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Formal Synthesis of Brefeldin A from (+)-Limonen-10-ol

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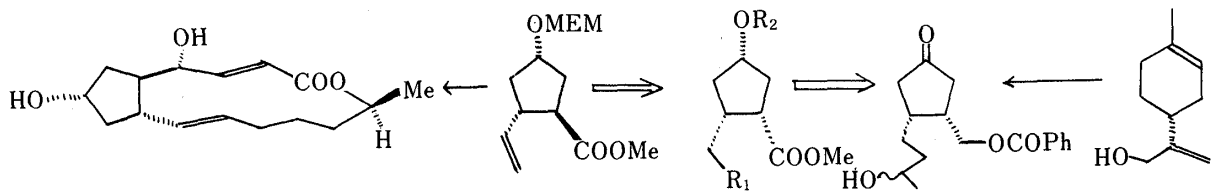
The conversion of naturally abundant (+)-limonen-10-ol (**2**) into the synthetic intermediate (**3**) for brefeldin A is described. The *cis*-3,4-disubstituted cyclopentanone (**4**), which was easily obtained from **2** by Rh(I)-catalyzed cyclization reaction *via* the 4-pentenal derivative, could be converted to the target compound **3** *via* the appropriate modification of substituents on the five-membered ring.

Keywords——*cis*-3,4-disubstituted cyclopentanone; cyclopentanol; stereospecific reduction; dehydroiodination; brefeldin A

Brefeldin A[1] (**1**) has been isolated from *Penicillium decumbens*, and is known to possess a wide range of biological activities including antiviral, antifungal, antimitotic and antitumor actions. The structure of this fungal metabolite was determined by Sigg *et al.*[2] by means of X-ray diffraction analysis. In addition to the biological activities, its characteristic framework makes it an attractive target for synthetic chemists. Since the first total synthesis of (±)-**1** by Corey and Wollenberg[3] in 1976, partial[4] and total[5] syntheses of this compound have been achieved by several groups. (+)-Brefeldin A, the naturally occurring form, was first synthesized by Mori and Kitahara[6] using (+)-mannitol and (+)-glutamic acid as the chiral sources. Recently, alternative syntheses of (+)-**1** have been reported independently by Greene and Le Drian,[7] Winterfeld *et al.*[8] and Gais and Lied.[9]



1 3 4 2

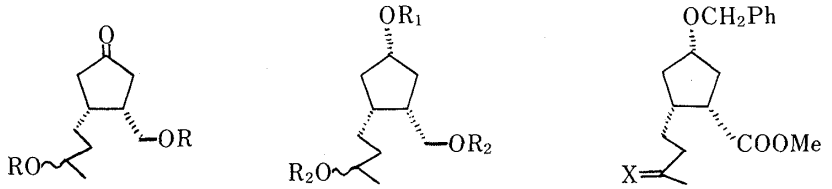
Chart 1

As a part of our synthetic studies on biologically active compounds containing a five-membered ring, such as prostaglandins, we have succeeded in a stereospecific synthesis[10] of *cis*-3,4-disubstituted cyclopentanones from 3,4-disubstituted 4-pentenals by using Rh(I)-complex. In this paper, we describe the synthesis of the optically active intermediate[6] (**3**) in the synthesis of (+)-**1**, starting from the *cis*-3,4-disubstituted cyclopentanone (**4**).

The retro synthesis of the ester (**3**) is shown in Chart 1. We have already reported that the optically active *cis*-3,4-disubstituted cyclopentanone[11] (**4**) could easily be obtained from naturally abundant (+)-limonen-10-ol (**2**) in a stereocontrolled fashion by means of Rh(I)-catalyzed cyclization.

Compound **4** seems to have several advantages for the synthesis of the target molecule **3**. For example, the α-site of the carbonyl function may be shielded by the C_3- and C_4-

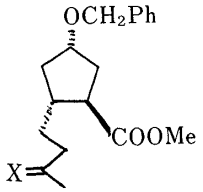
substituents. This shielding effect might permit stereospecific reduction to afford the desired $C_1\alpha$-alcohol in **3**, and the $C_3\alpha$-substituent should be convertible to the $C_3\beta$-configuration in **3** *via* the methyl ester. In addition to favorable configuration, the C_4-substituent seems appropriate for shortening from a C_4-unit to a C_2-unit *via* Baeyer–Villiger oxidation.



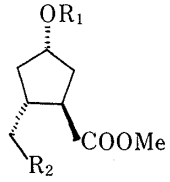
5 : R=H
6 : R=THP

7 : R_1=H, R_2=THP
8 : R_1=CH_2Ph, R_2=THP

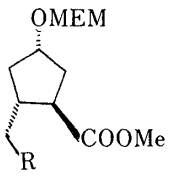
9 : X=O
10 : X=



11 : X= 
12 : X=O



13 : R_1=CH_2Ph, R_2=CH_2OAc
14 : R_1=H, R_2=CH_2OAc



15 : R=CH_2OAc
16 : R=CH_2OH
17 : R=CH_2OMs
18 : R=CH_2I

THP=tetrahydropyran

Chart 2

Methanolysis of **4** with K_2CO_3 in MeOH yielded the diol (**5**), which was protected with dihydropyran in the presence of *p*-toluenesulfonic acid to afford the bis-tetrahydropyranyl ether (**6**). In accord with our expectation, reduction of the carbonyl function in **6** with $NaBH_4$ afforded the alcohol (**7**) (78% from **4**) as a sole product, and no other isomeric alcohol was detected. On the basis of the steric hindrance caused by the 3,4-disubstituents, the configuration of the C_1-OH in **7** was concluded to be *cis* relative to the C_3- and C_4-substituents.

Reaction of **7** with benzyl chloride and NaH in dimethyl sulfoxide (DMSO) afforded the benzyl ether (**8**). Direct oxidation of **8** with Jones reagent, and subsequent esterification with CH_2N_2 afforded the *cis*-keto ester (**9**). Epimerization of the $C_3\alpha$-ester to the $C_3\beta$-ester was carried out as follows. After ketalization with ethylene glycol and *p*-toluenesulfonic acid, followed by heating in toluene with sodium methoxide at 110 °C for 3 h, **9** was isomerized to the corresponding *trans* isomer (**11**). The ketal group in **11** was deprotected with 10% HCl in MeOH at room temperature to afford the *trans*-keto ester (**12**) (61% from **7**).

Baeyer–Villiger oxidation of **12** with trifluoroperacetic acid and Na_2HPO_4 in CH_2Cl_2 at room temperature afforded the acetate (**13**), and the positional isomer was not detected. According to a conventional method, the protecting group of C_1-OH in **13** was converted from the benzyl ether to the methoxyethoxymethyl ether (**15**) (74% from **12**), and subsequent methanolysis of the acetoxy function in **15** with K_2CO_3 in MeOH afforded the corresponding alcohol (**16**). By mesylation with methanesulfonyl chloride and triethylamine, followed by treatment with NaI, **16** was converted to the iodide (**18**) (79% from **15**). Dehydroiodination of **18** with 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) in DMSO at room temperature afforded **3** (36% yield), which was identical with the standard sample in terms of the proton nuclear magnetic resonance (^{1}H-NMR) spectrum and the infrared (IR) spectrum.

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. Optical rotations were measured on a JASCO DIP-SL polarimeter. For column chromatography, silica gel (Merck, Kieselgel 60, 70—230 mesh) was used. Thin layer chromatography (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.

(3*S*,4*R*)-4-(3-Hydroxybutyl)-3-hydroxymethylcyclopentanone (5)——K_2CO_3 (0.20 g) was added portionwise to a stirred solution of **4** (3.20 g) in MeOH (50 ml) at room temperature. The mixture was stirred for 3 h, and neutralized with acetic acid (0.17 g). The solvent was removed *in vacuo* to afford an oily residue, which was purified by column chromatography on silica gel (30 g). The fraction eluted with 1—3% MeOH in AcOEt (v/v) was collected. Removal of the solvent *in vacuo* afforded **5** (1.91 g, 93%) as a colorless oil. IR (neat): 3400, 1738 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.19 (3H, d, J=7 Hz, CH_3), 3.56—4.00 (3H, m, C<u>H</u>$_2$OH, C<u>H</u>(OH)). MS *m/z*: 186 (M^+), 168, 150. *Anal.* Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.62; H, 9.81.

(3*S*,4*R*)-4-[3-(Tetrahydropyran-2-yl)oxybutyl]-3-(tetrahydropyran-2-yl)oxymethylcyclopentanone (6)——2,3-Dihydropyran (2.00 g) in CH_2Cl_2 (3 ml) was added dropwise to a stirred solution of **5** (1.85 g) in CH_2Cl_2 (50 ml) in the presence of *p*-toluenesulfonic acid (trace) at 0 °C. The reaction mixture was stirred for 2 h at room temperature, then poured into 5% aq. $NaHCO_3$ (50 ml) and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed and dried. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel (45 g). The fraction eluted with 20—25% AcOEt in hexane (v/v) was collected, and the solvent was removed *in vacuo*, yielding **6** (3.25 g, 92%) as a colorless oil. IR (neat): 1745, 1140, 1120 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.13, 1.24 (1.5H each, d, J=7 Hz, CH_3), 3.45 (3H, m, CH_2O–THP, CH(O–THP)), 3.80 (4H, m, CH_2O–×2), 4.63 (2H, m, O–CH–O×2). MS *m/z*: 354 (M^+), 270, 186. *Anal.* Calcd for $C_{20}H_{34}O_5$: C, 67.76; H, 9.67. Found: C, 67.53; H, 9.81.

(1*S*,3*S*,4*R*)-4-[3-(Tetrahydropyran-2-yl)oxybutyl]-3-(tetrahydropyran-2-yl)oxymethyl-1-cyclopentanol (7)——$NaBH_4$ (175 mg) was added portionwise to a stirred solution of **6** (3.20 g) in MeOH (50 ml) at below 5 °C. The whole was stirred for 1 h, and quenched with acetone (1 ml), then the solvent was removed *in vacuo* to afford an oily residue, which was diluted with brine and extracted with AcOEt. 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 (40 g). The fraction eluted with 50% AcOEt in hexane (v/v) was collected, and the solvent was evaporated off *in vacuo* to afford **7** (2.93 g, 91%) as a colorless oil. IR (neat): 3445, 1140, 1120 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.13, 1.24 (1.5H each, d, J=7 Hz, CH_3), 2.82 (1H, br, OH), 4.24 (1H, m, C_1-H), 4.63 (2H, m, O–CH–O×2). MS *m/z*: 356 (M^+), 338, 271. *Anal.* Calcd for $C_{20}H_{36}O_5$: C, 67.38; H, 10.18. Found: C, 67.55; H, 10.28.

(1*S*,3*S*,4*R*)-1-Benzyloxy-4-[3-(tetrahydropyran-2-yl)oxybutyl]-3-(tetrahydropyran-2-yl)oxymethylcyclopentane (8)——The alcohol **7** (1.30 g) in DMSO (10 ml) was added dropwise to sodium methylsulfinylmethide [prepared from NaH (50% content, 0.53 g) and DMSO (15 ml) in a conventional manner] with stirring at room temperature under an N_2 atmosphere. After 1 h, benzyl chloride (0.90 g) in DMSO (3 ml) was added dropwise, and the whole was stirred for 6 h at room temperature, poured into ice-water, and extracted with ether. The ether extract was washed and dried. The solvent was removed *in vacuo* to afford an oily residue, which was purified by column chromatography on silica gel (30 g). The fraction eluted with 25% AcOEt in hexane (v/v) afforded **8** (1.54 g, 95%) as a colorless oil. IR (neat): 1500, 1140, 735 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.13, 1.24 (1.5H each, d, J=7 Hz, CH_3), 4.45 (2H, s, C<u>H</u>$_2$Ph), 4.58 (2H, m, O–CH–O), 7.29 (5H, m, Ph). MS *m/z*: 446 (M^+), 361, 277. *Anal.* Calcd for $C_{27}H_{42}O_5$: C, 72.61; H, 9.48. Found: C, 72.68; H, 9.55.

(1*S*,3*S*,4*R*)-1-Benzyloxy-3-methoxycarbonyl-4-(3-oxobutyl)-cyclopentane (9)——Jones reagent (7.1 ml) was added dropwise to a stirred solution of **8** (1.70 g) in acetone (25 ml) at below 5 °C. After 1.5 h, isopropanol (1 ml) was added to decompose excess reagent, and the resulting precipitate was filtered off. The filtrate was concentrated *in vacuo* to yield an oily residue, which was dissolved in ether (70 ml). The acidic fraction was extracted with 10% NaOH (30 ml). The alkaline extract was made acidic with 10% HCl, and then extracted with AcOEt. The AcOEt extract was treated with diazomethane in a usual manner to yield a crude oil (1.30 g), which was subjected to column chromatography on silica gel (25 g). The fraction eluted with 25% AcOEt in hexane (v/v) was collected, and the solvent was removed *in vacuo* to give **9** (0.92 g, 80%) as a colorless oil. $[\alpha]_D^{27}$ +3.1° (c=3.2, EtOH). IR (neat): 1735, 1715, 1500, 1165 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.09 (3H, s, $COCH_3$), 3.65 (3H, s, $COOCH_3$), 4.47 (2H, s, C<u>H</u>$_2$Ph), 7.28 (5H, m, Ph). MS *m/z*: 304 (M^+), 273, 261. *Anal.* Calcd for $C_{18}H_{24}O_4$: C, 71.02; H, 7.95. Found: C, 70.89; H, 8.10.

(1*S*,3*S*,4*R*)-1-Benzyloxy-4-(3,3-ethylenedioxybutyl)-3-methoxycarbonylcyclopentane (10)——The mixture of **9** (0.91 g), ethylene glycol (0.40 ml), and benzene (30 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 successively washed with 5% aq. $NaHCO_3$ and water, then dried. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel (20 g). The fraction eluted with 20% AcOEt in hexane (v/v) afforded **10** (0.97 g, 94%) as a colorless oil. IR (neat): 1735, 1500, 1175, 1070 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, s, CH_3), 3.66 (3H, s, $COOCH_3$), 3.88 (4H, s, OCH_2CH_2O), 4.48 (2H, s, C<u>H</u>$_2$Ph), 7.30 (5H, m, Ph).

(1*S*,3*R*,4*R*)-1-Benzyloxy-4-(3,3-ethylenedioxybutyl)-3-methoxycarbonylcyclopentane (11)——Freshly prepared

NaOMe (0.15 g) was added in one portion to a stirred solution of **10** (0.95 g) in toluene (20 ml). The mixture was stirred at room temperature for 1 h, and then refluxed for 3 h. The reaction mixture was washed and dried. The solvent was removed *in vacuo* to leave an oily residue, which was subjected to column chromatography on silica gel (20 g). The fraction eluted with 20% AcOEt in hexane (v/v) was collected, and the solvent was evaporated off *in vacuo* to afford **11** (0.85 g, 88%) as a colorless oil. IR (neat): 1732, 1495, 1160, 1065 cm^{-1}.

(1*S*,3*R*,4*R*)-1-Benzyloxy-3-methoxycarbonyl-4-(3-oxobutyl)-cyclopentane (12)——An aliquot of 10% HCl (1 ml) was added dropwise to a stirred solution of **11** (0.85 g) in MeOH (20 ml) at room temperature. The whole was stirred for 1.5 h, diluted with brine (50 ml), and extracted with AcOEt. The AcOEt extract was washed, dried, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (20 g). The fraction eluted with 20% AcOEt in hexane (v/v) was collected, and the solvent was removed *in vacuo* to afford **12** (0.71 g, 96%) as a colorless oil. $[\alpha]_D^{27}$ −38.8° (c=1.3, EtOH). IR (neat): 1735, 1720, 1500, 1170 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.11 (3H, s, $COCH_3$), 3.65 (3H, s, $COOCH_3$), 4.43 (2H, s, CH_2Ph), 7.28 (5H, m, Ph). MS m/z: 304 (M^+), 273, 261. *Anal.* Calcd for $C_{18}H_{24}O_4$: C, 71.02; H, 7.95. Found: C, 71.12; H, 7.92.

(1*S*,3*R*,4*R*)-4-(2-Acetoxyethyl)-1-benzyloxy-3-methoxycarbonylcyclopentane (13)——CF_3COOOH [freshly prepared from $(CF_3CO)_2O$ (20 ml) and 60% H_2O_2 (7 ml) in CH_2Cl_2 (45 ml) at 0 °C] was added dropwise with stirring to **12** (0.70 g) in CH_2Cl_2 (30 ml) in the presence of Na_2HPO_4 (13 g) at room temperature, and the whole was stirred for 4 h. The reaction mixture was poured into 5% aq. $NaHCO_3$ (100 ml) under ice-water cooling, and extracted with AcOEt. The AcOEt extract was successively washed with 5% aq. KI, 5% aq. $Na_2S_2O_3$ and brine, then dried. Removal of the solvent *in vacuo* afforded an oily residue, which was subjected to column chromatography on silica gel (20 g). The fraction eluted with 20% AcOEt in hexane (v/v) gave **13** (0.64 g, 87%) as a colorless oil. $[\alpha]_D^{27}$ −21.0° (c=3.5, EtOH). IR (neat): 1735, 1500, 1245, 1070 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.03 (3H, s, CH_3COO), 3.67 (3H, s, $COOCH_3$), 4.44 (2H, s, CH_2Ph), 7.29 (5H, m, Ph). MS m/z: 320 (M^+), 289, 261. *Anal.* Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.72; H, 7.64.

(1*S*,3*R*,4*R*)-4-(2-Acetoxyethyl)-3-methoxycarbonyl-1-cyclopentanol (14)——A solution of **13** (0.50 g) in EtOH (25 ml) was hydrogenated in the presence of 5% Pd/C 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 purified by column chromatography on silica gel (10 g). The fraction eluted with 50% AcOEt in hexane (v/v) was collected, and the solvent was removed *in vacuo* to yield **14** (0.34 g, 95%) as a colorless oil. $[\alpha]_D^{27}$ −34.9° (c=1.0, CH_2Cl_2). IR (neat): 3450, 1735, 1248, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.04 (3H, s, CH_3COO), 3.68 (3H, s, $COOCH_3$), 4.41 (1H, m, C_1-H). MS m/z: 230 (M^+), 212, 186. *Anal.* Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.41; H, 7.79.

(1*S*,3*R*,4*R*)-4-(2-Acetoxyethyl)-3-methoxycarbonyl-1-(2-methoxyethoxymethoxy)cyclopentane (15)——2-Methoxyethoxymethyl chloride (275 mg) in CH_2Cl_2 (2 ml) was added dropwise to a stirred solution of **14** (0.325 mg) and diisopropyl ethylamine (290 mg) in CH_2Cl_2 (5 ml) at room temperature. After 3 h, the reaction mixture was diluted with CH_2Cl_2 (30 ml), washed successively with 2% HCl, 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 (10 g). The fraction eluted with 50% AcOEt in hexane (v/v) afforded **15** (421 mg, 89%) as a colorless oil. $[\alpha]_D^{27}$ −32.2° (c=1.0, $CHCl_3$). IR (neat): 1735, 1245, 1045 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.04 (3H, s, CH_3COO), 3.38 (3H, s, OCH_3), 3.67 (3H, s, $COOCH_3$), 4.68 (2H, s, O–CH_2–O). MS m/z: 318 (M^+), 212. *Anal.* Calcd for $C_{15}H_{26}O_7$: C, 56.59; H, 8.23. Found: C, 56.51; H, 8.15.

(1*S*,3*R*,4*R*)-4-(2-Hydroxyethyl)-3-methoxycarbonyl-1-(2-methoxyethoxymethoxy)cyclopentane (16)——K_2CO_3 (300 mg) was added portionwise to a stirred solution of **15** (402 mg) in MeOH (15 ml) at room temperature. After 3 h, the reaction mixture was diluted with brine (30 ml), and extracted with AcOEt. The AcOEt extract was washed and dried, then the solvent was removed *in vacuo* to leave an oily residue, which was purified by column chromatography on silica gel (10 g). The fraction eluted with 70% AcOEt in hexane (v/v) gave **16** (328 mg, 94%) as a colorless oil. $[\alpha]_D^{27}$ −18.5° (c=1.0, $CHCl_3$). IR (neat): 3460, 1735, 1045 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.68 (1H, m, C_3-H), 3.38 (3H, s, OCH_3), 3.68 (3H, s, $COOCH_3$), 4.21 (1H, m, C_1-H), 4.69 (2H, s, O–CH_2–O).

(1*S*,3*R*,4*R*)-4-(2-Mesyloxyethyl)-3-methoxycarbonyl-1-(2-methoxyethoxymethoxy)cyclopentane (17)——Mesyl chloride (200 mg) in benzene (3 ml) was added dropwise to a stirred solution of **16** (312 mg) and triethylamine (240 mg) in benzene (10 ml) at 10 °C. After 1 h, the reaction mixture was diluted with benzene (30 ml), washed successively with 2% HCl, 5% aq. $NaHCO_3$ and brine, then dried. The solvent was removed *in vacuo* to afford an oily residue, which was purified by column chromatography on silica gel (10 g). The fraction eluted with 70% AcOEt in hexane (v/v) was collected, and removal of the solvent *in vacuo* afforded **17** (389 mg, 94%) as a colorless oil. $[\alpha]_D^{26}$ −17.7° (c=1.5, $CHCl_3$). IR (neat): 1730, 1355, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.66 (1H, m, C_3-H), 3.00 (3H, s, SO_2CH_3), 3.38 (3H, s, OCH_3), 3.68 (3H, s, $COOCH_3$), 4.24 (3H, m, CH_2OMs, C_1-H), 4.69 (2H, s, O–CH_2–O). MS m/z: 354 (M^+), 278. *Anal.* Calcd for $C_{14}H_{26}O_6S$: C, 47.45; H, 7.40. Found: C, 47.72; H, 7.53.

(1*S*,3*R*,4*S*)-4-(2-Iodoethyl)-3-methoxycarbonyl-1-(2-methoxyethoxymethoxy)cyclopentane (18)——A mixture of NaI (200 mg), **17** (354 mg), and hexamethylphosphoric triamide (HMPA, 0.5 ml) in benzene (5 ml) was stirred for 1 h at 70 °C, diluted with brine (50 ml), and extracted with ether. The ether extract was washed with 5% aq. $Na_2S_2O_3$ and brine, then dried. Removal of the solvent *in vacuo* gave an oily residue, which was subjected to column chromatography on silica gel (8 g). The fraction eluted with 25% AcOEt in hexane (v/v) afforded **18** (366 mg, 95%) as

a colorless oil. $[\alpha]_D^{23}$ $-42.5°$ ($c=1.0$, $CHCl_3$). IR (neat): 1735, 1040 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.63 (1H, m, C_3-H), 3.16 (2H, m, CH_2I), 3.38 (3H, s, OCH_3), 3.68 (3H, s, $COOCH_3$), 4.23 (1H, m, C_1-H), 4.69 (2H, s, O–CH_2–O). MS *m/z*: 386 (M^+), 355, 310. *Anal.* Calcd for $C_{13}H_{23}IO_5$: C, 40.43; H, 6.00. Found: C, 40.48; H, 6.17.

(1*S*,3*R*,4*S*)-3-Methoxycarbonyl-1-(2-methoxyethoxymethoxy)-4-vinylcyclopentane (3)——The mixture of **18** (305 mg), DBU (130 mg), and 10% DMSO in benzene (v/v) (5 ml) was stirred for 5 h at 60 °C, diluted with brine, and extracted with ether. The ether extract was successively washed with 3% aq. HCl, 5% aq. $NaHCO_3$ and brine, then dried. The solvent was removed *in vacuo* to yield an oily residue, which was purified by column chromatography on silica gel (8 g). The fraction eluted with 25% AcOEt in hexane (v/v) was collected, and the solvent was evaporated off *in vacuo* to afford **3** (72 mg, 36%) as a colorless oil. $[\alpha]_D^{16}$ $-31.0°$ ($c=1.0$, $CHCl_3$). IR (neat): 1735, 1640, 1167, 1045 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 3.38 (3H, s, OCH_3), 3.46—3.80 (4H, m, OCH_2CH_2O), 3.67 (3H, s, $COOCH_3$), 4.27 (1H, m, C_1-H), 4.70 (2H, s, O–CH_2–O), 5.02 (2H, m, $=CH_2$), 5.83 (1H, m, –CH=). MS *m/z*: 258 (M^+), 227, 151. *Anal.* Calcd for $C_{13}H_{22}O_5$: C, 58.51; H, 9.00. Found: C, 58.38; H, 9.15.

References and Notes

1) For a review, see M. Harre, P. Raddatz, R. Walenta, and E. Winterfeldt, *Angew. Chem. Int. Ed. Engl.*, **21**, 480 (1982), and references cited therein.
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11) Compound (**4**) consists of a mixture of the epimeric alcohols.