Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 10181–10185

General and systematic synthetic entry to carotenoid natural products

Young Cheol Jeong, Minkoo Ji, Jun Sup Lee, Jae-Deuk Yang, Jingquan Jin, Woonphil Baik and Sangho Koo*

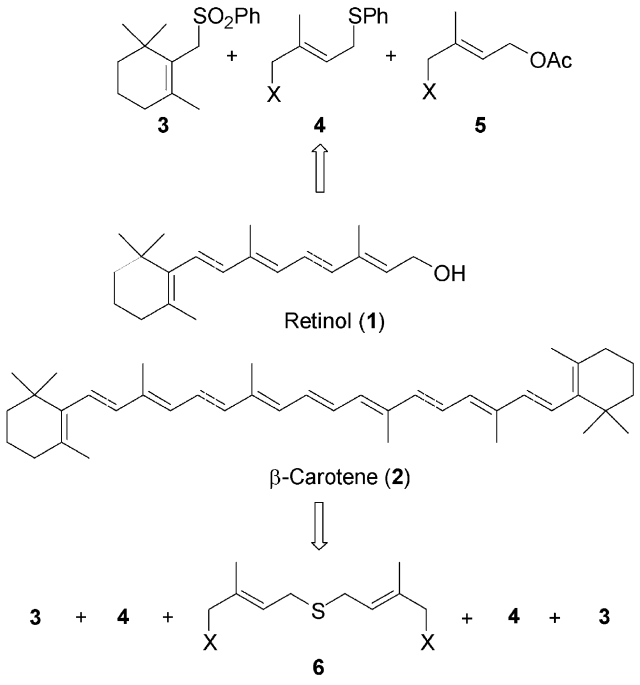
Department of Chemistry, Myong Ji University, San 38-2, Nam-Dong, Yongin, 449-728 Kyunggi-Do, South Korea

Received 4 August 2004; revised 2 September 2004; accepted 2 September 2004

Abstract—A general synthetic method of carotenoid natural products has been developed, in which the systematic chain extension and termination processes were applied. The syntheses of the chain extension and termination units were greatly improved by the use of the common intermediate, 1-bromo-4-chloro-3-methyl-2-butene (**8**), in a short and highly efficient way. The C_{10} chain initiation β-cyclogeranyl sulfone (**3**) was coupled with the C_5 chain extension unit to give the C_{15} chain-extended allylic sulfone after chemoselective sulfide oxidation. This chain-extended C_{15} allylic sulfone underwent the Julia olefination reaction with the C_5 and the C_{10} chain termination units to give retinol (**1**) and β-carotene (**2**), respectively.

1. Introduction

Carotenoids are biologically, medicinally, and commercially important natural products, which include retinol (vitamin A), retinoic acid, β-carotene, canthaxanthin, and astaxanthin etc.[1] Retinol is an essential nutrient for higher animals required for cell growth and differentiation, fertilization, and visual action. Retinoic acid shows broad treatment effects on skin disorders including acne and even on emphysema.[2] β-Carotene and astaxanthin have wide industrial applications especially in animal feeds and the coloration of foodstuffs. These carotenoids belong to the isoprenoid family according to their biogenetic origin, which are enzymatically assembled by repeated uses of isopentenyl pyrophosphate (IPP) or dimethylallyl pyrophosphate (DMAP) as building blocks.[1] Chemical syntheses of these carotene compounds,[3] therefore, can be generalized in a systematic way by utilizing 'the C_5 building blocks,' as chemical mimics for IPP or DMAP. The Julia sulfone olefination protocol[4] is the best method to construct these highly unstable carotenoid structures through the much more stable allylic sulfone intermediates that can be transformed to the fully conjugated polyene chains in the final stage. Retrosynthetic analyses of the two representative carotenoid compounds, retinol (**1**) and β-carotene (**2**) utilizing the sulfone chemistry disintegrate these carotenoid structures systematically into the chain initiation allylic sulfone **3**, the chain extension C_5 unit **4**, and the chain termination C_5 and C_{10} units, **5** and **6**, respectively (Scheme 1). We herein report the details of our systematic studies on



Scheme 1. Disconnection approaches to retinol (**1**) and β-carotene (**2**).

Keywords: Carotenoid; Olefination; Retinol; β-Carotene; Total synthesis.
* Corresponding author. Tel.: +82 31 330 6185; fax: +82 31 335 7248; e-mail: sangkoo@mju.ac.kr

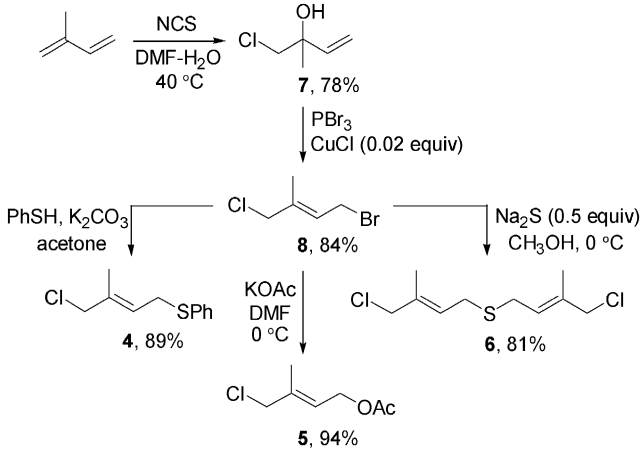
0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.09.002

the efficient syntheses of each unit, the chain extension process, and the total syntheses of retinol (**1**) and β-carotene (**2**).

2. Results and discussion

β-Cyclogeranyl sulfone (**3**)[5] which can be readily prepared by the electrophilic cyclization of geranyl sulfone was used as a chain initiation unit for our carotenoid synthesis. The C_5 chain extension unit was so designed as to give the 1,5-arrangement of the methyl substituents, which is the general substitution pattern of the carotenoid compounds, and to give the chain-extended allylic sulfones again after the Julia coupling reaction with the chain-initiating allylic sulfone **3**. 4-Halo-3-methyl-2-butenyl sulfide **4** instead of the corresponding sulfone compound was selected in order to facilitate the Julia coupling reaction with β-cyclogeranyl sulfone **3**, where the undesirable dehydrohalogenation reaction could be prevented.[6] The resulting chain-extended allylic sulfide can be oxidized to the corresponding allylic sulfone. The chain-extended allylic sulfone then undergoes olefination process with the C_5 and the C_{10} chain termination units **5** and **6** to give retinol (**1**) and β-carotene (**2**), respectively. Bis(haloallylic) sulfide **6** has proven to be a stable substitute for highly unstable 1,8-dihalo-2,7-dimethyl-2,4,6-octatriene as the C_{10} chain termination unit for β-carotene and lycopene syntheses.[6,7]

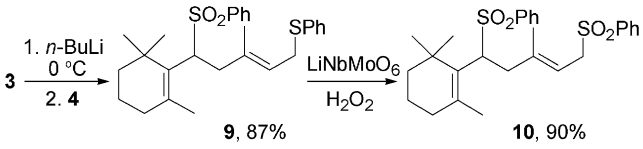
It was envisioned that the chain extension unit **4**[8] and the chain termination units **5**[9] and **6**[6,7] might be obtained in a highly efficient and convenient way from the common intermediate **8** in proviso that the ambidextrous allylic halide **8** could show different electrophilic reactivity (Scheme 2). In fact, the nucleophiles of PhS^- (PhSH, K_2CO_3 in acetone), AcO^- (AcOK in DMF) and S^{2-} (Na_2S in CH_3OH) discriminated allylic bromide from allylic chloride of 1-bromo-4-chloro-3-methyl-2-butene (**8**) to directly give rise to the C_5 chain extension unit, phenyl 4-chloro-3-methyl-2-butenyl sulfide (**4**)[10] in 89% yield and the C_5 and the C_{10} chain termination units, 4-chloro-3-methyl-2-butenyl acetate (**5**)[10] and bis(4-chloro-3-methyl-2-butenyl) sulfide (**6**) in 94 and 81% yields, respectively.



Scheme 2. Syntheses of the chain-extension unit **4** and the chain-termination units **5** and **6**.

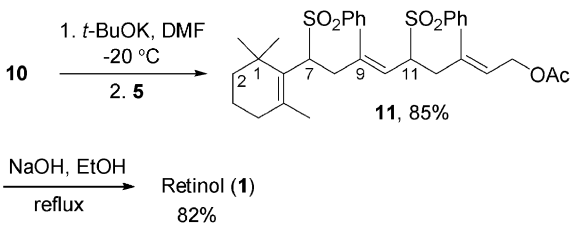
The ambidextrous allylic halide **8** was prepared from readily available isoprene in two steps: chlorohydrin formation using *N*-chlorosuccinimide in H_2O-DMF (78% yield), followed by PBr_3-promoted bromination of the resulting chlorohydrin **7** under CuCl catalyst (84% yield), where the allylic-transposed bromination product **8** was exclusively obtained with a high *E*:*Z* ratio of 10:1.[10]

The chain extension unit **4** that was proposed as a chemical mimic for IPP or DMAP was then utilized in the chain extension process. The Julia coupling reaction of β-cyclogeranyl sulfone (**3**) with the C_5 chain extension unit **4** produced the chain-extended allylic sulfides **9** (Scheme 3).[11] This coupling reaction works well (87% yield) with *n*-BuLi as a base. Chemoselective sulfur oxidation of **9** proceeded smoothly with 2.5 equiv H_2O_2 under $LiNbMoO_6$ catalyst[12] to give the C_{15} disulfone compound **10** (90% yield), where no epoxidation at the tetra-substituted double bond in the cyclohexene ring was observed contrary to the case of the conventional electrophilic oxidant such as MCPBA. The white crystalline disulfone compound **10** was easily purified by washing with diethyl ether.



Scheme 3. Chain extension process to obtain the C_{15} disulfone compound **10**.

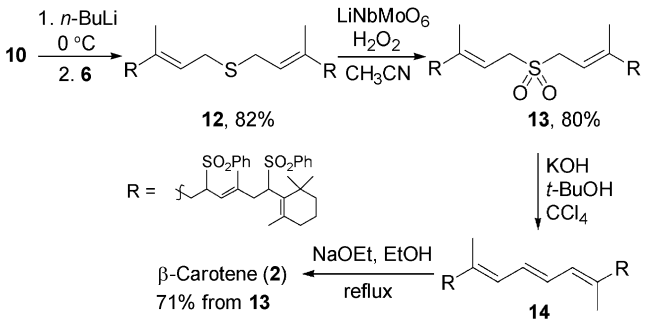
The Julia olefination reaction of the chain-extended allylic sulfone **10** with the C_5 chain termination unit **5** produced retinol (**1**). The coupling reaction of the C_{15} disulfone **10** and the C_5 unit **5** under *t*-BuOK/DMF condition provided the C_{20} compound **11** in 85% yield (Scheme 4). Deprotonation at the α-carbons to the benzenesulfonyl groups of the disulfone **10** can be completed by the use of 2 equiv of a strong base such as *t*-BuOK or *n*-BuLi, where the coupling reaction proceeded only at the less-substituted secondary carbanion. The dehydrosulfonation reaction of the C_{20} coupling product **11** using NaOH as a base in EtOH then produced all-(*E*)-retinol (**1**) in 82% yield after chromatographic separation of a small amount (less than 10%) of 13-(*Z*)-retinol.[13] It is beneficial to use NaOH as a base in EtOH and to operate the reaction initially at room temperature and then at the reflux temperature of EtOH to facilitate the hydrolysis of acetate first, and then promote dehydrosulfonation reaction in order to minimize the possibility of the base-promoted elimination of acetate producing anhydro vitamin A. Base-promoted



Scheme 4. Retinol synthesis.

dehydrosulfonation reaction produces a *E*-double bond in the Julia sulfone olefination.[14] Dehydrosulfonation at C(7,8) in the compound **11** proceeded rapidly even at room temperature presumably due to steric congestion, however, dehydrosulfonation at C(11,12) requires a stronger condition of boiling EtOH.

The Julia olefination reaction of the chain-extended allylic sulfone **10** with the C_{10} chain termination unit **6** in combination with the Ramberg-Bäcklund reaction produced β-carotene (**2**). The coupling reaction of the C_{15} disulfone **10** (2 equiv) with the C_{10} unit **6** (1 equiv) provided the C_{40} compound **12** (Scheme 5). To complete the deprotonation and the coupling reaction at the secondary α-carbon to the benzenesulfonyl group in compound **10**, 2 equiv *n*-BuLi was used as a base to give the optimized yield of 82%. Chemoselective oxidation of the bisallylic sulfide **12** to the corresponding bisallylic sulfone **13** proceeded by H_2O_2 (2.5 equiv) under $LiNbMoO_6$ catalyst (0.05 equiv) in 80% yield,[12] where MeCN was used as a solvent to improve the solubility of the compound **12** containing tetra-benzenesulfonyl groups. The Ramberg-Bäcklund reaction of bisallylic sulfone **13** under Meyers condition[15] produced the C_{40} compound **14** containing the central triene moiety. It was necessary to apply the dehydrosulfonation reaction to the crude product **14** without purification because the C_{40} compound **14** was not stable under air, and furthermore, some of the premature dehydrosulfonation products at C(7) were also observed at the Ramberg-Bäcklund reaction stage. Dehydrosulfonation reaction of the crude product **14** under excess NaOEt in refluxing EtOH, which presumably allowed thermal isomerization of the (*Z*)-isomers, then produced all-(*E*)-β-carotene (**2**) in 71% overall yield after two steps from the bisallylic sulfone **13**.



Scheme 5. β-Carotene synthesis.

3. Conclusion

We have developed a general and systematic synthetic method of carotenoid natural products. This biomimetic approach highlights the use of the C_5 chain extension unit **4** and the C_5 and the C_{10} chain termination units **5** and **6** that are prepared from the common intermediate **8** in a highly efficient way. The usefulness and general applicability of our systematic approach have been demonstrated in the synthesis of retinol (**1**) and β-carotene (**2**). This approach for carotenoid syntheses can be applied to the systematic syntheses of other isoprenoid natural products including terpenoids and steroids, which have the same biogenetic origin as the carotenoid compounds.

4. Experimental

4.1. General information

^1H (300 MHz) and ^{13}C NMR (75.5 MHz) spectra were recorded in deuterated chloroform ($CDCl_3$). Solvents for extraction and chromatography were reagent grade and used as received. The column chromatography was performed by the method of Still with silica gel 60, 230–400 mesh ASTM supplied by Merck. Solvents used as reaction media were dried over pre-dried molecular sieve (4 Å) by microwave oven. All reactions were performed under a dry argon atmosphere in oven-dried glassware except for those used H_2O as a reaction medium.

4.2. Bis(4-chloro-3-methyl-2-butenyl) sulfide (6)

To a stirred solution of 1-bromo-4-chloro-3-methyl-2-butene (**8**) (15.6 g, 80.7 mmol) in THF (100 mL) at 0 °C was added Na_2S (6.76 g, 40.3 mmol). The reaction mixture was stirred at that temperature for 6 h, and H_2O was added. The mixture was extracted with ether, washed with H_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by SiO_2 flash column chromatography to give **6** [7.83 g, 32.7 mmol; (*E*,*E*):(*E*,*Z*)=5:1] in 81% yield.

4.2.1. Data for (*E*,*E*)-6.[7] ^1H NMR δ 1.78 (s, 6H), 3.10 (d, J=7.6 Hz, 4H), 4.03 (s, 4H), 5.62 (t, J=7.6 Hz, 2H) ppm. Data for (*E*,*Z*)-**6**: ^1H NMR δ 1.78 (s, 3H), 1.83 (s, 3H), 3.10 (d, J=7.6 Hz, 2H), 3.12 (d, J=8.1 Hz, 2H), 4.01 (s, 2H), 4.03 (s, 2H), 5.44 (t, J=8.1 Hz, 1H), 5.62 (t, J=7.6 Hz, 1H) ppm.

4.3. 3-Methyl-5-(2,6,6-trimethyl-1-cyclohexenyl)-1,5-dibenzenesulfonyl-2-pentene (10)

To a stirred solution of **3** (2.78 g, 10.00 mmol) in THF (50 mL) at 0 °C was added 1.6 M solution of *n*-BuLi in hexane (7.5 mL, 12.00 mmol). The mixture was stirred for 1 h, and a solution of **4** (2.55 g, 12.00 mmol) in THF (10 mL) was added. The mixture was stirred at 0 °C for 1.5 h, quenched with 1 M HCl (20 mL), and extracted with ether. The organic layer was washed with 1 M HCl and H_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to give **9**[11] (2.96 g, 8.71 mmol) in 87% yield.

To a stirred solution of **9** (2.94 g, 6.50 mmol) in CH_3OH (30 mL) and benzene (10 mL) at 0 °C were added $LiNbMoO_6$ (94 mg, 0.30 mmol) and 30% H_2O_2 solution (1.84 g, 16.25 mmol). The reaction mixture was warmed up and stirred at 25 °C for 6 h, and most of solvent was removed under reduced pressure. The crude material was diluted with $CHCl_3$ (50 mL), washed with 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 **10** (2.83 g, 5.80 mmol) in 90% yield. The product was further purified by recrystallization with ether to give the (*E*)-**10** (2.55 g, 5.23 mmol) in 72% yield.

4.3.1. Data for (*E*)-10. ^{1}H NMR δ 0.76 (s, 3H), 0.98 (s, 3H), 1.11 (s, 3H), 1.33–1.60 (m, 4H), 1.95–2.18 (m, 2H), 1.99 (s, 3H), 2.57 (d of ABq, $J_{AB}=14.6$ Hz, $J_d=6.2$ Hz, 1H), 3.10 (d of ABq, $J_{AB}=14.6$ Hz, $J_d=7.1$ Hz, 1H), 3.64 (d of ABq, $J_{AB}=15.4$ Hz, $J_d=7.8$ Hz, 1H), 3.70 (d of ABq, $J_{AB}=15.4$ Hz, $J_d=7.8$ Hz, 1H), 3.87 (dd, $J=7.1$, 6.2 Hz, 1H), 5.23 (dt, $J_d=1.0$ Hz, $J_t=7.8$ Hz, 1H), 7.43–7.70 (m, 6H), 7.76–7.93 (m, 4H) ppm; ^{13}C NMR δ 15.7, 18.9, 23.3, 28.4, 28.9, 34.5, 36.0, 39.6, 41.1, 55.9, 65.2, 114.7, 128.2, 128.5, 128.8, 129.1, 130.5, 133.2, 133.7, 138.2, 138.7, 141.6 ppm; IR (KBr) 1448, 1385, 1144, 1084 cm^{-1}; HRMS (CI$^+$) calcd for $C_{27}H_{35}O_4S_2$ 487.1977, found 487.1990.

4.4. 1-Acetoxy-5,9-dibenzenesulfonyl-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexenyl)-2,6-nonadiene (11)

To a stirred solution of **10** (0.50 g, 1.03 mmol) in DMF (20 mL) at −20 °C was added *t*-BuOK (0.29 g, 2.47 mmol). The mixture was stirred at that temperature for 1 h, and a solution of C_5 chloroacetate **5** (0.25 g, 1.54 mmol) in DMF (5 mL) was added. The resulting mixture was stirred at −20 °C for 3 h, and 2 M HCl solution (10 mL) was added to quench the reaction. The mixture was extracted with ether, washed with 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 **11** (0.54 g, 0.88 mmol) in 85% yield, which was a 2:1 mixture of diastereomers

4.4.1. Data for the major isomer of 11. ^{1}H NMR δ 0.68 (s, 3H), 0.80 (s, 3H), 1.12 (s, 3H), 1.27–1.68 (m, 4H), 1.57 (s, 3H), 1.95–2.09 (m, 2H), 1.96 (s, 3H), 2.01 (s, 3H), 2.24 (dd, $J=14.3$, 11.3 Hz, 1H), 2.62 (dd, $J=15.0$, 5.9 Hz, 1H), 2.87 (br d, $J=14.3$ Hz, 1H), 3.05 (dd, $J=15.0$, 5.9 Hz, 1H), 3.78 (t, $J=5.9$ Hz, 1H), 3.91 (ddd, $J=11.3$, 10.3, 3.3 Hz, 1H), 4.38–4.55 (m, 2H), 4.95 (d, $J=10.3$ Hz, 1H), 5.28 (t, $J=6.7$ Hz, 1H), 7.47–7.70 (m, 6H), 7.75–7.95 (m, 4H) ppm; ^{13}C NMR δ 15.9, 16.3, 18.9, 20.9, 23.5, 28.7, 28.7, 34.5, 35.6, 38.4, 39.5, 41.6, 60.9, 63.0, 65.6, 120.8, 122.3, 128.8, 129.0, 129.0, 129.4, 131.5, 133.4, 133.8, 136.2, 137.3, 138.0, 140.9, 142.1, 170.9 ppm; IR (KBr) 2934, 1737, 1446, 1304, 1233, 1145 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{22}H_{33}O_2$ ($C_{34}H_{45}O_6S_2-2C_6H_6SO_2$) 329.2481, found 329.2485.

4.5. Retinol (1)[4]

To a stirred solution of **11** (7.53 g, 12.27 mmol) in 99.9% EtOH (100 mL) was added NaOH (4.91 g, 0.12 mol). The mixture was stirred at room temperature for 1 h and then heated to reflux for 15 h. The reaction mixture was cooled to room temperature, and most of the solvent was removed under reduced pressure. The mixture was carefully treated with H_2O and 3 M HCl (40 mL) solution, extracted with $CHCl_3$, washed with H_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product which contained a small amount (less than 10%) of 13-(*Z*)-retinol was purified by silica gel flash column chromatography to give all-(*E*)-retinol (**1**) (2.88 g, 10.06 mmol) in 82% yield.

4.6. Bis[3,7-dimethyl-5,9-dibenzenesulfonyl-9-(2,6,6-trimethyl-1-cyclohexenyl)-2,6-nonadienyl] sulfide (12)

To a stirred solution of **10** (4.00 g, 8.21 mmol) in THF (50 mL) at 0 °C was added 1.6 M solution of *n*-BuLi in hexane (11.3 mL, 18.1 mmol). The mixture was stirred at that temperature for 20 min, and a solution of **6** (1.18 g, 4.11 mmol) in THF (15 mL) was added. The resulting mixture was stirred at 0 °C for 1 h, quenched with 1 M HCl solution, extracted with ether, washed with 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 **12** (3.85 g, 6.75 mmol) in 82% yield. This coupling product was composed of a mixture of diastereomers, which were not easily separable.

4.6.1. Data for the major diastereomer of 12. ^{1}H NMR δ 0.77 (s, 6H), 0.82 (s, 6H), 1.16 (s, 6H), 1.23–1.43 (m, 4H), 1.43–1.52 (m, 4H), 1.50 (s, 6H), 1.86–2.12 (m, 4H), 1.97 (s, 6H), 2.03–2.32 (m, 2H), 2.44–3.00 (m, 6H), 2.90–3.20 (m, 4H), 3.72–3.99 (m, 4H), 4.83–5.00 (m, 2H), 5.12–5.27 (m, 2H), 7.43–7.68 (m, 12H), 7.74–7.95 (m, 8H) ppm; ^{13}C NMR δ 15.8, 18.7, 23.2, 28.5, 28.7, 34.4, 35.5, 35.7, 38.4, 39.4, 40.9, 41.4, 62.6, 65.4, 120.7, 124.3, 124.9, 128.6, 128.9, 129.0, 129.0, 131.3, 133.4, 133.7, 137.4, 137.7, 140.9, 141.8 ppm; IR (KBr) 2931, 1447, 1304, 1144 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{52}H_{71}S_3O_4$ [$C_{64}H_{83}S_5O_8-2\times(C_6H_6SO_2)$] 855.4514, found 855.4511.

4.7. Bis[3,7-dimethyl-5,9-dibenzenesulfonyl-9-(2,6,6-trimethyl-1-cyclohexenyl)-2,6-nonadienyl] sulfone (13)

To a stirred solution of **12** (1.61 g, 1.41 mmol) in MeCN (20 mL) at 0 °C were added $LiNbMoO_6$ (20 mg, 0.07 mmol) and a 35% aqueous solution of H_2O_2 (0.34 g, 3.53 mmol). The resulting mixture was stirred at 0 °C for 1 h and at room temperature for 12 h. The mixture was then extracted with CH_2Cl_2, washed with 1 M HCl and H_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to give **13** (1.36 g, 1.13 mmol) in 80% yield. This coupled product was composed of a mixture of diastereomers, which were not easily separable.

4.7.1. Data for the major diastereomer of 13. ^{1}H NMR δ 0.67 (s, 6H), 0.79 (s, 6H), 1.28 (s, 6H), 1.23–1.54 (m, 8H), 1.67 (s, 6H), 1.93–2.03 (m, 4H), 2.00 (s, 6H), 2.05–2.66 (m, 4H), 2.71–2.92 (m, 2H), 2.98–3.32 (m, 2H), 3.42–3.70 (m, 4H), 3.74–4.02 (m, 4H), 4.86–5.10 (m, 2H), 5.13–5.40 (m, 2H), 7.45–7.69 (m, 12H), 7.72–7.92 (m, 8H) ppm; ^{13}C NMR δ 15.8, 18.9, 23.4, 28.4, 28.7, 34.6, 35.7, 36.1, 38.4, 39.5, 41.5, 51.7, 62.3, 65.4, 113.8, 114.5, 120.4, 128.6, 129.0, 129.0, 129.2, 131.1, 133.5, 133.8, 137.2, 137.8, 140.8, 142.2 ppm; IR (KBr) 2931, 1447, 1305, 1144 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{46}H_{65}S_2O_4$ [$C_{64}H_{83}S_5O_{10}-3\times(C_6H_6SO_2)$] 745.4324, found 745.4333.

4.8. β-Carotene (2)[3,7]

To a stirred solution of **13** (0.98 g, 0.84 mmol, 1 equiv) in CCl_4 (15 mL) and *t*-BuOH (10 mL) at 0 °C was added pulverized KOH (0.47 g, 8.36 mmol, 10 equiv). The resulting mixture was stirred at 0 °C for 1 h and at room

temperature for 10 h, and carefully quenched with H_2O. The mixture was then neutralized with 1 M HCl (10 mL), extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product (1.15 g) was not stable and directly used for the next dehydrosulfonation reaction without purification.

A solution of the crude product **14** (1.15 g) in 99.9% EtOH (20 mL) was added to a solution of NaOEt which was prepared by adding Na (1.20 g, 52.14 mmol) to 99.9% EtOH (50 mL). The resulting mixture was heated to reflux for 12 h, and cooled to room temperature. Most of the solvent was removed under reduced pressure. The crude mixture was treated with 1 M HCl solution, extracted with $CHCl_3$, washed with 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 all-(*E*)-β-carotene (**2**) (0.32 g, 0.60 mmol) in 71% overall yield from **13**.

Acknowledgements

This work was supported by the RRC (Regional Research Center) program of MOST (Ministry of Science and Technology), KOSEF (Korea Science and Engineering Foundation), and Kyunggi-Do.

References and notes

1. (a) Koskinen, A. *Asymmetric Synthesis of Natural Products*; Wiley: Chichester, 1993; pp 168–191. (b) Cane, D. E. Comprehensive Natural Products Chemistry; Barton, D., Nakanishi, K., Eds.; Elsevier: Oxford, 1999; Vol. 2, pp 1–13.
2. (a) Orfanos, C. E.; Ehlert, R.; Gollnick, H. *Drugs* **1987**, *34*, 459–503. (b) Leid, M.; Kastner, P.; Chambon, P. *Trends Biochem. Sci.* **1992**, *17*, 427–433.
3. Reviews for carotenoid synthesis, (a) Pommer, H. *Angew. Chem.* **1960**, *72*, 911–915. (b) Isler, O. *Pure Appl. Chem.* **1979**, *51*, 447–462. (c) Widmer, E. *Pure Appl. Chem.* **1985**, *57*, 741–752. (d) Paust, J. *Pure Appl. Chem.* **1991**, *63*, 45–58. (e) Bernhard, K.; Mayer, H. *Pure Appl. Chem.* **1991**, *63*, 35–44.
4. (a) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, 4833–4836. (b) Julia, M.; Arnould, D. *Bull. Soc. Chim. France* **1973**, 743–746. (c) Julia, M.; Launay, M.; Stacino, J.-P.; Verpeaux, J.-N. *Tetrahedron Lett.* **1982**, *23*, 2465–2468. (d) Bremner, J.; Julia, M.; Launay, M.; Stacino, J.-P. *Tetrahedron Lett.* **1982**, *23*, 3265–3266.
5. Torii, S.; Uneyama, K.; Isihara, M. *Chem. Lett.* **1975**, 479–482.
6. Ji, M.; Choi, H.; Park, M.; Kee, M.; Jeong, Y. C.; Koo, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 3627–3629.
7. Choi, H.; Ji, M.; Park, M.; Yun, I.-K.; Oh, S.-S.; Baik, W.; Koo, S. *J. Org. Chem.* **1999**, *64*, 8051–8053.
8. Koo, S.; Yang, J.-D.; Kim, J.-S.; Lee, S.; Park, M. WO 037854 A1, 2003.
9. (a) Oroshnik, W.; Mallory, R. A. *J. Am. Chem. Soc.* **1950**, *72*, 4608–4613. (b) Babler, J. H.; Olsen, D. O. *Tetrahedron Lett.* **1974**, 351–354. (c) Babler, J. H.; Buttner, W. J. *Tetrahedron Lett.* **1976**, 239–242.
10. Lee, J.-S.; Jeong, Y. C.; Ji, M.; Baik, W.; Lee, S.; Koo, S. *Synlett* **2004**, 1937–1940.
11. 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.
12. Choi, S.; Yang, J.-D.; Ji, M.; Choi, H.; Kee, M.; Ahn, K.-H.; Byeon, S.-H.; Baik, W.; Koo, S. *J. Org. Chem.* **2001**, *66*, 8192–8198.
13. Dehydrosulfonation reaction of the C_{20} disulfone compound to produce the ester of retinoic acid had been reported: Uneyama, K.; Torii, S. *Chem. Lett.* **1977**, 39–40.
14. Manchand, P. S.; Rosenberger, M.; Saucy, G.; Wehrli, P. A.; Wong, H.; Chambers, L.; Ferro, M. P.; Jackson, W. *Helv. Chim. Acta* **1976**, *59*, 387–396.
15. Meyers, C. Y.; Malte, A. M.; Matthews, W. S. *J. Am. Chem. Soc.* **1969**, *91*, 7510–7512.