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Convergent synthesis of new types of stabilized carotenoid compounds*

Soo Bong Kim, Hyungjun Kim, Boram Lim, Juwan Meang, Sung-Hee Bae, Eunho Choi, Jung Taek Oh, Inseok Hong, Se-Young Jung, Jung Eun Yeo, and Sangho Koo‡

Department of Chemistry, Department of Nano Science and Engineering, Myong Ji University, Yongin, Kyunggi-Do, 449-728, Korea

Abstract: A convergent synthetic method for new types of carotenoid compounds containing phenyl substituents at C(13) and C(13') has been developed by the coupling of allylic sulfone and 2,7-diphenyloct-4-enedials, followed by the double elimination strategy. These carotenoid compounds are fairly stable and legitimate candidates for nanosized molecular wires, which show diverse conductance values according to the electronic nature of the substituent group in the phenyl ring.

Keywords: carotene; conjugated polyenes; double elimination; molecular wires; sulfone.

INTRODUCTION

Carotenoids play three important roles in plant and bacterial photosynthesis as a light-harvesting pigment, a photoprotective agent, and a structural stabilizing element. The red to yellow pigments absorb visible light in the green to blue wavelength region (400~550 nm) complementary to chlorophyll, and thus transfer energy to the photosynthetic reaction center [1]. Carotenoids also protect the photosynthetic apparatus by reversibly quenching the hazardous singlet oxygen and the chlorophyll triplet state [2]. The structural stabilizing effect of carotenoids was postulated by the π-stacking interactions of the polyenes with the porphyrins of chlorophylls within van der Waals distances [3]. There have been extensive studies to elucidate the modified carotenoid molecules containing electro-active polar end groups as electronic devices for intramolecular charge transfer, electro-chromic, semiconducting, or nonlinear optical properties [4]. The synthesis of these modified carotenoids **1a**–**d** has been based on the reaction of the natural crocetin dialdehyde **2** with the Wittig salts of the polar end groups, which restricted not only the structures but also the properties of these potential molecular wires (Scheme 1).

Strictly speaking, the potential of these ideal molecular wires has not been fully investigated due to their thermal and photochemical instabilities, which is an inevitable consequence of their antioxidant activities by quenching the reactive oxygen species. We serendipitously found that the stability of retinoids has been significantly improved by the covalent attachment of a phenyl group [5]. The synergistic protective effect of carotenoids and vitamin E, which contains a phenyl moiety, against photodynamic cell damage has been also reported [6]. It was thus envisioned that the synthesis of the novel carotenoids containing phenyl substituents, while maintaining the conjugated polyene chains, would provide a new type of stabilized carotenoids for practical applications to electronic devices.

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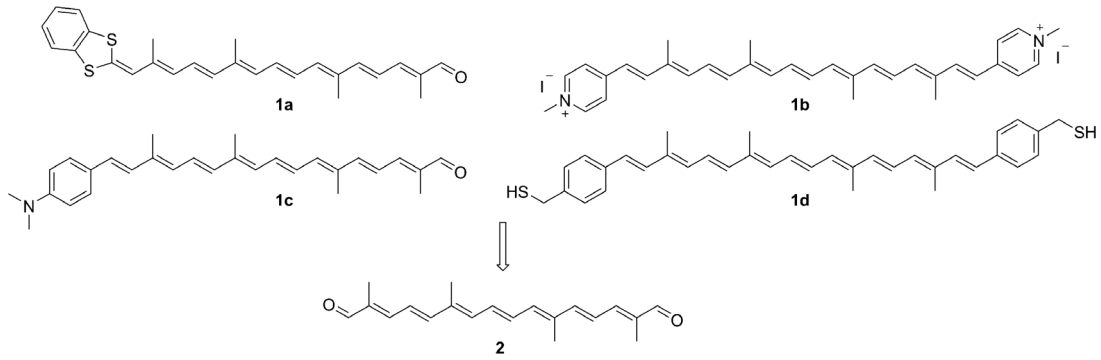
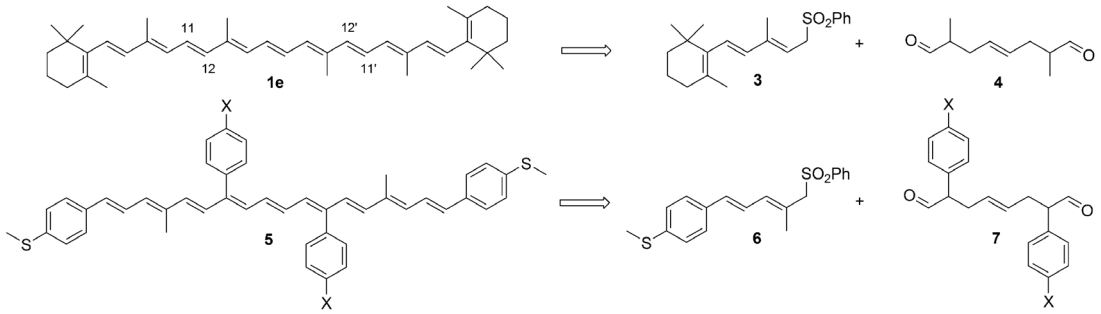
‡Corresponding author



Scheme 1 Typical modified carotenoid compounds synthesized from crocetin dialdehyde **2**.

A variety of unnatural carotenoids can be assembled by the convergent synthetic pathways utilizing the sulfone-mediated coupling and the double elimination protocol, which was introduced in the synthesis of β-carotene (Scheme 2) [7]. The disconnection at the C(11)/C(11')-double bonds is believed to be efficient for a convenient preparation of the subunits and the selective formation of *E*-alkenes. The C_{15}-allylic sulfone **3** [8] thus coupled with a half equivalent of (*E*)-2,7-dimethyloct-4-enedial (**4**) to provide the required carbon skeleton. Protection of the resulting diols followed by the double elimination reaction produced all-(*E*)-β-carotene (**1e**). In the same manner, the carotenoid compounds **5** containing phenyl substituents at C(13) and C(13') can be obtained by the convergent synthesis which makes use of the coupling between allylic sulfone **6** and 2,7-diphenyloct-4-enedials **7**, and the double elimination reaction of the coupling products.

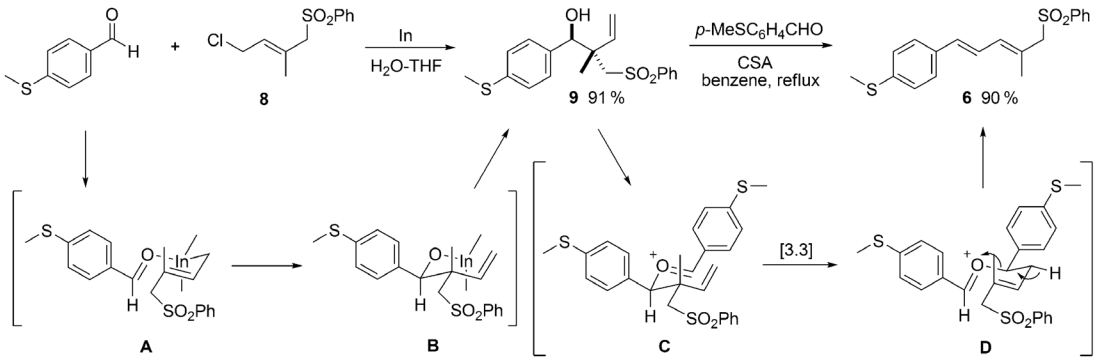


Scheme 2 Disconnection approaches to carotenoids by a convergent synthesis.

The methylthio groups at the terminal benzene rings of **5** are required for self-assembly of the carotenoids on a gold plate or a gold nanoparticle in order to observe their *I–V* characteristics by c-AFM (conducting atomic force microscopy) measurement. We found that the phenyl substituents at C(13) and C(13') not only provided the conjugated polyenes with enhanced stability, but also variable conductance depending upon the electronic characters (either electron-donating or -withdrawing) of the substituent group X [9]. The detailed syntheses of allylic sulfone **6**, phenyl-substituted oct-4-enedials **7**, and their couplings and the double elimination reactions are explained in the following text.

ALLYLIC SULFONE

The key issue in the synthesis of allylic sulfone **6** is to construct the all-(*E*)-dienyl moiety which is attached to the *para*-position of methylthio-benzene. We adapted the tandem sequence of indium-mediated addition of chloroallylic sulfone **8** to *para*-methylthiobenzaldehyde [10], followed by the oxonia-Cope rearrangement of the adduct (Scheme 3) [11]. Chloroallylic sulfone **8** is a useful C_5-building block for the synthesis of terpenoids such as Coenzyme Q-10, and has been conveniently prepared from isoprene [12]. Both of these reactions are highly stereoselective so that all-(*E*)-**6** was obtained exclusively in 82 % overall yield. The origins of the stereoselectivity are delineated by the Zimerman–Traxler transition-state models in Scheme 3.

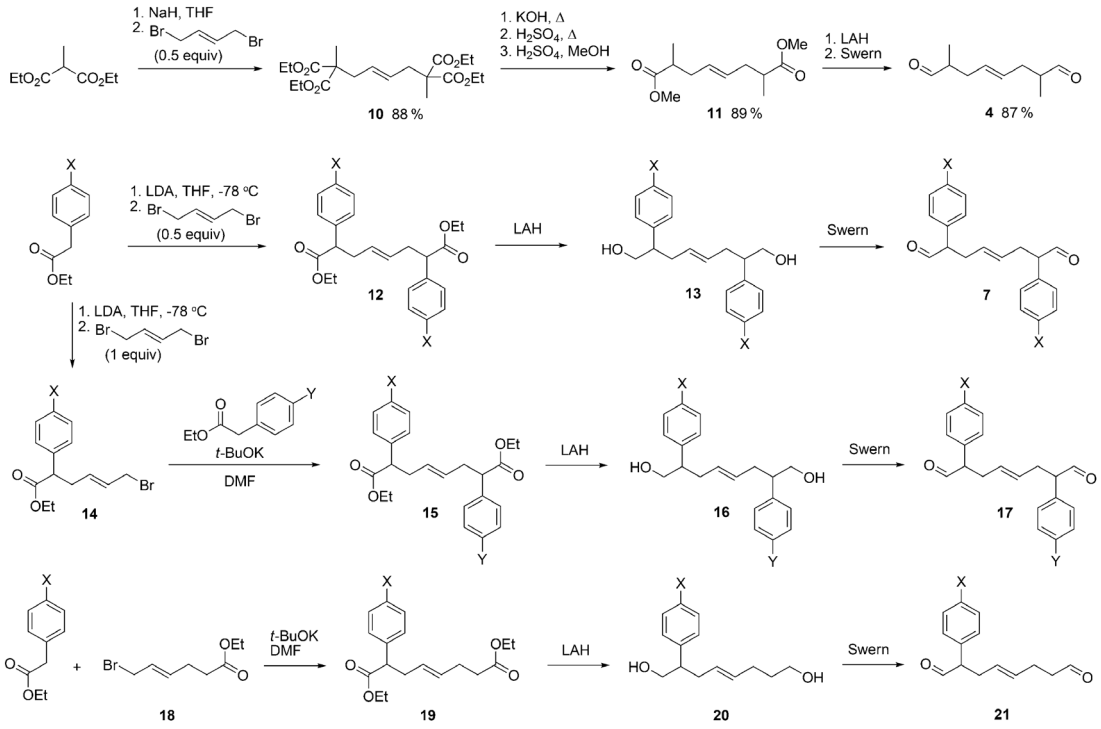


Scheme 3 Stereoselective synthesis of allylic sulfone **6** by the indium-mediated addition of **8** to *para*-methylthiobenzaldehyde, followed by the oxonia-Cope rearrangement.

The allyl indium-chelated six-membered ring transition state **A** (Scheme 3) placed the bulky *para*-methylthiophenyl group of the aldehyde preferentially into an equatorial position so that *anti*-**9** (OH vs. $PhSO_2CH_2$) was obtained as the major product (13:1 selectivity) in 91 % yield after the addition reaction through the model **B**. The equatorial dispositions of the two bulky *para*-methylthiophenyl groups in the transition-state model **C** for the [3.3]-oxonia-Cope rearrangement of aryl oxonium ion derived from **9** and *para*-methylthiobenzaldehyde under acidic conditions (stoichiometric 10-camphorsulfonic acid, CSA) produced all-(*E*)-**6** after elimination of *para*-methylthiobenzaldehyde in the model **D**. We were not able to detect any other stereoisomer from the rearrangement. Allylic sulfone **6** was easily purified by recrystallization from 95 % EtOH.

OCT-4-ENEDIALS

The key to success in the β-carotene synthesis by the double elimination protocol was the utilization of 2,7-dimethyloct-4-enedial (**4**), which was prepared from diethyl 2-methylmalonate and 1,4-dibromo-2-butene (first row in Scheme 4) [7]. All of the reaction steps involved were high yielding, but the overall sequence was somewhat lengthy and tedious. Instead of going through the malonate synthesis which required an extra decarboxylation procedure, we utilized the direct deprotonation/alkylation of *para*-X-substituted phenylacetic acid esters (X = OMe, Me, H, and Br) with 1,4-dibromo-2-butene for the synthesis of 2,7-diphenyloct-4-enedials (**7**) (second row in Scheme 4). The mono alkylation products **12** of phenylacetic acid esters were exclusively obtained in 80~91 % yields under the condition using LDA at –78 °C. Reduction (lithium aluminum hydride) and then oxidation (Swern: DMSO, oxalic chloride, triethylamine) of **12** smoothly produced the desired symmetric 2,7-diphenyloct-4-enedials (**7**) in high yields (see Table 1 for the yield of each product).



Scheme 4 Preparation of oct-4-enedials **4**, **7**, **17**, and **21** with various 2,7-substitutions.

Table 1 Isolated yields (by SiO_2 column chromatography) of each compound in the preparation of oct-4-enedials **7**, **17**, and **21**.

X	**12** (%)	**13** (%)	**7** (%)	**14** (%)	Y	**15** (%)	**16** (%)	**17** (%)
OMe	82	92	85	80	Me	60	97	82
					H	66	70	76
					Br	66	96	45
Me	80	90	84	92	H	62	70	74
					Br	67	80	61
H	91	85	91	81	Br	78	58	73
Br	80	90	82	84				

X	**19** (%)	**20** (%)	**21** (%)
OMe	80	84	82
Me	92	93	80
H	81	82	82
Br	84	84	81

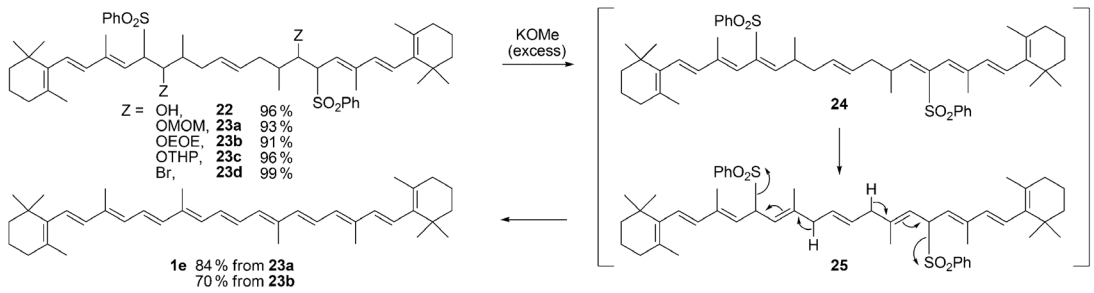
Asymmetrically substituted diesters **15** (X ≠ Y) can be prepared by the carefully controlled alkylation between *para*-X-substituted phenylacetic acid esters (X = OMe, Me, H, and Br) and 1,4-dibromo-2-butene (third row in Scheme 4): the couplings with a 1:1 stoichiometry produced bromoesters **14** in 80~92 % yields, and the subsequent couplings of **14** with phenylacetic acid esters with different *para*-substitution Y provided diesters **15** in 60~78 % yields. The first deprotonation should be carried out under the kinetic condition using LDA at –78 °C, and the second deprotonation might as well be executed under the condition using *t*-BuOK at –20 °C in dimethylformamide (DMF). Reduction and then

oxidation of **15** produced asymmetrically substituted 2,7-diphenyloct-4-enedials (**17**) in high yields (see Table 1 for the yield of each product).

Either bromoester **14** or **18** was required for the synthesis of mono-substituted oct-4-enedials **21** (fourth row in Scheme 4). The reaction of lithium enolate of ethyl acetate and bromoester **14** did not provide the desired coupling product **19**, but most of bromoester **14** was recovered presumably due to extensive self-coupling of ethyl acetate. On the other hand, bromoester **18** underwent smooth coupling with *para*-X-substituted phenylacetic acid esters using *t*-BuOK in DMF to give the mono-substituted diesters **19** in 80~92 % yields. Preparation of bromoester **18** by the reaction of ethyl acetate and 1,4-dibromo-2-butene was again problematic. Three-fold excess of the lithium enolate of ethyl acetate should be used for the coupling with 1,4-dibromo-2-butene at –78 °C to overcome the self-coupling problem to some degree, thereby producing bromoester **18** in 37 % yield. The yield of **18** was not improved by the use of more than 3 equiv of ethyl acetate. No dialkylation of 1.4-dibromo-2-butene was observed in any of these reaction conditions. Reduction and then oxidation of **19** produced 2-phenyloct-4-enedials (**21**) in high yields (see Table 1 for the yield of each product).

DOUBLE ELIMINATION

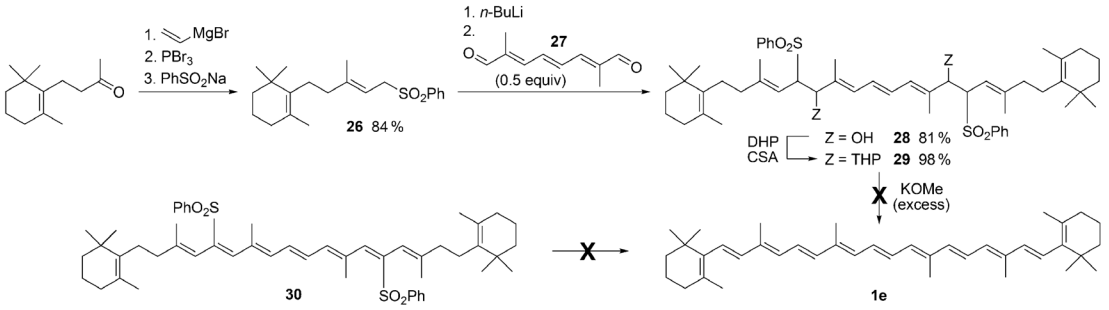
Double elimination means two consecutive E2 reactions to afford a conjugated diene moiety, which was originally introduced by Otera in the synthesis of vitamin A derivatives [13]. This reaction is well suited for the coupling products of allylic sulfones and aldehydes, in which the sulfonyl and the protected hydroxyl groups are served as leaving groups in the base-promoted elimination reactions. We extended this protocol to the expeditious synthesis of β-carotene and lycopene by the invention of the novel C_{10}- and C_{20}-dialdehydes [7,14]. The 2:1 coupling of C_{15}-allylic sulfone **3** and 2,7-dimethyloct-4-enedial (**4**) produced the C_{40}-diol **22** containing the required carbon skeleton for β-carotene (Scheme 5). Various protecting groups of OH such as methoxymethyl (MOM), 1-ethoxyethyl (EOE), and tetrahydro-2*H*-pyranyl (THP) were tested to be effective for the elimination reactions. Two consecutive double elimination reactions of **23** efficiently produced β-carotene (**1e**). It is believed that the initial E2 reactions proceed to give disulfone **24**, which can be isolated from the C_{40}-dibromide **23d** (Z = Br) under carefully controlled conditions using 5 equiv of KOMe at room temperature for 3 h (Scheme 5). The second eliminations would be E2' reactions of the intermediate **25** which might be transiently formed by the migration of the C(11)/C(11')-double bonds from **24** under the thermodynamic condition.



Scheme 5 Mechanism of the double elimination of **23a–d** in the synthesis of β-carotene **1e**.

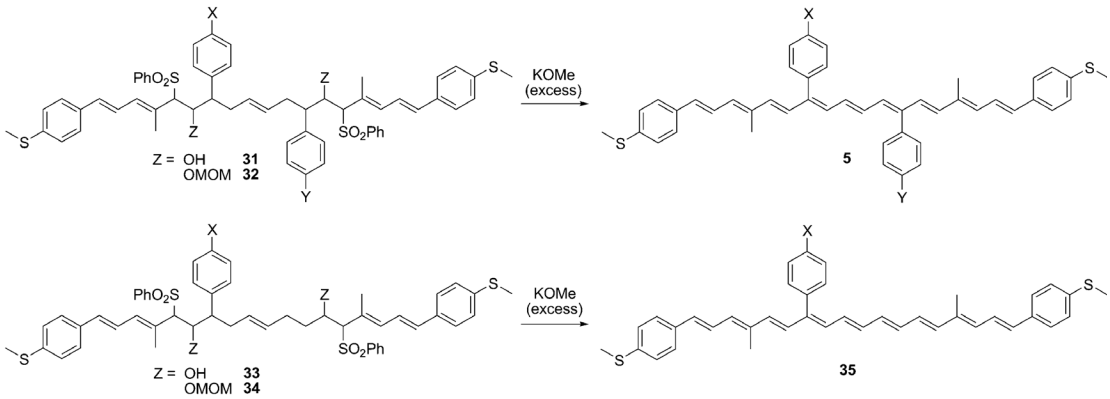
We then studied the scope of the above quadruple elimination reactions in the carotenoid synthesis. We were especially interested in the relative positions of the leaving groups and the C=C bonds for the successful quadruple elimination reactions. A new scheme was devised to make use of 2,7-dimethylocta-2,4,6,-trienedial (**27**) which has been widely utilized for the carotenoid synthesis by the Wittig reaction [15]. Since dialdehyde **27** contains two more C=C bonds than dialdehyde **4**, 2 equiv of

the C_{15}-sulfone **26** containing one fewer C=C bond would be a good coupling partner to give the substrate for the double elimination reactions (Scheme 6). The C_{15}-allylic sulfone **26** was prepared from 7,8-dihydro-β-ionone by the three-step sequence of vinyl Grignard addition, bromination (PBr_3), and sulfonation in 84 % overall yield. The 2:1 coupling of the C_{15}-allylic sulfone **26** with the C_{10}-dialdehyde **27** was promoted by the deprotonation with *n*-BuLi at –78 °C to produce the C_{40}-diol **28** in 81 % yield. Protection of the hydroxyl groups in **28** with 3,4-dihydro-2*H*-pyran (DHP) under acidic condition (CSA) proceeded almost quantitatively. Unfortunately, the intended double elimination reactions of **29** utilizing 20 equiv of KOMe in a mixed solvent of cyclohexane and benzene at 60~80 °C was not successful in producing β-carotene **1e**. The initial E2 reactions of **29** would provide the conjugated heptaenyl disulfone **30**, in which E2' reactions to liberate the sulfonyl groups may not be possible. Complicated decomposition products with no vinylic protons were obtained under the forcing conditions (higher temperature for a prolonged time) [16]. It was thus concluded that only one C=C bond should reside in between the two alkoxy leaving groups as a requirement for the successful double elimination reactions to the carotenoids.



Scheme 6 Unsuccessful approach to β-carotene by the double elimination reactions of the compound **29**.

The new carotenoid compounds with phenyl substitutions at C(13) and C(13') can be assembled with no difficulty by the coupling and double elimination reactions of allylic sulfone **6** and oct-4-enedials **7**, **17**, and **21**. Deprotonation of allylic sulfone **6** with *n*-BuLi at –78 °C and then coupling with a half equivalent of 2,7-diphenyloct-4-enedials **7** and **17** produced the compounds **31** in 56~95 % yield (Scheme 7). After MOM protection of the two hydroxyl groups in **31** (82~96 % yield), the quadruple eliminations efficiently provided the 13,13'-diphenyl-substituted carotenoids **5** in 74~98 % yield as red solids, which were purified by recrystallization to give a single stereoisomer of all-(*E*)-configurations except the C(13)/C(13')-double bonds (see Table 2 for the yield of each product) [17]. The unsymmetrical carotenoids **35** with a mono-phenyl substitution at C(13) were also prepared in the same manner by the 2:1 coupling of allylic sulfone **6** with oct-4-enedials **21** to give **33** (60~82 % yield), and then protection of the two hydroxyl groups in **33** (72~89 % yield), followed by the quadruple eliminations of **34**. The carotenoids **35** with mono-phenyl substitution at C(13) were purified by recrystallization to give a single stereoisomer of all-(*E*)-configurations except the C(13)-double bond in 31~56 % yield (see Table 2 for the yield of each product) [17]. These unnatural carotenoids **5** and **35** are stable enough to be stored at 0 °C in the dark under argon atmosphere for several years without any decomposition. Their c-AFM measurements showed that diverse conductance values were obtained according to the electronic nature of the substituent group X or Y in the phenyl rings [9].



Scheme 7 Synthesis of the new types of carotenoid compounds by the double elimination protocol.

Table 2 Yields of each compound in the preparation of the carotenoid compounds **5** and **35**.[a]

X	Y	**31** (%)	**32** (%)	**5** (%)
OMe	OMe	**a** 91	**a** 96	**a** 58 (88)
	Me	**b** 85	**b** 94	**b** 43 (98)
	H	**c** 75	**c** 86	**c** 53 (98)
	Br	**d** 56	**d** 82	**d** 39 (94)
Me	Me	**e** 92	**e** 92	**e** 52 (74)
	H	**f** 62	**f** 86	**f** 43 (93)
	Br	**g** 66	**g** 82	**g** 43 (80)
H	H	**h** 95	**h** 96	**h** 56 (93)
	Br	**i** 60	**i** 85	**i** 33 (93)
Br	Br	**j** 63	**j** 84	**j** 38 (86)
X	**33** (%)	**34** (%)	**35** (%)	
OMe	**a** 66	**a** 79	**a** 56	
Me	**b** 82	**b** 77	**b** 36	
H	**C** 60	**c** 89	**c** 31	
Br	**d** 79	**d** 72	**d** 53	

[a]Isolated yield by SiO_2 column chromatography for **31**, **32**, **33**, and **34**.
Purified yield after recrystallization for **5** and **35**; Crude yield in parenthesis for **5**.

In summary, we were able to develop a convergent synthetic pathway for the new types of carotenoid compounds containing phenyl substituents at C(13) and C(13'). The coupling of allylic sulfone **6** and oct-4-enedials **7**, **17**, or **21** and the double elimination reactions efficiently and expeditiously produced the carotenoids **5** or **35**. These unnatural carotenoids are fairly stable due to the phenyl substituents at C(13) and C(13'), and diverse conductance values are observed by c-AMF measurement according to the electronic nature of the substituent group in the phenyl ring.

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16. Unpublished results.
17. This is the same type of C=C bond configurations as those of all-(*E*)-carotenoids from the natural origin.

