Studies on Vitamin D (Calciferol) and Its Analogues. 19. Rearrangement of Vinylallenes to 1-Hydroxylated Vitamin D Model Systems Lacking the D Ring and Side Chain[1]

Patrick Condran, Jr., and William H. Okamura*

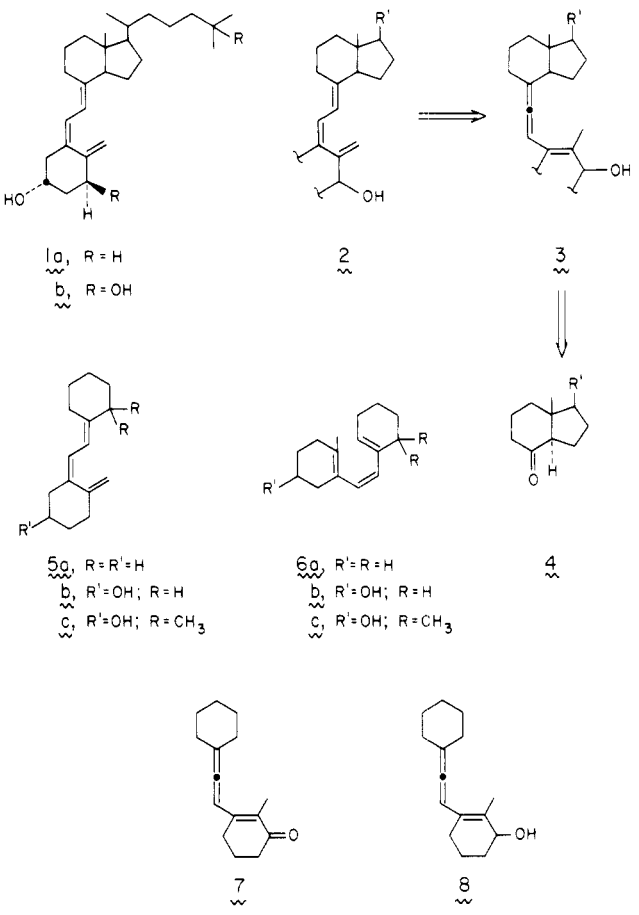
Department of Chemistry, University of California, Riverside, California 92521

Received February 19, 1980

The thermally induced sigmatropic shifts of vinylallenone **7** and vinylallenol **8** were studied. The former (**7**) rearranges (~100 °C, 18 h) to previtamin ketone model system **13** in essentially quantitative yield; further thermolysis (~180 °C, 10 h) of **13** afforded pyrocalciferone analogue **14** (57%) and a new member of the vitamin D thermal manifold, spiro ketone **15** (17%). Thermolysis of the alcohol **8** at ~100 °C (8 h) afforded what was shown to be an ~1:4 equilibrium mixture of model vitamin alcohol **11** (14% yield) and previtamin alcohol **12** (65% yield). The lithium salt **10b** obtained from bromoallene **10a** was reacted with 3-isobutoxy-2-methylcyclohex-2-en-1-one, and then the resulting 1,2-adduct was isomerized to **7** with aqueous acetic acid. The latter was reduced with sodium borohydride to afford allenol **8**. The salt **10b** could also be iodinated with 1,2-diiodoethane to give iodoallene **10c** or protonated with methanol to afford hydrocarbon **10d**. A mechanistic rationale for the formation of the various thermal products is given and spectral properties are discussed.

The physiologically active form of vitamin D_3 (**1a**, cholecalciferol) is considered to be the steroid hormone 1α,25-dihydroxyvitamin D_3 (**1b**).[2] The 1-hydroxyvitamin D skeleton **2** (see Chart I) seems to be characteristic of analogues and metabolites of vitamin D_3 possessing unusual biological properties.[3] We recently reported a convergent vinylallene approach[4,5] for synthesizing the hydroxy triene moiety **2**. In this new approach,[4] which we believe greatly simplifies the preparation of analogues of the type **2**, the appropriate vinylallene **3** (a *cis*-alkyl enallene)[6] is thermally rearranged via a [1,5] sigmatropic[7] shift to **2**. The allene **3** must be synthesized ultimately from Grundmann's ketone$_3$ (**4**) which in turn is preparable by degradation of **1a** or its side chain analogue vitamin D_2.[8] It is not usually economical to carry out extensive exploratory studies on **4**, however, because of its expense. Accordingly, we have chosen cyclohexanone as a simple and obviously inexpensive model for **4**. The resulting vinylallene model system should be useful for testing new synthetic procedures as well as for serving as a point of reference in studies of [1,5] sigmatropic rearrangements of allenes. As a prelude to the total synthesis of the parent vitamin D_3 and/or a study of the vitamin D_3–previtamin D_3 equilibrium, Havinga,[9] Lythgoe,[10] Inhoffen,[11] and co-

Chart I



(1) (a) For paper 18, see: Condran, P.; Hammond, M. L.; Mouriño, A.; Okamura, W. H. *J. Am. Chem. Soc.*, in press. (b) Taken in part from the Ph.D. Thesis submitted to the University of California, Riverside, by P. Condran, Jr. (Mar 1980).

(2) For general reviews on the subject of vitamin D, see: (a) Fieser, L. F.; Fieser, M. "Steroids"; Reinhold: New York, 1959; Chapter 4; (b) Georghiou, P. E. *Chem. Soc. Rev.* **1977**, *6*, 83; (c) DeLuca, H. F.; Paaren, H. E.; Schnoes, H. K. *Top. Curr. Chem.* **1979**, *83*, 1–65; (d) Norman, A. W. "Vitamin D, the Calcium Homeostatic Steroid Hormone"; Academic Press: New York, 1979.

(3) See for example: Okamura, W. H.; Norman, A. W.; Wing, R. M. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 4194.

(4) Hammond, M. L.; Mouriño, A.; Okamura, W. H. *J. Am. Chem. Soc.* **1978**, *100*, 4907.

(5) For leading references to convergent approaches to vitamin D, see: (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.

(6) For a review of enallenes (vinylallenes), see: (a) Eigenburg, I. Z. *Russ. Chem. Rev. (Engl. Transl.)* **1978**, *47*, 900–933; (b) Crowley, K. J. *Proc. Chem. Soc., London* **1964**, 17; (c) Mikolajczak, K. L.; Bagby, M. O.; Bates, R. B.; Wolff, I. A. *J. Org. Chem.* **1965**, *30*, 2983; (d) Skattebøl, L. *Tetrahderon* **1969**, *25*, 4933; (e) Bakker, S. A.; Lugtenburg, J.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 1459; (f) Havinga, E. *Experientia* **1973**, *29*, 1181; (g) van Koeveringe, J. A.; Lugtenburg, J. *Recl. Trav. Chim. Pays-Bas* **1976**, *95*, 80; (h) Minter, D. E.; Fonken, G. F.; Cook, F. T. *Tetrahedron Lett.* **1979**, 711.

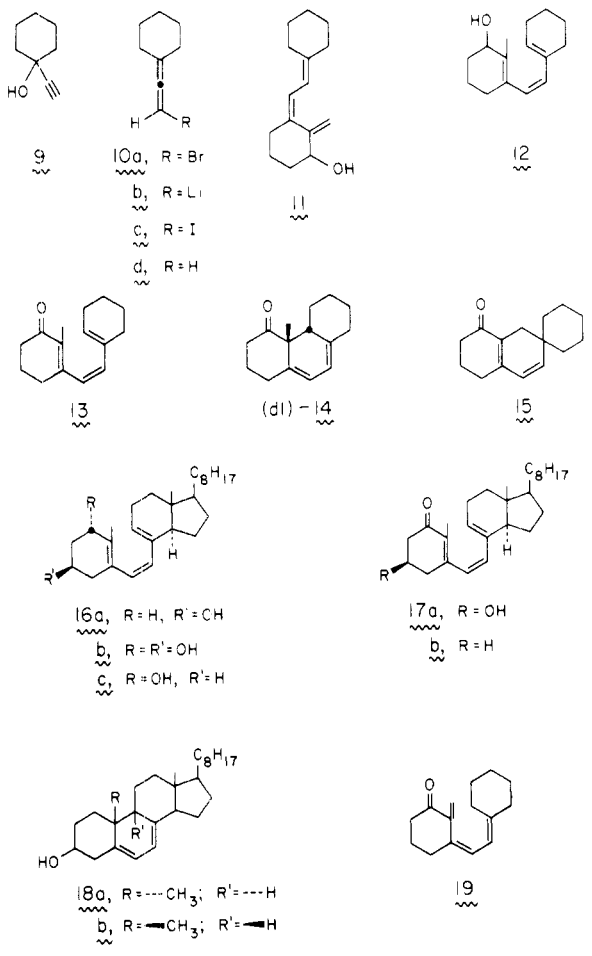
(7) For a review of [1,j] sigmatropic shifts, see: Spangler, C. W. *Chem. Rev.* **1976**, *76*, 187.

(8) (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.

(9) (a) Verloop, A.; Koevoet, A. L.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1957**, *76*, 689. (b) Schlatmann, J. L. M. A.; Havinga, E. *Ibid.* **1961**, *80*, 1101. (c) Schlatmann, J. L. M. A.; Pot, J.; Havinga, E. *Ibid.* **1964**, *83*, 1173. (d) Havinga, E.; Schlatmann, J. L. M. A. *Tetrahedron* **1961**, *16*, 146. (e) Sanders, G. M.; Pot, J.; Havinga, E. *Fortschr. Chem. Org. Naturst.* **1969**, *27*, 129.

0022-3263/80/1945-4011$01.00/0

Chart II



workers reported some time ago the synthesis of several related models which, however, lacked the important allylic hydroxyl function. This paper concerns the syntheses of the allylically oxygenated **7** and **8** and the characterization of the products which result from their thermal rearrangement.

Results and Discussion

The bromoallene **10a** was prepared in 86% yield from 1-ethynylcyclohexanol (**9**) by a modification of Landor's procedure[12] (see Chart II). That the action of *n*-butyllithium/hexane on **10a** in ether affords allenyllithium[13] reagent **10b** (or at least its equivalent in reactions with the electrophiles used) was established by quenching with 1,2-diiodoethane which gave **10c** (70%). The use of crystalline 1,2-diiodoethane instead of iodine proved most convenient, and its use has analogy to a similar reaction of 1,2-dibromoethane.[14] The bromoallene **10a** could also be lithiated with methyllithium in ether containing hexamethylphosphoramide (HMPA). Quenching the latter solution with methanol afforded ethenylidenecyclohexane (**10d**) in 71% yield.[13e] Reaction of **10b** from *n*-butyllithium–ether with 3-isobutoxy-2-methylcyclohex-2-en-1-one (−78 °C → ambient) followed by hydrolysis (aqueous HOAC) and purification afforded crystalline allenone **7** (79%).[15] Reduction of the latter with $NaBH_4$ afforded 91% of the highly labile, crystalline allenol **8**. The allenes described in this study displayed varying degrees of air sensitivity and were stored most effectively under nitrogen in a low-temperature freezer (−80 °C).

Thermolysis of allenone **7** in decalin or isooctane at ~100 °C for ~18 h afforded the previtamin ketone analogue **13** in essentially quantitative yield (^1H NMR pure). Further thermolysis of the latter in decalin at 180 °C for ~10 h afforded, after preparative high-pressure liquid chromatographic separation, 57% of the pyrocalciferone analogue **14**, 8% of starting trienone **13**, and 17% of spiro ketone **15**. Thermolysis of allenol **8** in isooctane at ~100 °C for 8 h resulted in the complete isomerization of starting material. NMR analysis of the crude product mixture (approximately quantitative) disclosed the presence of two principal components in a ratio of 1:4. Preparative high-pressure LC afforded 14% of model vitamin analogue **11** and 65% of its previtamin form **12**. When either **11** or **12** was heated at ~100 °C for 3 h, the same 22/78 equilibrium ratio of **11**/**12** was obtained.

The spectral data (supplementary material: ^1H NMR, IR, UV, mass spectra, and in some cases ^{13}C NMR) for the substances whose syntheses are described in this paper are in accord with their structural assignments. Several anomalies in the UV spectral data should be noted, however. The model vitamin **11** exhibits λ_{max} (EtOH) 256 nm (ϵ 19 100), which is considerably blue-shifted from that of vitamin D_3 [**1a**, λ_{max} (EtOH) 264.5 nm with ϵ 18 200],[16] 1α-hydroxyvitamin D_3 [λ_{max} (Et_2O) 264–265 nm with ϵ 18 000],[17] and the various model systems **5** (λ_{max} (MeOH) 261–262.5 nm with ϵ 14 800–17 000).[9b,c,10e,h]

The model previtamin **12** exhibits λ_{max} (EtOH) 244 nm (ϵ 13 000) which is similar to that of the models **6** (λ_{max} (MeOH) 240 nm with ϵ 11 500–12 300)[9b,c,10e] but strikingly blue-shifted from that of the previtamins **16a** (262 nm, ϵ 9000),[18,10g] **16b** (259 nm, ϵ 10 000 in ether),[17a] and **16c** (257 nm, ϵ 8900 in EtOH).[1] A logical rationale for the 13–22-nm shift in the λ_{max} values is that the models (240–244 nm) exist primarily in a somewhat twisted s-trans,s-trans conformation whereas the steroids (257–262 nm) exist predominantly in a twisted s-trans,s-cis form.[19] A similar large spectral difference, however, is not observed for the model ketone **13** [λ_{max} (EtOH) 290 and 233 nm with ϵ 9500

(10) (a) Harrison, I. T.; Lythgoe, B. *Proc. Chem. Soc., London* **1957**, 261. (b) Lythgoe, B. *Ibid.* **1959**, 141. (c) Harrison, I. T.; Lythgoe, B.; Trippett, S. *J. Chem. Soc.* **1955**, 4016. (d) Lythgoe, B.; Trippett, S.; Watkins, J. C. *Ibid.* **1956**, 4060. (e) Harrison, I. T.; Lythgoe, B. *Ibid.* **1958**, 837. (f) Harrison, I. T.; Lythgoe, B. *Ibid.* **1958**, 843. (g) Dawson, T. M.; Dixon, J.; Littlewood, P. S.; Lythgoe, B.; Saksena, A. K. *J. Chem. Soc. C* **1971**, 2960. (h) Frosch, J. V.; Harrison, I. T.; Lythgoe, B.; Saksena, A. K. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2005.

(11) (a) Inhoffen, H. H.; Weissermel, K.; Quinkert, G.; Irmscher, K. *Chem. Ber.* **1955**, *88*, 1321. (b) Inhoffen, H. H.; Quinkert, G. *Ibid.* **1954**, *87*, 1418.

(12) Landor, S. R.; Patel, A. N.; Whiter, P. F.; Greaves, P. M. *J. Chem. Soc. C* **1966**, 1223.

(13) (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.; Schults, R. H.; Waterhouse, A.; Hennion, G. F. *J. Org. Chem.* **1978**, *43*, 1389.

(14) (a) Greene, A. E.; Muller, J.-C.; Ourisson, G. *Tetrahedron Lett.* **1972**, 2489. (b) Greene, A. E.; Muller, J.-C.; Ourrison, G. *J. Org.Chem.* **1974**, *39*, 186. (c) Whitesides, G. M.; Casey, C. P.; Krieger, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1379. The corresponding reaction of the allenyllithium with iodine afforded only low yields of iodide **10c** along with substantial amounts of **10d**.

(15) (a) Stiles, M.; Longroy, A. L. *J. Org. Chem.* **1967**, *32*, 1095 and references cited therein. (b) Eschenmoser, A.; Schreiber, J.; Julia, S. A. *Helv. Chim. Acta* **1953**, *36*, 482.

(16) Huber, W.; Ewing, G. W.; Kriger, J. *J. Am. Chem. Soc.* **1945**, *67*, 609.

(17) (a) Sheves, M.; Friedman, N.; Mazur, Y. *J. Org. Chem.* **1977**, *42*, 3597. (b) Paaren, H. E.; Schnoes, H. K.; DeLuca, H. F. *J. Chem. Soc., Chem. Commun.* **1977**, 890.

(18) Velluz, L.; Armiard, G.; Petit, A. *Bull. Soc. Chim. Fr.* **1949**, 501.

(19) (a) Allinger, N. L.; Miller, M. A. *J. Am. Chem. Soc.* **1964**, *86*, 2811. (b) See also ref 9e, pp 139–140. (c) For a recent example of the s-cis effect, see: Squillacote, M. E.; Sheridan, R. A.; Chapman, O. L.; Anet, F. A. L. *J. Am. Chem. Soc.* **1979**, *101*, 3657.

and 14 500, respectively] when compared to the steroid systems **17a** [λ_{max} (ether) plus a 7-nm correction for solvent,[20] 294 and 243 nm with ϵ 10 000 and 9500, respectively][17] and **17b** [λ_{max} (EtOH) 296 and 242 nm with ϵ 10 400 and 10 600, respectively].[1]

The rearrangements of **7** and **8** presumably first afford **19** and **11**, respectively, through an initial [1,5] sigmatropic shift.[6,7] Under the reaction conditions, **11** equilibrates with **12** through a reversible [1,7] sigmatropic shift. The **11** $\rightleftarrows$ **12** equilibrium (22% **11**) is shifted further to the left than is the analogous **5b** $\rightleftarrows$ **6b** equilibrium (5% **5b**).[6f] This difference can be rationalized in terms of an increased steric strain in **12** similar to that characteristic of other 2-methylcyclohex-2-en-1-ol systems.[21] By analogy, we can expect that the natural hormone 1α,25-dihydroxyvitamin D_3 (**1b**) should at equilibrium be less on the previtamin side than the parent system, vitamin D_3 (**1a**). By contrast to the alcohol **11**, the corresponding ketone **19** was not observed at all. Instead, the presumed [1,7]-hydrogen-shifted product, the previtamin model ketone **13**, was the sole product observed. This is logically explicable on the basis that, whereas the putative **19** is cross conjugated, **13** has the more stable linearly conjugated chromophore. Thus, the presumed equilibrium **19** $\rightleftarrows$ **13** is shifted completely to the right. Similar examples in the steroid series are known.[17]

At higher temperatures (180 °C), the formation of the pyro structure **14** via a disrotatory electrocyclization of **13** as a major pathway is a kind of process well-known (e.g., **1a** or **16a** $\rightarrow$ **18**) in the vitamin D field.[2,5a,9e] By contrast, the minor product, spiro ketone **15**, is a new member in the thermal manifold of the vitamin D series. Its formation is logically envisaged as being the result of direct six-electron electrocyclization of the putative ketone **19** (the keto form of **11**), which in turn is presumably in reversible equilibrium to a small degree with **13** via a [1,7] sigmatropic shift. The observed UV maximum for **15** (λ_{max} 311 nm; calculated[20] 324 nm) is indicative of a homoannular diene, while the remaining spectral data are nicely accommodated by the assigned structure. Its ^{13}C NMR spectrum reveals the 13 expected signals including the five at low fields (carbonyl carbon at δ 198.9, two low-intensity quaternary olefinic carbons at δ 149.3 and 127.9, two other olefinic carbons at δ 145.8 and 125.6). Its ^1H NMR reveals the expected AB pattern ($J \approx 10.0$ Hz) in the olefinic region, and the IR exhibits an intense carbonyl stretch at 1661 cm^{-1}. Moreover, the formation of such a valence isomer from **13** is mechanistically logical. The spirane **15** is of some interest since such a valence isomer was once considered as a possible structure for previtamin D_3 (**16a**).[22] As mentioned earlier, **16a** equilibrates with vitamin D_3 (**1a**) at moderate temperatures ($\lesssim$100 °C), but at high temperatures (>150 °C) **16a** (or **1a**) rearranges irreversibly to pyrocalciferol (**18a**) and isopyrocalciferol (**18b**).[2,5a,9e] Unfortunately, the model system alcohol **12** (or **11**) affords a complex mixture of products under the high-temperature conditions used for rearranging the ketone **13**. The high-temperature thermal behavior of 1-oxygenated vitamin D metabolites or analogues (e.g., **1b**, **16bc**, and **17**) has not yet been studied in any detail.

(20) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. "Spectrometric Identification of Organic Compounds", 3rd ed.; Wiley: New York, 1974; pp 241–247.

(21) (a) Johnson, F. *Chem. Rev.* **1968**, *68*, 375–413 (1968). (b) Senda, Y.; Imaizumi, S.; Ochiai, S.; Fujita, K. *Tetrahedron* **1974**, *30*, 539. The 2-methylcyclohex-2-en-1-ol system should exhibit nonbonded steric strain in either half-chair conformation. In the pseudoequatorial OH conformer, there is allylic strain between the OH and methyl. In the pseudoaxial OH conformer, the OH bears a 1,3-diaxial relationship to the *cis*-hydrogen at C_5. In an analogous system lacking the allylic OH, there are fewer such nonbonded interactions.

(22) See ref 5a, p 77.

Experimental Section

General Methods. Ultraviolet (UV) and infrared (IR) spectra, nuclear magnetic resonance spectra (NMR), mass spectra, and other analytical data are given as supplementary material; melting points (uncorrected) were obtained with a Thomas-Hoover capillary apparatus. Dry tetrahydrofuran (THF) or dry ether was freshly distilled (nitrogen) from $LiAlH_4$ or potassium–benzophenone; lbpe (30–60 °C low-boiling petroleum ether) was redistilled. Kugelrohr distillation boiling points refer to the external oven air-bath temperatures. Reactions involving air- and/or moisture-sensitive organometallic reagents or substrates were handled under a blanket of dry nitrogen. Air-sensitive allenes or other polyenes were normally stored in the cold under nitrogen.

Chromatographic Methods. High-pressure liquid chromatography (LC) was carried out on a Waters 6000A solvent-delivery system equipped with a U6K injector and a dual detector system (UV at 2537 Å and a refractive index detector). A Whatman M9 10/50 partisil (10 μm, 9.4 mm i.d. × 50 cm), Whatman M9 10/50 ODS-2 Partisil (10 μm, 9.4 mm i.d. × 50 cm), or Waters μ-porasil (10 μm, 3.9 mm i.d. × 30 cm) column was used. Diisopropyl ether (chromatographed over activity I alumina and then distilled from CaH_2), reagent grade isopropyl alcohol, isobutyl alcohol, and Skellysolve B (distilled from CaH_2) were used as solvents for the normal phase columns. Solvent combinations were vacuum filtered through a 0.45-μm Millipore filter immediately before use. For gravity column chromatography, Baker analyzed reagent silica gel (60–200 mesh) or Woelm neutral grade III alumina was used. For thin-layer chromatography (TLC), silica gel G (EM reagents, type 60) was used to prepare analytical plates (0.38 mm).

Preparation of (2′-Bromoethenylidene)cyclohexane (10a). To a 1-L, three-necked, round-bottom flask fitted with a mechanical stirrer and a nitrogen inlet were added 1-ethynylcyclohexanol (20 g, 0.161 mol), cuprous bromide (157.6 g, 1.61 mol), ammonium bromide (157.6 g, 1.61 mol), and copper powder (10.2 g, 0.161 mol). The flask was ice cooled and 570 mL of 48% hydrobromic acid solution, previously cooled to −40 °C, was added all at once. The deep violet solution was then stirred for 1.5 h at 0 °C prior to workup. The crude mixture was transferred without warming to a separatory funnel and the reaction mixture thoroughly extracted with lbpe (500 mL). The aqueous layer was separated and the organic fraction washed with small portions of 48% HBr until no further violet coloration was obtained. A column was constructed with a 6-cm layer of 1:1 $MgSO_4/Na_2CO_3$, which was layered atop an equally thick band of silica gel. The lbpe solution was passed down this column along with an additional 500 mL of lbpe. Evaporation of the eluant under diminished pressure afforded nearly pure product (TLC and NMR examination). Kugelrohr distillation gave 26.0 g (86%) of **10a** [bp 41–45 °C (0.35 mm), lit.[12] bp 39–41 °C (0.5 mm)] contaminated with approximately 6% of the isomeric propargylic bromide.

Preparation of (2′-Iodoethenylidene)cyclohexane (10c) from Bromoallene 10a. To a stirred solution of 1.43 mL (1.87 g, 10.0 mmol) of **10a** in dry ether at −78 °C was added (syringe) 7.19 mL (11.0 mmol) of 1.53 M *n*-butyllithium in hexane solution. Stirring was continued for 30 min at −78 °C to afford a pale yellow solution of the desired lithium anion. Alternatively, the anion could be prepared in THF solution by following the same procedure. To the stirred anion solution in ether (−78 °C) was added a solution of 1,2-diiodoethane (3.38 g, 12.0 mmol) in ether (20 mL). The flask was immediately warmed to 0 °C by immersion in an ice bath and stirring continued at this temperature for 1 h followed by 10 min at room temperature. After removal of the solvent under vacuum, the light brown residual oil was dissolved in 40 mL of acetone. Liberated iodine was immediately titrated with 1 M sodium thiosulfate until the solution became colorless and stirring continued for an additional 10 min with periodic addition of thiosulfate solution as needed. The crude mixture was poured into a separatory funnel containing 100 mL of ether and 100 mL of distilled water. After the mixture was shaken briefly the aqueous fraction was run off and the ethereal layer washed with water (2 × 100 mL) and brine (1 × 50 mL). Drying ($MgSO_4$), filtration, and removal of the solvent under reduced pressure

afforded a pale yellow liquid. Kugelrohr distillation of the crude material [bp 70 °C (0.15 mm), lit.[23] bp 62 °C (2 mm)] gave 1.65 g (70%) of iodoallene **10c** as a pale yellow liquid.

Preparation of Ethenylidenecyclohexane (10d) from Bromoallene 10a. A dry 100-mL flask containing 1.43 mL (1.87 g, 10.0 mmol) of **10a** in 39 mL of dry ether containing 1 mL of HMPA was cooled to −50 °C with stirring over a 5-min period. To this solution was added 6.86 mL (12.0 mmol) of 1.75 M methyllithium in ether by syringe in a slow stream. The resulting pale yellow solution was stirred at −50 °C for 1 h during which some precipitation was observed. The solution was quenched by addition of 5.0 mL of anhydrous methanol followed by warming of the mixture to room temperature. The resulting biphasic mixture was poured into a separatory funnel containing 50 mL of ether and 50 mL of distilled water. After the mixture was shaken, the aqueous layer was run off and the ethereal fraction washed with portions of distilled water (5 × 50 mL) and a 25-mL portion of brine. The solution was dried ($MgSO_4$) and filtered, and then most of the ether was evaporated on a steam bath by using a Vigreaux column. The crude product was transferred to a smaller vessel, the remaining ether distilled off, and the yellow-brown residue distilled bulb-to-bulb at 2×10^{-4} torr to yield 0.72 g (71%) of ethenylidenecyclohexane (**10d**): colorless liquid; bp 135–136 °C (lit.[24] bp 138–141).

Preparation of [2′-(2″-Methyl-3″-oxocyclohex-1″-en-1″-yl)ethenylidene]cyclohexane (7). An ether solution of the anion **10b** in ether (20 mL) was prepared as described above from **10a** (1.87 g, 10.0 mmol) and *n*-butyllithium in hexane (7.19 mL, 1.53 M, 11.0 mmol). After anion formation was complete, a solution of 2.19 g (12.0 mmol) of 3-isobutoxy-2-methylcyclohex-2-en-1-one in ether (10 mL) was added by syringe in a rapid dropwise manner. Any residual ketone adhering to the walls of the vessel was rinsed in with a small additional volume of ether. Stirring was continued at −78 °C for 10 min prior to warming of the mixture to room temperature for 1 h. The reaction was quenched by addition of 20 mL of 1.0 N aqueous acetic acid followed by vigorous stirring for 5 min. After the mixture was allowed to stand an additional 5 min, the aqueous layer was drawn off with a pipet and replaced with 20 mL of fresh acid solution. Continued vigorous stirring at room temperature for a period of 30 min resulted in complete deprotection and dehydration of the initially formed 1,2-adduct.[15] The crude mixture was transferred to a separatory funnel with ether and water washings. After brief shaking of the separatory funnel, the aqueous layer was decanted and extracted with 50 mL of additional ether. The combined extracts were washed sequentially with saturated bicarbonate (2 × 50 mL), distilled water (50 mL), and brine (50 mL). Drying ($MgSO_4$) and removal of the solvent afforded a yellow liquid which was immediately chromatographed: dry silica gel (150 × 30 mm dry column; 25-mL fractions) successively eluted with 200 mL of lbpe and 600 mL of benzene. Product detection was carried out by TLC with diisopropyl ether as solvent. Those fractions containing the desired allene (fractions 12–26) were combined and evaporated under reduced pressure to give 1.71 g (79%) of a colorless liquid which crystallized on storage overnight at 0 °C. Recrystallization from pentane in the freezer gave 1.24 g (57%) of **7** as stout, colorless needles, mp 64–65 °C.

Thermolysis of Vinylallenone 7 to (*Z*)-1-(Cyclohex-1′-en-1′-yl)-2-(2″-methyl-3″-oxocyclohex-1″-en-1″-yl)ethene (13). A solution of allenone **7** (108 mg, 0.50 mmol) in 50 mL of purified isooctane was held at reflux for a period of 18 h. Complete consumption of the starting material was ascertained by UV and NMR analyses. After the mixture cooled to room temperature, the solvent was removed under reduced pressure and then the colorless residue dried under vacuum. Examination of the crude reaction mixture by NMR showed that **7** had been converted to the model previtamin **13** in essentially quantitative yield. Preparative high-pressure LC afforded the pure material.

High-Temperature Thermolysis of Model Previtamin Ketone 13. Preparation of *cisoid*-1,2,4a,4b,5,6,7,8,-Octahydro-4a-methyl-4(3*H*)-phenanthrone (14) and 5′,6′-Dihydrospiro[cyclohexane-1,2′(1′*H*)-naphthalen]-8′(7′*H*)-one (15). A solution of 432 mg (2.0 mmol) vinylallenone **7** in dry, purified decalin (200 mL) was stirred at 100 °C for a period of 18 h (NMR analysis indicated the presence of only **13**) and then heated at 180 °C for an additional 10 h. The progress of the reaction was monitored by analytical high-pressure LC (10% diisopropyl ether/Skellysolve B on μ-Porasil) until no further significant changes in product distribution were detectable. The mixture was cooled to room temperature, the solvent removed under reduced pressure (60 °C at 1.5 torr), and the residual pale yellow liquid resolved by preparative high-pressure LC utilizing 40% diisopropyl ether/Skellysolve B on Partisil. Three major fractions were collected, and each was evaporated under reduced pressure and vacuum dried. Isolated in this manner were, in order of elution, 247 mg (57%) of pyrocalciferone model **14**, 33 mg (8%) of starting trienone **13**, and 113 mg (26%) of a third fraction which, on the basis of NMR evidence, appeared to contain two distinct components. This third fraction was resolved by preparative reverse-phase high-pressure LC by using 10% water/methanol on Partisil ODS-2. Two major peaks were collected; dilution with distilled water, back-extraction into pentane, drying ($MgSO_4$), and evaporation of the solvent afforded, in order of elution, 74 mg (17%) of spiro ketone **15** and 15 mg (~3%) of an apparently homogeneous but as yet uncharacterized second product.

Preparation of [2′-(3″-Hydroxy-2″-methylcyclohex-1″-en-1″-yl)ethenylidene]cyclohexane (8). A solution of 433 mg (2.0 mmol) of vinylallenone **7** in 20 mL of absolute ethanol at room temperature was treated with 378 mg (10.0 mmol) of powdered sodium borohydride added in one portion. After the mixture was stirred at room temperature for 4 h, the excess borohydride was quenched by slow, dropwise addition of 8.0 mL (8.0 mmol) of 1.0 N aqueous acetic acid. A clear, colorless solution resulted after the mixture was stirred for 5 min at room temperature. The mixture was then transferred to a separatory funnel containing 100 mL of ether and 50 mL of saturated Na_2CO_3 solution, the funnel was shaken briefly, and the aqueous layer was decanted and extracted with an additional 50 mL of ether. The combined extracts were washed with aqueous saturated bicarbonate (2 × 50 mL), distilled water (2 × 50 mL), and brine (30 mL). Evaporation under reduced pressure followed by brief vacuum drying gave a colorless oil. TLC examination of this material with benzene as eluant indicated the presence of some highly polar contaminants; these were removed by filtration through a short (50 mm × 10 mm) silica gel column. Elution with benzene containing 1% pyridine (v/v) and collection of the total eluant afforded, after evaporation of the solvent, 396 mg (91%) of a pale yellow oil which was free from polar materials but slightly contaminated with the products of apparent dehydration (TLC, NMR). The pure alcohol **8** deposited fine, colorless, air-sensitive needles from hexane; mp 74.2–75 °C.

Thermolysis of Vinylallenol 8. Preparation of (*Z*)-1-Cyclohexylidene-2-(3′-hydroxy-2′-methylenecyclohexylidene)ethane (11) and (*Z*)-1-(Cyclohex-1′-en-1′-yl)-2-(3″-hydroxy-2″-methylcyclohex-1″-en-1″-yl)ethene (12). A solution of 109.2 mg (0.50 mmol) of allenic alcohol **8** in 50 mL of dry isooctane was held at reflux (100 °C) for a period of 8 h. This resulted in complete consumption of the starting material as evidenced by UV and high-pressure LC with 25% diisopropyl ether/Skellysolve B on Partisil. The mixture was cooled to room temperature and the solvent removed by distillation at reduced pressure. Examination of the colorless residue by NMR disclosed the presence of two principal components in a ratio of 20:80. The residue was taken up in approximately 0.5 mL Skellysolve B and a minimum amount of benzene, and the components were resolved by preparative high-pressure LC with 40% diisopropyl ether/Skellysolve on Partisil with shave/recycling techniques. Each component was collected, the solvent evaporated under reduced pressure, and the residue dried under vacuum. Isolation in this manner afforded, in the order of elution, 16 mg (14%) of model vitamin **11** and 71 mg (65%) of the corresponding previtamin model system **12**. Each component was obtained as a colorless air-sensitive oil. Thermolysis of **8** at higher temperatures (≥180 °C) appeared to be complicated by extensive dehydration with the formation of at least seven products (by high-pressure LC).

Model Vitamin–Previtamin Thermal Equilibrium 11 ⇌ 12. A solution of 19.6 mg (0.09 mmol) of model vitamin **11** in 9.0 mL of dry isooctane was transferred to a round-bottom flask

(23) (a) Gore, J.; Roumestant, M. *Tetrahedron Lett.* **1971**, 1027. (b) Roumestant, M.; Gore, J. *Bull. Soc. Chim. Fr.* **1972**, 591.
(24) Bailey, W. J.; Pfeifer, C. R. *J. Org. Chem.* **1955**, *20*, 95.

equipped with an efficient condenser. The vessel was purged with a flow of dry nitrogen and the solution heated to reflux (100 °C). The solution composition was monitored throughout the reaction by analytical high-pressure LC (25% diisopropyl ether/Skellysolve B on μ-Porasil) at 1-h intervals until no further changes were observed. After 3 h, the solution was cooled, the solvent distilled off under reduced pressure, and the residual oil examined by NMR. Comparison of integrated peak intensities in the olefinic region of the spectrum indicated that a 22:78 equilibrium mixture of model vitamin **11** and previtamin **12** had been established. A similar experiment starting from the previtamin gave an identical result.

Acknowledgment. The U.S. Public Health Service (NIH Grant No. AM-16595) and the Intramural Fund of the University of California, Riverside, provided the financial support for this study. We thank Badische-Anilin and Sodafabrik (Ludwigshafen) and Hoffmann-La Roche (Nutley) for providing several of the starting materials used in this study. Dr. Milton Hammond (Ph.D. Thesis, University of California, Riverside, March 1978) is acknowledged for carrying out several preliminary investigations on vitamin D model systems which led to this investigation.

Registry No. **7**, 74483-09-3; **8**, 74483-10-6; **9**, 78-27-3; **10a**, 10575-77-6; **10b**, 65150-03-0; **10c**, 31814-67-2; **10d**, 5664-20-0; **11**, 74483-11-7; **12**, 74483-12-8; **13**, 74483-13-9; **14**, 74483-14-0; **15**, 74483-15-1; 1,2-diiodoethane, 624-73-7; 3-isobutoxy-2-methylcyclohex-2-en-1-one, 37457-15-1.

Supplementary Material Available: Spectral and analytical data (6 pages). Ordering information is given on any current masthead page.

Studies on Vitamin D (Calciferol) and Its Analogues. 20. Synthesis of 3-Deoxy-3,3-dimethyl-1-hydroxyvitamin D_3 from Vinylallene Intermediates and Related Thermal and Configurational Studies[1]

Antonio Mouriño, Sabina Lewicka-Piekut, Anthony W. Norman, and William H. Okamura*

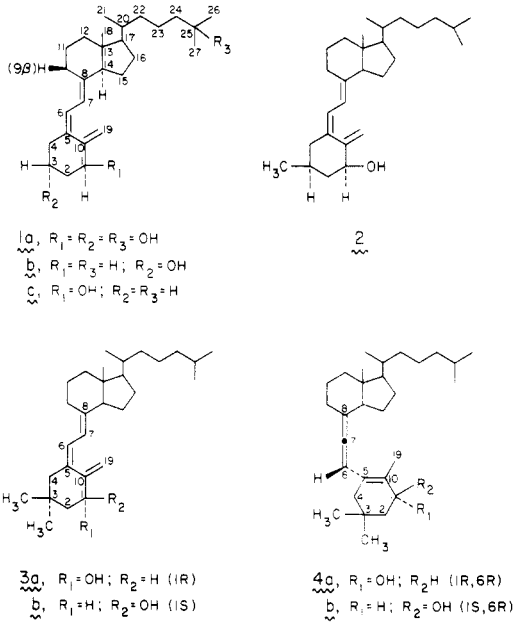
Departments of Chemistry and Biochemistry, University of California, Riverside, California 92521

Received April 11, 1980

The diastereomeric vinylallenols **4a** (1*R*,6*R*) and **4b** (1*S*,6*R*) were synthesized by coupling the known propargylic benzoate **9** with the heterocuprate **8**. The latter was prepared in five steps from 2-methyldimedone (**5**). By use of model systems **10a–c**, **11a–c**, and **12**, comparison of ^{13}C NMR data lends support to the 6*R* configuration assigned to **4a** and **4b**. Comparisons of the specific rotations of **10a,b**, **11a,b**, **4a,b**, and other chiral cyclohexenols previously described lend support to the C_1 configuration assigned to **4a** (1*R*) and **4b** (1*S*). Thermolysis of **4a** (~100 °C, 10 h) affords an ~6.8 to 1 ratio of 7*E* (**3a**) to 7*Z* manifold (**15a + 16a + 17a**) products. Similar thermolysis of **4b** affords a reversed ~1 to 8.3 ratio of 7*E* (**3b**) to 7*Z* manifold (**15b + 16b + 17b**) products. How the reversal in the 7*E* to 7*Z* ratio supports the C_1 configurational assignment is discussed. Neither vitamin (**3a** or **3b**) exhibits any in vivo vitamin D biological activity.

Analogues of 1α,25-dihydroxyvitamin D_3 (**1a**), the hormonally active form of vitamin D_3 (**1b**, cholecalciferol),[2] modified at the 3-position possess biological properties of unusual interest[3] (see Chart I). In earlier papers[4] we reported the synthesis and biological evaluation of 3-deoxy-1α-hydroxyvitamin D_3 (**1c**) in order to evaluate the relative contributions of the various hydroxy groups to the biological properties of **1a**. Interestingly, the 3-unsubstituted analogue **1c** was found to possess a significant ability to elicit intestinal calcium absorption (ICA) but only minimal bone calcium mobilization (BCM). This selectivity in biological action is of potential clinical interest

Chart I



in as much as the natural hormone **1a** is the most active substance known for eliciting both of these classical vitamin D mediated physiologic responses, ICA and BCM. In order to further pursue the notion that 3-substitution might impart interesting biological properties to other

(1) (a) For paper 19, see: Condran, P.; Okamura, W. H. *J. Org. Chem.*, preceding paper in this issue. For earlier vinylallene papers, see also: (b) Hammond, M. L.; Mouriño, A.; Okamura, W. H. *J. Am. Chem. Soc.* **1978**, *100*, 4907; (c) Condran, P.; Hammond, M. L.; Mouriño, A.; Okamura, W. H. *J. Am. Chem. Soc.*, in press.

(2) For general reviews on the subject of vitamin D, see: (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*, 1–65; (c) Georghiou, P. E. *Chem. Soc. Rev.* **1977**, *6*, 83; (d) Fieser, L. F.; Fieser, M. "Steroids"; Reinhold: New York, 1959; Chapter 4.

(3) Okamura, W. H.; Norman, A. W.; Wing, R. M. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 4194.

(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.; Procsal, D. A.; Norman, A. W. *Ibid.* **1975**, *65*, 24. (c) Lam, H.-Y.; Onisko, B. L.; Schnoes, H. K.; DeLuca, H. F. *Ibid.* **1974**, *59*, 845. (d) Mitra, M. N.; Norman, A. W.; Okamura, W. H. *J. Org. Chem.* **1974**, *39*, 2931. (e) Norman, A. W.; Mitra, M. N.; Okamura, W. H.; Wing, R. M. *Science* **1975**, *188*, 1013. (f) Onisko, B. L.; Lam, H.-Y.; Reeve, L. E.; Schnoes, H. K.; DeLuca, H. F. *Bioorg. Chem.* **1977**, *6*, 203.

0022-3263/80/1945-4015$01.00/0