A plus B (^{1}H NMR indicated the presence of 50% A, 10% 11-cis isomer, and 40% 11,13-dicis isomer) and 47 mg (16%) of B (^{1}H NMR revealed the presence of 70% 11-cis isomer and 30% 11,13-dicis isomer).

Pure A was identified as (11*Z*)-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. (11*Z*)-Retinol (14) and (11*Z*,13*Z*)-Retinol (15). To 47 mg (0.12 mmol) of fraction B (^{1}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 (^{1}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. (11*Z*)-20,14-*retro*-Retinol (13b). To silyl ether **13a** (533 mg, 1.08 mmol) was added freshly prepared tetra-*n*-butylammonium fluoride solution (6 mL, 1 M in THF, 5.5 mmol) under N_2, 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_2OH). A 50-mg sample of vinylallenol **7** (Y = CH_2OH) in isooctane (165 mL) was thermolyzed (100 °C, 4 h) under N_2 as described earlier for the case of the corresponding silyl ether **7** (Y = $CH_2OTBDMS$). Concentration (<40 °C) under vacuum afforded 50 mg (~100%) of material whose composition (^{1}H NMR) revealed the presence of 63% (11*Z*)-20,14-*retro*-retinol (**13b**), 13% (11*Z*,13*Z*)-retinol (**15**), and 24% (11*Z*)-retinol (**14**). The ^{1}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 ^{1}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_2–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.

Acknowledgment. We are grateful to the National Institutes of Health (USPHS Grant EY-02452), the Cancer Research Coordinating Committee (Grant No. 79R4, University of California), and the Intramural Committee on Research (UC Riverside) for financial support. J.S. is a postdoctoral fellow supported by a grant from the Program of the United States–Spanish Joint Committee for Scientific and Technological Cooperation. Badische-Anilin und Sodafabrik (Ludwigshafen) and Hoffman-La Roche (Nutley) generously provided several of the chemicals used in this study; Mr. Christopher Knudsen also provided comparison spectral data for various isomeric retinols.

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[†] [1]

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Abstract: The thermally induced [1,5]-sigmatropic hydrogen shift of the diastereomeric vitamin D type vinylallenols **6a** (1*R*,6*R*), **6b** (1*R*,6*S*), **7a** (1*S*,6*R*), and **7b** (1*S*,6*S*) and vinylallenones **5a** (6*R*) and **5b** (6*S*) were studied. The 1*S*,6*S* (**7b**) and 1*R*,6*R* (**6a**) alcohols afforded ~60% yields of the biologically active 3-deoxy-1α-hydroxyvitamin D_3 (**3a**) and its inactive 1β epimer **3b**, respectively. By contrast, the major products (70–79%) from the 1*R*,6*S* (**6b**) and 1*S*,6*R* (**7a**) allenols were products of an equilibrium manifold (**23** ⇄ **25** ⇄ **24** and **26** ⇄ **28** ⇄ **27**, respectively) resulting from successive [1,7]-sigmatropic hydrogen shifts of an initially formed putative intermediate, (7*Z*)-3-deoxy-1-hydroxyvitamin D_3. 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 6*R* 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$_3$ **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 (6*S*)-vinylallenes **5–7** were obtained by photoequilibration of the more readily available 6*R* 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 1α,25-dihydroxyvitamin D_3 (**2a**), the active form of vitamin D_3 (**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-

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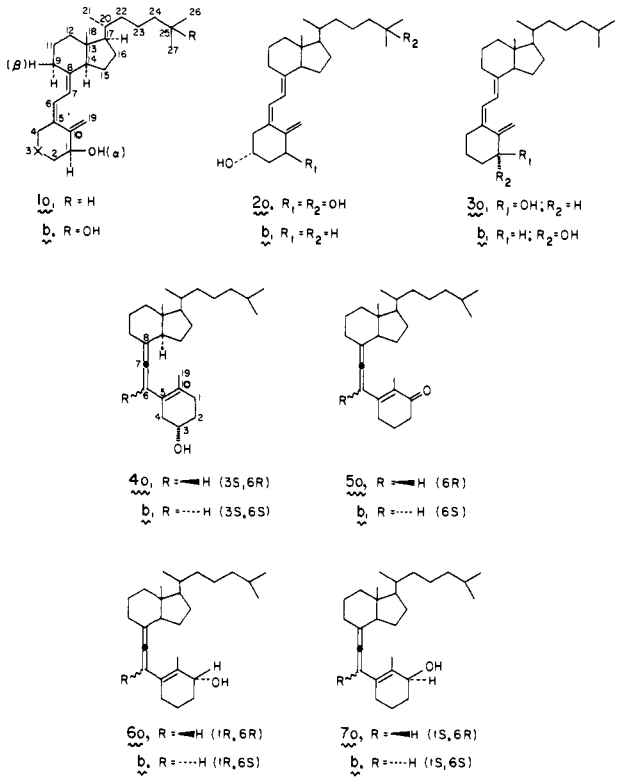

Figure 1.

hydroxy-$\Delta^{5,7,10(19)}$-triene moiety (see Figure 1).[2]

Classical steroid syntheses have usually been employed for constructing the triene group stereoselectively. In the most commonly used procedure, a steroidal Δ^5 olefin is brominated and then dehydrobrominated to produce a $\Delta^{5,7}$ diene.[2a] 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[3] of a hydrogen atom, is an excellent reaction. However, the two other late steps, introduction of the Δ^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.[4]

In the preliminary communication,[1b] we reported a method using vinylallene intermediates[5] for constructing the 1-hydroxyvitamin D system in a convergent manner. As the first application of the new method, synthesis of 3-deoxy-1α-hydroxyvitamin D_3 (**3a**)[1b,6] and its 1β 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.

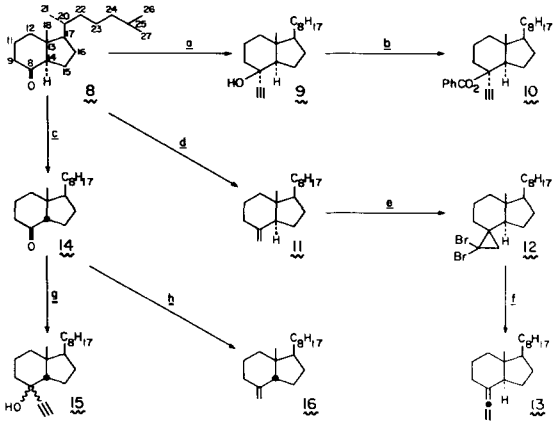

Figure 2. Synthesis of C/D fragments. Reagents: (a) LiC_2H, THF, −78 °C (90%); (b) *n*-BuLi–THF, PhCOCl, −78 °C–RT (88%); (c) CF_3C-OOH, C_6H_6 (58%); (d) Ph_3PCH_2, THF, heat (88%); (e) $CHBr_3$, KO-*t*-Bu, hexane, 0 °C (97%); (f) CH_3Li, ether, 0 °C (97%); (g) LiC_2H, THF, −78 °C (87%); (h) Ph_3PCH_2, THF, heat (74%). See ref 7–9 in the text.

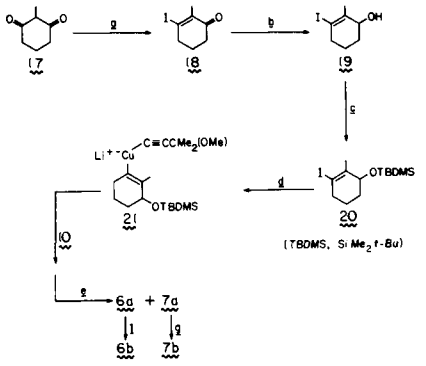

Figure 3. The A-ring cuprate coupling method. Reagents: (a) Ph_3PI_2, CH_3CN, Et_3N (77%); (b) $NaBH_4$, CH_3CH_2OH (88%); (c) TBDMS-Cl, imidazole, DMF (92%); (d) 2-*t*-BuLi/Et_2O, CuC≡CCMe$_2$(OMe), and then **10** (−78) °C; (e) (*n*-Bu)$_4$NF, THF, and then MPLC (31% **6a** + 38% **7a**); (f) *hν*, hexane 1 h (58%); (g) *hν*, hexane, 1 h (50%). See ref 10, 11, and 5g in the text.

Our vinylallene approach to the 1-hydroxyvitamin D system is based on some earlier photochemical studies of Havinga, Lugtenburg, and co-workers.[5e-g] They characterized the vinylallenes **4a** and **4b** as minor photoproducts (~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 silyl ether of vitamin D_3 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

† 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.

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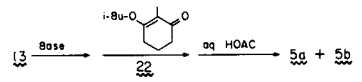

Figure 4. The C/D allenyllithium coupling method. See Tables I and II and ref 12 and 13 in the text

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[5d] and Crowley[5b] 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 Δ^5 double bond. The stereochemistry expected for the Δ^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$_3$ (**8**),[7] which in turn was prepared in 73% yield by ozonolysis of vitamin D_3 (**2b**) in propionaldehyde by the method of Story.[8] The key C/D fragments **10** and **13** were prepared as outlined.[9] 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.[7] 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 8β alcohol.[7] 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),[5g,10,11] 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)[12] operationally simpler approach, the nucleophilic lithium salt of allene **13** is coupled to an electrophilic A-ring fragment.

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

base[a]	5a/5b (% yield mixture)
t-BuLi/ether/−78 to −55 °C[b]	13.5/1.0 (90)
t-BuLi/THF/−78 to −10 °C	1.6/1.0 (80)
n-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)$_2$/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. [b] Experimental details are given for the first entry. The 5a/5b ratios were determined by ^{1}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 5b 6b/7b (% yield)
$NaBH_4$/EtOH	1/1 (77)[a]	1/1.3 (90)[a]
9-BBN/THF	1.2/1 (88)	1/1.1 (87)
LiAl(O-*t*-Bu)$_3$H/THF	1/1.2 (71)	1.1/1 (75)
L-selectride/THF	1/1.2 (100)	1.4/1 (100)
PBPH/THF	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 $NaBH_4$ 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.

As shown in Figure 3, 2-methylcyclohexane-1,3-dione (**17**) was converted in three steps (62% overall) to the silyl ether **20**.[10a,b] The latter was converted to its lithium salt (*t*-BuLi/ether),[10d] 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.[10c] 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** (~87%). Medium-pressure liquid chromatography (MPLC)[14] afforded pure **6a** (31%, less polar) and **7a** (38%, more polar). We were unable to detect the presence of the 6*S* allenes **6b** and **7b**. Irradiation[5g] 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_3, 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.[12] It was allowed to react with the isobutyl enol ether **22**[13] 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[5g] 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)[14] in 41% yield (75% based on recovered **5a**). Table II summarizes the reduction of **5a** and **5b** under a variety of conditions.[15] In view of the lack of really significant stereoselectivity,

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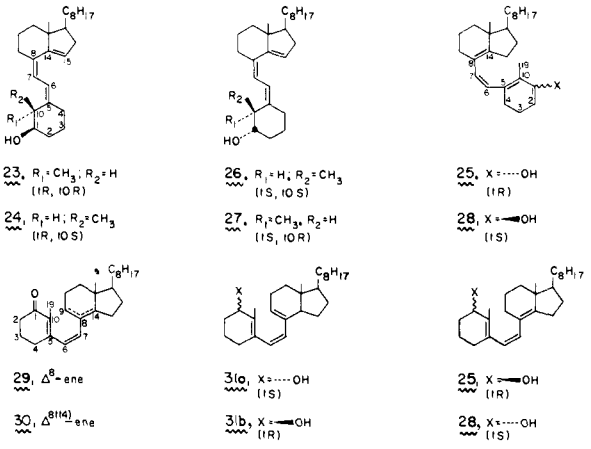

Figure 5. Thermal rearrangement products.

$NaBH_4$ 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 (1*S*)-3-deoxy-1-hydroxyvitamin D_3 (**3a**) obtained in this study (see the thermal studies below) with that synthesized independently from 1α-hydroxycholest-5-ene as described earlier.[6] The two epimers (**3a** and **3b**) are easily distinguishable by chromatography (20% $AgNO_3$ impregnated silica gel, 4:1 benzene–chloroform) but exhibit only subtle differences in their spectral characteristics (^1H 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_3 ^1H NMR chemical shifts with those of model compounds (**4a,b**[5e] and **13**). The C-18 CH_3 signals of **4a**, **4b**, and **13** appear at τ 9.35, 9.27, and 9.36, respectively. It appears that a C-18, CH_3 signal near τ 9.35 ± 0.03 ppm is characteristic of allenes possessing a β hydrogen (β 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_3 signal at τ 9.27 ± 0.03 is characteristic of the substances with a β substitutent at C_6.[16] The C-18 angular methyl group signals for the 6*R* allenes **5a**, **6a**, and **7a** appear at τ 9.32, 9.35, and 9.35, respectively. The corresponding signals for the 6*S* allenes **5b**, **6b**, and **7b** appear at τ 9.24, 9.29, and 9.29, respectively. Yet another small, but significant characteristic which distinguishes the 6*R* and 6*S* allenes is the magnitude of the long-range triplet splitting of the allenic H at C-6.[17] For the 6*R* allenes (**5a**, **6a**, and **7a**), the apparent coupling constants are 2.9, 3.1, and 3.1 Hz, respectively. For the 6*S* 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 (~0.01 M) in isooctane was heated at reflux (~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 (1*S*,6*S*)- (**7b**) and (1*R*,6*R*)-vinylallenols (**6a**) afforded as main products 3-deoxy-1α-hydroxyvitamin D_3 (**3a**, the vitamin with the natural 1*S* configuration)[6] and its 1β epimer (**3b**), respectively. As mentioned earlier, **3a** was chromatographically distinguishable from **3b** and proved identical with an authentic specimen obtained from 1α-hydroxycholest-5-ene.[6] The overall yield of **3a** from vitamin D_3 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.

Table III. Summary of Thermal Studies under Standard Conditions[a]

substrate (reaction time)	products (% yield; given in order of elution)
5a (20 h)	**30** (47), **29** (47)
5b (20 h)	**30** (62), **29** (30)
6a (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** (~9), **7a** + **31a** (~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
3a or **31a** (60 °C, 8 h)	**3a** (79), **31a** (10); 9:1 ratio by ^1H NMR with a ±1% av dev
3b or **31b** (60 °C, 8 h)	**3b** (74), **31b** (11); 9:1 ratio by ^1H NMR with a ±1% av dev

[a] Refluxing isooctane (~100 °C unless otherwise indicated) under nitrogen for the time periods indicated.

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

Similar hydride reduction of **30** afforded a ~1:1 mixture of **25** (1*R*) and **26** (1*S*). 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,[1b] 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 ^1H 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** ⇄ **25** ⇄ **24** and **26** ⇄ **28** ⇄ **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,[18b] upon reexamination of earlier work of Havinga and co-workers,[18a] have meanwhile reported closely

(16) The allenyl anion of **13** (*t*-BuLi/ether, Table I) was quenched with 1,2-diiodoethane to afford an inseparable 13:1 mixture (^1H NMR analysis) of what has been assigned the 6*R* (major) and 6*S* (minor) iodoallenes. Their C-18 CH_3 chemical shifts were τ 9.38 and 9.27, respectively.

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

(18) *cis*-Isotachysterol$_3$ 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.

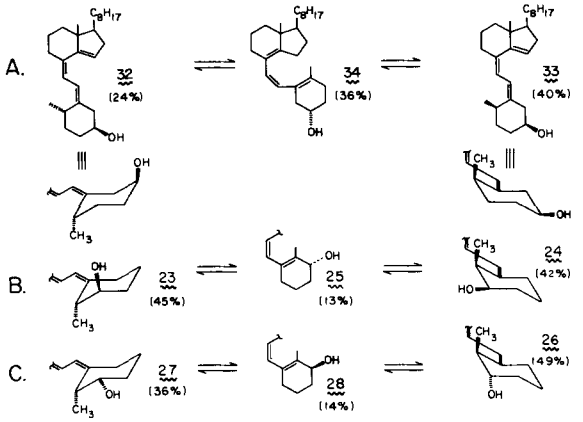

Figure 6. Thermal equilibria.

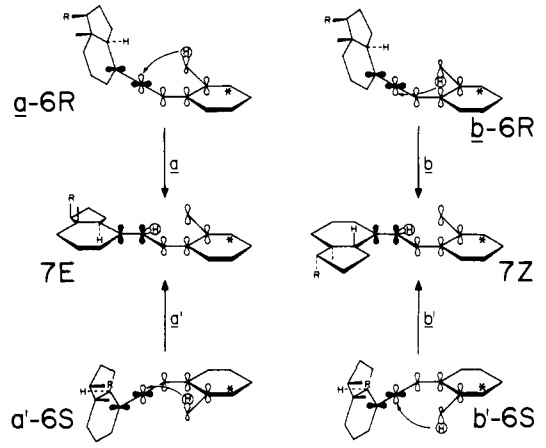

Figure 7. The possible stereochemical pathways of the primary thermal step of the vinylallenes **5**, **6**, and **7** are depicted. The asterisk (*) denotes C-1 which bears a hydroxyl or carbonyl function; the migrating hydrogen atom is circled.

related equilibria, **32** ⇄ **34** ⇄ **33** (Figure 6A). For comparison, Figures 6B and 6C summarize the results from this study for **23** ⇄ **25** ⇄ **24** and **27** ⇄ **28** ⇄ **26**. The close correspondence of the equilibrium behavior and of spectral properties (UV and ^{1}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 → 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 7*E* manifold, which consists of a mixture of the vitamin and previtamin (**3a** ⇄ **31a**, **3b** ⇄ **31b** or 1-keto-**3** ⇄ **29**). The other path (b or b′) leads to the 7*Z* manifold, in which the product of the primary [1,5] process (7*Z* 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 → 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_α or C_{15}-H_β → C_{10}) were actually isolated.

Referring to Figure 7, the 1*R*,6*R* alcohol prefers rearrangement via path a over path b by a ~2.7:1 ratio; the ratio is reversed (a/b ~1:4.1 ratio) for the 1*S*,6*R* diastereomer. For the 1*S*,6*S* and 1*R*,6*S* isomers, the a′/b′ ratios were ~3.7:1 and ~1:6.6, respectively. These values were calculated from the data of Table III, wherein for each allenol diastereomer the sum of the 7*Z* manifold products corresponds to b or b′ and that of the 7*E* products (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 → C-7) is always *opposite* to the A-ring face bearing the C-1 OH group (the 7*E* manifold is favored for the 1*R*,6*R* and 1*S*,6*S* alcohols; the 7*Z* manifold is preferred for the 1*R*,6*S* and 1*S*,6*R* alcohols). The most desirable diastereomer for thermolysis is the 1*S*,6*S* allenol **7b**, since it is this isomer that produces the greatest proportion of the natural vitamin configuration, 1*S*,7*E*. Whether this C-1 configurational effect is general for optimizing entry into the desired 7*E* 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 6*R* ketone **5a**, in which each face of the A ring at C-1 is sterically the same, produces equal proportions of 7*E*- (**29**) and 7*Z* 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/D fragment significantly influences the path a to b ratio. This implies that for the two 6*R* alcohols, **6a** and **7a**, only the A ring is influencing the final Δ^7 stereochemistry. However, in the case of the 6*S* ketone **5b**, which affords a ~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 6*S* alcohols, **6b** and **7b**, both the C/D fragment and the A ring are probably collectively influencing the ultimate Δ^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.[19] 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 ~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.[20] 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).[18] 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[1b] and in detail for **32**/**33** in the paper by Schnoes and co-workers,[18b] the C-10 CH_3 group is strongly biased in an axial orientation[21] as depicted in Figure 6. The opposite chair form in each case would suffer steric congestion between an equatorial methyl (C-10 CH_3) 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.[21] In the equilibrium of Figure 6A, the 1.67/1 ratio of **33**/**34** is readily rationalized on the basis that the hydroxyl prefers to be equatorial.[18b] 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

(19) 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.

(20) (a) Johnson, F. *Chem. Rev.* **1968**, *68*, 375–413. (b) Senda, Y.; Imaizumi, S.; Ochiai, S.; Fujita, K. *Tetrahedron* **1974**, *30*, 539. The 2-methylcyclohex-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,[18b] it was noted that the [1,7]-sigmatropic shift **34** → **36** occurred ca. two times faster than **34** → **33**. In this study, the reactions **25** → **23** and **28** → **26** proceed faster than **25** → **24** and **28** → **27**, respectively. Assuming the theoretically predicted antarafacial pathway for the [1,7] migration[3] of the 15α- or 15β-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.[22] 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_N2' fashion.[11] In similar reactions involving alkyl rather than vinyl cuprates, both selective syn[11c,d] and anti[11b] displacements have been reported. Although it has recently been stated[11d] 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.[11g,h] Claesson and Olsson[11f] have nicely reiterated the current notion regarding the stereochemical course of 1,3-substitution reactions (S_N2') 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 1*S*,6*S* stereoisomer **7b**, future efforts will center around attempts to reverse the stereoselectivity of the coupling reaction to give 6*S* allenes. Furthermore, there will be a need to study the prototype transformation **18** → **19** (Figure 3) in an asymmetric sense to obtain the natural 1*S* 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 ~13.5 to 1 6*R*/6*S* 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).[23] 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 α and β faces of the C/D fragment. Some degree of sp^3 character at C-8 of the lithium salt of **13** would more satisfactorily account for the observed α-face stereoselectivity. A tetrahedral propargylic lithium structure can, for example, be considered. Another possibility obtains from the work of Schleyer and co-workers.[23c] 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 (~1.9 and 2.3 Å) from the terminal carbons. Extrapolation of the C_3H_3Li structural parameters to **13** leads to nonplanarity at C-8 of **13** in such a manner as to impart partial axial (β-lithio-**13**) or partial equatorial (α-lithio-**13**) character to the lithium atom. Thus it can be argued that the seemingly more favorable α-lithio-13 structure reacts with electrophile on the same face as the lithium atom to give the observed major 6*R* steroisomer. Whether the theoretical gas-phase structural parameters of C_3H_3Li 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 lithium–carbon 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[6a,d] 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[24] variations, is in principle a general method for producing polyene chains possessing central cis double bonds (e.g., 11-cis retinoids).[25] These possibilities are being explored.

Experimental Section

1. General. 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. Dry tetrahydrofuran (THF) or dry ether was freshly distilled (nitrogen) from $LiAlH_4$ or potassium–benzophenone; lbpe refers to redistilled 30–60° 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 ϵ_{254} obtained for appropriate samples. A Whatman M9 10/50 Partisil (10 μ, 9.4 mm i.d. × 50 cm) or Waters μ-Porasil (10 μ, 3.9 mm i.d. × 30 cm) column was used. Diisopropyl ether (chromatographed over activity I alumina and then distilled from CaH_2), reagent grade isopropyl and isobutyl alcohols, and Skellysolve B (distilled from CaH_2) were used as solvents. Solvent combinations were vacuum filtered through a 0.45-μ Millipore filter immediately before use. Medium-pressure liquid chromatography (MPLC) was carried out on an apparatus designed by Meyers and co-workers.[14] The absorbant was silica gel 60 (40-600 μm) from E. Merck and the columns used were either 25 mm × 1 m or 15 mm × 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),

(22) 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.

(23) (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.

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

(25) (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$_3$). Ozone was passed through a solution of vitamin D_3 (**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 $NaHCO_3$, 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 × 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; $LiAlH_4$ workup; back-oxidation with CrO_3/pyridine).[7,8]

4. De-*A*,*B*-8α-ethynyl-8β-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.[9a] Grundmann's ketone$_3$ (**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 ($MgSO_4$). Filtration, concentration, and Kugelrohr distillation (117 °C (3 × 10^{-4} mm)) yielded **9** (3.35g, 90%) as a colorless viscous oil.

5. De-*A*,*B*-8α-ethynyl-8β-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_2, −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 ($MgSO_4$) and concentrated. Crystallization of the residue from lbpe afforded pure benzoate **10**: 2.36 g (88%); mp 96–97 °C.[9g]

6. De-*A*,*B*-8-methylenecholestane (11). Grundmann's ketone$_3$ (**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 × 10^{-4} mm)) afforded 1.16 g (88%) of **11**.[7]

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_2SO_4), and then concentrated to give a viscous residual oil. Kugelrohr distillation (bp 140–145 °C (2 × 10^{-4} mm)) afforded the dibromocyclopropane adduct **12** as a colorless oil in excellent yield (2.12 g, 97%).[9b,d]

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_2SO_4). The oily residue (quantitative) resulting after concentration was Kugelrohr distilled (bp 110–115 °C (2.5 × 10^{-4} mm)) to afford pure allene **13** (133 mg, 97%) as a colorless oil.[9c-f]

9. De-*A*,*B*-14-epi-8-cholestanone (14, 14-Epi-Grundmann's ketone$_3$). Two drops of trifluoroacetic acid were added to a solution of Grundmann's ketone$_3$ (**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^{-4} mm)) afforded **14** as a colorless liquid with little loss of material.[7]

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$_3$ **8**.[9a]

11. De-*A*,*B*-14-epi-8-methylenecholestane (16). Epi-Grundmann's ketone$_3$ (**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 × 10^{-4} mm)). The product **16** was readily distinguishable from its C-14 epimer **11** by ^1H 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 × 100 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.[10a] 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 $NaHCO_3$ (30 mL) and water (30 mL), dried (Na_2SO_4), 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_2, 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 $NaHCO_3$ (50 mL), and water (50 mL). Upon drying (Na_2SO_4) 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.[10b]

15. (1*R*,6*R*)- (6a) and (1*S*,6*R*)-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_2) *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_2). The resulting orange cuprous acetylide suspension was stirred at room temperature for 45 min, cooled to −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_2, −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 reaction mixture was quenched by the addition of water (20 mL). The resulting mixture was stirred for 10 min and then poured into a mixture of ether and saturated aqueous $NaHCO_3$. The organic layer was washed (H_2O, 1% HCl), filtered, and dried ($MgSO_4$). Removal of solvent afforded a pale yellow oil which was evacuated on an oil pump for at least 1 day.[10c,d,11]

A solution of freshly prepared anhydrous tetrabutylammonium fluoride in dry THF (~0.5 M, 19 mL, 9.6 mmol) was added (room temperature, N_2) and the resulting solution stirred for 5 h. Workup (lbpe and saturated aqueous $NaHCO_3$ solution, brine, $MgSO_4$; 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.[10b]

16. (1*R*,6*S*)-1-Hydroxy-9,10-secocholesta-5(10),6,7-triene (6b). Irradiation of 6a. An aliquot (10 mL) of a standard solution of the (1*R*,6*R*)-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 × 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 (1*R*,6*R*)-vinylallene **6a** (19 mg). Fractions 25–27 contained a mixture of isomeric vinylallenes. Concentration of fractions 28–35 yielded pure 1*R*,6*S* allene **6b** (16 mg).

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

17. (1*S*,6*S*)-1-Hydroxy-9,10-secocholesta-5(10),6,7-triene (7b). Irradiation of 7a. A solution of the (1*S*,6*R*)-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 × 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 (1*S*,6*S*)-vinylallene **7b** (17.4 mg). Fractions 26–29 contained a mixture of allene isomers (16.0 mg). Fractions 30–36 yielded, after concentration, the (1*S*,6*R*)-vinylallene **7a** (14 mg).

Fractions 26–29 were rechromatographed on a silica gel column, 70 × 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**.[5g]

18. (6*R*)- (5a) and (6*S*)-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 $NaHCO_3$ (2 × 50 mL), water (50 mL), and brine (25 mL). Drying ($MgSO_4$) 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 Skellysolve 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.[12]

19. Photolysis of (6*R*)-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 ~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 ~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 (6*R*)-vinylallenone (115 mg, 0.30 mmol) in absolute ethanol (6 mL) was treated with $NaBH_4$ (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 $NaBH_4$/ethanol, several other reducing agents were utilized in attempts to enhance the 1*R*/1*S* stereoselection. The results are compiled in Table II.

21. Reduction of 5b to 6b and 7b. The $NaBH_4$/ethanol reduction of (6*S*)-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 1*R* alcohol **6b** and 63.6 mg (55%) of its 1*S* 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 6*R* Ketone 5a. (6*Z*)-9,10-Secocholesta-5(10),6,8(14)-trien-1-one (30) and (6*Z*)-9,10-Secocholesta-5(10),6,8-trien-1-one (29). A solution of 6*R* ketone **5a** (383 mg, 1.0 mmol) in freshly distilled dry isooctane (100 mL, bp 100 °C) was refluxed (N_2) 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 6*S* 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. (1*R*,6*Z*)- and (1*S*,6*Z*)-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 $NaBH_4$ (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_2SO_4) 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. (1*R*,6*Z*)- and (1*S*,6*Z*)-1-Hydroxy-9,10-secocholesta-5(10),6,8-triene (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 $NaBH_4$ (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_3 (**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 (1*R*,6*R*)-Vinyllallenol 6a. (1*R*)-3-Deoxy-1-hydroxy-vitamin D_3 (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%); (1*R*, 10*R*)-(5*Z*,7*Z*)-trienol **23** (19 mg, 10%); (1*R*)-(6*Z*)-trienol **25** (4.5 mg, ~2%); starting material **6a** (5.3 mg, ~3%, slightly impure); (1*R*,10*S*)-(5*Z*,7*Z*)-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 1α-hydroxycholesterol.[6]

27. Thermolysis of (1*R*,6*S*)-Vinylallenol 6b. (1*R*,10*R*)-(5*Z*,7*Z*)- and (1*R*,10*S*)-(5*Z*,7*Z*)-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%); (1*R*, 10*R*)-(5*Z*,7*Z*)-triene **23** (61 mg, 45%); (1*R*)-(6*Z*)-trienol **25** (12 mg, 9%); (1*R*,10*S*)-(5*Z*,7*Z*)-triene **24** (33 mg, 25%). No starting material was detected and the total mass balance after separation was 91%.

28. Thermolysis of (1*S*,6*R*)-Vinylallenol 7a. (1*S*,10*S*)-(5*Z*,7*Z*)- and (1*S*,10*R*)-(5*Z*,7*Z*)-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 1*S* vitamin **3a** (23 mg, 17%); (1*S*,10*S*)-(5*Z*,7*Z*)-trienol **26** (50 mg, 37%); (1*S*)-(6*Z*) isomer **28** (13 mg, 9%); **7a/31a** (10.2 mg, 7%); (1*S*,10*R*)-(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 (1*S*,6*S*)-Vinylallenol 7b. (1*S*)-3-Deoxy-1-hydroxyvitamin D_3 (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 1*S* vitamin **3a** (114 mg, 59%); the (1*S*,10*S*)-(5*Z*,7*Z*) alcohol **26** (14 mg, 7%); the *cis*-isotachysterol analog (1*S*)-(6*Z*) **28** (6 mg, 3%); the previtamin–allene mixture **7b/31a** (23 mg, 12%); the 1*S*,10*R*)-(5*Z*,7*Z*)-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 (1*R*)-*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/μ-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 Equllibration of the 1*S* Alcohols 26, 27, and 28. The (1*S*)-*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% 1*S*,10*S* isomer **26**, 37% 1*S*,10*R* 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 analysis 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 1*S* Previtamin 31a to Vitamin 3a. The 1*S* 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, μ-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.

Acknowledgment. The U.S. Public Service (NIH Grant No. AM-16595) and the Intramural Fund of the University of California, Riverside, provided the financial support for this study. We thank Dr. M. Rappoldt of Philips-Duphar (Weesp, the Netherlands) for generous gifts of vitamin D_3. M.L.H. was a recipient of a Regents Graduate Fellowship from the University of California and A.M. was a postdoctoral fellow supported by a grant from the Program of the United States–Spanish Joint Committee for Scientific and Technological Cooperation. The reaction conditions for the cuprate coupling method described in Figure 3 were developed during the course of vitamin A studies by Mr. Christopher G. Knudsen of this laboratory.

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