(Z)-9, 125972-66-9; (E)-9, 125972-80-7; 10, 1487-18-9; (Z)-11, 125972-67-0; (E)-11, 125972-81-8; 12, 1759-28-0; (Z)-13, 125972-68-1; (E)-13, 125972-82-9; (Z)-14, 125972-69-2; (E)-14, 125972-83-0; (Z)-15, 125972-70-5; (E)-15, 125972-84-1; 16, 271-89-6; 17, 125972-71-6; 18, 536-74-3; 19, 17257-10-2; 20, 4298-52-6; 21, 36687-75-9; 22, 125972-72-7; 23, 18649-64-4; 24, 125972-73-8; 25, 125972-74-9; 26, 125972-75-0; 27, 125972-76-1; 28, 125972-77-2; 30, 3437-95-4.

Hydroxyl-Directing Effects on [1,7]-Sigmatropic Hydrogen Migrations[1]

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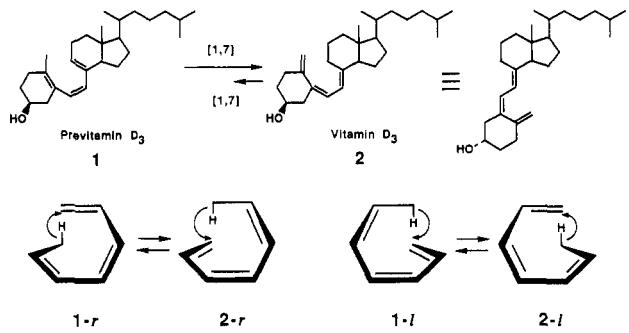
Previous stereomechanistic investigations of thermally induced [1,7]-sigmatropic shifts of *cis*-isotachysterol analogues **8** and **14** revealed that an allylic hydroxyl exerts a syn-directing effect on the helicity of this antarafacial process. Studies of *cis*-isotachysterols **17** and **18**, wherein the allylic hydroxyl control element at C_1 is relocated to a new position on the steroid, namely C_4, were undertaken to develop a better understanding of this eight-electron pericyclic reaction. The rearrangement in isooctane at 98.4 °C of **17** to **24** and **25** and of **18** to **26** and **27** and their equilibrations were studied quantitatively. The results reveal that the hydroxyl syn-facial directing effect on the antarafacial helicity of this rearrangement is retained for **17** and **18** and that the magnitude of this π-facial selectivity is similar to that observed for **8** and **14**.

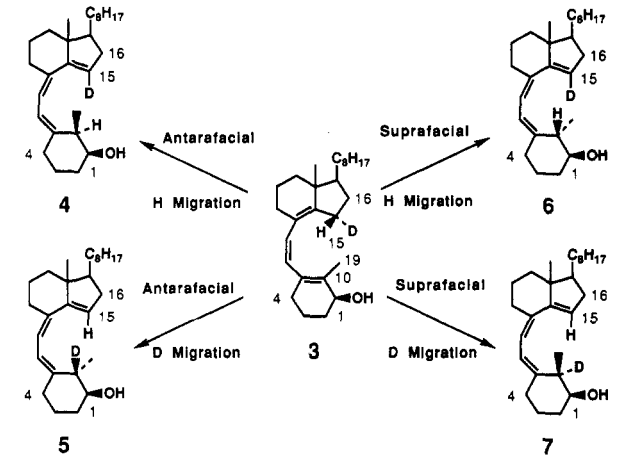
Introduction

The intramolecular nature of the thermal equilibrium between previtamin D_3 (**1**) and vitamin D_3 (**2**)[2] involving a [1,7]-sigmatropic hydrogen migration[3] (Scheme I) was established in 1965 by a tritium-labeling experiment.[4] In the same year Woodward and Hoffmann on the basis of orbital symmetry considerations predicted that thermal [1,7]-sigmatropic hydrogen shifts should be an antarafacial, allowed and suprafacial, forbidden process.[5] Thus for the rearrangement of **1** to **2**, the hydrogen transfer may occur either via the right-handed or left-handed helical pathway depicted as **1**-*r* to **2**-*r* or **1**-*l* to **2**-*l*. However, it was not until recently that the antarafaciality of this rearrangement process was demonstrated[6a,b] wherein an appropriate deuterium-labeling experiment was carried out. The *cis*-isotachysterol analogue **3** and its hydroxyl epimer (both with deuterium label at the C_{15}-α position) were synthesized and then their thermal rearrangements were studied. The antarafacial nature of this rearrangement was established by the finding that only **4** and **5** (and no **6** and **7**) were observed within experimental error (>98%) from thermolysis of *cis*-isotachysterol analogue **3** (Scheme II). Parallel conclusions were reached for the C_1 epimer of **3**.

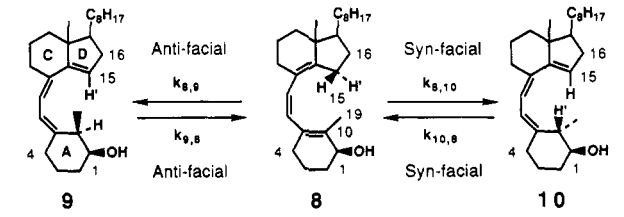
Scheme I



Scheme II



Scheme III



(1) (a) This is Paper 36 in the series Studies of Vitamin D (Calciferol) and Its Analogues. For paper 35, see: Okamura, W. H.; Aurrecoechea, J. M.; Gibbs, R. A.; Norman, A. W. *J. Org. Chem.* **1989**, *54*, 4072. (b) This paper was taken in part from the Ph.D. Thesis submitted to the University of California, Riverside, by K.-M. Wu, September, 1989.

(2) For selected studies of the previtamin D–vitamin D system, see: (a) Verloop, A.; Koevoet, A. L.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1957**, *76*, 689. (b) Havinga, E.; Schlatmann, J. L. M. A. *Tetrahedron* **1961**, *16*, 146. (c) Velluz, L.; Amiard, G.; Petit, A. *Bull. Soc. Chim. Fr.* **1949**, 501. (d) Havinga, E. *Experientia* **1973**, *29*, 1181. (e) Jacobs, H. J. C.; Havinga, E. *Adv. Photochem.* **1979**, *11*, 305. (f) Schlatmann, J. L. M. A.; Pot, J.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1964**, *83*, 1173. (g) Holick, M. F.; Frommer, J. E.; McNeill, S. C.; Richtand, N. M.; Henley, J. W.; Potts, J. T., Jr. *Biochem. Biophys. Res. Commun.* **1977**, *76*, 107. (h) Hanewald, K. H.; Rappoldt, M. P.; Roborgh, J. R. *Recl. Trav. Chim. Pays-Bas* **1961**, *80*, 1003. (i) Sheves, M.; Berman, E.; Mazur, Y.; Zaretskii, Z. V. I. *J. Am. Chem. Soc.* **1979**, *101*, 1882.

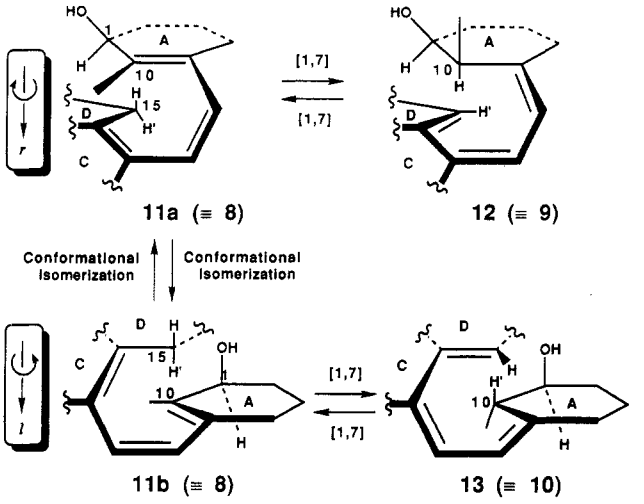
(3) For a general review of [1,*j*]-sigmatropic shifts, see: Spangler, C. W. *Chem. Rev.* **1976**, *76*, 187.

(4) (a) Akhtar, M.; Gibbons, C. J. *Tetrahedron Lett.* **1965**, *509*. (b) Akhtar, M.; Gibbons, C. J. *J. Chem. Soc.* **1965**, 5964.

(5) Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 2511.

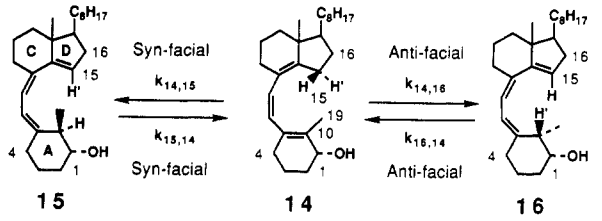
(6) (a) Hoeger, C. A.; Okamura, W. H. *J. Am. Chem. Soc.* **1985**, *107*, 268. (b) Hoeger, C. A.; Johnston, A. D.; Okamura, W. H. *J. Am. Chem. Soc.* **1987**, *109*, 4690. For other studies of [1,7]-sigmatropic hydrogen migrations, see: (c) Palenzuela, J. A.; Elnagar, H. Y.; Okamura, W. H. *J. Am. Chem. Soc.* **1989**, *111*, 1770. (d) Baldwin, J. E.; Reddy, V. P. *J. Am. Chem. Soc.* **1988**, *110*, 8223. (e) Baldwin, J. E.; Reddy, V. P. *J. Org. Chem.* **1988**, *53*, 1129. (f) Okamura, W. H.; Hoeger, C. A.; Miller, K. J.; Reischl, W. *J. Am. Chem. Soc.* **1988**, *110*, 973. (g) Baldwin, J. E.; Reddy, V. P. *J. Am. Chem. Soc.* **1987**, *109*, 8051. See also, ref 2–5.

Scheme IV[a]



[a] A, C, and D refer to standard steroid ring labels; the hydroxyl is located at C_1 which is allylic to the $\Delta^{5(10)}$ steroid double bond in **11a** and **11b** and the methyl is located at C_{10}.

Scheme V

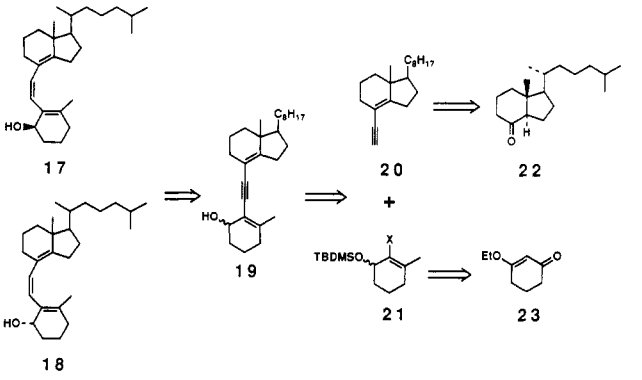


During the investigations of the thermally induced [1,7]-sigmatropic hydrogen shifts of the unlabeled *cis*-isotachysterol analogue **8** and its C-1 epimer (vide infra), an interesting syn-directing effect imparted by the neighboring hydroxyl group was detected. At 98 °C in isooctane, *cis*-isotachysterol analogue **8** was smoothly equilibrated with trienol **9** and **10** as depicted in Scheme III, wherein the ratio of the forward reaction rates ($k_{8,9}/k_{8,10}$) was determined to be 1.0/2.8 and the ratio of the reverse reaction rates ($k_{9,8}/k_{10,8}$) was found to be 1.0/2.3.[6b]

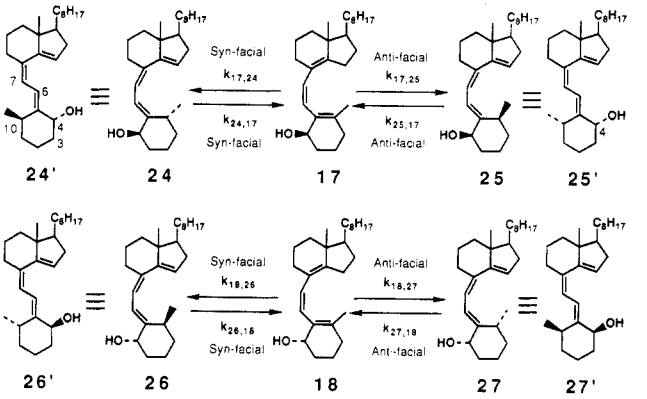
Structures **11a** and **11b** (Scheme IV) represent the two helical ground-state conformers of **8** involved in the [1,7]-shifts. These conformers correspond to the right-handed (*r*) and left-handed (*l*) helices, respectively. Antarafacial migration of H_β (labeled as H in Scheme IV) at C_{15} of conformer **11a** to the bottom face at C_{10} of the A ring anti to the hydroxyl group at C_1 gives **12** (same as **9**). On the other hand, antarafacial delivery of H_α (labeled as H′ in Scheme IV) of **11b** to the top face at C_{10} of the A ring syn to the neighboring hydroxyl group at C_1 leads to **13** (same as **10**). The observed rate constant ratio of 1.0/2.8 ($k_{8,9}/k_{8,10}$) indicates that the hydrogen prefers to migrate with a trajectory syn to the neighboring hydroxyl group. The same syn effect is true for the reverse process ($k_{9,8}/k_{10,8}$ ~ 1.0/2.3).

That the syn-directing effect imparted by the neighboring hydroxyl group is general was shown by an analogous study of the C_1 epimer of **8**, namely **14** (Scheme V). The C_{15}-H in *cis*-isotachysterol analogue **14** migrates faster syn to the C_1-OH relative to rearrangement of H′ (which migrates anti to the C_1-OH) by a rate ratio of 5.8/1.0 ($k_{14,15}/k_{14,16}$). The same effect was seen for the reverse process, namely **15** to **14** versus **16** to **14**, wherein the syn effect was dominant, affording a rate ratio of 5.4/1.0 ($k_{15,14}/k_{16,14}$).

Scheme VI



Scheme VII



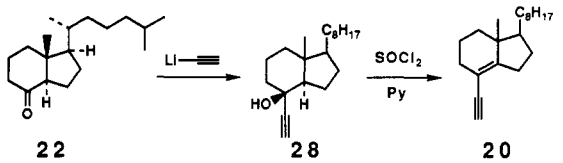
To summarize, it is helix **11b** (of *cis*-isotachysterol **8**) in Scheme III (the one with the hydroxyl group syn to the migrating hydrogen trajectory) that is favored over **11a** in the [1,7]-shift. And when the carbinol center (C_1) is inverted, as in Scheme V, it is the C_1-epimer of helix **11a** that is favored over the corresponding helical array **11b**. A study of the *cis*-isotachysterol analogue **17**, wherein the hydroxyl control element is relocated to C_4 from the previously evaluated C_1, and its hydroxyl epimer **18** was undertaken to develop a better understanding of this eight-electron pericyclic reaction. The trienols **17** and **18** were anticipated to be obtainable by catalytic Lindlar hydrogenation of a mixture of dienynols **19** followed by separation (Scheme VI). Palladium-catalyzed coupling of enyne **20** and a racemic mixture of protected alcohol **21** with a suitable leaving group followed by deprotection was expected to afford dienynol **19**. Synthesis of enyne **20** has been previously reported by this laboratory[6] from Grundmann's ketone (**22**) and the protected alcohol **21** was anticipated to be easily obtained from the keto enol ether **23**. It is hoped that the results of the thermal studies of **17** and **18** would stimulate further computational probing[7] of the origin of the π-facial selectivities involved in these [1,7]-shifts.

Results and Discussion

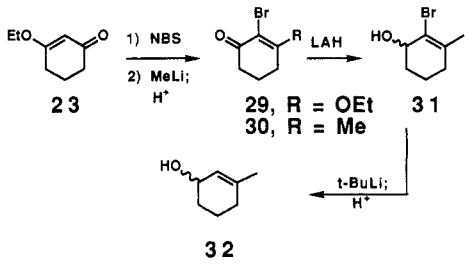
Syntheses of both optically active forms of the A ring **21** were ultimately developed to facilitate the preparation of diastereomerically pure trienols **17** and **18** and to assign the absolute configuration of the carbon bearing the hydroxyl group. It should be noted that establishment of the absolute configuration at C_4 is not really necessary to determine the degree of π-facial selectivity involved in the [1,7]-sigmatropic hydrogen shift. The ^{1}H NMR spectra

(7) Hess, B. A., Jr.; Schaad, L. J.; Pancir, J. *J. Am. Chem. Soc.* **1985**, *107*, 149.

Scheme VIII



Scheme IX

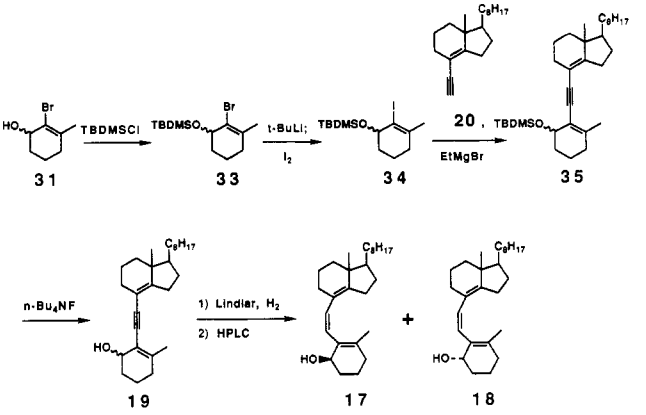


(±)-seudenol

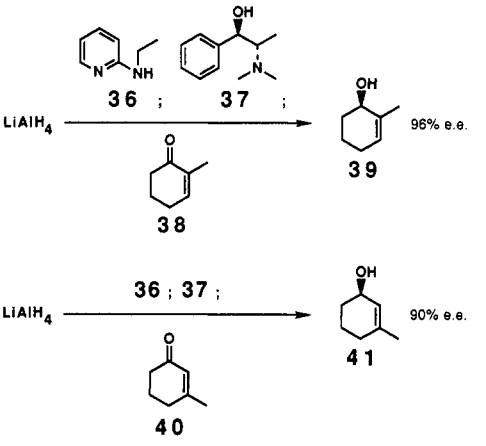
of two of the expected thermolysis products **24** and **26** (Scheme VII), which correspond to the products from syn-facial hydrogen migrations, are expected to exhibit larger peak widths[8] of their C_4 hydrogens than those of the products **25** and **27**, the products of anti-facial hydrogen migrations. By analogy with similar products derived from heating **8** (products: syn-facial, **10**; anti-facial, **9**) and **14** (products: syn-facial, **15**; anti-facial, **16**) (see Schemes III and V), the expected thermal products **24**–**27** (including **9**, **10**, **15**, and **16**) exist predominately in the 6-*s*-*trans* conformations **24′**–**27′** (Scheme VII). As a consequence of $A_{1,3}$ strain[9] between the C_{10}-methyl and C_7-H, these molecules all exist with the C_{10}-methyl axially disposed, presumably with chair-like A rings. As a further consequence, in the syn-facial products **24′** and **26′**, the C_4-hydroxyl groups are equatorially disposed and therefore the C_4-H's are axially disposed. By a similar analysis, in **25′** and **27′**, the anti-facial products, the corresponding C_4-H's are equatorially disposed. From the well-known larger coupling constants between vicinal pairs of axial protons relative to the smaller vicinal equatorial–axial and equatorial–equatorial couplings in cyclohexanes,[10] it follows that the peak widths of the observed H_4 signals should be larger (due to $J_{3,4}$) for syn-facial products **24′** and **26′** than for anti-facial products **25′** and **27′**. Despite the fact that knowledge of the absolute configuration at C_4 was not completely necessary for detecting π-facial selectivity, a knowledge of C_4 configuration is necessary for establishing the preferred sense (*r* or *l* as in Scheme IV; vide supra) of helicity. Accordingly, it was necessary to establish absolute stereochemistry.

The CD-ring enyne **20** (Scheme VIII)[6a,b] and the A-ring bromide **31** (Scheme IX)[11] were prepared as previously described. For stereochemical purposes, the plan was to prepare the optically active form of the bromo alcohol **31** and, therefore, it was first shown that reduction of (±)-**31**

Scheme X



Scheme XI



with *t*-BuLi gave racemic seudenol (**32**) (82%), an enantiomer of which is the pheromone of the Douglas fir beetle.[12]

The racemic bromo alcohol **31** was converted (Scheme X) to its *tert*-butyldimethylsilyl (TBDMS) ether **33** (93%), but despite extensive efforts, bromide **33** failed to couple to the alkynyl Grignard reagent of enyne **20**[13] wherein primarily starting **20** and **33** were obtained. However, the iodide **34** (54% from **33**)[14] did couple smoothly with the acetylenic Grignard reagent derived from **20** to afford the diastereomeric mixture **35** (contaminated by ~7% of the $\Delta^{8,9}$ isomers) (68%). The pure diastereomers of **35** were barely separated by a tedious HPLC shave–recycle technique, even by injecting only a few milligrams of material. The less polar diastereomer (later identified as (4*S*)-(+)-**35**) and the more polar diastereomer (later shown to be (4*R*)-(+)-**35**) were obtained in a ~1:1 ratio. Deprotection of the diastereomeric mixture of the dienyne **35** gave an inseparable diastereomeric mixture of dienynol **19** (72%). Lindlar catalytic hydrogenation followed by a difficult HPLC separation afforded a less polar trienol A [later determined to be 4*R*-(+) isomer **17** (49%)] and a more polar trienol B [later established as the 4*S*-(−) isomer **18** (41%)]. A synthesis utilizing the optically active forms of A-ring alcohol **31** was employed to minimize the sepa-

(8) (a) Condran, P., Jr.; Hammond, M. L.; Mouriño, A.; Okamura, W. H. *J. Am. Chem. Soc.* **1980**, *102*, 6259. (b) Hammond, M. L.; Mouriño, A.; Okamura, W. H. *J. Am. Chem. Soc.* **1978**, *100*, 4907. (c) Mouriño, A.; Okamura, W. H. *J. Org. Chem.* **1978**, *43*, 1653. (d) Okamura, W. H.; Hammond, M. L.; Rego, A.; Norman, A. W.; Wing, R. M. *J. Org. Chem.* **1977**, *42*, 2284. (e) Onisko, B. L.; Schnoes, H. K.; Deluca, H. F. *J. Org. Chem.* **1978**, *43*, 3441. (f) Verloop, A.; Corts, G. J. B.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1960**, *79*, 164.

(9) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.

(10) For example, see: Günther, H. *NMR Spectroscopy, An Introduction*; John Wiley: New York, 1980; pp 106–107.

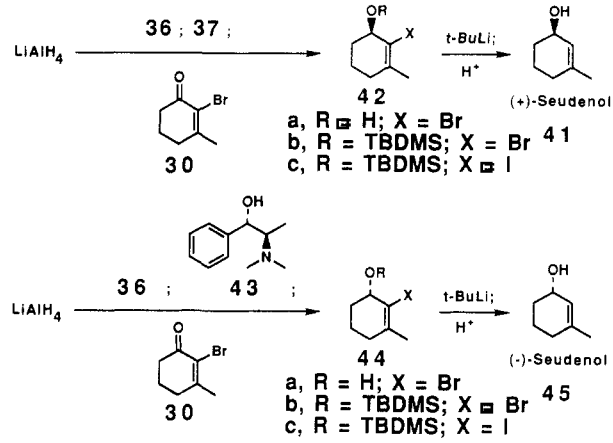
(11) (a) Belmont, D. T.; Paquette, L. A. *J. Org. Chem.* **1985**, *50*, 4102. (b) Paquette, L. A.; Zon, G. *J. Am. Chem. Soc.* **1974**, *96*, 224.

(12) Mori, K.; Tamada, S.; Uchida, M.; Mizumachi, N.; Tachibana, Y.; Matsui, M. *Tetrahedron* **1978**, *34*, 1901.

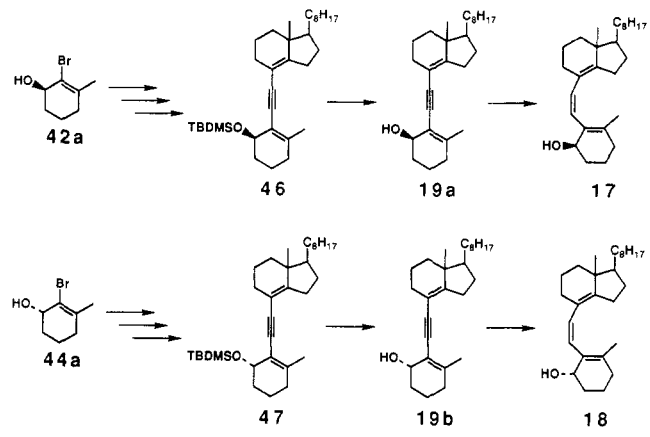
(13) For leading references, see: Chauhan, Y. S.; Chandraratna, R. A. S.; Miller, D. A.; Kondrat, R. W.; Reischl, W.; Okamura, W. H. *J. Am. Chem. Soc.* **1985**, *107*, 1028.

(14) Methanol-*d* quenching experiments indicated that metal–halogen exchange proceeded smoothly at −50 °C in about 1 h and the resulting vinyllithium was relatively stable at this temperature. Upon warming to −22 °C, almost all of the vinyllithium decomposed in 1 h.

Scheme XII



Scheme XIII



ration problems and to establish the C_4 absolute configuration, which, in turn, should also lead to assignment of the C_{10} configuration.

The procedure developed by Terashima[15] was chosen for enantioselective reduction of bromo ketone **30** since reduction of similar cyclohexenones such as **38** and **40** to **39** and **41**, respectively, with high degrees of optical purity had been achieved (Scheme XI). Both antipodes of *N*-methylephedrine (**37** and **43**) are commercially available and thus the necessary reagents (**36**, **37**, and **43**) are easily accessed.[15,16] The ketone **30** was converted to the optically enriched bromo alcohol **42a** (63%) as shown in Scheme XII. Debromination of **42a** by the same procedure as used for the racemic bromo alcohol **31** (Scheme IX) gave (*R*)-(+)-seudenol (**41**)[12] in 80% yield. The enantiomerically enriched bromo alcohol **44a** prepared similarly was unambiguously determined to possess the *S* configuration by its conversion to (*S*)-(−)-seudenol[12] (**45**) in 77% yield. The enantiomeric purities of the bromo alcohols **42a** (87% ee) and **44a** (89% ee) were based on lanthanide-induced shift (LIS) studies using tris[[(3-heptafluoropropyl)hydroxymethylene]-(+)-camphorato]europium(III) [Eu(hfc)$_3$] and the details are presented in the supplementary material section. LIS studies were also conducted on their reduction products **41** (89% ee) and **45** (88% ee), respectively, to further confirm the reliability of these determinations. Not only were the latter values in good agreement with those of the bromo compounds [(+)-**42a**, 87% ee; (−)-**44a**, 89% ee], they also agreed well with optical purities estimated by comparison of literature specific rotation values[12] with those obtained in this study [(+)-**41**, 85% ee; (−)-**45**, 88% ee].

Following the procedure for synthesis of the diastereomeric mixture of dienyne **35** described above, both optically active bromo alcohols **42a** and **44a** were converted (Scheme XIII) to the dienynes **46** (38%, three steps) and **47** (52%, three steps), respectively. The dienynes were further transformed into the trienols **17** (60%) and **18** (56%), respectively, thus also establishing the C_4 configurational assignments.

Each trienol was thermolyzed in refluxing isooctane under a nitrogen atmosphere to afford a mixture of **24** (22%), **17** (32%), and **25** (15%) from **17** and a mixture of **26** (25%), **18** (39%), and **27** (19%) from **18** (see Scheme VII). The ^{1}H NMR spectra of the individually purified

(15) Kawasaki, M.; Suzuki, Y.; Terashima, S. *Chem. Pharm. Bull.* **1985**, *33*, 52.

(16) Nakajima, K. *J. Chem. Soc. Jpn., Pure Chem. Sect.* **1960**, *81*, 1476. The reagents are also commercially available from the Aldrich Chemical Co.

Table I. Results for the Thermal [1,7]-Sigmatropic Hydrogen Shifts of *cis*-Isotachysterol Analogues 17 and 18

4*R*-OH isomers,[a] $\times 10^5$ s^{-1}		4*S*-OH isomers,[b] $\times 10^5$ s^{-1}	
$k_{17,24}$	10.1 ± 0.8[c]	$k_{18,26}$	10.6 ± 1.1[c]
$k_{24,17}$	14.4 ± 1.3[c]	$k_{26,18}$	21.7 ± 2.4[c]
$k_{17,25}$	4.92 ± 0.37[c]	$k_{18,27}$	2.53 ± 0.24[c]
$k_{25,17}$	10.7 ± 0.9[c]	$k_{27,18}$	5.68 ± 0.56[c]

[a] 98.5 ± 0.2 °C. [b] 98.42 ± 0.08 °C. [c] The mean of three separate runs together with the standard deviations.

compounds **24**–**27** were appropriately similar to those of trienols **9**, **10**, **15**, **16**, **49**, and **50**, which were characterized previously.[6a,b,8a,b,e] The ten thermally rearranged trienols (**9**, **10**, **15**, **16**, **24**, **25**, **26**, **27**, **49**, and **50**) all exhibit UV absorption maxima at ~273 nm, which is about 20 nm red-shifted from their corresponding starting *cis*-isotachysterol analogues (**8**, **14**, **17**, **18**, and **48**). As discussed above, **24** and **26**, the products of syn-facial migration, were expected to exhibit in their ^{1}H NMR spectra broader peak widths for the C_4-H signal than for **25** and **27**, the products of anti-facial migration. The more polar and less polar alcohols derived from heating **17** were thus assigned as **24** and **25**, respectively. The C_4 methinyl proton of **24** exhibits a peak width of 11.6 Hz, which is larger than that observed for **25** ($w_{1/2}$ = 7.1 Hz), clearly indicative of the former having a 10*R* configuration such that the C_4 methinyl proton occupies an axial orientation and the latter possessing a 10*S* configuration and an equatorially disposed C_4 methinyl proton. Similarly, the 10*S* configuration was assigned to **26** (more polar thermal product of **18**), which showed a larger C_4-H peak width ($w_{1/2}$ = 10.8 Hz), and 10*R* to **27** (less polar thermal product of **18**), which exhibited a smaller C_4-H peak width ($w_{1/2}$ = 7.2 Hz).

Kinetic Results for the Thermal Rearrangement of *cis*-Isotachysterol Analogues 17 and 18. The thermal [1,7]-sigmatropic hydrogen migrations of **17** and **18** were also investigated quantitatively in order to determine the effects of relocation of the neighboring allylic hydroxyl group from C_1 (**8** and **14**; earlier work[6]) to C_4 (**17** and **18**; this study). Details of the kinetic studies are presented in the supplementary material section and the results are summarized in Table I. Note that the forward rate constants ($k_{17,24}$, $k_{17,25}$, $k_{18,26}$, and $k_{18,27}$) were calculated from data taken to ca. 25% conversion within which irreversible first-order kinetic behavior was observed. The reverse rate constants ($k_{24,17}$, $k_{25,17}$, $k_{26,18}$, and $k_{27,18}$) were calculated from the forward rate constants and the experimentally determined equilibrium constants as determined from the ratios of **24**/**17**/**25** and **26**/**18**/**27** determined at long reaction

Table II. Kinetic Results for the Thermal [1,7]-Sigmatropic Hydrogen Shifts of *cis*-Isotachysterol Analogues 8 and 14

1*S*-OH isomers,[a] $\times 10^5$ s^{-1}		1*R*-OH isomers,[a] $\times 10^5$ s^{-1}	
$k_{8,10}$	16.95 ± 2.2[b]	$k_{14,15}$	21.9 ± 1.8[b]
$k_{10,8}$	4.34[c]	$k_{15,14}$	6.06[c]
$k_{8,9}$	5.82 ± 0.79[b]	$k_{14,16}$	3.77 ± 0.30[b]
$k_{9,8}$	1.93[c]	$k_{16,14}$	1.13[c]

[a] 98.36 ± 0.05 °C. [b] The uncertainties are maximum errors (absolute deviations from the mean). [c] The value was calculated from the forward reaction rate and the equilibrium constant. See ref 17.

Table III. π-Facial Selectivities for the Thermal [1,7]-Sigmatropic Hydrogen Shifts of *cis*-Isotachysterol Analogues

	syn/anti[a]	syn/anti[b,c]
α-OH	$k_{8,10}/k_{8,9}$ = 2.84	$k_{17,24}/k_{17,25}$ = 2.05 ± 0.22
	$k_{10,8}/k_{9,8}$ = 2.25	$k_{24,17}/k_{25,17}$ = 1.35 ± 0.17
β-OH	$k_{14,15}/k_{14,16}$ = 5.81	$k_{18,26}/k_{18,27}$ = 4.19 ± 0.59
	$k_{15,14}/k_{16,14}$ = 5.37	$k_{26,18}/k_{27,18}$ = 3.82 ± 0.57

[a] Computed from Table II. [b] Computed from Table I. [c] The uncertainties are standard deviations.

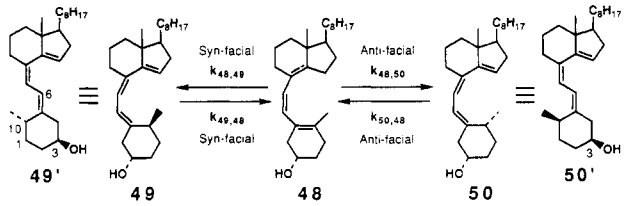
times. Trienols **25** and **26** were independently subjected to the thermal conditions of the kinetic runs to ascertain that a true equilibrium had been established for both cases. Thermolysis of **25** afforded an equilibrium mixture consisting of a **17/24/25** ratio of (46.4 ± 0.7)/(32.5 ± 0.5)/(21.1 ± 0.6), which was in good agreement with that obtained at long reaction times during the kinetic experiment starting from **17** [(46.3 ± 1.2)/(32.4 ± 1.0)/(21.3 ± 0.5)]. The results for the thermolysis of **26** afforded a **18/26/27** equilibrium ratio of (51.8 ± 1.2)/(25.3 ± 0.5)/(23.0 ± 0.3), which is also in good agreement with the ratio observed [(51.8 ± 1.0)/(25.2 ± 0.6)/(23.1 ± 0.5)] starting from **18** in the kinetic run.

π-Facial Selectivity Effects. For comparison, the corrected[17] results from thermolyses of the 1-hydroxylated trienols **8** and **14** reported earlier by Hoeger[6b] of this laboratory are tabulated in Table II. As discussed in the Introduction, these kinetic data can be expressed as π-facial selectivities in terms of the ratios of certain rate constants (syn–anti ratios) both in the forward and reverse directions as tabulated in the first column of data in Table III. It is the C_1 hydroxyl group that determines which of the two helical (*l* or *r* as in Scheme IV) antarafacial modes of [1,7]-sigmatropic hydrogen migratons is preferred; more specifically, the hydroxyl prefers to be syn to the trajectory of the migrating hydrogen.

From the kinetic results of this study (Table I), analogous π-facial selectivities can be calculated and these are tabulated in the second column of Table III. The important thing to discern from comparison of data in the two columns of Table III is that there is a parallel in the thermal behavior of the *cis*-isotachysterols irrespective of whether the hydroxyl is located at C_1 (earlier work of Hoeger[6b,17]) or C_4 (this study). Whether the [1,7]-sigmatropic hydrogen shift is in the *forward direction* (**8** to **10** vs **8** to **9**; **14** to **15** vs **14** to **16**; **17** to **24** vs **17** to **25**; and **18** to **26** vs **18** to **27**) or *reverse direction* (**10** to **8** vs **9** to **8**; **15** to **14** vs **16** to **14**; **24** to **17** vs **25** to **17**; and **26** to **18** vs **27** to **18**), there is a distinct preference for the syn directive

(17) The values for $k_{10,8}$ and $k_{9,8}$ differ from those previously reported due to a miscalculation of the equilibrium constants $K_{8,9}$ and $K_{8,10}$ in the earlier paper (listed as $K_{1,2}$ and $K_{1,3}$, respectively, in the earlier report, ref 6b). The data presented in Tables II and III utilize the corrected data.

Scheme XIV



effect of the hydroxyl group. Thus, in reference to Scheme IV, it is the left-handed (*l*) helical arrangement (interconversion between **11b** and **13**) that is preferred when the hydroxyl is 1α or 4α oriented (nomenclature of the hydroxyl on the A ring of *cis*-isotachysterol analogues throughout this article is based on the vitamin D system). For the 1β- or 4β-oriented hydroxyl, it is the right-handed helical arrangement (corresponding to **11a** and **12** but of the opposite hydroxyl orientation) that is preferred.

To be sure, the effects are small. Nonetheless, the selectivity effects (Table III) seem to be general and it remains for future experiments to determine whether other substituents might impart a larger effect than a hydroxyl group. Hehre and Kahn have briefly examined by computation the effect of a neighboring fluorine (a surrogate for the hydroxyl) on the preferred facial selectivity of the [1,5]-sigmatropic hydrogen shift[18] and their results indicate that the anti-facial effect should be favored over the syn-facial effect, just the opposite of the [1,7]-shift processes involving **8** and **14**. Besides further computational probing of these phenomena (the anti effect observed for the suprafacial [1,5]-hydrogen shift and the opposite syn effect observed for the [1,7]-shift),[18] it will be necessary to determine whether this effect will be observed for systems skeletally different from the *cis*-isotachysterols (**8**, **14**, **17**, and **18**). Since the effects are small, as of yet not understood steric effects may be the origin of these facial selectivities.

Returning to Table III, one other trend that bears noting is the fact that the β-OH effect is somewhat larger by a factor of $\geq$2 than the α-OH effect. Mention should be made of the earlier kinetic studies of Schnoes, De Luca, and co-worker[8e] on the parent system **48** (Scheme XIV), which possesses a 3β-OH on a nonallylic site (the 3α-OH epimer was not investigated). From their kinetic data the π-facial selectivity can be calculated to be k_{syn}/k_{anti} = $k_{48,49}/k_{48,50}$ = 1.9/1.0 at 98 °C. If it can be assumed that these selectivities are intrinsic to the *cis*-isotachysterol skeleton (i.e., wherein the hydroxyl has a negligible effect because it is further removed from the allylic position), then it can be seen that there is a built-in ~1.9:1.0 bias toward the right-handed helix in this system.[19] Therefore, with the 3β-OH system as a reference (Scheme XIV), the intrinsic magnitude of the syn-directing π-facial effect by

(18) For studies of [1,5]-shifts, see: Kahn, S. Ph.D. Dissertation, University of California, Irvine, 1986. An allylic fluorine, a surrogate for a hydroxyl group, in [1,5]-shifts exerts an anti-facial effect in line with experimental observations. (For a recent example, see ref 1a. For a review of earlier examples, see: Okamura, W. H. *Acc. Chem. Res.* **1983**, *16*, 81). W. Hehre and S. Kahn (unpublished preliminary computations) have attempted similar computations at the 3-21G level transition structure for the [1,7]-shift. For this latter case, a neighboring fluorine positioned as in **8** or **14** exerted a syn-directing effect.

(19) Molecular mechanics computations on a model CD fragment possessing a $\Delta^{8(14)}$ double bond as in **48** and the other *cis*-isotachysterol analogues (**8**, **14**, **17** and **18**) described in this study reveal that the 15β-CH bond is approximately coplanar with the p orbitals of the π bond whereas the 15α-CH bond is almost orthogonal. Thus, there is a built in bias for the right-hand helix (cf. **11a** versus **11b** in Scheme IV) as C_{15} rehybridizes from sp^3 to sp^2 in the formation of **12**. However, from a steric standpoint, molecular models seem to indicate that the right-hand helical arrangement **11a** is sterically more congested than the helical system **11b**.

Table IV. Equilibrium Ratios for the Theraml [1,7]-Sigmatropic Hydrogen Shifts of *cis*-Isotachysterol Analouges 17, 18, 48, 8, and 14

	product ratio (%) at equilibrium	
	α-OH series	β-OH series
4-OH	**17/24/25**[a] = 46/33/21	**18/26/27**[b] = 52/25/23
3-OH		**48/49/50**[c] = 36/24/40
1-OH	**8/10/9**[d] = 13/48/38	**14/15/16**[d] = 13/45/42

[a] 98.5 ± 0.2 °C. [b] 98.42 ± 0.08 °C. [c] 120 °C. [d] 98.36 ± 0.05 °C.

an allylic hydroxyl can be estimated with a correction for the built-in ~1.9/1.0 bias of the *cis*-isotachysterol system for the right-handed helix (cf. **11a** in Scheme IV). This leads to the conclusion that for the forward processes (the first and third rows of data presented in Table III), the π-facial selectivities for the α-alcohols (**8** and **17**) are smaller than they are estimated to be whereas those for the β-alcohols (**14** and **18**) are larger than they are calculated to be (perhaps by a factor of ~1.9 in each series). This analysis however does not at all account for nonbonded steric interactions that may characterize the *cis*-isotachysterol ring systems studied nor does this analysis pertain to the reverse processes (the second and fourth rows of data in Table III).

Equilibrium of *cis*-Isotachysterol Analogues. The equilibrium ratios for the 4α-OH series (**24**, **17** and **25**) and the 4β-OH series (**18**, **26**, and **27**) were discussed earlier in connection with the kinetic data presented in Table I. These equilibrium ratio data together with the data for the other *cis*-isotachysterol systems studied (**8**, **10**, **9**; **14**, **15**, **16**; and **48**, **49**, **50**) are summarized in Table IV. Interestingly, the relocation of the hydroxyl substituent from C_1 (the earlier Hoeger study[6b]) to C_4 (this study) or C_3 (Schnoes, Deluca, and co-worker[8e]) leads to a significant increase in the proportion of *cis*-isotachysterol (**8**, **14** versus **17**, **18** and **48**) at equilibrium. For **8** and **14**, 13% of the triad of isomers prefers the *cis*-isotachysterol form. By contrast, for **17**, **18**, and **48**, the percent *cis*-isotachysterol ranges from 36 to 52% of the equilibrium mixture. At least qualitatively, we attribute this to the $A_{1,2}$ strain[9] between the C_1-OH and C_{19}-CH_3 present in **8** and **14**, which is absent when the hydroxyl is relocated to C_4 (**17** and **18**) or C_3 (**48**).

Experimental Section[20]

(4*R*)-(+)- and (4*S*)-(−)-(6*Z*)-9,10-Secocholesta-5(10),6,8-(14)-trien-4-ol (17, Less Polar Isomer A, and 18, More Polar Isomer B). To a well-stirred solution of a ~1:1 4*S*/4*R* diastereomeric mixture of dienynol **19** (122.8 mg, 0.321 mmol) and quinoline (1.47 mL, 0.2 mL quinoline/10 mL hexanes) in hexanes (20 mL) was introduced Lindlar catalyst (491 mg). The mixture was degassed and then exposed to a hydrogen atmosphere. This process was repeated three times and the mixture was allowed to stir under a hydrogen atmosphere for 2 h. Celite and ether (20 mL) were added to the black mixture and the resulting grey suspension was filtered. The solvent was removed and the residue was purified by HPLC (partisil, 7% EtOAc/hexanes) to give the desired trienols as pale yellow oils in the following order of elution: (4*R*)-**17** (60.3 mg, 49%, less polar, diastereomer A, $[\alpha]_D$ +277° (*c* 0.740, $CHCl_3$) and then (4*S*)-**18** (51.2 mg, 41%, more polar, diastereomer B, $[\alpha]_D$ −206° (*c* 0.890, $CHCl_3$).

The 4*S* dienynol **19b** enriched starting material was subjected to similar catalytic semihydrogenation to establish the absolute configuration of the hydroxyl bearing C-4 configuration of these trienols. Thus, **19b** enriched dienynol (26.1 mg, 0.0682 mmol; contaminated by ~3–4% of its 4*R* epimer based on the 93% ee optical purity of the A-ring bromo alcohol **44a** described elsewhere in the Experimental Section), quinoline (1.87 mL, 0.05 mL of quinoline/5 mL of hexanes), and Lindlar catalyst (104 mg) in hexanes (10 mL) was hydrogenated as described above for 28 min. The crude product was purified by flash column chromatography (silica gel, 25% ether/hexanes) followed by HPLC (partisil, 7% EtOAc/hexanes) to give the desired trienols with the expected elution order: 4*R* trienol **17** (isomer A; 1 mg, 4%; contaminated with a small amount of overhydrogenated product) and 4*S* trienol **18** (isomer B; 24.1 mg, 92%; contaminated with ~2% of overhydrogenated products), which was sufficiently pure for use in large-scale thermolysis. A pure sample of 4*S* trienol **18** can be obtained by further HPLC purification on a few milligram scale for kinetic studies and characterization purposes.

A complementary experiment in the 4*R* series, which further confirmed the configuration at the hydroxyl bearing center C-4, was carried out as follows. A diastereomerically enriched dienynol **19a** (28.8 mg, 0.0753 mmol; contaminated by ~12% of its 4*S* epimer based on the 77% ee optical purity of A-ring bromo alcohol **42a** described elsewhere in the Experimental Section), quinoline (2.06 mL, 0.05 mL of quinoline/5 mL of hexanes), and Lindlar catalyst (115 mg) in hexanes (10 mL) was exposed to hydrogen gas for 28 min in a manner analogous to that described above for the preparation of the more polar trienol B (**18**). After filtration of the reaction mixture through Celite with ether to remove the catalyst, the filtrate was concentrated on a rotary evaporator. The residue was purified by flash column chromatography (silica gel, 25% ether/hexanes) followed by HPLC separation (partisil, 7% EtOAc/hexanes) to give the desired trienols in the following elution order: 4*R* trienol **17** (24.5 mg, 85%, less polar, diastereomer A; contaminated with ~4% of overhydrogenated products) and 4*S* trienol **18** (1.2 mg, 4%, more polar diasteromer B; contaminated with a small amount of overhydrogenated products). The 4*R* trienol **17** thus produced was used for large-scale thermolysis without further purification. For kinetic studies and characterization purposes, a pure sample was obtained by further HPLC purification on a few milligram scale.

It should in summary be carefully noted that 4*R*-(+) trienol diastereomer A in this experiment ultimately derives from the reduction product (*R*-(+)-bromo alcohol **42a**) of ketone **30** using the $LiAlH_4$ complex of (1*R*,2*S*)-(−)-*N*-methylephedrine (**37**). All of the A-ring fragments of the *R*-(+) series are related to the TBDMS protected dienynol 4*R*-(+) diastereomer B **46** with the latter related to trienol 4*R*-(+) diastereoisomer A **17**. Hence, these should be carefully distinguished from the complementary series of stereoisomers leading to trienol 4*S*-(−) diastereoisomer B **18** (ultimately derived using (1*S*,2*R*)-(+)-*N*-methylephedrine (**43**)).

9,10-Secocholesta-5(10),8(14)-dien-6-yn-4-ol (19). A solution of *n*-Bu_4NF (3.00 mL, 1.1 M in THF, 3.3 mmol) was introduced via syringe to a flask containing silyl ether **35** (545.7 mg, 1.10 mmol; contaminated with ~7% of the $\Delta^{8,9}$ isomers) under a nitrogen atmosphere and the resulting mixture was stirred for 16 h. Saturated $NaHCO_3$ (22 mL) was added, the mixture was extracted with ether (3 × 20 mL), and the combined organic solution was then dried over $MgSO_4$. The solvent was removed on a rotary evaporator and the residue was purified by HPLC (partisil, 18% EtOAc/hexanes) to give the desired alcohol **19** (302.7 mg, 72%) as a pale yellow oil. The latter material was not contaminated by $\Delta^{8,9}$ isomers as determined by ^1H NMR analysis. This diastereomeric mixture of alcohols could be separated after catalytic semihydrogenation to the corresponding trienols.

(4*R*)-9,10-Secocholesta-5(10),8(14)-dien-6-yn-4-ol (19a). A sample of diastereomerically enriched **46** (654.7 mg, 1.32 mmol; contaminated with a small amount of its 4*S* epimer and ~8% of $\Delta^{8,9}$ isomers) was deprotected (*n*-Bu_4NF, 3.96 mmol) as described above. Purification by HPLC (partisil, 20% EtOAc/hexanes) gave the desired dienynol **19a** (353.0 mg, 70%, contaminated by its inseparable 4*S* epimer but free from $\Delta^{8,9}$ olefinic impurities) as a pale yellow oil and a small amount of the recovered starting material (70.6 mg, 11%, contaminated with the same impurities in the starting material). This diastereomeric mixture consisting mainly of the desired 4*R* dienynol **19a** could be separated after catalytic semihydrogenation to the corresponding trienols.

(4*S*)-9,10-Secocholesta-5(10),8(14)-dien-6-yn-4-ol (19b). Diastereomerically enriched silyl ether **47** (896.3 mg, 1.80 mmol; contaminated by a small amount of its 4*R* epimer and ~8% of

(20) General procedures and spectral data and a detailed description of the kinetic studies are given in the supplementary material section.

$\Delta^{8,9}$ isomers) was reacted with n-Bu_4NF (4.92 mL, 1.1 M in THF, 5.41 mmol) for 18 h as described above to afford a residue, which, upon HPLC (partisil, 20% EtOAc/hexanes) purification, gave the desired alcohol **19b** free from contamination by its $\Delta^{8,9}$ isomers (as determined by ^1H NMR analysis; 417.7 mg, 61%; contaminated by its inseparable 4*R* epimer) as a pale yellow oil and some recovered starting material (228.5 mg, 25%, contaminated with the same impurities indicated for the starting material). This diastereomeric mixture consisting mainly of the desired 4*S* dienynol **19b** could be separated after catalytic semihydrogenation to the corresponding trienols.

De-*A*,*B*-8-ethynylcholest-8(14)-ene (20). Using the procedure reported previously,[6a,b] propargyl alcohol **28** was converted to the enyne **20** (66%, contaminated with ~8% of its $\Delta^{8,9}$ regioisomer) as a colorless liquid, which was carried through to the next step without further purification. A small amount of the $\Delta^{8(14)}$ enyne was purified by HPLC (partisil, 100% hexanes) for characterization purposes. In the previous report,[6b] only the formation of the $\Delta^{9(14)}$ dehydration product **20** was observed.

(4*R*,10*S*)-(-)- and (4*R*,10*R*)-(-)-(5*E*,7*Z*)-9,10-Secocholesta-5,7,14-trien-4-ol (25, Diastereomer A_1, and 24, Diastereomer A_2). A solution of (4*R*)-**17** (trienol diastereomer A; 66.9 mg, contaminated with up to ~29% of overhydrogenated material) in isooctane (20 mL) was refluxed under a nitrogen atmosphere for 58 h. The mixture was cooled to room temperature and the isooctane was removed by passage of the solution through a flash chromatography column (silica gel) with hexane. Passage of 30% Et_2O–hexanes resulted in elution of the product mixture free of isooctane. The solvent was removed on a rotary evaporator and then the residue (after ^1H NMR analysis) was purified by HPLC (partisil, 5% EtOAc/hexanes) to afford in order of elution: 4*R*,10*S* trienol **25** (7.7 mg, 15%, less polar, diastereomer A_1; $[\alpha]_D$ -390° (*c* 0.574, $CHCl_3$)), 4*R*,10*R* trienol **24** (11.3 mg, 22%, more polar diastereomer A_2; $[\alpha]_D$ -441° (*c* 0.758, $CHCl_3$), and then starting 4*R* trienol **17**, (19.2 mg, 37%; contaminated with ~5% of the initially present overhydrogenated impurities). The ratio of A_1/A_2/starting material A (corrected for overhydrogenated impurities) was 21/32/47 (by ^1H NMR analysis, 21/30/49; by HPLC, 21/34/45; by isolated weight, 20/31/49). For more quantitative studies, refer to the kinetic studies described elsewhere in the Experimental Section. In later more quantitative experiments, the equilibrium ratio of A_1/A_2/starting material A was determined to be 21/33/46 at 98.5 °C in isooctane.

(4*S*,10*R*)-(-)- and (4*S*,10*S*)-(-)-(5*E*,7*Z*)-9,10-Secocholesta-5,7,14-trien-4-ol (27, Diastereomer B_1, and 26, Diastereomer B_2). In a flask equipped with a reflux condenser and a magnetic stirring bar, a solution of (4*S*)-**18** (126.6 mg, 0.329 mmol, contaminated with ~4% of possible overhydrogenated impurities) in isooctane (15 mL, freshly distilled over $LiAlH_4$) was brought to reflux under a nitrogen atmosphere for 24 h. The solution was cooled to room temperature and the isooctane was removed by passage through a flash chromatography column (silica gel) using hexanes. The total product mixture free of isooctane was eluted with 40% ether–hexanes and after the solvent was removed under vacuum, the product distribution was estimated by ^1H NMR analysis. The sample was again concentrated under vacuum and the pale yellow residue was subjected to HPLC purification (partisil, 5% EtOAc/hexanes) to give three compounds in the following elution order: (4*S*,10*R*)-**27** (23.7 mg, 19%, less polar, diastereomer B_1; $[\alpha]_D$ -358° (*c* 1.54, $CHCl_3$)); 4*S*,10*S* isomer **26** (31.2 mg, 25%, more polar, diastereomer B_2; $[\alpha]_D$ -231° (*c* 1.40, $CHCl_3$)); and starting 4*S*,6*Z* isomer **18** (63.4 mg, 50%, contaminated with ~11% of the overhydrogenated impurities mentioned above). The ratio of B_1/B_2/starting material B (corrected for overhydrogenated material) was 21/27/52 (by ^1H NMR analysis, 21/26/53; by HPLC, 22/28/50; by isolated weight, 21/28/51). For more quantitative studies, refer to the kinetic investigations given in the Experimental Section. In these later quantitative experiments, the equilibrium ratio of B_1/B_2/starting material B was estimated to be 23/25/52 at 98.4 °C in isooctane.

(8*S*)-De-*A*,*B*-8-ethynylcholestan-8-ol (28). The propargylic alcohol **28** was obtained in 95% yield using a previously described procedure.[8a,b,21]

(21) Haces, A.; van Kruchten, E. M. G. A.; Okamura, W. H. *Israel J. Chem.* **1985**, *26*, 140.

2-Bromo-3-ethoxycyclohex-2-en-1-one (29). Commercial ketone **23** was converted to the crude, vacuum-dried bromide **29** as a pale yellow solid, which was carried on to the next step without further purification. Recrystallization from a CH_2Cl_2/hexanes mixture gave the pure bromide **29** as white crystals (mp 86.0–86.5 °C; lit.[11] mp 85–87 °C).

2-Bromo-3-methylcyclohex-2-en-1-one (30). Methyllithium was reacted with the crude bromo enone **29** as previously described[11] to give the desired **30** (74%) as a pale yellow oil. The vacuum-dried material was used directly in the next step without further purification.

(±)-2-Bromo-3-methylcyclohex-2-en-1-ol (31). To a well-stirred suspension of $LiAlH_4$ (772 mg, 95%, 19.3 mmol) in anhydrous ether (28 mL) at -78 °C under a nitrogen atmosphere was added slowly a solution of ketone **30** (1.52 g, 8.05 mmol) in ether (8 mL) via cannula. Ether (2 × 1 mL) was used to rinse the ketone residue into the reaction mixture and the stirring was continued at -78 °C for 20 min and at 0 °C for 30 min. After an aqueous solution of 1 M H_2SO_4 (48 mL) was added cautiously, the mixture was allowed to warm to room temperature. The organic layer was separated from the aqueous layer and the latter was extracted with ether (3 × 30 mL). The combined organic extracts were washed with saturated $NaHCO_3$ and then dried over $MgSO_4$. Solvent evaporation followed by flash column chromatographic purification (silica gel, 30% ether/hexanes) gave after vacuum drying the desired alcohol **31** (1.50 g, 98%) as a white solid (mp 42.6–43.2 °C).

(±)-3-Methylcyclohex-2-en-1-ol (32). To a solution of racemic vinyl bromide **31** (96.5 mg, 0.505 mmol) in anhydrous ether (10.1 mL) at -78 °C was added *t*-BuLi (1.21 mL, 1.76 M in pentane, 2.13 mmol) via syringe under a nitrogen atmosphere. The mixture was stirred at -78 °C for 20 min and at 0 °C for 10 min and the reaction was quenched carefully with saturated $NaHCO_3$ (7 mL). The resulting mixture was extracted with ether (3 × 10 mL), the organic extracts were then dried over $MgSO_4$, and then the latter was concentrated. Flash column chromatographic purification (silica gel, 50% Et_2O/hexanes) of the residue gave the desired alcohol **32** (46.2 mg, 82%) as a pale yellow liquid. This material was further purified by HPLC (partisil, 20% EtOAc/hexanes) for spectral characterization.

(±)-2-Bromo-1-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclohex-2-ene (33). To a solution of racemic alcohol **31** (1.50 g, 7.85 mmol) in anhydrous ether (8 mL) were added imidazole (2.138 g, 99%, 31.4 mmol) and *tert*-butyldimethylchlorosilane (2.367 g, 97%, 15.7 mmol) with stirring under a nitrogen atmosphere. The mixture was stirred for 12 h and then the reaction was quenched with water (31 mL). The resulting mixture was extracted with ether (3 × 20 mL) and the combined organic solution was washed with saturated $NaHCO_3$ (20 mL) and then dried over $MgSO_4$. Solvent evaporation gave a pale yellow residue, which was purified by flash column chromatography (silica gel, 1% Et_2O/hexanes) to give the desired compound **33** (2.238 g, 93%) as a pale yellow liquid. The vacuum-dried material was used directly in the next step.

(±)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-iodo-3-methylcyclohex-2-ene (34). A solution of *t*-BuLi (9.16 mL, 1.76 M in pentane, 16.1 mmol) was added slowly to a solution of racemic vinyl bromide **33** (2.238 g, 7.329 mmol) in ether (36.6 mL) by syringe at -50 °C under a nitrogen atmosphere and the mixture was stirred for 2 h. An iodine solution (2.604 g, 10.26 mmol) in ether (24 mL) was introduced via cannula and the stirring was continued for 15 min. After addition of a saturated aqueous $Na_2S_2O_3$ solution (25 mL), the mixture was warmed to room temperature. The organic layer was separated from the aqueous layer and the latter was extracted with ether (3 × 15 mL). The combined organic extracts were washed with saturated $NaHCO_3$ and then dried over $MgSO_4$. The solvent was removed in the dark to give a yellow residue, which was subjected to flash column chromatographic purification (silica gel, 1% ether/hexanes). The solvent of the resulting eluant was evaporated on a rotary evaporator and dried on a vacuum pump in the dark to give the desired vinyl iodide **34** (1.400 g, 54%) as a pale yellow liquid. Since this material was not very stable, it was stored cold in the dark and used directly in the next step as obtained.

4-[(*tert*-Butyldimethylsilyl)oxy]-9,10-secocholesta-5-(10),8(14)-dien-6-yne (35). To a solution of enyne **20** (1.011 g,

3.71 mmol; contaminated with ~8% of its $\Delta^{8,9}$ isomer) in anhydrous THF (3.7 mL) at 0 °C under a nitrogen atmosphere was introduced a solution of EtMgBr (1.92 mL, 1.93 M in THF, 3.71 mmol) cautiously via syringe. The mixture was warmed to room temperature and a reflux condenser was attached to the flask. The mixture was brought to reflux for 1 h and the heating mantle was removed and then $Pd(PPh_3)_4$ (143 mg, 99%, 0.123 mmol) was added. A solution of racemic vinyl iodide **34** (871.7 mg, 2.47 mmol) in dry benzene (3 mL) was introduced via cannula and benzene (2 × 1 mL) was used to rinse the residue into the mixture. The resulting pale yellow solution was brought to reflux for 16 h and the mixture was then cooled to room temperature. Water (50 mL) was added and the mixture was extracted with ether (3 × 40 mL). The combined red orange solution was washed with saturated $NaHCO_3$ (30 mL) and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash column chromatography (silica gel, 100% hexanes) to give the desired coupled product **35** (828.3 mg, 68%; contaminated with ~7% of what appears to be $\Delta^{8,9}$ isomers as determined by ^1H NMR analysis) as a yellow oil, which was sufficiently pure for the next step. A small amount of the sample was purified by HPLC (silica gel, 100% hexanes) for characterization. The diastereomers could only be separated by a tedious shave–recycle technique by HPLC and providing only a few milligrams of mixture is injected each time. Therefore, the diastereomeric mixture was carried to the next step without separation. For characterization of the diastereomerically pure material, the synthesis of the same substrate was carried out using optically pure A-ring iodides. The less polar diastereomer A (synthesized from *S*-(−) iodide **44c**) proved to be the 4*S*-(+) isomer; the more polar diastereomer B (synthesized from *R*-(+) iodide **42c**) was the 4*R*-(+) isomer (refer to the details given elsewhere in this Experimental Section).

2-(Ethylamino)pyridine (36). Commercial 2-aminopyridine was converted as previously described[16] to **36** (34%) as a pale yellow oil. The vacuum-dried material was used without further purification.

(1*R*,2*S*)-(−)-*N*-Methylephedrine (37). This material is commercially available or can be prepared easily from (1*R*,2*S*)-(−)-ephedrine as previously described.[16] Recrystallization from MeOH afforded **37** (71%) as colorless crystals: mp 86.9–87.9 °C, $[\alpha]_D$ −29.1° (*c* 4.54, MeOH); lit.[16] mp 86.5–87.5 °C, $[\alpha]^{20}_D$ −29.5 (*c* 4.54, MeOH).

(*R*)-(+)-3-Methylcyclohex-2-en-1-ol (41). A solution of *t*-BuLi in pentane (1.25 mL, 1.76 M, 2.20 mmol) was added slowly with stirring to a solution of vinyl bromide **42a** (100.4 mg, 0.525 mmol, 87% ee, $[\alpha]_D$ +87.4° (*c* 5.06, $CHCl_3$)) in anhydrous ether (10.5 mL) at −78 °C under a nitrogen atmosphere. The stirring was continued at −78 °C for 20 min and at 0 °C for 10 min and then the mixture was quenched with saturated $NaHCO_3$ (7 mL). The resulting mixture was extracted with ether (3 × 10 mL) and the combined organic solution was dried over $MgSO_4$. Solvent evaporation on a rotary evaporator followed by flash column chromatographic purification (silica gel, 50% Et_2O/hexanes) gave the desired alcohol **41** (47.2 mg, 80%) as a pale yellow liquid. ($[\alpha]_D$ +81.4 (*c* 0.408 $CHCl_3$); lit.,[12] $[\alpha]^{20}_D$ +96.0 ± 0.3° (*c* 0.423, $CHCl_3$)). A shift study using Eu(hfc)$_3$ showed an optical purity of 85% ee; from the specific rotation, an optical purity of 85% ee can be calculated (see supplementary material).

(*R*)-(+)-2-Bromo-3-methylcyclohex-2-en-1-ol (42a). To a suspension of $LiAlH_4$ (147 mg, 95%, 3.69 mmol) in anhydrous ether (3.2 mL) in a flask equipped with a reflux condenser and a magnetic stirring bar under a nitrogen atmosphere was added a solution of (1*R*,2*S*)-(−)-*N*-methylephedrine (**37**, 723 mg, 4.03 mmol) in ether (5.2 mL) cautiously via cannula. Ether (2 × 1 mL) was used to rinse the residual ligand into the mixture and the resulting mixture was refluxed. After 1 h, a solution of amine **36** (985 mg, 8.06 mmol) in ether (2.2 mL) was introduced slowly by cannula into the mixture and ether (2 × 0.5 mL) was used for rinsing the residue into the mixture. The mixture was brought to refluxing for 1 h and the resulting light green mixture was then cooled to −78 °C. A solution of ketone **30** (212 mg, 1.12 mmol) in ether (1 mL plus 2 × 0.5 mL rinse) was added dropwise via cannula into the mixture. The stirring was continued for 3 h and methanol (0.19 mL) followed by water (6 mL) was added cautiously. The mixture was warmed to 0 °C and 15% NaOH solution (12 mL) was added. The resulting mixture was extracted with ether (3 × 15 mL) and the ethereal extract was washed with saturated Na_2CO_3 and dried over $MgSO_4$. The solvent was removed on a rotary evaporator and the residue was purified by flash column chromatography (silica gel, 30% Et_2O/hexanes) to give the desired alcohol **42a** (134 mg, 63%) as white crystals: mp 43.3–46.3 °C, $[\alpha]_D$ +87.4° (*c* 5.06, $CHCl_3$). A ^1H NMR shift study using Eu(hfc)$_3$ showed an optical purity of 87% ee (see supplementary material). The yield was improved in another run, which was carried out on a larger scale (starting with 828 mg of ketone; 80% yield of **42a**; 77% ee by a ^1H NMR shift study; $[\alpha]_D$ +78.7° (*c* 5.64, $CHCl_3$).

(*R*)-(+)-2-Bromo-1-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclohex-2-ene (42b). To a solution of *R* alcohol **42a** (669 mg, 3.50 mmol, 77% ee by the shift study, $[\alpha]_D$ +78.7° (*c* 5.64, $CHCl_3$) in anhydrous ether (3.5 mL) were introduced imidazole (953 mg, 99%, 13.9 mmol) and *tert*-butyldimethylchlorosilane (1.088 g, 97%, 7.00 mmol) with stirring under a nitrogen atmosphere. The reaction was quenched with water (14 mL) after 16 h and the mixture was extracted with ether (3 × 10 mL). The combined ethereal solution was washed with saturated $NaHCO_3$ and then dried over $MgSO_4$. The solvent was evaporated on a rotary evaporator and the resulting residue was purified by flash column chromatography (1% Et_2O/hexanes) to give the desired protected alcohol **42b** (944 mg, 88%; $[\alpha]_D$ +47.3° (*c* 2.48, $CHCl_3$)) as a pale yellow liquid. This material is assumed to be 77% ee based on the optical purity of the starting alcohol.

(*R*)-(+)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-iodo-3-methylcyclohex-2-ene (42c). To a solution of *R* vinyl bromide **42b** (944.2 mg, 3.09 mmol, $[\alpha]_D$ +47.3 (*c* 2.48, $CHCl_3$) in anhydrous ether (15.4 mL) was introduced a solution of *t*-BuLi (3.95 mL, 1.72 M in pentane, 6.79 mmol) dropwise with stirring at −50 °C under a nitrogen atmosphere. The stirring was continued for 2 h and the mixture was cooled to −78 °C. A solution of iodine (1.098 g, 4.33 mmol) in anhydrous ether (8.7 mL) was added to the mixture via cannula and the resulting mixture was stirred at −50 °C for 15 min and then warmed to room temperature. The reaction was quenched with water (31 mL) cautiously and then the mixture was transferred to a separatory funnel. Sodium thiosulfite was added with shaking until the mixture became colorless and then the mixture was extracted with ether (3 × 20 mL). The combined organic solution was washed with saturated NH_4Cl and then dried over $MgSO_4$. Solvent evaporation in the dark followed by flash column chromatographic purification (silica gel, 1% ether/hexanes) also in the dark gave the desired vinyl iodide **42c** (469.8 mg, 43%, $[\alpha]_D$ +34.6° (*c* 2.53, $CHCl_3$)) as a pale yellow liquid. Based on the assumed enantiomeric purity (77% ee) of the starting bromide, this iodide is also assumed to possess an enantiomeric purity of 77% ee.

(1*S*,2*R*)-(+)-*N*-Methylephedrine (43). This material is commercially available or can be prepared as previously described[16] from (1*S*,2*R*)-(+)-ephedrine hydrochloride. Recrystallization from MeOH gave **43** (83%) as colorless needles: mp 86.5–87.0 °C, $[\alpha]_D$ + 28.8° (*c* 4.52, CH_3OH).

(*S*)-(−)-2-Bromo-3-methylcyclohex-2-en-1-ol (44a). A solution of (1*S*,2*R*)-(+)-*N*-methylephedrine (**43**, 645 mg, 3.60 mmol) in anhydrous ether (4.7 mL) was introduced cautiously via cannula to a well-stirred suspension of LAH (132 mg, 95%, 3.29 mmol) in ether (2.8 mL) in a flask equipped with a magnetic stirring bar and a reflux condenser under a nitrogen atmosphere. Ether (2 × 1 mL) was used to rinse the residual ligand into the reaction mixture. The mixture was then brought to reflux for 1 h and then a solution of amine **36** (880 mg, 7.20 mmol) in ether (2.9 mL) was added to the mixture by cannula. The resulting mixture was refluxed for another hour. The resulting light green mixture was cooled to −78 °C and a solution of ketone **30** (189 mg, 1.00 mmol) in ether (1 mL) was introduced via cannula. Ether (2 × 0.5 mL) was used to rinse the residual ketone to the reaction mixture and the stirring was continued for 3 h. Methanol (0.17 mL) was added cautiously to the reaction mixture and, after 5 min, water (5 mL) was introduced dropwise. The mixture was warmed to 0 °C and 15% NaOH (10 mL) was added. The resulting mixture was extracted with ether (3 × 15 mL) and the combined ethereal extract was washed with saturated Na_2CO_3 and then dried over Mg_2SO_4. Flash column chromatographic purification (silica gel, 40% Et_2O/hexanes) gave the desired alcohol **44a** (149 mg, 78%) as pale yellow crystals: mp 45.5–47.0 °C; $[\alpha]_D$ −87.0° (*c* 4.14,

$CHCl_3$). A ^1H NMR shift study using $Eu(hfc)_3$ gave an optical purity of 89% ee (see supplementary material). The yield was improved in another run carried out on a larger scale (733 mg of ketone afforded 667 mg (90%) of alcohol; 93% ee by ^1H NMR shift study; $[\alpha]_D$ −93.1 (*c* 4.96, $CHCl_3$)).

(*S*)-(−)-2-Bromo-1-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclohex-2-ene (44b). Using the procedure for preparation of the protected alcohol **42b**, *S* alcohol **44a** (93% ee) was converted to the silyl ether **44b** ($[\alpha]_D$ −55.0 (*c* 2.45, $CHCl_3$)) in 95% yield as a pale yellow liquid. This material is estimated to be 93% ee based on the optical purity of starting alcohol.

(*S*)-(−)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-iodo-3-methylcyclohex-2-ene (44c). Using the procedure for preparation of vinyl iodide **42c** described above, *S* vinyl bromide **44b** ($[\alpha]_D$ −55.0° (*c* 2.45, $CHCl_3$)) was converted to the desired vinyl iodide **44c** ($[\alpha]_D$ −36.4° (*c* 2.53, $CHCl_3$)) in 58% yield as a pale yellow liquid. Based on the assumed optical purity (93% ee) of the starting bromide, this iodide is also assumed to possess an enantiomeric purity of 93% ee.

(*S*)-(−)-3-Methylcyclohex-2-en-1-ol (45). A solution of *S* vinyl bromide **44a** (189 mg, 1.00 mmol, 89% ee, $[\alpha]_D$ −87.0 (*c* 4.14, $CHCl_3$)) in anhydrous ether (15 mL) was treated with *t*-BuLi (1.80 mL, 1.76 M in pentane, 3.17 mmol) as described above for the preparation of *R* alcohol **41** to afford the desired alcohol **45** (65.3 mg, 77%) as a pale yellow liquid ($[\alpha]_D$ −84.6° (*c* 0.527, $CHCl_3$); lit.[12] $[\alpha]^{20}_D$ −96.3 ± 0.3 (*c* 0.458, $CHCl_3$)). A ^1H NMR shift study using $Eu(hfc)_3$ showed an optical purity of 89% ee (see supplementary material). The enantiomeric purity of the material obtained in this study is 88% ee based on comparison of its specific rotation with that of the literature report.

(4*R*)-(+)-4-[(*tert*-Butyldimethylsilyl)oxy]-9,10-secocholesta-5(10),8(14)-dien-6-yne (46). In a dry flask, a solution of EtMgBr (1.08 mL, 1.84 M in THF, 1.99 mmol) was added dropwise by syringe to a solution of enyne **20** (575 mg, 2.11 mmol, contaminated with ~8% of its $\Delta^{8,9}$ isomer) in THF (2.1 mL) with stirring at 0 °C under a nitrogen atmosphere. The mixture was warmed to room temperature and a reflux condenser was attached to the flask. The mixture was refluxed for 1 h and after the heating was stopped, a small amount of $Pd(PPh_3)_4$ catalyst (76.3 mg, 99%, 0.0654 mmol) was introduced and a solution of *R* vinyl iodide **42c** (464.9 mg, 1.32 mmol; contaminated with a small amount of its 4*S* diastereomer as described elsewhere in the Experimental Section) in dry benzene (0.9 mL) was added via cannula. Benzene (2 × 0.9 mL) was used to rinse the residue into the mixture and the solution was then refluxed for 18 h. After the resulting red orange solution was cooled to room temperature, water (28 mL) was introduced to quench the reaction. The mixture was extracted with ether (3 × 30 mL) and then the combined organic solution was washed with saturated $NaHCO_3$ and dried over $MgSO_4$. The solvent was removed on a rotary evaporator to afford a residue, which was purified by flash column chromatography (silica gel, 1% ether/hexanes) to yield the desired dienyne **46** quantitatively as a yellow oil (contaminated with ~8% of $\Delta^{8,9}$ isomers and a small amount of 4*S* epimer). The latter was sufficiently pure for use in the next (deprotection) step. A small amount of the product was further purified by HPLC (silica, 100% hexanes) to give the pure 4*R* dienyne **46** for structure characterization purposes (more polar, diastereomer B, $[\alpha]_D$ +108° (*c* 1.38 ($CHCl_3$)).

(4*S*)-(+)-4-[(*tert*-Butyldimethylsilyl)oxy]-9,10-secocholesta-5(10),8(14)-dien-6-yne (47). A solution of EtMgBr (1.56 mL, 1.84 M in THF, 2.87 mmol) was introduced slowly via syringe to a solution of enyne **20** (832.3 mg, 3.05 mmol, contaminated with ~8% of its $\Delta^{8,9}$ isomer) in THF (3.1 mL) in a dry flask equipped with a magnetic stirring bar at 0 °C under a nitrogen atmosphere. The mixture was warmed to room temperature and a reflux condenser was mounted on the flask. The mixture was brought to reflux under a nitrogen atmosphere for 1 h and the heating mantle was removed. Tetrakis(triphenylphosphine)palladium(0) (110.3 mg, 99%, 0.0945 mmol) was added and then a solution of *S* vinyl iodide **44c** (672.6 mg, 1.91 mmol, contaminated with a small amount of its 4*R* enantiomer as described elsewhere in the Experimental Section) in dry benzene (1.8 mL) was introduced by cannula. Benzene (2 × 1 mL) was used to rinse the flask and the rinsings were also added to the mixture. The mixture was refluxed for 16 h and the resulting red-orange solution was cooled to room temperature. Water (40 mL) was introduced and the mixture was then extracted with ether (3 × 40 mL). The combined etheral solution was washed with saturated $NaHCO_3$ and dried over $MgSO_4$. Solvent evaporation followed by flash column chromatographic purification (silica gel, 1% ether/hexanes) gave the desired dienyne **47** (896.3 mg, 94%; contaminated with ~8% of $\Delta^{8,9}$ isomers and a small amount of 4*R* epimer) as a yellow oil, which was sufficiently pure for the next (deprotection) step. A small amount of product was further purified by HPLC (silica, 100% hexanes) to afford the dienyne **47** for characterization purposes (less polar, diastereomer A, $[\alpha]_D$ +28.0° (*c* 2.42, $CHCl_3$).

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Supplementary Material Available: Spectral data for all new compounds and general experimental details (20 pages). Ordering information is given on any current masthead page.