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A-ring hydroxymethyl 19-nor analogs of the natural hormone 1α,25-dihydroxyvitamin D_3: synthesis and preliminary biological evaluation

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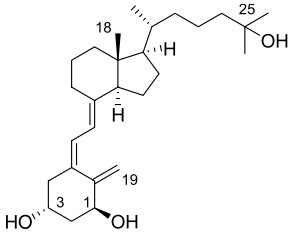
Abstract—A series **5**–**8** of 1- and 3-CH_2OH 19-nor analogs of the hormone calcitriol (**1**) has been prepared. Surprisingly, 19-nor 1α-CH_2OH analog **5a** is more antiproliferative at 100 nM concentration than the corresponding regioisomeric analog **6a** with the natural 1α-OH group, and 1α-CH_2OH hybrid analog **7a** is similar in antiproliferative potency to calcitriol (**1**) even at low nanomolar concentrations.

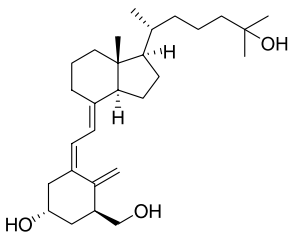
1. Introduction

The natural hormone 1α,25-dihydroxyvitamin D_3 (**1**, calcitriol) regulates not only calcium and phosphorus levels in our bodies, but it regulates also proliferation and differentiation of human cells.[1,2] Medicinal organic chemists have prepared a series of calcitriol analogs that are relatively nontoxic (low calcemic) and that are efficacious in chemotherapy of such human diseases as secondary hyperparathyroidism, psoriasis, and osteoporosis.[3,4] More than six analogs of calcitriol are now clinically used designer drugs promoting healthier living.[4]

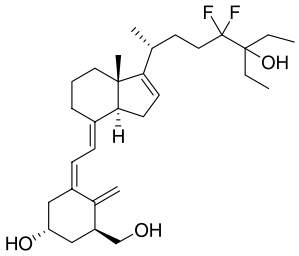
Challenging the accepted wisdom in the vitamin D field at the time, we prepared a homolog of the natural hormone containing a 1-hydroxymethyl group in place of the natural 1-OH group that had been considered essential for biological activity; homolog **2a** had measurable but somewhat lower in vitro antiproliferative activity and desirably much lower calcemic activity than the natural hormone calcitriol (**1**).[5] Combining this 1-hydroxymethyl replacement with a potentiating side chain led to hybrid analog **3a** that incorporated the calcemia



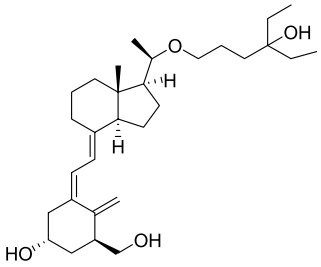
1 (calcitriol)
[1α,25-$(OH)_2D_3$]



2a



3a (QW-1624F_2-2)



4a (MCW-YB)

Keywords: Calcitriol; 19-Nor; Hydroxymethyl A-ring; Novel analogs.
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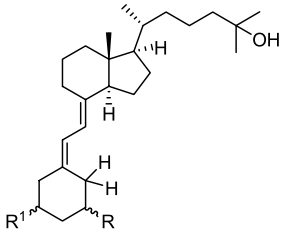
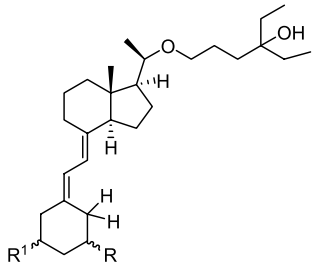
ablating 1-hydroxymethyl group, a potentiating 16,17-double bond, and a catabolism-blocking 24,24-difluoro unit.[6] We have reported that this hybrid analog **3a** is 80–100 times less calcemic than calcitriol,[7] inhibits multistage skin tumorigenesis when administered topically to mice,[8] and reduces the size of xenograft tumors of human neuroblastoma cells when administered systemically (IP) to mice.[9] Hybrid analog **3a** is significantly more antiproliferative than the natural hormone.[6] Hybrid analog **4a** having a 1-CH_2OH group and a KH-1060 potentiating side chain is as antiproliferative in vitro as the natural hormone **1** even at low nanomolar concentrations and is substantially less calcemic than calcitriol (**1**).[10] Now we report synthesis and preliminary biological evaluation of a new series **5**–**8** of calcitriol analogs lacking the 19-methylene group (i.e., 19-nor analogs)[11] but containing a hydroxymethyl group either at the 1-position (analogs **5** and **7**) or at the 3-position (analogs **6** and **8**).



Compound	R	R^1
5a	1α-CH_2OH	3β-OH
5b	1β-CH_2OH	3α-OH
6a	1α-OH	3β-CH_2OH
6b	1β-OH	3α-CH_2OH



Compound	R	R^1
7a	1α-CH_2OH	3β-OH
7b	1β-CH_2OH	3α-OH
8	1α-OH	3β-CH_2OH

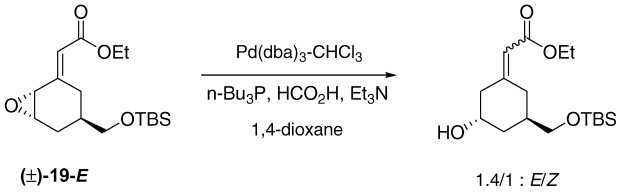
2. Results

2.1. Chemistry

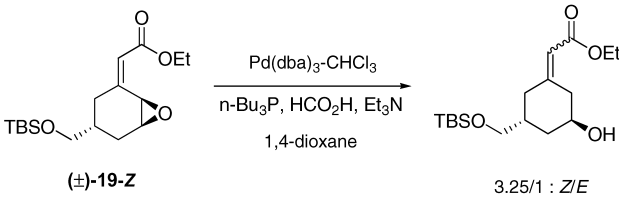
Preparation of the 19-nor hybrid analogs **5**–**8** can be retrosynthetically envisioned through the disconnections shown in Scheme 1. Analogs **5a** and **5b** can be prepared through Horner–Wadsworth–Emmons coupling of C,D-ring ketone (+)-**9**[12,13] and 1-hydroxymethyl-A-ring phosphine oxide (±)-**10**. Likewise, analogs **6a** and **6b** can be prepared through coupling of C,D-ring ketone (+)-**9** and 3-hydroxymethyl-A-ring phosphine oxide (±)-**11**. The two isomeric A-ring phosphine oxides (±)-**10** and (±)-**11** can be further disconnected back to readily available 3-cyclohexene-1-carboxylic acid (±)-**12**.[14–18]

As shown in Scheme 2, carboxylic acid (±)-**12** was reacted under standard iodolactonization conditions to give exclusively the *trans*-iodolactone (±)-**13** in excellent yield.[16–18] After elimination of the iodide with fresh DBU and reductive opening of lactone (±)-**14**, diol (±)-**15** was selectively protected at the primary alcohol position with *tert*-butyl dimethylsilyl chloride to give the mono-silyl protected allylic alcohol (±)-**16** in 71% yield.[16]

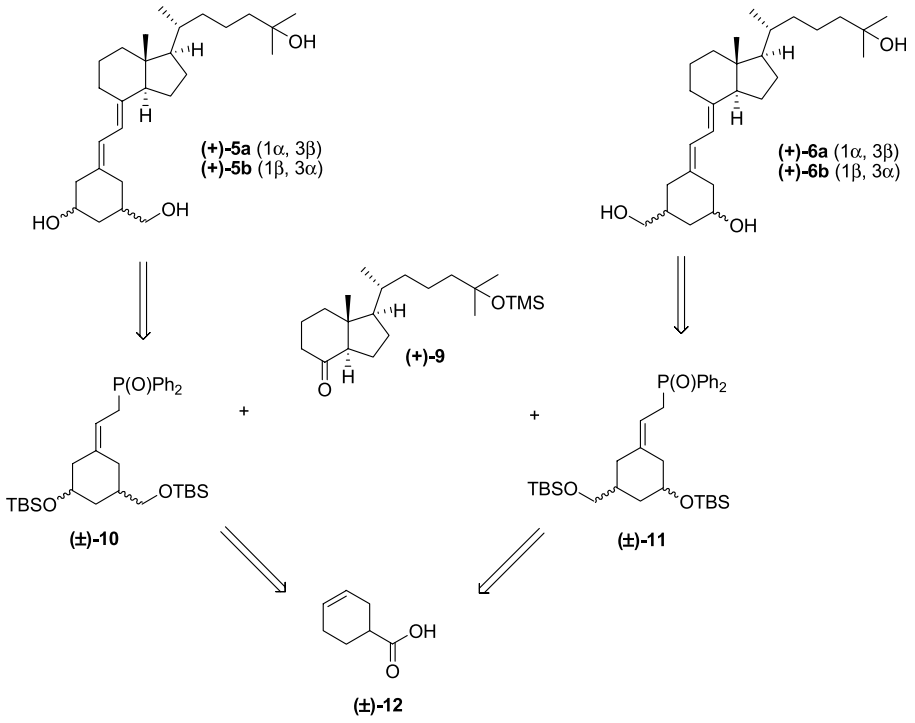
This allylic alcohol was oxidized to enone (±)-**17**, which was then selectively epoxidized with hydrogen peroxide to give epoxy ketone (±)-**18** in predominantly the trans-orientation (>95%).[19,20] Wittig reaction using triethyl phosphonoacetate and epoxy ketone (±)-**18** gave a 1.5:1 ratio of (±)-**19-*Z*** to (±)-**19-*E*** in overall 95% yield. These two geometrical isomers could be cleanly separated by standard flash column chromatography and taken on to their respective A-ring phosphine oxides (Scheme 2). The olefin geometry of (±)-**19-*Z*** was easily assigned by ^1H NMR in which the downfield doublet (4.62 ppm) correlates to the proton attached to the epoxide at the γ-position with respect to the ethyl ester. This doublet proton is much more downfield with respect to the proton of (±)-**19-*E*** (3.36 ppm) due to the deshielding effect of the ethyl ester carbonyl group in (±)-**19-*Z***.[21,22] As seen in Eqs. 1 and 2, γ-epoxy-α,β-unsaturated esters (±)-**19-*E*** and (±)-**19-*Z*** were subjected separately to a palladium catalyzed reductive opening, which unfortunately gave inseparable mixtures of *E* and *Z* products.[19,20,23]



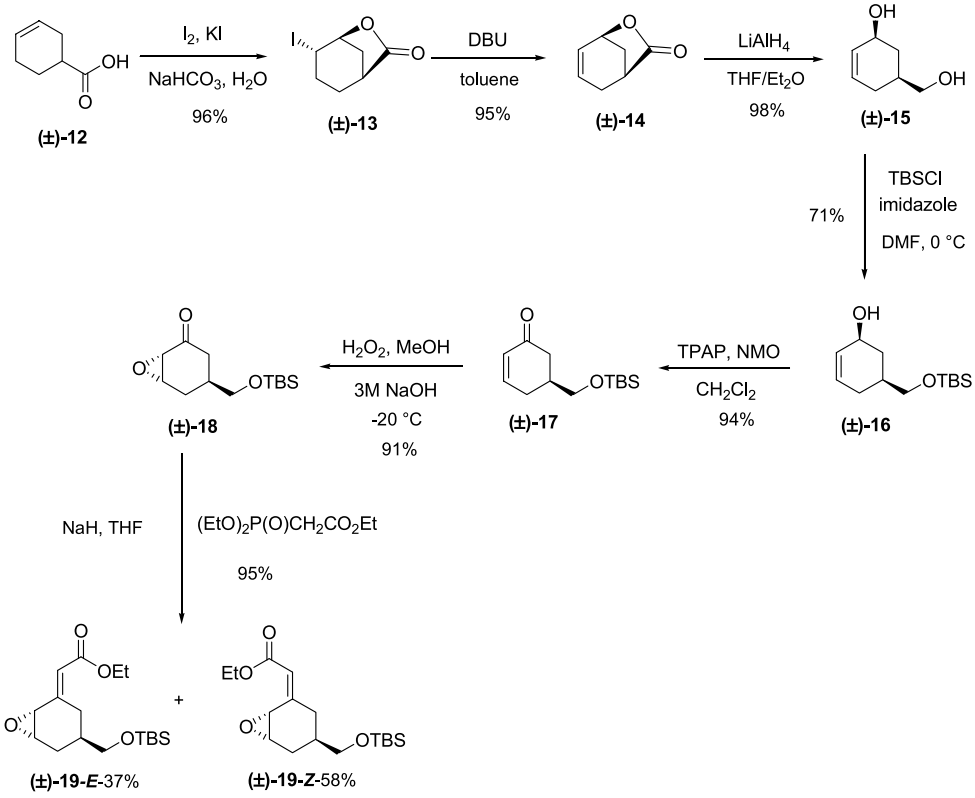
(1)



(2)

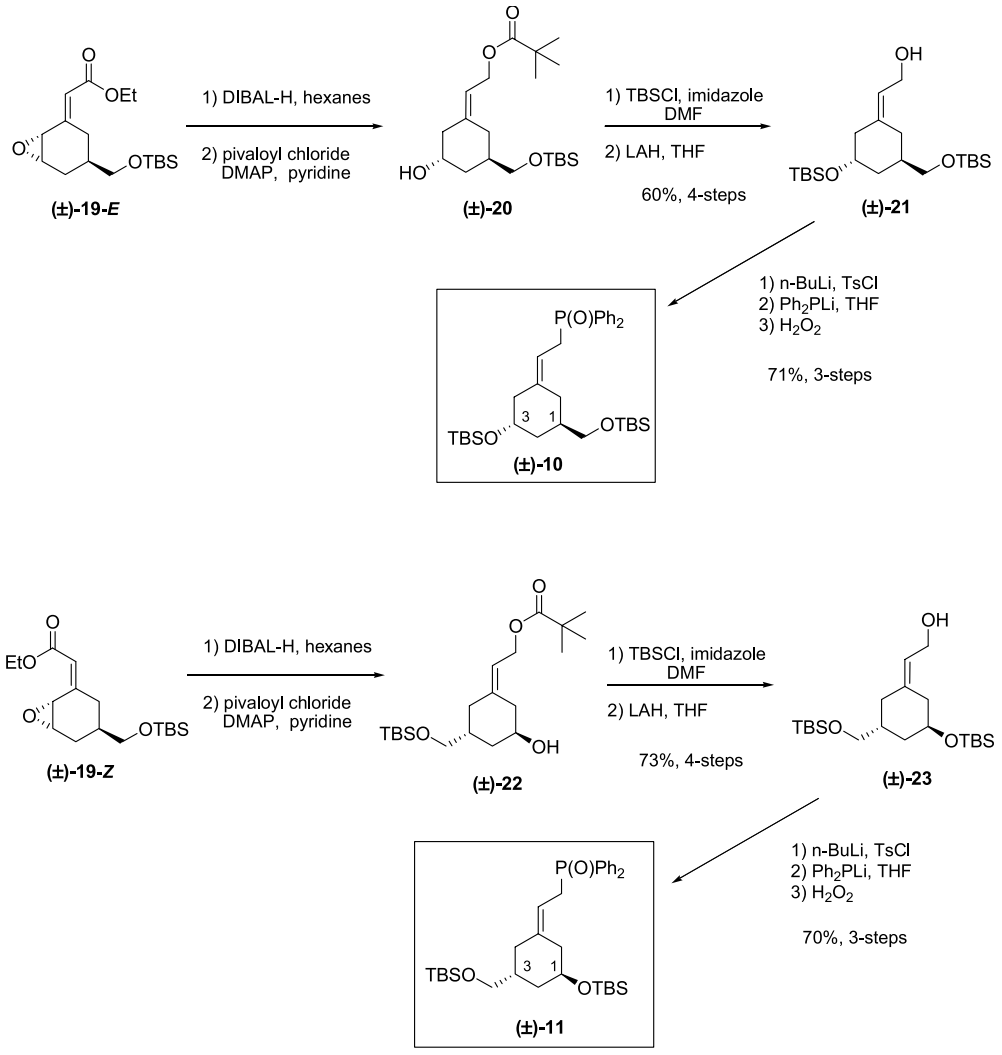


Scheme 1.



Scheme 2.

This setback steered us in a new direction for the synthesis of the A-ring phosphine oxides using an in situ regioselective bis-reduction of both the epoxide and ester moiety (Scheme 3). Epoxy ester (±)-**19-*E*** was reacted with DIBAL-H to open the epoxide as well as to reduce the ester to the allylic alcohol. The hydride was selectively delivered to the γ carbon as expected from good literature analogy.[24]



Scheme 3.

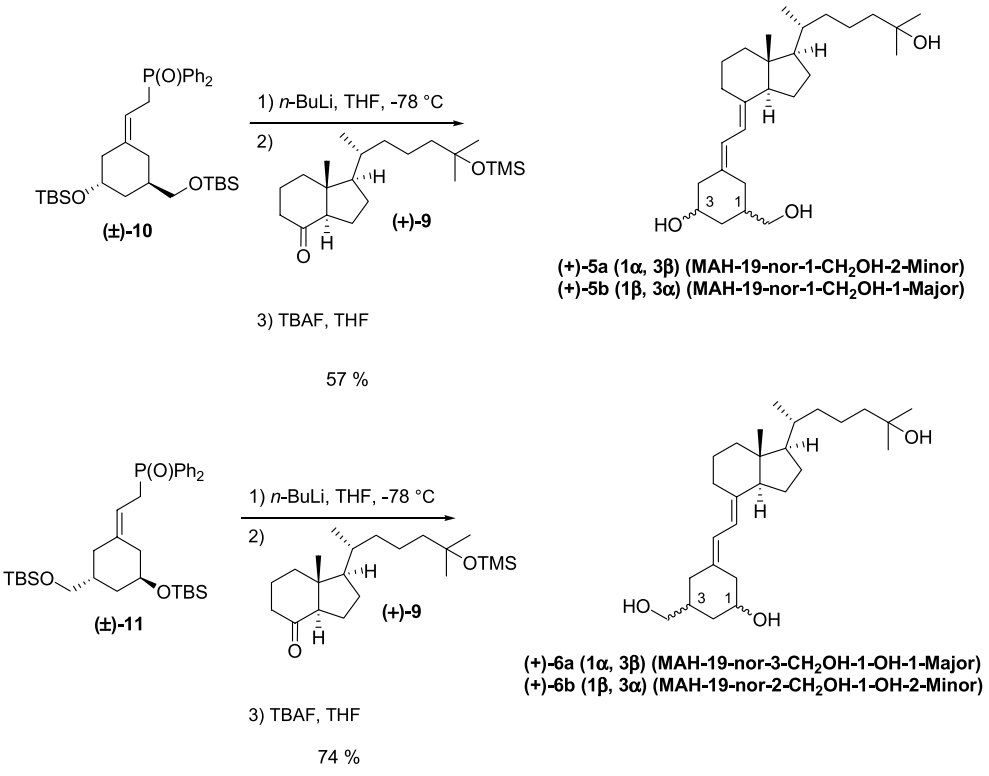
The resulting bis-alcohol was then selectively protected at the primary allylic alcohol to give the pivaloyl ester (±)-**20**.[25] After protection of the secondary alcohol as the *tert*-butyl dimethylsilyl ether and removal of the pivaloyl ester by lithium aluminum hydride (LAH) reduction, allylic alcohol (±)-**21** was tosylated, reacted with lithium diphenylphosphide, and finally oxidized with hydrogen peroxide to give the desired 19-nor-1-hydroxymethyl-A-ring phosphine oxide (±)-**10** in a total of 14 steps and 9% overall yield from (±)-**12**. The 19-nor-3-hydroxymethyl-A-ring phosphine oxide (±)-**11** was prepared in a similar fashion in 14 steps and 16% overall yield (Scheme 3). Coupling of the natural calcitriol C,D-ring (+)-**9** with the 1-hydroxymethyl-A-ring (±)-**10** and subsequent deprotection with TBAF gave the desired 19-nor-1-hydroxymethyl hybrid analogs **5a** and **5b** as 1:2 ratio of diastereomers in 57% yield (Scheme 4).[26] Separation of the diastereomers by HPLC gave enantiomerically pure analogs (+)-**5a** and (+)-**5b**.

Following the same procedure, 3-hydroxymethyl-A-ring (±)-**11** was coupled with C,D-ring ketone (+)-**9** to give 19-nor-3-hydroxymethyl hybrid analogs **6a** and **6b** in 74% yield, which upon HPLC separation gave enantiomerically pure (+)-**6a** and (+)-**6b**. The more potentiating KH-1060 C,D-ring side chain (−)-**24**[10,27,28] was coupled with the 1-hydroxymethyl-A-ring (+)-**10** with subsequent deprotection using TBAF to give analogs **7a** and **7b** as a 1:2 ratio of diastereomers in 50% yield, which then gave enantiomerically pure (−)-**7a** and (−)-**7b** after HPLC separation (Scheme 5).

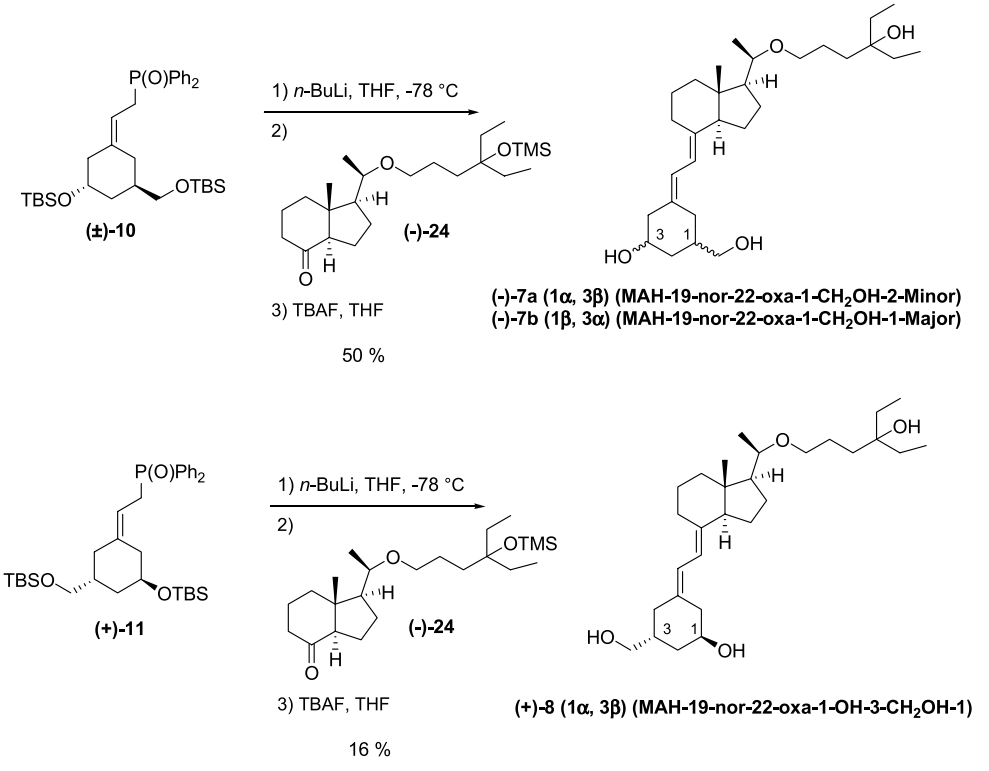
Coupling of the KH-1060 C,D-ring side chain (−)-**24** with enantiomerically pure (1α,3β)-3-hydromethyl A-ring (+)-**11** (99.5% ee by Chiral HPLC) followed by TBAF deprotection gave enantiomerically pure analog (+)-**8** in 16% yield.

The stereochemical assignment of these 19-nor-hybrid analogs is based on three grounds: first, enantiomerically enriched 1-hydroxymethyl-A-ring (−)-**10** and 3-hydroxymethyl-A-ring (−)-**11** were synthesized using enantiomerically enriched (*R*)-3-cyclohexene-1-carboxylic acid (+)-**12**, prepared by recrystallization of the corresponding brucine salt (Scheme 6).[17]

With both enantiomerically enriched A-rings in hand, they were both coupled once again with C,D-ring ketone

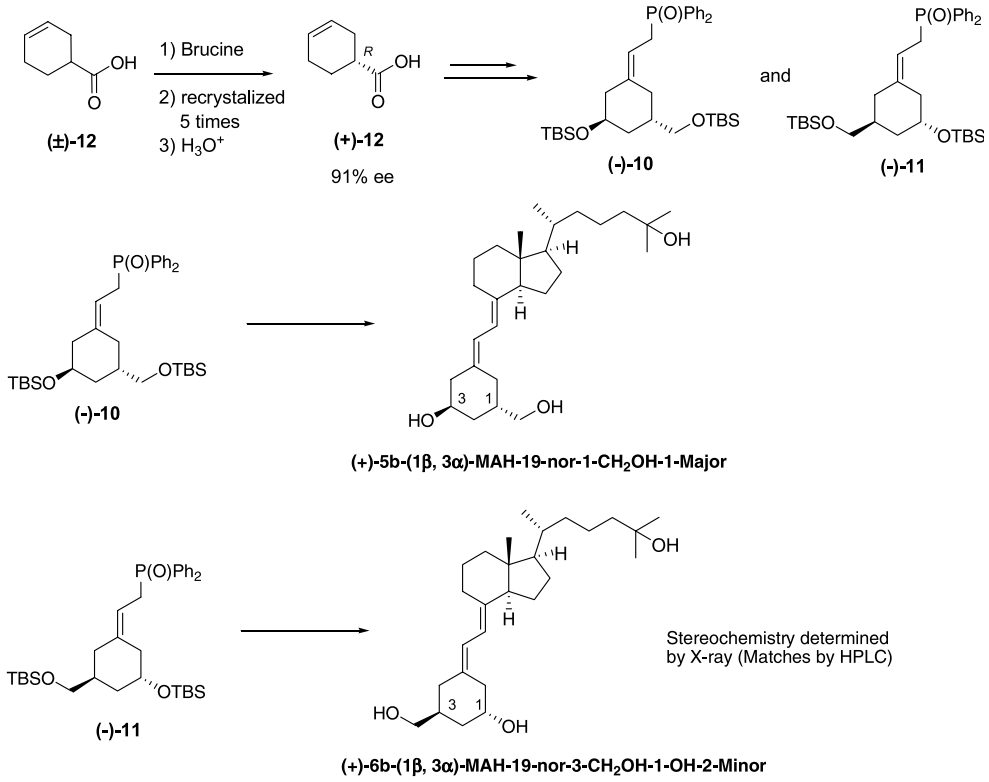


Scheme 4.



Scheme 5.

(+)-**9** to give analogs (+)-**5b** and (+)-**6b**, respectively. These enantiomerically pure analogs were characterized by both ^{1}H NMR and by co-injection on HPLC with previously prepared analogs. Second, a sufficiently resolved X-ray crystal structure[29] was obtained of analog (+)-**6b**.



Scheme 6.

As depicted in Figure 1, analog (+)-**6b** has the 1-OH in the β-position and the 3-hydroxymethyl in the α-position. This X-ray evidence of the 1β,3α stereochemistry in analog (+)-**6b** was then correlated to show that analog (+)-**5b** indeed has the 1β,3α stereochemistry as well. Finally, all the analogs containing a 1-hydroxy-A-ring, 19-methylene or 19-nor, share similar characteristic ^{1}H NMR signals as well as optical rotation trends. As seen in Table 1, the analogs containing the 1α,3β stereochemistry have a more upfield C-18 methyl signal in the ^{1}H NMR spectrum and a more positive optical rotation.[30]

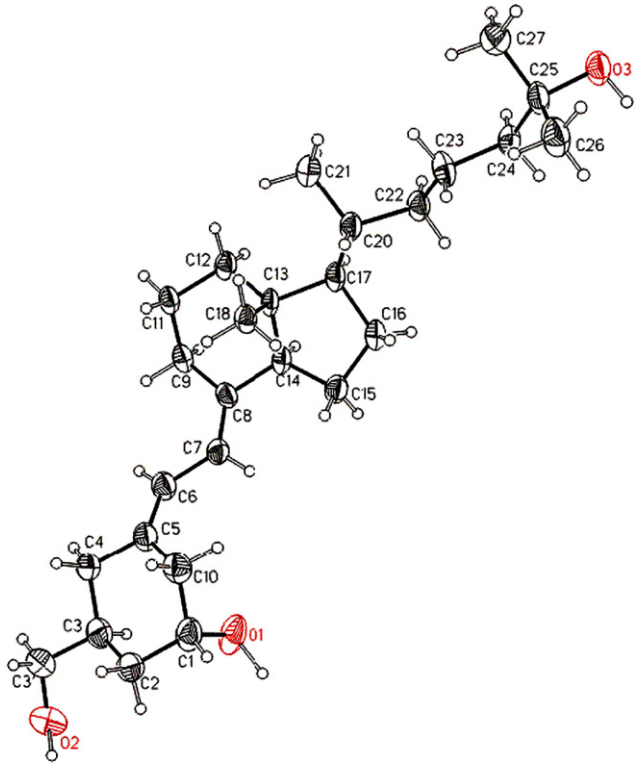


Figure 1. X-ray structure of 19-nor VD_3 analog **6b**.

2.2. Biology

Our standard murine keratinocyte assay for in vitro antiproliferative activity[6] showed that 1-α-CH_2OH analog **5a** is as expected, considerably more potent than its diastereomeric 1-β-CH_2OH analog **5b** (Fig. 2). Surprisingly, however, 19-nor 1-α-CH_2OH analog **5a** is more antiproliferative at 100 nM concentration than the corresponding regioisomeric analog **6a** containing the natural 1-α-OH group (Fig. 2); this is the first report of any 1-α-CH_2OH analog with the natural hormonal C,D-ring side chain being more antiproliferative than the corresponding 1-α-OH analog. This unusually high antiproliferative activity of the 1-α-CH_2OH analog **5a** is precedented to some degree by the exceptionally high antiproliferative activity of 1-α-CH_2OH hybrid analog **3a**;[6] the 1-α-CH_2OH group (being larger than a 1-α-OH group) may alter the A-ring conformation so as to raise antiproliferative potency. A similar but less pronounced trend was seen between hybrid KH-1060-like analogs **7a** and **8** (Fig. 3). It is noteworthy also that 1-α-CH_2OH hybrid analog **7a** is comparable in antiproliferative potency to calcitriol **1** even at low nanomolar concentrations (Fig. 3).

Table 1. Characteristic ^{1}H NMR C-18 methyl signals (ppm) and optical rotations of hybrid analogs **2**–**5** and **7**

Analog	**2a** (1α,3β)	**2b** (1β,3α)	**3a** (1α,3β)	**3b** (1β,3α)	**4a** (1α,3β)	**4b** (1β,3α)	**5a** (1α,3β)	**5b** (1β,3α)	**7a** (1α,3β)	**7b** (1β,3α)
C-18	0.50	0.54	0.66	0.68	0.52	0.55	0.54	0.56	0.55	0.57
$[\alpha]_D^{25}$	+24.0	−64.0	+78.0	−1.3	+4.0	−140.0	+40.3	+24.1	−8.0	−36.7

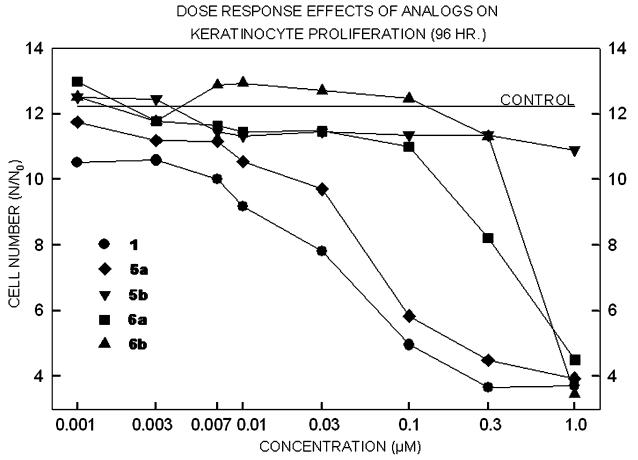


Figure 2.

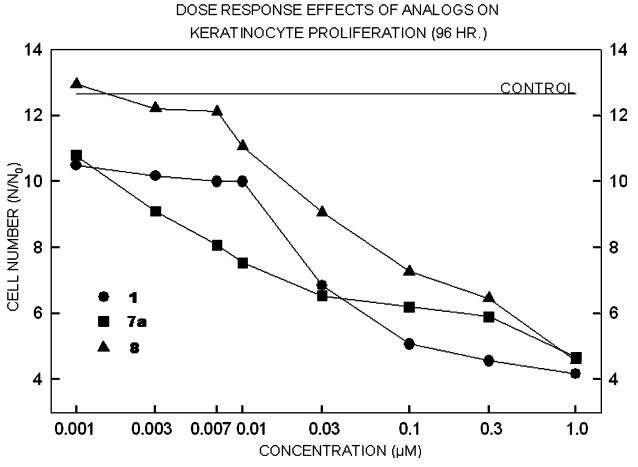


Figure 3.

Our standard protocol[31] for VDR-mediated in vitro transcriptional activity uses CV-1 cells co-transfected with the recombinant human VDR plasmid and the osteocalcin VDRE attached to the thymidine kinase promoter-growth hormone reporter. This assay showed 1-α-hydroxymethyl analog **5a** to be active but significantly less potent (ED_{50} = 300 nM) than calcitriol (**1**, ED_{50} = 1.0 nM, data not shown). Thus, as we have observed before, transcriptional potency does not always correlate directly with in vitro antiproliferative potency.[30]

3. Conclusion

We present here the first example in which a 1α-CH_2OH analog (**5a**) with the natural hormonal C,D-ring side chain is more antiproliferative in vitro than the corresponding regioisomeric analog (**6a**) having the natural 1α-OH group. Incorporating in one new analog a 1α-CH_2OH group, the absence of a 19-methylene group, and a KH-1060 potentiating side chain makes analog **7a** comparable to the natural hormone calcitriol (**1**) in antiproliferative potency even at physiologically relevant low nanomolar concentrations. These SAR generalizations should facilitate design of even more potent and safe new vitamin D analogs.

4. Experimental

Unless otherwise noted, all reactions were performed in oven-dried glassware stirred under an atmosphere of ultra-high-purity argon. THF was distilled from Na/benzophenone ketyl and CH_2Cl_2 distilled from CaH_2 immediately prior to use. Organolithiums were titrated prior to use following known methods. All other reagents were used as received from commercial suppliers. Analytical TLC analysis was conducted on precoated glass-backed silica gel plates (Merck Kieselgel 60 F254, 250 mm thickness) and visualized with *p*-anisaldehyde or $KMnO_4$ stains. Column chromatography was performed using flash silica gel (particle size 230–400 mesh). Preparative-plate chromatography was performed using silica-gel-coated glass preparative plates (500–1000 μm) from Analtech and analyzed by UV. HPLC was carried out using a Rainin HPLX™ system equipped with two 25 mL/min preparative pump heads using (1) a Chiral Technologies Chiralcel® OJ 10 mm × 250 mm (semipreparative) column packed with cellulose tris(4-methylbenzoate) on a 10 μm silica-gel substrate or (2) a Chiral Technologies Chiralcel® OD 10 mm × 250 mm (semipreparative) column and a Rainin Dynamax™ UV-C dual-beam variable-wavelength detector set at 254 nm. Yields are reported for pure products (>95% based on their chromatographic and spectroscopic homogeneity) and are unoptimized. Melting points were determined in open capillaries using a Mel-Temp metal-block apparatus and are uncorrected. Optical rotations were measured at the Na line using a Perkin–Elmer 141 Polarimeter. NMR spectra were obtained on a Varian XL-400 spectrometer operating at 400 MHz for 1H, 376 MHz for ^{19}F, and 100 MHz for ^{13}C and a Bruker 300 AMX spectrometer operating at 300 MHz for ^{1}H. Chemical shifts are reported in ppm (δ) and are referenced to $CDCl_3$ (7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C), tetramethylsilane (TMS, 0.00 ppm for ^{1}H), and $CFCl_3$ (0.00 ppm for ^{19}F). IR spectra were obtained using a Perkin–Elmer 1600 Series FT-IR instrument. HRMS were obtained at the mass spectrometry facility at the Ohio State University on a Micromass QTOF Electrospray mass spectrometer. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA.

4.1. Iodolactone (±)-13

A 250 mL flask was charged with carboxylic acid (±)-**12** (1.770 g, 14.04 mmol) and a solution of $NaHCO_3$ (3.54 g, 42.12 mmol) in water (35 mL) and stirred until homogeneous. To this mixture was added a solution of iodine (3.74 g, 14.75 mmol) and KI (13.98 g, 84.24 mmol) in water (35 mL) and then immediately protected from light by wrapping aluminum foil around the flask. The reaction was stirred for 24 h at room temperature followed by extraction with $CHCl_3$ (3×30 mL). The organics were combined, washed with $Na_2S_2O_3$ (100 mL, 10% in water) and $NaHCO_3$ (100 mL, 10% in water), dried over $MgSO_4$, and then removed under reduced pressure to give 3.397 g (96%) of iodolactone **13** as a yellow solid. Mp 132–134 °C; ^{1}H NMR ($CDCl_3$): δ 4.82 (t, $J = 5.6$ Hz, 1H), 4.5 (t, $J = 4.4$ Hz, 1H), 2.79 (d, $J = 12.4$ Hz, 1H), 2.68–2.65 (m, 1H), 2.48–2.35 (m, 3H), 2.10 (dd, $J = 16.8$, 5.2 Hz, 1H), 1.94–1.79 (m, 2H); identical in all respects to literature reports.[16,17]

4.2. Olefinic lactone (±)-14

Iodolactone (±)-**13** (3.394 g, 13.46 mmol) was dissolved in toluene (40 mL, anhydrous) and fresh 1,3-diazabicyclo-[5.4.0]undec-7-ene (DBU, 3.06 mL, 20.19 mmol). This was heated at reflux for 6 h and then cooled down to room temperature. The reaction was filtered, concentrated under reduced pressure, and purified by silica gel chromatography (60% hexanes/40% ethyl acetate) to give 1.593 g (95%) of olefinic lactone **14** as a pale-yellow oil. ^{1}H NMR ($CDCl_3$): δ 6.20 (m, 1H), 5.83–5.79 (m, 1H), 4.72 (m, 1H), 2.87 (m, 1H), 2.52–2.38 (m, 3H), 2.06 (d, $J = 11.2$ Hz, 1H); identical in all respects to literature reports.[16,17]

4.3. Diol (±)-15

Lactone (±)-**14** (1.54 g, 13.46 mmol) was dissolved in THF (4 mL, anhydrous) and then added (cannula) to a flask containing a solution of $LiAlH_4$ (0.470 g, 12.40 mmol, 1 M/ether) in THF (25 mL) at 0 °C. The reaction was stirred for 2 h and then quenched with water (1 mL), 15% NaOH (1 mL) and the more water (2 mL) and let stir vigorously for 1.5 h at room temperature. The mixture was dried over $MgSO_4$, concentrated under reduced pressure, and then purified by silica gel chromatography (60% hexanes/40% ethyl acetate) to give 1.557 g (98%) of diol **15** as an oil. ^{1}H NMR ($CDCl_3$): δ 5.81–5.76 (m, 1H), 5.73–5.69 (m, 1H), 4.32 (m, 1H), 3.58 (d, $J = 6$ Hz, 2H), 2.16–2.09 (m, 2H), 1.98–1.88 (m, 1H), 1.84–1.76 (m, 1H), 1.35–1.26 (m, 1H); identical in all respects to literature reports.[16,17]

4.4. Diol monosilyl ether (±)-16

Diol (±)-**15** (1.45 g, 11.32 mmol) was dissolved in DMF (15 mL, anhydrous) and then imidazole (1.542 g, 22.65 mmol) was added. The reaction was cooled to 0 °C and then *tert*-butyldimethylsilyl chloride (1.70 g, 11.32 mmol) was added. The reaction was stirred at 0 °C for 1 h and then slowly warmed to room temperature and stirred for another 5 h. The reaction was quenched with ice cold water (20 mL) and then extracted with diethyl ether. The organics were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (80% hexanes/20% ethyl acetate) to give 1.967 g (71%) of diol monosilyl ether **16** as an oil. ^{1}H NMR ($CDCl_3$): δ 5.76–5.59 (m, 2H), 4.29 (m, 1H), 3.55–3.44 (m, 2H), 2.15–2.02 (m, 2H), 1.98–1.70 (m, 3H), 1.22–1.18 (m, 1H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 131.10, 128.30, 67.53, 67.45, 35.73, 28.18, 25.88, 18.29, −5.41; identical in all respects to literature reports.[16]

4.5. Enone (±)-17

Diol monosilyl ether (±)-**16** (1.658 g, 6.818 mmol) was dissolved in methylene chloride (25 mL, anhydrous) and then 4 Å molecular sieves (7 g) was added. To this mixture was added *N*-methylmorpholine oxide (1.597 g, 13.63 mmol) and then tetrapropyl ammonium perruthenate (0.120 g, 0.341 mmol). The reaction was stirred at room temperature for 1.5 h. The reaction was then passed over a plug of silica and the organics were combined, dried over $MgSO_4$, concentrated under reduced pressure, and purified by column chromatography (80% hexanes/20% ethyl acetate) to give 1.460 g (89%) of enone **17** as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 6.97 (ddd, $J = 10.0$, 6.0, 2.8 Hz, 1H), 6.01 (d, $J = 9.2$ Hz, 1H), 3.59–3.51 (m, 2H), 2.50–2.33 (m, 2H), 2.32–2.20 (m, 3H), 0.88 (s, 9H), 0.037 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 199.78, 149.71, 129.63, 66.05, 40.82, 37.69, 28.57, 25.83, 18.25, −5.47, −5.49; IR (neat, cm^{-1}) 2929, 2857, 1682, 1471, 1386, 1113, 837; HRMS (CI) *m/z* (M+Na) calcd 263.143775 for $C_{13}H_{24}O_2SiNa^+$, found 263.144255.

4.6. Epoxy ketone (±)-18

Enone (±)-**17** (1.437 g, 5.977 mmol) was dissolved in methanol (100 mL) and then hydrogen peroxide (30%, 6.78 mL, 59.77 mmol) was added and the mixture was cooled to −20 °C. To this mixture was added an aqueous solution of sodium hydroxide (3 M, 300 μL, 0.897 mmol). The reaction was stirred at −20 °C for 5 h and upon disappearance of starting material (TLC) saturated ammonium chloride was added (5 mL). The reaction was extracted with diethyl ether (3×25 mL) and the organics were combined, dried over $MgSO_4$, concentrated under reduced pressure and then purified by column chromatography (90% hexanes/10% ethyl acetate) to give 1.400 g (91%) of epoxy ketone **18** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 3.59 (m, 1H), 3.51–3.44 (m, 2H), 3.23 (d, $J = 4$ Hz, 1H), 2.49 (dd, $J = 18.0$, 4.8 Hz, 1H), 2.32–2.20 (m, 2H), 2.01 (dd, $J = 18.4$, 10.8 Hz, 1H), 1.83 (ddd, $J = 14.4$, 10.0, 0.8 Hz, 1H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 205.55, 65.95, 55.02, 54.68, 39.41, 30.34, 26.09, 25.81, 18.21, −5.55; IR (neat, cm^{-1}) 2930, 2857, 1715, 1471, 1252, 1106, 837; HRMS (CI) *m/z* (M+Na) calcd 279.138690 for $C_{13}H_{24}O_3SiNa^+$, found 279.138261.

4.7. Enoate esters (±)-19-*E* and (±)-19-*Z*

To a 25 mL flask was added NaH (0.103 g, 4.08 mmol) and THF (5 mL, anhydrous). The slurry was cooled to

0 °C and then triethyl phosphonoacetate (0.809 μL, 4.08 mmol) was added via syringe. This was then warmed to room temperature and stirred for 30 min. The reaction was then cooled back to 0 °C and then a 3 mL THF solution of epoxy ketone (±)-**18** (0.523 g, 2.04 mmol) was added via cannula. The reaction was stirred at 0 °C until complete disappearance of starting material (TLC, ~3 h). The reaction was quenched with satd NH_4Cl and extracted with diethyl ether (3 × 25 mL). The organics were combined, dried over $MgSO_4$, concentrated under reduced pressure, and then purified by column chromatography (90% hexanes/10% ethyl acetate) to give 0.248 g (37%) of enoate ester (±)-**19-*E*** and 0.388 g (58%) of enoate ester (±)-**19-*Z*** (95% total) as colorless oils. Compound (±)-**19-*E***: ^{1}H NMR ($CDCl_3$): δ 6.03 (m, 1H), 4.16 (q, J = 7.2 Hz, 2H), 3.52–3.46 (m, 2H), 3.42 (dd, J = 9.6, 5.6 Hz, 1H), 3.36 (d, J = 4 Hz, 1H), 3.10 (dd, J = 18, 4 Hz, 1H), 2.26–2.13 (m, 2H), 1.95–1.84 (m, 1H), 1.64 (ddd, J = 14.4, 12, 1.2 Hz, 1H), 1.27 (t, J = 7.2 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 165.46, 153.31, 121.98, 66.74, 59.89, 55.04, 54.23, 30.18, 28.60, 26.80, 25.87, 18.26, 14.24, −5.46; IR (neat, cm^{-1}) 2930, 2857, 1717, 1646, 1471, 1384, 1255, 1106, 837; HRMS (CI) *m*/*z* (M+Na) calcd 349.180555 for $C_{17}H_{30}O_4SiNa^+$, found 349.182443. Compound (±)-**19-*Z***: ^{1}H NMR ($CDCl_3$): δ 5.96 (m, 1H), 4.62 (d, J = 3.6 Hz, 1H), 4.18 (dq, J = 7.2, 1.6 Hz, 2H), 3.45–3.36 (m, 3H), 2.37 (dd, J = 14.8, 3.2 Hz, 1H), 2.18 (dd, J = 14.8, 4.8 Hz, 1H), 1.97 (ddd, J = 15.2, 10.0, 2.0 Hz, 1H), 1.89–1.81 (m, 1H), 1.68–1.61 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H), 0.87 (s, 9H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 165.69, 152.75, 122.77, 66.31, 60.08, 54.38, 49.54, 33.77, 31.82, 26.69, 25.82, 18.21, 14.23, −5.50; IR (neat, cm^{-1}) 2930, 2857, 1717, 1646, 1471, 1384, 1255, 1106, 837; HRMS (CI) *m*/*z* (M+Na) calcd 349.180555 for $C_{17}H_{30}O_4SiNa^+$, found 349.180774.

4.8. Pivaloate ester (±)-20

To a 25 mL flask was added enoate ester (±)-**19-*E*** (0.085 g, 0.260 mmol) and hexanes (1.5 mL). This mixture was cooled to 0 °C and then DIBAL-H (1.04 mL, 1.04 mmol, 1.0 M in hexanes) was added slowly via syringe. The reaction was stirred for an additional 1.5 h and then quenched with a saturated Na^+, K^+ tartrate solution (2 mL), and stirred at room temperature for another 30 min. The reaction was extracted with ethyl acetate (3 × 25 mL) and the organics were combined, dried over $MgSO_4$ and concentrated under reduced pressure to give the crude diol (0.077 g), which was carried forward without further purification.

The crude diol (0.260 mmol) was placed in a 25 mL flask and dissolved in pyridine (2 mL, anhydrous). DMAP (0.035 g, 0.286 mmol) was added and the reaction was cooled to 0 °C. To this mixture was added trimethylacetyl chloride (35 μL, 0.286 mmol) dropwise via syringe. The reaction was then stirred at 0 °C for 3 h and then quenched with water (2 mL), extracted with diethyl ether (3 × 25 mL), dried over $MgSO_4$, and purified by silica gel chromatography (80% hexanes/20% ethyl acetate) to give 0.068 g of pivaloate ester **20** (72%, two steps) as a colorless oil. ^{1}H NMR ($CDCl_3$): 5.40 (t, J = 6.8 Hz, 1H), 4.58 (d, J = 7.2 Hz, 2H), 4.10 (m, 1H), 3.50–3.43 (m, 2H), 2.55 (dd, J = 13.2, 3.6 Hz, 1H), 2.35 (d, J = 13.6 Hz, 1H), 2.22 (dd, J = 13.2, 4.0 Hz, 1H), 1.96–1.86 (m, 1H), 1.81–1.68 (m, 4H), 1.48 (ddd, J = 13.6, 10.8, 2.8 Hz, 1H), 1.17 (s, 9H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 178.50, 140.52, 120.32, 67.39, 67.14, 60.37, 43.88, 38.68, 35.87, 35.74, 31.32, 27.16, 25.87, 18.26, −5.41; IR (neat, cm^{-1}) 3502, 2929, 1724, 1459, 1280, 1155; HRMS (CI) *m*/*z* (M+Na) calcd 393.243155 for $C_{20}H_{38}O_4SiNa^+$, found 393.24329.

4.9. Allylic alcohol (±)-21

To a 10 mL flask was added pivaloate ester (±)-**20** (0.068 g, 0.183 mmol) and DMF (3.0 mL). To this mixture was added imidazole (0.050 g, 0.734 mmol) and *tert*-butyldimethylsilyl chloride (0.083 g, 0.550 mmol) and then the reaction was heated to 60 °C for 3 h. After full consumption of the starting material (TLC), the reaction was poured into ice water and then extracted with diethyl ether (3 × 25 mL). The organics were combined, dried over $MgSO_4$, and concentrated under reduced pressure to give the crude bis-silyl ether product, which was carried forward without further purification.

In a 25 mL flame-dried flask was placed lithium aluminum hydride (0.004 g, 0.092 mmol) and THF (2 mL) that was cooled to 0 °C. In a separate 10 mL pear shaped flask was placed the bis-silyl ether (0.183 mmol) and THF (1.5 mL), which was cannulated over into the reaction flask. The reaction was then stirred at 0 °C for 1.5 h and then quenched by adding $Na_2SO_4{\cdot}10H_2O$. This was stirred together for 30 min and then the salts were filtered off and washed with diethyl ether. The organics were concentrated under reduced pressure and then purified by silica gel chromatography (80% hexanes/20% ethyl acetate) to give 0.061 g of allylic alcohol **21** (83%, two steps) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 5.49 (t, J = 7.6 Hz, 1H), 4.16 (dd, J = 12.0, 7.6 Hz, 1H), 4.03 (dd, J = 12.4, 7.2 Hz, 1H), 3.94 (m, 1H), 3.50–3.42 (m, 2H), 2.33–2.24 (m, 2H), 2.11–1.98 (m, 3H), 1.68–1.62 (m, 1H), 1.52–1.46 (m, 1H), 0.89 (s, 9H), 0.85 (s, 9H), 0.04 (d, J = 1.2 Hz, 6H), 0.02 (d, J = 4.8 Hz, 6H);^{13}C NMR ($CDCl_3$): δ 139.36, 124.46, 68.09, 66.26, 58.24, 45.32, 36.99, 36.11, 30.02, 25.86, 25.78, 18.24, 18.09, −4.73, −4.79, −5.26, −5.36; IR (neat, cm^{-1}) 3354, 2928, 2856, 1471, 1254, 1115, 1073, 836; HRMS (CI) *m*/*z* (M+Na) calcd 423.272117 for $C_{21}H_{44}O_3Si_2Na^+$, found 423.27055.

4.10. Allylic phosphine oxide (±)-10

Allylic alcohol (±)-**21** (0.113 g, 0.282 mmol) was placed in a 25 mL flask with THF (1.5 mL) and cooled to 0 °C. To this was added *n*-BuLi (194 μL, 0.310 mmol, 1.6 M in hexanes) dropwise via syringe. The reaction was stirred for 10 min and then a THF solution (1.5 mL) of *p*-toluenesulfonyl chloride (0.059 g, 0.310 mmol) was added via cannula and stirred for 3 h at 0 °C. In a separate flask was added diphenyl phos-

phine (245 μL, 1.409 mmol) and THF (3 mL). To this was slowly added *n*-BuLi (0.881 mL, 1.409 mmol) via syringe and then stirred for 10 min. This lithium diphenyl phosphine solution was then cannulated into the previous reaction flask until a dark orange color persisted for 2 min. This was stirred at 0 °C for another 1 h, after which water was added (2 mL) and the organics were brought to dryness under reduced pressure. To this oily water mixture was added methylene chloride (3 mL) and hydrogen peroxide (2 mL, 30%) and stirred vigorously overnight. The reaction was then extracted with methylene chloride (3 × 25 mL), the organics were concentrated under reduced pressure and then purified by silica gel chromatography (60% hexanes/40% ethyl acetate) to give 0.117 g of allylic phosphine oxide **10** (71%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.75–7.69 (m, 4H), 7.52–7.40 (m, 6H), 5.22 (m, 1H), 3.95 (m, 1H), 3.37–3.30 (m, 2H), 3.20–3.05 (m, 2H), 2.26–2.21 (m, 1H), 2.16–2.04 (m, 2H), 1.90–1.80 (m, 2H), 1.63–1.59 (m, 1H), 1.49–1.44 (m, 1H), 1.37–1.30 (m, 1H), 0.87 (s, 9H), 0.81 (s, 9H), 0.01 (s, 6H), −0.03 (d, J = 5.2 Hz, 6H); ^{13}C NMR ($CDCl_3$): δ 140.16, 140.04, 131.63, 131.60, 131.13, 131.04, 130.95, 128.50, 128.46, 128.39, 128.34, 112.25, 112.17, 67.79, 67.10, 44.70, 36.72, 35.22, 30.90, 30.65, 29.94, 25.87, 25.79, 18.20, 18.08, −4.79, −4.87, −5.35, −5.38; IR (neat, cm^{-1}) 2926, 2854, 1470, 1252, 1117, 836; HRMS (CI) *m*/*z* (M+Na) calcd 607.316304 for $C_{33}H_{53}O_3PSi_2Na^+$, found 607.322159.

4.11. Pivaloate (±)-22

To a 25 mL flask was added enoate ester (±)-**19-*Z*** (0.075 g, 0.229 mmol) and hexanes (1.5 mL). This mixture was cooled to 0 °C and then DIBAL-H (0.918 mL, 0.918 mmol, 1.0 M in hexanes) was added slowly via syringe. The reaction was stirred for an additional 1.5 h and then quenched with a saturated Na^+, K^+ tartrate solution (2 mL), and stirred at room temperature for another 30 min. The reaction was extracted with ethyl acetate (3 × 25 mL) and the organics were combined, dried over $MgSO_4$ and concentrated under reduced pressure to give the crude diol (0.067 g), which was carried forward without further purification.

The crude diol (0.229 mmol) was placed in a 25 mL flask and dissolved in pyridine (2 mL, anhydrous). DMAP (0.031 g, 0.253 mmol) was added, and the reaction was cooled to 0 °C. To this mixture was added trimethylacetyl chloride (31 μL, 0.253 mmol) dropwise via syringe. The reaction was then stirred at 0 °C for 3 h and then quenched with water (2 mL), extracted with diethyl ether (3 × 25 mL), dried over $MgSO_4$, and purified by silica gel chromatography (80% hexanes/20% ethyl acetate) to give 0.076 g of pivaloate ester **22** (90%, two steps) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 5.46 (t, J = 6.8 Hz, 1H), 4.77 (dd, J = 12.0, 8.8 Hz, 1H), 4.37 (dd, J = 12.4, 6.0 Hz, 1H), 4.16 (m, 1H), 3.44 (ddd, J = 10.0, 9.2, 5.2 Hz, 2H), 2.80–2.76 (m, 1H), 2.28–2.24 (m, 1H), 2.12–1.78 (m, 5H), 1.39 (dt, J = 13.6, 2.4 Hz, 1H), 1.17 (s, 9H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 179.07, 141.70, 119.83, 67.42, 66.96, 60.63, 39.22, 38.76, 36.28, 36.03, 35.59, 27.10, 25.91, 18.32, −5.41; IR (neat, cm^{-1}) 3504, 2928, 1725, 1459, 1283, 1155; HRMS (CI) *m*/*z* (M+Na) calcd 393.243155 for $C_{20}H_{38}O_4SiNa^+$, found 393.24347.

4.12. Allylic alcohol (±)-23

To a 10 mL flask was added pivaloate ester (±)-**22** (0.085 g, 0.229 mmol) and DMF (2.0 mL). To this mixture was added imidazole (0.047 g, 0.689 mmol) and *tert*-butyldimethylsilyl chloride (0.070 g, 0.459 mmol) and then the reaction was heated to 60 °C for 3 h. After full consumption of the starting material (TLC), the reaction was poured into ice water and then extracted with diethyl ether (3 × 25 mL). The organics were combined, dried over $MgSO_4$, and concentrated under reduced pressure to give the crude bis-silyl ether (0.115 g), which was carried forward without further purification.

In a 25 mL flame-dried flask was placed lithium aluminum hydride (0.004 g, 0.115 mmol) and THF (2 mL) that was cooled to 0 °C. In a separate 10 mL pear shaped flask was placed the bis-silyl ether (0.229 mmol) and THF (1.5 mL), which was cannulated over into the reaction flask. The reaction was then stirred at 0 °C for 1.5 h and then quenched by adding $Na_2SO_4{\cdot}10H_2O$. This was stirred together for 30 min and then the salts were filtered off and washed with diethyl ether. The organics were concentrated under reduced pressure and then purified by silica gel chromatography (80% hexanes/20% ethyl acetate) to give 0.067 g of allylic alcohol **23** (81%, two steps) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 5.66 (t, J = 7.2 Hz, 1H), 4.19 (m, 1H), 4.12 (dd, J = 11.6, 7.2 Hz, 1H), 3.96 (dd, J = 11.6, 7.2 Hz, 1H), 3.47–3.39 (m, 2H), 2.61–2.56 (m, 1H), 2.25–2.21 (m, 1H), 2.05–1.94 (m, 2H), 1.82–1.73 (m, 2H), 1.35 (dt, J = 10.8, 2.8 Hz, 1H), 0.88 (s, 9H), 0.86 (s, 9H), 0.05 (d, J = 4.0 Hz, 6H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 140.69, 123.82, 68.14, 67.59, 58.02, 39.33, 36.72, 36.67, 36.60, 25.90, 25.85, 18.29, 18.13, −4.75, −4.83, −5.37, −5.40; IR (neat, cm^{-1}) 3358, 2928, 2856, 1471, 1360, 1253, 1116, 1073, 839; HRMS (CI) *m*/*z* (M+Na) calcd 423.272117 for $C_{21}H_{44}O_3Si_2Na^+$, found 423.27122.

4.13. Allylic phosphine oxide (±)-11

Allylic alcohol (±)-**23** (0.180 g, 0.449 mmol) was placed in a 25 mL flask with THF (3 mL) and cooled to 0 °C. To this was added *n*-BuLi (309 μL, 0.494 mmol, 1.6 M in hexanes) dropwise via syringe. The reaction was stirred for 10 min and then a THF solution (2 mL) of *p*-toluenesulfonyl chloride (0.094 g, 0.494 mmol) was added via cannula and stirred for 3 h at 0 °C. In a separate flask was added diphenyl phosphine (391 μL, 2.24 mmol) and THF (4 mL). To this was slowly added *n*-BuLi (1.40 mL, 2.24 mmol) via syringe and then stirred for 10 min. This lithium diphenyl phosphine solution was then cannulated into the previous reaction flask until a dark orange color persisted for 2 min. This was stirred at 0 °C for another 1 h, after which water was added (2 mL) and the organics were brought to dryness under reduced pressure. To this oily water mixture was added

methylene chloride (5 mL) and hydrogen peroxide (3 mL, 30%) and stirred vigorously overnight. The reaction was then extracted with methylene chloride (3 × 25 mL), the organics were concentrated under reduced pressure and then purified by silica gel chromatography (60% hexanes/40% ethyl acetate) to give 0.184 g of allylic phosphine oxide **11** (71%) as a colorless oil. ^{1}H NMR ($CDCl_3$) 7.75–7.66 (m, 4H), 7.54–7.41 (m, 6H), 5.27 (m, 1H), 3.94 (m, 1H), 3.37–3.29 (m, 2H), 3.23–3.13 (m, 1H), 3.05–2.96 (m, 1H), 2.19–2.12 (m, 2H), 2.01–1.86 (m, 2H), 1.78–1.74 (m, 2H), 1.64–1.59 (m, 1H), 1.35 (dt, J = 10.0, 2.8 Hz, 1H), 0.85 (s, 9H), 0.84 (s, 9H), 0.01 (d, J = 3.2 Hz, 6H), −0.01 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 140.87, 140.75, 131.70, 131.64, 131.16, 131.08, 131.03, 130.94, 128.51, 128.40, 112.02, 111.94, 67.60, 67.05, 38.93, 36.96, 36.66, 36.05, 30.31, 29.62, 25.88, 25.74, 18.24, 18.00, −4.71, −4.90, −5.36, −5.40; IR (neat, cm^{-1}) 2928, 2855, 1470, 1252, 1253, 1118; HRMS (CI) m/z (M+Na) calcd 607.316304 for $C_{33}H_{53}O_3PSi_2Na^+$, found 607.31423.

4.14. Analogs (+)-5a and (+)-5b

Prior to reaction, phosphine oxide (±)-**10** and CD-ring ketone (+)-**9** were azeotrophically dried with benzene and left under vacuum for 48 h. A solution of *n*-BuLi in hexanes (81 μL, 0.121 mmol, 1.5 M) was added dropwise to a cold (−78 °C) solution of phosphine oxide (±)-**10** (0.071 g, 0.121 mmol) in THF (1.0 mL) under dry argon. The resulting deep red solution was stirred for 40 min, at which time a cold (−78 °C) solution of C,D-ring ketone (+)-**9** (0.025 g, 0.072 mmol) in THF (1.5 mL) was added dropwise via cannula. The resulting solution was stirred at −78 °C in the dark for approximately 3 h, after which the dark red color had faded to a light orange color. The reaction mixture was quenched with pH 7.0 phosphate buffer (1 mL), warmed to rt, extracted with Et_2O (3 × 20 mL), and washed with brine. The organics were dried over $MgSO_4$, filtered, concentrated, and purified by silica gel column chromatography (90% hexanes, 10% ethyl acetate) to afford the coupled products as a clear oil (0.031 g, 60%). This oil was immediately dissolved in THF (1.0 mL) and treated with triethylamine (30 μL, 0.215 mmol) followed by TBAF (215 μL, 0.215 mmol, 1.0 M in THF) and stirred in the dark for 16 h. The reaction mixture was quenched with H_2O (1 mL), extracted with EtOAc (3 × 25 mL), dried over $MgSO_4$, filtered, concentrated, and purified by silica gel column chromatography (80% ethyl acetate, 20% hexanes) to afford analogs **5a/b** (0.017 g, 95%) as a 1/2 mixture of diastereomers. This diastereomeric mixture was separated by HPLC (Chiralcel-OD, 9% *i*-PrOH/hexanes, 2.5 mL/min) giving enantiomerically pure, vitamin-D_3 analogs (+)-**5a** and (+)-**5b**. Compound (+)-**5a** (1α,3β): (Ret. time = 34.8 min); $[\alpha]_D^{25}$ +40.3 (*c* 0.046, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.22 (d, J = 11.2 Hz, 1H), 5.87 (d, J = 11.2 Hz, 1H), 4.13 (m, 1H), 3.56 (m, 2H), 2.81–2.78 (d, J = 12.0 Hz 2H), 2.43 (d, J = 14.4 Hz, 1H), 2.30–2.26 (m, 1H), 2.04–1.84 (m, 5H), 1.76–1.25 (m, 23H), 1.21 (s, 6H), 0.94 (d, J = 6.8 Hz, 3H), 0.54 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 142.41, 133.20, 122.29, 115.25, 71.09, 67.64, 67.50, 56.47, 56.26, 45.74, 44.68, 44.38, 40.45, 36.36, 36.09, 36.02, 35.93, 31.15, 29.69, 29.35, 29.19, 28.93, 27.65, 23.52, 22.27, 20.77, 18.79, 12.00; IR (neat, cm^{-1}) 3358, 2930, 2871, 1465, 1374, 1214; UV (EtOH) λ_{max} 251 (ε 22,738); HRMS m/z (M^+) calcd 441.333913 for $C_{27}H_{46}O_3Na^+$, found 441.33351. Compound (+)-**5b** (1β,3α): (Ret. time = 24.6 min); $[\alpha]_D^{25}$ +24.1 (*c* 0.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.21 (d, J = 11.2 Hz, 1H), 5.85 (d, J = 11.2 Hz, 1H), 4.10 (m, 1H), 3.56 (m, 2H), 2.82–2.72 (m, 2H), 2.43 (d, J = 13.6 Hz, 1H), 2.27 (dd, J = 14.0, 4.4 Hz, 1H), 2.01–1.74 (m, 7H), 1.69–1.25 (m, 21H), 1.21 (s, 6H), 0.94 (d, J = 6.4 Hz, 3H), 0.56 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 142.28, 133.02, 122.28, 115.28, 71.10, 67.55, 67.48, 56.48, 56.26, 45.72, 44.71, 44.38, 40.47, 36.36, 36.09, 35.78, 30.91, 29.69, 29.35, 29.19, 28.80, 27.64, 23.41, 22.31, 20.78, 18.79, 12.13; IR (neat, cm^{-1}) 3357, 2926, 2871, 1466, 1377, 1214; UV (EtOH) λ_{max} 251 (ε 31,195); HRMS m/z (M^+) calcd 441.333913 for $C_{27}H_{46}O_3Na^+$, found 441.334625.

4.15. Analogs (+)-6a and (+)-6b

Prior to reaction, phosphine oxide (±)-**11** and C,D-ring ketone (+)-**9** were azeotrophically dried with benzene and left under vacuum for 48 h. A solution of *n*-BuLi in hexanes (80 μL, 0.128 mmol, 1.6 M) was added dropwise to a cold (−78 °C) solution of phosphine oxide (±)-**11** (0.075 g, 0.128 mmol) in THF (1.0 mL) under dry argon. The resulting deep red solution was stirred for 40 min, at which time a cold (−78 °C) solution of C,D-ring ketone (+)-**9** (0.029 g, 0.081 mmol) in THF (1.5 mL) was added dropwise via cannula. The resulting solution was stirred at −78 °C in the dark for approximately 2 h, after which the dark red color had faded to a light orange color. The reaction mixture was quenched with pH 7.0 phosphate buffer (1 mL), warmed to rt, extracted with Et_2O (3 × 20 mL), and washed with brine. The organics were dried over $MgSO_4$, filtered, concentrated, and purified by silica gel column chromatography (95% hexanes/5% ethyl acetate) to afford the coupled products as a clear oil (0.047 g, 80%). This oil was immediately dissolved in THF (1.0 mL) and treated with triethylamine (54 μL, 0.392 mmol) followed by TBAF (392 μL, 0.392 mmol, 1.0 M in THF) and stirred in the dark for ∼16 h. The reaction mixture was quenched with H_2O (1 mL), extracted with EtOAc (3 × 25 mL), dried over $MgSO_4$, filtered, concentrated, and purified by silica gel column chromatography (80% ethyl acetate/20% hexanes) to afford analogs **6a/b** (0.025 g, 93%) as a 1.5/1 mixture of diastereomers. This diastereomeric mixture was separated by HPLC (Chiralcel-OD, 10% *i*-PrOH/hexanes, 2.5 mL/min) giving enantiomerically pure, vitamin-D_3 analogs **6a** and **6b**. Compound (+)-**6a** (1α,3β): (Ret. time = 21.3 min); $[\alpha]_D^{25}$ +82.3 (*c* 0.095, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.35 (d, J = 11.6 Hz, 1H), 5.83 (d, J = 10.8 Hz, 1H), 4.11 (m, 1H), 3.55–3.48 (m, 2H), 2.75 (ddd, J = 36.0, 12.4, 4.4 Hz, 2H), 2.33 (dd, J = 35.6, 10.4 Hz, 2H), 2.01–1.82 (m, 6H), 1.72–1.22 (m, 22H), 1.21 (s, 6H), 0.93 (d, J = 6.4 Hz, 3H), 0.54 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 142.49, 133.12, 122.75, 115.24, 71.10, 67.44, 67.26, 56.49, 56.28, 45.74, 44.39, 40.48, 39.34, 36.71, 36.40, 36.37, 36.07, 29.36, 29.17,

28.86, 27.64, 23.45, 22.24, 20.78, 18.79, 12.07; IR (neat, cm^{-1}) 3356, 2942, 2871, 1371, 1031, 756; UV (EtOH) λ_{max} 251 (ε 27,340); HRMS *m/z* (M^+) calcd 441.333913 for $C_{27}H_{46}O_3Na^+$, found 441.333921. Compound (+)-**6b** (1β,3α): (Ret. time = 26.9 min); $[\alpha]_D^{25}$ +47.6 (*c* 0.35, MeOH); ^1H NMR (400 MHz, $CDCl_3$): δ 6.37 (d, *J* = 11.2 Hz, 1H), 5.83 (d, *J* = 11.2 Hz, 1H), 4.16 (m, 1H), 3.58–3.48 (m, 2H), 2.83–2.76 (m, 2H), 2.38 (d, *J* = 10.4 Hz, 1H), 2.20 (d, *J* = 13.6 Hz, 1H), 2.01–1.84 (m, 6H), 1.72–1.23 (m, 23H), 1.21 (s, 6H), 0.94 (d, *J* = 6.4 Hz, 3H), 0.54 (s, 3H); ^{13}C NMR (CD_3OD): δ 141.56, 135.42, 122.43, 117.22, 71.47, 68.05, 67.07, 57.96, 57.53, 46.72, 45.28, 41.92, 40.19, 37.76, 37.59, 37.49, 37.24, 37.13, 29.76, 29.25, 29.13, 28.79, 24.53, 23.31, 21.90, 19.38, 12.39; IR (neat, cm^{-1}) 3309, 2921, 2855, 1450, 1377, 1141; UV (EtOH) λ_{max} 251 (ε 33,152); HRMS *m/z* (M^+) calcd 441.333913 for $C_{27}H_{46}O_3Na^+$, found 441.333592.

4.16. Analogs (−)-7a and (−)-7b

Prior to reaction, phosphine oxide (±)-**10** and C,D-ring ketone (−)-**24** were azeotrophically dried with benzene and left under vacuum for 48 h. A solution of *n*-BuLi in hexanes (44 μL, 0.071 mmol, 1.6 M) was added dropwise to a cold (−78 °C) solution of phosphine oxide (±)-**10** (0.041 g, 0.071 mmol) in THF (1.0 mL) under dry argon. The resulting deep red solution was stirred for 40 min, at which time a cold (−78 °C) solution of C,D-ring ketone (−)-**24** (0.014 g, 0.035 mmol) in THF (1.5 mL) was added dropwise via cannula. The resulting solution was stirred at −78 °C in the dark for approximately 3 h, after which the dark red color had faded to a light orange color. The reaction mixture was quenched with pH 7.0 phosphate buffer (1 mL), warmed to rt, extracted with Et_2O (3 × 20 mL), and washed with brine. The organics were dried over $MgSO_4$, filtered, concentrated, and purified by silica gel column chromatography (90% hexanes/10% ethyl acetate) to afford the coupled products as a clear oil (0.015 g, 55%).

The coupled product (0.034 g, 0.045 mmol) was dissolved in THF (1.0 mL) and treated with triethylamine (94 μL, 0.677 mmol) followed by TBAF (452 μL, 0.452 mmol, 1.0 M in THF) and stirred in the dark for ~16 h. The reaction mixture was quenched with H_2O (1 mL), extracted with EtOAc (3 × 25 mL), dried over $MgSO_4$, filtered, concentrated, and purified by silica gel column chromatography (80% ethyl acetate/20% hexanes) to afford analogs **7a/b** (0.019 g, 90%) as a 1/2 mixture of diastereomers. This diastereomeric mixture was separated by HPLC (Chiralcel-OD, 5% EtOH/hexanes, 2.5 mL/min) giving enantiomerically pure, vitamin-D_3 analogs (−)-**7a** and (−)-**7b**. Compound (−)-**7a** (1α,3β): (Ret. time = 41.2 min); $[\alpha]_D^{25}$ −8.02 (*c* 0.32, MeOH); ^1H NMR (400 MHz, $CDCl_3$): δ 6.21 (d, *J* = 11.2 Hz, 1H), 5.85 (d, *J* = 11.2 Hz, 1H), 4.12 (m, 1H), 3.61–3.51 (m, 2H), 3.30–3.18 (m, 2H), 2.83–2.76 (m, 2H), 2.43 (d, *J* = 13.6 Hz, 1H), 2.27 (d, *J* = 14.0 Hz, 1H), 2.15 (d, *J* = 12.4 Hz, 1H), 2.07–1.18 (m, 23H), 1.08 (d, *J* = 6.0 Hz, 3H), 0.85 (dt, *J* = 7.2, 1.6 Hz, 6H), 0.55 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 142.38, 133.20, 122.27, 115.21, 78.26, 74.10, 68.79, 67.64, 67.51, 56.78, 55.76, 45.68, 44.71, 40.30, 36.05, 35.95, 35.65, 31.16, 31.12, 30.83, 28.99, 25.12, 24.22, 23.47, 22.47, 18.25, 12.65, 7.86, 7.82; IR (neat, cm^{-1}) 3370, 2940, 2874, 1454, 1371, 1214, 1102, 949, 755; UV (EtOH) λ_{max} 251 (ε 38,978); HRMS *m/z* (M^+) calcd 485.360128 for $C_{29}H_{50}O_4Na^+$, found 485.36118. Compound (−)-**7b** (1β,3α): (Ret. time = 34.1 min); $[\alpha]_D^{25}$ −36.7 (*c* 0.28, MeOH); ^1H NMR (400 MHz, $CDCl_3$): δ 6.21 (d, *J* = 11.2 Hz, 1H), 5.83 (d, *J* = 11.2 Hz, 1H), 4.10 (m, 1H), 3.56–3.49 (m, 2H), 3.30–3.19 (m, 2H), 2.82–2.72 (m, 2H), 2.43 (d, *J* = 14.0 Hz, 1H), 2.27 (d, *J* = 14.0 Hz, 1H), 2.15 (d, *J* = 12.8 Hz, 1H), 2.03–1.17 (m, 23H), 1.09 (d, *J* = 6.4 Hz, 3H), 0.91–0.78 (m, 6H), 0.57 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 142.22, 133.05, 122.26, 115.27, 78.26, 74.13, 68.80, 67.56, 67.44, 56.81, 55.76, 45.65, 44.75, 40.33, 36.14, 35.80, 35.66, 31.13, 30.94, 30.83, 28.86, 25.10, 24.23, 23.37, 22.51, 18.26, 12.79, 7.85, 7.83; IR (neat, cm^{-1}) 3371, 2940, 2874, 1454, 1371, 1215, 1103, 754; UV (EtOH) λ_{max} 251 (ε 36,203); HRMS *m/z* (M^+) calcd 485.360128 for $C_{29}H_{50}O_4Na^+$, found 485.35879.

4.17. Analog (+)-8

Prior to reaction, phosphine oxide (+)-**11** and C,D-ring ketone (−)-**24** were azeotrophically dried with benzene and left under vacuum for 48 h. A solution of *n*-BuLi in hexanes (49 μL, 0.078 mmol, 1.6 M) was added dropwise to a cold (−78 °C) solution of phosphine oxide (+)-**11** (0.046 g, 0.078 mmol) in THF (1.0 mL) under dry argon. The resulting deep red solution was stirred for 40 min, at which time a cold (−78 °C) solution of C,D-ring ketone (−)-**24** (0.021 g, 0.053 mmol) in THF (1.5 mL) was added dropwise via cannula. The resulting solution was stirred at −78 °C in the dark for approximately 1 h, after which the dark red color had faded to a light orange color. The reaction mixture was quenched with pH 7.0 phosphate buffer (1 mL), warmed to rt, extracted with Et_2O (3 × 20 mL), and washed with brine. The organics were dried over $MgSO_4$, filtered, concentrated, and purified by silica gel column chromatography (95% hexanes/5% ethyl acetate) to afford the coupled product as a clear oil (0.009 g, 23%). This oil was immediately dissolved in THF (1.0 mL) and treated with triethylamine (25 μL, 0.177 mmol) followed by TBAF (118 μL, 0.118 mmol, 1.0 M in THF) and stirred in the dark for ~16 h. The reaction mixture was quenched with H_2O (1 mL), extracted with EtOAc (3 × 25 mL), dried over $MgSO_4$, filtered, concentrated, and purified by silica gel column chromatography (80% ethyl acetate/20% hexanes) to afford analog (+)-**8** (0.005 g) in 93% yield. This analog was purified by HPLC (Chiralcel-OD, 9% EtOH/hexanes, 2.5 mL/min). Compound (+)-**8** (1α,3β): (Ret. time = 31.0 min); $[\alpha]_D^{25}$ +8.5 (*c* 0.25, MeOH); ^1H NMR (400 MHz, $CDCl_3$): δ 6.35 (d, *J* = 11.2 Hz, 1H), 5.81 (d, *J* = 11.2 Hz, 1H), 4.12 (m, 1H), 3.58–3.48 (m, 2H), 3.30–3.19 (m, 2H), 2.75 (ddd, *J* = 38.0, 12.4, 4.4 Hz, 2H), 2.37 (d, *J* = 9.6 Hz, 1H), 2.27 (d, *J* = 10.0 Hz, 1H), 2.15 (d, *J* = 12.4 Hz, 1H), 2.03–1.18 (m, 23H), 1.09 (d, *J* = 6.0 Hz, 3H), 0.85 (dt, *J* = 7.6, 2.0 Hz, 6H), 0.55 (s,

3H); ^{13}C NMR ($CDCl_3$): δ 142.49, 133.09, 122.78, 115.19, 78.25, 74.08, 68.81, 67.48, 67.28, 56.80, 55.78, 45.68, 40.32, 39.36, 36.75, 36.41, 36.12, 35.67, 31.12, 30.82, 28.92, 25.11, 24.22, 23.41, 22.44, 18.25, 12.79, 7.87, 7.84; IR (neat, cm^{-1}) 3374, 2925, 2874, 1453, 1370, 1103; UV (EtOH) λ_{max} 251 (ε 26,975); HRMS *m/z* (M^+) calcd 485.360128 for $C_{29}H_{50}O_4Na^+$, found 485.36278.

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29. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 263794. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 (0)1223 336033 or deposit@ccdc.cam.ac.uk).
30. The (1α,3β) stereochemistry for analogs **2a**, **3a**, and **4a** has been revised from the previously reported (1β,3α) stereochemistry.[7]
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