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9-CIS AND 11-CIS ISOMERS OF 18,18,18-, 19,19,19- AND 20,20,20-TRIFLUORORETINAL†

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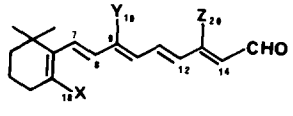
Summary - The preparation and properties of the 9-cis and 11-cis isomers of three trifluoromethylated retinals are described.

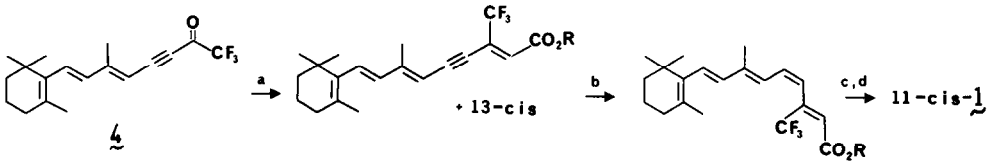
The preparations of several stable isomers of trifluorinated retinals with the fluorine labels located at the 13-, 9- and 5-methyl positions, 1-3, have recently been reported (see below). Because of the preference for the E-configuration (cis isomer) of CF_3 bearing olefins,[1] the synthesis of the 11-cis and 9-cis isomers of such retinals, those important for vision research, is far from routine. We now report the successful preparation of such isomers.



1: X = Y = CH_3 Z = CF_3
2: X = Z = CH_3 Y = CF_3
3: Y = Z = CH_3 X = CF_3

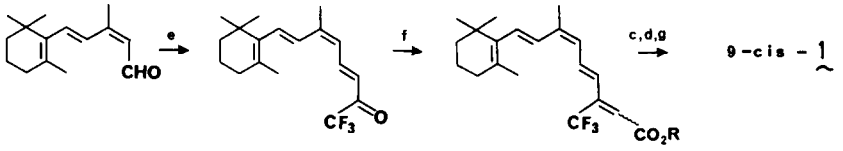
The synthesis of 20,20,20-trifluororetinal (1) was first reported in the literature.[2] The thermodynamically most stable isomer was first assigned the all-trans geometry but was subsequently corrected to the 13-cis.[1,3] Attempts to prepare the 11-cis and the 9-cis isomers via photoisomerization in acetonitrile[4] were unsuccessful. For this system, the photochemical method only led to an unseparable mixture of isomers containing the 13-cis geometry accompanied by degradation of the compound. Instead, the recently reported syntheses[3,5] of the relatively unstable all-trans isomer have provided new routes to the 9-cis and 11-cis isomers. Thus, the Tokyo group reported the preparation of the key trifluoro-C_{18}-ketone, 4.[3] Elaboration of this intermediate has now afforded the 11-cis isomer.

†New Geometric Isomers of Vitamin A 14. For previous paper in the series, see ref. 5. The work done in Hawaii was supported by a grant from the U.S. Public Health Services (AM-17806).



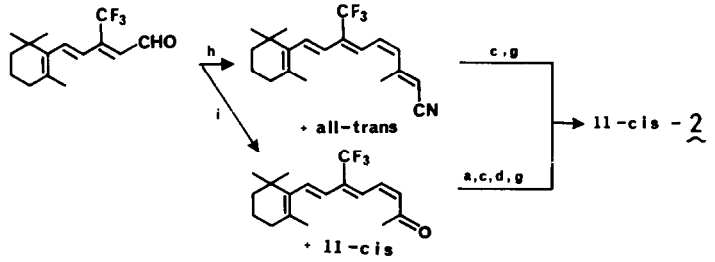
a. $TMSCH_2CO_2Et$ + LICA. b. H_2/Lindlar cat. c. DIBAL. d. MnO_2.

Modification of the Hawaii route[5] led to 9-*cis*-1:



e. CF_3COCH_3/piperidine + CH_3CO_2H. f. $(EtO)_2P(O)CH_2CO_2Et$, LDA. g. hplc separation.

The syntheses of the stable 9-cis and 9,13-dicis isomers of 19,19,19-trifluororetinal (2) are in the literature.[1,5,6] Irradiation of the 9-cis isomer led to one bond isomerization giving the 9,13-dicis and 7,9-dicis isomers[7] plus a trace amount of the trans isomer. The absence of the 11-cis isomer in the irradiation mixture made necessary the design of an independent synthetic route. Two separate synthetic sequences have now successfully provided the isomer. The first route featured the key step of modified Wittig reaction reported for cis selective formation of simple olefins.[8] The same 11-cis isomer was also obtained in a step-wise process involving the intermediacy of the C_{18}-ketone:



h. $(CF_3CH_2O)_2POCH_2C(CH_3)=CHCN$, K_2CO_3 + 18-crown-6. i. $TMSCH_2C(CH_3)=NtBu$[9], LDA.

The synthesis of the all-trans isomer of 18,18,18-trifluororetinal (3) has recently been reported by the Tokyo group.[10] In this case, the CF_3 group is too remote to change the normal course of photoisomerization of the polyene. Therefore, irradiation of the isomer in

Table 1. Uv-vis absorption maxima of analogs and nmr data of isomers of 20,20,20-trifluoro-(1), 19,19,19-trifluoro-(2), and 18,18,18-trifluororetinals (3)[a]

	Absorption maxima, nm		Chemical Shift, ppm										Coupling constants (Hz)		
Compounds	Retinal[b]	Rhodopsin[c]	CH_3-18	CH_3-19	CH_3-20	H_7	H_8	H_{10}	H_{11}	H_{12}	H_{14}	H_{15}	$J_{7,8}$	$J_{10,11}$	$J_{11,12}$
11-cis-1	380(s),310	542(D)	1.72	2.02	-56.4[d]	6.40	6.14	6.39	6.96	5.98	6.39	10.13	16.0	12.0	11.8
9-cis-1	390,300(s)	516(C)	1.72	2.02	-58.3	6.38	6.62	6.07	7.37	6.15	6.32	10.07	16.0	11.2	15.7
11-cis-2	336	456(D)	1.72	-58.9[d]	2.30	6.48	5.96	6.82	6.78	6.20	6.03	10.10	16.3	9.9	12.4
9-cis-2[e]	333,286(s)	447(D)	1.77	-64.7	2.32	6.56	6.22	6.65	7.11	6.60	6.05	10.14	16.4	10.9	15.1
7c,9c-2	--	--	1.43	-63.8	2.28	6.39	6.01	6.66	6.80	6.53	6.01	10.12	13.1	11.2	15.2
9c,13c-2[e]	330	453(C)	1.75	-64.9	2.12	6.51	6.20	6.67	6.95	7.50	5.95	10.18	16.5	11.0	14.5
11-cis-3[f]	326,248(s)	457(D)	-59.2	1.96	2.35	6.30	6.11	6.56	6.66	5.97	6.07	10.09	16.1	12.5	11.6
9-cis-3[d]	327,276(s)	454(D)	-58.4	2.02	2.33	6.33	6.63	6.14	7.17	6.32	5.97	10.11	16.3	11.6	15.1
13-cis-3[f]	339	None	-55.8	1.99	2.12	6.32	6.13	6.23	6.99	7.30	5.86	10.19	16.1	11.2	14.9

a. ^{1}H-nmr spectra recorded on a 300 MHz Nicolet NM-300 spectrometer or a 400 MHz Bruker AM-400 spectrometer. Solvent: 20% acetone-d_6 in CCl_4, with TMS and $CFCl_3$ as internal H and F standards respectively, unless otherwise specified. ^{19}F-nmr spectra recorded on an IBM NR-80 spectrometer. b. In hexane; (s) ≡ shoulder. c. In digitonin (D) or CHAPS (C). d. In $CDCl_3$ with $CF_3C_6H_5$ as internal standard recorded on a JEOL FX-200 spectrometer, the value readjusted relative to $CFCl_3$. e. From ref. 5. f. In $CDCl_3$/TMS.

acetonitrile led to the formation of four new isomers (13-cis, 11,13-dicis, 11-cis and 9-cis). The 11-cis (major) isomers have been isolated by preparative hplc. The minor isomer with lc retention time between those of 11-cis and all-trans was partially purified. By comparison of relative lc retention time with those of the parent retinal isomers, its partial spectral data, and reactivity toward bovine opsin, we tentatively assigned the 9-cis geometry.[11]

Preliminary binding studies with these fluorinated 9-cis and 11-cis retinal isomers with bovine opsin showed that stable pigments can be formed.[12] Their absorption maxima are listed in Table 1. Other information on these pigment analogs will be reported in a separate paper in the future.

In summary, these retinal and pigment analogs are now available for detailed investigation of protein substrate interactions whether using the fluorine atoms as nmr probes[13] or possible source of specific electronic interactions as recently observed in the photobleaching process of 10-fluororhodopsin.[14]

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12. For 9-*cis*-2, the negative result reported earlier[1] was most likely due to a combination of a low yield of pigment formation in digitonin plus the employment of a less sensitive absorption spectrometer at that time.
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