Pure A was identified as (11Z)-20,14-retro-retinyl tert-butyldimethylsilyl ether (13a). Fraction B could not be readily resolved chromatographically at this point and was therefore deprotected first as described below.

Deprotection of Fraction B. (11Z)-Retinol (14) and (11Z,13Z)-Retinol (15). To 47 mg (0.12 mmol) of fraction B (<sup>1</sup>H NMR analysis indicated the presence of 70% 11-cis isomer and 30% of the 11,13-dicis isomer) was added freshly prepared tetra-*n*-butylammonium fluoride solution (1 mL, 0.5 M in THF, 0.5 mmol). The mixture was stirred at room temperature under nitrogen for 3 h and then quenched by pouring it into brine and lbpe. Conventional workup afforded 33 mg of crude product which was subjected to MPLC (70:30 lbpe–ether; 8 mL of pyridine was added to each liter of the lbpe–ether mixture). Chromatographically and spectrally pure 11-*cis*,13-*cis*-retinol (15, 5 mg, 50%) and 11-*cis*-retinol (14, 19 mg, 77%) were obtained. Each was characterized by direct chromatographic and spectral (<sup>1</sup>H NMR) comparisons with authentic specimens provided by Mr. Christopher Knudsen of this laboratory and by the Hoffman-La Roche Co. of Nutley, N.J.

**Deprotection of Fraction A.** (11Z)-20,14-retro-Retinol (13b). To silyl ether 13a (533 mg, 1.08 mmol) was added freshly prepared tetra-*n*-bu-tylammonium fluoride solution (6 mL, 1 M in THF, 5.5 mmol) under N<sub>2</sub>, and then the solution was stirred at ambient temperatures for 3 h. The reaction mixture was poured into brine and then thoroughly extracted with lbpe. Conventional workup afforded crude material (398 mg) which was subjected to MPLC (70:30 lbpe-ether; 8 mL of pyridine was added to each 1000-mL portion of the lbpe-ether mixture). Combination and concentration of appropriate fractions afforded 350 mg (87%) of pure alcohol 13b.

Thermolysis of Vinylallenol 7 (Y = CH<sub>2</sub>OH). A 50-mg sample of vinylallenol 7 (Y = CH<sub>2</sub>OH) in isooctane (165 mL) was thermolyzed (100 °C, 4 h) under N<sub>2</sub> as described earlier for the case of the corresponding silyl ether 7 (Y = CH<sub>2</sub>OTBDMS). Concentration (<40 °C) under vacuum afforded 50 mg (~100%) of material whose composition (<sup>1</sup>H NMR) revealed the presence of 63% (11Z)-20,14-*retro*-retinol (13b), 13% (11Z,13Z)-retinol (15), and 24% (11Z)-retinol (14). The <sup>1</sup>H NMR analysis was conveniently carried out by integrating the signals due to protons on carbon adjacent to oxygen. Thermolysis of the above mixture for an additional 7.5 h at 100 °C revealed by <sup>1</sup>H NMR that slow deterioration was occurring as evidenced by an increase in the appearance of very broad, but weak signals appearing in the aromatic, olefinic, and CH<sub>2</sub>–O regions of the spectrum. The apparent ratio of 13b to 14 to 15 had changed to 76:14:10 from the initial 63:24:13 ratio given above.

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

# Studies on Vitamin D (Calciferol) and Its Analogues. 18. The Vinylallene Approach to the 1-Hydroxyvitamin D System. New Sigmatropic Reactions in the Vitamin D Series<sup>† 1</sup>

## Patrick Condran, Jr., Milton L. Hammond, Antonio Mouriño, and William H. Okamura\*

Contribution from the Department of Chemistry, University of California, Riverside, California 92521. Received March 24, 1980

Abstract: The thermally induced [1,5]-sigmatropic hydrogen shift of the diastereomeric vitamin D type vinylallenols 6a (IR,6R), **6b** (1R,6S), **7a** (1S,6R), and **7b** (1S,6S) and vinylallenones **5a** (6R) and **5b** (6S) were studied. The 1S,6S (7b) and 1R,6R(6a) alcohols afforded  $\sim 60\%$  yields of the biologically active 3-deoxy-1 $\alpha$ -hydroxyvitamin D<sub>1</sub> (3a) and its inactive 1 $\beta$  epimer 3b, respectively. By contrast, the major products (70–79%) from the  $1R_{6}S$  (6b) and  $1S_{6}R$  (7a) allenols were products of an equilibrium manifold ( $23 \Rightarrow 25 \Rightarrow 24$  and  $26 \Rightarrow 28 \Rightarrow 27$ , respectively) resulting from successive [1,7]-sigmatropic hydrogen shifts of an initially formed putative intermediate, (7Z)-3-deoxy-1-hydroxyvitamin D<sub>3</sub>. Thermolyses of ketones 5a or 5b afforded good yields of a mixture of the previtamin ketone 29 and the *cis*-isotachysterone 30. Reduction of 29 afforded the previtamins **31a** and **31b**, which could be equilibrated with the corresponding vitamins **3a** and **3b**, respectively ( $K_{eq} = 1/9$  for each stereoisomer at 60 °C). Reduction of 30 afforded the cis-isotachysterol analogues 25 and 28. The former could be equilibrated with 23 and 24 (45%, 23; 13%, 25; and 42%, 24 at 100 °C); the latter could be similarly equilibrated with 26 and 27 (49%, 26; 36%, 27, and 14%, 28 at 100 °C). The 6R vinylallenes 5-7 were synthesized by two different methods. The first method involves an anti-1,3-addition of a nucleophilic A-ring component (A-ring cuprate 21 obtained in four steps from 2-methylcyclohexane-1,3-dione) to the electrophilic propargylic ester 10 (obtained in two steps from Grundmann's ketone; 8). The second method involves as a key step the nucleophilic 1,2-addition (followed by acid-catalyzed rearrangement) of the lithium salt of allene 13 (obtained in four steps from 8) to the electrophilic component, keto enol ether 22. The (6S)-vinylallenes 5-7 were obtained by photoequilibration of the more readily available 6R allenes 5-7. The vinylallene approach gave good overall yields of vitamins 3 (8.3-16% in six to eight steps) which compares favorably with a classical steroid approach (0.2% in 11 steps). The allene strategy should be general for A-ring analogues of the physiologically important 1-hydroxyvitamin D system and could be applicable for preparing other polyenic systems characterized by centrally located Z-olefinic units.

## Introduction

The stereostructure 1 is characteristic of the physiologically important  $1\alpha$ ,25-dihydroxyvitamin D<sub>3</sub> (2a), the active form of vitamin D<sub>3</sub> (2b, cholecalciferol), as well as analogs possessing biological properties of unusual interest. Among steroid hormones, such as cortisol, aldosterone, testosterone, estradiol, and others, the calcium regulating hormone 2a is structurally unique because the usual steroid B-ring is absent and is replaced by a 1-



#### Figure 1.

hydroxy- $\Delta^{5,7,10(19)}$ -triene moiety (see Figure 1).<sup>2</sup>

Classical steroid syntheses have usually been employed for constructing the triene group stereoselectively. In the most commonly used procedure, a steroidal  $\Delta^5$  olefin is brominated and then dehydrobrominated to produce a  $\Delta^{5,7}$  diene.<sup>2a</sup> The latter is photochemically opened through an electrocyclic process to the previtamin form, and then the previtamin is thermally transformed to the vitamin. This last step, a [1,7]-sigmatropic shift<sup>3</sup> of a hydrogen atom, is an excellent reaction. However, the two other late steps, introduction of the  $\Delta^7$  double bond and the photoelectrocyclic ring opening, are inefficient. Moreover, the linearity of the steroid route makes it less flexible for the construction of analogs of the type 1. A convergent route seemed more desirable.<sup>4</sup>

In the preliminary communication,<sup>1b</sup> we reported a method using vinylallene intermediates<sup>5</sup> for constructing the 1-hydroxyvitamin D system in a convergent manner. As the first application

<sup>†</sup>This paper is dedicated to Professor E. Havinga on the occasion of his

retirement in 1979 after a distinguished career at the University of Leiden. (1) (a) For part 17, see Messing, A. W.; Ross, F. P.; Norman, A. W.; Okamura, W. H. *Tetrahedron Lett.* **1978**, 3635. (b) For the preliminary communication to this paper, see Hammond, M. L.; Mouriño, A.; Okamura, W. H. *J. Am. Chem. Soc.* **1978**, 100, 4907. (c) Taken in part from the Ph.D theses submitted to the University of California, Riverside, by P. Condran, L. (Mourin, 1980) and M. L. University of California, Riverside, by P. Condran, Jr. (March, 1980), and M. L. Hammond (March, 1978).

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Figure 2. Synthesis of C/D fragments. Reagents: (a)  $LiC_2H$ , THF, -78 °C (90%); (b) n-BuLi-THF, PhCOCl, -78 °C-RT (88%); (c) CF<sub>3</sub>C-OOH, C<sub>6</sub>H<sub>6</sub> (58%); (d) Ph<sub>3</sub>PCH<sub>2</sub>, THF, heat (88%); (e) CHBr<sub>3</sub>, KOt-Bu, hexane, 0 °C (97%); (f) CH<sub>3</sub>Li, ether, 0 °C (97%); (g) LiC<sub>2</sub>H, THF, -78 °C (87%); (h) Ph<sub>3</sub>PCH<sub>2</sub>, THF, heat (74%). See ref 7-9 in the text.



Figure 3. The A-ring cuprate coupling method. Reagents: (a) Ph<sub>3</sub>PI<sub>2</sub>, CH<sub>3</sub>CN, Et<sub>3</sub>N (77%); (b) NaBH<sub>4</sub>, CH<sub>3</sub>CH<sub>2</sub>OH (88%); (c) TBDMS-Cl, imidazole, DMF (92%); (d) 2-t-BuLi/Et<sub>2</sub>O, CuC=CCMe<sub>2</sub>(OMe), and then 10 (-78) °C; (e) (n-Bu)<sub>4</sub>NF, THF, and then MPLC (31% 6a + 38% 7a); (f) hv, hexane 1 h (58%); (g) hv, hexane, 1 h (50%). See ref 10, 11, and 5g in the text.

of the new method, synthesis of 3-deoxy-1 $\alpha$ -hydroxyvitamin D<sub>3</sub>  $(3a)^{1b,6}$  and its 1 $\beta$  epimer (3b) were described. This full report describes several significant modifications of the original route and the results of a more detailed examination of sigmatropic reactions in the vitamin D series.

Our vinylallene approach to the 1-hydroxyvitamin D system is based on some earlier photochemical studies of Havinga, Lugtenburg, and co-workers.<sup>5e-g</sup> They characterized the vinylallenes 4a and 4b as minor photoproducts ( $\sim 11\%$ ) upon irradiating the parent vitamin  $D_3$  (2b). The trimethylsilyl ether of either allene 4a or 4b was observed to rearrange under gas chromatography conditions (225 °C) to several products including the silyl ethers of isopyrocalciferol and pyrocalciferol. The two pyroisomers were identical with the two products obtained by subjecting the silvl ether of vitamin D<sub>3</sub> to the same gas chromatography conditions. It was suggested that the gas chromatographic behavior of the allenes 4 could be rationalized if they were to undergo first a [1,5]-sigmatropic shift to 2b. We reasoned, therefore, on the basis of this likely hypothesis, that vinylallenes 5, 6, and 7 would be attractive thermal precursors to the desired 1-hydrovitamin D system. If 5, 6, and 7 required temperatures

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Sigmatropic Reactions of Vinylallenes, Vitamin D

Figure 4. The C/D allenyllithium coupling method. See Tables I and II and ref 12 and 13 in the text

much in excess of 150 °C for inducing [1,5]-sigmatropic shifts, then it was likely that the desired vitamin would undergo an undesirable irreversible rearrangement to the pyrocalciferols corresponding to those of 2b. This was not an anticipated problem since the thermal studies of Skattebøl<sup>5d</sup> and Crowley<sup>5b</sup> on simple vinylallenes suggested that such [1,5] shifts should occur at much lower temperatures. The presumed concertedness of the intramolecular [1,5] shift necessarily imparts the desired Z stereochemistry to the central  $\Delta^5$  double bond. The stereochemistry expected for the  $\Delta^7$  double bond was uncertain, and this study was therefore necessarily exploratory in this respect. Penultimate to the thermal studies was the more critical problem of synthesizing allenes 5-7. Two different satisfactory solutions to the latter synthetic problem have been achieved, and new or improved details concerning the thermal behavior of vinylallenols (6, 7), vinylallenones (5), and their rearrangement products are described.

#### Results

Synthesis of Vinylallenes. Figure 2 summarizes the syntheses of various C/D/side-chain fragments prepared from Grundmann's ketone<sub>3</sub> (8),<sup>7</sup> which in turn was prepared in 73% yield by ozonolysis of vitamin  $D_3$  (2b) in propional dehyde by the method of Story.<sup>8</sup> The key C/D fragments 10 and 13 were prepared as outlined.<sup>9</sup> In order to ensure the stereochemical homogeneity of the trans C/D ring junction in 10 and 13, two of their earlier precursors (9 and 11, respectively) were also prepared in their cis C/D forms (15 and 16, respectively) for comparison purposes.<sup>7</sup> The C-8 stereochemistry of 9 and 10 is assigned as indicated in as much as the corresponding  $LiAlH_4$  reduction of 8 occurs completely stereoselectively to produce the  $8\beta$  alcohol.<sup>7</sup> While the C-8 stereochemistry of 15 is uncertain, it appears to be chromatographically mainly a single isomer. The overall distilled yields of 10 and 13 from vitamin  $D_3$  were 58% (three steps) and 60% (four steps), respectively.

The vinylallenes 5-7 were synthesized by two different methods. In the first (Figure 3: A-ring cuprate coupling),<sup>5g,10,11</sup> the coupling reaction involves a nucleophilic A-ring component and an electrophilic C/D fragment (10). In the second (Figure 4 C/D allenyllithium coupling)<sup>12</sup> operationally simpler approach, the

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Table I. Deprotonation-Coupling-Dehydration of Allene 13 with Keto-Enol Ether 22

base <sup>a</sup>	5a/5b (% yield mixture)
t-BuLi/ether/-78 to -55 °C <sup>b</sup>	13.5/1.0 (90)
<i>t</i> -BuLi/THF/ $-78$ to $-10$ °C	1.6/1.0 (80)
<i>n</i> -BuLi/THF/ $-78$ to $-10$ °C	1.9/1.0 (81)
$LiN(i-Pr)_2/THF/25$ °C	3.4/1.0 (88)
LiN(cyclohexyl) <sub>2</sub> /THF/25 °C	4.0/1.0 (80)
Li(2,2,4,4-tetramethylpiperidide)/THF/25 °C	3.0/1.0 (91)

 $^{a}$  The temperatures indicate deprotonation conditions. In all cases, 22 was added at -78 °C and then the mixture was warmed to room temperature. See also Figure 4. <sup>b</sup> Experimental details are given for the first entry. The 5a/5b ratios were determined by <sup>1</sup>H NMR integration of the C-18 methyl group peak or by HPLC. See ref 12 and 13 in the text.

Table II. Reduction of 5a to 6a/7a and 5b to 6b/7b

hydride	from 5a 6a/7a (% yield)	from <b>5b</b> 6b/7b (% yield)
NaBH <sub>4</sub> /EtOH	$\frac{1}{1}(77)^{a}$ 1.2/1.(88)	$\frac{1}{1.3}(90)^{a}$ $\frac{1}{1}(1,1,(87))^{a}$
LiAl(O-t-Bu) <sub>3</sub> H/THF	1/1.2 (71)	1.1/1 (75)
L-selectride/THF	1/1.2 (100)	1.4/1 (100)
PBPH/ I HF	1.3/1 (95)	1/2.0 (95)

 $^{a}$  The details for the first entries are given in the Experimental Section. The ratios of isomers were determined by HPLC. The yields for the NaBH<sub>4</sub> entries are for the mixture after separation. The yields for all other entries are for the crude but chromatographically homogeneous mixtures. See ref 15 in the text.

nucleophilic lithium salt of allene 13 is coupled to an electrophilic A-ring fragment.

As shown in Figure 3, 2-methylcyclohexane-1,3-dione (17) was converted in three steps (62% overall) to the silvl ether 20.<sup>10a,b</sup> The latter was converted to its lithium salt (t-BuLi/ether),<sup>10d</sup> and then the salt was transferred to a freshly prepared suspension of the cuprous salt of 3-methoxy-3-methyl-1-butyne (*n*-butyllithium and then CuI/ether) at -78 °C.<sup>10c</sup> The cuprate (formally 21) was treated with benzoate 10,11 and then the resulting material was deprotected with  $(n-Bu)_4 NF/THF^{10b}$  to give a mixture of **6a** and 7a ( $\sim$ 87%). Medium-pressure liquid chromatography (MPLC)<sup>14</sup> afforded pure 6a (31%, less polar) and 7a (38%, more polar). We were unable to detect the presence of the 6S allenes 6b and 7b. Irradiation<sup>5g</sup> of 6a afforded a quantitative yield of a 1:1 mixture of 6a and 6b. Chromatography afforded 6b in 53% yield (based on recovered 6a). Exactly parallel results were obtained from 7a (50% yield of 7b based on recovered 7a). From starting vitamin D<sub>3</sub>, the overall absolute yields of 6a, 7a, 6b, and 7b were 18, 22, 9.5, and 11%, respectively.

In the second procedure (Figure 4), the allenic hydrocarbon 13 was treated with a variety of strong bases (Table I) to produce the allenyllithium species.<sup>12</sup> It was allowed to react with the isobutyl enol ether 22<sup>13</sup> and then hydrolyzed to afford vinylallenones 5a and 5b, which were not interconvertible under the hydrolysis condition. Under the best conditions (t-BuLi/ether), the yield of chromatographically and spectrally pure 5a was 80%. Photolysis<sup>5g</sup> of **5a** as above for **6a** and **7a** afforded a 1:1 mixture (quantitative) of 5a and 5b from which pure 5b could be isolated (MPLC)<sup>14</sup> in 41% yield (75% based on recovered **5a**). Table II summarizes the reduction of 5a and 5b under a variety of conditions.<sup>15</sup> In view of the lack of really significant stereoselectivity,

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PBPH, lithium perhydro-9b-boraphenalylhydride.



Figure 5. Thermal rearrangement products.

NaBH<sub>4</sub> probably represents the most convenient reagent for reduction. Under the latter conditions, **5a** afforded **6a** and **7a** in 43 and 34% yields, respectively; **5b** afforded **6b** and **7b** in 35 and 55% yields, respectively. Based on starting vitamin  $D_3$ , **6a**, **7a**, **6b** and **7b** were obtained in 21, 16, 13, and 20% overall yields, respectively.

Stereochemistry of the Vinylallenes. The C-1 configuration for all alcohols described in this paper obtains ultimately from a direct comparison of a sample of (1S)-3-deoxy-1-hydroxyvitamin D<sub>3</sub> (3a) obtained in this study (see the thermal studies below) with that synthesized independently from  $1\alpha$ -hydroxycholest-5-ene as described earlier.<sup>6</sup> The two epimers (3a and 3b) are easily distinguishable by chromatography (20% AgNO<sub>3</sub> impregnated silica gel, 4:1 benzene-chloroform) but exhibit only subtle differences in their spectral characteristics (<sup>1</sup>H NMR, UV, IR).

The C-6 (allene) configuration of each of six vinylallenes (5a,b, 6a,b and 7a,b) was assigned by comparing C-18 CH<sub>3</sub> <sup>1</sup>H NMR chemical shifts with those of model compounds  $(4a, b^{5e} and 13)$ . The C-18 CH<sub>3</sub> signals of 4a, 4b, and 13 appear at  $\tau$  9.35, 9.27, and 9.36, respectively. It appears that a C-18, CH<sub>3</sub> signal near  $\tau$  9.35 ± 0.03 ppm is characteristic of allenes possessing a  $\beta$ hydrogen ( $\beta$  to the C/D fragment) at C-6 as in 4a and 13. In the cases thus far studied (4-7), a C-18 CH<sub>3</sub> signal at  $\tau$  9.27 ± 0.03 is characteristic of the substances with a  $\beta$  substitutent at  $C_6$ .<sup>16</sup> The C-18 angular methyl group signals for the 6*R* allenes 5a, 6a, and 7a appear at  $\tau$  9.32, 9.35, and 9.35, respectively. The corresponding signals for the 6S allenes 5b, 6b, and 7b appear at  $\tau$  9.24, 9.29, and 9.29, respectively. Yet another small, but significant characteristic which distinguishes the 6R and 6S allenes is the magnitude of the long-range triplet splitting of the allenic H at C-6.<sup>17</sup> For the 6R allenes (5a, 6a, and 7a), the apparent coupling constants are 2.9, 3.1, and 3.1 Hz, respectively. For the 6S allenes (5b, 6b, and 7b), the values are 3.6, 3.5, and 3.5 Hz, respectively. This triplet splitting of the allenyl proton  $(H_6)$  is likely due to essentially equivalent splitting by the axial protons,  $H_{9\alpha}$  and  $H_{15\alpha}$ .

**Thermal Studies.** Each of the vinylallenes ( $\sim 0.01$  M) in isooctane was heated at reflux ( $\sim 100$  °C) under nitrogen for 10 h (alcohols 6 and 7) or 20 h (ketones 5). Figure 5 and, in part, Figure 1 give structures for the products obtained (LC preparative separation) and Table III summarizes the product distributions.

Thermolysis of the (1S,6S)- (7b) and (1R,6R)-vinylallenols (6a)afforded as main products 3-deoxy-1 $\alpha$ -hydroxyvitamin D<sub>3</sub> (3a,the vitamin with the natural 1S configuration)<sup>6</sup> and its 1 $\beta$  epimer (3b), respectively. As mentioned earlier, 3a was chromatographically distinguishable from 3b and proved identical with an

Table III.	Summary	of	Thermal	Studies	under
Standard C	Conditions <sup>a</sup>	1			

· · · _ · · · · · · · · · · · · · · · ·	<u></u>
substrate	products
(reaction time)	(% yield; given in order of elution)
5a (20 h)	30 (47), 29 (47)
5b (20 h)	30 (62), 29 (30)
<b>6a</b> (10 h)	3b (60), 23 (~10), 25 (~2), 6a (~3), 24 (~10)
6b (10 h)	3b (12), 23 (45), 25 (~9), 24 (25)
7a (10 h)	$3a(17), 26(37), 28(\sim 9), 7a + 31a(\sim 7), 27(24)$
7b (10 h)	3a (59), 26 (~7), 28 (~3), 7b + 31a (~12), 27 (~6)
23, 24, or 25 (26-36 h)	23 (45), 25 (13), 24 (42); ±2% max av dev
26, 27, or 28 (26-36 h)	26 (49), 27 (36), 28 (14); ±3% max av dev
<b>3a</b> or <b>31a</b> (60 °C, 8 h)	<b>3a</b> (79), <b>31a</b> (10); 9:1 ratio by <sup>1</sup> H NMR with a ±1% av dev
<b>3b</b> or <b>31b</b> (60 °C, 8 h)	<b>3b</b> (74), <b>31b</b> (11); 9:1 ratio by <sup>1</sup> H NMR with a ±1% av dev

<sup>a</sup> Refluxing isooctane ( $\sim 100$  °C unless otherwise indicated) under nitrogen for the time periods indicated.

authentic specimen obtained from  $1\alpha$ -hydroxycholest-5-ene.<sup>6</sup> The overall yield of **3a** from vitamin D<sub>3</sub> was 8.3% (cuprate method, Figure 3) or 15% (allenyllithium method, Figure 4). The overall yield of **3b** calculated similarly was 13 or 16%, respectively.

The key minor products (13-22%) from 7b (26, 27, and 28) and 6a (23, 24, and 25) were obtained as major products (70-80%) by heating the diastereomeric vinylallenols (1*S*,6*R*)-7a and (1*R*,6*S*)-6b, respectively; the vitamins 3a and 3b, which were the major products (59-60%) from heating 7b and 6a, were now the minor products (12-17%). In separate experiments (Table III), it was shown that an equilibrium could be established between 26, 27, and 28 and between 23, 24, and 25. Thus, it is clear from the product proportions given in Table III that 23 is kinetically favored over 24 when 6b is heated, and that 26 is kinetically preferred over 27 when 7a is heated. Moreover, since 3b, 6a, 6b, and 23-25 belong to one thermal manifold while 3a, 7a, 7b, and 26-28 belong to the other, and since the C-1 configuration of 3a has been established as (1*S*), the C-1 configurations are established as assigned in Figure 5.

The thermolysis of (6R)-vinylallenone **5a** afforded a ~1:1 mixture of previtamin ketone **29** and *cis*-isotachysterone<sup>18</sup> **30**; by contrast, the 6S isomer **5b** afforded a ~1:2 mixture of the same pair of substances. Hydride reduction of **29** afforded a separable ~1:1 mixture of 1S- (**31a**) and 1R previtamins (**31b**). The C-1 configurations were established by their thermal isomerization through the classical [1,7]-sigmatropic shift pathway<sup>3</sup> to (1S)-**3a** and (1R)-**3b**, respectively. The vitamin-previtamin equilibrium ratio was 9:1 (Table III) for each C-1 epimer.

Similar hydride reduction of 30 afforded a  $\sim 1:1$  mixture of 25 (1R) and 26 (1S). The former, 25, was identical with one of the minor products obtained from heating 6a and 6b; the latter, 26, was the same as that derived from the thermal experiments involving 7a and 7b.

In the preliminary communication,<sup>1b</sup> the four diastereomers 23-24 and 26-27 were assigned the stereostructures shown in Figure 5 on the basis of their close spectral similarities (UV and <sup>1</sup>H NMR) with one another and on the basis of a rational mechanistic pathway for their formation involving two consecutive [1,7] shifts. The then proposed intermediates 25 and 28 have now been synthesized via reduction of ketone 30 and the existences of the equilibria  $23 \rightleftharpoons 25 \rightleftharpoons 24$  and  $26 \rightleftharpoons 28 \rightleftharpoons 27$  have been established. These new results leave little doubt as to the stereostructural assignments of 23-28 as well as 30. Moreover, Schnoes and co-workers,<sup>18a</sup> have meanwhile reported closely

<sup>(16)</sup> The allenyl anion of 13 (*t*-BuLi/ether, Table I) was quenched with 1,2-diiodoethane to afford an inseparable 13:1 mixture (<sup>1</sup>H NMR analysis) of what has been assigned the 6R (major) and 6S (minor) iodoallenes. Their C-18 CH<sub>3</sub> chemical shifts were  $\tau$  9.38 and 9.27, respectively. (17) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic

<sup>(17)</sup> Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: Oxford, 1969; pp 328-330.

<sup>(18)</sup> cis-Isotachysterol<sub>3</sub> is **34** in Figure 6. See (a) Verloop, A.; Corts, G. J. B.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1960**, *79*, 164. (b) Onisko, B. L.; Schnoes, H. K.; DeLuca, H. F. J. Org. Chem. **1978**, *43*, 3441.



Figure 6. Thermal equilibria.



Figure 7. The possible stereochemical pathways of the primary thermal step of the vinylallenes 5, 6, and 7 are depicted. The asterisk (\*) denotes C-1 which bears a hydroxyl or carbonyl function; the migrating hydrogen atom is circled.

related equilibria,  $32 \Rightarrow 34 \Rightarrow 33$  (Figure 6A). For comparison, Figures 6B and 6C summarize the results from this study for 23  $\Rightarrow$  25  $\Rightarrow$  24 and 27  $\Rightarrow$  28  $\Rightarrow$  26. The close correspondence of the equilibrium behavior and of spectral properties (UV and <sup>1</sup>H NMR data) of the various related isomers given in Figure 6 further attests to the assigned structures.

### Discussion

Thermal Studies. The thermal rearrangement of the vinylallenes 5-7 presumably proceeds through competing suprafacial [1,5]sigmatropic shifts of hydrogen from C-19  $\rightarrow$  C-7 (Figure 7; C-1, which bears the hydroxyl or carbonyl oxygen, is indicated by an asterisk). One path (a or a') leads to the desired 7E manifold, which consists of a mixture of the vitamin and previtamin (3a  $\rightleftharpoons$ **31a**, **3b**  $\rightleftharpoons$  **31b** or 1-keto-3  $\rightleftharpoons$  **29**). The other path (b or b') leads to the 7Z manifold, in which the product of the primary [1,5]process (7Z in Figure 7) is not observed, but rather the product (25, 28, or 30) of the secondary process ([1,7]-sigmatropic shift of the  $C_{14}$ -H  $\rightarrow$   $C_{19}$ ) as well as the products (23 + 24 from 25; 26 + 27 from 28; corresponding products from 30 were not observed) from the tertiary processes ([1,7]-sigmatropic shift of  $C_{15}$ - $H_{\alpha}$  or  $C_{15}$ - $H_{\beta} \rightarrow C_{10}$ ) were actually isolated.

Referring to Figure 7, the 1R,6R alcohol prefers rearrangement via path a over path b by a  $\sim$ 2.7:1 ratio; the ratio is reversed (a/b ~1:4.1 ratio) for the 1S,6R diastereomer. For the 1S,6S and 1R,6S isomers, the a'/b' ratios were  $\sim$ 3.7:1 and  $\sim$ 1:6.6, respectively. These values were calculated from the data of Table III, wherein for each allenol diastereomer the sum of the 7Zmanifold products corresponds to b or b' and that of the 7Eproducts (excluding the previtamin not quantitatively accounted for) corresponds to a or a'. Thus, the preferred A-ring face for the trajectory of the migrating hydrogen (C-19  $\rightarrow$  C-7) is always opposite to the A-ring face bearing the C-1 OH group (the 7E

manifold is favored for the 1R.6R and 1S.6S alcohols; the 7Zmanifold is preferred for the 1R,6S and 1S,6R alcohols). The most desirable diastereomer for thermolysis is the 1S,6S allenol 7b, since it is this isomer that produces the greatest proportion of the natural vitamin configuration, 1S.7E. Whether this C-1 configurational effect is general for optimizing entry into the desired 7E manifold remains to be determined through studies of other analogs.

As regards a rationale for the C-1 configurational effect, it is tempting to attribute the phenomenon to a steric effect. In support of this notion, thermolysis of the 6R ketone 5a, in which each face of the A ring at C-1 is sterically the same, produces equal proportions of 7E- (29) and 7Z manifold products (30). Models imply that for the isomerization of 5a, trajectories a and b seem to be influenced by nearly equivalent steric environments (path b by the axial  $H_{9\alpha}$  and path a by the axial  $H_{14\alpha}$  with minimal influence by the D ring). In other words, the observed product ratio from 5a is rationalized on the basis that neither the A ring nor the C/Dfragment significantly influences the path a to b ratio. This implies that for the two 6R alcohols, 6a and 7a, only the A ring is influencing the final  $\Delta^7$  stereochemistry. However, in the case of the 6S ketone 5b, which affords a  $\sim 2:1$  ratio of 30 and 29, the two possible trajectories of the migrating hydrogen atom (paths b' and a') encounter different steric environments with respect to the C-9 and C-14 substituents. Path a' resides syn to the steric environment of the D ring and C-18 angular methyl group; path b' resides anti to these same moieties. Thus, that path b' is favored over path a' can be accounted for in terms of a steric effect. This suggests that for the rearrangement of the two 6S alcohols. 6b and 7b, both the C/D fragment and the A ring are probably collectively influencing the ultimate  $\Delta^7$  stereochemistry. A study of the effects by other C-1 substituents on the stereochemical course of these vinlyallene rearrangements is obviously desirable. One can certainly not yet rule out the possible influence of electronic factors.

The previtamin  $D_3$ -vitamin  $D_3$  equilibrium has been established to be 16/84 at 60 °C.<sup>19</sup> In this study, where the OH is located at C-1 rather than C-3 (31 and 3 in Table III), the equilibrium ratio for the analogous process was  $\sim 10/90$ . This slightly larger bias to the vitamin side when a C-1 OH is present is likely due to the increased steric strain in 31 characteristic of 2-methylcyclohex-2-en-1-ol systems.<sup>20</sup> The results summarized in Figure 6 can be rationalized in a similar way. The proportion of 34 is similar to that of 33 and 32 (Figure 6A).<sup>18</sup> The proportions of the analogous 25 (Figure 6B) and 28 (Figure 6C) are attenuated in their respective equilibria, presumably again because of the same type of steric strain ascribed to 31.20

As discussed briefly for 23/24 and 26/27 in our earlier communication<sup>1b</sup> and in detail for 32/33 in the paper by Schnoes and co-workers,<sup>18b</sup> the C-10 CH<sub>3</sub> group is strongly biased in an axial orientation<sup>21</sup> as depicted in Figure 6. The opposite chair form in each case would suffer steric congestion between an equatorial methyl (C-10 CH<sub>3</sub>) and the vinyl-H at C-7 assuming that the intercyclic diene fragment prefers to be planar. The situation is akin to several 10,19-dihydrovitamins reported from this laboratory several years ago.<sup>21</sup> In the equilibrium of Figure 6A, the 1.67/1ratio of 33/34 is readily rationalized on the basis that the hydroxyl prefers to be equatorial.<sup>18b</sup> In the equilibria of Figures 6B and 6C, the ratios for 23/24 and 26/27 are closer to unity. The preference for the equatorial OH conformer is presumably partially

<sup>(19)</sup> Hanewald, K. H.; Rappoldt, M. P.; Roborgh, J. R. Recl. Trav. Chim. Pays-Bas, 1961, 80, 1003, and the references to Velluz and Havinga and their co-workers

<sup>(20) (</sup>a) Johnson, F. Chem. Rev. 1968, 68, 375-413. (b) Senda, Y.; Imaizumi, S.; Ochiai, S.; Fujita, K. Tetrahedron 1974, 30, 539. The 2methylcyclohex-2-en-1-ol system is expected to possess steric strain in either pseudo-chair conformation. In one conformer (pseudo-equatorial hydroxyl), there is allylic strain between the methyl and hydroxyl. In the other (pseudo-axial hydroxyl), the hydroxyl is 1,3-diaxial to the cis hydrogen at C-5. In the absence of an allylic hydroxyl, there are fewer nonbonded interactions. (21) (a) Mouriño, A.; Okamura, W. H. J. Org. Chem. **1978**, 43, 1653. (b) Okamura, W. H.; Hammond, M. L.; Rego, A.; Norman, A. W.; Wing, R. M.

Ibid. 1977, 42, 2284.

offset by the gauche interaction between the equatorial OH and the axial C-10  $CH_3$ .

In the quantitative studies of Schnoes and co-workers,<sup>18b</sup> it was noted that the [1,7]-sigmatropic shift  $34 \rightarrow 36$  occurred ca. two times faster than  $34 \rightarrow 33$ . In this study, the reactions  $25 \rightarrow 23$ and  $28 \rightarrow 26$  proceed faster than  $25 \rightarrow 24$  and  $28 \rightarrow 27$ , respectively. Assuming the theoretically predicted antarafacial pathway for the [1,7] migration<sup>3</sup> of the  $15\alpha$ - or  $15\beta$ -H to C-10, there is a kinetic preference for the migrating hydrogen to attack C-10 from the face that also bears the OH giving a trans relationship between vicinal OH and methyl groups. It is surprising that what seems to be the sterically more congested mode of rearrangement is kinetically preferred.

That the C-1 ketone 29 lies entirely on the previtamin side is not unexpected. The linear conjugation in the previtamin ketone 29 should be favored over the cross-conjugation which would be present in the putative vitamin C-1 ketone.<sup>22</sup> The analogous situation obtains for the *cis*-isotachysterone 30. The reduction of 30 constitutes a practical way for synthesizing reasonable amounts of 25 and 28. As is apparent from the data in Table III and Figure 6, only small amounts of the alcohols 25 and 28 can be made available by thermolyzing vinylallenols (6, 7) or trienes 23, 24, 26, or 27.

Coupling Reaction. Vinyl cuprate 21 reacts with propargylic ester 10 in a completely anti S<sub>N</sub>2' fashion.<sup>11</sup> In similar reactions involving alkyl rather than vinyl cuprates, both selective syn<sup>11c,d</sup> and anti<sup>11b</sup> displacements have been reported. Although it has recently been stated<sup>11d</sup> that organocuprate syn 1,3-substitution predominates in 17-ethylnyl-17-hydroxy steroidal esters and that analogous anti reaction dominates in nonsteroidal cases, considerably more detailed investigations would be desirable.<sup>11g,h</sup> Claesson and Olsson<sup>11f</sup> have nicely reiterated the current notion regarding the stereochemical course of 1,3-substitution reactions  $(S_N 2')$  involving propargylic and allylic derivatives. They emphasize that the mechanistic course of such reactions is strongly dependent on both the type of leaving group and the nature of the nucleophile. Since our thermal results suggest that the most desirable vinylallenol is the 1S, 6S stereoisomer 7b, future efforts will center around attempts to reverse the stereoselectivity of the coupling reaction to give 6S allenes. Furthermore, there will be a need to study the prototype transformation  $18 \rightarrow 19$  (Figure 3) in an asymmetric sense to obtain the natural 1S epimer of the alcohol.

Perhaps the most remarkable stereochemical observation encountered in this study concerns the formation of vinylallene 5. It is difficult to rationalize the observed  $\sim 13.5$  to 1.6R/6S ratio  $(5a/5b)^{16}$  on the basis of an allenyl anion (from 13) whose three-carbon framework is linear (either planar or allene-like in geometry).<sup>23</sup> Although it can be argued that stereochemical control can be attributed to subtle solution aggregation effects, the site of electrophilic attack (C-6 of 13) seems too remote from the sterically differentiated  $\alpha$  and  $\beta$  faces of the C/D fragment. Some degree of sp<sup>3</sup> character at C-8 of the lithium salt of 13 would more satisfactorily account for the observed  $\alpha$ -face stereoselectivity. A tetrahedral propargylic lithium structure can, for example, be considered. Another possibility obtains from the work of Schleyer and co-workers.<sup>23c</sup> They have on the basis of theoretical computations predicted an unusual bent carbon framework for the lithium-substituted allene,  $C_3H_3Li$ . The structure consists of a C-C-C bond angle of 158° with an in-plane lithium atom located nearly equidistant ( $\sim$ 1.9 and 2.3 Å) from the terminal carbons. Extrapolation of the C<sub>3</sub>H<sub>3</sub>Li structural parameters to 13 leads to nonplanarity at C-8 of 13 in such a manner as to impart partial axial ( $\beta$ -lithio-13) or partial equatorial ( $\alpha$ -lithio-13) character to

the lithium atom. Thus it can be argued that the seemingly more favorable  $\alpha$ -lithio-13 structure reacts with electrophile on the same face as the lithium atom to give the observed major 6R steroisomer. Whether the theoretical gas-phase structural parameters of C<sub>3</sub>H<sub>3</sub>Li can be applied to solution structures is obviously uncertain. We note, however, that (Table I) in the most nonpolar solvent (ether), wherein lithium coordination to carbon would be expected to be tighest, the highest stereoselectivity is observed. As the lithiumcarbon bond becomes more polarized in solvents of increased polarity, one might expect a more linear allenyl anion-like structure with a resultant decrease in stereoseolectivity. Since we have not yet established whether the conjugate base of 13 is produced under kinetic or thermodynamically controlled conditions (Table I), further speculation at this time is not warranted. Nevertheless, useful information regarding the structure of allenic anions may be obtainable through further studies of the stereochemically well-defined system 13. In this regard, le Noble and co-workers have nicely exploited allenic adamantyl systems for studying the structure of chloroallenic anions.23a

Synthetic Studies. The main thrust of this study was to demonstrate by way of example the general utility of the vinylallene approach in synthesis. Two methods have been developed for synthesizing 1-hydroxyvitamin D type vinylallenes which could be converted to the vitamins 3 in 8.3-16% yields (six to eight steps from vitamin  $D_3$ ). By way of comparison the classical steroid route from cholesterol used in our original synthesis<sup>6a,d</sup> required 11 steps with a 0.2% overall yield. Not only does the vinylallene approach compare favorably with classical approaches, it is made especially attractive by the fact that a host of A-ring fragments should be obtainable from the many very commonly available 2-methyl-1,3-cycloalkanediones (e.g., 2-methyldimedone, 2-methylcyclopentanedione, 2-methylcycloheptanedione, and 5-thia-, 5-oxa-, and other 5-substituted-2-methyl-1,3-cyclohexanediones). The vinylallene approach, including vinyllogous and homologous<sup>24</sup> variations, is in principle a general method for producing polyene chains possessing central cis double bonds (e.g., 11-cis retinoids).<sup>25</sup> These possibilities are being explored.

#### **Experimental Section**

1. General. Ultraviolet (UV) and infrared (IR) spectra, <sup>1</sup>H 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. Dry tetrahydrofuran (THF) or dry ether was freshly distilled (nitrogen) from LiAlH<sub>4</sub> or potassium-benzophenone; lbpe refers to redistilled  $30-60^{\circ}$  C low-boiling petroleum ether. Kugelrohr distillation boiling points (bp) refer to the external oven air bath temperatures. It can be assumed that 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 under nitrogen.

2. Chromatographic Methods. High-pressure liquid chromatography (HPLC) was carried out on a Waters 6000A solvent delivery system equipped with a U6K injection and a dual detector system (UV at 2537 Å and a refractive index detector). Integrations of UV peak intensities were normalized on the basis of  $\varepsilon_{254}$  obtained for appropriate samples. A Whatman M9 10/50 Partisil (10  $\mu$ , 9.4 mm i.d.  $\times$  50 cm) or Waters  $\mu$ -Porasil (10  $\mu$ , 3.9 mm i.d.  $\times$  30 cm) column was used. Diisopropyl ether (chromatographed over activity I alumina and then distilled from CaH<sub>2</sub>), reagent grade isopropyl and isobutyl alcohols, and Skellysolve B (distilled from CaH<sub>2</sub>) were used as solvents. Solvent combinations were vacuum filtered through a  $0.45-\mu$  Millipore filter immediately before use. Medium-pressure liquid chromatography (MPLC) was carried out on an apparatus designed by Meyers and co-workers.<sup>14</sup> The absorbant was silica gel 60 (40-600  $\mu$ m) from E. Merck and the columns used were either 25 mm  $\times$  1 m or 15 mm  $\times$  1 m. We are grateful to Professor Meyers for providing the details for constructing the MPLC apparatus well in advance of publication. For ordinary column chromatography, Baker Analyzed Reagent silica gel (60-200 mesh) or Woelm neutral grade III alumina was used. For thin layer chromatography (TLC),

<sup>(22)</sup> For a related case, see (a) Sheves, M.; Friedman, N.; Mazur, Y. J. Org. Chem. 1977, 42, 3597. (b) Paaren, H. E.; Schnoes, H. K.; DeLuca, H. F. J. Chem. Soc., Chem. Commun. 1977, 890.

<sup>(23) (</sup>a) le Noble, W. J.; Chiou, D.-M.; Okaya, Y. J. Am. Chem. Soc. 1979
101, 3244; 1978, 100, 7743. (b) Bushby, R. J.; Patterson, A. S.; Ferber, G. J.; Duke, A. J.; Whitman, G. H. J. Chem. Soc., Perkin Trans. 2 1978, 807.
(c) Jemmis, E. D.; Chandrasekhar, J.; Schleyer, P. v. R. J. Am. Chem. Soc. 1979, 101 2848.

<sup>(24) (</sup>a) Minter, D. E.; Fonken, G. J. Tetrahedron Lett. 1977, 1717. (b) Ibid. 1977, 4149. (c) See also ref 5h.

<sup>(25) (</sup>a) Knudsen, C. G.; Carey, S. C.; Okamura, W. H. J. Am. Chem. Soc. in press. (b) Sueiras, J.; Okamura, W. H., preceding paper in this issue.

silica gel G (EM reagents, type 60) was used to prepare analytical plates (0.25 mm).

3. De-A,B-8-cholestanone (8, Grundmann's ketone<sub>3</sub>). Ozone was passed through a solution of vitamin D<sub>3</sub> (2b, 10.0 g, 26.0 mmol) in propionaldehyde (150 mL) for 2.5 h (-78 °C). Slow warming (>1 h) to ambient temperatures followed by suitable workup (aqueous NaHCO<sub>3</sub>, ice, water, and ether) and then concentration afforded crude product. Short dry column chromatography (silica gel, lbpe, and benzene) followed by concentration and then Kugelrohr distillation ( $125 °C/3 \times 10^{-4}$  mm) afforded 5.0 g (73%) of 8 as a colorless oil. The material obtained in this experiment was identical with that obtained using Inhoffen's procedure (ozonation; LiAlH<sub>4</sub> workup; back-oxidation with CrO<sub>3</sub>/ pyridine).<sup>7,8</sup>

4. De-A, B-8 $\alpha$ -ethynyl-8 $\beta$ -cholestanol (9). Lithium acetylide (THF, 50 mL, -78 °C; *n*-butyllithium, 1.56 *M* in hexane, 16.5 mL, 25.7 mmol: dry purified acetylene, 675 mL, 27 mmol) was prepared according to Midland's procedure.<sup>9a</sup> Grundmann's ketone<sub>3</sub> (8, 3.39 g, 12.8 mmol) in THF (8 mL plus 16 mL of rinsings) was added dropwise to the acetylide solution (-78 °C, over 30 min), the cooling bath was removed (10 min), and then the reaction was quenched with water (5 mL). Anhydrous  $K_2CO_3$  was added until a thick paste was formed, and then the organic phase was decanted and dried (MgSO<sub>4</sub>). Filtration, concentration, and Kugelrohr distillation (117 °C (3 × 10<sup>-4</sup> mm)) yielded 9 (3.35g, 90%) as a colorless viscous oil.

5. De-A, B-8 $\alpha$ -ethynyl-8 $\beta$ -cholestanol benzoate (10). To a solution of propargyl alcohol (9, 1.99 g, 6.83 mmol) in THF (20 mL) was added *n*-butyllithium (1.63 M, 4.35 mL, 7.1 mmol; syringe, magnetically stirred, N<sub>2</sub>, -78 °C). The cooling bath was removed and the mixture stirred for 30 min. The solution was cooled (-78 °C) and then benzoyl chloride (0.99 g, 0.82 mL, 7.1 mmol; freshly distilled) was added by means of a syringe. The cooling bath was removed, the mixture was stirred at ambient for 2 h, and then the reaction was quenched with water. The THF was removed (vacuum), the residue was extracted (ether-water), and then the ether solution was dried (MgSO<sub>4</sub>) and concentrated. Crystallization of the residue from lbpe afforded pure benzoate 10: 2.36 g (88%); mp 96-97 °C.<sup>98</sup>

6. De-A,B-8-methylenecholestane (11). Grundmann's ketone<sub>3</sub> (8, 1.32 g, 5.0 mmol; dry THF, 25 mL) was allowed to react at reflux (15 min) with methylenetriphenylphosphorane (5.5. mmol in THF, 25 mL). Conventional workup followed by Kugelrohr distillation (100–105 °C ( $3.7 \times 10^{-4}$  mm)) afforded 1.16 g (88%) of 11.<sup>7</sup>

7. 2,2-Dibromospiro[cyclopropane-1,8'-de-A,B-cholestane] (12). Bromoform (2.16 mL, 6.31 g, 25.0 mmol) was added over a 2-h period (syringe drive) to a stirred ice-cooled suspension of KO-t-Bu (2.80 g, 25.0 mmol; freshly prepared and powdered) in a dry hexane (25 mL) solution of 11 (1.31 g, 5.0 mmol). After the addition and a 15-min reaction period, the reaction mixture was poured rapidly into a mixture of lbpe (100 mL) and water (100 mL). The organic phase was separated and then the aqueous phase was extracted with an additional portion of lbpe (100 mL). The combined organic extracts were back-washed (2 × 100 mL water), dried (Na<sub>2</sub>SO<sub>4</sub>), and then concentrated to give a viscous residual oil. Kugelrohr distillation (bp 140-145 °C (2 × 10<sup>-4</sup> mm)) afforded the dibromocyclopropane adduct 12 as a colorless oil in excellent yield (2.12 g, 97%).<sup>9b,d</sup>

8. De-A,B-8-ethenylidenecholestane (13). Methyllithium (0.40 mL, 0.60 mmol, 1.52 M in ether) was added over a 1.5-h period (syringe drive) to an ice-cooled solution of dibromocyclopropane 12 (217 mg, 0.50 mmol). During the addition, LiBr appeared to precipitate. After 10 min, the reaction mixture was poured into a separatory funnel containing lbpe (50 mL) and water (50 mL). The aqueous layer was separated and extracted with an additional 50 mL of lbpe. The combined lbpe extracts were washed with water (50 mL) and brine (20 mL) and then dried (Na<sub>2</sub>SO<sub>4</sub>). The oily residue (quantitative) resulting after concentration was Kugelrohr distilled (bp 110–115 °C ( $2.5 \times 10^{-4}$  mm)) to afford pure allene 13 (133 mg, 97%) as a colorless oil.<sup>9c-f</sup>

9. De-A, B-14-epi-8-cholestanone (14, 14-Epi-Grundmann's ketone<sub>3</sub>). Two drops of trifluoroacetic acid were added to a solution of Grundmann's ketone<sub>3</sub> (8, 264 mg, 1.0 mmol) in benzene (10 mL). After stirring for 4 h at ambient temperatures (monitored by gas chromatography, 5% SE-30, 10 ft ×  $^{1}/_{8}$  in., 225 °C), an additional 8 drops of acid were added and the stirring was continued for 20 h. An apparent equilibrium ratio of 4.3/1 (14/8) was attained. Concentration under vacuum followed by chromatography (75 × 1 cm, dry silica gel column, 40% toluene/lbpe, 8-mL fractions) afforded, after solvent removal, 152 mg (58%) of epiketone 14 ( $R_f$  0.66, diisopropyl ether, silica gel G) and 26 mg (10%) of 8 ( $R_f$  0.62). Kugelrohr distillation (~120 °C (3 × 10<sup>-4</sup> mm)) afforded 14 as a colorless liquid with little loss of material.<sup>7</sup>

10. De-A,B-8ξ-ethynyl-14-epicholestan-8ξ-ol (15). Epi-Grundmann's ketone 14 (284 mg, 1.1 mmol) was treated with lithium acetylide in a manner exactly analogous to that described for Grundmann's ketone 8

to give 9. Primarily a single propargyl alcohol 15 (270 mg, 87% crude yield) was obtained. Direct spectroscopic and TLC comparison (benzene-lbpe, 1:1) showed this material to be distinctly different from the propargyl alcohol 9 derived from Grundmann's ketone<sub>3</sub>  $8.^{9a}$ 

11. De-A, B-14-epi-8-methylenecholestane (16). Epi-Grundmann's ketone<sub>3</sub> (14, 132 mg, 0.50 mmol) in THF (4 mL) was allowed to react with methylenetriphenylphosphorane (0.55 mmol in THF, 2.5 mL) exactly as described for 8 to afford pure olefin 16 (97.5 mg, 74%; Kugelrohr distilled, 105–110 °C ( $3 \times 10^{-4}$  mm)). The product 16 was readily distinguishable from its C-14 epimer 11 by <sup>1</sup>H NMR.

12. 2-Methyl-3-iodocyclohex-2-en-1-one (18). To a mechanically stirred solution of triphenylphosphine (previously recrystallized from ethyl acetate/methanol, 5.78 g, 22.1 mmol) in acetonitrile (freshly distilled from phosphorus pentoxide, 100 mL) was added iodine (5.58 g, 22.0 mmol) and the mixture allowed to stir for 3 h at room temperature. Triethylamine (freshly distilled from lithium aluminum hydride, 3 mL, 21.8 mmol) was added to the resulting yellow suspension of triphenylphosphonium diiodide followed by 2-methylcyclohexane-1,3-dione 17 (2.52 g, 20.0 mmol). The reaction mixture immediately turned a dark brown color and was heated at reflux for 3 h. After cooling, the solvent was removed on a rotary evaporator and the resulting dark brown residue was taken up in ether  $(3 \times 100 \text{ mL})$  and filtered through a short column of silica gel. The column was eluted thoroughly with ether (1500 mL) and the total eluent was concentrated. The residue was Kugelrohr distilled (94 °C (12 mm)) to yield pure 18 (3.65 g, 77.4%), which crystallized as a pale yellow solid: mp 58.5-60 °C (lit.<sup>10a</sup> 57.5-59.5 °C).

13. 2-Methyl-3-iodocyclohex-2-en-1-ol (19). To a solution of 18 (997 mg, 4.2 mmol) in absolute ethanol (10 mL) was added sodium borohydride (175 mg, 4.6 mmol) in portions to minimize foaming. The reaction mixture was allowed to stir under nitrogen for 3 h at room temperature and then quenched with 1 M HCl dropwise until a clear solution was obtained (4 mL). The resulting solution was poured into water (30 mL) and extracted with ether (30 mL). The ether extract was washed with saturated aqueous NaHCO<sub>3</sub> (30 mL) and water (30 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated to yield a pale yellow oil (974 mg). Crystallization from lbpe in the freezer afforded 19 (883 mg, 87.8%) as small white needles that formed in clumps: mp 66.5–67.0 °C. The A-ring fragment is best stored at this stage rather than as the ketone 18 or the silyl ether 20. In practice this alcohol was stored in the dark in the refrigerator.

14. 1-tert-Butyldimethylsiloxy-2-methyl-3-iodocyclohex-2-ene (20). A mixture of imidazole (895 mg, 12.6 mmol) and tert-butyldimethylsilyl chloride (963 mg, 6.4 mmol) was dissolved with stirring in dimethylformamide (freshly distilled from CaH<sub>2</sub>, 4.2 mL) under a nitrogen atmosphere. After about 5 min a clear solution was obtained and alcohol 19 (999 mg, 4.2 mmol) was added. The resulting solution was allowed to stir for 3 h at room temperature and then quenched by pouring into water (100 mL). The resulting mixture was extracted with ether (100 mL) and the extract was washed sequentially with 1 M HCl (50 mL), saturated aqueous NaHCO<sub>3</sub> (50 mL), and water (50 mL). Upon drying (Na<sub>2</sub>SO<sub>4</sub>) and concentrating, the crude product was obtained as a yellow liquid. Kugelrohr distillation afforded 20 (1.36 g, 92.2%) as a colorless liquid: bp 99 °C/0.15 mm.<sup>10b</sup>

15. (1R,6R)- (6a) and (1S,6R)-1-Hydroxy-9,10-secocholesta-5(10), 6,7-triene (7a). Cuprate Coupling Method. To an ice-cooled solution of 3-methoxy-3-methyl-1-butyne (474 mg, 4.84 mmol) in dry ether (5 mL) was added (syringe, N<sub>2</sub>) *n*-butyllithium (1.57 M, 4.84 mmol, 3.08 mL) and the resulting mixture stirred for 20 min. A portion (4.5 mL) of this cooled solution was transferred (double-ended needle) to a reaction flask containing cuprous iodide (489 mg, 2.57 mmol, 5% excess, purified by Soxhlet extraction with THF under N<sub>2</sub>). The resulting orange cuprous acetylide suspension was stirred at room temperature for 45 min, cooled in -78 °C, and then reacted with the vinyllithium reagent described immediately below.

To a solution of iodosilyl ether **20** (852 mg, 2.42 mmol) in dry ether (5 mL) was added (syringe, N<sub>2</sub>, -78 °C, stirred) *tert*-butyllithium (1.47 M, 3.28 mL, 4.84 mmol). The resulting mixture was stirred (1.5 h, -78 °C; 1 h, -30 °C; and 3.5 h, from -30 to -50 °C) and then added (-78 °C, double-ended needle) to the above freshly prepared cuprous acetylide. Stirring was continued at -78 °C for 45 min. To the resulting mixture was added (slowly, doubled-ended needle) a solution of the ethynyl benzoate **10** (788 mg, 2 mmol) in dry ether (4 mL, 1 mL to wash the remaining benzoate). The resulting mixture was stirred (1 h, -78 °C; 3 h, -50 °C) and then allowed to reach room temperature (35 min). The resulting mixture was stirred for 10 min and then poured into a mixture of ether and saturated aqueous NaHCO<sub>3</sub>. The organic layer was washed (H<sub>2</sub>O, 1% HCl), filtered, and dried (MgSO<sub>4</sub>). Removal of solvent afforded a pale yellow oil which was evacuated on an oil pump for at least 1 day.<sup>10c,d,11</sup>

A solution of freshly prepared anhydrous tetrabutylammonium fluoride in dry THF (~0.5 M, 19 mL, 9.6 mmol) was added (room temperature, N<sub>2</sub>) and the resulting solution stirred for 5 h. Workup (lbpe and saturated aqueous NaHCO<sub>3</sub> solution, brine, MgSO<sub>4</sub>; filtration and concentration) and chromatography (silica gel, 10 × 4 cm; eluent: lbpe, 10 × 100 mL; 10% ether-lbpe 10 × 100 mL; 20% ether-lbpe 10 × 100 mL) afforded, after pumping for 40 h, a colorless viscous oily mixture of vinylallene alcohols (670 mg, 87%) which was separated on the MPLC system (eluent: 20% ether-lbpe, 20-mL fractions) to give the (1*R*,6*R*)-vinylallene alcohol **6a** (white foam, 237 mg, 31%) and the (1*S*,6*R*)-vinylallene alcohol **7a** (white foam, 290 mg, 38%). The allenols were chromatographically and spectrally homogeneous, but neither could be induced to crystallize.<sup>106</sup>

16. (1R,6S)-1-Hydroxy-9,10-secocholesta-5(10),6,7-triene (6b). Irradiation of 6a. An aliquot (10 mL) of a standard solution of the (1R,6R)-vinylallene 6a (61 mg, 0.16 mmol) in hexane (40 mL) was transferred to a quartz irradiation well equipped with a nitrogen flow and a dry ice/acetone condenser. The solution was diluted with hexane (40 mL) and the system flushed with nitrogen for 15 min. A Hanovia 100-W, medium-pressure mercury lamp was lowered into the well and the solution irradiated for 1 h. Three additional aliquots were irradiated in an analogous manner. The combined crude irradiation products were concentrated and chromatographed on a silica gel column,  $72 \times 1.5$  cm, eluted with 15% ether in lbpe; 15-mL fractions were collected and the products detected by TLC (isopropyl ether). Fractions 20-24 were combined and concentrated to afford the (1R,6R)-vinylallene 6a (19 mg). Fractions 25-27 contained a mixture of isomeric vinylallenes. Concentration of fractions 28-35 yielded pure 1R,6S allene 6b (16 mg).

Rechromatography of fractions 25-27 was performed on a silica gel column,  $70 \times 1.5$  cm eluted with 15% ether in lbpe; 15-mL fractions were collected and the products detected as before. Additional amounts of the (1R,6R)-vinylallene **6a** (fractions 20-24, 3.5 mg) and the (1R,6S)-vinylallene **6b** (fractions 27-33, 4.5 mg) were obtained. The total yield of the (1R,6S)-vinylallene was 33% (53% based on recovered **6a**).<sup>5g</sup>

17. (15,6S)-1-Hydroxy-9,10-secocholesta-5(10),6,7-triene (7b). Irradiation of 7a. A solution of the (1S,6R)-vinylallene 7a (68 mg, 0.18 mmol) in hexane (80 mL) was flushed with nitrogen for 15 min in a quartz irradiation well fitted with a dry ice/acetone condenser. A Hanovia 100-W medium-pressure mercury lamp was lowered into the well and the solution irradiated for 1 h. The reaction mixture was concentrated to give a colorless viscous oil (67 mg) which was chromatographed on a silica gel column,  $70 \times 1.5$  cm, eluted with 15% ether in lbpe; 15-mL fractions were collected and the products detected by TLC (isopropyl ether). Fractions 19-25 were combined and concentrated to yield the (1S,6S)-vinylallene 7b (17.4 mg). Fractions 26-29 contained a mixture of allene isomers (16.0 mg). Fractions 30-36 yielded, after concentration, the (1S,6R)-vinylallene 7a (14 mg).

Fractions 26-29 were rechromatographed on a silica gel column, 70  $\times$  1.5 cm, eluted with 15% ether in lbpe; 15-mL fractions were collected and the products detected as before. Fractions 22-26 were combined and concentrated to afford an additional amount of the (1*S*,6*S*)-vinylallene **7b** (5.0 mg, total yield of 7b was 33%; 50% based on recovered **7a**). Fractions 27-35 afforded additional material (9.0 mg) which was primarily the (1*S*,6*R*)-vinylallene **7a**.<sup>5g</sup>

18. (6R)- (5a) and (6S)-9,10-Secocholesta-5(10),6,7-triene-1-one (5b). Allenyllithium Coupling Method. A solution of tert-butyllithium (6.95 mL, 10.5 mmol, 1.5 M in pentane) was added to a stirred solution of allene 13 (2.75 g, 10.0 mmol) in dry ether (75 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 cooling the allenyllithium solution to -78 °C (5 min), 3-isobutoxy-2-methylcyclohex-2-en-1-one (2.00 g, 11.0 mmol) in ether (25 mL) was introduced (syringe) resulting in an immediate discharge of the color. Stirring was continued at -78 °C for 5 min and then at ambient temperatures (the cooling bath was removed) for 1 h. Aqueous acetic acid (20 mL, 1 M) was added and then the mixture was stirred vigorously for 5 min. The aqueous layer was withdrawn, a fresh portion of aqueous acetic acid (20 mL, 1 M) was added, and then the stirring was continued for 0.5 h. After transferring the mixture to a separatory funnel along with an additional quantity of ether rinsings (100 mL), the aqueous layer was separated and the ether layer was washed successively with saturated aqueous NaHCO<sub>3</sub> (2  $\times$  50 mL), water (50 mL), and brine (25 mL). Drying (MgSO<sub>4</sub>) and then concentrating under vacuum afforded a viscous yellow oil. Passage of the oil through a short dry silica column (14 × 3.5 cm; 50-mL fractions; 100 mL of lbpe and then 500 mL of benzene) afforded fractions (nos. 3-11) which, after evaporation and vacuum drying, afforded 3.45 g (90%; pale viscous oil) of a 13.5:1 mixture of allenones 5a to 5b (NMR integration of the C-18 angular methyl peaks and HPLC). MPLC (100 × 2.5 cm column; 8:1 Skellysolve B-diisopropyl ether; 25-mL fractions) afforded 5b (27 mg, 1%; eluted first) and

**5a** (3.03g, 80%). The latter was obtained as a very viscous pale yellow oil in a chromatographically and spectroscopically pure state. For TLC analyses of **5a–5b** mixtures on silica gel, three elutions with 4:1 Skelly-solve B to diisopropyl ether were effective.

Besides the *tert*-butyllithium/ether method described above, other base/solvent systems were also examined for their effectiveness in the allene coupling reaction. The results are summarized in Table I.<sup>12</sup>

19. Photolysis of (6R)-Vinylallenone 5a. Using the procedure essentially identical with that described for the photochemical allene isomerization of 6a (expt. 16), 200-400-mL aliquots of 0.005 M isooctane solutions of 5a (ice-cooled) were irradiated. After  $\sim 15$  min, HPLC analysis (Whatman Partisil column; 40% diisopropyl ether/Skellysolve B) indicated that an equimolar proportion of vinylallenone stereoisomers 5a and 5b were present. Prolonged irradiation effected no further change in the 5a/5b ratio. Concentration of photolysate (from 1.91 g of 5a in 1000 mL of isooctane) afforded a quantitative yield (HPLC and NMR) of the 5a/5b mixture as a pale yellow oil. MPLC as described in the preceding experiment (expt. 18) afforded 5a, 5b, and a  $\sim 0.5$ -g mixture of 5a and 5b. The latter 0.5-g mixture was subjected to preparative HPLC (Whatman Partisil column; 40% isopropryl ether/Skellysolve B) for further separation. Combination and vacuum drying of appropriate materials afforded chromatographically and spectrally pure 5b (0.78 g, 41%; 75% based on recovered 5a) and 5a (0.88g, 46%).5g

20. Reduction of 5a to 6a and 7a. A solution of (6R)-vinylallenone (115 mg, 0.30 mmol) in absolute ethanol (6 mL) was treated with NaBH<sub>4</sub> (114 mg, 3.0 mmol). After 4 h of stirring at room temperature, conventional processing (1 M aqueous HCl quench and then ether-water workup) afforded a 1:1 mixture (HPLC) of 6a and 6b. Preparative HPLC (Whatman Partisil; 2% *i*-BuOH/Skellysolve B; recycle), followed by concentrating and drying appropriate eluates, afforded 49.9 mg (43%) of 6a and 38.9 mg (34%) of 7a. The isomers were obtained as chromatographically and spectrally pure viscous oils and were identical with the isomers produced by the cuprate coupling procedure described above (expt. 15).

Besides NaBH<sub>4</sub>/ethanol, several other reducing agents were utilized in attempts to enhance the 1R/1S stereoselection. The results are compiled in Table II.

21. Reduction of 5b to 6b and 7b. The NaBH<sub>4</sub>/ethanol reduction of (6S)-vinylallenone 5b was carried out exactly as described for 5a in the preceding experiment. The crude mixture consisted of a 1/1.3 ratio of 6b/7b (HPLC). Preparative HPLC as above afforded 40.9 mg (35%) of the more polar 1R alcohol 6b and 63.6 mg (55%) of its 1S epimer 7b. The isomeric colorless oils were each chromatographically and spectrally homogeneous. A summary of results using various other reducing agents is described in Table II.

22. Thermolysis of the 6R Ketone 5a. (6Z)-9,10-Secocholesta-5-(10),6,8(14)-trien-1-one (30) and (6Z)-9,10-Secocholesta-5(10),6,8trien-1-one (29). A solution of 6R ketone 5a (383 mg, 1.0 mmol) in freshly distilled dry isooctane (100 mL, bp 100 °C) was refluxed (N<sub>2</sub>) for 20 h. Monitoring by analytical HPLC (40% diisopropyl ether/ Skellysolve B, Partisil) indicated the absence of 5a by this time. Concentration and then preparative HPLC (recycling) of the resulting residue under the same conditions afforded three fractions (each of which was concentrated and vacuum dried). NMR analysis indicated that the two most predominant components were present in a 1:1 ratio. The first least polar fraction contained 14 mg of an apparently heterogeneous material which could not be further resolved and characterized. The second component (179 mg, 47% colorless oil) was identified as the cis isotachysterone 30, and the most polar substance (180 mg, 47%) was characterized as the previtamin ketone 29.

23. Thermolysis of the 65 Ketone 5b to give 29 and 30. A solution of 5b (191 mg, 0.50 mmol) in isooctane (50 mL) was thermolyzed, analyzed, and separated exactly as in the preceding experiment. A 65:35 ratio of 30/29 was present in the crude mixture; preparative HPLC afforded 119 mg (62%) of 30 and 57 mg (30%) of 29, each as a colorless oil.

24. (1R,6Z)- and (1S,6Z)-1-Hydroxy-9,10-secocholesta-5(10),6,8-(14)-triene (25 and 28, respectively). Reduction of *cis*-Isotachysterol Ketone 30. The ketone 30 (230 mg, 0.60 mmol) in absolute ethanol (7 mL) was allowed to react with NaBH<sub>4</sub> (113.5 mg, 3.0 mmol) for 2.5 h at ambient temperatures. After quenching (0.1 M aq HOAc, 5.4 mL) and conventional workup (ether-water), concentration of the dried (Na<sub>2</sub>SO<sub>4</sub>) ether solution afforded a residual oil. Analytical HPLC indicated the 1*R*/1*S* epimer ratio to be 1.06:1. Preparative HPLC with recycling (40% diisopropyl ether/Skellysolve B on Partisil) afforded first the 1*S* alcohol 28 (109 mg, 47%) and then second its 1*R* epimer 25 (105 mg, 46%). Both were obtained as homogeneous colorless oils.

25. (1R,6Z)- and (1S,6Z)-1-Hydroxy-9,10-secocholesta-5(10),6,8triene (31b and 31a). Reduction of Previtamin Ketone 29. A solution of ketone 29 (153 mg, 0.40 mmol) in absolute ethanol (5 mL) was treated with NaBH<sub>4</sub> (76 mg, 2.0 mmol) for 2.5 h at room temperature. Workup as in the preceding experiment afforded a crude oil; analysis showed a ~1:1 mixture of epimeric alcohols. After the crude material was passed through a short, dry column (40 × 5 mm) of silica gel with benzene, the eluate was evaporated (<30 °C) to afford a yellow oil. Multiple recycle preparative HPLC (40% diisopropyl ether/Skellysolve B; partisil) afforded in order of elution: 19 mg (12%) of an oily mixture of (1*R*) and (1*S*)-3-deoxy-1-hydroxyvitamin D<sub>3</sub> (3b and 3a, respectively); 44 mg (29%) of the 1*S* previtamin 31a as an oil; and 49 mg (32%) of the 1*R* previtamin 31b also as an oil.

26. Thermolysis of (1R,6R)-Vinyllallenol 6a. (1R)-3-Deoxy-1hydroxy-vitamin D<sub>3</sub> (3b). A solution of 6a (192.3 mg, 0.50 mmol) in dry isooctane (50 mL) was refluxed under nitrogen for 10 h. Preparative HPLC (40% diisopropyl ether–Skellysolve B, Partisil) with a single injection multiple shave/recycling technique allowed the isolation of five pure components eluted in the following order: vitamin 3b (115 mg, 60%); (1R, 10R)-(5Z,7Z)-trienol 23 (19 mg, 10%); (1R)-(6Z)-trienol 25 (4.5 mg, ~2%); starting material 6a (5.3 mg, ~3%, slightly impure); (1R,10S)-(5Z,7Z)-trienol 24 (19 mg, 10%). Each of the five components was obtained as colorless oil and found to be homogeneous (except for recovered 6a) by HPLC (~85% yield after separation).

Vitamin 3b could be readily distinguished chromatographically from 3a (expts 28 and 29 below). The latter was chromatographically and spectroscopically identical with 3a prepared earlier from  $1\alpha$ -hydroxy-cholesterol.<sup>6</sup>

27. Thermolysis of (1R,6S)-Vinylallenol 6b. (1R,10R)-(5Z,7Z)and (1R,10S)-(5Z,7Z)-1-Hydroxy-9,10-secocholesta-5,7,14-triene (23 and 24, respectively). A solution of 6b (134.6 mg, 0.35 mmol) in isooctane (35 mL) was thermolyzed (10 h, nitrogen), and then the reaction residue was subjected to preparative HPLC exactly as described in the preceding experiment. Four chromatographically and spectrally pure components (colorless oils) were eluted as follows: vitamin 3b (16 mg, 12%); (1R, 10R)-(5Z,7Z)-triene 23 (61 mg, 45%); (1R)-(6Z)-trienol 25 (12 mg, 9%); (1R,10S)-(5Z,7Z)-triene 24 (33 mg, 25%). No starting material was detected and the total mass balance after separation was 91%.

28. Thermolysis of (15,6R)-Vinylallenol 7a. (15,10S)-(5Z,7Z)- and (15,10R)-(5Z,7Z)-1-Hydroxy-9,10-secocholesta-5,7,14-triene (26 and 27, respectively). As described in expt 26, thermolysis of 7a (134.6 mg, 0.35 mmol; 35 mL isooctane; 100 °C/10 h, nitrogen) and then similar workup and preparative HPLC afforded in order of elution: the 1S vitamin 3a (23 mg, 17%); (15,10S)-(5Z,7Z)-trienol 26 (50 mg, 37%); (1S)-(6Z) isomer 28 (13 mg, 9%); 7a/31a (10.2 mg, 7%); (15,10R)-(5Z,7Z)-trienol 27 (33 mg, 24%). All of the components were obtained as colorless oils or foams and the overall mass balance was ~95%.

29. Thermolysis of (15,6S)-Vinylallenol 7b. (1S)-3-Deoxy-1hydroxyvitamin D<sub>3</sub> (3a). As in expt 26, 7b (192 mg, 0.50 mmol) in isooctane was refluxed (100 °C) for 10 h under nitrogen. The usual workup followed by preparative HPLC afforded in order of elution: the 1S vitamin 3a (114 mg, 59%); the (1S,10S)-(5Z,7Z) alcohol 26 (14 mg, 7%); the *cis*-isotachysterol analog (1S)-(6Z) 28 (6 mg, 3%); the previtamin-allene mixture 7b/31a (23 mg, 12%); the 1S,10R)-(5Z,7Z)trienol 27 (11 mg, 6%). The total material balance was 87% of colorless oils.

**30.** Thermal Equilibration of the 1*R* Alcohols 23, 24, and 25. A solution of (1R)-*cis*-isotachysterol analog 25 (115.4 mg, 0.30 mmol) in isooctane (30 mL) was refluxed under nitrogen over a 36-h period while monitoring by HPLC (0.5% isopropyl alcohol in Skellysolve B/ $\mu$ -Porasil or 2% isobutyl alcohol in Skellysolve B/Partisil). After 36 h, HPLC analysis (UV detector) indicated the presence of an equilibrium mixture of 45% (1*R*,10*R*)(5*Z*,7*Z*) isomer 23, 43% of the C-10 epimer 24, and 12% starting material 25. During the early time points of the reaction,

it was apparent that 23 was produced more rapidly than 24. Preparative HPLC as above on a Partisil column (two recycles) afforded, in order of elution, 23 (52 mg, 45%), 25 (16 mg, 13%), and then 24 (46 mg, 40%), all as colorless oils.

Thermal studies (100 °C) on an analytical scale were also carried out on the 1*R*,10*R* isomer 23 (0.38 mg, 0.001 mmol; 5 mL of isooctane) and the 1*R*,10*S* isomer 24 (0.38 mg, 0.001 mmol; 5 mL of isooctane). At 26 h, the 1*R*,10*R* isomer 23 produced 47% 23, 13% 25, and 40% 24. Similarly, at 26 h, the 1*R*,10*S* isomer 24 produced a mixture consisting of 43% 23, 12% 25, and 45% 24.

**31.** Thermal Equilibration of the 1S Alcohols 26, 27, and 28. The (1S)-cis-isotachysterol analog 28 (115.4 mg, 0.30 mmol) in isooctane (30 mL) was thermolyzed (100 °C, 36 h, nitrogen) exactly as in the preceding experiment. At equilibrium, the composition was 48% 1S,10S isomer 26, 37% 1S,10R epimer 27, and 15% starting material. Preparative HPLC, as in expt 30, produced, in order of elution, 26 (41 mg, 35%), 28 (12 mg, 11%), and 27 (36 mg, 31%) as colorless oils. During the early time points of the reaction, it was apparent that 26 was produced more rapidly than 27. In analytical runs, 0.38 mg (0.001 mmol) each of 26 and 27 was heated separately for 26 h in refluxing isooctane (100°C, nitrogen). HPLC canalysis indicated that 26 produced a mixture of 52% 26, 15% 28, and 33% 27. Similar analysis of the mixture produced from 27 indicated the presence of 52% 26, 13% 28, and 35% 27.

32. Thermal Rearrangement of 1S Previtamin 31a to Vitamin 3a. The 1S previtamin alcohol 31a (38.4 mg, 0.10 mmol) in isooctane (10 mL) was maintained at 60 °C for 8 h (nitrogen). Monitoring of the reaction by HPLC (10% diisopropyl ether/Skellysolve B,  $\mu$ -Porasil) revealed that the ratio of 3a/31a had reached a constant value. NMR analysis (ratio of the C-18 angular methyl groups) revealed an 89:11 ratio of 3a/31a. Removal of solvent under vacuum (<30 °C) afforded a residue which was subjected to preparative HPLC (40% diisopropyl ether/Skellysolve B, Partisil). Pure 3a (30.3 mg, 79%; 88% based on recovered 31a) and 31a (3.7 mg, 10%) were obtained as oily white foams.

When pure 3a was heated (60 °C, 8 h) in a similar manner, a 90:10 ratio of 3a/31a was obtained.

33. Thermal Rearrangement of 1*R* Previtamin 31b to Vitamin 3b. The preceding experiment was repeated in exactly the same way for 31b (38.4 mg/0.10 mmol; 10 mL of isooctane; 8 h, 60 °C, nitrogen). NMR analysis of the resulting crude product revealed the presence of 89% vitamin 3b and 11% previtamin 31b. Preparative HPLC as above afforded 28.3 mg (74%; 83% based on recovered 31) of 3b (white foam) and 4.1 mg (~11%) of starting material (colorless liquid).

When pure 3b was heated (60 °C, 8 h) in a similar way, a 90:10 ratio of 3b/31b was obtained.

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Supplementary Material Available: Spectral and analytical data (32 pages). Ordering information is given on any current masthead page.