COMMUNICATION
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First total synthesis of crassostreaxanthin B

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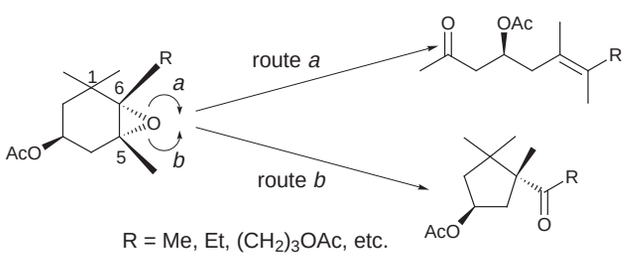
The first total synthesis of crassostreaxanthin B 1 was accomplished *via* the tetrasubstituted olefinic compound 5, prepared by stereoselective rearrangement of epoxides 3a,b using a Lewis acid.

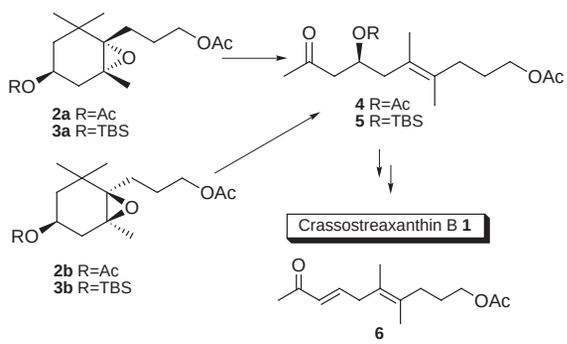
Crassostreaxanthin B **1** having a novel acyclic tetrasubstituted olefinic end group was isolated from *Crassostrea gigas*[1] and its stereostructure including C-3 chirality (3*R*) was determined by Matsuno's group in 1992. However, the absolute configuration at C-3′ has remained undetermined. We assumed that this end group was formed in nature from the epoxide end group of 5,6-epoxy carotenoids† by opening of the C-6–oxygen bond of the oxirane ring (Scheme 1, route *a*). Thus, the absolute



Scheme 1

configuration at C-3′ in crassostreaxanthin B **1** is considered to be *S*, since chiralities at C-3 in most of the known natural epoxy carotenoids are *R*. In previous papers,[2,3] we reported that the novel acyclic tetrasubstituted olefinic end group and cyclopentyl end group of carotenoids were obtained by Lewis acid-promoted stereoselective rearrangement of the epoxy end group of 5,6-epoxy carotenoids as shown in Scheme 1. This is the first example of biomimetic formation of end groups possessing an acyclic tetrasubstituted olefin. Herein, we wish to describe the first total synthesis of crassostreaxanthin B **1** applying the stereoselective rearrangement of epoxides with a Lewis acid and the determination of the absolute configuration at C-3′ in native samples.

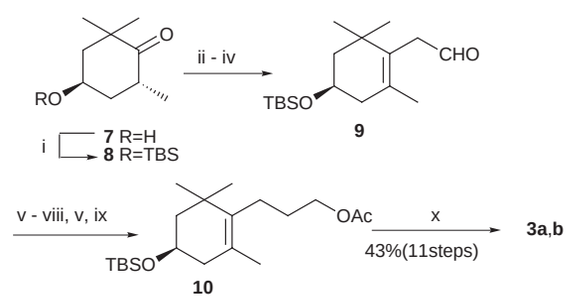
Toward the biomimetic synthesis of crassostreaxanthin B **1**, we previously investigated[3] the reaction of epoxides having several functional groups at the C-6 position with $BF_3{\cdot}OEt_2$. As a result, a promising rearrangement reaction was found; epoxides **2a**,**b** possessing the acetoxy propane group provided the tetrasubstituted olefinic compound **4** in reasonable yield, however, accompanied by the elimination product **6** (Scheme 2). Thus, epoxides **3a**,**b** having a TBS (*tert*-butyldimethylsilyl) ether



Scheme 2

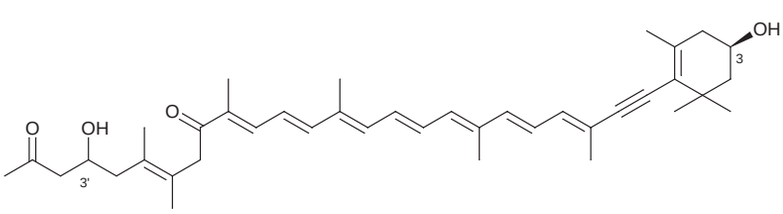
as the protecting group should be appropriate synthons for the biomimetic synthesis of **1**.

Epoxides **3a**,**b** were prepared in 11 steps from the known optically active ketone **7**[4] in good overall yield (43%) as shown in Scheme 3. Introduction of an ethynyl group to the silyloxy

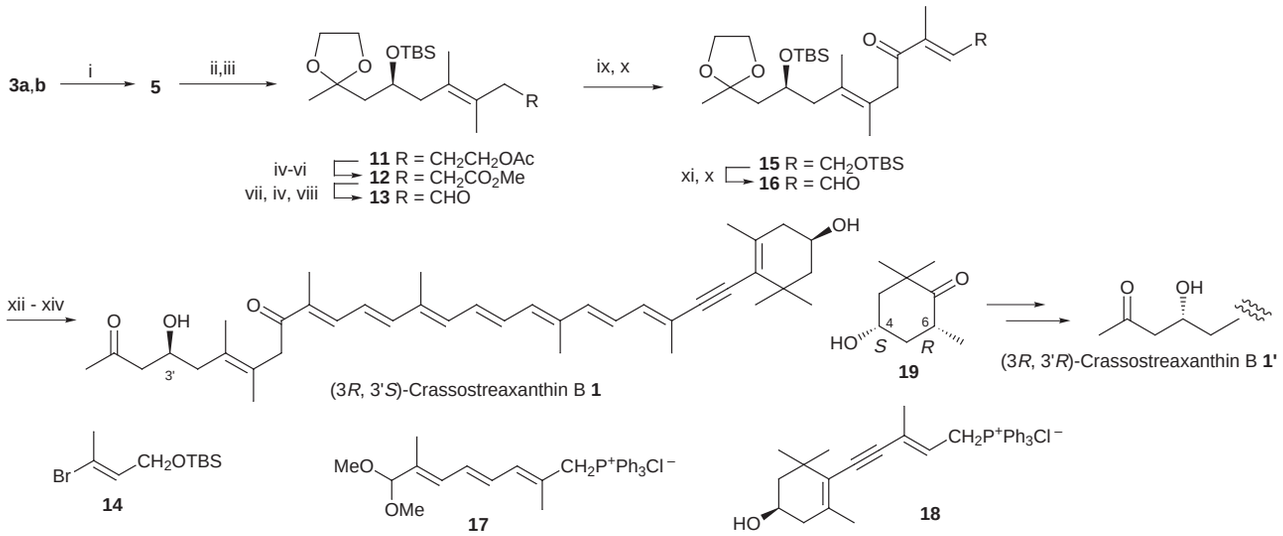


Scheme 3 *Reagents and conditions*: i, TBSCl, Et_3N, DMAP; ii, LiC≡CTMS; iii, 10% aq. KOH; iv, $(Ph_3SiO)_3VO$, $PhCO_2H$, xylene, reflux; v, $NaBH_4$; vi, MsCl, Py; vii, KCN, 18-crown-6, DMSO, 120 °C; viii, DIBAL-H; ix, Ac_2O, Py; x, MCPBA.

ketone **8**[5] and subsequent rearrangement of the resulting product using tris(triphenylsilyl)vanadate[6] as the catalyst yielded the aldehyde **9**, whose carbon chain extension was accomplished by the usual method to give compound **10**. Epoxidation of **10** with MCPBA led to both isomers (*anti*:*syn* = 2:3) of **3** which, without separation were treated with $SnCl_4$ to provide the stereoselective rearranged product, *E*-tetrasubstituted olefin **5**, in reasonable yield (60%). Ketaliz-



Crassostreaxanthin B **1**



Scheme 4 *Reagents and conditions*: i, $SnCl_4$, −78 °C; ii, $(CH_2OTMS)_2$, TMSOTf; iii, TBSOTf, 2,6-lutidine(2,6-dimethylpyridine); iv, LAH; v, PDC, DMF; vi, $TMSCHN_2$; vii, LDA, (+)-camphorylsulfonyloxaziridine; viii, $NaIO_4$; ix, **14**, *t*-BuLi; x, MnO_2; xi, TBAF; xii, **17**, 1 M NaOMe then H^+; xiii, **18**, 1 M NaOMe; xiv, *p*-TsOH.

ation of this olefin **5** and reprotection of the hydroxy group gave compound **11**, which was converted into the ester **12** by LAH reduction followed by PDC oxidation and subsequent methylation (Scheme 4). Introduction of a hydroxy group into the ester **12** by use of (+)-camphorylsulfonyloxaziridine[7] in the presence of LDA followed by reduction with LAH afforded the glycol, which was subjected to glycol cleavage with $NaIO_4$ to give the aldehyde **13** (23% from **5**). Reaction of this aldehyde **13** with vinyl bromide **14**[8] in the presence of *t*-BuLi and subsequent oxidation of the resulting hydroxy group with MnO_2 yielded the ketone **15**. Partial deprotection of the allylic TBS group in **15** with TBAF (tetrabutylammonium fluoride) afforded the allylic alcohol, which was oxidized with MnO_2 to provide the keto-aldehyde **16** (59%, from **13**). Then a double Wittig condensation of the aldehyde **16** with the Wittig salts **17**[9] and **18**[10] in the presence of 1 M NaOMe as base, followed by deprotection of ketal and TBS groups using *p*-TsOH led to (3*R*,3′*S*)-crassostreaxanthin B **1** (6%, from **16**). Spectral data (IR, UV–VIS, ^{1}H-NMR and MS) of synthetic crassostreaxanthin B **1** were in good agreement with those of a natural specimen.[11] However, the absolute configuration at C-3′ in the native sample could not be confirmed by comparison of synthetic and natural samples of CD data because these did not exhibit a clear Cotton effect. Therefore, (3*R*,3′*R*)-crassostreaxanthin B **1′** was independently synthesized from the (4*S*,6*R*)-hydroxy ketone **19**.[4] HPLC separation of **1** and **1′** was clearly accomplished using a chiral column (Chiralcel OD; Daicel). Synthetic (3*R*,3′*S*)-crassostreaxanthin B **1** was confirmed to be identical with a natural specimen by co-chromatography. Consequently, the absolute configuration at C-3′ in the natural specimen was determined to be *S*.

This is the first biomimetic total synthesis of the optically active crassostreaxanthin B **1** using the stereoselective rearrangement of epoxides **3a**,**b** with Lewis acid.

Acknowledgements

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Notes and references

† We have employed the numbering system used in carotenoids.

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11 An authentic sample of natural crassostreaxanthin B was kindly furnished by Dr T. Maoka, Kyoto Pharmaceutical University.

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