chloride. The layers were separated, the aqueous layer was extracted with ether, and the combined ethereal layers were dried over $MgSO_4$. After evaporation of the solvent 9.38 g (0.053 mol) of 2,2-dichloropropanoic acid was obtained contaminated with about 2% of 2,2,3,3-tetrachloropropanoic acid.

p-Methoxyphenyl 2,2-Dichloropropionate (2). A mixture of 6.87 g (0.048 mol) of 2,2-dichloropropanoic acid (containing about 2% of 2,2,3,3-tetrachloropropanoic acid) and 6.5 g (0.055 mol) of $SOCl_2$ was refluxed for 3 h. Distillation of the reaction mixture under reduced pressure (50 °C at ca. 100 mmHg) gave 3.8 g (0.024 mol) of 2,2-dichloropropanoyl chloride. The chloride was converted into **2** by following the same procedure as described for **1** (yield 86%). The ester was purified by using HPLC [silica gel (60 mesh) column, 5 μm; CH_2Cl_2/n-hexane, 50:50]: mp 25.0–26.4 °C; ^1H NMR ($CDCl_3$, Me_4Si) δ 2.38 (3 H, s), 3.72 (3 H, s), 6.70–7.15 (4 H, m); IR 1760 cm^{-1} (C=O). Anal. Calcd for $C_{10}H_{10}Cl_2O_3$: C, 48.22; H, 4.05; Cl, 28.47. Found: C, 48.09; H, 4.05; Cl, 28.34.

Compound **3** was synthesized by following the same procedure as used for **1**. The ester (mp 77.0–77.7 °C, lit.[27] mp 79–80 °C) was recrystallized from 60% EtOH. Ester **4** was synthesized according to the procedure of Funasaki.[28] Recrystallization from 80% EtOH–H_2O gave crystals with a melting point of 61.7–62.2 °C (lit.[29] mp 62–63 °C).

The water used in the kinetic and the solubility measurements was demineralized and distilled twice in an all-quartz distillation unit. t-BuOH was obtained from Merck and 2-n-butoxyethanol from Aldrich. Both solvents were of the highest grade available and were used as such. The solvent mixtures employed in the experiments were all made up by weight. The cosolvent was added to the appropriate amount of water containing 10^{-2} mol kg^{-1} of HCl in the kinetic experiments and 10^{-3} mol kg^{-1} of HCl in the solubility measurements.

Solubility measurements (5–30 °C) were carried out as follows. To 5 mL of the solvent mixture under study in a Slenk vessel was added 5–50 mg of the solute (**3** or **4**). The mixture was magnetically stirred in a thermostated bath (±0.05 °C) for ca. 6 h in order to obtain a saturated solution. This solution was filtered under pressure. After dilution with water containing 10^{-3} mol kg^{-1} of HCl, the concentration of the solute was determined in duplicate by measuring the absorbance at 273 nm (the absorption maximum of **3** and **4**). A correction was made for the absorbance of p-nitrophenol, which was formed by hydrolysis. The concentrated solution was diluted until the absorbance at 273 nm was between 0.5 and 1.0. The original solution was stirred for an additional 2 h, after which the concentration of the solute was again determined in duplicate. If any discrepancy was observed between both sets of measurements, the procedure was repeated a third time.

The solubilities were reproducible to within 1%, and they were determined at five or six temperatures between 5 and 30 °C. The Gibbs free energy, enthalpy, and entropy of transfer were determined by standard methods.[2b] Estimated errors in ΔC_{tr}^{θ}, ΔH_{tr}^{θ}, and ΔS_{tr}^{θ} are 0.02 kcal mol^{-1}, 0.3 kcal mol^{-1}, and 1 eu, respectively. Transfer parameters for transfer of a water molecule can be neglected[30] relative to those for transfer of **1** and **2**.

Kinetic Measurements. Reaction rates and thermodynamic activation parameters for hydrolysis of **1** and **2** were determined as outlined previously.[31] The solvolysis rates of t-BuCl in 2-BE–H_2O were determined conductometrically by using a Wayne–Kerr Autobalance Universal Bridge B642 connected with a Philips P.W. 9512/01 electrode (cell constant C = 0.71 cm^{-1}). To 11 mL of the neutral solvent mixture was added 22 μL of a 0.1 mol kg^{-1} HCl solution to obtain a suitable starting conductivity. The reaction medium was thermostated (±0.01 °C), and 3–10 μL of a concentrated solution of t-BuCl in acetonitrile was added (resulting in a substrate concentration between 0.8×10^{-4} and 2.0×10^{-4}M). The reactions were followed for at least 5 half-lives, and from the change in conductivity (recorded with a Kipp recorder), the rate constants were calculated by using the Guggenheim method. The rate constants were determined at nine temperatures between 15 and 35 °C and could be reproduced within 0.7%.

The estimated errors in $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ are 0.02 kcal mol^{-1}, 0.2 kcal mol^{-1}, and 1 eu, respectively.

Registry No. **1**, 26921-58-4; **2**, 75265-14-4; **3**, 830-03-5; **4**, 1956-06-5.

Supplementary Material Available: Tables VI and VII containing calculated rate constants for hydrolysis of **1** (2 pages). Ordering information is given on any current masthead page.

(27) Bruice, T. C.; Schmir, G. L. *J. Am. Chem. Soc.* **1957**, *79*, 1663.
(28) Funasaki, N. *J. Colloid Interface Sci.* **1978**, *64*, 461.
(29) Williams, A.; Salvadori, G. *J. Chem. Soc. B* **1971**, 2401.
(30) Cf.: Reference 2b. Gillet, H.; Avédikian, L.; Morel, J. P. *Can. J. Chem.* **1975**, *53*, 455.
(31) Holterman, H. A. J.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* 1982, *104*, 6382.

Effect of Seven-Membered Ring Fusion on Thermal Pericyclic Processes of Vinylallenes and Other Seco Steroids Related to A-Homovitamin D[1]

John M. Gerdes[2] and William H. Okamura*

Department of Chemistry, University of California, Riverside, California 92521

Received May 12, 1983

Reaction of the allenylcopper species **10** and iodo ketone **13** produced a 2.4:1 mixture of A-homovinylallenones **1c** (6R) and **2c** (6S). The absolute configurations of **1c** (6R) and **2c** (6S) were assigned by comparison of their ^{13}C NMR and ^1H NMR spectra to the six- (**1b** and **2b**) and five-membered-ring (**1a** and **2a**) vinylallenes. Thermolysis of **1c** (100 °C, 3 h) yielded **3c** (12%), **14** and **15** (12%), **16** (25%), **17** (24%), and **18** (10%). A similar distribution was obtained for **2c**: **3c** (12%), **14** and **15** (16%), **16** (24%), **17** (24%), and **18** (16%). The thermal rearrangements of the A-homovinylallenes **1c** and **2c** occur under much milder conditions than the previously studied six- (**1b** and **2b**) and five-membered-ring (**1a** and **2a**) vinylallene series, and the product distributions differ significantly.

Vitamin D type vinylallenes (**1** and **2**, Scheme I) undergo competitive thermal [1,5]-sigmatropic shifts to afford *E* (**3**) or *Z* (**4**) intermediate trienes. Thermal studies of the five- (**1a** and **2a**) and six-membered (**1b** and **2b**) A-ring vinylallene ketones have revealed that the required thermal

(1) Paper 26 in the series "Studies on Vitamin D (Calciferol) and Its Analogues". For paper 25, see: Toh, H. T.; Okamura, W. H. *J. Org. Chem.* **1983**, *48*, 1414.

(2) This article was taken in part from the Ph.D. thesis submitted to the University of California, Riverside, by J.M.G., Aug 1982.

0022-3263/83/1948-4030$01.50/0

Scheme I

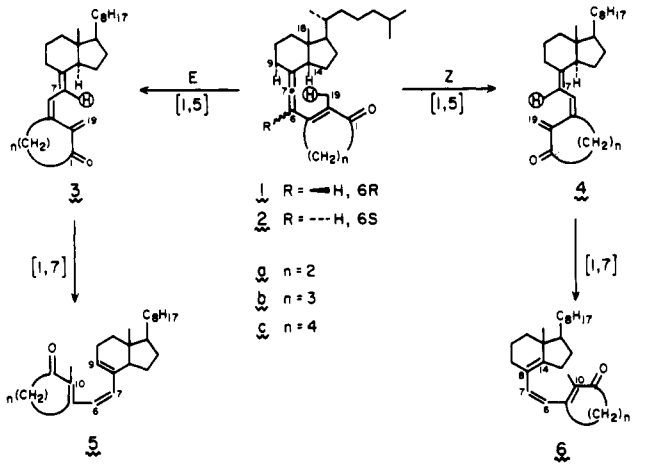
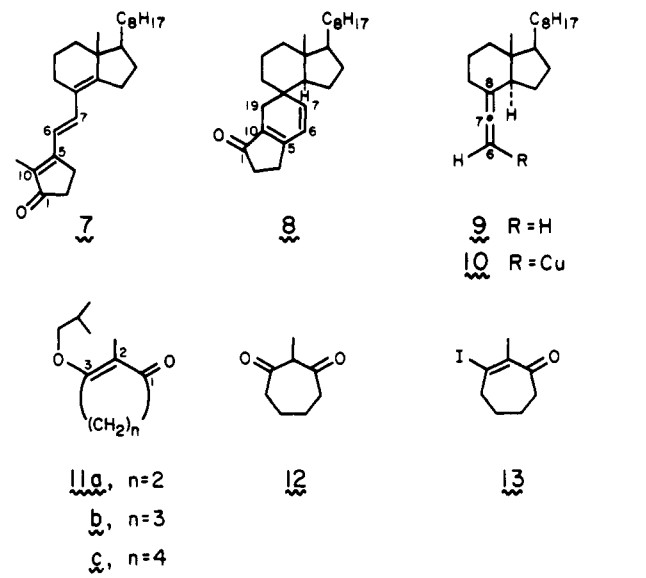


Chart I



isomerization conditions are sensitive to A-ring size.[3,4] Either of the epimeric parent six-membered-ring vinylallene ketones **1b** or **2b**, when heated at 100 °C for 20 h, afforded nearly equal amounts of previtamin ketone **5b** and *cis*-isotachysterone **6b**.[3] These secondary products are believed to be formed by way of [1,7]-sigmatropic hydrogen shifts of the initially formed but not observed intermediates **3b** and **4b**, respectively. The presence of the more stable linear conjugation in **5b** and **6b** readily accounts for their facile formation from the putative cross-conjugated trienones **3b** and **4b**, respectively.

In stark contrast to the six-membered-ring series, thermal rearrangement of the coresponding five-membered-ring vinylallene ketones required significantly harsher conditions.[4] Both **1a** and **2a** were less than 10% reacted under the same conditions (refluxing isooctane, 20 h); the six-membered analogues were completely rearranged. However, heating the *A*-norvinylallenes **1a** and **2a** at 140 °C for 24 h afforded **5a**, **6a**, and also two new isomers, **7** and **8** (Chart I), products of more deep-seated rearrangement processes than those depicted in Scheme I.

(3) (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. *Ibid.* **1978**, *100*, 4907.

(4) Gerdes, J. M.; Lewicka-Piekut, S.; Condran, P., Jr.; Okamura, W. H. *J. Org. Chem.* **1981**, *46*, 5197.

Table I. NMR Data[a,b] for Allenic Ketones 1a-c and 2a-c

compd	J^c	^{1}H NMR[d]	^{13}C NMR[d]
		6*R* ketone	
1a	2.9	0.68	11.94
1b	2.9	0.68	11.97
1c	3.4	0.68	11.91
		6*S* ketone	
2a	3.6	0.74	12.38
2b	3.5	0.75	12.45
2c	4.0	0.74	12.30

[a] Recorded in $CDCl_3$ with $(CH_3)_4Si$ as an internal standard for 1a, 2a, 1b, and 2b: ^{1}H NMR, 90 MHz, Varian EM-390, δ values; ^{13}C NMR, Bruker WH90D-18, FT NMR, δ values. [b] Recorded in $CDCl_3$ with $CHCl_3$ as an internal standard for compounds 1c and 2c: ^{1}H NMR, 200 MHz, JEOL FX-200, δ values; ^{13}C NMR, JEOL FX-200, FT NMR, δ values. [c] ^{1}H NMR *J* values in hertz; H_6 appears as a triplet due to equivalent splitting by $H_{9\alpha}$ and $H_{14\alpha}$. [d] C_{18} methyl.

In order to further probe the effect of structural changes on the course of [1,5]-sigmatropic shifts of vinylallenes, efforts were focused on the *A*-homovinylallenes **1c** and **2c**. In this paper, we report the synthesis and thermal properties of these seven-membered-ring systems.

Results

The synthesis of **1c** and **2c** was initially devised to follow the known allenyl anion coupling procedure, wherein the lithium salt of allene hydrocarbon **9** was condensed with isobutyl enol ether **11b**[3] to afford **1b** and **2b**. Similarly, the five-membered-ring system **1a** and **2a** had been prepared from **9** and enol ether **11a**.[4] Despite numerous trials, preparation of the corresponding enol ether **11c** (isobutyl alcohol, *p*-toluenesulfonic acid, refluxing benzene, 5 h) from the known 2-methylcycloheptane-1,3-dione (**12**)[5] afforded only a complex mixture of products (GLC and ^{1}H NMR analyses).[6] Numerous other known methods, several of which had been successful in our earlier investigations of vinylallenes in the vitamin D series, failed.[7] Consequently, a new method for coupling a seven-membered A ring with the CD fragment was successfully devised. The allenylcopper species **10** was reacted with β-iodo ketone **13** in the presence of a catalytic quantity of tetrakis(triphenylphosphine)palladium to afford after separation **1c** and **2c** in 43% and 18% yields, respectively. The former (**10**) was generated by successive treatment of **9** with *tert*-butyllithium[3a] and then cuprous iodide[8] in THF. The latter (**13**) was simply prepared by refluxing **12** in a mixture of triphenylphosphine, iodine, and triethylamine in CH_3CN for 42 h.[9] It must be mentioned that after our work had progressed, two other groups published[10] a detailed account

(5) Lewicka-Piekut, S.; Okamura, W. H. *Synth. Commun.* **1981**, *10*, 415.

(6) (a) Similar conditions afford the five- (**11a**) and six-membered (**11b**) keto–enol ethers in excellent yield (see ref 3 and 4). (b) It is possible that the acidic conditions employed caused dione **12** to undergo an acid-catalyzed retro-aldol condensation followed by cyclization to a mixture of five-membered-ring adducts. Base-catalyzed ring opening and reclosure of cycloheptane-1,3-dione are known: Maclean, T.; Sneeden, R. P. A. *Tetrahedron* **1965**, *21*, 31.

(7) The various methods reported in the earlier studies as well as the failures encountered in this study are reviewed in Ref 2.

(8) Cuprous iodide was purified according to the method communicated to us by Dr. Bruce Lipshutz, University of California, Santa Barbara.

(9) Dr. Sabina Lewicka-Piekut is acknowledged for providing the details for the preparation of **13**. The method is that of: Piers, E.; Nagakura, I. *Synth. Commun.* **1975**, *94*, 6190.

(10) (a) Ruitenberg, K.; Keijn, H.; Meijer, J.; Oostveen, E. A.; Vermeer, P. *J. Organomet. Chem.* **1982**, *224*, 399. (b) Jeffrey-Luong, T.; Linstrumelle, G. *Synthesis* **1982**, 738.

Scheme II

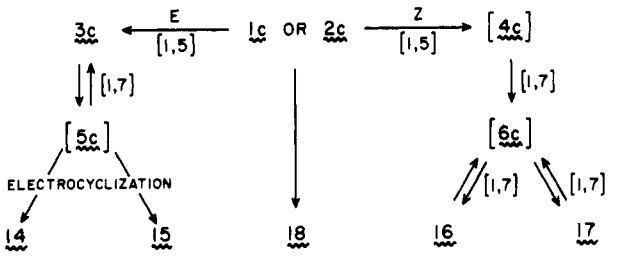
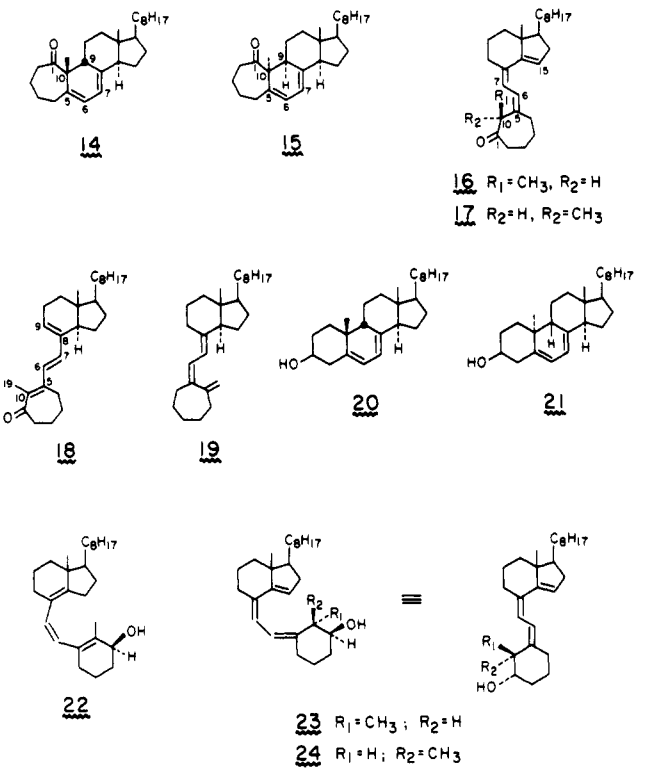


Chart II



of a similar vinylallene synthesis using simple vinyl halides, but not the presumably more reactive β-halo ketones of the kind (**13**) used in this study.

The absolute configurations of the allene groups in **1c** and **2c** were assigned on the basis of three pieces of NMR data[3,4,11] (Table I): the magnitude of the coupling constants between H_6 and the axial protons on C_9 and C_{14}, the ^1H NMR C_{18} angular methyl group chemical shifts, and the ^{13}C NMR C_{18} signals. The allene stereochemical assignments for **1c** and **2c** were thus based on a parallel between these data and those reported for the five- and six-membered vinylallene ketones **1a**,**2a** and **1b**,**2b**,[12] respectively.

Under optimized conditions (isooctane, 100 °C, 3), the 6*R* ketone **1c** produced the vitamin ketone **3c** (12%), an inseparable mixture of cyclized *A*-homoisopyro- and *A*-homopyrocalciferols **14** and **15** (12% total), respectively, methyl epimers **16** (25%) and **17** (24%), and *trans*-*A*-homotachysterone **18** (10%). Identical heating of the 6*S* ketone **2c** gave similar results: **3c** (12%), **14** and **15** (16%), **16** (24%), **17** (24%), and **18** (16%). Thermal control experiments involving the thermolysis of each of the products are described and discussed below. The structures of **3c** and **14**–**18** (Chart II) follow from comparison of their spectral data to those of similar molecules previously reported in the six- and five-membered-ring series and/or in the literature, inferences derived from the thermal control experiments, and consideration of mechanistic arguments concerning their formation.

To more succinctly describe the product distribution for the seven-membered-ring case (**1c**, **2c**) in terms of a rational mechanistic hypothesis, Scheme I is best expanded in the form of Scheme II. In stark contrast to the six-membered-ring case (**1b**, **2b**), which affords only **5b** (*E*-pathway product) and **6b** (*Z*-pathway product), the seven-membered-ring case affords **3c** plus **14**/**15** (but no **5c**) for the *E* pathway and **16** plus **17** (but no **6c**) for the *Z* pathway. In regard to Scheme II, the results of thermal control experiments are important. First, it was shown that **14**/**15** and **18** were completely stable to the reaction conditions (refluxing isooctane, 100 °C, >3 h) and that **18** results only from heating **1c** or **2c** but not from any of the other isomers (**3c**, **14**–**17**). Second, **3c**, after being heated in refluxing isooctane for 21 h, is completely rearranged to the inseparable mixture of **14** and **15**. And third, heating **16** or **17** under the reaction conditions of their formation from **1c** (**2c**) affords the same ~1:1 equilibrium mixture of **16** and **17**. To establish that this equilibrium (**16** ⇌ **17**) does not proceed through simple keto–enol tautomerism, we repeated this last experiment in *n*-butanol-*d*. The experiment afforded **16** and **17** with no detectable deuterium (^1H NMR) incorporation at the tertiary carbon (C-10) α to the carbonyl. While the products and the proposed isomerization pathways depicted for **1c** (**2c**) in Scheme II differ significantly from the six-membered-ring ketone case **1b** (**2b**), they are not unknown for related vitamin D systems.

The vitamin ketone **3c** exhibited a ^1H NMR C_{18}-methyl at δ 0.54 and an $H_{6,7}$ vinyl coupling constant of $J \approx 11.7$ Hz. These are similar to those reported for the known 3-deoxy-*A*-homovitamin D_3 **19** (C_{18}-methyl: δ 0.54, $H_{6,7}$, $J \approx 11.0$ Hz).[13] The observed UV λ_{max} of 254 nm is also similar to that reported for **19**. Further rearrangement of **3c** to **14** and **15** (Scheme II) presumably proceeds through the *A*-homoprevitamin ketone intermediate **5c**, which subsequently undergoes a six-electron electrocyclization, providing the mixture **14** and **15**. This kind of rearrangement is well-known in the vitamin D field.[14] The parent vitamin D_3 has been observed to rearrange at ≳150 °C to isopyro- (**20**) and pyrocholecalciferol (**21**). Although we were unsuccessful in separating **14** and **15**, the ^1H NMR of the mixture revealed the presence of olefinic signals ($J_{6,7}$ ≈ 5.9 Hz for one isomer and 5.2 Hz for the other) characteristic of related cyclohexadiene structures. Moreover, the UV spectra of the **14** and **15** mixture (λ_{max} 285 and 275 nm) is similar to isopyro- and pyrocalciferols **20** and **21**, respectively[14] (**20**, λ_{max} 280, 262 nm; **21**, λ_{max} 294, 274 nm). It is most striking, however, that **3c** rearranges to **14** and **15** under significantly milder conditions than does vitamin D_3 to **20** and **21**.

As regards the 7*Z*-pathway products **16** and **17**, a close analogy (and now one of many examples[3b,11,15]) is the ternary equilibrium system **23** ⇌ **22** ⇌ **24**. For this par-

(11) Mouriño, A.; Lewicka-Piekut, S.; Norman, A. W.; Okamura, W. H. *J. Org. Chem.* **1980**, *45*, 4015.

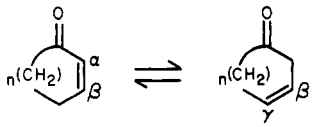
(12) The configuration of the allenes **1c** and **2c** also follows from the method of synthesis. As discussed in ref 4, the major coupling isomers are the 6*R* ketones **1a** and **1b** and the minor isomers are the 6*S* ketones **2a** and **2b**. A similar but attenuated trend is observed for the *A*-homo ketones **1c** and **2c**.

(13) Sine, S. M.; Conklin, T. E.; Okamura, W. H. *J. Org. Chem.* **1974**, *39*, 3797.

(14) (a) Fieser, L. F.; Fieser, M. "Steroids"; Reinhold: New York, 1959, Chapter 4. (b) Pelc, B.; Marshall, D. H. *Steroids* **1978**, *31*, 23.

(15) Leyes, G. A.; Okamura, W. H. *J. Am. Chem. Soc.* **1982**, *104*, 6099.

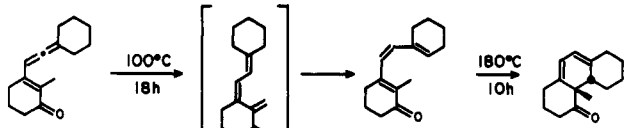
Scheme III



25 26

(a, n = 2; b, n = 3)

Scheme IV



27 28 29 30

ticular example,[3b] the observed equilibrium proportions (100 °C, >26 h) were 49% **23**, 14% **22**, and 36% **24**. When the secondary alcohol group of **22–24** is replaced by a carbonyl, the equilibrium is logically shifted completely to **22**.[3b] As inferred above, the seven-membered-ring carbonyl analogues of **22–24** (namely, **6c**, **16**, and **17**) exhibit an equilibirum completely shifted to the unconjugated analogues of **23** plus **24** (namely, **16** plus **17**)! The spectral data for **16** and **17** are similar to one another and, with not unexpected differences, to the alcohols **23** and **24**. For example, the ^{1}H NMR of **16** and **17** reveal the following: C_{18}-CH_3, δ 0.89, 0.91; C_{19}-CH_3, δ 1.12–1.17, d, $J \approx$ 6.8 Hz; H_{10}, δ 3.6, q, $J \approx$ 6.8 Hz; H_{15}, δ 5.5, br; $H_{6,7}$, $J \approx$ 11.0 Hz. It was not surprising to find that equilibration of **16** and **17** is complete within 3 h at 100 °C, whereas **23** and **24** required about 1 day for equilibration at this same temperature.

The unexpected *trans-A*-homotachysterone **18** arises from an as yet undefined process. The structure of **18** follows from ^{1}H NMR (particularly the trans $H_{6,7}$ vinyl coupling constant of $J \approx$ 16.1 Hz and the appearance of the C_9-vinyl signal of δ 5.89) and UV (λ_{max} 321 nm) spectral comparisons to the six-membered-ring cis counterpart **5b** and A-nor trans isomer **7**.[4] As shown by the thermal control experiments, its thermal stability (100 °C, 3 h) toward rearrangement to or from the other assumed Woodward–Hoffmann correlated products (**3c** and **14–17** in Scheme II) also attests to its *E* geometry.

Discussion

The thermal results are most simply discussed by comparing the behavior of **1c** with that of **1b**[16] and other related six-membered-ring systems described in the literature. Aside from the unanticipated formation of **18** from **1c**, the thermal reactions of Schemes I and II are *assumed* to proceed via simple orbital symmetry controlled, concerted processes.[17] These include suprafacial [1,5]-sigmatropic and antarafacial [1,7]-sigmatropic hydrogen shifts and six-electron disrotatory electrocyclizations. The change in ring size from six to seven not only increases the rate of these pericyclic processes but also effects the product distributions (Scheme II).

Dreiding models[18] reveal that the distance between the migrating hydrogen termini, C_{19} to C_7, for a [1,5]-sigmatropic shift differ significantly for the five-, six-, and seven-membered-ring cases (**1a**, 2.9 Å; **1b**, 2.6 Å; and **1c**, 2.4 Å, respectively). The milder thermal isomerization conditions for A-homo ketone **1c** (100 °C, 3 h) in comparison to the six-membered allene **1b** (100 °C, 20 h) are attributed to the decrease in this migration distance.[19] The strain characteristic of α,β-unsaturated cycloheptenones, not present in analogous cyclohexenones, very likely also plays a role in accelerating the rate of the A-homo case **1c**. Equilibration studies between **25** and **26** (Scheme III) from six- to nine-membered rings have revealed that an increase in ring size progressively favors the β,γ-unsaturated ketone.[20] It has been suggested that destabilization of the conjugated isomer as the ring becomes larger is due to increasing prohibition of the conformation in which the double bond and carbonyl are coplanar. Thus, the resonance stabilization energy in conjugated enones is not as large as might have been anticipated. It should also be noted that in the present case **1**, there is likely to be some vicinal steric strain between the C_{10}-methyl and the C_5-allene group. This vicinal strain should increase on going from **1b** to **1c** since the external bond angles decrease. Upon rearrangement of **1c** to **3c** plus **4c**, one can expect some relief of strain by twisting about the two single bonds between the three sp^2 centers in **3** or **4**. Thus, we feel that the ring strain (conjugated cycloheptenone strain and vicinal strain) and the distance effect factors are collectively accelerating the [1,5] hydrogen shift of **1c** relative to that of **1b**.

Considering next **3c** and the other components (**5c**, **14**, and **15**) of the *E* manifold (Scheme II), it is likely that under the reaction conditions (100 °C, 3 h) of their formation from **1c**, **3c** and the putative **5c** are in rapid equilibrium[21] but that **3c** is favored thermodynamically because of the same conjugated cycloheptenone and vicinal strain factors (see preceding paragraph) present in **5c**, but not in **3c**. On going to the six-membered-ring case, the **5b** $\rightleftharpoons$ **3b** equilibrium is shifted toward **5b**, because **5b** is linearly conjugated while **3b** is not.[22] As mentioned in the Results section, the rate of electrocyclization of **3c** (via **5c**) to **14** plus **15** is faster than that of the parent vitamin D_3 molecule, which affords **20** and **21**.[14] A yet more closely related six-membered-ring system previously investigated in this laboratory is depicted in Scheme IV.[23] A comparison of reaction conditions (six-membered-ring case **28**/**29**, 180 °C/10 h; seven-membered ring case **3c**/**5c**, 100 °C/21 h) further illustrates that **3c** electrocyclizes unusually rapidly. This accelerating effect may again be attributed to conjugated cycloheptenone and vicinal strain factors in the intermediate **5c**, but a topological effect,

(16) Since the thermal results for the 6*S* isomers **2c** and **2b** are similar to those obtained for the 6*R* isomers **1c** and **1b**, respectively, only the latter pair are compared.

(17) Woodward, R. B.; Hoffmann, R. "The Conservation of Orbital Symmetry"; Verlag Chemie: Weinheim Bergstr., Germany, 1970.

(18) Bond angle corrected Dreiding models were used.

(19) A planar 5-*s*-cis conformation of the vinylallenes **1** was assumed. The actual trajectory of the migrating hydrogen is open to speculation (for a recent discussion, see: Kwart, H.; Brechbiel, M. W.; Acheson, R. M.; Ward, D. C. *J. Am. Chem. Soc.* **1982**, *104*, 4671). For simplicity, the linear distance between the carbon termini was measured. Dr. Alberto Haces of this laboratory is acknowledged for first suggesting the notion of distance effects in these systems.

(20) Heap, N.; Whitham, G. H. *J. Chem. Soc. B* **1966**, 164. The equilibrium ratios were as follows: **25a**/**26a**, 99/1; **25b**/**26b**, 73/27. Another example of the unusual behavior of cycloheptenones has been described recently. See: Heathcock, C. H.; DelMar, E. G.; Graham, S. L. *J. Am. Chem. Soc.* **1982**, *104*, 1907.

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

(22) In the absence of the carbonyl, **3** is favored over **5** for other reasons, which have to do with CD ring strain. See Ref 3a and 13 and the earlier discussion by Havinga and co-workers: Havinga, E. *Experientia* **1973**, *29*, 1181.

(23) Condran, P., Jr.; Okamura, W. H. *J. Org. Chem.* **1980**, *45*, 4011.

wherein C_9 and C_{10} are better oriented[24] in **5c** than in **5b** for electrocyclization, may also be a factor.[25]

We now turn finally to the products of the *Z* manifold, namely, **16** and **17**. That the presumed ternary equilibrium **16** ⇌ [**6c**] ⇌ **17** avoids **6c**, while in the six-membered case this anlogous equilibrium favors linearly conjugated **6b** completely, is readily rationalized on the same basis as the ring size factors delineated for the equilibrium **3** ⇌ **5** (preceding paragraph). What is most striking, however, is that **16** equilibrates with **17**, presumably via the double [1,7] hydrogen shift through intermediate **6c**, under such mild conditions (100 °C for 3 h vs. over 1 day for the six-membered-ring case, **23** ⇌ **22** ⇌ **24**). We can only conjecture that the seven-membered-ring case is more optimally set up for a putative ideal topology for a [1,7]-sigmatropic hydrogen shift than is the corresponding six-membered-ring case.

Summary

Although the correlations are qualitative, it seems that seven-membered-ring annulation onto a polyene framework undergoing a [1,5] or [1,7] hydrogen shift,[26] or even electrocyclization,[24,27] results in accelerated rates compared to that of similar six-membered-ring systems. In addition, product distributions differ significantly for the two ring sizes, at least for the vitamin D seco steroids studied. It remains for future experiments to generalize the notion of seven-membered-ring accelerated pericyclizations.

Experimental Section

General Methods. Spectroscopic (^1H and ^{13}C NMR, IR, UV, and high- and low-resolution mass spectroscopy) and other analytical data are given in the supplementary material.

Air-sensitive reactions, including those involving alkyllithium reagents, metal catalysts, sensitive allenes, etc., were performed under an atmosphere of dry argon. References to aqueous $NaHCO_3$, NH_4Cl, or NaCl during the experimental workup procedures refer to saturated aqueous solutions of the above reagents unless otherwise stated. Dry ether or THF (tetrahydrofuran predried over 4-Å molecular sieves) refers to regent-grade material freshly distilled from $LiAlH_4$ under nitrogen. Skellysolve B and lbpe (low-boiling petroleum ether, bp 30–60 °C) were distilled from CaH_2 prior to use. Kugelrohr distillation boiling points refer to the external air-bath temperature; the pressure is expressed in millimeters of Hg. Melting points (uncorrected) were obtained on a Thomas-Hoover capillary apparatus.

High-pressure liquid chromatography (high-pressure LC) was performed by using a Waters 6000A delivery system equipped with a UK6 injector and a dual detector system (M450 variable-wavelength UV and R401 refractive index detectors). A Whatman M9 10/50 Partisil (10-μm particle size, 9.4 mm i.d. × 50 cm) column was used for normal-phase conditions unless otherwise noted. The column used for reverse-phase conditions was a Whatman ODS-2 M9 10/50 Partisil column (10-μm silica packing with 10% by weight octadecylsilane stationary phase). A Waters RCM-100 module radial compression system with a silica (5 μm) radial pack cartridge (5 mm i.d.) was used for analytical high-pressure LC. All chromatography solvents were distilled prior to use. Solvents and solvent mixtures were vacuum filtered through a 0.45-μm Millipore filter and vacuum degassed immediately prior to use. Open column chromatography was performed by using J. T. Baker silica gel (60–200 mesh).

3-Iodo-2-methyl-2-cyclohepten-1-one (13). Triphenylphosphine (5.07 g, 19.4 mmol, recrystallized from ether) and iodine (4.9 g, 19.4 mmol) were stirred in acetonitrile (88 mL; freshly distilled from P_2O_5) for 3 h (N_2). The diketone **12** (2.47 g, 17.6 mmol) and triethylamine (2.6 mL, 19.0 mmol, distilled from $LiAlH_4$) were added, and the solution was refluxed (42 h). The solvent was removed under reduced pressure, affording a residue which was taken up in ether and passed through a silica gel column (20 × 2 cm, ether, 800 mL). The solvent was evaporated, affording a yellow oil which was washed repeatedly with pentane. Removal of solvent and Kugelrohr distillation (65–67 °C, 0.4 mm) yielded pure iodo ketone **13** (3.35 g, 76%).

(6*R*)-1c and (6*S*)-*A*-Homo-9,10-secocholesta-5(10),6,7-trien-1-one (2c). A solution of *tert*-butyllithium (0.25 mL, 0.5 mmol, 2.0 M in pentane) was added to a stirred solution of allene **9** (137 mg, 0.5 mmol) in dry THF (3 mL) at −78 °C. The solution was stirred at −78 °C (5 min) and then at −55 °C (40 min) to produce a pale yellow solution of allenyllithium species. To a stirred suspension of cuprous iodide (95 mg, 0.5 mmol) in dry THF (1 mL) at −78 °C was added the cooled (−78 °C) allenyllithium species. The mixture was stirred at −78 °C (10 min) and then at −25 °C (30 min) to afford the clear brown allenylcopper species **10**. After the copper solution was cooled to −78 °C, a solution of iodo ketone **13** (50 mg, 0.2 mmol) and tetrakis(triphenylphosphine)palladium(0) (15 mg, 0.125 mmol) in dry THF (3 mL) was added. The mixture was stirred at −78 °C (1 h), −50 °C (1 h), −25 °C (1 h), and room temperature (1 h) and then quenched with saturated aqueous ammonium chloride (2 mL). The aqueous layer was withdrawn, and the ethereal layer was washed successively with aqueous $NaHCO_3$ (10 mL) and brine. Drying ($MgSO_4$) and then concentration under vacuum afforded an orange oil which was chromatographed (silica gel, 10 × 1.5 cm) by eluting first with lbpe (200 mL) and then with 20% ethyl acetate/lbpe (200 mL). The ethyl acetate fraction was concentrated under reduced pressure, affording a pale yellow oil which was further chromatographed (high-pressure LC, Partisil, 15% ethyl acetate/Skellysolve B), yielding a 1:2.4 mixture (by ^1H NMR) of (6*S*)- and (6*R*)-*A*-homovinylallenones **2c** and **1c**, respectively (50 mg, 63%). Separation of diastereomers **2c** and **1c** was achieved by reverse-phase high-pressure LC (acetonitrile/acetone, 1:1) to afford **2c** (14 mg, 18%) and **1c** (34 mg, 43%) as clear pure oils.

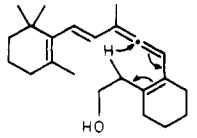
Thermolysis of 6*R* Ketones 1c. A solution of 6*R* ketone **1c** (51 mg, 0.130 mmol) in freshly distilled isooctane (8 mL) was heated (100 °C, Ar) for 3 h. Monitoring by analytical high-pressure LC (15% ethyl acetate/Skellysolve B) revealed that **1c** was completely consumed after 3 h. Removal of isooctane under reduced pressure and then preparative high-pressure LC (5% ethyl acetate/Skellysolve B) of the resulting residue afforded two significant fractions. Reverse-phase chromatographic separation of the less polar fraction (high-pressure LC, reverse phase, shave/recycle, 1:1 acetonitrile/acetone) afforded **3c** (6.0 mg, 12%), **14** and **15** (6.0 mg, 12%), and **18** (5 mg, 10%). Normal-phase rechromatography of the more polar fraction (high-pressure LC on Partisil, 5% ethyl acetate/Skellysolve B, multiple shave/recycle) yielded **16** (13 mg, 25%) and **17** (12 mg, 24%). Each of

(24) A perusal of a recent treatise on electrocyclizations (Marvell, E. N. "Thermal Electrocyclic Reactions"; Academic Press: New York, 1980; p 311) revealed a single example of a ring size effect on an electrocyclic process. See: Schiess, P.; Seeger, R.; Suter, C. *Helv. Chim. Acta* **1970**, *53*, 1713. The case reported involved electrocyclic tautomerism of a conjugated dienal possessing five- and six-membered ring fusion across the α,β double bond of the dienal. The *smaller*, five-membered ring fused system appeared to electrocyclize faster, but the cyclized product itself was not directly observed.

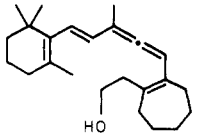
(25) Besides the acceleration of **5c** to **14** plus **15**, it seems likely that the back-reaction of **5c** to **3c**, a [1,7] shift, is also accelerated. This is supported by an earlier observation during our studies of **19** (see ref 13).

(26) For a study of ring size effects on [1,5]-sigmatropic shifts analogous to those being discussed here, we know of only one example (Wolinsky, J.; Chollar, B.; Baird, M. D. *J. Am. Chem. Soc.* **1962**, *84*, 2775). In this only analogous study, a six-membered ring fused system appeared to undergo the [1,5]-sigmatropic hydrogen shift slightly more slowly than did a five-membered ring fused case.

(27) In connection with research in the retinoids area (Chandraratna, R. A. S.; Okamura, W. H. *J. Am. Chem. Soc.* **1982**, *104*, 6114), we recently observed in the six-membered ring fused vinylallene i that complete [1,5]-sigmatropic rearrangement required heating at 69 °C for 4 h. By contrast, the seven-membered ring system ii rearranged at room temperature (Chandraratra, R. A. S.; Bayerque, A. L.; Okamura, W. *Ibid.* **1983**, *105*, 3588.



i



ii

the five components was obtained as an oil.

Analysis of **14** and **15** by ^{13}C NMR revealed that this fraction is a mixture of isomers which proved inseparable by both normal and reverse-phase high-pressure LC under a variety of solvent conditions. Separate control experiments (see below) revealed that the mixture of **14** and **15** is stable to the reaction conditions and results from the further rearrangement of **3c**, that **16** and **17** are interconvertible, but otherwise stable to the conditions, and that **18** is unchanged under the conditions.

Thermolysis of 6*S* Ketone 2c. As described in the preceding experiment, thermolysis of **2c** (25 mg, 0.06 mmol; 6 mL of isooctane, 100 °C, 3 h, Ar) and then a similar workup followed by semipreparative high-pressure LC afforded **3c** (4.0 mg, 16%), **14** and **15** (3.0 mg, 12%), **18** (4.0 mg, 16%), **16** (6.0 mg, 24%), and **17** (6.0 mg, 24%)

Thermal Control Experiments of Ketones 3c, 14, 15, and 18. In side-by-side experiments, the vitamin ketone **3c** (1 mg), a mixture of cyclized isomers **14** and **15** (1 mg), and *trans*-tachysterone **18** (1.5 mg) were individually heated in refluxing isooctane (8 mL, freshly distilled from $LiAlH_4$, 100 °C, Ar atmosphere). Monitoring by high-pressure LC (3% ethyl acetate/Skellysolve B) revealed that the vitamin ketone was completely consumed in 21 h, affording only a mixture of cyclized products **14** and **15** (LC comigration with the cyclized isomers; the ^1H NMR spectrum including the integration of the signals due to the C_{18}-methyls; UV spectral comparisons). The cyclized isomers **14** and **15** were stable to the thermolysis conditions (analytical high-pressure LC using the UV detector and ^1H NMR and UV spectra). The *trans*-tachysterone **18** was also stable to the thermolysis conditions (^1H NMR and UV spectra).

Thermal Equilibration of Ketones 16 and 17. In side-by-side experiments, isomer **16** (1 mg) and the methyl epimer **17** (1 mg) were heated for 3 h in refluxing isooctane (8 mL, freshly distilled from $LiAlH_4$, 100 °C, Ar atmosphere). Separation by high-pressure LC (3% ethyl acetate/Skellysolve B, recycle) afforded equilibrium ratios of the two isomers **16** and **17**. The ratio resulting from **16** was 46% and 54%, respectively, while that obtained from **17** was 48% and 52%, respectively. Ratios obtained by ^1H NMR were carried out by integrating the signals due to the C_{18}-methyl groups. High-pressure LC values were obtained by integration of the UV detector traces. The overall average equilibrium product distribution for the two thermolyses was 47 ± 2% **16** and 53 ± 1% **17**.

A similar control experiment where ketone **17** (6 mg) was heated (100 °C) in *n*-butanol-*d* (2 mL) for 3 h afforded an equilibrium mixture of **16** and **17**. Analysis of this mixture or the individually separated isomers revealed no deuterium incorporation at C_{10} in either **16** or **17** (^1H NMR integration of the signals attributed to the C_{10} hydrogens relative to the C_{15}-vinyl hydrogens).

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Registry No. **1a**, 79421-01-5; **1b**, 74398-26-8; **1c**, 87190-97-4; **2a**, 79421-04-8; **2b**, 74398-27-9; **2c**, 87190-98-5; **3c**, 87190-99-6; **9**, 74398-28-0; **12**, 5601-78-5; **13**, 83788-28-7; **14**, 87191-00-2; **15**, 87247-58-3; **16**, 87191-01-3; **17**, 87247-59-4; **18**, 87191-02-4.

Supplementary Material Available: Spectral and analytical data (5 pages). Ordering information is given on any current masthead page.

Structure of the Antibiotic Cyanobacterin, a Chlorine-Containing γ-Lactone from the Freshwater Cyanobacterium *Scytonema hofmanni*

Joseph J. Pignatello, Joseph Porwoll, Robert E. Carlson, Antonio Xavier, Florence K. Gleason,* and John M. Wood

Gray Freshwater Biological Institute, University of Minnesota, Navarre, Minnesota 55392

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The structure of cyanobacterin, an allelopathic substance, has been determined by MS, IR, and ^1H and ^{13}C NMR experiments. Nuclear Overhauser effect (NOE) enhancements have been used to determine the relative stereochemistry, the substitution pattern in the chlorinated aromatic ring, and the geometry of the exocyclic double bonds in cyanobacterin and its anhydro isomers.

We have reported the isolation of an antibiotic, **1**, from a freshwater cyanobacterium (blue-green alga), *Scytonema hofmanni*, that is highly toxic toward other cyanobacteria and green algae.[1] Our studies suggest that **1** is an allelopathic substance, allowing a slow-growing organism like *S. hofmanni* to compete with more prolific species. Electron micrographs of cyanobacterin treated *Synechococcus* sp. and *Euglena gracilis* indicate that the primary target of the antibiotic is the thylakoid membranes.[2] Halogenated metabolites have not been previously isolated from freshwater algae, although marine species are known to produce a variety of chlorinated and brominated compounds.[3] The γ-ylidene-γ-butyrolactone structure is also unusual in that cyanobacterin does not contain any additional α,β-unsaturation as found in other natural products.[4] We report here the structural elucidation of cyanobacterin and anhydro isomers A and B.

Results and Discussion

The high-resolution mass spectrum of **1** has molecular ion peaks at m/z 430.1167 and 432.1128 which correspond to chlorine isotope peaks in the molecular formula $C_{23}H_{23}ClO_6$ (calcd m/z 430.1184 and 432.1154). Other fragments exhibiting characteristic chlorine isotope peaks are m/z 412/414 ($M^+ - H_2O$), 369/371 ($M^+ - H_2O - C_3H_7$), and 169/171 ($C_8H_6ClO_2^+$).

(1) Mason, C. P.; Edwards, K. R.; Carlson, R. E.; Pignatello, J.; Gleason, F. K.; Wood, J. M. *Science (Washington, D.C.)* **1982**, *215*, 400.
(2) Gleason, F. K.; Paulson, J. manuscript in preparation.
(3) Moore, R. E. "Marine Natural Products"; Scheuer, P. J., Ed.; Academic Press: New York, 1981; Vol. IV, pp 1–52.
(4) (a) Niwa, M.; Iguchi, M.; Yamamura, S. *Tetrahedron Lett.* **1975**, 1539. (b) Niwa, M.; Iguchi, M.; Yamamura, S. *Chem. Lett.* **1975**, 655. (c) Niwa, M.; Iguchi, M.; Yamamura, S. *Tetrahedron Lett.* **1975**, 4395. (d) Kazlauskas, R.; Murphy, P. T.; Quinn, R. J.; Wells, R. J. *Ibid.* **1977**, 37. (e) Petters, J. A., Jr.; Wing, R. M.; Sims, J. J. *Ibid.* **1977**, 41.

0022-3263/83/1948-4035$01.50/0