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Calcitriol Derivatives with Two Different Side Chains at C-20. V. Potent Inhibitors of Mammary Carcinogenesis and Inducers of Leukemia Differentiation†

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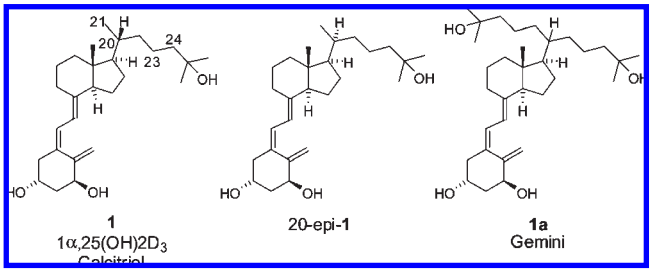
Calcitriol is implicated in many cellular functions including cellular growth and differentiation, thus explaining its antitumor effects. It was shown that gemini, the calcitriol derivative containing two side chain at C20, is also active in gene transcription with enhanced antitumor activity. We have now further optimized both the A-ring and the two side chains. The chemical structures of the resulting 18 geminis were correlated with biological activities. Those containing the 1α-fluoro A-ring are the least active. Those featuring 23-yne and 23(*E*) side-chains are generally more active in human breast cancer cell growth inhibition and human leukemia cell differentiation induction than their 23(*Z*) counterparts. On the basis of these evaluations, we selected as lead compound a 20(*R*) gemini, related to calcitriol in terms of it is A-ring, where one side chain was modified by introduction of a 23-yne function and replacement of the geminal methyl groups with trifluoromethyl groups, the other created by extension of C21 with a 3-hydroxy-3-trideuteromethyl-4,4,4-trideutero-butyl moiety.

Introduction

Gemini is the cumulative term for vitamin D analogues with two side chains emanating at C-20. In the first generation of this compound category, both side chains were identical as in **1a**. The arrangement comprises the unaltered chain of 1α,25(OH)$_2$D$_3$ (**1**) and a duplicate thereof as an extension of the methyl group 21.[1] From a historical viewpoint, it was argued that 20-epi-**1** exhibited transcriptional activities that were some 200−5000 times higher than the "natural" counterpart;[2−4] therefore, a biologically active derivative featuring two side chains was a tenable proposition. The presence of two side chains in one molecule raised the prospect of enhanced gene transactivation but, on the other hand, it dimmed the ability for such a compound to function as a ligand as it might overwhelm the space allotment provided by the VDR[a] with concomitant loss of receptor affinity.[5] Even if binding would occur, there was no guarantee for induction of the specific conformational change in the receptor essential for transcriptional activity.



A number of important discoveries were made in subsequent studies. Most significantly, gene transcription of gemini was demonstrated[1,6] and the ligand binding pocket was shown to be sufficiently malleable to allow the ligand to determine the conformation of the LBD suitable for its accommodation.[7] The ligand-dependent conformation of the LBD was investigated, and access to a channel that can accommodate the second side chain of gemini was discovered.[7,8] Molecular dynamics simulations, likewise, confirmed that the additional side chain, tantamount to a 25% increase in volume, could be domiciliated by minor reorganizations of some 30 amino acids and major realignments of several others without disturbing the overall structure of the LBD.[9,10] In this arrangement, one of the gemini side chains assumes the same position as the one of the natural ligand **1**, while the other has actually two spatial opportunities for residence.[11]

It is further perceived that two distinct receptors, the nuclear VDR and the membrane VDR, recognize different shapes of the conformationally flexible **1** to elicit gene transcriptions and rapid signal transduction pathways, respectively.[12] If the LBD is, to a certain extent, indiscriminate toward ligands of variegated chemical makeup, the prospect of designing specifically targeted ligands exists[7] and, with the

† Atomic coordinates for compounds **11S-b** and **2R-2** have been deposited with the Cambridge Crystallographic Data Center (deposition numbers 734110 and 734109, respectively). Copies of the CIF files can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK, via e-mail at deposit@ccdc.cam.ac.uk.

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[a] Abbreviations: VDR, vitamin-D receptor; LBD, ligand binding domain; INF, interferon; MLR, mixed lymphocyte reaction; DCM, dichloromethane; THF, tetrahydrofuran; TBAF, tetrabutylammonium fluoride; TMS, trimethylsilyl; TBSO, *t*-butyl-dimethylsilyloxy; TEMPO, 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical; PDC, pyridinium dichromate.

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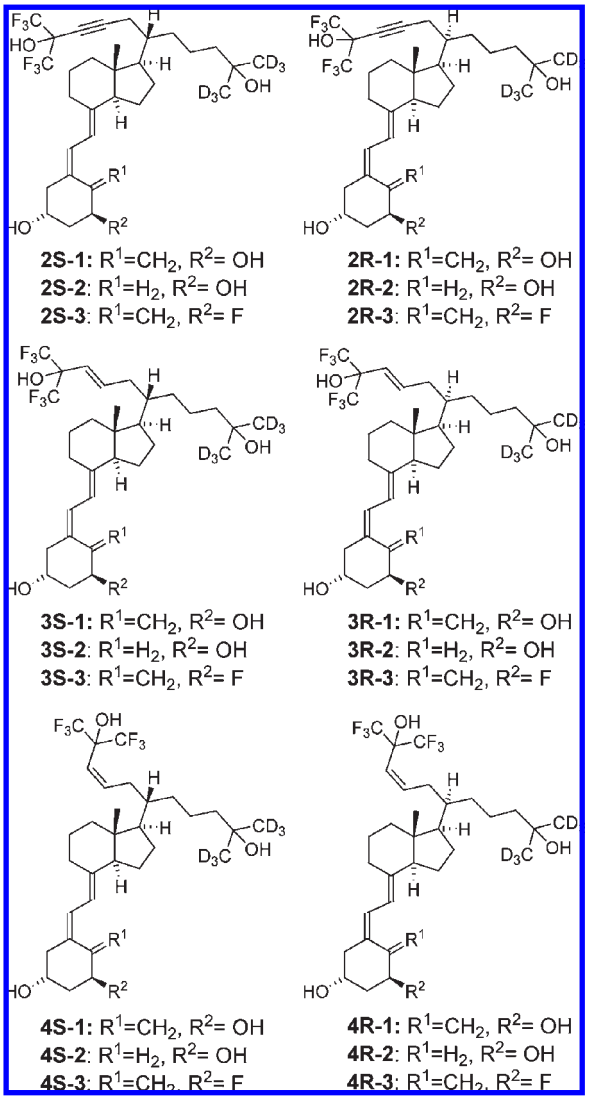
resulting conformational changes, targeted biochemical responses can be envisioned.

Complementary to the classical role of $1\alpha,25(OH)_2D_3$, a multitude of previously unexpected physiological and biochemical activities have come to light. Most prominent are the antitumor effects based on antiproliferation, prodifferentiation, and reduced angiogenesis. In view of the apparent VDR's promiscuity toward ligands, we incorporated into the gemini side chains those features that were previously established for the "one-side-chain" analogues as enhancements of biological activities. These augmentations are, at least in part, due to the prevention, or retardation, of biological degradation, most notably the degradative cascade initiated by 24-hydroxylation, and include replacement of the geminal methyl groups with trifluoromethyl entities and introduction of C23-unsaturation. This 24-hydroxylation, occurring preferentially at the pro-R side chain of **1a**,[13] entails higher drug dosages to increase blood calcium levels and to suppress INF-γ release in MLR.[14,15] Thus, the resulting new generation gemini maintain the side chain of **1** but feature a different second chain. In view of the physiological precariousness of vitamin D analogues, including gemini, we argued that a gemini's half-life could be extended by replacing the geminal methyl groups at the calcitriol side chain with trideuteromethyl moieties.[16] Such a modification was expected to alter, neither the propensity of this arm to assume the customary position within the VDR nor the kinetically controlled binding affinity, but contemporaneously, to prolong the intracellular life span due to increased lipophilicity and bond strengths. This lemma, together with the assurance of side chain similarity to the natural hormone, led to the expectation that gemini with deuterated methyl groups to be superior drugs in an in vivo environment. Fortunately, this proposition was subsequently substantiated[1,17−20] and is corroborated in the present study comprising 18 derivatives of **1a** as shown in Scheme 1.

Results and Discussion

Chemical Syntheses. The first part of the syntheses, illustrated in Schemes 2 and 3, is concerned with the preparation of the so-called CD-ring synthones and commences with the previously described methyl ester **5**,[21] which was treated with trideuteromethyl magnesium bromide in ether to afford alcohol **6**. An *ene*-reaction with paraformaldehyde and dimethylaluminum chloride in DCM gave the pair of diols **7*E*** and **7*Z***. Although this pair of epimers was readily separated by flash chromatography, it was hydrogenated as a mixture to furnish **8S** and **8R**, again easily separable by preparative HPLC. These two intermediates are the starting points for the entire cascade of the "S" and "R" series of the CD-ring systems. Subsequent TEMPO/chloramine-T mediated oxidations led to the aldehydes **9**, which were homologated to the alkynes **10**.[22] Conversion of the tertiary hydroxyl group to the TMS ether, prior to deprotonation with butyllithium and condensation with hexafluoracetone, gave higher yields of the diols **11S-a** and **11R-a** when compared to the use of the unprotected counterparts. Deprotection with fluorosilicic acid[23] furnished the triols **11S-b** and **11R-b**. The stereochemical assignments of the epimeric alcohols **8a** and **8b**, obtained after chromatographic separation (Scheme 2), was confirmed by a crystallographic analysis of **11S-b** whose ORTEP rendition is depicted in Figure 1. Subsequent oxidation with PDC in DCM gave **12S-a** and 12R-**a** and a following silylation of the tertiary hydroxyl groups led to the ketones **12S-b** and **12R-b**, respectively. The trimethylsilyloxy groups at the *gem*-trifluoromethyl positions, however, are of limited stability and partially lost upon purification of the reaction mixtures.

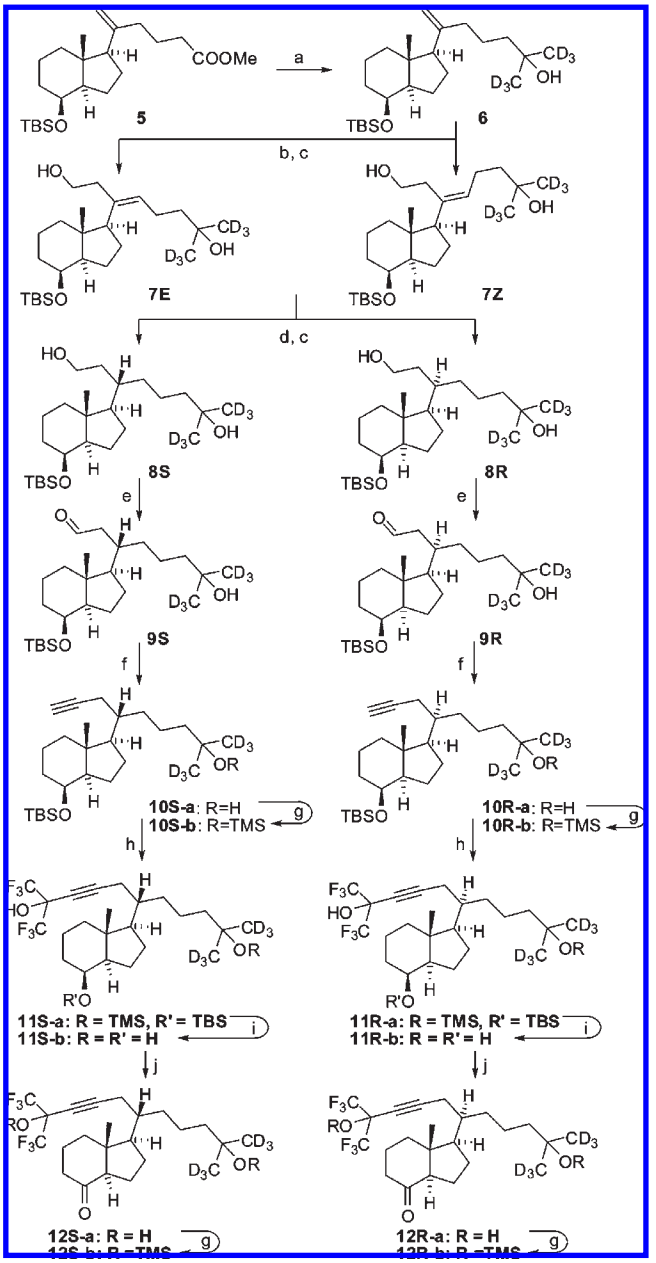
Scheme 1. Summary of Synthetic Targets



The intermediate triols **11S-b** and **11R-b** served as starting materials for the preparation of the alkene series of CD-ring synthones as shown in Scheme 3. Reduction with sodium bis(2-methoxyethoxy)aluminum hydride led to the (*E*)-alkene-triols **13S** and **13R**, whereas catalytic hydrogenation with Lindlar catalyst furnished the (*Z*)-alkene-triols **15S** and **15R**. The members of both pairs were oxidized with PDC to the ketones and then further protected by silylation to lead to the (*E*)-alkene-ketones **14S-b** and **14R-b** and the (*Z*)-alkene-ketones **16S-b** and **16-b**, respectively. The previous sequence, comprising oxidation at C8 and silylation of the tertiary hydroxyl groups, converted the triol pairs **13** and **15** to the protected ketone pairs **14S-b**/**14R-b** and **16S-b**/**16R-b**, which served as suitable coupling partners with the A-ring synthones.

The second phase of the synthesis included the coupling reactions of the CD-ring moieties with three different A-ring synthones as depicted in Scheme 4. The three A-rings, in the form of the allyldiphenylphosphane oxides **17**,[24−26] **18**,[27−29]

Scheme 2[a]



[a] Reagents and conditions: (a) CD_3MgI, ether; (b) $(CH_2O)_n$, Me_2AlCl; (c) chromatography, (d) PtO_2-C, EtOAc; (e) TEMPO, chloramine-T, DCM, buffer; (f) $N_2CHP(O)(OMe)_2$, MeOH, K_2CO_3; (g) TMS-imidazole, cyclohexane; (h) BuLi, THF, hexafluoroacetone; (i) fluorosilicic acid, AcCN; (j) PDC, DCM.

and **19**,[30−32] were used in Wittig−Horner reactions with the six CD-ring units **12S-b**, **14S-b**, **16S-b**, and their (*R*)-counterparts, which, after deprotection with TBAF, afforded 18 combinations as final products ranging from **2S-1** to **4R-3** (Scheme 4). The crystal structure of one of them (**2R-2**) is shown in Figure 2. While the crystal structure of **11S-b** (Figure 1) corroborated the configurational assignments in the 20S series, the structure of **2R-2** authenticates the stereochemical veracity of the 20R series.

Biological Studies. It became apparent that the side chain modification, the resulting configurational duality at C20, and the nature of the A-ring exert different biological responses. In a recent study with nondeuterated gemini, the

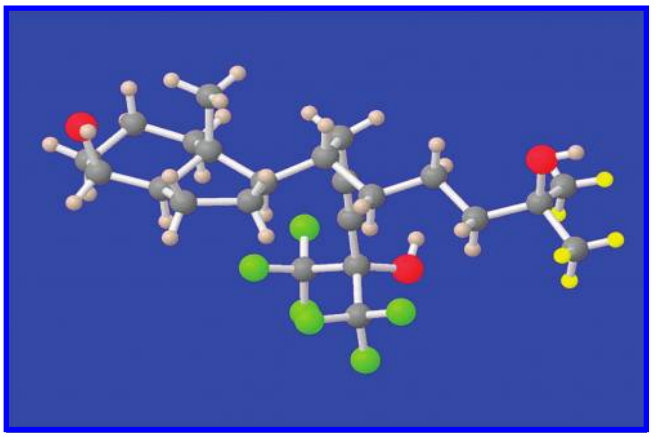
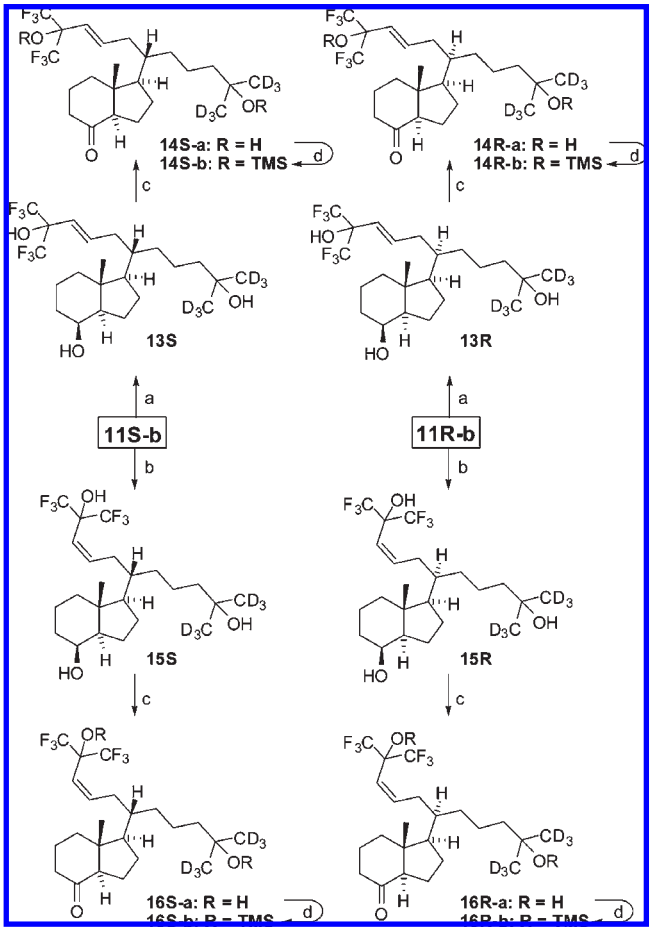


Figure 1. ORTEP drawing of **11S-b**.

Scheme 3[a]



[a] Reagents and conditions: (a) sodium bis(2-methoxyethoxy)-aluminum hydride, toluene; (b) Lindlar catalyst, H_2, EtOH; (c) PDC, DCM; (d) TMS-imidazole, THF.

analogue of **2S-1** was preferred and suggested gemini to modulate the expression and activity of proteins associated in cancer cell proliferation by inhibition of the Akt-mTOR pathway.[33] The effect, generated by introduction of deuterium, was underscored when **2S-2** was compared with the analogous, nondeuterated, epimeric pair **2S-2** and **2R-2** in the mouse MC-26 colon cancer model.[19] While the nondeuterated analogue of **2R-2** exerted little effect, the epimeric nondeuterated analogue of **2S-2** caused a significant

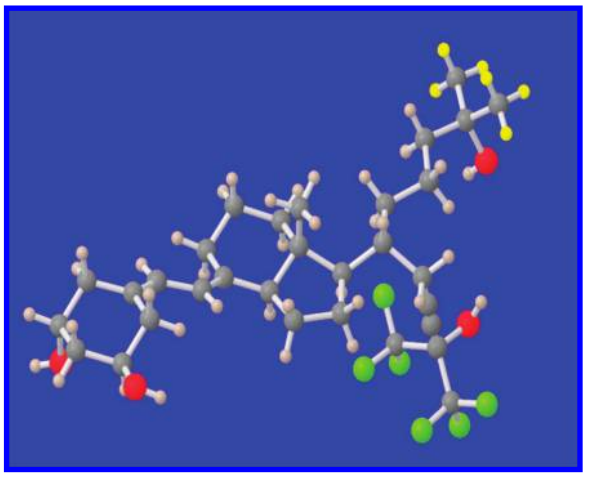
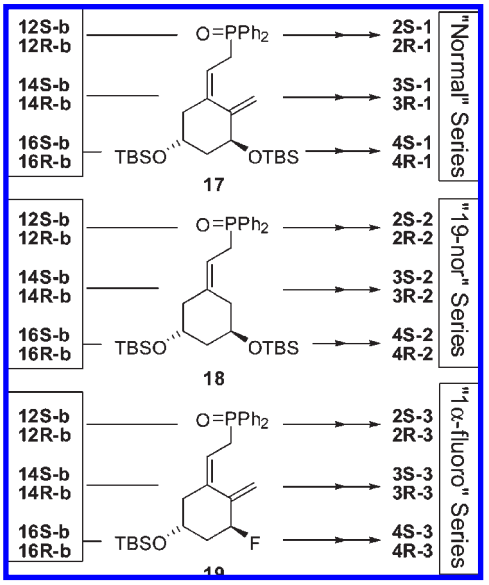


Figure 2. ORTEP drawing of **2R-2**.

Scheme 4. Assembly of Target Compounds **2S-1** to **4R-3**



reduction of colon tumor growth and tumor weight when administered at equal concentrations. The replacement of the hydrogen atom at the geminal methyl groups with deuterium, as in **2S-2**, enhanced the antitumor effect 10-fold. This remarkable C20 epimeric effect was also observed in the alteration of VDR-dependent monocytic differentiation in human leukemia cells[34] and in the present study of MCF10CA1a cell proliferation, but, surprisingly, it was largely unpronounced in the gemini series containing the 23-yne side chain. Different antitumor activities among epimers are somewhat remarkable, as it is generally contended that they assert their antiproliferative activity as ligands inside the LBD of the VDR. If a certain epimer of a given pair is established as a superior ligand capable to engender an antitumor effect, one would expect this bias to persevere in all antitumor responses. In view of the huge difference in antiproliferative effects between **1** and epi-**1**, as a result of disparate LBD conformations, different antineoplastic responses of two C20-epimeric geminis are not surprising. The observation that the partners of such an epimeric pair actually function differently, much like tailor-made entities for very specific antiproliferative activities, is unexpected and warrants further exploration.

Table 1. IC_{50} Values of Gemini Vitamin D Analogues in MCF10CA1a Human Breast Cancer Cells[a]

compd	IC_{50} (nM)	compd	IC_{50} (nM)
1	3.3		
2S-1	0.062	**2R-1**	0.053
2S-2	0.12	**2R-2**	0.19
2S-3	0.56	**2R-3**	1.6
3S-1	0.33	**3R-1**	0.13
3S-2	0.008	**3R-2**	0.23
3S-3	0.18	**3R-3**	2.3
4S-1	1.6	**4R-1**	0.56
4S-2	3.2	**4R-2**	0.43
4S-3	> 10	**4R-3**	6.9

[a] MCF10CA1a cells were incubated with gemini at concentrations of 0.001, 0.01, 0.1, 1, 10 nM in 5% horse serum DMEM/F12 medium for 3 days. IC_{50} values were determined using TableCurve 2D software (version 5.01, Systat).

We now report the effects of gemini on cell proliferation of MCF10CA1a human breast cancer cells and on differentiation of NB4 human promyelocytic leukemia cells. The current study centers on the gemini pairs **2**, **3**, and **4**, formal derivatives of **1** (**2S**, **3S**, and **4S**, left column in Scheme 1) and 20-epi-**1** (**2R**, **3,R** and **4R**, right column in Scheme 1), respectively. They feature the two traditional six-carbon chains of gemini (**1a**); the significant differences in a comparison to **1a**, however, are manifold, i.e., the inequality of the two chains, the replacement of the geminal methyl groups of calcitriol's "natural chain" by deuteromethyl moieties, and the transmutation of the other to incorporate geminal trifluoromethyl groups, and 23-yne, 23(*E*) and 23(*Z*)-ene unsaturations. To continue the theme of pharmacophoric periodicity, we also commuted the "natural" 1-hydroxy A-ring part to 19-nor and 1α-fluoro analogues. In the designations used, the first letter refers to the unsaturation of the side chain, e.g., **2** for 23-yne, **3** for 23(*E*)-ene, and **4** for 23(*Z*)-ene. The symbols R and S refer to the absolute configuration at C20 and the extensions -1, -2, and -3 refer to the A-ring characteristics, i.e., 1-hydroxy or "normal", 19-nor, and 1α-fluoro arrangements, respectively. As per example, **2S-2** has an alkyne side chain, the configuration at C20 is (*S*), and the A-ring portion is of the 19-nor type.

Gemini-type compounds were shown to be more active in inhibiting cell proliferation of breast-cancer cells than **1**,[35,36] and in BMP/Smad-specific signaling in human breast epithelial cells.[37] In preclinical animal studies, **2S-2** and **2R-2** prevented estrogen receptor (ER)-positive mammary tumorigenesis induced by *N*-methyl-*N*-nitrosourea in rats.[36,15] In addition, **2R-2** exhibited significant tumor growth suppression in the ER-negative MCF10DCIS.com xenograft model without hypercalcemic toxicity.[38] A mode of action study suggested the inhibitory effect of **2R-2** to be associated with an increase of cyclin-dependent kinase inhibitor p21 and the insulin-like growth-factor binding-protein 3 in both animal models. Spina et al. also reported that **2S-2** significantly reduced tumor growth of mouse colorectal cancer cells in BALB/c mice[9] and inhibited the invasive spread of the tumor into the surrounding muscle.[17]

We first studied the inhibitory effect of gemini on MCF10CA1a cell proliferation. The biological activities in cell growth inhibition are compared in terms of IC_{50} values and illustrated in Table 1. Most geminis are superior inhibitors of cell growth when compared to **1**, the naturally occurring 1α,25$(OH)_2D_3$, and significant differences ensue as a result of changes in A-rings, C20 configuration, and side

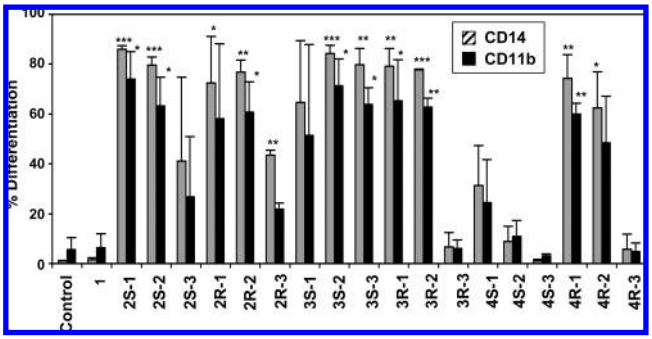


Figure 3. Differentiation induction of NB4 leukemia cell line by analysis of differentiated cell surface markers CD14 and CD11b. Two independent experiments were performed and combined, and values shown are averages ± SD. Statistical significances between **1** and the geminis were evaluated using Student's *t* test (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).

chain unsaturation. Those containing the 1α-fluoro A-rings (rows 4, 7, and 10) exerted relatively weak activities; in general, gemini featuring an alkyne side-chain (rows 2−4) or the 23(*E*) function (rows 5−7), inhibited MCF10CA1a cell proliferation most effectively.

In view of the well-known ability of vitamin D as an inducer of cell differentiation, we investigated the gemini's potential as differentiation inducers in NB4 human leukemia cells by measuring the induction of monocyte cell-surface markers CD11b and CD14. In general, gemini induced NB4 cell-differentiation stronger than **1**. Conforming to the trend observed in growth inhibition of breast cancer cells, the 1α-fluoro analogues were less active in inducing cell differentiation markers. Those containing the 1-hydroxy A-rings and the 19-nor A-rings exerted similar effects. The 23(*Z*)-ene side chains were generally less active than those with the 23-yne and 23(*E*)-ene chains, as illustrated in Figure 3. While the C20 epimeric effect was not perceivable among members containing the 23-yne or 23(*E*)-ene side chain, the differentiation was markedly enhanced in the 20R-series of those containing the 23(*Z*)-ene chain (**4R-1**, **4R-2**, and **4R-3** versus their *S*-counterparts).

Conclusion

In summary, we have synthesized 18 closely related geminis. The structural features incorporated into these molecules comprise established lead optimizations including side chain unsaturations, geminal trifluoromethyl and trideuteromethyl functions, A-ring variations, and duality due to C20 diastereotopicity. The resulting plexus affords an insight into the diverse structural requirements for specific biological activities. Compounds related to 1-fluoro-1-desoxy-calcitriol were less active than those containing the A-ring of calcitriol or 19-nor-calcitriol based on all parameters evaluated. As judged on the basis of IC_{50} values in MCF10CA1a human breast cancer cells, compounds containing the 23-yne and 23(*E*)-ene side chains were more potent than those featuring the *Z*-alkene chains. Members of the 23-yne category showed little differences between the C20 epimers; members of the 23(*E*)-ene category, however, were generally more active in the 20S series, while those in the 23(*Z*)-ene category were more active in the 20R series. This preference of the 20S configuration in the 23(*E*)-ene category is reflected in the extraordinary activity of **3S-2**, where the *E*-alkene chain gives rise to a compound that surpasses the alkyne counterpart. The activity profile associated with the nature of the A-rings was generally upheld in the study of induction potentials of monocyte cell surface markers CD11b and CD14. The C20 epimeric effect was only discernible among members containing the 23(*Z*) side chain, where the *20*(*R*) epimers were profoundly more active. Most significantly, however, the 20S epimers were more active than the 20R counterparts in the colon cancer models, while the C20 epimeric effect among members containing the 23-yne side chain was unpronounced in the present study of MCF10CA1a cell proliferation. Guided by the notion that this C20 epimeric effect was minimally expressed in gemini containing the 23-yne side chain, we focused our attention on a member of that category with the hope to select a compound with a broader spectrum of anticancer activities.

Experimental Section

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded at on a Varian 400 MHz spectrometer. The relatively long relaxation times of ^{13}C at the trideuteromethyl positions and the multiplicity due to their spin coupling to deuterium renders these ^{13}C resonances difficult to observe. Mass spectra were recorded on Waters ZQ (low resolution) and Bruker APEX II spectrometers (high resolution). Crystallographic data were obtained on a Bruker-Nonius Kappa CCD diffractometer. TLC was performed on silica gel GF_{254} plates (Merck), flash chromatography employed 40−65 μ silica gel and for preparative column chromatography 15−20 μ silica gel was used. The trimethylsilyl groups at the *gem*-trifluoromethyl carbinol position in the ketones **12**, **14**, and **16** are unstable and cause small losses of the TMS groups during purification. Further losses of the TMS groups occur during the quench of the coupling reactions with the A-rings, and after extractive and chromatographic workup, these losses are almost complete so that the TBAF treatments commence with partially deprotected products. Progress of deprotection of the final condensation products was monitored by TLC using 1:19 and 1:9 EtOAc−hexane, 1:1 EtOAc−hexane, and EtOAc were the mobile phases for the detection of the final materials. Detection was by UV light and/or phosphomolybdic acid spray. Preparative HPLC was performed on a 2" × 18" 15−20 μ silica YMC column using a flow rate of 100 mL/min and RI-detection. All final materials were of at least 95% purity; the major contaminants of noncrystalline materials were limited to solvent traces. Elemental analyses of the final materials are supplied in the Supporting Information. Solutions were dried with sodium sulfate unless specified otherwise.

6-[(1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-7a-methyl-octahydro-inden-1-yl]-1,1,1-trideutero-2-trideuteromethyl-hept-6-en-2-ol (6). A solution of ester **5** (18.92 g, 47.94 mmol) in ether (330 mL) was cooled in an ice-bath and a 1 M solution of deuteromethylmagnesium iodide in ether (130 mL) was added dropwise. Stirring was continued at ambient temperature for 2 h, the soln was cooled again in an ice bath, and a sat. ammonium chloride solution (100 mL) was added dropwise followed by water (150 mL) to dissolve the white precipitate present. The aqueous layer was re-extracted with ether (30 mL), and the combined ether layers were washed with 1:4 sat. ammonium chloride solution−water (100 mL) and then dried ($MgSO_4$), filtered, and evaporated. The residue was flash-chromatographed on silica gel using hexane → 1:19 EtOAc−hexane as mobile phase to afford **6** as a colorless oil (19.2 g, 100%); TLC (1:3 EtOAc−hexane) R_f 0.58; $[\alpha]_D^{28}$ +22.1 (c 0.4, methanol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (br s, 3 H), 0.02 (br s, 3 H), 0.80 (s, 3 H), 0.89 (s, 9 H), 1.17 (td, J = 13.5, 3.4 Hz, 1 H), 1.32−1.87 (m, 15 H), 1.97−2.09 (m, 3 H), 3.99−4.05 (m, 1 H), 4.78 (s, 1 H), 4.89 (s, 1 H). LRMS-EI(+) *m*/*z* 400 (12, M^+), 382 (80, M-H_2O), 382 (42, M-H_2O-CH_3). HRMS-ES(+) calcd for $C_{24}H_{40}D_6O_2Si$ (M + H)1^+ 401.3717, found 401.3713. Calcd for $C_{24}H_{40}D_6O_2Si$ (M + Na)1^+ 423.3536, found 423.3535.

(*E*)-3-[(1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyldimethyl-silanyloxy)-7a-methyl-octahydro-inden-1-yl]-8,8,8-trideutero-7-trideuteromethyl-oct-3-ene-1,7-diol (7*E*). A mixture of **6** (19.2 g, 48 mmol), paraformaldehyde (1.72 g, 57 mmol), and DCM (160 mL) was stirred under nitrogen for 10 min, cooled to −20 °C, and a 1 M dimethylaluminum chloride solution in hexane (122 mL) was added dropwise within 15 min. The mixture was then stirred in an ice bath for 1 h to complete the reaction (TLC, 1:1 EtOAc−hexane), cooled again to −20 °C, water (125 mL) was added dropwise, causing the temperature to rise to 10 °C, and then transferred to a separatory funnel with ether washes (2 × 30 mL). The milky soln was allowed to separate; the aqueous layer was extracted with ether (3 × 100 mL), the combined ether layers were washed with dilute pH 7 phosphate buffer (50 mL), dried, and evaporated to an oily residue. This material was chromatographed on a silica gel column using 1:9 → 1:4 → 1:1 EtOAc−hexane to yield **7*E*** as a major geometric isomer that was further purified by fractional crystallization (13.34 g). A second chromatography of the mixture fractions and the mother liquors gave an additional 1.67 g of crystalline product (total yield 72.6%). The *E*-geometry for **7*E*** was assigned by default based on the ^{1}H NMR NOE difference observed for the **7*Z*** isomer; TLC (1:1 EtOAc−hexane); R_f 0.27; $[\alpha]_D^{30}$ +14.4 (c 0.5, methanol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 3 H), 0.02 (s, 3 H), 0.79 (s, 3 H), 0.89 (s, 9 H), 1.12 (td, J = 12.6, 3.3 Hz, 1 H), 1.31−1.49 (m, 6 H), 1.53 (t, J = 8.1 Hz, 2 H), 1.58−1.84 (m, 6 H), 2.03 (t, J = 9.2 Hz, 1 H), 2.11−2.28 (m, 3 H), 2.54 (dt, J = 13.3, 7.5 Hz, 1 H), 3.61 (t, J = 7.0 Hz, 2 H), 3.98−4.06 (m, 1 H), 5.37 (t, J = 7.0 Hz, 1 H). LRMS-EI(+) m/z 430 (5, M+), 412 (62, M-H_2O), 394 (78, M-H_2O-CD_3). HRMS-ES(+) calcd for $C_{25}H_{42}D_6O_3Si$ 431.3822 (M + H); found 431.3818. Anal. calcd for $C_{25}H_{42}D_6O_3Si$: C, 69.71; found C, 69.70.

(*Z*)-3-[(1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyldimethyl-silanyloxy)-7a-methyl-octahydro-inden-1-yl]-8,8,8-trideutero-7-trideuteromethyl-oct-3-ene-1,7-diol (7*Z*). The chromatographic band preceding the major one, as described above, was rechromatographed to give the *Z*-isomer (1.2 g); TLC (1:1 EtOAc−hexane); R_f 0.36; $[\alpha]_D^{24}$ −43.6 (c 0.3, methanol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 3 H), 0.01 (s, 3 H), 0.86 (s, 3 H), 0.88 (s, 9 H), 1.09 (td, J = 12.6, 3.7 Hz, 1 H), 1.29−1.86 (m, 14 H), 1.98−2.43 (m, 4 H), 2.53 (t, J = 9.0 Hz, 1 H), 3.40−3.53 (m, 1 H), 3.57−3.70 (m, 1 H), 3.99−4.08 (m, 1 H), 5.35 (dd, J = 8.2, 5.7 Hz, 1 H). LRMS-EI(+) m/z 430 (9, M^+), 412 (92, M-H_2O). ^{13}C NMR (300 MHz, $CDCl_3$) δ 0.01, 0.38, 21.01, 22.76, 23.17, 28.71, 28.80, 28.93, 30.96, 39.75, 43.28, 44.37, 49.00, 51.36, 56.66, 57.50, 67.81, 74.38, 75.82, 81.72, 82.14, 82.58, 136.31, 139.81. HRMS-ES(+) calcd for $C_{25}H_{42}D_6O_3Si$ 453.3641(M + Na)1$^+$, found 453.3640. Anal. calcd for $C_{25}H_{42}D_6O_3Si$: C, 69.71; found C, 69.64.

(*S*)-3-[(1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-7a-methyl-octahydro-inden-1-yl]-8,8,8-trideutero-7-trideuteromethyl-octane-1,7-diol (8S, 047-094-4-5). A mixture of **7*E*** and **7*Z*** (16.59 g, 38.5 mmol), 5% PtO_2−C (2.2 g), and EtOAc (250 mL) was hydrogenated at hydrostatic pressure (500 mm) overnight; the catalyst was filtered off (celite), washed with EtOAc, and the filtrate and washes evaporated to a thick syrupy material (16.34 g) then prepurified on a silica gel column (50 mm × 130 mm) using 1:4 → 1:1 EtOAc−hexane. The resulting prepurified epimeric mixture (14.6 g) was resolved by preparative HPLC using 2:1 EtOAc−hexane as mobile phase and operating at 100 mL/min in 9 consecutive runs. The peak with the elution maximum of 3.4 L was evaporated to give **8S** as a sticky syrup (total quantity of 6.45 g). TLC (1:1 EtOAc−hexane); R_f 0.28; $[\alpha]_D^{32}$ +34.8 (c 0.83, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.03 (s, 3 H), −0.02 (s, 3 H), 0.86 (s, 9 H), 0.89 (s, 3 H), 1.00−1.85 (m, 22 H), 1.93 (d, J = 12.1 Hz, 1 H), 3.53−3.67 (m, 2 H), 3.94−4.02 (m, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$) δ −5.21, −4.83, 13.87, 17.62, 17.96, 19.74, 22.82, 25.75, 26.57, 31.63, 34.09, 34.39, 35.98, 40.44, 42.15, 44.21, 52.98, 53.45, 60.44, 69.32, 70.67. LRMS-EI(+) m/z 414 (18, M-H_2O)$^+$, 396 (21, M-H_2O-CD_3). HRMS-ES(+) calcd for $C_{25}H_{44}D_6O_3Si$: 455.3798 (M + Na)1$^+$; found 455.3795.

(*R*)-3-[(1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-7a-methyl-octahydro-inden-1-yl]-8,8,8-trideutero-7-trideuteromethyl-octane-1,7-diol (8R). The peak of the chromatograms described above, with the elution maximum of 4.2 L, was also evaporated to give **8R** (total quantity of 6.24 g); TLC (1:1 EtOAc−hexane); R_f 0.25; $[\alpha]_D^{30}$ +34.1 (c 0.57, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.01 (s, 3 H), 0.00 (s, 3 H), 0.88 (s, 9 H), 0.91 (s, 3 H), 1.13 (td, J = 12.8, 3.4 Hz, 1 H), 1.20−1.62 (m, 17 H), 1.62−1.72 (m, 2 H), 1.72−1.84 (m, 2 H), 1.84−1.91 (m, 1 H), 3.56−3.71 (m, 2 H), 3.99 (br s, 1 H). LRMS-ES(+) m/z 415 (100, M-17)$^+$. HRMS-ES(+) calcd for $C_{25}H_{44}D_6O_3Si$: 455.3798 [M + Na]1$^+$; found 455.3797.

(*S*)-3-[(1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy-7a-methyl-octahydro-inden-1-yl]-8,8,8-trideutero-7-hydroxy-7-trideuteromethyl-octanal (9S). A mixture of **8S** (1.13 g, 2.61 mmol), DCM (20 mL), TEMPO (84 mg), and tetrabutylammonium chloride hydrate (146 mg), dissolved in 0.5 M potassium hydrogen carbonate soln was stirred at ambient temperature and chloramine-T (1.46 g) was added and vigorous stirring continued for 1.5 h. Production of the aldehyde was followed by TLC (1:1 EtOAc−hexane, R_f 0.84). The mixture was diluted with DCM (50 mL); the organic layer was washed with water (25 mL), dried, and evaporated. The resulting residue was triturated with hexane, and the suspension filtered onto a silica gel column. Elution with 1:39 → 1:9 → 1:4 EtOAc−hexane furnished pure **9S** (1.05 g, 93.4%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 3 H), 0.01 (s, 3 H), 0.89 (s, 9 H), 0.95 (s, 3 H), 1.08−1.19 (m, 1 H), 1.19−.47 (m, 13 H), 1.51−1.61 (m, 1 H), 1.62−1.72 (m, 1 H), 1.72−1.87 (m, 3 H), 1.91−2.04 (m, 1 H), 2.42 (ddd, J = 16.7, 7.7, 3.0 Hz, 1 H), 2.59 (ddd, J = 16.7, 4.3, 1.8 Hz, 1 H), 3.98−4.02 (m, 1 H), 9.78 (dd, J = 3.0, 1.8 Hz, 1 H). LRMS-EI(+) m/z 355 (73, M-H_2O−C_4H_9); 354 (100, M-HOD-C_4H_9). HRMS-ES(+) calcd for $C_{25}H_{42}D_6O_3Si$: 453.3641 (M + Na)1$^+$; found 453.3649.

(*R*)-3-[(1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-7a-methyl-octahydro-inden-1-yl]-8,8,8-trideutero-7-hydroxy-7-trideuteromethyl-octanal (9R). To a soln of diol **8R** (6.24 g, 14.4 mmol) in DCM (110 mL) was added 0.5 M aqueous potassium hydrogen carbonate soln containing tetrabutylammonium chloride hydrate and TEMPO (0.44 g, 2.8 mmol). The two-phase system was stirred vigorously, and chloramine-T (8.0 g, 28.6 mmol) was added. The conversion to the aldehyde **9R** was complete after 1 h as monitored by TLC (1:1 EtOAc−hexane, R_f 0.84). The mixture was diluted with DCM (100 mL), and the organic layer washed with water (50 mL), dried, and evaporated. The resulting residue was triturated with hexane; the resulting suspension was filtered onto a silica gel column and then eluted with 1:39 and 1:4 EtOAc−hexane. The fractions containing **9R** were pooled, evaporated, and taken up in methanol (55 mL) for the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.01 (s, 3 H), 0.01 (s, 3 H), 0.88 (s, 9 H), 0.95 (s, 3 H), 1.15 (td, J = 12.7, 3.1 Hz, 1 H), 1.21−1.45 (m, 12 H), 1.45−1.85 (m, 5 H), 1.90 (ddd, J = 12.3, 3.3, 3.1 Hz, 1 H), 2.06 (br s, 1 H), 2.31 (ddd, J = 16.3, 7.5, 3.0 Hz, 1 H), 2.44 (ddd, J = 16.3, 4.5, 1.8 Hz, 1 H), 3.97−4.02 (m, 1 H), 9.78 (dd, J = 3.0, 1.8 Hz, 1 H). LRMS-EI(+) m/z 430 (7, M^+), 412 (30, M-CD_3), 394 (79, M-CD_3-H_2O), 393 (95, M-CD_3-HOD). HRMS-ES(+) calcd for $C_{25}H_{42}D_6O_3Si$: 431.3822 (M + H)1$^+$; found 431.2916.

(*S*)-6-[(1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-7a-methyl-octahydro-inden-1-yl]-1,1,1-trideutero-2-trideuteromethyl-non-8-yn-2-ol (10S-a). A stirred soln of **9S** (1.35 g, 3.13 mmol), methanol (20 mL), and dimethyl diazomethylphosphonate (0.725 g, 4.83 mmol) was cooled in an ice bath and powdered potassium carbonate (0.705 mg, 5.1 mmol) was added. The mixture was stirred in the ice bath for 30 min and then at room temperature for 6 h. Reaction progress was monitored by TLC (1:4 EtOAc−hexane, R_f 0.19 → 0.42). The mixture was equilibrated with hexane (80 mL) and water (40 mL), the aqueous layer was re-extracted with hexane (20 mL), and the combined extracts were washed with water

(30 mL) and brine (10 mL), dried, and evaporated. The resulting oily residue was chromatographed on a silica gel column using hexane → 1:19 → 1:9 EtOAc−hexane to lead to **10S-a** (1.14 g, 85%) as a colorless oil; $[\alpha]_D^{29}$ +33.3° (c 0.49, methanol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 3 H), 0.02 (s, 3 H), 0.89 (s, 9 H), 0.91 (br s, 3 H), 1.15−1.90 (m, 20 H), 1.93 (t, J = 2.2 Hz, 1 H), 2.22−2.46 (m, 2 H), 4.00 (br s, 1 H). ^{13}C NMR (300 MHz, $CDCl_3$) δ −5.18, −4.80, 13.83, 17.63, 17.99, 20.57, 20.78, 22.84, 25.76, 26.83, 31.83, 34.08, 34.32, 37.92, 40.13, 41.94, 44.06, 52.57, 52.85, 69.33, 69.63, 70.67, 82.88. LRMS-EI(+) m/z 351 (45, M-H_2O−C_4H_9); 295 (4, M-C_4H_9). HRMS-ES(+) calcd for $C_{26}H_{42}D_6O_2Si$: 449.3692 (M + Na)1$^+$; found 449.3696.

(1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-7a-methyl-1-((*S*)-6,6,6-trideutero-1-prop-2-ynyl-5-trideuteromethyl-5-trimethylsilanyloxy-hexyl)-octahydro-indene (10S-b). To a soln of **10S-a** (1.25 g, 2.93 mmol) in cyclohexane (20 mL) was added TMS-imidazole (2.0 mL, 13.6 mmol) and the mixture was allowed to stand overnight. The suspension was filtered and the filtrate chromatographed on silica gel; the column was eluted with hexane → 1:100 → 1:79 EtOAc−hexane to furnish **10R-a**; 1.28 g, 87.6%; TLC (1:19, EtOAc−hexane) R_f 0.68. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 3 H), 0.01 (s, 3 H), 0.11 (s, 9 H), 0.89 (s, 9 H), 0.91 (s, 3 H), 1.11−1.95 (m, 20 H), 2.28−2.41 (m, 2 H), 4.00 (br s, 1 H). ^{13}C NMR (300 MHz, $CDCl_3$) δ −5.14, −4.76, 2.65, 13.89, 17.69, 18.04, 20.58, 20.86, 22.91, 25.82, 26.86, 31.84, 34.39, 37.95, 40.17, 42.00, 44.87, 52.68, 52.91, 69.42, 69.54, 73.71, 83.02. LRMS-EI(+) m/z 367 (22, M-OTBS), 351 (28, M-C_4H_9-TMSOH). HRMS-EI(+) calcd for $C_{29}H_{50}D_6O_3Si_2$: 498.4189 (M$^+$); found 498.4203. Calcd for $C_{29}H_{50}D_6O_3Si_2$: 480.3772 (M-CD_3)$^+$; found 480.3788.

(*R*)-6-[(1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy-7a-methyl-octahydro-inden-1-yl]-1,1,1-trideutero-2-trideuteromethyl-non-8-yn-2-ol (10R-a). The stirred methanolic soln of **9R** obtained as described above was cooled in an ice bath and dimethyl diazomethylphosphonate (3.24 g, 21.6 mmol) was added, followed by powdered potassium carbonate (3.0 g, 21.6 mmol). The cooling bath was removed after 1 h and stirring continued for an additional 5 h. Reaction progress was monitored by TLC (1:1 EtOAc−hexane, R_f 0.72 → 0.86). The mixture was equilibrated with hexane (300 mL) and water (100 mL), the aqueous layer re-extracted with hexane (2 × 50 mL), and all extracts were evaporated. For analysis, a small portion was dissolved in hexane and chromatographed using hexane → 1:19 → 1: 9 EtOAc−hexane to furnish pure **10R-a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 3 H), 0.01 (s, 3 H), 0.89 (s, 9 H), 0.92 (s, 3 H), 1.13−1.77 (m, 17 H), 1.77−1.95 (m, 4 H), 2.10−2.18 (m, 1 H), 2.30−2.37 (m, 1 H), 3.95−4.06 (m, 1 H). LRMS-EI(+) m/z 408 (100, M + H−H_2O). HRMS-ES(+) calcd for $C_{26}H_{42}D_6O_2Si$: 449.3692 (M + Na)1$^+$; found 449.3692. The material was used without further purification in the next step.

(1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-7a-methyl-1-((*R*)-6,6,6-trideutero-1-prop-2-ynyl-5-trideuteromethyl-5-trimethylsilanyloxy-hexyl)-octahydro-indene (10R-b). The bulk of **10R-a**, together with the purified material described above, was dissolved in cyclohexane (80 mL) and TMS-imidazole (8 mL). After 4 h, the suspension was filtered onto a silica gel column, together with hexane washes, and the column was eluted with hexane → 1:79 EtOAc−hexane to give **10R-b** as a colorless oil (5.41 g, 75.3% from diol **8R**). ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.01 (s, 3 H), 0.00 (s, 3 H), 0.10 (s, 9 H), 0.88 (s, 9 H), 0.91 (s, 3 H), 1.12−1.45 (m, 11 H), 1.46−1.62 (m, 4 H), 1.62−1.72 (m, 1 H), 1.72−1.86 (m, 2 H), 1.88 (t, J = 2.5 Hz, 1 H), 1.92 (dt, J = 12.3, 2.8 Hz, 1 H), 2.12 (ddd, J = 16.9, 5.3, 2.6 Hz, 1 H), 2.32 (dt, J = 16.9, 3.0 Hz, 1 H), 3.93−4.03 (m, 1 H). ^{13}C NMR (300 MHz, $CDCl_3$) δ −5.10, −4.73, 2.65, 14.05, 17.75, 18.07, 20.74, 22.95, 25.86, 27.04, 31.52, 34.50, 38.63, 40.63, 42.11, 44.96, 53.03, 53.12, 68.93, 69.52, 73.72, 83.02. LRMS-ES(+) m/z 409 (35, M-TMSO), 295 (100, M-TMSO-TBS + H). HRMS-ES(+) calcd for $C_{29}H_{50}D_6O_3Si_2$: 521.4087 (M + Na)1$^+$; found 521.4088.

(*S*)-6-[(1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-7a-methyl-octahydro-inden-1-yl]-11,11,11-trideutero-1,1,1-trifluoro-10-trideuteromethyl-2-trifluoromethyl-10-trimethylsilyloxy-undec-3-yn-2-ol (11S-a). The condensation of **10S-b** (1.034 g, 2.07 mmol) with hexafluoroacetone was repeated as described below for the synthesis of **11R-a**. The crude product was purified by chromatography with hexane → 1:200 → 1:100 → 1:79 EtOAc−hexane as mobile phases to give **11S-a** as a colorless oil, 1.276 g, 92.7%. ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.007 (s, 3 H), −0.009 (s, 3 H), 0.11 (s, 9 H), 0.88 (s, 9 H), 0.91 (s, 3 H), 1.15−1.50 (m, 14 H), 1.63−1.89 (m, 4 H), 2.41 (dd, J = 17.4, 5.3 Hz, 1 H), 2.49 (m, J = 17.4, 4.0 Hz, 1 H), 3.49 (br s, 1 H), 3.96−4.03 (m, 1 H). ^{13}C NMR (300 MHz, $CDCl_3$) δ −5.15, −4.77, 2.58, 13.87, 14.14, 17.68, 18.04, 20.60, 20.89, 22.87, 25.81, 27.00, 31.62, 32.11, 34.30, 37.92, 40.18, 41.97, 44.66, 52.88, 53.09, 69.32, 70.47, 71.24, 73.95, 91.11, 121.13. LRMS-EI(+) m/z 664 (3, M+), 646 (48, M-H_2O), 607 (29, M-C_4H_9). HRMS-ES(+) calcd for $C_{32}H_{50}D_6O_3Si_2F6$: 687.3941 (M + Na)1$^+$; found 687.3937.

(*S*)-11,11,11-Trideutero-1,1,1-trifluoro-6-((1*R*,3a*R*,4*S*,7a*R*)-4-hydroxy-7a-methyl-octahydro-inden-1-yl]-10-trideuteromethyl-2-trifluoromethyl-undec-3-yne-2,10-diol (11S-b). A stirred soln of **11S-a** (0.406 g, 0.61 mmol) in acetonitrile (6 mL) was cooled in an ice bath and 25% aqueous fluorosilicic acid was added. Stirring was continued at ambient temperature for 4 h. The mixture was equilibrated with EtOAc (40 mL) and water (15 mL), the organic layer was washed with water (2 × 15 m) and 2:1 brine−satd sodium hydrogen carbonate soln (10 mL) and then dried and evaporated. The residue was chromatographed using 1:4 → 1:2 EtOAc−hexane as mobile phases to afford **11S-b** as a syrup that crystallized when treated with DCM−hexane. This material was recrystallized from the same solvent; TLC (1:19 methanol−DCM); R_f 0.25; (1:1 EtOAc−hexane); R_f 0.68; mp 132−3 °C; $[\alpha]_D^{25}$ +15.6 (c 0.72, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (s, 3 H), 1.09−1.55 (m, 16 H), 1.60−1.71 (m, 1 H), 1.74−1.96 (m, 4 H), 2.32 (dd, J = 17.4, 7.0 Hz, 1 H), 2.55 (dd, J = 17.4, 4.3 Hz, 1 H), 4.08 (br s, 1 H), 5.60 (s, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.60, 17.31, 20.07, 21.42, 22.26, 26.95, 32.15, 33.17, 38.46, 40.06, 41.77, 43.15, 52.45, 53.06, 69.28, 69.50, 70.61, 71.03, 71.91, 89.95, 121.41. LRMS-ES(+) m/z 478 (15, M+), 477 (100 M-H). HRMS-ES(+) calcd for $C_{23}H_{28}D_6O_3F6$: 501.2681 (M + Na)1$^+$; found 501.2680. Anal. calcd for $C_{23}H_{28}D_6F_6O_3$: C, 57.73; found 57.87. Roentgen diffraction analysis (Figure 1): $C_{23}H_{34}F_6O_3$, orthorhombic, space group $P2_12_12_1$ with unit cell dimensions of a = 6.8335(14), b = 18.386(4), c = 18.871(4) Å, volume 2371.0(8) Å^3 (Z = 4).

(*R*)-6-[(1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-7a-methyl-octahydro-inden-1-yl]-11,11,11-trideutero-1,1,1-trifluoro-10-trideuteromethyl-2-trifluoromethyl-10-trimethylsilyloxy-undec-3-yn-2-ol (11R-a). A three-neck flask equipped with a magnetic stirrer, an addition funnel in the center surrounded by a dry ice bath and topped by a dry ice condenser with a hexafluoroacetone inlet, and a Claisen adapter with nitrogen sweep connected to the exhaust slot of the hood and a rubber septum, was charged with **10R-b** (5.41 g, 10.8 mmol) and THF (31.13 g). The soln was immersed into a dry ice/acetone bath and a 1.6 M butyllithium soln in hexane (9 mL) was added dropwise over an 8 min period. Immediately after the addition, the dry ice condenser and the dry ice bath surrounding the addition funnel were filled dry ice and, after stirring for 5 min, hexafluoroacetone was condensed in. The condensate, ca. 1 mL, was then added to the reactor. The starting material was no longer detectable after 1.5 h (TLC, 1:19 EtOAc−hexane). The system was flushed with nitrogen and then pH 7 phosphate buffer (20 mL) was added, the stirred mixture allowed to reach room temperature, further diluted with hexane (50 mL), and transferred to a separatory funnel with a hexane rinse (25 mL).

The organic layer was washed with brine (15 mL), dried, and evaporated. From this oily residue, most of a self-condensation product derived from hexafluoroacetone could be removed by high-vacuum distillation at a bath temperature of 30−40 °C. For analysis, a small aliquot was purified on a silica gel column using hexane → 1:200 → 1:100 → 1: 79 EtOAc−hexane to furnish pure **11R-a**, TLC (cyclohexane, R_f 0.14). ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.01 (s, 3 H), 0.00 (s, 3 H), 0.10 (s, 6 H), 0.88 (s, 9 H), 0.92 (s, 3 H), 1.13 (td, J = 12.9, 3.0 Hz, 1 H), 1.18−1.46 (m, 15 H), 1.48−1.72 (m, 8 H), 1.72−1.87 (m, 3 H), 1.91 (d, J = 12.1 Hz, 1 H), 2.22 (dd, J = 17.4, 6.0 Hz, 1 H), 2.42 (dd, J = 17.4, 3.7 Hz, 1 H), 3.33 (br s, 1 H), 3.96−4.03 (m, 1 H). LRMS (ES(−) m/z 628 (38, M-H_2O-CD_3). HRMS-ES(+) calcd for $C_{32}H_{50}D_6F_6O_3Si_2$: 687.3941 (M + Na)1$^+$; found 687.3928.

(*R*)-11,11,11-Trideutero-1,1,1-trifluoro-6-((1*R*,3a*R*,4*S*,7a*R*)-4-hydroxy-7a-methyl-octahydro-inden-1-yl]-10-trideuteromethyl-2-trifluoromethyl-undec-3-yne-2,10-diol (11R-b). The bulk of the crude **11R-a**, together with the purified material described above, was dissolved in acetonitrile (100 mL), cooled in an ice bath, and a 25% aqueous fluorosilicic acid solution (24 mL) was added. The mixture was stirred in the ice bath for 5 min and then at room temperature for 5 h. The mixture was equilibrated with EtOAc (200 mL) and water (50 mL), the organic phase was washed with water (2 × 50 mL) and then 2:1 brine−sat. sodium hydrogen carbonate (50 mL), dried, and evaporated. This material was charged to a silica gel column and eluted with 1:4 → 1:2 EtOAc−hexane to yield **11R-b** as a colorless foam, 5.1 g, 98.6% from the acetylene **10R-b**; TLC (1:1, EtOAc−hexane, R_f 0.43); $[\alpha]_D^{26}$ +6.1 (c 0.70, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (s, 3 H), 1.09−1.70 (m, 13 H), 1.70−1.89 (m, 3 H), 1.93 (d, J = 12.7 Hz, 1 H), 2.18 (dd, J = 17.2, 6.3 Hz, 1 H), 2.41 (dd, J = 17.2, 3.3 Hz, 1 H), 3.38 (br s, 3 H), 4.08 (br s, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.60, 17.31, 20.07, 21.42, 22.26, 26.95, 32.15, 33.17, 38.46, 40.06, 41.77, 43.15, 52.45, 53.06, 69.28, 69.50, 70.61, 71.03, 71.91, 89.95, 121.41. ^{19}F NMR (376.31 MHz, $CDCl_3$) δ −78.12 (br s). HRMS-EI(+) calcd for $C_{23}H_{28}D_6O_3F_6$: 501.2681 (M + Na)1$^+$; found 501.2679.

(1*R*,3a*R*,7a*R*)-7a-Methyl-1-[(*S*)-6,6,6-trifluoro-5-hydroxy-1-(5,5,5-trideutero-4-hydroxy-4-trideuteromethyl-pentyl)-5-trifluoromethyl-hex-3ynyl]-octahydro-inden-4-one (12S-a). To a stirred soln of **11S-b** (0.239 mg, 0.500 mmol) in DCM (6.5 g) was added, in succession, celite (0.43 g) and PDC (0.83 g, 2.20 mmol). The suspension was diluted with ether (15 mL) after 7 h, stirred for 5 min, and applied to a silica gel plug. The eluate and ether washes were combined and evaporated to a colorless oil, which was allowed to crystallize. Recrystallization from DCM−hexane gave pure **12S-a**, 0.23 g, 96.5%; mp 176−177 °C; $[\alpha]_D^{26}$ −7.7 (c 0.44, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.64 (s, 3 H), 1.58 (s, 13 H), 1.83−2.11 (m, 4 H), 2.15−2.33 (m, 2 H), 2.39 (dd, J = 17.6, 5.9 Hz, 1 H), 2.48 (dd, J = 11.4, 7.7 Hz, 1 H), 2.57 (dd, J = 17.6, 3.7 Hz, 1 H), 5.67 (br s, 1 H). ^{19}F NMR (376.31 MHz, $CDCl_3$) δ −78.28 br s. LRMS(EI)(+) m/z 476 (7, M+). HRMS-EI calcd for $C_{23}H_{26}D_6O_3F_6$: 499.2524 (M + Na)1$^+$; found 499.2527. Anal. calcd for $C_{23}H_{26}D_6O_3F_6$: C, 57.97; found C, 57.92.

(1*R*,3a*R*,7a*R*)-7a-Methyl-1-[(*S*)-6,6,6-trifluoro-1-(5,5,5-trideutero-4-trideuteromethyl-4-trimethylsilanyloxy-pentyl)-5-trifluoromethyl-5-trimethylsilanyloxy-hex-3-ynyl]-octahydro-inden-4-one (12S-b). To a suspension of the ketone **12S-a** (0.22 g) in ether (3 mL) was added TMS-imidazole (0.3 mL), whereupon a soln was obtained. TLC (1:19 methanol−DCM and 1:39 EtOAc−hexane) confirmed the absence of educt and the conversion to **12S-b** after 1.5 h. The resulting suspension was filtered onto a flash column, which was then eluted with hexane → 1:39 EtOAc−hexane eluting **12S-b** (0.229 g, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.11 (s, 9 H), 0.29 (s, 9 H), 0.65 (s, 3 H), 1.05−1.48 (m, 8 H), 1.63−2.14 (m, 8 H), 2.14−2.40 (m, 2 H), 2.51 (br s, 3 H). LRMS(EI)(+) m/z 602 (68, M-CD_3). HRMS-EI(+) calcd for $C_{29}H_{42}D_6O_3Si_2F_6$: 643.3315 (M + Na)1$^+$; found 643.3333. Continued elution with 1:19 → 1:4 EtOAc−hexane gave the corresponding mono-TMS ether (0.023 g, 9%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.12 (s, 9 H), 0.65 (s, 3 H), 1.58 (s, 14 H), 2.12−2.61 (m, 7 H), 3.57 (br s, 1 H).

(1*R*,3a*R*,7a*R*)-7a-Methyl-1-[(*R*)-6,6,6-trifluoro-5-hydroxy-1-(5,5,5-trideutero-4-hydroxy-4-trideuteromethyl-pentyl)-5-trifluoromethyl-hex-3-ynyl]-octahydro-inden-4-one (12R-a). To a stirred soln of **11R-b** (0.330 g, 0.69 mmol) in DCM (9 g) was added, in succession, celite (06 g) and PDC (1.16 g, 3 mmol). The mixture was stirred for 14 h, diluted with ether (15 mL), stirred for 5 min, and applied to a silica gel G column. Elution was completed with 1:9 EtOAc−DCM, the effluent containing the ketone was evaporated, the residue taken up in DCM, diluted with hexane, and allowed to crystallize, 0.24 g (73%); mp 156−7 °C; TLC (1:4, 2-PrOH−cyclohexane) R_f 0.80; mp 156−7 °C; $[\alpha]_D^{23}$ −15.3 (c 0.43, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.65 (s, 3 H), 1.24−1.82 (m, 13 H), 1.82−1.98 (m, 2 H), 1.98−2.11 (m, 2 H), 2.17−2.35 (m, 3 H), 2.44−2.52 (m, 2 H), 5.81 (br s, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 12.71, 19.02, 20.06, 21.95, 24.02, 27.44, 32.91, 38.65, 38.81, 40.89, 42.67, 49.74, 53.53, 61.85, 70.79, 70.87, 71.26, 72.17, 89.99, 121.20, 211.47. ^{19}F NMR (376.31 MHz, $CDCl_3$) δ −78.35 (br m). LRMS(ES)(−) m/z 475 (100, M − H); HRMS-ES(+) calcd for $C_{23}H_{26}D_6O_3F_6$ 499.2524 (M + Na)1$^+$; found 499.2520. Anal. calcd for $C_{23}H_{26}D_6O_3F_6$: C, 57.97; found C, 57.77.

(1*R*,3a*R*,7a*R*)-7a-Methyl-1-[(*R*)-6,6,6-trifluoro-1-(5,5,5-trideutero-4-trideuteromethyl-4-trimethylsilanyloxy-pentyl)-5-trifluoromethyl-5-trimethylsilanyloxy-hex-3-ynyl]-octahydro-inden-4-one (12R-b). To a suspension of **12R-a** (0.22 g, 0.46 mmol) in cyclohexane (3 mL) was added TMS-imidazole (0.30 mL, 2 mmol) to form a solution that was stored overnight and then filtered onto a silica gel column. Elution with hexane → 1:79 → 1:39 → 1:19 EtOAc−hexane gave **12R-b** as a colorless oil, 0.26 g (91%); TLC (1:39 EtOAc−hexane) R_f 0.11. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.11 (s, 9 H), 0.29 (s, 9 H), 0.67 (s, 3 H), 1.17−1.50 (m, 6 H), 1.57−1.68 (m, 4 H), 1.71−1.84 (m, 2 H), 1.84−1.99 (m, 2 H), 1.99−2.14 (m, 2 H), 2.20−2.36 (m, 3 H), 2.43−2.53 (m, 2 H). ^{19}F NMR (376.31 MHz, $CDCl_3$) δ −8 2.41(s). LRMS(ES)(+) m/z 531 (100, M-OTMS). HRMS-EI(+) calcd for $C_{29}H_{42}D_6O_3Si_2F_6$: 643.3315 (M + Na)1$^+$; found 643.3311.

(*S*)-11,11,11-Trideutereo-1,1,1-trifluoro-6-((1*R*,3a*R*,4*S*,7a*R*)-4-hydroxy-7a-methyl-octahydro-indene-1-yl)-10-trideuteromethyl-2-trifluoromethyl-undec-3(*E*)-ene-2,10 diol (13S). A three-neck flask equipped with a magnetic stirrer, an addition funnel, and a Claisen adapter with nitrogen sweep and a rubber septum was charged with a 3.5 M soln of sodium bis(2-methoxyethoxy)-aluminum hydride in toluene and THF (50 mL) and cooled to −30 °C. To this soln was added a soln of triol **11S-b** (1.1 g, 2.3 mmol) in THF (45 mL) dropwise below −20 °C and the mixture was allowed to warm to 0 °C within 25 min and then maintained at that temperature for 3 h. The mixture was diluted with ether (50 mL), refrigerated overnight, filtered through celite, and the filtrate was evaporated. The residue was chromatographed on a silica gel column with 1:4 → 1:3 → 1:2 EtOAc−hexane. The pooled product fractions were evaporated and the residue allowed to crystallize from DCM−hexane to afford **13S**, 1.03 g (93%); TLC (1:9 methanol−DCM) R_f 0.69; mp 141 °C; $[\alpha]_D^{30}$ +10.55° (c 0.44, methanol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 3 H), 1.10−1.64 (m, 16 H), 1.75−1.89 (m, 3 H), 1.94 (d, J = 12.8 Hz, 1 H), 2.07−2.18 (m, 1 H), 2.48 (dt, J = 14.3, 4.7 Hz, 1 H), 4.03−4.10 (m, 1 H), 5.58 (d, J = 15.6 Hz, 1 H), 6.28 (ddd, J = 15.6, 7.6, 7.5 Hz, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.66, 17.40, 19.77, 22.36, 26.85, 31.91, 33.51, 35.23, 38.91, 40.32, 41.89, 43.34, 52.53, 53.52, 69.29, 71.34, 76.13, 118.92, 122.29, 138.59. ^{19}F NMR (376.31 MHz) δ −77.97, 3F, q, $^4J_{F,F}$ = 8.78 Hz, −77.80, 3F, q, $^4J_{F,F}$ = 9.40 Hz. LRMS-ES(−) m/z 480 (20, M) 479 (39, M − H). HRMS-ES(+) found 503.2838 (M + Na)1$^+$, calcd for $C_{23}H_{30}D_6O_3F_6$: 503.2837. Anal. calcd for $C_{23}H_{30}D_6O_3F_6$: C, 57.48; found 57.38.

(*R*)-11,11,11-Trideutereo-1,1,1-trifluoro-6-((1*R*,3a*R*,4*S*,7a-*R*)-4-hydroxy-7a-methyl-octahydro-indene-1-yl)-10-trideutero-methyl-2-trifluoromethyl-undec-3(*E*)-ene-2,10 diol (13R). The triol **13R** was prepared as described for the isomer **13S** and was obtained as a white powder (88.6% yield); $[\alpha]_D^{28}$ +17.3° (c 0.22, methanol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 3 H), 1.13−1.66 (m, 17 H), 1.75−1.91 (m, 3 H), 1.90−2.09 (m, 2 H), 2.37 (dt, J = 14.7, 5.1 Hz, 1 H), 3.79 (br s, 1 H), 4.05−4.10 (m, 1 H), 5.60 (d, J = 15.6 Hz, 1 H), 6.29 (ddd, J = 15.3, 8.8, 6.3 Hz, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.78, 17.55, 19.82, 22.45, 27.11, 31.65, 33.54, 35.06, 39.24, 40.23, 42.03, 43.35, 52.58, 53.31, 69.35, 71.35, 76.08, 118.87, 122.23, 138.43. ^{19}F NMR (376.31 MHz) δ −78.08, 3F, q, $^4J_{F,F}$ = 9.53 Hz, −77.87, 3F, q, $^4J_{F,F}$ = 9.28 Hz. LRMS-ES(+) m/z 463 (100, M−OH), 445 (25, M−OH-H_2O). HRMS-ES(+) found 503.2835 (M + Na)1$^+$, calcd for $C_{23}H_{30}D_6O_3F_6$: 503.2837. Anal. calcd for $C_{23}H_{30}D_6O_3F_6$: C, 57.48; found 57.38.

(1*R*,3a*R*,7a*R*)-7a-Methyl-1-[(*S*)-6,6,6-trifluoro-5-hydroxy-1-(5,5,5-trideutero-4-hydroxy-4-trideuteromethyl-pentyl)-5-trifluoromethyl-hex-3-enyl]-octahydro-inden-4-one (14S-a). The triol **13S** was oxidized as described for the preparation of the alkyne analogue **12S-a** to obtain crystalline **14S-a** from DCM−hexane (96% yield) TLC (1:9 MeOH−DCM); R_f 0.75; $[\alpha]_D^{31}$ −9.5° (c 0.45, methanol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.64 (s, 3 H), 1.11−1.44 (m, 7 H), 1.45−1.96 (m, 8 H), 1.97−2.08 (m, 2 H), 2.12−2.33 (m, 3 H), 2.45 (dd, J = 11.4, 7.6 Hz, 2 H), 5.06 (br s, 1 H), 5.59 (d, J = 15.4 Hz, 1 H), 6.30 (ddd, J = 15.4, 7.6, 7.5 Hz, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 12.56, 18.86, 19.69, 23.96, 26.94, 31.64, 34.94, 38.73, 38.97, 40.76, 43.47, 49.88, 53.37, 61.80, 71.33, 75.83, 119.50, 122.47, 137.71, 212.42. ^{19}F NMR (376.31 MHz) δ −77.83, 3F, q, $^4J_{F,F}$ = 8.27 Hz, −77.73, 3F, q, $^4J_{F,F}$ = 7.53 Hz. LRMS-ES(−) m/z 523 (100, M + $HCOO^-$), 477 (30, M − H). HRMS-ES(+) calcd for $C_{23}H_{28}D_6O_3F_6$: 501.2681 (M + Na)1$^+$, found 501.2685. Anal. calcd for $C_{23}H_{28}D_6O_3F_6$: C, 57.13; found C, 57.08.

(1*R*,3a*R*,7a*R*)-7a-Methyl-1-[(*S*)-6,6,6-trifluoro-1-(5,5,5-trideutero-4-trideuteromethyl-4-trimethylsilanyloxy-pentyl)-5-trifluoromethyl-5-trimethylsilanyloxy-hex-3(*E*)-enyl]-octahydro-inden-4-one (14S-b). The ketone-diol **14S-a** was silylated as described for the preparation of the disilyl ether **12R-b** to give **14S-b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.09 (s, 9 H), 0.22 (s, 9 H), 0.67 (s, 3 H), 1.08−1.46 (m, 7 H), 1.46−2.10 (m, 9 H), 2.16−2.43 (m, 4 H), 2.46 (dd, J = 11.3, 7.7 Hz, 1 H), 5.56 (d, J = 15.4 Hz, 1 H), 6.15 (dt, J = 15.4, 7.3 Hz, 1 H).

(1*R*,3a*R*,7a*R*)-7a-Methyl-1-[(*R*)-6,6,6-trifluoro-5-hydroxy-1-(5,5,5-trideutero-4-hydroxy-4-trideuteromethyl-pentyl)-5-trifluoromethyl-hex-3(*E*)-enyl]-octahydro-inden-4-one (14R-a). To a stirred suspension of triol **13R** (1.68 g), DCM (26 g) and celite (1.6 g) was added PDC (2.60 g, 6.64 mmol) and the mixture stirred for 5.5 h and then diluted with ether (30 mL) and applied to a silica gel-G plug. The column was washed exhaustively with 1:9 EtOAc−ether; the fractions containing the ketone were evaporated and the residue crystallized from DCM−hexane; TLC (1:9 methanol−DCM); R_f 0.75, $[\alpha]_D^{31}$ −4.1° (c 0.32, methanol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.65 (s, 3 H), 1.22−1.69 (m, 12 H), 1.69−1.81 (m, 1 H), 1.81−1.97 (m, 2 H), 1.97−2.12 (m, 3 H), 2.16−2.42 (m, 3 H), 2.46 (dd, J = 11.5, 7.7 Hz, 1 H), 4.27 (br s, 1 H), 5.61 (d, J = 15.4 Hz, 1 H), 6.29 (ddd, J = 15.4, 8.7, 6.2 Hz, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 12.71, 19.00, 19.74, 24.08, 27.34, 31.75, 34.91, 38.77, 39.37, 40.90, 43.30, 49.93, 53.35, 61.86, 71.24, 75.80, 119.19, 122.24, 137.92, 211.76. ^{19}F NMR (376.31 MHz) δ −77.84, 3F, q, $^4J_{F,F}$ = 8.91 Hz, −77.99, 3F, q, $^4J_{F,F}$ = 11.92 Hz. LRMS-ES(+) m/z 479 (100, M + H). HRMS-ES(+) calcd for $C_{23}H_{28}D_6O_3F_6$: 479.2862 (M + H)1$^+$; found 479.2861. Anal. calcd for $C_{23}H_{28}D_6O_3F_6$: C, 57.73; found 57.90.

(1*R*,3a*R*,7a*R*)-7a-Methyl-1-[(*R*)-6,6,6-trifluoro-1-(5,5,5-trideutero-4-trideuteromethyl-4-trimethylsilanyloxy-pentyl)-5-trifluoromethyl-5-trimethylsilanyloxy-hex-3(*E*)-enyl]-octahydro-inden-4-one (14R-b). The silylation of **14R-a** was repeated as described for the preparation of the disilyl ether **12R-b** to give **14R-b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.10 (s, 9 H), 0.22 (s, 9 H), 0.66 (s, 3 H), 1.10−1.46 (m, 7 H), 1.46−2.12 (m, 9 H), 2.17−2.43 (m, 4 H), 2.45 (dd, J = 11.6, 7.6 Hz, 1 H), 5.55 (d, J = 15.6 Hz, 1 H), 6.13 (m, 1 H). ^{19}F NMR (376.31 MHz) δ −76.64, 3F, q, $^4J_{F,F}$ = 9.41 Hz, −76.48, 3F, q, $^4J_{F,F}$ = 9.41 Hz.

(*S*)-11,11,11-Trideutereo-1,1,1-trifluoro-6-((1*R*,3a*R*,4*S*,7a*R*)-4-hydroxy-7a-methyl-octahydro-indene-1-yl)-10-trideuteromethyl-2-trifluoromethyl-undec-3(*Z*)-ene-2,10 diol (15S). A suspension comprising the triol **11S-b** (1.00 g, 2.09 mmol), hexane (25 mL), EtOAc (10 mL), and 5% Pd-$CaCO_3$ containing 3.5% Pb (0.3 g, Degussa) was stirred under hydrogen, near hydrostatic balance, for 30 min, and then filtered. The suspension was filtered, and the filtrate was evaporated to a white foam (1.03 g) and further purified by chromatography on a silica gel using 1:4 → 1:3 → 1:2 EtOAc−hexane to afford **15S** in the form of white solids after evaporation of a soln in methyl formate (0.99 g, 98.5%); TLC (1:1, EtOAc−hexane); R_f 0.75; $[\alpha]_D^{29}$ +6.70° (c 0.49, methanol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 3 H), 1.16 (td, J = 13.4, 3.4 Hz, 1 H), 1.21−1.63 (m, 15 H), 1.69−1.96 (m, 4 H), 2.52−2.70 (m, 2 H), 4.02−4.10 (m, 1 H), 5.42 (d, J = 12.4 Hz, 1 H), 5.95 (ddd, J = 12.4, 7.4, 7.2 Hz, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.59, 17.39, 18.34, 22.30, 26.51, 29.71, 31.38, 33.36, 39.14, 40.07, 43.50, 52.42, 52.52, 69.42, 71.71, 116.99, 122.90, 141.95. ^{19}F NMR (376.31 MHz) δ −77.76, 3F, q, $^4J_{F,F}$ = 9.78 Hz, −78.25, 3F, q, $^4J_{F,F}$ = 9.78 Hz. LRMS-ES(−) m/z 480 (20, M) 479 (100, M − H). HRMS-ES(+) calcd for $C_{23}H_{30}D_6O_3F_6$: 503.2837 (M + Na)1$^+$; found 503.2837.

(*R*)-11,11,11-Trideutereo-1,1,1-trifluoro-6-((1*R*,3a*R*,4*S*,7a-*R*)-4-hydroxy-7a-methyl-octahydro-indene-1-yl)-10-trideutero-methyl-2-trifluoromethyl-undec-3(*Z*)-ene-2,10 diol (15R). The hydrogenation with Lindlar catalyst was repeated with **11R-b** as described above to yield **15R** as white solids; $[\alpha]_D^{29}$ +16.9 ° (c 0.34, methanol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 3 H), 1.10−1.25 (m, 1 H), 1.26−1.64 (m, 16 H), 1.72−1.89 (m, 3 H), 1.93 (d, J = 13.0 Hz, 1 H), 2.39−2.50 (m, 1 H), 2.51−2.63 (m, 1 H), 4.07 (br s, 1 H), 5.36−5.44 (m, 2 H), 5.96 (ddd, J = 12.1, 7.9, 6.4 Hz, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.71, 17.55, 18.60, 22.40, 26.96, 29.89, 31.28, 33.42, 39.62, 40.04, 43.52, 52.39, 52.58, 69.43, 71.65, 116.92, 122.87, 141.90. ^{19}F NMR (376.31 MHz) δ −77.82, 3F, q, $^4J_{F,F}$ = 9.91 Hz, −78.23, 3F, q, $^4J_{F,F}$ = 9.90 Hz. LRMS-ES(−) m/z 480 (20, M) 479 (100, M − H). HRMS-ES(+) calcd for $C_{23}H_{30}D_6O_3F_6$: 503.2837 (M + Na)1$^+$; found 503.2834.

(1*R*,3a*R*,7a*R*)-7a-Methyl-1-[(*S*)-6,6,6-trifluoro-5-hydroxy-1-(5,5,5-trideutero-4-hydroxy-4-trideuteromethyl-pentyl)-5-trifluoromethyl-hex-3(*Z*)-enyl]-octahydro-inden-4-one (16S-a). A solution of triol **15S** (0.957 g, 2 mmol) in DCM (27.3 g) was stirred and a mixture of PDC (2.65 g, 7 mmol) and celite (1.64 g) was added. The oxidation was complete after 7 h as judged by TLC (1:9 MeOH−DCM, R_f 0.68 → 0.75). The suspension was diluted with ether (30 mL) and filtered through silica gel G. Filtrate and ether washed were combined and evaporated to an oil, which was flash-chromatographed using 1:6 → 1:4 → 1:3 EtOAc−hexane as mobile phases to afford **16S-a** as a white solid, 0.74 g (77.3%); TLC (1:19 MeOH−DCM, R_f 0.48; 1:4 EtOAc−hexane, R_f 0.07); $[\alpha]_D^{34}$ +13.2° (c 0.38, methanol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.63 (s, 3 H), 1.16−1.45 (m, 7 H), 1.45−1.79 (m, 6 H), 1.78−1.94 (m, 2 H), 1.94−2.08 (m, 2 H), 2.14−2.33 (m, 2 H), 2.45 (dd, J = 11.4, 7.6 Hz, 1 H), 2.65 (t, J = 6.4 Hz, 2 H), 5.46 (d, J = 12.2 Hz, 1 H), 5.54 (br s, 1 H), 5.96 (dt, J = 12.2, 7.2 Hz, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 12.50, 18.39, 18.86, 23.99, 26.70, 29.88, 31.35, 38.63, 39.35, 40.82, 43.39, 49.83, 52.63, 61.84, 71.63, 77.07, 117.49, 122.93, 141.40, 212.30. ^{19}F NMR (376.31 MHz) δ −77.73, 3F, q, $^4J_{F,F}$ = 9.91 Hz, −78.22, 3F, q, $^4J_{F,F}$ = 9.91 Hz. LRMS-ES(−) m/z 478 (15, M) 477 (90, M − H). HRMS-ES(+) calcd for $C_{23}H_{28}D_6O_3F_6$: 479.2862 (M + H)1$^+$; found 479.2863.

(1*R*,3a*R*,7a*R*)-7a-Methyl-1-[(*S*)-6,6,6-trifluoro-1-(5,5,5-trideutero-4-trideuteromethyl-4-trimethylsilanyloxy-pentyl)-5-trifluoromethyl-5-trimethylsilanyloxy-hex-3(*Z*)-enyl]-octahydro-inden-4-one (16S-b). The ketone-diol **16S-a** (0.74 g, 1.55 mmol)

was silylated as described for the preparation of the disilyl ether **12R-b** to give **16S-b** (0.864 g, 90%); TLC (1:9 EtOAc−hexane) R_f 0.43. This material was divided into three nearly equal parts and reserved for the syntheses of **4S-1**, **4S-2**, and **4S-3** described below.

(1*R*,3a*R*,7a*R*)-7a-Methyl-1-[(*R*)-6,6,6-trifluoro-5-hydroxy-1-(5,5,5-trideutero-4-hydroxy-4-trideuteromethyl-pentyl)-5-trifluoromethyl-hex-3(*Z*)-enyl]-octahydro-inden-4-one (16R-a). The triol **15R** (0.90 g, 1.87 mmol) was oxidized as described for the preparation of the ketone analogue **16S-a** to afford, after chromatography, a white foam (0.82 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.62 (s, 3 H), 1.30 (br s, 7 H), 1.44−1.79 (m, 6 H), 1.79−1.96 (m, 2 H), 2.02 (d, J = 9.8 Hz, 2 H), 2.12 - 2.32 (m, 2 H), 2.45 (dd, J = 11.4, 7.8 Hz, 2 H), 2.59 (ddd, J = 16.3, 8.3, 8.2 Hz, 1 H), 5.42 (d, J = 12.2 Hz, 1 H), 5.54 (br s, 1 H), 5.94 (ddd, J = 12.2, 8.0, 6.3 Hz, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 12.62, 18.65, 18.94, 24.09, 27.18, 29.87, 31.38, 38.57, 39.75, 40.83, 43.47, 50.03, 52.58, 61.88, 71.54, 77.23, 117.21, 122.83, 141.35, 212.31. ^{19}F NMR (376.31 MHz) δ −77.81, 3F, q, $^4J_{F,F}$ = 9.78 Hz, −78.20, 3F, q, $^4J_{F,F}$ = 9.91 Hz. LR MS-ES(−) m/z 478 (18, M) 477 (100, M − H). HRMS-ES(+) calcd for $C_{23}H_{28}D_6O_3F_6$: 501.2681 (M + Na)1$^+$; found 501.2682.

(1*R*,3a*R*,7a*R*)-7a-Methyl-1-[(*R*)-6,6,6-trifluoro-1-(5,5,5-trideutero-4-trideuteromethyl-4-trimethylsilanyloxy-pentyl)-5-trifluoromethyl-5-trimethylsilanyloxy-hex-3(*Z*)-enyl]-octahydro-inden-4-one (16R-b). The ketone-diol **16R-a** (0.82 g) was silylated as described for the preparation of the disilyl ether **12R-b** to give **16R-b** (1.03 g, 97%); TLC (1:4 and 1:39 EtOAc−hexane) R_f 0.71 and 0.08, respectively. This material was divided into three nearly equal parts and reserved for the syntheses of **4R-1**, **4R-2**, and **4R-3** described below.

(20*S*)-1α,25-Dihydroxy-21-(3-hydroxy-3-trifluoromethyl-4,4,4-trifluoro-but-1-ynyl)-26,26,26,27,27,27-hexadeutero-cholecalciferol (2S-1). A three-neck flask equipped with a magnetic stirrer, thermometer, and a Claisen adapter with addition funnel, nitrogen sweep, and a rubber septum was charged with **17** (0.2973 g, 0.52 mmol) and THF (2 mL). The flask was cooled to −75 °C and a 1.6 M butyllithium soln in hexane (0.325 mL, 0.52 mmol) was added dropwise over a 10 min period, followed by a soln of **12S-b** (0.1337 g, 0.215 mmol) in THF, at the same rate. Although no starting ketone was detectable after 4 h, the condensation product was a mixture of tri- and tetra-silyl ethers with R_f values of 0.30 and 0.57, respectively (TLC, 1:19 EtOAc−hexane). The reaction was quenched by the addition of a satd ammonium chloride soln (5 mL) at −65 °C, allowed to warm to 10 °C, and then distributed between hexane (35 mL) and water (10 mL). The organic layer was washed with 5:2 brine−pH 7 buffer (1 M, 7 mL), dried, and evaporated. At this stage only the trisilyl ether was detectable. This material was chromatographed on a flash column, using hexane → 1:72 → 1:39 → 1:19 EtOAc−hexane as mobile phases to yield the protected **2S-1** as colorless residue (0.1561 g). This residue was taken up in pentane, filtered, evaporated to a white foam, and dried at 0.5 Torr for 1 h, 0.1503 g. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 6 H), 0.06 (s, 6 H), 0.11 (s, 9 H), 0.53 (s, 3 H), 0.87 (s, 18 H), 1.14−1.53 (m, 13 H), 1.62−1.81 (m, 3 H), 1.82−1.95 (m, 3 H), 2.01 (t, J = 9.7 Hz, 1 H), 2.22 (dd, J = 13.1, 7.4 Hz, 1 H), 2.37−2.56 (m, 3 H), 2.83 (d, J = 15.8 Hz, 1 H), 3.45 (s, 1 H), 4.13−4.23 (m, 1 H), 4.34−4.40 (m, 1 H), 4.86 (d, J = 2.1 Hz, 1 H), 5.18 (d, J = 1.5 Hz, 1 H), 6.02 (d, J = 11.3 Hz, 1 H), 6.23 (d, J = 11.3 Hz, 1 H). LRMS-ES(−) m/z 958(18, M − H + HCOOH), 856 (100, M-C_4H_9). HRMS-ES(+) calcd for $C_{47}H_{74}D_6O_4Si_3F_6$: 913.5718 (M + H)1$^+$, found 913.5723. This material was dissolved in a 1 M TBAF soln in THF (3 mL) and allowed to stand for 45 h and then diluted with brine (5 mL), stirred for 5 min, and transferred to a separatory funnel with EtOAc (40 mL) and water (8 mL). The aqueous phase was extracted once with EtOAc (10 mL), and the combined layers were washed with water (5 × 10 mL) and brine (10 mL) and then dried and evaporated (0.1261 g). The resulting residue was chromatographed using 1:1→ 2:1 → 4:1 EtOAc−hexane as mobile phases. The product fractions were pooled and evaporated (0.100 g). This residue was taken up in methyl formate, filtered, and transferred to a 5 mL flask and then evaporated to yield **2S-1** as a solid, white foam that was dried at 0.5 Torr for 2 h; UV λ_{max} (ε) 212 (14801), 264 (16493) nm; $[\alpha]_D^{29}$ +16.9° (c 0.37, methanol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.53 (s, 3 H), 1.21−1.63 (m, 12 H), 1.63−1.77 (m, 2 H), 1.80−2.13 (m, 8 H), 2.26−2.42 (m, 2 H), 2.52 (dd, J = 17.7, 2.8 Hz, 1 H), 2.57 (dd, J = 14.3, 2.6 Hz, 1 H), 2.75−2.89 (m, 1 H), 3.75 (s, 1 H), 4.14−4.25 (m, 1 H), 4.42 (dd, J = 6.9, 4.2 Hz, 1 H), 4.98 (s, 1 H), 5.32 (s, 1 H), 6.01 (d, J = 11.2 Hz, 1 H), 6.23 (br s, 1 H), 6.35 (d, J = 11.2 Hz, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 12.18, 20.19, 21.71, 22.17, 23.58, 27.42, 29.01, 32.95, 38.73, 40.10, 42.64, 43.13, 45.08, 45.64, 53.19, 56.14, 66.84, 70.78, 71.15, 71.94, 89.89, 111.88, 117.22, 121.35, 124.75, 133.08, 142.42, 147.30. ^{19}F NMR (376.31 MHz) δ −78.28, 6F, s. LRMS-EI(+) m/z 612 (4, M), 594 (40, M-H_2O); 594 (39, M-2H_2O), 558 (100, M-3H_2O). HRMS-ES(+) calcd for $C_{32}H_{38}D_6O_4F_6$: 635.3412 (M + Na)1$^+$; found 35.3407.

(20*R*)-1α,25-Dihydroxy-21-(3-hydroxy-3-trideuteromethyl-4,4,4-trideutero-butyl)- 26,26,26,27,27,27-hexafluoro-23-yne-cholecalciferol (2R-1). A two-neck flask, equipped with magnetic stirrer, thermometer, and a Claisen adapter containing a nitrogen sweep and rubber septum, was charged with diphenylphosphine oxide **17** (0.465 g) and THF (3.5 mL). The solution was cooled to −70 °C, and a 1.6 M solution of butyl lithium in hexane (0.50 mL) was added dropwise over a 10 min period. To this red soln was added, via syringe, dropwise, within 20 min, ketone **12R-b** (0.2895 g, 0.466 mmol) dissolved in THF (3 mL). After 5 h, the mixture was allowed to warm to −35 °C and a satd ammonium chloride soln (10 mL) was added. The mixture was allowed to warm to 10 °C and was then distributed between hexane (60 mL) and enough water (5 mL) to dissolve all salts. The extract was washed with 5:1 brine−pH 7 buffer (10 mL) and then dried and evaporated. The resulting residue (0.71 g) was flash-chromatographed using hexane → 1:72 → 1:39 EtOAc−hexane as mobile phases to give a mixture (0.38 g) of the tetrasilyl (TLC 1:19, EtOAc−hexane, R_f 0.76) and the trisilyl ether, which lacks the silyl function at the *gem*-trifluoromethyl-carbinol site (TLC 1:19, EtOAc−hexane, R_f 0.33). This mixture was dissolved in a 1 M soln of TBAF (4 mL) and allowed to remain at room temperature in the dark for 45 h. The soln was diluted with brine (5 mL) and equilibrated with EtOAc (40 mL) and water (10 mL). The aqueous phase was extracted once with EtOAc (10 mL), and the combined extracts were washed with water (5 × 10 mL) and brine (10 mL) and then dried and evaporated. The residue was flash-chromatographed using 1:4 → 1:2 → 1:1 → 2:1 EtOAc−hexane → EtOAc as mobile phases. The product fractions were pooled, filtered, and evaporated and then coevaporated twice from hexane to furnish a residue (0.25 g) that was taken up in methyl formate and allowed to crystallize. The suspension was concentrated, diluted with pentane, and refrigerated. The ML was decanted from the crystalline **2R-1**, 0.198 g, 69.3%; UV λ_{max} (ε) 211 (17454), 265 (18463) nm; $[\alpha]_D^{29}$ +13.2° (c 0.25, methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.51 (s, 3 H), 1.09−1.69 (m, 15 H), 1.73−1.87 (m, 2 H), 1.87−1.99 (m, 2 H), 2.16 (dd, J = 13.5, 5.4 Hz, 1 H), 2.26 (d, J = 16.9 Hz, 1 H), 2.35 (d, J = 11.7 Hz, 1 H), 2.42 (d, J = 16.9 Hz, 1 H), 2.49 (s, 1 H), 2.73−2.83 (m, 1 H), 3.92−4.02 (m, 1 H), 4.05 (s, 1 H), 4.13−4.23 (m, 1 H), 4.56 (d, J = 3.6 Hz, 1 H), 4.75 (d, J = 1.6 Hz, 1 H), 4.86 (d, J = 4.6 Hz, 1 H), 5.22 (br s, 1 H), 5.98 (d, J = 11.1 Hz, 1 H), 6.18 (d, J = 11.1 Hz, 1 H), 8.93 (s, 1 H). ^{13}C NMR (400 MHz, DMSO-d_6) δ 11.89, 20.17, 20.51, 21.82, 23.14, 26.71, 28.38, 31.52, 38.76, 39.82, 43.13, 43.83, 44.94, 45.13, 52.29, 55.75, 65.07, 68.40, 68.50, 70.20, 70.40, 89.59, 109.89, 117.60, 121.47, 122.37, 135.87, 139.64, 149.33. ^{19}F NMR (376.31 MHz) δ −76.77 Hz, 6F, s; LRMS-ES(−) m/z 611 (100, M − 1). HRMS-ES(+) calcd for $C_{32}H_{38}D_6O_4F_6$: 635.3412 (M + Na)1$^+$; found 635.3412.

(20*S*)-1α,25-dihydroxy-21-(3-hydroxy-3-trifluoromethyl-4,4,4-trifluoro-but-1-ynyl)-26,26,26,27,27,27-hexadeutero-19-nor-cholecalciferol (2S-2). A three-neck flask, equipped with magnetic

stirrer, thermometer, and a Claisen adapter containing a nitrogen sweep and rubber septum, was charged with diphenylphosphine oxide **18** (0.2973 g, 0.52 mmol) and THF (2 mL) freshly distilled from sodium benzophenone ketyl. The solution was cooled to −70 °C, and a 1.6 M solution of butyllithium in hexane (0.325 mL, 0.52 mmol) was added dropwise over a 10 min period. To this soln was added, via syringe, dropwise over a 10 min period, a soln of **12S-b** (0.1271 g) in a soln of THF (2 mL). Starting material (TLC 1:4 EtOAc−hexane) was no longer observed after 4 h. and a mixture of tri- and tetrasilylated condensation products was present (TLC 1:19 EtOAc−hexane). The mixture was allowed to warm to −55 °C, and a satd ammonium chloride soln (5 mL) was added and then allowed to warm further to 10 °C. The resulting mixture was equilibrated with hexane (35 mL) and water (10 mL), and the aqueous layer was re-extracted once with hexane (15 mL). The combined extract, now containing mostly the trisilyl ether, was washed with 5:2 brine/pH 7 buffer and then dried and evaporated and chromatographed using hexane → 1:72 → 1:39 EtOAc−hexane as mobile phases. The product fractions were pooled and evaporated to give a colorless oil (0.1737 g) that was taken up in pentane, filtered, and evaporated. The resulting white foam was dried at 0.5 Torr and represents the trisilyl ether of **2S-2**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 9 H), 0.06 (br s, 3 H), 0.11 (s, 9 H), 0.54 (s, 3 H), 0.87 (d, J = 6.0 Hz, 18 H), 1.17−1.54 (m, 13 H), 1.57−1.74 (m, 3 H), 1.74−1.83 (m, 1 H), 1.84−1.96 (m, 2 H), 2.03 (t, J = 9.6 Hz, 1 H), 2.10 (dd, J = 12.9, 8.0 Hz, 1 H), 2.21−2.31 (m, 1 H), 2.33−2.57 (m, 4 H), 2.82 (m, J = 2.3 Hz, 1 H), 3.45 (s, 1 H), 3.99−4.16 (m, 2 H), 5.82 (d, J = 11.1 Hz, 1 H), 6.16 (d, J = 11.1 Hz, 1 H). The trisilyl ether obtained as described above was dissolved in a 1 M soln of TBAF (3 mL) and allowed to remain in the dark for 38 h. The mixture was diluted with brine (5 mL), stirred for 5 min, and equilibrated with EtOAc (40 mL) and water (8 mL). The aqueous phase was extracted once with EtOAc (10 mL), and the combined extracts were washed with water (5 × 10 mL) and brine (10 mL), dried (sodium sulfate), and evaporated. The residue was chromatographed using 1:1→ 2:1→ 4:1 EtOAc−hexane → EtOAc as mobile phases. The product fractions were pooled and evaporated. The residue (0.1038 g) was taken up in methyl formate, filtered, and evaporated to afford **2S-2** as a white, solid foam, dried at 0.5 Torr (0.1009 g); UV λ_{max} (ε) 242 (33349), 251(39366), 260 (26943) nm (methanol); $[\alpha]_D^{29}$ +46.0° (c 0.55, methanol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.55 (s, 3 H), 1.22−1.48 (m, 9 H), 1.48−1.62 (m, 4 H), 1.61−1.76 (m, 4 H), 1.74−1.85 (m, 1 H), 1.85−2.09 (m, 5 H), 2.17−2.27 (m, 2 H), 2.35 (dd, J = 17.3, 7.0 Hz, 1 H), 2.48 (dd, J = 13.3, 2.9 Hz, 1 H), 2.57 (dd, J = 17.3, 3.8 Hz, 1 H), 2.74 (dd, J = 13.3, 3.8 Hz, 1 H), 2.81 (m, 1 H), 4.04 (br s, 1 H), 4.12 (br s, 1 H), 5.61 (br s, 1 H), 5.86 (d, J = 11.3 Hz, 1 H), 6.31 (d, J = 11.3 Hz, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 12.29, 20.13, 22.03, 22.18, 23.48, 27.45, 28.86, 33.23, 37.19, 38.66, 40.16, 42.13, 42.89, 44.61, 45.54, 53.40, 56.11, 67.23, 67.43, 71.04, 72.15, 90.22, 115.48, 121.26, 123.65, 131.31, 142.30. LRMS-ES(−) m/z 599 (100, M − H). HRMS-ES(+) calcd for $C_{31}H_{38}D_6O_4F_6$: 623.3412 (M + Na)1$^+$; found 623.3414.

(20*R*)-1α,25-Dihydroxy-21-(3-hydroxy-3-trideuteromethyl-4,4,4-trideutero-butyl)- 26,26,26,27,27,27-hexafluoro-23-yne-19-nor-cholecalciferol (2R-2). The diphenylphosphine oxide **18** (0.4222 g, 0.74 mmol) was deprotonated with a 1.6 M solution of butyllithium in hexane and allowed to react with the ketone **12R-b** (0.257 g, 0.414 mmol) as described for the preparation of **2S-1**. The condensation product (0.31 g) was purified as described for the epimer **2S-2** and then dissolved in a 1 M soln of TBAF (5 mL). After 18 h, the temperature was increased and maintained at 30 °C for 16 h. The deprotected product was isolated and purified by chromatography as described for the epimer **2S-2**. The resulting colorless syrup (0.20 g) was crystallized from methyl formate, 0.15 g (60% from ketone **12R-b**); mp 165−167 °C; UV λ_{max} (ε) 243 (35935), 251(41886), 261 (228440) nm (methanol); $[\alpha]_D^{30}$ +58.4° (c 0.31, methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.52 (s, 3 H), 1.13−1.73 (m, 17 H), 1.79−2.11 (m, 5 H), 2.23−2.32 (m, 2 H), 2.39−2.48 (m, 2 H), 2.70−2.83 (m, 1 H), 3.74−3.84 (m, 1 H), 3.84−3.93 (m, 1 H), 4.05 (s, 1 H), 4.39 (d, J = 3.6 Hz, 1 H), 4.49 (d, J = 3.6 Hz, 1 H), 5.81 (d, J = 11.1 Hz, 1 H), 6.08 (d, J = 11.1 Hz, 1 H), 8.94 (br s, 1 H). ^{13}C NMR (400 MHz, DMSO-d_6) δ 12.01, 20.17, 21.72, 23.01, 26.79, 28.22, 31.48, 36.95, 38.79, 39.82, 42.23, 43.81, 44.99, 52.26, 55.71, 65.28, 65.55, 68.38, 70.19, 70.39, 89.58, 116.04, 120.81, 121.46, 134.70, 139.02. ^{19}F NMR (376.31 MHz) δ −76.76 Hz, 6F, s. LRMS-ES(−) m/z 599 (30, M − H). HRMS-ES(+) calcd for $C_{31}H_{38}D_6O_4F_6$: 623.3412 (M + Na)1$^+$; found 623.3410. Roentgen diffraction analysis (Figure 2): $C_{31}H_{44}F_6O_4$, orthorhombic, space group $P2_12_12_1$ with unit cell dimensions of a = 7.3400(15), b = 16.6070(3), c = 25.9300(5) Å, volume 3160.9(11) Å^3 (Z = 4).

(20*S*)-1α-Fluoro-21-(3-hydroxy-3-trifluoromethyl-4,4,4-trifluoro-but-1-ynyl)-25-hydroxy-26,26,26,27,27,27-hexadeutero-cholecalciferol (2S-3). The diphenylphosphine oxide **19** (0.286 g, 0.61 mmol) was deprotonated with a 1.6 M solution of butyllithium in hexane and allowed to react with the ketone **12S-b** (0.159 g, 0.256 mmol), and the resulting condensation product was purified as described for **2S-2**; the residue was dissolved in a 1 M soln of TBAF (3 mL) and allowed to stand for 24 h at ambient temperature. The deprotected product was isolated and purified by chromatography as described for **2S-2** to afford **2S-3** as a white solid foam (75 mg, 47% from **12S-b**); UV λ_{max} (ε) 210 (14386), 242(14376), 270 (14177) nm (methanol); $[\alpha]_D^{23}$ +27.4° (c 0.25, methanol).; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.50 (s, 3 H), 1.03−2.01 (m, 20 H), 2.05−2.20 (m, 2 H), 2.43−2.56 (m, 2 H), 2.84 (d, J = 12.4 Hz, 1 H), 3.83−3.99 (m, 1 H), 4.05 (s, 1 H), 4.86 (d, J = 4.5 Hz, 1 H), 4.99 (s, 1 H), 5.15 (d, J = 48.4 Hz, 1 H), 5.39 (br s, 1 H), 5.94 (d, J = 11.2 Hz, 1 H), 6.37 (d, J = 11.2 Hz, 1 H), 8.93 (s, 1 H). ^{13}C NMR (400 MHz, DMSO-d_6) δ 11.73, 20.30, 20.36, 21.63, 23.11, 26.75, 28.39, 31.93, 38.16, 40.70, 43.79, 44.88, 45.12, 52.22, 55.59, 64.52, 68.41, 7.45, 70.82, 89.41, 91.29, 92.96, 115.55, 117.09, 121.57, 124.16, 133.12, 141.75, 143.19. ^{19}F NMR (376.31 MHz) δ −76.64 Hz, 6F, br m. LRMS-ES(−) m/z 613 (100, M − H). HRMS-ES(+) calcd for $C_{32}H_{37}D_6O_3F_7$: 637.3369 (M + Na)1$^+$, found 637.3362.

(20*R*)-1α-Fluoro-21-(3-hydroxy-3-trideuteromethyl-4,4,4-trideutero-butyl)-25-hydroxy-26,26,26,27,27,27-hexafluoro-23-yne-cholecalciferol (2R-3). The diphenylphosphine oxide **19** (0.3042 g, 0.646 mmol) was deprotonated with a 1.6 M solution of butyllithium in hexane and allowed to react with the ketone **12R-b** (0.159 g, 0.61 mmol) and the condensation product was purified as described for **2S-2**. The resulting material (0.24 g) was dissolved in a 1 M soln of TBAF (3 mL) and allowed to stand for 24 h at ambient temperature. The deprotected product was isolated (0.17 g) and purified by chromatography as described to afford **2R-3** as a white, solid foam (0.1552 g, 41% from ketone; UV λ_{max} (ε) 209 (15954), 242(14652), 270 (14328) nm (methanol); $[\alpha]_D^{29}$ +34.3° (c 0.24, methanol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.55 (s, 3 H), 1.16−1.79 (m, 16 H), 1.80−2.07 (m, 5 H), 2.12−2.26 (m, 2 H), 2.30 (dd, J = 12.9, 8.0 Hz, 2 H), 2.44 (dd, J = 17.3, 3.2 Hz, 1 H), 2.62 (dd, J = 13.1, 2.9 Hz, 1 H), 2.76−2.89 (m, 1 H), 4.16−4.27 (m, 1 H), 5.13 (ddd, J = 49.6, 6.0, 3.6 Hz, 1 H), 5.10 (s, 1 H), 5.39 (br s, 1 H), 6.02 (d, J = 11.2 Hz, 1 H), 6.39 (d, J = 11.2 Hz, 1 H). ^{19}F NMR (376.31 MHz) δ −78.36 Hz, 6F, br m. LRMS-ES(−) m/z 659 (35, M + HCOOH-H), 613 (100, M − H). HRMS-ES(+) calcd for $C_{32}H_{37}D_6O_3F_7$: 637.3369 (M + Na)1$^+$; found 637.3365.

(20*S*)-1α,25-Dihydroxy-21-(3-hydroxy-3-trifluoromethyl-4,4,4-trifluoro-but-1(*E*)-enyl)-26,26,26,27,27,27-hexadeutero-cholecalciferol (3S-1). The diphenylphosphine oxide **17** (0.3042 g, 0.522 mmol) was deprotonated with a 1.6 M solution of butyllithium in hexane, allowed to react with the ketone **12R-b** (0.3296 g, 0.529 mmol), and the condensation product was purified as described for **2S-2**; the resulting material (0.51 g) was dissolved in a 1 M soln of TBAF (5 mL) and allowed to stand for 41 h at ambient temperature. The deprotected material was isolated (0.17 g) and purified by chromatography

as described to afford **3S-1** as a white, solid foam (0.2844 g, 87% from ketone); UV λ_{max} (ε) 213 (16297), 266 (17812) nm (methanol); $[\alpha]_D^{30}$ +9.9° (c 0.30, methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.53 (s, 3 H), 1.03−1.56 (m, 13 H), 1.56−1.72 (m, 3 H), 1.72−1.85 (m, 2 H), 1.87−2.03 (m, 2 H), 2.17 (dd, J = 13.5, 5.2 Hz, 1 H), 2.20−2.29 (m, 1 H), 2.36 (d, J = 11.5 Hz, 2 H), 2.80 (d, J = 10.2 Hz, 1 H), 3.98 (br s, 1 H), 4.02 (s, 1 H), 4.19 (br s, 1 H), 4.55 (d, J = 3.4 Hz, 1 H), 4.76 (br s, 1 H), 4.87 (d, J = 4.5 Hz, 1 H), 5.23 (br s, 1 H), 5.61 (d, J = 15.3 Hz, 1 H), 5.99 (d, J = 11.0 Hz, 1 H), 6.20 (d, J = 11.0 Hz, 1 H), 6.27 (ddd, J = 15.1, 7.4, 7.1 Hz, 1 H), 8.03 (s, 1 H). ^{13}C NMR (400 MHz, DMSO-d_6) δ 11.85, 19.26, 21.76, 23.17, 26.66, 28.39, 31.06, 33.31, 38.98, 43.13, 44.12, 44.94, 45.32, 52.20, 55.62, 65.10, 68.41, 68.53, 75.51, 109.97, 117.66, 119.31, 122.49, 122.74, 135.95, 137.55, 139.92, 149.52. ^{19}F NMR (376.31 MHz) δ −75.85 Hz, 6F, m). LRMS-ES(−) m/z 613 (40, M − H). HRMS-ES(+) calcd for $C_{32}H_{40}D_6O_4F_6$: 637.3569 (M + Na)1$^+$; found 637.3569.

(20*R*)-1α,25-Dihydroxy-21-(3-hydroxy-3-trideuteromethyl-4,4,4-trideutero-butyl)- 26,26,26,27,27,27-hexafluoro-23(*E*)-ene-cholecalciferol (3R-1). The diphenylphosphine oxide **17** (0.3546 g, 0.608 mmol) was deprotonated with a 1.6 M solution of butyllithium in hexane and allowed to react with the ketone **12R-b** (0. 0.2639 g, 0.424 mmol) as described. The condensation product was purified as described for **2S-2**; the resulting material was dissolved in a 1 M soln of TBAF (5 mL) and allowed to stand for 41 h at ambient temperature. The deprotected material was isolated and purified by chromatography as described to afford **3S-1** as a white, solid foam (0.1842 g, 70% from ketone **14R-b**; UV λ_{max} (ε) 205 (14284), 211 (15019), 265 (16299) nm (methanol); $[\alpha]_D^{30}$ +14.1° (c 0.20, methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.52 (s, 3 H), 1.10−1.57 (m, 13 H), 1.57−1.71 (m, 3 H), 1.73−1.85 (m, 2 H), 1.90 (d, J = 9.6 Hz, 1 H), 1.96 (t, J = 9.4 Hz, 1 H), 2.01−2.12 (m, 1 H), 2.16 (dd, J = 13.4, 5.5 Hz, 1 H), 2.22−2.32 (m, 1 H), 2.36 (d, J = 11.7 Hz, 1 H), 2.79 (m, J = 9.6 Hz, 1 H), 3.98 (br s, 1 H), 4.03 (s, 1 H), 4.15−4.26 (m, 1 H), 4.56 (d, J = 3.2 Hz, 1 H), 4.76 (d, J = 1.9 Hz, 1 H), 4.87 (d, J = 4.7 Hz, 1 H), 5.23 (d, J = 1.1 Hz, 1 H), 5.61 (d, J = 15.6 Hz, 1 H), 5.99 (d, J = 11.3 Hz, 1 H), 6.19 (d, J = 11.3 Hz, 1 H), 6.22−6.32 (m, 1 H), 8.03 (br s, 1 H). LRMS-ES(−) m/z 613 (35, M − H). HRMS-ES(+) calcd for $C_{32}H_{40}D_6O_4F_6$: 637.3569 (M + Na)1$^+$; found 637.3570.

(20*S*)-1α,25-Dihydroxy-21-(3-hydroxy-3-trifluoromethyl-4,4,4-trifluoro-but-1(*E*)-enyl)-26,26,26,27,27,27-hexadeutero-19-nor-cholecalciferol (3S-2). The diphenylphosphine oxide **18** (0.5340 g, 0.936 mmol) was deprotonated with a 1.6 M solution of butyllithium in hexane, allowed to react with the ketone **14S-b** (0.3498 g, 0.561 mmol), and the condensation product was purified as described for **2S-2**; the resulting partially desilylated material (0.48 g) was dissolved in a 1 M soln of TBAF (5 mL) and allowed to stand for 63 h at ambient temperature. The deprotected material was isolated and purified by chromatography as described to afford **3S-2** as a white, solid foam (0.2862 g, 84%); UV λ_{max} (ε) 243 (34631), 251(40591), 261 (27593) nm (methanol); $[\alpha]_D^{28}$ +42.3° (c 0.25, methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.53 (s, 3 H), 1.01−1.72 (m, 17 H), 1.72−2.12 (m, 5 H), 2.15−2.31 (m, 2 H), 2.31−2.47 (m, 2 H), 2.66−2.83 (m, 1 H), 3.76−3.95 (m, 2 H), 4.04 (s, 1 H), 4.40 (d, J = 3.5 Hz, 1 H), 4.50 (d, J = 3.5 Hz, 1 H), 5.61 (d, J = 15.2 Hz, 1 H), 5.81 (d, J = 11.0 Hz, 1 H), 6.08 (d, J = 11.0 Hz, 1 H), 6.28 (ddd, J = 15.2, 7.4, 7.1 Hz, 1 H), 8.03 (s, 1 H). ^{13}C NMR (400 MHz, DMSO-d_6) δ 11.98, 19.26, 21.66, 23.04, 26.72, 28.23, 31.06, 33.29, 36.98, 39.01, 42.23, 44.15, 44.61, 45.19, 52.20, 55.59, 65.32, 65.59, 68.43, 75.51, 116.12, 119.31, 120.95, 122.74, 134.76, 137.58, 139.34. LRMS-ES(−) m/z 601 (30, M − H). HRMS-ES(+) calcd for $C_{31}H_{40}D_6O_4F_6$: 625.3569 (M + Na)1$^+$; found 625.3572.

(20*R*)-1α,25-Dihydroxy-21-(3-hydroxy-3-trideuteromethyl-4,4,4-trideutero-butyl)- 26,26,26,27,27,27-hexafluoro-23(*E*)-ene-19-nor-cholecalciferol (3R-2). The diphenylphosphine oxide **18** (0.244 g, 0.427 mmol) was deprotonated with a 1.6 M solution of butyllithium in hexane and allowed to react with the ketone **14R-b** (0.152 g, 0.244 mmol). The condensation product was purified as described for **2S-2**; the resulting partially desilylated material was dissolved in a 1 M soln of TBAF (3 mL) and allowed to stand for 50 h at ambient temperature. The deprotected material was isolated and purified by chromatography as described to afford **3R-2**, which was crystallized from methyl formate (90 mg, 0.1493 mmol, 61% from ketone **14R-b**); UV λ_{max} (ε) 243 (33111), 251(35071), 261 (26178) nm (methanol); $[\alpha]_D^{28}$ +44.2° (c 0.22, methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.52 (s, 3 H), 1.10−1.73 (m, 17 H), 1.76−2.14 (m, 6 H), 2.16−2.33 (m, 2 H), 2.43 (d, J = 10.2 Hz, 1 H), 2.75 (d, J = 10.0 Hz, 1 H), 3.73−3.84 (m, 1 H), 3.84−3.94 (m, 1 H), 4.04 (s, 1 H), 4.40 (d, J = 3.7 Hz, 1 H), 4.50 (d, J = 3.7 Hz, 1 H), 5.62 (d, J = 15.2 Hz, 1 H), 5.80 (d, J = 11.1 Hz, 1 H), 6.08 (d, J = 11.1 Hz, 1 H), 6.26 (ddd, J = 15.2, 7.5, 7.4 Hz, 1 H), 8.03 (s, 1 H). ^{13}C NMR (400 MHz, DMSO-d_6) δ 11.99, 19.34, 21.79, 23.09, 26.87, 28.27, 30.92, 33.39, 36.97, 42.24, 44.03, 44.63, 45.19, 52.10, 55.65, 65.31, 65.58, 68.43, 75.47, 116.00, 119.13, 120.86, 122.62, 134.62, 137.55, 139.21. LRMS-ES(−) m/z 601 (34, M − H). HRMS-ES(+) calcd for $C_{31}H_{40}D_6O_4F_6$: 625.3569, found 625.3575.

(20*S*)-1α-Fluoro-25-hydroxy-21-(3-hydroxy-3-trifluoromethyl-4,4,4-trifluoro-but-1(*E*)-enyl)-26,26,26,27,27,27-hexadeutero-cholecalciferol (3S-3). The diphenylphosphine oxide **19** (0.35 g, 0.743 mmol)) was deprotonated with a 1.6 M solution of butyllithium in hexane and allowed to react with the ketone **14S-b** (0.295 g, 0.474 mmol). The condensation product was purified as described for **2S-2**; the resulting partially desilylated material was dissolved in a 1 M soln of TBAF (4 mL) and allowed to stand for 25 h at ambient temperature. The deprotected material was isolated and purified by chromatography as described to afford a crystalline residue. This material was coevaporated twice from hexane and then taken up in methyl formate, filtered, concentrated to a volume of ca. 1−2 mL, and warmed to dissolve most crystals and then allowed to crystallize, first at room temperature, then refrigerated. The mother liquor was decanted, the solids washed with pentane then dried to give **3S-3** (0.14 g, 48%); mp 148−50 °C; UV λ_{max} (ε) 212 (16206), 242(15668), 271 (15186) nm (methanol); $[\alpha]_D^{28}$ +30.72° (c 0.23, methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.52 (s, 3 H), 1.03−1.58 (m, 13 H), 1.59−1.85 (m, 4 H), 1.92 (d, J = 11.5 Hz, 1 H), 1.99 (t, J = 9.2 Hz, 1 H), 2.05−2.18 (m, 2 H), 2.18−2.29 (m, 1 H), 2.29−2.42 (m, 1 H), 2.52−2.56 (m, 1 H), 2.83 (d, J = 12.6 Hz, 1 H), 3.82−3.98 (m, 1 H), 4.02 (s, 1 H), 4.86 (d, J = 4.3 Hz, 1 H), 5.00 (s, 1 H), 5.15 (d, J = 49.7 Hz, 1 H), 5.39 (br s, 1 H), 5.61 (d, J = 15.6 Hz, 1 H), 5.95 (d, J = 11.1 Hz, 1 H), 6.20−6.33 (m, 1 H), 6.37 (d, J = 11.1 Hz, 1 H), 8.03 (s, 1 H). ^{13}C NMR (400 MHz, DMSO-d_6) δ 11.89, 19.27, 21.62, 23.09, 26.63, 28.38, 31.05, 33.24, 38.94, 40.70, 44.11, 44.88, 45.40, 52.14, 55.55, 64.52, 68.40, 75.50, 91.28, 92.94, 15.51, 117.02, 119.30, 122.73, 124.17, 133.05, 137.52, 141.91, 143.21. ^{19}F NMR (376.31 MHz) δ −75.86 Hz, 6F, m. LRMS-ES(−) m/z 661 (100, M + HCOO$^-$), 615 (10, M − H). HRMS-ES(+) calcd for $C_{32}H_{39}D_6O_3F_7$: 639.3526 [M + Na]1$^+$; found 639.3515.

(20*R*)-1α-Fluoro-25-hydroxy-21-(3-hydroxy-3-trideuteromethyl-4,4,4-trideutero-butyl)- 26,26,26,27,27,27-hexafluoro-23(*E*)-ene-cholecalciferol (3R-3). The diphenylphosphine oxide **19** (0.374 g, 0.795 mmol) was deprotonated with a 1.6 M solution of butyllithium in hexane and allowed to react with the ketone **14R-b** (0.262 g, 0.421 mmol). The condensation product was purified as described for **2S-2**; the resulting partially desilylated material was dissolved in a 1 M soln of TBAF (3 mL) and allowed to stand for 24 h at ambient temperature. The deprotected material was isolated and purified by chromatography as described to afford **3R-3** as a white, solid foam (0.153 g, 59%; UV λ_{max} (ε) 209 (23061), 241 (15755), 270 nm (14829); $[\alpha]_D^{28}$ +29.2° (c 0.26, methanol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.55 (s, 3 H), 1.17−1.78 (m, 16 H), 1.78−2.13 (m, 7 H), 2.12−2.42 (m, 3 H), 2.61 (dd, J = 13.1, 3.1 Hz, 1 H), 2.77−2.87 (m, 1 H), 4.20

(ddd, J = 7.4, 3.8, 3.7 Hz, 1 H), 5.12 (ddd, J = 49.7, 6.1, 3.5 Hz, 1 H), 5.10 (s, 1 H), 5.38 (br s, 1 H), 5.58 (d, J = 15.4 Hz, 1 H), 6.02 (d, J = 11.1 Hz, 1 H), 6.27 (ddd, J = 15.4, 8.5, 6.5 Hz, 1 H), 6.39 (d, J = 11.1 Hz, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 12.21, 19.70, 22.12, 23.56, 27.44, 29.05, 31.70, 34.83, 39.95, 40.26, 40.67, 43.50, 44.93, 45.95, 53.08, 56.26, 66.50, 71.40, 75.83, 90.89, 92.60, 115.23, 117.14, 119.07, 122.42, 125.43, 131.48, 138.09, 142.84, 143.00. ^{19}F NMR (376.31 MHz) δ −77.80, 3F, q, $^4J_{F,F}$ = 7.90 Hz, −77.88, 3F, q, $^4J_{F,F}$ = 7.80 Hz. LRMS-ES(−) m/z 661 (100, M + $HCOO^-$), 615 (20, M − H). HRMS-ES(+) calcd for $C_{32}H_{39}D_6O_3F_7$: 639.3526 [M + Na]1$^+$; found 639.3523.

(20*S*)-1α,25-Dihydroxy-21-(3-hydroxy-3-trifluoromethyl-4,4,4-trifluoro-but-1(*Z*)-enyl)-26,26,26,27,27,27-hexadeutero-cholecalciferol (4S-1). The diphenylphosphine oxide **17** (0.497 g, 0.853 mmol) was deprotonated with a 1.6 M solution of butyllithium in hexane and allowed to react with the ketone **16S-b** (0.288 g, 0.462 mmol). The condensation product was purified as described for **2S-2**; the resulting partially desilylated material was dissolved in a 1 M soln of TBAF (5 mL) and allowed to stand for 19 h at ambient temperature. The deprotected material was isolated and purified by chromatography as described to afford **4S-1** as a white, solid foam (0.238 g, 84%); UV λ_{max} (ε) 210 (66396), 264 (16769) nm; $[\alpha]_D^{28}$ +29.2° (c 0.26, methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.52 (s, 3 H), 1.09−1.37 (m, 8 H), 1.37−1.58 (m, 5 H), 1.58−1.70 (m, 3 H), 1.74−1.86 (m, 2 H), 1.90−2.03 (m, 2 H), 2.17 (dd, J = 13.4, 5.1 Hz, 1 H), 2.32−2.47 (m, 2 H), 2.71−2.86 (m, 2 H), 3.99 (br s, 1 H), 4.02 (s, 1 H), 4.19 (br s, 1 H), 4.55 (d, J = 2.1 Hz, 1 H), 4.76 (br s, 1 H), 4.87 (d, J = 4.3 Hz, 1 H), 5.23 (br s, 1 H), 5.42 (d, J = 11.5 Hz, 1 H), 5.96−6.10 (m, 2 H), 6.19 (d, J = 11.5 Hz, 1 H), 8.01 (s, 1 H). ^{13}C NMR (400 MHz, DMSO-d_6) δ 11.80, 19.27, 21.79, 23.17, 26.34, 28.41, 29.44, 31.43, 43.12, 44.33, 45.23, 52.30, 55.61, 65.08, 68.49, 76.78, 109.94, 116.77, 117.57, 122.50, 123.02, 135.88, 140.02, 141.37, 149.52. ^{19}F NMR (376.31 MHz) δ −75.87 Hz, 6F, m. LRMS-ES(−) m/z 659 (85, M + $HCOO^-$), 613 (100, M − H). HRMS-ES(+) calcd for $C_{32}H_{40}D_6O_4F_6$: 637.3569 [M + Na]1$^+$; found 637.3574.

(20*R*)-1α,25-Dihydroxy-21-(3-hydroxy-3-trideuteromethyl-4,4,4-trideutero-butyl)-26,26,26,27,27,27-hexafluoro-23(*Z*)-ene-cholecalciferol (4R-1). The diphenylphosphine oxide **17** (0.429 g, 0.736 mmol) was deprotonated with a 1.6 M solution of butyllithium in hexane and allowed to react with the ketone **16S-b** (0.3518 g, 0.565 mmol). The condensation product was purified as described for **2S-2**; the resulting partially desilylated material was dissolved in a 1 M soln of TBAF (4 mL) and allowed to stand for 32 h at ambient temperature. The deprotected material was isolated and purified by chromatography as described to afford **4R-1** as a white, solid foam (0.250 g, 72%); UV λ_{max} (ε) 212 (14818), 266 (17067) nm; $[\alpha]_D^{28}$ +18.1 (c = 0.29%, methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.52 (s, 3 H), 1.12−1.58 (m, 13 H), 1.58−1.70 (m, 3 H), 1.70−1.84 (m, 2 H), 1.89 (d, J = 11.1 Hz, 1 H), 1.93−2.04 (m, 1 H), 2.17 (dd, J = 13.4, 5.1 Hz, 1 H), 2.31−2.45 (m, 2 H), 2.53−2.62 (m, 1 H), 2.80 (d, J = 10.2 Hz, 1 H), 3.97 (br s, 1 H), 4.02 (s, 1 H), 4.18 (br s, 1 H), 4.55 (d, J = 3.4 Hz, 1 H), 4.76 (br s, 1 H), 4.87 (d, J = 4.5 Hz, 1 H), 5.23 (br s, 1 H), 5.41 (d, J = 11.9 Hz, 1 H), 5.99 (d, J = 11.1 Hz, 1 H), 6.02−6.11 (m, 1 H), 6.19 (d, J = 11.1 Hz, 1 H), 7.98 (s, 1 H). ^{13}C NMR (400 MHz, DMSO-d_6) δ 11.99, 19.39, 21.80, 23.20, 26.48, 28.40, 29.39, 31.39, 43.12, 44.17, 44.91, 45.35, 52.23, 55.55, 65.04, 68.47, 76.73, 109.85, 116.69, 117.49, 122.37, 122.89, 135.74, 139.85, 141.22, 149.33. ^{19}F NMR (376.31 MHz) δ −75.83 Hz, 6F, m. LRMS-ES(−) m/z 659 (30, M + HCOOH-H^-), 613 (100, M − H). HRMS-ES(+) calcd for $C_{32}H_{40}D_6O_4F_6$: 637.3569 [M + Na]1$^+$; found 637.3562.

(20*S*)-1α,25-Dihydroxy-21-(3-hydroxy-3-trifluoromethyl-4,4,4-trifluoro-but-1(*Z*)-enyl)-26,26,26,27,27,27-hexadeutero-19-nor-cholecalciferol (4S-2). The diphenylphosphine oxide **18** (0.4436, 0.778 mmol) was deprotonated with a 1.6 M solution of butyllithium in hexane and allowed to react with the ketone **16S-b** (0.2869 g, 0.460 mmol) and the condensation product was purified as described for **2S-2**; the resulting partially desilylated material was dissolved in a 1 M soln of TBAF (5 mL) and allowed to stand for 32 h at ambient temperature. The deprotected material was isolated and purified by chromatography as described to afford **4S-2** as a white, solid foam (0.243 g, 87.6%); UV λ_{max} (ε) 243 (34246), 252 (39955), 261 (27120) nm; $[\alpha]_D^{28}$ +31 (c = 0.31%, methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.52 (s, 3 H), 1.07−1.72 (m, 17 H), 1.72−2.15 (m, 5 H), 2.26 (d, J = 11.3 Hz, 1 H), 2.32−2.47 (m, 2 H), 2.70−2.83 (m, 2 H), 3.80 (br s, 1 H), 3.87 (br s, 1 H), 4.02 (s, 1 H), 4.38 (d, J = 3.6 Hz, 1 H), 4.49 (d, J = 3.6 Hz, 1 H), 5.42 (d, J = 11.9 Hz, 1 H), 5.80 (d, J = 11.1 Hz, 1 H), 5.98 - 6.13 (m, 2 H), 8.01 (s, 1 H). ^{13}C NMR (400 MHz, DMSO-d_6) δ 11.91, 19.25, 21.69, 23.02, 26.40, 28.24, 29.43, 31.43, 36.96, 42.21, 44.34, 45.07, 52.31, 55.56, 65.29, 65.57, 68.47, 76.76, 116.02, 116.75, 120.94, 123.02, 134.69, 139.40, 141.38. ^{19}F NMR (376.31 MHz) δ −75.85 Hz, 6F, m. LRMS-ES(−) m/z 647 (55, M + HCOOH-H^-), 602 (28, M), 601 (100, M − H). HRMS-ES(+) calcd for $C_{31}H_{40}D_6O_4F_6$: 625.3569 [M + Na]1$^+$; found 625.3576.

(20*R*)-1α,25-Dihydroxy-21-(3-hydroxy-3-trideuteromethyl-4,4,4-trideutero-butyl)-26,26,26,27,27,27-hexafluoro-23(*Z*)-ene-19-nor-cholecalciferol (4R-2). The diphenylphosphine oxide **18** (0.5078 g, 0.889 mmol) was deprotonated with a 1.6 M solution of butyllithium in hexane and allowed to react with the ketone **16R-b** (0.3298 g, 0.529 mmol). The condensation product was purified as described for **2S-2**; the resulting partially desilylated material was dissolved in a 1 M soln of TBAF (4 mL) and allowed to stand for 48.5 h at ambient temperature. The deprotected material was isolated and purified by chromatography as described to afford **4R-2** as a white, solid foam (0.2446 g, 76.7%); UV λ_{max} (ε) 243 (32530), 252 (38012), 261 (25710) nm; $[\alpha]_D^{25}$ +51.4° (c = 0.33%, methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.52 (s, 3 H), 1.13−1.72 (m, 17 H), 1.80 (br s, 1 H), 1.89 (d, J = 11.3 Hz, 1 H), 1.93−2.12 (m, 3 H), 2.27 (d, J = 11.1 Hz, 1 H), 2.32−2.48 (m, 2 H), 2.53−2.62 (m, 1 H), 2.69−2.81 (m, 1 H), 3.76−3.84 (m, 1 H), 3.88 (br s, 1 H), 4.02 (s, 1 H), 4.38 (d, J = 3.5 Hz, 1 H), 4.48 (d, J = 3.5 Hz, 1 H), 5.42 (d, J = 11.9 Hz, 1 H), 5.80 (d, J = 11.1 Hz, 1 H), 6.01−6.11 (m, 2 H), 7.99 (s, 1 H). ^{13}C NMR (400 MHz, DMSO-d_6) δ 12.11, 19.42, 21.71, 23.06, 26.55, 28.25, 29.40, 31.39, 36.95, 39.57, 42.23, 44.17, 45.20, 52.25, 55.51, 65.27, 65.54, 68.44, 76.73, 115.94, 116.70, 120.83, 122.92, 134.56, 139.25, 141.22. ^{19}F NMR (376.31 MHz) δ −75.82 Hz, 6F, m. LRMS-ES(−) m/z 647 (30, M + $HCOO^-$), 602 (25, M), 601 (100, M − H). HRMS-ES(+) calcd for $C_{31}H_{40}D_6O_4F_6$: 625.3569 [M + Na]1$^+$; found 625.3583.

(20*S*)-1α-Fluoro-25-hydroxy-21-(3-hydroxy-3-trifluoromethyl-4,4,4-trifluoro-but-1(*Z*)-enyl)-26,26,26,27,27,27-hexadeutero-cholecalciferol (4S-3). The diphenylphosphine oxide **19** (0.3557 g, 0.756 mmol) was deprotonated with a 1.6 M solution of butyllithium in hexane and allowed to react with the ketone **16S-b** (0.2700 g, 0.433 mmol) and the condensation product was purified as described for **2S-2**; the resulting partially desilylated material was dissolved in a 1 M soln of TBAF (5 mL) and allowed to stand for 24.5 h at ambient temperature. The deprotected material was isolated and purified by chromatography as described to afford **4S-3** as a white, solid foam (0.1714 g, 64%); UV λ_{max} (ε) 209 (13713), 243 (13893), 271 (13673) nm; $[\alpha]_D^{25}$ +16.8° (c = 0.20%, methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.51 (s, 3 H), 1.06−1.88 (m, 18 H), 1.88−2.04 (m, 2 H), 2.04−2.21 (m, 2 H), 2.33−2.46 (m, 1 H), 2.70−2.88 (m, 2 H), 3.83−3.97 (m, 1 H), 4.01 (s, 1 H), 4.86 (d, J = 4.3 Hz, 1 H), 5.00 (s, 1 H), 5.15 (d, J = 49.9 Hz, 1 H), 5.33−5.46 (m, 2 H), 5.95 (d, J = 11.1 Hz, 1 H), 6.04 (ddd, J = 12.1, 6.4, 6.2 Hz, 1 H), 6.37 (d, J = 11.1 Hz, 1 H), 8.01 (s, 1 H). ^{13}C NMR (400 MHz, DMSO-d_6) δ 11.83, 19.27, 21.66, 23.09, 26.34, 28.42, 29.39, 31.42, 40.70, 44.31, 44.87, 45.31, 52.26, 55.55, 64.52, 68.46, 76.77, 91.27, 92.94, 115.47, 116.77, 116.94, 123.01, 133.00, 141.34, 141.99, 143.23. ^{19}F NMR (376.31 MHz) δ −75.85 Hz, 6F, m. LRMS-ES(−) m/z 661 (55, M + HCOOH-H^-), 616 (20, M), 615 (100,

M − H). HRMS-ES(+) calcd for $C_{32}H_{39}D_6O_3F_7$: 639.3526 [M + Na]1$^+$; found 639.3523.

(20*R*)-1α-Fluoro-25-hydroxy-21-(3-hydroxy-3-trideuteromethyl-4,4,4-trideutero-butyl)-26,26,26,27,27,27-hexafluoro-23(*Z*)-ene-cholecalciferol (4R-3). The diphenylphosphine oxide **19** (0.5632 g, 1.20 mmol) was deprotonated with a 1.6 M solution of butyllithium in hexane and allowed to react with the ketone **16R-b** (0.3354 g, 0.538 mmol) and the condensation product was purified as described for **2S-2**; the resulting partially desilylated material was dissolved in a 1 M soln of TBAF (4 mL) and allowed to stand for 23 h at ambient temperature. The deprotected material was isolated and purified by chromatography as described to afford **4R-3** as a white solid that was crystallized from methyl formate (0.285 g, 86%); UV λ_{max} (ε) 208 (17000), 242 (16068), 270 (15615) nm; $[\alpha]_D^{25}$ +36.2° (c = 0.31%, methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.51 (s, 3 H), 1.12−1.58 (m, 13 H), 1.58−1.84 (m, 4 H), 1.90 (d, J = 11.3 Hz, 1 H), 2.00 (t, J = 9.2 Hz, 1 H), 2.04−2.20 (m, 2 H), 2.32−2.46 (m, 1 H), 2.52−2.61 (m, 2 H), 2.83 (d, J = 12.6 Hz, 1 H), 3.82−3.95 (m, 1 H), 4.02 (s, 1 H), 4.86 (d, J = 4.3 Hz, 1 H), 4.99 (s, 1 H), 5.14 (ddd, J = 50.1, 5.1, 3.2 Hz, 1 H), 5.37−5.44 (m, 2 H), 5.94 (d, J = 11.3 Hz, 1 H), 6.00−6.10 (m, 1 H), 6.37 (d, J = 11.3 Hz, 1 H), 7.98 (s, 1 H). ^{13}C NMR (400 MHz, DMSO-d_6) δ 12.03, 19.37, 21.69, 23.13, 26.49, 28.41, 29.39, 31.37, 40.70, 44.17, 44.87, 45.42, 52.19, 55.49, 64.50, 68.44, 76.73, 91.19, 92.86, 115.35, 116.70, 116.88, 122.90, 124.07, 132.88, 141.22, 141.82, 143.07. ^{19}F NMR (376.31 MHz) δ −75.83 Hz, 6F, m, −170.48 Hz, 1F, m). LRMS-ES(−) m/z 661 (20, M + HCOO$^-$), 616 (30, M), 615 (100, M − H). HRMS-ES(+) calcd for $C_{32}H_{39}D_6O_3F_7$: 639.3526 [M + Na]1$^+$, found 639.3522.

Cell Culture. The MCF10CA1a human breast epithelial cell line was developed and provided by Dr. Fred Miller's group at the Karmanos Cancer Institute (Detroit, MI). The cells were maintained in DMEM/F12 medium supplemented with 5% horse serum, 1% penicillin/streptomycin, and 1% HEPES solution at 37 °C, 5% CO_2. The cells were passaged every 3−4 days. Human promyelocytic leukemia NB4 cells (Dr. Ethan Dmitrovsky, Dartmouth Medical School, Hanover, NH) were grown in suspension culture at 37 °C with 5% CO_2 in RPMI 1640 (Sigma, St. Louis, MO) with 10% heat-activated, defined iron-supplemented bovine calf serum (Hyclone, Logan, UT). The NB4 cells were passaged two to three times a week to maintain log-phase growth.

Determination of Cell Proliferation by [^{3}H]Thymidine Uptake Assay. The MCF10CA1a human breast epithelial cells (10000 cells/well in a 24-well plate) were incubated with compounds in DMEM/F12 medium supplemented with 5% horse serum, 1% penicillin/streptomycin, and 1% HEPES solution for 3 days. One μCi of [^{3}H]thymidine was added to each well 3 h before the harvest. The cells were washed with PBS and precipitated with 10% trichloroacetic acid for 10 min. The cells were solubilized with the NaOH solution containing the salmon sperm DNA, and the radioactivity of [^{3}H] thymidine incorporated to the cells was analyzed with a liquid scintillation counter (Beckman Coulter, Fullerton, CA).

Determination of Differentiation Markers. The NB4 cells were incubated with test compounds at 1 nM concentrations for 48 h. Aliquots of 1 × 10^6 cells were washed twice with PBS and then incubated with 0.5 μL of MY4-RD1 and 0.5 μL of Mo1-FITC (Coulter, Miami, FL) to analyze the expression of differentiated cell surface markers CD14 and CD11b. The cells were suspended in 0.5 mL of PBS and analyzed with an Epics Profile II instrument (Coulter Electronics, Hialeah, FL).

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Supporting Information Available: Elemental analyses results of all final compounds and crystallographic data of **11S-b** and **2R-2**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Norman, A. W.; Manchand, P. S.; Uskokovic, M. R.; Okamura, W. H; Takeuchi, J. A; Bishop, J. E.; Hisatake, J. I.; Koeffler, H. P.; Peleg, S. Characterization of a novel analogue of 1alpha,25(OH)$_2$ vitamin D3 with two side chains: interaction with its nuclear receptor and cellular actions. *J. Med. Chem.* **2000**, *43*, 2719–2730.
(2) Liu, Y.-Y.; Collins, E. D.; Norman, A. W.; Peleg, S. Differential interaction of 1α,25-dihydroxyvitamin D3 analogs and their 20-epi homologs with vitamin D receptor. *J. Biol. Chem.* **1997**, *272*, 3336–3345.
(3) Liu, Y.-Y.; Nguyen, C.; Gradezi, S.; Schnirer, I.; Peleg, S. Differential regulation of heterodimerization by 1α,25-dihydroxyvitamin D3 and its 20-epi analog. *Steroids* **2001**, *66*, 203–212.
(4) Jaaskelainen, T.; Ryhanen, S.; Mahonen, A.; Deluca, H. F.; Maenpaa, P. H. Mechanism of action of superactive vitamin D analogs through regulated receptor degradation. *J. Cell. Biochem.* **2000**, *76*, 548–558.
(5) Gonzalez, M.; Perez, S.; Pedro, L.; Fall, Y.; Gomez, G. Quantitative structure−activity relationship studies of vitamin D receptor affinity for analogues of 1α,25-dihydroxyvitamin D3. 1: WHIM descriptors. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5165–5169.
(6) Weyts, F. A.; Dhawan, P.; Zhang, X.; Bishop, J. E.; Uskokovic, M. R.; Ji, Y.; Studzinski, G. P.; Norman, A. W.; Christakos, S. Novel Gemini analogs of 1α, 25-dihydroxyvitamin D3 with enhanced transcriptional activity. *Biochem. Pharmacol.* **2004**, *67*, 1327–1336.
(7) Ciesielski, F.; Rochel, N.; Moras, D. Adaptability of the Vitamin D nuclear receptor to the synthetic ligand Gemini: Remodelling the LBP with one side chain rotation. *J. Steroid Biochem. Mol. Biol.* **2007**, *103*, 235–242.
(8) Ciesielski, F.; Rochel, N.; Mitschler, A.; Kouzmenko, A.; Moras, D. Structural investigation of the ligand binding domain of the zebrafish VDR in complexes with 1α,25(OH)2D3 and Gemini: purification, crystallization and preliminary X-ray diffraction analysis. *J. Steroid Biochem. Mol. Biol.* **2004**, *89−90*, 55–59.
(9) Molnar, F.; Peraekylae, M.; Carlberg, C. Vitamin D Receptor Agonists Specifically Modulate the Volume of the Ligand-Binding Pocket. *J. Biol. Chem.* **2006**, *281*, 10516–10526.
(10) Molnar, F.; Perakyla, M.; Carlberg, C. Vitamin D receptor agonists specifically modulate the volume of the ligand-binding pocket. *J. Biol. Chem.* **2006**, *281*, 10516–10526.
(11) Vaisanen, S.; Perakyla, M.; Karkkainen, J. I.; Uskokovic, M. R.; Carlberg, C. Structural evaluation of the agonistic action of a vitamin D analog with two side chains binding to the nuclear vitamin D receptor. *Mol. Pharmacol.* **2003**, *63*, 1230–1237.
(12) Norman, A. W.; Henry, H. L.; Bishop, J. E.; Song, X.-D.; Bula, C.; Okamura, W. H. Different shapes of the steroid hormone 1α,25-(OH)2-vitamin D3 act as agonists for two different receptors in the vitamin D endocrine system to mediate genomic and rapid responses. *Steroids* **2001**, *66*, 147–158.
(13) Maehr, H.; Uskokovic, M. R.; Adorini, L.; Reddy, G. S. Calcitriol Derivatives with Two Different Side Chains at C-20. II. Diastereoselective Syntheses of the Metabolically Produced 24(*R*)-Hydroxygemini. *J. Med. Chem.* **2004**, *47*, 6476–6484.
(14) Maehr, H.; Uskokovic, M.; Reddy, G. S.; Adorini, L. Calcitriol derivatives with two different side chains at C20. 24-Hydroxy derivatives as metabolic products and molecular probes for VDR exploration. *J. Steroid Biochem. Mol. Biol.* **2004**, *89−90*, 35–38.
(15) Maehr, H.; Uskokovic, M.; Adorini, L.; Penna, G.; Mariani, R.; Panina, P.; Passini, N.; Bono, E.; Perego, S.; Biffi, M.; Holick, M.; Spina, C.; Suh, N. Calcitriol derivatives with two different side chains at C-20. III. An epimeric pair of the gemini family with unprecedented antiproliferative effects on tumor cells and renin mRNA expression inhibition. *J. Steroid Biochem. Mol. Biol.* **2007**, *103*, 277–281.
(16) Baggiolini, E. G.; Hennessy, B.; Uskokovic, M. R. Deuterated analogs of 1,25-dihydroxycholecalciferol. U.S. Patent US 5087619, **1992**.

(17) Spina, C. S.; Ton, L.; Yao, M.; Maehr, H.; Wolfe, M. M.; Uskokovic, M.; Adorini, L.; Holick, M. F. Selective vitamin D receptor modulators and their effects on colorectal tumor growth. *J. Steroid Biochem. Mol. Biol*. **2007**, *103*, 757–762.
(18) Spina, C. S.; Tangpricha, V.; Uskokovic, M.; Adorini, L.; Maehr, H.; Holick, M. F. Vitamin D and Cancer. *Anticancer Res*. **2006**, *26* (4A), 2515–2524.
(19) Spina, C. S.; Tangpricha, V.; Yao, M.; Zhou, W.; Wolfe, M. M.; Maehr, H.; Uskokovic, M.; Adorini, L.; Holick, M. F. Colon cancer and solar ultraviolet B radiation and prevention and treatment of colon cancer in mice with vitamin D and its gemini analogs. *J. Steroid Biochem. Mol. Biol*. **2005**, *97*, 111–120.
(20) Adorini, L.; Penna, G.; Uskokovic, M. R.; Maehr, H. Preparation and formulation of gemini vitamin D3 compounds for the treatment of vitamin D3 associated states. WO 2004098522, **2004**.
(21) Maehr, H.; Uskokovic, M. R. Formal desymmetrization of the diastereotopic chains in gemini calcitriol derivatives with two different side chains at C-20. *Eur. J. Org. Chem*. **2004**, 1703–1713.
(22) Maehr, H.; Uskokovic, M.; Schaffner, C. P. A concise synthesis of dimethyl (2-oxopropyl)phosphonate and homologation of aldehydes to alkynes in a tandem process. *Synth. Commun*. **2009**, *39*, 299–310.
(23) Pilcher, A. S.; DeShong, P. Improved protocols for the selective deprotection of trialkylsilyl ethers using fluorosilicic acid. *J. Org. Chem*. **1993**, *58*, 5130–5134.
(24) Daniewski, A. R.; Garofalo, L. M.; Huchings, S. D.; Kabat, M. M.; Liu, W.; Okabe, M.; Radinov, R.; Yannikouros, G. P. Efficient Synthesis of the A-ring Phosphine Oxide Building Block useful for 1α,25-dihydroxy vitamin D3 and analogs. *J. Org. Chem*. **2002**, *67*, 1580–1587.
(25) Daniewski, A. R.; Garofalo, L. M.; Kabat, M. M. Improved preparation of A-ring phosphine oxides for the synthesis of vitamin D analogs. *Synth. Commun*. **2002**, *32*, 3031–3039.
(26) Saha, U. Process for producing phosphine oxide vitamin D precursors. U.S. Patent US 20088300427, **2008**.
(27) Hilpert, H.; Wirz, B. Novel versatile approach to an enantiopure 19-nor,des-C,D vitamin D3 derivative. *Tetrahedron* **2001**, *57*, 681–694.
(28) Courtney, L. F.; Lange, M.; Uskokovic, M. R.; Wovkulich, P. M. Asymmetric synthesis of a key ring-A synthon for 1α-hydroxy-19-nor vitamin D. *Tetrahedron Lett*. **1998**, *39*, 3363–3366.
(29) Perlman, K. L.; Swenson, R. E.; Paaren, H. E.; Schnoes, H. K.; DeLuca, H. F. *Tetrahedron Lett*. **1991**, *32*, 7663–7666.
(30) Kabat, M. M.; Garofalo, L. M.; Daniewski, A R.; Huchings, S. D.; Liu, W.; Okabe, M.; Radinov, R.; Zhou, Y. Efficient synthesis of 1α-fluoro A-ring phosphine oxide, a useful building block for vitamin D analogues, from (*S*)-carvone via a highly selective palladium-catalyzed isomerization of dieneoxide to dieneol. *J. Org. Chem*. **2001**, *66*, 6141–6150.
(31) Barber, P.; Mohr, P.; Muller, M; Masciadri, R. Efficient fluorination with tertabutylammonium dihydrogen trifluoride in a novel approach toward 1α-fluoro-25-hydroxy-vitamin D3 analogs. *J. Org. Chem*. **1998**, *63*, 6984–6989.
(32) Shiuey, S. J.; Kulesha, I.; Baggiolini, E. G.; Uskokovic, M. R. Total synthesis of 1α-fluoro-25-hydroxycholecalciferol and -ergocholecalciferol. *J. Org. Chem*. **1990**, *55*, 243–247.
(33) O'Kelly, J.; Uskokovic, M.; Lemp, N.; Vadgama, J.; Koeffler, H. P. Novel gemini-vitamin D3 analog inhibits tumor cell growth and modulates the Akt/mTOR signaling pathway. *J. Steroid Biochem. Mol. Biol*. **2006**, *100*, 107–116.
(34) Garay, E.; Jankowski, P.; Lizano, P.; Marczak, S.; Maehr, H.; Adorini, L.; Uskokovic, M. R.; Studzinski, G. P. Calcitriol derivatives with two different side-chains at C-20. Part 4: Further chain modifications that alter VDR-dependent monocytic differentiation potency in human leukemia cells. *Bioorg. Med. Chem*. **2007**, *15*, 4444–4455.
(35) Saito, T.; Okamoto, R.; Haritunians, T.; O'Kelly, J.; Uskokovic, M.; Maehr, H.; Marczak, S.; Jankowski, P.; Badr, R.; Koeffler, H. P. Novel gemini vitamin D3 analogs have potent antitumor activity. *J. Steroid Biochem. Mol. Biol*. **2008**, *112*, 151–156.
(36) Lee, H. J.; Liu, H.; Goodman, C.; Ji, Y.; Maehr, H.; Uskokovic, M.; Notterman, D.; Reiss, M.; Suh, N. Gene expression profiling changes induced by a novel Gemini Vitamin D derivative during the progression of breast cancer. *Biochem. Pharmacol*. **2006**, *72*, 332–343.
(37) Lee, H. J.; Wislocki, A.; Goodman, C.; Ji, Y.; Ge, R.; Maehr, H.; Uskokovic, M.; Reiss, M.; Suh, N. A novel vitamin D derivative activates bone morphogenetic protein signaling in MCF10 breast epithelial cells. *Mol. Pharmacol*. **2006**, *69*, 1840–1848.
(38) Lee, H. J.; Paul, S.; Atalla, N.; Thomas, P. E.; Lin, X.; Yang, I.; Buckley, B.; Lu, G.; Zheng, X.; Lou, Y.-R.; Conney, A. H.; Maehr, H.; Adorini, L.; Uskokovic, M.; Suh, N. Gemini vitamin D analogues inhibit estrogen receptor-positive and estrogen receptor-negative mammary tumorigenesis without hypercalcemic toxicity. *Cancer Prev. Res*. **2008**, *1*, 476–484.