Expedited Articles

Conceptually New Sulfone Analogues of the Hormone 1α,25-Dihydroxyvitamin D_3: Synthesis and Preliminary Biological Evaluation

Gary H. Posner,*,† Qiang Wang,† Gyoonhee Han,† Jae Kyoo Lee,† Kenneth Crawford,† Sarvenaz Zand,‡ Henry Brem,‡ Sara Peleg,§ Patrick Dolan,⊥ and Thomas W. Kensler⊥

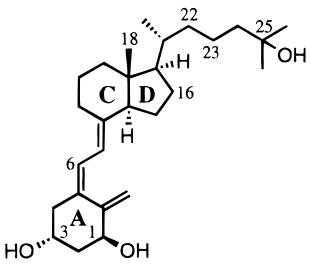
Department of Chemistry, School of Arts and Sciences, The Johns Hopkins University, Baltimore, Maryland 21218, Department of Neurosurgery, School of Medicine, and Division of Toxicological Sciences, School of Hygiene and Public Health, The Johns Hopkins University, Baltimore, Maryland 21205, and Department of Medical Specialties, The University of Texas, M.D. Anderson Cancer Center, Houston, Texas 77030

Received May 28, 1999

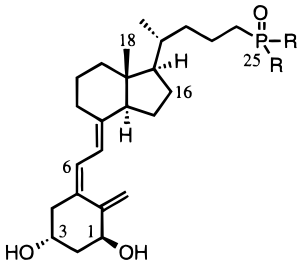
A conceptually new series of vitamin D_3-like nonfluorinated and fluorinated 16-ene side chain *tert*-butyl sulfones **3**−**7** has been synthesized. Even though these novel C,D-ring side chain analogues of the hormone 1α,25-dihydroxyvitamin D_3 (**1**, 1,25D_3) lack a terminal OH group, thought previously to be essential for high biological activity, they are highly antiproliferative and, in several cases, transcriptionally active in vitro but desirably noncalcemic in vivo. The side chain sulfone group may be binding to the nVDR as a hydrogen-bond acceptor, in contrast to the hydrogen-bond donor function of the 25-OH group of natural 1,25D_3.

Introduction

Clinical use of vitamin D_3 analogues as effective drugs requires separating desirable antiproliferative and pro-differentiating activities from undesirable calcemic activity.[1,2] Toward this end, structural changes in the C,D-ring and side chain region of hormonally active 1α,25-dihydroxyvitamin D_3 (1,25D_3, calcitriol, **1**) have been made. Important international examples of such therapeutically promising 1,25D_3 analogues include the following: Leo Pharmaceutical Company's KH-1060,[3]



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



2a, R = Me
2b, R = OMe

EB-1089,[4] and C_{18}-attached side chain analogues;[5] Hoffmann-LaRoche's 16-ene-23-yne and 16,23-diene series;[6] Chugai Pharmaceutical Company's 22-oxa series;[7] the Riverside group's arocaliferols;[8] and the Belgian C- and D-ring nor analogues.[9,10] Structural changes have been made also exclusively in the A-ring region, leading to separation of antiproliferative from calcemic activities. Important examples include the following: the Madison,[11] the Riverside,[12] and the Providence[13] 3-epi-vitamin D_3 analogues, DeLuca's 19-nor analogues,[14] the Austrian aromatic analogues,[15] and our 1-hydroxyalkyl series.[16] Structural changes in both the A-ring and also the C,D-ring side chain regions have produced transcriptionally active, noncalcemic, highly antiproliferative **hybrid** analogues.[17] The only side chain phosphorus-containing analogues of 1,25D_3 ever reported, phosphine oxide **2a** and phosphonate **2b**, showed very low antiproliferative activity.[18] Although several side chain sulfide analogues are known,[19−21] no 16-ene side chain sulfone-containing analogues have been reported. We describe now for the first time a series of natural A-ring 16-ene 24- and 25-sulfones, some of which are noncalcemic but potently antiproliferative and transcriptionally active even at physiologically relevant low nanomolar levels.

Results and Discussion

Having prepared a 16-**saturated** 24-*tert*-butyl sulfone (−SO_2Bu-*t*) analogue and a 24-dimethylsulfonamide (−SO_2NMe_2) analogue of 1,25D_3 (**1**) and having found them to be only weakly antiproliferative, we prepared also the corresponding **unsaturated** 16-ene 24-*tert*-butyl sulfone analogue **3a** with natural A-ring substituents and stereochemistry (Scheme 1). The final convergent coupling step to form enantiomerically pure vitamin D sulfone **3a** was performed with enantiomerically pure keto sulfone (+)-**13** and enantiomerically pure A-ring phosphine oxide (−)-**14**.[22] The characteristic ^{1}H NMR spectral data for the C_{18} methyl group and especially the C_6 vinyl hydrogen atom[12] of adduct **3a** are listed in Table 1. Sulfone analogue **3a** was found to be as antiproliferative in vitro as 1,25D_3 (**1**) in murine keratinocytes even at 7 nM concentration, using our previously described protocol (Figure 1).[23] Likewise, in

† Department of Chemistry.
‡ Department of Neurosurgery.
§ Department of Medical Specialties.
⊥ Division of Toxicological Sciences.

10.1021/jm990267c CCC: $18.00 © 1999 American Chemical Society
Published on Web 08/14/1999

Scheme 1

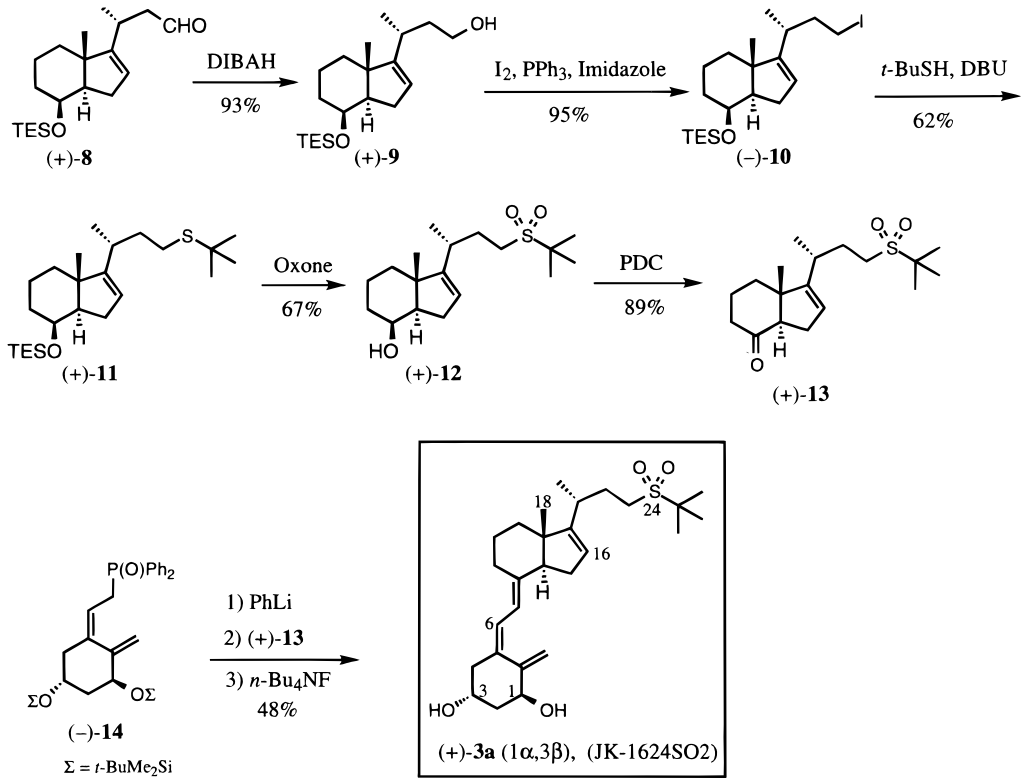


Table 1. ^{1}H NMR (δ) and Optical Rotation (deg) Characteristics of Sulfone Analogues

analogue	C_{18}-CH_3	C_6-H	C_7-H	$[\alpha]^{25}_D$
3a	0.68	6.35	6.09	+63.0
4a	0.69	6.37	6.11	+6.7
4b	0.68	6.39	6.09	−8.9
5a	0.68	6.36	6.10	+0.1
5b	0.68	6.39	6.10	−24.1
6a	0.70	6.36	6.10	−2.5
6b	0.69	6.38	6.09	−10.9
7a	0.69	6.36	6.10	+3.2
7b	0.69	6.38	6.09	−16.7

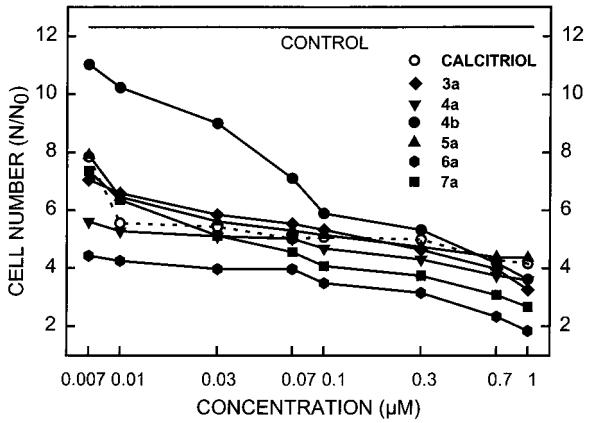


Figure 1. Dose−response effects of analogues on murine keratinocyte proliferation (96 h).

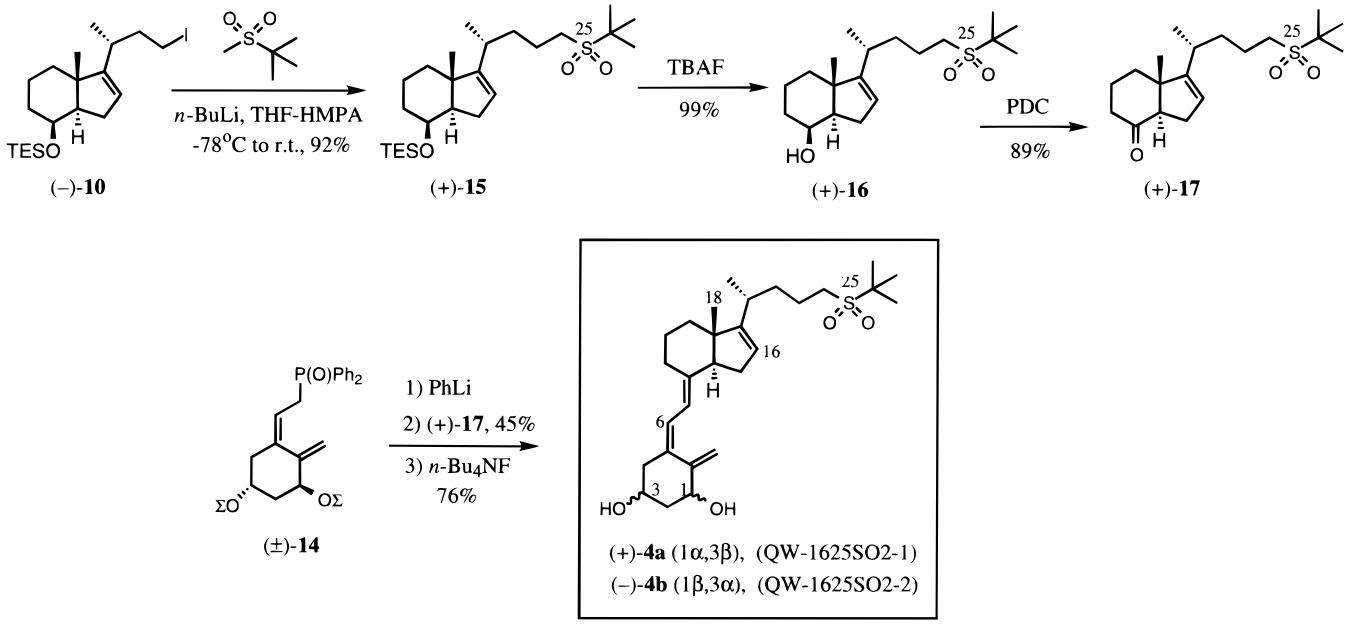
murine malignant melanoma cells (data not shown), 16-ene 24-sulfone **3a** was at least as antiproliferative as 1,25D$_3$ (**1**). The 1-hydroxymethyl[22] **hybrid** analogue of 16-ene 24-*tert*-butyl sulfone **3a**, however, was only weakly antiproliferative.

16-Ene-25-*tert*-butyl sulfone analogue **4a**, a homologue of analogue **3a**, was prepared also in a straightforward manner (Scheme 2), was characterized stereochemically as 1α,3β by ^{1}H NMR spectroscopy (Table 1), and was found to be comparable in vitro to 1,25D$_3$ (**1**) in terms of antiproliferative activity in murine keratinocytes. The diastereomer **4b**, with unnatural stereochemistry in the A-ring (see Table 1), was only weakly antiproliferative (Figure 1). Replacing the *tert*-butyl group in 25-sulfone analogues **4** by a phenyl group produced analogues that had only weak in vitro antiproliferative activities. Similarly, replacing the 25-*tert*-butyl sulfone group in analogues **3** or **4** by a diethyl phosphonate group [i.e. 24- or 25-P(O)(OEt)$_2$] produced only weakly antiproliferative analogues.

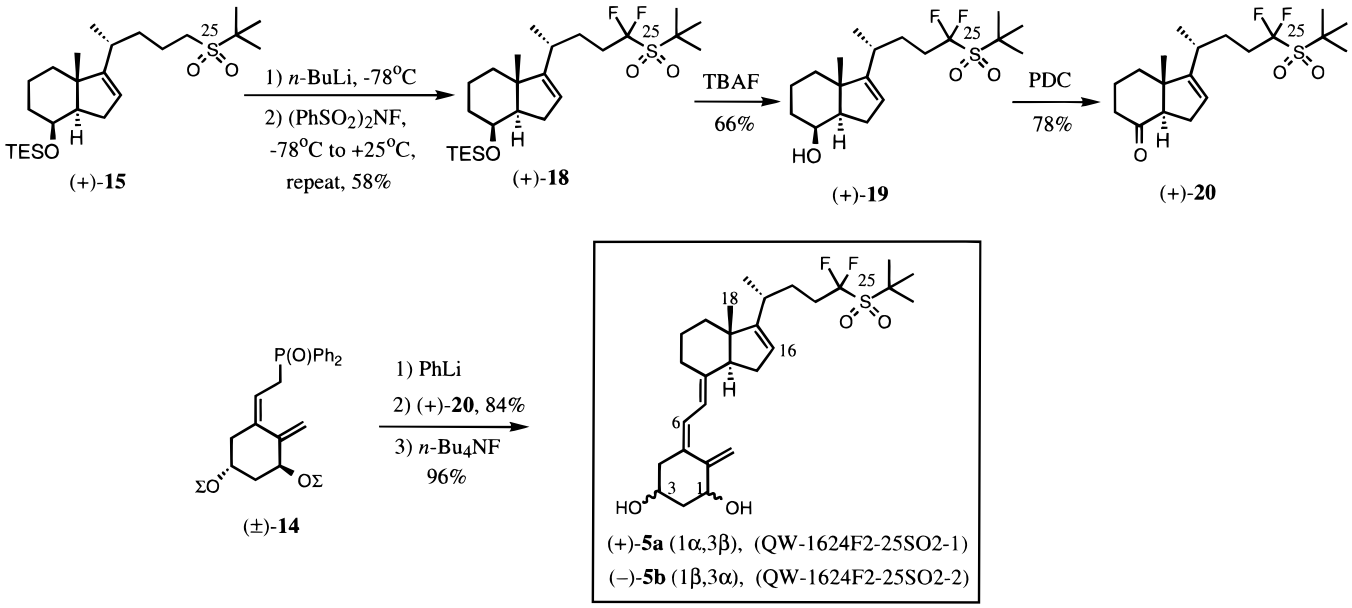
As expected based on our recent success with some 24-fluorinated analogues of 1,25D$_3$ (**1**),[24] 24,24-difluorinated 25-*tert*-butyl sulfone analogue **5a**, in contrast to its A-ring unnatural diastereomer **5b** (Scheme 3), was found in vitro to be comparable to 1,25D$_3$ (**1**) in terms of antiproliferative activity in both murine keratinocyte and malignant melanoma cells (Figures 1 and 2). Electrophilic fluorination[25,26] of *tert*-butyl sulfone (+)-**15** in Scheme 3 was achieved without addition of fluorine to the Δ^{16}-ene double bond, and convergent coupling of A-ring phosphine oxide ($\pm$)-**14** with α,α-difluorosulfone ketone (+)-**20** proceeded in high yield without loss of a fluorine atom (i.e. without dehydrofluorination).

Guided by the pioneering work at Hoffmann-LaRoche on 16,23-unsaturated analogues of 1,25D$_3$ (**1**),[6] we have prepared also 16,23-diene 25-*tert*-butyl sulfones **6** and the corresponding 24-fluoro 25-*tert*-butyl sulfones **7** (Schemes 4 and 5). Dehydration of β-hydroxy sulfones **21** gave exclusively (*E*)-alkenyl sulfone **22** (Scheme 4). Whereas tetra-*n*-butylammonium fluoride caused Michael addition of fluoride anion to alkenyl sulfone **22** (but not

Scheme 2



Scheme 3



to the less electrophilic alkenyl α-fluoro sulfone **25**), HF in acetonitrile effected removal of the silyl ether protecting group (**22** → **23**) without Michael addition. In both the nonfluorinated and the fluorinated series, only the A-ring diastereomers **6a** and **7a** having natural stereochemistry at both the 1- and 3-positions were found in vitro to be at least comparable to and perhaps more effective than 1,25D$_3$ in terms of antiproliferative activity in murine keratinocytes and in malignant melanoma cells over a wide range of concentrations (Figures 1 and 2).

The in vitro vitamin D receptor-mediated transcriptional potencies of several of these new analogues were determined, as described previously,[24] in rat osteosarcoma ROS 17/2.8 cells. The ED$_{50}$ values for transcriptional activity are as follows:[27] 1,25D$_3$, 0.35 nM; nonfluorinated sulfone **3a**, 0.8 nM; fluorinated sulfones **5a** and **7a**, 0.65 and 4.0 nM, respectively (Figure 3). Thus, sulfones **3a** and **5a** are only 2-fold less transcriptionally active than natural 1,25D$_3$ (**1**). These results are particularly significant because they indicate that sulfones **3a** and **5a**, both lacking a 25-OH group, are able to bind to the nuclear vitamin D receptor (nVDR) and thus to initiate genomic responses. Indeed, competitive binding affinities for these analogues [relative to 100% binding of 1,25D$_3$ (**1**)] are as follows: **3a**, 21%; **5a**, 7.9%; **7a**, 4%. Thus, despite the modest (7.9%) relative binding of fluorinated analogue **5a** to the nVDR, it has relatively strong transcriptional activity.[27] It is possible that one of the sulfone oxygen atoms in these analogues is serving as a polar group surrogate in place of a terminal OH group for binding to the nVDR; sulfones via their oxygen atoms have been reported to form hydrogen bonds with various proton donors.[28] Thus, the side chain sulfone groups in these analogues represent the first examples of a new class of hydrogen-bond **acceptors**[29–32]

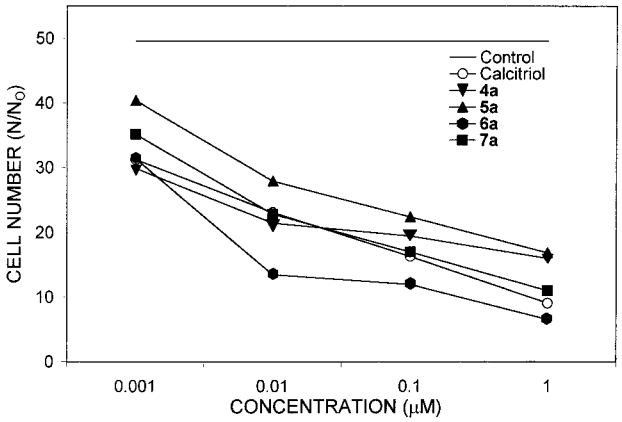


Figure 2. Dose−response effects of analogues on murine B16 malignant melanoma cell proliferation.

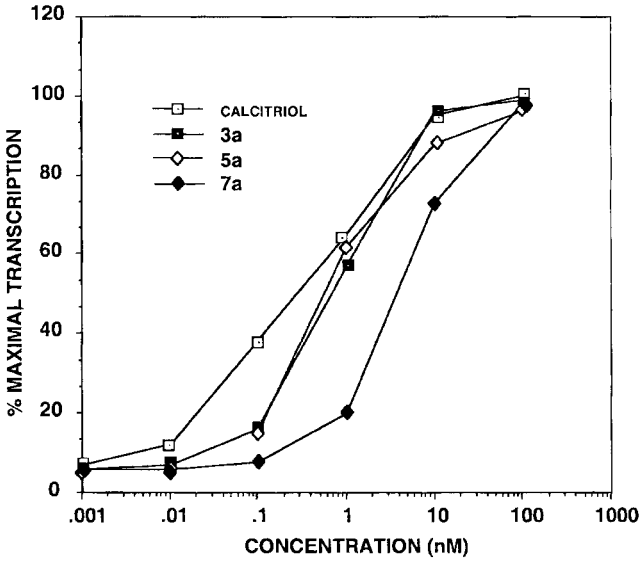


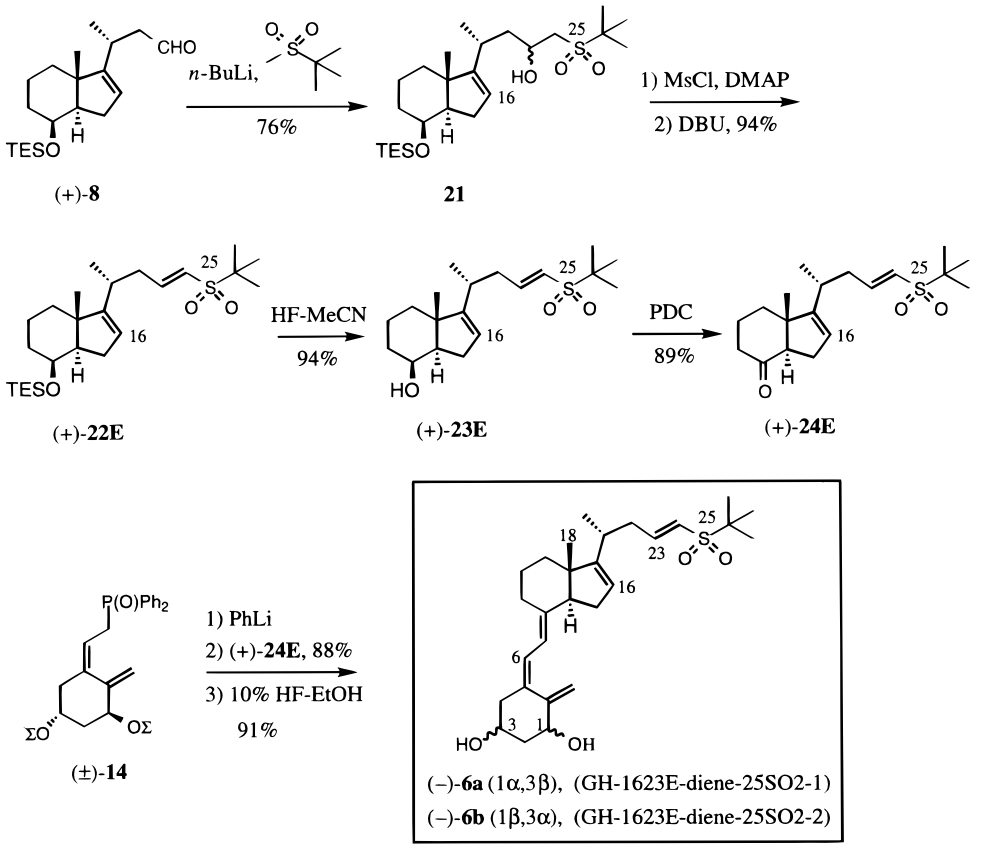
Figure 3. Transcriptional activity of vitamin D_3 analogues in ROS 17/2.8 cells.

that complement the normal hydrogen-bond **donor** function of the 25-OH group in natural 1,25D_3 (**1**) and in the thousand 1,25D_3 analogues prepared previously.[33]

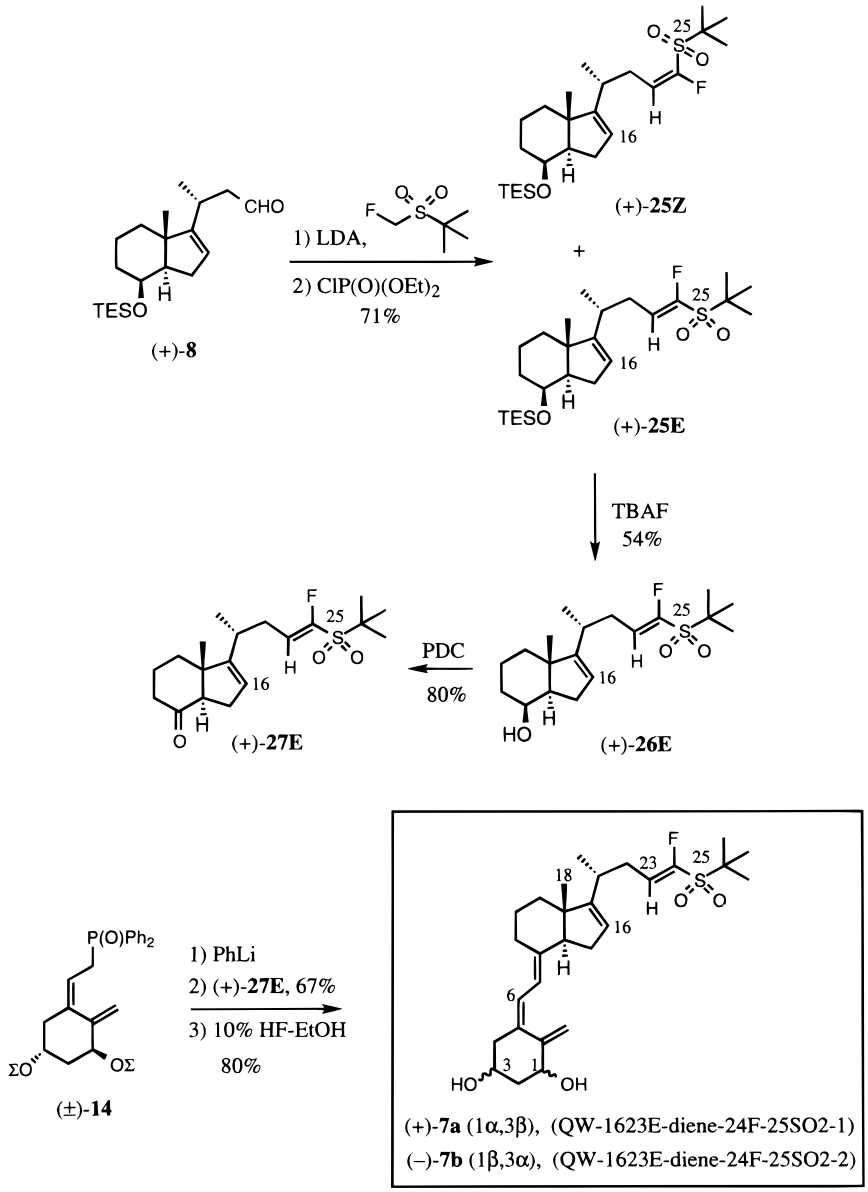
For practical chemotherapeutic uses of these new chemical entities, they would have to be weakly active or, even better, inactive in raising animals' calcium levels in their blood and urine. Using our previously reported protocol in which rats are treated orally with 1,25D_3 and the new analogues daily for 1 week, several of the sulfones (**3a**, **5a**, **7a**) produced no calcium elevation above control under identical treatment regimens (Figure 4). 16,23-Diene sulfone **6a**, however, was moderately calcemic. Interestingly, a substantial difference in calcemic activity was observed between the homologous sulfones **3a** and **4a**, large molecules differing by only a single CH_2 group: whereas 24-sulfone **3a** was noncalcemic, 25-sulfone **4a** was calcemic (Figure 4). A reasonable explanation of these considerable differences in calcemic activities induced by only small structural changes in the vitamin D skeleton awaits synthesis of additional analogues for structure−activity studies.

In summary, we have established for the first time that 16-ene side chain *tert*-butyl sulfones **3a**, **4a**, **5a**, **6a**, and **7a**, conceptually new analogues of 1,25D_3 (**1**), are potently antiproliferative and transcriptionally active even though they lack the natural hormone's 25-hydroxyl group and even though no terminal methine

Scheme 4



Scheme 5



C−H group is present that might undergo metabolic conversion (oxidation) into a terminal OH group. The side chain terminal 25-OH group in 1,25D$_3$ (**1**) has been considered up until now essential for effective recognition and binding to the nVDR. Therefore, these new 16-ene side chain *tert*-butyl sulfone analogues, because they are transcriptionally potent, are likely to serve well as molecular probes to elucidate fine details of ligandbinding to nVDR and, more generally, to advance understanding of how 1,25D$_3$ and its analogues elicit diverse biological responses. The effective separation of desirable antiproliferative activity from undesirable calcemic activity makes sulfones **3a**, **5a**, and **7a** promising candidates for further evaluation as potential chemotherapeutic or prophylactic agents in various human diseases.

Experimental Section

General. Unless otherwise noted, reactions were run in flame-dried round-bottomed flasks under an atmosphere of ultra-high-purity (UHP) argon. Diethyl ether (ether) and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl prior to use. Methylene chloride (CH_2Cl_2) was distilled from calcium hydride prior to use. All other compounds were purchased from Aldrich Chemical Co. and used without further purification. Analytical thin-layer chromatography (TLC) was conducted with silica gel 60 F_{254} plates (250-μm thickness; Merck). Column chromatography was performed using short path silica gel (particle size < 230 mesh), flash silica gel (particle size 400−230 mesh), or Florisil (200 mesh). Yields are not optimized. Purity of products was judged to be >95% based on their chromatographic homogeneity. High-performance liquid chromatography (HPLC) was carried out with a Rainin HPLX system equipped with two 25-mL/min preparative pump heads using Rainin Dynamax 10-mm × 250-mm (semipreparative) columns packed with 60 Å silica gel (8-μm pore size), either as bare silica or as C-18-bonded silica. Melting points were measured using a Mel-Temp metal-block apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were obtained either on a Varian XL-400 spectrometer, operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C, or on a Varian XL-500 spectrometer, operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C. Chemical shifts are reported in parts per million (ppm, δ) downfield from tetramethylsilane. Infrared (IR) spectra were obtained using a Perkin-Elmer 1600 FT-IR spectrometer. Absorption bands are reported in wave-

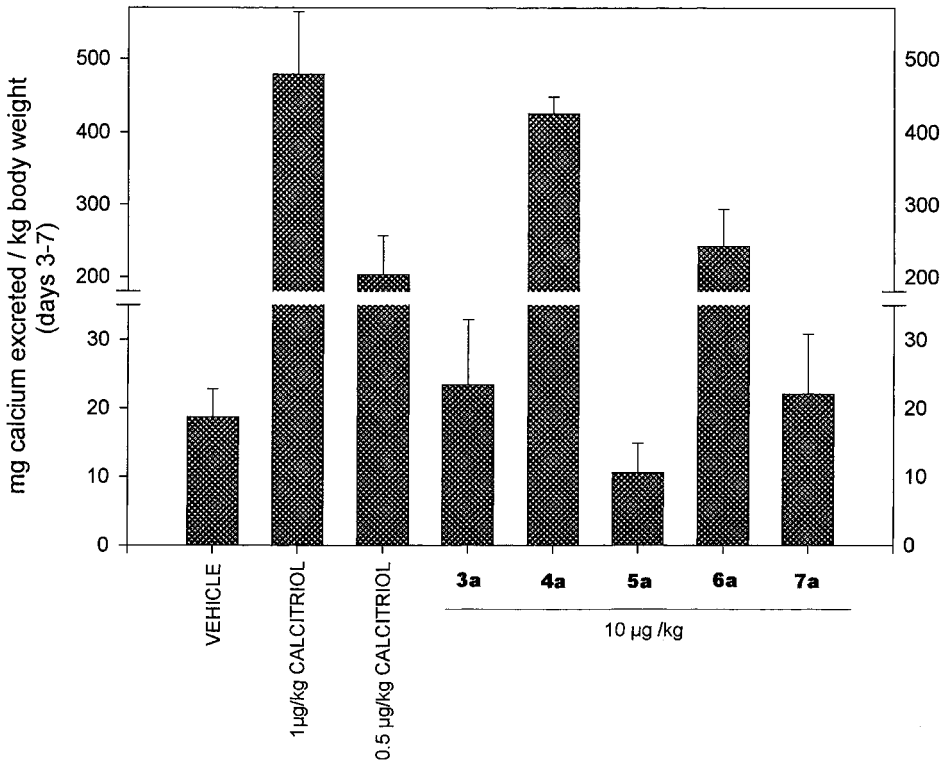


Figure 4. Effects of vitamin D_3 analogues on urinary calcium excretion in rats. Animals were treated with 0.5−10 μg/kg body weight of test compound po for 7 consecutive days, and urinary excretion of calcium was measured during days 3−7. Values are mean ± SE from three animals in each group.

numbers (cm^{-1}). Low- and high-resolution mass spectra (LRMS and HRMS) were obtained with electronic or chemical ionization (EI or CI) either (1) at Johns Hopkins University on a VG Instruments 70-S spectrometer run at 70 eV for EI and run with ammonia (NH_3) as a carrier gas for CI or (2) at the University of Illinois at Champaign−Urbana on a Finnigan-MAT CH5, a Finnigan-MAT 731, or a VG Instruments 70-VSE spectrometer run at 70 eV for EI and run with methane (CH_4) for CI.

23-Hydroxy Silyl Ether (+)-9. To a solution of aldehyde (+)-**8**[24] (361 mg, 1.07 mmol) in 20 mL of THF was added 3.2 mL (3.20 mmol) of a 1.0 M solution of diisobutylaluminum hydride (DIBAH) in hexanes at −78 °C. After 30 min, the reaction mixture was diluted with ether, quenched with 10% HCl, and then extracted with EtOAc (100 mL × 2). The combined extracts were successively washed with saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, concentrated in vacuo, and then purified by chromatography (10% EtOAc/hexanes) to give 353 mg (97%) of the alcohol (+)-**9** as a colorless oil: $[\alpha]^{25}_D$ +26.2 (*c* 5.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29 (t, J = 1.6 Hz, 1H), 4.12 (m 1H), 3.57−3.67 (m, 2H), 2.19−2.29 (m, 2H), 1.61−1.92 (m, 7H), 1.24−1.51 (m, 4H), 1.01 (s, 3H), 1.01 (d, J = 6.8 Hz, 3H), 0.95 (t, J = 8.0 Hz, 9H), 0.56 (q, J = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.90, 120.04, 68.91, 61.59, 55.06, 46.75, 39.26, 35.75, 34.92, 30.73, 28.29, 22.60, 18.73, 18.07, 6.96, 4.93; IR (neat, cm^{-1}) 3322, 2953, 2931, 2875, 1456, 1030; HRMS *m/z* (M^+) calcd 338.2641 for $C_{20}H_{38}O_2Si$, found 338.2644.

23-Iodo Silyl Ether (−)-10. To a solution of triphenylphosphine (990 mg, 3.77 mmol) and imidazole (580 mg, 8.52 mmol) in 40 mL of CH_2Cl_2 was slowly added a solution of iodine (1060 mg, 4.18 mmol) in 60 mL of CH_2Cl_2 at 0 °C. After 15 min, a solution of alcohol (+)-**9** (353 mg, 1.04 mmol) in 5 mL of CH_2Cl_2 was added into the mixture. After being stirred for 20 min at 0 °C followed by 16 h at room temperature, the reaction mixture was extracted with EtOAc (100 mL × 2), washed with brine, dried over $MgSO_4$, concentrated in vacuo, and then purified by column chromatography (100% hexanes) to give 443 mg (95%) of iodide (−)-**10** as a colorless oil: $[\alpha]^{25}_D$ −17.0 (*c* 6.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29 (t, J = 1.6 Hz, 1H), 4.12 (m, 1H), 3.07−3.22 (m, 2H), 2.27 (ddt, J = 14.4, 12.0, 1.2 Hz, 1 H), 2.18−2.22 (m, 1H), 2.02−2.11 (m, 2H), 1.86−1.95 (m, 3H), 1.61−1.76 (m, 3H), 1.42−1.52 (m, 2H), 1.35 (td, J = 12.4, 4.0 Hz, 1H), 1.04 (s, 3H), 1.00 (d, J = 6.8 Hz, 3H), 0.96 (t, J = 8.0 Hz, 9H), 0.57 (q, J = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.77, 120.39, 68.88, 55.05, 46.69, 35.57, 34.92, 32.70, 30.78, 22.02, 18.96, 18.07, 6.99, 5.66, 4.96; IR (neat, cm^{-1}) 2954, 2930, 2874, 1466, 1143, 1029; HRMS *m/z* (M^+) calcd 448.1658 for $C_{20}H_{37}IOSi$, found 448.1659.

TES 24-Sulfide (+)-11. A 5-mL hydrolysis tube was charged with iodide (−)-**10** (257 mg, 0.57 mmol), 0.1 mL (0.92 mmol) of 2-methyl-2-propanethiol, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 131 mg, 0.86 mmol), and 1.5 mL of benzene. After being stirred for 16 h at 130 °C, the reaction mixture was extracted with ether (50 mL × 2), washed with 5% HCl solution and brine, dried over $MgSO_4$, concentrated in vacuo, and then purified by chromatography (5% EtOAc/hexanes) to give 147 mg (62%) of the sulfide (+)-**11** as a colorless oil: $[\alpha]^{25}_D$ +18.0 (*c* 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29 (t, J = 1.6 Hz, 1H), 4.12 (m, 1H), 2.41−2.54 (m, 2H), 2.26 (ddt, J = 14.4, 12.0, 1.2 Hz, 1 H), 2.13−2.20 (m, 1H), 1.85−1.93 (m, 2H), 1.57−1.81 (m, 5H), 1.26−1.51 (m, 3H), 1.31 (s, 9H), 1.02 (s, 3H), 1.00 (d, J = 6.8 Hz, 3H), 0.96 (t, J = 8.0 Hz, 9H), 0.57 (q, J = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.66, 120.00, 68.96, 55.11, 46.70, 41.86, 36.58, 35.75, 34.96, 31.06, 30.78, 26.50, 22.28, 18.76, 18.09, 6.98, 4.65; IR (neat, cm^{-1}) 2956, 2928, 2875, 1457, 1029; HRMS *m/z* ($M + H^+$) calcd 411.3117 for $C_{24}H_{46}OSSi$, found 411.3109.

8-Hydroxy 24-Sulfone (+)-12. To a solution of sulfide (+)-**11** (72 mg, 0.18 mmol) in MeOH (2.0 mL) was added 1.2 mL (0.38 mmol) of 20% aqueous solution of potassium peroxymonosulfate ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$, Oxone) at 0 °C. The resulting white suspension was warmed to room temperature and then stirred for 1 h. Upon the disappearance of the starting material and the intermediate sulfoxide (monitored by TLC), the mixture was diluted with water, extracted with EtOAc, washed with brine, dried over $MgSO_4$, concentrated in vacuo, and then purified by chromatography (40% EtOAc/hexanes) to give 39 mg (68%) of 8-hydroxy 24-sulfone (+)-**12** as a colorless oil: $[\alpha]^{25}_D$ +4.6 (*c* 2.7, $CHCl_3$); ^{1}H NMR (400 MHz,

$CDCl_3$) δ 5.38 (t, J = 1.6 Hz, 1H), 4.18 (m, 1H), 2.75−2.95 (m, 2H), 2.28 (ddt, J = 14.4, 12.0, 1.2 Hz, 1 H), 2.16−2.23 (m, 1H), 1.96−2.10 (m, 3H), 1.71−1.90 (m, 4H), 1.41−1.45 (m, 3H), 1.39 (s, 9H), 1.06 (d, J = 6.8 Hz, 3H), 1.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.10, 121.04, 68.90, 58.82, 54.30, 46.27, 43.90, 35.27, 33.91, 31.20, 30.27, 26.29, 23.47, 22.49, 18.41, 17.74; IR (neat, cm^{-1}) 3516, 2929, 2875, 1454, 1277; HRMS m/z ($M + NH_4^+$) calcd 346.2416 for $C_{18}H_{32}O_3S$, found 346.2420.

8-Keto 24-Sulfone (+)-13. A flame-dried 5-mL flask was charged with 66 mg (0.20 mmol) of the C,D-ring alcohol (+)-**12**, 3 mL of anhydrous CH_2Cl_2, 150 mg of oven-dried Celite, and 150 mg (0.40 mmol) of pyridinium dichromate (PDC). The reaction mixture was stirred overnight at room temperature and then passed through a 2-cm pad of flash silica gel and washed with EtOAc. The filtrate was concentrated and purified by column chromatography (50% EtOAc/hexanes) to give 58 mg (88%) of 8-keto 24-sulfone (+)-**13** as a colorless oil: $[\alpha]^{25}_D$ +5.8 (*c* 5.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (t, J = 1.2 Hz, 1H), 2.75−2.90 (m, 3H), 2.44 (ddt, J = 16.0, 10.8, 1.2 Hz, 1 H), 2.25−2.35 (m, 3H), 1.93−2.12 (m, 5H), 1.86−1.93 (m, 1H), 1.77 (ddd, J = 18.0, 12.8, 5.6 Hz, 1H), 1.37 (s, 9H), 1.10 (d, J = 6.8 Hz, 3H), 0.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.45, 156.04, 121.55, 68.91, 58.86, 53.63, 43.40, 40.40, 34.15, 32.04, 27.09, 26.27, 23.91, 23.40, 21.67, 17.19; IR (neat, cm^{-1}) 2939, 1715, 1456, 1276, 1114; HRMS m/z ($M + NH_4^+$) calcd 344.2259 for $C_{18}H_{30}O_3S$, found 344.2267.

24-Sulfone Analogue (+)-3a. A solution of 70 mg (0.12 mmol) of phosphine oxide (−)-**14**[34] in 1.5 mL of anhydrous THF was cooled to −78 °C and treated with 75 μL (0.12 mmol) of a 1.7 M solution of phenyllithium in cyclohexane−ether. The resulting reddish orange solution was stirred for 30 min at −78 °C. To the solution was added dropwise a solution of 40 mg (0.12 mmol) of the C,D-ring ketone (+)-**13** in 1 mL of anhydrous THF. After being stirred for 2 h at the same temperature, the reaction was quenched with 2 mL of a 1:1 mixture of 2 N sodium potassium tartrate and 2 N K_2CO_3, extracted with EtOAc (50 mL × 2), and washed with brine. The combined organic portions were dried over anhydrous $MgSO_4$, concentrated in vacuo, and then purified by chromatography (20% Et_2O/hexanes) to afford 45 mg of the coupled product as a colorless oil.

The silyl ether was dissolved in 2 mL of anhydrous THF. To this solution were added 0.26 mL (0.26 mmol) of a 1.0 M solution of tetra-*n*-butylammonium fluoride (TBAF) in THF and 35 μL of triethylamine. After being stirred for 16 h at room temperature, the mixture was extracted with EtOAc (50 mL × 2) and washed with brine. The combined organic portions were dried over anhydrous $MgSO_4$, concentrated in vacuo, and then purified by chromatography (90% EtOAc/hexanes) to afford 27 mg (48%, two steps) of enantiomerically pure sulfone analogue (+)-**3a** as a white solid: mp 84−86 °C; $[\alpha]^{25}_D$ +63 (*c* 1.2, EtOH). The solid was further purified by reverse-phase HPLC (C-18 semipreparative column, 47% MeCN/H_2O, 3.0 mL/min, 262 nm) to afford 20 mg of (+)-**3a** (1α,3β, t_R 37.0 min) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.35 (d, J = 11.2 Hz, 1H), 6.09 (d, J = 11.2 Hz, 1H), 5.37 (br s, 1H), 5.33 (br s, 1H), 4.99 (br s, 1H), 4.41−4.44 (m, 1H), 4.22 (septet, J = 3.2 Hz, 1H), 2.76−2.94 (m, 3H), 2.18−2.39 (m, 5H), 1.88−2.10 (m, 5H), 1.48−1.71 (m, 4H), 1.39 (s, 9H), 1.09 (d, J = 6.8, 3H), 0.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.79, 147.52, 141.89, 133.28, 124.67, 121.70, 117.02, 111.71, 70.68, 66.76, 58.87, 58.27, 49.92, 45.16, 43.77, 42.83, 35.07, 32.23, 29.44, 28.69, 26.30, 23.49, 21.72, 16.87; IR (neat, cm^{-1}) 3406, 2930, 1457, 1277, 1114; UV (MeOH) λ_{max} 263 nm (ϵ 16 100); HRMS m/z (M^+) calcd 462.2804 for $C_{27}H_{42}O_4S$, found 462.2794.

TES 25-Sulfone (+)-15. A solution of *tert*-butyl methyl sulfone (118 mg, 0.87 mmol) and THF (3.0 mL) was cooled to −78 °C and treated dropwise under argon with 0.61 mL (0.85 mmol) of a 1.4 M solution of *n*-BuLi in hexanes. The solution was stirred for 15 min at −78 °C. To the solution was added 0.3 mL of HMPA, and then the solution was stirred for another 15 min. A precooled (−78 °C) solution of iodide (−)-**10** (78 mg, 0.17 mmol) in 2.0 mL of THF was added slowly via cannula. The reaction mixture was then warmed to room temperature and quenched with water, extracted with EtOAc (50 mL × 2), washed with brine, dried over anhydrous $MgSO_4$, concentrated in vacuo, and then purified by column chromatography (20% EtOAc/hexanes) to give 73 mg (92%) of the desired sulfone (+)-**15** as a colorless oil: $[\alpha]^{25}_D$ +18.5 (*c* 7.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.26 (s, 1H), 4.10 (m, 1H), 2.87 (t, J = 7.8 Hz, 2H), 2.24 (t, J = 13.2 Hz, 1H), 2.07 (m, 1H), 1.94−1.76 (m, 4H), 1.72−1.56 (m, 4H), 1.55−1.28 (m, 13H), 0.98 (d, J = 6.8 Hz, 3H), 0.98 (s, 3H), 0.93 (t, J = 7.8 Hz, 9H), 0.54 (q, J = 7.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.41, 120.15, 68.85, 58.73, 54.99, 46.61, 45.68, 35.71, 35.64, 34.83, 31.55, 30.68, 23.39, 22.16, 18.87, 18.77, 17.98, 6.88, 4.84; IR (neat, cm^{-1}) 2943, 2872, 1455, 1284, 1108, 1079, 1026; HRMS m/z (M^+) calcd 456.3093 for $C_{25}H_{48}O_3SSi$, found 456.3090.

8-Hydroxy 25-Sulfone (+)-16. To a solution of silyl ether (+)-**15** (83 mg, 0.18 mmol) in THF (3.0 mL) was added 0.45 mL (0.45 mmol) of a 1.0 M solution of TBAF in THF, and then it was stirred overnight at room temperature. The reaction mixture was quenched with water and extracted with EtOAc (50 mL × 2). The combined organic portions were washed with brine, dried, concentrated in vacuo, and then purified by chromatography (20% EtOAc/hexanes) to give 61 mg (99%) of the desired alcohol (+)-**16** as a colorless oil: $[\alpha]^{25}_D$ +4.2 (*c* 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.30 (d, J = 1.2 Hz, 1H), 4.15 (m, 1H), 2.87 (t, J = 8.0 Hz, 2H), 2.25 (t, J = 13.4 Hz, 1H), 2.07 (m, 1H), 2.00−1.45 (m, 12H), 1.38 (s, 9H), 1.02 (s, 3H), 0.99 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.23, 120.26, 68.94, 58.75, 54.31, 46.28, 45.62, 35.56, 35.38, 33.75, 31.57, 30.15, 23.38, 22.06, 18.88, 18.37, 17.71; IR (neat, cm^{-1}) 3519, 2919, 1461, 1367, 1284, 1108; HRMS m/z (M^+) calcd 342.2229 for $C_{19}H_{34}O_3S$, found 342.2235.

8-Keto 25-Sulfone (+)-17. To a solution of the C,D-ring alcohol (+)-**16** (60 mg, 0.18 mmol) in CH_2Cl_2 (5.0 mL) were added 130 mg of oven-dried Celite and PDC (132 mg, 0.35 mmol) at room temperature. The reaction mixture was stirred overnight and then passed through a 2-cm pad of flash silica gel and washed with EtOAc. The filtrate was concentrated and purified by column chromatography (50% EtOAc/hexanes) to give 56 mg (94%) of the desired C,D-ring ketone (+)-**17** as a colorless oil: $[\alpha]^{25}_D$ +14.7 (*c* 5.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.27 (t, J = 1.4 Hz, 1H), 2.86 (t, J = 7.8 Hz, 2H), 2.81 (m, 1H), 2.40 (ddt, J = 15.8, 10.6, 1.4 Hz, 1H), 2.29−2.19 (m, 2H), 2.17−1.90 (m, 4H), 1.90−1.58 (m, 5H), 1.56−1.40 (m, 1H), 1.36 (s, 9H), 1.04 (d, J = 6.8 Hz, 3H), 0.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.72, 157.10, 120.67, 62.92, 58.73, 53.64, 45.37, 40.35, 35.40, 34.24, 32.64, 26.95, 23.86, 23.31, 21.47, 18.79, 17.24; IR (neat, cm^{-1}) 2954, 1713, 1455, 1367, 1284, 1108; HRMS m/z (M^+) calcd 340.2072 for $C_{19}H_{32}O_3S$, found 340.2073.

25-Sulfone Analogues (+)-4a and (−)-4b. A solution of 108 mg (0.19 mmol) of racemic phosphine oxide (±)-**14** in 2.0 mL of anhydrous THF was cooled to −78 °C and treated with 107 μL (0.16 mmol, 1.5 M solution in cyclohexane−ether) of phenyllithium under argon atmosphere. The mixture turned reddish orange and was stirred for 30 min at −78 °C. To the solution was added dropwise a solution of 40 mg (0.12 mmol) of the C,D-ring ketone (+)-**17** in 1.0 mL of anhydrous THF. The reaction kept going until the reddish orange color faded to yellow (about 5 h). The reaction was quenched by adding 3.0 mL of a 1:1 mixture of 2 N sodium potassium tartrate and 2 N K_2CO_3 solution. The reaction mixture was extracted with EtOAc (50 mL × 2), washed with brine, dried over anhydrous $MgSO_4$, concentrated in vacuo, and then purified by column chromatography (20% EtOAc/hexanes) to afford 37 mg (45%) of the coupled product as a colorless oil.

The coupled product (37 mg, 0.053 mmol) was dissolved in 3.0 mL of anhydrous THF, and to this solution were added 0.21 mL (0.21 mmol) of a 1.0 M solution of TBAF in THF and 29 μL (0.21 mmol) of triethylamine. The reaction was run in darkness overnight, then quenched with water, extracted with EtOAc (50 mL × 2), washed with brine, dried over anhydrous $MgSO_4$, concentrated in vacuo, and then purified by silica gel chromatography (90% EtOAc/hexanes) to give 19 mg (76%) of

a mixture of two diastereomers as a colorless oil. The diastereomers were separated by reverse-phase HPLC (C-18 semipreparative column, 49% MeCN/H_2O, 3.0 mL/min) to afford 6 mg (11%) of (+)-**4a** (1α,3*β*, t_R 47.9 min) and 4 mg (7%) of (−)-**4b** (1*β*,3α, t_R 43.2 min) as colorless oils. (+)-**4a**: $[\alpha]^{25}_D$ +6.7 (*c* 0.6, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 6.37 (d, *J* = 11.2 Hz, 1H), 6.11 (d, *J* = 10.4 Hz, 1H), 5.34 (s, 2H), 5.01 (s, 1H), 4.45 (m, 1H), 4.24 (m, 1H), 3.00−2.75 (m, 3H), 2.60 (d, *J* = 12.8 Hz, 1H), 2.40−1.50 (m, 16H), 1.40 (s, 9H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 158.85, 147.62, 142.31, 133.09, 124.83, 120.84, 116.91, 111.64, 70.63, 66.86, 58.81, 58.31, 50.04, 45.62, 45.14, 42.82, 35.53, 35.28, 32.65, 29.39, 28.74, 23.57, 23.46, 21.59, 18.73, 16.98; IR (neat, cm^{-1}) 3425, 2919, 1284, 1108, 1049; UV (EtOH) λ_{max} 263 nm (*ϵ* 12 000); HRMS *m*/*z* (M^+) calcd 476.2960 for $C_{28}H_{44}O_4S$, found 476.2952. (−)-**4b**: $[\alpha]^{25}_D$ −8.9 (*c* 0.5, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 6.39 (d, *J* = 11.2 Hz, 1H), 6.09 (d, *J* = 10.6 Hz, 1H), 5.32 (s, 2H), 5.01 (d, *J* = 1.6 Hz, 1H), 4.45 (m, 1H), 4.22 (m, 1H), 2.94−2.76 (m, 3H), 2.62 (m, 1H), 2.42−1.46 (m, 16H), 1.41 (s, 9H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 158.84, 147.02, 142.40, 132.88, 124.89, 120.83, 116.91, 113.00, 71.55, 66.74, 58.82, 58.30, 50.06, 45.63, 45.53, 42.73, 35.54, 35.26, 32.65, 29.43, 28.73, 23.56, 23.47, 21.61, 18.72, 16.99; IR (neat, cm^{-1}) 3401, 2919, 1455, 1284, 1108, 1049; UV (EtOH) λ_{max} 264 nm (*ϵ* 13 200); HRMS *m*/*z* (M^+) calcd 476.2960 for $C_{28}H_{44}O_4S$, found 476.2955.

TES 24-Difluoro 25-Sulfone (+)-18. To a solution of the TES-protected C,D-ring sulfone (+)-**15** (56 mg, 0.12 mmol) in THF (3.0 mL) was added 0.18 mL (0.29 mmol) of a 1.6 M solution of *n*-BuLi in hexanes at −78 °C. After being stirred for 30 min, a precooled (−78 °C) solution of *N*-fluorobenzenesulfonimide (NFSI; 77 mg, 0.24 mmol) in 1.0 mL of THF was added slowly to the reaction mixture, and then it was warmed to room temperature. The reaction was quenched with water and extracted with EtOAc (50 mL × 2). The combined organic portions were washed with brine, dried, and concentrated in vacuo. Purification by column chromatography (20% EtOAc/hexanes) gave a mixture of mono- and difluorinated sulfones.

The mixture (58 mg) was dissolved in THF (3.0 mL), and the solution was cooled to −78 °C. To the solution was added 0.18 mL of *n*-BuLi (1.6 M solution in hexanes, 0.29 mmol), and the reaction mixture was stirred for 30 min at −78 °C. A precooled (−78 °C) solution of NFSI (96 mg, 0.30 mmol) in 1.0 mL of THF was then added slowly via cannula. The reaction mixture was warmed to room temperature, quenched with water, extracted with EtOAc (50 mL × 2), washed with brine, and concentrated. Purification by column chromatography (20% EtOAc/hexanes) gave 35 mg (58%) of the desired difluorinated C,D-ring sulfone (+)-**18** as a colorless oil: $[\alpha]^{25}_D$ +16.7 (*c* 3.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 5.30 (d, *J* = 1.2 Hz, 1H), 4.11 (m, 1H), 2.45−2.02 (m, 4H), 1.94−1.58 (m, 9H), 1.56−1.20 (m, 10H), 1.02 (d, *J* = 6.8 Hz, 3H), 1.00 (s, 3H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.56 (q, *J* = 7.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 158.80, 129.63 (t, *J* = 287.9 Hz), 120.94, 69.08, 63.30, 55.28, 46.81, 35.92, 35.10, 31.65, 30.99, 29.02 (t, *J* = 19.3 Hz), 27.00, 24.36, 22.49, 18.91, 18.25, 7.17, 5.11; ^{19}F NMR (376 MHz, $CDCl_3$, $CFCl_3$ as internal) *δ* −97.76 (t, *J* = 16.9 Hz); IR (neat, cm^{-1}) 2955, 2933, 2876, 1458, 1324, 1136, 1082, 1029; HRMS *m*/*z* (M^+) calcd 492.2905 for $C_{25}H_{46}F_2O_3SSi$, found 492.2907.

8-Hydroxy 24-Difluoro 25-Sulfone (+)-19. A solution of silyl ether (+)-**18** (89 mg, 0.18 mmol) in THF (2.0 mL) and 0.45 mL of 1.0 M solution of TBAF in THF was stirred overnight at room temperature. The mixture was quenched with water and extracted with EtOAc (50 mL × 2). The combined organic portions were washed with brine, dried, concentrated in vacuo, and then purified by column chromatography (20% EtOAc/hexanes) to give 45 mg (66%) of the desired alcohol (+)-**19** as a colorless oil: $[\alpha]^{25}_D$ +3.4 (*c* 3.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 5.34 (t, *J* = 1.4 Hz, 1H), 4.16 (m, 1H), 2.34−1.36 (m, 23H), 1.03 (d, *J* = 6.8 Hz, 3H), 1.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 158.62, 129.52 (t, *J* = 287.7 Hz), 121.04, 69.19, 63.29, 54.57, 46.47, 35.57, 33.96, 31.63, 30.42, 28.96 (t, *J* = 19.8 Hz), 26.93, 24.32, 22.37, 18.50, 17.96; ^{19}F NMR (376 MHz, $CDCl_3$, $CFCl_3$ as internal) *δ* −97.83 (m); IR (neat, cm^{-1}) 3568, 2930, 2870, 1458, 1320, 1134; HRMS *m*/*z* (M^+) calcd 378.2040 for $C_{19}H_{32}F_2O_3S$, found 378.2047.

8-Keto 24-Difluoro 25-Sulfone (+)-20. A flame-dried 5-mL flask was charged with 40 mg (0.11 mmol) of the C,D-ring alcohol (+)-**19**, 3.0 mL of anhydrous THF, 100 mg of oven-dried Celite, and 100 mg (0.27 mmol) of PDC. The reaction mixture was stirred overnight at room temperature and then passed through a 2-cm pad of flash silica gel and washed with EtOAc. The filtrate was concentrated and purified by column chromatography (20% EtOAc/hexanes) to give 31 mg (78%) of the desired C,D-ring ketone (+)-**20** as a colorless oil: $[\alpha]^{25}_D$ +12.9 (*c* 3.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 5.33 (d, *J* = 1.2 Hz, 1H), 2.83 (dd, *J* = 10.4, 6.4 Hz, 1H), 2.45 (dd, *J* = 15.6, 10.8 Hz, 1H), 2.36−1.56 (m, 12H), 1.50(s, 9H), 1.09 (d, *J* = 6.8 Hz, 3H), 0.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 210.87, 156.51, 129.38 (t, *J* = 287.8 Hz), 121.68, 63.36, 63.23, 53.83, 40.63, 34.50, 32.64, 28.85 (t, *J* = 19.6 Hz), 27.31, 26.90, 24.31, 24.14, 21.70, 17.47; ^{19}F NMR (376 MHz, $CDCl_3$, $CFCl_3$ as internal) *δ* −97.79 (m); IR (neat, cm^{-1}) 2939, 2873, 1718, 1458, 1377, 1320, 1130; HRMS *m*/*z* (M^+) calcd 376.1884 for $C_{19}H_{30}F_2O_3S$, found 376.1889.

24-Difluoro 25-Sulfone Analogues (+)-5a and (−)-5b. Racemic phosphine oxide (±)-**14** (89 mg, 0.15 mmol) was dissolved in 2.0 mL of anhydrous THF and cooled to −78 °C under argon atmosphere. To this solution was added 100 *μ*L (0.16 mmol) of phenyllithium (1.6 M solution in cyclohexane−ether) dropwise. The mixture turned deep reddish orange and persisted. After stirring at −78 °C for 30 min, a precooled (−78 °C) solution of C,D-ring ketone (+)-**20** (30 mg, 0.080 mmol) dissolved in 1.0 mL of anhydrous THF was added dropwise via cannula. The reaction kept going until the reddish orange color faded to yellow (about 4 h). The reaction was quenched by adding 3.0 mL of a 1:1 mixture of 2 N sodium potassium tartrate and 2 N K_2CO_3 solution. The reaction mixture was allowed to warm to room temperature, extracted with EtOAc (50 mL × 2), washed with brine, dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and then purified by column chromatography (10% EtOAc/hexanes) to afford 50 mg (84%) of the coupled product as a colorless oil.

The coupled product (50 mg, 0.067 mmol) was dissolved in 3.0 mL of anhydrous THF with 37 *μ*L of Et_3N, and to this solution was added 0.27 mL (0.27 mmol) of TBAF (1.0 M solution in THF) at room temperature. The reaction was run in darkness overnight, then quenched with water, extracted with EtOAc (50 mL × 2), washed with brine, dried over anhydrous $MgSO_4$, concentrated in vacuo, and then purified by column chromatography (90% EtOAc/hexanes) to give 33 mg (96%) of a mixture of two diastereomers as a colorless oil. The diastereomers were separated by reverse-phase HPLC (C-18 semipreparative column, 52% MeCN/H_2O, 3.0 mL/min) to afford 17 mg (41%) of (+)-**5a** (1α,3*β*, t_R 145.3 min) as a foaming solid and 7 mg (17%) of (−)-**5b** (1*β*,3α, t_R 129.2 min) as a colorless oil. (+)-**5a**: $[\alpha]^{25}_D$ +0.1 (*c* 1.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 6.36 (d, *J* = 11.2 Hz, 1H), 6.10 (d, *J* = 11.2 Hz, 1H), 5.40−5.30 (m, 2H), 5.00 (s, 1H), 4.43 (dd, *J* = 8.0, 4.4 Hz, 1H), 4.23 (m, 1H), 2.81 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.59 (dd, *J* = 13.2, 2.8 Hz, 1H), 2.43−2.13 (m, 5H), 2.09−1.96 (m, 2H), 1.95−1.63 (m, 9H), 1.51 (s, 9H), 1.07 (d, *J* = 6.8 Hz, 3H), 0.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 158.19, 147.85, 142.36, 133.43, 129.60 (t, *J* = 287.7 Hz), 124.99, 121.67, 117.21, 111.88, 70.82, 67.07, 63.34, 58.52, 50.18, 45.35, 43.02, 35.42, 32.58, 29.65, 28.94, 28.70 (t, *J* = 19.6 Hz), 26.81, 24.36, 23.77, 21.79, 17.05; ^{19}F NMR (376 MHz, $CDCl_3$, $CFCl_3$ as internal) *δ* −97.86 (m); IR (neat, cm^{-1}) 3601, 2931, 2837, 1455, 1314, 1126, 1043; UV (EtOH) λ_{max} 263 nm (*ϵ* 16 100); HRMS *m*/*z* (M^+) calcd 512.2772 for $C_{28}H_{42}F_2O_4S$, found 512.2781. (−)-**5b**: $[\alpha]^{25}_D$ −24.1 (*c* 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 6.39 (d, *J* = 11.2 Hz, 1H), 6.10 (d, *J* = 11.2 Hz, 1H), 5.35 (t, *J* = 1.2 Hz, 1H), 5.32 (s, 1H), 5.01 (d, *J* = 2.0 Hz, 1H), 4.44 (dd, *J* = 6.0, 4.0 Hz, 1H), 4.22 (m, 1H), 2.82 (dd, *J* = 11.8, 4.2 Hz, 1H), 2.62 (dd, *J* = 13.2, 4.0 Hz, 1H), 2.42−2.12 (m, 5H), 2.10−1.96 (m, 2H), 1.95−1.55 (m, 9H), 1.52 (s, 9H), 1.07 (d, *J* = 6.8 Hz, 3H), 0.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 158.20, 147.22,

142.49, 133.18, 129.62 (t, J = 288.0 Hz), 125.09, 121.66, 117.20, 113.29, 71.80, 66.96, 63.35, 58.53, 50.20, 45.78, 42.94, 35.40, 32.58, 29.70, 28.94, 28.69 (t, J = 19.1 Hz), 26.82, 24.38, 23.77, 21.81, 17.07; ^{19}F NMR (376 MHz, $CDCl_3$, $CFCl_3$ as internal) δ −97.88 (m); IR (neat, cm^{-1}) 3683, 3601, 2931, 1314, 1132, 1043; UV (EtOH) λ_{max} 263 nm (ϵ 15 000); HRMS m/z (M^+) calcd 512.2772 for $C_{28}H_{42}F_2O_4S$, found 512.2776.

16-Ene 23-Hydroxy 25-Sulfones 21. To a solution of *tert*-butyl methyl sulfone (103 mg, 0.76 mmol) in 10 mL of THF was added 0.52 mL of *n*-BuLi in hexanes (1.6 M, 0.83 mmol) dropwise at −78 °C. After 1 h at −78 °C, a solution of aldehyde (+)-**8** (45 mg, 0.13 mmol) in 10 mL of THF was added dropwise at −78 °C. After 2 h at −78 °C, the reaction mixture was quenched with saturated ammonium chloride solution (20 mL) and extracted with EtOAc (50 mL × 3). The combined organic portions were washed with brine (30 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by flash column chromatography (33% EtOAc/hexanes) to give 45 mg (76%) of diastereomeric alcohols **21** as colorless oils: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33 (m, 1H), 5.27 (m, 1H), 4.48 (m, 1H), 4.38 (m, 1H), 4.12 (m, 1H), 3.47 (m, 1H), 3.37 (m, 1H), 3.09−2.94 (m, 2H), 2.41 (m, 1H), 2.26 (m, 1H), 1.91−1.41 (m, 13H), 1.42 (m, 9H), 1.04 (m, 6H), 0.95 (t, J = 8.0 Hz, 9H), 0.56 (q, J = 8.0 Hz, 6H); IR (neat, cm^{-1}) 3523, 2932, 1290, 1114; HRMS m/z (M^+) calcd 472.3043 for $C_{25}H_{48}O_4SSi$, found 472.3037.

16,23-Diene 25-Sulfone (+)-22E. To a solution of alcohols **21** (42 mg, 0.089 mmol) in 10 mL of dry CH_2Cl_2 were added 0.20 mL of triethylamine and methanesulfonyl chloride (0.050 mL, 0.65 mmmol) at 0 °C. The mixture was stirred for 1 h at 0 °C. The solution was concentrated in vacuo. The residue was diluted with brine (20 mL) and extracted with EtOAc (30 mL × 3). The combined organic portions were dried over $MgSO_4$ and concentrated. The crude mesylates were used for the next step without further purification.

To a solution of the mesylates in 7 mL of dry benzene was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.050 mL, 0.33 mmol). The solution was gently refluxed for 15 min and then allowed to cool to room temperature. The reaction mixture was diluted with brine (20 mL) and extracted with EtOAc (30 mL × 3). The combined organic portions were dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (33% EtOAc/hexanes) to give 38 mg (94%) of the unsaturated sulfone (+)-**22E** as a colorless oil: $[\alpha]^{25}_D$ +20.0 (c 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (dt, J = 14.8, 7.6 Hz, 1H), 6.23 (d, J = 15.2 Hz, 1H), 5.29 (s, 1H), 4.11 (m, 1H), 2.51 (m, 1H), 2.41−2.02 (m, 3H), 1.91 (m, 2H), 1.73−1.37 (m, 10H), 1.04 (d, J = 6.4 Hz, 3H), 1.01 (s, 3H), 0.94 (t, J = 8.0 Hz, 9H), 0.56 (q, J = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.38, 150.43, 124.31, 121.34, 68.75, 58.17, 54.95, 46.75, 38.76, 35.78, 34.74, 30.91, 30.70, 23.23, 21.83, 18.84, 17.96, 6.88, 4.83; IR (neat, cm^{-1}) 2932, 1294, 1115; HRMS m/z ($M + H^+$) calcd 455.3015 for $C_{25}H_{46}O_3SSi$, found 455.3009.

16,23-Diene 8-Hydroxy 25-Sulfone (+)-23E. To a solution of the sulfone (+)-**22E** (24 mg, 0.053 mmol) in 10 mL of acetonitrile was added hydrofluoric acid (2% in H_2O, 0.10 mL, 0.10 mmol) at 0 °C. After 2 h at 0 °C, the reaction mixture was quenched with saturated $NaHCO_3$ solution (20 mL) and extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by flash chromatography (50% EtOAc/hexanes) to give 17 mg (94%) of the alcohol (+)-**23E** as a colorless oil: $[\alpha]^{25}_D$ +5.9 (c 2.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (dt, J = 15.2, 7.6 Hz, 1H), 6.25 (dt, J = 15.2, 1.6 Hz, 1H), 5.35 (s, 1H), 4.18 (m, 1H), 2.54−2.22 (m, 4H), 2.02−1.52 (m, 14H), 1.35 (s, 9H), 1.06 (d, J = 8.0 Hz, 3H), 1.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.30, 150.22, 124.45, 121.45, 68.89, 58.19, 54.31, 46.46, 38.72, 35.47, 33.79, 30.99, 30.22, 23.28, 21.84, 18.46, 17.70; IR (neat, cm^{-1}) 3526, 2927, 1290, 1120; HRMS m/z ($M + NH_4^+$) calcd 358.2416 for $C_{19}H_{32}O_3S$, found 358.2408.

16,23-Diene 8-Keto 25-Sulfone (+)-24E. To a solution of the alcohol (+)-**23E** (28 mg, 0.083 mmol) in 10 mL of dry CH_2Cl_2 was added 57 mg of oven-dried Celite and pyridinium dichromate (57 mg, 0.15 mmol) at room temperature. After 16 h, the reaction mixture was filtered through a flash silica gel pad and then eluted with EtOAc. The filtrate was concentrated and purified by flash chromatography (50% EtOAc/hexanes) to give 25 mg (89%) of the ketone (+)-**24E** as a colorless oil: $[\alpha]^{25}_D$ +22.2 (c 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (dt, J = 15.2 7.6 Hz, 1H), 6.25 (d, J = 15.2 Hz, 1H), 5.33 (s, 1H), 2.85(m, 1H), 2.55−2.27 (m, 6H), 2.15−1.74 (m, 7H), 1.33 (s 9H), 1.11 (d, J = 6.4 Hz, 3H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.43, 156.21, 149.49, 124.89, 121.80, 62.89, 58.19, 53.69, 40.34, 38.56, 34.35, 27.09, 23.86, 23.25, 21.35, 17.32; IR (neat, cm^{-1}) 2935, 1715, 1289, 1113; HRMS m/z ($M + NH_4^+$) calcd 356.2259 for $C_{19}H_{30}O_3S$, found 356.2266.

16,23-Diene 25-Sulfone Analogues (−)-6a and (−)-6b. To a solution of racemic phosphine oxide (±)-**14** (60 mg, 0.10 mmol) in 1 mL of anhydrous THF was treated dropwise with phenyllithium (1.22 M in cyclohexane−ether, 0.082 mL, 0.10 mmol) at −78 °C. The resulting reddish orange solution was stirred at −78 °C for 30 min, and then a solution of the ketone (+)-**24E** (24 mg, 0.071 mmol) in 1 mL of anhydrous THF was added dropwise. The reaction mixture was stirred until reddish color turned to pale yellow and then quenched with 3 mL of a 1:1 mixture of 2 N sodium potassium tartrate solution and 2 N K_2CO_3 solution. The aqueous layer was extracted with EtOAc (50 mL × 3). The combined organic portions were washed with brine (50 mL), dried over $MgSO_4$, and concentrated. The residue was purified by preparative TLC (EtOAc) to give 44 mg (88%) of the coupled product as a colorless oil.

To a solution of the coupled product (44 mg, 0.062 mmol) in 2 mL of anhydrous ethanol was added hydrofluoric acid (49% in H_2O, 0.50 mL, 12.3 mmol). The solution was stirred at room temperature for 2 h in the dark. The reaction mixture was quenched with $NaHCO_3$ solution (20 mL), and the aqueous layer was extracted with EtOAc (30 mL × 3). The combined organic portions were washed with brine (20 mL), dried over $MgSO_4$, and concentrated. The residue was purified by preparative TLC (EtOAc) to give 27 mg (91%) of diastereomeric diols **6** as colorless oils. The diastereomers were separated by reverse-phase HPLC (C-18 semipreparative column, 52% MeCN/48% H_2O, 3 mL/min) to give 12 mg (36%) of (−)-**6a** (1α,3β, t_R 30.2 min) and 9 mg (27%) of (−)-**6b** (1β,3α, t_R 27.1 min) as colorless oils. (−)-**6a**: $[\alpha]^{25}_D$ −2.5 (c 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (dt, J = 15.2, 7.4 Hz, 1H), 6.36 (d, J = 11.2 Hz, 1H), 6.24 (d, J = 15.2 Hz, 1H), 6.10 (d, J = 11.6 Hz, 1H), 5.34 (m, 2H), 5.00 (s, 1H), 4.44 (m, 1H), 4.24 (m, 1H), 2.88 (dd, J = 12.4, 4.2 Hz, 1H), 2.61−2.48 (m, 3H), 2.38−2.14 (m, 7H), 2.06−1.51 (m, 18H), 1.34 (s, 9H), 1.09 (d, J = 6.4 Hz, 3H), 0.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.86, 150.15, 147.63, 141.81, 133.37, 124.70, 124.50, 122.98, 117.14, 111.64, 70.62, 66.83, 58.28, 58.21, 50.02, 45.12, 42.84, 38.64, 35.29, 32.00, 29.43, 28.67, 23.49, 23.29, 21.29, 17.03; IR (neat, cm^{-1}) 3606, 2931, 1291, 1113; UV (EtOH) λ_{max} 263 nm (ϵ 11 793); HRMS m/z (M^+) calcd 474.2804 for $C_{28}H_{42}O_4S$, found 474.2800. (−)-**6b**: $[\alpha]^{25}_D$ −10.9 (c 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (dt, J = 15.2, 7.6 Hz, 1H), 6.38 (d, J = 11.6 Hz, 1H), 6.24 (d, J = 15.2 Hz, 1H), 6.09 (d, J = 11.2 Hz, 1H), 5.34 (m, 2H), 5.01 (s, 1H), 4.46 (m, 1H), 4.23 (m, 1H), 2.83 (dd, J = 12.8, 4.0 Hz, 1H), 2.64−2.48 (m, 3H), 2.34−2.15 (m, 7H), 2.05−1.52 (m, 20H), 1.35 (s, 9H), 1.09 (d, J = 6.4 Hz, 3H), 0.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.86, 150.15, 147.09, 141.91, 133.18, 124.76, 124.52, 121.98, 117.14, 112.82, 71.42, 66.74, 58.28, 58.22, 50.03, 45.47, 42.78, 38.64, 35.28, 32.01, 29.47, 28.66, 23.48, 23.30, 21.32, 17.05; IR (neat, cm^{-1}) 3606, 2931, 1291, 1112; UV (EtOH) λ_{max} 263 nm (ϵ 11 572); HRMS m/z (M^+) calcd 474.2804 for $C_{28}H_{42}O_4S$, found 474.2796.

TES 16,23-Diene 24-Fluoro 25-Sulfones (+)-25E and (+)-25Z. A solution of 5.0 mL of THF and 0.53 mL of *n*-BuLi (1.5 M solution in hexanes, 0.80 mmol) was cooled to −78 °C, and then 0.11 mL (0.80 mmol) of diisopropylamine was added dropwise to the solution. After 15 min, monofluorinated *tert*-butyl methyl sulfone (58 mg, 0.38 mmol) was added via cannula, and the resulting reaction mixture was stirred for another 15 min. Diethyl chlorophosphate (52 μL, 0.36 mmol) was added, and the reaction was stirred at −78 °C for 1 h. A

precooled (−78 °C) solution of TES-protected aldehyde (+)-**8** (75 mg, 0.22 mmol) in 1.0 mL of THF was added slowly via cannula. The reaction mixture was then warmed to room temperature, quenched with water, extracted with EtOAc (50 mL × 2), washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo, and then the mixture (75 mg, 71%) was separated by column chromatography (2% Et_2O/hexanes) to give 45 mg of the desired *E* isomer and 30 mg of the *Z* isomer as colorless oils. (+)-**25E**: $[\alpha]^{25}_D$ +28.2 (*c* 2.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.05 (dt, J = 32.8, 7.6 Hz, 1H), 5.31 (t, J = 1.6 Hz, 1H), 4.11 (m, 1H), 2.54−2.18 (m, 4H), 1.98−1.20 (m, 17H), 1.06 (d, J = 6.8 Hz, 3H), 1.00 (s, 3H), 0.94 (t, J = 8.0 Hz, 9H), 0.56 (q, J = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.62, 151.81 (d, J = 294.8 Hz), 122.33 (d, J = 6.4 Hz), 121.38, 69.02, 59.73, 55.19, 46.95, 35.98, 35.01, 31.41, 31.33, 30.96, 23.47, 22.16, 19.05, 18.22, 7.15, 5.10; ^{19}F NMR (376 MHz, $CDCl_3$, $CFCl_3$ as internal) δ −119.77 (d, J = 33.5 Hz); IR (neat, cm^{-1}) 2954, 2931, 2860, 1666, 1455, 1320, 1132, 1026; HRMS *m/z* (M^+) calcd 472.2843 for $C_{25}H_{45}FO_3SSi$, found 472.2851. (+)-**25Z**: $[\alpha]^{25}_D$ +22.7 (*c* 2.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 (dt, J = 24.0, 7.2 Hz, 1H), 5.34 (t, J = 1.6 Hz, 1H), 4.11 (m, 1H), 2.76−2.54 (m, 2H), 2.34−2.14 (m, 2H), 1.96−1.82 (m, 2H), 1.76−1.20 (m, 15H), 1.03 (d, J = 6.8 Hz, 3H), 1.01 (s, 3H), 0.95 (t, J = 8.0 Hz, 9H), 0.56 (q, J = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.56, 149.56 (d, J = 286.1 Hz), 123.89 (d, J = 12.3 Hz), 121.73, 69.05, 60.56, 55.25, 46.88, 35.85, 35.05, 32.08, 31.39, 30.99, 23.19, 22.18, 18.99, 18.22, 7.17, 5.12; ^{19}F NMR (376 MHz, $CDCl_3$, $CFCl_3$ as internal) δ −107.80 (d, J = 24.4 Hz); IR (neat, cm^{-1}) 2954, 2919, 2860, 1649, 1455, 1314, 1132, 1026; HRMS *m/z* (M^+) calcd 472.2843 for $C_{25}H_{45}FO_3SSi$, found 472.2837.

16,23-Diene 8-Hydroxy 24-Fluoro 25-Sulfone (+)-26E. A solution of silyl ether (+)-**25E** (74 mg, 0.16 mmol) and TBAF (0.39 mL, 1.0 M solution in THF, 0.39 mmol) in 2.0 mL of THF was stirred for 4 h at room temperature. The mixture was quenched with water and extracted with EtOAc (30 mL × 2). The combined organic portions were washed with brine, dried, concentrated in vacuo, and then purified by column chromatography (50% EtOAc/hexanes) to give 30 mg (54%) of the desired alcohol as a colorless oil: $[\alpha]^{25}_D$ +6.8 (*c* 1.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.05 (dt, J = 33.2, 7.8 Hz, 1H), 5.36 (t, J = 1.6 Hz, 1H), 4.17 (m, 1H), 2.55−2.20 (m, 4H), 2.06−1.30 (m, 17H), 1.06 (d, J = 6.8 Hz, 3H), 1.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.45, 151.92 (d, J = 295.2 Hz), 122.07 (d, J = 6.3 Hz), 121.51, 69.14, 59.72, 54.52, 46.63, 35.64, 34.03, 31.34, 31.32, 30.45, 23.48, 22.14, 18.64, 17.93; ^{19}F NMR (376 MHz, $CDCl_3$, $CFCl_3$ as internal) δ −119.62 (d, J = 33.5 Hz); IR (neat, cm^{-1}) 3542, 2919, 2872, 1666, 1455, 1137, 1114; HRMS *m/z* (M^+) calcd 358.1978 for $C_{19}H_{31}FO_3S$, found 358.1985.

16,23-Diene 8-Keto 24-Fluoro 25-Sulfone (+)-27E. A flame-dried 5-mL flask was charged with 30 mg (0.084 mmol) of the C,D-ring alcohol (+)-**26E**, 3.0 mL of anhydrous CH_2Cl_2, 70 mg of oven-dried Celite, and 63 mg (0.17 mmol) of PDC. The reaction mixture was stirred overnight at room temperature and then passed through a 2-cm pad of flash silica gel and washed with EtOAc. The filtrate was concentrated and purified by column chromatography (50% EtOAc/hexanes) to give 24 mg (78%) of the desired C,D-ring ketone (+)-**27E** as a colorless oil: $[\alpha]^{25}_D$ +26.0 (*c* 2.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03 (dt, J = 32.8, 7.6 Hz, 1H), 5.35 (t, J = 1.2 Hz, 1H), 2.85 (dd, J = 10.8, 6.6 Hz, 1H), 2.60−2.20 (m, 6H), 2.18−1.60 (m, 5H), 1.38 (s, 9H), 1.13 (d, J = 6.4 Hz, 3H), 0.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.70, 156.35, 152.31 (d, J = 295.7 Hz), 121.95, 121.38 (d, J = 6.4 Hz), 63.15, 59.74, 53.90, 40.60, 34.56, 32.24, 31.25, 27.34, 24.12, 23.47, 21.62, 17.54; ^{19}F NMR (376 MHz, $CDCl_3$, $CFCl_3$ as internal) δ −119.06 (d, J = 33.1 Hz); IR (neat, cm^{-1}) 2943, 1713, 1666, 1455, 1314, 1120, 1038; HRMS *m/z* (M^+) calcd 356.1821 for $C_{19}H_{29}FO_3S$, found 356.1822.

16,23-Diene 24-Fluoro 25-Sulfone Analogues (+)-7a and (−)-7b. Racemic phosphine oxide (±)-**14** (49 mg, 0.084 mmol) was dissolved in 2.0 mL of anhydrous THF and cooled to −78 °C under argon atmosphere. To this solution was added 65 μL (0.080 mmol) of phenyllithium (1.2 M solution in cyclohexane−ether) dropwise. The mixture turned deep reddish orange and persisted. After stirring at −78 °C for 30 min, a precooled (−78 °C) solution of C,D-ring ketone (+)-**27E** (24 mg, 0.068 mmol) dissolved in 1.0 mL of anhydrous THF was added dropwise via cannula. The reaction kept going on until the reddish orange color faded to yellow (about 4 h). The reaction was quenched by adding 3.0 mL of a 1:1 mixture of 2 N sodium potassium tartrate and 2 N K_2CO_3 solution. The reaction mixture was allowed to warm to room temperature, extracted with EtOAc (50 mL × 2), washed with brine, dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and then purified by column chromatography (8% EtOAc/hexanes) to afford 33 mg (67%) of the coupled product as a colorless oil.

The coupled product (31 mg, 0.043 mmol) was dissolved in 2.0 mL of anhydrous ethanol, then 0.34 mL of HF (49% solution in water) was added, and the resulting reaction mixture was stirred for 1 h at room temperature. The reaction was quenched with diluted $NaHCO_3$ solution, extracted with EtOAc (50 mL × 2), washed with brine, dried over anhydrous $MgSO_4$, concentrated in vacuo, and then purified by column chromatography (80% EtOAc/hexanes) to give 17 mg (80%) of a mixture of two diastereomers as a colorless oil. The diastereomers were separated by reverse-phase HPLC (C-18 semi-preparative column, 52% MeCN/H_2O, 3.0 mL/min) to afford 6 mg (17%) of (+)-**7a** (1α,3β, t_R 77.3 min) as a foaming solid and 4 mg (12%) of (−)-**7b** (1β,3α, t_R 70.4 min) as a colorless oil. (+)-**7a**: $[\alpha]^{25}_D$ +3.2 (*c* 0.57, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36(d, J = 11.2 Hz, 1H), 6.10 (d, J = 10.8 Hz, 1H), 6.05 (dt, J = 33.2, 7.6 Hz, 1H), 5.37 (s, 1H), 5.34 (t, J = 1.6 Hz, 1H), 5.00 (s, 1H), 4.44 (dd, J = 7.8, 4.2 Hz, 1H), 4.24 (m, 1H), 2.82 (dd, J = 12.2, 4.6 Hz, 1H), 2.60 (d, J = 13.6 Hz, 1H), 2.54−1.18 (m, 23H), 1.10 (d, J = 6.4 Hz, 3H), 0.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.03, 152.01 (d, J = 295.3 Hz), 147.86, 142.11, 133.56, 124.97, 122.12, 121.88 (d, J = 6.3 Hz), 117.36, 111.90, 70.89, 67.07, 59.73, 58.51, 50.20, 45.37, 43.08, 35.46, 32.30, 31.26, 29.66, 28.90, 23.72, 23.50, 21.52, 17.21; ^{19}F NMR (376 MHz, $CDCl_3$, $CFCl_3$ as internal) δ −119.50 (d, J = 33.1 Hz); IR ($CHCl_3$, cm^{-1}) 3707, 3601, 2919, 1654, 1455, 1314, 1220, 1038; UV (EtOH) λ_{max} 263 nm (ϵ 14 700); HRMS *m/z* (M^+) calcd 492.2710 for $C_{28}H_{41}FO_4S$, found 492.2715. (−)-**7b**: $[\alpha]^{25}_D$ −16.7 (*c* 0.42, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38(d, J = 11.6 Hz, 1H), 6.09 (d, J = 10.4 Hz, 1H), 6.05 (dt, J = 33.6, 7.6 Hz, 1H), 5.37 (s, 1H), 5.33 (s, 1H), 5.01 (d, J = 1.6 Hz, 1H), 4.46 (m, 1H), 4.22 (m, 1H), 2.82 (dd, J = 12.0, 4.4 Hz, 1H), 2.62 (dd, J = 13.2, 3.6 Hz, 1H), 2.56−1.20 (m, 23H), 1.10 (d, J = 6.8 Hz, 3H), 0.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.03, 152.01 (d, J = 295.7 Hz), 147.34, 142.20, 133.38, 125.02, 122.12, 121.89 (d, J = 5.9 Hz), 117.36, 113.03, 71.65, 67.00, 59.73, 58.51, 50.22, 45.71, 43.01, 35.45, 32.32, 31.27, 29.70, 28.89, 23.71, 23.51, 21.54, 17.23; ^{19}F NMR (376 MHz, $CDCl_3$, $CFCl_3$ as internal) δ −119.51 (d, J = 32.0 Hz); IR ($CHCl_3$, cm^{-1}) 3601, 2919, 2849, 1655, 1455, 1314, 1214, 1038; UV (EtOH) λ_{max} 263 nm (ϵ 14 900); HRMS *m/z* (M^+) calcd 492.2710 for $C_{28}H_{41}FO_4S$, found 492.2720.

Competition Assays. Competition assays were performed with homogenates of COS-1 cells transfected with the human VDR expression plasmid. The homogenates were incubated with 1 nM [^{3}H]1,25D_3, in the absence or presence of 0.2−20 nM competitor (1,25D_3 or analogue). The VDR-bound ligand was separated from unbound by hydroxyapatite. RCIs were calculated by plotting the inverse of the percent of maximum binding of [^{3}H]1,25D_3 × 100 on the ordinate versus competitor concentration (nM) on the abscissa, dividing the slope of the linear plot for analogue binding by the slope of the linear plot for 1,25D_3 binding, and then multiplying by 100. By definition the RCI for 1,25D_3 is 100. The linear regression coefficients of the competition plots were 0.95−0.98.

Acknowledgment. We thank the NIH (Grants CA44530 to G.H.P. and T.W.K., CA52857 to H.B., and DK50583 to S.P.) for financial support and Prof. Henry Linschitz (Brandeis University) and Dr. Beth Lunney (Parke-Davis) for helpful discussions on hydrogen bonding.

References

(1) Holick, M. F. *Vitamin D: Molecular Biology, Physiology, and Clinical Applications*; Humana Press: Totowa, NJ, 1999.

(2) Feldman, D.; Glorieux, F.; Pike, J. W. *Vitamin D*; Academic Press: San Diego, CA, 1997.

(3) Binderup, L. International Bone Forum: Bone Metabolism. The Second International Forum on Calcified Tissue and Vitamin D and Its Analogues; Potts, J. T., Ogata, E., Eds.; 1993; pp 52−55.

(4) Mathiasen, I. S.; Colston, R. W.; Binderup, L. EB 1089, A Novel Vitamin D Analogue, Has Strong Antiproliferative and Differentiation-Inducing Effects on Cancer Cells. *J. Steroid Biochem. Mol. Biol.* **1993**, *46*, 365−371.

(5) Grue-Sorensen, G.; Hansen, C. M. New 1α,25-Dihydroxy Vitamin D$_3$ Analogues with Side Chains Attached to C-18: Synthesis and Biological Activity. *Bioorg. Med. Chem.* **1998**, *6*, 2029−2039.

(6) Uskokovic, M. R.; Studzinski, G. P.; Gardner, J. P.; Reddy, S. G.; Campbell, M. J.; Koeffler, H. P. The 16-Ene Vitamin D Analogues. *Curr. Pharm. Des.* **1997**, *3*, 99−123.

(7) Abe, J.; Nakano, T.; Nishii, Y.; Matsumoto, T.; Ogata, E.; Ikeda, K. A Novel Vitamin D$_3$ Analogue, 22-Oxa-1,25-Dihydroxyvitamin D$_3$, Inhibits the Growth of Human Breast Cancer in vitro and in vivo without Causing Hypercalcemia. *Endocrinology* **1991**, *129*, 832−837.

(8) Figadère, B.; Norman, A. W.; Henry, H. L.; Koeffler, H. P.; Zhou, J.-Y.; Okamura, W. H. Arocalciferols, Synthesis and Biological Evaluation of Aromatic Side-Chain Analogues of 1α,25-Dihydroxyvitamin D$_3$. *J. Med. Chem.* **1991**, *34*, 2452−2463.

(9) Zhu, G.-D.; Chen, Y.; Zhou, X.; Vanderwalle, M.; DeClercq, P. J.; Bouillon, R.; Verstuyf, A. Synthesis of CD-ring Modified 1α,25-Dihydroxy Vitamin D Analogues: C-ring Analogues. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1703−1708.

(10) Sabbe, K.; D'Hallewyn, C.; De Clercq, P.; Vandewalle, M. Synthesis of CD-ring Modified 1α,25-Dihydroxyvitamin D Analogues. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1697−1702.

(11) Paaren, H. E.; Mellon, W. S.; Schnoes, H. K.; DeLuca, H. F. Ring A-Stereoisomers of 1-Hydroxyvitamin D$_3$ and Their Relative Binding Affinities for the Intestinal 1α,25-Dihydroxyvitamin D$_3$ Receptor Protein. *Bioorg. Chem.* **1985**, *13*, 62−75.

(12) Muralidharan, K. R.; de Lera, A. R.; Isaeff, S. D.; Norman, A. W.; Okamura, W. H. Studies on the A-Ring Diastereomers of 1α,25-Dihydroxyvitamin D$_3$. *J. Org. Chem.* **1993**, *58*, 1895−1899.

(13) Reddy, S. Synthesis and Activity of 3-Epi-vitamin D$_3$ Compounds for Use in Treatment of Disorders Involving Aberrant Activity of Hyperproliferative Skin, Parathyroid, and Bone Cells. PCT Int. Patent Appl. WO 98 51,663; *Chem. Abstr.* **1999**, *130*, 25,229X.

(14) Perlman, K. L.; Sicinski, R. R.; Schnoes, H. K.; DeLuca, H. F. 1α,25-Dihydroxy-19-nor-vitamin D$_3$, A Novel Vitamin D-Related Compound with Potential Therapeutic Activity. *Tetrahedron Lett.* **1990**, *31*, 1823−1824.

(15) Kanzler, S.; Halkes, S.; Van de Velde, J. P.; Reischl, W. A Novel Class of Vitamin D Analogues: Synthesis and Preliminary Biological Evaluation. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1865−1868.

(16) Posner, G. H.; Dai, H. 1-(Hydroxyalkyl)-25-hydroxyvitamin D$_3$ Analogues of Calcitriol. 1. Synthesis. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1829−1834.

(17) Posner, G. H.; Lee, J. K.; White, M. C.; Hutchings, R. H.; Dai, H.; Kachinski, J. L.; Dolan, P.; Kensler, T. W. Antiproliferative Hybrid Analogues of 1α,25-Dihydroxyvitamin D$_3$: Design, Synthesis, and Preliminary Biological Evaluation. *J. Org. Chem.* **1997**, *62*, 3299−3314.

(18) Dauben, W. G.; Ollmann, R. R., Jr.; Funhoff, A. S.; Leung, S. S.; Norman, A. W.; Bishop, J. E. 25-Phosphorus Analogues of Vitamin D$_3$. *Tetrahedron Lett.* **1991**, *32*, 4643−4646.

(19) Kubodera, N.; Miyamoto, K.; Akiyama, M.; Matoumoto, M.; Mori, T. Synthetic Studies of Vitamin D Analogues. IX. Synthesis and Differentiation-Inducing Activity of 1α,25-Dihydroxy-22-oxa-, thia-, and azavitamin D$_3$. *Chem. Pharm. Bull.* **1991**, *39*, 3221−3224.

(20) Kawase, A.; Hirata, M.; Endo, K.; Kubodera, N. Synthesis of 1α,25-Dihydroxy-22-Thiavitamin D$_3$ and Related Analogues. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 279−282.

(21) Grue-Sorensen, G.; Binderup, E.; Binderup, L. Chemistry and Biology of 23-Oxa-aro- and 23-Thio-aro-vitamin D Analogues with High Antiproliferative and Low Calcemic Activity. In *Vitamin D: A Pleuripotent Steroid Hormone*; Norman, A. W., Bouillon, R., Thomasett, M., Eds.; Walter de Gruyter: Berlin, 1994; Poster No. 075, pp 75−78.

(22) Dai, H.; Posner, G. H. Synthetic Approaches to Vitamin D. *Synthesis* **1994**, 1383−1398.

(23) Posner, G. H.; Nelson, T. D.; Guyton, K. Z.; Kensler, T. W. New Vitamin D$_3$ Derivatives with Unexpected Antiproliferative Activity: 1-Hydroxymethyl-25-hydroxyvitamin D$_3$ Homologues. *J. Med. Chem.* **1992**, *35*, 3280−3287.

(24) Posner, G. H.; Lee, J. K.; Wang, Q.; Peleg, S.; Burke, M.; Brem, H.; Dolan, P.; Kensler, T. W. Noncalcemic, Antiproliferative, Transcriptionally Active, 24-Fluorinated Hybrid Analogues of the Hormone 1α,25-Dihydroxyvitamin D$_3$. Synthesis and Preliminary Biological Evaluation. *J. Med. Chem.* **1998**, *41*, 3008−3014.

(25) Differding, E.; Duthaler, R. O.; Krieger, A.; Riegg, G. M.; Schmit, C. Electrophilic Fluorinations with *N*-Fluorobenzenesulfonimide: Convenient Access to α-Fluoro- and α,α-Difluorophosphonates. *Synlett* **1991**, 395−396.

(26) McAtee, J. J.; Schinazi, R. F.; Liotta, D. C. A Completely Diastereoselective Electrophilic Fluorination of a Chiral, Noncarbohydrate Sugar Ring Precursor: Application to the Synthesis of Several Novel 2′-Fluoronucleosides. *J. Org. Chem.* **1998**, *63*, 2161−2167.

(27) Peleg, S.; Liu, Y. Y.; Reddy, S.; Horst, R. L.; White, M. C.; Posner, G. H. A 20-Epi Side Chain Restores Growth-Regulatory and Transcriptional Activities of an A Ring-Modified Hybrid Analogue of 1α,25-Dihydroxyvitamin D$_3$ without Increasing Its Affinity to the Vitamin D Receptor. *J. Cell. Biochem.* **1996**, *63*, 149−161.

(28) Mase, N.; Watanabe, Y.; Toru, T. Discrimination of Diastereotopic Sulfonyl Oxygens by Intramolecular Hydrogen Bonding: Stereoselective Hydrogenation of α-Sulfonyl Radicals. *Tetrahedron Lett.* **1999**, *40*, 2797−2800.

(29) Lange-Savage, G.; Berchtold, H.; Liesum, A.; Budt, K.-H.; Peyman, A.; Knolle, J.; Sedlacek, J.; Fabry, M.; Hilgenfeld, R. Structure of HOE/BAY 793 Complexed to Human Immunodeficiency Virus (HIV-1) Protease in Two Different Crystal Forms. *Eur. J. Biochem.* **1997**, *248*, 313−322.

(30) McGrath, M. E.; Klaus, J. L.; Barnes, M. G.; Brömme, D. Crystal Structure of Human Cathepsin K Complexed with a Potent Inhibitor. *Nature Struct. Biol.* **1997**, *4*, 105−109.

(31) Abraham, M. H.; Duce, P. P.; Prior, D. V. Hydrogen Bonding. Part 9. Solute Proton Donor and Proton Acceptor Scales for Use in Drug Design. *J. Chem. Soc., Perkin Trans. II* **1989**, 1355−1375.

(32) Gennari, C.; Gude, M.; Potenza, D.; Piarulli, U. Hydrogen-Bonding Donor/Acceptor Scales in β-Sulfonamidopeptides. *Chem. Eur. J.* **1998**, *4*, 1924−1931.

(33) Bouillon, R.; Okamura, W. H.; Norman, A. W. Structure−Function Relationships in the Vitamin D Endocrine System. *Endocrine Rev.* **1995**, *16*, 200−257.

(34) Posner, G. H.; Nelson, T. D.; Guyton, K. Z.; Kensler, T. W. New Vitamin D$_3$ Derivatives with Unexpected Antiproliferative Activity. *J. Med. Chem.* **1992**, *35*, 3280−3287.

JM990267C