state that is located at the same position on the x axis. The published energy diagrams show an energy well or no barrier along the x axis for the proton transfer,[23,24] but it is likely that there is some such barrier[62] because proton transfer between electronegative atoms at $\Delta pK = 0$ is considerably slower than expected for a diffusion-controlled reaction[33] and shows a significant deuterium isotope effect.[63] This barrier may represent proton transfer over a barrier, tunneling through the barrier, and/or motion of the heavy atoms toward each other that decreases the barrier.[22,41,63] The proton transfer may involve tunneling, but tunneling does not require that the proton transfer must occur as a separate step. There is experimental and theoretical support for tunneling in E2 elimination reactions and the mutarotation of tetramethylglucose, which involve concerted transfer of one or more protons and changes in bonding to heavy atoms in the transition state.[64]

The reaction will follow the path of lowest Gibbs energy from reactants to products, which passes through the transition state at a saddle point. If the reaction path does not proceed through the corners of the diagram, the saddle point will ordinarily be located somewhere in the central area of the diagram because of the high energy of the intermediate structures at the corners. We can characterize the ground states of the reaction and the transition state at the saddle point; we do not know the path that is followed to reach the transition state, although it is likely that it is close to the path of steepest descent from the saddle point. The position of the transition state can be defined, within the limits of the uncertainty principle, even if the curvature along the coordinate for proton transfer is zero or negative.

Empirical energy contour diagrams that are defined by structure–reactivity parameters provide a self-consistent description of changes in these parameters with changing reactant structure. Appendix 1 of ref 19 shows that there is a linear relationship between the Brønsted β value, $\partial \log k/\partial pK_{BH}$, and the coordinate for proton transfer at the saddle point, x, when a linear energy perturbation is applied to an energy contour diagram. This conclusion holds for small perturbations regardless of the nature of the energy surface or its edges. The reason for the conclusion is obvious for changes in pK_{BH} (the energy of the right side of Figure 13) when the position of the transition state on the y coordinate is constant because the x coordinate is defined by β, so that the fraction of the perturbation at x is equal to β. The conclusion is less obvious but is still true when the y coordinate of the transition state changes. Consider the case in which the curvatures a and b are equal to zero for energy contour lines that pass through the saddle point parallel to the x and y axes, respectively. The reaction coordinate is then diagonal and the curvatures of the surface perpendicular and parallel to the reaction coordinate at the saddle point are equal but opposite. When $b = 0$ the change in energy of the transition state is independent of the y coordinate of the transition state and $x = \beta$. Appendix 1 shows that this conclusion holds also when the curvatures are not zero.[19] If significant changes in x do occur they will appear as curvature in the observed Brønsted plots.

If proton transfer occurs by tunneling through a barrier the exact position of the proton in the transition state cannot be specified. However, tunneling is likely to take place at an approximately constant distance below the top of the barrier so that the position and movements of the barrier will appear in the observed structure–reactivity behavior. We conclude that energy contour diagrams that are defined by structure–reactivity parameters provide a useful description of the characteristics of a reaction even if tunneling occurs and that they are indicators of reaction progress, to the extent that this can be defined when tunneling is significant.

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Thermal [1,7]-Sigmatropic Hydrogen Shifts: Stereochemistry, Kinetics, Isotope Effects, and π-Facial Selectivity[1,2]

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Abstract: The antarafacial stereochemistry of the thermal [1,7]-sigmatropic hydrogen shift has been demonstrated. The substrates studied include the epimeric *cis*-isotachysterol analogues **1** and **4** and their stereospecifically 15α-deuterium-labeled derivatives **7** and **10**, respectively. Two different synthetic routes to the key labeled intermediate **23b** are described; the highly stereoselective transformation of **18** to **19** to **20** proved to be a particularly useful observation for expeditious completion of this study and may be useful for *trans*-hydrindane syntheses in general (e.g., in steroid applications). The observations that heating **7** produces only **8** and **9**, and no **8′** and **9′**, and, likewise, that heating **10** produces only **11** and **12**, and no **11′** and **12′**, demonstrate antarafaciality. Kinetic investigations in the temperature range 67–98 °C of the thermal isomerization of unlabeled **1** and **2** reveal that they undergo [1,7]-sigmatropic shifts with activation parameters characteristic of other [1,7]-shifts. The kinetic studies of **1** and **2** also reveal that the configurational orientation of the allylic hydroxyl group exerts a significant syn-π-facial directive effect on the helicity of this antarafacial, pericyclic process. This is just the opposite to the anti-π-facial selectivity previously reported for thermal, suprafacial [1,5]-sigmatropic shifts of allylic hydroxyl substituted systems. Lastly, the kinetic studies of **1** and **2** coupled with those of labeled isomers **4** and **10** reveal primary deuterium kinetic isotope effects (k_H/k_D) of 4.0 and 2.6 [for the processes **1(7)** → **3(9)** and **4(10)** → **6(12)**, respectively]. These relatively normal kinetic isotope effect values are an order of magnitude smaller than the only other value previously recorded for the thermal [1,7]-sigmatropic hydrogen shift.

The thermal [1,5]- and [1,7]-sigmatropic hydrogen shifts are subsets of pericyclic processes first systematically defined in 1965 by Woodward and Hoffmann[3] (see Chart I). The classic metabolic transformation of previtamin D_3 to vitamin D_3 is a pivotal

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Chart I

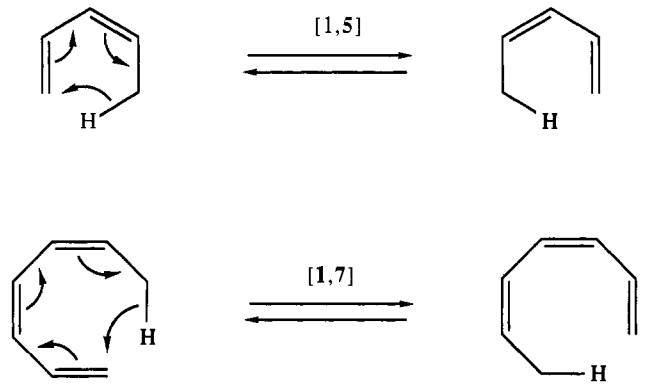
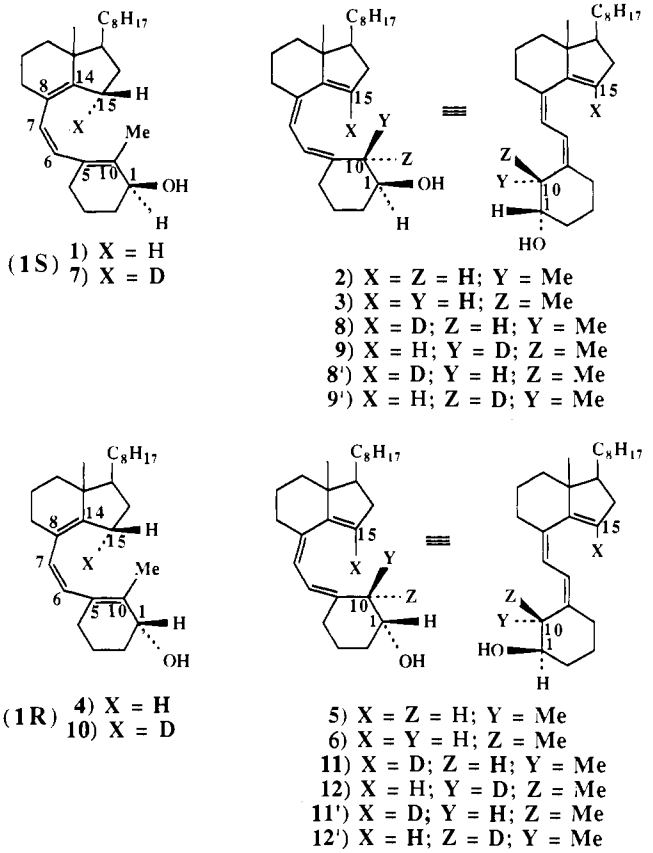


Chart II



(1S) 1) X = H
7) X = D

2) X = Z = H; Y = Me
3) X = Y = H; Z = Me
8) X = D; Z = H; Y = Me
9) X = H; Y = D; Z = Me
8') X = D; Y = H; Z = Me
9') X = H; Z = D; Y = Me

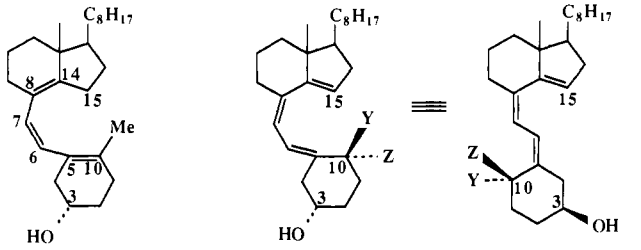
(1R) 4) X = H
10) X = D

5) X = Z = H; Y = Me
6) X = Y = H; Z = Me
11) X = D; Z = H; Y = Me
12) X = H; Y = D; Z = Me
11') X = D; Y = H; Z = Me
12') X = H; Z = D; Y = Me

event in calciferol (vitamin D) biosynthesis[4,5] and can be considered to be an example of a biological [1,7]-sigmatropic hydrogen shift (vide infra). Although the intramolecular nature of the in vitro thermal variant of this *specific* transformation has been established,[5] and although the stereochemistry of the related [1,5]-migration has been demonstrated to occur suprafacially,[6] no direct demonstration of the predicted antarafacial stereochemistry of the [1,7]-shift has been previously reported prior to this study.

The [1,7]-sigmatropic hydrogen shift[7] of *cis*-isotachysterol analogue **1** to afford **2** and **3** (and also its C-1 carbinol epimer **4** to afford **5** and **6**) was described in 1978,[8,9a] a full account of which was subsequently reported in 1980[9b] (see Chart II). More recently, the corresponding isotopically labeled (deuterium) substrates **7** and **10** were synthesized and subjected to thermal isomerization at ca. 100 °C.[2] It was established that **7** afforded only the antarafacial [1,7]-sigmatropic hydrogen shifted isomers **8** and **9**; the stereoisomers **8'** and **9'** resulting from suprafacial isomerization pathways were absent. Similarly, the carbinol

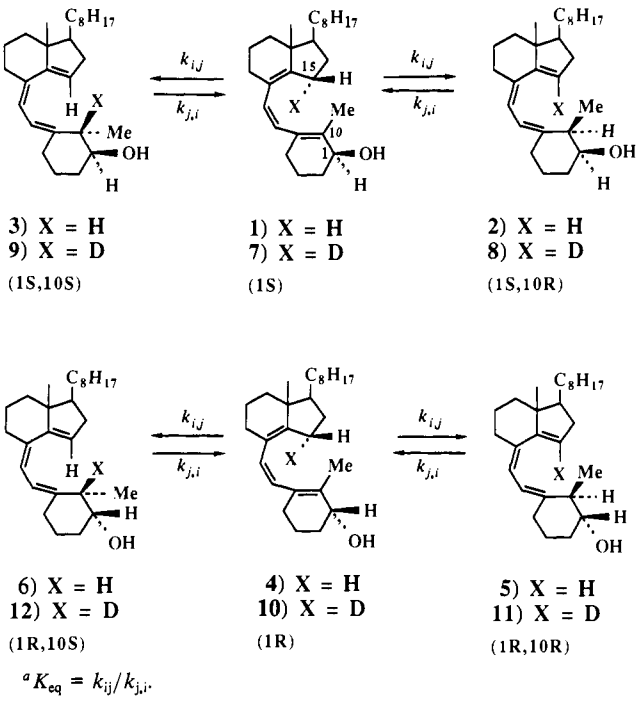
Chart III



13 (3S)

14) Y = Me; Z = H (3S,10S)
15) Y = H; Z = Me (3S,10R)

Scheme I[a]



3) X = H
9) X = D
(1S,10S)

1) X = H
7) X = D
(1S)

2) X = H
8) X = D
(1S,10R)

6) X = H
12) X = D
(1R,10S)

4) X = H
10) X = D
(1R)

5) X = H
11) X = D
(1R,10R)

[a] $K_{eq} = k_{ij}/k_{j,i}$.

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(8) The steroid numbering system including absolute configuration is used throughout this article.

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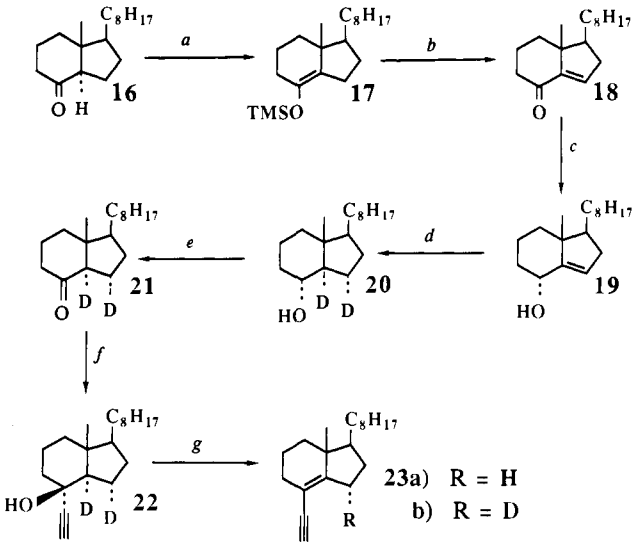
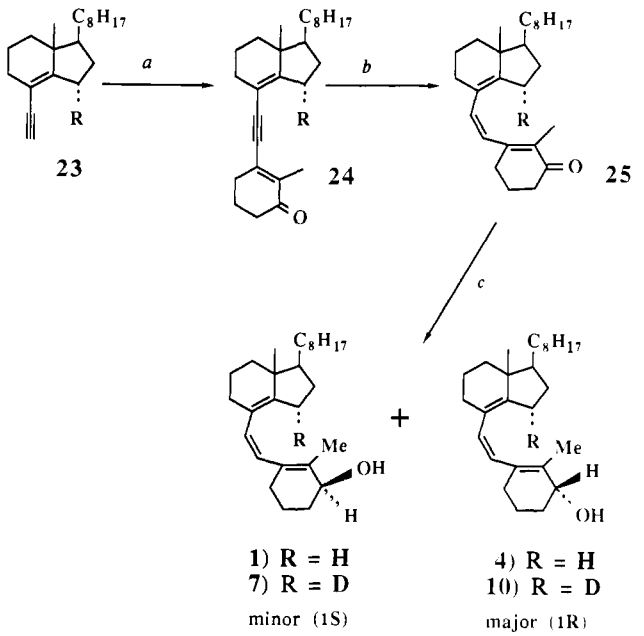
Scheme II



[a] Me_3Si-Cl, LiI, $(Me_3Si)_2NH$, CH_2Cl_2 (96%). [b] [(i) PhSeCl, C_5H_5N; (ii) MCPBA, CH_2Cl_2] (71%). [c] $NaBH_4$, $CeCl_3{\cdot}7H_2O$, CH_3OH (94%; >200:1 8R:8S ratio). [d] D_2, $RhCl(PPh_3)_3$, C_6H_6 (85%; >37:1 trans:cis ratio). [e] PDC, PTFA, CH_2Cl_2 (91%). [f] LiC_2H, THF (97%). [g] $SOCl_2$, C_5H_5N (unlabeled, 67%; labeled, 70% of regioisomers, 8-(14)-ene/8(9)-ene ratio = 7.5/1.0).

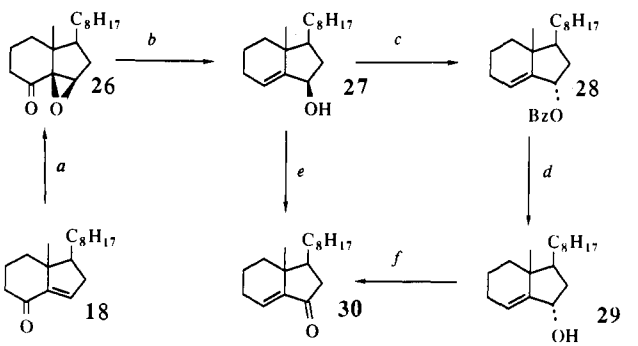
Scheme III



[a] [(i) *n*-BuLi, Et_2O; (ii) 3-isobutoxy-2-methylcyclohex-2-en-1-one; (iii) 1 M HOAc] (R = H, 86%; R = D, 76%). [b] H_2 or D_2, Lindlar catalyst, quinoline, C_5H_5N (R = H, 67%; R = D, 66%). [c] $NaBH_4$, $CeCl_3{\cdot}7H_2O$, CH_3OH and HPLC separation [R = H, 32% (minor) and 53% (major); R = D, 36% (minor) and 52% (major)].

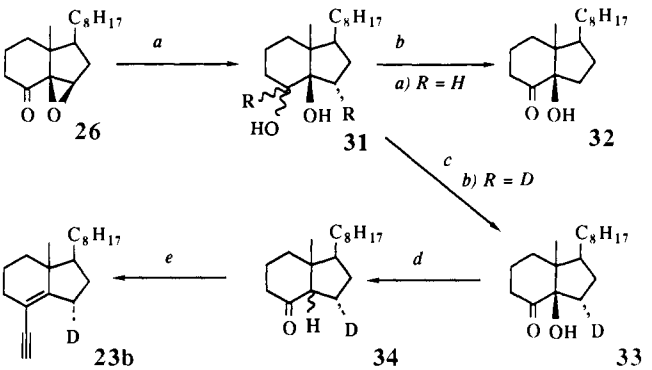
epimer **10** afforded **11** and **12** while **11′** and **12′** were absent. These stereochemical results demonstrated directly for the first time the antarafacial nature of the thermal [1,7]-sigmatropic hydrogen shift. Substrates similar to *cis*-isotachysterol analogues **1** and **4** have been previously reported.[10] The parent system,

Scheme IV



[a] H_2O_2, NaOH, CH_3OH (57%). [b] $NH_2NH_2{\cdot}H_2O$ (~100%). [c] Diethyl azodicarboxylate, Ph_3P, $PhCO_2H$, C_6H_6 (19%). [d] 5% KOH, CH_3OH (75%). [e] MnO_2, low boiling petroleum ether (75%). [f] Reagent e (79%).

Scheme V



[a] $LiAlH_4$ or $LiAlD_4$, THF (~100%, less polar/more polar = ~1:16). [b] H_2CrO_4, acetone (68%). [c] [(i) $(COCl)_2$, Me_2SO, CH_2Cl_2; (ii) Et_3N] (83%). [d] HI, H_2O, HOAc (85%, cis/trans = ~2.4:1.0). [e] (i) LiC_2H, THF; (ii) $POCl_3$, C_5H_5N].

cis-isotachysterol$_3$ (**13**), was reported in as early as 1960,[10a] and its isomerization to **14** and **15** was quantitatively assessed in 1978[10b] (see Chart III).

It is the purpose of this article to describe the complete experimental details of the preliminary report[2] on the stereospecific isomerization of **7** to **8** plus **9** and of **10** to **11** plus **12** and also to report on new experiments. Most notably, a kinetic study of the isomerization processes involving **1**–**12** as shown in Scheme I is described.

Results and Discussion

Synthesis of Substrates. The synthesis of the key substrates **1**, **4**, **7**, and **10** utilized in this stereochemical and kinetic investigation are shown in Schemes II and III. After transformation of Grundmann's ketone[11] **16** to enone **18** by a standard procedure,[12,13] the latter was reduced with $NaBH_4$ in the presence[14] or absence of $CeCl_3{\cdot}7H_2O$ to allylic alcohol **19** in >200:1 selectivity. By contrast, reduction with diisobutylaluminum hydride afforded a ~1:1 mixture of **19** and its alcohol epimer. Catalytic reduction (D_2/Wilkinson's catalyst) of **19** occurred with >37:1 selectivity from the face syn to the hydroxyl group to afford **20**.[15]

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Table I. ^{1}H NMR Chemical Shifts (δ) and Relative Integrations[a]

compd		$H_{6,7}$[b]		H_{15}		H_1		H_{10}	
3	(1*S*,10*S*)	6.22	(2.08 ± 0.01)	5.52	(0.95 ± 0.05)	3.84	(0.92 ± 0.01)	3.06	(0.99 ± 0.06)
[**9**]			[2.03 ± 0.02]		[0.98 ± 0.03]		[0.97 ± 0.02]		*c*
2	(1*S*,10*R*)	6.17	(2.05 ± 0.04)	5.50	(0.88 ± 0.03)	3.71	(0.95 ± 0.04)	3.24	(1.02 ± 0.05)
[**8**]			[2.00 ± 0.06]		[0.033 ± 0.007]		[0.99 ± 0.06]		[0.88 ± 0.07]
6	(1*R*,10*S*)	6.14	(2.08 ± 0.02)	5.49	(0.91 ± 0.02)	3.70	(0.92 ± 0.02)	3.20	(0.89 ± 0.05)
[**12**]			[2.06 ± 0.01]		[0.89 ± 0.03]		[0.94 ± 0.01]		[0.053 ± 0.011]
5	(1*R*,10*R*)	6.25	(2.06 ± 0.01)	5.49	(0.97 ± 0.04)	3.82	(0.94 ± 0.01)	3.10	(0.99 ± 0.04)
[**11**]			[2.08 ± 0.03]		[0.022 ± 0.002]		[0.92 ± 0.03]		[1.02 ± 0.07]

[a] The chemical shifts are for the unlabeled compounds, which at 300 MHz (Nicolet 300, $CDCl_3$) were identical with the observable resonances of the labeled series. See Figure 1 and the Supplementary Material. The values given in parentheses are the relative integrated values for the unlabeled derivative; those given in brackets are for the corresponding labeled derivative obtained by heating **7** or **10**. [b] Chemical shift for $H_{6,7}$ is that for the center of the AB pattern. [c] No signal was observed for the labeled material.

It should be noted that the sequence **18** to **19** to **20** provides a precedent for a very simple solution to a general problem in steroid synthesis, namely the production of *trans*-hyndrindanes characteristic of steroid CD fragments.[16] After transformation of **20** to **22** in a straightforward manner, the latter was dehydrated regioselectively to monodeuteriated enyne **23b** [7.5:1.0 ratio of 8(14)-ene/8(9)-ene].[17] Analogous dehydration experiments with unlabeled propargyl alcohol **22** revealed regioselectively homogeneous production of **23a**, apparently a reflection of the absence of a primary deuterium isotope effect expectedly present in the dehydration of **22** to **23b**.[18]

With enynes **23a** and **23b** in hand, *cis*-isotachysterols **1**, **4**, **7**, and **10** were prepared essentially by a method described previously (Scheme III).[13c,17] The spectral properties of both deuterium-labeled and unlabeled substances are presented in detail in the Supplementary Material. For the labeled thermolysis substrates **7** and **10**, the deuterium content was estimated to be >98% d_1 at C-15 by ^{1}H NMR integration analysis of labeled precursor enyne **23b** and unlabeled **23a**.

Schemes IV and V outline alternative schemes which were explored as possible routes to stereospecifically labeled *cis*-isotachysterol derivatives such as **7** and **10** and their C-15 epimers. This alternative route is based on the stereoselective formation of the β-epoxide **26** from enone **18**.[19] As given in Scheme IV, Wharton reaction[20] of epoxy ketone **26** afforded 15β alcohol **27** which could be transformed via the Mitsunobu route[21] in only poor yield to 15α alcohol **29**. Both **27** and **29** could be oxidized to the same ketone **30**, and an LIS shift reagent ^{1}H NMR study (Experimental Section) of the alcohols supported their C-15 configurational assignments. The result also supports the assigned epoxide stereochemistry of **26** but attempts to stereospecifically replace the alcohol function of **27** with isotope proved unsuccessful.

However, as shown in Scheme V, $LiAlD_4$ reduction of **26** did afford labeled diol **31** with high C-8 stereoselectivity (~16:1). Interestingly, Jones oxidation of unlabeled **31** to acyloin **32** occurred uneventfully, but little if any of **33** was produced from labeled **31**. Neither characterizable products nor starting labeled **31** were isolated. This result is interpreted to be a reflection of a significant primary deuterium isotope effect on the Jones oxidation of labeled **31**. A competing pathway, possibly oxidative cleavage of the glycol moiety in **31**, is conjectured to now dominate because of the attenuated rate of the Jones oxidation of **31** as a consequence of deuterium label at C-8. Swern oxidation of labeled **31** did, however, afford monodeuteriated **33** in good yield, and the latter was easily reduced to the cis and trans mixture of 15α-deuteriated hydrindanones **34**. The ~2.4:1 cis/trans bicyclic ketone mixture **34** was transformed to enyne **23b** in two steps as previously described.[13c,17] This procedure, however, leads to a regioisomeric mixture of enynes. In short, the finding that **18** can be transformed directly to **20** with excellent stereoselectivity renders the route shown in Scheme II the method of choice.

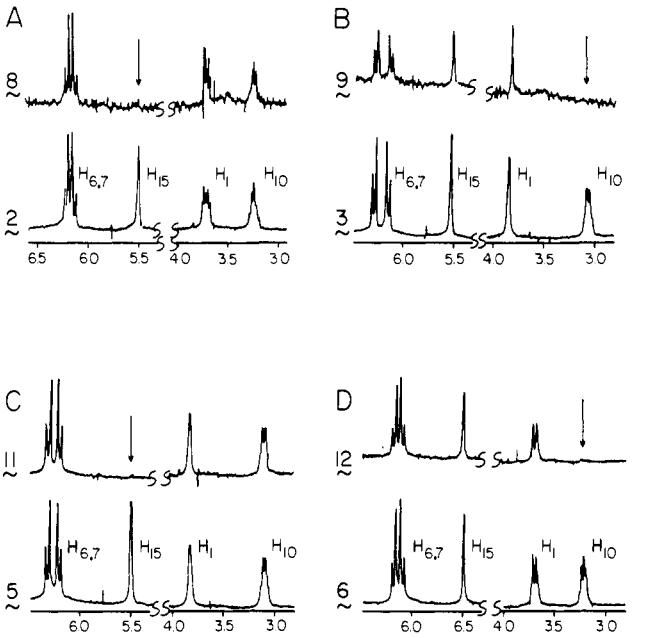

Figure 1. ^{1}H NMR (300-MHz) spectra of the δ 3.0–6.5 region (signals assigned to H-6, 7, 15, 1, and 10 for each case) of labeled (d_1, above) and unlabeled (d_0, below) trienes resulting from the thermal rearrangement of **1**, **4**, **7**, and **10**. (A) **8** vs. **2** (1*S*,10*R*); (B) **9** vs. **3** (1*S*,10*S*); (C) **11** vs. **5** (1*R*,10*R*); (D) **12** vs. **6** (1*R*,10*S*). The arrow indicates for the d_1 species the resonance which has been suppressed by labeling. Table I summarizes quantitatively the relative integrations of the peaks.

Antarafacial Stereochemistry of the [1,7]-Sigmatropic Shift. Previous investigations from this laboratory[9] indicated that the resonances assigned to the protons at C-1, C-6, C-7, C-10, and C-15 in the ^{1}H NMR spectra (see Figure 1) of the thermal products of unlabeled (1*S*)-alcohol **1**, namely **2** and **3**, were well separated and thus easily integrated. Similarly, the corresponding ^{1}H NMR resonances of the thermal products of unlabeled (1*R*)-alcohol **4**, namely **5** and **6**, were also easily analyzed. With this information and with the 15α-deuterium-labeled *cis*-isotachysterols **7** and **10** in hand, it was a simple matter to dem-

(15) (a) Thompson, H. W.; McPherson, E. *J. Am. Chem. Soc.* **1974**, *96*, 6232. (b) Stork, G.; Kahne, D. E. *J. Am. Chem. Soc.* **1983**, *105*, 1072. (c) Crabtree, R. H.; Davis, M. W. *Organometallics* **1983**, *2*, 681. (d) Corey, E. J.; Engler, T. A. *Tetrahedron Lett.* **1984**, *26*, 149. (e) Evans, D. A.; Morissey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866.

(16) For example, bridgehead enones of the type **18** are easy to synthesize. (a) Marfat, A.; Helquist, P. *Tetrahedron Lett.* **1978**, 4217. (b) Bal, S. A.; Marfat, A.; Helquist, P. *J. Org. Chem.* **1982**, *47*, 5045.

(17) The unlabeled *cis*-hydrindane system corresponding to **22** is dehydrated with only moderate regioselectivity (~2:1 $\Delta^{8(14)}$:$\Delta^{8(9)}$-ene ratio). Jeganathan, S.; Johnston, A. D.; Kuenzel, E. A.; Norman, A. W.; Okamura, W. H. *J. Org. Chem.* **1984**, *49*, 2152.

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(19) Wasson, R. L.; House, H. O. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol 4, p 552.

(20) (a) Wharton, P. S.; Bohlen, D. H. *J. Org. Chem.* **1961**, *26*, 3615. (b) Benn, W. R.; Dodson, R. M. *J. Org. Chem.* **1964**, *29*, 1742. (c) Ohloff, G.; Uhde, G. *Helv. Chim. Acta.* **1970**, *53*, 531.

(21) (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Mitsunobu, O.; Eguchi, M. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3427. (c) Grynkiewicz, G.; Burzynska, H. *Tetrahedron* **1976**, *32*, 2109.

Scheme VI

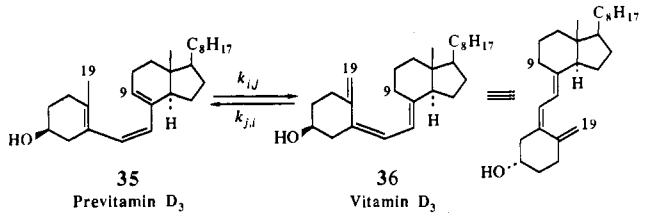

Table II. Summary of Kinetic Data[a] for **1** and **4** and Activation Parameters[b]

		$k_{i,j}$[d] × 10^5, s^{-1}			
T,[c] °C i,j[d] →		1,2	1,3	4,5	4,6
67.70		0.321	1.18	1.48	0.184
80.35		1.16	3.16	4.91	0.770
88.35		2.30	6.85	9.40	1.27
98.36		5.82	16.5	21.9	3.77
	E_a	23.7 ± 0.4	21.7 ± 1.0	22.0 ± 0.3	24.2 ± 1.5
	log A	9.7 ± 0.1	9.0 ± 0.4	9.3 ± 0.1	9.8 ± 0.6
	$\Delta H^{\ddagger}$	22.9 ± 0.3	21.0 ± 1.0	21.3 ± 0.3	23.5 ± 1.5
	$\Delta S^{\ddagger}$	−16.7 ± 0.2	−19.9 ± 0.9	−18.4 ± 0.2	−16.1 ± 1.0
	$\Delta G^{\ddagger}$	29.1 ± 0.4	28.3 ± 1.3	28.1 ± 0.3	29.4 ± 1.9

[a] Complete details are presented in the Experimental and Supplementary Material Sections. [b] At 95 °C for comparison with data in ref 10b of the text. Activation energies are given in kcal/mol; activation entropy is given in cal/mol K. Standard deviations are given. [c] ±0.05 °C. [d] Refer to Scheme I for definition of i,j and $k_{i,j}$.

onstrate the antarafaciality of the [1,7]-sigmatropic shift.

Heating labeled (1*S*)-alcohol **7** (ca. 10^{-3} M solutions in isooctane in sealed capillaries) for 26 h at 98.4 °C afforded 22% **7**, 47% **9**, and 31% **8**; similar heating of labeled (1*R*)-alcohol **10** afforded 22% **10**, 15% **12**, and 63% **11**. Table I and Figure 1 summarize the deuterium analyses of the products (**8** and **9** from **7** and **11** and **12** from **10**) and thus the stereochemical results reported in the preliminary account[2] demonstrated directly for the first time the antarafacial nature of the thermal [1,7]-sigmatropic shift.

Kinetic Studies. In the stereochemical study of labeled **7** and **10** just discussed, it was initially anticipated that the hydrogen migration process would be *highly* dominant over deuterium migration under the reaction conditions (i.e., nearly exclusive formation of **8** and **11** would result from heating **7** and **10**, respectively). This qualitative expectation was based on a previous investigation of the transformation of previtamin D_3 (**35**) to vitamin D_3 (**36**) (Scheme VI), for which a remarkably large primary kinetic deuterium isotope effect, k_H/k_D, of ~45 was reported by Mazur and co-workers.[7c] Mazur's investigation appears to be the only previous kinetic isotope effect (KIE) study reported for a [1,7]-sigmatropic shift. At least qualitatively, the thermal results for the *cis*-isotachysterols (Scheme I) suggested more normal primary KIE's. It was of interest therefore to examine the isomerization of **1**, **7**, **4**, and **10** quantitatively.

In the initial study, the kinetics of the thermal isomerization of the unlabeled isomers **1** and **4** were examined. Studies were conducted at four different temperatures (~67–98 °C) in a manner completely analogous to that previously reported by Onisko et al. for the parent system **13**,[10a,b] which possesses a 3*S*-hydroxyl rather than an allylic 1*S*- or 1*R*-hydroxyl (**1** and **4**, respectively) as in this study. The kinetic data and activation parameters from this investigation are summarized in Table II. For the four processes, **1** to **2**, **1** to **3**, **4** to **5**, and **4** to **6**, the enthalpies of activation are in the range 21.0–23.5 kcal/mol. The entropies of activation vary from −19.9 to −16.1 cal/mol K. These results are in good agreement with those of Onisko et al. who reported activation parameters of 23.0–23.2 kcal/mol and −16.3 to −17.1 cal/mol K, respectively, for the corresponding isomerization of **13** to **14** and **13** to **15**.[10b] For the transformation of previtamin D_3 (**35**) to vitamin D_3 (**36**), skeletally different systems, the corresponding parameters were 18.5 kcal/mol and −21.8 cal/mol K, respectively.[7a]

A particularly interesting consequence of these investigations of unlabeled *cis*-isotachysterols **1** and **4** concerns the effect of the allylic hydroxyl on the preferred helicity (a π-radical selectivity effect)[22] of the antarafacial [1,7]-sigmatropic shift. Comparisons were made at 98.36 °C, the highest temperature studied,[23] and the results are summarized in Table III. Referring to Scheme I and the π-facial selectivity computation in Table III, the 15α-hydrogen of **1** migrates antarafacially to C-10 in a manner syn to the (1*S*)-hydroxyl faster than the 15β-hydrogen of **1** to C-10 anti to the (1*S*)-hydroxyl by a factor of 2.8 (i.e., **1** to **3** is faster than **1** to **2**). The reverse processes are correspondingly faster (i.e., **3** to **1** is faster than **2** to **1**) by a factor of 3.6. That is, the kinetically favored trajectory for the antarafacially migrating hydrogen is syn to the neighboring hydroxyl, and this is represented

Table III. Kinetic and Equilibrium Data and π-Facial Selectivities

1*S*-Alcohols	
$k_{1,2} = 5.82 \times 10^{-5}$ [a]	$k_{1,3} = 16.5 \times 10^{-5}$ [a]
$K_{1,2} = 3.80$ [b]	$K_{1,3} = 3.02$ [b]
$k_{2,1} = 1.53 \times 10^{-5}$ [c]	$k_{3,1} = 5.46 \times 10^{-5}$ [c]
1*R*-Alcohols	
$k_{4,5} = 21.9 \times 10^{-5}$ [a]	$k_{4,6} = 3.77 \times 10^{-5}$ [a]
$K_{4,5} = 3.61$ [d]	$K_{4,6} = 3.33$ [d]
$k_{5,4} = 6.06 \times 10^{-5}$ [c]	$k_{6,4} = 1.13 \times 10^{-5}$ [c]
π-Facial Selectivity Calculations[e]	
$k_{1,3}/k_{1,2} = 2.84$ (±0.88)[c]	$k_{4,5}/k_{4,6} = 5.81$ (± 1.02)[c]
$k_{3,1}/k_{2,1} = 3.57$ (± 1.13)[c]	$k_{5,4}/k_{6,4} = 5.36$ (± 0.75)[c]

[a] Data (98.36 ± 0.05 °C) from Table II and the Supplementary Material Section. The equilibrium and the first-order rate constants (s^{-1}) are defined in Scheme I. [b] At equilibrium (98.36 °C, ~40 h): 48.2% **3**, 12.7% **1**, and 38.4% **2** [in good agreement with previously reported data (ref 9b of text): 49% **3**, 14% **1**, and 36% **2**]. [c] Calculated from the appropriate $k_{i,j}$ and $K_{i,j}$ in this table. [d] At equilibrium (98.36 °C, ~40 h): 41.9% **6**, 12.6% **4**, and 45.5% **5** [in good agreement with previously reported data (ref 9b of text): 42% **6**, 13% **4**, and 45% **5**]. The equilibrium constants $K_{i,j}$ were computed from these data. [e] The uncertainties are maximum errors (absolute deviations from the mean). See ref 23 in the text.

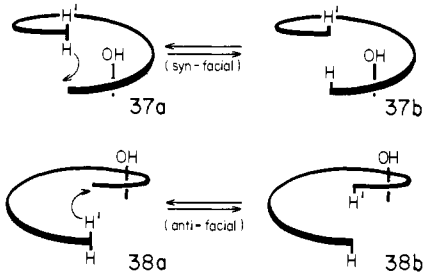

Figure 2. Helical representation of the antarafacial [1,7]-sigmatropic shift. The transformation of **37a** ⇌ **37b** is a schematic representation for **1** ⇌ **3** and **38a** ⇌ **38b** for **1** ⇌ **2**. In **37a** and **38a**, H′ and H represent the 15α- and 15β-hydrogens, respectively.

(22) π-Facial selectivity: (a) Inagaki, S.; Fujimoto, H.; Fukui, K. *J. Am. Chem. Soc.* **1976**, *98*, 4054. (b) Jones, D. W. *J. Chem. Soc., Chem. Commun.* **1980**, 739. (c) Gleiter, R.; Paquette, L. A. *Acc. Chem. Res.* **1983**, *16*, 328. (d) Brown, F. K.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 1971. (e) Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 2099. (f) Dolbier, W. R., Jr.; Koroniak, H.; Burton, D. J.; Bailey, A. R.; Shaw, G. S.; Hansen, S. W. *J. Am. Chem. Soc.* **1984**, *106*, 1871. (h) Washburn. W. N.; Hilson, R. A. *J. Am. Chem. Soc.* **1984**, *106*, 4575.

(23) The precision of the kinetic studies was hampered by an apparent instability of the triene reactants and/or products especially above ~100 °C and to a modest but acceptable extent at lower temperatures. Moreover, in the label studies, the prolonged reaction times necessary for equilibration prevented accurate determination of equilibrium constants and hence the $k_{i,j}$ (for the reverse process in Scheme I) values. Although satisfactory Arrhenius parameters (Table II) were obtained, the uncertainties obtained for the computed π-facial selectivities (Tables III) and KIE's (Table IV) were significant. Nevertheless, the data are satisfactory in regard to the discussion given in the text. Ultimately, for a more detailed mechanistic evaluation of [1,7]-sigmatropic shifts, a study of the temperature dependence of the primary kinetic isotope effect would be helpful, see: (a) Kwart, H. *Acc. Chem. Res.* **1982**, *15*, 401. (b) More O'Ferrall, R. A. *J. Chem. Soc. B* **1970**, 785. (c) Chrisope, D. R.; Beak, P. *J. Am. Chem. Soc.* **1986**, *108*, 334. Because of the limited temperature stability of the trienes described in this investigation, they are unlikely to be of further use in this regard. A search for new systems is in progress.

Table IV. Kinetic Isotope Effect Data[a]

substrate	$_{i,j}$[a]	$k_{i,j} \times 10^5$[a] (s^{-1})	k_H/k_D[b,c]
1	1,3	16.5	4.03 ± 0.62
7	7,9	4.09	
4	4,6	3.77	2.58 ± 0.55
10	10,12	1.46	

[a] Data (98.36 ± 0.05 °C) from Table II and the Supplementary Material Section. The first-order rate constants (s^{-1}) are defined in Scheme I of the text. [b] The uncertainties are maximum errors (absolute deviations from the mean). See ref 23 in the text. [c] Similar values can be calculated for the reverse processes if a negligible equilibrium isotope effect is assumed.

schematically in Figure 2. Structures **37** and **38** represent the two possible helical conformations of the heptatrienyl framework of **1** undergoing the two possible antarafacial shifts (**1** to **3** is represented by **37a** to **37b** and **1** to **2** by **38a** to **38b**) wherein the hydroxyl group is within the helix cavity (**37**) or outside of the cavity (**38**). The former is preferred kinetically in both the forward and reverse direction (**37a** ⇄ **37b** is faster than **38a** ⇄ **38b**). Precisely the same hydroxyl syn directive effect is observed for the epimeric alcohol series; **4** to **5** is faster than **4** to **6** by a factor of 5.8 and **5** to **4** is faster than **6** to **4** by a 5.4 factor. If one imagines each of the hydroxyl groups in Figure 2 inverted, the opposite helical arrangement for the [1,7]-sigmatropic shift is preferred (i.e., **38a** ⇄ **38b** is kinetically preferred over **37a** ⇄ **37b** for the epimeric carbinols). Thus, inversion of carbinol configuration (i.e., comparison of **1** vs. **4**) results in a 16.2-fold (2.8 × 5.8) reversal in preferred helicity handedness (comparing **37a** vs. the carbinol epimer of **38a**). For the reverse processes, a 19.4-fold factor (3.6 × 5.4) is observed. These correspond to $\Delta\Delta G^{\ddagger}$ differences of >2 kcal/mol for both the forward and reverse processes at the temperature (98 °C) studied.

It is most intriguing that for the corresponding six-electron suprafacial process, the thermal [1,5]-sigmatropic hydrogen shift, a neighboring allylic hydroxyl group exerts an anti directive effect.[24] Whether this reversal of π-facial selectivity by a neighboring hydroxyl on an eight-electron process ([1,7]-shift) vs. a six-electron process ([1,5]-shift) is a reflection of quantum mechanical alternation (i.e., the reversed stereochemical result observed between $4n$ and $4n + 2$ electron pericyclic processes) or some other factor remains to be further delineated. A recent theoretical treatment by Kahn and Hehre of this π-facial selectivity reversal by neighboring functional group makes a prediction in accordance with experiment.[25]

Finally, as summarized in Table IV, at 98.36 °C, the primary deuterium KIE could be determined for the processes **1** to **3** (**7** to **9**) and **4** to **6** (**10** to **12**), and the values were 4.0 and 2.6, respectively. The magnitude of these KIE's (4.0 and 2.6)[23] are relatively unexceptional and *about an order of magnitude smaller than the value of ~45* reported[7c] for the parent previtamin D_3 to vitamin D_3 transformation (Scheme VI). Studies are currently in progress in this laboratory to prepare a 19,19,19-trideuterio previtamin D_3 (**35** and analogues) to not only reexamine the validity of the exceptional $k_H/k_D \sim 45$ value previously reported[7c] but also to consider the intriguing question of the biological mechanism of the metabolic transformation of previtamin D_3 (**35**) to vitamin D_3 (**36**). A thermally more stable variant of previtamin D_3 by virtue of a KIE would be a most useful biochemical research tool.

(24) (a) Okamura, W. H. *Acc. Chem. Res.* **1983**, *16*, 81. (b) See, also: ref 1, 9, and 17. (c) Mouriño, A.; Lewicka-Piekut, S.; Norman, A. W.; Okamura, W. H. *J. Org. Chem.* **1980**, *45*, 4015. (d) Leyes, G. A.; Okamura, W. H. *J. Am. Chem. Soc.* **1982**, *104*, 6099. (e) Haces, A.; Okamura, W. H. *J. Am. Chem. Soc.* **1982**, *104*, 6105.

(25) Theoretical models for these [1,5]- and [1,7]-hydrogen shifts have been constructed in the 3-21G level transition structure. The experimentally observed preference for suprafacial [1,5]-sigmatropic migration to ocur anti to an electronegative hydroxyl and preference for antarafacial [1,7]-sigmatropic migration to occur syn to an electronegative hydroxyl are explained in part by an electrostatic model by Hehre and Kahn (Hehre, W. J.; Kahn, S. D. University of California, Irvine, unpublished studies). We are grateful to Professor Hehre for valuable discussions.

Summary

The antarafacial stereochemistry of the thermal [1,7]-sigmatropic hydrogen shift has been demonstrated for the first time.[2] When a cisoid heptatrienyl framework is constrained to, for example, a seven-membered ring,[26] a system capable of undergoing a suprafacial but not an antarafacial [1,7]-shift, thermolysis leads to an allowed suprafacial [1,5]-sigmatropic shift instead. The acyclic heptatrienyl framework characteristic of the systems **1–12** examined in this study are in principle capable of undergoing suprafacial [1,7]-shifts, but the antarafacial topography (Figure 2) appears sterically less demanding. Despite the antarafaciality predicted by orbital symmetry considerations,[3a] there would appear to be no simple way to avoid a built in bias for the thermal antarafacial topography. To this extent, it would appear difficult to imagine designing a system with equivalent steric constraints, unbiased topographically either for the suprafacial or antarafacial *thermal* pathways.

Finally, regarding the matter of the profound influence of a neighboring allylic hydroxyl on the π-facial selectivity of [1,5]- and [1,7]-sigmatropic shifts and the question of the interpretation of kinetic isotope effects in this series, a secure interpretation is not yet available. It remains for future studies to delineate the detailed facets of these phenomena for [1,*j*]-sigmatropic shifts and possibly other pericyclic processes.

Experimental Section

De-*A*,*B*-8-(trimethylsiloxy)cholest-8(14)-ene (17). To a dry, 100-mL round-bottomed flask equipped with a magnetic stirring bar and nitrogen inlet was added Grundmann's ketone **16** (8.77 g, 33 mmol), hexamethyldisilazane (5.8 g, 7.6 mL, 36 mmol), lithium iodide (4.8 g, 36 mmol), chlorotrimethylsilane (3.9 g, 4.6 mL, 36 mmol), and dry CH_2Cl_2 (30 mL). The flask was covered (to keep out light) and vigorously stirred at ambient temperature under an atmosphere of nitrogen for 18 h. To this light brown solution was added dry triethylamine (5 mL), and the resulting mixture was poured into a beaker containing a stirred ice-cold 7% solution of aqueous $NaHCO_3$ (100 mL) and ether (50 mL). Separation of the organic layer followed by a brine wash (25 mL), and drying over K_2CO_3 gave an orange solution. Concentration yielded a dark orange oil, which upon distillation (Kugelrohr, 0.25 mm, 140 °C) yielded 10.6 g (96% yield) of the desired silyl enol ether **17** as a light yellow liquid.

De-*A*,*B*-cholest-14-en-8-one (18). To a dry, 25-mL flask containing dry THF (10 mL) was added silyl enol ether **17** (2.3 g, 6.8 mmol) and dry pyridine (0.6 mL, 7.5 mmol). The reaction mixture was cooled to −78 °C and benzeneselenenyl chloride (1.4 g, 7.5 mmol) in THF (4 mL) was added via cannula. After stirring at −78 °C for 10 min, the reaction mixture was poured into 15 mL of acidic (HCl) brine and extracted with CH_2Cl_2. After having been dried over Na_2SO_4, the organic layer was concentrated to yield a yellow oil. Although the selenide could be purified by flash chromatography (5% EtOAc–lbpe) (lbpe, 30–60 °C low boiling petroleum ether), the crude selenide (CH_2Cl_2, 50 mL, 0 °C) was normally directly oxidized with *m*-chloroperoxybenzoic acid (MCPBA, 85% titer, 3.2 g, 16 mmol; added in 1 portion). After having been stirred at 0 °C for 5 min, the cooled mixture was poured into basic (NaOH) brine, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (10 mL). The combined organic extracts were washed with acidic (HCl) brine, dried over Na_2SO_4, and concentrated to give a dark oil. Purification of the crude oil by flash chromatography (5% EtOAc–lbpe) gave the enone **18** (1.3 g, 71% yield) as a light yellow oil.

(8*R*)-De-*A*,*B*-cholest-14-en-8-ol (19) and the C_8 Epimer. Into a dry, 100-mL, round-bottomed flask equipped with a magnetic stirring bar was placed enone **18** (0.82 g, 3.1 mmol), cerium(III) chloride (heptahydrate, 0.5 g, 1.4 mmol), and 50 mL of distilled methanol. The mixture was then cooled to 0 °C, and $NaBH_4$ (~0.25 g) was added in small portions until the reaction mixture no longer foamed on addition of borohydride. The reaction was then cautiously quenched with 20 mL of 1 M HCl, and the resulting mixture was extracted with 3 50-mL portions of ether. The combined ether extracts were dried over Na_2SO_4, filtered, and concentrated to give a yellow oil. Flash chromatography (20% EtOAc–lbpe) gave the desired alcohol **19** as a clear liquid (0.76 g, 94% yield). HPLC analysis (Partisil, 20% EtOAc-SSB, 3 mL/min) indicated the 8α:8β alcohol ratio to be >200:1 (uncalibrated; retention times, 22.5 and 20.0

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min, respectively). Essentially similar results were obtained in the absence of cerium chloride.

Treatment of enone **18** (789 mg, 3 mmol) in hexanes (15 mL) with diisobutylaluminum hydride (20% by weight in hexanes; 5 mL, ~5 mmol) at −78 °C (1 h) and then at room temperature (4 h) was followed by addition of ethyl formate (4 mL). After 5 min at room temperature, the mixture was treated with NH_4Cl and then with 1 M HCl (80 mL). Ether extraction followed by conventional workup, and then flash chromatography afforded a mixture containing comparable amounts of the epimeric alcohols. A small portion was subjected to HPLC (M-9 Whatman Partisil column, 20% EtOAc-SSB, 4 mL/min) to afford β- (C_8 epimer of **19**; retention time, 13 min) and α-alcohols (**19**; retention time, 16 min) in a 1:1 ratio.

LIS studies using tris(2,2,6,6-tetramethyl-3,5-heptanedionato)europium [Eu(thd)$_3$] were carried out. ^1H NMR samples (~0.1 M) of the epimeric alcohols in dry $CDCl_3$ were prepared, and the C_{18} angular methyl group chemical shifts were determined (β, 224.2 Hz; α, 172.0 Hz) at 200 MHz. After each incremental addition of Eu(thd)$_3$ (3–5 mg per increment), the C_{18}-methyl group chemical shift was determined. A titration plot extrapolated to a 1:1 mole ratio of Eu(thd)$_3$/alcohol for each sample afforded ΔHz values of 1405 and 378 Hz for β- and α-alcohols, respectively. This result and the hydrogenation results described below confirm the β- and α-OH configurational assignments.

(8*R*,14*R*,15*S*)-De-*A*,*B*-14,15-dideuteriocholestan-8-ol (20). Into a dry, 100-mL flask equipped with a magnetic stirring bar was placed Wilkinson's catalyst ($RhCl(PPh_3)_3$, 0.20 g) and dry, deoxygenated benzene (15 mL). After connection to a hydrogenation system, the mixture was degassed (water aspirator vacuum) and flushed with deuterium gas (99.7% d) 3 times. The allylic alcohol **19** (1.2 g, 4.4 mmol) in dry, deoxygenated benzene (10 mL) was added to the catalyst solution, and the ensuing reaction mixture degassed and flushed with deuterium gas one additional time. The system was then charged with deuterium gas, and the mixture was allowed to stir under a positive pressure at ambient temperature. After 21 h, TLC (20% EtOAc–lbpe) indicated the reaction was essentially complete. The reaction was then filtered through a sintered glass funnel containing a CH_2Cl_2 slurry of Celite covered with a CH_2Cl_2 slurry of Florisil. The Florisil–Celite pad was rinsed with 3 15-mL portions of CH_2Cl_2, and the combined organic layers were concentrated to give a dark oil. Flash chromatography (20% EtOAc–lbpe) followed by HPLC (20% EtOAc–SSB, Partisil M-90, 3.0 mL/min) gave 0.99 g (85% yield) of the desired deuteriated alcohol **20** (14*R*,15*S*-isomer) as a light yellow liquid. In addition, a small amount of the 14*S*,15*R* dideuterio alcohol was obtained; the ratio of this specie to the desired product was <1:37 based on HPLC-RI peak ratios.

(14*R*,15*S*)-De-*A*,*B*-14,15-dideuteriocholestan-8-one (14α,15α-Dideuterio Grundmann's Ketone, 21). In a dry, 10-mL, round-bottomed flask equipped with a magnetic stirring bar and nitrogen inlet was placed the dideuteriated 8α-alcohol **20** (0.32 g, 1.2 mmol), pyridinium trifluoroacetate (0.13 g, 0.67 mmol), and 5 mL of dry, distilled CH_2Cl_2. Pyridinium dichromate (1.3 g, 3.5 mmol) was then added, and the mixture was allowed to stir at ambient temperature for 12 h. The reaction mixture was then filtered through a short column of silica gel, and the column was rinsed with 75 mL of CH_2Cl_2. Concentration, followed by Chromatotron purification (2-mm silica-coated rotor, 20% EtOAc–lbpe, fastest moving band) gave the pure ketone **21** as a light yellow oil (0.29 g, 91% yield).

14α,15α-Dideuterio-de-*A*,*B*-8α-ethynylcholestan-8β-ol (22). This compound was prepared as previously reported for the unlabeled derivative of **22**.[9b] Thus, 14α,15α-dideuterio Grundmann's ketone (**21**) (0.265 g, 1.0 mmol) gave, after reaction with lithium acetylide and purification, 0.283 g (97%) of the labeled ethynyl alcohol **22**.

De-*A*,*B*-8-ethynylcholest-8(14)-ene (23a) and Its 15α-Deuterio Derivative 23b. To a dry, nitrogen-flushed, 10-mL flask was added the unlabeled derivative of ethynyl alcohol **22** (0.24 g, 0.83 mmol) and 5 mL of dry pyridine. After having cooled the mixture to 0 °C, $SOCl_2$ (0.09 mL, 1.24 mmol) was added, and then the mixture was allowed to stir at 0 °C for 30 min. The reaction mixture was then quenched at 0 °C with 1.5 mL of H_2O and then extracted with 50 mL of ether. The ether layer was washed with 30 mL of 1.2 M HCl followed by 30 mL of basic ($NaHCO_3$) brine. After drying over Na_2SO_4, the solvent was removed to give an orange oil. The crude product was chromatographed through a short column of silica gel with 100 mL of lbpe to afford upon concentration a light yellow oil. Chromatotron purification (2-mm silica-coated rotor, lbpe) gave the unlabeled enyne **23a** as a clear oil (0.15 g, 0.56 mmol, 67% yield). Only the $\Delta^{8,14}$-isomer was formed.

When this reaction was carried out on the 14α,15α dideuterio ethynyl alcohol **22** (0.187 g, 0.64 mmol), the enyne **23b** was obtained in 70% yield (0.123 g, 0.45 mmol) as a 7.5:1 mixture of the $\Delta^{8,14}/\Delta^{8,9}$ enynes. These enynes could be separated by reverse phase HPLC (Whatman ODS-2 M9 10/50 Partisil column, 100% CH_3CN, 4.0 mL/min) but were typically carried on without further separation as the mixture and separated at a later stage.

9,10-Secocholesta-5(10),8(14)-dien-6-yn-1-one (24a) and Its 15α-Deuterio Derivative 24b. To a solution of unlabeled enyne **23a** (0.30 g, 1.1 mmol) in ether (5 mL at 0 °C) was added dropwise *n*-butyllithium (1.0 mL, 1.54 mmol, 1.54 M in hexanes). After having been stirred at 0 °C for 25 min, 3-isobutoxy-2-methylcyclohex-2-en-1-one (0.5 g, 2.7 mmol) was added as the neat liquid, and the ensuing reaction was allowed to stir at ambient temperature for 2.5 h. The reaction was quenched by addition of 5 mL of 1 M HOAc. After having been stirred for 5 min, the aqueous layer was removed by pipet, and another 5-mL portion of 1 M HOAc was added to the reaction mixture. After having been stirred at ambient for 30 min, the layers were separated, and the aqueous layers were combined and extracted with 15 mL of ether. The ether layers were then combined and washed with 10 mL of 7% $NaHCO_3$ (aqueous) and then 10 mL of brine. After having been dried over Na_2SO_4, concentration gave a light yellow oil. Chromatotron purification (2-mm silica-coated rotor 10% EtOAc–lbpe) gave the desired dienynone as a clear liquid (0.36 g, 86% yield). When the reaction was carried out by using the corresponding 15α-deuterio enyne **23b** (0.100 g, 0.37 mmol), the corresponding labeled dienynone **24b** was obtained in 76% yield (0.110 g).

(6*Z*)-9,10-Secocholesta-5(10),6,8(14)-trien-1-one (25a) and Its 15α-Deuterio Derivative 25b. A solution of dienynone **24a** (0.55 g, 1.4 mmol), Lindlar catalyst (0.16 g), and quinoline (4 drops) in benzene (12 mL) was exposed to hydrogen gas until absorption decreased (2.5 h, room temperature). The solution was filtered, and then the vacuum dried residue was subjected to HPLC (5% EtOAc/SSB, 3.0 mL/min, Partisil M-9 column) to afford after concentration the known *cis*-isotachysterone **25a** (0.37 g, 67%) as an oil. The corresponding 15α-deuterio dienynone **24b** (80 mg, 0.20 mmol; also 40-mg catalyst, 4 drops of quinoline and 5 mL of benzene) reacted in the same manner gave 51.6 mg (66% yield) of the desired 15α-deuterated *cis*-isotachysterone **25b**.

(1*S*,6*Z*)- and (1*R*,6*Z*)-1-Hydroxy-9,10-secocholesta-5(10),6,8-(14)-triene (1 and 4, Respectively) and the Corresponding 15α-Deuterio Derivatives 7 and 10, Respectively. The unlabeled *cis*-isotachysterone **25a** (138 mg, 0.35 mmol) and $CeCl_3{\cdot}7H_2O$ (0.2 g) in methanol (12 mL) were cooled to 0 °C, and then $NaBH_4$ (0.5 g) was added in portions such that excessive foaming did not occur. Ice-cold 1.2 M HCl and then ether were added. After conventional workup, HPLC (M-9 Partisil, 3.0 mL/min, 10% EtOAc-SSB) of the resulting residue afforded pure 1*S*- (**1**; retention time, 24.8 min; 44.6 mg, 32%) and 1*R*-alcohols (**4**; retention time, 27.5 min; 72.5 mg, 53%) in 85% total yield. By a precisely analogous procedure, the 15α-deuterio derivative **25b** (50 mg, 0.13 mmol; also ~100 mg $CeCl_3{\cdot}7H_2O$, 2 mL of CH_3OH and 200 mg of $NaBH_4$) afforded 18.5 mg (36%) of 1*S*- and 26.7 mg (52%) of 1*R*-alcohols (**7** and **10**, respectively; 88% total yield).

De-*A*,*B*-14β,15β-oxidocholestan-8-one (26). In a dry, nitrogen-flushed, 300-mL, round-bottomed flask containing a magnetic stirring bar was placed 1.80 g of enone **18** (6.9 mmol) and 69 mL of methanol. The solution was cooled to 0 °C and then stirred while 3.5 mL of 1 M NaOH solution (3.5 mmol) was added. The solution turned bright yellow. After slowly adding 1.8 mL of 30% H_2O_2 solution (20.7 mmol), the reaction mixture was stirred at 0 °C for 15 min and then at room temperature for 7.5 h. Analysis by TLC (20% EtOAc–lbpe) revealed the absence of starting material and the appearance of a new more polar spot. The reaction mixture was directly extracted with 3 × 100 mL of ether. The ether layers were combined, washed with water (3 × 250 mL) and brine (1 × 200 mL), and then dried over $MgSO_4$. Removal of solvent left a residue of the epoxy ketone **26** (1.11 g, 57%) sufficiently pure for use in the next step. For further purification the material was distilled (130–135 °C, 0.10 mmHg) on a Kugelrohr.

(15*R*)-De-*A*,*B*-cholest-8(14)-en-15-ol (27). In a 10-mL flask (nitrogen atmosphere) was placed epoxy ketone **26** (20 mg, 0.072 mmol) and a magnetic stirring bar. Upon adding hydrazine hydrate (1 mL, 20.6 mmol) at room temperature, the yellow epoxy ketone appeared to be insoluble, but some gas evolution was observed. After 10 min of stirring at room temperature, the reaction was heated slowly (40 min) to reflux (120 °C) and kept at reflux for 15 min. The epoxy ketone dissolved as the temperature increased. After cooling, the reaction mixture was diluted with 35 mL of ether, and then the solution was washed with water (3 × 20 mL) and brine (1 × 20 mL) and then dried over $MgSO_4$. Filtration and removal of solvent yielded 19 mg (100%) of **27** which could be further purified by distillation (130–135 °C, 0.15 mmHg).

(15*S*)-De-*A*,*B*-cholest-8(14)-en-15-ol Benzoate (28). In a dry, nitrogen-flushed, 25-mL round-bottomed flask was placed the allylic alcohol **27** (293 mg, 1.11 mmol), triphenylphosphine (recrystallized from EtOH, 320 mg, 1.22 mmol, 1.1 equiv), and 5.5 mL of dry benzene (freshly distilled from $LiAlH_4$ under nitrogen). In a separate 10-mL flask was placed benzoic acid (149 mg, 1.22 mmol, 1.1 equiv) dissolved in 2.2

mL of dry benzene. In a third flask was placed diethyl azodicarboxylate (DEAD) diluted with dry benzene to give a 0.55 M solution. To the alcohol **27**–triphenylphosphine solution was added the benzoic acid–benzene solution at once and then the DEAD solution (2.22 mL, 0.55 M solution, 1.22 mmol, 1.1 equiv) was added dropwise at room temperature. The solution was stirred for 3 h at room temperature. The solvent was removed leaving a yellow solid, which was washed with 5% EtOAc–lbpe. The EtOAc–lbpe rinsing was filtered through a small column of silica gel (1 in. × 3 in.) to yield a yellow oil after removal of the solvent. Chromatography on reversed phase HPLC (40% acetone/60% MeOH, ODS-2 column, 3.0 mL/min) afforded after vacuum concentration pure benzoate **28** as an oil (77 mg, 19%).

(15*S*)-De-*A*,*B*-cholest-8(14)-en-15-ol (29). Into a dry, 50-mL flask equipped with a magnetic stirring bar, rubber septum, and nitrogen inlet was added the benzoate **28** (59 mg, 0.16 mmol) and then 5% KOH in methanol (10 mL). The reaction was stirred (nitrogen) at room temperature for 5.5 h. The reaction mixture was extracted with ether (3 × 10 mL), washed with water (10 mL), aqueous $NaHCO_3$ (10 mL), and aqueous NaCl (10 mL), and then dried over $MgSO_4$. The solvent was removed, and the residue was subjected to HPLC (10% EtOAc–SSB, 4.0 mL/min, normal phase) to yield the C-15 inverted alcohol **29** (31.9 mg, 75% yield).

De-*A*,*B*-cholest-8(14)-en-15-one (30). Ten milligrams (0.038 mmol) of each allylic alcohol (15*S*-**29** and 15*R*-**27**) were placed in separate dry flasks equipped with a magnetic stirring bar and a rubber septum. After flushing the flasks with dry nitrogen, lbpe (2 mL) and MnO_2 (33 mg, 0.38 mmol) were introduced. After 1 h of stirring at room temperature, TLC (5% EtOAc–lbpe) revealed the absence of starting material in the 15*S*-alcohol **29** reaction mixture. After 4 h, TLC (5% EtOAc–lbpe) revealed the absence of starting material in the 15*R*-alcohol **27** reaction mixture. Each reaction was worked up separately as follows. The mixture was filtered through a sintered glass filter (filled with layers of Celite at the bottom, silica gel in the middle, and $MgSO_4$ at the top) with ether. The filtrate was concentrated leaving a yellow residue. The residue was dissolved in ether, the solution was dried over $MgSO_4$ and filtered, and then the solvent was evaporated under vacuum. The ^1H NMR spectra of the crude residue showed no signals attributable to starting alcohol in either case. The residue was then filtered through a short column of silica gel (1/2 in. × 6 in., 5% EtOAc–lbpe) and then concentrated. The residue was subjected to a final HPLC purification (5% EtOAc–SSB, 4.0 mL/min) to yield 7.5 (75%) and 7.8 mg (79%) of unsaturated ketone **30** from the 15*R*- and 15*S*-alcohols, respectively. The ketones exhibited identical ^1H NMR and ^{13}C NMR spectra as well as identical chromatographic behavior.

^1H NMR LIS Study of (15*R*)- and (15*S*)-De-*A*,*B*-cholest-8(14)-en-15-ol (27 and 29, Respectively). The 15*R*-alcohol **27** (20.2 mg, 0.08 mmol in 0.5 mL dry $CDCl_3$) and the 15*S*-alcohol **29** (22.6 mg, 0.09 mmol in 0.6 mL dry $CDCl_3$) were each placed in NMR tubes. The ^1H NMR spectrum (90 MHz) was recorded, and then each sample was treated with a carefully measured amount (2–4 mg) of tris(2,2,6,6-tetramethyl-3,5-heptanedionato)europium [Eu(thd)$_3$], and the spectrum was recorded again. Additional quantities of shift reagent were added followed by recording of the spectrum until a Eu(thd)$_3$/alcohol mole ratio of 0.6 was reached. The initial chemical shifts at 90 MHz of the C_{18}–Me groups were 99 and 81 Hz for the 15*R*- and 15*S*-alcohols, respectively. At the 0.6 Eu(thd)$_3$/alcohol mole ratio, the downfield chemically shifted values were 276 and 162 Hz, respectively, relative to $(CH_3)_4Si$. These values correspond to Δ(Hz) values of 126 and 81 Hz for the β-15*R*- and α-15*S*-alcohols, respectively, consistent with their stereochemical assignments.

(8ξ_1,14*R*)- and (8ξ_2,14*R*)-Cholestane-8,14-diol (31a) and the 15α-Deuteriated Derivatives 31b. In a dry (nitrogen atmosphere, magnetic stirring bar) 50-mL flask was introduced $LiAlH_4$ (43 mg, 1.1 mmol) followed by dry THF (3 mL). The epoxy ketone **26** (31 mg, 0.11 mmol) in THF (3 mL) was transferred (syringe) to the $LiAlH_4$ solution at room temperature. Additional quantities of THF (3 × 1 mL) were used for rinsings to ensure complete transfer. The reaction mixture was stirred at reflux (4 h) until TLC (20% EtOAc–lbpe) indicated an absence of starting material. The cooled mixture was quenched by the dropwise addition of aqueous NH_4Cl solution (2 mL). The solution was decanted, and the remaining solids were washed with ether (15 mL). The solid material was dissolved in 1 M HCl (20 mL), and then the aqueous solution was extracted with ether (3 × 20 mL). The ether layers were combined, washed with aqueous $NaHCO_3$ (30 mL) and brine (30 mL), and then dried over $MgSO_4$. Concentration followed by distillation (165–170 °C, 0.1 mmHg) afforded the two diols **31** (31 mg, ~ quantitative yield) as a mixture.

For preparative purposes, the mixture of diols **31** without separation is best oxidized to the pure acyloin **32**. The diol mixture **31** could, however, be separated by HPLC (40% EtOAc–SSB, normal phase Partisil column, 5.0 mL/min). The minor, less polar isomer (8ξ_1,14*R*) eluted first followed by the major, more polar isomer (8ξ_2,14*R*) in a 1:16 ratio (uncorrected RI detector response). The minor isomer was contaminated by 10–20% of the major isomer, but the latter was obtained pure (^1H and ^{13}C NMR). Either isomer (viscous liquids) could be oxidized in acceptable yield to the same acyloin **32** as described below.

The epoxide **26** (390 mg, 1.4 mmol) in THF (2 mL) was reacted with $LiAlD_4$ (100 mg, 2.4 mmol) in THF (10 mL), and then the reaction mixture was worked up as above. The vacuum dried diol mixture **31b** (~quantitative yield) was subjected to Swern oxidation directly without further purification.

(14*R*)-De-*A*,*B*-14-hydroxycholestan-8-one (32) by Jones Oxidation. The Jones reagent consisted of $K_2Cr_2O_7$ (11.8 g), H_2O (120 mL), H_2SO_4 (57 mL), and glacial HOAc (36 mL). To a solution of major, more polar diol **31a** (8ξ_2,14*R*-isomer; 14 mg, 0.05 mmol) in acetone (5 mL) at 0 °C was added dropwise Jones reagent (0.36 mL). The green reaction mixture was diluted with water (5 mL) and then extracted with ether (5 × 20 mL). The ether extracts were combined, washed with aqueous $NaHCO_3$ (2 × 15 mL) and brine (15 mL), and then dried over $MgSO_4$. Concentration and then filtration of the residual oil through a short column of silica gel with ether removed excess chromium salts. Further concentration afforded a yellow oil, which upon HPLC purification (5% EtOAc–SSB, partisil, 4.0 mL/min) yielded the acyloin **32** as a homogeneous clear oil (9.5 mg, 68% yield). This material was identical (HPLC, ^1H NMR) with the product obtained from the Jones oxidation of the epimeric (8ξ_1,14*R*)-alcohol **31a**, which was oxidized as follows. To a solution of minor, less polar diol **31a** (4 mg, 0.014 mmol) in acetone (1.4 mL) at 0 °C was added dropwise Jones reagent (0.1 mL). After 1 min of stirring, the orange solution turned green, and then the mixture was diluted with water (5 mL). Workup as above yielded the same ketol (2.7 mg, 68% yield, determined by HPLC and ^1H NMR) identical with that described above. For preparative purposes, there is no need to separate the diols **31a** before oxidation to **32**.

(14*R*,15*S*)-De-*A*,*B*-15-deuteriocholestan-14-ol-8-one (33). Into a dry, 25-mL flask equipped with a magnetic stirring bar and nitrogen inlet was placed a solution of oxalyl chloride (0.36 g, 0.25 mL, 2.8 mmol) in CH_2Cl_2 (7 mL). The flask was cooled to −60 °C, and then a solution of dry dimethyl sulfoxide (Me_2SO, 0.44 g, 0.43 mL, 5.6 mmol) in CH_2Cl_2 (2 mL) was cautiously added via syringe over the course of 3 min. A vigorous evolution of gas occurred immediately upon the addition of the Me_2SO. After having been stirred at −60 °C for 3 min, deuteriated 8,14-diol **31b** (0.40 g, 1.4 mmol) in CH_2Cl_2 (2 mL) was added via cannula. After having been stirred further at −60 °C for 15 min, triethylamine (0.84 mL, 6 mmol) was added to the cold reaction mixture, which was kept at −60 °C for 5 min and then warmed to 22 °C over the course of 10 min. The thick reaction mixture was quenched with 5 mL of water and extracted with 3 15-mL portions of CH_2Cl_2, and then the separated organic layer was washed with brine. After having been dried over Na_2SO_4, the CH_2Cl_2 layer was concentrated to yield an evil smelling yellow oil. Flash chromatography (20% EtOAc–lbpe) gave the desired hydroxy ketone **33** (0.33 g, 83% yield) as a light yellow oil. Although the Jones procedure was successful in the unlabeled series, it failed in the labeled case.

Reduction of Ketol (32) to Grundmann's Ketone (16) and Its C-14 Epimer (Epi Grundmann's Ketone). Similar Reduction of Labeled 33 to 34. Hydroxy ketone **32** (23.3 mg, 0.083 mmol) was dissolved in acetic acid (1 mL) in a 10-mL flask equipped with a magnetic stirring bar and condenser. Five drops (~0.5 mL) of 57% hydriodic acid were added, and the brown solution was refluxed (30 min) until TLC (5% EtOAc–lbpe) indicated a complete disappearance of starting **32**. The red solution was poured into an ice cooled mixture of $NaHSO_3$ (0.5 g) and 1 M aqueous NaOH (5 mL). A small quantity of ether was used for rinsing. The colorless solution was then extracted with ether (4 × 20 mL). The combined ether extracts were washed successively with aqueous $NaHCO_3$ (3 × 25 mL) and brine (25 mL) and then dried over $MgSO_4$, filtered, and concentrated. The 200-MHz ^1H NMR spectrum of the crude residue disclosed a mixture of epi-Grundmann's and Grundmann's ketone **16** in a ~2.4:1 ratio. Separation by HPLC (5% EtOAc/SSB, Partisil M-9 column) yielded epi Grundmann's ketone (13.1 mg, 60% yield) and Grundmann's ketone **16** (5.4 mg, 25% yield) as clear oils (total yield, 85%). The ^1H NMR spectral properties and chromatographic behavior of the two ketones were identical with those of authentic specimens. This experiment establishes the structure of the ketol **32**.

The labeled hydroxy ketone **33** (244 mg, 0.87 mmol) and 57% hydriodic acid (1.5 mL) in acetic acid (10 mL) was reacted and then processed in a manner similar to that described above. Flash chromatography (20% EtOAc–lbpe) afforded a 71% yield of **34**, which could be used directly for transformation into **23b**.

Preparation of Labeled Enyne 23b from Epimeric Ketone Mixture 34. The labeled ketone mixture **34** (164 mg, 0.62 mmol) in THF (2 mL) was

reacted at −78 °C with lithium acetylide (100 mL of acetylene; *n*-BuLi, 1.0 mL, 1.5 M in hexanes; 15 mL THF) in the manner previously described.[17] After workup, the vacuum dried crude material (185 mg, ~0.63 mmol) in dry pyridine (5 mL) was treated with $POCl_3$ (1.0 mL, 93 μL/mmol, 10.8 mmol). After having refluxed the mixture for 6 h and then having stirred at room temperature for 12 h, standard workup afforded 103 mg (60% yield) of a mixture of enynes. The desired major enyne **23b** can be purified by reversed phase chromatography, but it is more efficient to couple this material via Scheme III and separate afterwards as described previously.[17]

Thermolysis of *cis*-Isotachysterols 1, 4, 7, and 10, Stereochemical and Kinetic Studies. Samples of the *cis*-isotachysterols were ascertained to be pure by HPLC (M-9 Partisil column, 3.0 mL/min flowrate, 10% EtOAc-SSB) and ^1H NMR and ^{13}C NMR spectra prior to the thermal investigations. The thermolysis solvent (spectral grade isooctane) was purified as previously described.[1] Isooctane stock solutions of **1**, **4**, **7**, and **10** were prepared under nitrogen at concentrations of ca. 2×10^{-3}–10^{-4} molar. From these stock solutions, 0.05-mL aliquots were taken and sealed under vacuum into 1 × 90 mm capillaries, which were stored at −80 °C until needed. The capillaries were fashioned from the narrow end of recleaned 9-in. disposable Pasteur pipets similar to that previously described.[1] For the kinetic studies, the sealed capillaries, after warming to ambient temperature, were placed in a thermostatically controlled oil bath (±0.05 °C) after temperature calibration. As the samples were removed after appropriate time intervals, the capillaries were stored at −80 °C until they were ready for analysis. Sample analyses were carried out by using HPLC with a UV detector set at 254 nm. The column was an analytical Waters μ-Porasil column (30 cm) with use of 1% isopropyl alcohol in Skellysolve B (SSB) as solvent and was calibrated with standard solutions of **1**–**6**. Table V in the Supplementary Material Section summarizes the data from 34 kinetic runs.

For the stereochemical studies, the product mixture from heating **7** (several capillaries were combined) for 26 h at 98.4 °C consisted of 22% **7**, 47% **9**, and 31% **8**; that from heating **10** under identical conditions consisted of 22% **10**, 15% **12**, and 63% **11**. Preparative separation was readily achieved by HPLC (Whatman M9 Partisil column, 10% EtOAc–hexanes). As summarized in Figure 1 and Table I, the deuterium analyses of the products **8**, **9**, **11**, and **12** were conveniently carried out by ^1H NMR integration of resonances assigned to H_1, $H_{6,7}$, H_{10}, and H_{15} of the products.

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Supplementary Material Available: Spectral and other experimental data (10 pages). Ordering information is given on any current masthead page.

^{13}C NMR Spectroscopy as a Biosynthetic Probe: The Biosynthesis of Purines in Yeast

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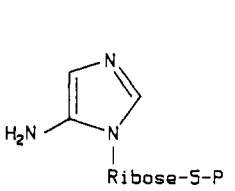
Abstract: It is shown by ^{13}C NMR spectroscopy that, in *Saccharomyces cerevisiae*, the skeleton of adenine and guanine arises from bicarbonate, which enters C-6, from formate, which enters C-2 and C-8, and from an intact glycine moiety, which gives rise to the C_2N unit, C-4, C-5, N-7. The findings substantiate general assumptions concerning the origin of the purines in yeast that had hitherto been based on fragmentary evidence. In *S. cerevisiae* the ring skeleton of the pyrimidine unit of vitamin B_1 (thiamin) and that of the purines do not originate from a common intermediate, unlike in bacteria where they do.

In *Salmonella typhimurium*,[1-5] and presumably in bacteria in general,[6] the pyrimidine unit **4** of thiamin is derived from 5-aminoimidazole ribonucleotide (AIR) (**1**), a compound that is an intermediate of purine biosynthesis.[7,8] Thus, in bacteria the biosynthesis of the thiamin pyrimidine unit is linked to that of the purines.

The pathway from AIR to the purines (e.g., guanine (**2**)) is well documented,[9,10] mainly on the basis of investigations with avian liver preparations. Individual steps of the pathway have been examined also in mammals (e.g., ref 11), bacteria (e.g., ref 12–15), and yeast,[14-17] and it is generally accepted[9,10] that the route from AIR to the purines is common to all organisms.



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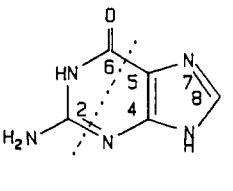

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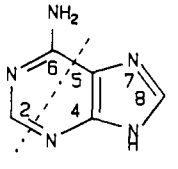

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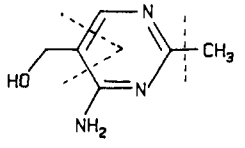

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