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Fluorinated Astaxanthins

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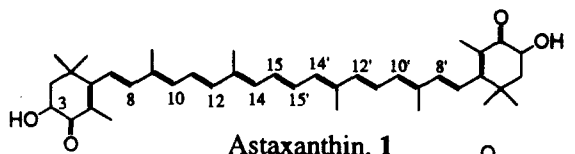
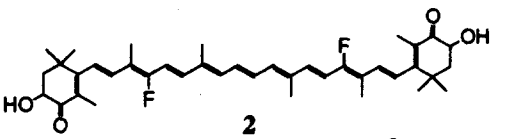
Abstract. The syntheses and spectral data of three fluorinated astaxanthins (10-F, 14-F and 10,10'-F_2) are reported. © 1997 Published by Elsevier Science Ltd.

In recent years there have been an increasing number of studies demonstrating new usages of carotenoids in biomedical[1] and material science[2] fields as well as for understanding of fundamental processes in natural occurring caroteno-protein complexes. In the latter front, considerable effort has been devoted toward structural properties of the crustacyanins.[3] For example, an important recent contribution is the use of ^{13}C-labelled astaxanthins for solid state NMR studies of α-crustacyanins.[4]

Fluorine labels have been widely applied in retinoid studies both for its high sensitivity as an NMR label[5] and regiospecific perturbation on properties of protein complexes[6] as well as for potential medicinal usages.[7] We have now initiated a program to study properties of fluorinated caroteno-protein complexes. However, for such studies one must first demonstrate possible preparation of the somewhat sensitive carotenoids substituted with the highly electronegative fluorine atom. In this paper the preparation of three fluorinated astaxanthins (**2-4**) is described.



Astaxanthin, **1**



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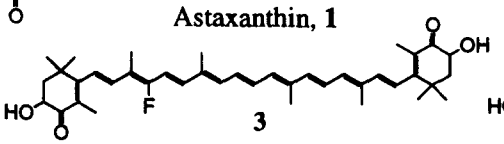

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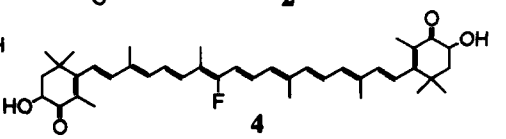

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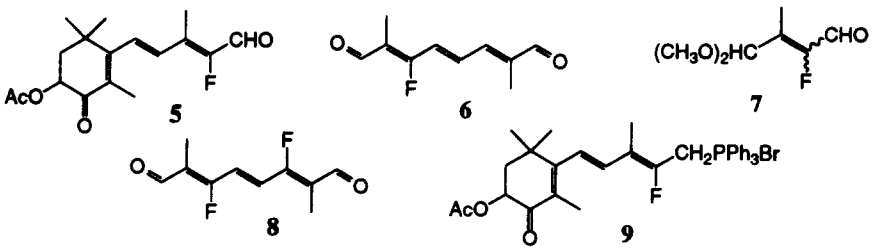
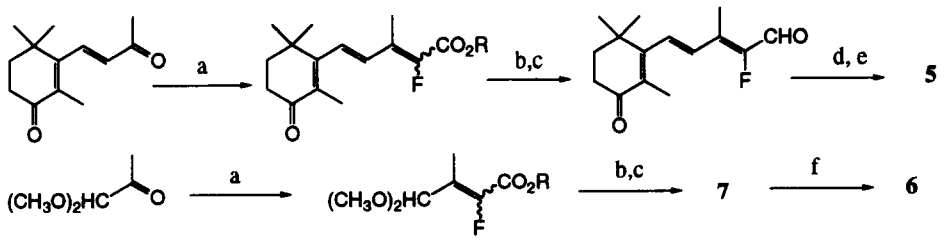
For preparation of chain fluorinated astaxanthins, we chose to adopt the $C_{15} + C_{10} + C_{15}$ synthetic strategy established for the parent astaxanthin.[8] The development of several key fluorinated intermediates (**5-9**) became necessary. The 10-fluoro-C_{15} intermediate **5** was prepared



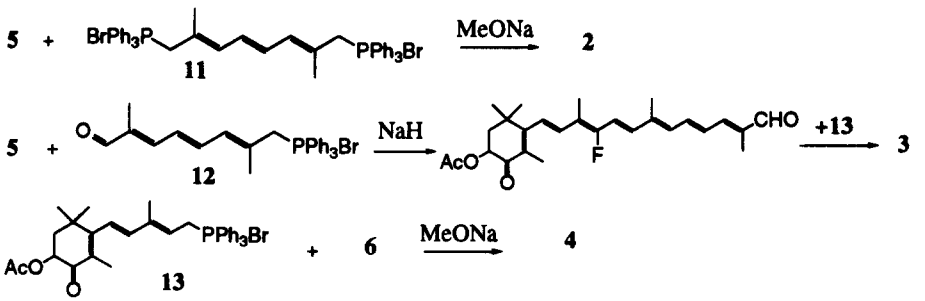
by condensing the fluorinating C_2-phosphonoester reagent with 4-keto-β-ionone followed by standard reactions for conversion to the aldehyde. The all-trans isomer was isolated by column chromatography, followed by introduction of the acetoxy group at the 3-position with lead tetraacetate. For 3-fluoro-C_{10}-dialdehyde **6** (a 2-cis/trans mixture), the F-atom was introduced using the same C_2-ester followed by Wittig reaction of the protected C_5-fluoroaldehyde **7** with C_5 phosphonium salt **10**. Satisfactory spectral data were obtained for all these compounds. An attempt to prepare 3,7-difluoro-C_{10}-dialdehyde **8**, a necessary intermediate to 14,14'-F_2-astaxanthin, via McMurry coupling of **7** was, however, unsuccessful, most likely due to low stability of **8**.



a. $(EtO)_2POCHFCO_2Et$, NaH. b. DIBAL-H, -78°C. c. MnO_2. d. column chrom. to isolate the all-trans isomer. e. $Pb(OAc)_4$. f. $(CH_3O)_2CH(CH_3)C{=}CHCH_2PPh_3Br$, **10**, NaOMe.

The more direct route to the 10,10'-difluoroastaxanthin **2** using the C_{15}-fluorophosphonium salt **9** was unsuccessful due to elimination of HF upon addition of a base. Instead, Wittig reaction of 10-fluoroaldehyde **5** with the C_{10}-bisphosphonium salt **11** and NaOMe (-25°C) was attempted, yielding the symmetrical, racemic 10,10'-F_2-astaxanthin, **2**, in 10% isolated yield, (the major side reaction being a competing elimination reaction of the bisphosphonium salt). Reaction of **5** with the phosphonium-C_{10}-CHO **12** followed by Wittig reaction with the C_{15} phosphonium salt **13**[9] yielded an isomeric mixture 10-F-astaxanthin, **3**. The major all-trans isomer was readily isolated by column chromatography (silica gel, 30% ethyl acetate-hexane in 35% yield). Reaction of the fluoro-C_{10}-dialdehyde, **6**, with a two fold excess of the C_{15} phosphonium salt **13** yielded an isomeric mixture of 14-fluoroastaxanthin in 70% yield. The major all-trans isomer was partially purified by column chromatography then isolated by hplc (Y M Corp., 10mm, 5 μ, C_{30} column, CH_3CN/EtOAc/MeOH, 3:1:1).

Compounds **2-4** are oxygen-sensitive red-solids. The structures were confirmed by their H, C & F NMR spectra, HRMS and UV-Vis data and by comparison with those of the parent



system.[10] The H NMR spectra of 14-F-astaxanthin, **4**, (simpler for the symmetrical **2** or the related **3**) is shown in Figure 1 as a representative example and key H NMR data and UV-absorption maxima for the fluorinated and unsubstituted astaxanthins for comparison are listed in Table 1 appended at the end of the paper (C NMR data are not shown due to limited space).

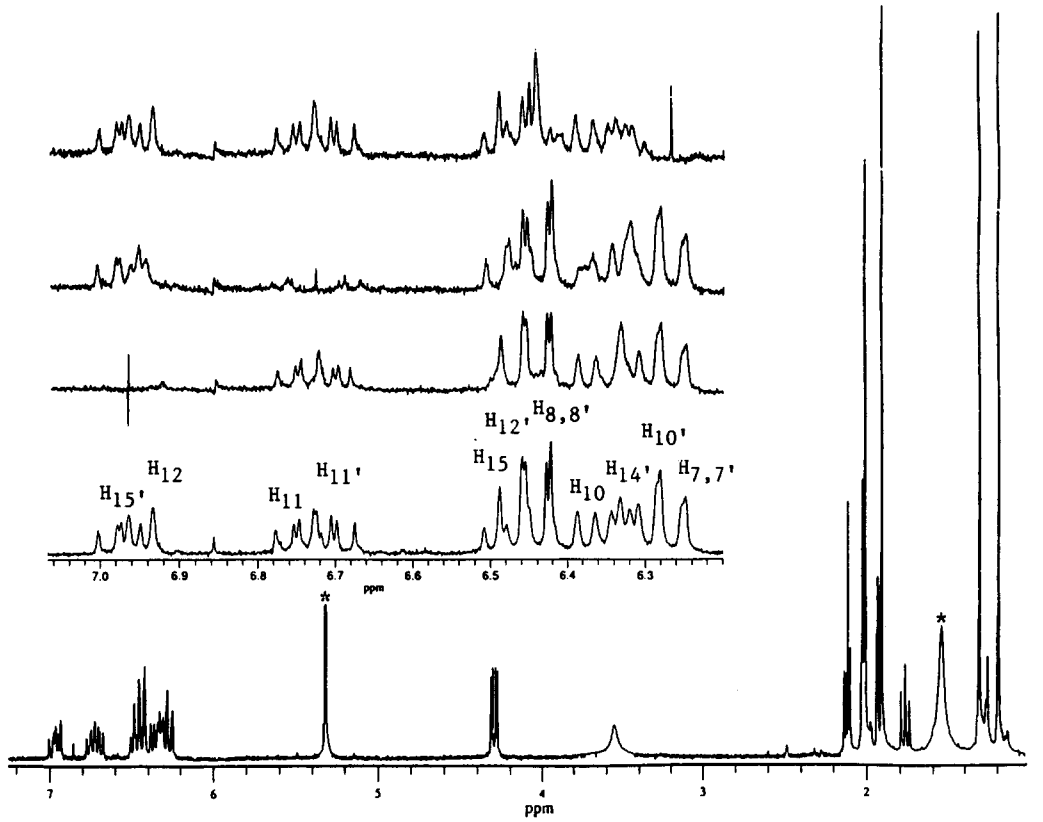


Figure 1. H NMR spectrum (500 MHz, CD_2Cl_2) of 14-F-astaxanthin; insert, vinyl region expanded (bottom) and decoupled (top three). *Solvent impurities.

In summary, in this paper we have demonstrated possible preparation of astaxanthin substituted with the highly electronegative fluorine atom. These compounds are not only

useful in studies of caroteno-protein complexes, but also they represent a new set of carotenoids in their increasingly broadened applicational usages.[11]

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11. The work was supported by a grant from the U. S. Public Health Services (DK-17806). We thank Drs. Hengartner and Bernhard of Hoffmann-La Roche for the gift sample of astaxanthin.

Table 1. Partial H NMR (in $CDCl_3$ 300MHz) data, chemical shift and coupling constants of astaxanthin and UV-Vis absorption maxima of fluorinated astaxanthins.

Compounds	H-3,3′	H-7,7′	H-8,8′	H-10,10′	H-11,11′	H-12,12′	H-14,14′	H-15,15′
Astaxanthin	4.30	6.21	6.43	6.30	6.66	6.45	6.30	6.68
10-fluoro	4.33	6.22	7.00	-120.26[b]	6.41	6.76	6.41	6.68
		6.21	6.43	6.31	6.68	6.45	6.31	6.68
14-fluoro[a]	4.30	6.26	6.44	6.38	6.75	6.95	-121.69[b]	6.46
	4.30	6.26	6.44	6.32	6.70	6.47	6.33	6.98
10,10′-F_2	4.33	6.22	7.01	-120.26[b]	6.39	6.77	6.41	6.71
	$J_{2,3}$	$J_{7,8}$	$J_{10,11}$	$J_{11,12}$	$J_{14,15}$	$J_{15,15'}$		λ_{max}[d]
Astaxanthin	13.6	16.4	-[c]	14.9	-			478.4
	5.6							
10-fluoro	13.0	16.3	-	15.0	-	-		475.2
	5.8	15.9		15.0				
14-fluoro	13.6	16.0	11.8	14.6	28.6	14.7		473.6
	5.6	16.0	11.3	15.1	11.4			
10,10′-F_2	13.7	16.2	27.1	15.6	-			472.8
	5.6							

a. In CD_2Cl_2, 500MHz. b. Chemical shifts for F NMR. c. Broad peak, not sufficiently well resolved for measurement. d. nm, in acetone.

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