98-2; **20**, 83135-99-3; **21**, 83136-00-9; **23**, 83152-06-1; **26**, 83136-01-0; **27**, 83136-02-1; **28a**, 83136-03-2; **28b**, 83136-05-4; **28c**, 83198-40-7; **29**, 83136-04-3; **30**, 81600-36-4; 3-[(*tert*-butyldimethylsilyl)oxy]-1-iodopropane, 78878-05-4; 2,2'-dipyridyl sulfide, 4262-06-0; phenylmercuric perchlorate, 19664-02-9; *p*-toluenesulfenyl chloride, 933-00-6.

Supplementary Material Available: X-ray stereostructure for compound **28a** plus Tables 1–10, including fractional atom coordinates, bond lengths, bond angles, hydrogen coordinates, and temperature factors for both structures **6a** and **28a**. Full experimental section for both structure determinations is also included (49 pages). Ordering information is given on any current masthead page.

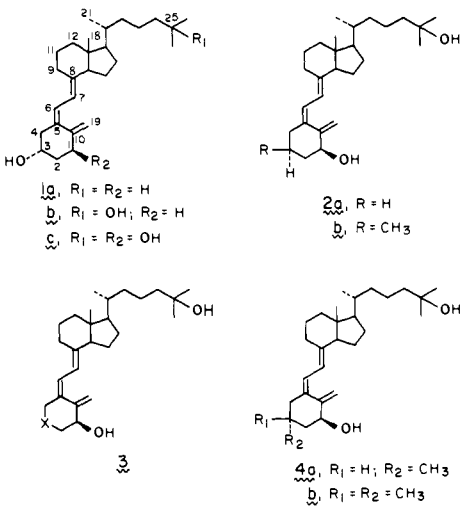
Effect of 3-Methyl Substituents on the Thermal [1,5]- and [1,7]-Sigmatropic Hydrogen Shifts of Vinylallenes and Other Seco Steroids Related to Vitamin D: Synthesis of 3-Methyl- and 3,3-Dimethyl-Substituted Analogues of 3-Deoxy-1α,25-dihydroxyvitamin D_3[1]

Gregory A. Leyes and William H. Okamura*

Contribution from the Department of Chemistry, University of California, Riverside, California 92521. *Received December 21, 1981*

Abstract: The 3-methyl-substituted analogues of 1α,25-dihydroxyvitamin D_3 (**2b**, **4a**, and **4b**), useful for probing structure–function relationships in the vitamin D_3–endocrine system, were synthesized by using vinylallenols **21–26** as key intermediates. The vinylallenols and their rearrangement products were studied to determine the effect of 3-methyl substitutents on their thermal behavior. The thermal rearrangement (100 °C) of vinylallenols of this type involves a [1,5]-sigmatropic hydrogen shift by either of two competing pathways. While one pathway affords a product containing the vitamin D triene, the products in the competing process consist of a triad of seco steroids related by [1,7]-sigmatropic hydrogen shifts. The vinylallenols **21**, **22**, **25**, and **26** were synthesized by coupling the C/D fragment, de-*A*,*B*-8α-ethynyl-25-cholesten-8β-ol benzoate (**16b**), with a heterocuprate derived from silyl ethers of *cis*-2,5-dimethyliodocyclohex-2-en-1-ol (**19b**) or 2,5,5-trimethyliodocylohex-2-en-1-ol (**20**) (followed by deprotection). The epimeric vinylallenols **23** and **24** were obtained by an S_N2 displacement process at C-1 of the corresponding *cis*-vinylallenols **21** and **22**, respectively. The thermolysis products of each vinylallenol rearrangement in the 3-methyl series were separated and characterized. The major products from the 1*R* alcohols **21** and **24** were the corresponding vitamins **27** and **39** whereas vitamins **31** and **35** were minor products of the thermolysis of the 1*S* alcohols **22** and **23**. In each case, the remaining products consisted of a triad of thermally interconvertible isomers of the type **8**, **9**, and **10**. The vitamin isomers possessing the side-chain double bond (**31**, **27**, and **43**) were further elaborated to the desired 1α,25-dihydroxyvitamin analogues **2b**, **4a**, and **4b**.

The principal metabolic pathway of vitamin D_3 (**1a**, cholecalciferol) involves successive hydroxylation to produce 25-hydroxyvitamin D_3 (**1b**) and then 1α,25-dihydroxyvitamin D_3 (**1c**).[2] This latter metabolite (**1c**) is the biologically most active substance known for eliciting the classic vitamin D mediated responses, intestinal calcium absorption (ICA) and bone-calcium mobilization (BCM). It is believed to be the physiologically active form of **1a**, and it should be considered to behave as a steroid hormone both from a functional and a structural point of view. The synthesis of analogues related to this steroid hormone continues to be of considerable interest in order to better understand its mode of action. Although previous studies had established that the hydroxyl functionalities at the C-1 and C-25 positions were most critical for optimum biological activity,[3] modifications at the C-3 position imparted biological properties of unusual interest to this hormone. Unlike the natural metabolite **1c**, which elicits both ICA and BCM, the 3-deoxy analogue **2a** exhibited only ICA activity.[4] Since this selective agonist ability is potentially useful



(1) Paper 23 in the series Studies on Vitamin D (Calciferol) and Its Analogues. For paper 22, see: Gerdes, J. M.; Lewicka-Piekut, S.; Condran, P., Jr.; Okamura, W. H. *J. Org. Chem.* **1981**, *46*, 5197.

(2) For reviews of the chemistry and biochemistry of the vitamin D field, see: (a) Norman, A. W. "Vitamin D, the Calcium Homeostatic Steroid Hormone"; 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.

(3) (a) Okamura, W. H.; Norman, A. W.; Wing, R. M. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 4194. (b) Procsal, D. A.; Okamura, W. H.; Norman, A. W. *J. Biol. Chem.* **1975**, *250*, 8382. (c) Proscsal, D. A.; Okamura, W. H.; Norman, A. W. *Am. J. Clin. Nutr.* **1976**, *29*, 1271. (d) Wecksler, W. R.; Okamura, W. H.; Norman, A. W. *J. Steroid Biochem.* **1978**, *9*, 927.

(4) (a) Okamura, W. H.; Mitra, M. N.; Wing, R. M.; Norman, A. W. *Biochem. Biophys. Res. Commun.* **1974**, *60*, 179. (b) Okamura, W. H.; Mitra, M. N.; Procsal, D. A.; Norman, A. W. *Ibid.* **1975**, *65*, 24. (c) Lam, H. Y.; Onisko, B. L.; Schnoes, H. K.; De Luca, H. F. *Ibid.* **1974**, *59*, 845. (d) Onisko, B. L.; Lam, H. Y.; Reeve, L.; Schnoes, H. K.; De Luca, H. F. *Bioorg. Chem.* **1977**, *6*, 203.

0002-7863/82/1504-6099$01.25/0

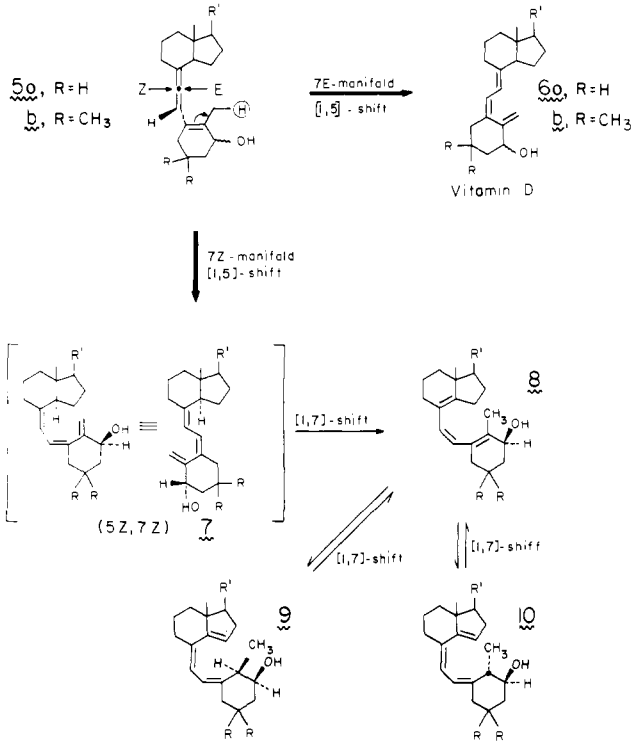


Figure 1. 7*E* and 7*Z* thermal manifolds. The pathway leading to the secondary products of the presumed intermediate **7** is shown for only one of the two C-1 hydroxyl epimers (1*S*).

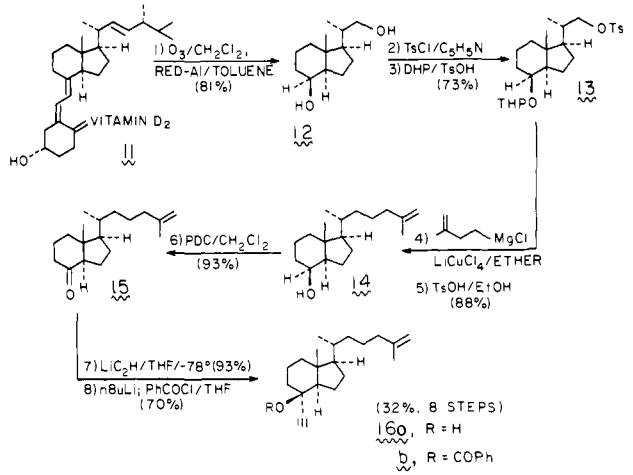
clinically, other studies were performed to probe the relationship between functional modification at C-3 and biological activity. Interestingly, the 3α-methyl analogue **2b** retained the ability to elicit both ICA and BCM.[5] In order to further evaluate this effect, it was of interest to develop a general method for synthesizing and studying a series of analogues possessing general structure **3**. To illustrate the method, in this article we report a new synthesis of **2b** as well as its epimer **4a** and the 3,3-dimethyl analogue **4b** to complete the 3-methyl series for biological evaluation. Of primary importance in developing the method was the incorporation of the biologically required C-1α and C-25 hydroxyl groups while allowing for isotopic labeling at the side chain at the latest possible stage in the synthesis.

Although the previous synthesis of **2b** involved a classical approach, it was more feasible to utilize our recently developed convergent approach involving vinylallenes as key intermediates. This approach had previously been employed for the synthesis of the 25-deoxy compounds **6a** and **6b**.[6,7] As shown in Figure 1, the thermal [1,5]-sigmatropic hydrogen shift of each vinylallenol **5a,b** affords products arising from rearrangement by either the 7*E* of 7*Z* manifold.[6,7] Whereas rearrangement via the 7*E* manifold produces the desired vitamin D–triene system (**6a** and **6b**), the products of the 7*Z* manifold (**7a** or **7b**) rearranged via [1,7]-sigmatropic shifts under the reaction conditions to provide a thermally interconvertible triad of secondary and tertiary products (**8**, **9**, and **10** in Figure 1). Besides the interesting finding that the C-1 hydroxyl stereochemistry provides a marked influence on the preferred pathway of vinylallene rearrangement, it was also noted that substituents at the C-3 position significantly influenced the 7*E*/7*Z* ratio (vide infra, Table I). Whereas the 1*R*,6*R* alcohol **5a** gave a 7*E*/7*Z* ratio of ~2.7:1, the corresponding 1R,6R alcohol **5b** gave a 7*E*/7*Z* ratio of ~6.8:1. The epimeric 1S,6R alcohols gave 7*E*/7*Z* ratios of ~1:4.1 and ~1:8.3 for **5a** and **5b**, respectively. The product distribution and reactivity of the trienes (**8–10**) of the 7*Z* manifold were also influenced by substituents at the C-3 position. It was thus of interest to synthesize the 3α, 3β, and 3,3-dimethyl analogues **2b**, **4a**, and **4b** not only to probe the structure–activity relationships in the vitamin D–endocrine system but also to study the effects of 3-substituents on the [1,5]- and [1,7]-sigmatropic hydrogen shift processes depicted in Figure 1.

Table I. Thermal Rearrangement of 3-Substituted Vinylallenols

vinylallenol	7*E*/7*Z*
21 (1*R*,3*R*)	4.6:1
22 (1*S*,3*S*)	1:4.6
23 (1*S*,3*R*)	1:4.3
24 (1*R*,3*S*)	3.5:1
(1*R*)-5a	2.7:1
(1*S*)-5a	1:4.1
(1*R*)-5b	6.8:1
(1*S*)-5b	1:8.3

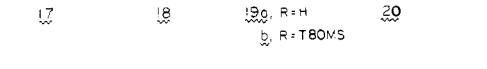
Scheme I



Results

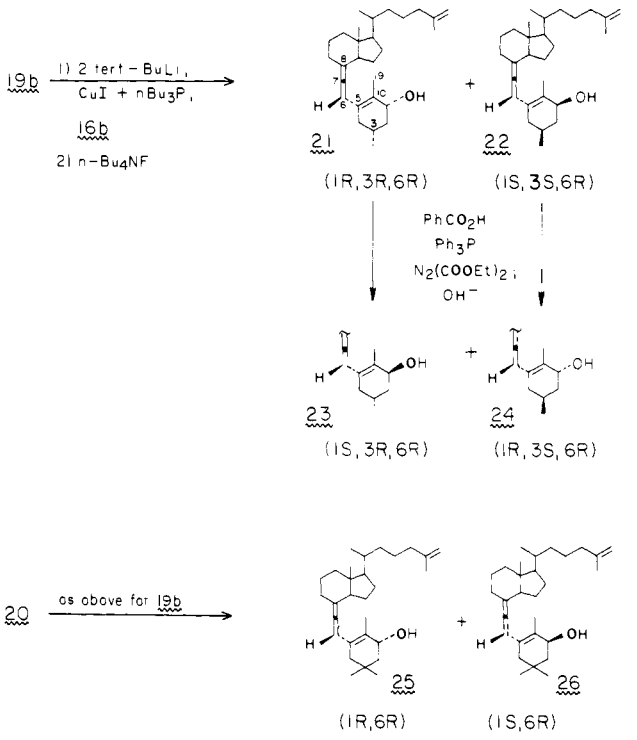
C/D and A-Ring Fragments. Scheme I summarizes the synthesis of the C/D fragment, propargyl benzoate **16b**. This is a technically improved modification of a procedure described by Lythgoe[8] for the synthesis of alcohol **14**, and the details are presented elsewhere.[9] The C-8 stereochemical assignment and the trans C/D ring junction of **16a** and **16b** were made on the basis of their similarity to the analogous side chain saturated derivatives previously described in the literature.[6,7,10]

The A-ring fragment utilized for the subsequent coupling step was obtained by iodination of **17** to provide **18**.[11] Reduction using $NaBH_4$/EtOH afforded **19a**,[12] which was protected as the silyl ether **19b**.[13] The 5,5-dimethyl A-ring fragment **20** was prepared in a similar way.[7]



(5) Okamura, W. H.; Mitra, M. N.; Pirio, M. R.; Mouriño, A.; Carey, S. C.; Norman, A. W. *J. Org. Chem.* **1978**, *43*, 574.
(6) Condran, P., Jr.; Hammond, M. L.; Mouriño, A.; Okamura, W. H. *J. Am. Chem. Soc.* **1980**, *102*, 6259.
(7) Mouriño, A.; Lewicka-Piekut, S.; Norman, A. W.; Okamura, W. H. *J. Org. Chem.* **1980**, *45*, 4015.
(8) Lythgoe, B.; Roberts, D. A.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2608.
(9) Leyes, G. A. Ph.D. Dissertation, University of California, Riverside, CA, December 1981.
(10) Hammond, M. L.; Mouriño, A.; Okamura, W. H. *J. Am. Chem. Soc.* **1978**, *100*, 4907. Hammond, M. L. Ph.D. Dissertation, University of California, Riverside, CA, March 1978.
(11) Piers, E.; Nagakura, I. *Synth. Commun.* **1975**, *5*, 193.
(12) The reduction afforded a ~5:1 ratio of *cis* and *trans* isomers. The cis isomer **19a** was purified by fractional crystallization.
(13) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

Scheme II



Synthesis of Vinylallenes. Scheme II shows the procedure used for preparing the 3-methyl and 3,3-dimethyl vinylallenols **21–26**. In each coupling reaction the iodosilyl ether (**19b** or **20**) was reacted with 2 equiv of *tert*-butyllithium in ether,[14] and then the lithium salt was transferred to a solution of CuI and $(n\text{-Bu})_3P$[15] in ether at −78 °C. The resulting mixed cuprate was treated with propargyl benzoate **16b** followed by deprotection using $(n\text{-Bu})_4NF$ in THF.[13] Separation by high-pressure LC afforded pure **21** (less polar) and **22** (more polar) in 25% and 24% yields, respectively. Analogously, in the 3,3-dimethyl series, **25** (less polar) and **26** (more polar) were obtained in 24% and 28% yields, respectively. All allene products were of the 6*R* configuration, consistent with previous reports of cuprate couplings in related systems.[6,7] No (6*S*)-allenes were isolated or detected spectroscopically.[6,7,16] The (6*R*)-allene assignments for **21** and **22** were made by comparison of the C-18 methyl ^1H NMR chemical shifts for each with those of previously reported compounds.[6,7,17] Allenes of the 6*R* configuration exhibit a C-18 methyl signal at τ 9.35 ± 0.03, whereas (6*S*)-allenes exhibit a signal at τ 9.27 ± 0.03. The C-18 resonances for **21** and **22** were found at τ 9.34. Similarly, the C-18 methyl resonances for **25** and **26** appeared at τ 9.35.

The epimeric vinylallenols **23** and **24** were prepared from **21** and **22**, respectively, as shown in Scheme II.[18] These trans isomers could be distinguished from the cis precursors by a much narrower signal of the C-1 proton ($w_{1/2} \sim 8.1$ Hz) in **23** and **24** compared to **21** and **22** ($w_{1/2} \sim 20$ Hz). The narrower signal is characteristic[19] of the increased population of pseudoaxial hydroxyl conformer in the trans isomers **23** and **24**.

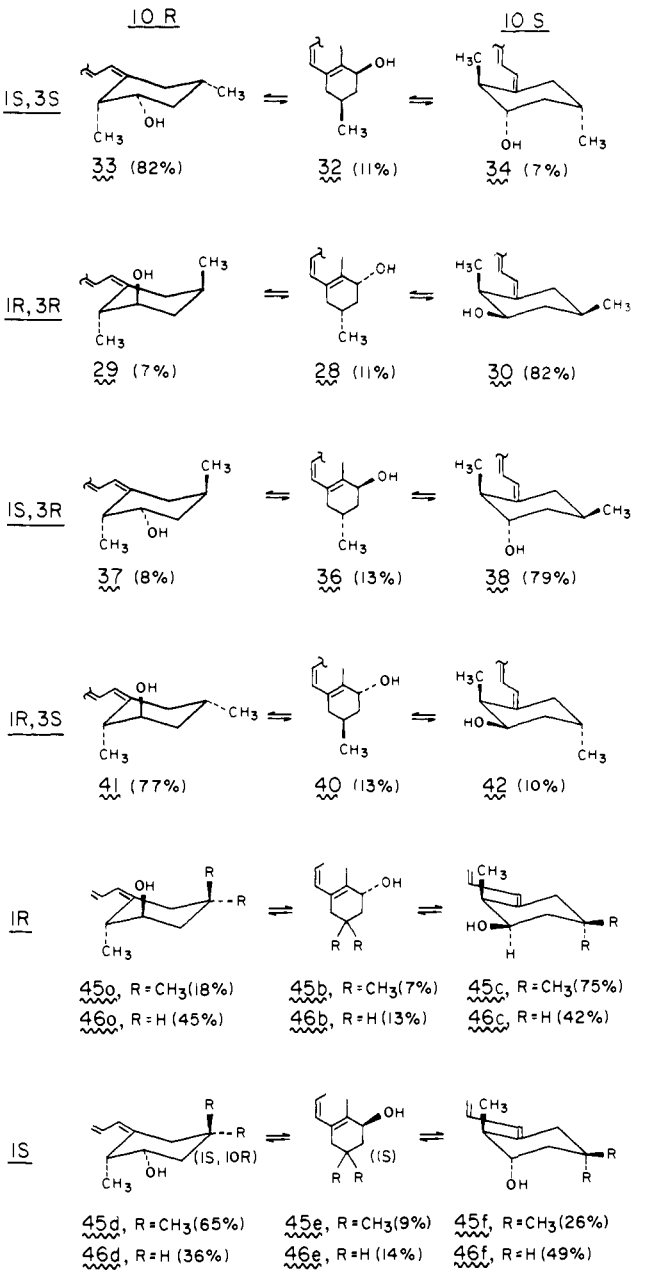
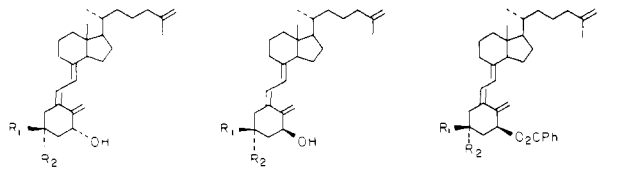


Figure 2. Thermal equilibrations of the 7*Z* manifold products. The left and right columns of structures depict the more stable of the two chair conformers of the (10*R*)- and (10*S*)-$\Delta^{5,7,14}$-trienes. The center column of structures correspond to the *cis*-isotachysterols. The C-1 (hydroxyl) and C-3 (non-allylic methyl) configurations for each row are given in the left-hand margin; the C-10 configurations (allylic methyl) are given at top of the first and third column of structures. The equilibrium data for **45** and **46** were taken from ref 6 and 7 of the text.

Thermal Studies. The 3-methylvinylallenols **21–24** were each heated in refluxing isooctane (~0.01 M, 100 °C) under nitrogen for 11 h, and a summary of products (**27–42**) and yields is given in the Experimental Section. The major products from the (1*R*)-vinylallenol thermolyses (**21** and **24**) were the vitamin analogues **27** and **39**. Vitamins **31** and **35** were produced in minor amounts from the epimeric (1*S*)-vinylallenols **22** and **23**, respectively. These findings are consistent with the results of previous studies in which the (1*R*,6*R*)-vinylallenols produced vitamin products preferentially, whereas vitamin products were

(14) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 9256.
(15) Suzuki, M.; Suzuki, T.; Kawagishi, T.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1247.
(16) The 6*R* stereochemistry is that resulting from a formal S_N2' displacement in a completely anti fashion. See: (a) Rona, P.; Crabbé, P. *J. Am. Chem. Soc.* **1968**, *90*, 4733; (b) *Ibid.* **1969**, *91*, 3289. (c) Luche, J. L.; Berreiro, E.; Dollat, J. M.; Crabbé, P. *Tetrahedron Lett.* **1975**, 4615. (d) Van Dijck, L. A.; Lankwerden, B. J.; Vermeer, J. G. C. M.; Weber, A. J. M. *Recl. Trav. Chim. Pays-Bas* **1971**, *90*, 801. (e) Westmijze, H.; Vermeer, P. *Tetrahedron Lett.* **1979**, 4101. (f) Amos, R. A.; Katzenellenbogen, J. A. *J. Org. Chem.* **1978**, *43*, 555. (g) Haces, A.; van Kruchten, E. M. G. A.; Okamura, W. H. *Tetrahedron Lett.* **1982**, *23*, 2707 and references cited therein.
(17) Bakker, S. A.; Lugtenburg, J.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 1459. Havinga, E. *Experientia* **1973**, *29*, 1181.
(18) (a) Mitsunobu, O.; Eguchi, M. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3427. (b) Grynkiewicz, G.; Burzynska, H. *Tetrahedron* **1976**, *32*, 2109. (c) For a review, see: Mitsunobu, O. *Synthesis* **1981**, 1.
(19) Senda, Y.; Imaizumi, S.; Ochiai, S.; Fujita, K. *Tetrahedron* **1974**, *30*, 539.



27, R_1=H, R_2=CH_3 31, R_1=CH_3, R_2=H 47a, R_1=H, R_2=CH_3
39, R_1=CH_3, R_2=H 35, R_1=H, R_2=CH_3 b, R_1=R_2=CH_3
43, R_1=R_2=CH_3 44, R_1=R_2=CH_3

formed in minor amounts from (1*S*,6*R*)-vinylallenols.[6,7] In a similar manner, thermolysis of **25** produced the (1*R*)-vitamin **43** in 65% isolated yield, while the (1*S*)-vitamin **44** was obtained in only 10% yield from **26**.

Also isolated in each thermolysis were the products obtained in the 7*Z* thermal manifold, namely, **28–30**, **32–34**, **36–38**, and **40–42**. These 7*Z* products exist in thermal equilibrium, and the results are shown in Figure 2. The ratios shown for each triad were obtained by separately heating each isomer (100 °C, 36 h) and analyzing the product distribution. Also shown in Figure 2 are the equilibrium ratios for the previously reported 7*Z* manifold products for the 3,3-dimethyl (**45a–f**)[7] and 3,3-didemethyl series (**46a–f**).[6] It is apparent from comparison of vinylallenol thermolysis products (see Experimental Section) and Figure 2 that equilibria within the 7*Z* manifold has not been established at the earlier time point (11 h). Monitoring the vinylallene thermolyses by means of analytical high-pressure LC indicates that in two cases studied, thermolysis of **21** and **22**, the two $\Delta^{5,7,14}$-triene isomers that form fastest, **29** and **34**, respectively, are not the thermodynamic products. It had also been previously noted in compounds **45** and **46** that the kinetic product was not the thermodynamically favored isomer.[6,7] The stereostructural assignment of each isomer in Figure 2 was made on the basis of spectral similarities (UV and ^{1}H NMR, supplementary material) to the aforementioned series **45** and **46**.[6,7]

Preparation of the 3-Methyl-Substituted 1α,25-(OH)$_2$-Vitamin D$_3$ Analogues. Elaboration of the vitamin **27** to the 3β-methyl-1α,25-(OH)$_2$-vitamin **4a** was accomplished through the intermediacy of the (1S)-benzoate **47a** (eq 1). The attenuated yield

$$\mathbf{27} \xrightarrow[N_2(COOEt)_2]{PhCO_2H,\ Ph_3P} \mathbf{47a} \xrightarrow[3.\ HO^-]{1.\ Hg(OAc)_2,\ 2.\ NaBH_4} \mathbf{4a} \qquad (1)$$

$$\mathbf{43} \xrightarrow[N_2(COOEt)_2]{PhCO_2H,\ Ph_3P} \mathbf{47b} \xrightarrow[3.\ HO^-]{1.\ Hg(OAc)_2,\ 2.\ NaBH_4} \mathbf{4b} \qquad (2)$$

$$\mathbf{31} \xrightarrow[2,\ NaBH_4]{1,\ Hg(OAc)_2} \mathbf{2b} \qquad (3)$$

(32%) was presumably due to the propensity for dehydration in this system using the triphenylphosphine–diethyl azodicarboxylate–benzoic acid reagents for formation of the benzoate with inversion of configuration at C-1.[18] Oxymercuration/demercuration of **47a** gave a single product which was isolated in 41% yield (not optimized) after saponification to afford **4a**. Identical manipulation of **47b** afforded **4b** in 67% yield (eq 2). It was surprising that oxymercuration was so selective in attacking only the Δ^{25} double bond. The original synthetic strategy entailed selective side chain epoxidation using *m*-chloroperbenzoic acid followed by $LiAlH_4$ reduction.[20] However, attempted epoxidation of **47b** resulted in almost instantaneous attack on the triene system with no noticeable reaction at the side chain. Formation of **2b** was accomplished in 70% yield by oxymercuration/demercuration of **31** (eq 3).

Discussion

Thermal Studies. The thermal rearrangement of the vinylallenols studied is assumed to involve a suprafacial [1,5]-sigmatropic hydrogen shift via either of two competing pathways (Figure 1). The 7*E*/7*Z* ratios for the 3-methylvinylallenols **21–24** are summarized in Table I. In cases reported previously, the preferred pathway of the 1*R*,6*R* alcohols leads to the 7*E* (vitamin) product.[6,7] Alternatively, thermolysis of the 1*S*,6*R* alcohols produces primarily products arising from [1,7]-sigmatropic shifts within the 7*Z* manifold (Figure 1). This result is consistent with a model wherein the migrating hydrogen prefers a pathway from the face of the A-ring opposite that of the C-1 hydroxyl.[6] It appears that this preference is not markedly affected by the relative stereochemistry of the C-3 methyl substituent. Thus, the 7*E*/7*Z* ratio for **22** (~1:4.6) is comparable to that for **23** (~1:4.3), while the ratio for **21** (~4.6:1) is only slightly larger than that for **24** (~3.5:1). These data are similar to the demethyl series **5a** discussed earlier in the introduction. The nearly complementary reversal of 7*E*/7*Z* ratios in the 1*R* and 1*S* series, e.g., **21** vs. **22**, **23** vs. **24**, and (1*R*)-**5a** vs. (1*S*)-**5a**, indicates that the major influence in migratory preference can be attributed to the relative orientation of the C-1 hydroxyl and the trajectory of the migrating C-19 hydrogen. The unusually enhanced *E*/*Z* ratios for the 3,3-dimethyl allenes **5b** also mentioned in the introduction is reminiscent of the exceptional behavior of *gem*-dialkyl-substituted six-membered rings studied in another context,[21] but there is no satisfactory correlation or rationale at present for this type of effect. The propensity for hydrogen migration anti to the hydroxyl is also not easily rationalized. Although this effect is possibly steric in origin, it could be argued that the effect is due to electronic factors. A π-facial perturbation,[22] that is, the relative location and orientation of the hydroxyl or other substituents with respect to the rearranging moiety, could be expected to influence the 7*E*/7*Z* ratio. For example, very strong conformational biasing (preferably locking) of the A ring would specifically orient the hydroxyl or the translocation (for example, to C-4) of the hydroxyl should prove informative. The results of theoretical molecular orbital calculations as well as the study of the vinylallene rearrangements with other substitution patterns should support or possibly refute this electronic argument, and such studies are in progress.

The thermal rearrangements in the 7*Z* manifold depicted in Figure 2 are presumed to occur via antarafacial [1,7]-sigmatropic hydrogen shifts. The conformers shown for the epimeric C-10 isomers in Figure 2 are the chair forms which would be expected to predominate. In each case, the $\Delta^{5,7,14}$-triene is of the planar 6,7-trans conformation and the C-19 methyl group is placed in an axial orientation. This C-19 methyl axial preference has been discussed earlier[6,7,23] and is due to an unfavorable steric interaction with the C-7 proton when the methyl group is oriented equatorially. The marked preference for one epimer over the other is then easily rationalized by examining the relative orientations of the C-1 hydroxyl and C-3 methyl. The usual generalizations that methyl and hydroxyl prefer equatorial orientations and that methyl groups are larger than hydroxyls readily rationalizes which of two diastereomers, 10*R* vs. 10*S* of the $\Delta^{5,7,14}$-trienes, is preferred. The *cis*-isotachysterol analogues are present in minor quantities at equilibrium, presumably due to the steric congestion in these types of compounds possessing (*Z*)-Δ^6-ene moieties. At least qualitatively, there is observed a kinetic preference for [1,7]-sigmatropic rearrangment of the *cis*-isotacysterols to that $\Delta^{5,7,14}$ isomer, 10*R* or 10*S*, which possesses a trans relationship between the C-10 methyl and C-1 hydroxyl. In other words, the rearrangement always favors the isomer formed by hydrogen migration to the A-ring face syn to the hydroxyl group, irrespective of steric congestion. With respect to Figure 1, **8** → **10** is faster than **8** →

(20) (a) Crandall, J. K.; Paulson, D. R. *J. Org. Chem.* **1968**, 32, 991. (b) Anderson, W. K.; Veysoglu, T. *Ibid.* **1973**, *38*, 2267.

(21) (a) Allinger, N. A.; Zalkow, V. *J. Org. Chem.* **1960**, *25*, 701. (b) Rickborn, B.; Wuesthoff, M. T. *J. Am. Chem. Soc.* **1970**, *92*, 6894.

(22) For treatments of orbital distortion in other systems, see: (a) Liotta, C. L. *Tetrahedron Lett.* **1975**, 519, 523. (b) Inagaki, S.; Fujimoto, H.; Fukui, K. *J. Am. Chem. Soc.* **1976**, *98*, 4054. (c) Burgess, E. M.; Liotta, C. L. *J. Org. Chem.* **1981**, *46*, 1703. For recent experimental examples, see: (d) Jones, D. W. *J. Chem. Soc., Chem. Commun.* **1980**, 739. (e) Mazzocchi, P. H.; Stahly, B.; Dodd, J.; Rondan, N. G.; Dommelsmith, L. N.; Rozeboom, M. D.; Caramella, P.; Houk, K. N. *J. Am. Chem. Soc.* **1980**, *102*, 6482. (f) Böhm, M. C.; Carr, R. V. C.; Gleiter, R.; Paquette, L. A. *Ibid.* **1980**, *102*, 7218.

(23) Onisko, B. L.; Schnoes, H. K.; De Luca, H. F. *J. Org. Chem.* **1978**, *43*, 3441.

9. In the monomethyl series, **29**, **34**, **38**, and **41** are formed faster than **30**, **33**, **37**, and **42**, respectively. In the cases of **38** and **41**, the kinetic and thermodynamic products are identical. Again, the notion of a π-facial orbital perturbation[22] caused by the allylic hydroxyl group provides an attractive rationale for the observed kinetic preferences. A steric rationale certainly seems unlikely in this case, and it is reasonable that the hydroxyl is producing a similar type of effect in both the [1,5] and [1,7] shifts occurring in these seco steroids. These results await a theoretical and experimental evaluation through studies involving translocation or other changes of the hydroxyl group.

Conclusion

The vinylallene approach for producing the important 1-hydroxyvitamin D system has now been extended for preparing 25-hydroxylated systems. The analogues **2b**, **4a**, and **4b** synthesized in this study have been submitted for biological evaluation. In vitro studies[24] have shown that the 3α-methyl isomer **2b** binds to the chick intestinal receptor most effectively of the three analogues studied. This isomer binds 3 times more effectively than its epimer **4a** and 48 times more effectively than the dimethyl isomer **4b**. In vivo evaluations are in progress and will be reported at a later date. The approach used in this study not only is extremely versatile but also lends itself conveniently to isotopic labeling using tritiated $NaBH_4$ at the final stage (oxymercuration/demercuration) of the synthesis. The inclusion of the biologically key hydroxyl functionalities at both the 1α and 25 positions allows for more direct comparisons of synthetic analogues with the biologically active form (**1c**) of vitamin D in structure–function studies.

Experimental Section

General Procedures. Spectroscopic (^{1}H NMR, IR, UV, and high- and low-resolution MS) and other analytical data are given in the supplementary material.

Air-sensitive reactions, including those involving alkyllithium reagents, metal catalysts, sensitive allenes, etc., were performed under an atmosphere of dry nitrogen. Commercial purified nitrogen was further dried by passing it through a tower containing KOH and anhydrous $CaSO_4$ prior to use. References to aqueous $NaHCO_3$, NH_4Cl, or NaCl during experimental workup procedures refer to saturated aqueous solutions of the above reagents unless otherwise stated. Dry ether or THF (tetrahydrofuran) refers to reagent-grade material freshly distilled from $LiAlH_4$ under nitrogen. THF was normally predried over 4-Å molecular sieves. Skellysolve B and lbpe (low-boiling petroleum ether, bp 30–60 °C) were distilled from CaH_2 prior to use. Benzene was purified by distillation from potassium/benzophenone ketyl. Pyridine was distilled from CaH_2 or KOH and stored over 4-Å molecular sieves. Acetonitrile (CH_3CN) was distilled from P_2O_5 prior to use. Isooctane (2,2,4-trimethylpentane) was freshly distilled from $LiAlH_4$ for all thermolyses. Dimethylformamide (DMF) was distilled from CaH_2. Kugelrohr distillation boiling points (bp) refer to the external-air-bath temperature; pressure is expressed in mmHg. Melting points (mp) (uncorrected) were obtained on a Thomas-Hoover capillary apparatus.

High-pressure liquid chromatography (high-pressure LC) was performed on a Waters 6000A solvent delivery system equipped with a U6K injector and dual detector system (M450 variable wavelength UV and R401 refractive index detectors). A Whatman M9 10/50 Partisil (10-μm particle size, 9.4 mm i.d. × 50 cm) column was used for normal-phase conditions unless otherwise noted. The column used for reverse-phase conditions was Whatman ODS-2 M9 10/50 Partisil (10-μm silica packing with 10% by weight octadecylsilane stationary phase). All chromatography solvents were distilled prior to use. Solvents and solvent mixtures were vacuum filtered through a 0.45-μm Millipore filter and vacuum degassed immediately prior to use.

Medium-ressure LC refers to a system designed by Meyers and co-workers.[25] Columns used were 1000 × 15 mm (<2 g of material) and 1000 × 25 mm (>2 g of material). Flash chromatography refers to a system described by Still and co-workers.[26] Silica gel 60 (230–300 mesh) obtained from MCB-Merck was used in the medium-pressure LC and flash chromatography systems. Ordinary column chromatography was performed on J. T. Baker silica gel (60–200 mesh). Thin-layer chromatography (TLC) was performed on either silica gel G (0.4-mm-thick analytical plates) or precoated plates with silica gel 60 F-254 from MCB-Merck.

(1*S*,3*S*)-3-Deoxy-1,25-dihydroxy-3-methylvitamin D_3 (2b). Mercuric acetate (4.1 mg, 0.013 mmol) was added to the (1*S*)-vitamin **31** (4.9 mg, 0.012 mmol) in a mixture of THF (0.2 mL) and water (0.05 mL) at 0 °C. The solution was stirred for 2 h followed by the addition of 3 M aqueous NaOH (12 μL) and a solution of 0.5 M sodium borohydride in aqueous NaOH (12 μL) and stirred for an additional 30 min. Solid K_2CO_3 was added, the liquid decanted, and the residue washed with ether. The organic fractions were combined and evaporated under reduced pressure, and then the residual oil was passed down a short silica column (1:1 ether/lbpe) to remove elemental mercury. Purification by high-pressure LC (μ-Porasil column, 20% EtOAc/Skellysolve B) gave pure dihydroxyvitamin **2b** (3.5 mg, 70%) as a colorless oil.

(1*S*,3*R*)-3-Deoxy-1,25-dihydroxy-3-methylvitamin D_3 (4a). The (1*S*)-vitamin benzoate **47a** (12 mg, 0.023 mmol) was dissolved in THF (0.2 mL) and water (0.05 mL). Mercuric acetate (8 mg, 0.026 mmol) was added and the solution stirred for 2 h. A solution of 0.5 M sodium borohydride in 3 M aqueous NaOH (25 μL) was added and the solution stirred for an additional 30 min. The flask was equipped with a reflux condenser, and the mixture was then stirred with 5% KOH/MeOH (1.5 mL) at 60 °C for 1.5 h. The majority of solvent was removed, ether (1 mL) was added, and then solid K_2CO_3 was added. The organic solvent was decanted and the residue washed with additional ether. Removal of insoluble material was accomplished by short silica gel column chromatography (20% ether/lbpe). High-pressure LC (μ-Porasil column, 20% ethyl acetate/Skellysolve B, 2.0 mL/min flow rate) gave the pure dihydroxyvitamin **4a** (4 mg, 41%).

(1*S*)-3-Deoxy-1,25-dihydroxy-3,3-dimethylvitamin D_3 (4b). Mercuric acetate (2.1 mg, 6.6 μmol) was added to a solution of the benzoate **47b** (3.4 mg, 6.6 μmol) in a mixture of THF (0.2 mL) and water (0.05 mL) cooled to 0 °C. The solution was stirred for 1.5 h followed by addition of 3 M aqueous NaOH solution (6.6 μL) and 0.5 M sodium borohydride in 3 M aqueous NaOH (6.6 μL) and stirred for an additional 20 min. Solid K_2CO_3 was added, and the organic layer was decanted. The flask was washed with ether (1 mL), and the organic layers were combined. The product was purified by short-column chromatography (silica gel, 40% ether/lbpe) to give a hydroxybenzoate (2.8 mg) of sufficient purity for saponification. The latter was stirred in a mixture of 5% KOH/MeOH (0.35 mL) and THF (0.07 mL) for 1.5 h at 60 °C. The crude saponification product was purified by high-pressure LC (20% ethyl acetate/Skellysolve B, μ-Porasil column, 2.0 mL/min flow rate) to give pure vitamin **4b** (1.9 mg, 67%).

De-*A*,*B*-25-cholesten-8-one (15). The alcohol **14**[8,9] (2.716 g, 10.27 mmol) was added to a solution of pyridinium dichromate (11.58 g, 30.8 mmol) and pyridinium trifluoroacetate (0.793 g, 4.1 mmol) in dry dichloromethane (27 mL), and then the mixture was magnetically stirred (4.5 h). The solution was passed through a fritted-glass funnel containing a slurry of diatomaceous earth (CH_2Cl_2) covered by a slurry of silica gel (CH_2Cl_2). Solvent evaporation under reduced pressure followed by purification by Kugelrohr distillation afforded **15** (2.526 g, 94%) as a colorless oil: bp 112 °C (0.05 mm).

De-*A*,*B*-8α-ethynyl-25-cholesten-8β-ol (16a). Acetylene (547 mL, 21.88 mmol) was slowly added (gas syringe to dry THF (−78 °C, N_2) followed by *n*-butyllithium (1.57 M, 13.3 mL, 20.84 mmol). After 10 min of stirring, ketone **15** (2.734 g, 10.42 mmol) was added via syringe (dissolved in 1 mL dry THF) and stirred (1 h, −78 °C). The cooling bath was removed and the reaction stirred at ambient temperature (1 h). The reaction was quenched by addition of water (5 mL). Solid K_2CO_3 was added, and the solution was decanted and dried over Na_2SO_4. The crude brown liquid was Kugelrohr distilled to afford the propargyl alcohol **16a** (2.80 g, 93%) as a clear liquid; bp 100 °C (0.005 mm).

De-*A*,*B*-8α-ethynyl-25-cholesten-8β-ol Benzoate (16b). *n*-Butyllithium (1.57 M, 6.5 mL, 10.14 mmol) was added dropwise (syringe) to a solution (−78 °C, N_2) of propargyl alcohol **16a** (2.80 g, 9.71 mmol) in dry THF (28 mL). The solution was stirred at ambient temperature (30 min) and then recooled (−78 °C) for addition (syringe, dropwise) of freshly distilled benzoyl chloride (1.13 mL, 9.71 mmol). The solution was then stirred (room temperature) for an additional 3 h. Water (5 mL) was added to quench the reaction mixture, followed by additional stirring (10 min). The solvent was evaporated under reduced pressure, and the resulting oil was taken up in water (30 mL) and extracted with ether (30 mL). The aqueous layer was extracted with additional ether (30 mL). The organic layers were combined, washed with aqueous $NaHCO_3$ (60 mL), dried over $MgSO_4$, and concentrated to a yellow oil. The product **16b** was purified by a combination of crystallization from pentane and medium-pressure LC (15% ether/lbpe eluant) of the concentrated mother

(24) Mayer, E.; Kadowaki, S.; Okamura, W. H., Ohnuma, N.; Leyes, G. A.; Schmidt-Gayk, H.; Norman, A. W. *J. Steroid Biochem.* **1981**, *15*, 145.
(25) Meyers, A. I.; Slade, J.; Smith, R. K.; Mihelich, E. D.; Hershenson, F. M.; Liang, C. D. *J. Org. Chem.* **1979**, *44*, 2247.
(26) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

liquor, leaving a white solid: 2.78 g, 70%, mp 81–82 °C.

3-Iodo-2,5-dimethylcyclohex-2-en-1-one (18). The iodination was performed by first reacting iodine (1.992 g, 7.85 mmol) with triphenylphosphine (2.05 g, 7.85 mmol) in acetonitrile (35 mL) for 3 h. The diketone **17**[27] (1.00 g, 7.13 mmol) and triethylamine (1.1 mL, 7.85 mmol) were added, and the resulting solution was refluxed (6–14 h). The amount of time required for reflux varied from reaction to reaction, so that monitoring (TLC, diisopropyl ether eluant) was necessary to determine optimum reflux time. After evaporation of acetonitrile under reduced pressure (water-bath temperature 32 °C), ether (50 mL) was added, resulting in the formation of a precipitate. The flask was washed with ether (4 × 100 mL) and the eluant passed down a silica column for purification (3 × 32 cm column). Evaporation of solvent followed by Kugelrohr distillation (bp 92 °C (0.15 mm) afforded pure iodoketone **18** (1.171 g, 66%).

***cis*-3-Iodo-2,5-dimethylcyclohex-2-en-1-ol (19a).** The iodo ketone **18** (2.903 g, 11.6 mmol) was reacted with sodium borohydride (0.482 g, 12.7 mmol) in absolute ethanol (27 mL) for 20 min. The reaction was quenched by dropwise addition of 2 M aqueous HCl (10 mL). The clear solution was poured into water (120 mL) and extracted with ether (2 × 100 mL). The organic layer was washed with aqueous $NaHCO_3$ and brine and then dried over Na_2SO_4. The ether was evaporated and the crude product dissolved in pentane. The flask was chilled to induce fractional crystallization of the cis-3-iodo alcohol **19a**: 1.966 g, 67%, mp 59–60 °C. The mother liquor consisted of an approximately 1.6:1 ratio of cis to trans isomers, whereas the initial mixture contained ~5:1 ratio of cis to trans isomers. Separation of the isomeric pair could be achieved with some difficulty by a multiple shave–recycle technique using semipreparative high-pressure LC (10% ethyl acetate/Skellysolve B, 8.0 mL/min flow rate). The trans isomer thus obtained could not be purified in sufficient quantities for further use, but its ^1H NMR spectrum is compared to that of the major cis isomer as evidence for relative configuration (see supplementary material).

***cis*-1-(*tert*-Butyldimethylsiloxy)-3-iodo-2,5-dimethylcyclohex-2-ene (19b).** The iodo alcohol **19a** (524 mg, 2.08 mmol) was reacted with *tert*-butyldimethylsilyl chloride (470 mg, 3.12 mmol) and imidazole (425 mg, 6.24 mmol) in a manner exactly analogous to that described for the preparation of the 2,5,5-trimethyl derivative **20**.[7] The iodo silyl ether **19b** was purified by Kugelrohr distillation: 658 mg, 83%, bp 95 °C (0.15 mm).

(1*R*,3*R*,6*R*)- and (1*S*,3*S*,6*R*)-1-Hydroxy-3-methyl-9,10-secocholesta-5(10),6,7,25-tetraenes (21 and 22, Respectively). The iodo silyl ether **19b** (613 mg, 1.67 mmol) was coupled with propargyl benzoate **16b** (597 mg, 1.52 mmol) and then deprotected in a manner exactly as described for the preparation of **25** and **26**. Purification by high-pressure LC (10% EtOAc/Skellysolve B) afforded two isomeric vinylallenols: 1*R*,3*R*,6*R* isomer **21** (153 mg, 25%) and 1*S*,3*S*,6*R* isomer **22** (146 mg, 24%) as white foams.

(1*S*,3*R*,6*R*)-1-Hydroxy-3-methyl-9,10-secocholesta-5(10),6,7,25-tetraene (23). Triphenylphosphine (328 mg, 1.25 mmol) and benzoic acid (305 mg, 2.5 mmol) were added to a solution of the (1*R*,3*R*)-vinylallenol 21 (110 mg, 0.25 mmol) in dry benzene (2 mL, dried over potassium/benzophenone; magnetically stirred, N_2 atmosphere). A solution of diethyl azodicarboxylate (0.2 mL, 1.25 mmol, freshly distilled) in dry benzene (2 mL) was added dropwise, and the mixture was stirred for 30 min. The solvent was evaporated under reduced pressure, the product was taken up in ether (35 mL), and then the organic extract was washed with aqueous $NaHCO_3$ (35 mL). The aqueous layer was back-extracted with ether, and then the organic layers were combined and dried over Na_2SO_4. The solution was concentrated and purified by high-pressure LC (reverse phase, 40% acetone/methanol) to afford the (1*S*)-vinylallenol benzoate (40 mg, 32%) as a yellow foam.

The (1*S*)-vinylallenol benzoate (obtained from epimerization of **21**; 44 mg, 0.088 mmol) was saponified by stirring with 5% KOH/MeOH (5.5 mL) in THF (1.1 mL) for 21 h at ambient temperature. The solvent was evaporated under reduced pressure and the product taken up in ether (10 mL). The organic solution was washed with aqueous $NaHCO_3$ (10 mL) and the aqueous layer back-extracted with ether (10 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated. Purification by high-pressure LC (10% ethyl acetate/Skellysolve B, 4.0 mL/min flow rate) afforded (1*S*,3*R*,6*R*)-vinylallenol **23** (24 mg, 69%) as a white foam.

(1*R*,3*S*,6*R*)-1-Hydroxy-3-methyl-9,10-secocholesta-5(10),6,7,25-tetraene (24). The (1*S*,3*S*)-vinylallenol **22** (158 mg, 0.40 mmol) was reacted with benzoic acid (488 mg, 4.0 mmol), triphenylphosphine (839 mg, 3.2 mmol), diethyl azodicarboxylate (0.5 mL in 0.5 mL benzene, 3.2 mmol) in benzene (3 mL) exactly as described for the 1*R*,3*R* isomer **21**. High-pressure LC (40% acetone/methanol, reverse phase, 5.0 mL/min flow rate) afforded pure benzoate (65 mg, 32%) as a foam.

The vinylallenol benzoate (obtained from epimerization of **22**; 87 mg, 0.17 mmol) was stirred in a mixture of 5% KOH/MeOH (10.8 mL) and THF (2.2 mL) for 18 h at ambient temperature. After the solvent was evaporated under reduced pressure, the remaining oil was taken up in ether (25 mL) and washed with aqueous $NaHCO_3$ (25 mL). The aqueous layer was back-extracted with ether (20 mL), and then the combined organic layers were dried (Na_2SO_4). After concentration, the crude product was purified by high-pressure LC (10% EtOAc/Skellysolve B) to give the vinylallenol **24** as a white foam (55 mg, 80%).

(1*R*,6*R*)- and (1*S*,6*R*)-1-Hydroxy-3,3-dimethyl-9,10-secocholesta-5(10),6,7,25-tetraenes (25 and 26, Respectively). A pentane solution of *tert*-butyllithium (1.57 mL, 2.1 M, 3.3 mmol) was added dropwise via syringe to a solution (N_2, −78 °C) of the iodo silyl ether **20** (628 mg, 1.65 mmol) in dry ether (4 mL). The reaction was stirred at −78 °C for 2 h, transferred to a −30 °C cooling bath (1 h), and then recooled to −78 °C prior to the addition of the following copper solution.

Copper iodide (314 mg, 1.65 mmol), tri-*n*-butylphosphine (1.06 mL, 4.27 mmol), and dry ether (25 mL) were stirred in a long-neck 100-mL round-bottomed flask until dissolved (10 min, ambient temperature). The solution was cooled (−78 °C), and then the vinyllithium compound formed above (cooled to −78 °C) was added via cannula and stirred (20 min). A precooled solution (−78 °C) of propargyl benzoate **16b** (500 mg, 1.22 mmol) in dry ether (5 mL) was added dropwise via syringe. Additional dry ether (1.4 mL) was used for rinsing in order to insure complete transfer of benzoate. The solution was stirred at −78 °C (1 h) and then at −40 °C (2.5 h). The reaction was quenched by addition of aqueous NH_4Cl (13 mL). The solution was removed from the cooling bath and warmed slowly to room temperature (20 min). The two layers were separated, and the aqueous layer was extracted with ether (15 mL). The organic portions were combined, dried over Na_2SO_4, filtered, and concentrated to a green liquid. The crude coupling products were separated from polar impurities by flash chromatography (1% ether/lbpe, 0.1% pyridine). The crude product was reacted (5 h, N_2) with tetra-*n*-butylammonium fluoride solution (5 mL, 1.0 M solution in THF) in order to remove the silyl protecting group. The mixture was poured into a mixture of ether (25 mL), lbpe (25 mL), and water (50 mL). The layers were separated, and the aqueous layer was extracted with additional ether/lbpe mixture (20 mL). The organic fractions were combined, washed with aqueous $NaHCO_3$ (50 mL), dried over $MgSO_4$, filtered, and concentrated. High-pressure LC (10% EtOAc/Skellysolve B) afforded two major products: less polar fraction A (119 mg, 24%) and more polar fraction B (140 mg, 28%) obtained as white foams. A and B were assigned as the 1*R*,6*R* (**25**) and 1*S*,6*R* (**26**) isomers, respectively.

Thermolysis of Vinylallenols 21–24. Each vinylallenol (**21–24**) was stirred in refluxing isooctane (0.01 M solution, 100 °C) for 11 h (N_2 atmosphere). The solvent was evaporated under reduced pressure, followed by high-pressure LC purification (10% ethyl acetate/Skellysolve B, 4.0 mL/min flow rate) involving a multiple shave–recycle technique when necessary.

The thermolysis results are summarized below.

vinylallenol	7*E*[28]	7*Z*	mass recovery
21	27 (82%)	28 (7%), 29 (4%), 30 (7%)	83%
22	31 (18%)	32 (25%), **33** (41%), 34 (16%)	88%
23	35 (19%)	36 (19%), 37 (14%), 38 (48%)	75%
24	39 (78%)	40 (13%), 41 (6%), 42 (3%)	79%

Thermolysis of Vinylallenol 25: (1*R*)-25,26-Didehydro-3-deoxy-1-hydroxy-3,3-dimethylvitamin D_3 (43). The vinylallenol **25** (103 mg, 0.22 mmol) was stirred in refluxing isooctane (25 mL, distilled from $LiAlH_4$, 100 °C) for 9 h (N_2 atmosphere). The solvent was removed by evaporation under reduced pressure, followed by purification of the vitamin **43** by high-pressure LC (10% EtOAc/Skellysolve B). The vitamin eluted as the least polar fraction (67 mg, 65%). Four more polar components

(27) Sardina, F. J.; Johnston, A. D.; Mouriño, A.; Okamura, W. H. *J. Org. Chem.* **1982**, *47*, 1576.

(28) The previtamin D (~10–20%) form is known to be in equilibrium with the vitamin D (~80–90%) via a [1,7]-sigmatropic shift of the C-9 hydrogen to C-19 of the latter with concomitant shift of the 5,7,10(19)-triene to the 5(10),6,8-triene position.[2,6,7] In calculating the percentage of *E* products, the vitamin and previtamin D forms were combined. Previtamin forms could be isolated from the thermolysis of **21** and **24** since the vitamins were major products. However, the relatively low percentage of vitamins isolated from **22** and **23** precluded isolation of their corresponding previtamin forms.

accounted for the remainder of the material. The results were similar to that reported for the side-chain-saturated derivative, (1*R*)-**5b**.[7]

Thermolysis of Vinylallenol 26: (1*S*)-25,26-Didehydro-3-deoxy-1-hydroxy-3,3-dimethylvitamin D_3 (44). Thermolysis of vinylallenol **26** (75 mg, 0.18 mmol) was performed as described for vinylallenol **25** (refluxing isooctane, 20 mL, 100 °C, 9 h). High-pressure LC (10% EtOAc/Skellysolve B) afforded the vitamin plus impurity, which was reinjected to afford pure vitamin **44** (8 mg, 10%). Collection of polar fractions accounted for an additional 78% of rearrangement products, giving an 88% mass balance of recovered material. The results were similar to that reported for the side-chain-saturated analogue, (1*S*)-**5b**.[7]

Thermal Equilibration of 7*Z* Manifold Products 28–30, 32–34, 36–38, and 40–42. Each isomer in each 7*Z* thermal manifold (i.e., 12 separate experiments) was heated for 36 h in refluxing isooctane (100 °C, N_2 atmosphere). The thermolysis reaction mixtures were analyzed by integration of the refractive index detector traces. The individually separated components (three for each experiment) were also quantitated by UV analysis using the calculated extinction coefficients given in the supplementary material. The complete experimental details are presented elsewhere.[9] The overall average equilibrium product distributions are summarized in Figure 2.

(1*S*,3*R*)-25,26-Didehydro-3-deoxy-1-hydroxy-3-methylvitamin D_3 Benzoate (47a). Triphenylphosphine (26 mg, 0.1 mmol) and benzoic acid (61 mg, 0.5 mmol) were added to a flask containing the (1*R*,3*R*)-1-hydroxy-3-methylvitamin **27** (20 mg, 0.05 mmol) in dry benzene (0.6 mL). Diethyl azodicarboxylate (16 μL, 0.1 mmol) was added, and the reaction was monitored by TLC (1:1 ether/lbpe). Additional triphenylphosphine and diethyl azodicarboxylate were added after 30 min (2 equiv of each) and 1 h (1 equiv of each). The solvent was evaporated under reduced pressure, and then the crude product was passed down a short silica column (8 × 1 cm, 20% ether/lbpe). High-pressure LC (reverse phase, 40% acetone/methanol, 5.0 mL/min) afforded pure **47a**: 9.2 mg, 37%.

(1*S*)-25,26-Didehydro-3-deoxy-1-hydroxy-3,3-dimethylvitamin D_3 Benzoate (47b). Triphenylphosphine (11.8 mg, 0.045 mmol, recrystallized from ether) and benzoic acid (16.4 mg, 0.134 mmol, sublimed) were added to a solution of the (1*R*)-vitamin **43** (9.2 mg, 22.4 μmol) in dry benzene (0.4 mL) with magnetic stirring (N_2 atmosphere). Diethyl azodicarboxylate (7 μL, 0.045 mmol, freshly distilled) was added and the mixture stirred for 1 h. Additional triphenylphosphine and diethyl azodicarboxylate (2 equiv of each) were added and stirring was continued for 1 h. The solvent was evaporated under reduced pressure, and the crude product was partially purified by separation on a small silica gel column (8 × 1 cm; 20% ether/lbpe solvent). Purification by high-pressure LC (reverse phase, 40% acetone/methanol, 5.0 mL/min flow rate) afforded pure benzoate **47b** (3.6 mg, 31%).

Acknowledgment. The National Institutes of Health (USPHS Grant AM-16595) and the Intramural Committee on Research (University of California, Riverside, CA) provided the financial support for this project. G.A.L. acknowledges the University of California Regents Graduate Fellowship and the Chancellor's Patent Fund Committees for partial support. We are grateful to Dr. M. Rappoldt of Duphar B.V. (Weesp, The Netherlands) for generous gifts of ergocalciferol (vitamin D_2). Badische-Anilin und Soda-Fabrik (Ludwigshafen, West Germany) and F. J. Sardina also provided chemicals used in this study.

Registry No. **2b**, 64252-58-0; **4a**, 83076-48-6; **4b**, 83076-49-7; **4b** benzoate, 83076-50-0; **11**, 50-14-6; **12**, 64190-52-9; **13**, 66774-81-0; **14**, 66774-82-1; **15**, 83076-51-1; **16a**, 83076-52-2; **16b**, 83076-53-3; **17**, 61621-47-4; **18**, 83095-44-7; (±)-*cis*-**19a**, 83076-54-4; (±)-*trans*-**19a**, 83076-55-5; (±)-**19b**, 83076-56-6; (±)-**20**, 83076-57-7; **21**, 83076-58-8; **22**, 83076-59-9; **23**, 83076-60-2; **23** benzoate, 83076-61-3; **24**, 83076-62-4; **24** benzoate, 83076-63-5; **25**, 83076-64-6; **26**, 83076-65-7; **27**, 83076-66-8; **28**, 83076-67-9; **29**, 83076-68-0; **30**, 83148-30-5; **31**, 83076-69-1; **32**, 83148-31-6; **33**, 83076-70-4; **34**, 83148-32-7; **35**, 83076-71-5; **36**, 83095-45-8; **37**, 83198-15-6; **38**, 83148-33-8; **39**, 83076-72-6; **40**, 83095-46-9; **41**, 83076-73-7; **42**, 83148-34-9; **43**, 83076-74-8; **44**, 83076-75-9; **47a**, 83076-76-0; **47b**, 83076-77-1; LiC_2H, 1111-64-4; 4-chloro-2-methyl-1-butene, 10523-96-3.

Supplementary Material Available: Spectral and analytical data (36 pages). Ordering information is given on any current masthead page.

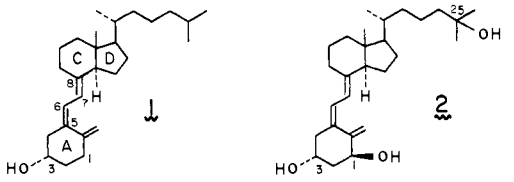
Heterocalciferols: Novel 3-Thia and 3-Sulfinyl Analogues of 1α-Hydroxyvitamin D_3[1]

Alberto Haces[2] and William H. Okamura*

Contribution from the Department of Chemistry, University of California, Riverside, California 92521. *Received January 25, 1982*

Abstract: Upon coupling of the allenyllithium salt obtained from hydrocarbon **6** with thia enol ether **7**, a diastereomeric mixture of vinylallenones **5a** (6*R*) and **5b** (6*S*) was obtained in an 8:1 ratio. Reduction of pure **5a** afforded vinylallenols **11a** and **11b**, which upon separate thermolysis isomerized via a [1,5]-sigmatropic hydrogen shift to afford the 3-thia vitamins **3a** (55%) and **4a** (25%). The C-1 hydroxyl stereochemistries were assigned on the basis of ^1H NMR lanthanide induced shift (LIS) studies. Peracid oxidation of **3a** and **4a** afforded the sulfoxides **3bc** and **4bc**, respectively, whose configurations were also established by LIS studies. Iodine catalyzed isomerization of **3b** and **3c** afforded the corresponding 5*E* derivatives **12a** and **12b**.

It is now well established that in order for vitamin D_3 (**1**) to elicit its physiological action, it must be successively hydroxylated in the liver and then in the kidney to produce the metabolite 1α,25-dihydroxyvitamin D_3 (**2**). The latter is considered to be



the active form of the vitamin, which regulates intestinal calcium absorption (ICA) and bone calcium mobilization (BCM). This

(1) This is paper 24 in the series "Studies on Vitamin D (Calciferol) and Its Analogues". For paper 23, see: Leyes, G. A.; Okamura, W. H. *J. Am. Chem. Soc.*, preceding paper in this issue.

(2) Graduate fellowship from Gran Mariscal de Ayacucho Foundation (Venezuela).

0002-7863/82/1504-6105$01.25/0