Synthetic Photochemistry. XX. Dye Sensitized Photooxidation and m-Chloroperbenzoic Acid Oxidation of Aristoladienes : A Biomimetic Rearrangement to the Nardosane Skeleton

Takeshita, Hitoshi
Department of Molecular Science and Technology, Interdisciplinary Graduate School of Engineering Sciences, Kyushu University

Shimooda, Isao
Faculty of Engineerings, Kyushu University

Toshihide, Hatsui
Department of Molecular Science and Technology, Interdisciplinary Graduate School of Engineering Sciences, Kyushu University

https://doi.org/10.15017/17503

出版情報：九州大学大学院総合理工学報告. 2 (1), pp.23-30, 1980-08-08. 九州大学大学院総合理工学研究科
バージョン：
権利関係：

Synthetic Photochemistry. XX.[1] Dye Sensitized Photooxidation and *m*-Chloroperbenzoic Acid Oxidation of Aristoladienes: A Biomimetic Rearrangement to the Nardosane Skeleton

Hitoshi TAKESHITA, Isao SHIMOODA*
and Toshihide HATSUI

(Received May 22, 1980)

Abstract: Dye-sensitized photooxygenation of aristoladienes (**3** and **4**) formed skeletal rearrangement products, but did no ene-reaction product. A formation of a nardosatrienone (**5**) *in vitro* is parallel to a biogenetic hypothesis for nardosinone (**1**), a natural dioxolane. An accompanied trisnoraldehyde (**2**) is assumed to be derived from a common precursor with **5**. *m*-Chloroperbenzoic acid oxidation of **3** and **4** gave, along with normal epoxy derivatives, debilone and **7**.

Nardosinone (**1**)[2], a congener of isonardosinone (**2**)[3] of *Nardostachys chinensis* Betalin, possesses a rare five-membered peroxide structure, but this unique ring system has not been synthesized to date. We will herein describe the derivation from the aristoladienes, co-metabolites of the plant, by the dye-sensitied photooxidations and *m*-chloroperbenzoic acid oxidation; the formers might be of interest in the biomimetic point of view. We have shown[4] that the dye-sensitized photooxygenation of Δ^2-carene gave no C=C cleavage product despite being an α-vinylcyclopropane, but gave some *seco*-cyclopropane derivatives by a solvolysis. This solvolytic ring-opening seems to be applicable to a construction of the frame-work of **1** from an appropriate aristolane.

The aristoladienes (**3** and **4**, *ca.*1 : 1)[1] were made from calarene by selenium dioxide oxidation, but were inseparable even on a silver nitrate-impregnated silica gel column chromatography. The mixture was therefore irradiated in methanol by means of a tungsten lamp under an oxygen atmosphere with a sensitizer, Rose Bengal (RB), to give three products as follows: The least polar product (**5**, *m/e*, 216 (M^+)), 2.5%, was a triene. The UV spectrum of **5** revealed a conjugated dienone chromophore as λ_{max}: 260 nm ($\varepsilon = 6500$), which is consistent to the IR carbonyl absorption, $\nu_{C=O} = 1665\,cm^{-1}$, and the NMR spectrum (**Fig. 1**) exhibiting the three mutually coupled olefinic protons in a row [δ: 5.88 (H-7, ddd, J=9.3, 6.3,

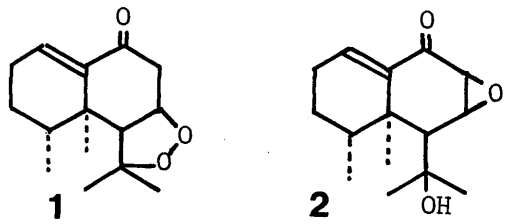

Chart 1.

Department of Molecular Science and Technology.
* Faculty of Engineerings, Kyushu University.

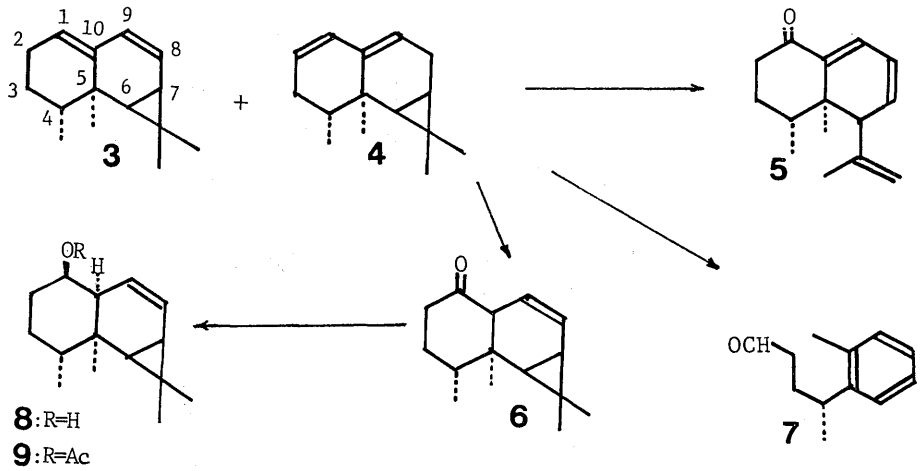

Chart 2. Photo-sensitized Oxidation of Aristoladienes (**3** and **4**).

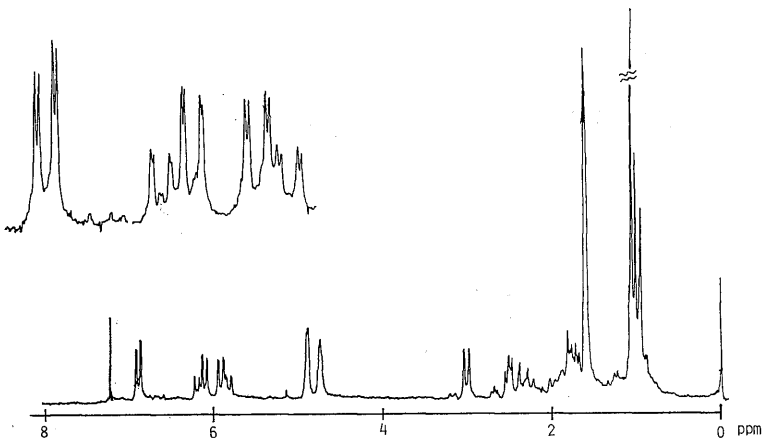

Figure 1. The NMR spectrum of **5**.

1.3 Hz), 6.15 (H-8, ddd, J=9.3, 5.5, 1 Hz), and 6.89 (H-9, ddm, J=5.5, 1.3 Hz)]. An absence of the cyclopropane ring was also evident on the NMR spectrum showing a newly formed vinyl methyl signal at δ: 1.60 (3H, br. s) as well as the signal of terminal methylene at δ: 4.88 (2H, br. s). According to the NMDR experiments, the methine signal (H-6) at δ: 3.00 was adjacent to H-7. The intactness of the secondary methyl and the adjacent angular methyl part was evident. Therefore, the structure of **5** must be a trienone with the nardosane skeleton as depicted.

From the subsequent fractions, a β,γ-unsaturated ketone (**6**), mp 64-65°C, 27 %, having the cyclopropane ring intact, and a trisnoraldehyde (**7**), a colorless oil, 5 %, were eluted. Their structures were obtained on the following physicochemical evidence. Thus, the IR spectrum of **6** showed $\nu_{C=O}$ at 1715 cm^{-1}, a typical cyclohexanone, and the NMR spectrum revealed two olefinic protons at δ: 5.86 (H-9, dm, J=10 Hz) and 5.96

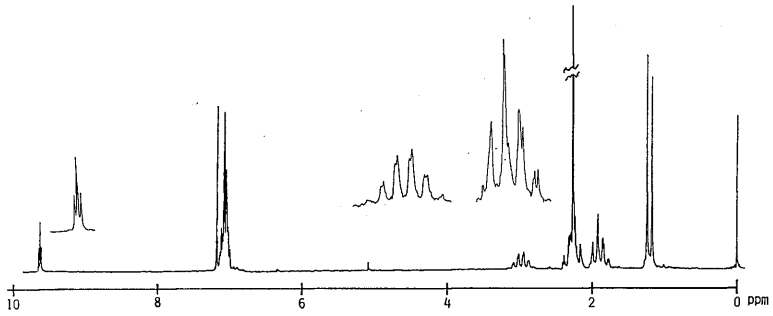

Figure 2. The NMR spectrum of **7**.

(H-8, ddd, J=10, 5.5, 3 Hz). The splitting patterns of these signals retained after derivation to the dihydro derivative (**8**) and its acetate (**9**) by the LAH reduction of **6** and further acetylation; for **8**, 5.45 (H-9, dd, J=10, 2.3 Hz) and 6.00 (H-8, ddd, J=10, 5.5, 3.1 Hz), and for **9**, 5.39 (H-9, dd, J=10, 3 Hz) and 5.92 (H-8, ddd, J=10, 5, 3 Hz). Consequently, the molecular conformations of **6**, **8**, and **9** should be similar. This was further confirmed by the chemical shift comparisons with the other signals. The compounds in this series commonly show characteristic doublet signals (J=7 to 10 Hz) due to the methine protons (H-6) in δ: *ca.* 0.5-0.8. In the case of **6**, **8**, and **9**, they were at 0.80 (d, J=8 Hz), 0.72 (d, J=8 Hz), and 0.70 (dm, J=7 Hz). In addition, the methine protons at the carbon bearing oxygen functions (H-1) have small splittings, *i.e.*, the half-hight widths are 6 to 10 Hz. Hence, the hydroxy and acetoxy groups of **8** and **9** have the *axial*-conformation.

In the same time, the chemical shift differences for the substituents on the α-side of **6**, **8**, and **9** were very small, and this means that the oxygen functions are β-orientation with the *cis*-A/B juncture: *e.g.*, 0.57 (3 H, s) of **6**, which can be ascribable to one of the *gem*-dimethyl group, has suffered an anisotropy from the carbonyl group. The lithium aluminum hyfride (LAH) reduction of **6** to **8** has caused a high-field shift to 0.86 (3 H, s). But the change of the chemical shift due to the acetylation, **8** to **9** [δ: 0.82 (3 H, s)], was a small high-field shift. These observations all together clarified the stereostructures as depicted.

Similarly, the NMR spectroscopy of **7** deduced it to be an aromatic derivative with an aldehyde side chain. Thus, the overlapped multiplets at δ: 7.10 (4 H) indicated a presence of 1, 2-disubstituted benzene structure, and the exhibition of only two methyl signals at 1.23 (d) and 2.29(s) showed a degrated nature. By the mass-spectral molecular weight determination and the mechanistic implications of splitting-off of acetone, the structure was obtained as shown.

On the other hand, the Methylene Blue (MB)-sensitized photooxygenation of the mixture (**3** and **4**) in methanol and chloroform (1 : 30) gave only **5** (5 %). An absence of the monooxygenation product, **6**, is not contradicted to the recent view[5]. Although the yields were poor[6], the formation of **5** should be attributable to a *transoid*-diene system conjugated with the cyclopropane ring,

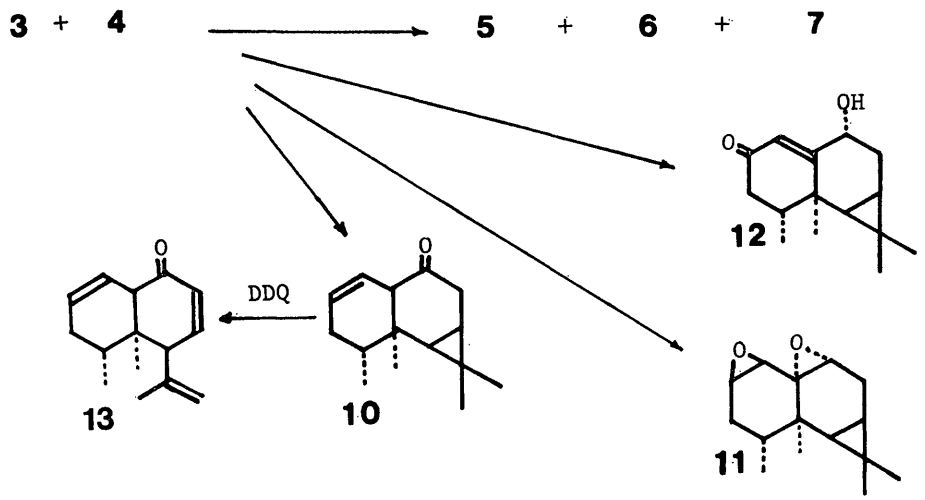

Chart 3. MCPA-oxidation of Aristoladienes (**3** and **4**).

to make capable of causing a solvolytic cleavage,[7] *via* a polar transition state.[8),9)]

This was supported by an independent MCPA-oxidation of **3** and **4** in dichloromethane: In one occasion, the reaction needed a long time; the products identified after 2 d were **6** (25%) and **5** (6.3%). However, unexpected formation of **5**, which is corresponding to the dioxygenation product, was rather odd, and probably, an autooxidation must be involved during the prolonged period. The oxidation with freshly purified reagent gave a clean products within 2 h. The mixture was separated by only the high-pressure liquid chromatography to characterize four products, the aromatic aldehyde **7** (4.5%) and the new products, **10** (colorless needles, mp 59–61°C, 1.1%), **11** (colorless crystals, mp 57–59 °C, 2%), and debilone (**12**).[10-12)] Some unidentified oily products were also detected.

According to the IR spectrum [$\nu_{C=O}$: 1710 cm^{-1}], **10** is an isomer of **6**. Its NMR spectrum exhibited two olefinic protons and the methine proton on the cyclopropane ring at δ: 5.65 (H-1, m), 5.98 (H-2, m), and 0.73 (H-6, d, J=10 Hz). The NMDR experiments confirmed H-6 is coupled with the other methine (H-7) at 0.92 (ddd, J=10, 8, 1.3 Hz). An irradiation with resonance frequency of H-7 has raised a pair of doubets having large spin-splitting at 2.35 (d, J=18.5 Hz) and 3.67 (d, J=18.5 Hz) which are only attributable to the signals of the α-methylene protons of the carbonyl group. Therefore, the structure of **10** left no ambiguity.

Similarly, the IR spectrum of **11** showed no absorption in the range of carbonyl and hydroxy groups. Therefore, **11** must be a diepoxide. The NMR spectrum of **11** was again confirmative; the characteristic methine signal (H-6) was in an extremely high field at δ: 0.17 (d, J=10 Hz), suffering the anisotropy from one of the epoxide rings, and the NMDR experiments proved the presence of a methylene group adjacent to the other methine proton of the cyclopropyl group, and these methylene protons were also spin-coupled with an epoxide

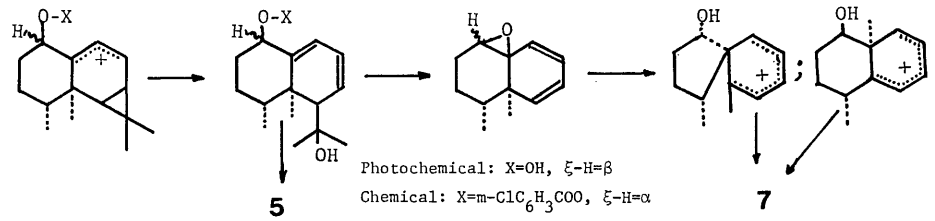

Chart 4. Mechanism leading to **5** and **7**.

methine signal at 2.25 with J=18 and 8 Hz. The two epoxide rings are adjacent in each other, because the signal at 2.58 and 3.14 are mutually coupled with J=0.5 Hz. Furthermore, the signal at 2.58 was sharpened by irradiation with the frequency of 3.14. Thus, the full stereostructure of **11** is established as shown.

In a regard of the absence of any dioxetane or ene-reaction product, the mechanism of a one-pot formation of **7** can be explained as illustrated in chart 4.

Finally, **10** was refluxed in toluene for **22** h with 2, 3-dichloro-5, 6-dicyano-1, 4-benzoquinone (DDQ) and a catalytic amount of boron trifluoride etherate to yield two products: A less polar product (**13**, *m/e*, 216 (M^+)) could be isolated by means of a high-pressure liquid chromatograph as a colorless oil (30 %). The NMR spectrum of **13**, which is corresponding to a double bond isomer of the hydroiodic acid reduction product of **2**[3], was suggestive; especially, the chemical shifts of three methyl signals [δ: 0.85 (3H, s), 0.96 (3H, d, J=6 Hz), 1.88 (3H, br. s)] and four olefinic protons [δ: 5.45-5.8 (H-1 and H-2, m), 6.04 (H-8, dd, J=10, 1.2 Hz), and 6.56 (H-7, dd, J=10, 5.5 Hz)] together with additional olefinic protons of β, γ-unsaturated ketone system [δ: 5.04 (2H, br. s)] indicated the carbon frame work of **13** to be a nardosane. Two chracteristc methine signals were also exhibited at δ: 3.12 (H-6) and 3.46 (H-10), and remaining signals were in 1.0-2.0 (3H, m). From this intactness of the secondary methyl and angular methyl groups, the change of **10** to **13** is explained only by the dehydrogenative ring-openening of the cyclopropane as depicted. The other product, whose NMR spectrum resembled to that of **13**, was not isolated in the pure form.

Although the cyclopropane of **3** is conjugated with the diene system, an absence of the C=C cleavage product is worthy to note. Probably, this could be attributable to the preferable reactivity of the trisubstituted C=C toward singlet oxygen. The initially oxygenated species might be converted to the *seco*-cyclopropane derivative *via* the delocalized species. In view of a streochemically crowded C-4 to C-6 arrangement, this facile formation of nardosane skeleton with unsaturated functions to lead **1** or **2** might be interesting. Due to a limited amount of the material available[13], a further transformation will be a subject of another study.

Experimental

RB-sensitized Photooxidation of Aristoladienes (**3** *and* **4**): *A Formation of* **5**, **6**, *and* **7**. A mixture of **3** and **4** (450 mg) was dissolved in MeOH (20 cm^3) and was irra-

diated by means of a 500-W tungsten lamp in a presence of RB (113 mg) under an oxygen atmosphere for 7 h. The mixture was then extracted with $CHCl_3$, and the extract was chromatographed on a silica gel column; from the eluent of hexane-ether (92 : 8), a colorless oil (**5**), 6 mg (2.5 %) [Found: *m/e*, 216 (M^+). δ: 0.98 (3H, d, J=6 Hz), 1.04 (3H, s), 1.60 (3H, br. s), 1.6-2.9 (5H, m), 3.00 (1H, ddm, J=6.3, 1 Hz), 4.73 (1H, br. s), 4.88 (1H, br. s), 5.88 (1H, ddd, J=9.3, 6.3, 1 Hz), 6.15 (1H, ddd, J=9.3, 5.5, 1 Hz), and 6.89 (1H, dd, J=5.5, 1.3 Hz). ν: 1665 cm^{-1} λ_{max}: 260 nm (ε=6500), 319 (350)]. Subsequently, from the elution of hexane-ether (9 : 1), colorless needles (**6**), mp 64-65°C (from methanol) 66 mg (27 %) [Found: M. W., 218.1682. Calcd for $C_{15}H_{22}O$: 218.1670. δ : 0.57 (3H, s), 0.80 (1H, d, J=8 Hz), 1.02 (3H, s), 1.06 (3H, d, J=7 Hz), 1.17 (3H, s), 1.22 (1H, ddm, J=8, 5.5 Hz), 1.5-2.1 (3H, m), 2.2-2.5 (2H, m), 2.58 (1H, m), 5.86 (1H, dm, J=10 Hz), and 5.96 (1H, ddd, J=10, 5.5, 3 Hz). ν: 1670 cm^{-1}], and a colorless oil (**7**), 10 mg (5 %) [Found: *m/e*, 180 (M^+). δ: 1.23 (3H, d, J=7 Hz), 1.8-2.1 (2H, m), 2.1-2.4 (2H, m), 2.29 (3H, s), 3.01 (1H, qm, J=7, Hz), 7.10 (4H, m), and 9.64 (1H, t, J=1.7 Hz). ν: 2720, 1725 cm^{-1}].

MB-sensitized Photooxidation of **3** *and* **4**. A mixture of **3** and **4** (435 mg) was dissolved in a mixture of MeOH (1 cm^3) and $CHCl_3$ (30 cm^3) containing MB (75 mg) and irradiated with a 500-W tungsten lamp for 10 h. The reaction mixture was then diluted by water and extracted with ether. A silica-gel column chromatography of the extracts gave a colorless oil (**5**), 12 mg (5 %) as the sole isolable product.

LAH Reduction of **6** *: Formation of* **8**. An anhydrous ether solution (20 cm^3) of **6** (25 mg) was treated with LAH (5 mg) at room temperature for 2 h. The mixture was then diluted with water and extracted with ethyl acetate. Silica-gel column chromatography of the extraxt gave a colorless oil (**8**), 22 mg (87 %) [Found: *m/e*, 220 (M^+). ν: 3640 cm^{-1}. δ: 0.72 (1H, d, J=8 Hz), 0.87 (3H, s), 0.98 (3H, d, J=8 Hz), 0.99 (3H, s), 1.12 (3H, s), 1.2-2.2 (8H, m), 4.06 (1H, m, $W_{h/2}$=7 Hz), 5.45 (1H, dd, J=10, 2.3 Hz), and 6.00 (1H, ddd, J=10, 5.5, 3.1 Hz)].

Acetylation of **8** *: Formation of* **9**. A mixture of acetic anhydride (0.3 cm^3) and pyridine (0.1 cm^3) was added to **8** (10 mg) and kept at room temperature for 24 h. An ordinary work up of the mixture gave colorless needles (**9**), mp 67-69°C, 9 mg (76 %) [Found : M. W., 262.1889. Calcd for $C_{17}H_{26}O_2$: 262.1933. ν: 1737, 1240 cm^{-1}. δ: 0.70 (1H, d, J=7 Hz), 0.82 (3H, s), 0.96 (3H, d, J=6 Hz), 0.99 (3H, s), 1.12 (3H, s), 1.2-2.1 (7H, m), 2.00 (3H, s), 5.22 (1H, m, $W_{h/2}$=6 Hz), 5.39 (1H, dd, J=10, 3 Hz), and 5.92 (1H, ddd, J=10, 5, 3 Hz)].

MCPA-oxidation of **3** *and* **4**. *a*). To a dichloromethane solution (10 cm^3) of **3** and **4** (68.5 mg), powdered MCPA (175 mg, activity=40 %) was added in portions and kept at room temperature for 2 d with an occasional monitoring of **3** and **4** on thin-layer chromatograms. The mixture was then treated with aqueous $NaHCO_3$, and extracted with $CHCl_3$. A silica gel column chromatography of the extract yielded, from hexane-ethyl acetate (92 : 8), colorless needles (**6**), mp 64-65°C, 18.6 mg (25 %), and a colorless oil (**5**), 4.7 mg (6.3 %). No other product was identified other than poly-

meric materials.

b). To a CH_2Cl_2 solution (100 cm^3) of **3** and **4** (1270 mg), powdered MCPA (1150 mg, activity=85 %) was added in portions. After 2 h, the mixture was washed with aqueous $NaHCO_3$, and extracted with $CHCl_3$. The silica gel column chromatography and the repeated high-pressure liquid chromatography of the extract yielded: **7** (51.2 mg, 4.4 %), **10** 15.9 mg, 1.1 %) [Found: M. W., 218.1668. Calcd for $C_{15}H_{22}O$: 218.1770. δ: 0.73 (1 H, d, J=10 Hz), 0.80 (3 H, s), 0.92 (1 H, ddd, J=10, 8, 1.3 Hz), 0.99 (3 H, d, J=8 Hz), 1.11 (3 H, s), 1.32 (3 H, s), 1.7–2.0 (3 H, m), 2.35 (1 H, dd, J=18.5, 1.3 Hz), 2.67 (1 H, ddd, J=18.5, 8, 1.3 Hz), 3.10 (1 H, br. s), 5.65 (1 H, m), and 5.98 (1 H, m). ν: 1710 cm^{-1}], **11** (29 mg, 4 %) [Found: 234.1649. Calcd for $C_{15}H_{22}O$: 234.1620. δ: 0.17 (1 H, d, J=8 Hz), 0.54 (1 H, tm, J=8 Hz), 0.96 (3 H, d, J=8 Hz), 0.98 (9 H, s), 1.4–2.1 (4 H, m), 2.25 (1 H, ddd, J=16, 8, 0.5 Hz), 2.58 (1 H, d, J=4 Hz), 3.14 (1 H, ddm, J=4, 0.5 Hz), and 3.24 (1 H, dm, J=4 Hz), ν: 1370, 1225, 1210, 1000, 975, 895, 835 cm^{-1}], and **12** (30 mg, 4 %) which was identical with debilone.[10-12] Subsequently, a colorless oil was eluted from the mixture of hexane-ethyl acetate (9 :1), but the NMR spectroscopy indicated to be a mixture containing some chlorobenzoates, and no further work was attempted.

DDQ-Dehydrogenation of **10**. To an anhydrous benzene solution (10 cm^3) of **10** (10 mg) containing a trace amount of BF_3 etherate, powdered DDQ (31 mg) was added and kept at room temperature for 20 d. After washings by aqueous $NaHCO_3$, the mixture was purified on a preparative thin-layer chromatography to give a colorless oil, 7 mg. The NMR spectrometry indicated it to be composed of two products. The high-pressure liquid chromatography furnished to collect an analytical specimen of oily **13**, *ca.* 1 mg [Found : *m/e*, 218 (M^+). δ: 0.85 (3 H, s), 0.96 (3 H, d, J=6 Hz), 1.88 (3 H, br. s), 1.8–3.0 (3 H, m), 3.12 (1 H, m), 3.46 (1 H, ddm, J=5.5, 1.3 Hz), 5.06 (2 H, m), 5.5–5.8 (2 H, m), 6.04 (1 H, dd, J=10, 1.3 Hz), and 6.56 (1 H, dd, J=10, 5.5 Hz). ν: 1670 cm^{-1}].

References and Notes

1) Part XIX: H. Takeshita, I. Kouno, M. Iino, H. Iwabuchi and D. Nomura, *Bull. Chem. Soc. Jpn.* in press, **53**, xxx (1980).
2) G. Rucker, *Chem. Ber.*, **102**, 2707 (1969).
3) G. Rucker, *Ann. Chem.*, **733**, 152 (1970).
4) H. Takeshita and I. Kouno, *Kyushu Daigaku Seisan Kagaku Kenkyusho Hokoku*, **63**, 13 (1977).
5) H. Takeshita and T. Hatsui, *J. Org. Chem.*, **43**, 3080 (1978).
6) The dienes are relatively unstable; an exposure to oxygen in the dark causes a rapid decomposition, but no product could be isolated.
7) Solvolytic cleavage of the cyclopropane during a dye-sensitized photooxygenation was observed in the reaction of tricyclo [3.2.1.$0^{2,4}$] octene derivatives. See H. Takeshita, T. Hatsui, and O. Jinnai, *Kyushu Daigaku Seisan Kagaku Kenkyusho Hokoku*, **65**, 1 (1977).
8) For current accounts of mechanisms, see a) A. Frimer, *Chem. Rev.*, **79**, 359 (1979), and b) E. Toromanoff, *Tetrahedron*, **36**, 207 (1980).
9) In the literature, there is an example on the dye-sensitized photooxidation of the *transoid*-diene; 2-ethylidene-6, 6-dimethyl-bicyclo [3.1.1] hept-3-ene was shown to give a bisnorketone, presumably being a Hock cleavage product (*K.* Gollnick, *Adv. in Photochem.*, **6**, 1 (1968)). An absence of the similar cleavage product in the present case must be attributable to a delocalization effect of the cyclopropane ring.
10) J. Krepinski, G. Jommi, Z. Samek, and F. Sorm, *Coll. Czech. Chem. Commun.*, **35**,

745 (1970).
11) G. Rucker and U. Kretzschmar, *Ann. Chem.*, **748**, 211 (1971).
12) R. Nishida and Z. Kumazawa, *Agr. Biol. Chem.*, **37**, 341 (1973).
13) We thank Prof. K. Suga and Dr. S. Watanabe, Chiba University, for a generous gift of raw calarene oil.