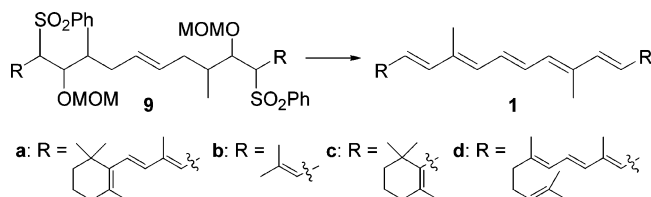## Sulfone Coupling and Double-Elimination Strategy for Carotenoid Synthesis

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A highly efficient synthetic method of carotenoid compounds has been developed on the basis of the sulfone coupling and double-elimination strategy. This method highlighted the sulfone-mediated coupling with the novel C_{10} dialdehyde, 2,7-dimethyl-4-octenedial, which was easily prepared and efficiently utilized in the synthesis of the conjugated polyene chains.

The sulfone-stabilized carbanion is an efficient nucleophile to couple with alkyl or allyl halides in carbon–carbon bond-forming reactions.[1] A single or a double bond can be obtained according to the sulfone elimination of either a radical[2] or a basic[3] condition. When aldehydes are used as an electrophile in the sulfone-mediated coupling reaction, the corresponding sulfone elimination reactions generate either a C=C bond[4] or a C≡C bond.[5] The above C=C bond formation reactions, known as the Julia sulfone olefination protocol, have been successfully utilized in the synthesis of carotenoid compounds, which have a general structure of the conjugated polyene chain.[6] The above C≡C bond formation reactions are, however, limited to the case of α,β-unsaturated aldehydes, and the conjugated dienes are generally obtained for saturated aldehydes by the double elimination of the sulfone and the protected hydroxyl groups under the basic condition.[7] This double-elimination reaction is ideally suited for the preparation of conjugated polyene chains, and retinol has

SCHEME 1. Disconnection Approach to β-Carotene (1a) Utilizing the Double-Elimination Strategy
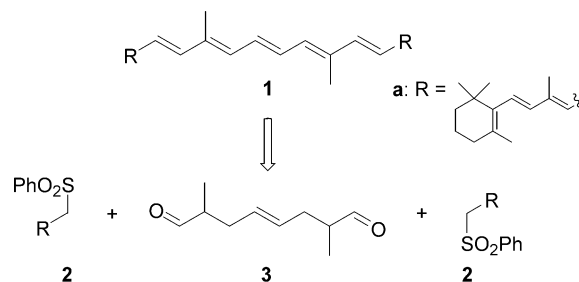
been prepared by this method.[8] It was envisioned that an efficient synthesis of β-carotene (**1a**) would be realized by the sulfone-mediated coupling and double-elimination strategy utilizing the novel C_{10} dialdehyde, 2,7-dimethyl-4-octenedial (**3**) (Scheme 1). This sulfone chemistry is believed to be more effective than the Wittig reaction[9] for the preparation of the conjugated polyene chains of carotenoids, especially in the production of the (*E*)-configuration of C=C bonds and the treatment of byproducts.[6d] We thus devised a practical synthetic method of the C_{10} dialdehyde **3** and then carried out the β-carotene synthesis by the coupling with the C_{15} allylic sulfone **2a**[10] and the double-elimination reaction in a highly efficient manner. The preparation of **3**, details of the double-elimination reaction exemplified for β-carotene synthesis, and the application of this strategy to other carotenoid syntheses are reported herein.

The synthesis of the symmetrical C_{10} dialdehyde **3** starting from the readily available (*E*)-1,4-dibromo-2-butene (**4**) was delineated in Scheme 2. Diethyl methylmalonate (2 equiv) was used in the reaction with **4** (1 equiv) to secure the efficient coupling to give rise to the tetraester **5** (88% yield). The standard decarboalkoxylation sequence[11] of basic hydrolysis, acidification, and thermolysis, followed by esterification in MeOH for **5**, produced the methyl diester **6** in 89% yield. Direct reduction[12] of the diester **6** to the dialdehyde **3** was not a trivial transformation. Instead, LAH reduction all the

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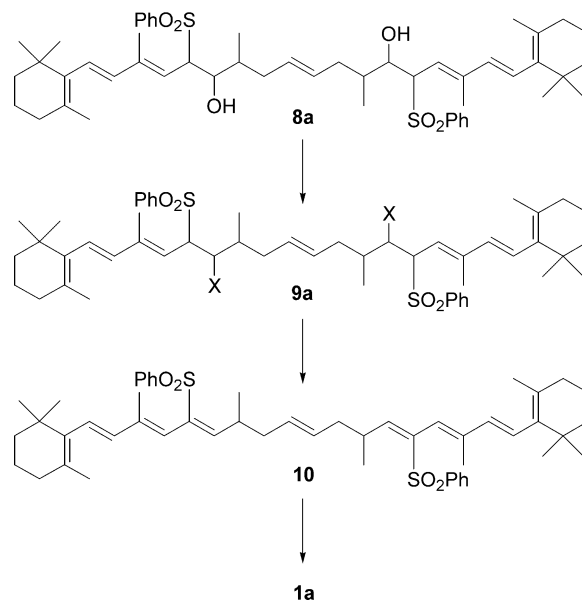
SCHEME 2. Preparation of the Novel C_{10} Dialdehyde 3[a]
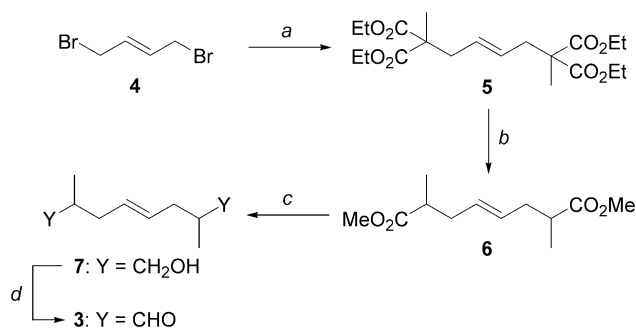
way to the diol **7**, followed by the Swern oxidation[13] to the dial **3** (87% yield) was the method of choice. The diester **6**, the diol **7**, and the dial **3** contained a 1:1 mixture of diastereomers[14] generated from the two stereocenters.

The coupling reaction of the C_{15} allylic sulfone **2a** and the C_{10} dial **3** in a 2:1 molar ratio produced the C_{40}-coupled product **8a** (Scheme 3). This coupling reaction can be carried out efficiently (96% yield) under the kinetic condition using *n*-BuLi as a base in THF at −78 °C. The reverse aldol-type reaction of the diol **8a** prevailed at temperatures higher than −20 °C to give the starting C_{15} sulfone **2a** again. Many diastereomers were generated in this coupling reaction from the six chiral centers of **8a**; however, these stereoisomers did not perturb the stereoselective formation of all-(*E*)-β-carotene (**1a**) in the double-elimination step.[8] Protections of the two hydroxy groups were required to prevent the reverse reaction of **8a** under a basic condition. The base-promoted double elimination of **9a** proceeded presumably through the initial formation of the vinyl sulfone **10**, which was isolated under the mild elimination condition at room temperature for 3 h. The double bond migrations to the allylic sites and the dehydrosulfonylation reactions completed the double elimination process to produce the fully conjugated polyene chain of β-carotene (**1a**).[6e]

Various protections of the diol **8a** and the subsequent double-elimination reactions of the protected **9a** to give rise to β-carotene (**1a**) are summarized in Table 1. The bromide **9a-1** and the chloride **9a-2**, which were prepared by the reaction with PBr_3 and $SOCl_2$, respectively, in the presence of pyridine, could not be purified because no

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(14) The 1:1 ratios of diastereomers were estimated on the basis of their ^{13}C NMR spectra, which were included in the Supporting Information.

SCHEME 3. Preparation of β-Carotene (1a) by the Double-Elimination Reaction[a]

TABLE 1. Preparation of 9a and the Double-Elimination Reaction To Give β-Carotene (1a)

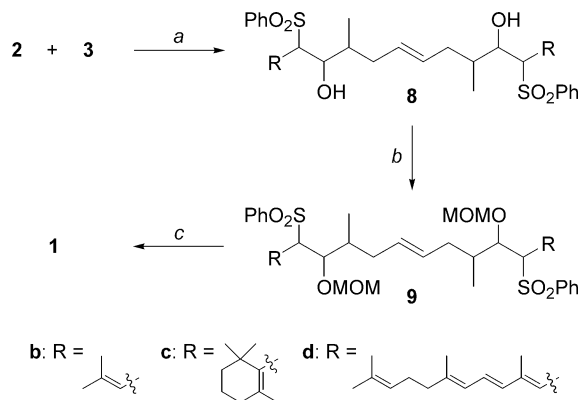| entry	9a	X[a]	yield of 9a (%)	elim cond[b]	yield of 1a[c,d] (%)	purified 1a[e] (%)
1	**9a-1**	Br	100[d]	**A**	80	38[f]
2				**B**	84	60[g]
3	**9a-2**	Cl	88[d]	**A**	h	0
4	**9a-3**	THPO	96[f]	**A**	100	29[f]
5				**C**	h	11[f]
6	**9a-4**	EOEO	91[f]	**A**	98	70[g]
7	**9a-5**	MOMO	93[f]	**A**	100	84[g]

[a] Preparation conditions for X = Br: PBr_3 (1 equiv) and pyridine (5 equiv) in CH_2Cl_2; X = Cl: $SOCl_2$ (2.2 equiv) and pyridine (4 equiv) in CH_2Cl_2; X = THPO: 3,4-dihydro-2*H*-pyrane (6 equiv) and CSA (0.3 equiv) in CH_2Cl_2; X = EOEO: ethyl vinyl ether (6 equiv) and PPTS (0.3 equiv) in CH_2Cl_2; X = MOMO: $CH_2(OCH_3)_2$ (20 equiv) and P_2O_5 (0.6 equiv × 2). [b] Elimination conditions for **A**: KOMe (20 equiv) in cyclohexane at 80 °C for 16 h; **B**: *t*-BuOK (20 equiv) in cyclohexane at 80 °C for 16 h; **C**: NaOEt (20 equiv) in EtOH at 80 °C for 16 h. [c] A 4:1 mixture of all-(*E*)- and 13-(*Z*)-β-carotene was obtained. [d] Crude yield. [e] Yield of pure all-(*E*)-β-carotene (**1a**). [f] Yield after SiO_2 column chromatography. [g] Yield after recrystallization from THF/MeOH. [h] A complicated mixture was obtained.

clear spot was seen in TLC, and the peaks of the ^1H NMR spectra were very broad. The alkyl ethers of tetrahydropyranyl (THP) **9a-3**, 1-ethoxyethyl (EOE) **9a-4**, and methoxymethyl (MOM) **9a-5** were prepared in high yields (91−96%) under acidic conditions.[8b] Three different elimination conditions **A** (KOMe in cyclohexane), **B** (*t*-BuOK in cyclohexane), and **C** (NaOEt in EtOH) at 80 °C were tested for **9a**. There was no significant difference according to the base used (conditions **A** and **B**), and the similar crude yields of **1a** were obtained (entries 1 and 2). The protic solvent (condition **C**) was not favorable, retarding this double-elimination reaction to give a complicate mixture, contrary to the case of the general dehydrosulfonylation reaction (entry 5).[15] The alkyl ethers seemed to be better protecting groups than bromide in providing

SCHEME 4. Application to the Synthesis of Other Carotenoids[a]

[a] Reagents: (a) **2** (1.1 equiv) and *n*-BuLi (1.2 equiv) in THF at −78 °C, then **3** (0.5 equiv), 91% for **8b**, 79% for **8c**, 88% for **8d**; (b) P$_2$O$_5$ (0.6 equiv × 2), CH$_2$(OCH$_3$)$_2$ (20 equiv), and **8** (1 equiv) at rt, 92% for **9b**, 90% for **9c**, 67% for **9d**; (c) KOMe (20 equiv) and **9** (1 equiv) in cyclohexane at 80 °C for 16 h, 49% (recrystallization) for **1b**, 77% (SiO$_2$) for **1c**, 28% (recrystallization) for **1d**.

a little higher crude yields of **1a**, while no double elimination has been observed in the case of chloride under condition **A**. The crude double elimination product **1a** contained two major stereoisomers of all-(*E*) and 13-(*Z*) in a 4:1 ratio.[16] Purification by careful SiO$_2$ column chromatography provided all-(*E*)-**1a** only in 29−38% yield presumably due to the abstraction by silica gel. Recrystallization from MeOH and THF, on the other hand, gave all-(*E*)-**1a** in 60−84% yields as a dark-red crystal.

The above double-elimination strategy has been applied to the synthesis of other carotenoid compounds **1b−d** (Scheme 4). Allylic sulfones **2b**, **2c**,[17] and **2d**[18] coupled with the dialdehyde **3** to produce the diols **8b−d** in 79−91% yields. Protections of the diols to MOM ethers **9b** and **9c** proceeded in 92% and 90% yields, respectively. A much lower 67% yield was obtained for **9d**, presumably due to the instability of the conjugated triene moiety. The KOMe-mediated double-elimination reactions of **9b−d** in cyclohexane at 80 °C for 16 h (condition **A**) produced all-(*E*)-carotenoids **1b**[19] (49% yield), **1c**[20] (77% yield), and **1d**[6f] (28% yield) after purifications. The lower yields of the carotenoids **1b** and **1d** may be ascribed to the intrinsic instability of the acyclic conjugated polyene chains.

In conclusion, we have developed a highly efficient synthetic method of carotenoid compounds by the sulfone coupling and double elimination strategy. This method highlighted the sulfone-mediated coupling with the novel 2,7-dimethyl-4-octenedial (**3**), which was easily prepared and efficiently utilized in the synthesis of the conjugated polyene chains. Applications of this method to the

syntheses of organic conducting materials based on the conjugated polyene chain structure are currently underway.

Experimental Section

General Procedure of the Carotenoid Synthesis by the Doubl-Elimination Process Exemplified for β-Carotene (1a). (1) Coupling. 5,14-Bis(benzenesulfonyl)-3,7,12,16-tetramethyl-1,18-bis(2,6,6-trimethyl-1-cyclohexenyl)octadeca-1,3,9,15,17-pentaene-6,13-diol (8a). To a stirred solution of 1-benzenesulfonyl-3-methyl-5-(2,6,6-trimethyl-1-cyclohexenyl)-2,4-pentadiene (**2a**) (3.09 g, 8.97 mmol) in THF (40 mL) was added a 1.6 M solution of *n*-BuLi in hexane (6.6 mL, 10.61 mmol) at −78 °C. The mixture was stirred at that temperature for 20 min, and a solution of 2,7-dimethyl-4-octenedial (**3**) (686 mg, 4.08 mmol) in THF (10 mL) was added. The resulting mixture was stirred at −78 °C for 1 h and quenched with 1 M HCl solution (20 mL). The mixture was diluted with ether, washed with 1 M HCl solution, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by SiO$_2$ flash column chromatography (hexanes/EtOAc = 4:1−3:2) to give the diol **8a** (3.35 g, 3.91 mmol) in 96% yield as a white solid, which contained many stereoisomers due to the presence of six chiral centers. The major stereoisomer, which was presumed to be the all-(*E*)-isomer, was carefully purified again by preparative TLC for spectroscopic analysis.

Data for **8a**: R_f = 0.15−0.23 (hexanes/EtOAc = 4:1); ^{1}H NMR (major) δ 0.75 (d, *J* = 6.8 Hz, 6H), 0.96 (s, 6H), 0.99 (s, 6H), 1.22 (s, 6H), 1.40−1.50 (m, 4H), 1.50−1.70 (m, 6H), 1.67 (s, 6H), 1.90−2.25 (m, 8H), 2.65 (br s, 2H), 4.04 (dd, *J* = 11.0, 9.3 Hz, 2H), 4.37 (dd, *J* = 9.2, 1.8 Hz, 2H), 4.98 (d, *J* = 11.0 Hz, 2H), 5.32−5.50 (m, 2H), 5.96 (s, 4H), 7.44−7.55 (m, 4H), 7.58−7.68 (m, 2H), 7.75−7.85 (m, 4H); ^{13}C NMR (major) δ 11.5, 12.2, 19.2, 21.6, 28.8, 28.9, 32.9, 34.1, 36.3, 37.3, 39.4, 70.0, 71.0, 117.7, 128.7, 128.8, 129.4, 129.8, 130.5, 133.8, 135.7, 137.1, 137.3, 141.9; IR (KBr) 3524, 2928, 1446, 1298, 1143 cm^{-1}; HRMS (FAB$^+$) calcd for C$_{40}$H$_{61}$O$_2$ (C$_{52}$H$_{73}$O$_6$S$_2$ − 2C$_6$H$_6$O$_2$S) 573.4672, found 573.4681.

(2) MOM Protection. 5,14-Bis(benzenesulfonyl)-3,7,12,16-tetramethyl-1,18-bis(2,6,6-trimethyl-1-cyclohexenyl)octadeca-1,3,9,15,17-pentaene-6,13-diol, Bis(methoxymethyl) Ether (9a-5). To a stirred solution of the diol **8a** (1.183 g, 1.38 mmol) in dimethoxymethane (2.45 mL, 27.6 mmol) was added P$_2$O$_5$ (0.12 g, 0.83 mmol) at room temperature. After the mixture was stirred for 5 h, an additional portion of P$_2$O$_5$ (0.12 g, 0.83 mmol) was added again to the mixture. After being stirred for 20 h at room temperature, the mixture was extracted with toluene, and 10% NaHCO$_3$ solution was added. The organic layer was washed again with 10% NaHCO$_3$ solution, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product (1.42 g) was purified by SiO$_2$ flash column chromatography (hexanes/EtOAc = 8:1−2:1) to give the MOM diether **9a-5** (1.212 g, 1.282 mmol) in 93% yield as a white solid, which contained many stereoisomers due to the presence of six chiral centers. The major stereoisomer, which was presumed to be all-(*E*)-isomer, was carefully purified again by preparative TLC for spectroscopic analysis.

Data for **9a-5**: R_f = 0.17−0.25 (hexanes/EtOAc = 4:1); ^{1}H NMR (major) δ 0.93 (s, 6H), 0.95 (s, 6H), 0.98 (d, *J* = 5.9 Hz, 6H), 1.16 (s, 6H), 1.35−1.50 (m, 4H), 1.50−1.70 (m, 6H), 1.62 (s, 6H), 1.70−1.87 (m, 2H), 1.92−2.13 (m, 6H), 3.41 (s, 6H), 4.16 (d, *J* = 7.7 Hz, 2H), 4.29 (dd, *J* = 11.4, 7.7 Hz, 2H), 4.77 (d, *J* = 7.2 Hz, 2H), 4.94 (d, *J* = 7.2 Hz, 2H), 5.16 (d, *J* = 11.4 Hz, 2H), 5.20 (br s, 2H), 5.88 (s, 4H), 7.38−7.48 (m, 4H), 7.50−7.60 (m, 2H), 7.72−7.84 (m, 4H); ^{13}C NMR (major) δ 12.3, 16.7, 19.1, 21.6, 28.0, 28.0, 32.8, 34.0, 34.2, 37.0, 39.3, 56.2, 68.7, 82.4, 99.0, 119.5, 128.5, 128.6, 129.0, 129.6, 130.2, 133.1, 135.8, 137.2, 139.2, 141.6; IR (KBr) 2928, 1454, 1306, 1146, 1033 cm^{-1}; HRMS (FAB$^+$) calcd for C$_{42}$H$_{65}$O$_3$ (C$_{56}$H$_{81}$O$_8$S$_2$ − 2C$_6$H$_6$O$_2$S − C$_2$H$_4$O) 617.4928, found 617.4951.

(3) Double-Elimination Reaction. β-Carotene (1a). Condition D. To a stirred solution of the MOM diether **9a-5** (0.945 g, 1.0 mmol) in cyclohexane (25 mL) was added KOMe (1.403 g,

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20.0 mmol). The mixture was heated to 80 °C for 16 h and cooled to room temperature. The mixture was then diluted with hexanes, washed three times with H_2O, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product (0.548 g), which consisted of a 4:1 mixture of all-(E) and 13-(Z) stereoisomers, was purified by recrystallization (THF/MeOH = 1:5) to give all-(E)-**1a** (0.453 g, 0.84 mmol) in 84% yield as a red solid.

The ^{1}H NMR data of **1a** were identical with those of the authentic sample.

Supporting Information Available: Experimental procedures and analytical data for **5**−**7**, **3**, **9a-1**, **9a-3**, **9a-4**, **10**, **1a**−**d**; ^{1}H NMR spectra of **1a**−**d**, **3**, **5**−**7**, **8a**, **9a-1**, **9a-3**, **9a-5**, and **10**; and ^{13}C NMR spectra of **6**, **7**, and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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