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 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 annuum1,2) and pumpkin Cucurbita maxima3) 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 a), 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 accomplished41) using regio- and stereoselective rearrangement of the C-15-epoxy dienial with a silyloxy group at C-3, as shown in Chart 1 (route b).

There has been a report6) concerning the attempted synthesis of cycloviolexanthin, 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 epoxide dienolate and dienonitrile.

First, we investigated the ring opening of epoxides 6a—f7) (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 108) 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 dienolate 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 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-
nate 15 gave the all-\(E\) dienoate 13 (67%) and its 9Z isomer (26%), while the reaction of 12 with the phosphonate 16 afforded the all-\(E\) dienonitrile 14 (80%) accompanied by its 9Z 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 LiAlH4 and subsequent oxidation of the resulting alcohol with MnO2 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 disobutylaluminium hydride (DIBAL-H).

Unfortunately, the Wittig condensation of the aldehyde 18 with the C10-phosphonium salt 21 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-\(E\) C25-apocarotenal 19 (53%) accompanied by some isomers.

Finally, apocarotenal 19 was condensed with C10-Wittig salt 22, 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. To the best of our knowledge, this is the first report of the total synthesis of optically active cucurbitaxanthin A.

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References and Notes


5) We employed the numbering system used in carotenoids.


7) These epoxides were prepared from the ketone 11.


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

### Table 1. Ring Opening of 3-Hydroxy Epoxides 6a—f

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conditions</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6a SnCl4 (2 eq), rt, 1 h</td>
<td>—</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>6a 10 (0.1 eq), rt, 3 h</td>
<td>—</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>6b SnCl4 (2 eq), rt, 1 h</td>
<td>—</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>6c SnCl4 (2 eq), 0°C, 20 min</td>
<td>—</td>
<td>44</td>
</tr>
<tr>
<td>5</td>
<td>6e 10 (0.1 eq), rt, 30 min</td>
<td>20</td>
<td>47</td>
</tr>
<tr>
<td>6</td>
<td>6d 10 (0.1 eq), rt, 30 min</td>
<td>9</td>
<td>68</td>
</tr>
<tr>
<td>7</td>
<td>6e SnCl4 (2 eq), 0°C, 15 min</td>
<td>16</td>
<td>32</td>
</tr>
<tr>
<td>8</td>
<td>6e 10 (0.1 eq), rt, 20 min</td>
<td>45</td>
<td>35</td>
</tr>
<tr>
<td>9</td>
<td>6f 10 (0.2 eq), rt, 2 h</td>
<td>54</td>
<td>—</td>
</tr>
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</table>

a) Isomeric mixture. rt, room temperature.
Compound 7e: 1H-NMR (CDCl₃) 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 (CHCl₃) cm⁻¹: 3609, 3489, 1702, 1683, 1620. HR-MS m/z: 294.1831 (Calcd for C₁₇H₂₆O₄: 294.1830). [α]D²⁵ = 24.6° (c = 1.06 in MeOH).

Compound 7f: 1H-NMR (CDCl₃) 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 (CHCl₃) cm⁻¹: 3605, 3484, 2214, 1640, 1591. HR-MS m/z: 247.1569 (Calcd for C₁₅H₂₁O₂: 247.1571). [α]D²⁵ = 26.0° (c = 1.00 in MeOH).

15) This was kindly supplied by Dr. T. Maoka, Research Institute of Production Development, Kyoto. The CD spectrum of the synthetic sample was superimposable on that of a natural specimen.