New Strategies for the Synthesis of Vitamin D Metabolites via Pd-Catalyzed Reactions

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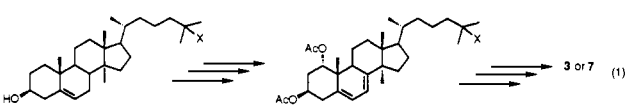
Abstract: The invention of new palladium-catalyzed reactions offers new insights into synthetic strategies directed toward the vitamin D system. The palladium-catalyzed cycloisomerization of 1,6- and 1,7-enynes to dialkylidenecycloalkanes permits a lynchpin approach to the A ring of vitamin Ds. Using the thioacetal of formaldehyde, the proper subunits containing the olefin and the acetylene were attached. Pd(2+) effected cycloisomerization to an A ring subunit. A more effective strategy evolved from the evolution of a Pd-catalyzed alkylative cyclization of enynes. Whereas prior work established the feasibility of this process for 1,6-enynes, model studies reported herein demonstrate the feasibility of its extension to 1,7-enynes. This reaction permits the creation of a new concept for vitamin D synthesis wherein A ring formation is concomitant with its attachment to an appropriate CD fragment. An asymmetric synthesis of the requistite 1,7-enyne required six steps. Bromomethylenation of Grundmann's ketone and its side chain hydroxylated derivative proceeded with excellent geometrical selectivity (>30:1) using the Wittig reaction. A Pd catalyst generated from $(dba)_3Pd_2 \cdot CHCl_3$ and triphenylphosphine stitched together these two units in a single step resulting in syntheses of alphacalcidiol and calcitriol.

The discovery that vitamin D_3 was a provitamin greatly stimulated research into its chemistry and biology.[1-3] Early studies revealed that one of its metabolites, 1α,25-dihydroxyvitamin D_3 (calcitriol, **3**), is the "active" form with the 1α-hydroxy group being the key for the classical biological function of bone deposition and resorption.[1] Other metabolites possessing differing side chains as well as the 1α-hydroxy group have been isolated, some of which are summarized in Figure 1.[4] Many different cell types have been identified as targets for the action of vitamin D metabolites. Its activity in cell proliferation and differentiation leads to its exploration for treatment of disorders ranging from psoriasis to cancer. Separation of the myriad of biological functions becomes a major goal. While the 1α-hydroxy group appears necessary for activity, modification of the side chains not only is tolerated but also has led to some separation of function.[3,5] The potential clinical applications require fuller examination of the effect of structural variation on biological profile.

The enhanced clinical indications for 1α-hydroxyvitamin D_3 (alphacalcidiol, **7**) and/or calcitriol and the further exploration of structure–activity relationships require partial or total syntheses.[6] Two fundamental approaches have been pursued. The first entails starting with an intact steroid as illustrated by the work of Barton and co-workers on the synthesis of alphacalcidiol and calcitriol (eq 1).[7,8]



(1)

A modular approach provides the greatest flexibility. Thus, the vitamin D may be viewed as consisting of three zones—the

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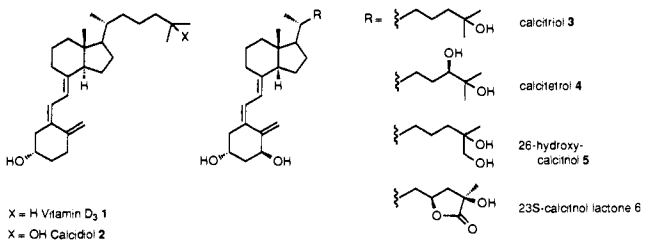
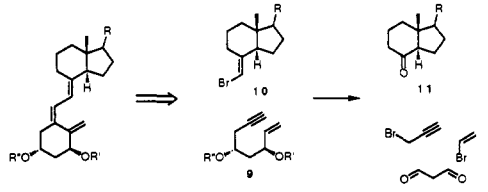
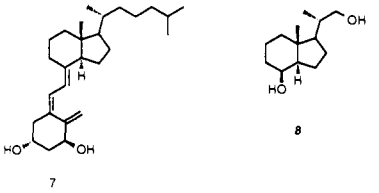


Figure 1. Some vitamin D_3 metabolites.

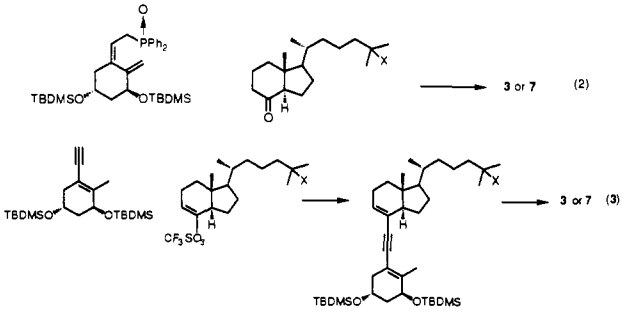
Scheme I. Retrosynthetic Analysis

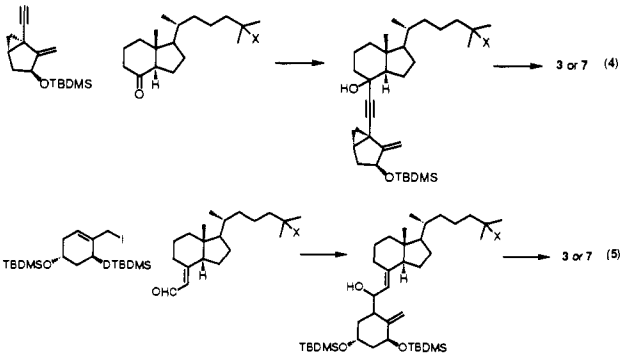


A ring, the CD fragment, and the side chain. The Lythgoe–Inhoffen diol **8**[9] commonly serves the role of the CD fragment onto

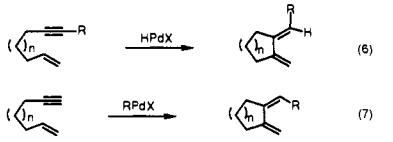


which the side chain and the A ring are attached. Equations 2–5[6] illustrate some of the innovative ways the A ring and the accompanying unsaturation have been created including olefination (eq 2),[10] cross coupling (eq 3),[11] and carbonyl additions (eqs 4[12] and 5[13]). All cases involve prefabrication of the A ring followed by its attachment to the CD unit.

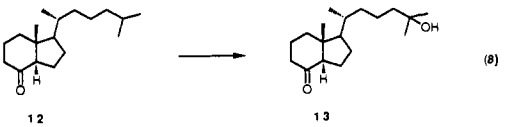




In developing our approach to 1,2-dialkylidenecycloalkanes, we have explored the cyclization of enynes by cycloisomerization (eq 6) which generates the *E* isomers.[14] The postulation that hydropalladation initiates the cyclization[15] suggested that the complementary *Z* isomers might be available by a chemoselective alkyl-, aryl-, or vinylpalladation as the initiation step (eq 7).[16] This concept offers a quite distinct modular approach to the vitamin D system whereby creation of the requisite triene, formation of the A ring, and attachment of this entire unit to the CD fragment would occur in a single reaction! A key question that needed to be answered involves the effect of tether length and substitution on the efficacy of the cyclization. In this paper, we record the realization of this sequence which culminated in syntheses of alphacalcidiol (**7**) and calcitriol (**3**).[17] Considering the atom economy of the cycloisomerization (eq 6), we also explored the independent synthesis of an A ring synthon using a Pd-catalyzed cycloisomerization.



Synthetic Strategy. Scheme I represents the retrosynthetic analysis using Pd-catalyzed alkylative cyclization. The bond disconnection generates two simple building blocks, an acyclic 1,7-enyne (**9**) and a vinyl bromide (**10**), the latter presumably arising from a geometrically defined olefination of a carbonyl compound which, in the cases of alphacalcidiol and calcitriol, corresponds to the well-known Grundmann's ketone **12**[18] and its hydroxylated analogue (**13**). Recently, the direct hydroxylation of the former to generate the latter has been reported (eq 8).[19] The enyne derives from the 2-fold addition of a propargyl and vinyl unit to a malondialdehyde equivalent.



Preparation of Vinyl Halides. Initial efforts for haloolefination of a ketone focussed on the Takai method using low valent chromium with a haloform (eq 9).[20,21] While reaction with

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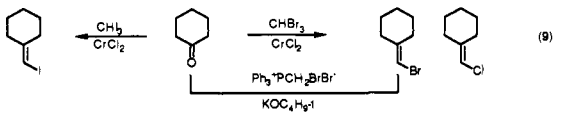
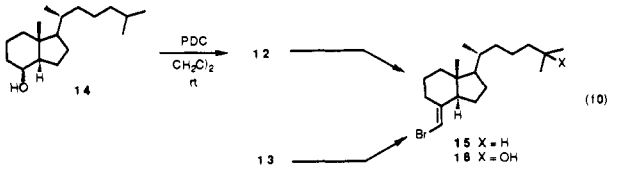


iodoform proceeded moderately well, the instability of the vinyl iodide (complete degradation after 1 week at 0 °C) led to our exploration of the reaction of bromoform. In contrast to the iodoform reaction which generated only the vinyl iodide, a mixture of the vinyl bromide and chloride was obtained.

Although the bromoolefination of cyclohexanone using (bromomethylene)triphenylphosphorane had been reported to proceed in only 15% yield,[21] the higher yields of olefination with this reagent by changing the base to potassium *tert*-butoxide led us to explore its reaction.[22] Indeed, without optimization, (bromomethylene)cyclohexane was obtained in 50% yield.

The key issue in the olefination was geometrical selectivity since we required the (*E*)-vinyl bromide **10**. Trepidation arose from the observation of *Z*-selectivity in reactions with aldehydes;[22] nevertheless, the observation of a 3:1 *E*:*Z* ratio in the reaction of a methyl ketone inspired us.[23] A strategy for making the desired vinyl bromide based upon reductive vicinal elimination produced a 1:1 geometric mixture in 38% yield.[24]

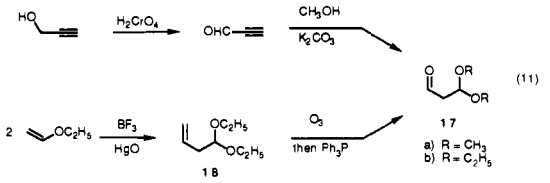
In the event, exposing an unpurified sample of Grundmann's ketone, generated by oxidation of the corresponding alcohol **14**, to a solution of the phosphorane generated using sodium hexamethyldisilylamide gave the bromoolefin in 62% overall yield from **14**. ^{1}H NMR spectroscopy of the crude mixture revealed two



broad singlets at δ 5.62 and 5.92 in the ratio of 30:1. Comparison of these chemical shifts to that for the vinyl proton of (bromomethylene)cyclohexane at δ 5.84 suggested that the major isomer had the desired *E* geometry with the upfield shift to δ 5.62 due to the anisotropy of the C–C single bond of the five-membered ring. This tentative conclusion was subsequently verified by the ultimate success of the synthesis. The authors who previously reported the 1:1 mixture did not separate the geometric isomers nor assign their stereochemistry.[24]

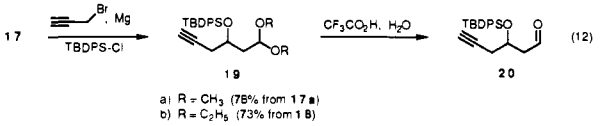
Extension of this methodology to the hydroxy ketone **13** without protection appeared unlikely in light of the reported failure of its olefination under Wittig–Horner conditions analogous to eq 2.[10a] Nevertheless, our desire to minimize the use of protecting groups led us to explore the direct olefination. In contrast to the Wittig–Horner protocol, the Wittig bromomethylenation proceeded well to give the desired product **16** with a 50:1 *E*:*Z* (δ 5.63 vs δ 5.93) selectivity (eq 10). In this case, the NMR spectrum (δ 5.89) revealed a small amount (<4%) of a third vinyl proton which we tentatively assign as the cis-fused ring juncture isomer which may derive from a small amount of the cis-fused ketone contaminating our starting material or by isomerization of the starting ketone under the basic conditions of the olefination. No attempt was made to optimize the conditions. Both compounds, although oils, were obtained analytically pure and were stored at 0 °C for substantial periods without significant degradation.

Preparation of 1,7-Enyne. A differentiated malondialdehyde equivalent that can serve as an acceptor for the organometallic additions is the monoacetal. Using the literature protocol,[25] oxidation of propargyl alcohol to the unstable propynal followed by reaction with basic methanol gave the monomethyl acetal **17a** albeit in low yields in our hands. A more reliable procedure

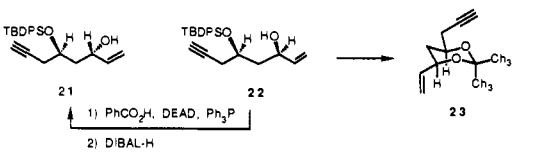


created the diethyl acetal **17b** by ozonolysis of 1,1-diethoxy-3-butene which, in turn, derived by a most remarkable but efficient mercuric ion catalyzed dimerization of ethyl vinyl ether.[26]

Addition of propargylmagnesium bromide[27] and direct silylation provided the monosilyl ethers **19a** and **19b** (eq 12). In the case



of the ethyl acetal, the crude ozonolysis product was reacted directly and the resultant alcohol purified by distillation prior to silylation. Hydrolysis with trifluoroacetic acid in aqueous THF provided the labile aldehyde **20**. The approximately 4-fold increase in rate of hydrolysis of the ethyl acetal **19b** compared to the methyl acetal **19a** minimized product decomposition and led to an enhanced yield as revealed after the next step. The lability of the aldehyde led us to react it immediately with vinylmagnesium bromide to give a 1:1.5 ratio of the two diastereomers **21** and **22** (61% from **19a**, 78% from **19b**). To assign stereochemistry, the



major diastereomer was converted to the acetonide **23** whose proton NMR spectrum suggested a rigid chair and whose ^{13}C NMR spectrum showed the signals for the *gem*-dimethyl group at δ 19.6 and 29.9—both indicative of a syn 1,3-diol stereochemistry.[28]

Efforts to modify the diastereoselectivity by changing the metal proved futile as summarized in Table I. In an attempt to force chelation control to generate the anti isomer by use of a titanium(4+) species, only decomposition resulted. The lack of chelation control with the TBDPS ether was not surprising due to its known low Lewis basicity.[29] Attempts using no protecting group were thwarted by the lability of the aldehydes corresponding to **20**.

In the meantime, a very efficient conversion of the syn isomer **22** into the anti isomer **21** evolved using a Mitsonobu inversion[30]

Table I. Diastereoselectivity for Formation of 1,3-Diol

entry	reagent	conditions	syn:anti
1	$(CH_2{=}CH)_2CuMgBrI$	THF, −78 °C	1.5:1
2	$CH_2{=}CHZnCl$	THF, −20 °C	2.5:1
3	$CH_2{=}CHCeCl_2$	THF, −78 °C	1.5:1
4	$CH_2{=}CHBr$, $CrCl_2$, cat. NBr_2	DMF, rt[b]	1.4:1
5[a]	$CH_2{=}CHTi(O\textit{i}\text{-}C_3H_7)_4MgBr$		

[a] Only decomposition observed. [b] Room temperature.

(21) For alternative bromoolefination methods, see: Wolinsky, J.; Erickson, K. L. *J. Org. Chem.* **1965**, *30*, 2208.
(22) Matsudo, M.; Kurida, K. *Tetrahedron Lett.* **1980**, *21*, 4021. Rollin, P.; Pougny, J. R. *Tetrahedron* **1986**, *42*, 4021. For a recent example, see: Avignon-Tropis, M.; Berjeaud, J. M.; Pougny, J. R.; Frechard-Ortuno, I.; Guillerm, D.; Linstrumelle, G. *J. Org. Chem.* **1992**, *57*, 651.
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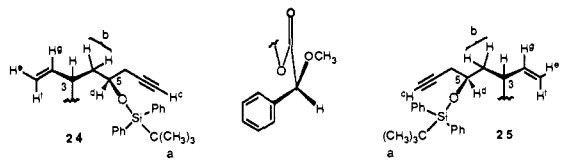


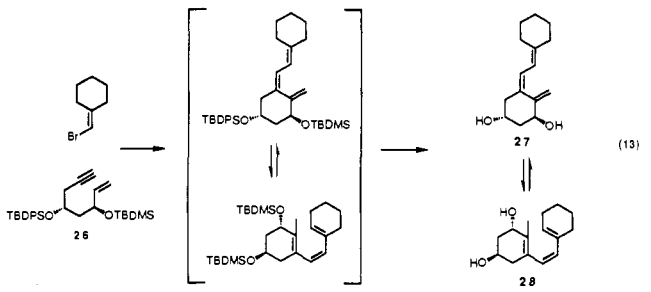
a	1.04	0.98
b	2.20, 2.29	2.03, 2.10
c	1.96	1.90
d	3.83	3.63
e	4.88	5.09
f	4.76	5.15
g	5.51	5.68

Figure 2. ^{1}H NMR correlation for assignment of absolute configuration.

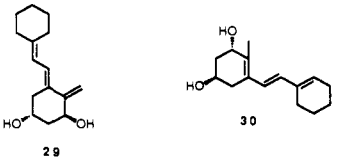
in 73% yield. In this way, a 70% overall yield of the desired anti monosilyl ether **21** from acetal **19b** was obtained. Silylation completed the synthesis of the enyne unit. Use of two different silyl protecting groups maintains differentiation of the two alcohols for greater synthetic flexibility if it should be desired for preparation of analogues.

In order to obtain the enyne unit enantiomerically pure, the racemic allyl alcohol **21** was subjected to a kinetic resolution via asymmetric epoxidation.[31] At −20 °C, in the presence of titanium tetraisopropoxide, dicyclohexyl D-(+)-tartrate in dichloromethane gave a 46% recovery (theoretical 50%, 92% yield) of (−)-allyl alcohol of 98% ee even in the presence of excess *tert*-butyl hydroperoxide. The optical purity and absolute configuration were established by conversion of the (−)- and (+)-allyl alcohols to their (*S*)-(+)-*O*-methylmandelate esters **24** and **25** as shown in Figure 2. The upfield shifts for the protons a–d and downfield shifts for protons e–g for the (−)-isomer compared to the (+)-isomer led to the assignment of the 3*S*,5*R* configuration for the former and 3*R*,5*S* for the (+)-enantiomer.

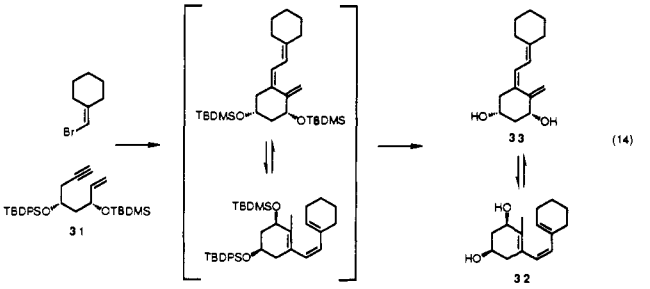
Model Study. To establish the feasibility of the alkylative cyclization, we subjected a mixture of the anti enyne **26** and (bromomethylene)cyclohexane to 10 mol % palladium acetate and 30 mol % triphenylphosphine (TPP) in 1:1 toluene–triethylamine at reflux for 1.5 h. The crude product was directly desilylated to give a mixture of two main products as depicted in eq 13.



Comparison of the spectral properties to those reported established the major product (50% yield) as the triene **28** and the minor product (18% yield) as the triene **27**.[32] That this triene mixture derives from a thermal equilibration under the reaction conditions is established by the equilibration of the separated isomers to give a 1:8 ratio of **27**:**28** which is in good agreement with previous work.[33] This equilibrium is remarkably sensitive to substituents since the silyl ethers show a diminished ratio of 1:2. These compounds were remarkably air sensitive. Exposure of the pure compounds to air for only 15 min effected 50% degradation with formation of a product corresponding to $M^+ + O_2$.[34] Trace amounts of two additional isomers tentatively assigned as **29** [δ 6.48 (d, *J* = 12 Hz, 1 H), 6.01 (d, *J* = 12 Hz, 1 H), 5.09 (bs, 1 H), 4.93 (bs, 1 H), 4.46 (m, 1 H), 4.20 (m, 1 H)] and **30** [δ 6.45 (d, *J* = 17 Hz, 1 H), 6.28 (d, *J* = 17 Hz, 1 H), 5.80 (m, 1 H), 4.21 (bs, 1 H), 4.10 (m, 1 H)] on the basis of the ^{1}H NMR spectra were detected.



The stereochemistry of the enyne partner had no effect on the alkylative cyclization. Performing the reaction with the syn enyne **31** gave a 65% yield of the isomeric mixture from which only the major isomer **32** was obtained pure and therefore fully characterized (eq 14). The presence of the isomeric **33** was suggested

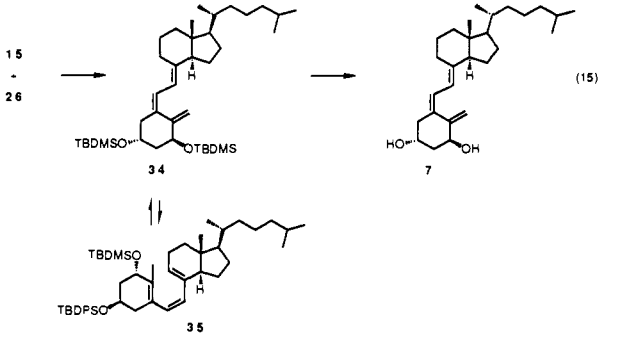


by appropriate signals in the NMR spectra of mixtures [δ 6.38 (d, *J* = 12 Hz, 1 H), 6.12 (d, *J* = 12 Hz, 1 H), 5.27 (bs, 1 H), 4.99 (bs, 1 H), 4.33 (m, 1 H), 4.07 (m, 1 H)].

Bidentate ligands were not satisfactory. Replacing TPP by dppp dramatically slowed the reaction, giving only 10% conversion after 2.5 h at reflux.

Synthesis of Alphacalcidiol. The synthesis of alphacalcidiol requires the alkylative cyclization of the enantiomerically pure enyne **26** with bromoolefin **15**. To minimize the presence of extraneous compounds that might interfere, we switched from generating the active Pd(0) catalyst by in situ reduction of palladium acetate to use of a preformed Pd(0) complex, tris(dibenzylideneacetone)dipalladium–chloroform solvate (**33**).[35]

Heating a solution of the enyne **26** and the vinyl bromide **15** with 5 mol % complex **33** and 30 mol % TPP in 1:1 toluene–triethylamine gave a clean reaction to form a 90:10 mixture of



the silylated alphacalcidiol **34** and its tautomer **35** [δ 5.72 (d, *J* = 12 Hz, 1 H), 5.67 (d, *J* = 12 Hz, 1 H), 5.61 (t, *J* = 2 Hz, 1 H)]. Chromatographic separation of the mixture, thermal equilibration of the silylated previtamin fraction by heating in toluene at 80 °C, and purification of the silylated vitamin from the latter gave a combined yield of 76%. Unlike the model re-

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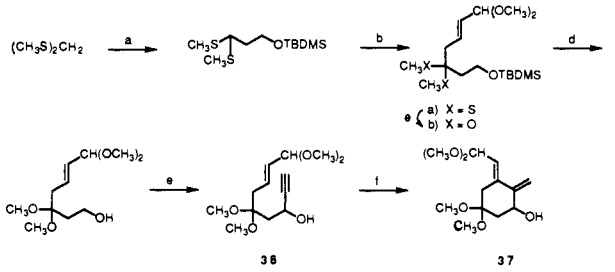
Scheme II. A Pd-Catalyzed Cycloisomerization to a Vitamin D A Ring Synthon[a]

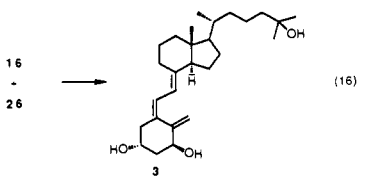


[a] (a) n-C_4H_9Li, THF, −20 °C then $BrCH_2CH_2OTBDMS$, −78 °C to −20 °C, 91%; (b) n-C_4H_9Li, THF, −12 °C, then $BrCH_2CH{=}CHCH(OCH_3)_2$, 75%; (c) $CdCO_3$, $Hg(OAc)_2$, $(CH_3O)_3CH$, CH_3OH, room temperature. (d) TBAF, THF, room temperature, 81% overall; (e) $(COCl)_2$, DMSO, $(C_2H_5)_3N$, CH_2Cl_2 then HC≡C—Li, THF, −78 °C, 49% overall; (f) 20% Ph_3P, 10% $Pd(OAc)_2$, PhH, reflux, 30%.

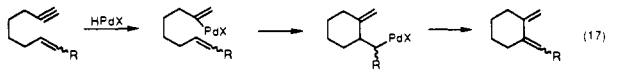
actions, no other geometrical isomers were observed.

Desilylation with TBAF in THF at room temperature occurred slowly but cleanly to give crystalline alphacalcidiol (79% yield) whose physical (mp, specific rotation) and spectroscopic (IR, UV, and ^1H and ^{13}C NMR) properties are in excellent accord with the literature.[7a,36]

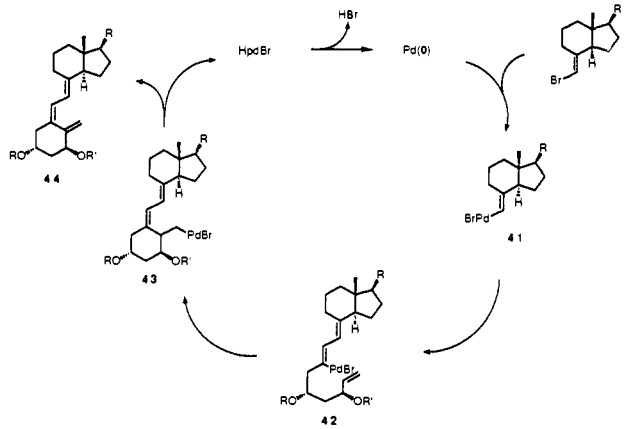
Synthesis of Calcitriol. Application of this coupling reaction to calcitriol raised the question of the compatibility with the free side chain hydroxyl group. The relatively poor coordination of hard Lewis bases like oxygen to palladium suggested it might be compatible. Without modification of the above protocol, a solution of scalemic enyne **26** and vinyl bromide **16** was subjected to the Pd(0) catalyst and the product directly desilylated to give crystalline calcitriol (**3**) in 52% overall yield (eq 16). Physical (mp, specific rotation) and spectroscopic (IR, UV, and ^1H and ^{13}C NMR) properties are in excellent accord with those recorded in the literature.[7b,10-13,37] In this case, the fraction containing the previtamin was not isolated and equilibrated which should enhance the yield of the desired product.



Cycloisomerization to A Ring Synthon. An alternative palladium based approach envisions intersecting one of the strategies illustrated in eq 2, 3, or 5 by synthesis of an A ring unit by cycloisomerization (eq 17).[14,38] Such a study would also provide



Scheme III



insight into the effect of both the R group and ligands on palladium on the cyclization. Furthermore, a conceptually simple strategy for the requisite substrate can be envisioned in which the olefinic and acetylenic arms can be joined to a thioacetal. Scheme II outlines such an approach where bis(methylthio)methane became the lynchpin for attaching the proper units. The requisite allylic bromide as the pure E isomer was readily available by bromoetherification of 1-methoxybutadiene with NBS in methanol.[39] Attempts to cyclize the thioketal analogue of **36** failed. Assessing the problem as incompatibility of a thioketal with our cycloisomerization, we transmuted it into a ketal at an earlier step in the sequence. We chose an acyclic ketal to optimize the Thorpe–Ziegler effect in promoting cyclization. The requisite substrate was available in only six steps.

The cycloisomerization of enyne **36** to diene **39** proceeded significantly less efficiently in spite of the presence of geminal substitution. The possibility that the lower yield relative to our alkylative cyclization arose because of the presence of a free hydroxyl group was ruled out by the fact that no improvement was observed when the corresponding silyl ether and acetate were cyclized. A major problem was the palladium catalyzed dimerization of the terminal acetylene[40]—a process which was minimized by its slow addition to a warm solution of the catalyst. Only one geometrical isomer was formed which, on the basis of mechanistic considerations, was assigned as E. Support for this assignment derived from a NOE experiment which showed a significant enhancement of the acetal proton at δ 5.12 upon irradiating the signal at δ 2.82 which corresponds to the protons of the isolated ring methylene group. Since only a small NOE was observed upon irradiating its partner at δ 2.40, the former must correspond to the equatorial and the latter to the axial hydrogen at C(4).

While the further transformation of the dialkylidenecyclohexane **37** to the correct A ring geometry was not pursued, the E to Z isomerization of related derivatives is well-documented.[10] Further, based upon our earlier work, the Z isomer should be available by cycloisomerizing the Z-olefin isomer corresponding to **36** which should be a more facile process.[41]

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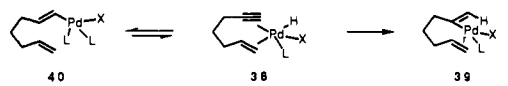
(38) For other approaches to A ring synthons, see ref 6, 10a, 19, and: (a) Takano, S.; Yamane, T.; Takahashi, M.; Ogasawara, K. *Synlett.* **1992**, 410. (b) Nagasawa, K.; Zako, Y.; Ishihara, H.; Shimizu, I. *Tetrahedron Lett.* **1991**, *32*, 4937. (c) Posner, G. H.; Nelson, T. D. *J. Org. Chem.* **1991**, *56*, 4339. (d) Posner, G. H.; Crouch, R. D.; Kinter, C. M.; Carry, J.-C. *J. Org. Chem.* **1991**, *56*, 6981. (e) Batty, D.; Crich, D. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2894. (f) Koboyashi, S.; Shibata, J.; Shimada, M.; Ohno, M. *Tetrahedron Lett.* **1990**, *31*, 1577. (g) Posner, G. H.; Kinter, C. M. *J. Org. Chem.* **1990**, *55*, 3967. (h) Hatakeyama, S.; Numata, H.; Osanai, K.; Takano, S. *J. Org. Chem.* **1989**, *54*, 3515. (i) Aurrecoechea, J. M.; Okamura, W. H. *Tetrahedron Lett.* **1987**, *28*, 4947. (j) Castedo, L.; Mascarenas, J. L.; Mourino, A. *Tetrahedron Lett.* **1987**, *28*, 2099. (k) Baggiolini, E. G.; Hennessy, B. M.; Iacobelli, J. A.; Uskokovic, M. R. *Tetrahedron Lett.* **1987**, *28*, 2095. (l) Desmaele, D.; Tanier, S. *Tetrahedron Lett.* **1985**, *26*, 4941.

(39) Makin, S. M.; Nazarova, D. V.; Kirsanova, E. A.; Smirnova, L. N. *J. Gen. Chem. USSR* **1962**, *32*, 1088. Paust, J.; Reif, W.; Schumacher, H. *Justus Liebigs Ann. Chem.* **1976**, 2194.

(40) Trost, B. M.; Chan, C.; Ruhter, G. *J. Am. Chem. Soc.* **1987**, *109*, 3486.

Discussion

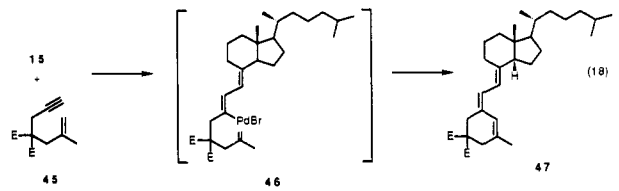
Previous work on the cycloisomerization of enynes (eq 6) indicated that the efficacy of the reaction depended upon tether length and substitution. Optimum but not necessarily required for cyclization is a tether length of three atoms (to form a five-membered ring) and geminal substituents. This, combined with the observation that a bidentate ligand shut down the reaction,[41] suggested that an initial complex such as **38** wherein the enyne functions as a bidentate ligand to Pd(2+) is a mandatory intermediate. Slippage from a π to a σ complex (**38** → **39**) then



40 **38** **39**

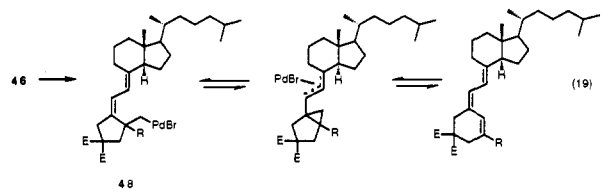
initiates the sequence of bond-forming reactions. Subsequent cyclization of **39** to form the cyclopentane ring appears less sensitive to tether length and substitution since cyclizations involving generation of the vinylpalladium species **39** via oxidative addition of Pd(0) to a vinyl bromide show diminished dependence on these factors. Bidentate coordination may also account for the chemo- and regioselectivity of the hydropalladation step although, to the extent that errors may occur, they can be rectified by β-hydrogen insertion by palladium. Obviously increasing tether length and removing geminal substituents diminishes the favorability of the bidentate coordination.

Extrapolating from the proposed mechanism for the cycloisomerization using a catalytic system derived from a Pd(0) complex, acetic acid, and a ligand,[15] we propose the mechanism for this alkylative cyclization as depicted in Scheme III. As above, bidentate coordination may be important in controlling the chemo- and regioselectivity of the conversions of **41** and **42**. If so, neither a three-atom tether nor geminal substitution plays an important role in alkylative cyclization considering the efficiency of the cyclization reported herein. Regioselectivity for the intramolecular carbapalladation (**42** → **43** → **44**) may also depend upon both tether and substituents. For example, alkylative cyclization of enyne **45** with vinyl bromide **15** produces only triene **47** which arises by a formal intramolecular carbametalation of **46** in the reverse sense (eq 18). The increased tether length of the enyne would be expected to disfavor an analogous process.



15 **45** **46** **47** (18)

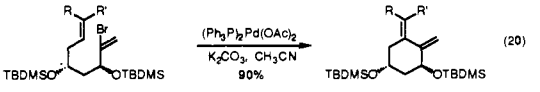
Alternatively, rearrangement of the kinetic carbametalation product **48** as in eq 19 may account for the abnormal alkylative cyclization. If this mechanism should be operative, the difference



46 **48** (19)

may be attributed to the inability of **48** (R = CH_3) to undergo β-hydrogen insertion, whereas that is not the case with enyne **26**. However, since the presence of such a quaternary center is not required in other cases, this explanation is less appealing.

The effectiveness of the internal carbapalladation is clearly related to the method of generation of the vinylpalladium species. The contrast between the hydropalladation and carbapalladation approaches for creation of the A ring illustrates the sensitivity toward the exact environment around palladium. Intramolecular Heck vinylations further highlight this point.[43] The palladium-catalyzed cyclization depicted in eq 20 produced the di-

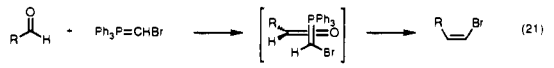


a) R = CO_2CH_3, R' = H b) R = H, R' = CO_2CH_3 (20)

alkylidenecyclohexane with high stereospecificity in excellent yield regardless of olefin geometry.[38b] Since the nature of the exact ligands on palladium at the time of cyclization for the various methods is not known, we can only suggest that exploration of this point would likely be quite revealing in optimizing palladium-catalyzed cyclizations.[44]

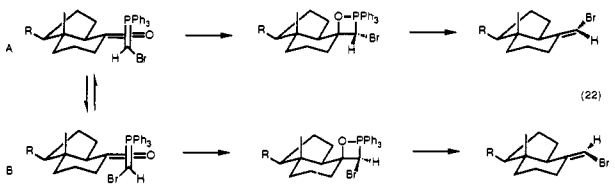
The danger of model studies is also illustrated by these studies since the model reactions proved more difficult than the main objective. The source of the complication in the model system lay with the high reactivity of the product. As noted, the simple trienes **27** and **28** showed a high sensitivity to oxygen. They also showed a tendency to undergo *Z* to *E* olefin isomerizations as revealed by the detection of small amounts of the trienes **29** and **30**. Similar isomers were not detected in the synthesis of either alphacalcidiol or calcitriol.

The high *E* geometrical selectivity of the olefination is remarkable in light of the known propensity of (bromomethylene)triphenylphosphorane to undergo *Z*-selective additions to aldehydes.[22] The latter is nicely rationalized in terms of the $\pi_{2a} + \pi_{2s}$ type addition according to eq 21.[45] Applying this



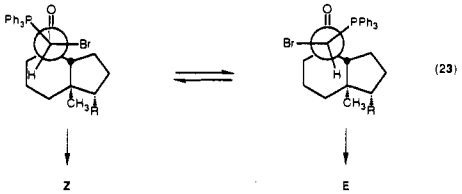
(21)

mechanism to the reaction with Grundmann's ketone should lead to a *Z* selectivity (eq 22, path A) that is not seen. On the other hand, the dipole–dipole effect present in this transition-state geometry should disfavor it relative to the alternative depicted in eq 22, path B. Because of the relatively small steric bulk of bromide, such dipole effects may become dominant.



(22)

However, such an asychronous cycloaddition mechanism, while reasonably established for aldehyde partners, may not apply to ketone partners. A mechanism involving nucleophilic addition to a betaine as in eq 23 should also be considered. In this case,



(23)

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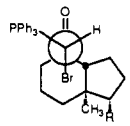
the steric bias might be anticipated to parallel the Wittig–Horner olefination which produces the *E* isomer. These two results may be understood by invoking a nearly eclipsed transition state as depicted in eq 23 arising from the charge attraction between phosphorus and oxygen. Steric effects then favor the observed *E* isomer. Nevertheless, the very small effective steric bulk of bromide (*A* value, 0.38 kcal/mol)[46] makes steric effects alone a less appealing rationale. Thus, a transition-state geometry leading to a betaine that minimizes both eclipsing and dipole interactions as depicted in **49** may be most appealing.



49

Conclusion

Palladium-catalyzed reactions offer new insights into synthetic strategies with construction of steroids and related compounds, as represented by the vitamin D metabolites, being very attractive targets. The extraordinary developments in the clinical prospects for vitamin D metabolites and analogues make them especially important. Methods for attaching the steroid side chain based upon allylic alkylations may apply for construction of the vitamin D side chains.[47] Alkylative cyclization now provides a simple convergent strategy for creating in a single step by a very simple operation not only the requisite triene but also the A ring of vitamin Ds and their analogues from a simple enyne and a CD unit. The effectiveness of this strategy is indicated by the approximately 10% overall yield for the 10 linear steps plus two for correction of diastereochemistry from ethyl vinyl ether and Grundmann's ketone for the synthesis of alphacalcidiol. The excellent chemoselectivity of such palladium-catalyzed reactions should allow broad application for the synthesis of analogues. Only the CD unit remains as a target for new synthetic designs based upon newly developed palladium-catalyzed reactions.

Experimental Section

General. All reactions were run under a nitrogen atmosphere in flame-dried glassware unless otherwise indicated. Anhydrous solvents or reaction mixtures were transferred via an oven-dried syringe or cannula. The following solvents and reagents were distilled prior to use: ethereal solvents from sodium benzophenone ketyl; toluene and benzene from LAH or sodium metal. Other solvents were utilized at their commercial level of purity. Palladium acetate was used as provided by Johnson–Matthey. Tris(dibenzylideneacetone)dipalladium–monochloroform complex ($Pd_2dba_3 \cdot CHCl_3$) was prepared by the procedure of Ibers.[35] Flash chromatography, according to the method of Still,[48] employed E. Merck silica gel (kieselgel 60, 200–400 mesh). Analytical thin-layer chromatography was performed with 0.2-mm coated commercial silica gel plates (E. Merck, DC-Plastikfolien, kieselgel 60 F_{254}). Melting points were obtained on a Thomas-Hoover apparatus in open capillary tubes and are uncorrected. Boiling points are also uncorrected. Kugelrohr distillation was performed in a Büchi GKR-50 glass tube oven.

Proton nuclear magnetic resonance (^1H NMR) data were obtained at 200 MHz on a Varian-200, at 300 MHz on a Varian GEM-300, or at 400 MHz on a Varian XL-400 spectrometer. Chemical shifts are reported in delta (δ) units, in parts per million (ppm) downfield from tetramethylsilane, or in ppm relative to the singlet at 7.24 ppm for chloroform-*d*. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet; and b, broad. Coupling constants are reported in herz (Hz). Carbon-13 nuclear magnetic resonance (^{13}C NMR) data were obtained at 75 MHz on a Varian GEM-300 or at 100 MHz on a Varian XL-400 and are reported in ppm with the center line of a triplet at 77.00 ppm for chloroform-*d*. Routine ^{13}C NMR spectra were fully decoupled by broad-band decoupling.

Infrared data were recorded in 0.1-mm path length sodium chloride cavity cells on a Nicolet 205 spectrophotometer. Absorbance frequencies are reported in reciprocal centimeters (cm^{-1}). Elemental analyses were performed by M-H-W of Phoenix, AZ. High-resolution mass spectral data (MS) were obtained from the Mass Spectrometry Resource, School of Pharmacy, University of California—San Francisco, on a Kratos MS9 spectrometer at an ionizing current of 98 mA and an ionizing voltage of 70 eV and are reported as an *m/e* (relative intensity), with accurate mass reported for the molecular ion (M^+) or suitable fragment ions.

Gas chromatographic analyses were performed on a Varian Model 3700 gas chromatograph using a 25-m × 0.25-mm poly(dimethylsiloxane) column from Alltech. Optical rotations were measured on a Jasco DIP-360 digital polarimeter using either 5- or 10-cm cells at ambient temperature.

Preparation of (Bromomethylene)cyclohexane. Potassium *tert*-butoxide (9.76 g, 79.8 mmol) was added portionwise to a mechanically stirred suspension of (bromomethylene)triphenylphosphonium bromide (34.8 g, 79.8 mmol) at −70 °C and the mixture was stirred 1 h. Slow addition of cyclohexanone (5.88 g, 6.22 mL, 60.0 mmol) at this temperature was followed by removal of the cooling bath and stirring for 2.5 h. The reaction was poured into water and extracted with hexane. After drying ($MgSO_4$), concentrating in vacuo, and chromatographing (hexane), distillation [bp 73 °C at 12 mmHg (lit. bp 77 °C at 25 mmHg)] gave 5.3 g (50% yield) of the titled compound. Rechromatographing and a second distillation gave analytically pure product. ^1H NMR ($CDCl_3$, 200 MHz): δ 5.84 (q, J = 0.4 Hz, 1 H), 2.31 (m, 2 H), 2.15 (m, 2 H), 1.10–1.00 (m, 6 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 145.3, 97.6, 35.5, 30.9, 27.6, 26.3, 26.0. Anal. Calcd for $C_7H_{11}Br$: C, 48.03; H, 6.33. Found: C, 48.14; H, 6.31.

Preparation of Vinyl Bromide 15. PDC (141 mg, 0.375 mmol) was added to a room temperature suspension of alcohol **14** (67 mg, 0.25 mmol) in 3 mL of dichloromethane. The resulting suspension was stirred 5 h and then filtered through a small pad of silica gel which was washed with ether. Concentration in vacuo gave 67 mg (100% yield) of crude Grundmann's ketone which was reacted directly.

Sodium hexamethyldisilazide (1 M in THF, 1.2 mL, 1.2 mmol) was added to (bromomethylene)triphenylphosphonium bromide (545 mg, 1.25 mmol) in 3 mL of THF at −60 °C. After 1 h, a solution of the above ketone in 0.5 mL of THF was added, and the cooling bath was then removed. After 1 h at room temperature, hexanes were added and the suspension was filtered over a small pad of silica gel which was washed with hexanes. After concentration, the oily residue was chromatographed (pentane, R_f = 0.92) to afford the bromide **15** as a colorless viscous oil (53 mg, 62% over two steps), $[\alpha]_D$ = +103° (*c* 1.63, CH_2Cl_2). IR (neat): 2952, 2869, 1632, 1467 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 5.62 (bs, 1 H), 2.85 (m, 1 H), 2.22–0.95 (m, 19 H), 0.90 (d, 3 H, J = 6 Hz), 0.83 (d, 6 H, J = 7 Hz), 0.52 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 145.5, 97.4, 55.8 (double peak), 45.4, 39.7, 39.3, 35.9 (double peak), 30.9, 27.8, 27.4, 23.6, 22.6, 22.4, 21.8, 18.6, 11.6. Anal. Calcd for $C_{19}H_{33}Br$: C, 66.85; H, 9.74; MW, 342.1745 and 340.1765. Found: C, 67.00; H, 9.49; MW, 342.1750 and 340.1746.

Preparation of Vinyl Bromide 16. According to the above procedure, hydroxylated Grundmann's ketone **13** (840 mg, 3 mmol), (bromomethylene)triphenylphosphonium bromide (6.54 g, 1.50 mmol), and sodium hexamethyldisilazide (1 M in THF, 15 mL, 1.50 mmol) in 30 mL of THF gave, after 30 min at room temperature the same workup, 490 mg (46% yield) of the titled compound as a colorless oil which yellows upon standing, $[\alpha]_D$ = +91.4° (*c* 2.79, $CHCl_2$). IR (neat): 3400 (b), 2962, 1631, 1467, 1377 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 5.64 (bs, 1 H), 2.88 (m, 1 H), 2.05–0.85 (m, 23 H, including a singlet, 6 H, at 1.21 ppm), 0.93 (d, 3 H, J = 6 Hz), 0.56 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 145.4, 97.4, 71.0, 55.8, 55.7, 45.4, 44.2, 36.2, 35.8, 30.9, 29.2, 29.0, 27.4, 22.4, 21.8, 20.6, 18.6, 11.6. Anal. Calcd for $C_{19}H_{33}BrO$: C, 63.86; H, 9.31; MW, 358.1694 and 356.1715. Found: C, 63.66; H, 9.46; MW, 358.1681 and 356.1727.

Preparation of 1,1-Dimethoxy-3-(*tert*-butyldiphenylsiloxy)-5-hexyne (19a). A solution of 3,3-dimethoxypropanal[25] (1.18 g, 10 mmol) in 10 mL of ether was added dropwise to a solution of allenylmagnesium bromide at 0 °C prepared from 1.8 g (15 mmol) of propargyl bromide and magnesium (400 mg, 16.5 mg·atom) in 40 mL of ether containing a trace of mercuric chloride. Upon completion of the addition, addition of water quenched the reaction. After further extraction of the water layer with ether, drying the combined ether layers ($MgSO_4$) and concentrating in vacuo gave 1.6 g of the crude alcohol. To the above alcohol (1.6 g) in dry DMF (10 mL) were successively added imidazole (1.7 g, 25 mmol) and *tert*-butyldichlorodiphenylsilane (3.33 mL, 12.5 mmol). The resulting brown solution was heated at 55 °C for 18 h, cooled, and poured into water (150 mL) and ethyl ether (150 mL). The organic layer was separated and then extracted with ethyl ether (50 mL). The combined organic phases were carefully washed with 10% aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo. Chromatography of the oily residue (hexanes/ethyl ether 5:1, R_f = 0.4) afforded the titled compound

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(3.96 g, 78% from 3,3-dimethoxypropanal) as a colorless oil. IR (neat): 3305, 2929, 2850, 2102, 1580, 1458, 1420 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.60–7.55 and 7.45–7.30 (2 m, 10 H), 4.55 (dd, 1 H, J = 6 and 7 Hz), 3.97 (m, 1 H), 3.18 and 3.13 (2 s, 6 H), 2.37 (complex AB, 2 H), 1.92 (m, 3 H), 1.05 (s, 9 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 136.1, 134.2, 133.8, 129.9, 129.8, 127.8, 127.7, 101.7, 80.8, 70.5, 68.3, 52.8, 51.9, 38.8, 27.0, 26.7, 19.7. HRMS: calcd for $C_{19}H_{19}O_2Si$ ($M^+ - t\text{-}C_4H_9 - CH_3OH$) 307.1154, found 307.1165.

Preparation of 1,1-Diethoxy-3-(*tert*-butyldiphenylsiloxy)-5-hexyne (19b). Boron trifluoride etherate (0.07 mL) was added to a suspension of mercuric oxide (0.7 g) in 15 mL of dry acetone. While we carefully maintained a temperature of 0 °C, 90 mL (0.93 mmol) of ethyl vinyl ether was added dropwise. Upon completion of the addition, the temperature was allowed to rise to ambient temperature. After 1 h at room temperature, potassium carbonate (0.5 g) was added and the resulting suspension was vigorously stirred for 2 h. Filtration to remove the inorganic salts followed by distillation (two times) afforded 45 g (67%) of 1,1-diethoxy-3-butene (**18**) as a colorless liquid, bp 134 °C.[26]

At −78 °C, ozone in oxygen was bubbled into a solution of 1,1-diethoxy-3-butene (2.88 g, 20 mmol) in dichloromethane (40 mL) until a blue color persisted. The flask was then purged with oxygen for 30 min. Decantation at low temperature allowed the separation of most of the condensed water. Triphenylphosphine (5.25 g) was added in one portion, and the cold bath was then removed since reduction of the ozonide which is slightly exothermic occurred smoothly only around room temperature. After being stirred 2 h at room temperature, the solution was dried ($MgSO_4$) and concentrated in vacuo. The triphenylphosphine oxide present in the oily residue was crystallized by successive addition of pentane (20 mL) and ethyl ether (50 mL) and removed by filtration. The resulting pentane/ethyl ether solution of 3,3-diethoxypropanal (**17b**) was redried ($MgSO_4$) and added dropwise to a solution of allenylmagnesium bromide (prepared from 40 mmol of propargyl bromide and 40 mg·atom magnesium in 50 mL of ethyl ether) at 0 °C. After 15 min at room temperature, water (5 mL) was slowly added. After decantation and extraction of the wet salts with ethyl ether (2 × 20 mL), the combined organic phases were dried ($MgSO_4$), concentrated, and distilled (Kugelrohr) to afford 2.71 g (73% from **18**) of 1,1-diethoxy-3-hydroxy-5-hexyne, bp 140–145 °C at 0.1 mmHg. IR (neat): 3450 (b), 2398, 2977, 2931, 1376, 1346 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 4.72 (t, 1 H, J = 6.5 Hz), 3.95 (m, 1 H), 3.80–3.45 (m, 4 H), 2.44 and 2.33 (complex AB, 2 H), 2.06 (t, 1 H, J = 2.5 Hz), 1.95 and 1.82 (complex AB, 2 H), 1.21 (t, 6 H, J = 7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 101.6, 80.6, 70.3, 66.6, 62.0, 61.2, 38.9, 26.7, 14.9, 14.8. HRMS: calcd for $C_{10}H_{18}O_3$ 186.1255, found 186.1244.

Silylation of 1.86 g (10 mmol) of the alcohol as above with imidazole (2.1 g, 30 mmol) and *tert*-butylchlorodiphenylsilane (4.12 g, 15 mmol) in 10 mL of DMF gave 3.52 g (83% yield) of the titled products. IR (neat): 3311, 2973, 2932, 2859, 1473, 1428, 1377 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.75–7.65 and 7.50–7.30 (2 m, 10 H), 4.68 (bt, 1 H J = 6.5 Hz), 4.00 (m, 1 H), 3.62–3.17 (m, 4 H), 2.34 and 2.23 (complex AB, 2 H), 2.08–1.86 (m, 3 H), 1.12 (t, 3 H, J = 7 Hz), 1.08 (t, 3 H, J = 7 Hz), 1.06 (s, 9 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 136.1, 134.2, 133.9, 129.8, 127.8, 127.7, 100.1, 80.9, 70.4, 68.3, 61.0, 60.3, 27.0, 26.8, 19.1, 15.1, 15.0. Anal. Calcd for $C_{26}H_{36}O_3Si$: C, 73.54; H, 8.54. Found: C, 73.75; H, 8.74.

Preparation of *anti*- and *syn*-3-Hydroxy-5-(*tert*-butyldiphenylsiloxy)-1-octen-7-yne (21 and 22). A. From Dimethyl Acetal. A mixture of acetal **19a** (3.1 g, 7.8 mmol) and 4 mL of trifluoroacetic acid in 10 mL of THF containing 2 mL of water was stirred for 6.5 h at room temperature. The reaction was quenched by being poured into a mixture of 30 mL of water containing 5 g of potassium carbonate and ether. After the aqueous phase was extracted with ether, the combined organic fractions were washed with 10% aqueous sodium chloride, dried ($MgSO_4$), and concentrated in vacuo to give 2.7 g of product which was immediately dissolved in 10 mL of THF. The resultant solution was added dropwise to vinylmagnesium bromide (1 M in THF, 20 mL, 20 mmol) at −78 °C. After 45 min, water was added to the cold reaction and the resultant mixture was poured into a two-phase ether–aqueous ammonium chloride mixture. After the aqueous phase was extracted with ether, the combined organic fractions were washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated. The oily residue was chromatographed (hexanes/ethyl ether, 3:1, R_f = 0.3) to afford 1.79 g (61% yield from **19a**) of a diastereoisomeric mixture of **21** and **22** (ca. 1:1.5). This mixture was separated by MPLC (hexanes/ethyl ether, 4:1, R_f = 0.37 (major) and 0.42 (minor) with three developments) to afford successively 590 mg of the anti isomer **21**, 100 mg of diastereomeric mixture, and 980 mg of the syn isomer **22**.

B. From Diethyl Acetal. According to the above procedure, the diethyl acetal **19b** (510 mg, 1.2 mmol) in a mixture of 2 mL of trifluoroacetic acid, 1 mL of water, and 5 mL of THF for 1.5 h followed immediately by reaction with vinylmagnesium bromide gave 355 mg (78%) of the same diastereomeric mixture as above.

20. IR (neat): 3300, 2980, 2850, 1730, 1580, 1470, 1425 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 9.71 (bs, 1 H), 7.75–7.60 and 7.50–7.30 (2 m, 10 H), 4.31 (q, 1 H, J = 5 Hz), 2.68 (m, 2 H), 2.36 (m, 2 H), 1.95 (t, 1 H, J = 2.5 Hz), 1.00 (s, 9 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 201.5, 136.0, 135.0, 133.6, 130.2, 130.1, 128.0, 127.9, 80.0, 71.3, 67.3, 49.7, 26.9, 26.7, 19.0. MS (GC-MS): m/z = 293 ($M^+ - t$-Bu), 249, 236, 199, 183.

21. IR (neat): 3410 (b), 3298, 2912, 2851, 2117, 1585, 1465, 1420 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.75–7.65 and 7.48–7.32 (2 m, 10 H), 5.79 (ddd, 1 H, J = 6, 11, and 17 Hz), 5.18 (bd, 1 H, J = 17 Hz), 5.03 (bd, 1 H, J = 11 Hz), 4.36 (m, 1 H), 4.11 (m, 1 H), 2.33 (complex AB, 2 H), 1.90 (t, 1 H, J = 2 Hz), 1.71 (complex AB, 2 H), 1.05 (s, 9 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 141.1, 136.1, 133.7, 133.3, 130.2, 130.1, 128.0, 127.9, 114.2, 80.5, 70.6, 69.6, 69.2, 42.0, 26.8, 26.3, 19.0. Anal. Calcd for $C_{24}H_{30}O_2Si$: C, 76.14; H, 7.99. Found: C, 76.36; H, 7.77.

22. IR (neat): 3410 (b), 3298, 2912, 2851, 2117, 1585, 1465, 1420 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.75–7.57 and 7.47–7.32 (2 m, 10 H), 5.76 (ddd, 1 H, J = 6, 11, and 17 Hz), 5.13 (bd, 1 H, J = 17 Hz), 5.02 (bd, 1 H, J = 11 Hz), 4.31 (m, 1 H), 4.03 (bq, 1 H, J = 7 Hz), 2.28 (complex AB, 2 H), 1.95–1.78 (m, 3 H), 1.05 (s, 9 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 140.8, 136.0, 133.9, 133.3, 130.1, 130.0, 127.9, 127.8, 114.5, 80.7, 70.7 (double peak), 70.4, 42.7, 26.9, 26.7, 19.0. Anal. Calcd for $C_{24}H_{30}O_2Si$: C, 76.14; H, 7.99. Found: C, 76.13; H, 8.07.

Determination of Relative Stereochemistry by Formation of Acetonide 23. To a stirred solution of alcohol **22** (190 mg, 0.5 mmol) in THF (2 mL) was added TBAF (1 M solution in THF, 0.6 mL, 1.2 equiv) at 0 °C. After 1.5 h, the reaction mixture was diluted with hexanes (2 mL) and filtered through silica gel (hexanes/ethyl acetate, 1:1, R_f = 0.5) to afford 63 mg of a pale yellow oil (90%). To a solution of this oil in 2,2-dimethoxypropane (2 mL) was added camphorsulfonic acid (10 mg, ca. 0.01 equiv). The mixture was stirred overnight at room temperature, poured into ethyl ether (20 mL), and washed with 5% aqueous $NaHCO_3$. The organic phase was dried ($MgSO_4$) and carefully concentrated to afford 48 mg of acetonide **23** (45% from **22**). IR (neat): 3312, 2933, 2924, 2855, 1464, 1380 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 5.81 (ddd, 1 H, J = 6, 11, and 17 Hz), 5.26 (dt, 1 H, J = 1.5 and 17 Hz), 5.12 (dt, 1 H, J = 1.5 and 11 Hz), 4.35 (dddt, 1 H, J = 1.5, 2.5, 6, and 11.5 Hz), 4.00 (dddd, 1 H, J = 2.5, 5.5, 7.5, and 11.5 Hz), 2.46 (ddd, 1 H, J = 2.5, 5.5, and 17 Hz), 2.24 (ddd, 1 H, J = 2.5, 7.5, and 17 Hz), 1.99 (t, 1 H, J = 2.5 Hz), 1.71 (dt, 1 H, J = 2.5 and 13 Hz), 1.45 (s, 3 H), 1.40 (s, 3 H), 1.2–1.4 (m, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.6, 115.8, 112.4, 99.0, 80.1, 70.4, 70.1, 67.4, 35.7, 29.9 (CH_3), 26.0, 19.6 (CH_3). HRMS: calcd for $C_9H_{13}O_2$ ($M^+ - CH_3$) 165.0915, found 165.0924.

Conversion of *syn*-23 to *anti*-21. DEAD (0.70 mL, 4.45 mmol) was added to a stirred solution of triphenylphosphine (1.62 g), benzoic acid (720 mg), and alcohol **22** (1.53 g, 4.05 mmol) in THF (40 mL) at room temperature. Since TLC analysis indicated the presence of some starting material after 1 h, an additional portion of DEAD (0.05 mL) was added. The reaction mixture was then poured into a suspension of water (100 mL) and pentane (100 mL). The organic phase was separated and the aqueous phase extracted with another 100 mL of pentane. The combined organic phases were dried, concentrated, and chromatographed (pentane/ethyl ether, 10:1, R_f = 0.4) to afford 1.57 g of colorless oily material **12**, which still contained a small amount of triphenylphosphine. IR (neat): 3300, 2930, 2855, 1740, 1440, 1270 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.90–7.00 (m, 15 H), 5.73 (ddd, 1 H, J = 6, 11, and 17 Hz), 5.51 (m, 1 H), 5.18 (d, 1 H, J = 17 Hz), 5.08 (d, 1 H, J = 11 Hz), 3.88 (m, 1 H), 2.33–1.85 (m, 5 H), 0.93 (s, 9 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.8, 136.8, 136.0, 135.9, 134.2, 132.9 (double peak), 130.5, 129.7, 128.3, 127.7, 127.6, 116.7, 80.6, 72.3, 70.8, 68.1, 41.0, 27.3, 26.8, 19.0.

To a stirred solution of the above benzoate in dichloromethane (50 mL) at −78 °C was added DIBAL-H (1.47 M in hexanes, 6.5 mL, 9.56 mmol). The solution was stirred 15 min, water (2 mL) was added, and the resulting suspension was stirred another 30 min at this temperature. The cold bath was removed, and the reaction mixture was poured into saturated ammonium chloride (100 mL) and dichloromethane (100 mL). The aqueous phase was extracted with dichloromethane (100 mL). The combined organic phases were dried and concentrated, and the oily residue (1.47 g) was subjected to MPLC (same column and conditions as previously) to afford 1.12 g (73% from **22**) of pure **21**.

Preparation of *anti*-3-(*tert*-Butyldimethylsiloxy)-5-(*tert*-butyldiphenylsiloxy)-1-octen-7-yne (26). A solution of alcohol **21** (378 mg, 1.00 mmol), imidazole (210 mg, 3.00 mmol), and *tert*-butylchlorodimethylsilane (225 mg, 1.50 mmol) in 3 mL of dry DMF was heated at 55 °C for 3 h at which time it was poured into a mixture of water and ether.

After extraction of the aqueous layer with additional ether, the combined organic layers were washed with water, dried ($MgSO_4$), and concentrated in vacuo to give, after chromatographic purification (hexanes/ethyl acetate, 20:1, R_f = 0.35), 430 mg (87% yield) of the titled compound. Repeating this reaction using scalemic alcohol (100 mg, 0.264 mmol, 98% ee) gave 117 mg (90% yield) of scalemic silyl ether **26** $[\alpha]_D$ = −5.3° (*c* 1.74, CH_2Cl_2). IR (neat): 3313, 3073, 2957, 2931, 2858, 2132, 1590, 1473, 1428 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.73–7.63 and 7.47–7.30 (2 m, 10 H), 5.59 (ddd, 1 H, *J* = 6.5, 11, and 17 Hz), 5.02–4.85 (m, 2 H), 4.21 (bq, 1 H, *J* = 6.5 Hz), 3.90 (bq, 1 H, *J* = 5.5 Hz), 2.29 (complex AB, 2 H), 1.91 (t, 1 H, *J* = 2 Hz), 1.84 (t, 2 H, *J* = 6 Hz), 1.05 (s, 9 H), 0.80 (s, 9 H), −0.3 (s, 6 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 141.3, 136.1, 134.3, 134.0, 129.8, 127.8, 127.7, 114.3, 81.1, 71.0, 70.3, 68.5, 44.1, 26.8, 26.6, 25.6, 19.1, 17.9, −4.7, −5.2. Anal. Calcd for $C_{30}H_{44}O_2Si_2$: C, 73.11; H, 9.00. Found C, 73.27; H, 8.88.

Preparation of *syn*-3-(*tert*-Butyldimethylsiloxy)-5-(*tert*-butyldiphenylsiloxy)-1-octen-7-yne (31). According to the above procedure starting with syn alcohol **22** (378 mg, 1.00 mmol) gave 435 mg (88% yield) of the titled compound as a colorless oil. IR (neat): 3313, 3073, 2957, 2931, 2858, 2132, 1590, 1473, 1428 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.75–7.65 and 7.48–7.32 (2 m, 10 H), 5.63 (ddd, 1 H, *J* = 6.5, 11, and 17 Hz), 5.06–4.90 (m, 2 H), 4.09 (bq, 1 H, *J* = 6.5 Hz), 3.94 (bq, 1 H, *J* = 5.5 Hz), 2.31 (complex AB, 2 H), 2.06–1.58 (m, 3 H), 1.07 (s, 9 H), 0.81 (s, 9 H), −0.03 (s, 3 H), −0.06 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 141.8, 136.1, 134.4, 134.2, 129.8, 127.8, 127.7, 114.3, 81.2, 71.7, 70.2, 69.1, 45.0, 27.2, 26.8, 25.7, 19.1, 17.9, −4.4, −5.1. Anal. Calcd for $C_{30}H_{44}O_2Si_2$: C, 73.11; H, 9.00. Found C, 72.91; H, 8.86.

Kinetic Resolution of 21. Freshly distilled titanium tetraisopropoxide (1.1 mL, 3.7 mmol) was added to a stirred suspension of freshly activated molecular sieves (400 mg), racemic allyl alcohol **21** (1.4 g, 3.7 mmol, azeotropically dried prior to use), and D-(+)-dicyclohexyl tartrate (1.39 g, 1.2 equiv, recrystallized four times) in dichloromethane (30 mL) at −20 °C. The reaction mixture was swirled for 30 min, and then *tert*-butyl hydroperoxide (3 M in isooctane, 0.82 mL, 0.66 equiv, dried over sieves prior to use) was added at −40 °C. The reaction mixture was placed in the freezer (−20 °C without stirring) for 19 days and then poured in an ice cold suspension of ferrous sulfate heptahydrate (17.5 g), tartaric acid (9 g), water (120 mL), and dichloromethane (100 mL). The organic layer was separated, and the aqueous phase was extracted with dichloromethane (3 × 100 mL). The organic phases were combined, washed with brine, dried, and concentrated. Chromatography of the residue (pentane/ethyl ether, 2:1, R_f = 0.6) afforded 642 mg (46%) of scalemic starting material **21** (98% ee by NMR analysis of the (*S*)-(+)-*O*-methylmandelic ester with signals at δ 3.35, major, and δ 3.32, minor) $[\alpha]_D$ = −19.7° (*c* 1.25, CH_2Cl_2).

Reaction of (Bromomethylene)cyclohexane and Enyne 26. A suspension of palladium acetate (2.2 mg, 0.01 mmol) and triphenylphosphine (7.8 mg, 0.03 mmol) in toluene (1 mL) and triethylamine (1 mL) was stirred for 30 min at room temperature and for 3 min at reflux. After the suspension was cooled to room temperature, (bromomethylene)-cyclohexane (40 mg, 0.23 mmol) and enyne **26** (50 mg, 0.1 mmol) were successively added. The resulting dark red-brown solution was heated at reflux for 1.5 h. Hexanes (5 mL) were added, and the resulting suspension was filtered through a small pad of silica gel, washing with 1:4 ethyl ether/hexanes. After concentration in vacuo, 90 mg of crude yellow oil was obtained and immediately dissolved in THF (2 mL). To this solution was added TBAF (1 M solution in THF, 0.5 mL, 0.5 mmol) at −78 °C in the dark, and the reaction was slowly warmed to room temperature and stirred at this temperature for 16 h and then purified by MPLC (hexanes/ethyl acetate, 1:1 with 0.1% NEt_3, R_f = 0.2) to afford 4.5 mg (20%) of **27**, contaminated by 10% of **29**, 12 mg (50%) of **28**, and 2 mg of a mixture containing **28** (major) and its presumed *E* isomer **30**. The spectral data for the products agreed with the reported data.

27. ^1H NMR ($CDCl_3$, 300 MHz): δ 6.30 and 6.08 (AB, 2 H, *J* = 12 Hz), 5.30 (bs, 1 H), 4.99 (bs, 1 H), 4.41 (bt, 1 H, *J* = 5 Hz), 4.19 (m, 1 H), 2.57 (dd, 1 H, *J* = 4 and 12 Hz), 2.34–1.90 (m, 7 H), 1.60–1.40 (m, 6 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 147.6, 144.2, 133.2, 125.0, 118.4, 112.4, 71.2, 66.8, 55.4, 42.7, 37.4, 29.0, 28.3, 27.5, 26.6. HRMS calcd for $C_{15}H_{22}O_2$: 234.1620, found: 234.1612.

28. ^1H NMR ($CDCl_3$, 300 MHz): δ 5.85 (d, 1 H, *J* = 12 Hz), 5.70–5.60 (m, 2 H), 4.17 (bs, 1 H), 4.08 (m, 1 H), 2.42 (dd, 1 H, *J* = 4 and 12 Hz), 2.19–1.92 (m, 5 H), 1.58 (s, 3 H), 1.55–1.45 (m, 4 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 136.3, 133.8, 131.4, 129.6, 126.7, 70.3, 64.0, 40.5, 39.0, 26.9, 25.6, 22.7, 21.9, 17.0.

Reaction of (Bromomethylene)cyclohexane and Enyne 31. According to the above procedure, enyne **31** (50 mg, 0.10 mmol) gave 15 mg (65%) of desilylated products **32** and **33** as well as trace amounts of the corresponding *E* isomer. Further chromatography gave 5.5 mg (24%) of pure triene **32**. ^1H NMR ($CDCl_3$, 300 MHz): δ 5.87 (d, 1 H, *J* = 12 Hz), 5.60–5.70 (m, 2 H), 4.22 (m, 1 H), 3.99 (m, 1 H), 1.80–2.35 (m, 8 H), 1.73 (bs, 3 H), 1.45–1.65 (m, 4 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 136.4, 133.7, 130.2, 129.3, 128.7, 127.2, 69.0, 65.9, 38.4, 36.7, 26.9, 25.6, 22.7, 21.9, 17.4.

Preparation of Alphacalcidiol (7). After a solution of $(dba)_3Pd_2$·$CHCl_3$ (25 mg, 0.016 mmol) and TPP (40 mg, 0.153 mmol) in 2.5 mL of toluene and 2.5 mL of triethylamine was stirred 15 min, a solution of scalemic enyne **26** (156 mg, 0.316 mmol) and vinyl bromide **15** (162 mg, 0.475 mmol) in 0.5 mL of toluene was added. The resultant mixture was heated at reflux for 1.5 h and directly filtered through a pad of silica gel, washing with pentane. After concentration in vacuo, chromatography (pentane/dichloromethane, 10:1) gave 49 mg (30% recovery) of vinyl bromide **15**, 33 mg of silylated prvitamin **35**, and 163.5 mg of silylated vitamin **34**. Heating the silylated previtamin fraction in toluene at 80 °C for 1 h, concentrating in vacuo, and purifying by chromatography as above gave an additional 17.5 mg of silylated vitamin for a total of 181 mg (76% yield) as a colorless oil. IR (neat): 2952, 2930, 1471, 1428, 1361, 1252 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.72–7.63 and 7.45–7.30 (2 m, 10 H), 6.09 (AB, 2 H, *J* = 12 Hz), 5.22 (bs, 1 H), 4.88 (bs, 1 H), 4.47 (m, 1 H), 4.23 (m, 1 H), 2.79 (bs, 1 H, *J* = 13 Hz), 2.30 (bs, 1 H, *J* = 13 Hz), 2.18 (dd, 1 H, *J* = 6.5 and 13 Hz), 2.03–0.80 (m, 49 H), 0.51 (s, 3 H), 0.03 and 0.01 (2 s, 6 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 149.0, 141.3, 136.1, 136.0, 135.1, 134.8, 134.4, 129.7 (double peak), 127.8, 127.7, 123.7, 117.9, 110.5, 71.2, 68.7, 56.6, 56.3, 45.7, 45.0, 44.4, 40.5, 39.3, 36.0, 28.8, 27.8, 27.5, 26.8, 25.7, 23.7, 23.4, 22.6, 22.4, 22.0, 19.0, 18.6, 18.1, 11.7, 5.1, −5.4.

TBAF (1 M in THF, 2 mL, 2.0 mmol) was added dropwise to the above product **34** (181 mg, 0.24 mmol) in 1 mL of THF at room temperature. After 40 h, the mixture was filtered through a pad of silica gel, eluting with ethyl acetate, concentrated in vacuo, and chromatographed (ethyl acetate) to give 75 mg (79%) of the titled compound, mp 133–134 °C (lit.[7a] mp 132–133 °C), $[\alpha]_D$ = +26.5° (*c* 0.89, ethyl ether), after recrystallization from pentane. IR (neat): 3400 (b), 2954, 2869, 1645, 1631, 1605, 1467, 1377, 1366, 1054, 956, 909 cm^{-1}. UV (ethyl ether): λ_{max} 263 nm, ε = 18 800 (lit.[7a] λ_{max} 264 nm, ε = 20 200). ^1H NMR ($CDCl_3$, 400 MHz): δ 6.39 (d, 1 H, *J* = 12 Hz), 6.02 (d, 1 H, *J* = 12 Hz), 5.32 (bs, 1 H), 5.01 (bs, 1 H), 4.43 (m, 1 H), 4.23 (m, 1 H), 2.82 (bd, 1 H, *J* = 11.5 Hz), 2.60 (dd, 1 H, *J* = 3.5 and 13.5 Hz), 2.32 (dd, 1 H, *J* = 7 and 13.5 Hz), 2.05–1.83 (m, 4 H), 1.73–0.95 (m, 18 H), 0.92 (2d, 3 H, *J* = 5 Hz), 0.87 (2d, 6 H, *J* = 6.5 Hz), 0.55 (3 H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 147.8, 143.6, 132.9, 125.2, 117.0, 111.9, 70.8, 66.8, 56.5, 56.3, 45.8, 45.1, 42.7, 40.3, 39.3, 36.0, 28.9, 27.8, 27.5, 23.7, 23.4, 22.6, 22.4, 22.1, 18.6, 11.8. HRMS: calcd for $C_{27}H_{44}O_2$ 400.3341, found 400.3342.

Preparation of Calcitriol (3). After a mixture of $(dba)_3Pd_2$·$CHCl_3$ (30 mg, 0.0192 mmol) and TPP (47 mg, 0.179 mmol) in 2 mL of toluene and 3 mL of triethyl amine was stirred for 10 min at room temperature, a solution of bromide **16** (327 mg, 0.916 mmol) and scalemic enyne **26** (299 mg, 0.61 mmol) in 1 mL of toluene was added. After being heated at reflux for 2 h and diluted with 5 mL of pentane, the reaction mixture was filtered through a pad of silica gel, eluting with ether. Rapid chromatography (ethyl ether/pentane, 2:1) gave 650 mg of a mixture of the vinyl bromide, silylated previtamin, and silylated calcitriol. TBAF (0.5 M in THF, 6 mL, 3.0 mmol) was added to the mixture. After 30 h at room temperature, chromatography (ethyl acetate) gave 132 mg (52% from **26**) of calcitriol, mp 109–114 °C (lit.[7b] mp 106–112 °C) after recrystallization from chloroform, $[\alpha]_D$ = +45.3° (*c* 0.44, ethanol). IR (neat): 1652, 1627, 1470, 1364, 1320, 1140, 1075, 1054, 915, 909 cm^{-1}. ^1H NMR (acetone-d_6, 400 MHz): δ 6.28 (d, 1 H, *J* = 12 Hz), 6.08 (d, 1 H, *J* = 12 Hz), 5.31 (bs, 1 H), 4.85 (bs, 1 H), 4.38 (m, 1 H), 4.16 (m, 1 H), 2.74 (m, 1 H, overlapped with the water peak at 2.80), 2.49 (bd, *J* = 13 Hz), 2.27 (dd, 1 H, *J* = 7 and 13.5 Hz), 1.21–2.10 (m, 19 H), 1.13 (s, 6 H), 1.06 (m, 1 H), 0.96 (d, 3 H, *J* = 6 Hz), 0.57 (s, 3 H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 150.6, 141.3, 136.5, 123.9, 118.8, 110.8, 70.5, 70.0, 66.8, 57.4, 57.0, 46.4, 46.3, 45.3, 44.3, 41.3, 37.4, 36.9, 29.5, 28.3, 24.2, 23.0, 21.4, 19.2, 12.3, total of 25 peaks out of 27 with two peaks overlapped. HRMS: calcd for $C_{27}H_{40}O$ ($M^+ - 2H_2O$) 380.3079, found 380.3079.

Preparation of 1,1,5,5-Tetramethoxy-7-hydroxy-(*E*)-2-nonen-8-yne (36). After addition of *n*-butyllithium (0.73 M in hexane, 115.6 mL, 85 mmol) to 1,1-bis(methylthio)methane (9.2 g, 85 mmol) in 210 mL of THF at −50 °C, the solution was allowed to warm to −20 °C over a period of 1 h and stirred for 2 h. Once the solution was recooled to −78 °C, 1-bromo-2-(*tert*-butyldimethylsiloxy)ethane (18.0 g, 75 mmol) was added dropwise, at which point the reaction was allowed to warm to −20 °C and kept there for 2 h. It was diluted with 300 mL of pentane, and the organic layer washed with aqueous sodium bicarbonate. After the aqueous layers were washed with additional pentane, the combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo to give 20.5 g of 1,1-bis(methylthio)-3-(*tert*-bu-

tyldimethylsiloxy)propane which was used directly in the next step. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.84 (t, J = 6 Hz, 1 H), 3.78 (t, J = 6 Hz, 2 H), 2.10 (s, 6 H), 1.94 (q, J = 6 Hz, 2 H), 0.89 (s, 9 H), 0.07 (s, 6 H).

After addition of *n*-butyllithium (7.4 M, in hexane, 9.2 mL, 68 mmol) to a solution of 1,1-bis(methylthio)-3-(*tert*-butyldimethylsiloxy)propane in 100 mL of THF at −78 °C, the solution was stirred 2 h at −12 °C. Once the solution was recooled to −78 °C, 1-bromo-4,4-dimethoxy-(*E*)-2-butene[39] (10.0 g, 51.3 mmol) was added, and the resultant reaction mixture was warmed to −20 °C over a 1-h period and stirred at that temperature for 30 min, at which point the reaction was quenched by addition of 50 mL of 5% aqueous sodium bicarbonate. Extraction with ether followed by washing of the organic layer with water and brine and drying ($MgSO_4$) gave 14.5 g (75% yield) of 1,1-dimethoxy-5,5-bis-(methylthio)-7-(*tert*-butyldimethylsiloxy)-(*E*)-2-heptene after chromatographic purification (9:1 hexane/ether). IR (CCl_4): 1700, 1680, 1255, 1055 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.99 (dt, J = 15.3 and 7.5 Hz, 1 H), 5.54 (dd, J = 15.3 and 5.9 Hz, 1 H), 4.77 (d, J = 5.9 Hz, 1 H), 3.84 (t, J = 7.1 Hz, 2 H), 3.33 (s, 6 H), 2.48 (d, J = 7.5 Hz, 2 H), 2.03 (s, 6 H), 1.93 (t, J = 7.1 Hz, 2 H), 0.89 (s, 9 H), 0.07 (s, 6 H).

Trimethyl orthoformate (2.17 g, 10 mmol) and the above thioketal (4.0 g, 10.5 mmol) were added to a suspension of cadmium carbonate (2.24 g, 13 mmol) in 36 mL of methanol at room temperature. After 15 min, four equal portions of mercuric acetate (total 3.34 g, 10.5 mmol) were added over 1 h. The reaction mixture was then filtered through Celite, washing with ethyl acetate. After the mixture was concentrated in vacuo, the residue was redissolved in ethyl acetate. The resulting solution was washed with aqueous sodium bicarbonate and brine, dried ($MgSO_4$), and concentrated in vacuo to give 3.41 g of product used directly in the next step. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.58 (dt, J = 16.0 and 6.8 Hz, 1 H), 5.53 (dd, J = 16.0 and 5.0 Hz, 1 H), 4.74 (d, J = 5.0 Hz, 1 H), 3.64 (t, J = 7.2 Hz, 2 H), 3.30 (s, 6 H), 3.18 (s, 6 H), 2.42 (d, J = 6.8 Hz, 2 H), 1.89 (t, J = 7.2 Hz, 2 H), 0.88 (s, 9 H), 0.04 (s, 6 H).

After dropwise addition of TBAF (1 M in THF, 10 mL, 10 mmol) to a solution of a the above crude product (3.41 g) in 10 mL of THF at room temperature, the reaction was stirred 2 h at which point it was quenched by addition of aqueous sodium bicarbonate. After extraction with ethyl acetate, the organic layer was washed with water and brine and dried (Na_2SO_4) to give 2.0 g (81% from thioketal) of 1,1,5,5-tetramethoxy-(*E*)-2-hepten-7-ol after chromatographic purification (silica gel, 35:65 hexane/ethyl acetate). IR (CCl_4): 3500, 1680, 1670, 1460 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.77 (dt, J = 7.2 and 16 Hz, 1 H), 5.55 (dd, J = 5.0 and 16 Hz, 1 H), 4.74 (d, J = 5.0 Hz, 1 H), 3.71 (q, J = 6 Hz, 2 H), 3.31 (s, 6 H), 3.23 (s, 6 H), 2.50 (d, J = 7.2 Hz, 2 H), 2.46 (t, J = 6 Hz, 1 H), 1.91 (t, J = 6 Hz, 1 H).

A solution of the above alcohol (1.50 g, 6.45 mmol) in 4.3 mL of dichloromethane followed by triethylamine (0.69 g, 6.88 mmol) was added to a solution of DMSO (1.30 g, 16.6 mmol) and oxalyl chloride (1.05 g, 8.25 mmol) in 14 mL of methylene chloride at −65 °C. After 15 min, additional triethylamine (2.78 g, 27.5 mmol) was added, and the reaction was allowed to stir 2 h at 0 °C, at which point it was quenched by addition of aqueous sodium bicarbonate. After extraction with ethyl acetate, the organic layer was washed with water and brine followed by drying ($MgSO_4$) and concentration in vacuo to give 1.55 g of aldehyde, which was utilized directly in the next step. IR (CCl_4): 2820, 1725, 1190, 1125, 1100 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.72 (t, J = 3 Hz, 1 H), 5.76 (dt, J = 16 and 7.0 Hz, 1 H), 5.57 (dd, J = 16 and 4.8 Hz, 1 H), 4.76 (d, J = 4.8 Hz, 1 H), 3.30 (s, 6 H), 3.25 (s, 6 H), 2.67 (d, J = 3.0 Hz, 2 H), 2.55 (d, J = 7 Hz, 2 H).

A solution of the above aldehyde (1.55 g) in 1.5 mL of THF was added to a solution of lithium acetylide prepared by adding *n*-butyllithium (1.4 M in hexane, 5.1 mL, 7.1 mmol) to acetylene (0.21 g, 8.1 mmol) in 15 mL of THF at −78 °C. Over 2 h, the temperature was raised to 0 °C, and the reaction was then quenched with aqueous sodium bicarbonate and worked up as above. Chromatographic purification (silica gel, 60:40 hexane/ethyl acetate) gave 1.12 g (49% from alcohol) of pure product. IR (CCl_4): 3840 (b), 3300, 2840, 2820, 1740, 1730, 1460, 1185, 1115, 1045 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.76 (dd, J = 16 and 8 Hz, 1 H), 5.57 (dd, J = 16 and 4.8 Hz, 1 H), 4.76 (d, J = 4.68 Hz, 1 H), 4.59 (bd, J = 9.2 Hz, 1 H), 3.45 (bs, 1 H), 3.31 (s, 3 H), 3.30 (s, 3 H), 3.25 (s, 3 H), 3.23 (s, 3 H), 2.66 (dd, J = 14.4 and 6 Hz, 1 H), 2.45 (dd, J = 14.4 and 8.0 Hz, 1 H), 2.44 (d, J = 2 Hz, 1 H), 2.20 (ddd, J = 14.8, 9.2, and 1.2 Hz, 1 H), 1.99 (dd, J = 14.8 and 2.8 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 130.7, 129.3, 102.5, 102.0, 84.2, 72.4, 58.6, 52.6, 48.2, 40.0, 36.9. Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.44; H, 8.58. Found: C, 60.51; H, 8.61.

Preparation of 2-Methylene-3-(2′,2′-dimethoxyethylidene)-5,5-dimethoxycyclohexan-1-ol (37). A portion (10%) of a solution of enyne **47** (13 mg, 0.05 mmol) in 1 mL of benzene was added to a solution of palladium acetate (1.12 mg, 0.006 mmol) and TPP (2.62 mg, 0.01 mmol) in 1 mL of benzene which had been allowed to stir at room temperature for 20 min. The mixture was warmed to 70 °C, at which point the remainder of the solution of enyne was added by syringe pump over 2 h. After an additional hour at 70 °C followed by concentration in vacuo, chromatographic purification (silica gel, 1:1 hexane/ethyl acetate) gave 4.0 mg (30% yield) of the titled product as a colorless oil. IR (CCl_4): 3500, 2950, 2920, 2825, 1538, 1250, 1123, 1100, 1050 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.74 (d, J = 6.0 Hz, 1 H), 5.15 (bs, 1 H), 5.12 (d, J = 6 Hz, 1 H), 5.03 (bs, 1 H), 4.30 (ddd, J = 5.6, 4 and 3 Hz, 1 H), 3.33 (s, 3 H), 3.32 (s, 3 H), 3.26 (s, 3 H), 3.24 (s, 3 H), 2.82 (d, J = 14.8 Hz, 1 H), 2.40 (d, J = 14.8 Hz, 1 H), 2.15 (ddd, J = 13.2, 5.6 and 2 Hz, 1 H), 2.21 (dd, J = 13.2 and 4 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.0, 138.7, 125.1, 111.4, 100.6, 99.2, 70.2, 52.3, 51.7, 48.1, 47.9, 39.4, 35.4. Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.44; H, 8.58; MW, 258.1461. Found: C, 60.51; H, 8.58; MW, 258.1471.

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