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]

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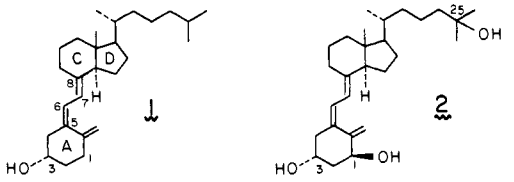
Contribution from the Department of Chemistry, University of California, Riverside, California 92521. *Received January 25, 1982*

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).

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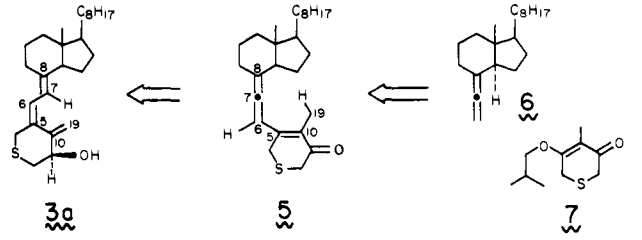
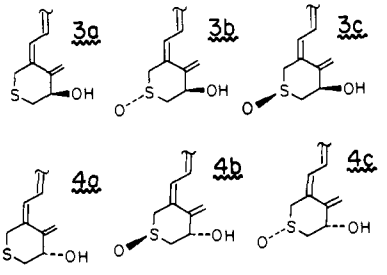
Scheme I



latter metabolite (**2**) should also now be considered to function as a steroid hormone.[3]

Recently, our group has reported the synthesis of 3-deoxy-1α,25-dihydroxyvitamin D_3 (3-deoxy-**2**) and its 25-deoxy analogue (i.e., 3-deoxy-1α-hydroxyvitamin D_3),[4] which have the interesting property of selectively stimulating ICA without significantly mobilizing bone calcium. This result prompted us to synthesize new A-ring analogues of 1α,25-dihydroxyvitamin D_3 in which the 3-position has been modified. This was expected to allow us to assess the relative contribution and importance of this position to the biological responses of the vitamin D_3 endocrine system. In this paper we report the synthesis of the *first vitamin D steroid analogues bearing an annular heteroatom.* In particular, we report the preparation and characterization of **3a–c** and **4a–c**, in which

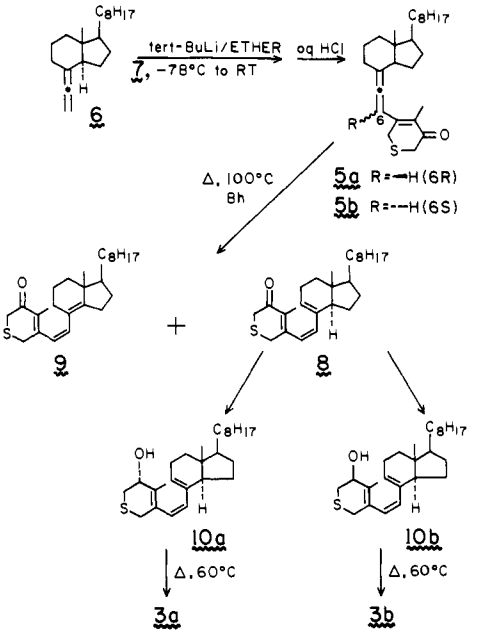


the C-3 carbon and its 3β-hydroxyl have been substituted by a sulfide or a sulfoxide functionality. Besides the analogy to the 3-deoxy system cited above, the reasons for selecting this pattern of substitution include the following: these substituents should further assist in evaluating such factors as hydrogen bonding, electronegativity, or steric effects on the activity of the hormone; there are a number of synthetic heterocyclic steroid hormone analogues that ave exhibited useful and/or unusual biological properties.[5]

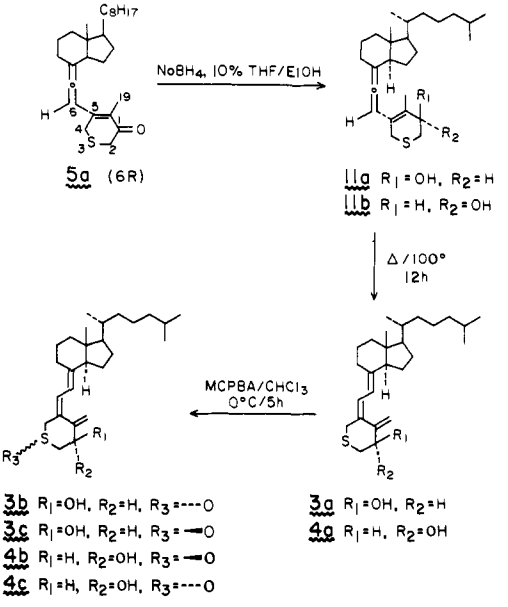
Results and Discussion

The synthesis was achieved by the convergent vinylallene approach reported earlier for producing the 1-hydroxyvitamin D system.[6] The route (shown in Scheme I) includes as the key step the thermally induced [1,5]-sigmatropic hydrogen shift of the vinylallene intermediate **5**. The latter, after reduction, was expected to afford the hydroxy triene system, for example, **3a**.

Scheme II



Scheme III



The synthesis of the requisite vinylallene **5** was accomplished by coupling the C,D moiety **6**[6a] previously reported by this laboratory with the A-ring fragment **7**. The latter can be easily prepared (isobutyl alcohol, TsOH, C_6H_6) from the known[7] 4-methyl-1-thiacyclohexane-3,5-dione. As shown in Scheme II, deprotonation of allene **6** followed by addition of electrophile **7** affords, after hydrolysis of the intermediate β-hydroxy enol ether, a mixture of (6*R*)-vinylallenone **5a** (61%) and (6*S*)-vinylallenone **5b** (7%). Thermolysis of this mixture of vinylallenones produced keto previtamin **8** and *cis*-isotachysterone **9** in 40% and 60% yields, respectively. Reduction ($NaBH_4$, 10% THF/EtOH) of the pure keto previtamin **8** followed by thermal equilibration of the corresponding alcohols **10a,b** yielded a thus far inseparable mixture of the desired epimeric vitamins **3a** and **4a**. The thermal lability of the previtamin alcohols **10a,b** precluded attempts at their separation. In the corresponding carbon case (**10a,b** with S= CH_2), the [1,7]-sigmatropic rearrangement to the vitamin was slower and this strategy was successful.[6a]

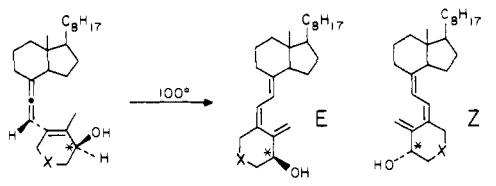
(3) For reviews on the chemistry and biochemistry of the vitamin D field, see: (a) Norman, A. W. "Vitamin D, the Calcium Homeostatic Steroid Hormone"; Academic Press: New York, 1979. (b) Deluca, H. F.; Paaren, H. E.; Schnoes, H. K. *Top. Curr. Chem.* **1979**, *83*, 1. (c) Georghiou, P. E. *Chem. Soc. Rev.* **1977**, *6*, 83. (d) Fieser, L. F.; Fieser, M. "Steroids"; Reinhold: New York, 1959.

(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.; Proscal, D. A.; Norman, A. W. *Ibid.* **1975**, *65*, 24. (c) Lam, H. Y.; Onisko, B. L.; Schnoes, H. K.; DeLuca, H. F. *Ibid.* **1974**, *59*, 845. (d) Onisko, B. L.; Lam, H. Y.; Reeve, L.; Schnoes, H. K.; DeLuca, H. F. *Bioorg. Chem.* **1977**, *6*, 203.

(5) Singh, H.; Kapoor, V. K.; Paul, D. *Prog. Med. Chem.* **1979**, *16*, 37–149. For some recent examples of thiasteroids, see: Kano, S.; Tanaka, K.; Hibino, S.; Shibuya, S. *J. Org. Chem.* **1979**, *44*, 1580. Terasawa, T.; Okada, T. *Ibid.* **1981**, *46*, 381.

(6) (a) Condran, P., Jr.; Hammond, M. L.; Mouriño, A.; Okamura, W. H. *J. Am. Chem. Soc.* **1980**, *102*, 6259. (b) Mouriño, A.; Lewicka-Piekut, S.; Norman, A. W.; Okamura, W. H. *J. Org. Chem.* **1980**, *45*, 4015.

(7) Terasawa, T.; Okada, T. *J. Org. Chem.* **1977**, *42*, 1163.



		E/Z
(1R,6R)	X = S	≈1.6
(1S,6R)	X = CH_2	0.3
	Epi-alcohol *	
(1S,6R)	X = S	≈0.5
(1R,6R)	X = CH_2	3.0

Figure 1. Comparison of rearrangement pathway ratios for the sulfur and carbon cases. The upper set of data is for the 1α-OH series shown in the reaction scheme. The lower set of data is for the epimeric 1β-OH series (not shown). The proportion of *Z*-triene, which is itself not observed, is discussed in the Experimental Section.

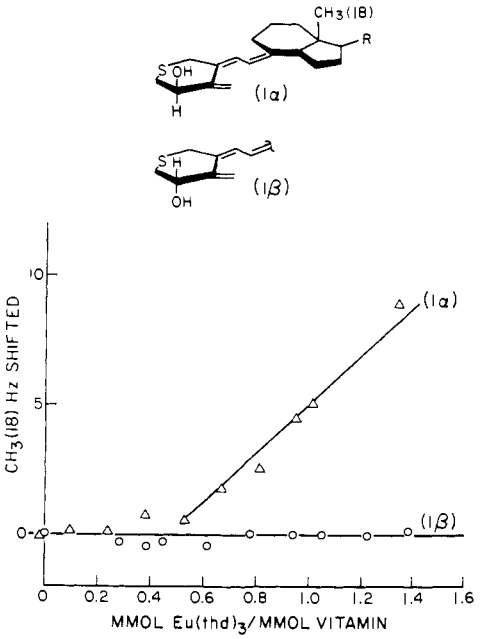


Figure 2. ^{1}H NMR LIS studies of sulfides **3a** (1α) and **4a** (1β). Tris-(2,2,6,6-tetramethyl-3,5-heptanedionato)europium [Eu(thd)$_3$] was used as shift reagent. the Eu(thd)$_3$ was quantitatively added in 2–4-mg increments to 7–11-mg solutions of vitamin in $CDCl_3$ (~0.5 mL in 5-mm tubes, 90 MHz). The C-13 angular methyl group (CH_3-18) was monitored.

In order to circumvent this problem, we carried out the separation of vinylallenones **5a** and **5b** first (Scheme III). Reduction of the major vinylallenone (**5a**) afforded a separable mixture of vinylallenols **11a** (41%) and **11b** (39%). Thermolysis of each of these vinylallenols produced the desired vitamins **3a** and **4a** in 55% and 25% yields, respectively. Finally, MCPBA oxidation[8] of each vitamin produced the corresponding epimeric pairs of sulfoxides **3bc** (29% and 41%, respectively) and **4bc** (29% and 47%, respectively). It should be noted that the cis sulfoxides **3c** and **4c** were produced in higher yield relative to their trans forms **3b** and **4b**. This is likely due to a hydroxyl directing effect[8a] such as that observed in the epoxidation of allylic alcohols with this same reagent.[8] These sulfoxides exhibit a λ_{max} of 268–269 nm, which is somewhat red shifted from that observed for triene chromophores of other vitamin D derivatives (usually 260–265 nm). This kind of red-shifted maximum is observed when vitamin D is

(8) For similar oxidations, see: (a) Terasawa, T.; Okada, T. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1254. (b) Johnson, C. R.; McCants, D., Jr. *J. Am. Chem. Soc.* **1965**, *87*, 1109.

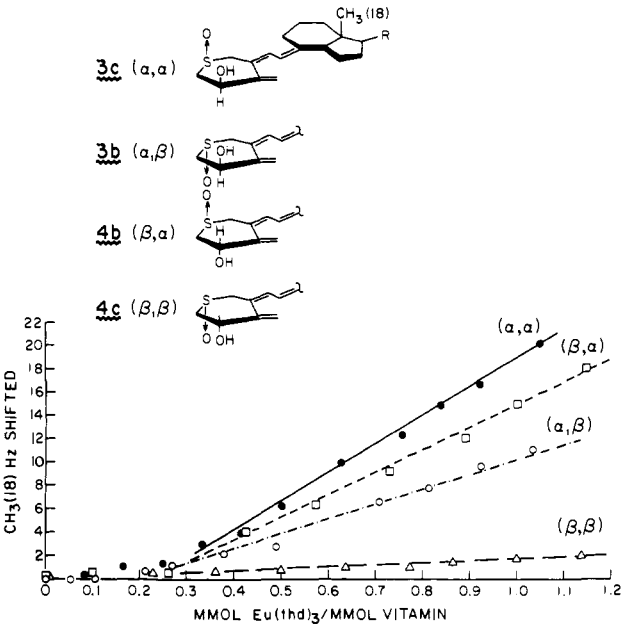


Figure 3. ^{1}H NMR LIS studies of sulfoxides **3bc** and **4bc**. For details, see the caption to Figure 2.

contaminated by varying amounts of the $\Delta^{5,6}$-*trans* isomer, which absorbs at ~272 nm when pure. However, the ^{1}H NMR spectrum and LC behavior of all four sulfoxides indicated that they were pure substances. Two of the isomers, **3b** and **3c**, were isomerized (see below for further discussion) to their 5,6-trans forms (**12a** and **12b**, respectively) to further substantiate their geometric homogeneity. They were readily separated and characterized and were found to absorb in the UV at λ_{max} 273–274 nm. Thus, both the 5,6-cis and 5,6-trans forms of the sulfoxides exhibit UV λ_{max} values to the red of most typical vitamin D systems. This may be due to a homoallylic electronic interaction of the sulfoxide group with the triene chromophore.

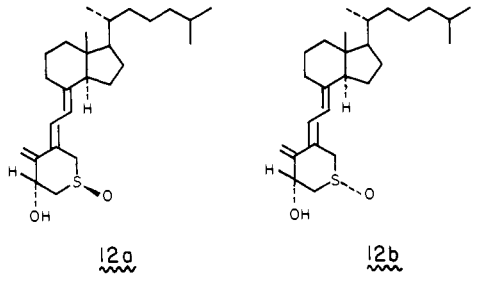
Another unusual feature concerning the parent thiavitamins **3a** and **4a** concerns their formation from the vinylallenols via [1,5] shifts. Two possible pathways for the [1,5]-sigmatropic hydrogen shift are available: one leading preferentially to the triene system of natural vitamin D in which the intercyclic diene possesses the 5*Z*,7*E* configuration, and the other that leads to the unnatural 5*Z*,7*Z* configuration. In other words, the desirable pathway is that which gives a large 7*E*/7*Z* ratio of products. Figure 1 compares the thermal behavior of the 3-thia vinylallenols **11a** and **11b** with that of the non-sulfur-containing 3-deoxyvinylallenols.[6] The latter non-sulfur cases (X = CH_2) typify the usual behavior wherein the 1α-hydroxyallenes (natural configuration of C-1 in the vitamin) produce minor amounts of the (7*E*)-vitamin. The corresponding unnatural 1β-hydroxyallene produces mainly the desired (7*E*)-vitamin. As can be seen, the 3-thia vinylallenols exhibit the opposite behavior: the vinylallenol with the natural 1α-OH group rearranges to give a higher percentage of 7*E*-geometry product.[9] Since this was not the expected behavior, it was necessary to independently establish the C-1 configuration.

(9) The thermolysis reaction conditions (~100 °C, 10–12 h) for the vinylallenols (both X = S and X = CH_2 cases) given in Figure 1 were similar. The difference may be due to an anisotropic distribution of electron density on the two faces of the π system. In the non-sulfur case, π-facial perturbation is due to the orientation of the allylic hydroxyl, whereas in the sulfur case, there is an additional perturbation by an allylic sulfur. The perturbation by the latter presumably overrides the hydroxyl effect common to both systems. The notion of π-facial perturbations on stereoselectivities of other pericyclic processes have been previously discussed. For example, 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*, 1073. (d) Jones, D. W. *J. Chem. Soc., Commun.* **1980**, 739. We note too that the ketone **5a** rearranged under distinctly milder conditions (100 °C, 8 h) than the corresponding alcohols **11a** or **11b**. The corresponding carbon analogue **5a** (sulfur replaced by CH_2) required nearly 20 h for complete rearrangement.[6a]

For the non-sulfur case, the stereochemistry at C-1 had already been rigorously established. Accordingly, lanthanide induced shift (LIS)[10] studies on the 3-thia vitamins were carried out and the results are shown in Figure 2. The chemical shift value for the C-18 angular methyl group vs. increasing ratios of LIS reagent to vitamin were plotted. The isomer exhibiting a slope of near 0 was assigned as the 1β-hydroxyvitamin **4a**; the other exhibiting a slope of ~1.0 was assigned the 1α-hydroxy configuration (**3a**). To test the validity of this method of assigning configurations, we carried out analogous LIS studies on the 3-deoxy-1α- and 3-deoxy-1β-hydroxyvitamins (as per Figure 2 for X = CH_2), which had previously been synthesized in our laboratory by means of a classical route. As mentioned above, their stereochemistries are firmly established. These non-sulfur-containing analogues exhibited the same trend as for the 3-thiavitamins.

With the stereochemistry at C-1 thus established, analogous LIS studies were carried out to determine the stereochemistry of the sulfoxides. Again, similar LIS studies on all four diastereomers, **3b,c** and **4b,c**, produced the plots given in Figure 3. The most straightforward analysis of the results consists of differentiating compounds in a pairwise manner (i.e., *cis*- from *trans*-hydroxy sulfoxides). For example, in the case of the 1α-hydroxy sulfoxides **3b** and **3c**, one would expect that the analogue with both the sulfoxide and the hydroxyl groups syn to the C-18 angular methyl group [(α,α) isomer **3c** in Figure 3] should exhibit a steeper slope than for its corresponding epimeric sulfoxide [(α,β), **3b**]. This is in fact the experimental observation. Analogously, one would expect that for the 1β-hydroxyl pair of sulfoxides (**4b** and **4c**), the one in which the hydroxy group and sulfoxide group are both anti (**4c**) to the C-18 methyl group should show a less steep slope than the case **4b**, in which only the sulfoxide group is syn to the C-18 methyl group. Again, this was the result observed. As regards other cross comparisons, it seems trivially clear why α,α (**3c**) exhibits a steeper slope than β,β (**4c**). It is less obvious why β,α (**4b**) exhibits a steeper slope than α,β (**3b**) since hydroxyl binds to LIS reagents better than the sulfoxide moiety.[11] However, we are fully aware of the fact that each sulfoxide-containing A ring should be viewed as a pair of rapidly equilibrating chair forms, each of which may bind in several ways with shift reagent.[12]

Mention was made above regarding the 5*E* analogues of the 1α-hydroxy sulfoxides **3b** and **3c**. This was accomplished by iodine-catalyzed Δ^5-ene equilibration (1:1 ratio after 8 h). These analogues (**12a,b**) besides being of interest as regards their UV maximum (vide supra) are stereochemically unique. In particular, the 1α-hydroxyl of the 5,6-trans forms of **3b** and **3c** occupies a pseudo-3β-OH position. Moreover, in the case of 5,6-*trans*-**3b**, the sulfoxide oxygen occupies a pseudo-1α-OH topology. These 5,6-trans sulfoxides may also be useful probes to assess the differential binding of these functional groups in different receptor environments. The biological evaluation of these analogues is currently underway in the laboratories of Professor Anthony W. Norman of our Department of Biochemistry, and the results will be reported elsewhere.



12a 12b

Experimental Section

General Procedures. Ultraviolet (UV) and infrared (IR) spectra, ^1H nuclear magnetic resonance spectra (NMR), mass spectra (MS), and other analytical data are summarized in the supplementary material; melting points (mp, uncorrected) were obtained with a Thomas-Hoover capillary apparatus. Ether was freshly distilled (nitrogen) from $LiAlH_4$; dry isooctane and pyridine were freshly distilled from CaH_2; lbpe refers to redistilled 30–60 °C low-boiling petroleum ether. Kugelrohr distillation boiling points (bp) refer to the external-oven air-bath temperatures. Reactions involving air- and/or moisture-sensitive organometallic reagents or substrates were handled under a blanket of dry nitrogen. Air-sensitive allenes or other polyenes were normally stored in the cold (usually <−70 °C) under nitrogen.

For ordinary column chromatography, Baker Analyzed Reagent silica gel (60–200 mesh) was used. For thin layer chromatography (TLC), silica gel 60 F-254 (0.20 mm) precoated plates (E. Merck) were used. High-pressure liquid chromatography (high-pressure LC) was carried out on a Waters 6000A solvent delivery system equipped with a U6K injector, and a dual detector system (UV at 254 nm and a refractive index detector). A Whatman M-9 10/50 ODS-2 partisil [10 μm, 9.4 mm (i.d.) × 50 cm] column was used for reverse-phase separations unless otherwise specified. Solvents were distilled prior to use, and solvents and solvent combinations were vacuum filtered through a 0.45-μm Millipore filter immediately before use.

5-Isobutoxy-4-methyl-1-thiacyclohex-4-en-3-one (7). A solution of 4-methyl-1-thiacyclohexane-3,5-dione[7] (2.00 g, 13.8 mmol), *sec*-butyl alcohol (3.00 g, 40.1 mmol), and *p*-toluenesulfonic acid monohydrate (100 mg) in dry benzene (250 mL) was refluxed (Dean Stark apparatus) for 5 h. The benzene was periodically removed during the reflux period, and an equal amount of solvent was added. After the mixture was cooled, the solvent was removed under vacuum, and then the resulting crude product was dissolved in ether (200 mL). The ethereal solution was washed consecutively with aqueous $NaHCO_3$ (10% solution, 15 mL), brine (20 mL), and water (20 mL) and then dried ($MgSO_4$). Removal of the ether followed by Kugelrohr distillation (115 °C, 2 mm) afforded keto enol ether **7** (2.46 g, 88%) as a white solid with mp 52–53 °C.

(6*R*)- (5a) and (6*S*)-3-Thia-9,10-secocholesta-5(10),6,7-trien-1-one (5b). A solution of *tert*-butyllithium (1.28 mL, 25.5 mmol, 1.99 M) in pentane was added to a stirred solution of allene **6** (700 mg, 25.5 mmol) in dry ether (20 mL) at −78 °C. The solution was stirred at −78 °C (5 min) and then at −55 °C (40 min) to produce a pale yellow solution of the allenyllithium species. After the allenyllithium solution was cooled to −78 °C (5 min), keto enol ether **7** (510 mg, 25.5 mmol) in ether (5 mL) was introduced (syringe). There was an immediate discharge of the color followed by reappearance of a more intense yellow color. Stirring was continued at −78 °C for 5 min and then at ambient temperature for 1 h. After the addition of 1M HCl (5 mL), the mixture was stirred vigorously for 5 min. The aqueous layer was withdrawn, a fresh portion of HCl (5 mL, 1M) was added, and stirring was continued for 4 h. The mixture was transferred to a separatory funnel with additional portions of ether (30 mL). The ethereal phase was washed successively with saturated aqueous $NaHCO_3$ (5 mL) and brine, dried ($MgSO_4$), and then concentrated under vacuum at room temperature to afford a red oil. Chromatography of the oil on silica gel (elution with lbpe, 5% ether in lbpe, and then 10% ether in lbpe) afforded, after concentration of appropriate fractions, 70 mg of unreacted allene **6** followed by 830 mg of a mixture of diasteromeric vinylallenones as a viscous yellow-greenish oil. The ^1H NMR spectrum (C_{18} angular methyl group peak) revealed an 8:1 ratio of (6*R*)-**5a** and (6*S*)-**5b**. Preparative high-pressure LC separation (1:1 acetonitrile/acetone, two recycles) gave pure (6*R*)-**5a** (620 mg, 61%) and (6*S*)-vinylallenone **5b** (79 mg, 7%) as light yellow oils.

(1*R*,6*R*)- (11a) and (1*S*,6*R*)-1-Hydroxy-3-thia-9,10-secocholesta-5(10),6,7-trlene (11b). A solution of (6*R*)-vinylallenon **5a** (260 mg, 0.64 mmol) in 10% THF in ethanol (10 mL) was reacted with $NaBH_4$ (100 mg, 2.6 mmol) over a 1-h period with stirring. The mixture was quenched by adding lbpe (20 mL) followed by a dropwise addition of aqueous acetic acid (1 M, 10 mL). The two-phase system was transferred to a separatory funnel, the organic layer was separated, and then

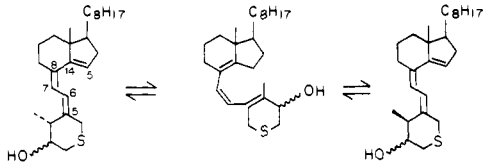
(10) For a related LIS study, see: Gerdes, J. M.; Norman, A. W.; Okamura, W. H. *J. Org. Chem.* **1981**, *46*, 599.

(11) Andersen, K. K.; Uebel, J. J. *Tetrahedron Lett.* **1970**, 5253.

(12) For examples of the chairlike nature of A rings of vitamin D, see: Wing, R. M.; Okamura, W. H.; Rego, A.; Pirio, M. R.; Norman, A. W. *J. Am. Chem. Soc.* **1975**, *97*, 4980. A Dreiding model of the vitamin D skeleton possessing 1α- and 3β-hydroxyl groups (as an approximation of **3b**) and another possessing 1β- and 3α-hydroxyls (as an approximation of **4b**) were constructed. If each of these models are assumed to be biased in the 1-hydroxyl equatorial conformation, thus placing the sulfoxide oxygen in the favored axial orientation (see ref 8b), the distance from the hydroxyl oxygen to the C-18 angular methyl carbon is about the same for **3b** and **4b** (~7.5 Å). On the other hand, the corresponding distances between their sulfoxide oxygen and this same methyl carbon are ~8.5 (**3b**) and ~7 Å (**4b**). This provides a rationale for the steeper LIS slope observed for **4b** vs. **3b**. Note too that the cis isomers **3c** and **4c** are also assumed to coordinate predominantly with the LIS reagent in the axial sulfoxide oxygen orientation (with a 1,3-diaxial relationship between it and the C-1 hydroxyl). In all cases, sulfoxide oxygen rather than sulfur is considered to bind to LIS reagent (ref 11).

the aqueous layer was extracted with additional lbpe (2 × 30 mL). The combined organic extracts were washed with aqueous $NaHCO_3$ (10 mL, saturated solution) and brine (10 mL). Concentration (room temperature) of the dried ($MgSO_4$) solution afforded 260 mg of the vinylallenols as a clear oil. Preparative high-pressure LC (methanol, 1 recycle) yielded in order of elution (1*R*,6*R*)-vinylallenol **11a** (107 mg, 41%) and (1*S*,6*R*)-vinylallenol **11b** (102 mg, 39%).[13]

Thermolysis of (1*S*,6*R*)-Vinylallenol 11b. (1*S*)-3-Deoxy-3-thia-1-hydroxyvitamin D_3 (4a). A solution of (1*S*,6*R*)-vinylallenol **11b** (190 mg, 0.47 mmol) in dry isooctane (2 L) was refluxed under nitrogen for 12 h. A necessary initial purification (high-pressure LC, 10% water in ethanol) of the crude mixture afforded 95 mg of vitamin **4a** (60% pure). A second high-pressure LC separation of this mixture (20:1 methanol/water, 3 recycles) afforded pure vitamin **4a** (51 mg, 27%).[13] In a separate experiment, the ^1H NMR of the crude thermolysis reaction mixture allowed the estimate of the *E*/*Z* ratio (~0.5) given in Figure 1. The *Z* product shown in Figure 1 is not directly observed, but rather, a triad of secondary rearrangement products of the type, i, ii, and iii, related to one



i ii iii

another by [1,7]-sigmatropic shifts, is observed. The methyl epimers i and iii constitute ~90% of the total *Z* products. The ~0.5 *E*/*Z* ratio was estimated by ^1H NMR integration of one of the C-19 proton resonances (δ 4.8 or 5.25) of vitamin **4a** and the total signal corresponding to the C-15 proton (m, δ 5.5) of i and iii. The ^1H NMR of the mixture of thermal products exhibited close correspondence to the carbon counterparts.[6]

Thermolysis of (1*R*,6*R*)-Vinylallenol 11a. (1*R*)-3-Deoxy-3-thia-1-hydroxyvitamin D_3 (3a). Essentially the same procedure used for thermolyzing vinylallenol **11b** was followed. Vinylallenol **11a** afforded compound **3a** in 55% yield.[13] The high-pressure LC refractive index trace of the crude thermal product revealed a major component (**3a**, *E* product) and two minor components (*Z* products; a mixture corresponding to trienes of the type i and iii shown in the preceding section), which were produced in a ~1.6:1 ratio. The mixture of minor components was also isolated by semipreparative high-pressure LC and identified by ^1H NMR comparison to the previously reported carbon analogues.[6]

(1*R*,3*R*)- (3b) and (1*R*,3*S*)-3-Deoxy-3-sulfinyl-1-hydroxyvitamin D_3 (3c). To a cooled solution (0 °C, under nitrogen) of **3a** (57 mg, 0.14 mmol) in chloroform (5 mL) was added (syringe) *m*-chloroperbenzoic acid [27.4 mg (89%) in 3 mL of chloroform]. The mixture was stirred for 4 h and then quenched with saturated $NaHCO_3$ solution (2 mL). The two-phase system was transferred to a separatory funnel, the aqueous phase discarded, and the organic layer washed with distilled water (2 mL). Then, the organic layer was azeotropically dried by adding absolute ethanol (10 mL) followed by vacuum evaporation of the solvent to afford a crude mixture of products. High-Pressure LC (20:1 H_2O/MeOH) of this mixture afforded pure **3b** (17 mg, 29%) and **3c** (24 mg, 41%) as semisolid compounds.

(1*S*,3*S*)- (4b) and (1*S*,3*R*)-3-Deoxy-3-sulfinyl-1-hydroxyvitamin D_3 (4c). A similar procedure as that for compound **3a** was followed with vitamin **4a**, and compounds **4b** (30%) and **4c** (48%) were obtained.

(1*R*,3*R*)-(5*E*)-3-Deoxy-3-sulfinyl-1-hydroxyvitamin D_3 (12a). To a solution of **3b** (7 mg, 0.02 mmol) in dry ether (6 mL) was added iodine (0.01 mg in 1 mL of ethyl ether). The mixture was allowed to stand under fluorescent laboratory lights for 8 h. A drop of pyridine was added, and then the solvent was evaporated. High-pressure LC (Whatman M-9 partisil column, ethyl acetate) of this mixture afforded, in order of elution, (5*E*)-vitamin **12a** (40%) and starting material **3b** (49%).[14]

(1*R*,3*S*)-(5*E*)-3-Deoxy-3-sulfinyl-1-hydroxyvitamin D_3 (12b). A similar procedure as that used for compound **3b** was followed with vitamin **3c**. Compounds **12b** and **3c** were obtained in 42% and 48% yields, respectively.[14]

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Registry No. 3a, 83044-48-8; **3b**, 83044-49-9; **3c**, 83044-50-2; **4a**, 83044-51-3; **4b**, 83044-52-4; **4c**, 83044-53-5; **5a**, 83044-54-6; **5b**, 83044-55-7; **6**, 74398-28-0; **7**, 83044-56-8; **11a**, 83044-57-9; **11b**, 83044-58-0; **12a**, 83044-59-1; **12b**, 83113-66-0; 4-methyl-1-thiacyclohexane-3,5-dione, 61363-53-9; isobutyl alcohol, 78-83-1.

Supplementary Material Available: Spectral and analytical data (6 pages). Ordering information is given on any current masthead page.

(13) To avoid confusion, it should be noted that the presence of sulfur in the A ring reverses the *S*,*R* notation at the hydroxyl-bearing C-1 center due to a priority order reversal in substituents about C-1 (see Figure 1). The 1α- and 1β-OH configuration notations are less confusing.

(14) As per the preceding footnote, the presence of sulfur at position 3 also reverses the *Z*,*E* notation of the Δ^5 double bond. The *Z*,*E* notation used in this article ignores the presence of sulfur to avoid confusion.