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Synthesis of an insecticidal tetrahydroisocoumarin, (3*R*,4*S*,4a*R*)-4,8-dihydroxy-3-methyl-3,4,4a,5-tetrahydro-1*H*-2-benzopyran-1-one

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Abstract—The insecticidal tetrahydroisocoumarin, (3*R*,4*S*,4a*R*)-4,8-dihydroxy-3-methyl-3,4,4a,5-tetrahydro-1*H*-2-benzopyran-1-one, was synthesized as a racemate and as an optically active form using one-pot esterification–Michael addition–aldol reaction of δ-hydroxy-α,β-unsaturated aldehyde and diketene as a key step.

1. Introduction

In 1995, Findlay et al.[1] isolated a tetrahydroisocoumarin, (3*R*,4*S*,4a*R*)-4,8-dihydroxy-3-methyl-3,4,4a,5-tetrahydro-1*H*-2-benzopyran-1-one (**1**, Fig. 1), from culture filtrates of conifer endophytic fungi [*Canoplea elegantula* (Cooke) M. B. Ellis 7BS37C1 and 6BS10K1] together with five new compounds and two known isocoumarins **2**[2] and **3**.[3] Some of these compounds including **1** show toxicity to cells and larvae of spruce budworm (*Choristoneura fumiferana* Clem.). Because the two known compounds **2** and **3** isolated in Findlay's work were identical in spectroscopic characteristics and signs of the specific rotations with those previously isolated,[2,3] the C-3 absolute configurations common to these co-metabolites were represented as such. Many of the naturally occurring 8-hydroxy-3-methyl-3,4-dihydroisocoumarins (mellein[4–9] or ramulosin[2,10,11] derivatives) exhibit a variety of biological activities,[12,13] but there have been no reports of toxicity to insects. Aiming at the development of efficient method to construct this tetrahydroisocoumarin, we started synthesizing **1** as a racemate and the results had already been reported as a communication.[14] Herein, we describe the details of the first synthesis of this compound both as a racemate and as an optically active form.

2. Results and discussion

Our synthetic strategy is shown in Scheme 1. We expected the target skeleton (**A**) to be constructed from two segments, diketene (**B**) and δ-hydroxy-α,β-unsaturated aldehyde (**C**) by successive esterification (**a**) to open the diketene β-lactone to give an acetoacetate, Michael addition (**b**) to the unsaturated aldehyde, and aldol condensation (**c**) of the methyl ketone with the aldehyde. In the Michael addition step, the angular hydrogen atom would be controlled to be in an axial orientation via the chair-form transition state (**D**) with all equatorial substituents.

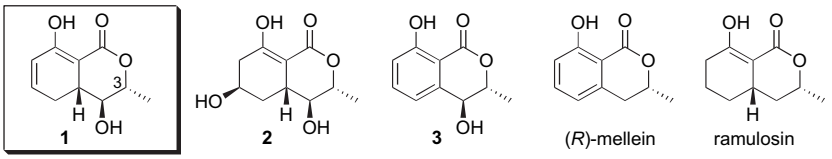

Figure 1.

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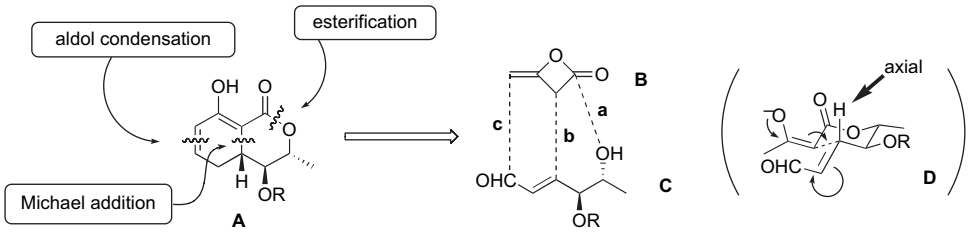
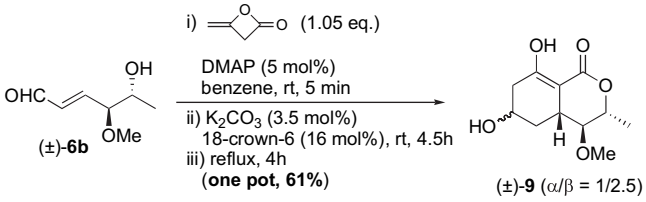


Scheme 1. Synthetic plan of tetrahydroisocoumarin (**1**).

Initially, synthesis of the racemate was investigated to establish the synthetic route.[14] Oxidation of ethyl sorbate (**4**) using *m*CPBA afforded the known epoxide (±)-**5**.[15] Acid-catalyzed epoxide opening of (±)-**5** gave hydroxy ester (±)-**6a**, whose ester group was reduced with 2 equiv of diisobutylaluminum hydride to afford aldehyde (±)-**6b**. Esterification of (±)-**6b** with diketene was promoted by catalytic amount of 4-(dimethylamino)pyridine[16] in tetrahydrofuran easily at room temperature to give β-keto ester (±)-**7**. When (±)-**7** was treated with potassium carbonate and 18-crown-6 in benzene at room temperature, the desired Michael addition occurred to afford bicyclic hemiacetal (±)-**8** (inseparable mixture of α- and β-hydroxy isomers in a 1:1.7 ratio). When the reaction was continued under reflux for additional 2 h, the hemiacetal ring of (±)-**8** reopened and aldol reaction proceeded to give the desired bicyclic compound (±)-**9** in a high yield (73% from (±)-**7**, inseparable mixture of α- and β-hydroxy isomers in a 1:3.3 ratio, Scheme 2).

Now that the step-by-step reaction was successful, we then tried the one-pot esterification–Michael addition–aldol reaction from (±)-**6b** to (±)-**9** (Scheme 3). With 1.05 equiv of diketene, esterification smoothly proceeded also in benzene. Then treatment with a catalytic amount of potassium carbonate and 18-crown-6 at room temperature and heating lead to the further reactions to give (±)-**9** in 61% yield in one-pot. Although some similar methods for the preparation of a simple six-membered ring have been reported,[17–20] we were not aware of any such applications to the construction of a bicyclic system in one-pot with control of stereochemistry. At that time, only the stereochemistry at C-4a could not be clarified because (±)-**9** was an inseparable mixture and showed a complicated ^{1}H NMR spectrum, and therefore the determination of its configuration was carried out at the later stage.

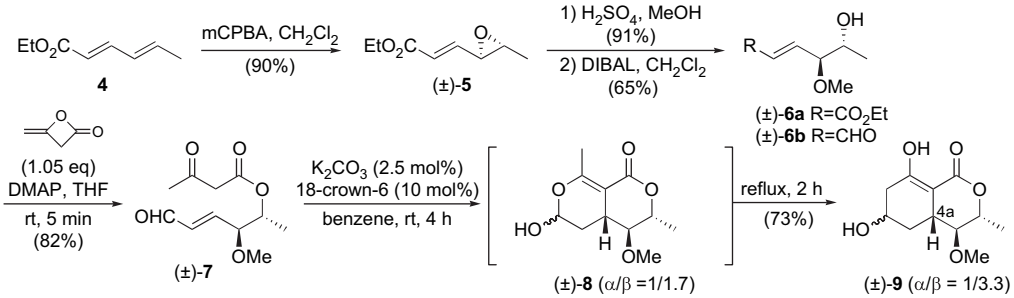
As further dehydration of (±)-**9** to (±)-**10** did not occur under the conditions shown in Scheme 3 against our expectation, it was investigated in the next step (Scheme 4). Although the



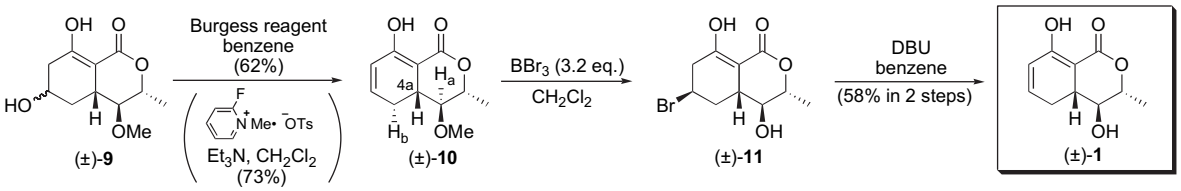
Scheme 3. Synthesis of bicyclic compound (±)-**9** by one-pot reaction.

best yield was obtained using 2-fluoro-*N*-methylpyridinium tosylate[21] at room temperature overnight (73% yield), it was not reproducible. On the other hand, Burgess reagent[22,23] gave (±)-**10** in more invariable yield (62%). At this stage, the stereochemistry at C-4a was confirmed as depicted in Scheme 4 from the coupling constants (9.6 Hz with H_a, 17.0 Hz with H_b). Treatment of (±)-**10** with excess boron tribromide gave bromide (±)-**11** as a colorless solid via the desired demethylation with a concomitant conjugate addition of bromide ion almost from β (axial)-face. This was easily dehydrobrominated with DBU at room temperature for 15 min to give (±)-**1** as colorless needles (mp 134.0–135.0 °C). The IR, ^{1}H NMR, and ^{13}C NMR spectra were identical with those of the natural **1**.[1]

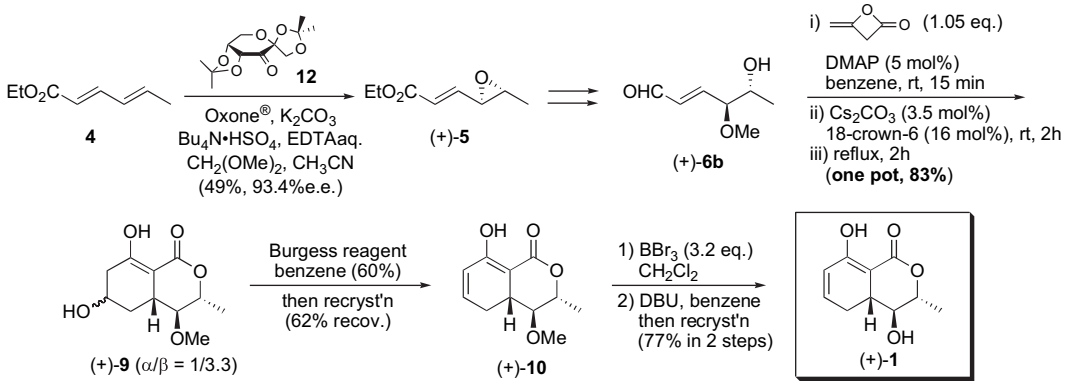
Since our strategy had been established by accomplishing the synthesis of the racemate, we adopted it for optically active **1** (Scheme 5). The known asymmetric epoxidation[24] of ethyl sorbate (**4**) afforded optically active epoxide (+)-**5** (93.4% ee), and then aldehyde (+)-**6b** was obtained in the same manner as above. In the one-pot reaction from (+)-**6b** to (+)-**9**, cesium carbonate was found to be a better base than potassium carbonate for improving the yield (83%) and reproducibility. Dehydration of (+)-**9** afforded the methyl analog (+)-**10**, whose enantiomeric purity was determined to be 93.6% ee (before recrystallization) by ^{1}H NMR of its Mosher ester.[25] After recrystallization of (+)-**10**, ^{1}H NMR peaks attributed to the diastereomer disappeared. After two steps



Scheme 2. Synthesis of bicyclic compound (±)-**9** by stepwise reactions.



Scheme 4. Synthesis of (±)-**1**.



Scheme 5. Synthesis of (+)-**1**.

as above, the optically active **1** was obtained; mp 141.0–143.5 °C, $[\alpha]_D^{22}$ +150 (*c* 0.545, $CHCl_3$). Although they have a slight difference from those of natural **1**[1] (mp 120–123 °C, $[\alpha]_D^{20}$ +164 (*c* 0.014, $CHCl_3$)), the enantiomeric purity of synthetic **1** was estimated to be >98% ee by HPLC analysis of its Mosher esters. From the sign of the specific rotations, the presumed absolute configuration was confirmed to be correct.

In summary, the insecticidal tetrahydroisocoumarin **1** was efficiently synthesized as a racemate and as almost optically pure form. The overall yield of (±)-**1** was 12% in six steps from commercially available ethyl sorbate, and that of (+)-**1** was 13% in six steps from the known epoxide **5**. The key step, one-pot esterification–Michael addition–aldol reaction from **6b** to **9**, succeeded in a high yield and in a stereoselective manner to help construct tetrahydroisocoumarin skeleton very concisely.

3. Experimental

3.1. General

Optical rotations were recorded with a Jasco DIP-371 polarimeter. IR spectra were measured with a Jasco FT/IR-230 spectrophotometer. ^{1}H NMR spectra were recorded on a Jeol JNM AL-300 spectrometer (300 MHz), Bruker AC-300 (300 MHz) or a Jeol JNM GSX-500 spectrometer (500 MHz). ^{13}C NMR spectra were recorded on a Jeol JNM GSX-500 (125 MHz). Chemical shifts (δ) were referenced to the residual solvent peak as the internal standard ($CDCl_3$: δ_H=7.26, δ_C=77.0). Refractive indices were measured with Atago 1T refractometer. HPLC was performed using Shodex DS-4 and SSC UV detector 3000B (254 nm) or Shimadzu LC-6A and Shimadzu SPD-6A UV detector (254 nm). Column chromatography was performed using Merck Kieselgel 60 (Ord. No. 107734). Preparative silica gel TLC was carried out on Merck Kieselgel 60 F_{254}, 0.5 mm (Ord. No. 105744). Melting points were measured with Yanako micro-melting point apparatus. Boiling points and melting points are uncorrected values.

3.2. Synthetic studies

3.2.1. Ethyl (2*E*,4*R*,5*R*)-4,5-epoxy-2-hexenoate (5). (a) *Racemate*:[15] to a solution of ethyl sorbate (19.1 g, 0.136 mol) in dichloromethane (300 ml) was added 80% *m*CPBA (41.0 g, 0.190 mol) at 0 °C. After the reaction mixture was stirred at 4 °C for 2 d, it was poured into a mixture of saturated sodium bicarbonate solution and excess sodium thiosulfate, and extracted with ether. The organic layer was washed with saturated sodium bicarbonate solution and brine, dried with anhydrous magnesium sulfate, and concentrated in vacuo. The residue was distilled to give known epoxide (±)-**5** (19.5 g, 92%) as a colorless oil.

Bp 70.0 °C/2.0 mmHg; IR (film): ν=2980, 2940, 1745, 1730, 1675, 1455, 1425, 1370, 1340, 1280, 1240, 1200, 1030, 965 cm^{-1}; ^{1}H NMR (300 MHz in $CDCl_3$): δ=1.28 (3H, t, *J*=7.4 Hz, $-CO_2CH_2CH_3$), 1.38 (3H, t, *J*=5.4 Hz, 6-H), 2.97 (1H, dq, *J*=1.7, 5.4 Hz, 5-H), 3.17 (1H, dd, *J*=7.2, 1.7 Hz, 4-H), 4.20 (2H, q, *J*=7.4 Hz, $-CO_2CH_2CH_3$), 6.12 (1H, d, *J*=15.6 Hz, 2-H), 6.68 (1H, dd, *J*=15.6, 7.2 Hz, 3-H).

(b) *(4R,5R)-Isomer*: optically active **5** was prepared according to the procedure of Shi et al.[24] $Na_2B_4O_7$ (1.9 g, 4.98 mmol) was added to aq EDTA (4×10^{-4} M, 100 ml) with stirring. Methylal (100 ml), acetonitrile (50 ml), ethyl sorbate (1.40 g, 10.0 mmol), tetra-*n*-butylammonium hydrosulfate (150 mg), and ketone **12** (1.30 g, 5.03 mmol) were added successively to the solution. The mixture was cooled to 0 °C, a solution of Oxone® (6.90 g, 11.2 mmol) in aq EDTA (4×10^{-4} M, 60 ml) and a solution of potassium carbonate (6.90 g, 50.0 mmol) in water (60 ml) were slowly added at the same rate using peristaltic pump for 4.5 h.

After the addition, ether (150 ml) was added to the mixture and the aqueous layer was extracted with ether. The combined organic layer was washed with brine, dried with anhydrous magnesium sulfate, and concentrated in vacuo. The residue was chromatographed over silica gel (60 g) and elution with hexane/ethyl acetate (15:1) gave (4*R*,5*R*)-**5** (770 mg, 49%) as a colorless oil. The enantiomeric purity was established to be 93.4% ee by HPLC analysis [(4*R*,5*R*)-**5**: t_R=30.6 min (96.7%), (4*S*,5*S*)-**5**: t_R=39.1 min (3.3%), Chiralcel® OD (4.6 $\phi\times$250 mm), hexane/2-propanol (400:1), 1.0 ml/min].

$[\alpha]_D^{20}$ +11.5 (*c* 1.52, $CHCl_3$); IR and ^1H NMR spectra were identical with those of (±)-**5**.

3.2.2. Ethyl (2*E*,4*S*,5*R*)-5-hydroxy-4-methoxy-2-hexenoate (6a). (a) *Racemate*: to a solution of the epoxide (±)-**5** (508 mg, 3.26 mmol) in methanol (10 ml) was added concd sulfuric acid (five drops) at 0 °C, and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was washed with brine, dried with anhydrous magnesium sulfate, and concentrated in vacuo. The residue was chromatographed over silica gel (18 g) and elution with hexane/ethyl acetate (3:1–1:1) gave hydroxy ester (±)-**6a** (558 mg, 91%) as a colorless oil. For analysis, a portion of this oil was distilled to give pure (±)-**6a**.

Bp 91.0–92.0 °C/1.5 mmHg; n_D^{22} 1.4607; IR (film): ν=3480 (br), 2980, 2940, 2900, 2830, 1725, 1715, 1660, 1460, 1455, 1370, 1300, 1270, 1240, 1180, 1110, 1040, 985 cm^{-1}; ^1H NMR (300 MHz in $CDCl_3$): δ=1.14 (3H, d, *J*=6.8 Hz, 6-H), 1.30 (3H, t, *J*=7.2 Hz, $-CO_2CH_2CH_3$), 2.15 (1H, d, *J*=5.3 Hz, 5-OH), 3.36 (3H, s, 4-OMe), 3.71 (1H, ddd, *J*=7.2, 3.8, 1.2 Hz, 4-H), 3.93 (1H, m, 5-H), 4.22 (2H, q, *J*=7.2 Hz, $-CO_2CH_2CH_3$), 6.04 (1H, dd, *J*=16.1, 1.2 Hz, 2-H), 6.83 (1H, dd, *J*=16.1, 7.2 Hz, 3-H). Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.20; H, 8.45.

(b) *(4S,5R)-Isomer*: in the same procedure as above, (4*R*,5*R*)-**5** (3.30 g, 21.2 mmol) was treated with concd sulfuric acid (0.35 ml) in methanol (35 ml) to give (4*R*,5*R*)-**6a** (3.72 g, 93%) as a colorless oil.

Bp 88.0–91.0 °C/0.6 mmHg; $[\alpha]_D^{26}$ +47.3 (*c* 2.07, $CHCl_3$); n_D^{27} 1.4667; its IR and ^1H NMR spectra were identical with those of (±)-**6a**. Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.35; H, 8.54.

3.2.3. (2*E*,4*S*,5*R*)-5-Hydroxy-4-methoxy-2-hexenal (6b). (a) *Racemate*: a solution of diisobutylaluminum hydride in hexane (0.95 M, 52.5 ml, 49.9 mmol) was added dropwise to a solution of (±)-**6a** (4.26 g, 22.7 mmol) in dry dichloromethane (150 ml) at −78 °C under argon. After the mixture was stirred at −78 °C for 1 h, methanol (3 ml) was added dropwise to this reaction mixture. Saturated aqueous potassium sodium tartrate solution was then added at −30 °C and the mixture was stirred at room temperature for 2 h. This was separated and the aqueous layer was extracted six times with ethyl acetate. The combined organic layer was washed with saturated ammonium chloride solution and brine, dried with anhydrous magnesium sulfate, and concentrated in vacuo. The residue was chromatographed over silica gel (100 g) and elution with hexane/ethyl acetate (1:1) gave (±)-**6b** (2.12 g, 65%) as a colorless oil. A portion of this oil was distilled for analysis to give pure (±)-**6b**.

Bp 80.0–84.0 °C/1.5 mmHg; n_D^{23} 1.4862; IR (film): ν=3460 (br), 2980, 2940, 2900, 2830, 1695, 1680, 1640, 1465, 1455, 1400, 1380, 1360, 1325, 1285, 1195, 1110, 1065, 1050, 980, 960 cm^{-1}; ^1H NMR (300 MHz in $CDCl_3$): δ=1.15 (3H, d, *J*=6.8 Hz, 6-H), 2.32 (1H, br, 5-OH), 3.38 (3H, s, 4-OMe), 3.81 (1H, ddd, *J*=6.9, 3.7, 0.7 Hz, 4-H), 4.00 (1H, dq, *J*=3.7, 6.8 Hz, 5-H), 6.30 (1H, ddd, *J*=15.4, 7.3, 0.7 Hz, 2-H), 6.76 (1H, dd, *J*=15.4, 6.9 Hz, 3-H), 9.61 (1H, d, *J*=7.3 Hz, 1-H). Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.20; H, 8.42.

(b) *(4S,5R)-Isomer*: in the same manner as above, a solution of (4*S*,5*R*)-**6a** (3.35 g, 17.8 mmol) in dry dichloromethane (100 ml) was treated with a solution of diisobutylaluminum hydride in hexane (0.95 M, 42.0 ml, 39.9 mmol) to afford (4*S*,5*R*)-**6b** (1.55 g, 60%) as a colorless oil.

Bp 72.0–73.0 °C/0.75 mmHg; $[\alpha]_D^{26}$ +44.6 (*c* 1.09, $CHCl_3$); n_D^{25} 1.4864; its IR and ^1H NMR spectra were identical with those of (±)-**6b**. Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 57.90; H, 8.38.

3.2.4. (3*R*,4*S*,4a*R*)-6,8-Dihydroxy-4-methoxy-3-methyl-3,4,4a,5,6,7-hexahydro-1*H*-2-benzopyran-1-one (9).

3.2.4.1. Method A: stepwise reaction. (a) *Esterification*: to a solution of δ-hydroxy-α,β-unsaturated aldehyde (±)-**6b** (2.12 g, 14.7 mmol) and DMAP (90.0 mg, 0.738 mmol) in dry THF (60 ml) was added diketene (1.2 ml, 15.6 mmol) slowly at room temperature under argon. After stirring for 5 min, the reaction mixture was poured into saturated ammonium chloride solution and extracted with ether. The organic layer was washed with saturated sodium bicarbonate solution and brine, dried with anhydrous magnesium sulfate, and concentrated in vacuo. The residue was chromatographed over silica gel (60 g) and elution with hexane/ethyl acetate (3:1–1:1) gave (±)-**7** (2.74 g, 82%) as a colorless oil. Though this oil contained small amount of impurities, it was used in the next step without further purification.

IR (film): ν=3440 (br), 2990, 2940, 2830, 1750, 1725, 1690, 1640, 1450, 1410, 1360, 1315, 1270, 1200, 1155, 1100, 1080, 1060, 980 cm^{-1}; ^1H NMR (300 MHz in $CDCl_3$): δ= 1.27 (3H, d, *J*=6.0 Hz, 6-H), 2.26 (3H, s, $-CO_2CH_2COCH_3$), 3.38 (3H, s, 4-OMe), 3.47 (2H, s, $-CO_2CH_2COCH_3$), 3.97 (1H, ddd, *J*=5.5, 4.0, 0.5 Hz, 4-H), 5.12 (1H, dq, *J*=4.0, 6.0 Hz, 5-H), 6.32 (1H, ddd, *J*=15.1, 7.4, 0.5 Hz, 2-H), 6.68 (1H, dd, *J*=15.1, 5.5 Hz, 3-H), 9.61 (1H, d, *J*=7.4 Hz, 1-H).

(b) *Michael addition*: to a solution of (±)-**7** (503 mg, 2.21 mmol) in benzene (20 ml) was added potassium carbonate (8.0 mg, 0.055 mmol) and 18-crown-6 (60.0 mg, 0.227 mmol) and the mixture was stirred at room temperature for 3 h under argon. It was concentrated in vacuo and the residue was chromatographed over silica gel (20 g) and elution with hexane/ethyl acetate (3:1–2:1) gave a mixture of hemiacetals (±)-**8** (459 mg, α-OH/β-OH=1:1.7) as

a slightly yellow viscous oil. Though this oil contained small amount of impurities, it was used in the next step without further purification.

IR (film): ν=3380 (br), 2990, 2980, 2960, 2940, 1680, 1590, 1450, 1380, 1360, 1320, 1310, 1285, 1265, 1205, 1140, 1120, 1105, 1085, 1030, 1020, 980 cm^{-1}; ^1H NMR (300 MHz in $CDCl_3$) *for β-isomer*: δ=1.43 (3H, d, J=6.0 Hz, 3-Me), 1.51 (1H, m, 5-H_{ax}), 2.31 (3H, s, 8-Me), 2.33 (1H, m, 5-H_{eq}), 2.81 (1H, m, 4a-H), 2.83 (1H, dd, J=10.0, 9.0 Hz, 4-H), 3.51 (3H, s, 4-OMe), 4.12 (1H, br, 6-OH), 4.24 (1H, dq, J=9.0, 6.0 Hz, 3-H), 5.64 (1H, br, 6-H); *for α-isomer*: δ=1.42 (3H, d, J=6.1 Hz, 3-Me), 1.51 (1H, m, 5-H_{ax}), 2.31 (3H, s, 8-Me), 2.50 (1H, ddd, J=12.4, 5.0, 2.5 Hz, 5-H_{eq}), 2.61 (1H, m, 4a-H), 2.81 (1H, dd, J=10.0, 9.2 Hz, 4-H), 3.54 (3H, s, 4-OMe), 4.14 (1H, dq, J=9.2, 6.1 Hz, 3-H), 4.49 (1H, br, 6-OH), 5.36 (1H, br d, J=9.0 Hz, 6-H).

(c) *Aldol reaction*: to a solution of (±)-**8** (434 mg, 2.07 mmol) in benzene (15 ml) was added potassium carbonate (7.5 mg, 0.054 mmol) and 18-crown-6 (60.0 mmol, 0.227 mmol), and the mixture was refluxed for 2 h under argon. After cooling, it was concentrated in vacuo and the residue was chromatographed over silica gel (15 g). Elution with hexane/ethyl acetate (1:1) gave a mixture of aldol products (±)-**9** (370 mg, α-OH/β-OH=1:3.3, 78% in two steps from (±)-**7**) as a yellow oil.

n_D^{25} 1.4864; IR (film): ν=3440 (br), 2980, 2940, 2910, 2840, 1650, 1645, 1630, 1615, 1455, 1410, 1355, 1305, 1270, 1230, 1175, 1140, 1095, 1080, 1060 cm^{-1}; ^1H NMR (500 MHz in $CDCl_3$) *for β-isomer*: δ=1.34 (1H, m, 5-H_{ax}), 1.45 (3H, d, J=6.3 Hz, 3-Me), 1.75 (1H, br, 6-OH), 2.31 (1H, m, 5-H_{eq}), 2.44 (1H, d, J=19.5 Hz, 7-H_{ax}), 2.63 (1H, ddd, J=19.5, 4.6, 1.6 Hz, 7-H_{eq}), 2.84 (2H, m, 4-H and 4a-H), 3.53 (3H, s, 4-OMe), 4.25 (1H, dq, J=9.0, 6.3 Hz, 3-H), 4.42 (1H, m, 6-H), 13.23 (1H, s, 8-OH); *for α-isomer*: δ=1.30 (1H, m, 5-H_{ax}), 1.46 (3H, d, J=6.3 Hz, 3-Me), 1.75 (1H, br, 6-OH), 2.36 (1H, dt, J=2.7, 10.0 Hz, 7-H_{ax}), 2.43 (1H, m, 4a-H), 2.51 (1H, m, 5-H_{eq}), 2.80 (1H, m, 4-H and 7-H_{eq}), 3.56 (3H, s, 4-OMe), 4.01 (1H, dddd, J=11.4, 10.0, 6.4, 3.5 Hz, 6-H), 4.17 (1H, dq, J=9.4, 6.3 Hz, 3-H), 13.17 (1H, s, 8-OH). Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found: C, 58.11; H, 7.37.

(d) *Michael-aldol reaction*: to a solution of (±)-**7** (95.6 mg, 0.419 mmol), obtained by the above procedure (a), in benzene (5 ml) was added potassium carbonate (1.5 mg, 0.011 mmol) and 18-crown-6 (12.0 mg, 0.0455 mmol) and the mixture was stirred for 4 h under argon. After confirming the completion of hemiacetal formation by TLC, the reaction mixture was heated and refluxed for further 2 h. It was concentrated in vacuo and the residue was chromatographed over silica gel (4 g) and elution with hexane/ethyl acetate (2:1–1:1) gave a mixture of hemiacetals (±)-**9** (69.4 mg, α-OH/β-OH=1:3.3, 73%) as a slightly yellow oil.

3.2.4.2. Method B: one-pot reaction. (a) *Racemate*: diketene (60.0 ml, 0.778 mmol) was added dropwise to a solution of δ-hydroxy-α,β-unsaturated aldehyde (±)-**6b** (105.7 mg, 0.734 mmol) and DMAP (4.6 mg, 0.038 mmol) in benzene (3 ml) at room temperature under argon. The mixture was stirred at room temperature, and the esterification completed within 15 min (by TLC monitoring). Potassium carbonate (3.6 mg, 0.026 mmol) and 18-crown-6 (30.6 mg, 0.116 mmol) were then added to the mixture and the whole was stirred at room temperature for 4.5 h. After TLC indicated the completion of the hemiacetal formation, the reaction mixture was heated and refluxed for further 4 h. It was concentrated in vacuo and the residue was chromatographed over silica gel (5 g) and elution with hexane/ethyl acetate (2:1–0:1) gave a mixture of hemiacetals (±)-**9** (102 mg, α-OH/β-OH=1:2.5, 61%) as a slightly yellow oil.

(b) *(3R,4S,4aR)-Isomer*: in the same manner as above, (4*S*,5*R*)-**6b** (597.7 mg, 4.15 mmol) in benzene (30 ml) was treated successively with DMAP (25.0 mg, 0.205 mmol), diketene (335 ml, 4.34 mmol), cesium carbonate (47.0 mg, 0.144 mmol), and 18-crown-6 (175 mg, 0.663 mmol) to give (3*R*,4*S*,4a*R*)-**9** (788 mg, α-OH/β-OH=1:3.3, 83%) as a slightly yellow oil.

$[\alpha]_D^{26}$ +89.0 (*c* 0.900, $CHCl_3$); n_D^{25} 1.5229; its IR and ^1H NMR spectra were identical with those of (±)-**9**. Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found: C, 57.84; H, 7.26.

3.2.5. (3*R*,4*S*,4a*R*)-8-Hydroxy-4-methoxy-3-methyl-3,4,4a,5-tetrahydro-1*H*-2-benzopyran-1-one (10). (a) *Racemate*: to a solution of (±)-**9** (270 mg, 1.18 mmol) in dry benzene (20 ml) was added Burgess reagent (320 mg, 1.34 mmol) at room temperature and the mixture was refluxed for 2.5 h under argon. After cooling, it was concentrated in vacuo and the residue was chromatographed over silica gel (9 g). Elution with hexane/ethyl acetate (2:1) gave (±)-**10** (154.5 mg, 62%) as colorless solid. A portion of this solid was recrystallized from hexane/ethyl acetate (10:1) for analysis to give pure (±)-**10** as colorless leaflets.

Mp 71.5–72.0 °C; IR (KBr): ν=2990, 2980, 2940, 2930, 2885, 2840, 1650, 1620, 1580, 1440, 1410, 1390, 1380, 1360, 1340, 1315, 1250, 1180, 1095, 1080 cm^{-1}; ^1H NMR (500 MHz in $CDCl_3$): δ=1.48 (3H, d, J=6.2 Hz, 3-Me), 2.05 (1H, ddt, J=3.0, 2.5, 17.0 Hz, 5-H), 2.06 (1H, dt, J=17.0, 6.4 Hz, 5-H), 2.79 (1H, ddd, J=17.0, 9.6, 6.4 Hz, 4a-H), 3.04 (1H, t, J=9.6 Hz, 4-H), 3.55 (3H, s, 4-OMe), 4.16 (1H, dq, J=9.6, 6.2 Hz, 3-H), 6.08 (1H, dd, J=9.8, 3.0 Hz, 7-H), 6.49 (1H, ddd, J=9.8, 6.4, 2.5 Hz, 6-H), 12.85 (1H, s, 8-OH). Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.79; H, 6.70.

(b) *(3R,4S,4aR)-Isomer*: in the same manner as above, a solution of (3*R*,4*S*,4a*R*)-**9** (788 mg, 3.46 mmol) in dry benzene (50 ml) was treated with Burgess reagent (1.03 g, 4.33 mmol) to afford (3*R*,4*S*,4a*R*)-**10** (437 mg, 60%) as colorless solid. This was recrystallized twice from hexane/ethyl acetate (20:1) to give pure (3*R*,4*S*,4a*R*)-**10** (270 mg, 62% recovery) as colorless needles.

Mp 92.0–93.5 °C; $[\alpha]_D^{19}$ +253 (*c* 0.595, $CHCl_3$); its IR and ^1H NMR spectra were identical with those of (±)-**10**. Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.91; H, 6.69.

3.2.6. Mosher ester of 10 [determination of enantiomeric purity of (3*R*,4*S*,4a*R*)-10]. (a) *From racemate*: a solution of (±)-**10** (2.0 mg, 9.5 μmol) in dry dichloromethane (0.5 ml)

were added triethylamine (0.1 ml) and DMAP (trace amount). (*S*)-MTPACl (20 μl, 107 μmol) was added to this mixture at room temperature and stirred for 2 h. The reaction mixture was purified directly using preparative silica gel TLC with hexane/ether (1:2) to give (*R*)-MTPA ester of (±)-**10** (3.0 mg, 74%).

(b) *From (3R,4S,4aR)-isomer*: in the same procedure as above, a solution of (3*R*,4*S*,4a*R*)-**10** (2.9 mg, 13.8 μmol) in dry dichloromethane (0.5 ml) was treated with triethylamine (0.1 ml), DMAP (trace amount), (*S*)-MTPACl (30 μl, 161 μmol) to give (*R*)-MTPA ester of (3*R*,4*S*,4a*R*)-**10** (**13a**) (4.0 mg, 68%).

^{1}H NMR (300 MHz in $CDCl_3$) *for (R)-MTPA ester of (3R,4S,4aR)-**10***: δ=1.47 (3H, d, *J*=6.3 Hz, 3-Me), 2.19 (1H, tt, *J*=18.3, 2.8 Hz, 5-H_{ax}), 2.58 (1H, dt, *J*=18.3, 6.3 Hz, 5-H_{eq}), 2.92 (1H, ddd, *J*=18.3, 9.5, 6.3 Hz, 4a-H), 3.22 (1H, t, *J*=9.5 Hz, 4-H), 3.54 (3H, s, 4-OMe), 3.72 (3H, br s, –OMe of MTPA), 4.20 (1H, dq, *J*=9.5, 6.3 Hz, 3-H), 5.76 (1H, dd, *J*=10.2, 2.8 Hz, 7-H), 6.46 (1H, ddd, *J*=10.2, 6.3, 2.8 Hz, 6-H), 7.44 (3H, m, Ar-H), 7.72 (2H, m, Ar-H); *for (R)-MTPA ester of (3S,4R,4aS)-**10*** (partial): δ=3.65 (3H, br s, –OMe of MTPA), 5.80 (1H, dd, *J*=10.0, 3.2 Hz, 7-H).

From the integral values of each MeO group of MTPA, the enantiomeric purities of (3*R*,4*S*,4a*R*)-**10** were established to be 93.6% ee (before recrystallization) and ~100% ee (after recrystallization).

3.2.7. (3*R*,4*S*,4a*R*,6*R*)-6-Bromo-4,8-dihydroxy-3-methyl-3,4,4a,5,6,7-hexahydro-1*H*-2-benzopyran-1-one (11). (a) *Racemate*: a solution of BBr_3 in dichloromethane (1.0 M, 2.6 ml, 2.6 mmol) was added to a solution of (±)-**10** (170 mg, 0.810 mmol) in dry dichloromethane (10 ml) at 0 °C under argon, and the mixture was stirred for 1 h. It was poured into water and extracted with ether. The organic layer was washed with brine, dried with anhydrous magnesium sulfate, and concentrated in vacuo. The residue was chromatographed over silica gel (5 g) and elution with hexane/ethyl acetate (3:1–1:1) gave (±)-**11** (168 mg, containing small amount of (±)-**1**) and trace amount of (±)-6-*epi*-**11** (<1%) both as slightly brown oils. A portion of (±)-**11** was purified with preparative silica gel TLC using benzene/ethyl acetate (3:1) to give pure (±)-**11** as slightly brown viscous oil. The α-bromo isomer was purified with preparative silica gel TLC using hexane/ethyl acetate (1:1) to give a solid, which was recrystallized from hexane/ether (1:1) to afford pure (±)-isomer as slightly pink needles.

*Compound (±)-**11***: IR (film): ν=3410 (br), 2960, 2860, 1650, 1640, 1610, 1455, 1410, 1380, 1350, 1300, 1285, 1260, 1230, 1185, 1165, 1120, 1060, 1040 cm^{-1}; ^{1}H NMR (500 MHz in $CDCl_3$): δ=1.48 (3H, d, *J*=6.3 Hz, 3-Me), 1.53 (1H, ddd, *J*=13.8, 11.0, 2.5 Hz, 5-H_{ax}), 2.07 (1H, br, 4-OH), 2.53 (1H, br ddt, *J*=13.8, 1.5, 4.0 Hz, 5-H_{eq}), 2.90 (1H, br dd, *J*=20.0, 1.5 Hz, 7-H_{eq}), 3.01 (1H, br m, 4a-H), 3.16 (1H, ddd, *J*=20.0, 5.4, 2.5 Hz, 7-H_{ax}), 3.34 (1H, dd, *J*=10.0, 9.2 Hz, 4-H), 4.30 (1H, dq, *J*=9.2, 6.3 Hz, 3-H), 4.71 (1H, br, 6-H), 13.21 (1H, s, 8-OH). Anal. Calcd for $C_{10}H_{13}BrO_4$: C, 43.34; H, 4.73. Found: C, 43.29; H, 4.68.

*Compound (±)-6-epi-**11***: IR (KBr): ν=3520, 2930, 2920, 1640, 1590, 1455, 1420, 1410, 1375, 1340, 1310, 1280, 1260, 1235, 1190, 1060 cm^{-1}; ^{1}H NMR (500 MHz in $CDCl_3$): δ=1.47 (3H, d, *J*=6.3 Hz, 3-Me), 1.69 (1H, q, *J*=12.0 Hz, 5-H_{ax}), 1.97 (1H, br d, *J*=5.5 Hz, 4-OH), 2.55 (1H, br m, 4a-H), 2.80 (1H, m, 5-H_{eq}), 2.85 (1H, ddd, *J*=18.5, 10.8, 2.4 Hz, 7-H_{ax}), 3.05 (1H, br dd, *J*=18.5, 6.2 Hz, 7-H_{eq}), 3.28 (1H, br ddd, *J*=10.0, 9.2, 5.5 Hz, 4-H), 4.14 (1H, m, 6-H), 4.18 (1H, dq, *J*=9.2, 6.3 Hz, 3-H), 13.15 (1H, s, 8-OH).

(b) *(3R,4S,4aR,6R)-Isomer*: in the same manner as above, a solution of (3*R*,4*S*,4a*R*)-**10** (210 mg, 1.00 mmol) in dry dichloromethane (15 ml) was treated with a solution of BBr_3 in dichloromethane (1.0 M, 3.3 ml, 3.3 mmol) at 0 °C for 2 h to give a mixture of (3*R*,4*S*,4a*R*,6*R*)-**11** and (3*R*,4*S*,4a*R*)-**1** (190 mg, ~80%, **11/1**=54:46) as a slightly brown amorphous solid, and the (6*S*)-isomer (3.9 mg, 1%) as colorless solid. A portion of (3*R*,4*S*,4a*R*,6*R*)-**11** was purified for analysis with preparative silica gel TLC using benzene/ethyl acetate (3:1) to give a solid, which was recrystallized from hexane/ethyl acetate (1:1) to give pure (3*R*,4*S*,4a*R*,6*R*)-**11** as slightly pink prisms. And the α-Br-isomer was purified with preparative silica gel TLC using hexane/ethyl acetate (1:1) to give a solid, which was recrystallized from hexane/ether (2:1) to afford pure (3*R*,4*S*,4a*R*,6*S*)-isomer as slightly pink needles.

*Compound (3R,4S,4aR,6R)-**11***: mp 123.0–123.5 °C; $[\alpha]_D^{20}$ +111 (*c* 0.320, $CHCl_3$); its IR and ^{1}H NMR spectra were identical with those of (±)-**11**. Anal. Calcd for $C_{10}H_{13}BrO_4$: C, 43.34; H, 4.73. Found: C, 43.80; H, 4.75.

(6S)-Isomer: mp 131.0–132.0 °C (sealed tube); its IR and ^{1}H NMR spectra were identical with those of the racemate.

3.2.8. (3*R*,4*S*,4a*R*)-4,8-Dihydroxy-3-methyl-3,4,4a,5-tetrahydro-1*H*-2-benzopyran-1-one (1). (a) *Racemate*: to a solution of (±)-**11** (164 mg, containing small amount of (±)-**1**) in benzene (5 ml) was added DBU (90.0 μl, 0.603 mmol) dropwise under argon, and the mixture was stirred at room temperature for 30 min. It was poured into water and extracted with ether. The organic layer was washed with brine, dried with anhydrous magnesium sulfate, and concentrated in vacuo. The residue was chromatographed over silica gel (5 g) and elution with hexane/ethyl acetate (5:1–1:1) gave (±)-**1** (89.9 mg, 58% in two steps from **10**) as colorless solid. This was recrystallized from hexane/ethyl acetate (3:2) to afford pure (±)-**1** as colorless needles.

Mp 134.0–135.0 °C; IR (KBr): ν=3400, 2980, 2920, 2880, 1650, 1610, 1580, 1410, 1390, 1370, 1345, 1310, 1250 (sh), 1240, 1190, 1065 cm^{-1}; ^{1}H NMR (500 MHz in $CDCl_3$): δ=1.47 (3H, d, *J*=6.3 Hz, 3-Me), 2.01 (1H, dddd, *J*=17.0, 16.8, 3.0, 2.2 Hz, 5-H_{ax}), 2.26 (1H, d, *J*=6.0 Hz, 4-OH), 2.67 (1H, dt, *J*=17.0, 6.3 Hz, 5-H_{eq}), 2.76 (1H, ddd, *J*=16.8, 9.5, 6.3 Hz, 4a-H), 3.46 (1H, dt, *J*=6.0, 9.5 Hz, 4-H), 4.16 (1H, dq, *J*=9.5, 6.3 Hz, 3-H), 6.08 (1H, dd, *J*=9.8, 3.0 Hz, 7-H), 6.51 (1H, ddd, *J*=9.8, 6.3, 2.2 Hz, 6-H), 12.81 (1H, s, 8-OH); ^{13}C NMR (125 MHz in $CDCl_3$): δ=17.8, 27.6, 37.5, 74.4, 78.1, 90.5, 124.4, 140.3, 169.2, 170.9. Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.13; H, 6.13.

(b) *(3R,4S,4aR)-Isomer*: in the same manner as above, a mixture of (3*R*,4*S*,4a*R*,6*R*)-**11** and (3*R*,4*S*,4a*R*)-**1** (46.2 mg, **11/1**=54:46) was treated with DBU (30.0 μl, 0.201 mmol) in benzene at room temperature to give (3*R*,4*S*,4a*R*)-**1** as slightly orange solid. This was recrystallized from hexane/ethyl acetate (1:1) to afford pure (3*R*,4*S*,4a*R*)-**1** (36.9 mg, 77% in two steps from **10**) as colorless needles.

Mp 141.0–143.5 °C; $[\alpha]_D^{22}$ +150 (*c* 0.545, $CHCl_3$); its IR, ^1H NMR, and ^{13}C NMR spectra were identical with those of (±)-**1**. Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 60.85; H, 6.07.

3.2.9. Bis Mosher ester of 1 [determination of enantiomeric purity of (3*R*,4*S*,4a*R*)-1]. (a) *Bis (R)-MTPA ester of (±)-**1***: to a mixture of (±)-**1** (2.6 mg, 13.3 μmol) in dichloromethane (0.5 ml) were added triethylamine (0.1 ml), DMAP (trace amount), and (*S*)-MTPACl (30 μl, 161 μmol) and the mixture was stirred at room temperature for 2.5 h. It was purified directly using preparative TLC with hexane/ethyl acetate (1:1) to give bis (*R*)-MTPA ester of (±)-**1** (5.0 mg, 91%).

(b) *Bis (R)-MTPA ester of (3R,4S,4aR)-**1***: in the same procedure as above, a solution of (3*R*,4*S*,4a*R*)-**1** (2.0 mg, 10.2 mmol) in dichloromethane (0.5 ml) was treated with triethylamine (0.1 ml), DMAP (trace amount), (*S*)-MTPACl (30 ml, 161 mmol) to give bis (*R*)-MTPA ester of (3*R*,4*S*, 4a*R*)-**1** (3.8 mg, 90%).

^1H NMR (300 MHz in $CDCl_3$): δ=1.20 (3H, d, *J*=6.4 Hz, 3-Me), 2.23 (2H, m, 5-H), 3.12 (1H, m, 4a-H), 3.55 (3H, s, –OMe), 3.69 (3H, s, –OMe), 4.34 (1H, dq, *J*=9.5, 6.4 Hz, 3-H), 5.14 (1H, t, *J*=9.5 Hz, 4-H), 5.79 (1H, dd, *J*=10.7, 1.3 Hz, 7-H), 6.40 (1H, m, 6-H), 7.44 (6H, m, Ar-H), 7.56 (2H, m, Ar-H), 7.70 (2H, m, Ar-H).

Enantiomeric purity of (3*R*,4*S*,4a*R*)-**1** was determined to be 98.8% ee by HPLC analysis of its bis (*R*)-MTPA ester [(3*R*,4*S*,4a*R*)-isomer: t_R=28.9 min (99.4%), (3*S*,4*R*,4a*S*)-isomer: t_R=31.6 min (0.6%), Senshu Pack Silica-1251-N (4.6 mm ϕ×250 mm), hexane/EtOAc (8:1), 1.0 ml/min].

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