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Chemical Transformation of Terpenoids. VIII.[1] Anodic Oxidation of Geranyl Acetate

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Constant-current electrolysis of geranyl acetate (2) in CH_3CN–H_2O afforded eight oxidation products (3—10) which were presumed to be formed through initial oxidation of the double bond at C_6–C_7. Based on the results of electrolysis of 2 in CH_3CN–$H_2{}^{18}O$, we have found that the oxygen atom(s) in the products (3—10) is(are) derived from water used as the reaction medium.

Keywords anodic oxidation; geraniol; geranyl acetate; geranyl acetate 6,7-epoxide; water-^{18}O; constant-current electrolysis

Many chemical studies on the cyclization of acyclic terpenoids have been reported.[2] On the other hand, oxidation–reduction reactions have been shown to play important roles in the biogenesis of cyclic terpenoids. In this connection, we have been interested in the electrochemical modification of acyclic terpenoids, since only a limited number of studies on chemical transformation of acyclic terpenoids by means of electrochemical reactions have been reported.[3] As part of our continuing studies on chemical transformation of readily available acyclic terpenoids[4] and electrochemical modification of naturally abundant materials[5] leading to biologically active substances, we have been investigating the electrochemical modification of acyclic terpenoids. In this paper, we report the anodic oxidation of geranyl acetate (**2**), prepared from geraniol (**1**) by acetylation, yielding various oxidation products.[6]

After several preliminary examinations of anodic oxidation of geranyl acetate (**2**) under various reaction conditions, it was found that the constant-current electrolysis of **2** in CH_3CN–H_2O (10 : 1) containing $NaClO_4$ as the supporting electrolyte afforded eight products with a total conversion yield of 53%. The product mixture was subjected to silica gel column chromatography and subsequently to high-performance liquid chromatography (HPLC) to furnish **3** (in 7% yield), **4** (42%), **5** (3%), **6** (8%), **7** (8%), **8** (2%), **9** (7%), and **10** (1%).

The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **3**, a colorless oil, $C_{12}H_{20}O_3$, showed signals due to one olefinic proton and one methine proton attached to a carbon bearing an oxygen function. In addition, it showed the presence of one acetoxyl group, one vinyl methyl group, two tertiary methyl groups on a carbon having an oxygen function, and one methylene proton attached to a carbon bearing an acetoxyl function. The infrared (IR) spectrum of **3** showed an ester carbonyl absorption band (1738 cm^{-1}), while a fragment ion peak [m/z 152 ($M^+ -$ AcOH)] was observed in its mass spectrum (MS). Based on these spectral data, the structure of **3** was determined to be geranyl acetate 6,7-epoxide [*i.e.*, (2*E*)-1-*O*-acetyl-3,7-dimethyl-2-octen-1-ol 6,7-epoxide]. The structure was chemically substantiated by an alternative synthesis of **3** from **2** by *m*-chloroperbenzoic acid oxidation.

The IR spectrum of the major product **4**, a colorless oil, $C_{12}H_{20}O_4$, showed absorption bands ascribable to hydroxyl (3430 cm^{-1}) and ester (1726 cm^{-1}) groups. The ^{1}H-NMR spectrum of **4** showed signals attributable to two tertiary methyl groups on a carbon bearing an oxygen function, one vinyl methyl group, one methine proton geminal to a hydroxyl function, and one olefinic proton. Thus, **4** was concluded to be 6,7-dihydroxygeranyl acetate [(2*E*)-1-*O*-acetyl-3,7-dimethyl-6,7-dihydroxy-2-octen-1-ol].

The IR spectrum of **5**, a colorless oil, $C_{12}H_{20}O_3$, showed two carbonyl absorption bands at 1739 and 1720 cm^{-1} (an ester and a ketone). In its ^{1}H-NMR spectrum, signals due to a methyl group on a carbonyl residue and a secondary methyl group were observed. The ^{1}H-NMR spectrum also showed the presence of one vinyl methyl group and one acetoxyl group. From these findings, **5** was shown to be (2*E*)-1-*O*-acetyl-3,6-dimethyl-7-oxo-2-octen-1-ol, which was presumably formed through a 1,2-shift of a methyl group at C-7 to C-6 in the carbenium ion **i**.

The IR spectrum of **6**, a colorless oil, $C_{12}H_{20}O_3$, showed absorption bands due to hydroxyl (3614 cm^{-1}) and ester (1715 cm^{-1}) groups. The ^{1}H-NMR spectrum of **6** showed signals assignable to three olefinic protons [δ 5.37 (t, $J=$ 6.5 Hz, 2-H); δ 5.61 (B in ABM$_2$, $J_{AB}=15.5$ Hz, $J_{BM}=$ 6.5 Hz, 5-H); δ 5.67 (A in ABM$_2$, $J_{AB}=15.5$ Hz, $J_{AM}=0$ Hz, 6-H)], two tertiary methyl groups on a carbon having a hydroxyl group, and one vinyl methyl group, as well as an acetoxyl group. Based on these data, the structure of **6** was determined to be (2*E*,5*E*)-1-*O*-acetyl-3,7-dimethyl-7-hydroxy-2,5-octadien-1-ol.

The IR spectrum of **7**, a colorless oil, $C_{12}H_{20}O_3$, exhibited two carbonyl absorption bands at 1741 and 1715 cm^{-1} (an ester and a ketone). The ^{1}H-NMR spectrum of **7** showed signals attributable to two secondary methyl groups,

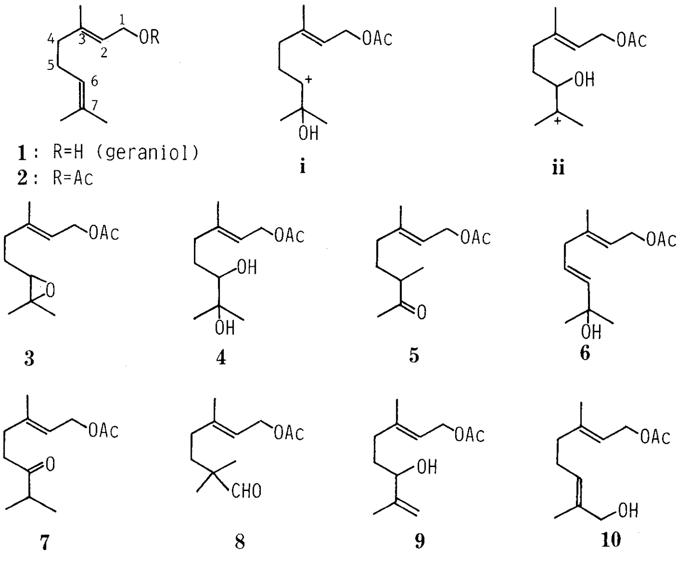
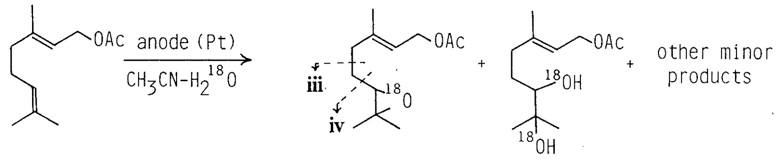


Chart 1



2 3a 4a

Chart 2

one vinyl methyl group, and one olefinic proton. From these findings, **7** was concluded to be (2*E*)-1-*O*-acetyl-3,7-dimethyl-6-oxo-2-octen-1-ol, which was presumably formed through a 1,2-hydride shift from C-6 to C-7 in the carbenium ion **ii**.

The ^{1}H-NMR spectrum of **8**, a colorless oil, $C_{12}H_{20}O_3$, showed a signal due to a formyl proton besides signals due to two tertiary methyl groups, one vinyl methyl group, and one acetoxyl group. The IR spectrum of **8** exhibited two carbonyl absorption bands due to an ester function and an aldehyde function (1735, 1720 cm^{-1}). Thus, the structure of **8** was determined to be (2*E*)-1-*O*-acetyl-3,6-dimethyl-6-formyl-2-hepten-1-ol, which was assumed to be formed by a 1,2-shift of the C_5–C_6 bond from C-6 to C-7 in the carbenium ion **ii**.

The IR spectrum of **9**, a colorless oil, $C_{12}H_{20}O_3$, showed absorptions due to hydroxyl (3434 cm^{-1}), ester (1735 cm^{-1}), and exomethylene (903 cm^{-1}) groups. The ^{1}H-NMR spectrum of **9** showed signals assignable to one methine proton geminal to hydroxyl function, two vinyl methyl groups, and one exomethylene group. Thus, the structure of **9** was concluded to be (2*E*)-1-*O*-acetyl-3,7-dimethyl-6-hydroxy-2,7-octadien-1-ol.

The structure of the final product **10** was assigned as ω-hydroxygeranyl acetate [*i.e.*, (2*E*,6*E*)-1-*O*-acetyl-3,7-dimethyl-8-hydroxy-2,6-octadien-1-ol] on the basis of the physicochemical evidence. The assignment was corroborated by the direct comparison (IR, ^{1}H-NMR, and MS) of **10** with an authentic sample.[4a)]

In order to improve the selectivity of the reaction and obtain a better yield of the products, cyclic voltammetry of geranyl acetate (**2**) in CH_3CN–H_2O containing $NaClO_4$ was carried out. It has been found that **2** possesses two oxidation potentials (1.65 and 2.16 V) *vs.* a standard calomel electrode (S.C.E.). In consequence, **2** was subjected to controlled potential electrolysis at 1.65 V *vs.* S.C.E. in CH_3CN–H_2O (10 : 1) containing $NaClO_4$. However, the resulting products were similar to those obtained above under constant-current electrolytic conditions.

To shed light on the source of the oxygen atom(s) in the products obtained by the electrolysis of **2**, we next examined the constant-current electrolysis of **2** in CH_3CN–$H_2{}^{18}O$ (10:1) containing $NaClO_4$. The reaction mixture, which contained eight products, the same as those obtained above by electrolysis of **2** in CH_3CN–H_2O, as shown by thin layer chromatography (TLC) analysis, was purified by silica gel column chromatography to furnish **3a** (6%) and **4a** (35%) as the major products. The IR and ^{1}H-NMR spectra of **3a** and **4a** were quite similar to those of **3** and **4**. In the MS of **3a**, characteristic fragment ion peaks were observed at *m*/*z* 154 (M^+ – AcOH), *m*/*z* 87 (**iii**), and *m*/*z* 73 (**iv**), which are larger by 2 mass units than those obtained in the MS of **3**. Furthermore, the high-resolution MS of **3a** revealed the following compositions of those ions: $C_{10}H_{16}{}^{18}O$ for the ion of *m*/*z* 154, $C_5H_9{}^{18}O$ for *m*/*z* 87, and $C_4H_7{}^{18}O$ for *m*/*z* 73, respectively. In the same manner as for **3a**, the elemental composition of a fragment ion peak at *m*/*z* 174 observed in the MS of **4a** was clarified to be $C_{10}H_{18}{}^{18}O_2$ (M^+ – AcOH). Based on these findings, it has been ascertained that the oxygen atom(s) in the anodic oxidation products, **3a** and **4a**, is(are) derived from water used as the reaction medium.

Furthermore, constant-current electrolysis of geranyl acetate 6,7-epoxide (**3**) under the same reaction conditions as for geranyl acetate (**2**) gave **4** (40%), **6** (4%), **9** (4%), and **10** (1%) in 52% conversion. It has been presumed therefore that, among the eight anodic oxidation products, four products (**4**, **6**, **9**, and **10**) are formed *via* the carbenium ions (**i**, **ii**) and/or **3**, whereas the other products (**5**, **7**, and **8**) may not be formed by way of **3**.

In conclusion, it has been found that anodic oxidation of geranyl acetate (**2**) results in the formation of eight kinds of products (**3**—**10**) which may be derived from the oxidation of the double bond at C_6–C_7 of **2**.

Experimental

The following instruments were used to obtain physical data: IR spectra, a Hitachi 260-30 infrared spectrometer; ^{1}H-NMR spectra, a JEOL JMN FX-90Q (90 MHz) NMR spectrometer or a JEOL JMN GX-500 (500 MHz) NMR spectrometer [in $CDCl_3$ solution with tetramethylsilane (TMS) as an internal standard unless otherwise specified]; MS and high-resolution MS, a JEOL JMS-D300 mass spectrometer or a JEOL JMN-01SG-2 mass spectrometer. For HPLC, a Shimadzu LC-5A chromatograph with an refraction index detector was used. Silica gel (Merck, Kieselgel 60, 70—230 mesh) and precoated TLC plates (Merck, Kieselgel $60F_{254}$) were used for column chromatography and TLC. Detection of spots on TLC was done by spraying 1% $Ce(SO_4)_2$–10% H_2SO_4 or 5% vanillin–concentrated H_2SO_4 with subsequent heating. Water-^{18}O (90% atom ^{18}O) was purchased from Amersham Japan Co. Ltd. Cyclic voltammetry was carried out on a three-electrode system using a linear scanning unit (Hokuto Denko Co., Model HB-101) connected with a potentiostat (Hokuto Denko Co., Model PS-500B). As electrode systems, a glassy-carbon indicator electrode, a glassy-carbon electrode, and a S.C.E. were used. The indicator electrode was prepared from a cut of glassy carbon (GC-20, Tokai Carbon Co.), coated on one side with epoxy resin, in a glass cylinder. The S.C.E. was separated by an agar plug containing 0.1 M sodium perchlorate. Current-potential curves were recorded on a Toa XYR-2A XY recorder at a scanning rate of 50 mV·s^{-1}. For preparative oxidations, a potentiostat/galvanostat apparatus (Hokuto Denko Co., Model HA-105) was used.

Constant-Current Electrolysis of 2 A solution of geranyl acetate (**2**, 250 mg) in CH_3CN (116 ml)–H_2O (11.6 ml) containing $NaClO_4 \cdot H_2O$ (1.57 g) was subjected to constant-current electrolysis (Pt electrode, 1 mA/cm^2) in an ice-cooling bath for 1 h. The reaction mixture was concentrated under reduced pressure to *ca.* 20 ml, then the whole was poured into water and extracted with EtOAc. The EtOAc extract was taken and washed with aqueous saturated NaCl, then dried over $MgSO_4$. Removal of the solvent under reduced pressure from the EtOAc extract gave a product, which was purified by column chromatography (SiO_2 25 g, *n*-hexane : EtOAc = 15 : 1→8 : 1→3 : 2) to furnish **3** (9.5 mg, 7%), **4** (37.1 mg, 42%), a mixture of **5**, **7**, and **8**, and a mixture of **6**, **9**, and **10** along with recovered **2** (47% recovery). The mixture of **5**, **7**, and **8** was further separated by HPLC (YMC-A014, *n*-hexane : EtOAc = 10 : 1) to give **5** (3.6 mg, 3%), **7** (10.7 mg, 8%), and **8** (2.6 mg, 2%). The mixture of **6**, **9**, and **10** was also separated by HPLC (YMC-A014, *n*-hexane : EtOAc = 5 : 1) to give **6** (10.5 mg, 8%), **9** (9.4 mg, 7%), and **10** (2.1 mg, 1%).

3: A colorless oil. IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 1738. ^{1}H-NMR (90 MHz) δ: 1.27, 1.31 (3H each, both s, 7-CH$_3$ × 2), 1.73 (3H, s, 3-CH$_3$), 2.06 (3H, s, OAc), 2.71 (1H, t, J = 6 Hz, 6-H), 4.59 (2H, d, J = 7 Hz, 1-H$_2$), 5.40 (1H, t, J = 7 Hz, 2-H). MS m/z (%): 152 (M$^+$ − AcOH, 0.3), 85 (100), 71 (79). *Anal.* Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.61; H, 9.63.

4: A colorless oil. IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 3430, 1726. ^{1}H-NMR (90 MHz) δ: 1.17, 1.21 (3H each, both s, 7-CH$_3$ × 2), 1.73 (3H, s, 3-CH$_3$), 2.06 (3H, s, OAc), 3.35 (1H, dd, J = 3, 9 Hz, 6-H), 4.59 (2H, d, J = 7 Hz, 1-H$_2$), 5.40 (1H, t-like, 2-H). MS m/z (%): 170 (M$^+$ − AcOH, 1), 59 (100). *Anal.* Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.48; H, 9.45.

5: A colorless oil. IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 1739, 1720. ^{1}H-NMR (90 MHz) δ: 1.10 (3H, d, J = 6.5 Hz, 6-CH$_3$), 1.70 (3H, s, 3-CH$_3$), 2.06 (3H, s, OAc), 2.15 (3H, s, 7-CH$_3$), 4.58 (2H, d, J = 7 Hz, 1-H$_2$), 5.31 (1H, t, J = 7 Hz, 2-H). MS m/z (%): 152 (M$^+$ − AcOH, 1), 84 (100). *Anal.* Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.88; H, 9.46.

6: A colorless oil. IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 3614, 1738. ^{1}H-NMR (500 MHz) δ: 1.33 (6H, s, 7-CH$_3$ × 2), 1.69 (3H, s, 3-CH$_3$), 2.06 (3H, s, OAc), 2.75 (2H, M$_2$ in ABM$_2$, J_{AM} = 0 Hz, J_{BM} = 6.5 Hz, 4-H$_2$), 4.60 (2H, d, J = 6.5 Hz, 1-H$_2$), 5.37 (1H, t, J = 6.5 Hz, 2-H), 5.61 (1H, B in ABM$_2$, J_{AB} = 15.5 Hz, J_{BM} = 6.5 Hz, 5-H), 5.67 (1H, A in ABM$_2$, J_{AB} = 15.5 Hz, J_{AM} = 0 Hz, 6-H). MS m/z (%): 152 (M$^+$ − AcOH, 14), 81 (100). *Anal.* Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.82; H, 9.56.

7: A colorless oil. IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 1741, 1715. ^{1}H-NMR (90 MHz) δ: 1.10 (6H, d, J = 7 Hz, 6-CH$_3$ × 2), 1.71 (3H, s, 3-CH$_3$), 2.05 (3H, s, OAc), 4.57 (2H, d, J = 7 Hz, 1-H$_2$), 5.34 (1H, t, J = 7 Hz, 2-H). MS m/z (%): 152 (M$^+$ − AcOH, 4), 68 (100). *Anal.* Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.78; H, 9.73.

8: A colorless oil. IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 1735, 1720. ^{1}H-NMR (90 MHz) δ: 1.08 (6H, s, 6-CH$_3$ × 2), 1.72 (3H, s, 3-CH$_3$), 2.06 (3H, s, OAc), 4.59 (2H, d, J = 7 Hz, 1-H$_2$), 5.36 (1H, t, J = 7 Hz, 2-H), 9.46 (1H, s, CHO). MS m/z (%): 152 (M$^+$ − AcOH, 15), 71 (100). *Anal.* Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.78; H, 9.61.

9: A colorless oil. IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 3618, 1735, 903. ^{1}H-NMR (90 MHz) δ: 1.73, 1.78 (3H each, both s, 3-CH$_3$, 7-CH$_3$), 2.05 (3H, s, OAc), 4.09 (1H, t-like, 6-H), 4.59 (2H, d, J = 7 Hz, 1-H$_2$), 4.85, 4.95 (1H each, both br s, 8-H$_2$), 5.36 (1H, t, J = 7 Hz, 2-H). MS m/z (%): 152 (M$^+$ − AcOH, 12), 84 (100). *Anal.* Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.84; H, 9.79.

10: A colorless oil. IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 3434, 1732. ^{1}H-NMR (90 MHz) δ: 1.69, 1.73 (3H each, both s, 3-CH$_3$, 7-CH$_3$), 2.07 (3H, s, OAc), 4.02 (2H, s, 8-H$_2$), 4.60 (2H, d, J = 7 Hz, 1-H$_2$), 5.36 (2H, m, 2-H, 6-H). MS m/z (%): 152 (M$^+$ − AcOH, 10), 68 (100). *Anal.* Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.88; H, 9.71.

Oxidation of 2 with *m*-Chloroperbenzoic Acid A solution of **2** (50 mg) in CH_2Cl_2 (10 ml) was treated with *m*-chloroperbenzoic acid (80%, 62 mg) at 0 °C for 10 min. After quenching of the reaction by adding aqueous saturated Na_2SO_3 (10 ml), the reaction mixture was poured into water and the whole was extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with aqueous saturated NaCl, then dried over $MgSO_4$. Removal of the solvent under reduced pressure from the CH_2Cl_2 extract gave a product, which was purified by column chromatography (SiO_2 10 g, *n*-hexane : EtOAc = 5 : 1) to furnish **3** (51 mg). The product was identical with **3** obtained above by anodic oxidation of **2**, based on a comparison of physical data.

Cyclic Voltammetry of 2 Cyclic voltammetry of **2** (25 mg) was carried out in CH_3CN (12 ml)–H_2O (1.2 ml) containing $NaClO_4 \cdot H_2O$ (157 mg) at 25 °C, and two potential peaks were observed at 1.65 and 2.16 V *vs.* S.C.E.

Constant-Potential Electrolysis of 2 A solution of **2** (196 mg) in CH_3CN (91 ml)–H_2O (9.1 ml) was subjected to constant-potential electrolysis (1.65 V *vs.* S.C.E.) in an ice-cooling bath for 19 h. Work-up of the reaction mixture in the usual manner gave the same products as those obtained by the constant-current electrolysis of **2**. These products were identical with authentic samples (**3**—**10**) as judged from TLC and HPLC comparisons.

Constant-Current Electrolysis of 2 in CH_3CN–$H_2{}^{18}O$ A solution of **2** (100 mg) in CH_3CN (5 ml)–$H_2{}^{18}O$ (0.5 ml) containing $NaClO_4 \cdot H_2O$ (66 mg) was subjected to constant-current electrolysis (Pt electrode, 1 mA/cm^2) in an ice-cooling bath for 1 h. The reaction mixture was poured into water and the whole was extracted with EtOAc. Work-up of the EtOAc extract as described above gave a product, which was purified by column chromatography (SiO_2 10 g, *n*-hexane : EtOAc = 8 : 1 → 3 : 2) to furnish **3a** (3.0 mg, 6%) and **4a** (19 mg, 35%) along with recovered **2** (54 mg, 54% recovery).

3a: A colorless oil. IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 1738. ^{1}H-NMR (90 MHz) δ: 1.27, 1.31 (3H each, both s, 7-CH$_3$ × 2), 1.73 (3H, s, 3-CH$_3$), 2.06 (3H, s, OAc), 2.71 (1H, t, J = 6 Hz, 6-H), 4.59 (2H, d, J = 7 Hz, 1-H$_2$), 5.40 (1H, t, J = 7 Hz, 2-H). MS m/z (%): 154 (M$^+$ − AcOH, 8), 87 (**iii**, 84), 73 (**iv**, 100). High-resolution MS m/z: Calcd for $C_{10}H_{16}{}^{18}O$: 154.124; Found: 154.125 (M$^+$ − AcOH), Calcd for $C_5H_9{}^{18}O$: 87.069; Found: 87.069 (**iii**), Calcd for $C_4H_7{}^{18}O$: 73.045; Found: 73.052 (**iv**).

4a: A colorless oil. IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 3430, 1726. ^{1}H-NMR (90 MHz) δ: 1.17, 1.21 (3H each, both s, 7-CH$_3$ × 2), 1.73 (3H, s, 3-CH$_3$), 3.35 (1H, dd, J = 3, 9 Hz, 6-H), 4.59 (2H, d, J = 7 Hz, 1-H$_2$), 5.40 (1H, t, J = 7 Hz, 2-H). MS m/z (%): 174 (M$^+$ − AcOH, 0.6), 61 (100). High-resolution MS m/z: Calcd for $C_{10}H_{18}{}^{18}O_2$: 174.139; Found: 174.140 (M$^+$ − AcOH).

Constant-Current Electrolysis of 3 A solution of **3** (200 mg) in CH_3CN (86 ml)–H_2O (8.6 ml) containing $NaClO_4 \cdot H_2O$ (1.15 g) was subjected to constant-current electrolysis (Pt electrode, 1 mA/cm^2) in an ice-cooling bath for 2 h. The reaction mixture was concentrated under reduced pressure to *ca.* 10 ml, then the whole was poured into water and extracted with EtOAc. Work-up of the EtOAc extract as described above gave a product, which was purified by column chromatography (SiO_2 20 g, *n*-hexane : EtOAc = 8 : 1 → 3 : 2) to furnish **4** (44 mg, 40%) and a mixture of **6**, **9**, and **10** along with recovered **3** (90 mg, 45% recovery). The mixture of **6**, **9**, and **10** was separated by HPLC (YMC-A014, *n*-hexane : EtOAc = 5 : 1) to give **6** (4.4 mg, 4%), **9** (4.3 mg, 4%), and **10** (1.2 mg, 1%).

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