Antiproliferative Hybrid Analogs of the Hormone 1α,25-Dihydroxyvitamin D_3: Design, Synthesis, and Preliminary Biological Evaluation†

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The combination of 10−12 kbar pressure plus Lewis acidic zinc dichloride promotes highly regioselective and stereoselective Diels−Alder cycloaddition between 3-bromo-2-pyrone, prepared in a new way, and unactivated terminal alkene 4-(*tert*-butyldimethylsiloxy)-1-butene. The conjugate base of A-ring allylic phosphine oxide **20** adds chemospecifically to the C-8 keto group of some C-8,C-24-diketones to form directly metabolically resistant 24-oxo analogs of 1α,25-dihydroxyvitamin D_3 (calcitriol). Several of these new hybrid analogs are as efficacious *in vitro* as calcitriol at inhibiting growth of murine keratinocytes even at physiologically relevant 10−100 nanomolar concentrations.

The hormone 1α,25-dihydroxyvitamin D_3 (calcitriol, **1**) is now known in humans to promote cell differentiation, to inhibit cell proliferation, and to regulate phosphorus metabolism, intestinal calcium absorption, and bone calcium mobilization.[1] This seco-steroid also affects the human immune system, and it is used in chemotherapy of diverse human diseases including osteoporosis and skin disorders such as psoriasis.[1−3] A serious practical medical problem occurs when administration of therapeutic amounts of calcitriol causes harmful hypercalcemia.[1] To minimize this undesirable calcemic activity, various low-calcemic or noncalcemic analogs of calcitriol that still retain desirable antiproliferative activity have been prepared. Outstanding examples of such beneficial calcitriol analogs contain structural modifications on the C,D-ring side chain like Leo Pharmaceutical Company's KH 1060 (**2**) and EB-1089 (**3**)[4] as well as Hoffmann-La Roche's Ro-23-7553 (**4**) (Chart 1).[5] Despite conventional wisdom in the early 1990's that considered any change to the 1α-hydroxyl group on the A-ring to severely undermine biological activity, we have designed and synthesized a conceptually new class of hybrid analogs incorporating an anticalcemic 1β-(hydroxymethyl) group on the A-ring[6] with a powerful antiproliferative structural unit on the C,D-ring side chain (*e.g.*, KH-1060 analog MCW-YB, **5**).[7] This new type of hybrid analog shows very weak calcemic activity but very strong regulation of growth and transcriptional activities.[8] Such new hybrid analogs combining structural modifications on both the A-ring and on the C,D-ring side chain also have strong nongenomic activity even at low nanomolar levels in stimulating rapid calcium flux in rat osteosarcoma cells.[9] Because this kind of hybrid analog **5** is so physiologically potent even though it does not bind well to the nuclear vitamin D receptor (nVDR) and does not have much calcemic activity, we have now prepared similar 1-(hydroxymethyl) hybrid analogs **6**−**12** with emphasis on C,D-ring side-chain substituents (*e.g.*, unsaturated as well as oxygenated versions) that might retard *in vivo* catabolism[10] and, therefore, that might cause these new hybrid analogs to have therapeutically desirable *in vivo* pharmacological properties. Preparation of these new hybrid analogs has involved development of useful new synthetic methodology, including a highly stereocontrolled inverse-electron-demand Diels−Alder cycloaddition using an unactivated 1-alkene plus 3-bromo-2-pyrone and including also an unexpectedly chemospecific monocoupling of an A-ring allylic phosphine oxide anion with some C,D-ring diketones.

Results and Discussion

Although the literature records a very poor yield in preparation of a metabolically characteristic 25-hydroxylated derivative of the 22-oxa analog KH-1060 (**2**),[11] we have discovered that the appropriate 25-hydroxylated primary tosylate (−)-**17** (Scheme 1), prepared enantiomerically pure according to literature protocol from chiral pool (−)-malic acid,[12] can be attached successfully to the

† Dedicated to Professor Dieter Seebach with admiration and friendship on the occasion of his 60th birthday.

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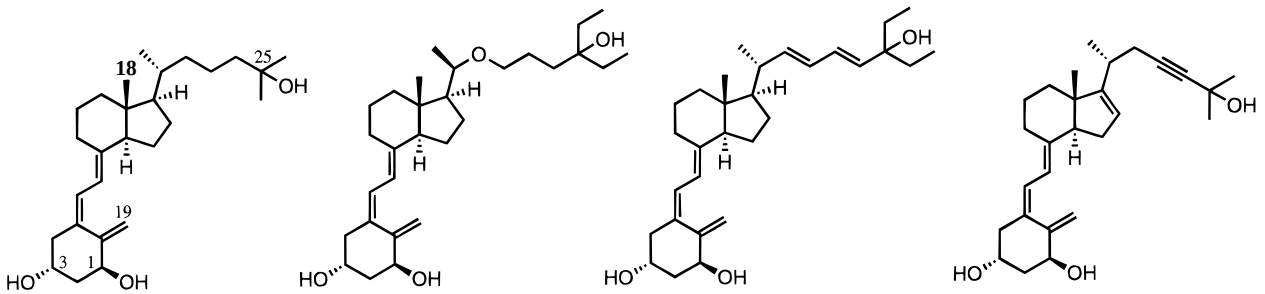
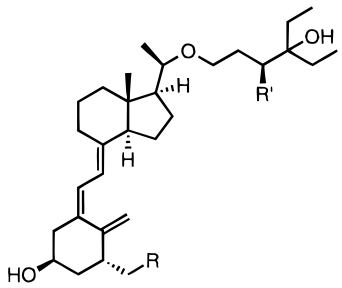
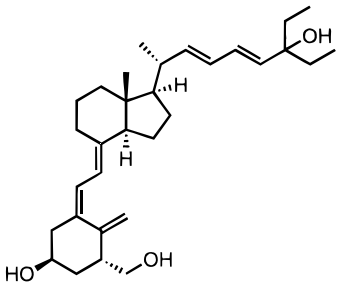
Chart 1



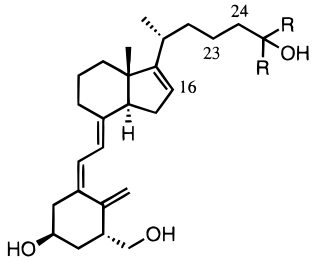
Calcitriol (**1**) KH-1060 (**2**) EB-1089 (**3**) Ro 23-7553 (**4**)



R = OH, R' = H, MCW-YB (**5**)
R = OH, R' = OH, MCW-GB-2 (**6b**)
R = CH_2F, R' = H, RHH-45b (**7b**)



MCW-EE (**8b**)



R = Me, 23-yne, JK-7-2 (**9b**)
R = Me, 23-H_2,24-H_2, JK-132-2 (**10b**)
R = Et, 23-H_2,24-H_2, JK-1626-2 (**11b**)
R = Me, 24-oxo, JK-1624-2 (**12b**)

C,D-ring secondary alcohol **16** *via* a Williamson ether coupling reaction (Scheme 1). Several attempts failed to prepare the corresponding O-protected 25-hydroxylated primary bromide for use in the Wilson coupling protocol.[13] A crucial step involved oxidation of the C-8 hydroxyl group in alcohol **18**; tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO) in the presence of molecular sieves were highly successful.[14] In this way, 22-oxa-25-hydroxylated C,D-ring ketone (−)-**19** was prepared starting from commercial vitamin D_2 [(+)-**13**] *via* secondary alcohol **16** (Scheme 1).[7] Convergent Horner−Wadsworth−Emmons[15,16] coupling of this enantiomerically pure C,D-ring ketone (−)-**19** with the racemic 1-(hydroxymethyl) A-ring allylic phosphine oxide **20**, followed by fluoride-induced silyl ether deprotection, gave two diastereomeric seco-steroids that were easily separated by preparative HPLC; Dowex resin-promoted deketalization[17] then produced hybrid analogs (−)-**6a** and (−)-**6b**. Assignment of stereochemistry at C-1 and C-3 in these diastereomers was achieved tentatively as in previous cases[18,19] using HPLC retention times, optical rotations, and especially 400 MHz ^{1}H NMR spectroscopy (Table 1).

As a new, direct, and efficient method for preparation of hydroxyethyl bicyclic synthon (±)-**21**,[20] we have discovered that Lewis acidic zinc dichloride promotes Diels−Alder 4 + 2 cycloaddition of 3-bromo-2-pyrone and an unactivated terminal alkene under 10−12 kbar pressure to form regioselectively and stereoselectively the desired *syn-endo* cycloadduct (±)-**21** (Scheme 2). This important new cycloaddition protocol combining a Lewis acid activator and high pressure[21] more than doubles the chemical yield of bicyclic primary alcohol (±)-**21** over that reported previously from 3-bromo-2-pyrone *via* a multistep protocol.[20] Furthermore, we report here a modified, milder experimental procedure that considerably raises the yield obtained relative to our previous method[22] for preparation of 3-bromo-2-pyrone from commercial 5,6-dihydro-2-pyrone (see the Experimental Section). Introduction of a fluorine atom was achieved smoothly *via* fluoride displacement of the primary mesylate corresponding to alcohol (±)-**21**, and removal of the bridgehead bromine atom (but not the primary fluorine atom) was achieved chemospecifically under radical conditions (Scheme 2). Fluorinated and debrominated bicyclic lactone (±)-**23** was then methanolyzed with concomitant formation of the conjugated enoate ester (±)-**24**. One-flask, regiospecific formation of a two-carbon-extended dienoate ester was achieved *via* a Claisen rearrangement using a sulfinyl orthoester,[23] and photochemical isomerization[16] formed the desired *Z*-dienoate ester (±)-**25**. Ester reduction, allylic alcohol chlorination, allylic chloride displacement with lithium diphenylphosphide, and finally phosphorus oxidation[16] gave racemic fluoroethyl A-ring allylic phosphine oxide (±)-**26**. Coupling of this phosphine oxide **26** with the enantiomerically pure C,D-ring ketone[7] shown in Scheme 2, followed by silyl ether deprotection, produced the two diastereomeric, fluorinated hybrid analogs

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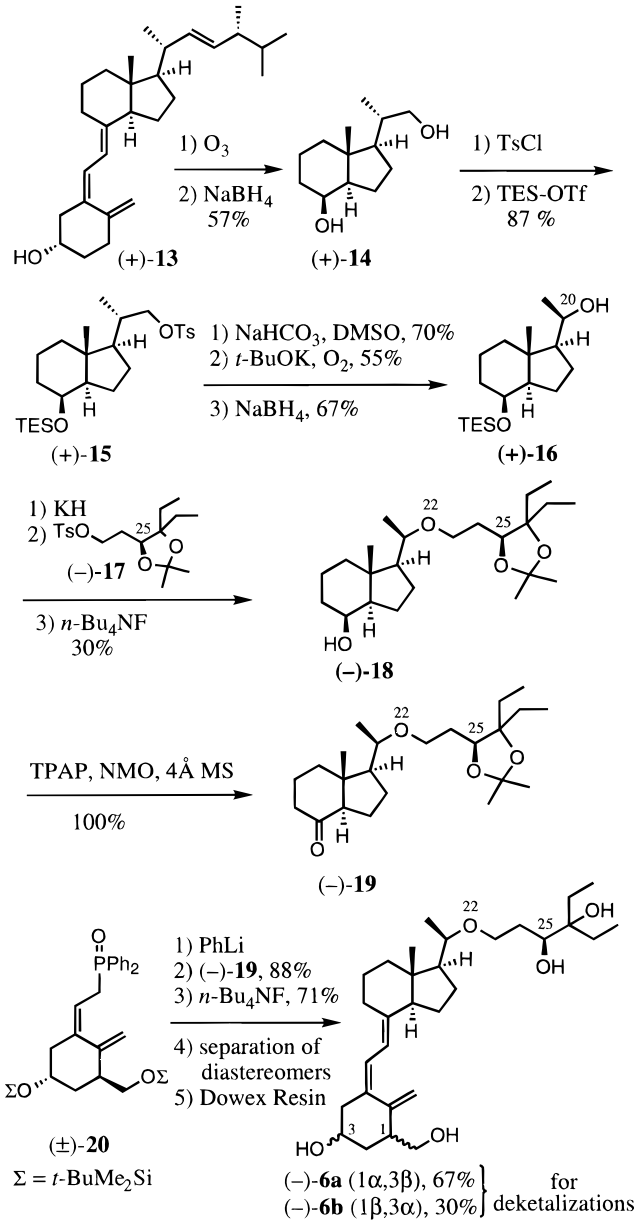
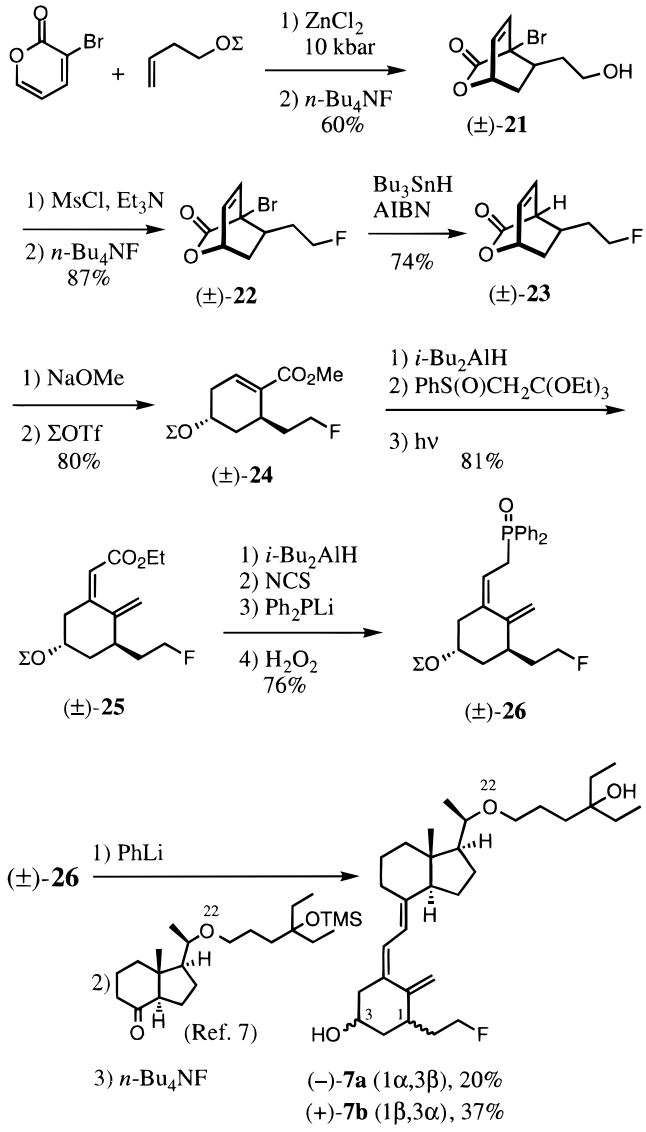
Scheme 1



Scheme 2



(−)-**7a** and (+)-**7b** (Scheme 2). It is noteworthy that the primary fluorine substituent survived many different radical and ionic reaction conditions during conversion of fluorinated bicycloadduct (±)-**22** into the final fluorinated hybrid analogs (−)-**7a** and (+)-**7b**. Separation of each enantiomerically pure diastereomer by preparative HPLC was followed by stereochemical characterization using mainly 400 MHz ^{1}H NMR (Table 1).

Because of the high biological activity and medical potential of C,D-ring side-chain diene analog EB-1089 (**3**)[4] and because preparation of the C,D-ring ketone precursor to EB-1089 has not been reported in the open literature, we describe here our synthesis (Scheme 3) of the EB-1089 C,D-ring ketone (+)-**34** carrying the characteristic 22,24-diene and 26,27-homoalkyl units that slow normal *in vivo* catabolism at the side chain.[24] Two important highlights of the reactions in Scheme 3 leading to enantiomerically pure C,D-ring diene ketone (+)-**34** are as follows: (1) the allylic phosphonate **29** was successfully added to side-chain aldehyde (+)-**28**, in sharp contrast to several failed attempts to prepare an allylic phosphine oxide already carrying an O-protected tertiary alcohol characteristic of EB-1089; and (2) although oxidation of the C-8 secondary hydroxyl group of diol **32** into the corresponding desired ketone failed with pyridinium chlorochromate (PCC) and with the Dess−Martin protocol, success was achieved using solid tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO) in the presence of molecular sieves.[14] Coupling of this enantiomerically pure C,D-ring diene ketone (+)-**34** with O-silylated 1-(hydroxymethyl) A-ring allylic phosphine oxide (±)-**20** gave, after silyl ether deprotection, the two diastereomeric hybrid analogs (−)-**8a** and (+)-**8b**, easily separable by preparative HPLC. Distinguishing between each enantiomerically pure diastereomer (−)-**8** and (+)-**8b** was based primarily on 400 MHz ^{1}H NMR spectroscopy (Table 1).

The Hoffmann-La Roche protocol allowed preparation of enantiomerically pure C,D-ring 16-en-23-yne ketone (+)-**35**[25,26] for coupling with our O-protected 1-(hydroxy-

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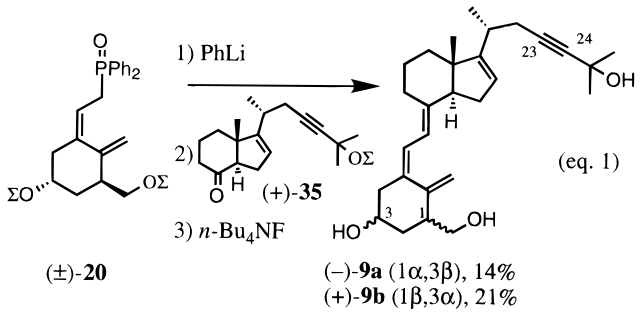
Table 1. Characteristics of New Hybrid Analogs

analogs	C-18	C-19a	C-19b	$[\alpha]^{25}_D$
6a	0.56	5.17 (d, 1.6 Hz)	5.01 (d, 2.0 Hz)	−175°
6b	0.54	5.15 (d, 1.2 Hz)	4.98 (d, 2.0 Hz)	−12°
7a	0.53	5.07 (d, 2.4 Hz)	4.91 (d, 2.4 Hz)	−176°
7b	0.49	5.04 (d, 2.0 Hz)	4.87 (d, 2.0 Hz)	+2.5°
8a	0.56	5.16 (s)	5.01 (d, 2.0 Hz)	−4.3°
8b	0.54	5.14 (s)	4.98 (d, 2.0 Hz)	+176°
9a	0.71	5.18 (d, 1.6 Hz)	5.03 (d, 2.0 Hz)	−86°
9b	0.69	5.15 (d, 1.2 Hz)	5.50 (d, 2.0 Hz)	+91°
10a	0.68	5.17 (d, 1.6 Hz)	5.02 (d, 2.0 Hz)	−49°
10b	0.66	5.1 (dd, 1.2, 0.8 Hz)	5.00 (d, 2.0 Hz)	+91°
11a	0.70	5.13 (d, 1.2 Hz)	4.89	−48°
11b	0.65	5.12 (br d, 2.0 Hz)	4.86 (d, 2.4 Hz)	+91°
12a	0.67	5.16 (broad s)	5.00 (broad s)	−29°
12b	0.65	5.15 (broad s)	5.00 (d, 1.6 Hz)	+94°
55a	0.914	5.15 (d, 2.0 Hz)	4.99 (d, 2.0 Hz)	−65°
55b	0.912	5.13 (d, 2.0 Hz)	4.97 (d, 2.0 Hz)	+100°

methyl) A-ring phosphine oxide (±)-**20** to form, after silyl ether deprotection, the HPLC-separated diastereomers (−)-**9a** and (+)-**9b** (eq 1); each enantiomerically pure diastereomer is distinguishable by 400 MHz ^{1}H NMR spectroscopy (Table 1).

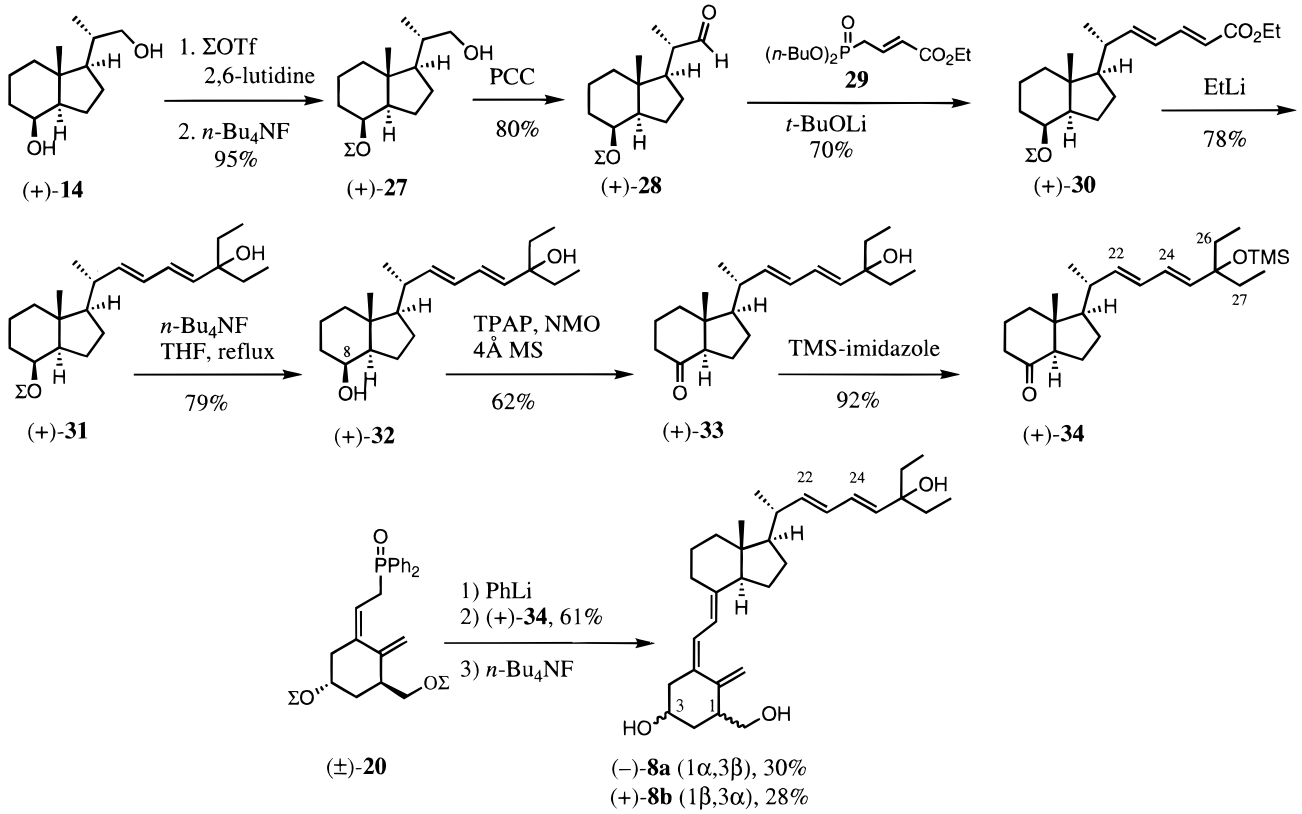
To examine what effect, if any, the 23-yne unsaturation has on the biological activities of such 16-en-23-yne



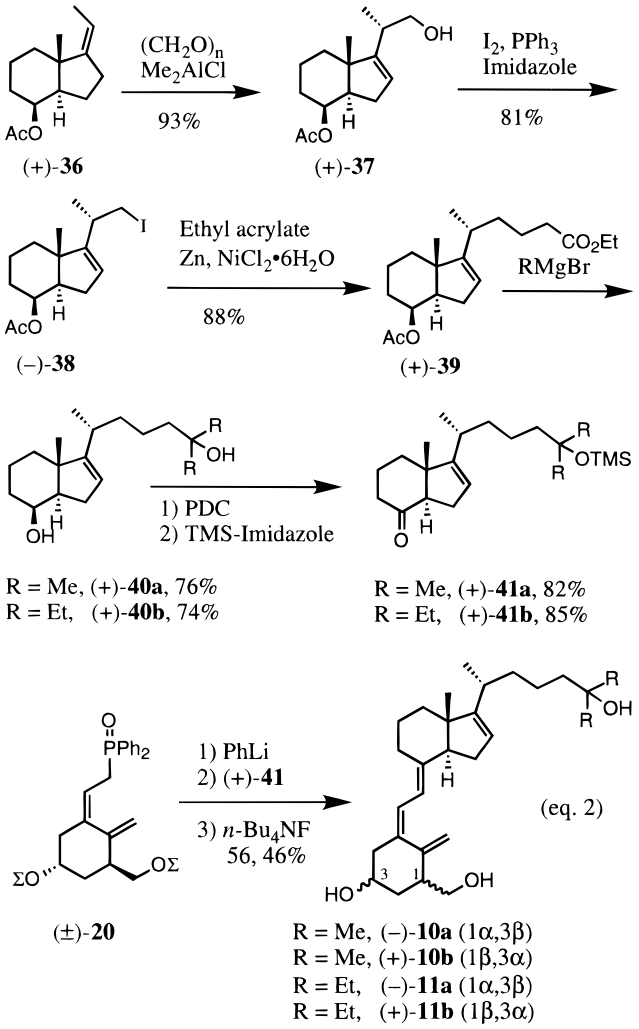
hybrid analogs, we prepared the corresponding 16-ene hybrid analog lacking 23-yne unsaturation; specifically, the 1-(hydroxymethyl)-16-ene hybrid analogs (−)-**10a** and (+)-**10b** were prepared *via* Scheme 4 and eq 2. Characteristic properties of these new hybrid analogs are listed in Table 1. Noteworthy aspects of Scheme 4 are as follows: (1) the successful dimethylaluminum chloride-promoted ene reaction[27−29] of the exocyclic olefinic group in C,D-ring chiron (+)-**36** and (2) the successful conjugate addition of multifunctional primary iodide (−)-**38** to ethyl acrylate[30] to produce the side chain ester (+)-**39** in excellent yield. Also, the 1-(hydroxymethyl)-26,27-homoalkyl 16-ene hybrid analogs (−)-**11a** and (+)-**11b** were desired to probe whether the additional 26,27-methylene groups would retard or alter *in vivo* catabolism of the side chain relative to that of the lower homologs (−)-**10a** and (+)-**10b** carrying the natural substitution pattern at the terminus of the C,D-ring side chain. Thus, homologs (−)-**11a** and (+)-**11b** were also prepared *via* Scheme 4 and eq 2; the characteristic ^{1}H NMR properties of these new hybrid analogs are listed in Table 1.

Finally, another type of 16-ene hybrid analog carrying a metabolically typical 24-oxo functionality[31,32] was desired. The presence of such a C-24 ketone, however, posed a significant chemical challenge. Constructing a

Scheme 3

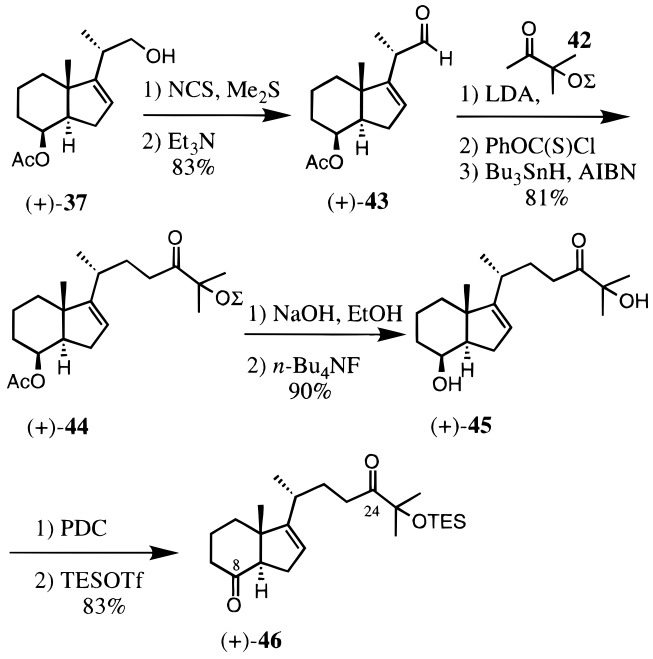


Scheme 4

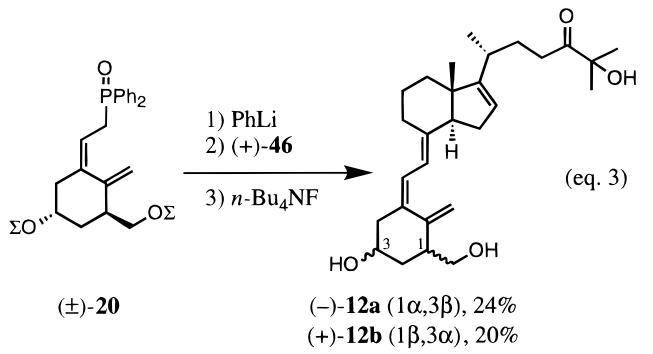


complete calcitriol analog with a protected 24-oxo group would entail a lengthy synthesis and a final deprotection of this functionality in the presence of the 16-ene double bond and of the reactive conjugated triene unit characteristic of these vitamin D_3 systems. Although there is precedent for using an acidic inorganic polymer[17] to deprotect ketal-bearing calcitriol side chains successfully (for example, see Scheme 1), the presence of the 16-ene functionality was of concern; neighboring group participation by the trisubstituted δ-16,17 carbon−carbon double bond nucleophically attacking the electrophilic C-24 carbon atom of a polarized C-24 ketone (*e.g.*, an ene reaction[33−35]) or a protonated C-24 ketal (a Prins-type reaction[36,37]) might be a serious unwanted side reaction. On the other hand, monocoupling of an A-ring allylic phosphine oxide at C-8 of a C-8,24-diketone would be shorter but risky because it would have to occur with high chemoselectivity at C-8 for this direct approach to be practical (*i.e.*, to avoid chromatographic separation of two very similar alkylidenation products). The more direct approach, using C-8,24-diketone (+)-**46** prepared as in Scheme 5, proved surprisingly C-8 chemospecific (only one product was detected by analytical TLC and ^{13}C NMR), thereby allowing efficient and, most importantly,

Scheme 5



direct synthesis of the desired and unprotected 24-oxo analogs (−)-**12a** and (+)-**12b** (eq 3), distinguished from each other mainly by high-field ^1H NMR (Table 1).



That this Horner−Wadsworth−Emmons olefination actually occurred exclusively with the C-8 ketone group was confirmed by a control experiment in which the conjugate base of the A-ring allylic phosphine oxide (±)-**20** was treated, under the same reaction conditions as in eq 3, with the C,D-ring 24-oxo compound (+)-**47** lacking a C-8 ketone functionality; no reaction was observed! Furthermore, when C-8,24-diketone (+)-**46** was treated with only 1.1 equiv of methylmagnesium bromide, only the corresponding C-8 tertiary alcohol was detected, thereby confirming the relative inertness of the 24-keto group toward even small nucleophiles; using 6 equiv of this Grignard reagent led to formation of the corresponding bis-tertiary alcohol.

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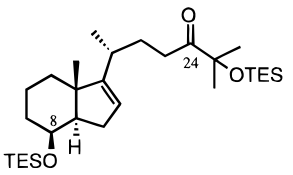
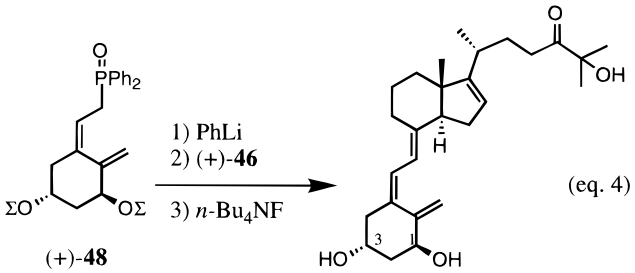


(+)-**47**

Because this highly chemoselective monocoupling (eq 3) was so useful for direct preparation of unprotected 24-oxo calcitriol analogs (−)-**12a** and (+)-**12b**, its generality was probed by using the slightly different enantiomerically pure (having natural structure and natural absolute stereochemistry) A-ring allylic phosphine oxide (+)-**48**[38] to give 24-oxo 16-ene analog (−)-**49** (eq 4)[31,32,39] and

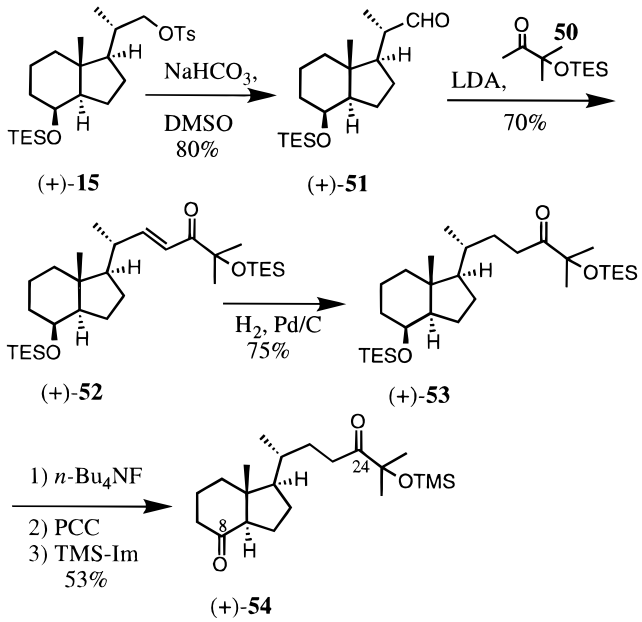


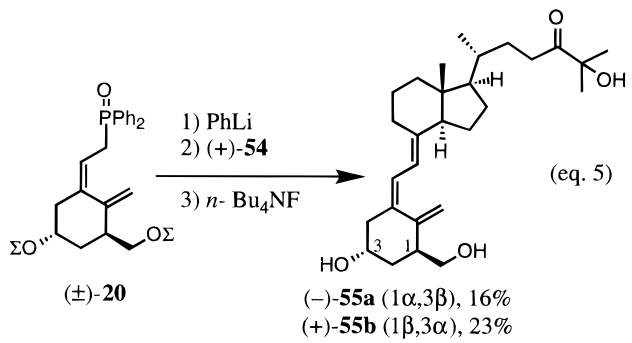
(+)-**48** (eq. 4)

(-)-**49** (1α,3β), 37%

separately by using the slightly different 16-saturated C,D-ring diketone (+)-**54** to give 1-(hydroxymethyl)-24-oxo hybrid analogs (−)-**55a** and (+)-**55b** (Scheme 6, eq 5).[40] In contrast to the chemospecific fluoride deprotection of the primary but not of the secondary silyl ether functionality[41] in the bis-silyl ether in Scheme 3 (*i.e.*, conversion **14** into **27**), double fluoride deprotection of secondary/tertiary bis-silyl ether (+)-**53** in Scheme 6 was accomplished upon prolonged treatment with tetra-*n*-butylammonium fluoride. In both eqs 4 and 5, virtually only C-8-chemoselective coupling occurred smoothly, with no spectroscopic evidence in the crude products of coupling at the C-24 ketone group. Thus, this extremely chemoselective olefination reaction should find widespread application as an easy, reliable, and direct approach for synthesis also of other side-chain-hindered ketone analogs of calcitriol (**1**).

Scheme 6





(±)-**20**

(−)-**55a** (1α,3β), 16%
(+)-**55b** (1β,3α), 23%

Each of these new hybrid analogs was evaluated initially for *in vitro* antiproliferative activity in murine keratinocytes, using our previously described protocol.[6] As seen previously with 1-(hydroxymethyl)-3-hydroxy diastereomeric pairs of hybrid analogs differing only in relative stereochemistry at the 1- and 3-positions (*i.e.*, 1α,3*β* *vs* 1*β*,3α), only those diastereomers with the unnatural 1*β*,3α stereochemistry (*i.e.*, the *β* series in this paper) showed significant antiproliferative activities. As shown in Figure 1, for the most antiproliferative of the hybrid analogs synthesized, 1*β*-(hydroxymethyl)-16-ene hybrid analogs (+)-**10b** and (+)-**11b** parallel the high antiproliferative activity of natural 1α,25-dihydroxyvitamin D_3 even at the physiologically relevant low nanomolar levels. The 24-oxo 16-ene analog (+)-**49**, prepared from the asymmetrically synthesized A-ring allylic phosphine oxide (+)-**48** having the natural substituents and stereochemistry, also is at least as efficacious as calcitirol (**1**) in antiproliferative activity even at low nanomolar concentrations. Results of broad biological screening of these hybrid analogs will be reported in due course. Small samples of these hybrid analogs are available upon request for further biological evaluation.

In conclusion, new chemistry reported here includes the following: (1) combining a Lewis acid with high pressure to promote an efficient and highly regioselective and stereoselective Diels−Alder 4 + 2-cycloaddition between 3-bromo-2-pyrone and an unactivated alkene, (2) developing a mild protocol for high-yield synthesis of 3-bromo-2-pyrone, and especially (3) highly chemoselective monoaddition of a carbanion to only one keto group of a diketone. Also, a new series of hybrid analogs of calcitriol characterized by a 1-(hydroxymethyl) substituent and a metabolically resistant sp^2-carbon-containing side chain modification has been prepared. Initial *in vitro* biological evaluation shows some of these new hybrid analogs to be comparable in efficacy to calcitriol (**1**) even at physiologically important low nanomolar concentrations; the expected low calcemic activity and slow metabolism of these 1-(hydroxymethyl) hybrid analogs is being evaluated and will be reported separately.

Experimental Section[6]

The purity of products was judged to be at least 95% on the basis of their chromatographic homogeneity.

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(39) Sui-Caldera, M.-L.; Clark, J. W.; Santos-Moore, A.; Peleg, S.; Liu, Y. Y.; Uskokovic, M. R.; Sharma, S.; Reddy, G. S. *J. Steroid Biochem. Molec. Biol.* **1996**, *59*(5/6), in press. We thank Professor Reddy for a preprint of this article.

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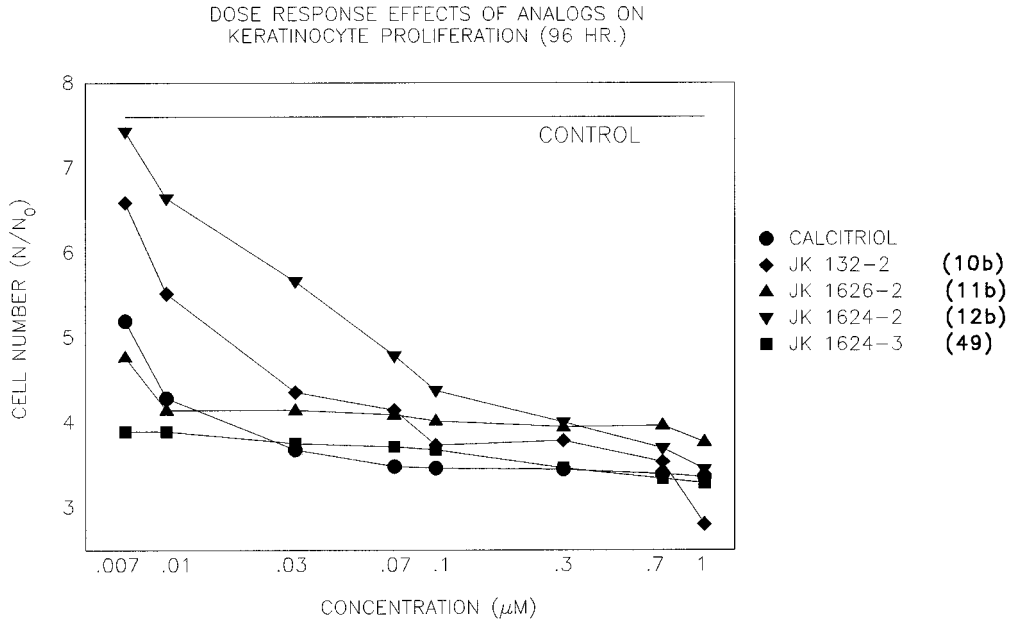

Figure 1. Growth inhibition of murine keratinocyte cell line PE according to the protocol in ref 6.

Lythgoe−Inhoffen Diol (+)-14. A flame-dried 500 mL three-necked flask was charged sequentially with 70 mg (0.83 mmol) of $NaHCO_3$, 50.0 mL of anhydrous MeOH, 170.0 mL of anhydrous CH_2Cl_2, and 4.82 g (12.15 mmol) of ergocalciferol [(+)-**13**, vitamin D_2, $[\alpha]^{25}_D$ +100°, *c* 1.5, EtOH]. The solution was cooled to −78 °C and treated with O_3 (O_2 pressure = 7.5 psi) until a deep blue color developed and persisted (approximately 1.5−2.0 h). The solution was subsequently flushed with O_2 (7.5 psi) for 10−15 min until the blue color faded. Solid sodium borohydride (4.0 g, 105.7 mmol) was added portionwise over a period of 10 min at −78 °C until complete disappearance of starting material was observed by TLC. The reaction mixture was warmed to 0 °C and stirred for 3 h. After being stirred for an additional 30 min at rt, the mixture was quenched with 1 N HCl, extracted with EtOAc (3 × 200 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (30% EtOAc/hexanes) afforded 1.45 g (6.86 mmol) of diol (+)-**14** in 57% yield as a white solid (R_f = 0.5, 50% EtOAc/hexanes): mp 108−110 °C (lit.[42] mp 109−110 °C); ^{1}H NMR ($CDCl_3$) δ 4.05 (m, 1H), 3.62 and 3.59 (2 d, J = 3.6, 3.2 Hz, 1H), 3.34 (dd, J = 10.4, 6.8 Hz, 1H), 1.97 (m, 1H), 1.86−1.77 (m, 3H), 1.59−1.13 (m, 11H), 1.0 (d, J = 6.8Hz, 3H), 0.93 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 69.1, 67.7, 52.9, 52.3, 41.8, 40.2, 38.2, 33.5, 26.6, 22.5, 17.4, 16.6, 13.5; IR ($CDCl_3$, cm^{-1}) 3621, 3464, 3017, 2943; HRMS (EI) *m*/*z* (M^+) calcd 212.1776 for $C_{13}H_{24}O_2$, found 212.1779.

(Triethylsilyl)oxy Tosylate (+)-15. A solution of diol (+)-**14** (993.3 mg, 4.70 mmol) in 10.0 mL of anhydrous pyridine was cooled to −25 °C. A precooled solution of tosyl chloride (1.1 g, 5.8 mmol) in 2.0 mL of anhydrous pyridine was added dropwise to the diol solution *via* cannula. Upon stirring for 3.5 h at −25 °C, the reaction mixture was warmed to 0 °C and allowed to stir for an additional 20 h. The mixture was extracted with CH_2Cl_2, washed with 1 N HCl, dried over $MgSO_4$, filtered, and concentrated to give a residue that was chromatographed on a silica gel column (30% EtOAc/hexanes) to afford 1.71 g (4.67 mmol) of the corresponding tosylate alcohol in quantitative yield. Spectroscopic data of this tosylate alcohol are identical to those previously reported in the literature.[43] To a 0 °C solution of this C-8-hydroxy tosylate (1.71 g, 4.67 mmol) in 15 mL of anhydrous CH_2Cl_2 was added 2,6-lutidine (0.65 mL, 5.60 mmol) followed by triethylsilyl trifluoromethanesulfonate (TES-OTf, 1.4 mL, 6.43 mmol). The solution was stirred at 0 °C for 15 min and then quenched with water (10.0 mL). The mixture was extracted with CH_2Cl_2 (3 × 40 mL), and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated to give a residue that was chromatographed on a silica gel column (20% EtOAc/hexanes) to afford 1.96 g of O-silylated tosylate (+)-**15** in 87% yield: $[\alpha]^{25}_D$ 31.8° (*c* 5.4, EtOH); ^{1}H NMR ($CDCl_3$) δ 7.77 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 4.01 (m, 1H), 3.95 (dd, J = 9.2, 2.8 Hz, 1H), 3.78 (dd, J = 9.2, 6.4 Hz, 1H), 2.44 (s, 3H), 0.94 (d, J = 6.4 Hz, 3H), 0.93 (t, J = 8.0 Hz, 9H), 0.85 (s, 3H), 0.53 (q, J = 8.0 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 144.5, 133.0, 129.7, 127.9, 75.7, 69.1, 52.7, 52.3, 42.1, 40.4, 35.7, 34.5, 26.5, 22.9, 21.6, 17.6, 16.8, 13.5, 6.9, 4.9; IR ($CDCl_3$, cm^{-1}) 2954, 2860, 1455, 1355; HRMS (CI) *m*/*z* (M + H^+) calcd 481.2808 for $C_{26}H_{44}O_4SSi$, found 481.2799.

20-*epi* Alcohol (+)-16. A solution of primary tosylate (+)-**15** (931.7 mg, 1.94 mmol) in DMSO was added to the suspension of 724 mg (8.62 mmol) of $NaHCO_3$ in 6 mL of DMSO at rt, and the mixture was heated at 150 °C under argon for 10 min. The mixture was cooled rapidly to room temperature, and H_2O (40 mL) followed by EtOAc (40 mL) were successively added. The aqueous phase was extracted with EtOAc (3 × 40 mL), and the combined organic phases were washed with water (40 mL), dried with $MgSO_4$, filtered, and concentrated to give a residue that was chromatographed on a silica gel column (0.5% EtOAc/hexanes) to afford the O-silylated aldehyde (442.0 mg) in 70% yield. O_2 was bubbled through a solution of KO-*t*-Bu (1.64 mL, 1.64 mmol) in dry *t*-BuOH (6.0 mL, freshly distilled from CaH_2) for 10−15 min. A solution of the O-silylated aldehyde (442.0 mg, 1.36 mmol) in 2.0 mL of *t*-BuOH was added, and O_2 was bubbled through the solution for an additional 15 min followed by argon for 10 min. The solution was quenched with 20 mL of H_2O and extracted with EtOAc (3 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered, concentrated, and chromatographed on a silica gel column (15% EtOAc/hexanes) to afford 231.0 mg of the corresponding O-silylated 20-ketone in 55% yield: ^{1}H NMR ($CDCl_3$) δ 4.04 (m, 1H), 2.45 (t, J = 8.8 Hz, 1H), 2.06 (s, 3H), 0.91 (t, J = 8.0 Hz, 9H), 0.82 (s, 3H), 0.52 (q, J = 8.0 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 209.4, 68.8, 64.4, 53.2, 43.7, 39.8, 34.3, 31.5, 23.1, 21.7, 17.6, 15.3, 6.9, 4.8; IR ($CDCl_3$) 2956, 2912, 2877, 1698 cm^{-1}; HRMS (CI) *m*/*z* (M + H^+) calcd 311.2406 for $C_{18}H_{34}O_2Si$, found 311.2410. A flame-dried 25 mL round-bottomed flask was charged with 141.0 mg (0.45 mmol) of this O-silylated ketone, dissolved in 10 mL of anhydrous MeOH, and cooled to 0 °C. Sodium borohydride (34.0 mg, 0.90 mmol, 2 equiv) was added portionwise to the solution until the disappearance of all starting material was observed by TLC. The reaction mixture was quenched with water, extracted with Et_2O (3 × 25 mL), dried over $MgSO_4$, filtered, concentrated, and then purified by silica gel column chromatography (10%

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EtOAc/hexanes) to afford 94.0 mg of the desired (20*R*) alcohol epimer and 30.0 mg of the undesired (20*S*) alcohol epimer (2.5:1), both as light yellow oils in 67% and 22% yields, respectively. (20*R*)-(+)-**16**: $[\alpha]^{25}_D$ 27° (*c* 1.0, EtOAc); ^{1}H NMR ($CDCl_3$) δ 4.04 (m, 1H), 3.73 (m, 1H), 1.11 (d, J = 6.0 Hz, 3H), 0.99 (s, 3H), 0.94 (t, J = 8.4 Hz, 9H), 0.55 (q, J = 8.0 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 70.14, 69.05, 59.10, 52.60, 41.93, 40.97, 34.60, 24.74, 23.33, 23.18, 17.56, 14.17, 6.95, 4.92; IR ($CDCl_3$) 3615, 2956, 2876, 1456, 1376 cm^{-1}; HRMS (CI) *m/z* (M + H$^+$) calcd 313.2563 for $C_{18}H_{36}O_2Si$, found 313.2557.

Side-Chain Tosylate (−)-17. To a 0 °C solution of the corresponding primary alcohol (synthesized as previously described in the literature,[44] 767.0 mg, 3.8 mmol) in 10.0 mL of pyridine was added under argon a precooled (0 °C) solution of tosyl chloride (1.1 g, 5.8 mmol) in 12.0 mL of pyridine. After the mixture was stirred overnight, 60.0 mL of EtOAc was added, and the mixture was washed with water. The organic layer was dried over $MgSO_4$, filtered, concentrated, and purified *via* silica gel chromatography (30% EtOAc/hexanes) to afford 1.2 g of tosylate (−)-**17** in 90% yield as an oil; $[\alpha]^{25}_D$ −12° (*c* 2.3, EtOAc); ^{1}H NMR ($CDCl_3$) δ 7.79 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 4.17 (m, 2H), 3.84 (dd, J = 8.0, 4.8 Hz, 1H), 2.43 (s, 3H), 1.80 (m, 2H), 1.52 (m, 4H), 1.33 (s, 3H), 1.22 (s, 3H), 0.87 (t, J =7.6 Hz, 3H), 0.83 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 144.69, 132.94, 129.78, 127.82, 106.81, 83.80, 76.72, 68.33, 29.39, 28.36, 27.15, 26.82, 25.36, 21.6, 8.19, 7.23; IR ($CDCl_3$, cm^{-1}) 2941, 2860, 1732, 1592, 1458, 1354; HRMS (CI) *m/z* (M + H$^+$) calcd 357.1736 for $C_{18}H_{28}O_5S$, found 357.1741.

Hydroxy Ether (−)-18. To a suspension of 60.0 mg of KH (1.5 mmol) in 0.25 mL of anhydrous THF was cannulated a solution of the alcohol (+)-**16** (136.8 mg, 0.44 mmol) in 0.5 mL of THF at rt. After 15 min, a solution of side-chain tosylate (−)-**17** (320.0 mg, 0.9 mmol, 2 equiv) in 0.25 mL of anhydrous THF was added to the alkoxide solution *via* syringe, and the reaction mixture was heated to reflux. After 30 min, 2 equiv of additional side-chain tosylate (−)-**17** was added in the same manner, and this process was repeated two more times over a period of 2 h. The reaction mixture was cooled to rt, diluted with EtOAc, quenched with H_2O, and then extracted with EtOAc (3 × 25 mL). The combined organic phases were dried over $MgSO_4$, filtered, concentrated, and purified by silica gel chromatography (5% EtOAc/hexanes) to afford 112.0 mg of the desired *O*-silyl-protected ether. The resulting 112.0 mg of the *O*-silyl-protected ether was treated with 510.0 mg (1.90 mmol) of tetrabutylammonium fluoride hydrate (TBAF) in 7.0 mL of anhydrous THF in the presence of 20.0 mg of 4 Å MS (oven dried) at rt. After 1 h, the reaction mixture was concentrated *in vacuo* and then purified with silica gel column chromatography (20% EtOAc/hexanes) to afford 48.4 mg of the C-8-hydroxy ether (−)-**18** in 30% overall yield from the alcohol (+)-**16**: $[\alpha]^{25}_D$ −12° (*c* 0.95, EtOAc); ^{1}H NMR ($CDCl_3$) δ 4.09 (m, 1H), 3.97 (dd, J = 10.0, 2.4 Hz, 1H), 3.63 (m, 1H), 3.38 (m, 1H), 3.31 (m, 1H), 2.12 (m, 1H), 1.41 (s, 3H), 1.33 (s, 3H), 1.07 (d, J = 5.6 Hz, 3H), 0.95 (s, 3H), 0.91 (t, J = 7.6 Hz, 3H), 0.88 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 106.43, 83.98, 78.16, 77.43, 69.27, 65.62, 56.92, 52.16, 41.75, 40.26, 33.83, 30.41, 28.53, 27.07, 26.89, 25.57, 24.76, 22.71, 18.20, 17.43, 14.26, 8.17, 7.34; IR ($CDCl_3$, cm^{-1}) 3613, 2954, 2931, 2872, 1455, 1373; HRMS *m/z* (M + H$^+$) calcd 383.3161 for $C_{23}H_{42}O_4$, found 383.3167.

22-Oxa C,D-Ring Ketone (−)-19. Solid tetrapropylammonium perruthenate (TPAP) was added (0.01 mmol, 3.7 mg) in one portion to a stirring mixture of hydroxy ether (−)-**18** (48.4 mg, 0.13 mmol), 4-methylmorpholine *N*-oxide (NMO, 23.4 mg, 0.2 mmol, 1.5 equiv), and 4 Å MS (65.0 mg) in anhydrous CH_2Cl_2 (2 mL) at rt under argon. Completion of the reaction was determined ^{1}H NMR analysis of a small aliquot of solution that was crudely purified by filtration through a silica gel plug. The reaction could not be monitored by TLC due to the similarity in R_f values of the starting material and product. Upon completion, the reaction mixture was diluted with EtOAc and filtered through a silica gel plug. The filtrate was concentrated *in vacuo* and then purified by silica gel column chromatography (30% EtOAc/hexanes) to yield 48.0 mg of the ketone (−)-**19** in quantitative yield: $[\alpha]^{25}_D$ −50° (*c* 1.74, EtOAc); ^{1}H NMR ($CDCl_3$) δ 3.97 (dd, J = 10.4, 2.4 Hz, 1H), 3.64 (m, 1H), 3.37 (m, 1H), 3.28 (m, 1H), 2.47 (m, 1H), 1.41 (s, 3H), 1.33 (s, 3H), 1.1 (d, J = 10.8 Hz, 3H), 0.91 (t, J = 7.6 Hz, 3H), 0.88 (t, J = 7.6 Hz, 3H), 0.65 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 211.97, 106.47, 83.91, 78.08, 77.36, 65.70, 61.46, 56.81, 49.90, 41.18, 38.91, 30.39, 28.50, 27.08, 26.89, 25.54, 25.02, 24.22, 19.38, 18.23, 13.03, 8.19, 7.31; IR ($CDCl_3$, cm^{-1}) 2969, 2939, 2879, 1705, 1462, 1370; HRMS (CI) *m/z* (M + H$^+$) calcd 381.3005 for $C_{23}H_{40}O_4$, found 381.3010.

20-*epi*-22-Oxa-25-hydroxy Hybrid Analogs (−)-6a and (−)-6b. Racemic phosphine oxide (±)-**20** and C,D-ring ketone (−)-**19** were separately azeotropically dried three times with freshly distilled benzene and held under vacuum for 24 h immediately prior to use. The racemic phosphine oxide (±)-**20** (113.7 mg, 0.19 mmol) was dissolved in 2.0 mL of anhydrous THF and cooled to −78 °C under argon atmosphere. To this was added 110 μL (0.19 mmol) of PhLi (1.8 M in THF) dropwise over 2−3 min, during which time a deep reddish orange color developed and persisted. The mixture was allowed to stir for an additional 5 min at −78 °C, at which time a precooled (−78 °C) solution of C,D-ring ketone (−)-**19** (60.0 mg, 0.16 mmol) dissolved in 1.0 mL of freshly distilled anhydrous THF was transferred dropwise *via* cannula. The deep redddish orange solution was stirred in the dark for approximately 5 h, during which time the color faded. Upon observation of a light yellow color, the reaction mixture was quenched at −78 °C with 4 mL of 2 N sodium potassium tartrate followed by addition of 2 mL of dilute aqueous potassium carbonate. The mixture was allowed to warm to rt, extracted with EtOAc (3 × 20 mL), dried over $MgSO_4$, filtered, concentrated, and purified by silica gel column chromatography (10% EtOAc/1% NEt_3/hexanes) to afford 110.6 mg of the coupled product in 88% yield [based on (−)-**19**]. This was immediately placed in a flame-dried 25 mL flask and dissolved in 5 mL of anhydrous THF with 20 μL of NEt_3 under argon. To this solution was added 533.0 mg (2.04 mmol) of TBAF and 270.0 mg of dry 4 Å MS. The reaction mixture was stirred at rt for 12 h in the dark. The solvent was evaporated, and the mixture was purified by silica gel chromatography (1% NEt_3/EtOAc) to afford 52.0 mg (0.10 mmol, 71%) of a mixture of two desilylated ketal diastereomers ketal pre-(−)-**6a** and ketal pre(−)-**6b**. The mixture of diastereomers was separated with reversed-phase HPLC (C18 semipreparative column, 15% H_2O/CH_3CN, 2.0 mL/min, 260 nm) to give ketal pre-(−)-**6a** (t_R 51.0 min) in 25% yield and ketal pre-(−)-**6b** (t_R 54.4 min) in 37% yield. Ketal pre-(−)-**6a**: $[\alpha]^{25}_D$ −170° (*c* 0.46, MeOH); ^{1}H NMR ($CDCl_3$) δ 6.32 (d, J = 11.2 Hz, 1H), 5.93 (d, J = 11.2 Hz, 1H), 5.17 (m, 1H), 5.02 (d, J = 2.4 Hz, 1H), 3.97 (dd, J = 10.0, 2.4 Hz, 1H), 3.96 (m, 1H), 3.62 (m, 1H), 3.55 (m, 2H), 3.37 (m, 1H), 3.28 (m, 1H), 2.82 (m, 1H), 2.62 (m, 2H), 2.25 (m, 1H), 1.41 (s, 3H), 1.33 (s, 3H), 1.08 (d, J = 6.0 Hz, 3H), 0.90 (m, 6H), 0.56 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 145.15, 143.06, 133.83, 123.74, 116.94, 114.48, 106.45, 83.98, 78.16, 78.05, 67.13, 65.66, 64.32, 56.83, 55.79, 46.37, 45.86, 45.06, 40.28, 37.44, 30.4, 29.15, 28.52, 27.07, 26.90, 25.57, 25.03, 23.64, 22.49, 18.30, 12.58, 8.18, 7.34; UV (MeOH) λ_{max} 264 nm (ϵ 17 712); HRMS (EI) *m/z* (M$^+$) calcd 530.3971 for $C_{33}H_{54}O_5$, found 530.3974. Ketal pre-(−)-**6b**: $[\alpha]^{25}_D$ −7.0° (*c* 0.65, MeOH); ^{1}H NMR ($CDCl_3$) δ 6.32 (d, J = 11.2 Hz, 1H), 5.92 (d, J = 11.2 Hz, 1H), 5.14 (m, 1H), 4.98 (d, J = 2.0 Hz, 1H), 4.0 (m, 1H), 3.97(dd, J = 10.0, 2.0 Hz, 1H), 3.60 (m, 3H), 3.37 (m, 1H), 3.27 (m, 1H), 2.82 (m, 1H), 2.62 (m, 2H), 2.27 (m, 1H), 1.41 (s, 3H), 1.33 (s, 3H), 1.08 (d, J = 5.6 Hz, 3H), 0.90 (m, 6H), 0.53 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 145.33, 143.16, 134.06, 123.63, 116.84, 113.84, 106.43, 83.98, 78.16, 78.03, 67.11, 65.65, 64.31, 56.77, 55.75, 46.25, 45.80, 44.52, 40.29, 37.40, 30.40, 29.14, 28.52, 27.07, 26.89, 25.57, 25.10, 23.53, 22.43, 18.31, 12.53, 8.17, 7.33; UV (MeOH) λ_{max} 263 nm (ϵ 16 980); HRMS (EI) *m/z* (M$^+$) calcd 530.3971 for $C_{33}H_{54}O_5$, found 530.3969. To a solution of the ketal pre-(−)-**6a** (8.1 mg, 0.015 mmol) in 3.0 mL of MeOH was added 211.0 mg of cation-exchange resin (Dowex 50WX4−200 mesh from Aldrich, prewashed with MeOH). The mixture was stirred at rt under argon atmosphere in the dark for 17 h. After filtration, the filtrate was concentrated to give 5.0 mg of alcohol (−)-**6a** in 68% yield. HPLC purification (semipreparative reversed-

(44) Andersen, N. R.; Buchwald, F. A.; Grue-Sorensen, G. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 341.

phase C18 column, 15% H_2O/CH_3CN, 2.0 mL/min, t_R 9.5 min) gave the diastereomer (−)-**6a** in 67% yield. (−)-**6a**: $[\alpha]^{25}_D$ −175° (*c* 0.23, MeOH); ^{1}H NMR ($CDCl_3$) δ 6.32 (d, J = 11.2 Hz, 1H), 5.93 (d, J = 11.6, 1H), 5.17 (m, 1H), 5.01 (d, J = 2.0 Hz, 1H), 3.96 (m, 1H), 3.76 (m, 1H), 3.69 (m, 1H), 3.54 (m, 3H), 3.33 (m, 1H), 3.08 (m, 1H), 2.82 (m, 1H), 1.10 (d, J = 5.6 Hz, 3H), 0.88 (t, J = 7.2 Hz, 6H), 0.56 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 145.15, 142.79, 133.97, 123.69, 117.05, 114.45, 78.41, 75.82, 74.02, 67.11, 66.47, 64.30, 56.63, 55.66, 46.34, 45.70, 45.02, 40.10, 37.40, 30.96, 29.05, 27.46, 26.19, 24.88, 23.57, 22.35, 18.55, 12.77, 7.71, 7.52; UV (MeOH) λ_{max} 264 nm (ϵ 16 650); HRMS (EI) *m*/*z* (M^+) calcd 490.3658 for $C_{30}H_{50}O_5$, found 490.3657. The ketal pre-(−)-**6b** (12.7 mg, 0.024 mmol) was deprotected with 370.0 mg of cation-exchange resin as described above. Purification with reversed phase HPLC afforded 3.5 mg (30%) of (−)-**6b** and 6.5 mg (50%) of recovered starting ketal. (−)-**6b**: $[\alpha]^{25}_D$ −12.0° (*c* 0.23, MeOH); ^{1}H NMR ($CDCl_3$) δ 6.32 (d, J = 10.8 Hz, 1H), 5.93 (d, J = 11.2 Hz, 1H), 5.15 (m, 1H), 4.98 (d, J = 2.0 Hz, 1H), 4.0 (m, 1H), 3.76 (m, 1H), 3.71 (m, 1H), 3.65−3.48 (m, 3H), 3.32 (m, 1H), 3.09 (m, 1H), 2.82 (m, 1H), 1.1 (d, J = 6.0 Hz, 3H), 0.88 (t, J = 7.6 Hz, 6H), 0.54 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 145.32, 142.91, 134.18, 123.59, 116.96, 113.87, 78.41, 75.82, 74.03, 67.11, 66.47, 64.31, 56.58, 55.64, 46.25, 45.67, 44.53, 40.13, 37.39, 30.97, 29.06, 27.46, 26.19, 24.96, 23.47, 22.30, 18.56, 12.73, 7.72, 7.52; UV (MeOH) λ_{max} 263 nm (ϵ 18 782); HRMS (EI) *m*/*z* (M^+) calcd 490.3658 for $C_{30}H_{50}O_5$, found 490.3659.

3-Bromo-2*H*-pyran-2-one. In 3 mL of dimethylformamide (DMF) were heated 200.0 mg (0.78 mmol) of 3,5-dibromo-5,6-dihydro-2-pyrone (prepared from commercial 5,6-dihydro-2-pyrone as described previously)[22] and 69.9 mg (0.95 mmol) of lithium carbonate at 110 °C for 10 min. After the reaction mixture was cooled to rt, 40 mL of water was added, and the aqueous phase was then extracted three times with chloroform. The combined choloroform extracts were washed with brine, dried over Na_2SO_4, and then concentrated *in vacuo*. Caution: the product bromopyrone sublimes easily. The last traces of DMF were removed by flash silica gel chromatography (30% EtOAc/hexane) to provide 102.0 mg (77%) of the desired bromopyrone product as a colorless solid having the spectroscopic and physical characteristics reported previously.[22] If desired for prolonged storage, this solid can be recrystallized from EtOAc/hexanes; such recrystallized material is stable for months.

4-Bromo-5-*endo*-(2-hydroxyethyl)-3-oxo-2-oxabicyclo-[2.2.2]oct-7-ene (21). A solution of 3-bromo-2*H*-pyran-2-one (600 mg, 3.42 mmol) and 3-butenyl *tert*-butyldimethylsilyl ether (2.55 g, 13.71 mmol) in CH_2Cl_2 (3 mL) was treated with $ZnCl_2$ (1.71 mL, 1.71 mmol, 1.0 M in ethyl ether) placed in a sealed tube[45] and held at 10−12 kbar[46] at rt for 5 days. Upon removal from the high-pressure generator, the whole reaction mixture was subjected to flash silica gel chromatography (5−15% ethyl acetate/hexanes) to give 730 mg (60%) of 4-bromo-5-*endo*-[(*tert*-butyldimethylsiloxy)ethyl]-3-oxo-2-oxabicyclo[2.2.2]-oct-7-ene: mp 71−72 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.42 (br d, J = 8.0 Hz, 1H), 6.36 (dd, J = 8.0, 5.2 Hz, 1H), 5.16 (m, 1H), 3.56−3.74 (m, 2H), 2.47 (ddd, J = 13.2, 9.2, 4.0 Hz, 1H), 2.22−2.38 (m, 2H), 1.63 (ddd, J = 13.2, 3.2, 1.2 Hz, 1H), 1.14−1.26 (m, 1H), 0.86 (s, 9H), 0.15(s, 3H), 0.01(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 136.3, 130.8, 72.9, 64.7, 60.6, 37.2, 36.4, 33.5, 25.8, 18.2, −5.3, −5.4; IR (CCl_4, cm^{-1}) 1762. The solution of this bromo cycloadduct (680 mg, 1.89 mmol) in dry THF (20 mL) was cooled to 0 °C, treated with TBAF (3.78 mL, 3.78 mmol, 1.0 M in THF), and stirred for 4 h at rt. The reaction mixture was extracted with EtOAc, washed with brine, dried with Na_2SO_4, and concentrated to a crude oil. Purification by flash silica gel chromatography (30% EtOAc/hexanes) provided 361 mg (78%) of alcohol (±)-**21** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41 (broad d, J = 8.0 Hz, 1H), 6.37(dd, J = 8.0, 4.8 Hz, 1H), 5.17 (m, 1H), 3.68−3.76 (m, 1H), 3.56−3.64 (m, 1H), 2.49 (ddd, J = 13.2, 9.2, 4.0 Hz, 1H), 2.24−2.38 (m, 2H), 1.96 (br m, 1H), 1.58 (ddd, J = 13.2, 3.2, 1.2Hz, 1H), 1.20−1.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 136.1, 130.9, 72.9, 64.5, 60.1, 36.8, 36.3, 33.3; IR (CCl_4, cm^{-1}) 3620, 1762; HRMS *m*/*z* calcd 183.9888 for C_8H_9Br ($M^+ - CO_2 - H_2O$), found 183.9881.

4-Bromo-5-*endo*-(2-fluoroethyl)-3-oxo-2-oxabicyclo[2.2.2]-oct-7-ene (22). To a solution of the free alcohol **21** (162 mg, 0.66 mmol) and triethylamine (129 μL, 0.92 mmol, 1.4 equiv) in dichloromethane (3 mL) was added methanesulfonyl chloride (56.3 μL, 0.72 mmol, 1.1 equiv) at 0 °C. After 30 min at 0 °C, the reaction mixture was quenched with water (3 mL), the organic layer was separated, and the aqueous component was extracted twice with dichloromethane (10 mL). The organic layers were combined, washed with brine, dried with Na_2SO_4, and concentrated to give 260 mg of a crude oil that was dissolved in dry THF (5 mL) and treated with tetrabutylammonium fluoride (1.00 mL, 1.00 mmol, 1.0 M in THF). This solution was immersed in a preheated oil bath (95 °C) and refluxed for 16 min. During this period, the reaction mixture turned from milky white to clear yellow and then to red. After the mixture was cooled to rt, H_2O (10 mL) was added, and a typical extraction with EtOAc furnished the crude product (400 mg), which was purified by flash silica gel chromatography (30% EtOAc/hexanes) to afford the bicyclic fluoride **22** (145 mg, 87%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.46 (dm, J = 7.4 Hz, 1 H), 6.43 (dd, J = 8.0, 4.8 Hz, 1 H), 5.21 (m, 1 H), 4.54−4.65 (m, 1 H), 4.42−4.52 (m, 1 H), 2.59 (ddd, J = 13.6, 9.2, 4.4 Hz, 1 H), 2.42−2.54 (m, 1 H), 2.39 (tt, J = 8.8, 2.8 Hz, 1 H), 1.67 (ddd, J = 13.4, 3.4, 1.5 Hz, 1 H), 1.3 −1.56 (m, 1 H); ^{13}C NMR δ 168.8, 135.8, 131.3, 81.8 (d, J = 166 Hz), 72.7, 64.2, 37.0 (d, J = 3 Hz), 34.3 (d, J = 19.5 Hz), 33.2; IR (neat, cm^{-1}) 1764; HRMS *m*/*z* calcd 203.9950 for $C_8H_{10}BrF$ ($M - CO_2^+$), found 203.9956.

5-*endo*-(2-Fluoroethyl)-3-oxo-2-oxabicyclo[2.2.2]oct-7-ene (23). A solution of the bicyclic fluoride **22** (250 mg, 1.00 mmol), tributyltin hydride (268 μL, 1.40 mmoL, 1.4 equiv) and azabisisobutyronitrile (AIBN, 22 mg, 0.20 mmoL, 0.2 equiv) in benzene (5 mL) was refluxed for 3 h. After the mixture was cooled to rt and the solvent was removed *in vacuo*, the residue was taken up in wet ether (20 mL) and treated with a solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 200 mg, 10 drops, 1.3 mmol) in ether (2 mL). The resulting mixture was stirred (15 min), and the resulting precipitate was removed by filtration through Celite. The solvent was evaporated, and the resulting oil was purified by flash silica gel chromatography (20% EtOAc/hexanes) to afford 125 mg of the norbromo adduct **23** (74%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (ddd, J = 6.4, 3.6, 1.2 Hz, 1 H), 6.38 (apparent t, J = 4.8 Hz, 1 H), 5.15 (m, 1 H), 4.45−4.54 (m, 1 H), 4.36−4.44 (m, 1 H), 3.52 (d, J = 5.2 Hz, 1 H), 2.44 (ddd, J = 10.8, 7.6, 3.2 Hz, 1 H), 2.24−2.32 (m, 1 H), 1.48−1.76 (m, 2 H), 1.22 (dd, J = 10.0, 2.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 132.1, 129.6, 81.8 (d, J = 165 Hz), 73.7, 45.2 , 35.0 (d, J = 19.2 Hz), 32.0, 28.3 (d, J = 3.2 Hz); IR 1749 cm^{-1}; HRMS (EI) *m*/*z* calcd 126.0845 for $C_8H_{11}F$ ($M - CO_2^+$), found 126.0847.

Methyl Ester 24. To a solution of the norbromocycloadduct **23** (205 mg, 1.2 mmol) in 7 mL of $MeOH/CH_2Cl_2$ (1:1) at −78 °C was added 1.0 M solution of sodium methoxide in methanol (3.0 mL, 3.0 mmol). The cold bath was removed, and the resulting mixture was allowed to warm to rt for 4 h. The reaction was quenched with water, the solvents were removed *in vacuo*, and the residue was taken up in CH_2Cl_2 (10mL), washed with water, dried with Na_2SO_4, and concentrated to give the crude hydroxy ester as a colorless oil. A solution of the latter material and 2,6-lutidine (181 μL, 1.56 mmol) in CH_2Cl_2 (3 mL) was cooled to 0 °C and treated with *tert*-butyldimethylsilyl trifflate (330 μL, 1.44 mmol). After the solution was stirred at 0 °C for 30 min, water (4 mL) was added. The organic layer was separated, dried with Na_2SO_4, and concentrated *in vacuo* to give a crude oil. Purification by flash silica gel chromatography (10% EtOAc/hexanes) afforded 305 mg (80%) of the silyl ether **24** as a colorless oil: ^{1}H NMR δ 6.83 (dd, J = 4.8, 2.8 Hz, 1 H), 4.54−4.62 (m, 1 H), 4.40−4.50 (m, 1 H), 3.92−4.02 (m, 1 H), 3.69 (s, 3 H), 2.82−2.90 (m, 1 H), 2.47 (dt, J = 19.2, 5.2 Hz , 1 H), 2.10 (dddd, J = 19.2, 8.4, 2.6, 2.4 Hz, 1 H), 1.85−2.03 (m, 2 H), 1.55−1.73 (m, 2 H), 0.86 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR δ 167.0,

(45) The sealed tube consists of a 3/8 × 6 in. length of heat-shrinkable Teflon tubing (Ace Glass) that is plugged at both ends by a 1 in. length of glass rod.

(46) High-pressure generator Model #PG-200-HPC, LECO Corporation/Tem-Press Division, P.O. Box 390, Bellefonte, PA 16823.

138.1, 133.1, 83.1 (d, J = 165 Hz), 63.7, 51.5, 35.9, 35.8, 34.7 (d, J = 18.9 Hz), 31.7 (d, J = 4.5 Hz), 25.8, 18.1, −4.6, −4.7; IR (neat, cm^{-1}) 1708, 1646; HRMS (EI) m/z calcd 259.1166 for $C_{12}H_{20}FO_3Si$ ($M^+ - Bu^t$), found 259.1169

(*Z*)-Dienoate 25. To a solution of methyl ester **24** (110 mg, 0.34 mmol) in THF (5 mL) at −78 °C was slowly added diisobutylaluminum hydride (1.04 mL, 1.04 mmol, 1.0 M in THF, 3.0 equiv). This mixture was allowed to warm to rt and stirred for 1 h. The reaction was quenched with aqueous sodium potassium tartrate (1 mL, 2 N), aqueous HCl (2 mL, 2 N), and H_2O (6 mL), and then the mixture was extracted with CH_2Cl_2 (3 × 6 mL). The combined organic layers were washed with H_2O (4 mL), dried with Na_2SO_4, and concentrated *in vacuo* to afforded the crude allylic alcohol (80 mg) as a colorless oil that was pure enough to be carried directly on to the next step. A 25 mL hydrolysis tube containing a solution of the allylic alcohol (crude product from last step, 0.28 mmol), 1-(phenylsulfinyl)-2,2,2-triethoxyethane (209 mg, 0.73 mmol, 2.6 equiv),[23] and 2,4,6-trimethylbenzoic acid (8 mg, 0.03 mmol, 0.1 equiv) in CH_2Cl_2 (1 mL) was heated to 110 °C for 24 h. After the mixture was cooled to rt, the solvent was removed *in vacuo* and the resulting light yellow oil (500 mg) was purified by flash silica gel chromatography (5% ethyl ether/hexanes) to afford the (*E*)-dienoate as a colorless oil. A borosilicate test tube containing a solution of the (*E*)-dienoate and 9-fluorenone (10 mg) in *tert*-butyl methyl ether (10 mL) was placed in a solution of 2 M sodium orthovanadate and irradiated[16] with a medium-pressure mercury arc lamp for 16 h at rt, at which time the reaction was determined to be complete by ^{1}H NMR analysis.[47] The yellow oily residue was purified by flash silica gel chromatography (5% ethyl ether/hexane) to give 100 mg (81%) of the (*Z*)-dienoate **25** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 (br s, 1 H), 4.97 (s, 2 H), 4.55−4.64 (m, 1 H), 4.45−4.54 (m, 1 H), 4.05−4.15 (m, 2 H), 3.93−4.02 (m, 1 H), 2.70−2.78 (m, 1 H), 2.47 (dd, J = 12.4, 4.0 Hz, 1 H), 2.26 (ddd, J = 12.4, 9.2, 1.8 Hz, 1 H), 1.70−1.90 (m, 4 H), 1.24 (t, J = 7.1 Hz, 3 H), 0.87 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.06, 153.27, 146.10, 117.33, 112.92, 82.13 (d, J = 162 Hz), 67.64, 59.85, 47.45, 41.57, 38.10 (d, J = 5.2 Hz), 33.52 (d, J = 19.5 Hz), 25.72, 18.05, 14.07, −4.79; IR 1716, 1637 cm^{-1}; HRMS (EI) m/z (M^+) calcd 356.2183 for $C_{19}H_{33}FO_3Si$ found 356.2186.

A-Ring Phosphine Oxide 26. To a solution of dienoate **25** (145 mg, 0.407 mmol) in $PhCH_3/CH_2Cl_2$ (6 mL, 2:1) at −78 °C was slowly added diisobutylaluminum hydride (0.90 mL, 1.0 M in $PhCH_3$, 0.90 mmol, 2.2 equiv). The reaction was maintained at −78 °C for 1 h and then slowly warmed to −50 °C, at which time the reaction was complete by TLC analysis. The reaction was quenched with 2 N aqueous sodium potassium tartrate (1 mL), HCl (1 mL, 2 N), and H_2O (2 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 3 mL), dried with Na_2SO_4, and concentrated to give the desired allylic alcohol (130 mg) as a colorless oil that was pure enough to be carried directly onto the next step. To a solution of *N*-chlorosuccinimide (NCS, 165 mg, 1.25 mmol, 3.2 equiv) in CH_2Cl_2 (3 mL) at 0 °C was slowly added Me_2S (100 mL, 1.30 mmol, 3.2 equiv). The resulting white cloudy solution was stirred for 15 min at 0 °C and then cooled to −20 °C and treated with a solution of the allylic alcohol (crude product from last reaction, 0.407 mmol) in CH_2Cl_2 (1.0 mL). After being stirred for 30 min at −20 °C, the reaction mixture was allowed to warm to 0 °C and then quenched with H_2O (4 mL) and diluted with CH_2Cl_2 (4 mL). The organic layer was separated, dried with $MgSO_4$, and concentrated. This colorless oil was then redissolved in 10% ether/hexanes with the help of a little CH_2Cl_2 and applied to a prepacked silica gel bed (3 g, 2 cm thick). Rapid filtration and subsequent washing with ether/hexane (10%, 50 mL) gave an essentially pure allylic chloride (136 mg) as a colorless oil that was immediately taken to the next step. A solution of the allylic chloride (136 mg) in THF (1.0 mL) at −78 °C was treated with a freshly prepared solution of Ph_2PLi [~0.3 M, addition of *n*-butyllithium (0.63 mL, 1.5 M in hexane, 0.94 mmol, 0.94 equiv) to a solution of Ph_2PH (174 mL, 1.0 mmol) in THF (3 mL) at 0 °C under N_2] until the orange color persisted for 5 min. To the reaction mixture was added H_2O (0.5 mL), and the resulting colorless mixture was allowed to warm to rt. The solvent was evaporated, and the residue was taken up in CH_2Cl_2 (4.5 mL). To this solution was added hydrogen peroxide (2 mL, 5%), and the resulting biphasic mixture was stirred vigorously for 45 min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with aqueous Na_2SO_3 and water, dried with $MgSO_4$, and concentrated to give a colorless oil (400 mg) that was purified by chromatography (10−30% EtOAc/hexanes) to afford 154 mg (76%) of the phosphine oxide **26** as a colorless oil: mp 115−116.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62−7.74 (m, 4 H), 7.38−7.54 (m, 6 H), 5.40 (q, J = 7.2 Hz, 1 H), 4.92 (d, J = 1.2 Hz, 1 H), 4.75 (d, J = 1.2 Hz, 1 H), 4.32−4.44 (m, 1 H), 4.18−4.30 (m, 1 H), 3.78 (septet, J = 4.4 Hz, 1 H), 3.12−3.33 (m, 2 H), 2.53 (m, 1 H), 2.38 (dd, J = 12.8, 3.6 Hz, 1 H), 2.12−2.20 (m, 1 H), 1.68−1.75 (m, 2 H), 1.47−1.55 (m, 1 H), 1.43 (q, J = 6.0 Hz, 1 H), 0.81 (s, 9 H), 0.00 (s , 3 H), −0.01 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6 (d, J = 2.2 Hz), 141.5 (d, J = 11.7 Hz), 133.2 (d, J = 36.0 Hz), 132.1 (d, J = 36.0 Hz), 131.8 (d, J = 2.2 Hz), 131.7 (d, J = 2.2 Hz), 131.0 (d, J = 5.8 Hz), 130.8 (d, J = 5.8 Hz), 128.5 (d, J = 5.1Hz), 128.3 (d, J = 5.1 Hz), 114.7 (d, J = 8.0 Hz), 112.3 , 82.1 (d, J = 164 Hz), 67.2 (d, J = 2.2 Hz), 46.9 (d, J = 1.5 Hz), 41.3, 38.0 (d, J = 3.6 Hz), 33.0 (d, J = 19.5 Hz), 31.1 (d, J = 69.8 Hz), 25.8, 18.1, −4.6, −4.7; IR ($CHCl_3$, cm^{-1}) 2956, 2931, 2899, 2858, 1818, 1794, 1636, 1471, 1438, 1383, 1172, 1066, 894, 846. Anal. Calcd for $C_{29}H_{40}FO_2PSi$: C, 69.80; H, 8.09; F, 3.81; P, 6.21; Si, 5.61. Found: C, 69.74; H, 8.17; F, 3.64; P, 6.40; Si, 5.20.

(1-Fluoroethyl)hydroxyvitamin D_3 Homologs (−)-7a and (+)-7b. To a solution of phosphine oxide **26** (50 mg, 0.10 mmol, 1.25 equiv) in THF (2.0 mL) at −78 °C was added PhLi (68 μL, 0.11 mmol, 1.6 M in 7/3 cyclohexane/ether, 1.4 equiv). After the solution was stirred at −78 °C for 10 min, a precooled solution of the C,D-ring ketone shown in Scheme 2[7] (32 mg, 0.08 mmol, 0.8 equiv) in THF (0.3 mL) was slowly canulated into the red-orange solution. The reaction mixture was maintained at −78 °C for 3 h and then slowly warmed to rt for 4 h. During this time, the red-orange color faded to light yellow. The reaction was quenched with potassium sodium tartrate (1.5 mL, 2 M), extracted with EtOAc, dried with Na_2SO_4, and concentrated to give a crude product that was purified by flash silica gel chromatography (5% ether/hexanes) to give silyl protected products (50 mg). The mixture was subsequently dissolved in THF (3.0 mL), treated with TBAF (0.4 mL, 0.40 mmol, 1 M in THF), and stirred at rt for overnight. The solvent was removed *in vacuo*, and the residue was purified by flash silica gel chromatography (90% EtOAc/hexanes) to give 23 mg (57%) of a 1:1.75 mixture of 1α- and 1β-(2-fluoroethyl)hydroxyvitamin D_3 homologs. This mixture of diastereomers was separated by the reversed phase HPLC (C-18 semipreparative column, 85% MeOH/water) to give diastereomers (−)-**7a** and (+)-**7b**. (−)-**7a**: $[\alpha]^{25}_D$ −176° (*c* 0.015, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (d, J = 10.4 Hz, 1 H), 5.90 (d, J = 11.4 Hz, 1 H), 5.07 (d, J = 2.4 Hz, 1 H), 4.91 (d, J = 2.4 Hz, 1 H), 4.44−4.54 (m, 1 H), 4.32−4.42 (m, 1 H), 3.90−4.02 (m, 1 H), 3.50−3.60 (m, 1H), 3.18−3.30 (m, 2H), 2.77 (dd, J = 12.0, 4.0 Hz, 1 H), 2.62−2.70 (m, 1 H), 2.60 (ddd, J = 12.0, 4.2, 0.8 Hz, 1 H), 2.21 (apparent t, J = 10.8 Hz, 1H), 2.12 (br d, J = 12.4 Hz, 1H), 1.05−2.00 (m, 24H), 1.07 (d, J = 6.0 Hz, 3H), 0.83 (t, J = 7.6 Hz, 3H), 0.82 (t, J = 7.6 Hz, 3H), 0.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7, 142.5, 134.1, 123.5, 117.1, 113.4, 82.0 (d, J = 131 Hz), 78.2, 74.0, 68.7, 67.0, 56.8, 55.7, 46.7, 45.7, 41.0, 40.2, 38.5 (d, J = 3.6 Hz), 35.6, 33.5 (d, J = 15.7 Hz), 31.1, 30.8, 29.0, 25.0, 24.2, 23.5, 22.4, 18.2, 12.5, 7.9, 7.8; IR ($CHCl_3$, cm^{-1}) 3605, 3260−3500, 2967, 2940, 2875, 1646, 1452, 1375; HRMS m/z (M^+) calcd 490.3822 for $C_{31}H_{51}O_3F$, found 490.3827; UV (EtOH) λ_{max} 264 nm (ϵ 15 600). (+)-**7b**: $[\alpha]^{25}_D$ 2.5 (*c* 0.40, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (d, J = 11.4 Hz, 1 H), 5.89 (d, J = 11.4 Hz, 1 H), 5.04 (d, J = 1.8 Hz, 1 H), 4.87 (d, J = 1.8 Hz, 1 H), 4.46−4.54 (m, 1 H), 4.34−4.42 (m, 1 H), 3.92−4.20 (m, 1 H), 3.50−3.60 (m, 1H), 3.16−3.28 (m, 2H), 2.77 (dd, J = 12.4, 4.0 Hz, 1 H),

(47) (*E*)-Dienoate is characterized by its ^{1}H NMR spectrum having three vinyl proton singlets at δ 5.81, 5.06, and 4.78 ppm (1:1:1). The (*Z*)-dienoate is characterized by two vinyl singlets at δ 5.62 and 4.93 ppm (1:2).

2.56−2.68 (m, 2 H), 2.22 (apparent t, J = 10.0 Hz, 1H), 2.12 (br d, J = 12.4 Hz, 1H), 1.98 (dd, J = 12.0, 7.2 Hz, 1H), 1.05−1.85 (m, 23H), 1.06 (d, J = 6.0 Hz, 3H), 0.83 (t, J = 7.6 Hz, 3H), 0.82 (t, J = 7.6 Hz, 3H), 0.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.9, 142.7, 134.2, 123.3, 116.9, 112.9, 82.1 (d, J = 163 Hz), 78.2, 74.0, 68.7, 67.0, 56.7, 55.7, 46.7, 45.7, 41.0, 40.2, 38.2 (d, J = 4.9 Hz), 35.6, 33.3 (d, J = 19.4 Hz), 31.1, 30.8, 29.0, 25.1, 24.2, 23.5, 22.3, 18.2, 12.4, 7.9, 7.8; IR ($CHCl_3$, cm^{-1}) 3605, 3260−3500, 2967, 2940, 1645, 1601, 1452; HRMS m/z (M^+) calcd 490.3822 for $C_{31}H_{51}O_3F$, found 490.3822; UV (EtOH) λ_{max} 264 nm (ϵ 17 000).

C,D-Ring Primary Alcohol (+)-27. To a solution of Lythgoe−Inhoffen diol (+)-**14** (101.2 mg, 0.47 mmol) in 5 mL of DMF was added 0.16 mL (1.41 mmol) of 2,6-lutidine followed by 0.36 mL (1.41mmol) of TBDMS-OTf at 0 °C. Further addition of 2,6-lutidine (0.16 mL) and TBDMS-OTf (0.36 mL) was made until the reaction was complete. The reaction mixture was quenched with H_2O and extracted with EtOAc, and the organic portion was dried over $MgSO_4$, filtered, concentrated by rotary evaporation, and immediately purified by silica gel chromatography (100% hexanes) to afford 198.7 mg (0.45 mmol) of bis-silylated diol intermediate in 96% yield. A flame-dried 25 mL flask was charged with 198.7 mg (0.45 mmol) of the bissilylated diol, 5 mL of anhydrous THF, 0.3 mL of NEt_3, 100 mg of dried 4 Å MS, and 118 mg (0.45 mmol) of TBAF. The resulting reaction mixture was stirred at rt for 2 h, concentrated by rotary evaporation, and purified by silica gel column chromatography (20% EtOAc/hexanes) to afford 167 mg (0.43 mmol) of the desired alcohol (+)-**27** in 95% yield. Spectroscopic data of the primary alcohol (+)-**27** are identical to those previously reported in the literature.[27]

C,D-Ring Aldehyde (+)-28. A flame-dried 100 mL flask was charged with 278 mg (1.29 mmol) of pyridinium chlorochromate and 185 mg (2.25 mmol) of sodium acetate. Approximately 35 mL of anhydrous CH_2Cl_2 was added, and the mixture was stirred for 10 min at rt. To this was added dropwise a solution of the alcohol (+)-**27** (167 mg, 0.43 mmol) in 5 mL of CH_2Cl_2. After 1 h, the solution was filtered through a plug of silica gel, concentrated, and purified by silica gel chromatography (50% EtOAc/hexanes) to afford 111 mg (0.34 mmol) of the corresponding somewhat unstable aldehyde (+)-**28** (80% yield) that was used immediately in the next step.

Side-Chain Phosphonate 29. A mixture of ethyl 4-bromocrotonate (5.0 g, 25.9 mmol) and tributyl phosphite (0.75g, 3.0 mol) was heated at 85−90 °C for 12 h under argon atmosphere. Standard workup followed by purification by preparative TLC (30% EtOAc/hexanes) gave the phosphonate **29** (858 mg, 2.8 mmol) in 93% yield: ^{1}H NMR ($CDCl_3$) δ 6.81 (m, 1H), 5.89 (ddt, J = 15.6, 5.2, 1.2 Hz, 1H), 4.13 (q, J = 7.2 Hz, 2H), 3.99 (m, 4H), 2.69 (ddd, J = 22.8, 8.0, 1.6 Hz, 2H), 1.62−1.55 (m, 4H), 1.38−1.29 (m, 4H), 1.22 (t, J = 7.2 Hz, 3H), 0.87 (t, J = 7.2 Hz, 6H); HRMS (CI) m/z ($M + H^+$) calcd 307.1674 for $C_{14}H_{27}O_5P$, found 307.1674.

C,D-Ring Dienoate (+)-30. To a solution of the phosphonate **29** in 5 mL of anhydrous THF was added 2.4 mL (2.4 mmol) of 1.0 M solution of lithium *tert*-butoxide in THF at −78 °C. The mixture was stirred at rt for 15 min and subsequently cooled to −78 °C. After 10 min, the brown phosphonate anion solution was cannulated into the solution of aldehyde (+)-**28** (111 mg, 0.34 mmol) in 2 mL of THF at rt. Upon being stirred for 3 h at rt, the solution was concentrated *in vacuo* and purified by preparative TLC (silica gel, 2000 μm, 10% EtOAc/hexanes) to afford 95.0 mg of dienoate (+)-**30** in 70% yield: $[\alpha]^{25}_D$ 90° (*c* 1.9, EtOAc); ^{1}H NMR ($CDCl_3$) δ 7.22 (dd, J = 15.6, 10.8 Hz, 1H), 6.07 (dd, J = 15.2, 10.4 Hz, 1H), 5.95 (dd, J = 15.2, 8.8 Hz, 1H), 5.75 (d, J = 15.6 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 3.98 (m, 1H), 2.24−1.11 (m, 13H), 1.27 (t, J = 7.2 Hz, 3H), 1.02 (d, J = 6.8 Hz, 3H), 0.93 (bs, 3H), 0.87 (s, 9H), −0.01 (s, 3H), −0.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 167.22, 150.67, 145.46, 125.83, 118.95, 69.27, 60.05, 55.99, 52.89, 42.30, 40.55, 39.99, 34.36, 27.39, 25.78, 22.99, 19.59, 17.99, 17.62, 14.31, 13.97, −4.82, −5.20; IR ($CHCl_3$, cm^{-1}) 3011, 2953, 2929, 2860, 1702, 1639, 1464, 1365; HRMS, m/z (M^+) calcd 420.3060 for $C_{25}H_{44}O_3Si$, found 420.3056.

C,D-Ring *tert*-Alcohol (+)-31. Lithium (1.1 g, 0.16 mol) was extruded from a 99% mineral oil suspension as wire fragments 3.2 mm in diameter directly into anhydrous *n*-pentane (20 mL). The lithium wire was cut into small fragments and washed twice with *n*-pentane under argon atmosphere. The lithium pieces were resuspended in 20 mL of *n*-pentane, and a solution of ethyl bromide (4.48 mL, 0.06 mmol) in pentane (20 mL) was added continuously over a 5−6 h period. Gentle refluxing was periodically invoked by a warm (40 °C) bath, and the mixture was vigorously stirred. Stirring under reflux was continued for 1 h after addition of the ethyl bromide solution was complete to afford a 1.5 M solution of ethyllithium. To a solution of dienoate (+)-**30** (95 mg, 0.23 mmol) in THF (2mL) was added a 1.5 M solution of ethyllithium (0.77 mL, 1.15 mmol) in *n*-pentane at −78 °C. Further addition of EtLi was made until the reaction was deemed complete by TLC. Upon completion, the reaction was quenched with aqueous NH_4Cl, warmed to rt, diluted in EtOAc, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. Preparative chromatography (silica, 2000 μm, 10% EtOAc/hexanes) afforded the desired *tert*-alcohol (+)-**31** (79.4 mg) in 78% yield: $[\alpha]^{25}_D$ 60° (*c* 1.7, EtOAc); ^{1}HNMR ($CDCl_3$) δ 6.14 (dd, J = 15.2, 10.4 Hz, 1H), 5.94 (dd, J = 15.2, 10.4 Hz, 1H), 5.51 (m, 2H), 3.99 (m, 1H), 2.14−1.1 (m, 18H), 1.01 (d, J = 6.8 Hz, 3H), 0.93 (bs, 3H), 0.88 (s, 9H), 0.86 (t, J = 7.6 Hz, 6H), 0.004, −0.014 (2s, 6H); ^{13}C NMR ($CDCl_3$) δ 140.58, 136.04, 128.94, 127.17, 75.40, 69.38, 56.51, 53.02, 42.15, 40.61, 39.57, 34.42, 33.01, 27.62,25.80, 23.01, 20.07, 18.02, 17.67, 13.91, 7.91, −4.79, −5.17; IR ($CHCl_3$, cm^{-1}) 3019, 29339, 2857, 1731, 1472, 1462, 1374; HRMS m/z (M^+) calcd 434.3580 for $C_{27}H_{50}O_2Si$, found 434.3577.

Diol (+)-32. A flame-dried 25 mL flask was charged with 79.4 mg (0.18 mmol) of the monosilylated diol (+)-**31**, 5 mL of THF, 30 μL of NEt_3, and 94 mg (0.36 mmol) of TBAF. The mixture was refluxed for 2 days, during which time excess TBAF (94 mg) was periodically added. The reaction mixture was cooled to rt, concentrated *in vacuo*, and purified by silica gel chromatography (30% EtOAc/hexanes) to afford 34.0 mg (61% yield) of the desired diol (+)-**32** and 14 mg of recovered starting material (+)-**31** (79% yield based on recovered starting material): $[\alpha]^{25}_D$ 44° (*c* 2.1, EtOAc); mp 107−108°C; ^{1}H NMR ($CDCl_3$) δ 6.13 (dd, J = 15.2, 10.4 Hz, 1H), 5.95 (dd, J = 15.2, 10.4 Hz, 1H), 5.50 (m, 2H), 4.06 (m, 1H), 2.14−1.10 (m, 19H), 1.02 (d, J = 6.4 Hz, 3H), 0.95 (bs, 3H), 0.85 (t, J =7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 140.26, 136.23, 128.83, 127.32, 75.41, 69.30, 56.33, 52.56, 41.85, 40.26, 39.58, 33.53, 33.00, 27.50, 22.48, 20.04, 17.43, 13.69, 7.91; IR ($CHCl_3$, cm^{-1}) 3612, 3018, 2938, 2871, 1459, 1225, 1220; HRMS m/z (M^+) calcd 320.2715 for $C_{21}H_{36}O_2$, found 320.2714.

C,D-Ring Ketone (+)-33. Tetrapropylammonium perruthenate (TPAP) was added (0.01 mmol, 3.7 mg) in one portion to a stirring mixture of diol (+)-**32** (67.9 mg, 0.21 mmol), 4-methylmorpholine *N*-oxide (NMO, 198.0 mg, 1.69 mmol, 8.0 equiv), and 4 Å MS (614 mg) in anhydrous CH_2Cl_2 (3 mL) at rt. Completion of the reaction was determined by ^{1}H NMR analysis of a small aliquot of solution, which was crudely purified by filtration through a silica gel plug. The reaction could not be monitored by TLC due to the similarity in R_f values of the starting material and product. Upon completion, the reaction mixture was diluted with EtOAc and filtered through a silica gel plug. The filtrate was evaporated, and the residue was purified by silica gel column chromatography (15% EtOAc/hexanes) to yield 40.4 mg of ketone (+)-**33** in 62% yield: $[\alpha]^{25}_D$ +31° (*c* 0.27, EtOAc); ^{1}H NMR ($CDCl_3$) δ 6.13 (dd, J = 10.4, 15.2 Hz, 1H), 5.96 (dd, J = 15.2, 10.4 Hz, 1H), 5.49 (m, 2H), 2.58−1.1(m, 18H), 1.06 (d, J = 6.4 Hz, 3H), 0.84 (t, J = 7.6 Hz, 6H), 0.64 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 211.79, 139.17, 136.69, 128.56, 127.89, 75.35, 61.87, 56.35, 49.79, 40.91, 39.61, 38.77, 33.01, 27.59, 24.02, 20.30, 19.02, 12.67, 7.87; IR ($CHCl_3$, cm^{-1}) 3621, 3019, 2967.3, 2878, 1706, 1459, 1379; HRMS m/z (M^+) calcd 318.2559 for $C_{21}H_{34}O_2$, found 318.2555.

O-Silylated C,D-Ring Ketone (+)-34. To a solution of 40.4 mg (0.13 mmol) of the alcohol (+)-**33** in 2.0 mL of CH_2Cl_2 was added dropwise 1-(trimethylsilyl)imidazole (40.0 μL, 2.1 equiv). The mixture was stirred at rt overnight, quenched with 2 mL of H_2O, extracted with EtOAc, dried over $MgSO_4$, filtered, concentrated, and then purified by silica gel column chromatography (30% EtOAc/hexanes) to afford 46.4 mg of the desired product (+)-**34** in 92% yield: $[\alpha]^{25}_D$ +26° (*c* 0.29, EtOAc); ^{1}H NMR ($CDCl_3$) δ 6.03 (dd, J = 14.8, 10.0 Hz, 1H), 5.95 (dd, J =

14.8, 10.0 Hz, 1H), 5.48 (m, 2H), 2.46−1.1 (m, 17H), 1.08 (d, J = 6.8 Hz, 3H), 0.80 (t, J = 7.6 Hz, 6H), 0.65 (s, 3H), 0.09 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 211.83, 138.77, 137.16, 128.73, 128.28, 78.59, 61.94, 56.42, 49.82, 40.95, 9.66, 38.81, 32.53, 32.50, 27.59, 24.05, 20.39, 19.04, 12.69, 8.29, 2.55; IR ($CHCl_3$, cm^{-1}) 3019, 2965, 2878, 1705, 1460, 1378; HRMS m/z (M^+) calcd 390.2954 for $C_{24}H_{42}O_2Si$, found 390.2958.

Hybrid Analogs (−)-8a and (+)-8b. Racemic phosphine oxide (±)-**20** (102.6 mg, 0.171 mmol) was dissolved in 1.5 mL of freshly distilled anhydrous THF and cooled to −78 °C under argon atmosphere. To this was added 121 μL (0.189 mmol) of PhLi (1.56 M in THF) dropwise over 2−3 min. The mixture was stirred for an additional 7−8 min at −78 °C, at which time a precooled (−78 °C) solution of C,D ring ketone (+)-**34** (68.5 mg, 0.175 mmol) in 1.0 mL of anhydrous THF was added dropwise *via* cannula. The deep red-orange solution was stirred in the dark for approximately 3 h and was quenched at −78 °C with 4 mL of 2 N sodium potassium tartrate followed by addition of 2 mL of dilute aqueous potassium carbonate. The mixture was allowed to warm to rt, extracted with EtOAc (3 × 20 mL), dried over $MgSO_4$, filtered, concentrated, and purified by silica gel column chromatography (10% EtOAc/1% NEt_3/hexanes) to afford 80.8 mg of the coupled product in 61% yield (based on (±)-**20**). This was immediately placed in a flame-dried flask and dissolved in 5 mL of freshly distilled anhydrous THF with 20 μL of NEt_3 under argon. To this solution was added 580.0 mg (2.22 mmol) of TBAF and 325.0 mg of dry 4 Å MS. The reaction mixture was stirred at rt for 12 h in the dark. The solvent was evaporated, and the mixture was purified by silica gel chromatography (1% NEt_3/EtOAc) to afford 34.42 mg (70%) of a mixture of two diastereomers (−)-**8a** and (+)-**8b**. The mixture of diastereomers was separated by HPLC [semipreparative Si column, 2% 2-propanol/0.1% NEt_3/0.1% hexanes/EtOAc, 2.5 mL/min, t_R (−)-**8a** 18.90 min, (+)-**8b** 17.4 min] to give pure diastereomers in 30% and 28% yields, respectively. (−)-**8a**: $[\alpha]^{25}_D$ −4.3° (c 0.21, MeOH); ^{1}H NMR ($CDCl_3$) δ 6.31 (d, J = 11.2 Hz, 1H), 6.14 (dd, J = 15.2, 10.4 Hz, 1H), 5.96 (m, 2H), 5.53 (m, 2H), 5.16 (m, 1H), 5.01 (d, J = 2.0 Hz, 1H), 3.98−3.92 (m, 1H), 3.56−3.53 (m, 2H), 2.83−2.79 (m, 2H), 2.65−2.58 (m, 2H), 1.05 (d, J = 6.8 Hz, 3H), 0.86 (t, J = 7.6 Hz, 6H), 0.56 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 145.11, 142.81, 140.17, 136.28, 133.99, 128.86, 127.45, 123.68, 117.11, 114.50, 75.43, 67.10, 64.28, 56.33, 56.23, 46.34, 45.92, 45.04, 40.27, 40.13, 37.38, 32.98, 29.03, 27.54, 23.59, 22.25, 20.40, 12.19, 7.92; UV (MeOH) λ_{max} 262 nm (ϵ 19 700); HRMS m/z calcd 439.3212 for $C_{31}H_{48}O_3 - Et^+$, found 439.3216. (+)-**8b**: $[\alpha]^{25}_D$ +176° (c 0.26, MeOH); ^{1}H NMR ($CDCl_3$) δ 6.31 (d, J = 11.2 Hz, 1H), 6.14 (dd, J = 15.6, 10.4 Hz, 1H), 5.96 (m, 2H), 5.53 (m, 2H), 5.14 (m, 1H), 4.98 (d, J = 2.0 Hz, 1H), 4.03−3.97 (m, 1H), 3.65−3.55 (m, 2H), 2.84−2.80 (m, 1H), 2.65−2.57 (m, 2H), 1.05 (d, J = 6.4 Hz, 3H), 0.86 (t, J = 7.6 Hz, 6H), 0.54 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 145.29, 142.95, 140.17, 136.29, 134.20, 128.85, 127.45, 123.60, 117.00, 113.87, 75.43, 67.11, 64.30, 56.26, 56.20, 46.23, 45.88, 44.47, 40.30, 40.11, 37.38, 33.01, 29.03, 27.61, 23.50, 22.18, 20.40, 12.16, 7.92; UV (MeOH) λ_{max} 262 nm (ϵ 19 370); HRMS m/z (M^+) calcd 468.3603 for $C_{31}H_{48}O_3$, found 468.3612.

16-En-23-yne Analogs (−)-9a and (+)-9b. A solution of 175 mg (0.29 mmol, 1.5 equiv) of phosphine oxide (±)-**20** in 3 mL of anhydrous THF was cooled to −78 °C and treated dropwise with 290 μL (0.29 mmol, 1.5 equiv) of a 1 M solution of phenyllithium in THF under argon. The resulting orange solution was stirred for 30 min at −78 °C. To the solution was added dropwise a solution of 80.2 mg (0.20 mmol, 1 equiv) of the C,D-ring ketone (+)-**35**[26] in 2 mL of anhydrous THF. After being stirred for 6 h at the same temperature, the reaction mixture was allowed to warm to rt for 10 h, quenched with 6 mL of a 1:1 mixture of 2 N sodium potassium tartrate and 2 N K_2CO_3, extracted with EtOAc (50 mL × 2), and washed with brine. The combined organic portions were dried with anhydrous $MgSO_4$, concentrated *in vacuo*, and then purified by chromatography (3% EtOAc/hexanes) to afford 76.0 mg of the coupled product as a colorless oil. The silyl ethers were dissolved in 5 mL of anhydrous THF. To the solution were added 0.5 mL (0.5 mmol, 5 equiv) of a 1 M solution of tetrabutylammonium fluoride in THF and 60 μL (0.4 mmol, 4 equiv) of triethylamine. After 16 h at rt, the mixture was extracted with EtOAc (50 mL × 2) and washed with brine. The combined organic portions were dried over anhydrous $MgSO_4$, concentrated *in vacuo*, and then purified by chromatography (Et_2O/MeOH/NEt_3 = 97/3/1) to afford 41.2 mg (48%) of a mixture of two diastereomers as a white solid (mp 68−70 °C). The diastereomers were separated by reversed phase HPLC (C-18 semipreparative column, 50% MeCN/H_2O, 3 mL/min) to afford 12.0 mg (14%) of **9a** (1α,3β, t_R 32.3 min) and 17.8 mg (21%) of **9b** (1β,3α, t_R 41.5 min) as a white solid. (−)-**9a** (1α,3β): mp 180 °C dec; $[\alpha]^{25}_D$ −86° (c 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (d, J = 11.2 Hz, 1H), 6.04 (d, J = 11.2 Hz, 1H), 5.31 (t, J = 1.2 Hz, 1H), 5.18 (dd, J = 1.6, 0.8 Hz, 1H), 5.03 (d, J = 2 Hz, 1H), 3.97 (m, 1H), 3.57 (m, 2H), 2.81 (br d, J = 12.4, 1H) 2.64 (m, 2H), 2.38−2.16 (m, 6H), 2.03−1.97 (m, 2H), 1.77 (m, 5H), 1.68 (m, 1H), 1.49 (s, 6H), 1.13 (d, J = 6.4, 3H), 0.71 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 159.85, 147.56, 141.92, 136.66, 123.91, 122.41, 118.94, 114.08, 87.23, 81.75,67.39, 65.57, 64.69, 59.67, 51.09, 47.36, 46.49, 37.64, 36.51, 33.56, 32.06, 32.03, 29.69, 30.44, 26.92, 24.69, 21.17, 17.21; IR ($CHCl_3$, cm^{-1}) 3603, 3018, 2934, 1435; UV (MeOH) λ_{max} 263 nm (ϵ 19 000); MS m/z (70 eV, EI) 424 (M^+); HRMS m/z (M^+) calcd 424.2997 for $C_{28}H_{40}O_3$, found 424.2981. (+)-**9b** (1β,3α): $[\alpha]^{25}_D$ + 91° (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (d, J = 11.2 Hz, 1H), 6.05 (d, J = 11.2 Hz, 1H), 5.37 (t, J = 1.2 Hz, 1H), 5.15 (d, J = 1.2, 1H), 5.00 (d, J = 2 Hz, 1H), 4.01 (m, 1H), 3.61 (m, 2H), 2.80 (br d, J = 12.4, 1H), 2.62 (m, 2H), 2.38−2.15 (m, 6H), 1.97−2.03 (m, 2H), 1.77 (m, 5H), 1.65 (m, 1H), 1.48 (s, 6H), 1.12 (d, J = 6.8, 3H), 0.69 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 159.91, 147.67, 142.06, 136.77, 123.83, 122.39, 118.90, 113.79, 87.23, 81.74, 67.43, 65.57, 64.62, 59.63, 51.05, 47.35, 46.32, 37.58, 36.57, 33.55, 32.07, 32.05, 30.27, 29.70, 26.93, 24.60, 21.17, 17.30; IR ($CHCl_3$, cm^{-1}) 3603, 3011, 2933, 1454, 1366, 1330, 1218, 1162, 1035; UV (MeOH) λ_{max} 263 nm (ϵ 17 000); MS m/z (70 eV, EI) 424 (M^+); HRMS m/z (M^+) calcd 424.2997 for $C_{28}H_{40}O_3$, found 424.2985.

(1′*S*,3a*R*,4*S*,7a*S*)-1′-(1′-Methyl-2′-hydroxyethyl)-1-octahydro-7a-methyl-22-hydroxy-1*H*-inden-4-ol Acetate [(+)-37]. To a suspension of paraformaldehyde (264 mg, 4 equiv) in 40 mL of CH_2Cl_2 was added 13 mL (5 equiv) of a 1 M solution of dimethylaluminum chloride in hexanes at −78 °C. After 30 min, a solution of 487 mg (2.2 mmol) of trisubstituted olefin (+)-**36**[48] in 5 mL of CH_2Cl_2 was added into the mixture at −78 °C, and then the reaction mixture was warmed to −40 °C. After being stirred for 16 h at −40 °C, it was quenched with 10% K_2HPO_4 at −40 °C and then warmed to rt. The reaction mixture was extracted with EtOAc (100 mL × 2), washed with 10% HCl, saturated aqueous $NaHCO_3$ solution, and brine, successively, dried over $NaSO_4$, concentrated *in vacuo*, and then purified by chromatography (30% EtOAc/hexanes) to give 513 mg (93%) of homoallylic alcohol (+)-**37** as a colorless oil: $[\alpha]^{25}_D$ +1.63° (c 3.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40 (t, J = 1.6 Hz, 1H), 5.21 (m, 1H), 3.57 (m, 2H), 2.34 (m, 1H), 2.10 (m, 2H), 2.04 (s, 3H), 1.81(m, 4H), 1.57 (m, 3H), 1.41 (m, 1H), 1.01 (d, J = 6.8 Hz, 3H), 1.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.76, 156.97, 121.66, 70.56, 66.57, 52.85, 46.52, 34.82, 34.60, 30.65, 21.34, 18.41, 18.12, 17.90 (2C); MS m/z (150 eV, CI) 270 (M + NH_4^+); HRMS m/z (M + NH_4^+) calcd 270.2069 for $C_{15}H_{24}O_3$, found 270.2068; IR ($CHCl_3$, cm^{-1}) 3579, 2937, 1727.

(1′*S*,3a*R*,4*S*,7a*S*)-1-(1′-Methyl-2′-iodoethyl)-1-octahydro-7a-methyl-22-hydroxy-1*H*-inden-4-ol Acetate [(−)-38]. To a solution of triphenylphosphine (1.10 g, 3.5 equiv) and imidazole (0.64 g, 7.9 equiv) in 50 mL of CH_2Cl_2 was slowly added a solution of iodine (1.06 g, 3.5 equiv) in 80 mL of CH_2Cl_2 at 0 °C. After 15 min, a solution of alcohol (+)-**37** (297 mg, 1.18 mmol) in 7 mL of CH_2Cl_2 was added into the mixture. After being stirred for 20 min at 5 °C followed by 3.5 h at rt, the reaction mixture was extracted with EtOAc (100 mL × 2), washed with brine, dried over $MgSO_4$, concentrated *in vacuo*, and then purified by chromatography (5% Et_2O/pentane) to give 404 mg (85%) of iodide (−)-**38** as a colorless oil: $[\alpha]^{25}_D$ −26.0° (c 5.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39 (m, 1H), 5.20 (m, 1H), 3.32 (dd, J = 9.6, 5.6 Hz, 1H), 3.20 (dd, J = 9.6, 8.4 Hz, 1H), 2.38 (m, 1H), 2.04 (s, 3H), 2.00−2.16 (m, 2H),

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1.74−1.91 (m, 4H), 1.52−1.62 (m, 2H), 1.20 (m, 1H), 1.15 (d, J = 6.8 Hz, 3 H), 1.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.74, 157.04, 122.00, 70.51, 52.65, 46.53, 34.95, 34.85, 30.60, 22.09 (2C), 21.37, 18.11, 18.04, 14.40; MS m/z (70 eV, EI) 362 (M^+); HRMS m/z (M^+) calcd 362.0743 for $C_{15}H_{23}IO_2$, found 362.0745.

Diester (+)-39. A flame-dried 30 mL flask was charged with activated Zn powder (365 mg, 5 equiv), anhydrous pyridine (7.0 mL), and ethyl acrylate (0.61 mL, 5 equiv) at rt and then warmed to 50 °C. To this was added $NiCl_2 \cdot 6H_2O$ (320 mg, 1.2 equiv) with vigorous stirring. The mixture was warmed to 65 °C and stirred for 1−2 h until the green slurry mixture turned to a reddish brown solution. To the resulting mixture cooled to 0 °C was added a solution of the iodide (−)-**38** (404 mg, 1.16 mmol) in pyridine (4 mL), and then the mixture was stirred for 3 h at rt. The reaction mixture was poured into 50 mL of EtOAc, and the resulting precipitates were filtered off through a pad of Celite. The filtrate was washed with 5% HCl (50 mL × 2), brine, dried over $MgSO_4$, concentrated *in vacuo*, and then purified by chromatography (5% Et_2O/pentane) to give 331 mg (88%) of diester (+)-**39** as a colorless oil: $[\alpha]^{25}_D$ +0.23° (*c* 10.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24 (m, 1H), 5.16 (m, 1H), 4.07 (q, J = 7.2 Hz, 2H), 2.23 (t, J = 7.2 Hz, 2H), 1.95−2.10 (m, 4H), 2.00 (s, 3H), 1.70−1.83 (m, 4H), 1.43−1.60 (m, 4H), 1.30−1.40 (m, 2H), 1.21 (t, J = 7.2 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H), 0.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.58, 170.63, 159.21, 119.88, 70.66, 60.04, 52.88, 46.38, 35.82, 35.01, 34.37, 31.42, 30.65, 30.46, 23.02, 22.24, 21.26, 18.13, 17.78, 14.17; MS m/z (150 eV, CI) 354 (M + NH_4^+); HRMS m/z (M + NH_4^+) calcd 354.2644 for $C_{20}H_{32}O_4$, found 354.2639; ($CHCl_3$, cm^{-1}) 2936, 2854, 1724, 1456.

C-8,25-Diol (+)-40a. To a solution of the diester (+)-**39** (99 mg, 0.30 mmol) in 3 mL of THF was added 0.60 mL (1.8 mmol) of 3 M solution of MeMgBr in ether at 0 °C, and then the mixture was stirred for 1.5 h at rt. The mixture was cooled to 0 °C, diluted with ether (10 mL), and then quenched with saturated NH_4Cl solution. The mixture was extracted with EtOAc (50 mL × 2), washed with brine, dried over $MgSO_4$, concentrated *in vacuo*, and then purified by chromatography (30% EtOAc/hexanes) to give 63 mg (76%) of diol (+)-**40a** as a colorless oil: $[\alpha]^{25}_D$ +11.9° (*c* 5.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.30 (m, 1H), 4.18 (m, 1H), 2.0 Hz, 1H), 2.39 (ddt, J = 14.4, 12.0, 1.72−2.11 (m, 5H), 1.25−1.60 (m, 10H), 1.20 (s, 6H), 1.04 (s, 3H), 0.99 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.20, 119.58, 70.95, 69.04, 54.36, 46.29, 44.05, 36.97, 35.41, 33.81, 31.49, 30.17, 29.13, 22.30, 22.12, 18.33, 17.76; MS m/z (150 eV, CI) 298 (M + NH_4^+); HRMS m/z (M^+) calcd 280.2402 for $C_{18}H_{32}O_2$, found 280.2401; IR ($CHCl_3$, cm^{-1}) 3460, 2943, 2872, 1455.

Homologous C-8,25-Diol (+)-40b. Compound (+)-**39** (137 mg, 0.41 mmol) was treated with 0.80 mL (2.5 mmol) of a 3 M solution of EtMgBr in THF as described for the preparation of (+)-**40a**. After the same workup as described above, followed by chromatography (30% EtOAc/hexanes), 95 mg (74%) of diol (+)-**40b** was obtained as a colorless oil: $[\alpha]^{25}_D$ +9.0° (*c* 7.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.27 (m, 1H), 4.14 (m, 1H), 2.24 (tm, J = 14.4 Hz, 1H), 1.67−2.05 (m, 5H), 1.41 (q, J = 7.6 Hz, 4H), 1.22−1.55 (m, 10H), 1.01 (s, 3H), 0.95 (d, J = 6.8 Hz, 3H), 0.82 (t, J = 7.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.18, 119.58, 74.55, 69.06, 54.36, 46.29, 38.36, 37.12, 35.42, 33.82, 31.59, 30.95, 30.94, 30.16, 22.09, 21.31, 18.34, 17.76, 7.76, 7.73; MS m/z (150 eV, CI) 326 (M + NH_4^+); HRMS m/z (M^+) calcd 308.2715 for $C_{18}H_{32}O_2$, found 308.2720; IR ($CHCl_3$, cm^{-1}) 3409, 2930, 1459.

25-(Silyloxy) C-8-Ketone (+)-41a. To a solution of alcohol (+)-**40a** (62 mg, 0.22 mmol) in CH_2Cl_2 (10 mL) were added 120 mg of oven-dried Celite and PDC (120 mg, 1.5 equiv) at rt. After being stirred for 3.5 h at rt, the mixture was passed through 2 cm of flash silica gel pad and washed with EtOAc. The filtrate was concentrated and chromatographed with 20% EtOAc in hexanes to give 61 mg of the desired ketone as a colorless oil. The resulted keto alcohol (61 mg, 0.22 mmol) was protected with TMS-imidazole (65 μL, 2 equiv) in CH_2Cl_2 (5 mL) at rt. After being stirred for 4 h at rt, the mixture was was concentrated *in vacuo* and then chromatographed with 5% EtOAc in hexanes to give 63 mg (82%) of ketone (+)-**41a** as a colorless oil: $[\alpha]^{28}_D$ +21.0 ° (*c* 6.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.26 (m, 1H), 2.84 (dd, J = 10.4, 5.6 Hz, 1H), 2.43 (ddt, J = 15.6, 10.4, 1.2 Hz, 1H), 2.25−2.29 (m, 2H), 1.87−2.13 (m, 5H), 1.73−1.80 (m, 1H), 1.24−1.52 (m, 6H), 1.17 (s, 3H), 1.16 (s, 3H), 1.03 (d, J = 6.8 Hz, 3H), 0.80 (s, 3H), 0.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.04, 158.14, 119.95, 73.89, 63.14, 53.82, 44.84, 40.52, 36.86, 34.38, 32.68, 29.92, 29.76, 27.02, 24.02, 22.20, 21.71, 17.22, 2.60; MS m/z (150 eV, CI) 368 (M + NH_4^+); HRMS m/z (M − CH_3^+) calcd 335.2406 for $C_{21}H_{38}O_2Si - CH_3^+$, found 335.2398; IR ($CHCl_3$, cm^{-1}) 2967, 2858, 1709.

Homologous 25-(Silyloxy) C-8-Ketone (+)-41b. Compound (+)-**40b** (70.5 mg, 0.23 mmol) was treated with 172 mg (2 equiv) of PDC in CH_2Cl_2 as described for the preparation of (+)-**41a**. After the same workup followed by chromatography (20% EtOAc/hexanes), 64 mg (92%) of the desired keto alcohol was obtained as a colorless oil. The resulting keto alcohol (48 mg, 0.16 mmol) was treated with TMS-imidazole (45 μL, 2 equiv) in CH_2Cl_2 (3 mL) as described for the preparation of (+)-**41a**. After the same workup followed by chromatography (20% EtOAc/hexanes), 54 mg (92%) of ketone (+)-**41b** was obtained as a colorles oil: $[\alpha]^{28}_D$ +19.7° (*c* 4.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 (m, 1H), 2.84 (dd, J = 10.8, 6.4 Hz, 1H), 2.43 (ddt, J = 15.6, 10.8, 1.2 Hz, 1H), 2.26−2.30 (m, 2H), 1.84−2.13 (m, 5H), 1.73−1.81 (m, 1H), 1.15 −1.47 (m, 6H), 1.42 (qd, J = 7.2, 2.4 Hz, 6H), 1.04 (d, J = 6.8 Hz, 3H), 0.80 (s, 3H), 0.78 (td, J = 7.2, 1.6 Hz, 8H), 0.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.07, 158.08, 120.00, 78.75, 63.15, 53.83, 40.53, 38.70, 37.08, 34.41, 32.81, 31.38, 31.17, 27.02, 24.04, 21.72, 21.54, 17.25, 8.23 (2C), 2.72; MS m/z (150 eV, CI) 396 (M + NH_4^+); HRMS m/z (M + NH_4^+) calcd 396.3298 for $C_{23}H_{42}O_2Si$, found 396.3290; IR ($CHCl_3$, cm^{-1}) 2962, 2858, 1721.

16-Ene Calcitriol Analogs (−)-10a and (+)-10b: A solution of 74 mg (0.12 mmol, 1.35 equiv) of phosphine oxide (±)-**20** in 2 mL of anhydrous THF was cooled to −78 °C and treated with 70 μL (0.12 mmol, 1.35 equiv) of a 1.8 M solution of phenyllithium in THF under argon atmosphere. The resulting reddish orange solution was stirred for 30 min at −78 °C. To the solution was added dropwise a solution of 31 mg (0.09 mmol, 1 equiv) of the C,D-ring ketone (+)-**41a** in 1 mL of anhydrous THF. The reaction was allowed to warm to rt for 10 h, quenched with 3 mL of a 1:1 mixture of 2 N sodium potassium tartrate and 2 N K_2CO_3, extracted with EtOAc (50 mL × 2), and washed with brine. The combined organic portions were dried over anhydrous $MgSO_4$, concentrated *in vacuo*, and then purified by chromatography (3% EtOAc/hexanes) to afford 36 mg of the coupled product as a colorless oil. The silyl ethers were dissolved in 3 mL of anhydrous THF. To the solution were added 0.3 mL (0.3 mmol, 6 equiv) of a 1 M solution of tetrabutylammonium fluoride in THF and 30 μL (0.3 mmol, 6 eq) of triethylamine. After 16 h at rt, the mixture was extracted with EtOAc (50 mL × 2) and washed with brine. The combined organic portions were dried over anhydrous $MgSO_4$, concentrated *in vacuo*, and then purified by chromatography (Et_2O/MeOH/NEt_3 = 97/3/1) to afford 21 mg (56%) of a mixture of two diastereomers as a white solid. The diastereomers were separated by reversed-phase HPLC (C-18 semipreparative column, 55% MeCN/H_2O, 4 mL/min) to afford 6.4 mg (17%) of (−)-**10a** (1α,3β, t_R 27.4 min) and 8.0 mg (21%) of (+)-**10b** (1β,3α, t_R 33.8 min) as a white solid. (−)-**10a** (1α,3β): $[\alpha]^{25}_D$ −49° (*c* 0.30, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (d, J = 11.6 Hz, 1H), 6.04 (d, J = 11.6 Hz, 1H), 5.28 (t, J = 1.2 Hz, 1H), 5.17 (d, J = 1.6 Hz, 1H), 5.03 (d, J = 2.0 Hz, 1H), 3.93−4.00 (m, 1H), 3.52−3.61 (m, 2H), 2.78−2.83 (m, 1H), 2.58−2.66 (m, 2H), 2.10−2.41 (m, 4H), 1.95−2.01 (m, 2H), 1.25−1.84 (m, 12H), 1.19 (s, 6H), 1.02 (d, J =6.4, 3H), 0.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.91, 145.06, 142.50, 133.95, 123.74, 120.08, 116.89, 114.60, 71.08, 67.10, 64.33, 58.38, 50.09, 46.35, 45.09, 44.08, 37.40, 36.91, 35.27, 32.65, 29.39, 29.25, 28.28, 23.67, 22.16, 21.52, 16.91; UV (MeOH) λ_{max} 262 nm (ϵ 18 400); MS m/z (150 eV, CI) 429 (M + H^+); HRMS m/z (M^+) calcd 428.3290 for $C_{28}H_{44}O_3$, found 428.3290; IR (neat, cm^{-1}) 3341, 2930, 1367, 1043. (+)-**10b** (1β,3α): $[\alpha]^{25}_D$ +91° (*c* 0.62, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.31 (d, J = 11.2 Hz, 1H), 6.04 (d, J = 11.2 Hz, 1H), 5.28 (t, J = 1.2 Hz, 1H), 5.15 (dd, J = 2.0, 1.6 Hz, 1H), 5.00 (d, J =2

Hz, 1H), 3.99−4.05 (m, 1H), 3.56−3.65 (m, 2H), 2.79−2.83 (m, 1H), 2.58−2.66 (m, 2H), 2.10−2.38 (m, 4H), 1.90−2.01 (m, 2H), 1.25−1.84 (m, 12H), 1.19 (s, 6H), 1.02 (d, J = 6.4 Hz, 3H), 0.66 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.96, 145.33, 142.60, 133.24, 123.61, 120.07, 116.77, 113.75, 71.08, 67.12, 64.32, 58.34, 50.04, 46.21, 44.35, 44.08, 37.39, 36.92, 35.32, 32.65, 29.23, 29.26, 28.80, 23.61, 22.17, 21.54, 16.84; UV (MeOH) λ_{max} 261 nm (ϵ 10 600); MS m/z (150 eV, CI) 429 (M + H$^+$), 446 (M + NH_4^+); HRMS m/z (M$^+$) calcd 428.3290 for $C_{28}H_{44}O_3$, found 428.3299; IR (neat, cm^{-1}) 3342, 2929, 1367, 1040.

Homologous 16-Ene Calcitriol Analogs (−)-11a and (+)-11b. Ketone (+)-**41b** (39 mg, 0.10 mmol) was coupled with phosphine oxide (±)-**20** (67 mg, 1.1 equiv) in THF (1 mL) as described for preparation of **10**. After the same workup followed by deprotection with TBAF, 21.4 mg (46%) of a mixture of two diastereomers and 20.4 mg (30.4 mg, 44% recovery) of unreacted starting material (±)-**20** were obtained as a white solid. The diastereomers were separated by reversed-phase HPLC (C-18 semipreparative column, 65% MeCN/H_2O, 4 mL/min) to afford 7.9 mg (16%) of (−)-**11a** (1α,3β, t_R 41 min) and 7.2 mg (15%) of (+)-**11b** (1β,3α, t_R 52 min) as a white solid. (−)-**11a** (1α,3β): [α]$^{25}_D$ −48° (c 0.70, EtOH); ^{1}H NMR (400 MHz, CD_3OD) δ 6.27 (d, J = 10.8 Hz, 1H), 6.11 (d, J = 10.8 Hz, 1H), 5.31 (br m, 1H), 5.13 (d, J = 2.0 Hz, 1H), 4.89 (overlapping with CD_3OD, 1H), 3.84−3.90 (m, 1H), 3.40−3.51 (m, 2H), 2.82−2.86 (m, 1H), 2.53−2.61 (m, 2H), 2.34−2.40(m, 1H), 2.07−2.23 (m, 4H), 1.91−1.98 (m, 1H),1.25−1.80 (m, 12H), 1.42 (q, J = 7.6 Hz, 4H), 1.03 (d, J =6.8, 3H), 0.83 (t, J = 7.6 Hz, 6H), 0.70 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 161.23, 147.54, 142.07, 136.65, 123.94, 121.36, 118.84, 114.12, 75.47, 67.38, 64.68, 59.81, 51.17, 47.38, 46.52, 39.16, 38.39, 37.64, 36.64, 34.12, 31.77, 31.62, 30.37, 29.75, 24.74, 22.42, 22.19, 17.42, 8.12; UV (MeOH) λ_{max} 262 nm (ϵ 17 800); MS m/z (150 eV, CI) 429 (M + H$^+$), 446 (M + NH_4^+); HRMS m/z (M$^+$) calcd 456.3603 for $C_{30}H_{48}O_3$, found 456.3609; IR (neat, cm^{-1}) 3341, 2930, 1367, 1043. (+)-**11b** (1β,3α): [α]$^{25}_D$ +91° (c 0.65, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ 6.30 (d, J = 10.8 Hz, 1H), 6.12 (d, J = 10.8 Hz, 1H), 5.31 (br m, 1H), 5.11 (d, J = 2.0 Hz, 1H), 4.82 (d, J = 2.4 Hz, 1H), 3.85−3.92 (m, 1H), 3.41−3.53 (m, 2H), 2.82−2.86 (m, 1H),2.53−2.61 (m, 2H), 2.34−2.48(m, 1H), 2.07−2.23 (m, 4H), 1.91−1.97 (m, 1H), 1.42 (q, J = 7.6 Hz, 4H), 1.25−1.80 (m, 12H), 1.03 (d, J = 6.8, 3H), 0.83 (t, J = 7.6 Hz, 6H), 0.68 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 161.26, 147.65, 142.22, 136.66, 123.87, 121.35, 118.79, 113.78, 75.47, 67.43, 64.68, 59.76, 51.17, 47.37, 46.34, 39.16, 38.40, 37.61, 36.70, 34.11, 31.77, 31.63, 30.21, 29.77, 24.66, 22.43, 22.20, 17.41, 8.12; UV (MeOH) λ_{max} 261 nm (ϵ 18 100); MS m/z (150 eV, CI) 429 (M + H$^+$); HRMS m/z (M$^+$) calcd 456.3606 for $C_{30}H_{48}O_3$, found 456.3605; IR (neat, cm^{-1}) 3342, 2929, 1367, 1040.

16-Ene Aldehyde (+)-43. To a suspension of NCS (513 mg, 3.84 mmol, 2.5 equiv) in 20 mL of anhydrous toluene was added dimethyl sulfide (372 μL, 3.3 equiv) at 0 °C under argon. After being stirred for 15 min at the same temperature, the resulting white suspension was cooled to −30 °C. To this was added dropwise a solution of the alcohol **37** (387 mg, 1.53 mmol) in 2 mL of anhydrous toluene at −30 °C. The reaction mixture was stirred for an additional 2.5 h, and then the reaction was quenched with a solution of triethylamine (0.75 mL, 3.5 equiv) in 1.5 mL of anhydrous toluene at −30 °C. The reaction mixture was warmed to rt, stirred for 10 min, and then extracted with ether. The combined organic extracts were washed with 5% HCl and brine, dried over $MgSO_4$, concentrated *in vacuo*, and then purified by chmatography (15% EtOAc/hexanes) to afford 320 mg (83%) of the desired aldehyde (+)-**43** as a colorless oil: [α]$^{25}_D$ +32° (c 5.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (d, J = 2.0 Hz, 1H), 5.41 (m, 1H), 5.17 (m, 1H), 2.96 (q, J = 7.2 Hz, 1H), 2.06−2.16 (m, 2H), 2.09 (s, 3H), 1.72−1.85 (m, 3H), 1.47−1.61 (m, 2H), 1.32 (td, J = 12.0, 3.6 Hz, 1H), 1.13 (d, J = 6.8 Hz, 3H), 0.97 (s, 3H; ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.57, 170.53, 151.21,126.12, 70.23, 52.46, 46.48, 45.23, 34.43, 30.90, 30.40, 21.22, 17.93, 17.65, 14.40; MS m/z (150 eV, CI) 268 (M + NH_4^+); HRMS m/z (M + NH_4^+) calcd 268.1913 for $C_{15}H_{22}O_3$, found 268.1916; IR ($CHCl_3$, cm^{-1}) 2936, 2853, 1733.

16-Ene 24-ketone (+)-44. To a solution of diisopropylamine (197 μL, 1.50 mmol, 1.3 equiv) in THF (5 mL) was added a 1.6 M solution of *n*-BuLi in hexanes (1.0 mL, 1.3 equiv) at −78 °C, and then it was stirred for an additional 30 min at −78 °C and another 30 min at −35 °C. A solution of 2-[(*tert*-butyldimethylsilyl)oxy]-2-methyl-3-butanone (**42**) (325 mg, 1.5 mmol, 1.3 equiv) in THF (3.0 mL) was added to the LDA solution at −78 °C. After being stirred for 1 h, the enolate solution was treated with a solution of the aldehyde (+)-**43** (289 mg, 1.16 mmol, 1 equiv) in THF (5 mL) by dropwise addition. The reaction mixture was stirred for 15 min at the same temperature, quenched with the solution of phenyl chlorothionocarbonate (0.3 mL, 2.0 equiv) in THF (5 mL), and then warmed to rt. After being stirred for 30 min at rt, the reaction mixture was extracted with ether (100 mL × 2), washed with saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, concentrated *in vacuo*, and then purified by chromatography (10% Et_2O/hexanes) to give 597 mg (88%) of the desired phenylthiocarbonate as a diastereomeric mixture: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (bt, J = 7.2, 2H), 7.28 (bd, J = 7.2, 1H), 7.07−7.08 (m, 2H), 5.84 (m, 1H), 5.50 (m, 1H), 5.20 (m, 1H), 3.17 (ddd, J = 78.0, 18.8, 7.2 Hz, 1H), 2.67 (m, 1H), 2.06−2.17 (m, 2H), 2.05 (s, 3H), 1.78−1.89 (m, 4H), 1.57−1.64 (m, 2H), 1.38−1.44 (m, 1H), 1.35 (s, 3H),1.34 (s, 3H), 1.12 (d, J = 7.2 Hz, 3H), 1.08 (s, 3H), 0.91 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H). To the solution of the resultant phenylthiocarbonates (622 mg, 1.06 mmol) in anhydrous benzene (40 mL) were added AIBN (30 mg) and Bu_3SnH (0.35 mL, 1.2 equiv) at rt. After reflux for 3.5 h, the mixture was cooled to 0 °C and diluted with ether (10 mL), and then it was quenched with 5 mL of water. The reaction mixture was extracted with EtOAc (100 mL × 2), washed with brine, dried over $MgSO_4$, concentrated *in vacuo*, and then purified by chromatography (0−10% EtOAc/hexanes) to give 445 mg (93 %) of (+)-**44** as a colorless oil: [α]$^{25}_D$ −3.0° (c 8.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.25 (m, 1H), 5.18 (m, 1H), 2.60−2.65 (m, 2H), 2.03 (s, 3H),1.95−2.10 (m, 3H), 1.73−1.86 (m, 3H), 1.63−1.69 (m, 2H), 1.54−1.58 (m, 2H), 1.36−1.45 (m, 1H), 1.29 (s, 6H), 0.99 (d, J = 6.8 Hz, 3H), 0.95 (s, 3H), 0.88 (s, 9H),0.10 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.57, 170.71, 158.70, 126.29, 80.12, 70.73, 52.92, 46.61, 35.04, 34.53, 30.70, 30.52, 29.53, 27.28, 27.19, 25.75, 22.44, 21.32, 18.18, 18.04, 17.88, −2.27; MS m/z (150 eV, CI) 451 (M + H$^+$); HRMS m/z (M + H$^+$) calcd 451.3244 for $C_{26}H_{46}O_4Si$, found 451.3237; IR (neat, cm^{-1}) 2932, 2856, 1738, 1717.

24-Keto 8,25-Diol (+)-45. A mixture of tertiary silyl ether (+)-**44** (445 mg, 1.0 mmol) and 1.0 g of 10 N NaOH (10 equiv) in EtOH (4.0 mL) was stirred for 20 h at 30−35 °C. The mixture was cooled to 0 °C, diluted with ether (10 mL), and then neutralized with 10% HCl. It was extracted with EtOAc (50 mL × 2), washed with aqueous saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The resultant oil was treated with TBAF in THF followed by normal aqueous workup and then purified by chromatography (40% EtOAc/hexanes) to give 261 mg (90%) of diol (+)-**45** as a colorless oil: [α]$^{25}_D$ +10.7° (c 4.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29 (m, 1H), 4.16 (m, 1H), 3.83 (s, 1H), 2.40−2.58 (m, 2H), 2.26 (tm, J = 13.2, Hz, 1H), 2.06−2.09 (m, 1H), 1.96 (ddd, J = 14.4, 6.0, 2.8 Hz, 1H), 1.68−1.89 (m, 5H), 1.48−1.57 (m, 2H), 1.37−1.47 (m, 1H), 1.33 (s, 6H), 1.01 (s, 3H), 1.00 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.70, 159.00, 120.28, 70.08, 68.95, 52.33, 46.24, 35.33, 33.87, 33.66, 31.20, 30.20, 29.84, 27.19, 26.59, 22.33, 18.41, 17.75; MS m/z (150 eV, CI) 312 (M + NH_4^+); HRMS m/z (M$^+$) calcd 294.2195 for $C_{18}H_{30}O_3$, found 294. 2195; IR (neat, cm^{-1}) 3456, 2929, 2808, 1738, 1706.

16-Ene 8,24-diketone (+)-46. To a solution of C-8 alcohol (+)-**45** (94.6 mg, 0.32 mmol) in CH_2Cl_2 (10 mL) were added 0.36 g of oven-dried Celite and PDC (0.36 g, 3.0 equiv) at rt. After being stirred at rt for 6 h, the mixture was passed through 2 cm of flash silica gel pad and washed with EtOAc. The filtrate was concentrated *in vacuo* and then chromatographed with 30% EtOAc in hexanes to give 79.0 mg (84%) of the diketo alcohol as a colorless oil: [α]$^{25}_D$ +24.3° (c 7.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.31 (m, 1H), 3.74 (s, 1H), 2.86 (dd, J = 10.8, 6.8 Hz, 1H), 2.42−2.59 (m, 3H), 2.28−2.33 (m, 2H), 1.97−2.20 (m, 4H), 1.67−1.94 (m, 4H), 1.36 (s,

3H), 1.35 (s, H), 1.08 (d, J = 7.2 Hz, 3H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.47, 210.69, 156.84, 120.69, 70.06, 62.89, 53.61, 34.14, 33.28, 30.02, 29.62, 26.95, 26.52, 23.87, 21.50, 17.17; MS *m/z* (70 eV, CI) 310 (M + NH_4^+); HRMS *m/z* (M+ H^+) calcd 293.2117 for $C_{18}H_{28}O_3$, found 293.2116; IR (neat, cm^{-1}) 3470, 2965, 2835, 1713. To a solution of the diketo alcohol (75 mg, 0.26 mmol) and 2,6-lutidine (120 μL, 4.0 equiv) in CH_2Cl_2 (5 mL) was added triethylsilyl triflate (72 μL, 1.2 equiv) at −78 °C. After being stirred for 15 min, the mixture was extracted with Et_2O, washed with 5% HCl, aqueous saturated $NaHCO_3$ solution, and brine, dried over $MgSO_4$, concentrated *in vacuo*, and then purified by chromatography (15% Et_2O/hexanes) to give 92 mg (88%) of silyl ether (+)-**46** as a colorless oil: $[\alpha]^{25}_D$ +17.2° (*c* 6.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24 (m, 1H), 2.81 (dd, J = 10.8, 6.8 Hz, 1H), 2.51−2.70 (m, 2H), 2.40 (ddm, J = 15.6, 10.8 Hz, 1H), 2.23−2.26 (m, 2H), 1.85−2.15 (m, 5H), 1.54−1.77 (m, 3H), 1.26 (s, 3H), 1.25 (s, 3H), 1.02 (d, J = 6.8 Hz, 3H), 0.56 (t, J = 8.0 Hz, 9H), 0.76 (s, 3H), 0.56 (q, J = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.70, 210.89, 157.11, 120.46, 79.81, 63.00, 53.65, 40.43, 34.24, 34.02, 32.22, 29.46, 27.30, 27.22, 26.97, 23.94, 21.74, 17.02, 6.96, 6.49; MS *m/z* (70 eV, CI) 407 (M + H^+); HRMS *m/z* (M + H^+) calcd 407.2981 for $C_{24}H_{42}O_3Si$, found 407.2988; IR (neat, cm^{-1}) 2956, 2876, 1717.

16-Ene 24-Keto Calcitriol Analogs (−)-12a and (+)-12b. A solution of 89 mg (0.15 mmol, 1.0 equiv) of phosphine oxide (±)-**20** in 3 mL of anhydrous THF was cooled to −78 °C and treated with 90 μL (0.15 mmol, 1.0 equiv) of a 1.7 M solution of phenyllithium in THF. The resulting reddish orange solution was stirred for 30 min at −78 °C. To the solution was added dropwise a solution of 60 mg (0.15 mmol, 1 equiv) of the C,D-ring diketone (+)-**46** in 2 mL of anhydrous THF. After being stirred for 6 h at the same temperature, the reaction was quenched with 4 mL of a 1:1 mixture of 2 N sodium potassium tartrate and 2 N K_2CO_3, extracted with EtOAc (50 mL × 2) and washed with brine. The combined organic portions were dried with anhydrous $MgSO_4$, concentrated *in vacuo*, and then purified by chromatography (3% Et_2O/hexanes) to afford 70.3 mg of the coupled product as a colorless oil. The silyl ethers were dissolved in 3 mL of anhydrous THF. To the solution were added 0.55 mL (0.55 mmol, 6 equiv) of a 1 M solution of TBAF in THF and 75 μL (0.55 mmol, 6 equiv) of triethylamine. After being stirred for 16 h at rt, the mixture was extracted with EtOAc (50 mL × 2) and washed with brine. The combined organic portions were dried with anhydrous $MgSO_4$, concentrated *in vacuo*, and then purified by chromatography (10% MeOH/CH_2Cl_2) to afford 40 mg (62%) of a mixture of two diastereomers. The diastereomers were separated by reversed-phase HPLC (C-18 semipreparative column, 60% MeCN/H_2O, 3 mL/min, 262 nm) to afford 15.3 mg (24%) of (−)-**12a** (1α,3β, t_R 31 min) and 12.7 mg (19.7%) of (+)-**12b** (1β,3α, t_R 38 min) as a white solid. (−)-**12a** (1α,3β): mp 49−50 °C; $[\alpha]^{25}_D$ −29° (*c* 1.5, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (d, J = 11.2 Hz, 1H), 6.04 (d, J = 11.2 Hz, 1H), 5.30 (bs, 1H), 5.16 (bs, 1H), 5.00 (bs,1H), 3.93−4.05 (m, 1H), 3.82 (bs, 1H), 3.50−3.57 (m, 2H), 3.33 (bs, 1H), 2.79−2.83 (m, 1H), 2.33−2.67 (m, 5H), 2.10−2.30 (m, 4H), 1.92−2.03 (m, 3 H), 1.65−1.85 (m, 4 H), 1.42−1.54 (m, 2H), 1.35 (s, 6H), 1.05 (d, J = 7.2, 3H), 0.67 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 214.68, 158.67, 145.89, 141.89, 134.37, 123.49,120.94, 117.07, 114.37, 76.12, 66.91, 64.23, 58.31, 49.95, 46.28, 45.06, 37.29, 35.14, 33.45, 32.32, 29.80, 29.40, 28.72, 26.62, 23.57, 21.59, 16.88; UV (EtOH) λ_{max} 262 nm (ϵ 11 800); MS *m/z* (70 eV, CI) 460 (M + NH4$^+$); HRMS *m/z* (M^+) calcd 442.3083 for $C_{28}H_{42}O_4$, found 442.3087; IR (neat, cm^{-1}) 3356, 2930, 1707. (+)-**12b** (1β,3α): mp 56−57 °C; $[\alpha]^{25}_D$ +94° (*c* 1.3, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.31 (d, J = 11.2 Hz, 1H), 6.04 (d, J = 11.2 Hz, 1H), 5.30 (m, 1H), 5.13 (bs, 1H), 5.00 (b, J = 1.6 Hz, 1H), 3.98−4.04 (m, 1H), 3.55−3.65 (m, 2H), 2.77−2.85 (m, 1H), 2.13−2.65 (m, 9H), 1.90−2.03 (m, 3 H), 1.64−1.85 (m, 4 H), 1.47−1.55 (m, 2H), 1.36 (s, 3H), 1.35 (s, 3H), 1.05 (d, J = 7.2, 3H), 0.65 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 214.69, 158.70, 145.31, 142.19, 134.42, 123.50, 120.89, 116.90, 113.80, 76.13, 67.08, 64.31, 58.28, 49.93, 46.20, 44.39, 37.37, 35.19, 33.45, 32.31, 29.80, 29.30, 28.74, 26.63, 23.53, 21.66, 16.83; UV (EtOH) λ_{max} 262 nm (ϵ 15 000); MS *m/z* (70 eV, CI) 460 (M + NH_4^+); HRMS *m/z* (M^+) calcd 442.3092 for $C_{28}H_{42}O_4$, found 442.3087; IR (neat, cm^{-1}) 3360, 2928, 1701.

16-Ene 24-Oxo Calcitiol Analog (−)-49. A solution of 63 mg (0.11 mmol, 1.2 equiv) of enantiomerically pure phosphine oxide (+)-**48**[38] in 1.5 mL of anhydrous THF was cooled to −78 °C and treated dropwise under argon with 70 μL (0.11 mmol, 1.2 equiv) of a 1.7 M solution of phenyllithium in THF. The resulting orange solution was stirred for 30 min at −78 °C. To the solution was added a solution of 37.4 mg (0.15 mmol, 1 equiv) of enantiomerically pure C,D-ring (+)-**46** in 1.5 mL of anhydrous THF dropwise. After being stirred for 7 h at the same temperature followed by the same workup as described above, 40 mg of the desired product was obtained. The silyl ether was dissolved in 3 mL of anhydrous THF. To the solution were added 0.31 mL (0.31 mmol, 6 equiv) of a 1 M solution of TBAF in THF and 45 μL (0.31 mmol, 6 equiv) of triethylamine. After 16 h at rt, the mixture was extracted with EtOAc (50 mL × 2) and washed with brine. The combined organic portions were dried with anhydrous $MgSO_4$, concentrated *in vacuo*, and then purified by chromatography (5−15% MeOH/CH_2Cl_2) to afford 23 mg (57%) of the desired product. The diastereomerically pure product was purified by reversed-phase HPLC (C-18 semipreparative column, 50% MeCN/H_2O, 3 mL/min) to afford 15.1 mg (37%) of (−)-**49** (1α,3β, t_R 30 min) as a white solid. (+)-**49** (1α,3β): $[\alpha]^{25}_D$ +13° (*c* 0.5, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (d, J = 11.2 Hz, 1H), 6.09 (d, J = 11.2 Hz, 1H), 5.32 (t, J = 1.6 Hz, 1H), 5.30 (m, 1H), 5.00 (m, 1H), 4.42−4.44 (m, 1H), 4.20−4.4.26 (m, 1H), 3.80 (bs, 1H), 2.78−2.83 (m, 1H), 2.40−2.61 (m, 3H), 2.29−2.38 (m, 2H), 2.13−2.24 (m, 2H), 1.90−1.93 (m, 2 H), 1.60−1.89 (m, 6 H), 1.45−1.54 (m, 1H), 1.35 (s, 3H), 1.34 (s, 3H), 1.04 (d, J = 6.8 Hz, 3H), 0.67 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 214.68, 158.69, 147.55, 142.25, 133.09, 124.82, 120.97, 116.92, 111.70, 76.12, 70.72, 66.83, 58.34, 49.96, 45.18, 42.85, 35.18, 33.46, 32.31, 29.80, 29.40, 28.74, 26.64, 26.63, 23.56, 21.64, 16.95; UV (EtOH) λ_{max} 262 nm (ϵ 11 800); MS *m/z* (70 eV, CI) 446 (M + NH_4^+); HRMS *m/z* (M^+) calcd 428.2927 for $C_{27}H_{40}O_4$, found 428.2928; IR (neat, cm^{-1}) 3396, 2930, 1706.

Aldehyde (+)-51. According to the method of Kornblum,[49] a solution of primary tosylate (+)-**15** (220 mg, 0.45 mmol) in DMSO (1 mL) was added to a slurry of $NaHCO_3$ (168 mg, 2.0 mmol) in DMSO (2 mL) and heated to 150 °C. When the evolution of gas had ceased (10 min), the reaction mixture was cooled rapidly to rt (water bath), diluted with water (50 mL), and extracted (4 × 10 mL) with chloroform. The organic fractions were combined, washed repeatedly with brine, dried with Na_2SO_4, and concentrated to a light oil. Purification by flash silica gel chromatography (2% EtOAc/hexanes) provided 120 mg (80%) of aldehyde (+)-**51** as a colorless oil: $[\alpha]^{25}_D$ +40.7 (*c* 2.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (d, J = 3.2 Hz, 1H), 4.03 (m, 1H), 2.32 (ddq, J = 10.0, 6.8, 3.2 Hz, 1H), 1.73−1.92 (m, 3H), 1.58−1.71 (m, 2H), 1.28−1.44 (m, 5H), 1.10−1.26 (m, 2H), 1.06 (d, J = 6.8 Hz, 3H), 0.93 (s, 3H), 0.91 (t, J = 8.0 Hz, 9H), 0.52 (q, J = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.2, 69.0, 52.3, 51.6, 49.1, 42.6, 40.4, 34.5, 26.2, 23.3, 17.6, 13.9, 13.3, 6.9, 4.9; IR (thin film, cm^{-1}) 2948, 2872, 1724, 1456, 1164.

α,β-Unsaturated Ketone (+)-52. To a solution of the enolate formed by treatment of 3-(triethylsilyloxy)-3-methyl-2-butanone (**50**) (324 mg, 1.5 mmol) in THF (5 mL) at −78 °C with LDA (3.0 mL, 1.5 mmol, 0.5 M in THF) was added the aldehyde (+)-**51** (420 mg, 1.3 mmol) as a solution in THF (4 mL). The resulting mixture was removed from the low-temperature bath and allowed to warm to rt for 4 h. The reaction mixture was quenched with water and extracted three times with EtOAc. The organic fractions were combined, washed with brine, dried with Na_2SO_4, and concentrated to a light oil. Purification by flash silica gel chromatography (2% EtOAc/hexanes) provided 477 mg (70%) of conjugated ketone (+)-**52** as a colorless oil: $[\alpha]^{25}_D$ +45.4 (*c* 1.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (dd, J = 15.6, 8.8 Hz, 1H), 6.66 (d, J = 15.6 Hz, 1H), 4.01 (m, 1H), 2.48 (m, 1H), 1.88−1.96 (m, 1H), 1.73−1.87 (m, 1H), 1.48−1.70 (m, 3H), 1.32 (s, 6H), 1.26−1.42

(49) Kornblum, N.; Jones, W. J.; Anderson, G. J. *J. Am. Chem. Soc.* **1959**, *81*, 4113.

(m, 3H), 1.10−1.25 (m, 4H), 1.04 (d, J = 6.8 Hz, 3H), 0.936 (t, J = 8.0 Hz, 9H), 0.93 (s, 3H), 0.92 (t, J = 8.0 Hz, 9H), 0.58 (q, J = 8.0 Hz, 6H), 0.53 (q, J = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.1, 153.8, 121.4, 78.7, 69.2, 55.7, 52.8, 42.4, 40.6, 39.7, 34.5, 27.3, 27.2, 27.1, 23.0, 19.1, 17.6, 13.7, 7.0, 6.9, 6.5, 4.9; IR (thin film, cm^{-1}) 2951, 2875, 1697, 1622, 1458; HRMS m/z (M + H^+) calcd 523.4003 for $C_{30}H_{58}O_3Si_2$, found 523.4007.

Saturated Ketone (+)-53. A solution of α,β unsaturated ketone (+)-**52** (341 mg, 0.73 mmol) in benzene (20 mL) was hydrogenated (50 psi) for 12 h in the presence of 15 of mg 10% Pd/C until the absence of starting material was indicated by TLC. The reaction mixture was filtered through a bed of Celite with several benzene washes, and the filtrate was concentrated to a light oil. Purification by flash silica gel chromatography (2% EtOAc/hexanes) provided 255 mg (75%) of saturated ketone (+)-**53** as a colorless oil: $[\alpha]^{25}_D$ +32.7 (c 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 (m, 1H), 2.66 (ddd, J = 17.6, 10.4, 5.2 Hz, 1H), 2.56 (ddd, J = 17.6, 10.0, 6.0 Hz, 1H), 1.89−1.97 (m, 1H), 1.73−1.86 (m, 2H), 1.50−1.71 (m, 3H), 1.30 (s, 3H), 1.29 (s, 3H), 1.00−1.42 (m, 9H), 0.95 (t, J = 8.0 Hz, 9H), 0.92 (t, J = 8.0 Hz, 9H), 0.88 (s, 3H), 0.86 (d, J = 6.8 Hz, 3H), 0.61 (q, J = 8.0 Hz, 6H), 0.53 (q, J = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.3, 79.9, 69.3, 56.7, 53.0, 42.1, 40.8, 35.0, 34.6, 32.8, 29.5, 27.3, 27.2, 23.0, 18.4, 17.7, 13.5, 7.0, 6.9, 6.6, 4.9; IR (thin film, cm^{-1}) 2952, 2875, 1718, 1458, 1166, 1017; HRMS m/z (M + H^+) calcd 525.4159 for $C_{30}H_{60}O_3Si_2$, found 525.4164.

C,D-Ring Diketone (+)-54. The saturated bis-silylated ketone (+)-**53** (320 mg, 0.61 mmol) in THF (2 mL) was treated with TBAF (2.44 mL, 2.44 mmol, 1.0 M in THF) and allowed to stir at rt for 16 h. A general workup and flash silica gel chromatography (25% EtOAc/hexanes) provided 162 mg (88%) of the corresponding diol as a colorless oil: $[\alpha]^{25}_D$ +33.44 (c 2.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.03 (m, 1H), 2.52 (ddd, J = 17.2, 10.0, 5.2 Hz, 1H), 2.43 (ddd, J = 17.2, 9.6, 6.0 Hz, 1H), 1.91−1.97 (m, 1H), 1.70−1.89 (m, 4H), 1.2−1.6 (m, 7H), 1.35 (s, 3H), 1.34 (s, 3H), 1.00−1.16 (m, 2H), 0.89 (s, 3H), 0.87 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.9, 76.1, 69.2, 56.3, 52.5, 41.8, 40.3, 34.8, 33.5, 32.3, 29.6, 27.0, 26.54, 26.51, 22.4, 18.3, 17.4, 13.5; IR (thin film, cm^{-1}) 3456, 2934, 2871, 1706; HRMS m/z (M + NH_4^+) calcd 314.2695 for $C_{18}H_{32}O_3$, found 314.2700. A solution of this diol (162 mg, 0.54 mmol) in CH_2Cl_2 (2 mL) was added to a slurry of pyridinium chlorochromate (235 mg, 1.09 mmol) and Celite (235 mg) in CH_2Cl_2 (2 mL) at 0 °C and allowed to warm to rt. After being stirred for 5 h at rt, the whole reaction mixture was subsequently placed on a silica gel column and eluted with hexanes/ethyl acetate (3:2) to give 142 mg (87%) of the corresponding diketone tertiary alcohol as a colorless oil: $[\alpha]^{25}_D$ +12.00 (c 0.5, $CHCl_3$),^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64 (br s, 1H), 2.36−2.58 (m, 3H), 1.61−2.29 (m, 8H), 1.2−1.6 (m, 6H), 1.32 (s, 3H), 1.31 (s, 3H), 0.90 (d, J = 6.0 Hz, 3H), 0.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.6, 211.7, 76.1, 61.8, 56.4, 49.8, 40.8, 38.8, 35.0, 32.3, 29.5, 27.4, 26.6, 26.7, 23.9, 19.0, 18.4, 12.4; IR (thin film, cm^{-1}) 3478, 2958, 2871, 1711; HRMS (M + NH_4^+) calcd 312.2539 for $C_{18}H_{32}O_3$, found 312.2538. A solution of the diketone (62 mg, 0.21 mmol) in THF (2 mL) was treated with 1-(trimethylsilyl)imidazole and then allowed to warm to rt for 1 h. The solvent was removed *in vacuo*, and the residue was purified by flash silica gel chromatography to give 88 mg (70%) of diketone silyl ether (+)-**54** as a colorless oil: $[\alpha]^{25}_D$ +56.0 (c 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.58 (m, 2H), 2.43 (dd, J = 11.6, 7.6 Hz, 1H), 2.05−2.30 (m, 3H), 1.80−2.04 (m, 3H), 1.64−1.76 (m, 2H), 1.30 (s, 3H), 1.29 (s, 3H), 1.14−1.62 (m, 6H), 0.92 (d, J = 6.0 Hz, 3H), 0.61 (s, 3H), 0.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.7, 211.9, 80.1, 61.9, 56.6, 49.8, 40.9, 38.9, 35.2, 32.8, 29.6, 27.4, 27.2, 24.0, 19.0, 18.5, 12.5, 2.3; IR ($CHCl_3$, cm^{-1}) 2957, 2875, 1714, 1251, 1038, 841; HRMS m/z (M + H^+) calcd 367.2668 for $C_{21}H_{38}O_3Si$, found 367.2673.

Hybrid Analogs (−)-55a and (+)-55b. To a solution of phosphine oxide (±)-**20** (113 mg, 0.19 mmol) in THF (1.5 mL) at −78 °C was added PhLi (105 μL, 0.19 mmol, 1.8 M in 7/3 cyclohexane−ether). The resulting red-orange solution was allowed to stir for 15 min and then treated, *via* cannula, with a precooled (−78 °C) solution of the C,D-ring diketone (+)-**54** (35 mg, 0.10 mmol) in THF (1.5 mL). The reaction mixture was maintained at −78 °C for 6 h during which time the orange color faded slightly. The reaction mixture was quenched at −78 °C with 1 M potassium sodium tartrate (2 mL), warmed to rt, diluted with water (25 mL), and then extracted (4 × 5 mL) with EtOAc. The combined extracts were washed with brine, dried with Na_2SO_4, and concentrated to a crude oil *in vacuo*. Purification by flash silica gel chromatography (3% EtOAc/hexanes) provided 41 mg (58%) of the coupled products (45:55 mixture of diastereomers by ^{1}H NMR) as a colorless oil. A portion of this diastereomeric mixture (24 mg, 0.032 mmol) was subsequently dissolved in dry THF (1 mL), treated with excess TBAF (1.0 mL, 1.0 mmol, 1.0 M in THF), and stirred for 24 h at rt. The solvent was removed, and the residue was passed through a short column of silica gel (100% EtOAc) in preparation for HPLC purification. The diastereomers were then purified by reversed-phase HPLC (C-18 semipreparative column, 60% EtOH/water, 3 mL/min, 254 nm) to give 4.0 mg of (−)-**55a** (28%) and 6.0 mg (+)-**55b** (40%) as colorless oils. (−)-**55a**: $[\alpha]^{25}_D$ −23.75 (c 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (d, J = 10.8 Hz, 1H), 5.93 (d, J = 10.8 Hz, 1H), 5.15 (d, J = 2.0 Hz, 1H), 4.99, (d, J = 2.0 Hz, 1H), 3.94 (m, 1H), 3.80 (s, 1H), 3.53 (m, 2H), 2.80 (dd, J = 12.0, 4.0 Hz, 1H), 2.40−2.66 (m, 4H), 2.23 (dd, J = 11.2, 9.2 Hz, 1H), 1.16−2.02 (m, 18H), 1.36 (s, 6H), 0.91 (d, J = 6.4 Hz, 3H), 0.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.8, 145.1, 142.7, 134.0, 123.6, 117.1, 114.5, 76.1, 67.1, 64.3, 56.3, 56.2, 46.3, 45.9, 45.0, 40.4, 37.4, 35.6, 32.3, 29.8, 29.0, 27.4, 26.5, 23.6, 22.2, 18.6, 11.9; IR ($CHCl_3$, cm^{-1}) 3470, 2940, 2871, 1704, 1603, 1382, 1162; HRMS m/z (M^+) calcd 444.3240 for $C_{28}H_{44}O_4$, found 444.3244; UV (EtOH) λ_{max} 264 nm (ϵ 7500). (+)-**55b**: $[\alpha]^{25}_D$ +44.10 (c 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (d, J = 11.2 Hz, 1H), 5.93 (d, J = 11.2 Hz, 1H), 5.13 (d, J = 2.0 Hz, 1H), 4.97, (d, J = 2.0 Hz, 1H), 3.99 (m, 1H), 3.80 (s, 1H), 3.58 (m, 2H), 2.79 (dd, J = 12.4, 4.4 Hz, 1H), 2.40−2.66 (m, 4H), 2.25 (dd, J = 12.8, 8.4 Hz, 1H), 1.16−2.02 (m, 18H), 1.36 (s, 6H), 0.91 (d, J = 6.4 Hz, 3H), 0.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.8, 145.2, 142.8, 134.2, 123.5, 117.0, 113.8, 76.1, 67.1, 64.3, 56.3, 56.2, 46.2, 45.8, 44.4, 40.4, 37.4, 35.6, 32.3, 29.8, 29.0, 27.5, 26.5, 23.5, 22.2, 18.6, 11.9; HRMS m/z (M^+) calcd 444.3240 for $C_{28}H_{44}O_4$, found 444.3248; IR ($CHCl_3$, cm^{-1}) 3470, 2940, 2871, 1704, 1603, 1382, 1162; UV (EtOH) λ_{max} 264 nm (ϵ 9400).

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Supporting Information Available: Proton and ^{13}C NMR spectra for compounds **6**−**12**, **15**−**19**, **21**−**26**, **29**−**41**, **43**−**49**, and **51**−**55** (107 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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