Olefin metathesis in carotenoid synthesis†

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Olefin metathesis is a powerful and widely applicable synthetic method for carbon–carbon double bond formation. However, its application to the synthesis of conjugating polyene chains has been very limited because of possible undesired side reactions. We attempted to apply this method to the synthesis of symmetrical carotenoids. In this paper, the syntheses of violaxanthin and mimulaxanthin are described using the olefin metathesis protocol.

Over the past decade, olefin metathesis has emerged as a powerful and widely applicable olefin forming reaction,[1] and been utilized for many complicated natural product syntheses. Obviously, this reaction has been accepted as one of the most general and convenient protocols for C–C double bond formation. Although this reaction is also used for the ene–yne metathesis[2] and polymerization,[3] application to the synthesis of conjugating polyene chains is very limited because of possible undesired side reactions.[4]

Carotenoids are ubiquitous natural pigments distributed widely, and their isolation from a variety of species such as bacteria, yeast, algae, plants, animals and even humans has been documented.[5] They generally possess 40 carbon atoms and contain a long conjugated polyene chain. The representative coupling methods for the functionalized polyene skeleton construction of carotenoids are the utilization of the Wittig reaction,[6] Stille coupling,[7] and modified Julia olefination.[8] In these methods, characteristic functional groups are needed. We then attempted to apply the olefin metathesis reaction to the synthesis of symmetrical carotenoids such as violaxanthin (**1**) and mimulaxanthin (**2**) (Fig. 1).[9] In these syntheses, we need only one kind of synthon for the metathesis, and hence their synthesis is rather simple and convenient. In addition, we anticipated that the desired *all-trans* compounds would be obtained based on the thermodynamic stability of the products. In this paper, the syntheses of violaxanthin (**1**) and mimulaxanthin (**2**) using the olefin metathesis protocol are described, as shown in Fig. 1.

Violaxanthin (**1**) was isolated from *Viola tricolor* by Kuhn and Winterstein,[10] and its structure was determined by synthesis, utilizing the Wittig and Horner-Wadsworth-Emmons (HWE) reactions,

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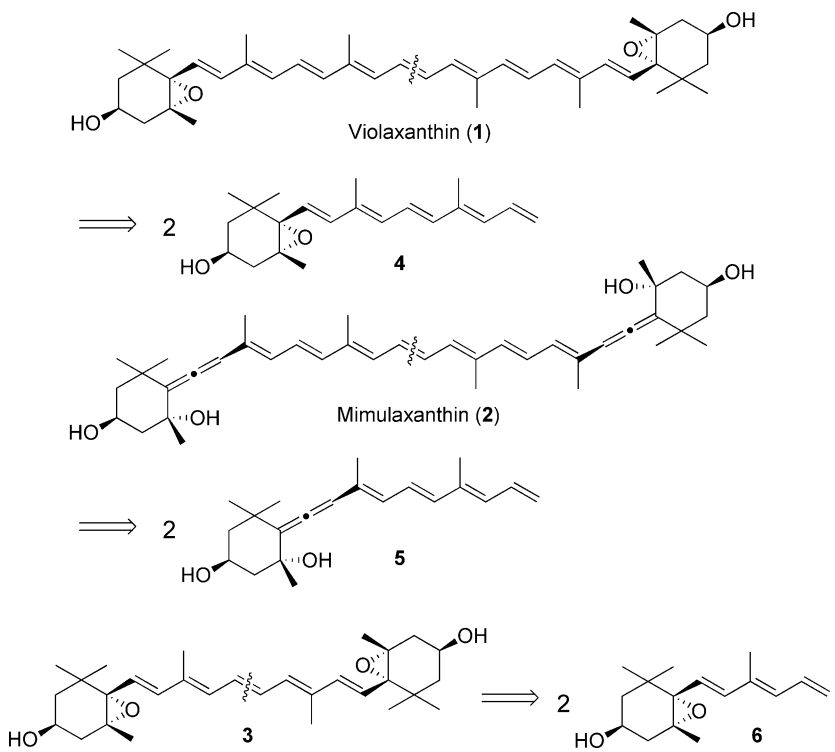

Fig. 1 Synthons for olefin metathesis.

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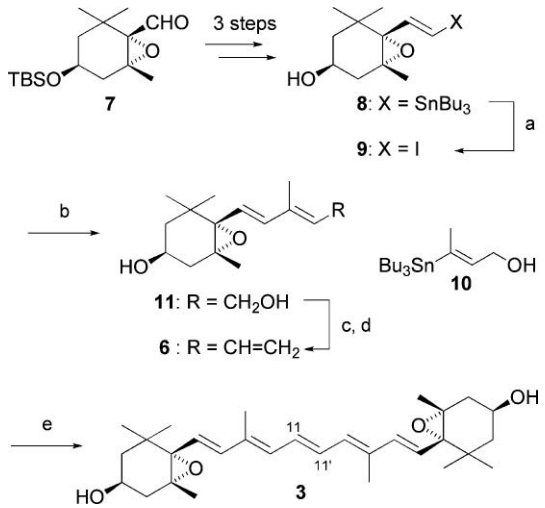
by Eugster's group.[11] Prior to the synthesis of violaxanthin (**1**), we targeted the shorter C30 violaxanthin analogue **3** to understand the applicability of the olefin metathesis reaction to the polyene synthesis (Fig. 1). Thus, vinyl stannane **8**, which was prepared starting from the known (–)-epoxyaldehyde **7**[12] according to the reported procedure,[7,8] was transformed into the corresponding vinyl iodide **9** in excellent yield (Scheme 1). The Stille cross-coupling reaction of iodide **9** with the known vinyl stannane **10**[13] afforded the desired alcohol **11**, which was transformed in good yield into triene **6**, the synthon for the metathesis, by MnO_2 oxidation followed by the Wittig reaction. Fortunately, the homo-coupling of the obtained **6** in the presence of Grubbs second-generation catalyst (5 mol%) at 45 °C produced the expected product **3** in 53% yield. In this case, it was estimated to be 92% of the desired *all-trans* **3**, based on HPLC and 400 MHz NMR analyses of the product.[14] Thus, the pentaene analogue **3** of violaxanthin was rapidly synthesized.

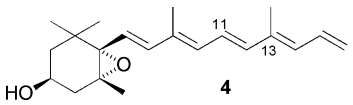


Scheme 1 Synthesis of C30 violaxanthin analogue **3**. *Reagents and Conditions*: (a) I_2, Na_2CO_3, CH_2Cl_2, 0 °C, 15 min, 98%; (b) **10**, $Pd(CH_3CN)_2Cl_2$, LiCl, DMF, r.t., 20 min, 86%; (c) MnO_2, THF, r.t., 20 min; (d) methyltriphenylphosphonium bromide, NaHMDS, THF, r.t., 5 min, 72% for 2 steps; (e) Grubbs 2nd generation cat., toluene, 45 °C, 20 min, 53%.

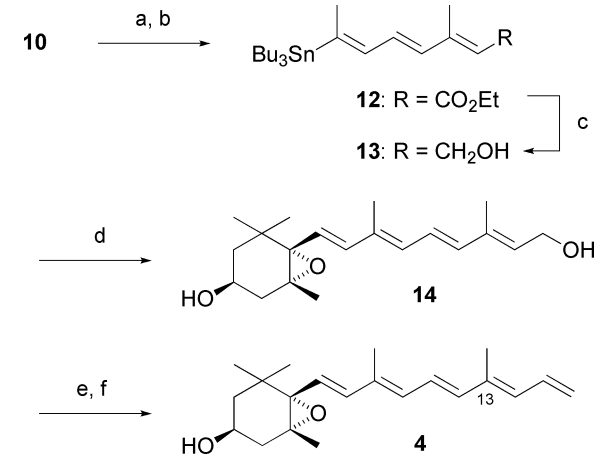
Next, we tried to synthesize violaxanthin (**1**) using the olefin metathesis. The stereocontrolled synthesis of precursor **4** is shown in Scheme 2. Vinyl stannane **13** was prepared in good yield from **10** by the sequence of MnO_2 oxidation, HWE reaction of the resulting aldehyde,[15] and then DIBAL reduction. The Stille cross-coupling reaction of vinyl iodide **9** with vinyl stannane **13** in the presence of $Pd(PPh_3)_4$, LiCl and $^iPr_2NEt$ gave the desired alcohol **14** in 64% yield as a single isomer. The obtained alcohol **14** was transformed into the pentaene **4** by MnO_2 oxidation followed by the Wittig reaction. The product of the Wittig reaction at –20 °C was mainly the 13*E*-isomer (13*E*/13*Z* = 7/1). The reaction at –78 °C produced a higher stereoselectivity (13*E*/13*Z* = 15/1), but in low yield (32%), while the reaction at a higher temperature (0 °C) gave a lower stereoselectivity (13*E*/13*Z* = 3/1). We then used the mixture of stereoisomers of **4** (13*E*/13*Z* = 7/1) for the coupling reaction.

The results of the metathesis of **4** are shown in Table 1. The reaction did not proceed in dichloromethane at 40 °C, but

Table 1 Synthesis of violaxanthin (**1**)



entry	cat. (mol%)		temp. (°C)	time (min)	yield of crude products (%)
1	Grubbs 2nd	(5)	rt	20	trace
2		(5)	45	20	37
3		(5)	45	120	trace
4		(10)	45	20	56
5		**(10)**	**60**	**10**	**67**
6		(5)	80	10	13
7	Hoveyda–Grubbs 2nd	(10)	60	10	23
8	Grubbs 1st	(10)	60	10	10



Scheme 2 Synthesis of pentaene **4**. *Reagents and Conditions*: (a) MnO_2, THF, r.t., 2 h; (b) triethyl 3-methyl 4-phosphonocrotonate, ^{n}BuLi, DMPU, THF, 0 °C, 10 min, 85% for 2 steps; (c) DIBAL, CH_2Cl_2, –78 °C, 10 min, 84%; (d) **9**, $Pd(PPh_3)_4$, LiCl, ^{i}PrNEt, DMF, 65 °C, 30 min, 64%; (e) MnO_2, THF, r.t., 50 min; (f) methyltriphenylphosphonium bromide, NaHMDS, THF, –20 °C, 5 min, 70% for 2 steps.

in toluene at 45 °C violaxanthin (**1**) was obtained in about 35% yield. Next, we surveyed the equivalents of the catalyst used, temperature, and the reaction time using Grubbs second-generation catalyst in toluene (Table 1). The reaction of 5 mol% of the catalyst in 45 °C gave the coupling products in 37% yield, but the products gradually decomposed with a longer reaction time (entries 2 and 3). The use of 10 mol% catalyst improved the yield (56%), and the coupling products were obtained in about 67% amount at 60 °C (entries 4 and 5). A higher reaction temperature, 80 °C, led to a lower yield (entry 6). On the other hand, the Hoveyda–Grubbs catalyst and Grubbs first-generation catalyst gave undesirable results (entries 7 and 8).

The detailed analysis of the coupling products obtained in entry 5 by mobile-phase HPLC showed two major peaks (A–C of Fig. 2). As shown in (A) of Fig. 2, the HPLC detection at a 470 nm wavelength, which indicates the C40 violaxanthin derivatives, was different from that detected at a 423 nm wavelength, which was mainly ascribed to the C35 violaxanthin analogues, as shown in (B) of Fig. 2. We then isolated both compounds and elucidated their structures based on NMR, mass and UV spectra. Thus, we clarified that peak 1 was the *all-trans* violaxanthin (**1**)

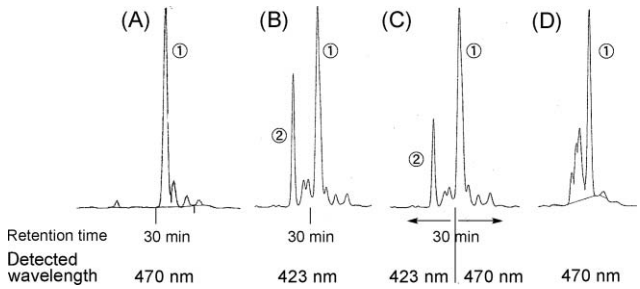
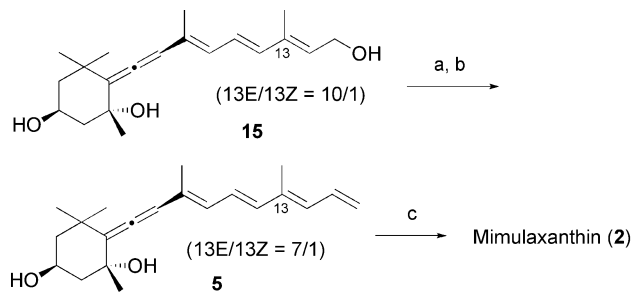


Fig. 2 Results of HPLC analysis of violaxanthin (A–C) and mimulaxanthin (D).

(λ_{max} = 470 nm). Meanwhile, we estimated that peak 2 was the C35 violaxanthin analogue (λ_{max} = 423 nm) by mass, UV and NMR spectra. The spectral data of the isolated *all-trans* violaxanthin (**1**) were in good agreement with those already reported.[11] Next, in order to determine the ratio of these compounds, we changed the wavelength for the detection from 423 nm to 470 nm after 30 minutes. As shown in (C) of Fig. 2, the ratio between the compounds of peak 1 and peak 2 was approximately 5 to 1. Analysis of the compounds detected by 470 nm revealed that this mixture consisted of the desired *all-trans* violaxanthin (**1**) (peak 1; 84%), its three stereoisomers (7, 5 and 2%) and others (2%) by HPLC and mass spectroscopy. Thus, the *all-trans* violaxanthin (**1**) was rapidly synthesized by the olefin metathesis protocol in 49% estimated yield .

Next was the synthesis of mimulaxanthin (**2**), which was isolated from the flowers of *Mimulus guttatus* and *Lamium montanum*[16] and its structure determined by synthesis, utilizing the Wittig and HWE reactions, by Eugster and Buchecker.[17] The C20-allenic triol **15** (Scheme 3), which was previously synthesized by us, was a synthetic intermediate and was prepared as a *E*/*Z* mixture at the C13 position (13*E*/13*Z* =10/1).[6c] The coupling precursor, allenic tetraene **5**, was prepared from **15** by MnO_2 oxidation followed by the Wittig reaction as in the case of violaxanthin (**1**). Olefin metathesis of the obtained allenic tetraene **5** proceeded within



entry	cat. (mol %)		temp. (°C)	time (min)	amount of crude product (%)
1	Grubbs 2nd	(10)	60	10	34
2		(20)[a]	60	20	56

[a]adding at 4 times of 5 mol % at 5 min intervals.

Scheme 3 Synthesis of mimulaxanthin (**2**). *Reagents and Conditions*: (a) MnO_2, AcOEt, r.t., 20 min; (b) methyltriphenylphosphonium bromide, NaHMDS, THF, 0 °C, 10 min, 44% for 2 steps; (c) Grubbs 2nd generation cat., toluene, 60 °C, 20 min, 56%.

10 min under the same conditions as those for the violaxanthin synthesis, and produced a mixture of products in a 34% yield. Meanwhile, the addition of Grubbs second-generation catalyst (5 mol%) for four times at 5 min intervals provided a 56% yield. The detailed analysis of the coupling products by HPLC detected at a 470 nm wavelength showed one major peak and some minor peaks as shown in (D) of Fig. 2. In this case, the major peak 1 comprised 52% of the reaction products. We then isolated the major peak 1 and elucidated its structure based on NMR, mass and UV spectra. Fortunately, peak 1 was the desired *all-trans* mimulaxanthin (**2**) (λ_{max}= 470 nm).[18] The spectral data of the isolated *all-trans* mimulaxanthin (**2**) were in good agreement with those already reported.[17]

In summary, we demonstrated that the olefin metathesis protocol could be applied to the synthesis of conjugated polyene compounds, in particular to symmetrical carotenoid synthesis. Violaxanthin (**1**) possessing a conjugating nonaene system and mimulaxanthin (**2**) possessing a heptaene system conjugating to two allenic functions were synthesized by utilizing the olefin metathesis as a key reaction at the final step. In carotenoid synthesis, the isolation of the desired compound from a mixture of stereoisomers is usually troublesome, and for the product obtained by the olefin metathesis strategy this is also unavoidable. The above results, however, would provide a new strategy for the synthesis of symmetrical carotenoids.

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Notes and references

1 For recent reviews on olefin metathesis, see: R. H. Grubbs, Ed. *Handbook of Metathesis*, Wiley-VCH, Weinheim, Germany, 2003; R. H. Grubbs and T. M. Trnka in *Ruthenium in Organic Synthesis*, S.–I. Murahashi, Ed.; Wiley-VCH, Weinheim, 2004, chapter 6.; A. Deiters and S. F. Martin, *Chem. Rev.*, 2004, **104**, 2199; T. Katz, *Angew. Chem., Int. Ed.*, 2005, **44**, 3010.

2 For reviews on enyne metathesis, see: C. Aubert, O. Buisine and M. Malacria, *Chem. Rev.*, 2002, **102**, 813; A. J. Giessert and S. T. Diver, *Chem. Rev.*, 2004, **104**, 1317.

3 For recent reports on polymerization, see: A. Hejl, M. W. Day and R. H. Grubbs, *Organometallics*, 2006, **25**, 6149; I. A. Gorodetskaya, T. Choi and R. H. Grubbs, *J. Am. Chem. Soc.*, 2007, **129**, 12672; I. A. Gorodeskayam, A. A. Gorodetsky, E. V. Vinogradova and R. H. Grubbs, *Macromolecules*, 2009, **42**, 2895.

4 For recent reports in retinoid and polyene macrolide synthesis, see: A. Wojtkielewicz, J. Maj and J. W. Morzycki, *Tetrahedron Lett.*, 2009, **50**, 4734; M. J. Mitton-Fry, A. J. Cullen and T. Sammakia, *Angew. Chem., Int. Ed.*, 2007, **46**, 1066.

5 For authorized monographs, see: G. Britton, S. Liaaen-Jensen and H. Pfander, Eds. *Carotenoids. Volume 1 and 2*, Birkhauser, Basel, 1995.

6 C. Tode, Y. Yamano and M. Ito, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1581; Y. Yamano and M. Ito, *Chem. Pharm. Bull.*, 2004, **52**, 780; Y. Murakami, M. Nakano, T. Shimofusa, N. Furuichi and S. Katsumura, *Org. Biomol. Chem.*, 2005, **3**, 1372; F. Khachik and A. Chang, *J. Org. Chem.*, 2009, **74**, 3875.

7 B. Vaz, R. Alvarez and A. R. de Lera, *J. Org. Chem.*, 2002, **67**, 5040; B. Vaz, M. Dominguez, R. Alvarez and A. R. de Lera, *Chem.–Eur. J.*,

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2007, **13**, 1273; J. Burghart and R. Brückner, *Angew. Chem., Int. Ed.*, 2008, **47**, 7664.
8 N. Furuichi, H. Hara, T. Osaki, H. Mori and S. Katsumura, *Angew. Chem., Int. Ed.*, 2002, **41**, 1023; N. Furuichi, H. Hara, T. Osaki, M. Nakano, H. Mori and S. Katsumura, *J. Org. Chem.*, 2004, **69**, 7949; T. Olpp and R. Brückner, *Angew. Chem., Int. Ed.*, 2006, **45**, 4023.
9 For the synthesis of symmetrical carotenoids by using one kind of synthon, see: J. E. McMurry and M. P. Fleming, *J. Am. Chem. Soc.*, 1974, **96**, 4708.
10 R. Kuhn and A. Winterstein, *Chem. Ber.*, 1931, **64**, 326.
11 M. Acemoglu, P. Uebelhardt, M. Rey and C. H. Eugster, *Helv. Chim. Acta*, 1988, **71**, 931.
12 M. Kuba, N. Furuichi and S. Katsumura, *Chem. Lett.*, 2002, 1248.
13 J. F. Betzer, F. Delaloge, B. Muller, A. Pancrazi and J. Prunet, *J. Org. Chem.*, 1997, **62**, 7768.
14 It was difficult to determine the *E*-geometry at the C11-C11′ position of the product **3** by NOE and J-coupling because of the symmetrical structure of **3**. We then estimated it by referring ^{1}H NMR spectra of violaxanthin (**1**), because the environment around the central olefin of the both compounds is almost same. Our conclusion agrees well with the empirical ^{1}H NMR data of carotenoids, see ref. 5.
15 B. Dominguez, B. Iglesias and A. R. de Lera, *Tetrahedron*, 1999, **55**, 15071.
16 H. Z. Nitsche, *Naturforsch*, 1973, **28C**, 481; R. Buchecker and C. H. Eugster, *Helv. Chim. Acta*, 1980, **63**, 2531.
17 R. Buchecker and C. H. Eugster, *Helv. Chim. Acta*, 1991, **74**, 469.
18 Other minor peaks of (D) in Fig. 2 were assumed to be stereoisomers of C40 mimulaxanthin resulting from the mass spectra. In order to estimate the yield of the obtained mimulaxanthin (**2**) in a similar manner to that of violaxanthin (**1**), we also measured HPLC detected by 423 nm wavelength that could detect C35 mimulaxanthin analogues. Unfortunately, C35 mimulaxanthin analogues could not be separated from the stereoisomers of C40 mimulaxanthin, and the yield of mimulaxanthin (**2**) synthesized was not estimated.