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Stereoselective Synthesis of 9-*trans*-9-Desmethyl-9-fluororetinals Based on the Four-Components Coupling Approach

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Abstract: 9-*trans*-9-Desmethyl-9-fluororetinal analogs were synthesized by the four-components coupling approach. Horner-Emmons olefination of **3** afforded the undesired 2*E*-isomer **5** which was transformed to 6*E*-triene **8** via the Stille coupling reaction. Isomerization of 6*E*-triene **8** with an iodine catalyst proceeded in a highly regioselective manner to give the 6*Z*-isomer **9**. Wittig reaction of **13** derived from oxidation of **9** followed by reduction and oxidation provided 13-*cis*-9-desmethyl-9-fluororetinal **17**. The 13-*cis*-analog **17** was regioselectively converted to the all-*trans*-isomer **19** by treatment with trifluoroacetic acid.

Retinal proteins play an important role in the light-energy converting process for vision, phototaxis, and light-driven ion pumping.[1,2] The primary photochemical events for the light-energy converting process involve the regioselective isomerization of retinal chromophore linked to the retinal protein.[3] Recently, the crucial role of the methyl group at C-9 for the conformational change in the retinal protein induced by the isomerization has been indicated (Fig 1).[4] This evidence has been provided by a retinal analog modified at the methyl group at C-9. For example, in the study of visual signal transduction, a rhodopsin analog incorporated 9-desmethylretinal allowed diminished activation of a peripheral membrane protein of the G-protein family, transducin, as compared to that of native rhodopsin.[4c,e] Our continuous efforts to clarify the mechanism using retinal analogs as well as the facts along these lines prompted us to explore stereoselective syntheses of 9-*trans*-retinal analogs modified at C-9 (9-R-retinal) .[5] Several 9-R-retinal analogs have been reported to date.[5,6] However, there are a limited number of successful examples with respect to their stereoselective construction at C-9 with the 9-*trans*-configuration, [5,6a-c] despite the fact that the 9-*trans*-analogs are usually required for biological evaluation. Herein, we describe stereoselective syntheses of 9-*trans*-9-desmethyl-9-fluororetinals (9-F-retinals) which are of potential use for the elucidation of the crucial role of the methyl group at C-9 by ^{19}F-NMR study.[7]

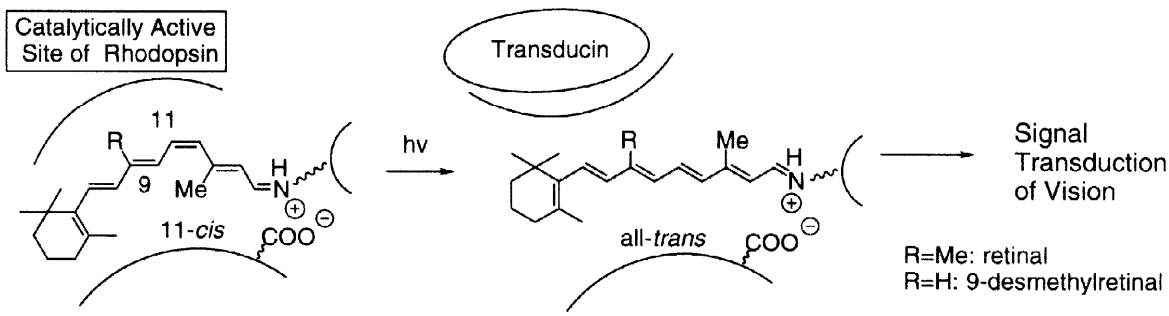

Figure 1. 11-*cis*-Retinal chromophore linked to rhodopsin is converted to an all-*trans*-form (photo-activated rhodopsin R*) by light absorption. The isomerization is accompanied with an intramolecular rearrangement of a catalytically active site of rhodopsin. Activated rhodopsin (R*) binds with transducin known as a peripheral membrane protein of the G-protein family. A single R* catalizes the activation of ~1000 transducin molecules.

† *Dedicated with respect and deep appreciation to the memory of the late Sir Derek H. R. Barton.*

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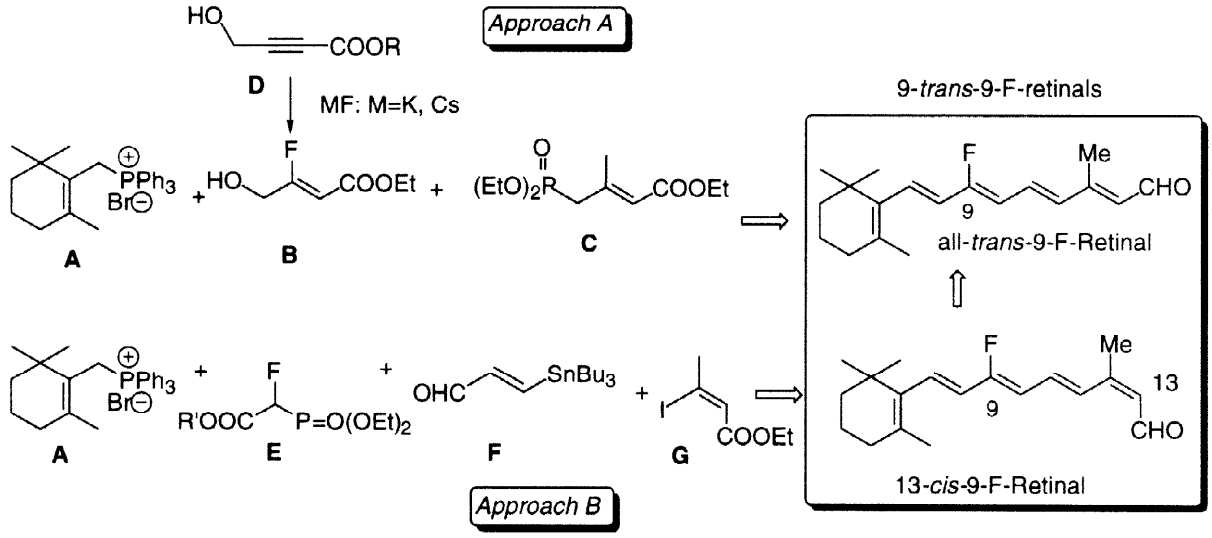
Synthetic Plan

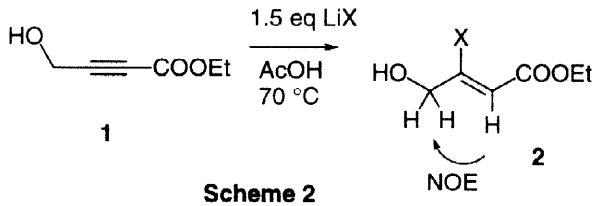
Our approaches for the stereoselective synthesis of 9-*trans*-9-F-retinal analogs are depicted in Scheme 1. In approach A, the three components **A**, **B** and **C** are sequentially linked by Wittig and Horner-Emmons olefinations to give all-*trans*-9-F-retinal. The key to this approach is the stereoselective construction of the fluoroolefin **B**. We have reported that 4-hydroxybutynoate **D** is a favorable chloride, bromide, or iodide anion acceptor to provide the corresponding *Z*-β-haloacrylates.[5a] We envisaged that the fluoroolefin **B** would be accessible by a similar manner as the reported method.[5a] The second approach B consisted of the coupling of four components **A**, **E**, **F**, and **G**. The introduction of the fluorine atom by this approach would be made by the Horner-Emmons reaction of **E** with stannyl acrylaldehyde **E**, followed by the Stille coupling and Wittig reactions to afford 13-*cis*-9-F-retinal. It is also envisioned that the 13-*cis*-isomer would be isomerized to all-*trans*-9-F-retinal.



Scheme 1

Synthesis of 9-Fluororetinals

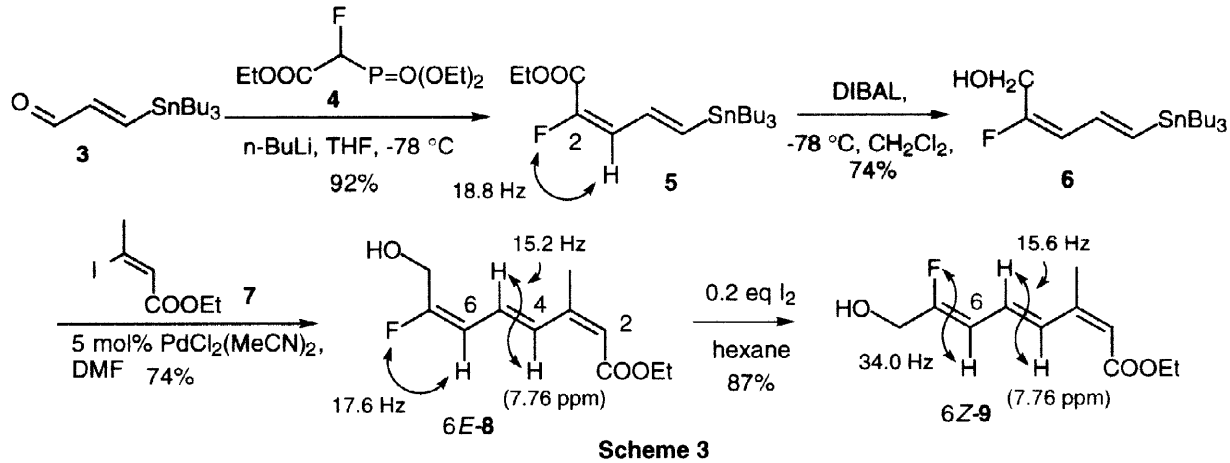
Synthesis of all-*trans*-9-F-retinal was begun with approach A. The addition reaction of lithium chloride to **1** in acetic acid at 70 °C proceeded in a highly stereoselective manner to give *Z*-**2a** (Scheme 2, Table 1).[5a,8] Lithium bromide and lithium iodide also underwent the stereoselective addition reaction to give *Z*-**2b,c**. Stereostructures of **2a-c** were confirmed to the desired *Z*-form by their NOE experiments, respectively. On the other hand, the addition of potassium fluoride to **1** in acetic acid at 70 °C led to only the recovered starting material. The use of more nucleophilic fluorides, *e.g.*, cesium fluoride and tetrabutylammonium fluoride, also failed even under reflux conditions due probably to the poor nucleophilicity of the fluoride anion.



Scheme 2

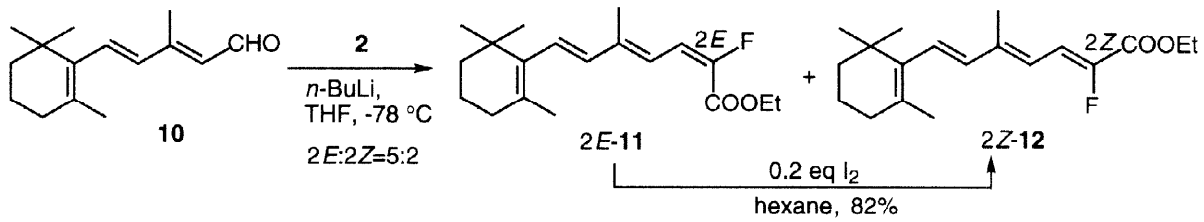
Table 1. Addition of LiX

Compound	X	time (h)	Yield (%)	NOE (%)
2a	F	24	0	-----
2b	Cl	16	50	3.25
2c	Br	2	84	4.60
2d	I	1	72	5.99



Scheme 3

We next turned our attention to approach B. Horner-Emmons olefination of **3**[9] with commercially available phosphonate **4** afforded ester **5** as a single isomer. Product **5** was thought to be the undesired *E*-isomer by comparison of the three bond coupling constants between the fluorine at C-2 and the proton at C-3 (^3J = 18.8 Hz) with those of other fluoroolefins reported [*E*-isomers (^3J = 20-25 Hz); *Z*-isomer (^3J = 30-40 Hz)][12]. The stereochemistry of **5** could be determined in a later evaluation of the configuration of **8** and **9**, both of which are related in the regioisomers with respect to the fluoroolefin moiety. The stereochemical outcome affording the *E*-isomer as opposed to the representative results using phosphonoacetates having an alkyl group instead of the fluorine atom is ascribed to the neighboring group participation of the fluorine atom.[10,11] Conversion of 2*E*-**5** into the requisite 2*Z*-isomer using iodine,[13] irradiation with uv lights,[14] and the phenylthio radical[15] resulted in either recovery of the starting material or decomposition. Isomerization with allyl alcohol **6** obtained by reduction of **5** was also unsuccessful. Since the stannylolefin compounds of **5** and **6** were unstable under these isomerization reaction conditions,[16] we decided to test the feasibility late in the transformation. Thus, alcohol **6** was subjected to the Stille coupling reaction with *Z*-**7** to give 6*E*-triene **8**, which was found to be more stable than **5** and **6**.[17] We found that 6*E*-triene **8** underwent isomerization by treatment with a catalytic amount of iodine to give the 6*Z*-olefin **9** as a single isomer in high yield (Scheme 3). Comparison of the ^{1}H-NMR data of **8** and **9** suggested that only the fluoroolefin moiety was isomerized (Scheme 3). We also examined the isomerization reaction with 2*E*-fluoroolefin **11** which was easily obtained as a major isomer by the Horner-Emmons olefination of **10** with **2**.[10d] Similarly, 2*E*-**11** was regioselectively transformed into the *Z*-isomer **12** (Scheme 4).



Scheme 4

The previous observations wherein the *E*-fluoroolefins were selectively inverted indicated the participation of the fluorine atom. It has been reported that 2-fluoropropene reacts faster with electrophiles, *e.g.*, trifluoroacetic

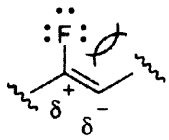
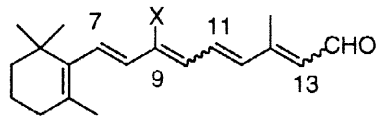


Figure 2 Charge distribution of fluoroolefin:Steric repulsion between lone-pair electrons on the fluorine atom and the π-orbital of olefin induces the charge distribution.

acid and sulfuric acid, than propene.[18] The enhanced reactivity of fluoroolefin toward the electrophile was explained by the positive inductive effect (+*I*π effect) (Fig. 2).[18] In order to assess the electron delocalization of fluoroolefins, we compared the ^{1}H-NMR data of all-*trans*-9-desmethylretinal,[19] all-*trans*-retinal,[20] and 9-Cl, Br, I-retinals[5a] with those of the 9-F-retinals (Table 2). It is clear that the protons at C-10 of all-*trans*- and 13-*cis*-9-F-retinals markedly shifted to a higher magnetic field than those of the others.

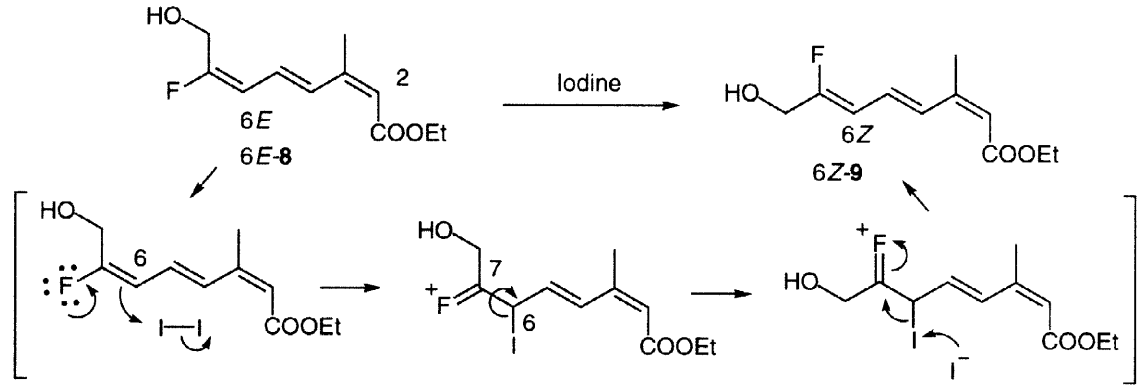
Table 2. NMR Data of 9-X-Retinal



Compound	Chemical Shift Value [400 MHz, $CDCl_3$, ppm]									Coupling Constants (*J* in Hz)					
	7	8	10	11	12	13-Me	14	15	9-F[d]	7-8	10-11	11-12	14-15	8-9	9-10
9-F[a,b] all-*trans*	6.66	6.01	5.79[c]	7.19	6.48	2.34	5.95	10.06	-119.64	16.4	11.2	15.6	8.0	26.4	33.6
13-*cis*	6.66	6.01	5.83	7.08	7.43	2.15	5.85	10.16	-119.80	16.8	11.6	15.6	7.6	26.4	33.6
9-Cl all-*trans*	6.79	6.21	6.46	7.25	6.38	2.35	5.99	10.13		15.2	10.8	15.6	7.6		
13-*cis*	6.79	6.22	6.41	7.15	7.39	2.17	5.91	10.18		15.2	10.8	15.6	8.0		
9-Br all-*trans*	6.78	6.17	6.56	7.23	6.55	2.35	6.00	10.13		15.2	10.4	15.2	7.2		
13-*cis*	6.78	6.19	6.60	7.13	7.43	2.17	5.92	10.18		15.2	10.4	15.2	7.6		
9-*cis*	6.74	6.51	6.69	7.01	6.39	2.31	6.02	10.12		15.2	11.2	15.2	8.4		
9-I all-*trans*	6.64	5.86	6.50	7.16	6.56	2.37	6.01	10.14		14.8	10.4	15.6	8.0		
13-*cis*	6.68	5.86	6.55	7.06	7.48	2.19	5.92	10.19		14.4	10.4	15.2	8.0		
9-*cis*	6.56	6.06	7.02	7.09	6.33	2.30	6.02	10.11		14.4	11.2	14.4			
9-H[e] all-*trans*	6.34	6.19	6.31	6.81	6.34	2.29	5.96	10.10							
9-Me[f] all-*trans* (retinal)	6.36	6.18	6.20	7.15	6.37	2.33	5.98	10.12							

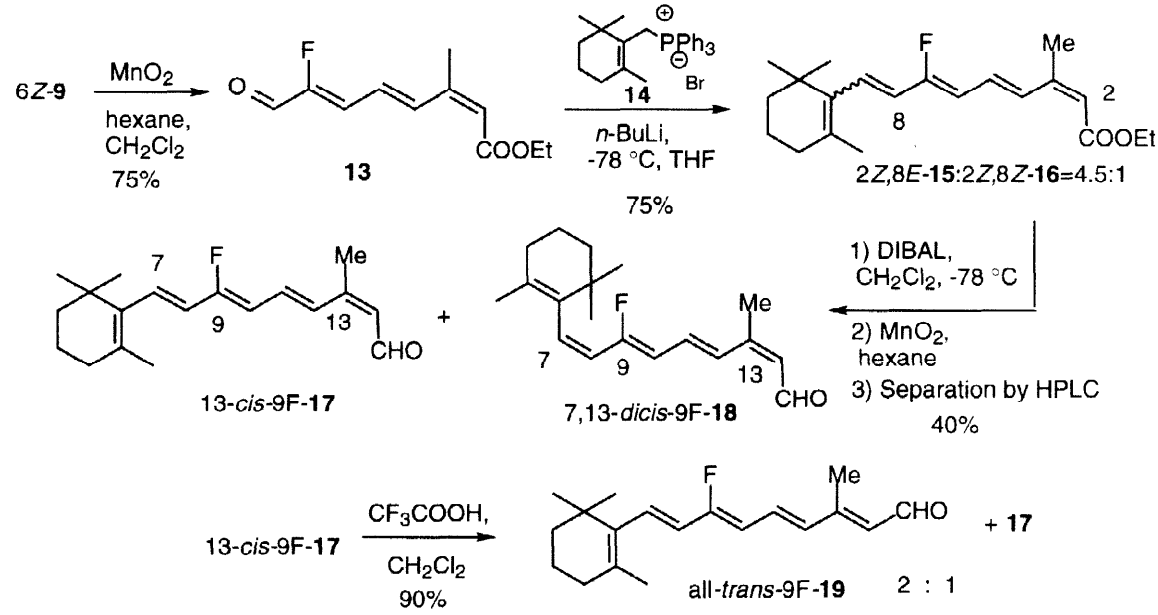
[a] The Numbering system and designations *cis* and *trans* in this table are according to the retinoid structure. [b] Methanol-d_4. [c] 5.57 ppm in C_6D_6 for all-*trans*-9F. see ref. 6b [d] ^{19}F-NMR [376 MHz, methanol-d_4 ,Trifluoroacetic acid (-76.50 ppm) as the external standard]. [e] ref. 19, [f] ref. 20.

These results would imply that the C-10 position of the fluororetinals appear to be electronically enhanced due to the +*I*π effect. Accordingly, the highly regioselective isomerization previously observed would be conducted by the fluorine atom attached directly to the olefin and take place *via* an electrophilic ionic addition of iodine followed by the elimination of iodine from **c** accompanied by the single-bond rotation between C-6 and C-7 to afford the more stable isomer **9** (Scheme 5)



Scheme 5

We next subjected the conversion of 6*Z*-**9** to 9-F-retinals. Oxidation of 6*Z*-**9** followed by Wittig olefination of the resulting aldehyde **13** with **14**[21] gave a 4.5:1 mixture of **15** and **16**. Without separation, the mixture of regioisomers was transformed to the corresponding 9-F-retinals **17** and **18** by treatment with diisobutylaluminum hydride followed by oxidation with activated manganese dioxide (Scheme 6). The resulting 13-*cis*-**17** and its 7-*cis*-isomer **18** were separated by HPLC. The final attempt of this approach is comprised of the isomerization of 13-*cis*-**17** to all-*trans*-**19**. For this operation, we initially examined an iodine-catalyzed isomerization which has been applied to the isomerization of the 13-*cis*-retinal to the all-*trans*-isomer.[12b] However, the isomerization was sluggish to yield a small amount of a mixture of regioisomers. During the course of these manipulations, we found that the 13-*cis*-**17** was isomerized to the all-*trans*-isomer **19** upon standing in a solution of $CDCl_3$ to provide nearly a 1:2 mixture of **17** and **19**. The all-*trans*-isomer **19** was also isomerized to afford the same mixture. These results would be considerably affected by an acid contaminated in $CDCl_3$. Thus, the synthesis of all-*trans*-9-fluororetinal was accomplished by treatment of 13-*cis*-**17** with trifluoroacetic acid affording a 2:1 mixture of all-*trans*- and 13-*cis*-**17**.[22]



Scheme 6

Conclusions

We have achieved stereoselective syntheses of all-*trans*- and 13-*cis*-9-*trans*-9-F-retinal analogs by the four-components coupling approach B. Although the key Horner-Emmons reaction with fluorophosphonate **2** afforded fluoroolefin **3** accompanied with the undesired stereochemistry, the problem was circumvented by regioselective isomerization using an iodine catalyst. We also found that trifluoroacetic acid is superior to iodine for the regioselective isomerization of 13-*cis*-**17** to all-*trans*-**19**. The 9-F-retinals would be a mimic of the retinal because of the similar steric bulkiness to the methyl group at C-9.[23]

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Experimental Section

General. All nonaqueous reactions were carried out under a nitrogen atmosphere with dry, freshly distilled solvents under anhydrous conditions. Analytical thin-layer chromatography (TLC) was carried out on silica-courted plates (silica gel 60 F-254, 0.25 mm layer thickness, manufactured by E. Merck). Flash column chromatography (fcc) was performed with E. Merck silica gel 60 (230-400 mesh ASTM). Infrared spectra were measured on a Elmer FT-IR 1640 spectrometer. High-resolution mass spectra (HRMS) were recorded on a JOEL JMS-HX 110 for fast atom bombardment ionization (FAB). ^{1}H-NMR spectra were recorded on a JOEL EX-400 spectrometer. Chemical shifts of ^{1}H-NMR are reported in perts per million (ppm, δ) using $CHCl_3$ (7.26 ppm) as the internal reference. Chemical shifts of ^{19}F-NMR are reported in ppm (δ) using trifluoroacetic acid (-76.95 ppm) as the external reference. *J* values were given in Hz. Absorption spectra were measured on a Shimadzu UV-vis 2100 recording spectrometer at 20 °C equipped with a temperature control unit, TOC 280 (Kyoto, Japan). High-performance liquid chromatography (HPLC) was performed with a Shimadzu HPLC system [LC-6AD (system controller), SCL-6B (pump), SPD-6AV (UV-VIS spectrophotometric detector), and C-R4A (chromatopack)] equipped with a Cosmosil® 5SL packed column (20x250) purchased from Nacalai Tesque. The syntheses, purifications, and separations of **15-19** were carried out under subdued red light.

General procedure for the addition of lithium halides to (1).

To a mixture of **1** (384 mg, 3 mmol) in acetic acid (3 mL) was added a lithium halide (4.5 mmol) at 70°C. The mixture was stirred for the period shown in Table 1 and neutralized with saturated sodium bicarbonate at 0°C. The mixture was extracted with dichloromethane. The organic phase was washed with brine, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by fcc (hexane-diethyl ether, 3:2) to give **2a-c**.

Ethyl *Z*-3-Chloro-4-hydroxy-2-butenoate (2a).

According to the general procedure described above, **1** was treated with lithium chloride (191 mg) to give **2a** (246 mg, 50%) as a colorless oil. *Rf*=0.23 (hexane-ether, 3:2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.41 (1H, d, *J*=1.6 Hz), 4.28 (2H, d, *J*=6.8 Hz), 4.23 (2H, q, *J*=6.8 Hz), 2.07 (1H, t, *J*=6.8 Hz), 1.31 (3H, t, *J*=6.8 Hz). HRMS (FAB$^+$) *m/z*: Calcd for $C_6H_{10}O_3{}^{35}Cl$ (M+H) 165.0318, Found: 165.0300.

Ethyl *Z*-3-Bromo-4-hydroxy-2-butenoate (2b).

According to the general procedure described above, **1** was treated with lithium bromide (391 mg) to give **2b** (524 mg, 84%) as a pale yellow oil. *Rf*=0.24 (hexane-ether, 3:2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.71 (1H, s), 4.35 (2H, brs), 4.24 (2H, q, *J*=6.8 Hz), 2.11 (1H, br s), 1.31 (3H, t, *J*=6.8 Hz). HRMS (FAB$^+$) *m/z*: Calcd for $C_6H_{10}O_3{}^{79}Br$ (M+H) 208.9813, Found: 208.9809.

Ethyl *Z*-3-Iodo-4-hydroxy-2-butenoate (2c).

According to the general procedure described above, **1** was treated with lithium iodide (602 mg) to give **2c** (553 mg, 74%) as a pale yellow oil. *Rf*=0.11 (hexane-ether, 3:1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.80 (1H, s), 4.37 (2H, brs), 4.24 (2H, q, *J*=6.8 Hz), 2.20 (1H, brs), 1.38 (3H, t, *J*=6.8 Hz). HRMS (FAB$^+$) *m/z*: Calcd for

$C_6H_{10}O_3I$ (M+H) 256.9675, Found: 256.9675.

Ethyl (2*E*,4*E*)-2-Fluoro-5-(tributylstannyl)-2,4-pentadienoate (5).

To a solution of triethyl 2-fluoro-2-phosphonoacetate **4** (533 mg, 2.2 mmol) in tetrahydrofuran (5 mL) was added *n*-butyllithium (1.28 mL, 2 mmol, 1.65 M solution in hexane) at -78°C. Aldehyde **3** was added to the mixture and stirred for 30 min at -78°C. The mixture was diluted with hexane, filtered through a thin silica gel pad, and concentrated *in vacuo*. The residue was purified by fcc (hexane) to give **5** as a pale yellow oil (640 mg, 98%). *Rf*=0.68 (hexane/diethyl ether, 6:1); IRν_{max}cm^{-1} (neat): 2957, 2926, 2872, 2854, 1728, 1631, 1464, 1417, 1394, 1373, 1340, 1302, 1238, 1203, 1140, 1107, 1074, 1022, 999, 900, 864; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.41 (1H, dd, *J*=18.8, 11.2 Hz), 6.70 (1H, d, *J*=19.2 Hz), 6.40 (1H, dd, *J*=19.2, 11.2 Hz), 4.33 (2H, q, *J*=6.8 Hz), 1.50 (6H, m), 1.38 (3H, t, *J*=6.8 Hz), 1.30 (6H, m), 0.95 (6H, m), 0.89 (9H, t, *J*=8.8 Hz); HRMS (FAB$^+$) *m/z* : Calcd for $C_{19}H_{36}FO_2{}^{120}Sn$ (M^++H) 435.1722, Found: 435.1693.

(2*E*,4*E*)-2-fluoro-5-(tributylstannyl)-2,4-pentadien-1-ol (6).

To a solution of **5** (580 mg, 1.34 mmol) in dichloromethane (5 mL) was added diisobutylaluminum hydride (3 mL, 3 mmol, 1 M solution in toluene) at -78°C. The mixture was stirred at -78°C for 15 min and quenched with a wet silica gel. The mixture was warmed to room temperature, filtered through a thin silica gel pad, and concentrated *in vacuo*. The residue was purified by fcc (hexane/diethyl ether, 5:1) to give **6** as a colorless oil (390 mg, 74%). The resulting alcohol was immediately employed for the following cross-coupling reaction. *Rf*=0.39 (hexane/diethyl ether, 3:1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.50 (1H, dd, *J*=18.8, 10.8 Hz), 6.28 (1H, d, *J*=18.8 Hz), 5.9 (1H, dd, *J*=19.6, 10.8 Hz), 4.38 (2H, dd, *J*=21.2, 6.4 Hz), 1.5 (6H, m), 1.3 (6H, m), 0.93 (15H, m).

Ethyl (2*Z*,4*E*,6*E*)-7-Fluoro-8-hydroxyl-3-methyl-2,4,6-octatrienoate (8).

To a mixture of **6** (390 mg, 1 mmol) and ethyl *Z*-3-iodo-2-butenoate **7**[8] (240 mg, 1 mmol) in *N,N*-dimethylformamide (3 mL) was added bis(acetonitrile)palladium(II) dichloride (13 mg, 5 mol%). The mixture was stirred for 30 min at room temperature and concentrated *in vacuo*. The residue was purified by fcc (hexane/diethyl ether, 1:1) to give 6*E*-**8** as a pale yellow oil (160 mg, 74%). *Rf*=0.44 (hexane/diethyl ether, 1:2); IRν_{max}cm^{-1} (neat): 3450, 2982, 2960, 2933, 2872, 1709, 1614, 1587, 1448, 1381, 1336, 1242, 1165, 1076, 1051, 1022, 981, 900, 858; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.76 (1H, d, *J*=15.2 Hz), 6.61 (1H, dd, *J*=15.2, 11.6 Hz), 6.08 (1H, dd, *J*=17.6, 11.6 Hz), 5.69 (1H, s), 4.40 (2H, dd, *J*=20, 6.4 Hz), 4.17 (2H, q, *J*=7.2 Hz), 2.02 (3H, d, *J*=0.8 Hz), 1.64 (1H, m), 1.29 (3H, t, *J*=7.2 Hz); HRMS (FAB$^+$) *m/z* : Calcd for $C_{11}H_{15}FO_3$ (M^++H) 215.1006, Found: 215.1003.

Ethyl (2*Z*,4*E*,6*Z*)-7-Fluoro-8-hydroxyl-3-methyl-2,4,6-octatrienoate (9).

To a solution of *E*-**8** (160 mg, 0.74 mmol) in dichloromethane (5 mL) was added iodine (38 mg, 0.14 mmol) in hexane (15 mL). The solution was stirred at room temperature for 20 min and poured into ice. Sodium bisulfite was added to the mixture until the solution became colorless. The organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by fcc

(hexane/diethyl ether, 1:1) to give 6*Z*-**9** (140 mg, 87%). Recrystallization of **9** (hexane/diethyl ether) gave colorless needles (mp 60-61°C). *Rf*=0.44 (hexane/diethyl ether, 1:2); IRν_{max}cm^{-1} (neat): 3439, 2958, 2928, 2870, 1703, 1662, 1614, 1583, 1454, 1381, 1280, 1242, 1161, 1140, 1049, 1024, 974, 862; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.76 (1H, d, *J*=15.6 Hz), 6.82 (1H, dd, *J*=15.6, 10.4 Hz), 5.76 (1H, dd, *J*=34, 10.4 Hz), 5.70 (1H, s), 4.22 (2H, dd, *J*=14.4, 7.2 Hz), 4.16 (2H, q, *J*=7.2 Hz), 2.04 (3H, s), 1.75 (1H, t, *J*=7.2 Hz), 1.29 (3H, t, *J*=7.2 Hz); HRMS (FAB$^+$) *m/z* : Calcd for $C_{11}H_{15}FO_3$ (M^++H) 215.1006, Found: 215.1010.

Isomerization of 2*E*-(11) to 2*Z*-(12).

According to the procedure for isomerization of **8**,[10c] 2*E*-**11** (20 mg, 0.066 mmol) in hexane (2 mL) was treated with iodine (1 mg) at room temperature with stirring for 10 min. After the work up, the residue was purified by fcc (hexane/diethyl ether, 98:2) to give 2*Z*-**12** 16.4 mg (82%) as a yellow oil.

2*Z*-**12**: IRν_{max}cm^{-1} (neat): 2963, 2933, 2863, 1800, 1754, 1733, 1466, 1447, 1397, 1376, 1334, 1233, 1219, 1137, 1019, 971, 897; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (6H, s), 1.37 (3H, t, *J*= 7.2 Hz), 1.47 (2H, m), 1.62 (2H, m), 1.71 (3H, s), 1.96 (3H, s), 2.02 (2H, m), 4.33 (2H, q, *J*=7.2 Hz), 6.21 (1H, d, *J*=16.1 Hz), 6.35 (1H, d, *J*=16.1 Hz), 6.86 (1H, dd, *J*=20.3, 12.7 Hz), 6.97 (1H, d, *J*=12.7 Hz). HRMS (FAB$^+$) *m/z* : calcld for $C_{19}H_{27}O_2F$ 306.1995 (M^++H), Found 306.1992.

2*E*-**11**: IRν_{max}cm^{-1} (neat): 2934, 1798, 1730, 1634, 1449, 1373, 1319.1262,1181,1099,1024, 976, 885, 855, 725, 708; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (6H, s), 1.36 (3H, t, *J*= 7.2 Hz), 1.47 (2H, m), 1.61 (2H, m), 1.72 (3H, s), 2.01 (3H, s), 2.03 (2H, m), 4.31 (2H, q, *J*=7.2 Hz), 6.21 (1H, d, *J*=16.1 Hz), 6.34 (1H, d, *J*=12.2 Hz), 6.39 (1H, d, *J*=16.1 Hz), 6.99 (1H, dd, *J*=30.5, 12.2 Hz). HRMS (FAB$^+$) *m/z* : calcld for $C_{19}H_{27}O_2F$ 306.1995 (M^++H), Found 306.1995.

Ethyl (2*Z*,4*E*,6*E*)-7-Fluoro-8-oxo-3-methyl-2,4,6-octatrienoate (13).

To a solution of *Z*-**9** (130 mg, 0.61 mmol) in dichloromethane (2mL) and hexane (8mL) was added activated manganese dioxide (1.5 g) at room temperature. The suspension was vigorously stirred for 30 min, filtrated through a thin silica gel pad, and concentrated *in vacuo*. The residue was purified by fcc (hexane/diethyl ether, 2:1) to give **13** as a colorless solid (75 mg, 58%). Recrystallization of **13** (hexane/dichloromethane) gave colorless needles (mp 92-93°C): *Rf*=0.44 (hexane/diethyl ether, 1:1); IRν_{max}cm^{-1} (neat): 2987, 2939, 2833, 1685, 1629, 1612, 1577, 1541, 1450, 1354, 1280, 1248, 1178, 1051, 1022, 902, 877, 839, 736; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.30 (1H, d, *J*=18.8 Hz), 8.19 (1H, d, *J*=15.6 Hz), 6.95 (1H, dd, *J*=15.6, 11.2 Hz), 5.9 (1H, s), 4.19 (2H, q, *J*=7.2 Hz), 2.01 (1H, d, *J*=1.2 Hz), 1.3 (3H, t, *J*=7.2 Hz); HRMS (FAB$^+$) *m/z* : Calcd for $C_{11}H_{13}FO_3$ (M^++H) 213.0916, Found: 213.0913.

Ethyl (2*Z*,4*E*,6*Z*,8*E*) and (2*Z*,4*E*,6*Z*,8*Z*)-7-Fluoro-3-methyl-9-(2,6,6-trimethyl-1-cyclohexene-1-yl)-2,4,6,8-nonatetraenoates (15) and (16).

To a suspension of phosphonium bromide **14** (190 mg, 0.4 mmol) in tetrahydrofuran (5 mL) was added *n*-butyllithium (0.26 mL, 0.4 mmol, 1.64 M solution in hexane) at -78°C. The mixture was stirred for 15 min and warmed to 0°C. The mixture was stirred for 15 min and cooled to -78°C. To the resulting dark red mixture was added a solution of **13** (70 mg, 0.33 mmol) in tetrahydrofuran (3 mL). The mixture was stirred for 15 min

at -78°C and diluted with hexane. The suspension was filtered through a thin silica gel pad and concentrated *in vacuo*. The residue was purified by fcc (hexane/diethyl ether, 10:1) to give a 4.5:1 mixture of **15** and **16** (yellow oil, 82 mg, 75%). *Rf*=0.59 (hexane/diethyl ether, 5:1); IRν_{max}cm^{-1} (neat): 3065, 2957, 2930, 2866, 2827, 1709, 1597, 1454, 1379, 1361, 1338, 1155, 1095, 1051, 1024, 977, 904, 850; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.76 (9/11H, d, *J*=16 Hz), 7.72 (2/11H, d, *J*=15.6 Hz), 6.95 (9/11H, dd, *J*=16, 11.2 Hz), 6.89 (2/11H, dd, *J*=15.6, 11.2 Hz), 6.59 (9/11H, br d, *J*=16 Hz), 6.08 (2/11H, br d, *J*=12.4 Hz), 5.89 (2/11H, dd, *J*=29.2, 12.4 Hz), 5.87 (9/11H, dd, *J*=26.4, 16 Hz), 5.69 (2/11H, dd, *J*=32, 11.2 Hz), 5.66 (1H, s), 5.63 (9/11H, dd, *J*=34, 11.2 Hz), 4.16 (2H, q, *J*=7.2 Hz), 2.06 (27/11H, s), 2.04 (6/11H, s), 2.03 (2H, br t, *J*=5.6 Hz), 1.74 (27/11H, s), 1.61 (2H, m), 1.56 (6/11H, s), 1.47 (2H, m), 1.28 (3H, t, *J*=7.2 Hz), 1.04 (6H, s); HRMS (FAB$^+$) *m/z* : Calcd for $C_{21}H_{29}FO_2$ (M^++H) 333.2152, Found: 333.2153.

13-*cis*- and 7,13-*dicis*-9-desmethyl-9-fluororetinals (17) and (18) [9-desmethyl(2*Z*,4*E*,6*Z*,8*E*)- and (2*Z*,4*E*,6*Z*,8*Z*)-7-Fluoro-3-methyl-9-(2,6,6-trimethyl-1-cyclohexene-1-yl)-2,4,6,8-nona-tetraenals].

To a solution of a 4.5:1 mixture of **15** and **16** (25 mg, 0.075 mmol) in dichloromethane (3 mL) was added diisobutylaluminum hydride (0.17 mL, 0.17 mmol, 1 M solution in toluene) at -78°C. The mixture was stirred at -78°C for 15 min and quenched with a wet silica gel. The mixture was allowed to warm to room temperature, filtered through a thin silica gel pad, and concentrated *in vacuo*. The residue was purified by fcc (hexane/diethyl ether, 2:1) to give the corresponding alcohol as a pale yellow oil (18 mg). The resulting alcohol was immediately employed for the following oxidation reaction. *Rf*=0.08 (hexane/diethyl ether, 3:1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.70-6.51 (3H, m), 6.02 (2/11H, d, *J*=12.4 Hz), 5.86 (2/11H, dd, *J*=28.8, 12.4 Hz), 5.84 (9/11H, dd, *J*=26.4, 16 Hz), 5.62 (2/11H, t, *J*=7.2 Hz), 5.60 (9/11H, t, *J*=7.2 Hz), 5.51 (9/11H, dd, *J*=34.4, 10.4 Hz), 4.31 (2H, d, *J*=7.2 Hz), 2.02 (2H, br t, *J*=5.6 Hz), 1.93 (27/11H, s), 1.91 (6/11H, s), 1.73 (3H, s), 1.61 (2H, m), 1.46 (2H, m), 1.04 (6H, s). To a solution of the alcohol (18 mg) obtained above in hexane (5 mL) was added activated manganese dioxide (100 mg). The mixture was stirred for 30 min at room temperature, filtered through a thin silica gel pad, and concentrated *in vacuo*. The residue was purified by fcc (hexane-diethyl ether, 5:1) to give a 4:1 mixture of 13-*cis*-**17** and 7,13-*dicis*-**18** as a yellow oil (9 mg, 50%). *Rf*=0.46 (hexane/diethyl ether-3:1) The mixture of regioisomers was separated by HPLC (hexane-ethyl acetate, 91:9 at 300 nm) to give **17** and **18**, respectively.

13-*cis*-**17**: retention time 13.394 min. ^{1}H-NMR (400 MHz, CD_3OD) δ: 10.16 (1H, d, *J*=7.6 Hz), 7.43 (1H, d, *J*=15.6 Hz), 7.08 (1H, 15.6, 11.6 Hz), 6.66 (1H, br d, *J*= 16.8 Hz), 6.01 (1H, dd, *J*=26.4, 16.8 Hz), 5.85 (1H, d, *J*=7.6 Hz), 5.83 (1H, dd, *J*=33.6, 11.6 Hz), 2.15 (3H, d, *J*=0.8 Hz), 2.07 (2H, t, *J*=6.4 Hz), 1.75 (3H, d, *J*=0.8 Hz), 1.64 (2H, m), 1.5 (2H, m), 1.06 (6H, s); ^{19}F-NMR (376 MHz, CD_3OD) δ: -119.8 (dd, *J*=33.6, 26.4 Hz); HRMS (FAB$^+$) *m/z*: Calcd for $C_{19}H_{25}OF$ (M^++H) 289.1967, Found: 289.1945.

7,13-*dicis*-**18**: retention time 14.373 min. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.18 (1H, d, *J*=8 Hz), 7.24 (1H, d, *J*=15.6 Hz), 6.96 (1H, dd, *J*=11.2, 15.6 Hz), 6.16 (1H, brd, *J*=12.4 Hz), 5.92 (1H, dd, *J*=29.2, 12.4 Hz), 5.87 (1H, brd, *J*=8 Hz), 5.70 (1H, dd, *J*=31.2, 11.2 Hz), 2.11 (3H, s), 1.99 (2H, brs), 1.64 (2H, m), 1.55 (3H, s), 1.49 (2H, m), 1.01 (6H, brs); HRMS (FAB$^+$) *m/z*: Calcd for $C_{19}H_{25}OF$ (M^++H) 289.1967, Found: 289.1960.

Isomerization of 13-*cis*-(17) to all-*trans*-(19).

To a solution of 13-*cis*-**17** (1 mg, 0.0034 mmol) in dichloromethane (0.2 mL) was added 34 μL of trifluoroacetic acid (0.01 M dichloromethane solution). The mixture was stirred at room temperature for 15 min and concentrated *in vacuo*. The residue was purified by HPLC (hexane-ethyl acetate, 89:11 at 300 nm) to give all-*trans*-**19** (0.6 mg, 60%) and 13-*cis*-**17** (0.3 mg, 30%). All-*trans*-**19**: retention time, 13.579 min.; ^{1}H-NMR (400 MHz, CD_3OD) δ 10.06 (1H, d, *J*=8 Hz), 7.19 (1H, dd, *J*=15.6, 11.2 Hz), 6.66 (1H, br d, *J*=16.4 Hz), 6.48 (1H, d, *J*=15.6 Hz), 6.01 (1H, dd, *J*=26.4, 16.4 Hz), 5.95 (1H, d, *J*=8Hz), 5.79 (1H, dd, *J*=33.6, 11.2 Hz), 2.34 (3H, d, *J*=0.8 Hz), 2.07 (2H, brt, *J*=6 Hz), 1.75 (3H, d, *J*=1.2 Hz), 1.64 (2H, m), 1.50 (1H, m), 1.05 (6H, s); ^{19}F-NMR (376 MHz, CD_3OD) δ -119.64 (dd, *J*=33.6, 26.4 Hz); HRMS (FAB$^+$) *m/z*: Calcd for $C_{19}H_{25}OF$ (M^++H) 289.1967, Found: 289.1988.

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analogs and native bR.

Absorption Maxima of All-*trans*-9-X-Retinal and Their Bacteriorhodopsin Analogs.

Compound	Aldehyde (nm)[a]	SB (nm)[b]	PSB (nm)[c]	bR Analog (nm)[d]	OS (cm^{-1})[e]	E.N.[f]
retinal	381	355	444	568	4920	2.3[g]
9-H	373	357	436	548	4690	2.1[h]
9-F	369	357	426	530	4603	4.0[h]
9-Cl	375	364	430	548	5010	3.0[h]
9-Br	375	364	429	545	4900	2.8[h]
9-I	379	369	432	553	5060	2.3

[a] In EtOH, [b] SB; shiff base with *n*-$BuNH_2$ in EtOH, [c] PSB; Protonated Schiff base with dil. HCl in EtOH , [d] bR; bacteriorhodopsin in 20 mM Tris-buffer after light adaptation. [e] OS; Opsin- shift. Difference in λ_{max} of bR and PBS, in cm^{-1}. [f] Electronegativity, [g] Mullay's scale for methyl group, [h] Pauling's scale.