Asymmetric Induction Reactions. VI.[1,2] Asymmetric Synthesis of a Cyclopentene Derivative by Transition Metal-Catalyzed Asymmetric Vinylcyclopropane–Cyclopentene Rearrangements with Chiral Phosphine Ligands

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Asymmetric synthesis of a cyclopentene derivative was accomplished by transition metal-catalyzed vinylcyclopropane–cyclopentene rearrangements with chiral phosphine ligands. A dramatic solvent effect was observed on the nickel-catalyzed asymmetric rearrangement of a cyclopropane system into an optically active cyclopentene derivative with chiral phosphine ligands. The absolute configuration of the product was determined by chemical correlation to the compound of known absolute configuration. The stereochemistry of the product was readily controlled by selecting the catalyst, nickel or palladium, with extremely high enantioselectivity.

Keywords asymmetric synthesis; cyclopropane; cyclopentene; transition metal catalyst; chiral phosphine ligand; enantioselectivity

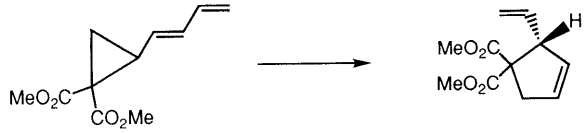
Transition metal-promoted carbon–carbon bond formation reaction[3] is a useful tool for the stereoselective construction of complex organic structures and has recently received much attention owing to its stereoselectivity and stereospecificity.[4]

Construction of cyclopentane frameworks for the preparation of five-membered natural products such as prostaglandins[5] and terpenoids[6] has been well investigated, and many methodologies for five-membered ring annelations have been devised.[7] Recently much interest has been focussed on asymmetric synthesis of biologically active five-membered compounds.[8] We wish to report here asymmetric synthesis of a cyclopentene derivative by a transition metal-promoted asymmetric carbon–carbon bond formation reaction using a chiral phosphine ligand as a chiral source.

The thermal rearrangement of vinylcyclopropanes to cyclopentenes[9] requires in general a high reaction temperature, whereas transition metals such as nickel,[10] palladium,[11] rhodium,[12] copper,[13] molybdenum,[14] chromium,[15] and iron[16] mediate the reactions under much milder reaction conditions. We have achieved a highly enantioselective asymmetric synthesis of a cyclopentene derivative by means of nickel- or palladium-catalyzed asymmetric vinylcyclopropane–cyclopentene rearrangements with chiral phosphine ligands. We also wish to report a dramatic solvent effect on the nickel-catalyzed asymmetric rearrangement and control of the enantioselection of the product by the catalyst employed.

A model compound for this transformation, dimethyl 2-(1,3-butadienyl)-1,1-cyclopropanedicarboxylate (**1**), was readily prepared by cyclopropanation of acrolein with dimethyl bromomalonate followed by Wittig condensation of the resulting aldehyde with allyltriphenylphosphonium ylide.[10]

Upon treatment with a nickel catalyst, bis(cyclooctadiene)nickel [$Ni(COD)_2$], in the presence of a chiral phosphine ligand, a cyclopropane compound **1** underwent facile conversion into an optically active cyclopentene derivative, dimethyl 2-vinyl-3-cyclopentene-1,1-dicarboxylate (**2**), in good yield with extremely high enantioselectivity, depending on the solvent used. Effects of chiral ligands on the asymmetric induction were examined using (*S*)-(−)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP),[17] (4*R*,5*R*)-(−)-4,5-bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolane (DIOP),[18] (4*R*,5*R*)-(+)-4,5-bis[bis(4-methoxy-3,5-dimethylphenyl)-phosphinomethyl]-2,2-dimethyl-1,3-dioxolane (MOD-DIOP),[19] and neomenthyldiphenylphosphine (NMDPP).[20] The enantiomeric excess of **2** was calculated on the basis of the optical rotation ($[\alpha]_D$ −158.4°) of optically pure (*R*)-(−)-**2**, which was determined by NMR spectral analysis with a shift reagent, tris[3-(2,2,2-trifluoro-1-hydroxyethylidene)-*d*-camphorato]europium [$Eu(tfc)_3$]. The results obtained are listed in Table I.



1 (*R*)-(−)-**2**

Chart 1

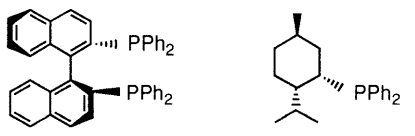


Fig. 1

TABLE I. Nickel-Catalyzed Asymmetric Rearrangements of **1** with Chiral Phosphine Ligands[a)]

Ligand	Solvent	Reaction temperature (°C)	Reaction time (h)	Yield (%)	Product **2** $[\alpha]_D$ (MeOH) (*c*, °C)	ee (%)
PPh_3	DMSO	r.t.	24	89	—	—
PPh_3	CH_3CN	50	4	48	—	—
(−)-BINAP	DMSO	r.t.	4	97	−133.9° (2.9, 26)	84.1
(−)-BINAP	CH_3CN	50	4	50	−123.0° (2.2, 25)	77.2
(−)-DIOP	DMSO	r.t.	2	76	−2.6° (2.2, 25)	1.6
(−)-DIOP	CH_3CN	50	5	44	−7.5° (2.1, 24)	4.7
(+)-MOD-DIOP	DMSO	r.t.	4	77	−144.0° (3.5, 28)	90.4
(+)-MOD-DIOP	CH_3CN	50	5	63	−108.0° (1.9, 17)	68.4
(+)-MOD-DIOP	DME	r.t.	12	71	−4.2° (2.1, 26)	2.6
(+)-MOD-DIOP	THF/HMPA (10:1)	r.t.	12	68	−5.4° (2.1, 26)	3.4
(+)-MOD-DIOP	DMF	r.t.	12	66	−7.2° (1.8, 27)	4.5
(+)-MOD-DIOP	THF	r.t.	12	56	−1.2° (1.7, 27)	0.7
(+)-MOD-DIOP	Benzene	r.t.	12	20	−5.0° (0.6, 27)	3.1
(+)-MOD-DIOP	THF/DMSO (10:1)	r.t.	12	67	−120.1° (2.3, 26)	75.0
(+)-MOD-DIOP	THF/DMSO (100:1)	r.t.	12	57	−12.3° (2.0, 27)	7.5
(+)-MOD-DIOP	THF/$DMSO_2$ (10:1)	r.t.	12	50	−1.4° (0.7, 26)	0.8
(+)-MOD-DIOP	THF/DMS (100:1)	r.t.	12	0	—	—
(+)-MOD-DIOP	DMSO/DMS (100:1)	r.t.	12	26	−1.5° (0.4, 27)	0.9
(+)-MOD-DIOP	THF/CH_3CN (10:1)	50	12	52	−9.1° (1.2, 27)	5.8

a) The cyclopropanedicarboxylate **1** was treated with $Ni(COD)_2$ (0.15 eq) in the presence of a chiral phosphine ligand (0.2 eq). $DMSO_2$, dimethyl sulfone. DMS, dimethyl sulfide. r.t. = room temperature.

The chiral phosphines (+)-MOD-DIOP and (−)-BINAP served as extremely efficient ligands in the nickel-catalyzed reactions to give (*R*)-(−)-**2** in very high optical yields (84—90%), whereas the phosphine (−)-DIOP was less effective for asymmetric induction. The nickel-catalyzed reaction was successfully executed at room temperature in dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), 1,2-dimethoxyethane (DME), and tetrahydrofuran (THF), though not benzene, but heating at 50 °C was required in acetonitrile. Dramatic solvent effects were observed on the chemical yields and the enantioselectivity in this nickel-catalyzed reaction of **1**. The nickel–(+)-MOD-DIOP-catalyzed reactions in benzene, DMF, DME, and THF at room temperature provided (*R*)-(−)-**2** with extremely low enantiomeric excess (1—4%). However, rather high optical yields were observed in DMSO or acetonitrile; the highest optical yield (90.4%) of (*R*)-(−)-**2** was obtained in the nickel–(+)-MOD-DIOP-catalyzed reaction with the use of DMSO as a solvent.

In order to rationalize the dramatic solvent effect of DMSO on asymmetric induction, other sulfur functionalities such as the sulfonyl (dimethyl sulfone) and sulfenyl groups (dimethyl sulfide) were used in this catalytic reaction. The optical yield decreased with increasing dilution ratio of THF in DMSO; in a 10:1 or 100:1 mixture of THF and DMSO, the nickel–(+)-MOD-DIOP-catalyzed reaction produced (*R*)-(−)-**2** in 75.0 or 7.5% optical yields, respectively. Use of dimethyl sulfone in THF (THF–dimethyl sulfone, 10:1), instead of DMSO, was not effective for asymmetric induction, leading to (*R*)-(−)-**2** in 50% yield with very low enantiomeric excess. The reaction in THF–dimethyl sulfide (100:1) at room temperature gave no rearranged product.

The use of (−)-BINAP as a chiral ligand in DMSO or acetonitrile produced (*R*)-(−)-**2** with high enantiomeric excess. In this case, rather severe solvent effects were observed.

Stereochemical studies on the transition metal-catalyzed reactions of the cyclopropane system **1** were carried out employing various other kinds of transition metal catalysts such as tetrakis(triphenylphosphine)palladium[$Pd(PPh_3)_4$], tetrakis(triphenylphosphine)platinum [$Pt(PPh_3)_4$], hexacarbonylchromium [$Cr(CO)_6$], hexacarbonylmolybdenum [$Mo(CO)_6$], and hexacarbonyltungsten [$W(CO)_6$]. In contrast to the afore-mentioned nickel-catalyzed reactions, the palladium-catalyzed reactions of **1** in the presence of the chiral phosphines described above led to smooth formation of (*S*)-(+)-**2** in good yields with rather low enantiomeric excess, as listed in Table II.

Unexpectedly, in the palladium-catalyzed reaction, (+)-MOD-DIOP was a less effective ligand for asymmetric induction, while other chiral phosphine ligands such as (−)-DIOP, (−)-BINAP, and NMDPP provided (*S*)-(+)-**2** in moderate optical yields. In this palladium-catalyzed reaction an unequivocal solvent effect of DMSO was observed.

In the case of the platinum and molybdenum catalysts, heating at 50—110 °C in DMSO or acetonitrile was required to complete the rearrangement of **1** in the presence of (+)-MOD-DIOP and (−)-BINAP, producing (*R*)-(−)-**2** with rather low enantiomeric excess. The results are summarized in Table III, indicating that (−)-BINAP was not a useful chiral ligand and DMSO was not a good solvent for the platinum-catalyzed asymmetric rearrangement of **1**, whereas in the molybdenum-catalyzed reaction they were more effective, giving (*R*)-(−)-**2** in about 30% optical yield. In the molybdenum-(+)-MOD-DIOP-catalyzed reaction, a strong solvent effect was observed (DMSO was a more efficient solvent for the asymmetric transformation than acetonitrile).

The chromium- or tungsten-catalyzed reactions of **1** in

Table II. Palladium-Catalyzed Asymmetric Rearrangements of **1** with Chiral Phosphine Ligands[a]

Ligand	Solvent	Reaction temperature (°C)	Reaction time (h)	Yield (%)	Product **2** $[\alpha]_D$ (MeOH) (*c*, °C)	ee (%)	Absolute configuration
PPh_3	DMSO	r.t.	12	64	—	—	—
PPh_3	CH_3CN	50	12	83	—	—	—
(−)-BINAP	DMSO	r.t.	2	68	+64.4° (1.2, 26)	40.4	(*S*)
(−)-BINAP	CH_3CN	r.t.	6	52	+20.5° (2.6, 28)	12.9	(*S*)
(−)-DIOP	DMSO	r.t.	6	72	+32.5° (4.2, 25)	20.4	(*S*)
(−)-DIOP	CH_3CN	50	5	68	+16.7° (2.1, 24)	10.0	(*S*)
(+)-MOD-DIOP	DMSO	r.t.	2	100	+3.0° (2.2, 23)	1.9	(*S*)
(+)-MOD-DIOP	CH_3CN	50	2	100	−16.9° (3.1, 26)	10.1	(*R*)
(+)-NMDPP	DMSO	r.t.	4	65	+50.0° (2.1, 25)	31.4	(*S*)
(+)-NMDPP	CH_3CN	50	4	50	+2.3° (2.1, 24)	1.4	(*S*)

a) The cyclopropanedicarboxylate **1** was treated with $Pd(PPh_3)_4$ (0.15 eq) in the presence of a chiral phosphine ligand (0.2 eq). r.t. = room temperature.

Table III. Platinum-, Chromium-, Molybdenum-, or Tungsten-Catalyzed Rearrangements of **1** with Chiral Phosphine Ligands[a]

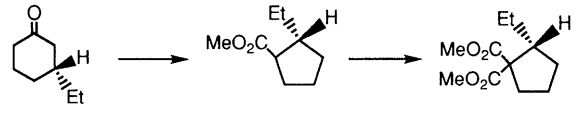
Catalyst	Ligand	Solvent	Reaction temperature (°C)	Reaction time (h)	Yield (%)	Product **2** $[\alpha]_D$ (MeOH) (*c*, °C)	ee (%)
$Pt(PPh_3)_4$	PPh_3	DMSO	110	12	83	—	—
$Pt(PPh_3)_4$	PPh_3	CH_3CN	80	12	38	—	—
$Pt(PPh_3)_4$	(−)-BINAP	DMSO	110	12	69	−4.6° (2.1, 26)	2.9
$Pt(PPh_3)_4$	(−)-BINAP	CH_3CN	80	12	99	—	—
$Pt(PPh_3)_4$	(−)-BINAP	CH_3CN	50	24	52	−4.2° (1.7, 25)	2.6
$Pt(PPh_3)_4$	(+)-MOD-DIOP	DMSO	110	12	72	−0.5° (2.1, 24)	0.1
$Pt(PPh_3)_4$	(+)-MOD-DIOP	CH_3CN	80	12	87	−27.2° (2.5, 23)	17.1
$Pt(PPh_3)_4$	(+)-MOD-DIOP	CH_3CN	r.t.	32	18	−34.5° (0.5, 27)	21.7
$Cr(Co)_6$	(+)-MOD-DIOP	DMSO	110	12	6	−2.3° (0.5, 25)	1.4
$Cr(Co)_6$	(−)-BINAP	DMSO	110	12	4	−1.3° (0.6, 27)	0.1
$Mo(CO)_6$	(−)-BINAP	DMSO	110	12	60	−45.0° (1.8, 26)	28.2
$Mo(CO)_6$	(−)-BINAP	DMSO	50	12	43	−47.0° (1.3, 27)	29.5
$Mo(CO)_6$	(−)-BINAP	CH_3CN	80	12	13	—	—
$Mo(CO)_6$	(+)-MOD-DIOP	DMSO	110	12	37	−43.2° (1.1, 27)	27.1
$Mo(CO)_6$	(+)-MOD-DIOP	CH_3CN	80	12	10	−9.2° (1.3, 28)	5.8
$W(CO)_6$	(+)-MOD-DIOP	DMSO	110	36	2	−0.9° (0.5, 26)	0.1
$W(CO)_6$	(−)-BINAP	DMSO	110	36	4	—	—

a) The cyclopropanedicarboxylate **1** was treated with a catalyst (0.15 eq) in the presence of a chiral phosphine ligand (0.2 eq). r.t. = room temperature.

DMSO did not work well, even under heating at 110 °C, resulting in a very poor yield (2—6%) of (*R*)-(−)-**2** with low enantiomeric excess. The cobalt-, rhodium-, and ruthenium-catalyzed reactions of **1** at 80—90 °C in DMSO or acetonitrile gave no rearranged product.

The absolute configuration of the product **2** was determined as follows. Oxidative ring contraction of (*R*)-(+)-3-ethylcyclohexanone (**3**) ($[\alpha]_D$ +4.2° (MeOH))[21] with selenium dioxide-hydrogen peroxide in refluxing pyridine, followed by esterification, afforded (*R*)-**4**.[22] α-Methoxycarboxylation of the ester (*R*)-**4** thus obtained with methyl chloroformate was carried out in THF at −78 °C for 4 h in the presence of lithium diisopropylamine (LDA), giving (*R*)-(−)-**5** ($[\alpha]_D$ −12.9° (MeOH), 59% ee). The Raney Ni-catalyzed hydrogenation of (*R*)-(−)-**2** ($[\alpha]_D$ −105° (MeOH), 68% ee) obtained above gave (*R*)-(−)-**5** ($[\alpha]_D$ −14.4° (MeOH), 68% ee). Thus, the absolute configuration of the product **2** obtained by the afore-mentioned nickel-catalyzed asymmetric synthesis was determined as (*R*)-(−)-**2**.

The stereochemistry of this palladium- and nickel-catalyzed asymmetric synthesis can be rationalized as follows. The cyclopropane ring in **1** would be dissected by



(*R*)-(+)-**3** (*R*)-(−)-**4** (*R*)-(−)-**5**

Chart 2

the reactions with transition metals (palladium and nickel catalysts), forming π-allylmetal complexes having the sterically preferred zig-zag structures as depicted in **6**. The chiral phosphine ligands would chelate to the transition metals in the above complexes to provide chiral intermediates **6**. The carbonucleophiles in **6** would undergo intramolecular asymmetric carbon–carbon bond-forming reactions from the opposite direction to the metal (palladium),[23] or from the same direction as the metal (nickel)[24] presumably *via* chiral π-allylnickel complexes **7** formed by the enantiospecific coordination of the carbanion to the metal, producing a chiral cyclic compound, (*S*)- or (*R*)-**2**, respectively.

In conclusion, the sulfinyl function played an important role for induction of new chirality with high efficiency in the nickel-catalyzed asymmetric rearrangements of a

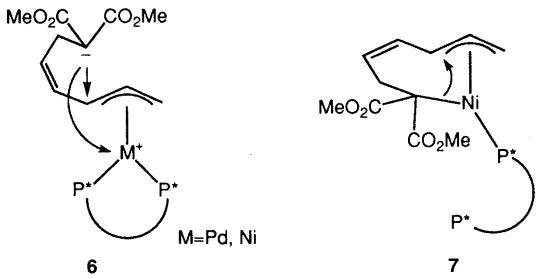


Fig. 2

cyclopropane system **1** with chiral phosphine ligands (+)-MOD-DIOP and (−)-BINAP, presumably because of the direct coordination of the sulfinyl function of DMSO to the metal catalysts or the solvation. Furthermore, the selection of the catalyst, $Ni(COD)_2$ or $Pd(PPh_3)_4$, allowed easy control of the stereochemistry of the product, producing an optically active cyclopentene derivative **2** of (*R*)- or (*S*)-configuration, respectively. This nickel-(+)-MOD-DIOP-catalyzed reaction provides a facile entry to optically active cyclopentane derivatives, which are expected to be synthetically useful chiral intermediates for interesting five-membered ring natural products.

Experimental

Infrared (IR) spectra were obtained in the indicated state with a JASCO DR-81 Fourier-transform infrared spectrometer. NMR spectra were determined in the indicated solvent with a JEOL GSX-400 (^{1}H-NMR, 400 MHz; ^{13}C-NMR, 100 MHz), EX-270 (^{1}H-NMR, 270 MHz; ^{13}C-NMR, 67.5 MHz), JNM PMX-60SI (60 MHz) high-resolution NMR spectrometer; chemical shifts are given in ppm from tetramethylsilane as an internal standard. Splitting patterns are designated as s, singlet; ss, singlet singlet; d, doublet; dd, doublet doublet; t, triplet; m, multiplet. Mass spectra (MS) were taken on a JEOL JMS-DX 303/JMA-DA 5000 system. Optical rotations were measured with a JASCO DIP-370 or DIP-360 polarimeter. High-performance liquid chromatographic data (HPLC) were obtained with Tosoh UV-8010, CCPM (column, Tosoh TSK-GEL ODS-80TM). Flash column chromatography was performed with using Merck Silica gel 60 (230—400 mesh). Thin layer or thick layer plates (preparative TLC) were made of Merck Silica gel 60PF-254 activated by drying at 140 °C for 3.5 h.

Transition Metal-Catalyzed Asymmetric Rearrangements of Dimethyl 2-(1,3-Butadienyl)-1,1-cyclopropanedicarboxylate (1) with Chiral Phosphine Ligands General Procedure: A solution of **1** (50 mg, 0.24 mmol) in a solvent (DMSO, THF or CH_3CN) (1 ml) was stirred under N_2 in the presence of a catalyst ($Pd(PPh_3)_4$, $Ni(COD)_2$, $Pt(PPh_3)_4$, $Cr(CO)_6$, $Mo(CO)_6$, or $W(CO)_6$ (0.036 mmol) and a chiral phosphine ((+)-MOD-DIOP, (−)-DIOP, (−)-BINAP, or NMDPP) (0.048 mmol) at the temperature and for the time shown in Tables I—III. The reaction mixture was diluted with ether. The solution was filtered and the filtrate was concentrated under reduced pressure. The residual oil was subjected to preparative TLC (ether–hexane, 1:3) to give dimethyl 2-vinyl-3-cyclopentene-1,1-dicarboxylate (**2**). The chemical yields, the optical rotations, and the enantiomeric excess of the product **2** are listed in Tables I—III.

2: IR ν_{max}^{film} cm^{-1}: 1735 (ester), 1635 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 2.71—2.79, 3.25—3.27 (2H, d, J=5.4 Hz, CH_2), 3.66, 3.74 (6H, ss, $COOCH_3$), 4.15—4.18 (1H, dd, J=0.14, 1.68 Hz, $CHCH=CH_2$), 5.04—5.19 (2H, m, CH=CH), 5.54—5.73 (3H, m CH_2=CH). MS *m/z*: 210 (M^+). Exact mass determination: 210.1207 (Calcd for $C_{11}H_{14}O_4$: 210.1207).

Catalytic Hydrogenation of (*R*)-(−)-2 A solution of (−)-**2** (25 mg, 0.12 mmol, $[\alpha]_D^{23}$ −105° (c=1.0, MeOH) in MeOH (4 ml) was stirred in the presence of Pd/C (20 mol%, 50 mg) at room temperature for 12 h under a hydrogen atmosphere. The reaction mixture was diluted with ether and filtered through Celite. The filtrate was concentrated *in vacuo*. The crude product was subjected to flash column chromatography (ether–hexane, 1:3) to give dimethyl (*R*)-(−)-2-ethyl-1,1-cyclopentanedicarboxylate (**5**) (24 mg, 95% yield, $[\alpha]_D^{23}$ −14.4° (c=1.0, MeOH). IR ν_{max}^{film} cm^{-1}: 1735 (ester). ^{1}H-NMR ($CDCl_3$) δ: 0.90—0.95 (3H, t, J=1.6 Hz, CH_3), 1.53—1.67 (2H, m, $-CH_2CH_3$), 1.78—1.86 (2H, m, $CHCH_2CH_2$), 1.90—2.07 (3H, m, CH, $-CH_2CH_2CH_2-$), 2.36—2.49 (2H, m, $-CCH_2-$), 3.69, 3.72 (6H, ss, CO_2CH_3). MS *m/z*: 214 (M^+). Exact mass determination: 214.1205 (Calcd for $C_{11}H_{18}O_4$: 214.1205).

Chemical Correlation of (*R*)-(+)-3-Ethylcyclohexanone (3) to (*R*)-(−)-5 Conversion of (*R*)-(+)-**3** into Methyl (*R*)-(−)-2-Ethylcyclopentanecarboxylate (**4**): A solution of selenium dioxide (84 mg, 0.7 mmol) in 30% H_2O_2 (1 ml) was refluxed for 1.5 h, then cooled to room temperature. A mixture of pyridine (0.1 ml) and 30% H_2O_2 (1 ml) was added to the above solution, followed by a solution of (*R*)-(+)-**3**[21] (46 mg, 0.37 mmol, $[\alpha]_D^{25}$ +4.2°, (c=1.0, MeOH)) in *tert*-BuOH (1 ml). The reaction mixture was refluxed for 20 h, then concentrated *in vacuo*. The residual oil was diluted with ether and extracted with saturated aqueous $NaHCO_3$. The aqueous layer was washed with ether, neutralized with 10% aqueous H_2SO_4, and extracted with ether. The organic layer was dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residual oil (32 mg, $[\alpha]_D^{22}$ +26.0°, (c=1.0, MeOH)) was dissolved in MeOH (7 ml) and the solution was refluxed for 12 h in the presence of a catalytic amount of concentrated H_2SO_4. The reaction mixture was concentrated *in vacuo*. The crude product was dissolved in ether, and the solution was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residual oil was subjected to flash column chromatography (ether–hexane, 1:3) to give (*R*)-(−)-**4** (31 mg, 54% overall yield from (*R*)-(+)-**3**, $[\alpha]_D^{22}$ −16.0°, (c=2.1, MeOH)).[18] IR ν_{max}^{film} cm^{-1}: 1735 (ester). ^{1}H-NMR ($CDCl_3$) δ: 0.84—0.95 (3H, t, J=1.6 Hz, CH_3), 1.22—1.31 (2H, m, CH_2CH_3), 1.40—1.51 (1H, m, $CHCH_2CH_3$), 1.62—1.80 (2H, m, $CHCH_2CH_2$), 1.80—1.92 (2H, m, $-CH_2CH_2CH_2-$), 1.98—2.12 (2H, m, $CH_2CHCO_2CH_3$), 2.72—2.84 (1H, m, $CHCO_2CH_3$), 3.66 (3H, s, CO_2CH_3). MS *m/z*: 156 (M^+). Exact mass determination: 156.115 (Calcd for $C_9H_{16}O_2$: 156.115).

Conversion of (*R*)-(−)-**4** into (*R*)-(−)-**5**: A dry 15 ml two-necked flask equipped with a septum inlet and a magnetic stirring bar was flushed with nitrogen, and maintained under a positive pressure of nitrogen. A solution of diisopropylamine (77.7 mg, 0.77 mmol) in THF (2 ml) was added to the flask. A 1.5 M butyllithium hexane solution (0.512 ml, 0.77 mmol) was added to the above solution at 0 °C and the mixture was stirred at 0 °C for 15 min. A solution of (*R*)-(−)-**4** (100 mg, 0.64 mmol) in THF (1 ml) was added to the above solution at −78 °C. The mixture was stirred at −78 °C for 1 h, then a solution of methyl chloroformate (73 mg, 0.77 mmol) in THF (1 ml) was added and the reaction mixture was further stirred at −78 °C for 4 h, then diluted with ether. The reaction was quenched with 10% aqueous HCl, and the organic layer was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residual oil was subjected to flash column chromatography (ether–hexane, 1:3) to give (*R*)-(−)-**5** (94 mg, 69% yield, $[\alpha]_D^{25}$ −12.9° (c=1.0, MeOH)). The spectral data were identical with those of the sample obtained from (*R*)-(−)-**2**, as described earlier.

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