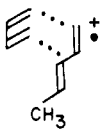
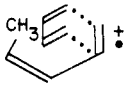
teraction. Indeed, the HOMO-LUMO interaction is expected to be greatly enhanced in the cation-radical version because of the stabilization of the cation-radical LUMO, mentioned earlier. A MINDO/3 calculation yields a HOMO/LUMO energy gap of 1.1339 - (-9.0995) = 10.23 eV for the uncatalyzed reaction and only -5.3067 - (-9.0995) = 3.79 eV for the cation-radical version. Although it may now seem curious, superficially, that the SUB-SOMO interaction, though energetically less important, should control chemo/regioselection, the appropriate basis for this was prepared earlier and related to the miniscule differentiation of the diene terminal carbons in the diene HOMO.

The simple PMO approach therefore appears to provide a potentially plausible basis for enhanced endo stereoselection in the cation-radical Diels-Alder as a consequence of the decreased energy gap, although one might legitimately wonder to what extent the SUB-SOMO effect, with its secondary antibonding interaction, may diminish the HOMO-LUMO stabilization. The *cis*-propenyl effect, fortunately, provides further insights to guide the evolution of the theory of endo stereoselection. In particular, it appears highly unlikely that a methyl group on the terminal (exocyclic) dienophile carbon could significantly affect the choice of endo vs. exo transition states for a dienophile in an s-trans conformation (**12**). In contradistinction, a cis terminal alkyl group in an s-cis




**12**




**13**

dienophile would be expected to encounter very appreciable steric repulsions (**13**). The proposal of an s-cis diene cation-radical conformation, at least for those dienes which exhibit high endo stereoselection, is also plausible in terms of PMO theory. In this conformation a new interaction ($C_3$-$C_8$) is potentially incurred in the transition state, and FMO theory (**10**) reveals this also to be bonding in the HOMO-LUMO interaction. In fact, since the LUMO coefficient at $C_8$ is considerably larger than at $C_7$, the new interaction could be expected to augment the familiar $C_2$-$C_7$ interaction in a major way, and thus provides a further and probably more important reason for the enhanced stereoselection in the cation-radical Diels-Alder.

These considerations and conclusions arouse curiosity concerning the questions of whether s-cis dienophile conformations are important in the uncatalyzed Diels-Alder and, if not, why they are uniquely important in the cation-radical version. Although the first question is not easily answered at present, some useful insights are available apropos of the second. Evidence is available that anion radicals of $\alpha$-diketones and dienes often prefer the s-cis conformation, especially in less polar solvents, as a consequence of chelate-like ion pairing.[20] A similar effect should be capable of stabilizing diene cation radicals, and methylene chloride is a solvent in which ion pairing would reasonably be anticipated. It is, of course, unnecessary to assume that the diene cation radical exist exclusively in the s-cis conformation, but if they do not, the s-cis conformation must be assumed to be more reactive. Specifically, this enhanced reactivity could emanate from the stabilizing secondary interactions. In accord with these conclusions, the endo:exo ratio in the addition of *t,t*-2,4-hexadiene to cyclohexadiene is decreased to 8:1 in acetonitrile, a solvent in which ion pairing should be attenuated. In contrast, the endo selectivity in the cation-radical dimerization of cyclohexadiene (a rigidly s-cis diene) is increased to 8:1 in acetonitrile (from 5:1).

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**Registry No. 1**, 504-60-9; **2**, 926-56-7; **3**, 1000-86-8; **4**, 28823-41-8; **5**, 4313-57-9; **6**, 586-63-0; **7**, 2161-90-2; **8**, 104-46-1; 1,3-cyclohexadiene, 592-57-4.

(20) Bauld, N. L. *J. Am. Chem. Soc.* **1962**, *84*, 4347.

# 12-s-Cis Conformationally Locked 11-*cis*-Retinoids: A Delineation of the Thermal Requirements for [1,5]-Sigmatropic Shifts and Electrocyclizations in the Vitamin A Series and Novel Spectral Properties[1]

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*Contribution from the Department of Chemistry, University of California, Riverside, California 92521.* *Received November 19, 1982*

**Abstract:** The thermally induced [1,5]-sigmatropic rearrangement (69 °C, 4 h) of the six-membered ring fused vinylallenol **5b**, a process specific for preparing 11-*cis*-retinoids, afforded **24** (12%) and the 12-s-cis-locked retinols 11-*cis*-**7a** (14%), 11-*cis*,13-*cis*-**8a** (33%), and 9-*cis*,11-*cis*,13-*cis*-**9a** (23%). The formation of the tetracyclic compound **24** is rationalized on the basis of further electrocyclizations of the putative 9-cis,11-cis-isomer **25**. In the corresponding seven-membered ring fused vinylallenol **6b**, the thermal threshold (room temperature) for [1,5]-sigmatropic hydrogen shift was sufficiently lowered to enable the isolation of all four possible geometrically isomeric 11-*cis*-retinols **10a**, **12a**, **13a** and the previously elusive 9-cis,11-cis-isomer **11a**. In a separate experiment, the latter (**11a**) was shown to isomerize to the tetracyclic compound **29** analogous to the putative transformation of **25** to **24** in the six-membered ring fused series. Oxidation of the retinol analogues **7a**-**13a** yielded the corresponding retinals **7b**-**13b**. Unlike in most previously reported retinals, which exhibit prominent ultraviolet $\alpha$ bands and weak $\beta$ bands, in these 12-s-cis-locked retinals, there is a dramatic reversal in the intensity of these bands. In fact, the 12-s-cis-locked aldehydes exhibit their main maximum (~288-300 nm) slightly to lower wavelengths than the corresponding alcohols (~298-309 nm).

## Introduction

A multitude of findings in recent years has clearly established the position of retinoids (vitamin A) as ubiquitous substances of importance in biological systems. Retinoids of interest include 11-*cis*- and 9-*cis*-retinal in vision,[2] 13-*cis*- and *all-trans*-retinal in energy transduction,[3] 13-*cis*-retinoic acid in acne therapy,[4]

(1) For a preliminary account of this work, see: Chandraratna, R. A. S.; Okamura, W. H. *J. Am. Chem. Soc.* **1982**, *104*, 6114.

(2) Wald, G. *Science* (Washington, *D.C.*) **1968**, *162*, 230.

(3) Stoeckenius, W. *Sci. Am.* **1975** (Nov.), 38.

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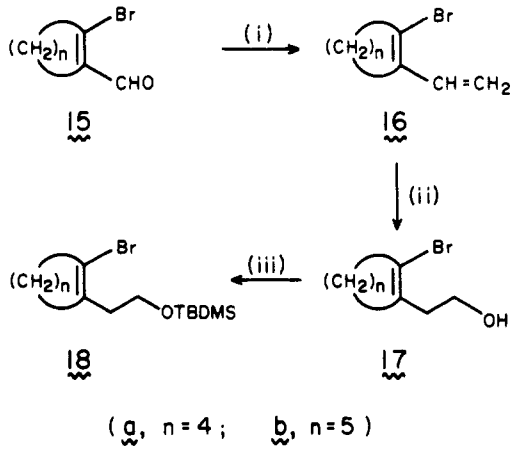
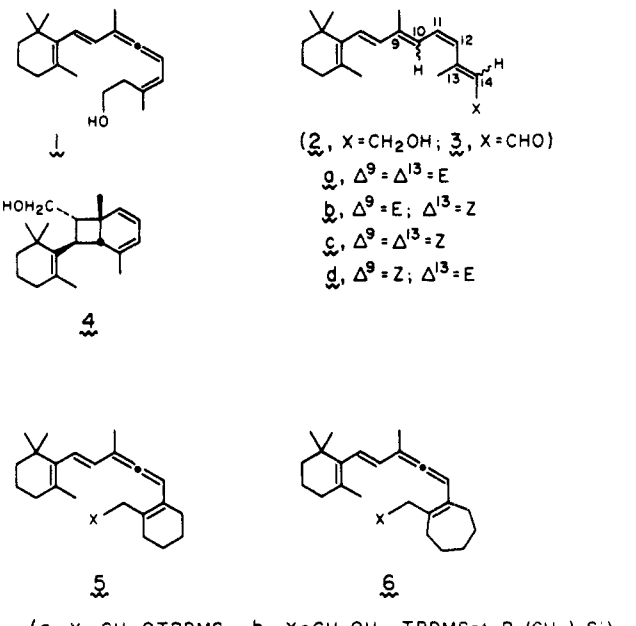
Scheme I



(i) $Ph_3PCH_3Br$, *n*-BuLi, ether. (ii) 9-BBN, THF; $H_2O_2$, NaOH, $H_2O$–$CH_3OH$. (iii) TBDMSCl, imidazole, DMF.

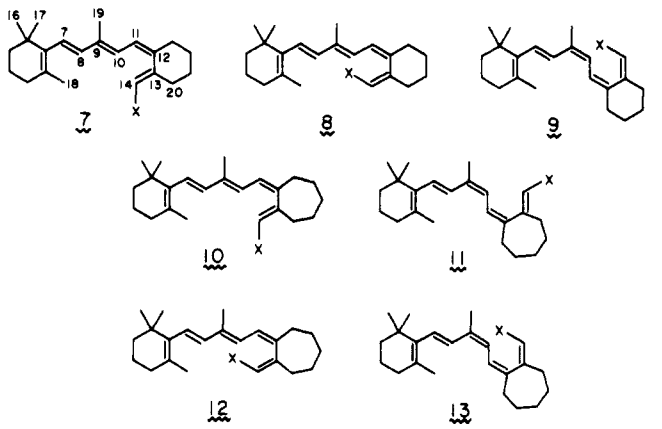
*all-trans*-retinoic acid, its 13-cis-isomer, and numerous other retinoid analogues in cancer prophylaxis and therapy.[5] It is apparent that various biological responses are elicited by a wide range of geometrically isomeric retinoids. We have recently utilized [1,5]-sigmatropic hydrogen shifts of vinylallenes to synthesize the (3*Z*)-1,3,5-hexatriene moiety characteristic of 11-*cis*-retinoids[6,7] and other natural product systems.[8] In our application of this pericyclic process to retinoid syntheses, the vinylallene **1** was thermolyzed to yield 11-*cis*-**2a**, 11-*cis*,13-*cis*-**2b**, and 9-*cis*,11-*cis*,13-*cis*-retinols **2c**.[6] However, the fourth possible geometric isomer, which should have resulted from a concerted [1,5]-sigmatropic hydrogen shift of **1**, namely, 9-*cis*,11-*cis*-retinol **2d**,[9] was not observed as a product but presumably underwent further thermally induced electrocyclizations to form **4**.[7] In this paper, we describe the thermal requirements for the [1,5]-sigmatropic shift in the 12-cis-locked 9,10-allenic retinoids **5b** and **6b** and how these requirements were manipulated to produce for the first time a 9-*cis*,11-*cis*-retinoid by a vinylallene route in addition to the 11-cis-, 11-cis,13-cis-, and 9-cis,11-cis,13-cis-isomers. The vinylallenes **5** and **6** were obtained by an approach employing a cuprate-mediated coupling reaction as the key step. As reported in the preliminary communication,[1] thermally induced sigmatropic rearrangement of the six-membered-ring analogue **5b**, like **1**, yielded only the three 12-s-cis-locked retinols: 11-*cis*-**7a**, 11-*cis*,13-*cis*-**8a**, and 9-*cis*,11-*cis*,13-*cis*-**9a**. Besides describing the details of the earlier report,[1] we now show that the milder thermal conditions required for the rearrangement of the seven-membered-ring analogue **6b** enabled the isolation of all four possible geometric isomers **10a–13a**, including the previously unobserved 9-cis 11-cis-isomer **11a**.



(**2**, X = $CH_2OH$; **3**, X = CHO)
**a**, $\Delta^9 = \Delta^{13} = E$
**b**, $\Delta^9 = E$; $\Delta^{13} = Z$
**c**, $\Delta^9 = \Delta^{13} = Z$
**d**, $\Delta^9 = Z$; $\Delta^{13} = E$

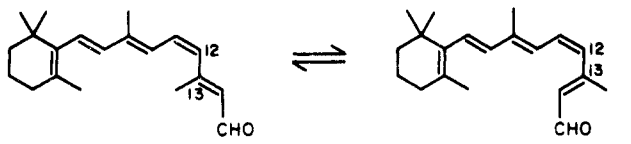


(**a**, X = $CH_2OTBDMS$; **b**, X = $CH_2OH$; TBDMS = t-Bu$(CH_3)_2Si$)



(**a**, X = $CH_2OH$; **b**, X = CHO)

The original impetus for preparing these 12-s-cis-locked analogues concerned a study directed toward developing a better understanding of the unusual electronic properties of 11-*cis*-retinal **3a**. By way of background, the UV absorption maxima exhibited by retinals and retinols (at ~360 and ~320 nm, respectively) are indicative of considerably distorted chromophoric groups.[10] For example, the chromophore of the visual pigment rhodospin,[2,11] 11-*cis*-retinal **3a**, exists in solution as an equlibrium mixture of twisted 12-s-trans (**14a**) and 12-s-cis (**14b**) conformers.[12] We recently observed that the highly hindered 11-*cis*,13-*cis*-**3b** and



**14a** (12-s-trans) **14b** (12-s-cis)

(4) Peck, G. L.; Olsen, T. G.; Yoder, F. W.; Strauss, J. S.; Downing, D.; Pandya, M.; Balkus, D.; Arnand-Baltandier, J. *N. Engl. J. Med.* **1979**, *300*, 329.

(5) (a) Bollag, W. *Cancer Chemother. Rep.* **1971**, *55*, 53. (b) Bollag, W. *Europ. J. Cancer* **1972**, *8*, 689. (c) Sporn, M. B. *Nutr. Rev.* **1977**, *35*, 65. (d) Mayer, H.; Bollag, W.; Hänni, R.; Rüegg, R. *Experientia* **1978**, *34*, 1105.

(6) Knudsen, C. G.; Carey, S. C.; Okamura, W. H. *J. Am. Chem. Soc.* **1980**, *102*, 6355.

(7) Knudsen, C. G. Chandraratna, R. A. S.; Walkeapää, L. P.; Chauhan, Y. S.; Carey, S. C.; Cooper, T. M.; Birge, R. R.; Okamura, W. H. *J. Am. Chem. Soc.*, in press.

(8) For applications in the vitamin D field, see: (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. *J. Am. Chem. Soc.* **1980**, *102*, 6259. (c) Mouriño, A.; Lewicka-Piekut, S.; Norman, A. W.; Okamura, W. H. *J. Org. Chem.* **1980**, *45*, 4015. (d) Condran, P., Jr.; Okamura, W. H. *Ibid.* **1980**, *45*, 4011. (e) Gerdes, J. M.; Lewicka-Piekut, S.; Condran, P., Jr.; Okamura, W. H. *Ibid.* **1981**, *46*, 5197.

(9) For recent studies of 9-*cis*,11-*cis*-retinals, see: Kini, A.; Matsumoto, H.; Liu, R. S. H. *Bioorg. Chem.* **1980**, *9*, 406.

(10) Zechmeister, L. "*Cis-Trans* Isomeric Carotenoids: Vitamins A and Arylpolyenes"; Academic Press: New York, 1962; p 126. Application of Woodward's Rules suggest $\lambda_{max}$ values of 414 and 334 nm for an undistorted pentaalkyl pentaenal (a reference point for retinals) and a hexaalkyl pentaene (a reference point for retinols), respectively. See: Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. "Spectrometric Identification of Organic Compounds", 4th ed.; Wiley: New York, 1981.

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

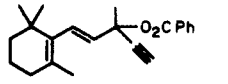
(12) (a) Rowan, R.; Warshel, A.; Sykes, B. D.; Karplus, M. *Biochemistry* **1974**, *13*, 970. (b) Becker, R. S.; Berger, S.; Dalling, D. K.; Grant, D. M.; Pugmire, R. J. *J. Am. Chem. Soc.* **1974**, *96*, 7008.

9-*cis*,11-*cis*,13-*cis*-retinals **3c** exhibit their main maxima at 302 nm, which is actually to the blue of the corresponding alcohols.[7] This and other considerations led us to suggest that these two retinals exist in solution predominantly as 12-s-cis conformers. Thus, in this paper we also describe the details of the effect of 12-s-cis conformational locking on the absorption spectra of four 11-*cis*-retinals, geometrically isomeric about the $\Delta^9$ and $\Delta^{13}$ double bonds.

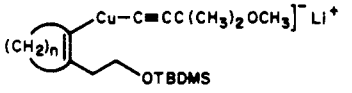
## Results and Discussion

The six- and seven-membered bromosilyl ethers **18a** and **18b** were synthesized according to the sequence outlined in Scheme I. Reaction of the known,[13] unstable bromoaldehydes **15a** and **15b** under Wittig conditions gave the corresponding bromodienes **16a** and **16b**. Hydroboration–oxidation of the dienes using 9-BBN afforded the primary alcohols **17a** and **17b**, which were then protected as their *tert*-butyldimethylsilyl ethers **18a** and **18b**.

The vinylallene moieties **5** and **6** were obtained by formal $S_N2'$ couplings[6,7,14] of the propargyl benzoate **19** with the corresponding vinylcuprates **20a** or **20b**. The mixed cuprates **20a** and **20b** were

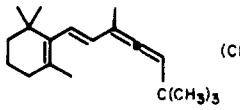



19




20

(a, n = 4; b, n = 5)

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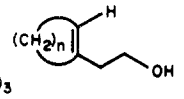


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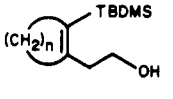
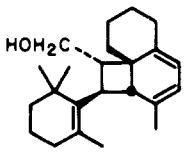



23

(a, n = 4; b, n = 5)

obtained by lithiation of the corresponding bromosilyl ethers **18a** and **18b** using 2.1 equiv of *tert*-butyllithium and subsequent reaction of the lithio species with $CuC{\equiv}CC(CH_3)_2OCH_3$.[15] It was our experience that the coupling reactions did not give satisfactory yields of the vinylallenes unless a slight excess of *tert*-butyllithium was used in the lithiation step. As a consequence, a constant contaminant in the coupling product was the known *tert*-butylallene **21**.[7] Also identified as minor byproducts of the coupling reaction were the alcohols **22** and **23**. The presence of the vinylallene in the coupling product mixtures was ascertained by a characteristic absorption in the IR at ~1925 $cm^{-1}$ and by a quartet assigned to $H_{11}$ in the $^1H$ NMR at ~6.4 ppm ($J \approx 3.0$ Hz). The partially purified vinylallene silyl ethers **5a** and **6a** were deprotected to afford the corresponding alcohols by using $(n\text{-Bu})_4NF$.[16] The vinylallenol **5b** was isolated in pure form by high-pressure LC. However, the corresponding seven-membered vinylallenol **6b** was not isolated as it rearranged to the retinols **10a–13a** under the conditions of deprotection.

The thermal rearrangement of the vinylallenol **5b** was carried out in refluxing hexanes (~69 °C, 4 h). Preparative high-pressure LC of the product mixture afforded four components (82% mass balance) in the following order of elution: the cyclized compound **24** (12%) and the 12-s-cis-locked retinols, 11-*cis*,13-*cis*-**8a** (33.1%), 11-*cis*-**7a** (13.5%), and 9-*cis*,11-cis,13-*cis*-**9a** (22.8%).[17] The four thermolysis products were separately subjected to the conditions of the vinylallene thermolysis and were found to be unchanged by $^1H$ NMR spectroscopy and high-pressure LC. The occurrence of **24** as a thermolysis product is particularly enlightening given the absence of 9-cis,11-cis-isomers as products in the thermolysis of **5b** and **1**. It is readily apparent from an examination of the

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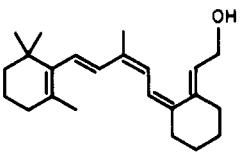
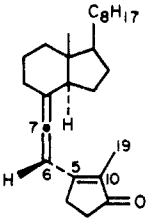



25

structure of the putative 9-cis,11-cis intermediate **25** that **24** can reasonably be derived from **25**. The 9-cis,11-cis-isomer **25** possesses a *trans*,*cis*,*cis*,*trans*-octatetraene moiety and such tetraenes undergo very facile eight-electron conrotatory electrocyclization to cycloocta-1,3,5-trienes which can further electrocyclize in a six-electron disrotatory manner to bicyclo[4.2.0]octa-2,4-dienes.[18] Such a series of electrocyclizations would result in the conversion of the putative 9-cis,11-cis-isomer **25** to **24**.

These results indicated that the thermal conditions required to effect the [1,5]-sigmatropic hydrogen shift in vinylallenes of the type **5** and **1** were too vigorous to enable the isolation of the thermally labile 9-*cis*,11-*cis*-retinols. It had been observed in studies in our laboratories on vinylallenes of the vitamin D series that the thermal thresholds for [1,5]-sigmatropic hydrogen shifts in the five-membered-ring series **26**[8c] were considerably higher

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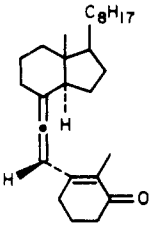


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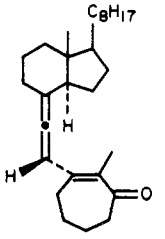


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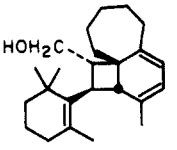


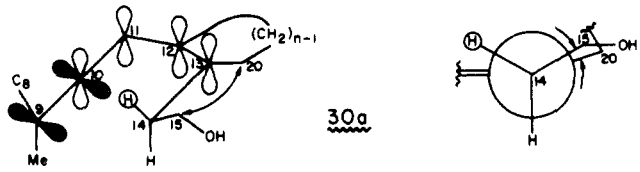

29

than for the six-membered-ring series **27**.[8b] This difference in reactivity was rationalized on the basis that the distance between the carbon atoms involved in the [1,5]-sigmatropic hydrogen shift ($C_{19}$ and $C_7$) is much greater in the five-membered-ring compounds **26** than in the six-membered-ring compounds **27**.[19] Since Dreiding models revealed that this distance was shorter in the seven-membered-ring case, it was predicted that **28** should rearrange faster than **27**.[19] We therefore envisaged that in a seven-membered vinylallene, such as **6**, the distance between the relevant carbon termini ($C_{10}$ and $C_{14}$) would be shorter and consequently the thermal threshold for the [1,5]-sigmatropic shift would be lowered sufficiently to enable the isolation of a 9-cis,11-cis-isomer. Indeed, the vinylallenol **6b** was not isolated in a pure form since it rearranged under the deprotection conditions (room temperature, 3 h) to give four geometrically isomeric retinols

(13) Arnold, Z.; Holy, A. *Collect. Czech. Chem. Commun.* **1961**, *26*, 3059.
(14) Rona, P.; Crabbé, P. *J. Am. Chem. Soc.* **1968**, *90*, 4733; **1969**, *91*, 3289.
(15) (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.
(16) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(17) All new compounds were characterized by $^1H$ and $^{13}C$ NMR, IR, low- and high-resolution MS, and UV spectroscopy as appropriate (see supplementary material).
(18) (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 **24** and **29** via the alternative disrotatory closure is also possible, but only a single diastereomer was obtained in each case.
(19) We thank Mr. Alberto Haces of this laboratory for suggesting the distance effect rationale.

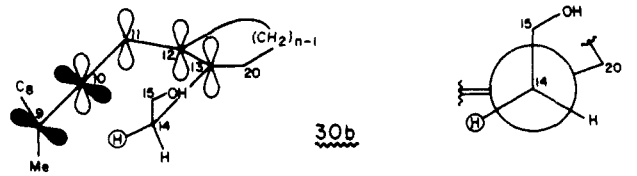
including the elusive 9-cis,11-cis-isomer **11a**. The four 12,20-tetramethyleneretinols, listed in their order of elution, were isolated by high-pressure LC in the following yields (based on **18b**): 11-*cis*-**10a** (5.4%), 11-*cis*,13-*cis*-**12a** (10.0%), 9-*cis*,11-*cis*,13-*cis*-**13a** (15.0%), and 9-*cis*,11-*cis*-**11a** (6.8%). When the 9-*cis*,11-*cis*-retinol **11a** was thermolyzed (69 °C, 3 h), it underwent electrocyclization (presumably in the manner hypothesized above for the putative six-membered-ring analogue **25**) to yield **29**. However, the 9-*cis*-11-*cis*,13-*cis*-retinol **13a** was unchanged upon heating (69 °C, 4 h).

An interesting feature of the product distributions obtained from the thermolyses of the vinylallenols **5b** and **6b** is the preferential formation of the sterically more congested 13-cis-isomers (13-cis/13-trans = 2.2 for **5b** and 2.1 for **6b**). The transition-state conformation **30a** adopted by the vinylallenols in order to yield 13-trans-isomers results in considerable eclipsing interaction between the $C_{15}$ and $C_{20}$ methylenes. This interaction is absent




30a




30b




in the transition-state conformation **30b** leading to 13-cis-isomers and hence there is a slight preference for this conformation, which leads to an excess of 13-cis product. Migration of the hydrogen to $C_{10}$ from the top and bottom faces of the vinylallene results in 9-trans- and 9-cis-isomers, respectively. However, little stereodifferentiation is observed between the substituents at $C_9$ (vinyl and methyl) in **5b** and **6b** as evidenced by the approximately equal amounts of 9-cis- and 9-trans-isomers produced.

The presumed concerted nature of the thermal [1,5]-sigmatropic rearrangement utilized to synthesize the retinol analogues **7a–13a** predicates that they be of 11-cis geometry. A 9-cis geometry was assigned to the compounds **9a**, **11a**, and **13a** on the basis of deshielding of $H_8$ (~0.6 ppm relative to the 9-trans-isomers; see Table I) by a steric polarization mechanism[20] due to interaction with $H_{11}$.[21] Compounds **7a**, **10a**, and **11a** were considered to be of 13-trans geometry as a result of deshielding of the $H_{15}$ signal (~0.3 ppm) due to interaction of the $C_{15}$ methylene with the $C_{20}$ methylene, an interaction which is absent in a 13-cis-isomer. Furthermore, in the 13-trans-isomers, $H_{10}$ is deshielded (~0.3 ppm) due to interaction with $H_{14}$. The relief of the deshielding interaction between $H_{14}$ and $H_{10}$ on going from a 13-trans to a 13-cis geometry is counterbalanced in the case of $H_{14}$ by a new deshielding interaction with the $C_{20}$ methylene.

Each of the retinols was oxidized to the corresponding retinal and the chemical shifts of these retinals **7b–13b** (see Table II) are in accord with the assigned geometries. The 13-cis geometry for the compounds **8a**, **8b**, **9a**, and **9b** was further confirmed by the observation of an NOE effect between $H_{15}$ and $H_{10}$ while there was no observable NOE between these protons in **7a** and **7b**. A salient feature of the data listed in Table II is the chemical shift of $\delta$ ~9.5 for the aldehydic protons in the 11-cis,13-cis- (**8b** and **12b**) and 9-cis,11-cis,13-cis-isomers (**9b** and **13b**). This upfield shift is attributable to elimination of the deshielding interaction between the aldehyde proton and the $C_{20}$ methylene that is present

Table I. $^1$H NMR Chemical Shifts (ppm) of 12-s-Cis-Locked Retinals[a]

| | 9-*cis*,11-*cis*- | 11-*cis*- | | 11-*cis*,13-*cis*- | | 9-*cis*,11-*cis*,13-*cis*- | |
|---|---|---|---|---|---|---|---|
| | **11a** | **7a** | **10a** | **8a** | **12a** | **9a** | **13a** |
| $H_7$ | 6.12 | 6.09 | 6.08 | 6.10 | 6.03 | 6.14 | 6.14 |
| $H_8$ | 6.66 | 6.04 | 6.08 | 6.02 | 6.13 | 6.63 | 6.63 |
| $H_{10}$ | 6.18 | 6.21 | 6.27 | 5.85 | 5.91 | 5.79 | 5.82 |
| $H_{11}$ | 6.38 | 6.31 | 6.27 | 6.26 | 6.32 | 6.37 | 6.40 |
| $H_{14}$ | 5.52 | 5.52 | 5.52 | 5.51 | 5.58 | 5.52 | 5.59 |
| $H_{15}$ | 4.30 | 4.28 | 4.29 | 3.94 | 3.95 | 3.99 | 3.97 |
| $C_{16}$,$C_{17}$-$CH_3$ | 1.04 | 1.00 | 1.02 | 1.00 | 1.01 | 1.02 | 1.04 |
| $C_{18}$-$CH_3$ | 1.76 | 1.69 | 1.71 | 1.68 | 1.69 | 1.77 | 1.75 |
| $C_{19}$-$CH_3$ | 1.92 | 1.93 | 1.93 | 1.91 | 1.92 | 1.90 | 1.91 |

Table II. $^1$H NMR Chemical Shifts (ppm) of 12-s-Cis-Locked Retinals

| | 9-*cis*,11-*cis*- | 11-*cis*- | | 11-*cis*,13-*cis*- | | 9-*cis*,11-*cis*,13-*cis*- | |
|---|---|---|---|---|---|---|---|
| | **11b** | **7b** | **10b** | **8b** | **12b** | **9b** | **13b** |
| $H_7$ | 6.21 | 6.16 | 6.19 | 6.15 | 6.17 | 6.20 | 6.19 |
| $H_8$ | 6.64 | 6.04 | 6.05 | 5.99 | 6.00 | 6.608 | 6.62 |
| $H_{10}$ | 6.08 | 6.17 | 6.18 | 6.01 | 5.95 | 5.92 | 5.86 |
| $H_{11}$ | 6.55 | 6.39 | 6.46 | 6.53 | 6.57 | 6.613 | 6.66 |
| $H_{14}$ | 5.97 | 5.94 | 5.96 | 5.93 | 5.99 | 5.94 | 6.00 |
| $H_{15}$ | 10.12 | 10.12 | 10.11 | 9.52 | 9.51 | 9.53 | 9.51 |
| $C_{16}$,$C_{17}$-$CH_3$ | 1.05 | 1.00 | 1.02 | 0.97 | 1.01 | 1.02 | 1.04 |
| $C_{18}$-$CH_3$ | 1.76 | 1.69 | 1.70 | 1.60 | 1.68 | 1.74 | 1.75 |
| $C_{19}$-$CH_3$ | 1.93 | 1.94 | 1.95 | 1.88 | 1.94 | 1.89 | 1.89 |

in the 13-trans geometry. However, in the corresponding 12-s-trans-locked 11-cis,13-cis- and 9-cis,11-cis,13-cis analogues synthesized by Nakanishi and co-workers, the aldehyde signals are downfield shifted due to mutually deshielding interactions between $H_{15}$ and $H_{12}$.[22] In the parent retinals possessing 13-cis geometry, a similar deshielding interaction should occur if the molecules exist in 12-s-trans conformations. This, in fact, is found to be the case for the 13-*cis*-, 7-*cis*,13-*cis*-, 9-*cis*,13-*cis*-, and 7-*cis*,9-*cis*,13-*cis*-retinals.[23] Conspicuously, the 11-*cis*,13-*cis*- and 9-*cis*,11-*cis*,13-*cis*-retinals (**3b** and **3c**) exhibit shielded aldehyde signals, indicating that these isomers exist in twisted 12-s-cis conformations. Accordingly, we anticipate in general that retinals of 13-cis geometry biased in a 12-s-trans conformation should exhibit deshielded aldehyde signals while those of 13-cis geometry with 12-s-cis conformation should exhibit shielded aldehyde signals.[24]

The electronic absorption spectral data for the retinals **7b–13b** are listed in Table III. The major bands of the absorption spectra of retinals along with the states associated with these transitions have been assigned as follows: $\lambda_\alpha \approx 360$ nm ($^1B^*_u{}^+$ and $^1A^*_g{}^-$),[25a] $\lambda_\beta \approx 280$ nm ($^1A^*_g{}^+$),[25b] and $\lambda_\gamma \approx 250$ nm (unassigned).[25c] Retinals, in general, exhibit very strong $\alpha$ bands and either weak (in retinals with no cis bonds) or moderate intensity (in retinals with cis bonds in middle of chain) $\beta$ bands.[26] However, in the 12-s-cis-locked retinals **7b–13b**, this order is strikingly reversed and the $\beta$ bands are much more intense than the $\alpha$ bands (see Figure 1). This observation is especially true for the 11-cis,13-cis-isomers (**8b** and **12b**) and the 9-cis,11-cis,13-cis-isomers (**9b** and **13b**). Interestingly, the corresponding 12-s-trans-locked analogues exhibit normal spectra with prominent $\alpha$ bands.[22] Thus, the presence of prominent $\beta$ or so-called "cis" bands with concomitantly weak $\alpha$ bands appears to be a feature characteristic

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(21) (a) Patel, D. J. *Nature (London)* **1969**, *221*, 825. (b) Rowan, R., III; Sykes, B. D. *J. Am. Chem. Soc.* **1975**, *97*, 1023.
(22) Akita, H.; Tanis, S. P.; Adams, M.; Balogh-Nair, V.; Nakanishi, K. *J. Am. Chem. Soc.* **1980**, *102*, 6370.
(23) Liu, R. S. H.; Asato, A. E. *Methods Enzymol.* **1982**, *88*, 506.
(24) Chandraratna, R. A. S.; Okamura, W. H., unpublished observation: the $H_{15}$ chemical shift of 12,20-tetramethylene-13-*cis*-retinal is $\delta$ 9.64. The corresponding value for 13-*cis*-retinal is $\delta$ 10.2.
(25) (a) Birge, R. R.; Bennett, J. A.; Hubbard, L. M.; Fang, H. L.; Pierce, B. M.; Kliger, D. S.; Leroi, G. E. *J. Am. Chem. Soc.* **1982**, *104*, 2519. (b) Honig, B.; Dinur, U.; Birge, R. R.; Ebrey, T. G. *Ibid.* **1980**, *102*, 488. (c) Birge, R. R. *Annu. Rev. Biophys. Bioeng.* **1981**, *10*, 315.
(26) Menger, E. L. *Acc. Chem. Res.* **1975**, *8*, 81, and accompanying articles. Ottolenghi, M. *Adv. Photochem.* **1980**, *12*, 97.

Table III. Electronic Absorption Spectral Data of 12-s-Cis-Locked Retinals

| | | 11-*cis*- | | 11-*cis*,13-*cis*- | | 9-*cis*,11-*cis*,13-*cis*- | |
|---|---|---|---|---|---|---|---|
| | 9-*cis*,11-*cis*-**11b** | **7b** | **10b** | **8b** | **12b** | **9b** | **13b** |
| $\lambda_\alpha$, nm ($\epsilon$) | 370 (8000) | 358 (10 000) | 376 (12 000) | 357 (5000) | 370 (7000) | 362 (3000) | 365 (3000) |
| $\lambda_\beta$, nm ($\epsilon$) | 294 (14 000) | 288 (19 000) | 292 (18 000) | 300 (27 000) | 295 (21 000) | 299 (23 000) | 300 (21 000) |
| $\lambda_\gamma$, nm ($\epsilon$) | 252 (13 000) | 251 (20 000) | 256 (20 000) | | | | |
| $\lambda_\delta$, nm ($\epsilon$) | 232 (15 000) | 235 (18 000) | 232 (18 000) | 236 (20 000) | 227 (23 000) | 233 (19 000) | 235 (18 000) |

[a] In 95% EtOH. For data in other solvents, see the Supplementary Material.

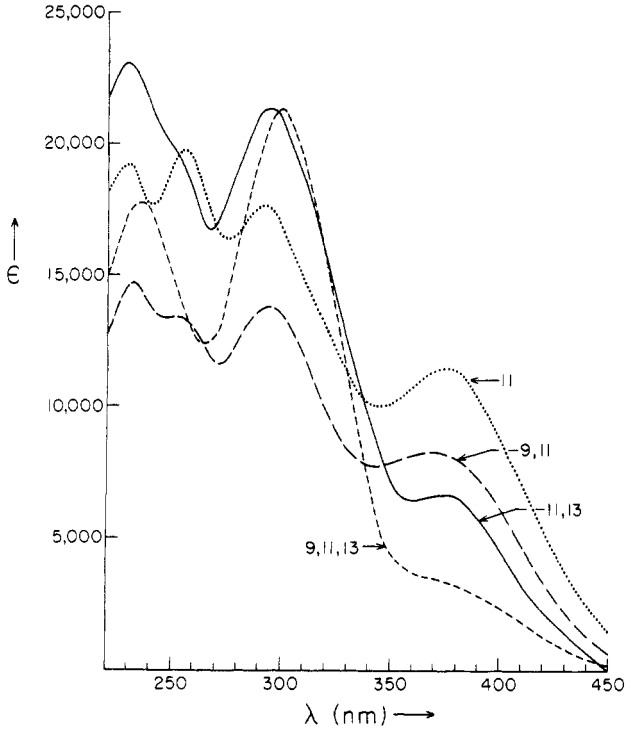


**Figure 1.** UV absorption spectra (95% ethanol) of the 12,20-tetramethyleneretinals: 11-*cis*-**10b**, 9-*cis*,11-*cis*-**11b**, 11-*cis*,13-*cis*-**12b**, and 9-*cis*,11-*cis*,13-*cis*-**13b**. See supplementary material for UV data in other solvents.

of 12-s-cis conformations in retinals. On this basis, we postulate that the parent 11-*cis*,13-*cis*- and 9-*cis*,11-*cis*,13-*cis*-retinals (**3b** and **3c**, respectively), which also exhibit similarly anamolous absorption spectra, exist primarily in twisted 12-s-cis conformations.[6,7]

The reversal in intensity of the $\alpha$ and $\beta$ bands is not as marked in the 11-cis- (**7b** and **10b**) and 9-cis,11-cis-isomers (**11b**). These isomers exhibit very prominent $\gamma$ bands ($\sim$250 nm) and, in fact in the 11-cis-isomers **7b** and **10b**, the main maxima are at 251 and 256 nm, respectively. In contrast, the corresponding 12-s-trans-locked 11-cis-isomer exhibits a weak $\gamma$ band and the 9-cis,11-cis isomer does not exhibit an observable $\gamma$ band.[22] That the parent 11-*cis*- and 9-*cis*,11-*cis*-retinals exhibit fairly strong and moderate $\gamma$ bands,[9] respectively, seems to suggest that these isomers exist at least partially as 12-s-cis conformers. It appears that while the combination of 11-cis geometry and 12-s-cis conformation in retinals results in prominent $\gamma$ bands, the concomitant introduction of 9-cis geometry decreases the intensity of this band and of 13-cis geometry results in the absence of this band.

The electronic absorption spectrum of the natural chromophore 11-*cis*-retinal **3a** exhibits most unusual properties. At low temperatures, especially in polar solvents, the intensity of the $\alpha$ band is increased while that of the $\beta$ and $\gamma$ bands is somewhat decreased. This temperature dependence has been interpreted in terms of preferential stabilization of the 12-s-trans conformer at low temperatures.[27] Calculations utilizing singly and doubly excited configurations in the PPP formalism predict that the oscillator strength for the $^1B^*_u{}^+$ absorption ($\alpha$ band) is increased for the 12-s-trans conformations of 11-*cis*-retinal while the oscillator strength for the $^1A^*_g{}^+$ absorption ($\beta$ band) is increased for the 12-s-cis conformations.[28] Our results on the 12-s-cis-locked 11-*cis*-retinals **7b** and **10b** (strong $\beta$ and $\gamma$ bands and moderate $\alpha$ bands) taken in conjunction with those on Nakanishi's 12-s-trans-locked analogue (strong $\alpha$ band and moderate $\beta$ and $\gamma$ bands)[22] are in accord with the calculations and are supportive of a scenario in which 11-*cis*-retinal exists in solution as an equlibrium mixture of 12-s-cis and 12-s-trans conformers with increased population of the 12-s-trans conformation at low temperatures.

In summary, this study provides a clear delineation of the thermal requirements of the [1,5]-sigmatropic hydrogen shift of 9,10-allenes of the vitamin A series and reveals how a manipulation of these requirements can provide direct access to 11-*cis*-,9-*cis*,11-*cis*, 11-*cis*,13-*cis*-, and 9-*cis*,11-*cis*-13-*cis*-retinoids. The unusual propensity of 9-*cis*,11-*cis*-retinyl polyenes to rearrange to polycyclic compounds has been firmly established. Finally, the class of retinoids resulting from this study, besides exhibiting unusual electronic absorption spectral properties, constitute potentially interesting probes of the binding site of the vertebrate pigment rhodopsin. And, in addition, in light of recent reports[29] ascribing high activity in the chemoprophylaxis of epithelial cancer to retinoids possessing 12-s-cis topologies, the new analogues **7–13** are attractive candidates for related biological evaluation.

## Experimental Section

**General Data.** Spectroscopic ($^1$H NMR, $^{13}$C NMR, IR, UV, and high- and low-resolution mass spectra) data are given in the supplementary material. Air-sensitive materials were generally stored under argon in a −80 °C freezer, and reactions involving organometallic materials were performed under an atmosphere of dry argon. References to aqueous $NaHCO_3$, $NH_4Cl$, or NaCl during experimental workup procedures refer to saturated aqueous solutions unless otherwise stated. Dry ether or THF (tetrahydrofuran) refers to reagent grade material freshly distilled from $LiAlH_4$ under argon. 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 by 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-$\mu$m particle size, 9.4 mm i.d. × 50 cm) column was used for normal-phase conditions unless otherwise noted. All chromatography solvents were distilled prior to use. Solvents and solvent mixtures were vacuum filtered through a 0.45-$\mu$m Millipore filter and vacuum degassed immediately prior to use. Open-column chromatography was performed by using J. T. Baker silica gel (60–200 mesh). Thin-layer chromatography (TLC) was performed by using precoated plates (silica gel 60 F-254 from MCB-Merck).

**1-Bromo-2-ethenylcyclohexene (16a).** To a suspension of methyltriphenylphosphonium bromide (18.9 g, 0.053 mol) in dry ether (150 mL) in a three-necked, 500-mL round-bottom flask (magnetic stir bar, reflux condenser with a nitrogen inlet, dropping funnel, and a rubber septum) was added dropwise *n*-butyllithium in hexane (34.6 mL, 1.53 M, 0.053

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mol). The mixture was heated at reflux for 4 h and then cooled to room temperature. A solution of the bromo aldehyde **15a** (10 g, 0.053 mol) in dry ether (25 mL) was added to the mixture, and then the mixture was successively heated at reflux for 14 h, cooled to room temperature, and filtered. The filtrate was dried over $MgSO_4$ and then concentrated under vacuum. The residue was chromatographed (silica gel/ether) and then distilled to yield the bromodiene **16a** (5.3 g, 54%; bp 68 °C (3.7 mm)).

**1-Bromo-2-(2-hydroxyethyl)cyclohexene (17a).** To a solution of bromo diene **16a** (5 g, 26.7 mmol) in dry THF (25 mL) in a three-necked, 100-mL round-bottom flask (magnetic stir bar, condenser with a nitrogen inlet, and a rubber stopple) was added dropwise a solution of 9-borabicyclo[3.3.1]nonane in THF (9-BBN; 53.4 mL, 0.5 M, 26.7 mmol). The mixture was stirred at room temperature for 26 h and then quenched by the addition of methanol (25 mL). The mixture was transferred to a 200-mL round-bottom flask, cooled in ice, and then treated successively with 37.5 mL of 3 M NaOH and 37.5 mL of 30% $H_2O_2$. The mixture was heated at reflux for 3 h and cooled to room temperature. The aqueous layer was saturated with $K_2CO_3$, and then the mixture was extracted repeatedly with ether. The organic extracts were combined, washed with saturated brine, dried over $MgSO_4$, and then concentrated under vacuum. The residual oil was chromatographed [silica gel; 25% ether (lbpe)] and then distilled to yield the bromo alcohol **17a** (94 °C (1.1 mm); 4.7 g, 86%).

**1-Bromo-2-(2-(*tert*-butyldimethylsiloxy)ethyl)cyclohexene (18a).** To a solution of *tert*-butyldimethylsilyl chloride (4.4 g, 29.2 mmol) and imidazole (4.0 g, 58.7 mmol) in dry DMF (35 mL) was added dropwise under nitrogen a solution of bromo alchol **17a** (4.00 g, 19.5 mmol) in dry DMF (10 mL). The mixture was stirred at room temperature for 3 h, quenched with 80 mL of 1 M HCl, and then extracted with 5 × 150 mL of ether. The ether extracts were combined, washed with 1 × 100 mL of saturated $NaHCO_3$, 1 × 100 mL of saturated brine, dried over $MgSO_4$ and then concentrated under vacuum. The residue was chromatographed (silica gel, lbpe) and then distilled to afford the silyl ether **18a** (bp 94 °C (0.05 mm); 5.25 g, 84.3%).

**Preparation of 12,20-Trimethylene-10,14-*retro*-retinyl *tert*-Butyldimethylsilyl Ether (5a).** (A) The bromosilyl ether **18a** (515 mg, 1.61 mmol) was placed in a dry, long-necked 10-mL round-bottom flask equipped with a stirring bar. The flask was flushed with dry argon, through a stopple, charged with 3 mL of dry ether, and cooled to −78 °C. To the stirred solution was added dropwise via syringe a solution of *tert*-butyllithium in pentane (1.65 mL of 2.05 M, 3.38 mmol), and the mixture was stirred for 4.5 h.

(B) 2-Methoxy-2-methylbut-3-yne (160 mg, 1.63 mmol) was placed in a dry, long-necked 10-mL round-bottom flask equipped with a stirring bar. The flask was flushed with argon through a stoppled inlet, charged with 2 mL of dry ether, and then cooled to −10 °C (dry ice/ethylene glycol bath). A solution of *n*-butyllithium in hexane (1.02 mL of 1.6 M; 1.63 mmol) was added slowly via syringe and the mixture stirred for 15 min.

(C) Cuprous iodide (308 mg, 1.62 mmol) was placed in a dry, long-necked 50-mL round-bottom flask equipped with a stirring bar. The stoppled flask was flushed with dry argon, charged with 5 mL of dry ether, and than cooled to −10 °C. The suspension of lithioalkyne (prepared in part B above) was transferred into the flask via a double-ended needle, and the mixture was stirred for 20 min and then cooled to −78 °C. The solution of vinyllithium (prepared in part A above) was then transferred into the flask via a double-ended needle and the mixture stirred for 1 h. After a cold (−78 °C) solution of the benzoate **19** (496 mg, 1.54 mmol) in 4 mL of dry ether was added to the reaction mixture via a double-ended needle, the mixture was stirred for 6 h and warmed to room temperature over 0.5 h. The reaction was quenched with 0.5 mL of water, the resultant solids were removed by vacuum filtration through Celite, and the filtrate was concentrated under vacuum. The residue was passed through a short column (silica gel; 2% pyridine/lbpe) and then the vacuum-dried product was used in the next step without further purification.

**Preparation of 12,20-Trimethylene-10,14-*retro*-retinol (5b).** The crude vinylallene silyl ether **5a** (preceding experiment) was placed in a 25-mL round-bottom flask equipped with a stirring bar and stoppled with an argon inlet. A solution of tetra-*n*-butylammonium fluoride in THF (10 mL of 1 M) was added via syringe and the mixture stirred for 4.5 h. The reaction was quenched with 50 mL of saturated brine and the mixture extracted with 2 × 100 mL of 1:1 ether/lbpe and 1 × 50 mL of ether. The organic extracts were combined, washed with 1 × 30 mL of saturated $NaHCO_3$ solution and 1 × 30 mL of saturated brine, dried ($MgSO_4$), and then concentrated under vacuum. The residue was chromatographed on a short silica column. After elution with 2% pyridine/lbpe, the fraction eluting with 2% pyridine/30% ether/lbpe was collected and then concentrated. The residue was subjected to preparative high-pressure LC (Whatman Partisil M9 10/50; 15% ethyl acetate/skellysolve B; 4.0 mL/min) to yield the desired product **5b** (213 mg; 42.5% yield for the coupling and deprotection steps based on benzoate **19**).

**Thermolysis of 12,20-Trimethylene-10,14-*retro*-retinol (5b).** To 250mL of refluxing hexane (freshly distilled from $LiAlH_4$ and then deaerated by argon bubbling) was added a solution of the vinylallenol **5b** (167 mg, 0.51 mmol) in 50 mL of hexane. The mixture was heated for 4 h and cooled, and then the solvent was removed under vacuum. The residue was subjected to preparative high-pressure LC (Whatman Partisil M9 10/50; 15% ethylacetate/skellysolve B; 4.0 mL/min) to yield four products eluted as follows: cyclized compound **24** (20 mg, 12%) 11-*cis*,13-*cis*-**8a** (55 mg, 33%), 11-*cis*-**7a** (23 mg, 14%), and 9-*cis*,11-*cis*,13-*cis*-**9a** (38 mg, 23%). Each of the thermal products when individually heated under the reaction conditions (refluxing hexanes, 4 h) remained unchanged.

**12,20-Trimethyleneretinals 7b, 8b, and 9b. General Procedure.** The 12,20-trimethyleneretinol **8a** (20 mg, 0.061 mmol) was dissolved in 3 mL of lbpe in a 10-mL round-bottom flask covered with aluminum foil and equipped with a $N_2$ inlet. The solution was cooled (ice bath), and then activated $MnO_2$ (300 mg) was added with stirring. The reaction mixture was stirred at 0 °C until no starting material was observable (1 h for a typical procedure) by TLC (silica gel; 30% $Et_2O$/lbpe). The reaction mixture was filtered through Celite under vacuum and the $MnO_2$ residue washed several times with ether. The filtrate was concentrated in vacuo and the product **8b** isolated (14 mg, 70%) by high-pressure LC (Whatman Partisil M9 10/50; 5% ethyl acetate/skellysolve B; 4.0 mL/min). The 12,20-trimethylene-11-*cis*- (**7b**) and 9-*cis*,11-*cis*,13-*cis*-retinals (**9b**) were prepared by the same procedure. Yields of ~80% were typical.

**1-Bromo-2-ethenylcycloheptene (16b).** To methyltriphenylphosphonium bromide (18.5 g, 53 mmol) in dry ether (200 mL) in a three-necked round-bottom flask under nitrogen was added *n*-butyllithium (1.5 M in hexane, 52 mmol) by syringe, and then the solution was refluxed for 4 h. The reaction mixture was allowed to cool, and then the bromoaldehyde **15b** (10.65 g, 52 mmol) was added slowly via dropping funnel. The mixture was refluxed for 17 h (monitored by TLC). The cooled mixture was filtered and the solid extracted with ether. The ether extracts were washed with water and then with aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated under vacuum at room temperature. The product was purified by flash chromatography and then Kugelrohr distilled (bp 75–80 °C (0.65 mm)) to afford 8.45 g (81%) of **16b**.

**1-Bromo-2-(2-hydroxyethyl)cycloheptene (17b).** The bromide **16b** (8.05 g, 0.04 mmol) in dry THF (100 mL) was reacted with a THF solution of 9-BBN (180 mL, 0.5 M, 0.09 mmol) and then oxidized (40 mL of $CH_3OH$, 50 mL of 3 M NaOH, 50 mL of 30% $H_2O_2$) in the same manner as in the preparation of the six-membered-ring derivative **17a**. After the prescribed workup, chromatography followed by vacuum drying afforded 5.7 g (65%) of **17b**, which was silylated directly as described in the next section.

**1-Bromo-2-(2-(tert-butyldimethylsiloxy)ethyl)cycloheptene (18b).** The bromo alcohol **17b** (4.9 g, 22.4 mmol) was reacted with *tert*-butyldimethylsilyl chloride (5.19 g, 34.4 mmol) according to the procedure described for the six-membered-ring silyl ether **18a** to give **18b** (bp 125 °C (1.0 mm); 7.2 g, 96%).

**Preparation of 12,20-Tetramethylene-10,14-*retro*-retinyl *tert*-Butyldimethylsilyl Ether (6a).** The bromosilyl ether **18b** (425 mg, 1.275 mmol) was coupled with the propargyl benzoate **19** (415 mg, 1.29 mmol) by using the procedure described for the corresponding six-membered-ring ether **5a**. The product was partially purified as before by short column chromatography (silica gel; 2% pyridine/lbpe), but it was apparent by $^1H$ NMR that rearrangement had already commenced. However, the presence of allene **6a** was signal by the presence of an IR band at $\nu$ ~1920 $cm^{-1}$. The crude material was subjected to deprotection conditions, which produced directly the rearranged retinols **10a**, **11a**, **12a**, and **13a**, as described in the next step.

**Preparation of 12,20-Tetramethyleneretinols 10a, 11a, 12a, and 13a.** The crude vinylallene silyl ether **6a** (preceding experiment) was deprotected with $(n\text{-}Bu)_4NF$ as described for the preparation of 12,20-trimethylene-10,14-*retro*-retinol (**5b**). After workup, the product was passed through a short column (silica gel; 2% pyridine/30% ether/lbpe) and concentrated under vacuum. Examination of the product at this stage by $^1H$ NMR and IR spectroscopy indicated that the vinylallene had undergone complete rearrangement to the retinols. The mixture was subjected to preparative high pressure LC (Whatman Partisil M9 10/50; 15% ethyl acetate/skellysolve B; 4.0 mL/min) to give in order of elution: a mixture of 11-*cis*-**10a** and 11-*cis*,13-*cis*-**12a**; 9-*cis*,11-*cis*,13-*cis*-**3a**; and 9-*cis*,11-*cis*-**11a**. The mixture of 11-*cis*-**10a** and 11-*cis*,-13-*cis*-**12a**, the former eluting first, was separated by further subjection to reversed-phase high-pressure LC (Whatman Partisil M9 10/50 ODS-2, $CH_3CN$, 4.0 mL/min). The four 12,20-tetramethyleneretinols were obtained in the following yields (a 37% total mass balance after separation based on the

bromo silyl ether **18b**): 11-*cis*-**10a** (23.4 mg, 5.4%), 11-*cis*,13-*cis*-**12a** (43.4 mg, 10%), 9-*cis*,11-*cis*,13-*cis*-**13a** (65.2 mg, 15%), and 9-*cis*,11-*cis*-**11a** (29.6 mg, 6.8%).

**12,20-Tetramethyleneretinals 10b, 11b, 12b, and 13b. General Procedure.** The seven-membered ring 12,20-tetramethyleneretinals were prepared by $MnO_2$ oxidation of the corresponding retinols according to the procedure described for the six-membered-ring 12,20-trimethyleneretinals **7b**, **8b**, and **9b**. The four seven-membered-ring isomers 11-*cis*-**10b**, 9-*cis*,11-*cis*-**11b**, 11-*cis*,13-*cis*-**12b**, and 9-*cis*,11-*cis*,13-*cis*-**13b** were prepared in yields ranging from 50 to 80%.

**Preparation of Cyclized Product 29: Thermolyses of 12,20-Tetramethylene-9-*cis*,11-*cis*-retinol (11a) and -9-*cis*,11-*cis*,13-*cis*-retinol (13a).** The 9-cis,11-cis-isomer **11a** (~2 mg) in freshly distilled hexanes (10 mL) was added under argon to a refluxing solution of hexanes (100 mL). Aliquots were removed at various time intervals and analyzed by high-pressure LC (Waters μ-porasil column, 15% ethyl acetate/skellysolve B). Essentially quantitative conversion of the retinol **11a** to the cyclized product **29** was complete in ~3 h. By contrast, the 9-cis,11-cis,13-cis-isomer **13a** was recovered unchanged ($^1$H NMR, high-pressure LC) after 4 h in refluxing hexanes.

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**Registry No. 5a**, 83043-81-6; **5b**, 83043-82-7; **6a**, 85236-03-9; **6b**, 85236-04-0; **7a**, 83043-76-9; **7b**, 83043-75-8; **8a**, 83043-78-1; **8b**, 83043-77-0; **9a**, 83043-80-5; **9b**, 83043-79-2; **10a**, 85236-05-1; **10b**, 85236-06-2; **11a**, 85236-07-3; **11b**, 85236-08-4; **12a**, 85236-09-5; **12b**, 85236-10-8; **13a**, 85236-11-9; **13b**, 85236-12-0; **15a**, 38127-47-8; **15b**, 85236-13-1; **16a**, 83043-84-9; **16b**, 85236-14-2; **17a**, 85236-15-3; **17b**, 85236-16-4; **18a**, 83043-83-8; **18b**, 85236-17-5; **19**, 74723-00-5; **24**, 83060-55-3; **29**, 85236-18-6; 2-methoxy-2-methylbut-3-yne, 13994-57-5.

**Supplementary Material Available:** Spectral and analytical data (12 pages). Ordering information is given on any current masthead page.

# Unified Stereochemical Model of Polyether Antibiotic Structure and Biogenesis[1a]

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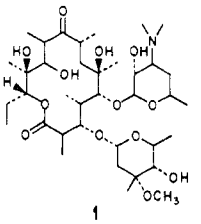
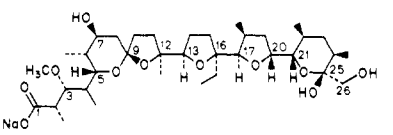
**Abstract:** A unified stereochemical model is proposed which correlates the structure and stereochemistry of a large number of polyether antibiotics and which suggests the biosynthetic basis for this perceived structural regularity. Two stereochemical prototypes, illustrated in Figure 3, parts A and B, summarize the stereochemical patterns of more than 30 different polyether antibiotics of the APPA and PAPA structural families.

Macrolide lactones[2] such as erythromycin (**1**) and the polyether antibiotics[3] typified by monensin (**2**) and lasalocid (**3**) are two important classes of antibiotics produced by actinomycetes. The two classes have been compared because the polyethers are branched-chain, polyoxygenated carboxylic acids and the macrolides are branched-chain, polyoxygenated carboxylic lactones. Apart from this formal resemblance, however, the structures, biochemical modes of action, and antimicrobial spectra of these two groups of metabolites are quite distinct. Specifically, whereas most macrolides act as inhibitors of protein biosynthesis at the ribosomal level,[4] the polyethers exert their effects by interfering with permeability barriers to ion transport across biological membranes.[3a,5] Erythromycin is one of the most widely used antibiotics in human medicine, whereas monensin and lasalocid are major agents in the control of coccidiosis in poultry and in the improvement of feed utilization in ruminant livestock. Nonetheless, intriguing structural parallels exist between these two important groups of natural products. The biogenetic basis of this structural similarity is the common origin of these complex natural products from the simple precursors acetate, propionate, and butyrate by a sequence of transformations analogous to, but certainly not identical, with classical saturated fatty acid biosynthesis.



1



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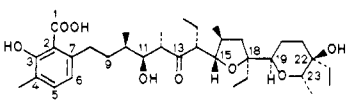

3

Some 150 macrolides have been characterized since the discovery of pikromycin in 1951.[6] In spite of the diversity of

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