A-Homo-11-hydroxy-3-deoxyvitamin D: Ring Size and π-Facial Selectivity Effects on the [1,7]-Sigmatropic Hydrogen Shift of Previtamin D to Vitamin D[1]

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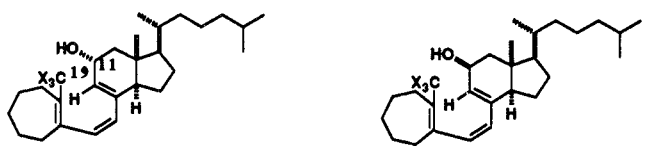
Abstract: The previtamin D–vitamin D interconversion, a [1,7]-sigmatropic hydrogen shift, provides a convenient system with which to evaluate the structural requirements of this hydrogen migration process. Thus, the A-homoprevitamin D analogues **7a,b** and **8a,b** were synthesized and their thermal [1,7]-sigmatropic hydrogen rearrangements studied. Relative to the parent previtamin D_3 system, the presence of the seven membered A-ring not only accelerates the rate of the rearrangement but also shifts the equilibrium to lie completely in favor of the vitamin. In addition, the 11-hydroxyl group was found to exert a modest effect (~2:1 to ~5:1) on the preferred helicity of the antarafacial rearrangement (a π-facial selectivity effect). In both cases a syn directive effect by the 11-hydroxyl was observed.

Introduction

The thermal [1,7]-sigmatropic hydrogen shift of previtamin D_3 (**1**) to vitamin D_3 (**2,2'**)[2] is of continuing interest in our laboratory because of its role in the biosynthesis of the biologically active forms of vitamin D (Scheme I).[3] For the thermal [1,7]-sigmatropic hydrogen shift,[4] the antarafaciality of the process as depicted by Woodward and Hoffmann[5] has recently been demonstrated by appropriate deuterium labeling experiments.[6]

Although antarafaciality for the conversion of the parent previtamin D_3 (**1**) to vitamin D_3 (**2**) has not been explicitly established, the intramolecular nature of this process has been demonstrated by isotopic labeling,[7] and the activation enthalpy and entropy were estimated to be 19.2 kcal/mol and −19.6 cal/mol K, respectively.[8]

Chart I



7 **8**

a, X = H; b, X = D

Recently, Dauben[9a] has provided computational evidence, supported by ^{1}H NMR (NOESY) studies,[9b] for the existence of two main triene types (5-s-cis,7-s-cis conformers **3** and **4**; 5-s-trans,7-s-cis conformers **5** and **6**) of ground-state conformations of previtamin D_3 in solution as depicted in Scheme I. Each of the conformers **3–6** may also exist in the opposite half-chair like conformer, resulting in a pseudoaxial orientation of the hydroxyl. Dauben's molecular mechanics calculations (MMP2) indicate that there exist eight lowest energy minima, and conformer **6** is the global minimum. This conformer places the C_{19} methyl group in the A-ring below the plane defined by C_5–C_6–C_7–C_8. The 5,6-single bond is in the s-trans conformation, and the C_3 hydroxyl is pseudoequatorially oriented. At the time of the [1,7]-shift however, the triene portion of the previtamin **1** must assume either one of the two possible doubly cisoid, helical conformations depicted approximately by **3** or **4**. Mazur[10] has shown that an inherent preference exists in the previtamin for the triene to assume the right-handed helical transition-state topography **4** as opposed to the left-handed one **3** by a ratio of ~2:1 at the time of the

(1) This is paper No. 37 in the series, Studies on Vitamin D (Calciferol) and Its Analogues. For paper No. 36, see: Wu, K.-M.; Okamura, W. H. *J. Org. Chem.* **1990**, *55*, 4025.

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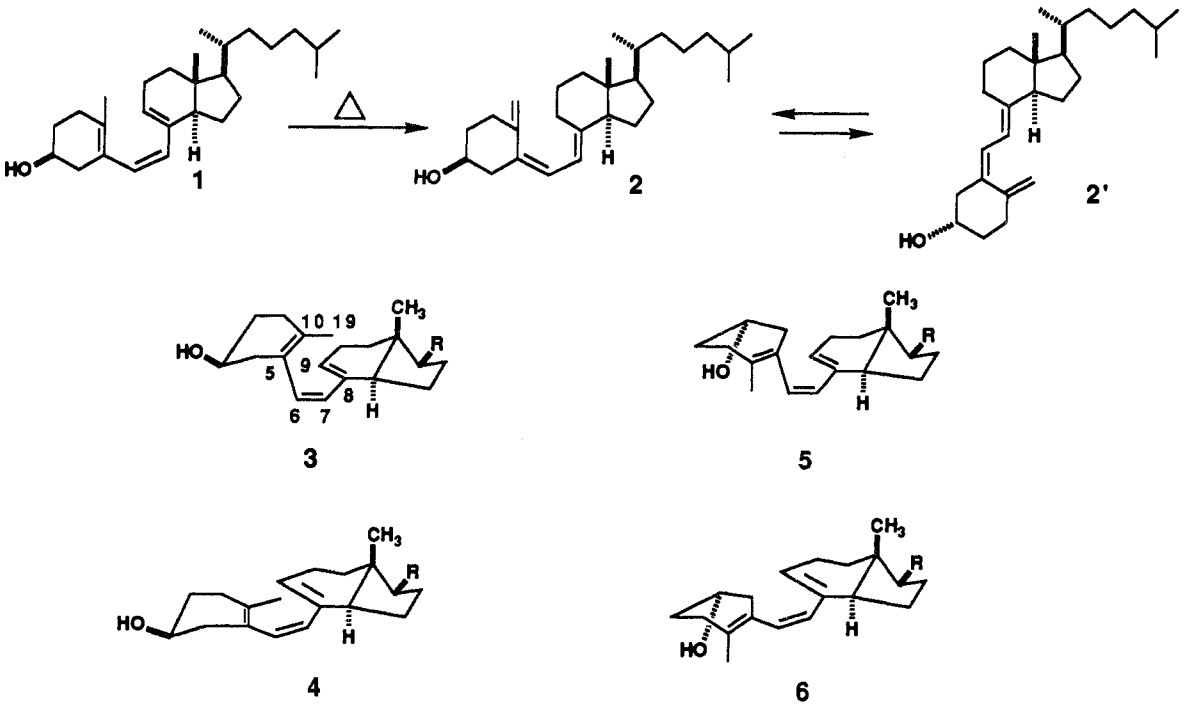
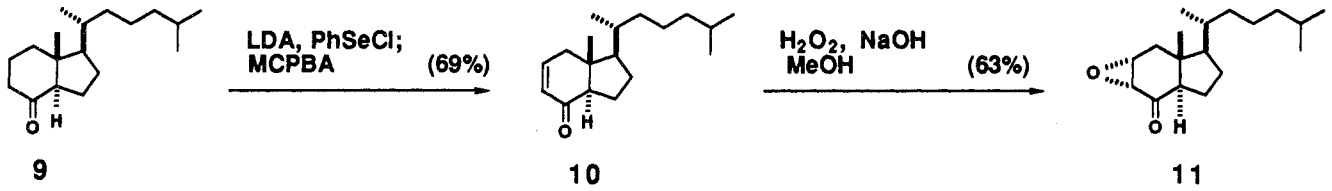
Scheme I



Scheme II



[1,7]-shift. This ratio can be explained by the notion that the right-handed helix permits the migrating hydrogen to be delivered axially to C_9 of the $\Delta^{8,9}$ double bond of the six-membered C-ring (**4**) and the left-handed helix (**3**) allows for only formal, equatorial delivery of the migrating hydrogen. Axial delivery of hydrogen from C_{19} to C_9 should be preferred since this would lead directly to the ring C chair conformer of **2**, the latter then equilibrating to the more stable s-trans conformer.[9c-o]

Other studies have shown that an allylic hydroxyl group flanking the heptatriene network in *cis*-isotachysterol analogues directs the antarafacial hydrogen migration so that the hydrogen prefers to migrate in a syn fashion relative to the allylic hydroxyl (π-facial selectivity).[6b,c,11]

In an effort to develop a more detailed understanding of [1,7]-sigmatropic hydrogen shifts, this paper describes a synthesis of the *A*-homo-11-hydroxy-3-deoxyprevitamin D_3 analogues **7** and **8** (Chart I) and a study of their thermal [1,7]-sigmatropic hydrogen shifts. The presence of the enlarged A-ring (seven-membered) was expected to help assess the topographical demands of [1,7]-shifts through a change in ring size in the previtamin–vitamin system. The strategic positioning of an α- or β-hydroxyl group at C_{11} was anticipated to allow an assessment of any directing effect by the hydroxyl on the [1,7]-shift (π-facial selectivity). A viable method for incorporation of a trideuteriomethyl group at C_{19} in **7** and **8** was a necessary goal of this study as a means of assessing the latter effects.

Finally, it should be noted that 11α-hydroxyvitamin D_3[12] and the 11α- and 11β-hydroxylated epimers of 1α,25-dihydroxyvitamin D_3[13] are the only 11-hydroxylated vitamin D substrates previously reported.

Results and Discussion

Synthesis of Substrates. The required CD fragment, epoxy ketone **11**, was synthesized as shown in Scheme II. Grundmann's ketone **9** was converted to the known $\Delta^{9,11}$-enone **10**[14,15] and then diastereoselectively epoxidized with basic peroxide to afford the epoxy ketone **11** as a single diastereomer. Initially, enone **10** itself without epoxidation was envisaged as the requisite CD fragment for preparing **7** and **8**. However, as will be seen later, the overall utility of this substrate was limited by purification problems and the low yields obtained in subsequent steps of the synthesis.

For the synthesis of the protio A-ring portion **16a**, cycloheptanone was transformed to the aldehyde **15a** (Scheme III) following the procedure of Lugtenburg[16] for the corresponding six-membered ring aldehyde. This involved formation of the acetal **13** followed by addition of methyllithium to yield the alcohol **14a** and hydrolysis of the latter to afford the unsaturated aldehyde **15**. Wittig reaction of **15a** under Corey–Fuchs conditions[17]

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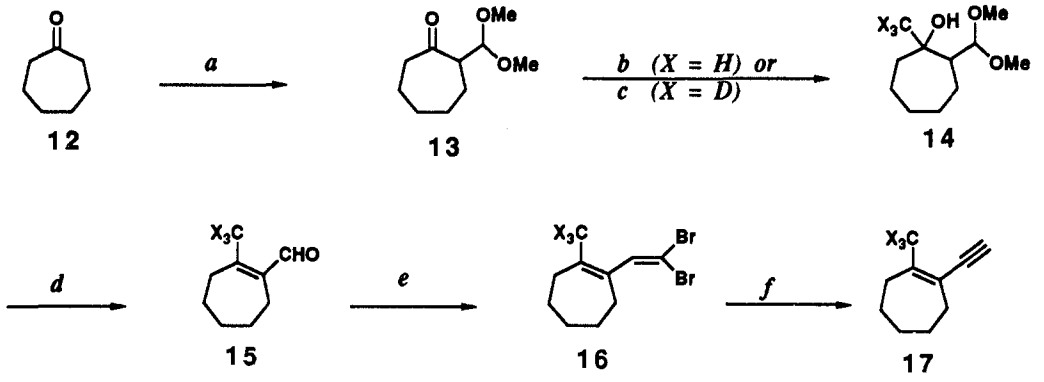
Scheme III[a]



(a, X = H; b, X = D)

[a] Reagents: (a) NaH, HCOOEt; CH_3COCl, MeOH (53%); (b) CH_3Li (crude hydrolyzed directly); (c) CD_3MgI (crude hydrolyzed directly); (d) H_3O^+ (X = H, 71%; X = D, 48% containing 77.9% d_3, 19.9% d_2, and 2% d_1 by MS); (e) Zn, Ph_3P, CBr_4, CH_2Cl_2 (X = H, 90%; X = D, 70%); (f) *n*-BuLi, THF (62%, unstable).

produced the requisite vinyl dibromide **16a** in good yield. Although the latter could be transformed to the hydrocarbon enyne **17a** by using *n*-butyllithium, the instability of the latter prompted the direct use of **16a** (vide infra).

Unlike that for the protio A-ring fragment, the synthesis of the deuterio A-ring proved less straightforward. It was initially thought that the trideuteriomethyl group could be introduced by replacing methyllithium in the transformation of **13** to **15b**[16] (Scheme III) with commercially available trideuteriomethylmagnesium iodide. However, while the transformation **13** to **15b** could be achieved (48% yield), undesirable deuterium–hydrogen exchange occurred to a significant extent during the subsequent hydrolysis step so that actual deuterium incorporation of **15b** was not satisfactory (<80% d_3 as shown in Scheme III). Introduction of the trideuteriomethyl group (**15b**) was best achieved by subjecting protio **15a** to a thermal deuterium–hydrogen exchange reaction. A mechanism involving a [1,5]-sigmatropic shift of the methyl hydrogens to the proximal carbonyl oxygen followed by exchange of the proton of the resulting enol with a deuteron from D_2O and subsequent [1,5]-deuterium migration to yield the labeled methyl group seems mechanistically plausible.[18] Four cycles were carried out to ensure that each methyl hydrogen was replaced with deuterium (**15b**).

With the labeled aldehyde **15b** in hand, Wittig transformation to the labeled dibromide **16b** (Scheme III) proceeded smoothly as for the unlabeled case **16a**. For the subsequent steps of the synthesis, both protio (**16a**) and deuterio (**16b**) A-ring fragments were subjected to the same transformations.

The A-ring dibromide **16** (Scheme IV) was treated with 2 equiv of *n*-BuLi to generate the corresponding lithium acetylide which was coupled in situ[17] with the CD epoxy ketone **11** to afford the epoxy propargyl 8β-alcohol **18** as a single diastereomer. The 8β-alcohol was then converted to the corresponding benzoate (**19**), which reacted smoothly with SmI_2 in the presence of Pd(0) to produce the 11α-dienynol **20** as a single diastereomer, both unlabeled **20a** and labeled **20b**.[14a,19]

Once the details of the 11α-OH-*A*-homodienynol (**20**) synthesis had been worked out, the synthesis of the 11β-OH epimer **22** was relatively straightforward. As shown in Scheme IV, the 11α-dienynol **20** was oxidized to the dienynone **21** followed by treatment of the dienynone with the sterically hindered reducing agent L-Selectride to give the C_{11} inverted alcohol **22** as the only product. In an earlier and less successful attempt to synthesize **20–22**, the enone **10**, the precursor to epoxy ketone **11** (Scheme II), was reacted directly with the lithium anion of **17a** to afford enynol **23**.[14a] Oxidative 1,3-transposition[20,21] of the latter under several different conditions afforded only low yields (~33%) of **21**. It was also noted that sodium borohydride reduction of the latter under Luche conditions[22] afforded an ~1.5/1 mixture of **20**/**22** in low yield after separation.

Preparation of Previtamins and Equilibrium Studies. Because of the thermal lability of the previtamins **7a–8a** (Scheme V) toward a [1,7]-sigmatropic hydrogen shift, the dienynes **20** and **22** were catalytically reduced to previtamins only immediately before use. The protio 11α-dienynol **20a** was subjected to semihydrogenation under Linldar conditions at room temperature to afford after standing the vitamin **24a** (Scheme V) in 64% yield via the intermediacy of the previtamin **7a** which underwent a relatively facile [1,7]-sigmatropic hydrogen shift at room temperature. The purified vitamin was heated at 80 °C for 5 h and cooled to room temperature. The expanded ^1H NMR spectrum (in $CDCl_3$, 25.4 °C) of the heated material revealed the absence of any signals corresponding to the 11α-OH-previtamin **7a**. Thus, the previtamin–vitamin equilibrium ratio at 25.4 °C was estimated to be ~0:100 favoring the vitamin completely.

The protio 11β-dienynol **22a** was reduced and rearranged under similar conditions at room temperature to yield the 11β-OH-vitamin **25a** (61%) (Scheme V). The purified vitamin was also heat treated to confirm that the previtamin–vitamin equilibrium ratio for the 11β-OH-vitamin at 25.4 °C was ~0:100 favoring the vitamin **25a** over the previtamin **8a** completely.

Previous work in this laboratory[23] revealed that photochemical ring opening of *A*-homo-3-deoxy-7-dehydrocholesterol afforded only the *A*-homo-3-deoxyvitamin D_3. There was no indication of the intermediacy of the corresponding previtamin. This is in stark contrast to the six-membered ring case such as the parent previtamin D_3–vitamin D_3 (**1** and **2**, Scheme I). When 7-dehydrocholesterol is photolyzed at ambient temperature, previtamin D_3 (**1**) is produced, and it needs to be heated typically at 60 °C for several hours to induce the formation of vitamin D_3 (**2**). The previtamin D_3–vitamin D_3 equilibrium is ~8/92 at room temperature[8] in contrast to ~0/100 observed for the epimeric A-homo systems just described. It can be inferred that the introduction of the C_{11} hydroxyl group (α or β) has no observable effect on the position of the *A*-homoprevitamin–vitamin equilib-

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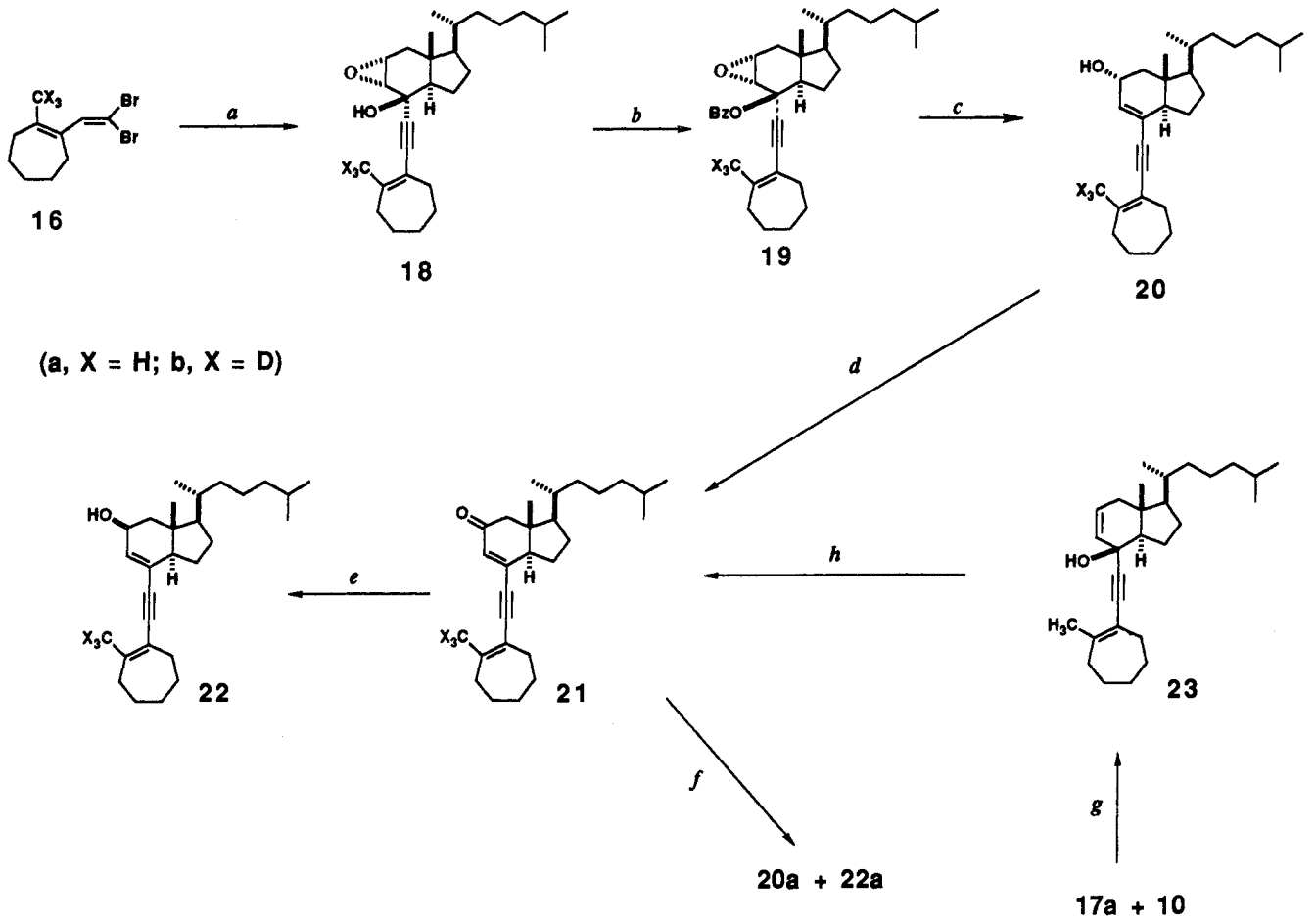
Scheme IV[a]



[a] Reagents: (a) *n*-BuLi and then epoxy ketone **11** (X = H, 76%; X = D, 75%); (b) *n*-BuLi and then PhCOCl (X = H, 87%; X = D, 83%); (c) SmI_2, $Pd(PPh_3)_4$ (X = H, 74%; X = D, 83%); (d) MnO_2 (X = H, 78%; X = D, 77%); (e) L-Selectride (X = H, 90%; X = D, 76%); (f) $NaBH_4$, $CeCl_3$, MeOH (19% **20a** plus 13% **22a**); (g) *n*-BuLi, **17a** and then **10** (59%); (h) PDC, CH_2Cl_2 (33%) or Dess-Martin periodinane (33%).

Table I. ^1H NMR Chemical Shifts and Relative Integration for 11α-Deuterio **24b′** and **24b″**[a]

compound	δ 6.16, $H_{6,7}$[b]	δ 3.90, H_{11}	δ 3.16, $H_{9\beta}$[c]	δ 1.72, $H_{9\alpha}$[c]
11α-ol protio	(1.96 ± 0.02)	(1.04 ± 0.03)	(1.00 ± 0.04)	(1.01 ± 0.02)
11α-ol deuterio	(2.03 ± 0.01)	(0.97 ± 0.01)	(0.85 ± 0.01)	(0.19 ± 0.01)

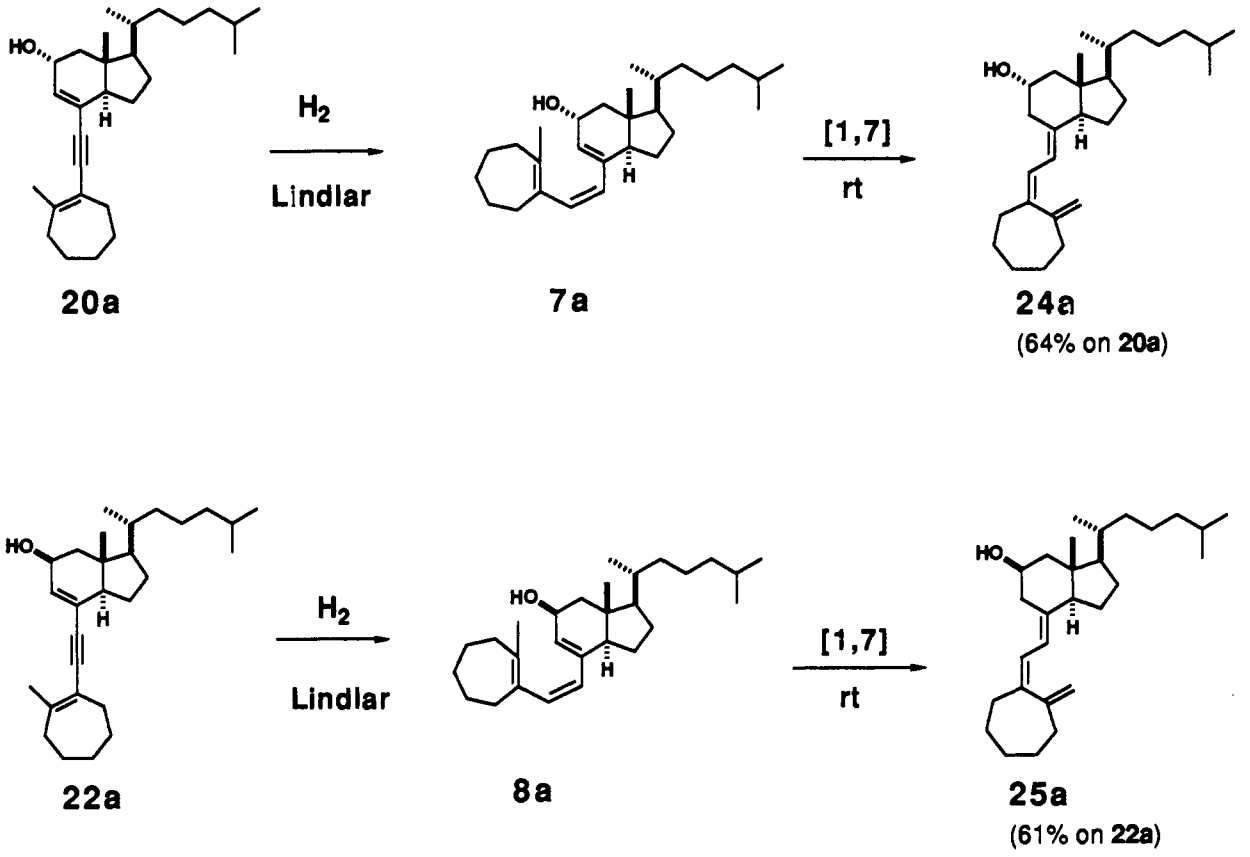
[a] ^1H NMR data were recorded at 500 MHz in $CDCl_3$. The relative peak areas (given in parentheses) were obtained from expanded spectra by the cut and weigh method. The peak areas represent the average of three integrations, and the uncertainties represent absolute deviations from the mean. [b] This signal actually consists of two doublets centered at δ 6.08 and δ 6.25. [c] The integrated ratio of the $H_{9\alpha}/H_{9\beta}$ signal leads to a correction factor of 1.01 (1.01 ÷ 1.00) for the protio derivative. Applying this correction factor to the observed $H_{9\alpha}/H_{9\beta}$ ratio of 0.224 (0.19 ÷ 0.85) [18:82] affords a similar value of 0.226 [18:82] for this ratio.

rium at 25 °C. The notion that the observed equilibrium constant for the 11-OH-*A*-homoprevitamins is mainly a reflection of a significant amount of strain in the A-ring of the *A*-homoprevitamin (**7a** or **8a**) versus that of the vitamin (**24a** or **25a**) seems plausible. This hypothesis is currently being further evaluated by computational procedures.

The tendency for protio *A*-homoprevitamin D analogues to undergo rapid [1,7]-hydrogen migrations was further demonstrated (Scheme VI) in an effort to lock the *A*-homo analogue in the previtamin form by retaining a carbonyl group at C_{11}. Semihydrogenation of dienynone **21a** gave instead a 62:38 mixture of ketones **26** amd **27**, respectively, in 32% yield. The rate of equilibration between **26** and **27** is reflected by the observation that upon attempted HPLC purification, the two chromatographic peaks attributable to these ketones are highly skewed and ill-defined, indicating their interconversion during elution. By contrast, the 300-MHz ^1H NMR spectrum of the mixture revealed the presence of signals attributable to two distinct isomers, not interconverting on the time scale of the ^1H NMR experiment. In the latter case, the observation of a significant proportion (38%) of **27** at an apparent equilibrium attests to the suggested A-ring strain in **26** despite the presence of the conjugated α,β-unsaturated enone moiety.

π-Facial Selectivity Studies. The synthesis of the labeled 11α-OH previtamin **7b** (Scheme VII) was achieved by subjecting the trideuteriated 11α-dienynol **20b** to semihydrogenation with Lindlar's catalyst at room temperature as above for the protio case (Scheme V). The labeled previtamin was allowed to rearrange completely to the vitamins **24b′** and **24b″**, and then purification led to a 68% yield of the mixture **24b** . Integration of the signals corresponding to $H_{9\alpha}$ and $H_{9\beta}$ in the 500-MHz ^1H NMR spectrum of the vitamin **24b** gave a relative ratio of 4.6:1 ($H_{9\alpha}/H_{9\beta}$) (Table I). To ensure that this ratio was a true reflection of a kinetic process and not perturbed by partial equilibration, the ratio of the intensity of the $H_{9\beta}$ signal of the vitamin **24b** to that of the H_6 signal (also of the vitamin) was monitored over the time period of the kinetic studies described for the labeled 11α-OH-previtamin **7b** described below and in the supplementary material section. This ratio remained constant (300 MHz). Monitoring the $H_{9\alpha}/H_{9\beta}$ ratio over time would have been better, but this study was precluded by the fact that the $H_{9\alpha}$ signal was obscured by other signals in the same region of the ^1H NMR

Scheme V



Scheme VI

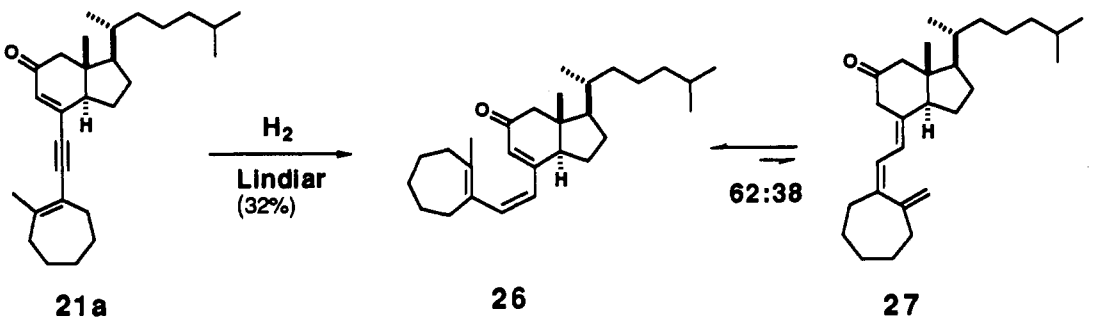


Table II. ^{1}H NMR Chemical Shifts and Relative Integration for 11β-Deuterio **25b′** and **25b″**[a]

compound	δ 6.23, $H_{6,7}$	δ 4.21, H_{11}	δ 2.90, $H_{9\beta}$[b]	δ 2.14, $H_{9\alpha}$[b]
11β-ol protio	(2.00 ± 0.02)	(1.01 ± 0.01)	(0.94 ± 0.01)	(0.97 ± 0.03)[c]
11β-ol deuterio	(2.00 ± 0.01)	(1.00 ± 0.01)	(0.39 ± 0.01)	(0.66 ± 0.01)[c]

[a] ^{1}H NMR data were recorded at 500 MHz in $CDCl_3$. The relative peak areas (given in parentheses) were obtained from expanded spectra by the cut and weigh method. The peak areas represent the average of three integrations, and the uncertainties represent absolute deviations from the mean. [b] The integrated ratio of the $H_{9\alpha}/H_{9\beta}$ signal leads to a correction factor of 1.032 (0.97 ÷ 0.94) for the protio derivative. Applying this correction factor to the observed $H_{9\alpha}/H_{9\beta}$ ratio of 1.692 (0.66 ÷ 0.39) [63:37] affords a similar value of 1.746 [64:36]. [c] The signal assigned to $H_{9\alpha}$ was obtained by integration of the two proton multiplet centered at δ 2.1–2.2 and dividing by two.

spectrum (300 MHz). Thus, the deuterium which migrates in the [1,7]-shift of the labeled previtamin **7b** to the vitamin **24b** prefers to do so in a syn facial fashion (presumably via the antarafacial mode) relative to the $C_{11\alpha}$-hydroxyl group.

The synthesis of the labeled 11β-OH-previtamin **8b** (Scheme VII) was completed by semihydrogenation of the trideuterio 11β-dienynol **22b** under Lindlar conditions at room temperature to afford the labeled 11β-OH-previtamin **8b**, which was allowed to rearrange completely to the vitamins **25b′** and **25b″**. A 52% yield was obtained after HPLC purification of the vitamin mixture. Integration of the $H_{9\alpha}$ and $H_{9\beta}$ signals in the 500-MHz ^{1}H NMR spectrum of the vitamin afforded a relative ratio of 1:1.7 ($H_{9\alpha}/H_{9\beta}$) (Table II). Once again a preference for the deuterium at C_{19} to migrate syn to the C_{11}-hydroxyl was observed. To also ensure that this ratio reflected a kinetic process and not one due to perturbation by partial equilibration, the ratio of the intensities of the $H_{9\beta}$ and H_6 signals of the vitamin in the 300-MHz ^{1}H NMR spectrum was monitored over the time frame described for the kinetic studies of the 11β-OH-previtamin **8b** described below and in the supplementary material section. This ratio was determined to remain constant. As in the case of the labeled 11α-OH-previtamin, the $H_{9\alpha}/H_{9\beta}$ ratio was not monitored over time due to the overlap of the $H_{9\alpha}$ signal by other proton signals in the 300-MHz spectrum.

In summary, a modest π-facial selectivity effect has been observed for the rearrangement of the deuterio 11α- and 11β-OH-

Scheme VII

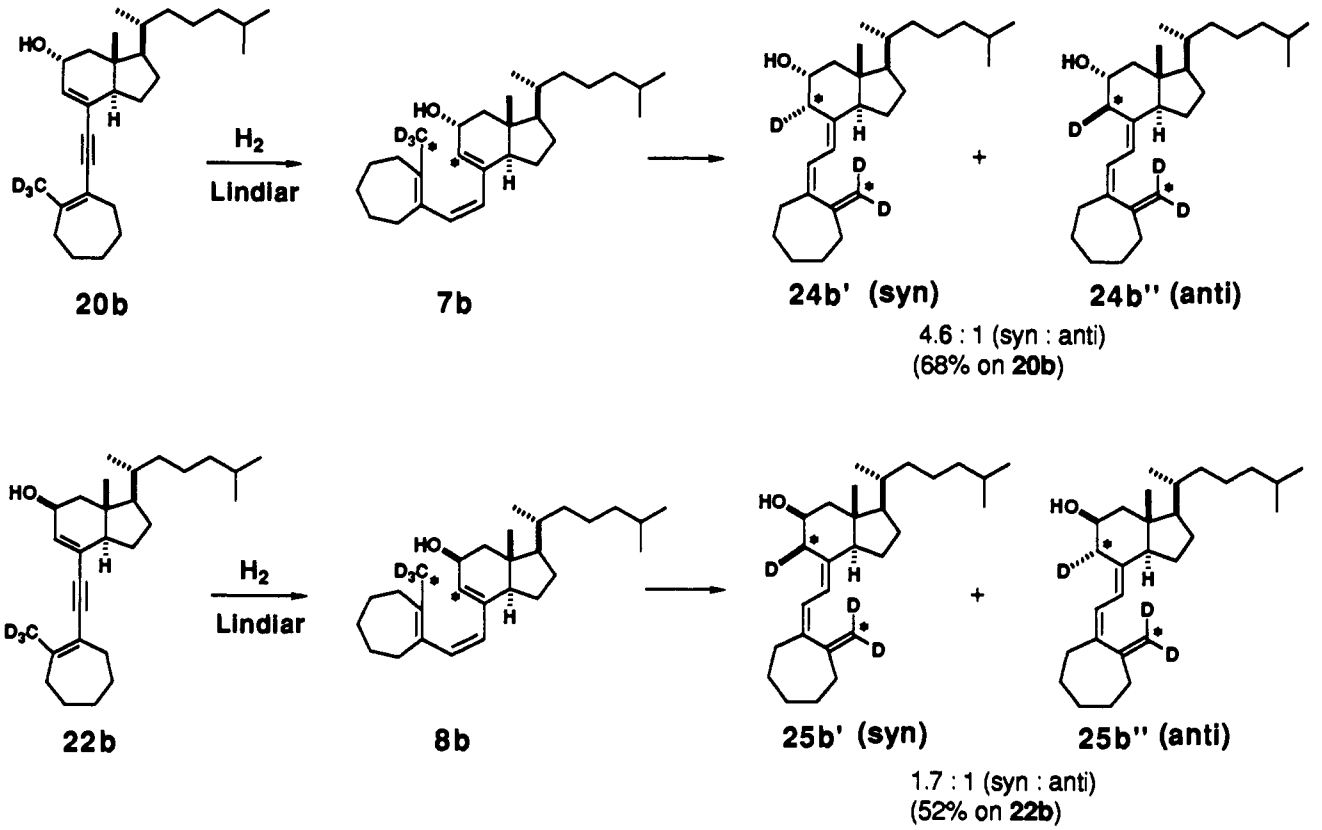


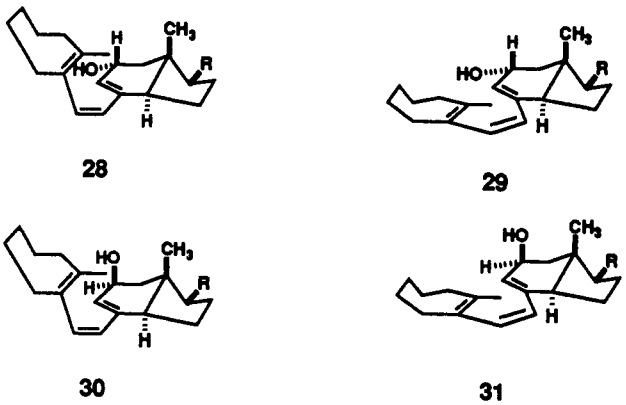
Table III. Activation Parameters[a] for the Rearrangement of **7a** and **8a** at 25.4 °C ($CDCl_3$)

compd	E_a, kcal/mol	log A, s^{-1}	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, cal/mol K	$\Delta G^{\ddagger}$, kcal/mol	$k_H \times 10^4$, s^{-1}
22a	13.8 (±0.5)	7.0 (±0.3)	13.2 (±0.5)	−28.4 (±1.0)	21.7 (±0.8)	8.23 (±0.44)
23a	14.2 (±0.1)	7.3 (±0.1)	13.7 (±0.1)	−26.9 (±0.1)	21.7 (±0.1)	8.01 (±0.30)

[a] Uncertainties are standard deviations for the activation parameters and absolute deviations from the mean for the rate constants.

A-homoprevitamins **7b** and **8b**. The syn directing effect by the C_{11} hydroxyl group agrees well with the similar effect observed by Hoeger[6a] and Wu[11] for the 1- and 4-hydroxy-*cis*-isotachysterol systems, respectively. This lends credence to the notion that this is a general effect. Inspection of Chart II indicates that of the two possible helical conformers (**28** and **29**) accessible at the time of [1,7]-hydrogen migration for the 11α-OH-*A*-homoprevitamin, the preferred helical conformation **29** disposes the A-ring below the plane of the CD ring (right-handed helix) rather than above (left-handed helix) by a factor of 4.6. This achieves a modest syn facial migration selectivity of hydrogen relative to the hydroxyl. Conversely, for the [1,7]-sigmatropic hydrogen shift of the 11β-OH-*A*-homoprevitamin (**30** and **31**) the preferred helical conformation places the A-ring above the CD ring, as in **30** (left-handed helix), rather than below (right-handed helix) by a factor of 1.7. This too leads to a hydrogen migration syn to the neighboring C_{11} hydroxyl. However, as mentioned earlier, Mazur[10] has shown that for the parent previtamin D_3 triene **1** (Scheme I), which has the hydroxyl group further removed from the triene portion of the molecule, an inherent preference for the right-handed helical conformation exists by a factor of ~2:1 over the left-handed conformation. To the extent that this "built-in" preference for the A-ring to be below the CD ring applies in the A-homo analogues **7b** and **8b**, the π-facial selectivity ratio of 4.6:1 for the 11α-OH isomer **7b** favoring **29** is actually smaller by a factor of about 2. Conversely, the π-facial selectivity ratio of 1:1.7 for the 11β-OH isomer **8b**, which indicates a smaller preference for the left-handed helix **30**, is actually larger by a factor of about 2 because it must overcome the characteristic tendency of the triene to rearrange via the right-handed helix.

Chart II



Kinetics Studies. Since it was already established that the [1,7]-sigmatropic hydrogen shift of the protio 11α-OH-previtamin **7a** to the vitamin **24a** was inconveniently rapid at room temperature to carry out rate studies, the synthesis of **7a** had to be carried out at lower temperatures. Thus, the hydrogenation of the unlabeled 11α-dienynol **20a** was performed at ice temperatures as was the corresponding workup. Purification of the resulting previtamin was precluded because of its thermal lability. The [1,7]-hydrogen rearrangement of the previtamin to the vitamin was then monitored by ^1H NMR analysis at various temperatures ranging from ~ −10–25 °C for the Arrhenius study. The rate constants (k_H) were calculated from the slope of the line obtained upon plotting the natural logarithm of the mole fraction of pre-

vitamin versus time. The k_H and activation parameters for the rearrangement of the 11α-OH-previtamin **7a** at 25.4 °C are summarized in Table III. The mean rate constant 8.23×10^{-4} s^{-1} corresponds to a half-life of 14.0 min at 25.4 °C. By contrast, naturally occurring previtamin D_3 (**1**) rearranges to vitamin D_3 (**2**) with a calculated half-life of ~70 h at this same temperature.[8] Thus an approximate 300-fold rate acceleration is observed for the [1,7]-shift of the *A*-homo-11α-OH-previtamin **7a**. The incorporation of a trideuteriomethyl group at C_{19} as in the 11α-OH-previtamin **7b** slowed down the [1,7]-shift enough to allow HPLC purification of the labeled previtamin after hydrogenation of the corresponding trideuterio 11α-dienynol **20b** at room temperature. The rate of the [1,7]-deuterium migration was then monitored by ^1H NMR analysis at 25.4 °C. The rate constant (k_D) calculated from the slope obtained by plotting the natural logarithm of the mole fraction of previtamin versus time was 7.99×10^{-5} s^{-1} ($\tau_{1/2}$ = 2.4 h). Thus, k_H/k_D = 10.3 for the [1,7]-sigmatropic hydrogen shift of the 11α-OH-previtamin **7a,b** to the vitamin **24a,b** at 25.4 °C.[24]

In order to study the [1,7]-shift of the protio 11β-OH-previtamin **8a** to the vitamin **25a**, the hydrogenation and subsequent workup of the corresponding unlabeled 11β-dienynol **22a** was also carried out at ice temperatures as in the case of the unlabeled 11α-OH epimer. The rearrangement was then monitored by 300-MHz ^1H NMR analysis at room temperatures ranging from ~ −10–25 °C. The k_H and activation parameters for the [1,7]-shift of the 11β-OH-previtamin at 25.4 °C are given in Table III. The mean rate constant 8.01×10^{-4} s^{-1} corresponds to a half-life of 14.4 min at 25.4 °C. As in the case of the rearrangement of the protio 11α-OH-previtamin **7a**, this also represents a rate acceleration of ~300 fold when compared to the rate of the [1,7]-shift of the parent previtamin D_3 (**1**). As was the case for the labeled 11α-OH-previtamin **7b**, the introduction of a trideuteriomethyl group at C_{19} in the 11β-OH-previtamin **8b** attenuated the [1,7]-hydrogen shift sufficiently to allow for isolation of the pure labeled previtamin upon hydrogenation of the corresponding trideuteriated 11β-dienynol **22b** at room temperature. The [1,7]-shift was then monitored by 300-MHz ^1H NMR analysis at 25.4 °C. The rate constant (k_D) calculated from the slope of the line obtained by plotting the natural logarithm of the mole fraction of previtamin versus time was 6.74×10^{-5} s^{-1} ($\tau_{1/2}$ = 2.9 h). Thus, k_H/k_D = 11.9 (similar to that obtained for rearrangement of **7a,b**),[24] for the [1,7]-hydrogen migration of the 11β-OH-previtamin **8a,b** to the vitamin **25a,b** at 25.4 °C.

Summary

In both the 11α-OH- and 11β-OH-*A*-homovitamin D series, the allylic hydroxyl exerts a modest effect (~2:1 to ~5:1) in π-facially directing in a syn facial sense the [1,7]-hydrogen migration.[6,11] Also, in both series, the [1,7]-sigmatropic hydrogen shift of the previtamin analogues **7a** and **8a** to the vitamin forms **24a** and **25a** is fast relative to the parent six-membered A-ring system, with **24a** and **25a** being thermodynamically more stable than **7a** and **8a**, respectively. The large rate acceleration observed for the [1,7]-sigmatropic hydrogen shift of the *A*-homoprevitamin analogues may be attributed to an increase in A-ring strain which is relieved upon rearrangement to the vitamin coupled with a possibly more favorable C_{19}–H–C_9 transition-state geometry obtained when the size of the A-ring is increased from a six-membered ring to a seven-membered ring. Additionally, computational probing to evaluate whether conformational effects are operating in the six- and seven-membered ring systems leading to the observed rate perturbation of the [1,7]-shift is being considered.[25]

(24) (a) Baldwin, J. E.; Reddy, V. P. *J. Org. Chem.* **1988**, *53*, 1129. (b) Baldwin, J. E.; Reddy, V. P. *J. Am. Chem. Soc.* **1987**, *109*, 8051. (c) Baldwin, J. E.; Reddy, V. P. *J. Am. Chem. Soc.* **1988**, *110*, 8223. (d) Extrapolation of Baldwin's temperature-dependent kinetic isotope effect data in the latter reference for the [1,7]-shift leads coincidentally to a similar k_H/k_D value of ~10 at 25 °C. (e) See, also: Palenzuela, J. A.; Elnagar, H. Y.; Okamura, W. H. *J. Am. Chem. Soc.* **1989**, *111*, 1770.

(25) Besides footnote 9, see also: Hofmann, H.-J.; Cimiraglia, R. *J. Org. Chem.* **1990**, *55*, 2151.

Experimental[26] Section

De-*A*,*B*-cholest-9(11)-en-8-one (10). This material was prepared as previously described.[14a] The enone **10** was obtained as a yellow-orange oil in 69% yield sufficiently pure for use in the next epoxidation state.

De-*A*,*B*-9α,11α-oxidocholestan-8-one (11). To a 0 °C solution of enone **10** (0.108 g, 0.41 mmol) in methanol (10 mL) was added 30% H_2O_2 (1.76 mL). After stirring for a few minutes, 5 M NaOH (0.16 mL) was added slowly to the mixture via syringe. The solution was stirred at 0 °C for 5 h, then diluted with water (10 mL), and extracted with CH_2Cl_2 (2×). The organic layer was washed with brine, dried, and concentrated. The residue was subjected to HPLC purification (5% EtOAc/hexanes) to afford the epoxide **11** (0.072 g, 63%) as a colorless oil.

2-(Dimethoxymethyl)cycloheptanone (13). This substance was prepared following a procedure for the analogous six-membered ring ketone.[16] Ketone **13** was obtained as a pale yellow liquid in 53% yield sufficiently pure for use in the next step.

2-Methyl-1-cycloheptenecarboxaldehyde (15a). This compound was prepared as previously described for the corresponding six-membered ring aldehyde.[16] The aldehyde **15a** was obtained as a colorless oil in 71% yield.

2-(Trideuteriomethyl)-1-cycloheptenecarboxaldehyde (15b). The protio aldehyde **15a** (246 mg, 1.78 mmol) was dissolved in dry benzene (3 mL) and placed in a tube equipped with a high-pressure seal screw-cap. The solution was subjected to two freeze–thaw cycles under vacuum, and then D_2O (1 mL) was added. The mixture was then flushed with nitrogen and sealed with the high-pressure screw-cap. After covering the entire tube with aluminum foil, it was placed in an oil bath at 140 °C and allowed to heat for 20 h. After cooling, the mixture was extracted with ether, and the organic layer was washed with saturated $NaHCO_3$, dried, and concentrated. The above procedure was repeated three more times to allow for near-complete deuterium exchange as monitored by ^1H NMR analysis. The deuteriated aldehyde **15b** (216 mg, 88%) was obtained as a volatile oil. The deuterium content was best determined by mass spectrometry at a later stage in the synthesis (as the 8β-ol **18b**). An attempt to prepare this trideuterated material from ketoacetal **13** using CD_3MgBr (see Scheme III) led to less satisfactory levels of deuterium incorporation. This was plausibly a result of solvent exchange during the acetal hydrolysis–dehydration reaction.

1-(2,2-Dibromoethenyl)-2-methylcyclohept-1-ene (16a). To a mixture of zinc dust (2.151 g, 32.9 mmol) and triphenylphosphine (8.629 g, 32.9 mmol, recrystallized from ether) in dry CH_2Cl_2 (30 mL) was added CBr_4 (10.901 g, 32.9 mmol) in dry CH_2Cl_2 (30 mL) via cannula at room temperature. The resulting suspension was stirred for 23 h at room temperature. The aldehyde **15a** (0.756 g, 5.48 mmol) in CH_2Cl_2 (2 mL) was then introduced to the reaction mixture via syringe, and the latter was stirred for 1 h at room temperature. Workup was accomplished by dilution of the mixture with pentane (240 mL), filtration through Celite to remove the insoluble material, and evaporation of the pentane/CH_2Cl_2. The insoluble material was subjected to additional cycles (2×) of CH_2Cl_2 extraction and pentane precipitation to remove all of the olefinic product. After concentration the resulting oil was taken up in pentane and passed through a short column of silica gel (7 × 1.5 cm) to afford, after evaporation of solvent, the dibromoolefin **16a** (1.442 g, 90%) as a light yellow oil.

1-(2,2-Dibromoethenyl)-2-(trideuteriomethyl)cycloheptene (16b). This compound was prepared in the same manner as the protio dibromide

(26) Spectral and other analytical data along with a detailed description of the kinetic studies are presented in the supplementary material section. All experiments involving air- and/or moisture-sensitive materials were carried out under a nitrogen or argon atmosphere, which was dried prior to use by passage through a column of KOH layered with $CaSO_4$. Tetrahydrofuran, ether, and benzene were distilled from sodium benzophenone ketyl immediately prior to use. Hexanes was distilled from CaH_2. Unless otherwise indicated for workup procedures, organic solutions were dried over $MgSO_4$, filtered, and then finally concentrated on a rotary evaporator at reduced pressure. High-pressure liquid chromatography (HPLC) was performed by using a Rheodyne 7125 sample injector, Waters 6000A or 510 pump, a Waters R401 refractive index detector, and a Rainin Dynamax 60A silica column or Whatman Partisil M9 column unless otherwise noted. Flash chromatography was performed by using silica gel (EM Science, 230–400 mesh), and thin-layer chromatography (TLC) was run on a plastic plate precoated with silica gel (Kodak, 0.25 mm) and developed by spraying with a 15% ethanol solution of phosphomolybdic acid. The purity of all new compounds were judged by a combination of HPLC and ^1H and ^{13}C NMR analysis before mass spectral determination. Satisfactory combustion analyses were also obtained for selected compounds. For other new compounds, the level of purity is indicated by the inclusion of copies of NMR spectra presented in the supplementary material.

(27) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *Chem. Commun.* **1987**, 1625.

16a except that the deuterated aldehyde **15b** (210 mg, 1.42 mmol) was used to afford the deuterated dibromide **16b** (309 mg, 70%) as a colorless oil sufficiently pure for use in the next step.

2-Methyl-1-ethynylcyclohept-1-ene (17a). To a −78 °C solution of dibromoolefin **16a** (1.1 g, 3.7 mmol) in dry THF (15 mL) was added *n*-BuLi (1.57 M in hexanes, 5.9 mL, 9.3 mmol). The solution was allowed to stir at −78 °C for 30 min and at room temperature for 1 h. The reaction was quenched at 0 °C with water and then warmed to room temperature. Ether (25 mL) was added, and the layers were separated. The organic layer was washed with water and brine and then dried. Concentration of the organic layer yielded a dark orange oil which was purified by flash chromatography (hexanes) to afford the unstable enyne **17a** (306 mg, 62%) as a colorless oil.

***A*-Homo-9α,11α-oxido-9,10-secocholest-5(10)-en-6-yn-8β-ol (18a).** To a −78 °C solution of dibromide **16a** (0.485 g, 1.65 mmol) in dry THF (7.5 mL) was added *n*-butyllithium (2.1 mL, 1.57 m solution in hexanes, 3.3 mmol) dropwise. The resulting orange solution was stirred at −78 °C for 30 min and at room temperature for 1 h. The solution was then cooled to −78 °C, and epoxy ketone **11** (0.312 g, 1.12 mmol) in THF (3 mL plus 1 mL rinse) was added via syringe. The solution was warmed to room temperature and stirred for 30 min. The reaction was quenched with water and extracted with ether (2 × 25 mL). After drying, concentration of the ether extract afforded a dark orange oil which was purified by flash chromatography (5% EtOAc/hexanes) to yield the epoxy propargyl alcohol **18a** (0.351 g, 76%) as a yellow amorphous solid (mp 92–94 °C). This material, despite its coloration, was spectrally homogenous (^{1}H and ^{13}C NMR analysis) and was sufficiently pure for use in the next step.

***A*-Homo-9α,11α-oxido-19,19,19-trideuterio-9,10-secocholest-5(10)-en-6-yn-8β-ol (18b).** This compound was prepared in precisely the same manner as the protio analogue **18a** except that the deuteriated dibromide **16b** (155 mg, 0.52 mmol) was coupled with the epoxy ketone **11** (106 mg, 0.38 mmol) to afford the deuteriated epoxy alcohol **18b** (119 mg, 75%) as a white foam. This material was used for spectral characterization and in the next step without further purification.

***A*-Homo-9α,11α-oxido-9,10-secocholest-5(10)-en-6-yn-8β-yl Benzoate (19a).** To a −78 °C solution of epoxy propargyl alcohol **18a** (0.351 g, 0.85 mmol) in dry THF (6 mL) was added *n*-butyllithium (0.60 mL, 1.57 M solution in hexanes, 0.94 mmol) dropwise via syringe. The solution was warmed to room temperture and stirred for 1 h. After cooling the solution again to −78 °C, benzoyl chloride (0.12 mL, 1.0 mmol) was added as the neat liquid. The solution was then brought to room temperature and stirred for 30 min. Water (10 mL) was added, and the mixture was extracted with Et_2O (2 × 20 mL). The combined ether extracts were washed with saturated aqueous $NaHCO_3$, dried, and then concentrated. The residual orange oil was subjected to HPLC purification (5% EtOAc/hexanes) to yield the epoxy propargyl benzoate **19a** (0.382 g, 87%) as a white foam.

***A*-Homo-9α,11α-oxido-19,19,19-trideuterio-9,10-secocholest-5(10)-en-6-yn-8β-yl Benzoate (19b).** This compound was prepared in the same manner as the protio analogue **19a** except that the deuteriated propargylic alcohol **18b** (0.313 g, 0.0075 mmol) was used to afford the deuteriated propargylic benzoate **19b** (0.325 g, 83%) as a white foam.

***A*-Homo-9,10-secocholesta-5(10),8-dien-6-yn-11α-ol (20a).** To a suspension of samarium powder (0.588 g, 3.9 mmol, Aldrich) in dry THF (5 mL) was added a solution of 1,2-diiodoethane (0.933 g, 3.3 mmol) in THF (6 mL) under argon at room temperature via cannula. After stirring for 1 h, a deep blue solution was obtained, and a solution of epoxy propargyl benzoate **19a** (0.339 g, 0.66 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.026 g, 3 mol %) in THF (14 mL) was added via cannula. The deep blue color persisted, and the solution was stirred for 1 h. Water (15 mL) was added, and the mixture was stirred for a few minutes. Solid Na_2CO_3 was added to separate the layers, the entire mixture was extracted with ether (2 × 20 mL), and the organic layers were dried. Concentration gave a dark orange oil which was flash chromatographed (10% EtOAc/hexanes) to yield the alcohol **20a** (0.193 g, 74%) as a white foam.

***A*-Homo-19,19,19-trideuterio-9,10-secocholesta-5(10),8-dien-6-yn-11α-ol (20b).** This compound was prepared analogously to the protio dienynol **20a** except that the deuteriated epoxy propargyl benzoate **19b** (0.257 g, 0.0005 mol) was used to furnish the labeled dienynol **20b** (0.164 g, 83%) as a white foam.

***A*-Homo-9,10-secocholesta-5(10),8-dien-6-yn-11-one (21a). By MnO_2 Oxidation.** To a suspension of MnO_2 (39 mg, 0.45 mmol) in hexanes (2 mL) was added dienynol **20a** (9 mg, 0.023 mmol) in hexanes (1 mL) at room temperature. The mixture was stirred for 1.5 h and then filtered through Celite. Concentration afforded the dienynone **21a** (7 mg, 78%) as a viscous oil sufficiently pure for use in the next step. An analytical sample was prepared by subjecting the dienynone to HPLC purification (Whatman Partisil M9 column, 5% EtOAc/hexanes).

By Oxidation of Propargyl Alcohol 23. Method A. To a suspension of PDC (pyridinium dichromate, 369 mg, 0.98 mmol) in dry CH_2Cl_2 (2 mL) under argon at room temperature was added propargyl alcohol **23** (259 mg, 0.65 mmol) in dry CH_2Cl_2 (2 mL) via syringe. The mixture was allowed to stir at room temperature for 10 h, after which it was filtered through Celite and concentrated. The resulting residue was purified by HPLC (Whatman Partisil M10 20/50 column; 10% EtOAc/hexane) to give the dienynone **21a** (84 mg, 33%) as a viscous oil. Also obtained was enone **10** (17 mg) resulting from formal oxidative cleavage of the A-ring fragment **17a**.

Method B. To a suspension of Dess–Martin periodinane (Aldrich, 48 mg, 0.11 mmol) in dry CH_2Cl_2 (2 mL) under argon was added pyridine (0.04 mL) followed by propargyl alcohol **23** (30 mg, 0.076 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred at room temperature for 5 h after which it was diluted with ether (10 mL) and poured into a 7:1 saturated $Na_2S_2O_3$/saturated $NaHCO_3$ solution. The mixture was stirred until the solid material dissolved. The layers were then separated, and the ether layer was washed with saturated $NaHCO_3$ (1 × 20 mL) and with water (1 × 20 mL) and dried. Concentration afforded a residue which was purified by HPLC (5% EtOAc/hexanes) to give the desired dienynone **21a** (10 mg, 35%) as a viscous oil. There was also obtained a second, less polar component (~5 mg, 17%) believed to be a dehydration product, but this material was not characterized.

***A*-Homo-19,19,19-trideuterio-9,10-secocholesta-5(10),8-dien-6-yn-11-one (21b).** This compound was prepared in the same manner (MnO_2 oxidation) as the protiodienynone **21a** except that the deuteriated dienynol **20b** (113 mg, 0.28 mmol) was used to furnish the deuteriated dienynone **21b** (87 mg, 77%) as a viscous oil.

***A*-Homo-9,10-secocholesta-5(10),8-dien-6-yn-11β-ol (22a). L-Selectride.** To a −78 °C solution of dienynone **21a** (10 mg, 0.025 mmol) in dry THF under argon (2 mL) was added L-Selectride (Aldrich, 1.0 M solution in THF, 0.05 mL, 0.05 mL) dropwise via syringe. The solution was stirred at −78 °C for 2 h and then warmed to 0 °C. The reaction was then quenched with water (1 mL), and then 1 M NaOH (0.06 mL) and 30% H_2O_2 (0.06 mL) were added sequentially to oxidize the organoborane. The mixture was then taken up in ether (10 mL), and then the aqueous layer was extracted with ether (1×). The organic layers were combined and dried. Concentration yielded the dienynol **22a** (9 mg, 90%) as a white foam sufficiently pure for use in the next step. A sample for spectral characterization was prepared by subjecting the dienynol to HPLC purification (10% EtOAc/hexanes).

$NaBH_4$/$CeCl_3$. To a 0 °C solution of dienynone **21a** (31 mg, 0.077 mmol) dissolved in a 0.4 M $CeCl_3$/MeOH solution (3 mL) was added $NaBH_4$ (Aldrich, 99%, 5.8 mg, 0.15 mmol) in portions. The mixture was stirred for 0 °C for 5 min and then allowed to warm to room temperature. Ether (10 mL) was added, and the layers were separated. The aqueous layer was extracted with ether (2 × 10 mL), and the ether layers were combined and washed with water (30 mL) and dried. Concentration afforded a residue which was subjected to HPLC purification (10% EtOAc/hexanes). Eluted first was the starting dienynone **21a** (2 mg). Eluted second was the 11β-dienynol **22a** (4 mg, 13%) followed by the 11α-dienynol **20a** (6 mg, 19%). Both dienynols were obtained as colorless oils.

***A*-Homo-19,19,19-trideuterio-9,10-secocholesta-5(10),8-dien-6-yn-11β-ol (22b).** This compound was prepared in the same manner using L-Selectride as the protiodienynol **22a** except that the deuteriated dienynone **21b** (67 mg, 0.17 mmol) was used to afford the deuteriated dienynol **22b** (51 mg, 76%) as an oil. A sample for spectroscopic characterization was obtained by HPLC purification (10% EtOAc/hexanes).

***A*-Homo-9,10-secocholesta-5(10),9(11)-dien-6-yn-8β-ol (23).** To a solution of enyne **17a** (0.534 g, 3.99 mmol) in dry ether (5 mL) at 0 °C was added *n*-BuLi (2.5 mL, 1.59 M in hexanes, 3.99 mmol). The reaction mixture was stirred for 30 min, and then enone **10** (0.950 g, 3.62 mmol) in ether (5 mL) was added to the acetylide solution via cannula. The cooling bath was removed, and the reaction mixture was stirred at room temperature for 1 h. Water (5 mL) was added, the layers were separated, and the organic layer was dried. Concentration yielded a dark red-orange oil which was flash chromatographed (5% EtOAc/hexanes) to afford the propargyl alcohol **23** (0.850 g, 59%) as an orange, viscous oil. HPLC purification (Whatman, Partisil 10 Magnum 20/50; 10% EtOAc/hexanes) afforded the alcohol as a yellow oil, sufficiently pure for the next step.

(5*Z*,7*E*)-*A*-Homo-9,10-secocholesta-5,7,10(19)-trien-11α-ol (24a). For preparative purposes, a stirred mixture of dienynol **20a** (47 mg, 0.12 mmol), Lindlar catalyst (180 mg), and quinoline (0.60 mL, 0.17 M solution in hexanes, 0.10 mmol) in hexanes (11 mL) was exposed to hydrogen gas for 2 h at ~23 °C. Filtration of the reaction mixture through Celite and concentration afforded a residue, the ^{1}H NMR spectrum of which already revealed the complete conversion of the intermediate previtamin form (**7a**, absence of signals assigned to its $C_{6,7}$

protons) to the vitamin. The vacuum dried residue was then subjected to HPLC purification (10% EtOAc/hexanes) to yield the vitamin D analogue **24a** (30 mg, 64%) as a white foam.

For the kinetic studies, the dienynol **20a** was reduced and then worked up with ice cooling as described in the supplementary material section.

(5*Z*,7*E*)-*A*-Homo-9α,19,19-trideuterio-9,10-secocholesta-5,7,10(19)-trien-11α-ol (24b′) and (5*Z*,7*E*)-*A*-Homo-9β,19,19-trideuterio-9,10-secocholesta-5,7,10(19)-trien-11α-ol (24b″). This mixture of *A*-homovitamin D trienols was prepared by stirring a mixture of deuteriated dienynol **20b** (28 mg, 0.07 mmol), Lindlar catalyst (72 mg), and quinoline (0.24 mL, 0.17 M solution in hexanes, 0.04 mmol) in hexanes (5 mL) under a hydrogen atmosphere for ~2 h. Filtration of the reaction mixture through Celite and then concentration of the filtrate afforded a residue which was allowed to stand overnight under vacuum at room temperature. The residue was then subjected to HPLC purification (10% EtOAC/hexanes) to yield the deuteriated trienols **24b′** and **24b″** (19 mg, 68%) in a ratio of 82:18 (500 MHz, ^{1}H NMR), respectively. No previtamin **7b** was detected as determined by the absence of the signals assigned to the $C_{6,7}$ protons.

The 82:18 ratio, which reflects the π-facial selectivity of the [1,7]-sigmatropic hydrogen shift, was estimated by ^{1}H NMR analysis at 500 MHz. The two doublets at δ 6.08 and 6.25 ($H_{6,7}$) as well as the one proton signal at δ 3.90 (H_{11}) were used as internal standards and are compared to the $H_{9\beta}$ (δ 3.16) and $H_{9\alpha}$ (δ 1.72) signals of both the protio and deuterio compounds. The integration data and analysis are presented in Table I.

In order to ensure that the computed ratio of 82/18 describes a kinetic effect and not a value distorted by the reversibility of the process (resulting in H/D scrambling between the *Z* and *E* positions of C_{19} and the α and β positions of C_9), a control experiment was carried out. The signal assigned to $H_{9\beta}$ was integrated relative to that assigned to H_6 over the period of time described for the kinetic runs at 25 °C (see supplementary material). No change was observed in the ratio of the relative peak areas. In addition, it was also established that the equilibrium is shifted completely to the vitamin side by the lack of appearance of olefinic signals assigned to the previtamin run even after heating (80 °C, 5 h) samples of vitamin.

For the kinetic studies, the deuteriated dienynol **20b** was reduced and then worked up as described elsewhere in the Experimental Section.

(5*Z*,7*E*)-*A*-Homo-9,10-secocholesta-5,7,10(19)-trien-11β-ol (25a). For preparative purposes, a stirred mixture of dienynol **22a** (49 mg, 0.12 mmol), Lindlar catalyst (180 mg), and quinoline (0.60 mL, 0.17 M solution in hexanes, 0.10 mmol) in hexanes (11 mL) was exposed to hydrogen gas for 2 h. Filtration of the reaction mixture through Celite and then concentration afforded a residue, which by ^{1}H NMR analysis revealed that the intermediate previtamin form (absence of signals assigned to its $C_{6,7}$ protons) had already completely rearranged to the vitamin form. The vacuum dried residue was subjected to HPLC purification (10% EtOAc/hexanes) to yield the 11β-trienol **25a** (30 mg, 61%) as a colorless oil.

For the kinetic studies, the dienynol **22a** was reduced and then worked up with ice cooling as described in the supplementary material section.

(5*Z*,7*E*)-*A*-Homo-9α,19,19-trideuterio-9,10-secocholesta-5,7,10(19)-trien-11β-ol (25b″) and (5*Z*,7*E*)-*A*-Homo-9β,19,19-trideuterio-9,10-secocholesta-5,7,10(19)-trien-11β-ol (25b′). This mixture of *A*-homovitamin D trienols was prepared by stirring a mixture of deuteriated dienynol **22b** (5 mg, 0.01 mmol), Lindlar catalyst (36 mg), and quinoline (0.09 mL, 0.17 M solution in hexanes, 0.02 mmol) in hexanes (4 mL) under a hydrogen atmosphere for 2 h. Filtration of the reaction residue through Celite and then concentration of the filtrate afforded a residue which was allowed to stand overnight under vacuum at room temperature. The residue was subjected to HPLC purification (10% EtOAc/hexanes) to furnish the deuteriated vitamin D analogues **25b′** and **25b″** (2.6 mg, 52%) in a ratio of 64:36, respectively. No previtamin (**8b**) was detected as determined by the absence of the signals assigned to the $C_{6,7}$ proton.

The 64:36 ratio, which reflects the π-facial selectivity of the [1,7]-sigmatropic hydrogen shift, was estimated by ^{1}H NMR analysis at 500 MHz. The two proton signals at δ 6.23 ($H_{6,7}$) as well as the one proton signal at δ 4.21 (H_{11}) were used as internal standards and were compared to the $H_{9\beta}$ (δ 2.90) at $H_{9\alpha}$ (δ 2.14) signals of both the protio and deuterio compounds. The integration data are presented in Table II.

In order to ensure that the computed ratio of 64/36 describes a kinetic effect and not a value distorted by the reversibility of the process (resulting ion H/D scrambling between the *Z* and *E* positions of C_{19} and the α and β position of C_9), a control experiment was carried out. The signal assigned to $H_{9\beta}$ was integrated relative to that assigned to H_6 over the period of time described for the kinetic runs at 25 °C (see supplementary material). No significant change was observed in the ratio of the relative peak areas. In addition, it was also established that the equilibrium is shifted completely to the vitamin side as evidenced by the lack of appearance of olefinic signals assigned to the previtamin form even after heating (80 °C, 6 h) samples of vitamin.

For the kinetic studies, the deuteriated dienynol **22b** was reduced and then worked up as described in the supplementary material section.

(6*Z*)-*A*-Homo-9,10-secocholesta-5(10),6,8-trien-11-one (26, Previtamin) and (5*Z*,7*E*)-*A*-Homo-9,10-secocholesta-5,7,10(19)-trien-11-one (27, Vitamin). A mixture of dienynone **21a** (22 mg, 0.063 mmol) in hexanes (6 mL), Lindlar catalyst (32 mg), and quinoline (15.5 μL) was exposed to hydrogen gas for 2 h. Filtration through Celite and concentration afforded a residue which was subjected to HPLC purification (5% EtOAc/hexanes) to yield the trienones **26** and **27** (7 mg, 32%) in a ratio of 62:38 (equilibrium at ~23 °C), respectively (300-MHz ^{1}H NMR). The ketones are obtained as a rapidly equilibrating mixture which partially decomposes during attempts at purification. The HPLC trace indicated that the two trienones equilibrated too quickly on the HPLC time scale, thus precluding separation. The HPLC trace revealed two diffuse broad peaks interconnected by a plateau, and re-injection of fractionated material afforded the same behavior. It was not clear whether sample deterioration to some extent during HPLC elution caused the poor chromatographic behavior as well. Even lower yields were obtained by, for example, Dess–Martin or tetrapropylammonium perruthenate ($Pr_4N^+RuO_4^-$)[27] oxidation of the vitamin trienol **24a** or **25a**.

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Supplementary Material Available: Spectral data for all new compounds, general experimental details, and details of the kinetic investigations (46 pages). Ordering information is given on any current masthead page.