Allylic Sulfones Containing Triene Moieties as Key Synthons for Carotenoid Synthesis

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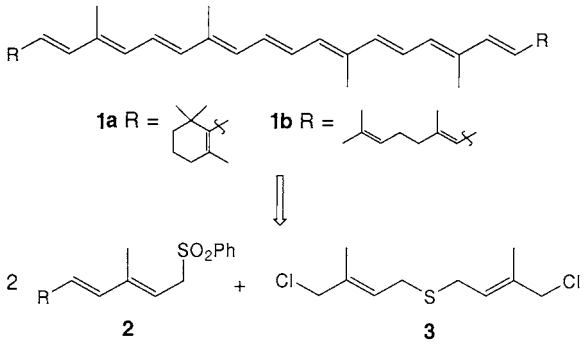
An efficient synthetic method for the allylic sulfone **2** containing a conjugated triene moiety has been proposed involving *i*) coupling of allylic sulfones **4** with the C_5 bromoallylic sulfide **5**, *ii*) base-promoted dehydrosulfonation in the presence of allylic sulfide, and *iii*) selective oxidation of the resulting trienyl sulfide to the corresponding sulfone. Total synthesis of lycopene starting from the C_{15} allylic sulfone **2b** has been described, where the new C_{10} bis(chloroallylic) sulfone **11** proved to be a useful substitute for the C_{10} bis(chloroallylic) sulfide **3**, which did not require the problematic chemoselective sulfur oxidation in a conjugated polyene.

Introduction. – Carotenoids such as β-carotene (**1a**) and lycopene (**1b**) are characterized by long conjugated polyene chains that show distinctive red colors and are ideally utilized as nonhazardous dyes for foodstuffs. High reactivity of these polyenes with activated carcinogenic oxygen or radicals provides carotenoids with prophylactic effects against certain cancers of the pancreas, the mouth, and the bladder, *etc.* [1]. Among the numerous approaches that have appeared in the literature to build the conjugated polyene chains of carotenoids [2], methods based on acetylide coupling/partial hydrogenation [3] and *Wittig* olefination [4] have been the two main synthetic approaches. The *Julia* sulfone olefination protocol [5], which has been applied to retinol synthesis [6], is presumed to be the best method to produce double bonds with the (*E*)-configuration [7]. We have introduced the C_{10} bis(chloroallylic) sulfide **3** as a stable substitute for the highly unstable 1,8-dichloro-2,7-dimethylocta-2,4,6-triene, and successfully accomplished total syntheses of β-carotene (**1a**) and lycopene (**1b**) based on the *Julia* sulfone-olefination protocol [8]. To generalize this process with C_{10} bis(chloroallylic) sulfide **3** for carotenoid syntheses, an efficient method should be devised to build allylic sulfones containing conjugated C=C bonds such as **2** (*Scheme 1*). We herein report our strategy to synthesize allylic sulfones comprising a conjugated triene moiety and total synthesis of lycopene [9] by means of the allylic sulfone **2b**.

Results and Discussion. – The number of C-atoms in carotenoids is generally a multiple of 5 due to the biogenetic origin [2][10], and, thus, we started the synthetic procedure for allylic sulfones **2** from C_{10} cyclogeranyl [11], geranyl, and C_5 prenyl sulfones **4a**, **4b**, and **4c**, respectively (*Scheme 2* and *Table*). The coupling reaction of the anions of the allylic sulfones **4a**–**4c** with our chain-extending C_5 unit **5** [8b] produced

Scheme 1. *Retro Synthesis of Carotenoids by Utilization of Sulfur Chemistry*



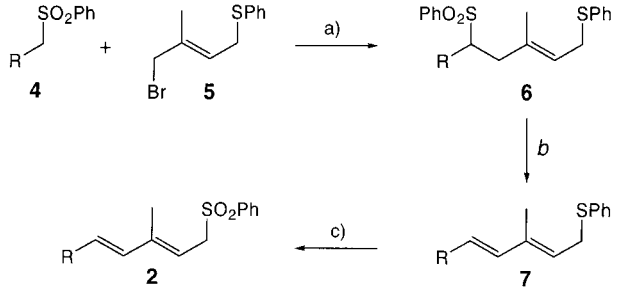
the chain-extended allylic sulfides **6a**–**6c**. The anion-stabilizing ability of sulfone is far superior to that of sulfide, and, therefore, no proton exchange occurred during their coupling reactions with the bromoallylic sulfide **5** to give excellent yields of the coupling products. It is also this difference in anion-stabilizing ability that makes sulfone a better leaving group than sulfide, and, thus, chemoselective base-promoted dehydrosulfonation reactions of **6** proceeded to bring two isolated C=C bonds into conjugation, producing the allylic sulfides **7a**–**7c** with a conjugated triene moiety. Chemoselective oxidation of sulfur was then accomplished by the $LiNbMoO_6$–H_2O_2 oxidant system [12], without any oxidation of the C=C bonds, to produce the desired allylic sulfones **2a**–**2c** containing conjugated triene moieties.

Table. *Yields and Stereoisomer Ratios of the Reaction Products* **6**, **7**, *and* **2** (see *Scheme 2*) *and UV Absorption Values of* (all-E)-**2** *in* $CHCl_3$

4	**6** ((*E*)/(*Z*))	**7** ((2*E*)/(2*Z*))	**2** ((2*E*)/(2*Z*))	UV [λ_{max} (ε_{max})] of (*all-E*)-**2**
(**a**) R = 	93% (4:1)	80% (3:1)	93% (3:1)	279 nm (15,590)
(**b**) R = 	93% (4:1)	75% (2.5:1)	77% (2.5:1)	294 nm (13,235)
(**c**) R = 	95% (5:1)	78% (3:1)	73% (3:1)	291 nm (7,978)

The *Table* summarizes the yields and the stereoisomer ratios of the products in the above reaction sequence and UV absorption characteristics of the allylic sulfones **2a**–**2c** containing conjugated (all-*E*)-triene moieties. The stereoisomer ratios of the C=C bond in **6** reflect those of the C_5 bromoallylic sulfide **5**, which was generated in a 4–5:1 (*E*)/(*Z*) ratio [8b]. It is believed that there is no stereoisomerization during the

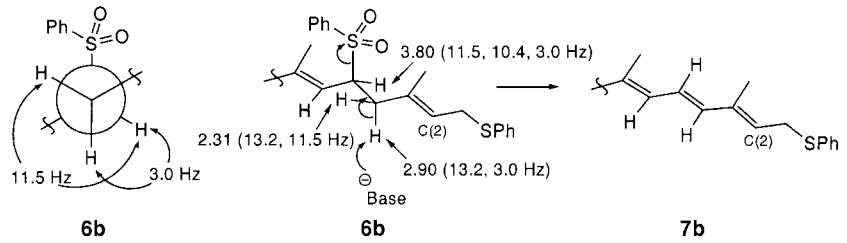
Scheme 2. *Synthesis of the Allylic Sulfones* **2** *Containing a Conjugated Triene Moiety*



a) 1) BuLi in THF at −78°; 2) **5** at −78° to r.t. *b*) NaOEt in refluxing EtOH. *c*) $LiNbMoO_6$ (0.05 equiv.) and H_2O_2 (2.5 equiv.) in MeOH at 0° to r.t.

coupling reaction between **4** and **5** under the above reaction conditions. Base-promoted dehydrosulfonation of **6** requires anti-disposition of one of the H-atoms at C(4) and the $PhSO_2$ group at C(5), which is tentatively depicted for **6b** in *Scheme 3*. The conformation of **6b** is based on the coupling constants of the H_α-atom to the $PhSO_2$ group in the ^{1}H-NMR spectrum, which are 11.5, 10.4, and 3.0 Hz. These values are typical for strain-free acyclic sulfones. Two vicinal coupling constants with diastereotopic sp^3-hybridized H-atoms at C(4) are 11.5 and 3.0 Hz, which indicate dihedral angles of *ca.* 180° and *ca.* 60°, respectively, according to the *Karplus* correlation [13]. Base-promoted *anti*-elimination of the H-atom and the $PhSO_2$ group then produced the (*E*)-C=C bond at C(4) in conjugation with the other two C=C bonds [7]. The (*E*)/(*Z*) stereoisomer ratios of the C=C bond at C(2) in **7**, however, deteriorated during this elimination process presumably due to an allylic migration of the anion at C(4), which might be formed under the harsh conditions in boiling EtOH. This indicated that the elimination process proceeded by an E_{1cb}-like E_2 mechanism. These stereoisomers of the allylic sulfide **7** were not separable. However, the corresponding sulfones **2** can be separated and unambiguously identified as (*E*)- and (*Z*)-isomers at C(2) by NOE experiments.

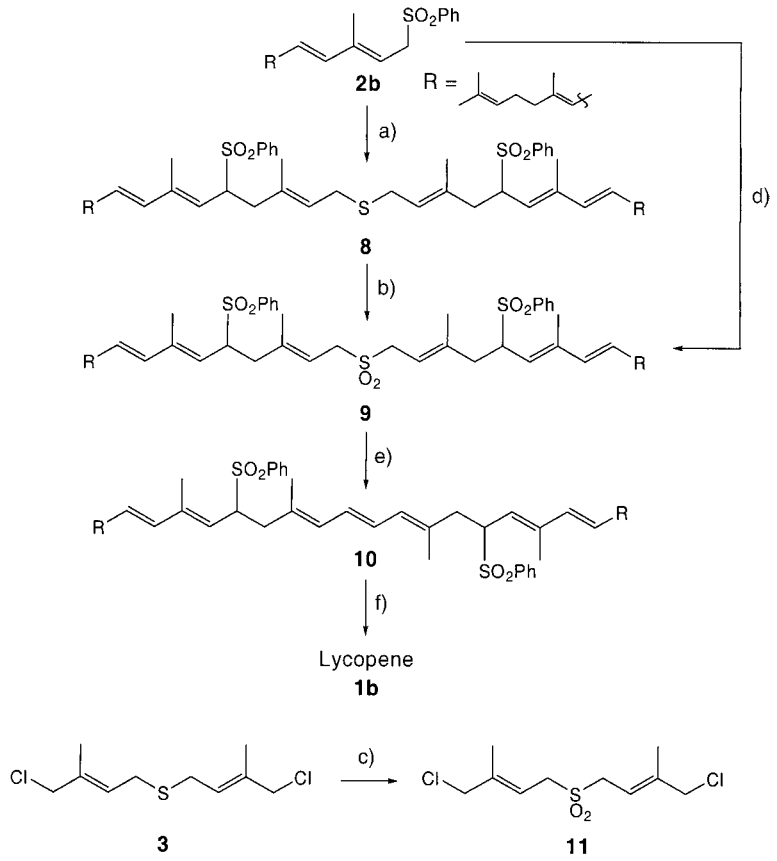
Scheme 3. *The Conformation of* **6b** *and the Course of Base-Promoted Dehydrosulfonation Reaction*



Since the allylic sulfone **2a** has been successfully applied to β-carotene synthesis [8a], we wanted to show the generality of our carotenoid synthesis utilizing C_{10} bis(chloroallylic) sulfide **3** in the lycopene synthesis, starting from the allylic sulfone **2b** containing the (all-*E*)-triene (*Scheme 4*). Deprotonation of **2b** with NaH in THF,

followed by the coupling reaction with 0.5 equiv of **3** at both termini, produced the C_{40} coupling product **8** in 90% yield with the required C-skeleton for lycopene synthesis. Chemoselective sulfur oxidation of **8** to **9**, however, was problematic due to the presence of the conjugated C=C bonds, probably leading to various oxidation products. The best yield of 40% was obtained by the oxidation with monoperphthalic acid that was generated *in situ* by the reaction of phthalic anhydride and a urea–H_2O_2 complex in Me_3CN [14].

Scheme 4. *Synthesis of Lycopene Starting from the Allylic Sulfone* **2b**



a) 1) NaH in THF at 0°; 2) **3** (0.5 equiv.) at 0°; 3) NaI at 0° to r.t.; 90%. *b*) Urea-H_2O_2 (5 equiv.) and phthalic anhydride (2.5 equiv.) in MeCN at 0°; 40%. *c*) $LiNbMoO_6$ (0.05 equiv.) and H_2O_2 (4 equiv.) in MeOH; 71%. *d*) 1) ^{t}BuOK in DMF at –20°; 2) **11** (0.5 equiv.) at –20°; 86%. *e*) KOH in ^{t}BuOH and CCl_4; 63%. *f*) EtONa in refluxing EtOH; 78%.

At this point, the possibility of utilizing the new C_{10} bis(chloroallylic) sulfone **11** in the coupling reaction with the allylic sulfone **2b** to directly produce the C_{40} bis(allylic) sulfone **9** has been studied in order to avoid the problematic sulfur oxidation reaction of **8** to **9**. The C_{10} bis(chloroallylic) sulfone **11** can be obtained in 71% yield from the C_{10} bis(chloroallylic) sulfide **3** by chemoselective sulfur oxidation with H_2O_2 under

$LiNbMoO_6$ catalyst. The choice of deprotonating base and solvent is crucial in the coupling reaction of the allylic sulfone **2b** and the allylic chloride **11**. The use of NaH or BuLi in THF produced an appreciable amount of the dehydrochlorination product from the bis(chloroallylic) sulfone **11**. The coupling reaction of **2b** and **11**, on the other hand, proceeded efficiently with ^{t}BuOK as a base in DMF to produce the coupling product **9** in 86% yield.

The *Ramberg–Bäcklund* reaction of the bisallylic sulfone **9** under *Meyer*'s conditions [15] at ambient temperature produced compound **10** containing the central conjugated triene moiety in 63% yield. The presence of a small amount (less than 10%) of a stereoisomer of compound **10**, presumably the (15*Z*)-isomer, was also observed in ^{1}H-NMR spectrum. Compound **10** is unstable under air especially in solution, and it must be handled and stored under inert atmosphere. EtONa-Promoted dehydrosulfonation of **10** in refluxing EtOH produced lycopene (**1b**) in 78% yield under the condition where thermal isomerization to (*all-E*)-double bonds occurred.

In conclusion, we have developed an efficient synthetic method of allylic sulfones containing a conjugated triene. The allylic sulfone **2a** has previously been efficiently used for the syntheses of retinal [6], retinoic acid [6a], and β-carotene [8a]. We also demonstrated the total synthesis of lycopene (**1b**) by means of the allylic sulfone **2b**, where the new C_{10} bis(chloroallylic) sulfone **11** was proved to be a useful substitute for the C_{10} bis(chloroallylic) sulfide **3**. Furthermore, these allylic sulfones may well be applied to the synthesis of conducting organic compounds containing fully conjugated polyene chains.

Experimental Part

General. Solvents used as reaction media were dried over molecular sieves (5 Å) pre-dried in a microwave oven. All reactions were performed under dry Ar in oven-dried glassware, except for those reactions with H_2O as a solvent, which were run in air. Solvents for extraction and chromatography were reagent-grade and were used as received. Column chromatography (CC): silica gel *60*, 230–400 mesh ASTM supplied by *Merck*. ^{1}H-(300 MHz) and ^{13}C-NMR (75.5 MHz) spectra: in $CDCl_3$ with Me_4Si ($\delta = 0$ ppm) as an internal standard.

3-Methyl-1-(phenylsulfanyl)-5-(phenylsulfonyl)-5-(2,6,6-trimethylcyclohex-1-enyl)pent-2-ene (**6a**). To a stirred soln. of *β-cyclogeranyl phenyl sulfone* (**4a**) (2.06 g, 7.40 mmol) in THF (30 ml) at $-78°$ was slowly added 1.6M soln. of BuLi in hexane (5.1 ml, 8.14 mmol). The mixture was stirred at that temp. for 30 min and then treated with a soln. of *4-bromo-3-methylbut-2-enyl phenyl sulfide* (**5**) [8b] (2.31 g, 9.00 mmol, 4:1 (*E*)/(*Z*)) in THF. The mixture was slowly warmed and stirred at r.t. for 14 h, diluted with Et_2O, washed with 1M HCl soln. and water, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by SiO_2 flash column chromatography to give **6a** (3.14 g, 6.90 mmol) in 93% yield. The (2*E*)/(2*Z*) ratio of 4:1 was based on ^{1}H-NMR analysis.

Data of (2*E*)-**6a**: IR (neat) 1446, 1304, 1143. ^{1}H-NMR: 0.81 (*s*, 3 H); 1.05 (*s*, 3 H); 1.24 (*s*, 3 H); 1.33–1.77 (*m*, 4 H); 1.90–2.20 (*m*, 2 H); 2.00 (*s*, 3 H); 2.62 (*d* of A of *ABq*, $J_{AB} = 14.5$, $J_d = 6.4$, 1 H); 3.00 (*d* of *B* of *ABq*, $J_{AB} = 14.5$, $J_d = 6.6$, 1 H); 3.40 (*dd*, $J = 7.6$, 2.7, 2 H); 3.90 (*dd*, $J = 6.6$, 6.4, 1 H); 5.35 (*t*, $J = 7.6$, 1 H); 7.15–7.33 (*m*, 5 H); 7.43–7.65 (*m*, 3 H); 7.80–7.96 (*m*, 2 H). ^{13}C-NMR: 15.4; 18.9; 23.3; 28.4; 29.1; 31.9; 34.5; 35.9; 39.6; 40.9; 65.4; 123.8; 126.1; 128.3; 128.7; 128.7; 129.5; 130.0; 130.5; 133.0; 134.9; 137.9; 141.9. CI-HR-MS (pos.): 455.2087 ($C_{27}H_{35}O_2S_2^+$; calc. 455.2079).

3,7,11-Trimethyl-1-(phenylsulfanyl)-5-(phenylsulfonyl)dodeca-2,6,10-triene (**6b**) [8b]. According to the general procedure for **6a**, *geranyl phenyl sulfone* (**4b**; 28.7 g, 103 mmol) in THF (150 ml) at 0° was deprotonated with a 1.6M soln. of BuLi in hexane (64 ml, 103 mmol), and then reacted with **5** (29.1 g, 113 mmol; (*E*)/(*Z*) 4:1) for 11 h at r.t. to give **6b** (43.6 g, 96 mmol) in 93% yield. The (2*E*)/(2*Z*) ratio of 4:1 was based on ^{1}H-NMR analysis.

3,7-Dimethyl-1-(phenylsulfanyl)-5-(phenylsulfonyl)octa-2,6-diene (**6c**) [8b]. According to the general procedure for **6a**, *phenyl prenyl sulfone* (**4c**, 14.72 g, 70.0 mmol) in THF (70 ml) at −78° was deprotonated with 1.6M soln. of BuLi in hexane (45.9 ml, 73.5 mmol), and then reacted with **5** (18.0 g, 70.0 mmol; (*E*)/(*Z*) 5:1) for 2 h at −78° to give **6c** (25.58 g, 66.2 mmol) in 95% yield. The (2*E*)/(2*Z*) ratio of 5:1 was based on ^{1}H-NMR analysis.

3-Methyl-1-(phenylsulfanyl)-5-(2,6,6-trimethylcyclohex-1-enyl)penta-2,4-diene (**7a**). Na (1.19 g, 51.7 mmol) was added to anh. EtOH (30 ml) at 0°. The mixture was then heated to reflux for 1 h and cooled to r.t. A soln. of **6a** (2.35 g, 5.17 mmol) in EtOH (5 ml) was added, and the mixture was heated to reflux for 10 h. Upon cooling to r.t., the reaction was quenched with H_2O, and the mixture was extracted with hexanes, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by SiO_2 flash column chromatography to give **7a** (1.30 g, 4.15 mmol) in 80% yield, which was composed of a 3:1 mixture of stereoisomers according to ^{1}H-NMR analysis. These isomers were inseparable by CC; however, they were separated after oxidation to sulfones **2a** in the next step and unambiguously identified as (2*E*)- and (2*Z*)-isomers, respectively, by NOE experiments.

Data of (2*Z*)-**7a**: ^{1}H-NMR: 1.01 (*s*, 6 H); 1.42–1.48 (*m*, 2 H); 1.56–1.64 (*m*, 2 H); 1.69 (*s*, 3 H); 1.88 (*s*, 3 H); 1.99 (*t*, *J* = 5.7, 2 H); 3.71 (*d*, *J* = 8.0, 2 H); 5.44 (*t*, *J* = 8.0, 1 H); 6.27 (*A* of *ABq*, *J* = 16.2, 1 H); 6.37 (*B* of *ABq*, *J* = 16.2 Hz, 1 H); 7.13–7.27 (*m*, 3 H); 7.27–7.38 (*m*, 2 H). ^{13}C-NMR: 12.5; 19.2; 19.8; 21.7; 28.9; 31.3; 32.9; 34.1; 39.5; 117.8; 125.9; 126.2; 126.4; 128.9; 129.1; 130.4; 136.2; 137.9; 139.0.

*Data of (all-*E*)-***7a***: IR (neat): 1477, 1440, 966. ^{1}H-NMR: 0.99 (*s*, 6 H); 1.42–1.48 (*m*, 2 H); 1.56–1.64 (*m*, 2 H); 1.67 (*s*, 3 H); 1.70 (*s*, 3 H); 1.99 (*t*, *J* = 5.7, 2 H); 3.68 (*d*, *J* = 7.9, 2 H); 5.53 (*t*, *J* = 7.9, 1 H); 6.02 (br. *s*, 2 H); 7.13–7.27 (*m*, 3 H); 7.27–7.38 (*m*, 2 H). ^{13}C-NMR: 12.1; 19.2; 19.8; 21.6; 28.9; 32.8; 32.9; 34.2; 39.5; 112.9; 124.5; 126.3; 126.5; 128.7; 129.3; 130.4; 136.9; 137.5; 137.6. CI-HR-MS (pos.): 313.1999 ($C_{21}H_{29}S^+$; calc. 313.1990).

3,7,11-Trimethyl-1-(phenylsulfanyl)dodeca-2,4,6,10-tetraene (**7b**). According to the general procedure for **7a**, EtONa, prepared by reacting Na (15.5 g, 0.673 mol) with anh. EtOH (160 ml), was reacted with **6b** (15.3 g, 33.7 mmol) to give **7b** (7.92 g, 25.3 mmol) in 75% yield, composed of a 2.5:1 mixture of stereoisomers according to ^{1}H-NMR analysis. These isomers were inseparable by CC; however, they were separated after oxidation to sulfones **2b** in the next step and unambiguously identified as (2*E*)- and (2*Z*)-isomers, respectively, by NOE experiments.

*Data of (2*Z*)-***7b***: ^{1}H-NMR: 1.60 (*s*, 3 H); 1.68 (*s*, 3 H); 1.79 (*s*, 3 H); 1.88 (*s*, 3 H); 2.10 (br. *s*, 4 H); 3.73 (*d*, *J* = 7.9, 2 H); 5.10 (br. *s*, 1 H); 5.44 (*t*, *J* = 7.9, 1 H); 5.93 (*d*, *J* = 11.5, 1 H); 6.16 (*d*, *J* = 15.2, 1 H); 6.47 (*dd*, *J* = 15.2, 11.0, 1 H); 7.12–7.44 (*m*, 5 H). ^{13}C-NMR: 12.3; 16.9; 20.4; 25.7; 26.6; 31.3; 40.1; 123.1; 123.9; 126.0; 126.3; 127.1; 128.8; 129.4; 130.3; 131.8; 136.2; 136.3; 140.5 ppm.

*Data of (all-*E*)-***7b***: IR (neat): 1480, 1440, 1378. ^{1}H-NMR: 1.60 (*s*, 3 H); 1.68 (*s*, 3 H); 1.71 (*s*, 3 H); 1.78 (*s*, 3 H); 2.09 (br. *s*, 4 H); 3.67 (*d*, *J* = 8.0, 2 H); 5.10 (br. *s*, 1 H); 5.57 (*t*, *J* = 8.0, 1 H); 5.89 (*d*, *J* = 11.0, 1 H); 6.16 (*d*, *J* = 15.2, 1 H); 6.40 (*dd*, *J* = 15.2, 11.0, 1 H); 7.12–7.44 (*m*, 5 H). ^{13}C-NMR: 12.3; 16.8; 17.7; 25.7; 26.6; 32.8; 40.1; 123.9; 124.7; 125.1; 125.4; 126.3; 128.8; 129.4; 130.3; 131.7; 134.4; 137.5; 139.4. CI-HR-MS (pos.): 313.1988 ($C_{21}H_{29}S^+$; calc. 313.1990).

3,7-Dimethyl-1-(phenylsulfanyl)octa-2,4,6-triene (**7c**). According to the general procedure for **7a**, EtONa, prepared by reacting Na (0.612 g, 26.6 mol) with anh. EtOH (30 ml), was reacted with **6c** (1.03 g, 2.66 mmol) to give **7c** (0.507 g, 2.08 mmol) in 78% yield, composed of a 3:1 mixture of stereoisomers according to ^{1}H-NMR analysis. These isomers were inseparable by CC; however, they were separated after oxidation to sulfones **2c** in the next step and unambiguously identified as (2*E*)- and (2*Z*)-isomers, respectively, by NOE experiments.

*Data of (2*Z*)-***7c***: ^{1}H-NMR: 1.81 (*s*, 3 H); 1.86 (*s*, 3 H); 3.72 (*d*, *J* = 7.5, 2 H); 5.43 (*t*, *J* = 7.5, 1 H); 5.91 (*d*, *J* = 9.3, 1 H); 6.46 (*dd*, *J* = 11.1, 9.3, 1 H). ^{13}C-NMR: 18.5; 20.4; 26.2; 31.3; 123.0; 125.8; 125.9; 127.1; 129.3; 136.3; 136.7; 137.9.

*Data of (2-*E*)-***7c***: IR (neat): 1480, 1439. ^{1}H-NMR: 1.71 (*s*, 3 H); 1.78 (*s*, 3 H); 1.80 (*s*, 3 H); 3.67 (*d*, *J* = 8.1, 2 H); 5.56 (*t*, *J* = 7.9, 1 H); 5.86 (*d*, *J* = 10.7, 1 H); 6.12 (*d*, *J* = 15.4, 1 H); 6.37 (*dd*, *J* = 15.4, 10.7, 1 H); 7.15–7.40 (m, 5 H). ^{13}C-NMR: 12.3; 18.5; 26.2; 32.8; 124.7; 125.3; 125.5; 126.3; 128.8; 130.3; 133.9; 135.8; 136.2; 137.5. CI-HR-MS (pos.): 245.1370 ($C_{16}H_{21}S^+$; calc. 245.1364).

3-Methyl-1-(phenylsulfonyl)-5-(2,6,6-trimethylcyclohex-1-enyl)penta-2,4-diene (**2a**) [6b]. To a stirred soln. of **7a** (1.30 g, 4.15 mmol) in MeOH (10 ml) and benzene (5 ml) were added $LiNbMoO_6$ (26.3 mg, 0.09 mmol) and 30% aq. H_2O_2 soln. (2.78 g, 8.58 mmol) consecutively at 0°. After the mixture was slowly warmed and stirred at r.t. for 6 h, it was concentrated under reduced pressure. The crude mixture was dissolved in $CHCl_3$, washed with H_2O, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by SiO_2 flash column chromatography to give (2*Z*)-**2a** (0.33 g, 0.96 mmol) and (all-*E*)-**2a** (0.99 g, 2.88 mmol) in 23 and 70% yields, resp.

3,7,11-Trimethyl-1-(phenylsulfonyl)dodeca-2,4,6,10-tetraene (**2b**) [12]. According to the general procedure for **2a**, a soln. of **7b** (16.1 g, 51.5 mmol) in benzene (30 ml) and MeOH (70 ml) was reacted with $LiNbMoO_6$ (301 mg, 1.03 mmol) and 35% aq. H_2O_2 soln. (12.5 g, 0.129 mol) at r.t. for 6 h to give (2*Z*)-**2b** (3.91 g, 11.4 mmol) and (all-*E*)-**2b** (9.79 g, 28.4 mmol) in 22 and 55% yields, resp.

3,7-Dimethyl-1-(phenylsulfonyl)octa-2,4,6-triene (**2c**) [16]. According to the general procedure for **2a**, a soln. of **7c** (0.42 g, 1.73 mmol) in MeOH (20 ml) was reacted with $LiNbMoO_6$ (25 mg, 0.09 mmol) and 30% aq. H_2O_2 soln. (0.65 g, 5.71 mmol) at r.t. for 6 h to give (2*Z*)-**2c** (87 mg, 0.31 mmol) and (all-*E*)-**2c** (262 mg, 0.95 mmol) in 18 and 55% yields, resp.

Bis[3,7,11,15-tetramethyl-5-(phenylsulfonyl)hexadeca-2,6,8,10,14-pentaenyl] Sulfide (**8**). To a stirred soln. of **2b** (7.29 g, 21.2 mmol) in THF (50 ml) at 0° was added 60% NaH (1.02 g, 25.4 mmol). The mixture was stirred for 30 min, and then bis(chloroallylic) sulfide **3** (2.53 g, 10.6 mmol) and NaI (3.81 g, 25.4 mmol) were added consecutively. The mixture was stirred at r.t. for 15 h, diluted with Et_2O, washed with 1M HCl and H_2O, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by SiO_2 flash column chromatography to give **8** (8.15 g, 9.53 mmol) in 90% yield. IR (neat): 1447, 1304, 1146, 1084. ^{1}H-NMR: 1.29 (*s*, 6 H); 1.50 (*s*, 6 H); 1.61 (*s*, 6 H); 1.69 (*s*, 6 H); 1.76 (*s*, 6 H); 2.10 (br. *s*, 8 H); 2.34 (*dd*, *J* = 13.0, 11.7, 2 H); 2.91 (*d*, *J* = 7.5, 4 H); 2.75–3.18 (*m*, 2 H); 4.00 (*dd*, *J* = 10.3, 9.2, 2 H); 5.09 (br. *s*, 4 H); 5.19 (*t*, *J* = 7.5, 2 H); 5.85 (*d*, *J* = 10.6, 2 H); 6.06 (*d*, *J* = 15.2, 2 H); 6.30 (*dd*, *J* = 15.2, 10.6, 2 H); 7.43–7.55 (*m*, 4 H); 7.55–7.66 (*m*, 2 H); 7.73–7.86 (*m*, 4 H). ^{13}C-NMR: 12.5; 15.9; 16.9; 17.7; 25.7; 26.5; 28.1; 37.5; 40.1; 63.8; 110.0; 121.8; 123.8; 124.7; 124.8; 126.2; 128.8; 129.1; 131.7; 133.2; 133.5; 137.7; 140.9; 142.2. FAB-HR-MS (pos.): 713.4446 ($C_{46}H_{65}O_2S_2^+$, $[C_{52}H_{71}O_4S_3 - C_6H_6O_2S]^+$; calc. 713.4426).

Bis[3,7,11,15-tetramethyl-5-(phenylsulfonyl)hexadeca-2,6,8,10,14-pentaenyl) Sulfone (**9**). *Method A* (Oxidation of **8**). The mixture of urea–H_2O_2 (UHP; 3.42 g, 36.4 mmol) and phthalic anhydride (2.70 g, 18.2 mmol) in MeCN (50 ml) were stirred vigorously at r.t. to give a clear soln. This soln. was slowly added with a dropper to a soln. of **8** (6.23 g, 7.28 mmol) in MeCN (50 ml) at 0° for 3 h. The mixture was stirred for another 2 h and, the reaction was quenched with 1M HCl soln. This mixture was extracted with AcOEt, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a white solid, which was then dissolved in $CHCl_3$. The insoluble solid material was removed by filtration, and the filtrate was concentrated under reduced pressure. The crude product was purified by SiO_2 flash column chromatography to give **9** (2.58 g, 2.91 mmol) in 40% yield.

Method B (Coupling of **2b** and **11**). To a stirred soln. of **2b** (4.29 g, 12.45 mmol) in DMF (25 ml) at −20° under Ar was added ^{t}BuOK (1.62 g, 13.7 mmol) in several portions. The mixture was stirred for 30 min at that temp., and a soln. of bis(allylic) sulfone **11** (1.69 g, 6.22 mmol) in DMF (10 ml) was added slowly for 2 h. Stirring the mixture for 1 h at −20°, 1M HCl (100 ml) and AcOEt (70 ml) were added. The org. layer was separated, washed with sat. $NaHCO_3$ soln. and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by SiO_2 flash column chromatography to give **9** (4.77 g, 5.38 mmol) in 86% yield. IR (neat): 1447, 1305, 1146, 1084. ^{1}H-NMR: 1.29 (*s*, 6 H); 1.61 (*s*, 6 H); 1.62 (*s*, 6 H); 1.69 (*s*, 6 H); 1.75 (*s*, 6 H); 2.09 (br. *s*, 8 H); 2.43 (*dd*, *J* = 13.5, 11.2, 2 H); 3.02 (br. *d*, *J* = 13.5, 2 H); 3.48 (*d*, *J* = 7.4, 4 H); 4.04 (*ddd*, *J* = 11.2, 9.7, 3.1, 2 H); 5.08 (*d*, *J* = 9.7, 2 H); 5.10 (br. *s*, 2 H); 5.23 (*t*, *J* = 7.4, 2 H); 5.85 (*d*, *J* = 10.9, 2 H); 6.05 (*d*, *J* = 15.2, 2 H); 6.33 (*dd*, *J* = 15.2, 10.9, 2 H); 7.45–7.57 (*m*, 4 H); 7.57–7.68 (*m*, 2 H); 7.74–7.85 (*m*, 4 H). ^{13}C-NMR: 12.5; 16.9; 17.0; 17.7; 25.7; 26.6; 37.7; 40.1; 51.3; 63.5; 114.1; 121.2; 123.7; 124.7; 126.8; 128.9; 129.2; 131.9; 132.8; 133.7; 137.3; 140.9; 141.5; 142.7. FAB$^+$-HR-MS: 603.4240 ($C_{40}H_{59}O_2S^+$, $[C_{52}H_{71}O_6S_3 - 2\ C_6H_6O_2S]^+$; calc. 603.4236).

Bis(4-chloro-3-methylbut-2-enyl) Sulfone (**11**). According to the general procedure for **2a**, a soln. of **3** (1.00 g, 4.18 mmol) in MeOH (20 ml) was reacted with $LiNbMoO_6$ (60 mg, 0.21 mmol) and 35% aq. H_2O_2 soln. (1.62 g, 16.72 mmol) at r.t. for 3 h to give **11** (0.80 g, 2.95 mmol) in 71% yield. IR (neat): 1444, 1307, 1117. ^{1}H-NMR: 1.86 (*s*, 6 H); 3.74 (*d*, *J* = 7.7, 4 H); 4.07 (*s*, 4 H); 5.69 (*t*, *J* = 7.7, 2 H). ^{13}C-NMR: 15.0; 50.1; 51.9; 115.2; 141.5. Anal. calc. for $C_{10}H_{16}Cl_2O_2S$: C 44.29, H 5.95, S 11.82; found: C 44.25, H 5.99, S 11.76.

11,11′,12,12′-Tetrahydro-11,11′-bis(phenylsulfonyl)lycopene (**10**). To a soln. of **9** (627 mg, 0.71 mmol) in ^{t}BuOH (15 ml) and CCl_4 (15 ml) was added pulverized KOH (793 mg, 14.1 mmol) at r.t. under Ar. This mixture was stirred vigorously for 7 h at that temp., diluted with CH_2Cl_2, washed with 1M HCl soln. and H_2O, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by SiO_2 flash column chromatography to give **10** (367 mg, 0.48 mmol) in 63% yield, which contained a small amount (*ca.* 10%) of a stereoisomer, presumably the (15*Z*)-isomer. This compound is very unstable in air, and the actual yield should be higher than that sited above. IR (neat): 1448, 1305, 1147, 1085. ^{1}H-NMR: 1.28 (*s*, 6 H); 1.60 (*s*, 6 H); 1.65 (*s*, 6 H); 1.68 (*s*, 6 H); 1.74 (*s*, 6 H); 2.08 (br. *s*, 8 H); 2.41 (*dd*, *J* = 13.2, 11.8, 2 H); 3.03 (*d*, *J* = 13.2, 2 H); 4.04 (*ddd*, *J* = 11.8, 9.0, 2.1, 2 H); 5.10 (br. *s*, 4 H); 5.87 (br. *s*, 4 H); 6.07 (*d*, *J* = 15.0, 2 H); 6.20 (*m*, 2 H); 6.31 (*dd*, *J* = 15.0, 10.1, 2 H); 7.40–7.70 (*m*, 6 H); 7.73–7.88 (*m*, 4 H). ^{13}C-NMR: 12.4; 16.8; 17.1; 17.6; 25.6; 26.5; 38.1; 40.0; 63.9; 121.7; 123.7; 124.8; 126.1; 127.8; 128.4; 128.8; 129.1; 131.7; 133.0; 133.3; 133.5; 137.6; 140.9; 142.1.

Lycopene (**1b**) [8b][9c]. According to the general procedure for **7a**, EtONa, prepared by reacting Na (414 mg, 18.0 mol) with anh. EtOH (20 ml), was reacted with **10** (367 mg, 0.45 mmol) in benzene (10 ml) at 90° for 12 h to give **1b** (188 mg, 0.35 mmol) in 78% yield. The possible (*Z*)-stereoisomers at C(13), C(13′), C(15), and C(15′) were presumably isomerized to (all-*E*)-lycopene during this thermolysis reaction. The ^{1}H-NMR spectrum of the synthetic sample was identical with that of an authentic sample. ^{1}H-NMR: 1.61 (*s*, 6 H); 1.68 (*s*, 6 H); 1.82 (*s*, 6 H); 1.96 (*s*, 12 H); 2.11 (br. *s*, 8 H); 5.11 (br. *s*, 2 H); 5.95 (*d*, *J* = 10.8, 2 H); 6.18 (*d*, *J* = 12.1, 2 H); 6.24 (*d*, *J* = 14.9, 2 H); 6.20–6.30 (*m*, 2 H); 6.35 (*d*, *J* = 14.8, 2 H); 6.49 (*dd*, *J* = 14.9, 10.8, 2 H); 6.63 (*dd*, *J* = 14.8, 12.1, 2 H); 6.55–6.70 (*m*, 2 H).

HPLC Analysis of the synthetic lycopene (**1b**) was performed on *YMC Carotenoid S-5* column (4.6 × 250 mm) with BuOH/MeCN/CH_2Cl_2 3 : 7 : 1 as mobile phase (*Fig.*).

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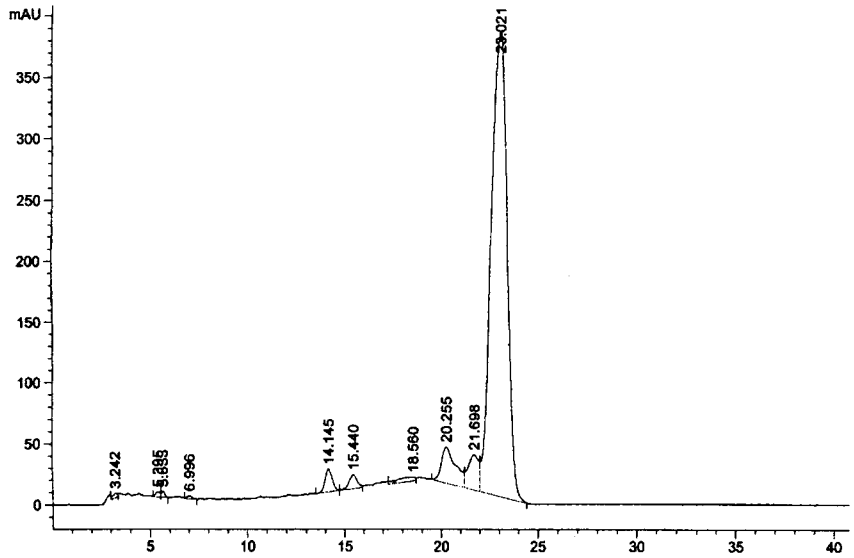

Figure. *HPLC of the synthetic lycopene* (**1b**) *showing mostly (all-*E*)-lycopene* (23.021 min). *YMC Carotenoid S-5* column (4.6 × 250 mm) with BuOH/MeCN/CH_2Cl_2 3 : 7 : 1.

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