COMMUNICATION

Stereoselective rearrangement of 5,6-epoxy carotenoid model compounds

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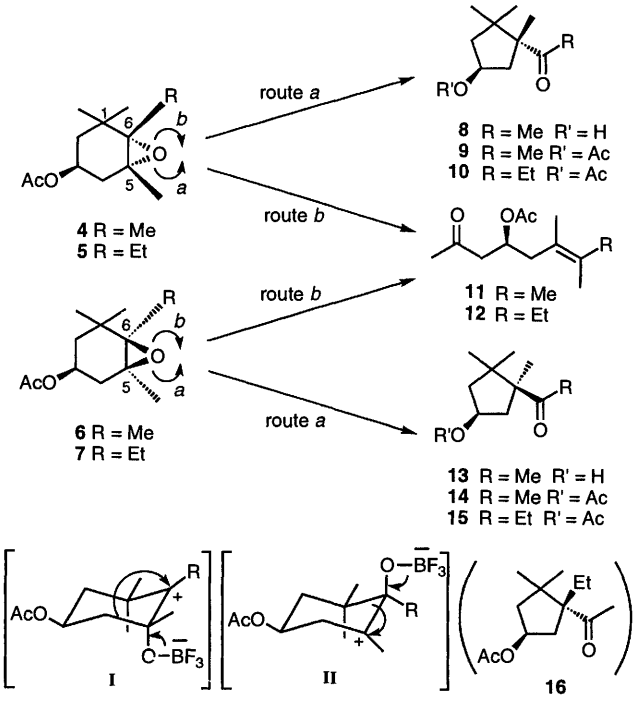
Carotenoids with novel acyclic tetrasubstituted olefinic and cyclopentyl end groups are obtained by Lewis acid-promoted stereoselective rearrangement of the epoxide end group of 5,6-epoxy carotenoids.

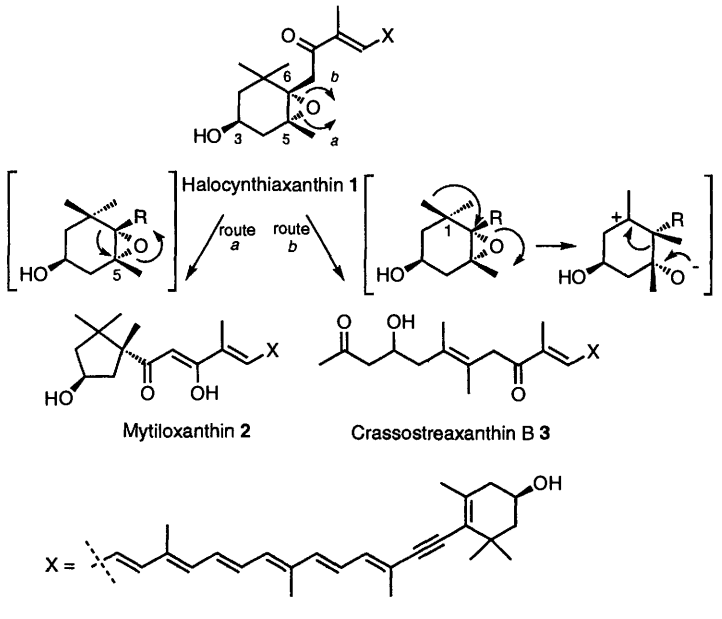
Marine carotenoids halocynthiaxanthin **1**,[1] mytiloxanthin **2**[2] and crassostreaxanthin B **3**[1b,3] (Scheme 1) have characteristic structures, commonly possessing a monoacetylenic end group. The cyclopentyl end group of mytiloxanthin **2** is believed[4] to be formed in nature from the epoxide end group of 5,6-epoxy carotenoids† such as halocynthiaxanthin **1** by cleavage of the oxirane ring at the C-5 position and successive ring contraction (a pinacolic rearrangement) (Scheme 1, route *a*). It is also conceivable that crassostreaxanthin B **3**, including the novel tetrasubstituted olefinic end group, arises from epoxy carotenoids by opening of the C-6–oxygen bond of the oxirane ring and subsequent migration of the methyl group at the C-1 position (route *b*). In order to confirm chemically the hypothetical biosynthetic mechanism of these carotenoids, we examined the reaction of epoxides **5** and **7** (Scheme 2) having a part structure of epoxy carotenoids with Lewis acids.

Rüttimann reported[5] that treatment of epoxides **4** and **6** with BF_3·OEt_2 followed by hydrolysis yielded cyclopentyl methyl ketones **8** and **13**, respectively, each as a single product in up to 70% yield. Then he proposed the possible intermediates I and II deriving from 'axial' cleavage of the respective epoxides. However, the mechanism for the formation of the methyl ketone **8** from the *anti*-epoxide **4** is in conflict with the proposed biosynthetic mechanism[4] of mytiloxanthin **2**. Since substituents at the C-5 and C-6 positions of these epoxides are both methyl groups, the direction of the oxirane ring opening can not be proved. Thus, epoxides **5** and **7** having an ethyl group at C-6 were treated with BF_3·OEt_2.



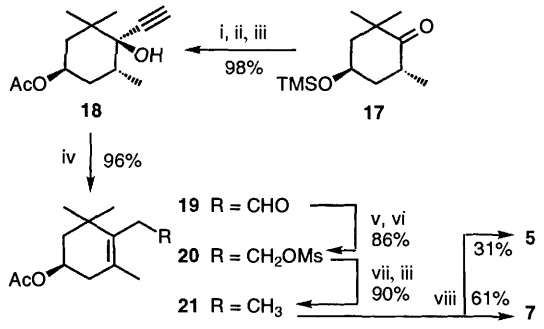
Scheme 2

† We have employed the numbering system used in carotenoids.



Scheme 1

Epoxides **5** and **7** were prepared in 9 steps from the known[6] optically active ketone **17** in good overall yield as shown in Scheme 3. The key step was the effective conversion of the



Scheme 3 *Reagents and conditions:* i, LiC≡CTMS; ii, 10% aq. KOH; iii, Ac_2O, py; iv, TPSV, $PhCO_2H$, xylene, reflux; v, $NaBH_4$; vi, MsCl, py; vii, $LiAlH_4$, THF, reflux; viii, MCPBA

α-acetylenic alcohol **18** into the β,γ-unsaturated aldehyde **19** using tris(triphenylsilyl)vanadate (TPSV) as the catalyst.[7] Application of the modified conditions [TPSV (0.02 equiv.) and $PhCO_2H$ (0.02 equiv.) in the absence of triphenylsilanol] to the alcohol **18** afforded the desired aldehyde **19** in high yield. Relative configurations between acetoxy and epoxy groups in epoxides **5** and **7** were confirmed by their ^1H NMR spectroscopic data.[6]

Reaction of the *anti*-epoxide **5** with BF_3·OEt_2 (3 equiv.; CH_2Cl_2; −78 °C for 3 h, then 0 °C for 1 h) gave the acyclic tetrasubstituted olefinic methyl ketone **12** (54%) having the partial structure of crassostreaxanthin B **3**, and the cyclopentyl ethyl ketone **10** (31%) possessing the same configuration as mytiloxanthin **2** (Scheme 2). In this reaction, the cyclopentyl methyl ketone **16** arising through the intermediate I[5] was not obtained. Thus, it was found that in the epoxide **5** cleavage of the oxirane ring at C-6 (route *b*) did not induce the skeletal transformation into the compound **16** but caused the migration of the methyl group at C-1 to give the compound **12**. On the other hand, the five-membered ethyl ketone **10** was formed in the same pathway as the proposed biosynthetic mechanism[4] of mytiloxanthin **2** (route *a*). Then, the same treatment of the *syn*-epoxide **7** provided the cyclopentyl ethyl ketone **15** (44%) and the compound **12** (49%). In addition, predominant formation of the novel olefinic methyl ketone **12** was found by treatment of the epoxide **5** with $SnCl_4$ (2 equiv.; −20 °C for 30 min, then 0 °C for 3 h) (**10**: trace; **12**: 70%) and tris(4-bromophenyl)aminium hexachloroantimonate[8] (0.1 equiv.; room temp. for 1.5 h) (**10**: 12%; **12**: 71%).

Stereostructures of cyclopentyl ethyl ketones **10** and **15** were determined by the comparison of their ^1H NMR data with those of the known[9] five-membered methyl ketones **9** and **14**. The structure of the novel compound **12** was confirmed on the basis of its spectral data (see Experimental section), which failed to prove the geometry of the tetrasubstituted double bond. Thus, it was chemically determined by the synthesis of both isomers **12′** and **29** as shown in Scheme 4.

Reaction of the ketone **22** with phosphorothioate **24** prepared according to the literature[10] and following reduction of the products gave alcohols **25** and **26**, whose stereochemistries were determined by their NOESY measurements, shown in Scheme 4. Spectral properties of the *E*-olefinic methyl ketone **12′** derived from the alcohol **26** were in good agreement with those of the compound **12** obtained from rearrangement of epoxides **5** and **7**. In the NOESY spectra of the *Z*-isomer **29**, cross-peaks between the methylene protons of the ethyl group and methylene protons at the C-5 position were observed. Hence, the stereoselective formation of the compound **12** from both *anti*- and *syn*-epoxides **5** and **7** could be accounted for through a concerted antiperiplanar pathway.

In addition, reaction of epoxides **4** and **6** with BF_3·OEt_2 was reinvestigated. In the case of *syn*-epoxide **6**, only the five-membered methyl ketone **14** was obtained, whereas in the case of the *anti*-epoxide **4**, the olefinic ketone **11** was found to be formed together with compound **9** (*ca.* 1:1).

This is the first report of novel acyclic tetrasubstituted olefinic compounds being produced by rearrangement of tetrasubstituted epoxides. These results support the proposed metabolism of 5,6-epoxy carotenoids.

Work is in progress on the biomimetic synthesis of **2** and **3** using the present results.

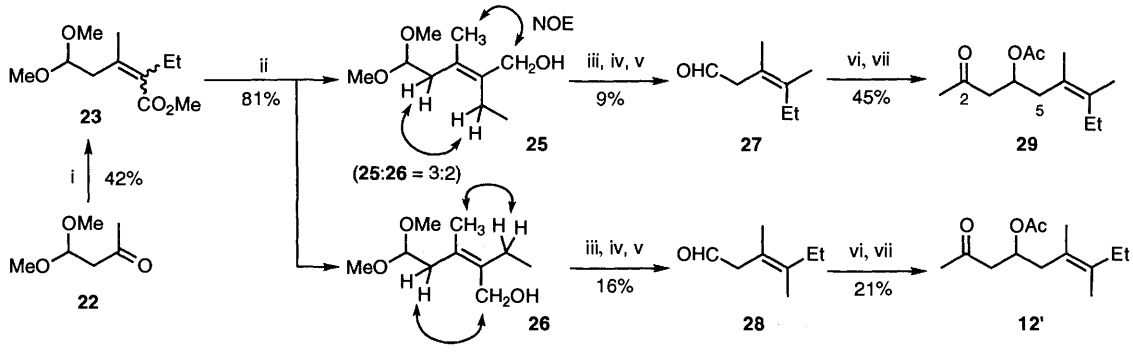
Experimental

Treatment of the *anti*-epoxide 5 with BF_3·OEt_2

To a stirred solution of the *anti*-epoxide **5** (300 mg, 1.3 mmol) in CH_2Cl_2 (10 cm^3) was added dropwise 47% boron trifluoride diethyl ether complex (1.20 g, 4.0 mmol) at −78 °C under N_2. After being stirred at −78 °C for 3 h and at 0 °C for 1 h, the reaction mixture was diluted with CH_2Cl_2 and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine. Evaporation of the dried (Na_2SO_4) solution gave a residue which was purified by column chromatography on silica gel (Et_2O–hexane, 3:7) to furnish the cyclopentyl ethyl ketone **10** (92 mg, 31%) and the tetrasubstituted olefinic methyl ketone **12** (163 mg, 54%).

Compound **10**: $[\alpha]_D^{21}$ −6.54 (*c* 0.92, MeOH); ν/cm^{-1} 1725 and 1700; δ_H(500 MHz; $CDCl_3$; *J*/Hz) 0.83, 1.14 and 1.26 (each 3 H, s), 1.01 (3 H, t, *J* 7), 1.54 (1 H, dd, *J* 15, 3.5), 1.71 (1 H, dd, *J* 14.5, 4.5), 2.02 (3 H, s), 2.06 (1 H, dd, *J* 14.5, 8.5), 2.45 (2 H, qd-like, *J* 7, 1.5), 2.86 (1 H, dd, *J* 15, 8.5) and 5.22 (1 H, m) (Found: *m/z* 226.1568. $C_{13}H_{22}O_3$ requires *M*, 226.1570).

Compound **12**: $[\alpha]_D^{25}$ −1.69 (*c* 1.18, MeOH); ν/cm^{-1} 1730; δ_H(500 MHz; $CDCl_3$; *J*/Hz) 0.92 (3 H, t, *J* 7.5), 1.67 (3 H, d-like, *J* 1), 1.69 (3 H, d-like, *J* 1), 1.98 (3 H, s), 2.10 (2 H, q, *J* 7.5), 2.16 (3 H, s), 2.19 (1 H, dd, *J* 13.5, 6), 2.42 (1 H, dd, *J* 13.5, 8), 2.60 (1 H, dd, *J* 16.5, 4.5), 2.70 (1 H, dd, *J* 16.5, 8) and 5.40 (1 H, tdd, *J* 8, 6, 4.5); δ_C(125 MHz; $CDCl_3$), 12.3, 18.1, 18.3, 21.0, 27.6,



Scheme 4 *Reagents and conditions:* i, $(EtO)_2P(O)SCH(Et)CO_2Me$ **24**, LDA; ii, $LiAlH_4$; iii, MsCl, py; iv, $LiAlH_4$; v, *p*-TsOH; vi, LDA, acetone; vii, Ac_2O, py

30.3, 39.2, 47.8, 69.3, 122.7, 134.1, 170.1 and 205.7 (Found: m/z 226.1566. $C_{13}H_{22}O_3$ requires M, 226.1570).

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