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2,2-Disubstituted Analogues of the Natural Hormone 1α,25-Dihydroxyvitamin D_3: Chemistry and Biology

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Abstract—Six new 2,2-disubstituted analogues of the natural hormone calcitriol have been prepared. Chemical novelty includes (1) the first example of an inverse-electron-demand Diels–Alder cycloaddition using a pyrone diene and a difluorinated vinyl ether dienophile, leading to difluorinated analogues **7** and (2) a conceptually streamlined approach to dimethylated 19-nor analogues **8**. Analogues **7a** and **8a** are similar to calcitriol in terms of in vitro antiproliferative activity, but they are different from calcitriol in terms of transcriptional activity: difluorinated analogue **7a** is 2–3 times more active transcriptionally than calcitriol, whereas dimethylated analogue **8a** is 7.5 times less active transcriptionally. Whereas the in vivo calcemic activity of difluorinated analogue **7a** is similar to that of calcitriol, dimethylated analogue **8a** is considerably less calcemic than calcitriol. Dimethylated analogue **8a** strongly suppresses parathyroid hormone (PTH) secretion.

Introduction

The vitamin D family of steroid hormones is being studied by diverse scientists interested in issues ranging from fundamental organic and medicinal chemistry to molecular biology, endocrinology, and new drug development.[1] Much of the motivation for this widespread interest and effort is the growing appreciation that the natural hormone 1α,25-dihydroxyvitamin D_3 (calcitriol, **1**) has many different human biological functions ranging from regulating calcium and phosphorus homeostasis to governing cell growth and differentiation.[2] Medical use of the natural hormone calcitriol (**1**), however, is often risky due to the hypercalcemia typically induced by the supraphysiological levels of this hormone required to treat humans with diseases such as cancer, psoriasis, and autoimmune disorders.[1,2] Small chemical changes at various positions in the structure of the natural hormone have produced thousands of synthetic analogues, some of which have desirably low calcemic activity and high antiproliferative and pro-differentiation activities.[3] Several of such designer analogues are now undergoing preclinical evaluation for chemotherapy of diverse human diseases, and some of these synthetic analogues are U.S. FDA-approved drugs (e.g. calcipotriol for treatment of psoriasis and 1α,25-dihydroxy-19-nor-vitamin D_2 for treatment of secondary hyperparathyroidism).[2]

Structural changes specifically at the 2-position of the natural hormone in several cases produce analogues having desirable physiological properties. For example, the Chugai pharmaceutical company designed some 2-alkoxy and 2-alkyl analogues (e.g., **2** and **3**), among which ED-71 (**2**) is a leading drug candidate to treat women who have osteoporosis.[4] Also, we[5,6] and others[7–9] designed a series of 2-alkyl analogues (**4**–**6**) and showed that some of these 2-monosubstituted analogues have strong affinity for the vitamin D receptor (VDR). Additionally, 2β-fluoro-19-norcalcitriol[10] and 2β-fluorocalcitriol[11,12] have been prepared, and 4,4-difluorocalcitriol has been prepared to probe A-ring conformation.[13] No 2,2-disubstituted analogue of calcitriol (**1**), however, has been reported. Now, we describe a series of six 2,2-disubstituted analogues, prepared using

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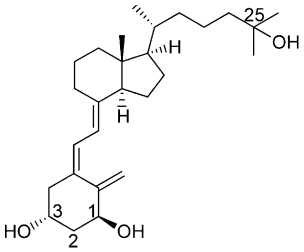
some novel organic chemistry. Strong electronic influence by two powerfully electronegative fluorine atoms[14] at position-2 was expected to enhance the hydrogen-bonding ability of the 1- and 3-OH groups and to afford new analogues **7** with enhanced VDR affinity and lipophilicity. Considerable steric hindrance (but minimal electronic influence) by two methyl groups at position-2 was expected to diminish the reactivity of the 1- and 3-OH groups (e.g., retarding 3-epimerization and A-ring dehydration)[15] in new 19-nor analogues **8** but probably also to interfere with VDR binding.

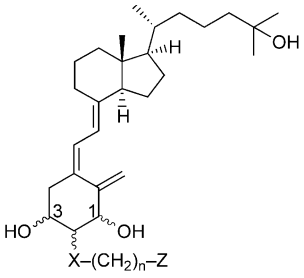
Chemistry

We have extensively developed Diels–Alder cycloaddition reactions of heteroaromatic 2-pyrones with electronically matched dienophiles to form synthetically versatile and stereochemically rich bicyclic lactone adducts.[16] We report here the first example of a successful high pressure 4+2-cycloaddition between commercial electron-poor 3-methoxycarbonyl-2-pyrone and a new geminally difluorinated electron-rich vinyl ether dienophile (Scheme 1); chromatographically pure racemic cycloadduct **9** was isolated in 73% yield, formed regiospecifically and stereospecifically with the desired 1,3-*trans* dioxygenation pattern necessary for ultimate transformation into calcitriol analogues **7**. Nucleophilic opening of the lactone in **9** using lithium allyloxide[17] proceeded smoothly to form polyfunctionalized cyclohexene **10** without intermolecular or intramolecular displacement of fluoride ion. Also, no loss of fluoride was encountered during the several subsequent steps in Scheme 1 using powerful nucleophiles (e.g., $LiAlH_4$, Ph_2PLi) or using high temperature for Claisen rearrangement of the sulfoxide-containing vinyl ether derived from allylic alcohol **12**; conjugated dienyl ester **13** was formed after in situ sulfoxide pyrolytic elimination.[18] Standard protocol[19] allowed smooth conversion of dienyl ester **13** into racemic 2,2-difluorinated A-ring phosphine oxide **14**. Coupling of phosphine oxide (±)-**14** with enantiomerically pure C,D-ring ketone (+)-**15**, followed by desilylation, produced the desired 2,2-difluorinated analogues (−)-**7a** and **7b** in a 5:1 ratio. Distinction between these two diastereomers was based, as in previous related cases, on their characteristic ^1H NMR (Table 1).[19] Based on chromatographic comparison and as expected based on the presence of two fluorine atoms, difluorinated analogue **7a** is noticeably more lipophilic than calcitriol (**1**).

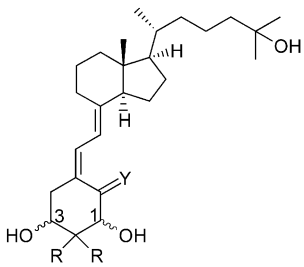
To simplify preparation of some 2,2-dimethyl analogues of calcitriol (**1**), we chose to design analogues lacking the 19-methylene group; DeLuca's pioneering work has shown that many 19-nor analogues of calcitriol (**1**) retain much of the hormone's desirable cell growth regulatory properties while having low calcemic activities.[20] Our streamlined synthetic approach, outlined in



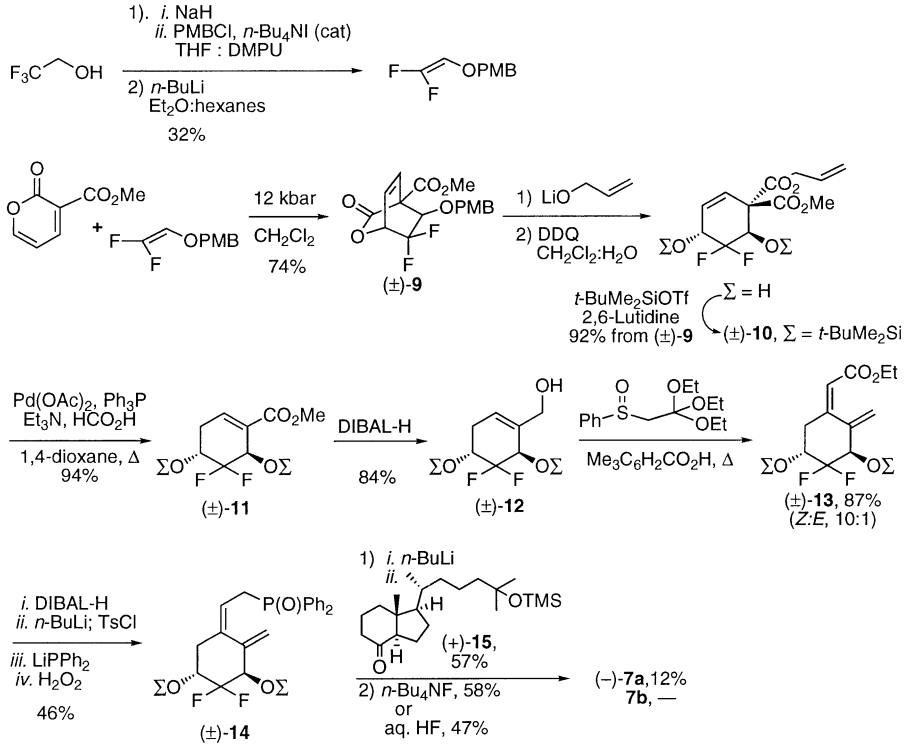
1α,25-dihydroxyvitamin D_3
(1,25D_3, calcitriol, **1**)



	1	X	n	Z	
2	α	β-O	3	OH	(ED-71)
3	α	β-CH_2	3	OH	(ED-120)
(–)-**4**	α	α-CH_2	3	OH	
(–)-**5**	α	α-CH_2	3	F	
(–)-**6**	β	β-CH_2	2	F	



	1	3	R	Y	
(–)-**7a**	α	β	F	CH_2	(KRC-2,2-F_2-1)
7b	β	α	F	CH_2	(KRC-2,2-F_2-2)
(+)-**8a**	α	β	CH_3	H_2	(BTW-1α,3β-2,2-Me_2-nor)
(+)-**8b**	β	α	CH_3	H_2	(BTW-1β,3α-2,2-Me_2-nor)
(+)-**8c**	α	α	CH_3	H_2	(BTW-1α,3α-2,2-Me_2-nor)
(+)-**8d**	β	β	CH_3	H_2	(BTW-1β,3β-2,2-Me_2-nor)



Scheme 1.

Table 1. ^{1}H NMR (δ) and optical rotation characteristics of new analogues

Analogue	C_{18}-CH_3	C_6-H	C_7-H	$[\alpha]_D^{25}$
7a	0.55	6.45	6.02	
7b	0.54	6.47	6.00	
8a	0.54	6.29	5.84	+29
8b	0.55	6.30	5.83	+21
8c	0.54	6.31	5.85	+94
8d	0.55	6.33	5.86	+42

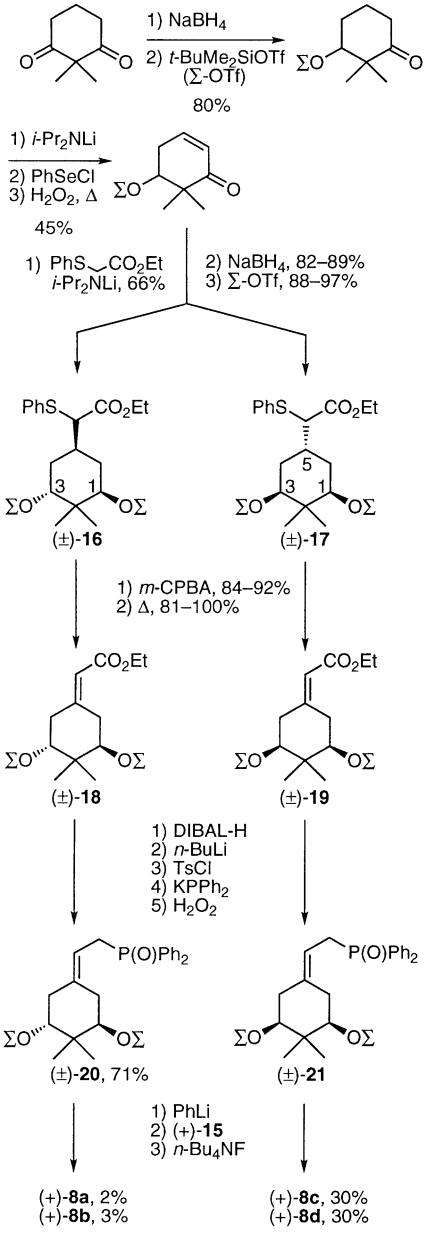
Scheme 2 starting with symmetrical 2,2-dimethyl-1,3-cyclohexanedione, involves a series of intermediates grouped into two families: (1) a pair of diastereomeric *trans*-1,3-dihydroxycyclohexanes **16** and (2) the corresponding *cis*-1,3-dihydroxycyclohexane **17** having symmetrical substitution about a plane through C-2 and C-5 of the cyclohexane ring and, therefore, having also a simplified ^{1}H NMR spectrum especially in the δ 3.7 region (see Experimental). Noteworthy is the Michael addition of a phenylthioacetate enolate that occurs exclusively *trans* to the resident siloxy group leading to two 3-siloxy-5-phenylthioacetate cyclohexanone precursors to adducts **16** and **17**. In these two cyclohexanone precursors to adducts **16** and **17**, proton NMR shows clearly that the 3- and 5-substituents are *trans* to each other, with the 3-siloxy group axial and with the equatorial C-3 H appearing at δ 3.8 as a doublet of doublets with coupling constants of 2.2 and 4.0 Hz. Sulfide oxidation of thioether adducts **16** and **17** into the corresponding sulfoxides (as a mixture of diastereomers that were not separated) and then pyrolysis gave the pure α,β-unsaturated esters **18** and **19** in high yields. Standard transformations[19] then produced the A-ring phosphine oxides **20** and **21**. Each of these racemic A-ring units underwent separate Horner–Wadsworth–Emmons coupling with enantiomerically pure C,D-ring ketone (+)-**15** to form chromatographically separated 2,2-dimethyl-19-nor analogues **8a** and **8b** (in low yields) and also **8c** and **8d** (in good yields). Distinction between 1,3-*trans* diastereomers **8a** and **8b** and between 1,3-*cis* diastereomers **8c** and **8d** was based on optical rotations and ^{1}H NMR (Table 1)[19] and also on analogy with analogues of calcitriol (**1**) having similar 1,3-diol stereochemical relationships.[21]

Biology

Motivation for interest in non-calcemic analogues of calcitriol (**1**) rests not only on their potential chemotherapeutic applications but also on using these analogues as sensitive probes of the fundamental molecular mechanisms underlying the varied biological effects that such analogues elicit. For example, we have discovered that there is an inverse relationship between some analogues' transcriptional potencies and their interaction specifically with AF-2 residues of VDR[22] and that some A-ring analogues with low affinity for VDR modulate chondrocyte growth via membrane effects that are dependent on the stage of cell maturation.[23] New 2,2-difluoro analogues **7** and 2,2-dimethyl analogues **8** now provide some surprising observations; understanding the molecular biology underlying these results may advance this field in significant ways.

The antiproliferative activity, determined in vitro using murine keratinocytes as previously described,[24] of only one of the four 2,2-dimethyl diastereomers (i.e., **8a** with

natural A-ring diol stereochemistry) is similar to that of calcitriol (**1**, Fig. 1). Likewise, 2,2-difluoro diastereomer **7a** with natural A-ring diol stereochemistry has antiproliferative activity similar to that of calcitriol (**1**, Fig. 1). The VDR-mediated transcriptional potencies of 2,2-disubstituted analogues **7a** and **8a**, determined in vitro using a previously described protocol in rat osteosarcoma ROS 17/2.8 cells,[25] are different from that of calcitriol (**1**). The ED_{50} values for transcriptional activity are as follows: calcitriol (**1**), 0.4 nM; difluoro analogue **7a**, 0.15 nM; dimethyl analogue **8a**, 3.0 nM. Competition assays[25] using the recombinant human vitamin D receptor revealed the affinities of these two analogues [relative to 100% binding of calcitriol (**1**)] to be 9.6% for **7a** and 1.3% for **8a**. Thus, as rationally designed, the presence of two methyl groups at the 2-position in analogue **8a** strongly diminishes (by a factor of 75) binding of this analogue to the human VDR.



Scheme 2.

Remarkably however, this 2,2-dimethyl analogue **8a** is only 7.5-fold less active transcriptionally than calcitriol (**1**) in rat osteosarcoma cells. Likewise, although 2,2-difluoro analogue **7a** binds to the human VDR only about 1/10 as well as the natural hormone **1**, **7a** is 2–3 times more transcriptionally active in the rat osteosarcoma cells than the natural hormone **1**. Therefore, as in some related instances,[22,26] the levels of genomic activity produced by analogues **7a** and **8a** are not directly proportional to their affinities for the nuclear VDR.

2,2-Dimethyl analogue **8a** with natural 1α,3β-diol stereochemistry (but not the diastereomeric 1α,3α-diol analogue **8c**) is a strong inhibitor in vitro of parathyroid hormone (PTH) secretion (Fig. 2). Confluent cultures of bovine parathyroid cells were incubated for 72 h with various concentrations of dimethlylated analogues **8a**, **8c** or calcitriol (**1**). The steady state levels of PTH secretion were then determined during a 3-h incubation with fresh medium. As shown in Fig. 2, *trans* diol ana-

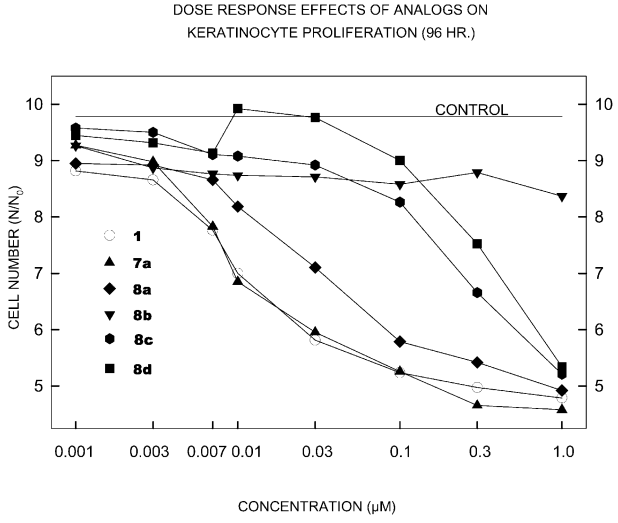


Figure 1.

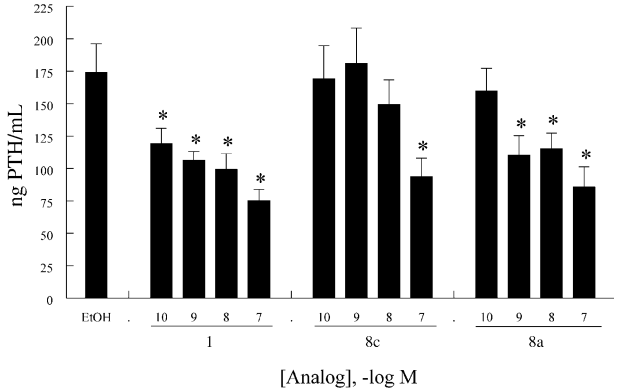


Figure 2. Suppression of PTH secretion. Confluent cultures of bovine parathyroid cells were treated for 72 h with the designated concentration of the vitamin D compounds. The cells were then incubated in fresh medium, and the amount of PTH secreted during a 3-h period was determined by RIA. The values are expressed as mean ± SD ($n = 6$). *$p < 0.001$.

logue **8a** appeared to be about 10 times less active than calcitriol (**1**), whereas *cis* diol analogue **8c** appeared to be several hundred times less active than calcitriol (**1**). Inhibition of PTH by calcitriol (**1**) is well established to involve repression of PTH gene transcription[27,28] and vitamin D response elements (VDREs) have been identified in the promoters of the human,[29] rat,[30] and chick[31] PTH genes. Further characterization of these negative VDREs and establishment of transcriptional assays have been hampered by the lack of a parathyroid cell line and the lack of activity of the PTH gene promoter in non-parathyroid cells. The suppression of PTH by vitamin D compounds is known to be VDR-dependent, but the other components of the negative regulatory complex have not been characterized. In fact, while VDR/RXR dimers appear to bind the rat and chick VDREs,[30,31] the dimerization partner for VDR binding to the human PTH VDRE has not been identified.[32] Thus, the molecular details of the mechanism for transcriptional repression by liganded VDR are not known. The VDR present in the parathyroid glands is functionally indistinguishable from that in other tissues. Studies examining structure–activity relationships for the suppression of PTH by vitamin D analogues have revealed a close correlation between the VDR affinity and suppressive activity. [33] The suppressive activity of PTH by *trans* diol analogue **8a** correlates well with the transcriptional potency of this analogue in the rat osteosarcoma cells, further substantiating that this suppressive activity is mediated by the vitamin D receptor.

The in vivo calcemic activities of difluoro analogue **7a** and dimethyl analogue **8a** were determined using our standard protocol[19] in which rats are treated daily with calcitriol (**1**) at 0.5 μg/kg body weight and with our new analogues at either 10.0 μg/kg body weight (Fig. 3) or 1.0 μg/kg body weight (Fig. 4) daily for 1 week. At a 20-fold higher dose than calcitriol (**1**), dimethyl analogue **8a** caused only slight elevation of urinary calcium levels (Fig. 3) but no slowing of animal weight gain (data not shown). In sharp contrast, even at only a 2-fold higher dose than calcitriol (**1**), difluoro analogue **7a** elevated urinary calcium levels more than did calcitriol (**1**, Fig. 4). This strong calcemic activity of difluoro analogue **7a** was not expected based on its relatively low VDR binding affinity (9.6% that of the natural hormone **1**) or based on the low calcemic effect of the closely related 2β-fluorocalcitriol.[12]

In conclusion, rationally designed and newly synthesized 2,2-disubstituted chemical entities **7a** and **8a** illustrate how even very small structural changes in large molecules can produce powerful and different biological effects. Specifically, the desirable characteristics of high antiproliferative and PTH-suppression activities with low calcemic activity make new dimethylated analogue **8a** suitable for further in vivo testing as a potential chemotherapeutic drug candidate. The new knowledge presented here about the relationships between chemical structure and biological activity may allow also other analogues of calcitriol (**1**) to be prepared for medicinal use and/or for use as sensitive probes of vitamin D molecular biology and mechanism of action.[34–36]

Experimental[19]

***p*-Methoxybenzyl 2,2,2-trifluoroethyl ether.** Trifluoroethanol (10 g, 0.10 mol) in THF (10 mL) was added dropwise via addition funnel to a stirred suspension of NaH (2.9 g, 0.12 mol) in THF (10 mL) at 0 °C over a period of 30 min. To the resulting mixture was added a

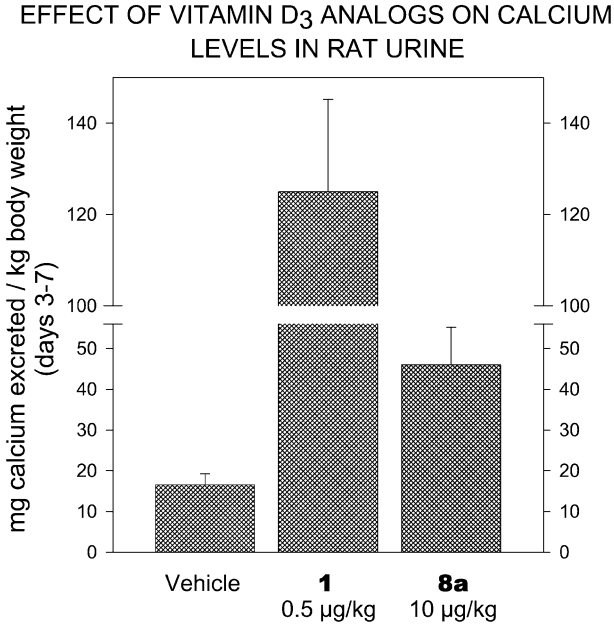


Figure 3. Effects of vitamin D_3 analogues on urinary calcium excretion in rats. Animals were treated with 0.5–10.0 microgram/kg body weight of test compound po for 7 consecutive days, and urinary excretion of calcium was measured during days 3–7. Values are mean + SE from three animals in each group.

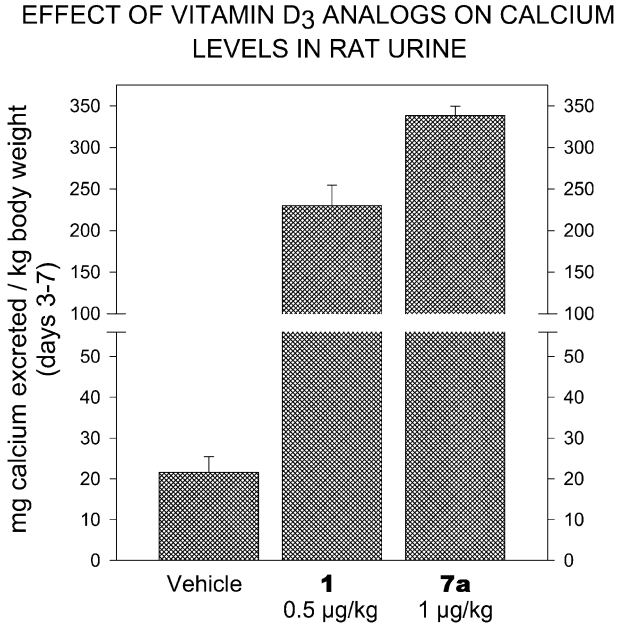


Figure 4. Effects of vitamin D_3 analogues on urinary calcium excretion in rats. Animals were treated with 0.5–10.0 microgram/kg body weight of test compound po for 7 consecutive days, and urinary excretion of calcium was measured during days 3–7. Values are mean + SE from three animals in each group.

solution of *p*-methoxybenzyl chloride (PMB-Cl, 19 g, 0.12 mol) in THF (10 mL) and *N,N'*-dimethylpropyleneurea (DMPU, 6 mL) via addition funnel over 1 h. After this addition, tetrabutylammonium iodide (*n*-Bu_4NI, 11 g, 0.03 mol) was added and the mixture warmed slowly to rt overnight. After acidic workup, the crude product was vacuum distilled to afford the desired ether as a pale orange liquid (25 g, quantitative): bp 100–101 °C/0.5 mm Hg; ^1H NMR ($CDCl_3$) δ 7.30–7.21 (m, 2H), 6.93–6.85 (m, 2H), 4.58 (s, 2H), 3.78 (s, 3H), 3.76 (q, $J=9.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 159.7, 129.6, 128.5, 124.1 (q, $J=278.0$ Hz), 113.9, 73.6, 66.6 (q, $J=33.7$ Hz), 55.1; ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −74.2 to −74.4 (m); IR (neat) 2937, 2837, 1613, 1515, 1280, 1250, 1164, 1117, 1034, 998, 965, 827, 665. Anal. Calcd for $C_{17}H_{16}F_2O_6$: C, 54.55; H, 5.04, found: C, 54.51; H, 5.24.

***p*-Methoxybenzyl 2,2-difluorovinyl ether.** A solution of *n*-BuLi (26 mL, 0.26 mol, 10 M in hexanes) was added dropwise via addition funnel to a 1 L flask fitted with an argon inlet and outlet bubbler charged with a cold (−78 °C), stirred solution of the aforementioned ether (23 g, 0.10 mol) in Et_2O (210 mL). The resulting solution was allowed to reach rt gradually overnight. Upon cooling the mixture to 0 °C, the reaction was quenched with dropwise addition of saturated aq NH_4Cl (50 mL). The reaction mixture was then extracted with Et_2O (3×50 mL) and the combined organics filtered through Celite, washed with H_2O (2×250 mL), dried (Na_2SO_4), filtered, and carefully concentrated to a brown oil. Vacuum distillation gave the desired 2,2-difluorovinyl ether as a pale yellow, somewhat unstable liquid (6.6 g, 32%) followed by a mixture of starting material and desired product (3.4 g, ∼1:1). PMB-2,2-difluorovinyl ether: bp 98 °C/0.5 mm Hg; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.24 (m, 2H), 6.94–6.87 (m, 2H), 5.65 (dd, $J=22.0$, 3.8 Hz, 1H), 4.67 (s, 2H), 3.82 (s, 3H). Due to its instability, this 2,2-difluorovinyl ether was used immediately.

4-Carbomethoxy-5-*endo*-[(*p*-methoxybenzyl)oxy]-6,6-difluoro-3-oxo-2-oxabicyclo-[2.2.2]oct-7-ene (±)-9. A five-inch length of heat shrinkable Teflon tubing (Ace Glass #12685–40) was heat sealed at one end with a stainless steel plug. To the tube were added 3-carbomethoxy-2-pyrone (1.0 g, 6.5 mmol), CH_2Cl_2 (10 mL), and PMB-2,2-difluorovinyl ether (6.5 g, 32 mmol). The tube was sealed at the other end with a stainless steel plug and placed under high pressure (10–12 kbar) for 5 days.[37] The tube was opened, the reaction mixture was transferred to a flask and concentrated in vacuo, and the residue purified by silica gel chromatography (5–40% EtOAc/hexanes). The fractions containing the desired *syn,endo* isomer (±)-**9** were combined and concentrated to a faint yellow oil, which afforded white crystals on standing (1.7 g, 74%): mp 74–76 °C; ^1H NMR ($CDCl_3$) δ 7.23–7.17 (m, 2H), 6.96–6.92 (m, 1H), 6.91–6.85 (m, 2H), 6.57–6.49 (m, 1H), 5.17–5.09 (m, 1H), 4.72 (d, $J=11.2$ Hz, 1H), 4.49 (d, $J=11.2$ Hz, 1H), 4.36 (d, $J=8.0$ Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.5, 165.1, 159.7, 132.5, 130.3, 127.7, 126.6 (d, $J=5.3$ Hz), 118.6 (t, $J=259.6$ Hz), 113.7, 75.3 (t, $J=8.7$ Hz), 74.9 (t, $J=8.4$ Hz), 74.7, 74.2 (d, $J=2.2$ Hz), 61.0 (d, $J=6.1$ Hz), 55.2, 53.2; ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ−103.3 (ddd, $J=244.9$, 15.8, 5.1 Hz), −113.8 (d, $J=244.9$ Hz); IR (neat) 2954, 1780, 1751, 1613, 1515, 1340, 1295, 1250, 1171, 1131, 1103, 1049, 826. Anal. Calcd for $C_{17}H_{16}F_2O_6$: C, 57.63; H, 4.55, found: C, 57.64; H, 4.62.

Bis-silylated mixed malonate (±)-10. A solution of *n*-BuLi (1.6 M in hexanes, 0.900 mL, 1.44 mmol) was added dropwise to freshly distilled allyl alcohol (5 mL) at 0 °C. Bicyclic lactone (±)-**9** (300 mg, 0.847 mmol) was then added in solution (5 mL CH_2Cl_2, 2.5 mL allyl alcohol) over 10 min. The reaction was stirred at 0 °C for 3 h and quenched with saturated aq NH_4Cl. The aqueous phase was extracted with EtOAc (3×25 mL), the combined organics dried over $MgSO_4$, and the solvents removed in vacuo to provide crude hydroxy mixed malonate as a pale yellow oil requiring no further purification for the following deprotection.

To the crude hydroxy mixed malonate was added CH_2Cl_2, H_2O (4.25 and 0.25 mL, respectively), and DDQ (297 mg, 1.31 mmol). Additional DDQ (297 mg) was added after 6 h of stirring to complete the deprotection. After 12 h, the reaction was cautiously quenched with saturated aq $NaHCO_3$, decanted into H_2O (50 mL), extracted with CH_2Cl_2 (3×20 mL), dried over Na_2SO_4, filtered through silica (1 inch plug), and concentrated to an oil requiring no further purification for the following bis-silylation.

The crude diol was dissolved in CH_2Cl_2 (8.0 mL), cooled to −78 °C, and treated with 2,6-lutidine (195 μL, 1.68 mmol) and TBSOTf (339 μL, 1.48 mmol). After stirring for 3 h, additional 2,6-lutidine and TBSOTf were added (same amounts as above). The reaction mixture was allowed to warm to 0 °C, at which time additional 2,6-lutidine and TBSOTf were added (same amounts as above) and the solution stirred at 0 °C overnight. Additional 2,6-lutidine and TBSOTf were added (3×s, same amounts as above) to complete the reaction. After normal aqueous workup, the crude oil was passed though flash silica gel (5% EtOAc/hexanes) to afford (±)-**10** as a pale yellow oil [323 mg, 92% from (±)-**9**]: ^1H NMR ($CDCl_3$) δ 6.02 (dq, $J=10.4$, 1.6 Hz, 1H), 5.85 (ddt, $J=17.2$, 10.4, 5.7 Hz, 1H), 5.73 (ddd, $J=10.4$, 6.4, 2.4 Hz, 1H), 5.25 (dddd, $J=10.4$, 6.4, 1.6, 1.2 Hz, 2H), 5.05 (d, $J=11.6$ Hz, 1H), 4.61 (apparent dddt, $J=29.5$, 13.1, 5.7, 1.2 Hz, 2H), 4.63–4.54 (m, 2H), 3.74 (s, 3H), 0.90 (s, 9H), 0.84 (s, 9H), 0.15 (d, $J=2.8$ Hz, 3H), 0.10 (s, 6H), 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 167.2, 166.3, 131.2, 129.4 (d, $J=7.6$ Hz), 123.6, 119.3 (t, $J=249.4$ Hz), 118.6, 71.8 (dd, $J=24.7$, 6.0 Hz), 66.4 (dd, $J=19.8$, 5.4 Hz), 63.0 (d, $J=5.4$ Hz), 53.1, 25.6, 18.2, 18.0, −4.5 (d, $J=6.0$ Hz), −4.9 (d, $J=5.4$ Hz), −5.3; ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −115.7 (d, $J=246.7$ Hz),−124.9 (dd, $J=246.7$, 15.2 Hz); IR (neat) 2954, 2931, 2858, 1749, 1255, 1221, 1200, 1180, 1135, 1111, 1040, 870, 838, 780; HRMS: calcd for $C_{24}H_{48}F_2O_6Si_2+Na$ 453.2386, found 453.2386.

Methyl ester (±)-11. A mixture of (±)-**10** (266 mg, 0.511 mmol), formic acid (24 μL, 0.638 mmol), Et_3N (93

μL, 0.664 mmol), Ph_3P (27 mg, 0.102 mmol), and palladium (II) acetate (12 mg, 0.051 mmol) in 1,4-dioxane (1.6 mL) was heated to 100 °C in a sealed tube for 16 h. Upon cooling, the tube was carefully purged under argon and dilute HCl added (1 mL, 1 M aq). The contents of the tube were transferred to a separatory funnel and partitioned between H_2O and CH_2Cl_2, extracted (3×10 mL CH_2Cl_2), dried ($MgSO_4$), filtered, concentrated, and passed through flash silica gel (5% EtOAc/hexanes) to give (±)-**11** (210 mg, 94%) as a clear oil which solidified on standing: mp 42–43 °C; ^{1}H NMR ($CDCl_3$) δ 6.91 (dd, J=4.8, 2.8 Hz, 1H), 4.69 (t, J=6.4 Hz, 1H), 4.40–4.24 (m, 1H), 3.75 (s, 3H), 2.75–2.60 (m, 1H), 2.45 (ddd, J=19.4, 9.0, 2.8 Hz, 1H), 0.91 (s, 9H), 0.85 (s, 9H), 0.17 (d, J=1.6 Hz, 3H), 0.14 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.6, 139.6, 130.5 (d, J=6.1 Hz), 119.3 (t, J=249.4 Hz), 67.8 (dd, J=87.9, 20.2 Hz), 64.8 (t, J=20.2 Hz), 51.8, 34.0, 25.7, 18.14, 18.11,−4.9,−5.0,−5.1; ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ−121.6 (d, J=241.0 Hz),−130.4 (ddd, J=241.0, 25.1, 6.8 Hz); IR (neat) 2954, 2930, 2858, 1725, 1258, 1177, 1123, 1082, 900, 838, 781; HRMS: calcd for $C_{20}H_{38}F_2O_4Si_2$ + Na 459.2174, found 459.2177.

Allylic alcohol (±)-12. To a solution of (±)-**11** (200 mg, 0.458 mmol) in CH_2Cl_2 (5 mL) at −78 °C was slowly added diisobutylaluminum hydride (DIBAL-H, 1.01 mL, 1.01 mmol, 1.0 M in $PhCH_3$). This mixture was allowed to warm to rt and stirred (1 h) until the reaction was complete by TLC analysis (20% EtOAc/hexanes). The reaction was quenched with aqueous sodium potassium tartrate (1 mL, 2 N), the mixture was extracted with CH_2Cl_2 (3×6 mL), the combined organic layers were washed with H_2O (4 mL), dried (Na_2SO_4), concentrated under reduced pressure, and passed through flash silica gel (5–10% EtOAc/hexanes) to afford (±)-**12** (158 mg, 84%) as a white solid: mp 42–44 °C; ^{1}H NMR ($CDCl_3$) δ 5.67 (m, 1H), 4.47 (t, J=9.2 Hz, 1H), 4.24–4.06 (m, 1H), 4.11 (s, 2H), 2.58–2.40 (m, 1H), 2.34–2.17 (m, 1H), 1.63 (br s, 1H), 0.91 (s, 9H), 0.89 (s, 9H), 0.15 (s, 6H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 136.5 (m), 123.2, 120.1 (t, J=247.5 Hz), 68.7 (t, J=25.8 Hz), 67.0 (t, J=24.0 Hz), 63.8, 33.0 (m), 25.8, 25.6, 18.2, 18.1,−4.7, −4.9, −5.1; ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ−122.5 to−124.5 (m); IR (neat) 3601–3094 (br), 2954, 2930, 2859, 1472, 1463, 1256, 1186, 1126, 1102, 1080, 896, 878, 862, 837, 778. Anal. Calcd for $C_{20}H_{38}F_2O_4Si_2$: C, 55.84; H, 9.37, found: C, 56.10; H, 9.49.

***Z*-dienoate ester (±)-13.** A 25-mL hydrolysis tube containing a solution of (±)-**12** (158 mg, 0.387 mmol), 1-phenylsulfinyl-2,2,2-triethoxyethane[38] (289 mg, 1.01 mmol) and 2,4,6-trimethylbenzoic acid (TMBA, 6.8 mg, 0.041 mmol) in CH_2Cl_2 (2 mL) was heated to 115 °C for 16 h. After cooling to rt, the solvent was removed in vacuo and the resulting light yellow oil was purified by flash silica gel chromatography (2–5% EtOAc/hexanes) to afford a mixture of *Z*- and *E*-dienoate esters (64 mg, ∼2.2:1.0) and pure *Z*-dienoate ester (±)-**13** (104 mg). Separation of the remaining *Z*/*E* mixture using preparative plate chromatography (1000 μm, 5% EtOAc / hexanes) afforded pure *E*-dienoate ester (14 mg, 8%) and pure (±)-**13** (42 mg, 146 mg total, 79%) both as clear oils. (±)-**13**: ^{1}H NMR ($CDCl_3$) δ 5.72 (br s, 1H), 5.42 (t, J=1.6 Hz, 1H), 5.26 (br s, 1H), 4.59–4.47 (m, 1H), 4.21–4.04 (m, 1H), 4.13 (q, J=7.0 Hz, 2H), 2.53 (dt, J=13.6, 1.4 Hz, 1H), 2.33 (ddd, J=13.6, 4.8, 1.4 Hz, 1H), 1.23 (t, J=7.0 Hz, 3H), 0.92 (s, 9H), 0.88 (s, 9H), 0.11 (d, J=12.4 Hz, 6H), 0.10 (d, J=8.8 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 165.4, 149.0, 141.1, 119.7, 119.6 (t, J=250.2 Hz), 115.9, 72.6 (t, J=23.5 Hz), 69.4 (t, J=25.8 Hz), 60.0, 41.4, 25.6, 25.5, 18.3, 18.0, 14.1, −5.0, −5.1, −5.3; ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −120.7 (d, J=242.3 Hz), −123.7 (d, J=242.3 Hz); IR (neat) 2956, 2931, 2896, 2858, 1730, 1646, 1473, 1366, 1255, 1222, 1184, 1161, 1122, 1098, 1037, 1006, 940, 893, 838, 800; HRMS: calcd for $C_{23}H_{42}F_2O_4Si_2$ 476.2590, found 476.2587.

A-ring phosphine oxide (±)-14. To a solution of (±)-**13** (104 mg, 0.218 mmol) in $PhCH_3/CH_2Cl_2$ (3.0 mL, 2:1) at −78 °C was slowly added a solution of DIBAL-H (480 μL, 1.0 M in $PhCH_3$, 0.480 mmol) via syringe. The reaction was maintained at −78 °C (1 h), then slowly warmed to −50 °C at which time the reaction was complete by TLC analysis (25% EtOAc/hexanes). The reaction was quenched with aqueous sodium potassium tartrate (1 mL, 2 N), HCl (1 mL, 1 M aqueous) and H_2O (1 mL), the organic layer was separated and the aq layer extracted with CH_2Cl_2 (3×6 mL), the combined organics dried (Na_2SO_4) and concentrated to give the desired allylic alcohol (103 mg) as a colorless oil which was pure enough to be carried forward directly.

To a cold (−78 °C) solution of the crude allylic alcohol in THF (2.5 mL) was added a solution of *n*-BuLi (178 μL, 0.283 mmol, 1.53 M in hexanes) dropwise via syringe. The resulting solution was warmed (0 °C) for 30 min, cooled (−20 °C), and treated with a precooled solution of TsCl (62 mg, 0.327 mmol) in THF (0.5 mL). After stirring for 30 min at 0 °C, the reaction mixture was cooled (−78 °C) and treated with enough of a precooled solution of lithium diphenylphosphide [generated from the addition of *n*-BuLi (623 μL, 0.990 mmol, 1.53 M in hexanes) to a cold (−78 °C) solution of Ph_2PH (172 μL, 0.990 mmol) in THF (2.6 mL)] until an orange color persisted for 5 min (∼2.1 mL). The reaction mixture was quenched with H_2O (three drops), warmed to rt, the solvent removed in vacuo, the residual oil dissolved in CH_2Cl_2 (3.5 mL), treated with hydrogen peroxide (2 mL, 5% aqueous H_2O_2), and stirred vigorously for 1 h. After general aqueous workup, the crude reaction mixture was passed through flash silica (20–50% EtOAc/hexanes) to afford 62 mg [46% from (±)-**13**] of (±)-**14** as a clear oil: ^{1}H NMR ($CDCl_3$) δ 7.75–7.65 (m, 4H), 7.56–7.41 (m, 6H), 5.45 (apparent dd, J=14.6, 7.0 Hz, 1H), 5.36 (t, J=1.6 Hz, 1H), 4.96 (br s, 1H), 4.42–4.30 (m, 1H), 4.10–3.99 (m, 1H), 3.35 (dt, J=14.2, 8.4 Hz, 1H), 3.17 (dt, J=15.6, 6.9 Hz, 1H), 2.45 (d, J=14 Hz, 1H), 2.31–2.21 (m, 1H), 0.91 (s, 9H), 0.81 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 141.8 (d, J=2.2 Hz), 137.8 (d, J=11.4 Hz), 133.1 (d, J=33.4 Hz), 132.1 (d, J=33.4 Hz), 131.9 (t, J=2.2 Hz), 130.9 (dd, J=9.1, 3.8 Hz), 128.6 (dd, J=11.4, 3.1 Hz), 120.0 (t, J=245.2 Hz), 117.5 (d,

$J=7.6$ Hz), 114.9, 72.7 (t, $J=22.3$ Hz), 69.5 (t, $J=26.5$ Hz), 40.9, 31.5 (d, $J=70.6$ Hz), 25.62, 25.57, 18.3, 18.0, −5.0, −5.1; ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −118.0 to −125.0 (m); IR (neat) 2952, 2929, 2856, 1472, 1438, 1255, 1166, 1120, 1093, 939, 892, 837, 780, 695, 552, 509; HRMS: calcd for $C_{33}H_{49}F_2O_3PSi_2$ 618.2926, found 619.3007.

General HWE Coupling: 2,2-difluorocalcitriol analogues (−)-7a and 7b. Prior to reaction, phosphine oxide (±)-**14** and C,D-ring ketone (+)-**15**[39] were azeotropically dried with benzene and left under vacuum for 48 h. To a solution of (±)-**14** (63 mg, 0.102 mmol) in THF (1.1 mL) at −78 °C was added a solution of *n*-BuLi (64 μL, 0.101 mmol, 1.59 M in hexanes). After stirring in the dark for 1 h, a precooled (−78 °C) solution of (+)-**15** (32 mg, 0.08 mmol) in THF (0.3 mL) was slowly cannulated into the flask containing the red-orange ylide. The reaction mixture was maintained at −78 °C (3 h) then warmed to −40 °C (2 h). During this time the red-orange color faded to light yellow. The reaction was quenched with H_2O (3 mL), extracted with Et_2O (3×5 mL), dried ($MgSO_4$), filtered, and concentrated to give a crude product which was purified by flash silica gel chromatography (1% EtOAc/hexanes) to give a mixture of silyl protected analogues (23 mg, 57%), followed by recovered (+)-**15** (elution with 20% EtOAc/hexanes, 7 mg, 37%) and (±)-**14** (elution with 50% EtOAc/hexanes, 27 mg, 43%).

Half of the mixture of silyl-protected analogues was dissolved in THF (1.5 mL), treated with tetrabutylammonium fluoride (TBAF, 68 μL, 0.068 mmol, 1 M in THF), allowed to stir at rt overnight, and concentrated to an oil. Purification by flash silica gel chromatography (40% EtOAc/hexanes) gave 4.2 mg (58%) of a mixture of (−)-**7a** and **7b**. The other half of this mixture was dissolved in EtOH (3.0 mL), cooled to 0 °C, and treated with a solution of hydrogen fluoride (100 μL, 49% aq HF), warmed to room temperature over 2 h, and treated with additional HF solution (3×100 μL) to complete global deprotection. Upon completion by TLC analysis (50% EtOAc/hexanes), the reaction mixture was cautiously quenched with saturated $NaHCO_3$ solution and subjected to a general extraction. Purification by flash silica gel chromatography (40% EtOAc/hexanes) afforded 3.4 mg (47%) of the diastereomeric mixture. The combined mixture of diastereomers was subjected to HPLC separation (CHIRALCEL® OJ semipreparative column, 15% *i*-PrOH/hexanes, 3 mL/min) to afford only pure diastereomer **7a**. (−)-**7a**: (3 mg, 12%, 1α,3β, R_f 37.2 min); [α]-12.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.45 (d, $J=11.2$ Hz, 1H), 6.02 (d, $J=11.2$ Hz, 1H), 5.62–5.55 (m, 1H), 5.26–5.20 (m, 1H), 4.60–4.46 (m, 1H), 4.28–4.15 (m, 1H), 2.81 (dd, $J=14.0$, 4.8 Hz, 1H), 2.68 (d, $J=14.0$ Hz, 1H), 2.45 (ddd, $J=14.0$, 4.8, 3.8 Hz, 1H), 1.22 (s, 6H), 0.94 (d, $J=6.4$ Hz, 3H), 0.55 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 144.8, 141.4, 129.0, 126.9, 118.1 (t, $J=247.0$ Hz), 116.7, 115.7, 71.9 (t, $J=22.0$ Hz), 71.1, 69.4–68.5 (m), 56.5, 56.4, 46.0, 44.4, 40.4, 39.3, 36.3, 36.1, 29.4, 29.2, 27.6, 23.7, 22.2, 20.8, 18.8, 12.0; ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −121.6 to −126.0 (m); IR (neat) 3636–3072 (br), 2937, 2869, 1377, 1215, 1156, 1077, 757; HRMS: calcd for $C_{27}H_{42}F_2O_3+Na$ 475.3000, found 475.3002.

5-(*t*-Butyldimethylsilyl)oxy-6,6-dimethyl-2-cyclohexenone. 3-Hydroxy-2,2-dimethylcyclohexanone (2.39 g, 16.8 mmol), prepared according to literature procedures,[40] was dissolved in CH_2Cl_2 (50 mL), cooled to −78 °C, and treated with 2,6-lutidine (2.92 mL, 25.2 mmol) and TBSOTf (3.84 mL, 16.8 mmol). The solution was stirred for 30 min at −78 °C, quenched with H_2O (30 mL), and extracted with CH_2Cl_2. The combined organics were dried over $MgSO_4$ and concentrated in vacuo. Silica gel chromatography (3% EtOAc/hexanes) provided 3-(*t*-butyldimethylsilyl)oxy-2,2-dimethylcyclohexanone as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 3.64 (dd, $J=7.2$, 2.8 Hz, 1H), 2.34 (apparent t, $J=6.8$ Hz, 2H), 2.04–1.85 (m, 2H), 1.77–1.66 (m, 1H), 1.65–1.53 (m, 1H) 1.08 (s, 3H), 1.04 (s, 3H), 0.84 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 214.6, 78.2, 51.4, 37.1, 29.2, 25.6, 23.1, 20.4, 17.9, −4.4, −5.2; IR ($CHCl_3$) 2954, 2858, 1713, 1472, 1255, 1120, 1082, 1002, 869, 835, 775; HRMS (EI) *m*/*z* (M^+) calcd 256.1859 for $C_{14}H_{28}O_2Si$, found 256.1856.

3-(*t*-Butyldimethylsilyl)oxy-2,2-dimethylcyclohexanone (1.53 g, 5.96 mmol) in THF (15 mL) was cooled to −78 °C and then cannulated into a freshly prepared solution of LDA (6.55 mL, 1 M in THF/hexanes). The reaction mixture was stirred for 15 min and then cooled in liquid nitrogen until the THF just begins to form a slurry. A solution of PhSeCl (3.30 g, 17.2 mmol) in CH_2Cl_2 (15 mL) was added all at once. The reaction temperature increased to −55 °C upon addition. Dilute HCl (6.5 mL, 1 N aq) was added and the reaction mixture was warmed to rt, dried ($MgSO_4$), and the organic solvents removed in vacuo. The residue was taken up in CH_2Cl_2 (40 mL), the mixture cooled to 0 °C, and H_2O_2 (3 mL, 29% aqueous) was added over 1 h. The reaction mixture was dried over $MgSO_4$, the organic solvents removed in vacuo, and the residue purified by silica gel chromatography (3% EtOAc/hexanes) to provide the desired 5-(*t*-butyldimethylsilyl)oxy-6,6-dimethyl-2-cyclohexenone (757 mg, 50%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.73 (ddd, $J=10.0$, 5.2, 3.2 Hz, 1H), 5.96 (ddd, $J=10.0$, 2.2, 1.6 Hz, 1H), 3.83 (dd, $J=7.6$, 4.8 Hz, 1H), 2.53 (ddt, $J=18.8$, 4.8, 1.6 Hz, 1H), 2.39 (dddd, $J=18.8$, 7.6, 3.0, 2.6 Hz, 1H), 1.12 (s, 3H), 1.05 (s, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 204.1, 144.5, 128.4, 74.4, 48.6, 32.8, 25.7, 21.3, 18.2, 17.9, −4.3, −5.0; IR ($CDCl_3$) 2956, 2931, 2857, 1681, 1253, 1099, 876, 837, 776; HRMS (EI) *m*/*z* (M^+) calcd 254.1702 for $C_{14}H_{26}O_2Si$, found 254.1698.

1,3-*trans* Bis protected diols (±)-16. To ethyl phenylthioacetate[41] (3.23 g, 16.5 mmol) in THF (30 mL) at −78 °C was added a freshly prepared solution of LDA (15.0 mL, 1 M in THF/hexanes) and the reaction mixture was stirred for 30 min. A solution of 5-(*t*-butyldimethylsilyl)oxy-6,6-dimethyl-2-cyclohexenone (952 mg, 3.74 mmol) in THF (30 mL) was added, the reaction was warmed to −30 °C, stirred for 12 h, quenched with H_2O (30 mL), and extracted with CH_2Cl_2. The combined organics were washed once with brine and dried

over $MgSO_4$, then concentrated in vacuo. Silica gel chromatography of the residue (3% EtOAc/hexanes) provided two diastereomeric thioethers (609 mg, 36%; 504 mg, 30%). Less polar thioether: ^{1}H NMR ($CDCl_3$) δ 7.48–7.24 (m, 5H), 4.22–4.05 (m, 2H), 3.82 (dd, J = 4.2, 2.2 Hz, 1H), 3.57 (d, J = 7.6 Hz, 1H), 2.79 (ddddd, J = 12.4, 12.4, 7.6, 4.8, 3.8 Hz, 1H), 2.70 (ddd, J = 14.6, 4.8, 2.0 Hz, 1H), 2.44 (dd, J = 14.6, 12.4 Hz, 1H), 2.09 (ddd, J = 13.6, 12.4, 2.2 Hz, 1H), 1.83 (dddd, J = 13.6, 4.2, 3.8, 2.0 Hz, 1H), 1.20 (t, J = 7.2 Hz, 3H), 1.13 (s, 3H), 1.07 (s, 3H), 0.83 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 213.0, 171.1, 134.1, 132.2, 129.1, 127.8, 77.7, 61.4, 57.4, 50.1, 41.0, 34.8, 31.8, 25.8, 24.3, 21.3, 18.0, 14.0, −4.5, −5.1; IR ($CHCl_3$) 2956, 2930, 2857, 1732, 1714, 1472, 1258, 1151, 1063, 1025, 832, 776; HRMS (EI) m/z ($M+H^+$) calcd 451.2338 for $C_{24}H_{38}O_4SSi$, found 451.2343. More polar thioether: ^{1}H NMR ($CDCl_3$) δ 7.47–7.23 (m, 5H), 4.19–4.06 (m, 2H), 3.84 (dd, J = 3.8, 2.2 Hz, 1H), 3.62 (d, J = 6.8 Hz, 1H), 2.83 (ddddd, J = 12.4, 12.0, 6.8, 4.8, 4.0 Hz, 1H), 2.68 (dd, J = 14.4, 12.4 Hz, 1H), 2.37 (ddd, J = 14.4, 4.8, 2.0 Hz, 1H), 2.12 (dddd, J = 14.0, 4.0, 3.8, 2.0 Hz, 1H), 2.01 (ddd, J = 14.0, 12.0, 2.2 Hz, 1H), 1.19 (t, J = 7.2 Hz, 3H), 1.14 (s, 3H), 1.07 (s, 3H), 0.85 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 212.9, 171.0, 133.6, 132.6, 129.0, 127.9, 77.7, 61.3, 57.0, 50.2, 40.9, 34.7, 32.4, 25.7, 24.3, 21.3, 18.0, 14.1, −4.5, −5.1; IR ($CHCl_3$) 2956, 2930, 2857, 1732, 1714, 1472, 1257, 1154, 1102, 1063, 1027, 833, 776; HRMS (EI) m/z ($M+H^+$) calcd 451.2338 for $C_{24}H_{38}O_4SSi$, found 451.2338.

To a solution of the less polar thioether (585 mg, 1.30 mmol) in MeOH (40 mL) was added $NaBH_4$ (5 mg, $1.5H^-$ equiv) in portions until starting material was consumed. The reaction was quenched with H_2O and extracted with EtOAc. The combined organics were washed with brine and dried over $MgSO_4$. After removal of the organic solvents in vacuo, silica gel chromatography provided two diastereomeric alcohols (162 mg, 27%; 362 mg, 62%) as colorless oils. Less polar 1,3-*cis* alcohol: ^{1}H NMR ($CDCl_3$) δ 7.47–7.22 (m, 5H), 4.19–4.02 (m, 2H), 3.95 (d, J = 10 Hz, 1H), 3.70–3.66 (m, 1H), 3.56 (d, J = 8.0 Hz, 1H), 3.55–3.50 (m, 1H), 2.66–2.54 (m, 1H), 2.26–2.18 (m, 1H), 1.86–1.58 (m, 3H), 1.18 (t, J = 7.2 Hz, 3H), 1.14 (s, 3H), 0.89 (s, 9H), 0.88 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.5, 134.0, 132.5, 128.9, 127.6, 77.5, 75.7, 61.0, 57.2, 37.6, 33.4, 32.4, 28.1, 25.8, 24.7, 24.4, 17.8, 14.1, −4.7, −5.2; IR ($CHCl_3$) 3511 (br), 2954, 2930, 2858, 1732, 1472, 1258, 1151, 1094, 1052, 838, 778; HRMS (EI) m/z ($M+H^+$) calcd 453.2495 for $C_{24}H_{40}O_4SSi$, found 453.2494. More polar 1,3-*trans* alcohol: ^{1}H NMR ($CDCl_3$) δ 7.46–7.20 (m, 5H), 4.19–4.00 (m, 2H), 3.80 (dd, J = 11.4, 4.6 Hz, 1H), 3.59–3.55 (m, 1H), 3.52 (d, J = 8.8 Hz, 1H), 2.47–2.35 (m, 1H), 2.26–2.18 (m, 1H), 1.68–1.50 (m, 3H), 1.17 (t, J = 7.2 Hz, 3H), 1.03 (s, 3H), 0.88 (s, 9H), 0.82 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.5, 134.1, 132.3, 128.9, 127.5, 76.6, 72.5, 61.0, 57.4, 40.0, 34.4, 33.0, 32.9, 25.8, 24.4, 18.1, 18.0, 14.0, −4.5, −5.1; IR ($CHCl_3$) 3426 (br), 2954, 2930, 2857, 1732, 1472, 1256, 1150, 1070, 833, 775; HRMS (EI) m/z ($M+H^+$) calcd 453.2495 for $C_{24}H_{40}O_4SSi$, found 453.2503.

Likewise, the more polar thioether (504 mg, 1.12 mmol), MeOH (30 mL), and $NaBH_4$ (13 mg, $1.5H^-$ equiv) provided two diastereomeric alcohols (257 mg, 51%; 162 mg, 31%) as colorless oils. Less polar, 1,3-*cis* alcohol: ^{1}H NMR ($CDCl_3$) δ 7.46–7.22 (m, 5H), 4.19–4.05 (m, 2H), 3.72–3.68 (m, 1H), 3.61 (d, J = 6.8 Hz, 1H), 3.53–3.49 (m, 1H), 2.69–2.57 (m, 1H), 2.10–2.02 (m, 1H), 1.91–1.79 (m, 2H), 1.75–1.66 (m, 1H), 1.26 (t, J = 7.2 Hz, 3H), 1.14 (s, 3H), 0.91 (s, 9H), 0.90 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.5, 134.7, 131.9, 128.9, 127.4, 77.5, 75.7, 61.1, 57.9, 37.5, 33.5, 32.2, 28.3, 25.7, 24.6, 24.3, 17.8, 14.0, −4.7, −5.3; IR ($CHCl_3$) 3512, 2954, 2930, 2858, 1733, 1472, 1257, 1150, 1095, 1052, 837, 777; HRMS (EI) m/z ($M+H^+$) calcd 453.2495 for $C_{24}H_{40}O_4SSi$, found 453.2489. More polar 1,3-*trans* alcohol: ^{1}H NMR ($CDCl_3$) δ 7.46–7.21 (m, 5H), 4.17–4.04 (m, 2H), 3.79 (dd, J = 11.6, 4.8 Hz, 1H), 3.62–3.58 (m, 1H), 3.55 (d, J = 8.0 Hz, 1H), 2.49–2.37 (m, 1H), 1.98–1.91 (m, 1H), 1.83–1.76 (m, 1H), 1.58–1.38 (m, 3H), 1.17 (t, J = 7.2 Hz, 3H), 1.04 (s, 3H), 0.89 (s, 9H), 0.83 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.7, 134.6, 132.0, 128.9, 127.4, 76.6, 72.5, 61.1, 57.7, 40.0, 34.4, 33.3, 32.6, 25.9, 24.4, 18.1, 18.0, 14.0, −4.4, −5.1; IR ($CHCl_3$) 3428 (br), 2954, 2929, 2857, 1733, 1472, 1255, 1153, 1071, 980, 832, 775; HRMS (EI) m/z ($M+H^+$) calcd 453.2495 for $C_{24}H_{40}O_4SSi$, found 453.2585.

Each of the 1,3-*trans* alcohols from above was protected as follows: to a solution of alcohol (1 equiv) in CH_2Cl_2 at −30 °C were added 2,6-lutidine (1.25 equiv) and TBSOTf (1.1 equiv). The reaction mixture was stirred for 30 min, quenched with H_2O, and extracted with CH_2Cl_2. The combined organics were dried over $MgSO_4$, the solvents removed in vacuo, and the residue purified by column chromatography to provide two 1,3-*trans* bis silyl ethers (±)-**16** both as a colorless oils. First 1,3-*trans* bis silyl ether (197 mg, 347 μmol, 97%); ^{1}H NMR ($CDCl_3$) δ 7.47–7.20 (m, 5H), 4.20–4.10 (m, 1H), 4.09–3.99 (m, 1H), 3.75 (dd, J = 7.2, 4.4 Hz, 1H), 3.56–3.53 (m, 1H), 3.48 (d, J = 8.0 Hz, 1H), 2.42–2.29 (m, 1H), 2.11–2.02 (m, 1H), 1.66–1.56 (m, 1H), 1.52–1.43 (m, 1H), 1.29–1.18 (m, 1H), 1.18 (t, J = 7.2 Hz, 3H), 0.93 (s, 3H), 0.884 (s, 9H), 0.882 (s, 9H), 0.78 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.6, 134.2, 132.4, 128.9, 127.5, 72.7, 61.0, 57.5, 42.6, 33.2, 32.4, 31.1, 25.9, 25.8, 18.1, 18.0, 14.0, −4.0, −4.4, −5.0; IR ($CHCl_3$) 2955, 2929, 2857, 1735, 1472, 1256, 1096, 1072, 833, 774; HRMS (EI) m/z ($M+H^+$) calcd 567.3360 for $C_{30}H_{54}O_4SSi_2$, found 567.3349. Second 1,3-trans bis silyl ether: (182 mg, 322 μmol, 93%); ^{1}H NMR ($CDCl_3$) δ 7.45–7.20 (m, 5H), 4.11 (ddd, J = 14, 7.2, 1.6 Hz, 2H), 3.74 (dd, J = 11.2, 4.8 Hz, 1H), 3.59–3.56 (m, 1H), 3.54 (d, J = 8.0 Hz, 1H), 2.43–2.31 (m, 1H), 1.95–1.87 (m, 1H), 1.66–1.36 (m, 3H), 1.19 (t, J = 7.2 Hz, 3H), 0.94 (s, 3H), 0.90 (s, 9H), 0.87 (s, 9H), 0.79 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.7, 134.8, 131.8, 128.9, 127.3, 76.7, 72.7, 61.0, 57.8, 40.5, 35.1, 33.3, 32.7, 25.91, 25.86, 25.2, 18.5, 18.1, 18.0, 14.1, −4.1, −4.3, −5.0, −5.1; IR ($CHCl_3$) 2929, 2857, 1737, 1472, 1368, 1256, 1150, 909, 873, 833, 775, 691; HRMS (EI) m/z ($M+H^+$) calcd 567.3360 for $C_{30}H_{54}O_4SSi_2$, found 567.3355.

1,3-trans unsaturated ester (±)-18. Each 1,3-*trans* bis silyl ether (±)-**16** was separately subjected to the following oxidation: to a solution of bis silyl ether (182 mg, 321 μmol) in CH_2Cl_2 (7–8 mL) at 0 °C was added a solution of *m*-CPBA (55 mg, 321 μmol) in CH_2Cl_2 (1 mL) dropwise, maintaining the solution at less than 5 °C at all times. Upon disappearance of the starting material, the reaction was quenched with saturated $NaHCO_3$ solution, dried over $MgSO_4$, and chromatographed over silica to provide two diastereomeric sulfoxides as colorless oils. From first 1,3-*trans* bis silyl ether above: (less polar sulfoxide, 52 mg, 90 μmol, 28%); ^{1}H NMR ($CDCl_3$) δ 7.70–7.43 (m, 5H), 3.88–3.74 (m, 3H), 3.63–3.60 (m, 1H), 3.33 (d, J = 6.8 Hz, 1H), 2.95–2.82 (m, 1H), 1.91–1.68 (m, 3H), 1.56–1.44 (m, 1H), 0.99 (t, J = 7.2 Hz, 3H), 0.96 (s, 3H), 0.93 (s, 9H), 0.87 (s, 9H), 0.79 (s, 3H), 0.09 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 167.1, 142.8, 131.8, 128.9, 125.5, 78.3, 76.7, 72.5, 61.1, 40.6, 34.1, 33.5, 31.1, 25.92, 25.88, 25.2, 18.5, 18.1, 18.0, 13.9, −4.0, −4.3, −5.1; IR ($CHCl_3$) 2955, 2930, 2885, 2857, 1726, 1472, 1252, 1098, 1083, 1070, 1053, 833, 775; HRMS (EI) m/z ($M+H^+$) calcd 583.3309 for $C_{30}H_{54}O_5Si_2S$, found 583.3313; (more polar sulfoxide, 112 mg, 192 μmol, 60%); ^{1}H NMR ($CDCl_3$) δ 7.63–7.47 (m, 5H), 4.10–3.89 (m, 2H), 3.70 (dd, J = 10.8, 4.4 Hz, 1H), 3.59–3.56 (m, 1H), 3.23 (d, J = 8.0 Hz, 1H), 2.54–2.40 (m, 1H), 1.86–1.78 (m, 1H), 1.68–1.59 (m, 2H), 1.52–1.41 (m, 1H), 1.08 (t, J = 7.2 Hz, 3H), 0.92 (s, 3H), 0.86 (s, 9H), 0.82 (s, 9H), 0.78 (s, 3H), 0.08 (s, 6H), 0.02 (s, 3H), −0.01 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 166.2, 142.0, 131.5, 129.1, 124.7, 76.2, 75.5, 72.4, 61.2, 40.6, 34.4, 33.0, 29.7, 25.8, 25.8, 25.1, 18.5, 18.0, 14.0, −4.1, −4.4, −5.0, −5.2; IR ($CHCl_3$) 2955, 2929, 2857, 2855, 1732, 1472, 1255, 1094, 1057, 834, 775; HRMS (EI) m/z ($M+H^+$) calcd 583.3309 for $C_{30}H_{54}O_5Si_2S$, found 583.3318. From second 1,3-*trans* bis silyl ether above: (less polar sulfoxide, 89 mg, 153 μmol, 44%); ^{1}H NMR ($CDCl_3$) δ 7.70–7.45 (m, 5H), 3.96–3.80 (m, 3H), 3.64–3.60 (m, 1H), 3.45 (d, J = 5.6 Hz, 1H), 2.95–2.86 (m, 1H), 1.86–1.72 (m, 3H), 1.01 (t, J = 7.2 Hz, 3H), 0.96 (s, 3H), 0.93 (s, 9H), 0.88 (s, 9H), 0.78 (s, 3H), 0.11 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 167.1, 142.6, 131.8, 128.9, 125.5, 77.7, 76.4, 72.6, 61.1, 40.6, 35.6, 31.0, 30.0, 25.92, 25.88, 25.2, 18.4, 18.1, 18.0, 14.0, −4.0, −4.3, −5.0, −5.1; IR ($CHCl_3$) 2955, 2930, 2857, 1725, 1250, 1074, 834, 775; HRMS (EI) m/z ($M+H^+$) calcd 583.3309 for $C_{30}H_{54}O_5Si_2S$, found 583.3324; (more polar sulfoxide, 81 mg, 140 μmol, 40%); ^{1}H NMR ($CDCl_3$) δ 7.63–7.47 (m, 5H), 4.00–3.90 (m, 1H), 3.86–3.72 (m, 2H), 3.58–3.55 (m, 1H), 3.18 (d, J = 9.6 Hz, 1H), 2.82–2.68 (m, 1H), 2.20–2.11 (m, 1H), 1.70–1.35 (m, 3H), 1.01 (t, J = 7.6 Hz, 3H), 0.96 (s, 3H), 0.91 (s, 9H), 0.90 (s, 9H), 0.81 (s, 3H), 0.08 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.6, 141.9, 131.1, 128.9, 124.5, 76.4, 74.5, 72.2, 61.0, 40.6, 34.9, 33.2, 29.7, 25.94, 25.91, 25.1, 18.5, 18.1, 18.0, 13.9, −3.9, −4.3, −5.17, −5.12; IR ($CHCl_3$) 2955, 2928, 2881, 2855, 1722, 1471, 1257, 1072, 833, 774; HRMS (EI) m/z ($M+H^+$) calcd 583.3309 for $C_{30}H_{54}O_5Si_2S$, found 583.3318.

A mixture of all four aforementioned sulfoxides (334 mg, 573 μmol total) was taken up in benzene and heated at reflux for 36 h. After removing the solvent in vacuo, silica gel chromatography (1–3% EtOAc/hexanes) provided (±)-**18** (212 mg, 81%) as a colorless oil with the following physical characteristics: ^{1}H NMR ($CDCl_3$) δ 5.66 (br s, 1H), 4.18–4.06 (m, 2H), 3.69 (dd, J = 8.0, 4.0 Hz, 1H), 3.67 (dd, J = 6.4, 3.6 Hz, 1H), 3.03 (dd, J = 14.4, 6.4 Hz, 1H), 2.94 (ddd, J = 14.4, 3.6, 1.6 Hz, 1H), 2.38 (ddd, J = 14.0, 4.0, 0.6 Hz, 1H), 2.22 (ddd, J = 14.0, 4.0, 1.2 Hz, 1H), 1.25 (t, J = 7.2 Hz, 3H), 0.94 (s, 3H), 0.93 (s, 3H), 0.87 (s, 9H), 0.85 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H), 0.018 (s, 3H), 0.016 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 166.4, 157.7, 116.9, 75.6, 74.9, 59.5, 41.8, 40.8, 33.4, 25.82, 25.76, 22.3, 21.1, 18.03, 17.97, 14.3, −4.1, −4.6, −5.0, −5.1; IR ($CHCl_3$) 2954, 2929, 2894, 2857, 1716, 1652, 1472, 1251, 1162, 1091, 1045, 835, 776; HRMS (EI) m/z ($M+H^+$) calcd 457.3169 for $C_{24}H_{48}O_4Si_2$, found 457.3176.

1,3-trans phosphine oxide (±)-20. To a solution of (±)-**18** (120 mg, 263 μmol) in Et_2O (5 mL) at −40 °C was added a solution of lithium aluminum hydride (LAH, 660 μL, 1 M in Et_2O) and the reaction mixture was warmed to 0 °C over 2 h. The reaction was quenched with a few drops of 1 N NaOH and the precipitated salts were washed with several portions of EtOAc. The combined organics were dried over $MgSO_4$ and the solvents removed in vacuo. Chromatographic purification of the residue over silica gel (5–10% EtOAc/hexanes) provided the corresponding allylic alcohol (104 mg, 96%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 5.49–5.39 (m, 1H), 4.11 (d, J = 6.8 Hz, 2H), 3.66–3.59 (m, 2H), 2.42–2.30 (m, 2H), 2.22–2.08 (m, 2H), 0.91 (s, 6H), 0.88 (s, 9H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 138.4, 124.4, 75.12, 75.09, 58.7, 41.1, 40.8, 32.9, 25.9, 25.8, 21.8, 21.7, 18.1, 18.0, −4.1, −4.2, −5.0; IR ($CHCl_3$) 3317 (br), 2956, 2930, 2887, 2857, 1472, 1252, 1090, 878, 836, 724; HRMS (EI) m/z ($M+NH_4^+$) calcd 432.3329 for $C_{22}H_{46}O_3Si_2$, found 432.3338.

Following the procedure for the synthesis of (±)-**14** above, this allylic alcohol (157 mg, 378 μmol) in THF (5 mL) was tosylated with *n*-BuLi (310 μL, 1.58 M in hexanes) and TsCl (97 mg, 510 μmol) in THF (1 mL), treated with potassium diphenylphosphide ($KPPh_2$, 1.2 mL, 0.5 M in THF) at 0 °C, oxidized with H_2O_2 (200 μL, 29% aq), and purified upon passage through silica gel (30–40% EtOAc/hexanes) to provide (±)-**20** (161 mg, 269 μmol, 71%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.75–7.40 (m, 10H), 5.26–5.17 (m, 1H), 3.54 (dd, J = 6.8, 3.6 Hz, 1H), 3.51 (dd, J = 8.0, 4.0 Hz, 1H), 3.18–2.97 (m, 2H), 2.31–2.22 (m, 1H), 2.06–1.96 (m, 1H), 1.81–1.72 (m, 1H), 0.84 (s, 9H), 0.83 (s, 3H), 0.81 (s, 3H), 0.809 (s, 9H), −0.026 (s, 3H), −0.029 (s, 3H), −0.04 (s, 3H), −0.05 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 139.7 (d, J = 12.1 Hz), 133.0 (d, J = 26.6 Hz), 132.0 (d, J = 27.4 Hz), 131.7, 131.0 (t, J = 10.2 Hz), 128.4 (dd, J = 11.4, 3.8 Hz), 112.7 (d, J = 9.1 Hz), 75.2 (d, J = 1.5 Hz), 74.5 (d, J = 1.5 Hz), 40.9, 40.6 (d, J = 2.2 Hz), 33.0 (d, J = 1.5 Hz), 30.2 (d, J = 69.8 Hz), 25.8, 25.7, 22.0, 21.2, 18.0, 17.9, −4.2, −5.0, −5.1; IR ($CHCl_3$) 3058, 2956, 2929, 2893, 2856, 1472, 1462, 1438, 1361, 1252, 1201, 1105,

1076, 1054, 877, 862, 838, 820, 804, 775; HRMS (EI) m/z ($M+H^+$) calcd 599.3506 for $C_{34}H_{55}O_3Si_2P$, found 599.3513.

2,2-Dimethyl-19-norcalcitriol analogues (+)-8a and (+)-8b. Following the general procedure for HWE coupling found above for (−)-**7a** and **7b**, phosphine oxide (±)-**20** (92 mg, 0.154 mmol) in THF (1.5 mL), PhLi (95 μL, 1.68 M solution in cyclohexane/Et_2O), and (±)-**15** (54 mg, 0.154 mmol) in THF (0.75 mL) provided 11 mg (10%) of a mixture of silyl protected analogues as a colorless oil after column chromatography (0–10% EtOAc/hexanes). This mixture was immediately taken up in EtOH (1.5 mL) and 2 mL of 20% HF in EtOH/H_2O was added. After 48 h at rt, water was added and the mixture was extracted with EtOAc. The organic fractions were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Silica gel chromatography (3–6% EtOH/CH_2Cl_2) provided a mixture of (+)-**8a** and (+)-**8b** as a white solid. Further purification by chiral HPLC (Daicel-Chiralpak AS, 5% EtOH/hexanes) provided the more polar analogue (+)-**8a** [1.0 mg, 1.5% from (+)-**15**] followed by analogue (+)-**8b** [1.9 mg, 2.8% from (+)-**15**] both as white solids. (+)-**8a**: [α]+29 (*c* 0.7, EtOH); ^{1}H NMR ($CDCl_3$) δ 6.30 (d, $J=11.0$ Hz, 1H), 5.83 (d, $J=11.0$ Hz, 1H), 3.68–3.60 (m, 2H), 2.83–2.74 (m, 1H), 2.66 (dd, $J=13.6$, 3.8 Hz, 1H), 2.56 (dd, $J=13.6$, 4.0 Hz, 1H) 2.35 (dd, $J=14.0$, 7.6 Hz, 1H), 2.23 (dd, $J=14.0$, 6.8 Hz, 1H), 1.22 (s, 6H), 1.06 (s, 3H), 1.04 (s, 3H), 0.93 (d, $J=6.4$ Hz, 3H), 0.55 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 143.0, 131.5, 123.7, 115.2, 77.2, 75.4, 75.0, 71.1, 56.5, 56.3, 45.8, 44.4, 40.8, 40.6, 40.3, 36.4, 36.1, 32.7, 31.6, 29.4, 29.2, 28.9, 23.5, 22.6, 22.3, 21.2, 20.8, 20.7, 18.8, 14.1, 12.1; UV (EtOH) λ_{max} 251 nm (ε 17600). IR ($CHCl_3$) 3460 (br), 3021, 2962, 2928, 2854, 1602, 1458, 1377, 1261, 1097, 1031, 811; HRMS (EI) m/z (M^+) calcd 432.3603 for $C_{28}H_{48}O_3$, found 432.3597. (+)-**8b**: [α]+21 (*c* 1.4, EtOH); ^{1}H NMR ($CDCl_3$) δ 6.29 (d, $J=11.2$ Hz, 1H), 5.84 (d, $J=11.2$ Hz, 1H), 3.70–3.58 (m, 2H), 2.84–2.74 (m, 1H), 2.70 (dd, $J=14.0$, 4.0 Hz, 1H), 2.59 (dd, $J=14.0$, 3.4 Hz, 1H), 2.29 (dd, $J=13.6$, 9.0 Hz, 1H), 2.21 (dd, $J=14.0$, 6.4 Hz, 1H), 1.22 (s, 6H), 1.07 (s, 3H), 1.03 (s, 3H), 0.94 (d, $J=6.4$ Hz, 3H), 0.54 (s, 3H); ^{13}C NMR (CD_3OD) δ 143.0, 131.6, 123.7, 115.1, 77.2, 75.6, 74.8, 71.1, 60.4, 56.5, 56.3, 45.8, 44.4, 40.7, 40.4, 40.3, 36.4, 36.1, 32.9, 29.4, 29.2, 28.9, 27.6, 23.5, 22.3, 20.8, 18.8, 14.2, 12.0; UV (EtOH) λ_{max} 252 nm (ε 33,000). IR ($CHCl_3$) 3021, 2927, 1602, 1457, 1377, 1032; HRMS (EI) m/z (M^+) calcd 432.3603 for $C_{28}H_{48}O_3$, found 432.3593.

Leading to 1,3-*cis* compounds

1,3-*cis* Bis protected diol (±)-17. Each of the 1,3-*cis* alcohols from above [see (±)-**16** experimental] was protected separately in an analogous manner to the 1,3-*trans* alcohols to afford an identical bis silyl ether (±)-**17** (from first 1,3-*cis* alcohol: 397 mg, 701 μmol, 88%; from second 1,3-*cis* alcohol, 257 mg, 453 μmol, 80%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.49–7.28 (m, 5H), 4.19–3.95 (m, 2H), 3.71 (d, $J=12.0$ Hz, 1H), 3.50–3.33 (m, 2H), 2.34–2.24 (m, 1H), 2.14–2.06 (m, 1H), 1.74–1.60 (m, 2H), 1.46–1.37 (m, 1H), 1.13 (t, $J=7.2$ Hz, 3H), 0.96 (s, 3H), 0.90 (s, 9H), 0.85 (s, 9H), 0.81 (s, 3H), 0.09 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H), −0.05 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 172.1, 133.3, 133.0, 128.9, 128.1, 73.0, 72.8, 61.1, 54.1, 42.6, 33.2, 32.4, 31.1, 25.9, 25.8, 18.1, 18.0, 14.0, −4.0, −4.4, −5.0; IR ($CHCl_3$) 2955, 2929, 2857, 1738, 1472, 1256, 1150, 1074, 872, 837, 774; HRMS (EI) m/z ($M+H^+$) calcd 567.3360 for $C_{30}H_{54}O_4SSi_2$, found 567.3366.

1,3 *cis* Unsaturated ester (±)-19. Following the oxidation procedure of (±)-**16** above, ether (±)-**17** (654 mg, 1.15 mmol) and *m*-CPBA (198 mg, 1.15 mmol) in CH_2Cl_2 (35 mL total) provided two diastereomeric sulfoxides as colorless oils: (less polar sulfoxide, 271 mg, 464 μmol, 40%); ^{1}H NMR ($CDCl_3$) δ 7.70–7.40 (m, 5H), 3.81–3.72 (m, 2H), 3.66 (d, $J=10.4$ Hz, 1H), 3.58 (dd, $J=10.0$, 4.0 Hz, 1H), 3.43 (dd, $J=10.0$, 4.0 Hz, 1H), 2.86–2.77 (m, 1H), 2.21–2.13 (m, 1H), 1.84 (ddd, $J=13.8$, 10.0, 5.0 Hz, 1H), 1.73 (ddd, $J=14.0$, 10.0, 5.2 Hz, 1H), 1.52–1.44 (m, 1H), 0.98 (t, $J=7.2$ Hz, 3H), 0.96 (s, 3H), 0.91 (s, 9H), 0.86 (s, 12H), 0.13 (s, 3H), 0.09 (s, 3H), 0.00 (s, 3H), −0.05 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 167.3, 141.8, 132.0, 128.8, 125.8, 75.9, 73.1, 72.9, 61.3, 42.0, 33.5, 32.2, 31.3, 25.9, 25.8, 25.7, 18.1, 18.0, 13.7, −4.1, −4.4, −4.98, −5.03; IR ($CHCl_3$) 2955, 2930, 2885, 2857, 1726, 1472, 1298, 1253, 1113, 1074, 872, 837, 775; HRMS (EI) m/z ($M+H^+$) calcd 583.3309 for $C_{30}H_{54}O_5SSi_2$, found 583.3302; (more polar sulfoxide, 349 mg, 598 μmol, 52%); ^{1}H NMR ($CDCl_3$) δ 7.58–7.47 (m, 5H), 3.84–3.74 (m, 1H), 3.71–3.60 (m, 1H), 3.48 (dd, $J=11.6$, 4.0 Hz, 1H), 3.40 (d, $J=12.4$ Hz, 1H), 3.34 (dd, $J=11.4$, 4.2 Hz, 1H), 2.85–2.76 (m, 1H), 2.23–2.15 (m, 1H), 1.86–1.75 (m, 2H), 1.41–1.32 (m, 1H), 0.99 (s, 3H), 0.89 (s, 9H), 0.85 (t, $J=7.6$ Hz, 3H), 0.83 (s, 3H), 0.82 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H), −0.05 (s, 3H), −0.13 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.5, 140.9, 131.2, 129.0, 124.2, 72.9, 72.8, 69.7, 61.1, 43.0, 33.1, 30.6, 29.4, 25.8, 25.71, 25.66, 18.0, 17.8, 13.5, 12.4, −4.1, −4.5, −4.8, −5.1; IR ($CHCl_3$) 2955, 2930, 2885, 2857, 1733, 1473, 1253, 1115, 1073, 871, 837, 775; HRMS (EI) m/z ($M+H^+$) calcd 583.3309 for $C_{30}H_{54}O_5SSi_2$, found 583.3296.

A mixture of these diastereomeric sulfoxides (594 mg, 1.02 mmol total) was taken up in benzene and heated at reflux for 6 h. After removing the solvent in vacuo, silica gel chromatography (1–3% EtOAc/hexanes) provided (±)-**19** (489 mg, 100%) as a colorless oil with the following physical characteristics: ^{1}H NMR ($CDCl_3$) δ 5.67 (t, $J=1.6$ Hz, 1H), 4.15 (q, $J=7.2$ Hz, 2H), 3.82 (ddd, $J=13.6$, 4.8, 1.6 Hz, 1H), 3.22 (ddd, $J=11.6$, 7.0, 4.6 Hz, 1H), 2.39–2.30 (m, 1H), 2.13 (ddd, $J=13.2$, 4.8, 1.6 Hz, 1H), 2.04–1.95 (m, 1H), 1.28 (t, $J=7.2$ Hz, 3H), 0.97 (s, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.88 (s, 3H), 0.12 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 166.2, 155.1, 116.2, 75.8, 75.5, 59.7, 42.6, 42.5, 34.3, 25.82, 25.79, 25.4, 18.02, 18.00, 14.3, 12.1, −4.1, −5.0, −5.1; IR ($CHCl_3$) 2956, 2930, 2894, 2858, 1717, 1652, 1472, 1362, 1253, 1241, 1161, 1140, 1112, 1079, 1051, 871, 837, 804, 775; HRMS (EI) m/z ($M+H^+$) calcd 457.3169 for $C_{24}H_{48}O_4Si_2$, found 457.3178.

1,3-*cis* Phosphine oxide (±)-21. To a solution of (±)-19 (460 mg, 1.01 mmol) in Et_2O (15 mL) at −78 °C was added a solution of DIBAL-H (6 mL, 1 M in hexanes) and the reaction mixture was warmed to room temperature over 2 h. After stirring at room temperature overnight, the reaction was quenched with dilute HCl and extracted with several portions of EtOAc. The combined organics were washed with brine, dried over $MgSO_4$, and the solvents removed in vacuo. Chromatographic purification of the residue over silica gel provided the target allylic alcohol (194 mg, 468 μmol, 46%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 5.46 (tt, J=6.8, 1.6 Hz, 1H), 4.14 (d, J=6.8 Hz, 1H), 3.19 (dd, J=11.4, 5.0 Hz, 1H), 3.13 (dd, J=11.6, 4.8 Hz, 1H), 2.47 (ddd, J=13.4, 4.6, 1.4 Hz, 1H), 2.28–2.18 (m, 1H), 2.08 (ddd, J=13.2, 4.8, 1.6 Hz, 1H), 2.00–1.90 (m, 1H), 0.95 (s, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.86 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.030 (s, 3H), 0.028 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 136.9, 123.9, 76.1, 75.9, 58.6, 42.8, 41.6, 33.8, 25.8, 25.6, 18.02, 17.99, 11.9, −4.06, −4.10, −5.0; IR ($CHCl_3$) 3313 (br), 2956, 2930, 2887, 2857, 1472, 1463, 1362, 1255, 1078, 1050, 1006, 874, 837, 803, 774, 671; HRMS (EI) m/z ($M+H^+$) calcd 415.3064 for $C_{22}H_{46}O_3Si_2$, found 415.3058.

In a manner analogous to the synthesis of (±)-**20**, this allylic alcohol (194 mg, 468 μmol), *n*-BuLi (385 μL, 1.58 M in hexanes), TsCl (120 mg, 632 μmol), $KPPh_2$ (1.4 mL, 0.5 M in THF), and H_2O_2 (250 μL, 29% aqueous) afforded (±)-**21** (225 mg, 80%) as an amorphous solid after silica gel chromatography (30–40% EtOAc/hexanes): ^{1}H NMR ($CDCl_3$) δ 7.75–7.42 (m, 10H), 5.37–5.27 (m, 1H), 3.06 (dd, J=14.8, 7.6 Hz, 1H), 3.00 (dd, J=11.0, 5.0 Hz, 1H), 2.85 (dd, J=11.4, 4.6 Hz, 1H), 2.19–2.01 (m, 2H), 1.60–1.49 (m, 1H), 0.87 (s, 9H), 0.86 (s, 12H), 0.75 (s, 3H), 0.06 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 138.0 (d, J=11.4 Hz), 132.9 (d, J=47.9 Hz), 131.9 (d, J=47.8 Hz), 131.8 (d, J=5.4 Hz), 131.1 (t, J=9.1 Hz), 128.5 (d, J=11.4 Hz), 112.8 (d, J=8.4 Hz), 75.7 (d, J=3.1 Hz), 75.2 (d, J=2.3 Hz), 42.6, 41.6 (d, J=2.2 Hz), 33.7, 30.4 (d, J=69.1 Hz), 25.74, 25.71, 25.4, 17.94, 17.91, 11.7, −4.0, −4.1, −4.9, −5.0; IR ($CHCl_3$) 3058, 2956, 2929, 2893, 2856, 1472, 1438, 1361, 1252, 1201, 1105, 1076, 1054, 877, 862, 838, 820, 804, 775; HRMS (EI) m/z ($M+H^+$) calcd 599.3506 for $C_{34}H_{55}O_3Si_2P$, found 599.3501.

2,2-Dimethyl-19-norcalcitriol Analogues (+)-8c and (+)-8d. Following the general procedure for HWE coupling found above for (−)-**7a** and **7b**, (±)-**21** (62 mg, 0.104 mmol), PhLi (62 μL, 1.68 M solution in cyclohexane/Et_2O), and (+)-**15** (40 mg, 0.114 mmol) gave 32 mg (42%) of a mixture of silyl protected analogues as a colorless oil after silica gel chromatography (0–10% EtOAc/hexanes). The mixture of diastereomers was then deprotected without separation. The mixture was taken up in THF (1.5 mL) and Et_3N (35 μL) and a solution of TBAF (250 μL, 1 M in THF) added. After 48 h at room temperature, H_2O was added and the mixture was extracted with EtOAc (3×). The organic fractions were combined, washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Silica gel chromatography (3–6% EtOH/CH_2Cl_2) provided a mixture of (+)-**8c** and (+)-**8d** as a white solid. Further purification by C-18HPLC (69% MeCN/H_2O) provided the more polar analogue (+)-**8c** [5.8 mg, 30% from (±)-**21**], followed by analogue (+)-**8d** [5.7 mg, 30% from (±)-**21**] both as white solids. (+)-**8c**: [α] +94 (*c* 5.8, EtOH); ^{1}H NMR ($CDCl_3$) δ 6.31 (d, J=11.2 Hz, 1H), 5.85 (d, J=11.2 Hz, 1H), 3.53–3.43 (m, 2H), 2.88–2.75 (m, 1H), 2.64–2.46 (m, 3H), 2.30 (dd, J=14.0, 6.8 Hz, 1H), 1.22 (s, 6H), 1.09 (s, 3H), 1.05 (s, 3H), 0.93 (d, J=6.4 Hz, 3H), 0.54 (s, 3H); ^{13}C NMR (CD_3OD) δ 142.6, 133.0, 122.5, 117.1, 77.2, 76.7, 71.6, 58.1, 57.6, 47.0, 45.4, 42.6, 42.3, 42.0, 37.9, 37.6, 34.1, 30.9, 30.0, 28.9, 25.3, 24.7, 23.4, 22.0, 19.5, 13.1; UV (EtOH) λ_{max} 250 nm (ε 344,000). IR ($CHCl_3$) 3362, 2927, 2872, 1616, 1468, 1378, 1214, 1146, 1082, 1052, 1015, 994, 934, 880; HRMS (EI) m/z (M^+) calcd 432.3603 for $C_{28}H_{48}O_3$, found 432.3601. (+)-**8d**: [α] +42 (*c* 5.0, EtOH); ^{1}H NMR ($CDCl_3$) δ 6.33 (d, J=11.6 Hz, 1H), 5.86 (d, J=11.6 Hz, 1H), 3.58–3.48 (m, 2H), 2.86–2.77 (m, 1H), 2.66–2.51 (m, 3H), 2.30 (dd, J=14.0, 5.6 Hz, 1H), 1.22 (s, 6H), 1.11 (s, 3H), 1.05 (s, 3H), 0.94 (d, J=6.8 Hz, 3H), 0.55 (s, 3H); ^{13}C NMR (CD_3OD) δ 142.6, 133.0, 122.5, 117.1, 77.1, 76.7, 71.6, 58.1, 57.6, 47.0, 45.4, 42.6, 42.3, 42.0, 37.9, 37.6, 35.0, 30.9, 29.4, 29.3, 28.9, 25.3, 24.7, 23.4, 22.0, 19.5, 13.3, 12.6; UV (EtOH) λ_{max} 250 nm (ε 33,000). IR ($CHCl_3$) 3374, 2925, 1618, 1467, 1378, 1082, 1052, 1015, 934, 864; HRMS (EI) m/z (M^+) calcd 432.3603 for $C_{28}H_{48}O_3$, found 432.3597.

PTH cell culture. Bovine parathyroid glands were obtained from a local slaughterhouse and transported to the laboratory in cold PBS. The glands were digested with collagenase as previously described[42] and seeded at a density of 80,000 cells/cm^2 in DMEM–Ham's F-12 (1:1) containing 4% heat-inactivated newborn calf serum, 15 mM HEPES, 100 IU/mL penicillin, 100 μg/mL streptomycin, 5 μg/mL insulin, 2 mM glutamine, 5 μg/mL holo-transferrin and 1% non-essential amino acids. After 24 h cells were placed in medium containing 0.1% bovine serum albumin in place of the serum. Except for the initial 24 h, the cells were grown to confluency (6 days) in serum-free medium.

Analysis of parathyroid hormone secretion. Parathyroid cell cultures were prepared as described above. On the third day of culture the cells were treated with the vitamin D compounds (calcitriol or its analogues) at concentrations ranging from 10 pM to 100 nM with daily changes of the medium for 3 days. Steady state PTH secretion was determined by washing the cells three times with Dulbecco's PBS and then placing them in treatment media for 3 h. The media were collected, centrifuged at 4 °C and analyzed for PTH using CH9 antibody as described previously.[43]

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