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 C_{15}-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-6[3] 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 group[5] concerning its synthesis. Here, we describe the total synthesis of **1** *via* regio- and stereoselective rearrangement of the C_{15}-epoxide **12** (Chart 3) having a conjugated olefinic group at C-6, which was efficiently derived from the optically active (4*R*,6*R*)-4-hydroxy-2,2,6-trimethylcyclohexanone.[6]

It has been known that the rearrangement of the epoxide **4b**[7] (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 **4a**[8] 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**—**e**[9] 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 $SnCl_4$ was found to give predominantly the desired cyclopentyl ketone **6d** (91%). On the other hand, the reaction of the epoxides **4c** and **4e** with $SnCl_4$ preferentially provided flanoids **5c** (86%; 5,8-*trans*[10] : 5,8-*cis*[10] = 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**, C_{15}-epoxide **12** was prepared *via* stereo-controlled cross-coupling reaction of the vinylstannane **8** with the vinyl triflate **15**[11] as shown in Chart 3. The known[12] terminal alkyne **7**, prepared (62%) from (4*R*,6*R*)-4-hydroxy-2,2,6-trimethylcyclohexanone,[6] was heated at 130 °C for 20 min with an excess amount (4 eq) of Bu_3SnH 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 **15**[11] by combined use of tris(dibenzylidene-acetone)dipalladium (Pd_2dba_3) and $AsPh_3$ (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*-butlydimethylsilyl (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 $LiAlH_4$ followed by MnO_2-oxidation gave the C_{15}-epoxy-aldehyde **12** in 98% yield.

Treatment of the epoxide **12** with $SnCl_4$ followed by desilylation yielded the regio- and stereoselective rearranged product **13**[15] in good yield, which was then condensed with the Wittig salt **16**[16] 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* C_{25}-apocarotenal **14a** (39%), the 11*Z* isomer **14b** (28%) and 13*Z* 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

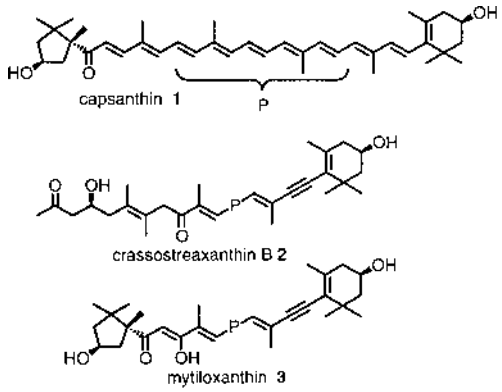

Fig. 1

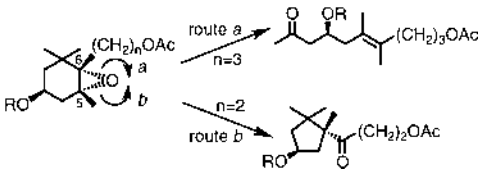

Chart 1

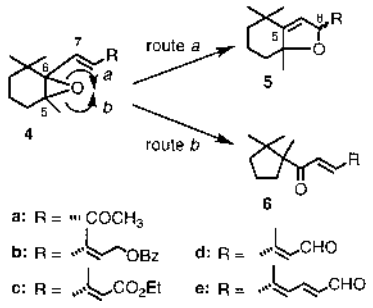

Chart 2

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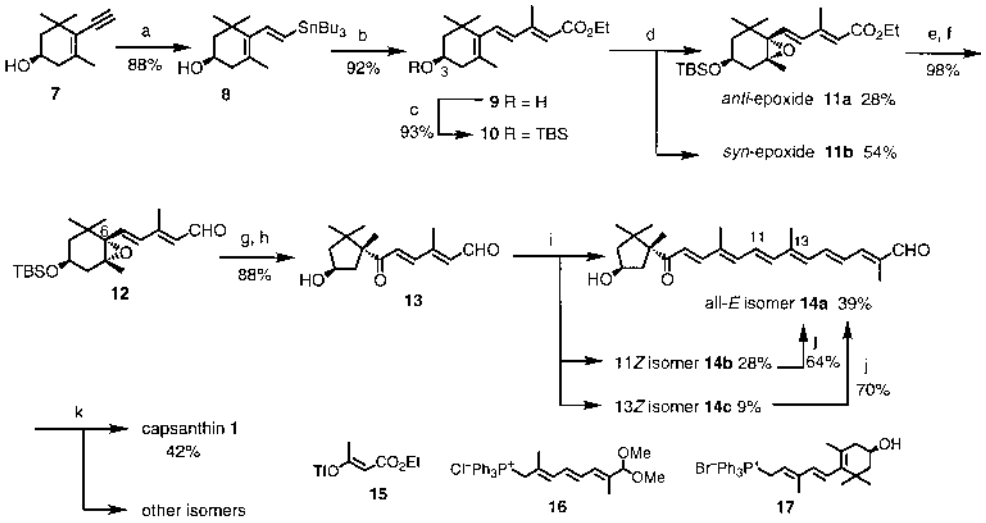

a) Bu_3SnH, cat. AIBN / 130°C; b) **15**, cat. $AsPh_3$, cat. $Pd_2dba_3{\cdot}CHCl_3$ / 50°C; c) TBSCl, DMAP, Et_3N; d) *m*-CPBA; e) $LiAlH_4$; f) MnO_2; g) $SnCl_4$; h) HF; i) **16**, NaOMe then Dowex(H^+); j) cat. $PdCl_2(MeCN)_2$, Et_3N; k) **17**, NaOMe

Chart 3

palladium-catalyzed isomerization.[17] Finally, C_{25}-apocarotenal **14a** was condensed with C_{15}-Wittig salt **17**,[18] which was prepared from trienoate **9** by reduction with $LiAlH_4$ followed by treatment with $PPh_3 \cdot HBr$, to give the condensed products (quant.), which was purified by preparative HPLC to afford all-*E* capsanthin (42%). Its spectral data [IR, UV-VIS, ^{1}H- and ^{13}C-NMR, MS, and CD (circular dichroism)] were in good agreement with those reported.[5]

Biological activities of capsanthin **1** except for the antioxidant function are now extensively under investigation.

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References and Notes

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15) Compound **13**: ^{1}H-NMR ($CDCl_3$) 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=1.5 Hz), 2.91 (1H, dd, J=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=8 Hz). IR ($CHCl_3$) cm^{-1}: 3605, 3466, 1667, 1589. HR-MS *m*/*z*: 250.1560 (Calcd for $C_{15}H_{22}O_3$: 250.1568). $[\alpha]_D^{25}$ −15.2° (*c*=1.12 in MeOH).
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