CH_2CH_2OCO), 4.5 (m, 4 H, CH_2OCO), 7.6 (t, 2 H, ArH), 8.2 (d. 2 H, ArH), 8.3 (d, 2 H, ArH); mass spectrum, m/e M^+ 500. Anal. Calcd for $C_{24}H_{20}O_8S_2$: C, 57.59; H, 4.03; S, 12.81. Found: C, 57.53; H, 3.91; S, 12.78.

7,7'-Bis(((2-((2-((2-methoxyethylene)oxy)ethylene)oxy)ethylene)-oxy)carbonyl)thioindigo (T-2). The synthetic procedure was the same as for T-1. Triethylene glycol monomethyl ether was used instead of ethylene glycol monomethyl ether: ^1H NMR (Me_2SO-d_6) 3.3 (s, 6 H, CH_3), 3.5 (m, 16 H, CH_2), 3.8 (m, 4 H, CH_2CH_2OCO), 4.5 (m, 4 H, CH_2OCO), 7.6 (t, 2 H, ArH), 8.2 (d, 2 H, ArH), 8.3 (d, 2 H, ArH); mass spectrum, m/e M^+ 676. Anal. Calcd for $C_{32}H_{36}O_{12}S_2$: C, 56.79; H, 5.36; S, 9.48. Found: C, 56.76; H, 5.53; S, 9.55.

Photoisomerization. A xenon lamp (Osram 450 W) was used as a light source. Monochromatic light of 550 and 450 nm was obtained by passing the light through a band-pass interference filter (Toshiba KL-55 or KL-45) and a cutoff filter (Toshib VY-42). Lines of the Ar ion laser (Spectra-Physics 165) of 488 and 529 nm were also used to isomerize T-1 from the cis to the trans and from the trans to the cis form, respectively, in a single test tube or in a H-type ion transport cell. A laser beam is convenient for irradiation to the limited area. When used for the ion transport experiments, the laser beam irradiated a small area just below the aqueous-organic phase boundary.

Solvent Extraction. Equal volumes (15 mL) of benzene (or 1,2-dichloroethane) containing 4×10^{-5} mol/1 T-1 or T-2 and an aqueous solution containing 1×10^{-2} mol/1 metal nitrate and 2×10^{-5} mol/1 picric acid was vigorously agitated for 30 min with a shaker (Yamato SA-31). T-1 and T-2 were irradiated with 450- or 550-nm light for 10 min prior to the extraction experiments. A similar extraction was performed with pure benzene (or 1,2-dichloroethane). The extractability was determined from the difference between these two absorbances of metal picrate in the aqueous phase. All the extractions were conducted at 25 °C.

Ion Transport across a Liquid Membrane. A H-type cell containing 40 mL of organic liquid membrane (1,2-dichloroethane) and two aqueous phases (15 mL each) was used. The cell was immerced in a water bath thermostated at 25 °C. The liquid membrane was stirred gently. Dissolved in the liquid membrane was 4×10^{-5} mol/1 T-1. Aqueous phase I contained 1×10^{-2} mol/1 $AgNO_3$ and 2×10^{-5} mol/1 picric acid, and phase II was pure water. The ion transport was followed by measuring the decrease of the absorption of metal picrate in phase I and the increase in phase II.

Acknowledgment. We thank Prof. K. Hayashi for helpful discussions and L. Katsikas for her kind correction of the English.

On a Tandem 1,2-Elimination/[1,7]-Sigmatropic Shift: Synthesis of Double Bond Shifted Isomers of Vitamin A

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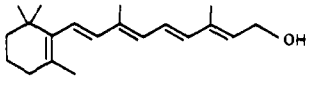
Abstract: The syntheses of four geometrical isomers of 18,14-*retro*-retinol (**7a–10a**) and two dehydro derivatives (**31b** and **32b**) are described. Treatment of the *cis*-benzoate **19** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded an 80% yield of the trienyne **20a**. Evidence for the formation of the latter by an initial 1,2-elimination to afford the putative **21** followed by a [1,7]-sigmatropic shift is provided. Thus, treatment of the pentadeuteriobenzoate **23** under identical conditions afforded **25**, in which a single deuterium atom is incorporated at the C_3 methyl position by way of an intramolecular process. Palladium-catalyzed coupling of the Grignard salt of **20a** (**20f**) with (*E*)-bromide **30a** followed by deprotection afforded dehydro-*retro*-retinol **31b**. The latter was catalytically reduced to the (10*Z*)-*retro*-retinol **8a**. A similar sequence applied to the (*Z*)-bromide **30b** afforded **32b** and the (10*Z*,12*Z*)-*retro*-retinol **10a**. A standard three-step sequence was used to convert **20a** to the tetraenal **33b**, which was condensed in a Wittig reaction with ylide **35** to afford after separation the *all-trans*- and (12*Z*)-*retro*-retinols, **7a** and **9a**, respectively.

A significant correlation between the role of retinoids (vitamin A) in controlling differentiation of epithelial cells and the development of malignancy in epithelial tissues has been clearly established.[1] The natural vitamin A (**1**) exhibits therapeutic and prophylactic activity in certain types of carcinomas but unfortunately causes toxic liver damage due to excessive localization in the liver. In contrast, the unnatural geometric isomer 13-*cis*-



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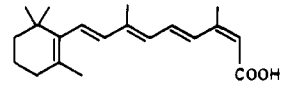

2

retinoic acid (**2**) is far less toxic yet possesses similar biological efficacy in controlling cell differentiation.[1,2] Success of this sort has spurred a search for increasingly more effective retinoidal anticancer drugs.[3] The signal importance of retinoids in photobiological research (energy transduction and vision)[4] and acne therapy[5] provides further impetus for synthetic endeavors in the vitamin A field.

In the case of compounds which show toxic side effects, acceptable therapeutic indexes can still be obtained by designing analogues which show greatly enhanced beneficial activity. Although exactly how a retinoid such as **2** exerts its various biological effects is unclear, it would be quite plausible that it does so by binding to one or more proteins in one topologically specific form or another. For example, 13-*cis*-retinoic acid (**2**) may bind to a putative receptor in a side chain conformation, such as **3–6** or one

(1) Sporn, M. B. *Nutr. Rev.* **1977**, *35*, 65.

(2) (a) Sporn, M. B.; Squire, R. A.; Brown, C. C.; Smith, J. M.; Wenk, M. L.; Springer, S. *Science (Washington, D.C.)* **1977**, *195*, 487. (b) Grubbs, C. J.; Moon, R. C.; Squire, R. A.; Farrow, G. M.; Stinson, S. F.; Goodman, D. G.; Brown, C. C.; Sporn, M. B. *Ibid.* **1977**, *198*, 743.

(3) For a compilation of biological data for analogues, see: (a) Newton, D. L.; Henderson, W. R.; Sporn, M. B. "Structure-Activity Relationships of Retinoids: Tracheal Organ Culture Assay of Activity of Retinoids"; Laboratory of Chemoprevention, Division of Cancer Cause and Prevention, National Cancer Institute: Bethesda, MD, 1980. (b) *Cancer Res.* **1980**, *40*, 3413.

(4) For a recent overview, see: Ottolenghi, M. *Adv. Photochem.* **1980**, *12*, 97.

(5) Peck, G. L.; Olsen, T. G.; Yoder, F. W.; Strauss, J. S.; Downing, D.; Pandya, M.; Butkus, D.; Arnand-Battandier, J. *New Engl. J. Med.* **1979**, *300*, 329.

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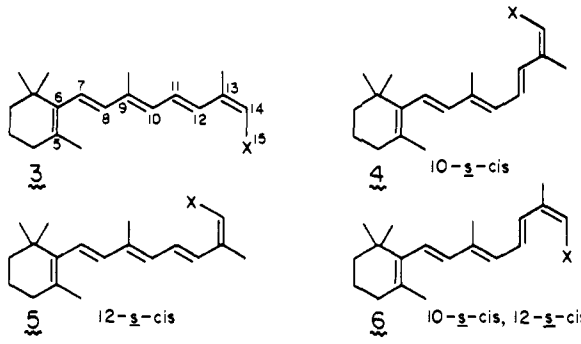
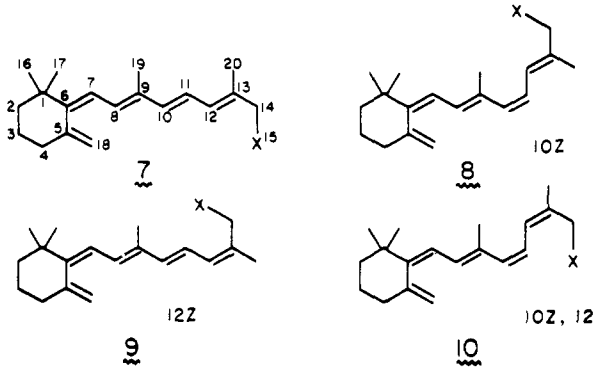
of a number of other rotamers, which is not necessarily the lowest energy conformation. Thus, a conformationally locked analogue



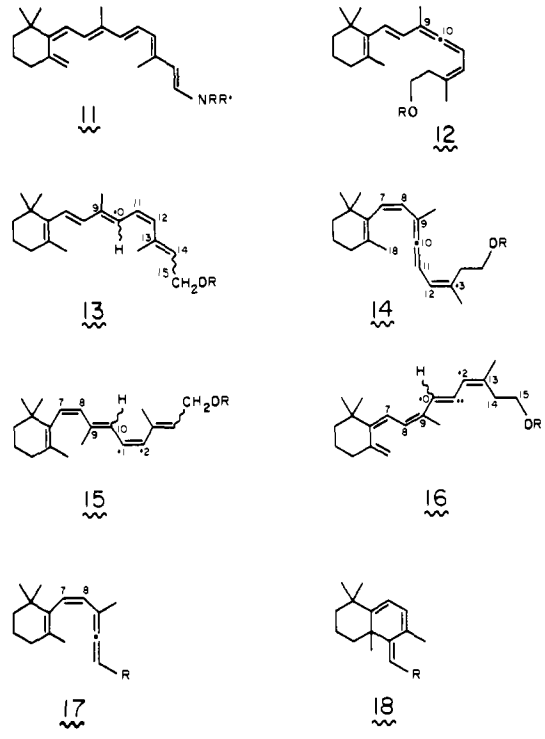
which mimics the "active topology" would be expected to bind preferentially and exhibit enhanced biological activity. The systematic fusion of rings to the retinoid side chain has produced conformationally locked analogues which in some cases have been extraordinarily active.[6] We envisage an alternative mode of conformational locking where the interchange of double and single bond positions along the side chain would produce the locked equivalents of various conformations of different geometric isomers. With this concept in mind, we became interested in synthesizing and studying the polyenes **7–10** which in their most extended conformations would be topological mimics of the conformational isomers of 13-*cis*-retinoic acid **3–6**, respectively.



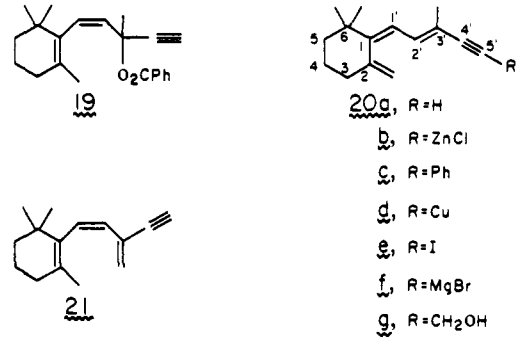
a, X=CH_2OH; **b**, X=COOH

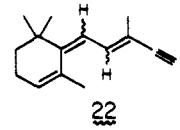
The 18,14-*retro*-retinols **7–10** possess the partial chromophore of the hexaenamine **11**, a substance hypothesized as an intermediate in the visual process.[7] Thus, these *retro*-retinoids are also of interest as possible synthetic precursors of **11** and its geometric isomers.

In previous synthetic endeavors in the retinoid area, we utilized thermally induced [1,5]-sigmatropic hydrogen shifts in 9,10-allenes of the type **12** to obtain geometrically isomeric 11-*cis*-retinoids **13** and various conformationally locked analogues.[8] While a similar [1,5]-hydrogen migration of the corresponding 7-*cis*-9,10-allene **14** would result in various 7-*cis*,11-*cis*-retinoids **15**, we anticipated instead that **14** would preferentially undergo a



thermal [1,7]-sigmatropic hydrogen shift from C_{18} to C_{10} to give **16** and hence provide us initial access to the *retro*-retinoid series. However, in studies directed toward this end, we observed that the model compounds **17** did not undergo the desired [1,7]-hydrogen shift but instead underwent very facile six-electron electrocyclizations to give the bicyclic products **18**,[9] indicating that the allene approach to *retro*-retinoids was probably not a viable one. The unexpected discovery was made, however, that the *cis*-benzoate **19**, utilized previously[9] in preparing some derivatives of **18** via **17**, could be transformed into trienyne **20a** (vide infra), which possessed the desired 18-*retro* skeleton. It is the purpose





of this article to describe the synthesis of the double bond shifted isomers **7a–10a** and related substances from the trienyne **20a** and to show that the latter is in fact produced by a most unusual tandem 1,2-elimination/[1,7]-sigmatropic shift via **21** from **19**.

Results and Discussion

The base-induced (DBU, refluxing acetonitrile) elimination of benzoic acid from *cis*-benzoate **19**[9] surprisingly afforded a single

(6) For leading references, see: Dawson, M. I.; Hobbs, P. D.; Chan, R. L.; Chao, W.-R.; Fung, V. A. *J. Med. Chem.* **1981**, *24*, 583.

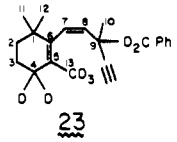
(7) (a) Fransen, M. R.; Luyten, W. C. M. M.; van Thuijl, J.; Lugtenburg, J.; Jansen, P. A. A.; van Breugel, P. J. G. M.; Daemen, F. J. M. *Nature (London)* **1976**, *260*, 726. (b) van der Meer, K.; Mulder, J. J. C.; Lugtenburg, J. *Photochem. Photobiol.* **1976**, *24*, 363. (c) See for a more recent discussion: Fransen, M. R.; Palings, I.; Lugtenburg, J.; Jansen, P. A. A.; Groenendijk, G. W. T. *Recl. Trav. Chim. Pays-Bas* **1980**, *99*, 384.

(8) (a) Knudsen, C. G.; Carey, S. C.; Okamura, W. H. *J. Am. Chem. Soc.* **1980**, *102*, 6355. (b) Chandraratna, R. A. S.; Okamura, W. H. *Ibid.* **1982**, *104*, 6114. (c) Knudsen, C. G.; Chandraratna, R. A. S.; Walkeapää, L. P.; Chauhan, Y. S.; Carey, S. C.; Copper, T. M.; Birge, R. R.; Okamura, W. H. *Ibid.* **1983**, *105*, 1626. (d) Chandraratna, R. A. S.; Bayerque, A. L.; Okamura, W. H. *Ibid.* **1983**, *105*, 3588. (e) Chandraratna, R. A. S.; Okamura, W. H. *Tetrahedron Lett.* **1984**, *25*, 1003. (f) Chandraratna, R. A. S.; Birge, R. R.; Okamura, W. H. *Ibid.* **1984**, *25*, 1007.

(9) Reischl, W.; Okamura, W. H. *J. Am. Chem. Soc.* **1982**, *104*, 6115. For the full paper, see: Okamura, W. H.; Peter, R.; Reischl, W. *J. Am. Chem. Soc.*, following paper in this issue.

hydrocarbon (80%) as ascertained by ^1H and ^{13}C NMR spectroscopy as well as chromatography. Its ^1H NMR clearly revealed the presence of a terminal vinyl group consistent with either **20a** or **21**, but a more detailed analysis revealed it to be the former. The appearance of appropriate allylic couplings (between $H_{2'}$ and the $C_{3'}$ CH_3, $J \sim 1.4$ Hz; H_3 and the *Z* hydrogen of the exocyclic methylene group, $J \sim 1.4$ Hz)[10] and the vicinal s-trans coupling (between $H_{1'}$ and $H_{2'}$ of $J \sim 10.8$ Hz)[11] provide the most convincing evidence for structure **20a** rather than **21**. The formation of only **20a**, to the exclusion of its three other possible geometric isomers and of structural isomers of the type **22**, cannot satisfactorily be rationalized on the basis of a direct 1,6-elimination of benzoic acid. However, a 1,2-elimination of benzoic acid leading to the initial formation of **21** followed by a subsequent [1,7]-sigmatropic hydrogen shift would readily explain the formation of a single, more stable, linearly conjugated trienyne (**20a**) from the cross-conjugated (**21**) system.

Since the geometry assigned to the trienyne **20a** (and also to the *retro*-retinols and intermediates subsequently derived from **20a**) is based on the above mechanistic hypothesis, it was imperative that we unequivocally establish this mechanistic scheme. All attempts made to isolate the putative intermediate **21** by inducing the reaction of **19** at lowered temperatures were unsuccessful. We envisaged that reaction of the deuteriobenzoate **23** under elimination conditions would, if the postulated mechanism were operative, lead through the intermediacy of **24** to **25** with the incorporation of a single deuterium atom at the $C_{3'}$ CH_3 and net retention of deuterium content. Alternatively, if a direct



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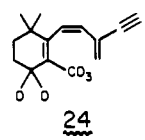

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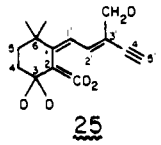
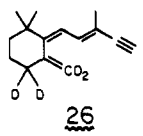


25



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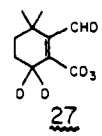

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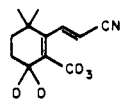

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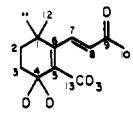
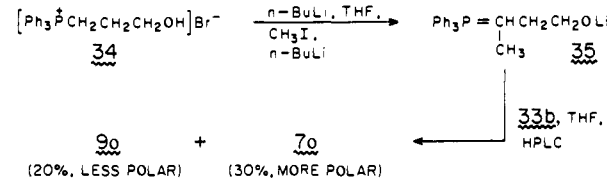


29

1,6-elimination were to occur, reaction of **23** would likely result in **26** with a net loss of a single deuterium. The desired benzoate **23** was synthesized starting from the known pentadeuterio-β-cyclocitral **27**,[12] which upon condensation with diethyl (cyanomethyl)phosphonate[13] followed by treatment of the resultant diene nitrile **28** with methyllithium gave upon acidic workup[14] the pentadeuterio-β-ionone **29**. The latter (**29**) was then converted to **23** by a sequence identical with that used for the synthesis of **19**.[9] Treatment of **23** under conditions identical with those used for the synthesis of **20a** afforded a single hydrocarbon product **25** in which we could demonstrate clearly by ^1H and ^{13}C NMR the presence of a single deuterium in the $C_{3'}$ methyl group. Mass spectroscopic analysis of **23** and **25** also revealed that the conversion proceeds with retention of deuterium content. These data

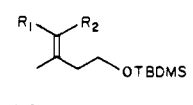
Scheme I



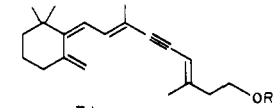
clearly indicate that the formation of **25** (and **20a**) must proceed by a [1,7]-sigmatropic hydrogen shift of the cross-conjugated **24** (or **21** in the undeuterated case) and hence confirms the stereochemistry assigned to **25** (and **20a**).

Parenthetically, it is interesting to note at this stage the dichotomy in reaction pathway of the putative intermediates **17** and **21**. While the 7-*cis*-vinylallenes **17** react exclusively by six-electron electrocyclization, the corresponding triene **21** reacts by a [1,7]-hydrogen shift. Apparently, the extraordinarily facile six-electron electrocyclization pathway accessible to vinylallenes of the type **17** results from the central carbon of the allene being a site of minimal steric demand. The introduction of even a small amount of steric hindrance in the form of the hydrogens in the terminal vinyl group of the putative **21** results in a total crossover to the [1,7]-hydrogen shift pathway. However, at higher temperatures, electrocyclizations will very likely occur in the latter case as exemplified by the thermal behavior of β-carotene.[13]

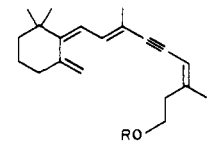
It was envisaged that cross-coupling[15] of the zinc salt **20b** derived from the trienyne **20a** with the protected vinyl bromides **30a** (*E*) and **30b** (*Z*) in the presence of palladium catalyst would lead to tetraenynes **31** and **32**, respectively. Subsequent catalytic



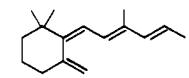
30o, R_1=Br, R_2=H (E)
b, R_1=H, R_2=Br (Z)



31o, R=TBDMS
b, R=H



32o, R=TBDMS
b, R=H



33o, R=CH2OH
b, R=CHO

reduction should afford two (**8a** and **10a**, respectively) of the four *retro*-retinols. This process, reported to be applicable to alkenyl bromides as well as iodides,[15a] was not successful. The zinc salt **20b** also failed to react when **30** was replaced by iodobenzene in order to produce the phenyl derivative **20c**.[15b] However the terminal copper derivative **20d** derived from **20a** reacted with iodobenzene in the presence of catalyst to afford an 83% yield of **20c** but failed to react with **30a**, **30b**, or bromobenzene.[16] The iodoacetylene **20e** also failed to reat with the copper salt derived from the bromide **30a**.[17] The successful route[18] entailed conversion of **20a** to its magnesium salt **20f**, which in the presence of catalytic amounts of tetrakis(triphenylphosphine)palladium reacted with **30a** (benzene; 2 h, room temperature, and 10 h, 60 °C) to give after deprotection [$(n\text{-Bu})_4$NF, THF] pure *E* isomer **31b** in 69% yield. Reaction of the (*Z*)-bromide **30b** in a similar manner afforded the *Z* isomer **32b** contaminated by *E* isomer **31b**, which after separation were obtained in 63% and 6.2% yields, respectively.

(10) The triene portion of the molecule exhibits a ^1H NMR pattern very similar to that of vitamin D_3 and the even more closely related 4,4-dimethyl-vitamin D_3. See: (a) Wing, R. M.; Okamura, W. H.; Rego, A.; Pirio, M. R.; Norman, A. W. *J. Am. Chem. Soc.* **1975**, *97*, 4980. (b) Berman, E.; Friedman, N.; Mazur, Y.; Sheves, M. *Ibid.* **1978**, *100*, 5626.

(11) The observed cis vicinal coupling in **19**, a model for the putative **21**, is $J \sim 13.5$ Hz. The value of 10.8 Hz observed for the hydrocarbon assigned **20a** would appear to also be at variance with that expected for **21**.

(12) Dawson, M. I.; Hobbs, P. D.; Chan, R. L.-S.; Chao, W.-R. *J. Med. Chem.* **1981**, *24*, 1214.

(13) Byers, J. *J. Org. Chem.* **1983**, *48*, 1515.

(14) Pawson, B. A.; Chueng, H.-C.; Gurbaxani, S.; Saucy, G. *J. Am. Chem. Soc.* **1970**, *92*, 336.

(15) (a) King, A. O.; Okukado, N.; Negishi, E. *J. Chem. Soc., Chem. Commun.* **1977**, 683. (b) King, A. O.; Negishi, E.; Villani, F. J., Jr.; Silveira, A., Jr. *J. Org. Chem.* **1978**, *43*, 358.

(16) For related examples, see: (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (b) Ames, D. E.; Bull, D.; Takundwa, C. *Synthesis* **1981**, 364.

(17) (a) Normant, J. F.; Commercon, A.; Villieras, J. *Tetrahedron Lett.* **1975**, 1465. (b) Knight, D. W.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1975**, 641.

(18) Rossi, R.; Carpita, A.; Quirici, M. G. *Tetrahedron* **1981**, *37*, 2617.

Lindlar reduction of **31b** and **32b** afforded after high-pressure LC purification the desired Δ^{10}-*cis-retro*-retinols **8a** (58%) and **10a** (61%), respectively.

The Δ^{10}-*trans* isomers **7a** and **9a** were prepared form **20a** by a chain extension procedure. Reaction of the lithium salt of **20a** with paraformaldehyde[19] afforded the propargyl alcohol **20g** (82%), which was reduced ($LiAlH_4$, THF)[20] to the allylic alcohol **33a** (~quantitative) and then the latter oxidized (MnO_2, petroleum ether) to aldehyde **33b** (81%). Wittig condensation of **33b** with ylide **35** (Scheme I),[21] prepared in situ from **34**,[22] afforded after separation the desired Δ^{10}-*trans* isomers **9a** (20%) and **7a** (30%).

In summary, we have developed a simple route to 18,14-*retro*-retinols through the intermediacy of the novel trienyne **20a**. The unusual formation of **20a** was clearly established as a tandem β-elimination/[1,7]-sigmatropic shift by appropriate labeling studies. The new 18,14-*retro*-retinols reported here (**7a–10a**), besides being promising candidates for evaluation as potential chemotherapeutic and chemoprophylactic agents, provide prototypes for preparing related end group modified analogues such as the acids **7b–10b** as well as **11** for future biological evaluation.

Experimental Section

General. ^1H nuclear magnetic resonance spectra (^1H NMR), 90-MHz Varian EM-390 or 200-MHz Jeol FX-200 spectrometers, were performed with deuteriochloroform ($CDCl_3$) with tetramethylsilane (TMS) as the internal standard; chemical shifts are given in delta (δ) values, and the coupling constants (J) are given in hertz (Hz). ^{13}C nuclear magnetic resonance spectra (^{13}C NMR), 50.4-MHz Jeol FX-200 spectrometer were performed with deuteriochloroform ($CDCl_3$) as the solvent and internal standard; chemical shifts are given in delta (δ) values and coupling constants (J) in hertz (Hz). Infrared spectra (IR), Perkin-Elmer Model 283 grating spectrophotometer, 0.1 mm NaCl plates, were performed in $CDCl_3$ or CCl_4 solutions as indicated. Mass spectra low resolution (MS) and mass spectra exact mass (MS exact mass), m/e (rel intensity), 70 eV, were performed on Varian MAT 711 and Kratos MS-50 and MS-80 mass spectrometers (the National Science Foundation Midwest Center for Mass Spectrometry). Ultraviolet spectra (UV) were performed on a Cary 17 or Cary 219D (Varian) spectrophotometer with 95% ethanol as the solvent unless otherwise indicated.

Air sensitive materials were generally stored under nitrogen in a −80 °C freezer, and reactions involving organometallic materials were performed under an atmosphere of dry nitrogen or argon. Dry ether or THF (tetrahydrofuran) refers to reagent grade material freshly distilled from $LiAlH_4$ under nitrogen. Skellysolve B, hexanes, and lbpe (low-boiling petroleum ether, bp 30–60 °C) were distilled from CaH_2 prior to use. Pyridine was distilled from CaH_2 or KOH and stored over 4-Å molecular sieves. Kugelrohr distillation boiling points (bp) refer to the external air bath temperature.

High-pressure liquid chromatography (high-pressure LC) was performed using a Waters 6000A solvent delivery system equipped with a U6K injector and dual-detector system (M450 variable wavelength UV and R401 refractive index detectors). A Whatman M9 10/50 Partisil (10-μm particle size, 9.4 mm i.d. × 50 cm) column was used except as noted. All chromatographic solvents were distilled prior to use. Solvents and solvent mixtures were vacuum-filtered through a 0.45-μm Millipore filter and vacuum degassed immediately prior to use. Ordinary column chromatography was performed using J. T. Baker silica gel (60–200 mesh). Thin-layer chromatography (TLC) was performed using precoated plates (silica gel 60 F-254 from MCB-Merck).

(6*Z*,8*E*,10*E*,12*E*)- and (6*Z*,8*E*,10*E*,12*Z*)-18,14-*retro*-Retinol (7a and 9a, respectively). Normal butyllithium (0.52 mL, 1.6 M, 0.83 mmol) was added dropwise to a stirred suspension of phosphonium salt **34** (121 mg, 0.3 mmol) in dry THF (2.5 mL) under argon at room temperature. The initial yellow color turned a dark brick red color after 10 min. After 15 min, iodomethane (86 mg, 0.6 mmol) was added dropwise, producing an immediate white precipitate. After stirring for 15 min, *n*-BuLi (0.27 mL, 1.6 M, 0.43 mmol) was added, producing again a deep brick red coloration. After 15 min, the aldehyde **33b** (58 mg, 0.25 mmol) in dry THF (1 mL) was introduced and the mixture was stirred for 1 h. Water was added, and the mixture was extracted with ether (3 × 15 mL). The dried ether layer was evaporated to dryness and then the residue was filtered with ether through a short column of silica gel. Removal of ether left a residue which was subjected to purification by high-pressure LC (Whatman M9 10/50 partisil column, 25% ethyl acetate/Skellysolve B, 4 mL/min flow rate). The pure products were eluted as follows: the less polar 12*Z* isomer A, **9a** (14.6 mg, 20.4%); an unidentified substance (7.2 mg) with a UV λ_{max} 289 nm (similar to tetraenol **20a**); and finally the more polar 12*E* isomer B, **7a** (21.2 mg, 29.6%).

Retinol 7a: ^1H NMR (200 MHz) δ 1.10 ($C_{16,17}$ $2CH_3$, s), 1.82 (C_{20} CH_3, d, $J \sim 1.2$ Hz), 1.92 (C_{19} CH_3, d, $J \sim 1.2$ Hz), 2.22 (C_4 CH_2, m), 2.36 (C_{14} CH_2, t, $J \sim 6.0$ Hz), 3.71 (C_{15} CH_2, t, $J \sim 6.0$ Hz), 4.69 (C_{18} CH_E, d, $J \sim 3$ Hz), 5.10 (C_{18} CH_Z, dt, $J \sim 3$, 1.2 Hz), 5.99 (H_{12}, br d, $J \sim 10.3$ Hz), 6.25 (H_7, d, $J \sim 11.4$ Hz), 6.26 (H_{10}, d, $J \sim 14.5$ Hz), 6.41 (H_{11}, dd, $J \sim 14.5$, 10.3 Hz), 6.49 (H_8, br d, $J \sim 11.4$ Hz); ^{13}C NMR δ 152.7, 146.0, 137.4, 133.9, 129.5, 128.4, 122.8, 116.7, and 113.3 (nine peaks, ten olefinic carbons); 60.5, 43.1, 41.6, 38.5, 37.2, 23.3, 16.6, and 12.7 ($C_{1-4,14+15,19+20}$), 27.7, and 27.6 ($C_{16,17}$); UV (95% EtOH) λ_{max} 333 nm (ϵ 40 500), 318 (ϵ 46 000), 306 (sh, ϵ 34 800); IR (CCl_4) ν_{max} 3360 (s, OH), 2950, 2880, 1550, 1245, 1040, 855, 760 cm^{-1}; MS exact mass, m/e 286.2291 (calcd for $C_{20}H_{30}O$, 286.2298); MS, m/e 287 (1, M + 1), 286 (7, M), 181 (34), 159 (base), 145 (28), 143 (35), 135 (26), 133 (30), 131 (73), 129 (30), 128 (26), 119 (67), 115 (29), 105 (54), 95 (35), 93 (37), 91 (51), 81 (29), 79 (29).

Retinol 9a: ^1H NMR (200 MHz) δ 1.10 ($C_{16,17}$ $2CH_3$, s), 1.85 (C_{20} CH_3, s), 1.93 (C_{19} CH_3, s), 2.23 (C_4 CH_2, m), 2.51 (C_{14} CH_2, t, $J \sim 6$ Hz), 3.73 (C_{15} CH_2, br q, $J \sim 6$ Hz), 4.68 (C_{18} CH_E, d, $J \sim 3$ Hz), 5.09 (C_{18} CH_Z, dt, $J \sim 3$, 1.5 Hz), 6.09 (H_{12}, br d, $J \sim 10.7$ Hz), 6.24 (H_{10}, d, $J \sim 15.0$ Hz), 6.25 (H_7, d, $J \sim 11.5$ Hz), 6.44 (H_{11}, dd, $J \sim 15.0$, 10.7 Hz), 6.48 (H_8, br d, $J \sim 11.5$ Hz); UV (95% EtOH) λ_{max} 333 nm (ϵ 36 000), 318 (ϵ 40 700), 306 (sh, ϵ 31 500); IR (CCl_4) ν_{max} 3380 (OH), 2960, 2880, 1550, 1245, 1040, 860, 760 cm^{-1}; MS exact mass, m/e 286.2303 (calcd for $C_{20}H_{30}O$, 286.2298); MS, m/e 287 (5, M + 1), 286 (26, M) 213 (17), 174 (16), 159 (base), 157 (19), 145 (18), 143 (24), 131 (22), 129 (20), 128 (16), 119 (19), 105 (27), 95 (19), 91 (26), 79 (18).

(6*Z*,8*E*,10*Z*,12*E*)-18,14-*retro*-Retinol (8a). A low-pressure hydrogenation vessel was charged with Lindlar catalyst (100 mg) in 6 mL of dry benzene and then the apparatus was evacuated and hydrogen admitted to a pressure of ~1 atm. The (12*E*)-acetylenic retinol **31b** (14 mg, 0.05 mmol) in 1.5 mL of dry benzene was injected via syringe and then the mixture was stirred at ~1 atm (room temperature) for ~0.5 h. Hydrogenation (~2 mL) slows down but does not stop. The vessel was removed, and the mixture was filtered through a celite–sodium sulfate pad and rinsed with ether (10 mL). After removing solvent under vacuum, the residue was passed through a short silica gel column (ether/lbpe, 1:1). Removal of solvent left a residue which was subjected to high-pressure LC purification (Whatman M9 10/50 partisil column, 20% ethyl acetate/Skellysolve B, 4.0 mL/flow rate) to give *retro*-retinol **8a** (8.2 mg, 58%): ^1H NMR (200 MHz) δ 1.10 ($C_{16,17}$ $2CH_3$, 6 H, s), 1.80 (C_{20} CH_3, 3 H, s), 2.0 (C_{19} CH_3, 3 H, s), 2.21 (C_4 CH_2, 2 H, m), 2.37 (C_{14} CH_2, 2 H, t, $J \sim 6.0$ Hz), 3.72 (C_{15} CH_2, t, $J \sim 6.0$ Hz), 4.69 (C_{18} CH_E, 1 H, d, $J \sim 2.3$ Hz), 5.08 (C_{18} CH_Z, 1 H, br m), 5.86 (H_{12}, 1 H, d, $J \sim 11.9$ Hz), 6.10 (H_{11}, 1 H, dd, $J \sim 11.9$ Hz, $J \sim 11.9$ Hz), 6.19 (H_7, 1 H, d, $J \sim 11.2$ Hz), 6.42 (H_{10}, 1 H, d, $J \sim 11.9$ Hz), 6.50 (H_8, 1 H, d, $J \sim 11.2$ Hz); ^{13}C NMR δ 152.6, 146.2, 135.3, 133.3, 129.5, 125.0, 123.2, 116.3, 113.1 (nine peaks, ten olefinic carbons), 60.6, 43.5, 41.5, 38.4, 37.2, 23.3, 17.2, 16.2 ($C_{1-4,14,15,19,20}$), and 27.6 ($C_{16,17}$); UV (95% EtOH) λ_{max} 333 nm (sh, ϵ 29 000), 319 (ϵ 34 700), 306 (sh, ϵ 29 000), 235 (ϵ 12 800); IR (CCl_4) ν_{max} 3367, 2930, 1545, 1245, 860 cm^{-1}. MS exact mass, m/e 286.2299 (calcd for $C_{20}H_{30}O$, 286.2298); MS, m/e 287 (10, M + 1), 286 (44, M), 271 (44), 213 (44), 185 (41), 175 (26), 173 (40), 171 (29), 159 (94), 157 (48), 145 (46), 143 (55), 133 (43), 131 (48), 129 (35), 121 (31), 119 (56), 117 (30), 109 (29), 107 (38), 105 (86), 95 (base), 93 (55), 91 (79), 83 (31), 81 (89), 79 (53).

(6*Z*,8*E*,10*Z*,12*Z*)-18,14-*retro*-Retinol (10a). The (12*Z*)-acetylenic retinol **32b** (12 mg, 0.042 mmol) was hydrogenated with Lindlar catalyst (50 mg) in benzene (4.5 mL total) in precisely the same manner as described for the *E* isomer **31b** (see preceding section). The high-pressure LC pure alcohol **10a** was obtained in 61% yield (7.2 mg): ^1H NMR (200 MHz) δ 1.10 ($C_{16,17}$ $2CH_3$, 6 H, s), 1.88 (C_{20} CH_3, 3 H, s), 2.01 (C_{19} CH_3, 3 H, s), 2.20 (C_4 CH_2, 2 H, m), 2.49 (C_{14} CH_2, 2 H, t, $J \sim 6.2$ Hz), 3.75 (C_{15} CH_2, 2 H, t, $J \sim 6.2$ Hz), 4.69 (C_{18} CH_E, 1 H, d, $J \sim 1.4$ Hz), 5.08 (C_{18} CH_Z, 1 H, br m), 5.83 (H_{12}, 1 H, d, $J \sim 11.8$ Hz), 6.13 (H_{11}, 1 H, dd, $J \sim 11.8$ Hz, $J \sim 11.6$ Hz), 6.20 (H_7, 1 H, d, $J \sim 11.6$ Hz), 6.48 (H_{10}, 1 H, d, $J \sim 11.8$ Hz), 6.55 (H_8, 1 H, d, $J \sim 11.6$ Hz); ^{13}C NMR δ 153.3, 146.8, 136.8, 133.7, 129.7, 126.8, 123.2, 116.6, and 113.2 (nine peaks, ten olefinic carbons), 60.5, 40.8, 37.3, 36.1, 34.4, 23.2, 22.1, 15.8 ($C_{1-4,14,15,19,20}$), and 27.2 ($C_{16,17}$); UV (95% EtOH) λ_{max} 331 nm (sh, ϵ 32 300), 318 (ϵ 38 700), 305 (sh, ϵ 32 300), 233 (ϵ 17 000); IR (CCl_4) ν_{max} 3370, 2930, 2860, 1550, 1255, 860 cm^{-1}. MS exact mass,

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m/e 286.2298 (calcd for $C_{20}H_{20}O$, 286.2298); MS, m/e 287 (2, M + 1), 286 (14, M), 201 (86), 175 (41), 173 (32), 159 (86), 157 (32), 147 (32), 145 (44), 143 (41), 133 (56), 131 (46), 121 (40), 119 (56), 109 (51), 107 (44), 105 (90), 97 (60), 95 (95), 93 (52), 91 (79), 85 (40), 83 (70), 81 (base), 79 (52).

1-[(1,1′-*Z*,2′-*E*)-3′-Methylpent-2′-en-4′-yn-1′-ylidene]-2-methylene-6,6-dimethylcyclohexane (20a). A mixture of benzoate **19** (1.28 g, 3.98 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.62 g, 4.0 mmol) in acetonitrile (25 mL) was refluxed for 4 h. The reaction was followed by TLC (8:2 lbpe/ether). The mixture was poured into water (25 mL) and lbpe (25 mL), the organic layer was removed, and the aqueous layer was further extracted with lbpe (25 mL). The combined lbpe extracts were washed successively with saturated aqueous solutions of NH_4Cl and $NaHCO_3$ and then water. After the solution was dried (Na_2SO_4), the lbpe was removed, and the residue was then chromatographed (silica gel). Elution with lbpe gave the trienyne **20a** in 80.5% yield (1.03 g as a viscous oil): ^1H NMR δ 1.03 (C_6 $2CH_3$, s), 1.88 ($C_{3'}$ CH_3, d, $J \sim 1.4$ Hz), 2.83 (1 H, $H_{5'}$, s), 4.62 (C_2 CH_E, d, $J \sim 2.7$ Hz), 5.02 (C_2 CH_Z, d of t, $J \sim 2.7$, 1.4 Hz), 6.05 (1 H, $H_{1'}$, d, $J \sim 10.8$ Hz), 6.78 (1 H, $H_{2'}$, d with fine structure, $J \sim 10.8$ Hz); ^{13}C NMR δ 154.74 (s), 145.54 (s), 135.28 (d, $^1J_{C-H} \sim 156$ Hz), 115.48 (d, $^1J_{C-H} \sim 157$ Hz), 88.23 ($C_{4'}$, s), 75.63 ($C_{5'}$, d, $^1J_{C-H} \sim 249$ Hz), 41.53 (t, $^1J_{C-H} \sim 128$ Hz), 38.51 (C_6, s), 37.10 (t, $^1J_{C-H} \sim 128$ Hz), 27.52 (C_6 $2CH_3$, q, $^1J_{C-H} \sim 125$ Hz), 23.19 (t, $^1J_{C-H} \sim 128$ Hz), 17.26 ($C_{3'}$ CH_3, q, $^1J_{C-H} \sim 129$ Hz); IR (CCl_4) ν 3320 (s, C≡C—H), 2080 (w, C≡C), 903 (s, CH_2), other prominent bands, 2935, 2870, 2850, 1450, 1385, 1205, 635 cm^{-1}; UV (95% EtOH) λ_{max} 280 nm (ϵ 21 200); MS exact mass, m/e 200.1556 (calcd for $C_{15}H_{20}$, 200.1566); MS, m/e 200 (41, M), 185 (base), 157 (20), 143 (30), 129 (52), 119 (30), 115 (54), 105 (33), 91 (65), 77 (33).

1-[(1,1′-*Z*,2′-*E*)-3′-Methyl-5′-phenylpent-2′-en-4′-yn-1′-ylidene]-2-methylene-6,6-dimethylcyclohexane (20c). To the trienyne **20a** (50 mg, 0.25 mmol) dissolved in dry THF (0.8 mL) was added *n*-butyllithium (0.2 mL, 1.6 M in hexanes, 0.32 mmol) slowly at 0 °C. After the solution was stirred for 15 min, a suspension of cuprous iodide (42.8 mg, 0.25 mmol) in dry THF (1 mL) was added, and the mixtures were stirred for 20 min at room temperature. The above solution was then added dropwise via cannula to a mixture of tetrakis(triphenylphosphine)palladium (15 mg, 0.0125 mmol) and iodobenzene (51 mg, 0.25 mmol) in dry THF (1 mL) at 0 °C. The mixture was stirred for 2 h at room temperature and then quenched with cold water. Lbpe (20 mL) was added, and the organic layer was separated and passed over a short alumina column. The concentrated residue was chromatographed through silica gel (elution with lbpe) to yield the product **20c** (57 mg, 83%): ^1H NMR δ 1.10 (C_6 $2CH_3$, s), 1.95 ($C_{3'}$ CH_3, d, $J \sim 1.5$ Hz), 4.67 (C_2 CH_E, d, $J \sim 2.8$ Hz), 5.08 (C_2 = CH_Z, d of t, $J \sim 2.8$, 1.5 Hz), 6.15 ($H_{1'}$, d, $J \sim 11.2$ Hz), 6.86 ($H_{2'}$, d of q, $J \sim 11.2$, 1.5 Hz), 7.20–7.52 (5 ArH, m); IR ($CHCl_3$) ν 3170 (w), 2250 (C≡C, w), 1465 (s), 1382 (m), 910 (C=CH_2 bend, s), 725 (s), 650 (s), cm^{-1}; UV (95% EtOH) λ_{max} 327 nm (sh), 311; MS exact mass, m/e 276.1868 (calcd for $C_{21}H_{24}$, 276.1879); MS, m/e 276 (4, M), 261 (6), 203 (12), 178 (10), 155 (6), 154 (34), 153 (13), 152 (12), 144 (17), 130 (10), 129 (base), 128 (6), 122 (13), 115 (9), 109 (8), 105 (31), 102 (7), 95 (9), 93 (6), 91 (14), 81 (5), 79 (5), 77 (22), 76 (5), 75 (7), 74 (5).

1-[(1,1′-*Z*,2′-*E*)-3′-Methyl-5′-iodopent-2′-en-4′-yn-1′-ylidene]-2-methylene-6,6-dimethylcyclohexane (20e). To a solution of trienyne **20a** (55 mg, 0.27 mmol) in dry THF (0.8 mL) was slowly added *n*-butyllithium (0.20 mL, 1.6 M in hexanes, 0.32 mmol) at −78 °C under a nitrogen atmosphere. After further stirring for 15 min at −78 °C, powdered iodine (78 mg, 0.31 mmol) was introduced as a THF solution (1 mL). After the bright yellow mixture was stirred for 1 h at −78 °C, the mixture was worked up in the usual fashion (H_2O quench followed by warming to room temperature; lbpe extraction; back wash with sodium thiosulfate solution, brine, and water; Na_2SO_4 drying). Removal of the solvent followed by chromatography (silica gel, lbpe) afforded 79 mg (89%) of pure iodo compound **20e** as an oil: ^1H NMR δ 1.06 (C_6 $2CH_3$, s), 1.89 ($C_{3'}$ CH_3, d, $J \sim 1.5$ Hz), 4.63 (C_2 CH_E, d, $J \sim 2.8$ Hz), 5.03 (C_2 CH_Z, d of t, $J \sim 2.8$ Hz, 1.4 Hz), 6.02 ($H_{1'}$, d, $J \sim 10.8$ Hz), 6.76 ($H_{2'}$, d with fine structure, $J \sim 10.8$ Hz); UV (95% EtOH) λ_{max} 287 nm (ϵ 22 500); MS exact mass, m/e 326.0511 (calcd for $C_{15}H_{19}I$, 326.0533); MS, m/e 327 (2, M + 1), 326 (4, M), 253 (base), 201 (37), 199 (23), 183 (21), 173 (27), 159 (42), 157 (28), 143 (28), 142 (38), 141 (32), 131 (22), 129 (27), 128 (69), 126 (81), 119 (22), 115 (32), 105 (32), 91 (34).

1-[(1,1′-*Z*,2′-*E*)-6′-Hydroxy-3′-methylhex-2′-en-4′-yn-1′-ylidene]-2-methylene-6,6-dimethylcyclohexane (20g). To a solution of trienyne **20a** (100 mg, 0.5 mmol) in ether (2 mL) was added *n*-butyllithium (0.4 mL, 1.6 M, 0.64 mmol at −10 °C), and the solution was stirred for 20 min under nitrogen. To the trienynyllithium suspension was added THF (1.5 mL) and then dry paraformaldehyde (30 mg, 1.0 mmol) whereupon a mildly exothermic reaction occurred. After the mixture was stirred for 1 h at room temperature, the flask was placed in an oil bath and heated under reflux for 3 h and then stirred overnight at room temperature. The reaction mixture was poured into cold water (20 mL) and then the aqueous layer was reextracted with ether (3 × 10 mL) and dried over sodium sulfate. After removal of the ether, the residue was chromatographed (medium-pressure LC, silica gel; lbpe/ether, 20:80) to afford the desired alcohol **20g** (94 mg, 82%): ^1H NMR δ 1.05 (6 H, C_6 $2CH_3$, s), 1.89 (3 H, $C_{3'}$ CH_3, d, $J \sim 1.5$ Hz), 4.31 (2 H, 2 $H_{6'}$, br s, $w \sim 1.5$ Hz), 4.60 (1 H, C_2 CH_E, d, $J \sim 2.8$ Hz), 5.03 (1 H, C_2 CH_Z, dt, $J \sim 2.8$, 1.5 Hz), 6.04 (1 H, $H_{1'}$, d, $J \sim 11.2$ Hz), 6.76 (1 H, $H_{5'}$, d with fine structure, $J \sim 11.2$ Hz); IR ($CHCl_3$) ν 3615 (OH, w), 3165, 2940, 2870, 2210 (C≡C), 1465, 1390, 1250, 1000, 910 cm^{-1} (C=CH_2 bend, s); UV (95% EtOH) λ_{max} 283 nm (ϵ 23 600); ^{13}C NMR δ 154.5, 145.6, 115.7 ($C_{1,2,3'}$), 134.4, 115.6, 113.8 ($C_{2',1'}$, exo-methylene carbon), 90.1, 85.8 ($C_{5',4'}$), 51.8, 41.5, 38.5, 37.1, 27.5, 23.2, 17.3 (remaining sp^3 seven carbons); MS exact mass; m/e 230.1681 (calcd for $C_{16}H_{22}O$, 230.1672); MS, m/e 230 (1, M), 163 (5), 159 (5), 149 (12), 147 (9), 145 (5), 137 (14), 136 (5), 135 (10), 133 (7), 131 (6), 125 (5), 123 (13), 121 (13), 119 (9), 111 (11), 109 (16), 107 (12), 105 (12), 98 (6), 97 (18), 96 (8), 95 (27), 93 (14), 91 (13), 85 (12), 84 (8), 83 (24), 82 (12), 81 (51), 79 (11), 77 (7), 71 (23), 70 (14), 69 (base), 68 (12), 67 (17), 65 (5), 57 (40), 56 (11), 55 (43), 53 (9).

(7*Z*)-4,4,13,13,13-Pentadeuterio-9-ethynyl-β-ionyl Benzoate (23). The pentadeuterio-β-ionone **29** was converted with lithium acetylide to the corresponding pentadeuterio-9-ethynyl-β-ionol according to the method previously described.[8c] The pentadeuterio-9-ethynyl-β-ionol was then converted to its 7*Z* isomer and then in turn to the *cis*-benzoate **23** according to the method of Reischl.[9] Purification of **23** was achieved by high-pressure LC (Whatman Partisil M-9 10/50, reverse-phase ODS-2, 100% CH_3CN, 2 mL/min flow rate). The deuterium content of the benzoate **23** could not be readily assessed from its ^1H NMR spectrum at 200 MHz in that the signals due to the allylic methylene (2 H_4, δ 1.95) and allylic methyl (C_5 CH_3, $\delta \sim 1.8$) overlap with the C_9 methyl (δ 1.98) and the remaining ring methylene groups (2 H_2 and 2 H_3, δ 1.4–1.9), respectively. However, in the ^{13}C NMR spectrum of **23**, the signals at δ 31.8 and 22.5 assigned to C_4 and C_{13}, respectively, in the undeuterated compound, have nearly completely degenerated into background noise as a result of multiple deuterium substitution at these carbons. Finally, although a complete deuterium content analysis (d_0–d_5 species) of **23** was not achieved by mass spectrometry due to intensity problems at the time of measurement, a ratio of the d_5 to d_4 species could be accurately determined to be 63.79% d_5 to 36.21% d_4. Of significance is that the deuterium content in terms of the d_5 to d_4 ratio of **25** prepared from this same sample of **23** was precisely identical. The exact masses of the molecular ions were as follows: m/e 327.2187 (calcd for $C_{22}H_{21}D_5O_2$, 327.2247); m/e 326.2187 (calcd for $C_{22}H_{22}D_4O_2$, 326.2185).

1-[(1,1′-*Z*,2′-*E*)-3′-Deuteriomethylpent-2′-en-4′-yn-1′-ylidene]-2-dideuteriomethylene-3,3-dideuterio-6,6-dimethylcyclohexane (25). The *cis*-benzoate **23** was reacted with DBU as described in the synthesis of **20a**. The reaction was worked up as before and the product subjected to high-pressure LC purification (Whatman Partisil M-9 10/50, 100% Skellysolve B, 3.0 mL/min flow rate). Mass spectral analysis of **25** analogous to that described for its precursor was carried out. The ratio of d_5 to d_4 species determined for **25** was 63.79% d_5 to 36.21% d_4, precisely identical with that obtained for its precursor **23**. The exact masses of the molecular ions were as follows: m/e 205.1875 (calcd for $C_{15}H_{15}D_5$, 205.1880); m/e 204.1817 (calcd for $C_{15}H_{16}D_4$, 204.1875). In another series of experiments, ^1H NMR was utilized to determine the isotopic composition by integration of the signal attributable to residual protons attached to the methyl carbon at $C_{3'}$ (δ 1.88). No signal was observed for residual protons attached to the allylic ring carbon C_3 (δ 2.20) or the exocyclic methylene carbon at C_2 (δ 4.62 and 5.02). Accordingly, it is assumed that the deuterium content at these positions is >95% for four deuterium atoms and, therefore, integral data are omitted below. As internal standards, the side chain olefinic ($H_{1'}$ and $H_{2'}$) and acetylenic ($H_{5'}$) protons were used. For comparison, the undeuterated hydrocarbon **20a** was analyzed. The integration results were as follows:

	$C_{3'}$ CH_3 or CH_2D	$H_{1'}$	$H_{2'}$	$H_{5'}$
20a	2.96 ± 0.24	0.96 ± 0.08	1.09 ± 0.09	0.95 ± 0.08
25	1.98 ± 0.09	0.92 ± 0.04	1.15 ± 0.07	0.93 ± 0.05

The integration data are the averages of three separate scans using the cut and weigh method; the uncertainties are standard deviations. Finally, ^{13}C NMR data fully support the presence of a single deuterium atom on the $C_{3'}$ methyl group. This and related data are presented in the supplementary material. Thus, the conversion of **23** to **25** occurs with complete retention of five deuterium atoms in support of the proposed pathway.

4,4,13,13,13-Pentadeuterio-β-ionone (29). The pentadeuterio-β-

cyclocitral **27** was prepared according to the procedure of Dawson[12] and converted to the corresponding nitrile **28** according to the procedure of Byers.[13] To a solution of methyllithium (7.2 mmol) in dry THF (1 mL) was added slowly a solution of **28** (259 mg, 1.43 mmol) in dry THF (3.3 mL) at 0 °C. After the solution was stirred at 0 °C for 30 min, a mixture of sulfuric acid (1.2 mL, 3 M) and THF (3 mL) was added slowly. The reaction mixture was warmed to room temperature and stirred for a further 1.25 h. Water (25 mL) and methylene chloride (25 mL) were then added to the reaction mixture, and the organic layer was separated. The aqueous layer was reextracted with methylene chloride (25 mL). The organic extracts were combined, washed with water (2 × 50 mL) and saturated NaCl solution (50 mL), dried ($MgSO_4$), and concentrated under vacuum. The residue was chromatographed (silica gel; 15% ether/Skellysolve B) to give **29** (149 mg, 53%). The ^1H NMR spectra of **27** and **29** are indicative of >95% deuterium incorporation; these spectra are compared with the data for their unlabeled counterparts in the supplementary material.

(6*Z*,8*E*,12*E*)-10,11-Didehydro-18,14-*retro*-retinol (31b). A solution of trienyne **20a** (100 mg, 0.50 mmol) in THF (0.8 mL) was slowly added to a solution of ethylmagnesium bromide (0.22 mL, 2.94 M, 0.64 mmol) in THF (1 mL). After the addition was complete, the mixture was heated at 55 °C for 1.5 h. The Grignard solution was added dropwise via cannula to a mixture of the (*E*)-bromide **30a** (140 mg, 0.50 mmol) and tetrakis(triphenylphosphine)palladium (30 mg, 0.025 mmol) in benzene (2 mL). The mixture was stirred for 2 h at room temperature and then for 10 h at 60 °C. After cooling to room temperature, the mixture was quenched with cold water. The organic layer was separated, and the water layer was further extracted with ether (3 × 5 mL). The combined extracts were washed with brine and water. After the solution was dried ($MgSO_4$) and concentrated (vacuum), the resulting crude residue was passed through a short alumina column (8:2 lbpe/ether) and then concentrated in vacuo to afford 157 mg of the silyl ether **31a**. To the crude silyl ether **31a** was added freshly prepared tetra-*n*-butylammonium fluoride (2 mL, 1 M in THF, 2.0 mmol) at room temperature under nitrogen. The solution was stirred for 4 h and then poured into 10 mL of brine and extracted with ether. The separated aqueous layer was reextracted with ether (10 mL) and then the combined ether extracts were washed successively with 15 mL each of 1 M HCl, saturated aqueous $NaHCO_3$, and water. Upon drying ($MgSO_4$), filtering, and concentrating, the crude product was subjected to silica gel column chromatography (70:30 lbpe/ether). Combination and concentration of appropriate fractions afforded 75 mg (69%) of pure alcohol **31b**. The corresponding *Z* isomer **32b** was not detected as a byproduct: ^1H NMR δ 1.06 ($C_{16,17}$ $2CH_3$, s), 1.88 (C_{20} CH_3, d, $J \sim 1.5$ Hz), 1.90 (C_{19} CH_3, d, $J \sim 1.5$ Hz), 2.31 (2 H_{14}, t, $J \sim 6.5$ Hz), 3.66 (2 H_{15}, t, $J \sim 6.5$ Hz), 4.67 (H_{18E}, d, $J \sim 2.9$ Hz), 5.07 (H_{18Z}, dt, $J \sim 2.9$, 1.5 Hz), 5.47 (H_{12}, br q, $J \sim 1.5$ Hz), 6.10 (H_7, d, $J \sim 11.3$ Hz), 6.73 (H_8, dq, $J \sim 11.3$, 1.5 Hz); ^{13}C NMR δ 153.7, 146.8, 145.6, 116.9 ($C_{5,6,9,13}$), 133.2, 115.9, 113.7, 107.8 ($C_{7,8,12,18}$), 97.3, 86.3 ($C_{10,11}$), 60.4 (C_{15}), 41.7, 41.5, 37.1 ($C_{2,3,4}$), 38.4 (C_1), 27.6 ($C_{16,17}$), 23.2, 19.2, and 17.6 ($C_{14,19,20}$); IR (neat) ν_{max} 3360 (s, br, OH), 2180 (w, C≡C), 900 (s, C=CH_2), other prominent bands at 2940, 1632, 1613, 1440, 1385, 1290, 1045 cm^{-1}; UV (95% EtOH), λ_{max} 311 nm (ϵ 27 600), 327 (sh, ϵ 22 500); MS exact mass, *m/e* 284.2137 (calcd for $C_{20}H_{28}O$, 284.2141); MS, *m/e* 285 (18, M + 1), 284 (72, M), 269 (base), 253 (21), 239 (8), 223 (10), 215 (10), 209 (9), 197 (20), 183 (28), 171 (13), 169 (24), 159 (27), 143 (23), 137 (28), 131 (23), 119 (37), 105 (40), 91 (52), 77 (29), 69 (42), 55 (45).

(6*Z*,8*E*,12*Z*)-10,11-Didehydro-18,14-*retro*-retinol (32b). The trienyne **20a** was coupled with the (*Z*)-bromide **30b** in precisely the same manner as described for the *E* isomer **30a** (see preceding section). The chromatographically pure alcohol **32b** was obtained in 63% yield from a silica gel column with lbpe/ether (60:40). Further elution with ether gave the *E* isomer **31b** in 6.2% yield: ^1H NMR δ 1.05 ($C_{16,17}$ $2CH_3$, s), 1.77 (C_{20} CH_3, d, $J \sim 1.5$ Hz), 1.87 (C_{19} CH_3, d, $J \sim 1.5$ Hz), 2.50 (2 H_{14}, t, $J \sim 6.3$ Hz), 3.67 (2 H_{15}, t, $J \sim 6.3$ Hz), 4.62 (H_{18E}, d, $J \sim 3.0$ Hz), 5.02 (H_{18Z}, dt, $J \sim 3.0$, 1.5 Hz), 5.47 (H_{12}, br s, $W \sim 4.5$ Hz), 6.03 (H_7, d, $J \sim 11.3$ Hz), 6.63 (H_8, dq, $J \sim 11.3$, 1.5 Hz); ^{13}C NMR δ 153.7, 147.2, 145.6, 116.9 ($C_{5,6,9,13}$), 133.2, 115.9, 113.7, and 108.1 ($C_{7,8,12,18}$), 96.8, 86.3 ($C_{10,11}$), 60.9 (C_{15}), 41.5, 38.1, 37.2 ($C_{2,3,4}$), 38.5 (C_1), 27.6 ($C_{16,17}$), 23.2, 23.0, 17.6 ($C_{14,19,20}$); IR (neat) ν_{max} 3360 (s, br, OH), 2180 (w, C≡C), 896 (s, C=CH_2), other prominent bands at 2930, 2870, 1630, 1440, 1385, 1040 cm^{-1}; UV (95% EtOH) λ_{max} 311 nm (ϵ 34 800), 326 (sh, ϵ 28 500); MS exact mass, *m/e* 284.2141 (calcd for $C_{20}H_{28}O$, 284.2141); MS, *m/e* 285 (10, M + 1), 284 (41, M), 269 (93), 253 (base), 239 (14), 223 (16), 213 (21), 209 (15), 197 (38), 183 (43), 173 (16), 169 (39), 159 (73), 155 (39), 143 (43), 133 (57), 119 (69), 105 (78), 91 (94), 77 (57), 69 (73), 55 (90).

1-[(1,1′-*Z*,2′-*E*,4′-*E*)-6′-Hydroxy-3′-methylhexa-2′,4′-dien-1′-ylidene]-2-methylene-6,6-dimethylcyclohexane (33a). A solution of $LiAlH_4$ (40 mg, 1.1 mmol) in dry THF (2 mL) was cooled to 0 °C while propargyl alcohol **20g** (50 mg, 0.2 mmol) in THF (1 mL) was added dropwise. The mixture was warmed to room temperature and then was heated under reflux for 3 h. After cautious addition of water, the reaction product was isolated by extraction with ether. The dried ether solution was concentrated and then the resulting residue was passed through a short silica gel column (50:50 lbpe/ether) to afford the tetraenol **33a** in essentially quantitative yield: ^1H NMR δ 1.10 (6H, C_6 $2CH_3$, s), 1.83 (3 H, $C_{3'}$ CH_3, d, $J \sim 1.4$ Hz), 4.16 (2H, 2 $H_{6'}$, br d, $J \sim 6.2$ Hz), 4.64 (1 H, C_2=CH_E, d, $J \sim 2.7$ Hz), 5.08 (1 H, C_2=CH_Z, dt, $J \sim 2.7$, 1.4 Hz), 5.81 (1 H, $H_{5'}$, dt, $J \sim 15.6$, 6.2 Hz), 6.23 (1 H, $H_{1'}$, d, $J \sim 10.8$ Hz), 6.35 (1 H, $H_{4'}$, d, $J \sim 15.6$ Hz), 6.57 (1 H, $H_{2'}$, d with fine structure, $J \sim 10.8$ Hz); IR (neat) ν_{max} 3370 and 3320 (OH), 3380, 2940, 2870, 1635, 1620, 1460, 1100, 970, 900 (C=CH_2 bend , m) cm^{-1}; UV (95% EtOH) λ_{max} 287 nm (ϵ 27 200); MS exact mass; *m/e* 232.1836 (calcd for $C_{16}H_{24}O$, 232.1828); MS, *m/e* 233 (2, M + 1), 214 (2, M − H_2O), 217 (21), 201 (36), 199 (38), 187 (21), 159 (25), 157 (27), 147 (23), 145 (40), 143 (50), 141 (28), 133 (56), 131 (42), 129 (56), 128 (50), 119 (41), 117 (39), 116 (21), 115 (80), 109 (21), 107 (26), 105 (78), 95 (26), 93 (32), 91 (base), 81 (30), 79 (48), 77 (61), 69 (52), 67 (35), 57 (30), 55 (76).

1-[(1,1′-*Z*,2′-*E*,4′-*E*)-6-Formyl-3′-methylhexa-2′,4′-dien-1′-ylidene]-2-methylene-6,6-dimethylcyclohexane (33b). Powdered MnO_2 (500 mg, 5.7 mmol) was added to a stirred solution of tetraenol **33a** (50 mg, 0.2 mmol) in 3 mL of lbpe at 0 °C. After the mixture was stirred for 3 h under nitrogen at this temperature, the MnO_2 was removed by vacuum filtration through celite with lbpe. The lbpe was evaporated on the rotary evaporator and residue was subjected to high-pressure LC (partisil, 3% ethyl acetate/Skellysolve B, 4 mL/min flow rate) to give the pure aldehyde **33b** (40 mg, 81% yield): ^1H NMR δ 1.10 (6 H, C_6 $2CH_3$, s), 1.93 (3 H, $C_{3'}$ CH_3, d, $J \sim 1.9$ Hz), 4.72 (1 H, C_2 CH_E, d, $J \sim 2.6$ Hz), 5.17 (1 H, C_2 CH_Z, dt, $J \sim 2.6$, 1.4 Hz), 6.20 (1 H, $H_{5'}$, dd, $J \sim 7.5$, 15.0 Hz), 6.33 (1 H, $H_{1'}$, d, $J \sim 11.3$ Hz), 6.97 (1 H, $H_{2'}$, br d, $J \sim 11.3$ Hz), 7.20 (1 H, $H_{4'}$, d, $J \sim 15.0$ Hz), 9.63 (CHO, d, $J \sim 7.5$ Hz); UV (95% EtOH) λ_{max} 342 nm (ϵ 30 000); IR (CCl_4) ν_{max} 2930 (s), 1685 (vs, CHO), 1595 (s, C=C), 1125, 970, 905 cm^{-1} (C=CH_2 bend, m); MS exact mass, *m/e* 230.1674 (calcd for $C_{16}H_{22}O$, 230.1672); MS, *m/e* 231 (7, M + 1), 230 (42, M), 215 (58), 201 (40), 159 (85), 147 (25), 146 (25), 145 (base), 143 (33), 141 (27), 133 (80), 131 (80), 129 (43), 128 (41), 121 (26), 119 (48), 117 (49), 115 (54), 107 (35), 105 (77), 95 (40), 93 (36), 91 (base), 81 (34), 79 (48), 77 (69), 69 (42), 67 (28), 65 (33), 55 (60), 52 (41) 50 (35).

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Supplementary Material Available: ^1H NMR data for deuterium-labeled derivatives (3 pages). Ordering information is given on any current masthead page.