Asymmetric Reaction of Diethylzinc with Aldehydes Catalyzed by *l*-Menthopyrazole Derivatives

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Received December 4, 2001

N-Hydroxyalkyl-*l*-menthopyrazoles acted as a chiral catalyst for the diethylzinc (**1**) addition to aromatic aldehydes, and 1-aryl-1-propanols were afforded enantioselectively. These reactions were carried out optimally in toluene at 40 °C in the presence of 30 mol% of (*2'S*)-2-(2-phenyl-2-hydroxyethyl)-3-phenyl-l-menthopyrazole ((*S*)-**16d**) to afford optically active 1-aryl-1-propanols up to 70% ee (*S*).

J. Heterocyclic Chem., **39**, 917(2002).

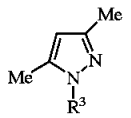
Recently we have developed the preparation and the utilities of 3-phenyl-*l*-menthopyrazole as a new chiral auxiliary [1], which has a unique structure and properties relative to the conventional chiral auxiliaries [2]. The most important characteristics of this auxiliary are that the substrate terminates at a nitrogen atom of the heteroaromatic pyrazole ring, and that the substrate is surrounded by the chiral environment. These structural features cause 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, *N*-acylheteroaromatics such as *N*-acylimidazoles are utilized as the activated acyl moiety in a wide varieties of organic syntheses [11]. As an analogue of these *N*-acylheteroaromatics, *N*-acylpyrazoles are easily converted into acyl derivatives by the action of nucleophiles such as alcohols [12], amines [13], Grignard reagents [14], or organozinc compounds [15] under basic or acidic conditions.

Many reports of chiral amino alcohols relating to enantioselective synthesis have appeared in the literature. The chiral amino alcohols behave as a ligand for a metal atom to form a complex, which takes the role of an optically active Lewis acid. Since *l*-menthopyrazole derivatives exhibit both the characteristic of Lewis basicity and asymmetric structure, the introduction of a hydroxyl group was expected to exploit the utilities of *l*-menthopyrazoles as a ligand for an optically active Lewis acid. On this strategy, the utility of *l*-menthopyrazole derivatives having an hydroxyalkyl group was investigated as an optically active catalyst for the borane reduction of ketones [16]. As a part of these investigations been hoped to extend the catalytic use of pyrazole derivatives in synthetic reactions especially in asymmetric reactions.

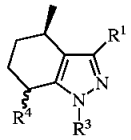
Recently, Soai and his co-workers focused their attention on the addition reaction of dialkylzinc toward aldehydes in the presence of chiral amino alcohols, and elucidated their enantioselective reaction mechanism, catalyzed by an optically active Lewis acid [17]. Since then, some papers using various amino alcohols followed to give similar enantioselective addition of dialkylzinc toward aldehydes [18]. With the background, we wish to report the reaction of diethylzinc with aldehydes catalyzed by *l*-menthopyrazoles having the hydroxylalkyl group.

Results and Discussion

N-(1-Hydroxyalkyl)pyrazoles were previously reported to be prepared by the action of aldehydes toward *N*-unsubstituted pyrazoles [16a]. From these facts, the Lewis acid complex of *N*-(1-hydroxyalkyl)pyrazoles with dialkylzinc should be formed *in situ* by aldehydes with pyrazoles. Moreover, this complex was expected to act as a self-catalyst in the addition reaction of dialkylzinc to aldehydes. Actually 1-(4-methylphenyl)-1-propanol (**3a**) was obtained by the action of diethylzinc (**1**) toward 4-methylbenzaldehyde (**2a**) in the presence of 3,5-dimethylpyrazole (**4**). This catalytic effect was observed with less than 30 mol% of **4**. These results indicated the catalytic effect of *N*-unsubstituted pyrazole for the addition reaction of dialkylzinc to aldehydes through the formation of Lewis acid complex.



4: R^3=H
12: R^3=CH_2CH_2OH



a:	R^1=Ph	R^3=H	R^4=(*S*)-*i*-Pr
b:	R^1=H	R^3=H	R^4=(*R*)-*i*-Pr
c:	R^1=2-MeO-C_6H_4	R^3=H	R^4=(*S*)-*i*-Pr
d:	R^1=2-HO-C_6H_4	R^3=H	R^4=(*S*)-*i*-Pr
e:	R^1=CH_2OH	R^3=H	R^4=(*S*)-*i*-Pr
f:	R^1=Ph	R^3=Me	R^4=(*S*)-*i*-Pr
g:	R^1=2-HO-C_6H_4	R^3=Me	R^4=(*S*)-*i*-Pr

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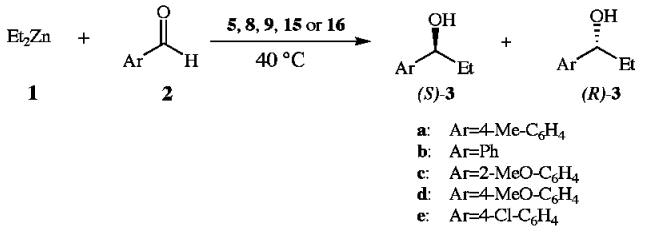
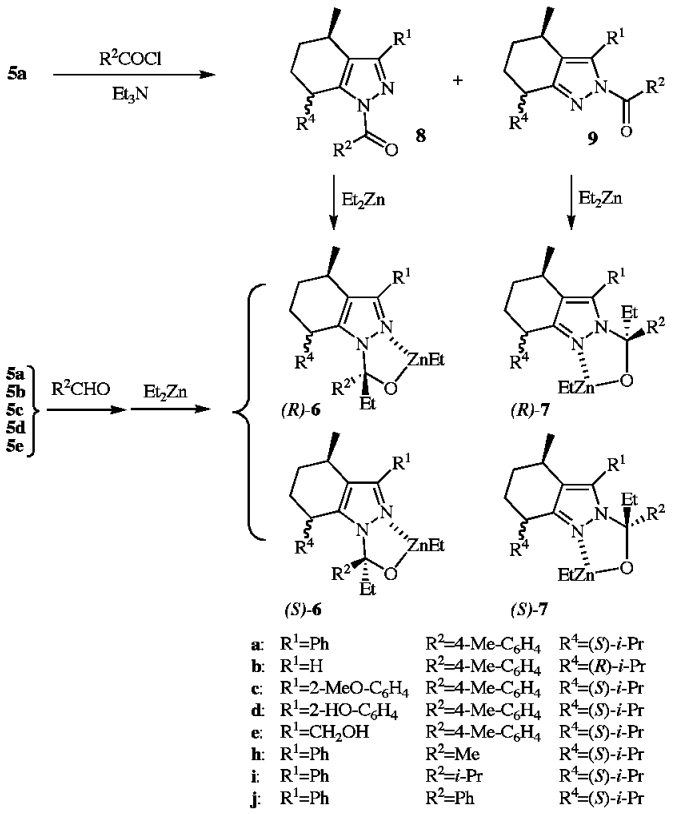
Next, the catalytic effect of 3-phenyl-*l*-menthopyrzole (**5a**), which was recently designed as an optically active pyrazole, was studied in the addition reaction of dialkylzinc to aldehydes. In the meanwhile, isomenthopyrazole [(4*R*,7*R*)-4-methyl-7-isopropyl-4,5,6,7-tetrahydro-indazole], (**5b**) was designed at an optically active pyrazole [19]. Therefore the catalytic effects of **5b** were also examined. In the various solvents, a mixture of 1.3 mmol of **2a**

Scheme 1



Scheme 2



was treated with 2 mmol of **1** at 40 °C in the presence of 0.3 mmol of **5**. The data in Table 1 indicate that a non-polar solvent was preferable, and that optically active **3a** was obtained in a moderate yield with an enantioselectivity of about 20% ee. The low enantioselectivity of this reaction was perhaps caused by the mixed formation of 4 isomers of *N*-hydroxymethylpyrazoles, which consisted of 2 diastereomers in each of 2 regioisomers, **6** and **7**. Although the catalyst in this reaction was easily formed *in situ* from **2a**, **5** and **1**, the regioselective and diastereoselective formation of these catalyst was difficult to control because of the labile properties of *N*-hydroxymethylpyrazoles.

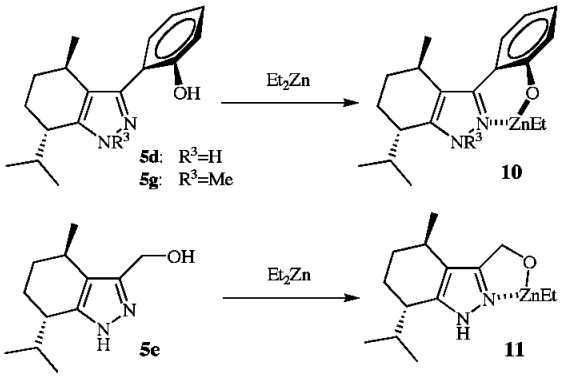
Previously the reactions of *N*-acylpyrazoles with organometallic substances such as lithium aluminum hydride [20], Grignard reagents [14] and Reformatsky reagents [15], were revealed to give carbonyl compounds, where the reaction intermediate was explained to be *N*-hydroxymethylpyrazoles. Since *N*-acyl-3-phenyl-*l*-menthopyrazoles (**8** and **9**) could be prepared regioselectively, the regioselective formation of zinc complex of *N*-(1-hydroxyalkyl)pyrazoles (**6** or **7**) was expected *in situ* by the reaction of *N*-acylpyrazoles with dialkylzinc. The catalytic effect of **8** and **9** in the addition reaction of **1** to **2a** is summarized in Table 1. As another attempt toward the regioselective formation of catalysts such as **10** and **11**, another Lewis base center consisting of hydroxyl or methoxy groups was introduced on pyrazole derivatives (**5d**, **5e**, and **5g**). However, the data in Table 1 illustrate that these attempts gave unsatisfactory results, and such

Table 1

Addition of **1** toward **2a** Catalyzed by Menthopyrazoles

Run	Catalyst				Mol %	Solvent	Yield (%)	Ee (%)
		R^1	R^3	R^4				
1			None		0	Toluene	0	–
2	**4**		3,5-Dimethylpyrazole		30	Toluene	51	–
3	**4**		3,5-Dimethylpyrazole		30	Hexane	58	–
4	**5a**	Ph	1-H	(*S*)-*i*-Pr	30	DMF	6	9 (*S*)
5	**5a**	Ph	1-H	(*S*)-*i*-Pr	30	THF	27	24 (*S*)
6	**5a**	Ph	1-H	(*S*)-*i*-Pr	30	Toluene	34	23 (*S*)
7	**5a**	Ph	1-H	(*S*)-*i*-Pr	30	Hexane	51	11 (*S*)
8	**5b**	H	1-H	(*R*)-*i*-Pr	30	Toluene	47	3 (*S*)
9	**5c**	2-MeO-C_6H_4	1-H	(*S*)-*i*-Pr	30	Toluene	23	22 (*S*)
10	**5d**	2-HO-C_6H_4	1-H	(*S*)-*i*-Pr	30	Toluene	9	14 (*S*)
11	**5e**	CH_2OH	1-H	(*S*)-*i*-Pr	30	Toluene	19	3 (*S*)
12	**5f**	Ph	1-Me	(*S*)-*i*-Pr	30	Toluene	10	7 (*S*)
13	**5g**	2-HO-C_6H_4	1-Me	(*S*)-*i*-Pr	30	Toluene	31	32 (*S*)
14	**8h**	Ph	1-Ac	(*S*)-*i*-Pr	30	Toluene	32	14 (*S*)
15	**9h**	Ph	2-Ac	(*S*)-*i*-Pr	30	Toluene	35	13 (*S*)
16	**8i**	Ph	1-CO-*i*-Pr	(*S*)-*i*-Pr	30	Toluene	38	11 (*S*)
17	**9i**	Ph	2-CO-*i*-Pr	(*S*)-*i*-Pr	30	Toluene	19	18 (*S*)
18	**8j**	Ph	1-CO-Ph	(*S*)-*i*-Pr	30	Toluene	22	11 (*S*)
19	**9j**	Ph	2-CO-Ph	(*S*)-*i*-Pr	30	Toluene	23	14 (*S*)

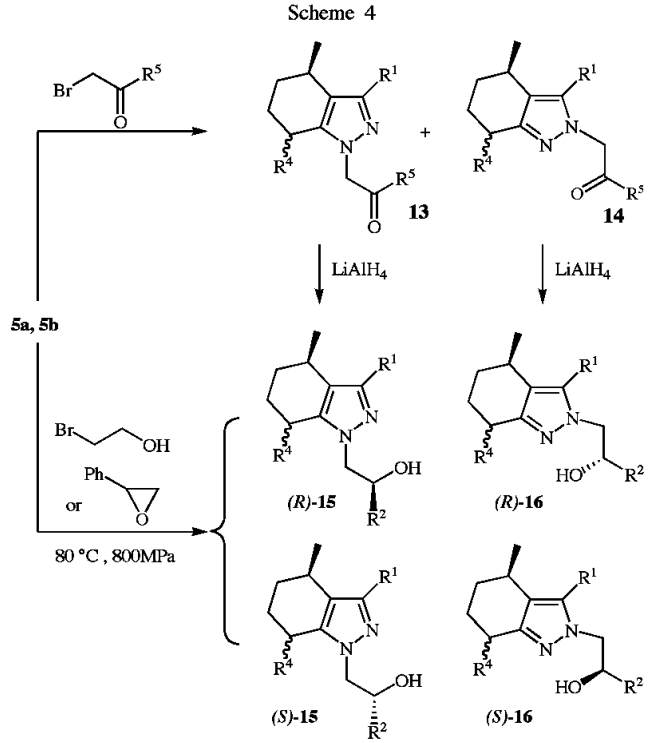
Scheme 3



Lewis basic centers do not affect the promotion of enantioselectivity in the addition reaction of dialkylzinc to aldehydes. From these facts, the formation of a chiral catalyst of *N*-(α-hydroxylalkyl)-*l*-menthopyrazoles was prepared *in situ* with ease, but the satisfactory results in enantioselectivity of dialkylzinc addition could not be obtained by less diastereoselective formation of these catalyst.

On the other hand, *N*-(2-hydroxyethyl)pyrazoles were prepared by the direct alkylation of the corresponding pyrazoles.

Scheme 4



Also *N*-(2-hydroxyethyl)pyrazoles were prepared by the hydride reduction of pyrazolylacetates (**13g**, **13h**, **14g** and **14h**) or aroylmethylpyrazoles (**13d-f** and **14d-f**), and were easily isolated regio- and diastereoselectively as stable substances [16]. The catalytic effect of *N*-(2-hydroxyethyl)pyrazoles was optimized by the reaction of **2a** with **1** in the presence of 1-(2-hydroxyethyl)-3,5-dimethylpyrazole (**12**) under various reaction conditions. The data in Table 2 exhibit that 30 mol% of **12** catalyzed sufficiently the addition reaction of dialkylzinc to aldehydes at 40 °C in toluene.

Table 2

Addition of **1** to **2a** Catalyzed by 1-(2-Hydroxyethyl)-3,5-dimethylpyrazole (**12**)

Run	**12** (mol %)	**1** (mmol)	**2a** (mmol)	Time (h)	Temp. (°C)	Yield of **3a** (%)
1	0	2.0	1.0	6.0	40	0
2	15	2.0	1.0	4.5	40	45
3	30	2.0	1.0	4.0	40	72
4	30	2.0	1.0	6.0	40	71
5	45	2.0	1.0	4.0	40	70
6	100	2.0	1.0	2.5	40	70
7	30	2.0	1.0	6.0	0	20
8	30	2.0	1.0	2.0	80	88
9	30	1.0	1.0	8.0	40	2
10	30	1.5	1.0	4.0	40	5

Table 3

Enantioselective Diethylzinc Addition to **2a** Catalyzed by *N*-(2-Hydroxyethyl)-menthopyrazole Derivatives

Run	Catalyst	R^1	R^2	Yield of **3a** R^4	(%)	Ee of **3a** (%)
1	**15a**	Ph	H	(*S*)-*i*-Pr	85	20 (*R*)
2	**16a**	Ph	H	(*S*)-*i*-Pr	75	7 (*S*)
3	**15b**	H	H	(*R*)-*i*-Pr	85	18 (*R*)
4	**16b**	H	H	(*R*)-*i*-Pr	79	12 (*S*)
5	(*S*)-**16c**	H	(*S*)-Ph	(*R*)-*i*-Pr	46	63 (*S*)
6	(*R*)-**16c**	H	(*R*)-Ph	(*R*)-*i*-Pr	65	33 (*R*)
7	(*S*)-**15d**	Ph	(*S*)-Ph	(*S*)-*i*-Pr	59	28 (*S*)
8	(*R*)-**15d**	Ph	(*R*)-Ph	(*S*)-*i*-Pr	74	65 (*R*)
9	(*S*)-**16d**	Ph	(*S*)-Ph	(*S*)-*i*-Pr	81	70 (*S*)
10	(*R*)-**16d**	Ph	(*R*)-Ph	(*S*)-*i*-Pr	21	55(*R*)
11	(*S*)-**15e**	Ph	(*S*)-4-Me-C_6H_4	(*S*)-*i*-Pr	17	25 (*S*)
12	(*R*)-**15e**	Ph	(*R*)-4-Me-C_6H_4	(*S*)-*i*-Pr	99	43 (*R*)
13	(*S*)-**16e**	Ph	(*S*)-4-Me-C_6H_4	(*S*)-*i*-Pr	83	72 (*S*)
14	(*R*)-**16e**	Ph	(*R*)-4-Me-C_6H_4	(*S*)-*i*-Pr	71	24 (*R*)
15	(*S*)-**15f**	Ph	(*S*)-1-Naph	(*S*)-*i*-Pr	37	56 (*S*)
16	(*R*)-**15f**	Ph	(*R*)-1-Naph	(*S*)-*i*-Pr	63	44 (*R*)
17	(*S*)-**16f**	Ph	(*S*)-1-Naph	(*S*)-*i*-Pr	78	70 (*S*)
18	(*R*)-**16f**	Ph	(*R*)-1-Naph	(*S*)-*i*-Pr	54	39 (*R*)

When various 1-(2-hydroxyethyl)- (**15**) and 2-(2-hydroxyethyl)-*l*-menthopyrazole derivatives (**16**) were used as the chiral catalyst, **1** reacted with **2a** in an enantioselective manner and the results are summarized in Table 3. The stereo structures of menthopyrazole moiety in **15** and **16** were affected to the formation of (*R*)-**3a** and (*S*)-**3a** respectively, but their effects were rather small. The enantioselective control of the product was governed mainly by the

Table 4

Enantioselective Diethylzinc Addition to Aldehydes Catalyzed by (*S*)-**1d**

Run	Aldehydes	Ar	Yield of **3** (%)	Ee of **3** (%)	Recovery of (*S*)-**16d** (%)
1	**2a**	4-Me-C_6H_4	81	70 (*S*)	77
3	**2b**	Ph	79	36 (*S*)	77
2	**2c**	2- MeO-C_6H_4	65	66 (*S*)	62
3	**2d**	4-MeO-C_6H_4	53	20 (*S*)	99
4	**2e**	4-Cl-C_6H_4	67	41 (*S*)	84

substituent group adjacent to the hydroxyl group, where the substituent group with (*S*)-configuration on the β-carbon preferably gave (*S*)-**3a**. In the case of (*2'S*)-2-(2-phenyl-2-hydroxyethyl)-3-phenyl-*l*-menthopyrazole ((*S*)-**16d**), the structures of menthopyrazole moiety and side chain were complementarily affected to the formation of (*S*)-**3a**. Furthermore, the addition reaction of **1** with some aromatic aldehydes (**2**) afforded the corresponding alcohols (**3**) enantioselectively, as summarized in Table 4.

N-Hydroxyalkyl-*l*-menthopyrazoles acted as a chiral catalyst for the diethylzinc (**1**) addition to 4-methylbenzaldehyde (**2a**), and 1-(4-methylphenyl)-1-proparnol (**3a**) was afforded enantioselectively. These reactions were carried out optimally in toluene at 40 °C in the presence of 30 mol% of (*S*)-**16d** to afford optically active 1-aryl-1-propanols up to 70% ee (*S*).

EXPERIMENTAL

Melting points are uncorrected. ^{1}H nmr and ^{13}C nmr spectra were obtained on JEOL JNM-EX270 (270 MHz) or Varian GEMINI 2000 (200 MHz) spectrometers in deuterochloroform with tetramethylsilane as an internal standard. The IR spectra were measured by Shimadzu IR-460 spectrophotometer. Specific rotations were measured on JASCO DIP-370 digital polarimeter. The enantiomer ratios were evaluated from the peak ratios of gas chromatography on SHIMADZU GC-14A gas chromatograph using Chrompack Chirasil DEX-CB capillary column (0.25 mm x 25 m). The yields of the products were evaluated by GL Science GC-353 gas chromatograph using dimethylsiloxane type capillary column (0.25 mm x 30 m) of GL Science TC-1.

Materials.

Ether and THF were dried over ketyl radical generated from sodium and benzophenone. Toluene was dried over calcium hydride with refluxing. Diethylzinc hexane solution (1 mol/L) was commercially available from Kanto Chemical CO. Compounds **5c**, **5d**, **5f**, **12**, **13h** and **14h** were prepared according to previously described method [16]. Isomenthopyrazole (**5b)** was prepared by the method of Bovens [19]. *N*-Acyl-3-phenyl-*l*-menthopyrazoles (**8** and **9**) were directly acylated with the corresponding acyl chloride from **5a** [3].

1-Acetyl-3-phenyl-*l*-menthopyrazole (**8h**).

This compound was obtained in 80% yield; bp 150 °C/ 5 mmHg; ^{1}H nmr: δ 0.88 (3H, d, *J*=7 Hz), 0.96 (3H, d, *J*=7 Hz), 0.99 (3H, d, *J*=7 Hz), 1.43-1.51 (1H, m), 1.76-1.83 (2H, m), 2.00-2.19 (2H, m), 2.73 (3H, s), 3.17-3.22 (1H, m), 3.37-3.42 (1H, m), 7.35-7.47 (3H, m), 7.75-7.80 (2H, m); ^{13}C nmr: δ 19.6 (CH_2), 19.7 (CH_3), 20.7 (CH_3), 21.2 (CH_3), 23.9 (CH_3), 25.7 (CH), 27.1 (CH_2), 31.4 (CH), 37.9 (CH), 124.6 (C), 127.6 (CH), 128.5 (CH), 133.3 (C), 145.8 (C), 152.2 (C), 171.4 (C).

Anal. Calcd. for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45; Found: C, 77.17; H, 8.23; N, 9.46.

2-Acetyl-3-phenyl-*l*-menthopyrazole (**9h**).

This compound was obtained as a colorless oil in 62% yield; ^{1}H nmr: δ 0.69 (3H, d, *J*= 7 Hz), 0.94 (3H, d, *J*=7 Hz), 1.09 (3H, d, *J*= 7 Hz), 1.18-1.31 (1H, m), 1.46-1.55 (1H, m), 1.83-2.00 (2H, m), 2.36-2.44 (1H, m), 2.59-2.79 (2H, m), 2.63 (3H, s), 7.27-7.41 (5H, m); ^{13}C nmr: δ 18.6 (CH_3), 20.2 (CH_3), 20.4 (CH_3), 23.0 (CH_2), 23.6 (CH_2), 27.3 (CH), 30.0 (CH), 32.1 (CH), 41.3 (CH_3), 126.2 (C), 127.9 (CH), 128.1 (CH), 129.3 (CH), 132.6 (C), 140.8 (C), 155.9 (C), 170.5 (C).

Anal. Calcd. for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45; Found: C, 76.75; H, 8.07; N, 9.42.

1-Isobutyryl-3-phenyl-*l*-menthopyrazole (**8i**).

This compound was obtained in 85% yield; bp 155-65°C/ 5 mmHg; ^{1}H nmr: δ 0.88 (3H, d, *J*=7 Hz), 0.96 (3H, d, *J*=7 Hz), 0.97 (3H, d, *J*=7 Hz), 1.28 (3H, d, *J*=7 Hz), 1.29 (3H, d, *J*=7 Hz), 1.43-1.50 (1H, m), 1.76-1.83 (2H, m), 2.02-2.14 (2H, m), 3.17-3.22 (1H, m), 3.41-3.46 (1H, m), 4.03-4.13 (1H, m), 7.34-7.46 (3H, m), 7.77-7.80 (2H, m); ^{13}C nmr: δ 18.9 (CH_3), 19.5 (CH_3), 19.8 (CH_3), 19.8 (CH_3), 20.7 (CH_3), 21.2 (CH_2), 25.8 (CH_2), 27.2 (CH), 31.6 (CH), 33.2 (CH), 38.1 (CH), 124.6 (C), 127.6 (CH), 128.4 (CH), 128.5 (CH), 133.5 (C), 145.8 (C), 151.9 (C), 178.3 (C).

Anal. Calcd. for $C_{21}H_{28}N_2O$: C, 77.74; H, 8.70; N, 8.63; Found: C, 77.86; H, 8.77; N, 8.63.

2-Isobutyryl-3-phenyl-*l*-menthopyrazole (**9i**).

This compound was obtained in 95% yield; bp 160-170 °C/ 5 mmHg; ^{1}H nmr: δ 0.70 (3H, d, *J*=7 Hz), 0.95 (3H, d, *J*=7 Hz), 1.09 (3H, d, *J*=7 Hz), 1.20 (3H, d, *J*=7 Hz), 1.24 (3H, d, *J*=7 Hz), 1.18-1.33 (1H, m), 1.45-1.58 (1H, m), 1.84-2.00 (2H, m), 2.37-2.45 (1H, m), 2.60-2.79 (2H, m), 3.88-3.99 (1H, m), 7.27-7.40 (5H, m); ^{13}C nmr: δ 18.6 (CH_3), 19.0 (CH_3), 19.4 (CH_3), 20.2 (CH_3), 20.4 (CH_3), 23.2 (CH_2), 27.4 (CH_2), 30.0 (CH), 32.3 (CH), 33.2 (CH), 41.4 (CH), 126.0 (C), 127.9 (CH), 128.0 (CH), 129.2 (CH), 132.9 (C), 141.0 (C), 155.6 (C), 177.1 (C).

Anal. Calcd. for $C_{21}H_{28}N_2O$: C, 77.74; H, 8.70; N, 8.63; Found: C, 77.49; H, 8.78; N, 8.62.

1-Benzoyl-3-phenyl-*l*-menthopyrazole (**8j**).

This compound was obtained as a colorless oil in 25% yield; ^{1}H nmr: δ 0.89 (3H, d, *J*=6.9 Hz), 1.01 (3H, d, *J*=6.9 Hz), 1.03 (3H, d, *J*=6.6 Hz), 1.47-1.55 (1H, m), 1.78-1.97 (2H, m), 2.03-2.18 (2H, m), 3.18-3.25 (1H, m), 3.54-3.60 (1H, m), 7.34-7.58 (6H, m), 7.73 (2H, d-d, *J*=7.3, 1.3 Hz), 8.03 (2H, d, *J*=6.9 Hz); ^{13}C nmr: δ 19.4 (CH_3), 19.8 (CH_3), 20.9 (CH_3), 21.1 (CH_2), 26.2 (CH_2), 27.8 (CH), 31.4 (CH), 38.1 (CH), 124.9 (C), 127.7 (CH), 127.8 (CH), 128.4 (CH), 128.4 (CH), 131.5 (CH), 132.3 (CH), 133.4 (C), 133.7 (C), 146.8 (C), 152.1 (C), 169.0 (C).

Anal. Calcd. for $C_{24}H_{26}N_2O$: C, 80.41; H, 7.31; N, 7.81. Found: C, 80.19; H, 7.34; N, 7.91.

2-Benzoyl-3-phenyl-*l*-menthopyrazole (**9j**).

This compound was obtained as colorless needles in 75% yield; mp 110-111°C (from Hexane); ^{1}H nmr: δ 0.80 (3H, d, *J*=6.6 Hz), 0.89 (3H, d, *J*=6.6 Hz), 1.04 (3H, d, *J*=6.9 Hz), 1.35-1.18 (1H, m), 1.52-1.60 (1H, m), 1.87-2.01 (2H, m), 2.34-2.41 (1H, m), 2.66 (1H, quint, *J*=4.9 Hz), 2.79-2.86 (1H, m), 7.36-7.56 (8H, m), 7.97-8.01 (2H, m); ^{13}C nmr: δ 18.3 (CH_3), 20.4 (CH_3), 22.8 (CH_2), 27.5 (CH_2), 29.9 (CH), 32.3 (CH), 41.3 (CH), 125.8 (C), 127.5 (C), 127.6 (CH), 127.9 (CH), 128.1 (CH), 129.3 (CH), 131.7 (CH), 132.3 (CH), 133.3 (C), 142.1 (C), 155.9 (C), 167.4 (C).

Anal. Calcd. for $C_{24}H_{26}N_2O$: C, 80.41; H, 7.31; N, 7.81. Found: C, 80.22; H, 7.39; N, 7.88.

3-Hydroxymethyl-*l*-menthopyrazole (**5e**).

Ethyl *l*-menthopyrazole-3-carboxylate (252 mg), which was prepared from *l*-menthone and diethyl oxalate, was reduced by lithium aluminum hydride (75 mg) in anhydrous ether (5 ml) at room temperature for 2 hours. The mixture was quenched with water, and the organic layer was washed with dilute hydrochloric acid, saturated sodium hydrogen carbonate, and sodium chloride. After removal of the solvent, the residue was chromatographed on silica gel with benzene-ethyl acetate mixture; yield 53%; mp 163-164°C (from Hexane); ^{1}H nmr: δ 0.76 (3H, d, *J*=6.9 Hz), 1.00 (3H, d, *J*=6.6 Hz), 1.18 (3H, d, *J*=6.9 Hz), 1.20-2.19 (5H, m), 2.59-2.65 (1H, m), 2.68-2.77 (1H, m), 4.69 (2H, s), 0.80 (3H, d, *J*=6.9 Hz), 1.01 (3H, d, *J*=6.6 Hz), 1.14 (3H, d, *J*=6.9 Hz), 1.20-2.19 (5H, m), 2.59-2.65 (1H, m), 2.80-2.90 (1H, m), 4.64 (2H, s); ^{13}C nmr: δ 18.0 (CH_3), 18.0 (CH_3), 19.3 (CH_3), 20.4 (CH_3), 20.5 (CH_3), 21.2 (CH_3), 21.8 (CH_2), 22.4 (CH_2), 25.0 (CH_2), 27.0 (CH_2), 30.0 (CH), 30.1 (CH), 32.1 (CH), 39.4 (CH), 39.5 (CH), 57.1 (CH_2), 57.7 (CH_2), 118.4 (C), 119.1 (C).

Anal. Calcd. for $C_{12}H_{20}N_2O$: C, 69.19; H, 9.68; N, 13.45. Found: C, 69.46; H, 9.82; N, 13.48.

1-Methyl-3-(2-hydroxyphenyl)-*l*-menthopyrazole (**5g**).

3-(2-Hydroxyphenyl)-*l*-menthopyrazole (**5e**, 145 mg, 0.54 mmol) in dry THF (3 ml) was treated with butyllithium hexane solution (1.5 *M*, 0.7 ml) at 0 °C for 30 minutes. Methyl iodide (148 mg) in THF (2 ml) was added to the mixture, and stirred for 17 hours at room temperature. The reaction mixture was extracted with ether, and the organic layer was washed with dilute hydrochloric acid, saturated sodium hydrogen carbonate and sodium chloride. After drying over anhydrous magnesium sulfate, the solvent was removed. By silica gel chromatography of the residue with hexane-ethyl acetate mixture, **5g** was isolated; yield 56%; mp 85-86.5 °C (from hexane); ^{1}H nmr: δ 0.93 (3H, d, *J*=6.8 Hz), 1.01 (3H, d, *J*=7.0 Hz), 1.11 (3H, d, *J*=6.8 Hz), 1.48-1.56 (1H, m), 1.75-1.89 (2H, m), 1.93-2.12 (2H, m), 2.53-2.61 (1H, m), 3.33-3.38 (1H, m), 3.79 (3H, s), 6.85-7.26 (3H, m), 7.66-7.70 (1H, m); ^{13}C nmr: δ 19.8 (CH_3), 20.1 (CH_3), 21.1 (CH_3), 21.4 (CH_2), 26.3 (CH_2), 27.0 (CH), 31.6 (CH), 37.0 (CH), 37.1 (CH_3), 116.9 (CH), 118.7 (CH), 119.2 (C), 126.8 (CH), 128.2 (CH), 128.6 (C), 142.0 (C), 146.0 (C), 156.2 (C).

Anal. Calcd. for $C_{18}H_{24}N_2O$: C, 76.02; H, 8.51; N, 9.85. Found: C, 75.60; H, 8.39; N, 10.19.

N-Aroylmethyl Menthopyrazoles from Phenacyl Bromide Analogues.

The mixture of menthopyrazoles (**5a** or **5b**, 2 mmol), phenacyl bromide analogues (2.1 mmol) and anhydrous potassium carbonate (350 mg, 2.5 mmol) in toluene (7 ml) was refluxed for 23 hours under an argon atmosphere. The reaction mixture was quenched with water, and the organic layer was washed with aqueous sodium hydroxide and saturated sodium chloride. After removal of the solvent, regioisomers of *N*-aroylmethyl-*l*-menthopyrazoles were purified by silica gel column chromatography with hexane-ethyl acetate mixture.

2-Benzoylmethyl-isomenthopyrazole (**14c**).

This compound was obtained as a colorless oil in 67% yield; ^{1}H nmr: δ 0.86 (3H, d, *J*=6.9 Hz), 1.03 (3H, d, *J*=6.9 Hz), 1.17 (3H, d, *J*=6.9 Hz), 1.43-1.52 (1H, m), 1.63-1.83 (3H, m), 2.21 (1H, sex, *J*=5.6 Hz), 2.58-2.65 (1H, m), 2.77-2.85 (1H, m), 5.50 (2H, AB-q, *J*=6.6 Hz), 7.20 (1H, s), 7.47 (2H, t, *J*=7.3 Hz), 7.56-7.63 (1H, m), 7.97 (2H, d, *J*=7.3 Hz); ^{13}C nmr: δ 16.6 (CH_3), 18.8 (CH_3), 19.5 (CH_3), 20.6 (CH_2), 24.4 (CH_2), 27.7 (CH), 28.8 (CH), 37.6 (CH), 55.7 (CH_2), 121.7 (C), 125.2 (CH), 126.1 (CH), 126.7 (CH), 131.7 (CH), 132.7 (C), 150.0 (C), 191.1 (C).

Anal. Calcd. for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 76.88; H, 7.89; N, 9.53.

1-[2-Oxo-2-(1-naphthyl)ethyl]-3-phenyl-*l*-menthopyrazole (**13f**).

This compound was obtained as a colorless oil in 20% yield; ^{1}H nmr: δ 0.86 (3H, d, *J*=6.6 Hz), 0.88 (3H, d, *J*=6.3 Hz), 1.00 (3H, d, *J*=6.9 Hz), 1.30-1.39 (1H, m), 1.58-1.80 (2H, m), 1.94-2.08 (2H, m), 2.50-2.57 (1H, m), 3.14-3.21 (1H, m), 5.55 (2H, AB-q, *J*=17.8 Hz), 7.23-7.67 (9H, m), 7.85 (2H, d-d, *J*=7.3, 1.0 Hz), 7.98 (1H, d, *J*=8.2 Hz), 8.60 (1H, d, *J*=8.2 Hz); ^{13}C nmr: δ 19.2 (CH_3), 20.1 (CH_3), 21.2 (CH_3), 21.3 (CH_2), 26.1 (CH_2), 28.1 (CH), 31.1 (CH), 37.8 (CH), 58.7 (CH_2), 120.3 (C), 124.1 (CH), 125.4 (CH), 126.6 (C), 127.1 (CH), 127.3 (C), 127.3 (C), 128.2 (CH), 128.5 (CH), 130.2 (C), 133.0 (C), 133.2 (CH), 133.9 (C), 134.8 (C), 143.2 (C), 148.9 (C), 197.3 (C).

Anal. Calcd. for $C_{29}H_{30}N_2O$: C, 82.43; H, 7.16; N, 6.63. Found: C, 82.58; H, 6.91; N, 6.63.

2-[2-Oxo-2-(1-naphthyl)ethyl]-3-phenyl-*l*-menthopyrazole (**14f**).

This compound was obtained as colorless needles in 19% yield; mp 119-120 °C (from hexane); ^{1}H nmr: δ 0.76 (6H, d, *J*=6.6 Hz), 1.02 (3H, d, *J*=6.9 Hz), 1.25 (1H, q, *J*=12.5 Hz), 1.50 (1H, q, *J*=12.2 Hz), 1.80-1.97 (2H, m), 2.38-2.45 (1H, m), 2.68-2.83 (2H, m), 5.40 (2H, s), 7.25-7.63 (9H, m), 7.81 (1H, d-d, *J*=5.9, 3.6 Hz), 7.93 (1H, d, *J*=8.3 Hz), 8.30 (1H, d-d, *J*=6.3, 3.6 Hz); ^{13}C nmr: δ 17.6 (CH_3), 20.5 (CH_3), 20.8 (CH_3), 22.6 (CH_2), 27.6 (CH_2), 29.8 (CH), 32.7 (CH), 40.8 (CH), 57.9 (CH_2), 121.1 (C), 124.0 (CH), 125.7 (CH), 126.5 (CH), 127.2 (CH), 127.9 (CH), 128.2 (C), 128.5 (CH), 128.5 (CH), 129.8 (CH), 130.2 (C), 131.6 (C), 133.0 (CH), 133.1 (C), 133.8 (C), 140.6 (C), 152.1 (C), 197.4 (C).

Anal. Calcd. for $C_{29}H_{30}N_2O$: C, 82.43; H, 7.16; N, 6.63. Found: C, 82.69; H, 7.23; N, 6.66.

Preparation of Ethyl Isomenthopyrazole-*N*-acetate.

After stirring a mixture of **5b** (514 mg) and sodium hydride (40% in oil, 151 mg) in THF (8 ml) for 15 minutes, ethyl bromoacetate (534 mg) in THF (2 ml) was added and continued stirring for 6 hours at room temperature. The reaction mixture was quenched with water and extracted with ether. The organic layer was washed with water and saturated sodium chloride, dried over anhydrous magnesium sulfate, and concentrated. By chromatog-

raphy on silica gel with hexane-ethyl acetate, the regioisomers were separated.

Ethyl Isomenthopyrazole-1-acetate (**13g**).

This compound was obtained as a colorless oil in 33% yield; ^{1}H nmr: δ 0.85 (3H, d, *J*=6.6 Hz), 1.03 (3H, d, *J*=6.9 Hz), 1.17 (3H, d, *J*=7.3 Hz), 1.27 (3H, t, *J*=6.9 Hz), 1.46-1.49 (1H, m), 1.64-1.82 (4H, m), 2.20 (1H, sex, *J*=6.3 Hz), 2.60 (1H, q, *J*=5.6 Hz), 2.65-2.80 (1H, m), 4.21 (2H, q, *J*=6.9 Hz), 4.82 (2H, AB-q, *J*=17.0 Hz), 7.26 (1H, s); ^{13}C nmr: δ 14.1 (CH_3), 18.6 (CH_3), 20.9 (CH_3), 21.5 (CH_3), 22.6 (CH_2), 26.4 (CH_2), 29.7 (CH), 30.8 (CH), 39.6 (CH), 53.0 (CH_2), 61.5 (CH_2), 123.6 (C), 127.0 (CH), 152.3 (C), 168.4 (C).

Anal. Calcd. for $C_{15}H_{24}N_2O_2$: C, 68.15; H, 9.15; N, 10.60. Found: C, 67.82; H, 8.99; N, 10.15.

Ethyl Isomenthopyrazole-2-acetate (**14g**).

This compound was obtained as a colorless oil in 37% yield; ^{1}H nmr: δ 0.86 (3H, d, *J*=6.9 Hz), 1.01 (3H, d, *J*=6.9 Hz), 1.21 (3H, d, *J*=6.9 Hz), 1.26 (3H, t, *J*=7.3 Hz), 1.37-1.46 (1H, m), 1.58-1.82 (2H, m), 1.91-2.00 (2H, m), 2.54-2.60 (1H, m), 2.67-2.76 (1H, m), 4.22 (2H, q, *J*=6.9 Hz), 4.82 (2H, AB-q, *J*=17.5 Hz), 7.40 (1H, s); ^{13}C nmr: δ 14.1 (CH_3), 19.4 (CH_3), 21.3 (CH_3), 21.7 (CH_3), 23.4 (CH_2), 27.0 (CH_2), 29.1 (CH), 31.4 (CH), 37.1 (CH), 51.3 (C), 61.6 (CH_2), 122.8 (C), 137.6 (CH), 141.6 (C), 168.3 (C).

Anal. Calcd. for $C_{15}H_{24}N_2O_2$: C, 68.15; H, 9.15; N, 10.6. Found: C, 67.99; H, 9.04; N, 10.76.

Preparation of *N*-(2-Hydroxyethyl)-menthopyrazoles.

Menthopyrazole-*N*-acetates (1.5 mmol) was reduced by treatment with lithium aluminum hydride (65 mg, 1.7 mmol) in anhydrous ether (5 ml) for 1.5 hour at room temperature. Similarly, *N*-aroylmethyl menthopyrazoles (0.5 mmol) were reduced with lithium aluminum hydride (60 mg, 1.6 mmol) in anhydrous ether (4 ml) for 1.5 hour at room temperature. After the mixture was quenched with water, the mixture was filtered. The organic layer was washed with saturated sodium chloride, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography with hexane-ethyl acetate mixture. *N*-(2-hydroxyethyl)-menthopyrazoles were also prepared by the alkylation of menthopyrazole (**5a** and **5b**) under high pressure conditions according to a previously described method [16].

1-(2-Hydroxyethyl)-3-phenyl-*l*-menthopyrazole (**15a**).

This compound was obtained as a colorless oil in 92% yield; ^{1}H nmr: δ 0.92 (3H, d, *J*=6.8 Hz), 0.99 (3H, d, *J*=6.4 Hz), 1.01 (3H, d, *J*=6.4 Hz), 1.42-1.49 (1H, m), 1.747-1.83 (2H, m), 2.05 (2H, m), 2.59 (1H, q, *J*=5.0 Hz), 4.04 (2H, s), 4.09-4.22 (2H, m), 4.63 (1H, m), 7.26-7.43 (3H, m), 7.73 (2H, d, *J*=8.0 Hz); ^{13}C nmr: δ 19.7 (CH_3), 20.3 (CH_3), 21.4 (CH_3), 21.4 (CH_2), 25.9 (CH_2), 27.7 (CH), 31.5 (CH), 37.2 (CH), 50.6 (CH_2), 62.1 (CH_2), 118.8 (C), 127.0 (CH), 127.3 (CH), 128.4 (CH), 134.5 (C), 142.7 (C).

Anal. Calcd. for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39. Found: C, 76.47; H, 8.78; N, 9.39.

2-(2-Hydroxyethyl)-3-phenyl-*l*-menthopyrazole (**16a**).

This compound was obtained as a colorless oil in 50% yield; ^{1}H nmr: δ 0.74 (3H, d, *J*=6.8 Hz), 0.88 (3H, d, *J*=6.8 Hz), 1.06 (3H, d, *J*=6.8 Hz), 1.20-1.59 (2H, m), 1.82-2.02 (2H, m), 2.32-2.47 (1H, m), 2.60-2.86 (2H, m), 3.75-4.11 (4H, m), 7.27-7.38 (2H, m), 7.41-7.46 (3H, m); ^{13}C nmr: δ 18.3 (CH_3), 20.6 (CH_3), 20.8 (CH_3), 23.2 (CH_2), 27.4 (CH_2), 29.9 (CH), 32.8 (CH), 41.0 (CH_2), 50.0 (CH_2), 62.4 (CH_2), 120.3 (C), 127.0 (C), 128.4 (CH), 128.5 (CH), 129.8 (CH), 131.5 (C), 151.4 (C).

Anal. Calcd. for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39. Found: C, 76.11; H, 8.71; N, 9.32.

1-(2-Hydroxyethyl)-isomenthopyrazole (**15b**).

This compound was obtained as a colorless oil in 87% yield; ^{1}H nmr: δ 0.86 (3H, d, *J*=6.9 Hz), 1.02 (3H, d, *J*=6.9 Hz), 1.15 (3H, d, *J*=6.9 Hz), 1.45-1.50 (1H, m), 1.62-1.81 (3H, m), 2.17 (1H, sex, 5.6 Hz), 2.50-2.60 (1H, q, *J*=5.9 Hz), 2.76 (1H, q, *J*=5.3 Hz), 3.92 (2H, t, *J*=4.6 Hz), 4.14 (2H, t, *J*=5.6 Hz), 7.13 (1H, s); ^{13}C nmr: δ 18.9 (CH_3), 20.8 (CH_3), 21.7 (CH_3), 22.7 (CH_2), 26.2 (CH_2), 29.7 (CH), 30.7 (CH), 39.7 (CH), 53.2 (CH_2), 62.1 (CH_2), 122.4 (C), 126.6 (CH), 151.8 (C).

Anal. Calcd. for $C_{13}H_{22}N_2O$: C, 70.23; H, 9.97; N, 12.6. Found: C, 69.95; H, 9.79; N, 12.62.

2-(2-Hydroxyethyl)-isomenthopyrazole (**16b**).

This compound was obtained as colorless needles in 86% yield; mp 98-99 °C (from Hexane) ; ^{1}H nmr: δ 0.87 (3H, d, *J*=6.9 Hz), 1.00 (3H, d, *J*=6.9 Hz), 1.21 (3H, d, *J*=6.9 Hz), 1.35-1.46 (1H, m), 1.55-1.68 (1H, m), 1.72-1.83 (1H, m), 1.94-2.05 (2H, m), 2.57-2.72 (2H, m), 3.88-4.19 (4H, m), 7.34 (1H, s); ^{13}C nmr: δ 19.7 (CH_3), 21.4 (CH_3), 21.7 (CH_3), 23.9 (CH_2), 27.0 (CH_2), 29.0 (CH), 31.6 (CH), 36.9 (CH), 50.7 (CH_2), 61.9 (CH_2), 121.9 (C), 136.3 (CH), 141.2 (C).

Anal. Calcd. for $C_{13}H_{22}N_2O$: C, 70.23; H, 9.97; N, 12.6. Found: C, 70.10; H, 10.08; N, 12.81.

(*2'S*)-2-(2-Phenyl-2-hydroxyethyl)-isomenthopyrazole (*S*)-(**16c**).

This compound was obtained as colorless oil in 36% yield; ^{1}H nmr: δ 0.91 (3H, d, *J*=6.9 Hz), 1.06 (3H, d, *J*=6.9 Hz), 1.10 (3H, d, *J*=6.9 Hz), 1.43-1.50 (1H, m), 1.61-1.81 (3H, m), 2.24 (1H, sex, *J*=5.3 Hz), 2.60 (1H, q, *J*=5.3 Hz), 2.70-2.78 (1H, m), 4.07-4.29 (2H, m), 5.04-5.08 (2H, m), 6.96 (1H, s), 7.24-7.38 (5H, m); ^{13}C nmr: δ 18.9 (CH_3), 20.8 (CH_3), 21.6 (CH_3), 22.7 (CH_2), 26.1 (CH_2), 29.8 (CH), 30.8 (CH), 39.8 (CH), 58.4 (CH_2), 73.8 (CH_2), 122.5 (C), 125.9 (CH), 127.2 (CH), 127.7 (CH), 128.3 (CH), 128.4 (CH), 140.9 (C), 152.3 (C).

Anal. Calcd. for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39. Found: C, 75.85; H, 8.59; N, 9.33.

(*2'R*)-2-(2-Phenyl-2-hydroxyethyl)-isomenthopyrazole (*R*)-(**16c**).

This compound was obtained as a colorless oil in 16% yield; ^{1}H nmr: δ 0.89 (3H, d, *J*=6.9 Hz), 1.04 (3H, d, *J*=6.9 Hz), 1.14 (3H, d, *J*=6.9 Hz), 1.43-1.52 (1H, m), 1.63-1.82 (3H, m), 2.21 (1H, sex, *J*=5.6 Hz), 2.59 (1H, q, *J*=5.6 Hz), 2.70-2.76 (1H, m), 4.06-4.219 (1H, m), 4.95-5.04 (2H, m), 6.95 (1H, s), 7.24-7.38 (5H, m); ^{13}C nmr: δ 18.9 (CH_3), 20.8 (CH_3), 21.7 (CH_3), 22.6 (CH_2), 26.2 (CH_2), 29.7 (CH), 30.8 (CH), 39.7 (CH), 58.5 (CH_2), 73.7 (CH_2), 122.5 (C), 126.0 (CH), 127.1 (CH), 127.8 (CH), 128.4 (CH), 140.8 (C), 152.2 (C).

Anal. Calcd. for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39. Found: C, 75.85; H, 8.69; N, 9.22.

(*2'S*)-1-(2-Phenyl-2-hydroxyethyl)-3-phenyl-*l*-menthopyrazole (*S*)-(**15d**).

This compound was obtained as colorless needles in 25% yield; mp 46-47 °C (from Hexane); ^{1}H nmr: δ 0.79 (3H, d, *J*=6.8 Hz), 0.89 (3H, d, *J*=6.8 Hz), 0.97 (3H, d, *J*=7.0 Hz), 1.23-2.09 (5H, m), 2.26-2.34 (1H, m), 3.17-3.29 (1H, m), 4.10 (1H, ABX, *J*=4.4, 13.4 Hz), 4.22 (3H, ABX, *J*=7.8, 13.8 Hz), 5.14 (1H, ABX, *J*=4.4, 7.8 Hz), 7.12-7.57 (7H, m), 7.73-7.79 (2H, m); ^{13}C nmr: δ 19.6 (CH_3), 20.1 (CH_3), 21.3 (CH_3), 21.5 (CH_2), 25.9 (CH_2), 27.5 (CH), 31.5 (CH), 37.1 (CH), 56.2 (CH_2), 73.7 (CH), 119.1 (C), 126.2 (CH), 127.1 (CH), 127.4 (CH), 127.9 (CH), 128.4 (CH), 128.5 (CH), 134.3 (C), 141.0 (C), 142.8 (C), 147.8 (C).

Anal. Calcd. for $C_{25}H_{30}N_2O$: C, 80.17; H, 8.07; N, 7.48. Found: C, 79.53; H, 8.26; N, 8.69.

(*2'R*)-1-(2-Phenyl-2-hydroxyethyl)-3-phenyl-*l*-menthopyrazole (*R*)-(**15d**).

This compound was obtained as a colorless oil in 38% yield; ^{1}H nmr: δ 0.80 (3H, d, *J*=6.8 Hz), 0.96 (3H, d, *J*=7 Hz), 0.99 (3H, d, *J*=7 Hz), 1.21-1.48 (1H, m), 1.51-1.64 (1H, m), 1.75-1.84 (1H, m), 1.85-2.21 (2H, m), 2.53-2.62 (1H, m), 3.04-3.14 (1H, m), 4.10-4.28 (4H, m),5.55-6.05 (1H, m), 7.24-7.63 (10H, m).

Anal. Calcd. for $C_{25}H_{30}N_2O$: C, 80.17; H, 8.07; N, 7.48. Found: C, 79.77; H, 8.21; N, 7.13.

(*2'S*)-2-(2-Phenyl-2-hydroxyethyl)-3-phenyl-*l*-menthopyrazole (*S*)-(**16d**).

This compound was obtained as a colorless oil in 39% yield; ^{1}H nmr: δ 0.69 (3H, d, *J*=6.9 Hz), 0.94 (3H, d, *J*=6.9 Hz), 1.10 (3H, d, *J*=6.9 Hz), 1.19-2.03 (4H, m), 2.39-2.55 (1H, m), 2.66-2.79 (2H, m), 3.97 (1H, ABX, *J*=6.9, 13.9 Hz), 4.21 (1H, ABX, *J*=2.6, 13.9 Hz), 5.06 (1H, d-d, *J*=2.6, 6.9 Hz), 5.7-5.9 (1H, broad), 6.98-7.02 (2H, m), 7.11-7.14 (2H, m), 7.20- 7.28 (3H, m), 7.32-7.41 (3H, m); ^{13}C nmr: δ 18.5 (CH_3), 20.8 (CH_3), 20.9 (CH_3), 23.2 (CH_2), 27.5 (CH_2), 30.2 (CH), 33.0 (CH), 41.0 (CH), 54.6 (CH_2), 73.8 (CH), 120.4 (C), 125.9 (CH), 127.5 (CH), 128.3 (CH), 128.5 (CH), 129.9 (CH), 131.3 (C), 140.8 (C), 141.3 (C), 151.7 (C).

Anal. Calcd. for $C_{25}H_{30}N_2O$: C, 80.17; H, 8.07; N, 7.48. Found: C, 80.05; H, 8.12; N, 7.42.

(*2'R*)-2-(2-Phenyl-2-hydroxyethyl)-3-phenyl-*l*-menthopyrazole (*R*)-(**16d**).

This compound was obtained as a colorless oil in 25% yield; ^{1}H nmr: δ 0.72 (3H, d, *J*=6.6 Hz), 0.94 (3H, d, *J*=6.9 Hz), 1.10 (3H, d, *J*=6.9 Hz), 1.22-2.03 (5H, m), 2.41-2.50 (1H, m), 2.66-2.85 (2H, m), 3.98 (1H, ABX, *J*=8.3, 13.9 Hz), 4.09 (1H, ABX, *J*=3.0, 13.9 Hz), 4.83 (1H, d-d, *J*=3.0, 8.3 Hz), 5.63-5.70 (1H, broad), 7.10-7.16 (2H, m), 7.17-7.20 (2H, m), 7.23-7.32 (3H, m), 7.33-7.42 (3H, m); ^{13}C nmr: δ 18.3 (CH_3), 20.6 (C), 20.8 (CH_3), 23.1 (CH_2), 27.4 (CH_2), 30.0 (CH), 32.7 (CH), 41.0 (CH), 55.3 (CH_2), 73.9 (CH), 120.7 (C), 126.0 (CH), 127.7 (CH), 128.3 (CH), 128.5 (C), 129.7 (C), 131.1 (C), 140.4 (C), 140.9 (C), 151.7 (C).

Anal. Calcd. for $C_{25}H_{30}N_2O$: C, 80.17; H, 8.07; N, 7.48. Found: C, 79.66; H, 8.05; N, 7.33.

(*2'S*)-1-[2-(4- Methylphenyl)-2-hydroxyethyl]-3-phenyl-*l*-menthopyrazole (*S*)-(**15e**).

This compound was obtained as colorless needles in 18% yield; mp 105 °C (from MeOH); ^{1}H nmr: δ 0.89 (3H, d, *J*=6.6 Hz), 0.93 (3H, d, *J*=6.9 Hz), 0.96 (3H, 6.9, *J*= Hz), 1.26-1.45 (2H, m), 1.53-1.71 (2H, m), 1.87-2.25 (2H, m), 2.32 (3H, s), 3.20-3.26 (1H, m), 4.08 (1H, ABX, *J*=6.6, 13.9 Hz), 4.34 (1H, ABX, *J*=2.3,13.9 Hz), 5.18-5.29 (1H, m), 5.62 (1H, s), 7.10 (4H, s), 7.29-7.45 (3H, m), 7.78 (2H, d, *J*=7.3 Hz); ^{13}C nmr: δ 20.0 (CH_3), 21.0 (CH_3), 21.4 (CH_3), 21.5 (CH_3), 25.8 (CH_2), 27.1 (CH_2), 31.6 (CH_2), 37.0 (CH), 55.7 (C), 73.5 (CH), 118.9 (CH), 125.6 (CH), 127.00 (CH), 127.4 (C), 128.4 (CH), 129.0 (CH), 137.3 (CH), 138.3 (CH).

Anal. Calcd. for $C_{26}H_{32}N_2O$: C, 80.37; H, 8.30; N, 7.21. Found: C, 79.84; H, 8.39; N, 6.84.

(*2'R*)-1-[2-(4- Methylphenyl)-2-hydroxyethyl]-3-phenyl-*l*-menthopyrazole (*R*)-(**15e**).

This compound was obtained as colorless needles in 32% yield; mp 50 °C (from MeOH); ^{1}H nmr: δ 0.82 (3H, d, *J*=6.9 Hz), 0.91 (3H, d, *J*=6.9 Hz), 0.99 (3H, d, *J*=6.9 Hz), 1.39-1.47 (1H, m), 1.65-2.06 (4H, m), 2.36 (3H, s), 2.41-2.47 (1H, m), 3.22-3.28 (1H, m), 4.09 (1H, ABX, *J*=1.6, 11.2 Hz), 4.17 (1H, ABX, *J*=5.3 Hz), 5.09 (1H, dd, *J*=4.3, 7.6 Hz), 5.67 (1H, s), 7.25 (4H, AB, *J*=8.2, 6.3 Hz), 7.30-7.43 (3H, m), 7.77 (2H, d, *J*=8.0 Hz); ^{13}C nmr: δ 19.5 (CH_3), 20.0 (CH_3), 21.0 (CH_3), 21.2 (CH_3), 21.2 (CH_3), 21.3 (CH_2), 25.8 (CH_2), 27.4 (CH_2), 31.3 (CH_2), 37.0 (CH), 56 (CH), 73.4 (CH), 118.9 (CH), 126.0 (CH), 126.9 (CH), 127.3 (CH), 128.2 (CH), 129.0 (CH), 134.2 (CH), 127.5 (CH), 127.9 (CH), 142.6 (CH).

Anal. Calcd. for $C_{26}H_{32}N_2O$: C, 80.37; H, 8.30; N, 7.21. Found: C, 80.82; H, 8.09; N, 6.84.

(*2'S*)-2-[2-(4-Methylphenyl)-2-hydroxyethyl]-3-phenyl-*l*-menthopyrazole (*S*)-(**16e**).

This compound was obtained as a colorless oil in 43% yield; ^{1}H nmr: δ 0.70 (3H, d, *J*=6.8 Hz), 0.93 (3H, d, *J*=6.8 Hz), 1.10 (3H, d, *J*=7.0 Hz), 1.22 (1H, q, *J*=10 Hz), 1.51 (1H, q, *J*=10 Hz), 1.83-1.99 (2H, m), 2.31 (3H, s), 2.38-2.50 (1H, m), 2.63-2.77 (2H, m), 3.94 (1H, ABX, *J*=7.2, 14.0 Hz), 4.17 (1H, ABX, *J*=2.6, 14.0 Hz), 5.04 (1H, d, *J*=6.8 Hz), 5.65 (1H, s), 7.04 (5H, s), 7.33-7.36 (4H, m); ^{13}C nmr: δ 18.3 (CH_3), 20.6 (CH_3), 20.8 (CH_3), 21.0 (CH_3), 23.1 (CH_2), 27.4 (CH_2), 30.9 (CH), 32.8 (CH), 40.0 (CH), 54.6 (CH_2), 73.5 (CH), 120.3 (CH), 125.7 (CH), 128.2 (CH), 128.8 (CH), 129.7 (CH), 129.9 (CH), 131.2 (CH), 137.0 (CH), 138.0 (CH), 140.6 (C), 151.5 (C).

Anal. Calcd. for $C_{26}H_{32}N_2O$: C, 80.37; H, 8.30; N, 7.21. Found: C, 80.12; H, 7.93; N, 7.31.

(*2'R*)-2-[2-(4-Methylphenyl)-2-hydroxyethyl]-3-phenyl-*l*-menthopyrazole (*R*)-(**16e**).

This compound was obtained as a colorless oil in 11% yield; ^{1}H nmr: δ 6.94 (3H, d, *J*=6.9 Hz), 0.93 (3H, d, *J*=6.6 Hz), 1.09 (3H, d, *J*=6.9 Hz), 1.22-1.32 (1H, m), 1.50-1.57 (1H, m), 1.85-2.01 (2H, m), 2.31 (3H, s), 2.42-2.49 (1H, m), 2.66-2.82 (2H, m), 3.97 (1H, ABX, *J*=8.0, 13.9 Hz),4.06 (1H, ABX, *J*=3.0, 13.9 Hz), 4.79 (1H, dd, *J*=3.0, 8.6 Hz), 5.55 (1H, s), 7.09 (4H, c, *J*= Hz), 7.13-7.19 (2H, m), 7.35-7.40 (3H, m); ^{13}C nmr: δ 18.4 (CH_3), 20.6 (CH_3), 21.1 (CH_3), 23.2 (CH_2), 27l4 (CH_2), 30.0 (CH), 32.7 (CH), 41.0 (CH), 53.4 (C), 55.4 (CH), 73.8 (CH), 120.7 (CH), 126.0 (CH), 128.4 (CH), 128.5 (CH), 129.0 (CH), 129.8 (CH), 131.2 (CH), 137.4 (CH), 138.0 (CH), 140.4 (C), 151.7 (C).

Anal. Calcd. for $C_{26}H_{32}N_2O$: C, 80.37; H, 8.30; N, 7.21. Found: C, 79.98; H, 8.54; N, 6.63.

(*2'S*)-1-[2-(1-Naphthyl)-2-hydroxyethyl]-3-phenyl-*l*-menthopyrazole (*S*)-(**15f**).

This compound was obtained as a colorless oil in 28% yield; ^{1}H nmr: δ 0.69 (3H, d, *J*=6.9 Hz), 0.75 (3H, d, *J*=6.9 Hz), 0.86 (3H, d, *J*=6.6 Hz), 0.92-1.02 (1H, m),1.18-1.37 (3H, m), 1.69-1.86 (2H, m), 3.11-3.17 (1H, m), 4.50 (2H, ABX, *J*=13.9, 5.0, 2.3 Hz), 5.76 (1H, d, *J*=5.9 Hz), 5.97 (1H, m), 7.28-7.60 (7H, m), 7.72-7.90 (4H, m), 8.06 (1H, d, *J*=8.6 Hz); ^{13}C nmr: δ 19.6 (CH_3), 19.7 (CH_3), 21.2 (CH_3), 21.4 (CH_2), 25.8 (CH_2), 27.0 (CH), 31.4 (CH), 36.4 (CH), 54.3 (CH_2), 70.3 (CH), 118.9 (C), 122.0 (CH), 123.3 (CH), 125.5 (CH), 125.6 (CH), 126.3 (CH), 127.0 (CH), 127.4 (CH), 127.9 (CH), 128.5 (CH), 129.1 (CH), 129.9 (C), 133.6 (C), 134.3 (C), 136.6 (C), 143.9 (C), 148.7 (C).

Anal. Calcd. for $C_{29}H_{32}N_2O$: C, 82.04; H, 7.60; N, 6.60. Found: C, 81.79; H, 7.64; N, 6.54.

(*2'R*)-1-[2-(1-Naphthyl)-2-hydroxyethyl]-3-phenyl-*l*-menthopyrazole (*R*)-(**15f**).

This compound was obtained as colorless needles in 53% yield; mp 72-73 °C (from MeOH); ^{1}H nmr: δ 0.69 (3H, d, *J*=6.6 Hz), 0.79 (3H, d, *J*=6.9 Hz), 0.97 (3H, d, *J*=6.9 Hz), 1.36-1.43 (1H, m), 1.62-1.82 (3H, m), 1.94-2.02 (1H, m), 2.36-2.42 (1H, m), 3.20-3.27 (1H, m), 4.35 (2H, ABX, *J*=13.9, 8.3, 3.0 Hz), 5.90-5.94 (2H, m), 7.30-7.56 (6H, m), 7.79-7.92 (5H, m), 8.02-8.06 (1H, m); ^{13}C nmr: δ 19.4 (CH_3), 20.0 (CH_3), 21.2 (CH_3), 21.4 (CH_2), 25.9 (CH_2), 27.7 (CH), 31.4 (CH), 37.0 (CH), 55.4 (CH_2), 70.5 (CH), 119.2 (C), 122.4 (CH), 124.2 (CH), 125.5 (CH), 125.7 (CH), 126.2 (CH), 127.1 (CH), 127.4 (CH), 128.3 (CH), 128.4 (CH), 129.1 (CH), 130.4 (C), 133.7 (C), 134.4 (C), 136.4 (C), 142.7 (C), 147.9 (C).

Anal. Calcd. for $C_{29}H_{32}N_2O$: C, 82.04; H, 7.60; N, 6.60. Found: C, 81.69; H, 7.29; N, 6.56.

(*2'S*)-2-[2-(1-Naphthyl)-2'-hydroxyethyl]-3-phenyl-*l*-menthopyrazole (*S*)-(**16f**).

This compound was obtained as colorless needles in 38% yield; mp 133-134 °C (from MeOH); ^{1}H nmr: δ 0.69 (3H, d, *J*=6.6 Hz), 1.01 (3H, d, *J*=6.9 Hz), 1.14 (3H, d, *J*=6.9 Hz), 1.23 (1H, q, *J*=11.9 Hz), 1.53 (1H, q, *J*=11.9 Hz), 1.83-1.95 (2H, m), 2.50-2.77 (3H, m), 4.25 (1H, ABX, *J*=14.2, 6.6, 2.3 Hz), 5.78-5.86 (2H, m), 6.83 (2H, d, *J*=6.3 Hz), 7.07-7.42 (6H, m), 7.55-7.81 (4H, m); ^{13}C nmr: δ 18.4 (CH_3), 20.7 (CH_3), 20.9 (CH_3), 23.1 (CH_2), 27.5 (CH_2), 30 (CH), 32.8 (CH), 41.0 (CH), 53.6 (CH), 70.4 (CH), 122.0 (CH), 123.6 (CH), 125. (CH), 125.4 (CH), 125.8 (CH), 127.9 (CH), 128.0 (CH), 128.1 (CH), 128.8 (CH), 129.5 (CH), 151.0 (C).

Anal. Calcd. for $C_{29}H_{32}N_2O$: C, 82.04; H, 7.60; N, 6.60. Found: C, 82.15; H, 7.66; N, 6.56.

(*2'R*)-2-[2-(1-Naphthyl)-2'-hydroxyethyl]-3-phenyl-*l*-menthopyrazole (*R*)-(**16f**).

This compound was obtained as a colorless oil in 18% yield; ^{1}H nmr: δ 0.76 (3H, 6.8, *J*=6.6 Hz), 0.98 (3H, d, *J*=6.9 Hz), 1.13 (3H, d, *J*=6.9 Hz), 1.26 (1H, q, *J*=12.5 Hz), 1.57 (1H, q, *J*=12.2 Hz), 1.86-2.05 (2H, m), 2.49-2.57 (1H, m), 2.70-2.91 (2H, m), 4.25 (2H, ABX, *J*=14.2, 8.9, 2.0 Hz), 5.30 (1H, s), 5.41 (1H, d, *J*=8.6 Hz), 7.06 (2H, d, *J*=3.3 Hz), 7.23-7.49 (7H, m), 7.71-7.83 (3H, m); ^{13}C nmr: δ 18.3 (CH_3), 20.6 (CH_3), 20.8 (CH_3), 23.2 (CH_2), 27.5 (CH_2), 29.9 (CH), 32.8 (CH), 41.15 (CH_2), 71.0 (CH), 121.8 (C), 123.5 (CH), 125.2 (CH), 125.6 (CH), 125.9 (CH), 128.0 (CH), 128.6 (CH), 128.8 (CH), 128.8 (CH), 129.8 (CH), 129.9 (C), 133.5 (C).

Anal. Calcd. for $C_{29}H_{32}N_2O$: C, 82.04; H, 7.60; N, 6.60. Found: C, 81.56; H, 7.58; N, 6.57.

Diethylzinc Addition Reaction on Aromatic Aldehyde.

With *N*-Unsubstituted Pyrazoles.

To the mixture of *N*-unsubstituted pyrazole(0.3 mmol), aromatic aldehyde (1.3 mmol) in toluene (4 ml) was added diethyl zinc hexane solution (1 mol/l, 2.0 ml) under argon atmosphere. The mixture was stirred for several hours at 40 °C. The small portion of reaction mixture was quenched with hydrochloric acid in some intervals, and was monitored by gas chromatography using naphthalene as the internal standard. The reaction mixture was quenched with dilute hydrochloric acid and the organic layer was washed with water, dilute sodium hydroxide and saturated sodium chloride. After drying over anhydrous magnesium sulfate, the solvent was evaporated, and the desired 1-aryl-1-propanol was distilled using a cold finger apparatus. The ee of distillate was evaluated by gas chromatography through a chiral phase column. From the residue of the distillation, pyrazole compounds were isolated by silica gel column chromatography.

With *N*-Acylpyrazoles.

To a mixture of *N*-acylpyrazole(0.3 mmol), aromatic aldehyde (1.3 mmol) in toluene (4 ml) was added diethylzinc hexane solution (1 mol/l, 2.0 ml) under argon atmosphere. The mixture was stirred for several hours at 40 °C. The reaction mixture was worked up described above.

With *N*-(2-Hydroxyethyl)-pyrazoles.

To the mixture of *N*-(2-hydroxyethyl)-pyrazole (0.3 mmol), aromatic aldehyde (1.0 mmol) in toluene (4 ml) was added diethylzinc hexane solution (1 mol/l, 2.0 ml) under argon atmosphere. The mixture was stirred for several hours at 40 °C. The reaction mixture was worked up described above.

Acknowledgement.

The authors are grateful to the Chemical Analysis Center, University of Tsukuba, for the measurement of various kinds of spectra and the elemental analyses.

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