Thermal Rearrangement of Vinylallenes: Synthesis of 3-Deoxy-1α-hydroxy-14-epiprevitamin D_3[1]

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The lithium salt of the terminal allene **12a** was reacted with keto enol ether **13** to give the vinylallenones **8a**(6*R*) and **9a**(6*S*). On reduction with sodium borohydride, **8a** afforded vinylallenols **8b**(1*R*,6*R*) and **8c**(1*S*,6*R*); similarly **9a** gave **9b**(1*R*,6*S*) and **9c**(1*S*,6*S*). Thermolysis of the four vinylallenols **8bc** and **9bc** in isooctane (100 °C) was studied. The (1*S*)-epiprevitamin **7b** and its (1*R*)-epimer **29** were obtained as major products from the thermolysis of **9c** and **8b**, respectively. By contrast, the vinylallenols **9b** and **8c** upon thermolysis produced the epiprevitamins (**29** and **7b**, respectively) only as minor products; the major products resulted from a competing [1,5]-sigmatropic shift process followed by subsequent [1,7]-shifts. Thermolysis of vinylallenones **8a** and **9a** afforded mainly an inseparable mixture of previtamin ketone **18** and *cis*-isotachysterone **19**, which were identified by comparison with samples prepared by independent synthesis. The vitamin–previtamin equilibrium (**28** ⇄ **29**) was found to be 5/95.

Introduction

Vitamin D_3 (**1a**) and its biologically active metabolies,[2] 25-hydroxyvitamin D_3 (**1b**) and 1α,25-dihydroxyvitamin D_3 (**1c**), may equilibrate with their previtamin forms **3**, wherein the [1,7]-sigmatropic hydrogen shift proceeds via the s-cis conformer **2**[3] (Chart I). That the equilibrium **1** ⇄ **3** favors **1** has long been known, and a particularly enlightening study on this subject was carried out by Havinga and co-workers.[4] They found that the analogue **4a**, possessing a *cis*-hydrindane C/D fragment, favors the previtamin form **5a** at equilibrium, just the opposite to *trans*-hydrindane systems **4b** and **1a**, for which the vitamin D is more stable than the previtamin D. An interesting question is whether previtamin-type structures possess biological activity. As early as 1961, Velluz and co-workers suggested the possibility that reversible isomerization of vitamin D to previtamin may be necessary for biological activity.[5] Also in 1961, Rappoldt and co-workers examined the question of the biological activity of previtamin D_3 (**3a**).[6] The latter proved to be about 35% as active in vivo as vitamin D_3, but the apparent antirachitic activity of **3a** was interpreted as originating exclusively from **1a** formed in the animal. That is, the rate of isomerization of **3a** to **1a** was such that the activity observed during the time course of the bioassay could be equally well attributed to the formed **1a** as well as to the administered **3a**.

Since vitamin D_3 (**1a**)[7] and the synthetic analogue 3-deoxy-1α-hydroxyvitamin D_3 (**6a**)[8] are known to be highly biologically active in terms of a classical vitamin D mediated response such as intestinal calcium absorption

Chart I

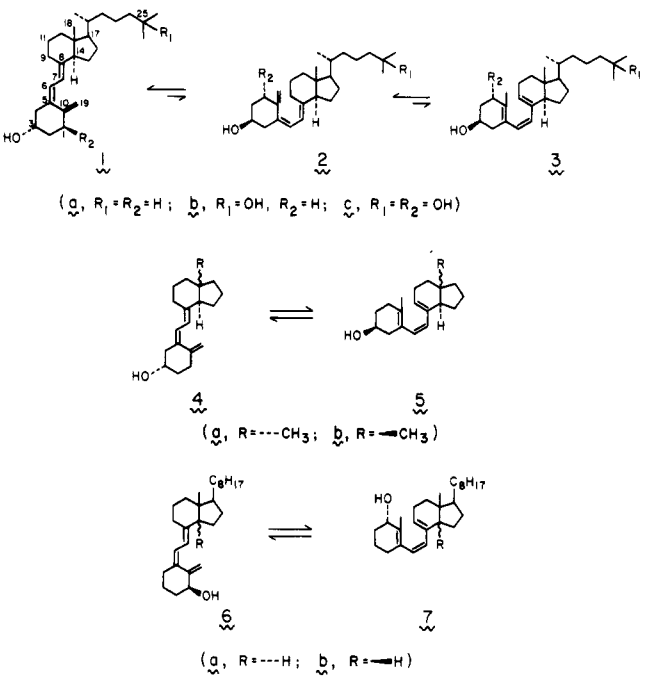
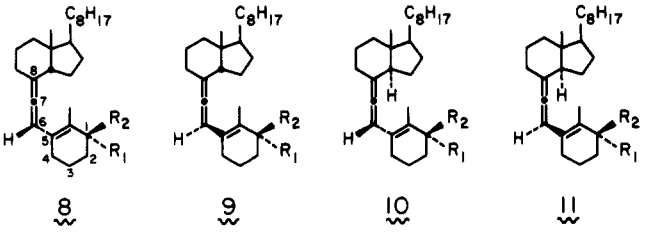


Chart II



(1) Paper 27 in the series "Studies on Vitamin D (Calciferol) and Its Analogues". For Paper 26, see: Gerdes, J. M.; Okamura, W. H. *J. Org. Chem.* **1983**, *48*, 4030.

(2) (a) Norman, A. W. "Vitamin D, the Calcium Homeostatic Steroid Hormone"; Academic Press: New York, 1979. (b) De Luca, H. F.; Paaren, H. E.; Schnoes, H. K. *Top. Curr. Chem.* **1979**, *83*, 1. (c) Georghiou, P. E. *Chem. Soc. Rev.* **1977**, *6*, 83. (d) Fieser, L. F.; Fieser, M. "Steroids"; Reinhold: New York, 1959.

(3) For a general review with leading references, see: Okamura, W. H.; Wing, R. M. In "Vitamin D: Molecular Biology and Clinical Nutrition"; Norman, A. W., Ed.; Marcel Dekker, Inc.: New York, 1980; pp 59–92 and 685–691.

(4) (a) Havinga, E. *Experientia* **1973**, *29*, 1181. (b) Takken, H. J. Ph.D. Thesis, February, 1971, State University of Leiden, the Netherlands. (c) See also: Sheves, M.; Berman, E.; Mazur, Y.; Zaretskŭ, Z. V. I. *J. Am. Chem. Soc.* **1979**, *101*, 1882.

(5) Velluz, L.; Amiard, G. *C. R. Hebd. Seances Acad. Sci.* **1961**, *253*, 603; *Chem. Abstr.* **1961**, *56*, 11662e.

(6) Hanewald, K. H.; Rappoldt, M. P.; Roborgh, J. R. *Recl. Trav. Chim. Pays-Bas* **1961**, *80*, 1003.

(7) For example, see: Hibberd, K.; Norman, A. W. *Biochem. Pharmacol.* **1969**, *18*, 2347.

(8) (a) Okamura, W. H.; Mitra, M. N.; Wing, R. M.; Norman, A. W. *Biochem. Biophys. Res. Commun.* **1974**, *60*, 179. (b) Okamura, W. H.; Mitra, M. N.; Procsal, D. A.; Norman, A. W. *Ibid.* **1975**, *65*, 24. (c) Lam, H. Y.; Onisko, B. L.; Schnoes, H. K.; De Luca, H. F. *Ibid.* **1974**, *59*, 845. (d) Onisko, B. L.; Lam, H. Y.; Reeve, L.; Schnoes, H. K.; De Luca, H. F. *Bioorg. Chem.* **1977**, *6*, 203.

0022-3263/84/1949-2152$01.50/0

Chart III

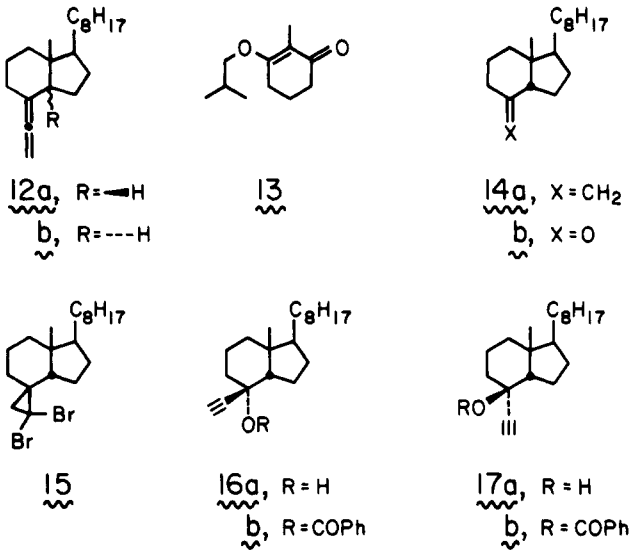
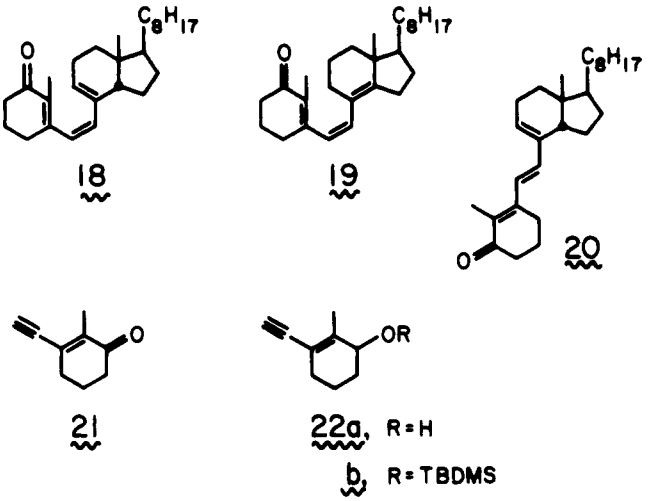


Chart IV

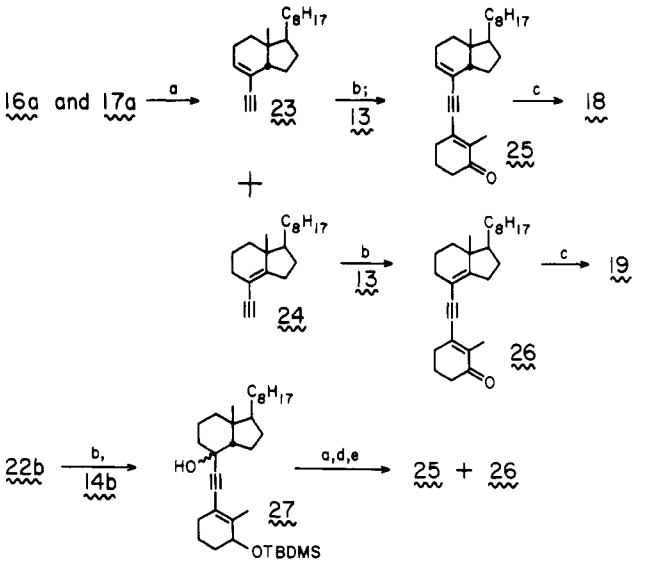


(ICA), it was of interest to prepare and biologically evaluate **6b**, which possesses a *cis*-hydrindane skeleton in contrast to **6a**. From Havinga's observations,[4a,b] it was anticipated that **6b** should easily revert to and favor **7b** and its biological evaluation was also of interest. It is the purpose of this article to describe the preparation and thermal rearrangement of the vitamin D-type vinylallenes[9] **8** and **9** as a means of preparing **6b** and **7b**. It was shown previously that thermolyses of the analogous *trans*-hydrindane systems **10** and **11** (Chart II) led to **6a** and **7a**.[10] The rearrangement of the vinylallenes **10** and **11** initially entails two competing [1,5]-sigmatropic hydrogen shifts, wherein a C_{19} hydrogen migrates to C_7. In this regard, we also describe in this article that the stereochemical course of the thermal rearrangement pathways of **8** and **9** appear to closely parallel[10b] those of **10** and **11**, respectively.

Results and Discussion

The preparation of vinylallenones **8a** ((6*R*)-isomer, 19%) and **9a** ((6*S*)-isomer, 45%) was achieved by treating allene **12a** (Chart III) with *tert*-butyllithium (pentane–ether, −55 °C) and then reacting the incipient lithium salt with keto enol ether **13** followed by acid hydrolysis. The starting allene **12a** was synthesized in two different ways. In the first method, the known olefin **14a**[10b] was converted to the dibromocyclopropane adduct **15** (*t*-BuOK, $CHBr_3$, 80%), which was treated with CH_3Li in ether to afford **12a** (98%). In the second, operationally more convenient method, the known epi Grundmann's ketone **14b**[11] was converted to a ~10:1 mixture of **16a** and **17a** (LiC≡CH, THF, −78 °C, 95%), which upon treatment with 3:1 $LiAlH_4$–$AlCl_3$ (THF, reflux) afforded **12a** in 80% yield.[12] Sodium borohydride reduction of vinylallenone **8a** afforded the alcohols **8b** and **8c** in 25% and 27% yields, respectively. Similarly, **9a** on reduction with $NaBH_4$ afforded **9c** and **9b** in 33% and 31% yields, respectively.

Scheme I[a]



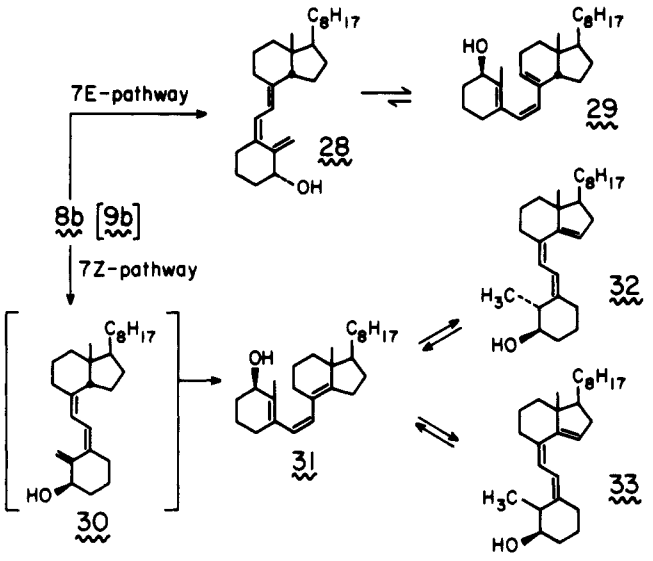
[a] Reagents: a, $POCl_3$, C_5H_5N; b, *n*-BuLi; c, H_2, 1 atm, Lindlar catalyst; d, $(n\text{-Bu})_4NF$, THF; e, PDC.

Thermolysis[13] of (6*R*)-vinylallenone **8a** (isooctane, N_2, 14 h) afforded an inseparable ~1:1.5 mixture of previtamin ketone **18** (Chart IV) and *cis*-isotachysterone (**19**) (75% yield) and the (6*E*)-isomer **20** (5% yield). Under the same conditions of thermolysis; (6*S*)-ketone **9b** afforded a 1:1.2 mixture of **18** and **19** (60%) and **20** (5%). The previtamin ketone **18** and isotachysterone **19** were synthesized independently as shown in Scheme I. The mixture of alcohols **16a** and **17a** were subjected to dehydration ($POCl_3$/C_5H_5N), followed by reverse-phase LC purification (CH_3CN) of the reaction mixture, to afford **23** and **24** in 23% and 46% yields, respectively. Each of the enynes (**23**, **24**) was treated separately with *n*-BuLi and isobutyl enol ether **13** and then hydrolyzed to give **25** and **26**. The dienynes **25** and **26** were then catalytically hydrogenated to previtamin ketone **18** and *cis*-isotachysterone **19**, respectively. In another approach, the enone **21** was reduced to the enynol **22a** ($NaBH_4$) and then converted to the silyl ether **22b**.[8] The lithium salt of silyl ether **22b** was reacted with epi ketone **14b** to afford a complex, isomeric mixture of

(9) Okamura, W. H. *Acc. Chem. Res.* **1983**, *16*, 81.
(10) (a) Hammond, M. L; Mouriño, A.; Okamura, W. H. *J. Am. Chem. Soc.* **1978**, *100*, 4907. (b) Condran, P., Jr.; Hammond, M. L.; Mouriño, A.; Okamura, W. H. *Ibid.* **1980**, *102*, 6259.
(11) Inhoffen, H. H.; Quinkert, G.; Siegismund, S.; Kampe, D.; Domaghk, G. F. *Chem. Ber.* **1957**, *90*, 664.
(12) For similar transformations in a closely related system along with leading references, see: (a) Haces, A.; van Kruchten, E. M. G. A.; Okamura, W. H. *Tetrahedron Lett.* **1982**, *23*, 2707. (b) van Kruchten, E. M. G. A.; Haces, A.; Okamura, W. H. *Ibid.* **1983**, *24*, 3939.

(13) These are standard conditions utilized in our earlier studies. Besides ref 10, see: (a) Leyes, G. A.; Okamura, W. H. *J. Am. Chem. Soc.* **1982**, *104*, 6099. (b) Haces, A.; Okamura, W. H. *Ibid.* **1982**, *104*, 6105.

Scheme II



Scheme III

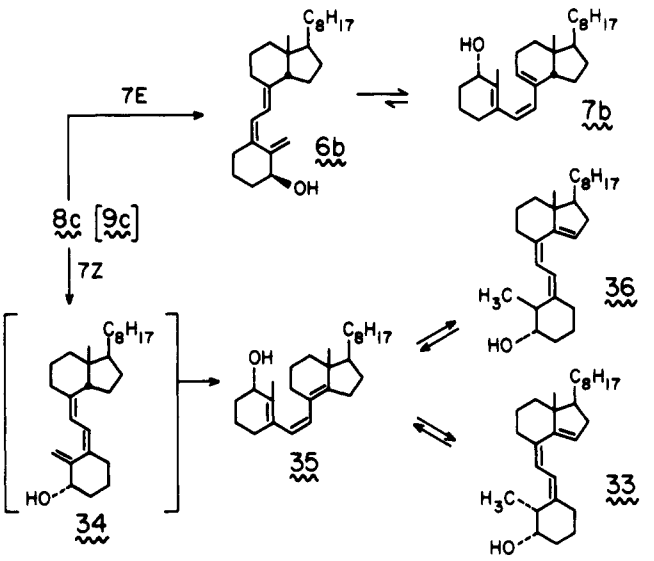


Table I

vinylallenols	7E/7Z ratios C/D cis	C/D trans
(1R,6R)-**8b**	2.9:1.0	2.7:1.0
(1S,6R)-**8c**	1.0:3.8	1.0:4.1
(1R,6S)-**9b**	1.0:4.4	1.0:6.6
(1S,6S)-**9c**	3.8:1.0	3.7:1.0

alcohols **27**, which was converted to **25** and **26** in a one-pot sequence ($POCl_3/C_2H_5N$; $(n\text{-}Bu)_4NF$, THF; PDC; HPLC separation).

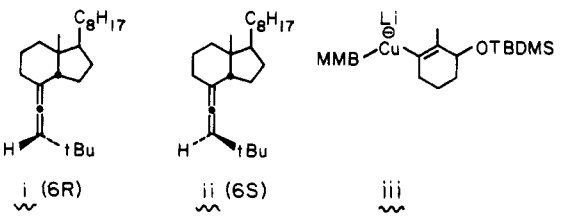
Each vinylallenol (**8bc–9bc**) in isooctane (~0.03 M) was heated at reflux (100 °C) for 10 h under nitrogen. The products expected from **8bc** and **9bc**, by analogy with the previously published[10] behavior of **10bc** and **11bc**, are summarized in Schemes II and III. The actual products and their yields are summarized in the Experimental Section and, in fact, the distribution of products from **8bc** and **9bc** closely resembled that from **10bc** and **11bc**. A notable exception was that the vitamin–previtamin equilibrium (**28** ⇄ **29** in Scheme II; **6b** ⇄ **7b** in Scheme III) strongly favored previtamin (**29** and **7b**), and this subject is discussed further below.

The products **31–33** (formed via **30**) and **35–37** (formed via **34**) were identical by direct comparison (^1H NMR, high-pressure LC) with the samples previously reported.[10] This provides definitive evidence for the 1*R* absolute configuration assigned to **8b** and **9b** (and the resultant thermal products in Scheme II) and the (1*S*)-configuration assigned to **8c** and **9c** (and the products in Scheme III). The C-1 configuration for the vinylallenes could also be assigned on the basis of their specific rotations: for each pair (**8b** vs. **8c** and **9b** vs. **9c**), the more dextrorotatary isomer was assigned the *R* configuration ($[\alpha]^{25}_D$ (*c* 1 g/100 mL, $CHCl_3$) +130° (**8b**); −100° (**8c**); +177° (**9b**); +35° (**9c**)). These configurational correlations are based on Mills rules[14] for cyclohexenols and have been applied previously by this laboratory for related vinylallenols.[15] The previtamin products **29** and **7a** were identified on the basis of their spectral characteristics.

With regard to the configurations of the allene moiety (6*R* for **8a–c** and 6*S* for **9a–c**), the assignments are based on the thermal results (see Table I). The thermal rearrangement of the vinylallenols (**8bc–9bc**) is believed to involve a suprafacial [1,5]-hydrogen shift from C_{19} to C_7. This [1,5]-shift can take place in two ways; namely, 7*E* and 7*Z* pathways as indicated in Schemes II and III. The 7*E* manifold gives the vitamin **28**, which further undergoes [1,7]-shift to afford previtamin **29**. Of particular significance with regard to the allene configuration is the resultant 7*E* (sum of **28** + **29** or **6b** + **7b**) to 7*Z* (sum of **31** + **32** + **33** or **35** + **36** + **37**, respectively) ratio. As can be seen in Table I, since it is known that the C-1 hydroxyl configuration appears to be the most significant factor in controlling these 7*E*/7*Z* ratios,[16] and since the C-1 absolute configurations of **8bc–9bc** are firmly established, the stereochemical assignments for **8b**, **8c**, **9c**, and **9b** follow accordingly from their parallel thermal behavior when compared to **10b**, **10c**, **11c**, and **11b**, respectively.[17]

(14) Mills, J. A. *J. Chem. Soc.* **1952**, 4976.
(15) Mouriño, A.; Lewicka-Piekut, S.; Norman, A. W.; Okamura, W. H. *J. Org. Chem.* **1980**, *45*, 4015.

(16) In general, the substituents on the allene terminus (i.e., the CD ring) play only a minimal role in effecting the 7*Z*/7*E* ratio. See ref 9 and 10 for detailed discussions.
(17) The previtamin was heated to 100 °C for 30 min and then the sample was cooled at once in an ice bath. Analysis of the mixture by ^1H NMR revealed the ~5/95 ratio of **6b**/**7b** indicated. Some attempt was made to correlate configuration with chromatographic behavior as well as with ^1H NMR data. Under similar conditions, the normal-phase high-pressure LC elution profile of the vinylallenols in the CD-cis and CD-trans system were very similar: **8b**(1*R*,6*R*) eluted before **8c**(1*S*,6*R*) as did **10b**(1*R*,6*R*) before **10c**(1*S*,6*R*); **9c**(1*S*,6*S*) eluted before **9b**(1*R*,6*S*) as did **11c**(1*S*,6*S*) before **11b**(1*R*,6*S*). However, whereas **8a**(6*R*) eluted before **10a**(6*S*) in the CD-cis series, **11a**(6*S*) eluted before **10a**(6*R*) in the CD-trans series. The C_{18} methyl shift for **8a** and **9a** are 0.95 and 0.97 ppm, respectively. In (6*R*)-allenes the C_{18} CH_3 group is known to resonate at higher field than its 6*S* counterpart (the difference is ~0.06 ppm; in this case the difference is ~0.02). A similar small difference for the C_{18} methyl group was noted for the (6*R*)- and (6*S*)-*tert*-butylallenes **i** (6*R*, 0.91) and **ii** (6*S*, 0.95). It is known that cuprates react with related



propargyl benzoates in a highly stereoselective anti S_N2' manner to give allenes. Reaction of $(t\text{-}Bu)_2CuCNLi_2$ with **16b** and **17b** afforded **ii** and **i**, respectively. See: Haces, A.; van Kruchten, E. M. G. A.; Okamura, W. H. *Tetrahedron Lett.* **1982**, *23*, 2707 and the references cited therein. All attempts to react cuprate **iii** with benzoate **16b** or **17b** to ultimately afford **9bc** and **8bc**, respectively, in a stereodefined manner failed.

Table II

vinylallenol	products (% relative yield), given in order of elution	mass balance
8b(1*R*,6*R*)	**28** (4), **29** (71), **31** (5), **32** (14), **8b** (0), **33** (7)	80%
8c(1*S*,6*R*)	**6b** (0), **35** (12), **36** (36), **7b** (18), **8c** (16), **37** (19)	81%
9c(1*S*,6*S*)	**6b** (0), **35** (0), **36** (12), **7b** (71), **8c** (11), **37** (7)	70%
9b(1*R*,6*S*)	**28** (0), **29** (17 ± 4), **31** (13), **32** (45), **8b** (8), **33** (17 ± 3)	75%

Of the four thermolysis experiments involving **8bc–9bc**, only in the case of heating **8b** was any vitamin (i.e., **28**) actually isolated in sufficient amounts to be characterized (~4% yield, ^{1}H NMR). In the other cases (**8c**, **9b**, and **9c**), only the previtamins (**7b**, **29**) could be isolated among the 7*E* pathway products. This observation is the reverse of the C/D trans systems where the previtamin D to vitamin D equilibrium is 90/10 at 60 °C (**6a** ⇄ **7a**). In the case of the C/D-cis system described here, an apparent equilibrium ratio for **6b** ⇄ **7b** was found to be 5/95.[18] Havinga also observed a previtamin–vitamin D equilibrium ratio of ~95/5 for their C/D-cis model system **5a** ⇄ **4a** and thus our results parallel the results from the earlier Havinga studies.[4]

To summarize, one of the desired analogues, 3-deoxy-1α-hydroxy-14-epiprevitamin D_3 (**7b**), has been successfully synthesized; its C-1 epimer **29** was also prepared. Preliminary biochemical evaluation[7] of **7b** and **29** revealed that neither of these substances were able to elicit intestinal calcium absorption or bone calcium mobilization in vivo in the chick. Several hypotheses may be put forward to account for these observations. For example, the vitamin form of **7b** (i.e., **6b**) may in fact be necessary for activity or the unnatural configuration of **7b** at C-14 precludes its eliciting activity. Because of the thermal conditions involved in the method of synthesis (thermolysis of vinylallenes) described herein, it appears impractical to obtain sufficient quantities of **6b** and **28** for further characterization and biological evaluation.

Experimental Section

General Procedures. Spectroscopic (^{1}H NMR, IR, UV, high- and low-resolution MS) and other data are given in the supplementary material.

Air-sensitive chemicals were stored under nitrogen, and reactions involving alkyllithiums were carried out under dry nitrogen. The cuprate coupling was done under dry Argon. References to aqueous NH_4Cl, $NaHCO_3$, and NaCl refer to the saturated solutions of the above unless otherwise specified. Dry ether and THF were distilled prior to use. Lbpe refers to low-boiling petroleum ether. Isooctane used for thermolyses was first purified (acidic ferrous ammonium sulfate, base, water, $MgSO_4$) and distilled over $LiAlH_4$. Kugelrohr distillation boiling points refer to the external air bath temperature; pressure is in mmHg.

High-pressure liquid chromatography (HPLC) was performed on a Waters 6000A system. A Whatman M9 10/50 Partisil (10 μm particle size, 9.4 mm × 50 cm) column was used for normal phase and Whatman ODS-2 M9 10/50 Partisil (10 μm, 9.4 mm × 50 cm) column was used for reverse-phase separations unless otherwise specified. For ordinary columns, Baker Analyzed Reagent silica gel (60-200 mesh) was used. For TLC precoated plastic plates (0.25 mm, Brinkmann) were used. Silica gel (230–400 mesh, Sigma) was used for flash chromatography.

(6*R*)- and (6*S*)-14-Epi-9,10-secocholesta-5(10),6,7-trien-1-one (8a and 9a). To a cooled (−78 °C) solution of allene **12a** (1.20 g, 4.38 mmol) in dry ether (30 mL) was added *tert*-butyllithium (1.7 mL, 4.4 mmol, 2.6 M in pentane). The mixture was stirred for 5 min at −78 °C and then at −55 °C for 1 h. After cooling the allenyllithium solution back to −78 °C, 3-isobutoxy-2-methylcyclohex-2-en-1-one[10a] (0.91 g, 5.0 mmol) in dry ether (5 mL) was added, the bath was removed, and then stirring was continued at ambient temperature for 1.5 h. Aqueous acetic acid (10 mL, 1 M) was added to the stirred mixture and then the latter was stirred vigorously for 5 min. The aqueous layer was removed, 10 mL of fresh acid was added, and then the stirring was resumed for 0.5 h. The mixture was taken up in 50 mL of ether and the organic layer was washed successively with aqueous $NaHCO_3$ (2 × 20 mL), H_2O (1 × 20 mL), and brine (1 × 25 mL). The ether solution was dried ($MgSO_4$), filtered, and concentrated to a yellow oil (~1:6 starting allene and allenone by ^{1}H NMR). Starting allene was removed by chromatography (short silica gel column, elution with 200 mL of lbpe followed by 400 mL of 15% ethyl acetate/lbpe) to afford 1.05 g (72%) of vinylallenone isomers. The mixture was separated by high-pressure LC (Whatman partisil column; 10% ethyl acetate/skellysolve B) followed by vacuum drying to afford **8a** (isomer A, eluted first, 0.28 g, 19%) and **9a** (isomer B, eluted second, 0.65 g, 45%) as colorless oils. Isomers A and B are tentatively assigned to possess the 6*R* (minor) and 6*S* (major) allene configurations, respectively.

Thermolysis of Vinylallenones 8a and 9a. A solution of each vinylallenone (~0.1 M) in isooctane (purified and then distilled from $LiAlH_4$) was refluxed for 14 h. The solvent was evaporated under vacuum and then the residue was subjected to preparative high-pressure LC (Whatman Partisil, 10% EtOAc/skellysolve B, 3 mL/min flow rate). The ketones **18** and **19** were obtained only as an inseparable mixture (normal or reverse-phase high-pressure LC in a variety of solvents) accompanied by the easily separated (6*E*)-trienone **20**. The results were as follows: (6*R*)-vinylallenone **8a** afforded 75% of pure trienone mixtue (1:1.5 ratio of preketone **18** to isotachysterone **19** by ^{1}H NMR analysis) and 5% of (6*E*)-isomer **20**; (6*S*)-vinylallenone **9a** afforded 60% of pure trienone mixture (1:1.2 ratio of preketone **18** to isotachysterone **19** by ^{1}H NMR analysis) and 5% of (6*E*)-isomer **20**. The preparation of individually purified samples of trienones **18** and **19** are described elsewhere in this article; mixtures of the ketones were readily analyzed by ^{1}H NMR integration of their olefinic signals. In control experiments, samples of the mixture of ketones **18** and **19** upon heating, under the reaction conditions (~14 h, isooctane, reflux) for their formation from allenones, afforded small amounts (~8%) of the (6*E*)-byproduct **20**.

(1*R*,6*R*)- (8b) and (1*S*,6*R*)-14-Epi-1-hydroxy-9,10-secocholesta-5(10),6,7-triene (8c). To a solution of vinylallenone **8a** (190 mg, 0.49 mmol) in absolute ethanol (5 mL) at 0 °C was added $NaBH_4$ (190 mg, 5 mmol). After stirring at room temperature for 3 h, the mixture was worked up in the usual manner (1 M aqueous HCl quenching, ether extraction, etc.). The residual mixture was separated by high-pressure LC (Whatman Partisil; 10% ethyl acetate/skellysolve B) to afrord (1*R*,6*R*)-**8b** (48 mg, 25%) and (1*S*,6*R*)-**8c** (51 mg, 27%) as viscous oils.

(1*S*,6*S*)- (9c) and (1*R*,6*S*)-14-Epi-1-hydroxy-9,10-secocholesta-5(10),6,7-triene (9b). The $NaBH_4$–ethanol reduction of the vinylallenone **9a** (360 mg, 0.93 mmol) was carried out exactly as described for **8a** in the preceding experiment. Preparative high-pressure LC (Whatman Partisil; 10% ethyl acetate/skellysolve B) followed by vacuum drying afforded (1*S*,6*S*)-**9c** (120 mg, 33%) and (1*R*,6*S*)-**9b** (110 mg, 31%) as colorless oils.

Thermolysis of Vinylallenols 8bc–9bc (Table II). A solution of each of four vinylallenols **8bc–8bc** in isooctane (~0.03 M) was refluxed for 10 h under nitrogen. The solvent was evaporated under reduced pressure and then the reaction mixture was subjected to preparative high-pressure LC (Whatman Partisil; 10% ethyl acetate/skellysolve B, 3 mL/min flow rate). The results of thermolyses are summarized below. The yields are the average values obtained by weight and by integration of the high-pressure LC RI detector traces. The percent average deviation between the two determinations was ≲±2% except as noted; a value of zero signifies that the isomer was not isolable in sufficient quantities (<3%) for identification. Only in the case of **8b**, vitamin **28** was obtained in 4% yield and characterized by ^{1}H NMR and UV. **28**: ^{1}H NMR δ 6.26 and 6.15 (2 H, $H_{6,7}$, AB_q, J ~ 11.3 Hz),

(18) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

5.32 (1 H, H_{19E}, bt, $J \sim 1.5$ Hz), 4.98 (1 H, H_{19Z}, bt, $J \sim 1.5$ Hz), 4.2 (1 H, $H_{1\alpha}$, $w_{1/2} \sim 13$ Hz); UV (95% EtOH) λ_{max} 262 and 234 nm, λ_{min} 225 nm. Its ^{1}H NMR also showed the presence of trace amounts of previtamin **29**. No further attempts were made to prepare this vitamin **28** because of its low yield and its tendency to equilibrate towards previtamin **29**.

De-A,B-14-epi-8-ethenylidenecholestane (12a). Methyllithium (7.7 mL, 10.5 mmol, 1.37 M in ether) was added dropwise (3 min) to an ice-cooled solution of dibromocyclopropyl compound **15** (4.70 g, 10.8 mmol) in dry ether (100 mL). After stirring overnight at ambient temperature, the mixture was poured into a separatory funnel containing lbpe (150 mL) and water (150 mL). The water layer was separated and extracted with an additional 150 mL lbpe. The organic extracts were combined, washed with brine (150 mL), dried ($MgSO_4$), filtered, and concentrated. Distillation (Kugelrohr, 130 °C (1.8 mm)) yielded 2.9 g (98%) of the colorless 14-epiallene **12a**.

In a second method, the propargyl alcohols **16a,17a** (1.2 g, 4.1 mmol) in THF (10 mL) were added dropwise to a mixture of $LiAlH_4$ (0.5 g, 13.2 mmol) and anhydrous $AlCl_3$ (0.6 g, 4.5 mmol) in THF (75 mL). The reaction mixture was refluxed under nitrogen for 14 h. The excess $LiAlH_4$ was destroyed by cautiously adding water and then the mixture was taken up in ether (100 mL). The organic layer was washed with water (2 × 20 mL) and dried ($MgSO_4$). Evaporation of ether afforded a colorless oil, which was chromatographed over silica (lbpe eluent) to afford, after distillation, 0.91 g (80%) of the allene (**12a**).

2,2-Dibromospiro[cyclopropane-1,8′-de-A,B-14′-epicholestane] (15). To an ice-cooled mixture of **14a**[10a] (6.3 g, 24 mmol), KO-*t*-Bu (13.5 g, 120 mmol), and 100 mL of dry Skellysolve B was added bromoform (10.7 mL, 30.9 g, 120 mmol) dropwise. The resulting suspension was stirred overnight and then poured into a separatory funnel containing lbpe (200 mL) and water (200 mL). The layers were separated, and then the aqueous fraction was extracted with an additional 100 mL of lbpe. The combined organic extracts were washed (150 mL of water), dried (Na_2SO_4), and concentrated. Kugelrohr distillation (160 °C (0.08 mm)) gave 8.3 g (80%) of the 14-epidibromocyclopropane product **15**.

De-A,B-8β-ethynyl-14-epicholestan-8α-ol (16a) and De-A,B-8α-ethynyl-14-epicholestan-8β-ol (17a). Epi Grundmann's ketone **14b**[11] (0.53 g, 2.0 mmol) in THF (5 mL) was added dropwise to a lithium acetylide solution (prepared from excess acetylene according to Midland's method: THF (50 mL), −78 °C, *n*-butyllithium (1.6 M in hexane, 2.57 mL, 4.02 mmol)) at −78 °C and then, after stirring for 1 h, the mixture was warmed to room temperature and stirred for an additional 30 min. The reaction mixture was quenched with water (2 mL), anhydrous K_2CO_3 was added, and then the organic layer was dried ($MgSO_4$) and filtered. Evaporation gave almost pure alcohol mixture (95% crude yield), which upon high-pressure LC (Whatman Partisil, 10% EtOAc/skellysolve b) separation afforded **16a** (415 mg, 71%, eluted first) and **17a** (42 mg, 7%, eluted second). High-pressure LC analysis (refractive index detection, uncorrected) of the mixture prior to separation indicated a 7.7 to 1.0 mixture of **16a** to **17a**. The configurations of the epimeric alcohols were established by a ^{1}H NMR–LIS study (see supplementary material section).

De-A,B-8β-ethynyl-14-epicholestan-8α-yl Benzoate (16b). *n*-Butyllithium (2.4 mL, 1.5 M, 3.6 mmol) was added to a solution of the propargyl alcohol (**16a**, 1.00 g, 3.45 mmol) in THF (20 mL) at −78 °C. After stirring at room temperature for 30 min, the mixture was cooled to −78 °C and then benzoyl chloride (0.506 g, 3.6 mmol) was added. The reaction mixture was stirred at room temperature for 2 h, quenched with water, and then THF was removed under vacuum. The residue was extracted with ether and then the ether layer was washed with water and dried ($MgSO_4$). Concentration afforded the crude product, which was chromatographed over silica gel (5% ether/lpbe) to afford, after appropriate processing of fractions, 1.11 g of **16b** (82%, viscous oil) and 0.12 g of the starting alcohol **16a** (12%).

De-A,B-8α-ethynyl-14-epicholestan-8β-yl Benzoate (17b). The propargyl alcohol **17a** (120 mg, 0.41 mmol) was treated with *n*-butyllithium (0.33 mL, 1.6 M, 0.53 mmol) and benzoyl chloride (75 mg, 0.53 mmol) in the same way as described for the epimeric alcohol **16a**. The reaction product was purified by silica gel chromatography (5% ether/lbpe) to afford the benzoate **17b** (75 mg, 46%) and starting alcohol **17a** (30 mg, 18%).

(6*Z*)-14-Epi-9,10-secocholesta-5(10),6,8-trien-1-one (18). A solution of dienynone **25** (10 mg, 0.027 mmol) and Lindlar catalyst (10 mg) in benzene (0.6 mL) was exposed to hydrogen gas (1 atm) for 6 h at room temperature. The solution was filtered and concentrated, and then the residue was subjected to high-pressure LC (4% EtOAc/skellysolve B, 4.0 mL/min, Partisil M-9) to yield the 14-epiprevitamin ketone **18** (4.2 mg, 42%).

(6*Z*)-9,10-Secocholesta-5(10),6,8(14)-trien-1-one (19). A solution of dienynone **26** (57 mg, 0.15 mmol), Lindlar catalyst (6 mg), and quinoline (1 drop) in benzene (1.5 mL) was exposed to hydrogen gas until absorption noticeably decreased (4 h, room temperature). The solution was filtered and then the residue was chromatographed on high-pressure LC (4% EtOAc/skellysolve B, 4.0 mgl/min, Partisal M-9 column) to afford after concentration the known *cis*-isotachysterone **19** (20 mg, 34%) as an oil. Significant quantities of other byproducts were also observed.

3-Ethynyl-2-methylcyclohex-2-en-1-one (21). A dry round-bottom flask equipped with magnetic stirring bar and rubber septum was charged with acetylene gas (2250 mL, 0.082 mmol) in cold (−78 °C) dry THF (50 mL). *n*-Butyllithium (20 mL, 0.031 mmol, 1.55 M in hexane) was added dropwise to the cooled (−78 °C) solution and stirred 10 min. Enol ether **13** (5 g, 0.027 mmol) in THF (5 mL), along with additional THF (2 × 5 mL) for rinsing, was then cannulated into the reaction flask. The reaction mixture was stirred (−78 °C, 30 min, room temperature, 1 h) and then quenched by the addition of water (5 mL). Solid K_2CO_3 was added and, after removal of the K_2CO_3 by filtration, the mixture was diluted with ether (200 mL). The ether layer was washed with water (100 mL) and brine (100 mL) and then dried over $MgSO_4$. Filtration followed by concentration afforded an orange-red oil. The oil was diluted with 20 mL of ether and stirred vigorously (1 h, room temperature) with 1 M HCl (10 mL). The layers were separated and the aqueous layer was extracted with ether (20 mL). The organic layers were combined and then washed with aqueous $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL). After drying over $MgSO_4$, the ether solution was filtered and then concentrated to afford a yellow-orange oil. Crystallization of the oil at −12 °C from pentane (10 mL) afforded **21** as yellow crystals [2.6 g, 72%, mp 40–41 °C (lit.[19] mp 41–42 °C)].

3-Ethynyl-2-methylcyclohex-2-en-1-ol (22a). In a 50-mL pear-shaped flask, equipped with a magnetic stirring bar, rubber septum, and nitrogen inlet needle, was placed enone **21** (1.70 g, 13.0 mmol) and 0.04 M $CeCl_3$ in MeOH (35 mL, 1.40 mmol $CeCl_3$). The orange solution was stirred at ambient temperature for 5 min for complete dissolution and then cooled to 0 °C in an ice bath. Sodium borohydride (0.984 g, 25.1 mmol) was added slowly in small portions to minimize foaming. When addition was complete, the ice bath was removed and the cloudy orange solution stirred at ambient temperature. Monitoring by TLC (10% EtOAc/skellysolve B) indicated the reaction was complete within 5 min. Acid (1 M HCl, 30 mL) was added until the solution turned clear orange. The methanol solution was extracted with ether (3 × 50 mL) and then the combined extracts were washed with aqueous $NaHCO_3$ (50 mL), water (50 mL), and brine (50 mL). Drying ($MgSO_4$), filtration, concentration, and then distillation (Kugelrohr, 80 °C (0.5 mm)) gave **22a** (1.26 g, 74%) as a clear oil.

1-(*tert*-Butyldimethylsiloxy)-3-ethynyl-2-methylcyclohex-2-ene (22b). In a 50-mL round-bottom flask, equipped with a magnetic stirring bar, rubber septum, and a nitrogen inlet needle, was placed *tert*-butyldimethylsilyl chloride (1.66 g, 11.0 mmol), imidazole (1.50 g, 22.0 mmol), and *N,N*-dimethylformamide (DMF, 3.0 mL, freshly distilled from CaH_2 under nitrogen). The alcohol **22a** (1.0 g, 7.34 mmol) was dissolved in DMF (2 mL) and added to the above solution at once. The flask and the syringe were rinsed with additional DMF (1.0 mL and then 1.5 mL). TLC (10% EtOAc/skellysolve B) analysis after 1 h indicated the reaction was complete. The mixture was poured into water (120 mL) and the resulting aqueous solution was extracted with ether (3 × 50 mL). The combined ethereal extracts were washed with 1 M HCl (50 mL), aqueous $NaHCO_3$ (3 × 50 mL), and water (50 mL). After drying ($MgSO_4$) and filtration, the solution was concentrated to a yellow oil. The residue was distilled on the Kugelrohr (70–72

(19) Eschenmoser, A.; Schreiber, J.; Julia, S. A. *Helv. Chim. Acta* **1953**, *36*, 482.

°C (0.2 mm)) to yield the product **22b** (1.66 g, 90%) as a clear oil.

De-A,B-8-ethynyl-14-epicholest-8-ene (23) and De-A,B-8-ethynylcholest-8(14)-ene (24). Epipropargyl alcohol **16a,17a** (80 mg, 0.27 mmol) was dissolved in pyridine (8 mL, freshly distilled from KOH, nitrogen atmosphere) and $POCl_3$ (0.5 mL, freshly distilled) was added. The solution was heated in an oil bath at reflux for 1 h and then cooled in an ice bath. The condenser was rinsed cautiously with water into the reaction vessel and then 5 mL of 1 M HCl was added. The reaction mixture was extracted thoroughly with ether (6 × 25 mL). The combined ethereal layer was washed with acid (1 M HCl, 3 × 50 mL), aqueous $NaHCO_3$ (2 × 50 mL), and brine (50 mL), and then dried over $MgSO_4$. Filtration followed by concentration gave a yellowish oil, which was subjected to high-pressure LC (100% CH_3CN, 4.0 mL/min, ODS-2 column). Of the two fractions collected, the first fraction corresponded to the Δ^8-isomer **23** (17.5 mg, 23%) and the second major fraction corresponded to the $\Delta^{8(14)}$-isomer **24** (34.3 mg, 46%).

14-Epi-9,10-secocholesta-5(10),8-dien-6-yn-1-one (25). To a solution (−78 °C) of enyne **23** (84.5 mg, 0.31 mmol, freshly distilled) in dry THF (0.31 mL) was added dropwise *n*-butyllithium (0.21 mL, 0.38 mmol, 1.8 M in hexane) and then the mixture was allowed to react with stirring as follows: 20 min, −78 °C; 20 min, room temperature; 20 min, −78 °C. The A ring fragment **13** (68.5 mg, 0.374 mmol) in dry THF (0.37 mL) was then added to the cooled solution. After the solution was stirred at −78 °C (45 min) and then at room temperature (45 min), aqueous HCl (1 M, 0.8 mL) was added. The resulting mixture was stirred vigorously for 1 h, followed by dilution with ether (5 mL), and then the ether and water layers were separated. The aqueous layer was back extracted with ether (5 mL). The combined ethereal extracts were washed with aqueous $NaHCO_3$ (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated. The crude reaction mixture was flash chromatographed (5% EtOAc/lbpe) to yield 28.2 mg (24%) of the product **25**.

9,10-Secocholesta-5(10),8(14)-dien-6-yn-1-one (26). To a solution of CD ring fragment **24** (100 mg, 0.37 mmol) in THF (0.37 mL at −78 °C) was added dropwise *n*-butyllithium (0.22 mL, 0.40 mmol, 1.8 M in hexane). After stirring at −78 °C for 1 h, the A ring fragment **13** (71.5 mg, 0.39 mmol) in THF (0.1 mL) was added dropwise over 5 min. Additional THF rinsings (3 × 0.1 mL) were utilized to insure complete transfer. The solution was stirred at −78 °C for 35 min and then the cooling bath was removed. After stirring the orange solution at room temperature for 80 min, the reaction was quenched by adding 1 M HCl (0.8 mL) and then the mixture was stirred for 30 min. The reaction mixture was diluted with ether (4 mL), washed with aqueous $NaHCO_3$ (4 mL) and brine (4 mL), and then dried over $MgSO_4$, filtered, and concentrated. The residue was flash chromatographed (5% EtOAc/lbpe) to yield recovered CD ring fragment **24** (30.1 mg, 30%) and the desired product **26**. The latter was further purified by high-pressure LC (5% EtOAc/skellysolve B, Partisal, M-9, 4.0 mL/min) to afford 69 mg (49%) of dienynone **26**.

14-Episecocholesta-5(10),8-dien-6-yn-1-one (25) and 9,10-Secocholesta-5(10),8(14)-dien-6-yn-1-one (26) from Epi Grundmann's Ketone (14b) and 1-(*tert*-Butyldimethylsiloxy)-3-ethynyl-2-methylcyclohex-2-ene (22b). To a solution (−78 °C, nitrogen) of freshly distilled A ring fragment **22b** (258 mg, 1.02 mmol) in THF (3 mL, freshly distilled from LAH) was added *n*-butyllithium (0.9 mL, 1.08 mmol, 1.2 M in hexane) dropwise, turning the colorless solution yellow. The solution was stirred (−78 °C, 1 h) and then freshly distilled epi Grundmann's ketone **14b**[11] (273 mg, 1.03 mmol) in THF (2 mL) was added. The ketone-holding flask and syringe were rinsed with THF (2 × 0.5 mL) to insure complete transfer. The solution was stirred (−78 °C, 2.5 h, room temperature, 3 h) and then quenched by the addition of water (1 mL). The reaction mixture was diluted with ether (10 mL) and washed with water (10 mL), and then the ether phase was separated. The aqueous layer was extracted with ether (3 × 10 mL) and then the combined ethereal layers were washed with aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The ether layer was dried ($MgSO_4$), filtered, and concentrated to yield a dark oil, which was chromatographed on a 1 in. × 6 in. flash column. The column was eluted sequentially with lbpe (250 mL) followed by mixtures of EtOAc/skellysolve B (200 mL, 1%; 200 mL, 2%; 100 mL, 3%; 100 mL, 4%; 400 mL, 5%). Fractions (~25 mL each) 10–22 yielded A ring fragment **22b** (3.7 mg), 27–33 afforded coupled products (303 mg, 58% based on A ring fragment), and 39–44 gave traces of C/D ring fragment **14b**. The ^1H NMR (200 MHz) spectrum of the mixture of isomers exhibited two singlets at 0.08 and 0.1 ppm corresponding to the methyl groups of the *tert*-butyldimethylsiloxy group, as well as signals at 0.85, 0.88, 0.90, 0.93, and 0.95 ppm, which probably correspond to $C_{26,27}$, *tert*-butyl, and C_{21} methyl groups of the various isomers. Signals at 1.00 and 1.05 ppm are attributed to the C_{18} methyl groups of various isomers and a broad signal at 4.07 ppm was assigned to their H_1 proton signals.

The mixture of alcohols (23 mg, 0.045 mmol) was dissolved (nitrogen atmosphere) in pyridine (5 mL, freshly distilled from KOH) and reacted with $POCl_3$ (8.3 μL, 0.09 mmol, freshly distilled) at reflux temperature. After 1.5 h, the reaction mixture was cooled (0 °C), quenched by slow addition of water (0.5 mL), and thoroughly extracted with ether (5 × 15 mL). The ethereal layers were combined, washed with dilute acid (1 M HCl, 5 × 20 mL), aqueous $NaHCO_3$ (20 mL), and brine (20 mL), and then dried ($MgSO_4$). Filtration and concentration yielded a brown oil, which upon examination by ^1H NMR, showed an olefinic peak near 6.0 ppm attributable to the Δ^8-isomer. The presence of the $\Delta^{8(14)}$-isomer was not determinable by ^1H NMR at this stage.

The crude olefin mixture (22 mg, 0.045 mmol) was exposed to $(n\text{-Bu})_4NF$ (2 mL, 1 M in THF) at room temperature under nitrogen (1 h) until the starting material had disappeared (by TLC, 10% EtOAc/lbpe eluant). After dilution with ether (15 mL), the mixture was washed with water (5 mL), aqueous $NaHCO_3$ (5 mL), and brine (5 mL), and then dried ($MgSO_4$). Filtration and concentration yielded a dark oil. High-pressure LC separation (15% EtOAc/skellysolve B, 4.0 mL/min, Partisil) yielded a mixture of alcohols (7.4 mg). Spectral analysis (^1H NMR) showed the absence of the *tert*-butylsiloxy group, the presence of $C_{26,27}$, C_{18}, and C_{19} methyl groups as signalled by peaks at 0.85, 0.87, 0.90, and 2.0 ppm, the presence of an olefinic peak at 6.9 ppm, and the presence of protons adjacent to hydroxyl groups as a broad signal at 4.08 ppm.

The alcohol mixture (7.4 mg) thus obtained was oxidized by addition of a solution (nitrogen atmosphere) of pyridinium dichromate (75 mg, 0.2 mmol) and pyridinium trifluoroacetate (4 mg, 0.02 mmol) in CH_2Cl_2 (0.2 mL). Stirring at room temperature (2 h) resulted in the disappearance of starting alcohol and the appearance of a less polar spot on TLC. The crude reaction mixture was poured through a sintered glass filter containing a layer of silica gel, a layer of $MgSO_4$, and a layer of Celite. The filtration pad was thoroughly washed with ether. The filtrate was concentrated and then subjected to high-pressure LC (100% MeOH, ODS-2 reverse-phase M-9 column, 4.0 mL/min) to yield two fractions in a 3:1 ratio. The earliest eluting substance by ^1H NMR comparison to previously synthesized compound was determined to be the Δ^8-isomer **25** (3.0 mg, ~41%) based on allylic alcohol. The second eluting substance by ^1H NMR comparison was determined to be the $\Delta^{8(14)}$-isomer (<1 mg, ~8%) based on allylic alcohol.

(1*R*,6*Z*)- and (1*S*,6*Z*)-9,10-Secocholesta-5(10),6,8(14)-trien-1-ol (31 and 35). To a solution of ketone **19** (20 mg, 0.052 mmol) in 0.4 M $CeCl_3$ in MeOH (1 mL) was added (0 °C, nitrogen atmosphere) $NaBH_4$ (20 mg, 0.52 mmol) at once. The ice bath was removed and the reaction mixture was stirred for 5 min. After quenching by the addition of 1 M HCl (2 mL), the mixture was extracted with ether (3 × 15 mL) and then combined ethereal layers were washed with aqueous $NaHCO_3$ (30 mL) and brine (30 mL). Drying over $MgSO_4$ followed by filtration, concentration, and then chromatography of the residue by high-pressure LC (10% EtOAc/skellysolve B, 4.0 mL/min on Partisil M-9 column) afforded two fractions. These were obtained in a ratio of 1.1:1.0 by integration of the UV traces. The first substance eluted was identified as the (1*S*)-isomer **35** (5.2 mg, 26%) by comparison of its HPLC retention time and by ^1H NMR spectra with those of an authentic sample. The second substance eluted (4.1 mg, 21%) was similarly identified as the (1*R*)-isomer **31**.

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Supplementary Material Available: Spectral and other analytical data (15 pages). Ordering information is given on any masthead page.

Defined Dimensional Alterations in Enzyme Substrates. *lin*-Naphthoadenine and *lin*-Naphthoadenosine

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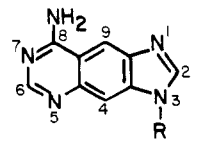
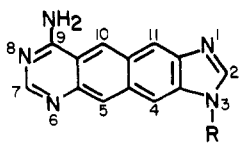
lin-Naphthoadenine (*lin* = linear) and *lin*-naphthoadenosine have been synthesized for the first time, on the basis of the availability of the intermediate *lin*-naphthohypoxanthine from a shortened, efficient synthesis. 5,6-Dimethylbenzimidazole, protected by a bulky group on N, was subjected to selective benzylic bromination. The tetrabromo product, when treated with sodium iodide under Finkelstein conditions, generated a dibromo-*o*-xylylene intermediate that could be trapped by maleic anhydride or *N*-hydroxymaleimide, with aromatization by loss of 2 HBr. This Diels–Alder cycloaddition approach to the otherwise difficultly available tetra-β-substituted naphthalenes was followed by stepwise conversions of the terminal anhydride or *N*-hydroxy imide ring to a suitably substituted pyrimidine ring. *lin*-Naphthoadenine and *lin*-naphthoadenosine are brilliantly fluorescent, exhibiting high fluorescent yields (Φ = 0.57, 0.64) and long lifetimes (τ = 20.5, 22.4 ns in ethanol purged of oxygen). Neither is a substrate for adenosine deaminase, showing that a lateral extension of 4.8 Å is too great for a satisfactory fit at the enzyme active site, whereas a 2.4-Å extension (*lin*-benzoadenine and *lin*-benzoadenosine) is tolerated.

The concept of utilizing defined dimensional probes for testing the spatial restrictions of enzyme binding regions for purine-containing substrates or cofactors has been advanced in this Laboratory with the synthesis and biological evaluation of laterally extended analogues of naturally occurring purines.[1] The lateral extensions are of known magnitude, brought about by the formal insertion of a benzo (2.4 Å), benzocyclobutadieno (3.9 Å), or naphtho (4.8 Å) unit between the terminal pyrimidine and imidazole rings. With synthetic dimensional probes of these types, we have been able to improve descriptions of binding and to define more accurately the spatial basis of activity and inhibition by comparison of the biochemical behavior of the synthetic analogues with those of the natural substrates and cofactors. As examples, *lin*-benzoadenine (1) and





1 R = H
2 R = β-D-Ribofuranosyl

3 R = H
4 R = β-D-Ribofuranosyl

lin-benzoadenosine (2) are excellent substrates for adenosine deaminase and show fluorescence characteristics that have made them, along with the mono-, di-, tri-, and cyclic phosphates of 2, useful in enzyme binding studies. The synthetic *lin*-naphthopurine analogues, *lin*-naphthoxanthine and *lin*-naphthohypoxanthine, which are intensely fluorescent, have been applied toward setting the spatial limits of the binding region of xanthine oxidase.[2] We have now provided a second method of synthesis of the *lin*-naphthopurine ring system that leads successfully to *lin*-naphthoadenine (3) and *lin*-naphthoadenosine (4).

The challenge of construction of the tetracyclic ring system in the *lin*-naphthopurine series lies in the synthesis of requisite tetra-β-substituted naphthalene intermediates. We have previously developed methodology for the regioselective synthesis of such intermediates via an *o*-xylylene precursor, 3,4-bis(trimethylsilyl)bicyclo[4.2.0]octa-1,3,5-triene, and an appropriate dienophile.[2] While we were convinced of the value of the Diels–Alder cycloaddition approach, we sought a more accessible substituted *o*-xylylene precursor. *o*-Xylylenes can also be obtained from substituted benzo[*c*]thiophene 2,2-dioxides by thermal cheleotropic elimination of sulfur dioxide.[3] Since these heterocycles are usually obtained from *o*-bis(bromomethyl)benzenes, which have themselves been shown to be precursors of *o*-xylylenes under the mild conditions of the Finkelstein reaction,[4] we perceived no obvious advantage in employing the thiophene dioxide route. Cava has shown that naphthalenes and anthraquinones can be synthesized from *o*-xylenes by benzylic bromination followed by dehalogenation with sodium iodide and in situ

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(2) Moder, K. P.; Leonard, N. J. *J. Am. Chem. Soc.* **1982**, *104*, 2613.
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