On the Thermal Sigmatropic Rearrangement of Allenic Retinoids: 12,14-*retro*-Retinol

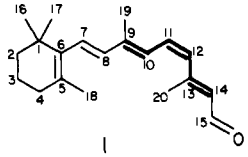
Javier Sueiras and William H. Okamura*

Contribution from the Department of Chemistry, University of California, Riverside, California 92521. *Received March 24, 1980*

Abstract: The 11,12-allenic retinoid **7** (Y = $CH_2OSi(CH_3)_2$-*t*-Bu) was synthesized in 51% yield by Wittig condensation of the ylide of β-ionyltriphenylphosponium bromide (**12**) with the allenic aldehyde **10c**. The latter was synthesized from isopentenyl alcohol **8a** in four steps (53% overall). Thermolysis of **7** (Y = $CH_2OSi(CH_3)_2$-*t*-Bu) afforded a ~1.9:1 ratio of the double bond shifted retinoid (a retro-ene isomer) **13a** and a mixture of retinol ethers (~2:1 ratio of the silyl ethers of 11-*cis*- (**14**) and 11-*cis*,13-*cis*-retinol (**15**)). Similar rearrangement of alcohol **7** (Y = CH_2OH) afforded a ~1.7:1 ratio of analogous alcohol isomers (**13b** and **14** + **15**). The formation of the products can be rationalized in terms of an initial competitive suprafacial [1,5]-sigmatropic hydrogen shift to afford the putative 12*E* and 12*Z* isomers of **17**, which undergo subsequent [1,7]-sigmatropic hydrogen shifts.

Introduction

The chromophoric group of the visual system, 11-*cis*-retinal (**1**),[1]



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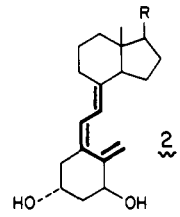

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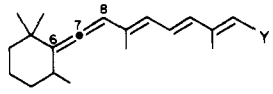
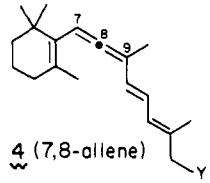
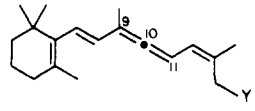


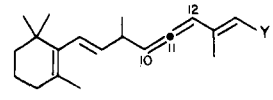
3 (6,7-allene)



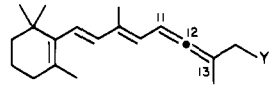
4 (7,8-allene)



5 (9,10-allene)



6 (10,11-allene)



7 (11,12-allene)

and the calcium-regulating steroid hormone, vitamin D (**2**),[2] while functionally unrelated, possess a common structural feature, namely, the (3*Z*)-1,3,5-hexatriene moiety. Recently we were able to establish the efficacy of utilizing a [1,5]-sigmatropic shift of a vinylallene as a key step in a new synthesis of the 1-hydroxy-vitamin D system.[3] Retinoids have recently attracted interest in what is seemingly a renaissance in the vision field[4] in addition to their emergence in the areas of energy transduction,[5] cancer prophylaxis,[6] and acne therapy.[7] These factors as well as our interest in defining the scope and limitations of the vinylallene scheme toward the synthesis of other polyenes directed our attention to the possibility of studying allenic retinoids analogous to those of vitamin D.

Five structurally isomeric side-chain allenic retinoids **3**–**7** were considered. Depending upon configuration, each of these can be related to a normal retinoid (i.e., a retinoid with the same structure as **1** with unspecified geometry) or a retro-ene (double-bond shifted) type retinoid valence isomer by [1,*j*]-sigmatropic shifts[8] or through other kinds of allylic rearrangements. Nakanishi and co-workers[9] have already prepared various geometric isomers of the 6,7-allene **3** and observed that several such isomers of the aldehyde (**3**, Y = CHO) produce visual pigment analogs (rhodopsins). Other allenic retinoids have also been reported as intermediates during the course of total synthetic work.[10] In the context of [1,5]-sigmatropic shifts we were most intrigued by **4**, **5**, and **7**. We envisaged that **4** could be isomerized to an exocyclic methylene isomer ($\Delta^{5(18)}$), a potential visual cycle intermediate eluded to by Lugtenburg;[11] that **5**, depending upon the stereochemistry of the Δ^{12} double bond, could be isomerized to 11-cis retinoids or to $\Delta^{13(20)}$-methylene isomers of the kind proposed recently by Mowery and Stoeckenius;[12] and that **7** might be convertible to 11-cis retinoids or to $\Delta^{9(19)}$ cross-conjugated isomers also considered as possible intermediates of the visual cycle by Mathies and Lugtenburg.[13] It is the purpose of this article to report on the preparation of **7** (Y = CH_2OSiMe_2-*t*-Bu and Y = CH_2OH) and on studies of their thermal reorganization. While diverse cases of [1,5]-sigmatropic shifts of vinylallenes to give (*Z*)-hexatrienes have now been reported,[14] there appear to be no

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(2) Norman, A. W. "Vitamin D, the Calcium Homeostatic Steroid Hormone"; Academic Press: New York, 1979.
(3) (a) Hammond, M. L.; Mouriño, A.; Okamura, W. H. *J. Am. Chem. Soc.* **1978**, *100*, 4907. (b) Condran, P.; Hammond, M. L.; Mouriño, A.; Okamura, W. H., following paper in this issue.
(4) Menger, E. L. *Acc. Chem. Res.* **1975**, *8*, 81, and accompanying articles.
(5) Stoeckenius, W. *Sci. Am.* **1975** (Nov), 38.
(6) Sporn, M. B. *Nutr. Rev.* **1977**, *35*, 65.
(7) See, for example, *Chem. Eng. News* **1979**, *57* (Feb), 6–7.
(8) Spangler, C. W. *Chem. Rev.* **1976**, *76*, 187.
(9) Nakanishi, K.; Yudd, A. P.; Crouch, R. K.; Olson, G. L.; Cheung, H.-C.; Govindjee, R.; Ebrey, T. G.; Patel, D. J. *J. Am. Chem. Soc.* **1976**, *98*, 236. See also, Baltchly, R. A.; Carriker, J. D.; Balogh-Nair, V.; Nakanishi, K. *ibid.* **1980**, *102*, 2495.
(10) Dr. Gary L. Olson, Hoffmann-La Roche, Nutley, N.J., personal communication.
(11) (a) v. d. Meer, K.; Mulder, J. J. C.; Lugtenburg, J. *Photochem. Photobiol.* **1976**, *24*, 363. (b) Fransen, M. R.; Luyten, W. C. M. M.; v. Thuijl, J.; Lugtenburg, J.; Jansen, P. A. A.; v. Breugel, P. J. G. M.; Daemen, F. J. M. *Nature (London)* **1976**, *260*, 726.
(12) Mowery, P. C.; Stoeckenius, W. *J. Am. Chem. Soc.* **1979**, *101*, 414.
(13) Eyring, G.; Curry, B.; Mathies, R.; Fransen, R.; Palings, I.; Lugtenburg, J., *Biochemistry* **1980**, *19*, 2410. And personal communications with Dr. R. Mathies and Dr. J. Lugtenburg.
(14) Besides ref 3, previous papers on the subject of sigmatropic shifts of vinylallenes include: (a) Crowley, K. J. *Proc. Chem. Soc.* **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. (d) Bakker, S. A.; Lugtenburg, J.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 1459. (e) Havinga, E. *Experientia* **1973**, *29*, 1181. (f) van Koeveringe, J. A.; Lugtenburg, J. *Recl. Trav. Chim. Pays-Bas* **1976**, *95*, 80. (g) Minter, D. E.; Fonken, G. F.; Cook, F. T. *Tetrahedron Lett.* **1979**, 711. For a very recent report on the 9,10-allene **5**, see Knudsen, C. G.; Carey, S. C.; Okamura, W. H. *J. Am. Chem. Soc.* in press.

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examples of using the concept to prepare higher polyenes. Because of the known thermal lability of certain retinoids,[15] it seemed that our objectives in the vitamin A field would provide a severe test of the vinylallene approach.

Results and Discussion

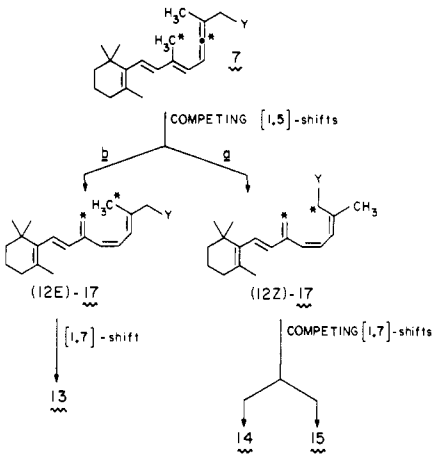
The key step in the synthesis of the 11,12-allene **7** (Y = $CH_2OTBDMS$; TBDMS = *tert*-butyldimethylsilyl) was the Wittig condensation of aldehyde **10c** with the ylide derived from the known phosphonium salt **12**.[16] Chromatographically and spectrally pure **7** (Y = $CH_2OTBDMS$), obtained in 51% yield, was converted by the action of $(n\text{-Bu})_4NF/THF$[17] to the alcohol **7** (Y = CH_2OH) in 50% yield. The highly air-sensitive allenes exhibited a characteristic allenic stretch at 1942 cm^{-1} in the IR, a maximum at 288 nm (ϵ 25 600 and 29 200 for the silyl ether and alcohol, respectively) in the UV, and appropriate signals in their ^1H NMR spectra. The *E* stereochemistry of the Δ^7 and Δ^9 double bonds is assigned on the basis of the method of synthesis[16] and on the stereochemistry of the products obtained from their thermolyses.

The aldehyde **10c** was synthesized in four steps (53% overall yield) from isopentenyl alcohol **8a**. After protection of **8a** as its *tert*-butyldimethylsilyl ether,[17] it was converted to dibromocyclopropane **9** and then to allene **10a** by standard procedures.[18] Metalation of **10a** (*tert*-butyllithium/THF) afforded a solution of **10b**[19] which was quenched with *N,N*-dimethylformamide[19c,20] to give **10c**. In a second, less satisfactory synthesis, **8a** was ozonized to the known ketone **11a**[21] which was allowed to react with lithium acetylide[22] to afford **11b**. The latter was converted to the bromo allene **10d** by the method (48% HBr, NH_4Br, CuBr, and Cu) of Landor.[23] The corresponding silyl ether **10e** (11% overall yield from **8a** in four steps) could be readily lithiated (*n*-butyllithium) to give **10b**, but several attempts to react the latter with *N,N*-dimethylformamide[19c,20] (in the same way as the process **10a** → **10c**) proceeded to afford mixtures of **10a** and **10c** among other contaminants. Further studies of this second route have been discontinued.

Thermolysis[3,14] of the allene **7** (Y = $CH_2OTBDMS$) in refluxing isooctane (~100 °C, 3 h) afforded a mixture (~100%) of pentaene **13a**, 11-*cis*-retinol silyl ether (**14**-OTBDMS), and 11-*cis*,13-*cis*-retinol silyl ether (**15**-OTBDMS). ^1H NMR analysis revealed the composition to be 66, 22, and 12%, respectively. Chromatography afforded pure **13a** in 19% yield (fraction A), a pure mixture of **14**-OTBDMS plus **15**-OTBDMS in 16% yield (fraction B), and a mixture of A + B (14%). Treatment of pure fraction B with $(n\text{-Bu})_4NF/THF$ afforded after chromatographic separation pure 11-*cis*-retinol (**14**) and 11-*cis*,13-*cis*-retinol (**15**) which proved identical with authentic specimens. Similar deprotection of fraction A (pure **13a**) afforded the corresponding alcohol **13b** in 87% yield.

Several control or comparison thermal experiments were also carried out. When **7** (Y = $CH_2OTBDMS$) was heated for shorter (2 h; trace amounts of starting material remained) or longer (4.5 h) reaction times, there was essentially no change in the composition of the reaction mixture. When pure major product (**13a**) was heated for 4 h under the reaction conditions, it was recovered unchanged in quantitative yield. Finally, thermolysis (100 °C/4 h) of the alcohol **7** (Y = CH_2OH) gave a product distribution

Scheme I



(15) (a) Hubbard, R. *J. Biol. Chem.* **1966**, *241*, 1814. (b) Oroshnik, W.; Brown, P. K.; Hubbard, R.; Wald, G. *Proc. Natl. Acad. Sci. U.S.A.* **1956**, *42*, 578. (c) Kini, A.; Matsumoto, H.; Liu, R. S. H. *J. Am. Chem. Soc.* **1979**, *101*, 5078.

(16) (a) Olivé, J.-L.; Mousseron-Canet, M.; Dornard, J. *Bull Soc. Chim. Fr.* **1969**, 3247. (b) Pommer, H. *Angew. Chem.* **1960**, *72*, 811. A referee has pointed out that *Z* olefins normally predominate when the ylide of **12** is allowed to react with aldehydes as described in the preceding articles. Direct spectroscopic evidence for the 9*E* stereochemistry for **7** obtains from the ^1H NMR chemical shift of the signal assigned to H_8 (τ 3.92). For a wide variety of retinoids including several possessing shortened side chains, those with 9*E* linkages exhibit H_8 chemical shifts in the range τ 3.82–4.04. The corresponding 9*Z* isomers exhibit signals in the range below τ 3.5. [Ramamurthy, V.; Tustin, G.; Yau, C. C.; Liu, R. S. H. *Tetrahedron* **1975**, *31*, 193. Patel, D. J. *Nature (London)* **1969**, *221*, 825. Knudsen, C. G. Ph.D. Dissertation, University of California, Riverside, 1980.] Unfortunately, we have not been able to isolate the corresponding 9*Z* isomer of **7** (see Experimental Section).

(17) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(18) (a) Doering, W. von E.; Hoffman, A. K. *J. Am. Chem. Soc.* **1954**, *76*, 6162. (b) Doering, W. von E.; LaFlamme, P. M. *Tetrahedron* **1958**, *2*, 75. (c) Skattebøl, L. *Acta Chem. Scand.* **1963**, *17*, 1683. (d) Moore, W. R.; Ward, H. R. *J. Org. Chem.* **1962**, *27*, 4179. (e) Untch, K. G.; Martin, D. J.; Castellucci, N. T. *Ibid.* **1965**, *30*, 3572.

(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.

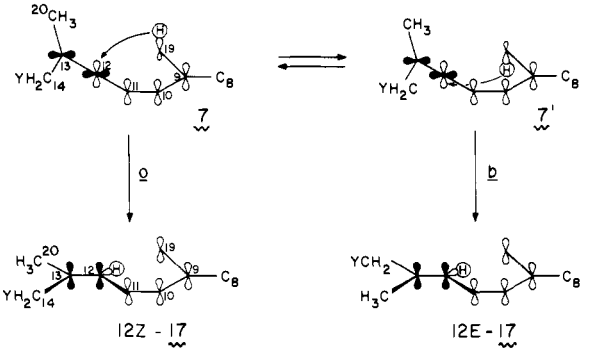
(20) Colvin, E. W.; Purcell, T. A.; Raphael, R. A. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1718.

(21) (a) Pappas, J. J.; Keaveney, W. P.; Gancher, E.; Berger, M. *Tetrahedron Lett.* **1966**, 4273. (b) Fêtizon, M.; Golfier, M.; Louis, J.-M. *J. Chem. Soc. D* **1969**, 1102.

(22) Midland, M. M. *J. Org. Chem.* **1975**, *40*, 2250.

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

Scheme II



similar to that from the silyl ether: 63% **13b**, 24% 11-*cis*-retinol (**14**), and 13% 11-*cis*,13-*cis*-retinol (**15**).[24]

The structural assignment of **13** is based on the mechanistic rationale discussed below and on spectral data. The ^{1}H NMR spectrum of alcohol **13b** in benzene-d_6 was particularly informative; that taken in $CDCl_3$ is complicated by second-order effects and overlapping signals. The appearance of signals at τ 3.27 (H_{10}, d, $J \sim 11.0$ Hz), 3.61 (H_{11}, t, $J \sim 10.8$ Hz), and 4.24 (H_{12}, d, $J \sim 10.8$ Hz) is consistent with the nearly isolated three-spin system which would be expected for **13b** having the (9*E*,11*Z*) configuration and (10,11-*s*-*trans*) conformation.[25] Moreover, the high-field two-proton signal at τ 5.00 and the pair of two proton triplets at τ 6.56 and 7.82 are in accord with the assigned structure. Using the base value of 255 nm for the $\Delta^{5,7,9}$ triene chromophore (5 nm was subtracted from the reported λ_{max} of 260 nm for **16**),[26] the Woodward's rule prediction for **13b** is λ_{max} 320 nm.[27] The observed values (λ_{max} 312 and 307 nm for **13b** and **13a**, respectively) are somewhat blue shifted from that predicted, as would be expected for such a sterically distorted system (**13**).

A possible mechanistic rationale for the formation of the observed products **13**, **14**, and **15** upon thermolyzing vinylallene **7** is depicted in Scheme I. Competing [1,5]-sigmatropic shifts (paths b and a) of a hydrogen from the C-9 CH_3 to the sp carbon (C-12) of the allene affords a ~2:1 mixture of the (12*E*) and (12*Z*) isomers, respectively, of the putative intermediate **17**. The observed **13** is presumably formed from (12*E*)-**17** via a [1,7]-sigmatropic shift of a C-13 CH_3 hydrogen to C-19. The (12*Z*)-**17** can be envisaged to undergo an analogous competitive [1,7]-sigmatropic hydrogen shift of a C-14 H to C-19 to afford a ~2:1 ratio[24] of 11-*cis*- and 11-*cis*,13-*cis*-retinols (**14** and **15**, respectively). Scheme II depicts the initial competing [1,5]-sigmatropic shift of **7** to **17** in greater detail where **7** and **7′** are the methyl rotamers which predetermine the $\Delta^{12,13}$ stereochemistry of **17**. The relative rates of path b to a is nearly 2:1 assuming the pathway depicted in Scheme I. That is, the ~1.9–1.7 ratio (for Y = CH_2OTBDMS and Y = CH_2OH, respectively) of **13** to **14** + **15** formed reflects the path b to a ratio.

Thus, for **7**, the favored trajectory (path b) of the migrating hydrogen from the C-9 methyl to the sp carbon of the allene is syn to the larger group, C-13 CH_2Y. This bias was not expected since we recently observed that in the vitamin D–vinylallene system **18**,[3b] the path b to path a ratio was about 1 to 2. That is, the favored trajectory (path a) of the migrating hydrogen was syn to the smaller C-9 methylene (steroid numbering with the D ring bearing C-14 considered the larger group). The *t*rans-hydrindan system of **18** is fairly rigid, of course, and it was not surprising in retrospect to find that the corresponding path b:a ratio for **19** was about 1:1.[3b] For **19**, we presume that there is little difference between paths b and a since the trajectory of the migrating hydrogen encounters only the nearly equivalent axial hydrogens at C-9 and C-14 (steroid numbering). In studies by Wolff and co-workers[14b] on the thermolysis of the crude cis enallene (vinylallene) obtained by base-catalyzed rearrangement of the cis enyne, methyl crepenynate, infrared analysis of the product suggested that the major conjugated triene product was the trans,cis,trans isomer. Like **7**, this corresponds to path b being favored, but the product components were not quantitated or thoroughly characterized. In very recent studies by Minter, Fonken, and co-workers,[14g] a cyclic enallene was suggested to undergo exclusive path b type rearrangement. In the latter case, however, a strictly mechanistic argument was used to suggest that the path a type products appeared to be strongly precluded because of the structural characteristics of the vinylallene. In concluding, it seems that to gain the full synthetic potential of related allene rearrangements, there is a need to delineate more systematically those factors which can influence the steric course of sigmatropic shifts. It is gratifying to find, however, that the polyene moieties of the retinols are *configurationally* stable to the conditions of the vinylallene rearrangement. Most specifically, the 11-cis geometry is maintained.

Experimental Section

General. Ultraviolet (UV) and infrared (IR) spectra, ^{1}H nuclear magnetic resonance spectra (NMR), mass spectra (MS), and other analytical data are summarized in the Supplementary Material; melting points (mp, 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 refers to redistilled 30–60 °C low-boiling petroleum ether. Kugelrohr distillation boiling points (bp) 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 (usually <−70 °C) under nitrogen.

Medium-pressure liquid chromatography (MPLC) was carried out on an apparatus designed by Meyers and co-workers.[28] The absorbant was silica gel 60 (40–600 μm) from E. Merck, and the columns used were either 25 × 1000 or 15 × 1000 mm. We are grateful to Professor A. I. Meyers for providing the details for constructing the MPLC apparatus well in advance of publication. Flash chromatography (silica gel as per MPLC) according to Still's procedure was also used.[29] For ordinary 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 (0.25 mm).

1-(*tert*-Butyldimethylsiloxy)-3-methyl-3-butene (8b). Imidazole (24.7 g, 0.36 mol) and *tert*-butyldimethylsilyl chloride (27.7 g, 0.18 mol) were added with stirring to *N*,*N*-dimethylformamide (126 mL, freshly distilled from BaO) under dry nitrogen. After 5 min, 3-methyl-3-buten-1-ol (**8a**, 10 g, 0.11 mol) was added to the clear solution. After the mixture was stirred for 4 h (room temperature), water and ether were added. The ether layer was separated and the water layer was further extracted with ether. The combined ether extracts were washed successively with aqueous HCl (1 M), saturated aqueous $NaHCO_3$, and water. After being dried ($MgSO_4$) and concentrated (vacuum), the resulting crude residue was passed through a short silica gel column (9:1 lbpe/ether) and then distilled (Kugelrohr, bp 50 °C (0.05 mm)) to afford 21.5 g (90%) of product.

1,1-Dibromo-2-[2′-(*tert*-butyldimethylsiloxyethyl)]-2-methylcyclopropane (9). A dry 500-mL round-bottom flask containing silyl ether **8b** (12.5 g, 0.062 mol) in dry hexane (250 mL) was charged with freshly prepared powdered potassium *t*ert-butoxide (35.7 g, 0.32 mol). The resulting suspension (magnetically stirred) was cooled to 0 °C and then bromoform (27.9 mL, 80.63 g, 0.31 mol) was added over a period of 3 h. The milky white mixture was allowed to stir 1 h after the addition was complete and then was quenched by pouring it into a rapidly stirred mixture of lbpe and water. The layers were separated and the aqueous fraction was extracted with an additional portion of lbpe. The combined extracts were washed with distilled water and dried over $MgSO_4$. Fil-

(24) Christopher G. Knudsen of this laboratory has established that 11-*cis*-retinol (**14**) and 11-*cis*,13-*cis*-retinol (**15**) are unchanged upon heating at ~69 °C for 2 h (refluxing Skellysolve B under N_2). In fact, over a 40-h period under these conditions, **14** and **15** do not interconvert.

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

tration, evaporation of solvent under reduced pressure, and then Kugelrohr distillation (bp 110–115 °C (0.5 mm)) of the resulting residue afforded 19.47 g (84%) of dibromocyclopropane derivative **9**.

1-(*tert*-Butyldimethylsiloxy)-3-methylpenta-3,4-diene (10a). An ice-cooled solution of dibromide **9** (19.47 g, 0.052 mol) in dry ether (250 mL) was prepared under nitrogen under anhydrous conditions. Methyllithium in ether (40 mL, 1.75 M, 0.07 mol) was added to the magnetically stirred solution over a 2-h period. A white precipitate, presumably lithium bromide, was observed. After an additional 1 h of stirring, the mixture was poured rapidly into an ether–water mixture. The layers were separated and the aqueous fraction was further extracted with ether. The combined organic extracts were washed, dried ($MgSO_4$), filtered, and then concentrated under vacuum. The resulting crude liquid was Kugelrohr distilled (by 70–75 °C/(1 mm)) to afford 10.60 g (95%) of allene **10a**.

6-(*tert*-Butyldimethylsiloxy)-4-methyl-2,3-hexadien-1-al (10c). To a stirred solution (−78 °C, N_2) of allene **10a** (4.0 g, 0.019 mol) in dry THF (60 mL) was added (syringe, 5 min) *tert*-butyllithium (16.0 mL, 1.30 M, 0.02 mol) in pentane. After 10 min at −78 °C, stirring of the mixture was continued at −50 °C for 1 h, the temperature was raised to −20 °C, dry *N,N*-dimethylformamide (5 mL, 4.7 g, 0.64 mol) was added, and then stirring was continued at −20 °C for 5 h. The mixture was poured into water and ether for quenching. The water layer was separated and then further extracted with ether. The combined ether extracts were back-washed with water, dried ($MgSO_4$), filtered, and then concentrated under vacuum. Kugelrohr distillation (100 °C/(0.1 mm)) of the residue afforded 3.33 g (74%) of the desired allenyl aldehyde **10c**.

4-Hydroxy-2-butanone (11a). A solution of 3-methyl-3-buten-1-ol (**8a**, 17 g, 0.20 mol) in methanol (150 mL) was prepared in a vessel equipped with a gas inlet tube connected to a three-way stopcock leading to an ozonized oxygen (Welsbach Ozonizer Model No. T-408) or nitrogen source. After the reaction solution was cooled to −78 °C, ozonized oxygen was passed through until the solution retained a blue color. While still at −78 °C, nitrogen gas was passed through the solution until the blue color disappeared. Dimethyl sulfide (40 mL) was added, and then the mixture was allowed to warm to ambient temperature and left standing overnight. The solution proved to be negative to starch–iodide test paper. The solvent was removed under vacuum, and then the residue was passed through a silica gel column (ether). The concentrated residue was Kugelrohr distilled (bp 110 °C/(22 mm)) to afford 15.1 g (86%) of pure keto alcohol **11a**.[21]

3-Methyl-4-pentyne-1,3-diol (11b). A dry 2000-mL three-necked round-bottom flask equipped with a stirring bar, septum-capped inlet, and dropping funnel was flushed with nitrogen and charged with dry THF (500 mL). The THF was cooled (−78 °C) with stirring, and then excess acetylene gas was passed through the solution (~2 h). An *n*-butyllithium/hexane solution (245 mL, 1.63 M, 0.40 mol) was introduced into the funnel, and then the alkyllithium was added dropwise (75 min) to the cold acetylene solution. After 55 min, the keto alcohol **11a** (11.76 g, 0.13 mol) in THF (30 mL) was added over 30 min to the lithium acetylide.[22] After overnight stirring (−78 °C to ambient, ~14 h), the mixture was ice cooled and water (200 mL) was added. Sufficient anhydrous K_2CO_3 was added until a pasty residue was obtained. The organic phase was decanted and the residue was washed thoroughly with ether. The combined organic phase was dried ($MgSO_4$), filtered, concentrated, and then chromatographed (silica gel column according to Still's procedure; lbpe/ether). The concentrated product was Kugelrohr distilled (bp 85–90 °C/(0.2 mm)) to afford 9.45 g (62%) of diol **11b**.

5-Bromo-3-methyl-3,4-pentadien-1-ol (10d). To an ice-cooled mixture of powdered cuprous bromide (11.48 g, 64 mmol), powdered ammonium bromide (7.84 g, 64 mmol), copper powder (80 mg), and 48% aqueous HBr (40 mL) was added the acetylene diol **11b** (3.37 g, 32 mmol). The well-agitated mixture was maintained at 0 °C for 5 h and then a mixture of ice and ether was added to quench the reaction. The organic phase was separated and then the aqueous phase was extracted with ether. The combined ether extracts were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered, and then concentrated. Chromatography through a short column of silica gel (6:4 lbpe/ether) and then concentration afforded 1.8 g (35%) of spectrally (^1H NMR) pure bromoallene **10d**. Since distillation (Kugelrohr, bp 60–70 °C (0.05 mm)) resulted in extensive decomposition, the allene was best carried through directly to the next step (silylation) without distillation.

5-Bromo-3-methyl-1-(*tert*-butyldimethylsiloxy)penta-3,4-diene (10e). Imidazole (2.04 g, 0.03 mol) and *tert*-butyldimethylsilyl chloride (2.31 g, 0.015 mol) were dissolved with stirring in *N,N*-dimethylformamide (6 mL, freshly distilled from BaO) under a dry nitrogen atmosphere. After 5 min, the bromoallene **10d** (1.78 g, 0.01 mol) was added to the clear solution. After 1 h of stirring at room temperature, the reaction mixture was poured into water and then extracted thoroughly with ether. The ether extract was washed sequentially with 1 M aqueous HCl, saturated aqueous $NaHCO_3$, and then water. Upon drying ($MgSO_4$), filtering, and concentrating, the crude product (3.29 g) was passed through a silica gel column (98:2 lbpe–ether). Concentration of appropriate chromatographic fractions afforded a residue which was Kugelrohr distilled (bp 80–85 °C/(0.05 mm)) to afford 1.728 g (58%) of pure bromoallene silyl ether **10e**.

Lithiation of Bromoallene 10e. To a stirred solution (−78 °C, N_2) of bromoallene **10e** (0.25 g, 0.85 mmol) in dry THF (8 mL) was added (syringe) *n*-butyllithium (0.64 mL, 1.47 M in hexane, 0.94 mmol). After 2 h at −78 °C, the temperature was raised to −20 °C and then *N,N*-dimethylformamide (DMF, 0.30 mL, 0.25 g, 3.4 mmol; dried and freshly distilled) was added. After stirring for 4 h at −20 °C, the mixture was quenched by pouring it into water and ether. The water layer was separated and then further extracted with ether. The combined ether extracts were back-washed with water, dried ($MgSO_4$), filtered, and then concentrated under vacuum. Analysis by ^1H NMR indicated the presence of comparable amounts of desired aldehyde **10c** and the protonated allene **10a**, trace amounts of unreacted bromide, and unidentified impurities (as indicated by considerable base-line noise in the olefinic and aldehyde CHO regions). In a separate experiment, quenching with water instead of DMF at −20 °C afforded hydrocarbon allene **10a** contaminated by only trace amounts of starting bromide **10e**. The use of **10e** as a precursor to **10c** was not investigated further.

12,14-*retro*-Retinyl *tert*-Butyldimethylsilyl Ether (7, Y = CH_2OSiMe_2-*t*-Bu). To a stirred suspension of β-ionyltriphenylphosphonium bromide (**12**, 22 g, 42.5 mmol) in dry THF (120 mL) at −20 °C (N_2 atmosphere) was added *n*-butyllithium (27.2 mL, 1.55 *M* in hexane, 42.2 mmol) dropwise by means of a syringe. The resulting red phosphorane solution was maintained at −20 °C for 0.5 h and then cooled to −40 °C for an additional 0.5 h. The allenyl aldehyde (9.20 g, 38.3 mmol) in dry THF (8 mL) was added as a steady stream (syringe) to the stirred phosphorane solution held at −40 °C, and then the reaction was allowed to continue at this temperature for 5 h; lbpe was added, the resulting precipitate was removed by suction filtration, and then the precipitate was washed thoroughly with additional portions of lbpe. The combined lbpe filtrate and washings were concentrated under vacuum to a syrup. The syrup was thoroughly extracted with several portions of lbpe which were separated by decantation. The combined lbpe extracts were again concentrated under vacuum and the resulting residue was subjected to MPLC (solvent system was 8:1000, v/v, pyridine–lbpe) to afford after concentration of appropriate fractions, 7.83 g (51%) of pure vinylallene silyl ether. Spectral and chromatographic analysis of the crude product mixture as well as chromatographic fractions revealed the presence of a complex mixture of other components as well. In our hands, despite repeated trials, only the major component **7** (Y = CH_2OSiMe_2-*t*-Bu) was isolable in a pure state.

12,14-*retro*-Retinol (7, Y = CH_2OH). To 200 mg (0.5 mmol) of vinylallene silyl ether **7** (Y = CH_2OSiMe_2-*t*-Bu) was added 4 mL (0.5 M in THF, 2.0 mmol) of freshly prepared tetra-*n*-butylammonium fluoride at room temperature under nitrogen. After a 3-h reaction period, the reaction mixture was poured into brine and then extracted with lbpe. Conventional workup afforded 149 mg of crude material which was subjected to chromatography by Still's procedure[29] (70:30 lbpe–ether with 8 mL of pyridine/L of the lbpe–ether mixture). Combination and concentration of appropriate fractions afforded 77 mg (50%) of pure vinylallenol **7** (Y = CH_2OH).

Thermal Isomerization of Vinylallene Silyl Ether 7 (Y = CH_2OSiMe_2-*t*-Bu). (11*Z*)-20,14-*retro*-Retinyl *tert*-Butyldimethylsilyl Ether (13a). Freshly distilled isooctane (750 mL) was brought to reflux (100 °C) under nitrogen in a 2-L round-bottom flask fitted with a water-cooled condenser and a rubber septum (N_2 inlet by means of a syringe needle). The vinylallene silyl ether (300 mg) was introduced to the preheated solution by means of a syringe, and then the mixture was heated at reflux under nitrogen for 3 h. The reaction solution was ice cooled, and then the solvent was removed under vacuum (<40 °C; first on a rotary evaporation and then second on a high-vacuum pump) to afford an essentially quantitative yield of product (~300 mg). Analysis (^1H NMR) of the crude mixture (conveniently carried out by integrating the protons on carbon adjacent to oxygen for all the substances) revealed the presence of a major component (66%; less polar fraction A below) and a minor component (34%; more polar fraction **B** below consisting of 22% 11-*cis*-retinol silyl ether and 12% 11-*cis*,13-*cis*-retinol silyl ether). In a 2-h reaction time experiment, small amounts of vinylallene could be detected, but the product distribution was essentially the same (68, 22, and 11%, respectively). In a 4.5-h reaction time experiment, the distribution was 67, 20, and 13%, respectively. It was also established that pure A (major) could be recovered unchanged in quantitative yield (50 mg experiment) upon heating as above (100 °C) for 4 h. MPLC (solvent system was 8:1000, v/v, pyridine–lbpe) of the mixture from the 3-h reaction time experiment afforded 58 mg (19%) of A, 43 mg (14%) of

A plus B (^{1}H NMR indicated the presence of 50% A, 10% 11-cis isomer, and 40% 11,13-dicis isomer) and 47 mg (16%) of B (^{1}H NMR revealed the presence of 70% 11-cis isomer and 30% 11,13-dicis isomer).

Pure A was identified as (11*Z*)-20,14-*retro*-retinyl *tert*-butyldimethylsilyl ether (**13a**). Fraction **B** could not be readily resolved chromatographically at this point and was therefore deprotected first as described below.

Deprotection of Fraction B. (11*Z*)-Retinol (14) and (11*Z*,13*Z*)-Retinol (15). To 47 mg (0.12 mmol) of fraction **B** (^{1}H NMR analysis indicated the presence of 70% 11-cis isomer and 30% of the 11,13-dicis isomer) was added freshly prepared tetra-*n*-butylammonium fluoride solution (1 mL, 0.5 M in THF, 0.5 mmol). The mixture was stirred at room temperature under nitrogen for 3 h and then quenched by pouring it into brine and lbpe. Conventional workup afforded 33 mg of crude product which was subjected to MPLC (70:30 lbpe–ether; 8 mL of pyridine was added to each liter of the lbpe–ether mixture). Chromatographically and spectrally pure 11-*cis*,13-*cis*-retinol (**15**, 5 mg, 50%) and 11-*cis*-retinol (**14**, 19 mg, 77%) were obtained. Each was characterized by direct chromatographic and spectral (^{1}H NMR) comparisons with authentic specimens provided by Mr. Christopher Knudsen of this laboratory and by the Hoffman-La Roche Co. of Nutley, N.J.

Deprotection of Fraction A. (11*Z*)-20,14-*retro*-Retinol (13b). To silyl ether **13a** (533 mg, 1.08 mmol) was added freshly prepared tetra-*n*-butylammonium fluoride solution (6 mL, 1 M in THF, 5.5 mmol) under N_2, and then the solution was stirred at ambient temperatures for 3 h. The reaction mixture was poured into brine and then thoroughly extracted with lbpe. Conventional workup afforded crude material (398 mg) which was subjected to MPLC (70:30 lbpe–ether; 8 mL of pyridine was added to each 1000-mL portion of the lbpe–ether mixture). Combination and concentration of appropriate fractions afforded 350 mg (87%) of pure alcohol **13b**.

Thermolysis of Vinylallenol 7 (Y = CH_2OH). A 50-mg sample of vinylallenol **7** (Y = CH_2OH) in isooctane (165 mL) was thermolyzed (100 °C, 4 h) under N_2 as described earlier for the case of the corresponding silyl ether **7** (Y = $CH_2OTBDMS$). Concentration (<40 °C) under vacuum afforded 50 mg (~100%) of material whose composition (^{1}H NMR) revealed the presence of 63% (11*Z*)-20,14-*retro*-retinol (**13b**), 13% (11*Z*,13*Z*)-retinol (**15**), and 24% (11*Z*)-retinol (**14**). The ^{1}H NMR analysis was conveniently carried out by integrating the signals due to protons on carbon adjacent to oxygen. Thermolysis of the above mixture for an additional 7.5 h at 100 °C revealed by ^{1}H NMR that slow deterioration was occurring as evidenced by an increase in the appearance of very broad, but weak signals appearing in the aromatic, olefinic, and CH_2–O regions of the spectrum. The apparent ratio of **13b** to **14** to **15** had changed to 76:14:10 from the initial 63:24:13 ratio given above.

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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. 18. The Vinylallene Approach to the 1-Hydroxyvitamin D System. New Sigmatropic Reactions in the Vitamin D Series† [1]

Patrick Condran, Jr., Milton L. Hammond, Antonio Mouriño, and William H. Okamura*

Contribution from the Department of Chemistry, University of California, Riverside, California 92521. *Received March 24, 1980*

Abstract: The thermally induced [1,5]-sigmatropic hydrogen shift of the diastereomeric vitamin D type vinylallenols **6a** (1*R*,6*R*), **6b** (1*R*,6*S*), **7a** (1*S*,6*R*), and **7b** (1*S*,6*S*) and vinylallenones **5a** (6*R*) and **5b** (6*S*) were studied. The 1*S*,6*S* (**7b**) and 1*R*,6*R* (**6a**) alcohols afforded ~60% yields of the biologically active 3-deoxy-1α-hydroxyvitamin D_3 (**3a**) and its inactive 1β epimer **3b**, respectively. By contrast, the major products (70–79%) from the 1*R*,6*S* (**6b**) and 1*S*,6*R* (**7a**) allenols were products of an equilibrium manifold (**23** ⇄ **25** ⇄ **24** and **26** ⇄ **28** ⇄ **27**, respectively) resulting from successive [1,7]-sigmatropic hydrogen shifts of an initially formed putative intermediate, (7*Z*)-3-deoxy-1-hydroxyvitamin D_3. Thermolyses of ketones **5a** or **5b** afforded good yields of a mixture of the previtamin ketone **29** and the *cis*-isotachysterone **30**. Reduction of **29** afforded the previtamins **31a** and **31b**, which could be equilibrated with the corresponding vitamins **3a** and **3b**, respectively (K_{eq} = 1/9 for each stereoisomer at 60 °C). Reduction of **30** afforded the *cis*-isotachysterol analogues **25** and **28**. The former could be equilibrated with **23** and **24** (45%, **23**; 13%, **25**; and 42%, **24** at 100 °C); the latter could be similarly equilibrated with **26** and **27** (49%, **26**; 36%, **27**; and 14%, **28** at 100 °C). The 6*R* vinylallenes **5–7** were synthesized by two different methods. The first method involves an *anti*-1,3-addition of a nucleophilic A-ring component (A-ring cuprate **21** obtained in four steps from 2-methylcyclohexane-1,3-dione) to the electrophilic propargylic ester **10** (obtained in two steps from Grundmann's ketone$_3$ **8**). The second method involves as a key step the nucleophilic 1,2-addition (followed by acid-catalyzed rearrangement) of the lithium salt of allene **13** (obtained in four steps from **8**) to the electrophilic component, keto enol ether **22**. The (6*S*)-vinylallenes **5–7** were obtained by photoequilibration of the more readily available 6*R* allenes **5–7**. The vinylallene approach gave good overall yields of vitamins **3** (8.3–16% in six to eight steps) which compares favorably with a classical steroid approach (0.2% in 11 steps). The allene strategy should be general for A-ring analogues of the physiologically important 1-hydroxyvitamin D system and could be applicable for preparing other polyenic systems characterized by centrally located *Z*-olefinic units.

Introduction

The stereostructure **1** is characteristic of the physiologically important 1α,25-dihydroxyvitamin D_3 (**2a**), the active form of vitamin D_3 (**2b**, cholecalciferol), as well as analogs possessing biological properties of unusual interest. Among steroid hormones, such as cortisol, aldosterone, testosterone, estradiol, and others, the calcium regulating hormone **2a** is structurally unique because the usual steroid B-ring is absent and is replaced by a 1-

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