Resolution and Utilization of Ethyl 5-Hydroxycyclopent-1-enecarboxylate: Enantioselective Synthesis of (+)-Mitsugashiwalactone and (−)-Dolichodial

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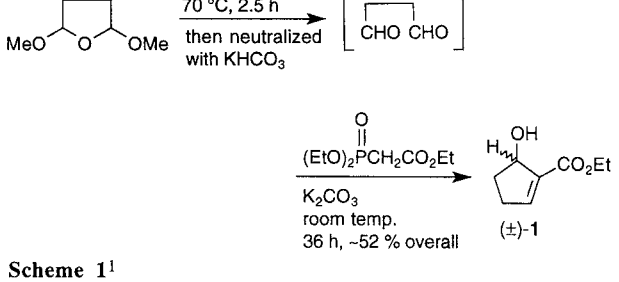
Received 17 October 1994

Optically pure ethyl 5-hydroxycyclopent-1-enecarboxylate has been obtained with its acetate in both enantiomeric forms in excellent optical yields from racemic ethyl 5-hydroxycyclopent-1-enecarboxylate by lipase-mediated kinetic resolution. The optically pure (*R*)-enantiomer thus obtained has been transformed into two naturally occurring iridoid monoterpenes, (+)-mitsugashiwalactone and (−)-dolichodial.

Racemic ethyl 5-hydroxycyclopent-1-enecarboxylate **(1)** was readily obtained in a single step operation by reaction of succinaldehyde, generated in situ from 2,5-dimethoxytetrahydrofuran, and a phosphonate ester in an aqueous potassium carbonate solution[1] (Scheme 1). Since the product **1** carries an ester functionality on a cyclic allylic alcohol system, we assumed that it would be a highly versatile chiral building block if we could resolve it in an efficient manner. We, therefore, examined the resolution of (±)-**1** employing the lipase-mediated kinetic acylation–deacylation method[2] and report here the successful acquisition of optically pure **1** and its utilization as a chiral building block[3] for the enantiocontrolled synthesis of two naturally occurring iridoid monoterpenes, (+)-mitsugashiwalactone[4] **(4)** and (−)-dolichodial[5] **(12)**.

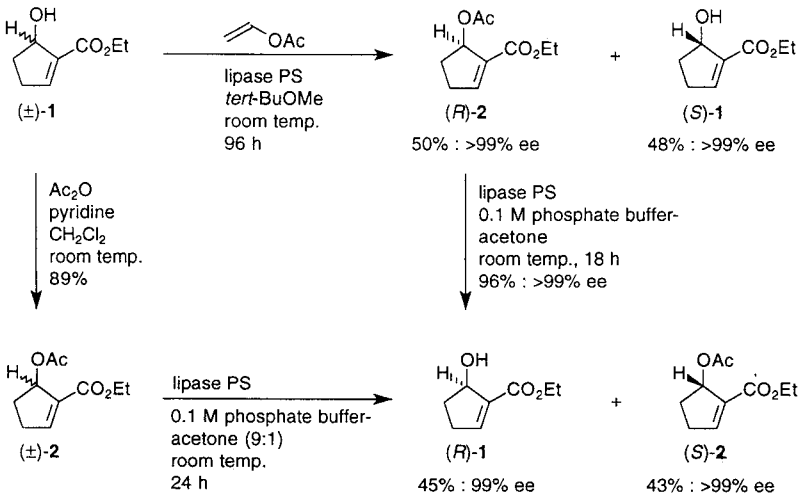


Scheme 1[1]

We first treated the racemic alcohol (±)-**1** with an excess of vinyl acetate in *tert*-butyl methyl ether in the presence of lipase PS on Celite (*Pseudomonas* sp., Amano) at room temperature.[6] The reaction terminated after 96 hours to give the (*R*)-acetate (*R*)-**2** and the unchanged (*S*)-alcohol (*S*)-**1** in yields of 50 and 48%, respectively. Optical purities of the both products were determined to be more than 99% ee by HPLC using a chiral column (Scheme 2).

We next treated the racemic acetate (±)-**2**, prepared from (±)-**1**, in a phosphate buffer solution in the presence of the same lipase above at room temperature. The reaction was terminated after 24 hours to give (*R*)-alcohol[7] (*R*)-**1** and the unchanged (*S*)-acetate[7] (*S*)-**2** in 45 and 43% yields. Optical purities of the both products could be determined by HPLC using a chiral column which revealed the former to be 99% ee and the latter to be more than 99% ee (Scheme 2).

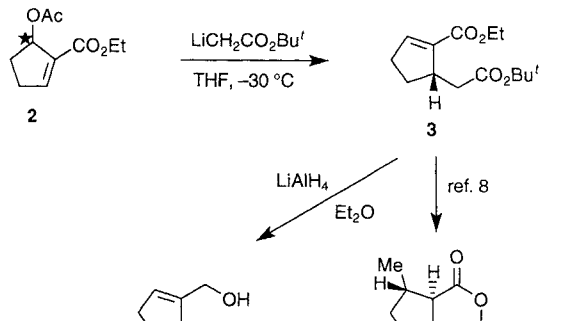
Although it is not unexpected that a lipase catalyzes both acylation and deacylation at the same particular chiral center, the observed clear-cut reactions in both directions at the *R*-center was noteworthy as enantiocomplementary preparation of the alcohol **1** and the acetate **2** is now possible depending on the conditions employed. This was also found to be particularly useful for the transformation of the optically pure (*R*)-acetate (*R*)-**2** into the (*R*)-alcohol (*R*)-**1** which could be accomplished in 96% yield without loss of the original optical purity. When the same acetate was subjected to ethanolysis conditions in the presence of potassium carbonate, the yield of (*R*)-**1** decreased to 32% accompanied by a considerable amount (49%) of the addition–elimination product although racemization of the former compound did not occur. On the other hand, the same acetate brought about complete racemization under acid-catalyzed hydrolysis although



Scheme 2

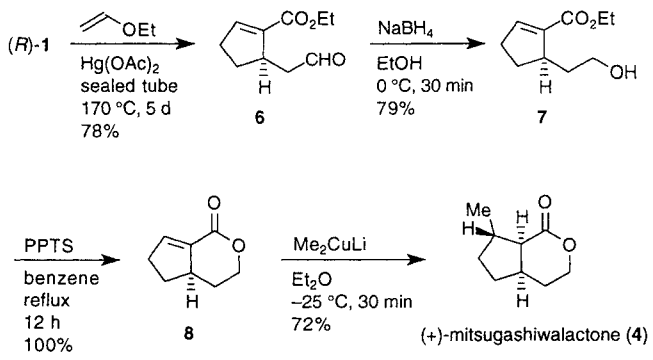
the reaction proceeded in a satisfactory manner (Scheme 2).

The report[8] that the racemic acetate (±)-**2** reacted with *tert*-butyl lithioacetate to give the diester **3** as the key intermediate for the synthesis of racemic mitsugashiwalactone **(4)**, prompted us to find out the stereochemical outcome of the same reaction between the optically active acetate **2** and the lithioacetate. We, therefore, treated (*R*)-**2** with *tert*-butyl lithioacetate under the established conditions[8] to give the diester **3** in 63% yield. However, the optical purity of the product was found to be only 33% ee (Scheme 3).



Scheme 3

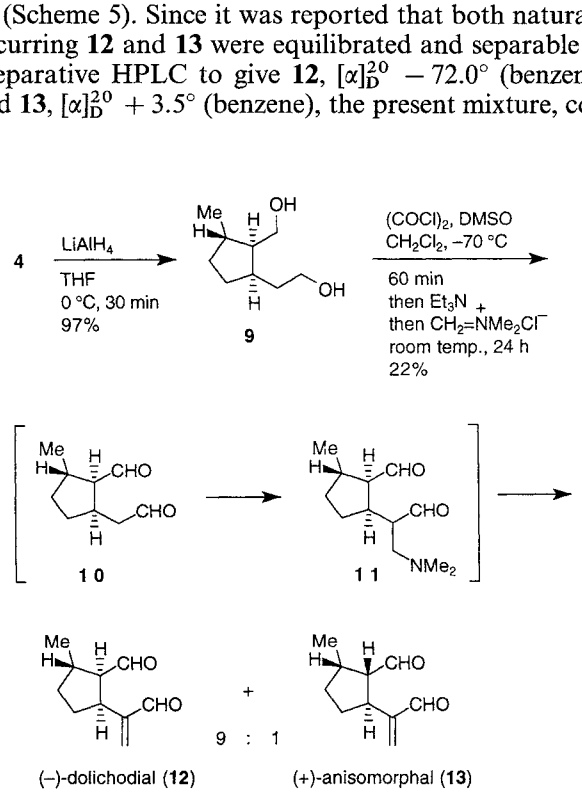
Having concluded the incapable applicability of the racemic procedure[8] to the chiral acetate **2**, an alternative procedure starting from the (*R*)-alcohol (*R*)-**1** by employing the Claisen rearrangement to acquire optically pure natural (+)-mitsugashiwalactone **(4)** was devised (Scheme 4). Thus (*R*)-**1** was first treated with ethyl vinyl ether in the presence of mercury(II) acetate[9] in a sealed tube at 170 °C to furnish to γ,δ-unsaturated aldehyde **6** in 78% yield. The original chiral integrity was retained intact under the conditions which was confirmed by HPLC using a chiral column. This compound was reduced with lithium aluminium hydride to give the diol **5** which was found to be enantiomeric with the diol **5** obtained from the diester **3** above. This clarified the stereochemistry of the reaction between the (*R*)-acetate (*R*)-**2** and *tert*-butyl lithioacetate which proceeded competitively via both S_N2 and S_N2' pathways.



Scheme 4

To obtain natural (+)-mitsugashiwalactone **(4)**, **6** was next treated with sodium borohydride to allow chemoselective reduction to give the hydroxy ester **7** in 79% yield which cyclized on reflux in benzene containing a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS)[10] to yield the δ-lactone **8**, quantitatively. Finally, **8** was exposed to lithium dimethylcuprate prepared in situ to furnish (+)-mitsugashiwalactone[11] **(4)**, isolated from *Menyanthes trifoliata*, in 72% yield as a single stereoisomer, in which the conjugate addition occurred stereoselectively from the less hindered face of the molecule.[8] The overall yield of **4** from (*R*)-**1** was 44% in 4 steps.

The synthesis of (−)-dolichodial **(12)**, a powerful lachrymatory monoterpene which occurs in both insects[5a] and a plant[5b] and whose stereochemistry was determined only by chemical correlations,[5] was attempted next starting from (+)-mitsugashiwalactone **(4)**. We previously discovered[12] the general one-pot procedure for the construction of α-methylenealdehyde functionality by treating a substrate having a 2-hydroxyethyl functionality with methylenedimethylammonium chloride[13] under Swern oxidation conditions.[14] To apply these Swern–Mannich conditions for the construction of the α-methylenealdehyde functionality of (−)-dolichodial **(12)**, (+)-mitsugashiwalactone **(4)** was first reduced with lithium aluminium hydride to give the diol **9** in 97% yield. On Swern oxidation followed by exposure to methylenedimethylammonium chloride in the same flask, the diol **9** furnished (−)-dolichodial[5] **(12)** accompanied by a minor amount of an epimerized product presumed[5b] to be another naturally occurring monoterpene (+)-anisomorphal[15] **(13)** in 22% total yield as a 9:1 mixture via transient intermediates, the dialdehyde **10** and the Mannich base **11** (Scheme 5). Since it was reported that both naturally occurring **12** and **13** were equilibrated and separable by preparative HPLC to give **12**, $[\alpha]_D^{20}$ −72.0° (benzene), and **13**, $[\alpha]_D^{20}$ +3.5° (benzene), the present mixture, con-



Scheme 5

sisting of 9 parts of **12** and 1 part of **13** showing $[\alpha]_D^{30}$ $-68.8°$ (benzene), could be safely concluded to be a mixture of the natural enantiomers having the absolute configurations shown. Thus, synthesis of (−)-dolichodial **(12)** has been accomplished for the first time and the configuration of the natural product has been established unambiguously.

In conclusion, we have demonstrated an efficient preparation of optically pure ethyl 5-hydroxycyclopent-1-enecarboxylate and its acetate in both enantiomeric forms by lipase-mediated enantiocomplementary resolution and an utilization of the (*R*)-enantiomers for the construction of naturally occurring monoterpenes, (+)-mitsugashiwalactone and (−)-dolichodial, the latter of which was synthesized for the first time.

IR spectra were recorded on a JASCO-IR-700 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Hitachi R-3000 (300 and 75 MHz) and JEOL FX 90A (90 MHz) and JNM-GX500 (500 MHz) spectrometers. Mass specta were measured on a JEOL JMS-DX303 instrument. Optical rotations were measured with a JASCO-DIP-370 digital polarimeter. Optical purities were determined on a Gilson Model-307 instrument equipped with a chiral column. For all new compounds satisfactory microanalyses obtained: C ± 0.29, H ± 0.31.

Racemic Ethyl 5-Hydroxycyclopent-1-enecarboxylate [(±)-1]:[1]

A mixture of 2,5-dimethoxytetrahydrofuran (13.0 mL, 100 mmol) and 0.6 N HCl (80 mL) was stirred at 70 °C for 2.5 h. After cooling to 0 °C, the mixture was neutralized with 10% (w/v) $KHCO_3$ and ethyl diethylphosphonoacetate (20.0 mL, 101 mmol) and 6.4 M K_2CO_3 (32.0 mL, 204 mmol) were added at the same temperature. The mixture was then stirred at r.t. for 36 h and extracted with EtOAc (3 × 200 mL). The extract was washed with brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was distilled under vacuum to give racemic alcohol (±)-**1** as a colorless oil; yield: 8.11 g (52%); bp 49–50 °C/0.06 Torr (Lit.[1] bp 70–71 °C/0.4 Torr).

IR (neat): $\nu = 3462, 1714, 1633\ cm^{-1}$.

^1H NMR ($CDCl_3$, 90 MHz): $\delta = 6.91$ (1 H, t, $J = 1.8$ Hz), 5.18 (1 H, br s), 4.24 (2 H, q, $J = 7.1$ Hz), 2.92 (1 H, d, $J = 2.2$ Hz), 2.75–2.41 (2 H, m), 2.38–2.24 (1 H, m), 2.02–1.75 (1 H, m), 1.32 (3 H, t, $J = 7.1$ Hz).

MS: $m/z = 156$ (M^+), 139 (100%).

Racemic Ethyl 5-Acetoxycyclopent-1-enecarboxylate [(±)-2]:

To a stirred solution of (±)-**1** (1.57 g, 10.1 mmol) in CH_2Cl_2 (20 mL) and pyridine (1.2 mL, 14.8 mmol) was added Ac_2O (2.0 mL, 21.2 mmol) dropwise at r.t. After 2 h, the mixture was diluted with Et_2O (50 mL) and washed with 10% (w/v) $CuSO_4$ (10 mL), brine (10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed on silica gel (70 g, eluent: EtOAc/hexane, 1:6) to give the racemic acetate (±)-**2** as a colorless oil; yield: 1.87 g (89%).

IR (neat): $\nu = 1720, 1639\ cm^{-1}$.

^1H NMR ($CDCl_3$, 90 MHz): $\delta = 7.09$ (1 H, t, $J = 1.8$ Hz), 6.1 (1 H, br s), 4.20 (2 H, q, $J = 7.1$ Hz), 2.66–2.44 (2 H, m), 2.43–2.20 (1 H, m), 2.04 (3 H, s), 2.00–1.84 (1 H, m), 1.28 (3 H, t, $J = 7.1$ Hz).

MS: $m/z = 198$ (M^+), 109 (100%).

Lipase-Mediated Acylation; Ethyl (*R*)-5-Acetoxycyclopent-1-enecarboxylate [(*R*)-2] and Ethyl (*S*)-5-Hydroxycyclopent-1-enecarboxylate [(*S*)-1]:

A suspension of (±)-**1** (4.97 g, 31.8 mmol), vinyl acetate (5.9 mL, 64 mmol), and lipase PS on Celite (*Pseudomonas* sp., Amano, 320 mg) in *t*-BuOMe (250 mL) was stirred at r.t. for 96 h. After filtering through a Celite pad, the filtrate was evaporated under reduced pressure and chromatographed on silica gel (300 g, eluent: EtOAc/hexane, 1:6) to give the acetate (*R*)-**2** as a colorless oil; yield: 3.14 g (50%); $[\alpha]_D^{29}$ $+2.6°$ ($c = 1.03$, $CHCl_3$) (> 99% ee by HPLC using chiral column, CHIRALCEL OD, eluent: 10% *i*-PrOH in hexane), and the alcohol (*S*)-**1** as a colorless oil; yield: 2.39 g (48%); $[\alpha]_D^{31}$ $-34.5°$ ($c = 1.10$, $CHCl_3$) (> 99% ee by HPLC using chiral column CHIRALCEL OD, eluent: 10% *i*-PrOH in hexane). Spectral data of (*S*)-**1** and (*R*)-**2** were identical with those of (±)-**1** and (±)-**2**, respectively.

Lipase-Mediated Deacylation; Ethyl (*R*)-5-Hydroxycyclopent-1-enecarboxylate [(*R*)-1] and Ethyl (*S*)-5-Acetoxycyclopent-1-enecarboxylate [(*S*)-2]:

A suspension of (±)-**2** (97 mg, 0.49 mmol) and lipase PS on Celite (51 mg) in a mixture of 0.1 M phosphate buffer and acetone (9:1, 5 mL) was stirred at r.t. for 24 h. After filtering through a Celite pad, the mixture was extracted with EtOAc (2 × 20 mL) and the extract was washed with brine (5 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed on silica gel (10 g, eluent: EtOAc/hexane, 1:4) to give the acetate (*S*)-**2** as a colorless oil; yield: 44 mg (45%); $[\alpha]_D^{29}$ $-2.6°$ ($c = 1.08$, $CHCl_3$) (> 99% ee by HPLC using chiral column, CHIRALCEL OD, eluent: 10% *i*-PrOH in hexane) and the alcohol (*R*)-**1** as a colorless oil; yield: 33 mg (43%); $[\alpha]_D^{30}$ $+34.2°$ ($c = 0.85$, $CHCl_3$) (99% ee by HPLC using chiral column, CHIRALCEL OD, eluent: 10% *i*-PrOH in hexane). Spectral data of (*R*)-**1** and (*S*)-**2** were identical with those of (±)-**1** and (±)-**2**, respectively.

Deacylation of Ethyl (*R*)-5-Acetoxycyclopent-1-enecarboxylate [(*R*)-2] by Ethanolysis:

A suspension of (*R*)-**2** (160 mg, 0.81 mmol) and K_2CO_3 (559 mg, 4.05 mmol) in EtOH (5 mL) was stirred at r.t. for 3 h. After being filtered through a Celite pad, the mixture was evaporated under reduced pressure and chromatographed on silica gel (5 g, eluent: Et_2O/hexane, 1:4) to give ethyl 5-ethoxycyclopent-1-enecarboxylate as a colorless oil; yield: 73 mg (49%) (34% ee by HPLC using chiral column, CHIRALCEL OD, eluent; 3% *i*-PrOH in hexane) and (*R*)-**1** as a colorless oil; yield: 40 mg (32%) (> 99% ee by HPLC using chiral column, CHIRALCEL OD, eluent: 10% *i*-PrOH in hexane).

Ethyl 5-Ethoxycyclopent-1-enecarboxylate:

IR (neat): $\nu = 1717, 1634\ cm^{-1}$.

^1H NMR ($CDCl_3$, 90 MHz): $\delta = 7.05–6.92$ (1 H, m), 4.80–4.60 (1 H, m), 4.22 (2 H, q, $J = 7.1$ Hz), 3.59 (2 H, q, $J = 7.1$ Hz), 3.00–2.35 (2 H, m), 2.35–1.80 (2 H, m), 1.30 (3 H, t, $J = 7.1$ Hz), 1.20 (3 H, t, $J = 7.1$ Hz).

MS: $m/z = 185$ ($M^+ + 1$), 140 (100%).

HRMS: m/z calc. for $C_{10}H_{17}O_3$ 185.1178 ($M^+ + 1$), found 185.1212.

Deacylation of Ethyl (*R*)-5-Acetoxycyclopent-1-enecarboxylate [(*R*)-2] by Lipase PS:

A suspension of (*R*)-**2** (> 99% ee: 3.60 g, 18.2 mmol) and lipase PS on Celite (1.83 g) in a mixture of 0.1 M phosphate buffer and acetone (9:1, 150 mL) was stirred at r.t. for 18 h. After filtering through a Celite pad, the mixture was extracted with EtOAc (300 mL × 2) and the extract was washed with brine (50 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed on silica gel (150 g, eluent: EtOAc/hexane, 1:4) to give the alcohol (*R*)-**1** as a colorless oil; yield: 2.73 g (96%); $[\alpha]_D^{30}$ $+34.4°$ ($c = 1.04$, $CHCl_3$) (> 99% ee by HPLC using chiral column, CHIRALCEL OD, eluent: 10% *i*-PrOH in hexane). Spectral data were identical with an authentic material.

Reaction of Ethyl (*R*)-5-Acetoxycyclopent-1-enecarboxylate with *tert*-Butyl Lithoacetate:

To a stirred solution of lithium diisopropylamide [prepared in situ from diisopropylamine (0.32 mL, 2.44 mmol) and 1.6 M BuLi (1.6 M in hexane, 1.5 mL, 2.4 mmol) in Et_2O (5 mL)] was added *tert*-butyl acetate (0.33 mL, 2.35 mmol) at −30 °C and stirring was continued for 30 min. To this stirred mixture was then added (*R*)-**2** (164 mg, 0.83 mmol) in Et_2O (5 mL) at the same temperature and stirring was continued for 50 min. The reaction was quenched by addition of sat. NH_4Cl solution and extracted with Et_2O (20 mL).

The extract was washed with brine (5 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed on silica gel (10 g, eluent: EtOAc/hexane, 1:20) to give the diester **3**; yield: 133 mg (63%) (33% ee by HPLC using chiral column, CHIRALCEL OD, eluent: 3% *i*-PrOH in hexane).

Diester **3**:

IR (neat): $\nu = 1715, 1629\ cm^{-1}$.

^1H NMR ($CDCl_3$, 300 MHz): $\delta = 6.84–6.76$ (1 H, m), 4.19 (2 H, dq, $J = 7.1, 2.6$ Hz), 3.31 (1 H, br s), 2.77 (1 H, dd, $J = 15.0, 3.3$ Hz), 2.60–2.32 (2 H, m), 2.32–2.13 (2 H, m), 1.82–1.69 (1 H, m), 1.44 (9 H, s), 1.29 (3 H, t, $J = 7.1$ Hz).

MS: $m/z = 198$ ($M^+ - 56$), 152 (100%).

Spectral data were virtually identical with those reported for racemic material (±)-**3**.[8]

Reduction of the Diester 3:

To a stirred suspension of $LiAlH_4$ (28 mg, 0.74 mmol) in Et_2O (2 mL) was added **3** (33% ee 95 mg, 0.37 mmol) in Et_2O (3 mL) dropwise at 0 °C. After stirring for 30 min at r.t., the reaction was quenched by addition of 29% NH_4OH (1 mL) and the mixture was filtered through a Celite pad and the filtrate was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica gel (5 g, eluent: MeOH/$CHCl_3$, 1:19) to give the diol **5**; yield: 22 mg (41%); $[\alpha]_D^{28} - 1.5°$ ($c = 0.25$, MeOH).

IR (neat): $\nu = 3340, 1649\ cm^{-1}$.

^1H NMR (CD_3OD, 300 MHz): $\delta = 5.62$ (1 H, br d, $J = 1.5$ Hz), 4.13 (2 H, br d, $J = 4.4$ Hz), 3.70–3.48 (2 H, m), 3.60 (1 H, s), 3.33 (1 H, br t, $J = 1.5$ Hz), 2.82–2.68 (1 H, m), 2.40–2.20 (2 H, m), 2.20–2.04 (1 H, m), 1.96–1.81 (1 H, m), 1.65–1.50 (1 H, m), 1.46–1.31 (1 H, m).

^{13}C NMR (CD_3OD, 75 MHz): $\delta = 146.1$ (s), 125.2 (d), 60.1 (t), 59.2 (t), 41.1 (d), 35.6 (t), 30.1 (t), 29.7 (t).

MS: $m/z = 142$ (M^+), 140 ($M^+ - 2$), 93 (100%).

HRMS: m/z calc. for $C_8H_{14}O_2$ 142.0994, found 142.0993.

(*R*)-(2-Ethoxycarbonylcyclopent-2-enyl)acetaldehyde (6):

A mixture of (*R*)-**1** (> 99% ee: 202 mg, 1.29 mmol) and $Hg(OAc)_2$ (52 mg, 0.16 mmol) in ethyl vinyl ether (10 mL) was heated in a sealed tube at 170 °C for 5 d. After cooling, the mixture was diluted with Et_2O (30 mL) and the ethereal solution was washed with sat. $NaHCO_3$ solution (5 mL), brine (5 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed on silica gel (15 g, eluent: Et_2O/hexane, 1:10) to give the aldehyde **6** as a colorless oil; yield: 183 mg (78%); $[\alpha]_D^{29} + 45.2°$ ($c = 1.16$, $CHCl_3$).

IR (neat): $\nu = 1710, 1626\ cm^{-1}$.

^1H NMR ($CDCl_3$, 300 MHz): $\delta = 9.79$ (1 H, t, $J = 1.8$ Hz), 6.87–6.81 (1 H, m), 4.20 (2 H, q, $J = 7.1$ Hz), 3.49–3.37 (1 H, m), 2.95 (1 H, ddd, $J = 16.9, 4.0, 1.5$ Hz), 2.62–2.22 (4 H, m), 1.70–1.56 (1 H, m), 1.30 (3 H, m, $J = 7.1$ Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 201.9$ (d), 164.7 (s), 145.0 (d), 138.1 (s), 60.3 (t), 48.3 (t), 38.7 (d), 31.6 (t), 30.2 (t), 14.3 (q).

MS: $m/z = 182$ (M^+), 136 (100%).

HRMS: m/z calc. for $C_{10}H_{14}O_3$ 182.0943, found 182.0943.

Reduction of the Aldehyde 6:

To a stirred suspension of $LiAlH_4$ (110 mg, 2.9 mmol) in Et_2O (7 mL) was added a solution of **6** (264 mg, 1.45 mmol) in Et_2O (3 mL) dropwise at 0 °C. After stirring for 30 min at r.t., the reaction was quenched by the addition of 29% NH_4OH (1 mL) and the mixture was filtered through a Celite pad and the filtrate was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica gel (15 g, eluent: MeOH/$CHCl_3$, 1:19) to give the diol **5**; yield: 118 mg (57%); $[\alpha]_D^{30} + 9.2°$ ($c = 0.68$, MeOH). Spectra data were identical with those of **5** obtained from **3**.

(*R*)-2-(2-Ethoxycarbonylcyclopent-2-enyl)ethanol (7):

To a stirred solution of **6** (523 mg, 2.87 mmol) in EtOH (12 mL) was added $NaBH_4$ (163 mg, 4.31 mmol) portionwise at 0 °C and stirring was continued for 30 min at r.t. The reaction was quenched by the addition of an appropriate amount of acetone and the mixture was evaporated under reduced pressure. The residue was extracted with EtOAc (30 mL) and the extract was washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica gel (40 g, eluent: EtOAc/hexane, 1:2) to give the primary alcohol **7**; yield: 415 mg (79%); $[\alpha]_D^{26} - 43.0°$ ($c = 1.01$, $CHCl_3$) (> 99% ee by HPLC using chiral column CHIRALCEL OB, eluent 3% *i*-PrOH in hexane).

IR (neat): $\nu = 3442, 1710, 1627\ cm^{-1}$.

^1H NMR ($CDCl_3$, 300 MHz): $\delta = 6.85–6.78$ (1 H, m), 4.21 (2 H, q, $J = 7.0$ Hz), 3.72–3.56 (2 H, m), 3.14–3.03 (1 H, m), 2.61–2.34 (2 H, m), 2.25–2.07 (2 H, m), 1.90–1.70 (1 H, m), 1.77–1.58 (2 H, m), 1.31 (3 H, t, $J = 7.0$ Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 165.6$ (s), 143.9 (d), 139.8 (s), 61.1 (t), 60.1 (t), 40.7 (d), 37.1 (t), 31.5 (t), 30.3 (t), 14.2 (q).

MS: $m/z = 184$ (M^+), 79 (100%).

HRMS: m/z calc. for $C_{10}H_{16}O_3$ 184.1099, found 184.1106.

(*R*)-5-(2-Hydroxyethyl)cyclopent-1-enecarboxylic Acid Lactone (8):

A solution of **7** (303 mg, 1.65 mmol) in benzene (10 mL) containing pyridinium *p*-toluenesulfonate (33 mg, 0.13 mmol) was refluxed for 12 h. After cooling, the mixture was diluted with EtOAc (30 mL) and the solution was washed with sat. $NaHCO_3$ solution (5 mL), brine ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica gel (20 g, eluent: EtOAc/hexane, 1:6) to give the δ-lactone **8**; yield: 228 mg (100%); $[\alpha]_D^{31} - 116.6°$ ($c = 0.93$, $CHCl_3$) (> 99% ee by HPLC using chiral column, CHIRALCEL OB, eluent: 3% *i*-PrOH in hexane).

IR (neat): $\nu = 1716, 1626\ cm^{-1}$.

^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.00$ (1 H, d, $J = 2.2$ Hz), 4.46 (1 H, ddd, $J = 11.4, 4.8, 1.8$ Hz), 4.32 (1 H, dt, $J = 11.7, 2.2$ Hz), 3.06–2.90 (1 H, m), 2.55–2.31 (3 H, m), 2.10 (1 H, br, dt, $J = 13.6, 2.2$ Hz), 1.76–1.53 (2 H, m).

^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 163.2$ (s), 144.9 (d), 134.8 (s), 69.5 (t), 42.0 (d), 32.6 (t), 31.6 (t), 30.8 (t).

MS: $m/z = 138$ (M^+), 79 (100%).

HRMS: m/z calc. for $C_8H_{10}O_2$ 138.0681, found 138.0684.

(+)-Mitsugashiwalactone (4):

To a solution of lithium dimethylcuprate [prepared in situ by mixing CuI (939 mg, 4.93 mmol) in Et_2O (5 mL) and MeLi in Et_2O (1.14 M, 87 mL, 9.92 mmol) at −25 °C] was added **8** (225 mg, 1.63 mmol) in Et_2O (5 mL) dropwise at −25 °C and stirring was continued for 30 min at the same temperature. The reaction was quenched by addition of sat. NH_4Cl solution and the mixture was extracted with Et_2O (30 mL × 3). The extract was washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica gel (10 g, eluent: EtOAc/hexane, 1:6) to give (+)-mitsugashiwalactone **(4)** as a colorless oil; yield: 180 mg (72%); $[\alpha]_D^{32} + 5.3°$ ($c = 0.92$, $CHCl_3$); $[\alpha]_D^{32} + 6.3°$ ($c = 0.96$, CCl_4) [natural: $[\alpha]_D + 6.4°$ (not described); synthetic[11b]: $[\alpha]_D^{24} + 4.6°$ ($c = 2$, $CHCl_3$)], as a colorless oil.

IR (neat): $\nu = 1732\ cm^{-1}$.

^1H NMR ($CDCl_3$, 500 MHz): $\delta = 4.32$ (1 H, ddd, $J = 11.0, 6.6, 3.3$ Hz), 4.20 (1 H, ddd, $J = 11.0, 8.6, 2.4$ Hz), 2.64–2.51 (1 H, m), 2.36 (1 H, t, $J = 10.0$ Hz), 2.28–2.17 (1 H, m), 2.08–1.96 (2 H, m), 1.95–1.85 (1 H, m), 1.57–1.47 (1 H, m), 1.38–1.27 (1 H, m), 1.20 (3 H, d, $J = 6.7$ Hz), 1.27–1.12 (1 H, m).

^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 174.1$ (s), 66.6 (t), 49.8 (d), 39.1 (d), 35.9 (d), 34.3 (t), 32.3 (t), 28.9 (t), 19.6 (q).

MS: $m/z = 154$ (M^+), 99 (100%).

HRMS: m/z calc. for $C_9H_{14}O_2$ 154.0994, found 154.1026.

(1*R*,2*R*,3*S*)-2-(2-Hydroxymethyl-3-methylcyclopentyl)ethanol (9):

To a stirred solution of **4** (368 mg, 2.39 mmol) in THF (15 mL) was added $LiAlH_4$ (100 mg, 2.63 mmol) portionwise at 0 °C and stirring was continued for 30 min at the same temperature. The reaction was quenched by addition of 29% NH_4OH (3 mL) and the mixture was diluted with CH_2Cl_2 (20 mL) and filtered through a Celite

pad. The filtrate was evaporated under reduced pressure and the residue was chromatographed on silica gel (30 g, eluent: MeOH/$CHCl_3$, 1:19) to give the diol **9** as a colorless oil; yield: 367 mg (97%); $[\alpha]_D^{29}$ + 52.6° (c = 0.91, $CHCl_3$).

IR (neat): ν = 3326 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 3.84–3.72 (1 H, m), 3.72–3.50 (3 H, m), 2.16 (1 H, br sextet, J = 7.0 Hz), 1.98–1.63 (7 H, m), 1.48–1.35 (1 H, m), 1.35–1.23 (1 H, m), 1.21–1.08 (1 H, m), 1.02 (3 H, d, J = 6.2 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 62.4 (t), 62.0 (t), 52.1 (d), 37.7 (d), 35.7 (d), 32.9 (t), 32.3 (t), 31.2 (t), 20.9 (q).

MS: m/z = 159 (M^+ + 1), 81 (100%).

HRMS: m/z calc. for $C_9H_{19}O_2$ 159.1385, found 159.1376.

(−)-Dolichodial (12):

To a stirred solution of DMSO (0.9 mL, 12.7 mmol) in CH_2Cl_2 (10 mL) was added oxalyl chloride (0.72 mL, 8.25 mmol) at − 70 °C and, after 20 min, the diol **9** (163 mg, 1.03 mmol) in CH_2Cl_2 (5 mL) was added dropwise and, after 60 min at the same temperature, Et_3N (1.0 mL, 7.17 mmol) was added, and the temperature was raised to r.t.. After stirring at r.t. for 60 min, to this mixture was added *N,N*-dimethylmethyleneammonium chloride (317 mg, 3.39 mmol) and stirring was continued for 24 h at r.t. The mixture was diluted with H_2O (5 mL) and the mixture was extracted with Et_2O (30 mL). The extract was washed with brine (5 mL), dried ($MgSO_4$), and chromatographed on silica gel (10 g, eluent: EtOAc/hexane) to give a colorless oil which was further purified by TLC (silica gel) (eluent: 2 × EtOAc/hexane, 1:4) to give (−)-dolichodial **(12)** containing 10% of the epimer **13** as a colorless oil; yield: 38 mg (22%); $[\alpha]_D^{30}$ − 68.8° (c = 0.41, benzene) [natural product: $[\alpha]_D^{20}$ − 72.0° (c = 4.2, benzene) for **12** and $[\alpha]_D^{20}$ + 3.5° (c = 4.3, benzene) for **13**].

IR (neat): ν = 1717, 1689, 1656 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 9.76 (0.1 H, d, J = 3.0 Hz), 9.54 (0.9 H, s), 9.52 (0.1 H, s), 9.43 (0.9 H, d, J = 3.1 Hz), 6.30 (1 H, d, J = 1.2 Hz), 6.14 (0.9 H, s), 6.00 (0.1 H, s), 3.45–3.38 (0.1 H, m), 3.36–3.27 (0.9 H, m), 2.83–2.73 (1 H, m), 2.66–2.56 (0.1 H, m), 2.50–2.40 (0.9 H, m), 2.13–1.97 (1 H, m), 1.97–1.83 (1 H, m), 1.78–1.64 (1 H, m), 1.36–1.23 (1 H, m), 1.10 (2.7 H, d, J = 6.7 Hz), 1.06 (0.3 H, d, J = 7.3 Hz).

MS: m/z = 166 (M^+), 41 (100%).

HRMS: m/z calc. for $C_9H_{14}O_2$ 166.0994, found 166.1011.

The ^1H NMR spectrum[5b] of the major component corresponds well to that of natural (−)-dolichodial[5] **(12)** and the ^1H NMR spectrum[5b] of the minor component corresponds well to that of natural (+)-anisomorphal[15] **(13)**.

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