

First Total Synthesis of Cucurbitaxanthin A Applying Regioselective Ring Opening of Tetrasubstituted Epoxides

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The synthesis of cucurbitaxanthin A **1** was accomplished via the C₁₅-3,6-epoxides **7e** and **7f** prepared by regioselective ring opening of the 3-hydroxy-5,6-epoxides **6e** and **6f**.

Key words cucurbitaxanthin A; 3,6-epoxide; tetrasubstituted epoxide; ring opening; total synthesis

There are many xanthophylls that hypothetically are assumed to be derived from 5,6-epoxy-carotenoids through ring opening of the epoxy moiety. Cucurbitaxanthin A **1** (Chart 1) with a 3,6-epoxy-end group is isolated from both the red paprika *Capsicum annuum*^{1,2)} and pumpkin *Cucurbita maxima*³⁾ and capsanthin **2** with a κ -end group is isolated from the former. Both carotenoids are also considered²⁾ to be formed in nature from 5,6-epoxy-carotenoids.

From the previous results⁴⁾ in the reaction of epoxides **3a–e** with an olefinic group at C-6⁵⁾ (Chart 2) with Lewis acid, we found that the direction of the oxirane ring cleavage depended upon both the length of conjugated double bond system and the electron-withdrawing ability of the substituents adjacent to the double bond. Epoxides **3a** and **3d** carrying a strong electron-withdrawing group (EWG) predominantly provided the cyclopentyl ketones **5a** and **5d**, respectively, via cleavage of the oxirane ring at the C-5 position (route *b*), whereas 5,6-epoxides **3b**, **3c**, and **3e** only gave 5,8-epoxides **4b**, **4c**, and **4e**, respectively, via opening of the

C-6-oxygen bond of the oxirane ring (route *a*). The biomimetic-type total synthesis of capsanthin **2** was accomplished⁴⁾ using regio- and stereoselective rearrangement of the C₁₅-epoxy dienal with a silyloxy group at C-3, as shown in Chart 1 (route *b*).

There has been a report⁶⁾ concerning the attempted synthesis of cycloviolaxanthin, a carotenoid with a 3,6-epoxy end group. Here we describe the first total synthesis of the 3,6-epoxy-carotenoid cucurbitaxanthin A **1** (Chart 1) applying biomimetic-type ring opening (route *a*) of the 3-hydroxy-C₁₅-epoxy dienone and dienitrile.

First, we investigated the ring opening of epoxides **6a–f**⁷⁾ (Chart 3, Table 1), which has a hydroxy group at C-3, toward the synthesis of cucurbitaxanthin A **1**. Treatment of epoxides **6a** and **6b** carrying a strong EWG with SnCl₄ or the aminium salt **10**⁸⁾ resulted in the formation of a complicated mixture including cyclopentyl ketones **9a** and **9b** (entries 1–3 in the Table 1). In the case of epoxides **6c** and **6d**, which do not have an EWG, the desired 3,6-epoxides **7c** and **7d** were formed by the opening of the C-6-oxygen bond of the oxirane ring and subsequent ring closing from the C-3-hydroxy group (entries 5, 6). However, preferential migration of the 7,8-double bond to the attack of the C-3-hydroxy group gave 5,8-epoxides **8c** and **8d** as major products. Introduction of weak EWGs (entries 8, 9) improved the yield of the desired 3,6-epoxides **7e** and **7f**.⁹⁾ Formation of the 3,6-epoxides would require both ease of ring opening at C-6 and difficult migration of the 7,8-double bond. Thus in dienoate and dienitrile systems, the conjugated double bond would tend to be retained in the original moieties.

As shown in Chart 4, epoxides **6e** and **6f** were prepared from the known C₁₀-epoxy aldehyde **12**, which was recently synthesized by Katsumura's group¹⁰⁾ via a Sharpless asymmetric epoxidation of the corresponding allylic alcohol derived from the optically active hydroxyketone **11**.¹¹⁾ Emmons-Horner reaction of the aldehyde **12** with the phospho-

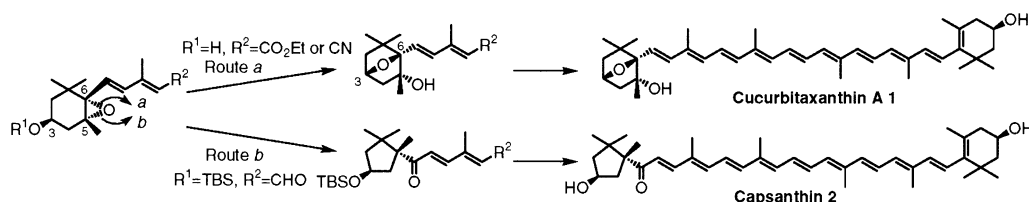


Chart 1

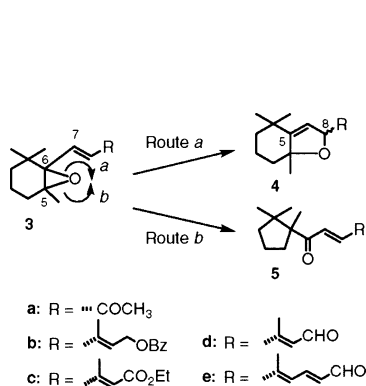


Chart 2

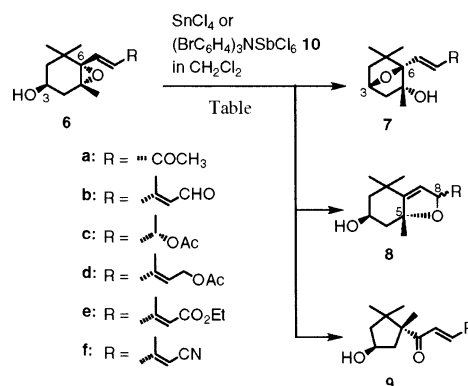
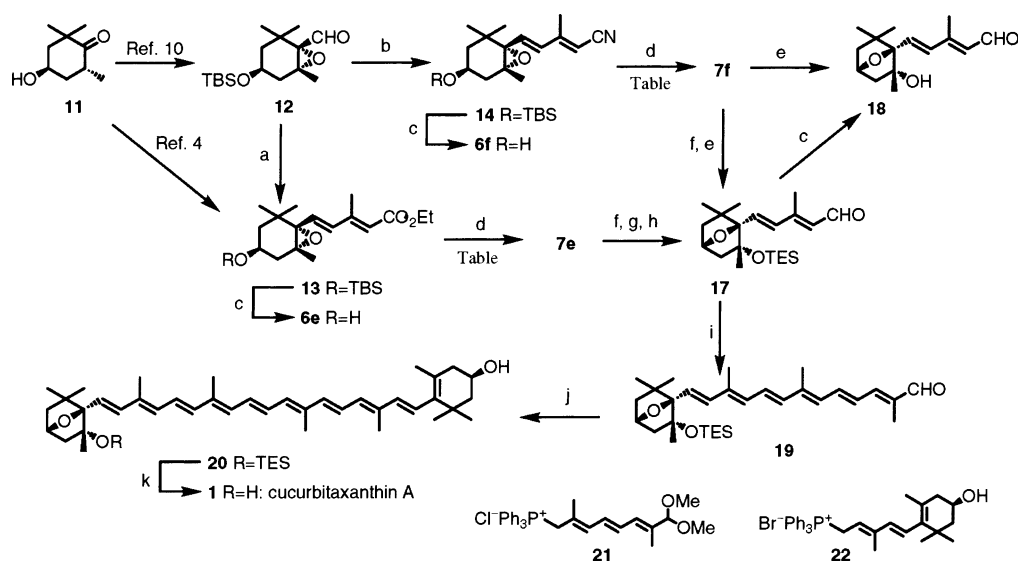


Chart 3

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a) $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{C}(\text{Me})=\text{CHCO}_2\text{Et}$ **15**/ $n\text{-BuLi}$; b) $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{C}(\text{Me})=\text{CHCN}$ **16**/ NaH ; c) $\text{HF}\cdot\text{Py}$; d) $(\text{BrC}_6\text{H}_4)_3\text{NSbCl}_6$ **10**; e) DIBAL-H; f) TESOTf/lutidine; g) LiAlH_4 ; h) MnO_2 ; i) **21**, NaOMe then Dowex (H^+); j) **22**, NaOMe; k) TBAF-AcOH, 50°C

Chart 4

Table 1. Ring Opening of 3-Hydroxy Epoxides **6a–f**

Entry	Substrate	Conditions	Isolated yield (%)		
			7	8 ^a	9
1	6a	SnCl_4 (2 eq), rt, 1 h	—	—	25
2	6a	10 (0.1 eq), rt, 3 h	—	—	6
3	6b	SnCl_4 (2 eq), rt, 1 h	—	—	20
4	6c	SnCl_4 (2 eq), 0°C , 20 min	—	44	—
5	6c	10 (0.1 eq), rt, 30 min	20	47	6
6	6d	10 (0.1 eq), rt, 30 min	9	68	—
7	6e	SnCl_4 (2 eq), 0°C , 15 min	16	32	—
8	6e	10 (0.1 eq), rt, 20 min	45	35	—
9	6f	10 (0.2 eq), rt, 2 h	54	—	—

a) Isomeric mixture. rt, room temperature.

nate **15** gave the all-*E* dienoate **13** (67%) and its 9*Z* isomer (26%), while the reaction of **12** with the phosphonate **16**¹²⁾ afforded the all-*E* dienonitrile **14** (80%) accompanied by its 9*Z* isomer (15%). *tert*-Butyldimethylsilyl (TBS) groups in compounds **13** and **14** were deprotected to give the hydroxy compounds **6e** (98%) and **6f** (96%), which were treated with the aminium salt **10** (Table 1, entries 8, 9) to provide 3,6-epoxides **7e** (45%) and **7f** (54%), respectively. This is the first example of 7-oxabicyclo[2.2.1]heptyl end group formation from a 3-hydroxy-5,6-epoxy end group.

Then compounds **7e** and **7f** were transformed into the dienal **18**. Reduction of the ester group in **7e** with LiAlH_4 and subsequent oxidation of the resulting alcohol with MnO_2 resulted in a complex mixture, probably due to oxidative cleavage of the C5–6 bond. Thus after protection of the C-5-hydroxy group in **7e** by a triethylsilyl (TES) group, the resulting silyl ether was converted into the aldehyde **17** (94%; three steps), which was deprotected to give compound **18** (84%). In the case of the nitrile **7f**, the aldehyde **18** was directly obtained (69%) by reduction with diisobutylaluminum hydride (DIBAL-H).

Unfortunately, the Wittig condensation of the aldehyde **18**

with the C_{10} -phosphonium salt **21**¹³⁾ was unsuccessful because of the instability of **18** under basic conditions. Thus the TES-protected aldehyde **17**, which could be also derived in two steps (81%) from the nitrile **7f**, was condensed with the phosphonium salt **21** in the presence of NaOMe as a base and then treated in one pot with ion-exchange resin, Dowex 50W-X8 (H^+), to lead a mixture of the all-*E* C_{25} -apocarotenal **19** (53%) accompanied by some isomers.

Finally, apocarotenal **19** was condensed with C_{15} -Wittig salt **22**,^{4,14)} followed by purification of the condensed products by preparative HPLC to provide the all-*E* skeletal compound **20** (56%), which was deprotected to furnish cucurbitaxanthin A **1** (54%) along with some recovery (32%) of **20**. Spectral data (IR, UV-VIS, ^1H -NMR, MS, and CD) of synthetic **1** were in good agreement with those of a natural specimen.^{1–3,15)} To the best of our knowledge, this is the first report of the total synthesis of optically active cucurbitaxanthin A.

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- 9) Compound **7e** was obtained (45%) together with the 5,8-epoxide **8e**

(35%) and compound **7f** was obtained (54%) accompanied by some unidentified compounds.

Compound **7e**: $^1\text{H-NMR}$ (CDCl_3) δ : 0.87, 1.19 (each 3H, s), 1.28 (3H, t, $J=7$ Hz), 1.44 (3H, s), 1.62 (1H, d, $J=11.5$ Hz), 1.68 (1H, d, $J=12.5$ Hz), 1.84 (1H, ddd, $J=11.5, 6, 2$ Hz), 2.05 (1H, ddd, $J=12.5, 6, 2$ Hz), 2.30 (3H, d, $J=1$ Hz), 4.17 (2H, q, $J=7$ Hz), 4.40 (1H, t, $J=6$ Hz), 5.80 (1H, brs), 6.15, 6.36 (each 1H, d, $J=15.5$ Hz). IR (CHCl_3) cm^{-1} : 3609, 3489, 1702, 1683, 1620. HR-MS m/z : 294.1831 (Calcd for $\text{C}_{17}\text{H}_{26}\text{O}_4$: 294.1830). $[\alpha]_{\text{D}}^{25} -24.6^\circ$ ($c=1.06$ in MeOH).

Compound **7f**: $^1\text{H-NMR}$ (CDCl_3) δ : 0.86, 1.19, 1.44 (each 3H, s), 1.63, 1.68 (each 1H, d, $J=12$ Hz), 1.84, 2.06 (each 1H, ddd, $J=12, 6, 2$ Hz), 2.18 (3H, d, $J=1$ Hz), 4.41 (1H, t, $J=6$ Hz), 5.23 (1H, brs), 6.15, 6.40 (each 1H, d, $J=16$ Hz). IR (CHCl_3) cm^{-1} : 3605, 3484, 2214, 1640, 1591. HR-MS m/z : 247.1569 (Calcd for $\text{C}_{15}\text{H}_{21}\text{O}_2$: 247.1571).

$[\alpha]_{\text{D}}^{25} -26.0^\circ$ ($c=1.00$ in MeOH).

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