Tetrahedron Vol. 40, No. 11, pp. 1931 to 1969, 1984
Printed in Great Britain.

0040-4020/84 $5.00 + .00
Pergamon Press Ltd.

TETRAHEDRON REPORT NUMBER 165

PHOTOCHEMISTRY AND SYNTHESIS OF STEREOISOMERS OF VITAMIN A

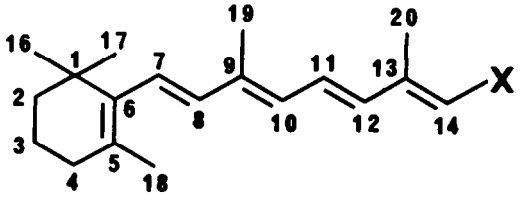
ROBERT S. H. LIU and ALFRED E. ASATO
Department of Chemistry, 2545 The Mall, University of Hawaii, Honolulu, HI 96822, U.S.A.

(*Received in U.S.A.* 31 *May* 1983)

CONTENTS

INTRODUCTION

The 1960 Symposium on Vitamin A and Metabolism held at Bürgenstock[1] marked the amazing progress in vitamin A research during the preceding years of this century. It all began with the description of the fat soluble active principal from egg yolk in 1909 by Stepp, which was subsequently designated as vitamin A by McCollum.[2] Elucidation of its structure by Karrer in 1931[3] and its first total synthesis in 1937[4] were followed by the development of the first industrial preparation by Isler and coworkers at Hoffman–La Roche[5] and several other industrial routes in rapid succession (see Section II), making vitamin A readily available. The importance of stereoisomerism of the pentaene chain was clearly recognized through the elegant work of Wald in elucidating the important role of the 11-cis and the all-trans isomers in the visual process[6] and the successful isolation, identification and synthesis of six geometric isomers of vitamin A.[7] Indeed, most of the cornerstones in vitamin A research were laid during that period.



a: X = CH_2OH
b: X = CHO
c: X = CO_2H
d: X = CO_2R
e: X = CH_2OAc
f: X = CN

Fig. 1. The structure and numbering system of all-*trans*-vitamin A.

During the last ten years, aided by rapid development of new synthetic techniques, separation methods and photochemical knowledge there has been a renewed interest in the syntheses of the missing isomers and structurally modified analogues. The discovery of new biological activities of vitamin A, dependent on geometry of the polyene chain and structural variation, also provided an added impetus for development of new methodologies for preparation of the pentaene derivatives. For example the toxicity and cancer-preventive-activity correlation studies,[8,9] acne therapy[10]—with the recent marketing of 13-*cis*-retinoic acid under the trade name of ACCUTANE,[11] and the proton pumping activities in bacteriorhodopsin as well as in vision demonstrated the importance of the polyene geometry.[12]

Of the six earlier known geometric isomers, four were labelled[13] as sterically unhindered (all-trans, 9-cis and 9,13-dicis) and two sterically hindered (11-cis and 11,13-dicis) because of 1,7-hydrogen,hydrogen interactions (Fig. 2a, b). These, however, represent only six of the possible sixteen geometric isomers (Fig. 3). For some time, missing were ten other hindered isomers

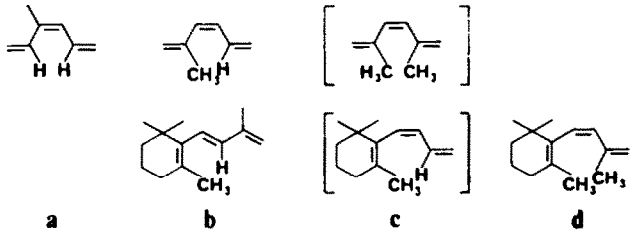


Fig. 2. Non-bonded hydrogen–hydrogen interactions in cis-isomers of vitamin A and carotenoids. (a) 1,6-interaction in 9-cis or 13-cis geometry. (b) 1,7-interaction in 11-cis or 7-trans geometry. (c) 1,8-interaction, not observed in vitamin A or naturally occurring carotenoid isomers. (d) 1,9-interaction in 7-cis geometry. Clearly, any deviation from planarity rapidly diminishes the steric crowding.

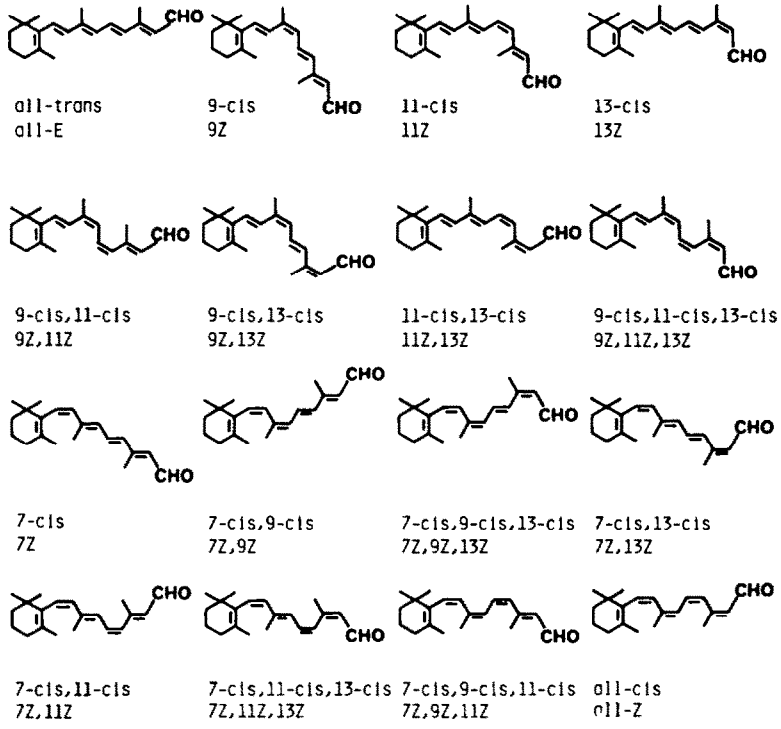


Fig. 3. Sixteen possible geometric isomers of vitamin A. While the alcohol form is commonly known as vitamin A, other derivatives also exhibit similar growth activities. To distinguish between these active compounds the following names have been recommended by IUPAC:[14,15] retinol for X = CH_2OH (**a**); retinal acetate (**e**) and retinonitrile (**f**) for X = CO_2R, CH_2OAc and CN, respectively, are also commonly used in the literature. (cf. Figure 1)

including the manifold of the eight much more sterically crowded (through 1,9-hydrogen,hydrogen interactions, Fig. 2d) isomers containing the 7-cis geometry. The syntheses of these isomers and methodologies for the stereoselective construction of the polyene chain have been of interest and is the main subject of the current review.

2. PHOTOISOMERIZATION OF POLYENES IN THE VITAMIN A SERIES

The importance of photochemical geometric isomerization of polyenes is evident not only in its role in the visual processes,[16] but also in the synthesis of geometric isomers of polyenes in general and vitamin A in particular. The studies by Zechmeister on carotenoids[17] and Hubbard and Wald on vitamin A[18] perhaps best reflect the pivotal roles played by photochemistry in the developments of the respective fields. Even the more recent activities of synthesis of stereoisomers of vitamin A and related compounds seemed to have been rekindled by new findings in the photoisomerization process.[19] It is therefore appropriate to begin this review on stereoisomers of vitamin A with a discussion on the photochemistry of homologous polyenes. The current survey will emphasize preparative aspects of the photoisomerization process and, in particular, as applied to synthesis of stereoisomers. Quantitative photochemical, photophysical and theoretical discussions on polyenes will be kept to a minimum. For detailed discussions on these subjects, particularly on the photochemistry,[20] spectroscopy and theory[20-22] on visual pigments and related chromophores, readers are referred to several excellent review articles which appeared recently in the literature.

The reactive states

Photoisomerization of polyenes in the vitamin A series can be brought about by direct irradiation[17,23] as well as by triplet photosensitization.[24] Cumulative evidence appear to suggest that different reactive states are involved under these two conditions of irradiation. For example, compounds without low lying n, π^* states (alcohols, esters, carboxylic acids, imines and hydrocarbons), generally exhibit strong fluorescence and give almost undetectable amounts of triplets.[20] (For details see later sections; reactions from the excited singlet states). For compounds with high intersystem crossing efficiencies (e.g. retinal, **Ib**), the quantum yield of triplet sensitized isomerization of the trans isomer was found to be more than an order of magnitude (< 0.002)[25,26] lower than that from direct irradiation (~ 0.10).[27-29] While the cis isomers give different sets of numbers,[28,30,31] it appears safe to conclude that direct irradiation of the trans isomer leads predominantly to reaction from the excited singlet state and sensitized irradiation results in reaction from the triplet state.

The triplet sensitized isomerization process

Selective sensitization of dienes. The photostationary state (PsS) composition of a two isomer system is a function of the product of the excitation and the decay ratios:[32,33]

$$\left(\frac{[\text{trans}]}{[\text{cis}]}\right)_{\text{PsS}} = \left(\frac{k_c}{k_t}\right)_{\text{excit.}} \left(\frac{k_t}{k_c}\right)_{\text{decay}}.$$

The decay ratio is unique to a given system and essentially independent of reaction conditions for photochemical processes (however see discussions below). Therefore, traditionally, manipulation of product composition has been accomplished through controlled variation of the excitation ratio.

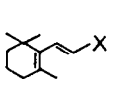
For direct irradiation the excitation ratio is the ratio of extinction coefficients ($C_c\epsilon_c/C_t\epsilon_t$) of the two isomers at the irradiation frequency. Hence the normally blue shifted absorption spectrum of the cis isomer allows the use of light of long wavelength for enrichment of the cis isomer. In the case of triplet sensitized isomerization, the excitation ratio is the rates of energy transfer from the sensitizer to the two isomeric acceptors. The possibility of varying product composition by varying rates of energy transfer was established by Hammond and coworkers in the classical study of sensitized isomerization of stilbenes and 1,3-pentadiene.[34]

The constant composition of isomers produced by high energy sensitizers could be changed by the employment of sensitizers of energy lower than that of the trans isomer. The resultant cis enriched product mixtures were due to selective pumping of the trans isomer as a result of the more favored rate of energy transfer. However, in these systems further systematic lowering of the donor energy failed to continue the increase of the cis isomer; in fact, instead a reversal of isomer

distribution resulted.[34] Measurement of rates of energy transfer showed a less rapid decrease of the transfer rates to the higher energy cis isomer than to the trans when the donor energy fell below those of each isomer.[35] The exact nature of such endothermic energy transfer generated much controversy[36] in the past but is not of concern here. Nevertheless the observation seemed to have diminished the synthetic value of the method.

Subsequently, it became evident that the latter difficulty could be eliminated in systems with a large difference in the excitation energies of the isomeric pair. One class of compound that fulfilled the condition was the sterically crowded conjugated systems with the cis isomer existing in a substantially non-planar conformation.[37] Therefore, it was shown[38] from the Saltiel plot[33] of a photostationary state study of β-ionol (**17b**) that the excitation energy difference between the two isomers exceeded ~15 kcal mol^{-1}. For the relatively planar trans isomer (NMR data of β-ionone suggest a ring-chain dihedral angle of 25–30°)[39] the excitation energy was assumed to be between 56–60 kcal mol^{-1}, a typical range of values for linear dienes.[40] However, for the non-planar cis isomer (NMR data suggested a minimum value of 40–53°),[41,42] a value of 75 kcal mol^{-1} was obtained.[38] Hence, it was not surprising that trans to cis isomerization under selective sensitization conditions was reported to be quantitative.[37,43]

Subsequent reports from this laboratory extended the method to a large number of dienes in the vitamin A series[38,44] including the simple dienes of the C_{11} (**17h**[45]), the C_{12} (**17c–g**[46]) or the C_{13} (**17a, b**[37,43]) framework and other more elaborately substituted dienes (**17k, m, n**[45–48]). Generally, any triplet sensitizer of energy between 53–60 kcal mol^{-1} [49] could be used. The common ones were α- and β-acetonaphthone. However for compounds with a highly substituted quaternary carbon at C_9 (**17p–s**[46]), isomerization was not observed under a variety of irradiation conditions. Presumably the excessive ring-chain steric repulsion in the excited state of these compounds changed the decay ratios prohibitively in favor of the trans isomer. Nevertheless, this photochemical method, including isomerization of the trienes (next section), represents a general procedure for introducing 7-cis geometry of compounds in the vitamin A series.



17

a: X = $COCH_3$
b: X = $CH(CH_3)OH$
c: X = CH_2OH
d: X = CN
e: X = CO_2Et
f: X = CO_2H
g: X = CH_3
h: X = Cl
i: X = C_2H_5
j: X = C_6H_5
k: X = $CH(CH_3)CHO$
m: X = $CH(CH_3)SO_2C_6H_5$
n: X = $CH_2CH(OH)C{\equiv}CC(CH_3){=}CH_2$
p: X = $C(CH_3)_2OH$
q: X = $C(OCH_2CH_2O)CH_3$
r: X = $C(SO_2C_6H_5)(CH_3)CH_2C_6H_5$
s: X = $C(OH)(CH_3)CH{=}CH_2$

Selective sensitization of trienes. Selective photosensitization of the trienes in the vitamin A series also resulted in the conversion of the 7-trans isomers to the two sterically crowded 7-cis isomers.[37,43] The lower triplet excitation energy of the trienes (47–8 kcal mole for the parent 1,3,5-hexatriene)[50] required the use of lower energy sensitizers. 9-Fluorenone and benzanthrone (51 and 46 kcal mol^{-1})[49] were the two most commonly used.[43] Recently, the phthalein dye sensitizers such as Rose Bengal and Eosin (E_T ~ 41 kcal mol^{-1})[51] were also found to be efficient sensitizers[52] for selective isomerization, uncomplicated by radical catalyzed side reactions reported to take place with other halogen containing sensitizers in sensitized isomerization of simple olefins.[53] The much red-shifted absorption characteristics of such dyes are clearly desirable properties for the sensitized isomerization process. The trienes examined so far included the simple C_{15} compounds (**18b–e**,[37,43] **a, f–k**[52]) and other substituted trienes (**19**,[53] **20, 21**,[47] **22, 23**[55]). Conversions to the 7-cis and 7,9-dicis isomers generally exceeded 90% and were sometimes nearly quantitative (Table 1). The early general statement[38,43] of quantitative conversions to the 7-cis isomers, based on analyses by low field NMR, now appears to be overly optimistic in most cases. Also, with the use of phthalein dye sensitizers, triplet sensitized isomerization of β-ionylideneacetaldehyde (**18a**) has been successfully demonstrated[52] (Table 2), thus superseding the earlier erroneous observation of failure to undergo isomerization at the 7,8-bond under sensitized irradiation conditions.[38] It was noted that the less crowded 11-cis-like system (alloocimene) did not result in selective isomerization to the cis isomer.[56]

The presence of four isomers in the trienes made the system more complicated than the dienes. It deserves a closer examination. The case of β-ionylideneacetonitrile (**18b**) is shown in Fig. 4. The primary products from the all-trans isomer were predominantly the mono-cis although small

Table 1. Photostationary state (PsS) compositions of isomers of trienes in the vitamin A series under selective sensitization[a]

Compound	Sensitizer[b]	Ratio of 7-cis to 7-cis,9-cis	7-trans isomers remaining, %
18a, X = CHO	RB	1.00 : 1.6[c]	9.5
18b, X = CN	RB	1.00 : 1.00[d]	9
18c, X = CO_2H	Bz	1.00 : 1.2[d]	5
18d, X = CO_2Et	Bz	1.00 : 1.90[d]	3.5
18e, X = $CONCH_3C_6H_5$	Eo	1.00 : 2.3[d]	4.5
18f, X = CO_2i-Pr[e]	Bz	1.00 : 1.8[d]	4.6
	RB	1.00 : 1.6[d]	7.9
18h, X = $CO_2CH\Phi_2$[e]	Bz	1.0 : 1.0	10
18k, X = COS-2-quin.[e]	RB	1.0 : 4.2	17
18m, 10-fluoro, X = CHO	RB	3.3 : 1.00[d]	18
19	RB	1.0 : 81[c]	9.4

a. Ref. 38 and 52. Some of the data in ref. 38 did not reach PsS.
b. RB = Rose Bengal; Bz = benzanthrone; Eo = Eosin. Deuterated acetone and Corning 3-67 filter with phthalein dyes and $CDCl_3$ and Corning 3-74 filter with Bz as sensitizer. c. By hplc. d. By ^{1}H-nmr. e. Unpublished results of A. Nakayama, H. White and R. S. H. Liu.

Table 2. Quantum yield of photoisomerization of retinal (1b) isomers

Isomer	Conditions of irradiation	Products (ratio)	$\Sigma\Phi_{iso}$
all-trans	Direct, hexane	9c/13c (1:4)	.06-.2[a]
1b	hexane		.07[b]
	3-methylpentane		.04[c], 0.11[d]
	Direct, ethanol		.33[d]
	methanol	7c/9c/11c/13c (1:10:30:60)	.04[c]
	Biacetyl sensitized, CH_3CN	13c	<.003[c]
	CCl_4	13c	.17[e]
9-cis	Direct, hexane	t/9c,13c (2:1)	.5[a]
2b	3-methylpentane		.18[c]
	methanol	(4:1)	.04[c]
	Biacetyl sensitized, CH_3CN	(5:1)	.20[c]
11-cis	Direct, hexane	t/11c,13c (5:1)	.2[a]
3b	hexane		.25[b]
	3-methylpentane		.24[c,f]
	methanol	t	.04[c]
	CCl_4	t	.2[e]
	Biacetyl sensitized, CH_3CN	t	.17[c]
	CCl_4	t	.75[e]
	Biacetyl sensitized, hexane	t	.15[g]
13-cis	Direct, hexane	t	.4[a]
4b	3-methylpentane	t	.21[c]
	methanol	t	.05[c]
	CCl_4	t	.4[e]
	Biacetyl sensitized, CH_3CN	t	.15[c]
	CCl_4	t	.35[e]
9-cis,13-cis	Direct, 3-methylpentane	9c/13c (1:1)	.20[c]
5b	methanol	t/9c/13c (1:8:10)	.04[c]
	Biacetyl sensitized, CH_3CN	(2:3:5)	.20[c]

a. Ref. 27. b. Ref. 29. c. Ref. 25. d. Ref. 28. e. Ref. 30. f. Ref. 26. g. Ref. 31.

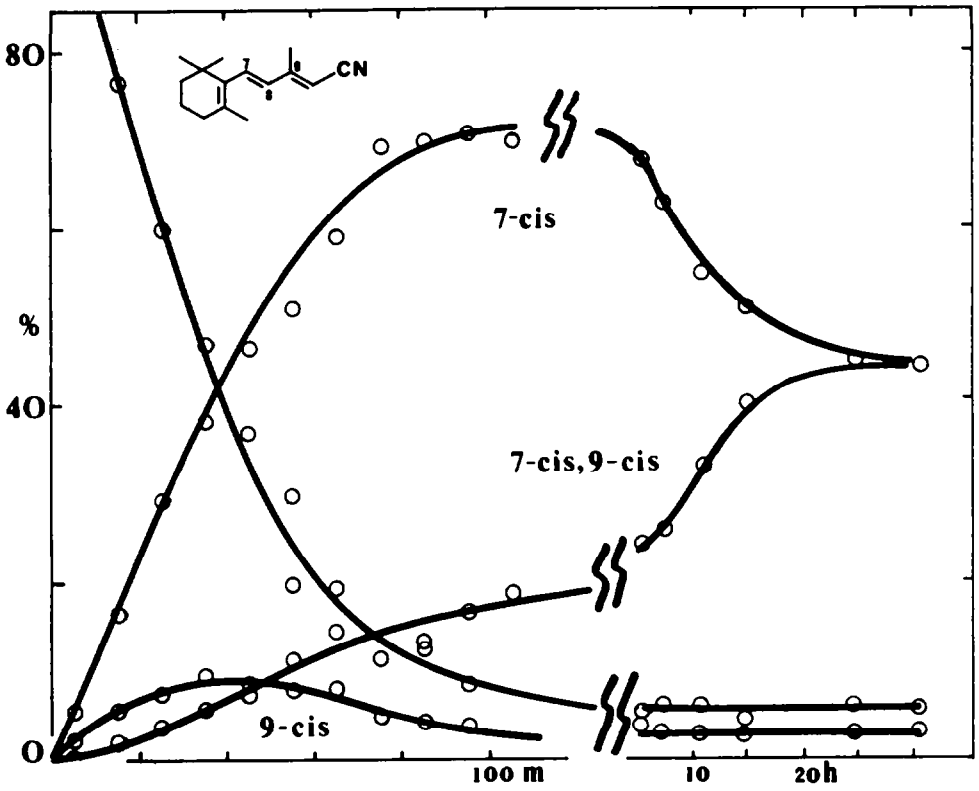
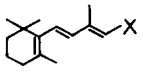


Fig. 4. Progress of Rose Bengal sensitized isomerization of all-*trans*-β-ionylideneacetonitrile in acetone-d_6 with light ≥480 nm. Two different time scales are shown with the initial periods in minutes and the latter in hours.

amounts of the dicis isomer were detectable even at very early stages of the reaction (<1% conversion). The same situation was observed for the linear triene, alloocimene.[56] Interconversion of excited intermediates in the form of activated processes could account for the minor amounts of the two-bond isomerized products.[57] The total amount of the two 7-trans isomers (all-trans and 9-cis) reached a photostationary state of less than 10% after the first two hours of irradiation. The two 7-cis isomers, on the other hand, did not reach a stationary state until several hours later. The latter result was probably due to a secondary selective sensitization process with the sensitizer transferring energy to the two nonplanar 7-cis isomers at much slower and slightly different rates.



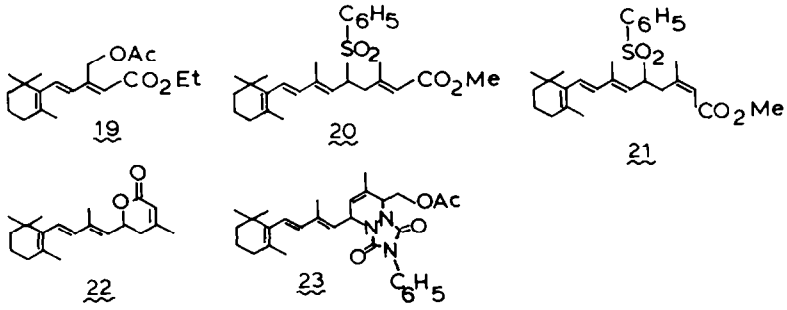
18

a: X = CHO
b: X = CN
c: X = CO_2H
d: X = CO_2Et
e: X = H
f: X = CO_2i-Pr
g: X = $(CON(CH_3)C_6H_5$
h: X = $CO_2CH(C_6H_5)_2$
i: X = CH_2OH
j: X = CH(OH)t-Bu
k: X = COS-2-quinoline
m: 10-fluoro, X = CHO

The slow rate of redistribution of the final products could be an additional experimental parameter for preparing mixtures enriched in either of the two 7-cis isomers, thus increasing the synthetic potential of the photochemical method.

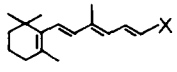
Examples of surprisingly highly regioselective and stereoselective photosensitized isomerization of trienes are known.[46,54,55] The report of conversion of the acetoxyester **19** to a final product mixture 10:1 in favor of the 7-cis,9-cis isomer[54] was followed by the observation of conversion of two isomeric sulfones **20** and **21** to mixtures containing predominantly respectively the 7-cis and the 7,13-dicis isomers.[46] In addition the C_{20}-lactone **22** and the Diels–Alder adduct **23** from vitamin A acetate under selective sensitization conditions were reported to give exclusively the 7-cis isomer.[55] Application of these photochemical observations to stereoselective synthesis of isomers of vitamin A will be described in the next section.

An explanation for these synthetically desirable photochemical observation was recently offered. The observed selectivity was attributed to a change of the direction of decay of the planar triplet from preferential twisting of one double bond to the other upon variation of the substitution pattern.[55] The increased amount of the 9-cis geometry in the final product mixture of the acetoxy



triene-ester (7-cis,9-cis/7-cis = 10) as compared to the parent triene-ester, **18d**, (7-cis,9-cis/7-cis = 1.2) was first rationalized in terms of increased steric crowding around the 9,10-double bond. The results of the remaining compounds, which shared the common feature of having the bulky substituents at the reaction center (the rotating C-10) was attributed to solvent induced hindered rotation of C-10 with the excited molecule opting for selective decay via twisting of the unaffected 7,8-bond. These situations could be depicted in terms of changes of the torsional potential curves near the Franck–Condon triplets (Fig. 5). It should be noted that similar arguments have been used to account for medium effects on luminescence properties of compounds (the Dellinger–Kasha model)[58,59] and viscosity effect on stilbene isomerization.[60]

Longer polyenes and 3-dehydro compounds. Polyenes with four or more double bonds in the vitamin A series were reported not to give 7-cis isomers under triplet sensitized conditions.[38,61] The early work based on qualitative NMR analyses with the retinal (**1b**)[24,38] was confirmed by more recent studies using HPLC analyses,[25,52] however with the C_{18}-ketone (**24a**) up to 11% of the 7-cis isomer has since been detected by HPLC.[52] The extensive study of Waddell *et al.* of biacetyl sensitized isomerization of all-*trans*-retinal and its cis isomers showed that only unhindered isomers were formed from the triplet state even when acetonitrile was used as solvent.[25] The lack of hindered isomers was attributed to a reversal of the shape of the excited torsional potential curve from one favoring the perpendicular intermediate for dienes and trienes to one favoring the planar intermediates for the longer polyenes.[38] The same reversal of the shape of the torsional potential curve was predicted by calculated (extended Hückel method) results by Hoffmann.[62]



24

a: X = $COCH_3$
b: X = CN
c: X = CHO

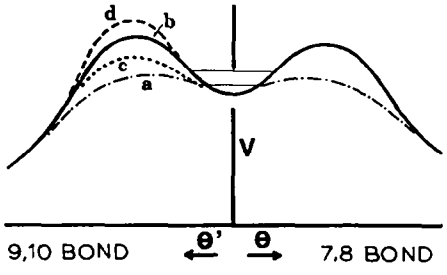


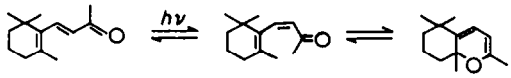
Fig. 5. Medium and substituent effects on the portion of the torsional potential curve nearby planar all-trans triene triplets. (a) Simple trienes (e.g. **18d**) in the absence of solvent cage induced barriers around the 9,10 (left) and the 7,8 bonds (right). (b) Simple trienes with added solvent induced barriers. (c) Internally reduced barrier due to steric repulsions such as in 9-substituted triene **19**. (d) Externally increased barrier due to increased volume of activation in 10-substituted trienes **20–23**.

Interconversion of isomeric triplets apparently was not sufficiently rapid to establish an equilibrium before deactivation to the ground state. The identical triplet–triplet absorption spectra of several retinal isomers[26,63] once were considered supporting evidence for equilibrated triplets.[63] However, the concept was not consistent with the different extinction coefficients of transient absorption of isomers[64] and the observation that only one-bond isomerization products (except when starting with the 9-cis,13-cis isomer) were obtained from sensitized isomerization of retinal isomers.[25]

The quantum yields of photosensitized isomerization of isomeric retinals determined by Kropf and Hubbard,[27] Ottolenghi and coworkers,[26] Weiss and coworkers[29] (both by UV analyses) and Waddell *et al.*[25] (by HPLC) (Table 2) showed that isomerization of the cis isomers was more efficient than the trans. Ottolenghi also concluded from the observation of the lack of oxygen quenching on sensitized isomerization of 11-*cis*-retinal that the 11-cis to trans isomerization involved non-relaxed "vibronic" triplets.[26] The triplet state was suggested to be involved in isomerization of cis isomers under direct irradiation.[29]

Compounds in the vitamin A_2 series (3-dehydro) were found not to undergo triplet sensitized isomerization to the 7-cis isomers.[65] For example 3-dehydro-β-ionone (**25**) was found to be stable under sensitized irradiation. Decay via the cyclohexadiene portion of the chromophore was considered the cause for the low reactivity.[65]

The sensitized geometric isomerization is rarely accompanied by unwanted side reactions. The only documented case of unimolecular reaction of β-ionone **17a** to the α-pyran **26**[60] can be



17a 26

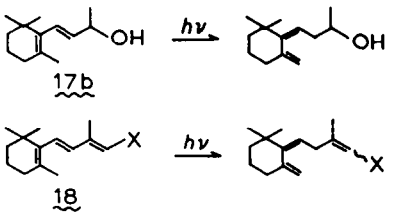
explained by the sequence of geometric isomerization and thermal 6e electrocyclization.[66] The lack of other concerted processes is most likely due to unfavorable energy changes associated with the conversion of a triplet polyene to a triplet rearranged product. Documented bimolecular reactions are few. Only a vitamin A acetate, cyclobutyl and cyclohexenyl dimers (apparently not identical with those from direct irradiation)[67] were isolated from product mixtures obtained from biacetyl sensitized irradiation.[68]

Polyenes in the vitamin A series (particularly the 3-dehydro derivatives) were reported to react with singlet oxygen efficiently.[69,70] Hence exclusion of oxygen is necessary not only for avoiding quenching triplet sensitizers but also for eliminating oxygenation of substrates.

Reactions from the excited singlet states

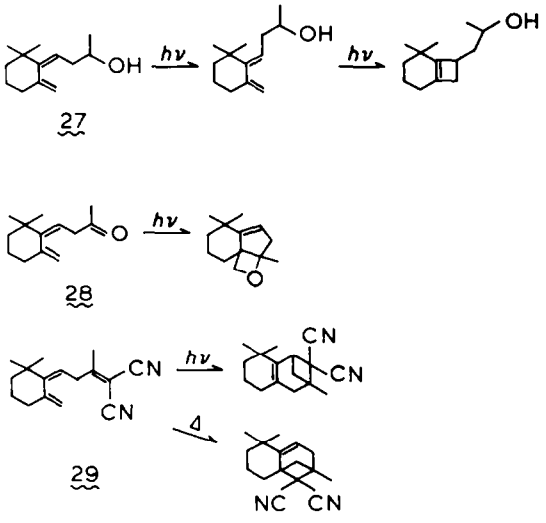
Concerted and other side reactions. Not restricted on energy grounds, polyenes in excited singlet states undergo a variety of concerted reactions such as electrocyclizations of 4, 6 and 8 electrons,[71] sigmatropic reactions including formation of allenic products[72] and internal 4 + 2 cycloadditions of hexatrienes.[71,73] Singlet state reactions of polyenes in the vitamin A series are on the other hand quite limited. Only two types of unimolecular reactions are known: sigmatropic hydrogen migration and electrocyclization. Even for these the scope is quite narrow. Only a brief summary of these two reactions, supplementing those covered in an earlier review,[23] will be attempted here.

When assuming the preferred twisted 6-*S*-cis conformation for compounds in the vitamin A series,[39] the C-8 of the side chain becomes ideally located for accepting a hydrogen atom from CH_3-5 in a sigmatropic process. Hence such 1,5-hydrogen migration is an efficient, and in fact the only known, sigmatropic photochemical reaction for polyenes in the series. The reaction was reported to be most efficient for the dienes. For example, in β-ionol (**17b**) the geometric isomerization was not competitive (cis isomer was not observed) with hydrogen migration.[74] The decrease in efficiency of the reaction in compounds of extended conjugation such as β-ionone **17a** and triene derivatives[74] was indicated by the extensive geometric isomerization process accompanying the sigmatropic process. However, because of the irreversible nature of the hydrogen migration process under the usual conditions of irradiation the rearranged retro-γ-products were usually the sole end products.

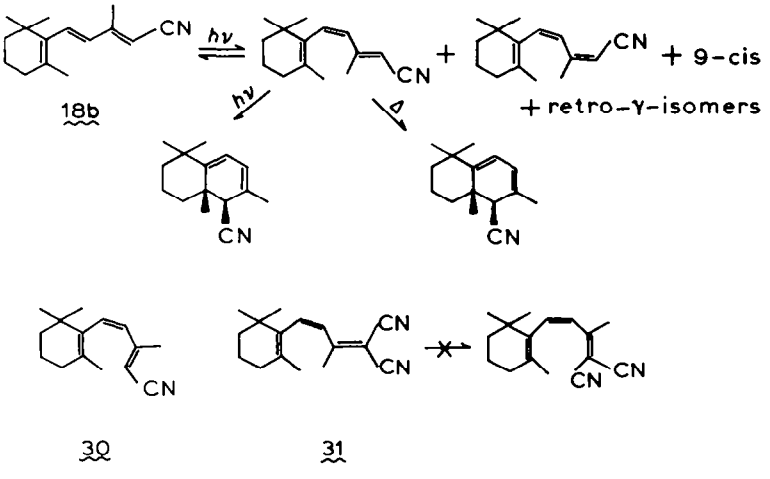


Rearrangements of the several dienes (**17a**,[75] **b, e, f**,[23] **d**[74]) and trienes (**18d–i**,[23] **b, c, e**[74]) were reported. Among tetraenes only **24b** was reported to give a similar product.[74]

Upon heating, several retro-γ-products were reported to revert back to the isomeric mixtures of the dienes.[74] Photoisomerization of retro-γ-ionol (**27**),[76] photochemical cycloaddition of retro-γ-ionone (**28**),[77] and photochemical and thermal[78] internal cycloaddition of retro-γ-ionylidenemalononitrile (**29**) have also been reported.



Photochemical electrocyclization for compounds in the vitamin A series is limited to the 6e process of the 5–6, 7–8 and 9–10 double bonds regardless of the length of the polyene chain. In the case of the trienenitrile **18b** the cyclization process was shown to proceed by way of photoisomerization to the 7-cis isomer followed by ring closure in a separate photochemical step.[74] The concerted nature of the process was indicated by the different stereochemistry of the photo and the thermal products from the same 7-cis isomer.[74] In the same vein different thermal and photochemical cyclized products were obtained from ethyl β-ionylideneacetate (**18d**) which were interconvertible through base catalyzed epimerization.[79] That the *S*-cis, *S*-cis conformer (e.g. **30**)

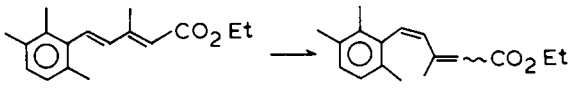


was involved in the ring closure process was indicated by the failure of the 7-cis,9-cis isomer of **18b** and the 7-cis isomer of β-ionylidenemalononitrile (**31**), both too crowded to exist in the bis-*S*-*S*-cis-conformation, to photocyclize. Retrocyclization could take place with light of shorter wavelengths. Reopening of the cyclohexadiene ring proceeded in a stereorandom manner.[80]

Several tetraenes (**24a**,[81] **b**,[74], **c**[82]) and a pentaene (retinal)[82] were also reported to produce cyclized products upon extended irradiation. In the last case, surprisingly only the 13-cis isomer was isolated.

The absence of electrocyclic and sigmatropic reactions at other portions of the polyene chain is probably due to the cumulative effects of a general preference for the *S*-trans conformation in the polyene chain[83] and the higher quantum yields of isomerization of the cis isomers back to the trans (see below). In that regard it will be of interest to study such processes in conformationally modified polyenes such as those with the trifluoromethyl group[84] where the cis isomers are more stable.

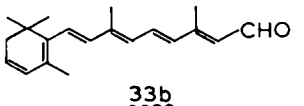
For shorter chain compounds the side reactions, particularly the irreversible sigmatropic rearrangement process, make direct irradiation a less desirable condition for the preparation of geometric isomers. Triplet sensitization is clearly preferred. However, for other modified compounds geometric isomerization may not be complicated by side reactions. Thus, for the aromatic diene-ester **32**[52] (and also hindered stilbenes)[85] the conversion to the two central cis isomers exceeded 90% when light of long wavelengths was employed. For longer chain compounds, geometric isomerization is competitively more favored, and therefore, the process can be profitably used for conversion of the trans isomer to the cis at the final stage, or occasionally in the middle of a synthetic sequence.



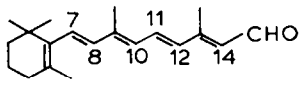
32

The geometric isomerization process. The early work of photoisomerization of compounds in the vitamin A series was of a preparative nature involving the isolation and identification of geometric isomers of retinal.[18,36] Irradiation of the more readily available all-trans isomer of retinal in hexane gave predominantly the 13-cis isomer plus a small amount of the 9-cis isomer. On the other hand when ethanol was used as solvent, the visually important 11-cis isomer constituted up to 25% of the product mixture (long wavelength excitation).[18] This observation reported many years ago is still the most direct route to small amounts of this hindered isomer, the most important one in vision research. Popularity of this simple procedure has been enhanced by the observation of increased amounts of cis isomers in dipolar aprotic solvents[87,88] and the recent advancement in chromatographic separation techniques. In fact, recently such methods allowed isolation of several of the minor components of the dicis geometry in the irradiation mixture of retinal.[89]

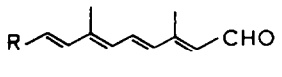
The exact cause for the solvent dependent photochemical behavior of the polyene, however, remains a mystery. In addition to the parent retinal many derivatives and analogues have since been shown to exhibit solvent dependent photochemistry: 3-dehydro- (**33b**),[90,91] 10-fluoro- (**34**), 14-fluoro- (**35**),[92] 9-demethyl (**36**),[93] 13-demethyl (**37**)[93-95] 9,13-didemethyl (**38**),[93] 14-methyl (**39**)[94] and several aromatic retinals (**41**).[96] Even in two polyene esters, similar photochemical behavior has been observed (methyl retinoate[97] and the aromatic retinoid **42**[98]). On the other hand, vitamin A alcohol[99] and vitamin A acetate[100] were shown to be solvent insensitive. Deuteration (**40**) was shown to have no effect on the isomerization process.[101]



33b

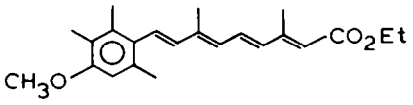


34: 10-fluoro
35: 14-fluoro
36: 9-demethyl
37: 13-demethyl
38: 9,13-didemethyl
39: 14-methyl
40: 14,15-dideutero



41

R = Phenyl, *o*-tolyl, mesityl, 2-chloro-6-fluorophenyl, 3,4,5-trimethoxyphenyl, piperonyl

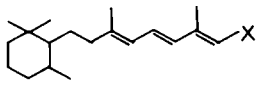


42

Recently it was shown that the 11-cis rich retinal product mixtures in ethanol could be mimicked even in isooctane when an excess of a Lewis acid such as $Eu(fod)_3$ was added.[102,103] Also, retinonitrile (**1f**) has since been added to the list of compounds showing solvent dependent photochemistry.[104] Results of all these systems, particularly those where quantitative data are available, are summarized in Table 3.

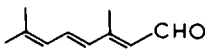
Two types of data are listed. The synthetically more meaningful data of photostationary state compositions were more frequently reported. However, such data are dependent on excitation wavelengths, the duration of the irradiation period and also sensitive to complicating degradation processes. Therefore, not too surprisingly, the data reported by different groups vary quite significantly. The initial ratios (relative quantum yields) are also included whenever available. These numbers are less sensitive to variation of the excitation wavelength when samples are analyzed after very low conversions. (For quantum yields of isomerization of retinal, data in Table 2 should be consulted.)

For compounds with shorter conjugation, the product mixtures are generally insensitive to solvent variation (Table 4). These include systems with the conjugation near the ring; e.g. the C_{15}-aldehyde (**18a**),[105] the C_{18}-ketone (**24a**)[105] and the C_{15}-ester (**18d**),[100] and those with conjugation on the chain portion of the vitamin A system, e.g. 5,6,7,8-tetrahydroretinal (**43a**),[106] 5,6,7,8-tetrahydroretinonitrile (**43b**),[104] dehydrocitral (**44**)[107] and 9-*cis*-retro-γ-retinal (**45**).[108]

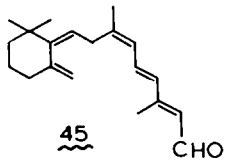


a: X = OH
b: X = OAc

43



44



45

Temperature dependent quantum yields of isomerization have been reported for both the all-trans[27,28] and the 11-cis isomers[25-28] of retinal. The latter result was unusual in that lowering the temperature actually increased the quantum yields.[27]

The low lying excited singlet states of polyenes. The identity of the reactive state, hence the nature of the low lying states and the relative ordering of the low lying excited states, are clearly of primary concern for understanding of the photochemical properties of polyenes. The extensive spectroscopic studies in recent years have yielded much meaningful information on the excited state properties (and the identity of the excited states) of compounds in the vitamin A series. In Table 5 are listed data of several derivatives of the homologues in the vitamin A series. The alcohols are representative of most of the derivatives in having low intersystems crossing efficiencies while aldehydes and ketones are exceptional in having higher triplet yields.

The uv-vis absorption spectra of vitamin A and related pentaenes are dominated by a strong absorption band near 325–270 nm (in nonpolar solvents).[109] It is associated with the $\pi \rightarrow \pi^*$

Table 3. Distribution of cis isomers formed during direct irradiation of all-*trans*-retinal and related compounds

Compound	Solvent	Photostationary states, %						Initial ratio
		λ_{ex}, nm	t	7c	9c	11c	13c	other	7c: 9c : 11c: 13c
Retinal	hexane	390	70	0	5	0	24	1[a]	0: .25: 0 :1.00[a]
		>380	40	0	5.5	3.5	51	-[b]	0: .28: 0 :1.00[c]
		430	62	0	5	0	31	2[a]	
		d	41	0	5	0	52	2[e]	
	3-methylpentane								0: .15: 0 :1.00[f]
	isooctane	355	67	0	7	0	27	0[g]	
	isooct. + Eu(fod)$_3$	515	33	0	17	33	8	8[g]	
	ether								0: .15: tr :1.00[f]
	diglyme	d	28	0	7	24	41	0[e]	
	pyridine	d	19	?	13	35	31	1[e]	
	DMSO	d	20	?	17	37	25	2[e]	
									.06: .29:1.51:1.00[f]
	ethanol	390	52.5	.5	7	19.5	24.5	1[a]	.01: .16: .50:1.00[a]
		430	45	1	12.5	20	21.5	1[a]	
									.04: .24: .81:1.00[f]
	methanol								.05: .23: .95:1.00[f]
	acetonitrile	>380	31	4.5	23	29	9.2	3[b]	.27: .70:1.9 :1.00[c]
		d	20	?	12	43	19	6[e]	
9-Demethyl-retinal	hexane	d	59	1.3	1.2	0	37	0[h]	
	acetonitrile	d	40	7.2	8.1	20	21	0[h]	
13-Demethyl-retinal	3-methylpentane	350	83	0	7	10	0	0[i]	
		430	83	0	9	7	0	0[i]	
	hexane	d	81	0	9.7	2.6	6.8	0[h]	
	acetonitrile	d	37	9.1	37	17	0	0[h]	
	ethanol	350	51	3	21	23	0	0[i]	
		430	37	3	30	27	0	0[i]	
	acetonitrile	350	44	6	24	25	0	0[i]	
			35	8	30	26	0	0[i]	
9,13-Dide-methylretinal	hexane	d	83	2.4	3.0	4.0	5.7	0[h]	
	acetonitrile	d	34	19	20	23	0	0[h]	
14-Methyl-retinal	hexane	390	41	0	3	0	49	5[i]	
		450	26	0	4	2	62	5[i]	
	ethanol	390	40	0	5	19	32	4[i]	
		450	23	0	7	35	32	3[i]	
	acetonitrile	350	32	0	7	37	22	1[i]	
		430	19	0	8	49	23	0[i]	
10-Fluoro-retinal	hexane	>380							0: .32:0 :1.00[f]
	acetonitrile	>380							.64: .27:1.12:1.00[f]
14-Fluoro-retinal	hexane	>380							0: .43: .11:1.00[f]
	ether	>380							0:1.14:1.31:1.00[f]
	acetonitrile	>380							.44:3.4 :6.2 :1.00[f]
3-Dehydro-retinal	hexane	d	82	0	1	0	17	10[j]	
	ethanol	d	52	4	19	17	8	0[j]	
	acetonitrile	d	44	12	26	13	5	0[j]	
Methyl retinoate	heptane	d	13	0	21	2	14	49[k]	
	DMSO		10	3	14	12	20	41[k]	
Retinoni-trile	hexane	360	41	0	13	0	35	11[ℓ]	
	ethanol	360	23	7	17	16	19	18[ℓ]	
	acetonitrile	360	22	7	16	20	23	12[ℓ]	

a. Ref. 25. b. Ref. 105. c. Ref. 87. d. Unfiltered fluorescent or tungsten lamps.
e. Ref. 88. f. Ref. 28. g. Ref. 102. h. Ref. 93. i. Ref. 94. j. Ref. 91. k. Ref. 97.
ℓ. Ref. 104.

Table 4. Initial product distribution and/or photostationary state compositions in direct irradiation of trienes or tetraenes in the vitamin A series

Compound	Solvents	Products	Initial ratio	PsS-composition (%)[a]
18a	Hexane	7c,7c9c,9c	1.00:.21: .57	37; 25; 16; 23[b]
	Benzene		1.00:.32:1.25	35; 24; 18; 23
	Chloroform			33; 25; 18; 24
	Methanol			36; 26; 15; 23
	Acetonitrile			37; 23; 17; 23
24a	Hexane	7c,7c9c,9c,11c	.21: 0 :1.00:1.5	7; 0; 11; 8; 74[b]
	Benzene			7; 0; 16; 8; 68
	Chloroform			13; 4; 25; 10; 48
	Methanol			15; 5; 24; 9; 45
	Acetonitrile			10; 3; 20; 6; 61
18d	Chloroform	7c,7c9c,9c		16; 32; 8; 45[c]
	Acetonitrile			16; 32; 8; 44
40a	Acetonitrile	9c,13c; no 11c[e]		
40b	Hexane	9c,11c,13c		20; 6; 29; 34[d,e]
	Acetonitrile			17; 8; 29; 32
41	Hexane	No central cis[f]		
	Acetonitrile	No central cis[f]		
20	Hexane	all t, 9c13c		15; 29; 56[g]
	Ethanol			9; 49; 42
	Acetonitrile			15; 36; 49

a. Last entry being the starting material. b. Ref. 105. c. Ref. 100. d. Ref. 104. e. Ref. 106. f. Ref. 107. g. Ref. 108. Not clear whether PsS was reached.

Table 5. Quantum yields of fluorsecence (Φ_F) and triplet yields (Φ_T) of representative polyenes in the vitamin A series

Compound	Solvent	Φ_F		Φ_T
		77°K	298°K	298°K
C_{15}-aldehyde, 18a	Hydrocarbon	.042[a]		.42[b]
	Alcohol			.45[c]
C_{15}-alcohol, 18g	Hydrocarbon	.083[d]		
C_{17}-aldehyde, 24b	Hydrocarbon	.0066[a]		.66[c]
	Alcohol	.0791[a]		.41[c]
	CH_3CN			.51[c]
C_{17}-alcohol	Hydrocarbon	.069[d]	.0007[d]	
C_{18}-ketone, 24a	Hydrocarbon	.23[a]		
Retinal (C_{20}), 1b	Hydrocarbon	.005[e]	.0001[e]	.43[f]
	Alcohol		.004[e]	.08-.12[c]
	Acetonitrile			.16[c]
Retinol, 1a	Hydrocarbon	.25[g]	.018[g]	.03[h]
	Alcohol	.33[g]	.016[g]	.03[h]
Methyl retinoate, 1d	Hydrocarbon	.61[i]		
N-butyl Schiff base of 1b	Hydrocarbon		$<10^{-3}$ h	<.01[h]
C_{22}-aldehyde	Hydrocarbon	.066[a]	.0098[a]	.41,[b] .54[c]
	Alcohol	.12[a]	.0007[a]	.033[c]
	CH_3CN			.095[c]
C_{22}-alcohol	Hydrocarbon	.019[d]	.0068[d]	

a. Ref. 113. b. R. S. Becker, R. V. Bensasson, J. Lefferty, T. G. Truscott and E. J. Land, Fara. Trans. II. 74, 2246 (1978). c. P. K. Das and R. S. Becker, J. Am. Chem. Soc., 101, 6348 (1979). d. Ref. 122. e. Ref. 29. f. R. Bensasson, E. J. Land and T. G. Truscott, Photochem. Photobiol., 21, 419 (1975). g. Ref. 111. h. Ref. 20. i. T. Takemura, K. Chihara, R. S. Becker, P. K. Das and G. L. Hug, J. Am. Chem. Soc., 102, 2604 (1980).

transition to the state of ^1B_u symmetry (a linear pentaene of the C_{2h} point group is generally used to approximate the chromophore of the all-trans isomer). However, the radiative lifetimes of most of these polyenes are found to be much too long for a symmetry allowed transition. For example the experimental radiative lifetime for retinol is 200 nsec while that calculated from the absorption intensity is 2.7 nsec.[110,111]

Two types of forbidden transitions are possible in at least some of the compounds. For polyenals and polyenones the n, π^* state is an obvious possibility. The recent comprehensive studies by Das and Becker[112,113] of homologous compounds in the series showed that the relative positions of the n, π^* and π, π^* states are chain length dependent. From the absorption[112] and the emission[113] properties, they concluded that for compounds with two to four double bonds the n, π^* state is the lowest, for those with five and six double bonds the n, π^* and the π, π^* states are close in energy, and for those with seven and more double bonds the π, π^* state is the lowest. However, even for compounds in the last group the radiative lifetimes are "anomalously" long.

The fluorescence intensity of retinal and related aldehydes and ketones was shown to be solvent dependent ranging from non-fluorescent in thoroughly dried hydrocarbon solvents to moderately strong in hydroxylic solvents.[112,114] The intensity could also be enhanced by the hydrogen bonding additives in hydrocarbon solvents[112,114] and cations in polar solvents,[115] presumably due to changes of relative ordering of the n, π^* and π, π^* states. The concentration of a substrate was also shown to have a marked effect on the fluorescent properties.[116,117] For example, it was reported that in a hydrocarbon solvent retinal was non-fluorescent at low concentration ($<10^{-4}$ M) but increasingly fluorescent at higher concentrations.[117] The once anomalous wavelength dependent fluorescent property of retinal was therefore explained in terms of selective excitation of dimers.[117] Selective excitation of different low-lying excited singlets was once suggested as a possible explanation.[118]

The presence of a low lying symmetry forbidden state in compounds without low lying n, π^* states is not at first an obvious one. However through a concerted effort of spectroscopic[119] and theoretical[120] studies first on the octatetraene system it was shown that the doubly excited state of the $^1A_g^-$ symmetry is in fact more stable than the singly excited ^1B_u state. Since these pioneering studies, much supporting evidence for this extraordinary conclusion have become available, including high resolution single photon absorption studies on model polyenes with varying length,[22,121] the radiative lifetime of vitamin A homologues (Table 5),[122] two photon absorption on retinol[123] and retinal[124] and other more refined calculations.[125] The relative levels of the two π, π^* states have been shown to be chain length dependent with longer polyenes favoring the forbidden $^1A_g^-$ state. For longer chain polyenes (more than 5 double bonds) in the vitamin A series there is now a general agreement that the "anomalous" long lifetimes are due to involvement of such states.[22]

Explanations for the photoisomerization process. Several attempts were made to explain the solvent dependent photochemistry of polyenes in the vitamin A series. That the 11-cis isomer of retinal was also obtained in aprotic dipolar solvents such as acetonitrile[87] showed that the ethanol result first observed by Wald was not due to any specific interaction of the aldehyde with the hydroxylic solvents. That the isomer distribution in different solvents (Table 3) seems to parallel with the dielectric constants of solvent rather than refractive indices (the latter significantly affect the position of the absorption band)[126,127] suggests that the bulk property of solvent polarity rather than polarizability of solvents has a more important effect on the photochemical properties. An attempt[92] was made to relate the solvent effect to the dipolar character of the orthogonal ethylene and polyenes (the Salem zwitterionic intermediates).[128,129] The directions of isomerization of retinal and several substituted retinals were rationalized in terms of selective stabilization of zwitterionic intermediates by the dipolar solvents, particularly those twisted at the central most double bonds.[92]

This explanation, however, was not consistent with the subsequent observation of a lack of solvent dependent photochemistry in a shorter chain homologue, the C_{15}-aldehyde (**18a**) and the negligible effect in the C_{18}-ketone (**24a**).[105] Furthermore, calculated results on the hexatriene system, which gave results in excellent agreement with the stereochemical properties of the photochemical internal cyclization reaction of hexatrienes to the bicyclo[3.1.0]hexenes,[130] suggested the excited trienes taking on the dipolar character only when approaching a geometry very close to that of the perpendicular structure (the sudden polarization effect).[131] It became doubtful that at such a late stage, solvent stabilization could have any effect on dictating the direction of photoisomerization of a polyene.

Instead, an explanation involving possible reversal of state level ordering in different solvents was put forward to account for the observed photochemistry. Parallel to what was concluded from the spectroscopic studies,[113] it was suggested that the n, π^* state remained as the lowest lying excited state in all solvents for the shorter chain C_{15}-aldehyde and the C_{18}-ketone, hence the solvent independent photochemistry. The closeness of the n, π^* and the π, π^* states in the pentaenes (retinal) and the hexaenes (3-dehydroretinal) and the expected dependence of the n, π^* level on solvent polarity led to the situation of having different reactive states in different solvents. In polar solvents, the photochemistry was dominated by the π, π^* state, and in non-polar solvents, by the n, π^* state.

In the same vein, the photochemistry of retinal-Eu(fod)$_3$ adduct, where the main absorption band was much red-shifted, was explained in terms of reordering of the π, π^* and n, π^* states.[103] The situation is probably related to Song's observation of enhanced retinal fluorescence by metal ions.[115]

It was noted that the directions of chemistry appeared to be in agreement with the expected π-electron distribution in these two states. The observed selective photoisomerization at the more highly substituted double bonds in nonpolar solvents was attributed to the higher bonding π-electron density of the n, π^* state; and the random photoisomerization in polar solvents, the lower π-electron density of the π, π^* state.[105] The exact positions of the n, π^* states in polyene esters have not been defined. Based on spacing of the n, π^* and π, π^* states in simple esters[132,133] it is conceivable that in longer polyenes the two states are also nearly degenerate which could account for the observed solvent dependent photochemistry of the pentaene esters.

A general trend of photoisomerization of the polyenes, when carried out in hydrocarbon solvents, is preferred isomerization at the more highly substituted double bonds, e.g. the trisubstituted double bonds in the regular vitamin A series,[86,87] the tetrahydro- (**43**)[104] and the aromatic (**41**) derivatives,[96] and the tetrasubstituted double bonds in the 14-methyl analogues (**39**).[94] The reduction of the 13-cis isomer to trace amounts in 13-demethylretinal[93 95] also falls into this general pattern. The trend indicates that steric relief is a dominant factor in determining the direction of relaxation of the planar excited polyenes.

Another general trend is the regioselective isomerization at the trisubstituted double bond near the end of the polyene chain, i.e. 13-cis > 9-cis (Table 3). The result was believed due to medium directed selective twisting of the partial double bonds in the planar excited singlets.[54] Preferential isomerization at the site involving the least amount of displacement of solvent molecules (usually at the double bond with the smallest end group) led to the observed results. A simple way to describe the situation is the different spatial requirements for isomerization at the 13,14 and the 9,10 double bonds as shown in Fig. 6. Therefore, it appears that medium directed preferential decay of the planar excited polyenes occurs in excited singlets as well as in the triplet states (see above).

The more complex mixtures of the pentaenes obtained during irradiation of these polyenes in polar solvents can be viewed as a result of diminishing influence of the steric effect with a concomitant loss of selectivity. Hence, isomerization took place at all four side chain double bonds with a slight preference for isomerization at the central most double bond as shown in 3-dehydro[90] and substituted retinals.[87,92] This result is consistent with the lower π-bond order as noted earlier.

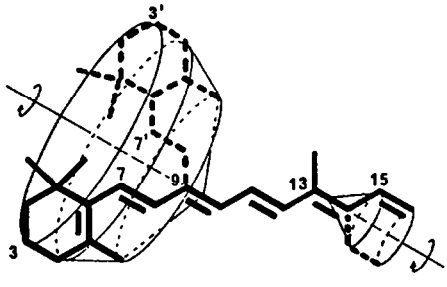


Fig. 6. Different spatial requirements for the isomerization of an all-*trans*-vitamin A derivative to 13-cis (right) and to 9-cis (left). For clarity the alternative process of rotating the right hand portion of the molecule for formation of the 9-cis isomer is not shown.

The n, π^* $-\pi$, π^* explanation, however, cannot be a unique one for all polyenes. The solvent dependent photochemistry of retinonitrile observed recently[107] demanded a different explanation because the nitriles are not likely to have low-lying n, π^* states. The cylindrical symmetry of the cyano group should make its n, π^* state similar to the second n, π^* state of a carbonyl group and similarly should be much higher in energy. In fact, such transitions in simple nitriles were detected in the far uv region.[134] Therefore, it would be highly unlikely that this state could cross the low lying π, π^* state as a result of interaction with solvent.

The forbidden $^1A_g^-$ state has been brought into the picture.[104] Reordering of the two π, π^* states (the "ionic" ^1B_u state and the "covalent" $^1A_g^-$ state)[22] in different solvents was suggested as a possible explanation for the retinonitrile result.[104] This explanation is in agreement with the now commonly accepted notion among spectroscopists of the low lying of the $^1A_g^-$ state in polyenes (see above). And it might not necessarily be in conflict with the n, π^* $-\pi$, π^* explanation discussed earlier. In fact, the different amounts of the 11-cis isomer in the product mixture of tetrahydroretinal and tetrahydroretinonitrile when irradiated in hexane could be an indication of the involvement of two different reactive states, even though forbidden in both cases. However, before embracing this idea as a general explanation, other issues must first be resolved. For example, it remains to be established that in polar solvents the position of the relaxed ^1B_u state indeed shifts dramatically to the extent sufficient to cross the lower "covalent" $^1A_g^-$ state. Also, it remains to be resolved of the different implications of the solvent dependent photochemistry suggesting a near degeneracy of the two π, π^* states at the pentaene stage and the spectroscopic studies indicating degeneracy at the triene stage.[22]

Other photochemical properties have been attributed to changes of relative heights of the n, π^* and/or the two π, π^* states. For example, the recently reported temperature dependent quantum yields of photoisomerization of all-*trans*-retinal were explained in terms of involvement of either the upper n, π^* or the $^1A_g^-$ state.[28] Adding to the complication of possible state reordering upon variation of temperatures is conformer population changes, a situation of particular concern for the cis isomers. Both the increase of the extinction coefficients of uv absorption spectra[109,135,136] and quantum yield of isomerization of 11-*cis*-retinal at lower temperatures[28] have been attributed to an increase of the 12-*S*-trans conformer.[137] Calculations further indicated possible dependence of ordering of excited singlet states on conformations and configurations of polyenes.[138]

That 13-cis methyl retinoate gave a noticeable amount of the hindered 11,13-dicis isomer (14%) among initial products during its irradiation in hexane[100] in contrast to zero amount of the 11-cis isomer when irradiating the all-trans isomer in the same solvent could possibly be an experimental evidence for variation of ordering of the low lying excited singlet states or their separation among different isomers.[138]

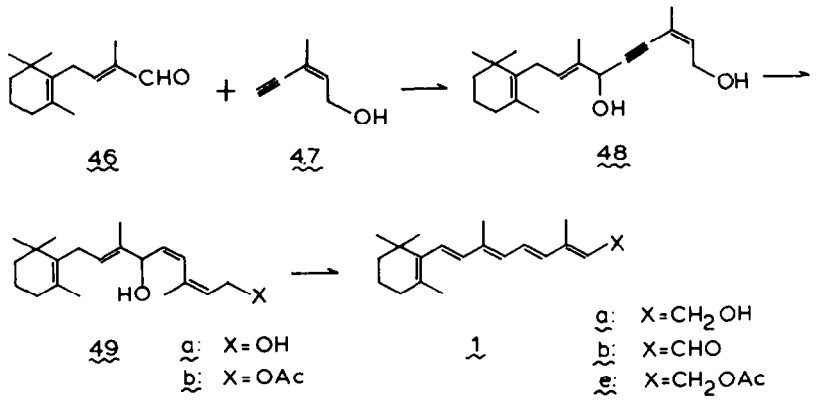
THE SYNTHESIS OF ISOMERS OF VITAMIN A AND RELATED COMPOUNDS

The synthetic chemistry of vitamin A has been reviewed on several occasions by a number of contributors to the field,[139-147] most notably, including Mayer and Isler with their important contribution in 1971 in the authoritative book "Carotenoids".[148] The purpose of the current effort is to describe methodologies for the stereoselective synthesis of configuration isomers of vitamin A, with particular emphasis on more recent advances in this field. No attempt will be made to provide an exhaustive coverage of all methods developed in vitamin A synthesis. With these constraints in mind, we are likely to omit some of the important contributions in the vitamin A area. To these contributors, we wish to offer our apology.

The early effort directed toward the synthesis of the all-trans and the five cis isomers containing the 7-trans geometry (9-cis, 11-cis, 13-cis, 9,13-dicis and 11,13-dicis) will first be reviewed. A section on new synthetic methodology will follow. The last section will be devoted to a review of recent effort in the synthesis of all missing stereoisomers.

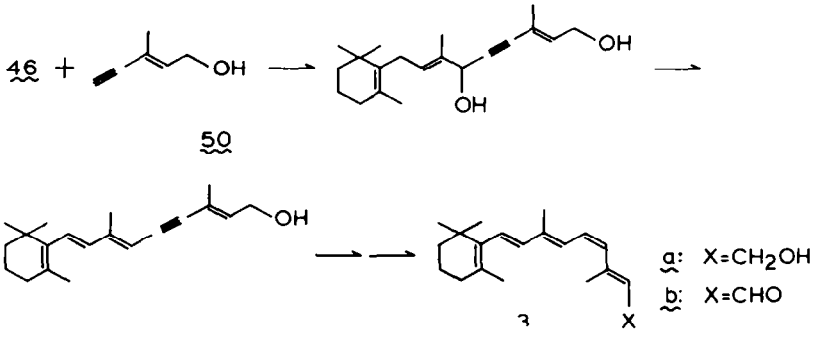
The synthesis of six 7-trans stereoisomers of vitamin A

The $C_{14} + C_6$ *route.* In 1947 Isler *et al.*[5] at Hoffmann–La Roche in Basel reported the first industrial synthesis of all-*trans*-vitamin A via a $C_{14} + C_6$ convergent sequence starting from the β-C_{14}-aldehyde, **46**:

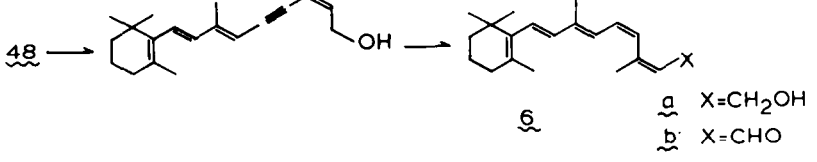


According to this reaction sequence, condensation of aldehyde **46** with the Grignard derivative of 2-*cis*-3-methyl-2-penten-4-yn-1-ol **47** (*cis*-"pentol") afforded the C_{20}-diol, **48** which was successively semihydrogenated over Lindlar catalyst to the 11-*cis*,13.*cis*-diol **49a**, regioselectively monoacetylated to **49b** and concomitantly dehydrated and isomerized at both cis double bonds to give all-*trans*-retinyl acetate **1e**. Lastly, saponification of the acetate provided crystalline all-*trans*-vitamin A, **1a**.

By replacing the cis form of C_6-alkenynol with its corresponding trans isomer (**50**) in the same sequence, Oroshnik[149] also prepared the hindered 11-cis isomer of retinol (**3a**) and retinal (**3b**).

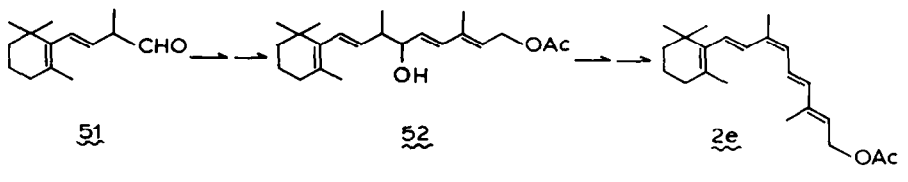


In the same paper Oroshnik[7,149] described the preparation of the 11-cis,13-cis isomer of vitamin A (**6a**). After MnO_2 oxidation, 1-*cis*,13-*cis*-retinal (**6b**) was obtained. Acknowledged only indirectly in the literature, Oroshnik apparently also prepared and supplied substantial amounts of the 13-cis



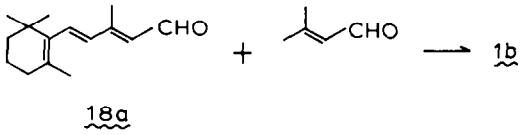
isomer of retinol and retinal.[18] The relatively unstable 11-cis,13-cis isomer has been isolated from a mixture produced by acid-catalyzed isomerization of 11-*cis*-retinal.[150]

In yet another variation of the versatile $C_{14}+C_6$ route, starting from the isomeric β-C_{14}-aldehyde **51**, Eiter *et al.*[151,152] effected the synthesis of 9-*cis*-vitamin A acetate **2e** by the following sequence of reactions. This synthetic scheme featured a surprisingly high degree of

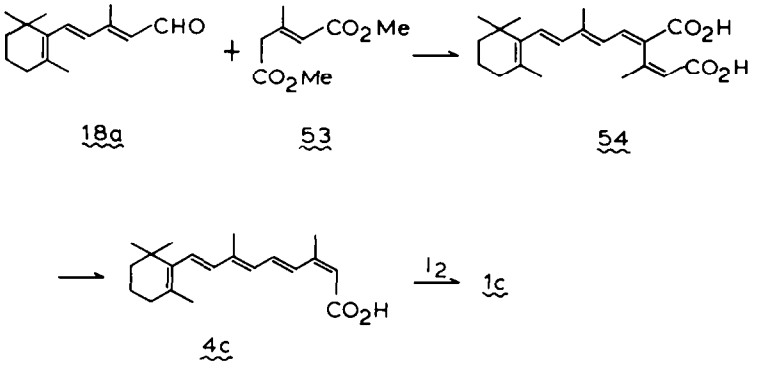


selectivity (85–89%) in the final base-induced (DBN) dehydrobromination of the bromide prepared by reaction of **52** with PBr_3, wherein the 9-cis configuration was introduced.

The $C_{15} + C_5$ *route.* Several isomers of retinal have been synthesized by $C_{15} + C_5$ approaches starting from either all-*trans*- or 9-*cis*-β-ionylideneacetaldehyde (**18a** or **56**) including the first reported total synthesis of vitamin A.[4]

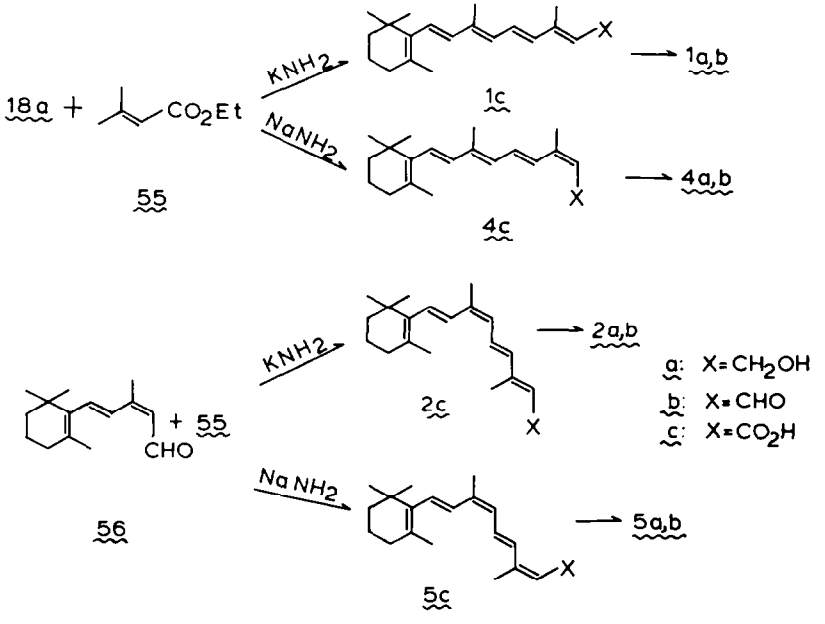


Using methyl β-methylglutaconate (**53**) as the C_5-chain extension unit, Robeson *et al.*[153–155] prepared and characterized the all-trans, 13-cis, 9-cis and 9-cis,13-cis isomers of retinal as illustrated for the all-trans and 13-cis forms. Recently, the diester of 11-*cis*,13-*cis*-diacid **54** has been shown

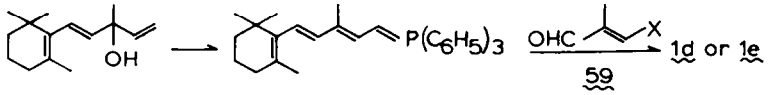


to be significantly distorted from planarity about the 12-*S*-single bond as a result of steric interaction between the two carbomethoxy substituents.[156]

The stereoselective syntheses of isomeric retinals whereby the C_{20} carbon skeleton was generated by the condensation of a metal dienolate derivative of ethyl senecioate (**55**) with β-C_{15}-aldehyde was first reported by Matsui *et al.*[157] in 1958. The stereochemical outcome of the Matsui condensation was governed by the nature of the solvent and counterion in the generation of the requisite dienolate form.



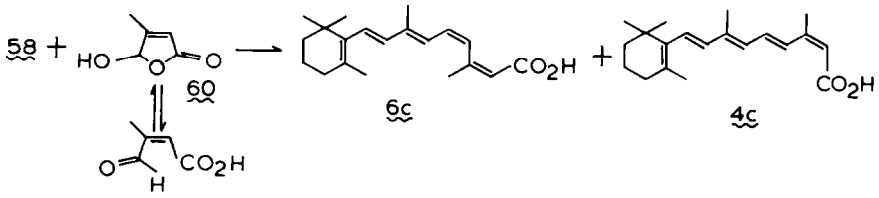
The BASF industrial preparation of all-*trans*-retinoic acid and its ester derivatives was developed by Pommer and Sarnecki[158] and featured the Wittig condensation of phosphorane **58** with the C_5-aldehydic ester (or acid) **59**.



57 58

The key intermediate, phosphorane **58**, was prepared from the reaction of vinyl-β-ionol (**57**) with triphenylphosphine hydrochloride followed by base-induced dehydrochlorination of the phosphonium chloride.

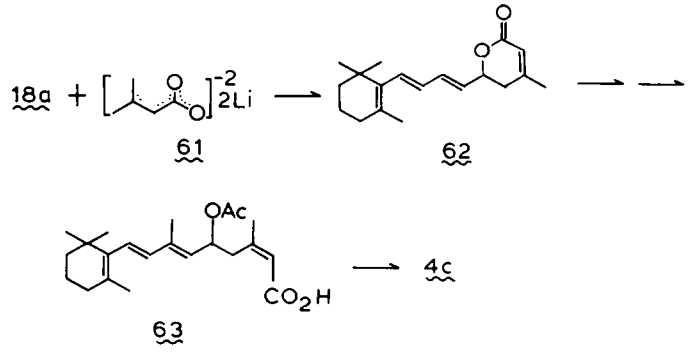
In 1965, Weedon and coworkers effected the first stereoselective synthesis of 11-*cis*, 13-*cis*-retinoic acid (**6c**) by the Wittig condensation of **58** with 4-hydroxy-3-methyl-2-butenolide **60** which underwent reaction as its tautomeric cis-aldehydic acid forms.[159]



The final product mixture, formed in 68–75% overall yield, consisted of the 11,13-dicis acid and its 13-cis isomer in a ratio of 64:36. These isomers were subsequently separated by fractional crystallization.[160,161]

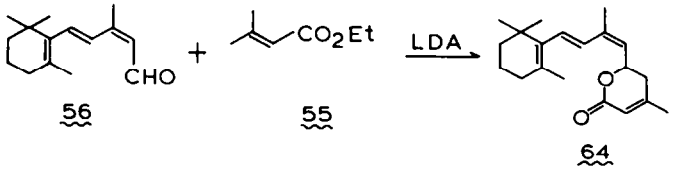
The predominant formation of the thermodynamically less stable 11-cis isomer in the Wittig reaction was unprecedented for polyene systems, although well established for simple olefinic systems where the cis configuration is stereoselectively formed.[162]

In a similar approach, the Italian group headed by Cainelli and Cardillo[147,163] used the lithium dienolate derivative of the sodium salt of senecioic acid **61a** in a stereoselective synthesis of 13-*cis*-retinoic acid, **4c**.

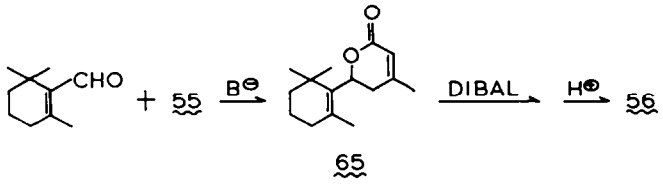


According to this procedure, the initially formed lactone **62** was stereoselectively ring-opened with base and then acetylated to acetoxy acid **63**. Lastly, base-induced elimination of acetic acid provided the desired isomerically pure 13-cis isomer of retinoic acid (**4c**).

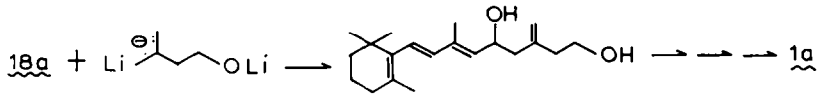
Alternatively, Heathcock and Dugger[164] prepared lactone **62** and its 9-cis form (**64**) from the respective reactions of all-*trans*-β-C_{15}-aldehyde or its 9-cis isomer with the lithium dienolate derivative of ethyl senecioate (**55**).



The method of choice for the stereoselective synthesis of the 9-*cis*-C_{15}-aldehyde (**56**)[165] involves the formation of the intermediate lactone **65**, which can be readily prepared by reaction of β-cyclocitral with either **55** or **61**.[166]

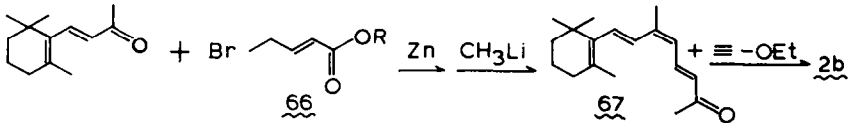


Cardillo has also reported on a stereospecific synthesis of all-*trans*-retinal using the dilithio derivative of 3-methyl-3-buten-1-ol.[167]



The $C_{13} + C_4 + C_1 + C_2$ *route.* This relatively cumbersome route represents the first successful synthesis of the 9-cis isomer of vitamin A.

The C_{18}-ketone was prepared by Reformatski reaction of the C_4-bromoester (**66**) with β-ionone followed by reaction with methyllithium. A substantial amount of the 9-cis isomer (**67**) was

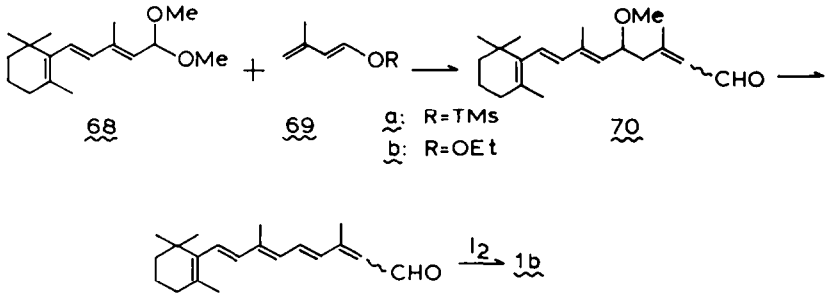


isolated[168] along with the all-*trans*-C_{18}-ketone (**24a**). Subsequent condensation of **67** with ethoxyacetylene followed by acid hydrolysis led to 9-*cis*-retinal (**2b**).[169]

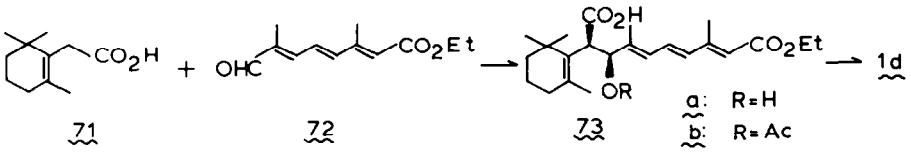
Recent developments in vitamin A synthesis

Several diverse approaches to the synthesis of isomers of vitamin A and its derivatives have recently been developed.

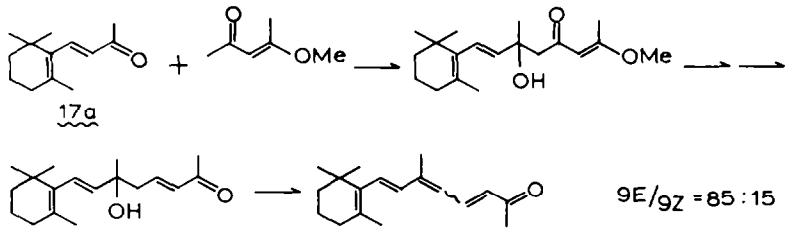
The Mukaiyama[170] approaches featured the Lewis acid catalyzed condensation of β-ionylideneacetaldehyde dimethyl acetal **68** with trimethylsilyl (or ethyl) dienol ether **69** to give isomeric 11-methoxy-11,12-dihydroretinals, **70**. Subsequent base-induced elimination of methanol followed by iodine catalyzed isomerization provided all-*trans*-retinal in 42% overall yield form **68**.



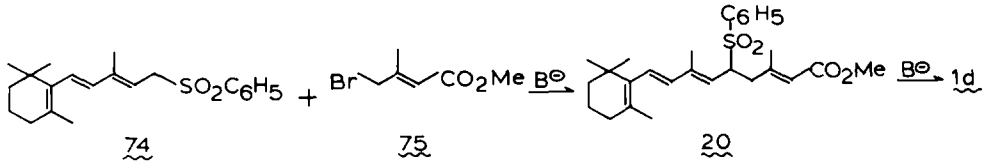
The all-trans form of ethyl retinoate was stereoselectively prepared by Trost and Fortunak[172] by the condensation of the dianion of C_{11} acid **71** with the C_{10} aldehydic ester **72**, acetylation of the relatively unstable hydroxy acid **73a** to give the threo diastereomeric acetoxy ester **73b** and, lastly, Pd(0) mediated decarboxylative elimination to produce isomerically pure C_{20} ester **1d**.



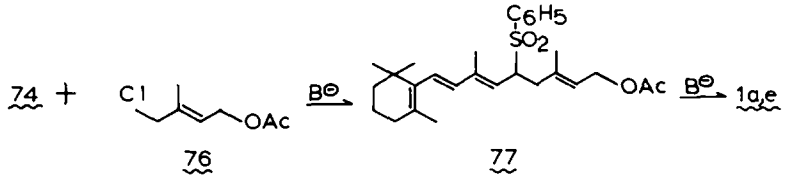
Stork and Kraus[173] have reported on a vinylogous aldolization reaction sequence to give an isomeric mixture of the important intermediate, C_{18}-ketone (**24a**:**67** = 85:15).



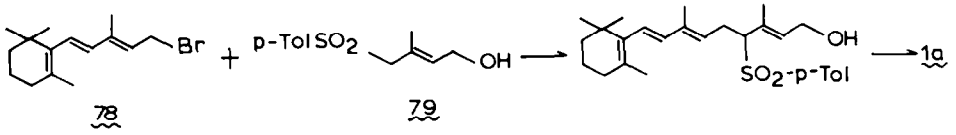
A highly stereoselective sulfone route to vitamin A wherein the tetraene side chain was generated by a sulfone alkylation–sulfinic acid elimination sequence, was first reported by Julia and Arnould[174] in 1973, and since then, has been successfully exploited by several research groups.



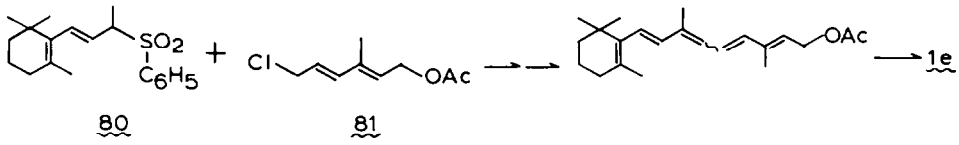
Hoffman–La Roche (New Jersey) chemists[175] and, quite independently, a French group headed by Decor[176] of Rhone–Poulenc Industries reported on the syntheses of all-*trans*-vitamin A and its acetate by similar reaction routes starting from all-*trans*-C_{15}-sulfone and C_5-chloro acetate, **76**. Both groups studied the final elimination step in considerable detail and attained excellent overall yields (83–89%) and product stereoselectivities (9-trans:9-cis ≈ 73:7 to 82:18).



Olson and coworkers,[177] also of Hoffmann–La Roche (New Jersey), developed an equally efficient "through process" perparation of crystalline all-*trans*-vitamin A acetate starting from all-*trans*-C_{15}-bromotriene**78** (prepared from vinyl-β-ionol, **57**) and C_5-*p*-tolylsulfone, **79**.

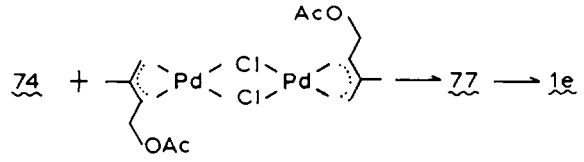


The Fischli–Mayer $C_{13} + C_7$ sulfone approach[178] to all-*trans*-vitamin A involved the alkylation of β-ionyl phenyl sulfone **80** with all-*trans*-C_7-chloro acetates (9-trans:9-cis = 0.63). Brief warming of the isomeric mixture with $Pd(C_6H_5CN)_2Cl_2$–Et_3N in acetonitrile resulted in a significant increase of the 9-trans to 9-cis ratio to 2.43. Lastly, fractional crystallization gave all-*trans*-vitamin A acetate of 95% isomeric purity in 71% overall yield.

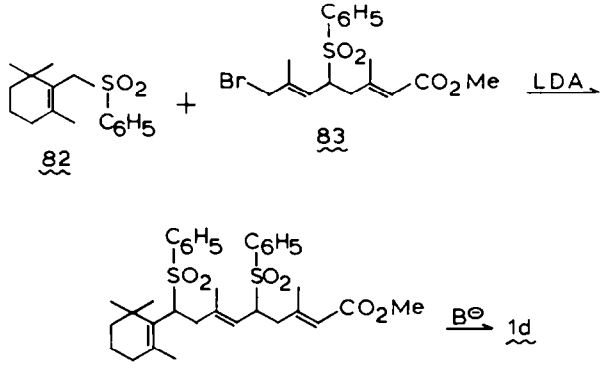


80 81

In 1978, Manchand and coworkers[179] reported a unique $C_{15} + C_5$ convergent approach to the synthesis of all-*trans*-vitamin A wherein the pi-allylpalladium complex of prenyl acetate was regio- and stereoselectively alkylated at the δ-position by the anion of C_{15}-sulfone **74** to give the acetoxy sulfone **77** in 53% yield. Subsequent base-induced elimination of benzenesulfinic acid followed by acetylation afforded vitamin A acetate of 95% isomeric purity.

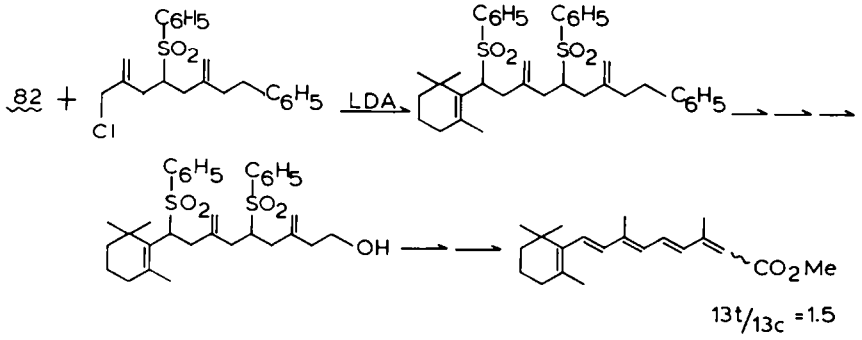


The first $C_{10} + C_{10}$ convergent synthesis of methyl retinoate by the coupling of β-cyclocitryl phenyl sulfone **82** with C_{10}-bromo derivative **83** (94%) followed by the double elimination of two equivalents of benzenesulfinic acid in 94% yield was described by Torii and Uneyama[180] in 1977.

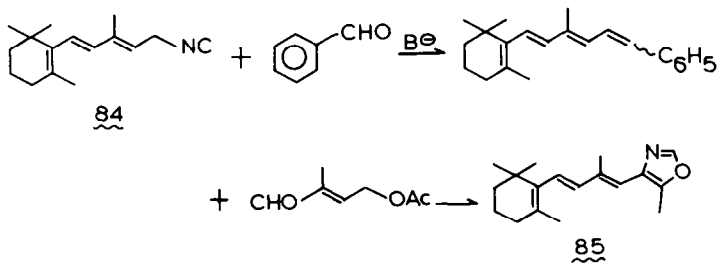


A final product ratio of 13-trans:13-cis = 5 was realized.

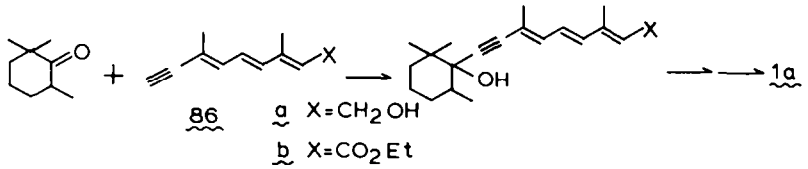
Otera *et al.*[181] have recently reported a novel synthesis of methyl retinoate by the sulfone route outlined below.



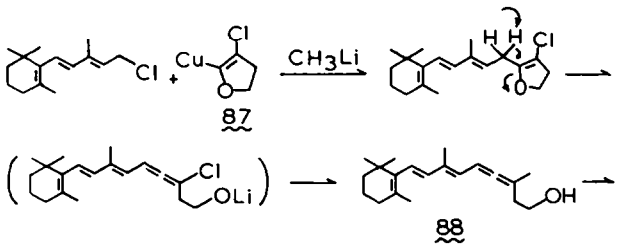
An interesting variation of the ylide condensation was the report of reaction of isonitrile **84** with benzaldehyde. However similar reaction with the C_5-acetate resulted in the formation of the oxazole **85**. The method was not successfully applied to vitamin A synthesis.[182]



The Grignard reaction of the C_{10}-component **86** with 2,2,6-trimethylcyclohexanone was reported to give the C_{20}-compounds in high yield.[183] However, subsequent conversion to vitamin A acetate was accomplished only in 20% yield.



A new retinal synthesis was recently reported by Ruzziconi and Schlosser.[184] A one pot reaction of β-ionylideneethyl chloride with the C_4–cuprate **87** and two equivalents of methyllithium gave isoretinal **88**. Oxidation of **88** with dimethyl sulfoxide in the presence of N,N-dicyclohexylcarbodiimide gave a mixture of four geometric isomers of retinal (11,13-dicis:11-cis:13-cis:all-trans = 1:1:4:5).

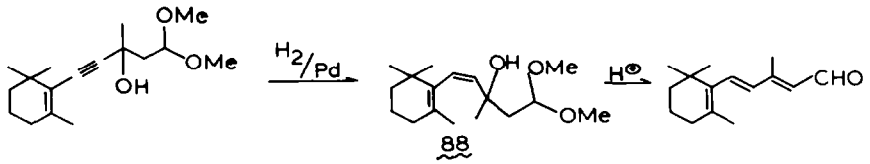


The synthesis of 7-cis and other missing 7-trans isomers of vitamin A

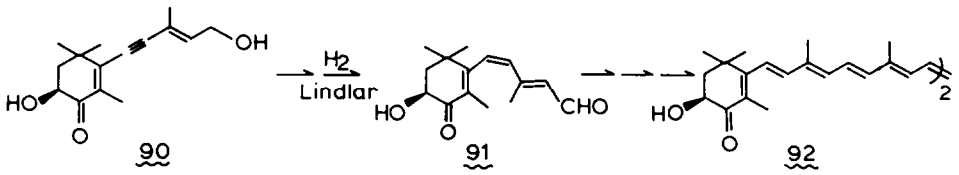
The eight isomers of retinal which constitute the 7-cis manifold (Fig. 3) were previously believed[13] to be synthetically unattainable due to excessive steric crowding between the methyl groups on the C_5- and C_9-positions (Fig. 2). This early misconception was effectively dispelled by several examples wherein the 7-cis configuration was invoked for intermediates in synthetic and photochemical investigations.

Thus, in 1957, Büchi and Yang[66] demonstrated that β-ionone underwent photoisomerization to the corresponding 7-cis form which was in rapid thermal equilibrium with its ring-closed pyran isomeric form (see previous section).[75] This result was later confirmed by Marvell and coworkers[185] by ^{1}H-NMR spectroscopy.

In 1964, Redel *et al.*[186] described the preparation of C_{15}–diene **89** which possessed the 7-cis configuration by catalytic semihydrogenation of its corresponding 7-dehydro precursor. In this experiment, acidic workup resulted in isomerization of the 7-cis bond to its trans form with the formation of β-ionylideneacetaldehyde.



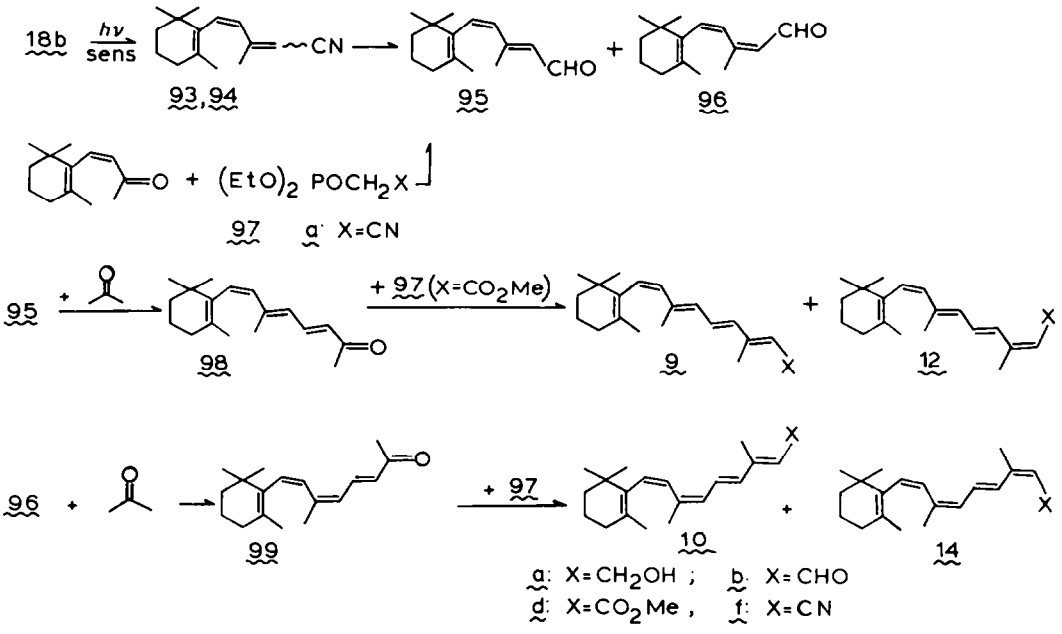
More recently, Kienzle and Mayer[187,188] reported the first total synthesis of the optically active carotenoid, (3S,3S)-astaxanthin, **92**, wherein the key intermediate **90** was converted to its corresponding aldehyde and catalytically hydrogenated over Lindlar catalyst to give the stable 7-*cis*-C_{15}-keto aldehyde **91**.



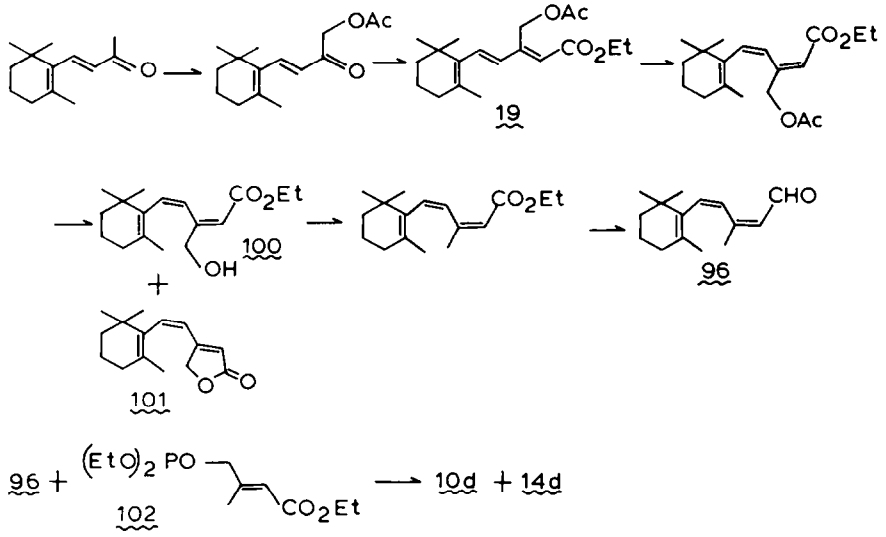
In the 1970's, Liu and Ramamurthy[37,43] at the University of Hawaii reported that the photosensitized isomerization of a series of β-ionyl and β-ionylidene derivatives resulted in the stereoselective formation of their stable 7-cis forms. The general nature of this photochemical isomerization process has been previously described in the earlier Section: The Triplet Sensitized Isomerization Process.

Thus, with procedures in hand for the facile introduction of the 7-cis configuration in key reaction intermediates, standard synthetic methodologies were employed for the first syntheses of 7-cis isomers of vitamin A.

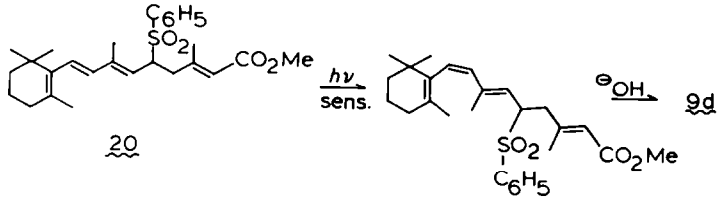
Irradiation of β-ionylideneacetonitrile **18b** in the presence of benzanthrone as photosensitizer generated in near quantitative yield a ~3:2 mixture of 7-*cis*- (**93**) and 7-*cis*,9-*cis*-C_{15}-nitriles (**94**). Alternatively, this same mixture of isomeric nitriles could be realized in 95% yield by the Emmons reaction of 7-*cis*-β-ionone with diethylphosphonoacetonitrile **97** (NaH, DMF). Reduction of the 7-*cis*- and 7-*cis*,9-*cis*-C_{15}-nitriles with diisobutylaluminum hydride (DIBAL) afforded in 75% yield a corresponding mixture of isomeric C_{15}-aldehydes. At this stage the isomers were isolable on silica gel columns giving 7-*cis*- (**95**) and 7-*cis*,9-*cis*-C_{15}-aldehyde (**96**).[43,189] Each of the aldehydes was subjected to base-catalyzed condensation with acetone to give 7-*cis*- (**98**) and 7-*cis*,9-*cis*-C_{18}-ketone (**99**).[189,190] However, reaction of these ketones with the C_2-phosphonate **97** gave two isomer mixtures of retinoate esters which were subjected to chromatographic separation to give pure 7-*cis*- (**9d**), 7-*cis*,9-*cis*- (**10d**), 7-*cis*,13-*cis*- (**12d**) and 7-*cis*,9-*cis*,13-*cis*-retinoate methyl esters (**14d**). Reduction with LAH and oxidation with MnO_2 yielded the corresponding retinols (**9a**, **10a**, **12a**, **14a**) and retinals (**9b**, **10b**, **12b**, **14b**) respectively.[189] Conversion of the ketones to the retinals was also accomplished via intermediate retinonitriles (**9f**, **10f**, **12f**, **14f**) using the C_2-nitrile **97** in the Emmons reaction.[190]



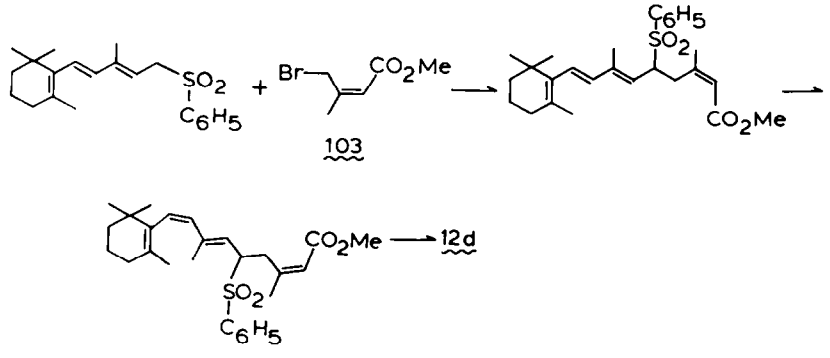
A stereoselective synthesis of 7-*cis*,9-*cis*-β-ionylideneacetaldehyde (**96**) was devised in these laboratories and employed in a $C_{15} + C_5$ synthetic sequence for the preparation of the readily separable isomeric pair, 7-*cis*,9-*cis*- and 7-*cis*,13-*cis*-retinal.[54] They key feature of this lengthy sequence was the high stereoselectivity of the benzanthrone-sensitized photoisomerization of C_{15}-acetoxyester **19** to the corresponding 7-cis,9-cis form (see Section IIB). Subsequent acid-catalyzed ethanolysis afforded 7-*cis*,9-*cis*-C_{15}-hydroxyester **100** and 7-*cis*-C_{15}-butenolide **101** which were readily separated by column chromatography on silica gel. Conversion of hydroxyester **100** to 7-*cis*,9-*cis*-C_{15}-aldehyde was effected by sequential treatment with (a) methanesulfonyl chloride, triethylamine; (b) sodium borohydride in HMPA; (c) LAH and (d) MnO_2. A standard $C_{15} + C_5$ chain extension reaction of **96** with **102** C_5-phosphonoester afforded a 1:1 mixture of 7-*cis*,9-*cis*-(**10d**) and 7-*cis*,9-*cis*,13-*cis*-retinoates (**14d**) which were chromatographically separated and routinely converted to the desired corresponding retinals (**10b, 14b**).



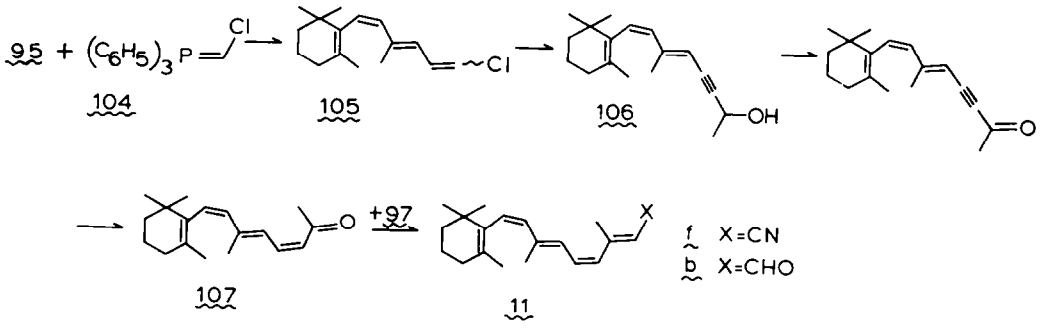
A highly stereoselective $C_{15} + C_5$ sulfone route to methyl 7-*cis*-retinoate which entailed the introduction of the 7-cis configuration by photosensitized isomerization at the C_{20} level has been



reported.[47] Alternatively, starting with *cis*-C_5-bromoester **103** the 7-*cis*,13-*cis*-retinoate, **12d**, was obtained stereoselectively.[47]

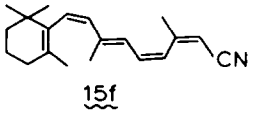


The doubly hindered 7-cis,11-cis isomer of retinal was prepared according to the following reaction sequence:[191]

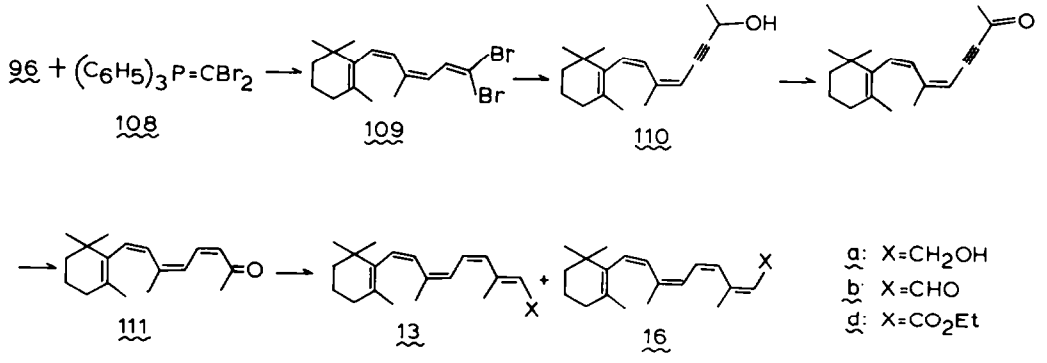


Starting from isomerically pure 7-*cis*-C_{15}-aldehyde (**95**), the Wittig reaction with chloromethylenetriphenylphosphorane (**104**) gave an isomeric mixture of chlorotetraenes, **105**, which, without isolation was reacted with two equivalents of butyllithium to give a dehydrochlorinated and lithiated derivative which when quenched with acetaldehyde produced 7-*cis*-11,12-didehydro-C_{18}-alcohol **106**. Oxidation with MnO_2 followed by catalytic semihydrogenation over Lindlar catalyst afforded the 7-*cis*,11-*cis*-C_{18}-ketone **107**. Next, the $C_{18} + C_2$ chain extension reaction with diethylphosphonoacetonitrile, **97** (NaH, DMF–benzene, 1:15) resulted in very high trans stereoselectivity for the newly formed 13-double bond (> 90%). Lastly, reduction of nitrile **11f** with DIBAL gave the doubly hindered 7-*cis*,11-*cis*-retinal(**11b**) in 95% yield.

The minor isomer formed in the Emmons reaction was also isolated and characterized as 7-*cis*,11-*cis*,13-*cis*-retinonitrile (**15f**). The corresponding retinal was not isolated, but instead underwent thermal isomerization to the 7-cis,13-cis isomer, from possibly two consecutive steps of 6e electrocyclization. A similar isomerization process was observed for 11-*cis*,13-*cis*-retinal.[7,192]



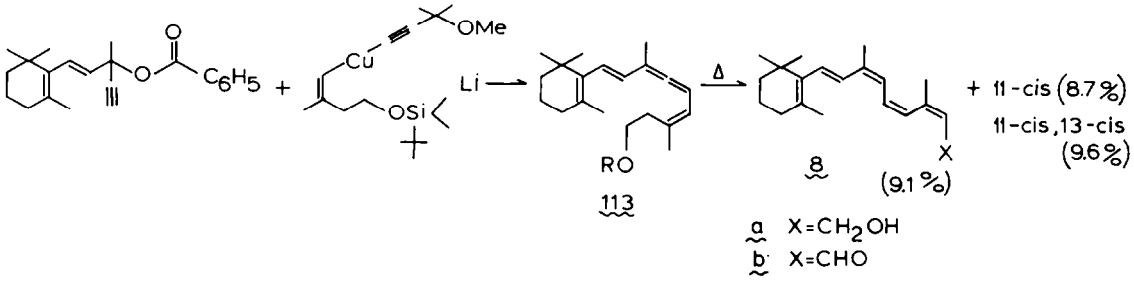
With only minor variations of the above reaction sequence, the ethyl esters of 7-*cis*,9-*cis*,11-*cis*-(**13c**) and all-*cis*-retinoic acid (**16c**) were recently prepared.[193]



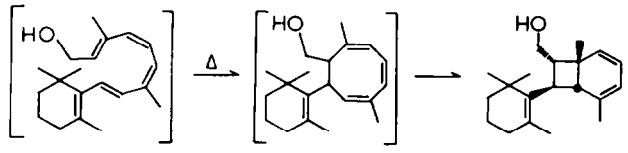
The Corey reaction[194] of 7-*cis*,9-*cis*-C_{15}-aldehyde (**96**) with dibromomethylenetriphenylphosphorane (**108**) afforded the relatively unstable 7-*cis*,9-*cis*-dibromotetraene **109**, which, after removal of phosphorus compounds, was converted to 7-*cis*,9-*cis*-11,12-didehydro-C_{18}-carbinol **110**. Manganese dioxide oxidation followed by catalytic semihydrogenation gave the all-*cis*-C_{18}-ketone, **111**. Lastly, $C_{18} + C_2$ elaboration of the side chain by treatment with ethyl lithiotrimethylsilylacetate (**112**) provided a 1:1 mixture of tricis and all-*cis*-retinoates, **13d** and **16d**.

After HPLC separation, the two esters were reduced separately with DIBAL to give the corresponding vitamin A derivatives (**13a, 16a**). Manganese dioxide oxidation converted the tricis alcohol to 7-*cis*,9-*cis*,11-*cis*-retinal (**13b**).

Progress has also been made on synthesis of the two missing 7-trans isomers: 9-cis,11-cis and 9-cis,11-cis,13-cis. A particularly elegant synthesis of 9-*cis*,11-*cis*,13-*cis*-retinal (**8b**) was recently reported by Okamura *et al.*[195] Their novel approach featured a thermally (69°, 2h) induced [1,5]-sigmatropic hydrogen shift in vinylallene **113** to give a mixture consisting of 11-cis, 11-cis,13-cis and the new 9-cis,11-cis,13-cis (**8a**) isomer of vitamin A. Subsequently a bicyclo[4.2.0]octadiene derivative (**114**) was isolated which was believed to derive from the missing 9-cis,11-cis isomer (**5a**) via consecutive 8e and 6e electrocyclization processes under conditions for sigmatropic hydrogen migration.[192]



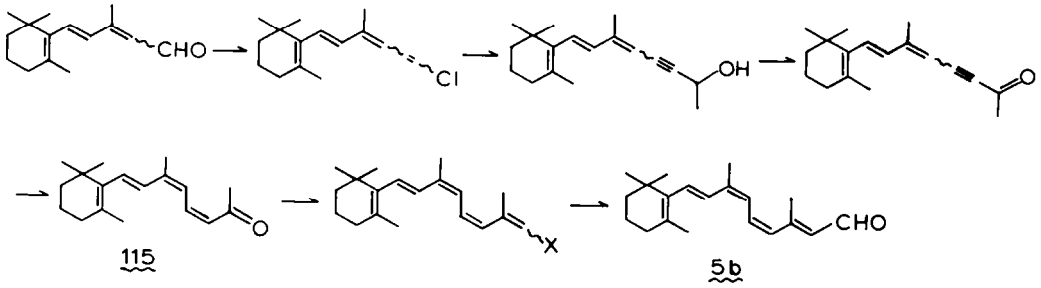
113 8



5a 103 114

Low temperature (4°) oxidation of retinol **8a** with MnO_2 afforded the relatively unstable 9-*cis*,11-*cis*,13-*cis*-retinal **8b**. This highly hindered isomer was found to undergo slow isomerization with a half-life of *ca* 2h at 45° to the thermodynamically more stable 9-cis,13-cis form of retinal, also probably by consecutive pyranylization and ring-opening processes (see above for 11,13-dicis and 7,11,13-tricis isomers). The steric congestion and resultant nonplanarity of the polyenal chromophore in **8b** is reflected in the large hypsochromic shift of the ultraviolet absorption maximum to 302 nm (ϵ = 15,500) in hexane.[195]

The final isomer in the 7-trans manifold, 9-*cis*,11-*cis*-retinal (**5b**) was prepared by Kini[196] according to the following six-step, non-stereoselective reaction sequence:



115 5b

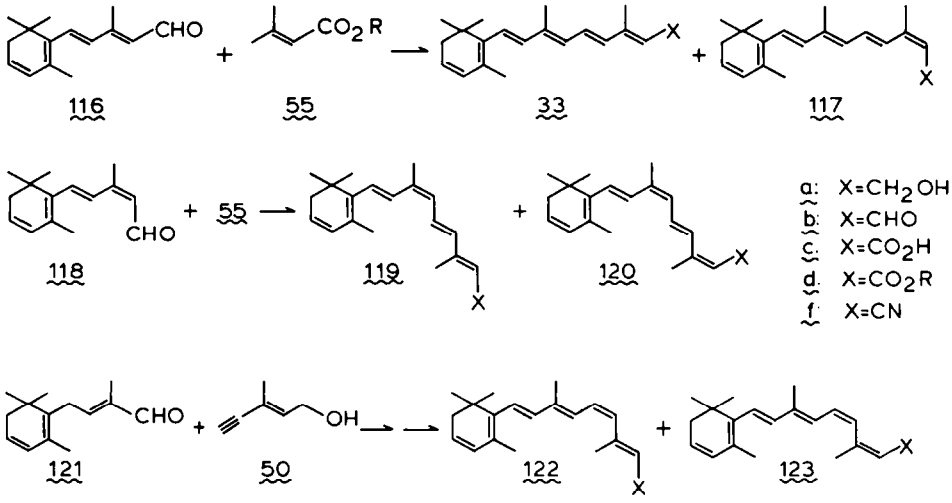
In this approach, the key intermediate, 9-*cis*,11-*cis*-C_{18}-ketone, **115** (together with its 11-cis isomer) was synthesized along with the corresponding 11-cis isomer from a mixture of 9-cis and all-*trans*-β-ionylideneacetaldehyde following a sequence of reactions similar to those in preparation of the 7,11-dicis isomers.[191] Emmons reaction with diethylphosphonacetonitrile (**97**) under conditions which favored the 13-trans configuration in the newly constructed double bond (nonpolar solvents) afforded a mixture of isomeric retinonitriles. After column chromatographic separation of two 13-*trans*-retinonitriles, the mixture was reduced with diisobutylaluminum hydride to the corresponding isomeric retinals which were readily separated by HPLC to give pure 9-*cis*,11-*cis*-retinal, **5b**. The presence of the dicis isomer in photo-mixtures from irradiation of all-*trans*-retinal was subsequently reported.[89]

In conclusion, all sixteen geometric isomers of vitamin A have been synthesized although the aldehyde form of two of the less stable 7-cis isomers have yet to be prepared and characterized (7-cis,11-cis, 13-cis and all-cis). The chapter of stereoisomers of vitamin A has therefore approached the final page. Nevertheless, improved synthetic methodologies in terms of increased stereoselectivity for preparation of these known isomers will remain a continued challenge to workers in the field.

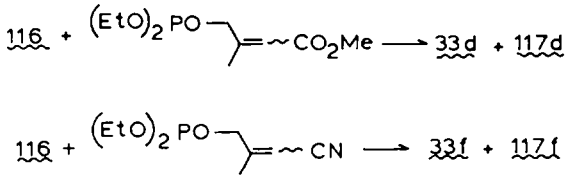
The synthesis of isomers of vitamin A_2 (3-dehydro) and other vitamin A analogues

In contrast to the vast amount of chemical literature for the preparation of stereoisomers of vitamin A_1, the less stable vitamin A_2 series of compounds has received far less attention. The major efforts have centered on the standard $C_{14} + C_6$ and $C_{15} + C_5$ methodologies previously described for the preparation of the structurally similar isomers of vitamin A.

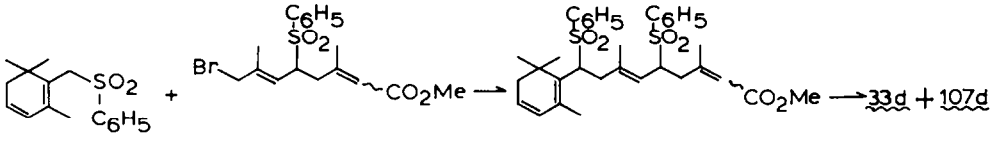
Thus, in 1962, Isler *et al.*[197,198] reported on the synthesis of six isomers of 3-dehydrovitamin A: all-trans (**33a, b**); 9-cis (**119a, b**); 11-cis (**122a, b**); 13-cis (**107a, b**); 9-cis,13-cis (**120a, b**) and 11-cis,13-cis (**123a, b**).



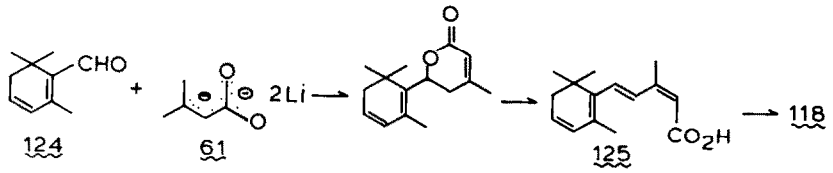
Vitamin A_2 acid (**33c**),[199] ester (**33d**)[200] and nitrile (**33f**)[200] have also been prepared by the reaction of 3-dehydro-β-ionylideneacetaldehyde (**116**)[198] with the C_5 phosphonate and phosphorane derivatives.



The methyl esters of all-*trans*- and 13-*cis*-vitamin A_2 acid were recently prepared by Uneyama and Torii[180] according to the following $C_{10} + C_{10}$ reaction sequence.

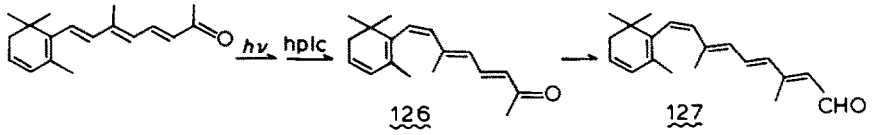


Cainelli and Cardillo[166] have also reported the stereoselective synthesis of 9-*cis*-3-dehydro-β-ionylideneacetic acid (**125**), a precursor to the key intermediate 9-*cis*-C_{15}-aldehyde **118** for the preparation of 9-cis isomers in the vitamin A_2 series, by the reaction of safranal (**124**) with the dilithio derivative of senecioic acid.



124 61 125

Of the eight isomers that possess the 7-cis configuration, only 7-*cis*-3-dehydroretinal (**127**) has been prepared to date. This isomer was synthesized by a standard $C_{18} + C_2$ reaction sequence starting from 7-*cis*-C_{18}-tetraene ketone **126** which had in turn been generated from its corresponding 7-trans form by photochemical isomerization.[90]



126 127

Because of the interest in structure-reactivity relationships in studies of cancer prevention,[8] visual pigment[19] and bacteriorhodopsin analogues,[12] a large number of structurally modified derivatives of vitamin A have been synthesized in recent years. This subject has been thoroughly reviewed by Balogh–Nair and Nakanishi.[201] Other new analogues have since been reported.[93,202]

SEPARATION METHODS AND SPECTROSCOPIC DATA

Separation of vitamin A isomers

The traditional method of fractional recrystallization was successful in separation of the earlier known six geometric isomers of vitamin A.[86,148,153] However, most of the recently prepared cis isomers are oils under common laboratory conditions. For these, chromatographic methods are preferred.

Because of the usual low thermal stability of the polyenes, gas chromatographic methods are rarely used in separation of geometric isomers of vitamin A and derivatives. Separation of the more stable isomers after their protection with silyl end groups has been reported.[203]

The most useful current method of separation of isomers is high pressure (performance) liquid chromatography, HPLC. Several reviews are available compiling conditions for separation of isomers on preparative scale,[204] on analytical or semi-preparative scale particularly on those derivatives of interest to the vision researchers,[205] and separations of vitamin A metabolites or retinoids in pharmaceutical or therapeutic studies.[206] In general uncoated silica gel columns are preferred in separation of isomers. The chromatogram for a photomixture of retinal isomer is shown as a representative example (Fig. 7).[89] Bonded columns, particularly those with cyanoalkyl side chains, were found attractive because of possible reversal of order of elution for a given set of isomers.[207] Reverse phase columns have been extensively used in separation of compounds with different end groups. Separation of isomers are usually limited to the all-trans and 13-cis pair.[206] Alumina based HPLC columns are rarely used. Even though the first successful separation of retinal isomers was done on alumina columns,[18,208] some of the more hindered isomers were found to isomerize on such columns.[52]

Separation of isomers of β-ionylideneacetaldehyde (**18a**) and the C_{18}-ketone (**24a**), the two key intermediates in synthesis of isomers of vitamin A and carotenoids are more readily achieved at the C_{15}-aldehyde stage. (See Figs. 8 and 9 for chromatographs of isomer mixtures of the two compounds.) The synthetic pair of all-trans and 9-cis isomers of the C_{15}-aldehyde were readily separated on silica gel columns. Even the more closely separated pair of isomers with the 7-cis geometry, could be separated on commercial preparative columns such as Waters Prep-500 columns[189] and other low pressure columns.

Spectroscopic properties of vitamin A isomers

Electronic spectroscopy, which only provides limited structural information on geometric isomers of vitamin A, nevertheless has been the most important tool in vision related studies.[209] The characteristic data on isomers of retinal recorded at room temperature are tabulated in Table 6. Low temperature spectra of several geometric isomers have been recorded.[109,135] The 11-cis isomer

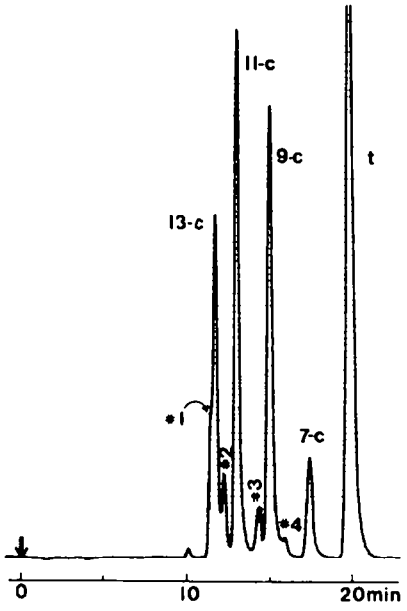


Fig. 7. A chromatogram (Si-60 HPLC column, 360 nm detection) of an irradiated mixture of retinal ($\geqslant$380 nm, in CH_3CN). The minor peaks have retention times identical to 7-cis,13-cis (# 1), 9-cis,13-cis (# 2), 9-cis,11-cis (#) and 7-cis,9-cis (# 4) isomers.

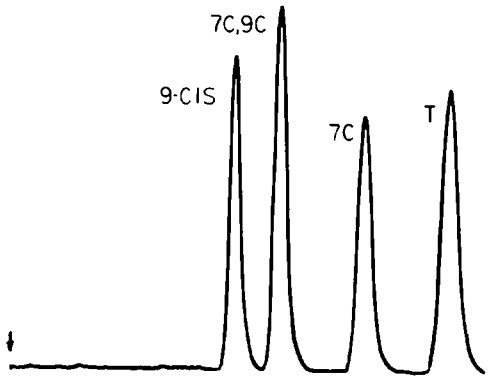


Fig. 8. A chromatogram (HPLC) of four isomers of C_{15}-aldehyde. A Si-60 10 μm preparative column (25 mm x 1/2 in) was used with 10% ether in hexane as solvent.

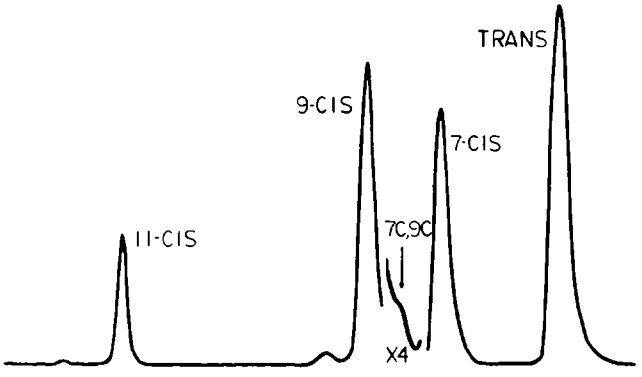


Fig. 9. A chromatogram (HPLC) of geometric isomers of the C_{16}-ketone. A Si-60 10 μm preparative column was used with 10% ether in hexane as solvent. The retention time of the 7-cis, 9-cis isomer was in between those of 9-cis and 7-cis isomers, while that of the 9-cis, 11-cis isomer was identical to that of the 11-cis isomer. The peak in front of the 9-cis isomer was that of the retro-γ-isomer.

Table 6. UV–vis absorption data of isomers of retinol

Isomer	Hexane		Ethanol	
	λ_{max}	ε	λ_{max}	ε
All trans[a]	368	48,000	383	42,884
7-cis	359[b]	44,100	377[d]	38,000
9-cis[a]	363	37,660	373	36,010
11-cis[a]	365	26,360	379.5	24,940
13-cis[a]	363	38,770	375	35,500
7,9-dicis	351[b]	42,500		
7,11-dicis	355[c]	18,800	374[d]	16,000
7,13-dicis[b,d]	357			
9,11-dicis[e]	352	30,600	368[d]	27,000
9,13-dicis[a]	359	34,170	368	32,380
11,13-dicis[f]			302	17,000
7,9,11-tricis[g]	345	22,000		
7,9,13-tricis	346[b]	36,600		
9,11,13-tricis[h]	302	15,500	302	14,300

a. Ref. 209. b. W. DeGrip, R. S. H. Liu, A. E. Asato and V. Ramamurthy, Nature, 262, 416 (1976). c. Ref. 191. d. M. Denny, A. Kini, H. Matsumoto and R. S. H. Liu, unpublished results. e. Ref. 196. f. Ref. 192. g. Ref. 193. h. Ref. 195.

showed the unusual feature of a large increase of extinction coefficient at lower temperatures. For obvious reasons, circular dichroism has not been used for studies of naturally occurring vitamin A isomers although extensive CD studies have recently been applied to carotenoids[210] and visual pigments.[211]

Vibrational spectroscopy (infrared) has been used in configurational assignments especially in the early synthetic work on the stereoisomers of vitamin A.

Recently the advent of Resonance Raman and FT–IR spectroscopy added a new dimension to vibrational spectroscopy in studies of polyene chromophores. The former is particularly useful for protein bond retinyl systems. Several excellent review articles are available.[212,213,214] We refer the readers to these papers for detailed information.

Nuclear magnetic resonance spectroscopy is currently the method of choice for structural assignments of geometric isomers. The general availability of high field spectrometers in recent years further enhanced the usefulness of the method. An excellent example is the recent extensive study of ^{13}C-NMR spectra of carotenoids.[215]

The most extensive compilation of ^{1}H-NMR data on isomers of vitamin A and derivatives was that of Englert and coworkers in the 1971 treatise of "Carotenoids"[216] and ^{13}C-NMR data by Englert in 1974.[217] We now attempt to update those listings by compiling recent data along with selected earlier ones on key proton chemical shifts and coupling constants (Table 7) and carbon shifts (Table 8) of vitamin A isomers. Also listed are isomers of the key synthetic intermediates, the C_{15}-aldehyde and the C_{18}-ketone (Tables 9 and 10). Limited data on compounds in the vitamin A_2 series are listed in Table 11. To limit the tables to a manageable length we have arbitrarily chosen to list, whenever possible, data obtained in the most commonly used solvent: deuterated chloroform. It should be noted that the possible presence of acidic impurites in this solvent sometimes introduces the complication of isomerization of the cis isomers, especially during extended storage.

The data in these tables are generally temperature independent. The exceptions are the chemical shifts of retinals in aromatic solvents (specific solvent solute interactions)[150] and that of 11-*cis*-retinal in acetone-d_6 (12-*S*-cis, and 12-*S*-trans equilibrium).[218] Also, for the 7-cis isomers the 1,1-dimethyl groups exhibit DNMR features characteristic of a two site exchange.[41,42,219] It was believed to be due to restricted rotation about the 6,7 single bond. The average barrier heights of 12–14 kcal mol^{-1} is, however, too low for resolution of chiral rotational isomers.[219]

Table 7. ^{1}H-NMR data of isomers of retinal, methyl retinoate, retinonitrile, retinol and vitamin A acetate from the literature (in $CDCl_3$ unless otherwise specified)

	Methyls (δ, ppm)				Vinyl hydrogens (δ, ppm)							Coupling Constant (J, Hz)			
C_{20}-compound	1	5	9	13	7	8	10	11	12	14	15	7,8	10,11	11,12	14,15
All-trans, 1															
CHO	1.04	1.72	2.03	2.33	6.36	6.18	6.20	7.15	6.37	5.98	10.12	16.5	12.0	15.4	8.0[a]
COOMe	1.03	1.72	2.01	2.37	6.26	6.16	6.15	7.01	6.30	5.79	--	16.0	11.4	15.0	b
CN	1.02	1.72	1.93	2.21							5.19				c
CH_2OH			1.97	1.85	6.14	6.09	6.08	6.60	6.27	5.67	4.29				d
CH_2OAc	1.03	1.70	1.95	1.89	6.18	6.12	6.09	6.65	6.27	5.61	4.70	16	11.1	15.2	7.0[a]
7-cis, 9															
CHO	1.05	1.52	1.93	2.31	5.99	6.18	6.25	7.86	6.37	5.98	10.12	11.3	11.5	15.0	8.2[e]
COOMe	1.04	1.52	1.90	2.34	5.95	6.11	6.22	6.93	6.26	5.78	--	13.0	11.8	14.6	b
CN	1.06	1.52	1.92	2.22	5.99	6.12	6.90	6.88	6.26	5.19	--	12	11.5	14.8	f
CH_2OH					5.68	5.92	5.49	6.41	6.00	5.58		11.3	14.5	7.2	f
9-cis, 2															
CHO	1.05	1.75	2.00	2.30	6.31	6.64	6.06	7.20	6.27	5.94	10.07	15.9	11.8	15.4	8.2[a]
COOMe	1.05	1.75	2.01	2.35	6.23	6.65	6.05	7.10	6.27	5.79	--	16.0	12.0	15.0	b
CN															
11-cis, 3															
CHO	1.02	1.71	1.99	2.36	6.32	6.14	6.54	6.69	5.92	6.07	10.10	16.0	13.0	11.5	8.0[a]
COOMe	1.03	1.71	2.00	2.35	6.35	6.21	6.63	6.67	6.00	5.84	--	16.0	11.9	10.8	b
CN	1.02	1.72	1.96	2.24	6.31	6.13	6.48	6.62	5.84	5.27	--	15.4	11.7	11.7	c
CH_2OH			1.96	1.93	6.17	6.10	6.13	6.65	6.60	5.55	4.30				d
CH_2OAc			1.93	1.92	6.20	6.12	6.56	6.39	5.87	5.63	4.71				d
13-cis, 4															
CHO	1.04	1.72	2.02	2.14	6.35	6.18	6.23	7.05	7.28	5.85	10.20	16.0	11.1	15.0	8.0[a]
COOMe	1.02	1.72	1.99	2.07	6.26	6.17	6.26	7.00	7.78	5.65	--	16.5	11.4	15.2	b
CN	1.02	1.70	1.99	2.04	6.30	6.15	6.18	6.97	6.79	5.05	--	16	11	15	f
CH_2OH			1.96	1.93	6.17	6.10	6.13	6.65	6.60	5.55	4.30				d
CH_2OAc			1.95	1.96	6.17	6.10	6.12	6.69	6.59	5.47	4.74				d
7-cis,9-cis, 10															
CHO	1.05	1.46	1.87	2.30	6.10	6.58	6.02	7.16	6.26	5.95	10.10	12.4	12.4	15.1	7.5[f]
COOMe	1.04	1.46	1.84	2.33	6.06	6.57	5.97	7.02	6.17	5.76	--	12.2	11.8	14.5	f
CN	1.05	1.48	1.88	2.22	5.79	6.56	6.08	6.99	6.20	5.19	--	12	11.5	15	f
CH_2OH	1.00	1.43	1.81	1.76	5.9	6.5	6.0	6.60	6.15	5.65	4.24	12.5	11.0	14.5	7.4[f]
7-cis,11-cis, 11															
CHO	1.02	1.50	1.88	2.33	5.95	6.07	6.58	6.59	5.92	6.02	10.05	12.4	i	i	7.8[f]
COOMe	1.01	1.50	1.85	2.31	5.90	6.04	6.6	6.5	5.86	5.80	--	12.8	11	12	f
CN	1.04	1.54	1.90	2.24	5.92	6.08	6.6	6.5	5.8	5.22	--	12.5	12[j]	12[j]	f
7-cis,13-cis, 12															
CHO	1.07	1.54	1.94	2.10	5.98	6.11	6.36	6.92	7.22	5.80	10.20	11.5	11.2	15.5	8.0[f]
COOMe	1.06	1.54	1.96	2.09	6.00	6.23	6.36	7.07	7.82	5.69	--	13.2	11.2	15.2	b
CN	1.04	1.5	1.92	2.06	5.99	6.14	6.27	6.85	6.8	5.08	--	12	10	15	f

Table 7 (*Contd*)

C_{20}-compound	Methyls (δ, ppm)				Vinyl hydrogens (δ, ppm)							Coupling Constant (J, Hz)			
	1	5	9	13	7	8	10	11	12	14	15	7,8	10,11	11,12	14,15
9-cis,11-cis, 5															
CHO	1.04	1.74	2.04	2.36	6.26	6.64	6.40	6.72	5.86	5.98	10.06	16.0	11.5	11.5	7.6[e]
CN															
9-cis,13-cis, 6															
CHO	1.05	1.77	2.05	2.15	6.36	6.68	6.16	7.16	7.25	5.87	10.27	16.0	10.5	15.0	8.0[a]
COOMe	1.03	1.74	1.99	2.06	6.28	6.66	6.17	7.09	7.72	5.65	--	16.0	10.5	15.0	b
11-cis,13-cis, 7															
CHO	1.01	1.68	1.96	2.07	6.28	6.08	6.20	6.77	6.11	5.98	9.71	16.0	12.5	11.8	8.1[a]
COOMe	1.02	1.71	1.96	2.17	6.27	6.12	6.41	6.63	6.99	5.70	--	16.3	12.1	11.6	b
CN	1.02	1.72	1.98	2.20	6.36	6.10	6.46	6.72	6.32	5.08	--	16.0	12.0	12.0	f
CH_2OH			1.93	1.88	6.16	6.04	6.03	6.49	5.86	5.54	4.04				d
CH_2OAc					6.19	6.08	6.09	6.49	5.87	5.49	4.73				d
7c,9c,11c, 13															
CHO	1.03	1.44	1.84	2.32	6.08	6.48	6.34	6.66	5.83	6.04	10.07	12.5	12.2	12.7	8.1[g]
COOEt	1.03	1.45	1.82	2.31	6.04	6.49	6.33	6.51	5.78	5.81	--	12.2	12.3	11.7	g
CN	1.05	1.45	1.86	2.23	6.32	6.47	6.07	6.58	5.80	5.25	--	12.5	11.5	11.5	f
7c,9c,13c, 14															
CHO	1.04	1.47	1.88	2.12	5.97	6.52	6.13	6.99	7.12	5.83	10.20	12.1	10.5	14.5	8.0[e]
COOMe	1.03	1.46	1.84	2.05	6.05	6.57	6.09	7.00	7.66	5.64	--	12.5	11.2	15.3	f
CN	1.05	1.52	1.90	2.06	6.01	6.58					--				f
7c,11c,13c, 15															
CHO	1.02	1.51	1.88	2.05				6.61			9.56				f
COOMe	1.01	1.48	1.94	2.14	5.90	6.03	6.5	6.5	6.9	5.66	--	12.5	i	i	f
CN	1.02	1.51	1.89	2.17	5.94	6.07	6.4	6.4	6.6	5.07	--	12.2	i	i	f
9c,11c,13c, 8															
CHO	1.04	1.47	1.88	2.12	5.97	6.52	6.13	6.99	7.12	5.83	10.20	12.1	10.5	14.5	8.0[h]
COOMe	1.03	1.73	1.99	2.18	6.29	6.68	6.30	6.71	6.90	5.70	--	16.0	11.1	11.8	b
CN															
CH_2OH	1.02	1.72	1.86	1.93	6.20	6.65	5.97	6.57	5.81	5.57	4.04	15.5	12	12	7.0[h]
all-cis, 16															
COOEt	1.03	1.44	1.81	2.13	6.04	6.50	6.84	6.57	6.21	5.67	--	12.8	12.0	12.2	g
CN	1.06	1.46	1.90	2.20						5.12	--	12[j]	11[j]	11.2[j]	f
CH_2OH	1.03	1.45	1.85	1.77	6.00	6.48	5.88	6.44	5.78	5.53	4.03	12.4	11.7	11.5	6.7[g]

a. Ref. 150. b. B. A. Halley and E. C. Nelson, J. Chromatogr., 175, 113 (1979). c. Ref. 104. d. Ref. 216. e. Ref. 189. f. Unpublished results of A. E. Asato, M. Denny, A. Kini and R. S. H. Liu. g. Ref. 193. h. 195. i. Not well resolved. j. J values obtained in C_6D_6.

Table 8. ^{13}C-NMR chemical shift data of isomers of vitamin A[a]

C_{20}-compound	C-1	C-2	C-3	C-4	16,17	C-18	C-19	C-20	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12	C-13	C-14	C-15
all-trans, 1																			
CHO	34.1	39.6	19.3	33.2	29.0	21.7	13.0	13.0	130.3	137.6	129.6	137.1	141.1	129.4	132.4	134.5	154.5	128.9	190.7[b]
COOMe	34.3	39.8	19.3	33.2	29.0	21.7	12.9	13.9	129.8	137.8	128.6	137.3	139.4	129.5	130.9	135.2	152.8	118.2	167.3[b]
CH_2OH	34.2	39.8	19.4	33.1	29.0	21.7	12.5	12.6	128.9	137.9	126.5	137.7	135.6	130.2	124.8	136.5	136.2	130.6	59.1[b]
CH_2OAc	34.3	39.8	19.4	33.1	29.0	21.7	12.7	12.7	129.3	138.0	127.0	137.7	136.5	130.0	125.8	135.9	139.0	124.6	61.3[b]
7-cis, 9																			
CHO	34.6	39.2	19.2	32.1	28.7	21.6	13.1	14.8	129.4	136.3	128.9	134.5	142.1	130.8	132.3	134.2	154.5	130.8	190.8[c]
9-cis, 2																			
CHO	34.1	39.7	19.3	33.2	29.0	21.8	20.9	13.2	130.4	138.1	131.1	129.4	140.0	127.9	131.2	133.8	154.3	128.9	190.6[b]
COOMe	34.3	39.7	19.4	33.2	29.1	21.8	20.9	13.9	130.0	138.1	130.2	129.6	138.3	128.1	129.9	134.5	152.3	118.2	167.4[b]
CH_2OH	34.3	39.8	19.4	33.2	29.0	21.8	20.7	12.7	129.4	138.2	128.6	130.0	134.8	128.7	124.0	135.7	136.7	130.0	59.4[b]
CH_2OAc	34.3	39.8	19.4	33.2	29.1	21.8	20.7	12.7	129.4	138.1	128.6	130.0	135.1	128.6	124.7	135.1	139.0	124.5	61.2[b]
11-cis, 3																			
CHO	32.9	38.4	17.9	31.6	27.3	19.9	10.4	15.9	128.5	136.5	127.9	136.5	139.7	125.0	129.6	129.6	153.9	128.7	189.2[d]
	34.6	39.6	19.5	33.3	29.0	21.6	11.9	17.4	130.0	138.1	129.3	138.3	141.1	126.6	130.9	131.2	154.6	130.5	190.8[e]
CH_2OH	34.3	39.7	19.4	33.1	29.0	21.7	12.2	17.1	129.1	138.0	127.1	138.1	137.1	126.4	125.2	132.6	136.1	130.5	59.4[b]
CH_2OAc	34.3	39.7	19.3	33.1	29.0	21.7	12.2	17.2	129.2	138.0	127.2	138.0	137.4	126.2	125.7	132.1	138.0	124.9	61.2[b]
13-cis, 4																			
CHO	34.3	39.7	19.3	33.2	29.0	21.7	13.0	21.1	130.3	137.6	129.6	137.0	141.3	129.4	133.4	126.5	154.2	127.7	189.6[b]
COOMe	34.3	39.7	19.4	33.2	29.0	21.7	12.8	20.8	129.9	137.7	128.5	137.5	139.6	130.4	132.1	129.5	151.1	116.2	166.5[b]
CH_2OH	34.3	39.8	19.4	33.1	29.0	21.6	12.7	20.4	129.3	137.9	127.1	137.6	136.8	130.2	127.1	128.6	135.6	128.7	58.4[b]
CH_2OAc	34.3	39.8	19.4	33.1	29.0	21.7	13.0	21.1	129.4	137.9	127.4	137.6	137.3	130.2	127.4	128.2	137.4	123.2	59.8[b]
7c,9c, 10																			
CHO	34.3	39.2	19.1	32.3	28.9	21.7	22.0	13.1	130.2	136.5	127.1	128.9	142.0	129.4	131.6	131.6	154.6	131.7	190.7[c]
11c,13c, 7																			
CH_2OH	34.3	39.8	19.4	33.1	29.0	21.7	12.5	23.9	129.3	137.9	127.5	137.8	137.3	126.2	126.8	128.2	135.7	127.9	60.6[b]
7c,9c,13c, 14																			
CHO	34.3	39.2	19.1	32.3	28.9	21.7	22.0	20.9	130.2	136.5	127.2	131.7	142.2	129.4	132.4	125.1	154.0	127.4	186.5[c]

a. In $CDCl_3$ unless otherwise specified. b. Ref. 217. c. Ref. 189, tentative assignments. d. R. Rowan III and B. D. Sykes, J. Am. Chem. Soc., 96, 7000 (1974). In acetone-d_6. e. R. S. Becker, S. Berger, D. K. Dalling, D. M. Grant and R. J. Pugmire, J. Am. Chem. Soc., 96, 7008 (1974). In dioxane-d_8.

Table 9. ^{1}H-NMR data of isomers of the C_{18}-ketone (**24a**) and the C_{15}-aldehyde (**18a**)[a]

	Chemical Shift									Coupling Constants		
	Methyls (δ, ppm)				Vinyl Hydrogens (δ, ppm)					J, Hz		
C_{15}-CHO	1	5	9	13	7	8	10	11	12	7,8	10,11	11,12
all-trans	1.02	1.68	2.18	--	6.63	6.11	5.79	--	--	16.0	--	b
7-cis	1.02	1.52	2.16	--	6.15	6.05	5.85	--	--	12.0	--	b
9-cis	1.02	1.68	2.00	--	6.56	7.03	5.79	--	--	15.5	--	b
all-cis	1.02	1.52	1.93	--	6.19	6.86	5.68	--	--	12.0	--	b
C_{18}-ketone												
all-trans	1.02	1.70	2.05	2.33	6.43	6.22	6.22	7.58	6.12	16.2	11.8	15.3[c]
7-cis	1.01	1.48	1.94	2.26	6.05	6.10	6.23	7.48	6.11	12.5	11.7	15.3[c]
9-cis	1.00	1.70	2.01	2.25	6.34	6.68	6.04	7.62	6.08	15.9	12.1	14.8[c]
11-cis	1.00	1.69	1.99	2.21	6.40	6.24	7.39	6.85	5.97	16.1	12.3	11.9[c]
7c,9c	1.02	1.43	1.87	2.26	6.14	6.62	6.00	7.55	6.03	12.3	12.1	15.2[c]
7c,11c	1.02	1.58	1.92	2.09	6.02	6.14	7.42	6.88	5.95	12.5	11.5	12.2[c]
9c,11c	1.00	1.70	2.04	2.21	6.36	6.69	7.29	6.94	5.93	16.0	12.5	11.8[c]
all-cis	1.06	1.48	1.94	2.22	6.15	6.61	7.28	6.88	5.94	12.5	12	11[d]

a. In $CDCl_3$. b. Ref. 43. c. Unpublished results of M. Denny, A. Kini and R. S. H. Liu. d. Ref. 193.

Table 10. ^{13}C-NMR (δ, ppm) data of isomers of C_{15}-aldehyde and C_{18}-ketone in $CDCl_3$

	C-1	C-2	C-3	C-4	16,17	C-18	C-19	C-20	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12	C-13
C_{15}-CHO																	
all-trans	34.1	39.7	19.4	33.4	28.9	21.6	12.9	--	132.5	137.2	135.4	135.7	154.6	128.7	190.9	--	a
7-cis	34.4	38.8	18.7	31.8	28.4	21.2	15.1	--	130.4	135.8	136.5	132.9	156.6	129.6	191.6	--	b
9-cis	34.3	39.8	19.2	33.3	29.0	21.8	21.1	--	132.4	137.4	136.4	128.0	154.6	127.8	189.6	--	a
7c,9c	34.2	38.9	18.8	32.2	28.7	21.7[c]	22.3[c]	--	131.7	?	136.3	128.9[c]	158.6	126.3[c]	190.9	--	b
C_{18}-ketone																	
all-trans	34.1	39.5	19.0	33.0	28.8	21.7	13.0	27.5	130.7	137.1	131.0	139.1	145.2	128.9	136.4	127.4	198.1[b]
9-cis	34.2	39.4	19.1	32.9	28.9	21.1	21.8	27.7	130.5	137.5	132.1	125.9	144.3	128.8	137.8	128.3	198.2[b]

a. Ref. 217. b. Unpublished results of D. Mead, A. E. Asato and R. S. H. Liu. c. The C-18, C-19 signals and the C-8, C-10 signals could be reversed.

Table 11. ^{1}H-NMR data of isomers of vitamin A_2 and 3-dehydroretinal (in $CDCl_3$ unless otherwise specified)

	Methyls (δ, ppm)				Vinyl hydrogens (δ, ppm)									Coupling Constant (J, Hz)			
C_{20}-compound	1	5	9	13	3	4	7	8	10	11	12	14	15	7,8	10,11	11,12	14,15
All-trans, 33																	
CHO	1.02	1.86	2.02	2.31	5.74	5.85	6.34	6.30	6.22	7.12	6.37	5.97	10.09	16.2	11.5	15.0	8.1[a]
CH_2OH		1.86	1.96	1.86	5.72	5.85	6.17	6.26	6.14	6.62	6.30	5.67	4.28				b
7-cis, 127																	
CHO	1.03	1.58	1.96	2.30	5.78	5.80	5.95	6.17	6.26	7.05	6.33	5.96	10.06	12.5	11.4	14.9	8.2[a]
9-cis, 119																	
CHO	1.04	1.91	2.02	2.29	5.77	5.86	6.31	6.80	6.10	7.21	6.32	5.95	10.16	15.9		15.0	8.2[a]
CH_2OH			1.99	1.92	5.74	5.88	6.17	6.80	6.04	6.72	6.24	5.69	4.32				b
11-cis, 122																	
CHO[c]	1.06	1.76	1.73	1.80	5.68	5.84	6.32	6.32	6.58	6.37	5.59	6.10	9.92	?	11.9	11.5	7.8[d]
13-cis, 117																	
CHO		1.87	2.03	2.14	5.74	5.84	6.33	6.33	6.25	7.03	7.29	5.86	10.16[a]	16.3[c]	11.4[c]	14.5[c]	7.6[c]
9-cis,13-cis, 120																	
CH_2OH			1.95	1.89	5.71	5.83	6.19	6.19	6.08	6.46	5.88	5.56	4.07				b

a. Ref. 90; also 300 MHz, ref. 52. b. Ref. 216. c. In C_6D_6. d. Ref. 52.

X-ray crystal structures of vitamin A isomers are limited to the following compounds: all-*trans*-,[220] 11-*cis*-,[221,222] and 13-*cis*-retinal,[223] all-*trans*-retinoic acid,[224,225] all-*trans*-vitamin A acetate[226] and methyl 7-*cis*,9-*cis*-retinoate.[227] For a given compound the ring-chain[225] conformation may change from *S*-*cis* to *S*-trans depending on the method of crystallization. A very unusual case is in 13-*cis*-retinal where simultaneous presence of both conformers in one unit cell was reported.[227] The crystal structure of all-*trans*-dehydroretinal has also been solved recently.[228]

Acknowledgements—The work carried out at the University of Hawaii was supported by grants from the National Science Foundation (CHE-15233, CHE-12686) and U.S. Public Health Service (AM-17806). We acknowledge with thanks the reprints and preprints from the following workers in the field: Prof. R. Becker, G. Cainelli, A.B. Ellis, W. H. Okamura, K. Tsukida, W.H. Waddell and Drs J. Lugtenburg, E. C. Nelson, G. Olson. Critical reading of and helpful suggestions to an earlier version of the review by Professors W. J. Waddell and Drs V. Balogh-Nair and J. Lugtenburg are much appreciated.

REFERENCES

[1]"Symposium on vitamin A and metabolism in honor of Prof. P. Karrer", *Vitamins and Hormones* **18**, 289–571 (1960).
[2]O. Isler, In *Carotenoids* (Edited by O. Isler), Chap. 1. Birkhauser Verlag, Basel (1971).
[3]P. Karrer, R. Morf and K. Schöpp, *Helv. Chim. Acta* **14**, 1431 (1931).
[4]R. Kuhn and C. J. O. R. Morris, *Ber.* **70**, 853 (1937).
[5]O. Isler, W. Huber, A. Ronco and M. Kofler, *Helv. Chim. Acta* **30**, 1911 (1947).
[6]G. Wald in Ref. 1. p. 417–430.
[7]See G. Wald, P. K. Brown, R. Hubbard and W. Oroshnik, *Proc. Nat. Acad. Sci. USA*, **41**, 438 (1955); **42**, 578 (1956).
[8]R. K. Boutwell, "Oncology overview, selected abstracts on vitamin A in cancer biology", HE 20.3173/3:OB–79/04, U.S. Dept. of Health, Education and Welfare, PHS, NIH, NCI, Washington, D.C., 11 Sept. 1979.
[9]D. L. Newton, W. R. Henderson and M. B. Sporn, *Cancer Res.* **40**, 3413 (1980).
[10]G. L. Peck, T. G. Olsen, F. W. Yoder, J. S. Strauss, D. T. Downing, M. Pandya, D. Butkis and J. Arnaud-Battandier, *New England J. Med.* **300**, 329 (1979).
[11]Produced by Hoffmann–La Roche Inc.
[12]W. Stoeckenius, *Acc. Chem. Res.* **13**, 337 (1980).
[13]L. Pauling, *Forschr. Chem. Org. Naturstoffe* **3**, 203 (1939).
[14]IUPAC Commission on "Definitive rules for the nomenclature of the vitamins", *J. Am. Chem. Soc.* **82**, 5581 (1960).
[15]IUPAC–IUB Joint Commission on Biological Nomenclature; Nomenclature of Retinoids, *Eur. J. Biochem.* **129**, 1 (1982).
[16]G. Wald, *Science* **162**, 230 (1968).
[17]L. Zechmeister, *Cis–trans Isomeric Carotenoids, Vitamin A and Arylpolyenes*. Academic Press, New York, 1962.
[18]R. Hubbard and G. Wald, *J. Gen. Physiol.* **36**, 269 (1952–53).
[19]R. S. H. Liu, In *Carotenoid Chemistry and Biochemistry* (Edited by G. Britton and T. W. Goodwin), p. 253. Pergamon Press, Oxford (1982).
[20]M. Ottolenghi, *Adv. Photochem.* **12**, 97 (1980).
[21]B. Honig, *Ann. Rev. Phys. Chem.* **29**, 31 (1978).
[22]R. R. Birge, *Ann. Rev. Biophys. Bioengng* **10**, 315 (1981).
[23]M. Mousseron, *Adv. Photochem.* **4**, 203 (1966).
[24]R. S. H. Liu, *Pure Appl. Chem.*, Suppl. **1**, 335 (1971).
[25]W. H. Waddell, R. Crouch, K. Nakanishi and N. J. Turro, *J. Am. Chem. Soc.* **98**, 4189 (1976).
[26]T. Rosenfeld, A. Alchalel and M. Ottolenghi, *J. Phys. Chem.* **78**, 336 (1974).
[27]A. Kropf and R. Hubbard, *Photochem. Photobiol.* **12**, 249 (1970).
[28]W. H. Waddell and K. Chihara, *J. Am. Chem. Soc.* **103**, 7389 (1981).
[29]B. Veyret, S. G. Davis, M. Yoshida and K. Weiss, *J. Am. Chem. Soc.* **100**, 3283 (1978).
[30]R. A. Raubach and A. V. Guzzo, *J. Phys. Chem.* **77**, 889 (1973).
[31]T. Rosenfeld, O. Kalisky and M. Ottolenghi, *J. Phys. Chem.* **81**, 1496 (1977).
[32]See e.g. N. J. Turro, *Modern Molecular Photochemistry*, pp. 476–480. Benjamin, New York (1978).
[33]J. Saltiel *et al.*, *Org. Photochem.* **3**, 1 (1972).
[34]G. S. Hammond, J. Saltiel, A. A. Lamola, N. J. Turro, J. J. Bradshaw, D. O. Cowan, R. E. Counsell, V. Vogt and C. Dalton, *J. Am. Chem. Soc.* **86**, 3197 (1964).
[35]W. G. Herkstroeter and G. S. Hammond, *J. Am. Chem. Soc.* **88**, 4769 (1966).
[36]See e.g., S. Yamauchi and T. Azumi, *J. Am. Chem. Soc.* **95**, 2709 (1973) and refs cited therein.
[37]V. Ramamurthy, Y. Butt, C. Yang, P. Yang and R. S. H. Liu, *J. Org. Chem.* **38**, 1247 (1973).
[38]V. Ramamurthy and R. S. H. Liu, *J. Am. Chem. Soc.* **98**, 2935 (1976).
[39]B. Honig, B. Hudson, B. D. Sykes and M. Karplus, *Proc. Nat. Acad. Sci., USA* **68**, 1289 (1971).
[40]R. E. Kellogg and W. T. Simpson, *J. Am. Chem. Soc.* **87**, 4230 (1965).
[41]V. Ramamurthy, T. T. Bopp and R. S. H. Liu, *Tetrahedron Letters* 3915 (1972).
[42]V. Ramamurthy and R. S. H. Liu, *Proc. Ind. Acad. Sci.* **88A**, 239 (1979).
[43]V. Ramamurthy, G. Tustin, C. C. Yau and R. S. H. Liu, *Tetrahedron* **31**, 193 (1975).
[44]For preparative procedures see: V. Ramamurthy and R. S. H. Liu, *Org. Photochem. Syn.* **2**, 70 (1976).
[45]A. Kini, Ph.D. Thesis, University of Hawaii, 1979.
[46]V. Ramamurthy, Ph.D. Thesis,University of Hawaii, 1976.
[47]D. Miller, M. Trammell, A. Kini and R. S. H. Liu, *Tetrahedron Letters* **22**, 409 (1981).
[48]V. Ramamurthy and R. S. H. Liu, *J. Org. Chem.* **40**, 3460 (1975).
[49]For tabulated triplet excitation energies, see: S. Murov, *Handbook of Photochemistry*, p. 27. Marcel Dekker (1973).
[50]N. G. Minnaard, Ph.D. Thesis, University of Leiden, 1970.
[51]K. Gollnick, *Adv. Photochem.* **6**, 1 (1968).
[52]Unpublished results of M. Denny, A. E. Asato and R. S. H. Liu.

[53]P. S. Engel and B. M. Monroe, *Adv. Photochem.* **8**, 245 (1971).
[54]A. E. Asato and R. S. H. Liu, *J. Am. Chem. Soc.* **97**, 4128 (1975).
[55]R. S. H. Liu, A. E. Asato and M. Denny, *J. Am. Chem. Soc.* **105**, 4829 (1983).
[56]R. S. H. Liu and Y. Butt, *J. Am. Chem. Soc.* **93**, 1532 (1971).
[57]Y. C. C. Butt, A. K. Singh, B. H. Baretz and R. S. H. Liu, *J. Phys. Chem.* **85**, 2091 (1981).
[58]B. Dellinger and M. Kasha, *Chem. Phys. Lett.* **36**, 410 (1975).
[59]B. Dellinger and M. Kasha, *Chem. Phys. Lett.* **38**, 9 (1976).
[60]J. Saltiel and J. L. Charlton, In *Rearrangements in Ground and Excited States* (Edited by P. de Mayo), Vol. 3, p. 25. Academic Press (1980).
[61]V. Ramamurthy and R. S. H. Liu, *J. Am. Chem. Soc.* **96**, 5625 (1974).
[62]R. Hoffmann, *Tetrahedron* **22**, 521 (1966).
[63]A. Harriman and R. S. H. Liu, *Photochem. Photobiol.* **26**, 29 (1977).
[64]R. Bensasson and E. J. Land, *Nouv. J. Chim.* **2**, 503 (1978).
[65]V. Ramamurthy and R. S. H. Liu, *Tetrahedron Letters* 441 (1973).
[66]G. Büchi and N. C. Yang, *J. Am. Chem. Soc.* **79**, 2318 (1957).
[67] M. Mousseron-Canet, J.-C. Mani and D. Lerner, *Bull. Soc. Chim. Fr.* 3043 (1966).
[68]C. Giannotti, *Can. J. Chem.* **46**, 3025 (1968).
[69]M. Mousseron-Canet, J.-P. Dalle and J.-C. Mani, *Tetrahedron Letters* 6037 (1968).
[70]C. S. Foote and M. Brenner, *Tetrahedron Letters* 6041 (1968).
[71]W. G. Dauben, E. L. McInnis and D. M. Michno, In *Rearrangements in Ground and Excited States* (Edited by P. de Mayo), Vol. 3, pp. 91–129 (1980).
[72]K. J. Crowley, *J. Org. Chem.* **33**, 3679 (1968).
[73]P. Courtot, R. Rumin and J.-Y. Salaün, *Pure Appl. Chem.* **49**, 317 (1977).
[74]V. Ramamurthy and R. S. H. Liu, *J. Org. Chem.* **41**, 1862 (1976).
[75]P. de Mayo, J. B. Stothers and R. W. Yip, *Can. J. Chem.* **39**, 2135 (1961).
[76]A. A. M. Roof, A. van Wageningen, C. Kruk and H. Cerfontain, *Tetrahedron Letters* 367 (1972).
[77]A. van Wageningen and H. Cerfontain, *Tetrahedron Letters* 3679 (1972).
[78]V. Ramamurthy and R. S. H. Liu, *J. Org. Chem.* **39**, 3435 (1974).
[79]G. Frater, *Helv. Chim. Acta* **57**, 2446 (1974).
[80]V. Ramamurthy and R. S. H. Liu, *Tetrahedron Letters* 1393 (1973).
[81]Unpublished results of L. Segundo, V. Ramamurthy and R. S. H. Liu.
[82]K. Tsukida, M. Ito and A. Kodama, *J. Nutr. Sci. Vitaminol.* **24**, 143 (1978).
[83]R. Rowan III, and B. D. Sykes, *J. Am. Chem. Soc.* **97**, 1023 (1975).
[84]A. E. Asato, D. Mead, M. Denny, T. T. Bopp and R. S. H. Liu, *J. Am. Chem. Soc.* **104**, 4979 (1982).
[85]D. Gegiou, K. A. Muszkat and E. Fischer, *J. Am. Chem. Soc.* **90**, 3907 (1968).
[86]P. K. Brown and G. Wald, *J. Biol. Chem.* **222**, 865 (1956).
[87]M. Denny and R. S. H. Liu, *J. Am. Chem. Soc.* **99**, 4865 (1977).
[88]K. Tsukida, A. Kodama and M. Ito, *J. Chromatogr.* **134**, 331 (1977).
[89]M. Denny, M. Chun and R. S. H. Liu, *Photochem. Photobiol.* **33**, 267 (1981).
[90]R. S. H. Liu, A. E. Asato and M. Denny, *J. Am. Chem. Soc.* **99**, 8095 (1977).
[91]K. Tsukida, R. Masahara and M. Ito, *J. Chromatogr.* **192**, 395 (1980).
[92]R. S. H. Liu, M. Denny, M. Grodowski and A. E. Asato, *Nouv. J. Chim.* **3**, 503 (1979).
[93]A. D. Broek, M. Muradin-Szweykowska, J. M. L. Courtin and J. Lugtenburg, *Recl. Trav. Chim. Pays Bas* **102**, 46 (1983).
[94a]W. H. Waddell, D. L. Hopkins, M. Uemura and J. L. West, *J. Am. Chem. Soc.* **100**, 1970 (1978); [b]W. H. Waddell and J. L. West, *J. Phys. Chem.* **84**, 134 (1980).
[95]W. Gartner, H. Hopf, W. E. Hull, D. Oesterhelt, D. Scheutzow and P. Towner, *Tetrahedron Letters* 347 (1980).
[96]H. Matsumoto, A. E. Asato, M. Denny, B. Baretz, Y.-P. Yen, D. Tong and R. S. H. Liu, *Biochemistry* **19**, 4589 (1980).
[97]B. A. Halley and E. C. Nelson, *Int. J. Vit. Nutr. Res.* **49**, 347 (1979).
[98]G. Englert, S. Weber and M. Klaus, *Helv. Chim. Acta* **61**, 2697 (1978).
[99]K. Tsukida, A. Kodama, M. Ito, M. Kawamoto and K. Takahashi, *J. Nutr. Sci. Vitaminol.* **23**, 263 (1977).
[100]A. Singh and R. S. H. Liu, unpublished results.
[101]W. H. Waddell, K. Chihara and U. E. Younes, *Photochem. Photobiol*, **34**, 501 (1981).
[102]A. B. Ellis, R. Schreiner and R. A. Ulkus, *Proc. Nat. Acad. Sci., USA* **78**, 3993 (1981).
[103]R. Schreiner and A. B. Ellis, *J. Am. Chem. Soc.* **104**, 3374 (1982).
[104]R. Fenstemacher, Ph.D. thesis, University of Hawaii, 1982.
[105]V. Ramamurthy, M. Denny and R. S. H. Liu, *Tetrahedron Letters* **22**, 2463 (1981).
[106]R. Fenstemacher, H. Matsumoto and R. S. H. Liu, *Bioorg. Chem.* **11**, 404 (1982).
[107]Unpublished results of R. Fenstemacher and R. S. H. Liu.
[108]M. Ito, A. Kodama and K. Tsukida, *Chem. Pharm. Bull.* **29**, 3385 (1981).
[109]See e.g., W. Sperling, In *Biochemistry and Physiology of Visual Pigments* (Edited by H. Langer), pp. 19–28. Springer, Berlin (1973).
[110]J. P. Dalle and B. Rosenberg, *Photochem. Photobiol.* **12**, 151 (1970).
[111]K. Chihara, T. Takemura, T.Yamaoka, N. Yamamoto, A. Schaffer and R. S. Becker, *Photochem. Photobiol.* **29**, 1001 (1979).
[112]P. K. Das and R. S. Becker,*J. Phys. Chem.* **82**, 2081 (1978).
[113]P. K. Das and R. S. Becker, *J. Phys. Chem.* **82**, 2093 (1978).
[114]T. Takemura, P. K. Das, G. Hug and R. S. Becker, *J. Am. Chem. Soc.* **100**, 2626 (1978).
[115]P.-S. Song, Q. Chae, M. Fujita and H. Baba, *J. Am. Chem. Soc.* **98**, 819 (1976).
[116]T. A. Moore and P. S. Song, *Nature, New Biol.* **243**, 30 (1973).
[117]T. Takemura, G. Hug, P. K. Das and R. S. Becker, *J. Am. Chem. Soc.* **100**, 2631 (1978).
[118]R. L. Christensen and B. E. Kohler, *Photochem. Photobiol.* **19**, 401 (1974).
[119]B. Hudson and B. Kohler, *Ann. Rev. Phys. Chem.* **25**, 437 (1974).
[120]K. Schulten and M. Karplus, *Chem. Phys. Lett.* **14**, 305 (1972).
[121]B. E. Kohler, *Biophys. Struc. Mech.* **3**, 101 (1977).

[122]P. K. Das and R. S. Becker, *Photochem. Photobiol.* **32**, 739 (1980).
[123]R. R. Birge, J. A. Bennett, B. M. Pierce, T. M. Thomas, *J. Am. Chem. Soc.* **100**, 1533 (1978).
[124]R. Birge, *Methods Enzymol.* **88**, 522 (1982).
[125]A. C. Lasaga, R. J. Aerni and M. Karplus, *J. Chem. Phys.* **73**, 5230 (1980).
[126]R. S. Becker, G. Hug, P. K. Das, A. M. Schaffer, T. Takemura, N. Yamamoto and W. Waddell, *J. Phys. Chem.* **80**, 2265 (1976).
[127]C. S. Irving, G. W. Byers and P. A. Leermakers, *Biochemistry* **9**, 858 (1970).
[128]L. Salem, *Science* **191**, 822 (1976).
[129]L. Salem and P. Bruckman, *Nature* **258**, 526 (1975).
[130]V. Bonacic-Koutecky, *J. Am. Chem. Soc.* **100**, 396 (1978).
[131]V. Bonacic-Koutecky, P. Bruckman, P. Hiberty, J. Koutecky, C. Leforestier and L. Salem, *Ang. Chem.* Int. Edn **14**, 575 (1975).
[132]W. D. Closson, S. F. Brady, E. M. Kosower and P. C. Hang, *J. Org. Chem.* **28**, 1161 (1963).
[133]J. A. Barltrop and J. Wills, *Tetrahedron Letters* 4987 (1968).
[134]M. N. R. Ashford, M. T. Macpherson, J. P. Simons, *Topics in Current Chem.* **86**, 76 (1979).
[135]J. N. Loeb, P. K. Brown and G. Wald, *Nature (London)* **184**, 617 (1959).
[136]A. M. Schaffer, W. H. Waddell and R. S. Becker, *J. Am. Chem. Soc.* **96**, 2063 (1974).
[137]B. Honig and M. Karplus, *Nature (London)* **229**, 558 (1971).
[138]R. R. Birge, K. Schulten and M. Karplus, *Chem. Phys. Lett.* **31**, 451 (1975).
[139]I. M. Heilbron, W. E. Jones and A. F. Bacharach, *Vitamins and Hormones* **2**, 155 (1944).
[140]N. A. Milas, *Vitamins and Hormones* **5**, 1 (1947).
[141]W. Oroshnik, in Encyclopedia of Chemical Technology, R. E. Kirk and D. F. Othmer [Eds], *Interscience Encyclopedia*, Vol. 14, p. 791. Interscience, New York (1955).
[142]O. Isler, R. Rüegg, U. Schwieter and J. Wursch, *Vitamins and Hormones* **18**, 295 (1960).
[143]K. Eiter, E. Truscheit and H. Oediger, *Angew. Chem.* **72**, 948 (1960).
[144]For a summary of industrial preparations of vitamin A, cee: F. Kienzle, *Pure Appl. Chem.* **47**, 183 (1976).
[145]B. C. L. Weedon, *Pure Appl. Chem.* **47**, 161 (1976).
[146]H. Pommer, *Angew. Chem. Int. Ed. Engl.* **16**, 423–429 (1977).
[147]G. Cainelli and G. Cardillo, *Acc. Chem. Res.* **14**, 89 (1981).
[148]H. Mayer and O. Isler, In *Carotenoids* (Edited by O. Isler), Chap. 6. Birkhauser-Verlag, Basel (1971).
[149]W. Oroshnik, *J. Am. Chem. Soc.* **78**, 2651 (1956).
[150]D. J. Patel, *Nature* **221**, 825 (1969).
[151]H. Oediger, H.-J. Kabbe, F. Moller and K. Eiter, *Chem. Ber.* **99**, 2012 (1966).
[152]H. Oediger and K. Eiter, *Ger. Pat.* 1,157,606 (1963); *Chem. Abstr.* **60**, 5568h (1964).
[153]C. D. Robeson, J. D. Cawley, L. Weisler, M. H. Stern, C. C. Eddinger and A. J. Chechak, *J. Am. Chem. Soc.* **77**, 4111 (1955).
[154]C. D. Robeson, W. P. Blum, J. M. Dieterle, J. D. Cawley and J. G. Baxter, *J. Am. Chem. Soc.* **77**, 4120 (1955).
[155]J. D. Cawley, *J. Am. Chem. Soc.* **77**, 4125 (1955).
[156]A. H. Lewin, F. I. Carroll and E. G. Moreland, *J. Am. Chem. Soc.* **103**, 6527–6529 (1981).
[157]M. Matsui, S. Okano, K. Yamashita, M. Miyano, S. Kidamura, A. Kobayashi, T. Sato and R. Mikami, *J. Vitaminol. (Kyoto)* **4**, 178 (1958).
[158]H. Pommer and W. Sarnecki, *Ger. Pat.* 1,068,702; *Chem. Abstr.* **55**, 10,812e (1961); *Ger. pat.* 1,059,900; *Chem. Abstr.* 14, 511a (1961).
[159]G. Pattenden, B. C. L. Weedon, C. F. Garbers, D. F. Schneider and J. P. van der Meerwe, *Chem. Commun.* 347 (1965).
[160]G. Pattenden and B. C. L. Weedon, *J. Chem. Soc., C*, 1984 (1968).
[161]G. F. Garbers, D. F. Schneider and J. P. van der Meerwe, *J. Chem. Soc., C*, 1982 (1968).
[162]L. D. Bergelson, L. I. Barsukow and M. M. Shemyakin, *Tetrahedron* **23**, 2709 (1967).
[163]G. Cainelli, G. Cardillo, M. Contento, P. Grasselli and A. Umani Ronchi, *Gazz. Chim. Ital.* **103**, 117 (1973).
[164]R. W. Dugger and C. H. Heathcock, *J. Org. Chem.* **45**, 1181 (1980).
[165]Unpublished results of A. E. Asato.
[166]G. Cainelli, G. Cardillo and M. Orena, *J. Chem. Soc.*, Perkin -I 1597 (1979).
[167]G. Cardillo, M. Contento and S. Sandri, *J. Chem. Soc.*, Perkin-I 1729 (1979).
[168]J. F. Arens and D. A. van Dorp, *Rec. Trav. Chim.* **66**, 759 (1947).
[169]W. Graham, D. A. van Dorp and J. F. Arens, *Rec. Trav. Chim.* **68**, 609 (1949).
[170]T.Mukaiyama and I. Ishida, *Chem. Lett.* 1201 (1975).
[171]S. M. Makin, *Pure Appl. Chem.* **47**, 173 (1976).
[172]B. Trost and J. M. D. Fortunak, *Tetrahedron Letters* 3459 (1981).
[173]G. Stork and G. A. Kraus, *J. Am. Chem. Soc.* **98**, 2351 (1976).
[174]M. Julia and D. Arnould, *Bull. Soc. Chim. Fr.* 746 (1973).
[175]P. S. Manchand, M. Rosenberger, G. Saucy, P. A. Wehrli, H. Wong, L. Chambers, M. P. Ferro and W. Jackson, *Helv. Chim. Acta* **59**, 387 (1976).
[176]P, Chabardes, J. P. Decor and J. Varagnat, *Tetrahedron* **33**, 2799 (1977).
[177]G. L. Olson, H.-C. Cheung, K. D. Morgan, C. Neukom and G. Saucy, *J. Org. Chem.* **41**, 3287 (1976).
[178]A. Fischli, H. Mayer, W. Simon and H.-J. Stoller, *Helv. Chim. Acta* **59**, 397 (1976).
[179]P. S. Manchand, H. S. Wong and J. F. Blount, *J. Org. Chem.* **43**, 4769 (1978).
[180]K. Uneyama and S. Torii, *Chem. Lett.* 39 (1977).
[181]T. Mandai, Y. Iuchi, K. Suzuki, M. Kawada and J. Otera, *Tetrahedron Letters* 4721 (1982).
[182]F. Kienzle, *Helv. Chim. Acta* **56**, 1671 (1973).
[183]F. Derguini, V. Balogh-Nair and K. Nakanishi, *Tetrahedron Letters* 4899 (1979).
[184]R. Ruzziconi and M. Schlosser, *Angew. Chem.* Int. Edn Engl. **1**, 855 (1982).
[185]E. N. Marvell, G. Caple. T. A. Gosink and G. Zimmer, *J. Am. Chem. Soc.* **88**, 619 (1966).
[186]J. Redel, J. Boch and S. Y. Tchen, *C. R. Acad. Sci.* **259**, 2466 (1964).
[187]F. Kienzle and H. Mayer, *Helv. Chim. Acta* **61**, 2609 (1978).
[188]H. Mayer, *Pure Appl. Chem.* **51**, 535 (1979).

[189]R. S. H. Liu and A. E. Asato, *Methods Enzymol.* **88**, 506 (1982).
[190]V. Ramamurthy and R. S. H. Liu, *Tetrahedron* **31**, 201 (1975).
[191]A. Kini, H. Matsumoto and R. S. H. Liu, *J. Am. Chem. Soc.* **101**, 5078 (1979).
[192]C. G. Knudsen, R. A. S. Chandraratna, L. P. Walkenpää, Y. S. Chauhan, S. C. Carey, T. M. Cooper, R. R. Birge and W. H. Okamura, *J. Am. Chem. Soc.* **105**, 1626 (1983).
[193]A. E. Asato, A. Kini, M. Denny and R. S. H. Liu, *J. Am. Chem. Soc.* **105**, 2023 (1983).
[194]E. J. Corey and P. L. Fuchs, *Tetrahedron Letters* 3769 (1972).
[195]C. G. Knudsen, S. C. Carey and W. H. Okamura, *J. Am. Chem. Soc.* **102**, 6355 (1980).
[196]A. Kini, H. Matsumoto and R. S. H. Liu, *J. Bioorg. Chem.* **9**, 406 (1980).
[197]U. Schwieter, G. Saucy, M. Montavan, C. V. Planta, R. Rüegg and O. Isler, *Helv. Chim. Acta* **45**, 517 (1962).
[198]U. Schwieter, C. V. Planta, R. Rüegg and O. Isler, *Helv. Chim. Acta* **45**, 528 (1962).
[199]J.-L. Olive and M. Mousseron-Canet, *Bull. Soc. Chim. Fr.* 3252 (1969).
[200]K. Eiter, H. Oediger and E. Truscheit, *Ger. Pat.* 1,110,633; *Chem. Abstr.* **56**, 3522c (1962).
[201]V. Balogh-Nair and K. Nakanishi, In *New Comprehensive Biochemistry* (Edited by A. Neuberger and L. L. M. van Deenen), IIIrd Edn, pp. 283–334. Elsevier (1982).
[202]L. J. P. van Amsterdam and J. Lugtenburg, *J. Chem. Soc.*, Chem. Commun. 946 (1982).
[203]M. Vecchi, J. Vesely and G. Oesterhelt, *J. Chromatography* **83**, 447 (1973).
[204]R. A. Blatchly and K. Nakanishi, *Methods Enzymol.* **88**, 491 (1982).
[205]G. W. T. Groenendijk, P. A. A. Jansen, S. L. Bonting and F. J. M. Daemen, *Methods Enzymol.* **67**, 203 (1980).
[206]A. M. McCormick, J. L. Napoli and H. F. DeLuca, *Methods Enzymol.* **67**, 220 (1980).
[207]F. G. Pilkiewicz, M. J. Pettei, A. P. Yudd and K. Nakanishi, *Expt. Eye Res.* **24**, 421 (1977).
[208]N. L. Wendler, C. Rosenblum and M. Tishler, *J. Am. Chem. Soc.* **72**, 234 (1950).
[209]See e.g. R. Hubbard, P. K. Brown and D. Bownds, *Methods Enzymol.* **18**, 615 (1971).
[210]See K. Noack, In *Carotenoid Chemistry and Biochemistry* (Edited by G. Britton and T. W. Goodwin), p. 135. Pergamon Press, Oxford (1982).
[211]See e.g. A. Kropf, B. P. Wittenberger, S. P. Goff and A. S. Waggoner, *Expt. Eye Res.* 591 (1973).
[212]R. H. Callender, A. Doukas, R. Crouch and M. Nakanishi, *Biochemistry* **15**, 1621 (1976).
[213] R. Callender and B. Honig, Ann. Rev. Biophys. Bioengng **6**, 33 (1977).
[214]A. Warshel, *Ann. Rev. Biophys. Bioengng* **6**, 273 (1977).
[215]G. Englert, In *Carotenoid Chemistry and Biochemistry* (Edited by G. Britton and T. W. Goodwin), p. 107. Pergamon Press, Oxford (1982).
[216]W. Vetter, G. Englert, N. Rigassi and U. Schwieter, In *Carotenoids* (Edited by O. Isler), pp. 213–225. Birkhauser-Verlag (1971).
[217]G. Englert, *Helv. Chim. Acta* **58**, 2367 (1975).
[218]R. Rowan III, A. Warshel, B. D. Sykes and M. Karplus, *Biochemistry* **13**, 970 (1974).
[219]R. S. H. Liu, J. Zingoni, A. Kini, M. Trammell, D. Chu, A. E. Asato and T. T. Bopp, *J. Org. Chem.*, in press.
[220]T. Hamanaka, T. Mistui, T. Ashida and M. Kakudo, *Acta Cryst.* **B28**, 214 (1972).
[221]R. D. Gilardi, I. L. Karle, J. Karle, *Acta Cryst.* **B28**, 2605 (1972).
[222]G. Drikos, H. Ruppel. H. Dietrich and W. Sperling, *FEBS Lett.* **131**, 23 (1981).
[223]C. J. Simmons, R. S. H. Liu, M. Denny and K. Seff, *Acta Cryst.* **B37**, 2197 (1981).
[224]C. H. Stam and C. H. MacGillavry, *Acta Cryst.* **16**, 62 (1963).
[225]C. H. Stam, *Acta Cryst.* **B28**, 2936 (1972).
[226]W. E. Oberhänsli, H. P. Wagner and O. Isler, *Acta Cryst.* **B30**, 161 (1974).
[227]H. Matsumoto, R. S. H. Liu, C. Simmons and K. Seff, *J. Am. Chem. Soc.* **102**, 4259 (1980).
[228]C. J. Simmons, A. E. Asato, M. Denny and R. S. H. Liu, unpublished results.