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9-CF_3 and 13-CF_3–β-carotene, canthaxanthin and related carotenoids. Synthesis, characterization and electrochemical data

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Dedicated to Prof. Yoshiro Kobayashi on the occasion of his 75th birthday

Abstract

The preparation and characterization of the following trifluoromethylated carotenoids are reported: 9-CF_3–, 13-CF_3–, 9,9′-bis-CF_3–, 13,13′-bis-CF_3–β-carotene, 9-CF_3– and 13-CF_3–canthaxanthin, 13′-CF_3– and, 9′-CF_3–4-oxo-β-carotene, 13′-CF_3–adonirubin and 3-dehydro-13′-CF_3–canthaxanthin. The CF_3 group exhibits a strong *cis*-directing effect leading primarily to the *cis* isomer (near the CF_3 group, i.e., all-*E*) in the synthetic mixtures. The minor all-*trans* isomer could be enriched by sensitized irradiation; however, they were found to be only marginally stable at room temperature. The CF_3 group also exhibits a stabilizing effect towards oxidation reactions. Spectral data and oxidation potentials of these fluorinated carotenoids are reported.

Keywords: Trifluoromethylated carotenoids; Synthesis; Spectral data; Oxidation potentials

1. Introduction

Carotenoids are naturally occurring pigments. Because of their involvement in light initiated biological processes (e.g., light harvesting and protection in the photosynthetic apparatus) as well as their nutritional and health values, their isolation, characterization and synthesis have attracted much attention of researchers in recent decades.[1] Fluorinated carotenoids, in contrast to the analogous retinoids [2–4], on the other hand attracted little attention in spite of potential benefits such as the possible use of F-atoms as NMR reporting labels[2], being more lipophilic[3] and as an effective perturbing unit on UV–Vis absorption properties of the polyene chromophore [8,9]. Recently, we reported the preparation of several vinyl fluoroastaxanthins [10] and formation of fluorinated α-crustacyanins [11]. Now, we would like to report the preparation of several trifluoromethylated carotenoids, their isolation, characterization and some of their properties.

2. Results and discussion

In the early stage of developing synthetic methodologies to trifluoromethylated carotenoids, we encountered unexpected difficulties arising from the high sensitivity of the polyene chromophore especially in cases of simultaneous presence of the CF_3 group and the 4-keto functionality under the alkaline conditions used in Wittig ylide formation. Neither were we successful in preparing the key trifluoromethylated central C_{10} unit by following sequences of reactions similar to those used for the parent systems [11–13]. Therefore, instead of the C_{15}+C_{10}+C_{15} route, successfully applied to the synthesis of several vinyl fluoro-carotenoids [10], we now describe results in applying the C_{20}+C_{20} or the C_{20}+C_5+C_{15} strategy to the trifluoromethylated carotenoids. These results illustrate the possible preparation and stability of such compounds.

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[1]See e.g., [1].

[2]See e.g., [5,6].

[3]See e.g., [7].

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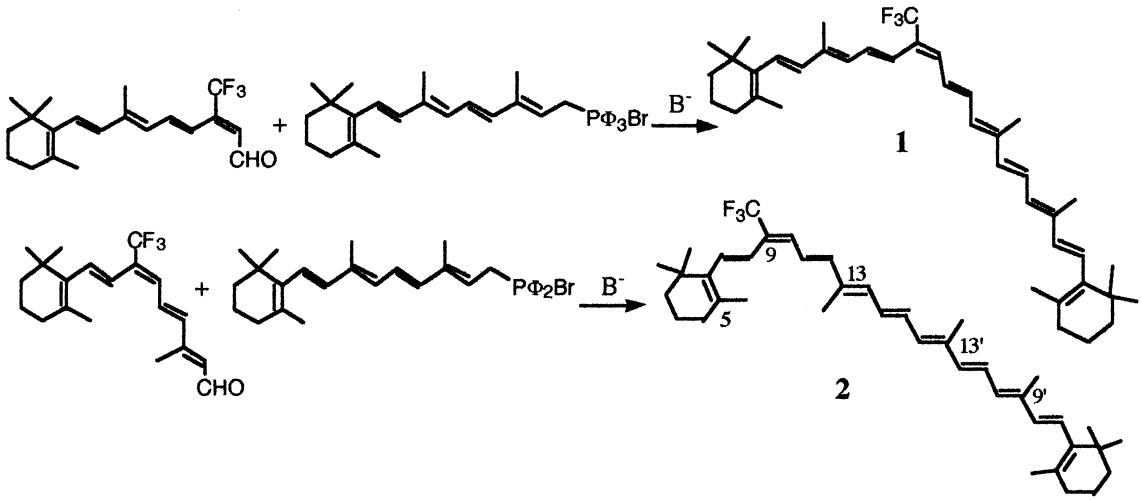
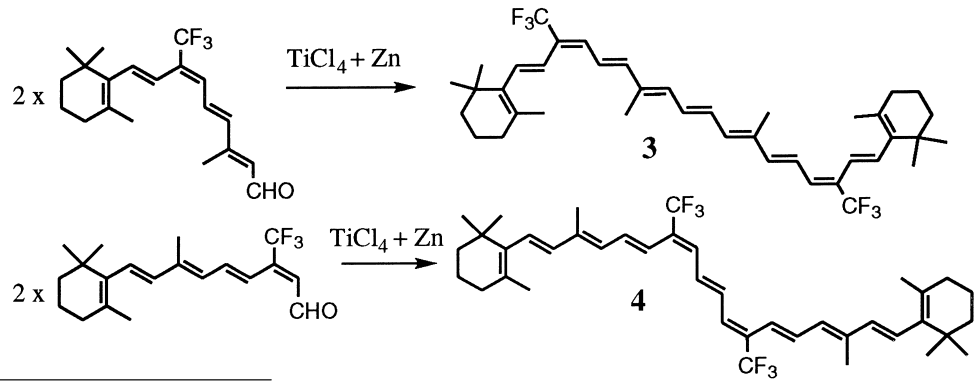
2.1. Trifluoromethylated-β-carotenes

13-*cis*-13-CF_3–β-carotene[4] (**1**) was prepared by reaction of the C_{20} Wittig salt with 13-*cis*-13-CF_3–retinal [14]. The 13-*cis* (13*E*) geometry, a result of the *cis*-directing property of the CF_3 group, was retained during the coupling reaction giving primarily the 13-*cis* (all-*E*) isomer (~80% based on F NMR) of the carotenoid, which was subsequently purified by preparative hplc. Starting with 9-*cis*-9-CF_3–retinal and following a similar C_{20}+C_{20} coupling reaction, 9-CF_3–β-carotene (**2**) was also prepared.[5] The predominant isomer in the product mixture was the 9-*cis* (all-*E*) isomer, again retaining the preferred *cis* (9*E*) stereochemistry during olefination.

By way of McMurry coupling reaction [15] of 9-*cis*-9-CF_3–retinal, 9-*cis*,9′-*cis*-9,9′-bis-CF_3–β-carotene (all-*E*), **3**, was prepared. And, starting with 13-CF_3–retinal, 13-*cis*,13′-*cis*-13,13′-bis-CF_3–β-carotene (all-*E*), **4**, was prepared.





2.2. Oxygenated trifluoromethylated carotenoids

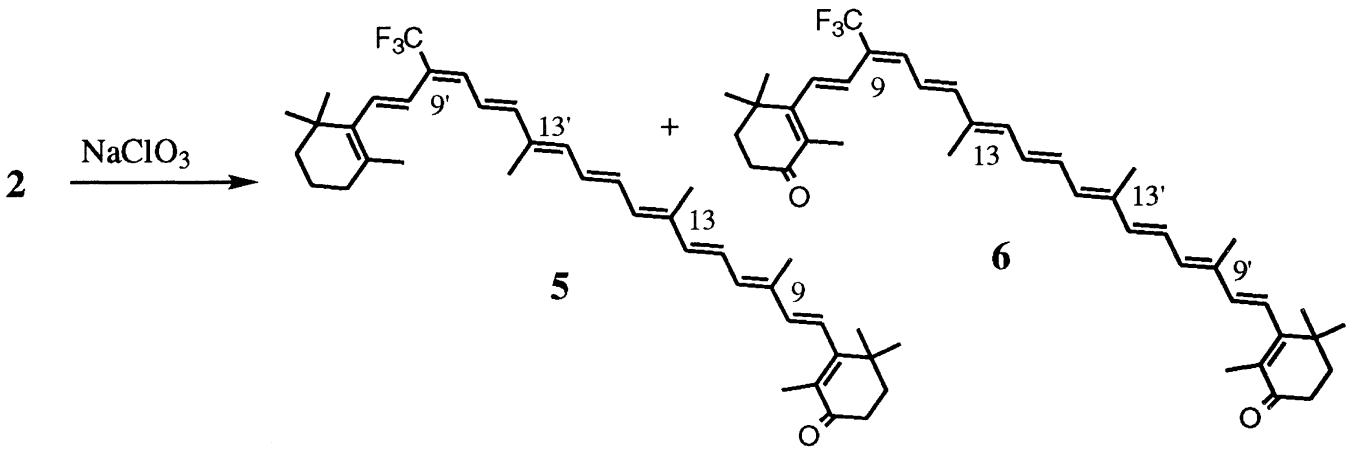
2.2.1. 9′-cis-9′-CF_3–4-oxo-β-carotene (5) and 9-cis-9-CF_3–canthaxanthin (6)

Oxidation of β-carotene by sodium hypochlorite was reported to be an effective procedure for its conversion to canthaxanthin [16]. When the reaction was applied to 9-CF_3–β-carotene, a more complex mixture of products was obtained from which the mono and bis-oxidized products were isolated (readily separated by column chromatography). The ring closer to the CF_3 group was found to be less reactive because only one mono-oxidized product was isolated with its H NMR spectrum (chemical shifts of H8 and H8′) being consistent with the structure shown. This

[4]The *cis*, *trans* designations used in this paper conform to the accepted nomenclature for carotenoids, i.e., according to the disposition of the substituents that constitute a continuation of the main polyene chain: see B.C.L. Weeden, G.P. Mass, in: G. Britton, S. Liaaen-Jensen, H. Pfander (Eds.), Carotenoids 1A, Isolation and Analysis, Birkhauser, Basel, 1995, p. 34.

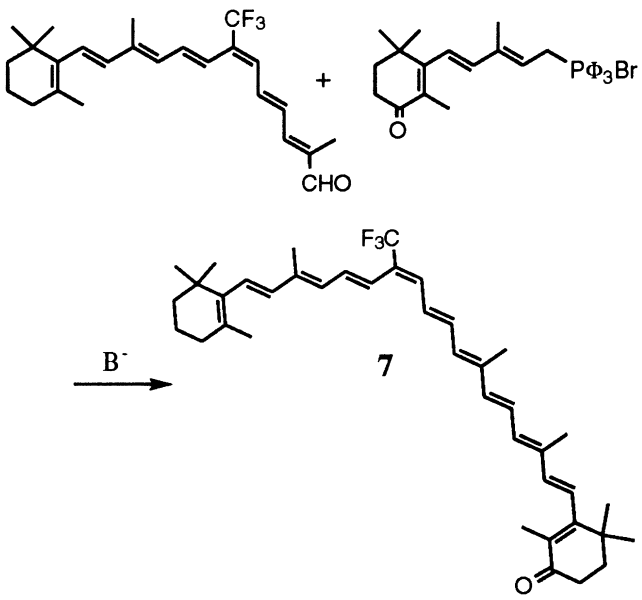
[5]Compound **2** was found to be surprisingly sensitive to molecular oxygen, undergoing allylic oxidation upon standing in NMR solvents to a product that was subsequently characterized to be 4-oxo-β-carotene **5** (see below).

selectivity also accounts for the low yield (slow rate of formation) of the bis-oxidized product and to the formation of other unidentified degradation products by prolonging the reaction time.



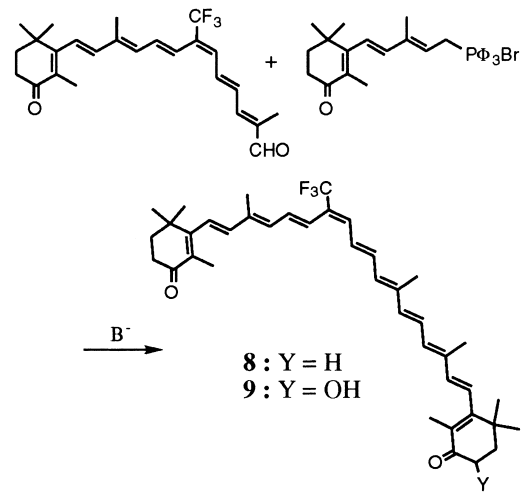
2.2.2. 13′-cis-13′-CF_3–4-oxo-β-carotene (7)

The compound was prepared from reaction of the C_{15} Wittig salt with the 13-*cis*-13-CF_3–C_{25}-apocarotenal. The latter was prepared in turn by reaction of the protected C_5 Wittig salt **10** (see Section 3) with 13-*cis*-13-CF_3–retinal. The product mixtures contained primarily the 13-*cis* (all-*E*) isomer. It was isolated by preparative hplc.



2.2.3. 13-cis-13-CF_3–canthaxanthin (8)

The compound was prepared from reaction of the C_5-Wittig salt **10** (see Section 3) with 13-*cis*-13-CF_3–4-oxo-retinal followed by coupling of the resulting C_{25}-apocarotenal with the C_{15}-Wittig salt. In addition to the major 13-*cis* (all-*E*) isomer (70%), three other isomers were also present. Two of them were isolated by preparative hplc. They were identified as 13-*cis*, 13′-*cis*- (13′-*Z*, 20%) and all-*trans* (13-*Z*, <5%) (see below for spectral data).



2.2.4. 13′-CF_3–Adonirubin, 3-hydroxy-13′-CF_3–canthaxanthin (9)

The compound was prepared from a Wittig reaction similar to that for **8**, using instead the 3-hydroxy-4-keto-C_{15}-Wittig salt. Under normal phase conditions for hplc separation, compound **9** was found to undergo ready dehydration, as indicated by the H NMR spectrum of the collected product: the disappearance of the 4.3 ppm signal for H3 and the appearance of a new set of two coupled vinyl hydrogens. The remaining vinyl hydrogen signals were nearly identical to those of **8** (Table 1). As a result, compound **9** had to be purified under reverse phase hplc conditions.

Table 1
Partial (vinyl region) H NMR data of isomers of trifluoromethylated carotenoids[a]

Compound	H7	H8	H10	H11	H12	H14	H15	H15′	H14′	H12′	H11′	H10′	H8′	H7′
13C,13-CF_3–β-car., **1** [b]	6.28	6.17	6.17	6.90	6.59	6.66	6.73	6.93	6.30	6.38	6.79	6.17	6.15	6.24
9C,9-CF_3–β-carotene, **2** [b]	6.29	6.43	[c]	6.72	[c]	[c]	[c]	[c]	[c]	[c]	[c]	6.16	6.14	6.21
9,9′C-bis-CF_3–β-car., **3** [b]	6.73	6.54	6.31	6.80	6.76	6.17	6.55							
9,9′C-bis-CF_3–β-car., **3**	6.45	6.29	6.70	6.61	6.67	6.39	6.74							
13,13′C-bis-CF_3–β-car, **4**	6.33	6.18	6.18	6.99	6.58	6.68	6.99							
9′C-9-CF_3-4-oxo-β-c., **5** [b]	6.44	6.29	6.67	6.61	6.68	6.42	6.68	6.75	6.32	6.45	6.72	6.29	6.37	6.28
9′C-9-CF_3-4-oxo-β-c., **5**	6.81	6.55	6.33	6.73	6.78	6.28	6.69	6.57	6.23	6.47	6.72	6.26	6.36	6.14
9-C,9-CF_3–canthax., **6**	6.64	6.57	6.78	6.56	6.31	6.30	6.71	6.56	6.25	6.48	6.73	6.27	6.36	6.15
9-C-9-CF_3–canthax., **6** [b]	6.51	6.51	6.79	6.63	6.69	6.44	6.68	6.78	6.32	6.45	6.73	6.29	6.37	6.28
all-*t*-9-CF_3–canthax., **6a**	6.07	6.50	6.41	7.00	6.40	6.28	6.73	6.56	6.33	6.48	6.70	6.27	6.36	6.15
13′C,13′-CF_3-4-oxo-β, **7** [b]	6.30	6.17	6.17	6.90	6.59	6.67	6.76	6.93	6.32	6.46	6.79	6.30	6.37	6.29
13C,13-CF_3–canthax., **8** [b]	6.34	6.37	6.31	6.91	6.67	6.72	6.76	6.96	6.34	6.46	6.80	6.30	6.37	6.31
13C,13-CF_3–canthax., **8**	6.16	6.34	6.12	7.22	6.58	6.21	6.56	6.58	6.71	6.40	6.74	6.22	6.31	6.10
13′C,13′-CF_3–adon., **9** [b]	6.34	6.37	6.29	6.92	6.67	6.72	6.76	6.96	6.34	6.46	6.80	6.30	6.37	6.31
13′C,13′-CF_3–adon., **9**	6.10	6.30	6.11	7.21	6.57	6.21	6.58	6.56	6.70	6.41	6.72	6.21	6.28	6.04
13C′,13′-CF_3-3-dhc., **11**	6.81	6.55	6.33	6.73	6.78	6.28	6.69	6.57	6.23	6.47	6.72	6.26	6.36	6.14

[a] In C_6D_6, unless otherwise specified.
[b] In CD_2Cl_2.
[c] Overlapping signals.

2.3. Enrichment of the all-trans isomer

Because of the potential use of such carotenoids in studies of caroteno–protein complexes where the all-*trans* isomer is required[6], we have carried out exploratory photochemical experiments to seek for conditions to enrich the all-*trans* isomer of the CF_3-substituted carotenoids. For 9-CF_3–canthaxanthin, the all-*trans* isomer was present in 4.6% of the synthetic mixture. Direct irradiation (light > 430 nm) of either the 9-*cis* isomer or the synthetic mixture resulted in doubling the amount of the *trans* isomer (according to F NMR). The amount was further increased (to ~20%) when the compound was subjected to triplet sensitization (Rose Bengal using light > 530 nm)[6]. The latter conditions were employed to enrich the all-*trans* isomer of 13-CF_3–canthaxanthin, 9-CF_3–canthaxanthin as well as 13′-CF_3–adonirubin and subsequently its isolation by hplc was attempted. However, the all-*trans* isomer was found only to be marginally stable at room temperature. Under the usual conditions of hplc separation (room temperature and storage at 0°C), ~40% of all-*trans* 9-CF_3–canthaxanthin (9*Z*) was found to have reverted back to the 9-*cis* isomer (all-*E*); while >90% of the 13-CF_3–canthaxanthin and the 13′-CF_3–adonirubin reverted to the 13-*cis* isomer. All-*trans*-9-CF_3–canthaxanthin (9*Z*) was eventually isolated in pure form when hplc fractions were kept at 0°C and the NMR solvent was pre-treated with K_2CO_3 for the removal of any possible acidic impurities.

2.4. Spectroscopic properties

The H NMR data of the fluorinated carotenoids are tabulated in Table 1 and the UV–Vis absorption maxima in Table 2. Initial assignment of proton signals was aided by comparison with the corresponding data of either the parent β-carotene or canthaxanthin[7] or the corresponding C_{25}-apo-β-carotenals and by selective decoupling. Thus, the magnitude of the *trans* coupling constants helped identify those signals corresponding to H8, H12 and H14 (larger near the end of the chain) [19]; and the broader width of the signals for H7 and H10 (long range coupling). The chemical shift of the vinyl hydrogen on the carbon adjacent to the CF_3-substituted carbon (H8 for 9-CF_3 and H12 for 13-CF_3) is

Table 2
Oxidation potentials, UV absorption maxima and calculated HOMO levels of trifluoromethylated carotenoids

Compound	E^{ox_1} (mV)	E^{HOMO} (eV)	λ_{max} [a] (nm)
All-*trans*-β-carotene	570	−7.66	461
13-*cis*-13-CF_3–, **1**	698	−8.96	451
9-*cis*-9-CF_3–, **2**	820 [b]	−7.88	448
9-*cis*,9′-*cis*-9,9′-bis-CF_3–, **3**	940	−8.20	436
13-*cis*,13′-*cis*-13,13′-bis-CF_3–, **4**	815 [c]	−8.22	452
All-*trans*-canthaxanthin	730	−7.84	477 [d]
9-*cis*-	739		472 [d]
13-*cis*-	722		468 [d]
9-*cis*-9-CF_3–, **6**	860	−8.07	474 [d]
13-*cis*-13-CF_3–, **8**	940	−8.16	451, 470 [d]
9′-*cis*-9′-CF_3-4-oxo-β-carot., **5**	827	−8.025	453
13′-*cis*-13′-CF_3-4-oxo-β-carot., **7**	795	−7.97	452, 464 [d]
13′-*cis*-13′-CF_3–adonirubin, **9**			462 [e]
All-*trans*-13′-CF_3–adonirubin			467 [e]

[a] In hexane.
[b] A broad band that began to resolve into two waves at a slower scan-rate.
[c] The beginning of four overlapping oxidative waves.
[d] CH_2Cl_2.
[e] 80:10:10 (acetonitrile:ethyl acetate:methanol).

[6] See e.g., [17].

[7] See e.g., [18].

at unusually high field as noted before [14,20] for retinoids although such signals for the *cis* isomer exhibit the same downfield shift from the *trans* isomer as in retinoids. Final peak assignments were aided by spectral simulation.

The F NMR chemical shift (see Section 3) is a sensitive measure of the *cis/trans* (*E/Z*) geometry where the CF_3 group is located. For the *trans* (*Z*) isomer, the F chemical shift is usually ~6 ppm downfield from that of the *cis* (*E*). The UV–Vis absorption spectra of the fluorinated carotenoids (Table 2) exhibit the general trend of blue shift from that of the parent systems.

2.5. Oxidation potentials

Because of the recent interest in oxidation processes of carotenoids [21], we have carried out electrochemical experiments to determine the oxidation potentials of several of these trifluoromethylated carotenoids. The cyclic voltammograms of two substituted β-carotenes along with that of the parent hydrocarbon is shown in Fig. 1 as representative examples. The oxidation potential data for these fluorinated carotenoids are summarized in Table 2.

There are three obvious features general to all these fluorinated carotenoids. First, unlike β-carotene and canthaxanthin, the fluorinated carotenoids do not exhibit reversible oxidative waves, as evidenced by the near zero amplitude of the reductive waves in all cases. We suspect that fluoro-substituents have introduced new (yet to be identified) reactions to the radical cation (or di-cation) of the carotenoids. Second, there is a noticeable increase of the first oxidation potential from that of the unsubstituted carotenoids (β-carotene and canthaxanthin) (see Table 2). This is an expected consequence when the highly electron-withdrawing CF_3 group is introduced onto the polyene chain, a feature pointed out by Kispert and Jeevarajan [22] in their extensive electrochemical studies of other electronegatively substituted carotenoids (e.g., the values of canthaxanthins are much higher than that of β-carotene) [22–24]. It is noteworthy that the degree of difficulty in removing an electron for these fluorinated carotenoids parallels with the calculated values (by AM1) of the HOMO energy levels and the absorption maxima (Table 2), a feature also discussed by Kispert and Jeevarajan [22]. Third, a general trend was observed in that electron withdrawing group on the β-carotene chain increases the difficulty of di-cation formation vis-a-vis first oxidation step. First reported by Kispert and coworkers, we concur that increasing gap between the two oxidation waves take place as in the β-carotene, 9-CF_3– and 13-CF_3–carotene and 4-keto series. However, in the canthaxanthin series, the trend is reversed. Addition of more electron withdrawing groups to the polyene chain decreases the gap between the two oxidation steps (believed to involve the two keto groups), especially when the CF_3 group is located near the middle of the chain.

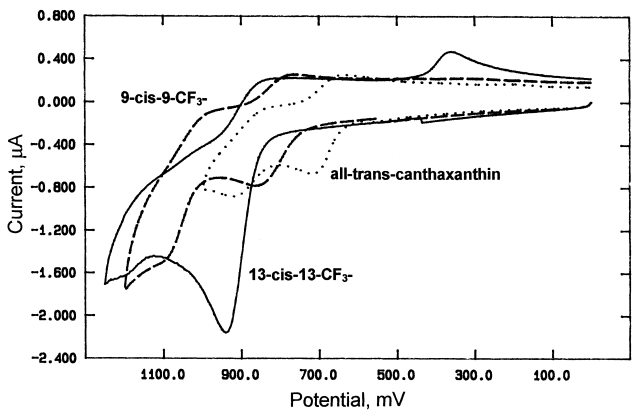


Fig. 1. Cyclic voltammograms for trifluoromethylated-β-carotenes: (a) 9-*cis*-9-CF_3, (b) 13-*cis*-13-CF_3, along with that of all-*trans*-β-carotene.

In conclusion, 9-CF_3– and 13-CF_3–β-carotenes and canthaxanthins can be prepared. The *cis* directing properties of the CF_3 group and the sensitivity of the compounds under strong basic conditions, however, made preparation of the all-*E* isomer difficult. The isolated isomers of CF_3–carotenoids exhibit spectroscopic and electrochemical properties characteristic of those polyenes with strong electron withdrawing groups. The increased oxidation potentials of the CF_3-substituted carotenoids agree with the noted preferential oxidation of the ring with no nearby CF_3-group in the preparation of 9′-CF_3–4-keto-canthaxanthin.

3. Experimental

3.1. General procedures

In general, normal phase hplc conditions were used for separation of isomers of fluorinated carotenoids: 5 μ, 4.6×25 mm Si column (Rainin Microsorb). Solvent conditions were: 0.125–0.25% ether in hexane for fluorinated β-carotenes and 5% acetone in hexane for fluorinated canthaxanthins. UV–Vis spectra were recorded on a PE λ-19 spectrometer. H NMR spectra were recorded either on a 400 (Varian Inova 400 WB) or a 500 MHz (GE Omega GN-500) spectrometer; F NMR spectra recorded on the Varian Inova spectrometer (376 MHz), using trifluorotrichloroethane (−82.2 ppm) as external standard. Simulation of H NMR spectra was carried out using gNMR software v 3.6. AM1 (Austin Model 1). Calculations were performed using HyperChem software with an AST Bravo PC.

For photosensitized irradiation, a catalytic amount of Rose Bengal was introduced to an acetonitrile solution of a carotenoid. The solution was deoxygenated by bubbling argon gas through the sample tube and irradiated with a 200 W Hanovia Hg lamp, using a Corning 3-70 filter plate.

3.2. Electrochemistry

Cyclic voltammetry measurements were carried out in a single compartment cell with a 2 mm diameter glassy

carbon disk electrode as a working electrode, a platinum wire as an auxiliary electrode and Ag/AgCl as a reference electrode.

Methylene chloride of hplc grade (Fisher Co.) was kept over CaH_2 under argon. The needed amount of solvent was distilled just before use. The supporting electrolyte, tetra-*n*-butylammonium hexafluorophosphate (TBAHFP) was used as supplied by Fluka and kept in the vacuum dessicator over Drierite. All carotenoids were purified by hplc before use.

A 0.1 M solution of TBAHFP in CH_2Cl_2 was employed with ca. 0.1–0.3 mM of the carotenoid with scan speed ranging from 50 to 1000 mV s^{-1}. During the measurements the electrochemical cell was purged by dry argon gas.

All the measurements were performed employing a Princeton Applied Research Potentiostat/Galvanostat Model 273 run by Model 250-270 Electrochemical Research software.

3.3. Materials

β-Carotene was generously supplied by Hoffmann La-Roche and Co. Canthaxanthin was prepared by oxidation of β-carotene according to published procedure [16].

3.3.1. 13-CF_3–β-carotene (1)

To a methylene chloride (2 ml) solution of 100 mg of 13-*cis*-13-CF_3–retinal and 200 mg C_{20}-Wittig salt was added at 0°C a methanol solution of sodium methoxide. Standard workup and chromatography on silica gel with 15% ether/hexane yielded 168 mg of 13-*cis*-13-CF_3–β-carotene. The major 13-*cis* isomer (80%) was purified by hplc. NMR signals for the vinylic protons are listed in Table 1. HRMS: calculated for $C_{40}H_{53}F_3$=590.4102, found=590.4096. F NMR (CD_2Cl_2): −63.5 ppm.

3.3.2. 9-*cis*-9-CF_3–β-carotene (2)

Following the same procedure as above, the coupling of 9-CF_3–retinal (80 mg) and C_{20}-triphenylphosphonium bromide (200 mg) yielded 140 mg of the desired product. The major 9-*cis* isomer (80%) was isolated by preparative hplc. F NMR: −64.1 ppm. Photosensitized (with Rose Bengal) isomerization resulted in formation of the all-*trans* isomer (∼20%). F NMR: −59.1 ppm.

3.3.3. 9-*cis*,9′-*cis*-9,9′-bis-CF_3–β-carotene (3)

Under argon, 30 mg of 9-*cis*-9-CF_3–retinal was added to a slurry of 68 mg $TiCl_4$, 12 mg Zn, 3 ml THF, 3 ml CH_2Cl_2. After 2 h, extraction and chromatography of the product mixture yielded 26 mg of the bis-CF_3–carotene (90% yield). The major (95%) di*cis* isomer was isolated by preparative hplc. HRMS: Calc. for $C_{40}H_{50}F_6$=644.3829, found 644.3811. F NMR (CD_2Cl_2): −65.0 ppm.

3.3.4. 13-*cis*,13′-*cis*-13,13′-bis-CF_3–β-carotene (4)

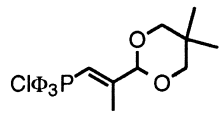
Under the same conditions as above, 30 mg of 13-*cis*-13-CF_3–retinal with 68 mg of $TiCl_4$, 12 mg of Zn in 3 ml of THF and 3 ml of CH_2Cl_2 yielded 20 mg of the bis-CF_3–carotene-**4** (68% yield). F NMR (CD_2Cl_2): −53.9 ppm.

3.3.5. 9′-*cis*-9′-CF_3–4-oxo-β-carotene (5) and 9-*cis*-9-CF_3–canthaxanthin (6)

A mixture of 110 mg of 9-CF_3–β-carotene in 3 ml of CH_2Cl_2, acatalytic amount of I_2 and 550 mg of $NaClO_3$ in 1 ml of H_2O was stirred at room temperature for 3 h. After usual workup and column chromatography, two carotenoids were isolated: 9′-CF_3–4-oxo-β-carotene (30 mg, 26% yield) and 9-CF_3–canthaxanthin (46 mg, 38%). The major (∼80%) 9-*cis* isomer for each compound was isolated by preparative hplc. F NMR (CD_2Cl_2): −64.0 and −63.9 ppm, respectively.

3.3.6. 13-*cis*-13-CF_3–canthaxanthin (8)

To a dry THF solution of 13-CF_3–4-oxo-retinal (200 mg) and the protected C_5-phosphonium salt **10** (380 mg) [25] was added at −78°C 0.2 ml of 2.5 M BuLi. Standard workup and chromatography (silica gel, 15% ether/hexane) yielded 170 mg of the C_{25} 13-CF_3–4-oxo-apocarotenal. Reaction of the above C_{25}-apocarotenal (30 mg) and 4-oxo-C_{15}-triphenylphosphonium salt (40 mg) in the same manner as described above yielded 32 mg of 13-*cis*-13-CF_3–canthaxanthin (70% yield). The major 13-*cis* isomer was isolated by preparative hplc. HRMS: Calc. for $C_{40}H_{49}F_3O_2$=618.3695, found 618.3695. F NMR (CD_2Cl_2): 13-*cis*, −63.6 ppm; all-*trans*, −59.1 ppm.



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3.3.7. 13′-*cis*-13′-CF_3–4-oxo-β-carotene (7)

Starting with 120 mg of 13-*cis*-13-CF_3–retinal and 0.208 g of the protected C_5-phosphonium salt **10** and following the same procedure as above, 136 mg (90% yield) of 13-CF_3–C_{25}-apocarotenal was prepared. Reaction of 20 mg of the apocarotenal with 30 mg of 4-oxo-C_{15}-triphenylphosphonium bromide gave 27 mg of 13-CF_3–4-oxo-β-carotene (88% yield). The major 13-*cis* isomer was isolated by preparative hplc. F NMR (CD_2Cl_2): −63.6 ppm.

3.3.8. 13′-CF_3–Adonirubin (9)

Reaction of 20 mg of the 13-CF_3–C_{25}-apocarotenal above with 33 mg of 3-hydroxy-4-oxo-C_{15}-triphenylphosphonium bromide in the same manner as described above gave 22 mg of the CF_3–adonirubin **9** (72% yield). HRMS: calculated for $C_{40}H_{49}F_3O_3$=634.3636, found=634.3641. A first attempt to purify the 13-*cis* isomer by preparative hplc on a normal phase silica gel column (10% acetone in hexane) resulted in a mixture of four major components. The principal component, **11**, (∼50%) gave a H NMR spectrum (Table 2) consistent with that of the cross-conjugated dienone end group from dehydration of the starting material (13′-*cis*-3-

dehydro-13′-CF_3–canthaxanthin). F NMR (CD_2Cl_2): −63.5 ppm. Purification by reverse phase hplc (C30 column) using acetonitrile:ethyl acetate:methanol (80:10:10) gave 13-*cis*-**9**. F NMR (CD_2Cl_2): −63.7, (CD_3CN): −63.1 ppm. The all-*trans* isomer was isolated from mixtures obtained from photosensitized irradiation. F NMR (CD_3CN): **4. −58.8 ppm**.

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