

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

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

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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 diolane. An accompanied trisnorldehyde (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-sensitized photooxidations and *m*-chloroperbenzoic acid oxidation; the formers might be of interest in the biomimetic point of view. We have shown⁴⁾ 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

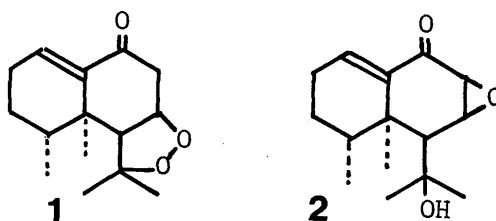


Chart 1.

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 $\lambda_{\max}$: 260 nm ($\epsilon = 6500$), which is consistent to the IR carbonyl absorption, $\nu_{C=O} = 1665\text{ cm}^{-1}$, and the NMR spectrum (Fig. 1) exhibiting the three mutually coupled olefinic protons in a row [δ : 5.88 (H-7, ddd, $J = 9.3, 6.3$,

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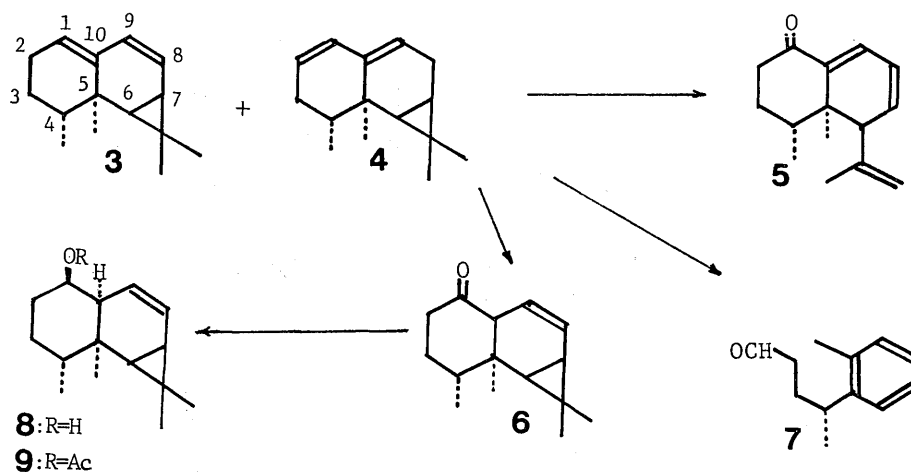


Chart 2. Photo-sensitized Oxidation of Aristoladienes (3 and 4).

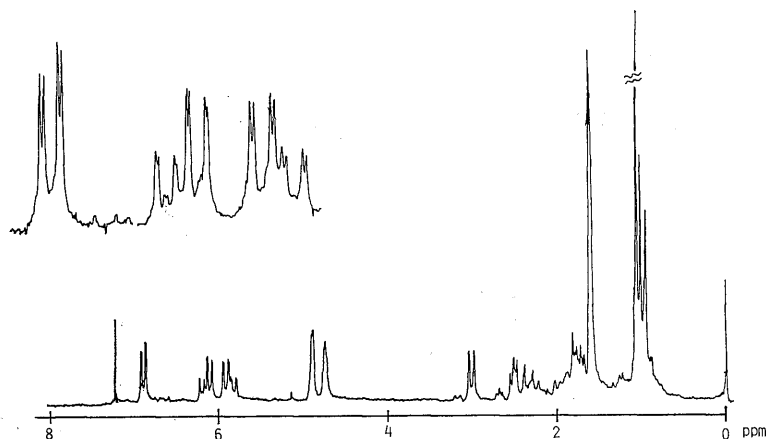


Figure 1. The NMR spectrum of 5.

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 trisnorldehyde (7), a colorless oil, 5%, were eluted. Their structures were obtained on the following physico-chemical 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

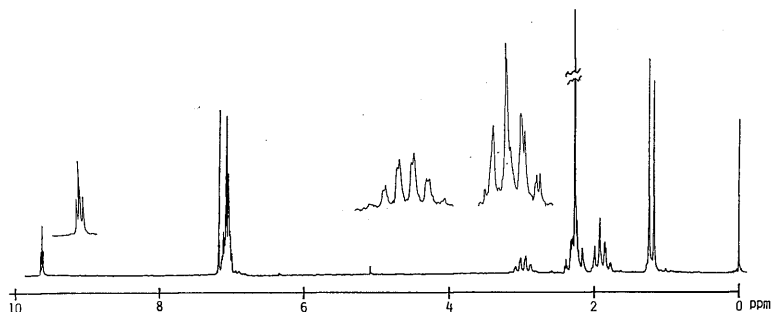


Figure 2. The NMR spectrum of 7.

(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-height 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 (3H, s) of **6**, which can be ascribable to one of the *gem*-di-

methyl group, has suffered an anisotropy from the carbonyl group. The lithium aluminum hydride (LAH) reduction of **6** to **8** has caused a high-field shift to 0.86 (3H, s). But the change of the chemical shift due to the acetylation, **8** to **9** [δ : 0.82 (3H, 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 (4H) 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 degraded 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 view⁵⁾. Although the yields were poor⁶⁾, the formation of **5** should be attributable to a *transoid*-diene system conjugated with the cyclopropane ring,

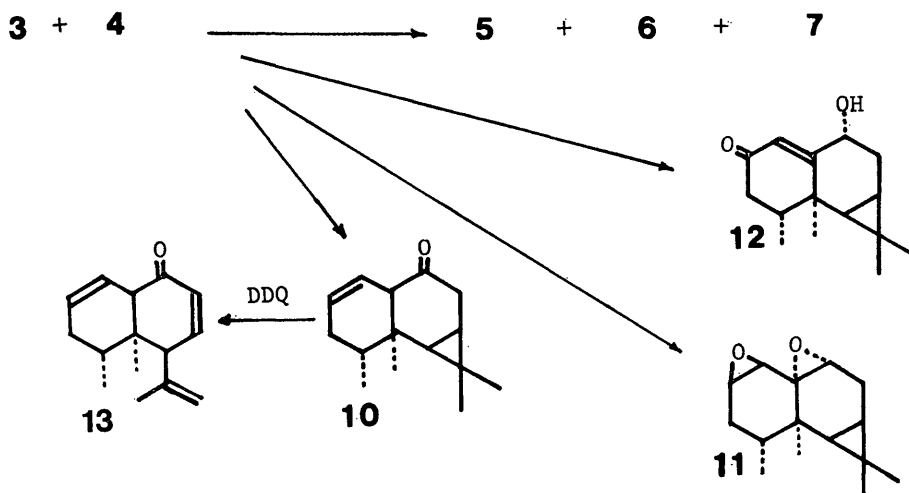


Chart 3. MCPA-oxidation of Aristoladienes (3 and 4).

to make capable of causing a solvolytic cleavage," *via* a polar transition state.^{9),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 NMR 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 doublets 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 NMR 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

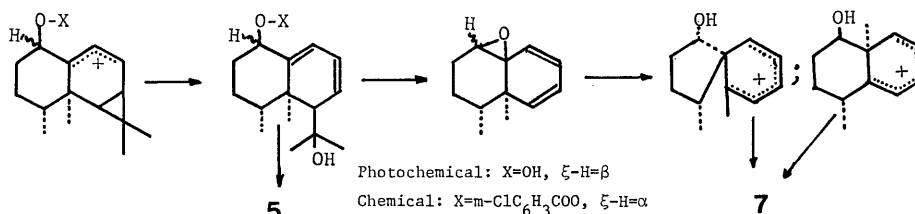


Chart 4. Mechanism leading to 5 and 7.

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 di-oxetane 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**⁹, 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 characteristic 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-opening 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 stereochemically 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 available¹³, 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 cm³) 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 ($\epsilon=6500$), 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 $\text{C}_{15}\text{H}_{22}\text{O}$: 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 extract 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 $\text{C}_{17}\text{H}_{26}\text{O}_2$: 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 $\text{C}_{15}\text{H}_{22}\text{O}$: 218.1770. δ : 0.73 (1 H, d, $J=10\text{ Hz}$), 0.80 (3 H, s), 0.92 (1 H, ddd, $J=10, 8, 1.3\text{ Hz}$), 0.99 (3 H, d, $J=8\text{ Hz}$), 1.11 (3 H, s), 1.32 (3 H, s), 1.7–2.0 (3 H, m), 2.35 (1 H, dd, $J=18.5, 1.3\text{ Hz}$), 2.67 (1 H, ddd, $J=18.5, 8, 1.3\text{ Hz}$), 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 $\text{C}_{15}\text{H}_{22}\text{O}$: 234.1620. δ : 0.17 (1 H, d, $J=8\text{ Hz}$), 0.54 (1 H, tm, $J=8\text{ Hz}$), 0.96 (3 H, d, $J=8\text{ Hz}$), 0.98 (9 H, s), 1.4–2.1 (4 H, m), 2.25 (1 H, ddd, $J=16, 8, 0.5\text{ Hz}$), 2.58 (1 H, d, $J=4\text{ Hz}$), 3.14 (1 H, ddm, $J=4, 0.5\text{ Hz}$), and 3.24 (1 H, dm, $J=4\text{ Hz}$), 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, $J=6\text{ Hz}$), 1.88 (3 H, br. s), 1.8–3.0 (3 H, m), 3.12 (1 H, m), 3.46 (1 H, ddm, $J=5.5, 1.3\text{ Hz}$), 5.06 (2 H, m), 5.5–5.8 (2 H, m), 6.04 (1 H, dd, $J=10, 1.3\text{ Hz}$), and 6.56 (1 H, dd, $J=10, 5.5\text{ Hz}$). ν : 1670 cm^{-1}].

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