2-Fluoroalkyl A-Ring Analogs of 1,25-Dihydroxyvitamin D_3. Stereocontrolled Total Synthesis *via* Intramolecular and Intermolecular Diels–Alder Cycloadditions. Preliminary Biological Testing

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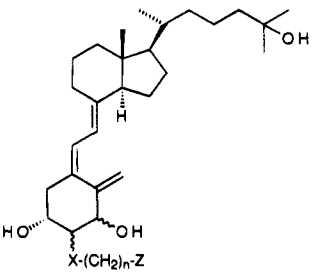
Intramolecular Diels–Alder (IMDA) cycloadditions of electron-rich *trans*-vinylic silaketal groups tethered *via* a chiral, nonracemic 1,3-butanediol auxiliary to electron-poor 2-pyrone-3-carboxylates (*e.g.* (*R*)-**9**, (*S*)-**14**) were promoted by zinc dibromide and proceeded unexpectedly in a stepwise, ionic fashion to form exclusively *cis*-4,5-disubstituted bicyclic lactones **10** and **15** with nearly complete asymmetric induction. Confirmation of the stereochemical outcome of these nonconcerted IMDA cycloadditions was achieved by ^{1}H NMR spectroscopy and by X-ray crystallography. Fluorinated bicycloadduct (−)-**15a** was converted smoothly in 13 steps into the lipophilic calcitriol analog 2β-(3′-fluoropropyl)-1β,25-dihydroxyvitamin D_3 ((−)-**5**). Intermolecular, concerted, 11 kbar, inverse-electron-demand 4 + 2-cycloaddition of bis-silylated *Z*-enol ether **22c**, carrying two different silyl groups, with commercial methyl 2-pyrone-3-carboxylate gave in gram amounts only vicinally *cis*-disubstituted bicycloadduct (±)-**23c**. Chemospecific monodesilylation using sodium azide and then fluorination using Et_2NSF_3 (DAST) gave fluoroalkyl bicyclic lactone (±)-**25**. This bicyclic lactone (±)-**25** was transformed into fluorinated, racemic, A-ring phosphine oxide (±)-**30** that was coupled with enantiomerically pure C,D-ring ketone (+)-**21** to form enantiomerically pure diastereomers (−)-**4** and (+)-**4′** as fluorinated, lipophilic, A-ring analogs of 1,25-dihydroxyvitamin D_3 (calcitriol). Preliminary biological testing (Table I) showed that only those diastereomers having the unnatural 1β-hydroxyl group stereochemistry (*i.e.* (+)-**3′**, (+)-**4′**, and (−)-**5**) had relatively high affinities for the calf thymus vitamin D receptor and significant antiproliferative and differentiation-inducing potencies in HL-60 cells.

Searching for new calcitriol analogs like ED-71 (**1**) and ED-120 (**2**) for chemotherapy of osteoporosis,[1] we have prepared 2-substituted analog primary alcohol (−)-**3** as well as its A-ring stereochemically inverted diastereomer (+)-**3′**, both having significant affinity for the vitamin D binding protein.[2] As part of our ongoing research program using electronically matched 2-pyrones and various dienophiles for stereocontrolled construction of isolable and versatile bicyclic lactone adducts,[3] we report here on the preparation of fluoro analog (−)-**4**, a fluorinated version of (−)-**3**, as well as on the results of Lewis acid-promoted, intramolecular Diels–Alder (IMDA) cycloadditions of 3-substituted 2-pyrones leading to an asymmetric total synthesis of 2-fluoroalkyl calcitriol analog (−)-**5**. Preliminary biological evaluations of these seco-



	⊥	X	n	Z	
1,	α	β-O	3	OH	(ED-71)
2,	α	β-CH_2	3	OH	(ED-120)
(−)-**3**,	α	α-CH_2	3	OH	
(−)-**4**,	α	α-CH_2	3	F	
(−)-**5**,	β	β-CH_2	2	F	

steroids are also presented. During the course of this study, a delicate balance was revealed between concerted and stepwise Diels–Alder cycloadditions.

Results and Discussions

A series of 2-pyrone-3-carboxylate esters with diverse olefinic ester groups was prepared for IMDA cycloadditions.[4] Allylic and vinylic silanes as well as a vinyl

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(3) (a) Posner, G. H.; Eydoux, F.; Lee, J. K.; Bull, D. S. *Tetrahedron Lett.* **1994**, *35*, 7541. (b) Posner, G. H.; Ishihara, Y. *Ibid.* **1994**, *35*, 7545. For reviews, see: (c) Afarinkia, K.; Vinader, V.; Nelson, T. D.; Posner, G. H. *Tetrahedron* **1992**, *48*, 9111. (d) Kvita, V.; Fischer, W. *Chimia* **1993**, *47*, 3. (e) Posner, G. H. In *Stereocontrolled Organic Synthesis - Chemistry for the 21st Century*; Trost, B. M., Beletskaya, I, P., Eds.; Blackwell Scientific Publications: Oxford, U.K., 1994; p 177. (f) Marko, I. E. *Organometallic Reagents in Organic Synthesis*; Academic Press: New York, 1994; Chapter 2, p 44.

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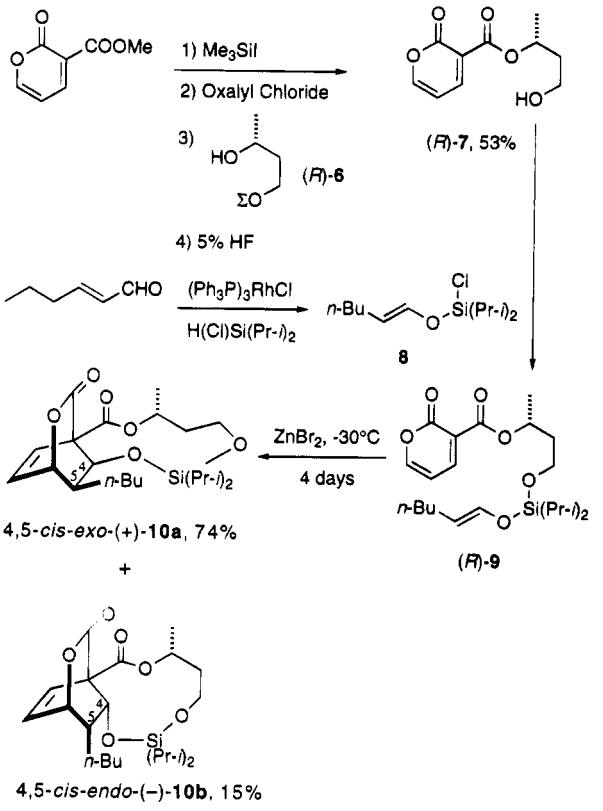
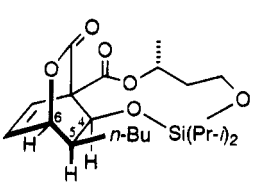
Scheme 1



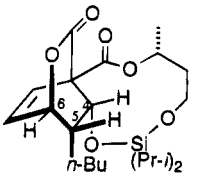
carbonate tethered[5] to the carboxylate group of 2-pyrone-3-carboxylate all failed to undergo thermal or 11 kbar intramolecular 4 + 2-cycloaddition. In contrast, unsymmetrical enolic silaketals tethered to the pyrone carboxylate group, as in structure (*R*)-**9** (Scheme 1), were successful;[6] enol silaketals like (*R*)-**9**, derived from commercial and enantiomerically pure (*R*)-1,3-butanediol, were found to undergo IMDA cycloaddition with higher chemical yields and higher stereocontrol than the corresponding enol silaketals derived from enantiomerically pure vicinal diols 1,2-propanediol or 2,3-butanediol. Also, two isopropyl groups attached to the silicon atom (as in silaketal (*R*)-**9**) were found to give better results than two methyl groups. Preparation exclusively of the *E*-geometric isomer enol silaketal **8** from (*E*)-2-hexenal followed literature precedent (Scheme 1);[7] ^{1}H NMR spectroscopy showed a coupling constant of 12 Hz for the two adjacent vinylic hydrogen atoms characteristic of E-double bond stereochemistry.[7] Lewis acid-promoted[8] IMDA cycloaddition of pyrone enol silaketal (*R*)-**9** proceeded as shown in Scheme 1 to produce chromatographically separable diastereomers (+)-**10a** and (−)-**10b**, isolated in pure form in 74 and 15% yields, respectively. This stereochemical result represents outstanding asymmetric induction by the lone stereogenic carbon center in the (*R*)-1,3-butanediol chiral auxiliary.

Unambiguously establishing the relative stereochemistry of the bicyclic lactone cycloadducts **10** was essential to understanding the course of this IMDA reaction. Assignment of the 4,5-regiochemistry and of the *cis*-4,5 relative stereochemistry to cycloadducts (+)-**10a** and (−)-**10b** was based on matching the 400 MHz ^{1}H NMR patterns of chemical shifts and the $J_{4,5}$ coupling constants with those of very close structural analogs, in contrast to the *trans*-4,5-disubstituted isomers, as shown in the accompanying structures.[2,3] ^{1}H NMR decoupling experiments were especially useful for these assignments. Within each pair of *cis*-4,5-disubstituted isomers, the H_4 chemical shifts were very different, but the H_6 chemical shifts were similar; in contrast, the *trans*-4,5-disubstituted isomers had similar H_4 chemical shifts but very different H_6 chemical shifts.



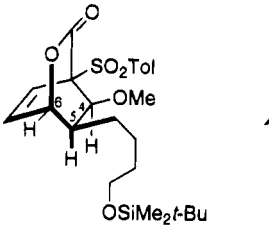
4,5-*cis*-*exo*-(+)-**10a**

H_4 4.38δ $J_{4,5}$ = 0 Hz
H_5 1.84δ
H_6 4.98δ



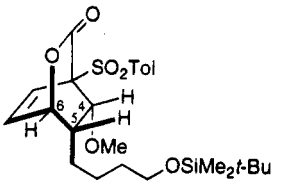
4,5-*cis*-*endo*-(−)-**10b**

H_4 4.94δ $J_{4,5}$ = 7.6 Hz
H_5 2.41δ
H_6 5.06δ



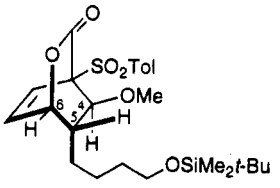
4,5-*cis*-*exo*

H_4 3.82δ $J_{4,5}$ = 0 Hz
H_5 1.74δ
H_6 4.95δ



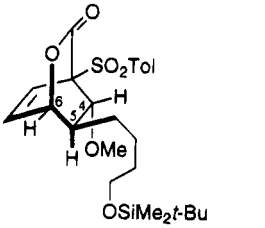
4,5-*cis*-*endo*

H_4 4.56δ $J_{4,5}$ = 8.9 Hz
H_5 2.55δ
H_6 5.04δ



trans-4-*exo*-5-*endo*

H_4 4.40δ $J_{4,5}$ = 1 Hz
H_5 2.30δ
H_6 3.80δ



trans-4-*endo*-5-*exo*

H_4 4.98δ $J_{4,5}$ = 3 Hz
H_5 1.70δ
H_6 4.40δ

(4) (a) Oppolzer, W. *Angew. Chem., Int. Ed. Eng.* **1977**, *16*, 10. (b) Brieger, G.; Bennet, J. N. *Chem. Rev.* **1980**, *80*, 63. (c) Taber, D. F. *Intramolecular Diels–Alder Reactions and Alder Ene Reactions;* Springer Verlag: New York, 1984. (d) Ciganek, E. *Org. React.* **1984**, *32*, 1. (e) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 238. (f) Carruthers, W. In *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: New York, 1990; p 140. (g) Brown, F. K.; Singh, U. C.; Kollman, P. A.; Raimondi, L.; Houk, K. N. *J. Org. Chem.* **1992**, *57*, 4862.

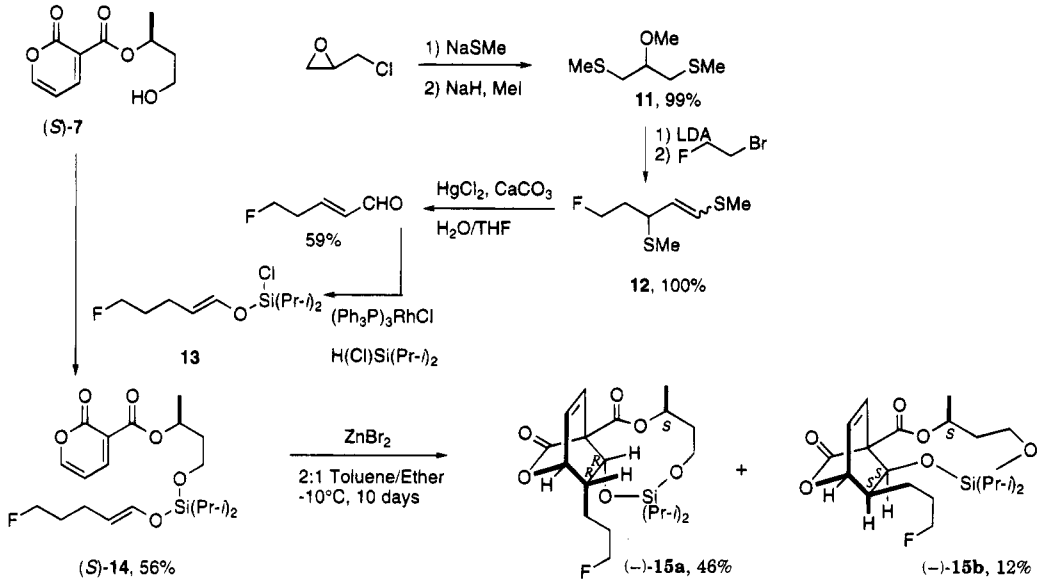
(5) (a) Stork, G.; Kim, G. *J. Am. Chem. Soc.* **1992**, *114*, 1087. (b) Stork, G.; Chan, T. Y.; Breaulet, G. A. *Ibid.* **1992**, *114*, 7578. (c) Stork, G.; Suh, H. S.; Kim, G. *Ibid.* **1991**, *113*, 7054. (d) Sieburth, S. M.; Fensterbank, L. *J. Org. Chem.* **1992**, *57*, 5279. (e) For 2 + 2-photocycloadditions, see also: Crimmins, M. T.; Guise, L. E. *Tetrahedron Lett.* **1994**, *35*, 1657.

(6) For examples of IMDA cycloaddition using a silaketal to tether a diene and a dienophile, see: (a) Gillard, J. W.; Fortin, R.; Grimm, E. L.; Maillard, M.; Tjepkema, M.; Bernstein, M. A.; Glaser, R. *Tetrahedron Lett.* **1991**, *32*, 1145. (b) Craig, D.; Reader, J. C. *Tetrahedron Lett.* **1992**, *33*, 6165. (c) Shea, K. J.; Gauthier, D. R., Jr. *Tetrahedron Lett.* **1994**, *35*, 7311. See also: (d) Garner, P. P.; Cox, P. B.; Klippenstein, S. J.; Young, W. J.; McConville, D. B. *J. Org. Chem.* **1994**, *59*, 6510. (e) Colombier, C.; Skrydstrup, T.; Beau, J.-M. *Tetrahedron Lett.* **1994**, *35*, 8167.

(7) Ojima, I.; Kogure, T. *Organometallics* **1982**, *1*, 1390.

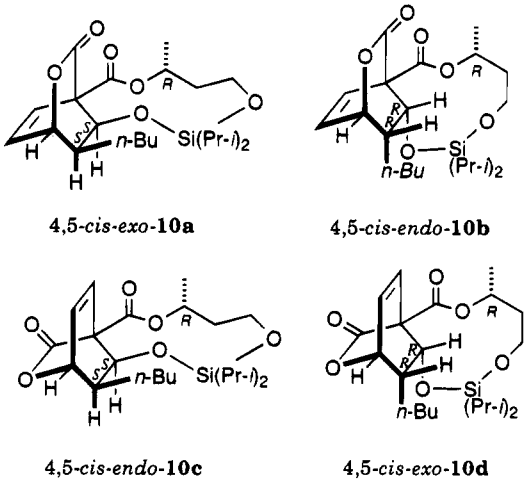
(8) Marwoka, K.; Yamamoto, H. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: 1994; Chapter 9, p 413.

Scheme 2



Thus, in sharp contrast to concerted intermolecular 4 + 2-cycloadditions of electron-rich enol silyl ethers with electron-poor methyl 2-pyrone-3-carboxylate,[3,4] this inverse-electron-demand, Lewis acid-promoted, intramolecular 4 + 2-cycloaddition must occur stepwise[9,10] because the exclusive *E*-geometry of the dienophile in (*R*)-**9** is lost during formation of only the *cis*-4,5-disubstituted cycloadducts **10**.[11] In the absence of zinc dibromide but under 11 kbar pressure, concerted cycloaddition occurred (albeit in low yield) with preservation of dienophile geometry to give mainly the expected *trans*-4,5-disubstituted cycloadducts. A control experiment showed that these kinetic *trans*-4,5-disubstituted cycloadducts are stable to the Lewis acid reaction conditions. Another control experiment showed by analytical TLC that an *E*-configured enol silaketal like **8** (formed via hydrosilylation of (*E*)-2-hexenal with *tert*-butyldimethylsilane and chromatographically separated from the corresponding *Z*-configured enol silaketal) is stable to zinc dibromide in 2/1 toluene/ether even at 0 °C, thereby ruling out the possibility of Lewis acid-promoted *trans* → *cis* isomerization of enol silaketal (*R*)-**9** before cycloaddition. Apparently therefore in Scheme 1, the Lewis acid polarizes the diene sufficiently to initiate nucleophilic attack by the pendant vinyl silaketal, forming a zwitterionic intermediate containing a siloxy-stabilized carbocation in which the original double bond geometry can be lost.[10] At this time, we do not have a convincing explanation to account for the exclusive formation of only *cis*-4,5-disubstituted cycloadducts **10** rather than a mixture of *cis*- and *trans*-4,5-disubstituted cycloadducts *via* the zwitterionic intermediate. It is noteworthy that the stepwise, ionic nature of this Lewis acid-promoted intramolecular cycloaddition would not have been noticed if only *trans*-4,5-disubstituted cycloadducts had been formed, as originally expected for a concerted cycloaddition starting with the *E*-vinylic silaketal precursor (*R*)-**9**.

Establishing the absolute stereochemistry of cycloadducts **10** was more difficult. The four possible *cis*-4,5-disubstituted cycloadducts are shown in the accompanying structures. Luckily, the minor cycloadduct **10b** was a crystalline solid; X-ray analysis established its absolute stereochemistry to be as shown for 4,5-*cis*-*endo*-**10b**. The major cycloadduct could not have 4,5-*cis*-*endo* stereochemistry because of its nearly zero ^{1}H NMR $J_{4,5}$ coupling constant; therefore, the major cycloadduct cannot be 4,5-*cis*-*endo*-**10c**. Thus, the major cycloadduct must be either 4,5-*cis*-*exo*-**10a** or 4,5-*cis*-*exo*-**10d**. Distinguishing between diastereomers **10a** and **10d** is difficult, and the following argument is offered only as a tentative working hypothesis. Molecular models suggest that diastereomers **10a** and **10d** might be distinguishable from each other by ^{1}H NMR spectroscopy. Specifically, it appears that the chemical environment of the original stereogenic carbon atom of (*R*)-1,3-propanediol should be similar for the two *R,R,R*-diastereomers **10b** and **10d**. In contrast, (*R,R,R*)-**10b** and (*R,S,S*)-**10a** should have different ^{1}H NMR chemical shifts for the methyl doublet and the methine multiplet characteristic of the stereogenic center.



4,5-*cis*-*exo*-**10a** 4,5-*cis*-*endo*-**10b**

4,5-*cis*-*endo*-**10c** 4,5-*cis*-*exo*-**10d**

(9) For a stepwise, ionic, intermolecular 4 + 2-cycloaddition of methyl 2-pyrone-5-carboxylate with 1,1-diarylethylenes, see: Behringer, H.; Heckmaier, P. *Chem. Ber.* **1969**, *102*, 2835.

(10) For other examples, see: (a) Gupta, R. B.; Franck, R. W. *J. Am. Chem. Soc.* **1987**, *109*, 5393. (b) Magnus, P.; Walker, C.; Jenkins, P. R.; Menear, K. A. *Tetrahedron Lett.* **1986**, *27*, dd651. (c) Padias, A. B.; Hedrick, S. T.; Hall, H. K., Jr. *J. Org. Chem.* **1983**, *48*, 3787. (d) See also: Potts, K. T.; Dery, M. O. *Ibid.* **1990**, *55*, 2884. (e) Storer, J. W.; Raimondi, L.; Houk, K. N. *J. Am. Chem. Soc.* **1994**, *116*, 96753.

(11) For concerted intramolecular 4 + 2-cycloaddition of a 2-pyrone tethered *via* a boron bridge to a dienophile, see: Narasaka, K.; Shimada, S.; Osoda, K.; Iwasawa, N. *Synthesis* **1991**, 1171.

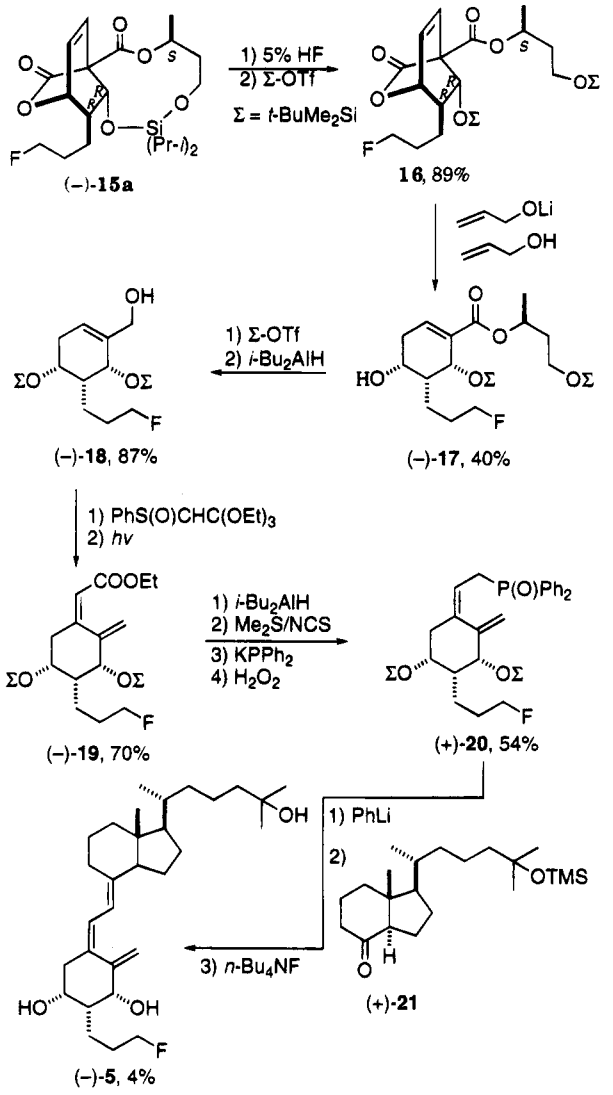
Indeed, the methyl doublet of (*R,S,S*)-**10a** is at 1.40 δ whereas that of (*R,R,R*)-**10b** is at 1.34 δ; likewise, the carbinol hydrogen atom at the stereogenic center in **10a** differs in chemical shift from that in **10b** by 0.5 ppm. Therefore, the major cycloadduct was tentatively assigned to have the absolute stereochemistry represented by structure **10a**.

To provide a second example of this type of stepwise, Lewis acid-promoted, IMDA cycloaddition and to prepare a 2-fluoroalkyl analog of vitamin D_3, we selected the enantiomeric chiral auxiliary (*S*)-1,3-butanediol to form pyrone fluorovinyl silaketal (*S*)-**14** (Scheme 2). The requisite fluorovinyloxysilyl chloride **13** was prepared by hydrosilylation[7] of 5-fluoro-(*E*)-2-pentenal, itself formed in several steps according to literature precedent from epichlorohydrin (Scheme 2).[12] Although fluorovinyl silaketal (*S*)-**14** was considerably less stable than its nonfluorinated analog (*R*)-**9**, when used immediately after its preparation, it underwent a similar zinc dibromide-promoted IMDA cycloaddition to give easily separable *cis*-4,5-disubstituted cycloadducts (−)-**15a** and (−)-**15b** in 46 and 12% yields, respectively. The 400 MHz ^{1}H NMR spectra of these cycloadducts very closely matched those of the *cis*-4,5-disubstituted cycloadducts (+)-**10a** and (−)-**10b** (Scheme 1). Using the (*S*)-1,3-butanediol chiral auxiliary to prepare pyrone vinyl silaketal (*S*)-**14** gave the cycloadducts **15** that are enantiomeric to cycloadducts **10**.

Using other Lewis acids[8] (*e.g.* $MgBr_2$, Et_2AlCl, $TiCl_4$, $LiClO_4$) to promote the IMDA cycloaddition of fluorovinyl silaketal (*S*)-**14** was successful but offered no advantage over zinc dibromide in the yield of *cis*-4,5-disubstituted cycloadducts (−)-**15a** and (−)-**15b** or in the ratio of these cycloadducts.

Diastereomerically pure fluorinated cycloadduct (−)-**15a** was carried on toward a 2-fluoroalkyl-1,25-dihydroxyvitamin D_3 analog. Opening of the silaketal ring using HF followed immediately by silylation gave O-protected bicyclic lactone **16** (Scheme 3). Opening of the lactone ring chemospecifically with a large excess of lithium allyl oxide gave an intermediate mixed allyl methyl malonate (isolated when only 1 equiv of allyl oxide was used) that, unexpectedly, underwent spontaneous decarboxylation[13] with concomitant conjugation of the olefinic double bond to the ester group to form stereospecifically tetrasubstituted cyclohexene (−)-**17**. After O-silylation, reduction of the conjugated enoate ester led to allylic alcohol (−)-**18** that underwent smooth, one-flask two-carbon homologation *via* a Claisen rearrangement followed by a spontaneous thermal sulfoxide elimination using our sulfinylated orthoester protocol;[14] photochemical isomerization[15] of *E* → *Z*-dienoate gave A-ring chiron (−)-**19**. Established reactions as shown in Scheme 3 provided the crucial, fully protected, enantiomerically pure, A-ring phosphine oxide (+)-**20**.[2] Lythgoe-type coupling[16] of the conjugate base of this phosphine oxide, generated using

Scheme 3



phenyllithium,[17] with C,D-ring ketone (+)-**21** of natural absolute configuration[15] produced an O-silylated product that underwent fluoride-promoted desilylation to form a fluorinated, lipophilic vitamin D analog with tentative stereochemical assignment as 2β-(3′-fluoropropyl)-1β,25-dihydroxyvitamin D_3 analog (−)-**5** having the unnatural 1β-hydroxyl group orientation.[18,19]

Having in hand the various synthetic intermediates leading up to 2-hydroxybutyl analog (−)-**3**,[2] we explored when it would be easiest to replace the primary alcohol

(12) Corey, E. J.; Erickson, B. W.; Noyori, R. *J. Am. Chem. Soc.* **1971**, *93*, 1724.
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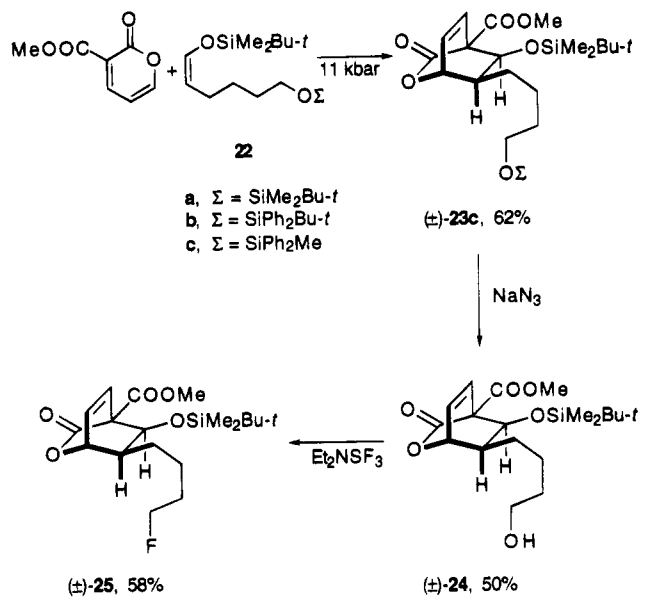
(18) For reviews of synthetic approaches to vitamin D, see: (a) Wilson, S. R.; Yasmin, A. In *Studies in Natural Products Chemistry*; Ur-Raman, A., Ed.; Stereoselective Syntheses; Elsevier Science Publishers: Amsterdam, 1992; p 43. (b) Dai, H.; Posner, G. H. *Synthesis* **1994**, 1383. (c) Zhu, G.-D.; Okamura, W. H. *Chem. Rev.*, in press, 1995.
(19) Examples of physiologically active 1β-hydroxyl vitamin D_3 analogs have been reported recently: (a) Norman, A. W.; Nemere, I.; Muralidharan, K. R.; Okamura, W. H. *Biochem. Biophys. Res. Commun.* **1992**, *189*, 1450. (b) Muralidharan, K. R.; de Lera, A. R.; Isaeffy, S. D.; Norman, A. W.; Okamura, W. H. *J. Org. Chem.* **1993**, *58*, 1895. (c) Posner, G. H., Guyton, K. Z.; Kensler, T. W.; Barsony, J.; Lieberman, M. E.; Reddy, G. S.; Clark, J. W.; Wankadiya, K. F.; Tserng, K.-Y. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1835. (d) Posner, G. H.; White, M. C.; Dolan, P.; Kensler, T. W.; Yukihiro, S.; Guggino, S. *Ibid.* **1994**, *4*, 2919. (e) See also ref 18.

Scheme 4



group by a fluorine atom,[20] leading to preparation of fluorinated vitamin D analog (−)-**4**. Toward this end, failed attempts included treating primary−secondary bis-silyl ether cycloadduct **23a** with tetra-*n*-butylammonium fluoride,[21] aiming for chemoselective deprotection of the sterically more accessible primary alcohol, and treating differently protected bis-silyl ether cycloadduct **23b** with sodium hydride/HMPA, a procedure reported to selectively desilylate *tert*-butyldiphenylsilyl ethers in the presence of *tert*-butyldimethylsilyl ethers.[22] Changing the primary alcohol protecting group to a diphenylmethylsilyl ether in the reactant enol silyl ether **22** produced cycloadduct (±)-**23c** in which somewhat capricious hydrolytic deprotection on silica gel formed free primary alcohol (±)-**24**. More reliable chemospecific deprotection of this primary silyl ether group in bis-silyl ether cycloadduct (±)-**23c** was finally achieved using sodium azide (Scheme 4).[23] Although the primary triflate corresponding to alcohol (±)-**24** failed to undergo nucleophilic displacement with fluoride ion, direct fluorination of primary alcohol (±)-**24** with Et_2NSF_3 (DAST) was successful (Scheme 4).[24] It should be noted that several attempts for converting 6-fluorohexanal into the corresponding enol silyl ether[25] for cycloaddition with methyl 2-pyrone-3-carboxylate as a direct approach to fluorinated cycloadduct (±)-**25** failed. Finally, it is worth emphasizing that the gram-scale, concerted cycloaddition of bis-silyl *Z*-enol ether **22c** led, as expected on the basis of a recent close analogy,[3] exclusively to vicinally *cis*-disubstituted bicyclic lactone (±)-**23c** in 62% yield, with starting commercial methyl 2-pyrone-3-carboxylate recovered in 15−20% yield.

Also in accord with recent precedent, fluorinated bicyclic lactone (±)-**25** was converted into racemic, fluorinated, A-ring phosphine oxide (±)-**30** (Scheme 5).[2] Noteworthy features of the transformations in Scheme 5 are as follows: (1) chemospecific lactone opening by lithium allyl oxide[2] to form cyclohexene (±)-**26** even in the presence of other electrophilic centers such as the methyl ester, the silyl ether, and the primary fluoralkyl group; (2) mild and non-high pressure deallyloxycarboxylation[26] with concomitant conjugation of the enoate double bond to form cyclohexene (±)-**27**; (3) survival of the primary fluoroalkyl group to *i*-Bu_2AlH reductions in preparation of alcohol (±)-**28** and of phosphine oxide (±)-**30**; and (4) stereoselective generation of the desired *Z*-dienoate (±)-**30**, easily separated chromatographically from its *E*-isomer, thereby avoiding the need for photochemical isomerization,[15] by one-pot two-carbon homologation using a phenylsulfinyl orthoester.[14] Coupling[2] of the conjugate base of racemic allylic phosphine oxide (±)-**30** with the enantiomerically pure C,D-ring ketone (+)-**21** gave HPLC-separable, enantiomerically pure fluoroalkyl seco-steroids (−)-**4** and (+)-**4′**.

Tentative assignment of A-ring stereochemistry to these fluoroalkyl A-ring analogs (−)-**4** and (+)-**4′** was made by comparing the characteristic portions of their ^1H NMR spectra with those of hydroxyalkyl A-ring analog (−)-**3** and its diastereomer (+)-**3′** (corresponding to (+)-**4′**) as well as their characteristic signs of optical rotation.[2,27] Specifically, the chemical shifts of the C_{18}-methyl group (δ 0.55 *vs* 0.53) and the C_{19}-methylene group (δ 5.01 *vs* 4.99) were diagnostic. The ^{19}F NMR spectra of diastereomers (−)-**4** and (+)-**4′** confirmed the presence of a primary alkyl fluoride group.[28] These steroidal alkyl fluorides were much more soluble in organic solvents (*i.e* more lipophilic) and much less polar on TLC than were the corresponding alcohols (−)-**3** and (+)-**3′**.

Replacing the primary hydroxyl group in analog (−)-**3** with a fluorine atom and inverting the stereochemistry at positions 1 and 2 (*i.e.* analog (−)-**5**) caused an attenuation in the relative binding affinity to the vitamin D binding protein (DBP) but an increase in the relative binding affinity to the calf thymus vitamin D receptor (VDR), as specified in Table 1, in which the data were generated *in vitro* according to the previously described protocol.[1,29] The relative *in vitro* potencies for inhibition of human leukemic HL-60 cell proliferation and induction of HL-60 cell differentiation as well as the relative VDR binding affinities were higher for the unnatural 1β-hydroxyl diastereomers (*i.e.* (+)-**3′** vs (−)-**3** and (+)-**4′** vs (−)-**4**). The strong similarity in the relative binding affinities of analogs (+)-**3′**, (+)-**4′**, and (−)-**5** as well as their similar activities in HL-60 cells support the absolute stereochemistry of (−)-**5** being the same as that in analogs (+)-**3′** and (+)-**4′** at the crucial 1- and 2-positions. The lipophilic fluorinated analogs (+)-**4′** and (−)-**5** are expected to have *in vivo* pharmacodynamics and transport characteristics different than those of osteoporosis

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Scheme 5

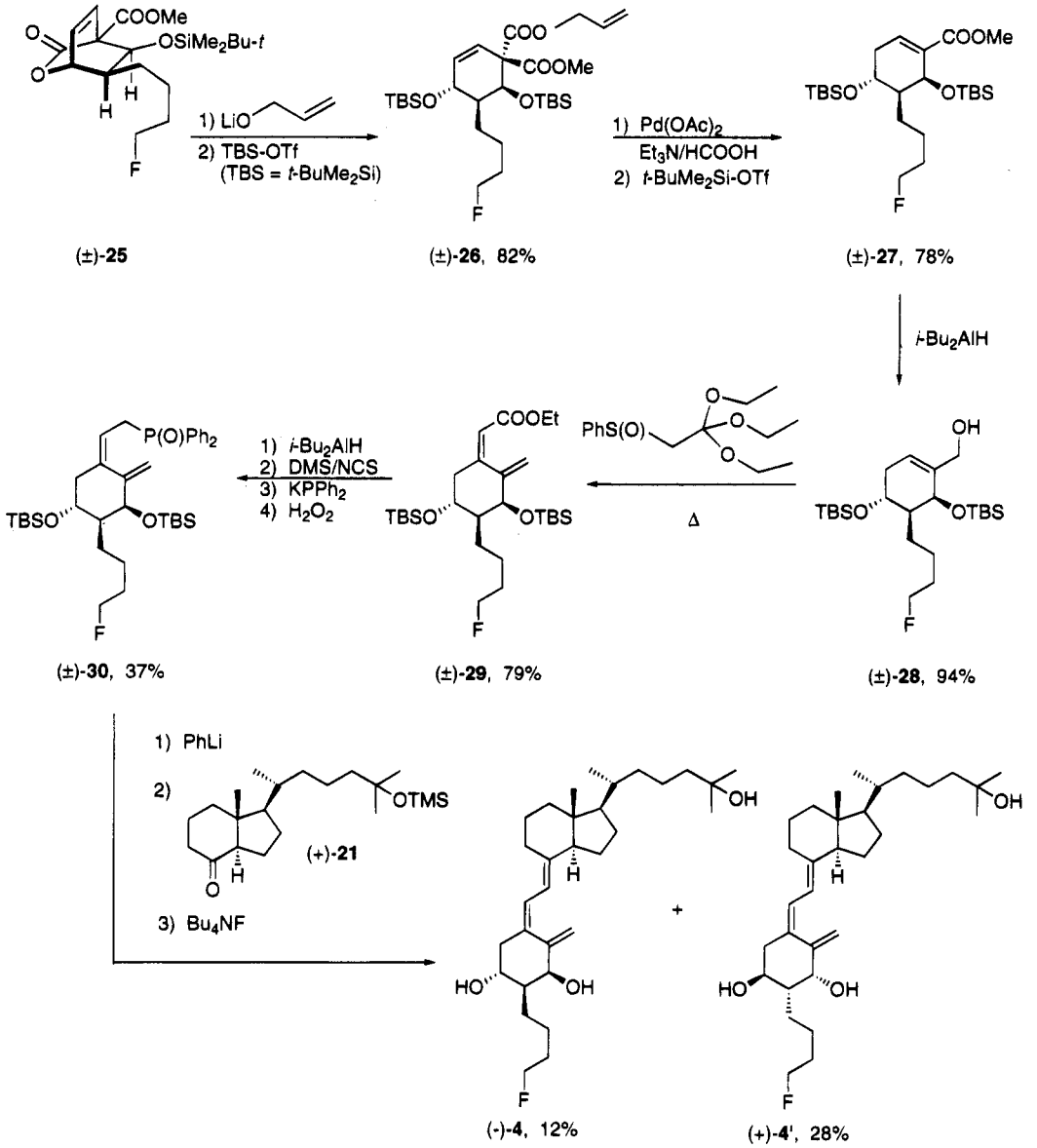

Table 1. Chemical Structure–Biological Activity Relationships

	relative binding affinities		inhibition of cell proliferation	induction of cell differentiation
	DBP	VDR		
$1,25\text{-}(OH)_2D_3$	1	1	1	1
ED-71	3.7	0.21		
ED-120	1.8	0.01		
(−)-**3**	5.0	0.01	<0.1	<0.1
(+)-**3'**	1.9	0.28	0.58	0.84
(−)-**4**	1.2	0.001	<0.1	<0.1
(+)-**4'**	0.40	0.16	0.50	0.23
(−)-**5**	0.83	0.10	0.20	0.41

drug candidate ED-71 (**1**), and, therefore, they deserve further *in vivo* biological evaluation to determine whether they have any practical value in preventing or curing osteoporosis.

The structure–activity relationships described here, along with those reported recently,[1-3,19] emphasize that considerable structural and stereochemical changes at the 1–3-positions of calcitriol can be made while still maintaining significant regulation of calcium metabolism and cell differentiation. These combined results, therefore, encourage design, synthesis, and biological evaluation of additional A-ring analogs of calcitriol that may have practical value in preventing or diminishing the bone mineral loss characteristic of osteoporosis and in restoring desirable differentiating ability to nondifferentiating cells.

Experimental Section[14]

The purity of most products was judged to be >95% on the basis of their chromatographic homogeneity. The only exceptions were the final coupling products in which the purity was somewhat lower due to the small amounts of seco-steroids produced, making their purification and spectroscopic characterization difficult.

Pyrone Ester (*R*)-7. A mixture of hexamethyldisilane (4.75 g, 32.4 mmol) and iodine (8.23 g, 32.4 mmol) was heated at 65 °C in a dry 500 mL round-bottomed flask equipped with a reservoir and a long reflux condenser. A violent exothermic reaction occurred, and a homogeneous reddish brown solution resulted, which was heated under reflux for 1.5 h to form a colorless liquid (hexamethyldisilane was quantitatively converted to iodotrimethylsilane). Methyl 2-oxo-2*H*-pyran-3-carboxylate (5.0 g, 32.4 mmol) in 50 mL of $CHCl_3$ was added, and the mixture heated at reflux until the reaction was complete by TLC analysis (*ca.* 25 h). The reaction mixture was cooled to 25 °C, and 2 mL of water was added. The

mixture was strirred for 10 min and then dissolved with CH_2Cl_2 (100 mL). Saturated aqueous sodium thiosulfate (5 mL) was added, and the mixture was stirred until complete decoloration was evident. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic solution was then washed with saturated sodium thiosulfate solution (1 × 20 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure, and the residue was dried using a vacuum pump. The 2-pyrone-3-carboxylic acid was recrystallized from toluene to afford 3.53 g (78% yield) as yellow crystals: mp 121−123 °C; ^{1}H NMR ($CDCl_3$) δ 8.56 (dd, J = 2.2, 6.5 Hz, 1H), 7.83 (dd, J = 2.2, 4.9 Hz, 1H), 6.68 (dd, J = 5.1, 6.9 Hz, 1H); IR ($CHCl_3$) 1749, 1690, 1555, 1414, 1390 cm^{-1}. Anal. Calcd for $C_6H_4O_4$: C, 51.44; H, 2.91. Found: C, 51.47; H, 2.89.

To 2.0 g (14.3 mmol) of this carboxylic acid in benzene (50 mL) was added oxalyl chloride (8 mL, 91.4 mmol). A few drops of DMF were added which initiated a vigorous reaction. The reaction mixture was stirred at rt for 2 h. The solvent was evaporated under reduced pressure. The residue was redissolved in benzene and evaporated again. The residue was dried under a vacuum pump and recrystallized from benzene to afford 2.26 g (100% yield) of the corresponding acid chloride as yellow crystals: mp 98−100 °C; ^{1}H NMR ($CDCl_3$) δ 8.51 (dd, J = 2.22, 7.08 Hz, 1H), 7.82 (dd, J = 2.24, 5.06 Hz, 1H), 6.51 (dd, J = 4.98, 7.05 Hz, 1H); IR ($CHCl_3$) 3013, 1813, 1784, 1743, 1625, 1543 cm^{-1}. Anal. Calcd for $C_6H_4ClO_3$: C, 45.45; H, 1.91; Cl, 22.39. Found: C, 45.61; H, 1.96; Cl, 22.24.

To 0.919 g (10.2 mmol) of (*R*)-1,3-butanediol, 1.414 mL (19.0 mmol) of triethylamine, 0.257 g (2 mmol) of 4-(dimethylamino)-pyridine (DMAP), and 20 mL of CH_2Cl_2 was added 1.543 g (10.2 mmol) of *tert*-butyldimethylsilyl chloride (TBDMSCl) dissolved in 10 mL of CH_2Cl_2 at −78 °C. Upon addition, the reaction mixture was allowed to warm to rt and stirred for 27 h. The reaction mixture was then diluted with 100 mL of ether, washed with H_2O and saturated NH_4Cl, dried over $MgSO_4$, concentrated *in vacuo*, and purified by column chromatography (silica gel, 80/20 hexane/EtOAc) to afford 1.789 g of the monoprotected diol (+)-**6** in 87% yield: ^{1}H NMR ($CDCl_3$) δ 4.02−3.94 (m, 1H), 3.90−3.83 (m, 1H), 3.80−3.74 (m, 1H), 1.69−1.55 (m, 2H), 1.16 (d, J = 6.4 Hz, 3H), 0.87 (s, 9H), 0.04 (bs, 6H); ^{13}C NMR ($CDCl_3$) δ 68.1, 25.8, 23.3, 18.1, −5.57, −5.62; FT-IR ($CHCl_3$) 3482, 2956, 2859, 1472, 1260 cm^{-1}.

To 1.85 g (9.1 mmol) of the monosilylated diol (*R*)-**6** in 20 mL of anhydrous CH_2Cl_2 were added 1.44 g (9.28 mmol) of 2-pyrone-3-carboxylic acid chloride in 20 mL of CH_2Cl_2 and 1.58 mL (11.3 mmol) of triethylamine at −78 °C. The reaction mixture was then slowly warmed to rt over 2 h, washed with H_2O, dried over $MgSO_4$, concentrated *in vacuo*, and purified by column chromatography (80/20 hexane/EtOAc) to give 1.89 g of the O-silylated derivative of pyrone ester (*R*)-**7** as a brown oil in 64% yield: ^{1}H NMR ($CDCl_3$) δ 8.10 (dd, J = 6.4, 2.4 Hz, 1H), 7.66 (dd, J = 5.2, 2.4 Hz, 1H), 5.24−5.17 (m, 1H), 3.74−3.64 (m, 2H), 1.95−1.86 (m, 1H), 1.81-1.73 (m, 1H), 1.32 (d, J = 6.4, 3.0 Hz, 3H), 0.84 (s, 9H), −0.01 (s, 3H), −0.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 162.5, 157.1, 156.1, 147.8, 118.4, 105.6, 70.2, 59.2, 38.7, 25.8, 20.0, 18.1, −5.5, −5.6; FT-IR ($CHCl_3$) 2930, 2927, 2857, 1758, 1705, 1552, 1463, 1362, 1292, 1259, 1244 cm^{-1}; HRMS m/e (M^+ − *t*-Bu) calcd for $C_{12}H_{17}O_5Si$ 269.0845, found 269.0849.

To 1.89 g (5.8 mmol) of this O-silylated derivative of (*R*)-**7** was added 30 mL of 5% HF in acetronitrile at rt. After 8 min, the reaction mixture was neutralized with aqueous $NaHCO_3$, extracted with $CHCl_3$ (2 × 100 mL), dried over $MgSO_4$, concentrated *in vacuo*, and purified by column chromatography (100% EtOAc) to afford 0.75 g of the alcohol (+)-**7** in 61% yield as a yellow oil. The alcohol (*R*)-**7** was used for the next reaction without a complete characterization due to its instability.

Enol Silaketal (*R*)-9. Into a 20 mL hydrolysis tube were placed 0.726 g (7.4 mmol) of *trans*-2-hexenal, 1.155 g (7.6 mmol) of chlorodiisopropylsilane, and 0.033 g of tris(triphenylphosphine)rhodium chloride. The tube was then sealed, stirred for 10 h at rt, and heated at 90 °C for 14 h. The reaction mixture was decanted and directly purified by a bulb to bulb distillation (60−70 °C at 0.5 mmHg) to afford 1.380 g of the enol silyl chloride **8** as a colorless liquid in 75% yield, contaminated with a trace amount of impurities: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.30 (dt, J = 12.0, 1.6 Hz, 1H), 5.13 (dt, J = 12.0, 7.6 Hz, 1H), 1.93−1.87 (m, 2H), 1.34−1.28 (m, 4H), 1.14−1.10 (m, 2H), 1.09 (d, J = 4.8 Hz, 6H), 1.08 (d, J = 4.8 Hz, 6H), 0.91−0.86 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 133.4, 113.4, 32.3, 26.8, 22.1, 16.6, 16.5, 16.3, 14.8, 13.9. Because of its lability, this material was carried on immediately.

To 71.3 mg (0.3 mmol) of the alcohol (*R*)-**7** and 10 mL of anhydrous CH_2Cl_2 were added 100.4 mg (0.4 mmol) of silyl chloride **8** in 10 mL of anhydrous CH_2Cl_2 and 0.05 mL (0.3 mmol) of triethylamine at −78 °C. Upon addition, the reaction mixture was allowed to warm to rt and stirred for 27 h. The reaction mixture was slowly warmed to rt over 7 h, diluted with 50 mL of ether, washed with H_2O and brine, dried over $MgSO_4$, concentrated *in vacuo*, and purified by column chromatography (20/80 EtOAc/hexane) to give 97.3 mg of the pyrone enol silaketal (*R*)-**9** in 67% yield as a greenish yellow oil (slowly decomposing): ^{1}H NMR ($CDCl_3$) δ 8.13 (dd, J = 6.8, 2.4 Hz, 1H), 7.66 (dd, J = 5.1, 2.3 Hz, 1H), 6.33 (dd, J = 6.8, 5.0 Hz, 1H), 6.30 (dt, J = 11.8, 1.4 Hz, 1H), 3.91−3.86 (m, 2H), 2.04−1.85 (m, 1H), 1.88−1.80 (m, 2H), 1.37 (d, J = 6.2 Hz, 3 H), 1.31−1.25 (m, 4H), 1.03 (d, J = 3.6 Hz, 12H), 1.03−1.00 (m, 1H, overlapped with doublet at δ 1.03), 0.89−0.85 (m, 3H). Because of its instability, silaketal (*R*)-**9** was carried on immediately.

Cycloadducts (+)-10a and (−)-10b. To a flame-dried 50 mL flask charged with 0.310 g (7.3 mmol) of the pyrone enol ether (*R*)-**9**, 3 mL of anhydrous ether, and 6 mL of anhydrous toluene was added 0.160 g (7.3 mmol) of $ZnBr_2$. Upon addition, the reaction mixture was cooled to −30 °C and stirred for 4 days. The reaction mixture was then concentrated by rotary evaporator and directly purified by column chromatography (97/3 hexane/EtOAc) to afford 0.230 g of the cycloadduct (+)-**10a** in 74% yield along with 0.045 g (15% yield) of the crystalline cycloadduct (−)-**10b**. For cycloadduct (+)-**10a**: ^{1}H NMR ($CDCl_3$) δ 6.77 (dt, J = 8.0, 1.2 Hz, 1H), 6.59 (dt, J = 8.0, 5.2 Hz, 1H), 5.54−5.46 (m, 1H), 4.98 (d, J = 5.2, 1.6 Hz, 1H), 4.38 (s, 1H), 3.89−3.77 (m, 2H), 1.88−1.28 (m, 8H), 1.324 (d, J = 6.4 Hz, 3H), 1.25−1.16 (m, 1H), 1.03 (d, J = 3.2 Hz, 3H), 1.01 (d, J = 3.6 Hz, 3H), 0.92−0.87 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 168.5, 167.0, 130.8, 129.3, 76.4, 75.4, 70.3, 62.6, 59.8, 49.2, 37.7, 30.1, 29.3, 22.4, 20.6, 17.6, 17.4, 17.3, 17.2, 13.8, 12.7, 10.5; FT-IR ($CHCl_3$) 2945, 2868, 1769, 1724, 1464, 1364, 1291, 1259 cm^{-1}; HRMS m/e (M^+ − *i*-Pr) calcd for $C_{19}H_{31}O_6Si$ 381.1733, found 381.1740; $[\alpha]^{24}_D$ 17.5 (c = 22 mg/mL, CH_2Cl_2). For cycloadduct (−)-**10b**: ^{1}H NMR ($CDCl_3$) δ 6.83 (dt, J = 8.0, 1.2 Hz, 1H), 6.51 (dd, J = 8.0, 5.0 Hz, 1H), 5.56−5.60 (m, 1H), 5.06 (m, 1H), 4.94 (d, J = 7.6 Hz, 1H), 3.95 (m, 1H), 3.84 (m, 1H), 2.41 (m, 2H), 1.85 (m, 2H), 1.5−1.2 (m, 9H), 1.40 (d, J = 6.4 Hz, 3H); HRMS m/e (M^+ − *i*-Pr) calcd for $C_{19}H_{13}O_6Si$ 381.1733, found 381.1739; $[\alpha]^{24}_D$ −1.8 (c = 35 mg/mL, CH_2Cl_2). Single crystal X-ray analysis showed the absolute stereochemistry of (−)-**10b** to be as shown in Scheme 1.

1,3-Bis(methylthio)-2-methoxypropane (11): colorless oil; ^{1}H NMR δ 3.49 (m, 1H), 3.41 (s, 3H), 2.73 (m, 4H), 2.14 (s, 6H); data consistent with literature data.[12]

***trans*-1,3-Bis(methylthio)-5-fluoro-1-pentene (12).** To diisopropylamine (5.11 g, 50.5 mmol) in THF (100 mL) was added *n*-BuLi (1.5 M in hexanes, 7.1 mL, 50.5 mmol) at −78 °C. After 10 min, 1,3-bis(methylthio)-2-methoxypropane (**11**, 4.2 g) in THF (20 mL) was added *via* cannula at −78 °C. After addition was completed, the reaction mixture was warmed to 0 °C (the reaction mixture changed from dark brown to a deep purple solution) and stirred for 2.5 h. The resulting purple solution was cooled to −78 °C, and 1-bromo-2-fluoroethane (3.53 g, 27.8 mmol) was added dropwise. The reaction mixture was warmed to rt, after which time reaction was complete by analytical TLC (*ca.* 4 h). The reaction mixture was diluted with ether and washed successively with aqueous NH_4Cl, water, and brine. The combined aqueous washes were extracted with ether (2 × 100 mL). The combined ethereal solution was dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residue was subjected to silica gel column chromatography (eluent, 95/5 hexanes/ethyl acetate) to give an inseparable *trans*/*cis* mixture of 1,3-bis(methylthio)-5-fluoro-1-pentene (**12**) (4.67 g, 100%) as a deep orange oil:

R_f 0.62 (70/30 hexane/ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 6.12 (d, J = 14.8 Hz, 1H), 5.16 (dd, J = 9.6, 14.6 Hz, 1H), 4.63–4.41 (m, 2H), 3.35 (m, 1H), 2.27 (s, 3H), 2.01 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 126.8, 124.9, 81.1 (d, J = 658.4 Hz), 45.7 (d, J = 18 Hz), 35.2 (d, J = 78.8 Hz), 14.7 (d, J = 13.8 Hz); IR ($CHCl_3$) 2978, 2906, 1596, 1467, 1425, 1390, 1220 cm^{-1}; HRMS m/e (M^+) calcd for $C_7H_{13}FS_2$ 180.0443, found 180.0444.

Enol Silyl Chloride 13. To a solution of 1,3-bis(methylthio)-5-fluoro-1-pentene (**12**) (1.5 g, 8.32 mmol) in THF (32 mL) was added powdered calcium carbonate (2.5 g, 24.96 mmol). The mixture was stirred, and a solution of mercuric chloride (6.8 g, 24.96 mmol) in water (17 mL) and THF (56 mL) was added. A pale green to dark yellow color change was observed. The mixture was heated at 65–70 °C for 20 h. The reaction mixture was filtered with suction through a pad of celite. The filter cake was washed with a 1/1 pentane/methylene chloride mixture. The filtrate was washed with saturated aqueous sodium chloride (3 × 50 mL). The combined aqueous solution was extracted with the 1/1 pentane/methylene chloride solution (2 × 100 mL). The combined organic solution was dried ($MgSO_4$), filtered, and concentrated *in vacuo* at 25 °C. After almost all the solvent was removed, the residue was purified by silica gel column chromatography (90/10 hexanes/ethyl acetate) to provide 0.50 g (59% yield) of *trans*-5-fluoro-2-pentenal as a bright yellow liquid: R_f 0.57 (20/80-ethyl ether/chloroform); ^{1}H NMR ($CDCl_3$) δ 9.53 (d, J = 8.0 Hz, 1H), 6.84 (m, 1H), 6.20 (m, 1H), 4.59 (dt, J = 6.0, 12.0 Hz, 2H), 2.77–2.67 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 193.42, 152.3 (d, J = 4.6 Hz), 134.7, 81.2 (d, J = 168.6 Hz), 33.3 (d, J = 20.6 Hz); IR ($CHCl_3$) 3013, 2966, 1731, 1690, 1637, 1461, 1373, 1243, 1138 cm^{-1}; HRMS m/e calcd for C_5H_7FO 102.0481, found 102.0483.

To a 5 mL hydrolysis tube charged with tris(triphenylphosphine)rhodium chloride (0.034 g, 0.037 mmol) was added chlorodiisopropylsilane (0.861 mL, 5.044 mmol). The resulting mixture was stirred for 5 min. *trans*-5-Fluoro-2-pentenal (0.500 g, 4.89 mmol) was then added *via* cannula. The tube was sealed and stirred at 25 °C for 20 h and then heated at 90 °C for 4 h, after which time the reaction was complete by ^{1}H NMR analysis. Because of its instability, the enol silyl chloride **13** was used for the next reaction without further purification: ^{1}H NMR ($CDCl_3$) δ 6.34 (dt, J = 12.0, 1.2 Hz, 1H), 5.10 (dt, J = 7.6, 12.0 Hz, 1H), 4.42 (dt, J = 6.0, 47.2 Hz, 2H), 2.53–2.17 (m, 2H), 2.01 (m, 2H), 1.71 (m, 2H), 1.09 (d, J = 4.8 Hz, 6H), 1.07 (d, J = 4.8 Hz, 6H).

Pyrone Enol Silaketal (*S*)-14. To pyrone alcohol (*S*)-**7** (1.00 g, 4.69 mmol) were added CH_2Cl_2 (10 mL) and triethylamine (1.3 mL, 9.39 mmol). The resulting dark brown solution was cooled to −78 °C and stirred for 5 min. Freshly prepared enol silyl chloride **13** (1.78 g, 7.04 mmol) was added *via* cannula. The dry ice bath was removed and the reaction mixture stirred at 25 °C until reaction was complete by TLC analysis (*ca.* 4 h). The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with water (20 mL). The aqueous wash was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic solution was dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was subjected immediately to silica gel column chromatography (85/15 hexanes/ethyl acetate) to provide 1.12 g of pyrone enol ether silaketal (*S*)-**14** in 56% yield as a bright yellow oil: R_f 0.44 (60/40 hexane/ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 8.13 (dd, J = 2.25, 6.78 Hz, 1H), 7.67 (dd, J = 2.28, 5.04 Hz, 1H), 6.35 (m, 2H), 5.28 (m, 1H), 5.01 (dt, J = 7.53, 15.0 Hz, 1H), 4.53–4.34 (m, 2H), 3.89 (m, 2H), 2.04–1.64 (m, 6H), 1.37 (d, J = 6.27 Hz, 3H), 1.03 (d, J = 2.4 Hz, 12H), 1.03–1.00 (m, 2H); IR ($CHCl_3$) 3013, 2943, 2860, 1760, 1702, 1549, 1284, 1260, 1226, 1202, 1096 cm^{-1}. Because of its instability, silaketal (*S*)-**14** was carried on immediately.

Bicyclic Lactones (−)-15. To 0.730 g (0.70 mmol) of pyrone enol ether (*S*)-**14**, 7 mL of anhydrous ethyl ether, and 14 mL of anhydrous toluene was added 0.463 g (2.04 mmol) of $ZnBr_2$ (98% purity) predried under a vacuum pump for at least 8 h. The reaction mixture was cooled to −10 °C and stirred until reaction was complete by TLC analysis (*ca.* 10 days). The reaction mixture was dissolved in ethyl acetate, filtered through a plug of silica gel, concentrated, and subjected to silica gel column chromatography (90/10 hexanes/ethyl acetate) to afford 0.337 g of the cycloadduct (−)-**15a** in 46% yield, R_f 0.56 (60/40 hexane/ethyl acetate), along with 0.088 g of cycloadduct (−)-**15b** in 12% yield. (−)-**15a**: ^{1}H NMR ($CDCl_3$) δ 6.81 (m, 1H), 6.62 (dd, J = 5.2, 7.6 Hz, 1H), 5.53 (m, 1H), 5.01 (dt, J = 1.2, 4.8 Hz, 1H), 4.54 (m, 1H), 4.44 (s, 1H), 3.92–3.82 (m, 2H), 1.84–1.77 (m, 6H), 1.37 (d, J = 6.4 Hz, 3H), 1.28–1.20 (m, 1H), 1.06–1.03 (m, 6H), 0.94–0.92 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 168.34, 167.0, 130.6, 129.6, 83.4 (d, J = 165.5 Hz), 76.2, 75.1, 70.6, 62.6, 60.1, 49.0, 37.8, 28.8 (d, J = 19.8 Hz), 26.3 (d, J = 4.5 Hz), 20.6, 17.7, 17.4, 17.3, 17.2, 12.7, 10.5; ^{19}F NMR ($CDCl_3$) δ −219.20; IR ($CHCl_3$) 2913, 2872, 1766, 1731, 1619, 1461, 1361, 1284, 1114, 1061, 1038 cm^{-1}; HRMS m/e (M^+ − *i*-Pr) calcd for $C_{18}H_{26}FO_6Si$ 385.1483, found 385.1489; $[\alpha]^{31}_D$ −20.5 (c = 8.2 mg/mL, $CHCl_3$). (−)-**15b**: ^{1}H NMR ($CHCl_3$) δ 6.86 (dt, J = 1.6, 7.6 Hz, 1H), 6.53 (dd, J = 4.8, 7.6 Hz, 1H), 5.60–5.55 (m, 1H), 5.07–5.05 (m, 1H), 4.99 (dd, J = 0.8, 7.2 Hz, 1H), 4.52–4.36 (m, 2H), 4.01–3.96 (m, 1H), 3.86–3.81 (m, 1H), 2.48-2.41 (m, 1H), 1.85–1.83 (m, 6H), 1.36 (d, J = 6.4 Hz, 3H), 1.06–1.01 (m, 6H), 0.96–0.93 (m, 9H); ^{19}F NMR ($CDCl_3$) δ −219.62; $[\alpha]^{31}_D$ −5.13 (c = 28 mg/mL, $CHCl_3$).

Bis-Silyl Ether 16. To adduct (−)-**15a** (0.337 g, 0.786 mmol) was added 35 mL of 5% HF in acetonitrile at 25 °C. After 60 min, the reaction mixture was neutralized with aqueous sodium bicarbonate and extracted with $CHCl_3$ (3 × 100 mL). The combined organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in 10 mL of *N,N*-dimethylformamide (DMF). To this solution were added *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) (0.867 mL, 3.774 mmol) and 2,6-lutidine (0.366 mL, 3.145 mmol). The progress of the reaction was monitored by TLC (*ca.* ~8 h). After the reaction was complete, the reaction mixture was dumped into 50 mL of water and extracted with ethyl ether (3 × 100 mL). The combined ethereal solution was dried ($MgSO_4$), concentrated under reduced pressure, and purified by silica gel column chromatography (93/7 hexanes/ethyl acetate) to afford 0.383 g (89% yield) of bis-silyl ether **16** as a colorless oil: R_f 0.63 (60/40 hexane/ethyl acetate); ^{1}H NMR ($CHCl_3$) δ 6.72 (dt, J = 1.6, 8.0 Hz, 1H), 6.58 (dd, J = 5.2, 8.0 Hz, 1H), 5.17 (m, 1H), 5.04 (dt, J = 1.6, 5.2 Hz, 1H), 4.61–4.38 (m, 2H), 4.19 (bs, 1H), 3.72 (t, 2H), 2.12–1.61 (m, 7H), 1.37 (d, J = 6.4 Hz, 3H), 0.89 (s, 9H), 0.79 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 168.8, 166.6, 130.5, 130.0, 83.4 (d, J = 166.3 Hz), 75.6, 73.4, 71.3, 62.9, 59.6, 49.0, 39.0, 28.0 (d, J = 18.8 Hz), 25.9(3), 25.5(3), 20.1, 18.2 (d, J = 3.8 Hz), 17.8, −4.4, −5.1, −5.3, −5.4; IR ($CHCl_3$) 2931, 2849, 1760, 1737, 1619, 1467, 1355, 1284, 1255, 1185, 1114, 1091, 908, 838 cm^{-1}; HRMS m/e (M^+ − *t*-Bu) calcd for $C_{23}H_{40}FO_6Si_2$ 487.2347, found 487.2352.

Cyclohexenol Ester (−)-17. To a 50 mL oven-dried round-bottomed flask charged with 155 mg (0.284 mmol) of the bis-silyl ether **16** was added at 0 °C 8.12 mL (20 equiv) of lithium allyl oxide in allyl alcohol (0.7 M). (The solution of lithium allyl oxide was prepared thusly: 4.92 mL of *n*-BuLi (1.42 M in hexanes) was added dropwise to a −78 °C solution of allyl alcohol. After addition was complete, the reaction mixture was allowed to warm to rt and stirred for 30 min.) The reaction mixture was stirred at 0 °C for 4 h and at 25 °C for 12 h. The reaction mixture was quenched with saturated NH_4Cl, and the product mixture was extracted with CH_2Cl_2 (3 × 50 mL), dried over $MgSO_4$, concentrated *in vacuo*, and chromatographed (90/10 hexanes/ethyl acetate) to provide 45 mg of cyclohexenol ester (−)-**17** in 40% yield: R_f 0.60 (60/40 hexane/ethyl acetate); ^{1}H NMR ($CHCl_3$) δ 6.87 (dd, J = 2.4, 5.2 Hz, 1H), 5.06 (m, 1H), 4.63 (d, J = 2.0 Hz, 1H), 4.49 (t, J = 6 Hz, 1H), 4.43–4.37 (m, 2H), 3.63 (m, 2H), 2.51 (dt, J = 5.60, 11.2 Hz, 2H), 2.14–2.06 (m, 2H), 1.91–1.85 (m, 2H), 1.77–1.70 (m, 1H), 1.28 (d, J = 6.4 Hz, 3H), 0.88 (s, 3H), 0.87 (s, 9H), 0.86 (s, 9H), 0.15 (s, 3H), 0.07 (s, 3H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 165.9, 139.1, 131.3, 84.1 (d, J = 164.8 Hz), 68.9, 67.7, 64.8, 59.5, 47.0, 39.2, 31.1, 29.1 (d, J = 19.8 Hz), 25.9(3), 25.8(3), 20.3, 19.1 (d, J = 5.3 Hz), 18.2, 18.0, −4.43, −4.87, −5.37, −5.42; IR ($CHCl_3$) 3613, 2943, 2919, 2849, 1702, 1467, 1249,

1067, 832 cm^{-1}; HRMS m/e ($M^+ - t$-Bu) calcd for $C_{22}H_{42}FO_5Si_2$ 461.2555, found 461.2560; $[\alpha]^{20}_D$ −12.5 (c = 7.5 mg/mL, $CHCl_3$).

Allylic Alcohol (−)-18. To 103 mg (0.198 mmol) of cyclohexenol ester (−)-**17** in 3.0 mL of DMF were added TBDMSOTf (0.100 mL, 0.436 mmol) and 2,6-lutidine (0.046 mL, 0.397 mmol) at 25 °C. After 24 h at rt, the product mixture was diluted with ether, washed with water, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Crude protected ester **17** was dissolved in 1 mL of CH_2Cl_2 and 2 mL of anhydrous toluene and cooled to −78 °C. To this solution was added i-Bu_2AlH (0.494 mL, 1 M in toluene). After 40 min, only a trace of starting material was present. The reaction mixture was quenched at −78 °C with 3 mL of sodium potassium tartrate (2 M in H_2O), and the resulting solution was warmed to rt. After 1 h, the reaction mixture was extracted with ethyl ether (3 × 50 mL), filtered, dried over anhydrous $MgSO_4$, evaporated under reduced pressure, and subjected to silica gel column chromatography (93/7 hexanes/ethyl acetate) to provide 75 mg of allylic alcohol (−)-**18** in 87% yield: R_f 0.55 (70/30 hexane/ethyl acetate); ^1H NMR ($CDCl_3$) 5.67 (m, 1H), 4.53−4.45 (m, 1H), 4.27−4.35 (m, 1H), 4.14 (d, J = 1.6 Hz, 1H), 4.06 (s, 2H), 2.18 (dt, J = 5.2, 11.2 Hz, 1H), 2.00 (m, 1H), 1.82−1.68 (m, 5H), 0.90 (s, 9H), 0.88 (s, 9H), 0.124 (s, 3H), 0.119 (s, 3H), 0.05 (s, 6H); ^{13}C NMR ($CDCL_3$) δ 136.9, 125.0, 84.3 (d, J = 164.8 Hz), 70.2, 66.03, 65.1, 47.3, 31.1, 29.3 (d, J = 19.8 Hz), 25.8(6), 19.7, 19.6, 18.0 (d, J = 7.5 Hz), −4.25, −4.61, −4.77, −4.84; IR ($CHCl_3$) 3613, 2943, 2919, 2849, 1466, 1249, 1213, 1096, 1044, 1005, 873 cm^{-1}; HRMS m/e ($M^+ - t$-Bu) calcd for $C_{18}H_{36}FO_3Si_2$ 375.2187, found 375.2184; $[\alpha]^{20}_D$ −41 (c = 14.4 mg/mL, $CHCl_3$).

Z-Dienoate (−)-19. A 25 mL oven-dried hydrolysis tube was charged with allylic alcohol (−)-**18** (0.070 g, 0.162 mmol) and 1-(phenylsulfinyl)-2,2,2-triethoxyethane (0.225 g, 0.785 mmol),[14] 2,4,6-trimethylbenzoic acid (TMBA) (0.003 g, 0.018 mmol) and 5 mL of anhydrous CH_2Cl_2. The tube was sealed and heated at 145 °C for 14 h. The product mixture was cooled to 25 °C and then filtered through a plug of silica gel, and the filter cake was washed with ether. The filtrate was evaporated under reduced pressure and the residue chromatographed (95/5 hexanes/ethyl acetate) to give 0.074 g of product as a mixture of E- and Z-dienoates. A 10 mL borosilicate test tube was charged with the E/Z dienoate mixture, 9-fluorenone (5.3 mg, 0.03 mmol), and 5 mL of *tert*-butyl methyl ether. The test tube was then placed in a 2 M aqueous solution of sodium orthovanadate (Na_3VO_4) and irradiated with a medium pressure mercury arc lamp for 20 h. The product mixture was filtered through a plug of Celite, and the filter cake was washed with CH_2Cl_2. The filtrate was evaporated *in vacuo*, and the residue was subjected to preparative TLC purification (75/25 hexanes/ethyl acetate) to afford 0.050 g of the Z-dienoate (−)-**19** in 70% overall yield: R_f 0.82 (70/30 hexane/ethyl acetate); ^1H NMR ($CDCl_3$) δ 5.62 (s, 1H), 5.18 (s, 1H), 5.07 (s, 1H), 4.48 (t, J = 6.0 Hz, 1H), 4.39−4.34 (m, 2H), 4.24 (m, 2H), 4.16−4.06 (m, 2H), 2.36−2.27 (m, 2H), 1.75−1.52 (m, 6H), 1.23 (t, J = 7.2 Hz, 3H), 0.91 (s, 9H), 0.87 (s, 9H), 0.08 (s, 3H), 0.07 (s, 6H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.8, 152.9, 128.3, 117.5, 112.3, 84.2 (d, J = 164.8 Hz), 74.3, 68.4, 59.7, 50.7, 44.2, 28.6 (d, J = 19.8 Hz), 25.79(3), 25.75(3), 21.8, 19.7, 18.1 (d, J = 6.8 Hz), 14.2, −4.22, −4.61, −5.03, −5.08; IR ($CHCl_3$) 2943, 2919, 2849, 1713, 1637, 1467, 1249, 1173, 1091 cm^{-1}; HRMS m/e calcd for $C_{26}H_{49}FO_4Si_2$ 500.3153, found 500.3156; $[\alpha]^{20}_D$ −40.2 (c = 12 mg/mL, $CHCl_3$).

Phosphine Oxide (+)-20. To Z-dienoate (−)-**19** (0.086 g, 0.172 mmol), CH_2Cl_2 (2 mL), and toluene (4 mL) was added i-Bu_2AlH (0.515 mL, 1.0 M in toluene) at −78 °C. After 1 h, the reaction was complete by TLC analysis (70/30 hexanes/ethyl acetate, R_f 0.56). The reaction was quenched at −78 °C with 6 mL of 2 M sodium potassium tartrate solution. Ethyl acetate (10 mL) was added, and the mixture was allowed to warm to 25 °C and stirred for 1 h. The product mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic solution was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide crude allylic alcohol.

To a separate flask charged with 0.183 g (1.37 mmol) of N-chlorosuccinimide (NCS) and CH_2Cl_2 (4 mL) was added 0.106 mL (1.44 mmol) of dimethyl sulfide (DMS) at 0 °C (the reaction mixture immediately turned to a white turbid solution). The NCS−DMS complex was allowed to stir at 0 °C for 30 min and then cooled to −20 °C with a dry ice ethylene glycol bath. To the NCS−DMS complex was added the allylic alcohol in 2 mL of CH_2Cl_2 *via* cannula at −20 °C. The reaction mixture was stirred at −20 °C for 15 min and then warmed to 0 °C and stirred for another 30 min, after which time reaction was complete by TLC analysis (70/30 hexanes/ethyl acetate, R_f 0.75). The product mixture was dissolved with water (10 mL) and CH_2Cl_2 (50 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was filtered through a plug of florisil with 80/20 hexanes/ethyl acetate and concentrated *in vacuo* to provide the allylic chloride as a tan oil.

A solution of this allylic chloride in 2 mL of THF was cooled to −78 °C, and potassium diphenylphosphide (0.5 M in THF) was added (~0.5 mL) until the red color persisted. The reaction mixture was stirred at −78 °C until the reaction was complete (*ca.* 2 h). The reaction was quenched with water (1 mL) at −78 °C, and the mixture was warmed to 25 °C and concentrated to a reduced volume (~2 mL). To this solution was added 10−15 drops of 30% H_2O_2. After 20 min, to the reaction mixture were added water (5 mL) and CH_2Cl_2 (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic solution was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography (70/30 hexanes/ethyl acetate) to afford 60 mg of phosphine oxide (+)-**20** as a white, viscous oil in 54% overall yield from Z- dienoate (−)-**19**: Rf 0.65 (75:25-hexane:ethyl acetate); ^1H NMR ($CDCl_3$) δ 7.74−7.68 (m, 4H), 7.75−7.44 (m, 6H), 5.29 (m, 1H), 5.09 (s, 1H), 4.77 (d, J = 1.6 Hz, 1H), 4.40 (dt, J = 6.4, 47.6 Hz, 2H), 4.15−4.08 (m, 2H), 3.42−3.12 (m, 2H), 2.30−2.18 (m, 2H), 1.78−1.53 (m, 5H), 0.89 (s, 9H), 0.82 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H), 0.00 (s, 3H), −0.03 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 146.2 (t, J = 2.3 Hz), 141.0 (d, J = 12.2 Hz), 133.2 (d, J = 7.6 Hz), 132.3 (d, J = 8.3 Hz), 131.7, 130.9 (t, J = 8.3 Hz), 128.5 (dd, J = 4.6, 11.5 Hz), 114.6 (d, J = 7.7 Hz), 111.9 (m), 84.2 (d, J = 164.8 Hz), 74.5, 68.4, 50.6, 43.3, 31.5, 30.8, 28.6 (d, J = 19.9 Hz), 25.8(6), 21.5 (d, J = 4.6 Hz), 18.1 (d, J = 6.8 Hz), −4.29, −4.45, −4.93, −5.08; IR ($CHCl_3$) 2943, 2931, 2895, 2849, 1467, 1431, 1390, 1355, 1249, 1167, 1114, 1091, 1067 cm^{-1}; HRMS m/e calcd for $C_{36}H_{56}FO_3PSi_2$ 642.3490, found 642.3483; $[\alpha]^{20}_D$ +5.5 (c = 5.7 mg/mL, CH_2Cl_2).

Fluoro Vitamin D Analog (−)-5. Phosphine oxide (+)-**20** (0.070 g, 0.108 mmol, 1.70 equiv, after being azeotropically dried three times with benzene and held under high vacuum for at least 30 h) was dissolved in 1 mL of freshly distilled anhydrous THF and the mixture cooled to −78 °C under argon. To this was added PhLi (0.080 mL, 0.115 mmol, 1.7 equiv, 1.48 M in ether) dropwise over a period of 5 min, during which time a deep red color change occurred and persisted. The mixture was allowed to stir for an additional 6−8 min. A precooled (−78 °C) solution of C,D-ring ketone (+)-**21** (0.024 g, 0.068 mmol, 1.0 equiv, dried in exactly the same manner as for the phosphine oxide) dissolved in 1 mL of THF was added dropwise *via* cannula. The deep red mixture was stirred at −78 °C in the dark for 1.5 h, after which time the red color began to fade and analytical TLC (90/10 hexanes/ethyl acetate) indicated that reaction was complete. The reaction was then quenched at −78 °C with 0.5 mL of 2 N sodium potassium tartrate, followed by addition of dilute aqueous K_2CO_3 (2 mL). After being warmed to rt, the reaction mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic solution was dried ($MgSO_4$), filtered, evaporated under reduced pressure, and chromatographed (eluent 95/5 hexanes/ethyl acetate) to provide 0.012 g (22% yield) of coupled product. To the coupled product in 0.5 mL of anhydrous THF were added solid n-Bu_4NF (0.023 g, 0.089 mmol, 5.5 equiv) and 4 Å molecular sieves. The mixture was then heated at 60 °C for 1 h, after which time only a trace of starting material was present by TLC analysis (20/80 hexanes/ethyl acetate). The reaction mixture

was filtered through a plug of Celite and immediately chromatographed rapidly (eluent 50/50 hexanes/ethyl acetate) to provide 0.0013 g (17% yield) of analog (−)-**5** as an oil: R_f 0.62 (20/80 hexane/ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 6.35 (d, J = 11.4 Hz, 1H), 6.02 (d, J = 11.0 Hz, 1H), 5.38 (t, J = 2.0 Hz, 1H), 5.03 (t, J = 2.0 Hz, 1H), 4.56−4.41 (m, 2H), 4.16−4.11 (m, 3H), 2.84−2.80 (m, 1H), 2.54−2.41 (m, 2H), 1.22 (s, 6H), 0.938 (d, J = 6.4 Hz, 3H), 0.549 (s, 3H); based on the ^{1}H NMR spectrum, the purity of this sample was judged to be at least 90%. Because of the small amount of (−)-**5** available, only a poor quality ^{13}C NMR spectrum could be obtained: ^{19}F NMR ($CDCl_3$) δ −218.11 (m, 1F); IR ($CHCl_3$) 2943, 2872, 1725, 1602, 1461, 1373, 1261 cm^{-1}; UV (MeOH) λ_{max} 264 nm (ϵ 16 000), HRMS m/e calcd for $C_{30}H_{47}FO_3$ 474.3509, found 474.3505; $[\alpha]^{20}_D$ −32.2 (c 3.0 mg/mL, $CHCl_3$).

Silyl Enol Ether 22c. To a solution of 4 g (35.0 mmol) of ϵ-caprolactone in 100 mL of toluene at −78 °C was added dropwise, over 30 min, 36 mL (36 mmol) of a 1 M solution of i-Bu_2AlH. After addition was complete, the reaction was stirred for 1 h at −78 °C. The reaction was then quenched with 10 mL of a saturated solution of potassium sodium tartrate, diluted with 100 mL of EtOAc, and stirred for 30 min while it was allowed to warm to rt. The layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. Column chromotography provided 3 g (25.9 mmol, 74% yield) of the desired hydroxy aldehyde. This material was dissolved in 50 mL of CH_2Cl_2. To this solution were added 3.6 mL (25.9 mmol) of Et_3N and approximately 20 mg of DMAP, followed by 5.44 mL (25.9 mmol) of chlorodiphenylmethylsilane. The reaction was allowed to run for 12 h, by which time a large amount of white solid had formed, signaling the completion of the reaction. Addition of 25 mL H_2O, followed by separation of the organic layer from the aqueous, drying the organic layer over $MgSO_4$, filtration, and concentration provided a yellow oil. This oil was purified by column chromatography to give 6 g (19.2 mmol, 55% yield from ϵ-caprolactone) of O-protected aldehyde: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (s, 1H), 7.58 (m, 4H), 7.38 (m, 6H), 3.70 (t, J = 3.2 Hz, 2H), 2.38 (m, 2 H), 1.65−1.35 (m, 6H), 0.62 (s, 3H); IR ($CHCl_3$) 2731, 1725, 1619, 1584 cm^{-1}.

The above aldehyde was then diluted with 35 mL of benzene and 3.2 mL (23 mmol) of triethylamine. The resulting mixture was cooled to 0 °C, and 5.3 mL (23 mmol) of *tert*-butyldimethylsilyl triflate was added. The reaction mixture was allowed to warm to rt and stirred for 1 h. The reaction was quenched with brine and the mixture diluted with Et_2O. The organic layer was separated, and the aqueous layer was washed with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography (hexane) on silica gel that was slurry-packed with 1% triethylamine/hexane. The silylated vinylic ether **22c** (3.6 g, 8.5 mmol, 65% yield) was a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (m, 4H), 7.38 (m, 6H), 6.15 (d, J = 7.5 Hz, 1H), 4.41 (dt, J = 7.5, 1.3 Hz, 1H), 3.69 (t, J = 3.4 Hz, 2H), 2.05 (m, 2H), 1.57 (m, 2H), 1.37 (m, 2H), 0.91 (s, 9H), 0.61 (s, 3H), 0.11 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 136.4, 134.3, 129.7, 127.9, 127.8, 110.6, 63.6, 32.4, 25.8, 23.5, −2.8, −5.2; IR ($CHCl_3$) 1648, 1472, 1431, 1255, 1114, 1084 cm^{-1}; HRMS m/e (M − t-Bu) calcd for $C_{21}H_{29}O_2Si_2$ 369.1706, found 369.1708.

Cycloadduct (±)-23c. A 12 cm piece of 3/8 in. heat shrinkable teflon tubing (Ace Glass catalog no. 12685-40) was sealed on one end with a glass dowel plug by using a heat gun. To this were added 0.50 g (3.24 mmol) of methyl 2-pyrone-3-carboxylate, 4.15 g (9.70 mmol) of silylated vinylic ether (±)-**22c**, 10 mg of barium carbonate, and 2 mL of dry CH_2Cl_2. The open end of the tubing was then sealed in a similar fashion with a second glass dowel plug. This "sealed tube" was then pressurized at 10−11 Kbar at rt for 5 days. The reaction mixture was concentrated on a rotary evaporator, and the residue was purified by column chromatography (5% EtOAc/hexane) to give 1.16 g (2.00 mmol, 62%) of the cycloadduct (±)-**23c** as a clear oil: R_f 0.65 (75/25 hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (m, 4H), 7.40 (m, 6H), 6.77 (dd, J = 5.0, 1.7 Hz, 1H), 6.44 (dd, J = 7.8, 5.0 Hz, 1H), 5.06 (ddd, J = 7.8, 4.7, 1.7 Hz, 1H), 4.78 (dd, J = 7.6, 1.0 Hz, 1H), 3.89 (s, 3H), 3.70 (t, J = 3.2 Hz, 2H), 2.34 (ddd, J = 7.6, 4.7, 1.0 Hz, 1H), 1.65−1.35 (m, 6H), 0.78 (s, 9H), 0.68 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 167.5, 134.2(4), 133.9(2), 130.5, 129.7(2), 128.6, 127.8(4), 76.1, 69.4, 63.3, 62.9, 52.7, 44.8, 32.5, 27.3, 25.7, 23.6, 18.1, −3.2, −3.9, −5.0; IR ($CHCl_3$) 1760, 1742, 1619, 1584 cm^{-1}; HRMS m/e (M − t-Bu) calcd for $C_{28}H_{35}O_6Si_2$ 523.1972, found 523.1976. A diastereomeric *cis*-4,5-disubstituted cycloadduct was also isolated (25 mg, 0.09 mmol, 3% yield): R_f 0.60 (75/25 hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (m, 4H), 7.40 (m, 6H), 6.55 (dd, J = 7.8, 5.2 Hz, 1H), 6.40 (dd, J = 7.8, 2.0 Hz, 1H), 4.99 (dd, J = 4.3, 0.6 Hz, 1H), 4.32 (d, J = 8.6 Hz, 1H), 3.80 (s, 3H), 3.70 (t, J = 3.2 Hz, 2H), 1.90 (ddt, J = 7.8, 2.0, 1.0 Hz, 1H), 1.65−1.35 (m, 6H), 0.85 (s, 9H), 0.62 (s, 3H), 0.02 (s, 6H).

Alcohol (±)-24. To 931 mg (1.6 mmol) of cycloadduct (±)-**23c** in 7 mL of DMF were added 114 mg (1.7 mmol) of NaN_3 and 95 mg (1.7 mmol) of anhydrous NH_4Cl. The reaction was run at rt for 1 day. After completion, 1 mL of water was added and the reaction mixture was diluted with 10 mL of ethyl acetate. The layers were separated, the aqueous layer was washed with 10 mL of ethyl acetate, and the organic layers were combined, dried ($MgSO_4$), filtered, and concentrated. The reaction mixture was purified *via* short-path column chromotography (10 g of silica gel, 25−75% EtOAc/hexane) to give 384 mg (1 mmol, 62%) of the alcohol (±)-**24** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (dd, J = 5.0, 1.7 Hz, 1H), 6.44 (dd, J = 7.8, 5.0 Hz, 1H), 5.06 (ddd, J = 7.8, 4.7, 1.7 Hz, 1H), 4.78 (dd, J = 7.6, 1.0 Hz, 1H), 3.89 (s, 3H), 3.70 (t, J = 3.2 Hz, 2H), 2.34 (ddd, J = 7.6, 4.7, 1.0 Hz, 1H), 1.65−1.35 (m, 6H), 0.78 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 167.5, 130.4, 128.7, 76.7, 69.4, 63.2, 62.1, 52.7, 44.8, 32.6, 27.4, 25.6, 23.5, 18.0, −3.9, −5.0; IR ($CHCl_3$) 3542, 1754, 1742, 1619, 1472, 1458, 1431 cm^{-1}; HRMS m/e (M − t-Bu) calcd for $C_{15}H_{23}O_6Si$ 384.1968, found 384.1975.

Fluorinated Cycloadduct (±)-25. To 78 μL (0.59 mmol) of diethylaminosulfur trifluoride in 1 mL of CH_2Cl_2 at −78 °C was added dropwise *via* cannula 205 mg (0.53 mmol) of alcohol (±)-**7** in 5 mL of CH_2Cl_2. The reaction mixture was warmed to 0 °C, and the reaction was followed by TLC till complete after 2 h. The reaction was then quenched with water and the mixture allowed to warm to rt. After it warmed, it was diluted with CH_2Cl_2, washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by column chromotography (5 g of silica, 0−25% EtOAc/hexane) to give 119 mg (0.31 mmol, 58%) of the fluoride (±)-**25** as a white solid: R_f 0.39 (75/25 hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (dd, J = 5.0, 1.7 Hz, 1H), 6.52 (dd, J = 7.8, 5.0 Hz, 1H), 5.13 (ddd, J = 7.8, 3.4, 1.7 Hz, 1H), 4.76 (dd, J = 7.2, 1.0 Hz, 1H), 4.45 (dt, J = 5.9 Hz, 41.5H), 3.88 (s, 3H), 2.41 (ddd, J = 7.2, 3.4, 1.0 Hz, 1H), 1.75−1.42 (m, 6H), 0.80 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 167.5, 130.7, 128.6, 83.5 (J_{CF} = 164 Hz), 76.1, 69.4, 63.3, 52.8, 44.9, 30.5 (J_{CF} = 19.7 Hz), 27.3, 25.7, 23.2, 18.1, −3.9, −4.9; ^{19}F NMR (375 MHz, CCl_3F) δ −218.71; IR ($CHCl_3$) 1760, 1743, 1473, 1461, 1437, 1284, 1260.7, 1132, 1102, 1073, 1008 cm^{-1}; HRMS m/e (M − t-Bu) calcd for $C_{15}H_{22}O_5FSi$ 329.1221, found 329.1224.

Mixed Malonate (±)-26. To 500 mg (0.80 mmol) of bicyclic lactone (±)-**25** and 3 mL of CH_2Cl_2 at 0 °C was added dropwise, *via* syringe, 1.34 mL (1.34 mmol) of a freshly made 1.0 M solution of lithium allyl oxide in allyl alcohol. Reaction was complete by TLC after 2 h. The reaction was quenched with 2 mL of aqueous NH_4Cl and the mixture extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered, and concentrated on a rotary evaporator. The residue was purified by column chromatography (0−20% EtOAc/hexane) to give 383 mg (0.86 mmol, 77%) of the desired malonate (±)-**26** as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97 (s, 2H), 5.85 (ddt, J = 16.2, 10.5, 4.9 Hz, 1H), 5.25 (ddd, J = 16.2, 5.3, 1.5 Hz, 2H), 4.78 (s, 1H), 4.64 (ddt, J = 7.6, 5.3, 1.5 Hz, 1H), 4.53 (dd, J = 7.6, 4.5, 1.5 Hz, 1H), 4.46 (dt, J = 41.5, 5.9 Hz, 2H), 4.07 (d, J = 8.6 Hz, 1H), 3.75 (s, 3H), 1.79−1.44 (m, 6H), 1.38 (s, 1H), 0.82 (s, 9H), 0.12 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 168.0, 134.0, 131.1, 122.4, 118.4, 83.5 (J_{CF} = 164 Hz), 71.7, 68.5, 65.8, 61.3, 52.6, 45.9, 30.1 (J_{CF} = 19 Hz), 26.6, 25.9, 22.6, 18.2, −3.9, −4.5; IR ($CHCl_3$) 1735, 1473,

1463.9, 1436, 1390, 1362, 1254 cm^{-1}; HRMS *m/e* (M − *t*-Bu) calcd for $C_{18}H_{28}O_6FSi$ 387.1639, found 387.1638.

Conjugated Ester (±)-27. A mixture of 380 mg (0.86 mmol) of allyl malonate (±)-**26**, 44 μL (1.07 mmol) of formic acid, 154 μL (1.11 mmol) of triethylamine, 18 mg (0.07 mmol) of triphenylphosphine, and 4 mg (0.02 mmol) of palladium(II) acetate in 2 mL of dioxane was sealed in a 5 mL hydrolysis tube and the tube heated at 100 °C for 12 h. After evaporation of dioxane, 1 N HCl (1mL) was added, and the mixture was extracted with CH_2Cl_2 (2 mL × 2). The organic solution was washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. The oily residue was purified by column chromatography (0−10% EtOAc/hexane) to give 266 mg (0.74 mmol, 86%) of a free alcohol conjugated ester that was then O-protected.

To 266 mg (0.74 mmol) of this alcohol ester, 104 μL (0.89 mmol) of 2,6-lutidine, and 2 mL of CH_2Cl_2 at 0 °C was added dropwise *via* syringe 204 μL (0.89 mmol) of *tert*-butyldimethylsilyl triflate. The reaction was complete by TLC after 10 min. The reaction was quenched at 0 °C with 1 mL of water and the mixture allowed to warm to rt. Extraction with CH_2Cl_2 followed by drying with $MgSO_4$, filtration, and concentration afforded a viscous oil which was purified by column chromatography (5% EtOAc/hexane), giving 310 mg (0.65 mmol, 88%) of ester (±)-**27** as a clear oil: ^1H NMR (400 MHz, $CDCl_3$) δ 6.89 (t, *J* = 3.2 Hz, 1H), 4.75 (d, *J* = 2.6 Hz, 1H), 4.46 (dt, *J* = 47.3, 6.1 Hz, 2H), 4.01 (ddd, *J* = 9.1, 6.1, 2.9 Hz, 1H), 3.73 (s, 3H), 2.63 (ddd, *J* = 19.7, 6.1, 4.7 Hz, 1H), 2.05 (ddd, *J* = 19.7, 9.1, 3.2 Hz, 1H), 1.79−1.32 (m, 7H), 0.90 (s, 9H), 0.82 (s, 9H), 0.12 (s, 3H), 0.06 (s, 6H), −0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 140.5, 133.0, 83.8 (J_{CF} = 163 Hz), 66.8, 65.1, 51.4, 47.4, 37.1, 30.6 (J_{CF} = 19 Hz), 26.0(3), 25.8(3), 25.0, 22.5, 18.4, 18.0, −4.2, −4.4, −4.8, −5.6; IR ($CHCl_3$) 1713, 1655, 1472, 1461, 1437, 1390, 1255 cm^{-1}; HRMS *m/e* (M − *t*-Bu) calcd for $C_{20}H_{38}O_4FSi_2$ 417.2293, found 417.2289.

Allylic Alcohol (±)-28. To 300 mg (0.63 mmol) of cyclohexene ester (±)-**27** in 2 mL of toluene at −78 °C was added dropwise *via* syringe 1.39 mL (1.39 mmol) of 1 M *i*-Bu_2AlH in toluene. The reaction was complete by TLC after 1 h. The reaction was quenched by addition at −78 °C of 2 mL of saturated potassium sodium tartrate followed by dilution with 5 mL of EtOAc. After the mixture was allowed to warm to rt and stirred for 0.5 h, two layers were visible. These were separated, and the aqueous layer was washed with EtOAc. The combined organic fractions were washed with water, and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (0−25% EtOAc/hexane) to give 262 mg (0.59 mmol, 94%) of allylic alcohol (±)-**28** as a clear oil: R_f 0.47 (75/25 hexane/ethyl acetate); ^1H NMR (400 MHz, $CDCl_3$) δ 5.51 (t, *J* = 1.50 Hz, 1H), 4.80 (d, *J* = 2.6 Hz, 1H), 4.45 (dt, *J* = 47.3, 6.1 Hz, 2H), 4.22 (d, *J* = 11.9 Hz, 1H), 4.04 (dd, *J* = 2.4, 0.5 Hz, 1H), 3.90 (d, *J* = 11.9 Hz, 1H), 2.36 (ddd, *J* = 19.7, 6.1, 4.7 Hz, 1H), 1.93 (ddd, *J* = 19.7, 9.1, 3.2 Hz, 1H), 1.79−1.62 (m, 6H), 0.93 (s, 9H), 0.89 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 122.2, 83.8 (J_{CF} = 163 Hz), 69.5, 68.1, 65.1, 46.3, 31.5, 30.6 (J_{CF} = 19 Hz), 25.8(3), 25.7(3), 24.5, 23.3, 17.9, −4.4, −4.9, −5.0(2); IR ($CHCl_3$) 3518, 1472, 1460, 1390, 1361, 1255, 1067 cm^{-1}; HRMS *m/e* (M − *t*-Bu) calcd for $C_{19}H_{38}O_3FSi_2$ 389.2344, found 389.2344.

Dienyl Ester (±)-29. To 262 mg (0.59 mmol) of allylic alcohol (±)-**28** in a sealable hydrolysis tube were added 420 mg (1.47 mmol) of (triethylphenyl)sulfinyl orthoacetate, 1.0 mg of 2,4,6-trimethylbenzoic acid, and 2 mL of CH_2Cl_2. The tube was purged with argon and sealed and then heated at 110 °C for 12 h. The reaction mixture was concentrated. Crude ^1H NMR showed a >8:1 mixture of *Z*:*E* isomers. The crude product was purified *via* PTLC (10% EtOAc/hexane) to give 239 mg (0.46 mmol, 79%) of *Z*-dienoate (±)-**29** as a clear oil: R_f 0.8 (75/25 hexane/ethyl acetate); ^1H NMR (400 MHz, $CDCl_3$) δ 5.62 (s, 1H), 5.19 (t, *J* = 1.5 Hz, 1H), 5.11 (t, *J* = 1.1 Hz, 1H), 4.52 (dd, *J* = 6.1, 1.1 Hz, 2H), 4.45 (dt, *J* = 47.3, 6.1 Hz, 2H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.97 (dd, *J* = 5.8, 2.0 Hz, 1H), 2.48 (dd, *J* = 5.2, 1.4 Hz, 1H), 2.16 (dd, *J* = 6.1, 1.7 Hz, 1H), 1.70 (m, 1H), 1.58 (m, 2H), 1.50 (s, 1H), 1.25 (m, 2H), 1.23 (m, 2H), 0.91 (s, 9H), 0.88 (s, 9H), 0.83 (s, 9H), 0.06 (s, 6H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 153.1, 145.2, 117.3, 117.3, 83.9 (J_{CF} 163 Hz), 72.7, 70.2, 59.7, 50.5, 44.9, 32.8, 30.8 (J_{CF} 19 Hz), 25.8(3), 25.7(3), 25.1, 23.6, 18.2, 17.9, 14.1, −4.6, −4.8, −4.9, −5.2, −5.17; IR ($CHCl_3$) 1719, 1637, 1472, 1461, 1390, 1373, 1361, 1255, 1185, 1096, 1078 cm^{-1}; HRMS *m/e* calcd for $C_{27}H_{51}O_4FSi_2$ 514.3310, found 514.3313.

Phosphine Oxide (±)-30. The same procedure used for the conversion of dienoate (−)-**19** into phosphine oxide (+)-**20** was used here. Dienoate (±)-**29** (170 mg, 0.33 mmol) gave a crude product that was purified by column chromatography (25−50% EtOAc/hexane) to give 80 mg (0.12 mmol, 37% from *Z*-dienoate (±)-**29**) of the phosphine oxide (±)-**30** as a clear oil: R_f 0.43 (25/75 hexane/ethyl acetate); ^1H NMR (400 MHz, $CDCl_3$) δ 5.31 (dd, *J* = 14.9, 6.6 Hz, 1H), 5.12 (s, 1H), 4.77 (s, 1H), 4.42 (d, *J* = 3.5 Hz, 1H), 4.41 (dt, *J* = 47.3, 6.1 Hz, 2H), 3.87 (dd, *J* = 9.1, 5.4 Hz, 1H), 3.40 (ddd, *J* = 15.1, 8.9, 1.5 Hz, 1H), 3.14 (ddd, *J* = 16.0, 9.8, 6.3 Hz, 1H), 2.4 (d, *J* = 3.7 Hz, 1H), 2.06 (dt, *J* = 14.2, 2.9 Hz, 1H), 1.68 (m, 1H), 1.53 (m, 2H), 1.43 (m, 2H), 1.35 (m, 2H), 0.88 (s, 9H), 0.82 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H), −0.01 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.1 (J_{CP} = 2 Hz), 140.9 (J_{CP} = 12 Hz), 131.7, 131.6 (J_{CP} = 3 Hz), 130.9 (J_{CP} = 3 Hz), 128.5 (J_{CP} = 11 Hz), 114.4 (J_{CP} = 8 Hz), 111.3, 83.9 (J_{CF} = 163 Hz), 72.5, 70.2, 50.6, 42.4, 31.5, 30.8, 25.8(3), 25.6(3), 25.1, 23.4, 18.1 (J_{CF} = 17 Hz), −4.6, −4.7, −4.9, −5.1; IR ($CHCl_3$) 1472, 1455, 1437, 1390, 1360, 1255, 1172, 1120, 1096, 1072 cm^{-1}; HRMS *m/e* calcd for $C_{37}H_{58}O_3FPSi_2$ 656.3646, found 656.3656.

2-Fluorobutyl analogs (−)-4 and (+)-4′. To 67 mg (0.10 mmol) of phosphine oxide (±)-**30** in 1 mL of THF at −78 °C was added dropwise 68 μl (0.10 mmol) of a 1.48 M solution of phenyllithium in THF. The resultant red solution was allowed to stir for 10 min. A solution of 27 mg (0.076 mmol) of C,D-ring ketone (+)-**21** in 1 mL of THF was added *via* cannula. The reaction was complete after 1.5 h by TLC following the disappearance of the C,D ring. The reaction was quenched by addition of 1 mL of 1/1 $KHCO_3$/2 M potassium sodium tartrate. The layers were separated, and the organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was rapidly purified by filtration through silica gel using 10% EtOAc/hexane as eluent to give 36 mg (0.045 mmol, 60% yield) of the coupled product. The silyl ether was cleaved by redissolving the product in 1 mL of THF with 10 mg of 4 Å molecular sieves, treating the mixture with 60 mg (0.23 mmol) of solid tetrabutylammonium fluoride, and heating the mixture at 60 °C. After 3.5 h, the reaction mixture was concentrated, diluted with EtOAc, passed through a plug of silica gel, and concentrated. Column chromotography gave 10 mg (0.02 mmol, 50% yield) of a 1/2.5 mixture of diastereomers (−)-**4** and (+)-**4′**, respectively. The diastereomers were separated and purified by reverse phase HPLC (20% H_2O/CH_3CN on a C-18 semipreparative column): Major product (+)-**4′**: $[\alpha]^{25}_D$ +23.3 (*c* = 1.5 mg/mL, CH_2Cl_2); UV (CH_2Cl_2) λ_{max} 259 nm (ε 18 600); ^1H NMR (400 MHz, $CDCl_3$) δ 6.40 (d, *J* = 10.3 Hz, 1H), 5.99 (d, *J* = 10.3 Hz, 1H), 5.27 (s, 1H), 4.99 (d, *J* = 2.4 Hz, 1H), 4.48 (dt, *J* = 41.5, 5.9 Hz, 2H), 4.37 (d, *J* = 2.4 Hz, 1H), 3.88 (m, 1H), 2.82 (d, *J* = 9.8 Hz, 1H), 2.67 (dd, *J* = 9.8, 3.2 Hz, 1H), 2.26 (dd, *J* = 10.2, 3.2 Hz, 1H), 1.98 (t, *J* = 7.5 Hz, 1H), 1.75−1.23 (m), 1.21 (s, 6H), 0.93 (d, *J* = 7.2 Hz, 3H), 0.53 (s, 3H); ^{19}F NMR (375 MHz, CCl_3F) δ −218.65; ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.6, 143.4, 132.5, 124.8, 116.7, 113.5, 94.75, 83.9 (J_{CF} = 163 Hz), 73.4 (J_{CF} = 18 Hz), 71.1, 70.3, 56.3, 49.5, 45.9, 44.4, 42.9, 40.5, 36.1, 29.7, 29.2(2), 27.6, 26.2, 22.2, 20.7, 18.8 (J_{CF} = 17 Hz); HRMS calcd for $C_{31}H_{51}O_3F$, 490.3822, found 490.3827. Minor product (−)-**4**: $[\alpha]^{25}_D$ −12.5 (*c* = 1.2 mg/mL, CH_2Cl_2); UV (CH_2Cl_2) λ_{max} 263 nm (ε 20 000); ^1H NMR (400 MHz, $CDCl_3$) δ 6.42 (d, *J* = 11.1 Hz, 1H), 6.03 (d, *J* = 11.1 Hz, 1H), 5.28 (s, 1H), 5.01 (s, 1H), 4.48 (dt, *J* = 41.5, 5.9 Hz, 2H), 4.35 (s, 1H), 3.85 (m, 1H), 2.82 (m, 1H), 2.65 (m, 1H), 2.26 (m, 1H), 1.98 (t, *J* = 7.5 Hz, 1H), 1.75−1.23 (m), 1.22 (s, 6H), 0.94 (d, *J* = 7.2 Hz, 3H), 0.55 (s, 3H); ^{19}F NMR (375 MHz, CCl_3F) δ −219.46; insufficient quantity available for ^{13}C NMR; HRMS calcd for $C_{31}H_{51}O_3F$ 490.3822, found 490.3822.

Antiproliferative and Cell Differentiation-Inducing Activity.[1] HL-60 cells were seeded at 3.0×10^5 cells/mL in 2.0 mL of RPMI1640 medium supplemented with 10% heat-inactivated fetal calf serum and kanamycin (60 μg/mL, Sigma). 1,25-$(OH)_2D_3$ or its analogs dissolved in 2 μL of ethanol were added. After 4 days of culture in a humidified atmosphere of 5% CO_2 in air at 37 °C, cells were mixed with an equivolume of 0.4% tripan blue, and then the viable cell number was counted under a microscope. Cell differentiation-inducing activities were examined by morphological obervations (Gimsa stain).

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Supporting Information Available: Spectroscopic data of all compounds and X-ray analysis of (−)-**10b** (53 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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