$P(CH_3NCH_2CH_2)_3N$ as a Dehydrobromination Reagent: Synthesis of Vitamin A Derivatives Revisited

Andrzej E. Wróblewski† and John G. Verkade*

Department of Chemistry, Iowa State University, Ames, Iowa 50011-3111

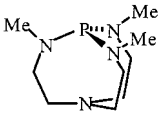
jverkade@iastate.edu

Received June 25, 2001

Although $P(CH_3NCH_2CH_2)_3N$ (**1**) was found to be less effective than 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in the removal of hydrogen bromide from vitamin A intermediates 13-*cis*-10-bromo-9,10-dihydroretinyl acetates (**6**) and 14-bromo-9,14-dihydroretinyl acetate (**11**) when the reaction was carried out in refluxing benzene, in acetonitrile at room temperature it was superior to DBN and DBU. A ^{31}P NMR study of this reaction suggests that the carbanion generated from acetonitrile-d_3 in the presence of **1** is the basic species that initiates the elimination step. Diastereoselectivity of the nucleophilic addition of (*Z*)-HC≡C(CH_3)=$CHCH_2OH$ to the carbonyl group of (*E*)-2-methyl-4-(2′,6′,6′-trimethyl-1′-cyclohexen-1′-yl)-3-butenal (**2**) was only moderate (20%), and (9*R**,10*S**)-13-*cis*-11,12-didehydro-9,10-dihydro-10-hydroxyretinol (**3b**) predominated. The $LiAlH_4$ reduction of the C≡C bond in the diastereoisomeric diols **3** afforded 13-*cis*-9,10-dihydro-10-hydroxyretinols **4a** and **4b** as major products together with 11-*cis*-13-*cis*-isomers and the deoxygenated compound (3*EZ*,5*EZ*,8*E*)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3,5,8-nonatetraene (**9**). Reaction of 15-acetates of the pure diastereoisomeric allylic alcohols **4a** and **4b** with PBr_3 occurred with significant but not identical retention of configuration, and with concomitant formation of the rearranged bromide **11**.

Introduction

The synthesis of compound **1** in this laboratory[1] and the discovery of its very strongly basic nature[2] prompted us to evaluate the reactivity of **1** in the elimination of H−X species (X = Cl, Br, I, OSO_3R, etc) from organic substrates.[3,4] As a part of this project we focused our attention on the application of this approach to the synthesis of *all*-trans Vitamin A and its various isomers by introducing the fifth C=C bond into the 9,10 position of the retinol skeleton.[5] Although the synthesis of *all*-trans Vitamin A has been successfully accomplished using DBN,[6] an improvement of this synthesis by the use of **1** could be envisioned due to higher basicity of the latter compound.[2] Here we report on such an improvement and propose a mechanism for the mode of action of **1**.

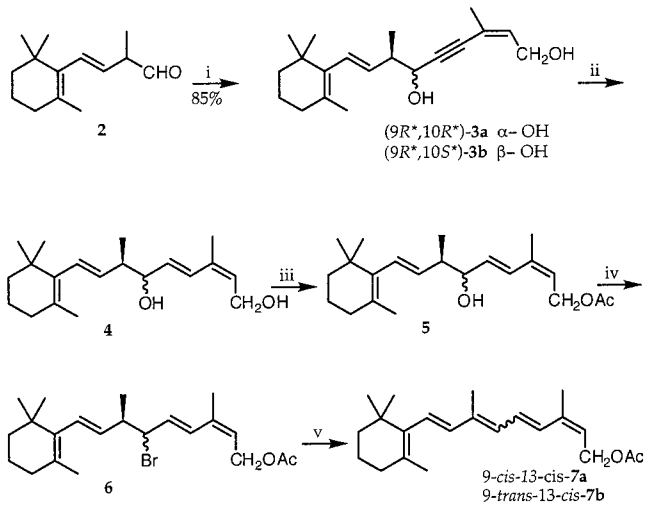


1

Results and Discussion

Synthesis. The major steps in the synthesis of vitamin A via the elimination of hydrogen bromide are depicted in Scheme 1 and parallel those described in the literature.[6] However, each step of the sequence was optimized, and the major byproducts of all the transformations were separated and identified. The required aldehyde **2** was obtained from β-ionone by introducing a carbon atom from trimethylsulfonium methyl sulfate under phase-transfer catalysis (PTC) conditions,[7] followed by transformation of the intermediate epoxide into **2** according to a literature procedure[8] in 98% overall yield. Attempts

Scheme 1[a]



[a] Reagents: (i) HC≡C(CH_3)C=$CHCH_2OH$, 2BuLi, THF, then water; (ii) $LiAlH_4$ in ether; (iii) Ac_2O in 2,4,6-collidine; (iv) PBr_3 in ether, −20° to rt; (v) **1**, DBN, or DBU.

* To whom correspondence should be addressed. Fax: 515-294-0105.
† On leave of absence from the Institute of Chemistry, Medical University, Lódz, Poland.

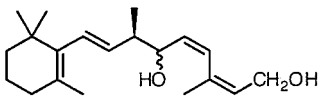
(1) Schmidt, H.; Lensink, C.; Xi, S. K.; Verkade, J. G. *Z. Anorg. Allg. Chem.* **1989**, *578*, 75.
(2) (a) Verkade, J. G. *Acc. Chem. Res.* **1993**, *26*, 483. (b) Kisanga, P.; Verkade, J. G.; Schwesinger, R. *J. Org. Chem.* **2000**, *65*, 5431.
(3) Arumugan, S.; Verkade, J. G. *J. Org. Chem.* **1997**, *62*, 4827.
(4) Liu, X.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 4840.
(5) Verkade, J. G.; Mohan, T.; Wroblewski, A. E. U.S. Pat. 5698737; *Chem. Abstr.* **1998**, *128*, 75536.
(6) Oediger, H.; Kabbe, H.-J.; Möller, F.; Eiter, K. *Chem. Ber.* **1966**, *99*, 2012. Oediger, H.; Eiter, K. Ger. Pat. 1157606; *Chem. Abstr.* **1964**, *60*, 5569a.

10.1021/jo010648+ CCC: $22.00
Published on Web 12/21/2001

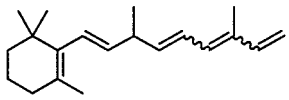
to synthesize pure **2** from β-ionone via the Darzens reaction[9] were unsuccessful, leading to mixtures containing **2** contaminated with its α,β isomer and other impurities which are possibly of a polymeric nature.

The synthesis of the retinol skeleton through a $C_{14} + C_6$ coupling has usually been accomplished by the addition of dimagnesium salts of 2-methyl-2-penten-4-yl-1-ols to the aldehyde **2** or preferentially to its α,β isomer.[6,10] Although the reaction is sluggish with **2**, it could be accelerated using lithium salts.[11] Thus, the dilithium salt of *cis*-2-methyl-2-penten-4-yl-1-ol (obtained by the addition of 2 equiv of butyllithium to a tetrahydrofuran (THF) solution of the alcohol) was treated with **2** to give a 2:3 mixture of the 13-*cis*-11,12-didehydro-9,10-dihydro-10-hydroxyretinols (9*R**,10*R**)-**3a** and (9*R**,10*S**)-**3b**, respectively, in 85% yield of crude product, which was found to be sufficiently pure, however, for the subsequent transformation. The ratio of diastereoisomers, established from ^{1}H NMR spectral data, was independent of the reaction conditions, as well as of the cation (i.e., Li^+ or Mg^{2+}).

The reaction of acetylenic bonds with $LiAlH_4$ usually leads to pure trans products, while the exclusive formation of cis isomers is expected when hydrogenation is performed over deactivated palladium catalysts.[12] In our hands, the $LiAlH_4$ reduction of **3** afforded a mixture of the required diastereoisomeric 11,12-trans diols **4** and 11,12-cis diols **8** in a ratio of approximately 4:1 in overall 65% yield. This mixture was easily separated by silica gel chromatography. In addition, a nonpolar fraction was also obtained (5%), which was later identified as a liquid mixture of four isomeric hydrocarbons, **9**. Partial separation of the diastereoisomeric diols **4** was achieved by column chromatography after which the more polar diol **4b** (eluting second from the column) crystallized. The ratio of (9*R**,10*R**)-**4a** to (9*R**,10*S**)-**4b** in the crude reduction product reflected a 2:3 ratio of diastereoisomeric compounds **3**. For NMR characterization, the diastereoisomeric *cis*-diols **8** were separated on silica gel after several chromatographic runs.

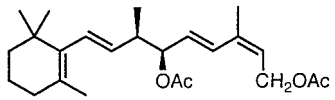


8



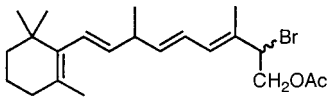
9

Selective protection of the primary hydroxy groups in **4a** and **4b** as the corresponding acetates was achieved with acceptable selectivity using an excess of acetic anhydride in 2,4,6-collidine.[13] Quantitative conversion of pure **4b** into a 9:1 mixture of monoacetate (9*R**,10*S**)-**5b** and diacetate **10b** was accomplished when 2 equiv of the anhydride and an excess of the base were employed. Using chloroform or methylene chloride as a solvent and pyridine as a base led only to incomplete conversion of the starting diols **4** and excessive formation of diacetates. An even more complex mixture was formed when acetyl chloride was used as an acetylation reagent.

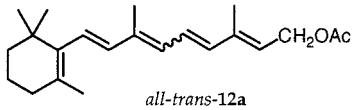


10b

Synthesis of diastereoisomeric bromides **6** from the secondary allylic alcohols **5** was most satisfactorily accomplished with phosphorus tribromide.[6] Other brominating reagents, namely, PPh_3/NBS[14] and PPh_3/CBr_4,[15] led only to traces of **6** in complex reaction mixtures. Transformation of the hydroxy group to a bromide with PBr_3 also provided interesting regio- and stereochemical results. Independent of the ratio of (9*R**,10*R**)-**5a** to (9*R**,10*S**)-**5b**, approximately 10−30% of the rearranged bromide **11** was formed. Furthermore, when pure **5a** was treated with PBr_3, nearly complete conversion to a mixture of (9*R**,10*R**)-**6a** and (9*R**,10*S**)-**6b** (3:1) containing ca. 10% of **11** was observed. Under the same conditions, pure **5b** gave a mixture of **6a** and **6b** (3:7) and 23% of **11**.



11



all-trans-**12a**
9-*cis*-**12b**

Initially we studied the conversion of mixtures of **6** and **11** into the isomeric retinyl acetates 9-*cis*-13-*cis*-**7a** and 9-*trans*-13-*cis*-**7b** in refluxing benzene (Table 1).[6] It was found that in the presence of equimolar amounts of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) or 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU), mixtures of diastereoisomers **6a** and **6b** were almost quantitatively transformed after 15 min into mixtures of **7a** and **7b**, while the rearranged bromide **11** underwent elimination only partially. The same transformation performed with DBN in refluxing toluene left only a trace of unreacted **11** after 15 min.

Progress of the elimination of hydrogen bromide from a mixture of **6a**, **6b**, and **11** with **1**, DBN, or DBU in acetonitrile at room temperature was monitored by ^{1}H NMR spectroscopy. It was found that **1** is more reactive than DBN or DBU, leading to disappearance of the signals of **6** and **11** in 30 min, while complete conversion with DBN was observed only after 1 h. Using DBU under these conditions, traces of unreacted **6** and **11** still remained after 1 h.

Purification of the products of the dehydrohalogenation reactions included a water workup and filtration through

(7) Bosansky, M.; Goemoery, J.; Kacina, R.; Styrakova, L. Czech Pat. 254032; *Chem. Abstr.* **1989**, *111*, P57525. Babler, H. J.; Schlidt, S. A. *Tetrahedron Lett.* **1992**, *33*, 7697.
(8) Rosenberger, M.; Jackson, W.; Saucy, G. *Helv. Chim. Acta* **1980**, *63*, 1665.
(9) Ramamurthy, V.; Tustin, G.; Yau, C. C.; Liu, R. S. H. *Tetrahedron* **1975**, *31*, 193.
(10) Isler, O.; Huber, W.; Ronco, A.; Kofler, M. *Helv. Chim. Acta* **1947**, *30*, 1911.
(11) Takahashi, J.; Oritani, T.; Yamashita, K. *Agric. Biol. Chem.* **1989**, *53*, 2711.
(12) Hudlicky, M. *Reductions in Organic Chemistry*; Ellis Horwood Ltd.: Chichester, England, 1984. Seyden-Penne, J. *Reductions by the Alumino- and Borohydrides in Organic Synthesis*; Wiley-VCH: New York, 1997.
(13) Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 3791.
(14) Bose, A. K.; Lal, B. *Tetrahedron Lett.* **1973**, 3937.
(15) Calzada, J. G.; Hooz, J. *Org. Synth.* **1974**, *54*, 63.

Table 1. Yields and Stereochemical Results of HBr Elimination from the Bromides 6 and 11

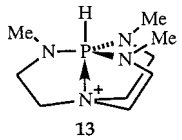
starting materials					products		
6a:**6b**[a]	**11**:(**6a** + **6b**)[b]	reagent	solvent	time, min	**7a**:**7b**[c]	**12**:**7**[d]	yield, %
75:25	9:91	DBN	benzene	15	66:34	15:85	*e*
40:60	30:70	DBU	benzene	15	40:60	20:80	*e*
31:69	23:77	DBN	benzene	30	36:64	34:66	61[f]
38:62	10:90	DBN	toluene	15	42:58	23:77	50[f]
31:69	23:77	DBN	acetonitrile	60	36:64	24:76	61[f]
31:60	23:77	DBU	acetonitrile	60	37:63	30:70	63[f]
35:65	20:80	**1**	acetonitrile	60	37:63	18:82	49[f]
31:69	23:77	**1**	acetonitrile	60	36:64	22:78	52[f]

[a] Based on relative intensities of H12 signals. [b] Based on integrals of H9 signals. [c] Based on integrals of H_3C18 signals. [d] Based on integrals of H14 signals. [e] Reaction proceeded to more than 95% completion. [f] For a mixture containing only **7a**, **7b**, and **12**.

a pad of deactivated alumina to give mixtures of isomeric retinyl acetates consisting of **7a** and **7b** as major products (see Table 1). Elimination of hydrogen bromide from **6a** and **6b** leads exclusively to the 13-*cis*-isomers **7a** and **7b**. On the other hand, from the rearranged bromide **11**, formation of *all-trans*-retinyl acetate (**12a**) and its 9-*cis*-isomer **12b** was found as expected rather than the more sterically strained 13-*cis*-isomers **7a** and **7b**. No improvement in the yield of vitamin A isomers was noticed when the dehydrobromination of the bromides **6** and **11** with **1** in acetonitrile was carried out at room temperature over 30 min. Comparison of the ^{1}H NMR spectra of the crude products from the DBU, DBN, and **1**-induced dehydrobrominations suggests that **1** in acetonitrile may induce some decomposition of highly conjugated products. When the mixture of the bromides **6** and **11** was treated with **1** in acetonitrile at 0 °C for 2 1/4 h, incomplete conversion was observed.

Structural, Stereochemical, and Mechanistic Considerations. Initially, we were disappointed with the lower dehydrobromination conversion rates using **1** compared with DBN or DBU in refluxing benzene. In hindsight, this observation can be rationalized on the greater steric bulk around the basic phosphorus center in **1** compared with DBN and DBU, especially as positive charge is built up on **1** as it becomes protonated and transannulated to the trigonal bipyramidal cation **13**. In acetonitrile, however, the superiority of **1** over DBN and DBU in effecting HBr elimination from **6** and **11** at room temperature stems from

the greater basicity of **1** (pK_a of **13** ≅ 33 in acetonitrile[2b]) compared with the basicities of DBU (pK_a ≅ 23.9)[16,17] and DBN (pK_a ≅ 23.4).[17] Although the pK_a of **13** is the same as a reported value of pK_{auto} = 33 of acetonitrile,[18] evidence has been put forth for a value of 44 for this autoprotolysis constant.[16] In any case we have found that nonionic bases such as **1** are capable of deprotonating acetonitrile to $^-CH_2CN$ with sufficient efficiency to allow it to act as a sterically small but potent base in affecting the dehydrohalogenation of primary, secondary and tertiary alkyl halides[19] and as a nucleophile in the synthesis of 3-hydroxy nitriles from its reactions with aldehydes and ketones.[20]



13

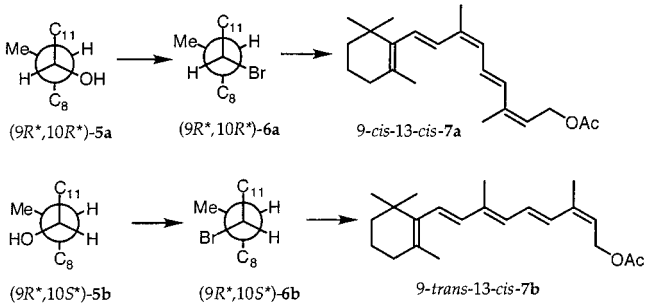
In the present work, the generation of $^-CH_2CN$ is supported by a ^{31}P NMR study of the elimination of hydrogen bromide from **6** and **11** with **1** in acetonitrile-d_3. Before addition of the bromides, the ^{31}P NMR spectrum of an acetonitrile-d_3 solution of **1** showed signals of **1** (singlet at 120.8 ppm) and of minute quantities of its deuterated cation (three lines of equal intensity at −10.0 ppm).[21] When the dehydrobromination[21] reaction was complete, a small excess of **1** was still present, while more than 80% of **1** was converted to its deuterated form and less than 20% was found as the protonated species.

Evidence for the 9-*cis*-configuration for **7a** and 9-*trans* for **7b** is provided by their ^{1}H NMR spectra. Although no differences between analogous coupling constants among the H7−H8 and H10−H11−H12 sets of protons in both isomers were found, it was noticed that H8 in **7a** is deshielded by 0.5 ppm relative to H8 in **7b**. The same phenomenon was found when the chemical shifts of H8 in *all-trans* and 13-*cis*-retinal and methyl retinoate were compared with the 9-*cis*- and 9-*cis*-13-*cis*-isomers, respectively.[22] The presence of *all-trans*-**12a** and possibly also 9-*cis*-**12b** was concluded from the observation of H14 triplets at δ 5.58 ppm[22] and a long-range correlation of this proton to H_3C2 at 1.86 ppm[22] in its ^{1}H−^{1}H COSY spectrum. Further evidence that **12a** and **12b** had been formed was the appearance of all of their ^{13}C signals[23] (except for some in the aliphatic region owing to overlaps) in the ^{13}C NMR spectra of the dehydrohalogenation reaction mixtures.

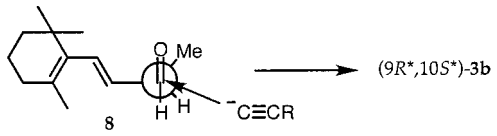
Elimination of hydrogen bromide with strong bases usually proceeds via an E2 mechanism with an anti orientation of departing substituents[24] (Scheme 2). Comparison of the ratios of starting bromides **6a** and **6b** with the ratios of the products **7a** and **7b** (Table 1) as well as the independence of the isomeric ratio of **7a** and **7b** from polarity changes of the solvents provides support for the E2 mechanism in our case. Thus, (9*R**,10*R**)-**6a** is expected to give 9-*cis*-13-*cis*-**7a**, while 9-*trans*-13-*cis*-**7b** should be formed from (9*R**,10*S**)-**6b** (Scheme 2). Moreover, the ratio of the bromides **6** and **11** are in reasonable correlation with the ratios of the 13-*cis*-**7** to 13-*trans*-**12**

(16) Kaljurand, I.; Rodima, T.; Leito, I.; Koppel, I. A.; Schwesinger, R. *J. Org. Chem.* **2000**, *65*, 6202, and references therein.
(17) Leffek, K.; Pruszynski, P.; Thanapaalasingham, K. *Can. J. Chem.* **1989**, *67*, 590.
(18) Kolthoff, I. M.; Chantooni, M. K., Jr. *J. Phys. Chem.* **1968**, *72*, 2270.
(19) Mohan, T.; Arumugam, S.; Wang, T.; Jacobson, R. A.; Verkade, J. G. *Heteroatom Chem.* **1996**, *7*, 455.
(20) Kisanga, P. B.; McLeod, D.; D'Sa, B. A.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 3090.
(21) D'Sa, B. A.; Kisanga, P.; Verkade, J. G. *J. Org. Chem.* **1998**, *63*, 3961.
(22) Liu, R. S. H.; Asato, A. E. *Tetrahedron* **1984**, *40*, 1931.
(23) Englert, G. *Helv. Chim. Acta* **1975**, *58*, 2367.
(24) March, J. *Advanced Organic Chemistry*; John Wiley & Sons: New York, 1992; pp 982−1050.

Scheme 2



Scheme 3

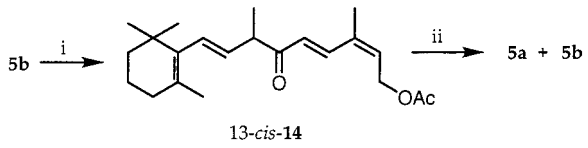


isomers, supporting the conclusion that **11** is the predominant, if not the sole, source of the latter compounds.

Transformation of the OH in **5a** and **5b** to a bromide in **6a** and **6b** (Scheme 2) undoubtedly involves an ionic intermediate,[25] because the formation of significant amounts of the rearranged bromide **11** was observed and because partial epimerization at C10 in **5a** and **5b** occurred. The close resemblance of the ^{1}H NMR patterns of **5a** and **6a**, as well as those of **5b** and **6b**, suggests that **6a** is the major product of bromination of pure **5a**, while **6b** is predominantly formed from pure **5b**. Thus, in our case, phosphorus tribromide converts the secondary allylic alcohols **5** into bromides **6** with predominant retention of configuration. To support this conclusion, the relative configurations in the diastereoisomeric alcohols **3a** and **3b** and/or **4a** and **4b** were established. At first we resorted to considerations of asymmetric induction in the addition of (*Z*)-HC≡C(CH$_3$)=CHCH$_2$OH to the carbonyl group of **2**. When nucleophilic attack occurs from the less hindered face in the conformation predicted from the Felkin−Anh model,[26] wherein the 2-(2,6,6-trimethylcyclohexene-1-yl)ethenyl group is viewed as the L substituent, then (9*R**,10*S**)-**3b** predominates (Scheme 3). Although the diastereoisomeric excess (de) in this addition is only moderate (20%), in reactions of closely structurally related 2-substituted propanals with lithium or magnesium salts of diverse acetylenes,[27−32] de's value never exceeded 33%, and the configuration of the major product was found to be in full agreement with that predicted from the Felkin−Anh model.[26]

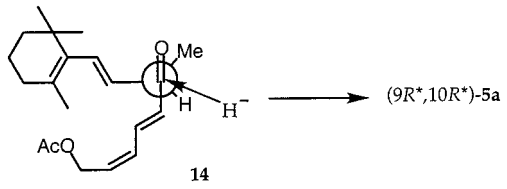
An additional argument for the (9*R**,10*S**) configuration in **3b**, as well as, in **4b** and **5b** was gained from the stereochemistry of the reduction of ketone **14** prepared by PCC oxidation[33] of the acetate **5b** (Scheme 4). Thus

Scheme 4[a]



[a] Reagents: (i) PCC; (ii) NaBH$_4$, MeOH/CH$_2$Cl$_2$, 1:1, 0°.

Scheme 5



when unstable **14** was reduced with NaBH$_4$ at 0 °C,[34] a 70:30 mixture of (9*R**,10*R**)-**5a** and (9*R**,10*S**)-**5b** was formed. Reports of precedents in the literature rationalize the stereochemistry of hydride reductions of structurally related α-methyl-*β*,*γ*-unsaturated ketones by invoking the Felkin−Anh model[26] in conjunction with $\pi^*_{C=O}$–$\pi^*_{C=C}$ attractive interactions that stabilize the transition state of the nucleophilic addition.[35−37] Application of this model (Scheme 5) to the reduction of **14** rationalizes the formation of (9*R**,10*R**)-**5a** as a major product. It has been reported that the ketone 13-*trans*-**14** can be reduced with NaBH$_4$[38] and with AlH(OtBu)$_3$,[39] but diastereoselectivity of the reactions was not disclosed.

The 11,12-*cis*-configuration in diastereoisomeric **8a** and **8b** was deduced from the lower values of H11−H12 coupling constants (11.2 Hz) compared with those in the respective 11,12-*trans*-isomers **4a** and **4b** (15.6 Hz). The structures of the isomeric hydrocarbons **9** in the mixture were deduced from ^{1}H and ^{13}C NMR spectral data, including ^{1}H−^{1}H COSY experiments. Thus, the ^{13}C NMR spectrum clearly shows four signals for the terminal methylene carbons in the 111.8−114.5 ppm region, and it lacks signals for carbons attached to oxygen. Two-dimensional ^{1}H−^{1}H correlation allowed us to assign ^{1}H resonances to two major constituents of the mixture **9a** and **9b** having the 10,11-*trans*-configuration ($J_{H10-H11}$ = 15.0 and 15.4 Hz, respectively). The cis arrangement of the substituents around the C12−C13 bond in **9a** can be assigned on the basis of the 0.5 ppm downfield shift of H14 relative to that in **9b**. This conclusion is expected from the structural resemblance of the C9−C15 and C13−C7 subunits in the pairs of compounds **9a** and **9b**, and **7a** and **7b**, respectively. The formulations of **9** were supported by MS data. The CI-MS spectrum showed a prominent peak for the molecular ion and two others resulting from scissions at the two allylic positions.

The mechanism of formation of the isomeric hydrocarbons **9** has not been investigated, but neither **8** nor **4** afforded detectable amounts of **9** when treated with

(25) March, J. *Advanced Organic Chemistry*; John Wiley & Sons: New York, 1992; pp 293−500.
(26) (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (b) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 146.
(27) Oka, T.; Murai, A. *Tetrahedron* **1998**, *54*, 1.
(28) Yamamoto, Y.; Nishii, S.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1986**, 102.
(29) Hirano Y.; Djerassi, C. *J. Org. Chem.* **1982**, *47*, 2420.
(30) Anastasia, M.; Ciuffreda, P.; Del Puppo, M.; Feicchi, A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 383.
(31) Fujimoto, Y.; Kimura, M.; Teresawa, T.; Khalifa, F. A. M.; Ikekawa, N. *Tetrahedron Lett.* **1984**, *25*, 1805.
(32) Craig, A. S.; Norman, A. W.; Okamura, W. H. *J. Org. Chem.* **1992**, *57*, 4374.
(33) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(34) Ward, D. E.; Rhee, C. K. *Can. J. Chem.* **1989**, *67*, 1206.
(35) Sato, F.; Takeda, Y.; Uchiyama, H.; Kobayashi, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 1132.
(36) Shimazaki, M.; Hara, H.; Suzuki, K. *Tetrahedron Lett.* **1989**, *30*, 5447.
(37) Suzuki, K.; Katayama, E.; Tsuchihashi, G. *Tetrahedron Lett.* **1984**, *25*, 2479.
(38) Baraldi, P. G.; Barco, A.; Benetti, S.; Guarneri, M.; Manfredini, S.; Pollini, G. P.; Simoni, D. *Tetrahedron Lett.* **1988**, *29*, 1307.
(39) Baraldi, P. G.; Bigoni, A.; Guarneri, M.; Manfredini, S.; Pollini, G. P.; Simoni, D. *Farmaco* **1993**, *48*, 1515.

lithium aluminum hydride for prolonged periods of time. On the other hand, all four isomers of **9** were found in the crude product when the 15-tetrahydropyranyl derivative of **3** was reduced with $LiAlH_4$.

In conclusion, it was found that (9*R**,10*S**)-13-*cis*-11,-12-didehydro-9,10-dihydro-10-hydroxyretinol (**3b**) was the major product of the addition of (*Z*)-LiC≡C(CH_3)═$CHCH_2OLi$ to the carbonyl group of (*E*)-2-methyl-4-(2′,6′,6′-trimethyl-1-cyclohexen-1′-yl)-3-butenal (**2**). In the presence of PBr_3 the 15-acetates of diols (9*R**,10*R**)-**4a** and (9*R**,10*S**)-**4b** were transformed into 13-*cis*-10-bromo-9,10-dihydroretinyl acetates (**6**) with significant retention of configuration. Proazaphosphatrane **1** in acetonitrile eliminates HBr from vitamin A precursors **6** and **11** faster than DBU and DBN.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Solvents were reagent grade, predried over molecular sieves, and when necessary, distilled from sodium−benzophenone ketyl prior to use (THF, ether). Removal of solvents from oily reaction products was carried out by applying vacuum and magnetically stirring at room temperature until 20 mTorr was achieved. However, residual hexane was still present, especially for viscous compounds as judged from their ^{1}H NMR spectra. Efforts to remove hexane by heating under vacuum resulted in decomposition.

^{1}H NMR spectra were measured on Nicolet NT-300 and Varian VXR-300 NMR spectrometers in chloroform-*d*, while ^{13}C and ^{31}P NMR spectra were recorded on a Varian VXR-300 NMR spectrometer in chloroform-*d* and acetonitrile-d_3, respectively. Chemical shifts are reported in parts per million downfield from tetramethylsilane using chloroform (^{1}H, 7.23 ppm) and chloroform-*d* (^{13}C, 77.07 ppm) resonances as secondary standards. ^{1}H and ^{13}C chemical shift assignments were supported by 2D ^{1}H−^{1}H correlations performed on **2**, **4b**, **8a**,**b**, **6,** and **11** as a mixture, **9**, and mixtures of **7a** and **7b**, and by 2D ^{1}H−^{13}C correlations recorded for **4b**, **8b** and a mixture of **7a** and **7b**. Two-dimensional spectra were obtained on a Varian VXR-300 spectrometer using standard COSY and HETCOR experiments. The CI-MS spectrum of **9** was determined on a Finnegan 4023 mass spectrometer.

For preparative chromatographic separations, silica gel (60−200 mesh, EM Science) was used, except for vitamin A isomers, for which only deactivated alumina (neutral, Baker) was found useful. TLC analyses were performed using plates precoated with silica gel (IB-2 and IB−F) or alumina (IB−F) (both Baker-flex from Baker). The following solvent systems were employed: 3:1 hexanes−ethyl acetate (v/v, for silica gel plates) and 10:1 hexanes−ethyl acetate (v/v, for alumina plates).

Trimethylsulfonium methyl sulfate was prepared (88% yield; lit.,[40] 70−75% yield), 2-methyl-2[2′-(2″,6″,6″-trimethyl-1″-cyclohexen-1″-yl)ethenyl]oxirane (98.3% yield, lit.[8] 94% yield), and (*RS*)-(*E*)-2-methyl-4,2′,6′,6′-trimethyl-1′-yl)-3-butenal (**2**) (quantitative; lit.[8] 85% yield) were prepared according to methods in the cited literature.

13-*cis*-11,12-Didehydro-9,10-dihydro-10-hydroxyretinols (3). The dilithium salt of *cis*-2-methyl-2-penten-4-yl-1-ol was prepared from the alcohol (3.715 g, 38.6 mmol) and *n*-butyllithium (30.9 mL, 2.5 M in hexane) in tetrahydrofuran (100 mL) below −15 °C. After stirring for 1 h below −15 °C, a room-temperature solution of **2** (5.63 g, 27.3 mmol) in THF (20 mL) was added while the reaction flask temperature was maintained below −15 °C. The reaction mixture was stirred for 1 h at this temperature, and then it was allowed to warm to room temperature. After addition of cold water (100 mL) the product was extracted with ether (2 × 200 mL). The organic phase was washed with brine until neutral and was dried over $MgSO_4$. Solvents were evaporated and unreacted alcohol was distilled off in vacuo (0.2 Torr, bath 95 °C). The yellow oil left in the flask (7.046 g, 85%) was identified by NMR spectroscopy as a mixture of **3a** and **3b** of sufficient purity (TLC) to be used in the next step. A sample was purified on a silica gel column with hexanes−ethyl acetate (10:1 to 3:1, v/v) to give pure **3a** and **3b** (a 2:3 mixture) as a colorless oil.

Reduction of 3 with $LiAlH_4$. To a suspension of $LiAlH_4$ (1.736 g, 45.75 mmol) in ether (75 mL) cooled under argon to 2 °C, a solution of **3** (7.05 g, 23.3 mmol) in ether (25 mL) was added dropwise at a rate just slow enough to keep the temperature of the reaction mixture below 6 °C. Then the mixture was stirred at room temperature for 16 h. After cooling to −10 °C, water was slowly added until the vigorous reaction ceased. The reaction mixture was acidified with dilute H_2SO_4 at 0 °C, the ether layer was separated, and the water phase was extracted with ether (2 × 50 mL). The combined organic phases were washed with water, aqueous $NaHCO_3$, then water again until neutral, dried over $MgSO_4$, and evaporated. The residue was kept in vacuo (0.1 Torr) at room temperature for 48 h to give 6.779 g of a very viscous yellow oil which was subjected to chromatography on silica gel (50 g) with hexanes−ethyl acetate mixtures to give a mixture of isomers **9** (oil, 0.315 g, 5%), a mixture of diastereoisomers **8** (0.898 mg, 12.6%), a partially separated mixture of diastereoisomers **4a** and **4b** (2.224 g, 31.3%), and crystalline **4b** (1.503 g, 21.2%) after solvent evaporation. Diastereoisomers **8** were further chromatographed on silica gel with 10:1 hexanes−ethyl acetate (v/v) to afford pure samples of **8a** and the more polar **8b**.

Synthesis of Monoacetates 5a and 5b. A mixture of **4b** (1.397 g, 4.588 mmol), 2,4,6-collidine (3.03 mL) and acetic anhydride (0.87 mL, 9.17 mmol) was left at room temperature for 48 h. After dilution with ether (50 mL) the mixture was washed with cold diluted H_2SO_4, water, aqueous $NaHCO_3$, and water again, and then it was dried over $MgSO_4$. Chromatography on silica gel with 10:1 and 5:1 hexanes−ethyl acetate (v/v) afforded diacetate **10b** (174 mg, 9.5%, oil) and **5b** (1.440 g, 89.5%, oil). In an analogous fashion, a mixture of **4a** and **4b** was esterified. Chromatography on silica gel with hexanes−ethyl acetate mixtures (100:5 to 2:1, v/v) allowed partial separation of **5a** and **5b**.

Reaction of Phosphorus Tribromide with 5 (General Procedure). To a solution of **5** (10 mmol) in ether (10 mL) PBr_3 (12 mmol) was injected at −20 °C under argon. The reaction mixture was stirred for 1 h while allowing it to reach room temperature during that time. It was then diluted with ether (40 mL), washed with cold brine, aqueous $NaHCO_3$, and then brine until neutral and dried over $MgSO_4$. After evaporation of the ether, the crude product was left in vacuo (0.02 Torr) to give a mixture of **6a**, **6b**, and **11** as a yellow oil in 85−95% yield. This material slowly turned brown when left at room temperature, and for this reason it was used immediately in the next step.

Elimination of HBr from a Mixture of 6a, 6b, and 11 with 1, DBN, or DBU (General Procedure). A mixture of **6a**, **6b**, and **11** obtained in a previous experiment was dissolved in benzene or toluene (1 mmol in 1 mL) and was refluxed with 1.2 equiv of **1**, DBN, or DBU. Alternatively, the mixture of bromides was dissolved in acetonitrile (1 mmol in 1 mL) and was stirred at room temperature with 1.2 equiv of **1**, DBN, or DBU. The reaction mixture was diluted with ether and washed with brine until neutral. The crude products were filtered through deactivated alumina (12 g for 5 mmol) to give mixtures of **7a** and **7b** (major) and **12a** and **12b** (minor).

Synthesis of the Ketone 14. The acetate **5b** (0.193 g, 0.55 mmol) was dissolved in CH_2Cl_2 (2 mL) and then PCC (0.178 g, 0.83 mmol) was added portionwise at 0 °C. After 3 h at 0 °C hexane (10 mL) was added, the organic solution was withdrawn by pipet and concentrated. The yellow residue was chromatographed on silica gel (5 g) with hexanes−ethyl acetate (20:1, v/v) to give **4** (60 mg, 31%) as a yellowish oil. On the basis of the NMR spectra (see Supporting Information) the material was judged to be ca. 90% pure.

(40) Mosset, P.; Gree, R. *Synth. Commun.* **1985**, *15*, 749.

Reduction of the Ketone 14. To a solution of **14** (77 mg, 0.22 mmol) in a 1:1 mixture of CH_2Cl_2 and methanol, $NaBH_4$ (8.4 mg, 0.22 mmol) was added portionwise at 0 °C. After 30 min, hexane (20 mL) was added, followed by aqueous H_2SO_4 (6%) (0.1 mL). The ice−water bath was then removed and the reaction mixture was dried with $MgSO_4$. The crude product was chromatographed on silica gel (5 g) with hexanes−ethyl acetate (10:1, v/v) to give a 7:3 mixture of **5a** and **5b**, respectively. ^1H NMR integrals of $H_3C16,17$, H_3C19, H_3C18, H_3C20, HC10, and HC12 in **5a** and **5b** were compared and averaged (see Discussion).

Acknowledgment. We thank the National Science Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for grant support.

Supporting Information Available: 1D and 2D NMR spectra and NMR and mass spectral assignments. This material is available free of charge via the Internet at http://pubs.org.

JO010648+