Stereocontrolled Total Synthesis of Calcitriol Derivatives: 1,25-Dihydroxy-2-(4′-hydroxybutyl)vitamin D_3 Analogs of an Osteoporosis Drug

Gary H. Posner* and Neil Johnson

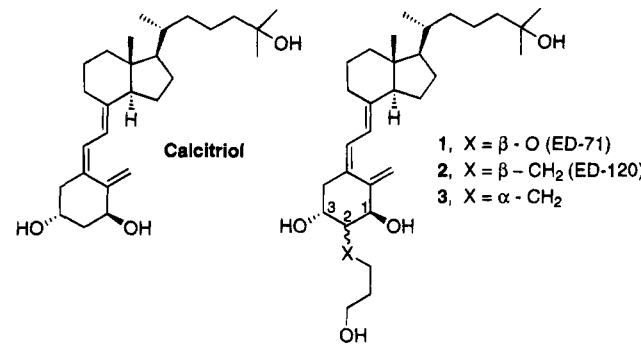
Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218

Received June 17, 1994[⊗]

The diastereomeric 2α- and 2β-(4′-hydroxybutyl) calcitriol analogs (−)-**3** and (+)-**3′** were prepared in only 11 chemical operations, starting with 4 + 2−cycloaddition of commercially available methyl 2-pyrone-3-carboxylate. Highlights of this convergent and stereocontrolled synthetic approach are as follows: (1) retention of reactant dienophile geometry in the product bicyclic lactone, characteristic of a concerted inverse-electron-demand Diels−Alder cycloaddition; (2) an improved decarboxylation procedure involving chemospecific allyloxide opening of a lactone ring in the presence of a methyl ester and then non-high pressure palladium-promoted allylic ester decarboxylation; and (3) use of the enantiomercially pure C,D-ring chiron (+)-**14** to resolve racemic A-ring phosphine oxide (±)-**13**. Relative binding affinities of the enantiomerically pure diastereomers (−)-**3** and (+)-**3′** to the vitamin D binding protein and to the vitamin D receptor showed some unexpected trends. Diastereomer (+)-**3′** surprisingly bound more effectively to the vitamin D receptor than did the established osteoporosis drug ED−71 (**1**).

Especially for postmenopausal women, osteoporosis is a very serious illness that causes physical deformity and high susceptibility to bone (e.g., hip) fractures. In the general population aged above 65 years, osteoporosis ranks third to heart disease and cancer in terms of prevalence.[1] It is estimated that 30% of women at 75 years and 40% of women at 85 years have abnormal bone loss.[2] Calcitriol is being used, especially in Japan where dietary intake of calcium is low, for treatment of osteoporosis.[3] The Chugai Pharmaceutical Co. has prepared ED−71 (**1**) and ED−120 (**2**) as synthetic derivatives of calcitriol, with ED−71 (**1**) having a better therapeutic index than calcitriol.[4] This 2β-((3′-hydroxypropyl)oxy)calcitriol (**1**) has a 2-fold stronger binding affinity to the rat plasma vitamin D-binding protein (DBP) than does calcitriol, perhaps due to the fact that it circulates in the plasma with a longer half-life than calcitriol.[4] Furthermore, in animal models with osteoporosis, ED−71 (**1**) is more effective than calcitriol.[4]

To probe structure−medicinal activity relationships in the hope of preparing a new osteoporosis drug with an even better therapeutic index than ED−71 (**1**), we targeted the 2-carba-analog **3** having a *cis*-1,2-stereochemical relationship in contrast to the *trans*-1,2-stereochemistry of ED−120 (**2**). This analog was chosen



because replacing one oxygen atom by a methylene group, a relatively small change in a large seco-steroid molecule, was anticipated, based on the current working model for receptor binding of ED−71 (**1**),[4] not to interfere with such critical receptor binding. Also, this analog was chosen for chemical reasons, probing whether recently developed Diels−Alder methodology[5] using 2-pyrones and monosubstituted alkenes could be extended to 1,2-disubstituted alkene dienophiles with reliable and faithful transfer of olefin geometry ultimately into the stereochemical relationships at the 1- and 2-positions of the steroid targets. We record here the results of these chemical explorations and biological evaluations.

Results and Discussion

Uncatalyzed Diels−Alder cycloadditions between highly polarized dienes and dienophiles can occur step-wise rather than in the usual concerted fashion.[6] To probe this issue within the context of inverse-electron-demand

[⊗] Abstract published in *Advance ACS Abstracts*, November 1, 1994.

(1) 1. Yamaguchi, K.; Matsumura, G.; Kagechika, H.; Azumaya, I.; Ito, Y.; Itai, A.; Shudo, K. *J. Am. Chem. Soc.* **1991**, *113*, 5474 and references therein.

(2) Tilyard, M. W. In *Vitamin D: Gene Regulation, Structure-Function Analysis, and Clinical Applications*; Norman, A. W., Bouillon, R., Thomasset, M., Eds.; W. de Gruyter: New York, 1991; p 779.

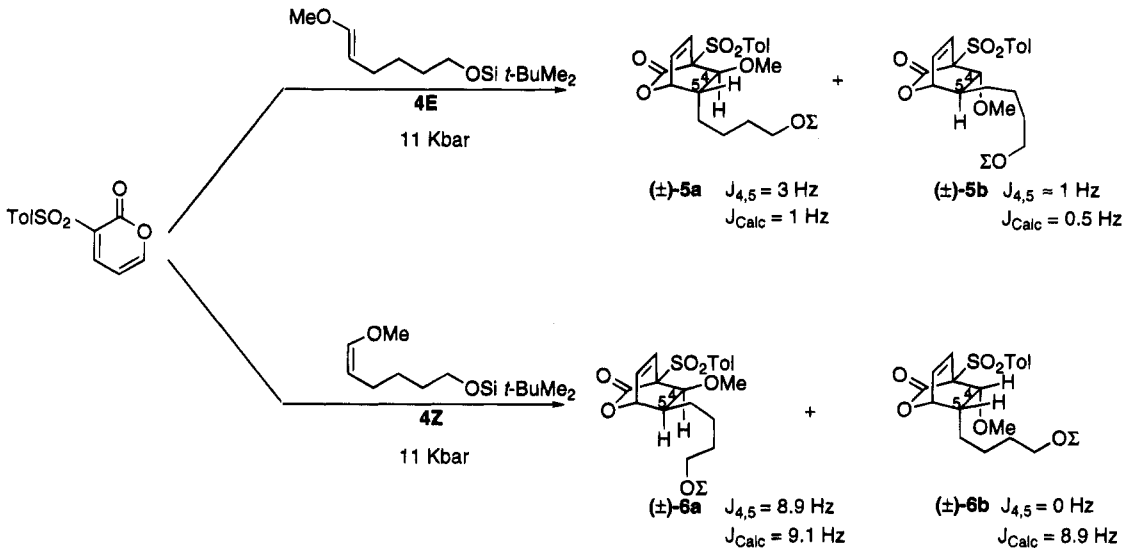
(3) Nordin, B. E. C.; Need, A. G.; Morris, H. A.; Horowitz, M. In *Vitamin D: Gene Regulation Structure−Function Analysis, and Clinical Applications*; Norman, A. W., Bouillon, R., Thomasset, M., Eds.; W. de Gruyter: New York, 1991; p 787.

(4) (a) Nishii, Y.; Abe, S.; Kobayashi, T.; Okano, T.; Tsugawa, N.; Slatopolsky, E.; Brown, A. J.; Dusso, A.; Raisz, L. G. In *Vitamin D: Gene Regulation, Structure−Function Analysis, and Clinical Applications*; Norman, A. W., Bouillon, R., Thomasset, R. R., Eds.; W. de Gruyter: New York, 1991; p 294. (b) Okano, T.; Tsugawa, N.; Masuda, S.; Takeuchi, A.; Kobayashi, T.; Takita, Y.; Nishii, Y. *Biochem. Biophys. Res. Commun.* **1989**, *163*, 1444. (c) Miyamoto, K.; Murayama, E.; Ochi, K.; Watanabe, H.; Kubodera, N. *Chem. Pharm. Bull.* **1993**, *41*, 1111. (d) Nishii, Y.; Sato, K.; Kobayashi, T. *Osteoporosis Int. Suppl.* **1993**, *1*, 190.

(5) (a) Posner, G. H.; Carry, J. C.; Lee, J. K.; Bull D. S.; Dai, H. *Tetrahedron Lett.*, **1994**, *35*, 1321. (b) Posner, G. H.; Nelson, T. D.; Kinter, C. M.; Johnson, N. *J. Org. Chem.* **1992**, *57*, 4083. (c) Posner, G. H.; Nelson, T. D.; Kinter, C. M., Afarinkia, K. *Tetrahedron Lett.* **1991**, *32*, 5295. (d) Afarinkia, K.; Posner, G. H. *Ibid.*, **1992**, *33*, 7839. (e) Marko, I; Evans, G. R. *Ibid.*, **1994**, *35*, 2767. (f) For reviews, see: Afarinkia, K.; Vinader, V.; Nelson, T. D.; Posner, G. H. *Tetrahedron* **1992**, *48*, 9111. Posner, G. H. In *Stereocontrolled Organic Synthesis−Chemistry for the 21st Century* Trost, B. M., Beletskaya, I. P., Eds.; Blackwell Scientific Publications: Oxford, 1994; p 177 Kvita, V.; Fischer, W. *Chimia* **1993**, *47*, 3.

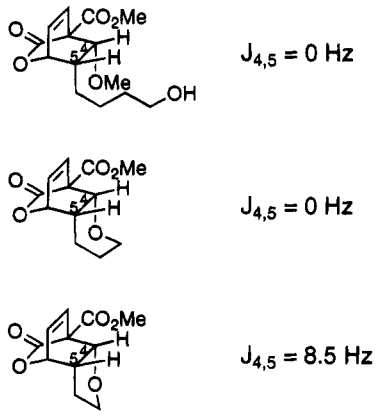
0022-3263/94/1959-7855$04.50/0

Scheme 1



Diels–Alder cycloadditions using 2-pyrones substituted at the 3-position with highly electron-withdrawing (e.g., 3-sulfonyl, 3-acyl) substituents,[5] 3-(*p*-toluenesulfonyl)-2-pyrone and 1,2-disubstituted alkenes **4E** and separately **4Z** were placed under high pressure. In both of these electronically matched cases, the electron-poor 2-pyrone diene and the electron-rich vinylic ether cycloadded to produce isolable bicyclic lactone adducts without undesirable and often-encountered extrusion of CO_2 (Scheme 1).

The most important aspect of these Diels–Alder reactions from a **mechanistic** viewpoint is that the cycloadducts retained the stereochemical information in the reactant vinylic ethers: dienophile **4E** led exclusively to *trans*-4,5-oriented products **5a** and **5b**, whereas dienophile **4Z** led exclusively to *cis*-4,5-oriented products **6a** and **6b**. Therefore, **these polarized 4 + 2-cycloadditions must occur in a concerted rather than in a stepwise fashion.**[6] The assignments of the 4,5-positional relationships were based on extensive precedent,[5] and the assignments of the 4,5-stereochemical relationships were based on the match of the 400 MHz ^{1}H NMR $J_{4,5}$ coupling constants with those calculated using the Karplus equation for energy-minimized structures generated using Chem-3D and Quanta (Scheme 1).[7] Bicyclic lactone **6a**, the very major cycloadduct, differed in a characteristic way[5] from bicyclic lactone **6b** in terms of the chemical shift of the bridgehead hydrogen atom (δ 5.04 vs 4.98) and the chemical shift of the C_4 hydrogen atom (δ 4.55 vs 3.83). Also, irradiation of the C_5 hydrogen atom of lactone **6a** caused an 11% NOE on the C_4 hydrogen atom, confirming their *cis*-relationship. Similar observations were made in distinguishing cycloadduct **5a** from cycloadduct **5b.** The large discrepancy between the observed and the calculated $J_{4,5}$ coupling constant for *cis*-4,5-disubstituted bicyclic adduct **6b**, the minor bicycloadduct, was of concern. Therefore, a series of similar *cis*-4,5-disubstituted bicyclic lactones was prepared. Examination of their $J_{4,5}$ coupling constants showed a very subtle effect of the nature of the substituents on the magnitude of the *vicinal* coupling constant. For example, the cycloadduct derived from the 6-membered cyclic vinyl ether showed $J_{4,5} = 0$ Hz, whereas that derived from the 5-membered cyclic vinyl ether showed $J_{4,5} = 8.5$ Hz.



Thus, the original concern about the low value of the observed $J_{4,5}$ coupling constant of minor bicycloadduct **6b** vanished. Finally, based on literature analogies in which E-alkenes underwent 4 + 2–cycloadditions more easily than Z-alkenes,[6e-g] we were surprised to find that vinylic ether geometric isomer **4Z** reacted considerably faster than isomer **4E** with 3-tolylsulfonyl-2-pyrone. Whereas vinylic ether isomer **4Z** yielded almost exclusively the cycloadduct **6a**, as expected from previous results,[5] vinylic ether isomer **4E** gave a 1:2 mixture of cycloadducts **5a: 5b** in low yield.

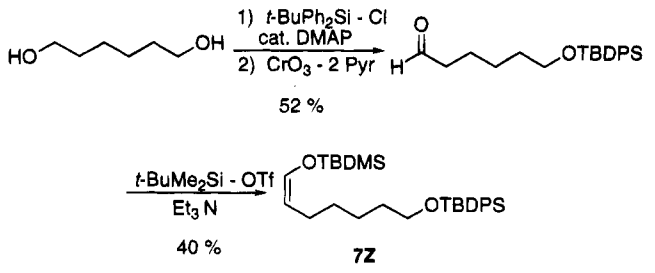
From a **synthesis** viewpoint, cycloadducts **5** and **6** turned out to be disappointing. Despite close structural similarity with other bridgehead-substituted toluenesulfonyl cycloadducts and related cyclohexene systems that underwent smooth reductive desulfonylation,[8] we

(6) (a) Gupta, R. B.; Frank, R. W. *J. Am. Chem. Soc.* **1987**, *109*, 5393. (b) Jensen, F.; Foote, C. S. *Ibid.* **1987**, *109*, 6376. (c) Baran, J.; Mayr, H.; Ruster, V.; Klarner, F.-G. *J. Org. Chem.* **1989**, *54*, 5016. (d) Gassman, P. G.; Gorman, D. B. *J. Am. Chem. Soc.* **1990**, *112*, 8624. (e) Reissig, H-U.; Hippeli, C.; Arnold, T. *Chem. Ber.* **1990**, *123*, 2403. (f) Van Mele, B.; Huybrechts, G. *Int. J. Chem. Kinetics* **1989**, *21*, 967. (g) Sauer, J.; Lang, D.; Wiest, H. *Chem. Ber.* **1964**, *97*, 3208. (h) *cf.* Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1993**, *115*, 7478 and references therein.

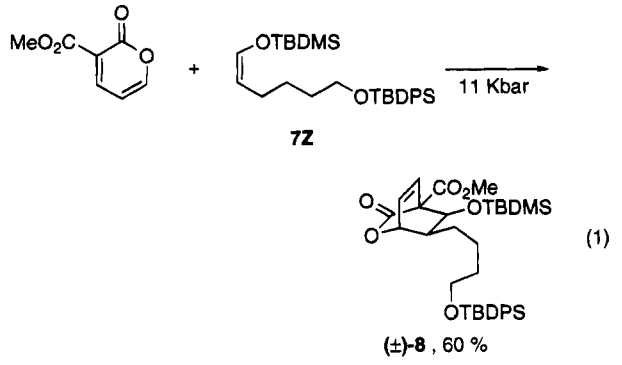
(7) (a) Karplus, M. *J. Chem. Phys.* **1959**, *30*, 11. (b) Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870. (c) Jackman, L. M.; Sternhell, S. *Applications of NMR Spectroscopy in Organic Chemistry*, 2nd ed.; Pergamon: New York, 1969.

(8) (a) Posner, G. H.; Kinter, C. M. *J. Org. Chem.* **1990**, *55*, 3967. (b) Posner, G. H.; Nelson, T. D. *Tetrahedron* **1990**, *46*, 4573. (c) Posner, G. H.; Wettlaufer, D. G. *J. Am. Chem. Soc.* **1986**, *108*, 7373.

Scheme 2



were unsuccessful using a variety of conditions [e.g., Al–Hg, Na–Hg, Raney nickel, Li/NH_3] to effect high-yielding reductive desulfonylation. Also, it was anticipated that ultimate conversion of the methyl ether functionality into the desired alcohol group would be more difficult than deprotection of a silyl ether. Therefore, silylated vinylic ether **7Z**, prepared according to literature precedent as illustrated in Scheme 2,[9] and commercially available methyl 2-pyrone-3-carboxylate were subjected to high pressure cycloaddition (eq 1).



(1)

Bicycloadduct **8** was the major product, isolated on gram scale in 60% yield (75% yield based on recovered pyrone reactant), with the oxygen substituent at position-4, as expected based on the polar nature of the Diels–Alder cycloaddition and also on literature precedent,[5] and with a *cis*-4,5-stereochemical relationship. This stereochemical outcome was expected based on the results in Scheme 1 with the 3-sulfonyl-2-pyrone and was confirmed by the observed large ^{1}H NMR $J_{4,5}$ coupling constant (8.6 Hz)[7] and by the characteristic chemical shifts of the bridgehead hydrogen atom at δ 5.1 and the C_4 hydrogen atom at δ 4.7. Also, irradiation of the C_5 hydrogen atom caused a 14% NOE on the C_4 hydrogen atom, confirming their *cis*-4,5-relationship. We have not succeeded in preparing cleanly the isomeric silylated vinylic ether **7E** for cycloaddition with methyl 2-pyrone-3-carboxylate.

Having served its chemical function of activating the pyrone diene (the unsubstituted parent 2-pyrone is unreactive)[5d,10] for cycloaddition with the electron-rich vinylic ether **7Z**, the bridgehead carboxylate ester group in bicyclic lactone adduct **8** had to be removed. To complement our two-step lactone methanolysis and high-pressure procedure for this type of decarboxylation,[11] we report now a new and more convenient (i.e., not high pressure) two-step protocol (Scheme 3). Although bicyclic lactone methyl ester **8** has two ester carbonyl groups, it was gratifying to find that the lactone ring was chemospecifically attacked by lithium allyloxide to produce mixed methyl allyl malonate **9** in 75% yield. In accord with literature precedent,[12] allyl ester **9** was smoothly decarboxylated using palladium acetate; an unexpected but desired benefit of this procedure was conjugation of the cyclohexene double bond, giving the contiguously tetrasubstituted cyclohexene **10** in 92% yield (Scheme 3).

Without any surprises, highly functionalized cyclohexene alcohol ester **10** was O-silylated and then reduced to form allylic alcohol **11** (Scheme 4). One-flask Claisen rearrangement followed by spontaneous thermal sulfoxide elimination was achieved using our sulfinylated orthoester protocol[13] giving an unusually favorable >10:1 Z:E ratio of dienoate esters from which the desired Z-dienoate **12** was isolated by chromatography in 80% yield, without the added and sometimes tedious step of having to photoisomerize the E → Z dienoate.[13] Established reactions as outlined in Scheme 4 provided the crucial, fully O-protected, racemic, A-ring phosphine oxide (±)-**13**. Lythgoe-type coupling[14] of the conjugate base of phosphine oxide (±)-**13**, generated using phenyllithium,[15] with C,D-ring ketone (+)-**14** of natural absolute configuration[14b] produced O-silylated derivatives of diastereomeric 2-(4′-hydroxylated) calcitriol analogs (−)-**3** and (+)-**3′**, isolated in 50% yield. Fluoride-induced cleavage of the silyl protecting groups proceeded easily at three of the four silylated alcohol groups; desilylation at the C_1 secondary alcohol position, however, was unexpectedly slow, requiring considerably more vigorous reaction conditions. In another context,[16] we have observed that the C_1 secondary alcohol unit in calcitriol is chemically less reactive than the C_3 secondary alcohol toward esterifying reagents. Nevertheless, fluoride-assisted quadruple desilylation under more vigorous conditions eventually yielded the desired calcitriol analogs (−)-**3** and (+)-**3′**. Easy HPLC separation gave each diastereomer in enantiomerically pure form. Tentative assignments of stereochemistry to diastereomers (−)-**3** and (+)-**3′** were made by ^{1}H NMR in analogy with closely related calcitriol analogs; in diastereomeric pairs differing only by inversions of stereochemistry at positions 1–3 but not in the C,D-ring or in the side chain, the 1α-substituted diastereomer characteristically showed lower field absorptions for the C_{18}-methyl group and for one proton of the C_{19}-methylene group (Table 1). Thus, in only 11 steps from commercially available methyl 2-pyrone-3-carboxylate, two new vitamin D_3 analogs have been prepared, and the C,D-ring chiron (+)-**14** has been used to resolve racemic A-ring phosphine oxide (±)-**13**.[17]

Preliminary biological evaluation of synthetic diastereomers (−)-**3** and (+)-**3′** involved measuring their relative

(9) Moeller, K. D.; Tinao, L. V. *J. Am. Chem. Soc.* **1992**, *114*, 1033 and references therein.

(10) 2-Pyrone, prone to rapid polymerization when heated, undergoes nonregioselective cycloadditions under very high pressure conditions (e.g., 18.5 Kbar): Markó, I. E.; Seres, P.; Swarbrick, T. M.; Staton, I.; Adams, H. *Tetrahedron Lett.* **1992**, *33*, 5649. For successful use of 2-pyrone under Lewis acid catalysis **and** 11 kbar pressure, see: Posner, G. H.; Ishihara, Y. *Ibid.* **1994**, *35*, 7545.

(11) Posner, G. H.; Carry, J.-C.; Anjeh, T. E. N.; French, A. N. *J. Org. Chem.* **1992**, *57*, 7012.

(12) Mandi, T.; Imaji, M.; Takada, H.; Kawata, M.; Nokami, J.; Tsuji, J. *J. Org. Chem.* **1989**, *54*, 5395.

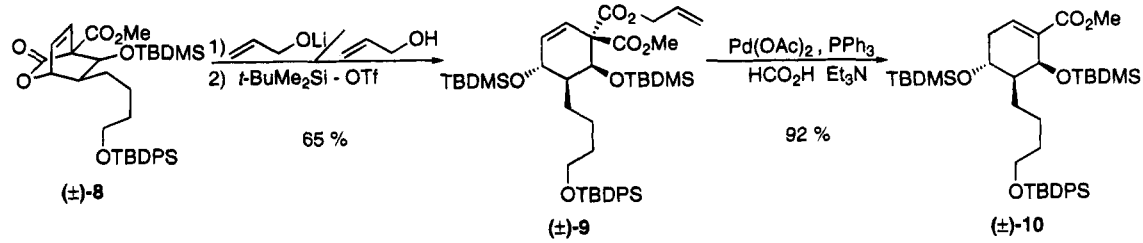
(13) (a) Posner, G. H.; Crouch, R. D.; Kinter, C. M.; Carry, J.-C. *J. Org. Chem.* **1991**, *56*, 6981. (b) Posner, G. H., Dai, H. *BioMed. Chem. Lett.* **1993**, *3*, 1829.

(14) (a) Lythgoe, B.; Moran, T. A.; Nambudiry, M. E. N.; Tideswell, J.; Wright, P. W. *J. Chem. Soc. Perkin Trans. 1* **1978**, 590. (b) Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Batcho, A. D.; Sereno, J. F.; Uskokovioć, M. R. *J. Org. Chem.*, **1986**, *51*, 3098.

(15) (a) Posner, G. H.; Nelson, T. C.; Guyton, K. Z.; Kensler, T. W. *J. Med. Chem.* **1992**, *35*, 3280. (b) Posner, G. H.; Dai, H.; Afarinkia, K.; Murthy, N. N.; Guyton, K. Z.; Kensler, T. W. *J. Org. Chem.* **1993**, *58*, 7209.

(16) Unpublished results of G. H. Posner and H. Liu.

Scheme 3



Scheme 4

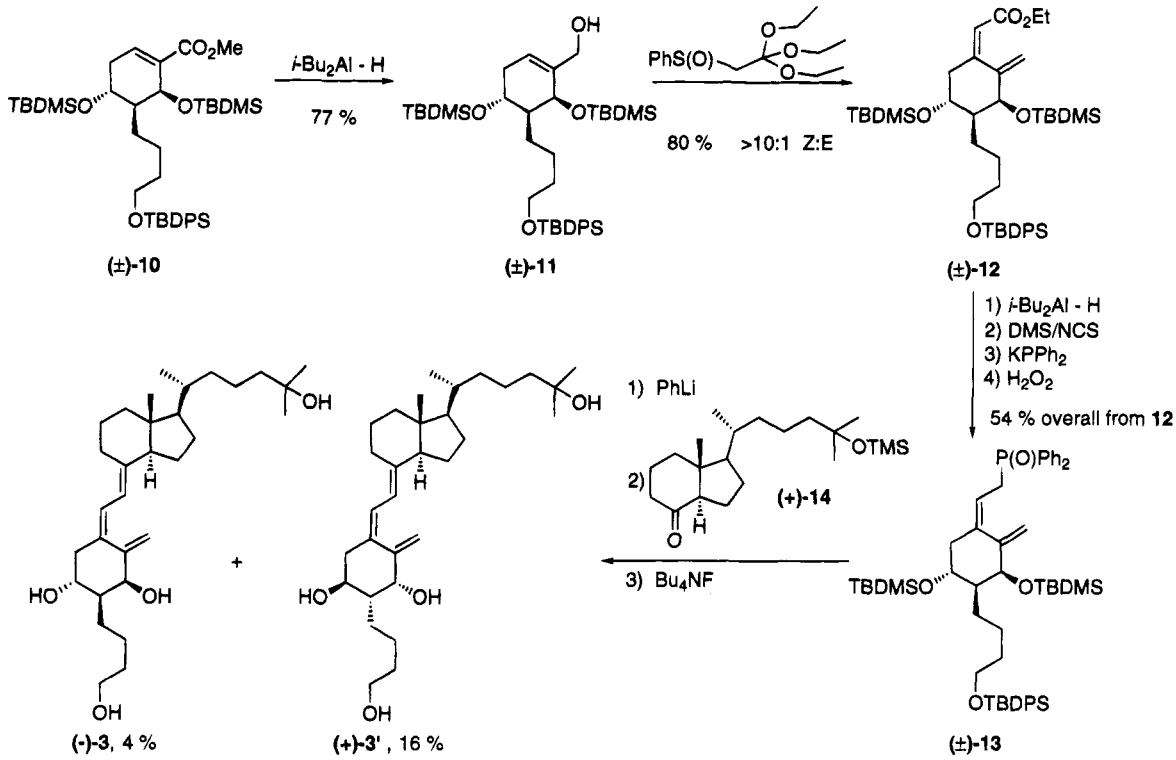
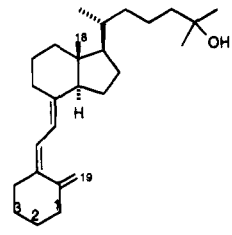


Table 1



			^{1}H NMR chemical shift (δ)		
1	2	3	C_{18}	C_{19}	ref
α-OH	α-OH	β-OH	0.54	5.14	18
β-OH	β-OH	α-OH	0.53	5.11	18
α-CH_2OH		β-OH	0.54	5.02	15
β-CH_2OH		α-OH	0.50	4.99	15
α-CH_2CH_2OH		β-OH	0.54	4.90	13b
β-CH_2CH_2OH		α-OH	0.51	4.88	13b
(−)-**3** 1α-OH	2α-$(CH_2)_4OH$	β-OH	0.54	5.00	this
(+)-**3′** 1β-OH	2β-$(CH_2)_4OH$	α-OH	0.52	4.98	work

binding affinities to rat vitamin D binding protein and also to the vitamin D receptor of bovine thymus (Table 2).[4] Diastereomer (−)-**3** had **higher** affinity than ED−71 (**1**) for the vitamin D binding protein, but it had extremely low affinity for the vitamin D receptor; whether this separation of binding affinities has important mechanistic and/or medicinal value remains to be established. Diastereomer (+)-**3′**, on the other hand, had **lower** affinity than ED−71 (**1**) for the vitamin D binding protein, but it had **higher** affinity than ED−71 (**1**) for the vitamin D receptor even though diastereomer (+)-**3′** has the **unnatural** 1β-OH stereochemistry. Determining the impact of these differences on possible use of these new analogs for chemotherapy of osteoporosis requires further (e.g., *in vivo*) biological testing.

Table 2. Relative Binding Affinities

	D-binding protein	D receptor
25(OH)-d_3	90	
1,25$(OH)_2$-d_3	1	1
ED−71 (**1**)	3.7	0.21
ED-120 (**2**)	1.8	0.01
(−)-**3**	5.0	0.01
(+)-**3′**	1.9	0.28

Experimental Section[15b]

Cycloadducts (±)-6a and (±)-6b. A 12 cm piece of 3/8 in. heat shrinkable teflon tubing (Ace Glass cat. #12685-40) was sealed on one end with a glass dowel plug by using a heat

(17) For reviews of synthetic approaches to vitamin D, see: (a) Wilson, S. R.; Yasmin, A. in *Topics in Natural Products Chemistry*; Ur-Raman, A., Ed.; Elsevier Science Publishers: Amsterdam, 1992. (b) Dai, H.; Posner, G. H. *Synthesis* **1994**, 1383.

(18) Unpublished results of G. H. Posner and T. D. Nelson.

gun. To this 99 mg (0.39 mmol) of 3-(*p*-tolylsulfonyl)-2-pyrone, 970 mg (3.9 mmol) of methyl enol ether **4Z**, 10 mg of barium carbonate, and 1 mL of dry CH_2Cl_2 was added. The open end of 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 room temperature for 5 days. The reaction mixture was concentrated on a rotary evaporator and the residue was purified by column chromatography (25% EtOAc/hexane) to give 70 mg (0.14 mmol, 38%) of the cycloadduct (±)-**6** as a mixture of adducts in a ratio of 18:1. This reaction mixture was dissolved in 2 mL of THF and 280 mL (0.28 mmol) of a 1M solution of *n*-Bu_4NF was added. After 2 hrs the reaction mixture was concentrated, diluted in 5 mL EtOAc, and filtered through a plug of silica gel. The filtrate was concentrated and purified by column chromotography (10−50% EtOAc/hexane) to give 35 mg (0.09 mmol 19%) of adduct (±)-**6a** and 6 mg (0.02 mmol 3%) of adduct (±)-**6b**, both as white solids. (±)-**6a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.4 Hz, 1H), 7.50 (d, J = 7.8 Hz, 1H), 7.31 (m, 2H), 6.85 (dd, J = 9.2, 6.9 Hz, 1H), 6.63 (dd, J = 9.2, 5.0 Hz, 1H), 5.04 (dd, J = 5.0, 1.6 Hz, 1H), 4.58 (8.9, 1H), 3.65 (t, J = 3.6 Hz, 2H), 3.63 (s, 3H), 2.55 (dd, J = 8.9, 1.6 Hz, 1H), 2.42 (s, 3H), 2.06 (s, 1H), 1.60 (m, 2H), 1.42 (m, 2H), 1.16 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 145.2, 137.5, 135.9, 133.9, 130.6, 129.5, 129.1, 127.6, 77.8, 75.5, 62.6, 61.5, 45.0, 32.4, 27.4, 26.7, 25.9, 21.7. (±)-**6b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (dd, J = 6.7, 1.2 Hz, 1H), 6.72 (dd, J = 6.7, 5.2 Hz, 1H), 4.98 (ddd, J = 5.2, 3.1, 2.2 Hz, 1H), 3.83 (bs, 1H), 3.66 (t, J = 3.5 Hz, 2H), 3.47 (s, 3H), 2.44 (s, 3H), 1.79 (dt, J = 3.4, 3.1 Hz, 1H), 1.68 (m, 2H), 1.42 (m, 2H), 1.38 (m, 2H).

Silylated Vinylic Ether 7Z. To a 100 mL round-bottomed flask containing 2.1 g (17.5 mmol) of 1,6-hexanediol, 2.7 mL (19.2 mmol) of triethylamine, and 10 mg of *N,N*-(dimethylamino)pyridine in 35 mL CH_2Cl_2 was added 5 mL (19.2 mmol) of *tert*-butylchlorodiphenylsilane. The reaction was stirred at room temperature for 12 h, or until complete by TLC. The reaction was quenched with 10 mL water, the organic layer was separated, and the aqueous layer was washed with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography (10−20% EtOAc/hexane) to afford 3.73 g (10.45 mmol, 60% yield) of the monosilated product as a clear oil.

To a 250 mL round-bottomed flask containing 10.14 mL (125.4 mmol) of pyridine in 50 mL of CH_2Cl_2 was slowly added 6.27 g (62.7 mmol) of chromium trioxide. The resultant deep burgandy solution was stirred for 15 min at room temperature. At the end of this period, a solution of the above monosilated diol in 50 mL CH_2Cl_2 was added via cannula. A tarry, black deposit separated immediately. This mixture was stirred for 1h at which time the CH_2Cl_2 was removed on a rotary evaporator and the tar was diluted with Et_2O. This heterogeneous mixture was filtered through silica gel to give a yellow liquid which was concentrated. The crude product was purified by column chromotography (5% EtOAc/hexane) to give 3.17 g (8.9 mmol, 85% yield) of the aldehyde as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (s, 1H), 7.675 (m, 4H), 7.40 (m, 6H), 3.66 (t, J = 6.2 Hz, 2H), 2.34 (m, 2H), 1.58 (m, 4H), 1.41 (m, 2H), 1.04 (s, 9H); IR ($CHCl_3$) 3013, 2931, 1713 cm^{-1}.

The above aldehyde was then diluted with 20 mL of benzene and 1.64 mL (11.75 mmol) of triethylamine. The resulting mixture was cooled to 0 °C and 2.45 ml (10.68 mmol) of *tert*-butyldimethylsilyl triflate was added. The reaction was allowed to warm to room temperature and stirred for 1 h. The reaction was quenched with brine and 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 **7Z** (1.67 g, 3.56 mmol, 40% yield) was a clear oil: R_f = 0.8 (25% EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 4H), 7.41 (m, 6H), 6.17 (dt, J = 5.9, 1.5 Hz, 1H), 4.43 (dd, J = 7.4, 5.9 Hz, 1H), 3.61 (t, J = 6.6 Hz, 2H), 2.09 (ddt, J = 14.7, 7.4, 1.5 Hz, 2H), 1.54 (m, 2H), 1.37 (m, 2H), 0.92 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.50, 135.54 (4), 134.15 (2), 129.50, 129.43, 127.55 (2), 127.53, 110.54, 63.93, 32.31, 26.87 (3), 25.99 (3), 25.80, 25.66, 23.36, 19.22, −2.92, −5.36; IR ($CHCl_3$) 3013, 2931, 1654, 1108 cm^{-1}; HRMS m/e calcd for $C_{24}H_{38}O_2Si_2$ 411.2176, found 411.2179.

Cycloadduct (±)-8. A 12 cm piece of 3/8 in. heat shrinkable teflon tubing (Ace Glass cat. #12685-40) was sealed on one end with a glass dowel plug by using a heat gun. To this 500.0 mg (3.24 mmol) of methyl 2-pyrone-3-carboxylate (Aldrich), 2 g (4.26 mmol) of silylated vinylic ether **7Z**, 10 mg of barium carbonate, and 2 mL of dry CH_2Cl_2 was added. The open end of 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 room temperature for 4 days. The reaction mixture was concentrated on a rotary evaporator and the residue was purified by column chromatography (5% EtOAc/hexane) to give 40 mg (8%) of recovered pyrone methyl ester and 1.21 g (1.94 mmol, 60%) of the cycloadduct (±)-**8** as a clear oil: R_f = 0.58 (25% EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 4H), 7.41 (m, 6H), 6.78 (dd, J = 7.8, 2.8 Hz, 1H), 6.46 (dd, J = 7.8, 5.1 Hz, 1H), 5.09 (ddd, J = 5.1, 3.8, 1.0 Hz, 1H), 4.71 (dd, J = 7.6, 1.00 Hz, 1H), 3.89 (s, 1H), 3.66 (t, J = 6.1 Hz, 3H), 2.35 (ddd, J = 7.6, 3.8, 2.8 Hz, 1H), 1.56 (m, 2H), 1.26 (m, 2H), 1.06 (s, 9H), 0.91 (m, 2H), 0.78 (s, 9H), 0.012 (s, 3H), 0.006 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.93, 167.51, 135.51 (4), 133.70 (2), 130.46, 129.53 (2), 128.64, 127.54 (4), 76.12, 69.36, 63.12, 52.7, 44.72, 32.37, 27.09, 26.75 (3), 25.64 (3), 25.56, 25.31, 23.34, 19.09, 18.04, −3.90, −5.03; IR ($CHCl_3$) 1760, 1743 cm^{-1}; HRMS m/e calcd for $C_{31}H_{41}O_6Si_2$ 565.2442, found 565.2450.

Mixed Malonate (±)-9. To a 25 mL round-bottomed flask with 500 mg (0.80 mmol) of cycloadduct **8** and 2 mL of CH_2Cl_2 at 0 °C was added dropwise, via syringe, 962 μL of a freshly made 1.0 M solution of lithium allyloxide in allyl alcohol. The reaction mixture was allowed to warm to room temperature after the addition. Reaction was complete by TLC after 2 h. The mixture was quenched with 2 mL aq. NH_4Cl and 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 410 mg (0.60 mmol, 75%) of the desired malonate as a clear oil: R_f = 0.42 (25% EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (m, 4H), 7.41 (m, 6H), 5.96 (s, 2H), 5.83 (ddt, J = 17.2, 10.5, 5.6 Hz, 1H), 5.36 (dd, J = 17.2, 1.5 Hz, 1H), 5.22 (dd, J = 10.5, 1.5 Hz, 1H), 4.76 (s, 1H), 4.63 (ddt, J = 13.3, 5.6, 1.4 Hz, 1H), 4.51 (ddt, J = 13.3, 5.6, 1.4 Hz, 1H), 4.02 (t, J = 8.6 Hz, 1H), 3.74 (s, 3H), 3.69 (t, J = 6.1 Hz, 2H), 1.71 (m, 2H), 1.64 (m, 2H), 1.57 (s, 1H), 1.28 (m, 2H), 1.05 (s, 9H), 0.81 (s, 9H), 0.07 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.11, 167.95, 135.41 (4), 134.07 (2), 133.89, 131.17, 129.34 (2), 127.44 (4), 122.47, 118.43, 71.70, 68.64, 65.72, 63.89, 61.38, 52.57, 46.04, 32.45, 26.76 (3), 25.94 (3), 23.25, 19.04, 18.27, 14.02, −3.79, −4.44; IR ($CHCl_3$) 1737 cm^{-1}; HRMS m/e calcd for $C_{34}H_{47}O_7Si_2$ 623.2860, found 623.2865.

To a 25 mL round-bottomed flask with 380 mg (0.56 mmol) of the allyl ester alcohol, 78 μL (0.67 mmol) of 2,6-lutidine, and 1.5 mL of CH_2Cl_2 at 0 °C was added 154 μL (0.67 mmol) of *tert*-butyldimethylsilyl trifluoromethanesulfonate dropwise via syringe. The reaction was complete by TLC after 10 min. The reaction was quenched at 0 °C with 1 mL water and allowed to warm to room temperature. 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 390 mg (0.49 mmol, 87%) of O-silylated mixed malonate (±)-**9** as a clear oil: R_f = 0.6 (25% EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (m, 4H), 7.41 (m, 6H), 5.87 (d, J = 2.68 Hz, 2H), 5.83 (ddt, J = 17.2, 10.5, 5.6 Hz, 1H), 5.36 (dd, J = 17.2, 1.5 Hz, 1H), 5.22 (dd, J = 10.5, 1.5 Hz, 1H), 4.76 (s, 1H), 4.63 (ddt, J = 13.3, 5.6, 1.4 Hz, 1H), 4.51 (ddt, J = 13.3, 5.6, 1.4 Hz, 1H), 4.13 (d, J = 9.2 Hz, 1H), 3.74 (s, 3H), 3.69 (t, J = 6.1 Hz, 2H), 1.76 (m, 2H), 1.61 (m, 2H), 1.55 (s, 1H), 1.28 (m, 2H), 1.06 (s, 9H), 0.88 (s, 9H), 0.83 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.27, 167.96, 135.45 (4), 133.99 (2), 133.97, 131.33, 129.38 (2), 127.48

(4), 121.83, 118.43, 71.70, 69.16, 65.69, 64.00, 61.47, 52.52, 46.10, 32.67, 26.81 (3), 25.99 (3), 25.80 (3), 23.25, 19.10, 18.35, 17.99, 14.11, −3.83, -4.20, −4.34, −4.70; IR ($CHCl_3$) 1737 cm^{-1}; HRMS *m/e* calcd for $C_{40}H_{61}O_7Si_3$ 737.3725, found 737.33730.

Cycohexene Ester (±)-10. A mixture of 380 mg (0.48 mmol) of malonate **9**, 23 μL (0.60 mmol) formic acid, 87 μL (0.62 mmol) triethylamine, 10 mg (0.04 mmol) triphenylphosphine, and 2 mg (0.01 mmol) palladium acetate in 1.5 mL dioxane was sealed in a 5 mL hydrolysis tube and 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 satd. $NaHCO_3$ and dried over $MgSO_4$, filtered, and concentrated. The oily residue was purified by column chromatography (0−10%EtOAc/hexane) to give 310 mg (0.44 mmol, 92%) of cyclohexene ester (±)-**10** as a clear oil: R_f = 0.50 (25% EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (m, 4H), 7.41 (m, 6H), 6.87 (t, *J* = 1.5 Hz, 1H), 5.76 (s, 1H), 4.72 (s, 1H), 4.16 (m, 1H), 3.99 (m, 1H), 3.74 (s, 3H), 3.69 (t, *J* = 6.1 Hz, 2H), 2.60 (dt, *J* = 14.3, 5.6 Hz, 1H), 2.10 (ddd, *J* = 16.9, 8.4, 1.5 Hz, 1H), 1.58 (m, 2H), 1.55 (s, 1H), 1.38 (m, 2H), 1.26 (m, 2H), 1.05 (s, 9H), 0.89 (s, 9H), 0.83 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H), −0.07 (s, 3H), −0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.01, 135.51 (4), 134.05 (2), 133.16, 132.35, 129.45 (2), 127.55 (4), 66.89, 64.16, 51.50, 47.43, 33.1, 26.87, 25.95, 25.92, 25.89, 25.84, 25.68, 23.31, 19.17, 18.42, 18.06, −4.09, −4.37, −4.74, −5.39; IR ($CHCl_3$) 1713 cm^{-1}; HRMS *m/e* calcd for $C_{36}H_{57}O_5Si_3$ 653.3514, found 653.3516.

Allylic Alcohol (±)-11. To a 25 mL round-bottomed flask containing 695 mg (0.98 mmol) of cyclohexene ester (±)-**10** in 8 mL toluene at −78 °C was added 2.15 ml (2.15 mmol) of 1 M diisobutylaluminum hydride in toluene dropwise via syringe. The reaction was complete by TLC after 1h. The reaction was quenched by addition at −78 °C of 5mL of 2 M potassium sodium tartrate followed by dilution with 10 mL EtOAc. After the mixture was allowed to warm to room temperature and stirred for 1/2 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, and dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (0−25% EtOAc/hexane) to give 518 mg (0.76 mmol, 77%) of allylic alcohol (±)-**11** as a clear oil: R_f = 0.35 (25% EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (m, 4H), 7.41 (m, 6H), 5.51 (t, *J* = 1.5 Hz, 1H), 4.80 (s, 1H), 4.22 (d, *J* = 12.0 Hz, 1H), 4.16 (m, 1H), 3.99 (m, 1H), 3.74 (s, 3H), 3.69 (t, *J* = 6.1 Hz, 2H), 2.60 (dt, *J* = 14.3, 5.6 Hz, 1H), 2.10 (ddd, *J* = 16.9, 8.4, 1.5 Hz, 1H), 1.58 (m, 2H), 1.55 (s, 1H), 1.38 (m, 2H), 1.26 (m, 2H), 1.05 (s, 9H), 0.89 (s, 9H), 0.83 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H), −0.07 (s, 3H), −0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.81, 135.51 (4), 134.04 (2), 129.47 (2), 127.55 (4), 122.65, 70.03, 68.32, 65.68, 63.77, 46.36, 33.11, 31.28, 26.85 (3), 25.90 (3), 25.82 (3), 25.51, 25.43, 24.52, 24.03, 19.21, 18.06, −4.20, −4.82 (2), −4.92; IR ($CHCl_3$) 3401, 1713 cm^{-1}; HRMS *m/e* calcd for $C_{34}H_{57}O_4Si_3$ 625.3565, found 625.3570.

Z-Dienoate (±)-12. To 510 mg (0.75 mmol) of allylic alcohol (±)-**11** in a sealable hydrolysis tube was added 642 mg (2.2 mmol) triethylphenylsulfinyl orthoacetate and 1.0 mg 2,4,6-trimethylbenzoic acid and 2 mL CH_2Cl_2. The tube was purged with argon and sealed, then heated at 100 °C for 12 h. The reaction mixture was concentrated. Crude ^1H NMR showed a >10:1 mixture of Z:E isomers. The crude product was purified via PTLC (10%EtOAc/hexane) to give 450 mg (0.60 mmol, 80%) of Z dienoate (±)-**12** as a clear oil: R_f = 0.61 (25% EtOAc/hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (m, 4H), 7.41 (m, 6H), 5.61 (s, 1H), 5.17 (t, *J* = 1.8 Hz, 1H), 5.09 (t, *J* = 1.3 Hz, 1H), 4.55 (dd, *J* = 5.5, 1.3 Hz, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.97 (t, *J* = 3.8 Hz, 1H), 3.66 (t, *J* = 6.1 Hz, 2H), 2.48 (dd, *J* = 5.5, 1.4 Hz, 1H), 2.15 (dd, *J* = 3.8, 1.7 Hz, 1H), 1.70 (m, 1H), 1.58 (m, 2H), 1.55 (s, 1H), 1.38 (m, 2H), 1.26 (m, 2H), 1.04 (s, 9H), 0.87 (s, 18H), 0.05 (s, 6H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.92, 157.09, 153.29, 145.39, 135.52 (4), 134.09 (2), 129.47 (2), 127.55 (4), 117.17, 70.23, 63.91, 59.67, 50.54, 32.98, 26.86 (3), 25.80 (3), 25.74 (3), 19.20, 18.18, 17.98, 14.30, 14.13, −4.66, −4.83, −4.87, -5.17; IR ($CHCl_3$) 3025, 2931, 1713 cm^{-1}; HRMS *m/e* calcd for $C_{43}H_{70}O_5Si_3$ 750.4531, found 750.4538.

Phosphine Oxide (±)-13. To a 25 mL round-bottomed flask containing 180 mg (0.24 mmol) of dienoate (±)-**12** in 2 mL toluene at −78 °C was added dropwise 530 μL (0.53 mmol) of a 1 M solution of diisobutylaluminum hydride via syringe. After 1 h the reaction was complete by TLC. The reaction was quenched at −78 °C by addition of 2 mL of 2 N potassium sodium tartrate and dilution with 5 mL EtOAc. The mixture was allowed to warm to room temperature and stirred 1/2 h until two distinct phases appeared. The organic phase was separated, and the aqueous phase was washed with EtOAc. The combined organic extracts were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. The crude mixture was quickly purified by column chromatography (10−20% EtOAc/hexane) to give 167 mg (0.24 mmol) of the desired allylic alcohol.

To a 10 mL round-bottomed flask containing 152 mg (1.14 mmol) N-chlorosuccinimide in 3 mL CH_2Cl_2 at 0 °C was added 90 mL (1.22 mmol) of dimethyl sulfide via syringe. A white precipitate formed immediately upon addition. This mixture was cooled to −20 °C and stirred for 20 min. The above allylic alcohol in 2 mL CH_2Cl_2 was then added to the heterogeneous mixture via cannula. The reaction was stirred for 1/2 h at −20 °C and then allowed to warm to room temperature and stirred for an additional 1 h. The organic layer was washed with water, brine, dried with $MgSO_4$, filtered, and concentrated. The crude product was passed through florisil (5% EtOAc/hexane) to afford 154 mg (0.21 mmol) of the desired allylic chloride as a yellow oil.

To a 10 mL round-bottomed flask containing the above allylic chloride in 2 mL THF at −78 °C was added dropwise via cannula a 0.5 M solution of potassium diphenylphosphide in THF. The addition was stopped once the red color persisted. After 1 h the reaction was allowed to slowly warm to 0 °C at which point it was complete by TLC. The reaction was quenched with 2 drops of water and the THF was removed. The residue was diluted with 2 mL CH_2Cl_2 and 10 drops of 30% H_2O_2 was added. After 1 h the reaction was diluted with CH_2Cl_2 and water and the layers were separated. The organic phase was concentrated. The crude product was purified by column chromatography (25−50% EtOAc/hexane) to give 121 mg (0.13 mmol, 54% from Z-dienoate (±)-**12**) of the phosphine oxide (±)-**13** as a clear oil: R_f = 0.56 (75% EtOAc/hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.74−7.36 (m, 20H), 5.3 (dd, *J* = 15.1 Hz, 6.6H), 5.11 (s, 1H), 4.75 (s, 1H), 4.42 (d, *J* = 3.2 Hz, 1H), 3.87 (dd, *J* = 8.9, 4.9 Hz, 1H), 3.65 (t, *J* = 6.6 Hz, 3H), 3.40 (dt, *J* = 15.1, 8.9 Hz, 1H), 3.14 (dt, *J* = 16.0, 6.7 Hz, 1H), 2.4 (dd, *J* = 13.3, 3.2 Hz, 1H), 2.06 (dd, *J* = 14.2, 2.9 Hz, 1H), 1.56 (m, 1H), 1.53 (m, 2H), 1.43 (m, 2H), 1.35 (m, 2H), 1.04 (s, 9H), 0.88 (s, 9H), 0.82 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H), −0.01 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.20 (2), 141.17, 135.50 (4), 134.06 (2), 131.71, 131.04, 130.92 (4), 129.45 (2), 128.63 (4), 128.47 (2), 127.53 (4), 114.39, 70.15, 63.90, 50.72, 32.97, 30.09, 26.83 (3), 25.79 (3), 25.05, 24.06, 19.18, 18.04, −4.58, −4.69, -4.89, −5.07; IR ($CHCl_3$) 3025, 2954, 1472, 1255 cm^{-1}; HRMS *m/e* calcd for $C_{49}H_{68}O_4Si_3$ 835.4163, found 835.4169.

Calcitriol Analogs (−)-3 and (+)-3'. To a 10 mL round-bottomed flask containing 95 mg (0.103 mmol) of phosphine oxide (±)-**13** in 1.4 mL of THF at −78 °C was added dropwise 67 μL (0.103 mmol) of a 1.54 M solution of phenyllithium in THF. The resultant red solution was allowed to stir for 10 minutes. A precooled (− 78 °C) solution of 20 mg (0.056 mmol) of C-D ring (+)-**14** in 1 mL of THF was added via cannula. The reaction was complete after 1 h by TLC following disappearance of C−D ring. The reaction was quenched by addition of 1 mL 1:1 $KHCO_3$/2 N 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 50% EtOAc/hexane as solvent to give 47 mg (0.052 mmol, 50% yield) of the coupled product. The silyl ethers were cleaved by redissolving the product in 1 mL of THF and treating with 220 μL (0.22 mmol) of tetrabutylammonium

fluoride. After 24 h the reaction was diluted with water and the layers were separated, dried over $MgSO_4$, filtered, and concentrated. The diastereomers were separated and purified by reverse phase HPLC (30–20% H_2O/CH_3CN on a C-18 semipreparative column) to afford 1.1 mg (0.002 mmol, 4% yield) of chromatographically pure analog (−)-**3**, and 4.4 mg (0.008 mmol, 16% yield) of chromatographically pure analog (+)-**3′**, both as white solids. (−)-**3**; $[\alpha]^{25}_D$ −13.3° (*c* 0.9 × 10^{-3}, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.41 (d, *J* = 11.6 Hz, 1H), 6.02 (d, *J* = 11.6 Hz, 1H), 5.29 (s, 1H), 5.02 (s, 1H), 4.35 (s, 1H), 3.82 (m, 1H), 3.68 (t, *J* = 6.1 Hz, 2H), 2.78 (d, *J* = 11.5 Hz, 1H), 2.62 (dd, *J* = 11.5, 3.5 Hz, 1H), 2.20 (dd, *J* = 10.2, 3.5 Hz, 1H), 1.98 (m, 2H), 1.68–1.20 (m), 0.92 (s, 3H), 0.90 (s, 3H), 0.54 (s, 3H); UV–vis (MeOH) λ_{max} 256 nm (ε 18 000). (+)-**3′**: $[\alpha]^{25}_D$ +22° (*c* 0.5 × 10^{-3}, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.40 (d, *J* = 11.6 Hz, 1H), 5.98 (d, *J* = 11.6 Hz, 1H), 5.27 (s, 1H), 4.98 (s, 1H), 4.38 (s, 1H), 3.87 (m, 1H), 3.68 (t, *J* = 6.1 Hz, 2H), 2.82 (d, *J* = 11.5 Hz, 1H), 2.65 (dd, *J* = 11.5, 3.5 Hz, 1H), 2.24 (dd, *J* = 10.2, 3.5 Hz, 1H), 1.68–1.20 (m), 0.92 (s, 3H), 0.90 (s, 3H), 0.52 (s, 3H); UV–vis (MeOH) λ_{max} 268 nm (ε 15 600); HRMS *m*/*e* calcd for $C_{31}H_{50}O_3$ 470.3760, found 470.3771.

Acknowledgment. We thank the NIH (GM-30052) for financial support and the Chugai Pharmaceutical Co. for assistance and for copies of the ^{1}H NMR spectra of ED–71 (**1**) and ED–120 (**2**), Professors T. Kobayashi and T. Okano (Kobe Pharmaceutical University, Japan) for comparison of the biological properties of (−)-**3** and (+)-**3′** vs ED–71 (**1**) and ED–120 (**2**), Dr. Milan Uskoković (Hoffmann-LaRoche) for a generous gift of C,D-ring chiron (+)-**14**, Mr. Hong Guo of this department for help with the use of Quanta, and Dr. J.-C. Carry and Dr. C.-G. Cho of this department for discovering the chemospecific allyl oxide opening of a related bicyclic lactone ester. We also thank a reviewer for some detailed suggestions.