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

KOHSHI UENO, HIROSHI SUEMUNE, SEITARO SAEKI,
and KIYOSHI SAKAI*

Faculty of Pharmaceutical Sciences, Kyushu University,
3-1-1, Maidashi, Higashi-ku, Fukuoka 812, Japan

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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-pentenol 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 A¹⁾ (**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 Wollenberg³⁾ in 1976, partial⁴⁾ and total⁵⁾ syntheses of this compound have been achieved by several groups. (+)-Brefeldin A, the naturally occurring form, was first synthesized by Mori and Kitahara⁶⁾ 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⁾

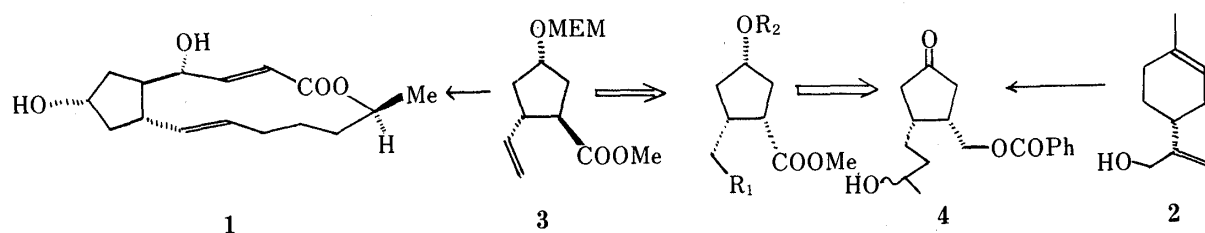


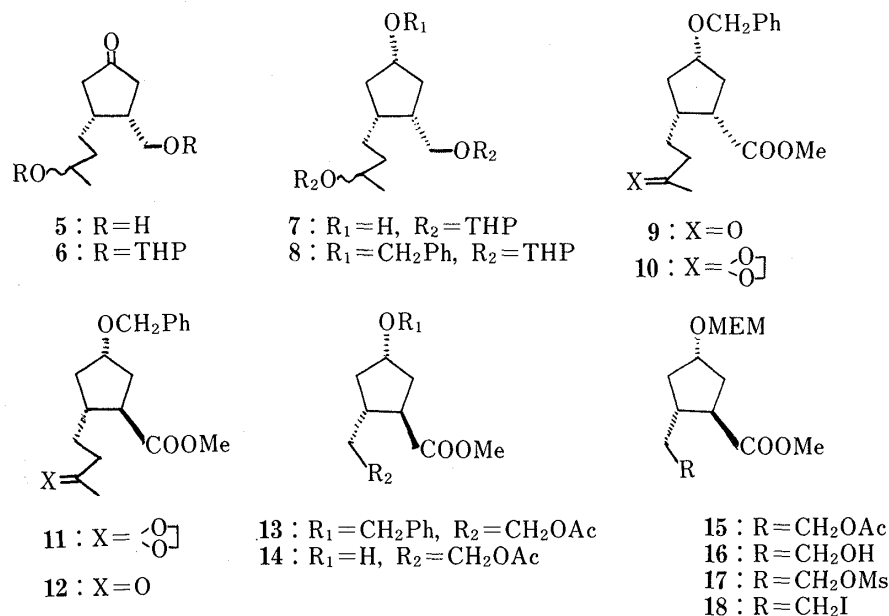
Chart 1

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 synthesis¹⁰⁾ 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 intermediate⁶⁾ (**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 cyclopentanone¹¹⁾ (**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 C₃- and C₄-

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.



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 trifluoroacetic 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 (1H -NMR) spectrum and the infrared (IR) spectrum.

Experimental

IR spectra were measured with a JASCO A-202 spectrometer. ^1H -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.

(3S,4R)-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} . ^1H -NMR (CDCl_3) δ : 1.19 (3H, d, $J=7$ Hz, CH_3), 3.56—4.00 (3H, m, CH_2OH , $\text{CH}(\text{OH})$). MS m/z : 186 (M^+), 168, 150. Anal. Calcd for $\text{C}_{10}\text{H}_{18}\text{O}_3$: C, 64.49; H, 9.74. Found: C, 64.62; H, 9.81.

(3S,4R)-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} . ^1H -NMR (CDCl_3) δ : 1.13, 1.24 (1.5H each, d, $J=7$ Hz, CH_3), 3.45 (3H, m, $\text{CH}_2\text{O-THP}$, $\text{CH}(\text{O-THP})$), 3.80 (4H, m, $\text{CH}_2\text{O} \times 2$), 4.63 (2H, m, $\text{O-CH-O} \times 2$). MS m/z : 354 (M^+), 270, 186. Anal. Calcd for $\text{C}_{20}\text{H}_{34}\text{O}_5$: C, 67.76; H, 9.67. Found: C, 67.53; H, 9.81.

(1S,3S,4R)-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} . ^1H -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, $\text{C}_1\text{-H}$), 4.63 (2H, m, $\text{O-CH-O} \times 2$). MS m/z : 356 (M^+), 338, 271. Anal. Calcd for $\text{C}_{20}\text{H}_{36}\text{O}_5$: C, 67.38; H, 10.18. Found: C, 67.55; H, 10.28.

(1S,3S,4R)-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} . ^1H -NMR (CDCl_3) δ : 1.13, 1.24 (1.5H each, d, $J=7$ Hz, CH_3), 4.45 (2H, s, CH_2Ph), 4.58 (2H, m, O-CH-O), 7.29 (5H, m, Ph). MS m/z : 446 (M^+), 361, 277. Anal. Calcd for $\text{C}_{27}\text{H}_{42}\text{O}_5$: C, 72.61; H, 9.48. Found: C, 72.68; H, 9.55.

(1S,3S,4R)-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. $[\alpha]_D^{27} + 3.1^\circ$ ($c=3.2$, EtOH). IR (neat): 1735, 1715, 1500, 1165 cm^{-1} . ^1H -NMR (CDCl_3) δ : 2.09 (3H, s, COCH_3), 3.65 (3H, s, COOCH_3), 4.47 (2H, s, CH_2Ph), 7.28 (5H, m, Ph). MS m/z : 304 (M^+), 273, 261. Anal. Calcd for $\text{C}_{18}\text{H}_{24}\text{O}_4$: C, 71.02; H, 7.95. Found: C, 70.89; H, 8.10.

(1S,3S,4R)-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} . ^1H -NMR (CDCl_3) δ : 1.28 (3H, s, CH_3), 3.66 (3H, s, COOCH_3), 3.88 (4H, s, $\text{OCH}_2\text{CH}_2\text{O}$), 4.48 (2H, s, CH_2Ph), 7.30 (5H, m, Ph).

(1S,3R,4R)-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} .

(1S,3R,4R)-1-Benzoyloxy-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. $[\alpha]_D^{27} - 38.8^\circ$ ($c = 1.3$, EtOH). IR (neat): 1735, 1720, 1500, 1170 cm^{-1} . $^1\text{H-NMR}$ (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 $\text{C}_{18}\text{H}_{24}\text{O}_4$: C, 71.02; H, 7.95. Found: C, 71.12; H, 7.92.

(1S,3R,4R)-4-(2-Acetoxyethyl)-1-benzoyloxy-3-methoxycarbonylcyclopentane (13)— CF_3COOOH [freshly prepared from $(\text{CF}_3\text{CO})_2\text{O}$ (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. $\text{Na}_2\text{S}_2\text{O}_3$ 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. $[\alpha]_D^{27} - 21.0^\circ$ ($c = 3.5$, EtOH). IR (neat): 1735, 1500, 1245, 1070 cm^{-1} . $^1\text{H-NMR}$ (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 $\text{C}_{18}\text{H}_{24}\text{O}_5$: C, 67.48; H, 7.55. Found: C, 67.72; H, 7.64.

(1S,3R,4R)-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. $[\alpha]_D^{27} - 34.9^\circ$ ($c = 1.0$, CH_2Cl_2). IR (neat): 3450, 1735, 1248, 1040 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 2.04 (3H, s, CH_3COO), 3.68 (3H, s, COOCH_3), 4.41 (1H, m, $\text{C}_1\text{-H}$). MS m/z : 230 (M^+), 212, 186. Anal. Calcd for $\text{C}_{11}\text{H}_{18}\text{O}_5$: C, 57.38; H, 7.88. Found: C, 57.41; H, 7.79.

(1S,3R,4R)-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. $[\alpha]_D^{27} - 32.2^\circ$ ($c = 1.0$, CHCl_3). IR (neat): 1735, 1245, 1045 cm^{-1} . $^1\text{H-NMR}$ (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, $\text{O-CH}_2\text{-O}$). MS m/z : 318 (M^+), 212. Anal. Calcd for $\text{C}_{15}\text{H}_{26}\text{O}_7$: C, 56.59; H, 8.23. Found: C, 56.51; H, 8.15.

(1S,3R,4R)-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. $[\alpha]_D^{27} - 18.5^\circ$ ($c = 1.0$, CHCl_3). IR (neat): 3460, 1735, 1045 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 2.68 (1H, m, $\text{C}_3\text{-H}$), 3.38 (3H, s, OCH_3), 3.68 (3H, s, COOCH_3), 4.21 (1H, m, $\text{C}_1\text{-H}$), 4.69 (2H, s, $\text{O-CH}_2\text{-O}$).

(1S,3R,4R)-4-(2-Mesyloxyethyl)-3-methoxycarbonyl-1-(2-methoxyethoxymethoxy)cyclopentane (17)—Mesityl 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. $[\alpha]_D^{26} - 17.7^\circ$ ($c = 1.5$, CHCl_3). IR (neat): 1730, 1355, 1040 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 2.66 (1H, m, $\text{C}_3\text{-H}$), 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 , $\text{C}_1\text{-H}$), 4.69 (2H, s, $\text{O-CH}_2\text{-O}$). MS m/z : 354 (M^+), 278. Anal. Calcd for $\text{C}_{14}\text{H}_{26}\text{O}_6\text{S}$: C, 47.45; H, 7.40. Found: C, 47.72; H, 7.53.

(1S,3R,4S)-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. $\text{Na}_2\text{S}_2\text{O}_3$ and brine, then dried. Removal of the solvent *in vacuo* gave an oily residue, which was 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. $[\alpha]_D^{23} -42.5^\circ$ ($c=1.0$, CHCl_3). IR (neat): 1735, 1040 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 2.63 (1H, m, $\text{C}_3\text{-H}$), 3.16 (2H, m, CH_2I), 3.38 (3H, s, OCH_3), 3.68 (3H, s, COOCH_3), 4.23 (1H, m, $\text{C}_1\text{-H}$), 4.69 (2H, s, $\text{O-CH}_2\text{-O}$). MS m/z : 386 (M^+), 355, 310. Anal. Calcd for $\text{C}_{13}\text{H}_{23}\text{IO}_5$: C, 40.43; H, 6.00. Found: C, 40.48; H, 6.17.

(1S,3R,4S)-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. $[\alpha]_D^{16} -31.0^\circ$ ($c=1.0$, CHCl_3). IR (neat): 1735, 1640, 1167, 1045 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 3.38 (3H, s, OCH_3), 3.46–3.80 (4H, m, $\text{OCH}_2\text{CH}_2\text{O}$), 3.67 (3H, s, COOCH_3), 4.27 (1H, m, $\text{C}_1\text{-H}$), 4.70 (2H, s, $\text{O-CH}_2\text{-O}$), 5.02 (2H, m, $=\text{CH}_2$), 5.83 (1H, m, $-\text{CH}=\text{}$). MS m/z : 258 (M^+), 227, 151. Anal. Calcd for $\text{C}_{13}\text{H}_{22}\text{O}_5$: C, 58.51; H, 9.00. Found: C, 58.38; H, 9.15.

References and Notes

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- 11) Compound (**4**) consists of a mixture of the epimeric alcohols.