fluorine atom of the other phenyl ring is disordered between the two ortho positions; the occupancy factor of F(26) is 0.563 and that of F(22) 0.437. Positions for the two partial fluorine atoms were refined with their isotropic thermal parameters constrained to be the same and with the sum of their occupancies, as well as the sum of the occupancies of the disordered ortho hydrogens, each constrained to be 1.0. The positions of the phenyl hydrogen atoms were calculated, and they were included as fixed contributors with isotropic thermal parameters fixed at 5.6 Å^2.

NMR Spectroscopy. Fluorine spectra at 282 MHz were collected with either a Nicolet NT300 or a General Electric GN300 spectrometer, while fluorine spectroscopy at 470 MHz employed a General Electric GN500spectrometer. In all cases 10-mm samples were used with acetone-d_6 (Aldrich) as the solvent for low-temperature (−90 to 25 °C) spectra and a mixture of cyclohexanone and acetone-d_6 (60/40) as the solvent at higher temperatures (25–100 °C). The deuterium of the solvent provided a lock signal. Samples were approximately 0.01 M in solute for the low temperature studies and 0.05 M at temperatures above ambient. Sample temperatures were regulated with the controllers supplied with each instrument and are believed to be accurate to at least ±1 °C. Fluorine COSY spectra were obtained with the phase cycle of Bax[20] to give quadrature detection in both dimensions and are displayed in absolute value mode.

Theoretical line shapes for a system undergoing two-site exchange were generated by using a program based on the derivation of Johnson[21] and run on an IBM-PC. Computed spectra were compared visually to experimental spectra and the input parameters for the calculations adjusted until good agreement between observed and calculated line shapes was obtained.

Acknowledgment. This work was supported by the Hellenic Ministry of Eduction and the National Institutes of Health (Grant GM-25975).

Supplementary Material Available: X-ray crystallographic data for compound II (5 pages). Ordering information is given on any current masthead page.

(20) Bax, A. *Bull. Magn. Reson.* **1985**, *7*, 167–183.
(21) Johnson, C. S., Jr. *Adv. Magn. Reson.* **1965**, *1*, 33.

Synthesis and Biological Activity of 9,11-Dehydrovitamin D_3 Analogues: Stereoselective Preparation of 6β-Vitamin D Vinylallenes and a Concise Enynol Synthesis for Preparing the A-Ring[1a-c]

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Received March 31, 1989

The $\Delta^{9(11)}$-unsaturated vitamin D analogues **5a** and **5b** are of biochemical interest because they are incapable of tautomerizing via a [1,7]-sigmatropic hydrogen shift to a previtamin structure related to **3** and also because they possess a perturbed π-system. Vitamin **5a** was prepared in eight steps from ketone **18**, with the key steps being the stannylcuprate S_N2' displacement reaction of propargyl benzoate **22** followed by the mild and highly selective fluorodestannylation of allene **23** to afford primarily the 6β-vinylallenes **24a,b**. The enantiomerically pure vitamin D A-ring enyne **38** was prepared in seven steps from (*S*)-(+)-carvone (**29**), with the novel step in this sequence being the SmI_2–Pd^0-mediated transformation of epoxy propargyl acetate **35** to enynol **37**. These two methods were then used to synthesize the trihydroxylated analogue **5b** in 13 steps from (*S*)-(+)-carvone. The analogue **5b** differs from the biologically active hormonal form of vitamin D, 1α,25-dihydroxyvitamin D_3 (**1c**, calcitriol), only by the presence of the double bond at the $\Delta^{9(11)}$-position. Initial in vitro biological screening of vitamins **5a** and **5b** indicate that the 9,11-double bond has only a modest effect on chick intestinal receptor binding, and it therefore seems likely that the vitamin D–previtamin D interconversion is not necessary for the expression of the calcitropic effects of vitamin D.

Introduction

The biosynthesis of vitamin D_3 (**1a**, Scheme I) involves two of the very few known biologically occurring pericyclic reactions.[2] First, 7-dehydrocholesterol (**2**) undergoes (in the skin) a photochemically induced six-electron electrocyclic ring opening to afford previtamin D_3 (**3a**).[3] Second, previtamin D_3 rearranges via a thermal [1,7]-sigmatropic hydrogen shift to afford vitamin D_3 (**1a**). Vitamin D_3 then undergoes hydroxylation in the liver to afford 25-hydroxyvitamin D_3 (**1b**) followed by hydroxylation in the kidney to produce 1α,25-dihydroxyvitamin D_3 [1α,25-$(OH)_2$-D_3, **1c**]. It is the latter compound that acts as a classical steroid hormone to induce the biological effects associated with vitamin D_3 via binding to a receptor protein, which then regulates the expression of certain genes.[4]

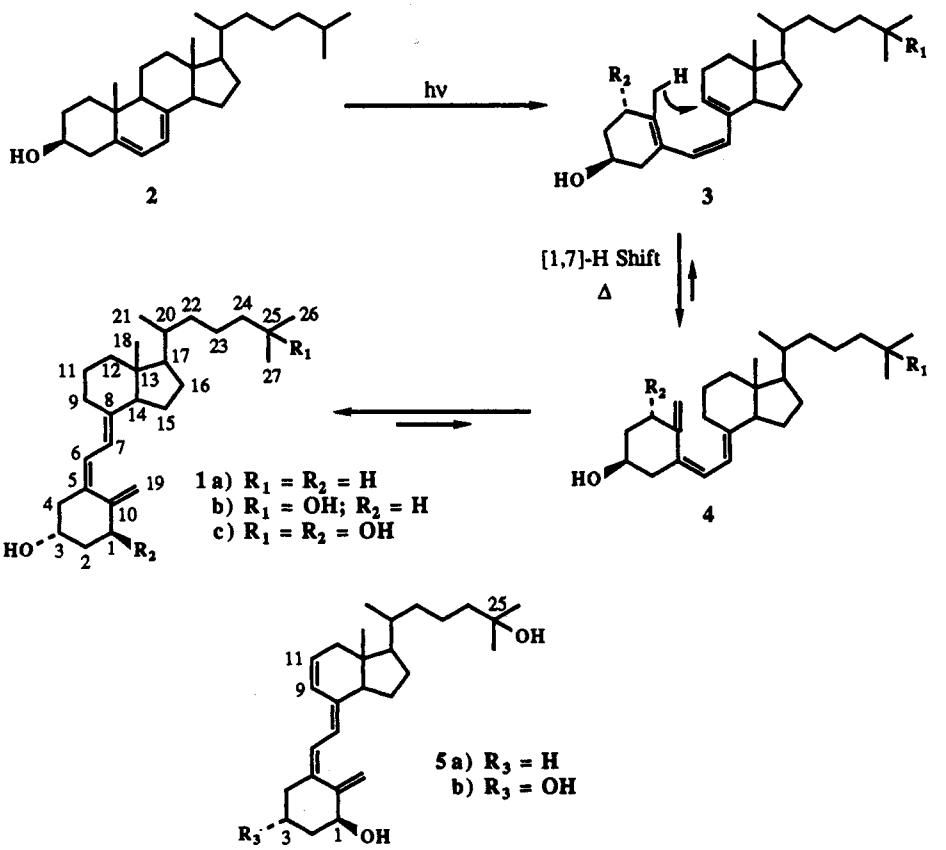
(1) (a) This is Paper 35 in the series, Studies of Vitamin D (Calciferol) and Its Analogues. For Paper 34, see: Barrack, S. A.; Gibbs, R. A.; Okamura, W. H. *J. Org. Chem.* **1988**, *53*, 1790. (b) This article was taken in part from the Ph.D. thesis submitted to the University of California, Riverside, by R. A. Gibbs, August, 1988. (c) For preliminary communications of this work, see: Aurrecoechea, J. M.; Okamura, W. H. *Tetrahedron Lett.* **1987**, *28*, 4947. Gibbs, R. A.; Okamura, W. H. *Tetrahedron Lett.* **1987**, *28*, 6021. (d) Department of Chemistry. (e) Current address: Dept. of Chemistry, Univ. del Pais Vasco, Bilbao, Spain. (f) Department of Biochemistry.

(2) For general reviews of vitamin D chemistry and biochemistry, see: (a) Norman, A. W. *Vitamin D, the Calcium Homeostatic Steroid Hormones*; Academic Press: New York, 1979. (b) De Luca, H. F.; Paaren, H. E.; Schnoes, H. K. *Top. Curr. Chem.* **1979**, *83*, 1. (c) Georghiou, P. E. *Chem. Soc. Rev.* **1977**, *6*, 83. (d) Fieser, L. F.; Fieser, M. *Steroids*; Reinhold: New York, 1959. (e) Norman, A. W.; Roth, J.; Orci, L. *Endocrine Rev.* **1982**, *3*, 331. (f) De Luca, H. F.; Schnoes, H. K. *Ann. Rev. Biochem.* **1983**, *52*, 411.

(3) (a) MacLaughlin, J. A.; Anderson, R. R.; Holick, M. F. *Science* **1982**, *216*, 1001. (b) Holick, M. F.; MacLaughlin, J. A.; Doppelt, S. H. *Science* **1981**, *211*, 590. (c) Holick, M. F.; MacLaughlin, J. A.; Clark, M. B.; Holick, S. A.; Potts, J. T., Jr.; Anderson, R. R.; Blank, I. H.; Parrish, J. A.; Elias, P. *Science* **1980**, *210*, 203. (d) For another possible example of a biological pericyclic reaction (the rearrangement of chorismate to prephenate) see: Guilford, W. J.; Copley, S. D.; Knowles, J. R. *J. Am. Chem. Soc.* **1987**, *109*, 5013 and references cited therein.

0022-3263/89/1954-4072$01.50/0

Scheme I



Recently, it has been found that in addition to its traditional role in calcium homeostasis, 1α,25-$(OH)_2$-D_3 also plays a role in cellular differentiation.[5] This has led to an increased interest in the chemistry and biochemistry of vitamin D_3[6] due to the potential utility of 1α,25-$(OH)_2$-D_3 (or an analogue) in the treatment of certain cancers and skin disorders.

The analogues described in this study (**5a** and **5b**) were targeted for synthesis in part because of our interest in the [1,7]-sigmatropic hydrogen shift, the pericyclic reaction which interconverts previtamin D_3 and vitamin D_3.[7] It is well established that 1α,25-$(OH)_2$-D_3 (**1c**) as well as 25-hydroxyvitamin D_3 (**1b**) and **1a** can be readily equilibrated (via their s-cis conformers **4a–c**) with their respective minor previtamin forms **3a–c** at physiological temperatures. Analogues **5a** and **5b**, due to the presence of the 9,11 double bond, are "locked" into the vitamin form and are thus incapable of undergoing a [1,7]-shift to give a previtamin analogous to **3**. Vitamins **5a,b** are the first analogues locked into the vitamin form, and they are thus a potential tool for exploring the biological relevance of the vitamin–previtamin equilibrium. These analogues are also of interest due to their modified π-system. Recently, several triene-modified analogues of vitamin D_3 have exhibited interesting biological properties.[8] Accordingly, analogues with electronically perturbed π-systems are of some interest in connection with assessing the significance of, for example, π-stacking in the ability of vitamin D to interact with its various enzymes, transport proteins, and other receptors.

The second major goal of this project was to develop improvements in our previously described vinylallene route to vitamin D analogues.[9] As shown in Scheme II, we have reported that the thermal [1,5]-sigmatropic hydrogen shift of the 6β-vinylallene **6** affords the vitamin D analogue **7** in 59% yield. However, rearrangement of the epimeric 6α-vinylallene **8** gives only a 17% yield of **7**,[9,10a] and the

(4) (a) Walters, M. R.; Hunziker, W.; Norman, A. W. *Trends Biol. Sci.* **1981**, 268. (b) Wecksler, W. R.; Norman, A. W. *J. Steroid Biochem.* **1980**, *13*, 977. For a discussion of the mechanism of action of classical steroids, see: (c) Buller, R. E.; O'Malley, B. W. *Biochem. Pharmacol.* **1976**, *25*, 1. (d) Grody, W. W.; Schrader, W. T.; O'Malley, B. W. *Endocrine Rev.* **1982**, *3*, 141. (e) Recently, the amino acid sequence of the human 1α,25-$(OH)_2$-D_3 receptor has been determined: Baker, A. R.; McDonnell, D. P.; Hughes, M.; Crisp, T. M.; Mangelsdorf, D. J.; Haussler, M. R.; Pike, J. W.; Shine, J.; O'Malley, B. W. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 3294.

(5) Differentiation of leukemia cells: (a) Abe, E.; Miyaura, C.; Sakagami, H.; Takeda, M.; Konno, K.; Yamazaki, T.; Yoshiki, S.; Suda, T. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 4990. (b) Honma, Y.; Hozumi, M.; Abe, E.; Konno, K.; Fukushima, M.; Hata, S.; Nishii, Y.; DeLuca, H. F.; Suda, T. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 201. (c) Koeffler, H. P.; Amatruda, T.; Ikekawa, N.; Kobayashi, Y.; DeLuca, H. F. *Cancer Res.* **1984**, *44*, 5624. (d) Munker, R.; Norman, A. W.; Koeffler, H. P. *J. Clinical Invest.* **1986**, *78*, 424. (e) Koeffler, H. P.; Hirji, K.; Itri, L.; the Southern California Leukemia Group *Cancer Treat. Rep.* **1985**, *69*, 1399. Differentiation of skin cells (psoriasis treatment): (f) MacLaughlin, J. A.; Gange, W.; Taylor, D.; Smith, E.; Holick, M. F. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 5409. (g) Morimoto, S.; Onishi, T.; Imanaka, S.; Yukawa, H.; Kozuka, T.; Kitano, Y.; Yoshikawa, K.; Kumahara, Y. *Calcif. Tissue. Int.* **1986**, *38*, 119.

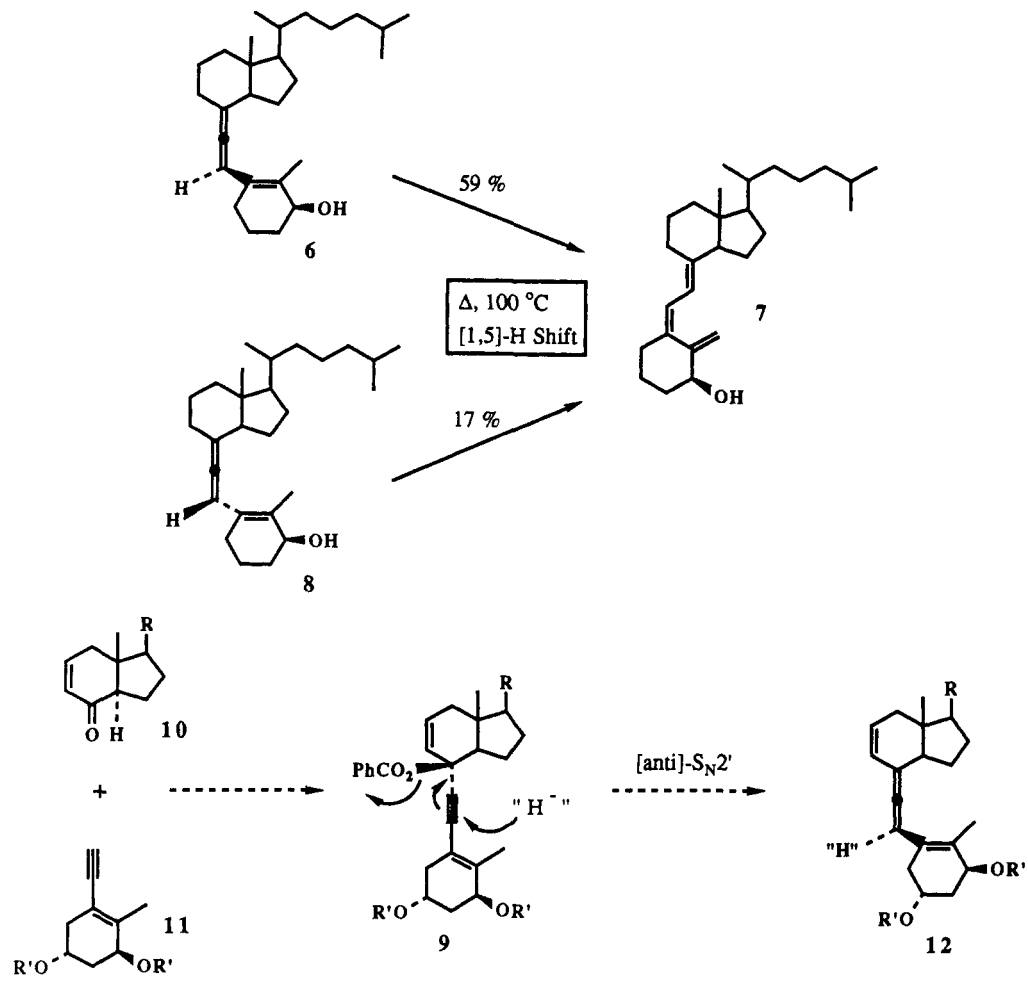
(6) For a recent review of synthetic endeavors in the vitamin D field, see: Pardo, R.; Santelli, M. *Bull. Chim. Soc. Fr.* **1985**, 98.

(7) (a) Hoeger, C. A.; Johnston, A. D.; Okamura, W. H. *J. Am. Chem. Soc.* **1987**, *109*, 4690. (b) Okamura, W. H.; Hoeger, C. A.; Miller, K. J.; Reischl, W. *J. Am. Chem. Soc.* **1988**, *110*, 973.

(8) (a) 6-Fluorovitamin D_3: Wilhelm, F.; Dauben, W. G.; Kohler, B.; Roesle, A.; Norman, A. W. *Arch. Biochem. Biophys.* **1984**, *233*, 127. Dauben, W. G.; Kohler, B.; Roesle, A. *J. Org. Chem.* **1985**, *50*, 2007. (b) 10-Keto-19-nor-25-hydroxyvitamin D_3: Stern, P. H.; Horst, R. L.; Gardner, R.; Napoli, J. L. *Arch. Biochem. Biophys.* **1985**, *236*, 555. Gray, T. K.; Millington, D. S.; Maltby, D. A.; Williams, M. E.; Cohen, M. S.; Dodd, R. C. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 8218. (c) 6,19-Epoxy-25-hydroxyvitamin D_3: Shiina, Y.; Miyaura, C.; Tanaka, H.; Abe, E.; Yamada, S.; Yamamoto, K.; Ino, E.; Takayama, H.; Matsunaga, I.; Nishii, Y.; Suda, T. *J. Med. Chem.* **1985**, *28*, 1153.

(9) Okamura, W. H. *Acc. Chem. Res.* **1983**, *16*, 81.

Scheme II



profound effect of the neighboring allylic hydroxyl in directing the π-facial course of the suprafacial [1,5]-sigmatropic hydrogen shift has already been noted.[10b] The natural 1*S* configuration of the carbinol center as in **6** and **8** is of course mandatory,[4b] but we have long been aware that the 6β rather than the 6α-allene configuration as in **6** and **8**, respectively, is crucial in order to obtain satisfactory yields in this reaction. The methods that have been previously employed in this laboratory for the preparation of vitamin D type vinylallenes unfortunately afforded primarily (or exclusively) the 6α allene stereochemistry. We anticipated that the S$_N$2' reaction of propargylic benzoate **9** (prepared via the coupling of CD ring enone **10** and enyne **11**) with a nucleophilic copper hydride equivalent would afford the desired 6β vinylallene **12** in a highly stereoselective fashion.[11] In addition, it would allow us for the first time to prepare a vitamin D analogue possessing all three biologically important hydroxyl groups via the vinylallene route. This paper describes in detail how the formal equivalent of this route has been developed for the synthesis of the 9,11-dehydrovitamins **5a** and **5b**. The full details of our concise method for the synthesis of the key A-ring synthon **11** are also presented. Finally, the preliminary results of in vitro biological evaluation of analogues **5a** and **5b** are described.

Results and Discussion

Synthesis of 3-Deoxy-1α,25-dihydroxy-9,11-didehydrovitamin D$_3$ (5a). An important assumption made in the proposed synthesis of 6β-vinylallenes outlined in Scheme II is that a nucleophile such as the anion of enyne **11** will add to enone **10** primarily (or exclusively) from the α-face. Although it is known that a wide variety of nucleophiles add to Grundmann's ketone (**13**, Scheme III) from the α-face (equatorial attack is presumably favored due to steric hinderance imparted by the 13β angular methyl group),[10] it is known that the 14,15-enone derived from Grundmann's ketone is reduced by NaBH$_4$ from the β-face[7a] and that acetylide anions show a high propensity for axial addition to enones.[12] Therefore it was important to unambiguously determine the stereochemistry of acetylide attack on a 9,11-enone. Grundmann's ketone (**13**)[10] was converted via Reich's method[13] to the 9,11-enone **14**, which upon treatment with lithium acetylide afforded a single propargyl alcohol **15** (by ^{1}H and ^{13}C NMR spectral analyses) in excellent yield. Enynol **15** was then exhaustively hydrogenated to produce the saturated tertiary alcohol **16**. Hydrogenation of the previously known pro-

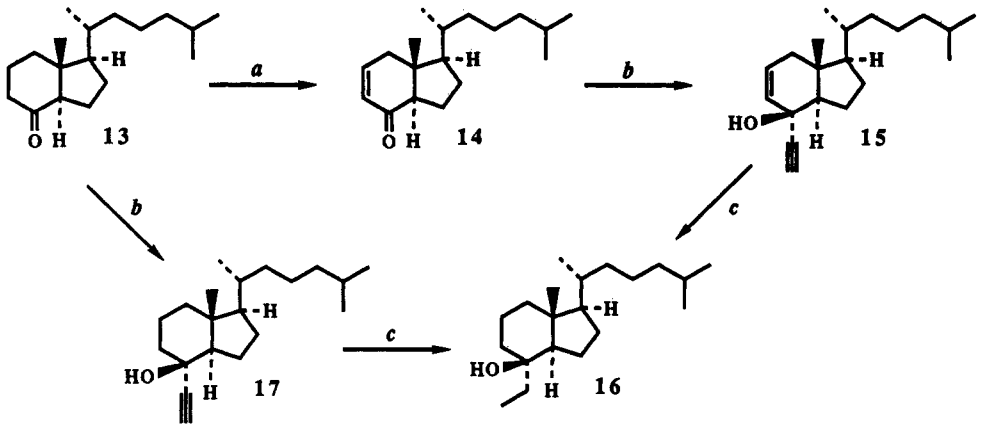
(10) (a) Condran, P., Jr.; Hammond, M. L.; Mouriño, A.; Okamura, W. H. *J. Am. Chem. Soc.* **1980**, *102*, 6259. (b) The origin of this effect is unclear, but it does not appear to be steric in nature: Barrack, S. A.; Okamura, W. H. *J. Org. Chem.* **1986**, *51*, 3201 and references cited therein.

(11) This sequence was based on the development of an improved route to vitamin A vinylallenes recently reported by this laboratory: (a) Silveira, M. H.; Okamura, W. H. *J. Org. Chem.* **1985**, *50*, 2390. (b) Shen, G.-Y.; de Lera, A. R.; Norman, T. C.; Haces, A.; Okamura, W. H. *Tetrahedron Lett.* **1987**, *28*, 2917.

(12) Stork, G.; Stryker, J. M. *Tetrahedron Lett.* **1983**, *24*, 4887.

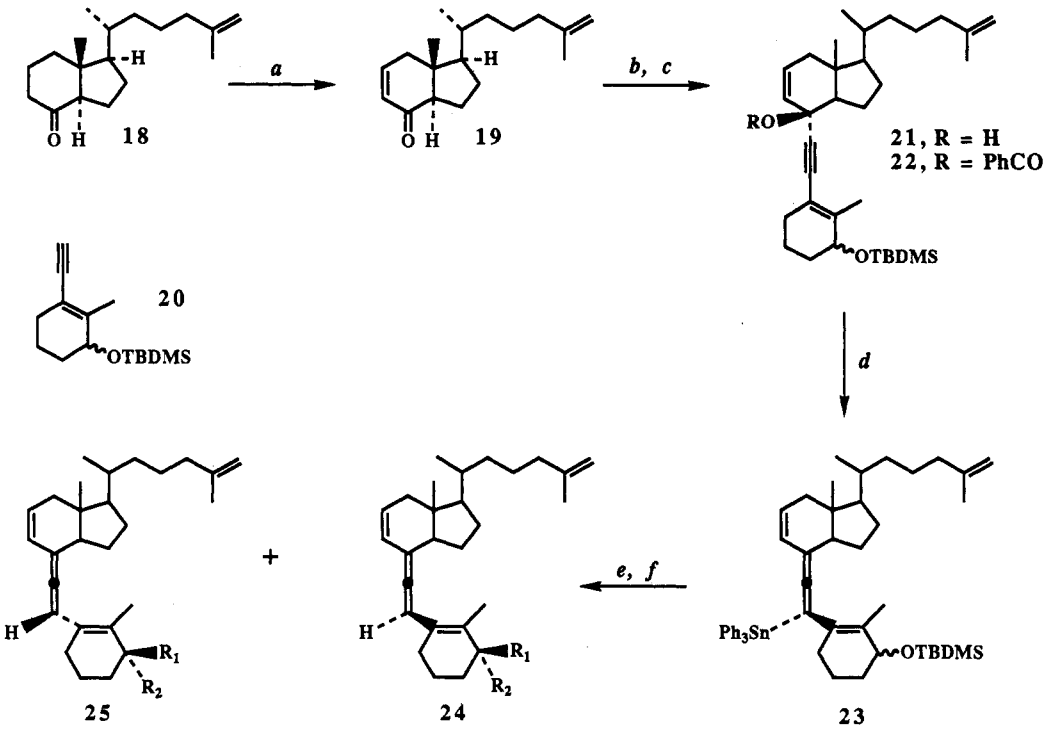
(13) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

Scheme III[a]



[a] (a) (i) LDA, THF, −78 °C; PhSeCl, −78 °C; (ii) MCPBA, CH_2Cl_2, 0 °C (50%); (b) LiC_2H, THF, −78 °C (15, 93%; 17, 90% from ref 10a); (c) H_2, Pt/C, hexanes, room temperature (83% from 15; 95% from 17).

Scheme IV[a]



a) R_1 = OTBDMS; R_2 = H
b) R_1 = H; R_2 = OTBDMS
c) R_1 = OH; R_2 = H
d) R_1 = H; R_2 = OH

[a] (a) (i) LDA, THF, −78 °C to room temperature; PhSeCl, −78 °C; (ii) MCPBA, C_5H_5N, CH_2Cl_2, −15 °C (51%); (b) **20**, *n*-BuLi, ether, 0 °C; **19**, 0 °C to room temperature (89%); (c) *n*-BuLi, ether, −78 °C to room temperature; PhCOCl, −78 °C to room temperature; (d) $(Ph_3Sn)_2Cu(CN)Li_2$, THF/ether, 0 °C (87% from **21**); (e) $(n\text{-}Bu)_4NF{\cdot}3H_2O$, THF, 0 °C (54%); (f) $(n\text{-}Bu)_4NF$, THF, room temperature (81%).

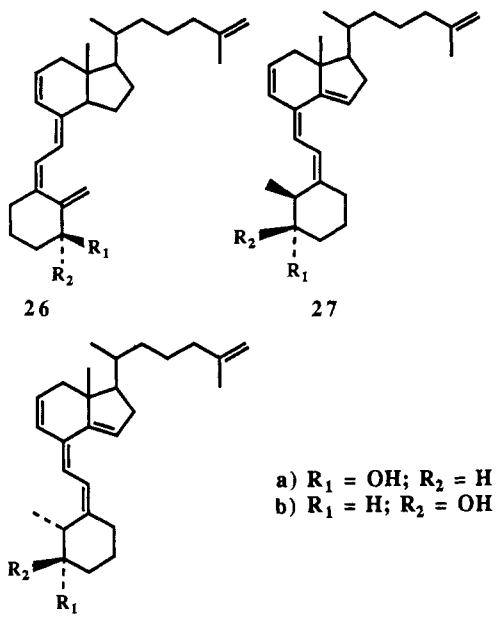
pargyl alcohol **17**[10,14] afforded the same saturated alcohol **16**, thus establishing that the acetylide anion did add to **14** in the desired fashion and also that **15** (as well as **14**) retained the trans CD ring junction of ketone **13**.

The synthesis of the vitamin **5a** began with the known C/D ring fragment **18**,[1a] which was readily transformed to the 9,11-enone **19** (Scheme IV).[13] The racemic A ring fragment **20**[15] was coupled with **19** to afford propargyl alcohol **21** in excellent yield. Alcohol **21** was then converted to the unstable benzoate **22**, which was used directly in the next reaction without purification. After some preliminary investigation, it was found that the conversion of benzoate **22** to the desired 6β-vinylallenols was best accomplished via a three-step sequence. Treatment of **22** with the higher order triphenylstannyl cyanocuprate reagent afforded the 6β-stannylallene **23** (only a single allene isomer was detected by ^1H and ^{13}C NMR spectral

(14) Haces, A.; van Kruchten, E. M. G. A.; Okamura, W. H. *Isr. J. Chem.* **1985**, *26*, 140.

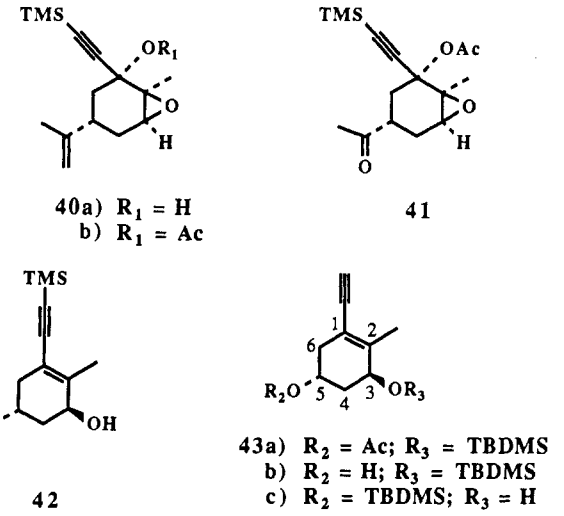
(15) Jeganathan, S.; Johnston, A. D.; Kuenzel, E. A.; Norman, A. W.; Okamura, W. H. *J. Org. Chem.* **1984**, *49*, 2152.

Chart I



analyses).[16-18] The triphenylstannyl moiety was then removed in a mild, selective manner by treatment of **23** with tetrabutylammonium fluoride trihydrate at 0 °C to afford a 13.5:1.0 mixture of the 6β TBDMS protected vinylallenols **24a** and **24b** and their 6α epimers **25a** and **25b**.[19] This mixture was then separated by HPLC and the two 6β isomers deprotected to afford the desired vinylallenols **24c** and **24d**. The selective cleavage of the carbon–tin bond in **23** in the presence of the oxygen–silicon bond may appear surprising at first, but Pearlman and his co-workers have recently reported a striking example of the greater kinetic affinity of fluoride ion for tin versus silicon.[20a,b]

Chart II



The thermal [1,5]-sigmatropic hydrogen shift [refluxing isooctane (100 °C), 3 h] of the 1α,6β vinylallenol **24c** afforded primarily the desired vitamin **26a** (63% yield) as expected (Chart I). The two tetraenes **27a** (19%) and **28a** (10%) were also isolated from the thermolysis of **24c**; the ratio of **26a** to **27a** + **28a** was 2.2:1.0. Thermolysis of the 1β,6β vinylallenol **24d** gave the 1β vitamin **26b** (12%) and tetraenes **27b** (33%) and **28b** (45%) in a ratio of 1.0:5.8.[21] The 9,11 double bond exerts a significant accelerating effect on the [1,5]-hydrogen shift; in the parent system, complete rearrangement of vinylallenols **6** and **8** required 10 h of heating at 100 °C. The 1α-hydroxyvitamin **26a** was subjected to selective oxymercuration–demercuration[22] to afford the desired 9,11 dehydrovitamin analogue **5a** in 57% yield. Due to its extra conjugated double bond, **5a** possesses a red-shifted UV maximum relative to the parent triene system (**5a**, λ_{max} = 288 nm; **1c**, λ_{max} = 262 nm).

Synthesis of the A-Ring Synthon. A concise, efficient method for the preparation of the A-ring enyne of the type **11** (Scheme II) would be useful not only for the preparation of the trihydroxylated 9,11-dehydrovitamin D analogue **5b** (via the method described above) but also for the synthesis of other vitamin D analogues of biological interest to these laboratories. Enynes of this type (**11**, R′ = H) were first prepared in 12 steps and 3% overall yield by Lythgoe and co-workers.[23a] More recently, Castedo et al. have described a more efficient synthesis (11 steps, 10% overall yield) of **11** (R′ = H)[23b] and the synthesis of a related A-ring fragment has been reported by the Hoffmann-La Roche group[23c] and by Desmaele and Tanier.[23d] We present here a detailed description of our concise (six steps) method for the preparation of **11** (R′ = H), which utilizes as the key step a novel SmI_2–Pd^0 induced transformation of an epoxy propargyl acetate to an enynol.

(16) (a) The stereochemistry of allene **23** was based on previous examples of anti addition of stannylcopper(I) species to propargylic substrates: Ruitenberg, K.; Westmijze, H.; Meijer, J.; Elsevier, C. J.; Vermeer, P. *J. Organomet. Chem.* **1983**, *241*, 417. In addition, see ref 14. (b) For a review of higher order cuprates, see: Lipschutz, B. H. *Synthesis* **1987**, 325. (c) Other recent uses of stannylcyanocuprates: Gilbertson, S. R.; Challener, C. A.; Bos, M. E.; Wulff, W. D. *Tetrahedron Lett.* **1988**, *29*, 4795. Piers, E.; Tillyer, R. D. *J. Org. Chem.* **1988**, *53*, 5366.

(17) (a) In preliminary studies with a side chain saturated variant of benzoate **22** (prepared in two steps from enone **14** and **20**[1b]) it was found that the use of $Ph_3SnCu{\cdot}Me_2S{\cdot}LiBr$[17b,c] or $Ph_3SnCu{\cdot}LiBr$[16a] also afforded the desired stannylallene, but in somewhat lower yields than were obtained with the cyanocuprate reagent. Preliminary attempts to employ trimethylstannyl or tributylstannyl copper reagents were unsuccessful. (b) Piers, E.; Chong, J. M.; Morton, H. E. *Tetrahedron Lett.* **1981**, *22*, 4905. (c) Piers, E.; Morton, H. E.; Chong, J. M. *Can. J. Chem.* **1987**, *65*, 78.

(18) (a) Note that although the stannylcopper reagent could have initiated (among other possibilities) either an allylic (attack at C_{11}) or propargylic (attack at C_8) S_N2' displacement reaction on benzoate **22**, only the product resulting from propargylic attack was seen. This finding is in accord with the results of Vermeer and co-workers[18b] and with the results previously obtained in this laboratory.[11] (b) Kleijn, H.; Westmijze, H.; Kruithof, K.; Vermeer, P. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 27.

(19) The stereochemical assignments of the 6α and 6β allenes are based on the ^{1}H NMR chemical shifts of their C-18 (or 13β) methyl groups (**24a,b**, δ 0.71; **25a,b**, δ 0.67). These signals are similar to those previously observed for a series of 6β and 6α allenes prepared in this laboratory[14] (for example: **6**, C-18 CH_3 δ 0.71; and **8**, C-18 CH_3 δ 0.65).[10] For additional evidence for the stereochemical assignments of **24** and **25**, see the discussion in ref 1a, 1b, 9, and 10.

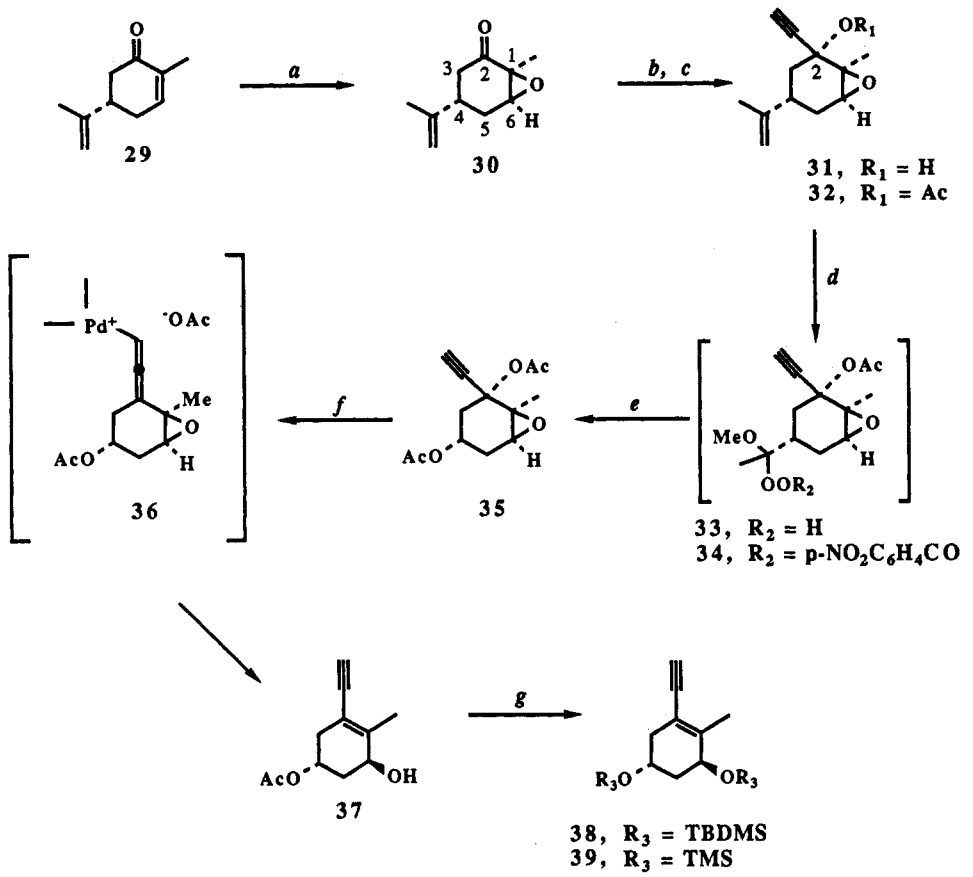
(20) (a) Pearlman, B. A.; Putt, S. R.; Fleming, J. A. *J. Org. Chem.* **1985**, *50*, 3622. For other examples of fluorodestannylation, see: Harpp, D. N.; Gingras, M. *J. Am. Chem. Soc.* **1988**, *110*, 7737 and references cited therein. (b) Treatment of allene **23** with commercial 1 M tetrabutylammonium fluoride in THF caused simultaneous removal of silicon and tin. However, while the four alcohols **24c** and **24d** and **25c** and **25d** could not be separated by HPLC, their TBDMS ethers were readily separable.

(21) The stereochemistry of the four tetraenes **27a–b** and **28a–b** is based on the similarity of their ^{1}H NMR spectra and chromatographic mobility to that of similar trienes previously isolated from the thermolysis of **6** and **8** and their 1β epimers.[7a,10] The ratios of **26** to **27** + **28** obtained from the thermolysis of **24c** and **24d** provide evidence for the stereochemistry of the 1-hydroxy group (for a discussion, see ref 9). Additional evidence for the assigned 1-hydroxy stereochemistry is the fact that **26a** was converted to **5a**, which is highly biologically active. It has been previously shown that the α-orientation of the 1-hydroxy group is necessary for biological activity.[4b]

(22) Leyes, G. A.; Okamura, W. H. *J. Am. Chem. Soc.* **1982**, *104*, 6099.

(23) (a) Harrison, R. G.; Lythgoe, B.; Wright, P. W. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2654. (b) Castedo, L.; Mascareñas, J. L.; Mouriño, A. *Tetrahedron Lett.* **1987**, *28*, 2099. (c) Baggiolini, E. G.; Hennessy, B. M.; Iacobelli, J. A.; Uskokovic, M. R. *Tetrahedron Lett.* **1987**, *28*, 2095. (d) Desmaele, D.; Tanier, S. *Tetrahedron Lett.* **1985**, *26*, 4941.

Scheme V[a]



[a] (a) H_2O_2, NaOH, MeOH, −10 to 0 °C (89%); (b) LiC_2H, THF, −78 °C (83%); (c) Ac_2O, DMAP, Et_3N, room temperature (92%); (d) (i) O_3, CH_2Cl_2/MeOH, −78 °C; (ii) p-$NO_2C_6H_4COCl$, CH_2Cl_2/C_5H_5N, 0 °C to room temperature; (e) 40 °C (75% from **32**); (f) SmI_2, $Pd(PPh_3)_4$, THF, room temperature (91%); (g) **38**, NaOMe, MeOH, 0 °C; TBDMS-Cl, imidazole, DMF, room temperature (70% from **35**); **39**, NaOMe, MeOH, 0 °C; TMS-Cl, imidazole, THF, room temperature.

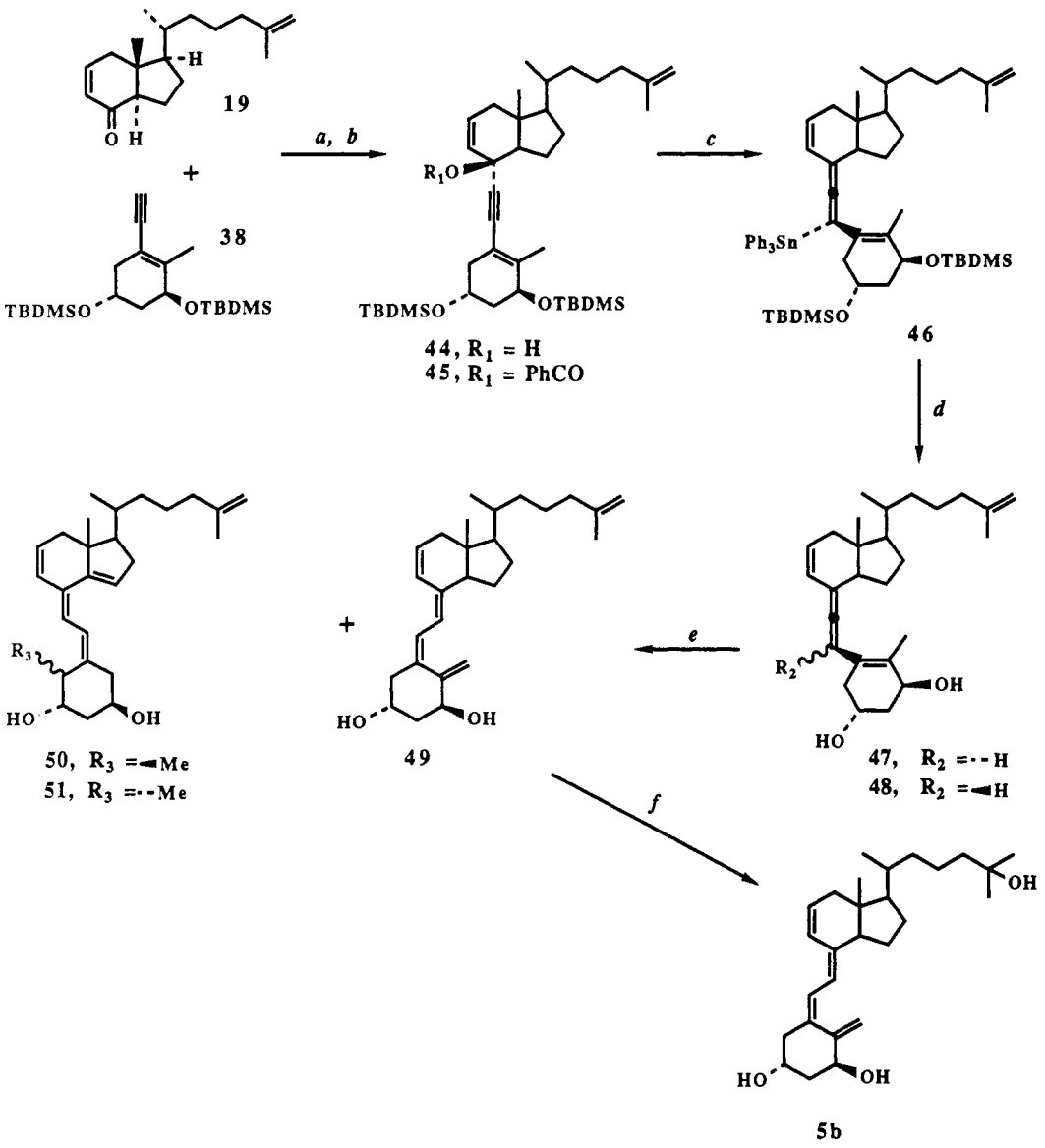
The preparation of the A-ring enyne began with the known stereoselective epoxidation of (*S*)-(+)-carvone (**29**, Scheme V) to afford epoxy ketone **30**.[24] Treatment of **30** with lithium acetylide[25] proceeded in a highly stereoselective fashion to afford **31**,[26] which was then converted in high yield to the epoxypropargyl acetate **32**. Selective ozonolysis of **32** afforded a diastereomeric mixture (^1H NMR spectral analysis) of the methoxy hydroperoxide **33**, which was then acylated to give **34**. In situ Criegee rearrangement of methoxy peroxy ester **34** proceeded smoothly to afford a 75% yield of diacetate **35** (based on **32**).[27]

The crucial step in this synthesis (the conversion of **35** to **37**) was effected using a variant of the method recently developed by Inanaga and co-workers for the conversion of propargyl acetates into allenes.[28] Palladium-catalyzed samarium iodide mediated displacement of propargyl acetate **35** presumably produces the allenylpalladium intermediate **36**. This intermediate then can be considered to undergo not only reduction but also epoxide ring opening to give the enynol **37**. Whereas in the Inanaga allene synthesis an in situ electrophile (a proton derived from an alcohol) is needed, the vicinal epoxide carbon–oxygen bond serves this purpose in the present case. In fact, there were indications that deleterious results (vide infra) were obtained if Inanaga's conditions (in situ proton quench) are used with our epoxy propargyl esters. Saponification of **37** followed by protection of the resulting diol gave the desired A-ring synthon **38** in seven steps (36% overall yield) from commercially available (*S*)-(+)-carvone. We have used this short and highly reproducible scheme to prepare multigram quantities of **38**. In order to confirm the structure and enantiomeric purity of enynol **37**, it was transformed to the bis(trimethylsilyl) ether **39**, which had been previously prepared by Lythgoe.[23a]

It is worthwhile to mention several preliminary studies on this route employing the trimethylsilyl-protected propargyl acetate **40b** (Chart II). Although the propargyl alcohol **40a** and acetate **40b** were readily prepared, all attempts to effect the selective ozonolysis–Criegee rearrangement of these substrates were unsuccessful. Acetate **40b** was converted in 68% yield (OsO_4, $NaIO_4$, THF/H_2O, room temperature) to the methyl ketone **41**, but attempts to transform **41** to a diacetate analogous to **35** via a Baeyer–Villiger reaction were unsuccessful.[29] Acetate **40b** was also transformed (SmI_2, $Pd(PPh_3)_4$, THF, room temperature) in 67% yield to enynol **42** using the variant of Inanaga's conditions described above for **35**.[28] However, attempts to selectively ozonize **42** also met with little success. It was found that the use of an in situ proton

(24) Klein, E.; Ohloff, G. *Tetrahedron* **1963**, *19*, 1091.
(25) Midland, M. M. *J. Org. Chem.* **1975**, *40*, 2250.
(26) The assignment of the stereochemistry of **31** was made on the basis of preferential attack at the less hindered face of the epoxy ketone, i.e., opposite to the 1β-methyl group. For a discussion on the stereochemistry of hydride attack on α-keto epoxides, see: Chautemps, P.; Pierre, J.-L. *Tetrahedron* **1976**, *32*, 549.
(27) Schreiber, S. L.; Liew, W.-F. *Tetrahedron Lett.* **1983**, *24*, 2363.
(28) Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 5237.
(29) For an analogous Baeyer–Villiger reaction of a carvone epoxide derivative, see: Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Batcho, A. D.; Sereno, J. F.; Uskokovic, M. R. *J. Org. Chem.* **1986**, *51*, 3098.

Scheme VI[a]



[a] (a) **38**, *n*-BuLi, ether, 0 °C; **19**, 0 °C to room temperature (85%); (b) *n*-BuLi, ether, −78 °C to room temperature; PhCOCl, −78 °C to room temperature; (c) $(Ph_3Sn)_2Cu(CN)Li_2$, THF/ether, 0 °C (70% from **44**); (d) $(n\text{-}Bu)_4NF$, THF, 0 °C to room temperature (47% from **44**); (e) Isooctane, reflux (65% **49**; 30% **50** + **51**); (f) $Hg(OAc)_2$, THF/H_2O, room temperature; $NaBH_4$, NaOH, room temperature (48%).

source (as described by Inanaga) during the reduction of **40b** resulted in significantly lower yields of **42**, and thus an in situ proton source was not used during the transformation of **35** to **37** (Scheme V).

Monoprotected derivatives of enynol **38** were also prepared in view of their potential value in the synthesis of A-ring modified vitamin D analogues. Silylation (TBDMS-Cl, imidazole, DMF, room temperature) of the monoacetate **37** gave **43a** (69% yield from diacetate **35**), which was then saponified (NaOMe, MeOH, room temperature) to give alcohol **43b** in 88% yield. The selective deprotection of the bis-TBDMS ether **38** (1 equiv of *n*-Bu_4NF, THF, room temperature) afforded (following HPLC separation) a mixture of **43b** (23%) and the isomeric mono-TBDMS ether **43c** (46% yield).

Synthesis of 1α,25-Dihydroxy-9,11-didehydrovitamin D_3 (5b). The development of the method for the preparation of 6β-vinylallenes and the concise synthesis of enyne **38** has enabled us to prepare the parent trihydroxylated 9,11-dehydrovitamin **5b** in a straightforward manner. The coupling of **38** and enone **19** produced propargyl alcohol **44** in good yield (Scheme VI).[30] Benzoylation of **44** followed by treatment of the resulting **45** with triphenylstannyl cyanocuprate gave the stannylallene **46**. Simultaneous fluoride-induced destannylation and desilylation of **46** afforded a 10:1 mixture of the desired 6β-vinylallenol **47** and its 6α epimer **48**. Thermolysis of **47** gave a mixture of vitamin **49** (65% yield after purification) and the epimeric tetraenes **50** and **51** (ratio of **49** to **50** + **51** = 2.5:1.0). Oxymercuration–demercuration of **49** produced the desired analogue **5b**.

Biological Evaluation. Analogues **5a** and **5b** have undergone preliminary in vitro biological evaluation in the vitamin D deficient chick. The 3-deoxy-9,11-dehydrovitamin **5a** exhibited significant binding to the chick intestinal 1α,25-$(OH)_2$-D_3 receptor in an in vitro competitive binding assay (RCI assay).[31] The RCI value for **5a** was 5.9, whereas the RCI value for 3-deoxy-1α,25-dihydroxy-

(30) We thank Dr. C. Pumar of this laboratory for first preparing and characterizing **44** in connection with other vitamin D analogue studies.

(31) (a) Wecksler, W. R.; Norman, A. W. *Methods in Enzymology: Vitamins and Co-Enzymes* **1980**, *67*, 488. (b) Mayer, E.; Kadowaki, S.; Okamura, W. H.; Ohnuma, N.; Leyes, G. A.; Schmidt-Gayk, H.; Norman, A. W. *J. Steroid Biochem.* **1981**, *15*, 145.

vitamin D_3 (differing only from **5a** by the lack of the 9,11-double bond) was 3.6,[31b] while the standard reference compound 1α,25-$(OH)_2$-D_3 had an RCI of 100. The RCI value for the trihydroxylated 9,11-dehydrovitamin **5b** [which unlike **5a** contains in its structure all three significant hydroxyls as in the natural hormone, 1α,25-$(OH)_2$-D_3 (**1c**)] was approximately half of that for the natural hormone 1α,25-$(OH)_2D_3$ [RCI of **5b** = 47; RCI of **1c** = 100 (by definition)].[31] These results indicate that the 9,11-double bond has only a modest effect[32] on the binding ability of an analogue to the chick intestinal 1α,25-$(OH)_2$-D_3 receptor and hence the vitamin–previtamin interconversion is not necessary for the primary calcitropic activities (intestinal calcium absorption and bone calcium mobilization)[33] of 1α,25-dihydroxyvitamin D_3 (**1c**).[34]

Summary

This study has resulted in the development of a method for the stereoselective preparation of 6β-vinylallenes and the development of an improved practical synthesis of the vitamin D A-ring enyne **38**. These methods are based upon the development of two novel synthetic transformations: (a) the mild and highly stereoselective fluorodestannylation of allene **23** to afford **24a,b** and (b) the SmI_2–Pd^0-mediated conversion of epoxypropargyl acetate **35** to enynol **37**. These methods can now be employed in the preparation of a wide variety of hydroxylated vitamin D analogues and they should also prove useful in other synthetic endeavors.[35] This study has resulted in the synthesis of the two novel 9,11-dehydro analogues of vitamin D, **5a** and **5b**. The results of initial in vitro biological testing of **5a** and **5b** indicate that the 9,11 double bond has only a modest attenuating affect on the biological activity of vitamin D and we are further pursuing the use of these analogues as biochemical research tools.

Experimental Section[36]

(1*S*)-9,11-Didehydro-3-deoxy-1,25-dihydroxyvitamin D_3 (5a). To the vacuum dried vitamin **26a** (3.2 mg, 0.0084 mmol) under nitrogen in a 5-mL flask were added THF (0.14 mL) and H_2O (0.035 mL). The solution was ice cooled, and then mercuric acetate (2.9 mg, 0.0091 mmol) was added in one portion and the reaction mixture was stirred for 2 h. To the reaction mixture was then added 3 M aqueous NaOH (8.5 μL) followed by 0.5 M $NaBH_4$ in 3 M aqueous NaOH (8.5 μL). The mixture was stirred an additional 30 min at 0 °C, diluted with ether (5 mL), treated with K_2CO_3, and then taken up in additional ether (20 mL). The ether solution was dried ($MgSO_4$), filtered, and then passed through a pad of silica gel. After removal of solvent, the crude residue was subjected to HPLC (Whatman Partisil M9 10/50 column, 35% EtOAc/hexanes) to give 1.9 mg (57%) of pure vitamin **5a**.

(1*S*)-9,11-Didehydro-1,25-dihydroxyvitamin D_3 (5b). Mercuric acetate (5.2 mg, 0.0163 mmol) was added in one portion to a stirred solution of dehydrovitamin **49** (6.0 mg, 0.0151 mmol) in THF (170 μL) and water (170 μL) at room temperature. The reaction mixture was stirred for 1.3 h, treated with 3 M NaOH (16 μL) and 0.5 M $NaBH_4$ in 3 M NaOH (16 μL), and then stirred for 20 min. Solid NaCl was then added, and the mixture was diluted with ethyl acetate (20 mL) and water (1 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (10 mL), and the organic layers were combined and dried (Na_2SO_4). The residue after evaporation was purified by HPLC (Rainin Dynamax 1 × 25 cm, 8 μm silica gel column, 70% ethyl acetate, 4 mL/min) to afford in order of elution the starting dehydrovitamin **49** (2.0 mg, 33%) and the side-chain hydroxylated vitamin **5b** (3.0 mg, 48%).

De-*A*,*B*-cholest-9(11)-en-8-one (14). A solution of lithium diisopropylamide was prepared by adding *n*-BuLi (9.6 mmol, 6.0 mL, 1.60 M in hexanes) to a solution of diisopropylamine (1.34 mL, 0.97 g, 9.6 mmol) in THF (32 mL) at 0 °C. After 15 min, the reaction mixture was cooled to −78 °C, and Grundmann's ketone **13**[10] (2.11 g, 8.0 mmol) in THF (8 mL) was added dropwise via cannula. After 1 h, PhSeCl (1.84 g, 9.6 mmol) in THF (10 mL) was added via cannula. The reaction mixture was worked up immediately by adding it to acidic brine (4:1 saturated brine–10% HCl) and extracting with CH_2Cl_2 (2 × 50 mL). The organic layers were combined and then dried ($MgSO_4$). After removal of solvent, the crude selenide was dissolved in CH_2Cl_2 (100 mL). The mixture was then cooled to 0 °C, and MCPBA (*m*-chloroperbenzoic acid, 3.46 g, 80%, 16 mmol) was added in several portions. After 15 min, the reaction mixture was quenched with basic brine (1:1 saturated brine–saturated aqueous $NaHCO_3$) and then extracted with CH_2Cl_2 (1 × 100 mL). The combined organic layers were dried ($MgSO_4$), and then the solvent was removed. The crude product was purified via flash chromatography (silica gel, 5% EtOAc/hexanes) followed by HPLC (Waters 500, one cartridge, Prepak 500, 5% EtOAc/hexanes) to give 1.04 g of enone **14** (3.96 mmol, 50%) as a colorless oil.

De-*A*,*B*-8α-ethynylcholest-9(11)-en-8β-ol (15). Enone **14** (1.04 g, 3.97 mmol) in THF (15 mL) was added dropwise to a lithium acetylide solution prepared from THF (100 mL), acetylene (725 mL, 29 mmol), and n-BuLi (5.0 mL, 8.0 mmol, 1.60 M in hexanes) according to Midland's procedure.[25] The reaction mixture was stirred at −78 °C for 1 h. The dry ice bath was removed, and stirring was continued for 1 h. The reaction was quenched with H_2O (2 mL), and then the mixture was treated with K_2CO_3 until a white paste had formed. The organic layer was decanted, dried ($MgSO_4$), and filtered. Evaporation of the solvent gave a crude brown oil, which was distilled (Kugelrohr, 120 °C, 0.05 mm) to give a clear oil. The oil solidified to give waxy white crystals of **15** (1.05 g, 92%, mp 55–56 °C).

De-*A*,*B*-8α-ethylcholestan-8β-ol (16). Propargyl alcohol **17**[10,14] (62 mg, 0.21 mmol) and a stirbar were placed in a 25-mL hydrogenation flask, and then the flask was evacuated and flushed with N_2. To this flask was added hexanes (5 mL, distilled over $LiAlH_4$ under N_2) and 5% platinum on powdered carbon (31 mg). The flask was then attached to a standard hydrogenation apparatus, evacuated, and then flushed with hydrogen gas (four times). The reaction mixture was stirred under a positive atmosphere for 16 h. The mixture was then taken up in ether and filtered through a pad of silica gel. Removal of solvent afforded a residue, which was purified by HPLC (Whatman Partisil M9 10/50 column, 5% EtOAc/hexanes) to give 59 mg (95%) of the desired alcohol **16** as a clear oil.

Treatment of propargyl alcohol **15** (30 mg, 0.10 mmol) derived from enone **14** with hydrogen gas under similar conditions (5 mL hexanes, 30 mg of 5% Pt on carbon, 18 h at room temperature) gave, after HPLC purification, 25 mg (83%) of pure alcohol **16**, identical (^1H NMR and ^{13}C NMR spectral analyses and HPLC retention time) with the alcohol produced from **17**.

De-*A*,*B*-cholesta-9(11),25-dien-8-one (19). A solution of lithium diisopropylamide (LDA) was prepared by adding *n*-BuLi (2.59 mL, 1.70 M in hexanes, 4.4 mmol) to a solution of diisopropylamine (0.67 mL, 0.48 g, 4.8 mmol) in THF at 0 °C. After 5 min, the solution was cooled to −78 °C, and ketone **18**[1a] (1.05 g, 4.0 mmol) was added via cannula in THF (4 mL plus 1 mL for rinsing). The reaction mixture was stirred for 10 min at −78 °C and 2 h at room temperature and then recooled to −78 °C. To the cooled solution, PhSeCl (0.92 g, 4.8 mmol; recrystallized from

(32) For the binding of **1c** to the chick intestinal receptor, K_d (the equilibrium dissociation constant) is $\sim 2 \times 10^{-10}$ M, while that for nonspecific binding is $\sim 10^{-5}$ to 10^{-6} M (see ref 2a, p 236). An RCI value of >1 should be considered highly selective including the RCI value of ~47 measured for **5b**.

(33) Using the standard in vivo biological assay in the chick for intestinal calcium absorption (ICA) and bone calcium mobilization (BCM) previously reported [see: Hibberd, K. A.; Norman, A. W. *Biochem. Pharm.* **1969**, *18*, 2347], both analogues **5a** and **5b** exhibited significant agonist activity. These results will be presented elsewhere.

(34) Previously, it had been proposed that the reversible isomerization of vitamin D to previtamin might be necessary for biological activity: Velluz, L.; Amiard, G. *C. R. Hebd. Seances. Acad. Sci.* **1961**, *253*, 603; *Chem. Abstr.* **1962**, *56*, 11662e.

(35) Enas, J. D., unpublished results; Palenzuela, J. A., unpublished results.

(36) General experimental details are presented in the supplementary material section. In all cases, samples after purification were shown to be homogeneous by analytical HPLC analysis and ^1H and ^{13}C NMR analyses before submission for mass spectrometric determination.

hexanes) was added via cannula in THF (5 mL plus 1 mL washing). The cold reaction mixture was immediately poured into a stirred mixture of 100 mL of 0.1 M citric acid and 100 mL of ether. The organic layer was removed and separated, and the aqueous layer was extracted with ether (50 mL). The combined organic layers were washed with 50 mL of water and 50 mL of brine, dried ($MgSO_4$), and filtered. Removal of solvent afforded the crude selenide as a yellow oil, which was dissolved in a mixture of 60 mL of CH_2Cl_2 and 2 mL of pyridine. The solution was then cooled to ~−15 °C (ice/methanol bath), and then MCPBA (1.29 g, 6.0 mmol, 80% titer) was added in several portions. After 15 min, the cold reaction mixture was poured into basic brine (100 mL 1:1 brine–saturated aqueous $NaHCO_3$). The organic layer was removed, and the aqueous layer extracted with 50 mL of CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 × 50 mL), dried ($MgSO_4$), and filtered. Removal of the solvent gave a brown oil, which was purified by flash chromatography (5% EtOAc/hexanes, 5 × 18 cm silica gel column) to afford 140 mg recovered ketone **18** and 527 mg (51%) enone **19** as an oil.

1-(*tert*-Butyldimethylsiloxy)-9,10-secocholesta-5(10),9(11),25-trien-6-yn-8β-ol (21). To a solution of enyne **20**[15] (0.66 g, 2.67 mmol) in ether (3.5 mL) at 0 °C was added *n*-BuLi (1.71 mL, 1.70 M in hexanes, 2.90 mmol). The reaction mixture was stirred for 30 min, and then enone **19** (0.33 g, 1.32 mmol) in ether (1 mL and 0.5 mL washing) was added to the yellow acetylide solution via cannula. The cooling bath was removed, and the reaction mixture was stirred at room temperature for 1 h. Water (1 mL) was added, and then the mixture was treated with K_2CO_3, dried ($MgSO_4$), and finally filtered. Concentration of the ether solution gave a red oil, which was purified via flash chromatography (5% EtOAc/hexanes, 5.0 × 14 cm silica gel) to afford 0.34 g of recovered enyne and 0.57 g (89% based on **19**) of pure propargyl alcohol **21** as a light yellow glass.

1-(*tert*-Butyldimethylsiloxy)-9,10-secocholesta-5(10),9(11),25-trien-6-yn-8β-yl Benzoate (22). A solution of propargyl alcohol **21** (0.67 g, 1.31 mmol) in ether (4.1 mL) under N_2 was cooled to −78 °C. *n*-Butyllithium (0.85 mL, 1.70 M in hexanes, 1.44 mmol) was then added dropwise to the reaction mixture, which was then stirred at room temperature for 30 min. It was then recooled to −78 °C, and benzoyl chloride (0.152 mL, 0.18 g, 1.31 mmol) was added neat via a syringe. The cooling bath was removed, and the reaction mixture was stirred at room temperature for 2 h and then quenched with 1 mL of saturated aqueous NH_4Cl. Ether (50 mL) was added, and then the mixture was extracted with saturated aqueous $NaHCO_3$ (3 × 25 mL). The organic layer was then dried ($MgSO_4$), filtered, and concentrated to give the crude benzoate. Due to its chromatographic instability, the benzoate was used directly in the next reaction.

1-(*tert*-Butyldimethylsiloxy)-6α-(triphenylstannyl)-9,10-secocholesta-5(10),6,7,9(11),25-pentaene (23). A 100-mL round-bottomed flask equipped with stopcock and solid addition funnel was evacuated and flushed with N_2. Copper(I) cyanide (0.233 g, 2.6 mmol) was then placed in the solid addition funnel, and a solution of diisopropylamine (0.80 mL, 5.7 mmol) in THF (5.2 mL) was placed in the flask. To the solution (cooled to 0 °C) was added *n*-BuLi (3.06 mL, 1.70 M, 5.2 mmol) dropwise, and the solution was stirred for ~5 min. Triphenyltin hydride (1.33 mL, 1.83 g, 5.2 mmol) was added to the LDA solution, and the resulting cloudy yellow mixture was stirred for 15 min.[37] After dilution with ether (12.6 mL), CuCN was added slowly through the solid addition funnel to the (triphenylstannyl)lithium solution. After 20 min at 0 °C, the crude benzoate **22** (~800 mg, ~1.3 mmol) in ether (3 mL plus 2 mL rinsing) was added via cannula. The yellow solution turned black immediately and was stirred for 1 h at 0 °C, at which point the original yellow color had returned. The reaction was then quenched by addition of ~5 mL saturated aqueous NH_4Cl to the mixture. The crude mixture was extracted with ether (2 × 50 mL), and the combined organic layers were washed with saturated aqueous NH_4Cl (2 × 50 mL) and H_2O (1 × 50 mL), dried ($MgSO_4$), and filtered. Removal of the solvent gave a yellow oil, which was purified by flash chromatography (1% EtOAc/hexanes, silica gel, 5.0 × 15 cm) to afford 950 mg of stannyl allene **23** (87% yield, based on propargyl alcohol **21**). Further purification by HPLC (Rainin Dynamax 2.24 × 25 cm, 5 μm silica gel column, 1% EtOAc/hexanes, 8.0 mL/min) gave spectrally pure material.

(1*S*,6*R*)- and (1*R*,6*R*)-9,10-Secocholesta-5(10),6,7,9(11),25-pentaen-1-ol (1α,6β Isomer 24c and 1β,6β Isomer 24d, Respectively). The stannylallene **23** (195 mg, 0.231 mmol) was dissolved in 2 mL of THF in a 25-mL flask equipped with stirbar under N_2. The solution was cooled to 0 °C, and tetra-*n*-butylammonium fluoride trihydrate (432 mg, 1.38 mmol) was added via cannula in THF (2 mL + 0.5 mL washing). After 15 min, the reaction solution was quenched by the addition of ~2 mL of brine. The resulting mixture was extracted with ether (2 × 35 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (1 × 25 mL), dried ($MgSO_4$), and filtered. Removal of the solvent gave a crude oil, which was purified, first by flash chromatography (100% hexanes, 2.5 × 15 cm silica gel), and then by preparative HPLC (100% hexanes, Whatman Partisil M10 20/50 column, 1 recycle) to give the major 1α,6β and 1β,6β vinylallenol silyl ethers **24a** and **24b** (62 mg, 54%) and the minor 1α,6α and 1β,6α vinylallenol silyl ethers **25a** and **25b**. By integration of the HPLC RI trace (cut and weigh), the 6β to 6α ratio was determined to be 13.3/1.0. The 6β vinylallenol silyl ether fractions were then combined, placed in a 25-mL flask with a stir bar under N_2, and treated with tetra-*n*-butylammonium fluoride (1 M in THF, 2 mL). After 2 h at room temperature, the reaction mixture was treated with 1 mL of brine and extracted with ether (2 × 25 mL), and then the combined organic layers were washed with saturated aqueous $NaHCO_3$ (1 × 20 mL), dried ($MgSO_4$), filtered, and concentrated to give the crude vinylallenol mixture of **24c** and **24d**. The crude oil was then passed through a short silica gel column (hexanes) and then purified by HPLC (Rainin Dynamax 1.0 × 25 cm 5 μm silica gel column, 5% EtOAc/hexanes) to give in order of elution the 1α,6β vinylallenol **24c** (19.0 mg, 40%) and the 1β,6β vinylallenol **24d** (19.3 mg, 41%). The overall yield of 6β vinylallenols **24c** and **24d** from stannylallene **23** was 44%.

(1*S*)-9,11,25,26-Tetradehydro-3-deoxy-1-hydroxyvitamin D_3 (26a) and (1*S*,10*S*)-(5*Z*,7*Z*)- and (1*S*,10*R*)-(5*Z*,7*Z*)-9,10-Secocholesta-5,7,9(11),14,25-pentaen-1-ol (27a and 28a, Respectively). The 1α,6β vinylallenol **24c** (16.6 mg, 0.0436 mmol) was placed in a 25-mL flask equipped with condenser and stirbar. The apparatus was then evacuated and flushed with N_2, and the vinylallenol was dissolved in isooctane (4.4 mL). The resulting solution was heated at reflux for 3 h, following which the solvent was removed and the residue was subjected to HPLC purification (Rainin Dynamax 1.0 × 25 cm 5 μm silica gel column, 5% EtOAc/hexanes), giving in order of elution the 1*S* vitamin **26a** (10.5 mg, 63%), the 1*S*,10*S* pentaene **27a** (3.2 mg, 19%), and the 1*S*,10*R* pentaene **28a** (1.6 mg, 10%). The ratio of *E* isomer (**26a**) to *Z* isomers (**27a** plus **28a**) was 2.0:1.0 by integration of the HPLC RI trace (2.4:1.0 by NMR spectral analysis; 2.2:1.0 by weight). The overall mass balance for the thermolysis after separation and purification was 92%.

(1*R*)-9,11,25,26-Tetradehydro-3-deoxy-1-hydroxyvitamin D_3 (26b) and (1*R*,10*R*)-(5*Z*,7*Z*)- and (1*R*,10*S*)-(5*Z*,7*Z*)-9,10-Secocholesta-5,7,9(11),14,25-pentaen-1-ol (28b and 27b, Respectively). The 1β,6β vinylallene **24d** (21.0 mg, 0.0552 mmol) was placed in a 25-mL flask equipped with condenser and stirbar. The apparatus was then evacuated and flushed with N_2, and the vinylallenol was dissolved in isooctane (5.5 mL). The resulting solution was heated at reflux for 3 h, following which the solvent was removed. The residue was subjected to HPLC purification (Rainin Dynamax 1.0 × 25 cm 5 μm silica gel column, 5% EtOAc/hexanes) to give in order of elution the 1β-vitamin **26b** (2.6 mg, 12%), the 1*R*,10*R* pentaene **28b** (9.4 mg, 45%), and the 1*R*,10*S* isomer **27b** (7.0 mg, 33%). The ratio of *E* isomer (**26b**) to *Z* isomers (**28b** plus **27b**) was 1.0:5.2 by integration of the HPLC (RI) trace (1.0:6.0 by NMR spectral analysis; 1.0:6.3 by weight). The overall mass balance for the thermolysis products after separation and purification was 90%.

(1*S*,4*S*,6*S*)-1-Methyl-4-isopropenyl-7-oxabicyclo[4.1.0]-heptan-2-one (30). (*S*)-(+)-Carvone (**29**, 48 g, 0.31 mol) was dissolved in methanol (320 mL), and the solution was cooled to 0 °C. Hydrogen peroxide (30%, 100 mL, 0.96 mol) was added slowly with stirring to the cooled solution, and then the mixture

(37) The procedure used is taken from a procedure used to prepare tributylstannyl lithium: Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481.

was cooled to −15 °C. To the well-stirred mixture was added 6 M NaOH (26.4 mL) at such a rate that the internal temperature of the reaction did not exceed −10 °C. The reaction mixture was stirred at −10 to −15 °C for 8 h and then at 0 °C for an additional 11 h, after which it was poured into water (500 mL) and saturated with sodium chloride. The mixture was extracted with ether (4 × 300 mL), and the combined organic extracts were washed with brine and then dried over $MgSO_4$. After filtering, the solvent was evaporated and the crude residue was distilled on a Kugelrohr apparatus to afford 47.5 g (89%) of product (bp 90 °C, 1.5 mm; lit.[24] bp 70 °C, 0.6 mm) as a colorless oil.

(1*S*,2*R*,4*S*,6*S*)-2-Ethynyl-2-hydroxy-4-isopropenyl-1-methyl-7-oxabicyclo[4.1.0]heptane (31). Dry THF (25 mL) was syringed into a graduated cylinder fitted with a septum and cooled to −78 °C under a positive pressure of acetylene gas. Once the volume of THF remained constant, acetylene gas was bubbled through the solvent until 5 mL of acetylene (~120 mmol; $d_{-78°C}$ = 0.6208) had been absorbed. The acetylene solution at −78 °C was transferred via cannula to a 500-mL three-neck round-bottomed flask containing THF (175 mL) that had been previously cooled to −78 °C under argon. *n*-Butyllithium (1.4 M, 64 mL, 90 mmol) was added via cannula to the well-stirred acetylene solution at −78 °C over a 45-min period. The temperature was kept below −70 °C throughout the addition, and the resulting clear lithium acetylide solution was stirred at −78 °C for 30 min after the addition. To the lithium acetylide solution at −78 °C was slowly (~30 min) added via cannula carvone epoxide **30** (10 g, 60 mmol) in THF (100 mL), the temperature being maintained below −75 °C during the addition. After the addition was complete, the mixture was stirred at −78 °C for 5.5 h, after which TLC (silica gel, 10% ethyl acetate/hexanes) showed the absence of starting carvone epoxide. The reaction mixture was then poured into brine (300 mL), the layers were separated, the aqueous layer was extracted with ether (2 × 200 mL), and the combined organic layers were washed with brine and dried ($MgSO_4$). Concentration of the ether solution afforded a residue, which could be crystallized from pentane after cooling in the refrigerator to afford 8.3 g of product. Evaporation of the pentane mother liquors left 3.067 g of a residue, which after flash chromatography (silica gel, 20% ethyl acetate/hexanes), afforded a further 1.34 g of product: 9.6 g total yield (83%); mp 55–56 °C; $[\alpha]_D^{25}$ 0° (*c* 2.0, $CHCl_3$).

(1*S*,2*R*,4*S*,6*S*)-2-Acetoxy-2-ethynyl-4-isopropenyl-1-methyl-7-oxabicyclo[4.1.0]heptane (32). Alcohol **31** (8 g, 0.034 mol) was dissolved in dry triethylamine (104 mL), and to this stirred solution at 25 °C was added freshly distilled acetic anhydride (32 mL, 0.34 mol) followed by (dimethylamino)pyridine (0.992 g, 8.1 mmol). The mixture was stirred at 25 °C under argon for 13 h, after which the solvent was evaporated, the residue was dissolved in ether (400 mL), and the ether layer was washed with 1 M HCl, 1 M NaOH, and brine. After drying ($MgSO_4$) and evaporation of the solvent, the crude residual oil was distilled on a Kugelrohr apparatus (bp 110 °C, 1.4 mm) to afford 8.9 g (92%) of acetate **32**: $[\alpha]_D^{25}$ +0.8° (*c* 1.8, $CHCl_3$).

(1*S*,2*R*,4*S*,6*S*)-2,4-Diacetoxy-2-ethynyl-1-methyl-7-oxabicyclo[4.1.0]heptane (35). Acetate **32** (4.39 g, 18.7 mmol) was dissolved in dry dichloromethane (290 mL) and methanol (65 mL), and the solution was cooled to −78 °C under nitrogen. A mixture of ozone/oxygen (Welsbach Ozonator, pressure 5.5 psi, flow rate 1, 75 V) was bubbled through the solution for 22 min at which time the solution had turned blue. Nitrogen was then bubbled through the solution at −78 °C until the reaction solution was colorless. The solution was then allowed to reach room temperature slowly while maintaining a slow flow of nitrogen. Dry benzene (100 mL) was added to the solution, and then the mixture was evaporated to dryness. The methoxy hydroperoxide intermediate can be checked by ^1H NMR at this stage. The residue was dissolved in dry dichloromethane (205 mL) and pyridine (25 mL) and cooled to 0 °C under N_2. Freshly distilled *p*-nitrobenzoyl chloride (9.5 g, 51.1 mmol) was added in one portion, and the mixture stirred at 0 °C for 1 h, allowed to warm to room temperature, and refluxed for 16.5 h. After cooling, the solution was evaporated to dryness, the residue was dissolved in ethyl acetate (250 mL), the solution was filtered, and the filtrate was extracted with water, 1 M HCl, 1 M NaOH, and brine. After drying ($MgSO_4$) and evaporation of the combined organic extracts, the remaining solid was purified by flash chromatography (silica gel, 25% ethyl acetate/hexanes) to afford 3.54 g (75%) of diacetate **35**: mp 115–116 °C; $[\alpha]_D^{25}$ −19.0° (*c* 0.5, $CHCl_3$).

(3*S*,5*R*)-5-Acetoxy-1-ethynyl-3-hydroxy-2-methylcyclohex-1-ene (37). Freshly purified 1,2-diiodoethane (1.6 g, 5.67 mmol) was dissolved in dry THF (14 mL), and the solution was added via cannula to a stirred suspension of samarium metal (1.17 g, 7.78 mmol) in THF (7 mL) under an argon atmosphere. An exothermic reaction took place, and the suspension became green at first and after a few minutes, blue. Stirring was continued at 25 °C for 1 h, after which the color of the solution was deep blue. To this SmI_2 solution, a solution of epoxy diacetate **35** (610 mg, 2.42 mmol) and $Pd(PPh_3)_4$ (65 mg, 0.056 mmol) in dry THF (28 mL) was added via cannula. The solution was stirred at 25 °C for 4 h, at which time the blue color persisted but no starting material remained (TLC). The solution was poured into water (50 mL) and after stirring for 5 min, the color changed to brown-green. Solid sodium carbonate was added until saturation and the mixture was extracted with ethyl acetate (3 × 50 mL). After drying ($MgSO_4$) and concentrating the solution, the residue was subjected to flash chromatography (silica gel, 25% ethyl acetate/hexanes) to afford 430 mg (91%) of product **37** as a light yellow oil that was best stored in the dark under argon and at low temperature (−80 °C): $[\alpha]_D^{25}$ −101.3° (*c* 3.0, $CHCl_3$).

(3*S*,5*R*)-3,5-Bis[(*tert*-butyldimethylsilyl)oxy]-1-ethynyl-2-methylcyclohex-1-ene (38). Epoxy acetate **35** (3.00 g, 11.9 mmol) was treated with SmI_2 as described before (see preparation of **37**). The crude hydroxy acetate **37** was dissolved in diethyl ether (120 mL) and filtered. The residue after evaporation (2.5 g) was dissolved in methanol (23 mL), and the solution was cooled to 0 °C and treated with 0.2 M sodium methoxide in methanol (150 mL). After stirring for 2.5 h at 0 °C, the solution was acidified with Dowex 50X4-400 resin (200–400 mesh). After removal of the resin by filtration, the solution was evaporated, and the residue was purified by flash chromatography (silica gel, ethyl acetate) to give a quantitative yield of the deprotected diol. The diol was then treated with *tert*-butyldimethylsilyl chloride (7.10 g, 47.1 mmol) and imidazole (6.34 g, 93.1 mmol) in DMF (62 mL) at 25 °C for 12 h protected from light. An ice–water slurry (60 mL) was added to the solution, and stirring was continued for $^1/_2$ h. The solution was extracted repeatedly with diethyl ether, and the combined ether extracts were washed with brine to afford, after drying and evaporation, a crude product that was purified by flash chromatography (silica gel, hexanes and then 2% ethyl acetate/hexanes) followed by vacuum drying. The protected enyne **38** was obtained as a colorless oil in 70% yield (3.15 g).

(3*S*,5*R*)-3,5-Bis[(trimethylsilyl)oxy]-1-ethynyl-2-methylcyclohex-1-ene (39). To a stirred solution of hydroxy acetate **37** (107 mg, 0.551 mmol) in dry methanol (1 mL) at 0 °C was added 0.20 M sodium methoxide in methanol (6.9 μL, 1.4 mmol) dropwise, and the mixture was stirred at 0 °C for 4 h. Glacial acetic acid was added to the reaction mixture until it was slightly acidic, and then the solution was evaporated to dryness. The residue was dissolved in dry THF (3 mL) and treated with imidazole (112 mg, 1.64 mmol) and trimethylsilyl chloride (0.20 μL, 1.57 mmol) at 25 °C, and then the mixture was allowed to stir for 0.5 h. After evaporation of the solvent, the residue was dissolved in benzene (10 mL), and the solution was filtered through a short column of neutral alumina (grade III). Evaporation of the solvent gave an oil that was purified by HPLC (2% ethyl acetate/hexanes, Whatman Partisil M10 20/50 column) to give the product **39** as an oil: $[\alpha]_D^{25}$ −102.5° (*c* 0.4, $CHCl_3$) [lit.[23a] $[\alpha]_D^{22}$ −90° ($CHCl_3$)].

(1*S*,2*R*,4*S*,6*S*)-2-Hydroxy-4-isopropenyl-1-methyl-7-oxa-2-[2-(trimethylsilyl)ethynyl]bicyclo[4.1.0]heptane (40a). Methyllithium–lithium bromide complex (1.30 M in pentane, 2.88 mL, 3.75 mmol) was added dropwise to a solution of bis(trimethylsilyl)acetylene (0.64, 3.75 mmol) in THF (10 mL) at 0 °C. The cloudy solution was warmed to room temperature, stirred for 3 h, and recooled to −78 °C. A solution of carvone epoxide **30** (0.52 g, 3.13 mmol) in THF (5 mL) was then added, and the resulting clear solution was allowed to warm to room temperature, stirred for 2 h, and poured into brine (15 mL). The mixture was extracted with diethyl ether (4 × 30 mL) and then the combined organic extracts were dried ($MgSO_4$). Evaporation of the solvent afforded a white solid, which was purified by flash chromatography (silica gel, hexanes/diethyl ether, 3/1) to afford 0.57 g (69%) of

alcohol **40a** (colorless needles, mp 70.5–71.0 °C) and a mixture of **40a** and its 2*S* epimer (0.17 g).

(1*S*,2*R*,4*S*,6*S*)-2-Acetoxy-4-isopropenyl-1-methyl-7-oxa-2-[2-(trimethylsilyl)ethynyl]bicyclo[4.1.0]heptane (40b). Alcohol **40a** (3.96 g, 15 mmol) was dissolved in dry triethylamine (2.27 g, 22.5 mmol), and to this solution (dimethylamino)pyridine (DMAP, 0.36 g, 3 mmol) was added followed by freshly distilled acetic anhydride (1.91 g, 18.75 mmol). The mixture was stirred for 19 h, more acetic anhydride (0.39 g) was added, and the solution was stirred for an additional 3 h. The reaction mixture was diluted with ether and poured onto ice. The layers were separated, and the organic layer was washed with 1 M HCl, saturated Na_2CO_3 and water, and dried ($MgSO_4$). Evaporation of the solvent left an oil, which was distilled (Kugelrohr, bp 105 °C, 1.5 mm) to afford acetate **40b** (3.63 g, 79%) as a thick, colorless oil.

(1*S*,2*R*,4*S*,6*S*)-2-Acetoxy-4-acetyl-1-methyl-7-oxa-2-[2-(trimethylsilyl)ethynyl]bicyclo[4.1.0]heptane (41). To a stirred solution of acetate **40b** (0.319 g, 1.04 mmol) dissolved in THF (7 mL) and water (7 mL) was added 1% OsO_4 (0.2 mL). The mixture was stirred for 5 min, and sodium periodate (0.541 g) was added in one portion. The reaction mixture was stirred for 23 h, the THF solvent was evaporated under vacuum, and then the residue was extracted with diethyl ether (3 × 5 mL). The combined organic extracts were washed with saturated sodium bisulfite (2 × 3 mL), saturated $NaHCO_3$ (1 × 3 mL), and brine (1 × 3 mL) and then dried ($MgSO_4$). The residue after evaporation was purified by flash chromatography (silica gel, 25% ethyl acetate/hexanes) to afford methyl ketone **41** (0.219 g, 68%) as an oil, which was further purified by Kugelrohr distillation (bp 90–95 °C, 1.5 mm).

(3*S*,5*R*)-3-Hydroxy-5-isopropenyl-2-methyl-1-[2-(trimethylsilyl)ethynyl]cyclohex-1-ene (42). A solution of epoxy acetate **40b** (0.139 g, 0.456 mmol) and $Pd(PPh_3)_4$ (0.026 g, 0.023 mmol) in THF (5 mL) was added via cannula to a solution of SmI_2 [prepared as described earlier from Sm (0.686 g, 4.56 mmol) and diiodoethane (1.223 g, 4.147 mmol)] in THF (5 mL), and the solution was stirred at room temperature for 3 h. The reaction mixture was poured over saturated Na_2CO_3 (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residual red oil was dissolved in hexanes (20 mL) and filtered. After evaporation, the crude alcohol **42** was purified by flash chromatography (silica gel, 10% ethyl acetate/hexanes) to afford **42** as a white amorphous solid (0.076 g, 67%), which proved homogeneous by HPLC and spectral characterization.

(3*S*,5*R*)-5-Acetoxy-3-[(*tert*-butyldimethylsilyl)oxy]-1-ethynyl-2-methylcyclohex-1-ene (43a). Diacetate **35** (1.160 g, 4.603 mmol) was treated with samarium diodide as described elsewhere. The crude hydroxy acetate **37** was dissolved in diethyl ether (100 mL) and filtered. The residual reddish oil after evaporation was dissolved in dry DMF (25 mL) and the solution treated with *tert*-butyldimethylsilyl chloride (1.42 g, 9.42 mmol) and imidazole (1.27 g, 18.67 mmol). The solution was stirred at room temperature for 11 h protected from the light. Ice-cold water (25 mL) was added, and the solution was stirred for 40 min and extracted with diethyl ether (3 × 40 mL). The combined organic extracts were washed with water (3 × 10 mL) and dried ($MgSO_4$). The residual oil after evaporation was purified by flash chromatography (silica gel, 5% ethyl acetate/hexanes and then 10% ethyl acetate/hexanes) to afford silyl ether **43a** (0.985 g, 69% from epoxy diacetate **35**).

(3*S*,5*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-1-ethynyl-5-hydroxy-2-methylcyclohex-1-ene (43b). Sodium methoxide (0.2 M in methanol, 19 mL, 3.80 mmol) was added dropwise to a solution of acetate **43a** (0.935 g, 3.03 mmol) in dry methanol (19 mL) at 0 °C. The solution was stirred for 3 h, neutralized with Dowex 50×4-400 resin (200–400 mesh), filtered, and concentrated. The residual crude alcohol **43b** was purified by flash chromatography (silica gel, 25% ethyl acetate/hexanes) to afford **43b** as white, crystalline plates (0.709 g, 88%) with mp 92.0–92.5 °C.

(3*S*,5*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-1-ethynyl-3-hydroxy-2-methylcyclohex-1-ene (43c). Tetra-*n*-butylammonium fluoride (1 M solution in THF, 0.066 mL, 0.066 mmol) was added to a solution of bissilyl ether **38** (25 mg, 0.065 mmol) in THF (1 mL) at room temperature, and the mixture was stirred for 40 min. Water (1 mL) was added, and the mixture was stirred for 50 min. After dilution with diethyl ether (10 mL) the layers were separated, the aqueous layer extracted with diethyl ether (2 × 5 mL), and then the organic layers were combined and dried ($MgSO_4$). The residue after evaporation was purified by HPLC (Rainin Dynamax 1 × 25 cm, 8 μm silica gel column, 10% ethyl acetate/hexanes, 4 mL/min) to afford in order of elution the allylic alcohol **43c** (8 mg, 46%) and the isomer alcohol **43b** (4 mg, 23%) (the latter was identified by direct ^1H NMR comparison with an authentic sample).

(1*S*,3*S*)-Bis[(*tert*-butyldimethylsilyl)oxy]-9,10-secocholesta-5(10),9(11),25-trien-5-yn-8β-ol (44).[30] To a solution of enyne **38** (522 mg, 1.38 mmol) in diethyl ether (1.6 mL) at 0 °C was added *n*-BuLi (0.86 mL, 1.60 M in hexanes, 1.4 mmol). The reaction mixture was stirred for 1 h, and then enone **19** (298 mg, 1.15 mmol) in diethyl ether (2 mL) was added dropwise. After stirring at 0 °C for 10 min, the cooling bath was removed and the reaction mixture was allowed to reach room temperature while stirring. After 1 h (total time since removal of the bath), brine (1 mL) was added, the mixture was diluted with diethyl ether (10 mL), the layers were separated, the aqueous layer was extracted with diethyl ether (2 × 5 mL), and the organic extracts were combined and dried ($MgSO_4$). The residual oil after evaporation was purified by flash chromatography (silica gel, 5% ethyl acetate/hexanes) to afford 626 mg (85%) of propargyl alcohol **44**.

(1*S*,3*S*)-Bis[(*tert*-butyldimethylsilyl)oxy]-9,10-secocholesta-5(10),9(11),25-trien-6-yn-8β-yl Benzoate (45). *n*-Butyllithium (0.67 mL, 1.60 M in hexanes, 1.1 mmol) was added dropwise to a stirred solution of alcohol **44** (0.626 g, 0.978 mmol) in diethyl ether (3 mL) at −78 °C. The stirred reaction mixture was then allowed to warm to room temperature, stirred for 2.3 h, and recooled to −78 °C. Freshly distilled benzoyl chloride (113 μL, 0.978 mmol) was added neat, and then the reaction mixture was allowed to reach room temperature, stirred for 2 h (total time since addition of benzoyl chloride), and quenched with saturated aqueous $NaHCO_3$ (1 mL). The mixture was diluted with diethyl ether (20 mL), and the layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 5 mL) and brine (1 × 5 mL), and then dried ($MgSO_4$). After filtration, the solvent was evaporated to yield the labile benzoate **45** (~700 mg) as a crude material containing some unreacted alcohol **44**, which, for preparative purposes, was best used without further purification. Alternatively, a 65–70% yield of pure benzoate **45** (white foam) could be obtained upon subjecting the crude material to flash chromatography (silica gel, hexanes/ethyl acetate/pyridine 97/2/1; the silica gel was thoroughly washed with this solvent mixture to insure saturation with pyridine) followed by HPLC purification (Whatman Partisil M 10 20/50 column, 5% ethyl acetate/hexanes, 4 mL/min).

(1*S*,3*S*,6*S*)-1,3-Bis[(*tert*-butyldimethylsilyl)oxy]-6-(triphenylstannyl)-9,10-secocholesta-5(10),6,7,9(11),25-pentaene (46). Triphenyltin hydride (1.0 mL, 3.9 mmol) was added dropwise to a solution of LDA [from diisopropylamine (0.60 mL, 4.3 mmol) and *n*-butyllithium (2.44 mL, 1.6 M in hexanes, 4.3 mmol)] in THF (3.9 mL) at 0 °C.[37] The resulting yellow suspension was stirred at 0 °C for 15 min and then diluted with diethyl ether (8 mL). To the well-stirred mixture at 0 °C was added CuCN (0.175 g, 1.96 mmol) in small portions through a solid addition funnel. After rinsing the funnel with THF (3 mL) the mixture was stirred at 0 °C for 30 min. To the resulting yellow-orange suspension a solution of the crude benzoate **45** (~0.7 g) in diethyl ether (3.2 mL) was added via cannula. After being stirred at 0 °C for 1.5 h the reaction mixture was quenched with saturated aqueous NH_4Cl (4 mL), the layers were separated, and the aqueous layer was extracted with diethyl ether (2 × 30 mL). The combined organic extracts were washed with saturated NH_4Cl (1 × 20 mL) and brine (1 × 10 mL) and dried ($MgSO_4$). The residue after evaporation was dissolved in hexanes (10 mL), and the remaining insoluble white solid was filtered and thoroughly washed with hexanes. The filtrate was evaporated to dryness, and the residue was subjected to flash chromatography (silica gel, 2.5% ethyl acetate/hexanes) to afford stannylallene **46** (~1.0 g), suitable for carrying on the synthetic scheme. Pure **46** was obtained by HPLC (Rainin Dynamax 2.24 × 25 cm, 5 μm silica gel column, 1% ethyl acetate/hexanes, 2 mL/min, one recycle). There

was no indication of the presence of a second diastereomeric allene.

(1S,3S,6R)-9,10-Secocholesta-5(10),6,7,9(11),25-pentaene-1,3-diol (47). Tetra-*n*-butylammonium fluoride (1 M in THF, 11 mL, 11 mmol) was added dropwise to a solution of stannylallene **46** (~978 mg, partially purified material from previous reaction) in THF (15 mL) at 0 °C. The solution was stirred at 0 °C for 20 min, slowly warmed to room temperature, and then stirred for 14 h. Water (15 mL) was added, the mixture was extracted with diethyl ether (3 × 30 mL), and then the combined organic extracts were washed with brine (1 × 10 mL) and dried ($MgSO_4$). The crude material obtained after evaporation was purified by flash chromatography (silica gel, 4/1 ethyl acetate/hexanes) to obtain in order of elution a mixture of the 3-TBDMS protected diol and its 6*S* isomer (~297 mg) and a mixture of diol **47** and its 6*S* isomer **48** (192 mg). The partially protected material was dissolved in THF (5 mL) and stirred with fresh tetra-*n*-butylammonium fluoride (1 M in THF, 3.3 mL) at room temperature for 38 h. A similar workup as described above yielded an additional 120 mg of the diol mixture **47** and **48** (total crude yield, 312 mg). The ratio of 6*R* vinylallene to its 6*S* isomer was 10:1 [by ^1H NMR integration of the C_{18}-CH_3 signals at δ 0.74 (major 6*R* isomer) and δ 0.67 (minor 6*S* isomer)]. This mixture was separated by HPLC (Rainin Dynamax 2.24 × 25 cm, 5 μm silica gel column, 4/1 ethyl acetate/hexanes, 8 mL/min) to give in order of elution the desired 6*R* vinylallene **47** (183 mg) and slightly impure (^1H NMR spectrum) 6*S* vinylallene **48** (~19 mg). The overall yield of the desired (1*S*,3*S*,6*R*)-vinylallene **48** was 47% from propargyl alcohol **44** (three steps).

(1S)-9,11,25,26-Tetradehydro-1-hydroxyvitamin D_3 (49). A solution of vinylallene **47** (43 mg, 0.108 mmol) in isooctane (11 mL) was refluxed under an argon atmosphere for 3.25 h. After cooling, the solvent was evaporated, and the residue was purified by HPLC (Rainin Dynamax 1 × 25 cm, 8 μm silica gel column, 7/3 ethyl acetate/hexanes, 3 mL/min) to afford in order of elution the vitamin **49** (28 mg, 65%) and an inseparable mixture of 7*Z*-pentaenes **50** and **51** (13 mg, 30%). The 7*Z* fraction was a mixture of C_{10} epimers (10*S* and 10*R*) analogous to **27** and **28**. These minor components were not separated (they appeared under optimized conditions as overlapping peaks on the HPLC trace), but were characterized as a mixture: the major component eluted slightly faster than the minor component; the major and minor components were identified as the 10*S* and 10*R* isomers, respectively, by ^1H NMR analysis of the mixture (2.7:1.0 ratio by ^1H NMR integration). The ratio of vitamin **49** to 7*Z* isomers (by integration of the HPLC trace) was 2.3:1.0. The overall mass balance of the reaction after separation was 95%.

1α,25-$(OH)_2$-D_3 Receptor Competition Assays. The assay of competitive binding was performed using the hydroxylapatite batch assay.[31a,32] Increasing amounts of unlabeled 1α,25-$(OH)_2$-D_3 or analogue were added to a constant amount of [^3H]-1α,25-$(OH)_2$-D_3 and incubated with chick intestinal cytosol. The relative competitive index (RCI) for **5a** or **5b** was calculated by plotting the percent maximum 1α,25-$(OH)_2$-[^3H]-D_3 bound × 100 on the ordinate versus [competitor]/[1α,25-$(OH)_2$-[^3H]-D_3] on the abscissa. The slope of the line obtained for the analogue is divided by the slope of the line obtained for 1α,25-$(OH)_2$-D_3; multiplication of this value by 100 results in the RCI.[31a] By definition, the RCI for 1α,25-$(OH)_2$-D_3 is 100. For the preparation of intestinal cytosol from vitamin D-deficient chicks, the duodenal loop was removed after decapitation, stripped of contents, and washed at 4 °C in 0.9% NaCl solution. All subsequent steps were carried out at 4 °C as previously described.[31a]

Acknowledgment. This study was generously supported by the NIH grants DK-16595, DK-9012, and CA-43277. R. A. Gibbs also acknowledges receipt of a Chancellor's Patent Fund Grant from UC Riverside for partial support. Grace Jones is acknowledged for the biological evaluation of the analogues described herein. Starting materials utilized in this study were generously provided by Badische-Anilin und Soda Fabrik, Lugwigshafen, and Dr. M. Rappodolt of Duphar B. V., Weesp, the Netherlands. We are grateful to A. Mouriño and L. Castedo (Universidad de Santiago de Compostela, Spain) and E. G. Baggiolini and M. Uskokovic (Hoffmann- LaRoche, Nutley, NJ) for informing us of their results prior to publication.

Supplementary Material Available: Spectral data for all new compounds and general experimental details (19 pages). Ordering information is given on any current masthead page.

Total Synthesis of (±)-Dimethyl Secologanoside *O*-Methyl Ether

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Received March 2, 1989

The synthesis of the iridoid monoterpene (±)-dimethyl secologanoside *O*-methyl ether is described. The key steps include the anionic oxy-Cope rearrangement of an *endo*-vinylnorbornenol, lead tetraacetate oxidative cleavage of an α-hydroxy ketone to an aldehyde ester, and ozonolytic cleavage of a β,γ-unsaturated ester followed by zinc–acetic acid reduction of the ozonide to a hemiacetal.

The iridoids,[1] with ca. 300 known naturally occurring compounds, represent a large class of natural products. They usually occur as the glucoside and are important for the biosynthesis of some types of indole alkaloids.[2] In addition, some possess significant biological activity of their own.[3] Most of the members of these iridoids, such as secologanoside (**1a**),[4] sweroside (**2**),[5] loganin (**3**),[6] allamandin (**4**),[7] and specionin (**5**),[8] are highly oxygenated and densely functionalized. These characteristics may explain

(1) El-Naggar, L. J.; Beal, J. L. *J. Nat. Prod.* **1980**, *43*(6), 649.
(2) Miles, D. H.; Kokpol, U.; Bhattacharya, J.; Atwood, T. L.; Stone, K. E.; Bryson, T. A.; Wilson, C. *J. Am. Chem. Soc.* **1976**, *98*, 1569.
(3) Trost, B. M.; Mao, M. K.-T.; Balkovec, J. M.; Buhlmayer, P. *J. Am. Chem. Soc.* **1986**, *108*, 4965.
(4) (a) Calis, I.; Sticher, D. *Phytochemistry* **1984**, *23*, 2539. (b) Isoe, S.; Katsumura, S.; Okada, T.; Yamamoto, K.; Takemoto, T.; Inaba, H.; Han, Q.; Nakatani, K. *Tetrahedron Lett.* **1987**, *28*, 5865. (c) Brown, R. T.; Curless, D. *Tetrahedron Lett.* **1986**, *27*, 6005. (d) Brown, R. T.; Jones, M. F. *J. Chem. Soc., Chem. Commun.* **1985**, 699; **1986**, 1818. (e) Hamilton, R. G.; Saunders, G. N.; McLean, S. *Can. J. Chem.* **1983**, *61*, 284. (f) For review about secologanin, see: Tietze, L.-F. *Angew. Chem., Int. Ed. Engl.* **1983**, 828.
(5) Inouye, H.; Ueda, S.; Nakamura, Y. *Chem. Pharm. Bull. (Tokyo)* **1970**, *18*, 1856.
(6) Lentz, P. L.; Rossmann, M. G. *Chem. Commun.* **1969**, 1269.

0022-3263/89/1954-4083$01.50/0