Synthesis of 19-Fluororetinal and 20-Fluororetinal

Michel Groesbeek and Steven O. Smith*

Department of Molecular Biophysics and Biochemistry, Yale University, New Haven, Connecticut 06520−8114

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We have investigated methods to monofluorinate the methyl positions 19 and 20 in retinal, and we describe a general, mild strategy that proceeds in high yields and is compatible with current carbon-13 labeling strategies. The new sequence consists of the conversion of *N*-methoxy-*N*-methylamides via the α-chloromethyl ketone to the corresponding γ-hydroxy nitrile, which can subsequently be fluorinated by (diethylamido)sulfur trifluoride (DAST).

The visual pigment rhodopsin is an integral membrane protein in the disk membranes of vertebrate rod cells. It contains 11-*cis*-retinal as a chromophore, bound as an imine to Lys_{296} (see Figure 1). When light is absorbed, the chromophore isomerizes to an *all-E* configuration and the resulting changes in the protein structure activate the G protein transducin. Rhodopsin shows a high sequence similarity to other G protein-coupled receptors and is probably the best understood model for the principles that govern G protein-coupled receptors in general. A high-resolution structure of rhodopsin is not available, and current knowledge about the protein stems from a host of biochemical and biophysical studies including those with engineered chromophores, containing isotope labels and chemical modifications.

Magic angle spinning (MAS) NMR spectroscopy can yield a wealth of information about membrane proteins, such as rhodopsin, which generally defy crystallization.[1] Chemical shift measurements using MAS NMR have been instrumental in identifying specific interactions in rhodopsin, *e.g.*, studies with rhodopsin using singly carbon-13-labeled retinals have led to a computational model of the chromophore docked in the protein binding pocket.[2] New pulse sequences have recently been developed to measure the direct magnetic dipole coupling which is related to the internuclear distance. Rotational-echo double-resonance (REDOR) methods to measure heteronuclear dipole couplings have revived interest in ^{19}F-labeled compounds. The high gyromagnetic ratio of ^{19}F allows for large distances to be measured, which in turn provide tight structural constraints.

We are currently extending our studies of rhodopsin with REDOR-based distance measurements between ^{13}C and ^{19}F labels in the chromophore. This allows accurate distance measurements of up to 11 Å to be made between the labeled sites inside the binding pocket of the protein. Retinoic acids, which are known to crystallize very easily, can serve as model compounds to calibrate REDOR distance measurements. Here we discuss the method we have developed to prepare retinal containing the fluoromethyl group. A prerequisite for our synthetic schemes is that they must be compatible with methods for introduction of carbon-13 labels; specifically, the same synthons (acetonitrile, ethyl acetate, and methyl iodide) should be used to allow for maximum flexibility and the reactions must proceed in high yields.

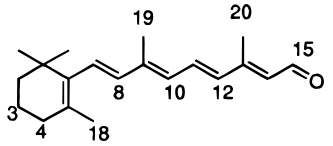
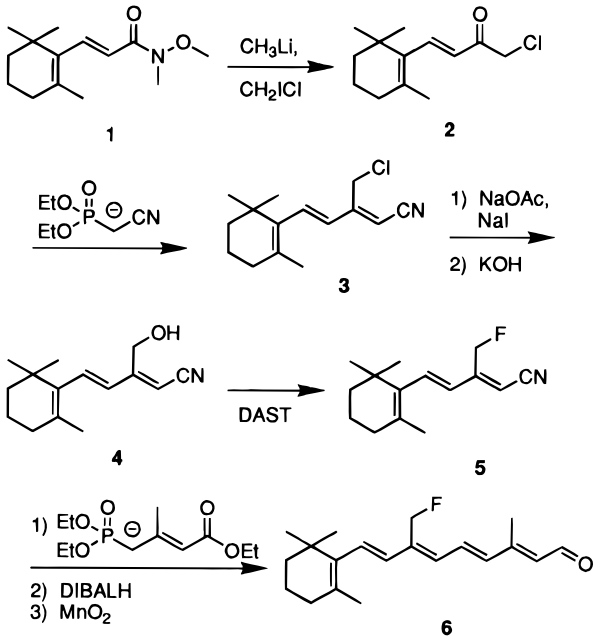


Figure 1. Structure and numbering of *all-E*-retinal.

Scheme 1. Synthesis of 19-Fluororetinal



Results

N-Methoxy-*N*-methylamide **1** is a convenient intermediate for the preparation of 19-derivatized retinals. Recently it was shown that α′-halo esters and chloroiodomethane react under addition of methyllithium to give α′-halo-α-chloro methyl ketones.[3] It is known that *N*-methoxy-*N*-methylamides react with methyllithium to give methyl ketones, presumably via a stabilized intermediate.[4] Using chloroiodomethane and methyllithium with *N*-methoxy-*N*-methylamide **1** gave the expected α-chloromethyl ketone **2** in almost quantitative yield, see Scheme 1.

The α-chloromethyl ketone **2** is a versatile new intermediate which we sought to convert to the fluororetinal. The classical method for selective introduction of fluorine

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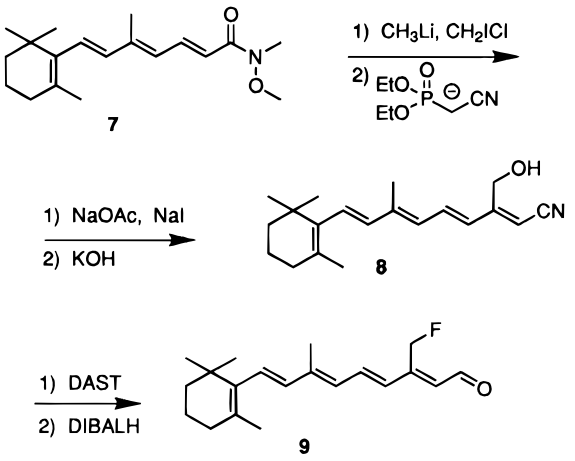
Scheme 2. Synthesis of 20-Fluororetinal



is the nucleophilic displacement of an appropriate leaving group by the fluoride anion.[5] However, no conditions were found to achieve the desired fluorination of **2**: either no reaction occurred or, under more forcing conditions, elimination appeared to be the main reaction. To avoid eliminations we first elongated chloromethyl ketone **2**, using the (diethylphosphono)acetonitrile anion. The resulting nitrile **3** (a mixture of isomers, with about 80% *E* configuration around the newly formed double bond) was acetylated using sodium acetate in acetone.[6] The acetate was cleaved off by treatment with cold KOH in methanol, yielding hydroxymethyl nitrile **4**. Reductive cleavage of the acetate with DIBALH failed. More vigorous base treatment would lead to decomposition of the material.[7] In dilute acid, the ester is very stable and does not cleave. This is a convenient and high-yield synthesis of the hydroxymethyl functionality, and no elimination was observed in the conversion of **2** to **4**. Direct oxidation at this position in retinoids and carotenoids is often difficult and gives substantial amounts of byproducts (especially oxidation at the 4-position).

For conversion of the hydroxyl group to a fluoride, we treated **4** with (diethylamido)sulfur trifluoride (DAST) and obtained the monofluoro product in 78% yield. Reaction of **4** with (2-chloro-1,1,2-trifluoroethyl)diethylamine (FAR) at −60 °C gave a clean conversion of the alcohol to the corresponding fluoride **5**. At room temperature, however, the reaction of FAR with **4** gave predominantly the 2-chloro-2-fluoroacetic ester of the alcohol. Standard polyene chain elongation[8] of **4** gives access to retinal **6**. DIBALH reduction of the nitrile function selectively afforded the γ-fluoro aldehyde, without reduction of the methyl fluoride being observed. The aldehyde was subsequently coupled with triethyl 3-methyl-4-phosphonocrotonate, and the resulting ester was converted to the aldehyde to give an isomeric mixture of 19-fluororetinal (**6**).

A mixture of isomers of 20-fluororetinal (**9**) was easily prepared from *N*-methoxy-*N*-methylamide **7**, employing the same strategy that was found to work for 19-fluororetinal, see Scheme 2. The fluorine was introduced through reaction of hydroxy nitrile **8** with DAST. Surprisingly, treatment of **8** with FAR led to two unidentified products, even at −100 °C, and the desired product could not be detected.

Although pure isomers can be obtained by column chromatography of the intermediates, an easier way to prepare the desired isomer is through irradiation in an appropriate solvent, followed by HPLC separation.[9] Irradiation of a dilute solution of **6** or **9** in acetonitrile with a 200-W tungsten lamp leads to a photostationary state consisting of predominantly the mono-*cis* isomers. Isocratic straight phase separation with HPLC affords the mono-*cis* isomers in pure form.

Discussion and Conclusion

We have developed a new, high-yield method for preparing the fluoromethyl group. Synthetic options for the fluoromethyl group are severely limited when compared to those of the trifluoromethyl group owing to its enhanced reactivity in reductions, eliminations, and substitutions. The key reaction, the conversion of **1** into **2**, likely proceeds through *in situ* generation of (chloromethyl)lithium. This reaction is known to work for esters with electron-withdrawing groups, but a complexing agent (LiBr) is required to stabilize the intermediate and prevent formation of the ketone before workup.[3] *N*-Methoxy-*N*-methylamides form a stable intermediate upon reaction with organolithium and Grignard reagents, and as expected, we found that the reaction of **1** to **2** proceeds equally well with and without LiBr. However, higher temperatures and longer reaction times dramatically decreased the yield of the reaction. The use of fresh reagents is also critical. Replacement of methyllithium by LDA has been reported to give products resulting from proton abstraction rather than lithium iodide exchange in the reaction of chloroiodomethane and esters;[10] similar observations were made in the reaction of CH_2Br_2 and esters, using butyllithium.[11] For the preparation of the fluoromethyl group, it would be of interest to use CH_2FI instead of CH_2ICl, but CH_2IF is not easily available.[12]

An attractive approach for selective introduction of fluorine consists of the reaction of enol acetates, enol silyl ethers, or lithium enolates with electrophilic fluorinating agents such as trifluoromethyl hypofluorite, acetyl hypofluorite, or pyridinium triflates.[13] Initial attempts to introduce a fluorine directly to the β-ionone skeleton through fluorination of its conjugated enolate using pyridinium triflates were unsuccessful, and we did not explore this approach further.

FAR generally fluorinates alcohols selectively at room temperature or higher.[5] We were surprised to find that FAR reacts with **4** and **8** instantaneously at −100 °C. **8** is probably fluorinated followed by rearrangement. Vinylic and allylic fluorides are prone to reduction by $LiAlH_4$ and DIBALH. In the case of [12,14-$^{13}C_2$]-8-fluororetinal, we observed small amounts of the corresponding hydrodefluoro product in every reduction step. Likewise, for the allylic fluorides in this work stringent temperature control is needed in the reduction steps to avoid undesired reduction of the fluoride.

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Vinylic fluorides in retinal at positions C8, C10, C12, and C14 have previously been prepared through the use of fluorophosphonate.[14,15] A few methods have been reported for the synthesis of (trifluoromethyl)retinals. We have described here a novel route to the monofluoromethyl methyl group that is compatible with our carbon-13 labeling schemes.[16,17] These procedures are easily expanded to various other carotenoids and polyenes and complement recently published elegant work on fluorinated methyl groups.[18] The number of fluorine-containing starting materials commercially available is still extremely limited, and although the synthesis of compounds containing both carbon-13 and fluorine-19 labels in the same molecule is primarily of interest for NMR studies, the methods developed may lead to new organofluorides with application in biochemical and medicinal chemistry, where the demand for fluorinated analogs is high.

Experimental Section

THF was distilled prior to use from $LiAlH_4$, and diethyl ether, petroleum ether (bp 35−60 °C), and *n*-hexane from P_2O_5. Other chemicals (reagent grade) were used without purification. *N*-Methoxy-*N*-methyl-3-(2,6,6-trimethylcyclohexenyl)propenoic acid amide (**1**), *N*,5-dimethyl-*N*-methoxy-7-(2,6,6-trimethylcyclohexenyl)heptenoic acid amide (**7**), and (2-chloro-2,1,1-trifluoroetyl)diethylamine[19] were prepared according to published methods. DIBALH was used as a 1.0 M solution in hexanes, *n*-butyllithium (BuLi) as a 1.6 M solution in hexanes, and methyllithium (MeLi) as a 1.4 M solution in diethyl ether. These solutions were introduced into the reaction mixture dropwise via a syringe. Reactions were carried out under a nitrogen atmosphere.

After completion of the reaction (according to TLC), the products were isolated as follows. First, unless stated otherwise, water was added to the reaction mixture. The layers were separated, and the aqueous phase was extracted three times with diethyl ether. The combined organic layers were washed with brine and dried with $MgSO_4$. The solids were filtered off over a glass-fritted funnel. The residue was rinsed with diethyl ether. The solvents in the filtrate were evaporated in vacuo (20 mmHg). Unless stated otherwise, purification was performed by column SiO_2 chromatography (60−200 mesh), using petroleum ether/diethyl ether mixtures as eluent. Proton and proton-decoupled carbon NMR spectra were run in $CDCl_3$ with tetramethylsilane ($\delta = 0$ ppm) as an internal standard at 500 and 125 MHz, respectively. Fluorine NMR spectra were recorded at 461 MHz, with CCl_3F ($\delta = 0$ ppm) as an internal standard. UV/vis spectra were run in methanol. FT-IR absorbance spectra were run on pure material dried down on a germanium crystal. The HRMS were recorded using EI at 70 eV. HPLC was performed using straight phase isocratic elution with diethyl ether/petroleum ether mixtures and detection of the absorbance at 360 nm.

1-Chloro-4-(2,6,6-trimethylcyclohexenyl)-3-butenone (2). To a stirred solution of chloroiodomethane (1.1 g, 6.5 mmol) and **1** (1.0 g, 4.2 mmol) in 30 mL of THF was added MeLi (4.2 mmol) at −78 °C. The solution was stirred for 15 min at −78 °C. Then water was added, and the product was isolated and purified, yielding 0.60 g (91%). ^{1}H NMR: δ 7.51 (d, $J = 16.5$ Hz, 1H), 6.38 (d, $J = 16.3$ Hz, 1H), 4.22 (s, 2H), 2.10 (t, $J = 6.2$ Hz, 2H), 1.81 (s, 3H), 1.63 (m, 2H), 1.51 (m, 2H), 1.09 (s, 6H). ^{13}C NMR: δ 191.3; 144.8; 138.4; 136.2; 125.8; 46.9; 40.0; 34.1; 33.9; 28.8; 21.7; 18.8. Anal. Calcd for $C_{13}H_{19}OCl$: C, 68.86; H, 8.45. Found: C, 68.70; H, 8.39.

3-(Chloromethyl)-5-(2,6,6-trimethylcyclohexenyl)-2,4-pentadienenitrile (3). (Diethylphosphono)acetonitrile (0.55 g, 3.1 mmol) was dissolved in THF (40 mL), and BuLi (3.0 mmol) was added at −60 °C. The mixture was stirred for 10 min; then **2** (0.6 g, 2.6 mmol) was added at −60 °C and the mixture was stirred for 15 min. Water was added, and the product was isolated and purified, yielding 0.41 g (63%) of the corresponding chloro nitrile as a mixture of isomers. ^{1}H NMR: trans, δ 6.76 (d, $J = 16.3$ Hz, 1H), 6.62 (d, $J = 16.4$ Hz, 1H), 5.49 (s, 1H), 4.34 (d, $J = 0.7$ Hz, 2H), 2.08 (m, 2H), 1.79 (s, 3H), 1.64 (m, 2H), 1.49 (m, 2H), 1.08 (s, 6H); 9-cis, 6.89 (d, $J = 16.4$ Hz, 1H), 6.08 (d, $J = 16.3$ Hz, 1H), 5.33 (s, 1H), 4.48 (s, 2H), 2.07 (m, 2H), 1.75 (s, 3H), 1.64 (m, 2H), 1.49 (m, 2H), 1.07 (s, 6H). Anal. Calcd for $C_{15}H_{20}ClN$: C, 72.13; H, 8.07; N, 5.61. Found: C, 72.31; H, 8.19; N, 5.45.

3-(Hydroxymethyl)-5-(2,6,6-trimethylcyclohexenyl)-2,4-pentadienenitrile (4). To a solution of chloro nitrile (0.41 g, 1.6 mmol) in 50 mL of acetone were added a solution of sodium acetate (1.0 g, 12 mmol) and NaI (0.5 g, 3.4 mmol) in 10 mL of water. After 12 h of reflux, the mixture was concentrated and the product was isolated and purified, yielding 0.38 g (85%) as a mixture of isomers. ^{1}H NMR: δ 6.62 (s, 1H); 5.39 (br s, 1H), 4.93 (d, $J = 1.4$ Hz, 2H), 2.16 (s, 3H), 2.06 (m, 2H), 1.77 (s, 3H), 1.62 (m, 2H), 1.48 (m, 2H), 1.05 (s, 6H). IR: 2214, 1749, 1607, 1456 cm^{-1}.

The acetate (0.38 g, 1.4 mmol) was dissolved in methanol (30 mL). At 0 °C 200 mg of KOH in water (1 mL) was added and the mixture was stirred at 0 °C for 10 min. Then acetic acid (2 mL) was added, and the mixture was concentrated in vacuo. Water was added, and the product was extracted with CH_2Cl_2. The organic layer was washed (brine) and dried ($MgSO_4$), and the solvents were evaporated, yielding 0.28 g (87%) of **4**. ^{1}H NMR: δ 6.59 (d, $J = 16.6$ Hz, 1H), 6.54 (d, $J = 16.7$ Hz, 1H), 5.56 (s, 1H), 4.52 (d, $J = 3.3$ Hz, 2H), 2.77 (s, 1H), 2.05 (t, $J = 6.2$ Hz, 2H), 1.76 (s, 3H), 1.62 (m, 2H), 1.49 (m, 2H), 1.04 (s, 6H). ^{13}C NMR: δ 159.1; 136.6; 134.7; 133.3; 127.1; 117.4; 92.5; 61.0; 39.3; 34.0; 33.1; 28.8; 21.6; 18.9. IR: 2212 cm^{-1}. Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 78.03; H, 9.34; N, 5.98.

3-(Fluoromethyl)-5-(2,6,6-trimethylcyclohexenyl)-2,4-pentadienenitrile (5). Alcohol **4** (0.28 g, 1.2 mmol) was dissolved in methylene chloride, and DAST (2.5 mmol) was added dropwise at −60 °C. The mixture was allowed to warm to room temperature and stirred for 30 min at −20 °C. After workup, a 78% yield (0.22 g) was obtained. ^{1}H NMR: δ 6.58 (dd, $J = 16.3$ Hz, 2.4 Hz, 1H), 6.48 (d, $J = 16.5$ Hz, 1H), 5.42 (s, 1H), 5.24 (d, $J = 46.0$ Hz, 2H), 2.05 (m, 2H), 1.75 (s, 3H), 1.63 (m, 2H), 1.46 (m, 2H), 1.03 (s, 6H). ^{13}C NMR: δ 153.8 (d, $J = 14.0$ Hz); 136.5; 135.7; 134.0; 116.4; 126.1; 93.7 (d, $J = 16.6$ Hz); 80.8 (d, $J = 176.0$ Hz); 39.4; 34.0; 33.2; 28.8; 21.7; 18.9. ^{19}F NMR: δ −224.1 (t, $J = 48.8$ Hz). IR: 2210 cm^{-1}. Anal. Calcd for $C_{15}H_{20}FN$: C, 77.22; H, 8.64; N, 6.00. Found: C, 77.18; H, 8.79; N, 5.76.

7-(Fluoromethyl)-3-methyl-9-(2,6,6-trimethylcyclohexenyl)-2,4,6,8-nonatetraenal (6). Nitrile **5** (0.22 g, 0.94 mmol) was dissolved in hexanes, and DIBALH (2 mmol) was added at −60 °C. The mixture was stirred for 10 min; then a slurry of 2 g of SiO_2 and 0.5 g of water was added. The mixture was allowed to warm to room temperature, $MgSO_4$ was added, and the solids were filtered off over Celite. After evaporation of the solvents, a 0.2 g (90%) yield was obtained. ^{1}H NMR: δ 10.18 (dd, $J = 1.3$ Hz, 7.6 Hz, 1H), 6.88 (d, $J = 16.5$ Hz, 1H), 6.52 (d, $J = 16.5$ Hz, 1H), 6.09 (d, $J = 7.6$ Hz, 1H), 5.23 (d, $J = 46.7$ Hz, 2H), 2.06 (t, $J = 6.1$ Hz, 2H), 1.76 (s, 3H), 1.63 (m, 2H), 1.49 (m, 2H), 1.05 (s, 6H). ^{13}C NMR: δ 190.2; 151.6; 137.1; 136.9; 133.4; 124.3 (d, $J = 10.8$ Hz); 123.9; 81.8 (d, $J = 175.9$ Hz); 39.4; 34.1; 33.2; 28.9; 21.8; 18.9. ^{19}F NMR: δ −220.8 (t, $J = 46.4$ Hz). IR: 1671 cm^{-1}.

Triethyl 3-methyl-4-phosphonocrotonate (0.26 g, 1 mmol) was dissolved in THF, and LDA (0.95 mmol) was added. The fluoro aldehyde (0.2 g, 0.85 mmol) was added at −40 °C, and the mixture was stirred at 0 °C for 20 min. After workup and

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purification, an isomeric mixture of the corresponding ester was obtained (0.24 g). IR: 1710 cm^{-1}.

The fluoro ester (0.24 g, 0.69 mmol) was dissolved in THF, and DIBALH (2 mmol) was added at −60 °C. After the solution was stirred for 10 min, a slurry of 2 g of SiO_2 and 0.5 g of water was added. The mixture was allowed to warm to room temperature, $MgSO_4$ was added, and the solids were filtered off over Celite. After evaporation of the solvents, 33% yield (0.07 g) was obtained. The isomeric mixture of alcohols was dissolved in 30 mL of dichloromethane, and 1 g of MnO_2 was added. The mixture was stirred for 1 h; then the solids were filtered off over Celite. The residue was purified to give an isomeric mixture of aldehyde **6** (58 mg, 85%). HRMS: calcd 302.2046, found 302.2036. The pure mono-*cis* isomers were obtained by irradiation in acetonitrile (1 mg/mL) and subsequent HPLC separation. ***all-E***. IR: 1664 cm^{-1}. ^{1}H NMR: δ 10.12 ppm (d, J = 8.0 Hz (15-CH)); 7.15 (dd, J = 11.2, 15.9 Hz (11-CH)); 6.51 (d, J = 16.1 Hz (8-CH)); 6.45 (d, J = 12.8 Hz (10-CH)); 6.37 (d, J = 11.0 Hz (7-CH)); 6.30 (d, J = 11.5 Hz (12-CH)); 6.01 (d, J = 8.2 Hz (14-CH)); 5.13 (d, J = 47.1 Hz (19-CH_2)); 2.33 (s (20-CH_3)); 2.05 (t, J = 6.0 Hz (4-CH_2)); 1.76 (s (18-CH_3)); 1.61 (m (3-CH_2)); 1.49 (m (2-CH_2)); 1.04 (s (16,17-CH_3)). ^{19}F-NMR: δ −218.1 ppm (t, J = 47.0 Hz). Anal. Calcd for $C_{20}H_{27}FO$: C, 79.43; H, 9.00. Found: C, 79.65; H, 9.11.

3-(Hydroxymethyl)-7-methyl-9-(2,6,6-trimethylcyclohexenyl)-2,4,6,8-nonatetraenenitrile (8). Chloroiodomethane (2.1 g, 12 mmol) and **7** (1.9 g, 6.3 mmol) were dissolved in 70 mL of THF. At −60 °C MeLi (12 mmol) was added over 10 min and the mixture was stirred for 15 min more at −40 °C. Then water was added, and the product was isolated and purified, yielding 1.6 g (87%) of the chloromethyl ketone. ^{1}H NMR: δ 7.79 (dd, J = 12.2, 14.9 Hz, 1H), 6.49 (d, J = 16.0 Hz, 1H), 6.42 (d, J = 14.9 Hz), 6.20 (d, J = 10.5 Hz, 1H), 6.20 (d, J = 16.2 Hz), 4.19 (s, 2H), 2.08 (s, 3H), 2.04 (m, 2H), 1.72 (s, 3H), 1.63 (m, 2H), 1.49 (m, 2H), 1.04 (s, 6H).

(Diethylphosphono)acetonitrile (1.1 g, 6.2 mmol) was dissolved in THF (50 mL), and BuLi (6.2 mmol) was added at −60 °C. The mixture was stirred for 10 min; then the chloromethyl ketone (1.5 g, 5.1 mmol) was added at −60 °C and the mixture was stirred for 15 min. Water was added, and the product was isolated and purified, yielding 1.3 g (80%) of the corresponding chloronitrile as a mixture of 13-*E*/*Z* isomers. ^{1}H NMR: 13-*E*, δ 7.12 (dd, J = 11.4, 15.3 Hz, 1H), 6.69 (d, J = 15.4 Hz, 1H), 6.38 (d, J = 16.1 Hz, 1H), 6.21 (d, J = 12.9 Hz, 1H), 6.18 (d, J = 16.3 Hz), 5.43 (s, 1H), 4.33 (s, 2H), 2.04 (m, 2H), 2.03 (s, 3H), 1.72 (s, 3H), 1.63 (m, 2H), 1.49 (m, 2H), 1.04 (s, 6H).

The chloro nitrile (1.1 g, 3.5 mmol) was dissolved in acetone (70 mL) and added to sodium acetate (3.0 g, 35 mmol) and sodium iodide (0.5 g, 3.3 mmol) in water (15 mL). The mixture was refluxed for 6 h. The solvents were concentrated in vacuo, and the product was isolated and purified, yielding 1.1 g (%) of the acetate nitrile. ^{1}H NMR: δ 6.99 (dd, J = 11.4, 15.3 Hz, 1H), 6.71 (d, J = 15.4 Hz, 1H), 6.37 (d, J = 16.0 Hz, 1H), 6.19 (d, J = 11.3 Hz, 1H), 6.17 (d, J = 16.0 Hz, 1H), 5.36 (s, 1H), 4.94 (d, J = 1.2 Hz, 2H), 2.15 (s, 3H), 2.04 (m, 2H), 2.00 (s, 3H), 1.72 (s, 3H), 1.63 (m, 2H), 1.49 (m, 2H), 1.04 (s, 6H). ^{13}C NMR: δ 170.1; 153.1; 142.6; 137.5; 136.8; 132.7; 130.8; 130.4; 128.8; 125.2; 116.8; 94.5; 62.2; 39.6; 34.2; 33.1; 28.9; 21.7; 20.7; 19.2; 13.0. IR: 1751 cm^{-1}.

The acetate (0.78 g, 2.3 mmol) was dissolved in methanol (30 mL). At 0 °C 200 mg of KOH in water (2 mL) was added and the mixture was stirred at 0 °C for 10 min. Then acetic acid (2 mL) was added, and the mixture was concentrated in vacuo. Water was added, and the product was extracted with CH_2Cl_2. The organic layer was washed (brine) and dried ($MgSO_4$), and the solvents were evaporated. The residue was dissolved in diethyl ether (1 mL), petroleum ether (20 mL) was added, and the mixture was stored at −20 °C overnight. Crystals of the *all-E* hydroxymethyl nitrile **8** (480 mg, 70%) were obtained. ^{1}H NMR: δ 6.94 (dd, J = 1.4, 15.5 Hz, 1H), 6.71 (d, J = 15.5 Hz, 1H), 6.34 (d, J = 16.1 Hz, 1H), 6.18 (d, J = 11.2 Hz, 1H), 6.16 (d, J = 16.1 Hz, 1H), 5.53 (s, 1H), 4.55 (dd, J = 1.1, 5.6 Hz, 2H), 2.03 (t, J = 6.2 Hz, 2H), 1.99 (s, 3H), 1.85 (t, J = 5.8 Hz, 1H), 1.72 (s, 3H), 1.63 (m, 2H), 1.49 (m, 2H), 1.03 (s, 6H). ^{13}C NMR: δ 158.1; 141.9; 137.5; 136.9; 131.7; 130.6; 130.0; 129.0; 125.4; 117.5; 93.1; 61.6; 39.6; 34.2; 33.1; 29.0; 21.7; 19.1; 13.0. IR: 2214 cm^{-1}. Anal. Calcd for $C_{20}H_{27}NO$: C, 80.76; H, 9.15; N, 4.71. Found: C, 80.47; H, 8.96; N, 4.59.

3-(Fluoromethyl)-7-methyl-9-(2,6,6-trimethylcyclohexenyl)-2,4,6,8-nonatetraenal (9). The *all-E* hydroxymethyl nitrile **8** (0.26 g, 0.88 mmol) was dissolved in CH_2Cl_2 (20 mL) and cooled to −60 °C. DAST (0.5 g, mmol) was added, and the mixture was stirred for 2 h at room temperature. Then water was added, and the product was isolated and purified, yielding 0.22 g (73%) of the fluoromethyl nitrile. Some *cis*/*trans* isomerization had occurred. ^{1}H NMR: δ 6.88 (dd, J = 11.3 Hz, 15.6 Hz, 1H), 6.68 (dd, J = 15.6 Hz, 1.0 Hz, 1H), 6.37 (d, J = 16.1 Hz, 1H), 6.17 (d, J = 10.0 Hz, 1H), 6.17 (d, J = 16.4 Hz, 1H), 5.39 (s, 1H), 5.24 (d, J = 45.4 Hz, 2H), 2.04 (t, J = 5.9 Hz, 2H), 2.00 (s, 3H), 1.72 (s, 3H), 1.63 (m, 2H), 1.49 (m, 2H), 1.04 (s, 6H). ^{13}C NMR: δ 153.5 (d, J = 14.2 Hz); 142.6; 137.5; 136.8; 132.4; 130.8; 130.4; 128.7; 124.2; 116.6; 93.6 (d, J = 16.4 Hz); 81.0 (d, J = 176.0 Hz); 39.5; 34.2; 33.1; 28.9; 21.7; 19.1; 13.0. ^{19}F NMR: δ −223.1 (t, J = 47.6 Hz). IR: 2210 cm^{-1}.

The fluoro nitrile (0.2 g, mmol) was dissolved in petroleum ether (20 mL), and at -60 °C DIBALH (1 mL, 1 mmol) was added. The mixture was stirred for 10 min. Then a slurry of 1 g of water and 2 g of silica gel was added, and the mixture was stirred for 1 h at room temperature. The solids were filtered off, the solvents were evaporated, and the product was purified, yielding 0.18 g. IR: 1665 cm^{-1}. HRMS: calcd 302.2046, found 302.2036. The pure mono-*cis* isomers were obtained by irradiation in acetonitrile (1 mg/ mL) and subsequent HPLC separation.

all-E. ^{1}H NMR: δ 10.11 ppm (d, J = 7.2 Hz (15-CH)); 7.13 (d, J = 15.4 Hz (12-CH)); 6.95 (dd, J = 11.3, 15.4 Hz (11-CH)); 6.38 (d, J = 16.1 Hz (7- or 8-CH)); 6.20 (d, J = 11.0 Hz (10-CH)); 6.18 (d, J = 16.2 Hz (7- or 8-CH)); 6.06 (d, J = 7.2 Hz (14-CH)); 5.26 (d, J = 46.8 Hz (20-CH_2)); 2.03 (t, J = 6.0 Hz (4-CH_2)); 2.01 (s (19-CH_3)); 1.72 (s (18-CH_3)); 1.61 m (3-CH_2)); 1.49 (m (2-CH_2)); 1.03 (s (16,17-CH_3)). ^{13}C NMR: δ 190.0 ppm (15-C); 150.8 (d, J = 14.0 Hz (13-C)); 142.3 (q); 137.5 (q); 136.8; 133.4; 130.7 (q); 130.3; 129.2; 124.1 (d, J = 11.2 Hz (12-C)); 122.2 (14-C); 81.9 (d, J = 175.6 Hz (19-C)); 39.6; 34.2; 33.1; 28.9; 21.7; 19.1; 13.0. ^{19}F NMR: δ −223.4 ppm (t, J = 46.4 Hz). Anal. Calcd for $C_{20}H_{27}FO$: C, 79.43; H, 9.00. Found: C, 79.21; H, 9.15.

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