direct carbanion addition to 2,6-dimethylbenzoquinone under conditions where the anion was unaggregated, weakly solvated and had a small counterion.[9] However, in that study we noted that when the inherent steric requirements of the carbanion become very large (e.g., secondary carbanions), selective attack at the more hindered carbonyl carbon is no longer possible. Our mechanistic studies with **1** had led us to a simple solution to this problem. Since the ring-opening reaction (**2** → **3**) exhibits a much larger temperature dependence than the competing addition process (**2** → **5**), secondary carbanions can be cleanly added to **1** at very low temperatures (see last entry in Table I) to produce (after quenching and ketal hydrolysis) **7** in good yield.[10]

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Registry No. 1, 85268-20-8; **4**, 85268-21-9; **6** (R = Me), 85268-22-0; **6** (R = Bu), 85268-23-1; **6** (R = *sec*-Bu), 85268-24-2; **6** (R = *t*-Bu), 85268-25-3; $(CH_3)_2Cu{\cdot}Li$, 15681-48-8; CH_3Li, 917-54-4; CH_3MgBr, 75-16-1; *n*-C_4H_9Li, 109-72-8; *n*-C_4H_9MgBr, 693-03-8; *sec*-C_4H_9Li, 598-30-1; *t*-C_4H_9Li, 594-19-4; 1-lithio-5-hexene, 85268-26-4.

(9) Liotta, D.; Saindane, M.; Barnum, C. *J. Org. Chem.* **1981**, *46*, 3369.
(10) **4** can be easily separated from **6** by simple base extraction.

7-*cis*,9-cis,11-*cis*-Retinal, *all-cis*-Vitamin A, and 7-*cis*,9-*cis*,11-*cis*-12-Fluororetinal. New Geometric Isomers of Vitamin A and Carotenoids. 12[1]

Alfred E. Asato, Aravinda Kini, Marlene Denny, and R. S. H. Liu*

Department of Chemistry, University of Hawaii Honolulu, Hawaii 96822

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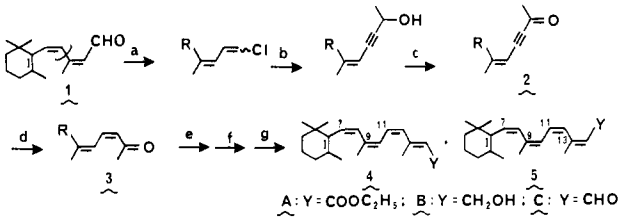
The geometric isomers of vitamin A occupy an important chapter in studies of stereospecificity of the binding site of the visual protein opsin.[2] Of its 16 possible geometric isomers, 14 are known. They are the six earlier reported 7-trans isomers (*all-trans*; 9-*cis*; 11-*cis*; 13-*cis*; 9-*cis*,13-*cis*; 11-*cis*,13-*cis*)[3] and the eight more recently reported hindered isomers (7-*cis*; 7-*cis*,9-*cis*; 7-*cis*,13-*cis*; 7-*cis*,9-*cis*,13-*cis*;[4] 7-*cis*,11-*cis*; 7-*cis*,11-*cis*,13-*cis*;[5] 9-*cis*,11-cis;[6] 9-*cis*,11-*cis*,13-*cis*[7]). Now we report the synthesis of the last two remaining isomers: 7-*cis*,9-*cis*,11-*cis* and the interesting all-*cis*.

The synthetic sequence used in the synthesis of the missing isomers of vitamin A was similar to that recently reported for the doubly hindered 7-*cis*,11-*cis* isomer[5] but with 7-*cis*,9-*cis*-β-ionylideneacetaldehyde (**1**)[4b,c] as the starting material (see Scheme I). Partial hydrogenation of the 11-dehydro-C_{18}-ketone **2** was the key step in the synthetic sequence because hydrogenation at later stages invariably led to complex mixtures. Even at the C_{18} stage, in order to avoid over hydrogenation, the reaction was carried out to only 70–80% completion. Since the 11-dehydro compounds were found more easily separated at a later stage, the *all-cis*-C_{18}-ketone **3** mixed with small amounts of the dehydro ketone was used in the chain-extension reaction. Ethyl lithio(trimethylsilyl)acetate, **6**, was chosen as the reagent because of its demonstrated higher reactivity and the concomitant lack of stereospecificity.[8] The crude condensation product mixture was partially separated by flash column chromatography. The early fractions were the 11-dehydro esters. The later fractions contained two components, subsequently separated by preparative HPLC. Their structures were readily deduced from their 300-MHz ^1H NMR spectra (see supplemental material).[9] The early eluting fraction was ethyl 7-*cis*,9-*cis*,11-*cis*-retinoate (**4A**) with the 13-trans geometry indicated by the low-field CH_3-13 signal, the 7-cis and the 11-cis geometry by the small coupling constants, and the 9-cis geometry by the low-field H_8 signal.[10] For similar reasons, the principal of the later eluting fraction was identified to be ethyl *all-cis*-retinoate (**5A**). The UV–vis absorption spectra of both compounds with the much blue shifted absorption maxima (328 and 330 nm in hexane) are consistent with the expected nonplanar conformation of these severely crowded isomers.

A mixture of the two C_{20} esters was converted to the corresponding aldehydes[4a] and separated by preparative HPLC with the mixtures of isomeric 11-dehydroretinals conveniently eluted in early fractions. The first eluted retinal isomer was 7-*cis*,9-*cis*,13-*cis*-retinal, identified by comparison of ^1H NMR spectra.[4b] Since all operations were carried out at room temperature, this was an expected isomer from facile thermal isomerization of

Scheme I



[a] Ph_3PCH_2Cl, X; BuLi. [b] 2BuLi; CH_3CHO. [c] MnO_2. [d] H_2–Lindlar catalyst. [e] $Me_3SiCHCO_2EtLi$, **6**. [f] Dibal-H. [g] MnO_2 (R = *cis*-$C_{11}H_{17}$ (see structure **1**)).

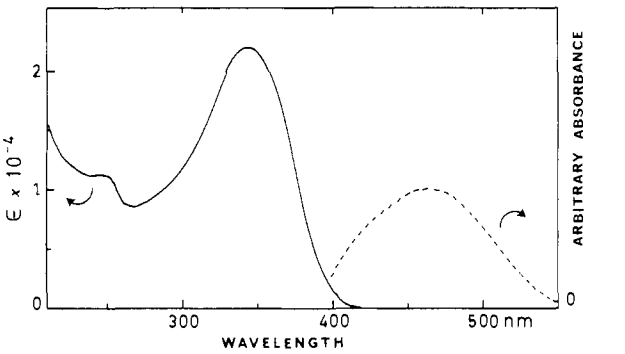


Figure 1. UV–vis absorption spectrum of 7-*cis*,9-*cis*,11-*cis*-retinal in cyclohexane (solid line), λ_{max} 345 nm (ε 22 000), and difference absorption spectrum of 7-*cis*,9-*cis*,11-*cis*-rhodopsin (dashed line) in 1% digitonin, obtained after taking the difference between the spectra of the pigment in an excess of hydroxylamine before and after photobleaching with yellow light.

(1) For previous paper in the series see: Asato, A. E.; Mead, D.; Denny, M.; Bopp, T. T.; Liu, R. S. H. *J. Am. Chem. Soc.* **1982**, *104*, 4979–4981.
(2) (a) Wald, G. *Science* (*Washington*, D.C.) **1968**, *162*, 230–239. (b) Liu, R. S. H. In "Carotenoid Chemistry and Biochemistry"; Britton, G., Goodwin, T. W., Eds.; Pergamon Press: New York, 1982; pp 253–264.
(3) Wald, G.; Brown, P. K.; Hubbard, R.; Oroshnik, W. *Natl. Acad. Sci. U.S.A.* **1955**, *41*, 438–450; **1956**, *42*, 578–580.
(4) (a) Ramamurthy, V.; Liu, R. S. H. *Tetrahedron* **1975**, *31*, 201–206. (b) Asato, A. E.; Liu, R. S. H. *J. Am. Chem. Soc.* **1975**, *97*, 4128–4130. (c) Liu, R. S. H.; Asato, A. E. *Methods Enzymol.* **1982**, *88*, 506–516.
(5) Kini, A.; Matsumoto, H.; Liu, R. S. H. *J. Am. Chem. Soc.* **1979**, *101*, 5078–5079.
(6) Kini, A.; Matsumoto, H.; Liu, R. S. H. *Bioorg. Chem.* **1980**, *9*, 406–410.
(7) Knudsen, C. G.; Carey, S. C.; Okamura, W. H. *J. Am. Chem. Soc.* **1980**, *102*, 6355–6356.
(8) Taguchi, H.; Shimoji, K.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 2529–2529.
(9) Recorded on a Nicolet NT-300 spectrometer acquired through a grant by the National Science Foundation (CHE 8100240) and the University of Hawaii.
(10) For ^1H NMR data of geometric isomers of retinoids, see: (a) Patel, D. *Nature* (*London*) **1969**, *221*, 825–827. (b) Vetter, W.; Englert, G.; Rigassi, N.; Schwieter, U. In "Carotenoids"t; Isler, O., Ed.; Birkhäuser Verlag: Basel, 1971; p 213–225. (c) Reference 4c.

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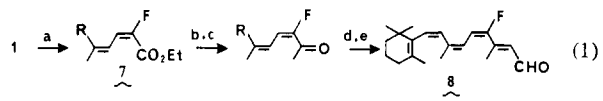
Scheme II



(1)

[a] $(EtO)_2POCFHCO_2Et$, 9, LDA. [b] MeOH/KOH. [c] MeLi. [d] $(EtO)_2POCH_2CO_2Me$, NaH, C_6H_5/DMF (9:1). [e] $LiAlH_4$ (-78 °C); MnO_2 (R = *cis*-$C_{11}H_{17}$).

all-cis-retinal via consecutive six-electron electrocyclization reactions known for all retinal isomers containing the 11-*cis*,13-*cis* geometry.[3,5,7] The ^1H NMR spectrum of the major product was that of a new retinal isomer. At 300 MHz, its spectrum was of first order, thus peaks readily were assignable. The assignments were confirmed by selective decoupling experiments. The chemical shifts of CH_3-5, H_8, and CH_3-13 revealed respectively the 7-cis, 9-cis, and 13-trans geometry while the magnitudes of $J_{7,8}$ and $J_{11,12}$ were consistent only with the cis geometry at both centers. Therefore, the new isomer must be 7-*cis*,9-*cis*,11-*cis*-retinal (**4C**). The UV spectrum (Figure 1) displayed features similar to those of 7-*cis*,11-*cis*-retinal.[5]

all-cis-Retinol (**5B**) was obtained in quantitative yield by reduction of ethyl *all-cis*-retinoate (**5A**) by Dibal-H at -70 °C. Its ^1H NMR spectrum was readily assigned after selective decoupling experiments. The magnitude of the vinyl coupling constants and chemical shifts of the vinyl and CH_2-15 hydrogens showed retention of the all-cis geometry.[10b] The compound, a colorless oil, was found to be stable even after several months of storage at 0 °C under nitrogen.

As in the case of other hindered isomers of retinal,[5,6,11] 7-*cis*,9-*cis*,11-*cis*-retinal was found to give a low yield (28%) of a pigment analogue (see Figure 1 for the difference absorption spectrum) when incubated with a digitonin solution of bovine opsin. The slow rate of pigment formation, $k_2 = 0.02\ M^{-1}\ s^{-1}$, is similar to that of 7-*cis*,11-*cis*-retinal.[12] Properties of the pigment analogue including the photobleaching characteristics will be examined in detail.

We have also prepared a fluorinated analogue of the tri-cis isomer 7-*cis*,9-*cis*,11-*cis*-12-fluororetinal, **8** (7*Z*,9*Z*,11*E*,13*E*), Scheme II. As observed earlier,[13] reaction of the fluoro-C_2-phosphonate, **9**, gave preferentially the cis geometry (12*E*) at the newlys formed double bond. The isolated C_{17}-fluoro ester, **7**, (flash column chromatography) was elaborated in the conventional fashion (17 + 1 + 2).[13] The conditions for the C_2-chain-extension reaction was for selective formation of the 13-trans geometry.[5] Assignment of the tri-cis geometry was again by its NMR data and by comparison with those of the other known isomers.[13]

In summary, the current effort not only brings to a conclusion of preparation of stereoisomers of vitamin A but also demonstrates further the stability of the hindered isomers, which was once questioned.[14]

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Supplementary Material Available: ^1H NMR data of *all-cis*-C_{18}-ketone, 7-*cis*,9-*cis*,11-*cis*- and *all-cis*-vitamin A, and 12-fluoro-7-*cis*,9-*cis*,11-*cis*-retinal, the complete ^1H NMR spectrum of 7-*cis*,9-*cis*,11-*cis*-retinal and selective decoupled vinyl signals, and chromatographic separation conditions (3 pages). Ordering information is given on any current masthead page.

(11) DeGrip, W. J.; Liu, R. S. H.; Ramamurthy, V.; Asato, A. E. *Nature (London)* **1976**, *262*, 416-418.
(12) The bimolecular rate constant for formation of 7-*cis*,11-*cis*-rhodopsin reported in ref 5 was incorrect. It should read 0.04 $M^{-1}\ s^{-1}$. For details, see: Liu, R. S. H.; Matsumoto, H.; Kini, A.; Asato, A. E.; Kropf, A.; deGrip, W. J. *Tetrahedron*, in press.
(13) Liu, R. S. H.; Matsumoto, H.; Asato, A. E.; Denny, M.; Shichida, Y.; Yoshizawa, T.; Dahlquist, F. W. *J. Am. Chem. Soc.* **1981**, *103*, 7195-7201.
(14) Pauling, L. *Fortschr. Chem. Org. Naturst.* **1939**, *3*, 203-235.

Stereochemistry of the Olefin Metathesis Reaction: Theoretical Extended Hückel Study of Substituted Metallacyclobutanes

B. Tinland*

ERA No. 600, CNRS Université Claude Bernard 69622 Villeurbanne, France

F. Quignard, M. Leconte, and J. M. Basset*

Institut de Recherches sur la Catalyse, CNRS 69626 Villeurbanne Cédex, France

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It has been claimed that the stereochemistry of the olefin metathesis reaction is governed by the various interactions occurring in the puckered metallacyclobutane intermediate.[1-6] This assumption was largely based on experimental data related to the metathesis of various olefins with group 6 metal-based catalysts.[5,6] The hypothesis of ring puckering was deduced from structural data related to a series of stable substituted or unsubstituted platinacyclobutanes.[7,8] Recent X-ray studies of a titanacyclobutane complex $Cp_2TiCH_2CHRCH_2$ (R = phenyl) indicate that a metallacyclobutane complex may be planar and may exhibit a moderate degree of activity and stereoselectivity in metathesis.[9,10] A similar system, $Cl_2TiCH_2CH_2CH_2$, studied by Goddard[11] using ab initio calculations was found to be planar. However, both systems have no substituents in the 1-3-positions. One may reasonably assume that if substituents were present in the 1-3-positions, a certain degree of puckering could have occurred.[12] It was therefore necessary to investigate (i) whether or not the presence of substituents in the metallacycle will favor a puckered conformation, (ii) what the favored conformations with substituents in the 1-2- or 1-3-positions are, and (iii) what the effect of the group 6 transition metal is.

As model of our extended Hückel calculations we took a six-coordinate metallacyclobutane complex, $Cl_4MCHR_1CHR_2CHR_3$ (M = Cr, W; $R_1 = CH_3$; R_2 = H, CH_3; R_3 = H, CH_3, C_2H_5) for which the d^4 electron count is assumed to be the most favored configuration.[13] The metallacyclobutane was assumed to be pseudooctahedral with classical M-C, M-Cl, and C-C bond lengths values,[14] with a C_1-M-C_3 angle close to that found in

(1) T. J. Katz and J. McGinnis, *J. Am. Chem. Soc.*, **97**, 1592 (1975).
(2) T. J. Katz and W. H. Hersh, *Tetrahedron Lett.*, 585 (1977).
(3) C. P. Casey, L. D. Albin, and T. J. Burkhardt, *J. Am. Chem. Soc.*, **99**, 2533 (1977).
(4) J. L. Bilhou, J. M. Basset, R. Mutin, and W. F. Graydon, *J. Am. Chem. Soc.*, **99**, 4083 (1977).
(5) M. Leconte and J. M. Basset, *J. Am. Chem. Soc.*, **101**, 7296 (1979).
(6) N. Calderon, J. P. Lawrence, and E. A. Ofstead, *Adv. Organomet. Chem.*, **17**, 449 (1979).
(7) R. D. Gillard, M. Keeton, R. Mason, M. F. Pilbrow, and D. R. Russell, *J. Organomet. Chem.*, **33**, 247 (1971).
(8) R. Schlodder, J. A. Ibers, M. Lenarda, and M. Graziani, *J. Am. Chem. Soc.*, **96**, 6893 (1974).
(9) T. R. Howard, J. B. Lee, and R. H. Grubbs, *J. Am. Chem. Soc.*, **102**, 6876 (1980).
(10) J. B. Lee, G. J. Gajda, W. P. Schaefer, T. R. Howard, T. Ikariya, D. A. Straus, and R. H. Grubbs, *J. Am. Chem. Soc.*, **103**, 7358 (1981).
(11) A. K. Rappé and W. A. Goddard III, *J. Am. Chem. Soc.*, **104**, 297 (1982).
(12) In fact, Goddard[11] calculates that the metallacycle is quite floppy since a fixed puckering angle of 10° increases the energy by only 0.3 kcal/mol above that of the optimum planar molecule.
(13) O. Eisenstein, R. Hoffmann, and A. R. Rossi, *J. Am. Chem. Soc.*, **103**, 5582 (1981).
(14) The following bond lengths (Å) and angles (deg) were selected from known X-ray structures:[7,10,15,16] Cr-C_1 = Cr-C_3 = 2.05, W-C_1 = W-C_3 = 2.20, C_1-C_2 = C_2-C_3 = 1.50, M-Cl = 2.38 (M = Cr, W); C_1-M-C_2 = 77.6, Cl-M-Cl = 90.
(15) R. R. Schrock and G. W. Parshall, *Chem. Rev.*, **76**, 243 (1976).
(16) J. H. Wengrovius, R. R. Schrock, M. R. Churchill, J. R. Missert, and W. J. Youngs, *J. Am. Chem. Soc.*, **102**, 4515 (1980).

0002-7863/83/1505-2924$01.50/0