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Novel synthesis of the allene moiety of carotenoids via biomimetic photosensitized oxygenation

Masayuki Nakano, Noriyuki Furuichi, Hajime Mori and Shigeo Katsumura*

School of Science, Kwansei Gakuin University, Uegahara 1-1-155, Nishinomiya, Hyogo 662-8501, Japan

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Abstract—A novel synthesis of the allene moiety of carotenoids was achieved by the regioselective ene reaction of the vinyl hydrogen rather than the allyl hydrogen of the significantly twisted 1,3-dienes, (3*R*)-alkoxy-*cis*-β-ionol derivative, followed by selective allyl rearrangement.

Among more than 600 natural carotenoids,[1] a considerable number possesses 3,5-dihydroxy-1,1,5-trimethylcyclo-hexylideneallene (carotenoid numbering) moiety in one terminal. This characteristic allene structure can be found in C40 carotenoids represented by neoxanthin, mimulaxanthin and fucoxanthin, in C37 carotenoid, peridinin, and in C31 paracentrone. As the acceptable biogenetic occurrence of this particular moiety, an isomerization of the 3-hydroxy-5,6-epoxypolyene (carotenoid numbering) such as voilaxanthin has been proposed.[2] Meanwhile, in the syntheses of allene carotenoids and their metabolic small molecule, grasshopper ketone,[3] intramolecular S_N2' hydride reduction of the 3-hydroxy-5,6-epoxyacetylene derivative (carotenoid numbering) is the only method established for the stereocontrolled synthesis on the C-5 hydroxy group and the C-8 allene hydrogen of the 5-hydroxy-1,1,5-trimethylcyclohexylideneallene function (carotenoid numbering), although the satisfactory stereocontrol between the 3-hydroxy group and the 5,6-epoxy function has not been achieved (Fig. 1).[4]

Previously, we found that in an ene reaction of significantly twisted 1,3-diene **1**, singlet oxygen preferentially abstracted the vinyl hydrogen Ha rather than the allyl hydrogen Hb to produce the corresponding allene **3** in good yield, and its relative configuration between the C-5 allyl hydroxy group and the C-8 vinyl hydrogen was the same as that of the natural allene carotenoids (Scheme 1).[5] This one-step pathway to produce the allene moiety from the twisted 1,1,5-trimethylcyclohexenylvinyl derivatives would be considered a possible biomimetic route, because the mechanism of the ene reaction with $^1O_2$ through the intermediary perepoxide, which has generally been accepted,[6] can be regarded to be equivalent to the two-step biogenetic pathway of the allene moiety, which involves epoxidation of the tetrasubstituted double bond of the polyolefin derivatives followed by isomerization to the allene moiety.[2] In order to realize the possible biomimetic synthesis of the allene moiety in carotenoids by utilizing our own novel allene formation with $^1O_2$, we have to overcome the problems caused by the presence of the C-3 OH group. The one problem is the creation of diastereomers due to the C-3 and C-9 asymmetric carbons, in addition to the rotational isomers in the precursor for $^1O_2$ oxygenation, compound **8**. Another is the unknown influence on

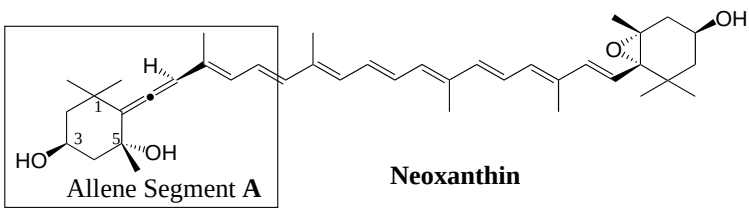

Figure 1.

Keywords: allene carotenoids; biomimetic reaction; twisted diene.

* Corresponding author. Tel.: +81-798-54-6381; fax: +81-798-51-0914; e-mail: katumura@kwansei.ac.jp

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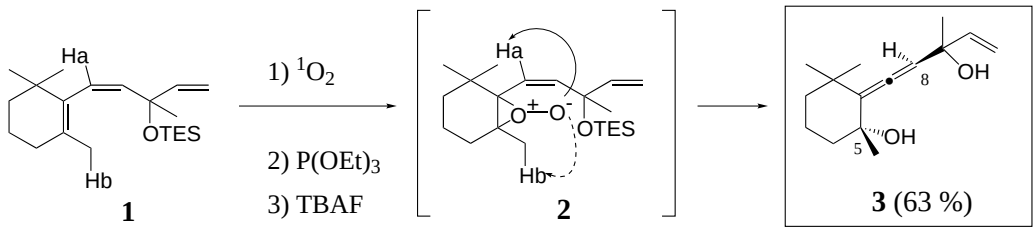
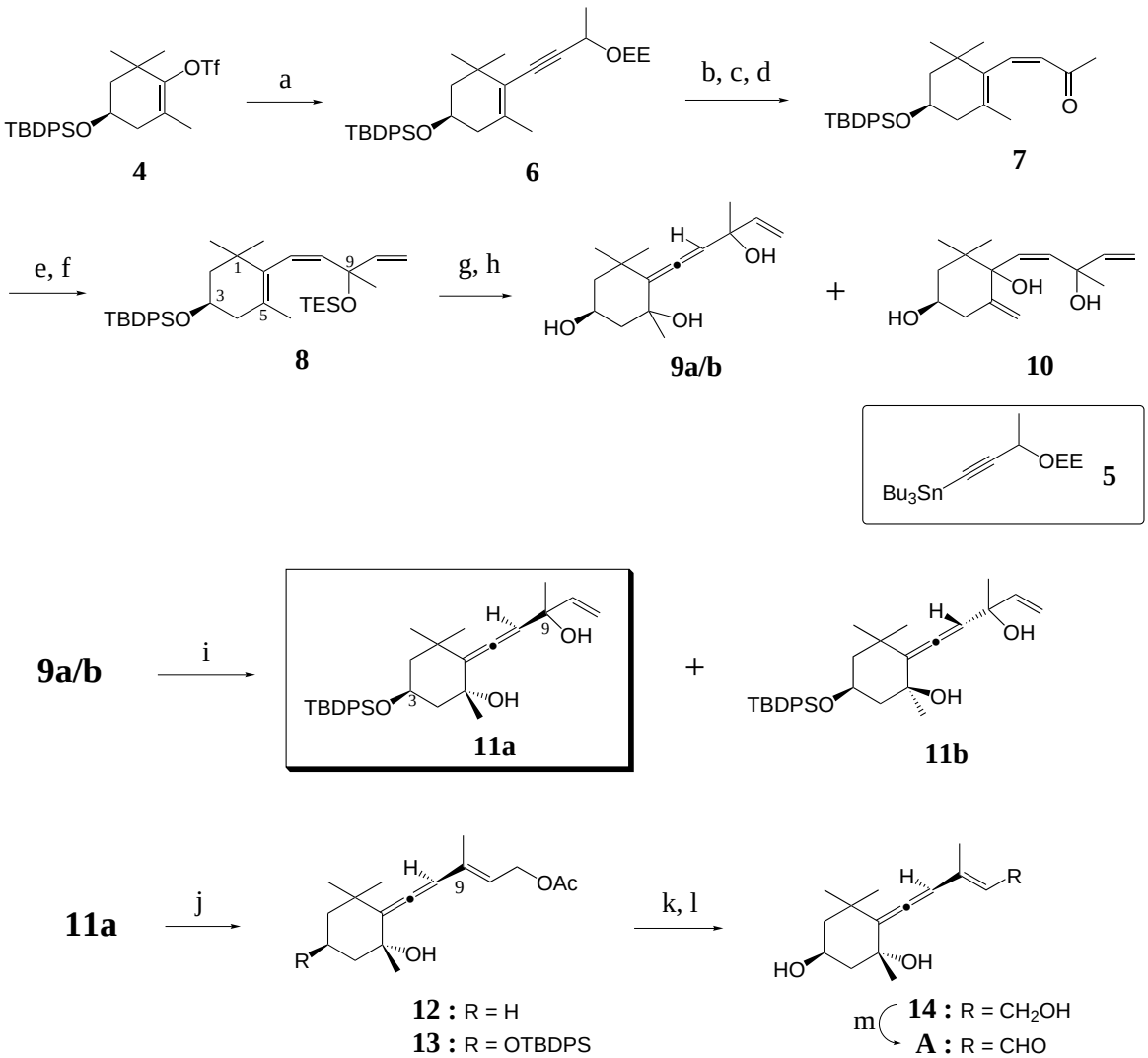


Scheme 1.

both the conformations of the cyclohexene ring in **8** for $^1O_2$ ene reaction and of the cyclohexylidene ring in **11a** for the chemoselective allyl rearrangement of the C-9 tertiary hydroxy group resulting from the $^1O_2$ oxygenation. Achievement of the biomimetic synthesis of this particular allene moiety is, therefore, very attractive and significant subject as an another route for the synthesis. In the present paper, we disclose a novel synthesis of the enantiomerically pure allene segment **A** by utilizing a new, the second, and, moreover, a biomimetic method.

The synthesis was started from enantiomerically pure vinyltriflate **4**.[4f] Cross-coupling of **4** with a tin acetylide



Scheme 2. *Reagents and conditions*: (a) **5**, Pd(PPh$_3$)$_4$, LiCl, abs. DMF, 60°C, 3 h, then 10% NH_3 aq, 89%; (b) 2N aqueous H_2SO_4, THF, rt, 5 h, quant.; (c) H_2, Lindlar catalyst (0.5% Pb poisoned), *n*-hexane, rt, 21 h, 96%; (d) Jones reagent, acetone, rt, 15 min, then 10% $NaHSO_4$ aq, 89%; (e) vinyl magnesium bromide, THF, 65°C, 1 h, 85%; (f) Et_3SiCl, DMAP, Et_3N, DMF, 35°C, 40 h, 96%; (g) O_2, TPP, P(OEt)$_3$, hυ, CH_2Cl_2, 0°C, 4 h, then P(OEt)$_3$, rt, 1 h; (h) TBAF, THF, rt, 24 h, 60% for **9a**/**b**, and 31% for **10** from **8**; (i) TBDPSCl, imidazole, DMF, rt, 40 h, 27% for **11a**, and 33% for **11b** from **8**; (j) Ac_2O, AcOH, rt, 18 h, 77% (9*E*/9*Z*=4/1); (k) 10% KOH aq, THF–MeOH (1:1), rt, 2 h, 87% (9*E*/9*Z*=4/1); (l) TBAF, THF, rt, 60 h, 81%; (m) MnO_2, acetone, rt, 2 h, 78% then HPLC purification.

derivative **5** catalyzed by palladium in the presence of LiCl in DMF gave **6** in 89% yield (Scheme 2). Then, selective reduction of the ethynyl group to the corresponding *cis*-olefin with the freshly prepared Lindlar catalyst (0.5% Pb poisoned), deprotection, and then oxidation with Jones reagent produced ketone **7**. The reaction of **7** with vinylmagnesium bromide in THF at 65°C, followed by introduction of the triethylsilyl group to the hydroxy group thus obtained to produce the key intermediate, (3*R*)-alkoxy-*cis*-β-ionol derivative **8**[7] in 67% overall yield as a mixture of diastereomers and rotamers. Photosensitized oxygenation of the resulting mixture in the presence of $P(OEt)_3$ followed by desilylation gave the desired allene triol **9a** and its diastereomer **9b** in 60% yield for three steps as an inseparable mixture along with exomethylene **10** (31% yield). Selective silylation at the C-3 hydroxy group of the obtained mixture of **9a** and **9b** produced a mixture of the corresponding allene diol **11a**[8,9] and **11b**, respectively, which were separable with column chromatography on silica gel. Thus, **11a** and **11b** were obtained as a diastereomeric mixture due to the C-9 asymmetric carbon, respectively. The selectivity attributable to the C-3 position of **8** in the photosensitized oxygenation was not observed, and the ratio between **11a** and **11b** was 1 to 1.2 in the ^{1}H NMR spectrum.

In order to realize the regio- and stereoselective allyl rearrangement of the hydroxy group in the side-chain of **11a**, dehydroxy derivative **3** was used as a model compound. Treatment of **3** with sodium *p*-toluenesulfinate, which is commonly used for allyl rearrangement,[10] gave the corresponding allyl sulfone along with its *Z* isomer in 40% yield (*E*:*Z* = 5:1). Meanwhile, acid treatment were also investigated under various trials, and we finally found that treatment of **3** with 1 equiv. of acetic anhydride in acetic acid successfully produced the desired **12** in 68% yield as a sole stereoisomer. The stereoselectivity of this rearrangement may be attributed to the [2,3] sigmatoropic rearrangement of the allyl acetate. Then, treatment of **11a** with the same reaction conditions successfully produced the desired allyl acetate **13** in 77% yield as a 4:1 mixture (by ^{1}H NMR) of the inseparable stereoisomers at C-9 double bond. Compound **13** was transformed into the separable aldehyde **A**[11] by deprotection of both the acetyl and silyl groups, and then oxidation. The physical and spectral data of the synthesized allene compound **A**, which was purified by HPLC,[12] were in good agreement with those reported[4a] [mp 181–183°C; $[\alpha]_D^{21}$ −60.7 (*c* 0.52, MeOH), literature, mp 178–179°C; $[\alpha]_D^{22}$ −63.0 (*c* 0.5, MeOH)].

In conclusion, we established a novel method for the synthesis of the allene moiety in allene carotenoids by utilizing the biomimetic photosensitized oxygenation, which involved the selective ene reaction of the vinyl hydrogen in preference to the allyl hydrogens with singlet oxygen.

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7. Compound **8** obtained was a mixture of diastereomers at the C-3 and C-9 asymmetric carbons, and this compound also exists as a mixture of rotamers. The ^{1}H NMR spectrum of the mixture showed complex signals even at 65°C; EI$^+$ HRMS found *m*/*z* 588.3828, calcd for $C_{37}H_{56}O_2Si_2$ M^+ 588.3816.
8. Data for **11a**: ^{1}H NMR (400 MHz, $CDCl_3$) (diastereomer mixture) δ 7.69 (m, 4H), 7.39 (m, 6H), 5.93 (dd, 1H, *J* = 17.3, 10.5 Hz), 5.32 (s, 1H), 5.26 (dd, 1H, *J* = 17.3, 1.2 Hz), 5.05 (dd, 1H, *J* = 10.7, 1.2 Hz), 4.29 (m, 1H), 2.13 (ddd, 1H, *J* = 13.2, 4.1, 2.2 Hz), 1.64 (ddd, 1H, *J* = 12.6, 4.0, 2.2 Hz), 1.50 (dd, 1H, *J* = 13.2, 11.0 Hz), 1.36 (s, 3H), 1.34 (dd, 1H), 1.30 (s, 3H), 1.08 (s, 9H), 0.96 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.67, 143.79, (135.79, 135.76), (134.60, 134.49), 129.52 (127.49, 127.47), 118.77, 111.88, 101.93, 72.50, 72.11, 65.80, 49.56, 49.06, 35.21, 32.05, 31.31, 28.82, 27.83, 27.01, 19.13; EI$^+$ HRMS found *m*/*z* 490.2919, calcd for $C_{31}H_{42}O_3Si$ M^+ 490.2901.

9. The stereochemistry of **11a** and **11b** could not be determined in this step. Then, these were transformed into the corresponding triol **14** and its diastereomer, the absolute configuration of which was determined by comparison with the reported optical rotation value and spectral data,[4a] respectively.
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11. Data for **A**: mp 181–183°C; $[\alpha]_D^{21}$ −60.7 (*c* 0.52, MeOH); IR (NaCl Nujol, cm^{-1}) 3876, 3344, 2344, 1928, 1662; ^1H NMR (400 MHz, $CDCl_3$) δ 10.03 (d, 1H, $J=8.1$ Hz), 6.08 (s, 1H), 5.94 (brdq, 1H, $J=8.1$, 1.2 Hz), 4.33 (m, 1H), 2.29 (ddd, 1H, $J=13.1$, 4.2, 2.2 Hz), 2.16 (d, 3H, $J=1.2$ Hz), 1.98 (ddd, 1H, $J=12.6$, 4.1, 2.2 Hz), 1.38 (s, 3H), 1.37 (s, 3H), 1.32–1.48 (m, 2H), 1.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.86, 190.84, 153.60, 127.19, 119.03, 102.06, 72.66, 63.97, 49.20, 48.84, 36.03, 31.90, 31.11, 29.14, 14.25; EI^+ HRMS found m/z 250.1577, calcd for $C_{15}H_{22}O_3$ M^+ 250.1567.
12. Preparative high-performance liquid chromatography (HPLC) was carried out on JASCO PU-1580 instruments with UV–vis detector, UV-1570 on Develosil CN-UG-5 column (0.6×25 cm) with isopropanol/hexane = 3/7 as the mobile phase, flow = 1.0 ml min^{-1}.