Total Synthesis of Capsanthin Using Lewis Acid-Promoted Regio- and Stereoselective Rearrangement of Tetrasubstituted Epoxide

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The synthesis of capsanthin 1 was accomplished via the C₁₅-cyclopentyl ketone 13 prepared by Lewis acid-promoted regio- and stereoselective rearrangement of the epoxide 12.

Key words capsanthin; tetrasubstituted epoxide; regio- and stereoselective rearrangement; total synthesis

Previously, we reported ¹) the first biomimetic type total synthesis of both crassostreaxanthin B 2 (Fig. 1) possessing a novel acyclic-tetrasubstituted olefinic end group and mytiloxanthin 3 containing a cyclopentyl enolic β-diketone group applying stereoselective rearrangement of tetrasubstituted epoxide.²) In these syntheses, we employed epoxides, in which substituents at the C-6³) position were alkyl groups having an oxygen functional group as shown in Chart 1.

Capsanthin 1 (Fig. 1), having a κ-end group, is a main pigment of red paprika Capsicum annuum and has become the center of attention due to its strong antioxidant activities.⁴) There has been only one report by Weedon’s group⁵) concerning its synthesis. Here, we describe the total synthesis of 1 via regio- and stereoselective rearrangement of the C₁₅-epoxide 12 (Chart 3) having a conjugated olefinic group at C-6, which was efficiently derived from the optically active (4R,6R)-4-hydroxy-2,2,6-trimethylcyclohexanone,⁶) It has been known that the rearrangement of the epoxide 4b⁷) (Chart 2) only provided the flanoid 5b by opening of C-6-oxygen bond of the oxirane ring (route a) and subsequent migration of the 7,8-double bond, whereas that of the epoxide 4a⁸) predominantly produced the cyclopentyl ketone 6a by cleavage of the oxirane ring at the C-5 position (route b) and successive ring contraction. It is considered that the selective cleavage of epoxide 4a at C-5 was promoted by destabilization of the cation at C-6 due to the electron deficiency of 7(β)-carbon on α,β-unsaturated carbonyl group.

Thus, the reaction of epoxides 4c–e⁹) having an olefinic group conjugated to a carbonyl group at C-6 (Chart 2) was investigated toward the synthesis of 1. As a result, treatment of the epoxide 4d with SnCl₄ was found to give predominantly the desired cyclopentyl ketone 6d (91%). On the other hand, the reaction of the epoxides 4c and 4e with SnCl₄ preferentially provided flanoids 5c (86%; 5,8-trans¹⁰):5,8-cis¹⁰) = 8:1) and 5e (53%; 5,8-trans:5,8-cis = 5:1). These results show that the direction of C–O bond cleavage in the oxirane ring depends upon both the length of conjugated double bond system and the electron-withdrawing ability of the substituent adjacent to the double bond.

In order to synthesize 1, C₁₅-epoxide 12 was prepared via stereo-controlled cross-coupling reaction of the vinylstannane 8 with the vinyl triflate 15¹¹ as shown in Chart 3. The known¹²) terminal alkyne 7, prepared (62%) from (4R,6R)-4-hydroxy-2,2,6-trimethylcyclohexanone,⁶) was heated at 130 °C for 20 min with an excess amount (4 eq) of Bu₃SnH in the presence of a catalytic amount of azobisisobutyronitrile (AIBN)¹³) to give stereoselectively the E-vinylstannane 8 in 88% yield. Cross-coupling reaction of 8 with 15¹¹) by combined use of tris(dibenzylidene-acetone)dipalladium (Pd₂dba₃) and AsPh₃ (ligand)¹⁴) in N,N-dimethylformamide (DMF) at 50 °C gave the all-E trienoate 9 (93%), whose hydroxy group at C-3 was protected (93%) with tert-butyldimethylsilyl (TBS) group. The resulting TBS ether 10 was then treated with m-chloroperbenzoic acid (m-CPBA) to give a mixture of the anti(α)-epoxide 11a (28%) and syn(β)-epoxide 11b (54%). Reduction of 11a with LiAlH₄ followed by MnO₂-oxidation gave the C₁₅-epoxy-aldehyde 12 in 98% yield.

Treatment of the epoxide 12 with SnCl₄ followed by desilylation yielded the regio- and stereoselective rearranged product 13¹⁵) in good yield, which was then condensed with the Wittig salt 16¹⁶) in the presence of NaOMe as a base followed by one-pot treatment with ion exchange resin, Dowex 50W-X8 (H⁺), to give a mixture of the all-E C₂₅-apocarotenal 14a (39%), the 11Z isomer 14b (28%) and 13Z one 14c (9%). Both isomers 14b and 14c could be transformed (64% from 14b; 70% from 14c) into the desired all-E one 14a by

\[ \text{capsanthin} \longrightarrow \text{crossostreaxanthin B} \rightarrow \text{mytiloxanthin} \]

\[ \text{route a} \]

\[ \text{route b} \]

\[ \text{Chart 1} \]

\[ \text{Chart 2} \]

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Finally, C25-apocarotene-14a was condensed with C15-Wittig salt 17,18, which was prepared from trienoate 9 by reduction with LiAlH4 followed by treatment with PPh3·HBr, to give the condensed products (quant.), which was purified by preparative HPLC to afford all-E capsanthin (42%). Its spectral data [IR, UV-VIS, 1H- and 13C-NMR, MS, and CD (circular dichroism)] were in good agreement with those reported.5

Biological activities of capsanthin except for the antioxidant function are now extensively under investigation.

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References and Notes

3) We have employed the numbering system used in carotenoids.
10) These epoxides were prepared from β-ionone.
15) Compound 13: 1H-NMR (CDCl3) δ: 0.85, 1.22 and 1.39 (each 3H, s), 1.52 (1H, dd, J=14.5, 3.5 Hz), 1.74 (1H, dd, J=13.5, 4.5 Hz), 1.99 (1H, dd, J=13.5, 8 Hz), 2.32 (3H, d, J=1=14.5, 8.5 Hz), 4.51 (1H, m), 6.21 (1H, br d, J=8 Hz), 6.88 (1H, d, J=15.5 Hz), 7.26 (1H, d, J=15.5 Hz), 10.18 (1H, d, J=15.5 Hz). IR (CHCl3) cm−1: 3605, 3466, 1567, 1589. HR-MS m/z: 250.1568 (Calcd for C15H22O3: 250.1566); [α]D25 = 15.2° (c=1.12 in MeOH).