Tetrahedron Vol. 49, No 9, pp 1831-1840, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

The Lewis Acid-catalyzed Intramolecular Asymmetric Ene Reaction Using a Chiral α-Cyanovinylic Sulfoxide as an Enophile†, 1)

Kunio Hiroi* and Masayuki Umemura

Department of Synthetic Organic Chemistry, Tohoku College of Pharmacy,

4-4-1 Komatsushima, Aoba-ku, Sendai, Miyagi 981, Japan

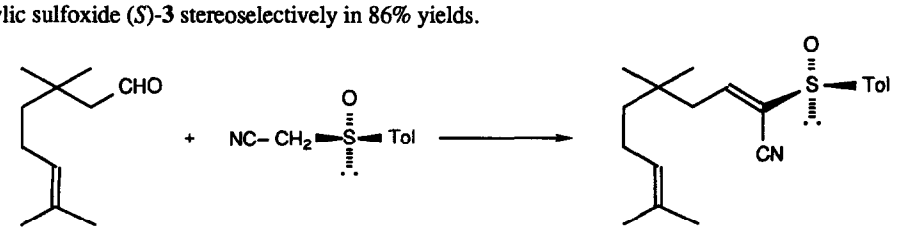
(*Received in Japan* 21 *September* 1992)

Abstract: A chiral α-cyanovinylic sulfoxide served as an efficient chiral enophile in a Lewis acid-catalyzed intramolecular ene reaction. Use of diethylaluminum chloride as a catalyst provided extremely high stereoselectivity in the ene reaction. The stereochemistry of the ene reaction products were determined by chemical correlation and the NMR spectral analysis. A mechanistic pathway for the asymmetric induction is presented on the basis of the stereochemical results obtained.

An ene reaction is one of the useful tools for stereoselective construction of complex organic structures.[2] During the past decade much efforts have been devoted to the development of new methodologies for the presentation of high stereoselectivity in organic synthesis by utilizing inter-[3] and intramolecular ene reactions.[4] In recent years an ene reaction has received much attention especially for asymmetric synthesis with high enantioselectivity by means of various kinds of chiral sources such as (-)-menthyl ester,[5] chiral olefins,[6] and chiral titanium,[7] aluminum,[8] and zinc Lewis acid catalysts.[9]

We have previously explored a novel method for asymmetric cyclization via Lewis acid-[10] or palladium-catalyzed[11] intramolecular ene reactions of chiral allylic sulfones obtained by chiral allylic sulfinate-sulfone rearrangements.[12] We wish to report here a great advantage of a chiral vinylic sulfoxide for an efficient enophile in an asymmetric ene reaction.[13]

A model compound (*S*)-**3** for the intramolecular asymmetric ene reaction was prepared as follows. Knoevenagel condensation of 3-methylcitronellal (**1**) with (*R*)-cyanomethyl *p*-tolyl sulfoxide (**2**)[14] was carried out in the presence of a catalytic amount of piperidinium acetate in benzene at room temperature for 24h to give a chiral vinylic sulfoxide (*S*)-**3** stereoselectively in 86% yields.



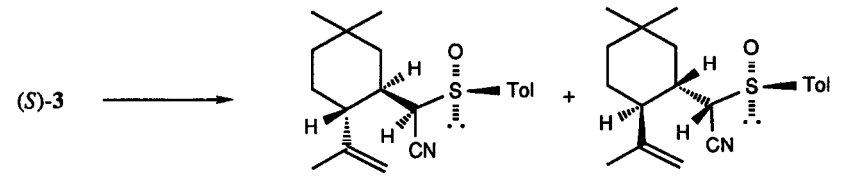
1 (*R*)-**2** (*S*)-**3**

† This paper is dedicated to Professor Shun-ichi Yamada on the occasion of the 77th anniversary of his birth.

Table I. The Lewis Acid-catalyzed Intramolecular Asymmetric Ene Reactions of (*S*)-**3**

Lewis acids[a)]	Solvent	Reaction temp.(°C)	Reaction time (h)	Yield of 4(%)[b)]	d.e.(%) of 4[c)]
$ZnCl_2$	CH_2Cl_2	r.t.	12	61(68)	78.2
$ZnCl_2$	toluene	r.t.	19	70(86)	74.3
$ZnBr_2$	CH_2Cl_2	r.t.	18	82(92)	76.8
$ZnBr_2$	CH_2Cl_2	0	26	42(69)	76.1
$ZnBr_2$	toluene	r.t.	20	76(89)	73.9
$Zn I_2$	CH_2Cl_2	r.t.	17	70(82)	66.3
$Zn I_2$	toluene	r.t.	17	58(69)	62.9
Et_2AlCl	CH_2Cl_2	0	1	77(91)	96.6
Et_2AlCl	CH_2Cl_2	-20	2	62(89)	97.3
Et_2AlCl	hexane	0	2	42(51)	80.8
$EtAlCl_2$	CH_2Cl_2	r.t.	1	43(52)	90.0
$EtAlCl_2$	CH_2Cl_2	0	1	48(80)	82.9
$EtAlCl_2$	CH_2Cl_2	-20	1	52(88)	94.9
$EtAlCl_2$	CH_2Cl_2	-78	12	34(71)	95.2
Me_3Al	CH_2Cl_2	0	4	22(73)	20.0
i-Bu_3Al	CH_2Cl_2	0	4	26(70)	31.2
$BF_3{\cdot}OEt_2$	CH_2Cl_2	r.t.	22	27(52)	56.7

a) The ene reactions of (*S*)-**3** were carried out in the presence of Lewis acids (1.5 equiv.).
b) The yields based on the recovered starting material are listed in parentheses.
c) The diastereomeric excess (d.e.) was determined by the high performance liquid chromatographic analysis.

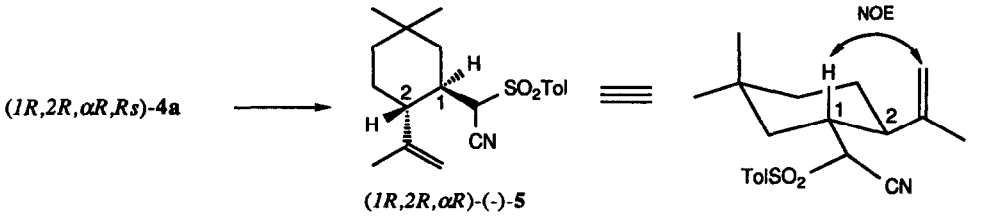


(*1R,2R,αR,Rs*)-**4a** (*1S,2S,αS,Rs*)-**4b**

The α–cyanovinylic sulfoxide (*S*)-**3** underwent an intramolecular asymmetric ene reaction to afford a two diastereomeric mixture of optically active cyclohexane derivatives, (*1R,2R,αR,Rs*)- and (*1S,2S,αS,Rs*)-5,5-dimethyl-2-isopropenyl-α-*p*-toluenesulfinylcyclohexaneacetonitrile(**4a**) and (**4b**) with extremely high diastereomeric excess, upon treatment in dichloromethane, toluene, or hexane at -78 °C ~ room temperature with various Lewis acids such as zinc(II) chloride, bromide and iodide, diethylaluminum chloride, or ethylaluminum dichloride. The diastereomeric excess of the products **4a,b** was determined by the high performance liquid chromatographic analysis and listed in Table I. Use of diethylaluminum chloride as a catalyst at -20 °C provided the highest diastereomeric selectivity (97.3%), as shown in Table I.

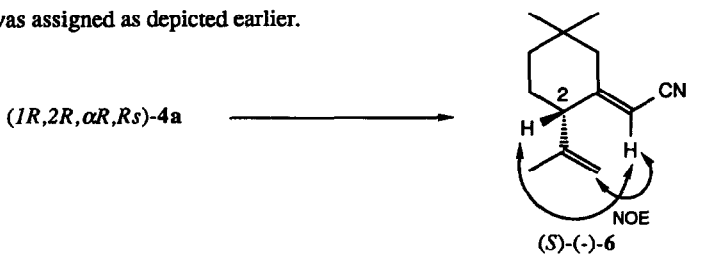
Three asymmetric carbons were newly created under these reaction conditions by the effect of the chirality of the starting sulfinyl groups. Oxidation of the sulfoxides in the products **4a** and **4b** with *m*-chloroperbenzoic acid afforded the enantiomeric sulfone (*1R,2R,αR*)-(-)- and (*1S,2S,αS*)-(+)-**5**, respectively, of which the spectral data were completely superimposable. This result indicates that the newly created three asymmetric carbons in the products should be enantiomeric. This was confirmed also by the following experimental results.

The nuclear overhauser effects (NOE) were observed between the olefinic hydrogen of the isopropenyl group and the hydrogen atom at C_1 in the sulfone (*1R,2R,αR*)-(-)- and (*1S,2S,αS*)-(+)-**5** derived from **4a** and **4b**. Therefore the relative stereochemistry of the isopropenyl and the α-*p*-toluenesulfonylcyanomethyl groups in (*1R,2R,αR*)-(-)- and (*1S,2S,αS*)-(+)-**5** was assigned as *trans* configuration.



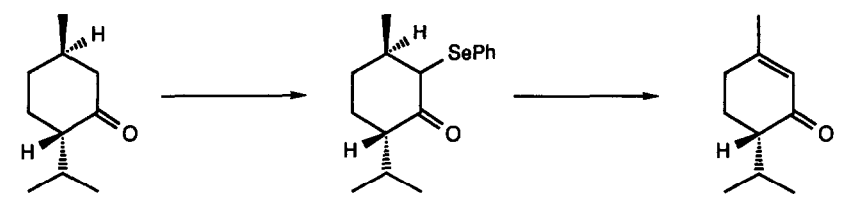
(*1R,2R,αR*)-(-)-**5**

Heating of **4a** or **4b** in refluxing carbon tetrachloride or toluene gave (*S*)-(-)- or (*R*)-(+)-**6**, respectively. The geometry of the olefin in **6** was determined on the basis of the observation of the NOE between the olefinic hydrogen in the cyanomethylene group, and the hydrogen atom at C_2 and the olefinic hydrogen of the isopropenyl group in the NMR spectrum. This dehydrosulfenylation has been well known to proceed in syn fashion.[15] Thus, on the basis of this stereochemical result, the relative stereochemistry of the C_1 and C_α position in **4a, b** was assigned as depicted earlier.

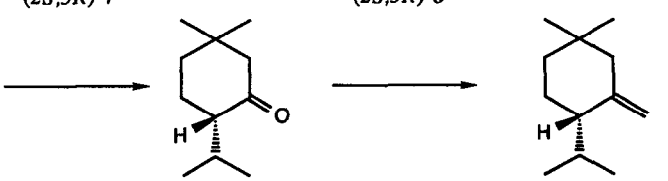


(*S*)-(-)-**6**

The absolute configuration of the newly created asymmetric carbons was determined by chemical correlation of the products **4a,b** to *l*-menthone. Regioselective selenenylation of *l*-menthone (**7**) with diphenyl diselenide was carried out in THF at -78 °C for 1h in the presence of lithium diisopropylamide (1.2 equiv.) to give an α–selenenyl ketone (*2S,5R*)-**8** in 72% yield. Upon treatment with 30% aqueous hydrogen peroxide in the presence of magnesium sulfate in acetone at room temperature for 4 h, the ketone (*2S,5R*)-**8** underwent oxidative



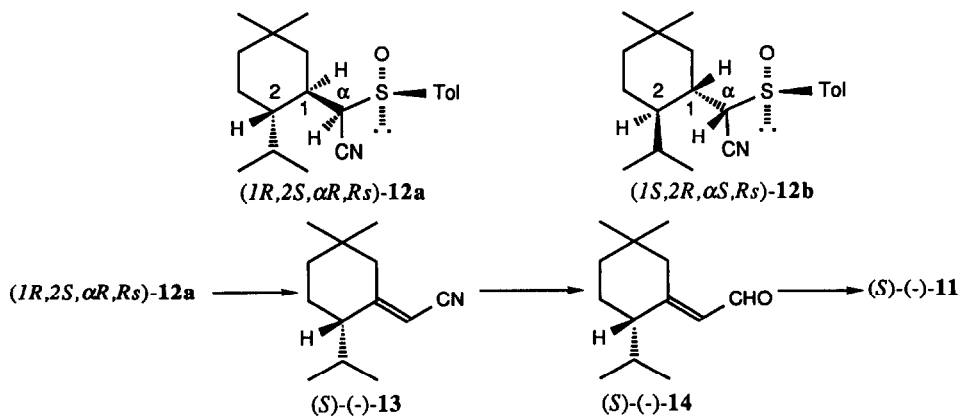
(*2S,5R*)-**7** (*2S,5R*)-**8** (*S*)-**9**



(*S*)-**10** (*S*)-**11**

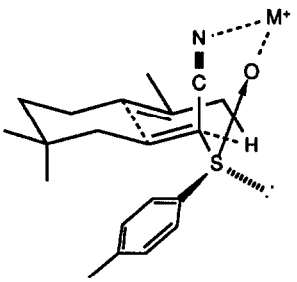
dehydroselenenylation to afford (*S*)-(+)-piperitone (**9**). 1,4-Addition of lithium dimethylcuprate to (*S*)-(+)-**9** (in THF at 0 °C for 2h) followed by the Wittig condensation of the resulting ketone (*S*)-**10** with triphenylphosphonium methylide (in THF at room temperature for 1h) gave (*S*)-(-)-**11**.

Hydrogenation of the isopropenyl groups in **4a** and **4b** was carried out in the presence of tris(triphenylphosphine)rhodium chloride under hydrogen in benzene at room temperature[16] to give (*1R,2S,αR,Rs*)-**12a** and (*1S,2R,αS,Rs*)-**12b**, respectively. Upon heating in carbon tetrachloride, the sulfoxide (*1R,2S,αR,Rs*)-**12a** underwent dehydrosulfenylation in *syn* fashion to give (*S*)-(-)-**13**. Reductive hydrolysis of the cyano group of (*S*)-(-)-**13** with diisobutylaluminum hydride followed by decarbonylation of the aldehyde (*S*)-(-)-**14** with tris(triphenylphosphine)rhodium chloride in refluxing benzene[17] produced (*S*)-(-)-**11**. Accordingly, the absolute configuration of the C_2 in the product **4a** was determined as (*2R*)-configuration. The relative stereochemistry of the product was determined by the NMR spectral analysis as mentioned earlier. Thus, the absolute configuration of the newly created asymmetric three carbons in the ene reaction products was unequivocally determined as (*1R,2R,αR*)-**4a** and (*1S,2S,αS*)-**4b**.

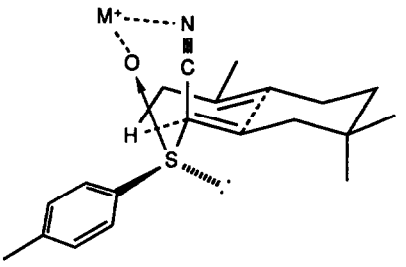


On the basis of stereochemical results obtained, a plausible mechanistic pathway was proposed for the high asymmetric induction in this Lewis acid-catalyzed intramolecular ene reaction with a chiral sulfinyl group. In the six-membered intermediates including the methyl hydrogen atom of the isopropylidene group in this ene reaction, the Lewis acids employed activate the reaction by forming six-membered transition states **15a** and **15b**, in which the Lewis acids chelate with the sulfinyl oxygen and the nitrogen atom of the cyano group. Rather severe steric repulsion is observed between the tolyl group and the cyclohexane ring in **15a**. Therefore the reaction would proceed preferentially through **15b** to give (*1R,2R,αR,Rs*)-**4a** as a main product. The other diastereomer (*1S,2S,αS,Rs*)-**4b** would be obtained through **15a** as a minor product.

Thus, a chiral α-cyanovinylic sulfoxide served as a highly efficient chiral enophile in an intramolecular asymmetric ene reaction. This Lewis acid-catalyzed intramolecular asymmetric ene reaction provides a useful method for asymmetric synthesis of optically active cyclohexane derivatives with high enantioselectivity.



15a



15b

Experimental

Infrared (IR) spectra were obtained in the indicated state with a JASCO DR-81 Fourier-transform infrared spectrometer. NMR spectra were determined in indicated solvent with a JEOL GSX-400 (^{1}H-NMR; 400MHz, ^{13}C-NMR; 100MHz), EX-270 (^{1}H-NMR; 270MHz, ^{13}C-NMR; 67.5MHz), JNM PMX-60SI (60MHz) 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, double doublet; t, triplet, q, quartet; m, multiplet. Mass spectra (MS) were taken on JEOL JMS-DX 303/JMA-DA 5000 system. Optical rotations were measured with 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). Flush column chromatography was performed with using Merck Silica gel 60 (230-400mesh). Thin layer or thick layer plates (preparative TLC) were made of Merck Silica gel 60PF-254 activated by drying at 140 °C for 3.5h.

(*R*)-(+)-Cyanomethyl *p*-Tolyl Sulfoxide (2)

A dry 200ml 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 acetonitrile (0.62g, 15.30mmol) in tetrahydrofuran (THF) (20ml) was added to the flask. A 1.5M butyllithium hexane solution (10.2ml, 15.30mmol) was added at -78 °C to the solution and the mixture was stirred for 30min. A solution of commercially available optically pure (-)-menthyl (*S*)-(-)-*p*-toluenesulfinate (3.00g, 10.20mmol) in THF (20ml) was added to the above solution at -78 °C and the reaction mixture was stirred at -78 °C for 1h. The reaction mixture was diluted with ether, washed with saturated aqueous NH_4Cl and saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was subjected to preparative TLC (ether) to give (*R*)-(+)-**2** (1.60g, 87% yield, $[\alpha]_D^{25}$ +252.7° (c 1.33, EtOH)).[14]

Knoevenagel Condensation of (*R*)-(+)-2 with 1

A catalytic amount of piperidinium acetate was added to a solution of (*R*)-(+)-**2** (295mg, 1.65mmol, $[\alpha]_D^{25}$+252.7° (c 1.33, EtOH)) obtained above and 3-methylcitronellal (**1**) (300mg, 1.81mmol)[9] in benzene (6ml). The reaction mixture was allowed to stir in the presence of molecular sieves 4A (2.00g) at room temperature for 24h, and then the mixture was diluted with dichloromethane and filtered through celite. The filtrate was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was subjected to preparative TLC (ether-hexane 1 : 2) to give (*S*)-

(+)-5,5,9-trimethyl-2-*p*-toluenesulfinyl-2,8-decadienonitrile (**3**) (464mg, 86% yield): $[\alpha]_D^{26}$+150.4° (c 2.84, $CHCl_3$). IRν_{max}^{film}cm^{-1} : 2220 (CN), 1670, 1620 (C=C), 1600 (aromatic), 1050 (S=O). ^{1}H-NMR (CCl_4) δ : 1.00 (6H, s, $(CH_3)_2C$), 1.00-2.15 (4H, m, $(CH_2)_2$), 1.55-1.66 (6H, d, $(CH_3)_2C$=C), 2.33-2.45 (2H, d, CCH_2), 2.45 (3H, s, $C_6H_4C\underline{H}_3$), 4.90-5.15 (1H, t, C=CH), 7.00-7.25 (1H, t, CH=CS), 7.33-7.60 (4H, q, C_6H_4). MS m/z : 329 (M+). Exact mass determination : 329.1797 (Calcd. for $C_{20}H_{27}NOS$: 329.1813).

Lewis Acid-catalyzed Ene Reactions of (*S*)-(+)-3

A dry 25ml 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 Lewis acid (0.45mmol) in dichloromethane (2ml) was added to the flask. A solution of (*S*)-(+)-**3** (100mg, 0.30mmol) in dichloromethane (2ml) was added to the above solution. The reaction mixture was allowed to stir at the reaction temperature for the reaction time listed in Table I. The reaction mixture was diluted with dichloromethane and the solution was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was subjected to preparative TLC (ether-hexane 1 : 2) to give (*1R,2R,αR,Rs*)-(+)- and (*1S,2S,αS,Rs*)-(+)-5,5-dimethyl-2-isopropenyl-α-*p*-toluenesulfinylcyclohexaneacetonitrile(**4a**) and (**4b**). The yields and the diastereomeric excess of the products are summarized in Table I.

(*1R,2R,αR,Rs*)-(+)-**4a** : $[\alpha]_D^{26}$+144.6° (c 1.93, $CHCl_3$). IRν_{max}^{film}cm^{-1} : 2250 (CN), 1640 (C=C), 1600 (aromatic), 1050 (S=O). ^{1}H-NMR ($CDCl_3$) δ : 0.91, 0.96 (6H, ss, $(CH_3)_2C$), 1.00-2.15 (6H, m, $(CH_2)_2CCH_2$), 1.47 (3H, s, CH_3C=C), 1.92-2.05 (2H, m, $(CH)_2$), 2.45 (3H, s, $C_6H_4C\underline{H}_3$), 3.61-3.62 (1H, d, CHS), 4.72-4.80 (2H, d, CH_2=C), 7.37-7.58 (4H, q, C_6H_4). ^{13}C-NMR ($CDCl_3$) δ : 18.5, 21.6, 24.4, 27.5, 30.7, 32.7, 35.0, 38.1, 41.3, 50.1, 62.0, 113.3, 113.7, 124.6, 130.2, 138.2, 143.4, 145.7. MS m/z : 329 (M^+). Exact mass determination : 329.1797 (Calcd. for $C_{20}H_{27}NOS$: 329.1813).

(*1S,2S,αS,Rs*)-(+)-**4b** : $[\alpha]_D^{26}$+97.3° (c 2.22, $CHCl_3$). IRν_{max}^{film}cm^{-1} : 2250 (CN), 1640 (C=C), 1600 (aromatic), 1050 (S=O). ^{1}H-NMR ($CDCl_3$) δ : 1.04 (6H, s, $(CH_3)_2C$), 1.26-1.92 (6H, m, $(CH_2)_2CCH_2$), 1.67 (3H, s, CH_3C=C), 2.00-2.06 (1H, m, CHCS), 2.44 (3H, s, $C_6H_4C\underline{H}_3$), 2.46-2.50 (1H, m, CCH), 3.48-3.49 (1H, d, CHS), 4.79-4.80 (2H, d, CH_2=C), 7.36-7.65 (4H, q, C_6H_4). ^{13}C-NMR ($CDCl_3$) δ : 18.6, 21.6, 24.6, 27.7, 30.9, 32.5, 32.9, 38.4, 40.2, 49.5, 62.3, 113.7, 113.9, 125.0, 130.2, 138.5, 143.4, 145.6. MS m/z : 329 (M^+). Exact mass determination : 329.1797 (Calcd. for $C_{20}H_{27}NOS$: 329.1813).

(*1R,2R,αR*)-(-)-5,5-Dimethyl-2-isopropenyl-α-*p*-toluenesulfonylcyclohexaneacetonitrile (5)

m-Chloroperbenzoic acid (35mg, 0.21mmol) was added to a solution of (*1R,2R,αR,Rs*)-(+)-**4a** (47mg, 0.14mmol) in dichloromethane (5ml) at 0 °C. The reaction mixture was stirred at 0 °C for 1h, and then quenched with saturated aqueous $NaHCO_3$, and diluted with dichloromethane. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was subjected to preparative TLC (ether-hexane 1 : 2) to give (*1R,2R,αR*)-(-)-**5** (47mg, 98% yield). The oxidation of (*1S,2S,αS,Rs*)-(+)-**4b** was carried out in the same procedure to give (*1S,2S,αS*)-(+)-**5** ($[\alpha]_D^{26}$+14.0° (c 0.50, $CHCl_3$)).

(*1R,2R,αR*)-(-)-**5**: $[\alpha]_D^{26}$-15.3° (c 1.89, $CHCl_3$). IRν_{max}^{film} cm^{-1} : 2250 (CN), 1640 (C=C), 1600 (aromatic), 1330, 1155 (SO_2). ^{1}H-NMR ($CDCl_3$) δ : 0.96, 0.99 (6H, ss, $(CH_3)_2C$), 1.25-1.95 (7H, m, $(CH_2)_2CCH_2CH$), 1.63 (3H, s, CH_3C=C), 2.48 (3H, s, $C_6H_4C\underline{H}_3$), 2.56-2.59 (1H, t, CHCS), 2.56-2.59 (1H, m, CCH), 4.03-4.04 (1H, d, CHS), 4.79-4.84 (2H, d, CH_2=C), 7.26-7.84 (4H, q, C_6H_4). MS m/z : 345 (M^+). Exact mass determination : 345.1743 (Calcd. for $C_{20}H_{27}NO_2S$: 345.1762).

Dehydrosulfenylation of (*1R,2R,αR,Rs*)-(+)-4a

A solution of (*1R,2R,αR,Rs*)-(+)-**4a** (100mg, 0.30mmol) in carbon tetrachloride (10ml) was refluxed for 4h. After being cooled, the solution was concentrated *in vacuo*. The crude product was subjected to preparative TLC (benzene-hexane 4 : 1) to give (*S*)-(-)-5,5-dimethyl-2-isopropenylcyclohexylideneacetonitrile (**6**) (56mg, 98% yield). Heating of (*1S,2S,αS,Rs*)-(+)-**4b** in refluxing toluene for 12h produced (*R*)-(+)-**6** (96% yield, $[\alpha]_D^{26}$+14.6° (c 3.49, $CHCl_3$)).

(*S*)-(-)-**6** : $[\alpha]_D^{26}$-12.4° (c 3.07, $CHCl_3$). IRν_{max}^{film} cm^{-1} : 2200 (CN), 1670, 1620 (C=C). ^{1}H-NMR ($CDCl_3$) δ : 0.91, 1.04 (6H, ss, $(CH_3)_2C$), 1.35-1.94 (4H, m, $C(CH_2)_2$), 1.71 (3H, s, CH_3C=C), 2.62-2.72 (2H, m, C=CCH_2), 4.81-5.03 (2H, d, CH_2=C), 5.08 (1H, s, CHCN).^{13}C-NMR ($CDCl_3$) δ : 21.9, 25.4, 28.0, 30.6, 35.0, 38.1, 46.4, 51.2, 93.6, 113.9, 117.3, 143.8, 167.8. MS m/z : 189 (M^+). Exact mass determination : 189.1534 (Calcd. for $C_{13}H_{19}N$: 189.1534).

Transformation of *l*-Menthone (7) into (+)-Piperitone (9) via α-Selenenylation

A dry 25ml 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 1.5M butyllithium hexane solution (6.50ml, 9.74mmol) was added to a solution of diisopropylamine (993mg, 9.74mmol) in THF (20ml) at -78 °C and the mixture was stirred for 45min. A solution of **7** (1.00g, 6.49mmol, $[\alpha]_D^{23}$-24.6° (c 4.55, MeOH)) in THF (10ml) was added to the above solution at -78 °C and the mixture was stirred for 1h. A solution of diphenyl diselenide (3.04g, 9.74mmol) in THF (20ml) was added to the solution at -78 °C and the reaction mixture was allowed to stir at -78 °C for 3h. The reaction mixture was diluted with ether, and the ethereal solution was washed with 10% aqueous HCl and saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was subjected to flush column chromatography (ether-hexane 1 : 10) to give (2S,5R)-6-phenylselenenylmenthone (**8**) (1.40g, 72% yield): IRν_{max}^{film} cm^{-1} : 1705 (C=O), 1580 (aromatic). ^{1}H-NMR ($CDCl_3$) δ : 0.50-2.33 (7H, m, $(CH)_2(CH_2)_2CH$), 0.85-1.00 (9H, m, $(CH_3)_2C$, CH_3), 4.66-4.85 (1H, d, CHSe), 6.95-7.45 (5H, q, C_6H_5). A solution of (*2S,5R*)-**8** (1.50g, 4.85mmol) obtained above in THF (10ml) was added to a mixture of 30% aqueous H_2O_2 (0.72ml, 5.83mmol) and anhydrous $MgSO_4$ (2.90g, 24.30mmol) in THF (5ml) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 4h. The mixture was diluted with ether. The ethereal solution was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was subjected to flush column chromatography (ether-hexane 1 : 10) to give (*S*)-(+)-6-isopropyl-3-methyl-2-cyclohexenone (piperitone) (**9**)[18] (429mg, 58% yield) :

$[\alpha]_D^{26}$+18.6° (c 3.45, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ : 1.10-1.70 (6H, m, $(CH_3)_2C$), 1.66-2.66 (6H, m, $(CH)_2(CH_2)_2$), 2.00 (3H, s, CH_3), 5.80-5.90 (1H, s, C=CH).

1,4-Addition of Lithium Dimethylcuprate to (*S*)-(+)-9

A dry 50ml two-necked flask equipped with a septum inlet and a magnetic stirring bar and containing copper(I) iodide (357mg, 1.88mmol) was flushed with nitrogen, and maintained under a positive pressure of nitrogen. THF (7ml) was added to the flask, and then a 0.98M methyllithium ether solution (3.75ml, 3.83mmol) was added to the above mixture at 0 °C. The mixture was stirred for 30min. A solution of (*S*)-(+)-**9** (190mg, 1.25mmol, $[\alpha]_D^{26}$+18.6° (c 3.45, CHCl3)) in THF (3ml) was added dropwise to the above mixture at 0 °C .The reaction mixture was stirred at 0°C for 1h, then quenched with saturated aqueous NH_4Cl at 0 °C, and diluted with ether. The ethereal layer was washed with saturated aqueous NH_4Cl and saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was subjected to flush column chromatography (ether-hexane 1 : 10) to give (*S*)-(-)-5,5-dimethyl-2-isopropylcyclohexanone (**10**) (105mg, 50% yield) : $[\alpha]_D^{27}$-38.3° (c 6.09, $CHCl_3$). IRν_{max}^{film}cm^{-1} : 1705 (C=O). ^{1}H-NMR ($CDCl_3$) δ : 1.15-1.66 (12H, ss, $(CH_3)_2C$, $(C\underline{H}_3)_2CH$), 1.15-2.33 (8H, m, $(CH)_2(CH_2)_2CCH_2$). MS m/z : 168 (M+). Exact mass determination : 168.1511 (Calcd. for $C_{11}H_{20}O$: 168.1514).

Wittig Condensation of (*S*)-(-)-10

A dry 25ml two-necked flask equipped with a septum inlet and a magnetic stirring bar and containing methyltriphenylphosphonium iodide (361mg, 0.89mmol) was flushed with nitrogen, and maintained under a positive pressure of nitrogen. THF (3ml) was added to the flask and a 1.5M butyllithium hexane solution (0.61ml, 0.89mmol) was added to the above mixture at 0 °C. The mixture was stirred and warmed to room temperature during 1h. A solution of (*S*)-(-)-**10** (100mg, 0,60mmol, $[\alpha]_D^{27}$-38.3° (c 6.09, CHCl3)) in THF (2ml) was added to the above mixture at 0 °C, and the reaction mixture was stirred for 1h. The reaction mixture was diluted with ether, washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was subjected to flush column chromatography (hexane) to give (*S*)-(-)-4,4-dimethyl-1-isopropyl-2-methylidenecyclohexane (**11**) (71mg, 72% yield) : $[\alpha]_D^{26}$-18.7° (c 0.91, $CHCl_3$). IRν_{max}^{film}cm^{-1} : 1650, (C=C). ^{1}H-NMR ($CDCl_3$) δ : 0.70-1.00 (12H, ss, $(CH_3)_2C$, $(C\underline{H}_3)_2CH$), 1.15-2.00 (8H, m, $(CH)_2(CH_2)_2CCH_2$), 4.66 (2H, s, CH_2=C). MS m/z : 166 (M^+). Exact mass determination : 166.1705 (Calcd. for $C_{12}H_{22}$: 166.1721).

Catalytic Hydrogenation of (*1R,2R,αR,Rs*)-(+)-4a

A dry 25ml two-necked flask equipped with a septum inlet and a magnetic stirring bar and containing tris(triphenylphosphine)rhodium chloride (185mg, 0.20mmol) was flushed with hydrogen, and maintained under a positive pressure of hydrogen. A solution of (*1R,2R,αR,Rs*)-(+)-**4a** (600mg, 1.82mmol) in benzene (10ml) was added to the flask and the reaction mixture was stirred at room temperature for 12h. The reaction mixture was concentrated *in vacuo*. The crude product was subjected to preparative TLC (ether-hexane 1 : 2) to give (*1R,2S,αR,Rs*)-(+)-5,5-dimethyl-2-isopropyl-α-*p*-toluenesulfinylcyclohexaneacetonitrile (**12a**) (592mg, 98%).

The hydrogenation of (*1S,2S,αS,Rs*)-(+)-**4b** under the same reaction conditions produced (*1S,2R,αS,Rs*)-(+)-**12b**.

(*1R,2S,αR,Rs*)-(+)-**12a** : $[\alpha]_D^{26}$+101.7° (c 1.18, $CHCl_3$). IRν_{max}^{film}cm^{-1} : 2250 (CN), 1600 (aromatic), 1040 (S=O). ^{1}H-NMR ($CDCl_3$) δ : 0.40-1.00 (12H, ss, $(CH_3)_2C$, $(C\underline{H}_3)_2CH$), 1.10-2.20 (9H, m, $(CH)_2(CH_2)_2CCH_2CH$), 2.45 (3H, s, $C_6H_4C\underline{H}_3$), 3.66-3.70 (1H, d, CHS), 7.33-7.70 (4H, q, C_6H_4). MS m/z: 331 (M^+). Exact mass determination : 331.1945 (Calcd. for $C_{20}H_{29}NOS$: 331.1970).

(*1S,2R,αS,Rs*)-(+)-**12b** : $[\alpha]_D^{26}$+52.3° (c 1.03, $CHCl_3$). IRν_{max}^{film}cm^{-1} : 2250 (CN), 1600 (aromatic), 1040 (S=O). ^{1}H-NMR ($CDCl_3$) δ : 0.66-1.33 (12H, ss, $(CH_3)_2C$, $(C\underline{H}_3)_2CH$), 1.33-2.00 (9H, m, $(CH)_2(CH_2)_2CCH_2CH$), 2.55 (3H, s, $C_6H_4C\underline{H}_3$), 3.60-3.66 (1H, d, CHS), 7.33-7.70 (4H, q, C_6H_4). MS m/z: 331 (M^+). Exact mass determination : 331.1945 (Calcd. for $C_{20}H_{29}NOS$: 331.1970).

Dehydrosulfenylation of (*1R,2S,αR,Rs*)-(+)-12a

A solution of (*1R,2S,αR,Rs*)-(+)-**12a** (120mg, 0.35mmol) in carbon tetrachloride (10ml) was refluxed for 4h. After being cooled, the solution was concentrated *in vacuo*. The crude product was subjected to preparative TLC (benzene-hexane 4 : 1) to give (*S*)-(-)-5,5-dimethyl-2-isopropylcyclohexylideneacetonitrile (**13**) (47mg, 72% yield) : $[\alpha]_D^{27}$-28.6° (c 1.54, $CHCl_3$). IRν_{max}^{film}cm^{-1} : 2200 (CN), 1620 (C=C). ^{1}H-NMR ($CDCl_3$) δ : 0.78-1.00 (12H, ss, $(CH_3)_2C$, $(C\underline{H}_3)_2CH$), 1.22-1.89 (6H, m, $(CH)_2(CH_2)_2C$), 2.13-2.37 (2H, dd, CH_2C), 5.11 (1H, s, CHCN). MS m/z : 191 (M+). Exact mass determination : 191.1722 (Calcd. for $C_{13}H_{21}N$: 191.1674).

Reductive Hydrolysis of the Nitrile (*S*)-(-)-13

A 0.98M diisobutylaluminum hydride hexane solution (0.81ml, 0.79mmol) was added to a solution of (*S*)-(-)-**13** (100mg, 0.53mmol, $[\alpha]_D^{27}$-28.6° (c 1.54, $CHCl_3$)) in diethyl ether (4ml) and the reaction mixture was stirred at 0°C for 1h. The reaction mixture was diluted with ether, quenched with 10% aqueous HCl, and warmed to room temperature during 30min. 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 crude product was subjected to preparative TLC (ether-hexane 1 : 5) to give (*S*)-(-)-5,5-dimethyl-2-isopropylcyclohexylideneacetaldehyde (**14**) (97mg, 96% yield) : $[\alpha]_D^{27}$-23.1° (c 4.80, $CHCl_3$). IRν_{max}^{film}cm^{-1} : 1675 (C=O), 1620 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 0.80-1.20 (12H, ss, $(CH_3)_2C$, $(C\underline{H}_3)_2CH$), 1.33-3.00 (8H, m, $(CH)_2(CH_2)_2CCH_2$), 5.82-6.00 (1H, d, C=CH), 9.90-10.10 (1H, d, CHO). MS m/z : 194 (M^+). Exact mass determination : 194.1669 (Calcd. for $C_{13}H_{22}O$: 194.1671).

Decarbonylation of (*S*)-(-)-14

A dry 25ml two-necked flask equipped with a septum inlet and a magnetic stirring bar and containing tris(triphenylphosphine)rhodium chloride (485mg, 0.52mmol) was flushed with nitrogen, and maintained under a positive pressure of nitrogen. A solution of (*S*)-(-)-**14** (83mg, 0.44mmol, $[\alpha]_D^{27}$-23.1° (c 4.80, $CHCl_3$)) in benzene (3ml) was added to the flask, and the reaction mixture was refluxed for 1h. After being cooled, the mixture was filtered and the filtrate was concentrated *in vacuo*. The crude product was subjected to flash column

chromatography (hexane) to give (*S*)-(-)-**11** (27mg, 39% yield, $[\alpha]_D^{27}$ -21.8° (c 2.71, $CHCl_3$)). The spectral data were completely identical with those of (*S*)-(-)-**11** obtained from (*S*)-(-)-**10**, as described earlier.

Acknowledgement Partial financial support of this research by the Japan Foundation for the Optically Active Compounds is gratefully acknowledged.

REFERENCES

1. This publication belongs to Studies on Chiral Organosulfur Compounds IV in the series of the papers by our groups. For the part III see Hiroi, K.; Umemura, M.; Fujisawa, A. *Chem. Pharm. Bull.* submitted.
2. For leading reviews see Hoffmann, H.M.R. *Angew. Chem. Int. Ed. Engl.* **1969**, 8, 556-577; Oppolzer, W.; Snieckus, V. *Angew. Chem.* **1978**, 90, 506-516; Snider, B.B. *Acc. Chem. Res.* **1980**, 13, 426-432; Fujita, Y.; Suzuki, S.; Kanehira, K. *Yuki Gosei Kagaku Kyokai Shi* **1983**, 41, 1152-1167; Dubae, J.; Laporterie, A. *Chem. Rev.* **1987**, 87, 319-334; Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, 92, 1021-1050.
3. For recent papers see Mikami, K.; Loh, T.-P.; Nakai, T. *J. Am. Chem. Soc.* **1990**, 112, 6737-6738; Mikami, K.; Loh, T.-P.; Nakai, T. *Tetrahedron Asymmetry* **1990**, 1, 13-16; Kamimura, A.; Yamamoto, A. *Chem. Lett.* **1990**, 1991-1994.
4. For recent papers see Mikami, K.; Takahashi, K.; Nakai, T. *Tetrahedron Lett.* **1989**, 30, 357-360; Mikami, K.; Takahashi, K.; Nakai, T. *Synlett.* **1989**, 45-46; Mikami, K.; Takahashi, K.; Nakai, T. *J. Am. Chem. Soc.* **1990**, 112, 4035-4037; Maruoka, K.; Ooi, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, 112, 9011-9012.
5. Achmatowicz, Jr., O.; Szechner, B. *J. Org. Chem.* **1972**, 37, 964-967; Whitesell, J.K.; Deyo, D.; Bhattacharya, A. *J. Chem. Soc., Chem. Commun.* **1983**, 802.
6. Stephenson, L.M.; Mattern, D.L. *J. Org. Chem.* **1976**, 41, 3614-3619; Mikami, K.; Narisawa, S.; Shimizu, M.; Terada, M. *J. Am. Chem. Soc.* **1992**, 114, 6566-6568.
7. Narasaka, K.; Hayashi, Y.; Shimada, S. *Chem. Lett.* **1988**, 1609-1612; Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1989**, 111, 1940-1941; Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, 112, 3949-3954; Terada, M.; Mikami, K.; Nakai, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1623-1624; Mikami, K.; Terada, M. *Tetrahedron* **1992**, 48, 5671-5680.
8. Maruoka, K.; Hoshino, Y.; Shirasaka, T.; Yamamoto, H. *Tetrahedron Lett.* **1988**, 29, 3967-3970.
9. Sakane, S.; Maruoka, K.; Yamamoto, H. *Tetrahedron* **1986**, 42, 2203-2209.
10. Hiroi, K.; Yamamoto, M.; Kurihara, Y.; Yonezawa, H. *Tetrahedron Lett.* **1990**, 31, 2619-2622.
11. Hiroi, K.; Kurihara, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 1778-1780.
12. Hiroi, K.; Kitayama, R.; Sato, S. *J. Chem. Soc., Chem. Commun.* **1983**, 1470-1472; *Chem. Pharm. Bull.* **1984**, 32, 2628-2638; *J. Chem. Soc., Chem. Commun.* **1984**, 303-305; *Chem. Lett.* **1984**, 929-932; Hiroi, K. *Yuki Gosei Kagaku Kyokai Shi* **1986**, 44, 907-917; Hiroi, K.; Makino, K. *Chem. Lett.* **1986**, 617-620; *Chem. Pharm. Bull.* **1988**, 36, 1744-1749.
13. Hiroi, K.; Umemura, M. *Tetrahedron Lett.* **1992**, 33, 3343-3346.
14. Numata, T.; Itoh, O.; Yoshimura, T.; Oae, S. *Bull. Chem. Soc. Jpn.* **1983**, 56, 257-265.
15. Trost, B.M.; Salzmann, T.N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, 98, 4887-4902.
16. Brown, M.; Piszkiewicz, L.W. *J. Org. Chem* **1967**, 32, 2013-2014.
17. Tsuji, J.; Ohno, K. *Tetrahedron Lett.* **1965**, 3969-3971.
18. von Rudloff, E. *Can. J. Chem.* **1964**, 42, 1057-1062.