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Intramolecular Diels-Alder Reactions of the Retinoid Side Chain

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Abstract: Retinyl propynyl ether (RPE) undergoes an intramolecular Diels-Alder reaction to form a tetrahydroisobenzofuran derivative by addition of the alkyne group at positions 11 and 14 of the retinoid side chain. The Diels-Alder product can be isolated after RPE has been heated in refluxing ethanol. The Diels-Alder reaction also occurs very slowly in the solid state at low temperatures. The tetrahydroisobenzofuran is readily dehydrogenated to an aromatic retinoid, a 1,3-dihydroisobenzofuran. 2-Butynyl and 2-propenyl retinyl ethers undergo intramolecular cyclization to similar Diels-Alder products that can be isolated in yields of 50-60% after the ethers have been heated in refluxing toluene.

INTRODUCTION

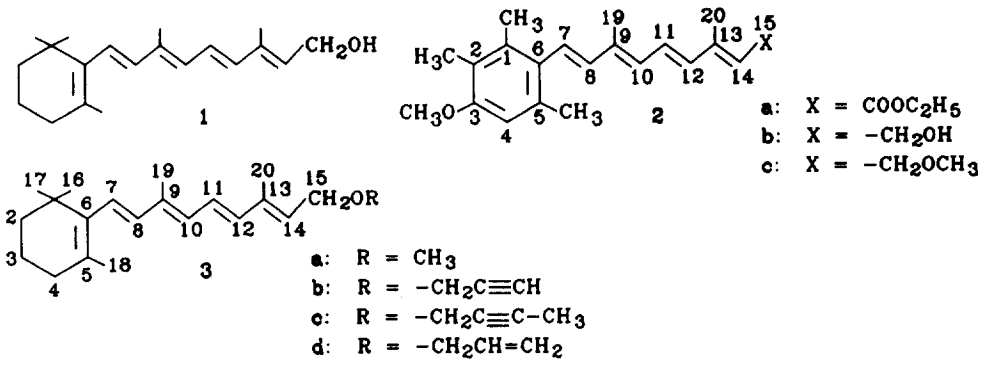
Certain retinoids, compounds that comprise the vitamin A group and their derivatives and analogues, suppress carcinogenesis.[1] The initial studies of cancer chemopreventive activity by retinoids were conducted with the natural retinoids or ester derivatives: retinol (1) or retinyl esters, all-*trans*-retinoic acid, 13-*cis*-retinoic acid, or esters of these retinoic acids.[2-5] However, the toxic effects[1c,1f,6-8] produced by the prolonged administration of these fundamental retinoids in pharmacological doses and their non-specific tissue distribution limit their usefulness.[1a-e] It was then shown that certain retinoid analogues[1c,9-11] also suppress carcinogen-induced malignancy *in vivo*, and some of these *in vivo*-active compounds are less toxic than are the natural retinoids.

Subsequent to these early observations, many types of retinoids have been synthesized and subjected to biological evaluations.[12,13] The synthetic retinoids have encompassed derivatives of the natural retinoid structures,[1a-b,14-16] aromatic analogues[1c,17] (*e.g.*, the 2,3,6-trimethyl-4-methoxyphenyl analogues, 2), arotenoids[18] and conformationally restricted retinoids,[19-22] and non-classical, retinoid-like structures.[23,24] Representatives of some of the various types of retinoid structures have demonstrated cancer chemopreventive activity, and clinical studies and clinical activity of certain retinoids have been reported.[25] These findings have generated widespread interest in the chemistry and biology of retinoids. Interest in retinoids has intensified because of the recent discoveries and investigations of nuclear retinoid receptors (RARs and RXRs), which appear to be crucial stages in the molecular mechanisms of action of retinoids.[26]

Retinyl methyl ether (RME, 3a, Chart I) was one of the earliest derivatives of retinol (1) that was shown to have cancer chemopreventive activity *in vivo*.[9] Interest in retinyl ethers waned because RME

is converted by microsomal oxidases to retinol;[27] therefore, only a few, simple retinyl ethers have been reported. The rationale for reviving investigations of retinyl ethers has been outlined.[28] Retinyl propynyl ether (RPE, **3b**), which has cancer chemopreventive activity,[28,29] is one of the new retinyl ethers that we have synthesized. A reaction of RPE and similar retinyl ethers that is new to retinoid chemistry is the subject of this report.

CHART I.



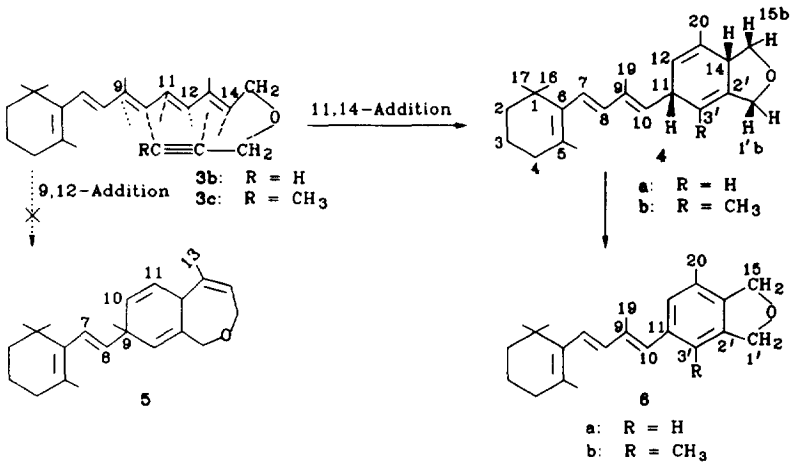
RESULTS AND DISCUSSION

Retinyl propynyl ether (RPE, **3b**), a new retinyl ether, was prepared from lithium retinoxide and 2-propynyl bromide. Analyses of specimens of RPE by HPLC indicated that this compound would change slowly to a new compound, depending upon conditions, during chromatographic purification at room temperature or during long-term storage at low temperatures. The transformation product was not observable by HPLC monitored by ultraviolet absorption at 340 nm, but was readily detected at 254 nm. Deliberate formation of the transformation product by heating RPE in refluxing ethanol resulted in the isolation of the new compound in 60% yield. The mass spectra of both RPE and the new compound showed molecular ions at *m/z* 324, but infrared bands in the spectrum of RPE at 3300 and 2115 cm^{-1} arising, respectively, from the C-H and C≡C stretching vibrations of the alkyne group were not present in the spectrum of the transformation product. Furthermore, the ultraviolet maximum at 258 nm (ethanol) showed that the conjugated double-bond system had been shortened. The virtual absence of ultraviolet absorption at 340 nm accounts for the fact that the transformation product is not detectable by HPLC monitored at that wavelength.

More definitively, initial proton NMR analysis indicated that the transformation product was formed by an intramolecular Diels-Alder reaction of the alkyne group with the conjugated double-bond system of the side chain (Chart II). Intramolecular addition of the alkyne group across the C11-C14 part of the side chain would produce a 1,3,5,7a-tetrahydroisobenzofuran (**4a**), whereas addition at the C9-C12

part would produce a 1,3,5a,8-tetrahydro-2-benzoxepin (5). The ^{1}H-NMR spectrum of the transformation product clearly reveals the presence of the β-ionylidene unit[30] (positions C1-C9). Also, the signal from the proton attached to C11 is shifted upfield from 6.61 ppm in the spectrum of RPE to 3.79 ppm in the spectrum of the transformation product, a fact which indicates that C11 has been converted from an sp^2 carbon atom to an sp^3 carbon atom. These data support **4a** as the structure of the transformation product. Interestingly, the ^{1}H-NMR spectrum of **4a** shows an unusually large five-bond coupling constant, $^5J_{11,14}$ = 10.0 Hz. However, precedents reported in the literature[31] show that large five-bond coupling constants are not unusual in 1,4-cyclohexadienes. The magnitude of the coupling suggests that H-11 and H-14 are *cis* to each other and that the cyclohexadiene is in the boat conformation.[32] This coupling provided further evidence for structure **4a**.

CHART II



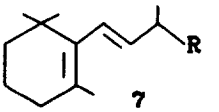
The structure was substantiated by the dehydrogenation of the 1,4-cyclohexadiene group of **4a** to a benzene ring. Treatment of **4a** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in benzene at room temperature produced the 1,3-dihydroisobenzofuran **6a**, which is a cyclic ether derivative of an aromatic analogue of retinol. The ^{1}H-NMR spectrum of this compound was consistent with structure **6a** and, therefore, also confirmed the structure (**4a**) of the transformation product of **3b**. Compounds **4a** and **6a** were fully characterized by ^{1}H-NMR spectroscopy with selective proton-proton decoupling and nuclear Overhauser experiments.

The ultraviolet absorption data are consistent with the changes represented by **3b** ⟶ **4a** ⟶ **6a** and display interesting correlations with other retinoid structures (Chart III). The ultraviolet absorption maximum (258 nm) of **4a** differs from the maximum calculated[33] (234 nm) for **5**, which is near reported maxima at 227-228 nm[34a] of similar dienes (**7a**). In contrast, the *broad* UV maximum of

CHART III.

UV MAXIMA (ETHANOL EXCEPT AS NOTED) AND HYPSOCHROMIC SHIFTS.

4a: 258nm
4b: 259nm
4a in hexane; 256.4nm
4b in hexane; 256.7nm
5: Calcd., 234nm



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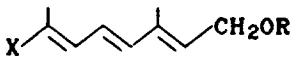
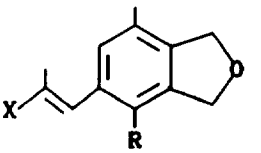
a: R = H, CH_3, C_2H_5; 227–228nm
b: R = $\diagup\!\!\diagdown CH_2OH$; 259, 237nm; in hexane, 262.5 (Band I). 238.5nm (Band II)



1, 3a, 3b: 325–326nm

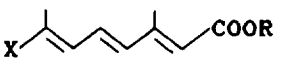
−30nm



6a: 295nm
6b: 284nm

−30nm

−19 to −24nm



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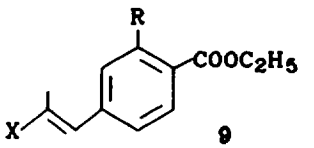
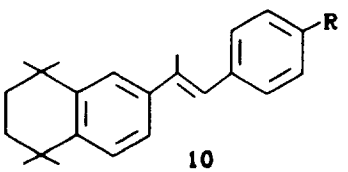
R = CH_3, C_2H_5; 355–356nm

−36 to −41nm



9

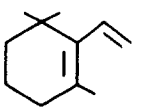
R = H or CH_3; 314–319nm



10

a: R = $-CH_2OCH_3$; 282nm
b: R = −COOEt; 306nm
−24nm

X =



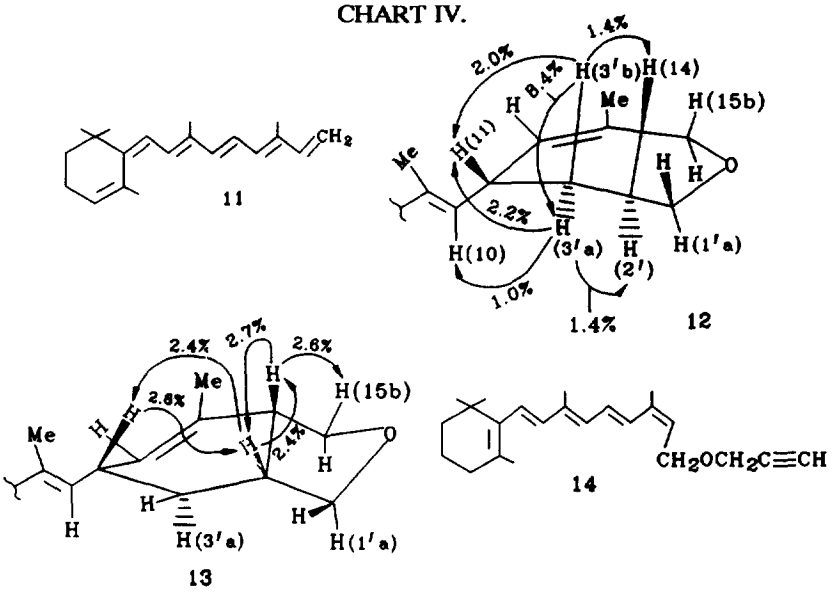
4a at 256.4 nm in hexane is near one of the maxima at 262.5 nm[34b] of a similar triene, β-ionylidene ethanol (**7b**), in a hexane (3-methylpentane), and UV maxima of **4a** and **4b** in ethanol are the same as the reported major maximum of **7b** at 259 nm.[35a]. The large hypsochromic shift (30 nm) of the absorption maximum of the aromatic ether (**6a**) relative to that of retinol (**1**) and retinyl ethers (**3**) (325-326 nm) is consistent with large hypsochromic shifts of the maxima of the aromatic retinoate analogues[19] (**9**) relative to that of retinoic acid esters (**8**). Furthermore, the hypsochromic relationship of the ultraviolet absorption maximum of aromatic retinoid **6a** relative to that of the aromatic retinoate analogues (**9**) is similar to the difference between the maximum of an arotenoid ether[18] (**10a**) relative to the maximum of an arotenoid ester[18] (**10b**).

The cyclization of RPE was investigated further by analyzing aliquots by high pressure liquid chromatography (HPLC). The frequently employed wavelengths of 254 nm and 340 nm for monitoring HPLC were used to analyze isolated retinoids (**3**, **4**, **6**), but they were not entirely suitable for examining the course of the reaction. The Diels-Alder products (**4**) are easily detectable at 254 nm because their UV maxima are near that wavelength, but retinyl ethers have much lower molar absorptivities at 254 nm (Table 1). The retinyl ethers (**3**) absorb UV light strongly at 340 nm (near their maxima of 325-326 nm), but the Diels-Alder products are virtually without UV absorption at 340 nm (Table 1, see Experimental Section). At 282 nm the molar absorptivities of RPE and **4a** are equal (Table 1); therefore, cyclization of **3b** was monitored at 282 nm. Aliquots were removed from a refluxing solution of RPE in ethanol at four, six, and twenty-four hours and analyzed by HPLC at 282 nm. The ratios of **4a** to **3b** after four and six hours were 2:1 and 4.2:1, respectively (Table 2). After twenty-four hours, **3b** was no longer observable; and the reaction mixture consisted of **4a**, a small amount of **6a**, and less than one percent of an unidentified component. Aliquots were also analyzed at 340 nm in order to look for other potential products such as **6a**, which absorbs more strongly at 340 nm than at 282 nm, and anhydroretinol (**11**). The facile formation of anhydroretinol (**11**) from certain retinyl ethers has been observed.[36] The presence of **6a** was confirmed, and small amounts of anhydroretinol were sometimes formed during the cyclizations of **3b**.

Retinyl 2-butynyl ether (**3c**) and retinyl 2-propenyl ether (**3d**), prepared from retinol and 2-butynyl bromide and 2-propenyl bromide, respectively, were shown to undergo similar intramolecular Diels-Alder reactions. Cyclization of **3c** at the temperature of refluxing ethanol proceeded more slowly than did the cyclization of **3b** and a small amount of **11** was formed, but the Diels-Alder reaction occurred readily at the higher temperature of refluxing toluene. Dehydrogenation of **4b** with DDQ furnished the dimethyl dihydroisobenzofuran **6b**.

Most of **3d** remained unchanged in refluxing ethanol after twenty-four hours; but, after the same time in refluxing toluene, two compounds with molecular ions of the same m/z (326) as **3d** were isolated. The two Diels-Alder products (**12**) and (**13**) were isolated with a total yield of 75%; the major isomer was **12**, which was isolated with a yield of 55%. The relative configurations of the two Diels-Alder products were shown by NOE experiments to have *trans*- (**12**) and *cis*-fused (**13**) bicyclic structures. Some selected NOE's of the two structures are shown in Chart IV. In the case of **13**, irradiation of the

CHART IV.



signal of H-2′ gave 2.4% and 2.6% enhancements of the signals of H-14 and H-11, respectively. These data show that H-2′, H-14, and H-11 are *cis*, that is, on the same side of the cyclohexenyl ring. In the case of **12**, irradiation of H-3′a gave 1.4% and 1.0% enhancements of the H-2′ and H-10 signals, respectively. Similarly, irradiation of H-3′b gave 2.0% and a 1.4% enhancements of the signals of H-11 and H-14, respectively. These NOE data confirm that H-11 and H-14 are *cis* to each other and that H-2′ and H-10 are *cis* to each other and, at the same time, show that H-11 and H-14 are *trans*, respectively, to H-10 and H-2′. Interestingly, H-3′a in **13** is shifted about 0.45ppm upfield compared to H-3′a in **12**; this shift is the result of the shielding of H-3′a by C-11 and C-2′ and indicates that C-11, C-2′, and H-3′a are *cis*.

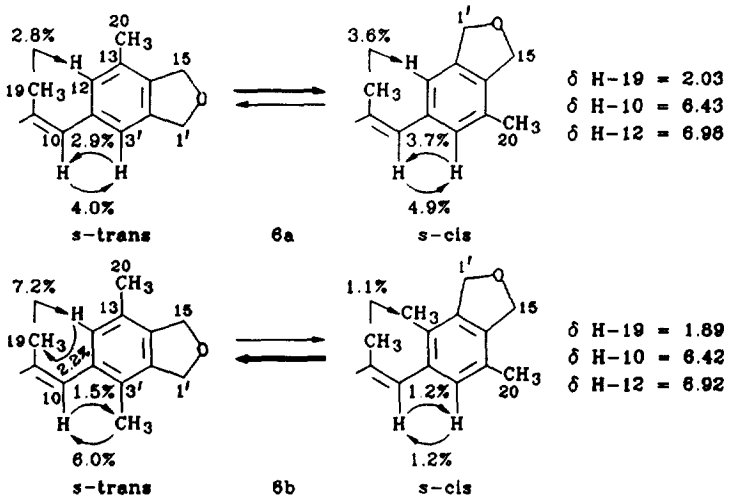
The formation of Diels-Alder structures **4a-b**, **12**, and **13**, which were established unequivocally by NMR couplings and NOE, as well as dehydrogenation of **4a** and **4b**, is consistent with preferred conformations of the retinoid side chain. The formation of **5** would require the 10-s-*cis* conformation in the transition state. The *cis*-oriented 19-methyl group and H-12 would then be brought in close proximity

in an unfavorable interaction that would prevent or slow-down the rate of formation of **5**. In contrast, the formation of **4** should proceed through the much less hindered 12-s-*cis* conformation in the transition state. Similarly, stereochemical orientations in the transition state[37-39] can account for the preferred formation of a *trans*-fused product (**12**) when the dienophile is an alkene (**3d**). There are two possible stereochemical orientations of an unsymmetrical dienophile relative to the diene in the transition state.[37-39] The exo-transition state with the substituent on the dienophile oriented away from the π-system of the diene leads to a *trans*-fused product. The *endo*-transition state has the substituent oriented toward the π-system of the diene and leads to a *cis*-fused product. Generally, in intramolecular Diels-Alder reactions with chains of one- or two-atoms connecting the substrates lead to *cis*-fused products and reactions with chains of three-atoms or more connecting the substrates lead a predominance of *trans*-fused products.

The UV spectra of **6a** and **6b** might be expected to be nearly the same, but the λ_{max} (284 nm) of **6b** shows a hypsochromic shift and loss in intensity as compared with λ_{max} (295 nm) of **6a**. In **6b** the introduction of a methyl group at C-3′, *ortho* to the alkenyl group at C-11, results in some loss in coplanarity between the alkenyl group and the aromatic ring, which is caused by steric interferences with the C-19 methyl group. This loss in π-orbital overlap in **6b** is reflected in the shorter wavelength and lower intensity of λ_{max} of **6b** (Table I).

The chemical shifts of the C-19 methyl group protons and NOE experiments support this loss of coplanarity of **6b** and also indicate the direction of the conformational equilibrium around the H-10, H-11 single bond (Chart V). For example, the irradiation of the CH_3-19 signal in **6a** gave a 2.8% enhancement of H-12 and 3.6% enhancement of H-8′ signals which indicate that for compound **6a** the

CHART V.



s-*cis* conformation is slightly more populated than the s-*trans* conformation. Where as, the irradiation of the CH_3-19 signal of **6b** gave a 7.2% enhancement of H-12 and a 1.1% enhancement of 3'-CH_3 signals,indicating that equilibrium is shift toward the s-*trans* conformation in **6b**. Furthermore the comparisons of the CH_3-19 proton chemical shifts in **6a** and **6b** showed that CH_3-19 protons in **6b** are more shielded than in **6a**, which indicates the C-19 methyl group lies more out of the plane of the aromatic ring.

Previously, a few reported examples of intermolecular Diels-Alder reactions of retinoids have been reported. The addition of maleic anhydride to retinol, and some of its isomers, and retinyl esters was reported during early investigations of retinol and its isomers.[35] Although addition at the end of the side chain was proposed and one of the adducts was obtained in crystalline form,[35a] the structure of such adducts apparently was never confirmed. Subsequently, the addition of methyl 3-formyl-2-butenoate[40] or tetracyanoethene[41] to retinoids was demonstrated.

The addition of maleic anhydride to 13-*cis*-retinol was much slower than addition to retinol.[36b] During studies reported here, the possibility of an intramolecular Diels-Alder reaction of 13-*cis*-retinyl 2-propynyl ether (13-*cis*-RPE; **14**, CHART IV) was investigated. After twenty-four hours under the conditions (refluxing ethanol) that readily produced **4a** from **3b** (with no detectable residual **3b**), the ratio of **14** to **4a** was 9.24:1 determined by HPLC monitored at 282 nm; after forty-eight hours, the ratio was 4:1.

EXPERIMENTAL SECTION[42]

General Methods. All operations involved in the preparation, isolation, purification, and transfer of retinoids were performed in an atmosphere, or under a current, of nitrogen or argon. All such operations were also performed in dim light or photographic darkroom light and, insofar as possible, with containers wrapped with aluminum foil or with black cloths. All retinoids were stored in an atmosphere of argon or nitrogen in hermetically sealed containers at -20 °C or -80 °C.

Melting temperatures were determined in capillary tubes heated in a Mel-Temp apparatus. Ultraviolet spectra (UV) were determined with ethanol solutions and were recorded with a Perkin Elmer Model Lambda 9 spectrophotometer; maxima are given in nanometers. Infrared spectra (IR) were determined from specimens in pressed potassium bromide discs, unless indicated otherwise, and were recorded with a Nicolet Model 10DX Fourier Transform IR spectrometer; vs = very strong, br = broad, sh = shoulder. Mass spectral (MS) data were taken from low-resolution, electron-impact spectra determined at 70 eV with a Varian MAT Model 311A double-focusing spectrometer. The direct-probe temperature was 20 °C unless indicated otherwise; M = molecular ion. Some of the other peaks are identified as probable fragments, *e.g.*, M minus a fragment. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were determined at 300.635 MHZ, and carbon-13 NMR spectra were determined at 75.602 MHZ with a Nicolet Model NT 300NB NMR spectrometer; tetramethylsilane was the internal reference.

Assignments of chemical shifts are designated by the position numbers shown on structures **2-6**. The numbering system for these structures is the retinoid numbering system with additional positions of structures **4a**, **4b**, **6a**, **6b**, **12**, and **13** designated 1′-3′. The position numbers (Hx, x = positions 1-20 or 1′-3′) are given parenthetically with each chemical shift, and multiplicity is designated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, br = broad. Protons of methylene groups are designated a or b when their chemical shifts differ. Carbon-13 assignments were established using APT, HETCOR, and selective hydrogen decoupling experiments. Thin-layer chromatography (TLC) was performed on plates of fluorescing silica gel, and developed plates were examined with UV lamps (254 and 365 nm). High-pressure liquid chromatography (HPLC) was performed with a Hewlett-Packard Model 1084B system or with components by Waters Associates systems and a Hewlett-Packard Model 3380-S integrator. HPLC was performed on columns packed with octadecylsilylated silica (Spherisorb ODS), 5μ particle size. Unless indicated otherwise, the eluting solvent was 85:15 acetonitrile-1% aqueous ammonium acetate, isocratic, 1 mL /min flow rate; and elution was monitored by UV absorption at 340, 282, or 254 nm as specified in parentheses. HPLC retention times are in minutes; h for reaction times = hour or hours. Commercial solutions of butyllithium were used.

Retinyl 2-Propynyl Ether (RPE, 3b). All-*trans*-retinol was prepared by treating commercial retinyl acetate with a solution of sodium hydroxide in methanol (2%) and crystallizing the crude product from cold ethyl formate. To a solution of 5 g (17.5 mmol) of all-*trans*-retinol in 80 mL of dry benzene at 20 °C was added 12 mL of *n*-butyl lithium in hexane (1.6 M). After the viscous red solution had been stirred for 5 min, it was added slowly to a stirring solution of 3 mL (*ca.* 34 mmol) of 2-propynyl bromide in 75 mL of dry dimethylformamide at 25 °C. The mixture was stirred for 45 min and then diluted with ether (100 mL), and the resulting solution was washed three times with cold water. The organic layer was dried ($MgSO_4$) and concentrated to an orange syrup that, according to HPLC analysis (340 nm), consisted of 85% retinyl propynyl ether (**3b**) and 15% retinol. A chloroform solution of the syrup was poured onto a column of silica gel 60. Elution of the column with chloroform was monitored by TLC, eluent fractions were combined into two portions, and both portions were concentrated *in vacuo* to viscous oils. The first portion amounted to 0.8 g; HPLC assay (340 nm), 98.9%. The second portion, which was used for bioassays *in vitro*, was characterized further: wt., 3.1 g (total yield, 78%); HPLC[43] (340 nm), 99.6%; IR (film, medium and strong bands) 3300 (C≡C), 3040, 3025, 2985 sh, 2955, 2925 vs, 2865, 2825, 1455 sh, 1440, 1380, 1375, 1360, 1335, 1270, 1120, 1100 sh, 1080 vs, 1065, 1025, 1010 sh, 965 vs, 940, 665, 630 cm^{-1}; IR, weak bank at 2115 (C≡C); MS *m/z* 325 (M + H), 324 (M), 309 (M - CH_3), 285 (M - $CH_2C{\equiv}CH$), 270, 269 (M -$OCH_2C{\equiv}CH$), 255 (M - $CH_2OCH_2C{\equiv}CH$); ^1H NMR ($CDCl_3$) δ 6.61 (dd, 1H, $J_{10,11}$ = 11.1 Hz, $J_{11,12}$ = 15.2 Hz, H_{11}), 6.29 (d, 1H, H_{12}), 6.16 (the B part of an AB spin system, 1H, $J_{7,8}$ = 16.0 Hz, H_7), 6.11 (the A part of an AB spin system, 1H, H_8), 6.09 (d, 1H, H_{10}), 5.62 (t, 1H, $J_{14,15}$ =

7.0 Hz, H_{14}), 4.24 (d, 2H, H_{15}), 4.15 (d, 2H, ^4J = 2.6 Hz, -CH_2-C≡C-H), 2.44 (t, 1H, ^4J = 2.6 Hz, -CH$_2$-C≡C-*H*), 2.01 (t, 2H, H_4), 1.95 (s, 3H, H_{19}), 1.88 (s, 3H, H_{20}), 1.71 (s, 3H, H_{18}), 1.65-1.59 (m, 2H, H_3), 1.48-1.44 (m, 2H, H_2), 1.02 (s, 6H, H_{16}, H_{17}). *Anal.* Calcd. for $C_{23}H_{32}O$: C, 85.13; H, 9.94. Found: C, 84.80; H, 10.23.

Retinyl 2-Butynyl Ether (3c). The procedure for the preparation of **3c** from 1-bromo-2-butyne and retinol was similar to that described for **3b**. The reaction mixture, initially at 10 °C, was allowed to warm to room temperature, stirred for 6 h, and poured into a mixture of ether, water, and ice. The solution obtained by combining the organic layer and an ether extract of the water layer was washed with an aqueous solution of NaCl, dried ($MgSO_4$), and concentrated to a syrup. The crude product was subjected to flash chromatography on silica gel 60 with chloroform as the eluting solvent. Eluent fractions that were shown by TLC to contain **3c** were combined, the solvent was evaporated under reduced pressure, and the residue was flash-chromatographed again in the same manner: yield of purified **3c**, 42%; HPLC, 99% (340 nm), 98% (254 nm); IR spectrum (liquid film), -C≡C- at 2290, 2245, 2225 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.60 (dd, 1H, $J_{10,11}$ = 11.2 Hz, $J_{11,12}$ = 15.2 H, H_{11}), 6.29 (d, 1H, H_{12}), 6.15 (the B part of an AB spin system, 1H, $J_{7,8}$ = 15.9 Hz, H_7), 6.10 (the A part of an AB spin system, 1H, H_8), 6.09 (d, 1H, H_{10}), 5.62 (t, 1H, $J_{14,15}$ = 6.9 Hz, H_{14}), 4.21 (d, 2H, H_{15}), 4.10 (q, 1H, ^5J = 2.3 Hz, -CH_2-C≡C-), 2.01 (t, 2H, H_4), 1.95 (s, 3H, H_{19}), 1.88 (s, 3H, H_{20}), 1.87 (t, 3H, ^5J = 2.3 Hz, CH_3-C≡C-CH$_2$-), 1.71 (s, 3H, H_{18}), 1.65-1.57 (m, 2H, H_3), 1.48-1.44 (m, 2H, H_2), 1.02 (s, 6H, H_{16}, H_{17}). *Anal.* Calcd. for $C_{24}H_{34}O{\cdot}H_2O$: C, 80.85; H, 10.18. Found: C, 80.90; H, 9.86.

Retinyl 2-Propenyl Ether (3d) was prepared from 2-propenyl bromide and retinol by a procedure similar to that outlined for the preparation of **3c**. The crude product was chromatographed on a column of silica gel 60; elution (gravity) with chloroform-hexane (1:1) was monitored by TLC: yield of **3d** (a syrup), 66%; HPLC, 99.6% (340 nm); MS *m/z* 326 (M); ^{1}H NMR ($CDCl_3$) δ 6.59 (dd, 1H, $J_{10,11}$ = 11.1 Hz, $J_{11,12}$ = 15.2 Hz, H_{11}), 6.29 (d, 1H, H_{12}), 6.15 (the A part of an AB spin system, 1H, $J_{7,8}$ = 16.0 Hz, H_7), 6.10 (the B part of an AB spin system, 1H, H_8), 6.09 (d, 1H, H_{10}), 5.93 (m, 1H, J = 17.2 Hz, J = 10.3 Hz, J = 5.7 Hz, -CH$_2$-C*H*=CH$_2$), 5.65 (t, 1H, $J_{14,15}$ = 6.7 Hz, H_{14}), 5.28 (dq, 1H, J = 1.6 Hz, J = 17.2 Hz, -CH=C*H*aHb), 5.19 (dq, 1H, J = 10.3 Hz, J = 1.6 Hz, -CH=CHa*H*b), 4.15 (d, 2H, $J_{14,15}$ = 6.7 Hz, H_{15}), 3.99 (dt, 2H, J = 1.6 Hz, J = 1.6 Hz, J = 5.7 Hz, -O-CH_2-CH=), 2.01 (t, 2H, H_4), 1.95 (s, 3H, H_{19}), 1.89 (s, 3H, H_{20}), 1.71 (s, 3H, H_{18}), 1.65-1.57 (m, 2H, H_3), 1.48-1.44 (m, 2H, H_2), 1.02 (s, 6H, H_{16}, H_{17}). *Anal.* Calcd. for $C_{23}H_{34}O$: C, 84.60; H, 10.50. Found: C, 84.28; H, 10.81.

Cyclization of Retinyl Propynyl Ether to *Cis*-5H,7aH - 1,3,5,7a-Tetrahydro-7-methyl-5-[2-methyl-4-(2,6,6-trimethylcyclohex-1-enyl)-*E,E*-1,3-butadienyl]isobenzofuran (4a). A solution of 1.0 g of **2b** in ethanol (25 mL) was boiled under reflux. Aliquot portions removed after 3 h and 20 h were examined by TLC and HPLC, (monitored by UV absorbance at 254 nm). A considerable amount of **4a** had formed

by 3 h; after 20 h, **2b** had been converted to **4a** (97.8% by HPLC) and small amounts of other components. The reaction mixture was concentrated to a syrup, and the residue (1 g) was subjected to chromatography, under nitrogen pressure, in chloroform-pentane (2:1) on a column of silica gel 60. The eluent fractions were combined into two portions and were concentrated *in vacuo* to syrups that were analyzed by HPLC at 254 nm: 200 mg (portion 1), 98.2% of **4a** and 1.8% of an unidentified component; 400 mg (portion 2), 99.3% of **4a** and 0.7% of the same unidentified component. After **6a** had been obtained, retrospective examination of the HPLC results indicated that **6a** was the unidentified component of portions 1 and 2. Portion 2 was characterized further and was shown by NMR analyses to be **4a**: IR (film, strong and medium bands) 3015, 2960, 2925 vs, 2910 sh, 2860, 2825, 1465 sh, 1450 sh, 1440, 1380, 1355, 1200, 1090, 1065, 1040 vs, 1020, 965, 905, 855, 825, 815, 750, 625 cm^{-1}; MS *m/z* 324 (M), 322 (M - 2H), 309 (M - CH_3), 307 (M - 2H - CH_3), 294, 177, 175; ^1H NMR ($CDCl_3$) δ 6.05 (the B part of an AB spin system, 1H, $J_{7,18}$ = 0.6 Hz, $J_{7,8}$ = 16.4 Hz, H_7), 6.00 (the A part of AB spin system, 1H, H_8), 5.41 (m, 1H, $J_{1',3'}$ = 1.4 Hz, $J_{1'b,3'}$ = 2.2 Hz, $H_{3'}$), 5.31 (m, 1H, H_{12}), 5.23 (dq, 1H, $J_{10,19}$ = 1.2 Hz, $J_{10,11}$ = 9.5 Hz, H_{10}), 4.44 (m, 1H, $J_{1'a,1'b}$ = 12.1 Hz, $J_{1'b,11}$ = 3.2 Hz, $J_{1'b,14}$ = 1.5 Hz, $J_{1'b,3'}$ = 2.2 Hz, $H_{1'b}$), 4.29 (m, 1H, $J_{1'a,11}$ = 2.0 Hz, $J_{1'a,14}$ = 1.8 Hz, $J_{1'a,3'}$ = 1.4 Hz, $H_{1'a}$), 4.24 (apparent t, 1H, $J_{15a,15b}$ = 7.3 Hz, $J_{14,15b}$ = 8.0 Hz, H_{15b}), 3.79 (a complex multiplet appearing as a br t, 1H, $J_{1'a,11}$ = 2.0 Hz, $J_{1'b,11}$ = 3.2 Hz, $J_{10,11}$ = 9.5 Hz, $J_{11,14}$ = 10.0 Hz, H_{11}), 3.33 (dd, 1H, $J_{15a,15b}$ = 7.3 Hz, $J_{14,15a}$ = 11.2 Hz, H_{15a}), 3.04 (a complex multiplet appearing as a br q, 1H, $J_{11,14}$ = 10.0 Hz, $J_{14,15a}$ = 11.2 Hz, $J_{1'b,14}$ = 1.5 Hz, $J_{1'a,14}$ = 1.8 Hz, H_{14}), 2.00 (t, 2H, H_4), 1.86 (d, 3H, $J_{10,19}$ = 1.2 Hz, H_{19}), 1.72 (m, 3H, $J_{12,20}$ = 1.4 Hz, $J_{11,20}$ = 1.8 Hz, $J_{14,20}$ = 1.4 Hz, H_{20}), 1.69 (d, 3H, $J_{7,18}$ = 0.6 Hz, H_{18}), 1.65-1.57 (m, 2H, H_3) 1.48-1.44 (m, 2H, H_2), 1.01 (s, 6H, H_{16}, H_{17}); ^{13}C NMR ($CDCl_3$) δ 137.90 ($C_{2'}$), 137.50 (C_6), 137.3 (C_8), 133.6 (C_9), 133.0 (C_{10}), 130.4 (C_{13}), 128.3 (C_5), 125.2 (C_7), 124.7 (C_{12}), 118.4 ($C_{3'}$), 71.5 (C_{15}), 69.4 ($C_{1'}$), 42.7 (C_{14}), 39.5 (C_2), 36.9 (C_{11}), 34.0 (C_1), 32.8 (C_4), 28.8 (C_{16}, C_{17}), 21.5 (C_{18}), 21.1 (C_{20}), 19.2 (C_3), 12.3 (C_{19}). *Anal.* Calcd. for $C_{23}H_{32}O \cdot 0.5H_2O$: C, 82.83; H, 9.97. Found: C, 82.94; H, 9.91.

From a larger run, the yield of the major (second) chromatography fraction was 60%; HPLC at 254 nm (retention time): 99.2% (13.3) of **4a**, 0.56% (12.5) of **6a**, 0.21% (11.6). The yield of the first chromatography fraction was 17%; HPLC at 254 nm (retention time): 95.5% (13.4) of **4a**, 2.7% (12.5) of **6a**, 0.4% (11.6), and several lesser components.

Cyclization of RPE Monitored By HPLC. In another experiment, the disappearance of RPE (**3b**); the formation of **4a**, **6a**, and anhydroretinol (**11**); and the presence of 13-*cis*-RPE (**14**) in boiling absolute ethanol were investigated by analyzing aliquot portions by HPLC at 0 h (before heating was begun) and at 4, 6, and 24 h. (Commercial specimens of retinyl acetate, the starting material for the preparation of RPE and other retinyl ethers *via* retinol, usually contain a small amount of the 13-cis isomer from which

13-*cis*-RPE is formed during the preparation of RPE.) The elution of components of the aliquots was monitored by UV absorption at 282 nm and at 340 nm. Compound **4a** is practically devoid of UV

Table 1. Ultraviolet Absorption Maxima and ϵ at Wavelengths at Which HPLC was Monitored.[a]

Compound[b]	UV λ_{max} nm (ϵ)	ϵ at 254 nm	ϵ at 282 nm	ϵ at 340 nm
RPE (**3b**)	326 (49,400) 251 (6,100)	6,000	12,400	38,400
RPE-CP (**4a**)	258 (18,400)	18,300	12,400	180
RPE-CDP (**6a**)	295 (27,800) 212 (15,600)	8,800	24,500	4,400
3c	326 (50,500) 251 (5,900)	5,800	12,800	39,100
4b	259 (19,300)	19,100	12,900	170
6b	284 (23,400) 214 (17,200)	12,500	23,200	1,550
11[c]	391 (86,300) 370 (94,100) 351 (60,800)	3,300	1,300	33,600
13-*Cis*-RPE (**10**)	329 (45,000) 252 (6,600)	6,500	11,200	37,700
3d	325 (46,600) 251 (5,700)	5,600	11,800	35,500
12	253 (17,800)	17,800	11,600	170
13	249 (15,500)	15,300	9,100	100

[a]Absolute ethanol solutions. [b]RPE-CP = RPE cyclization product; RPE-CDP = RPE cyclization-dehydrogenation product. [c]Smaller peaks appeared at 270 (ϵ 6 300), 261 (ϵ 5100), 254 (ϵ 3 300), and 214 (ϵ 9 600).

absorption at 340 nm; however, the molar absorptivities (ϵ) of RPE and **4a** are identical at 282 nm, and the ϵ's of RPE, 13-*cis*-RPE, and **7** are similar at 340 nm (Table 1). Data that demonstrate the disappearance of **3b**, the formation of **4a**, and the presence of **6a** and **14** are summarized in Table 2. After 4 h and 6 h about 2/3 and 3/4, respectively, of **2b** had been converted to **4a**. Because of the much slower rate of cyclization of **14** (described below), the small amount of **14** in the starting specimen of **3b** was practically unchanged after 6 h. Neither **3b** nor **14** was detectable after 24 h. A small amount of **6a**, which has stronger UV absorption at 282 and 340 nm than does **4a** (Table 1), was observed after 24 h. Although small amounts of anhydroretinol may sometimes be formed, it was not detectable at 340 nm, where it has strong UV absorption.

Table 2. Disappearance of RPE (3b) and Formation of 4a and 6a In Boiling Ethanol.

Time Hr.	Monitoring Wavelength,[a] nm	Retention Time nm.	Compound,[b,c] Area %
0	282	9.9	**3b**, 95.1
		9.5	**14**, 3.5
		14.7	**4a**, 1
0	340	9.9	**3b**, 96.8
		9.5	**14**, 3.0
		-	**4a**, NO
4	282	9.9	**3b**, 32.7
		9.5	**14**, 3.2
		14.8	**4a**, 64
	340	9.8	**3b**, 92.5[a,d]
		9.4	**14**, 7.5[a,d]
		-	**4a**, NO
6	282	9.8	**3b**, 18.6
		9.4	**14**, 3.2
		14.8	**4a**, 78.2
6	340	9.7	**3b**, 87.5[a,d]
		9.3	**14**, 12[a,d]
		-	**4a**, NO
24	282	-	**3b**, ND
		-	**14**, ND
		13.3	**6a**, 10.1[e]
		14.1	**4a**, 88.9[e]
24	340	-	**3b**, ND
		-	**14**, ND
		13.2	**6a**, Weak
		--	**4a**, NO

[a]Percentages determined from areas under the peaks at specified wavelengths obviously represent the relative amounts of the components based on the absorptivity of each component at that wavelength. [b]The source of 13-*cis*-RPE (**14**) was 13-*cis*-retinyl acetate in commercial specimens of retinyl acetate. [c]NO = Not observable at 340 nm. ND = Quantity too small to be detected. [d]Because **4a** is not observable at 340 nm, the percentages of **3b** and **14** are only the values relative to each other until both were no longer detectable at 24 hr. [e]At 282 nm, the ϵ of **6a** is about twice that of **4a**.

Cyclization of Retinyl 2-Butynyl Ether. *Cis*-5H,7aH-1,3,5,7a-Tetrahydro-4,7-dimethyl-5-[2-methyl-4-(2,6,6-trimethyl-1-cyclohex-1-enyl)-*E,E*-1,3-butadienyl]isobenzofuran (4b). A solution of 2.2 g of **3c** in 60 mL of dry toluene was boiled under reflux for 12 h and then concentrated under reduced pressure to a syrup that crystallized from acetonitrile: yield, 1.3 g (59%); mp 79-80 °C; HPLC (254 nm), 100%; MS *m/z* 339 (M); ^{1}H NMR ($CDCl_3$) δ 6.05 (the A part of an AB spin system, 1H, $J_{7,8}$ = 16.1 Hz, H_7), 6.03 (the B part of an AB spin system, 1H, H_8), 5.25 (m, 1H, $J_{12,14}$ = 1.6 Hz, $J_{12,20}$ = 1.4 Hz, H_{12}),

5.11 (dq, 1H, $J_{10,19}$ = 1.3 Hz, $J_{10,11}$ = 10.3 Hz, H_{10}), 4.38 (br s, 2H, $J_{1',3'\text{-}CH_3}$ = 1.3 Hz, $H_{1'}$), 4.21 (t, 1H, $J_{15a,15b}$ = 7.2 Hz, $J_{14,\ 15b}$ = 7.4 Hz, H_{15b}), 3.74 (a complex multiplet that appears as a br t, 1H, $J_{10,11}$ = 10.3 Hz, $J_{10,14}$ = 9.3 Hz, $J_{11,\ 3'\text{-}CH_3}$ = 1.3 Hz, H_{11}), 3.29 (dd, 1H, $J_{14,15a}$ = 11.4 Hz, $J_{15a,15b}$ = 7.2 Hz, H_{15a}), 3.04 (a complex multiplet that appears as a br q, 1H, $J_{14,15a}$ = 11.4 Hz $J_{14,15b}$ = 7.4 Hz, $J_{10,14}$ = 9.3 Hz, $J_{14,20}$ = 1.6 Hz, H_{14}), 2.00 (t, 2H, H_4), 1.87 (d, 3H, $J_{10,19}$ = 1.3 Hz, H_{19}), 1.70 (q, 3H, $J_{12,20}$ = 1.3 Hz, $J_{14,20}$ = 1.6 Hz, H_{20}), 1.69 (s, 3H, H_{18}), 1.65-1.56 (m, 2H, H_3), 1.55 (br s, 3H, $J_{1',3'\text{-}CH_3}$ = 1.3 Hz, 3'-CH_3), 1.48-1.44 (m, 2H, H_2), 1.02 (s, 6H, H_{16}, H_{17}); ^{13}C NMR ($CDCl_3$) δ 137.6 (C_6), 137.5 (C_8), 134.5 (C_9), 132.7 (C_{10}), 131.5 ($C_{2'}$), 130.3 (C_{13}), 128.6 (C_5), 125.1 (C_7), 124.9 (C_{12}), 124.0 ($C_{3'}$, 71.7 (C_{15}), 68.3 ($C_{1'}$), 44.0 (C_{11}), 41.3 (C_{14}) 39.6 (C_2), 34.2 (C_1), 33.0 (C_4), 28.9 (C_{16}, C_{17}), 21.6 (C_{18}), 21.1 (C_{20}), 19.3 (C_3), 17.0 (3'-CH_3), 12.5 (C_{19}). *Anal.* Calcd. for $C_{24}H_{34}O$: C, 85.16; H, 10.12. Found: C, 85.34; H, 10.15.

Cyclization product **4b** was also isolated by chromatography (silica gel 60, elution with chloroform) after prolonged heating of **3c** in refluxing benzene. In refluxing ethanol, cyclization of **3c** to **4b** occurred slowly; after 24 h, approximately half of **3c** had been converted to **4b** and a small amount of anhydroretinol (**11**) had also formed (about 0.6% of the total reaction residue).

1,3-Dihydro-7-methyl-5-[2-methyl-4-(2,6,6-trimethylcyclohex-1-enyl)-1,3-butadienyl]isobenzofuran (6a). 2,3-Dichloro-5,6-dicyanobenzoquinone (88 mg, 0.39 mmol) was added in 3 portions during 45 min to a stirred solution of 125 mg (0.38 mmol) of **4a** in 10 mL of dry benzene at room temperature. The reaction solution was stirred for 1.5 h after the last addition. (HPLC of an aliquot portion removed 0.5 h after the last addition showed that very little of **4a** remained.) The solution was washed successively with cold water, sodium bicarbonate solution (2 x 20 mL), and sodium chloride solution, and it was then dried ($MgSO_4$) and concentrated *in vacuo* to a syrup. A chloroform solution of the crude product was poured onto a column of silica gel 60, and the column was eluted with chloroform-pentane (1:1→1:3). Fractions containing **6a** (determined by TLC) were combined and concentrated to dryness *in vacuo*: weight, 70 mg; HPLC at 254 nm (retention time) 84.6% of **6a** (12.9), 8% of **4a** (13.8), 1.7% (10.2), and 5.7% (10.8) of the two unidentified components;[44] HPLC at 340 nm (retention time) 86.4% (12.9) of **6a**, 5.7% (10.2), and 7.9% (10.8) of two unidentified components. After this material crystallized partially, it was triturated three times with cold pentane. The residual solid was dried *in vacuo*: weight, 40 mg; HPLC at 254 nm (retention time) 98.3% (13.1) of **6a**, 0.34% (14.0) of **4a**, 1.37% (10.3) of an unidentified component; IR (medium and strong bands) 3030 (aromatic CH), 3015 sh, 2965, 2945, 2910, 2905, 2845, 2825, 1610 and 1590 (aromatic C=C), 1470, 1450, 1435 sh, 1425, 1365, 1355, 1315, 1060, 1025, 970, 905, 890 (aromatic CH), 880 sh, 860 cm^{-1}; MS *m/z* 323 (M + H), 322 (M), 307 (M - CH_3), 277, 251, 237, 221, 207; ^{1}H NMR ($CDCl_3$) δ 6.99 (br s, 1H, $H_{3'}$), 6.98 (br s, 1H, H_{12}), 6.43 (br s, 1H, $J_{10,19}$ = 1.1Hz, H_{10}), 6.19 (br s, 2H, H_7 and H_8), 5.12 (br s, 2H, $H_{1'}$), 5.07 (br s, 2H, H_{15}), 2.25 (s, 3H, H_{20}),

2.03 (d, 3H, $J_{10,19}$ = 1.1 Hz, H_{19}), 2.02 (t, 2H, H_4), 1.73 (s, 3H, H_{18}), 1.65-1.58 (m, 2H, H_3), 1.49-1.45 (m, 2H, H_2), 1.04 (s, 6H, H_{16},H_{17}). ^{13}C NMR ($CDCl_3$) δ 138.8 (C_6), 138.1 (C_8), 137.9, 137.7, 136.3, 136.1 ($C_{2'}$, C_{14}, C_{11}, C_{13}), 130.8 (C_9), 129.6 (C_{10}), 129.3 (C_{12}), 129.0 (C_5), 126.9 (C_7), 118.7 ($C_{3'}$), 74.0 ($C_{1'}$), 73.0 (C_{15}), 39.6 (C_2), 34.3 (C_1), 33.0 (C_4), 29.0 (C_{16}, C_{17}), 21.7 (C_{18}), 19.3 (C_3), 18.8 (C_{20}), 13.9 (C_{19}). *Anal.* Calcd. for $C_{23}H_{30}O \cdot 1/8H_2O$: C, 85.07; H, 9.39. Found: C, 85.04; H, 9.47.

1,3-Dihydro-4,7-dimethyl-5-[2-methyl-4-(2,6,6-trimethylcyclohex-1-enyl)-1,3-butadienyl]isobenzofuran (6b). To a solution of 650 mg of **4b** in 25 mL of anhydrous benzene at 10 °C was added 440 mg of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in three portions during 0.5 h. After 2 h of stirring, TLC showed that some **4b** remained. The temperature of the solution was raised to room temperature, and stirring was continued for 1 h, at which time **4b** was not observable by TLC. Ether (50 mL) was added, and the mixture was washed successively with water (3 x 50 mL), dilute aqueous sodium bicarbonate (3 x 25 mL), and sodium chloride solution. The organic layer was dried (Na_2SO_4) and concentrated to a syrup; the residue was triturated with acetonitrile; and a crystalline precipitate was collected and dried: yield, 567 mg (89%); mp 88-90 °C; HPLC, 98.6% at 254 nm, 99.0% at 280 nm; ^{1}H NMR ($CDCl_3$) δ 6.92 (s, 1H, H_{12}), 6.42 (br s, 1H, H_{10}), 6.24 (the A part of an AB spin system, $J_{7,8}$ = 16.2 Hz, H_8), 6.19 (the B part of an AB spin system, 1H, H_7), 5.11 (s, 4H, H_{15} and $H_{1'}$), 2.21 (s, 3H, H_{20}), 2.09 (s, 3H, 3'-CH_3), 2.03 (t, 2H, H_4), 1.89 (d, 3H, $J_{10,19}$ = 1.2 Hz, H_{19}), 1.76 (s, 3H, H_{18}), 1.68-1.59 (m, 2H, H_3), 1.50-1.47 (m, 2H, H_2), 1.06 (s, 6H, H_{16}, H_{17}). *Anal.* Calcd. for $C_{24}H_{32}O$: C, 85.67; H, 9.59. Found: C, 85.61; H, 10.13.

Anhydroretinol (11) was prepared by dehydrating retinol in an ethanol-hydrogen chloride solution (1/30 M), as described by Shantz *et al.*[45] The crude product in pentane was chromatographed on deactivated alumina (9:1 alumina-water). Eluent fractions, identified by TLC, that contained the partially purified product were combined and concentrated *in vacuo* to an orange syrup. Further purification by chromatography was repeated in the same way, and a pentane solution of the eluted product was stored overnight at -80 °C. A yellow crystalline precipitate was recrystallized in the same way and was then recrystallized again at -20 °C: mp 76-77 °C (lit.[40] 76-77 °C); MS *m/z* 268 (M); ^{1}H NMR ($CHCl_3$) δ 6.77 (d, 1H, $J_{7,8}$ = 12.5 Hz, H_8), 6.59 (dd, $J_{10,11}$ = 15.0 Hz, $J_{11,12}$ = 11.1 Hz, H_{11}), 6.44 (dd, 1H, H_{14}), 6.43 (dd, 1H, H_{10}), 6.38 (d, 1H, H_7), 6.19 (d, 1H, H_{12}), 5.78 (bt, 1H, $J_{3,4}$ = 4.5 Hz, H_4), 5.21 (d, 1H, $J_{14,15Z}$ = 17.3 Hz, H_{15Z}), 5.03 (d, 1H, $J_{14,15E}$ = 10.5 Hz, H_{15E}), 2.12 (apparent q, 2H, H_3), 1.95 (d, 3H, $J_{8,19}$ = 1.1 Hz, H_{19}), 1.92 (d, 3H, $J_{4,20}$ = 1.3 Hz, H_{20}), 1.91 (m, 3H, H_{18}), 1.51 (t, 2H, $J_{2,3}$ = 6.2 Hz, H_2), 1.30 (s, 6H, $H16$, H_{17}). *Anal.* Calcd. For $C_{20}H_{28}$: C, 89.50; H, 10.50. Found: C, 89.52; H, 10.61.

Cyclization of Retinyl 2-Propenyl Ether to 12 and 13. A solution of **3d** (2 g) in dry toluene (30 mL) was boiled under reflux during 24 h at which time TLC showed a large, intense spot; a small, intense spot in front of the large spot; and a faint faster-moving spot (unchanged **3d**). Subsequently, the two

intense spots were identified as **12** and **13**, respectively. The reaction mixture concentrated to a yellow syrup. A chloroform solution of the syrup was poured onto a column of silica gel 60; chloroform was the eluting solvent and the elution was monitored by TLC. Eluent portions were combined into three fractions that were concentrated to syrups (fraction designation, wt., HPLC % at 254 nm, retention time): A1, 0.3 g, 99%, 14.5 min; B1, 0.9 g; C1, 0.7 g, 100%, 13.4 min. According to TLC, fraction B1 was a mixture of A1 and C1 and was resolved by column chromatography into three similar fractions: A2, 0.1 g, 98.3%, 14.2 min; B2, 0.2 g (mixture), 90%, 13.4 min and 10%, 14.2 min; C2, 0.4 g, 99.8%, 13.4 min.

Ether solutions of fractions C1 and C2 were combined and concentrated to dryness: yield of **12**, 1.1 g (55%); HPLC (254 nm), 99.9%; MS *m/z* 326 (M); ^{1}H NMR ($CDCl_3$) δ 6.03 (A part of an AB spin system, 1H, $J_{7,8}$ = 16.2 Hz, H_7), 5.97 (B part of an AB spin system, 1H, H_8), 5.38 (dq, 1H, $J_{10,19}$ = 1.1Hz, $J_{10,11}$ = 9.3 Hz, H_{10}), 5.20 (m, 1H, H_{12}), 4.09 (apparent t, 1H, $J_{14,\ 15b}$ = 7.3 Hz, $J_{15a,15b}$ = 7.1 Hz, H_{15b}), 3.99 (apparent t, 1H, $J_{1'b,2'}$ = 7.0 Hz, $J_{1'a,1'b}$ = 7.3 Hz, $H_{1'b}$), 3.45 (dd, 1H, $J_{14,15a}$ = 11.4 Hz, $J_{15a,15b}$ = 7.1 Hz, H_{15a}), 3.41 (dd, 1H, $J_{1'a,2'}$ = 10.8 Hz, $J_{1'a,1'b}$ = 7.3 Hz, $H_{1'a}$), 3.36 (br m, 1H, H_{11}), 2.29 (a complex multiplet that appears as a br q, 1H, $J_{2',14}$ = 10.0 Hz, H_{14}), 2.12-2.00 (m, 1H, $H_{2'}$), 1.99 (t, 1H, H_4), 1.83 (d, 3H, $J_{10,19}$ = 1.1 Hz, H_{19}), 1.80-1.75 (m, 1H, $J_{3'a,3'b}$ = 12.6 Hz, $J_{3'b,2'}$ = 3 Hz, $H_{3'b}$), 1.72-1.64 (m, 1H, $H_{3'a}$), 1.69 (br s, 6H, H_{18}, H_{20}), 1.65-1.56 (m, 2H, H_3), 1.47-1.43 (m, 2H, H_2), 1.01 (s, 6H, H_{16}, H_{17}). ^{13}C NMR ($CDCl_3$) δ 137.7 (C_6), 137.6 (C_8), 134.3 (C_{10}), 132.7 and 132.5 (C_9 and C_{13}), 128.5 (C_5), 125.0 (C_7 and C_{12}), 71.9 ($C_{1'}$), 70.0 (C_{15}), 47.2 (C_{14}), 40.2 ($C_{2'}$), 39.6 (C_2), 35.1 (C_{11}), 34.2 (C_1), 32.9 (C_4), 30.0 ($C_{3'}$), 28.9 (C_{16} and C_{17}), 21.7 (C_{18}), 20.9 (C_{20}), 19.3 (C_3), 12.4 (C_{19}). *Anal.* Calcd. For $C_{23}H_{34}O{\cdot}2/3H_2O$: C, 81.60; H, 10.52. Found: C, 81.19; H, 10.88.

Fractions A1 and A2 were combined similarly and dried: yield of **13**, 0.4 g; mp 44-46 °C; HPLC, 100% (at 254 nm); MS *m/z* 326 (M); ^{1}H NMR ($CDCl_3$) δ 6.00 (br s, 2H, H_7, H_8), 5.29 (m, 1H, H_{12}), 5.20 (dq, 1H, $J_{10,19}$ = 1.2 Hz, $J_{10,11}$ = 9.3 Hz, H_{10}), 4.10 (apparent t, 1H, $J_{15a,15b}$ = 7.8 Hz, $J_{14,15b}$ = 8.5 Hz, H_{15b}), 4.02 (dd, 1H, $J_{1'b,2'}$ = 6.0 Hz, $J_{1'a,1'b}$ = 8.5 Hz, $H_{1'b}$), 3.64 (dd, 1H, $J_{1'a,1'b}$ = 8.5 Hz, $J_{1'a,2'}$ = 1.9 Hz, $H_{1'a}$), 3.46 (dd, $J_{15a,15b}$ = 7.8 Hz, $J_{14,15a}$ = 9.9 Hz, H_{15a}), 3.12 (m, 1H, H_{11}), 2.57 (a complex multiplet appearing as a br q, 1H, $J_{14,15a}$ = 8.5 Hz, $J_{14,15b}$ = 9.9 Hz, $J_{2',14}$ = 7.4 Hz, H_{14}), 2.42-2.31 (m, 1H, $J_{2',3'a}$ = 13 Hz, $J_{1'a,2'}$ = 1.9 Hz, $J_{1'b,2'}$ = 6.0 Hz, $J_{2',3'b}$ = 4.5 Hz, $J_{2',14}$ = 7.4 Hz, H_2), 2.00 (t, 1H, H_4), 1.82 (d, 3H, $J_{10,19}$ = 1.2 Hz, H_{19}), 1.69 (s, 3H, H_{18}), 1.67 (m, 3H, H_{20}), 1.71-1.64 (m, 1H, $J_{3'b,11}$ = 4.5 Hz, $J_{3'b,3'a}$ = 13 Hz, $H_{3'b}$), 1.64-1.57 (m, 2H, H_3), 1.47-1.44 (m, 2H, H_2), 1.29-1.16 (m, $J_{3'a,11}$ = 11 Hz, $J_{3'a,3'b}$ = 13 Hz, $J_{2',3'a}$ = 13 Hz, 1 H, $H_{3'a}$), 1.01 (s, 6H, H_{16}, H_{17}). ^{13}C NMR ($CDCl_3$) δ 137.9 (C_8), 137.8 (C_6), 134.8 (C_{10}), 133.8 and 133.1 (C_{13} and C_9), 128.4 (C_5), 126.7 (C_{12}), 124.8 (C_7), 74.6 (C_{15}), 72.1 ($C_{1'}$), 43.4 (C_{14}), 39.7 (C_2), 37.7 ($C_{2'}$), 35.4 (C_{11}), 34.3 (C_1), 33.0 (C_4), 32.2 ($C_{3'}$), 29.0 (C_{16} and C_{17}), 23.1 (C_{20}), 21.7 (C_{18}), 19.4 (C_3), 12.5 (C_{19}). *Anal.* Calcd. for $C_{23}H_{34}O{\cdot}H_2O$: C, 80.19; H, 10.53. Found: C, 80.41; H, 10.90.

In a prior experiment, **3d** was heated in boiling ethanol under reflux; TLC showed that little, or no, change had occurred after 6 h, that most of the **3d** remained after 24 h, and that a small amount of **11** had formed.

13-*Cis*-Retinyl 2-Propynyl Ether (14) was prepared from 13-*cis*-retinol and 2-propynyl bromide by a procedure similar to that outlined for the preparation of **3c**. After the reaction mixture had warmed to room temperature, it was stirred for 4 h. The crude product, a yellow oil, was shown by HPLC (340 nm) to be a mixture of **14** and the starting material (about 2:1). Flash chromatography of the crude product on a column of silica gel 60 with chloroform as the eluting solvent afforded **14**: yield, 47%; HPLC (340 nm), 99%; ^{1}H NMR ($CDCl_3$) δ 6.68 (A part of an ABX spin system, 1H, $J_{11,12}$ = 15.1 Hz, $J_{10,11}$ = 9.3 Hz, H_{11}), 6.62 (B part of an ABX spin system, 1H, H_{12}), 6.18 (A part of an AB spin system, 1H, $J_{7,8}$ = 16.1 Hz, H_7), 6.14 (d, 1H, $J_{10,11}$ = 9.3 Hz, H_{10}), 6.12 (B part of an AB spin system, 1H, H_8), 5.49 (t, 1H, $J_{14,15}$ = 7.1 Hz, H_{14}) 4.25 (d, 2H, $J_{14,15}$ = 7.1 Hz, H_{15}), 4.15 (d, 2H, ^4J = 2.5 Hz, -CH_2-C≡C), 2.45 (t, 1H, ^4J = 2.5 Hz, -C≡C-H), 2.02 (t, 2H, H_4), 1.97 (d, 3H, $J_{10,20}$ = 0.6 Hz, H_{20}), 1.95 (d, 3H, $J_{14,19}$ = 0.9 Hz, H_{19}), 1.71 (s, 3H, H_{18}), 1.66-1.58 (m, 2H, H_3), 1.49-1.45 (m, 2H, H_2), 1.03 (s, 6H, H_{16}, H_{17}). *Anal.* Calcd. for $C_{23}H_{32}O{\cdot}0.25H_2O$: C, 83.97; H, 9.96. Found: C, 84.07; H, 10.08. A second fraction eluted from the flash chromatography column was 13-*cis*-retinol (recovery, 40%).

Attempts to Cyclize Retinyl 13-*cis*-Propynyl Ether (14). A solution of **14** in absolute ethanol was boiled under reflux, and aliquot portions were analyzed by HPLC at 0 h (before heating was begun), 6 h, 24 h, and 48 h. Elution of components was monitored at 282 nm to determine the proportions of **14** and **4a** (see Table 1) and at 340 nm to look for anhydroretinol (**11**). The following reference standards (retention times) were employed during the HPLC analyses: **14** (9.15 ± 0.10 min), **4a** (14.18 ± 0.11 min), **3b** (9.47 ± 0.11 min), **11** (12.16 ± 0.10 min). At 0 h, HPLC revealed only **14** (98.7% at 282 nm, 97.3% at 340 nm) and an unknown impurity (1.3% and 2.7% at 282 and 340 nm, respectively) that eluted at about 5.6 min. At 282 nm, the ratios of **14** : **4a** and the sum of the percentages of **14** and **4a** in the total mixture were as follows: at 6 h, 16.4 : 1, 90.3%; at 24 h, 9.24 : 1, 89.1%; at 48 h, 4 : 1, 75.6%. Therefore, cyclization of **14** proceeded much slower than cyclization of **3b**. The minor impurity present at 0 h remained and 4-6 additional minor components appeared during the course of the experiment. Aliquots were analyzed at 340 nm immediately after aliquots were analyzed at 282 nm. Anhydroretinol (**11**), which absorbs strongly at 340 nm, was not present, and all-*trans*-RPE (**3b**) was not detectable at either 282 nm or 340 nm.

In boiling toluene, the cyclization proceeded somewhat faster, but the reaction was not complete after 44 h and other products were detected at 282 nm and 340 nm in the reaction mixture.

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42. In accordance with *Chemical Abstracts* nomenclature, retinoids **4a**, **4b**, **6a**, and **6b** are named as isobenzofurans.
43. In this determination, the retention times of **3b** and an impurity (0.4%) were 10.4 and 6.3 min, respectively. The retention time of retinol determined immediately afterward under the same conditions was 8.8 min; therefore, retinol was not present in determinable amounts in **3b**.
44. The unidentified components might be products of further dehydrogenation.
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