isomerization makes such a process very attractive. It is noteworthy that although the proton transfer in the conversion of I to II (eq 1) involves a 1,8 and a 1,13 shift, respectively, no competition of the simple vinyl epoxide isomerization to enones occurs.[11] This type of cyclization holds promise of being a general solution to normally unfavorable ring sizes. Furthermore, the juxtaposition of functionality in the specific cases chosen offers an opportunity for further elaboration toward natural products such as the polyene macrolides.[15] A simple illustration from **13** to muscone can be envisioned by conjugate addition of lithium dimethylcuprate followed by reductive desulfonylation.[16]

Acknowledgment. We thank the National Science Foundation and the General Medical Sciences Institute of the National Institutes of Health for their generous support of our programs. We are grateful to Rohm and Haas for a generous gift of the polystyrene resin and Englehardt Industries and Johnson Matthey for a generous supply of palladium chloride.

Registry No. **1** (R = CO_2CH_3) Na, 82902-78-1; **1** (R = $PhSO_2$) Na, 82917-43-9; **2**, 82902-79-2; **3**, 82902-80-5; **4**, 82902-81-6; **5**, 82917-44-0; **6**, 82902-82-7; **7**, 82902-83-8; **8**, 82902-84-9; **9**, 82902-85-0; **10**, 82902-86-1; **11**, 82902-87-2; **12**, 82902-88-3; **13**, 82902-89-4; **14**, 82902-90-7; ethyl 8-bromo-2-octenoate, 82902-91-8; ethyl 13-bromo-2-tridecenoate, 82902-92-9; 8-bromo-2,3-epoxyoctanol, 82902-93-0; 13-bromo-2,3-epoxytridecanol, 82902-94-1; 2-(5-bromopentyl)-3-ethenyloxirane, 82902-95-2; 2-(10-bromodecyl)-3-ethenyloxirane, 82902-96-3; 6-bromohexanol, 4286-55-9; 11-bromoundecanol, 1611-56-9; methyl 1-phenylsulfonyl-3-cyclononene-1-carboxylate, 70255-45-7; 4,4-diphenylsulfonylcyclononene, 70255-47-9; methyl 1-phenylsulfonyl-2-ethenylcycloheptanecarboxylate, 70255-46-8; 1,1-diphenylsulfonyl-2-ethenylcycloheptane, 70255-48-0; $(Ph_3P)_4Pd$, 14221-01-3; dppe, 1663-45-2.

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(15) Oroshnik, W.; Mebane, A. D. *Fortsch. Chem. Org. Naturst.* **1963**, *21*, 17. Hamilton-Miller, J. M. T. *Bacteriol. Rev.* **1973**, *37*, 166.

(16) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem.* **1980**, *102*, 4730. Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.

12-s-Cis-Locked Retinoids (Vitamin A): Synthesis and Novel Spectral Properties

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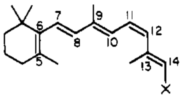
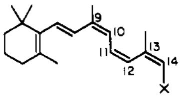
The chromophoric group of the visual pigment rhodopsin, 11-*cis*-retinal (**1a**),[1] is believed to exist in solution as an equilibrium mixture of twisted 12-s-cis and 12-s-trans conformers.[2] The observation that **1a** and the corresponding alcohol **1b** exhibit UV maxima at 377 and 319 nm,[3] respectively, is indicative of a highly distorted chromophore for each.[3] We recently made the unusual observation that the more hindered 9-*cis*,11-*cis*,13-*cis*-retinal (**2a**) exhibits its main maximum (302 nm) to the blue of the corresponding alcohol **2b** (306 nm).[4a] The ^1H NMR data indicated that a high degree of distortion exists about the C(12)–C(13) single bond.[4a] In order to further evaluate this effect, this communication describes the synthesis and spectral properties of highly twisted 12-s-cis-locked retinal analogues possessing 11-cis (**3a**), 11-cis,13-cis (**4a**), and 9-cis,11-cis,13-cis (**5a**) geometries. This study nicely complements that of Nakanishi and co-workers on twisted 12-s-trans-locked retinals **6**, which exhibit relatively normal electronic spectra (λ_{max} >350 nm) for both the 11-cis and 9-cis,11-cis,13-cis geometric isomers.[5] The synthetic route used for preparing **3–5** entails the [1,5] sigmatropic hydrogen shift of the vinylallene **7b** as a key step, a process specific for producing 11-*cis*-retinoids.[4] This process should have also produced a 9-cis,11-cis isomer, but the latter apparently undergoes further previously unrecognized[4a] pericyclic transformations. This study therefore also provides further insight into the stereochemical course of vinylallene rearrangements.



1



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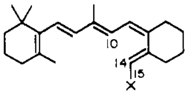

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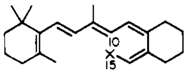

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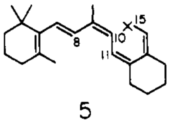
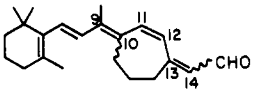


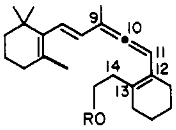
5

a, X = CHO; b, X = CH_2OH



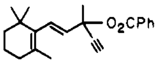
6

(TBDMS = t-$BuMe_2Si$)

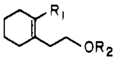


7a, R = TBDMS
b, R = H

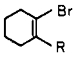
The vinylallene **7a** was obtained by the coupling of the propargyl benzoate **8** and the vinyl cuprate **9d**,[4,6] which was prepared as follows. Reaction of **10a** (prepared in 52% yield from cyclohexanone)[7] under Wittig conditions (ether, Ph_3PCH_3Br, *n*-BuLi; 54%) gave the bromodiene **10b**. Hydroboration–oxidation (THF, 9-BBN; H_2O_2, NaOH, H_2O–CH_3OH; 85%)[8] followed by protection (TBDMSCl, imidazole, DMF; 84%)[9] afforded the bromosilyl ether **9b**. Lithiation (2.1 equiv of *t*-BuLi, ether, −78 °C, 4 h) of **9b** followed by reaction with $CuC{\equiv}C{-}C(CH_3)_2OCH_3$[10] afforded the mixed cuprate **9d**, which was reacted with **8** to afford silyl ether **7a**. Deprotection ((*n*-Bu)$_4$NF, THF, room temperature, 4.5 h)[9] of **7a** followed by high-pressure liquid chromatography (HPLC) (15% ethyl acetate–skellysolve B) afforded pure vinyl-



8



9a, R_1 = Br; R_2 = H
b, R_1 = Br; R_2 = TBDMS
c, R_1 = Li; R_2 = TBDMS
d, R_1 = $[CuC{\equiv}CC(CH_3)_2OCH_3]^-Li^+$; R_2 = TBDMS



10a, R = CHO
b, R = CH=CH_2

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(1) (a) Wald, G. *Nature (London)* **1968**, *219*, 800. (b) Hubbard, R.; Kropf, A. *Proc. Natl. Acad. Sci. U.S.A.* **1958**, *44*, 130.

(2) (a) Rowan, R.; Warshel, A.; Sykes, B. D.; Karplus, M. *Biochemistry* **1974**, *13*, 970. (b) Becker, R. S.; Berger, S.; Dalling, D. K.; Grant, D. M.; Pugmire, R. J. *J. Am. Chem. Soc.* **1974**, *96*, 7008.

(3) Zechmeister, L. "Cis–Trans Isomeric Carotenoids: Vitamins A and Arylpolyenes"; Academic Press: New York, 1962; p 126. Woodward's rules predict λ_{max} values of 414 and 334 nm for a planar pentaalkyl pentaenal (a reference point for **1a**) and hexaalkyl pentaene (a reference point for **1b**), respectively. See: Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. "Spectrometric Identification of Organic Compounds", 4th ed.; Wiley: New York, 1981.

(4) (a) Knudsen, C. G.; Carey, S. C.; Okamura, W. H. *J. Am. Chem. Soc.* **1980**, *102*, 6355. The electronic spectrum of **2a** in ethanol exhibits a shoulder at 349 nm (ϵ 11 000) as well as the maximum at 302 nm (ϵ 14 000) reported previously. (b) Sueiras, J.; Okamura, W. H. *Ibid.* **1980**, *102*, 6255.

(5) Akita, H.; Tanis, S. P.; Adams, M.; Balogh-Nair, V.; Nakanishi, K. *J. Am. Chem. Soc.* **1980**, *102*, 6370.

(6) (a) Hammond, M. L.; Mourinño, A.; Okamura, W. H. *J. Am. Chem. Soc.* **1978**, *100*, 4907. (b) Condran, P.; Hammond, M. L.; Mouriño, A.; Okamura, W. H. *Ibid.* **1980**, *102*, 6259. (c) Rona, P.; Crabbé, P. *Ibid.* **1968**, *90*, 4733; **1969**, *91*, 3289.

(7) Arnold, Z.; Holy, A. *Coll. Czech. Chem. Commun.* **1961**, *26*, 3059.

(8) Brown, H. C.; Liotta, R.; Kramer, G. W. *J. Org. Chem.* **1978**, *43*, 1058.

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

(10) (a) Corey, E. J.; Floyd, D.; Lipshutz, B. H. *J. Org. Chem.* **1978**, *43*, 3418. (b) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210.

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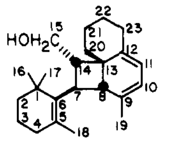
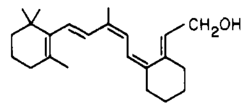
allene **7b** (43% based on **9b**).[11]

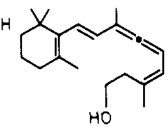
The thermally induced rearrangement of the vinylallenol **7b** (10^{-3} M in purified hexanes at reflux, ~69 °C, 4 h) followed by preparative HPLC afforded four components (82% mass balance) in the following order of elution: a substance characterized as **11** (12%) and the 12-s-cis-locked retinols, 11-*cis*,13-*cis*-**4b** (33.1%), 11-*cis*-**3b** (13.5%), and 9-*cis*,11-*cis*,13-*cis*-**5b** (22.8%). Each of the four thermolysis products was individually subjected to the conditions of thermolysis (refluxing hexanes, 4 h) and found to be unchanged by ^{1}H NMR and HPLC analyses.



11



12



13

The observation of **11** as one of the thermolysis products of **7b** is of particular interest since no retinol possessing the 9-cis,11-cis geometry was observed as a product in the thermolysis of the previously reported vinylallenol **13**.[4a] Structure **11** is proposed on the basis of spectral analysis[11] and on the reasonable mechanistic hypothesis that it can be derived from further rearrangement of the putative 9-cis,11-cis-isomer **12**. Examination of **12** reveals in it the presence of *trans,cis,cis,trans*-octatetraene moiety. Such tetraenes are known to undergo extraordinarily facile eight-electron conrotatory electrocyclization to cycloocta-1,3,5-trienes, which further electrocyclize to bicyclo[4.2.0]octa-2,4-dienes in a six-electron disrotatory manner.[12] A similar series of tandem electrocyclizations should result in the rearrangement of the putative intermediate **12** to **11**.

The retinol analogues **3b**, **4b**, and **5b** are considered to be of the 11-cis geometrical series on the basis of their method of synthesis via the thermal [1,5] sigmatropic rearrangement. The 13-cis geometry for **4b** and **5b** was based on observation of an NOE between H_{15} and H_{10} in these isomers while no NOE was observed between these protons in **3b**. Compound **5b** was assigned the 9-cis geometry on the basis of deshielding of H_8 (~0.6 ppm) as a result of interaction with H_{11}.[11,13] The retinols were individually oxidized (MnO_2, low-boiling petroleum ether, 0 °C, 1 h; ~80%) to the corresponding retinals, and the spectral data for these compounds were also in accord with the assigned geometries.[11]

The electronic absorption spectra of retinals generally exhibit prominent α bands (~360 nm) and weak β bands (~280 nm).[14] In striking contrast, the absorption spectra of the 12-s-cis-locked retinal analogues show marked enhancements of the β bands relative to the α bands,[11] a phenomenon also exhibited by 9-*cis*,11-*cis*,13-*cis*-retinal.[4a] Interestingly, the corresponding 12-s-trans-locked analogues exhibit maxima in the α region.[5] It thus appears that the appearance of a strong absorption at ~300 nm is a consequence of distortion of the chromophore into a twisted 12-s-cis conformation. The data also suggest that 9-*cis*,11-*cis*,13-*cis*-retinal (**2a**) exists predominantly in a twisted 12-s-cis conformation.

This paper further defines the scope of the vinylallene method for synthesizing 11-*cis*-retinoids. Apparently, the application of this approach to 9,10-allenes results in stereospecific production of 11-cis isomers, but there is little control of the stereochemistry of the lateral double bonds (Δ^9 and Δ^{13}) and the 9-cis,11-cis isomers are not stable to the thermal conditions. Future research will be directed toward addressing these problems. Despite these shortcomings, the method still allows rapid access to certain of the hindered 11-*cis*-retinoid analogues in sufficient quantities for further study. Recent reports[15,16] ascribing high activity in the chemoprophylaxis of epithelial cancer to retinoid analogues possessing 12-s-cis topologies make **3–5** attractive candidates for related biological evaluation.

Acknowledgment. The National Institutes of Health (USPHS Grant EY-02452 and NCI Contract CP-05715) provided financial support for this project. We also acknowledge the National Science Foundation Midwest Center for Mass Spectrometry for mass spectra, the Southern California Regional NMR Facility (supported by NSF Grant No. CHE79-16324) for 500-MHz spectra, and BASF (Ludwigshafen) for chemicals.

Registry No. **3a**, 83043-75-8; **3b**, 83043-76-9; **4a**, 83043-77-0; **4b**, 83043-78-1; **5a**, 83043-79-2; **5b**, 83043-80-5; **7a**, 83043-81-6; **7b**, 83043-82-7; **8**, 74723-00-5; **9b**, 83043-83-8; **9d**, 83043-86-1; **10a**, 38127-47-8; **10b**, 83043-84-9; **11**, 83060-55-3; **12**, 83043-85-0.

Supplementary Material Available: Spectral data for **7b**, **3ab**, **4ab**, **5ab**, and **11** (2 pages). Ordering information is given on any current masthead page.

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[11] All new compounds were characterized by ^{1}H and ^{13}C NMR, IR, and low- and high-resolution mass spectra and by UV as appropriate (see supplementary material section). The UV data (95% EtOH) for the retinals **3a–5a** and retinols **3b–5b** are as follows: (**3a**) λ_{max} 358 nm (sh, ϵ 9500), 288 nm (ϵ 19 300), 251 nm (ϵ 19 500), 235 nm (sh, ϵ 17 600); (**4a**) λ_{max} 357 nm (sh, ϵ 4900), 300 nm (ϵ 27 200), 236 nm (ϵ 20 300); (**5a**) λ_{max} 362 nm (sh, ϵ 3200), 299 nm (ϵ 23 000), 233 nm (ϵ 18 800); (**3b**) λ_{max} 308.5 nm (ϵ 19 700), 230 nm (ϵ 9700); (**4b**) λ_{max} 305 nm (ϵ 28 800), 230 nm (ϵ 11 000); (**5b**) λ_{max} 303 nm (ϵ 24 400), 223 nm (ϵ 9400).

[12] (a) Marvell, E. N.; Seubert, J. *J. Am. Chem. Soc.* **1967** *89*, 337. (b) Huisgen, R.; Dahmen, A.; Huber, H. *Ibid.* **1967**, *89*, 7130. Note that a sterically more congested diastereomeric structure for **11** formed via the alternative disrotatory closure is also possible, but only a single diastereomer is produced.

[13] (a) Patel, D. J. *Nature (London)* **1969**, *221*, 825. (b) Rowan, R., III; Sykes, B. D. *J. Am. Chem. Soc.* **1975**, *97*, 1023.

[14] (a) Birge, R. R.; Schulten, K.; Karplus, M. *Chem. Phys. Lett.* **1975**, *31*, 451. (b) Birge, R. R. *Annu. Rev. Biophys. Bioeng.* **1981**, *10*, 315.

[15] Loeliger, P.; Bollag, W.; Mayer, H. *Eur. J. Med. Chem.* **1980**, *15*, 9.

[16] Dawson, M. I.; Hobbs, P. D.; Chan, R. L.; Chao, W.; Fung, V. A. *J. Med. Chem.* **1981**, *24*, 583.

Electrocyclization of 1-Allenyldienes: Novel Synthesis of Drimatrienes and Related *trans*-Decalins

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Vinylallenes of the type **1** are useful intermediates for preparing polyenes such as vitamin D[1] and 11-*cis*-retinoids,[2] wherein a key step is a $C_6 \rightarrow C_2$ hydrogen migration, a thermal suprafacial [1,5]sigmatropic shift.[3,4] In order to further define the scope of this allene approach in organic synthesis, we considered the diene–allene[5] of the type **2**; it was initially assumed that it would undergo an exceptionally rapid $C_8 \rightarrow C_2$ antarafacial [1,7]sig-

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[1] (a) Hammond, M. L.; Mouriño, A.; Okamura, W. H. *J. Am. Chem. Soc.* **1978**, *100*, 4907. (b) Condran, P., Jr.; Hammond, M. L.; Mouriño, A.; Okamura, W. H., *Ibid.* **1980**, *102*, 6259. (c) Leyes, G. A.; Okamura, W. H. *Ibid.*, in press. (d) Haces, A.; Okamura, W. H. *Ibid.*, in press. (e) Condran, P., Jr.; Okamura, W. H. *J. Org. Chem.* **1980**, *45*, 4011. (f) Mouriño, A.; Lewicka-Piekut, S.; Norman, A. W.; Okamura, W. H. *Ibid.* **1980**, *45*, 4015. (g) Gerdes, J. M.; Lewicka-Piekut, S.; Condran, P., Jr.; Okamura, W. H. *Ibid.* **1981**, *46*, 5197.

[2] (a) Kundsen, C. G.; Carey, S. C.; Okamura, W. H. *J. Am. Chem. Soc.* **1980**, *102*, 6355. (b) Sueiras, J.; Okamura, W. H. *Ibid.* **1980**, *102*, 6255.

[3] Spangler, C. W. *Chem. Rev.* **1976**, *76*, 187.

[4] (a) For a review of enallenes (vinylallenes), see: Eigenburg, I. Z. *Russ. Chem. Rev. (Engl. Transl.)* **1978**, *47*, 900. (b) Crowley, K. J. *Proc. Chem. Soc.* **1964**, *17*. (c) Mikolajczak, K. L.; Bagby, M. O.; Bates, R. B.; Wolff, I. A. *J. Org. Chem.* **1965**, *30*, 2983. (d) Skattebøl, L. *Tetrahedron* **1969**, *25*, 4933. (e) Bakker, S. A.; Lugtenburg, J.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 1459. (f) Havinga, E. *Experientia* **1973**, *29*, 1181. (g) van Koeveringe, J. A.; Lugtenburg, J. *Recl. Trav. Chim. Pays-Bas* **1976**, *95*, 80. (h) Minter, D. E.; Fonken, G. J.; Cook, F. T. *Tetrahedron Lett.* **1979**, *711*. (i) Minter, D. E.; Fonken, G. J. *Ibid.* **1977**, 1717; **1977**, 4149.

0002-7863/82/1504-6115$01.25/0