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Conversion of (−)-Limonen-10-ol to 11-Deoxyprostaglandin

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This paper describes a conversion of (−)-limonen-10-ol to the key intermediate (**1**) for 11-deoxyprostaglandin. The 3,4-*cis*-disubstituted cyclopentanone (**2**), which was easily obtained from (−)-limonen-10-ol in a stereocontrolled fashion by means of Rh(I)-catalyzed cyclization *via* the 4-pentenal derivative, could be directly converted to the bicyclo[3.3.0]octenone (**3**) by treatment with $KHSO_4$ in boiling benzene. Compound **3** with a double bond at the favorable position was converted to **1** by way of fission of the double bond and subsequent modification of substituents on the five-membered ring.

Keywords——prostaglandin; deconjugation; bicyclo[3.3.0]octenone; aldol condensation; (−)-limonen-10-ol; lactonization; 11-deoxyprostaglandin

11-Deoxyprostaglandin has been an attractive target for chemical synthesis from the early stages of prostaglandin (PG) research,[1] because of its biological similarity to primary PG and relatively simple framework. As a part of our synthetic studies on functionalized cyclopentanone,[2] we have developed a stereospecific synthesis of *cis*-3,4-disubstituted cyclopentanone from 3,4-disubstituted 4-pentenals[3] by using the Rh(I)-complex. The present paper describes a conversion of (−)-limonen-10-ol to the key intermediate (**1**)[4] for 11-deoxy-PG.

The retro synthesis of **1** is shown in Chart 1. The β-hydroxymethyl function in **1** may be derived from the α-isomer (A) *via* the epimerization of the corresponding aldehyde. The lactone moiety of compound A may be built up after the concomitant lactonization with inversion of the α-ester function in compound B. The α-ester function in B may be obtained by Baeyer–Villiger oxidation of the corresponding ketone function. The carbonyl and ester functions in compound C may be formed *via* the oxidative cleavage of a double bond with the alkyl substituent (compound D). The carbonyl function in the side chain of compound F is suggestive of an intramolecular aldol condensation to afford compound E. Compound F[3] could be obtained from (−)-limonen-10-ol[5] in a stereocontrolled fashion by means of Rh(I)-catalyzed cyclization. Thus, the retro synthesis of **1** suggests that (−)-limonen-10-ol is a favorable compound as a starting material.

The designed sequence starts with cyclization of the diketone (**2**) to the bicyclo-[3.3.0]octenone (**3**). This cyclization, involving three steps of intramolecular aldol condensation, dehydration, and then deconjugation, was accomplished in 94% yield by heating under reflux in benzene in the presence of $KHSO_4$.[6] In the proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **3**, the methyl signal at δ 2.17 due to methyl ketone in **2** disappeared, and new signals attributable to vinyl methyl and olefinic protons were observed at δ 1.77 (3H, s) and 5.38 (1H, m), respectively. In addition to the ^{1}H-NMR spectrum, the infrared (IR) spectrum also supported the structure of **3** (absorption bands at 1655 (olefin) and 1740 (carbonyl) cm^{-1}).

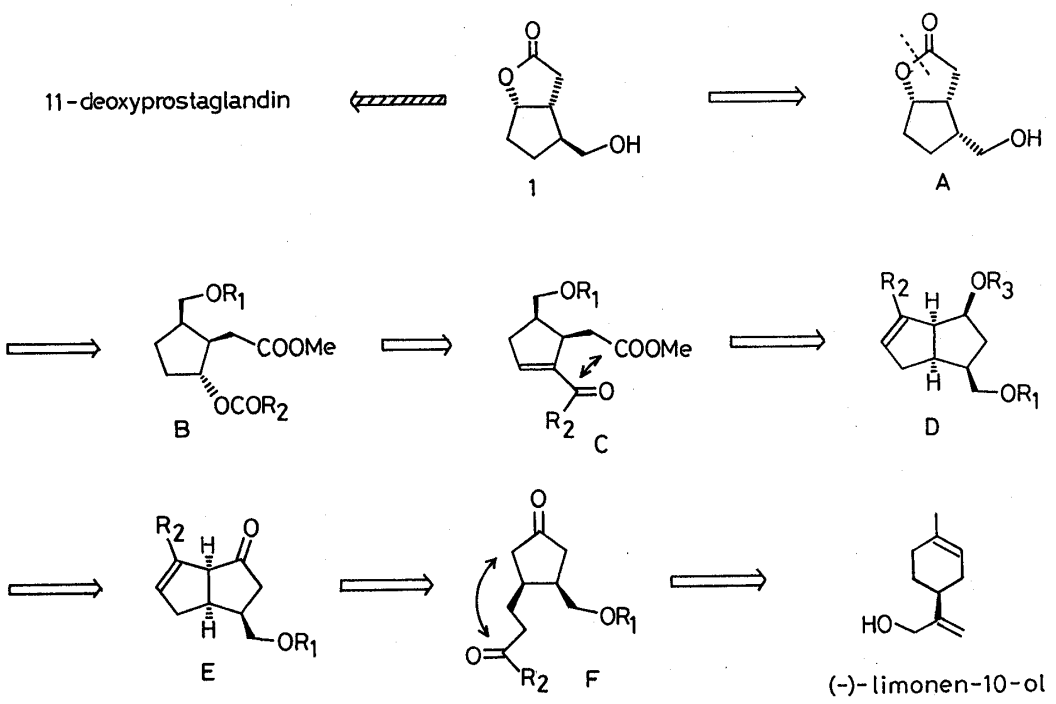

Chart 1

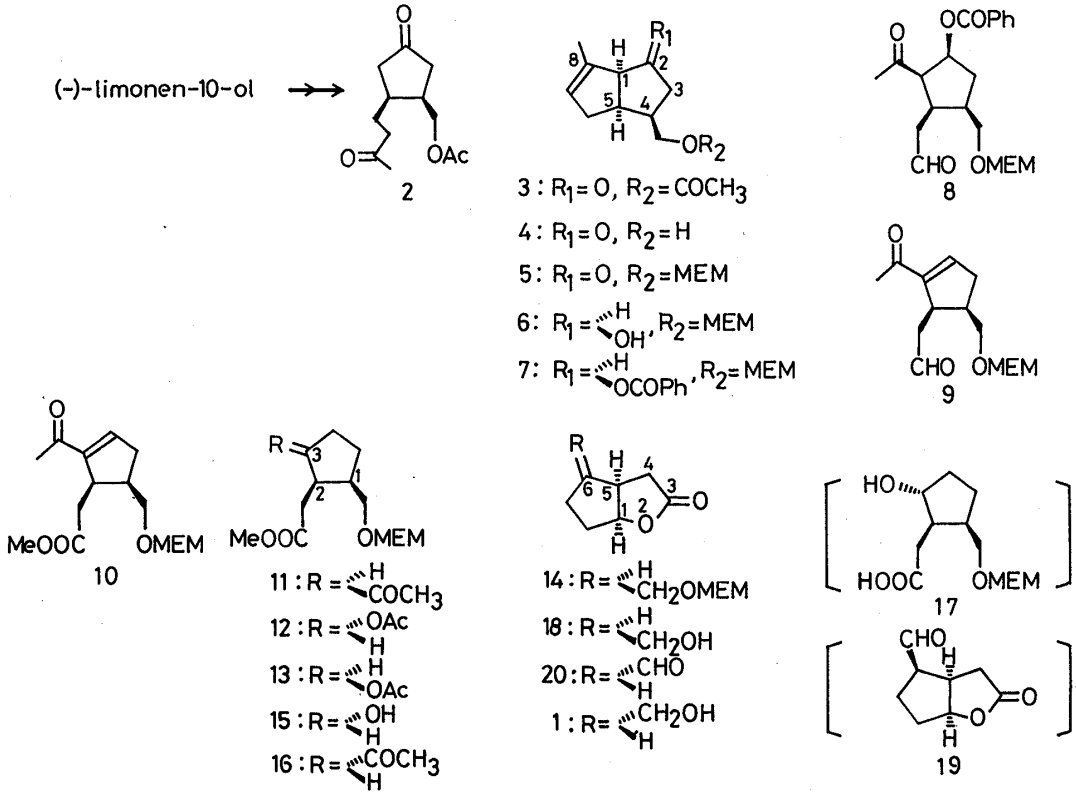

Chart 2

Compound **3** seems to have several advantages for the synthesis of the target (**1**). For example, the double bond occupies a favobable position to afford a C_2-unit as required for the introduction of the α-chain *via* oxidative cleavage of the double bond with ozone, and the resulting methyl ketone seems appropriate for conversion to the acetoxy function by Baeyer–Villiger oxidation. In addition the favorable position of the double bond, **3** retains the

stereochemistry of **2** intact, and the unnecessary carbonyl function in the five-membered ring may be removed without difficulty.

Compound **3** was smoothly converted to the 2-methoxyethoxymethyl ether (MEM ether) (**5**) in 50% yield by successive treatments with K_2CO_3/MeOH, and MEM chloride/*N*,*N*-diisopropylethylamine. Reduction of **5** with $NaBH_4$/MeOH afforded the alcohol (**6**) as a sole product; the configuration of the alcohol was determined to be β and *trans* relative to the hydrogen at the ring junction by taking the approach of the reagent from the convex site into consideration.

In order to facilitate the elimination of the alcohol function, the alcohol in **6** was protected as a benzoate. The benzoate (**7**) was subjected to oxidative cleavage of the double bond with ozone in CH_2Cl_2, followed by treatment with Zn/AcOH. The crude products displayed two spots on thin layer chromatography (TLC), and the ^{1}H-NMR spectrum showed the existence of the phenyl group (δ 7.5—8.2) and the β-hydrogen of an α,β-unsaturated ketone (δ 6.77). These data suggest that the crude product is a mixture of the keto-benzoate (**8**) and the enone (**9**). In accord with expectation, *trans* elimination of the crude product with KOH/MeOH at 0 °C proceeded smoothly to afford **9** in 77% yield from **7**.

By Jones oxidation followed by treatment with CH_2N_2, **9** was converted in 79% yield to the ester (**10**), which was submitted to catalytic hydrogenation with H_2/5% Pd–C in MeOH to yield the cyclopentane (**11**). In this reduction, other possible isomers could not be detected on TLC. The structure of **11** was determined to be 1,2-*cis*-2,3-*cis* by assuming the attack of hydrogen from the less hindered side of the sterically hindered double bond.

Baeyer–Villiger oxidation of a methyl ketone in **11** to the corresponding acetate with *m*-chloroperbenzoic acid (MCPBA) in the presence of $NaHCO_3$ in CH_2Cl_2 yielded a mixture of the *cis*-acetate (**13**) and the *trans*-acetate (**12**) derived from the methyl ketone epimerized under the reaction conditions employed. The structures of **12** and **13** were chemically determined by the findings that, on treatment with K_2CO_3/MeOH, **13** was readily converted into the γ-lactone (**14**), while **12** underwent hydrolysis of the acetoxy function to give the α-alcohol (**15**).

From a practical viewpoint, compound **11** was subjected to epimerization reaction to the α-methyl ketone (**16**) with K_2CO_3/MeOH prior to Baeyer–Villiger oxidation. Monitoring of this epimerization by TLC was difficult. However, ^{1}H-NMR spectroscopy was found to be effective for following the epimerization. In the ^{1}H-NMR spectrum of **16**, the C_3-H was observed at higher field (δ 2.80) than the the case of the β-methyl ketone (**11**, δ 3.10). The difference in this chemical shift[7] made it quite easy to distinguish **16** from **11**.

Baeyer–Villiger oxidation[8] of the α-methyl ketone (**16**) with MCPBA/$NaHCO_3$ in CH_2Cl_2 gave the *trans*-acetate (**12**) in 78% yield. By hydrolysis with KOH/aq. MeOH, followed by concomitant lactonization with inversion of the alcohol using diethyl azodicarboxylate (DEAD) and triphenylphosphine (Mitsunobu method),[9] and finally deprotection with $TiCl_4$ in CH_2Cl_2 at 0 °C, the *cis*-lactone (**18**) was obtained in 46% yield from **12**. The structure of **18** was supported by the signals of the C_1-H (γ-lactone) at δ 5.06 (1H, m), the OH function at δ 2.24 (1H, m), and the C_6-CH_2OH at δ 3.49—3.92 (2H, m) in the ^{1}H-NMR spectrum, in addition to the absorption bands at 3400 (OH) and 1760 (γ-lactone) cm^{-1} in the IR spectrum.

Swern oxidation[10] of **18** with oxalyl chloride/dimethyl sulfoxide (DMSO) in the presence of triethylamine afforded the *cis*-aldehyde (**19**),[11] which epimerized rapidly to the stable *trans*-isomer (**20**) under the reaction conditions employed; attempts to isolate **19** failed.

Reduction of the *trans*-aldehyde (**20**) with $NaBH_4$ in MeOH afforded the key intermediate (**1**), whose ^{1}H-NMR spectrum, IR spectrum, and specific rotation were identical with the reported values.[12]

Experimental

IR spectra were measured with a JASCO A-202 spectrometer. ^{1}H-NMR spectra were measured on a JEOL LNP-PS-100 spectrometer. Mass spectra (MS) were taken on a JEOL JMS-D 300 spectrometer. Optical rotations were measured on a JASCO DIP-4 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 satd. brine and dried over anhydrous sodium sulfate.

(1*S*,4*R*,5*R*)-4-Acetoxymethyl-8-methylbicyclo[3.3.0]oct-7-en-2-one (3)——Compound **2** (8.28 g) in benzene (600 ml) in the presence of $KHSO_4$ (30 g) was heated under reflux with azeotropic removal of formed H_2O. After 5 h, the $KHSO_4$ was filtered off and the filtrate was washed and dried. Removal of the solvent *in vacuo* afforded an oily residue, which was subjected to column chromatography on silica gel (250 g). The fraction eluted with 5—15% AcOEt in hexane (v/v) afforded **3** (8.63 g, 94%) as a colorless oil. $[\alpha]_D^{25}$ −447° (*c*=0.20, $CHCl_3$). IR (neat): 1740, 1655, 1240 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.77 (3H, s, C=C–CH_3), 2.06 (3H, s, $OCOCH_3$), 5.38 (1H, m, C=CH). MS *m/z*: 208 (M^+), 166, 148. High-MS for $C_{12}H_{16}O_3$ (M^+): Calcd *m/z* 208.10985; Found 208.11032.

(1*S*,4*R*,5*R*)-4-Hydroxymethyl-8-methylbicyclo[3.3.0]oct-7-en-2-one (4)——K_2CO_3 (2.20 g) was added portionwise to a stirred solution of **3** (8.02 g) in MeOH (50 ml) at room temperature. After 3.5 h, the reaction mixture was diluted with brine (80 ml) and extracted with AcOEt (100 ml × 4). The AcOEt extract was washed, and dried, then concentrated *in vacuo* to leave an oily residue, which was purified by column chromatography on silica gel (80 g). The fraction eluted with 5% AcOEt in hexane (v/v) afforded **4** (3.62 g, 58%) as a colorless oil. $[\alpha]_D^{27}$ −548° (*c*=0.18, $CHCl_3$). IR (neat): 3430, 1730, 1655, 1018 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.78 (3H, s, C=C–CH_3), 3.75 (2H, d, *J*=7.0 Hz, CH_2O), 5.38 (1H, m, C=C–H). MS *m/z*: 166 (M^+), 148, 135.

(1*S*,4*R*,5*R*)-4-(2-Methoxyethoxymethoxymethyl)-8-methylbicyclo[3.3.0]oct-7-en-2-one (5)——MEM chloride (5.23 g) was added dropwise to a stirred solution of **4** (1.74 g) and *N*,*N*-diisopropylethylamine (5.42 g) in CH_2Cl_2 (25 ml) at room temperature. After being stirred for 2 h at 30 °C, the reaction mixture was diluted with brine (40 ml) and extracted with AcOEt (100 ml × 3). The AcOEt extract was washed and dried. Removal of the solvent *in vacuo* gave an oily residue, which was subjected to column chromatography on silica gel (20 g). The fraction eluted with 2% AcOEt in hexane (v/v) afforded **5** (2.52 g, 95%) as a colorless oil. $[\alpha]_D^{26}$ −367° (*c*=0.25, $CHCl_3$). IR (neat): 1735, 1655, 1450, 1045 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.38 (3H, s, OCH_3), 3.48—3.76 (6H, m, OCH_2CH_2O, CH_2OMEM), 4.71 (2H, s,OCH_2O). MS *m/z*: 254 (M^+), 178, 89.

(1*S*,2*S*,4*R*,5*R*)-4-(2-Methoxyethoxymethoxymethyl)-8-methylbicyclo[3.3.0]oct-7-en-2-ol (6)——$NaBH_4$ (87 mg) was added portionwise to a stirred solution of **5** (114 mg) in MeOH (5 ml) at −10 °C. After 0.5 h, the reaction mixture was diluted with brine (20 ml), and extracted with AcOEt (100 ml × 3). The AcOEt extract was washed and dried. Removal of the solvent *in vacuo* gave an oily residue, which was chromatographed on silica gel (3 g). The fraction eluted with 3—5% AcOEt in hexane (v/v) afforded **6** (90 mg, 79%) as a colorless oil. $[\alpha]_D^{26}$ −15.2° (*c*=0.22, $CHCl_3$). IR (neat): 3450, 1660, 1450, 1045 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.81 (3H, s, C=C–CH_3), 4.69 (2H, s, OCH_2O), 5.47 (1H, m, C=C–H). MS *m/z*: 256 (M^+), 238, 226. High-MS for $C_{14}H_{24}O_4$ (M^+): Calcd *m/z* 256.16732; Found 256.16695.

(1*S*,2*S*,4*R*,5*R*)-2-Benzoyloxy-4-(2-methoxyethoxymethoxymethyl)-8-methylbicyclo[3.3.0]oct-7-ene (7)——Benzoyl chloride (178 mg) in CH_2Cl_2 (1 ml) was added dropwise to a stirred solution of **6** (93 mg) in CH_2Cl_2 (2 ml) in the presence of pyridine (200 mg) at room temperature. After 6 h, the reaction mixture was diluted with brine (5 ml) and extracted with AcOEt (30 ml × 3). The AcOEt extract was washed, and dried, then concentrated *in vacuo* to leave an oily residue, which was chromatographed on silica gel (2 g). The fraction eluted with 3% AcOEt in hexane (v/v) afforded **7** (121 mg, 80%) as a colorless oil. $[\alpha]_D^{28}$ −60.7° (*c*=1.21, $CHCl_3$). IR (neat): 1720, 1655, 1045 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.70, (3H, s, C=C–CH_3), 5.46 (2H, m, C=C–H, CHOCOPh), 7.30—7.56 (3H, m, Ph-3,4,5-H), 8.01 (2H, dd, *J*=8, 2 Hz, Ph-2,6-H). MS *m/z*: 284 (M^+ −76), 271, 254.

(1*R*,2*R*)-3-Acetyl-2-formylmethyl-1-(2-methoxyethoxymethoxymethyl)-3-cyclopentene (9)——Ozone gas[13] was bubbled into a solution of **7** (1.56 g) in CH_2Cl_2 (20 ml) at −78 °C and the reaction was monitored by TLC. The resulting ozonide was decomposed with Zn powder (4 g) and AcOH (10 ml) at 10 to 20 °C. The Zn powder was filtered off, and the filtrate was concentrated *in vacuo*, diluted with brine (50 ml), and then extracted with AcOEt (100 ml × 3). The AcOEt extract was washed and dried. The solvent was removed *in vacuo* to afford a mixture of **8** and **9**, which was subjected to the next elimination reaction without further purification.

KOH (0.4 g) in MeOH (4 ml) was added dropwise to a stirred solution of the above mixture in CH_2Cl_2 (70 ml) at −10 °C. After being stirred for 1 h at −10 to 0 °C, the reaction mixture was diluted with brine (50 ml) and extracted with AcOEt (100 ml × 3). The AcOEt extract was washed, dried, and then concentrated *in vacuo* to afford an oily residue, which was purified by column chromatography on silica gel (2 g). The fraction eluted with 5% AcOEt in hexane (v/v) gave **9** (896 mg, 77%) as a colorless oil. $[\alpha]_D^{28}$ −27.9° (*c*=1.36, $CHCl_3$). IR (neat): 2730, 1720, 1665, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.30 (3H, s, $COCH_3$), 6.77 (1H, m, CH=C), 9.69 (1H, m, CHO). MS *m/z*: 195 (M^+ −75), 181.

(1*R*,2*R*)-3-Acetyl-2-methoxycarbonylmethyl-1-(2-methoxyethoxymethoxymethyl)-3-cyclopentene (10)——Jones reagent (2.5 ml) was added dropwise to a stirred solution of **9** (726 mg) in acetone (20 ml) at −10 °C. After 0.5 h, the

excess reagent was decomposed with isopropanol, and the reaction mixture was diluted with brine (30 ml), and extracted with ether (150 ml × 3). The Et_2O extract was dried, and esterified with CH_2N_2 in the usual manner. Removal of the solvent *in vacuo* afforded an oily residue, which was subjected to column chromatography on silica gel (10 g). The fraction eluted with 5% AcOEt in hexane (v/v) gave **10** (637 mg, 79%) as a colorless oil. $[\alpha]_D^{31}$ −36.8° (c = 1.11, $CHCl_3$). IR (neat): 1735, 1665, 1610, 1250 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.29 (3H, s, $COCH_3$), 3.62 (3H, s, $COOCH_3$), 6.75 (1H, m, CH=C). MS m/z: 225 (M^+ − 75), 195, 164.

(1*R*,2*R*,3*S*)-3-Acetyl-2-methoxycarbonylmethyl-1-(2-methoxyethoxymethoxymethyl)cyclopentane (11)——Compound **10** (103 mg) in MeOH (25 ml) was hydrogenated in the presence of 5% Pd–C (100 mg) under an H_2 atmosphere at room temperature. The catalyst was filtered off, and the filtrate was concentrated *in vacuo* to afford an oily residue, which was subjected to column chromatography on silica gel (1.5 g). The fraction eluted with 5% AcOEt in hexane (v/v) afforded **11** (90 mg, 87%) as a colorless oil. $[\alpha]_D^{32}$ +14.5° (c = 1.19, $CHCl_3$). IR (neat): 1740, 1710, 1050 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.18 (3H, s, $COCH_3$), 3.10 (1H, m, C_3-H), 3.61 (3H, s, $COOCH_3$), 4.66 (2H, s, OCH_2O). MS m/z: 271 (M^+ − 31), 227, 198.

(1*R*,2*R*,3*R*)-3-Acetoxy-2-methoxycarbonylmethyl-1-(2-methoxyethoxymethoxymethyl)cyclopentane (12) and (1*R*,2*R*,3*S*)-3-Acetoxy-2-methoxycarbonylmethyl-1-(2-methoxyethoxymethoxymethyl)cyclopentane (13)——MCPBA (80%, 140 mg) and $NaHCO_3$ (50 mg) were successively added to a stirred solution of **11** (97 mg) in CH_2Cl_2 (3 ml) at room temperature. After 5 h, the reaction mixture was diluted with 5% $NaHCO_3$, and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed, and dried, then concentrated *in vacuo* to leave an oily residue, which was chromatographed on silica gel (2 g). The fraction eluted with 3—5% AcOEt in hexane (v/v) afforded **12** (43 mg, polar fraction) and **13** (9 mg, less polar fraction), each as a colorless oil. **12**: $[\alpha]_D^{23}$ −32.7° (c = 1.40, $CHCl_3$). IR (neat): 1735, 1435, 1245, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.03 (3H, s, $OCOCH_3$), 3.67 (3H, s, $COOCH_3$), 4.67 (2H, s, OCH_2O), 4.88 (1H, m, CHOAc). MS m/z: 319 (M^+ + 1), 243, 229. **13**: ^{1}H-NMR ($CDCl_3$) δ: 2.03 (3H, s, $OCOCH_3$), 3.72 (3H, s, $COOCH_3$), 4.67 (2H, s, OCH_2O), 5.00 (1H, m, CHOAc).

(1*S*,5*R*,6*R*)-6-(2-Methoxyethoxymethoxymethyl)-3-oxo-2-oxabicyclo[3.3.0]octane (14) and (1*R*,2*R*,3*R*)-3-Hydroxy-2-methoxycarbonylmethyl-1-(2-methoxyethoxymethoxymethyl)cyclopentane (15)——K_2CO_3 (10 mg) was added to a stirred solution of **13** (23 mg) in MeOH (2 ml). After 5 h, the reaction mixture was diluted with brine (10 ml) and extracted with AcOEt (20 ml × 3). The AcOEt extract was washed, and dried, then concentrated *in vacuo* to leave an oily residue, which was purified by column chromatography on silica gel (1 g). The fraction eluted with 5% AcOEt in hexane (v/v) afforded **14** (13 mg) as a colorless oil.

Similar treatment of **12** (197 mg) with K_2CO_3 (35 mg) in MeOH (3 ml) gave **15** (148 mg, 87%) as a colorless oil. **14**: IR (neat): 1760, 1170, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.48—3.78 (6H, m, OCH_2CH_2O, CH_2OMEM), 4.69 (2H, s, OCH_2O), 5.04 (1H, m, C_1-H). MS m/z: 244 (M^+), 169, 139. **15** $[\alpha]_D^{25}$ −10.6° (c = 0.97, $CHCl_3$). IR (neat): 3450, 1730, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.69 (3H, s, $COOCH_3$), 3.97 (1H, m, CHOH), 4.68 (2H, s, OCH_2O). MS m/z: 259 (M^+ − 17), 201, 171.

(1*R*,2*R*,3*R*)-3-Acetyl-2-methoxycarbonylmethyl-1-(2-methoxyethoxymethoxymethyl)cyclopentane (16)——K_2CO_3 (210 mg) was added portionwise to a stirred solution of **11** (465 mg) in MeOH (5 ml) at room temperature. After 2 h, the reaction mixture was diluted with brine (10 ml) and extracted with AcOEt (50 ml × 3). The AcOEt extract was washed and dried. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel (5 g). The fraction eluted with 5% AcOEt in hexane (v/v) afforded **16** (444 mg, 96%) as a colorless oil. $[\alpha]_D^{25}$ −35.5° (c = 1.0, $CHCl_3$). IR (neat): 1730, 1710, 1250, 1050 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.18 (3H, s, CH_3CO), 2.80 (1H, m, C_3-H) 3.65 (3H, s, $COOCH_3$), 4.67 (2H, s, OCH_2O). MS m/z: 302 (M^+), 227, 198. High-MS for $C_{15}H_{26}O_6$ (M^+): Calcd m/z 302.17278; Found 302.17201.

Compound 12 from 16——In a manner similar to that described for the synthesis of **12** from **11**, **16** (305 mg) afforded**12** (250 mg, 78%) as a colorless oil.

(1*S*,5*R*,6*R*)-6-Hydroxymethyl-3-oxo-2-oxabicyclo[3.3.0]octane (18)——KOH (200 mg) in H_2O (1 ml) was added to a stirred solution of **12** (57 mg, 0.18 mmol) in MeOH (2 ml) at room temperature. After being stirred for 2 h, the reaction mixture was made neutral with ion-exchange resin (Amberlite IR-120B). The filtrate was concentrated *in vacuo* to afford an oily residue (**17**), which was subjected to the next lactonization without purification.

Triphenylphosphine (70 mg, 0.27 mmol) was added to a stirred solution of the above oil in benzene (2 ml) at room temperature, DEAD (47 mg, 0.27 mmol) was added at 5—10 °C, and the whole was stirred for 3 h. Removal of the solvent afforded a crystalline residue, which was roughly chromatographed on silica gel (1 g). Next, the product contaminated with triphenylphosphine was added to a stirred solution of $TiCl_4$ (102 mg, 0.54 mmol) in CH_2Cl_2 (5 ml) at 0 °C. After 1 h, the reaction mixture was diluted with brine (10 ml) and extracted with AcOEt (50 ml × 3). The AcOEt extract was washed, and dried, then concentrated *in vacuo* to afford an oily residue, which was subjected to column chromatography on silica gel (3 g). The fraction eluted with 5—7% AcOEt in hexane (v/v) afforded **18** (13 mg) as a colorless oil. $[\alpha]_D^{21}$ +8.7° (c = 1.18, $CHCl_3$). IR (neat): 3400, 1760, 1190, 1070 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.25 (1H, m, OH), 3.49—3.92 (2H, m, CH_2OH), 5.06 (1H, m, C_1-H). MS m/z: 156 (M^+), 138, 126.

(1*S*,5*R*,6*S*)-6-Formyl-3-oxo-2-oxabicyclo[3.3.0]octane (20)——DMSO (50 mg, 0.65 mmol) in CH_2Cl_2 (0.5 ml) was added to a stirred solution of $(COCl)_2$ (38 mg, 0.3 mmol) in CH_2Cl_2 (0.7 ml) at −60 °C under an Ar atmosphere. After 10 min, **18** (42 mg, 0.27 mmol) in CH_2Cl_2 (1 ml) was added, and the whole was stirred for 15 min, then

triethylamine (137 mg, 1.37 mmol) in CH_2Cl_2 (0.5 ml) was added at $-60\,^{\circ}C$. After 0.5 h, the reaction mixture was warmed to room temperature, and diluted with brine (10 ml), then extracted with AcOEt (50ml × 3). The AcOEt extract was dried, and concentrated *in vacuo* to leave an oily residue, which was purified by column chromatography on silica gel (1 g). The fraction eluted with 5% AcOEt in hexane (v/v) afforded **20** (21 mg, 50%) as a colorless oil. $[\alpha]_D^{24}$ $-49.8\,^{\circ}$ ($c=0.8$, $CHCl_3$). IR (neat): 2740, 1770, 1720, 1175 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 5.01 (1H, m, C_1-H), 9.66 (1H, s, CHO). MS *m/z*: 154 (M^+), 126, 110. High-MS for $C_8H_{10}O_3$ (M^+): Calcd *m/z* 154.06293; Found 154.06420.

(1*S*,5*R*,6*S*)-6-Hydroxymethyl-3-oxo-2-oxabicyclo[3.3.0]octane (1)——$NaBH_4$ (10 mg) was added to a stirred solution of **20** (17 mg) in MeOH (1.5 ml) at 0 °C. After 0.5 h, the reaction mixrure was diluted with brine (10 ml), and extracted with AcOEt (50 ml × 3). The AcOEt extract was washed, and dried. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel (1 g). The fraction eluted with 10% AcOEt in hexane (v/v) afforded **1** (15 mg) as a colorless oil. $[\alpha]_D^{22}$ $-24.2\,^{\circ}$ ($c=0.72$, $CHCl_3$). IR (neat): 3400, 1765, 1170, 1035 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.35—3.01 (8H, m), 1.88 (1H, s, OH), 3.57 (2H, d, $J=6$ Hz, CH_2OH), 4.99 (1H, m, C_1-H). MS *m/z*: 156 (M^+), 138, 126, 110. High-MS for $C_8H_{12}O_3$ (M^+): Calcd *m/z* 156.07857; Found 156.07914.

References and Notes

1) S. M. Roberts and R. F. Newtons, "Prostaglandins and Thromboxanes," Butterworths Scientific Publications, London, 1982, pp. 109—114.
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6) The reaction could be monitored by TLC, but no attempt was made to isolate the product at each step.
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8) Bayer–Villiger oxidation using CF_3COOOH gave a complex mixture.
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11) In this oxidative process, two spots (suggesting a mixture of the *cis*- and *trans*-aldehyde) were observed on TLC, but the less polar spot had disappeared at the end of the oxidation. This finding suggests a rapid epimerization from the *cis*-aldehyde (**19**) to the *trans*-aldehyde (**20**).
12) Specific rotation ($[\alpha]_D^{22}$ $-24.2°$ ($c=0.72$, $CHCl_3$)) was slightly different from the reported value[4] ($[\alpha]_D^{27}$ $-20.4°$ ($c=0.66$, $CHCl_3$)).
13) An Ishii ozone generator was used for O_3 oxidation.