Preparation of (*all-E*)- and (*11Z*)-12-Haloretinals and (*11Z,13Z*)- and (*13Z*)-14-Haloretinals by the $C_{15} + C_5$ Route − Exploring the Possibility of Preparing any Retinoid Rationally Chemically Modified at any Position in the Conjugated Tail

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In this paper we describe how chemically modified ylides can be prepared by electrophilic substitution in a simple way. A subsequent Horner–Emmons reaction gives access to (*all-E*)- and (11Z)-12-chloro-, -12-bromo-, and -12-iodoretinal. It could be expected that many more retinals chemically modified at the 12-position could be prepared in this manner. Selectfluor®, a good reagent for introducing a fluorine atom by electrophilic substitution, does not give the 12-fluororetinal system. However, 14-fluororetinal is simply available by reaction of the anion with Selectfluor®. Cl, Br and I atoms were also introduced at the 14-position of retinal both in the (11Z,13Z)- and (13Z)-isomeric forms. This strategy could be extended to a whole range of electrophilic-substitution reactions. We also developed a novel method to prepare 4-hydroxy-substituted Horner–Emmons derivatives, which could be converted into the 4-fluoro derivatives by reaction with (diethylamino)sulfur trifluoride (DAST). This system could simply be converted into 12-fluororetinal in the (*all-E*)- and (11Z)-isomeric forms and we think that this strategy has a good scope to prepare a whole series of 12-modified retinals. We have also explored the essential steps to give access to retinoids modified at any position of the conjugated chain.

Introduction

Rhodopsin is the G-protein-coupled photoreceptor in the retinae of vertebrates that initiates the visual signal transduction cascade in dim-light vision. It is considered a paradigm for the super family of seven transmembrane α-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 signalling by neurotransmitters, hormones and neuropeptides and are therefore one of the major pharmaceutical targets for pharmacological intervention or in human (animal) pathology.[4]

We recently 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 information, with atomic resolution, allows the study of systems with rationally designed chemical changes in the chromophore.

Our first target in this program was a new strategy to synthesise (*all-E*)-, (9*Z*)- and (11*Z*)-α- and -β-retinals with various chemical modifications at the 9-position of the conjugated chain.[7,8] These molecules are designed to obtain essential information about the role of the 9-methyl group (or other substituent), which plays a pivotal role in rhodopsin and isorhodopsin as the G-protein-coupled light receptor.

The target of the present study was to prepare (*all-E*)- and (11*Z*)-retinals with a halogen substituent at the 12-position in order to elucidate the role of the 12-H (or other substituent) in the primary step in rhodopsin photochemistry (conversion of the electronically excited rhodopsin chromophore into the ground state of bathorhodopsin, the primary photochemical product). This step is completed in 200 fs after the absorption of a photon by rhodopsin;[9] it is the fastest photochemical reaction thus far known. Various groups have assumed that an out-of-plane rotation of 12-H is the essential step in this process.[10−12] In the region of such ultrafast reactions, the energy involved to initiate such rapid processes may be considerable. The chromophore of rhodopsin has a torsion angle of about 45° around the 12−13 bond (Figure 1).[13] A rotation of about 90° of this hydrogen means that the 11−12 *cis* bond will be moved into the 11−12 *transoid* region of 135°. To effect a H-rotation within 200 fs over 90°, the energy needed to generate this angular momentum per molecule is given by $^1/_2(m_H R^2_{C12\text{-}H})\pi^2/4$.[14] For a grammol, using the known constants $m_H = 1.66 \times 10^{-27}$ kg, $N_A = 6.02 \times 10^{23}$ mol^{-1}

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and $R = 1 \times 10^{-10}$ m, this formula gives a value of 0.3 kJ·mol^{-1}; repeating the same calculations for 12-F, 12-Cl, 12-Br and 12-I gives values of 2.4 kcal·mol^{-1}, 7.4 kcal·mol^{-1}, 20.4 kcal·mol^{-1} and 39.6 kcal·mol^{-1}, respectively. For the latter two situations the value is much higher than the 15 kcal difference between electronically excited rhodopsin and ground-state bathorhodopsin.[15] This means that the kinetics of the bromo and iodo system should be at least one order of magnitude slower if the same process still occurs. It is also known that in the photochemistry of rhodopsin, there is a linear relationship between the ultrafast kinetics and the quantum yield.[16] It is clear that studying the femtosecond kinetics and the quantum yield of bathorhodopsin formation with a series consisting of the native system and the 12-F, 12-Cl, 12-Br and 12-I derivatives will give direct information about the role of the substituent in the photochemical process in rhodopsin photochemistry.

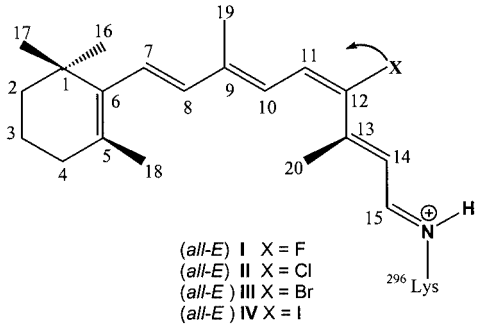


Figure 1. Structure of the retinylidene chromophore in the active site of rhodopsin (X = H) and its 12-F, 12-Cl, 12-Br and 12-I derivatives; the dihedral angle around the 12−13 bond is about 45°; the arrow indicates the direction of rotation of the 12-X substituent that converts the electronically excited state of rhodopsin into the ground-state primary photochemical product bathorhodopsin

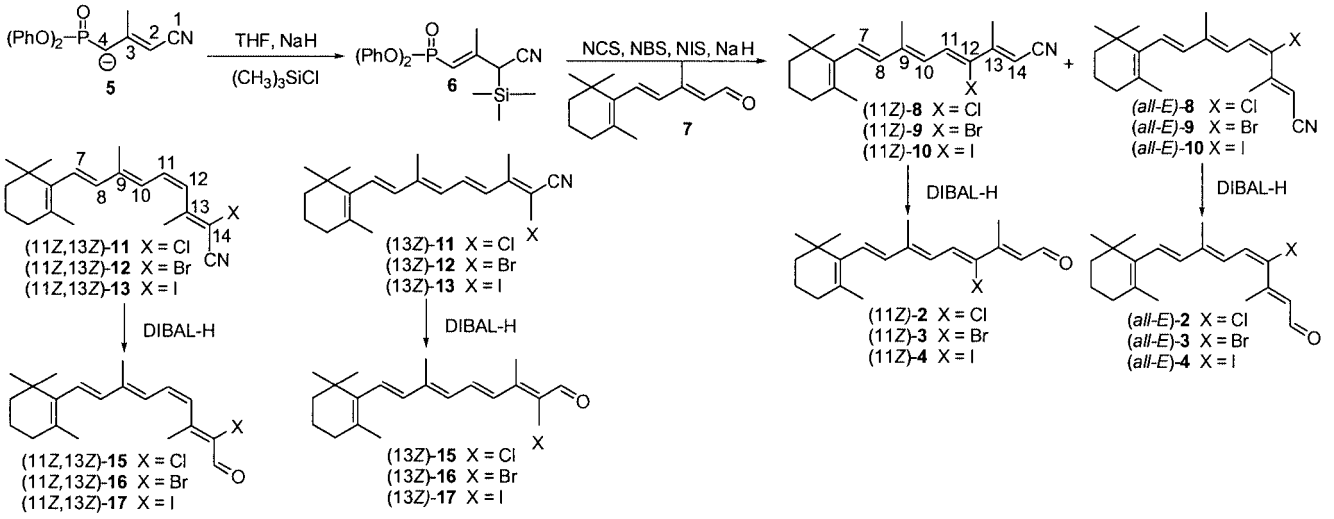
In this paper we describe a synthetic strategy to prepare 12-fluoro-, 12-chloro-, 12-bromo-, and 12-iodoretinal with both the (*all-E*) and (11*Z*) configurations. Due to the priority of halogens in IUPAC nomenclature, (*all-E*)-12-haloretinals are the systems that will provide the required 12-halorhodopsins. Based on this chemistry, we have also prepared 14-fluoro-, 14-chloro-, 14-bromo- and 14-iodoretinal with (11*Z*,13*Z*) and (13*Z*) configurations. In this case, the (11*Z*,13*Z*)-14-haloretinals are the precursors to form the 14-halorhodopsins.

The possibilities to chemically modify any retinoid on any specific positions in the ethylenic linkage conjugated tail-end are explored.

Results and Discussion

For the synthesis of (*all-E*)- and (11*Z*)-12-haloretinals, we used the known compound 4-(diphenoxyphosphoryl)-3-methyl-2-butenenitrile (**5**)[7] as synthon (Scheme 1). Treatment of **5** with 1 equiv. of NaH in THF gave the corresponding anion which, upon subsequent treatment with 1 equiv. of trimethylsilyl chloride, gave the 2-trimethylsilyl derivative **6**.[17,18] It is well known that allylic silyl compounds can react with electrophiles to introduce a substituent at the 4-position, with concomitant expulsion of the trimethylsilyl group and shift of the double bond to the 2−3 position.[17] Thus, treatment with 1 equiv. of base gave the Horner−Emmons reagent, and addition of 1 equiv. of β-(ionylidene)acetaldehyde (**7**) provided the Horner−Wadsworth−Emmons reaction product. The synthesis of (*all-E*)-**7** and its corresponding nitrile has been described by us before.[7] Treatment of **6** with *N*-chlorosuccinimide and subsequent addition of **7** gave a mixture of (*all-E*)-12-chlororetinonitrile (*all-E*)-**8** and (11*Z*)-12-chlororetinonitrile (11*Z*)-**8** (*all-E*/11*Z*, 3:2). Similarly, treatment of **6** with *N*-bromosuccinimide and subsequent addition of **7** gave a mixture of (*all-E*)-12-bromoretinonitrile (*all-E*)-**9** and (11*Z*)-12-bromoretinonitrile (11*Z*)-**9** (*all-E*/11*Z*, 3:2), and treatment of **6** with *N*-iodosuccinimide and subsequent addition of **7** gave a mixture of (*all-E*)-12-iodoretinonitrile (*all-E*)-**10** and (11*Z*)-12-iodoretinonitrile (11*Z*)-**10** (*all-E*/11*Z*, 3:2). This synthesis could be achieved in a one-pot procedure. The reaction mixture was then treated with aqueous sodium hydrogen carbonate. The resulting mixture was extracted with diethyl ether, the solution dried with $MgSO_4$ and the solvent was evaporated under reduced pressure. Pure (*all-E*)-**8** and (11*Z*)-**8**, (*all-E*)-**9** and (11*Z*)-**9** and (*all-E*)-**10** and (11*Z*)-**10**, respectively, were obtained in high yields by a preparative HPLC procedure. Subsequent reduction with DIBAL-H led to the corresponding retinals, although this synthesis had to be carried out for the (11*Z*)-9-halo system by a previously reported method.[7] (*all-E*)-**8** and (11*Z*)-**8** have been described before; their spectroscopic properties are in complete agreement with those published.[11] This method will also be applicable for many other (11*Z*)-12-substituted retinal systems by varying the electrophile. We hoped that the corresponding 12-fluoro derivatives could be prepared by treating **6** with Selectfluor® [1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)][19] as this commercially available compound allows the introduction of a fluoro substituent in an electrophilic-substitution reaction. However, treatment of **6** with 1 equiv. of Selectfluor® did not give any reaction at all.

In order to obtain the needed halo derivatives, the anion **5** was extended with *N*-chloro-, *N*-bromo- or *N*-iodosuccinimide to give mixtures of (*all-E*)-**8** and (11*Z*)-**8**, (*all-E*)-**9** and (11*Z*)-**9** and (*all-E*)-**10** and (11*Z*)-**10**, respectively, as well as the corresponding 14-chlorinated (11*Z*,13*Z*)-**11** and (13Z)-**11**, 14-brominated (11*Z*,13*Z*)-**12** and (13Z)-**12** and 14-iodinated (11*Z*,13*Z*)-**13** and (13Z)-**13**, respectively. This means that the electrophilic attack of the halo atom on **5** is not selective. The ratio of attack at the 2-position versus the 4-position in **5** is about 2:3. A similar situation holds for the corresponding Br and I systems **9**, **12** and **10**, **13**. The ratio of attack of the bromo on positions 2 and 4 is about the same as in the chloro case. In the case of iodo substitution it is 1:3. These systems were separated by preparative HPLC techniques.

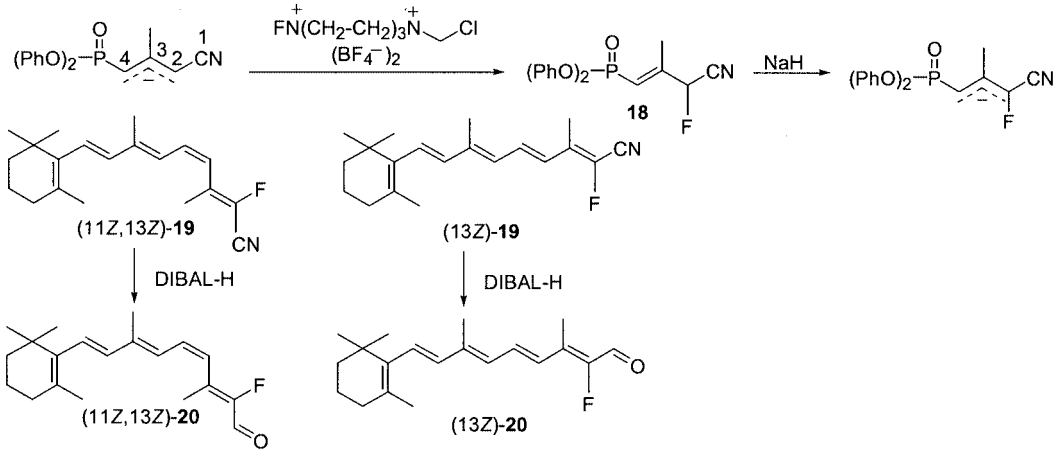


Scheme 1. Preparation of (*all-E*)-12-chlororetinal, (*all-E*)-12-bromoretinal, (*all-E*)-12-iodoretinal and their (11*Z*) isomers, together with (13*Z*)-14-chlororetinal, (13*Z*)-14-bromoretinal, (13*Z*)-14-iodoretinal and their (11*Z*,13*Z*) isomers

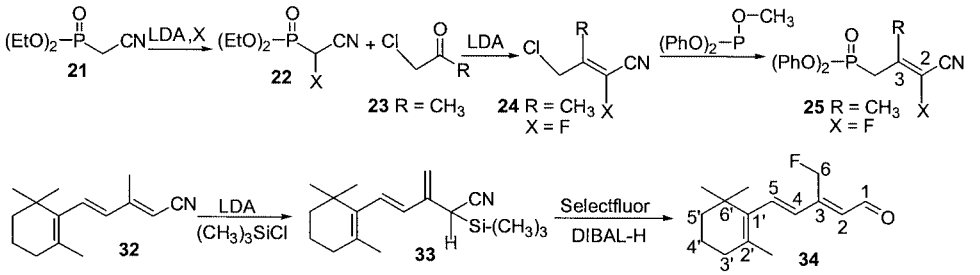
The nitriles **8**−**13** were reduced with DIBAL-H, as discussed before, to give the corresponding (11*Z*,13*Z*)- and (13*Z*)-14-halo-substituted retinals. In the case of the 14-iodo system, the 14-iodo atom is partially substituted by a hydrogen atom during the reduction. We have encountered this iodine loss during DIBAL-H reduction before and this fact has been previously reported.[20] Pure (11*Z*,13*Z*)-**17** and (13*Z*)-**17** were obtained in an isomeric ratio of 3:2 by preparative HPLC.

We reasoned that Selectfluor® might also react with the anion of **5** (Scheme 2). However, in the case of the reaction with trimethylsilyl chloride, complete fluorination occurred only at the 2-position to give a mixture of (11*Z*,13*Z*) isomers of 14-F-**19** and (13*Z*)-14-F-**19**. After the coupling reaction with β-(ionylidene)acetaldehyde (**7**), a DIBAL-H reduction gave (11*Z*,13*Z*)-14-F-retinal **20** and its (13*Z*) isomer. It is clear from our results that electronic and steric factors have a strong influence on the electrophilic attack at either the 2- or 4-position in the allylic anion: in the case of reaction with trimethylsilyl chloride or Selectfluor® the attack only takes place at the least hindered 2-position next to the very small CN group, indicating that these sterically very demanding reagents only attack at 2-position and not at all at 4-position, linked to the bulky phosphonate group. In the case of *N*-iodosuccinimide even more attack of the iodo takes place at position 2 than in the case of the other halogen reagents in a 2/4 selecting ratio of 1:3.

Taking into account these results, we decided to explore the possibility of simple site-directed introduction of substituents. 2-Substituted 4-(diphenoxyphosphoryl)-3-methyl-2-butenenitriles should be simply accessible by the reactions depicted in Scheme 3. 2-(Diethoxyphosphoryl)acetonitrile was treated with 1 equiv. of LDA in THF to give the corresponding anion, which was allowed to react with Selectfluor® to give the 2-fluoro derivative. Subsequent addition of a second equivalent of LDA and then 1 equiv. of



Scheme 2. Preparation of (11*Z*,13*Z*)-14-fluororetinal and (13*Z*)-14-fluororetinal



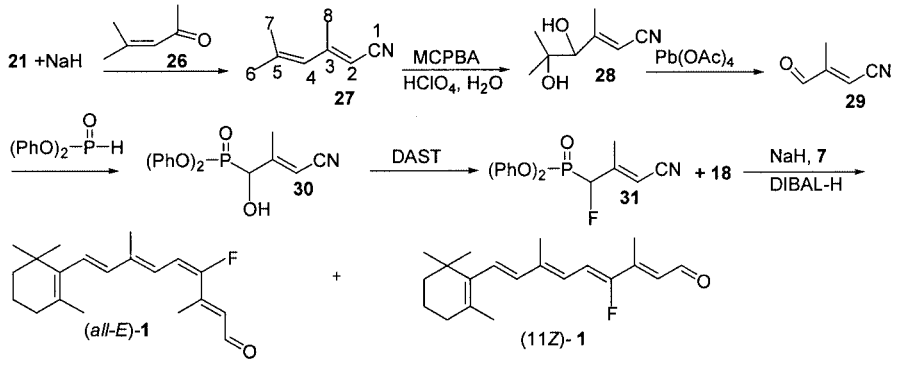
Scheme 3. Top: preparation of 4-(diphenylphosphoryl)-2-fluoro-3-methyl-2-butenenitrile by a method that allows chemical modification at positions 2 and 3; bottom: simple preparation of 19-fluoro-β-(ionylidene)acetaldehyde

1-chloroacetone (R = CH_3) led to 4-chloro-2-fluoro-3-methylbut-2-ene (**24**; R = CH_3, X = F). Arbuzov reaction with methyl diphenyl phosphite then gave 4-(diphenoxyphosphoryl)-2-fluoro-3-methyl-2-butenenitrile (**25**; R = CH_3, X = F). A Horner−Emmons reaction of the anion of **25** (R = CH_3, X = F) with β-(ionylidene)acetaldehyde gave a mixture of (11*Z*,13*Z*)-**19** and (13*Z*)-**19**, as described above. Based on our earlier work[28] it is known that the Horner−Emmons reaction of chloromethyl keto systems with the 2-phosphononitrile anion is very general, as is the subsequent Arbuzov reaction, which means that this route permits the synthesis of derivatives of **25** with many combinations of substituents (R and X) at positions 2 and 3, This means that a whole library of 13- and 14-substituted (11*Z*)- and (*all-E*)-retinals will be available in this way. It could also be expected that anions of type **25** can be chlorinated, brominated and iodinated, giving access to retinal chemically modified at position 14.

The only drawback in this general strategy is that we don't have a method to introduce the fluoro substituent at position 12 in (11*Z*)- and (*all-E*)-retinal. In order to effect this we explored a different approach. Commercially available 4-methyl-3-penten-2-one (**26**; Scheme 4) was treated with the anion of 2-(diethoxyphosphoryl)acetonitrile (**21**) in THF to yield 3,5-dimethyl-2,4-hexadienenitrile (**27**). Treatment of **27** with *m*-chloroperbenzoic acid (*m*CPBA) led, after removal of the *m*-chlorobenzoic acid by washing with aqueous sodium hydroxide solution, to the corresponding epoxide. Under these experimental conditions the double bond attached to the nitrile was not affected. We have described this type of selectivity before.[21] Treatment of this epoxide with a catalytic amount of perchloric acid in water gave the 4,5-diol **28** after extraction into a 10:1 diethyl ether/acetonitrile mixture. After subsequent evaporation of the solvent, **28** was dissolved in CH_2Cl_2. Oxidative cleavage of **28** with lead tetraacetate gave the 4-oxonitrile **29**, which reacted with dialkyl phosphite to give (1-hydroxyalkyl)phosphonates in high yield.[22,23] The 4-oxonitrile **29** reacted with diphenyl phosphite (diphenyl phosphonate according to the tautomer shown in Scheme 4) to give 4-(diphenoxyphosphoryl)-4-hydroxy-3-methyl-2-butenenitrile (**30**) in high yield. Phosphonate **30** was converted into a mixture of the required compounds **31** and **18** (Scheme 4) upon treatment with (diethylamino)sulfur trifluoride (DAST), although alkyl (1-hydroxyalkyl)phosphonates react with DAST only by γ-fluorination.[24] Treatment of β-(ionylidene)acetaldehyde with the anion of **31** gave a mixture of the corresponding 12-F-retinonitriles, which were separated by preparative HPLC. Subsequent careful DIBAL-H reduction gave pure (*all-E*)-12-fluororetinal (*all-E*)-**1** or (11*Z*)-12-fluororetinal (11*Z*)-**1**. The spectroscopic data of (*all-E*)-**1** and (11*Z*)-**1** are in agreement with those published in the literature.[25]

The allylic OH group in **30**, which can be converted into the corresponding fluoride by nucleophilic substitution with DAST, could also be replaced by a host of substituents by a Mitsunobu reaction.

The conversion of **26** can be carried out with various substituted (diethoxyphosphoryl)acetonitrile anions **22**, which



Scheme 4. Preparation of (*all-E*)-12-fluororetinal and (11*Z*)-12-fluororetinal

results in conjugated nitriles of type **27** with various substituents at C-2. This means that 4-(diphenoxyphosphoryl)-2-butenenitrile systems will be accessible with various substituents at carbon atoms 2, 3 and 4 (Scheme 4).

It is gratifying that the presence of substituents at positions 2 and 4 does not change the fundamental thermodynamic and kinetic factors, such that only reaction products with (11*Z*) and (11*E*) conformations are formed. In a previous paper we have reported a strategy to convert β- and α-cyclocitral into (*all-E*)-, (11*Z*)-retinal and α-retinal. This means that the chemically modified Horner−Emmons reagents reported here will allow an entry to (*all-E*)- and (11*Z*)-retinals chemically modified at positions 8, 9, 10, 12, 13 and 14 of the conjugated chain. Multisite-directed rationally designed chemical modification could also be used with the present chemically modified Horner−Emmons reagents. In our earlier study, we developed an alternative method to introduce chemical modifications in the conjugated chain at positions 9 and 13, which can easily be extended to positions 7 and 11. The only positions where no simple chemical modification has been realized thus far are 19 and 20. In order to show that these positions can also be made accessible, we carried out the reactions depicted in Scheme 3. β-(Ionylidene)acetonitrile (**32**) was treated with LDA in THF at −60 °C, and the resulting anion was reacted with trimethylsilyl chloride to give the allylic silyl derivative **33**. Treatment of **33** with Selectfluor® gave the 6-F-nitrile, which was subsequently reduced with DIBAL-H to obtain the 6-F-(ionylidene)acetaldehyde **34**.The 6-F-(ionylidene)acetonitrile and the corresponding aldehyde have been reported before.[26] The NMR spectra of our materials are in agreement with those reported earlier.[26] Hence, with this simple allylic trimethylsilyl derivative **33**, Selectfluor® gives the expected result, as has been described before.[27] This strategy could possibly be extended to other electrophiles. As the same type of factors rule the chemistry of the 13-methyl group in retinonitrile to those in β-(ionylidene)acetonitrile, atom 20 in retinoids can also be chemically modified. Based on the exploratory work in this paper, we can conclude that all positions in the conjugated chain of retinoids can now be rationally chemically modified and multi combinations, if not all chemical modifications, can be introduced in a rational manner.

Conclusion

The anion of 4-(diphenoxyphosphoryl)-3-methyl-2-butenenitrile gives the 2-trimethylsilyl derivative upon treatment with trimethylsilyl chloride. This system reacts with electrophilic halogenating agents to generate the corresponding 4-halogenated compounds, which, in a subsequent Horner−Emmons reaction, give (*all-E*)- and (11*Z*)-12-haloretinals. The corresponding 12-F derivative could not be prepared by this way. Due to the importance of site-directed fluorinated systems in biology, medicine and pharmacy, we have developed a new access to 4-(diphenoxyphosphoryl)-4-hydroxy-3-methyl-2-butenenitrile by a nucleophilic reaction with (diethylamino)sulfur trifluoride (DAST). The required 4-fluoro Horner−Emmons reagent can be prepared in a reasonable yield. In this way, (*all-E*)- and (11*Z*)-12-F-retinals can be made in a simple way. The chloro, bromo and iodo synthons also easily prepared to give the whole set of 12-halo-substituted derivatives. Based on the ease of access of these systems both with electrophilic and nucleophilic reagents in a rational site-directed way, it is clear that a whole library of various chemically modified Horner−Emmons reagents is now easily accessible by this route, which allows the entry to various site-directed chemically modified retinoids. The possibilities to extend this strategy to various positions in the carbon chain of retinoids have been explored and discussed.

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. Commercially available starting materials *N*-chlorosuccinimide, *N*-bromosuccinimide, *N*-iodosuccinimide, 4-methyl-3-pentene-2-one, 2-(diethoxyphosphoryl)acetonitrile, *m*-chloroperbenzoic acid, diphenyl phosphite (diphenyl phosphonate) and trimethylsilyl chloride, etc. were purchased from Sigma Aldrich. 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate) (= Selectfluor®) and (diethylamino)sulfur trifluoride (DAST) were purchased from Acros. All reagents were used without further purification, unless stated otherwise. In all cases, the chemically pure or higher quality grade of the chemicals was used. Sodium hydride refers to a 60% suspension in mineral oil. Petroleum ether refers to the fraction with a boiling range of 40−60 °C. Dry solvents and reagents were stored under dry argon. Dry THF was freshly distilled over sodium. Dry petroleum ether and dry diethyl ether were prepared by distilling over phosphorus pentoxide and were stored over sodium wire. Dry diisopropylamine and dichloromethane were freshly prepared by distilling over freshly grinded 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). HPLC purification was performed with an 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 recorded 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). ^{13}C NMR spectra were recorded at 75.5 MHz and were internally referenced to the carbon signal of deuterated methanol ($\delta = 49.0$ ppm) or deuterated chloroform ($\delta = 77.0$ ppm).

(11*Z*)-12-Chlororetinal [(11*Z*)-2]: A solution of 4-(diphenoxyphosphoryl)-3-methyl-2-butenenitrile (**5**; 122 mg, 0.39 mmol) in THF (5 mL) was added dropwise to sodium hydride (16 mg, 0.39 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. Trimethylsilyl chloride (43 mg, 0.39 mmol) in THF (10 mL) was added and stirring was continued at 0 °C for 1 h. After that, NCS (52 mg, 0.39 mmol) in THF (5 mL) was added. After stirring at 0 °C for an additional 1 h, sodium hydride (15 mg, 0.37 mmol) in THF (10 mL) was added to the mixture. The temperature was allowed to gradually rise to room temperature. After addition of β-(ionylid-

ene)acetaldehyde (**7**; 85 mg, 0.39 mmol) in THF (5 mL), the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with diethyl ether (2 × 15 mL) and the combined organic layers were washed with brine, dried with a mixture of K_2CO_3 and $MgSO_4$ (1:9, wt/wt), filtered and concentrated under reduced pressure. The crude product contained (11*Z*)-12-chlororetinonitrile and (*all-E*)-12-chlororetinonitrile isomer in an isomeric ratio of 2:3. Pure (11*Z*)-12-chlororetinonitrile (11*Z*)-**8** (44 mg) and (*all-E*)-12-chlororetinonitrile (*all-E*)-**8** (66 mg) were obtained by preparative HPLC (93%). The pure (11*Z*)-12-chlororetinonitrile (44 mg, 0.14 mmol) was dissolved in dry petroleum ether and cooled to −80 °C. DIBAL-H (0.37 mmol, 1.0 M in hexane) was added and the resulting solution was stirred and warmed to −40 °C in 1 h. Then homogeneous basic wet alumina (0.65 g; Al_2O_3/water, 5:1, wt/wt) was added and the mixture was stirred for an additional hour at 0 °C. The reaction mixture was dried with K_2CO_3/$MgSO_4$ (1:9, wt/wt). All solids were filtered off and washed with diethyl ether, yielding (11*Z*)-12-chlororetinal [(11*Z*)-**2**]; 42 mg (94%). ^{1}H NMR (300.1 MHz, CD_3OD): δ = 1.04 (s, 6 H, H-16, H-17), 1.49 (m, 2 H, H-2), 1.64 (m, 2 H, H-3), 1.72 (s, 3 H, H-18), 2.03 (m, 2 H, H-4), 2.06 (s, 3 H, H-19), 2.25 (s, 3 H, H-20), 5.76 (d, $^3J_{H14,H15}$ = 7.7 Hz, 1 H, H-14), 6.21 (d, $^3J_{H8,H7}$ = 16.1 Hz, 1 H, H-8), 6.45 (d, $^3J_{H7,H8}$ = 16.1 Hz, 1 H, H-7), 6.94 (d, $^3J_{H10,H11}$ = 11.5 Hz, 1 H, H-10), 7.23 (d, $^3J_{H11,H10}$ = 11.5 Hz, 1 H, H-11), 10.2 (d, $^3J_{H15,H14}$ = 7.7 Hz, 1 H, H-15) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 12.7 (C-19), 20.1 (C-3), 20.3 (C-20), 21.3 (C-18), 29.4 (C16, C17), 34.0 (C-4), 35.2 (C-1), 40.7 (C-2), 124.1 (C-14), 130.4 (C-11), 130.6 (C-10), 131.1 (C-5), 132.6 (C-7), 133.6 (C-12), 138.8 (C-6), 139.0 (C-8), 141.9 (C-9), 156.2 (C-13), 191.2 (C-15) ppm.

(*all-E*)-12-Chlororetinal [(*all-E*)-2]: The (*all-E*)-12-Chlororetinonitrile (66 mg, 0.21 mmol) was dissolved in dry petroleum ether and cooled to −80 °C. DIBAL-H (0.52 mmol, 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 alumina (0.91 g; Al_2O_3/water, 5:1, wt/wt) was added and the mixture was stirred at 0 °C for an additional 1 hour. The reaction mixture was dried by adding a mixture K_2CO_3 and $MgSO_4$ (1:9, wt/wt). All solids were filtered off and washed with diethyl ether, yielding (*all-E*)-12-chlororetinal [(*all-E*)-**2**]; 63 mg (95%). ^{1}H NMR (300.1 MHz, CD_3OD): δ = 1.01 (s, 6 H, H-16, H-17), 1.46 (m, 2 H, H-2), 1.61 (m, 2 H, H-3), 1.64 (s, 3 H, H-18), 1.96 (s, 3 H, H-19), 2.00 (m, 2 H, H-4), 2.36 (s, 3 H, H-20), 6.00 (d, $^3J_{H14,H15}$ = 7.7 Hz, 1 H, H-14), 6.05 (d, $^3J_{H8,H7}$ = 16.1 Hz, 1 H, H-8), 6.09 (d, $^3J_{H10,H11}$ = 11.1 Hz, 1 H, H-10), 6.33 (d, $^3J_{H7,H8}$ = 16.1 Hz, 1 H, H-7), 6.90 (d, $^3J_{H11,H10}$ = 11.9 Hz, 1 H, H-11), 10.1 (d, $^3J_{H15,H14}$ = 7.6 Hz, 1 H, H-15) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 12.7 (C-19), 20.3 (C-20), 20.4 (C-3), 21.9 (C-18), 29.4 (C16, C17), 34.0 (C-4), 35.1 (C-1), 40.7 (C-2), 124.1 (C-14), 124.1 (C-10), 130.2 (C-11), 131.1 (C-5), 131.3 (C-7), 137.3 (C-12), 137.8 (C-8), 138.8 (C-6), 141.9 (C-9), 157.0 (C-13), 193.6 (C-15) ppm.

(11*Z*)-12-Bromoretinal [(11*Z*)-3]: The procedure was the same as that described for the preparation of (11*Z*)-**2** and (*all-E*)-**2** by adding 4-(diphenoxyphosphoryl)-3-methyl-2-butenenitrile (**5**; 122 mg, 0.39 mmol) in THF (5 mL) dropwise to sodium hydride (16 mg, 0.39 mmol) at 0 °C. Subsequently, trimethylsilyl chloride (43 mg, 0.39 mmol) in THF (10 mL) was added followed by NBS (69 mg, 0.39 mmol) in THF (5 mL). After addition of further sodium hydride (15 mg, 0.37 mmol) in THF (10 mL), the temperature was allowed to gradually rise to room temperature. β-(Ionylidene)acetaldehyde (**7**; 85 mg, 0.39 mmol) in THF (5 mL) was then added. After work up, the crude product was found to contain (11*Z*)-12-bromoretinonitrile and (*all-E*)-12-bromoretionitrile isomer in an isomeric ratio of 2:3. Pure (11*Z*)-12-bromoretinonitrile, (11*Z*)-**9** (49 mg) and pure (*all-E*)-12-bromoretinonitrile, (*all-E*)-**9** (73 mg) were obtained by preparative HPLC (93% combined yield). Subsequent DIBAL-H (0.34 mmol, 1.0 M in hexane) reduction of the pure (11*Z*)-12-bromoretinonitrile (49 mg, 0.14 mmol) yielded (11*Z*)-**3**; 46 mg (94%). ^{1}H NMR (300.1 MHz, CD_3OD): δ = 1.03 (s, 6 H, H-16, H-17), 1.43 (m, 2 H, H-2), 1.54 (m, 2 H, H-3), 1.71 (s, 3 H, H-18), 1.96 (s, 3 H, H-19), 2.01 (m, 2 H, H-4), 2.28 (s, 3 H, H-20), 6.01 (d, $^3J_{H14,H15}$ = 7.9 Hz, 1 H, H-14), 6.14 (d, $^3J_{H8,H7}$ = 16.1 Hz, 1 H, H-8), 6.37 (d, $^3J_{H10,H11}$ = 11.5 Hz, 1 H, H-10), 6.57 (d, $^3J_{H7,H8}$ = 16.1 Hz, 1 H, H-7), 7.29 (d, $^3J_{H11,H10}$ = 11.5 Hz, 1 H, H-11), 10.2 (d, $^3J_{H15,H14}$ = 7.9 Hz, 1 H, H-15) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 13.1 (C-19), 20.3 (C-20), 20.5 (C-3), 22.1 (C-18), 29.3 (C16, C17), 34.0 (C-4), 35.1 (C-1), 40.7 (C-2), 127.6 (C-7), 130.7 (C-14), 131.1 (C-5), 131.4 (C-11), 133.3 (C-8), 134.6 (C-10), 137.2 (C-12), 138.3 (C-6), 144.9 (C-9), 158.7 (C-13), 192.6 (C-15) ppm.

(*all-E*)-12-Bromoretinal [(*all-E*)-3]: The procedure was the same as that described for the preparation of (*all-E*)-**8**. DIBAL-H (0.51 mmol, 1.0 M in hexane) reduction of pure (*all-E*)-12-bromoretinonitrile (*all-E*)-**9** (73 mg, 0.2 mmol) gave (*all-E*)-**3**; 69 mg (95%). ^{1}H NMR (300.1 MHz, CD_3OD): δ = 1.05 (s, 6 H, H-16, H-17), 1.46 (m, 2 H, H-2), 1.52 (m, 2 H, H-3), 1.68 (s, 3 H, H-18), 1.92 (s, 3 H, H-19), 1.99 (m, 2 H, H-4), 2.36 (s, 3 H, H-20), 5.95 (d, $^3J_{H14,H15}$ = 7.7 Hz, 1 H, H-14), 6.03 (d, $^3J_{H8,H7}$ = 16.1 Hz, 1 H, H-8), 6.34 (d, $^3J_{H7,H8}$ = 16.1 Hz, 1 H, H-7), 6.87 (d, $^3J_{H10,H11}$ = 11.6 Hz, 1 H, H-10), 7.07 (d, $^3J_{H11,H10}$ = 11.6 Hz, 1 H, H-11), 10.0 (d, $^3J_{H15,H14}$ = 7.7 Hz, 1 H, H-15) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 12.7 (C-19), 20.1 (C-20), 20.3 (C-3), 22.3 (C-18), 30.3 (C16, C17), 33.9 (C-4), 35.1 (C-1), 40.7 (C-2), 125.4 (C-7), 130.4 (C-11), 130.9 (C-14), 131.0 (C-5), 132.8 (C-8), 134.6 (C-10), 136.4 (C-12), 138.2(C-6), 145.2 (C-9), 160.2 (C-13), 194.7 (C-15) ppm.

(11*Z*)-12-Iodoretinal [(11*Z*)-4]: The procedure was the same as that described for the preparation of (11*Z*)-**2** and (*all-E*)-**2** by adding 4-(diphenoxyphosphoryl)-3-methyl-2-butenenitrile (**5**; 122 mg, 0.39 mmol) in THF (5 mL) dropwise to sodium hydride (16 mg, 0.39 mmol) at 0 °C. Subsequently, trimethylsilyl chloride (43 mg, 0.39 mmol) in THF (10 mL) was added, followed by NIS (88 mg, 0.39 mmol) in THF (5 mL). Sodium hydride (15 mg, 0.37 mmol) in THF (10 mL) was then added to the mixture and the temperature was allowed to gradually rise to room temperature. β-(Ionylidene)acetaldehyde (**7**; 85 mg, 0.39 mmol) in THF (5 mL) was then added. After work up, the crude product was found to contain (11*Z*)-12-iodoretinonitrile and (*all-E*)-12-retinonitrile isomers in an isomeric ratio of 2:3. Pure (11*Z*)-12-iodoretinonitrile [(11*Z*)-**10**] (58 mg) and pure (*all-E*)-12-iodoretinonitrile [(*all-E*)-**10**] (88 mg) were obtained by preparative HPLC (96%). DIBAL-H (0.37 mmol, 1.0 M in hexane) reduction of the pure (11*Z*)-12-iodoretinonitrile (58 mg, 0.14 mmol) gave (11*Z*)-12-iodoretinal [(11*Z*)-**4**]; 55 mg (94%). ^{1}H NMR (300.1 MHz, CD_3OD): δ = 1.01 (s, 6 H, H-16, H-17), 1.48 (m, 2 H, H-2), 1.64 (m, 2 H, H-3), 1.68 (s, 3 H, H-18), 1.93 (s, 3 H, H-19), 2.02 (m, 2 H, H-4), 2.23 (s, 3 H, H-20), 5.75 (d, $^3J_{H14,H15}$ = 7.8 Hz, 1 H, H-14), 6.02 (d, $^3J_{H10,H11}$ = 11.8 Hz, 1 H, H-10), 6.06 (d, $^3J_{H8,H7}$ = 16.1 Hz, 1 H, H-8), 6.36 (d, $^3J_{H7,H8}$ = 16.1 Hz, 1 H, H-7), 7.28 (d, $^3J_{H11,H10}$ = 11.8 Hz, 1 H, H-11), 10.1 (d, $^3J_{H15,H14}$ = 7.8 Hz, 1 H, H-15) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 12.6 (C-19), 20.3 (C-3), 21.6 (C-20), 21.8 (C-18), 29.5 (C16, C17), 34.1 (C-4), 35.3 (C-1), 40.7 (C-2), 95.1 (C-12), 125.9 (C-10), 129.8 (C-14), 131.2 (C-7), 131.0 (C-5), 138.5 (C-8), 138.7 (C-6), 140.7 (C-9), 142.4 (C-11), 162.5 (C-13), 194.6 (C-15) ppm.

(*all-E*)-12-Iodoretinal [(*all-E*)-4]: The procedure was the same as that described for the preparation of (*all-E*)-**2**. DIBAL-H (0.54 mmol, 1.0 M in hexane) reduction of pure (*all-E*)-12-iodoretinonitrile [(*all-E*)-**10**] (88 mg, 0.22 mmol) gave (11*Z*)-12-iodoretinal [(*all-E*)-**4**]; 84 mg (95%). ^{1}H NMR (300.1 MHz, CD_3OD): δ = 0.99 (s, 6 H, H-16, H-17), 1.29 (m, 2 H, H-2), 1.46 (m, 2 H, H-3), 1.63 (s, 3 H, H-18), 1.88 (m, 2 H, H-4), 1.98 (s, 3 H, H-19), 2.36 (s, 3 H, H-20), 5.94 (d, $^3J_{H14,H15}$ = 7.8 Hz, 1 H, H-14), 6.00 (d, $^3J_{H8,H7}$ = 16.1 Hz, 1 H, H-8), 6.02 (d, $^3J_{H10,H11}$ = 11.3 Hz, 1 H, H-10), 6.34 (d, $^3J_{H7,H8}$ = 16.1 Hz, 1 H, H-7), 7.25 (d, $^3J_{H11,H10}$ = 11.3 Hz, 1 H, H-11), 10.0 (d, $^3J_{H15,H14}$ = 7.8 Hz, 1 H, H-15) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 12.7 (C-19), 18.1 (C-20), 20.3 (C-3), 21.9 (C-18), 29.3 (C16, C17), 33.9 (C-4), 35.2 (C-1), 40.7 (C-2), 99.1 (C-12), 126.3 (C-10), 129.8 (C-14), 130.8 (C-7), 138.3 (C-8), 139.4 (C-11), 139.1 (C-6), 139.0 (C-5), 144.4 (C-9), 160.7 (C-13), 193.5 (C-15) ppm.

(11*Z*,13*Z*)-14-Chlororetinal [(11*Z*13*Z*)-15]: A solution of 4-(diphenoxyphosphoryl)-3-methyl-2-butenenitrile (**5**; 244 mg, 0.78 mmol) in THF (10 mL) was added dropwise onto sodium hydride (32 mg, 0.78 mmol) in THF (5 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h. After that, NCS (104 mg, 0.78 mmol) in THF (10 mL) was added. After stirring at 0 °C for an additional 1 h, sodium hydride (30 mg, 0.74 mmol) in THF (10 mL) was added to the mixture. The temperature was allowed to gradually rise to room temperature, followed by addition of β-(ionylidene)acetaldehyde (**7**; 170 mg, 0.78 mmol) in THF (10 mL). The reaction mixture was then quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with diethyl ether (2 × 15 mL) and the combined organic layers were washed with brine, dried with K_2CO_3/$MgSO_4$ (1:9, wt/wt), filtered and concentrated under reduced pressure. The crude product was found to be a complete conversion mixture of (11*Z*,13*Z*)-**11** and (13*Z*)-14-chlororetinonitrile [(13*Z*)-**11**], in an isomeric ratio of 3:2, and the corresponding 12-chlorinated retinonitriles (*all-E*)-**8** and (11*Z*)-**8** in an isomeric ratio of 3:2. Pure (11*Z*,13*Z*)-14-chlororetinonitrile [(11*Z*,13*Z*)-**11**] (58 mg) and (13*Z*)-14-chlororetinonitrile [(13*Z*)-**11**] (41 mg) were obtained by preparative HPLC (58%). Pure (11*Z*)-**8** (29 mg) and pure (*all-E*)-**8** (41 mg) were also obtained (39%). Pure (11*Z*,13*Z*)-14-chlororetinonitrile [(11*Z*,13*Z*)-**11**] (58 mg, 0.2 mmol) was dissolved in dry petroleum ether (10 mL) and cooled to −80 °C. DIBAL-H (0.46 mmol, 1.0 M in hexane) was added and the resulting solution was stirred and warmed to −40 °C over 1 h. Homogeneous basic wet alumina (0.81 g; Al_2O_3/water, 5:1, wt/wt) was added, and the mixture was stirred at 0 °C for an additional 1 h. The reaction mixture was then dried with K_2CO_3/$MgSO_4$ (1:9, wt/wt). All solids were filtered off and washed with diethyl ether to give (11*Z*,13*Z*)-14-chlororetinal [(11*Z*,13*Z*)-**15**]; 55 mg (95%). ^{1}H NMR (300.1 MHz, CD_3OD): δ = 1.03 (s, 6 H, H-16, H-17), 1.49 (m, 2 H, H-2), 1.63 (m, 2 H, H-3), 1.68 (s, 3 H, H-18), 1.99 (m, 2 H, H-4), 2.02 (s, 3 H, H-19), 2.32 (s, 3 H, H-20), 6.05 (d, $^3J_{H10,H11}$ = 11.7 Hz, 1 H, H-10), 6.32 (d, $^3J_{H8,H7}$ = 16.1 Hz, 1 H, H-8) 6.39 (d, $^3J_{H7,H8}$ = 16.1 Hz, 1 H, H-7), 6.59 (d, $^3J_{H12,H11}$ = 12.5 Hz, 1 H, H-12), 6.96 (dd, $^3J_{H11,H10}$ = 11.7, $^3J_{H11,H12}$ = 12.5 Hz, 1 H, H-11), 9.93 (s, 1 H, H-15) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 12.7 (C-19), 18.7 (C-20), 20.1 (C-3), 21.0 (C-18), 29.4 (C16, C17), 34.1 (C-4), 35.4 (C-1), 40.7 (C-2), 127.3 (C-7), 126.9 (C-10), 129.7 (C-12), 131.1 (C-5), 131.9 (C-11), 133.6 (C-14), 138.3 (C-8), 138.8 (C-6), 142.1 (C-9), 159.1 (C-13), 187.9 (C-15) ppm.

(13*Z*)-14-Chlororetinal [(13*Z*)-15]: (13*Z*)-14-Chlororetinonitrile, (13*Z*)-**11** (41 mg, 0.15 mmol) was dissolved in dry petroleum ether and cooled to −80 °C. DIBAL-H (0.32 mmol, 1.0 M in hexane) was then added and the resulting solution was stirred and warmed to −40 °C over 1 h. Subsequently, homogeneous basic wet alumina (Al_2O_3/water, 5:1, wt/wt; 0.56 g) was added and the mixture was stirred for an additional hour at 0 °C. The reaction mixture was dried by adding a mixture K_2CO_3/$MgSO_4$ (1:9, wt/wt). All solids were filtered off and washed with diethyl ether to give (13*Z*)-14-chlororetinal [(13*Z*)-**15**]; 38 mg (95%). ^{1}H NMR (300.1 MHz, CD_3OD): 1.02 (s, 6 H, H-16, H-17), 1.48 (m, 2 H, H-2), 1.62 (m, 2 H, H-3), 1.69 (s, 3 H, H-18), 1.96 (m, 2 H, H-4), 2.03 (s, 3 H, H-19), 2.30 (s, 3 H, H-20), 5.75 (d, $^3J_{H10,H11}$ = 11.8 Hz, 1 H, H-10), 6.12 (d, $^3J_{H8,H7}$ = 16.1 Hz, 1 H, H-8) 6.37 (d, $^3J_{H7,H8}$ = 16.1 Hz, 1 H, H-7), 6.90 (d, $^3J_{H12,H11}$ = 12.5 Hz, 1 H, H-12), 7.06 (dd, $^3J_{H11,H10}$ = 11.8, $^3J_{H11,H12}$ = 12.5 Hz, 1 H, H-11), 9.98 (s, 1 H, H-15) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 13.9 (C-19), 20.1 (C-20), 20.2 (C-3), 21.2 (C-18), 29.6 (C16, C17), 34.0 (C-4), 35.4 (C-1), 40.7 (C-2), 125.7 (C-7), 129.7 (C-12), 124.9 (C-10), 131.2 (C-5), 131.1 (C-11), 134.7 (C-14), 138.9 (C-8), 139.4 (C-6), 144.1 (C-9), 157.0 (C-13), 189.4 (C-15) ppm.

(11*Z*,13*Z*)-14-Bromoretinal [(11*Z*13*Z*)-16]: The procedure was the same as that described for the preparation of (11*Z*,13*Z*)-**15** and (13*Z*)-**15** by adding 4-(diphenoxyphosphoryl)-3-methyl-2-butenenitrile (**5**; 244 mg, 0.78 mmol) in THF (10 mL) dropwise to sodium hydride (32 mg, 0.78 mmol) at 0 °C, followed by NBS (104 mg, 0.78 mmol) in THF (10 mL). After addition of sodium hydride (30 mg, 0.74 mmol) in THF (10 mL) to the mixture, the temperature was allowed to gradually rise to room temperature. β-(Ionylidene)acetaldehyde (**7**; 170 mg, 0.78 mmol) in THF (10 mL) was then added. After workup, the crude product was found to be a complete conversion mixture of (11*Z*,13*Z*)-14-bromoretinonitrile [(11*Z*,13*Z*)-14-**12**] and (13*Z*)-14-bromoretinonitrile [(13*Z*)-14-**12**] in an isomeric ratio of 3:2 and the corresponding 12-brominated retinonitriles (11*Z*)-**9** and (*all-E*)-**9** in a ratio of 3:2. Pure (11*Z*,13*Z*)-14-bromoretinonitrile [(11*Z*,13*Z*)-14-**12**] (94 mg) and pure (13*Z*)-14-bromoretinonitrile [(13*Z*)-14-**12**] (63 mg; 59%) and corresponding pure (11*Z*)-**9** (40 mg) and (*all-E*)-**9** (59 mg; 37%) were obtained by preparative HPLC. Subsequent DIBAL-H (0.65 mmol, 1.0 M in hexane) reduction of the pure (11*Z*,13*Z*)-14-bromoretinonitrile [(11*Z*,13*Z*)-14-**12**] (94 mg, 0.26 mmol) yielded (11*Z*,13*Z*)-14-bromoretinal [(11*Z*,13*Z*)-**16**]; 88 mg (94%). ^{1}H NMR (300.1 MHz, CD_3OD): δ = 1.03 (s, 6 H, H-16, H-17), 1.451(m, 2 H, H-2), 1.65 (m, 2 H, H-3), 1.71 (s, 3 H, H-18), 2.02 (m, 2 H, H-4), 2.04 (s, 3 H, H-19), 2.25 (s, 3 H, H-20), 6.18 (d, $^3J_{H8,H7}$ = 16.1 Hz, 1 H, H-8), 6.27 (d, $^3J_{H10,H11}$ = 11.5 Hz, 1 H, H-10), 6.43 (d, $^3J_{H7,H8}$ = 16.1 Hz, 1 H, H-7), 6.76 (dd, $^3J_{H11,H10}$ = 11.5, $^3J_{H11,H12}$ = 12.1 Hz, 1 H, H-11), 7.28 (d, $^3J_{H12,H11}$ = 12.1 Hz, 1 H, H-12), 9.63 (s, 1 H, H-15) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 12.9 (C-19), 18.6 (C-20), 20.3 (C-3), 21.9 (C-18), 29.3 (C16, C17), 34.2 (C-4), 35.2 (C-1), 40.9 (C-2), 124.3 (C-14), 129.3 (C-12), 130.6 (C-10), 131.5 (C-7), 137.3 (C-8), 138.6 (C-11), 139.1 (C-6), 139.0 (C-5), 144.4 (C-9), 152.9 (C-13), 184.8 (C-15) ppm.

(13*Z*)-14-Bromoretinal [(13*Z*)-16]: The procedure was the same as that described for the preparation of (*all-E*)-**8**. DIBAL-H (0.44 mmol, 1.0 M in hexane) reduction of the pure (13*Z*)-retinonitrile (63 mg, 0.18 mmol) yielded (13*Z*)-14-bromoretinal [(13*Z*)-**16** isomer]; 61 mg (97%). ^{1}H NMR (300.1 MHz, CD_3OD): δ = 1.04 (s, 6 H, H-16, H-17), 1.48 (m, 2 H, H-2), 1.64 (m, 2 H, H-3), 1.71 (s, 3 H, H-18), 2.02 (m, 2 H, H-4), 2.07 (s, 3 H, H-19), 2.49 (s, 3 H, H-20), 6.22 (d, $^3J_{H8,H7}$ = 16.1 Hz, 1 H, H-8), 6.32 (d, $^3J_{H10,H11}$ = 11.6 Hz, 1 H, H-10), 6.45 (d, $^3J_{H7,H8}$ = 16.1 Hz, 1 H, H-7), 7.06 (d, $^3J_{H12,H11}$ = 15.0 Hz, 1 H, H-12), 7.49 (dd, $^3J_{H11,H10}$ = 11.5, $^3J_{H11,H12}$ = 15.0 Hz, 1 H, H-11), 9.84 (s, 1 H, H-15) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ =

13.1 (C-19), 15.6 (C-20), 20.3 (C-3), 22.0 (C-18), 29.4 (C16, C17), 34.1 (C-4), 35.2 (C-1), 40.8 (C-2), 124.6 (C-14), 131.2 (C-12), 131.5 (C-10), 134.1 (C-7), 137.4 (C-11), 138.7 (C-8), 139.1 (C-6), 139.0 (C-5), 144.5 (C-9), 153.9 (C-13), 185.1 (C-15) ppm.

(11*Z*,13*Z*)-14-Iodoretinal [(11*Z*13*Z*)-17]: The procedure was the same as that described for the preparation of (11*Z*,13*Z*)-**11** and (13*Z*)-**11** by adding 4-(diphenoxyphosphoryl)-3-methyl-2-butenenitrile (**5**; 244 mg, 0.78 mmol) in THF (10 mL) dropwise to sodium hydride (32 mg, 0.78 mmol) at 0 °C, followed by NIS (104 mg, 0.78 mmol) in THF (10 mL). After addition of further sodium hydride (30 mg, 0.74 mmol) in THF (10 mL) to the mixture, the temperature was allowed to gradually rise to room temperature. β-(Ionylidene)acetaldehyde (**7**; 170 mg, 0.78 mmol) in THF (10 mL) was then added. After workup, the crude product was found to be a complete conversion mixture of (11*Z*,13*Z*)-14-iodoretinonitrile [(11*Z*,13*Z*)-**13**] and (13*Z*)-14-iodoretinonitrile [(13*Z*)-**13**] in an isomeric ratio of 3:2 and the corresponding 12-iodinated retinonitriles (11*Z*)-**10** and (*all-E*)-**10**. Pure (11*Z*,13*Z*)-**13** (131 mg) and pure (13*Z*)-**13** (88 mg) were isolated with a total yield of 73%; the corresponding (11*Z*)-**9** (29 mg) and (*all-E*)-**9** (44 mg) isomers were obtained with a total yield of 23% by preparative HPLC. DIBAL-H (0.80 mmol, 1.0 M in hexane) reduction of the pure (11*Z*,13*Z*)-14-iodoretinonitrile (131 mg, 0.32 mmol) yielded (11*Z*,13*Z*)-14-iodoretinal [(11*Z*,13*Z*)-**17**]; 101 mg (77%). ^{1}H NMR (300.1 MHz, CD_3OD): δ = 1.02 (s, 6 H, H-16, H-17), 1.48 (m, 2 H, H-2), 1.63 (m, 2 H, H-3), 1.70 (s, 3 H, H-18), 1.98 (s, 3 H, H-19), 2.03 (m, 2 H, H-4), 2.27 (s, 3 H, H-20), 5.98 (d, $^3J_{H10,H11}$ = 11.0 Hz, 1 H, H-10), 6.17 (d, $^3J_{H8,H7}$ = 16.0 Hz, 1 H, H-8), 6.37 (d, $^3J_{H7,H8}$ = 16.0 Hz, 1 H, H-7), 6.57 (d, $^3J_{H12,H11}$ = 12.5 Hz, 1 H, H-12), 6.77 (d, $^3J_{H11,H10}$ = 11.0, $^3J_{H11,H12}$ = 11.9 Hz, 1 H, H-11), 9.96 (s, 1 H, H-15) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 12.7 (C-19), 18.3 (C-20), 20.1 (C-3), 21.7 (C-18), 29.4 (C16, C17), 34.0 (C-4), 35.1 (C-1), 40.8 (C-2), 99.1(C-14), 127.8 (C-7), 131.1 (C-5), 132.3 (C-10), 135.3 (C-8), 137.4 (C-11), 138.8 (C-12), 139.1 (C-6), 141.4 (C-9), 159.3 (C-13), 189.6 (C-15) ppm.

(13*Z*)-14-Iodoretinal [(13*Z*)-17]: The procedure was the same as that described for the preparation of (*all-E*)-**8**. DIBAL-H (0.55 mmol, 1.0 M in hexane) reduction of the pure (13*Z*)-14-iodoretinonitrile [(13*Z*)-**13**] (88 mg, 0.22 mmol) yielded (13*Z*)-**17**; 62 mg (70%). ^{1}H NMR (300.1 MHz, CD_3OD): δ = 1.03 (s, 6 H, H-16, H-17), 1.46 (m, 2 H, H-2), 1.63 (m, 2 H, H-3), 1.69 (s, 3 H, H-18), 2.01 (s, 3 H, H-19), 2.03 (m, 2 H, H-4), 2.34 (s, 3 H, H-20), 6.07 (d, $^3J_{H8,H7}$ = 16.0 Hz, 1 H, H-8), 6.18 (d, $^3J_{H10,H11}$ = 11.5 Hz, 1 H, H-10), 6.56 (d, $^3J_{H12,H11}$ = 15.2 Hz, 1 H, H-12), 6.77 (d, $^3J_{H7,H8}$ = 16.0 Hz, 1 H, H-7), 7.19 (d, $^3J_{H11,H10}$ = 11.5, $^3J_{H11,H12}$ = 15.2 Hz, 1 H, H-11), 9.99 (s, 1 H, H-15) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 12.9 (C-19), 18.3 (C-20), 20.3 (C-3), 22.0 (C-18), 29.4 (C16, C17), 33.9 (C-4), 35.2 (C-1), 40.7 (C-2), 99.7 (C-14), 130.6 (C-7), 131.0 (C-5), 132.3 (C-10), 136.3 (C-8), 137.4 (C-11), 138.2 (C-12), 138.3 (C-6), 140.1 (C-9), 160.2 (C-13), 190.3 (C-15) ppm.

3-(Fluoromethyl)-5-(2′,6′,6′-trimethyl-1′-cyclohexen-1′-yl)penta-2,4-dien-1-al (34): 3-Methyl-5-(2′,6′,6′-trimethyl-1′-cyclohexen-1′-yl)penta-2,4-dienenitrile (**32**; 1 g, 4.7 mmol) in freshly distilled dry THF (10 mL) was added dropwise, at −78 °C, to a solution of LDA prepared from freshly distilled diisopropylamine (0.5 g, 4.9 mmol) and *n*-butyllithium (2.9 mL, 1.6 M in hexane) in THF (10 mL). After stirring at this temperature for 30 min, freshly distilled trimethylsilyl chloride (0.51 g, 4.7 mmol) in THF (10 mL) was added through a syringe. The resulting mixture was warmed to room temperature over 2 h. Then the trimethylsilyl derivative **33** was treated by adding Selectfluor® (1.66 g, 4.7 mmol) in a mixture of dry THF (10 mL) and CH_3CN (10 mL). The resulting solution was stirred at room temperature overnight and the reaction was then quenched with saturated aqueous Na_2CO_3 (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 3-(fluoromethyl)-5-(2′,6′,6′-trimethyl-1′-cyclohexen-1′-yl)penta-2,4-dienenitrile (1.09 g, quantitative yield). A solution of this compound (1.09 g, 4.7 mmol) in dry petroleum ether (15 mL) was cooled to −60 °C, and DIBAL-H (1.8 mL, 1.0 M in hexane) was added. The resulting mixture was warmed to −40 °C over 1 h. Homogeneous wet silica gel (20.6 g; water/silica, 1:9, wt/wt) was added and stirring was continued at 0 °C for 1 h. The mixture was dried by adding Na_2SO_4, then all solids were filtered off and washed with diethyl ether. The organic solvent was evaporated and the residue was purified by column chromatography to yield **34** (1.0 g, 91%). ^{1}H NMR (300.1 MHz, CD_3OD): δ = 1.03 (s, 6 H, 2 × CH_3-6′), 1.48 (m, 2 H, H-5′), 1.63 (m, 2 H, H-4′), 1.81 (s, 3 H, 2′-CH_3), 2.08 (m, 2 H, H-3′), 5.29 (d, $^2J_{H6F6}$ = 7.8 Hz, 2 H, H-6), 5.43 (d, $^3J_{H2H1}$ = 7.8 Hz, 1 H, H-2), 6.13 (d, $^3J_{H4,H5}$ = 16.5 Hz, 1 H, H-4), 6.47 (d, $^3J_{H5,H4}$ = 16.5 Hz, 1 H, H-5), 10.1 (d, $^3J_{H1,H2}$ = 7.8 Hz, 1 H, H-1) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, $CDCl_3$): δ = 18.6 (C-4′), 22.3 (C-2′−CH_3), 31.2 (2 × 6′-CH_3), 35.1 (C-3′), 35.3 (C-6′), 39.1 (C-5′), 81.3 (d, $^1J_{C6,F6}$ = 175.3 Hz, C-6), 124.5 (d, $^3J_{C2,F6}$ = 6.4 Hz, C-2), 133.8 (C-4), 135.3 (C-2′), 136.6 (C-1′), 137.1 (d, C-5), 153.3 (d, $^2J_{C2,F6}$ = 16.4 Hz, C-3), 189.7 (d, C-1) ppm.

(11*Z*,13*Z*)-14-Fluororetinal [(11*Z*,13*Z*)-20]: A solution of 4-(diphenoxyphosphoryl)-3-methyl-2-buteneintrile (**5**; 122 mg, 0.39 mmol) in THF (5 mL) was added dropwise to sodium hydride (16 mg, 0.39 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. Selectfluor® (138 mg, 0.39 mmol) in THF (10 mL) was then added. After stirring at 0 °C for 1 h, sodium hydride (15 mg, 0.37 mmol) in THF (10 mL) was added to the mixture. The temperature was allowed to gradually rise to room temperature. After addition of β-(ionylidene)acetaldehyde (**7**; 85 mg, 0.39 mmol) in THF (5 mL) the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with diethyl ether (2 × 15 mL) and the combined organic layers were washed with brine, dried with a mixture of K_2CO_3 and $MgSO_4$ (1:9, wt/wt), filtered and concentrated under reduced pressure. The crude product was found to contain (11*Z*,13*Z*)-14-fluororetinonitrile [(11*Z*,13*Z*)-**19**] and (13*Z*)-14-fluororetinonitrile [(13*Z*)-**19**] in an isomeric ratio of 3:2. Pure (11*Z*,13*Z*)-**19** (62 mg) and pure (13*Z*)-**19** (41 mg) were obtained by preparative HPLC (93%). The pure (11*Z*,13*Z*)-retinonitrile (62 mg, 0.15 mmol) was dissolved in dry petroleum ether (10 mL) and cooled to −80 °C. DIBAL-H (0.54 mmol, 1.0 M in hexane) was added and the resulting solution was stirred and warmed to −40 °C over 1 h. Homogeneous basic wet alumina (0.95 g; Al_2O_3/water, 5:1, wt/wt) was then added and the mixture was stirred at 0 °C for an additional 1 hour. The reaction mixture was dried with K_2CO_3/$MgSO_4$ (1:9, wt/wt). All solids were filtered off and washed with diethyl ether to yield (11*Z*,13*Z*)-14-fluororetinal [(11*Z*,13*Z*)-**20**], 60 mg (96%). ^{1}H NMR (300.1 MHz, CD_3OD): δ = 1.03 (s, 6 H, H-16, H-17), 1.49 (m, 2 H, H-2), 1.64 (m, 2 H, H-3), 1.69 (s, 3 H, H-18), 2.00 (m, 2 H, H-4), 2.03 (s, 3 H, H-19), 2.36 (d, $^4J_{H20,F14}$ = 3.40 Hz, 3 H, H-20), 6.16 (d, $^3J_{H8,H7}$ = 16.1 Hz, 1 H, H-8), 6.38 (d, $^3J_{H7,H8}$ = 16.0 Hz, 1 H, H-7), 6.45 (d, $^3J_{H12,H11}$ = 12.6 Hz, 1 H, H-12), 6.84 (dd, $^3J_{H11,H10}$ = 11.6, $^3J_{H11,H12}$ = 12.6 Hz, 1 H, H-11), 7.26 (d, $^3J_{H10,H11}$ = 11.6 Hz, 1 H, H-10), 9.81 (d, $^3J_{H15,F14}$ = 18.0 Hz, 1 H, H-15) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 10.8 (d, $^3J_{C20,F14}$ = 1.54 Hz, C-

20), 12.7 (C-19), 20.1 (C-3), 21.3 (C-18), 29.4 (C16, C17), 34.1 (C-4), 35.3 (C-1), 40.8 (C-2), 127.3 (d, $^3J_{C12,F14}$ = 12.5 Hz, C-12), 130.3 (C-10), 130.6 (C-7), 131.1 (C-5), 135.2 (d, $^4J_{C11,F14}$ = 7.67 Hz, C-11), 137.5 (C-8), 138.8 (C-6), 139.3 (C-9), 141.0 (C-13), 154.7 (d, $^1J_{C14,F14}$ = 262.3 Hz, C-14), 188.7 (d, $^2J_{C15,F14}$ = 26.1 Hz, C-15) ppm.

(13*Z*)-14-Fluororetinal [(13*Z*)-20]: Pure (13*Z*)-**19** (41 mg, 0.14 mmol) was dissolved in dry petroleum ether and cooled to −80 °C. DIBAL-H (0.36 mmol, 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 alumina (Al_2O_3/water, 5:1, wt/wt; 0.63 g) was added and the mixture was stirred at 0 °C for an additional 1 h. The reaction mixture was dried with K_2CO_3/$MgSO_4$ (1:9, wt/wt). All solids were filtered off and washed with diethyl ether to yield (13*Z*)-14-fluororetinal [(13*Z*)-**20**]; 39 mg (95%). ^{1}H NMR (300.1 MHz, CD_3OD): δ = 1.03 (s, 6 H, H-16, H-17), 1.48 (m, 2 H, H-2), 1.63 (m, 2 H, H-3), 1.68 (s, 3 H, H-18), 2.00 (m, 2 H, H-4), 2.02 (s, 3 H, H-19), 2.28 (d, $^4J_{H20,F14}$ = 3.08 Hz, 3 H, H-20), 6.18 (d, $^3J_{H8,H7}$ = 16.1 Hz, 1 H, H-8), 6.28 (d, $^3J_{H10,H11}$ = 11.4 Hz, 1 H, H-10), 6.39 (d, $^3J_{H7,H8}$ = 16.0 Hz, 1 H, H-7), 6.82 (d, $^3J_{H12,H11}$ = 15.2 Hz, 1 H, H-12), 7.27 (dd, $^3J_{H11,H10}$ = 11.5, $^3J_{H11,H12}$ = 15.2 Hz, 1 H, H-11), 9.82 (d, $^3J_{H15,F14}$ = 18.2 Hz, 1 H, H-15) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 10.6 (d, $^3J_{C20,F14}$ = 1.58 Hz, C-20), 13.0 (C-19), 20.3 (C-3), 22.0 (C-18), 29.4 (C16, C17), 34.0 (C-4), 35.3 (C-1), 40.8 (C-2), 126.1 (d, $^3J_{C12,F14}$ = 12.7 Hz, C-12), 130.9 (C-7), 131.1 (C-10), 131.3 (C-5), 134.7 (d, $^4J_{C11,F14}$ = 7.95 Hz, C-11), 134.8 (C-6), 138.5 (C-8), 139.1 (C-9), 143.0 (C-13), 152.6 (d, $^1J_{C14,F14}$ = 262.1 Hz, C-14), 182.3 (d, $^2J_{C15,F14}$ = 28 Hz, C-15) ppm.

3,5-Dimethyl-2,4-hexadienenitrile (27): *n*-Butyllithium (21 mL, 1.6 M in hexane) was added dropwise with a syringe to a solution of 2-(diethoxyphosphoryl)acetonitrile (**21;** 6 g, 33.9 mmol) in THF (5 mL) at − 60 °C. The mixture was stirred at −60 °C for 1 h. Subsequently, 4-methyl-3-penten-2-one (**26**; 3.2 g, 33.9 mmol) in THF (15 mL) was added and the temperature was allowed to gradually rise to room temperature. The reaction mixture was then quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with diethyl ether (2 × 30 mL) and the combined organic layers were washed with brine, dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (diethyl ether/petroleum ether, 20:80, v/v) to give **27** (3.9 g, quantitative yield). ^{1}H NMR (300.1 MHz, CD_3OD): δ = 1.13 (s, 3 H, H-8), 1.32 (s, 3 H, H-7), 2.21 (s, 3 H, H-6), 5.17 (s, 1 H, H-4), 5.53 (s, 1 H, H-2) ppm,. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 19.3 (C-8), 25.1 (C-7), 27.5 (C-6), 103.7 (C-2), 117.0 (C-CN), 123.6 (C-4), 136.9 (C-5), 163.1 (C-3) ppm.

4,5-Dihydroxy-3,5-dimethyl-2-hexenenitrile (28): *meta*-Chloroperbenzoic acid (*m*CPBA; 12.5 g, 51 mmol) was added slowly to a stirred solution of 3,5-dimethyl-4-hexadienenitrile (**27**; 3.9 g, 33.9 mmol) in ethyl acetate (15 mL) at room temperature, and the mixture was stirred at room temperature for 3 h until TLC analysis indicated complete conversion. The reaction mixture was then quenched with saturated aqueous NaOH. The aqueous layer was extracted with diethyl ether (2 × 30 mL) and the combined organic layers were washed with brine, dried with $MgSO_4$, filtered and concentrated under reduced pressure. Subsequently, perchloric acid (0.14 M, 15 mL) in aqueous solution was added to the corresponding epoxide. After stirring at room temperature for 1 h, TLC analysis indicated the complete conversion of the epoxide to the 4,5-diol. Subsequently, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with acetonitrile in diethyl ether (2 × 50 mL, diethyl ether/acetonitrile, 10:1, v/v) and the combined organic layers were washed with brine, dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (diethyl ether/petroleum ether, 9:1, v/v) to give **28** (4.4 g, quantitative yield). ^{1}H NMR (300.1 MHz, CD_3OD): δ = 1.15 (s, 3 H, H-8), 1.28 (s, 3 H, H-7), 2.13 (s, 3 H, H-6), 3.12 (s, 1 H, OH), 3.97 (s, 1 H, H-4), 5.31 (s, 1 H, H-2) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 19.2 (C-6), 25.6 (C-7), 27.3 (C-8), 72.9 (C-5), 82.3 (C-4), 96.7 (C-2), 116.9 (C-CN), 163.3 (C-3) ppm. Corresponding epoxide: ^{1}H NMR (300.1 MHz, CD_3OD): δ = 1.16 (s, 3 H, H-8), 1.45 (s, 3 H, H-7), 2.11 (s, 3 H, H-6), 3.30 (s, 1 H, H-4), 5.27 (s, 1 H, H-2) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 16.3 (C-6), 18.7 (C-7), 24.7 (C-8), 60.9 (C-5), 65.4 (C-4), 95.4 (C-2), 116.5 (C-CN), 157.9 (C-3) ppm.

3-Methyl-4-oxobut-2-enenitrile (29): Lead tetraacetate (15.1 g, 33.9 mmol) was added slowly to the stirred solution of 4,5-dihydroxy-2-hexenenitrile (**28**; 4.4 g, 33.9 mmol) in dichloromethane (30 mL) at room temperature. Within 30 min TLC analysis indicated the complete conversion of the 4,5-diol to the aldehyde nitrile (**29**). The reaction mixture was then filtered and subsequently quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with diethyl ether (2 × 15 mL) and the combined organic layers were washed with brine, dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (diethyl ether/petroleum ether, 20:80, v/v) to give **29** (3.0 g, 91%). ^{1}H NMR (300.1 MHz, CD_3OD): δ = 2.14 (s, 1 H, H-4), 6.18 (s, 1 H, H-2), 9.62 (s, 1 H, H-4) ppm, − ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 12.7 (C-5), 114.4 (C-2), 115.7 (C-1), 155.8 (C-3), 190.3 (C-4) ppm.

4-(Diphenoxyphosphoryl)-4-hydroxy-3-methyl-2-butenenitrile (30): A mixture of diphenyl phosphite (diphenyl phosphonate) (7.7 g, 33 mmol) and **29** (3.0 g, 32 mmol) was refluxed at 131 °C for 6 h until ^{1}H NMR analysis indicated the reaction was complete. After column chromatography (ethyl acetate/petroleum ether, 1:1, v/v), **30** (9.1 g, 86%) was obtained. ^{1}H NMR (300 MHz, CD_3OD): δ = 2.25 (m, 3 H, H-5, *cis*), 2.37 (m, 3 H, H-5, *trans*), 3.12 (m, 1 H, −OH, *cis* and *trans*), 4.75 (dd, *J* = 23.7 Hz, 1 H, H-4, *trans*), 5.49 (dd, *J* = 24.0 Hz, 1 H, H-4, *cis*), 5.77 (m, 2 H, H-2, *cis* and *trans*), 7.24 (m, 10 H, arom.) 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 (dd, $^1J_{C4,P4}$ = 97.9 Hz, C-4, *trans*), 36.5 (dd, $^1J_{C4,P4}$ = 97.9 Hz, C-4, *cis*), 101.5 (C-2, *cis*), 102.7 (C-2, *trans*), 115.1 (C-1, *trans*, C-1, *cis*), 121.4 (C-2′, *trans*, C-2′, *cis;* C-6′, *trans*, C-6′, *cis*), 125.8 (C-4′, *trans*, C-4′, *cis*), 129.8 (C-3′, *trans*, C-3′, *cis;* C-5′, *trans*, C-5′, *cis*), 149.8 (C-1′, *trans*, C-1′, *cis*), 154.8 (C-3, *trans*, C-3, *cis*) ppm.

4-(Diphenoxyphosphoryl)-4-fluoro-3-methyl-2-butenenitrile (31): DAST (1.3 g, 8.1 mmol) was added dropwise through a syringe to a solution of **30** (2.3 g, 66 mmol) in dichloromethane (15 mL) at −80 °C. The resulting solution was slowly warmed to room temperature overnight. Subsequently, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with dichloromethane (2 × 30 mL) and the combined organic layers were washed with brine, dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate/petroleum ether, 1:1, v/v) to give **31** (0.67 g, 31%). ^{1}H NMR (300 MHz, CD_3OD): δ = 2.18 (m, 3 H, H-5, *cis*), 2.23 (m, 3 H, H-5, *trans*), 5.27 (dd, *J* = 23.9, *J* = 47.2 Hz H-4, 1 H, *trans*), 5.46 (dd, *J* = 22.3, *J* = 47.2 H-4, 1 H, *cis*), 5.68 (m, 2 H, H-2, *cis* and *trans*), 7.19 (m, 10 H, arom.) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled,

$CDCl_3$): δ = 23.8 (d, $^3J_{C5,F4}$ = 10.8 Hz, C-5, *cis*), 24.6 (d, $^3J_{C5,F4}$ = 10.7 Hz, C-5, *trans*), 83.7 (dd, $^1J_{C4,P4}$ = 91.3, $^1J_{C4,F4}$ = 266.2 Hz, C-4, *trans*), 86.4 (dd, $^1J_{C4,P4}$ = 91.3, $^1J_{C4,F4}$ = 266.2 Hz, C-4, *cis*), 101.3 (d, $^3J_{C2,F4}$ = 13.6 Hz, C-2, *cis*), 101.7 (d, $^3J_{C2,F4}$ = 13.6 Hz, C-2, *trans*), 113.1 (C-1, *trans*, C-1, *cis*), 120.3 (C-2′, *trans*, C-2′, *cis;* C-6′, *trans*, C-6′, *cis*), 124.5 (C-4′, *trans*, C-4′, *cis*), 126.3 (C-3′, *trans*, C-3′, *cis;* C-5′, *trans*, C-5′, *cis*), 148.7 (C-1′, *trans*, C-1′, *cis*), 154.2 (d, $^2J_{C3,F4}$ = 28.6 Hz, C-3, *trans*, C-3, *cis*) ppm.

(11*Z*)-12-Fluororetinal [(11*Z*)-1]: A solution of 4-(diphenoxyphosphoryl)-4-fluoro-3-methyl-2-butenenitrile (**31**; 131 mg, 0.39 mmol) in THF (5 mL) was added dropwise to sodium hydride (15 mg, 0.37 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h and then the temperature was allowed to gradually rise to room temperature. β-(Ionylidene)acetaldehyde (**7**; 85 mg, 0.39 mmol) in THF (5 mL) was then added and the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with diethyl ether (2 × 15 mL) and the combined organic layers were washed with brine, dried with a mixture of K_2CO_3 and $MgSO_4$ (1:9, wt/wt), filtered and concentrated under reduced pressure. The crude product was found to contain (11*Z*)-12-fluororetinonitrile and (*all-E*)-12-fluororetinonitrile in an isomeric ratio of 2:3. Pure (11*Z*)-12-fluororetinonitrile (40 mg) and pure (*all-E*)-12-fluororetinonitrile (61 mg) were obtained by preparative HPLC (96%). Pure (11*Z*)-12-fluororetinonitrile (40 mg, 0.14 mmol) was dissolved in dry petroleum ether and cooled to −80 °C. DIBAL-H (0.35 mmol, 1.0 M in hexane) was added and the resulting solution was stirred and warmed to −40 °C in 1 h. Then, homogeneous basic wet alumina (Al_2O_3/water, 5:1, wt/wt; 0.61 g) was added and the mixture was stirred at 0 °C for an additional 1 h. The mixture was then dried with a mixture of K_2CO_3 and $MgSO_4$ (1:9, wt/wt). All solids were filtered off and washed with diethyl ether to yield (11*Z*)-12-fluororetinal [(11*Z*)-**1**]; 39 mg (98%). ^{1}H NMR (300.1 MHz, CD_3OD): δ = 1.02 (s, 6 H, H-16, H-17), 1.48 (m, 2 H, H-2), 1.64 (m, 2 H, H-3), 1.70 (s, 3 H, H-18), 2.02 (m, 2 H, H-4), 2.03 (s, 3 H, H-19), 2.37 (d, $^4J_{H20,F12}$ = 3.40 Hz, 3 H, H-20), 6.03 (dd, $^3J_{H14,H11}$ = 7.9, $^4J_{H14,F12}$ = 7.6 Hz, 1 H, H-14), 6.12 (d, $^3J_{H8,H7}$ = 16.1 Hz, 1 H, H-8), 6.27 (d, $^3J_{H10,H11}$ = 11.5 Hz, 1 H, H-10), 6.79 (d, $^3J_{H7,H8}$ = 16.0 Hz, 1 H, H-7), 7.13 (dd, $^3J_{H11,H10}$ = 11.5, $^3J_{H11,F12}$ = 26.8 Hz, 1 H, H-11), 10.2 (d, $^3J_{H15,H14}$ = 7.9 Hz, 1 H, H-15) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 12.9 (C-19), 20.1 (d, $^3J_{C20,F12}$ = 2.6 Hz, C-20), 20.3 (C-3), 21.2 (C-18), 29.4 (C16, C17), 34.1 (C-4), 35.4 (C-1), 40.8 (C-2), 127.1 (C-7), 129.3 (d, $^3J_{C14,F12}$ = 11.7 Hz, C-14), 129.9 (d, $^3J_{C10,F12}$ = 7.2 Hz, C-10), 131.3 (C-5), 132.7 (d, $^3J_{C11,F12}$ = 18.5 Hz, C-11), 137.8 (C-8), 138.1 (C-6), 141.2 (C-9), 151.4 (d, $^3J_{C13,F12}$ = 22.3 Hz, C-13), 157.3 (d, $^1J_{C12,F12}$ = 261.0 Hz, C-12), 190.3 (d, $^4J_{C15,F12}$ = 2.56 Hz, C-15) ppm.

(*all-E*)-12-Fluororetinal [(*all-E*)-1]: Pure (*all-E*)-12-retinonitrile (61 mg, 0.21 mmol) was dissolved in dry petroleum ether and cooled to −80 °C. DIBAL-H (0.55 mmol, 1.0 M in hexane) was added and the resulting solution was stirred and warmed to −40 °C over 1 h. Then, homogeneous basic wet alumina (Al_2O_3/water, 5:1, wt/wt; 0.94 g) was added and the mixture was stirred at 0 °C for an additional 1 h. The mixture was dried with a mixture of K_2CO_3 and $MgSO_4$ (1:9, wt/wt). All solids were filtered off and washed with diethyl ether to yield (*all-E*)-12-fluororetinal [(*all-E*)-**1**]; 58 mg (95%). ^{1}H NMR (300.1 MHz, CD_3OD): δ = 1.03 (s, 6 H, H-16, H-17), 1.46 (m, 2 H, H-2), 1.63 (m, 2 H, H-3), 1.68 (s, 3 H, H-18), 1.98 (m, 2 H, H-4), 2.01 (s, 3 H, H-19), 2.28 (d, $^4J_{H20,F12}$ = 3.60 Hz, 3 H, H-20), 6.07 (d, $^3J_{H8,H7}$ = 16.1 Hz, 1 H, H-8), 6.11 (dd, $^3J_{H14,H11}$ = 7.8, $^4J_{H14,F12}$ = 7.6 Hz, 1 H, H-14), 6.23 (d, $^3J_{H10,H11}$ = 11.6 Hz, 1 H, H-10), 6.41 (d, $^3J_{H7,H8}$ = 16.0 Hz, 1 H, H-7), 6.56 (dd, $^3J_{H11,H10}$ = 11.6, $^3J_{H11,F12}$ = 18.6 Hz, 1 H, H-11), 10.1 (d, $^3J_{H15,H14}$ = 7.8 Hz, 1 H, H-15) ppm. ^{13}C NMR (75.5 MHz, ^{1}H-noise-decoupled, CD_3OD): δ = 12.9 (C-19), 18.3 (d, $^3J_{C20,F12}$ = 2.3 Hz, C-20), 20.3 (C-3), 21.0 (C-18), 29.4 (C16, C17), 34.0 (C-4), 35.4 (C-1), 40.7 (C-2), 123.7 (d, $^3J_{C11,F12}$ = 18.2 Hz, C-11), 126.3 (C-7), 127.9 (d, $^3J_{C14,F12}$ = 11.8 Hz, C-14), 129.1 (d, $^3J_{C10,F12}$ = 6.8 Hz, C-10), 131.3 (C-5), 138.8 (C-8), 138.1 (C-6), 139.3 (C-9), 152.3 (d, $^3J_{C13,F12}$ = 26 Hz, C-13), 157.8 (d, $^1J_{C12,F12}$ = 261.1 Hz, C-12), 189.7 (d, $^4J_{C15,F12}$ = 2.6 Hz, C-15) ppm.

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