Asymmetric Total Synthesis, X-ray Crystallography, and Preliminary Biological Evaluation of 1-(1′-Hydroxyethyl)-25-hydroxyvitamin D_3 Analogs of Natural Calcitriol†

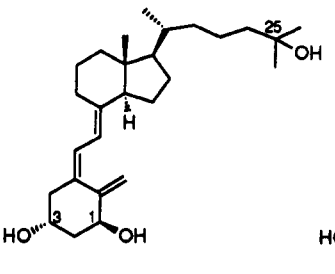
Gary H. Posner,*,‡ Haiyan Dai,‡ Kamyar Afarinkia,‡ N. Narasimha Murthy,‡,§ Kate Z. Guyton,∥ and Thomas W. Kensler*,∥

Department of Chemistry, School of Arts and Sciences, The Johns Hopkins University, Baltimore, Maryland 21218, and Division of Toxicological Sciences and the Environmental Health Sciences Center, Department of Environmental Health Sciences, School of Hygiene and Public Health, The Johns Hopkins University, Baltimore, Maryland 21205

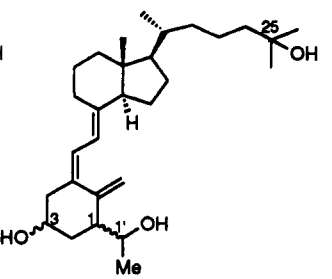
Received June 15, 1993•

With 3-bromo-2-pyrone as diene and acrolein as dienophile, thermally mild Diels–Alder cycloaddition led to an isolable bicyclic lactone aldehyde that underwent highly stereocontrolled methyl Grignard addition to form essentially only a single diastereomer of secondary alcohol (±)-**8a**. This bicyclic lactone alcohol (±)-**8a** was converted smoothly into A-ring phosphine oxide (±)-**15** which was coupled with the enantiomerically pure C,D-ring chiron **16** to produce separable diastereomers of 1-substituted calcitriol analogs (+)-**2** and (−)-**3** overall in 15 steps and approximately 4% yield. Single-crystal X-ray diffraction analysis revealed some unusual intermolecular hydrogen-bonding interactions as well as the absolute stereochemistry of diastereomer (+)-**2** and therefore also of its companion diastereomer (−)-**3**. Likewise, 1-substituted calcitriol analogs (+)-**4** and (−)-**5** were prepared with key steps involving mild Diels–Alder cycloaddition of 3-bromo-2-pyrone and methyl vinyl ketone followed by chemospecific reduction of the ketone carbonyl group. Preliminary biological evaluation showed all four of these 1-hydroxyethyl analogs **2–5** to be significant inhibitors of murine keratinocyte growth, with diastereomers (+)-**2** and (+)-**4** comparable in potency to calcitriol. Significantly, these four homologs of calcitriol were approximately 1000 times less effective than calcitriol in binding to the calf thymus $1,25(OH)_2D_3$ receptor. Also, these analogs were found to open calcium channels via a nongenomic process.

It has been commonly accepted that the 1α-hydroxyl group is required for the potent biological activities characteristic of the natural hormone 1α,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$, calcitriol, (+)-**1**].[1] Recently, however, we reported that small structural changes at the 1-position of calcitriol could be made while still maintaining significant biological activity. For example, we showed that 1-hydroxymethyl-25-hydroxyvitamin D_3 homologs of natural calcitriol retained calcitriol's antiproliferative activity in murine keratinocytes even though these synthetic homologs were less than 0.1% as effective as calcitriol in binding to the $1,25(OH)_2D_3$ receptor.[2a] Furthermore, we showed for the first time that such a small structural change at the 1-position significantly affected the rate of metabolism at the remote side chain (i.e., 24-hydroxylation).[2c] Also, a 1-(2′-hydroxyethyl)-25-hydroxyvitamin D_3 analog[2b] was shown to be antiproliferative in murine keratinocytes but to undergo side-chain metabolic hydroxylation much more rapidly than its 1-hydroxymethyl counterpart.[2c] To broaden this study of structure–function relationships of vitamin D_3 analogs,[3] we have achieved preparation, X-ray crystallography, and preliminary biological evaluation of four new synthetic homologs of natural calcitriol, namely, 1-(1′-hyroxylethyl)-25-hydroxyvitamin D_3 compounds **2–5**. Our results are described in this report.



(+)-**1**



	positions		
	3	1	1′
(+)-**2**	β	α	*S*
(−)-**3**	α	β	*R*
(+)-**4**	β	α	*R*
(−)-**5**	α	β	*S*

Results and Discussion

Although 2-pyrone is relatively unstable and unreactive as a diene in Diels–Alder cycloadditions,[4] 3-bromo-2-pyrone is an easily-prepared, crystalline, ambiphilic diene

† These analogs are the subject of a patent.

‡ Department of Chemistry.

§ Inquiries concerning X-ray crystallography should be addressed to N.N.M.

∥ Department of Environmental Health Sciences.

• Abstract published in *Advance ACS Abstracts,* October 15, 1993.

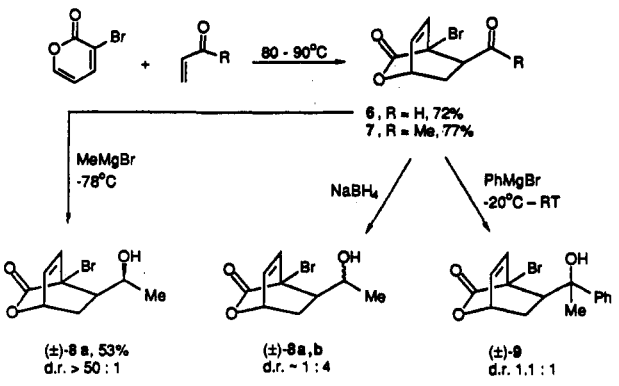
(1) (a) Kobayashi, Y.; Taguchi, T. *Biomedical aspects of fluorine chemistry*; Filler, R., Kobayashi, Y., Eds.; Kodansha LTD/Elsevier Biomedical: New York, 1982; pp 33–49. (b) Ikekawa, N. *Med. Res. Rev.* **1987**, *7*, 333–336. (c) de Costa, B. R.; Holick, S. A.; Holick, M. F. *J. Chem. Soc., Chem. Commun.* **1989**, 325–326.

(2) (a) Posner, G. H.; Nelson, T. D.; Guyton, K. Z.; Kensler, T. W. *J. Med. Chem.*, **1992**, *35*, 3280. (b) Posner, G. H.; Dai, H. *BioMed. Chem. Lett.* **1993**, *3*, 1829–1834. (c) Posner, G. H., Guyton, K. Z.; Kensler, T. W.; Barsony, J.; Lieberman, M.E.; Reddy, G. S.; Clark, J. W.; Wankadiya, K. F.; Tserng, K.-Y. *BioMed. Chem. Lett.* **1993**, *3*, 1835–1840.

(3) For other work showing interesting biological activity of calcitriol analogs modified at position-1, see: Norman, A. W.; Nemere, I.; Muralidharan, K. R.; Okamura, W. H. *Biochem. Biophys. Res. Commun.* **1992**, *189*, 1450. See also: Muralidharan, K. R.; de Lera, A. R.; Isaeff, S. D.; Norman, A. W.; Okamura, W.H. *J. Org. Chem.* **1993**, *58*, 1895–1899. Zhou, L.-X.; Nemere, I.; Norman, A. W. *J. Bone Mineral Res.* **1992**, *7*, 457–463.

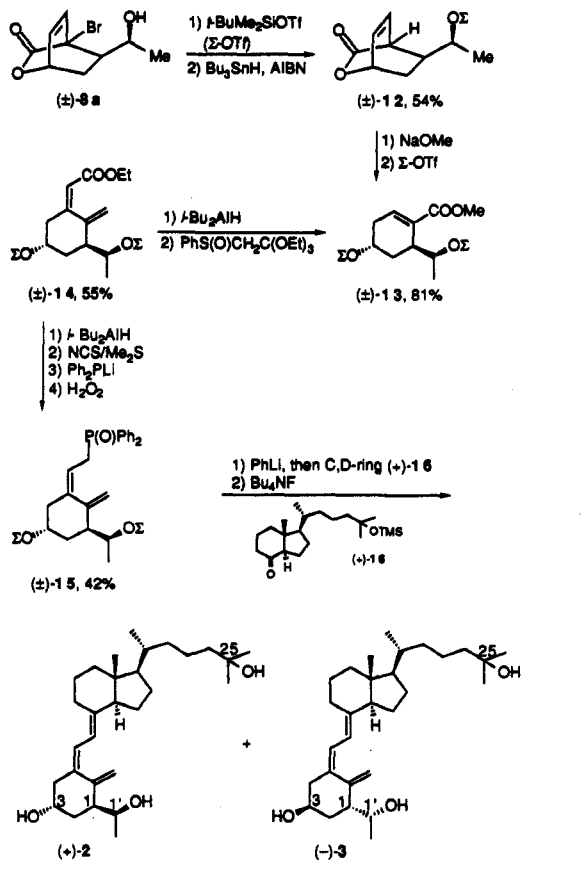
0022-3263/93/1958-7209$04.00/0

Scheme I

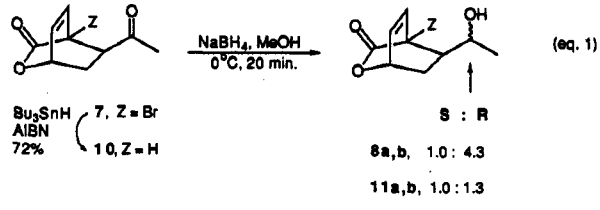


that undergoes mild (i.e., <95 °C) [4 + 2]-cycloadditions with both electron-poor and electron-rich dienophiles.[4,5] Thus, from stereochemically uninteresting (i.e., planar) precursors, stereochemcially rich and synthetically versatile bicyclic lactone adducts can be prepared conveniently on gram scale. Specifically, 3-bromo-2-pyrone reacted with acrolein and separately with methyl vinyl ketone to produce *endo*-bicyclo adducts **6** and **7** that were immediately subjected to side-chain carbonyl addition of methyl Grignard and of hydride, respectively (Scheme I). The methyl Grignard addition was chemospecific for the aldehyde carbonyl group and essentially stereospecific, generating only one diastereomer of a secondary alcohol (i.e., **8a**), the stereochemistry of which was later characterized unambiguously by X-ray crystallography. Similarly, *n*-hexylmagnesium bromide addition to bicyclic aldehyde **6** proceeded stereospecifically. The origin of this extraordinary stereocontrol (>50:1 diastereoselectivity) was thought to be due to a combination of two factors. First, the aldehyde's preference for a conformation in which the alkyl chain and the carbonyl oxygen atom are eclipsed has been documented;[6] for example, in propanal this conformer is 0.9 kcal/mol more stable than that with the α-hydrogen atom elcipsed with the carbonyl oxygen atom.[7] Second, the adjacent bulky bromine bridgehead substituent sterically shields approach of a nucleophile to one face of this conformationally-restricted prochiral aldehyde group. This steric argument may be complemented also by electronic factors involving 6-membered ring chelation of the Lewis basic bromine and adjacent aldehyde oxygen atoms with the Lewis acidic magnesium atom of the Grignard reagent.[8] In contrast to such highly stereocontrolled Grignard addition to this aldehyde, phenyl Grignard addition to and hydride reduction of the corresponding methyl ketone were only moderately stereoselective (Scheme I). Comparison of the stereoselectivity of methyl ketone reduction as a function of the

Scheme II



adjacent bridgehead substituent (i.e., Br vs H) showed the importance of the bridgehead bromine atom (eq 1).



Use of other reducing agents on bromo ketone **7** gave the following results: $LiBH_4$/THF/0 °C, dr (diastereomeric ratio) 1.0:1.2; *n*-Bu_4NBH_4/CH_2Cl_2/25 °C, dr 1.0:1.3; LiB-$[CH(CH_3)C_2H_5]_3H$/THF, 0 °C, dr 1.0:5.7. The lower diastereoselectivity of reduction using lithium vs sodium borohydride does not necessarily rule out chelation being important along with steric factors; for example, there is precedent for sodium trialkylborohydride reagents being more stereoselective than the corresponding lithium species for reducing highly coordinating heteroatom substituted ketones.[9]

The single racemic diastereomer of bromo alcohol (±)-**8a** prepared from cycloadduct **6** was transformed in 12 steps and 10.1% overall yield into 1-(1'-hydroxyethyl)-25-hydroxyvitamin D_3 analogs (+)-**2** and (−)-**3** as outlined in Scheme II.[2a] In a similar fashion, the racemic diastereomer of secondary alcohol (±)-**12'**, prepared from bromo alcohol (+)-**8b**, was converted into the corresponding calcitriol analogs (+)-**4** and (−)-**5** (Scheme III).

Important features of these schemes include the following: (1) the nonhydrolytic, neutral, radical condi-

(4) For a review of Diels–Alder cycloadditions using 2-pyrones and 2-pyridones, see: Afarinkia, K.; Vinader, V.; Nelson, T. D.; Posner, G. H. *Tetrahedron* **1992**, *48*, 9111–9171.

(5) (a) Posner, G. H.; Nelson, T. D.; Kinter, C. M.; Afarinkia, K. *Tetrahedron Lett.* **1991**, *32*, 5295. (b) Posner, G. H.; Carry, J.-C.; Anjeh, T. E. N.; French, A. N. *J. Org. Chem.* **1992**, *57*, 7012. (c) Posner, G. H.; Afarinkia, K.; Dai, H. *Org. Synth.*, in press.

(6) Karabatsos, G. J.; Hsi, N. *J. Am. Chem. Soc.* **1965**, *87*, 2864.

(7) Butcher, S. S.; Wilson, E. B. *J. Chem. Phys.* **1964**, *40*, 1671.

(8) For electronically related examples, see: (a) Takahashi, H.; Tsubuki, T.; Higashimaya, K. *Chem. Pharm. Bull.* **1991**, *39*, 3136 and references therein. (b) Kawanami, Y.; Fujita, I.; Ogawa, S; Katsuki, T. *Chem. Lett.* **1989**, 2063. (c) Eliel, E. L.; Morris-Natschke, S. *J. Am. Chem. Soc.* **1984**, *106*, 2937. (d) For the importance of electrostatic chelation factors in directing the stereochemistry of nucleophilic addition to the carbonyl of α-fluoro aldehydes, see: Wong, S. S.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.* **1991**, 327, and references therein.

(9) Manzoni, L.; Pilati, T.; Poli, G.; Scolastico, C. *J. Chem. Soc., Chem. Commun.* **1992**, 1027.

Scheme III

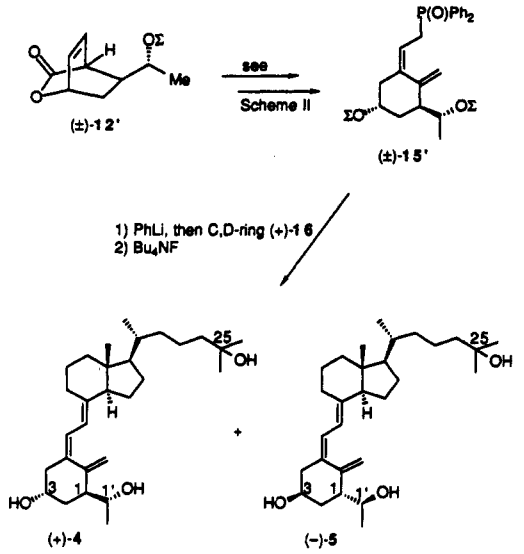


Chart I

compd	$[\alpha]^{25}_D$, deg	chemical shift data (δ)		
		C_{18}–CH_3	=CH_2	
(+)-2	+133	0.50	5.12	4.93
(−)-3	−64	0.54	5.14	4.96
(+)-4	+81	0.51	5.20	5.05
(−)-5	−21	0.54	5.22	5.09

tions for reductive cleavage of a bridgehead carbon–bromine bond leading to nonhalogenated bicyclic lactone (±)-**12**, a cycloadduct representing the synthetic equivalent of a Diels–Alder product derived from unsubstituted and unreactive 2-pyrone itself;[4,5a] (2) the one-flask, regiospecific formation of two-carbon-extended dienoate esters (±)-**14** using a new sulfinyl orthoester;[10] (3) the use of phenyllithium rather than *n*-butyllithium to generate the conjugate base of phosphine oxide (±)-**15**;[2a] and (4) the separability of diastereomers (+)-**2** and (−)-**3** and also diastereomers (+)-**4** and (−)-**5** by preparative HPLC.

Stereochemical analysis of crystalline diastereomer (+)-**2** by X-ray diffraction confirmed the absolute stereochemistry of this calcitriol analog and thereby allowed unambiguous stereochemical assignment to be made also for the companion diastereomer (−)-**3**. As shown in Scheme III, racemic diastereomer (±)-**12'** led to calcitriol analogs (+)-**4** and (−)-**5**, the identity of which was assigned tentatively on the following grounds: (1) shorter HPLC retention times of the dextrorotatory stereoisomers (i.e., **2** and **4**) vs the levorotatory stereoisomers (i.e., **3** and **5**); and especially (2) 400-MHz ^{1}H NMR spectroscopy showing a characteristic pattern of chemical shifts (Chart I) in which the dextrotatory stereoisomer **2** has slightly more upfield chemical shifts than does levorotatory diastereomer **3** and likewise for (+)-**4** vs (−)-**5**, consistent also with previous findings.[2a,b]

The X-ray crystallographic analysis of calcitriol analog (+)-**2** represents, as far as we can determine by searching the literature, the first reported diffraction study of a 1-substituted vitamin D_3 compound.[11] Important features of this X-ray analysis include the following: (1) in the asymmetric unit, there is only one crystallographically

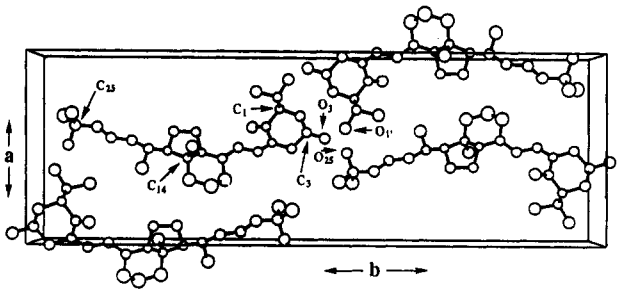


Figure 1. ORTEP drawing of the unit cell of (+)-**2** at 30% probability ellipsoids.

Table I. Competitive Binding Assays

compd	amount needed for 50% displacement of [^{3}H]-1,25(OH)$_2$D$_3$
(+)-**1**	46 pg
(+)**2**	544 ng
(−)-**3**	2208 ng
(+)-**4**	140 ng
(−)-**5**	1856 ng

independent molecule, and there are four molecules in the unit cell (Z = 4); (2) each molecule in the unit cell shows strong hydrogen bonding interactions as indicated by the short intermolecular bond distances (Figure 1) 1'-O --- 3-O, 2.63 Å; 1'-O --- 25-O, 2.67 Å; 3-O --- 25-O, 2.64 Å; (3) concerning ring A, only the α chair form is apparent showing the exocyclic CH_2 on ring A situated below the mean plane of that ring; (4) the 1'-hydroxyethyl substituent has an axial orientation; (5) the 3-hydroxyl group has an equatorial orientation; and (6) the side chain is extended in conformation. The dramatic ability of such trihydroxylated vitamin D analogs to undergo multiple intermolecular H-bonding interactions may ultimately prove relevant and even important in terms of how such calcitriol-like molecules are recognized and bound by transport and receptor proteins.

Preliminary biological evaluation of the synthetic analogs **2**–**5** showed them to be roughly 1000 times less effective than calcitriol for binding to the calf thymus 1,25(OH)$_2$D$_3$ receptor.[12] Specifically, as shown in Table I, the dextrorotatory stereoisomers (+)-**2** and (+)-**4** were several times more effective in binding to the calcitriol receptor than the levorotatory stereoisomers (−)-**3** and (−)-**5**, but still very much less effective than calcitriol itself which was active at the picogram level.

As shown in Figure 2, all four synthetic analogs **2**–**5** inhibited significantly the proliferation of murine keratinocytes, with the dextrorotatory diastereomers being more potent than the levorotatory diastereomers especially at 1 μM concentrations.[2a] Interestingly, now that we have prepared and tested several 1-substituted analogs of

(10) Posner, G. H.; Crouch, R. D.; Kinter, C. M.; Carry, J.-C. *J. Org. Chem.* **1991**, *56*, 6981.

(11) (a) Crowfoot, D.; Dunitz, J. D. *Nature* **1948**, *162*, 608. (b) Hodgkin, D. C.; Rimmer, B. M.; Duniz, J. D.; Trueblood, K. N. *J. Chem. Soc.*, **1963**, 4945. (c) Knobler, C.; Romers, C.; Braun, P. B.; Hornstra, J. *Acta Cryst.* **1972**, *B28*, 2097. (d) Hull, S. E.; Leban, I.; Main, P.; White, P. S.; Woolfson, M. M. *Ibid.*, **1976**, *B32*, 2374. (e) Trinh-Toan; DeLuca, H. F.; Dahl, L. F. *J. Org. Chem.* **1976**, *41*, 3476. (f) Trinh-Toan; DeLuca, H. F.; Dahl, L. F. *Vitam. D: Biochem., Chem. Clin. Aspects Relat. Calcium Metab. Proc. Workshop Vitam. D, 3rd;* Norman, A. W., Schaefer, K., Coburn, J. W., Eds.; deGruyter: Berlin, Germany, 1977; pp 927–36 (Eng.). (g) Jones, G.; Rosenthal, A.; Segev, D.; Mazur, Y.; Frolow, F.; Halfon, Y.; Rabinovich, D.; Shakked, Z. *Tetrahedron Lett.* **1979**, *2*, 177–180. (h) Trinh-Toan; Ryan, R. C.; Simon, G. L.; Calabrese, J. C.; Dahl, L.F.; DeLuca, H. F. *J. Chem. Soc., Perkin Trans. II* **1977**, 393–401. (i) Duax, W. L.; Strong, P. D.; Rohrer, D. C. *Acta Crystallogr.* **1980**, *B36*, 824–827.

(12) Reinhardt, T. A.; Horst, R. L.; Orf, J. W.; Hollis, B. W. *J. Clin. Endocrin. Metab.* **1984**, *58*, 91.

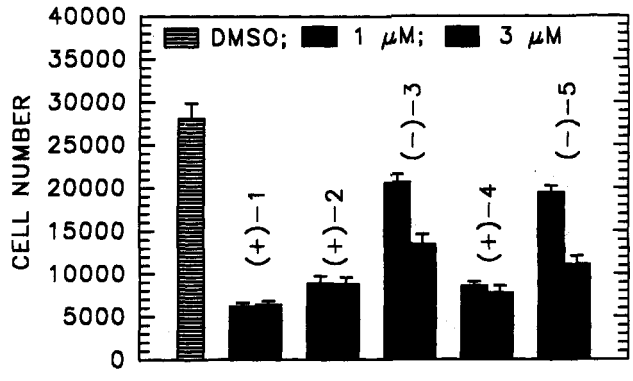


Figure 2. Effects of analogs 2–5 on PE cell growth.

calcitriol, structure–function analysis reveals generally that the dextrorotatory stereoisomers, including (+)-1-(2′-hydroxyethyl)-25-hydroxyvitamin D_3,[2b,c] are more potent than the levorotatory ones for inhibiting murine keratinocyte growth. Synthetic analogs (+)-2 and (+)-4 have antiproliferative activities similar to that of calcitriol.

Preliminary experiments show that, immediately upon administration, all four of these A-ring modified analogs 2–5 affect whole-cell barium currents in ROS 17/2.8 osteosarcoma cells using the perforated patch mode of the patch clamp technique.[13,14] At 0.5 nM concentration, analogs (-)-3 and (+)-4, each with the *R* configuration at the 1′-hydroxyl position, have about 88% and 75% of the potency of calcitriol, respectively. Analogs (+)-2 and (-)-5, with the *S* configuration at the 1′-hydroxyl group, are only 20–25% as potent as calcitriol. Recent screening of other vitamin D_3 analogs[15] has shown that 16-en-23-yne-25(OH)D_3 has the same potency as calcitriol for gating (opening) calcium currents in these cells via a nongenomic effect.[2,3]

Conclusions

The convergent synthetic route described here is easily modified for preparation of other 1-substituted calcitriol analogs, and we are actively engaged in such activity.

The higher antiproliferative activities of the various dextrorotatory analogs we have prepared here and previously, as well as the higher calcium channel gating potencies of the (*R*)-1′-hydroxyethyl diastereomers, suggest that molecular recognition is occurring as these synthetic analogs express their various biological activities. Synthesis and testing of additional analogs will help clarify the strength and significance of such molecular recognition.

The separation of the vitamin D receptor binding activity from the antiproliferative activity of calcitriol analogs 2–5 raises the possibility that these or related A-ring modified analogs may eventually be useful for practical clinical chemotherapy of skin diseases such as psoriasis.

Experimental Section

Chemistry. General. Tetrahydrofuran (THF) was distilled from sodium–benzophenone ketyl and dichloromethane (CH_2Cl_2) from calcium hydride prior to use. Anhydrous toluene, methanol, and HPLC grade benzene were purchased from Aldrich Chemical Co. and were and used directly. *tert*-Butyl ether was distilled from activated 4-Å molecular sieves. All other reagents were purchased from Aldrich and, unless otherwise specified, were used as received without further purification. FT-IR spectra were determined as solutions in $CHCl_3$ using a Perkin-Elmer 1600 FT-IR spectrometer. The ^1H NMR spectra were determined as solutions in $CDCl_3$ (unless noted otherwise) on a Varian XL-400 spectrometer and a Bruker AMX-300 spectrometer operating at 400 MHz and 300 MHz, respectively. The ^{13}C NMR spectra were recorded on Bruker AMX-300 operating at 75 MHz. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; m, multiplet; b, broad. High resolution mass spectra were obtained on a two sector high resolution VG-70S mass spectrometer run at 70 eV. Melting points are uncorrected. Preparative HPLC work was performed on a Rainin HPXL system with a Dynamax-60 Å 8-mm silica column. Optical rotation concentrations (*c*) are given in g/100 mL. Elemental analyses were performed by Atlantic Microlab, Atlantic, GA, and Galbraith Laboratories Inc., Knoxville, TN.

Bromo Cycloadduct 6. A mixture of 3-bromo-2-pyrone (2.43 g, 13.9 mmol, 1 equiv), acrolein (8 mL, 120 mmol, 8.6 equiv), 2,6-di-*tert*-4-methylphenol (BHT, a few crystals, catalytic), $BaCO_3$ (10–20 mg, catalytic), and CH_2Cl_2 (16 mL) was sealed in two hydrolysis tubes and heated to 80–90 °C for 4 days. After being cooled to room temperature, the tubes were opened and excess acrolein and CH_2Cl_2 were evaporated on a Rotavap. The residue was purified by flash silica gel chromatography (150 g silica, 10–50% EtOAc in hexane) to give bicyclic aldehyde 6 (2.30 g, 72%) as an yellow oil together with recovered bromopyrone (220 mg, 9% recovery): ^1H NMR δ 9.84 (s, 1 H), 6.48–6.56 (m, 2 H), 5.34 (bs, 1 H), 3.15 (ddd, *J* = 9.3, 3.3, 0.9 Hz, 1 H), 2.46 (ddd, *J* = 13.8, 9.4, 4.1 Hz, 1 H), 2.33 (ddd, *J* = 13.8, 4.2, 1.2 Hz, 1 H); ^{13}C NMR δ 197.78, 166.92, 135.22, 133.45, 73.30, 57.10, 50.05, 30.14; FT-IR 1772, 1730 cm^{-1}; HRMS, *m/z* cacld for C_7H_7BrO ($M^+ - CO_2$) 185.9680, found 185.9685.

Alcohol 8a. To a solution of aldehyde 6 (750 mg, 3.25 mmol) in THF (10 mL) at −78 °C under N_2 was slowly added MeMgBr (1.5 mL, 3.0 M in Et_2O, 4.5 mmol, 1.4 equiv). The resulting mixture was stirred at −78 °C for 1.5 h and then slowly warmed up to −30 °C during 1.5 h. The color was brown yellow. After the reaction was quenched with H_2O, normal workup furnished the crude product (790 mg, de ≥ 50:1 by NMR) which was purified by column chromatography (20 g of silica gel, 10–60% EtOAc/Hex) to give alcohol 8a (428 mg, 53%) as a white solid: mp 120–121 °C; ^1H NMR δ 6.41 (d, *J* = 7.9 Hz, 1 H), 6.31 (dd, *J* = 5.2, 8.0 Hz, 1 H), 5.24 (bs, 1 H), 4.52 (dq, *J* = 1.4, 5.1 Hz, 1 H), 2.35 (ddd, *J* = 4.5, 9.4, 13.1 Hz, 1 H), 2.04 (ddd, *J* = 1.6, 5.2, 9.2 Hz, 1 H), 1.91 (ddd, *J* = 1.2, 5.1, 12.7 Hz, 1 H), 1.68 (bs, 1 H), 1.13 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR δ 169.14, 135.54, 130.71, 73.64, 66.45, 64.05, 43.95, 27.68, 21.74; FT-IR 3613, 3401, 1765 cm^{-1}. Anal. Cacld for $C_9H_{11}BrO_3$: C, 43.75; H, 4.49; Br, 32.34. Found: C, 43.83; H, 4.50; Br, 32.46.

Norbromoadduct 12. To a mixture of bromo alcohol 8a (375 mg, 1.52 mmol) and 2,6-lutidine (250 μL, 2.17 mmol, 1.4 equiv) in dry CH_2Cl_2 (5 mL) at 0 °C under N_2 was slowly added *tert*-butyldimethylsilyl triflate (520 μL, 2.18 mmol, 1.4 equiv). The reaction mixture was stirred for 1 h at 0 °C before the reaction was quenched with H_2O (5 mL). The layers were separated. The aqueous layer was extracted twice with CH_2Cl_2. The combined layers were dried ($MgSO_4$) and concentrated to give crude product (701 mg) as a colorless oil which was carried directly on to the next step.

A solution of the above bromo TBS ether (701 mg), tributyltin hydride (600 μL, 2.22 mmoL, 1.5 equiv) and azabis(isobutyronitrile) (AIBN, 49 mg, 0.29 mmol, 0.19 equiv) in benzene (HPLC grade, 11 mL) was refluxed for 2 h. NMR analysis of an aliquot showed the reaction to be complete. After the solution was cooled to room temperature, benzene was evaporated on a Rotavap. The residue was taken up in wet ether (20 mL). To this was added a solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 400 mg, 2.6 mmol, 1.7 equiv) in wet ether (2 mL). The resulting mixture was stirred for 15 min after which time the white precipitate was removed by filtration through a plug of Celite with Et_2O. The solvent was evaporated and the resulting oil was purified by chromatography (40 g of silica, 5-20% Et_2O/Hex) to afford norbromo adduct 12 (232 mg, 54%) as a colorless viscous

(13) James Rae, Axobits 8, 1991, Axon Instruments Inc., Foster City, CA 94404.

(14) Nowycky, M. C.; Fox, A. P.; Tsien, R. W. *Nature* **1989**, *316*, 440–443.

(15) Caffrey, J. M.; Farach-Carson, M. C. *J. Biol. Chem.* **1989**, *264*(34), 20265–20274.

oil: ^{1}H NMR δ 6.49 (ddd, J = 1.6, 4.8, 7.6 Hz, 1 H), 6.32 (dt, J = 1.6, 8.0 Hz, 1 H), 5.18 (bs, 1 H), 3.44–3.51 (m, 2 H), 2.30 (ddd, J = 4.4, 7.2, 13.6 Hz, 1 H), 1.98–2.04 (bs, 1 H), 1.53 (ddd, J = 1.2, 4.4, 13.6 Hz, 1 H), 1.13 (d, J = 6.0 Hz, 3 H), 0.85 (s, 9 H), 0.016 (s, 3 H), −0.008 (s, 3 H); ^{13}C NMR δ 174.11, 132.19, 129.62, 74.34, 70.80, 44.18, 39.88, 29.69, 25.69, 22.23, 17.86, −4.00, −4.80; FT-IR 1747 cm^{-1}; HRMS, m/z calcd for $C_{11}H_{17}O_3Si$ ($M^+ - Bu^t$) 225.0947, found 225.0949.

Bis-silyl Ether 13. To a solution of norbromo adduct lactone **12** (232 mg, 0.85 mmol) in MeOH/CH_2Cl_2 (15 mL, 1:1) at −78 °C under N_2 was added NaOMe (0.45 mL, 4.37 M in MeOH, 2.3 equiv, Aldrich) dropwise. The cold bath was immediately removed and the resulting mixture was allowed to warm up to room temperature. In 2 h, it was quenched with H_2O. Most of the solvent was evaporated on a Rotavap (to remove MeOH, thus facilitating workup). The residue was taken up in CH_2Cl_2. Usual workup afforded a ring-opened hydroxy α,β-unsaturated ester (244 mg) as a colorless oil.

The above oil dissolved in CH_2Cl_2 (4 mL) was mixed with 2,6-lutidine (0.13 mL, 1.2 mmol, 1.3 equiv) and cooled to 0 °C under N_2. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (0.26 mL, 1.16 mmol, 1.3 equiv) was added dropwise. The resulting solution was stirred at 0 °C for 50 min. H_2O (4 mL) was added. Usual workup gave the crude product (450 mg) as a colorless oil which was purified by chromatography (20 g silica, 5% Et_2O/Hex) to afford bis-silyl ether **13** (284 mg, 80%) as a colorless oil: ^{1}H NMR δ 6.79–6.93 (m, 1 H), 4.47–4.38 (m, 1 H), 4.24–4.17 (m, 1 H), 3.72 (s, 3 H), 2.67–2.62 (m, 1 H), 2.48 (dt, J = 4.8, 18 Hz, 1 H), 2.14–2.00 (m, 2 H), 1.40–1.49 (m, 1 H), 1.21 (d, J = 6.2 Hz, 3 H), 0.89 (s, 9 H), 0.82 (s, 9 H), 0.08 (s, 3 H), 0.06 (s, 3 H), −0.05 (s, 3 H), −0.12 (s, 3 H); ^{13}C NMR δ 167.20, 140.22, 130.85, 68.62, 64.48, 51.30, 41.68, 35.88, 31.52, 25.85, 25.73, 21.84, 18.02, 17.81, −4.60, −4.72, −4.82, −5.28; FT-IR 1704, 1646 cm^{-1}; HRMS, m/z calcd for $C_{18}H_{35}O_4Si_2$ ($M^+ - Bu^t$) 371.2074, found 371.2083.

***Z* Dienoate 14.** To a solution of bis-silyl ether **13** (284 mg, 0.66 mmol) in $PhCH_3$/CH_2Cl_2 (9 mL, 2:1) at −78 °C under N_2 was slowly added diisobutylaluminum hydride (1.6 mL, 1.0 M in $PhCH_3$, 1.6 mmol, 2.4 equiv). This mixture was kept at −78 °C for 1 h. Reaction was complete by TLC analysis. After being quenched with sodium, potassium tartrate (3 mL, 2 N), aqueous HCl (3 mL, 2 N), and then H_2O (10 mL), the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed once with H_2O (5 mL) and dried ($MgSO_4$). Concentration under reduced pressure afforded the corresponding allylic alcohol as a colorless oil. This oil was pure enough to be carried directly on to the next step.

A 25-mL hydrolysis tube containing a solution of the above allylic alcohol, 1-(phenylsulfinyl)-2,2,2-triethoxyethane[8] (400 mg, 1.4 mmol, 2.1 equiv) and 2,4,6-trimethylbenzoic acid (10 mg, 0.06 mmol, 0.09 equiv) in CH_2Cl_2 (4 mL) was heated up to 110 °C for 16 h. Reaction was complete by TLC analysis. After the solution was cooled to room temperature, the solvent was evaporated. The resulting light yellow oil (Z:E = 6:1) was purified by chromatography (20 g of silica, 0–2–4% Et_2O/Hex) to afford Z dienoate **14** (171 mg, 55.4%) and a mixture of (Z + E) dienoates (25 mg, 8.1%) as colorless oils. ***Z* dienoate 14**: ^{1}H NMR δ 5.60 (s, 1 H), 5.03 (s, 2 H), 4.11 (q, J = 6.0 Hz, 2 H), 3.94–4.04 (m, 1 H), 3.66–3.76 (m, 1 H), 2.18–2.54 (m, 4 H), 1.52–1.64 (m, 1 H), 1.24 (t, J = 7.2 Hz, 3 H), 1.23 (d, J = 6.0 Hz, 3 H), 0.89 (s, 9 H), 0.86 (s, 9 H), 0.066 (s, 3 H), 0.060 (s, 3 H), 0.048 (s, 6 H); ^{13}C NMR δ 165.92, 154.40, 145.16, 116.20, 114.91, 68.22, 67.56, 59.81, 51.74, 48.04, 36.70, 26.00, 25.74, 22.86, 18.09, 17.93, 14.15, −3.46, −4.20, −4.49, −4.52; FT-IR 1719, 1636 cm^{-1}; HRMS, m/z calcd for $C_{25}H_{48}O_4Si_2$ 468.3091, found 468.3087.

A-Ring Phosphine Oxide 15. To a solution of Z dienoate **14** (108 mg, 0.23 mmol) in $PhCH_3$/CH_2Cl_2 (5 mL, 2:1) at −78 °C under N_2 was slowly added diisobutylaluminum hydride (0.50 mL, 1.0 M in $PhCH_3$, 0.50 mmol, 2.2 equiv). The reaction was kept at −78 °C for 1 h and then slowly warmed up to −50 °C in 0.5 h by which time the reaction was complete by TLC analysis. After being quenched with sodium, potassium tartrate (0.5 mL, 2 N), HCl (0.5 mL, 2 N), and H_2O (2 mL), the mixture was diluted with CH_2Cl_2 (2 mL). Extraction with CH_2Cl_2 (2 × 2 mL) followed by drying ($MgSO_4$) and concentration gave the desired allylic alcohol (90 mg) as a colorless oil. This oil was pure enough to be carried directly on to the next step.

To a solution of *N*-chlorosuccinimide (NCS, 89 mg, 0.68 mmol, 3.2 equiv) in CH_2Cl_2 (1.6 mL) at 0 °C under N_2 was slowly added Me_2S (50 μL, 0.66 mmol, 3.1 equiv). The resulting white cloudy solution was stirred for 15 min at 0 °C and then cooled to −20 °C. A solution of above allylic alcohol in CH_2Cl_2 (0.5 mL, rinsed with 0.2 mL) was slowly cannulated to this. After the solution was stirred for 30 min at −20 °C, the reaction was allowed to warm up slowly to 0 °C. After being quenched with H_2O (2 mL) and diluted with CH_2Cl_2 (2 mL), the layers were separated. The organic layer was dried ($MgSO_4$) and concentrated. This colorless oil was then redissolved in 10% Et_2O/ Hex with the help of a little CH_2Cl_2 and applied to a prepacked silica gel bed (3 g, 2 cm thick). Rapid filtration and subsequent washing with Et_2O/Hex (10%, 50 mL) gave an essentially pure allylic chloride (105 mg) as a colorless oil which was immediately taken on to the next step.

A solution of this allylic chloride (azeotropically dried with benzene) in THF (0.8 mL) at −78 °C under N_2 was very slowly cannulated into a freshly made, orange solution of Ph_2PLi [~0.3 M, addition of *n*-butyllithium (0.63 mL, 1.5 M in hexane, 0.94 mmol, 0.94 equiv) to a solution of Ph_2PH (174 μL, 1.0 mmol) in THF (3 mL) at 0 °C under N_2] until the orange color persisted for 20 min. The allylic chloride disappeared by TLC (3% Et_2O/ Hex). H_2O (0.5 mL) was added and the resulting colorless mixture was allowed to warm up to room temperature. THF was evaporated. The residue was taken up in CH_2Cl_2 (5 mL). To this was added H_2O_2 (5 mL, 10%), and the resulting solution was stirred vigorously for 45 min. The layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 2 mL). The combined organic layers were washed with Na_2SO_3 (3 mL, 2 N) and H_2O (2 mL) and dried ($MgSO_4$). Evaporation of solvents gave a colorless oily product (105 mg) which was purified by chromatography (4 g of silica, 10–30% EtOAc/Hex) to afford phosphine oxide **15** (76 mg, 54% from dienoate **14**) as a white solid: mp 102–104 °C; ^{1}H NMR δ 7.68–7.80 (m, 4 H), 7.43–7.58 (m, 6 H), 5.33 (dd, J = 10.2, 5.1 Hz, 1 H), 4.93 (d, J = 2.1 Hz, 1 H), 4.70 (d, J = 1.5 Hz, 1 H), 3.80–3.85 (m, 1 H), 3.50–3.58 (m, 1 H), 3.31–3.42 (m, 1 H), 3.07–3.18 (m, 1 H), 2.39–2.46 (m, 1 H), 2.07–2.27 (m, 3 H), 1.47–1.56 (m, 1 H), 1.00 (d, J = 4.5 Hz, 3 H), 0.87 (s, 9 H), 0.83 (s, 9 H), 0.040 (s, 3 H), 0.037 (s, 3 H), 0.016 (s, 6 H); ^{13}C NMR[16] δ 145.76 (d, J = 3.0 Hz), 142.36 (d, J = 12.8 Hz), 133.22 (d, J = 14 Hz), 131.80 (d, J = 2.2 Hz), 131.08 (d, J = 6.8 Hz), 130.96 (d, J = 6.8 Hz), 128.61 (d, J = 1.5 Hz), 128.46 (d, J = 1.5 Hz), 113.91, 113.35 (d, J = 8.2 Hz), 67.62, 67.32 (d, J = 2.2 Hz), 51.56, 47.33 (d, J = 1.5 Hz), 36.81, 31.74, 30.80, 25.89, 25.73, 23.10, 17.94 (d, J = 7.5 Hz), −3.54, -4.16, −4.58, −4.60; FT-IR 3019, 2958, 2930, 2887, 2857, 1472, 1463, 1438, 1255, 1224, 1120, 1104, 838 cm^{-1}; HRMS, m/z calcd for $C_{35}H_{55}O_3PSi_2$ 610.3427, found 610.3420.

1-(1′-Hydroxyethyl)-25-hydroxyvitamin D_3 Homologs (+)-2 and (−)-3. To a solution of phosphine oxide **15** (59 mg, 0.097 mmol, 1.3 equiv, azeotropically dried three times with benzene and then held under high vacuum overnight) in THF (1.0 mL) at −78 °C under N_2 was very slowly added PhLi (73 μL, 0.095 mmol, 1.3 M in 7/3 cyclohexane/ether, 1.3 equiv). The color turned yellow at the first drop, orange at the second drop, and deep orange at the end of the addition. After the solution was stirred at −78 °C for 10 min, a precooled (−78 °C) C,D-ring (26 mg, 0.074 mmol, 1 equiv, azeotropically dried three times with benzene and held under high vacuum for 12 h before use) in THF (0.5 + 0.2 mL) was slowly cannulated into the reaction mixture. The reaction was kept at −78 °C for 4 h and then slowly warmed up to −60 °C in 30 min at which time the color faded to orange. The reaction was quenched with potassium, sodium tartrate (1.5 mL, 2 M). Regular workup with EtOAc afforded a crude product (97 mg) which was further purified by chromatography (3 g of silica, sample loaded with toluene and a little CH_2Cl_2, 0–3-6–20–30% EtOAc in hexane as eluant) to give silylated products (37 mg) as a colorless oil. This oil was then immediately dissolved in THF (2 mL) and treated with tetrabutylammonium fluoride (0.25 mL, 0.25 mmol, 1 M in THF, 5 equiv) at rt under N_2. This yellow mixture was kept in dark stirring for 24 h. THF was evaporated on a Rotavap. The residue was purified by PTLC (1000 μm, applied to PTLC with 1:1 EtOH/EtOAc, eluted and

extracted with 5% EtOH in EtOAc) to give a mixture of 1α- and 1β-(1'-hydroxyethyl)-25-hydroxyvitamin D_3 homologs (+)-**2** and (−)-**3** (10 mg, 30% based on C,D-ring, 54% based on recovered phosphine oxide). This mixture of diastereomers was then subject to HPLC separation (EtOAc, normal phase, semiprep) to give pure diastereomers. (−)-**3**: $[\alpha]^{23}_D$ −64° (*c* 0.25, EtOH); ^{1}H NMR δ 6.26 (d, *J* = 11.4 Hz, 1 H), 5.99 (d, *J* = 11.6 Hz, 1 H), 5.14 (d, *J* = 2.1 Hz, 1 H), 4.96 (d, *J* = 2.4 Hz, 1 H), 3.98–4.12 (m, 1 H), 3.66–3.78 (m, 1 H), 2.76–2.84 (m, 1 H), 2.60–2.68 (m, 1 H), 2.20–2.46 (m, 3 H), 1.94–2.04 (m, 2 H), 1.21 (s, 6 H), 0.93 (d, *J* = 6.3 Hz, 3 H), 0.54 (s, 3 H); IR 3604, 3400, 3020, 2948, 1720, 1520, 1435, 1378, 1224, 1206 cm^{-1}; UV (EtOH) λ_{max} 264 nm (ε 16 700); MS *m/e* (rel intensity) 444 (12), 399 (20), 135 (100). (+)-**2**: $[\alpha]^{23}_D$ +133° (*c* 0.24, EtOH); ^{1}H NMR δ 6.27 (d, *J* = 11.1 Hz, 1 H), 5.98 (d, *J* = 10.8 Hz, 1 H), 5.12 (d, *J* = 2.7 Hz, 1 H), 4.93 (d, *J* = 2.1 Hz, 1 H), 4.00–4.16 (m, 1 H), 3.74–3.82 (m, 1 H), 2.76–2.86 (m, 1 H), 2.58–2.68 (m, 1 H), 2.20–2.44 (m, 3 H), 1.94–2.04 (m, 2 H), 1.21 (s, 6 H), 0.93 (d, *J* = 6.3 Hz, 3 H), 0.50 (s, 3 H); IR 3604, 3391, 3019, 2949, 1716, 1520, 1471, 1424, 1378, 1224, 1216, 929 cm^{-1}; UV (EtOH) λ_{max} 264 nm (ε 17 100); MS *m/e* (rel intensity) 444 (8), 399 (19), 135 (100). The analytical sample was recrystallized from ethyl acetate. Anal. A mixture of diastereomers **2** and **3** calcd for $C_{29}H_{48}O_3 \cdot 1.25\ C_4H_8O_2$: C, 73.59; H, 10.46. Found: C, 73.87; H, 10.62.

Bicycloadduct 7. A mixture of 3-bromo-2-pyrone (1.2 g, 6.86 mmol, 1 equiv), methyl vinyl ketone (4.5 mL, 54 mmol, 7.9 equiv), 2,6-di-*tert*-4-methylphenol (BHT, a few crystals, catalytic), $BaCO_3$ (10–20 mg, catalytic), and CH_2Cl_2 (5 mL) was sealed in two hydrolysis tubes, heated to 80–90 °C for 1 day, and cooled to room temperature. CH_2Cl_2 and excess methyl vinyl ketone were evaporated on a Rotavap. The residue was purified by silica gel chromatography (60 g of silica, 10–40% EtOAc/Hex) to give bicyclic bromo ketone **7** (1.30 g, 77%) as a white solid: mp 101–102 °C; ^{1}H NMR δ 6.57 (dd, *J* = 1.6, 8.0 Hz, 1 H), 6.43 (dd, *J* = 5.2, 8.0 Hz, 1 H), 5.30 (m, 1 H), 3.42 (dd, *J* = 4.5, 9.9 Hz, 1 H), 2.67 (ddd, *J* = 4.1, 9.9, 13.0 Hz, 1 H), 2.32 (s, 3 H), 1.86 (ddd, *J* = 1.3, 4.5, 13.0 Hz, 1 H); ^{13}C NMR δ 203.95, 167.46, 135.77, 130.44, 73.49, 57.87, 49.67, 32.96, 31.49; FT-IR 1768, 1725 cm^{-1}. Anal. Cacld for $C_9H_9BrO_3$: C, 44.11; H, 3.70; Br, 32.61. Found: C, 44.36; H, 3.82; Br, 32.70.

Norbromo Ketone 10. A solution of bromo ketone **7** (1.30 g, 5.3 mmol), tributyltin hydride (2.08 mL, 7.70 mmol, 1.45 equiv) and azabis(isobutyronitrile) (AIBN, 175 mg, 1.04 mmol, 0.19 equiv) in benzene (HPLC grade, 40 mL) was refluxed for 2 h. NMR analysis of an aliquot showed the reaction to be complete. The solution was cooled to rt, and benzene was evaporated on a Rotavap. The residue was taken up in wet ether (60 mL). To this was added a solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.4 g, 9.2 mmol, 1.7 equiv) in wet ether (10 mL). The resulting mixture was stirred for 15 min, at which time the white precipitate was removed by filtration through a plug of Celite with ether. The solvent was evaporated and the resulting oil was purified by chromatography (60-g short path silica gel, 5–20% Et_2O/Hex) to afford norbromo ketone **10** (465 mg, 53%) as a colorless oil: ^{1}H NMR δ 6.37–6.40 (m, 1 H), 6.28–6.32 (m, 1 H), 5.15–5.18 (m, 1 H), 3.72–3,74 (m, 1 H), 2.99 (ddd, *J* = 2.7, 4.0, 9.8 Hz, 1 H), 2.30 (ddd, *J* = 4.0, 9.8, 13.6 Hz, 1 H), 2.09 (s, 3 H), 1.90 (ddd, *J* = 1.4, 4.2, 13.5 Hz, 1 H); ^{13}C NMR δ 204.13, 172.45, 132.23, 129.41, 73.76, 43.70, 42.51, 27.96, 27.84; FT-IR 1754, 1717 cm^{-1}; HRMS, *m/z* calcd for $C_9H_{10}O_3$ 166.0630, found 166.0632.

TBS Ether 12'. To a solution of norbromo ketone **10** (465 mg, 2.8 mmol) in MeOH (25 mL) at −78 °C under N_2 was slowly cannulated a solution of $NaBH_4$ (106 mg, 2.8 mmol, 1.0 equiv) in MeOH (2 mL). After 3 h, another solution of $NaBH_4$ (175 mg, 4.6 mmol, 1.6 equiv) in MeOH (2 mL) was added slowly due to the incompleteness of reaction at that time. The reaction mixture was stirred at −78 °C for 1 h and then slowly warmed up to 0 °C. After dilution with EtOAc (100 mL), the reaction mixture was washed with H_2O (2 × 20 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to give a mixture of diastereomeric alcohols **11a,b** (1:1.2) (424 mg, 90%). This alcohol was pure enough to be carried directly on to next step.

The above alcohols **11a,b** (421 mg, 2.51 mmol), *tert*-butyldimethylsilyl chloride (700 mg, 4.66 mmol, 1.86 equiv) and imidazole (480 mg, 7.06 mmol, 2.8 equiv) in DMF (20 mL) were stirred at rt for 12 h. After dilution with EtOAc (100 mL), the organic layer was washed with H_2O (3 × 10 mL), dried ($MgSO_4$), and concentrated. This crude product was then subject to column chromatography (20 g, 5–10% EtOAc/Hex) to give pure higher R_f diastereomer **12** (36 mg, 5%), lower R_f diastereomer **12'** (162 mg, 23%), and a mixture of the above two products (200 mg, 28%) as colorless oils. **Lower R_f TBS ether 12'**: ^{1}H NMR δ 6.47–6.44 (m, 1 H), 6.30 (t, *J* = 6.1 Hz, 1 H), 5.09–5.11 (m, 1 H), 3.74–3.76 (m, 1 H), 3.20–3.27 (m, 1 H), 2.26 (ddd, *J* = 4.3, 9.5, 13.5 Hz, 1 H), 1.93–1.99 (m, 1 H), 1.04 –1.08 (m, 1 H), 1.06 (d, *J* = 5.9 Hz, 3 H), 0.85 (s, 9 H), −0.002 (s, 3 H), −0.006 (s, 3 H); ^{13}C NMR δ 174.43, 132.14, 129.88, 73.73, 69.96, 42.85, 39.89, 29.66, 25.62, 21.67, 17.75, -4.14, -5.06; FT-IR 1747 c^{-1}; HRMS, *m/z* calcd for $C_{11}H_{17}O_3Si$ (M^+ − Bu^t) 225.0947, found 225.0951.

Bis-silyl Ether 13'. As above, TBS ether lactone **12'** (163 mg, 0.578 mmol) was methanolyzed and silylated to give bis-silyl ether **13'** (189 mg, 80%) as a colorless oil: ^{1}H NMR δ 6.79 (m, 1 H), 4.15–4.20 (m, 1 H), 4.03–4.06 (m, 1 H), 3.70 (s, 3 H), 2.93 (bs, 1 H), 2.44 (ddd, *J* = 1.4, 5.4, 9.0 Hz, 1 H), 2.12 –1.99 (m, 2 H), 1.51–1.59 (m, 1 H), 0.99 (s, 9 H), 0.87 (s, 9 H), 0.064 (s, 3 H), 0.055 (s, 3 H), 0.041 (s, 3 H), 0.030 (s, 3 H); ^{13}C NMR δ 167.67, 138.24, 131.53, 68.80, 64.84, 51.37, 40.95, 35.49, 31.09, 25.83, 25.79, 20.69, 18.11, 17.98, −4.60, −4.76,-4.86, −4.93; FT-IR 1709 cm^{-1}; HRMS, *m/z* calcd for $C_{18}H_{35}O_4Si_2$ (M^+ − Bu^t) 371.2074, found 371.2079.

***Z* Dienoate 14'.** As above, bis-silyl ether ester **13'** (189 mg, 0.442 mmol) was reduced and subjected to Claisen rearrangement to give a light yellow oil (500 mg, *Z*:*E* = 1:1.2) which was purified by chromatography (20 g silica, 0–2–4% Et_2O/Hex) to afford *Z* dienoate **14'** (8 mg, 3.9%) and a mixture of (*Z* + *E*) dienoates (169 mg, 81.9%) as colorless oils. The (*Z* + *E*) mixture was subject to subsequent photoisomerization.

A borosilicate test tube containing a solution of the (*Z* + *E*) mixture (169 mg, 0.36 mmol) and 9-fluorenone (9 mg) in *tert*-butyl methyl ether (9 mL) was placed in a solution of 2 M sodium orthovanadate and irradiated with a medium pressure mercury arc lamp for 36 h at 26 °C. Reaction was still imcomplete by NMR analysis of an aliquot. Solvent was evaporated. The yellow oily residue was purified by PTLC (2 × 1000 μm, 15% Et_2O/Hex) to give *Z* dienoate **14'** (120 mg, 78%) and undesired *E* dienoate (20 mg, 9.7%) as colorless oils. ***Z* dienoate 14'**: ^{1}H NMR δ 5.53 (s, 1 H), 5.08 (s, 1 H), 4.96 (s, 1 H), 4.18–4.25 (m, 1 H), 2.64–2.70 (m, 1 H), 2.44 (dd, *J* = 7, 13.8 Hz, 1 H), 1.84–1.92 (m, 1 H), 1.73–1.80 (m, 1 H), 1.24 (t, *J* = 7.1 Hz, 3 H), 1.17 (d, *J* = 6.4 Hz, 3 H), 0.871 (s, 9 H), 0.868 (s, 9 H), 0.050 (s, 6 H), 0.040 (s, 6 H); ^{13}C NMR δ 166.21, 155.83, 144.87, 115.46, 114.02, 71.01, 68.06, 59.56, 47.60, 46.98, 36.35, 25.89, 25.76, 20.58, 18.04, 18.00, 14.09, −4.45, -4.61, −4.69, −4.70; FT-IR 1716, 1636 cm^{-1}; HRMS, *m/z* calcd for $C_{21}H_{39}O_4Si_2$ (M^+ − Bu^t) 411.2387, found 411.2393.

A-Ring Phosphine Oxide 15'. As above, *Z* dienoate **14'** (82 mg, 0.175 mmol) was reduced, chlorinated, converted into the corresponding diphenylphosphine, and oxidized to give phosphine oxide **15'** (57 mg, 52% from dienoate **14'**) as a white solid: mp 121–124 °C; ^{1}H NMR δ 7.76–7.69 (m, 4 H), 7.44–7.52 (m, 6 H), 5.25–5.30 (m, 1 H), 4.90 (s, 1 H), 4.84 (s, 1 H), 3.89- 3.97 (m, 2 H), 3.41–3.50 (m, 1 H), 3.13 (dt, *J* = 6.3, 15.5 Hz, 1 H), 2.45–2.49 (m, 1 H), 2.35–2.38 (m, 1 H), 2.13–2.17 (m, 1 H), 1.68–1.74 (m, 2 H), 1.08 (d, *J* = 6.1 Hz, 3 H), 0.85 (s, 9H), 0.82 (s, 9 H), 0.047 (s, 3 H), 0.026 (s, 3 H), 0.002 (s, 3 H), −0.024 (s, 3 H); ^{13}C NMR[16] δ 145.60 (d, *J* = 2.2 Hz), 142.98 (d, *J* = 12.8 Hz), 133.55 (d, *J* = 2.2 Hz), 132.26 (d, *J* = 16.5 Hz), 131.66 (d, *J* = 2.2 Hz), 131.60 (d, *J* = 2.2 Hz), 131.06 (d, *J* = 2.2 Hz), 130.94 (d, *J* = 2.2 Hz), 128.57 (d, *J* = 1.5 Hz), 128.42 (d, *J* = 1.5 Hz), 113.38 (d, *J* = 8.2 Hz), 113.04, 69.82, 67.61 (d, *J* = 3.0 Hz), 65.79, 47.74, 36.49, 31.87, 30.92, 25.92, 25.79, 20.68, 18.03, 15.22, −3.83, −4.53, −4.73, −4.74; FT-IR 3020, 2957, 2930, 2857, 1472, 1463, 1438, 1255, 1122, 1086 cm^{-1}; HRMS, *m/z* calcd for $C_{35}H_{55}O_3PSi_2$ 610.3428, found 610.3432.

1-(1'-Hydroxyethyl)-25-hydroxyvitamin D_3 Homologs (+)-4 and (−)-5. As above, a solution of phosphine oxide **15'** (60 mg, 0.098 mmol, 1.6 equiv), PhLi (73 μL, 0.095 mmol, 1.3 M in 7/3

(16) For ^{13}C–^{31}P NMR coupling, see: (a) Pretsch, E.; Simon, W.; Seibl, J.; Clerc, T. *Tables of Spectral Data for Structure Determination of Organic Compounds*, 2nd ed.; Springer-Verlag: Berlin, 1989. (b) Stothers, J. B. *Carbon-13 NMR Spectroscopy*; Academic Press: New York, 1972; p 376.

cyclohexane/ether, 1.5 equiv), and C,D-ring (22 mg, 0.062 mmol, 1 equiv) were reacted to give a mixture of 1-(1'-hydroxyethyl)-25-hydroxyvitamin D_3 homologs (+)-4 and (−)-5 (13 mg, 47% based on C,D-ring, 54% based on the recovered phosphine oxide) which was then subject to HPLC separation (EtOAc, normal phase, semiprep) to give pure diastereomers. (−)-5: $[\alpha]^{23}_D$ −21° (c 0.25, EtOH); ^{1}H NMR δ 6.33 (d, J = 11 Hz, 1 H), 5.97 (d, J = 10.8 Hz, 1 H), 5.22 (d, J = 2.4 Hz, 1 H), 5.09 (d, J = 2.7 Hz, 1 H), 3.92–4.04 (m, 1 H), 3.60–3.74 (m, 1 H), 2.76–2.92 (m, 1 H), 2.60–2.74 (m, 1 H), 2.20–2.38 (m, 2 H), 1.21 (s, 6 H), 0.93 (d, J = 6.0 Hz, 3 H), 0.54 (s, 3 H); IR 3604, 3020, 2935, 1716, 1520, 1424, 1377, 1224, 1207, 1128, 1043, 928 cm^{-1}; UV (EtOH) λ_{max} 262 nm (ε 12 500); MS m/e (rel intensity) 444 (5), 399 (16), 135 (100). (+)-4: $[\alpha]^{23}_D$ +81° (c 0.30, EtOH); ^{1}H NMR δ 6.33 (d, J = 12.3 Hz, 1 H), 5.94 (d, J = 12.0 Hz, 1 H), 5.21 (d, J = 2.4 Hz, 1 H), 5.06 (d, J = 2.4 Hz, 1 H), 3.92- 4.04 (m, 1 H), 3.60–3.74 (m, 1 H), 2.76–2.92 (m, 1 H), 2.60–2.74 (m, 1 H), 2.20–2.38 (m, 1 H), 1.21 (s, 6 H), 0.93 (d, J = 6.0 Hz, 3 H), 0.51 (s, 3 H); FT-IR 3604, 3020, 2950, 1721, 1521, 1472, 1424, 1377, 1216, 928, 910 cm^{-1}; UV (EtOH) λ_{max} 264 nm (ε 11 400); MS m/e (rel intensity) 444 (3), 399 (13), 135 (100). The analytical sample was recrystallized from ethyl acetate. Anal. Mixture of diastereomers 4 and 5 calcd for $C_{29}H_{48}O_3 \cdot 0.4C_4H_8O_2$: C, 76.56; H, 10.68. Found: C, 76.58; H, 10.65.

Crystal Structure of (+)-2.[19] A colorless plate crystal of (+)-2 with approximate dimensions of 0.20 × 0.20 × 0.5 mm (cleaved from a larger plate) mounted on a glass fiber was used. Cell constants were determined from the setting angles of 23 reflections in the range $10.0 < 2\theta < 16.1°$ corresponded to an othorhombic cell with dimensions a = 12.359(5) Å, b = 37.296(6) Å, c = 6.71(1) Å, V = 1858(1) Å^3 with Z = 4 and D_c = 1.039 g/cm^3. Based on systematic absences, space group $P2_12_12_1$ was determined.

The data were collected using the ω-scan mode with scan speed 2.0° min^{-1}, to 2θ = 50.0°. Intensities of three standard reflections measured after every 150 reflections did not show any significant variations. A total of 2520 reflections were measured, of which 1057 reflections with $I \geq 3.00\sigma(I)$ were used in the analysis.

The structure was solved by direct methods.[17] The chirality of the asymmetric carbon atom C13 was known (R) and the absolute configuration at carbon C1 was established (S). The non-hydrogen atoms were refined anisotropically and some hydrogen atoms were fixed in calculated positions. Full-matrix least-squares refinement of 289 parameters minimized the function $\Sigma w(|F_o| - |F_c|)^2$ (where $w = 4F_o^2/s^2(F_o^2)$) to final residuals R = 0.051 and R_w = 0.071, maximum shift/error = 0.04. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.17 and −0.18 e$^-$/Å^3, respectively. The ORTEP view of the molecule is shown in Figure 1.

All measurements were made on a Rigaku AFC6S diffractometer at room temperature with graphite monochromated MoKα (λ = 0.71069 Å) radiation. All calculations were performed using TEXSAN[18] crystallographic software package on a VAX computer.

Acknowledgment. We thank the NIH (GM 30052 and CA 44530) for generous financial support, Dr. Ron Horst (National Animal Disease Center, Ames, IA) for generating the data in Table I, Dr. James Strickland (NCI) for the keratinocyte cell line, Dr. Milan Uskoković (Hoffman-La Roche) for a generous gift of the C,D-ring ketone 16, and Dr. Sandra Guggino and Dr. Shigefumi Yukihiro (The Johns Hopkins University, School of Medicine) for the calcium channel studies.

Supplementary Material Available: ^{1}H and ^{13}C NMR spectra for new compounds (28 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(17) Gilmore, C. J.; Mithril, J. *Appl. Crystallogr.* **1984**, *17*, 42–46.
(18) Structure Analysis Package, Molecular Structure Corporation (1985).
(19) The authors have deposited atomic corrdinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.