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A New Selenium-Assisted Cyclization—A Biogenetic-type Synthesis of Safranal[1)]

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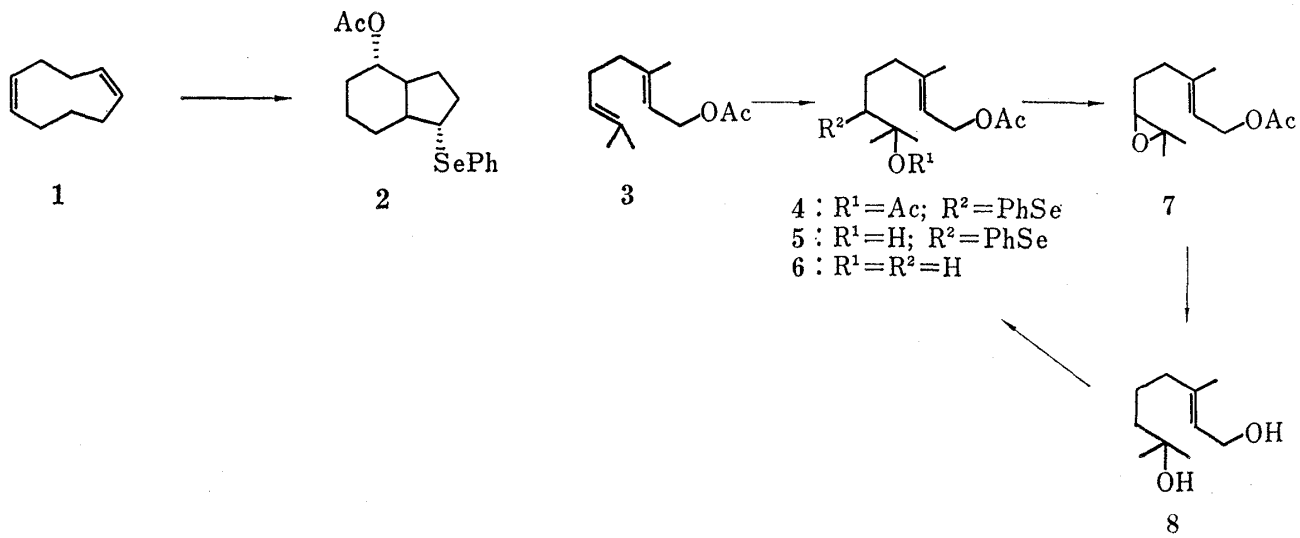
Cyclization of the olefinic β-hydroxy selenide (**5**) with various catalysts was carried out to give the cyclic compound (**9**) which was converted to safranal (**19**) *via* the olefinic alcohol (**14**), the diolefinic alcohol (**16**), and the aldehyde (**17**).

Keywords——Safranal; olefinic cyclization; β-hydroxy selenide; biogenetic-type synthesis; organoselenium compound; carbon-carbon bond formation

In contrast to the well-studied functional group manipulation and synthesis of heterocycles involving the use of organoselenium reagents,[3–10)] few studies[11)] have been carried out on cabon-carbon bond formation with selenium reagents. We hoped to find a cyclization reaction which would provide a product suitably functionalized for further elaboration. Although numerous investigations in the area of polyolefin cyclization have been reported,[12,13)] we became interested in developing a cyclization reaction induced by organoselenium reagents because of the versatility of the selenyl functional groups.[3)] We now wish to report a new selenium-assisted cyclization reaction that results in carbon -carbon bond formation.

As a preliminary experiment, geranyl acetate (**3**) was treated with phenylselenyl chloride in acetic acid in the presence of sodium acetate, under the conditions reported by Clive,[7)] to determine whether the cyclization (**1**→**2**)[7)] is generally applicable for carbon–carbon bond formation. However, the products isolated were found to be (**4**) and (**5**) and not the expected cyclic compound (**9**) and (**10**).

Since cyclization of (**3**) could not be achieved under the conditions described, we turned our attention to the possible cyclization of (**5**). Compound (**5**) was alternatively synthesized by epoxidation of (**3**) with *m*-chloroperbenzoic acid, followed by treatment of the resulting epoxide (**7**) with the phenylselenium anion.[14)] The carbonium ion generated by acid treatment of (**5**) may be stabilized by participation of the phenylselenyl group, with *in situ* formation



1 2 3 4 : R¹=Ac; R²=PhSe 5 : R¹=H; R²=PhSe 6 : R¹=R²=H 7 8

Chart 1

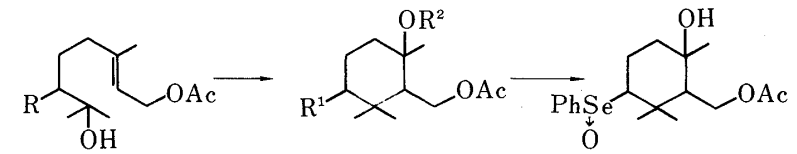
Table I. Cyclization of (5) initiated by Acid Catalysts[a]

Catalyst	Reaction time	Product yield[b] (%)	
		9	3
$BF_3 \cdot Et_2O$[c]	30 min	46	
$BF_3 \cdot Et_2O$	30 min	32.9	7.2
$SnCl_4$	40 min	26.3	7.1
CF_3CO_2H	15 min	65	
HCO_2H	2.5 hr	19.3	14.6

a) All the reactions were carried out at 0° in dry dichloromethane.
b) These figures indicate the isolated yields.
c) The reaction was run in wet dichloromethane.

of the seleniranium ion (**11**).[15] Thus, acid treatment of (**5**) under the conditions described in Table I gave the cyclic compound (**9**) [*m/e* 368, 370 (M^+)][16] and geranyl acetate (**3**).[15]

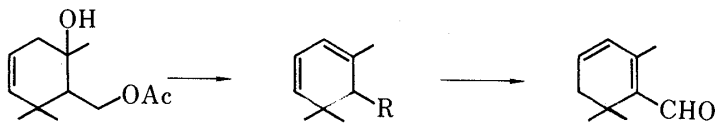
On the other hand, when the alcohol (**6**), obtained by reduction of (**7**) with lithium aluminium hydride in tetrahydrofuran followed by treatment of the resulting (**8**) with acetic anhydride in pyridine, was subjected to the same treatment as compound (**5**), the product obtained, although uncharacterized, was found not to be the corresponding cyclic compound (**12**). This remarkable difference in the reactivity of compounds (**5**) and (**6**) may be attributed to participation of the phenylselenyl group, as already mentioned. In order to demonstrate the facile manipulation of the functional groups thus introduced, the cyclic compound (**9**) was converted to safranal (**19**) as follows. Oxidation of (**9**) with 30% hydrogen peroxide gave the oxide (**13**), mp 139—140°, which on heating in carbon tetrachloride afforded the olefin (**14**) [*m/e* 212 (M^+)]. The diene alcohol (**16**) was obtained by dehydration of (**14**) with thionyl chloride in pyridine followed by hydrolysis of the resulting acetate (**15**) with 1 N potassium hydroxide in methanol. Oxidation of (**16**) with pyridinium chlorochromate in dichloromethane yielded



5 : R=PhSe
6 : R=H

9 : R^1=PhSe; R^2=H
10 : R^1=PhSe; R^2=Ac
12 : R^1=R^2=H

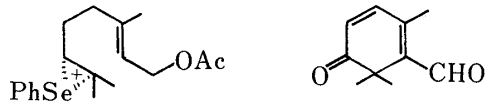
13



14

15 : R=CH_2OAc
16 : R=CH_2OH
17 : R=CHO

19



11

18

Chart 2

the 'over-oxidized' keto aldehyde (**18**) [IR 1660 and 1680 cm^{-1}, NMR δ 6.25 (1H, doublet, J=5 Hz) and 6.75 (1H, doublet, J=5 Hz)]. On the other hand, oxidation of (**16**) with chromium trioxide in pyridine gave the desired aldehyde (**17**) (IR 1710 cm^{-1}) which on reflux in pyridine furnished safranal (**19**). The NMR spectrum[17] of **19** was identical with that of an authentic sample.

Thus, a new cyclization reaction providing a product with suitable functionality for further elaboration has been developed and its application to the synthesis of safranal has been demonstrated.

Experimental

All melting points are uncorrected. IR spectra were recorded on a Hitachi EPI-3 spectrophotometer. NMR spectra were measured on a JEOL JNM-PMX-60 spectrometer. Chemical shifts are reported as δ values relative to internal tetramethylsilane. Mass spectra were taken on a Hitachi M-52G spectrometer.

Reaction of Geranyl Acetate (3) **with Phenylselenyl Chloride**——A solution of phenylselenyl chloride (200 mg) (1.04 mmol) in acetic acid (20 ml) was added to a solution of geranyl acetate (3) (200 mg) (1.02 mmol) and sodium acetate (85 mg) (1.04 mmol) in acetic acid (20 ml) under an atmosphere of nitrogen at 0°. The reaction mixture was stirred at room temperature for 15 min, then water (50 ml) was added. The resulting aqueous layer was extracted with benzene. The benzene layer was washed with saturated sodium hydrogen carbonate solution and saturated sodium chloride solution, and dried over Na_2SO_4. Removal of the solvent afforded the crude product, which was chromatographed on alumina (10 g) with benzene to give *trans*-1,7-diacetoxy-1,1,5-trimethyl-2-phenylselenyloct-5-ene (**4**) (290 mg; 69%) as a colorless oil. *Anal.* Calcd for $C_{20}H_{28}O_4Se$: C, 58.39; H, 6.86. Found: C, 58.33; H, 7.13. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (C=O). NMR ($CDCl_3$) δ: 1.57 (3H, singlet, CH_3), 1.60 (3H, singlet, CH_3), 1.88 (3H, singlet, CH_3), 2.04 (6H, singlet, $2\times CH_3$), 3.77 (1H, double doublet, J=1,5 Hz, >C<u>H</u>SePh), 4.60 (2H, doublet, J=7.0 Hz, -C<u>H</u>$_2$OAc), 5.30 (1H, triplet, J=7.0 Hz, olefinic proton), 7.20—7.86 (5H, multiplet, ArH). MS *m/e*: 410, 412 (M^+). Further elution with benzene gave *trans*-7-acetoxy-1,1,5-trimethyl-2-phenylselenyloct-5-en-1-ol (**5**) (94 mg; 25.0%) as a colorless oil. *Anal.* Calcd for $C_{18}H_{26}O_3Se$: C, 58.53; H, 7.10. Found: C, 58.87; H, 7.41. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3610 (OH) and 1720 (C=O). NMR ($CDCl_3$) δ: 1.26 (3H, singlet, CH_3), 1.33 (3H, singlet, CH_3), 1.67 (3H, singlet, CH_3), 2.00 (3H, singlet, CH_3), 3.70 (1H, double doublet, J=1,5 Hz, >C<u>H</u>SePh), 4.52 (1H, doublet, J=7.0 Hz, -C<u>H</u>$_2$OAc), 5.22 (1H, triplet, J=7.0 Hz, olefinic proton), 7.18—7.70 (5H, multiplet, ArH). MS *m/e*: 368, 370 (M^+).

Reaction of (7) **with Phenylselenium Anion**——A solution of diphenyl diselenide (2.4 g) (717 mmol) in ethanol (50 ml) was treated with sodium borohydride (0.5 g) (14.5 mmol) at 0°. The reaction mixture was stirred for 15 min at room temperature, then a solution of the epoxide (**7**) (2.78 g) (13.1 mmol) in ethanol (20 ml) was added and the stirring was continued for 1.5 hr at the same temperature. After removal of the solvent, water (20 ml) was added to the resulting crude product and the mixture was extracted with benzene. The benzene layer was washed with saturated sodium chloride solution and dried over Na_2SO_4. Removal of the solvent afforded β-hydroxy selenide (**5**) (4.6 g; 95.1%) as a colorless oil, which was identical with (**5**) (obtained above) as judged by IR ($CHCl_3$) and NMR ($CDCl_3$) spectral comparison.

Reaction of (5) **with Acid Catalyst**——A solution of selenide (**5**) (100 mg) (0.27 mmol) in dry dichloromethane (5 ml) was treated with trifluoroacetic acid (2.5 ml) under an atmosphere of nitrogen at 0°. After being stirred for 15 min at the same temperature, the reaction mixture was added to water (20 ml). The dichloromethane layer was washed with saturated sodium hydrogen carbonate solution and saturated sodium chloride solution, and dried over Na_2SO_4. Removal of the solvent afforded the crude product, which was chromatographed on alumina (2 g) with dichloromethane to give 2-acetoxymethyl-3-hydroxy-1,1,3-trimethyl-6-phenylselenylcyclohexane (**9**) (65 mg; 65%) as a colorless oil. *Anal.* Calcd for $C_{18}H_{26}O_3Se^{80}$: *m/e* 370.1045 (M^+). Found: *m/e* 370.1028 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3610 (OH) and 1720 (C=O). NMR ($CDCl_3$): 0.97 (3H, singlet, CH_3), 1.18 (3H, singlet, CH_3), 1.30 (3H, singlet, CH_3), 2.03 (3H, singlet, CH_3), 3.01 (1H, double doublet, J=2.5 and 5 Hz, >C<u>H</u>SePh), 5.1—4.7 (2H, multiplet, OC<u>H</u>$_2$OAc), 7.2—7.7 (5H, multiplet, ArH). Cyclization of (**5**) by using $BF_3\cdot Et_2O$, $SnCl_4$ and HCO_2H following the procedure described above was carried out to give (**9**) and (**3**) in the yields shown in Table I.

***trans*-7-Acetoxy-1,2-epoxy-1,1,5-trimethyloct-5-ene** (7)——A mixture of a solution of geranyl acetate (**3**) (1.9 g) (11.2 mmol) in dichloromethane (50 ml) and saturated sodium hydrogen carbonate solution (30 ml) was treated with *m*-chloroperbenzoic acid (2.0 g) (11.6 mmol). After being stirred for 2 hr at room temperature, the dichloromethane layer was washed with saturated sodium chloride solution and dried over Na_2SO_4. Removal of the solvent afforded the crude product, which was chromatographed on silica gel (40 g) with benzene to give the epoxide (**7**) (1.8 g; 87.4%) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (C=O). NMR ($CDCl_3$) δ: 1.22 (6H, singlet, $2\times CH_3$), 1.75 (3H, singlet, CH_3), 1.97 (3H, singlet, CH_3), 2.53 (1H, triplet, J=6 Hz, -C<u>H</u>-C), 4.53 (2H, doublet, J=7.0 Hz, C<u>H</u>$_2$OAc), 5.37 (1H, triplet, J=7.0 Hz, olefinic proton). MS *m/e*: 212 (M^+).

***trans*-1,1,5-Trimethyloct-4-en-1,7-diol (8)**——A solution of the epoxide (**7**) (1.8 g) (8.49 mmol) in dry ether (50 ml) was added to a suspension of lithium aluminium hydride (320 mg) (8.42 mmol) in dry ether (100 ml) and the whole was stirred for 2 hr at 0°. After addition of 10% aqueous sodium hydroxide solution, the inorganic material was removed by filtration and the solvent was distilled off. The aqueous layer was extracted with ether. The ethereal layer was washed with saturated sodium chloride solution and then dried over Na_2SO_4. Removal of the solvent by evaporation afforded the crude product, which was chromatographed on silica gel (40 g) with dichloromethane to give the alcohol (**8**) (780 mg; 55.3%) as a colorless oil. *Anal.* Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.37; H, 12.01. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3610 (OH). NMR ($CDCl_3$) δ: 1.23 (6H, singlet, $2\times CH_3$), 1.73 (3H, singlet, CH_3), 4.55 (2H, doublet, $J=7.0$ Hz, $C\underline{H}_2OAc$), 5.50 (1H, triplet, $J=7.0$ Hz, olefinic proton). MS *m/e*: 172 (M^+).

***trans*-7-Acetoxy-1,1,5-trimethyloct-5-en-1-ol (6)**——A solution of the alcohol (**8**) (780 mg) (4.7 mmol) and acetic anhydride (3 g) (29.4 mmol) in pyridine (30 ml) was stirred for 14 hr at room temperature. The reaction mixture was poured into water (50 ml) and extracted with benzene. The benzene layer was washed with saturated potassium hydrogen sulfate solution, saturated sodium hydrogen carbonate solution, and saturated sodium chloride solution, and dried over Na_2SO_4. Removal of the solvent afforded the crude product, which was chromatographed on silica gel (20 g) to give the acetate (**6**) (810 mg; 82.9%) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3610 (OH) and 1720 (C=O). NMR ($CDCl_3$) δ: 1.20 (6H, singlet, $2\times CH_3$), 1.73 (3H, singlet, CH_3), 2.07 (3H, singlet, CH_3), 4.63 (2H, doublet, $J=7.0$ Hz, $C\underline{H}_2OAc$), 5.40 (1H, triplet, $J=7.0$ Hz, olefinic proton). MS *m/e*: 208 (M^+).

2-Acetoxymethyl-3-hydroxy-1,1,3-trimethyl-6-phenylselenoxycyclohexane (13)——A solution of cyclohexane (**9**) (872 mg) (2.36 mmol) in methanol (2 ml) was treated with 5 drops of 30% hydrogen peroxide under stirring at 0°. After being stirred for 10 min at the same temperature, the reaction mixture was added to water (10 ml) and extracted with benzene. The benzene layer was washed with saturated sodium chloride solution and dried over Na_2SO_4. Removal of the solvent by evaporation gave a colorless solid, which was recrystallized from ethanol to give the selenoxide (**13**) (420 ml; 46.2%) as colorless needles, mp 139—140°, *Anal.* Calcd for $C_{18}H_{26}O_4Se$: C, 56.10; H, 6.80. Found: C, 56.08; H, 6.89. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3610 (OH) and 1720 (C=O). NMR ($CDCl_3$) δ: 1.23 (6H, singlet, $2\times CH_3$), 1.43 (3H, singlet, CH_3), 2.06 (3H, singlet, CH_3), 4.40 (2H, doublet, $J=2.5$ Hz, $C\underline{H}_2OAc$), 7.60 (5H, br singlet, ArH). MS *m/e*: 384, 386 (M^+).

2-Acetoxymethyl-3-hydroxy-1,1,3-trimethyl-5-cyclohexene (14)——A solution of selenoxide (**13**) (410 mg) (1.16 mmol) in carbon tetrachloride (50 ml) was refluxed for 16 hr under an atmosphere of nitrogen. Removal of the solvent afforded the crude product, which was chromatographed on silica gel (10 g) with benzene to give cyclohexane (**14**) (210 mg; 93.0%) as a colorless oil. *Anal.* Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.69; H, 9.22. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3610 (OH) and 1720 (C=O). NMR ($CDCl_3$) δ: 0.96 (3H, singlet, CH_3), 1.12 (3H, singlet, CH_3), 1.22 (3H, singlet, CH_3), 2.07 (3H, singlet, CH_3), 4.2—4.8 (2H, multiplet, $C\underline{H}_2OAc$), 5.18—5.75 (2H, multiplet, olefinic protons). MS *m/e*: 212 (M^+).

2-Acetoxymethyl-1,1,3-trimethyl-3,5-cyclohexadiene (15)——Thionyl chloride (115 mg) (0.97 mmol) and pyridine (90 mg) (1.2 mmol) were added to a solution of cyclohexane (**14**) (200 mg) (0.94 mmol) in dichloromethane (20 ml) under an atmosphere of nitrogen at 0°. The reaction mixture was stirred for 5 min, and water (50 ml) was added. The dichloromethane layer was separated and then washed with saturated potassium hydrogen sulfate solution, saturated sodium hydrogen carbonate and saturated sodium chloride solution, and dried over Na_2SO_4. Removal of the solvent afforded the crude product which was chromatographed on silica gel (5 g) with benzene to give the acetate (**15**) (162 mg) (88.5%) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (C=O). NMR ($CDCl_3$) δ: 0.97 (6H, singlet, $2\times CH_3$), 1.88 (3H, singlet, CH_3), 2.00 (3H, singlet, CH_3), 3.85—4.55 (2H, multiplet, $C\underline{H}_2OAc$), 5.15—5.88 (3H, multiplet, olefinic protons). MS *m/e*: 194 (M^+).

2-Hydroxymethyl-1,1,3-trimethyl-3,5-cyclohexadiene (16)——A solution of the acetate (**15**) (150 mg) (0.77 mmol) in methanol (10 ml) was treated with 1 N potassium hydroxide-methanol solution (3 ml) under stirring at room temperature. The reaction mixture was stirred for 4 hr at the same temperature, then water (50 ml) was added and the whole was extracted with benzene. The benzene layer was washed with saturated sodium chloride solution and dried over Na_2SO_4. Removal of the solvent afforded the crude product, which was chromatographed on silica gel (3 g) with dichloromethane to give the alcohol (**16**) (106 mg; 90.6%) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH). NMR ($CDCl_3$) δ: 1.00 (3H, singlet, CH_3), 1.11 (3H, singlet, CH_3), 1.86 (3H, singlet, CH_3), 3.58—3.95 (2H, multiplet, $C\underline{H}_2OH$), 5.20—5.87 (3H, multiplet, olefinic protons). MS *m/e*: 152 (M^+).

3-Keto-2,2,6-trimethylcyclohexa-4,6-dienocarboxaldehyde (18)——Pyridinium chlorochromate (300 mg) (1.39 mmol) was added to a solution of the alcohol (**16**) (100 mg) (0.66 mmol) in dichloromethane (20 ml) under an atmosphere of nitrogen at room temperature. The reaction mixture was stirred for 2 hr at the same temperature, then water (20 ml) was added. The dichloromethane layer was separated, washed with saturated sodium chloride solution, and dried over Na_2SO_4. Removal of the solvent afforded the crude product, which was chromatographed on silica gel (2 g) with benzene to give the keto aldehyde (**18**) (13 mg; 12.1%) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680 (C=O) and 1660 (C=O). NMR ($CDCl_3$) δ: 1.30 (6H, singlet, $2\times CH_3$), 2.31 (3H, singlet, CH_3), 6.25 (1H, doublet, $J=5$ Hz, olefinic proton), 6.75 (1H, doublet, $J=5$ Hz, olefinic proton), 10.50 (1H, singlet, $C\underline{H}O$): MS *m/e*: 164 (M^+).

2,3,6-Trimethylcyclohexa-3,5-dienocarboxaldehyde (17)——The alcohol (**16**) (85 mg) (0.56 mmol) was

added to a complex mixture of chromium trioxide (330 mg) (3.3 mmol) and pyridine (3.3 g) under an atmosphere of nitrogen at room temperature. The whole was stirred for 1 hr, then water (50 ml) was added to the reaction mixture. The resulting mixture was extracted with benzene. The benzene layer was washed with saturated potassium hydrogen sulfate solution, saturated sodium hydrogen carbonate solution and saturated sodium chloride solution, and dried over Na_2SO_4. Removal of the solvent afforded the crude product, which was chromatographed on silica gel (2 g) with benzene–hexane (1: 1) to give aldehyde (**17**) (23 mg, 27.4%) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (C=O). NMR ($CDCl_3$) δ: 1.05 (3H, singlet, CH_3), 1.10 (3H, singlet, CH_3), 1.82 (3H, singlet, CH_3), 2.38 (1H, doublet, $J=2.5$ Hz, C<u>H</u>–CHO), 5.40—6.10 (3H, multiplet, olefinic protons), 9.24 (1H, doublet, $J=2.5$ Hz, C<u>H</u>O), MS *m/e*: 150 (M^+).

Safranal (19)——A solution of the aldehyde (**17**) (23 mg) (0.15 mmol) in pyridine (2 ml) was refluxed under an atmosphere of nitrogen for 2.5 hr. Water (10 ml) was then added to the reaction mixture, and the whole was extracted with benzene. The benzene layer was washed with saturated potassium hydrogen sulfate solution, saturated sodium hydrogen carbonate solution and saturated sodium chloride solution, and dried over Na_2SO_4. Removal of the solvent afforded the crude mixture, which was chromatographed on silica gel (1 g) with benzene–hexane (1: 1) to give safranal (**19**) (9 mg) (39.1%) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1665 (C=O): NMR ($CDCl_3$) δ: 1.21 (6H, singlet, $2\times CH_3$), 2.17 (3H, singlet, CH_3), 2.83 (2H, singlet, $-C\underline{H}_2C$), 5.37—5.70 (2H, multiplet, olefinic protons), 10.20 (1H, singlet, C<u>H</u>O): MS *m/e*: 150 (M^+). The spectral data were identical with those of an authentic sample.

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