systems. The quinone monoketals are especially valuable as regiospecific quinone equivalents. They undergo reactions with a variety of organometallic reagents, the products of which serve as key intermediates in the formation of *p*-quinols and quinone methides. The annelation chemistry of the quinone monoketals allows regiospecific routes to linear polycyclic natural products. Since most of the chemistry reported here has been published since 1976,[35] new reactions and synthetic applications of quinone bisketals and monoketals remain to be reported.

(35) It has not been possible to discuss all of the applications of quinone monoketals in synthesis. References 18 and 21 cite most of the other published work.

We gratefully acknowledge support from the National Science Foundation that initially allowed this venture into organic electrochemistry and its application to organic synthesis. Much of the chemistry discussed herein was directed at the synthesis of quinone natural products and was supported by the National Institutes of Health. The author is grateful to his students who not only carried out the majority of the laboratory work but also contributed immeasurably in certain cases to the synthetic strategy. Thanks also go to B. Chenard, D. Henton, J. Richardson, and especially L. Spangler for numerous helpful comments and criticisms concerning this manuscript.

Pericyclic Reactions of Vinylallenes: From Calciferols to Retinoids and Drimanes

WILLIAM H. OKAMURA

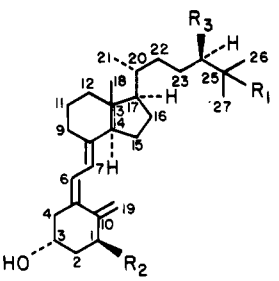
Department of Chemistry, University of California, Riverside, California 92521

Received June 18, 1982 (Revised Manuscript Received October 22, 1982)

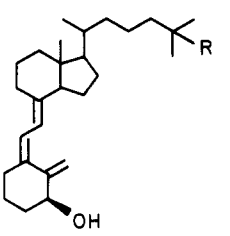
Vitamin D (Calciferol)

It is now established that, before vitamin D_3 (**1a**, D_3) can elicit its classic physiological responses, intestinal calcium absorption and bone calcium mobilization, it must undergo successive hepatic and renal hydroxylation to afford 25-hydroxyvitamin D_3 (**1b**) and 1α,25-dihydroxyvitamin D_3 (**1c**, 1α,25-$(OH)_2$-D_3), respectively.[1] Of the numerous metabolites of D_3 that have now been isolated and chemically characterized, **1b** and **1c** are considered the principal metabolites, although another renal metabolite, (24*R*)-24,25-dihydroxyvitamin D_3 (**1d**), appears to be required for at least some of the vitamin D mediated biological responses.[2] Particularly intriguing is the emergence of the notion that the vitamin D endocrine system resembles that of the classical steroid hormones such as estradiol, progesterone, testosterone, cortisone, and aldosterone. Thus, 1α,25-$(OH)_2D_3$ should no longer be considered a vitamin, but rather it should be considered a steroid hormone both structurally and functionally.[1a]

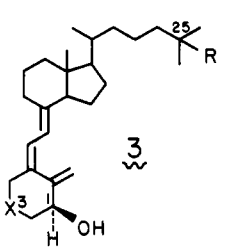
In order to develop a more detailed understanding of the vitamin D endocrine system, we and others have focussed attention on the chemical synthesis of metabolites and analogues of vitamin D. The studies at Riverside have progressed through collaborative efforts between the author's research group and that of Professor Anthony W. Norman of the Department of Biochemistry. Analogues of biologically active molecules, which can be classed as *agonists*, *antagonists*, or *synergists*, are useful biochemical research tools and are of potential value for clinical applications. Biologically



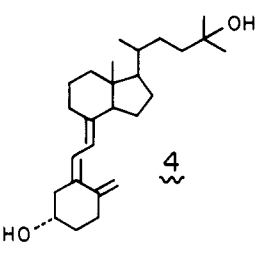
1a, $R_1=R_2=R_3=H$
b, $R_1=OH; R_2=R_3=H$
c $R_1=R_2=OH; R_3=H$
d $R_1=R_3=OH; R_2=H$



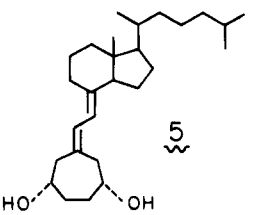
2a, R=OH
b R=H



3



4

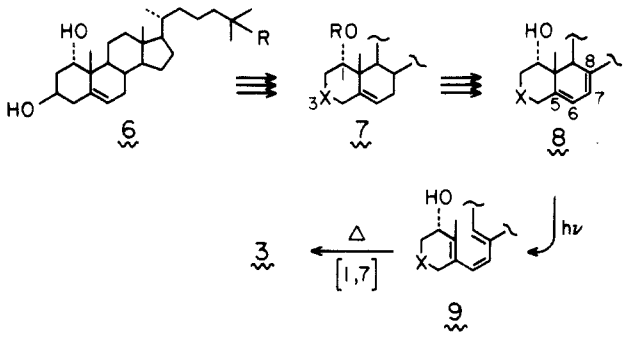


5

William Okamura was born in 1941 in Los Angeles, CA. He received his B.S. from UCLA in 1962 and his Ph.D. from Columbia University with Thomas J. Katz in 1966. After postdoctural studies at Cambridge University with the late Franz Sondheimer, he joined the faculty of the University of California, Riverside, in 1967; he is currently Professor of Chemistry at the same institution. His major research interests are in the synthetic organic chemistry area, especially synthetic and structure–activity studies of vitamins A and D, pericyclic reactions of allenes, and the synthesis of natural products and molecules of theoretical interest.

0001-4842/83/0116-0081$01.50/0

Scheme I



active analogues (agonists) of vitamin D are characterized by the presence of a 1α-hydroxyl, or better by the presence of both 1α- and 25-hydroxyl groups.[3] The analogues 3-deoxy-1α,25-dihydroxy-D_3 (**2a**) and 3-deoxy-1α-hydroxy-D_3 (**2b**), which differ from the natural hormone **1c** in that they lack the 3-hydroxyl or both the 3- and 25-hydroxyls, are particulrly interesting active agonists in that they exhibit significant intestinal calcium absorption activity but only minimal bone calcium mobilizing ability.[4] By contrast, the hormone **1c** is the most active substance known for eliciting *both* of these classical vitamin D mediated physiological responses. This unusual selectivity in biological action stimulated our interest in developing a short, flexible synthetic route to a family of analogues of **1c** modified in the A ring at position 3 as depicted by structure **3**, with or without the 25-hydroxyl. This could also include a total synthesis of the natural hormone **1c**. Our attempts to achieve these goals introduced us to the main subject of this Account, namely the chemistry of vinylallenes.[5] Before we delve into this topic, we should mention that antagonists and synergists of vitamin D metabolities are also now known. The first example of a vitamin D antagonist, 24-nor-25-hydroxy-D_3 (**4**), reported by our laboratories in 1975,[6] inhibits the normal action of vitamin D_3 (**1a**) by suppressing its metabolism to **1b**. Several additional examples of D_3 inhibitors have subsequently been reported,[7] but there is as of yet no report of an antagonist of **1c**. The only example of a vitamin D synergist, the A-homo-19-nor analogue **5**, which, when adminstered simultaneously with the parent hormone **1c**, stimulates the intestinal calcium absorption response of the latter above its normal levels when adminstered alone, was recently reported.[8]

Scheme I depicts the well-known classical vitamin D synthesis[1c,d] that was utilized in the synthesis of **2**.[4,9] Cholesterol or its 25-hydroxy counterpart was converted in three steps to **6** by Barton's method,[9b] and then the 3-position was modified to afford a suitably protected **7**. Introduction of the Δ^7 double bond to afford the provitamin **8** followed by photochemically induced ring opening gave the previtamin D **9**. Finally, thermal rearrangement of **9** completed the synthesis of the analogue **3**. In the case of **2b** (i.e., **3** X = CH_2; R = H), its preparation from cholesterol required 11 steps in an overall yield of 0.2%.[4a,9a] The introduction of the Δ^7 double bond (**7** → **8**) and the photochemical ring opening step (**8** → **9**), which proceeded in 10% and 8% yields, respectively, were primarily responsible for the low overall yield.[10] The linearity and length of this classical route also contributed to its inefficiency. It was obvious that a shorter and more flexible, convergent route[11] was highly desirable for preparing analogues of general structural type **3**.

Vinylallenes Related to Vitamin D

In 1972, Havinga and co-workers isolated two diastereomeric vinylallenes (**10a** and **10b**) as minor (~ 11%) photoproducts of D_3 (**1a**).[12] Under gas chromatographic conditions at 225 °C, **10a** or **10b** exhibited a trace characteristeric of **1a**. The latter is known to rearrange irreversibly to pyro- (**11a**) and isopyrocalciferol (**11b**) through the intermediacy of previtamin D (cf. **9**). These workers put forward the reasonable hypothesis that the vinylallenes undergo initial [1,5]-sigmatropic hydrogen shift to vitamin D_3, which then undergoes its characteristic thermal rearrangement. Crowley in 1964, Wolff in 1965, and Skattebøl in 1969 had also reported the same kind of rearrangement for the (*Z*)-vinylallenes **12**, **13**, and **14**, respectively.[13] Accordingly, we envisaged a synthetic strategy for synthesizing 1-oxygenated-3-substituted vitamin D systems of the type **3** wherein a C_{19} → C_7 [1,5]-sigmatropic hydrogen shift of a vinylallene **15** would be a key step. This strategy constitutes a general hexa-1,3,5-triene synthesis involving the transformation **16** → **17**. The subsequent irreversible electrocyclization[14] of **17** was not expected to be a problem since the [1,5] shifts of **12** and **14** were shown to occur under relatively mild

(1) (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.

(2) Henry, H. L.; Norman, A. W. *Science (Washington D.C.)* **1978**, *201*, 835.

(3) (a) Okamura, W. H.; Norman, A. W.; Wing, R. M. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 4194. (b) Proscal, D. A.; Okamura, W. H.; Norman, A. W. *J. Biol. Chem.* **1975**, *250*, 8382. (c) Procsal, D. A.; Okamura, W. H.; Norman, A. W. *Am. J. Clin, Nutr.* **1976**, *29*, 1271. (d) Wecksler, W. R.; Okamura, W. H.; Norman, A. W. *J. Steroid Biochem.* **1978**, *9*, 929. (e) Mayer, E.; Kadowaki, S.; Okamura, W. H.; Ohnuma, N.; Leyes, G. A.; Schmidt-Gayak, H.; Norman, A. W. *Ibid.* **1981**, *15*, 145.

(4) (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.; Proscal, D. A.; Norman, A. W. *Ibid.* **1975**, *65*, 24. (c) Lam, H.-Y.; Onisko, B. L.; Schnoes, H. K.; De Luca, H. F. *Biochem. Biophys. Res. Commun.* **1974**, *59*, 845. (d) Onisko, B. L.; Lam, H.-Y.; Reeve, L.; Schnoes, H. K.; De Luca, H. F. *Bioorg. Chem.* **1977**, *6*, 203.

(5) Egenburg, I. Z. *Rus. Chem. Rev. (Engl. Transl.)* **1978**, *47*, 900–933.

(6) (a) Johnson, R. L.; Okamura, W. H.; Norman, A. W. *Biochem. Biophys. Res. Commun.* **1975**, *67*, 797. (b) Johnson, R. L.; Carey, S. C.; Norman, A. W.; Okamura, W. H. *J. Med. Chem.* **1977**, *20*, 5. (c) Norman, A. W.; Johnson, R. L.; Okamura, W. H. *J. Biol. Chem.* **1979**, *254*, 11450.

(7) (a) Norman, A. W.; Hammond, M. L.; Okamura, W. H. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1977**, *36*, 914. (b) Gerdes, J. M.; Okamura, W. H.; Norman, A. W. *Arch. Biochem. Biophys.* **1981**, *210*, 238. (c) Paaren, H. E.; Moriarty, R. M.; Schnoes, H. K.; De Luca, H. F. *Biochemistry* **1980**, *19*, 5335. (d) Onisko, B. L.; Schnoes, H. K.; De Luca, H. F. *J. Biol. Chem.* **1979**, *254*, 3493. (e) Onisko, B. L.; Schnoes, H. K.; De Luca, H. F.; Glover, R. S. *Biochem. J.* **1979**, *182*, 1.

(8) Gerdes, J. M.; Norman, A. W.; Okamura, W. H. *J. Org. Chem.* **1981**, *46*, 599. See also ref 7b.

(9) Barton, D. H. R.; Hesse, R. H.; Pechet, M. M.; Rizzardo, E. *J. Am. Chem. Soc.* **1973**, *95*, 2748.

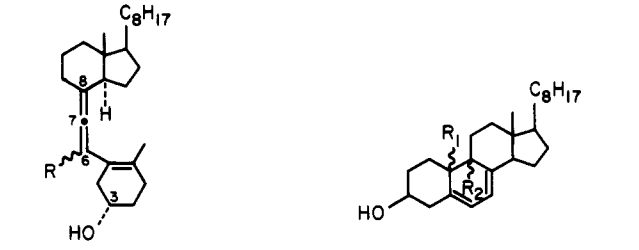
(10) For recent improvements: (a) Dauben, W. G.; Phillips, R. B. *J. Am. Chem. Soc.* **1982**, *104*, 355. (b) M. Rappoldt, Duphar (Weesp, The Netherlands), personal communication.

(11) (a) Inhoffen, H. H.; Irmscher, K. *Fortschr. Chem. Org. Naturst.* **1959**, *17*, 71. (b) Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1290. (c) Trost, B. M.; Bernstein, P. R.; Funfschilling, P. C. *J. Am. Chem. Soc.* **1979**, *101*, 4378. (d) Grieco, P. A.; Takigawa, T.; Moore, D. R. *Ibid.* **1979**, *101*, 4380.

(12) Bakker, S. A.; Lugtenburg, J.; Havinga, E. *Recl. Trav. Chim. Pays*-Bas **1972**, *91*, 1459.

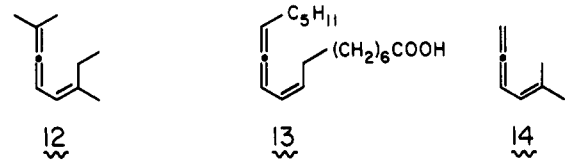
(13) (a) Crowley, K. J. *Proc. Chem. Soc., London* **1964**, 17. (b) Mikolajczak, K. L.; Bagby, M. O.; Bates, R. B.; Wolff, I. A. *J. Org. Chem.* **1965**, *30*, 2983. (c) Skattebøl, L. *Tetrahedron* **1969**, *25*, 4933.

(14) Marvell, E. N. "Thermal Electrocylic Reactions"; Academic Press: New York, 1980.

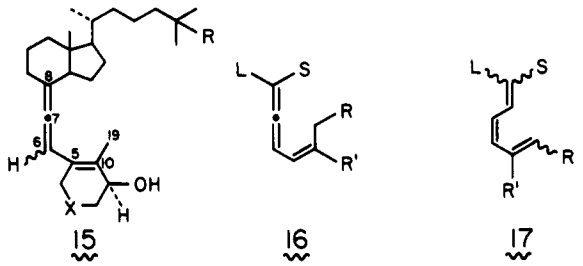


10a, R = H (6R)
b, R = H (6S)

11a, R_1 = CH_3; R_2 = H
b, R_1 = CH_3; R_2 = H



12 13 14

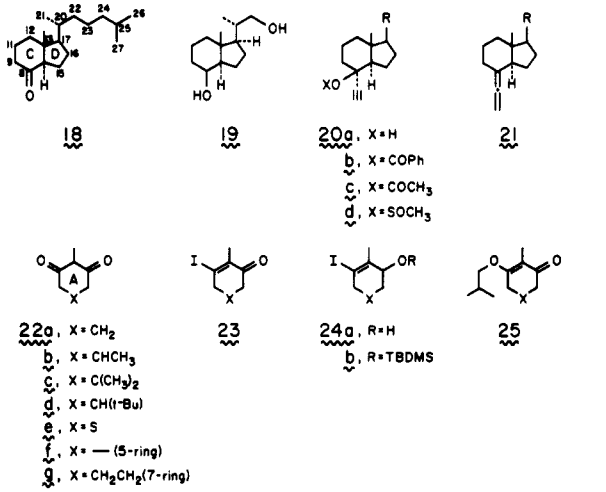


15 16 17

conditions (~100 °C).[13] As regards stereochemistry, the presumed intramolecular concertedness of the process **16** → **17** necessarily imparts the desired Δ^3 *Z* stereochemistry to the product triene, but that expected for the Δ^1 and Δ^5 double bonds was uncertain.[15,16] The thermal studies were therefore necessarily exploratory in this regard.

Synthesis of Vitamin D Vinylallenes

The optically active C/D fragments **20** and **21** (R = C_8H_{17} or functionalized side chains) were derived from Grundmann's ketone (**18**) and the Inhoffen–Lythgoe diol (**19**).[11,16a-g,17] The A-ring fragments **23–25** were obtained from the readily available 2-methylcycloalkane-1,3-diones **22**. Three routes have proven useful for effecting coupling of the A and C/D fragments

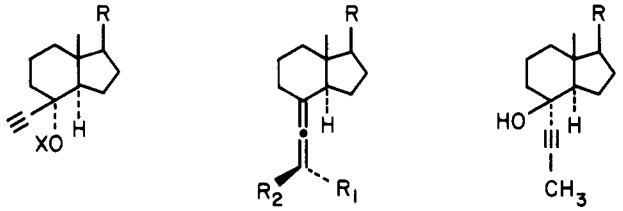


18 19 20a, X = H; b, X = COPh; c, X = $COCH_3$; d, X = $SOCH_3$ 21

22a, X = CH_2; b, X = $CHCH_3$; c, X = $C(CH_3)_2$; d, X = CH(t-Bu); e, X = S; f, X = — (5-ring); g, X = CH_2CH_2 (7-ring)

23 24a, R = H; b, R = TBDMS 25

(Scheme II). The A-ring vinylcuprate route A[16a,b,d,f,18] produces essentially exclusively the (6*R*)-allene **26**. The allenyllithium method B is less capricious than method A, but both (6*R*)-**27** and (6*S*)-**28** are produced.[16b,c,e,g-i,19] Most remarkably, the 6*R*/6*S* ratio is exceptionally large (e.g., 13.5/1.0 in the case of **25** derived from **22a**). Finally, the allenylcuprate method C was found to be necessary for one case, **23** derived from **22g**, but only a 2.2/1 ratio of **27** and **28** was observed.[16,20] In order to examine the possibility of producing mainly (6*S*)-allenes, the corresponding C_8 epimers of **20**, namely **29**, were prepared.[21] Oxidation of a >6:1 mixture of phenyl selenides **30a** and **30b**, prepared by reacting the lithium



29a, X = H; b, X = COPh; c, X = $COCH_3$; d, X = $SOCH_3$

30a, R_1 = SePh; R_2 = H; b, R_1 = H; R_2 = SePh; c, R_1 = CH_3; R_2 = H; d, R_1 = H; R_2 = CH_3; e, R_1 = t-Bu; R_2 = H; f, R_1 = H; R_2 = t-Bu; g, R_1 = CH_3; R_2 = SOPh

31

salt of **21** with diphenyl diselenide, afforded mainly **29a**. The reaction of lithium dimethylcuprate with **29b–d** resulted primarily in anti displacement: **29b–d** afforded mainly (6*S*)-allene **30d** (61–85%) along with **30c** (3–7%) and some reduction product **21** (0–10%); **20b–d** gave mainly **30c** (64–67%) and smaller amounts of **30d** (1–5%) and **21** (3–6%).[21] Even the presumably bulkier dilithium di-*tert*-butylcyanocuprate[22] reacted with the

(15) (a) Minter, D. E.; Fonken, G. J. *Tetrahedron* Lett. **1977**, 1717. (b) *Ibid.* **1977**, 4149. (c) Minter, D. E.; Fonken, G. J.; Cook, F. T. *Ibid.* **1979**, 711.

(16) For allenic vitamin D papers, see: (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. (c) Condran, P., Jr.; Okamura, W. H. *J. Org. Chem.* **1980**, *45*, 4011. (d) Mouriño, A.; Lewicka-Piekut, S.; Norman, A. W.; Okamura, W. H. *Ibid.* **1980**, *45*, 4015. (e) Gerdes, J. M.; Lewicka-Piekut, S.; Condran, P., Jr.; Okamura, W. H. *Ibid.* **1981**, *46*, 5197. (f) Leyes, G. A.; Okamura, W. H. *J. Am. Chem. Soc.* **1982**, *104*, 6099. (g) Haces, A.; Okamura, W. H. *Ibid.* **1982**, *104*, 6105. (h) Johnston, A.; Leyes, G. A.; Okamura, W. H. *Abstr. Pap.—Am. Chem. Soc.* **1982**, 183rd, ORGN-151. (i) Gerdes, J. M.; Lewicka-Piekut, S.; Condran, P., Jr.; Okamura, W. H. *Ibid.* **1982**, *183rd*, ORGN-33. For allenic vitamin A papers, see: (j) Sueiras, J.; Okamura, W. H. *J. Am. Chem. Soc.* **1980**, *102*, 6255. (k) Knudsen, C. G.; Carey, S. C.; Okamura, W. H. *Ibid.* **1980**, *102*, 6355. (l) Chandraratna, R. A. S.; Okamura, W. H. *Ibid.* **1982**, *104*, 6114. (m) Knudsen, C G.; Chandraratna, R. A. S.; Walkeapää, L. P.; Chauhan, Y. S.; Carey, S. C.; Copper, T. M.; Birge, R. R.; Okamura, W. H. *Ibid.*, in press.

(17) (a) Inhoffen, H. H.; Quinkert, G.; Siegismund, S.; Kampe, D.; Domagk, G. F. *Chem. Ber.* **1957**, 90, 664. (b) Lythgoe, B.; Roberts, D. A.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2608.

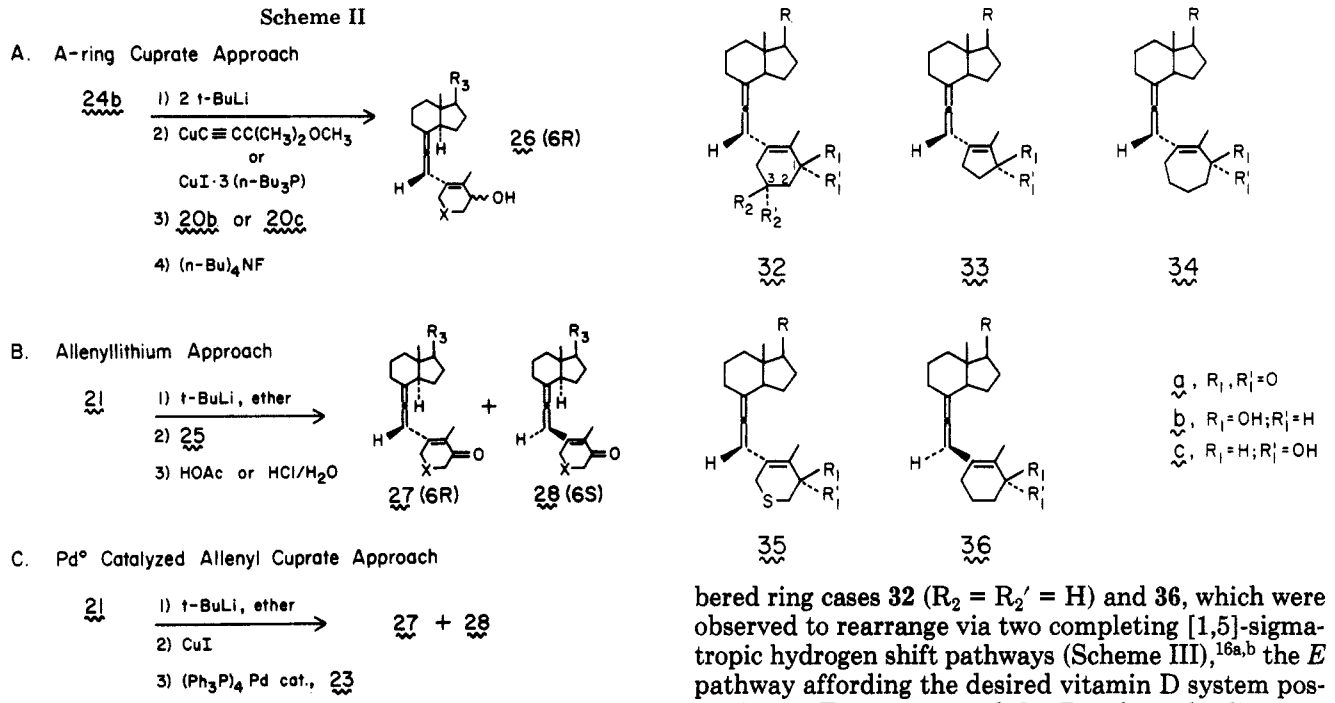
(18) Rona, P.; Crabbé, P. *J. Am. Chem. Soc.* **1969**, *91*, 3289.

(19) (a) Linstrumelle, G.; Michelot, D. *J. Chem. Soc., Chem. Commun.* **1975**, 561. (b) Michelot, D.; Linstrumelle, G. *Tetrahedron Lett.* **1976**, *275*. (c) Clinet, J. C.; Linstrumelle, G. *Nouv. J. Chim.* **1977**, 373. (d) Creary, X. *J. Am. Chem. Soc.* **1977**, *99*, 7632. (e) Pasto, D. J.; Chou, S.-K; Fritzen, E.; Shults, R. H.; Waterhouse, A.; Hennion, G. F. *J. Org. Chem.* **1978**, *43*, 1389.

(20) (a) Gerdes, J. M., unpublished observations. (b) Ruitenberg, K.; Kleijn, H.; Meijer, J.; Oostveen, E. A.; Vermeer, P. *J. Organomet. Chem.* **1982**, *224*, 399.

(21) Haces, A.; van Kruchten, E. M. G. A.; Okamura, W. H. *Tetrahedron Lett.* **1982**, *23*, 2707.

Scheme II



benzoates **29b** and **20b** with at least the same degree of anti selectivity.[23] To firmly establish the configuration of the allene, pure (6*R*)-allene **30c** was synthesized unambiguously from **31** by reacting the latter with phenylsulfenyl chloride to afford **30g** followed by CH_3Li desulfurization.[21,24] In addition, the direct reaction of **31** with $LiAlH_4$·$AlCl_3$ complex afforded the epimer **30d**, a product of anti displacement.[25] Thus, these results confirm[26] that cuprate reactions with propargylic esters occur primarily by anti S_N2' displacement with no known exceptions. They also suggest that (6*S*)-vinylallenes in the vitamin D series should be available stereoselectively from **29b** (Scheme IIA). A few (6*S*)-allenes have heretofore been obtained by photolyses of (6*R*)–allenes,[16a,b,e,27] which produce 1:1 mixtures.

Thermal Studies

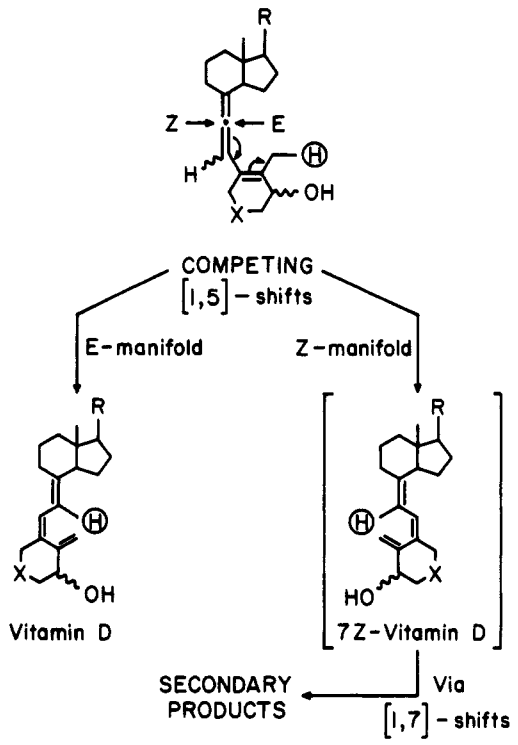
A variety of vitamin D type vinylallenes **32–36** have been synthesized. In all cases, the C-1 position possesses a carbonyl (**a** series), a 1α-OH (**b** series), or a 1β-OH[28] (**c** series) and the allenes are of the 6*R* configuration except for **36**. For **32**, various combinations of hydrogen or alkyl groups have been incorporated at C-3, including $R_2 = R_2' = H$, $R_2 = R_2' = CH_3$, $R_2 = CH_3$ or *t*-Bu and $R_2' = H$, $R_2 = H$ and $R_2' = CH_3$ or *t*-Bu.

The thermal studies (refluxing isooctane, ~10–12 h, ~100 °C) began with the 3-unsubstituted six-membered ring cases **32** ($R_2 = R_2' = H$) and **36**, which were observed to rearrange via two completing [1,5]-sigmatropic hydrogen shift pathways (Scheme III),[16a,b] the *E* pathway affording the desired vitamin D system possessing a 7*E* geometry and the *Z* pathway leading to a triad of secondary and tertiary products related by [1,7]-sigmatropic shifts to the putative 7*Z* geometric isomer of the vitamin D system.[29] The very interesting finding was that the C-1 hydroxyl configuration markedly influenced the 7*E*:7*Z* ratio, but the ratios are reversed for the (6*R*) and (6*S*)-allenes.[16g] In the 6*R* case, **32** ($R_2 = R_2' = H$), the 1α epimer **32b** afforded a 1:4.1 7*E*/7*Z* ratio, but this ratio was reversed (2.7:1) for the 1β epimer **32c**. In the 6*S* case, **36b** and **36c** afforded 7*E*/7*Z* ratios of products of 3.7:1 and 1:6.6, respectively. Although **36** represents the only (6*S*)-allene studied in detail, numerous other 3-alkyl substituted (6*R*)-allenes **32** have been synthesized (see above) and subjected to thermolysis.[16b,d,f,h] In all cases, the 1α-OH series **32b** resulted in an excess of the 7*Z* products (1:2.8–8.3) and the 1β-OH series **32c** afforded mainly 7E pathway products (2.7–6.8:1).

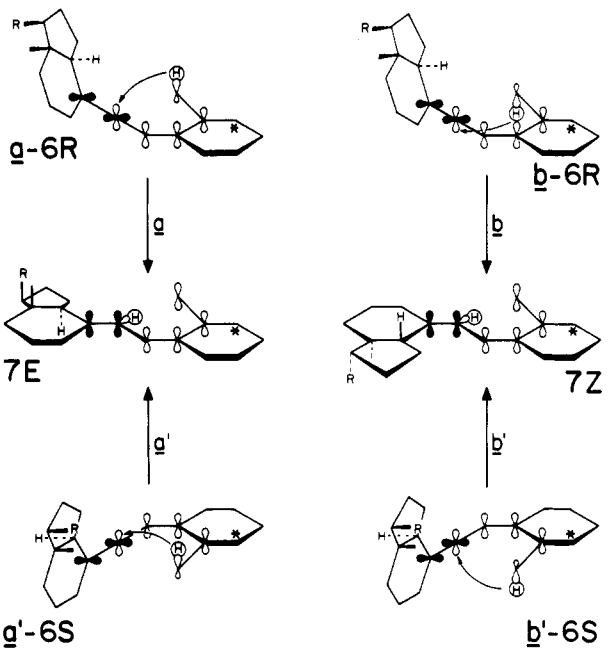
These results can be viewed more explicitly by referring to Scheme IV. Paths a and b are the competing 7*E*,7*Z* pathways starting from the (6*R*)-allenes **32**, wherein the asterisk indicates the position bearing the hydroxyl. When the hydroxyl is oriented above the A-ring plane as drawn for the (6*R*)-allene of Scheme IV, it corresponds to a 1α-OH group, and the favored path is b (or 7*Z*). Path a is favored if the hydroxyl is below the A-ring plane (or 1β). In contrast, for the (6*S*)-allene of Scheme IV, a hydroxyl on C* below the A-ring plane as drawn corresponds to a 1α-hydroxyl, and now path a′ leading to 7*E* isomer is favored. Reversal of the hydroxyl group configuration to 1β again gives the opposite result (path b′ favored). In other words, *the favored trajectory of the migrating hydrogen is always opposite or anti to the A-ring face bearing the hydroxyl.* Thermolysis of the parent ketones **32a** ($R_2 = R_2' = H$) and **36a**, wherein the two A-ring faces are now equivalent, resulted in an attenuated 7*E*/7*Z* ratio: 1:1 for the former and a 1:2 ratio for the later. While this

(22) Lipshutz, B. H.; Kozlowski, J.; Wilhelm, R. S. *J. Am. Chem. Soc.* **1982**, *104*, 2305.
(23) Haces, A., unpublished observations.
(24) Neef, G.; Eder, U.; Seeger, A. *Tetrahedron Lett.* **1980**, *21*, 903.
(25) Under similar conditions, a syn displacement has previously been reported [Claesson, A.; Olsson, L-I. *J. Am Chem. Soc.* **1979**, *101*, 7302 and references cited]. However, our result (**31** → **30d**; van Kruchten, E. M. G. A., unpublished observations) and those of others [Butler, W. M.; Tanaka, Y.; Koreeda, M. *J. Org. Chem.* **1981**, *46*, 4620 the references cited, and ref 26 below] suggest an anti displacement stereochemistry for this kind of process.
(26) Elsevier, C. J.; Meijer, J.; Westmijze, H.; Vermeer, P.; van Dijck, L. A. *J. Chem. Soc., Chem. Commun.* **1982**, 84.
(27) v. Koeveringe, J. A.; Lugtenburg, J. *Recl. Trav. Chim. Pays*-Bas **1976**, *95*, 80.
(28) The usual α and β configurational notations are reversed for the A ring of vitamin D, because this steroid is usually drawn in the 6-s-trans conformation as given in 1.
(29) The secondary and tertiary products of the 7*Z* manifold (Scheme III) related to one another by [1,7]-sigmatropic shifts are discussed in the earlier papers (ref 16a–i) and by: Onisko, B. L.; Schnoes, H. K.; De Luca, H. F. *J. Org. Chem.* **1978**, *43*, 3441.

Scheme III



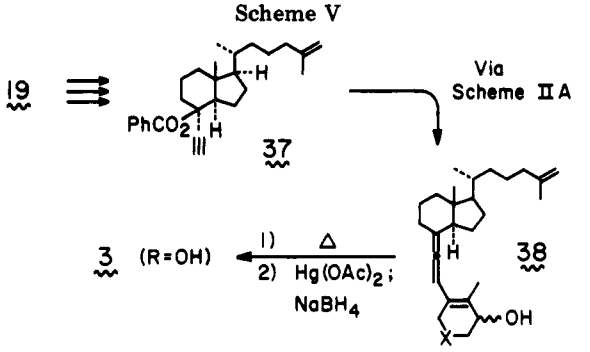
Scheme IV



suggests that the C-1 hydroxyl effect on the $7E/7Z$ ratios is steric in origin, an alternative electronic argument, one based on π facial selectivity,[30] seems more plausible because the reacting moiety (i.e., the hydrogen trajectory) as shown in Scheme IV seems too distant from the C-1 substituent. The results of theoretical calculations as well as the study of vinylallene rearrangements with other substitution patterns should assist in understanding this phenomenon.

(30) (a) Liotta, C. L. *Tetrahedron Lett.* **1975**, 519, 523. (b) Inagaki, S.; Fujimoto, H.; Fukui, K. *J. Am. Chem. Soc.* **1976**, *98*, 4054. (c) Burgess, E. M.; Liotta, C. L. *J. Org. Chem.* **1981**, *46*, 1703. (d) Jones, D. W. *J. Chem Soc., Chem. Commun.* **1980**, 739. (e) Mazzocchi, P. H.; Stahly, B.; Dodd, J.; Rondan, N. G.; Dommelsmith, L. N.; Rozeboom, M. D.; Caramella, P.; Houk, K. N. *J. Am. Chem. Soc.* **1980**, *102*, 6482. (f) Böhm, M. C.; Carr, R. V. C.; Gleiter, R.; Paquette, L. A. *Ibid.* **1980**, **102**, 7218.

Scheme V



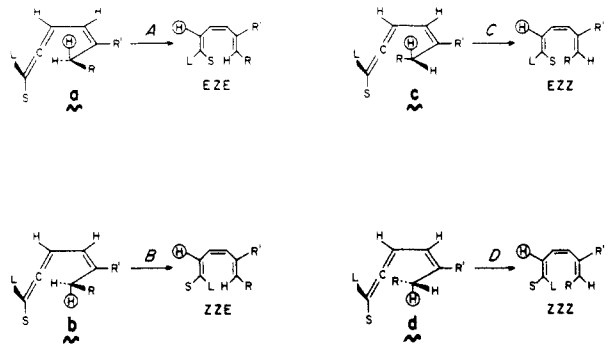
The effect of the size of the A ring has a marked effect on the relative ease of the [1,5]-sigmatropic shift. While the six-membered ring alcohol series **32** and **36** undergo virtually complete rearrangement (via Scheme III) after 10 h (20 h for the ketones) in refluxing isooctane (~100 °C), the five-membered A-nor series **33a–c**[16e] are virtually unchanged after 20 h. However, complete rearrangement of the ketone **33a** does occur after 24 h at 140 °C. Besides products related to those expected from the rearrangement pathways depicted in Scheme III, the major products observed are due to more deep-seated hydrogen shifts. The alcohols **33b** and **33c** undergo rearrangement to uncharacterized complex mixtures, but it was noted that they lacked UV absorption above 230 nm. In remarkable contrast, the rearrangement of the A-homo ketone **34** is complete in only 3 h in refluxing isooctane.[31] The alcohols **34b** and **34c** have been synthesized and are labile to [1,5] shifts even at room temperature. The ring size effect can be attributed to an effect of distance between the migrating hydrogen terminii, C_{19} and C_7, for the [1,5] shift. When bond angle corrected Dreiding models are used, these distances for the five- (**33**), six- (**32**, **36**), and seven-membered (**34**) A-ring cases are 2.9, 2.6, and 2.4 Å, respectively.[32] The situation is undoubtedly more complex, but the distance postulate may play a dominant role in the ring size effect. More recently, we have examined the six-membered A-ring sulfur cases **35**.[16g] Interestingly, the $7E/7Z$ ratio resulting from heating **35b** (1α-OH) and **35c** (1β-OH) were 1.6:1 and 1:2, respectively. This is just the opposite to that observed for the case where the sulfur is replaced by a carbon: in **32b** and **32c** where $R_2 = R_2' = H$, the $7E/7Z$ ratios were 1:4.1 and 2.7:1, respectively. Since the sulfur atom (like the C-1 hydroxyl oxygen) is allylic to the vinylallene π system in **35**, it is attractive to consider the combined electronic effect[30] of sulfur and oxygen to rationalize the reversed selectivity. It remains for future studies to test this hypothesis.

Applications in Vitamin D Synthesis

The vitamin D type vinylallenes have also proved useful for preparing a family of analogues of the type **3**, which was the initial goal. By way of comparison to the classical synthesis (Scheme I) of **2b** (11 steps, 0.2%) discussed earlier, this same analogue has been synthesized in 8.3–16% yield in only 6–8 steps[16b] using the vinylallene convergent approach. More recently, the vinylallene scheme was modified to allow incorporation of a 25-OH group (Scheme V).[16f] The C/D fragment **37**, prepared from Inhoffen–Lythgoe diol **19**, was con-

(31) Gerdes, J. M., unpublished observations. See also ref 16i.
(32) This suggestion was due to Alberto Haces of this laboratory.

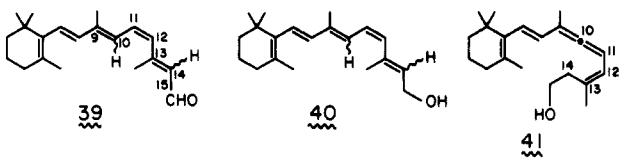
Scheme VI



verted to the vinylallene **38** and then to the side chain Δ^{25}-dehydro variant of **3**. Included in the design of this scheme was the introduction of the side chain hydroxyl in a manner that would allow radiolabel incorporation (for metabolism studies) at a late stage in the synthesis (i.e., the oxymercuration–demercuration step of Scheme V using labeled $NaBH_4$).

Retinoids

The chromophoric group of the visual system,[33] 11-*cis*-retinal (**39a**), and the calcium-regulating hormone 1α,25-$(OH)_2$-D_3 (**1c**), while functionally unrelated, incorporate a common structural feature, namely the (3*Z*)-hexa-1,3,5-triene unit **17**. By applying the process **16** → **17** to the 9,10-allenic retinoid **41**, we envisaged the shift of a C_{14} hydrogen to C_{10}, which would necessarily produce retinoids bearing an 11-cis geometry. It was not easy to predict beforehand whether heating **41** would result stereoselectively in one or more of the four possible 11-*cis*-retinols **40a–d**. Moreover, because of



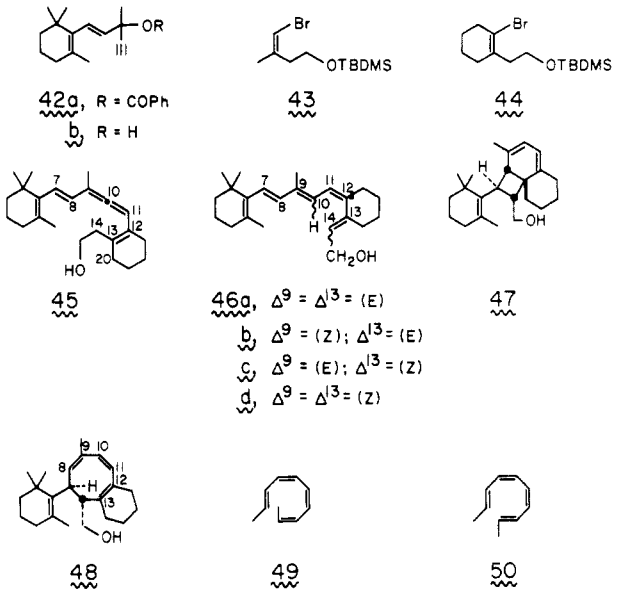
39 **40** **41**

a, $\Delta^9 = \Delta^{13} = (E)$
b, $\Delta^9 = (Z)$; $\Delta^{13} = (E)$
c, $\Delta^9 = (E)$; $\Delta^{13} = (Z)$
d, $\Delta^9 = \Delta^{13} = (Z)$

NOTE: (E) = trans; (Z) = cis

the known thermal lability of retinoids, this study was expected to provide a very severe test of the vinylallene method. Our interest in the retinoid problem was enhanced by virtue of its emerging biochemistry. Retinoids (vitamin A), besides playing pivotal roles in the visual process[33] as well as in the function of the purple membrame (the proton pump of *Halobacterium halobium*),[34] have recently been shown to be potentially useful in cancer prophylaxis[35] and acne therapy.[36]

The allene **41** was prepared from the β-ionone-derived propargyl ester **42a** and the vinyl bromide **43** by the cuprate approach used in Scheme IIA.[16k] Thermal rearrangement (69 °C, 2 h) of **41** was complex, but it produced (after separation) three 11-*cis*-retinols, **40a**, **40c**, and **40d**, in 10%, 12%, and 14% yields, respectively, but the absence of the fourth possible isomer **40b** was intriguing. More recently, application of the same condensation sequence (Scheme IIA) to **44** and **42a** afforded the more stable bridged allenic retinoid, **45**.[16l,37] Thermal rearrangement (hexanes, 69 °C, 4h) resulted in a four-component mixture in quantitative yield, which, after preparative high pressure LC separation, afforded **46a** (14%), **46c** (33%), **46d** (23%), and a fourth component, **47** (12%). The bicyclo[4.2.0]octadiene **47** is believed to be formed from the noticeably absent 9-cis,11-cis isomer **46b**[38] via the sequence: **46b** [eight-electron conrotatory closure across C_7–C_{14}] → **48** [six-electron disrotatory closure across C_8–C_{13}] → **47** (or a diastereomer).



42a, R = COPh
b, R = H

43 **44** **45**

46a, $\Delta^9 = \Delta^{13} = (E)$
b, $\Delta^9 = (Z)$; $\Delta^{13} = (E)$
c, $\Delta^9 = (E)$; $\Delta^{13} = (Z)$
d, $\Delta^9 = \Delta^{13} = (Z)$

47 **48** **49** **50**

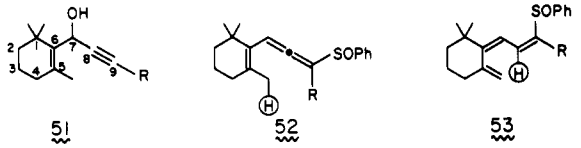
At first sight it was curious that the sterically more strained cis,cis,cis-isomer **46d**, but not the less hindered cis,cis isomer **46b**, was stable to the thermal conditions. This is now readily explicable on the basis of the analogous behavior of the octatetraenes **49** and **50**.[39] The trans,cis,cis,cis isomer **49**, a prototype for **46d**, has been shown to electrocyclize more slowly than **50**, a model for the less hindered and presumably more readily cyclized 9-cis,11-cis isomer **46b**. The parent allene **41**[16k] was recently shown to behave similarly.[16m]

Scheme VI depicts the process **16** → **17** (as a model for **45** → **46**) in greater detail wherein **a** through **d** are conformational isomers of **16**, which can undergo the four competing [1,5]-sigmatropic shifts A-D affording the four possible (3*Z*)-hexa-1,3,5-triene isomers of **17**. On the basis of product distribution for the rearrangement of **45**, the ratio for paths A:C and B:D were 1:2.4 and 1:1.9, respectively. This small preference for paths C or D over A or B probably reflects the relative importance of the eclipsing interaction between R and R′ in the transition states that result from conformers a and b compared to the nonbonded interaction between R and the allene moiety characteristic of the transition states that result from c and d. The ratio A:B

(33) Ottolenghi, M. *Adv. Photochem.* **1980**, *12*, 97–200.
(34) Stoeckenius, W. *Acc. Chem. Res.* **1980**, *13*, 337.
(35) Sporn, M. B. *Nutr. Rev.* **1977**, *35*, 65.
(36) See *Chem. Eng. News* **1979**, *57* (*Feb*), 6–7.
(37) Chandraratna, R. A. S.; Knudsen, C. G.; Walkeapää, L.; Chauhan, Y. S.; Cooper, T.; Birge, R. .; Okamura, W. H. *Abstr. Pap.—Am. Chem. Soc.* **1982**, *183rd*, ORGN-38.
(38) The parent 9-*cis*,11-*cis*-retinal has been reported: Kini, A.; Matsumoto, H.; Liu, R. S. H. *Bioorg. Chem.* **1980**, *9*, 406.
(39) (a) Marvell, E. N.; Seubert, J. *J. Am. Chem. Soc.* **1967**, *89*, 3377. (b) Huisgen, R.; Dahmen, A.; Huber, H. *Ibid.*, 7130, and *Tetrahedron Lett.* **1969**, 1461.

or C:D (1.2:1 or 1.4:1 for **45**) reflects the preference of the migrating hydrogen (circled) for the allene face either syn to L or syn to S, respectively, as it migrates to the sp carbon of the allene. For **45**, L and S are CH_3 and vinyl groups for which the relative contributions of steric and electronic effects are not clear.

In a more systematic study, treatment of propargyl alcohols **51** with PhSCl–Et_3N results in mainly the triene **53**.[40,41] The mirating hydrogen (circled) of vinylallene **52**, which rearranges even at room temperature to **53**, prefers to approach syn to the R group. For R = H, the ratio of **53** to its Δ^8-(*E*) isomer was 4.3 to 1. For R = CH_3 and R = $CH_2OTBDMS$, the corresponding ratios were >10:1 and ~8.6:1, respectively.

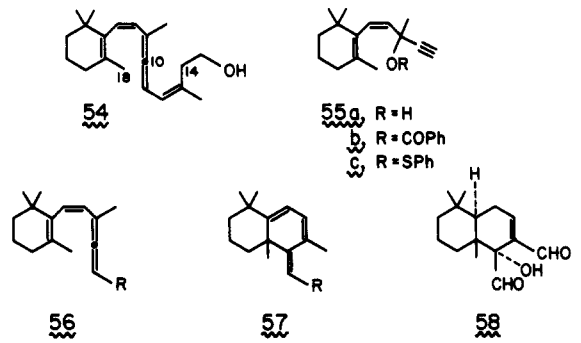


51 **52** **53**

In summary, the thermolysis of the 9,10-allenic retinoids **41** and **45** results in stereospecific production of 11-cis isomers, but there is little control of the stereochemistry of the lateral double bonds (Δ^9 and Δ^{13}) and the putative 9-cis,11-cis isomers appears not to be stable to the thermal conditions. Despite these present shortcomings, the method still allows ready access to certain of the hindered 11-*cis*-retinoid analogues in sufficient quantities for further study.

Drimanes

In order to examine the behavior of an allenyl diene (a diene–allene),[42] the synthesis and study of 7-cis allene **54** was considered. The putative allene **54**, however,



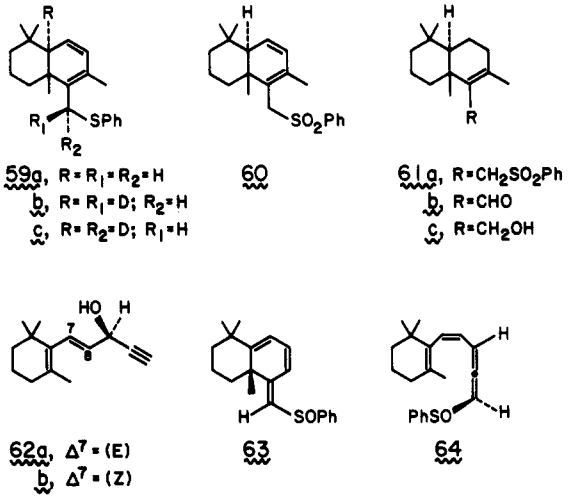
54 **55a**, R = H; **b**, R = COPh; **c**, R = SPh

56 **57** **58**

a, R = C_6H_5; **b**, R = t-Bu; **c**, R = n-Bu; **d**, R = CH_3; **e**, R = SOPh; **f**, R = SPh

was not expected to undergo the $C_{14} \rightarrow C_{10}$ [1,5] hydrogen shift observed for the closely related **41**, but rather a $C_{18} \rightarrow C_{10}$ [1,7] hydrogen shift accessible to **54**, but not **41**, was the anticipated observation.[43] However, upon reacting cuprates,[22] $R_2CuCNLi_2$, with 7-*cis*-benzoate **55b** with the expectation of obtaining diene–allenes **56**, the drimatriene **57** was obtained instead.[44] Thus, electrocyclization is more facile than [1,7]-sigmatropic shift, just the opposite for the *non*-allenic case.[43] The presumed allenic intermediate has not been observed at room temperature and the efficacy of synthesizing the phenyl (**57a**, 63%), *tert*-butyl (**57b**, 79%), *n*-butyl (**57c**, 77%), and methyl (**57d**, 32%) drimane derivatives attests to the generality of this process. The close relationship of **57** to the drimane class of natural products, which includes the novel insect antifeedant warburganal **58**,[45] was recognized, and we were therefore encouraged to exploit this serendipitous finding.

The preparation of **57** with a more synthetically useful handle R was achieved by reaction of **55a** with PhSCl–Et_3N, which afforded sulfoxide **57e** in ~80% yield as a ~3:2 diastereomeric mixture.[44] Either diastereomer reacted with zinc to afford the same vinyl sulfide **57f**, and quite remarkably, with excess $LiAlH_4$ to produce the trans-fused drimadiene **59a**. This latter



59a, R = R_1 = R_2 = H; **b**, R = R_1 = D; R_2 = H; **c**, R = R_2 = D; R_1 = H

60

61a, R = CH_2SO_2Ph; **b**, R = CHO; **c**, R = CH_2OH

62a, Δ^7 = (E); **b**, Δ^7 = (Z)

63 **64**

reduction, which requires a 12-fold excess of $LiAlH_4$ to achieve the ~90% observed yield, has been studied in some detail. Reduction with $LiAlD_4$ (H_2O workup) of one diastereomer of **57e** produces **59b** while the other produces **59c**, each with >9:1 diastereoselectivity. The trans ring fusion in **59** was established by its conversion to the known **61c**[46] through the sequence **59a** → **60** → **61a** → **61b** → **61c**.[44]

Since both the [2,3]-sigmatropic shift[41b–h] (**55c** → **56e**) and the six-electron electrocyclization (56e → 57e)[14] are considered to be stereospecific, it follows that a chiral center (**55a**) is translated into a chiral axis (**56e**) and then back to a chiral center (the bridgehead carbon of **57e**). This center → axis → center chirality transfer sequence is rare[47] and has been demonstrated in our case as follows. The one-way photosensitized isomerization[48] of **62a** (84% ee), prepared by asymmetric re-

(40) Tapia, R., unpublished observations.

(41) (a) van Kruchten, E. M. G. A.; Okamura, W. H. *Tetrahedron Lett.* **1982**, *23*, 1019. (b) Bickart, P.; Carson, F. W.; Jacobus, J.; Miller, E. G.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4869. (c) Tang, R.; Mislow, K. *Ibid.* **1970**, *92*, 2100. (d) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147. (e) Braverman, S.; Stabinsky, Y. *Isr. J. Chem.* **1967**, *5*, 125. (f) Smith, G.; Stirling, C. J. M. *J. Chem. Soc. C* **1971**, 1530. (g) Horner, L.; Binder, V. *Liebigs Ann. Chem.* **1972**, *757*, 33. (h) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 563.

(42) (a) Eglinton, G.; Raphael, R. A.; Willis, R. G.; Zabkiewicz, J. A. *J. Chem. Soc.* **1964**, 2597. (b) Hopf, H. *Chem. Ber.* **1971**, *104*, 3087.

(43) (a) Crowley, K. J.; Traynor, S. G. *Tetrahedron* **1978**, *34*, 2783. (b) Spangler, C. W. *Chem. Rev.* **1976**, *76*, 187.

(44) Reischl, W.; Okamura, W. H. *Abstr. Pap.—Am. Chem. Soc.* **1982**, ORGN-39; *J. Am. Chem. Soc.*, **1982**, *104*, 6115.

(45) (a) Kubo, I.; Lee, Y-W.; Pettei, M. J.; Pilkiewicz, F.; Nakanishi, K. *J. Chem. Soc. Chem. Commun.* **1976**, 1013. (b) Nakanishi, K.; Kubo, I. *Isr. J. Chem.* **1977**, *16*, 28.

(46) (a) Stadler, P. A.; Eschenmoser, A.; Schinz, H.; Stork, G. *Helv. Chim. Acta* **1957**, *40*, 2191. (b) Stoll, M..; Commarmont, A. *Ibid.* **1949**, *32*, 1836.

(47) For examples, see: Bertrand, M.; Roumestant, M. L.; Sylvestre-Panthet, P. *Tetrahedron Lett.* **1981**, *22*, 3589.

(48) Ramamurthy, V.; Butt, Y.; Yang, C.; Yang, P.; Liu, R. S. H. *J. Org. Chem.* **1973**, *38*, 1247. For **42b** → **55a** and **62a** → **62b**, 2′-acetonaphthone was used as sensitizer.

duction[49] of the corresponding ketone, afforded **62b** (also 84% ee),[50] which upon benzenesulfenyl chloride treatment afforded **63** with the same optical purity[51] as starting material. It is presumed that the stereospecifically produced intermediate **64** electrocyclizes disrotatorily to afford the less hindered *E* isomer **63** possessing the *R* bridgehead carbon.[49] Had disrotatory electrocyclization occurred in the opposite allowed sense, then the corresponding *Z,S* combination should have resulted. In other words, a novel situation emerges wherein *geometric* diastereomers correspond to optical antipodes.

Conclusion

Factors that influence *E* to *Z* pathways in the [1,5] hydrogen shift of vinylallenes of the general type **16** are not well-understood, but this process provides an efficacious route to the 1-hydroxyvitamin D system, certain 11-*cis*-retinoids, and other polyenes. Further exploratory investigations, both experimental and theoretical, should be useful and are continuing. The unexpected formation of drimatrienes, resulting from electrocyclization rather than [1,7]-sigmatropic hydrogen shifts of an allenyl diene, offers a new method for the stereospecific asymmetric synthesis of polycyclic ring systems. It is easy to envisage an extension of the transformation **62b** → [**64**] → **63** to a variety of substitution patterns including other sized rings. This Account clearly describes how new research areas may emerge from others, namely, from vitamin D to retinoids and drimanes.

The research described above was, of course, intellectually developed and then reduced to practice through the efforts of a number of undergraduate and graduate students, postdoctorals, and several colleagues who have been referenced throughout this article. I am deeply indebted to these individuals. Financial support was provided by the National Institutes of Health (Grant No. AM-16595 and EY-02452 and NCI Contract CP-05715), the Cancer Research Coordinating Committee of the University of California, and the Intramural Committee on Research (UC, Riverside). Duphar, B. V. (Weesp, the Netherlands), Hoffmann-LaRoche, Inc. (Nutley, NJ), BASF (Ludwigshafen, W. Germany), and Schering A.G. (Berlin, W. Germany) also provided support in various ways.

(49) Yamaguchi, S.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 1870. The configuration is predicted to be that shown for **62** and this stereochemistry is assumed to be transferred to **63** and **64** as shown.

(50) Determined by using ^{1}H NMR with a chiral shift reagent [Eu(hfc)$_3$] sold by Aldrich.

(51) The separated diastereomeric sulfoxides were analyzed by high pressure LC (chiral column, Regis *Chemical* Co.), but only one disastereomer could be resolved. See: Pirkle, W. H.; Finn, J. M.; Schreiner, J. L.; Hamper, B. C. *J. Am. Chem. Soc.* **1981**, *103*, 3964.

Infrared Fluorescence: A Versatile Probe of State-Selected Chemical Dynamics

STEPHEN R. LEONE

Joint Institute for Laboratory Astrophysics, National Bureau of Standards and University of Colorado, and Department of Chemistry, University of Colorado, Boulder, Colorado 80309

Received May 12, 1982 (Revised Manuscript Received October 11, 1982)

Early studies on chemical reactions were limited to measurements on the nature of the reaction products and the total reaction rate. Now chemists have many elegant methods for analysis of specific excited electronic, vibrational, and rotational states. These techniques have amply demonstrated the ability to analyze chemical reactions in much greater detail, from a state-selected point of view. Understanding the participation of excited states in a chemical reaction and the partitioning of energy among various states of the products provides a wealth of sensitive information pertaining to the dynamics, i.e., the molecular motions and forces that play a role in the reaction. Thus, the study of state-selected reactive and inelastic energy transfer collision events has come to form a cornerstone of modern chemical dynamics and kinetics.

The infrared emission technique was one of the earliest to be applied to detailed measurements of molecular states involved in reactions.[1] The infrared spectral region provides a means of analyzing vibrational state populations, and under high resolution, rotational state details as well. Overall, it has been a tremendously powerful technique for analysis of individual states in simple A + BC → AB(v,J) + C reaction dynamics[2] and in laser-excited vibrational energy transfer studies.[3] It is fair to say that the infrared studies completely opened up these fields, obtaining massive amounts of high quality detailed data and providing deep insights into the detailed mechanisms of these simple processes. State-selected optical studies and molecular beam scattering experiments provide ideal complements to each other in the study of collisional events. The former obtains precise information on product state popula-

Stephen R. Leone is a staff member of the Quantum Physics Division of the National Bureau of Standards, where he is currently a Fellow of the Joint Institute for Laboratory Astrophysics and a Professor Adjoint in Chemistry at the University of Colorado. He received his B.A. in Chemistry from Northwestern University in 1970 and his Ph.D. degree under the direction of C. Bradley Moore at the University of California, Berkeley, in 1974. From 1974 to 1976 he was a faculty member at the University of Southern California; he assumed his present position in Boulder in 1976. He is the 1982 recipient of the American Chemical Society Pure Chemistry Award, which recognizes his work employing state-of-the-art infrared techniques to the study of chemical dynamics.

(1) Smith, I. W. M. "Kinetics and Dynamics of Elementary Gas Reactions"; Butterworths: London, 1980.

(2) (a) Polanyi, J. C.; *Acc. Chem. Res.* **1972**, *5*, 161. (b) Anlauf, D. G.; Horne, D. S.; Macdonald, R. G.; Polanyi, J. C.; Woodall, K. B. *J. Chem. Phys.* **1972**, *57*, 1561.

(3) (a) Moore, C. B. *Acc. Chem. Res.* **1969**, *2*, 103. (b) Chen, H. L.; Moore, C. B. *J. Chem. Phys.* **1971**, *54*, 4072, 4081.