ORGANIC LETTERS

2013
Vol. 15, No. 20
5310–5313

Stereocontrolled First Total Syntheses of Amarouciaxanthin A and B

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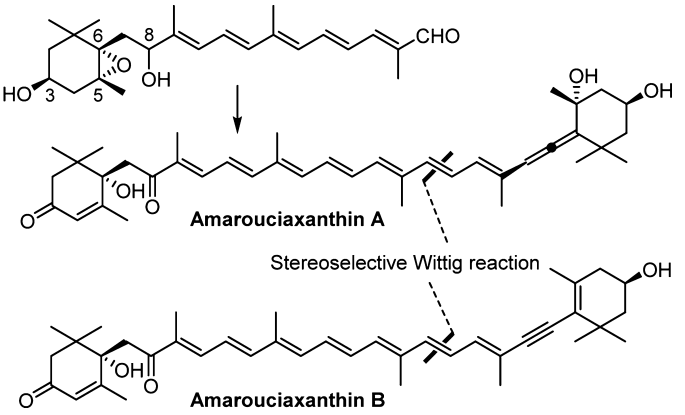
Received September 5, 2013

ABSTRACT



The first total syntheses of amarouciaxanthin A and B (C_{40}) via the stereoselective Wittig reaction of C_{15}-allenic and C_{15}-acetylenic tri-*n*-butylphosphonium salts with the unprecedented C_{25}-3,8-dihydroxy-5,6-epoxyapocarotenal have been completed. Oxidation of the two hydroxyl groups in the left part of the resulting condensation products followed by regioselective oxirane ring opening gave the target carotenoids.

Amarouciaxanthin A (**1**) and B (**2**) (Figure 1), which have a novel γ-hydroxy cyclohexenone moiety, were first isolated from the tunicate *Amaroucium pliciferum* and are thought to be metabolites of fucoxanthin (**3**) via oxirane ring opening.[1] Biotransformation of fucoxanthinol (**4**), a deacetylated metabolite of **3**, into **1** was indeed confirmed by incubation of **4** with mouse liver homogenate.[2] Fucoxanthin (**3**) is widely distributed in brown algae, most of which are edible, and has various physiological functions including anticarcinogenic[3] and antiobese activities.[4] Recently, amarouciaxanthin A (**1**) was reported to significantly suppress adipocyte differentiation in comparison with its metabolite precursor **4**.[4a] Thus, both **1** and **2** are expected to show strong or specific effects in various functions. However, because of their limited availability from natural sources, their properties and functions are not yet well understood. Moreover, the absolute configuration at C6 in these compounds has not been unequivocally established; the configuration is presumed to be *S* based on a simple comparison of their CD spectra with that of (*S*)-abscisic acid (**5**).[1] Thus, interest in their function and structure prompted us to undertake the first total synthesis of **1** and **2**.

Scheme 1 shows our retrosynthetic analyses. It is becoming common to utilize metal-catalyzed coupling reactions in polyene synthesis of carotenoids;[5] however, these

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10.1021/ol402540g
Published on Web 10/03/2013

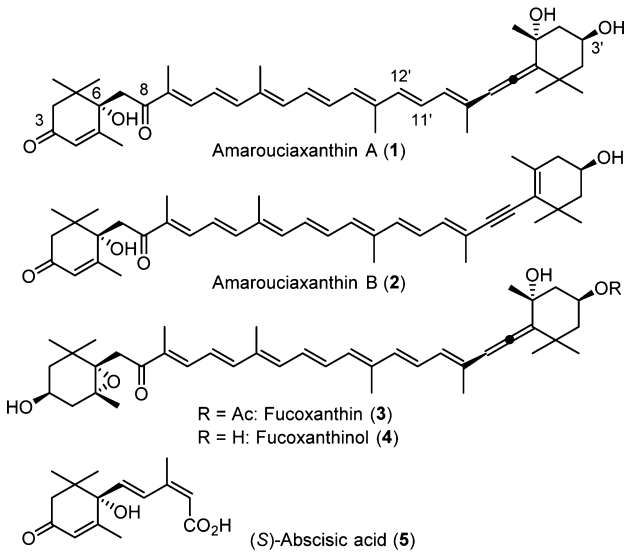
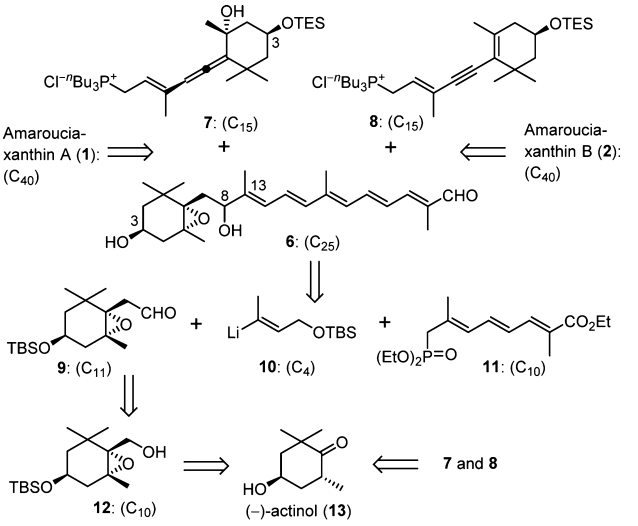


Figure 1. Structure of target carotenoids and related compounds.

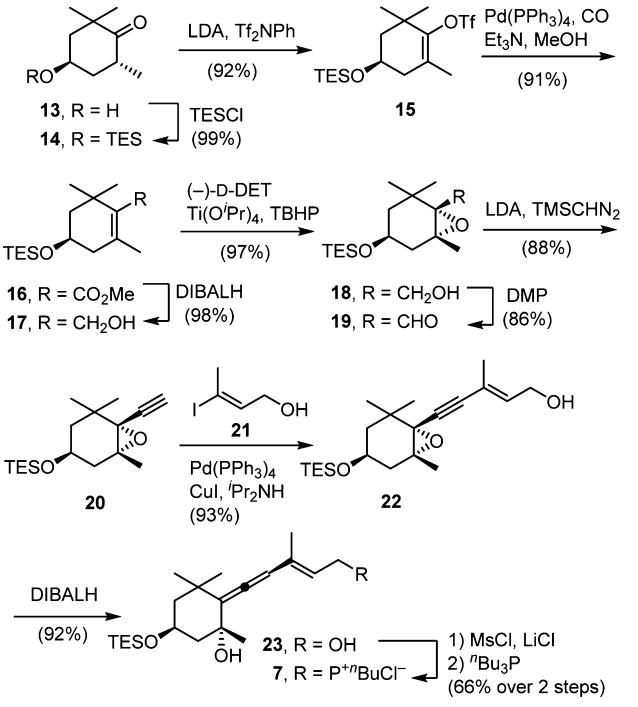
reactions may give unsatisfactory yields and produce hazardous waste. In the synthesis of acetylenic carotenoids in particular, isomerization of the C=C of the enyne moiety under the coupling conditions is a major flaw.[5c,e] We previously reported[6] that C_{15}-acetylenic tri-*n*-butylphosphonium salt **8** is a useful and versatile tool for stereoselective synthesis of acetylenic carotenoids. Thus, we planned to construct the polyene chain of **1** and **2** stereoselectively by using **8** and the corresponding allenic phosphonium salt **7**, which could be prepared from (−)-actinol (**13**).[7] The fact[1] that **1** and **2** are decomposed into methyl ketones, namely, paracentrone and triophaxanthin, via a retro-aldol reaction upon alkaline treatment prompted us to construct the alkali-labile *β*-hydroxy keto moiety of these carotenoids in the final step. We envisioned using the C_{25}-3,8-dihydroxy-5,6-epoxyapocarotenal[8] **6** as a condensation partner for the ylides derived from phosphonium salts **7** and **8**.[6] As a key step in constructing the left part of **1** and **2**, oxidation of both C3- and C8-hydroxyl groups of the condensation products was designed to obtain diketo compounds, which we envisioned would undergo regioselective oxirane ring opening via deprotonation of the more acidic C4 proton to afford our targets. The C_{25}-apocarotenal **6** was expected to be prepared by a three-component connection, which involves the addition of the C_4-alkenyllithium reagent **10**[9] to the C_{11}-epoxyaldehyde **9** and the Horner−Emmons condensation with the previously reported[10] C_{10}-phosphonate **11**. The challenging transformation of C_{10}-epoxyalcohol **12**, whose highly stereoselective preparation by Sharpless asymmetric epoxidation has been documented,[11] into C_{11}-epoxyaldehyde **9** would be achieved by C_1-homologation.

Scheme 1. Retrosynthetic Analyses



First, the C_{15}-allenic phosphonium salt **7** was prepared as shown in Scheme 2. After protecting the hydroxyl group in **13** with triethylsilyl (OTES) and subsequent triflation, the resulting vinyltriflate **15** was transformed into allylic alcohol **17** by palladium-catalyzed methoxycarbonylation[11,12]

Scheme 2. Synthesis of C_{15}-Allenic Phosphonium Salt **7**



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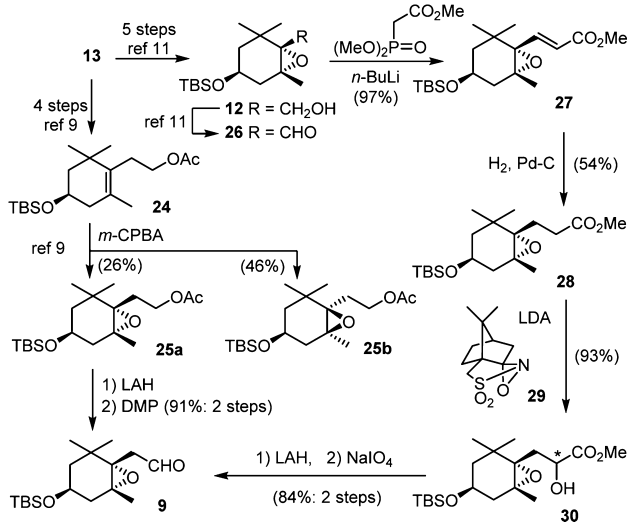
followed by DIBALH reduction. Sharpless oxidation of **17** assisted by (−)-diethy-D-tartrate (D-DET) provided diastereomerically pure *anti*(α)-epoxide **18**, which was oxidized by using Dess-Martin periodinane (DMP) to afford aldehyde **19**. C_1-extension of **19** by the Colvin/Shioiri protocol[13] gave the epoxyalkyne **20** similarly as described for closely related substrates.[5c,14] By using $Pd(PPh_3)_4$ and CuI as catalysts in diisopropylamine and by degassing the reaction mixture, Sonogashira cross-coupling between **20** and vinyl iodide **21**[11b] gave the desired epoxyalcohol **22** in high yield. The stereospecific S_N2' hydride reduction of **22** with DIBALH produced the known allenic diol **23**,[15] which was converted to tri-*n*-butylphosphonium salt **7** via the corresponding allylic chloride. The total yield of the phosphonium salt **7** from (−)-actinol (**13**) was 34% over 11 steps.

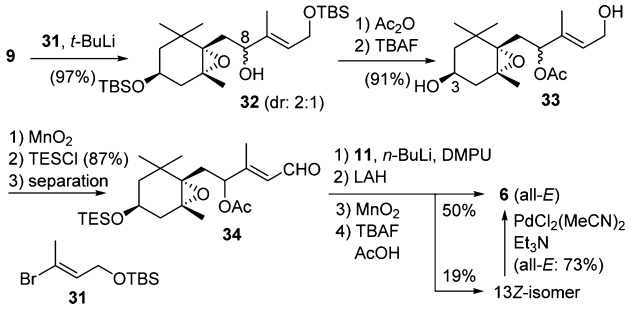
Scheme 3. Synthesis of C_{11}-Epoxyaldehyde **9**



Next, C_{11}-epoxyaldehyde **9**, the precursor of apocarotenal **6**, was prepared as shown in Scheme 3. Previously reported[9] epoxyacetate **25a** was easily converted into epoxyaldehyde **9** by LAH reduction followed by DMP oxidation, but the overall yield of **9** from **13** was as low as 19%, mainly due to the poor diastereoselectivity of epoxidizing alkene **24**. Thus, we investigated the transformation of C_{10}-epoxyalcohol **12**, which has been prepared[11] in a highly stereoselective manner, into C_{11}-compound **9**. Because several trials of the direct C_1-extension using alcohol **12** and corresponding aldehyde **26** were unsuccessful, aldehyde **26** was converted into a C_2-elongated conjugated ester **27** by the Horner−Emmons reaction. After a detailed investigation of reduction reagents and catalysts, it was found that hydrogenation of **27** by using Pd/C as a catalyst provided the desired saturated ester **28** in 54% yield, accompanied by some products of oxirane ring opening.[16] Ester **28** was transformed into the C_1-shortened aldehyde **9** in three steps. Treatment of **28** with commercially available oxaziridine **29**[17] in the presence of LDA yielded α-hydroxylated **30** as a single diastereomer; this was reduced with LAH, and the resulting glycol was cleaved with $NaIO_4$ to afford aldehyde **9** in high yield. The total yield of **9** from (−)-actinol (**13**) was 30% over 11 steps.

C_{11}-Epoxyaldehyde **9** was then converted into C_{25}-apocarotenal **6** as shown in Scheme 4. Aldehyde **9** was treated with a reagent obtained from alkenyl bromide **31**[9,18] and *t*-BuLi to give the diastereomeric alcohols **32** as an unassigned 2:1 mixture; without separating the diastereomers, **32** was acetylated and then desilylated to yield diol **33**. MnO_2 oxidation of **33** and protection of the C3-hydroxyl with TES afforded aldehyde **34**. The C8-acetoxy group on compound **34** is ultimately transformed into a carbonyl group, which destroys the stereogenic center and makes the separation of the diastereomers unnecessary. However, we separated the diastereomers in this step for the sake of convenience in spectral analyses of subsequent compounds. The major diastereomer of **34** was condensed with the previously reported[10] C_{10}-phosphonate **11**, and the resulting pentaenoate was subjected to LAH reduction followed by MnO_2 oxidation and subsequent deprotection to provide all-*E*-apocarotenal **6** and its 13*Z*-isomer in 50% and 19% yield from **34**, respectively. The 13*Z*-isomer was converted into the desired all-*E*-isomer (73%: HPLC yield) by isomerization[19] using a palladium catalyst. The minor diastereomer of **34** was also converted into the corresponding apocarotenal.

Scheme 4. Synthesis of C_{25}-Apocarotenal **6**



The next step toward amarouciaxanthin A and B was Wittig condensation of C_{25}-apocarotenal **6** with C_{15}-tri-*n*-butylphosphonium salts **7** and **8** (Scheme 5). We investigated the further transformation by using the major diastereomer

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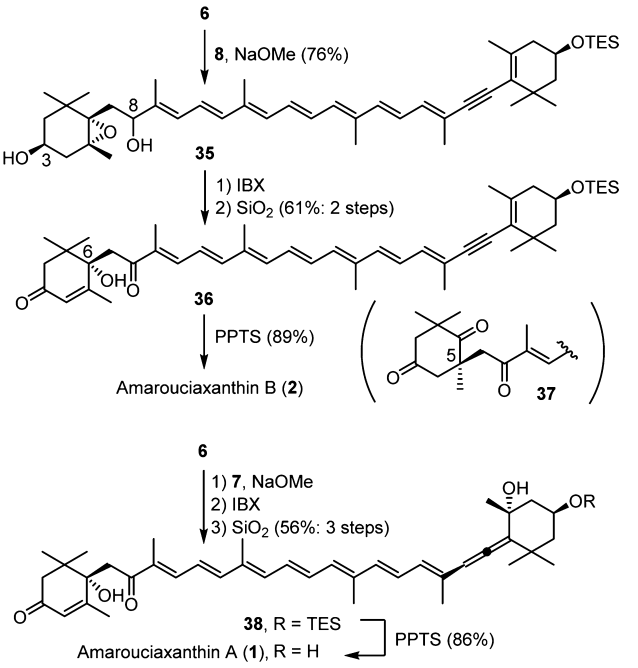
of apocarotenal **6**. As expected, the reaction of **6** with the acetylenic phosphonium salt **8** under previously reported[6] conditions (NaOMe in CH_2Cl_2) stereoselectively proceeded to afford the all-*E* condensed C_{40}-epoxydiol **35** in 76% yield. This diol was oxidized with 2-iodoxybenzoic acid (IBX) in the presence of Et_3N in DMSO/THF to afford the expected epoxydiketone. The latter gradually ring-opened to the desired γ-hydroxyenone **36** during purification using a flash silica gel column. However, this reaction did not proceed to completion. Therefore, the mentioned epoxydiketone/γ-hydroxyenone mixture was treated with a large amount of silica gel in AcOEt overnight. This provided the γ-hydroxyenone **36** without isomerization of the enyne moiety.[20] Finally, **36** was treated with pyridinium *p*-toluenesulfonate (PPTS) in MeOH to afford amarouciaxanthin B (**2**) in 89% yield. Desilylation of **36** with TBAF provided triophaxanthin via a retro-aldol reaction, whereas combined use of TBAF and acetic acid (1:1) led to the competing formation of triketone **37**.[21] Spectral data for the synthetic specimen of **2** were in good agreement with the reported data[1] including CD data. This shows that the proposed configuration at C6 is correct.

By the same approach, amarouciaxanthin A (**1**) was effectively synthesized by a sequence of stereoselective condensation of C_{25}-apocarotenal **6** with C_{15}-allenic phosphonium salt **7**, oxidation, regioselective oxirane ring opening, and removal of the TES group. Spectral data for the synthetic specimen of **1** were in good agreement with the reported data.[1]

Scheme 5. Syntheses of Amarouciaxanthin A and B



In summary, we achieved the first total syntheses of amarouciaxanthin A (**1**) and B (**2**) in a highly efficient and convergent manner. Phosphonium salts **7** and **8** proved and reproved[6] to be, respectively, versatile building blocks for allenic and acetylenic carotenoids because of their ease of use and stereocontrol. This method will provide materials needed for investigating the biological functions of **1** and **2**.

Supporting Information Available. Experimental details and characterization data on **6**, **7**, **9**, **14**–**20**, **22**, **23**, **27**–**30**, **32**–**34**, **36**, **37**, **1**, and **2**. This material is available free of charge via Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(20) Oxidation of **35** with DMP was poorly reproducible and often resulted in decomposition; oxidation with IBX in the absence of Et_3N was accompanied by the 3,8,3′-trioxo compound formed by removal of the TES group and subsequent oxidation.

(21) Treatment with TBAF in the presence of acetic acid gradually converted **2** into **37**. The chemical structure of **37** was determined by NMR and MS spectra. The plausible configuration of C5 in **37** was deduced to be *R* based on the following semipinacol-type rearrangement mechanism.