4,5-Didehydro-9-demethyl-9-halo-5,6-dihydroretinals and Their 9-Cyclopropyl and 9-Isopropyl Derivatives − Simple Preparation of α-Ionone Derivatives and Pure (*all-E*)-, (9*Z*)- and (11*Z*)-α-Retinals

Yajie Wang[a] and Johan Lugtenburg*[a]

Keywords: (11*Z*)-α-Retinal / α-Ionone derivatives / Cyclopropyl derivatives / Stereoisomeric synthesis

α-Ionone and several of its chemically modified derivatives have been prepared in high yield in full isomeric purity by a Wadsworth–Emmons procedure using imino-phosphonate anion reagents. Starting from α-ionone, 5-(2′,6′,6′-trimethyl-cyclo-2′-hexen-1′-yl)-4-penten-2-yn-1-al could be prepared in a high yielding one-pot procedure. The corresponding (9-Cl-, 9-Br- and 9-I-α-ionylidene)acetaldehyde system could be obtained in one step in a quantitative mixture of (9Z) and (*all-E*) isomers by 1,4-nucleophilic addition reactions. The pure (*all-E*) and (9Z) isomers could be separated by simple column chromatography. The corresponding [(9Z)- and (*all-E*)-9-demethyl-9-fluoro-α-ionylidene]acetaldehydes could also be obtained in pure form by simple column chromatography. These α-ionylidene systems could be easily converted either into the (*all-E*)-4,5-didehydro-9-demethyl-9-halo-5,6-dihydroretinals or the corresponding (9Z) isomers in two steps. Similar mixtures of the corresponding (9Z,11Z)- and (9Z)-nitriles could be obtained by normal chemistry. The (9Z,11Z) isomer is the main component of this mixture, and could be obtained in pure form. Subsequent reduction with DIBAL-H and careful workup gave the pure (9Z,11Z)-9-halo-retinals. These (9Z,11Z) isomers show a similar extreme acid sensitivity to the corresponding 9-halo-β-retinals. α-Retinal and its 9-demethyl, 19,19-ethano and 19,19-dimethyl derivatives have been prepared in the (*all-E*), (9Z), and (11Z) isomeric forms in a similar manner. The corresponding β-retinal and its 9-demethyl derivative in the various isomeric forms are known. In this paper the 19,19-ethano- and 19,19-dimethyl-β-retinals in the (*all-E*), (9Z), and (11Z) isomeric forms are also reported.

Introduction

Rhodopsin is the G-protein-coupled photoreceptor protein in the retina of vertebrates that initiates the visual signal transduction cascade in dim-light vision. It is considered a paradigm for the superfamily of seven transmembrane helix G-protein-coupled receptors (GPCRs),[1] which comprises a physiologically widespread and pharmacologically very significant class of signal mediators.[1−4] GPCRs trigger a wide variety of physiological processes that involve signaling by neurotransmitters, hormones, and neuropeptides and therefore are one of the major pharmaceutical targets for pharmacological intervention in human pathology. Recently, we published a solid-state ^{13}C NMR spectroscopic study of rhodopsin containing a uniformly labeled (11*Z*)-retinylidene chromophore.[5] From the ^{1}H and ^{13}C chemical shift data, we could derive the electric charge at each carbon atom in the conjugated chain and the non-bonding interactions between the protons in the β-ionone part and the aromatic residues in the active site. We have now extended this study to isorhodopsin with a uniformly ^{13}C-labeled (9*Z*)-retinylidene chromophore. A very interesting result is the fact that the non-bonding interactions of the β-ionone part in isorhodopsin with the aromatic residues in the active site are dramatically different from those in rhodopsin.[6] It is clear that the ^{1}H NMR parameters of the chromophore in the active site give otherwise unobtainable structural information in exquisite detail.

It is known that α-isorhodopsin is also a functional receptor protein system.[7−9] The difference between isorhodopsin and α-isorhodopsin is that, in the latter case, a 4−5 endocyclic double bond is present which is not conjugated with the other carbon−carbon double bonds, with the introduction of chirality on the sp^3-carbon atom 6 (Figure 1). There is no chiral discrimination upon regeneration of the α-isorhodopsin system.[10−12] The proper IUPAC name for α-retinal is (*all-E*)-4,5-didehydro-5,6-dihydroretinal. Thus far, the only other isomer available besides (*all-E*)-α-retinal is (9*Z*)-α-retinal. No other *cis* isomer, especially the (11*Z*) isomer, which is essential for rhodopsin studies, is accessible because it is not formed by the photochemical reaction of (*all-E*)-α-retinal. It is clear that a similar solid-state ^{1}H NMR study of α-rhodopsin and α-isorhodopsin with a uni-

[a] Leiden Institute of Chemistry, Leiden University, Gorlaeus Laboratories,
P. O. Box 9502, 2300 RA Leiden, The Netherlands
Fax: (internat.) + 31-71-527-4488
E-mail: Lugtenbu@chem.leidenuniv.nl
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

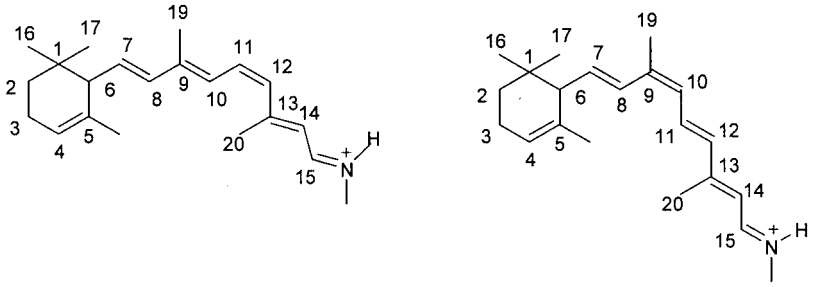


Figure 1. Structures and numbering of the chromophore in α-rhodopsin and α-isorhodopsin

formly ^{13}C-enriched chromophore will give new information about the interaction of the six-membered-ring part of the chromophore with the aromatic residues in the active site.

Of the chemically modified rhodopsins studied so far, 9-demethylrhodopsin shows properties that are very different from the native system. For example, the λ_{max} value shows a drastic blue shift of 460 nm vs. 498 nm,[7,8] and this system does not even form a signaling M_{II} intermediate.[9,13,14] It is very surprising that rhodopsin in a rod in a fully dark-adapted eye gives a nerve signal upon excitation with only one photon that leads to the sense of vision in the brain. In this way rhodopsin is the most sensitive photoreceptor known. The removal of the 9-methyl group to give 9-demethylrhodopsin leads to almost no receptor signal, even under intense light conditions.[5] This means that the 9-methyl group has a pivotal role in the function of the receptor.[15,16]

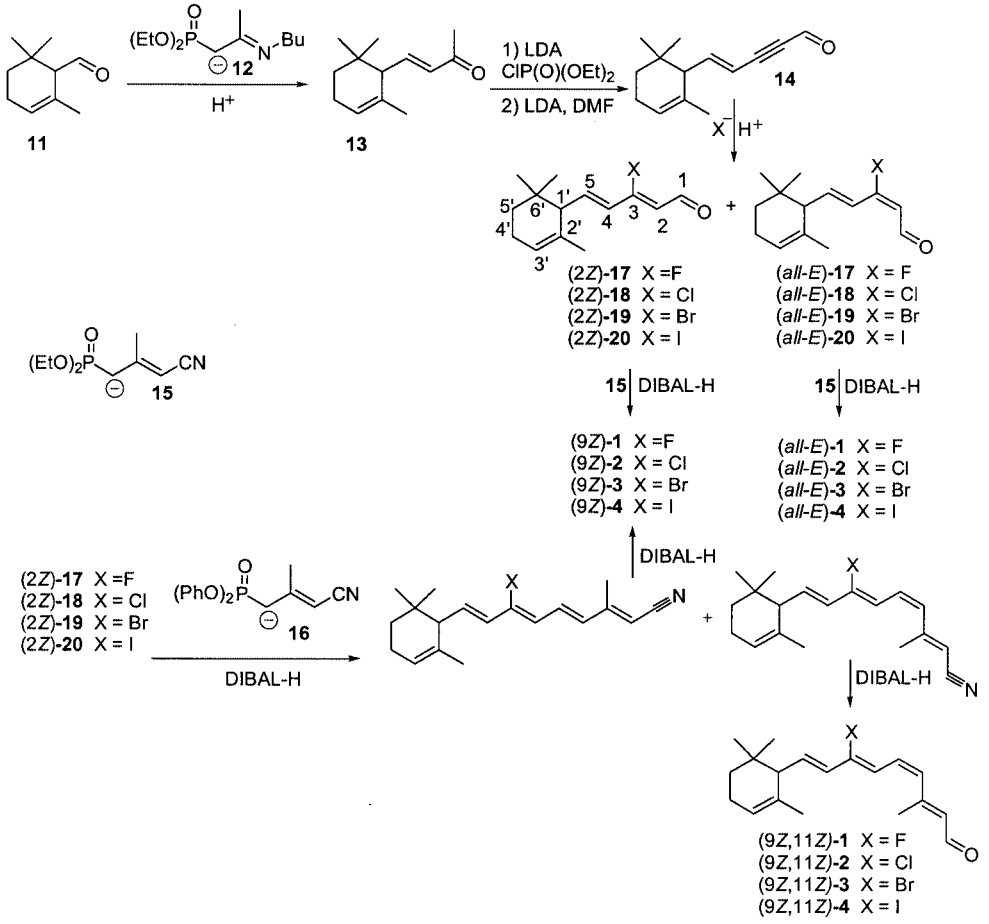
It is essential to establish whether in the case of α-rhodopsin and α-isorhodopsin the 9-methyl group has the same essential role as in rhodopsin and isorhodopsin. We think that by studying the receptor action of the as-yet-unknown 9-demethyl-9-fluoro-, 9-chloro-9-demethyl-, 9-bromo-9-demethyl-, and 9-demethyl-9-iodo-α-rhodopsin, and the related α-isorhodopsin derivatives, we will obtain direct information about the role of size and electronegativity of the substituent at the 9-position. Additional advantages of the halogens are the fact that ^{19}F has a spin quantum number of 1/2 with a high nuclear magnetic moment, which allows ^{19}F NMR studies of 9-demethyl-9-fluororhodopsin and its photochemical intermediates. The iodine atom has a high atomic weight, which allows efficient X-ray studies of the 9-demethyl-9-iodorhodopsin and its photo products. Besides the 9-halogen-α-retinal system, we also decided to prepare the (11*Z*)- and (9*Z*)-19,19-ethano- and -19,19-dimethyl-α-retinals, in which a 9-cyclopropyl and a 9-isopropyl group are present which are less than spherically symmetrical and are electron donors. The isopropyl group has been called a "Janus group", after the Roman god Janus, who looked both forward to the future and backwards to the past, as the freely rotating isopropyl group shows either a *tert*-butyl side or an ethyl side. The cyclopropyl group, which is sterically much smaller than the isopropyl group, can also be considered as a Janus group.[17,18]

In this paper we describe simple, efficient syntheses of the α-retinals directly as the (*all-E*) and (9*Z*) isomeric forms. The (11*Z*) isomer could also easily be prepared, leading to mixtures of the (11*Z*) and (*all-E*) isomers in which the (11*Z*) form is the predominant isomer and can be simply separated in pure form. The biochemical studies with the chemically modified α-rhodopsins and α-isorhodopsin will be published in a subsequent paper.

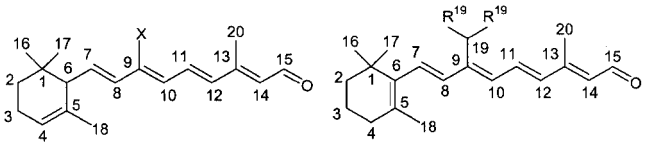
Results and Discussion

For the preparation of the 4,5-didehydro-9-demethyl-9-halo-5,6-dihydroretinals (9-demethyl-9-halo-α-retinals) we expected that, based on retrosynthetic analysis, a 1,4-nucleophilic addition to a conjugated ynal would be appropriate. Thus, 5-(2′,6′,6′-trimethylcyclohex-2′-en-1′-yl)pent-4-en-2-ynal (**14**; Scheme 1) is the central system for the synthesis of these retinals. It should be accessible from α-ionone (**13**). This α-ionone is commercially available; however, in view of later possible site-directed ^{13}C labeling, we preferred to start our synthetic scheme with α-cyclocitral (**11**). The efficient preparation of α-cyclocitral, which allows access to any site-directed ^{13}C-enriched form, has been described by our group before.[19] The reaction of α-cyclocitral with the anion of diethyl [2-(butylimino)propyl]phosphonate (**12**) leads to the formation of the α-ionone *n*-butylimine system which, upon aqueous acid treatment, gives pure (*all-E*)-α-ionone (**13**) in high yield. We feel that this is the best general method to prepare many chemically modified α-ionone systems; for the α- and β-ionone systems prepared here we always obtained only the systems with the (*E*)-2−3 double bond. The corresponding base-catalyzed aldol condensation of **11** with acetone gave only pure β-ionone and no α-ionone. α-Ionone (**13**) was converted into **14** in a one-pot strategy pioneered in the previous paper.[20] This process involves removal of a proton from the methyl group, treatment with diethyl chlorophosphate to form the enol phosphate ester, base-induced removal of diethyl phosphate and subsequent treatment of the acetylene anion with dimethylformamide to give the ynal 5-(2′,6′,6′-trimethylcyclohex-2′-en-1′-yl)pent-4-en-2-ynal (**14**). Treatment of **14** with LiCl, LiBr or LiI in acetic acid at 70 °C gave, in a clean conversion, mixtures of (2*Z*)-**18** and (*all-E*)-**18**, (2*Z*)-**19** and

(*all-E*)-**19** and (2*Z*)-**20** and (*all-E*)-**20**, respectively. Treatment of **14** with tetrabutylammonium dihydrogentrifluoride in 1,2-dichloroethane at 83 °C gave a mixture of the required fluorides (2*Z*)-**17** and (*all-E*)-**17** along with (2*Z*)-**18** and (*all-E*)-**18** and unchanged starting material.[20] Careful silica-gel column chromatography gave (2*Z*)-**17**, (2*Z*)-**18**, (2*Z*)-**19**, (2*Z*)-**20**, (*all-E*)-**17**, (*all-E*)-**18**, (*all-E*)-**19** and (*all-E*)-**20** as pure isomers in a ratio of 2:1. Comparison of the α-systems with the corresponding β-systems indicates that the separation parameters of the (2*Z*) and (*all-E*) pair in the α-systems differ much less than in the β-systems. This shows that lack of conjugation of the 4−5 double bond leads to a more similar chromatographic behavior than that of the fully conjugated β-case. Treatment of either the (2*Z*) or the (*all-E*) forms with the anion of diethyl (3-cyano-2-methylprop-2-enyl)phosphonate (**15**) at +20 °C gave the corresponding retinonitrile as the (9*Z*) or (*all-E*) isomer, respectively. The pure (2*Z*) systems (2*Z*)-**17**, (2*Z*)-**18**, (2*Z*)-**19** and (2*Z*)-**20** and their corresponding pure (*all-E*) isomers could therefore be simply converted into the pure (9*Z*)- or (*all-E*)-retinal systems (9*Z*)-**1**, (9*Z*)-**2**, (9*Z*)-**3**, (9*Z*)-**4** and (*all-E*)-**1**, (*all-E*)-**2**, (*all-E*)-**3** and (*all-E*)-**4** in high yield by DIBAL-H reduction. Reaction of the pure (2*Z*) forms **17**, **18**, **19** and **20** with the anion of diphenyl (3-cyano-2-methylprop-2-enyl)phosphonate (**16**) gave a mixture of (9*Z*)- and (9*Z*,11*Z*)-retinonitriles in the isomeric ratios 3:2, 7:3, 9:1 and 7:3, respectively, which were separated by column chromatography on silica gel. Subsequent DIBAL-H reduction of these nitriles and Al_2O_3 workup gave the corresponding (9*Z*,11*Z*)-**1**, (9*Z*,11*Z*)-**2**, (9*Z*,11*Z*)-**3** and (9*Z*,11*Z*)-**4**, which have the (11*Z*) structure. Normal workup with acidified silica gel results in complete conversion into the (9*Z*) forms. This acid lability of the (9*Z*,11*Z*)-9-demethyl-9-halo-α-retinals is similar to that of the β-systems described by us before.[20] For the preparation of the (*all-E*), (9*Z*), and (11*Z*) isomers of 9-demethyl-α-retinal (**5**), α-retinal (**6**), 19,19-ethano-α-retinal (**7**) and 19,19-dimethyl-α-retinal (**8** in Figure 2; X = H, CH_3, cyclopropyl, isopropyl, respectively), the starting material was α-cyclocitral (**11**; Scheme 2). Reaction of **11** with the anion of diethyl (cyanomethyl)phosphonate (**21**) gave the corresponding conjugated nitrile, which was subsequently converted into the conjugated aldehyde **23** by DIBAL-H reduction. The α-ionone systems **25** and **26** were prepared in a similar manner to the formation of α-ionone **13** from **11**. Namely, cyclopropyl methyl ketone and isopropyl methyl ketone were first converted into the corresponding ketimines, which were subsequently converted into the corresponding phosphonated anions **22b** and **22c**, respectively. Aqueous acid workup after the Wadsworth−Emmons coupling of **11** with **22b** and **22c** gave pure **25** and **26**, respectively, in high yield. These reactions once more show that this conversion has a very wide scope



Scheme 1. Preparation of 9-demethyl-9-halo-α-retinals in the pure (*all-E*), (9*Z*), and (9*Z*,11*Z*) isomeric forms



	X	R^{19} R^{19}
(9*Z*)-**1**	F	
(9*Z*)-**2**	Cl	
(9*Z*)-**3**	Br	
(9*Z*)-**4**	I	
(*all-E*)-**5**	H	
(*all-E*)-**6**	CH_3	
(*all-E*)-**7**	cyclopropyl	
(*all-E*)-**8**	isopropyl	
(*all-E*)-**9**		ethano
(*all-E*)-**10**		dimethyl

Figure 2. Structures and numbering of (9*Z*)-9-demethyl-9-fluoro-α-retinal [(9*Z*)-**1**], (9*Z*)-9-chloro-9-demethyl-α-retinal [(9*Z*)-**2**], (9*Z*)-9-bromo-9-demethyl-α-retinal [(9*Z*)-**3**], (9*Z*)-9-demethyl-9-iodo-α-retinal [(9*Z*)-**4**], (*all-E*)-9-demethyl-α-retinal [(*all-E*)-**5**], (*all-E*)-α-retinal [(*all-E*)-**6**], (*all-E*)-19,19-ethano-α-retinal [(*all-E*)-**7**], (*all-E*)-19,19-dimethyl-α-retinal [(*all-E*)-**8**], (*all-E*)-19,19-ethanoretinal [(*all-E*)-**9**] and (*all-E*)-19,19-dimethylretinal [(*all-E*)-**10**]

to prepare any α-ionone system starting from α-cyclocitral. Extension of the conjugated chain of the α-ionone and α-ionone derivatives **23**, **13**, **25** and **26** with the anion **21**, and subsequent DIBAL-H reduction, give mixtures of the corresponding [(*all-E*)- and (9*Z*)-α-ionylidene]acetaldehydes, which could easily be separated into pure (*all-E*)-**27**, (*all-E*)-**28**, (*all-E*)-**29**, (*all-E*)-**30** and (9*Z*)-**27**, (9*Z*)-**28**, (9*Z*)-**29**, (9*Z*)-**30**, respectively, in the isomeric ratio 2:1. These systems were converted into the pure (*all-E*)-, (9*Z*)-, and (11*Z*)-retinal systems by the strategy discussed for 9-demethyl-9-halo derivatives earlier in this paper. The (*all-E*) forms of the 9-demethyl-9-halo-α- and -β-retinals show an extreme acid sensitivity, which is unprecedented in the retinal field. Also, the (11*Z*)-9-cyclopropyl- and -9-isopropyl-α-retinals show a higher acid sensitivity than retinals with a smaller alkyl group. For the preparation of the corresponding new 19,19-ethano- and 19,19-dimethylretinal systems (*all-E*)-**9**, (9*Z*)-**9**, (11*Z*)-**9** and (*all-E*)-**10**, (9*Z*)-**10**, (11*Z*)-**10**, we carried out the same chemical steps as depicted in Scheme 2, starting in this case with β-cyclocitral (**11b**) instead of α-cyclocitral (**11**). Once more also the (11*Z*) derivatives (11*Z*)-**9** and (11*Z*)-**10** show a similar acid sensitivity to the corresponding (11*Z*)-α derivatives.

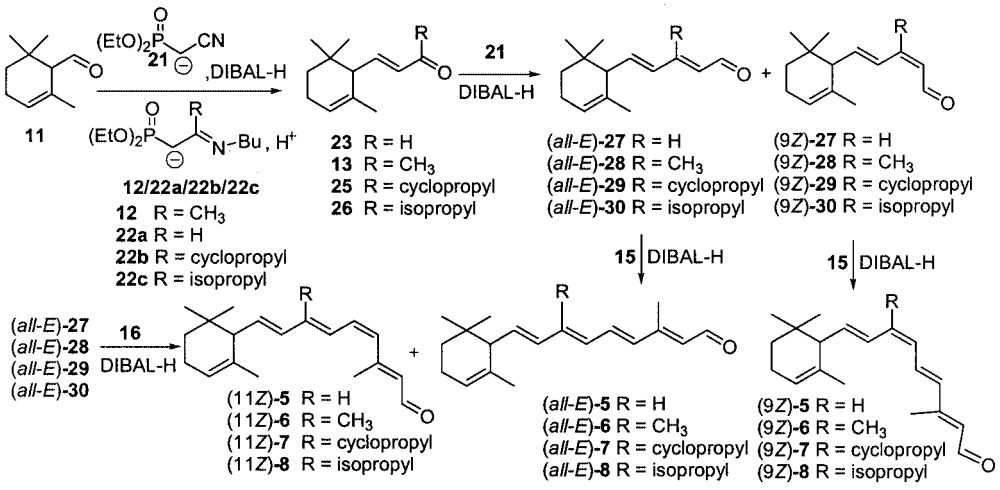
Spectroscopic Characterization

Mass Spectrometry

All retinals described in this paper are new, except (*all-E*)-**6** and (9*Z*)-**6**. In order to confirm the molecular constitution of those systems, double-focus mass spectra were obtained. The observed exact masses were the same (within experimental error) as the calculated values. This fully confirms their molecular formulae (Table 1). The structures of **2**, **3** and **4** found additional support in the following facts: In the mass spectrum of **2**, the peaks at *m*/*z* = 306 and 304 show an intensity ratio of 3:1, which is an indication of the presence of a chloro atom. In the fragmentation pattern a peak at *m*/*z* = 269 is also present, indicating that the system must contain one chloro atom. In the case of **3**, two peaks at *m*/*z* = 348 and 350 have a 1:1 intensity ratio, showing that the system has a bromo atom. In the fragmentation pattern a prominent peak at *m*/*z* = 269 is present indicating the presence of only one bromo atom. The mass spectrum of **4** shows much more fragmentation than those of **1**, **2** and **3**. In this spectrum a peak at *m*/*z* = 269 corresponds to the loss of a 127 mass unit corresponding to one iodo atom.

NMR Spectroscopy

In the ^{1}H NMR spectra, the location of the substituent at the 9-position could be established definitely. In the case of the three isomers of **5**, **6**, **7**, **8**, **9** and **10** the identity of the substituent was secured. The precise isomeric structure of each system was determined from ^{1}H NMR chemical shift values, coupling constants and NOESY spectra. This



Scheme 2. Preparation of 4,5-didehydro-9-demethyl-5,6-dihydroretinal (**5**), 4,5-didehydro-5,6-dihydro-9-methylretinal (**6**), 4,5-didehydro-19,19-ethano-5,6-dihydroretinal (**7**) and 4,5-didehydro-5,6-dihydro-19,19-dimethylretinal (**8**) in (*all-E*), (9*Z*), and (11*Z*) isomeric forms; for the preparation of **9** and **10** in the (*all-E*), (9*Z*), and (11*Z*) isomeric forms the corresponding β-derivatives are used

Table 1. Elemental composition of (*all-E*)-α- and -β-retinal derivatives **1**−**10**; experimental and calculated exact masses

Retinal Observed	Empirical formula Calculated	Exact mass [u] Observed	Exact mass [u] Calculated	Retinal	Empirical formula	Exact mass [u]	
(9*Z*)-**1**	$^{12}C_{19}{}^{1}H_{25}{}^{19}F^{16}O$	288.1888	288.1889	(*all-E*)-**6**	$^{12}C_{20}{}^{1}H_{28}{}^{16}O$	284.2143	284.2142
(9*Z*)-**2**	$^{12}C_{19}{}^{1}H_{25}{}^{35}Cl^{16}O$	304.1585	304.1594	(*all-E*)-**7**	$^{12}C_{22}{}^{1}H_{30}{}^{16}O$	310.2292	310.2297
(9*Z*)-**3**	$^{12}C_{19}{}^{1}H_{25}{}^{79}Br^{16}O$	348.1082	348.1089	(*all-E*)-**8**	$^{12}C_{22}{}^{1}H_{32}{}^{16}O$	312.2452	312.2453
(9*Z*)-**4**	$^{12}C_{19}{}^{1}H_{25}{}^{127}I^{16}O$	396.0940	396.0950	(*all-E*)-**9**	$^{12}C_{22}{}^{1}H_{30}{}^{16}O$	310.2302	310.2297
(*all-E*)-**5**	$^{12}C_{19}{}^{1}H_{25}{}^{16}O$	270.2091	270.2093	(*all-E*)-**10**	$^{12}C_{22}{}^{1}H_{32}{}^{16}O$	312.2448	312.2453

was supported by comparing the various isomers in the α-retinal series **1**−**6** with the corresponding isomers in the β-systems.[17] Similarly, the ^{1}H NMR characteristics of the isomers of **7** and **8** closely resemble those of **9** and **10**. The analytical data of (*all-E*)-**6** and (9*Z*)-**6** are in complete agreement with those published in the literature.[7]

All the ^{1}H NMR, ^{13}C NMR and UV/Vis spectroscopic data are given in the Exp. Sect. in the description of each individual retinal isomer.

Conclusion

This study shows that new α- and β-ionone systems are easily accessible in pure form and in high yield starting from either α- or β-cyclocitral by Wadsworth−Emmons couplings of imino-phosphonate anion reagents. In the present study, we have limited ourselves to α- and β-ionones with chemical modification at the carbonyl substituent, although we think that with simple adjustments of the synthetic schemes many more α- and β-ionone systems will be easily prepared. In the case of α-ionone, this molecule could be converted into 5-(2′,6′,6′-trimethylcyclohex-2′-en-1′-yl)pent-4-en-2-ynal in a high-yield one-pot procedure just as in the case of the β-ionone.[20] This 2-yn-1-al system undergoes an efficient 1,4-nucleophilic addition of halides to form a (halo-α-ionylidene)acetaldehyde system. Again, we think that this method has a wide scope and that many more nucleophiles can be used to prepare new chemically modified (α-ionylidene)acetaldehydes. An analogous method to prepare 9-*tert*-butyl-9-demethyl- and 9-demethyl-9-(trimethylsilyl)retinal and the corresponding 13-substituted retinals has been published.[21] These (ionylidene)acetaldehyde systems can be converted such that the newly formed bond is a (*E*) bond without changing the integrity of the other double bonds in the case of diethyl phosphate as leaving group. With diphenyl phosphate as leaving group a mixture of two isomers is formed,in which the main isomer has a (*Z*) structure as the newly formed bond.

The strategy of this paper and the previous one has been focused on the preparation of α- and β-retinal systems chemically modified at the 9-position. The syntheses have been effected with carbon-containing reagents, which are available with 99% ^{13}C enrichment on any carbon position or combinations of carbon positions. This means that all new retinals described in this paper can be simply obtained with high ^{13}C enrichment at any position and any combination of positions up to the uniformly enriched form.

We realize that, with appropriate adjustment, (*all-E*)-, (9*Z*)-, and (11*Z*)-α- and -β-retinals, and their ^{13}C isotopomers, will be available with chemical modifications at positions 11 and 13 in a similar way.

Experimental Section

General: All light-sensitive reactions were carried out in dim red light ($\lambda > 620$ nm) or in the dark. All experiments were carried out under dry nitrogen or argon. The commercially available starting materials lithium chloride, lithium bromide, lithium iodide, diethyl chlorophosphate, cyclopropyl methyl ketone and isopropyl methyl ketone were purchased from Sigma Aldrich. Tetrabutylammonium dihydrogentrifluoride was purchased from Acros. All reagents were used without further purification, unless stated otherwise. In all cases, chemically pure or higher quality chemicals were used. Sodium hydride refers to a 60% suspension in mineral oil. Petroleum ether refers to the distillate with a boiling range of 40−60 °C. Dry solvents and reagents were stored under dry argon. Dry THF was freshly distilled from sodium. Dry petroleum ether and dry diethyl ether were prepared by distilling from phosphorus pentoxide and were stored over sodium wire. Dry diisopropylamine, *n*-butylamine, *N*,*N*-dimethylformamide and dichloromethane were freshly prepared by distilling from freshly ground calcium hydride and stored over molecular sieves (4 Å). Silica-gel column chromatography was performed using Merck silica gel 60 (0.040−0.063 mm, 230−400 mesh). ^{1}H NMR spectra were record with a Bruker DPX-300 spectrometer operating at 300.13 MHz and were internally referenced to the proton of deuterated methanol ($\delta = 3.30$ ppm) or tetramethylsilane (TMS, $\delta = 0.00$ ppm). Solution ^{13}C NMR spectra were recorded using a Bruker DPX-300 spectrometer operating at 75.5 MHz and were internally referenced to the carbon signal of deuterated methanol ($\delta = 49.00$ ppm) or deuterated chloroform ($\delta = 77.0$ ppm). ^{19}F NMR spectra were recorded using a Bruker DMX-300 spectrometer operating at 282.4 MHz and were externally referenced to trifluoroacetic acid ($\delta = 0$ ppm). UV/Vis spectra were recorded with a PE-Lambda 18 or 300 spectrophotometer. Electron impact (EI) mass spectrometry was carried out using a JEOL JMS SX/SX 102A four-sector mass spectrometer coupled to a JEOL MS-MP9021D/UPD system program. The samples were introduced with a direct insertion probe into the ion source. During the high resolution EIMS measurement a resolving power of 10000 eV (10% valley definition) was used.

α-Ionone (13): The *n*-butylketimine of acetone was prepared by azeotropic distillation after refluxing acetone (5.8 g, 0.1 mol) with *n*-butylamide (7.3 g, 0.1 mol) in dry toluene (10 mL). LDA was prepared at −60 °C from a solution of diisopropylamine (1.94 g,

19.2 mmol) in dry THF (20 mL) and 11.1 mL of BuLi (17.7 mmol of a 1.6 M solution of BuLi in hexane). This solution was cooled to −80 °C and the *n*-butylketimine of acetone (0.83 g, 7.38 mmol) in 10 mL of THF was added dropwise. After stirring at −80 °C for 0.5 h, diethyl chlorophosphate (1.31 g, 7.38 mmol) in THF (10 mL) was added slowly to form the anion of **12**. A solution of **11** (1.12 g, 7.38 mmol) in THF (5 mL) was added slowly to the solution of the phosphonate anion keeping the temperature at −80 °C. Stirring was continued at room temperature for 2 h. Water (10 mL) was then added, followed by sufficient formic acid to bring the pH of the solution to 5. Workup was accomplished by adding water and extracting the reaction mixture three times with diethyl ether. The combined organic layers were washed with saturated $NaHCO_3$ and brine, and dried with K_2CO_3. Evaporation of the organic solvents in vacuo yielded a light-yellow liquid. The product was purified on silica (Et_2O/PE, 1:4, v/v), affording 1.36 g of **13** (96%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (s, 3 H, 6′-CH_3), 0.93 (s, 3 H, 6′-CH_3), 1.22 (m, 1 H, 5′-H[a]), 1.47 (m, 1 H, 5′-H[b]), 1.57 (s, 3 H, 2′-CH_3), 2.05 (m, 2 H, 4′-H), 2.25 (s, 3 H, 1-CH_3), 2.29 (d, $^3J_{1'\text{-H},3\text{-H}}$ = 9.60 Hz, 1 H, 1′-H), 5.45 (m, 1 H, 3′-H), 6.05 (d, $^3J_{2\text{-H},3\text{-H}}$ = 15.6 Hz, 1 H, 2-H), 6.62 (dd, $^3J_{3\text{-H},2\text{-H}}$ = 15.6, $^3J_{3\text{-H},1'\text{-H}}$ = 9.60 Hz, 1 H, 3-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, $CDCl_3$): δ = 22.5 (2′-CH_3), 22.7 (C-4′), 26.5 (6′-CH_3), 26.7 (1-CH_3), 27.5 (6′-CH_3), 30.9 (C-5′), 32.2 (C-6′), 54.0 (C-1′), 122.4 (C-3′), 131.6 (C-2′), 132.1 (C-2), 148.6 (C-3), 197.9 (C-1) ppm.

5-(2′,6′,6′-Trimethylcyclohex-2′-en-1′-yl)pent-4-en-2-ynal (14): α-Ionone (**13**; 5.36 g, 27.9 mmol) in dry THF (10 mL) was added dropwise at −78 °C to a solution of LDA prepared from diisopropylamine (3.1 g, 30.7 mmol) and *n*-butyllithium (17.6 mL, 1.6 M in hexane) in THF (100 mL). After stirring whilst maintaining the temperature for 1 h, freshly distilled diethyl chlorophosphate (4.0 mL, 28 mmol) was added and the resulting mixture was allowed to warm to room temperature in 2 h. In a separate flask, additional LDA was prepared from diisopropylamine (6.2 g, 61.4 mmol) and *n*-butyllithium (38.4 mL, 1.6 M in hexane) in THF (200 mL) at −78 °C. This batch of LDA was added to the main reaction mixture with a cannula at −78 °C. After stirring for 1 h, dry DMF (2.3 mL, 30.0 mmol) was added in one portion and the resulting mixture was allowed to warm to room temperature gradually. The reaction mixture was poured into a cold (−5 °C) vigorously stirred biphasic solution prepared from a 10% aqueous solution of KH_2PO_4 (85 mL, 59.8 mmol) and diethyl ether (100 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 100 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, diethyl ether/petroleum ether, 2:98, v/v) to give 3.52 g (95%) of the desired product. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (s, 3 H, 6′-CH_3), 0.92 (s, 3 H, 6′-CH_3), 1.21 (m, 1 H, 5′-H), 1.41 (m, 1 H, 5′-H), 1.58 (s, 3 H, 2′-CH_3), 2.03 (m, 2 H, 4′-H), 2.28 (d, $^3J_{1'\text{-H},5\text{-H}}$ = 9.71 Hz, 1 H, 1′-H), 5.50 (m, 1 H, 3′-H), 5.65 (d, $^3J_{4\text{-H},5\text{-H}}$ = 15.8 Hz, 1 H, 4-H), 6.45 (dd, $^3J_{5\text{-H},4\text{-H}}$ = 15.8, $^3J_{5\text{-H},1'\text{-H}}$ = 9.71 Hz, 1 H, 5-H), 9.29 (s, 1 H, 1-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, $CDCl_3$): δ = 22.6 (2′-CH_3), 22.8 (C-4′), 26.4 (6′-CH_3), 27.3 (6′-CH_3), 31.0 (C-5′), 32.5 (C-6′), 54.8 (C-1′), 87.8 (C-3), 94.4 (C-2), 122.4 (C-3′), 131.4 (C-2′), 134.2 (C-4), 154.8 (C-5), 176.4 (C-1) ppm.

3-Fluoro5-(2′,6′,6′-trimethylcyclohex-2′-en-1′-yl)penta-2,4-dien-1-al [(*all-E*)-17 + (2*Z*)-17]: A solution of **14** (300 mg, 1.5 mmol) in 1,2-dichloroethane (10 mL) was added to tetrabutylammonium dihydrogenfluoride (900 mg, 3.0 mmol, 50−55 wt.-% solution in 1,2-dichloroethane), contained in a 50-mL flask. The homogeneous reaction mixture was refluxed at 83 °C under argon for 6 h. After cooling to room temperature, the 1,2-dichloroethane was evaporated in vacuo. The residue was purified by chromatography on silica gel (30% hexane in dichloromethane, v/v). The first fraction is the unchanged starting material (**14**), the second is (*all-E*)-**17**, the third fraction (2*Z*)-**18**, and the fourth fraction pure (2*Z*)-**17**. The total amount of (2*Z*)-**17** and (*all-E*)-**17** (in the isomeric ratio 2:1) was 261 mg (80%).

(2*Z*)-17: ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 0.87 (s, 3 H, 6′-CH_3), 0.94 (s, 3 H, 6′-CH_3), 1.22 (m, 1 H, 5′-H), 1.42 (m, 1 H, 5′-H), 1.59 (s, 3 H, 2′-CH_3), 2.06 (m, 2 H, 4′-H), 2.31 (d, $^3J_{1'\text{-H},5\text{-H}}$ = 9.64 Hz, 1 H, 1′-H), 5.41 (dd, $^3J_{2\text{-H},1\text{-H}}$ = 7.92, $^3J_{2\text{-H},3\text{-F}}$ = 33.0 Hz, 1 H, 2-H), 5.52 (m, 1 H, 3′-H), 5.97 (dd, $^3J_{4\text{-H},5\text{-H}}$ = 15.5, $^3J_{4\text{-H},3\text{-F}}$ = 26.1 Hz, 1 H, 4-H), 6.49 (dd, $^3J_{5\text{-H},4\text{-H}}$ = 15.5, $^3J_{5\text{-H},1'\text{-H}}$ = 9.68 Hz, 1 H, 5-H), 10.1 (d, $^3J_{1\text{-H},2\text{-H}}$ = 8.00 Hz, 1 H, 1-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, $CDCl_3$): δ = 23.2 (2′-CH_3), 23.1 (C-4′), 28.7 (6′-CH_3), 28.9 (6′-CH_3), 31.2 (C-5′), 33.1 (C-6′), 53.1 (C-1′), 109.4 (d, $^2J_{C\text{-}2,3\text{-}F}$ = 6.4 Hz, C-2), 121.6 (d, $^2J_{C\text{-}4,3\text{-}F}$ = 18.6 Hz, C-4), 122.8 (C-3′), 131.7 (C-2′), 144.2 (dd, $^3J_{C\text{-}5,3\text{-}F}$ = 4.53 Hz, C-5), 169.5 (d, $^1J_{C\text{-}3,3\text{-}F}$ = 276.1 Hz, C-3), 188.7 (d, $^3J_{C\text{-}1,3\text{-}F}$ = 10.9 Hz, C-1) ppm. ^{19}F NMR (282.4 MHz): δ = −30.81 (dd, $^3J_{3\text{-F},4\text{-H}}$ = 26.0, $^3J_{3\text{-F},2\text{-H}}$ = 33.0 Hz, 3-F) ppm. UV/Vis: λ_{max} = 272 nm (*n*-hexane).

(*all-E*)-17: ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 0.87 (s, 3 H, 6′-CH_3), 0.93 (s, 3 H, 6′-CH_3), 1.25 (m, 1 H, 5′-H), 1.58 (m, 1 H, 5′-H), 1.60 (s, 3 H, 2′-CH_3), 2.06 (m, 2 H, 4′-H), 2.35 (d, $^3J_{1'\text{-H},5\text{-H}}$ = 9.71 Hz, 1 H, 1′-H), 5.53 (m, 1 H, 3′-H), 5.71 (dd, $^3J_{2\text{-H},1\text{-H}}$ = 7.4, $^3J_{2\text{-H},3\text{-F}}$ = 18.2 Hz, 1 H, 2-H), 6.48 (dd, $^3J_{5\text{-H},4\text{-H}}$ = 15.4, $^3J_{5\text{-H},1'\text{-H}}$ = 9.6 Hz, 1 H, 5-H), 6.66 (dd, $^3J_{4\text{-H},5\text{-H}}$ = 15.4, $^3J_{4\text{-H},3\text{-F}}$ = 27.8 Hz, 1 H, 4-H), 9.96 (dd, $^3J_{1\text{-H},2\text{-H}}$ = 7.32, $^4J_{1\text{-H},3\text{-F}}$ = 3.2 Hz, 1 H, 1-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, $CDCl_3$): δ = 23.3 (2′-CH_3), 23.5 (C-4′), 27.7 (6′-CH_3), 27.8 (6′-CH_3), 31.2 (C-5′), 34.0 (C-6′), 54.8 (C-1′), 109.1 (d, $^2J_{C\text{-}2,3\text{-}F}$ = 20.9 Hz, C-2), 117.9 (d, $^2J_{C\text{-}4,3\text{-}F}$ = 19.4 Hz, C-4), 122.7 (C-3′), 131.7 (C-2′), 145.1 (d, $^3J_{C\text{-}5,3\text{-}F}$ = 5.74 Hz, C-5), 171.7 (d, $^1J_{C\text{-}3,3\text{-}F}$ = 273.7 Hz, C-3), 189.1 (d, $^3J_{C\text{-}1,3\text{-}F}$ = 20.5 Hz, C-1) ppm. ^{19}F NMR (282.4 MHz): δ = −30.73 (ddd, $^3J_{3\text{-F},4\text{-H}}$ = 27.6, $^3J_{3\text{-F},2\text{-H}}$ = 18.2, $^4J_{3\text{-F},1\text{-H}}$ = 3.32 Hz, 3-F) ppm. UV/Vis: λ_{max} = 273 nm (*n*-hexane).

(9*Z*)-9-Demethyl-9-fluoro-α-retinal [(9*Z*)-1]: A solution of diethyl (3-cyano-2-methylprop-2-enyl)phosphonate (**15**; 126 mg, 0.58 mmol) in THF (5 mL) was added at 0 °C to a solution of NaH (23.2 mg, 0.57 mmol) in dry THF (5 mL). The reaction mixture was allowed to gradually warm to +20 °C and was maintained at that temperature for about 1 h. A solution of (2*Z*)-**17** (130 mg, 0.59 mmol) in THF (5 mL) was added to the anion solution with a syringe. The resulting solution was stirred for additional 3 h. Subsequently, the reaction was quenched with saturated aqueous NH_4Cl solution (20 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 20 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, filtered and the solvents evaporated. The crude product was purified by flash chromatography (diethyl ether/petroleum ether, 20:80, v/v) to give 160 mg of (9*Z*)-9-fluororetinonitrile in quantitative yield. A solution of (9*Z*)-9-fluororetinonitrile (160 mg, 0.56 mmol) in dry petroleum ether (15 mL) was cooled to −80 °C and DIBAL-H (1.4 mL, 1.0 M in hexane) was added. The resulting mixture was allowed to warm to −40 °C over 1 h. Subsequently, a homogeneous mixture of 2.5 g of wet silica gel (water/silica, 1:9, wt/wt) was added and stirring was continued at 0 °C for 1 h. After drying the mixture by adding Na_2SO_4, all solids were filtered off and washed thor-

oughly with diethyl ether. The organic solvent was evaporated and the resulting residue was purified by column chromatography. This procedure gave 160 mg of the (9*Z*) isomer in quantitative yield. ^{1}H NMR (300.1 MHz, CD_3OD): δ = 0.85 (s, 3 H, 16-H), 0.93 (s, 3 H, 16-H), 1.21 (m, 1 H, 2-H), 1.46 (m, 1 H, 2-H), 1.58 (s, 3 H, 18-H), 2.04 (m, 2 H, 3-H), 2.28 (d, $^3J_{6\text{-H},7\text{-H}}$ = 9.37 Hz, 1 H, 6-H), 2.32 (s, 3 H, 20-H), 5.45 (m, 1 H, 4-H), 5.74 (dd, $^3J_{10\text{-H},11\text{-H}}$ = 11.6, $^3J_{10\text{-H},9\text{-F}}$ = 33.7 Hz, 1 H, 10-H), 5.95 (d, $^3J_{14\text{-H},15\text{-H}}$ = 8.1 Hz, 1 H, 14-H), 5.97 (dd, $^3J_{7\text{-H},8\text{-H}}$ = 15.7, $^3J_{7\text{-H},6\text{-H}}$ = 9.37 Hz, 1 H, 7-H), 6.00 (dd, $^3J_{8\text{-H},7\text{-H}}$ = 15.7, $^3J_{8\text{-H},9\text{-F}}$ = 27.5 Hz, 1 H, 8-H), 6.47 (d, $^3J_{12\text{-H},11\text{-H}}$ = 15.3 Hz, 1 H, 12-H), 7.14 (dd, $^3J_{11\text{-H},10\text{-H}}$ = 11.4, $^3J_{11\text{-H},12\text{-H}}$ = 15.3 Hz, 1 H, 11-H), 10.1 (d, $^3J_{15\text{-H},14\text{-H}}$ = 8.17 Hz, 1 H, 15-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 12.9 (C-20), 23.2 (C-18), 24.0 (C-3), 27.2 (C-16), 28.2 (C-17), 32.4 (C-2), 33.6 (C-1), 55.6 (C-6), 110.2 (d, $^2J_{\text{C-10,9-F}}$ = 12.4 Hz, C-10), 122.9 (C-4), 124.2 (d, $^2J_{\text{C-8,9-F}}$ = 25.0 Hz, C-8), 129.6 (d, $^3J_{\text{C-11,9-F}}$ = 5.13 Hz, C-11), 130.7 (C-14), 134.3 (C-5), 135.6 (d, $^4J_{\text{C-12,9-F}}$ = 5.13 Hz, C-12), 137.5 (C-7), 157.8 (C-13), 160.3 (d, $^1J_{\text{C-9,9-F}}$ = 262 Hz, C-9), 193.5 (C-15) ppm. ^{19}F NMR (282.4 MHz): δ = −39.6 (m, $^3J_{9\text{-F},8\text{-H}}$ = 27.7, $^3J_{9\text{-F},10\text{-H}}$ = 33.6 Hz, 9-F) ppm. MS (EI): theoretical ion distribution calcd. 288.1889 mmu; found 288.1888 (error: −0.7 ppm/−0.2 mmu).

(*all-E*)-9-Demethyl-9-fluoro-α-retinal [(*all-E*)-1]: The procedure was the same as that described for the preparation of (9*Z*)-**1**. Dropwise addition of diethyl (3-cyano-2-methylprop-2-enyl)phosphonate (**15**; 62.9 mg, 0.29 mmol) to NaH (11.2 mg, 0.28 mmol) in dry THF at 0 °C gave (*all-E*)-**17** (66 mg, 0.30 mmol), which was subsequently treated with DIBAL-H (0.68 mL, 1.0 M in hexane). This procedure gave a total yield of 73 mg (93%) of the desired product. ^{1}H NMR (300.1 MHz, CD_3OD): δ = 0.86 (s, 3 H, 16-H), 0.94 (s, 3 H, 16-H), 1.23 (m, 1 H, 2-H), 1.49 (m, 1 H, 2-H), 1.60 (s, 3 H, 18-H), 2.06 (m, 2 H, 3-H), 2.36 (s, 3 H, 20-H), 2.38 (d, $^3J_{6\text{-H},7\text{-H}}$ = 9.0 Hz, 1 H, 6-H), 5.49 (m, 1 H, 4-H), 5.96 (d, $^3J_{14\text{-H},15\text{-H}}$ = 8.4 Hz, 1 H, 14-H), 5.90 (dd, $^3J_{10\text{-H},11\text{-H}}$ = 11.8, $^3J_{10\text{-H},9\text{-F}}$ = 18.9 Hz, 1 H, 10-H), 6.00 (dd, $^3J_{7\text{-H},8\text{-H}}$ = 15.2, $^3J_{7\text{-H},6\text{-H}}$ = 10.1 Hz, 1 H, 7-H), 6.40 (d, $^3J_{12\text{-H},11\text{-H}}$ = 15.2 Hz, 1 H, 12-H), 6.54 (dd, $^3J_{8\text{-H},7\text{-H}}$ = 15.2, $^3J_{8\text{-H},9\text{-F}}$ = 27.7 Hz, 1 H, 8-H), 6.92 (dd, $^3J_{11\text{-H},10\text{-H}}$ = 12.0, $^3J_{11\text{-H},12\text{-H}}$ = 15.2 Hz, 1 H, 11-H), 10.1 (d, $^3J_{15\text{-H},14\text{-H}}$ = 8.4 Hz, 1 H, 15-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 16.6 (C-20), 23.1 (C-18), 24.0 (C-3), 27.3 (C-16), 28.1 (C-17), 32.5 (C-2), 33.5 (C-1), 55.9 (C-6), 110.0 (d, $^2J_{\text{C-10,9-F}}$ = 31.1 Hz, C-10), 119.9 (d, $^2J_{\text{C-8,9-F}}$ = 21.7 Hz, C-8), 122.9 (C-4), 130.0 (d, $^6J_{\text{C-14,9-F}}$ = 2.71 Hz, C-14), 130.9 (d, $^3J_{\text{C-11,9-F}}$ = 5.52 Hz, C-11), 134.3 (C-5), 136.1 (d, $^4J_{\text{C-12,9-F}}$ = 5.03 Hz, C-12), 138.2 (d, $^3J_{\text{C-7,9-F}}$ = 3.91 Hz, C-7), 158.6 (C-13), 161.6 (d, $^1J_{\text{C-9,9-F}}$ = 263 Hz, C-9), 192.4 (C-15) ppm. ^{19}F NMR (282.4 MHz): δ = −33.2 (dd, $^3J_{9\text{-F},8\text{-H}}$ = 27.7, $^3J_{9\text{-F},10\text{-H}}$ = 18.9 Hz, 9-F) ppm.

(9*Z*,11*Z*)-9-Demethyl-9-fluoro-α-retinal [(9-*Z*,11-*Z*)-1]: A solution of diphenyl (3-cyano-2-methylprop-2-enyl)phosphonate (**16**; 122 mg, 0.39 mmol) in THF (5 mL) was added to sodium hydride (15 mg, 0.37 mmol) in THF (10 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h. A solution of (2*Z*)-**17** (86 mg, 0.39 mmol) in THF (5 mL) was then added. Stirring was continued at 0 °C for 1 h. The temperature was then allowed to gradually rise to room temperature. The reaction mixture was quenched with satd. aq. $NaHCO_3$. The aqueous layer was extracted with diethyl ether (2 × 10 mL) and the combined organic layers were washed with brine, dried with mixture of K_2CO_3 and $MgSO_4$ (1:9, wt/wt), filtered and concentrated in vacuo. The crude product, which was a 6:4 mixture of the (9*Z*,11*Z*)- and (9*Z*)-retinonitrile isomers was subjected to chromatography to yield pure (9*Z*,11*Z*)-retinonitrile (61 mg). The pure (9*Z*,11*Z*)-retinonitrile was dissolved in dry petroleum ether and cooled to −80 °C. DIBAL-H (0.65 mL, 1.0 M in hexane) was added and the resulting solution was stirred and allowed to warm to −40 °C in 1 h. Subsequently, 1.2 g of homogeneous basic wet Al_2O_3 (Al_2O_3/water, 5:1, wt/wt) was added and stirring was continued at 0 °C for 1 h. The mixture was dried by adding a mixture of K_2CO_3 and $MgSO_4$ (1:9, wt/wt). All solids were filtered off and thoroughly washed with diethyl ether. The organic solvent was evaporated to give the (9*Z*,11*Z*) isomer (58 mg, 94%). ^{1}H NMR (300.1 MHz, CD_3OD): δ = 0.84 (s, 3 H, 16-H), 0.92 (s, 3 H, 16-H), 1.20 (m, 1 H, 2-H), 1.44 (m, 1 H, 2-H), 1.58 (s, 3 H, 18-H), 2.03 (m, 2 H, 3-H), 2.30 (d, $^3J_{6\text{-H},7\text{-H}}$ = 9.43 Hz, 1 H, 6-H), 2.37 (s, 3 H, 20-H), 5.46 (m, 1 H, 4-H), 5.93 (dd, $^3J_{10\text{-H},11\text{-H}}$ = 12.1, $^3J_{10\text{-H},9\text{-F}}$ = 32.5 Hz, 1 H, 10-H), 5.99 (dd, $^3J_{7\text{-H},8\text{-H}}$ = 15.3, $^3J_{7\text{-H},6\text{-H}}$ = 9.43 Hz, 1 H, 7-H), 6.00 (dd, $^3J_{8\text{-H},7\text{-H}}$ = 15.3, $^3J_{8\text{-H},9\text{-F}}$ = 27.1 Hz, 1 H, 8-H), 6.02 (d, $^3J_{12\text{-H},11\text{-H}}$ = 12.1 Hz, 1 H, 12-H), 6.08 (d, $^3J_{14\text{-H},15\text{-H}}$ = 8.0 Hz, 1 H, 14-H), 6.65 (dd, $^3J_{11\text{-H},10\text{-H}}$ = 12.1, $^3J_{11\text{-H},12\text{-H}}$ = 12.1 Hz, 1 H, 11-H), 10.0 (d, $^3J_{15\text{-H},14\text{-H}}$ = 8.0 Hz, 1 H, 15-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 17.7 (C-20), 23.2 (C-18), 24.0 (C-3), 27.2 (C-16), 28.1 (C-17), 32.4 (C-2), 33.5 (C-1), 58.9 (C-6), 106.2 (d, $^2J_{\text{C-10,9-F}}$ = 10.3 Hz, C-10), 122.2 (C-4), 123.6 (d, $^2J_{\text{C-8,9-F}}$ = 40.6 Hz, C-8), 127.8 (d, $^3J_{\text{C-11,9-F}}$ = 6.74 Hz, C-11), 130.5 (d, $^6J_{\text{C-14,9-F}}$ = 2.62 Hz, C-14), 131.7 (d, $^4J_{\text{C-12,9-F}}$ = 4.03 Hz, C-12), 134.3 (C-5), 137.4 (d, $^3J_{\text{C-7,9-F}}$ = 3.61 Hz, C-7), 158.2 (C-13), 160.8 (d, $^1J_{\text{C-9,9-F}}$ = 263 Hz, C-9), 193.3 (C-15) ppm. ^{19}F NMR (282.4 MHz): δ −40.7 = (m, $^3J_{9\text{-F},8\text{-H}}$ = 27.1, $^3J_{9\text{-F},10\text{-H}}$ = 32.5 Hz, 9-F) ppm. UV/Vis: λ_{max} = 340 nm (*n*-hexane).

3-Chloro-5-(2′,6′,6′-trimethycyclohex-2′-en-yl′)penta-2,4-dienal [(*all-E*)-18 + (2*Z*)-18]: A solution of **14** (352 mg, 1.6 mmol) in acetic acid (5 mL) was added to a solution of lithium chloride (136.4 mg, 3.2 mmol) in acetic acid (10 mL). After stirring at 70 °C for 2 h, the solution was cooled to room temperature, the solvents were evaporated in vacuo. The crude product was purified by column chromatography (diethyl ether/petroleum ether, 3:97, v/v) to yield 371 mg, (97%) of the desired product as a 1:3 mixture of (*E*)/(*Z*) isomers.

(2*Z*)-18: ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 0.87 (s, 6 H, 6′-CH_3), 0.94 (s, 6 H, 6′-CH_3), 1.23 (m, 1 H, 5′-H), 1.47 (m, 1 H, 5′-H), 1.58 (s, 3 H, 2′-CH_3), 2.06 (m, 2 H, 4′-H), 2.35 (d, $^3J_{1'\text{-H},5\text{-H}}$ = 9.37 Hz, 1 H, 1′-H), 5.52 (m, 1 H, 3′-H), 6.12 (d, $^3J_{2\text{-H},1\text{-H}}$ = 7.2 Hz, 1 H, 2-H), 6.26 (d, $^3J_{4\text{-H},5\text{-H}}$ = 14.7 Hz, 1 H, 4-H), 6.59 (dd, $^3J_{5\text{-H},4\text{-H}}$ = 14.7, $^3J_{5\text{-H},1'\text{-H}}$ = 9.54 Hz, 1 H, 5-H), 10.2 (d, $^3J_{1\text{-H},2\text{-H}}$ = 7.20 Hz, 1 H, 1-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, $CDCl_3$): δ 22.7 (2′-CH_3), 22.9 (C-4′), 26.7 (6′CH_3), 27.6 (6′-CH_3), 31.0 (C-5′), 32.7 (C-6′), 54.2 (C-1′), 122.4 (C-3′), 124.0 (C-4), 128.5 (C-2), 132.0 (C-2′), 145.0 (C-5), 149.1 (C-3), 191.0 (C-1) ppm.

(*all-E*)-18: ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 0.88 (s, 3 H, 6′-CH_3), 0.95 (s, 3 H, 6′-CH_3), 1.23 (m, 1 H, 5′-H), 1.47 (m, 1 H, 5′-H), 1.60 (s, 3 H, 2′-CH_3), 2.06 (m, 2 H, 4′-H), 2.38 (d, $^3J_{1'\text{-H},5\text{-H}}$ = 9.37 Hz, 1 H, 1′-H), 5.52 (m, 1 H, 3′-H), 6.20 (d, $^3J_{2\text{-H},1\text{-H}}$ = 7.2 Hz, 1 H, 2-H), 6.51 (dd, $^3J_{5\text{-H},4\text{-H}}$ = 14.7, $^3J_{5\text{-H},1'\text{-H}}$ = 9.54 Hz, 1 H, 5-H), 7.04 (d, $^3J_{4\text{-H},5\text{-H}}$ = 14.7 Hz, 1 H, 4-H), 10.0 (d, $^3J_{1\text{-H},2\text{-H}}$ = 7.2 Hz, 1 H, 1-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, $CDCl_3$): δ = 22.7 (2′-CH_3), 22.9 (C-4′), 26.7 (6′-CH_3), 27.6 (6′-CH_3), 31.1 (C-5′), 32.7 (C-6′), 54.2 (C-1′), 122.9 (C-3′), 126.4 (C-4), 128.3 (C-2), 132.0 (C-2′), 147.0 (C-5), 152.5 (C-3), 187.0 (C-1) ppm.

(9*Z*)-9-Chloro-9-demethyl-α-retinal [(9*Z*)-2]: The procedure was the same as that described for the preparation of (9*Z*)-**1** by adding diethyl (3-cyano-2-methylprop-2-enyl)phosphonate (**15**; 107.7 mg,

0.503 mmol) dropwise to NaH (19.7 mg, 0.493 mmol) in dry THF (5 mL) at 0 °C. Subsequently, (2*Z*)-**18** (122 mg, 0.513 mmol) in dry THF (5 mL) was added, followed by DIBAL-H (1.3 mL, 1.0 M in hexane). Workup gave a total yield of 141 mg (96%) of the desired product. ^{1}H NMR (300.1 MHz, CD_3OD): δ = 0.84 (s, 3 H, 16-H), 0.93 (s, 3 H, 17-H), 1.20 (m, 1 H, 2-H), 1.48 (m, 1 H, 2-H), 1.57 (s, 3 H, 18-H), 2.05 (m, 2 H, 3-H), 2.32 (d, $^3J_{6\text{-H},7\text{-H}}$ = 9.54 Hz, 1 H, 6-H), 2.35 (s, 3 H, 20-H), 5.47 (m, 1 H, 4-H), 5.99 (d, $^3J_{14\text{-H},15\text{-H}}$ = 8.17 Hz, 1 H, 14-H), 6.12 (dd, $^3J_{7\text{-H},8\text{-H}}$ = 15.3, $^3J_{7\text{-H},6\text{-H}}$ = 9.71 Hz, 1 H, 7-H), 6.30 (d, $^3J_{12\text{-H},11\text{-H}}$ = 15.3 Hz, 1 H, 12-H), 6.54 (d, $^3J_{10\text{-H},11\text{-H}}$ = 11.0 Hz, 1 H, 10-H), 6.61 (d, $^3J_{8\text{-H},7\text{-H}}$ = 15.3 Hz, 1 H, 8-H), 7.27 (dd, $^3J_{11\text{-H},10\text{-H}}$ = 11.0, $^3J_{11\text{-H},12\text{-H}}$ = 15.3 Hz, 1 H, 11-H), 10.1 (d, $^3J_{15\text{-H},14\text{-H}}$ = 8.17 Hz, 1 H, 15-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 12.9 (C-20), 23.2 (C-18), 24.0 (C-3), 27.4 (C-16), 28.0 (C-17), 32.5 (C-2), 33.7 (C-1), 55.5 (C-6), 122.8 (C-4), 128.1 (C-10), 130.7 (C-8), 131.2 (C-14), 132.6 (C-11), 134.5 (C-5), 137.0 (C-9), 138.6 (C-12), 139.3 (C-7), 156.6 (C-13), 193.4 (C-15) ppm. MS (EI): theoretical ion distribution calcd. 304.1594 mmu; found 304.1585 (error: −2.8 ppm/−0.9 mmu).

(*all-E*)-9-Chloro-9-demethyl-α-retinal [(*all-E*)-2]: The procedure was the same as that described for the preparation of (9*Z*)-**1** by adding diethyl (3-cyano-2-methylprop-2-enyl)phosphonate (**15**; 62.9 mg, 0.29 mmol) dropwise to NaH (19.7 mg, 0.493 mmol) in dry THF (5 mL) at 0 °C. Subsequently, (*all-E*)-**18** (71.4 mg, 0.30 mmol) in dry THF (5 mL) was added, followed by DIBAL-H (0.68 mL, 1.0 M in hexane). Workup gave a total yield of 81 mg (98%) of the desired product. ^{1}H NMR (300.1 MHz, CD_3OD): δ = 0.84 (s, 3 H, 16-H), 0.92 (s, 3 H, 17-H), 1.18 (m, 1 H, 2-H), 1.47 (m, 1 H, 2-H), 1.57 (s, 3 H, 18-H), 2.04 (m, 2 H, 3-H), 2.16 (s, 3 H, 20-H), 2.31 (d, $^3J_{6\text{-H},7\text{-H}}$ = 9.60 Hz, 1 H, 6-H), 5.47 (m, 1 H, 4-H),), 5.89 (d, $^3J_{14\text{-H},15\text{-H}}$ = 8.00 Hz, 1 H, 14-H), 6.13 (dd, $^3J_{7\text{-H},8\text{-H}}$ = 15.0, $^3J_{7\text{-H},6\text{-H}}$ = 9.52 Hz, 1 H, 7-H), 6.30 (d, $^3J_{8\text{-H},7\text{-H}}$ = 15.0 Hz, 1 H, 8-H), 6.59 (d, $^3J_{10\text{-H},11\text{-H}}$ = 11.0 Hz, 1 H, 10-H), 7.15 (dd, $^3J_{11\text{-H},10\text{-H}}$ = 11.0, $^3J_{11\text{-H},12\text{-H}}$ = 15.3 Hz, 1 H, 11-H), 7.57 (d, $^3J_{12\text{-H},11\text{-H}}$ = 15.3 Hz, 1 H, 12-H), 10.2 (d, $^3J_{15\text{-H},14\text{-H}}$ = 8.0 Hz, 1 H, 15-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 21.0 (C-20), 23.3 (C-18), 24.1 (C-3), 27.3 (C-16), 28.2 (C-17), 32.5 (C-2), 33.7 (C-1), 55.4 (C-6), 122.7 (C-4), 128.2 (C-10), 130.0 (C-14), 130.7 (C-12), 130.8 (C-8), 133.5 (C-11), 134.5 (C-5), 137.1 (C-9), 139.3 (C-7), 156.8 (C-13), 192.2 (C-15) ppm.

(9*Z*,11*Z*)-9-Chloro-9-demethyl-α-retinal [(9*Z*,11*Z*)-2]: The procedure was the same as that described for the preparation of (9*Z*,11*Z*)-**1** by adding diphenyl (3-cyano-2-methylprop-2-enyl)-phosphonate (**16**; 122.1 mg, 0.39 mmol) dropwise to NaH (15 mg, 0.37 mmol) in dry THF (5 mL) at 0 °C. Subsequently, (2*Z*)-**18** (92.8 mg, 0.39 mmol) in dry THF (5 mL) was added to give a 7:3 mixture of the (9*Z*,11*Z*)- and (9*Z*)-retinonitrile isomers, followed by DIBAL-H reduction (0.65 mL, 1.0 M in hexane) of the pure (11*Z*)-nitrile to give pure (11*Z*)-retinal (74 mg, 94%). ^{1}H NMR (300.1 MHz, CD_3OD): δ = 0.82 (s, 3 H, 16-H), 0.91 (s, 3 H, 16-H), 1.21 (m, 1 H, 2-H), 1.46 (m, 1 H, 2-H), 1.58 (s, 3 H, 18-H), 2.04 (m, 2 H, 3-H), 2.32 (d, $^3J_{6\text{-H},7\text{-H}}$ = 9.54 Hz, 1 H, 6-H), 2.37 (s, 3 H, 20-H), 5.45 (m, 1 H, 4-H), 5.86 (d, $^3J_{12\text{-H},11\text{-H}}$ = 12.1 Hz, 1 H, 12-H), 5.93 (dd, $^3J_{7\text{-H},8\text{-H}}$ = 15.0, $^3J_{7\text{-H},6\text{-H}}$ = 9.54 Hz, 1 H, 7-H), 6.08 (d, $^3J_{14\text{-H},15\text{-H}}$ = 8.0 Hz, 1 H, 14-H), 6.13 (dd, $^3J_{11\text{-H},10\text{-H}}$ = 11.4, $^3J_{11\text{-H},12\text{-H}}$ = 12.6 Hz, 1 H, 11-H), 6.31 (d, $^3J_{8\text{-H},7\text{-H}}$ = 15.2 Hz, 1 H, 8-H), 6.81 (d, $^3J_{10\text{-H},11\text{-H}}$ = 11.4 Hz, 1 H, 10-H), 10.1 (d, $^3J_{15\text{-H},14\text{-H}}$ = 8.00 Hz, 1 H, 15-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 17.8 (C-20), 23.2 (C-18), 23.7 (C-3), 28.0 (C-16), 28.2 (C-17), 32.5 (C-2), 33.4 (C-1), 55.5 (C-6), 122.5 (C-4), 124.7 (C-14), 129.1 (C-8), 130.0 (C-10), 134.6 (C-5), 133.8 (C-11), 138.1 (C-9), 139.4 (C-7), 157.8 (C-13), 193.4 (C-15) ppm. UV/Vis: λ_{max} = 346 nm (*n*-hexane).

3-Bromo-5-(2′,6′,6′-trimethylcyclohex-2′-en-1′-yl)penta-2,4-dienal [(*all-E*)-19 + (2*Z*)-19]: The reaction procedure was repeated as described for the preparation of (*all-E*)-**17** and (9*Z*)-**17**, only now using **14** (436 mg, 1.98 mmol), lithium bromide (343 mg, 3.96 mmol) and acetic acid (15 mL). The desired product (532 mg, 95%) was obtained as a 1:3 mixture of (*E*)/(*Z*) isomers.

(2*Z*)-19: ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 0.87 (s, 3 H, 6′-CH_3), 0.93 (s, 3 H, 6′-CH_3), 1.22 (m, 1 H, 5′-H), 1.47 (m, 1 H, 5′-H), 1.58 (s, 3 H, 2′CH_3), 2.06 (m, 2 H, 4′-H), 2.38 (d, $^3J_{1'\text{-H},5\text{-H}}$ = 9.50 Hz, 1 H, 1′-H), 5.51 (m, 1 H, 3′-H), 6.23 (d, $^3J_{4\text{-H},5\text{-H}}$ = 15.0 Hz, 1 H, 4-H), 6.33 (d, $^3J_{2\text{-H},1\text{-H}}$ = 6.9 Hz, 1 H, 2-H), 6.57 (dd, $^3J_{5\text{-H},4\text{-H}}$ = 15.1, $^3J_{5\text{-H},1'\text{-H}}$ = 9.50 Hz, 1 H, 5-H), 10.1 (d, $^3J_{1\text{-H},2\text{-H}}$ = 6.9 Hz, 1 H, 1-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, $CDCl_3$): δ = 22.7 (2′-CH_3), 22.9 (C-4′), 26.7 (6′-CH_3), 27.6 (6′-CH_3), 31.2 (C-5′), 32.8 (C-6′), 54.2 (C-1′), 122.2 (C-3′), 127.4 (C-2), 129.8 (C-4), 132.0 (C-2′), 141.8 (C-3), 147.1 (C-5), 193.2 (C-1) ppm.

(*all-E*)-19: ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 0.87 (s, 3 H, 6′-CH_3), 0.93 (s, 3 H, 6′-CH_3), 1.22 (m, 1 H, 5′-H), 1.47 (m, 1 H, 5′-H), 1.59 (s, 3 H, 2′-CH_3), 2.05 (m, 2 H, 4′-H), 2.38 (d, $^3J_{1'\text{-H},5\text{-H}}$ = 9.50 Hz, 1 H, 1′-H), 5.51 (m, 1 H, 3′-H), 6.43 (dd, $^3J_{5\text{-H},4\text{-H}}$ = 15.0, $^3J_{5\text{-H},1'\text{-H}}$ = 9.57 Hz, 1 H, 5-H), 6.52 (d, $^3J_{2\text{-H},1\text{-H}}$ = 6.92 Hz, 1 H, 2-H), 6.95 (d, $^3J_{4\text{-H},5\text{-H}}$ = 15.0 Hz, 1 H, 4-H), 9.96 (d, $^3J_{1\text{-H},2\text{-H}}$ = 6.9 Hz, 1 H, 1-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, $CDCl_3$): δ = 18.7 (C-4′), 22.8 (6′-CH_3), 27.6 (2′-CH_3), 28.7 (6′-CH_3), 31.2 (C-5′), 34.1 (C-6′), 54.4 (C-1′), 124.5 (C-3′), 127.4 (C-2), 130.6 (C-4), 135.5 (C-2′), 145.7 (C-3), 149.2 (C-5), 186.8 (C-1) ppm.

(9*Z*)-9-Bromo-9-demethyl-α-retinal [(9*Z*)-3]: The procedure was the same as that described for the preparation of (9*Z*)-**1**, by adding diethyl (3-cyano-2-methylprop-2-enyl)phosphonate (**15**, 107.7 mg, 0.503 mmol) dropwise to NaH (19.7 mg, 0.493 mmol) in dry THF (5 mL) at 0 °C. Subsequently, (2*Z*)-**19** (145 mg, 0.513 mmol) in dry THF (5 mL) was added, followed by DIBAL-H (1.2 mL, 1.0 M in hexane). Workup gave a total yield of 157 mg (93%) of the desired product. ^{1}H NMR (300.1 MHz, CD_3OD): δ = 0.83 (s, 3 H, 16-H), 0.91 (s, 3 H, 17-H), 1.19 (m, 1 H, 2-H), 1.45 (m, 1 H, 2-H), 1.56 (s, 3 H, 18-H), 2.03 (m, 2 H, 3-H), 2.31 (d, $^3J_{6\text{-H},7\text{-H}}$ = 9.60 Hz, 1 H, 6-H), 2.33 (s, 3 H, 20-H), 5.45 (m, 1 H, 4-H), 5.98 (d, $^3J_{14\text{-H},15\text{-H}}$ = 8.17 Hz, 1 H, 14-H), 6.10 (dd, $^3J_{7\text{-H},8\text{-H}}$ = 15.0, $^3J_{7\text{-H},6\text{-H}}$ = 9.37 Hz, 1 H, 7-H), 6.24 (d, $^3J_{8\text{-H},7\text{-H}}$ = 14.5 Hz, 1 H, 8-H), 6.63 (d, $^3J_{12\text{-H},11\text{-H}}$ = 15.5 Hz, 1 H, 12-H), 6.69 (d, $^3J_{10\text{-H},11\text{-H}}$ = 11.0 Hz, 1 H, 10-H), 7.22 (dd, $^3J_{11\text{-H},10\text{-H}}$ = 11.0, $^3J_{11\text{-H},12\text{-H}}$ = 15.3 Hz, 1 H, 11-H), 10.1 (d, $^3J_{15\text{-H},14\text{-H}}$ = 8.17 Hz, 1 H, 15-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 13.1 (C-20), 23.4 (C-18), 24.1 (C-3), 27.3 (C-16), 28.2 (C-17), 32.5 (C-2), 33.7 (C-1), 55.4 (C-6), 122.8 (C-4), 130.5 (C-5), 130.9 (C-10), 131.3 (C-14), 132.0 (C-8), 134.5 (C-9), 134.8 (C-11), 139.1 (C-12), 141.3 (C-7), 156.4 (C-13), 193.3 (C-15) ppm. MS (EI): theoretical ion distribution calcd. 348.1089 mmu; found 348.1082 (error: −2.0 ppm/−0.7 mmu).

(*all-E*)-9-Bromo-9-demethyl-α-retinal [(*all-E*)-3]: The procedure was the same as that described for the preparation of (9*Z*)-**1** (5 mL) adding diethyl (3-cyano-2-methylprop-2-enyl)phosphonate (**15**; 67 mg, 0.31 mmol) dropwise to NaH (19.7 mg, 0.493 mmol) in dry THF at 0 °C. Subsequently, (*all-E*)-**19** (93.3 mg, 0.33 mmol) in dry THF (5 mL) was added, followed by DIBAL-H (0.73 mL, 1.0 M in hexane). Workup gave a total yield of 96 mg (95%) of the desired product. ^{1}H NMR (300.1 MHz, CD_3OD): δ = 0.86 (s, 3 H, 16-H),

0.94 (s, 3 H, 17-H), 1.26 (m, 1 H, 2-H), 1.49 (m, 1 H, 2-H), 1.58 (s, 3 H, 18-H), 2.09 (m, 2 H, 3-H), 2.18 (s, 3 H, 20-H), 2.44 (d, $^3J_{6\text{-H},7\text{-H}}$ = 9.90 Hz, 1 H, 6-H), 5.49 (m, 1 H, 4-H), 5.91 (d, $^3J_{14\text{-H},15\text{-H}}$ = 8.00 Hz, 1 H, 14-H), 6.07 (dd, $^3J_{7\text{-H},8\text{-H}}$ = 15.0, $^3J_{7\text{-H},6\text{-H}}$ = 9.90 Hz, 1 H, 7-H), 6.72 (d, $^3J_{8\text{-H},7\text{-H}}$ = 15.0 Hz, 1 H, 8-H), 6.79 (d, $^3J_{10\text{-H},11\text{-H}}$ = 11.5 Hz, 1 H, 10-H), 7.13 (dd, $^3J_{11\text{-H},10\text{-H}}$ = 11.4, $^3J_{11\text{-H},12\text{-H}}$ = 15.3 Hz, 1 H, 11-H), 7.47 (d, $^3J_{12\text{-H},11\text{-H}}$ = 15.0 Hz, 1 H, 12-H), 10.2 (d, $^3J_{15\text{-H},14\text{-H}}$ = 8.00 Hz, 1 H, 15-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 13.7.0 (C-20), 23.1 (C-18), 24.0 (C-3), 27.3 (C-16), 28.2 (C-17), 32.6 (C-2), 39.1 (C-1), 55.5 (C-6), 122.2 (C-4), 126.7 (C-14), 130.1 (C-8), 134.2 (C-5), 135.2 (C-10), 135.6 (C-7), 139.2 (C-11), 143.5 (C-12), 145.6 (C-9), 156.9 (C-13), 192.4 (C-15) ppm.

(9*Z*,11*Z*)-9-Bromo-9-demethyl-α-retinal [(9*Z*,11*Z*)-3]: The procedure was the same as that described for the preparation of (9*Z*,11*Z*)-**1** using diphenyl (3-cyano-2-methylprop-2-enyl)phosphonate (**16**; 122 mg, 0.39 mmol), sodium hydride (15 mg, 0.37 mmol) in THF (10 mL), and (2*Z*)-**19** (111 mg, 0.39 mmol). This procedure gave a 9:1 mixture of (9*Z*,11*Z*)- and (9*Z*)-retinonitrile isomers. Subsequent DIBAL-H reduction (0.93 mL, 1.0 M in hexane) of the pure (9*Z*,11*Z*)-nitrile gave pure (9*Z*,11*Z*)-retinal (123 mg, 98%). ^{1}H NMR (300.1 MHz, CD_3OD): δ = 0.84 (s, 3 H, 16-H), 0.93 (s, 3 H, 16-H), 1.21 (m, 1 H, 2-H), 1.46 (m, 1 H, 2-H), 1.57 (s, 3 H, 18-H), 2.04 (m, 2 H, 3-H), 2.34 (d, $^3J_{6\text{-H},7\text{-H}}$ = 9.54 Hz, 1 H, 6-H), 2.35 (s, 3 H, 20-H), 5.46 (m, 1 H, 4-H), 5.90 (d, $^3J_{14\text{-H},15\text{-H}}$ = 8.0 Hz, 1 H, 14-H), 6.11 (dd, $^3J_{7\text{-H},8\text{-H}}$ = 15.0, $^3J_{7\text{-H},6\text{-H}}$ = 9.30 Hz, 1 H, 7-H), 6.26 (d, $^3J_{12\text{-H},11\text{-H}}$ = 11.1 Hz, 1 H, 12-H), 6.65 (d, $^3J_{8\text{-H},7\text{-H}}$ = 15.4 Hz, 1 H, 8-H), 6.75 (dd, $^3J_{11\text{-H},10\text{-H}}$ = 11.5, $^3J_{11\text{-H},12\text{-H}}$ = 11.6 Hz, 1 H, 11-H), 6.98 (d, $^3J_{10\text{-H},11\text{-H}}$ = 11.4 Hz, 1 H, 10-H), 10.1 (d, $^3J_{15\text{-H},14\text{-H}}$ = 8.00 Hz, 1 H, 15-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 13.0 (C-20), 24.0 (C-3), 23.2 (C-18), 27.3 (C-16), 28.2 (C-17), 32.5 (C-2), 33.7 (C-1), 55.4 (C-6), 122.7 (C-4), 127.2 (C-14), 131.9 (C-5), 131.8 (C-8), 135.0 (C-7), 135.2 (C-10), 137.6 (C-9), 138.8 (C-11), 141.3 (C-12), 157.7 (C-13), 193.3 (C-15) ppm. UV/Vis: λ_{max} = 350 nm (*n*-hexane).

3-Iodo-5-(2′,6′,6′-trimethylcyclohex-2′-en-1′-yl)penta-2,4-dien-1-al [(*all-E*)-20 + (2*Z*)-20]: The procedure was the same as that described for the preparation of (*all-E*)-**18** and (2*Z*)-**18**. Compound **14** (262 mg, 1.19 mmol) was added to a solution of lithium iodide (319 mg, 2.38 mmol) in acetic acid (10 mL) to yield 367 mg (93%) of the desired product as a 1:3 mixture of (*E*)/(*Z*) isomers.

(*all-E*)-20: ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 0.87 (s, 3 H, 6′-CH_3), 0.93 (s, 3 H, 6′-CH_3), 1.22 (m, 1 H, 5′-H), 1.47 (m, 1 H, 5′-H), 1.57 (s, 3 H, 2′-CH_3), 2.05 (m, 2 H, 4′-H), 2.43 (d, $^3J_{1'\text{-H},5\text{-H}}$ = 9.60 Hz, 1 H, 1′-H), 5.50 (m, 1 H, 3′-H), 5.97 (d, $^3J_{4\text{-H},5\text{-H}}$ = 14.3 Hz, 1 H, 4-H), 6.31 (d, $^3J_{2\text{-H},1\text{-H}}$ = 6.53 Hz, 1 H, 2-H), 6.47 (dd, $^3J_{5\text{-H},4\text{-H}}$ = 14.3, $^3J_{5\text{-H},1'\text{-H}}$ = 9.60 Hz, 1 H, 5-H), 9.80 (d, $^3J_{1\text{-H},2\text{-H}}$ = 6.54 Hz, 1 H, 1-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, $CDCl_3$): δ = 22.9 (2′-CH_3), 22.9 (C-4′), 26.8 (6′-CH_3), 27.7 (6′-CH_3), 31.3 (C-5′), 32.9 (C-6′), 54.1 (C-1′), 122.5 (C-3′), 123.5 (C-3), 131.7 (C-4), 132.2 (C-2′), 132.6 (C-5), 150.3 (C-2), 197.6 (C-1) ppm.

(2*Z*)-20: ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 0.87 (s, 3 H, 6′-CH_3), 0.93 (s, 3 H, 6′-CH_3), 1.22 (m, 1 H, 5′-H), 1.47 (m, 1 H, 5′-H), 1.57 (s, 3 H, 2′-CH_3), 2.05 (m, 2 H, 4′-H), 2.42 (d, $^3J_{1'\text{-H},5\text{-H}}$ = 9.50 Hz, 1 H, 1′-H), 5.50 (m, 1 H, 3′-H), 6.21 (dd, $^3J_{5\text{-H},4\text{-H}}$ = 14.4, $^3J_{5\text{-H},1'\text{-H}}$ = 9.51 Hz, 1 H, 5-H), 6.56 (d, $^3J_{4\text{-H},5\text{-H}}$ = 14.3 Hz, 1 H, 4-H), 6.81 (d, $^3J_{2\text{-H},1\text{-H}}$ = 6.71 Hz, 1 H, 2-H), 9.91 (d, $^3J_{1\text{-H},2\text{-H}}$ = 6.72 Hz, 1 H, 1-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, $CDCl_3$): δ = 22.9 (2′-CH_3), 22.9 (C-4′), 26.7 (6′-CH_3), 27.6 (6′-CH_3), 31.3 (C-5′), 32.8 (C-6′), 54.2 (C-1′), 122.5 (C-3′), 122.6 (C-4), 123.5 (C-3), 132.2 (C-2′), 139.7 (C-5), 152.4 (C-2), 186.5 (C-1) ppm.

(9*Z*)-9-Demethyl-9-iodo-α-retinal [(9*Z*)-4]: The procedure was the same as that described for the preparation of (9*Z*)-**1** by adding diethyl (3-cyano-2-methylprop-2-enyl)phosphonate (**15**; 166 mg, 0.503 mmol) dropwise to NaH (19.7 mg, 0.493 mmol) in dry THF (5 mL) at 0 °C. Subsequently, (2*Z*)-**20** (169 mg, 0.513 mmol) in dry THF (5 mL) was added, followed by DIBAL-H (1.2 mL, 1.0 M in hexane). Workup gave a total yield of 178 mg (94%) of the desired product. ^{1}H NMR (300.1 MHz, CD_3OD): δ = 0.84 (s, 3 H, 16-H), 0.93 (s, 3 H, 17-H), 1.20 (m, 1 H, 2-H), 1.42 (m, 1 H, 2-H), 1.58 (s, 3 H, 18-H), 2.05 (m, 2 H, 3-H), 2.36 (s, 3 H, 20-H), 2.41 (d, $^3J_{6\text{-H},7\text{-H}}$ = 9.50 Hz, 1 H, 6-H), 5.47 (m, 1 H, 4-H), 5.90 (d, $^3J_{14\text{-H},15\text{-H}}$ = 8.10 Hz, 1 H, 14-H), 5.99 (d, $^3J_{12\text{-H},11\text{-H}}$ = 15.0 Hz, 1 H, 12-H), 6.06 (dd, $^3J_{7\text{-H},8\text{-H}}$ = 15.0, $^3J_{7\text{-H},6\text{-H}}$ = 9.50 Hz, 1 H, 7-H), 6.63 (d, $^3J_{10\text{-H},11\text{-H}}$ = 10.1 Hz, 1 H, 10-H), 6.72 (d, $^3J_{8\text{-H},7\text{-H}}$ = 15.0 Hz, 1 H, 8-H), 7.17 (dd, $^3J_{11\text{-H},10\text{-H}}$ = 10.2, $^3J_{11\text{-H},12\text{-H}}$ = 15.2 Hz, 1 H, 11-H), 10.1 (d, $^3J_{15\text{-H},14\text{-H}}$ = 8.10 Hz, 1 H, 15-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 12.9 (C-20), 22.9 (C-18), 23.2 (C-3), 27.2 (C-16), 28.2 (C-17), 28.2 (C-2), 33.7 (C-1), 55.2 (C-6), 112.7 (C-9), 122.7 (C-4), 134.7 (C-14), 135.1 (C-8), 136.8 (C-5), 136.9 (C-12), 139.4 (C-10), 139.6 (C-11), 144.7 (C-7), 156.5 (C-13), 193.5 (C-15) ppm. MS (EI): theoretical ion distribution calcd. 396.0950 mmu; found 396.0940 (error: −2.5 ppm/−1.0 mmu).

(*all-E*)-9-Demethyl-9-iodo-α-retinal [(*all-E*)-4]: The procedure was the same as that described for the preparation of the (9*Z*)-**1** by adding diethyl (3-cyano-2-methylprop-2-enyl)phosphonate (**15**; 62.9 mg, 0.29 mmol) dropwise to NaH (19.7 mg, 0.493 mmol) in dry THF (5 mL) at 0 °C. Subsequently, (*all-E*)-**20** (99 mg, 0.30 mmol) in dry THF (5 mL) was added, followed by DIBAL-H (0.68 mL, 1.0 M in hexane). Workup gave a total yield of 96 mg (91%) of the desired product. ^{1}H NMR (300.1 MHz, CD_3OD): δ = 0.75 (s, 3 H, 16-H), 0.83 (s, 3 H, 17-H), 1.08 (m, 1 H, 2-H), 1.35 (m, 1 H, 2-H), 1.48 (s, 3 H, 18-H), 1.96 (m, 2 H, 3-H), 2.27 (s, 3 H, 20-H), 2.29 (d, $^3J_{6\text{-H},7\text{-H}}$ = 9.67 Hz, 1 H, 6-H), 5.49 (m, 1 H, 4-H), 5.83 (d, $^3J_{14\text{-H},15\text{-H}}$ = 8.00 Hz, 1 H, 14-H), 5.87 (d, $^3J_{12\text{-H},11\text{-H}}$ = 15.2 Hz, 1 H, 12-H), 5.91 (dd, $^3J_{7\text{-H},8\text{-H}}$ = 15.3, $^3J_{7\text{-H},6\text{-H}}$ = 9.67 Hz, 1 H, 7-H), 6.62 (d, $^3J_{8\text{-H},7\text{-H}}$ = 15.3 Hz, 1 H, 8-H), 6.54 (d, $^3J_{10\text{-H},11\text{-H}}$ = 10.4 Hz, 1 H, 10-H), 7.08 (dd, $^3J_{11\text{-H},10\text{-H}}$ = 10.4, $^3J_{11\text{-H},12\text{-H}}$ = 15.2 Hz, 1 H, 11-H), 9.98 (d, $^3J_{15\text{-H},14\text{-H}}$ = 8.00 Hz, 1 H, 15-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 13.0 (C-20), 23.3 (C-18), 24.0 (C-3), 27.3 (C-16), 28.2 (C-17), 32.6 (C-2), 33.7 (C-1), 55.2 (C-6), 112.7 (C-9), 122.7 (C-4), 131.3 (C-14), 134.7 (C-7), 134.9 (C-5), 135.1 (C-12), 136.8 (C-10), 139.5 (C-11), 139.6 (C-8), 156.4 (C-13), 193.5 (C-15) ppm.

(9*Z*,11*Z*)-9-Demethyl-9-iodo-α-retinal [(9*Z*,11*Z*)-4]: The procedure was the same as that described for the preparation of (9*Z*,11*Z*)-**1**, using diphenyl (3-cyano-2-methylprop-2-enyl)phosphonate (**16**; 122 mg, 0.39 mmol), sodium hydride (15 mg, 0.37 mmol) in THF (10 mL), and (2*Z*)-**20** (129 mg, 0.39 mmol). This procedure gave a 7:3 mixture of (9*Z*,11*Z*)- and (9*Z*)-retinonitrile isomers. Subsequent DIBAL-H reduction (0.65 mL, 1.0 M in hexane) of the pure (11*Z*)-nitrile gave pure (11*Z*)-retinal (96 mg, 93%). ^{1}H NMR (300.1 MHz, CD_3OD): δ = 0.84 (s, 3 H, 16-H), 0.92 (s, 3 H, 17-H), 1.21 (m, 1 H, 2-H), 1.51 (m, 1 H, 2-H), 1.69 (s, 3 H, 18-H), 2.05 (m, 2 H, 3-H), 2.36 (s, 3 H, 20-H), 2.54 (d, $^3J_{6\text{-H},7\text{-H}}$ = 9.60 Hz, 1 H, 6-H), 5.46 (m, 1 H, 4-H), 6.05 (dd, $^3J_{7\text{-H},8\text{-H}}$ = 15.0, $^3J_{7\text{-H},6\text{-H}}$ = 9.54 Hz, 1 H, 7-H), 5.90 (d, $^3J_{14\text{-H},15\text{-H}}$ = 8.0 Hz, 1 H, 14-H), 6.20 (d, $^3J_{12\text{-H},11\text{-H}}$ = 11.8 Hz, 1 H, 12-H), 6.65 (dd,

$^3J_{11\text{-H},10\text{-H}}$ = 11.5, $^3J_{11\text{-H},12\text{-H}}$ = 11.9 Hz, 1 H, 11-H), 6.72 (d, $^3J_{8\text{-H},7\text{-H}}$ = 15.5 Hz, 1 H, 8-H), 6.86 (d, $^3J_{10\text{-H},11\text{-H}}$ = 11.4 Hz, 1 H, 10-H), 10.1 (d, $^3J_{15\text{-H},14\text{-H}}$ = 8.00 Hz, 1 H, 15-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 15.3 (C-20), 23.1 (C-18), 23.2 (C-3), 27.2 (C-16), 28.1 (C-17), 32.7 (C-2), 33.7 (C-1), 55.2 (C-6), 114.9 (C-9), 122.7 (C-4), 132.5 (C-8), 132.6 (C-14), 134.7 (C-7), 135.2 (C-5), 137.4 (C-10), 137.6 (C-12), 145.0 (C-11), 159.2 (C-13), 193.7 (C-15) ppm. UV/Vis: λ_{max} = 347 nm (*n*-hexane).

3-(2′,6′,6′-Trimethylcyclohex-2′-en-1′-yl)prop-2-enal (23): The experiment was carried out in a three-necked, conical-bottomed flask fitted with a reflux condenser, mercury-deal stirrer and dropping funnel packed in an ice-bath. It was charged with *n*-butylamine (7.3 g, 10 mmol), and freshly distilled acetaldehyde (4.4 g, 10 mmol) was added gradually over a period of 2 h. The reaction mixture was stirred for an additional 15 min, potassium hydroxide flakes were then added, and the mixture was allowed to stand until separation into two layers appeared complete. The organic layer was then removed, and was allowed to stand over crushed potassium hydroxide in the refrigerator overnight. The dry material was decanted and the product was obtained by careful fractional distillation. Yield: 9.6 g of *n*-acetaldimine (96%). The following procedure was repeated as described for the preparation of **13**. LDA was prepared at −60 °C from diisopropylamine (1.94 g, 19.2 mmol), dissolved in dry THF (20 mL), and 11.1 mL of BuLi (17.7 mmol, 1.6 M solution of BuLi in hexane). The solution was cooled to −80 °C and *n*-acetaldimine (0.73 g, 7.38 mmol) in THF (10 mL) was added dropwise. After stirring at −80 °C for 0.5 h, diethyl chlorophosphate (1.31 g, 7.38 mmol) in THF (10 mL) was added slowly to form the anion **22a**. While keeping the temperature at −80 °C, a solution of **11** (1.12 g, 7.38 mmol) in THF (5 mL) was added slowly to the solution of phosphonate anion. The reaction mixture was allowed to warm to 0 °C in 2 h followed by routine workup. Pure **23** (1.19 g, 91%) was obtained after column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (s, 3 H, 6′-CH_3), 0.93 (s, 3 H, 6′-CH_3), 1.24 (m, 1 H, 5′-H), 1.47 (m, 1 H, 5′-H), 1.58 (s, 3 H, 2′-CH_3), 2.08 (m, 2 H, 4′-H), 2.43 (d, $^3J_{1'\text{-H},5\text{-H}}$ = 9.68 Hz, 1 H, 1′-H), 5.53 (m, 1 H, 3′-H), 6.10 (dd, $^3J_{2\text{-H},1\text{-H}}$ = 7.92, $^3J_{2\text{-H},3\text{-H}}$ = 15.5 Hz, 1 H, 2-H), 6.69 (dd, $^3J_{3\text{-H},2\text{-H}}$ = 15.5, $^3J_{3\text{-H},1'\text{-H}}$ = 9.68 Hz, 1 H, 5-H), 9.53 (d, $^3J_{1\text{-H},2\text{-H}}$ = 7.92 Hz, 1 H, 1-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, $CDCl_3$): δ = 22.5 (2′-CH_3), 22.7 (C-4′), 26.4 (6′-CH_3), 27.5 (6′-CH_3), 30.8 (C-5′), 32.3 (C-6′), 54.3 (C-1′), 122.8 (C-3′), 131.2 (C-2), 133.8 (C-2′), 158.9 (C-3), 193.6 (C-1) ppm.

1-Cyclopropyl-3-(2′,6′,6′-trimethylcyclohex-2′-en-1′-yl)prop-2-en-1-one (25): The following procedure was repeated as described for the preparation of **13**. The *n*-butylketimine of cyclopropyl methyl ketone was obtained by azeotropic distillation after refluxing cyclopropyl methyl ketone (8.4 g, 10 mmol) with *n*-butylamide (7.3 g, 10 mmol) in dry toluene (10 mL). LDA was prepared at −60 °C from a solution of diisopropylamine (1.94 g, 19.2 mmol) in dry THF (20 mL) and 11.1 mL of BuLi (17.7 mmol, 1.6 M solution of BuLi in hexane). The solution was cooled to −80 °C and the *n*-butylketimine of cyclopropyl methyl ketone (1.03 g, 7.38 mmol) in THF (10 mL) was added dropwise. After stirring at −80 °C for 0.5 h, diethyl chlorophosphate (1.31 g, 7.38 mmol) in THF (10 mL) was added slowly to form the anion **22b**. While keeping the temperature at −80 °C, a solution of **11** (1.12 g, 7.38 mmol) in THF (5 mL) was added slowly to the solution of the phosphonate anion. The reaction mixture was allowed to warm to 0 °C in 1 h followed by routine workup. Pure **25** (1.50 g, 93%) was obtained after column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (s, 3 H, 6′-CH_3), 0.91 (m, 2 H, cyclopropyl-H$^{a,a'}$), 0.93 (s, 3 H, 6′-CH_3), 1.09 (m, 2 H, cyclopropyl-H$^{b,b'}$), 1.49 (m, 1 H, 5′-H), 1.59 (s, 3 H, 2′-CH_3), 2.06 (m, 1 H, 4′-H), 2.15 (m, 1 H, 5′-H), 2.16 (m, 1 H, cyclopropyl-H), 2.30 (d, $^3J_{1'\text{-H},5\text{-H}}$ = 9.8 Hz, 1 H, 1′-H), 5.50 (m, 1 H, 3′-H), 6.19 (d, $^3J_{2\text{-H},3\text{-H}}$ = 15.7 Hz, 1 H, 2-H), 6.72 (dd, $^3J_{3\text{-H},2\text{-H}}$ = 15.7, $^3J_{3\text{-H},1'\text{-H}}$ = 9.8 Hz, 1 H, 3-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, $CDCl_3$): δ = 11.0 (C-2 of cyclopropyl), 18.3 (C-1 of cyclopropyl), 22.7 (2′-CH_3), 22.9 (C-4′), 26.7 (6′-CH_3), 27.8 (6′-CH_3), 31.1 (C-5′), 32.4 (C-6′), 54.6 (C-1′), 124.4 (C-3′), 132.4 (C-2), 132.9 (C-2′), 145.9 (C-2), 200.1 (C-1) ppm.

Isopropyl-3-(2′,6′,6′-trimethylcyclohex-2′-en-1′-yl)prop-2-en-1-one (26): The following procedure was repeated as described for the preparation of **13**. The *n*-butylketimine of isopropyl methyl ketone was obtained by azeotropic distillation after refluxing isopropyl methyl ketone (8.6 g, 10 mmol) with *n*-butylamide (7.3 g, 10 mmol) in dry toluene (10 mL). LDA was prepared at −60 °C from a solution of diisopropylamine (1.94 g, 19.2 mmol) in dry THF (20 mL) and 11.1 mL of BuLi (17.7 mmol, 1.6 M solution of BuLi in hexane). The solution was cooled to −80 °C and the *n*-butylketineimine of isopropyl methyl ketone (1.04 g, 7.38 mmol) in THF (10 mL) was added dropwise. After stirring at −80 °C for 0.5 h, diethyl chlorophosphate (1.31 g, 7.38 mmol) in THF (10 mL) was added slowly to form the anion **22c**. While keeping the temperature at −80 °C, a solution of **11** (1.12 g, 7.38 mmol) in THF (5 mL) was added slowly to the solution of the phosphonate anion. The reaction mixture was allowed to warm to 0 °C in 1 h followed by routine workup. Pure **26** (1.54 g, 95%) was obtained after column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (s, 3 H, 6′-CH_3), 0.93 (s, 3 H, 6′-CH_3), 1.11 (m, 3 H, isopropyl-H^a), 1.12 (m, 3 H, isopropyl-H^b), 1.15 (m, 1 H, 5′-H), 1.42 (m, 1 H, 5′-H), 1.57 (s, 3 H, CH_3–2′), 2.04 (m, 2 H, 4′-H), 2.31 (d, $^3J_{1'\text{-H},5\text{-H}}$ = 9.72 Hz, 1 H, 1′-H), 2.92 (m, 1 H, isopropyl-H), 5.49 (m, 1 H, 3′-H), 6.12 (d, $^3J_{2\text{-H},3\text{-H}}$ = 15.1 Hz, 1 H, 2-H), 6.68 (dd, $^3J_{3\text{-H},2\text{-H}}$ = 15.1, $^3J_{3\text{-H},1'\text{-H}}$ = 9.72 Hz, 1 H, 3-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, $CDCl_3$): δ = 18.4 (CH_3 of isopropyl), 22.7 (2′-CH_3), 22.9 (C-4′), 26.7 (6′-CH_3), 27.6 (6′-CH_3), 31.2 (C-5′), 32.4 (C-6′), 38.1 (CH of isopropyl), 54.2 (C-1′), 122.4 (C-3′), 129.6 (C-2), 131.1 (C-2′), 147.5 (C-2), 203.6 (C-1) ppm.

5-(2′,6′,6′-Trimethylcyclohex-2′-en-1′-yl)penta-2,4-dien-1-al [(*all-E*)-27 and (9*Z*)-27]: A solution of diethyl (cyanomethyl)phosphonate (**21**; 1.73 g, 10 mmol) in THF (5 mL) was added to sodium hydride (348 mg, 8.7 mmol) in dry THF (10 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h. A solution of **23** (1.37 g, 7.7 mmol) in THF (5 mL) was added and stirring was continued at 0 °C for 1 h. The temperature was then allowed to gradually rise to room temperature and the reaction mixture was quenched with satd. aq. NH_4Cl. The aqueous layer was extracted with diethyl ether (2 × 10 mL) and the combined organic layers were washed with brine, dried with $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by column chromatography (diethyl ether/petroleum ether, 1:9, v/v) to yield 1.54 g (quantitative) of the desired product as the pure (*all-E*) and (9-*Z*) isomer, respectively in a ratio of 2:3. The pure (*all-E*) or (9*Z*) isomer was dissolved in dry petroleum ether (50 mL) and cooled to −80 °C. DIBAL-H (2.5 equiv.) was added and the resulting solution was stirred and allowed to warm to −40 °C in 1 h. Subsequently, homogeneous basic wet silica gel (silical gel/water, 5:1, wt/wt) was added and stirring was continued at 0 °C for 1 h. The mixture was dried by adding $MgSO_4$. All solids were filtered off and thoroughly washed with diethyl ether. After careful column chromatography (diethyl ether/petroleum ether, 1:9, v/v), pure (*all-E*)-**27** (0.62 g) and (9*Z*)-**27** (0.94 g) were obtained in a 2:3 isomeric ratio (quantitative).

(*all-E*)-27: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (s, 3 H, 6′-CH_3), 0.93 (s, 3 H, 6′-CH_3), 1.21 (m, 1 H, 5′-H), 1.46 (m, 1 H, 5′-H), 1.59 (s, 3 H, 2′-CH_3), 2.04 (m, 1 H, 4′-H), 2.29 (d, $^3J_{1'\text{-H},5\text{-H}}$ = 9.45 Hz, 1 H, 1′-H), 5.49 (m, 1 H, 3′-H), 6.10 (dd, $^3J_{2\text{-H},3\text{-H}}$ = 15.3, $^3J_{2\text{-H},1\text{-H}}$ = 8.20 Hz, 1 H, 2-H), 6.12 (dd, $^3J_{5\text{-H},4\text{-H}}$ = 15.0, $^3J_{5\text{-H},1'\text{-H}}$ = 9.45 Hz, 1 H, 5-H). 6.31 (dd, $^3J_{4\text{-H},5\text{-H}}$ = 15.0, $^3J_{4\text{-H},3\text{-H}}$ = 10.8 Hz, 1 H, 4-H). 7.11 (dd, $^3J_{3\text{-H},4\text{-H}}$ = 10.8, $^3J_{3\text{-H},2\text{-H}}$ = 15.3 Hz, 1 H, 3-H). 9.57 (d, $^3J_{1\text{-H},4\text{-H}}$ = 8.20 Hz, 1 H, 1-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, $CDCl_3$): δ = 22.8 (2′-CH_3), 23.0 (C-4′), 26.8 (6′-CH_3), 27.1 (6′-CH_3), 31.3 (C-5′), 32.6 (C-6′), 55.2 (C-1′), 122.2 (C-3′), 129.7 (C-2), 130.3 (C-4), 132.5 (C-2′), 147.9 (C-2), 152.6 (C-3), 193.7 (C-1) ppm.

(9*Z*)-27: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (s, 3 H, 6′-CH_3), 0.94 (s, 3 H, 6′-CH_3), 1.21 (m, 1 H, 5′-H), 1.45 (m, 1 H, 5′-H), 1.58 (s, 3 H, 2′-CH_3), 2.07 (m, 1 H, 4′-H), 2.31 (d, $^3J_{1'\text{-H},5\text{-H}}$ = 9.74 Hz, 1 H, 1′-H), 5.49 (m, 1 H, 3′-H), 5.80 (dd, $^3J_{2\text{-H},3\text{-H}}$ = 10.5, $^3J_{2\text{-H},1\text{-H}}$ = 8.10 Hz, 1 H, 2-H), 6.00 (dd, $^3J_{5\text{-H},4\text{-H}}$ = 14.0, $^3J_{5\text{-H},1'\text{-H}}$ = 9.74 Hz, 1 H, 5-H). 6.94 (dd, $^3J_{3\text{-H},4\text{-H}}$ = 10.8, $^3J_{3\text{-H},2\text{-H}}$ = 10.5 Hz, 1 H, 3-H), 7.02 (dd, $^3J_{4\text{-H},5\text{-H}}$ = 14.0, $^3J_{4\text{-H},3\text{-H}}$ = 10.8 Hz, 1 H, 4-H). 10.2 (d, $^3J_{1\text{-H},4\text{-H}}$ = 8.00 Hz, 1 H, 1-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, $CDCl_3$): δ = 22.8 (2′-CH_3), 22.9 (C-4′), 26.7 (6′-CH_3), 27.6 (6′-CH_3), 31.3 (C-5′), 32.6 (C-6′), 54.9 (C-1′), 122.1 (C-3′), 129.6 (C-2), 129.6 (C-4), 131.2 (C-2′), 148.0 (C-2), 152.4 (C-3), 193.8 (C-1) ppm.

3-Methyl-5-(2′,6′,6′-trimethylcyclohex-2′-en-1′-yl)penta-2,4-dien-1-al [(*all-E*)-28 and (9*Z*)-28]: The procedure was the same as that described for the preparation of (*all-E*)-**27** and (9*Z*)-**27**. Diethyl (3-cyano-2-methylprop-2-enyl)phosphonate (**15**; 1.73 g, 10 mmol) in THF (5 mL) was added to sodium hydride (348 mg, 8.7 mmol) in THF (10 mL) at 0 °C. The mixture was stirred at 20 °C for 1 h. Compound **13** (1.48 g, 7.7 mmol) in THF (5 mL) was then added. The crude product was purified by column chromatography (diethyl ether/petroleum ether, 1:9, v/v) to yield 1.66 g (quantitative) of the desired product as the pure (*all-E*) and (9-*Z*) isomer, respectively in a ratio of 2:3. The pure (*all-E*)- and (9*Z*)-nitriles were dissolved in dry petroleum ether (50 mL) and cooled to −80 °C. DIBAL-H (2.5 equiv.) reduction and column chromatography yielded pure (*all-E*)-**28** (0.65 g, 96%) and (9*Z*)-**28** (0.97 g, 96%).

(*all-E*)-28: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (s, 3 H, 6′-CH_3), 0.94 (s, 3 H, 6′-CH_3), 1.23 (m, 1 H, 5′-H), 1.46 (m, 1 H, 5′-H), 1.61 (s, 3 H, 2′-CH_3), 2.05 (m, 1 H, 4′-H), 2.07 (s, 3 H, 3-CH_3), 2.32 (d, $^3J_{1'\text{-H},5\text{-H}}$ = 9.60 Hz, 1 H, 1′-H), 5.48 (m, 1 H, 3′-H), 5.80 (d, $^3J_{2\text{-H},1\text{-H}}$ = 8.00 Hz, 1 H, 2-H), 6.02 (dd, $^3J_{5\text{-H},4\text{-H}}$ = 15.2, $^3J_{5\text{-H},1'\text{-H}}$ = 9.60 Hz, 1 H, 5-H). 7.08 (d, $^3J_{4\text{-H},5\text{-H}}$ = 15.2 Hz, 1 H, 4-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, $CDCl_3$): δ = 21.0 (3-CH_3), 22.4 (2′-CH_3), 22.6 (C-4′), 26.4 (6′-CH_3), 27.2 (6′-CH_3), 31.1 (C-5′), 32.1 (C-6′), 54.5 (C-1′), 121.5 (C-3′), 126.2 (C-4), 127.4 (C-2), 132.3 (C-2′), 140.7 (C-5), 153.8 (C-3), 189.1 (C-1) ppm.

(9*Z*)-28: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (s, 3 H, 6′-CH_3), 0.92 (s, 3 H, 6′-CH_3), 1.22 (m, 1 H, 5′-H), 1.45 (m, 1 H, 5′-H), 1.57 (s, 3 H, 2′-CH_3), 2.04 (m, 1 H, 4′-H), 2.26 (s, 3 H, 3-CH_3), 2.30 (d, $^3J_{1'\text{-H},5\text{-H}}$ = 8.74 Hz, 1 H, 1′-H), 5.47 (m, 1 H, 3′-H), 5.92 (d, $^3J_{2\text{-H},1\text{-H}}$ = 8.11 Hz, 1 H, 2-H), 6.10 (dd, $^3J_{5\text{-H},4\text{-H}}$ = 15.5, $^3J_{5\text{-H},1'\text{-H}}$ = 8.74 Hz, 1 H, 5-H). 6.20 (d, $^3J_{4\text{-H},5\text{-H}}$ = 15.5 Hz, 1 H, 4-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, $CDCl_3$): δ = 12.9 (3-CH_3), 22.7 (2′-CH_3), 22.8 (C-4′), 26.7 (6′-CH_3), 27.4 (6′-CH_3), 31.3 (C-5′), 33.0 (C-6′), 54.8 (C-1′), 121.8 (C-3′), 128.5 (C-2), 132.7 (C-2′), 134.3 (C-4), 140.0 (C-5), 154.4 (C-3), 190.8 (C-1) ppm.

3-Cyclopropyl-5-(2′,6′,6′-trimethylcyclohex-2′-en-1′-yl)penta-2,4-dien-1-al [(*all-E*)-29 and (9*Z*)-29]: The procedure was the same as that described for the preparation of (*all-E*)-**27** and (9*Z*)-**27**. Diethyl (cyanomethyl)phosphonate (**21**; 1.73 g, 10 mmol) in THF (5 mL) was added to sodium hydride (348 mg, 8.7 mmol) in THF (10 mL) at 0 °C. The mixture was stirred at 20 °C for 1 h. Compound **25** (1.68 g, 7.7 mmol) in THF (5 mL) was then added. The crude product was purified by column chromatography (diethyl ether/petroleum ether, 1:9, v/v) to yield 1.86 g (quantitative) of the desired product as the pure (*all-E*) and (9-*Z*) isomer, respectively in a ratio of 2:3. The pure (*all-E*)- and (9*Z*)-nitriles were dissolved in dry petroleum ether (50 mL) and cooled to −80 °C. DIBAL-H (2.5 equiv.) reduction and column chromatography yielded pure (*all-E*)-**29** (0.73 g, 97%) and (9*Z*)-**29** (1.1 g, 97%).

(*all-E*)-29: ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 0.69 (m, 2 H, cyclopropyl-$H^{a,a'}$), 0.84 (s, 3 H, CH_3–6′), 0.91 (s, 3 H, 6′-CH_3), 1.01 (m, 2 H, cyclopropyl-$H^{b,b'}$), 1.21 (m, 1 H, 5′-H), 1.42 (m, 1 H, 5′-H), 1.56 (s, 3 H, 2′-CH_3), 2.04 (m, 1 H, cyclopropyl-H), 2.04 (m, 2 H, 4′-H), 2.23 (d, $^3J_{1'\text{-H},5\text{-H}}$ = 9.72 Hz, 1 H, 1′-H), 5.47 (m, 1 H, 3′-H), 5.90 (d, $^3J_{4\text{-H},5\text{-H}}$ = 15.4 Hz, 1 H, 4-H), 5.98 (d, $^3J_{2\text{-H},1\text{-H}}$ = 8.4 Hz, 1 H, 2-H), 6.26 (dd, $^3J_{5\text{-H},4\text{-H}}$ = 15.4, $^3J_{5\text{-H},1'\text{-H}}$ = 9.7 Hz, 1 H, 5-H), 10.3 (d, $^3J_{1\text{-H},2\text{-H}}$ = 8.4 Hz, 1 H, 1-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, $CDCl_3$): δ = 7.21 (C-2 of cyclopropyl), 10.9 (C-1 of cyclopropyl), 21.4 (2′-CH_3), 22.3 (C-4′), 26.3 (6′-CH_3), 27.1 (6′-CH_3), 31.1 (C-5′), 32.3 (C-6′), 54.7 (C-1′), 121.5 (C-3′), 126.2 (C-4), 127.4 (C-2), 132.3 (C-2′), 141.7 (C-5), 153.8 (C-3), 190.2 (C-1) ppm.

(9*Z*)-29: ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 0.69 (m, 2 H, cyclopropyl-$H^{a,a'}$), 0.84 (s, 3 H, 6′-CH_3), 0.94 (s, 3 H, 6′-CH_3), 1.01 (m, 2 H, cyclopropyl-$H^{b,b'}$), 1.21 (m, 1 H, 5′-H), 1.42 (m, 1 H, 5′-H), 1.61 (s, 3 H, 2′-CH_3), 2.04 (m, 1 H, cyclopropyl-H), 2.05 (m, 2 H, 4′-H), 2.33 (d, $^3J_{1'\text{-H},5\text{-H}}$ = 9.52 Hz, 1 H, 1′-H), 5.48 (m, 1 H, 3′-H), 5.72 (d, $^3J_{2\text{-H},1\text{-H}}$ = 8.0 Hz, 1 H, 2-H), 6.15 (d, $^3J_{5\text{-H},4'\text{-H}}$ = 15.4, $^3J_{5\text{-H},1'\text{-H}}$ = 9.52 Hz, 1 H, 5-H), 6.63 (d, $^3J_{4\text{-H},5\text{-H}}$ = 15.4 Hz, 1 H, 4-H), 10.0 (d, $^3J_{1\text{-H},2\text{-H}}$ = 8.0 Hz, 1 H, 1-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, $CDCl_3$): δ = 7.23 (C-2 of cyclopropyl), 11.9 (C-1 of cyclopropyl), 22.4 (2′-CH_3), 22.7 (C-4′), 26.4 (6′-CH_3), 27.2 (6′-CH_3), 31.3 (C-5′), 33.1 (C-6′), 54.6 (C-1′), 121.4 (C-3′), 127.3 (C-4), 129.1 (C-2), 134.3 (C-2′), 142.8 (C-5), 156.2 (C-3), 191.0 (C-1) ppm.

3-Isopropyl-5-(2′,6′,6′-trimethylcyclohex-2′-en-1′-yl)penta-2,4-dien-1-al [(*all-E*)-30 and (9*Z*)-30]: The procedure was the same as that described for the preparation of (*all-E*)-**27** and (9*Z*)-**27**. Diethyl (cyanomethyl)phosphonate (**21**; 1.73 g, 10 mmol) in THF (5 mL) was added to sodium hydride (348 mg, 8.7 mmol) in THF (10 mL) at 0 °C. The mixture was stirred at 20 °C for 1 h. Compound **26** (1.69 g, 7.7 mmol) in THF (5 mL) was then added. The crude product was purified by column chromatography (diethyl ether/petroleum ether, 1:9, v/v) to yield 1.87 g (quantitative) of the desired product as the pure (*all-E*) and (9-*Z*) isomer, respectively in a ratio of 2:3. The pure (*all-E*)- and (9*Z*)-nitriles were dissolved in dry petroleum ether (50 mL) and cooled to −80 °C. DIBAL-H (2.5 equiv.) reduction and column chromatography yielded pure (*all-E*)-**30** (0.72 g, 95%) and (9*Z*)-**30** (1.08 g, 95%).

(*all-E*)-30: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (s, 3 H, 16-H), 0.93 (s, 3 H, 17-H), 1.20 (d, $^3J_{\text{CH3a,CHisopropyl}}$ = 6.93 Hz, 3 H, isopropyl-H^a), 1.22 (d, $^3J_{\text{CH3b,CHisopropyl}}$ = 6.94 Hz, 3 H, isopropyl-H^b), 1.22 (m, 1 H, 5′-H), 1.47 (m, 1 H, 5′-H), 1.63 (s, 3 H, 2′-CH_3), 2.03 (2 H, 4′-H), 2.32 (d, $^3J_{6'\text{-H},7\text{-H}}$ = 9.67 Hz, 6′-H), 3.65 (m, $^3J_{\text{CH3a,CHisopropyl}}$ = 6.93, $^3J_{\text{CH3b,CHisopropyl}}$ = 6.94 Hz, 1 H, isopropyl-H), 5.46 (m, 1 H, 3′-H), 6.10 (d, $^3J_{2\text{-H},1\text{-H}}$ = 8.2 Hz, 1 H, 2-H), 6.11 (dd, $^3J_{5\text{-H},4\text{-H}}$ = 15.2, $^3J_{5\text{-H},6'\text{-H}}$ = 9.67 Hz, 1 H, 5-H), 6.73 (d, $^3J_{4\text{-H},5\text{-H}}$ = 15.2 Hz, 1 H, 4-H), 10.1 (d, $^3J_{1\text{-H},2\text{-H}}$ = 8.2 Hz, 1 H,

1-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3Cl_3): δ = 22.1 (C-2 of isopropyl), 23.2 (2′-CH_3), 24.0 (C-4′), 27.4 (6′-CH_3), 28.2 (6′-CH_3), 29.7 (C-1 of isopropyl), 32.6 (C-5′), 33.5 (C-6′), 57.9 (C-1′), 123.1 (C-3′), 124.7 (C-2), 130.0 (C-5), 134.4 (C-2′), 141.3 (C-4), 169.7 (C-3), 192.3 (C-1) ppm.

(9*Z*)-30: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83 (s, 3 H, 16-H), 0.91 (s, 3 H, 17-H), 1.21 (d, $^3J_{CH3a,CHisopropyl}$ = 6.93 Hz, 3 H, isopropyl-H^{a,}), 1.23 (d, $^3J_{CH3b,CHisopropyl}$ = 6.94 Hz, 3 H, isopropyl-H^{b}), 1.26 (m, 1 H, 5′-H), 1.49 (m, 1 H, 5′-H), 1.63 (s, 3 H, 2′-CH_3), 2.08 (2 H, 4′-H), 2.36 (d, $^3J_{6'-H,7-H}$ = 9.50 Hz, 6′-H), 3.43 (m, $^3J_{CH3a,CHisopropyl}$ = 6.93, $^3J_{CH3b,CHisopropyl}$ = 6.94 Hz, 1 H, isopropyl-H), 5.47 (m, 2 H, 3′-H), 6.11 (d, $^3J_{2-H,1-H}$ = 8.2 Hz, 1 H, 2-H), 6.11 (dd, $^3J_{5-H,4-H}$ = 15.2, $^3J_{5-H,6'-H}$ = 9.67 Hz, 1 H, 5-H), 6.63 (d, $^3J_{4-H,5-H}$ = 15.2 Hz, 1 H, 4-H), 10.3 (d, $^3J_{1-H,2-H}$ = 8.2 Hz, 1 H, 1-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3Cl_3): δ = 17.6 (C-2 of isopropyl), 18.3 (C-4′), 22.3 (2′-CH_3), 27.2 (6′-CH_3), 28.3 (6′-CH_3), 32.7 (C-1 of isopropyl), 33.4 (C-6′), 38.3 (C-5′), 54.6 (C-1′), 123.1 (C-3′), 124.7 (C-2), 129.3 (C-5), 131.9 (C-2′), 136.8 (C-4), 165.5 (C-3), 192.6 (C-1) ppm.

Repeating the general procedures as described for the preparation of (9*Z*)-**1**, (*all-E*)-**1** and (9*Z*,11*Z*)-**1**, respectively, the following products were synthesized.

(*all-E*)-9-Demethyl-α-retinal [(*all-E*)-5]: ^{1}H NMR (300.1 MHz, CD_3OD): δ = 0.83 (s, 3 H, 16-H), 0.91 (s, 3 H, 17-H), 1.19 (m, 1 H, 2-H), 1.48 (m, 1 H, 2-H), 1.57 (s, 3 H, 18-H), 2.02 (m, 2 H, 3-H), 2.30 (d, $^3J_{6-H,7-H}$ = 9.57 Hz, 1 H, 6-H), 2.32 (s, 3 H, 20-H), 5.43 (m, 1 H, 4-H), 5.72 (dd, $^3J_{7-H,8-H}$ = 15.0, $^3J_{7-H,6-H}$ = 9.57 Hz, 1 H, 7-H), 5.93 (d, $^3J_{14-H,15-H}$ = 8.22 Hz, 1 H, 14-H), 6.16 (dd, $^3J_{8-H,7-H}$ = 15.0, $^3J_{8-H,9-H}$ = 10.7 Hz, 1 H, 8-H), 6.33 (dd, $^3J_{9-H,8-H}$ = 10.7, $^3J_{9-H,10-H}$ = 14.8 Hz, 1 H, H-9), 6.41 (dd, $^3J_{12-H,11-H}$ = 15.3 Hz, 1 H, 12-H), 6.54 (dd, $^3J_{10-H,11-H}$ = 10.7, $^3J_{10-H,9-H}$ = 14.8 Hz, 1 H, 10-H), 6.93 (dd, $^3J_{11-H,10-H}$ = 10.8, $^3J_{11-H,12-H}$ = 15.3 Hz, 1 H, 11-H), 10.0 (d, $^3J_{15-H,14-H}$ = 8.0 Hz, 1 H, 15-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 13.1 (C-20), 23.3 (C-18), 24.1 (C-3), 27.3 (C-16), 28.2 (C-17), 32.5 (C-2), 33.5 (C-1), 56.1 (C-6), 122.3 (C-4), 129.8 (C-14), 131.7 (C-9), 133.1 (C-8), 134.9 (C-5), 135.3 (C-12), 138.7 (C-11), 139.4 (C-10), 140.7 (C-7), 157.7 (C-13), 193.4 (C-15) ppm.

(9*Z*)-9-Demethyl-α-retinal [(9*Z*)-5]: ^{1}H NMR (300.1 MHz, CD_3OD): δ = 0.84 (s, 3 H, 16-H), 0.93 (s, 3 H, 17-H), 1.32 (m, 1 H, 2-H), 1.49 (m, 1 H, 2-H), 1.59 (s, 3 H, 18-H), 2.04 (m, 2 H, 3-H), 2.31 (d, $^3J_{6-H,7-H}$ = 9.60 Hz, 1 H, 6-H), 2.34 (s, 3 H, 20-H), 5.42 (m, 1 H, 4-H), 5.70 (dd, $^3J_{7-H,8-H}$ = 14.8, $^3J_{7-H,6-H}$ = 9.60 Hz, 1 H, 7-H), 5.96 (d, $^3J_{14-H,15-H}$ = 8.1 Hz, 1 H, 14-H), 6.07 (dd, $^3J_{10-H,11-H}$ = 11.2, $^3J_{10-H,9-H}$ = 10.8 Hz, 1 H, 10-H), 6.24 (dd, $^3J_{9-H,8-H}$ = 10.8, $^3J_{9-H,10-H}$ = 10.8 Hz, 1 H, H-9), 6.43 (dd, $^3J_{12-H,11-H}$ = 15.2 Hz, 1 H, 12-H), 6.74 (dd, $^3J_{8-H,7-H}$ = 14.8, $^3J_{8-H,9-H}$ = 11.3 Hz, 1 H, 8-H), 7.36 (dd, $^3J_{11-H,10-H}$ = 11.5, $^3J_{11-H,12-H}$ = 15.02 Hz, 1 H, 11-H), 10.1 (d, $^3J_{15-H,14-H}$ = 8.0 Hz, 1 H, 15-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 13.2 (C-20), 23.2 (C-18), 24.1 (C-3), 27.3 (C-16), 28.2 (C-17), 32.7 (C-2), 33.4 (C-1), 56.2 (C-6), 122.3 (C-4), 128.0 (C-10), 128.3 (C-8), 130.2 (C-14), 133.0 (C-11), 134.9 (C-5), 135.7 (C-9), 136.3 (C-12), 141.3 (C-7), 157.7 (C-13), 193.5 (C-15) ppm.

(11*Z*)-9-Demethyl-α-retinal [(11*Z*)-5]: ^{1}H NMR (300.1 MHz, CD_3OD): δ = 0.83 (s, 3 H, 16-H), 0.91 (s, 3 H, 17-H), 1.19 (m, 1 H, 2-H), 1.46 (m, 1 H, 2-H), 1.59 (s, 3 H, 18-H), 2.02 (m, 2 H, 3-H), 2.22 (d, $^3J_{6-H,7-H}$ = 9.59 Hz, 1 H, 6-H), 2.38 (s, 3 H, 20-H), 5.43 (m, 1 H, 4-H), 5.73 (dd, $^3J_{7-H,8-H}$ = 15.0, $^3J_{7-H,6-H}$ = 9.60 Hz, 1 H, 7-H), 5.91 (dd, $^3J_{12-H,11-H}$ = 11.2 Hz, 1 H, 12-H), 5.95 (d, $^3J_{14-H,15-H}$ = 8.2 Hz, 1 H, 14-H), 6.18 (dd, $^3J_{9-H,8-H}$ = 15.0, $^3J_{9-H,10-H}$ = 10.7 Hz, 1 H, H-9), 6.38 (dd, $^3J_{11-H,10-H}$ = 11.9, $^3J_{11-H,12-H}$ = 11.8 Hz, 1 H, 11-H), 6.45 (dd, $^3J_{8-H,7-H}$ = 15.0, $^3J_{8-H,9-H}$ = 11.0 Hz, 1 H, 8-H), 6.75 (dd, $^3J_{10-H,11-H}$ = 11.2, $^3J_{10-H,9-H}$ = 14.8 Hz, 1 H, 10-H), 10.0 (d, $^3J_{15-H,14-H}$ = 8.2 Hz, 1 H, 15-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 12.8 (C-20), 18.2 (C-19), 23.3 (C-18), 24.1 (C-3), 27.4 (C-16), 28.2 (C-17), 32.7 (C-2), 33.5 (C-1), 56.2 (C-6), 122.2 (C-4), 126.7 (C-14), 130.5 (C-10), 131.5 (C-12), 132.7 (C-11), 135.0 (C-7), 134.9 (C-5), 142.3 (C-9), 158.9 (C-13), 193.5 (C-15) ppm.

(*all-E*)-α-Retinal [(*all-E*)-6]: ^{1}H NMR (300.1 MHz, CD_3OD): δ = 0.84 (s, 3 H, 16-H), 0.92 (s, 3 H, 17-H), 1.20 (m, 1 H, 2-H), 1.45 (m, 1 H, 2-H), 1.59 (s, 3 H, 18-H), 1.97 (s, 3 H, H-19), 2.02 (m, 2 H, 3-H), 2.29 (s, 3 H, 20-H), 2.31 (d, $^3J_{6-H,7-H}$ = 9.50 Hz, 1 H, 6-H), 5.43 (m, 1 H, 4-H), 5.77 (dd, $^3J_{7-H,8-H}$ = 15.2, $^3J_{7-H,6-H}$ = 9.50 Hz, 1 H, 7-H), 5.93 (d, $^3J_{14-H,15-H}$ = 8.1 Hz, 1 H, 14-H), 6.07 (d, $^3J_{12-H,11-H}$ = 15.1 Hz, 1 H, 12-H), 6.28 (d, $^3J_{10-H,11-H}$ = 11.5 Hz, 1 H, 10-H), 6.68 (d, $^3J_{8-H,7-H}$ = 15.2 Hz, 1 H, 8-H), 7.21 (dd, $^3J_{11-H,10-H}$ = 11.5, $^3J_{11-H,12-H}$ = 15.0 Hz, 1 H, 11-H), 10.1 (d, $^3J_{15-H,14-H}$ = 8.1 Hz, 1 H, 15-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 13.3 (C-20), 13.6 (C-19), 23.6 (C-18), 24.1 (C-3), 27.6 (C-16), 28.3 (C-17), 32.7 (C-2), 33.5 (C-1), 56.1 (C-6), 122.2 (C-4), 129.8 (C-14), 130.4 (C-10), 134.0 (C-11), 134.9 (C-5), 134.9 (C-7), 135.8 (C-12), 137.0 (C-8), 141.8 (C-9), 157.1 (C-13), 192.7 (C-15) ppm.

(9*Z*)-α-Retinal [(9*Z*)-6]: ^{1}H NMR (300.1 MHz, CD_3OD): δ = 0.84 (s, 3 H, 16-H), 0.92 (s, 3 H, 17-H), 1.20 (m, 1 H, 2-H), 1.45 (m, 1 H, 2-H), 1.59 (s, 3 H, 18-H), 1.93 (s, 3 H, H-19), 2.02 (m, 2 H, 3-H), 2.29 (s, 3 H, 20-H), 2.31 (d, $^3J_{6-H,7-H}$ = 9.65 Hz, 1 H, 6-H), 5.42 (m, 1 H, 4-H), 5.70 (dd, $^3J_{7-H,8-H}$ = 15.3, $^3J_{7-H,6-H}$ = 9.65 Hz, 1 H, 7-H), 5.91 (d, $^3J_{14-H,15-H}$ = 8.2 Hz, 1 H, 14-H), 6.05 (d, $^3J_{10-H,11-H}$ = 11.5 Hz, 1 H, 10-H), 6.32 (d, $^3J_{12-H,11-H}$ = 15.1 Hz, 1 H, 12-H), 6.74 (d, $^3J_{8-H,7-H}$ = 15.3 Hz, 1 H, 8-H), 7.33 (dd, $^3J_{11-H,10-H}$ = 11.5, $^3J_{11-H,12-H}$ = 15.0 Hz, 1 H, 11-H), 10.0 (d, $^3J_{15-H,14-H}$ = 8.2 Hz, 1 H, 15-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 13.3 (C-20), 21.4 (C-19), 23.5 (C-18), 24.1 (C-3), 27.5 (C-16), 28.3 (C-17), 32.8 (C-2), 33.5 (C-1), 56.2 (C-6), 122.2 (C-4), 128.9 (C-10), 129.2 (C-8), 129.8 (C-14), 133.0 (C-11), 135.0 (C-5), 135.1 (C-12), 136.6 (C-7), 140.8 (C-9), 157.3 (C-13), 193.0 (C-15) ppm.

(11*Z*)-α-Retinal [(11*Z*)-6]: ^{1}H NMR (300.1 MHz, CD_3OD): δ = 0.83 (s, 3 H, 16-H), 0.92 (s, 3 H, 17-H), 1.43 (m, 2 H, 2-H), 1.58 (s, 3 H, 18-H), 1.99 (s, 3 H, H-19), 2.02 (m, 2 H, 3-H), 2.28 (d, $^3J_{6-H,7-H}$ = 9.42 Hz, 1 H, 6-H), 2.32 (s, 3 H, 20-H), 5.43 (m, 1 H, 4-H), 5.76 (dd, $^3J_{7-H,8-H}$ = 15.4, $^3J_{7-H,6-H}$ = 9.42 Hz, 1 H, 7-H), 5.98 (d, $^3J_{14-H,15-H}$ = 8.2 Hz, 1 H, 14-H), 5.99 (d, $^3J_{10-H,11-H}$ = 11.7 Hz, 1 H, 10-H), 6.06 (d, $^3J_{8-H,7-H}$ = 15.4 Hz, 1 H, 8-H), 6.55 (d, $^3J_{12-H,11-H}$ = 15.3 Hz, 1 H, 12-H), 6.73 (dd, $^3J_{11-H,10-H}$ = 11.9, $^3J_{11-H,12-H}$ = 12.1 Hz, 1 H, 11-H), 10.0 (d, $^3J_{15-H,14-H}$ = 8.2 Hz, 1 H, 15-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 13.2 (C-20), 21.6 (C-19), 24.0 (C-3), 27.3 (C-18), 28.0 (C-16), 28.2 (C-17), 32.5 (C-2), 33.4 (C-1), 55.1 (C-6), 122.5 (C-4), 128.5 (C-14), 129.1 (C-8), 130.0 (C-10), 134.6 (C-5), 133.8 (C-11), 138.1 (C-9), 139.4 (C-7), 157.8 (C-13), 193.4 (C-15) ppm.

(*all-E*)-19,19-Ethano-α-retinal [(*all-E*)-7]: ^{1}H NMR (300.1 MHz, CD_3OD): δ = 0.45 (m, 2 H, cyclopropyl-H$^{a,a'}$), 0.85 (s, 3 H, 16-H), 0.93 (s, 3 H, 17-H), 0.94 (m, 2 H, cyclopropyl-H$^{b,b'}$), 1.10 (s, 3 H, 16-H), 1.12 (s, 3 H, 17-H), 1.46 (m, 2 H, 2-H), 1.57 (s, 3 H, 18-H), 2.04 (m, 2 H, 3-H), 2.22 (d, $^3J_{6-H,7-H}$ = 6.52 Hz, 1 H, 6-H), 2.35 (s, 3 H, 20-H), 5.43 (m, 1 H, 4-H), 5.95 (d, $^3J_{14-H,15-H}$ = 8.2 Hz, 1 H, 14-H), 5.99 (d, $^3J_{8-H,7-H}$ = 15.4 Hz, 1 H, 8-H), 6.03 (dd, $^3J_{7-H,8-H}$ = 15.4, $^3J_{7-H,6-H}$ = 6.6 Hz, 1 H, 7-H), 6.24 (d,

$^3J_{10\text{-}H,11\text{-}H}$ = 11.5 Hz, 1 H, 10-H), 6.43 (d, $^3J_{12\text{-}H,11\text{-}H}$ = 15.3 Hz, 1 H, 12-H), 7.55 (dd, $^3J_{11\text{-}H,10\text{-}H}$ = 11.5, $^3J_{11\text{-}H,12\text{-}H}$ = 12.1 Hz, 1 H, 11-H), 10.1 (d, $^3J_{15\text{-}H,14\text{-}H}$ = 8.2 Hz, 1 H, 15-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 7.2 (C-2 of cyclopropyl), 10.9 (C-1 of cyclopropyl), 13.1 (C-20), 23.3 (C-18), 24.1 (C-3), 27.4 (C-16), 28.1 (C-17), 32.8 (C-2), 33.5 (C-1), 56.3 (C-6), 122.1 (C-4), 129.8 (C-14), 130.8 (C-10), 135.1 (C-11), 135.2 (C-8), 135.8 (12-C), 136.5 (C-7), 147.1 (C-9), 158.0 (C-13), 193.5 (C-15) ppm.

(9*Z*)-19,19-Ethano-α-retinal [(9*Z*)-7]: ^{1}H NMR (300.1 MHz, CD_3OD): δ = 0.50 (m, 2 H, cyclopropyl-H$^{a,a'}$), 0.87 (m, 2 H, cyclopropyl-H$^{b,b'}$), 0.87 (s, 6 H, 16-H + 17-H), 0.95 (m, 1 H, cyclopropyl-H), 1.34 (m, 2 H, 2-H), 1.62 (s, 3 H, 18-H), 2.06 (m, 2 H, 3-H), 2.33 (s, 3 H, 20-H), 2.33 (d, $^3J_{6\text{-}H,7\text{-}H}$ = 9.5 Hz, 1 H, 6-H), 5.46 (m, 1 H, 4-H), 5.94 (d, $^3J_{14\text{-}H,15\text{-}H}$ = 8.3 Hz, 1 H, 14-H), 6.04 (dd, $^3J_{7\text{-}H,8\text{-}H}$ = 15.2, $^3J_{7\text{-}H,6\text{-}H}$ = 9.5 Hz, 1 H, 7-H), 6.06 (d, $^3J_{10\text{-}H,11\text{-}H}$ = 11.1 Hz, 1 H, 10-H), 6.40 (d, $^3J_{12\text{-}H,11\text{-}H}$ = 15.3 Hz, 1 H, 12-H), 6.61 (d, $^3J_{8\text{-}H,7\text{-}H}$ = 15.0 Hz, 1 H, 8-H), 7.32 (dd, $^3J_{11\text{-}H,10\text{-}H}$ = 11.5, $^3J_{11\text{-}H,12\text{-}H}$ = 15.1 Hz, 1 H, 11-H), 10.0 (d, $^3J_{15\text{-}H,14\text{-}H}$ = 8.3 Hz, 1 H, 15-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 6.7 (C-2 of cyclopropyl), 6.8 (C-1 of cyclopropyl), 16.2 (C-20), 23.3 (C-18), 24.1 (C-3), 27.4 (C-16), 28.3 (C-17), 32.8 (C-2), 33.4 (C-1), 56.5 (C-6), 122.3 (C-4), 125.5 (C-7), 128.9 (C-8), 129.7 (C-14), 133.8 (C-11), 135.2 (12-C), 137.5 (C-10), 137.8 (C-5), 146.8 (C-9), 158.1 (C-13), 193.5 (C-15) ppm.

(11*Z*)-19,19-Ethano-α-retinal [(11*Z*)-7]: ^{1}H NMR (300.1 MHz, CD_3OD): δ = 0.44 (m, 2 H, cyclopropyl-H$^{a,a'}$), 0.96 (m, 2 H, cyclopropyl-H$^{b,b'}$), 0.87 (s, 6 H, 16-H + 17-H), 0.95 (m, 1 H, cyclopropyl-H), 1.57 (m, 2 H, 2-H), 1.62 (s, 3 H, 18-H), 2.03 (m, 2 H, 3-H), 2.20 (d, $^3J_{6\text{-}H,7\text{-}H}$ = 9.5 Hz, 1 H, 6-H), 2.37 (s, 3 H, 20-H), 5.42 (m, 1 H, 4-H), 5.97 (d, $^3J_{14\text{-}H,15\text{-}H}$ = 8.1 Hz, 1 H, 14-H), 5.98 (d, $^3J_{8\text{-}H,7\text{-}H}$ = 15.0 Hz, 1 H, 8-H), 6.00 (dd, $^3J_{7\text{-}H,8\text{-}H}$ = 15.0, $^3J_{7\text{-}H,6\text{-}H}$ = 9.5 Hz, 1 H, 7-H), 6.02 (d, $^3J_{12\text{-}H,11\text{-}H}$ = 12.3 Hz, 1 H, 12-H), 6.56 (d, $^3J_{10\text{-}H,11\text{-}H}$ = 12.0 Hz, 1 H, 10-H), 7.03 (dd, $^3J_{11\text{-}H,10\text{-}H}$ = 12.0, $^3J_{11\text{-}H,12\text{-}H}$ = 12.1 Hz, 1 H, 11-H), 10.0 (d, $^3J_{15\text{-}H,14\text{-}H}$ = 8.1 Hz, 1 H, 15-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 7.15 (C-1 of cyclopropyl), 7.25 (C-1 of cyclopropyl), 10.5 (C-1 of cyclopropyl), 18.2 (C-20), 23.3 (C-18), 24.1 (C-3), 27.5 (C-16), 28.1 (C-17), 32.9 (C-2), 33.4 (C-1), 57.6 (C-6), 122.1 (C-4), 127.1 (C-10), 133.4 (11-C), 137.8 (C-5), 135.3 (C-8), 136.4 (C-7), 131.5 (C-12), 129.7 (C-14), 147.2 (C-9), 159.0 (C-13), 196.7 (C-15) ppm.

(*all-E*)-19,19-Dimethyl-α-retinal [(*all-E*)-8]: ^{1}H NMR (300.1 MHz, CD_3OD): δ = 0.85 (s, 3 H, 16-H), 0.92 (s, 3 H, 17-H), 1.13 (d, $^3J_{CH3a,CHisopropyl}$ = 6.93 Hz, 3 H, isopropyl-H^{a,}), 1.15 (d, $^3J_{CH3b,CHisopropyl}$ = 6.94 Hz, 3 H, isopropyl-H^{b}), 1.46 (m, 2 H, 2-H), 1.59 (s, 3 H, 18-H), 2.04 (m, 2 H, 3-H), 2.21 (d, $^3J_{6\text{-}H,7\text{-}H}$ = 9.4 Hz, 1 H, 6-H), 2.34 (s, 3 H, 20-H), 3.12 (m, $^3J_{CH3a,CHisopropyl}$ = 6.93, $^3J_{CH3b,CHisopropyl}$ = 6.94 Hz, 1 H, isopropyl-H), (m, 1 H, isopropyl-H), 5.48 (m, 1 H, 4-H), 5.82 (dd, $^3J_{7\text{-}H,8\text{-}H}$ = 15.5, $^3J_{7\text{-}H,6\text{-}H}$ = 9.4 Hz, 1 H, 7-H), 5.95 (d, $^3J_{14\text{-}H,15\text{-}H}$ = 8.2 Hz, 1 H, 14-H), 6.06 (d, $^3J_{8\text{-}H,7\text{-}H}$ = 15.4 Hz, 1 H, 8-H), 6.23 (d, $^3J_{10\text{-}H,11\text{-}H}$ = 11.6 Hz, 1 H, 10-H), 6.45 (d, $^3J_{12\text{-}H,11\text{-}H}$ = 15.1 Hz, 1 H, 12-H), 7.25 (dd, $^3J_{11\text{-}H,10\text{-}H}$ = 11.6, $^3J_{11\text{-}H,12\text{-}H}$ = 15.1 Hz, 1 H, 11-H), 10.0 (d, $^3J_{15\text{-}H,14\text{-}H}$ = 8.2 Hz, 1 H, 15-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 13.2 (C-20), 22.1 (C-2 of isopropyl), 23.3 (C-18), 24.1 (C-3), 27.5 (C-16), 28.2 (C-17), 29.9 (C-1 of isopropyl), 32.8 (C-1), 33.5 (C-2), 56.5 (C-6), 122.2 (C-4), 125.6 (C-14), 129.8 (C-8), 132.2 (C-10), 133.6 (C-5), 135.2 (C-11), 135.9 (C-9), 152.7 (C-7), 158.1 (C-13), 193.5 (C-15) ppm.

(9*Z*)-19,19-Dimethyl-α-retinal [(9*Z*)-8]: ^{1}H NMR (300.1 MHz, CD_3OD): δ = 0.91 (s, 3 H, 16-H), 0.92 (s, 3 H, 17-H), 1.10 (d, $^3J_{CH3a,CHisopropyl}$ = 6.93 Hz, 3 H, isopropyl-H^{a,}), 1.26 (d, $^3J_{CH3b,CHisopropyl}$ = 6.94 Hz, 3 H, isopropyl-H^{b}), 1.51 (m, 2 H, 2-H), 1.65 (s, 3 H, 18-H), 2.05 (m, 2 H, 3-H), 2.21 (d, $^3J_{6\text{-}H,7\text{-}H}$ = 9.57 Hz, 1 H, 6-H), 2.31 (s, 3 H, 20-H), 2.68 (m, $^3J_{CH3a,CHisopropyl}$ = 6.93, $^3J_{CH3b,CHisopropyl}$ = 6.94 Hz, 1 H, isopropyl-H), 5.66 (m, 1 H, 4-H), 5.68 (dd, $^3J_{7\text{-}H,8\text{-}H}$ = 15.6, $^3J_{7\text{-}H,6\text{-}H}$ = 9.57 Hz, 1 H, 7-H), 5.94 (d, $^3J_{14\text{-}H,15\text{-}H}$ = 8.2 Hz, 1 H, 14-H), 6.13 (d, $^3J_{10\text{-}H,11\text{-}H}$ = 11.2 Hz, 1 H, 10-H), 6.42 (d, $^3J_{8\text{-}H,7\text{-}H}$ = 15.4 Hz, 1 H, 8-H), 6.43 (d, $^3J_{12\text{-}H,11\text{-}H}$ = 15.3 Hz, 1 H, 12-H), 7.3 (dd, $^3J_{11\text{-}H,10\text{-}H}$ = 11.2, $^3J_{11\text{-}H,12\text{-}H}$ = 15.2 Hz, 1 H, 11-H), 10.0 (d, $^3J_{15\text{-}H,14\text{-}H}$ = 8.2 Hz, 1 H, 15-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 13.2 (C-20), 22.6.0 (C-3), 23.3 (C-18), 24.1 (C-2 of isopropyl), 27.3 (C-16), 28.6 (C-17), 32.7 (C-2), 33.1 (C-1), 33.3 (C-1 of isopropyl), 56.7 (C-6), 122.4 (C-4), 124.7 (C-14), 128.6 (C-8), 129.7 (C-10), 135.1 (C-5), 135.2 (C-11), 137.7 (C-7), 152.7 (C-9), 158.0 (C-13), 193.2 (C-15) ppm.

(11*Z*)-19,19-Dimethyl-α-retinal [(11*Z*)-8]: ^{1}H NMR (300.1 MHz, CD_3OD): δ = 0.83 (s, 3 H, 16-H), 0.91 (s, 3 H, 17-H), 1.10 (d, $^3J_{CH3a,CHisopropyl}$ = 6.93 Hz, 3 H, isopropyl-H^{a,}), 1.11 (d, $^3J_{CH3b,CHisopropyl}$ = 6.94 Hz, 3 H, isopropyl-H^{b}), 1.18 (m, 1 H, 2-H), 1.43 (m, 1 H, 2-H), 1.58 (s, 3 H, 18-H), 2.02 (m, 2 H, 3-H), 2.21 (d, $^3J_{6\text{-}H,7\text{-}H}$ = 9.48 Hz, 1 H, 6-H), 2.36 (s, 3 H, 20-H), 3.12 (m, $^3J_{CH3a,CHisopropyl}$ = 6.93, $^3J_{CH3b,CHisopropyl}$ = 6.94 Hz, 1 H, isopropyl-H), 5.43 (m, 1 H, 4-H), 5.76 (dd, $^3J_{7\text{-}H,8\text{-}H}$ = 15.4, $^3J_{7\text{-}H,6\text{-}H}$ = 9.42 Hz, 1 H, 7-H), 5.98 (d, $^3J_{14\text{-}H,15\text{-}H}$ = 8.2 Hz, 1 H, 14-H), 5.99 (d, $^3J_{10\text{-}H,11\text{-}H}$ = 11.7 Hz, 1 H, 10-H), 6.06 (d, $^3J_{8\text{-}H,7\text{-}H}$ = 15.4 Hz, 1 H, 8-H), 6.55 (d, $^3J_{12\text{-}H,11\text{-}H}$ = 15.3 Hz, 1 H, 12-H), 6.73 (dd, $^3J_{11\text{-}H,10\text{-}H}$ = 11.9, $^3J_{11\text{-}H,12\text{-}H}$ = 12.1 Hz, 1 H, 11-H), 10.0 (d, $^3J_{15\text{-}H,14\text{-}H}$ = 8.2 Hz, 1 H, 15-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD: δ = 13.2 (C-20), 20.3 (C-2 of isopropyl), 24.0 (C-3), 26.3 (C-18), 27.3 (C-16), 28.2 (C-17), 29.3 (C-1 of isopropyl), 32.9 (C-2), 33.5 (C-1), 56.3 (C-6), 121.8 (C-10), 122.2 (C-4), 130.8 (C-14), 131.5 (C-11), 132.0 (C-8), 132.3 (C-10), 135.1 (C-5), 135.5 (C-7), 152.7 (C-9), 157.7 (C-13), 193.4 (C-15) ppm.

Acknowledgments

This investigation was supported by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for Scientific Research (NWO). The authors wish to thank H. Peeters, Universiteit van Amsterdam, Massa Spectrometrie SILS for acquiring the exact mass spectra; F. Lefeber and C. Erkelens for recording the NMR spectra; P. Bovee-Geurts, University of Nijmegen and J. van Brussels, Universiteit Leiden for UV/Vis spectra; and Dr. R. van der Steen for his careful reading of the final manuscript.

[1] S. Watson, S. Arkinstall, *The G-Protein Linked Receptor Facts Book*, Academic Press, San Diego, CA, **1994**.
[2] L. Tang, T. G. Ebrey, S. Subramaniam, *Isr. J. Chem.* **1995**, *35*, 193−209.
[3] I. R. Pogozheva, A. L. Lomize, H. I. Mosberg, *Biophys. J.* **1997**, *70*, 1963−1985.
[4] P. J. E. Verdegem, J. Lugtenburg, H. J. M. De Groot, *Pharmacochemistry Library*, vol. 26 ("Stable Isotopes in Pharmaceutical Research") (Ed.: T. R. Browne) Elsevier, Amsterdam, **1997**, chapter 10, 203−217.
[5] A. F. L. Creemers, S. K. Kiihne, P. H. M. Bovee-Geurts, W. J. DeGrip, J. Lugtenburg, H. J. M. de Groot, *Proc. Natl. Acad. Sci. USA* **2002**, *14*, 9101−9106.
[6] A. F. L. Creemers, P. H. M. Bovee-Geurts, W. J. DeGrip, J.

Lugtenburg, H. J. M. de Groot, *Proc. Natl. Acad. Sci. USA*, submitted.
[7] T. Okada, H. Kandori, Y. Shichida, T. Yoshizawa, M. Denny, B.-W. Zhang, A. Asato, R. S. H. Liu, *Biochemistry* **1991**, *30*, 4796−4802.
[8] C. E. Randall, J. W. Lewis, S. J. Hug, S. C. Bjoling, *J. Am. Chem. Soc.* **1991**, *11*, 3473−3485.
[9] T. L. Mah, J. W. Lewis, M. Sheves, M. Ottolenghi, D. S. Kligen, *Photochem. Photobiol.* **1995**, *62*, 356−360.
[10] M. Han, M. Groesbeek, T. P. Sakmar, S. O. Smith, *Proc. Natl. Acad. Sci. USA* **1998**, *94*, 13442−13447.
[11] T. P. Sakmar, R. R. Franke, H. G. Khorana, *Proc. Natl. Acad. Sci. USA* **1989**, *86*, 8309−8313.
[12] A. D. Broek, M. Muradin-Szweykowska, J. M. L. Courin, J. Lugtenburg, *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 46−51.
[13] R. Vogel, G.-B. Fan, M. Sheves, F. Siebert, *Biochemistry* **2000**, *39*, 8895−8908.
[14] C. K. Meyer, M. Bohme, A. Ockenfels, W. Gartner, K. P. Homann, O. P. Ernst, *J. Biol. Chem.* **2000**, *26*, 19713−19718.
[15] M. Ulrich, E. Ganter, D. Schmid, P.-S. Dolores, R. R. Rando, F. Siebert, *Biochemistry* **1989**, *28*, 5954−5962.
[16] M. Han, M. Groesbeek, S. O. Smith, T. P. Sakmar, *Biochemistry* **1998**, *37*, 538−545.
[17] A. T. Balaban, I. Ghiviriga, E. W. Czerwinski, P. R. De Faust, *J. Org. Chem.* **2004**, *69*, 536−542.
[18] C. Roussel, A. Liden, M. Chanon, J. Metzger, I. Sandstrom, *J. Am. Chem. Soc.* **1976**, *98*, 2847−2852.
[19] F. J. H. M. Jansen, J. Lugtenburg, *Eur. J. Org. Chem.* **2000**, 829−836.
[20] Y. Wang, W. S. Woo, I. van der Hoef, J. Lugtenburg, *Eur. J. Org. Chem.* **2004**, 2166−2175.
[21] L. Ernst, H. Hopf, N. Krause, *J. Org. Chem.* **1987**, *52*, 398−405.

Received March 25, 2004

