New Optically Active Pyrazoles: Syntheses and the Structural Characterization of Menthopyrazole Analogues

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New chiral pyrazoles, (4*R*,7*R*)-4-methyl-7-isopropyl-3-phenyl- (3-phenyl*iso*menthopyrazole; *cis*-**1**), (4*R*,7*S*)-4-methyl-7-isopropyl- (*l*-menthopyrazole; *trans*-**2**), (4*R*,7*R*)-4-isopropyl-7-methyl- (*iso*carvomenthopyrazole, *cis*-**3**) and (4*R*,7*S*)-4-isopropyl-7-methyl-4,5,6,7-tetrahydro-1*H*-indazole (carvomenthopyrazole, *trans*-**3**) were prepared. The diastereomeric pairs of these **1**-**3** were structurally characterized by NMR spectroscopy. The subtle differences of structures of **1**-**3** should induce the useful effects for a chiral auxiliary or a chiral catalyst.

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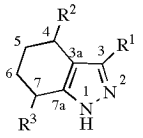
We have previously developed the preparation and the utilities of (4*R*,7*S*)-3-phenyl-4-methyl-7-isopropyl-4,5,6,7-tetrahydro-1*H*-indazole (3-phenyl-*l*-menthopyrazole; *trans*-**1**) as a chiral auxiliary [1]. This auxiliary is easily prepared from commercially available *l*-menthone in good yield with high optical purity, and has unique structure and properties relative to the conventional chiral auxiliaries [2]. The most important characteristics of this auxiliary are that the substrate terminates to nitrogen atom of heteroaromatic pyrazole ring and that the 3-phenyl ring of *trans*-**1** is close to the (4*R*)-methyl group. Subsequently, the steric repulsion is relaxed by rotation of the phenyl ring, and the substrate is located in the chiral environment. This structural feature causes the diastereofacial attack on the substrate moiety in the reactions with alkyl halides [3], diphenyldisulfide [4], acyl chloride [5], aldehydes [6], and C=N compounds [7]. Moreover, the asymmetric additions of Grignard reagents [8], dienes [9] and 1,3-dipolar compounds [10] on 2-(α,β-unsaturated)acyl-3-phenyl-*l*-menthopyrazoles have been reported. Otherwise, the extensive use of these optically active pyrazoles was studied as the chiral catalyst for the asymmetric borane reduction of ketones [11,12] and the asymmetric dialkylzinc addition on aldehydes [13].



3-Phenyl-*l*-menthopyrazole (*trans*-**1**):	R^1= Ph, R^2= (*R*)-Me, R^3= (*S*)-*i*Pr
3-Phenyl*iso*menthopyrazole (*cis*-**1**):	R^1= Ph, R^2= (*R*)-Me, R^3= (*R*)-*i*Pr
l-Menthopyrazole (*trans*-**2**):	R^1= H, R^2= (*R*)-Me, R^3= (*S*)-*i*Pr
*Iso*menthopyrazole (*cis*-**2**):	R^1= H, R^2= (*R*)-Me, R^3= (*R*)-*i*Pr
Carvomenthopyrazole (*trans*-**3**):	R^1= H, R^2= (*R*)-*i*Pr, R^3= (*S*)-Me
*Iso*carvomenthopyrazole (*cis*-**3**):	R^1= H, R^2= (*R*)-*i*Pr, R^3= (*R*)-Me

Figure

In the meanwhile, the preparation of (4*R*,7*R*)-4-methyl-7-isopropyl-4,5,6,7-tetrahydro-1*H*-indazole (*iso*menthopyrazole; *cis*-**2**) from *l*-menthone was reported, where (4*R*,7*S*)-4-methyl-7-isopropyl-4,5,6,7-tetrahydro-1*H*-indazole (*l*-menthopyrazole; *trans*-**2**) was formed in a yield too low to be isolated [14]. Some of *cis*-**2** derivatives were used as chiral catalysts in the asymmetric reactions such as bis(*iso*menthopyrazolyl)methanes in allylic alkylation [15], bis(*iso*menthopyrazolyl)pyridine in cyclopropanation [16] and tris(*iso*menthopyrazolyl)hydroborate in polymerization of lactides [17].

Because of difficulty in isolating the *trans*-**2**, this compound up until now had not been studied or characterized. Also (4*R*,7*R*)-4-methyl-7-isopropyl-3-phenyl-4,5,6,7-tetrahydro-1*H*-indazole (3-phenyl*iso*menthopyrazole; *cis*-**1**) should perhaps have a different twisting angle of the 3-phenyl ring against the pyrazole ring, relative to that of epimeric *trans*-**1**. Therefore, we have desired to investigate the isolation and the characterization of both *cis*-**1** and *trans*-**2**, which were expected to exhibit different steric effects as a chiral auxiliary and/or a chiral catalyst. Moreover, (4*R*,7*S*)-4-isopropyl-7-methyl-4,5,6,7-tetrahydro-1*H*-indazole (carvomenthopyrazole; *trans*-**3**) and (4*R*,7*R*)-4-isopropyl-7-methyl-4,5,6,7-tetrahydro-1*H*-indazole (*iso*carvomenthopyrazole; *cis*-**3**) attract our interest in their preparation and the characterization. These regioisomers of *cis*-/*trans*-**2** have a bulky isopropyl group on 3-position but not on 7-position.

In this paper we report the syntheses of new chiral pyrazoles *cis*-**1**, *trans*-**2**, *trans*-**3** and *cis*-**3**, which should exhibit useful properties which make them prospective chiral auxiliary or chiral catalyst in the asymmetric organic synthesis. Also the structural features of diastereomers of **1-3** were revealed by the comparison of their 1D and 2D NMR spectra.

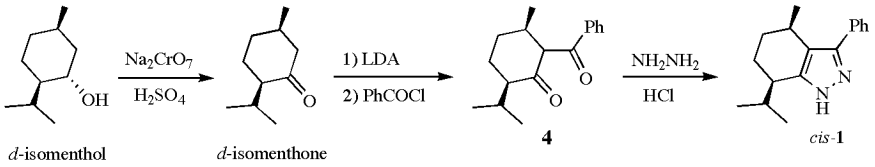
Results and Discussion.

3-Phenyl*iso*menthopyrazole (*cis*-**1**) was synthesized from (2*R*,5*R*)-2-isopropyl-5-methylcyclohexanone (isomenthone) according to the preparative method of *trans*-**1** (Scheme 1). Isomenthone was prepared by chromic acid oxidation of commercially available isomenthol. Isomenthone was acylated by benzoyl chloride in the presence of LDA to afford 2-benzoylisomenthone (**4**), which was treated with hydrazine monohydrate to give *cis*-**1** in moderate yield. During the benzoylation and pyrazole ring

formation, no epimerization and racemization was observed in GC through a chiral stationary-phase column.

13:1. On the contrary, *l*-menthone was formylated with LDA (Scheme 2, Method B) to give the mixture of *cis*-**5**

Scheme 1



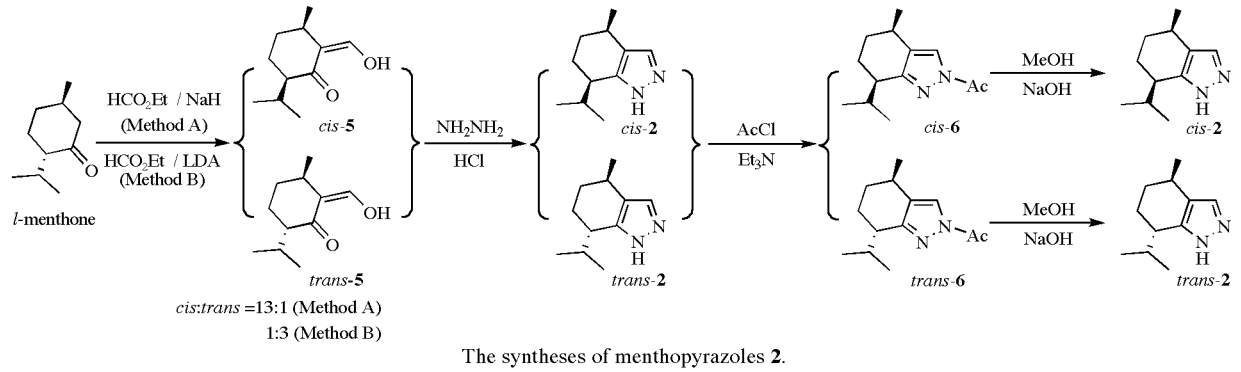
The syntheses of 3-phenyl*iso*menthopyrazole (*cis*-**1**).

As shown in the synthesis of *iso*menthopyrazole (*cis*-**2**) and *l*-menthopyrazole (*trans*-**2**), the mixture of (2*R*,5*R*)-(*cis*-**5**) and (2*S*,5*R*)-6-hydroxymethylene-2-isopropyl-5-methylcyclohexanone (*trans*-**5**) was prepared by the formylation of (2*S*,5*R*)-2-isopropyl-5-methylcyclohexanone *(l*-menthone) following a procedure that uses sodium hydride, which was modified from that method by using sodium methoxide [14b] (Scheme 2, Method A). In this formylation, the *l*-menthone skeleton was epimerized into isomenthone skeleton on *C*-2 carbon having 2*R* configuration, and *cis*-**5** was predominantly formed with the ratio of

and *trans*-**5** with the ratio of 1:3. When isomenthone was formylated according to either Method A or B, *cis*-**5** was predominantly formed with the ratio of 13:1, respectively. Namely, the formylation with sodium hydride afforded the *cis* isomer independent from the configuration of the menthone substrate, while the stereo structure of menthones was partly retained in the formylation using LDA.

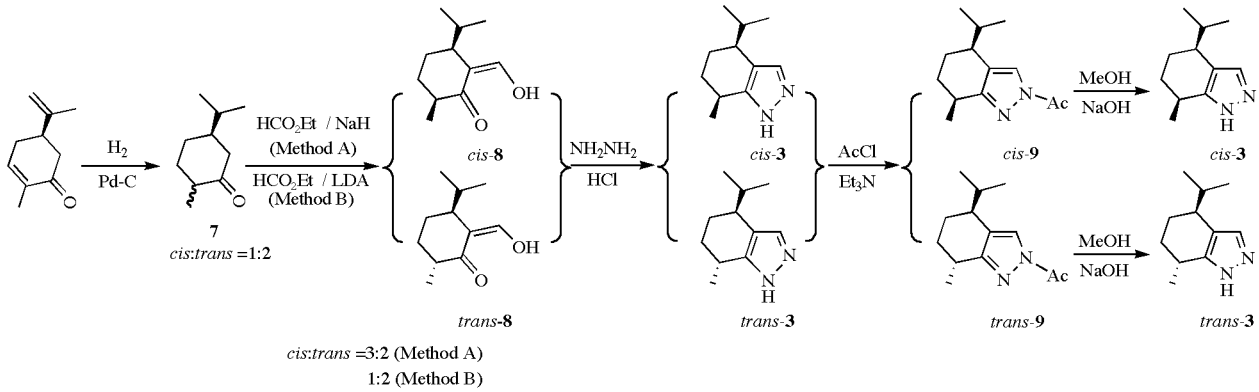
Since the separation of diastereomeric mixture of **5** was unsuccessful even by the careful chromatography, the mixture of *cis*-**5** and *trans*-**5** was treated with hydrazine hydrate without isolation. Subsequent mixture of

Scheme 2



The syntheses of menthopyrazoles **2**.

Scheme 3



The syntheses of carvomenthopyrazoles **3**.

diastereomeric pyrazoles *cis*-**2** and *trans*-**2** was obtained with the *cis*/*trans* ratio depending on that of **5**. Although the isolation of *cis*-**2** mixture was formerly accomplished by fractional recrystallization of their hydrochloride salts, the isolation of *trans*-**2** was unsuccessful by either chromatographic separation or fractional recrystallization.

Previously *N*-acylation of *trans*-**1** was studied to give *N*-acyl-3-phenyl-*l*-menthopyrazoles, isomers of which were easily purified by chromatographic separation [1]. Moreover, *N*-acyl-3-phenyl-*l*-menthopyrazoles were easily deacylated into *trans*-**1** by the action of nucleophiles such as alcohols [18] and amines [19]. On the basis of these facts, the resolution of the isomeric mixture of *cis*-**2** and *trans*-**2** was undertaken by means of the acylation, chromatographic separation and the subsequent deacylation. When the mixture of *cis*-**2** and *trans*-**2** was treated with acetyl chloride in the presence of triethylamine, acetylation occurred regioselectively at the *N*-2 position to afford a mixture of *cis*-**6** and *trans*-**6**. After chromatographic separation between *cis*-**6** and *trans*-**6**, the independent deacetylation of *cis*-**6** and *trans*-**6** gave *cis*-**2** and *trans*-**2** without epimerization by the action of sodium hydroxide or sulfuric acid, respectively. Both of resulting *cis*-**2** and *trans*-**2** were proven to be optically pure by chiral GC.

In order to clarify the substituent effect of methyl and isopropyl groups on *l*-menthopyrazoles and isomenthopyrazoles, the synthesis of (4*R*)-4-isopropyl-7-methyl-4,5,6,7-tetrahydro-1*H*-indazole (carvomenthopyrazole, **3**), which was the regioisomers of menthopyrazoles, was attempted from (*R*)-(-)-carvone ((5R)-2-methyl-5-propenyl-2-cyclohexenone) (Scheme 3). Commercially available (*R*)-(-)-carvone was hydrogenated over Pd/C to give carvomenthone (**7**) as 1:2 *cis*/*trans* mixture, which were the regioisomers of isomenthone and *l*-menthone. The *cis*/*trans* mixture of **7** was formylated by sodium hydride (Method A) or LDA (Method B) to afford a mixture of (4*S*,7*S*)- (*cis*-**8**) and (4*S*,7*R*)-2-hydroxymethylene-6-methyl-3-isopropylcyclohexanone (*trans*-**8**) in the ratios of 3:2 (Method A) and 1:2 (Method B), respectively. Since the isomeric separations of **7**, **8** and **3** were unsuccessful by chromatography, the mixture of *cis*-**8** and *trans*-**8** was converted into *cis*-**3** and *trans*-**3** by hydrazine monohydrate without any purification. Further the isomeric purification of **3** was carried out by way of acetylation, chromatography and then deacetylation, as described above. Chiral GC was used to determine the optical purities of *cis*-**3** and *trans*-**3**.

The stereo-chemical structure of these new chiral pyrazoles were studied by NMR spectroscopy using 1D- and 2D-measurement including HMQC and NOESY technique, as listed in Table 1. Although NMR data for *trans*-**1** [1] and *cis*-**2** [14b] have already been reported in papers, we took notice on the peaks attributable to the *C*-5 and *C*-6 protons. Both of *C*-5 axial and *C*-6 axial protons of *trans*-**1** are triplets of doublets of doublets due to two *trans*-diaxial *anti* vicinal couplings (J=6.7 Hz), an axial-equatorial

Table 1

^{1}H NMR Spectral Data of **1**-**3**

Chemical shift (δ)

	cis-**1**	*trans*-**1**	*cis*-**2**	*trans*-**2**	cis-**3**	*trans*-**3**
3	---	---	7.35 (s)	7.35 (s)	7.34 (s)	7.35 (s)
4	3.22	3.09	1.43-1.53 (m)	2.65	2.49	2.62
	(dq, 12.7, 6.4)	(sex, 6.7)		(d-quint, 11.1, 6.0)	(q, 6.4)	(dt, 10.3, 5.1)
5eq	1.67-1.73 (m)	2.04	1.43-1.53 (m)	1.95	1.57-1.65 (m)	1.82
		(dtd, 13.3, 6.7, 2.6)		(dm, 12.9)		(dtd, 12.4, 5.5, 2.0)
5ax	1.82-1.88 (m)	1.31	1.74-1.82 (m)	1.19	1.66-1.72 (m)	1.37
		(qd, 10.6, 2.6)		(qd, 12.9, 2.4)		(qd, 12.7, 2.2)
6eq	1.67-1.73 (m)	1.827	1.64-1.69 (m)	1.88	1.57-1.65 (m)	1.99-2.07 (m)
		(dtd, 13.2, 6.5, 2.6)		(dm, 13.0)		
6ax	1.67-1.73 (m)	1.56	1.74-1.82 (m)	1.46	1.81-1.85 (m)	1.31
		(qd, 10.9, 2.4)		(qd, 13.0, 2.4)		(qd, 12.5, 2.2)
7	2.71	2.59	2.61	2.74	2.90	2.78
	(dt, 9.1, 4.6)	(dt, 7.1, 4.5)	(q, 5.8)	(dt, 11.0, 5.5)	(sex, 6.4)	(d-quin, 10.2, 5.1)
4-Me	1.10 (d, 6.9)	0.99 (d, 6.7)	0.86 (d, 6.8)	1.20 (d, 6.8)	---	---
7-*i*Pr (Me)	0.86 (d, 6.9)	0.82 (d, 6.8)	1.04 (d, 6.8)	0.81 (d, 6.9)	---	---
	1.05 (d, 6.9)	0.99 (d, 6.6)	1.18 (d, 6.9)	1.03 (d, 6.9)	---	---
7-*i*Pr (CH)	2.26 (oct, 5.8)	2.16 (oct, 6.6)	2.11 (oct, 6.5)	2.27 (broad)	---	---
4-*i*Pr (Me)	---	---	---	---	0.88 (d, 6.8)	0.83 (d, 6.9)
	---	---	---	---	0.99 (d, 6.8)	0.99 (d, 6.9)
4-*i*Pr (CH)	---	---	---	---	1.89 (oct, 6.7)	1.99-2.07 (m)
7-Me	---	---	---	---	1.27 (d, 7.0)	1.301 (d, 6.8)
3-Ph (p)	7.31 (d, 7.4)	7.31 (d, 7.4)	---	---	---	---
3-Ph (m)	7.39 (d, 7.4)	7.38 (d, 7.4)	---	---	---	---
3-Ph (o)	7.68 (d, 7.5)	7.60 (d, 7.4)	---	---	---	---

geminal coupling (J=10.7 Hz) and an axial-equatorial vicinal coupling (J=2.5Hz). Also those of *trans*-**2** and *trans*-**3** appeared as the peaks of quartet (J=12.5~13.0 Hz) of doublet (J=2.2~2.4 Hz). These spectral features of *trans*-**1**-**3** supported their typical half chair form having the two substituent groups on equatorial positions of *C*-4 and *C*-7. On the contrary, both of *C*-5 and *C*-6 protons of *cis*-**2** were observed as the complicated multiplets, where the steric configuration was previously reported to be distorted from the chair form [13-15]. Similarly, the complicated multiplets were attributable to the axial proton signals on *C*-5 and *C*-6 of *cis*-**1** and *cis*-**3**. It is suggested that the distorted half-chair six-membered ring of tetrahydroindazole is responsible for the complicated coupling patterns observed for *cis*-**1**-**3**.

The methyl group on *C*-4 position and the *C*-4 proton of *trans*-**1** were shifted to higher and lower fields respectively by the anisotropic effect of the 3-phenyl group, comparing with those of *trans*-**2**. This anisotropic observation was supported by the X-ray structural analysis that the benzene ring of *trans*-1 was twisted about 40° against pyrazole ring. In the case of *cis*-**1**, the methyl group and the proton signals on *C*-4 were also shifted compared with those of *cis*-**2**, but to a lesser extent than those of *trans*-**1**. This difference in the magnitude of the anisotropic effect of the 3-phenyl group should reflected in the twisting angle of the benzene ring relative to the pyrazole ring of *cis*-**1** compared to that of *trans*-**1**, which causes most of the diastereofacial behaviors when used as a chiral auxiliary. In addition, the ^{13}C NMR spectra of *cis*-**1** were found to be the broad signals. This may be explained by a slow tautomerisation between 1*H*- and 2*H*-tetrahydroindazole. The predominant tautomer seemed to be the 1*H*-tetrahydroindazole form in this new chiral pyrazole.

In conclusion, new chiral pyrazoles, (4*R*,7*R*)-4-methyl-7-isopropyl-3-phenyl- (3-phenyl*iso*menthopyrazole; *cis*-**1**), (4*R*,7*S*)-4-methyl-7-isopropyl- (*l*-menthopyrazole; *trans*-**2**), (4*R*,7*R*)-4-isopropyl-7-methyl- (*iso*carvomenthopyrazole, *cis*-**3**) and (4*R*,7*S*)-4-isopropyl-7-methyl-4,5,6,7-tetrahydro-1*H*-indazole (carvomenthopyrazole, *trans*-**3**) were prepared. The diastereomeric pairs of these **1**-**3** were structurally characterized by NMR spectroscopy. The subtle differences of structures of **1**-**3** should induce useful effects for use as a chiral auxiliary or chiral catalyst.

EXPERIMENTAL

Melting points are uncorrected. NMR data were collected on Bruker AVANCE 600 (600 MHz) or JEOL ENM-EX270 (270 MHz) spectrometer in deuteriochloroform with tetramethylsilane as an internal standard. Optical rotations were observed using a JASCO DIP-370 digital polarimeter. Chiral GC chromatograms were obtained on SHIMADZU GC-14A gas chromatograph using Chrompak Chirasil DEX-CB capillary column (φ 0.25 mm x 25 m). THF and Et_2O were dried over benzophenone ketyl radical, and toluene was distilled over calcium hydride.

Preparation of 3-Phenyl*iso*menthopyrazole**.**

(3*R*,6*R*)-2-Benzoyl-3-methyl-6-isopropylcyclohexanone (**4**).

To the Et_2O solution (40 ml) of isomenthol (7.8 g, 50 mmol) in ice bath, sodium dichromate dihydrate (5.2 g, 17 mmol) in dilute sulfuric acid (25 ml, 7.2 *M*) was added dropwise over 1 hour. After stirring another hour at room temperature, the mixture was extracted with Et_2O. The combined organic layer was washed with saturated $NaHCO_3$ and saturated NaCl, and dried over anhydrous $MgSO_4$. After removal of the solvent, isomenthone (7.2 g, 47 mmol) was purified by Kugelrohr distillation. The subsequent isomenthone (1.5 g, 10 mmol) in THF (10 ml) was added to THF solution (10 ml) of LDA, which was prepared *in situ* from diisopropylamine (1.6 ml) and butyllithium solution (7.5 ml, 1.59 *M* in hexane) at –5 °C. After stirring for 15 minutes at –5 °C, the mixture was treated with benzoyl chloride (1.6 g, 11 mmol) in THF (5 ml), and then warmed up to room temperature with stirring for 1.5 hours. The mixture was quenched with dilute hydrochloric acid and extracted with Et_2O. The combined organic layer was washed with saturated NaCl, dried over anhydrous $MgSO_4$, and concentrated. The reaction residue was purified by recrystallization from methanol or hexane; yield 38 %; mp 108.5-109.5 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.87 (3H, d, J=6.6 Hz), 0.94 (3H, d, J=6.6 Hz), 1.01 (3H, d, J=6.9 Hz), 1.54-1.65 (1H, m), 1.86-2.02 (3H, m), 2.10-2.22 (2H, m), 2.63-2.70 (1H, m), 4.17 (1H, d, J=7.6 Hz), 7.41-7.59 (3H, m), 7.88-7.93 (2H, m); ^{13}C NMR (270 MHz, $CDCl_3$): δ 19.4 (CH_3), 20.4 (CH_3), 21.1 (CH_3), 26.2 (CH_2), 26.9 (CH_2), 28.0 (CH), 36.0 (CH), 56.8 (CH), 64.7 (CH), 128.4 (CH), 128.6 (CH), 133.2 (CH), 137.5 (C), 197.5 (C), 210.5 (C).

Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.24; H, 8.55.

(4*R*,7*R*)-3-Phenyl-4-methyl-7-isopropyl-4,5,6,7-tetrahydroindazole (*cis*-**1**).

The mixture of (3*R*,6*R*)-2-benzoyl-3-methyl-6-isopropylcyclohexanone (**4**, 970 mg, 3.7 mmol), hydrazine monohydrate (2.8 g, 56 mmol) and hydrazine hydrochloride (400 mg, 5.9 mmol) in methanol (20 ml) was refluxed for 6 hours. The reaction mixture was quenched with water and extracted with Et_2O. The organic layer was washed with aqueous $NaHCO_3$, and saturated NaCl, dried over anhydrous $MgSO_4$, and concentrated. The reaction residue was purified by recrystallization from aqueous methanol; yield 89 %; mp 124-126°C; $[\alpha]_D$ –10.8 (*c* 2.73, $CHCl_3$); ^{13}C NMR (270 MHz, $CDCl_3$): δ 17.8 (CH_3), 18.6 (CH_2), 20.4 (CH_3), 21.2 (CH_3), 25.8 (CH), 30.0 (CH), 30.3 (CH_2), 39.7 (CH), 119.2 (C), 126.7 (CH), 127.3 (CH), 128.5 (CH), 133.8 (C), 144.7 (C, broad), 145.3 (C, broad). The ^{1}H NMR data were summarized in Table 1 as well as those of *trans*-**1**.

Anal. Calcd for $C_{17}H_{22}N_2$: C, 80.27; H, 8.72; N, 11.01. Found: C, 79.99; H, 8.72; N, 10.88.

Preparation of *cis*-**2**, *trans*-**2**, *cis*-**3** and *trans*-**3**.

Hydrogenation of (*R*)-Carvone.

The MeOH (30 ml) solution of (*R*)-carvone (1.05 g, 7.0 mmol) was hydrogenated over Pd (50 mg, 5 % on carbon) under room pressure and temperature for 4 hours. After filtering off the catalyst, the solvent was removed to give the mixture (980 mg) of *cis*-

7 and *trans*-**7**. The product mixture was purified by Kugelrohr distillation, and was identical with the reported NMR data [20].

General Procedure for Formylation and the Pyrazole Ring Formation.

Method A.

To a suspension of NaH (1.9 g, 48 mmol, 60 % in oil) in Et_2O (40 ml), *l*-menthone or the mixture of *cis*-**7** and *trans*-**7** (42 mmol) in Et_2O (40 ml) was added, followed by ethyl formate (6.3 g, 85 mmol) in Et_2O (40 ml). After stirring for 18 hours under argon atmosphere, the mixture was dissolved in H_2O. The organic layer was extracted with 1 *M* NaOH. The combined aqueous layers were acidified with hydrochloric acid, and extracted with Et_2O. The Et_2O layers were washed with saturated NaCl, and dried over anhydrous $MgSO_4$. After removal of the solvent, the residual oil (6.7 g) was comprised of a 13:1 ratio of (3*R*,6*R*)- (*cis*-**5**) and (3*R*,6*S*)-2-hydroxymethylene-6-isopropyl-3-methylcyclohexanones (*trans*-**5**). In the case of **7**, the residual oil (2.4 g) was comprised of a 3:2 ratio of (3*R*,6*R*)- (*cis*-**8**) and (3*S*,6*R*)-2-hydroxymethylene-6-isopropyl-3-methylcyclohexanones (*trans*-**8**). The mixture was refluxed with hydrazine monohydrate (1.1 g, 22 mmol) and hydrazine hydrochloride (135 mg, 2.0 mmol) in methanol (30 ml) for 3 hours. The reaction mixture was quenched with H_2O and extracted with Et_2O. The Et_2O layer was washed with water and saturated NaCl, dried over anhydrous $MgSO_4$ and concentrated. The product (6.1 g) was found to be *cis*-**2** and *trans*-**2** mixture with the ratio of 13:1 after Kugelrohr distillation under reduced pressure. Otherwise, *cis*-**3** and *trans*-**3** mixture (2.2 g) was isolated with the ratio of 3:2 by Kugelrohr distillation under reduced pressure.

Method B.

To THF solution (40 ml) of LDA which was prepared *in situ* from diisopropylamine (9 ml) and butyllithium solution (40 ml, 1.59 *M* in hexane), *l*-menthone or the mixture of *cis*-**7** and *trans*-**7** (60 mmol) in THF (10 ml) was added at –5 °C. After standing for 15 minutes at –5 °C, ethyl formate (6.0 g, 81 mmol) in THF (30 ml) was added to the mixture and stirred for 1.5 hours. The mixture was quenched with H_2O and the organic layer was extracted 1 *M* NaOH. The combined aqueous layers were acidified with hydrochloric acid, and extracted with Et_2O. The Et_2O layer was washed with saturated NaCl, and dried over anhydrous $MgSO_4$. After removal of the solvent, the residual oil (5.1 g) was comprised of a 1:3 ratio of *cis*-**5** and *trans*-**5**. In the case of **7**, the residual oil (4.3 g) was comprised of a 1:2 ratio of *cis*-**7** and *trans*-**7**. The mixture was refluxed with hydrazine monohydrate (1.5 g, 30 mmol) and hydrazine hydrochloride (170 mg, 2.5 mmol) in methanol for 3 hours. The reaction mixture was extracted with Et_2O, and the organic layer was washed with water and saturated NaCl, dried over anhydrous $MgSO_4$ and concentrated. The product (5.6 g) was found to be *cis*-**2** and *trans*-**2** mixture with the ratio of 1:3 after Kugelrohr distillation under reduced pressure. Otherwise, *cis*-**3** and *trans*-**3** mixture (1.6 g) was isolated with the ratio of 1:2 by Kugelrohr distillation under reduced pressure.

Acetylation of *cis*-**2**, *trans*-**2**, *cis*-**3** and *trans*-**3**.

A mixture (5 mmol) of *cis*-**2** and *trans*-**2** or a mixture (5 mmol) of *cis*-**3** and *trans*-**3**, prepared as above, was acetylated by acetyl chloride (8.8 mmol) in toluene (20 ml) in the presence of triethylamine (15 mmol), according to the formerly described method [3]. The subsequent mixture was separated by silica gel column chromatography with benzene-hexane mixture (v/v 1:1), respectively. All products were obtained as colorless oils, and *cis*-**6** crystallized upon standing for a few days.

(4*R*,7*S*)-2-Acetyl-4-methyl-7-isopropyl-4,5,6,7-tetrahydro-2*H*-indazole (*trans*-**6**).

Trans-**6** showed bp 200 °C/4 mmHg; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.88 (3H, d, *J*= 6.9 Hz), 1.03 (3H, d, *J*= 6.9 Hz), 1.18 (1H, q, *J*= 12.2 Hz), 1.21 (3H, d, *J*= 6.6 Hz), 1.46 (1H, q, *J*= 12.2 Hz), 1.90-1.98 (2H, m), 2.38-2.45 (1H, m), 2.59-2.71 (2H, m), 2.64 (3H, s), 7.95 (1H, d, *J*= 1.3Hz); ^{13}C NMR (270 MHz, $CDCl_3$): δ 18.1 (CH_3), 19.9 (CH_3), 20.9 (CH_3), 21.5 (CH_2), 23.7 (CH_3), 28.1 (CH), 30.1 (CH), 32.2 (CH_2), 41.0 (CH), 123.7 (CH), 128.4 (C), 157.6 (C), 169.5 (C).

Anal. Calcd for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72. Found: C, 70.48; H, 9.17; N, 12.46.

(4*R*,7*R*)-2-Acetyl-4-methyl-7-isopropyl-4,5,6,7-tetrahydro-2H-indazole (*cis*-**6**).

Cis-**6** showed bp 200 °C/4mmHg; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.92 (3H, d, *J*= 6.9 Hz), 1.06 (3H, d, *J*= 6.9 Hz), 1.19 (3H, d, *J*= 6.9 Hz), 1.43-1.59 (1H, m), 1.65-1.88 (3H, m), 2.13-2.28 (1H, m), 2.53-2.67 (1H, m), 2.64 (3H, s), 2.78-2.88 (1H, m), 7.94 (1H, d, *J*= 1.3Hz); ^{13}C NMR (270 MHz, $CDCl_3$): δ 19.0 (CH_3), 20.6 (CH_3), 21.51 (CH_3), 21.58 (CH_2), 22.1 (CH_3), 26.3 (CH), 29.2 (CH_2), 30.6 (CH), 40.0 (CH), 124.0 (CH), 127.6 (C), 157.5 (C), 169.6 (C).

Anal. Calcd for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72. Found: C, 70.30; H, 9.14; N, 12.70.

(4*S*,7*R*)-2-Acetyl-4-isopropyl-7-methyl-4,5,6,7-tetrahydro-2*H*-indazole (*trans*-**9**).

Trans-**9** showed ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.84 (3H, d, *J*=6.9 Hz), 0.99 (3H, d, *J*=6.9 Hz), 1.22-1.43 (2H, m), 1.34 (3H, d, *J*=6.9 Hz), 1.78-1.94 (1H, m), 1.97-2.10 (2H, m), 2.56-2.77 (2H, m), 2.65 (3H, s), 2.78-2.88 (1H, m), 7.95 (1H, d, *J*= 1.6Hz); ^{13}C NMR (270 MHz, $CDCl_3$): δ 19.0 (CH_3), 20.6 (CH_3), 21.51 (CH_3), 21.58 (CH_2), 22.1 (CH_3), 26.3 (CH), 29.2 (CH_2), 30.6 (CH), 40.0 (CH), 124.0 (CH), 127.6 (C), 157.5 (C), 169.6 (C).

Anal. Calcd for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72. Found: C, 70.65; H, 9.15; N, 12.77.

(4*S*,7*S*)-2-Acetyl-4-isopropyl-7-methyl-4,5,6,7-tetrahydro-2*H*-indazole (*cis*-**9**).

Cis-**9** showed ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.89 (3H, d, *J*=6.9 Hz), 1.00 (3H, d, *J*=6.9 Hz), 1.29 (3H, d, *J*=6.6 Hz), 1.61-1.72 (3H, m), 1.76-1.97 (2H, m), 2.46-2.54 (1H, m), 2.65 (3H, s), 2.85-2.96 (1H, m), 7.94 (1H, d, *J*= 1.0Hz); ^{13}C NMR (270 MHz, $CDCl_3$): δ 18.6 (CH_3), 20.5 (CH_3), 20.6 (CH_3), 20.9 (CH_2), 21.6 (CH_3), 28.4 (CH), 29.3 (CH_2), 31.2 (CH), 38.5 (CH), 124.1 (C), 124.4 (CH), 160.1 (C), 169.5 (C).

Anal. Calcd for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72. Found: C, 70.69; H, 9.31; N, 12.68.

Deacetylation of *N*-Acetyl Derivatives.

All 2-acetyl derivatives (5.3 mmol), *cis*-**6**, *trans*-**6**, *cis*-**9** and *trans*-**9**, were refluxed with NaOH (1.1 mmol) in MeOH (15 ml), respectively. The resulting mixture was quenched with dil. hydrochloric acid, and extracted with Et_2O. The organic layer was washed with saturated NaCl, dried over anhydrous $MgSO_4$,

and concentrated. The products were purified by the silica gel column chromatography, and *cis*-**2** and *trans*-**3** were crystallized upon standing for a few days. The ^{1}H NMR spectral data were summarized in Table 1.

(4*R*,7*R*)-4-Methyl-7-isopropyl-4,5,6,7-tetrahydro-1*H*-indazole (*cis*-**2**).

Cis-**2** was obtained in 86 % yield; bp 160-165 °C/5 mmHg; mp 54-57 °C; $[\alpha]_D$: 18.45° (c 0.084, $CHCl_3$); ^{13}C NMR (270 MHz, $CDCl_3$): δ 18.5 (CH_3), 20.3(CH_3), 21.2 (CH_2), 21.8 (CH_3), 25.7 (CH), 29.2 (CH_2), 30.4 (CH), 38.4 (CH), 121.6 (C), 133.1 (CH), 144.3 (C).

(4*R*,7*S*)-4-Methyl-7-isopropyl-4,5,6,7-tetrahydro-1*H*-indazole (*trans*-**2**).

Trans-**2** was obtained in 95 % yield; bp 180 °C/7mmHg; $[\alpha]_D$ –98.1 (*c* 1.89, $CHCl_3$); ^{13}C NMR (270 MHz, $CDCl_3$): δ 17.7 (CH_3), 20.1 (CH_3), 21.4 (CH_3), 23.3 (CH_2), 27.7 (CH), 30.3 (CH), 32.7 (CH_2), 39.6 (CH), 122.4 (C), 132.1 (CH), 145.2 (C).

Anal. Calcd for $C_{11}H_{18}N_2$: C, 74.11; H, 10.18; N, 15.71. Found: C, 73.89; H, 10.12; N, 15.76.

(4*S*,7*S*)-4-Isopropyl-7-methyl-4,5,6,7-tetrahydro-1*H*-indazole (*cis*-**3**).

Cis-**3** was obtained in 95 % yield; bp 180 °C/7mmHg; $[\alpha]_D$ –9.3 (*c* 2.09, $CHCl_3$); ^{13}C NMR (270 MHz, $CDCl_3$): δ 19.0 (CH_3), 20.8 (CH_3), 20.8 (CH_3), 22.1 (CH_2), 27.3 (CH), 29.5 (CH_2), 31.5 (CH), 38.3 (CH), 118.1 (C), 133.0 (CH), 147.7 (C).

Anal. Calcd for $C_{11}H_{18}N_2$: C, 74.11; H, 10.18; N, 15.71. Found: C, 73.92; H, 10.18; N, 15.43.

(4*S*,7*R*)-4-Isopropyl-7-methyl-4,5,6,7-tetrahydro-1*H*-indazole (*trans*-**3**).

Trans-**3** was obtained in 95 % yield; mp 84-85 °C; $[\delta]_D$ –54.8 (*c* 2.07, $CHCl_3$); ^{13}C NMR (270 MHz, $CDCl_3$): δ 18.0 (CH_3), 19.7 (CH_3), 20.2 (CH_3), 24.2 (CH_2), 28.9 (CH), 31.3 (CH), 32.3 (CH_2), 38.9 (CH), 118.4 (C), 132.0 (CH), 148.3 (C).

Anal. Calcd for $C_{11}H_{18}N_2$: C, 74.11; H, 10.18; N, 15.71. Found: C, 74.16; H, 10.12; N, 15.64.

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REFERENCES AND NOTES

[1] C. Kashima, I. Fukuchi, K. Takahashi, and A. Hosomi, *Tetrahedron Lett*., **34**, 8305 (1993).

[2] For recent reviews, see: [a] 'Asymmetric Synthesis', Vol. **1**-**5**, ed. by D. J. Morrison, Academic Press Inc., New York, 1983-1985; [b] B. H. Kim and D. P. Curran, *Tetrahedron*, **49**, 298 (1993); [c] L. Deloux and M. Srebnik, *Chem. Rev.*, **93**, 763 (1993); [d] T. G. Gant and A. I. Meyers, *Tetrahedron*, **50**, 2297 (1994).

[3] C. Kashima, I. Fukuchi, and A. Hosomi, *J. Org. Chem*., **59**, 7821 (1994).

[4] C. Kashima, K. Takahashi, and A. Hosomi, *Heterocycles*, **42**, 241 (1996).

[5] C. Kashima, I. Fukuchi, K. Takahashi, and A. Hosomi, *Tetrahedron*, **52**, 10335 (1996).

[6] C. Kashima, I. Fukuchi, K. Takahashi, K. Fukusaka, and A. Hosomi, *Heterocycles*, **47**, 357 (1998).

[7] C. Kashima, K. Fukusaka, and K. Takahashi, *J. Heterocyclic Chem*., **34**, 1559 (1997).

[8] C. Kashima, K. Takahashi, K. Fukusaka, and A. Hosomi, *J. Heterocyclic Chem*., **35**, 503 (1998).

[9] C. Kashima, K. Fukusaka, K. Takahashi, and Y. Yokoyama, *J. Org. Chem*., **64**, 1108 (1999).

[10] C. Kashima, K. Takahashi, I. Fukuchi, and K. Fukusaka, *Heterocycles*, **44**, 289 (1997).

[11] C. Kashima, Y. Tsukamoto, K. Higashide, and H. Nakazono, *J. Heterocyclic Chem*., **37**, 983 (2000).

[12] C. Kashima, Y. Tsukamoto, Y. Miwa, and K. Higashide, *J. Heterocyclic Chem*., **38**, 601 (2001).

[13] C. Kashima, K. Higashide, Y. Miwa, and Y. Tsukamoto, *J. Heterocyclic Chem*., in press.

[14] D. D. LeCloux and W. B. Tolman, *J. Am. Chem. Soc*., **115**, 1153 (1993); [b] D. D. LeCloux, C. J. Tokar, M. Osawa, R. P. Houser, M. C. Keyes, and W. B. Tolman, *Organometallics*, **13**, 2855 (1994).

[15] M. Bovens, A. Togni, and L. M. Venanzi, *J. Organomet. Chem*., **451**, C28 (1993).

[16] D. L. Christenson, C. J. Tokar, and W. B. Tolman, *Organometallics*, **14**, 2148 (1995).

[17] M. H. Chisholm, N. W. Eilerts, J. C. Huffman, S. S. Iyer, M. Pacold, and K. Phomphrai, *J. Am. Chem. Soc.*, **122**, 11854 (2000).

[18] C. Kashima, H. Harada, I. Kita, I. Fukuchi, and A. Hosomi, *Synthesis*, 61 (1994).

[19] C. Kashima, I. Fukuchi, K. Takahashi, and A. Hosomi, *Heterocycles*, **38**, 1407 (1994).

[20] D. Savoia, E. Tagliavini, C. Trombini, and A. Ummani-Ronchi, *J. Org. Chem.*, **46**, 5344 (1981).