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Conversion of Limonene to Prostanoic Acid and 8-Isoprostanoic Acid

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Prostanoic acid (**18**) and 8-isoprostanoic acid (**1**) constitute the basic structures of primary prostaglandins and 8-isoprostaglandins. The conversion of commercially available (+)- and (−)-limonene to these compounds was accomplished by a sequence of reactions involving the Rh(I)-catalyzed cyclization of 3,4-disubstituted 4-pentenals, which were easily prepared from (+)- or (−)-limonene, to *cis*-3,4-disubstituted cyclopentanones and the appropriate modification of substituents on the five-membered ring.

Keywords——3,4-disubstituted cyclopentanone; prostanoic acid; 8-isoprostanoic acid; Wittig reaction; 3,4-disubstituted cyclopentane; limonene

Prostanoic acid (**18**) is the parent skeleton of primary prostaglandins (PGs), and serves as the basic structure for the PGs nomenclature[1] and for studies on the structure–activity relationships.[2] 8-Isoprostanoic acid (**1**) constitutes the basic skeleton of 8-isoprostaglandin E_1, which was isolated during studies on the biological conversion[3] of 8,11,14-icosatrienoic acid to PGs. Prostanoic acid was previously synthesized by our group[4] from the Corey lactone, and the absolute stereochemistry of this compound, which was incorrectly assigned by Hamon *et al.*,[5] was unambiguously established.

As a part of our synthetic studies[6] on functionalized cyclopentanone, we have succeeded in a stereospecific synthesis of *cis*-3,4-disubstituted cyclopentanones from 3,4-disubstituted 4-pentenals by using the Rh(I)-complex.[7] We describe here the stereospecific conversion of (−)- or (+)-limonene to prostanoic acid (**18**) or 8-isoprostanoic acid (**1**).

8-Isoprostanoic Acid (1)

The retro synthesis of 8-isoprostanoic acid (**1**) is shown in Chart 1. The designed

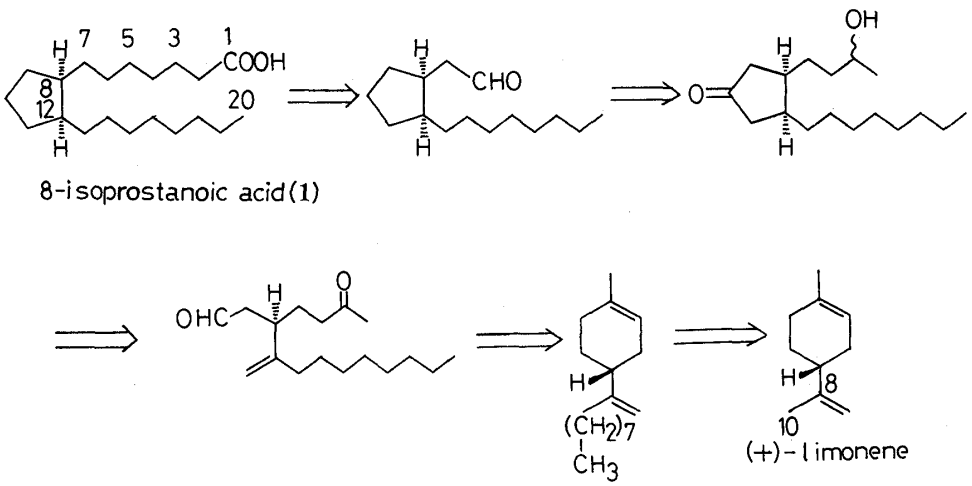

Chart 1

sequence starts with the alkylation of commercially available (+)-limonene, followed by fission of the cyclohexene ring to yield the substituted 4-pentenal, and subsequent cyclization to the *cis*-3,4-disubstituted cyclopentanone with the Rh(I)-complex. To introduce the ω-chain consisting of the C_8-unit, the C_{10}-position of (+)-limonene was alkylated with *sec*-BuLi-tetramethylethylenediamine (TMEDA)-complex and heptyl bromide,[8] and the heptyl limonene (**2**) was obtained in 71% yield. Selective epoxidation of the double bond on the cyclohexene ring in **2** was accomplished by treatment with *m*-chloroperbenzoic acid (MCPBA) in CH_2Cl_2. In this manner, the α- and β-epoxide were obtained as an inseparable mixture in almost equal amounts. Hydrolysis of the mixture with 1% aq. H_2SO_4 afforded the diol (**4**),[9] which, on oxidative cleavage with $NaIO_4$, yielded the keto-aldehyde (**5**, 68% from **2**).

Prior to the Rh(I)-catalyzed cyclization of **5** to the cyclopentanone, the ketone function

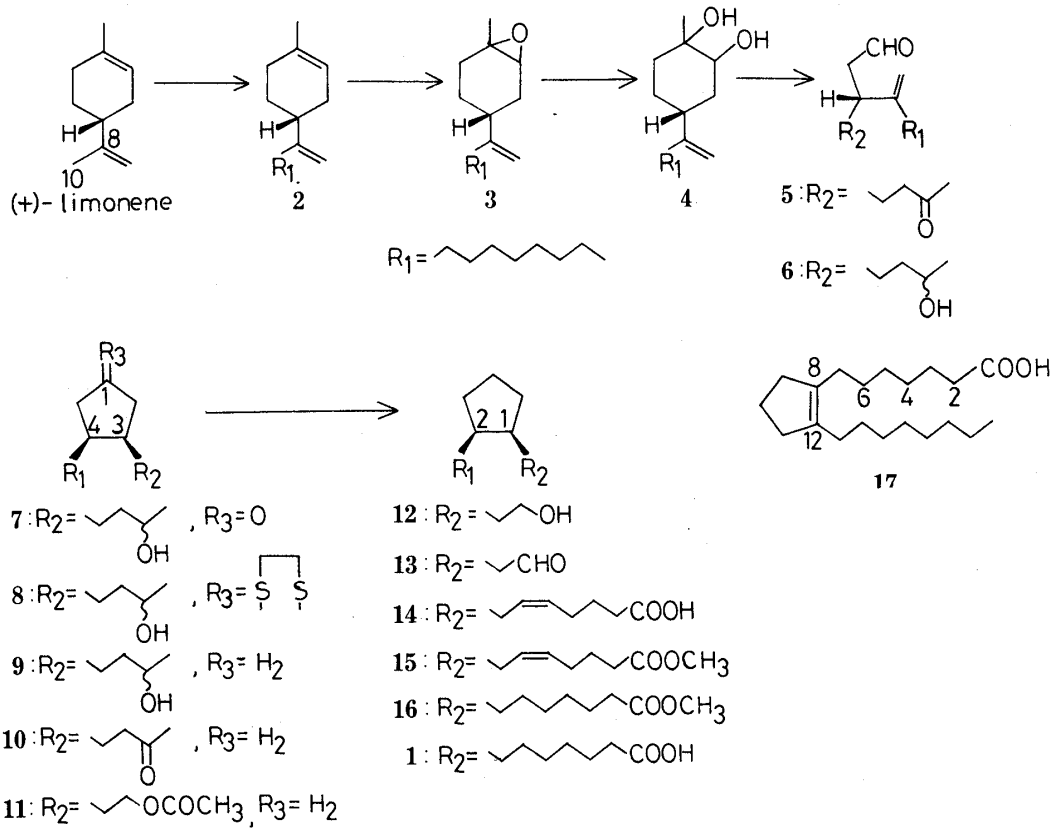

Chart 2

in **5** was subjected to selective reduction with $NaBH_4$ in the presence[10] of $CeCl_3$ in aq. EtOH, and the hydroxy aldehyde (**6**)[11] was obtained in 68% yield. The Rh(I)-catalyzed cyclization reaction of **6** proceeded stereospecifically to yield the desired cyclopentanone (**7**) in 85% yield. Thus, a stereochemical problem for the synthesis of **1** has been solved. The next problems are removal of the carbonyl function in the five-membered ring and the introduction of the α-chain. Removal of the undesired carbonyl function was effected in 64% yield by thioacetalization with ethanedithiol/BF_3 and subsequent desulfurization with Raney-Ni.

The α-chain could be introduced by means of the following reactions. Jones oxidation of the alcohol (**9**) to the corresponding ketone (**10**), followed by Baeyer–Villiger oxidation with trifluoroperacetic acid and Na_2HPO_4 in CH_2Cl_2 at room temperature, gave the acetate (**11**, 71% from **9**). Hydrolysis of **11** with K_2CO_3 in MeOH and subsequent oxidation with pyridinium dichromate (PDC) in CH_2Cl_2 yielded the aldehyde (**13**, 84% from **11**), which was

subjected to Wittig reaction using the sodium salt of (4-carboxybutylidene)triphenylphosphorane in dimethylsulfoxide (DMSO) to yield the acid (**14**). Thus, the synthesis of **1** has been achieved except for the catalytic hydrogenation of the Δ^5-double bond. However, the catalytic hydrogenation of **14** with H_2/5% Pd–C in MeOH gave an inseparable mixture[12] of 8-isoprostanoic acid (**1**) and the compound (**17**) in which the Δ^5-double bond has migrated to the $\Delta^{8(12)}$-position. This troublesome problem was overcome by catalytic hydrogenation[13] of the methyl ester (**15**) with H_2/Pt in MeOH at −20 °C; the hydrolysis of **16** with 5% aq. NaOH afforded **1**.

Prostanoic Acid (18)

As shown in the retro synthesis (Chart 3), (−)-limonene seems to be stereochemically favorable as a starting material for the synthesis of prostanoic acid (**18**). In order to introduce the ω-chain, the C_{10}-position of (−)-limonene should be oxidized to (−)-limonen-10-ol. This was effected by lithiation[8] with *sec*-BuLi–TMEDA-complex and subsequent oxidation with

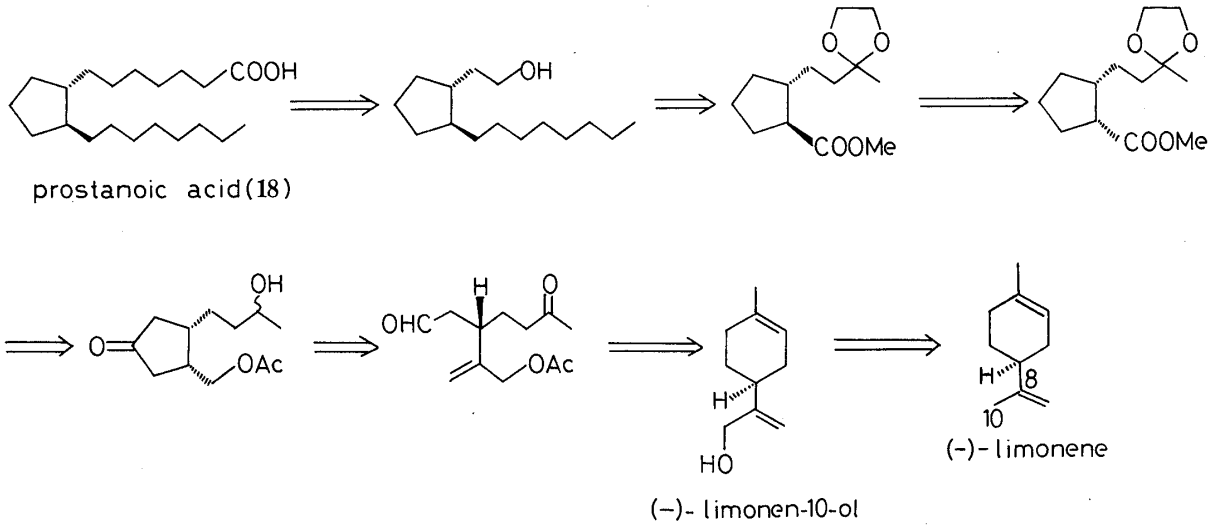

Chart 3

oxygen. In a manner similar to that described for the synthesis of **1**, (−)-limonen-10-ol was converted in 43% yield to the *cis*-3,4-disubstituted cyclopentanone (**22**) *via* the 3,4-disubstituted 4-pentenal (**21**). The functional groups of **22** seem to have several advantages for the synthesis of **18**. For example, the $C_4\alpha$-substituent should be easily isomerized to the more stable $C_4\beta$-configuration *via* the corresponding methyl ester, which may be extended to form the ω-chain. The C_3-substituent seems appropriate for shortening from the undesired C_4-unit to a C_2-unit as required for the introduction of the α-chain by means of the Wittig reaction. The unnecessary carbonyl function was removed in a manner similar to that used in the case of **1**, and the diol (**24**) was obtained in 49% yield from **22**. The two alcohol functions in **24** were concurrently oxidized with Jones reagent to give the keto-acid (**25**), which was converted to the ester by treatment with CH_2N_2. Thus, the keto-ester (**26**) was obtained in 57% yield. The acetal (**27**) was prepared in 83% yield from **26** in a usual manner, and could be epimerized into the desired *trans*-ester (**28**) by heating under reflux with NaOMe in toluene for 6 h. Monitoring this epimerization by thin layer chromatography (TLC) was difficult. However, proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy was found to be effective for the detection of this epimerization. In the ^{1}H-NMR spectrum of the *trans*-ester (**28**), the C_2-H was observed at higher field (δ 2.31) than in the case of the *cis*-ester (**27**, δ 2.84).[14] The difference in this chemical shift made it quite easy to distinguish the *trans*-ester **28** from the *cis*-ester **27**.

Reduction of **28** with $LiAlH_4$ followed by oxidation with Collins reagent afforded the

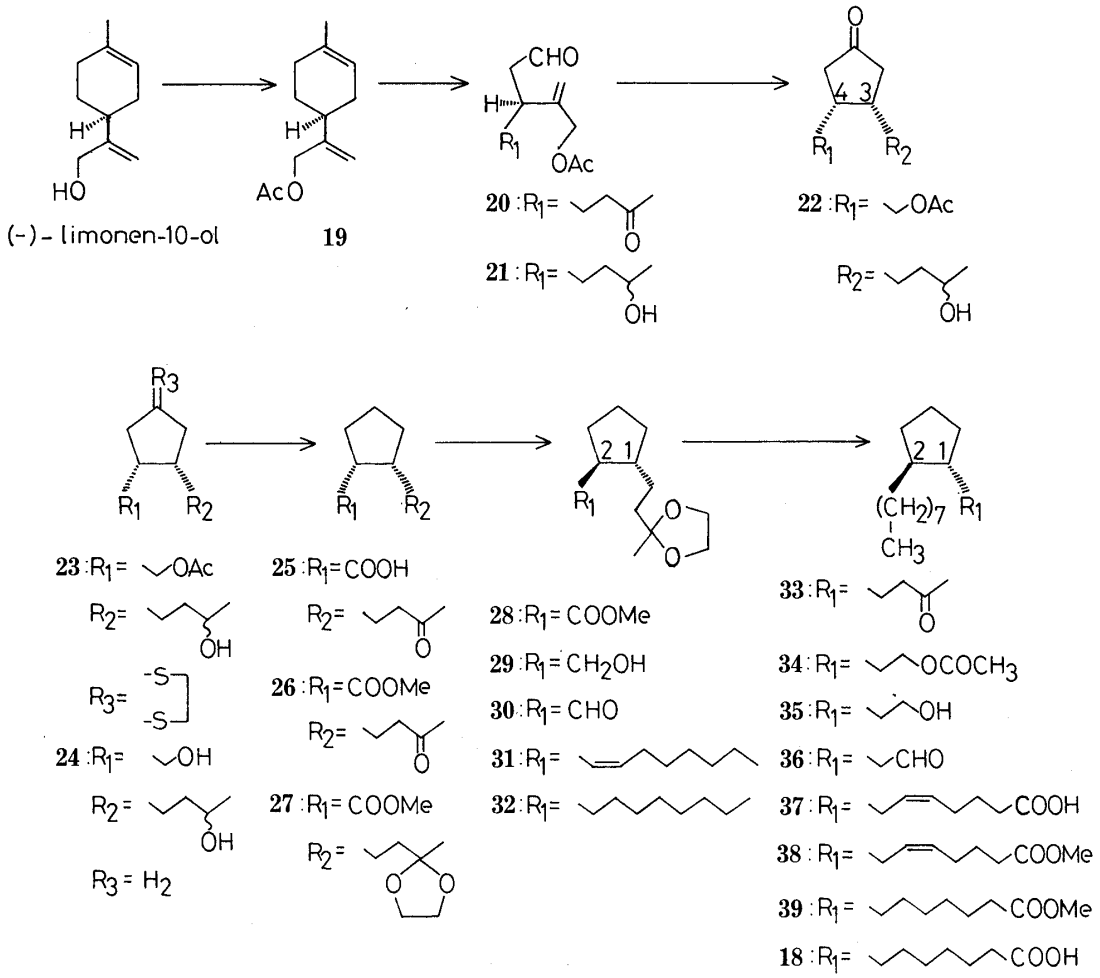

Chart 4

aldehyde (**30**), which was subjected to Wittig reaction with heptylidenetriphenylphosphorane[15] in ether. In this manner, **31** was obtained in 21% yield from **28**. Upon catalytic hydrogenation with H_2/Pt in MeOH and subsequent deprotection with 10% HCl, **31** afforded the ketone (**33**) possessing the ω-chain. The α-chain was introduced by a technique similar to that used in the case of **1**. Prostanoic acid (**18**) thus derived from (−)-limonene was identical with an authentic sample[4] in terms of the ^{1}H-NMR and the infrared (IR) spectra.

Experimental

IR spectra were measured with a JASCO A-202 spectrometer. ^{1}H-NMR spectra were measured on a JEOL JNM-PS-100 spectrometer with Me_4Si as an internal standard. Mass spectra (MS) were taken on a JEOL JMS-D 300 spectrometer. Specific rotations were measured on a JASCO DIP-SL polarimeter. For column chromatography, silica gel (Merck, Kieselgel 60, 70—230 mesh) was used. TLC was performed on Silica gel 60 F_{254} plates (Merck). All organic solvent extracts were washed with brine and dried over anhydrous sodium sulfate.

(4*R*)-9-Heptyl-*p*-mentha-1,8(10)-diene (2)——*sec*-BuLi (1.4 M in hexane, 114 ml) solution was added dropwise to a stirred solution of (+)-limonene (7.93 g) in TMEDA (24.4 ml) at −60 °C under an N_2 atmosphere. The whole was stirred for 0.5 h at −60 °C, and for 1 h at room temperature, then heptyl bromide (13.71 g) was added dropwise at −60 °C. After being stirred for 1 h at 0 °C, the reaction mixture was diluted with brine, and extracted with AcOEt. The AcOEt extract was washed, and dried. The solvent was removed *in vacuo* to afford an oily residue, which was distilled under reduced pressure, and the fraction (9.72 g, 71%) of bp 110—115 °C (3 mmHg) was collected. $[\alpha]_D^{28}$ +28.3° (c=1.45, $CHCl_3$). IR (neat): 1640, 1460, 885 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7 Hz, CH_3), 4.72 (2H, s, $=CH_2$), 5.41 (1H, s, C_2-H). MS m/z: 234 (M^+), 136, 121.

(4*R*)-1,2-Epoxy-9-heptyl-*p*-menth-8(10)-ene (3), (4*R*)-9-Heptyl-1,2-dihydroxy-*p*-menth-8(10)-ene (4), and (3*R*)-4-Methylene-3-(3-oxobutyl)dodecanal (5)——MCPBA (purity 80%, 22.41 g) in CH_2Cl_2 (260 ml) was added dropwise to

a well-stirred solution of **2** (16.22 g) in a mixture of CH_2Cl_2 (100 ml) and 5% aq. $NaHCO_3$ (300 ml) at room temperature. After 4 h, the reaction mixture was poured into brine, and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with 5% aq. Na_2CO_3, and brine, then dried. Removal of the solvent *in vacuo* afforded an oily residue, which was subjected to column chromatography on silica gel (120 g). The fraction eluted with 3% AcOEt in hexane (v/v) afforded **3** (15.21 g, 87%) as a mixture of the α- and β-oxide. The mixture of **3** (10.38 g), tetrahydrofuran (THF) (60 ml), and 1% aq. H_2SO_4 (100 ml) was stirred at room temperature for 24 h, then neutralized with 5% aq. $NaHCO_3$, and extracted with AcOEt. The AcOEt extract was dried, and concentrated *in vacuo* to afford **4** (10.35 g, 93%), which was subjected to the oxidative cleavage with $NaIO_4$ without purification.

$NaIO_4$ (5.54 g) in H_2O (45 ml) was added dropwise to a stirred solution of **4** (3.25 g) in THF (15 ml) at 0 °C. The whole was stirred for 1 h at 0 °C, and for 6 h at room temperature, then the resulting precipitate was filtered off. The filtrate was concentrated *in vacuo* to leave an oily residue, which was purified by column chromatography on silica gel (30 g). The fraction eluted with 15—20% AcOEt in hexane (v/v) afforded **5** (2.73 g, 84%). **3**; IR (neat): 1640, 1470, 1380, 890 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, s, CH_3), 3.01 (1H, m, C_2-H), 4.69 (2H, br s, $=CH_2$). **4**; IR (neat): 3400, 1640, 1460, 1380 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, s, CH_3), 3.61 (1H, t, J=3.5 Hz, C_2-H), 4.77 (2H, s, $=CH_2$).[9] **5**; $[\alpha]_D^{30}$ +0.48° (c=0.21, $CHCl_3$). IR (neat): 2730, 1720, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.14 (3H, s, $COCH_3$), 4.79, 4.86 (1H each, s, $=CH_2$), 9.67 (1H, t, J=2.5 Hz, CHO).

(3*R*)-3-[(3ξ)-3-Hydroxybutyl]-4-methylenedodecanal (6)——$NaBH_4$ (0.38 g) was added portionwise to a stirred solution of **5** (1.81 g) in a mixture of EtOH (24 ml), H_2O (15 ml), and $CeCl_3 \cdot 7H_2O$ (2.79 g) over 10 min at −15 °C, and the excess $NaBH_4$ was decomposed with acetone (0.5 ml). The reaction mixture was diluted with brine, and extracted with ether. The ether extract was washed, and dried, then concentrated *in vacuo* to yield an oily residue, which was chromatographed on silica gel (20 g). The fraction eluted with 30% AcOEt in hexane (v/v) afforded **6** (1.22 g, 68%) as a colorless oil. IR (neat): 3400, 2720, 1720, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.76 (1H, m, CH–O), 4.82 (2H, m, $=CH_2$), 9.68 (1H, s, CHO).

(3*R*,4*S*)-3-[(3ξ)-3-Hydroxybutyl]-4-octylcyclopentanone (7)——Compound **6** (308 mg) in CH_2Cl_2 (6 ml) was added dropwise to a stirred solution of tris(triphenylphosphine)chlororhodium (531 mg) in CH_2Cl_2 (12 ml) at room temperature. After 9 h, the solvent was removed *in vacuo* to leave a crystalline residue, and the material insoluble in ether was filtered off. The filtrate was concentrated *in vacuo* to afford an oily residue, which was purified by column chromatography on silica gel (3 g). The fraction eluted with 20—30% AcOEt in hexane (v/v) afforded **7** (261 mg, 85%) as a colorless oil. IR (neat): 3440, 1740, 1460 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.0 Hz, CH_3), 3.77 (1H, m, CH–O). MS *m/z*: 268 (M^+), 250, 195, 137.

(3*R*,4*S*)-3-[(3ξ)-3-Hydroxybutyl]-4-octylcyclopentanone Ethylene Dithioacetal (8) and (1*S*,2*S*)-1-[(3ξ)-3-Hydroxybutyl]-2-octylcyclopentane (9)——BF_3–etherate (0.5 ml) was added to a stirred solution of a mixture of **7** (252 mg) and ethanedithiol (140 mg) in CH_2Cl_2 (3 ml) at room temperature. After 3 h, the reaction mixture was diluted with 5% aq. $NaHCO_3$ (40 ml), and extracted with CH_2Cl_2. The CH_2Cl_2 extract was successively washed with 5% aq. $NaHCO_3$, and brine, then dried. Removal of the solvent *in vacuo* afforded an oily residue, which was roughly chromatographed on silica gel (1 g). The fraction eluted with 10% AcOEt in hexane (v/v) afforded **8** (258 mg, 80%) as a colorless oil.

A mixture of **8** (252 mg) and Raney-Ni (W-4, 1 ml) in EtOH (5 ml) was heated under reflux for 5 h. The Raney-Ni was filtered off, and the filtrate was concentrated *in vacuo* to yield an oily residue, which was chromatographed on silica gel (2.5 g). The fraction eluted with 10% AcOEt in hexane (v/v) afforded **9** (198 mg, 80%) as a colorless oil. **8**; IR (neat): 3350, 1460, 1375 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.36 (4H, s, SCH_2CH_2S), 3.81 (1H, m, CH–O). MS *m/z*: 344 (M^+), 283, 243. **9**; IR (neat): 3350, 1460, 1375 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.0 Hz, CH_3), 3.77 (1H, m, CH–O). MS *m/z*: 236 (M^+ − 18), 124, 96.

(1*S*,2*S*)-2-Octyl-1-(3-oxobutyl)cyclopentane (10)——Jones reagent (0.05 ml) was added to a stirred solution of **9** (28 mg) in acetone (2 ml) under ice-water cooling. After 0.5 h, a drop of isopropanol was added to decompose the excess reagent. The reaction mixture was diluted with brine, and extracted with ether. The ether extract was washed with 5% aq. $NaHCO_3$, and brine, then dried. Removal of the solvent *in vacuo* afforded an oily residue, which was subjected to column chromatography on silica gel (0.5 g). The fraction eluted with 5% AcOEt in hexane (v/v) afforded **10** (26 mg, 92%) as a colorless oil. $[\alpha]_D^{32}$ −1.7° (c=1.35, $CHCl_3$). IR (neat): 1720, 1460, 1360 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.05—1.97 (24H, m, CH_2 × 11, CH × 2), 2.15 (3H, s, $COCH_3$), 2.41 (2H, t, J=7.0 Hz, CH_2CO). MS *m/z*: 252 (M^+), 234, 194, 82.

(1*S*,2*S*)-1-(2-Acetoxyethyl)-2-octylcyclopentane (11)——CF_3COOOH [freshly prepared from $(CF_3CO)_2O$ (28.4 ml) and 60% H_2O_2 (6.6 ml) in CH_2Cl_2 (60 ml)] was added dropwise to a well-stirred solution of **10** (424 mg) in CH_2Cl_2 (14 ml) in the presence of Na_2HPO_4 (10 g) at room temperature. After 5 h, the reaction mixture was poured into 5% aq. $NaHCO_3$ (150 ml) and extracted with AcOEt. The AcOEt extract was successively washed with 2% aq. KI, 5% aq. $Na_2S_2O_3$, and brine, then dried. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel (4 g). The fraction eluted with 2% AcOEt in hexane (v/v) afforded **11** (347 mg, 77%) as a colorless oil. $[\alpha]_D^{29}$ +0.24° (c=1.70, $CHCl_3$). IR (neat): 1740, 1460, 1240 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.20—1.85 (24H, m, CH_2 × 11, CH × 2), 2.04 (3H, s, $COCH_3$), 4.04 (2H, dt, J=6.5, 2.0 Hz, CH_2–O). MS *m/z*: 268 (M^+), 208, 180. *Anal.* Calcd for $C_{17}H_{32}O_2$: C, 76.06; H, 12.02. Found: C, 76.19; H, 12.03.

(1*S*,2*S*)-1-(2-Hydroxyethyl)-2-octylcyclopentane (12)——K_2CO_3 (10 mg) was added to a stirred solution of **11** (23 mg) in MeOH (1.5 ml), and the whole was stirred for 3 h at room temperature. The reaction mixture was diluted with brine, and extracted with AcOEt. The AcOEt extract was washed, and dried. Removal of the solvent *in vacuo* afforded an oily residue, which was purified by column chromatography on silica gel (0.4 g). The fraction eluted with 10% AcOEt in hexane (v/v) afforded **12** (19 mg, 99%) as a colorless oil. $[\alpha]_D^{28}$ +1.71° (*c*=1.40, $CHCl_3$). IR (neat): 3350, 1465, 1380 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, *J*=7.0 Hz, CH_3), 3.63 (2H, dt, *J*=6.5, 2.0 Hz, CH_2–O). MS *m/z*: 226 (M^+), 208, 180.

(1*S*,2*S*)-1-(2-Formylmethyl)-2-octylcyclopentane (13)——Compound **12** (96 mg) in CH_2Cl_2 (3 ml) was added dropwise to a stirred solution of PDC (830 mg) in CH_2Cl_2 (5 ml) at 0 °C. After being stirred for 4 h at room temperature, the reaction mixture was diluted with ether, and the resulting precipitate was filtered off. The filtrate was concentrated *in vacuo* to afford an oily residue, which was subjected to column chromatography on silica gel (0.5 g). The fraction eluted with 5% AcOEt in hexane (v/v) afforded **13** (81 mg, 85%) as a colorless oil. $[\alpha]_D^{27}$ +10.0° (*c*=1.52, $CHCl_3$). IR (neat): 2700, 1735, 1375 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.03—2.00 (22H, m, CH_2 × 10, CH × 2), 2.25—2.54 (2H, m, CH_2CO), 9.77 (1H, m, CHO). MS *m/z*: 224 (M^+), 205, 180, 67.

8-Isoprost-5-enoic Acid (14)——The sodium salt of (4-carboxybutylidene)triphenylphosphorane was prepared by the reaction of (4-carboxybutyl)triphenylphosphonium bromide (1.16 g) with sodium methylsulfinylmethide, which was prepared from DMSO (5 ml) and NaH (60% content, 263 mg) in a usual manner. To the above Wittig reagent, **13** (98 mg) in DMSO (2 ml) was added dropwise with stirring at room temperature under an Ar atmosphere. After 2 h, the reaction mixture was poured into ice-water (40 ml) containing 5% HCl (5 ml), and extracted with AcOEt. The AcOEt extract was washed, and dried. Removal of the solvent *in vacuo* afforded an oily residue, which was purified by column chromatography on silica gel (0.4 g). The fraction eluted with 30—40% AcOEt in hexane (v/v) afforded **14** (66 mg, 51%) as a colorless oil. $[\alpha]_D^{26}$ −2.0° (*c*=1.95, $CHCl_3$). IR (neat): 2400—3600, 1715, 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.37 (2H, t, *J*=7.0 Hz, CH_2COO), 5.34 (2H, m, –CH=CH–), 8.85 (1H, br, COOH). MS *m/z*: 308 (M^+), 205, 180, 148.

Methyl 8-Isoprost-5-enoate (15)——The methyl ester **15** was obtained from **14** by treatment with CH_2N_2. IR (neat): 1740, 1660, 1165 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.34 (2H, t, *J*=7.0 Hz, CH_2COO), 3.64 (3H, s, $COOCH_3$), 5.34 (2H, m, –CH=CH–). MS *m/z*: 322 (M^+), 292, 143, 74. *Anal.* Calcd for $C_{21}H_{38}O_2$: C, 78.20; H, 11.88. Found: C, 78.33; H, 11.92.

Methyl 8-Isoprostanoate (16)——A solution of **15** (75 mg) in MeOH (10 ml) was hydrogenated in the presence of Pt (PtO_2 100 mg) under an H_2 atmosphere for 20 h at −20 °C. The catalyst was filtered off, and the filtrate was concentrated *in vacuo* to afford an oily residue, which was purified by column chromatography on silica gel (0.5 g). The fraction eluted with 5% AcOEt in hexane (v/v) afforded **16** (43 mg) as a colorless oil. IR (neat): 1740, 1260, 1165 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, *J*=7.0 Hz, CH_3), 1.04—1.94 (32H, m, CH_2 × 15, CH × 2), 2.32 (2H, t, *J*=7.0 Hz, CH_2COO), 3.65 (3H, s, $COOCH_3$). MS *m/z*: 324 (M^+), 292, 143, 74.

8-Isoprostanoic Acid (1)——A mixture of **16** (40 mg) and 5% aq. NaOH (2 ml) in EtOH (1 ml) was stirred for 4 h at 50 °C. The usual work-up afforded an oily residue, which was purified by column chromatography on silica gel (0.4 g). The fraction eluted with 30% AcOEt in hexane (v/v) afforded **1** (27 mg, 73%) as a colorless oil. $[\alpha]_D^{20}$ −1.90° (*c*=1.35, $CHCl_3$). IR (neat): 1710, 1415, 940 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, *J*=7.0 Hz, CH_3), 1.04—1.94 (32H, m, CH_2 × 15, CH × 2), 2.36 (2H, t, *J*=7.0 Hz, CH_2COO), 8.70 (1H, br, COOH). MS *m/z*: 310 (M^+), 292, 180, 134, 119. High-MS for $C_{20}H_{38}O_2(M^+)$: Calcd *m/z* 310.28710; Found 310.28695.

(4*S*)-9-Acetoxy-*p*-mentha-1,8(10)-diene (19)——The acetate **19** was prepared from (−)-limonen-10-ol by treatment with Ac_2O/pyridine. $[\alpha]_D^{20}$ −73.1° (*c*=1.35, $CHCl_3$). IR (neat): 1740, 1645, 1240, 1025 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.65 (3H, s, CH_3), 2.09 (3H, s, $COCH_3$), 4.97, 5.04 (1H each, s, $=CH_2$), 5.39 (1H, s, C_2-H).

(3*S*)-3-(3-Acetoxy-1-propene-2-yl)-6-oxo-1-heptanal (20)——The ketone **20** was prepared, in 62% yield, from **19** by a method similar to that used in the case of **5**. $[\alpha]_D^{16}$ −8.4° (*c*=1.02, $CHCl_3$). IR (neat): 2720, 1740, 1720, 1645 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.10 (3H, s, $OCOCH_3$), 2.16 (3H, s, $COCH_3$), 4.55 (2H, s, CH_2–O), 5.03, 5.20 (1H each, s, $=CH_2$), 9.69 (1H, m, CHO).

(3*S*,6ξ)-3-(3-Acetoxy-1-propene-2-yl)-6-hydroxy-1-heptanal (21)——The pentenal **21** was prepared, in 72% yield, from **20** in a manner similar to that described for the synthesis of **6**. IR (neat): 1740, 1725, 1655, 1240 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.10 (3H, s, $OCOCH_3$), 3.71 (1H, m, CH–O), 4.56 (2H, s, CH_2–O), 9.70 (1H, m, CHO).

(3*S*,4*R*)-4-Acetoxymethyl-3-[(3ξ)-3-hydroxybutyl]cyclopentanone (22)——The cyclopentanone **22** was prepared, in 96% yield, from **21** in a manner similar to that described for the synthesis of **7**. IR (neat): 1740, 1440, 1240, 1035 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.05 (3H, s, $OCOCH_3$), 3.77 (1H, m, CH–O), 4.17 (2H, m, CH_2–O). MS *m/z*: 228 (M^+), 184, 110.

(3*S*,4*R*)-4-Acetoxymethyl-3-[(3ξ)-3-hydroxybutyl]cyclopentanone Ethylene Dithioacetal (23) and (1*R*,2*R*)-1-[(3ξ)-3-Hydroxybutyl]-2-hydroxymethylcyclopentane (24)——The cyclopentane **24** was prepared, in 49% yield, from **22** *via* **23** in a manner similar to that described for the synthesis of **9**. **23**; IR (neat): 1740, 1450, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.03 (3H, s, $OCOCH_3$), 3.30 (4H, s, SCH_2CH_2S), 4.08 (2H, m, CH_2O). MS *m/z*: 304 (M^+), 286, 244. **24**; IR (neat): 3350, 1450, 1120, 1030 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, d, *J*=7.0 Hz, CH_3), 3.32—3.97 (3H, m, CH_2–O, CH–O). MS *m/z*: 172 (M^+), 154, 136.

(1*R*,2*R*)-1-(3-Oxobutyl)-2-carboxycyclopentane (25)——Jones reagent (12 ml) was added dropwise to a stirred solution of **24** (1.59 g) in acetone (30 ml) for 1 h at 0—10 °C. The excess reagent was decomposed by adding isopropanol (3 ml), and the reaction mixture was poured into brine (50 ml), then extracted with AcOEt. The AcOEt extract was washed with 5% aq. $NaHCO_3$ and brine, then dried. The solvent was removed *in vacuo* to leave an oily residue, which was purified by column chromatography on silica gel (20 g). The fraction eluted with 20—30% AcOEt in hexane (v/v) afforded **25** (0.96 g, 57%) as a colorless oil. $[\alpha]_D^{26}$ −20.8° (c=1.05, $CHCl_3$). IR (neat): 2500—3600, 1720, 1365 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.15 (3H, s, $COCH_3$), 2.51 (2H, t, J=8.0 Hz, CH_2CO), 2.88 (1H, m, CHCOO). MS m/z: 184 (M^+), 166, 138, 81.

(1*R*,2*R*)-1-(3-Oxobutyl)-2-methoxycarbonylcyclopentane (26)——The keto-ester **26** was prepared from **25** by treatment with CH_2N_2. $[\alpha]_D^{25}$ −29.6° (c=1.05, $CHCl_3$). ^{1}H-NMR ($CDCl_3$). δ: 2.13 (3H, s, $COCH_3$), 3.64 (3H, s, $COOCH_3$). MS m/z: 198 (M^+), 141, 81.

(1*R*,2*R*)-1-(3,3-Ethylenedioxybutyl)-2-methoxycarbonylcyclopentane (27)——The mixture of **26** (1.281 g), ethylene glycol (0.5 ml), and benzene (40 ml) in the presence of a catalytic amount of *p*-toluenesulfonic acid was heated under reflux with azeotropic removal of formed H_2O. After 3 h, the reaction mixture was washed with 5% aq. $NaHCO_3$, and brine, then dried. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel (10 g). The fraction eluted with 20% AcOEt in hexane (v/v) afforded **27** (1.301 g, 83%) as a colorless oil. $[\alpha]_D^{25}$ −25.3° (c=1.01, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 2.84 (1H, m, CHCOO), 3.64 (3H, s, $COOCH_3$), 3.90 (4H, s, OCH_2CH_2O). MS m/z: 242 (M^+), 227, 87.

(1*R*,2*S*)-1-(3,3-Ethylenedioxybutyl)-2-methoxycarbonylcyclopentane (28)——The *cis*-ester **27** (1.301 g) in toluene (30 ml) was heated under reflux for 6 h in the presence of MeONa [freshly prepared from Na (0.12 g) and MeOH] under an N_2 atmosphere. The reaction mixture was diluted with 1% aq. NH_4Cl (30 ml), and extracted with ether. The ether extract was washed, and dried. The solvent was removed *in vacuo* to afford an oily residue, which was subjected to column chromatography on silica gel (15 g). The fraction eluted with 5% AcOEt in hexane (v/v) afforded **28** (1.082 g, 83%) as a colorless oil. $[\alpha]_D^{25}$ +40.6° (c=1.20, $CHCl_3$). IR (neat): 1735, 1450, 1195, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.31 (1H, m, CHCOO), 3.64 (3H, s, $COOCH_3$), 3.90 (4H, s, OCH_2CH_2O). MS m/z: 242 (M^+), 227, 87.

(1*R*,2*S*)-1-(3,3-Ethylenedioxybutyl)-2-hydroxymethylcyclopentane (29)——The *trans*-ester **28** (1.082 g) in ether (10 ml) was added dropwise with stirring to a suspension of $LiAlH_4$ (152 mg) in ether (35 ml) at 0—5 °C. After 3 h, the reaction mixture was subjected to usual work-up, and the oily compound was purified by column chromatography on silica gel (10 g). The fraction eluted with 20—25% AcOEt in hexane (v/v) afforded **29** (853 mg, 89%) as a colorless oil. $[\alpha]_D^{24}$ +32.6° (c=1.15, $CHCl_3$). IR (neat): 3430, 1450, 1220, 1045 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.50 (2H, m, CH_2–O), 3.92 (4H, s, OCH_2CH_2O). MS m/z: 215 (M^++1), 199, 153.

(1*R*,2*S*)-1-(3,3-Ethylenedioxybutyl)-2-formylcyclopentane (30)——The *trans*-alcohol **29** (750 mg) in CH_2Cl_2 (10 ml) was added dropwise to Collins reagent [prepared from pyridine (3.4 ml), CrO_3 (2.15 g), and CH_2Cl_2 (50 ml)] with stirring at 0—5 °C. After 0.5 h, the reaction mixture was diluted with ether (100 ml), and the resulting precipitate was filtered off. The filtrate was washed with 5% aq. $NaHCO_3$, and brine, then dried. Removal of the solvent *in vacuo* afforded an oily residue, which was purified by column chromatography on silica gel (12 g). The fraction eluted with 5% AcOEt in hexane (v/v) afforded **30** (301 mg, 40%) as a colorless oil. IR (neat): 2720, 1725, 1220, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.92 (4H, s, OCH_2CH_2O), 9.57 (1H, d, J=4.0 Hz, CHO).

(1*R*,2*S*)-1-(3,3-Ethylenedioxybutyl)-2-(1-octenyl)cyclopentane (31)——Wittig reagent was prepared from heptyltriphenylphosphonium bromide (1 g) and BuLi (15% content, 2.3 ml) in a usual manner. To the above Wittig reagent, the *trans*-aldehyde **30** (289 mg) in ether (16 ml) was added dropwise with stirring at 5—10 °C under an N_2 atmosphere. After 1 h, the reaction mixture was diluted with brine, and extracted with ether. The ether extract was washed, and dried. The solvent was removed *in vacuo* to leave an oily residue, which was purified by column chromatography on silica gel (2 g). The fraction eluted with 5% AcOEt in hexane (v/v) afforded **31** (247 mg, 59%) as a colorless oil. $[\alpha]_D^{24}$ +9.50° (c=1.05, $CHCl_3$). IR (neat): 1660, 1375, 1220, 1060 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, t, J=7.0 Hz, CH_3), 3.88 (4H, s, OCH_2CH_2O), 5.20 (1H, dt, J=11.0, 8.0 Hz, =CH–), 5.38 (1H, dd, J=11.0, 7.0 Hz, =CH–). MS m/z: 294 (M^+), 279, 114, 87. *Anal.* Calcd for $C_{19}H_{34}O_2$: C, 77.49; H, 11.64. Found: C, 77.55; H, 11.72.

(1*R*,2*S*)-1-(3,3-Ethylenedioxybutyl)-2-octylcyclopentane (32)——Compound **31** was hydrogenated, in 97% yield, in a manner similar to that described for the hydrogenation of **15** to **16**. $[\alpha]_D^{24}$ +44.8° (c=1.03, $CHCl_3$). IR (neat): 1465, 1450, 1375, 1220 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.0 Hz, CH_3), 3.92 (4H, s, OCH_2CH_2O). MS m/z: 281 (M^+-CH_3), 234, 192.

(1*R*,2*S*)-2-Octyl-1-(3-oxobutyl)cyclopentane (33)——A mixture of **32** (238 mg), 10% HCl (0.5 ml), and MeOH (10 ml) was stirred at room temperature. After 1 h, the reaction mixture was neutralized with 5% aq. $NaHCO_3$, and diluted with brine, then extracted with AcOEt. The AcOEt extract was washed, and dried. The solvent was removed *in vacuo* to give **33** as an oily residue, which was purified by column chromatography on silica gel (1.5 g). The fraction eluted with 5% AcOEt in hexane (v/v) gave **33** (197 mg, 96%) as a colorless oil. $[\alpha]_D^{25}$ +48.8° (c=1.25, $CHCl_3$). IR (neat): 1720, 1470, 1360 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.15 (3H, s, $COCH_3$). MS m/z: 252 (M^+), 194, 82. *Anal.* Calcd for $C_{17}H_{32}O$: C, 80.88; H, 12.78. Found: C, 80.91; H, 12.83.

(1*R*,2*S*)-1-(2-Acetoxyethyl)-2-octylcyclopentane (34), (1*R*,2*S*)-1-(2-Hydroxyethyl)-2-octylcyclopentane (35), (1*R*,2*S*)-1-Formylmethyl-2-octylcyclopentane (36), Prost-5-enoic Acid (37), Methyl Prost-5-enoate (38), Methyl

Prostanoate (39), and Prostanoic Acid (18)——In a manner similar to that described for the synthesis of 8-isoprostanoic acid (**1**), compounds **34**, **35**, **36**, **37**, **38**, **39**, and **18** were synthesized in good yields (**34**, 89%; **35**, 93%; **36**,70%; **37**, 71%; **38**, 90%; **39**, 78%; **18**, 77%). **34**; $[\alpha]_D^{23}$ +41.4° (c=0.93, $CHCl_3$). IR (neat): 1740, 1465, 1365, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.0 Hz, CH_3), 2.04 (3H, s, $OCOCH_3$), 4.06 (2H, t, J=7.0 Hz, CH_2–O). MS m/z: 268 (M^+), 208. **35**; $[\alpha]_D^{24}$ +51.2° (c=0.94, $CHCl_3$). IR (neat): 3330, 1455, 1380 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.0 Hz, CH_3), 3.64 (2H, t, J=7.0 Hz, CH_2–O). MS m/z: 208 ($M^+ - H_2O$), 180, 82. **36**; $[\alpha]_D^{24}$ +43.6° (c=0.90, $CHCl_3$). IR (neat): 2720, 1730, 1380 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 9.75 (1H, m, CHO). MS m/z: 224 (M^+), 206, 180. **37**; $[\alpha]_D^{23}$ +35.3° (c=0.65, $CHCl_3$). IR (neat): 2500—3600, 1710, 1455, 1380 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.0 Hz, CH_3), 5.38 (2H, dt, J=12.0, 6.0 Hz, –CH=CH–). **38**; $[\alpha]_D^{25}$ +33.7° (c=0.95, $CHCl_3$). IR (neat): 1740, 1650, 1435, 1160 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.64 (3H, s, OCH_3), 5.36 (2H, dt, J=12.0, 6.0 Hz, –CH=CH–). **39**; IR (neat): 1740, 1460, 1165 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.63 (3H, s, OCH_3). **18**; $[\alpha]_D^{25}$ +45.0° (c=1.01, EtOH).[16] ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.0 Hz, CH_3), 1.10—1.88 (32H, m, CH_2 × 15, CH × 2), 2.37 (2H, t, J=8.0 Hz, CH_2COO), 8.34 (1H, br, COOH). MS m/z: 310 (M^+), 292, 180, 97. High-MS for $C_{20}H_{38}O_2$ (M^+): Calcd m/z 310. 28710; Found 310.28745.

References and Notes

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11) Compound (**6**) consists of a mixture of the epimeric alcohols.
12) In the ^{1}H-NMR spectrum of the reduction products, olefinic-H had completely disappeared, and the C_2-H was observed as two pairs of triplets at δ 2.28 (t, J=7.0 Hz) and 2.36 (t, J=7.0 Hz). Furthermore, the MS of the reduction products showed two M^+, 308 (M^+ corresponding to **17**) and 310 (M^+ of **1**) in almost equal amounts. On the basis of the above spectroscopic analysis, the reduction products were deduced to be a mixture of **1** and **17**.
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15) Compound (**31**) is considered to be a mixture of the geometrical isomers.
16) Prostanoic acid (**18**) ($[\alpha]_D^{25}$ +45°) was slightly different in specific rotation from the previous sample[4] ($[\alpha]_D^{20}$ +49.3°). This seems to be a result of the optical purity of the employed (−)-limonen-10-ol ($[\alpha]_D^{19}$ −95° (c=1.12, EtOH)), (commercially available (+)-limonene-10-ol: $[\alpha]_D^{21}$ +105° (c=1.03, EtOH)).