TOTAL SYNTHESIS OF PHOTOSYNTHETIC PIGMENT FUCOXANTHIN BY USE OF OXO-METALLIC CATALYST

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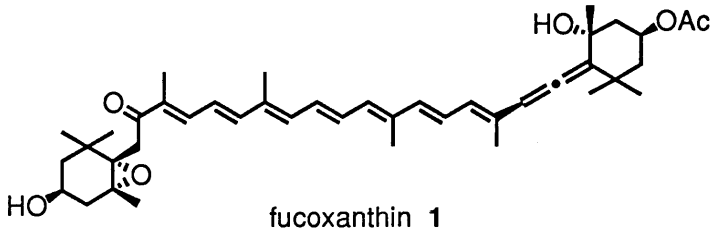
The first total synthesis of optically active fucoxanthin **1** has been accomplished *via* the 8-oxo-compound **7**, efficiently prepared by rearrangement of the α-acetylenic alcohol **2** using oxo-metallic catalyst and subsequent iodine catalyzed double bond-shift.

KEYWORDS fucoxanthin; carotenoid; rearrangement; oxo-metallic catalyst

The allenic carotenoid fucoxanthin **1**[1] is known to be widely distributed in brown algae and to function as a light harvesting pigment[2] for photosynthesis in the sea. In order to elucidate the fucoxanthin-protein interaction in algal photosynthetic pigment systems and to clarify the antenna function by chemical methods, development of a synthetic method for fucoxanthin molecule has been strongly desired for a long time. Moreover, it has recently been found[3] that **1** has effective antiproliferative and antitumor promoting activities. Here we wish to describe the first total synthesis of optically active **1**.

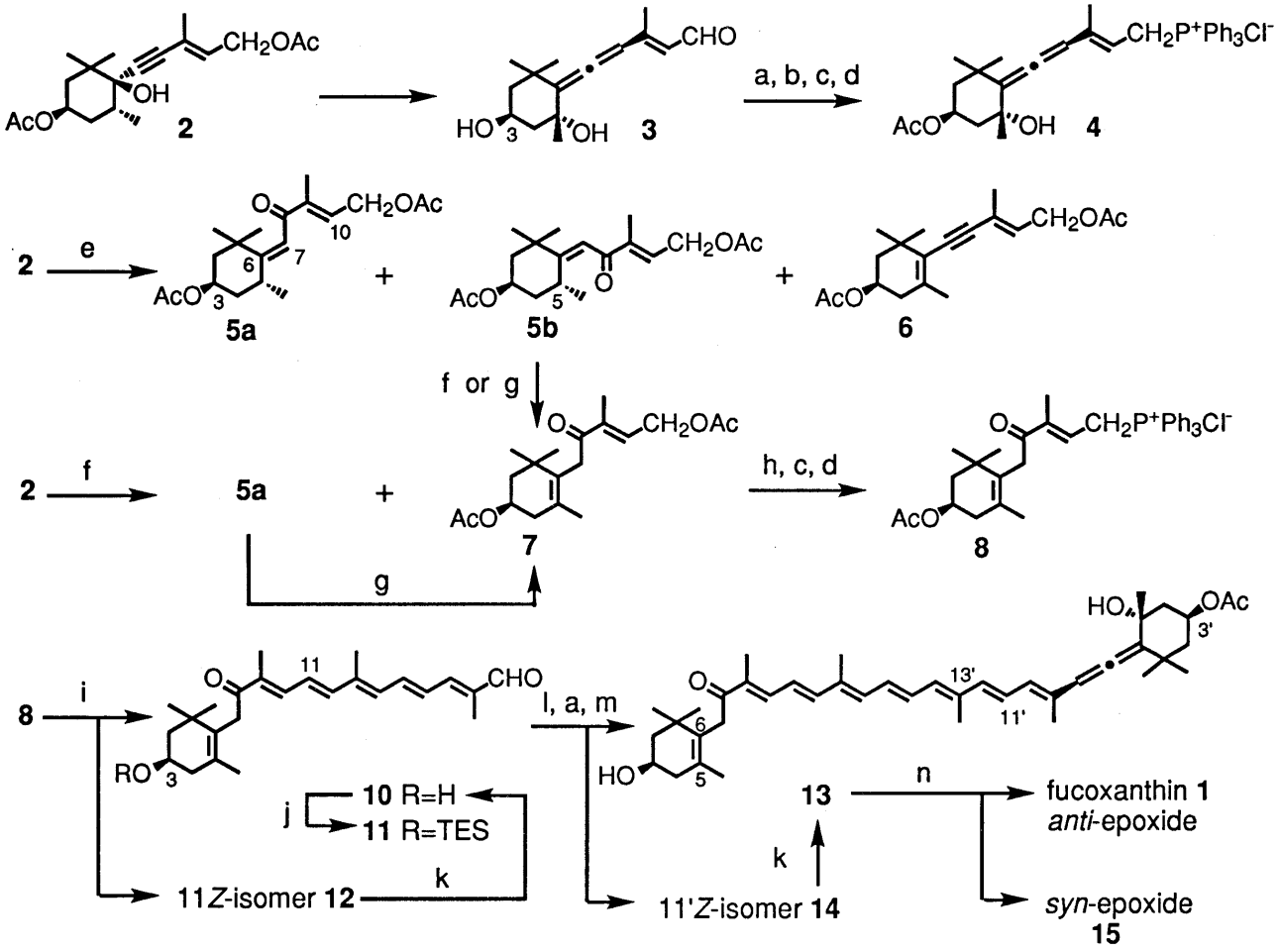


fucoxanthin **1**

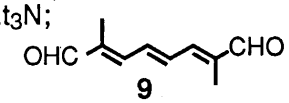
As shown in the Scheme, epoxidation of 5,6-double bond in the fucoxanthin skeletal compound **13** was employed at the final step because of an extreme alkali-lability[4] of β,γ-epoxy-keto-moiety in **1**. The compound **13** (C_{40}) was constructed by the Wittig reaction of C_{10}-dialdehyde **9** with two kinds of C_{15}-Wittig salts **4** and **8**, which were synthesized from the previously prepared[5] common intermediate **2** in an optically active form (97% ee) starting from the readily available (4*R*,6*R*)-4-hydroxy-2,2,6-trimethylcyclohexanone.

The allenic Wittig salt **4** was synthesized in 4 steps from the allenic aldehyde **3**, whose preparation from **2** was reported.[5] The 8-oxo-Wittig salt **8** was constructed by the application of the key reaction, i.e., the rearrangement of α-acetylenic alcohols to α,β-unsaturated carbonyl compounds by oxo-metallic catalysts[6] and subsequent iodine catalyzed double bond-shift. Reaction of the α-acetylenic alcohol **2** with catalytic amount of tetrabutylammonium perrhenate and *p*-toluenesulfonic acid[6a] at room temperature afforded the rearranged α,β-unsaturated ketones **5a** (6*Z*-isomer) (32%) and **5b** (6*E*-isomer) (50%) accompanied by the dehydrated product **6** (14%). On the other hand, treatment of **2** with tris(triphenylsilyl)vanadate catalyst[6b] in refluxing xylene gave α,β- and β,γ-unsaturated ketones **5a** (35%) and **7** (58%).[7] Under the reaction conditions, **5b** was converted to the β,γ-unsaturated ketone **7** (81%); nevertheless **5a** was not changed. Thus, **7** was assumed to be derived from the 6*E*-isomer **5b** by intramolecular hydrogen shift (C_5 to carbonyl oxygen). In addition, transformation of the

6*Z*-isomer **5a** to **7** was achieved in 80% yield by treatment with iodine in refluxing heptane. This reaction was found to proceed through the intermediate 6*E*-isomer **5b**, which was isolated in the course of the conversion. The structures of **5a,b** and **7** were determined on the basis of the IR and ^{1}H-NMR data[8] including NOE experiments. The 8-oxo-compound **7** was transformed in 3 steps into the Wittig salt **8** in 60% yield.



a) Ac_2O-Py; b) $NaBH_4$; c) LiCl-MsCl-γ-collidine; d) PPh_3; e) Bu_4NReO_4-*p*-TsOH, CH_2Cl_2, rt; f) $(Ph_3SiO)_3VO$-Ph_3SiOH-$PhCO_2H$, xylene, reflux; g) cat. I_2, heptane, reflux; h) 10%K_2CO_3; i) **9**, NaOMe then, 10% NaOH; j) TESOTf-γ-collidine; k) $PdCl_2(CH_3CN)_2$-Et_3N; l) **4**, NaOMe; m) TBAF-AcOH; n) MCPBA



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The Wittig condensation of **8** with C_{10}-dialdehyde **9** in the presence of NaOMe as a base and followed by hydrolysis afforded a mixture of the all-*E*-8-oxo-apocarotenal **10** (32%) and the 11*Z*-isomer **12** (29%). The latter was isomerized to the former in 94% yield by treatment[9] with palladium catalyst. After protection (79%) of the hydroxyl group of **10**, the product **11** was treated with the allenic Wittig salt **4** with NaOMe as a base to give a mixture of the condensed products which was acetylated and desilylated by the combined use of tetrabutylammonium fluoride (TBAF) and acetic acid to provide the all-*E*-fucoxanthin skeletal compound **13** (25%) and its 11'*Z*-isomer **14** (31%). These structures were characterized by spectral data.[8] Isomerization of the 11'*Z*-isomer

14 using palladium catalyst[9] afforded the all-*E*-isomer **13** in 45% yield. Finally, epoxidation of **13** with MCPBA followed by HPLC purification furnished a mixture (36%) of the *syn*-epoxide **15** and the *anti*-one **1** with the recovery (27%) of **13**. Separation of the epoxide mixture by preparative HPLC using a chiral column (CHIRALCEL OD; DAICEL) gave **15** (28%) and **1** (8%) in pure form, respectively. Spectral data (IR, UV-VIS, ^{1}H-NMR[10] and MS), including CD data of synthetic fucoxanthin **1**, were identical with those of natural specimen.

This is the first total synthesis of optically active fucoxanthin. Thus, this route has general applicability to the synthesis of a variety of fucoxanthin analogues.

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7) In this reaction, only a small amount of 6*E*-isomer **5b** was detected by HPLC.
8) Characteristic ^{1}H-NMR data (in $CDCl_3$) for compounds **5a,b**, **7**, **13** and **14** are as follows:
5a; δ(500 MHz): 1.12 (3H, d, *J* 6.5, 5-Me), 2.78 (1H, m, 5-H), 5.77 (1H, d-like, *J* 1.5, 7-H).
5b; δ(500 MHz): 1.31 (3H, d, *J* 7.5, 5-Me), 3.57 (1H, qdd, *J* 7.5, 6, 1.5, 5-H), 6.38 (1H, s, 7-H).
7; δ(200 MHz): 1.45 (3H, s, 5-Me), 3.43 (2H, s, 7-H_2). **13**; δ(500 MHz): 1.99 (3H, s, 13'-Me), 6.13 (1H, dd-like, *J* 11.5, 1, 10'-H), 6.35 (1H, d, *J* 15, 12'-H), 6.59 (1H, dd, *J* 15, 11.5, 11'-H).
14; δ(500 MHz): 2.12 (3H, s, 13'-Me), 5.98 (1H, d, *J* 12, 12'-H), 6.27 (1H, t, *J* 12, 11'-H), 6.63 (1H, br d, *J* 12, 10'-H).
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