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

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Experimental Section

General Experimental. \(^1\)H (300 MHz) and \(^{13}\)C NMR (75.5 MHz) spectra were recorded in CDCl\(_3\) with Me\(_4\)Si (\(\delta = 0\) ppm) as an internal standard. Solvents for extraction and chromatography were reagent grade and used as received. Column chromatography was performed by the method of Still using 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 dry argon in oven-dried glassware, except for those reactions with H\(_2\)O as a solvent, which were run in air.

\[
\text{Bis(5-benzenesulfonyl-3,7-dimethyl-9-(3-oxo-4-triisopropylsiloxy-2,6,6-trimethyl-1-cyclohexenyl)-2,6,8-nonatrienyl) sulfone (10c).}\]

Following the general procedure for 10b, keto-trisulfone 7 (3.82 g, 4.17 mmol) reacted with triisopropylsilyl trifluoromethanesulfonate (2.50 mL, 9.17 mmol) in CH\(_2\)Cl\(_2\) (40 mL) under Et\(_3\)N (3.00 mL, 20.85 mmol) at room temperature for 2 h to give 9c (6.71 g) as a white solid. The oxidation of 9c (6.71 g) with perphthalic acid, which was prepared by the reaction of urea-H\(_2\)O\(_2\) (UHP, 3.92 g, 41.70 mmol) and phthalic anhydride (3.09 g, 20.85 mmol) in CH\(_3\)CN (40 mL), under Na\(_2\)CO\(_3\) (4.42 g, 41.70 mmol) in CH\(_2\)Cl\(_2\) (40 mL) at room temperature for 10 h gave crude 10c as a light-yellow solid (4.52 g, 3.59 mmol, 86%). The crude product was purified by flash column chromatography on silica gel which was deactivated by Et\(_3\)N to give 10c (3.78 g, 3.00 mmol) in 72% yield, which was consisted of ~1:1 diastereoisomers presumably at the carbons containing the ethereal group.
Data for 10c: $^1$H NMR δ 1.05–1.18 (m, 48H), 1.20 (s, 6H), * 1.24 (s, 6H), 1.32 (s, 6H), 1.34 (s, 6H), * 1.69 (s, 6H), 1.77 (s, 6H), * 1.78 (s, 6H), 1.99 (d, $J = 8.3$ Hz, 4H), 2.48 (dd, $J = 12.6$, 11.9 Hz, 2H), 3.04 (d, $J = 14.6$ Hz, 2H), 3.40–3.63 (m, 4H), 4.09 (br t, $J = 9.6$ Hz, 2H), 4.43 (dd, $J = 8.8$, 2.2 Hz, 2H), 4.46 (dd, $J = 7.7$, 2.3 Hz, 2H), * 5.23 (d, $J = 10.8$ Hz, 2H), 5.28 (br s, 2H), 6.04 (d of A of ABq, $J_{AB} = 16.4$, $J_d = 1.7$ Hz, 2H), 6.10 (d of B of ABq, $J_{AB} = 16.4$, $J_d = 2.1$ Hz, 2H), 7.44–7.56 (m, 4H), 7.61–7.68 (m, 2H), 7.75–7.84 (m, 4H) ppm; $^{13}$C NMR δ 12.3, 12.4, 13.9, 17.0, 17.9, 18.0, 26.2, 30.2, 30.3,* 36.8, 37.5, 47.1, 51.3, 63.4, 70.8, 113.8, 124.6,* 124.7, 126.2, 128.8, 128.9, 129.2, 133.8, 137.1, 137.2,* 138.6, 138.6,* 140.9,* 141.0, 141.5, 141.6,* 158.1, 158.2,* 198.7 ppm; IR (KBr) 1685, 1447, 1307, 1148, 1084 cm$^{-1}$; HRMS (FAB$^+$) calcd for C$_{70}$H$_{107}$O$_{10}$S$_3$Si$_2$ 1259.6565, found 1259.6553.

* peaks from the other diastereoisomer.

Bis(5-benzenesulfonyl-3,7-dimethyl-9-(4-hydroxy-3-oxo-2,6,6-trimethyl-1-cyclohexenyl)-2,6,8-nonatrienyl) sulfone (10d). Following the general procedure for 10b, keto-trisulfone 7 (4.70 g, 5.13 mmol) reacted with trimethylsilyl trifluoromethanesulfonate (2.04 mL, 11.29 mmol) in CH$_2$Cl$_2$ (80 mL) under Et$_3$N (3.58 mL, 25.65 mmol) at room temperature for 10 min to give 9a (5.91 g) as a white solid.

The oxidation of 9a (5.91 g) with perphthalic acid, which was prepared by the reaction of urea-H$_2$O$_2$ (UHP, 4.83 g, 51.30 mmol) and phthalic anhydride (3.80 g, 25.65 mmol) in CH$_3$CN (80 mL), under Na$_2$CO$_3$ (5.44 g, 51.30 mmol) in CH$_2$Cl$_2$ (50 mL) at room temperature for 2.5 h, followed by the deprotection of TMS group
with a 50% HF solution (4.4 g, 0.11 mol) gave crude 10d as a light-yellow solid. The crude product was purified by washing with MeOH to give pure 10d (4.11 g, 4.33 mmol) in 85% yield, which was consisted of ~1:1 diastereoisomers presumably at the carbons containing the hydroxy group.

Data for 10d: \(^1\)H NMR \(\delta 1.10\) (s, 6H), 1.11 (s, 6H), \(^*\) 1.24 (s, 6H), \(^*\) 1.28 (s, 6H), 1.34 (s, 6H), 1.36 (s, 6H), \(^*\) 1.69 (s, 6H), 1.77 (dd, \(J = 14.1, 2.9\) Hz, 2H), 1.82 (s, 6H), \(^*\) 1.83 (s, 6H), 2.15 (ddd, \(J = 12.8, 5.7, 1.4\) Hz, 2H), 2.50 (dd, \(J = 12.5, 11.9\) Hz, 2H), 3.04 (d, \(J = 13.9\) Hz, 2H), 3.45–3.63 (m, 4H), 3.66 (br s, 2H), 4.09 (dt, \(J_d = 3.7, J_t = 10.5\) Hz, 2H), 4.29 (dd, \(J = 5.6, 3.4\) Hz, 2H), 4.34 (dd, \(J = 5.6, 3.4\) Hz, 2H), \(^*\) 5.25 (d, \(J = 10.5\) Hz, 2H), 5.28 (br s, 2H), 6.04 (d of A of ABq, \(J_{AB} = 16.3, J_d = 2.8\) Hz, 2H), 6.15 (d of B of ABq, \(J_{AB} = 16.3, J_d = 2.0\) Hz, 2H), 7.47–7.56 (m, 4H), 7.62–7.70 (m, 2H), 7.76–7.85 (m, 4H) ppm; \(^{13}\)C NMR \(\delta 12.4, 12.4, *\) 13.7, 17.1 25.9, 25.9, * 30.4, 30.5, * 36.7, 37.7, 37.7, * 45.2, 51.5, 63.4, 69.2, 113.9, 125.3, 125.3, * 125.8, 127.4, 127.4, * 129.0, 129.3, 133.9, 137.2, 137.2, * 139.3, 139.3, * 141.0, 141.0, * 141.4, 141.5, * 161.2, 161.3, * 200.4 ppm; IR (KBr) 3482, 1665, 1447, 1305, 1146, 913, 743 cm\(^{-1}\); Anal. Calcd for C\(_{52}\)H\(_{66}\)O\(_{10}\)S\(_{3}\): C, 65.93; H, 7.02; S, 10.16. Found: C, 65.79; H, 7.01; S, 10.35.

* peaks from the other diastereoisomer.

\[ \text{Bis(5-benzenesulfonyl-3,7-dimethyl-9-(3-oxo-4-tetrahydropyranyloxy-2,6,6-trimethyl-1-cyclohexenyl)-2,6,8-nonatrienyl) sulfone (10e).} \]

To a stirred solution of hydroxy-keto-trisulfone 10d (1.93 g, 2.04 mmol) in CH\(_2\)Cl\(_2\) (50 mL) were added 3,4-dihydro-2H-pyrane (DHP, 0.69 mL, 8.15 mmol) and 10-
camphorsulfonic acid (CSA, 0.19 g, 0.82 mmol). The mixture was stirred at room temperature for 30 min, diluted with CH₂Cl₂, washed with a saturated aqueous NaHCO₃ solution, dried over anhydrous K₂CO₃, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel which was deactivated by Et₃N to give 10e (1.98 g, 1.78 mmol) in 87% yield as a white crystalline solid, which was presumably consisted of diastereoisomers with ~1:1 and 3:1 ratios at the carbons containing the ethereal group and at the acetal carbons, respectively.

Data for the major stereoisomers of 10e: $^1$H NMR δ 1.10 (s, 6H),* 1.11 (s, 6H), 1.23 (s, 6H), 1.27 (s, 6H), 1.32 (s, 6H),* 1.35 (s, 6H), 1.50–1.68 (m, 6H), 1.69 (s, 6H), 1.76 (s, 6H), 1.77 (s, 6H),* 1.80–2.09 (m, 10H), 2.49 (dd, $J = 11.0, 10.1$ Hz, 2H), 3.04 (d, $J = 14.0$ Hz, 2H), 3.42–3.62 (m, 6H), 3.90 (dd, $J = 9.7, 8.4$ Hz, 2H), 4.09 (dd, $J = 11.4, 9.7$ Hz, 2H), 4.18 (m, 2H),* 4.44 (dd, $J = 6.2, 2.6$ Hz, 2H), 4.48 (dd, $J = 6.0, 2.9$ Hz, 2H),* 4.83 (br s, 2H),* 5.03 (br s, 2H), 5.21 (d, $J = 10.7$ Hz, 2H), 5.28 (t, $J = 6.8$ Hz, 2H), 6.03 (d of A of ABq, $J_{AB} = 16.4, J_d = 3.4$ Hz, 2H), 6.11 (d of B of ABq, $J_{AB} = 16.4, J_d = 2.7$ Hz, 2H), 7.47–7.56 (m, 4H), 7.61–7.69 (m, 2H), 7.77–7.84 (m, 4H) ppm; $^{13}$C NMR δ 12.3,* 12.4, 13.7, 17.1, 19.5, 25.5, 26.3,* 26.4, 30.2, 30.3,* 30.5, 37.0, 37.6,* 37.7, 44.5,* 44.5, 51.4, 61.6, 62.7,* 63.4, 72.2, 72.2,* 99.2, 99.2,* 113.9, 124.8, 124.9,* 126.2, 128.9, 129.2, 129.3, 129.4,* 133.9, 137.2, 138.8, 138.8,* 141.0, 141.0,* 141.5,* 141.6, 159.3, 159.4,* 199.0 ppm; IR (KBr) 1677, 1447, 1306, 1147, 1084, 996, 734 cm⁻¹; HRMS (FAB⁺) calcd for C₄₆H₆₂O₈S₂ (C₆₂H₈₃O₁₂S₃ – (2C₅H₈O + C₆H₅O₂S)) 806.3886, found 806.3878.

*: peaks from the 2nd major diastereoisomer
1,18-Bis(3-oxo-4-(t-butyldimethylsiloxy)-2,6,6-trimethyl-1-cyclohexenyl)-5,14-dibenzencesulfonyl-3,7,12,16-tetramethyl-1,3,7,9,11,15,17-eicosaheptaene (11b). Following the general procedure for 8, the reaction of C₄₀ keto-trisulfone compound 10b (663 mg, 0.56 mmol) with NaOCH₃ (305 mg, 5.65 mmol) and CCl₄ (6 mL) in CH₂Cl₂ (6 mL) at room temperature for 3.5 h gave 11b (173 mg, 0.18 mmol) in 32% yield as a mixture of diastereoisomers after purification by column chromatography on silica gel which was deactivated by Et₃N.

Data for the major stereoisomer of 11b: ¹H NMR δ 0.09 (s, 6H), 0.18 (s, 6H), 0.93 (s, 18H), 1.09 (s, 6H), 1.20 (s, 6H), 1.26 (s, 6H), 1.68 (s, 6H), 1.78 (s, 6H), 1.90–2.00 (m, 4H), 2.44 (dd, J = 13.2, 9.2 Hz, 2H), 3.03 (dd, J = 13.2, 8.8 Hz, 2H), 4.05 (dd, J = 9.2, 8.8 Hz, 2H), 4.25–4.37 (m, 2H), 5.24 (d, J = 10.3 Hz, 2H), 5.88 (br s, 2H), 5.93–6.16 (m, 4H), 6.20 (br s, 2H), 7.46–7.55 (m, 4H), 7.60–7.67 (m, 2H), 7.77–7.86 (m, 4H) ppm; ¹³C NMR δ -5.4, -4.5, 12.3, 13.8, 16.5, 18.5, 25.8, 26.2, 30.3, 36.8, 38.0, 46.8, 63.9, 71.0, 125.3, 125.6, 127.8, 128.7, 128.8, 129.2, 132.8, 132.9, 133.7, 137.5, 139.1, 141.1, 159.0, 198.8 ppm; IR (KBr) 1683, 1447, 1306, 1148, 1085 cm⁻¹; HRMS (FAB⁺) calcd for C₆₄H₉₃O₈S₂Si₂ 1109.5850, found 1109.5829.

1,18-bis(3-oxo-4-triisopropylsiloxy-2,6,6-trimethyl-1-cyclohexenyl)-5,14-dibenzencesulfonyl-3,7,12,16-tetramethyl-1,3,7,9,11,15,17-eicosaheptaene (11c). Following the general procedure for 8, the reaction of
C_{40} keto-trisulfone compound 10c (3.09 g, 2.45 mmol) with NaOCH\textsubscript{3} (1.32 g, 24.5 mmol) and CCl\textsubscript{4} (25 mL) in CH\textsubscript{2}Cl\textsubscript{2} (25 mL) at room temperature for 4 h gave 11c (2.25 g, 1.88 mmol) in 77% yield, that was consisted of ~1:1 diastereoisomers presumably at the carbons containing the ethereal group, after purification by column chromatography on silica gel which was deactivated by Et\textsubscript{3}N.

Data for 11c: \textsuperscript{1}H NMR δ 1.11 (s, 42H), 1.19 (s, 6H), 1.20 (s, 6H), \textsuperscript{*} 1.22 (s, 6H), \textsuperscript{*} 1.24 (s, 6H), 1.30 (s, 6H), 1.32 (s, 6H), \textsuperscript{*} 1.68 (s, 6H), 1.78 (s, 6H), 1.79 (s, 6H), \textsuperscript{*} 1.99 (d, J = 7.8 Hz, 4H), 2.32–2.55 (m, 2H), 2.88–3.15 (m, 2H), 4.05 (br t, J = 10.6 Hz, 2H), 4.35–4.50 (m, 2H), 5.24 (d, J = 10.1 Hz, 2H), 5.87 (br s, 2H), 6.00 (d of A of ABq, J\textsubscript{AB} = 16.2, J\textsubscript{d} = 6.5 Hz, 2H), 6.12 (br B of ABq, J\textsubscript{AB} = 16.2 Hz, 2H), 6.20 (br s, 2H), 7.43–7.68 (m, 6H), 7.76–8.07 (m, 4H) ppm; \textsuperscript{13}C NMR (major stereoisomer) δ 12.4, 12.4, 14.0, 16.6, 18.0, 18.0, 26.3, 30.3, 36.9, 38.1, 47.1, 64.2, 70.9, 125.3, 125.7, 127.9, 128.9, 128.9, 129.3, 132.8, 133.0, 133.7, 137.5, 139.1, 141.1, 158.4, 198.8 ppm; IR (KBr) 1686, 1447, 1306, 1147, 1084 cm\textsuperscript{-1}; HRMS (FAB\textsuperscript{+}) calcd for C\textsubscript{70}H\textsubscript{105}O\textsubscript{8}S\textsubscript{2}Si\textsubscript{2} 1193.6789, found 1193.6804.

\textsuperscript{*} peaks from the other diastereoisomer.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=0.2\textwidth]{image}};
\end{tikzpicture}
\end{center}

1,18-Bis(3-oxo-4-tetrahydropyranloxy-2,6,6-trimethyl-1-cyclohexenyl)-5,14-dibenzenesulfonyl-3,7,12,16-tetramethyl-1,3,7,9,11,15,17-eicosaheptane (11e). Following the general procedure for 8, the reaction of C\textsubscript{40} keto-trisulfone compound 10e (0.96 g, 0.86 mmol) with NaOCH\textsubscript{3} (0.56 g, 10.38 mmol) and CCl\textsubscript{4} (20 mL) in CH\textsubscript{2}Cl\textsubscript{2} (30 mL) at room temperature for 3 h gave 11e (0.84 g, 0.80 mmol) in 93% crude
yield as a yellow crystalline solid. The crude product, which contained diastereoisomers with ~1:1 and 3:1 ratios at the carbons containing the ethereal group and at the acetal carbons, respectively, was not stable under silica gel chromatographic condition, but was pure enough to be used in the next dehydrosulfonation step without further purification.

Data for the major stereoisomer of 11e: $^1$H NMR $\delta$ 1.12 (s, 6H), 1.23 (s, 6H), 1.30 (s, 6H), 1.48–1.65 (m, 6H), 1.70 (s, 6H), 1.78 (s, 6H), 1.80–2.10 (s, 10H), 2.44 (dd, $J = 13.4$, 10.8 Hz, 2H), 3.02 (d, $J = 13.7$ Hz, 2H), 3.52 (br s, 2H), 3.89 (br s, 2H), 4.05 (br t, $J = 9.5$ Hz, 2H), 4.43 (dd, $J = 6.4$, 2.9 Hz, 2H), 5.02 (br s, 2H), 5.24 (d, $J = 11.8$ Hz, 2H), 5.87 (br s, 2H), 5.93–6.15 (m, 4H), 6.21 (br s, 2H), 7.40–8.00 (m, 10H) ppm; $^{13}$C NMR $\delta$ 12.3, 13.6, 16.5, 19.5, 25.5, 26.4, 30.2, 30.4, 36.9, 38.1, 44.5, 62.7, 64.0, 72.2, 99.2, 123.9, 125.5, 127.8, 128.8, 129.2, 132.8, 133.7, 137.5, 139.2, 141.0, 144.5, 159.6, 199.0 ppm; IR (KBr) 1677, 1447, 1306, 1146, 1083, 1032, 732 cm$^{-1}$; HRMS (FAB$^+$) calcd for C$_{52}$H$_{65}$O$_8$S$_2$ (C$_{62}$H$_{81}$O$_{10}$S$_2$ – 2C$_5$H$_8$O) 881.4121, found 881.4106.

**Astaxanthin (2).** Following the general procedure for 1, C$_{40}$ keto-disulfone 11e (0.23 g, 0.22 mmol) in benzene (10 mL) reacted with NaOEt, that was prepared by the reaction of Na (98 mg, 4.26 mmol) and 99.9% EtOH (20 mL), at reflux for 16 h to give THP-protected astaxanthin (0.14 g, 0.18 mmol) in 83% crude yield.

THP-protected astaxanthin (0.14 g, 0.18 mmol) then reacted with MeOH (10 mL) and p-toluenesulfonic
acid (p-TsOH, 34 mg, 0.18 mmol) in CH$_2$Cl$_2$ (30 mL) at room temperature for 4 h to give crude astaxanthin.

The crude product was recrystallized from acetone/MeOH to give pure 2 (0.048 g, 0.08 mmol), and the mother liquor was purified again by silica gel column chromatography to give 2 (0.030 g, 0.05 mmol). The combined yield of 2 (0.078 g, 0.13 mmol) in the deprotection step was 72%, and the overall yield of astaxanthin (2) was 60% from 11e.

Data for 2: $^{1}$H NMR $\delta$ 1.21 (6H, s), 1.32 (6H, s), 1.81 (2H, dd, $J = 13.4, 13.2$ Hz), 1.94 (6H, s), 1.99 (6H, s), 2.00 (6H, s), 2.16 (2H, dd, $J = 13.2, 5.5$ Hz), 3.68 (2H, d, $J = 1.8$ Hz), 4.32 (2H, ddd, $J = 13.4, 5.5, 1.8$ Hz), 6.22 (2H, A of ABq, $J_{AB} = 16.0$ Hz), 6.26-6.34 (2H, m), 6.30 (2H, d, $J = 11.5$ Hz), 6.43 (2H, B of ABq, $J_{AB} = 16.0$ Hz), 6.45 (2H, d, $J = 15.0$ Hz), 6.65 (2H, dd, $J = 15.0, 11.5$ Hz), 6.63-6.70 (2H, m) ppm; $^{13}$C NMR $\delta$ 12.6, 12.8, 14.0, 26.1, 30.7, 36.8, 45.4, 69.2, 123.3, 124.6, 126.8, 130.7, 133.8, 134.6, 135.2, 136.7, 139.7, 142.3, 162.2, 200.4 ppm.

Astacene (3). Following the general procedure for 1, C$_{40}$ keto-disulfone 11c (0.70 g, 0.59 mmol) in benzene (10 mL) reacted with NaOEt, that was prepared by the reaction of Na (270 mg, 11.73 mmol) and 99.9% EtOH (20 mL), at reflux for 19 h to give crude astacene. The crude product was purified by silica gel flash column chromatography to give 3 (250 mg, 0.42 mmol) in 71% yield as a dark-red solid.

Data for 3: $^{1}$H NMR $\delta$ 1.30 (12H, s), 1.59 (2H, s), 2.00 (6H, s), 2.03 (6H, s), 2.10 (6H, s), 6.06 (2H, s), 6.31 (2H, d, $J = 15.9$ Hz), 6.34 (2H, d, $J = 10.7$ Hz), 6.43 (2H, s), 6.48 (2H, A of ABq, $J_{AB} = 15.6$ Hz), 6.52
(2H, B of ABq, $J_{AB} = 15.6$ Hz), 6.68 (2H, dd, $J = 15.9$, 10.7 Hz) ppm; $^{13}$C NMR $\delta$ 12.6, 12.8, 13.7, 28.2, 28.2, 39.3, 123.1, 124.6, 125.5, 128.3, 130.7, 133.9, 134.7, 135.4, 136.8, 139.8, 142.5, 144.5, 161.4, 182.5 ppm; IR (KBr) 3398, 1624, 1247, 1064, 968 cm$^{-1}$. 