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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<sup>1)</sup> and for studies on the structure-activity relationships.<sup>2)</sup> 8-Isoprostanoic acid (**1**) constitutes the basic skeleton of 8-isoprostaglandin E<sub>1</sub>, which was isolated during studies on the biological conversion<sup>3)</sup> of 8,11,14-icosatrienoic acid to PGs. Prostanoic acid was previously synthesized by our group<sup>4)</sup> from the Corey lactone, and the absolute stereochemistry of this compound, which was incorrectly assigned by Hamon *et al.*,<sup>5)</sup> was unambiguously established.

As a part of our synthetic studies<sup>6)</sup> 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.<sup>7)</sup> 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

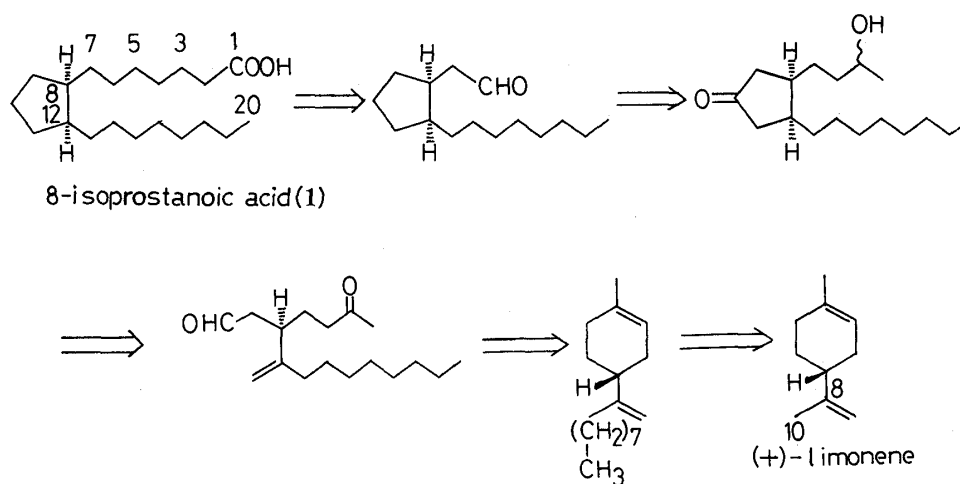


Chart 1

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  $\omega$ -chain consisting of the C<sub>8</sub>-unit, the C<sub>10</sub>-position of (+)-limonene was alkylated with *sec*-BuLi-tetramethylethylenediamine (TMEDA)-complex and heptyl bromide,<sup>8)</sup> 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<sub>2</sub>Cl<sub>2</sub>. In this manner, the  $\alpha$ - and  $\beta$ -epoxide were obtained as an inseparable mixture in almost equal amounts. Hydrolysis of the mixture with 1% aq. H<sub>2</sub>SO<sub>4</sub> afforded the diol (**4**),<sup>9)</sup> which, on oxidative cleavage with NaIO<sub>4</sub>, yielded the keto-aldehyde (**5**, 68% from **2**).

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

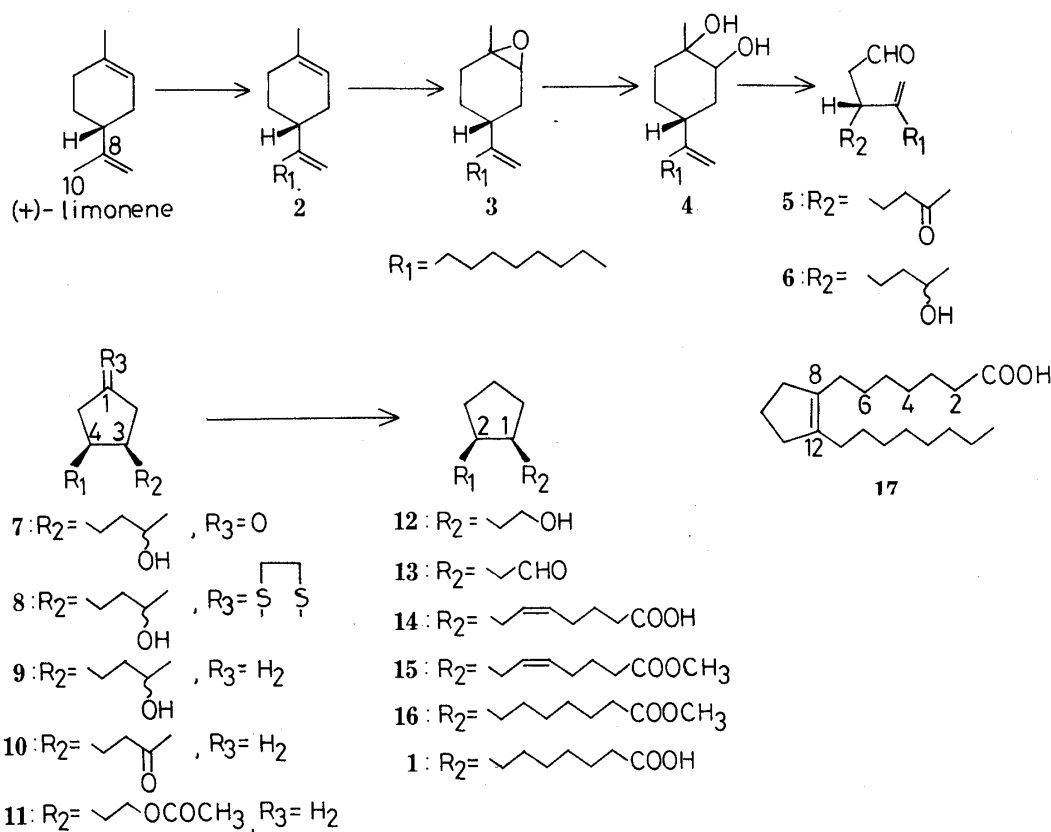


Chart 2

in **5** was subjected to selective reduction with NaBH<sub>4</sub> in the presence<sup>10)</sup> of CeCl<sub>3</sub> in aq. EtOH, and the hydroxy aldehyde (**6**)<sup>11)</sup> 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  $\alpha$ -chain. Removal of the undesired carbonyl function was effected in 64% yield by thioacetalization with ethanedithiol/BF<sub>3</sub> and subsequent desulfurization with Raney-Ni.

The  $\alpha$ -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<sub>2</sub>HPO<sub>4</sub> in CH<sub>2</sub>Cl<sub>2</sub> at room temperature, gave the acetate (**11**, 71% from **9**). Hydrolysis of **11** with K<sub>2</sub>CO<sub>3</sub> in MeOH and subsequent oxidation with pyridinium dichromate (PDC) in CH<sub>2</sub>Cl<sub>2</sub> 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  $\Delta^5$ -double bond. However, the catalytic hydrogenation of **14** with  $\text{H}_2/5\% \text{ Pd-C}$  in MeOH gave an inseparable mixture<sup>12)</sup> of 8-isoprostanoic acid (**1**) and the compound (**17**) in which the  $\Delta^5$ -double bond has migrated to the  $\Delta^{8(12)}$ -position. This troublesome problem was overcome by catalytic hydrogenation<sup>13)</sup> of the methyl ester (**15**) with  $\text{H}_2/\text{Pt}$  in MeOH at  $-20^\circ\text{C}$ ; 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  $\omega$ -chain, the  $\text{C}_{10}$ -position of (–)-limonene should be oxidized to (–)-limonen-10-ol. This was effected by lithiation<sup>8)</sup> with *sec*-BuLi–TMEDA-complex and subsequent oxidation with

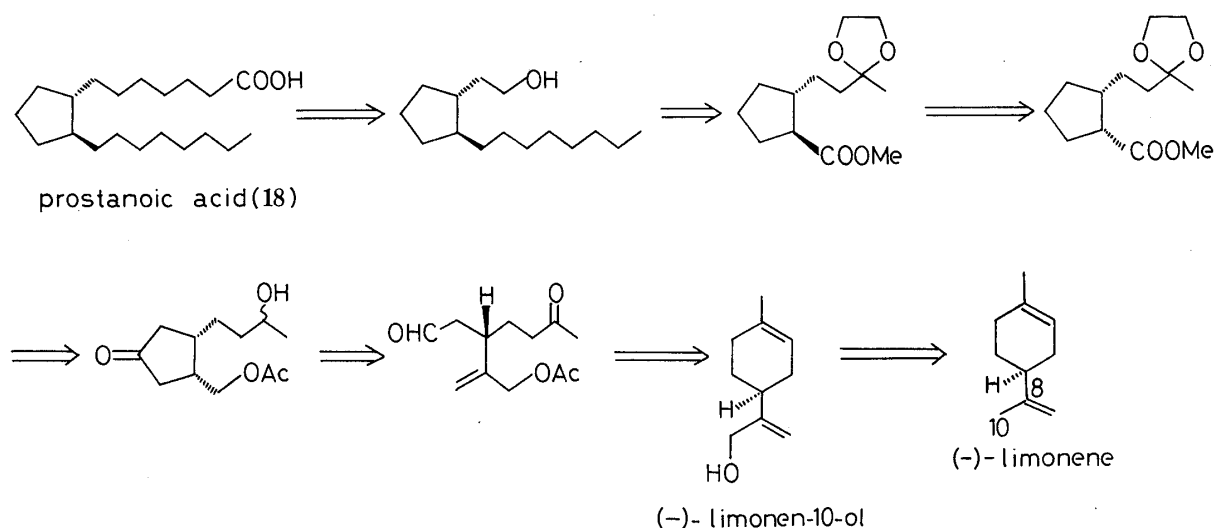


Chart 3

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  $\text{C}_4\alpha$ -substituent should be easily isomerized to the more stable  $\text{C}_4\beta$ -configuration via the corresponding methyl ester, which may be extended to form the  $\omega$ -chain. The  $\text{C}_3$ -substituent seems appropriate for shortening from the undesired  $\text{C}_4$ -unit to a  $\text{C}_2$ -unit as required for the introduction of the  $\alpha$ -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  $\text{CH}_2\text{N}_2$ . 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 ( $^1\text{H-NMR}$ ) spectroscopy was found to be effective for the detection of this epimerization. In the  $^1\text{H-NMR}$  spectrum of the *trans*-ester (**28**), the  $\text{C}_2\text{-H}$  was observed at higher field ( $\delta$  2.31) than in the case of the *cis*-ester (**27**,  $\delta$  2.84).<sup>14)</sup> 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  $\text{LiAlH}_4$  followed by oxidation with Collins reagent afforded the

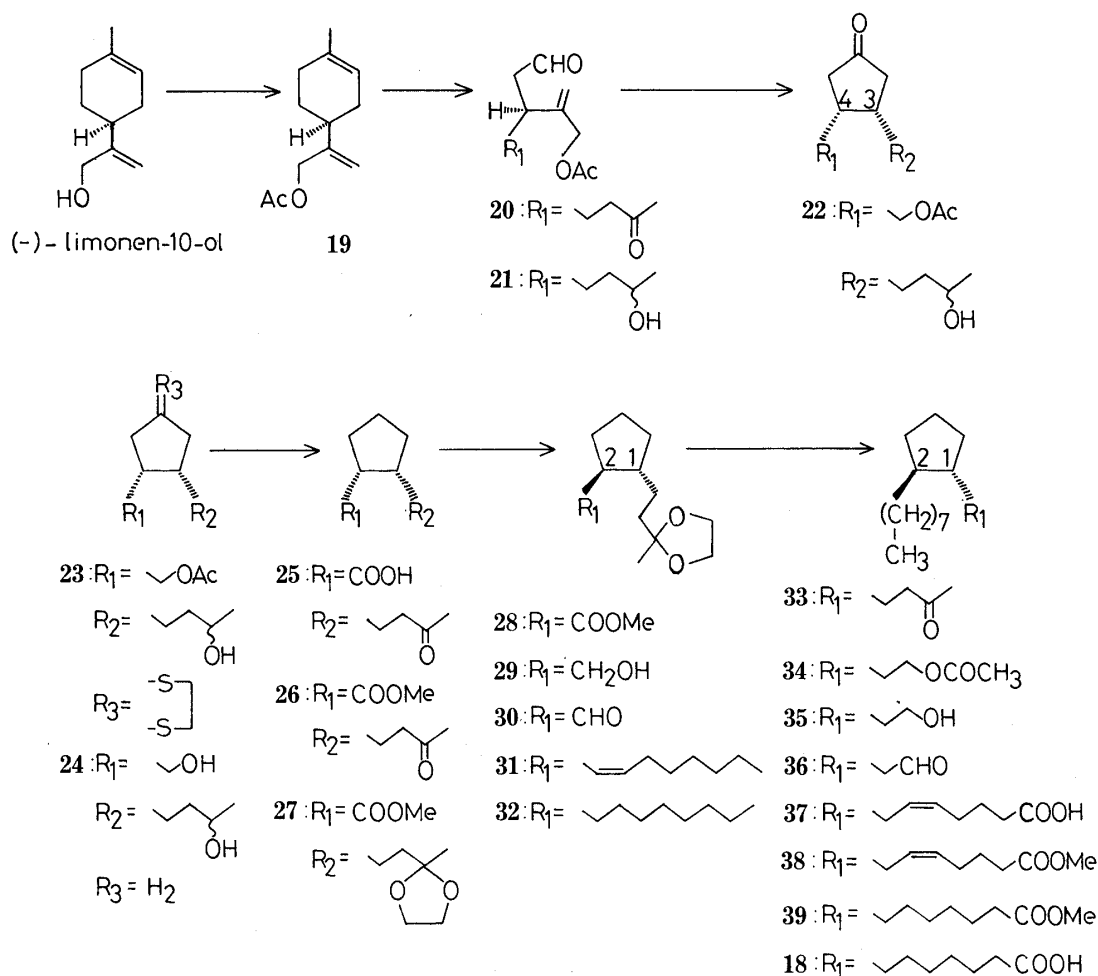


Chart 4

aldehyde (30), which was subjected to Wittig reaction with heptylidenetriphenylphosphorane<sup>15)</sup> in ether. In this manner, 31 was obtained in 21% yield from 28. Upon catalytic hydrogenation with H<sub>2</sub>/Pt in MeOH and subsequent deprotection with 10% HCl, 31 afforded the ketone (33) possessing the  $\omega$ -chain. The  $\alpha$ -chain was introduced by a technique similar to that used in the case of 1. Prostanic acid (18) thus derived from (-)-limonene was identical with an authentic sample<sup>4)</sup> in terms of the <sup>1</sup>H-NMR and the infrared (IR) spectra.

### Experimental

IR spectra were measured with a JASCO A-202 spectrometer. <sup>1</sup>H-NMR spectra were measured on a JEOL JNM-PS-100 spectrometer with Me<sub>4</sub>Si 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<sub>254</sub> plates (Merck). All organic solvent extracts were washed with brine and dried over anhydrous sodium sulfate.

**(4R)-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<sub>2</sub> 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. [ $\alpha$ ]<sub>D</sub><sup>28</sup> +28.3° (*c* = 1.45, CHCl<sub>3</sub>). IR (neat): 1640, 1460, 885 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 0.88 (3H, t, *J* = 7 Hz, CH<sub>3</sub>), 4.72 (2H, s, =CH<sub>2</sub>), 5.41 (1H, s, C<sub>2</sub>-H). MS *m/z*: 234 (M<sup>+</sup>), 136, 121.

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

a well-stirred solution of **2** (16.22 g) in a mixture of  $\text{CH}_2\text{Cl}_2$  (100 ml) and 5% aq.  $\text{NaHCO}_3$  (300 ml) at room temperature. After 4 h, the reaction mixture was poured into brine, and extracted with  $\text{CH}_2\text{Cl}_2$ . The  $\text{CH}_2\text{Cl}_2$  extract was washed with 5% aq.  $\text{Na}_2\text{CO}_3$ , 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  $\alpha$ - and  $\beta$ -oxide. The mixture of **3** (10.38 g), tetrahydrofuran (THF) (60 ml), and 1% aq.  $\text{H}_2\text{SO}_4$  (100 ml) was stirred at room temperature for 24 h, then neutralized with 5% aq.  $\text{NaHCO}_3$ , 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  $\text{NaIO}_4$  without purification.

$\text{NaIO}_4$  (5.54 g) in  $\text{H}_2\text{O}$  (45 ml) was added dropwise to a stirred solution of **4** (3.25 g) in THF (15 ml) at  $0^\circ\text{C}$ . The whole was stirred for 1 h at  $0^\circ\text{C}$ , 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,  $890\text{ cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.30 (3H, s,  $\text{CH}_3$ ), 3.01 (1H, m,  $\text{C}_2\text{-H}$ ), 4.69 (2H, br s,  $=\text{CH}_2$ ). **4**; IR (neat): 3400, 1640, 1460,  $1380\text{ cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.27 (3H, s,  $\text{CH}_3$ ), 3.61 (1H, t,  $J=3.5\text{ Hz}$ ,  $\text{C}_2\text{-H}$ ), 4.77 (2H, s,  $=\text{CH}_2$ ). **5**;  $[\alpha]_{\text{D}}^{30} +0.48^\circ$  ( $c=0.21$ ,  $\text{CHCl}_3$ ). IR (neat): 2730, 1720,  $1640\text{ cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.14 (3H, s,  $\text{COCH}_3$ ), 4.79, 4.86 (1H each, s,  $=\text{CH}_2$ ), 9.67 (1H, t,  $J=2.5\text{ Hz}$ , CHO).

**(3R,4S)-3-[(3S)-3-Hydroxybutyl]-4-methylenedodecanal (6)**— $\text{NaBH}_4$  (0.38 g) was added portionwise to a stirred solution of **5** (1.81 g) in a mixture of EtOH (24 ml),  $\text{H}_2\text{O}$  (15 ml), and  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$  (2.79 g) over 10 min at  $-15^\circ\text{C}$ , and the excess  $\text{NaBH}_4$  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,  $1640\text{ cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.76 (1H, m,  $\text{CH-O}$ ), 4.82 (2H, m,  $=\text{CH}_2$ ), 9.68 (1H, s, CHO).

**(3R,4S)-3-[(3S)-3-Hydroxybutyl]-4-octylcyclopentanone (7)**—Compound **6** (308 mg) in  $\text{CH}_2\text{Cl}_2$  (6 ml) was added dropwise to a stirred solution of tris(triphenylphosphine)chlororhodium (531 mg) in  $\text{CH}_2\text{Cl}_2$  (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,  $1460\text{ cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.88 (3H, t,  $J=7.0\text{ Hz}$ ,  $\text{CH}_3$ ), 3.77 (1H, m,  $\text{CH-O}$ ). MS  $m/z$ : 268 ( $\text{M}^+$ ), 250, 195, 137.

**(3R,4S)-3-[(3S)-3-Hydroxybutyl]-4-octylcyclopentanone Ethylene Dithioacetal (8) and (1S,2S)-1-[(3S)-3-Hydroxybutyl]-2-octylcyclopentane (9)**— $\text{BF}_3$ -etherate (0.5 ml) was added to a stirred solution of a mixture of **7** (252 mg) and ethanedithiol (140 mg) in  $\text{CH}_2\text{Cl}_2$  (3 ml) at room temperature. After 3 h, the reaction mixture was diluted with 5% aq.  $\text{NaHCO}_3$  (40 ml), and extracted with  $\text{CH}_2\text{Cl}_2$ . The  $\text{CH}_2\text{Cl}_2$  extract was successively washed with 5% aq.  $\text{NaHCO}_3$ , 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,  $1375\text{ cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.36 (4H, s,  $\text{SCH}_2\text{CH}_2\text{S}$ ), 3.81 (1H, m,  $\text{CH-O}$ ). MS  $m/z$ : 344 ( $\text{M}^+$ ), 283, 243. **9**; IR (neat): 3350, 1460,  $1375\text{ cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.88 (3H, t,  $J=7.0\text{ Hz}$ ,  $\text{CH}_3$ ), 3.77 (1H, m,  $\text{CH-O}$ ). MS  $m/z$ : 236 ( $\text{M}^+ - 18$ ), 124, 96.

**(1S,2S)-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.  $\text{NaHCO}_3$ , 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.  $[\alpha]_{\text{D}}^{32} -1.7^\circ$  ( $c=1.35$ ,  $\text{CHCl}_3$ ). IR (neat): 1720, 1460,  $1360\text{ cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.05–1.97 (24H, m,  $\text{CH}_2 \times 11$ ,  $\text{CH} \times 2$ ), 2.15 (3H, s,  $\text{COCH}_3$ ), 2.41 (2H, t,  $J=7.0\text{ Hz}$ ,  $\text{CH}_2\text{CO}$ ). MS  $m/z$ : 252 ( $\text{M}^+$ ), 234, 194, 82.

**(1S,2S)-1-(2-Acetoxyethyl)-2-octylcyclopentane (11)**— $\text{CF}_3\text{COOOH}$  [freshly prepared from  $(\text{CF}_3\text{CO})_2\text{O}$  (28.4 ml) and 60%  $\text{H}_2\text{O}_2$  (6.6 ml) in  $\text{CH}_2\text{Cl}_2$  (60 ml)] was added dropwise to a well-stirred solution of **10** (424 mg) in  $\text{CH}_2\text{Cl}_2$  (14 ml) in the presence of  $\text{Na}_2\text{HPO}_4$  (10 g) at room temperature. After 5 h, the reaction mixture was poured into 5% aq.  $\text{NaHCO}_3$  (150 ml) and extracted with AcOEt. The AcOEt extract was successively washed with 2% aq. KI, 5% aq.  $\text{Na}_2\text{S}_2\text{O}_3$ , 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.  $[\alpha]_{\text{D}}^{29} +0.24^\circ$  ( $c=1.70$ ,  $\text{CHCl}_3$ ). IR (neat): 1740, 1460,  $1240\text{ cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.20–1.85 (24H, m,  $\text{CH}_2 \times 11$ ,  $\text{CH} \times 2$ ), 2.04 (3H, s,  $\text{COCH}_3$ ), 4.04 (2H, dt,  $J=6.5, 2.0\text{ Hz}$ ,  $\text{CH}_2\text{-O}$ ). MS  $m/z$ : 268 ( $\text{M}^+$ ), 208, 180. Anal. Calcd for  $\text{C}_{17}\text{H}_{32}\text{O}_2$ : C, 76.06; H, 12.02. Found: C, 76.19; H, 12.03.

**(1S,2S)-1-(2-Hydroxyethyl)-2-octylcyclopentane (12)**—K<sub>2</sub>CO<sub>3</sub> (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.  $[\alpha]_D^{28} + 1.71^\circ$  ( $c = 1.40$ , CHCl<sub>3</sub>). IR (neat): 3350, 1465, 1380 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 0.88 (3H, t,  $J = 7.0$  Hz, CH<sub>3</sub>), 3.63 (2H, dt,  $J = 6.5, 2.0$  Hz, CH<sub>2</sub>-O). MS  $m/z$ : 226 (M<sup>+</sup>), 208, 180.

**(1S,2S)-1-(2-Formylmethyl)-2-octylcyclopentane (13)**—Compound **12** (96 mg) in CH<sub>2</sub>Cl<sub>2</sub> (3 ml) was added dropwise to a stirred solution of PDC (830 mg) in CH<sub>2</sub>Cl<sub>2</sub> (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.  $[\alpha]_D^{27} + 10.0^\circ$  ( $c = 1.52$ , CHCl<sub>3</sub>). IR (neat): 2700, 1735, 1375 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 1.03–2.00 (22H, m, CH<sub>2</sub>  $\times$  10, CH  $\times$  2), 2.25–2.54 (2H, m, CH<sub>2</sub>CO), 9.77 (1H, m, CHO). MS  $m/z$ : 224 (M<sup>+</sup>), 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.  $[\alpha]_D^{26} - 2.0^\circ$  ( $c = 1.95$ , CHCl<sub>3</sub>). IR (neat): 2400–3600, 1715, 1660 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 2.37 (2H, t,  $J = 7.0$  Hz, CH<sub>2</sub>COO), 5.34 (2H, m, -CH=CH-), 8.85 (1H, br, COOH). MS  $m/z$ : 308 (M<sup>+</sup>), 205, 180, 148.

**Methyl 8-Isoprost-5-enoate (15)**—The methyl ester **15** was obtained from **14** by treatment with CH<sub>2</sub>N<sub>2</sub>. IR (neat): 1740, 1660, 1165 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 2.34 (2H, t,  $J = 7.0$  Hz, CH<sub>2</sub>COO), 3.64 (3H, s, COOCH<sub>3</sub>), 5.34 (2H, m, -CH=CH-). MS  $m/z$ : 322 (M<sup>+</sup>), 292, 143, 74. Anal. Calcd for C<sub>21</sub>H<sub>38</sub>O<sub>2</sub>: 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<sub>2</sub> 100 mg) under an H<sub>2</sub> 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<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 0.88 (3H, t,  $J = 7.0$  Hz, CH<sub>3</sub>), 1.04–1.94 (32H, m, CH<sub>2</sub>  $\times$  15, CH  $\times$  2), 2.32 (2H, t,  $J = 7.0$  Hz, CH<sub>2</sub>COO), 3.65 (3H, s, COOCH<sub>3</sub>). MS  $m/z$ : 324 (M<sup>+</sup>), 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.  $[\alpha]_D^{20} - 1.90^\circ$  ( $c = 1.35$ , CHCl<sub>3</sub>). IR (neat): 1710, 1415, 940 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 0.88 (3H, t,  $J = 7.0$  Hz, CH<sub>3</sub>), 1.04–1.94 (32H, m, CH<sub>2</sub>  $\times$  15, CH  $\times$  2), 2.36 (2H, t,  $J = 7.0$  Hz, CH<sub>2</sub>COO), 8.70 (1H, br, COOH). MS  $m/z$ : 310 (M<sup>+</sup>), 292, 180, 134, 119. High-MS for C<sub>20</sub>H<sub>38</sub>O<sub>2</sub>(M<sup>+</sup>): Calcd  $m/z$  310.28710; Found 310.28695.

**(4S)-9-Acetoxy-*p*-mentha-1,8(10)-diene (19)**—The acetate **19** was prepared from (-)-limonen-10-ol by treatment with Ac<sub>2</sub>O/pyridine.  $[\alpha]_D^{20} - 73.1^\circ$  ( $c = 1.35$ , CHCl<sub>3</sub>). IR (neat): 1740, 1645, 1240, 1025 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 1.65 (3H, s, CH<sub>3</sub>), 2.09 (3H, s, COCH<sub>3</sub>), 4.97, 5.04 (1H each, s, =CH<sub>2</sub>), 5.39 (1H, s, C<sub>2</sub>-H).

**(3S)-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**.  $[\alpha]_D^{16} - 8.4^\circ$  ( $c = 1.02$ , CHCl<sub>3</sub>). IR (neat): 2720, 1740, 1720, 1645 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 2.10 (3H, s, OCOCH<sub>3</sub>), 2.16 (3H, s, COCH<sub>3</sub>), 4.55 (2H, s, CH<sub>2</sub>-O), 5.03, 5.20 (1H each, s, =CH<sub>2</sub>), 9.69 (1H, m, CHO).

**(3S,6 $\xi$ )-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<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 2.10 (3H, s, OCOCH<sub>3</sub>), 3.71 (1H, m, CH-O), 4.56 (2H, s, CH<sub>2</sub>-O), 9.70 (1H, m, CHO).

**(3S,4R)-4-Acetoxyethyl-3-[(3 $\xi$ )-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<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 2.05 (3H, s, OCOCH<sub>3</sub>), 3.77 (1H, m, CH-O), 4.17 (2H, m, CH<sub>2</sub>-O). MS  $m/z$ : 228 (M<sup>+</sup>), 184, 110.

**(3S,4R)-4-Acetoxyethyl-3-[(3 $\xi$ )-3-hydroxybutyl]cyclopentanone Ethylene Dithioacetal (23) and (1R,2R)-1-[(3 $\xi$ )-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<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 2.03 (3H, s, OCOCH<sub>3</sub>), 3.30 (4H, s, SCH<sub>2</sub>CH<sub>2</sub>S), 4.08 (2H, m, CH<sub>2</sub>O). MS  $m/z$ : 304 (M<sup>+</sup>), 286, 244. **24**; IR (neat): 3350, 1450, 1120, 1030 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 1.17 (3H, d,  $J = 7.0$  Hz, CH<sub>3</sub>), 3.32–3.97 (3H, m, CH<sub>2</sub>-O, CH-O). MS  $m/z$ : 172 (M<sup>+</sup>), 154, 136.

**(1R,2R)-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<sub>3</sub> 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.  $[\alpha]_D^{26} -20.8^\circ$  ( $c=1.05$ , CHCl<sub>3</sub>). IR (neat): 2500–3600, 1720, 1365 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 2.15 (3H, s, COCH<sub>3</sub>), 2.51 (2H, t,  $J=8.0$  Hz, CH<sub>2</sub>CO), 2.88 (1H, m, CHCOO). MS  $m/z$ : 184 (M<sup>+</sup>), 166, 138, 81.

**(1R,2R)-1-(3-Oxobutyl)-2-methoxycarbonylcyclopentane (26)**—The keto-ester **26** was prepared from **25** by treatment with CH<sub>2</sub>N<sub>2</sub>.  $[\alpha]_D^{25} -29.6^\circ$  ( $c=1.05$ , CHCl<sub>3</sub>). <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 2.13 (3H, s, COCH<sub>3</sub>), 3.64 (3H, s, COOCH<sub>3</sub>). MS  $m/z$ : 198 (M<sup>+</sup>), 141, 81.

**(1R,2R)-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<sub>2</sub>O. After 3 h, the reaction mixture was washed with 5% aq. NaHCO<sub>3</sub>, 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.  $[\alpha]_D^{25} -25.3^\circ$  ( $c=1.01$ , CHCl<sub>3</sub>). <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 2.84 (1H, m, CHCOO), 3.64 (3H, s, COOCH<sub>3</sub>), 3.90 (4H, s, OCH<sub>2</sub>CH<sub>2</sub>O). MS  $m/z$ : 242 (M<sup>+</sup>), 227, 87.

**(1R,2S)-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<sub>2</sub> atmosphere. The reaction mixture was diluted with 1% aq. NH<sub>4</sub>Cl (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.  $[\alpha]_D^{25} +40.6^\circ$  ( $c=1.20$ , CHCl<sub>3</sub>). IR (neat): 1735, 1450, 1195, 1040 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 2.31 (1H, m, CHCOO), 3.64 (3H, s, COOCH<sub>3</sub>), 3.90 (4H, s, OCH<sub>2</sub>CH<sub>2</sub>O). MS  $m/z$ : 242 (M<sup>+</sup>), 227, 87.

**(1R,2S)-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<sub>4</sub> (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.  $[\alpha]_D^{24} +32.6^\circ$  ( $c=1.15$ , CHCl<sub>3</sub>). IR (neat): 3430, 1450, 1220, 1045 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 3.50 (2H, m, CH<sub>2</sub>-O), 3.92 (4H, s, OCH<sub>2</sub>CH<sub>2</sub>O). MS  $m/z$ : 215 (M<sup>+</sup> + 1), 199, 153.

**(1R,2S)-1-(3,3-Ethylenedioxybutyl)-2-formylcyclopentane (30)**—The *trans*-alcohol **29** (750 mg) in CH<sub>2</sub>Cl<sub>2</sub> (10 ml) was added dropwise to Collins reagent [prepared from pyridine (3.4 ml), CrO<sub>3</sub> (2.15 g), and CH<sub>2</sub>Cl<sub>2</sub> (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<sub>3</sub>, 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<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 3.92 (4H, s, OCH<sub>2</sub>CH<sub>2</sub>O), 9.57 (1H, d,  $J=4.0$  Hz, CHO).

**(1R,2S)-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<sub>2</sub> 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.  $[\alpha]_D^{24} +9.50^\circ$  ( $c=1.05$ , CHCl<sub>3</sub>). IR (neat): 1660, 1375, 1220, 1060 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 0.85 (3H, t,  $J=7.0$  Hz, CH<sub>3</sub>), 3.88 (4H, s, OCH<sub>2</sub>CH<sub>2</sub>O), 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<sup>+</sup>), 279, 114, 87. Anal. Calcd for C<sub>19</sub>H<sub>34</sub>O<sub>2</sub>: C, 77.49; H, 11.64. Found: C, 77.55; H, 11.72.

**(1R,2S)-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**.  $[\alpha]_D^{24} +44.8^\circ$  ( $c=1.03$ , CHCl<sub>3</sub>). IR (neat): 1465, 1450, 1375, 1220 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 0.88 (3H, t,  $J=7.0$  Hz, CH<sub>3</sub>), 3.92 (4H, s, OCH<sub>2</sub>CH<sub>2</sub>O). MS  $m/z$ : 281 (M<sup>+</sup> – CH<sub>3</sub>), 234, 192.

**(1R,2S)-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<sub>3</sub>, 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.  $[\alpha]_D^{25} +48.8^\circ$  ( $c=1.25$ , CHCl<sub>3</sub>). IR (neat): 1720, 1470, 1360 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 2.15 (3H, s, COCH<sub>3</sub>). MS  $m/z$ : 252 (M<sup>+</sup>), 194, 82. Anal. Calcd for C<sub>17</sub>H<sub>32</sub>O: C, 80.88; H, 12.78. Found: C, 80.91; H, 12.83.

**(1R,2S)-1-(2-Acetoxyethyl)-2-octylcyclopentane (34), (1R,2S)-1-(2-Hydroxyethyl)-2-octylcyclopentane (35), (1R,2S)-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**:  $[\alpha]_D^{23} + 41.4^\circ$  ( $c=0.93$ ,  $\text{CHCl}_3$ ). IR (neat): 1740, 1465, 1365, 1040  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.88 (3H, t,  $J=7.0$  Hz,  $\text{CH}_3$ ), 2.04 (3H, s,  $\text{OCOCH}_3$ ), 4.06 (2H, t,  $J=7.0$  Hz,  $\text{CH}_2\text{-O}$ ). MS  $m/z$ : 268 ( $\text{M}^+$ ), 208. **35**:  $[\alpha]_D^{24} + 51.2^\circ$  ( $c=0.94$ ,  $\text{CHCl}_3$ ). IR (neat): 3330, 1455, 1380  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.88 (3H, t,  $J=7.0$  Hz,  $\text{CH}_3$ ), 3.64 (2H, t,  $J=7.0$  Hz,  $\text{CH}_2\text{-O}$ ). MS  $m/z$ : 208 ( $\text{M}^+ - \text{H}_2\text{O}$ ), 180, 82. **36**:  $[\alpha]_D^{24} + 43.6^\circ$  ( $c=0.90$ ,  $\text{CHCl}_3$ ). IR (neat): 2720, 1730, 1380  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 9.75 (1H, m, CHO). MS  $m/z$ : 224 ( $\text{M}^+$ ), 206, 180. **37**:  $[\alpha]_D^{23} + 35.3^\circ$  ( $c=0.65$ ,  $\text{CHCl}_3$ ). IR (neat): 2500—3600, 1710, 1455, 1380  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.88 (3H, t,  $J=7.0$  Hz,  $\text{CH}_3$ ), 5.38 (2H, dt,  $J=12.0, 6.0$  Hz,  $-\text{CH}=\text{CH}-$ ). **38**:  $[\alpha]_D^{25} + 33.7^\circ$  ( $c=0.95$ ,  $\text{CHCl}_3$ ). IR (neat): 1740, 1650, 1435, 1160  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.64 (3H, s,  $\text{OCH}_3$ ), 5.36 (2H, dt,  $J=12.0, 6.0$  Hz,  $-\text{CH}=\text{CH}-$ ). **39**: IR (neat): 1740, 1460, 1165  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.63 (3H, s,  $\text{OCH}_3$ ). **18**:  $[\alpha]_D^{25} + 45.0^\circ$  ( $c=1.01$ ,  $\text{EtOH}$ ).<sup>16)</sup>  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.88 (3H, t,  $J=7.0$  Hz,  $\text{CH}_3$ ), 1.10—1.88 (32H, m,  $\text{CH}_2 \times 15$ ,  $\text{CH} \times 2$ ), 2.37 (2H, t,  $J=8.0$  Hz,  $\text{CH}_2\text{COO}$ ), 8.34 (1H, br,  $\text{COOH}$ ). MS  $m/z$ : 310 ( $\text{M}^+$ ), 292, 180, 97. High-MS for  $\text{C}_{20}\text{H}_{38}\text{O}_2$  ( $\text{M}^+$ ): Calcd  $m/z$  310. 28710; Found 310.28745.

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- 15) Compound (**31**) is considered to be a mixture of the geometrical isomers.
- 16) Prostanoic acid (**18**) ( $[\alpha]_D^{25} + 45^\circ$ ) was slightly different in specific rotation from the previous sample<sup>4)</sup> ( $[\alpha]_D^{20} + 49.3^\circ$ ). This seems to be a result of the optical purity of the employed (–)-limonen-10-ol ( $[\alpha]_D^{19} - 95^\circ$  ( $c=1.12$ ,  $\text{EtOH}$ )), (commercially available (+)-limonene-10-ol:  $[\alpha]_D^{21} + 105^\circ$  ( $c=1.03$ ,  $\text{EtOH}$ )).