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Efficient Syntheses of the Keto-carotenoids Canthaxanthin, Astaxanthin, and Astacene

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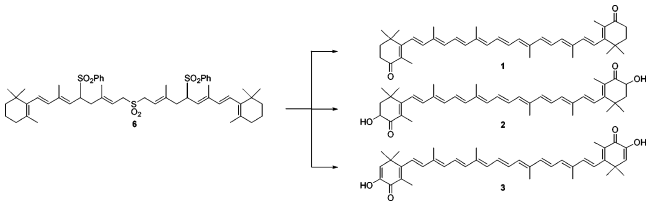
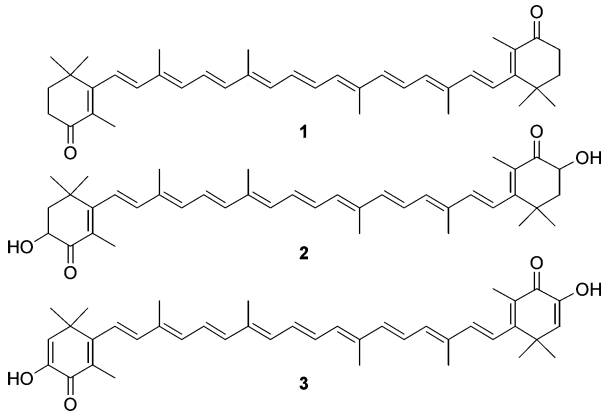


Three keto-carotenoids were prepared by the oxidation of the stable C_{40} trisulfone **6**, which has been used as the key compound in our β-carotene synthesis. The first allylic oxidation to the unsaturated ketone and the second oxidation to the α-hydroxyketone produced the C_{40} trisulfones **7** and **10**, respectively. The Ramberg−Bäcklund reaction of the oxidized C_{40} trisulfone was efficiently effected by the use of a mild base, NaOMe, in the presence of CCl_4 as a halogenating agent to give the C_{40} disulfones **8** and **11**. Base-promoted dehydrosulfonation reaction of the disulfone compounds produced the fully conjugated polyenes of canthaxanthin (**1**), astaxanthin (**2**), and astacene (**3**).

The rich pink color of salmons, feathers of flamingos, and shells of crustaceans are due to the natural pigments, keto-carotenoids. These are carotenoids oxidized in the cyclohexene ring moiety and include canthaxanthin (**1**), astaxanthin (**2**), and astacene (**3**) (Scheme 1). These carotenoids not only provide wonderful natural colors but also play important biological functions as antioxidants to relieve oxidative stresses.[1] These oxidative stresses, caused by reactive oxygen species such as superoxide, hydroxy and peroxy radicals, ozone, hydrogen peroxide, and singlet oxygen, induce protein oxidation, DNA and RNA damage, and lipid peroxidation.[2] Carotenoids are known to effectively scavenge these reactive oxygen species by chemical reactions with the conjugated polyene moiety in the structures,[3] thereby neutralizing the oxidative stresses.[4] Since carotenoids are not endogenously produced in higher animals, but ingested from dietary

SCHEME 1. Canthaxanthin (1), Astaxanthin (2), and Astacene (3)



sources,[5] and there have been no adverse reports on the toxicity, chemical syntheses of these valuable keto-carotenoids in large quantities for nutraceutical and pharmaceutical applications have been performed.[6−8]

Direct oxidation methods of β-carotene to canthaxanthin (**1**)[9] and of canthaxanthin (**1**) to astaxanthin (**2**)[10] have been reported. However, so far there are no practical syntheses based on direct oxidation methods especially due to the instability of carotenoids under the oxidation conditions. High adhesion of carotenoids also causes another problem of handling these unstable materials. We have recently established efficient synthetic methods for β-carotene[11] and lycopene[12] by the use of the Julia sulfone olefination method, in which the Ramberg−Bäcklund reaction played a key role to build up the central conjugated triene moiety. The major advantage of carotenoid synthesis utilizing sulfone chemistry is that

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(1) Krinsky, N. I. *Pure Appl. Chem.* **1994**, *66*, 1003−1010.

(2) Acworth, I. N.; McCabe, D. R.; Maher, T. J. In *Oxidants, Antioxidants and Free Radicals*; Baskin, S., Salem, H., Eds.; Taylor and Francis: Washington D.C., 1997; pp 23−77.

(3) (a) Zürcher, M.; Pfander, H. *Tetrahedron* **1999**, *55*, 2307−2310. (b) Zürcher, M.; Niggli, U. A.; Steck A.; Pfander, H. *Tetrahedron Lett.* **1997**, *38*, 7853−7856.

(4) (a) Tinkler, J. H.; Böhm, F.; Schalch, W.; Truscott, T. G. *J. Photochem. Photobiol. B: Biol.* **1994**, *26*, 283−285. (b) Palozza, P.; Krinsky, N. I. *Arch. Biochem. Biophys.* **1992**, *297*, 291−295. (c) Miki, W. *Pure Appl. Chem.* **1991**, *63*, 141−146.

(5) Deming, D. M.; Erdman, J. W., Jr. *Pure Appl. Chem.* **1999**, *71*, 2213−2223.

(6) General reviews (a) Ernst, H. *Pure Appl. Chem.* **2002**, *74*, 2213−2226. (b) Mayer, H. *Pure Appl. Chem.* **1994**, *66*, 931−938. (c) Rüttimann, A. *Pure Appl. Chem.* **1999**, *71*, 2285−2293.

(7) Canthaxanthin synthesis: (a) Rosenberger, M.; McDougal, P.; Bahr, J. *J. Org. Chem.* **1982**, *47*, 2130−2134. (b) Rosenberger, M.; McDougal, P.; Saucy, G.; Bahr, J. *Pure Appl. Chem.* **1979**, *51*, 871−886. (c) Surmatis, J. D. US Pat. 3,311,656, 1967; *Chem. Abstr.* **1967**, *67*, 22052.

(8) Astaxanthin synthesis: (a) Yamano, Y.; Sato, Y.; Watanabe, Y.; Namikawa, K.; Miki, W.; Ito, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1862−1869. (b) Widmer, E.; Zell, R.; Lukáč, T.; Casadei, M.; Schönholzer, P.; Broger, E. A. *Helv. Chim. Acta* **1981**, *64*, 2405−2418. (c) Becher, E.; Albrecht, R.; Bernhard, K.; Leuenberger, H. G. W.; Mayer, H.; Müller, R. K.; Schüep, W.; Wagner, H. P. *Helv. Chim. Acta* **1981**, *64*, 2419−2435. (d) Surmatis, J. D.; Thommen, R. *J. Org. Chem.* **1967**, *32*, 180−184.

(9) (a) Schloemer, G. C.; Schloemer, D. A.; Davis, J. L. US Pat. 6,372,946, 2002; *Chem. Abstr.* **2002**, *136*, 310051. (b) Jaedicke, H.; Paust, J.; Schneider, J. US Pat. 4,212,827, 1980; *Chem. Abstr.* **1981**, *94*, 30962.

(10) (a) Moldt, P. Eur. Pat. Appl. 400,037, 1991; *Chem. Abstr.* **1992**, *116*, 6778. (b) Bernhard, K.; Müeller, R. K.; Spruijtenburg, R. Eur. Pat. Appl. 101,597, 1984; *Chem. Abstr.* **1984**, *101*, 38712.

(11) (a) Choi, H.; Ji, M.; Park, M.; Yun, I.-K.; Oh, S.-S.; Baik, W.; Koo, S. *J. Org. Chem.* **1999**, *64*, 8051−8053. (b) Jeong, Y. C.; Ji, M.; Lee, J. S.; Yang, J.-D.; Jin, J.; Baik, W.; Koo, S. *Tetrahedron* **2004**, *60*, 10181−10185.

(12) (a) Ji, M.; Choi, H.; Jeong, Y. C.; Jin, J.; Baik, W.; Lee, S.; Kim, J. S.; Park, M.; Koo, S. *Helv. Chim. Acta* **2003**, *86*, 2620−2628. (b) Ji, M.; Choi, H.; Park, M.; Kee, M.; Jeong, Y. C.; Koo, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 3627−3629.

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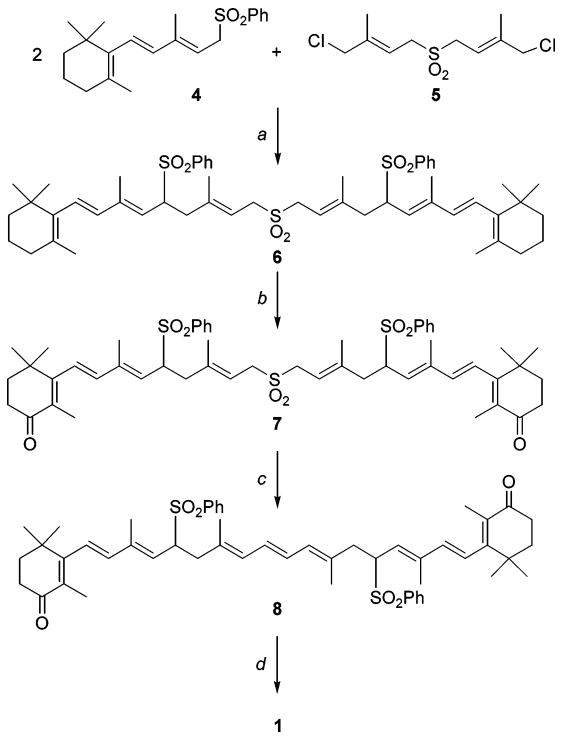
SCHEME 2. Synthetic Route to Canthaxanthin (1) via the Stable C_{40} Trisulfone Compound 6[a]



[a] Reagents: (a) **4**, *t*-BuOK in DMF at −20 °C then **5**, warm to rt, 85%; (b) $NaIO_4$ (3 equiv), I_2 (0.05) in $CHCl_3$ and H_2O, 82%; (c) NaOMe (8 equiv) and CCl_4 in CH_2Cl_2, 73%; (d) NaOEt (20 equiv) in EtOH and benzene at reflux, 86%.

the intermediate sulfone compounds are stable and easily purified by recrystallization. Furthermore, base-promoted dehydrosulfonation produces the conjugated double bonds with *E*-configuration.[12a] We thus attempted the synthesis of keto-carotenoids by oxidations of the stable C_{40} trisulfone which was the key compound in our β-carotene synthesis[11b] and accomplished efficient syntheses of canthaxanthin (**1**), astaxanthin (**2**), and astacene (**3**) by producing the conjugated polyene chains from the oxidized trisulfone compounds.

The synthesis of canthaxanthin (**1**), depicted in Scheme 2, started from the coupling reaction of the C_{15} allylic sulfone **4** and the C_{10} bischloroallylic sulfone **5** in a 2:1 molar ratio to produce the key C_{40} trisulfone **6**, which has been utilized in our β-carotene synthesis.[11b] This coupling reaction works well in DMF using *t*-BuOK as a base (85% yield). Upon addition of dilute HCl solution to the reaction mixture, the white solid product **6** was precipitated and was easily purified by recrystallization from MeOH. Base-promoted dehydrochlorination of the C_{10} bischloroallylic sulfone **5** was not observed under the above condition, which had forced us to devise the coupling reaction with a C_{10} bischloroallylic sulfide in our original β-carotene synthesis utilizing other coupling conditions (NaH in THF).[11b] It was expected and proved later that the stable C_{40} trisulfone **6** was the best substrate for the oxidation reactions. In fact, the C_{40} disulfone compound containing the central conjugated triene moiety, the Ramberg−Bäcklund reaction product of the C_{40} trisulfone **6**, was not stable under the general oxidation conditions. Allylic oxidation in the cyclohexene ring of the C_{40} trisulfone **6** produced the oxidized C_{40} trisulfone **7**. Due to the presence of many double bonds, the ordinary allylic oxidation conditions utilizing the Collins reagent,[13] CrO_3·DMP (3,5-dimethylpyrazole),[14] SeO_2,[15] and NBS/H_2O[16] did not produce the required oxidation product **7** in a reasonable yield. Iodine-catalyzed two-phase allylic oxidation reaction of **6** by $NaIO_4$,[17] on the other hand, proceeded in a highly efficient way to the desired oxidized trisulfone **7** in 82% yield.

TABLE 1. Ramberg−Bäcklund Reaction of the Keto-trisulfone 7 to the Keto-disulfone 8

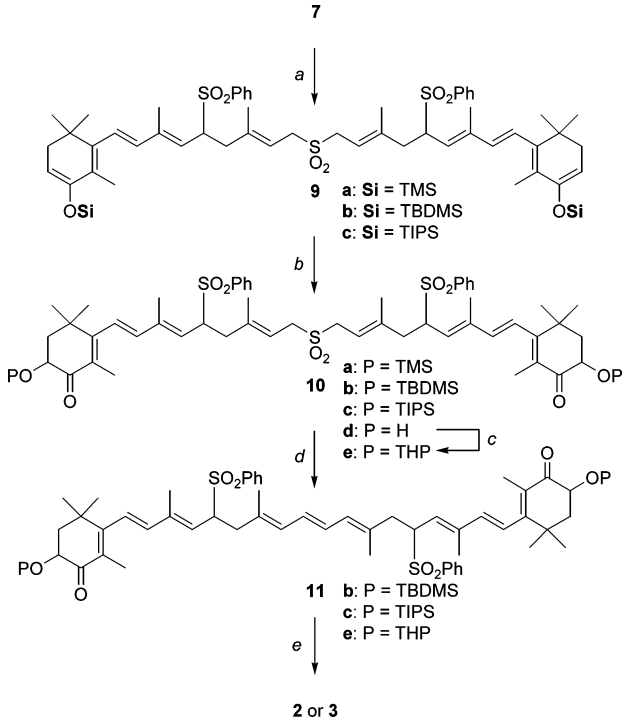
	reaction conditions[a]			
entry	base (equiv)	halogenating agent (equiv)[b]	time (h)	yield of **8** (%)
1	*t*-BuOK (8)	CCl_4	4	0
2	KOH (8) in *t*-BuOH	CCl_4	3.5	44
3	KOH (12) in *t*-BuOH	CCl_4	3.5	41
4	KOH (8) in *t*-BuOH	C_2Cl_6 (2)	6	42
5	KOH (12) in *t*-BuOH	C_2Cl_6 (2)	5.5	60
6	NaOMe (8)	CCl_4	4.5	73
7	NaOMe (12)	CCl_4	4	61
8	NaOMe (8)	C_2Cl_6 (2)	14	32
9	NaOMe (12)	C_2Cl_6 (2)	5	50

[a] CH_2Cl_2 was used as a solvent at room temperature. [b] A large excess of the reagent (~0.1 M) was used, unless otherwise stated.

The Ramberg−Bäcklund reaction of the oxidized trisulfone **7** under Meyer's condition[18] utilizing KOH/*t*-BuOH in CCl_4 produced the desired disulfone **8** only in about 40% yields. After a careful study on the conditions of the Ramberg−Bäcklund reaction of compound **7** (Table 1), the reaction was optimized to give **8** in 73% yield using a mild base, NaOMe in CCl_4 (entry 6). The yield was extremely low when a strong base, *t*-BuOK, was used in large excess (entry 1) and marginal under slowly generated *t*-BuOK (KOH/*t*-BuOH, entries 2 and 3), which indicated that the α-polychlorination of the ketone in the presence of excess strong base complicated the Ramberg−Bäcklund reaction. Unfavorable pK_a of NaOMe for the deprotonation at the α-carbon of the ketone, on the other hand, was in favor of the Ramberg−Bäcklund reaction of the compound **7** (entries 6 and 7). The effect of the halogenating agent was also elucidated by changing CCl_4 to C_2Cl_6. Formations of carbene from CCl_4 and the resulting adduct to the C=C of the Ramberg−Bäcklund reaction product had been reported.[18] However, no evidence of the carbene adduct was obtained in the Ramberg−Bäcklund reaction of the compound **7** using CCl_4. Hexachloroethane (C_2Cl_6) was a remarkable halogenating agent since no carbene can be formed and 2 equiv was enough to give a significant amount of the Ramberg−Bäcklund reaction product under Meyer's condition (entry 5). Hexachloroethane was, however, less effective for the reaction using NaOMe as a base (entries 8 and 9).

(13) Kerwin, S. M.; Paul, A. G.; Heathcock, C. H. *J. Org. Chem.* **1987**, *52*, 1686−1695.
(14) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057−2059.
(15) Bhalerao, U. T.; Rapoport, H. *J. Am. Chem. Soc.* **1971**, *93*, 4835−4840.
(16) Williams, D. R.; Benbow, J. W.; McNutt, J. G.; Allen, E. E. *J. Org. Chem.* **1995**, *60*, 833−843.
(17) Le Bris, L. DE Pat. 2,317,962, 1973; *Chem. Abstr.* **1974**, *80*, 15090.
(18) Meyers, C. Y.; Malte, A. M.; Matthews, W. S. *J. Am. Chem. Soc.* **1969**, *91*, 7510−7512.

SCHEME 3. Synthetic Route to Astaxanthin (2) and Astacene (3) from the Stable C_{40} Keto-trisulfone Compound 7[a]



[a] Reagents: (a) Si-OTf (2 equiv), Et_3N (5 equiv) in CH_2Cl_2, crude quantitative yields; (b) (i) urea−H_2O_2 (10 equiv), phthalic anhydride (5 equiv) in MeCN for 2 h and then Na_2CO_3 (10 equiv), **9** in CH_2Cl_2, 73% for **10b**, 72% for **10c**, (ii) HF, 85% for **10d** from **9a**; (c) DHP (4 equiv), CSA (0.4 equiv) in CH_2Cl_2, 87%; (d) NaOMe (10 equiv), CCl_4 in CH_2Cl_2, 32% for **11b** from **10b**, 77% for **11c** from **10c**, 93% crude for **11e** from **10e**; (e) (i) NaOEt (20 equiv) in EtOH and benzene at reflux, 71% for **3** from **11c**, (ii) *p*-TsOH (1 equiv), MeOH in CH_2Cl_2, 60% for **2** from **11e**.

NaOEt-promoted dehydrosulfonation reaction of the rearrangement product **8** in EtOH then produced canthaxanthin (**1**) in 86% yield, which was calculated by the ^{1}H NMR titration of an aliquot of the crude product with a known amount of phenethyl alcohol as a reference. Purification of the crude product by silica gel column chromatography provided only 40% isolated yield of **1** presumably due to the extensive abstraction by silica gel.

The syntheses of astaxanthin (**2**) and astacene (**3**), summarized in Scheme 3, started from the above oxidized C_{40} trisulfone **7** and required a second oxidation (α-hydroxylation to the ketone) in the cyclohexene ring moiety. Enolates of carbonyl compounds react with oxo-electrophiles such as MoO_5·Py·HMPA (MoOPH)[19] and oxaziridines[20] to give the α-hydroxycarbonyl compounds. Hypervalent iodine reagents[21] have also been used in the α-hydroxylation of ketones. It is crucial, however, to carefully control the position of the hydroxylation in the C_{40} trisulfone compound **7**, in which there are several allylic carbons containing acidic protons besides the α-carbons to the ketones. Trimethylsilyl trifluoromethanesulfonate (TMS·OTf) reacted selectively only with the carbonyl groups of **7** to give the silyl enol ethers **9a** quantitatively.[22] The oxidation of silyl enol ethers with percarboxylic acid provides α-siloxyketones via siloxyepoxide intermediates.[23] Perphthalic acid, which was generated in situ from the reaction of phthalic anhydride and anhydrous urea−H_2O_2 (UHP) in MeCN, was used for the oxidation of the silyl enol ethers **9**. Since the desilylation of the trimethylsiloxyketone **10a** was readily observed by TLC during the oxidation of **9a**, even in the presence of Na_2CO_3, crude **10a** was treated with HF solution to give rise to the α-hydroxy ketone **10d** in 85% overall yield from **7**.[24]

The attempted Ramberg−Bäcklund reaction of **10d** under various conditions produced no identifiable product, but complicated mixtures, which indicated that the protection of the hydroxy group was required. It was assumed that the silicon groups might be a perfect protecting group if they survived the oxidation and the Ramberg−Bäcklund reactions. The *tert*-butyldimethylsilyl enol ether **9b** was prepared quantitatively from **7** by the reaction with TBDMS·OTf. The oxidation of **9b** by perphthalic acid in the presence of Na_2CO_3 produced the *tert*-butyldimethylsiloxyketone **10b** in 73% yield. The Ramberg−Bäcklund reaction of **10b** using NaOMe (10 equiv) and CCl_4 provided the desired C_{40} disulfone **11b** in only 32% yield. Once again, the deprotection of the silicon protecting group under the basic conditions caused low yield of the rearrangement product. The Ramberg−Bäcklund reaction of the larger triisopropylsiloxy ketone **10c**, which was prepared in 72% yield from **7** by the silylation with TIPS·OTf, and the subsequent oxidation with perphthalic acid, proceeded well under the above improved condition to produce the C_{40} disulfone **11b** in 77% yield. The base-promoted dehydrosulfonation reaction of **11c** using NaOEt in refluxing EtOH/benzene gave rise to astacene (**3**) in 71% yield instead of astaxanthin (**2**). Apparently, the silicon protecting groups were desilylated in the course of the harsh dehydrosulfonation reaction, and the resulting astaxanthin (**2**) was readily oxidized to astacene (**3**) in the presence of base and traces of oxygen.[25]

The synthesis of astaxanthin (**2**) was completed by changing the silicon protecting group to THP and applying the above sequence of the reactions producing the fully conjugated polyene chain. The α-hydroxy ketone **10d** reacted with 3,4-dihydro-2*H*-pyran to give the THP-protected C_{40} trisulfone **10e** in 87% yield. The Ramberg−Bäcklund reaction of **10e** under the condition using NaOMe and CCl_4 produced the THP-protected disulfone **11e** in 93% crude yield. The THP protecting group survived in the dehydrosulfonation reaction of **11e**, and

(19) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188−196.

(20) (a) Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919−934. (b) Remiszewski, S. W.; Whittle, R. R.; Weinreb, S. M. *J. Org. Chem.* **1984**, *49*, 3241−3243.

(21) (a) Moriarty, R. M.; Berglund, B. A.; Penmasta, R. *Tetrahedron Lett.* **1992**, *33*, 6065−6068. (b) Moriarty, R. M.; Hou, K.-C. *Tetrahedron Lett.* **1984**, *25*, 691−694.

(22) Silylations at the allylic positions next to the central sulfone group have been also detected when the procedure of deprotonation by NaHMDS and silylation with TMS-Cl was utilized.

(23) Rubottom, G. M.; Gruber, J. M. *J. Org. Chem.* **1978**, *43*, 1599−1602.

(24) This α-hydroxylation was not stereoselective, and a statistical 1:1 mixture of *syn*- and *anti*-diols was observed in the ^{1}H NMR spectrum, which was comprised of a 1:2:1 stereoisomeric mixture of (3*R*,3′*R*)-, (3*R*,3′*S*,*meso*)-, (3*S*,3′*S*)-**10d**.

(25) Cooper, R. D. G.; Davis, J. B.; Leftwick, A. P.; Price, C.; Weedon, B. C. L. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2195−2204.

astaxanthin (**2**) was finally obtained in 60% yield after deprotection of the THP group.

In conclusion, we have developed practical and efficient synthetic methods for several keto-carotenoids, canthaxanthin (**1**), astaxanthin (**2**), and astacene (**3**), by the oxidations of the stable C_{40} trisulfone compound **6**. Our syntheses were accomplished by the improved Ramberg−Bäcklund reaction utilizing a mild NaOMe base for the C_{40} allylic sulfone compounds containing the carbonyl group.

Experimental Section

Coupling Reaction. Bis(5-benzenesulfonyl-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexenyl)-2,6,8-nonatrienyl) Sulfone (6). To a stirred solution of C_{15} allylic sulfone **4** (5.0 g, 14.51 mmol) in DMF (30 mL) at −20 °C was added *t*-BuOK (1.95 g, 17.42 mmol). The resulting dark red solution was stirred at that temperature for 30 min, and a solution of C_{10} bischloroallylic sulfone **5** (1.97 g, 7.26 mmol) in DMF (5 mL) was added. The mixture was stirred at −20 °C for 2 h and then at room temperature for another 2 h. A solid was precipitated upon addition of 1 M HCl (30 mL). This solid was filtered, rinsed with 1 M HCl and H_2O, and dried by air. The crude product was recrystallized from MeOH to give **6** (5.45 g, 6.15 mmol) in 85% yield as a white solid.

Allylic Oxidation (First Oxidation). Bis(5-benzenesulfonyl-3,7-dimethyl-9-(3-oxo-2,6,6-trimethyl-1-cyclohexenyl)-2,6,8-nonatrienyl) sulfone (7). To a stirred solution of C_{40} trisulfone compound **6** (7.10 g, 8.00 mmol) in $CHCl_3$ (60 mL) were added a solution of $NaIO_4$ (5.10 g, 24.0 mmol) in H_2O (60 mL) and I_2 (0.05 g, 0.40 mmol). The mixture was stirred at room temperature for 40 h, and the organic layer was separated. The aqueous layer was extracted with $CHCl_3$. The combined organic phase was washed with 1 M HCl solution, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by recrystallization from MeOH to give **7** (6.1 g, 6.6 mmol) in 82% yield as a white solid.

Data for **7**: ^{1}H NMR δ 1.10 (s, 6H), 1.13 (s, 6H), 1.34 (s, 6H), 1.70 (s, 6H), 1.75 (s, 6H), 1.84 (t, J = 6.8 Hz, 4H), 2.43−2.56 (m, 6H), 3.04 (d, J = 11.2 Hz, 2H), 3.50 (d of A of ABq, J_{AB} = 14.6, J_d = 7.8 Hz, 2H), 3.56 (d of B of ABq, J_{AB} = 14.6, J_d = 7.8 Hz, 2H), 4.10 (dt, J_d = 3.6, J_t = 10.5 Hz, 2H), 5.22 (d, J = 10.5 Hz, 2H), 5.28 (t, J = 7.8 Hz, 2H), 6.06 (A of ABq, J_{AB} = 17.2 Hz, 2H), 6.09 (B of ABq, J_{AB} = 17.2 Hz, 2H), 7.45−7.87 (m, 10 H) ppm; ^{13}C NMR δ 12.3, 13.5, 17.0, 27.3, 27.4, 34.1, 35.5, 37.1, 37.4, 51.2, 63.2, 113.8, 124.5, 126.5, 128.9, 129.2, 130.0, 133.8, 137.0, 138.2, 140.9, 141.6, 160.3, 199.0 ppm; IR (KBr) 1661, 1447, 1307, 1146, 913, 745 cm^{-1}. Anal. Calcd for $C_{52}H_{66}O_8S_3$: C, 68.24; H, 7.27; S, 10.51. Found: C, 68.03; H, 7.30; S, 10.24.

General Procedure for α-Hydroxylation (Second Oxidation). Bis(5-benzenesulfonyl-3,7-dimethyl-9-(4-*tert*-butyldimethylsiloxy-3-oxo-2,6,6-trimethyl-1-cyclohexenyl)-2,6,8-nonatrienyl) Sulfone (10b). To a stirred solution of keto-trisulfone **7** (2.00 g, 2.19 mmol) in CH_2Cl_2 (25 mL) were added Et_3N (1.50 mL, 10.95 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.10 mL, 4.82 mmol). The mixture was stirred at room temperature for 1.5 h, and a saturated aqueous $NaHCO_3$ solution was added. The reaction mixture was extracted with CH_2Cl_2, dried over K_2CO_3, filtered, and concentrated under reduced pressure to give silyl enol ether **9b** (3.02 g) as a white solid.

The mixture of urea−H_2O_2 (UHP, 2.06 g, 21.90 mmol) and phthalic anhydride (1.62 g, 10.95 mmol) in CH_3CN (25 mL) was stirred at room temperature for 2 h to give a clear solution. To the above solution were added Na_2CO_3 (2.32 g, 21.90 mmol) and a solution of **9b** (3.02 g) in CH_2Cl_2 (25 mL). The resulting mixture was stirred at room temperature for 7 h, diluted with $CHCl_3$, and filtered to remove the undissolved white solid. The filtrate was washed with a saturated aqueous $NaHCO_3$ solution, dried over anhydrous K_2CO_3, filtered, and concentrated under reduced pressure to give crude **10b** (1.89 g, 1.61 mmol) in 73% yield, which consisted of ∼1:1 diastereoisomers presumably at the carbons containing the etheral group. The product was not stable under silica gel chromatographic conditions and was not further purified.

Data for **10b**: ^{1}H NMR δ 0.10 (s, 6H), 0.19 (s, 6H), 0.93 (s, 18H), 1.09 (s, 6H), 1.10 (s, 6H),* 1.20 (s, 6H), 1.24 (s, 6H),* 1.31 (s, 6H), 1.34 (s, 6H),* 1.69 (s, 6H), 1.77 (s, 6H), 1.78 (s, 6H),* 1.85−2.04 (m, 4H), 2.49 (dd, J = 13.0, 11.2 Hz, 2H), 3.04 (br d, J = 13.0 Hz, 2H), 3.42−3.61 (m, 4H), 4.08 (br t, J = 9.7 Hz, 2H), 4.25−4.37 (m, 2H), 5.22 (d, J = 10.8 Hz, 2H), 5.27 (br s, 2H), 6.03 (d of A of ABq, J_{AB} = 16.2, J_d = 3.1 Hz, 2H), 6.10 (d of B of ABq, J_{AB} = 16.2, J_d = 2.0 Hz, 2H), 7.45−7.57 (m, 4H), 7.61−7.70 (m, 2H), 7.76−7.87 (m, 4H) ppm; ^{13}C NMR δ −5.4, −4.5, 12.2,* 12.3, 13.8, 17.0, 18.4, 25.8, 26.1, 30.2, 36.7, 37.5, 46.7, 51.3, 63.3, 70.9, 113.8, 124.6,* 124.7, 126.1, 128.7, 128.8, 129.2, 133.8, 137.1, 137.2,* 138.5,* 138.6, 140.9, 141.5, 158.7, 158.8,* 198.6 ppm; IR (KBr) 1682, 1447, 1307, 1148 cm^{-1}. Anal. Calcd for $C_{64}H_{94}O_{10}S_3Si_2$: C, 65.38; H, 8.06; S, 8.18. Found: C, 65.12; H, 7.99; S, 8.24. *Peaks from the other diastereoisomer.

General Procedure for the Ramberg−Bäcklund Reaction. 1,18-Bis(3-oxo-2,6,6-trimethyl-1-cyclohexenyl)-5,14-dibenzenesulfonyl-3,7,12,16-tetramethyl-1,3,7,9,11,15,17-eicosaheptaene (8). To a stirred solution of the C_{40} keto-trisulfone compound **7** (350 mg, 0.38 mmol) in CH_2Cl_2 (10 mL) were added CCl_4 (5 mL) and $NaOCH_3$ (0.17 g, 3.14 mmol). The mixture was stirred at room temperature for 4.5 h, and H_2O (5 mL) was added to the mixture. The reaction mixture was extracted with CH_2Cl_2, washed with a saturated aqueous $NaHCO_3$ solution and H_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography to give **8** (236 mg, 0.28 mmol) in 73% yield.

Data for **8**: ^{1}H NMR δ 1.10 (s, 6H), 1.13 (s, 6H), 1.31 (s, 6H), 1.68 (s, 6H), 1.76 (s, 6H), 1.84 (t, J = 5.5 Hz, 4H), 2.37−2.58 (m, 6H), 3.03 (d, J = 13.0 Hz, 2H), 4.06 (dd J = 10.5, 7.7 Hz, 2H), 5.23 (d J = 10.5 Hz, 2H), 5.83−5.93 (m, 2H), 6.03 (A of ABq, J_{AB} = 16.1 Hz, 2H), 6.10 (B of ABq, J_{AB} = 16.1 Hz, 2H), 6.14−6.27 (m, 2H), 7.35−8.00 (m, 10H) ppm; ^{13}C NMR δ 12.3, 13.6, 16.5, 27.4, 34.2, 35.5, 37.2, 38.0, 49.3, 63.9, 125.1, 126.0, 127.8, 128.8, 129.2, 130.1, 132.7, 133.7, 137.4, 138.7, 139.7, 141.1, 160.5, 199.1 ppm; IR (KBr) 1663, 1447, 1306, 1146 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{52}H_{65}O_6S_2$ 849.4223, found 849.4221.

General Procedure for Dehydrosulfonation. Canthaxanthin (1). Na (640 mg, 27.7 mmol) was added to 99.9% EtOH (30 mL), and the mixture was heated to reflux for 1 h and then cooled to room temperature. To this base solution was added a solution of the C_{40} keto-disulfone **8** (1.18 g, 1.39 mmol) in benzene (10 mL). The mixture was heated to reflux for 12 h and cooled to room temperature. Most of the solvent was removed under reduced pressure, and H_2O (20 mL) was carefully added. The reaction mixture was extracted with $CHCl_3$, washed with 1 M HCl solution and H_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Due to extensive abstraction by silica gel, purification of the crude product by silica gel flash column chromatography provided only 40% yield of canthaxanthin (314 mg, 0.55 mmol). The actual yield of **1**, calculated by ^{1}H NMR titration of an aliquot of the crude product with a known amount of phenethyl alcohol, was 86%.

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Supporting Information Available: Experimental procedures and characterization data for **2**, **3**, **10c**−**e**, and **11b**,**c**,**e** and ^{1}H NMR spectra of **1**−**3**, **7**, **8**, **10b**−**e**, and **11b**,**c**,**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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