9-Demethyl-9-haloretinals by Wadsworth−Emmons Coupling − Easy Preparation of Pure (*all-E*), (9*Z*) and (11*Z*) Isomers

Yajie Wang,[a] Wei Sein Woo,[a] Ineke van der Hoef,[a] and Johan Lugtenburg*[a]

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5-(2′,6′,6′-Trimethyl-1′-cyclohexen-1′-yl)-4-penten-2-yn-1-al has been prepared in a one-pot process starting from β-ionone in almost quantitative yield. Using 1,4-nucleophilic addition reactions, the corresponding 9-Cl, 9-Br, 9-I β-ionylideneacetaldehyde systems could be obtained in one step in quantitative yield as a mixture of (9Z) and (*all-E*) isomers. Even the corresponding fluoro derivative could be obtained in good yield as (9Z) and (*all-E*) isomers. In the case of a double bond having a halogen substituent, the IUPAC rules have the (*E*) nomenclature for a *cis* double bond and the (*Z*) for a *trans* double bond. Simple column chromatography gave the pure (9Z) and (*all-E*) form. Optimizing the Wadsworth–Emmons coupling gave the corresponding (*all-E*)- and (9Z)-retinonitriles in quantitative yield. Subsequent DIBAL-H reduction gave the corresponding retinals. For the preparation of the (11Z) isomers essential to vision, we found that Wadsworth–Emmons reactions with the diphenyl phosphonate group gave retinonitriles in quantitative yield, where the newly formed double bond is predominantly the (11Z) form (> 60%), together with the (9Z) isomer as minor component. The nitriles could be isolated in pure (9Z,11Z) and (9Z) forms by simple column chromatography. In the case of the (9Z,11Z)-9-demethyl-9-halo systems, a complication arose due to the unprecedented acid lability of these (9Z,11Z) aldehydes. By adjusting the DIBAL-H reduction workup procedure, these aldehydes are now available in pure form. We used this strategy to rationally synthesize (11Z)-retinal starting from β-cyclocitral as a first test for the generality of our new approach. β-Ionylideneacetaldehyde could be prepared in the (*all-E*) form in almost quantitative yield. Extending the conjugated chain of this molecule gave an almost quantitative yield of a mixture containing 80% (11Z)-retinal and 20% (*all-E*) as the minor component. Simple column chromatography gave pure (11Z)-retinal in 75% overall yield.

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. They are the major pharmaceutical targets for pharmacological intervention in human pathology. Recently we published a solid-state NMR study in which we established the charge distribution over each of the olefinic carbon atoms in the (11*Z*)-retinylidene chromophore,[5] together with the precise conformation of the central part of the chromophore.[6] This novel exquisite information with atomic resolution allows the study of the systems with rationally designed chemical changes in the chromophore. From the chemically modified rhodopsin studied thus far, 9-demethylrhodopsin shows properties that are very different from the native system. The $\lambda_{max.}$ value shows a drastic blue shift from 498 nm to 460 nm.[7,8] This system does not even form a signaling M_{II} intermediate.[9−11]

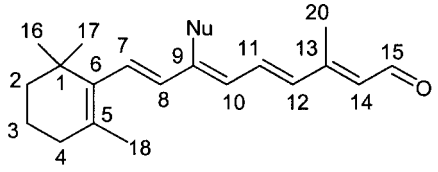
It is very surprising that rhodopsin in a rod in a fully dark-adapted eye upon excitation with only one photon gives a nerve signal that leads to the sense of vision in the brain. This response makes rhodopsin the most sensitive photoreceptor known, whereas the removal of the 9-methyl group in 9-demethyl rhodopsin leads to almost no receptor signal, even under intense light conditions.[9] This means that the 9-demethyl group has a pivotal role in the functioning of the receptor.[12,13]

We think that 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-iodorhodopsin may give so far unknown information about the steric and electronic factors of the 9-methyl group that contribute to its supreme role in photoreception. The F, Cl, Br and I substituents are spherical and differ in electronegativity and size. The F atom has the smallest van der Waals radius, not much bigger than that of hydrogen. The Br atom is about

[a] Leiden Institute of Chemistry, Leiden University, Gorlaeus Laboratories,
P. O. Box 9502, 2300 RA, Leiden, The Netherlands
Fax: (internat.) +31-71-5274488
E-mail: Lugtenbu@chem.leidenuniv.nl

the size of the 9-methyl group. The I atom is bigger than the 9-methyl group. By studying these rhodopsin derivatives, it is clear that we will get direct information about the role of size and electronegativity of the substituent on position 9. An additional advantage of the fluorine atom is the fact that ^{19}F has spin quantum number 1/2 with a high nuclear magnetic moment, which allows ^{19}F NMR studies of 9-demethyl-9-F-rhodopsin and its photochemical intermediates. The iodine atom has a high atomic weight, which allows efficient X-ray studies of the9-demethyl-9-iodo-rhodopsin and its photoproducts.

Thus far the synthesis of the (9*Z*) isomers (Figure 1) of 9-demethyl-9-F- [(9*Z*)-**1**], 9-Cl-9-demethyl- [(9*Z*)-**2**], 9-Br-9-demethyl- [(9*Z*)-**3**] and 9-demethyl-9-I-retinal [(9*Z*)-**4**] as well as the (*all-E*) isomer of 9-demethyl-9-F- [(*all-E*)-**1**], 9-Br-9-demethyl- [(*all-E*)-**3**] and 9-demethyl-9-I-retinal [(*all-E*)-**4**] have been published.[14,15] In the 9-demethyl-9-halo-retinal case, due to the high priority of halogens, the (*all-E*) system has the 9-*cis* retinal skeleton. The (9*Z*) has the *trans* retinal skeleton and (9*Z*,11*Z*) has the (11*Z*)-retinal carbon skeleton. The corresponding (11*Z*) isomers: (9*Z*,11*Z*)-**1**, (9*Z*,11*Z*)-**2**, (9*Z*,11*Z*)-**3**, (9*Z*,11*Z*)-**4**, as well as (*all-E*)-**2** (Scheme 1), which are essential for rhodopsin studies, are unknown. In general, the (9*Z*), (11*Z*) and (13*Z*) isomers of retinals are prepared via photochemistry of the (*all-E*) isomers in polar media. However, this method has at least three serious drawbacks. First of all, time-consuming preparative HPLC separation is necessary. In many cases the chromatographic properties are such that not all isomers can be obtained in pure form. In many cases the photostationary state is also dependent on the substitution pattern, such that not all mono *Z* derivatives are present in sufficient amount in the photostationary state.[16]



(9*Z*)-**1** Nu = F
(9*Z*)-**2** Nu = Cl
(9*Z*)-**3** Nu = Br
(9*Z*)-**4** Nu = I

Figure 1. Structures and numbering of (9*Z*)- 9-demethyl-9-fluoro-retinal [(9*Z*)-**1**], (9*Z*)-9-chloro-9-demethylretinal [(9*Z*)-**2**], and (9*Z*)-9- bromo-9-demethylretinal [(9*Z*)-**3**], (9*Z*)-9-demethyl-9-iodoretinal [(9*Z*)-**4**]

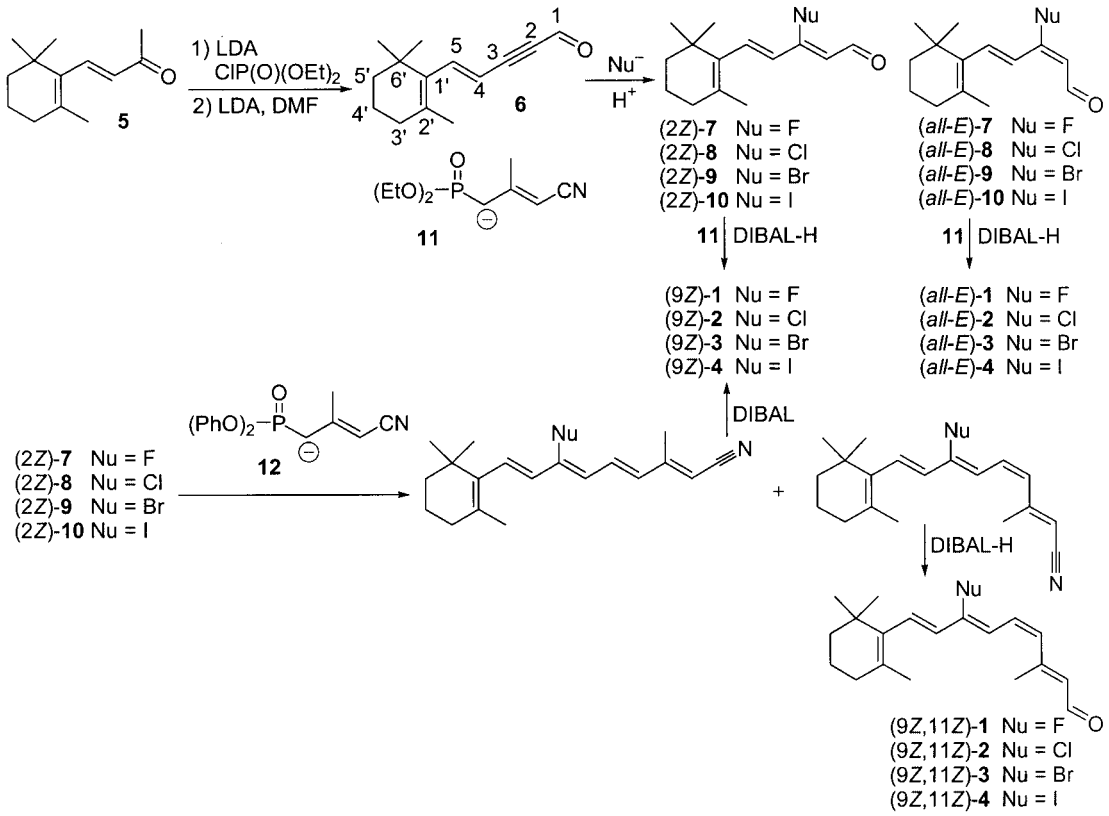
In this paper we describe a strategy in which the same starting material is used to prepare the required halogenated β-ionone derivative as mixtures of (*all-E*) and (9*Z*) isomers, which can be simply separated. These materials are used in a Wadsworth−Emmons coupling and final DIBAL-H reduction in such way that pure (*all-E*) and (9*Z*) isomers are formed via thermal chemistry only. We also describe a method to prepare the (9*Z*) and (11*Z*) isomer as part of approximately 2:1 mixtures of the (9*Z*,11*Z*) and (9*Z*) isomer, which can be simply separated via column chromatography.

Results and Discussion

For the preparation of the required 9-halogenated retinal systems, we worked out the reactions depicted in Scheme 1: A high-yield conversion of the methyl ketone function of β-ionone (**5**) into the corresponding acetylene compound has been published.[17] Recently an efficient extension of an acetylene into the α,β-unsaturated acetylenic aldehyde has been accomplished.[18] We have carried out this four-step procedure starting from β-ionone (**5**) into 5-(2′,6′,6′-trimethyl-1′-cyclohexen-1′-yl)-4-penten-2-yn-1-al (**6**) in one pot. After optimization, **6** was obtained in 97% yield (3.61 g, 17.9 mmol), starting from **5** (3.55 g, 18.5 mmol). The 2-yn-1-al **6** is a very versatile reagent, which is expected to be converted via a 1,4-nucleophilic addition reaction into an extended range of 9-substituted β-ionylideneacetaldehyde systems. Treatment of **6** with LiCl, LiBr and LiI respectively in acetic acid at 70 °C leads to complete conversion. The (*all-E*) and (9*Z*) mixtures of **8**, **9**, and **10** were obtained, which via simple chromatography gave (*all-E*)-**8**, (*all-E*)-**9**, (*all-E*)-**10**, (2*Z*)-**8**, (2*Z*)-**9**, and (2*Z*)-**10** in pure form. Similar treatment with LiF gave only the starting material **6**. Tetrabutylammonium dihydrogen trifluoride in 1,2-dichloroethane at 83 °C reacts with the starting α,β-unsaturated acetylenic aldehyde to the corresponding fluoro compounds.[19] After column chromatography (30% hexane in dichloromethane as eluent), the first fraction is the unchanged starting material **6**, the second fraction is (*all-E*)-**7** mixed with (2*Z*)-**8**, and the third fraction is pure (2*Z*)-**7**. The (*all-E*)-**7** could be isolated in pure form via preparative HPLC. The (*all-E*)-**8** and (2*Z*)-**8** are the result of Cl^- addition to **6**. The source of Cl^- is presumably the 1,2-dichloroethane solvent, which undergoes a thermal HCl elimination induced by the $H_2F_3^-$ ion. Reaction of Cl^- with **6** should give (2*Z*)-**8** besides (*all-E*)-**8**. ^1H NMR spectroscopy of the reaction mixture before chromatography establishes the presence of both (*all-E*)-**8** and (2*Z*)-**8**.

The β-ionylideneacetylaldehydes can be converted into the required retinals by Wadsworth−Emmons condensation with the anion of 4-(diethoxyphosphoryl)-3-methylbut-2-enenitrile (**11**) and subsequent DIBAL-H reduction of the resulting retinonitriles. In general, complex isomeric mixtures are obtained with the (*all-E*) isomer as the main component and the absence of the required (11*Z*) isomer. We reasoned that this complexity may arise in various ways. First, the anion **11** is prepared as an (*E*) and (*Z*) isomeric mixture giving at least two products, namely the (*all-E*)- and the (13*Z*)-retinal isomers. Second, the fact that both the starting aldehyde and the product nitrile may undergo base-induced *E*/*Z* isomerization[20,21] could also lead to the formation of isomers.

Using the following protocol, we aimed to prepare a single retinal isomer in the Wadsworth−Emmons coupling. 4-(Diethoxyphosphoryl)-3-methylbut-2-enenitrile, the precur-



Scheme 1. The preparation of 9-demethyl-9-halo-retinal in the pure (*all-E*,9*Z*) and (9*Z*,11*Z*) isomeric forms

sor of anion **11**, has been prepared by an efficient strategy that we have described before.[22,23] 4-(Diethoxyphosphoryl)-3-methylbut-2-enenitrile in THF is first treated at −80 °C with a little less than one equivalent of LDA resulting in the anion **11** (as an *E*,*Z* mixture) without any residual trace of LDA. We hoped that at higher temperature the isomeric mixture of the anions should form the thermodynamically most stable (*all-E*) isomer **11** only (Scheme 1). This expectation is based on the fact that **11** has a 1,3-disubstituted allylic anion structure, with a low activation barrier for the *E*/*Z* isomerization. The temperature of the solution was brought to −20 °C and kept at that temperature for 2 h; afterwards one equivalent of respectively (2*Z*)-**7**, (2*Z*)-**8**, (2*Z*)-**9** or (2*Z*)-**10** was added. After the reaction was finished a DIBAL-H reduction was effected. In each case the required (9*Z*) isomer could be obtained in almost quantitative yield, which after column chromatography give the pure (9*Z*) isomer. It is clear that the changes in the protocol for the Wadsworth−Emmons condensation led to the fundamental improvement, such that an almost quantitative yield pure (9*Z*) isomer was obtained. In a similar fashion, the pure (*all-E*) isomer was obtained via the same protocol starting from respectively (*all-E*)-**7**, (*all-E*)-**8**, (*all-E*)-**9** or (*all-E*)-**10**. The analytical data of (9*Z*)-**1**, (9*Z*)-**2**, (9*Z*)-**3**, (9*Z*)-**4**, (*all-E*)-**1**, **3** and (*all-E*)-**4** are in complete agreement with those prepared via other schemes.[14,15] The (*all-E*)-**2** is a new system. The 9-*cis* structure could be determined from ^{1}H NMR spectroscopy. The system showed a NOE between 8-H and 11-H in (*all-E*)-**2** in agreement with the expected *trans* structure for (*all-E*)-**2**. It is clear that from a Wadsworth−Emmons reaction with the diethyl phosphonate at −20 °C, the newly formed carbon−carbon double bond is only (*E*) within experimental error. Our changed protocol, in a simple way involving thermal reactions, leads to either only the (*all-E*) isomer or only the (9*Z*) isomer in pure form after simple column chromatography. The Wadsworth−Emmons condensation with the anion having two trifluoroethyl ester groups instead of two ethyl groups in **11** gives mixtures containing (11*Z*)-retinoids.[24,25] However, this type of Wadsworth−Emmons reagents is difficult to prepare.[26] We elected to prepare the corresponding diphenyl phosphonate system. Recently it has been found that in simple systems Wadsworth−Emmons coupling leads to predominately the formation of a new double bond in the (*Z*) configuration.[27] To obtain the diphenyl phosphonate system, we treated 4-chloro-3-methylbut-2-enenitrile with diphenyl methyl phosphite in an Arbuzov reaction. Diphenyl methyl phosphite was prepared via a simple literature procedure.[28] This system was converted into anion **12** by treating it with a little less than one equivalent of NaH in THF at −5 °C. After anion formation was complete, one equivalent of (2*Z*)-**7**, (2*Z*)-**8**, (2*Z*)-**9** or (2*Z*)-**10**, respectively, was added. These reactions resulted in complete conversion into a mixture of (9*Z*)- and (9*Z*)-retinoni-

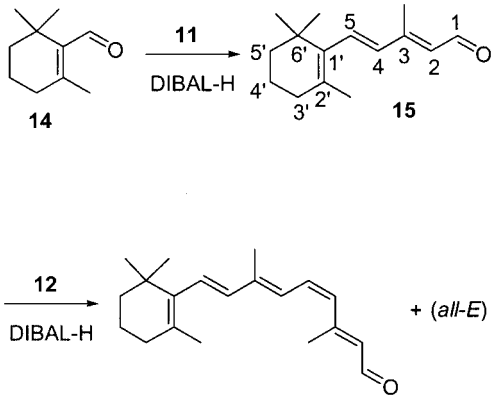
triles with the (9*Z*,11*Z*) form as the major isomer. The (11*Z*):(9*Z*) ratio for the fluoro derivative is 6:4, for the chloro 7:3, for the bromo 9:1 and for the iodo system 7:3. It is striking that such high percentages of (11*Z*) isomers are obtained. Simple chromatographic separation on silica gel in the presence of 20% diethyl ether in petroleum ether with a few drops of triethylamine gave the (9*Z*) and (9*Z*,11*Z*)-retinonitriles in pure form. Subsequent DIBAL-H reduction of the (9*Z*,11*Z*) isomers gave pure (9*Z*)-**1**, (9*Z*)-**2**, (9*Z*)-**3** and (9*Z*)-**4** only. We attributed this result to the extreme acid sensitivity of the (11*Z*) isomers. More rapid workup gave (9*Z*) and (9*Z*,11*Z*) mixtures, where *E*/*Z* isomerization has not gone to completion. Next we carried out the workup after DIBAL-H reduction with wet basic aluminum oxide. Using this procedure, we could obtain (9*Z*,11*Z*)-**1**, (9*Z*,11*Z*)-**2**, (9*Z*,11*Z*)-**3** and (9*Z*,11*Z*)-**4** in pure form. The ^{1}H and ^{13}C NMR spectroscopy of the (11*Z*) isomers had to be carried out in tetradeuterated methanol, because in either $CDCl_3$ or CD_2Cl_2, traces of acid present are sufficient to effect the acid catalyzed *E*/*Z* isomerization of (9*Z*,11*Z*)-**1**, (9*Z*,11*Z*)-**2**, (9*Z*,11*Z*)-**3** and (9*Z*,11*Z*)-**4**. It is interesting to observe that the corresponding (9*Z*,11*Z*) nitriles are less acid sensitive than the corresponding aldehydes. The (11*Z*) structure was established for each system by the value of the $^{3}J_{11\text{-}H,12\text{-}H}$ coupling constant. They are 12.2 Hz for (9*Z*,11*Z*)-**1**, 11.3 Hz for (9*Z*,11*Z*)-**2**, 11.4 Hz for (9*Z*,11*Z*)-**3** and 11.2 Hz for (9*Z*,11*Z*)-**4**, all of which lie within the range for double-bond (*Z*) couplings.

The discovery that Wadsworth−Emmons reagents **11** and **12** at higher temperatures are converted into the (*all-E*) system without traces of isomeric forms, allowed us to prepare both the (*all-E*) and the (9*Z*) isomers in almost quantitative yield. Using the diphenyl phosphonate **12** in a similar way gave mixtures of (9*Z*,11*Z*)- and (9*Z*)-retinoids with more than 60% of the (9*Z*,11*Z*) present. In the case of our target systems of the 9-demethyl-9-halo derivatives, a complication arose due to the extreme acid sensitivity of the required (9*Z*,11*Z*)-9-demethyl-9-halo-retinals. We could easily prepare the required (9*Z*,11*Z*)-retinals by a prior simple column separation at the retinonitrile stage. Subsequent adjustment of the DIBAL-H reduction procedure gave the expected (9*Z*,11*Z*)-retinals. This result shows that using Wadsworth−Emmons reactions with diphenyl phosphonate reagents gives a two-component mixture with the (9*Z*,11*Z*) component as the main isomer (60% or more) and the (9*Z*) isomer as minor component, which could be separated by simple column chromatography.

The schemes to prepare **6** and **11** or **12** will allow easy ^{13}C isotope incorporation, which means that there is no limitation to the preparation of any ^{13}C isotopomer up to unitary ^{13}C incorporation of any (*all-E*,9*Z*)- and (11*Z*)-retinoids prepared via these schemes. In this way solid-state ^{1}H NMR and ^{13}C NMR studies as mentioned for rhodopsin can now easily be extended to rhodopsins and isorhodopsins with chemically modified chromophores.

It is especially gratifying that now for the first time (11*Z*)-retinoids can be simply prepared via thermal reactions with simple column separation, without the difficult preparative HPLC separation of complex mixtures resulting from photochemical conversions.

To test if these improvements could also be applied for the simple high-yield preparation of (11*Z*)-[^{13}C-20]retinal, we treated β-cyclocitral (**14**, Scheme 2) at +20 °C with the diethyl phosphonate **11**. This results in pure (*all-E*)-β-ionylideneacetonitrile, which has been subsequently converted into (*all-E*)-β-ionylideneacetaldehyde (**15**). The latter molecule was treated with the diphenyl phosphonate **12**, which was formed at +20 °C. The resulting mixture of retinonitrile was (11*Z*) and (*all-E*), with more than 80% of (11*Z*). Simple column chromatography gave pure (11*Z*)-retinal in 75% overall yield starting from β-cyclocitral. This method is an important improvement for the preparation of (11*Z*)-[$^{13}C_{20}$]retinal compared to our earlier method.[23] It also means that (11*Z*)-retinal can now be prepared via a few simple chemical steps. In this way, the barriers for obtaining this essential (11*Z*) isomer for rhodopsin studies have been removed.



Scheme 2. The preparation of (11*Z*)-retinal starting from β-cyclocitral

Recently Nakanishi's group published an efficient synthesis of (11*Z*)-retinoids,[29] based on the semi-hydrogenation of 11-yne retinoid precursors with Cu/Ag-activated zinc dust. They also discussed all previous methods of obtaining (11*Z*)-retinoids.[24,30,31] Compared to the method in this paper, the drawback of this beautiful work is the fact that many more chemical steps are necessary. In some cases, the (11*Z*) form is mixed with up to 7% of the (*all-E*) isomer. Although the amount of (11*Z*) isomer is higher than in our case, column chromatography is still necessary. In their case the penultimate system is the (11*Z*)-retinol, which in some cases cannot easily be converted into the required (11*Z*)-retinal. In our strategy, the (11*Z*) nitrile is the penultimate intermediate, which can be quantitatively converted into the required aldehyde by simple DIBAL-H reduction. Thus far we have not found an (11*Z*) nitrile system that cannot easily be converted into the corresponding (11*Z*)-retinal. The strategy described in this paper also leads to easy introduction of ^{13}C isotopes at any position.

Conclusion

5-(2′,6′,6′-trimethyl-1′-cyclohexen-1′-yl)-4-penten-2-yn-1-al (**6**) has been prepared in a one-pot reaction in almost quantitative yield from β-ionone. Simple 1,4-nucleophilic addition reactions lead to quantitative yields of (*all-E*)-and (2*Z*)-3-chloro-, 3-bromo-, and 3-iodo-β-ionylideneacetaldehydes. Even the corresponding fluoro derivatives could be obtained in good yield. It is to be expected that the 1,4 nucleophilic reactions with **6** have a wide scope for the simple preparation of many new chemically modified β-ionylideneacetaldehydes. Using Wadsworth−Emmons coupling of these systems under careful conditions led to the formation of either the (9*Z*) or the (9*Z*,11*Z*) isomeric chemically modified retinonitriles and retinals. This means that we found the conditions under which Wadsworth−Emmons coupling gives only the (*E*) isomer of the newly formed double bond without changing the integrity of the double bonds present in the reagents or in the final product.

We think that this strategy will be very useful to obtain well-defined products, where Wadsworth−Emmons couplings are used. In this way, many isomeric retinoids and carotenoids will be accessible in a simple way. An important factor in this synthetic scheme is the fact that nitrile-containing Wadsworth−Emmons reagents are converted completely at higher temperature into the (*all-E*)-structure. It seems that the stereoelectronic properties of the nitrile substituent are essential, because there are papers in the literature describing cases in which the corresponding methyl esters led to thermodynamic equilibria in which both the (*Z*) and the (*E*) Wadsworth−Emmons reactions participate in comparable amounts.[32] In the case of stabilized Wadsworth−Horner reagents, the newly formed double bond is always (*E*), in agreement with the facts described above. However, changing the diethyl phosphonate group for the bis-trifluoroethylphosphonate groups leads to a situation in which the newly formed double bond is a mixture of both (*Z*) and (*E*).[24] We decided to prepare the diphenyl phosphonate reagents, which gave products with more than 60% of (9*Z*,11*Z*) isomer in the mixture with 40% or less (9*Z*) isomer. By treating (*all-E*)-β-ionylideneacetaldehyde, we could prepare normal (11*Z*)-retinal in about 80% yield. We feel this has great scope for the preparation of novel (11*Z*)-retinoids in a simple fashion. This is an important breakthrough in visual pigment research, because both (11*Z*)- and (9*Z*)-retinal (9*Z*,11*Z*) and (*all-E*) for the 9-demethyl-9-halo-retinal) isomers can now be obtained via simple chemical steps. Many biologically important retinoids have other functional groups besides aldehydes and nitriles. It is clear that our strategy only works for the retinonitriles as primary products of the synthesis. The nitriles can almost quantitatively be converted into the corresponding aldehydes without changing the structure of the polyene part. The aldehydes can easily be converted into other functional groups without changing the polyene part. Thus the corresponding alcohols, acids, esters, etc. are also accessible in a very simple 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 in a dry nitrogen atmosphere, unless aqueous conditions were used. Commercially available starting materials, methyl dichlorophosphite, β-ionone, lithium chloride, lithium bromide and lithium iodide, were purchased from Sigma Aldrich. Tetrabutylammonium dihydrogen trifluoride was purchased from Acros. All of these were used without further purification, unless stated otherwise. In all cases, the chemically pure or higher quality of the chemicals was used. Petroleum ether refers to the distillate with boiling range 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 with sodium wire. Dry diisopropylamine, dimethylformamide and dichloromethane were prepared by distilling from freshly ground calcium hydride and stored on 4-Å molecular sieves. Silica-gel column chromatography was performed using Merk silica gel 60 (0.040−0.063 mm, 230−400 mesh). HPLC purification was performed on a LKB Bromma system using a preparative Zorbax silica gel column 21.2 mm × 25 cm (Du Pont, Delaware). The eluent was hexane/diethyl ether (97:3, v/v). ^{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 (resonance at $\delta = 3.30$ 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 of the deuterated methanol which resonates at $\delta = 49.00$ ppm or with deuterated chloroform ($\delta = 77.0$ ppm). ^{19}F NMR spectra were recorded using a Bruker DMX-400 spectrometer operating at 376.0 MHz and were internally referenced to the fluorine of $CFCl_3$ ($\delta = -119.2$ ppm). UV/Vis spectra were recorded with a PE-Lambda 900 spectrophotometer.

5-(2′,6′,6′-Trimethyl-1′-cyclohexen-1′-yl)-4-penten-2-yn-1-al (6): Freshly distilled β-ionone (5.36 g, 27.9 mmol) in freshly distilled dry THF (10 mL) was added dropwise at −78 °C to a solution of LDA prepared from freshly distilled diisopropylamine (3.1 g, 30.7 mmol) and *n*-butyllithium (17.6 mL, 1.6 M in hexane) in THF (100 mL). After stirring and maintaining the temperature for 1 h, freshly distilled diethyl chlorophosphate (4.0 mL, 28 mmol) was added and the resulting mixture was warmed to room temperature over 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 through a cannula at −78 °C. After stirring for 1 h, freshly distilled dry DMF (2.3 mL, 30.0 mmol) was added in one portion and the resulting mixture was warmed to room temperature gradually. The reaction solution 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 3.6 g (97%) of the desired product **6**. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.06$ (s, 6 H, 2 × 6′-CH_3), 1.45 (m, 2 H, 5′-H), 1.60 (m, 2 H, 4′-H), 1.77 (s, 3 H, 2′-CH_3), 2.07 (m, 2 H, 3′-H), 5.67 (d, $^3J_{5\text{-H},4\text{-H}} = 16.4$ Hz, 1 H, 5-H), 7.05 (d, $^3J_{4\text{-H},5\text{-H}} = 16.4$ Hz, 1 H, 4-H), 9.32 (s, 1 H, 1-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, $CDCl_3$): $\delta = 18.7$ (C-4′),

21.5 (2′-CH_3), 28.6 (2 × 6′-CH_3), 34.0 (C-6′), 33.5 (C-3′), 39.6 (C-5′), 89.5 (C-2), 96.0 (C-3), 108.2 (C-8), 136.0 (C-2′), 136.7 (C-5), 149.2 (C-1′), 176.4 (C-1) ppm.

3-Fluoro-5-(2′,6′,6′-trimethyl-1′-cyclohexen-1′-yl)penta-2,4-dien-1-al [(*all-E*)-7 and (2*Z*)-7]: A solution of **6** (300 mg, 1.5 mmol) in 1,2-dichloroethane (10 mL) was added to tetrabutylammonium dihydrogen fluoride (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 for 6 h, under argon. After cooling to room temperature, 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 **6**, the second is (*all-E*)-**7** mixed with (2*Z*)-**8**, the third fraction is pure (2*Z*)-**7**. The (*all-E*)-**7** could be isolated in pure form by preparative HPLC. The total amount of (*all-E*)-**7** and (2*Z*)-**7** is 246 mg (75%).

(2*Z*)-7: ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.02 (s, 6 H, 2 × 6′-CH_3), 1.68 (m, 2 H, 5′-H), 1.73 (m, 2 H, 4′-H), 1.81 (s, 3 H, 2′-CH_3), 2.08 (m, 2 H, 3′-H), 5.43 (dd, $^3J_{2\text{-H},1\text{-H}}$ = 7.98, $^3J_{2\text{-H},3\text{-F}}$ = 33.1 Hz, 1 H, 2-H), 6.00 (dd, $^3J_{4\text{-H},5\text{-H}}$ = 16.5, $^3J_{4\text{-H},3\text{-F}}$ = 25.4 Hz, 1 H, 4-H), 7.09 (d, $^3J_{5\text{-H},4\text{-H}}$ = 16.5 Hz, 1 H, 5-H), 10.07 (d, $^3J_{1\text{-H},2\text{-H}}$ = 7.98 Hz, 1 H, 1-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, $CDCl_3$): δ = 19.1 (C-4′), 22.7 (2′-CH_3), 31.0 (C-2 and 6′-CH_3), 35.1 (C-3′), 35.2 (C-6′), 39.0 (C-5′), 109.5 (d, $^2J_{C2,3\text{-F}}$ = 6.4 Hz, C-2), 121.4 (d, $^2J_{C4,3\text{-F}}$ = 18.6 Hz, C-4), 136.8 (C-2′), 137.2 (C-1′), 138.8 (dd, $^3J_{C5,3\text{-F}}$ = 4.7 Hz, C-5), 170.3 (d, $^1J_{C3,3\text{-F}}$ = 275.5 Hz, C-3), 188.7 (d, $^3J_{C1,3\text{-F}}$ = 11.2 Hz, C-1) ppm. ^{19}F NMR (376.0 MHz, $CFCl_3$): δ = −110.5 (dd, $^3J_{3\text{-F},4\text{-H}}$ = 25.4, $^3J_{3\text{-F},2\text{-H}}$ = 33.9 Hz, F-3) ppm. UV/Vis: $\lambda_{max.}$ = 328 nm (*n*-hexane).

(*all-E*)-7: ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.07 (s, 6 H, 2 × 6′-CH_3), 1.50 (m, 2 H, 5′-H), 1.56 (s, 3 H, 2′-CH_3), 1.62 (m, 2 H, 4′-H), 2.09 (m, 2 H, 3′-H), 5.75 (dd, $^3J_{2\text{-H},1\text{-H}}$ = 7.2, $^3J_{2\text{-H},3\text{-F}}$ = 18.3 Hz, 1 H, 2-H), 6.74 (dd, $^3J_{4\text{-H},5\text{-H}}$ = 16.0, $^3J_{4\text{-H},3\text{-F}}$ = 27.4 Hz, 1 H, 4-H), 7.09 (d, $^3J_{5\text{-H},4\text{-H}}$ = 16.0 Hz, 1 H, 5-H), 9.94 (dd, $^3J_{1\text{-H},12\text{-H}}$ = 7.2, $^4J_{1\text{-H},3\text{-F}}$ = 3.5 Hz, 1 H, 1-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, $CDCl_3$): δ = 18.3 (C-4′), 20.6 (2′-CH_3), 30.0 (C-2 and 6′-CH_3), 34.2 (C-6′), 34.2 (C-3′), 38.0 (C-5′), 109.0 (d, $^2J_{C4,3\text{-F}}$ = 21.2 Hz, C-4), 118.0 (d, $^2J_{C2,3\text{-F}}$ = 17.4 Hz, C-2), 137.0 (C-2′), 137.2 (C-1′), 139.0 (d, $^3J_{C5,3\text{-F}}$ = 7.55 Hz, C-5), 165.2 (d, $^1J_{C3,3\text{-F}}$ = 267.6 Hz, C-3), 188.9 (d, $^3J_{C1,3\text{-F}}$ = 11.04 Hz, C-1) ppm. ^{19}F NMR (376.0 MHz, $CFCl_3$): δ = −94.41 (ddd, $^3J_{3\text{-F},4\text{-H}}$ = 27.4, $^3J_{3\text{-F},2\text{-H}}$ = 18.4, $^4J_{3\text{-F},1\text{-H}}$ = 3.39 Hz, F-3) ppm. UV/Vis: $\lambda_{max.}$ = 316 nm (*n*-hexane).

(9*Z*)-9-Demethyl-9-fluororetinal [(9*Z*)-1]: A solution of 4-(diethoxyphosphoryl)-3-methyl-2-butenenitrile (**11**) (126 mg, 0.58 mmol) in THF (5 mL) was added at −80 °C to a solution of LDA prepared from diisopropylamine (57.6 mg, 0.57 mmol) and *n*-butyllithium (350 μL, 1.6 M in hexane) in THF (10 mL). The reaction mixture was warmed gradually to −20 °C and was maintained at that temperature for about 2 h. (2*Z*)-**7** (130 mg, 0.59 mmol) in THF (5 mL) was added to the anion solution via a syringe. The resulting solution was stirred for a further 3 h. The temperature was allowed to rise gradually to room temperature; 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 (9*Z*)-9-fluororetinonitrile (160 mg, 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. DIBAL-H (1.4 mL, 1.0 M in hexane) was added. The resulting mixture was warmed to −40 °C over 1 h. Subsequently, homogeneous wet silica gel (2.5 g; water/silica, 1:9, g/g) was added and stirring was continued for 1 h at 0 °C. The mixture was dried by adding Na_2SO_4, then all solids were filtered off and thoroughly washed with diethyl ether. The organic solvent was evaporated and the residue was purified by column chromatography. This procedure gave the (9*Z*) isomer (160 mg, quantitative yield).

(9*Z*)-1: ^{1}H NMR (300.1 MHz, CD_3OD): δ = 1.04 (s, 6 H, 16-H and 17-H), 1.54 (m, 2 H, 2-H), 1.76 (s, 3 H, 18-H), 2.06 (m, 2 H, 4-H), 2.26 (s, 3 H, 20-H), 5.78 (dd, $^3J_{10\text{-H},11\text{-H}}$ = 11.1, $^3J_{10\text{-H},9\text{-F}}$ = 33.6 Hz, 1 H, 10-H), 5.94 (d, $^3J_{14\text{-H},15\text{-H}}$ = 8.0 Hz, 1 H, 14-H), 6.03 (dd, $^3J_{8\text{-H},7\text{-H}}$ = 16.4, $^3J_{8\text{-H},9\text{-F}}$ = 26.4 Hz, 1 H, 8-H), 6.67 (d, $^3J_{7\text{-H},8\text{-H}}$ = 16.4 Hz, 1 H, 7-H), 6.47 (d, $^3J_{12\text{-H},11\text{-H}}$ = 15.4 Hz, 1 H, 12-H), 7.19 (dd, $^3J_{11\text{-H},10\text{-H}}$ = 11.1, $^3J_{11\text{-H},12\text{-H}}$ = 15.4 Hz, 1 H, 11-H), 10.17 (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 = 13.0 (C-20), 20.1 (C-3), 21.9 (C-18), 29.3 (C16 and C17), 34.3 (C-4), 35.2 (C-1), 40.9 (C-2), 110.7 (d, $^2J_{C10,9\text{-F}}$ = 12.9 Hz, C-10), 124.70 (d, $^2J_{C8,9\text{-F}}$ = 20.52 Hz, C-8), 129.8 (d, $^3J_{C11,9\text{-F}}$ = 5.53 Hz, C-11), 130.3 (d, $^6J_{C14,9\text{-F}}$ = 2.7 Hz, C-14), 132.15 (d, $^3J_{C7H,9\text{-F}}$ = 3.9 Hz, C-7), 134.0 (C-5), 135.5 (C-12), 137.9 (C-6), 157.3 (C-13), 160.8 (d, $^1J_{9\text{-H},9\text{-F}}$ = 262 Hz, C-9), 193.5 (C-15) ppm. ^{19}F NMR (376.0 MHz, $CFCl_3$): δ = −119.2 (dd, $^3J_{9\text{-F},8\text{-H}}$ = 26.3, $^3J_{9\text{-F},10\text{-F}}$ = 33.8 Hz, F-9) ppm.

(*all-E*)-9-Demethyl-9-fluororetinal [(*all-E*)-1]: The general procedure was repeated as described for the preparation of (9*Z*)-**1** using 4-(diethoxyphosphoryl)-3-methyl-2-butenenitrile (62.9 mg, 0.29 mmol), LDA prepared from diisopropylamine (28.3 mg, 0.28 mmol), *n*-butyllithium (169 μL, 1.6 M in hexane), (*all-E*)-**7** (66 mg, 0.30 mmol) and DIBAL-H (0.68 mL, 1.0 M in hexane). This procedure gave a total yield of 75 mg (96%) of the desired product of (*all-E*)-**1** isomer.

(*all-E*)-1: ^{1}H NMR (300.1 MHz, CD_3OD): δ = 1.03 (s, 3 H, 16-H) 1.01 (s, 3 H, 17-H), 1.51 (m, 2 H, 2-H), 1.64 (m, 2 H, 3-H), 1.67 (s, 3 H, 18-H), 2.06 (m, 2 H, 4-H), 2.16 (s, 3 H, 20-H), 5.93 (d, $^3J_{14\text{-H},15\text{-H}}$ = 8.1 Hz, 1 H, 14-H), 6.00 (dd, $^3J_{10\text{-H},11\text{-H}}$ = 11.7, $^3J_{10\text{-H},9\text{-F}}$ = 9.3 Hz, 1 H, 10-H), 6.30 (d, $^3J_{7\text{-H},8\text{-H}}$ = 15.2 Hz, 1 H, 7-H), 6.64 (dd, $^3J_{8\text{-H},7\text{-H}}$ = 15.6, $^3J_{8\text{-H},9\text{-F}}$ = 19.6 Hz, 1 H, 8-H), 6.76 (d, $^3J_{12\text{-H},11\text{-H}}$ = 15.4 Hz, 1 H, 12-H), 7.07 (dd, $^3J_{11\text{-H},10\text{-H}}$ = 11.9, $^3J_{11\text{-H},12\text{-H}}$ = 15.4 Hz, 1 H, 11-H), 10.04 (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 = 19.1 (C-20), 20.0 (C-3), 21.8 (C-18), 29.2 (C16 and C17), 34.2 (C-4), 35.1(C-1), 40.8 (C-2), 110.2 (d, $^2J_{C10,9\text{-F}}$ = 12.4 Hz, C-10), 124.5 (d, $^2J_{C8,9\text{-F}}$ = 19.8 Hz, C-8), 129.1 (d, $^3J_{C7,9\text{-F}}$ = 3.9 Hz, C-7), 130.1 (d, $^3J_{C11,9\text{-F}}$ = 5.53 Hz, C-11), 132.1 (C-12), 131.3 (d, $^6J_{C14,9\text{-F}}$ = 2.7 Hz, C-14), 134.0 (C-5), 137.8 (C-6), 158.1 (C-13), 161.0 (d, $^1J_{C9,9\text{-F}}$ = 262 Hz, C-9), 193.4 (C-15) ppm. ^{19}F NMR (376.0 MHz, $CFCl_3$): δ = −119.5 (dd, $^3J_{9\text{-F},8\text{-H}}$ = 19.6, $^3J_{9\text{-F},10\text{-H}}$ = 19.3 Hz, F-9) ppm.

(9*Z*,11*Z*)-9-Demethyl-9-fluororetinal [(9*Z*,11*Z*)-1]: A solution of 4-(diphenoxyphosphoryl)-3-methyl-2-butenenitrile (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. (2*Z*)-**7** (86 mg, 0.39 mmol) in THF (5 mL) was added and stirring was continued at 0 °C for 1 h. After that the temperature was rised gradually to room temperature. The reaction mixture was quenched with satd. $NaHCO_3$. 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, g/g), filtered and concentrated in vacuo. The crude

product, which was a 6 to 4 mixture of (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 warmed to −40 °C over 1 h. Subsequently, homogeneous basic wet Al_2O_3 (1.2 g; Al_2O_3/water, 5:1, g/g) was added and stirring was continued for an additional 1 h at 0 °C. The mixture was dried by adding a mixture of K_2CO_3 and $MgSO_4$ (1:9, g/g). All solids were filtered off and thoroughly washed with diethyl ether. The organic solvent was evaporated and yielded (11*Z*) isomer (60 mg, 97%).

(9*Z*,11*Z*)-1: ^{1}H NMR (300.1 MHz, CD_3OD): δ = 1.04 (s, 6 H, 16-H and 17-H), 1.54 (m, 2 H, 2-H), 1.64 (m, 2 H, 3-H), 1.76 (s, 3 H, 18-H), 2.06 (m, 2 H, 4-H), 2.26 (s, 3 H, 20-H), 5.84 (d, $^3J_{14\text{-H},15\text{-H}}$ = 8.0 Hz, 1 H, 14-H), 5.98 (dd, $^3J_{10\text{-H},11\text{-H}}$ = 12.1, $^3J_{10\text{-H},9\text{-F}}$ = 27.2 Hz, 1 H, 10-H), 6.03 (dd, $^3J_{8\text{-H},7\text{-H}}$ = 16.2, $^3J_{8\text{-H},9\text{-F}}$ = 26.3 Hz, 1 H, 8-H), 6.15 (d, $^3J_{12\text{-H},11\text{-H}}$ = 12.2 Hz, 1 H, 12-H), 6.66 (d, $^3J_{7\text{-H},8\text{-H}}$ = 16.2 Hz, 1 H, 7-H), 6.69 (dd, $^3J_{11\text{-H},10\text{-H}}$ = 12.2, $^3J_{11\text{-H},12\text{-H}}$ = 12.2 Hz, 1 H, 11-H), 10.03 (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 = 13.0 (C-20), 20.1 (C-3), 21.9 (C-18), 29.3 (C16 and C17), 34.3 (C-4), 35.2 (C-1), 40.9 (C-2), 124.8 (d, $^2J_{C8,9\text{-F}}$ = 20.2 Hz, C-8), 126.1 (C-12), 127.1 (d, $^2J_{C10,9\text{-F}}$ = 7.34 Hz, C-10), 128.9 (d, $^3J_{C11,9\text{-F}}$ = 4.53 Hz, C-11), 130.32 (d, $^6J_{C14,9\text{-F}}$ = 2.61 Hz, C-14, 132.3 (d, $^3J_{C7,9\text{-F}}$ = 4.53 Hz, C-7), 133.9 (C-5), 137.9 (C-6), 157.3 (C-13), 160.0 (d, C-9, $^1J_{C9,9\text{-F}}$ = 268 Hz), 193.5 (C-15) ppm. ^{19}F NMR (376.0 MHz, $CFCl_3$): δ = −119.2 (dd, $^3J_{9\text{-F},8\text{-H}}$ = 26.3, $^3J_{9\text{-F},10\text{-H}}$ = 27.2 Hz, F-9) ppm.

3-Chloro-5-(2′,6′,6′-trimethyl-l′-cyclohexenyl)penta-2,4-dien-1-al [(*all-E*)-8 and (2*Z*)-8]: A solution of **6** (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 for 2 h at 70 °C and cooling to room temperature, the solvents were evaporated in vacuo. The crude product was purified via column chromatography (diethyl ether/petroleum ether, 3:97, v/v) to yield 358 mg, (94%) of the desired product as a 1 to 3 mixture of *E*/*Z* isomers.

(2*Z*)-8: ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.08 (s, 6 H, 2 × 6′-CH_3), 1.50 (m, 2 H, 5′-H), 1.64 (m, 2 H, 4′-H), 1.78 (s, 3 H, 2′-CH_3), 6.13 (d, $^3J_{2\text{-H},1\text{-H}}$ = 7.2 Hz, 1 H, 2-H), 6.30 (d, $^3J_{4\text{-H},5\text{-H}}$ = 15.4 Hz, 1 H, 4-H), 7.22 (d, $^3J_{5\text{-H},4\text{-H}}$ = 15.4 Hz, 1 H, 5-H), 10.18 (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 = 18.9 (C-4′), 21.7 (2′-CH_3), 28.8 (C-2 and 6′-CH_3) , 33.5 (C-3′), 34.2 (C-6′), 39.6 (C-5′), 125.2 (C-2), 128.5 (C-5), 135.6 (C-2′), 136.4 (C-1′), 139.8 (C-5), 150.1 (C-3), 191.2 (C-1) ppm.

(*all-E*)-8: ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.09 (s, 6 H, 2 × 6′-CH_3), 1.50 (m, 2 H, 5′-H), 1.64 (m, 2 H, 4′-H), 1.80 (s, 3 H, 2′-CH_3), 2.09 (m, 2 H, 3′-H), 6.23 (d, $^3J_{2\text{-H},1\text{-H}}$ = 6.9 Hz, 1 H, 2-H), 7.13 (s, 1 H, 4-H), 7.13 (s, 1 H, 5-H), 9.99 (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 = 19.4 (C-4′), 22.6 (2′-CH_3), 28.9 (C-2 and 6′-CH_3), 33.5 (C-3′), 33.3 (C-6′), 39.8 (C-5′), 124.6 (C-2), 128.4 (C-4), 131.3 (C-2′), 138.5 (C-1′), 138.6 (C-5), 147.1 (C-3), 190.1 (C-1) ppm.

(9*Z*)-9-Chloro-9-demethylretinal [(9*Z*)-2]: The general procedure was repeated as described for the preparation of (9*Z*)-**1** using 4-(diethoxyphosphoryl)-3-methyl-2-butenenitrile (107.7 mg, 0.503 mmol), LDA prepared from diisopropylamine (49.8 mg, 0.493 mmol) and *n*-butyllithium (302 μL, 1.6 M in hexane), (2*Z*)-**8** (122 mg, 0.513 mmol) and DIBAL-H (1.3 mL, 1.0 M in hexane). This procedure gave a total yield of 141 mg (96%) of the desired product of the (9*Z*)-**2** isomer.

(9*Z*)-2: ^{1}H NMR (300.1 MHz, CD_3OD): δ = 1.05 (s, 6 H, 16-H and 17-H), 1.50 (m, 2 H, 2-H), 1.64 (m, 2 H, 3-H), 1.74 (s, 3 H, 18-H), 2.06 (m, 2 H, 4-H), 2.27 (s, 3 H, 20-H), 6.00 (d, $^3J_{14\text{-H},15\text{-H}}$ = 8.04 Hz, 1 H, 14-H), 6.31(d, $^3J_{8\text{-H},7\text{-H}}$ = 15.3 Hz, 1 H, 8-H), 6.58 (d, $^3J_{10\text{-H},11\text{-H}}$ = 10.8 Hz, 1 H, 10-H), 6.63 (d, $^3J_{12\text{-H},11\text{-H}}$ = 15.4 Hz, 1 H, 12-H), 6.77 (d, $^3J_{7\text{-H},8\text{-H}}$ = 15.2 Hz, 1 H, 7-H), 7.31 (dd, $^3J_{11\text{-H},10\text{-H}}$ = 10.7, $^3J_{11\text{-H},12\text{-H}}$ = 15.3 Hz, 1 H, 11-H), 10.1 (d, $^3J_{15\text{-H},14\text{-H}}$ = 8.04 Hz, 1 H, 15-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 13.0 (C-20), 20.2 (C-3), 20.2 (C-18), 29.4 (C16 and C17), 34.2 (C-4), 35.3 (C-1), 40.8 (C-2), 128.4 (C-14), 131.1 (C-8), 131.6 (C-10), 132.8 (C-11), 133.3 (C-5), 134.4 (C-7), 137.6 (C-9), 138.1 (C-6), 138.5 (C-12), 158.4 (C-13), 193.4 (C-15) ppm.

(*all-E*)-9-Chloro-9-demethylretinal [(*all-E*)-2]: The general procedure was repeated as described for the preparation of (9*Z*)-**1** using 4-(diethoxyphosphoryl)-3-methyl-2-butenenitrile (62.9 mg, 0.29 mmol), LDA prepared from diisopropylamine (28.3 mg, 0.28 mmol), and *n*-butyllithium (69 μL, 1.6 M in hexane), (*all-E*)-**8** (71.4 mg, 0.30 mmol) and DIBAL-H (0.68 mL, 1.0 M in hexane). This procedure gave a total yield of 79 mg (96%) of the desired product of (*all-E*)-**2** isomer.

(*all-E*)-2: ^{1}H NMR (300.1 MHz, CD_3OD): δ = 1.01 (s, 3 H, 17-H), 1.05 (s, 3 H, 16-H), 1.49 (m, 2 H, 2-H), 1.63 (m, 2 H, 3-H), 1.73 (s, 3 H, 18-H), 2.06 (m, 2 H, 4-H), 2.24 (s, 3 H, 20-H), 5.98 (d, $^3J_{14\text{-H},15\text{-H}}$ = 8.00 Hz, 1 H, 14-H), 6.43 (d, $^3J_{12\text{-H},11\text{-H}}$ = 14.6 Hz, 1 H, 12-H), 6.49 (d, $^3J_{10\text{-H},11\text{-H}}$ = 11.4 Hz, 1 H, 10-H), 6.76 (d, $^3J_{7\text{-H},8\text{-H}}$ = 15.2 Hz, 1 H, 7-H), 6.80 (d, $^3J_{8\text{-H},7\text{-H}}$ = 15.4 Hz, 1 H, 8-H), 7.15 (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, $^3J_{15\text{-H},14\text{-H}}$ = 8.11 Hz, 1 H, 15-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 13.1 (C-20), 20.2 (C-3), 22.1 (C-18), 29.4 (C16 and C17), 34.2 (C-4), 34.1 (C-1), 40.6 (C-2), 127.3 (C-8), 129.7(C-9), 131.1 (C-11), 131.2 (C-14), 133.4 (C-10), 137.9 (C-12), 138.1 (C-5), 138.2 (C-6), 138.6 (C-7), 156.7(C-13), 193.4 (C-15) ppm.

(9*Z*,11*Z*)-9-Chloro-9-demethylretinal [(9*Z*,11*Z*)-2]: The general procedure was repeated as described for the preparation of (9*Z*,11*Z*)-**1** using 4-(diphenoxyphosphoryl)-3-methyl-2-butenenitrile (122.1 mg, 0.39 mmol), sodium hydride (15 mg, 0.37 mmol) in THF (10 mL) and (2*Z*)-**8** (92.8 mg, 0.39 mmol). This procedure gave a 7:3 mixture of (9*Z*,11*Z*)- and (9*Z*)-retinonitrile isomers, after DIBAL-H reduction (0.65 mL, 1.0 M in hexane) of the pure (11*Z*)-nitrile to obtain pure (11*Z*)-retinal [76 mg, 97% (11*Z*)].

(9*Z*,11*Z*)-2: ^{1}H NMR (300.1 MHz, CD_3OD): δ = 1.04 (s, 6 H, 16-H and 17-H), 1.50 (m, 2 H, 2-H), 1.63 (m, 2 H, 3-H), 1.74 (s, 3 H, 18-H), 2.07 (m, 2 H, 4-H), 2.17 (s, 3 H, 20-H), 5.98 (d, $^3J_{14\text{-H},15\text{-H}}$ = 8.1 Hz, 1 H, 14-H), 6.19 (d, $^3J_{8\text{-H},7\text{-H}}$ = 15.2 Hz, 1 H, 8-H), 6.20 (d, $^3J_{7\text{-H},8\text{-H}}$ = 15.1 Hz, 1 H, 7-H), 6.39 (d, $^3J_{10\text{-H},11\text{-H}}$ = 11.4 Hz, 1 H, 10-H), 6.48 (d, $^3J_{12\text{-H},11\text{-H}}$ = 11.4 Hz, 1 H, 12-H), 6.93 (dd, $^3J_{11\text{-H},10\text{-H}}$ = 11.4, $^3J_{11\text{-H},12\text{-H}}$ = 11.5 Hz, 1 H, 11-H), 9.60 (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 = 20.7 (C-20), 20.9 (C-3), 21.9 (C-18), 29.4 (C16 and C17), 34.2 (C-4), 37.2 (C-1), 40.8 (C-2), 128.5 (C-14), 129.9 (C-8), 130.4 (C-12), 131.6 (C-11), 133.3 (C-5), 133.6 (C-10), 134.4(C-7), 138.1 (C-6), 156.4 (C-9), 159.4 (C-13), 192.3 (C-15) ppm.

3-Bromo-5-(2′,6′,6′-trimethyl-1′-cyclohexen-1′-yl)penta-2,4-dien-1-al [(*all-E*)-9 and (2*Z*)-9]: The reaction procedure was repeated as described for the preparation of (*all-E*)-**8** and (9*Z*)-**8** only now

using **6** (436 mg, 1.98 mmol), lithium bromide (343 mg, 3.96 mmol) and acetic acid (15 mL). The desired product was obtained (519 mg, 93%) as a 1:3 mixture of *E*/*Z* isomers.

(2*Z*)-9: ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.08 (s, 6 H, 2 × 6′-CH_3), 1.50 (m, 2 H, 5′-H), 1.63 (m, 2 H, 4′-H), 1.77 (s, 3 H, 2′-CH_3), 2.09 (m, 2 H, 3′-H), 6.28 (d, $^3J_{4\text{-H},5\text{-H}}$ = 15.1 Hz, 1 H, 4-H), 6.34 (d, $^3J_{2\text{-H},1\text{-H}}$ = 6.9 Hz, 1 H, 2-H), 7.22 (d, $^3J_{5\text{-H},4\text{-H}}$ = 15.1 Hz, 1 H, 5-H), 10.08 (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 = 18.9 (C-4′), 21.7 (2′-CH_3), 28.8 (C-2 and 6′-CH_3), 33.5 (C-3′), 34.2 (C-6′), 39.6 (C-5′), 127.4 (C-2), 129.8 (C-4), 135.6 (C-2′), 136.4 (C-1′), 141.4 (C-5), 143.1(C-3), 193.6 (C-1) ppm.

(*all-E*)-9: ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.09 (s, 6 H, 2 × 6′-CH_3), 1.49 (m, 2 H, 5′-H), 1.64 (m, 2 H, 4′-H), 1.80 (s, 3 H, 2′-CH_3), 2.01 (m, 2 H, 3′-H), 6.51 (d, $^3J_{2\text{-H},1\text{-H}}$ = 6.7 Hz, 1 H, 2-H), 7.05 (s, 1 H, 4-H), 7.05 (s, 1 H, 5-H), 9.93 (d, $^3J_{1\text{-H},2\text{-H}}$ = 6.7 Hz, 1 H, 1-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, $CDCl_3$): δ = 18.9 (C-4′), 21.8 (2′-CH_3), 28.9 (C-2 and 6′-CH_3), 33.6 (C-3′), 34.2 (C-6′), 39.6 (C-5′), 124.8 (C-2), 130.3 (C-4), 136.0 (C-2′), 136.6 (C-1′), 144.2 (C-5), 146.9 (C-3), 186.9 (C-1) ppm.

(9*Z*)-9-Bromo-9-demethylretinal [(9*Z*)-3]: The general procedure was repeated as described for the preparation of (9*Z*)-**1** now using 4-(diethoxyphosphoryl)-3-methyl-2-butenenitrile (109.7 mg, 0.503 mmol), LDA prepared from diisopropylamine (49.9 mg, 0.493 mmol) and *n*-butyllithium (302 μL, 1.6 M in hexane), (*all-E*)-**9** (145 mg, 0.513 mmol) and DIBAL-H (1.2 mL, 1.0 M in hexane). This procedure gave a total yield of 160 mg (95%) of the desired product of (9*Z*)-**3** isomer.

(9*Z*)-3: ^{1}H NMR (300.1 MHz, CD_3OD): δ = 1.05 (s, 6 H, 16-H and 17-H), 1.51 (m, 2 H, 2-H), 1.64 (m, 2 H, 3-H), 1.73 (s, 3 H, 18-H), 2.07 (m, 2 H, 4-H), 2.36 (s, 3 H, 20-H), 6.00 (d, $^3J_{14\text{-H},15\text{-H}}$ = 8.1 Hz, 1 H, 14-H), 6.26 (d, $^3J_{8\text{-H},7\text{-H}}$ = 15.1 Hz, 1 H, 8-H), 6.66 (d, $^3J_{12\text{-H},11\text{-H}}$ = 15.3 Hz, 1 H, 12-H), 6.74 (d, $^3J_{10\text{-H},11\text{-H}}$ = 10.4 Hz, 1 H, 10-H), 6.77 (d, $^3J_{7\text{-H},8\text{-H}}$ = 15.1 Hz, 1 H, 7-H), 7.28 (dd, $^3J_{11\text{-H},10\text{-H}}$ = 10.4, $^3J_{11\text{-H},12\text{-H}}$ = 15.3 Hz, 1 H, 11-H), 10.09 (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 = 13.0 (C-20), 20.2 (C-3), 22.0 (C-18), 29.4 (C16 and C17), 34.2 (C-4), 35.3 (C-1), 40.8 (C-2), 131.3 (C-10), 131.7 (C-14), 133.3 (C-9), 135.1 (C-11), 136.7 (C-7), 137.1 (C-8), 138.0 (C-5), 138.1 (C-6), 139.0 (C-12), 156.6 (C-13), 193.5 (C-15) ppm.

(*all-E*)-9-Bromo-9-demethylretinal [(*all-E*)-3]: The general procedure was repeated as described for the preparation of (9*Z*)-**1** using 4-(diethoxyphosphoryl)-3-methyl-2-butenenitrile (67 mg, 0.31 mmol), LDA prepared from diisopropylamine (30.3 mg, 0.30 mmol) and *n*-butyllithium (181 μL, 1.6 M in hexane), (*all-E*)-**9** (93.3 mg, 0.33 mmol) and DIBAL-H (0.73 mL, 1.0 M in hexane). This procedure gave a total yield of 93 mg (92%) of the desired product of (*all-E*)-**3** isomer.

(*all-E*)-3: ^{1}H NMR (300.1 MHz, CD_3OD): δ = 1.06 (s, 6 H, 16-H and 17-H), 1.50 (m, 2 H, 2-H), 1.65 (m, 2 H, 3-H), 1.77 (s, 3 H, 18-H), 2.07 (m, 2 H, 4-H), 2.33 (s, 3 H, 20-H), 6.00 (d, $^3J_{14\text{-H},15\text{-H}}$ = 8.1 Hz, 1 H, 14-H), 6.50 (d, $^3J_{12\text{-H},11\text{-H}}$ = 15.0 Hz, 1 H, 12-H), 6.65 (d, $^3J_{8\text{-H},7\text{-H}}$ = 15.1 Hz, 1 H, 8-H), 6.72 (d, $^3J_{7\text{-H},8\text{-H}}$ = 15.1 Hz, 1 H, 7-H), 6.76 (d, $^3J_{10\text{-H},11\text{-H}}$ = 11.5 Hz, 1 H, 10-H), 7.19 (dd, $^3J_{11\text{-H},10\text{-H}}$ = 11.7, $^3J_{11\text{-H},12\text{-H}}$ = 15.0 Hz, 1 H, 11-H), 10.06 (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 = 13.1 (C-20), 20.2 (C-3), 22.1 (C-18), 29.4 (C-16 and C-17), 34.2 (C-4), 34.1 (C-1), 40.6 (C-2), 127.3 (C-8), 129.7 (C-9), 131.1 (C-11), 131.2 (C-14), 133.4 (C-10), 137.9 (C-12), 138.1 (C-5), 138.2 (C-6), 138.6 (C-7), 156.7 (C-13), 193.4 (C-15) ppm.

(9*Z*,11*Z*)-9-Bromo-9-demethylretinal [(9*Z*,11*Z*)-3]: The general procedure was repeated as described for the preparation of (9*Z*,11*Z*)-**1** using 4-(diphenoxyphosphoryl)-3-methyl-2-butenenitrile (122 mg, 0.39 mmol), sodium hydride (15 mg, 0.37 mmol) in THF (10 mL) and (*all-E*)-**9** (111 mg, 0.39 mmol). This procedure gave a 9:1 mixture of (9*Z*,11*Z*)- and (9*Z*)-retinonitrile isomers, giving, after DIBAL-H reduction (0.93 mL, 1.0 M in hexane) of the pure (9*Z*,11*Z*) nitrile, pure (9*Z*,11*Z*)-retinal (122 mg, 97%).

(9*Z*,11*Z*)-3: ^{1}H NMR (300.1 MHz, CD_3OD): δ = 1.04 (s, 6 H, 16-H and 17-H), 1.50 (m, 2 H, 2-H), 1.62 (m, 2 H, 3-H), 1.73 (s, 3 H, 18-H), 2.06 (m, 2 H, 4-H), 2.36 (s, 3 H, 20-H), 5.98 (d, $^3J_{14\text{-H},15\text{-H}}$ = 8.0 Hz, 1 H, 14-H), 6.20 (d, $^3J_{12\text{-H},11\text{-H}}$ = 11.4 Hz, 1 H, 12-H), 6.25 (d, $^3J_{8\text{-H},7\text{-H}}$ = 15.2 Hz, 1 H, 8-H), 6.72 (d, $^3J_{7\text{-H},8\text{-H}}$ = 15.2 Hz, 1 H, 7-H), 6.76 (dd, $^3J_{11\text{-H},10\text{-H}}$ = 11.4, $^3J_{11\text{-H},12\text{-H}}$ = 11.4 Hz, 1 H, 11-H), 7.01 (d, $^3J_{10\text{-H},11\text{-H}}$ = 11.4 Hz, 1 H, 10-H), 10.03 (d, $^3J_{15\text{-H},14\text{-H}}$ = 8.0 Hz, 1 H, 15-H) ppm. ^{13}C NMR (5.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 17.8 (C-20), 20.2 (C-3), 22.0 (C-18), 29.4 (C-16 and C-17), 34.2 (C-4), 35.3 (C-1), 40.7 (C-2), 40.7 (C-2), 132.3 (C-14), 132.6 (C-9), 133.0 (C-11), 133.1 (C-8), 135.1 (C-12), 137.0 (C-7), 138.0 (C-5), 138.1 (C-6), 157.8 (C-13), 193.4 (C-15) ppm.

3-Iodo-5-(2′,6′,6′-trimethyl-1′-cyclohexen-1′-yl)penta-2,4-dien-1-al [(*all-E*)-10 and (2*Z*)-10]: The general procedure was repeated as described for the preparation of (*all-E*)-**8** and (2*Z*)-**8**. **6** (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 369 mg (94%) of the desired product as a 1:3 mixture of *E*/*Z* isomers.

(2*Z*)-10: ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.08 (s, 6 H, 2 × 6′-CH_3), 1.50 (m, 2 H, 5′-H), 1.63 (m, 2 H, 4′-H), 1.77 (s, 3 H, 2′-CH_3), 2.08 (m, 2 H, 3′-H), 5.96 (d, $^3J_{4\text{-H},5\text{-H}}$ = 14.9 Hz, 1 H, 4-H), 6.31 (d, $^3J_{2\text{-H},1\text{-H}}$ = 6.6 Hz, 1 H, 2-H), 7.11 (d, $^3J_{5\text{-H},4\text{-H}}$ = 14.9 Hz, 1 H, 5-H), 9.86 (d, $^3J_{1\text{-H},2\text{-H}}$ = 6.6 Hz, 1 H, 1-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, $CDCl_3$): δ = 18.9 (C-4′), 21.8 (C-CH_3–2′), 28.9 (C-2 and 6′-CH_3), 33.5 (C-3′), 34.3 (C-6′), 39.7 (C-5′), 131.6 (C-2), 132.7 (C-4), 135.6 (C-2′), 136.4 (C-1′), 145.4 (C-5), 147.9 (C-2), 197.6 (C-1) ppm.

(*all-E*)-10: ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.08 (s, 6 H, 2 × 6′-CH_3), 1.48 (m, 2 H, 5′-H), 1.61 (m, 2 H, 4′-H), 1.79 (s, 3 H, 2′-CH_3), 2.09 (m, 2 H, 3′-H), 6.59 (d, $^3J_{4\text{-H},5\text{-H}}$ = 15.0 Hz, 1 H, 4-H), 6.83 (d, $^3J_{5\text{-H},4\text{-H}}$ = 15.0 Hz, 1 H, 5-H), 6.87 (d, $^3J_{2\text{-H},1\text{-H}}$ = 6.6 Hz, 1 H, 2-H), 9.88 (d, $^3J_{1\text{-H},2\text{-H}}$ = 6.6 Hz, 1 H, 1-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, $CDCl_3$): δ = 18.9 (C-4′), 21.9 (C-CH_3–2′), 28.9 (C-2 and 6′-CH_3), 33.6 (C-3′), 34.3 (C-6′), 39.7 (C-5′), 127.7 (C-2), 128.3 (C-3), 136.1 (C-2′), 136.6 (C-1′), 138.7 (C-4), 148.0 (C-5), 186.2 (C-1) ppm.

(9*Z*)-9-Demethyl-9-iodoretinal [(9*Z*)-4]: The general procedure was repeated as described for the preparation of (9*Z*)-**1** using 4-(diethoxyphosphoryl)-3-methyl-2-butenenitrile (166 mg, 0.503 mmol), LDA prepared from diisopropylamine (50 mg, 0.493 mmol) and *n*-butyllithium (302 μL, 1.6 M in hexane), (2*Z*)-**10** (169 mg, 0.513 mmol) and DIBAL-H (1.2 mL, 1.0 M in hexane). This procedure gave a total yield of 182 mg (96%) of the desired product of (9*Z*)-**4** isomer.

(9*Z*)-4: ^{1}H NMR (300.1 MHz, CD_3OD): δ = 1.04 (s, 6 H, 16-H and 17-H), 1.50 (m, 2 H, 2-H), 1.66 (m, 2 H, 3-H), 1.76 (s, 3 H, 18-H), 2.06 (m, 2 H, 4-H), 2.36 (s, 3 H, 20-H), 5.92 (d, $^3J_{8\text{-H},7\text{-H}}$ = 15.0 Hz, 1 H, 8-H), 5.99 (d, $^3J_{14\text{-H},15\text{-H}}$ = 8.0 Hz, 1 H, 14-H), 6.65

(d, $^3J_{7\text{-H},8\text{-H}}$ = 15.0 Hz, 1 H, 7-H), 6.66 (d, $^3J_{10\text{-H},11\text{-H}}$ = 10.3 Hz, 1 H, 10-H), 6.71 (d, $^3J_{12\text{-H},11\text{-H}}$ = 15.2 Hz, 1 H, 12-H), 7.21 (dd, $^3J_{11\text{-H},10\text{-H}}$ = 10.4, $^3J_{11\text{-H},12\text{-H}}$ = 15.2 Hz, 1 H, 11-H), 10.1 (d, $^3J_{15\text{-H},14\text{-H}}$ = 8.0 Hz, 1 H, 15-H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 12.6 (C-20), 20.2 (C-3), 21.9 (C-18), 29.4 (C16 and C17), 34.2 (C-4), 35.3 (C-1), 40.7 (C-2), 131.1 (C-14), 131.2 (C-10), 133.0 (C-8), 113.7 (C-9), 133.2 (C-5), 135.1 (C-11), 136.7 (C-7), 137.9 (C-6), 139.0 (C-12), 156.5 (C-13), 193.5 (C-15) ppm.

(*all-E*)-9-Demethyl-9-iodoretinal [(*all-E*)-4]: The general procedure was repeated as described for the preparation of (9*Z*)-**1** using 4-(diethoxyphosphoryl)-3-methyl-2-butenenitrile (62.9 mg, 0.29 mmol), LDA prepared from diisopropylamine (28.3 mg, 0.28 mmol) and *n*-butyllithium (169 μL, 1.6 M in hexane), (*all-E*)-**10** (99 mg, 0.30 mmol) and DIBAL-H (0.68 mL, 1.0 M in hexane). This procedure gave a total yield of 99.7 mg (94%) of the desired product of (*all-E*)-**4** isomer.

(*all-E*)-4: ^{1}H NMR (300.1 MHz, CD_3OD): δ = 1.06 (s, 6 H, 16-H and 17-H), 1.51 (m, 2 H, 2-H), 1.65 (m, 2 H, 3-H), 1.75 (s, 3 H, 18-H), 2.08 (m, 2 H, 4-H), 2.32 (s, 3 H, 20-H), 6.01 (d, $^3J_{14\text{-H},15\text{-H}}$ = 8.1 Hz, 1 H, 14-H), 6.20 (d, $^3J_{8\text{-H},7\text{-H}}$ = 15.0 Hz, 1 H, 8-H), 6.47 (d, $^3J_{12\text{-H},11\text{-H}}$ = 15.0 Hz, 1 H, 12-H), 6.70 (d, $^3J_{7\text{-H},8\text{-H}}$ = 15.0 Hz, 1 H, 7-H), 7.10 (d, $^3J_{10\text{-H},11\text{-H}}$ = 11.5 Hz, 1 H, 10-H), 7.26 (dd, $^3J_{11\text{-H},10\text{-H}}$ = 11.5, $^3J_{11\text{-H},12\text{-H}}$ = 15.0 Hz, 1 H, 11-H), 10.1 (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 = 13.01 (C-20), 20.2 (C-3), 22.1 (C-18), 29.4 (C-16 and C-17), 34.1 (C-4), 35.3 (C-1), 40.6 (C-2), 108.5 (C-9), 130.1 (C-8), 131.5 (C-14), 131.8 (C-11), 133.3 (C-5), 137.8 (C-12), 138.1 (C-6), 141.6 (C-10), 142.7 (C-7), 156.7 (C-13), 193.5 (C-15) ppm.

(9*Z*,11*Z*)-9-Demethyl-9-iodoretinal [(9*Z*,11*Z*)-4): The general procedure was repeated as described for the preparation of (9*Z*,11*Z*)-**1** using 4-(diphenoxyphosphoryl)-3-methyl-2-butenenitrile (122 mg, 0.39 mmol), sodium hydride (15 mg, 0.37 mmol) in THF (10 mL) and (9*Z*)-**10** (129 mg, 0.39 mmol). This procedure gave a 7:3 mixture of (9*Z*,11*Z*)- and (9*Z*)-retinonitrile isomers, yielding, after DIBAL-H reduction (0.65 mL, 1.0 M in hexane) of the pure (11*Z*) nitrile, pure (11*Z*)-retinal 100 mg, (97%).

(9*Z*,11*Z*)-4: ^{1}H NMR (300.1 MHz, CD_3OD): δ = 1.05 (s, 6 H, 16-H and 17-H), 1.50 (m, 2 H, 2-H), 1.63 (m, 2 H, 3-H), 1.73 (s, 3 H, 18-H), 2.26 (s, 3 H, 20-H), 2.05 (m, 2 H, 4-H), 5.92 (d, $^3J_{14\text{-H},15\text{-H}}$ = 8.00 Hz, 1 H, 14-H), 5.98 (d, $^3J_{8\text{-H},7\text{-H}}$ = 15.2 Hz, 1 H, 8-H), 6.20 (d, $^3J_{10\text{-H},11\text{-H}}$ = 11.1 Hz, 1 H, 10-H), 6.71 (dd, $^3J_{11\text{-H},10\text{-H}}$ = 11.0, $^3J_{11\text{-H},12\text{-H}}$ = 11.7 Hz, 1 H, 11-H), 6.72 (d, $^3J_{7\text{-H},8\text{-H}}$ = 15.4 Hz, 1 H, 7-H), 6.90 (d, $^3J_{12\text{-H},11\text{-H}}$ = 11.4 Hz, 1 H, 12-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), 20.2 (C-3), 22.0 (C-18), 29.4 (C-16 and C-17), 34.2 (C-4), 35.3 (C-1), 40.7 (C-2), 127.5 (C-10), 132.3 (C-14), 112.6 (C-9), 133.0 (C-11), 133.1 (C-8), 135.1 (C-12), 137.0 (C-7), 138.0 (C-5), 138.1 (C-6), 157.8 (C-13), 193.4 (C-15) ppm.

4-(Diphenoxyphosphoryl)-3-methyl-2-butenenitrile (12): Diphenyl methyl phosphite[27] was added to 4-chloro-3-methylbut-2-enenitrile. The mixture was heated to 180 °C and stirred for 36 h. The crude mixture was subjected to column chromatography to yield 60% of the desired product and 40% of starting materials. The starting materials were able to react with each other again at 180 °C to yield another 25% of the desired product. **12:** ^{1}H NMR (300 MHz, CD_3OD): δ = 2.17 (m, 5-H, CH_3, *cis*), 2.27 (m, 5-H, CH_3, *trans*), 3.06 (d, *J* = 23.7 Hz, 1 H, 2-H, *trans*), 3.31 (d, *J* = 24.0 Hz, 1 H, 2-H, *cis*), 5.36 (m, 4-H, CH_2, *cis* and *trans*), 7.24 (m, arom., 10 H) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, $CDCl_3$): δ = 22.5 (C-5, *cis*), 24.3 (C-5, *trans*), 34.7 (d, $^1J_{C4,P4}$ = 97.9 Hz, C-4, *trans*), 36.5 (d, $^1J_{C4,P4}$ = 97.9 Hz, C-4, *cis*), 100.5 (C-2, *cis*), 100.7 (C-2, *trans*), 116 (C-1, *trans*, C-1, *cis*), 120.4 (C-2′, *trans*, C-2′, *cis;* C-6′, *trans*, C-6′, *cis*), 125.4 (C-4′, *trans*, C-4′, *cis*), 129.8 (C-3′, *trans*, C-3′, *cis*; C-5′, *trans*, C-5′, *cis*), 149.3 (C-1′, *trans*, C-1′, *cis*), 154.2 (C-3, *trans*, C-3, *cis*) ppm.

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