Tetrahedron: *Asymmetry* 20 (2009) 457–460

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Isolation of (*E*)-9,10-dihydroxy-2-decenoic acid from royal jelly and determination of the absolute configuration by chemical synthesis

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ARTICLE INFO

Article history:
Received 5 January 2009
Accepted 23 January 2009
Available online 9 March 2009

ABSTRACT

(*E*)-9,10-Dihydroxy-2-decenoic acid **1** was isolated as a new compound from royal jelly. The planar structure was deduced by spectroscopic analyses, whereas the absolute configuration was established by chemical synthesis of both enantiomers of **1**. The natural product was revealed to be ca. 3.5:1 mixture of (*R*)- and (*S*)-acids by comparison of **1** with authentic samples.

1. Introduction

Royal jelly is the principal food for the queen honeybee and larva. This is secreted by the mandibular and hypopharyngeal glands of the worker bee (*Apis mellifera*), which is involved in the fertility and longevity of the queen, and has been used in folk medicine all over the world.

The chemical composition of royal jelly has been studied well, and proteins, sugars, fatty acids, vitamins, minerals, and free amino acids have been identified.[1–3] Of these, fatty acids have attracted much attention of researchers due to their chemically interesting features[4] and pharmacological activities.[5–7] (*E*)-10-Hydroxy-2-decenoic acid **2**, which is the major fatty acid in royal jelly, was firstly isolated by Butenandt and Rembold in 1957 (Fig. 1).[8,9] Subsequent studies revealed that **2** and its analogues[10,11] had antitumor, sebaceous lipid synthesis inhibitory, neurogenesis, and estrogenic effects.[12–14] The isolation of various hydroxy fatty acids, such as 3,10-dihydroxydecanoic acid **4**, (*E*)-9-hydroxy-2-decenoic acid, 11-hydroxydodecanoic acid, and 11,12-dihydroxydodecanoic acid, and their biological activities have also been reported.[15,16] The absolute stereochemistries of **4** and (*E*)-9-hydroxy-2-decenoic acid have been determined to be (3*R*) and (9*R*/9*S*) = 2:1, respectively,[15] by applying the modified Mosher's method,[17] whereas the absolute configurations of the other compounds have been determined to be (*S*) by comparison of the signs of the specific rotation with their analogues.[18,19]

In the course of our studies searching for biological active compounds in royal jelly, we found 9,10-dihydroxy-2-decenoic acid **1** as a new compound. Described herein are the isolation, structural determination, and total synthesis of **1**.

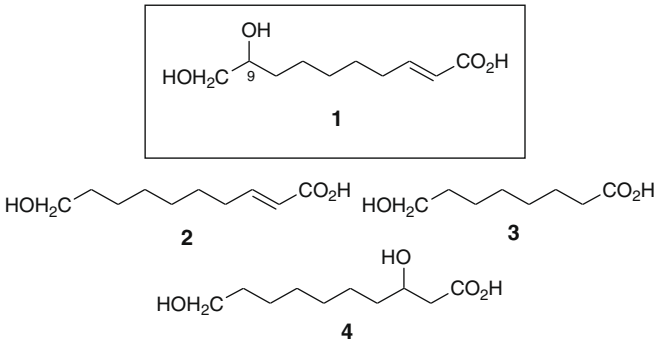

Figure 1. Structures of fatty acids in royal jelly.

2. Results and discussion

2.1. Isolation and structural determination

Royal jelly, collected in Zhejiang Sheng, China, was lyophilized and extracted with methanol. The crude extraction was successively subjected to ODS column chromatography, silica gel column chromatography, and finally reversed phase HPLC to give **1** along with **2**, 8-hydroxyoctanoic acid **3** and 3,10-dihydroxydecanoic acid **4**. The molecular formula of **1** was established as $C_{10}H_{18}O_4$ on the basis of MS and ^{13}C NMR. The NMR data for **1** revealed the presence of six methylenes (one of which oxygenated), two sp^2 methines, one oxygenated methine, and one carbonyl carbon, indicating that **1** has two free hydroxyl and one carboxyl groups. Treatment of **1** with diazomethane gave a monomethyl ester derivative, providing evidence for the presence of a carboxylic acid. Furthermore, the ^1H NMR chemical shift of sp^2 methine signals at 5.79 and 6.95 ppm indicated that the carboxyl group was attached to a double bond. Taking the

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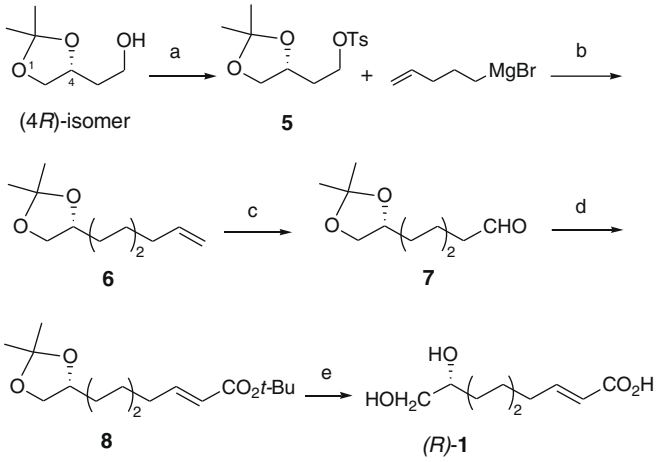
doi:10.1016/j.tetasy.2009.01.028

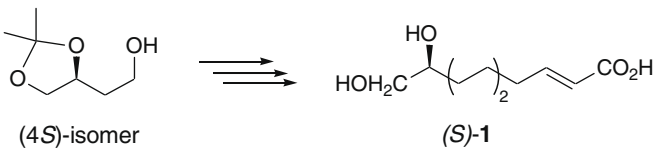
^{1}H–^{1}H COSY data into account, compound **1** has two partial structures: –$(CH_2)_mCH(OH)CH_2(OH)$, and –$(CH_2)_nCH{=}CHCOOH$. The $J_{H\text{-}2,H\text{-}3}$ value of 15.6 Hz revealed that the geometry of the double bond at C-2 had an *E* stereochemistry. Based on these partial structures, the structure of **1** was proposed to be (*E*)-9,10-dihydroxy-2-decenoic acid. The stereochemistry at the C-9 position was estimated to be (*R*) by comparison of the sign of the specific rotation $\{[\alpha]_D^{23} = +6.3$ (*c* 0.50, methanol)} of **1** with those of related compounds.[16,18,19]

2.2. Synthesis

In order to unambiguously establish the stereochemistry of **1** and to clarify its biological activity, we developed a facile method for the preparation of both enantiomers of **1**. Commercially available (4*R*)- and (4*S*)-4-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolane[20] were selected as the starting materials (Scheme 1). The tosylate (*R*)-**5**[21] obtained from the (4*R*)-isomer $\{[\alpha]_D^{21} = -2.0$ (*c* 5.0, chloroform)} was reacted with 4-pentenylmagnesium bromide in the presence of copper iodide in tetrahydrofuran to afford a terminal olefin **6** in 93% yield. Upon treatment with ozone in dichloromethane at −78 °C, followed by addition of methyl sulfide, **6** gave aldehyde **7** which was immediately subjected to the Wittig–Horner Emmons reaction $\{(EtO)_2P(=O)CH_2CO_2t\text{-Bu}$, NaH, THF} to provide the corresponding *E*-ester **8** in 82% yield. Finally, this was subjected to hydrolysis under acidic conditions, followed by treatment with potassium hydroxide to provide (*R*)-**1** in 72% yield. The spectroscopic data of synthetic **1** were identical to those of the natural product. However, the specific rotation of the synthetic product (*R*)-**1** was not in agreement with that of the natural product. The specific rotation of the natural acid was +6.3 (*c* 0.50, methanol), whereas synthetic (*R*)-**1** showed $[\alpha]_D^{25} = +11.9$ (*c* 0.51, methanol). The specific rotation of the enantiomer (*S*)-**1** prepared from the (4*S*)-isomer in a similar way (Scheme 2) was $[\alpha]_D^{26} = -11.8$ (*c* 0.50, methanol). Based on these results, we concluded that the natural acid was an epimeric mixture of (*R*)- and (*S*)-acids, and the enantiomeric purity was estimated to be ca. 53% ee. These results were also confirmed by the NMR analyses of the corresponding MTPA esters prepared from natural **1** in two steps (1. trimethylsilyldiazomethane, methanol, 0 °C; 2. MTPACl, *N*,*N*-dimethylaminopyridine, triethylamine, CH_2Cl_2, rt). As shown in Figure 2, the ^{1}H NMR spectra of MTPA esters prepared from natural **1** showed that it consisted of ca. 3.5:1 mixture of (9*R*)- and (9*S*)-isomers.



Scheme 1. (a) Ref. 21; (b) CuI, THF, rt→50 °C, 93%; (c) O_3, CH_2Cl_2, −78 °C, and then Me_2S, −78 °C→rt, quant.; (d) $(EtO)_2P(=O)CH_2CO_2t$-Bu, NaH, THF, 0 °C, 82% (two steps); (e) CF_3CO_2H, aq CH_2Cl_2, 0 °C, and then 1 M KOH, MeOH, rt, 72%.



Scheme 2. Synthesis of (*S*)-**1** from the (4*S*)-isomer.

The fact that some of the chiral fatty acids isolated from royal jelly were an epimeric mixture is of interest from the standpoint of biosynthesis, suggesting that enantiomeric purities of chiral acids from such sources should be confirmed.[22] We are currently studying the biological activities of the synthetic compounds.

3. Experimental

3.1. General procedures

All reactions were carried out under an argon atmosphere, unless otherwise noted. Melting points were determined using a

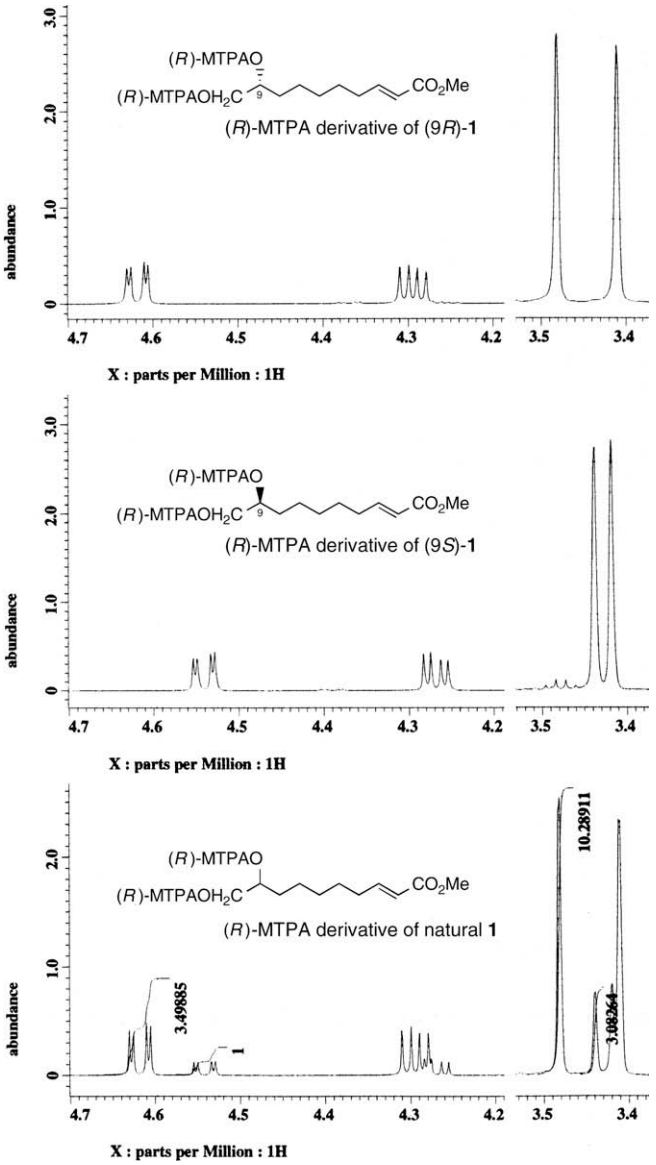


Figure 2. ^{1}H NMR spectra (600 MHz, $CDCl_3$) of (*R*)-MTPA derivatives.

Yanaco MP-500 apparatus, and are uncorrected. Optical rotations were measured with a JASCO DIP-370 polarimeter. IR spectra were recorded with a JASCO VALOR-III spectrophotometer by ATR method. ^{1}H NMR spectra were recorded at 400 MHz, 500 MHz or 600 MHz with JEOL JNM-A400, ECP500 or ECA600 spectrometers. Chemical shifts were referenced to a residual signal of $CDCl_3$ (δ_H 7.26, δ_C 77.0) and CD_3OD (δ_H 3.30, δ_C 49.0). ESIMS were recorded on a Waters Micromass Quattro Premier XE mass spectrometer or on a JEOL JMS-T100LC mass spectrometer. Column chromatography was performed on Kanto Silica Gel 60N (spherical, neutral; 40–100 μm). Merck precoated Silica Gel 60 F_{254} plates, 0.25 mm thickness, were used for analytical thin-layer chromatography. The solvent extracts were dried with magnesium sulfate, and the solutions were evaporated under reduced pressure at 40–42 °C.

3.2. Isolation

Fresh royal jelly (800 kg), which was collected in Zhejiang Sheng, China, was lyophilized to give a dry powder (280 kg); 200.4 g of the royal jelly powder was extracted with 1500 mL of methanol. After stirring at room temperature for 12 h, the extracts were filtered and evaporated in vacuo. The residue (108.9 g) was subjected to ODS column chromatography (Cosmosil 75C18-PREP, 80 × 205 mm), with 2500 mL (1250 mL × 2) each of 10% and 50% methanol as eluent. The second fraction eluted with 50% methanol was subjected to silica gel column chromatography (Daiso gel IR-60, 26 × 150 mm). Elution was performed with 600 mL (60 mL × 10) of 5% and 10% methanol in chloroform. The fourth to sixth fractions of 5% methanol in chloroform were combined and recrystallized from ethyl acetate/*n*-hexane to give **2** (5.9 g). The seventh to tenth fractions of 5% methanol in chloroform were combined and purified further by the same silica gel column chromatography (Daiso gel IR-60, 26 × 150 mm) with 600 mL (60 mL × 10) each of 0%, 5%, and 10% methanol in chloroform as the eluent. The fifth fraction, eluted with 5% methanol in chloroform, was purified by HPLC in a Cosmosil 5C18-AR column (Nacalai Tesque, 10 × 250 mm), with 13% acetonitrile in 0.1% TFA as solvent at the flow rate of 1.0 mL/min, monitoring at 220 nm) to give **1** (13.3 mg). The third fraction of 10% methanol in chloroform was subjected to silica gel column chromatography (Daiso gel IR-60, 16 × 60 mm) with 120 mL (12 mL × 10) of 5% methanol in chloroform as the eluent. The fifth and sixth fractions were combined to give **3** (6.2 mg). The fourth fraction of 10% methanol in chloroform was purified by silica gel column chromatography (Daiso gel IR-60, 26 × 100 mm) with 300 mL (20 mL × 15) each of 10% and 15% methanol in chloroform as the eluent. Fractions 13–19 were combined to give **4** (23.7 mg). Compound **1**. $[\alpha]_D^{26} = +6.3$ (*c* 0.50, methanol); IR (ZnSe) 3375, 3208, 2931, 1693, 1639, 1423, 1270, 1181, 979 cm^{-1}; ^{1}H NMR (CD_3OD, 500 MHz): δ 6.95 (1H, dt, *J* = 15.6, 7.1 Hz, H-3), 5.79 (1H, dt, *J* = 15.6, 1.5 Hz, H-2), 3.56 (1H, m, H-9), 3.46 (1H, dd, *J* = 11.1, 4.6 Hz, H-10a), 3.41 (1H, dd, *J* = 11.1, 6.5 Hz, H-10b), 2.23 (2H, ddt, *J* = 7.1, 1.5, 7.0 Hz, H-4), 1.50 (4H, m, H-5, 7a, 8a), 1.36 (4H, m, H-6, 7b, 8b); ^{13}C NMR (CD_3OD, 125 MHz) δ 170.1 (C-1), 151.2 (C-3), 122.5 (C-2), 73.2 (C-9), 67.4 (C-10), 34.3 (C-8), 33.1 (C-4), 30.3 (C-6), 29.2 (C-5), 26.2 (C-7); negative-ion ESIMS: *m*/z 201 $[M-H]^-$; HRMS (FAB) calcd for $C_{10}H_{17}O_4$ $[M-H]^-$ 201.1127, found 201.1136. Compound **2**. ^{1}H NMR (CD_3OD, 600 MHz) δ 6.94 (1H, dt, *J* = 15.6, 7.1 Hz, H-3), 5.78 (1H, dt, *J* = 15.6, 1.5 Hz, H-2), 3.53 (2H, t, *J* = 6.6 Hz, H-10), 2.22 (2H, ddt, *J* = 7.1, 1.5, 7.6 Hz, H-4), 1.52 (2H, m, H-9), 1.48 (2H, m, H-5), 1.35 (6H, m, H-6, 7, 8); ^{13}C NMR (CD_3OD, 150 MHz) δ 170.1 (C-1), 151.2 (C-3), 122.5 (C-2), 63.0 (C-10), 33.6 (C-9), 33.1 (C-4), 30.3 (C-7), 30.2 (C-6), 29.2 (C-5), 26.8 (C-8); negative-ion ESIMS: *m*/z 185 $[M-H]^-$; HRMS (FAB) calcd for $C_{10}H_{17}O_3$ $[M-H]^-$ 185.1178, found 185.1173. Compound **3**. ^{1}H NMR (CD_3OD, 600 MHz) δ 3.53 (2H, t, *J* = 6.6 Hz, H-8), 2.27 (2H, t, *J* = 7.3 Hz, H-2), 1.60 (2H, m, H-3), 1.52 (2H, m, H-7), 1.35 (6H, m, H-4, 5, 6); ^{13}C-NMR (CD_3OD, 150 MHz) δ 177.7 (C-1), 63.0 (C-8), 35.0 (C-2), 33.6 (C-7), 30.2 (C-4, 5), 26.8 (C-6), 26.1 (C-3); negative-ion ESIMS: *m*/z 159 $[M-H]^-$; HRMS (FAB) calcd for $C_8H_{15}O_3$ $[M-H]^-$ 159.1021, found 159.1015. Compound **4**. $[\alpha]_D^{22} = +2.3$ (*c* 1.07, methanol); ^{1}H NMR (CD_3OD, 600 MHz) δ 3.96 (1H, m, H-3), 3.53 (2H, t, *J* = 6.6 Hz, H-10), 2.43 (1H, dd, *J* = 15.1, 4.5 Hz, H-2a), 2.36 (1H, dd, *J* = 15.1, 8.0 Hz, H-2b), 1.52 (2H, m, H-9), 1.47 (4H, m, H-4, 5), 1.35 (2H, m, H-8), 1.34 (4H, m, H-6, 7); ^{13}C NMR (CD_3OD, 150 MHz) δ 175.8 (C-1), 69.4 (C-3), 63.0 (C-10), 43.3 (C-2), 38.1 (C-4), 33.7 (C-9), 30.6 (C-6), 30.5 (C-7), 26.9 (C-8), 26.6 (C-5); negative-ion ESIMS: *m*/z 203 $[M-H]^-$; HRMS (FAB) calcd for $C_{10}H_{19}O_4$ $[M-H]^-$ 203.1283, found 203.1279.

3.3. Preparation of MTPA esters

To a solution of methyl ester (1.1 mg, 0.0051 mmol) obtained by methylation of natural **1**, *N*,*N*-dimethylaminopyridine (1.25 mg, 0.01 mmol) and triethylamine (8.6 μL, 0.46 mmol) in dichloromethane (130 μL) was added (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPACl, 57.9 μL, 0.051 mmol) at 0 °C. After being stirred from 0 °C to room temperature for 16 h, the reaction mixture was diluted with ether, and the solution was washed successively with cold aqueous HCl, saturated aqueous $NaHCO_3$, water, brine, dried, and concentrated. The residue was purified by preparative TLC (*n*-hexane–ethyl acetate = 1:2) to give natural (*R*)-MTPA ester (3.3 mg, quant.). Using the same procedure, (*R*)-MTPA esters of (9*R*)- and (9*S*)-acids were prepared.

3.4. (*R*)-4-(Hept-6-enyl)-2,2-dimethyl-1,3-dioxolane 6

To a stirred solution of pentenylmagnesium bromide prepared from magnesium turnings (1.1 g, 45.2 mol) and 5-bromo-1-pentene (6.0 mL, 50.3 mol) in tetrahydrofuran (100 mL) was added a solution of **5** (5.4 g, 17.9 mmol) in tetrahydrofuran (20 mL) at 0 °C over 10 min. Then, CuI (384 mg, 2.0 mmol) was added, and the resulting mixture was stirred at 0 °C for 0.5 h, and 50 °C for 2.0 h. After addition of satd NH_4Cl solution, the resulting mixture was extracted with ether. The extracts were washed with water, brine, and concentrated. The residue was chromatographed on silica gel (*n*-hexane–ethyl acetate = 10:0→10:1→4:1) to give **6** (3.3 g, 93%) as a light-yellow liquid; $[\alpha]_D^{23} = -17.9$ (*c* 1.21, $CHCl_3$); IR (ZnSe) 3076, 2929, 1640, 1368, 1212, 1055, 907, 856 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.78 (1H, m), 4.97 (1H, dd, *J* = 17.1, 1.5 Hz), 4.91 (1H, br d, *J* = 10.3 Hz), 4.04 (1H, m), 4.00 (1H, t, *J* = 6.9 Hz), 3,47 (1H, t, *J* = 6.9 Hz), 2.02 (2H, m), 1.66–1.18 (8H, m), 1.38 (3H, s), 1.33 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.9, 114.3, 108.5, 76.1, 69.5, 33.6, 33.5, 29.1, 28.7, 26.9, 25.7, 25.6; HRMS (EI) calcd for $C_{11}H_{19}O_2$ $[M-Me]^+$ 183.1385, found 183.1375.

3.5. (*S*)-4-(Hept-6-enyl)-2,2-dimethyl-1,3-dioxolane 6

According to the procedure described above, (*S*)-tosylate **5** (1.85 g, 6.2 mmol) was converted into (*S*)-olefin **6** (1.13 g, 93%); $[\alpha]_D^{23} = +17.8$ (*c* 1.50, $CHCl_3$). HRMS (EI) calcd for $C_{11}H_{19}O_2$ $[M-Me]^+$ 183.1385, found 183.1421.

3.6. (*E*)-*tert*-Butyl 8-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)oct-2-enoate 8

To a stirred solution of **6** (640 mg, 3.23 mmol) in dichloromethane (8.0 mL) was bubbled ozone (O_3) at −78 °C for 20 min. After the excess O_3 was flushed out by the stream of nitrogen, dimethylsulfide (2.0 mL) was added. After stirring at −78 °C for 1.5 h and at 0 °C–rt for 3 h, the mixture was concentrated in vacuo to give the crude **7** (840 mg), which was employed in the next step without fur-

ther purification. To a stirred suspension of NaH (60% oil dispersion, 268 mg, 6.7 mmol) in tetrahydrofuran (10 mL) was added dropwise *tert*-butyl diethylphosphonoacetate (1.58 mL, 6.7 mmol) at 0 °C, after which the mixture was stirred at 0 °C for 1.5 h. To this solution was added a solution of the above aldehyde **7** (840 mg, ca. 3.23 mmol) in tetrahydrofuran (3.0 mL) at 0 °C, and the mixture was stirred at 0 °C for 1.5 h. After addition of water, the mixture was extracted with ether. The extracts were washed successively with water and brine, dried, and concentrated. The residue was chromatographed on silica gel (*n*-hexane–ether = 10:0→40:1→30:1→10:1) to give **8** (683 mg, 82% from **6**) as a light-yellow liquid; $[\alpha]_D^{23} = -10.4$ (*c* 1.39, $CHCl_3$); IR (ZnSe) 2932, 1711, 1653, 1366, 1148, 1055, 979 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.78 (1H, dt, *J* = 15.6, 6.8 Hz), 5.67 (1H, br d, *J* = 15.6 Hz), 3.99 (1H, m), 3.96 (1H, t, *J* = 6.4 Hz, 1H), 3.43 (1H, t, *J* = 6.4 Hz), 2.12 (2H, m), 1.57–1.20 (8H, m), 1.42 (9H, s), 1.34 (3H, s), 1.29 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 147.7, 122.9, 108.5, 79.8, 75.9, 69.3, 33.4, 31.8, 29.0, 28.0, 27.8, 26.8, 25.6, 25.4; HRMS (FAB) calcd for $C_{17}H_{30}O_4Na$ $[M+Na]^+$ 321.2042, found 321.2045.

3.7. (*E*)-*tert*-Butyl 8-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)oct-2-enoate 8

According to the procedure described above, (*S*)-olefin **6** was converted into (*S*)-ester **8** in 77% yield (two steps); $[\alpha]_D^{23} = +10.7$ (*c* 1.65, $CHCl_3$); HRMS (FAB) calcd for $C_{17}H_{30}O_4Na$ $[M+Na]^+$ 321.2042, found 321.2071.

3.8. (2*E*,9*R*)-9,10-Dihydroxy-2-decenoic acid 1

A solution of **8** (286 mg, 1.1 mmol) in dichloromethane–trifluoroacetic acid–water (20:10:1, 31 mL) was stirred at 0 °C for 6 h, and then concentrated in vacuo. The residue was dissolved in methanol (2.9 mL), and 1 M KOH solution (1.8 mL) was added. The resulting mixture was stirred at rt for 2.5 h, treated with Dowex-50W X-8 (H^+) resin, and the suspension was filtered. The filtrate was concentrated in vacuo to give a syrup, which was crystallized from ethyl acetate to afford **1** (160 mg, 72%) as white crystals. Mp 86.5–88 °C (ether); $[\alpha]_D^{25} = +11.9$ (*c* 0.51, methanol); HRMS (FAB) calcd for $C_{10}H_{17}O_4$ $[M-H]^-$ 201.1127, found 201.1137.

3.9. (2*E*,9*S*)-9,10-Dihydroxy-2-decenoic acid 1

According to the procedure described above, (*S*)-ester **8** (267 mg, 1.0 mmol) was converted into (*S*)-carboxylic acid **1** (132 mg, 64% in two steps); $[\alpha]_D^{23} = -11.8$ (*c* 0.50, methanol); HRMS (FAB) calcd for $C_{10}H_{17}O_4$ $[M-H]^-$ 201.1127, found 201.1121.

Acknowledgments

This work was supported in part by the Chemical Genomics Project (RIKEN) and a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture of Japan.

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