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A New Method for Selective Epoxidation and a Biogenetic-Type Synthesis of Linalyloxides[1]

TETSUJI KAMETANI, HIDEO NEMOTO,
AND KEIICHIRO FUKUMOTO

Pharmaceutical Institute, Tohoku University,
Aobayama, Sendai 980, Japan

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[2.3]Sigmatropic rearrangement and successive selective epoxidation of geranyl selenide (**2**), citronellyl selenide (**4**), and farnesyl selenide (**6**) are described, and a simple synthesis of *trans*-(**15**) and *cis*-linalyloxides (**16**) along biosynthetic lines is also reported.

INTRODUCTION

In pursuing biogenetic-type synthesis of natural products by using oxidation as a key reaction (*1*, *2*), we became interested in the epoxidation of olefins because of its important role in the biogenesis of natural products (*3*). Our approach involves the application of organoselenium-catalyzed epoxidation of olefins by hydrogen peroxide, which has not been reported previously as a useful synthetic method (*4*),[2] to the synthesis of *trans*- and *cis*-linalyloxides which have been isolated from *Lilium makinoi* (*5*) and *Humulus lupulus* (*6*) and assigned the structures (**15**) and (**16**), respectively, by Okazaki *et al.* (*5*).

Treatment of geraniol (**1**) with tri-*n*-butylphosphine and *o*-nitrophenyl selenocyanide in dry tetrahydrofuran (*7*) gave in a high yield the key intermediate (**2**). The selenides (**4**) and (**6**) were also obtained from citronellol (**3**) and farnesol (**5**), respectively, in a similar manner.

Second, oxidation of selenides **2**, **4**, and **6** with hydrogen peroxide was tried. Thus, intermediate (**2**) was treated with 30% hydrogen peroxide in the presence of pyridine in dichloromethane (*8*, *9*) to give quantitatively the epoxide (**7**), the structure of which was determined by direct comparison with authentic sample, prepared as follows. Oxidation of linalool (**12**) with *m*-chloroperbenzoic acid in dichloromethane in the presence of sodium hydrogen carbonate aqueous solution (*10*) gave in a high yield the epoxide (**7**), which was identical with the sample obtained as above. Since it had been reported that benzeneselenic acid generated by the elimination of the selenoxide group is further oxidized to benzeneseleninic acid with hydrogen peroxide (*11*), we considered that *o*-nitrobenzeneseleninic acid (**14**), which is produced by the [2.3]sigmatropic rearrangement of the selenoxide (**13**), followed by further oxidation of the *o*-nitrobenzeneselenic

[1] Dedicated to Professor William S. Johnson on the occasion of his 65th birthday.

[2] Hydrogen peroxide, in the presence of selenium dioxide, has been reported to hydroxylate (4*a*), acetoxylate (4*b*), and epoxidize (4*c*) the olefins. After completion of this work (4*d*), Grieco *et al.* (4*e*) reported the epoxidation of olefins with benzeneseleninic acid and hydrogen peroxide.

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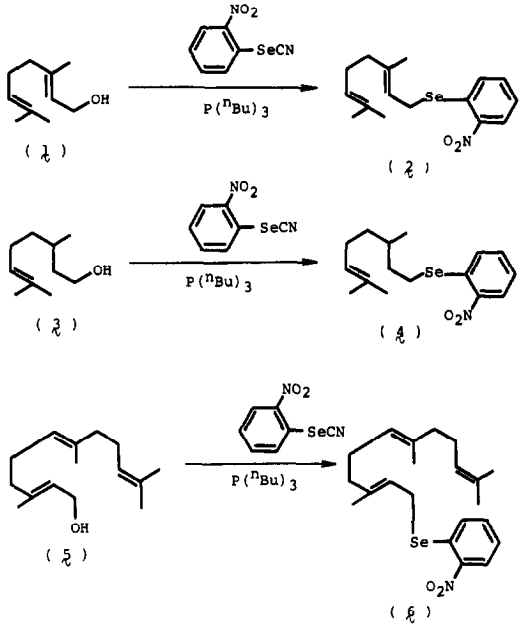
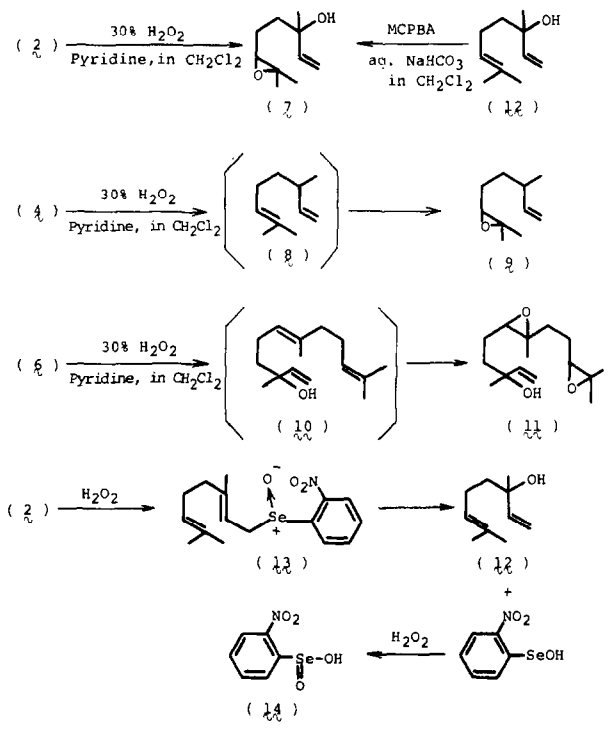
acid generated, catalyzes the epoxidation of the olefin system. Although the [2.3]sigmatropic rearrangement of selenoxide (*9*, *12*) and the olefin synthesis by elimination of phenyl selenoxide (*11*, *13*) using an excess amount of hydrogen peroxide have been reported, no epoxide formation has been described. Thus, we could demonstrate that the linalool which was formed during the reaction was epoxidized selectively at six and seven positions in the presence of a large excess of hydrogen peroxide. Selenide **4** seems to give olefin (**8**), which does not have the hydroxyl group of linalool (**12**) in the first stage of oxidation, and it was also oxidized under the same conditions used for the selenide (**2**) in order to determine whether the hydroxyl group of linalool (**12**) plays an important role in this selective epoxidation. Thus selenide (**4**) was subjected to the oxidation under the same conditions used for the selenide (**2**), and the



SCHEME 1

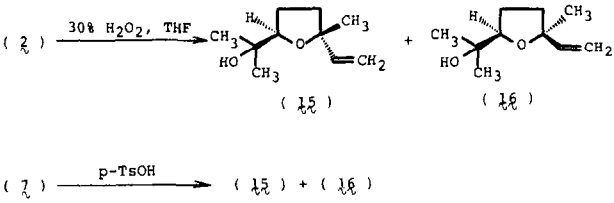
epoxide (**9**) was obtained as a single product in a high yield. This finding shows that the hydroxyl group of the olefinic compound is not important for the selectivity of epoxidation. Furthermore, the oxidation of the selenide (**6**), which seems to afford nerolidol (**10**) at first, was examined for selectivity of epoxidation of two trisubstituted olefins; the diepoxide (**11**) was obtained in a high yield. Thus we showed that monosubstituted olefins cannot be epoxidized, even if a large excess of hydrogen peroxide is used, and that both trisubstituted olefins are epoxidized unselectively under these conditions in the case of the selenide (**6**).

On the other hand, reaction of the selenide (**2**) with 30% hydrogen peroxide in tetrahydrofuran without any buffer gave directly in a high yield *trans*- (**15**) and *cis*-linalyloxide (**16**) in almost equal amounts formed via oxidation of the selenide, [2.3]sigmatropic rearrangement, epoxidation, and then ring closure. The spectroscopic data of our products (**15** and **16**) were found to be identical with those of the authentic specimens



SCHEME 2

described in the literature (*14*). The epoxide (**7**) was also treated with *p*-toluenesulfonic acid in ether to give (**15**) and (**16**) in almost the same yields as described above. Thus we could realize an effective synthesis of linalyloxides from geraniol by using a new method of epoxidation.



SCHEME 3

EXPERIMENTAL

Geranyl o-Nitrophenyl Selenide (**2**)

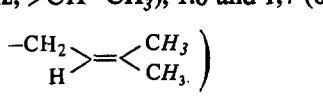
To a solution of 2.31 g (14.98 mmol) of geraniol (**1**) and 3.4 g (14.98 mmol) of *o*-nitrophenyl selenocyanate in 50 ml of anhydrous tetrahydrofuran, 3.63 g (17.97 mmol) of tri-*n*-butylphosphine was added dropwise at room temperature. After stirring for 2 hr, the solvent was removed *in vacuo*. Chromatography of the residue on silica gel (150 g) using benzene : hexane (1 : 2) afforded 4.5 g (89%) of geranyl *o*-nitrophenyl selenide as a

yellow oil, a part of which was distilled for spectral measurements and microanalysis, bp_3 160–165°C; nmr (CCl_4) δ 1.58, 1.66 and 1.74 (9H, each s, 3 × CH_3), 2.0–2.15 (4H, broad s, $-CH_2-CH_2-$), 3.5 (2H, d, J = 8 Hz, $-CH_2-$SeAr) 4.8–5.6 (2H, m, olefinic protons), 7.0–7.5 (3H, m, aromatic protons), 8.18 (1H, d, J = 8 Hz, aromatic proton); mass spectrum, *m/e* 337 and 339 (M^+).

Anal. Calcd for $C_{16}H_{21}NO_2Se$: C, 56.80; H, 6.26; N, 4.41. Found: C, 57.25; H, 6.45; N, 4.10.

Citronellyl o-Nitrophenyl Selenide (**4**)

In the same manner described above, a solution of 2.3 g (14.74 mmol) of citronellol (**3**) and 3.4 g (14.98 mmol) of *o*-nitrophenyl selenocyanate in 50 ml of anhydrous tetrahydrofuran was treated with 3.6 g (17.82 mmol) of tri-*n*-butylphosphine. After purification by chromatography on silica gel (150 g) using benzene:hexane (1:2), 4.8 g (95.8%) of citronellyl *o*-nitrophenyl selenide (**4**) was obtained as a yellow oil, a part of which was distilled for spectral determination and microanalysis, $bp_{0.05}$ 150–155°C; nmr (CCl_4) δ 0.96 (3H, d, J = 5 Hz, >CH–CH_3), 1.6 and 1,7 (6H, each s,



2.93 (2H, t, J = 7 Hz, $-CH_2-$Se–Ar), 4.8–5.3 (1H, m, olefinic proton), 7.1–7.6 (3H, m, aromatic protons), 8.2 (1H, d, J = 7 Hz, aromatic proton); mass spectrum, *m/e* 339 and 341 (M^+).

Anal. Calcd for $C_{16}H_{23}NO_2Se$: C, 56.47; H, 6.81; N, 4.12. Found: C, 56.26; H, 6.83; N, 4.10.

Farnesyl o-Nitrophenyl Selenide (**6**)

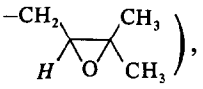
To a solution of 1.1 g (4.96 mmol) of farnesol (**5**) and 1.3 g (5.73 mmol) of *o*-nitrophenyl selenocyanate in 20 ml of anhydrous tetrahydrofuran was added 1.2 g (5.94 mmol) of tri-*n*-butylphosphine, and the same workup as used for the selenide (**2**) was carried out. After purification by chromatography on silica gel (50 g) using benzene:hexane (1:2), 1.7 g (84.3%) of farnesyl *o*-nitrophenyl selenide (**6**) was obtained as a yellow oil; nmr (CCl_4) δ 1.55 (6H, s, 2 × CH_3), 1.65 and 1.75 (6H, each s, 2 × CH_3), 1.85–2.25 (8H, m, 4 × CH_2), 3.5 (2H, d, J = 8 Hz, $-CH_2-$Se–Ar), 4.8–5.55 (3H, m, olefinic protons), 7.0–7.5 (3H, m, aromatic protons), and 8.2 (1H, d, J = 8 Hz, aromatic proton); mass spectrum, *m/e* 405 and 407 (M^+).

Anal. Calcd for $C_{21}H_{29}NO_2Se$: C, 62.06; H, 7.19; N, 3.45. Found: C, 61.60; H, 7.21; N, 3.44.

6,7-Epoxylinalool (**7**)

(*i*) *From geranyl selenide* (**2**). To a solution of 1 g (2.96 mmol) of geranyl selenide (**2**) in 3 ml of pyridine and 30 ml of dichloromethane, 4 ml (35.3 mmol) of 30% hydrogen peroxide was added dropwise at room temperature. After stirring for 13 hr at room temperature, the organic layer was washed with water, 10% sodium hydroxide aqueous solution, and saturated sodium chloride solution and was then dried over anhydrous sodium sulfate. After evaporation of solvent, the residue was distilled to give

483 mg (96%) of 6,7-epoxylinalool (**7**) as a colorless oil, bp_6 100–102°C; nmr (CCl_4) δ 1.25 (9H, s, 3 × CH_3), 1.4–1.8 (4H, m, $-CH_2-CH_2-$), 2.6 (1H, t, $J = 6$ Hz,



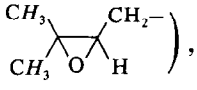
and 4.8–6.1 (3H, m, $-CH=CH_2$); mass spectrum, *m/e* 153 (M^+-17).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.20; H, 10.67.

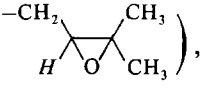
(*ii*) *From linalool* (**12**). To a mixture of 4.62 g (30 mmol) of linalool (**12**), 200 ml of dichloromethane, and 100 ml of saturated sodium hydrogen carbonate aqueous solution was added in small portions 7.4 g (42.9 mmol) of *m*-chloroperbenzoic acid under ice cooling. After stirring for 1 hr at 0°C, the organic layer was separated, washed with water, 10% sodium hydroxide solution, and saturated sodium chloride solution, and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was distilled to afford 4.93 g (96.7%) of 6,7-epoxylinalool (**7**) as a colorless oil, bp_6 100–102°C, which was identical with the sample obtained from geranyl selenide (**2**) in its ir ($CHCl_3$) and nmr (CCl_4) spectral comparison.

2,3-Epoxy-2,6-dimethylocta-7-ene (**9**)

In the same manner described for a synthesis of 6,7-epoxylinallol (**7**) from geranyl selenide (**2**), a solution of 1.02 g (3 mmol) of citronellyl selenide (**4**) in 30 ml of dichloromethane and 3 ml of pyridine was treated with 4 ml (35.3 mmol) of 30% hydrogen peroxide at room temperature and stirred for 13 hr at room temperature. After treatment of the reaction mixture as usual, 450 mg (96.7%) of 2,3-epoxy-2,6-dimethylocta-6-ene (**9**) was obtained as an oil, bp_6 73–75°C; nmr (CCl_4) δ 1.00 (3H, d, $J = 7$ Hz, $>CH-CH_3$), 1.2 and 1.25 (6H, each s,



2.55 (1H, broad s,



and 4.7–6.0 (3H, m, $-CH=CH_2$); mass spectrum, *m/e* 154 (M^+).

Anal. Calcd for $C_{10}H_{18}O \cdot 1/8H_2O$: C, 76.74; H, 11.75. Found: C, 76.85; H, 11.72.

6,7,10,11-Diepoxynerolidol (**11**)

A solution of 1.043 g (2.56 mmol) of farnesyl selenide (**6**) in 30 ml of dichloromethane and 3 ml of pyridine was treated with 4 ml (35.3 mmol) of 30% hydrogen peroxide and stirred for 13 hr at room temperature. After the usual workup and distillation of the reaction mixture, 592 mg (91%) of 6,7,10,11-diepoxynerolidol (**11**) was obtained as an oil, bp_3 115–120°C; nmr (CCl_4) δ 1.23 (12H, s, 4 × CH_3), 2.6 (2H, broad s, C_6-H and $C_{10}-H$), and 4.8–6.1 (3H, m, $-CH=CH_2$); mass spectrum, *m/e* 237 (M^+-OH), 239 (M^+-CH_3).

trans- (**15**) *and cis-Linalyloxides* (**16**)

(*i*) *From geranyl selenide* (**2**). To a solution of 3 g (8.87 mmol) of geranyl selenide (**2**) in 30 ml of tetrahydrofuran was added dropwise 12 ml (105.9 mmol) of 30% hydrogen peroxide, and the stirring was continued for 13 hr at room temperature. The reaction mixture was diluted with 100 ml of water and extracted with ether. The ethereal layer was washed with water, 10% sodium hydroxide solution, and saturated sodium chloride solution and then dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was subjected to chromatography on silica gel (120 g) using hexane:benzene (3:2) to give 604 mg (40%) of *trans*-linalyloxide (**15**) and 573 mg (38%) of *cis*-linalyloxide (**16**). The nmr spectra (CCl_4) of these compounds were superimposable upon those in the literature (*14*).

(*ii*) *From 6,7-epoxylinalool* (**7**). A solution of 1.25 g (7.35 mmol) of 6,7-epoxylinalool (**7**), 5 mg of *p*-toluenesulfonic acid, and 30 ml of ether was stirred for 1 hr at room temperature; then it was washed with saturated sodium hydrogen carbonate solution and saturated sodium chloride solution and finally dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was subjected to chromatography on silica gel (60 g) using hexane:benzene (3:2) to give 561 mg (45%) of *trans*-linalyloxide (**15**) and 525 mg (42%) of *cis*-linalyloxide (**16**), which were found to be identical with the samples described above.

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