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

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Received March 3, 2004; accepted April 5, 2004

The synthesis of cucurbitaxanthin A 1 was accomplished *via* the C_{15}-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 considered[2] to be formed in nature from 5,6-epoxy-carotenoids.

From the previous results[4] in the reaction of epoxides **3a**—**e** with an olefinic group at C-6[5] (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 accomplished[4] using regio- and stereoselective rearrangement of the C_{15}-epoxy dienal with a silyloxy group at C-3, as shown in Chart 1 (route *b*).

There has been a report[6] 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-C_{15}-epoxy dienonate and dienonitrile.

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 $SnCl_4$ 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 dienonitrile 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 C_{10}-epoxy aldehyde **12**, which was recently synthesized by Katsumura's group[10] *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-

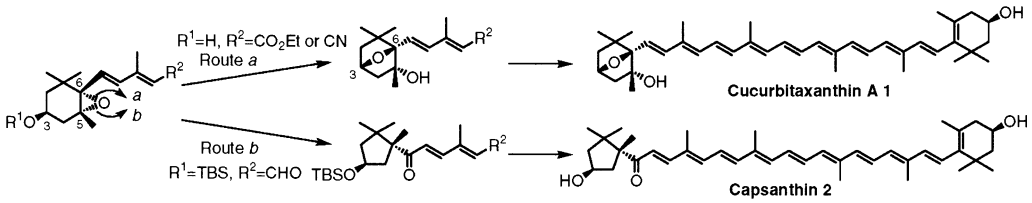

Chart 1

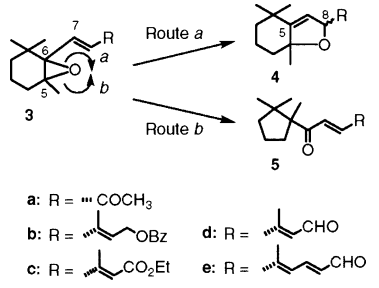

Chart 2

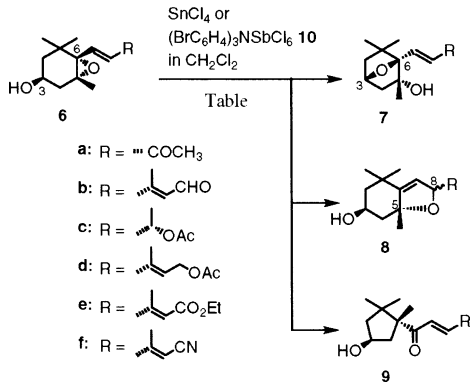

Chart 3

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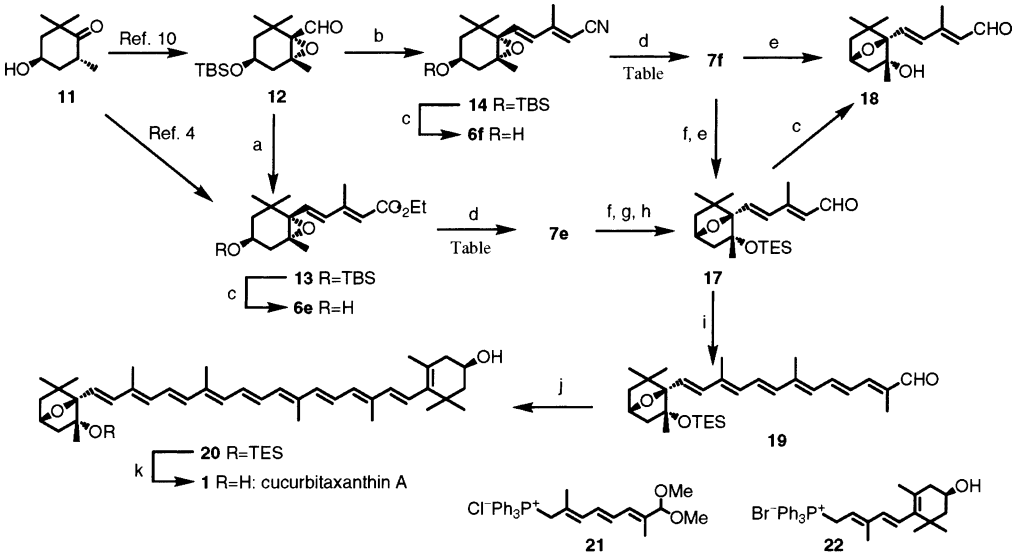

a) $(EtO)_2P(O)CH_2C(Me)=CHCO_2Et$ **15**/*n*-BuLi; b) $(EtO)_2P(O)CH_2C(Me)=CHCN$ **16**/NaH; c) HF•Py; d) $(BrC_6H_4)_3NSbCl_6$ **10**; e) DIBAL-H; f) TESOTf/lutidine; g) $LiAlH_4$; h) MnO_2; i) **21**, NaOMe then Dowex (H^+); j) **22**, NaOMe; k) TBAF-AcOH, 50°C

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 diisobutylaluminium 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, ^{1}H-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.

Acknowledgments We are indebted to Dr. T. Maoka, Research Institute of Production Development, Kyoto, for his invaluable gift of natural cucurbitaxanthin A. We appreciate Drs. U. Hengartner and K. Bernhard, Hoffmann-La Roche Ltd., Basel, Switzerland, for their gift of the optically active hydroxyketone **11**. We also thank Mr. M. Yamada and Miss K. Muranushi for technical assistance.

References and Notes

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7) These epoxides were prepared from the ketone **11**.
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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}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, br s), 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 $C_{17}H_{26}O_4$: 294.1830). $[\alpha]_D^{25}$ −24.6° (c=1.06 in MeOH).

Compound **7f**: ^{1}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, br s), 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 $C_{15}H_{21}O_2$: 247.1571). $[\alpha]_D^{25}$ −26.0° (c=1.00 in MeOH).

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