Organic LETTERS
Cite This: *Org. Lett.* XXXX, XXX, XXX−XXX
Letter
pubs.acs.org/OrgLett

Role of Ring *Ortho* Substituents on the Configuration of Carotenoid Polyene Chains

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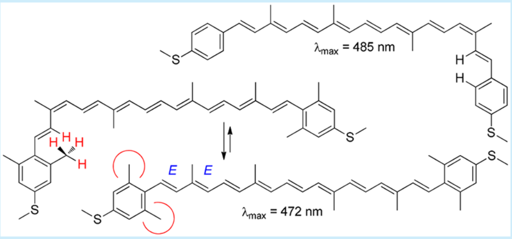
Supporting Information

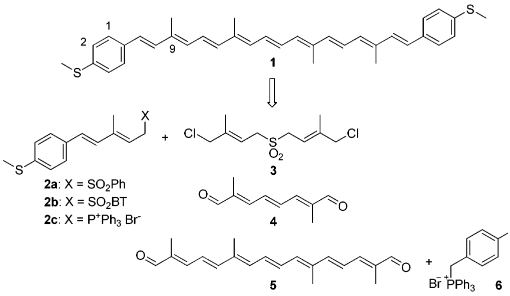
ABSTRACT: The 9-(Z)-configuration was exclusively obtained in the carotenoid polyene chain irrespective of olefination and disconnection methods for terminal *ortho*-unsubstituted benzene rings. The 2,6-dimethyl substituents in the terminal rings secure an all-(E)-polyene structure. The single molecular conductance of the pure 9-(Z)-carotene was measured for the first time to be $1.53 \times 10^{-4} \pm 6.37 \times 10^{-5} G_0$, whose value was 47% that of the all-(E)-carotene ($(3.23 \times 10^{-4}) \pm (1.23 \times 10^{-4})\ G_0$).



Carotenoids are structurally characterized by the conjugated polyene chain, which endows the red pigments with light-harvesting and energy transferring abilities[1] as well as strong antioxidant activity.[2] Even though 256 stereoisomers are theoretically obtainable by the palindromic structure containing nine C═C bonds, only a dozen stereoisomers were reported.[3] All-(E)-carotenes are generally the most stable form and can be prepared by chemical synthesis.[4] (Z)-Carotenes are also widespread in nature (e.g., bixin, phytofluene, prolycopene, etc.), 9-(Z)-isomers being prevalent.[5] Since the geometry of carotenoids determines their physicochemical characteristics as well as their biological activities,[6] it is desirable to develop a stereoselective synthetic method for each isomer.

In our research directed to the utilization of carotenoids as molecular wires, a series of phenyl-substituted all-(E)-carotenoids was designed[7] in which the phenyl groups not only stabilize the polyene chain[8] but also impart diverse electron-conducting abilities to the chain.[9] We were interested in the conductance behavior of carotene **1** containing the natural form of 9,9′,13,13′-tetramethyl substituents (Scheme 1).[10] Efforts to synthesize all-(E)-carotene **1** were unsuccessful, and on the contrary, it was found that the 9-(Z)-isomer was obtained exclusively. Since there have been controversial reports on the molecular conductance behaviors of E/Z isomers of azobenzene and diphenylethylene,[11,12] and since only the theoretical calculation for the conductance of (Z)-carotene was available,[13] it was a good opportunity to experimentally investigate the conductance of the (Z)-isomer. It was still necessary to synthesize the corresponding all-(E)-carotene in order to complete the conductance study on the E/Z isomerism of carotenoids. We devised a method to construct all-(E)-9,9′,13,13′-tetramethyl carotene based on the fact that β-carotene and isorenieratene[14] can be easily prepared in all-(E) form, in which the ring o-methyl substituents were conceived to play an important role in controlling the configuration of the polyene chain. We herein report the syntheses and conductance measurements of 9-(Z)- and all-(E)-9,9′,13,13′-tetramethylcarotenes.

Scheme 1. Disconnection Approaches to 9,9′,13,13′-Tetramethylcarotene Wire 1



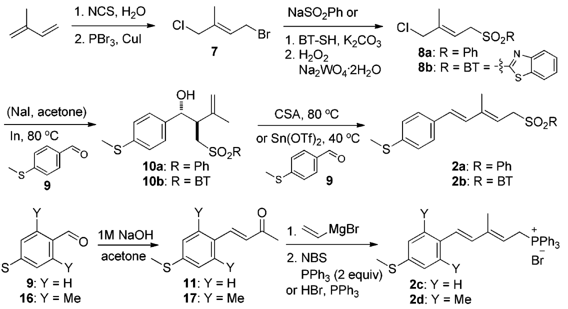
Typical disconnection approach to 9,9′,13,13′-tetramethylcarotene **1** was either using C_{10} dihalide **3**[15] or C_{10} dialdehyde **4**[16] (Scheme 1). The functional group X of the coupling partner **2** may be selected among benzenesulfonyl ($-SO_2Ph$), benzothiazolesulfonyl ($-SO_2BT$), and triphenylphosphonium bromide ($-PPh_3Br$) according to the olefination methods of Julia,[17] Julia−Kocienski,[18] and Wittig,[19] respectively (Scheme 1). The terminal methylthio group was designed as a linker to allow the carotene wire for reliable contact with gold electrodes for

Received: December 18, 2017

DOI: 10.1021/acs.orglett.7b03930

conductance measurement.[20] Other disconnection utilizing C_{20} crocetindial **5** and Wittig salt **6** was also tested.

Scheme 2. Synthesis of the Key Building Blocks 2 Containing a Methylthio Linker



The synthesis began with the preparation of the key building blocks **2** with methylthio linker (Scheme 2). Dienyl sulfones **2a** (X = $-SO_2Ph$) and **2b** (X = $-SO_2BT$) were synthesized by the application of the two step protocol utilizing indium-mediated addition of chloroallylic sulfones **8a** (R = Ph) and **8b** (R = BT) to 4-(methylthio)benzaldehyde (**9**),[21] followed by the oxonia-Cope rearrangement of the resulting homoallylic alcohols **10a** and **10b**, respectively.[22] The C_5 chloroallylic sulfones **8a** and **8b** were prepared from isoprene. Chlorohydrin formation (58% yield) by NCS in water/DMF followed by bromination (92% yield) with PBr_3 and catalytic CuI accompanying allylic migration produced allylic dihalide **7** (*E*:*Z* = 6:1).[23] Selective allylation at the more reactive carbon containing bromide by $NaSO_2Ph$ provided chloroallylic benzenesulfone **8a** (60% yield)[24] or by BT-SH using K_2CO_3 in acetone produced the corresponding BT-sulfide (95% yield). Sulfur oxidation by H_2O_2 with catalytic sodium tungstate ($Na_2WO_4{\cdot}2H_2O$) gave rise to chloroallylic benzothiazolesulfone **8b** (51% yield).[25] The *E*/*Z* alkene configurations were maintained as 6:1 through the allylation steps.

Indium-mediated Barbier addition of C_5 chloroallylic sulfone **8a** (R = Ph) to 4-(methylthio)benzaldehyde (**9**) was carried out at 80 °C in a 4:1 H_2O/THF to produce homoallylic alcohol **10a** (64% yield) with 2:1 anti (OH vs SO_2Ph) selectivity.[22] The same condition was not effective for the allylindium formation from chloroallylic sulfone **8b** (R = BT). Activation of the allylic chloride by Finkelstein reaction (NaI, acetone) was necessary to produce the corresponding homoallylic alcohol **10b** (R = BT) in 45% yield with 2:1 antiselectivity. A new *E*/*Z* ratio was established in the allyl indium species according to the alkenyl substituents regardless of the original *E*/*Z* ratio of allyl halide **8**.[24]

The oxonia-Cope rearrangement of homoallylic alcohol **10a** (R = Ph) was performed using stoichiometric camphoresulfonic acid and aldehyde **9** at 80 °C to provide dienyl sulfone **2a** in 77% yield (*E*/*Z* = 2:1 at C-2).[22] Milder condition of catalytic $Sn(OTf)_2$ and aldehyde **9** at 40 °C was utilized for the rearrangement of homoallylic alcohol **10b** (R = BT) to give dienyl sulfone **2b** in 61% yield (*E*/*Z* = 1.5:1 at C-2).[24] All-*E*-dienyl sulfone **2a** and **2b** can be easily obtained by recrystallization from MeOH or EtOH.

The corresponding Wittig salt **2c** (Y = H) was obtained from 4-(methylthio)benzaldehyde (**9**). Aldol condensation with acetone produced conjugated ketone **11** (87% yield), to which vinyl Grignard addition at −78 °C yielded the tertiary vinyl carbinol. The condition for bromination with allylic migration is crucial in the formation of Wittig salt **2c**. Acidic conditions allowing carbocation intermediate such as PBr_3 and HBr were complicated due to the formation of the regioisomer at the benzylic position. In situ generated triphenylphosphonium bromide from PPh_3 and NBS successfully activated the tertiary carbinol by forming triphenylphosphonium oxide, which was replaced by PPh_3 at the less hindered terminal vinyl carbon to provide the Wittig salt **2c** quantitatively.

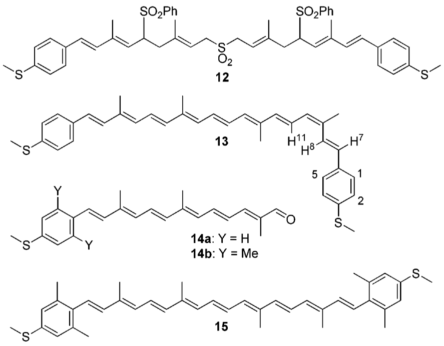


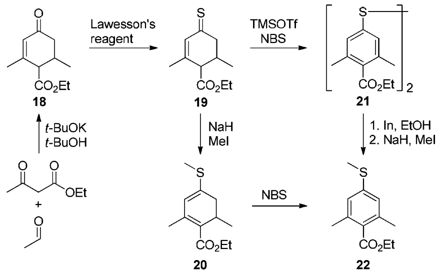
Figure 1. Products and intermediates obtained in the synthetic approaches to carotene wire **1**.

Sulfone-mediated 2:1 coupling between dienyl sulfone **2a** and C_{10} dihalide **3** was carried out with *t*-BuOK in DMF at −20 °C to produce C_{40} trisulfone **12** (92% yield, Figure 1). Olefinations were sequentially conducted first by the Ramberg−Bäcklund reaction (KOH, *t*-BuOH, CCl_4) and then by base-promoted (KOMe) double dehydro-desulfonation to exclusively and unexpectedly produce 9-(*Z*)-carotene **13** (overall 14% yield after recrystallization) instead of all-(*E*)-carotene **1**.[26] The 9-(*Z*)-configuration was assigned by the number of ^1H and ^{13}C peaks from the dissymmetrical structure and more specifically by NOE (7%) between H^{11} and H^8 in NMR analysis (see the Supporting Information for COSEY, NOESY, and 1D NOE).

The Julia−Kocienski olefination was then tried to minimize possible isomerization. Dienyl BT-sulfone **2b** (2 equiv) was coupled with C_{10} dial **4** at −78 °C and warmed to 25 °C to produce monocoupled all-(*E*)-apocarotenal **14a** (Y = H, 35% yield), which was reacted again with **2b** to exclusively give 9-(*Z*)-carotene **13** (37% yield). Olefination by the Wittig salt **2c** (5 equiv) and C_{10} dial **4** (NaOMe at 80 °C) also produced all-(*E*)-apocarotenal **14a** (56% yield) as a major product, which was reacted with the Wittig salt **2c** to give 9-(*Z*)-carotene **13** again (17% recrystallized yield). A different disconnection approach utilizing the Wittig reaction of benzyl triphenylphosphonium bromide **6** (5 equiv) and C_{20} crocetin dial **5** (NaOMe at 80 °C) provided again 9-(*Z*)-carotene **13** exclusively (13% yield after recrystallization).

A series of questions arose: Is the 9-(*Z*)-isomer **13** more stable than all-(*E*)-carotene **1**? How can *β*-carotene be easily obtained as all-(*E*)-form? Is it possible to synthesize all-(*E*)-9,9′,13,13′-tetramethylcarotene by introducing *o*-methyl substituents into the benzene rings (e.g., compound **15** in Figure 1) just like the ring *o*-methyl substituents of *β*-carotene? In order to answer these questions, we decided to synthesize Wittig salt **2d** (Y = Me, in Scheme 2). An efficient synthesis of 2,6-dimethyl-4-(methylthio)benzaldehyde (**16**) was devised from the Hagemman's ester **18**, which was prepared (95% yield) by a one-pot reaction between ethyl acetoacetate (2 equiv) and acetaldehyde (Scheme 3).[27] Lawesson's reagent allowed the formation of thione **19**, which was not easily purified. It was suspected to be consisted of a mixture of **19** and its dimeric form through a disulfide bond, because *S*-methylation (NaH, MeI) gave only

Scheme 3. Preparation of the Key Building Block 22 for All-(*E*)-Carotene 15



40% yield of methyl sulfide **20**; oxidation of the Lawesson's reaction product by NBS and catalytic TMS·OTf produced disulfide **21** in 73% yield.[28] Oxidative aromatization of **20** by NBS produced ethyl 2,6-dimethyl-4-(methylthio)benzoate (**22**) in 83% yield.[28] The key building block **22** can be better prepared by Indium reduction[29] of disulfide **21** to the monomeric thiol from, followed by *S*-methylation (NaH, MeI) in overall 80% yield.

Wittig salt **2d** was prepared as demonstrated for Wittig salt **2c** in Scheme 2. Ethyl benzoate **22** was converted to the corresponding aldehyde **16** by LAH reduction (50% yield) and PDC oxidation (73% yield). Aldol condensation with acetone provided unsaturated ketone **17** (94% yield), which was reacted with vinylmagnesium bromide to produce tertiary vinylcarbinol. Allylic bromination and phosphorylation at the terminal vinyl carbon were routinely carried out by HBr (1 equiv) and PPh_3 (1 equiv) to produce Wittig salt **2d** quantitatively (Scheme 2). Wittig reaction of **2d** (2.5 equiv) and C_{10} dialdehyde **4** (NaOMe in MeOH/toluene at reflux) eventually produced all-(*E*)-9,9′,13,13′-tetramethylcarotene **15** (23% yield) and mono-coupled all-(*E*)-apocarotenal **14b** (67% yield), which was coupled again with Wittig salt **2d** to give all-(*E*)-carotene **15** in 92% yield. The *o*-methyl ring substituents really play an important role in controlling the (*E*)-configuration of the polyene chain.

The distinctive triplet UV absorptions for 9-(*Z*)-carotene **13** were observed at 462, 485 (maximum), and 517 nm in CH_2Cl_2. On the other hand, only the maximum peak at 472 nm was discernible with a shoulder around 500 nm for all-(*E*)-carotene **15** (see the SI). It is interesting to note that λ_{max} for 9-(Z)-carotene **13** is red-shifted by 13 nm compared to that of all-(*E*)-carotene **15**, which may be the reason for the exclusive formation of 9-(*Z*)-form by effective conjugation of the polyene chain. DFT calculation (structure optimization: m062*x*/6-311G(d,p); basis set for free energy: cc-pVTZ) supports this result that 9-(Z)-carotene **13** is more stable than all-(*E*)-carotene **1** by 1.55 kcal/mol, and that all-(*E*)-carotene **15** with 2,6-dimethyl groups is more stable than its 9-(Z)-isomer by 2.64 kcal/mol (see SI).

The static version[30] of the STM break junction method[31] is a valuable tool to measure single molecule conductance for carotenoids without applying mechanical strains to the formed molecular junction. An electric circuit is stochastically formed and broken between a voltage-biased gold STM tip and supporting gold electrodes through a residing carotenoid molecule with methylthio-linkers in dilute mesitylene (0.5 μM) solution. The current is then monitored as a function of time. When a single carotenoid backbone transiently bridges the gap, a telegraphic signal is observed in the current transient (see Figure 2a,b). Tens of such current telegraphic traces are then accumulated in a single 2-dimensional map (blinking map, see Figure 2c,d) by setting all the current jumps to the same time origin and tunneling background subtraction. The averaged molecular conductance values (expressed versus the quantum of conductance, $G_0 = 77.4\ \mu S$) for both carotenoid molecules were statistically obtained by Gaussian fittings of the peaks in the 1-dimensional histogram representation of the two blinking maps (see Figures 2c,d): $((1.53 \times 10^{-4}) \pm (6.37 \times 10^{-5}))G_0$ and $((3.23 \times 10^{-4}) \pm (1.23 \times 10^{-4}))G_0$ for **13** and **15**, respectively. The experimental conductance value for 9-(*Z*)-carotene **13** was 47% of that of all-(*E*)-carotene **15**, which agrees well with the theoretical (DFT) calculations of 55% reduction for the 7-(*Z*)-isomer compared to the all-(*E*)-carotene.[13]

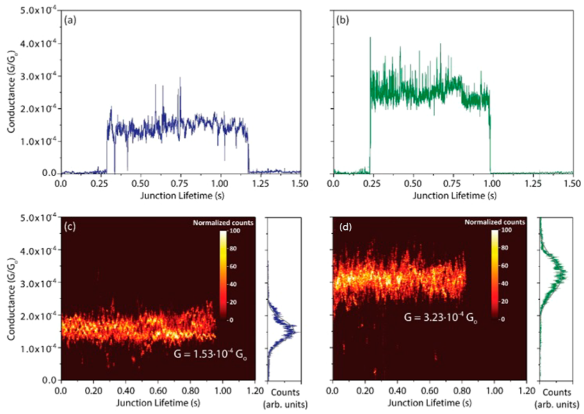


Figure 2. (a, b) Representative current transient for (a) 9-(*Z*)- and (b) all-(*E*)-9,9′,13,13′-tetramethylcarotenes, displaying blinking features as a result of transient single-carotene molecules being trapped in the tunneling junction. (c, d) 2-Dimensional blinking maps for (c) 9-(*Z*)- and (d) all-(*E*)-9,9′,13,13′-tetramethylcarotenes, respectively, built out of more than 30 individual current traces. The left panel of each 2-dimensional map shows vertically the 1-dimensional counts distribution. The maxima of the Gaussian fits (solid lines in the vertical 1-D histograms) projected over the *Y*-axis (*G*) provide the averaged conductance of the single-molecule junction. The applied bias voltage (*V*) was set to 7 mV.

It was assumed that both carotenes make stable interactions with the gold STM tip through methylthio linkers. The blinking signals in Figure 2 arise from strong tip-molecule interactions. Forces have been measured in break-junction experiments and the breaking features have been ascribed to the formation of a covalent Au−S bond.[32] The lower accessibility of the linker group might affect the yield of the single-molecule junction experiments, but the observed result shows that this is not the case. STM tips are known to present a number of asperities on their surface. They are far from being a smooth concave element, and such asperities can act as anchoring points to the methylthio group of 9-*Z*-isomer.

Short switching molecules under UV/vis irradiation such as azobenzene and diphenylethylene were reported to exhibit high conducting profile for *cis*-isomer, which is mainly because of the difference in tunneling length of the molecule spanned between the electrodes.[11] Controversially, *cis*-azobenzene was also reported to give lower conductance by breaking π-conjugation along the molecular frame.[12] We experimentally demonstrated that the *trans*-isomer is more conductive for the polyene chain of carotenoids. DFT calculations of frontier molecular orbitals in both cases show good delocalization of orbitals, being the HOMO−1 and −2 energetically the closest orbitals to the Au electrode Fermi level (−5 eV). The slight closer proximity in energy in all-(*E*) case (up to 70 mV in HOMO−2 case) might

DOI: 10.1021/acs.orglett.7b03930
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account for the observed factor of 2 difference in the conductance, given their exponential dependence nature (see Tables S1-1 and S1-2).

In conclusion, we were able to devise stereoselective synthetic methods for each of 9-(*Z*)- and all-(*E*)-carotene with the natural 9,9′,13,13′-tetramethyl substitution. Effective conjugation for 9-(*Z*)-carotene **13** and repulsive steric interaction at the ring *ortho*-substituents for all-(*E*)-carotene **15** seem to be the major controlling factors for the configurations. Molecular conductance measurements using the static STM break junction method revealed all-(*E*)-carotene **15** is almost twice more conducting than 9-(Z)-carotene **13**.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03930.

> Experimental procedure, analytical data, and DFT calculations for 9-(*Z*)-carotene **13** and all-(*E*)-carotene **15** (PDF)
>
> Analytical data and ^{1}H ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the Basic Science Research Program (NRF-2016R1A2B4007684) and by the Priority Research Centers Program (NRF-2009-0093816), both through the National Research Foundation of Korea, and also by the MINECO Spanish national project CTQ2015-64579-C3-3-P (MINECO/FEDER, EU) and start-up King's College London financial support.

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