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First Total Synthesis of Mytiloxanthin

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The first total synthesis of mytiloxanthin 2 was accomplished *via* the cyclopentyl ketone 7 prepared by stereoselective rearrangement of the epoxide 4a.

Key words mytiloxanthin; stereoselective rearrangement; cyclopentyl compound; conjugated enolic β-diketone; total synthesis

Recently, we found1) that the acyclic-tetrasubstituted olefinic compounds and cyclopentyl ketones were derived by Lewis acid-promoted stereoselective rearrangement of epoxy compounds as shown in Chart 1. Then, the first biomimetic total synthesis of crassostreaxanthin B **1** (Fig. 1) with a novel acyclic-tetrasubstituted olefinic end group was accomplished2) applying this rearrangement reaction.

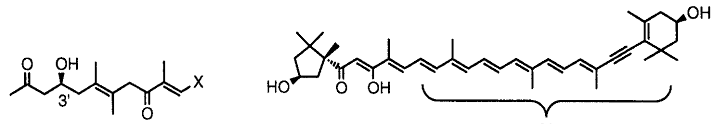
Mytiloxanthin **2** (Fig. 1), containing a unique cyclopentyl enolic β-diketone group conjugated to the polyene chain, was first isolated from *Mytilus californianus* by Scheer3) in 1940, and the structure and synthesis of the 9*Z*-isomer were reported by Weedon's group.4) Its absolute configuration was determined by Maoka and Fujiwara5) in 1996. The cyclopentyl end group of mytiloxanthin **2** is biogenetically believed4) to arise from a pinacollic rearrangement of the epoxy end group of 5,6-epoxy carotenoids.6) Here, we describe the biomimetic total synthesis of mytiloxanthin **2** by the application of the same rearrangement.

Among several epoxides (Chart 1) previously investigated,1*b*) epoxide **3** (Chart 2) with the acetoxy ethane group at the C-6 position provided the cyclopentyl compound by treatment with $BF_3 \cdot OEt_2$. However, this reaction proceeded very slowly and resulted in low-yield formation of the C-5 diastereomer **5** instead of the desired compound **6**. To obtain **6** effectively, we explored other Lewis acids involving aminium salts. As a result, treatment of epoxide **3** with tris(4-bromophenyl)aminium hexachloroantimonate7) was found to afford **6** in reasonable yield (69%). Thus we planned the biomimetic synthesis of **2** using a rearrangement of epoxide **4** with *tert*-butyldimethylsilyl (TBS) ether as a protecting group through the C_{15}-aldehyde **8** possessing an enolic β-diketone moiety as shown in Chart 2.

Epoxides **4a** and **b** were derived from the previously prepared optically active aldehyde **9**2) by reduction with $NaBH_4$, followed by acetylation and subsequent epoxidation with *m*-chloroperbenzoic acid (*m*-CPBA) (**4a**: 26% from **9**; **4b**: 46% from **9**) as shown in Chart 3. The *anti*(α)-epoxide **4a** was then treated with aminium salt7) to give the stereoselective rearranged product, cyclopentyl ketone **7**, in 63% yield, from which construction of an enolic β-diketone moiety was carried out as follows. Reduction of the ketone **7** with $NaBH_4$ and protection of the resulting hydroxy group with *p*-methoxybezyloxymethyl (PMBM) chloride8) gave compound **11**, which was converted to aldehyde **12** by reduction with $LiAlH_4$ and subsequent oxidation with *o*-iodoxybenzoic acid (IBX).9) The C_4-unit was then introduced into **12** by reaction with vinyl bromide **13**10) in the presence of *tert*-BuLi. The resulting alcohol was oxidized with IBX to yield the ketone **14**, which after deprotection of the PMBM group with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)8*b*) was transformed by dimethyl sulfoxide (DMSO) oxidation into the enolic β-diketone **16** (10% from **7**: 8 steps).

Unfortunately, direct conversion of **16** into the C_{15}-β-diketone-aldehyde **8a** (Chart 2) by deprotection of the allylic TBS group and subsequent oxidation of the resulting alcohol using several reagents (IBX, MnO_2, *etc.*) was unsuccessful, leading to the formation of complicated products, probably due to the instability of the β-diketone moiety. Thus after protection of the diketone moiety in **16** by an acetyl group, the resulting acetate **17** was transformed into the C_{15}-aldehyde **8b**.11) Partial deprotection of the allylic TBS group in **17** with tetrabutylammonium fluoride (TBAF) followed by oxidation with IBX and subsequent deprotection of the another TBS group with HF afforded **8b** (43% from **16**: 4 steps).

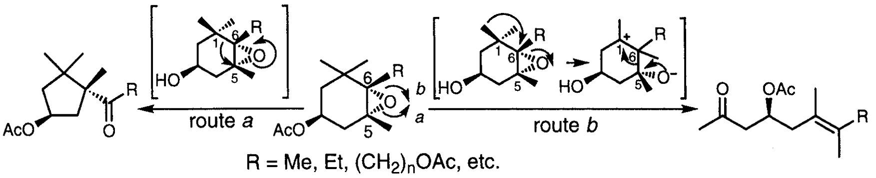
Next, the C_{15}-aldehyde **8b** was allowed to react with the C_{10}-phosphonium salt **18**12) in the presence of KOH as a base to give condensed products which were subjected to acid hydrolysis to afford an isomeric mixture of C_{25}-apocarotenals **19** (92% from **8b**). Finally, this mixture **19** was condensed with the acetylenic Wittig salt (C_{15}) **20**13) in the presence of KOH to give the condensed products (30%), repeated purification of which by preparative HPLC led to all-*E* mytiloxan-



Crassostreaxanthin B **1**

Mytiloxanthin **2**

Fig. 1



R = Me, Et, $(CH_2)_nOAc$, etc.

Chart 1

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thin **2** accompanied by 9*Z*, 9*Z*,11*Z* and unidentified isomers (all-*E* : 9*Z* : 9*Z*,11*Z*~1 : 1 : 1). The spectral data (IR, UV-VIS, ^{1}H-NMR, MS, and CD [circular dichroism]) of synthetic mytiloxanthin[14] were in good agreement with those of a natural specimen.[5] This is the first total synthesis of optically active all-*E* mytiloxanthin.

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References and Notes

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11) Compound **8b**: ^{1}H-NMR (CDCl$_3$) δ: 0.84 (3H, s), 1.19 (3H, s), 1.35 (3H, s), 1.46 (1H, dd, J=14.5, 3 Hz), 1.70 (1H, dd, J=14, 5 Hz), 1.96 (1H, dd, J=14, 8 Hz), 2.31 (3H, s), 2.33 (3H, s), 2.85 (1H, dd, J=14.5, 8.5 Hz), 4.47 (1H, m), 6.37 (1H, d, J=7.5 Hz), 6.60 (1H, s), 10.17 (1H, d, J=7.5 Hz). IR (CHCl$_3$) cm^{-1}: 3611, 3476, 1773, 1674, 1588. UV $\lambda_{\max}$ (EtOH) nm: 283. HRMS *m/z*: 308.1648 (calcd. for $C_{17}H_{24}O_5$: 308.1625). $[\alpha]_D^{26}$ $-10.0°$ (c=0.40 in CHCl$_3$).
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14) all-*E* Mytiloxanthin: ^{1}H-NMR (CDCl$_3$) δ: 0.85 (3H, s), 1.14 (3H, s), 1.19 (3H, s), 1.20 (3H, s), 1.35 (3H, s), 1.45 (1H, t), 1.55 (1H, m), 1.71 (1H, dd), 1.83 (1H, m), 1.92 (3H, s), 1.98 (6H, s), 1.99 (3H, s), 2.01 (3H, s), 2.07 (1H, m), 2.09 (1H, dd), 2.43 (1H, dd), 2.88 (1H, dd), 4.00 (1H, m), 4.52 (1H, m), 5.86 (1H, s), 6.28 (1H, d), 6.36 (1H, d), 6.38 (1H, d), 6.46 (1H, d), 6.55 (1H, dd), 6.60 (1H, dd), 6.64 (1H, dd), 6.65 (1H, d), 6.71 (1H, dd), 7.23 (1H, d). UV-VIS $\lambda_{\max}$ (EtOH) nm: 470. HRMS *m/z*: 598.4016 (calcd. for $C_{40}H_{54}O_4$: 598.4025).

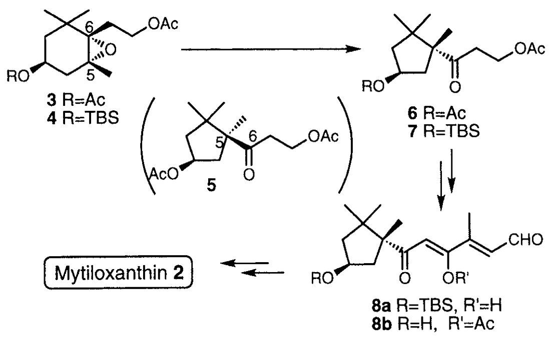
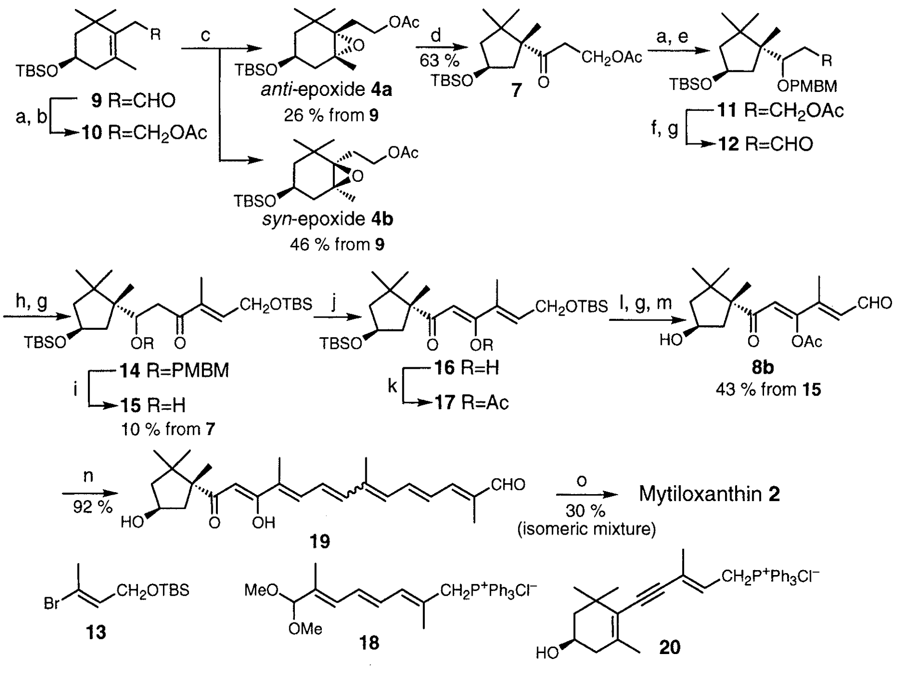


Chart 2



a) NaBH$_4$ / MeOH; b) Ac$_2$O, Py; c) *m*-CPBA / CH$_2$Cl$_2$; d) (p-BrC$_6$H$_4$)$_3$N$^{\bullet+}$SbCl$_6^-$ / CH$_2$Cl$_2$; e) PMBMCl, (*i*-Pr)$_2$EtN / CH$_2$Cl$_2$; f) LiAlH$_4$ / Et$_2$O; g) IBX / DMSO; h) **13**, *t*-BuLi / Et$_2$O; i) DDQ / CH$_2$Cl$_2$-H$_2$O (18 : 1); j) DMSO, Ac$_2$O; k) Ac$_2$O, DMAP, Et$_3$N / CH$_2$Cl$_2$; l) TBAF / THF; m) HF / CH$_3$CN-THF (9 : 1); n) **18**, KOH / *i*-PrOH then H$^+$; o) **20**, KOH / *i*-PrOH

Chart 3