DIASTEREOMERIC PREPARATION OF α- AND β-PHENYLTHIO SUBSTITUTED *N*-ACYLPYRAZOLES†

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Abstract— When 3-phenyl-*l*-menthopyrazole was used as a chiral auxiliary, the diastereomeric preparation of α– and β–phenylthio-substituted *N*-acylpyrazoles (**4** and **9**) was accomplished in high yield by the α–sulfenylation using diphenyl disulfide and the conjugate addition of thiophenol, respectively.

In many methodologies using various chiral auxiliaries,[1] three essential properties are required for the auxiliary compounds. The first is the easier preparation and the storage of the substrate-auxiliary intermediate. The second is either an optical or a chemical activation on the substrate moiety by the auxiliary. The last is the conversion of the substrate-auxiliary intermediate into the desired functionalities accompanied by the recovery of the auxiliary compound.

Recently we have investigated the utility of *N*-acylpyrazoles as the key intermediate compounds in this methodology. The formation of auxiliary-substrate intermediate was accomplished through the acylation of pyrazoles with carboxylic acids or their acid chlorides.[2,3] As the functionalization reactions, the nucleophilic reactions of *N*-acylpyrazoles such as alcoholysis,[2] aminolysis,[4] Grignard reactions[5] and Reformatsky reactions[6] proceeded chemoselectively under mild conditions with the recovery of pyrazoles. The α–alkylation on acyl group of *N*-acylpyrazoles was reported as the modification reaction of the substrate moiety.[7] Especially the α–alkylation was highly diastereoselective in the case of using 3-phenyl-*l*-menthopyrazole [(4*R*, 7*S*)-3-phenyl-4-methyl-7-isopropyl-4,5,6,7-tetrahydroindazole] as an optically active pyrazole.

In a meanwhile, the sulfur-containing substances are paid much attention in the pharmaceutical field. Also thio

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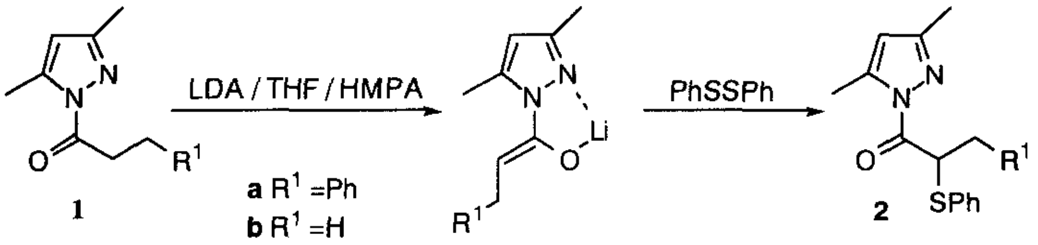
† This paper is dedicated to the memory of the late Prof. Yoshio Ban for his brilliant achievement in the field of heterocyclic chemistry.

groups, especially phenylthio group, are very labile and convertible to various functional groups.[8] Therefore the introduction of sulfur atom into the substrate moiety must raise up the usefulness of *N*-acylpyrazoles. In the course of studies concerning to *N*-acylpyrazoles, we will show the preparation of α– and β–phenylthio substituted *N*-acylpyrazoles. Also the diastereomeric sulfenylation will be discussed in the reactions using chiral 3-phenyl-*l*-menthopyrazole.

Previously α–alkylation of *N*-acylpyrazoles was accomplished by the action of alkyl halides on *N*-acylpyrazole lithium enolate.[7] When diphenyl disulfide was employed as an electrophile[9] instead of alkyl halides, 1-(2'-phenylthio-3'-phenyl)propanoyl- (**2a**) and 1-(2'-phenylthio)propanoyl-3,5-dimethylpyrazoles (**2b**) were prepared in high yields by the use of LDA in the presence of HMPA at -78°C. Similarly, various 2-acyl-3-phenyl-*l*-menthopyrazoles (**3**) were treated with diphenyl disulfide to obtain 2-(2'-phenylthio)acyl-3-phenyl-*l*-menthopyrazoles (**4**) in good yields as listed in Table 1. The configuration of the stereogenic center was deduced to be 2'*R* on the basis of both the reaction mechanism and the comparison of nmr data with those of the related



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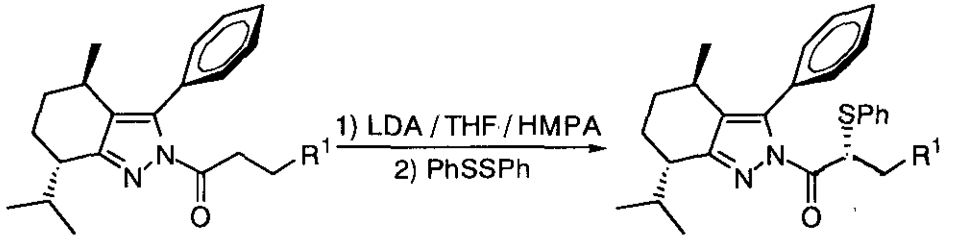

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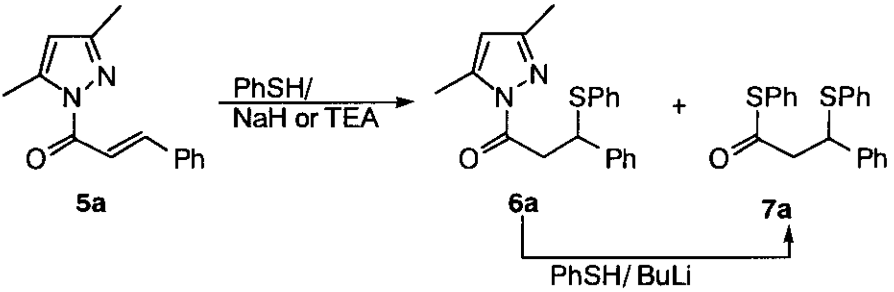
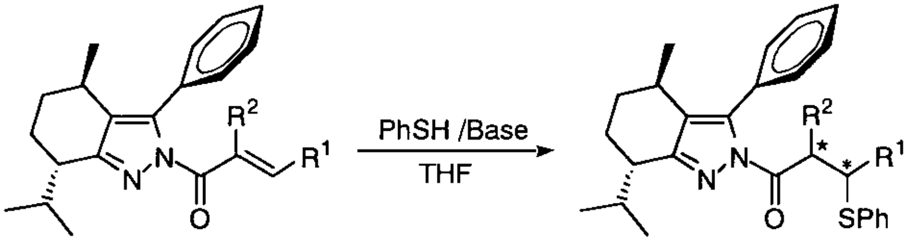
Table 1. α-Sulfenylation of 2-Acyl-3-phenyl-l-menthopyrazoles (**3**) with Diphenyl Disulfide

Substrate (3)	R^1	Yield (%)	De (%)[a]
a	Ph	85	76
b	H	35	43
c	Me	98	84
d	Et	84	80

a: The 2'*R* diastereomers were predominant, and the % de was evaluated from the nmr peak ratios.





8 **9**

Table 2. Conjugate Addition of Thiophenol on 2-(α,β-Unsaturated)acyl-3-phenyl-*l*-menthopyrazole (**8**)

Substrate (**8**)			Base	Conditions	Yield (%)	De (%)[a]
	R^1	R^2				
a	Ph	H	NaH	0°C, 2.5 h	99	23
a	Ph	H	TEA	20°C, 1 h	85	19
a	Ph	H	TEA	-78° to 0°C, 4 h	98	22
b	Me	H	TEA	20°C, 1 h	100	43
c	Et	H	TEA	20°C, 2.5 h	94	38
d	*i*-Pr	H	TEA	20°C, 1.5 h	84	33
e	*t*-Bu	H	TEA	20°C, 2 h	76	38
f	H	Me	TEA	20°C, 1 h	85	30
g	Me	Me	TEA	20°C, 1 h	78	b

a: The de % was evaluated from the nmr peak ratios.

b: The de % of *syn* and *anti* isomers were 33 and 32 % respectively, while the *syn*/ *anti* ratio was 8.4:1.

compounds. The diastereomeric excess (de) of the sulfenylated products (**4**) was found to be 43-84 % from the nmr peak ratios assigned to 4-Me protons.

Next, the conjugate addition of thiophenol to *N*-(α,β–unsaturated) acylpyrazoles was attempted for the introduction of phenylthio group on β–position of *N*-acylpyrazoles.[10] When 1-cinnamoyl-3,5-dimethylpyrazole

(**5a**) was treated with an excess amount of thiophenol in the presence of catalytic amount of sodium hydride at room temperature, β–sulfenylated product (**6a**) was formed accompanying with some 3-phenylthio-3-phenylpropanoic acid phenylthio ester (**7a**). Since **7a** was formed by the further attack of thiophenol on the conjugate adduct (**6a**), the reaction condition was optimized by either lowering the reaction temperature or the use of weaker base such as triethylamine (TEA). These optimal conditions were applied to the conjugate addition of thiophenol on the optically active 2-(α,β–unsaturated) acyl-3-phenyl-*l*-menthopyrazoles (**8**). The results were summarized in Table 2, in which β–sulfenylated products (**9**) were prepared in good yields. Although the configuration was still unrevealed, the diastereomeric excess values were evaluated from the nmr peak ratios of 7-iPr protons.

In the case of 2-methacryloyl-3-phenyl-*l*-menthopyrazole (**8f**), an asymmetric center was newly formed on the α-position. From the nmr data, the diastereomer ratio of **9f** was deduced to be 30 % de. When 2-(2'-methyl-2'-butenoyl)-3-phenyl-*l*-menthopyrazole (**8g**) was treated with thiophenol in the presence of TEA, two pairs of diastereomeric mixture of 2-(3'-phenylthio-2'-methyl)butanoyl-3-phenyl-*l*-menthopyrazole (**9g**) was obtained complicatedly. The nmr spectrum of α–proton showed that *syn* isomers (*syn*-**9g**) were predominant with the *syn*/*anti* ratio of 8.4 : 1. The diastereomeric excess of each *syn*-**9g** and *anti*-**9g** was found to be 33 and 32 % de, respectively.

In conclusion, the preparation of α– and β–phenylthio substituted *N*-acylpyrazoles was accomplished in high yield by the α–sulfenylation using diphenyl disulfide and the conjugate addition of thiophenol, respectively. By the use of chiral 3-phenyl-*l*-menthopyrazole, phenylthio group was able to introduce into acyl moiety with moderate diastereoselectivity.

EXPERIMENTAL

Nmr spectra were recorded on JEOL JNM-EX270 (270 MHz) spectrometers in $CDCl_3$ with TMS as an internal standard. IR spectrum was measured by Shimadzu IR-460 spectrophotometer. THF was dried over benzophenone ketyl radical generated from benzophenone and sodium metal, and distilled just before use.

General Procedure of α–Sulfenylation.

Under nitrogen atmosphere, butyllithium solution (1.6M in hexane, 940 μl, 1.5 mmol) was added to diisopropylamine (210 μl, 1.5 mmol) in THF (10 ml) at 0°C and stirred for 30 min. *N*-Acylpyrazole (1.08 mmol) and HMPA (500 μl, 2.9 mmol) in THF (1 ml) were slowly added to the chilled mixture at -78°C and stirring was continued for another 30 min. THF (1 ml) solution of diphenyl disulfide (350 mg, 1.6 mmol) was added to the mixture. After 1 h stirring, the reaction was quenched with several drops of acetic acid and diluted with water. Products were extracted with CH_2Cl_2 and organic layer was washed with saturated aq-$NaHCO_3$ and saturated aq-NaCl, dried over anhydrous $MgSO_4$ and solvent was evaporated. The residue was purified by silica gel column chromatography with the eluting solvent of benzene-hexane mixture.

1-(2-Phenylthio-3-phenyl)propanoyl-3,5-dimethylpyrazole (**2a**). Oil; yield 79 %; ^{1}H-nmr ($CDCl_3$) δ 2.14 (3H, s), 2.46 (3H, s), 3.22 (2H, ddd, J = 14.2, 8.6, 6.6 Hz), 5.43 (1H, dd, J = 8.6, 6.6 Hz), 5.90 (1H, s), 7.15-7.42 (10H, m). Anal. Calcd for $C_{20}H_{20}N_2OS$: C, 71.40; H, 5.99; N, 8.33. Found: C, 71.54; H, 6.06; N, 8.60.

1-(2-Phenylthio)propanoyl-3,5-dimethylpyrazole (**2b**). Oil; yield 75%; ^{1}H-nmr ($CDCl_3$) δ 1.53 (3H, d, J = 6.9 Hz), 2.19 (3H, s), 2.51 (3H, s), 5.24 (1H, q, J = 6.9 Hz), 5.96 (1H, s), 7.21-7.35 (3H, m), 7.40-7.47 (2H, m). Anal. Calcd for $C_{14}H_{16}N_2OS$: C, 64.59; H, 6.19; N, 10.76. Found: C, 64.67; H, 6.19; N, 10.67.

2-(2-Phenylthio-3-phenyl)propanoyl-3-phenyl-l-menthopyrazole (**4a**). Oil, yield 85%. Anal. Calcd for $C_{32}H_{34}N_2OS$: C, 77.69; H, 6.93; N, 5.66. Found: C, 77.71; H, 6.99; N, 5.67.

2'*R*-Diastereomer. ^{1}H-Nmr ($CDCl_3$) δ 0.67 (3H, d, J = 6.6 Hz), 0.88 (3H, d, J = 6.6 Hz), 1.02 (3H, d, J = 6.9 Hz), 1.14-1.27 (1H, m), 1.38-1.54 (1H, m), 1.78-1.97 (2H, m), 2.24-2.33 (1H, m), 2.48-2.55 (1H, m), 2.69-2.77 (1H, m), 3.18 (2H, ddd, J = 14.2, 8.9, 6.6 Hz), 5.60 (1H, dd, J = 8.9, 6.6 Hz), 7.11-7.47 (15H, m).

2'*S*-Diastereomer. ^{1}H-Nmr ($CDCl_3$) δ 0.67 (3H, d, J = 6.6 Hz), 0.92 (3H, d, J = 6.9 Hz), 1.07 (3H, d, J = 6.9 Hz), 1.14-1.27 (1H, m), 1.38-1.54 (1H, m), 1.78-1.97 (2H, m), 2.24-2.33 (1H, m), 2.48-2.55 (1H, m), 2.69-2.77 (1H, m), 3.18 (2H, ddd, J = 14.2, 8.9, 6.6 Hz), 5.60 (1H, dd, J = 8.9, 6.6 Hz), 7.11-7.47 (15H, m).

2-(2-Phenylthio)propanoyl-3-phenyl-l-menthopyrazole (**4b**). Oil, yield 35%. Anal. Calcd for $C_{26}H_{30}N_2OS$: C, 74.60; H, 7.22; N, 6.69. Found: C, 74.51; H, 7.37; N, 6.59.

2'*R*-Diastereomer. ^{1}H-Nmr ($CDCl_3$) δ 0.68 (3H, d, J = 6.6 Hz), 0.90 (3H, d, J = 6.9 Hz), 1.06 (3H, d, J = 6.9 Hz), 1.16-1.28 (1H, m), 1.41-1.61 (1H, m), 1.48 (3H, d, J = 6.9 Hz), 1.80-2.00 (2H, m), 2.28-2.40 (1H, m), 2.49-2.57 (1H, m), 2.70-2.80 (1H, m), 5.29 (1H, q, J = 7.3 Hz), 7.22-7.53 (10H, m).

2'*S*-Diastereomer. ^{1}H-Nmr ($CDCl_3$) δ 0.73 (3H, d, J = 6.9 Hz), 0.95 (3H, d, J = 6.6 Hz), 1.19 (3H, d, J = 6.9 Hz), 1.16-1.28 (1H, m), 1.41-1.61 (1H, m), 1.48 (3H, d, J = 6.9 Hz), 1.80-2.00 (2H, m), 2.28-2.40 (1H, m), 2.49-2.57 (1H, m), 2.70-2.80 (1H, m), 5.29 (1H, q, J = 7.3 Hz), 7.22-7.53 (10H, m).

2-(2-Phenylthio)butanoyl-3-phenyl-l-menthopyrazole (**4c**). Oil, yield 98%. Anal. Calcd for $C_{27}H_{32}N_2OS$:

C, 74.96; H, 7.46; N, 6.48. Found: C, 75.08; H, 7.55; N, 6.44.

2'*R*-Diastereomer. ^{1}H-Nmr ($CDCl_3$) δ 0.68 (3H, d, J = 6.9 Hz), 0.91 (3H, d, J = 6.9 Hz), 1.00 (3H, t, J = 7.4 Hz); 1.06 (3H, d, J = 6.9 Hz), 1.10-1.28 (1H, m), 1.42-1.56 (1H, m), 1.76-2.01 (4H, m), 2.29-2.44 (1H, m), 2.50-2.57 (1H, m), 2.73-2.81 (1H, m), 5.15 (1H, t, J = 6.9 Hz), 7.20-7.51 (10H, m).

2'*S*-Diastereomer. ^{1}H-Nmr ($CDCl_3$) δ 0.73 (3H, d, J = 6.6 Hz), 0.91 (3H, d, J = 6.9 Hz), 1.00 (3H, t, J = 7.4 Hz), 1.06 (3H, d, J = 6.9 Hz), 1.10-1.28 (1H, m), 1.42-1.56 (1H, m), 1.76-2.01 (4H, m), 2.29-2.44 (1H, m), 2.50-2.57 (1H, m), 2.73-2.81 (1H, m), 5.15 (1H, t, J = 6.9 Hz), 7.20-7.51 (10H, m).

2-(2-Phenylthio)pentanoyl-3-phenyl-l-menthopyrazole (**4d**). Oil, yield 84%; Anal. Calcd for $C_{28}H_{34}N_2OS$: C, 75.29; H, 7.67; N, 6.27. Found: C, 74.95; H, 7.73; N, 6.22.

2'*R*-Diastereomer. ^{1}H-Nmr ($CDCl_3$) δ 0.68 (3H, d, J = 6.6 Hz), 0.88 (3H, t, J = 7.3 Hz), 0.91 (3H, d, J = 6.6 Hz), 1.06 (3H, d, J = 6.9 Hz), 1.16-1.28 (1H, m), 1.32-1.57 (3H, m), 1.68-2.00 (4H, m), 2.29-2.41 (1H, m), 2.52-2.57 (1H, m), 2.63-2.81 (1H, m), 5.28 (1H, dd, J = 6.6, 8.3 Hz), 7.18-7.51 (10H, m).

2'*S*-Diastereomer. ^{1}H-Nmr ($CDCl_3$) δ 0.73 (3H, d, J = 6.9 Hz), 0.88 (3H, t, J = 7.3 Hz), 0.91 (3H, d, J = 6.6 Hz), 1.06 (3H, d, J = 6.9 Hz), 1.16-1.28 (1H, m), 1.32-1.57 (3H, m), 1.68-2.00 (4H, m), 2.29-2.41 (1H, m), 2.52-2.57 (1H, m), 2.63-2.81 (1H, m), 5.28 (1H, dd, J = 6.6, 8.3 Hz), 7.18-7.51 (10H, m).

General Procedure of Conjugate Addition.

Catalyzed by NaH. Under nitrogen atmosphere, NaH (60 % dispersed in mineral oil, 2.1 mg, 0.05 mmol) was suspended in THF (5 ml). Thiophenol (150 μl, 1.5 mmol) was added at 0°C and the mixture was kept stirring for 1 h. After the addition of THF (1 ml) solution of *N*-(α,β−unsaturated) acylpyrazole (0.5 mmol), the mixture was stirred for 3.5 h at 0°C. The reaction was quenched with several drops of acetic acid and diluted with water. The products were extracted with CH_2Cl_2, and the organic layer was washed with saturated aq-NaCl, dried over anhydrous $MgSO_4$, and the solvent was evaporated. The residue was chromatographed on silica gel column with the eluting solvent of benzene-hexane mixture.

Catalyzed by TEA. The mixture of *N*-(α,β−unsaturated) acylpyrazole (0.5 mmol), TEA (200 μl, 1.4 mmol) and thiophenol (500 μl, 4.9 mmol) in THF (5 ml) was stirred for 4 h at room temperature under nitrogen atmosphere. By the addition of 1N sodium hydroxide, the reaction was quenched. The product was extracted with CH_2Cl_2 and organic layer was worked up as described above.

1-(3-Phenylthio-3-phenyl)propanoyl-3,5-dimethylpyrazole (**6a**). Oil; yield 82%; ^{1}H nmr ($CDCl_3$) δ 2.19 (3H, s), 2.39 (3H, d, J = 1.0 Hz), 3.78 (2H, d, J = 6.9 Hz), 4.92 (1H, t, J = 6.9 Hz), 5.85 (1H, s), 7.13-7.35 (10H, m); ir (KBr) 1713 (s), 1588 (w), 1380 (s), 1310 (m), 970 (s), 815 (m), 751 (s), 692 (s) cm^{-1}. Anal.

Calcd for $C_{20}H_{20}N_2OS$: C, 71.40; H, 5.99; N, 8.33. Found: C, 71.50; H, 6.05; N, 8.35.

2-(3-Phenylthio-3-phenyl)propanoyl-3-phenyl-l-menthopyrazole (**9a**). Oil; yield 85%. Anal. Calcd for $C_{32}H_{34}N_2OS$: C, 77.69; H, 6.93; N, 5.66. Found: C, 77.86; H, 6.99; N, 5.81.

Major Diastereomer. ^{1}H-Nmr ($CDCl_3$) δ 0.66 (3H, d, J = 6.9 Hz), 0.97 (3H, d, J = 6.6 Hz), 1.12 (3H, d, J = 6.9 Hz), 1.19-1.28 (1H, m), 1.48-1.52 (1H, m), 1.84-1.96 (2H, m), 2.42-2.51 (1H, m), 2.60-2.73 (2H, m), 3.65-3.93 (2H, m), 4.87-4.93 (1H, m), 7.10-7.35 (15H, m).

Minor Diastereomer. ^{1}H-Nmr ($CDCl_3$) δ 0.66 (3H, d, J = 6.9 Hz), 0.93 (3H, d, J = 6.9 Hz), 1.11 (3H, d, J = 6.6 Hz), 1.19-1.28 (1H, m), 1.48-1.52 (1H, m), 1.84-1.96 (2H, m), 2.42-2.51 (1H, m), 2.60-2.73 (2H, m), 3.65-3.93 (2H, m), 4.87-4.93 (1H, m), 7.10-7.35 (15H, m).

2-(3-Phenylthio)butanoyl-3-phenyl-l-menthopyrazole (**9b**). Oil, yield 100%. Anal. Calcd for $C_{27}H_{32}N_2OS$: C, 74.96; H, 7.46; N, 6.48. Found: C, 74.92; H, 7.43; N, 6.48.

Major Diastereomer. ^{1}H-Nmr ($CDCl_3$) δ 0.68 (3H, d, J = 6.6 Hz), 0.93 (3H, d, J = 6.6 Hz), 1.09 (3H, d, J = 6.9 Hz), 1.17-1.29 (1H, m), 1.33 (3H, d, J = 6.9 Hz), 1.37-1.56 (1H, m), 1.83-1.98 (2H, m), 2.39-2.46 (1H, m), 2.57-2.65 (1H, m), 2.70-2.78 (1H, m), 3.16-3.25 (1H, m), 3.47-3.55 (1H, m), 3.77-3.86 (1H, m), 7.17-7.46 (10H, m).

Minor Diastereomer. ^{1}H-Nmr ($CDCl_3$) δ 0.68 (3H, d, J = 6.6 Hz), 0.92 (3H, d, J = 6.6 Hz), 1.09 (3H, d, J = 6.9 Hz), 1.17-1.29 (1H, m), 1.33 (3H, d, J = 6.9 Hz), 1.37-1.56 (1H, m), 1.83-1.98 (2H, m), 2.39-2.46 (1H, m), 2.57-2.65 (1H, m), 2.70-2.78 (1H, m), 3.16-3.25 (1H, m), 3.47-3.55 (1H, m), 3.77-3.86 (1H, m), 7.17-7.46 (10H, m).

2-(3-Phenylthio)pentanoyl-3-phenyl-l-menthopyrazole (**9c**). Oil; yield 94%. Anal. Calcd for $C_{28}H_{34}N_2OS$: C, 75.29; H, 7.67; N, 6.27. Found. C, 75.20; H, 7.64; N, 6.29.

Major Diastereomer. ^{1}H-Nmr ($CDCl_3$) δ 0.68 (3H, d, J = 6.6 Hz), 0.93 (3H, d, J = 6.9 Hz), 1.00-1.10 (6H, m), 1.16-1.28 (1H, m), 1.43-1.72 (3H, m), 1.82-1.97 (2H, m), 2.36-2.45 (1H, m), 2.57-2.65 (1H, m), 2.70-2.78 (1H, m), 3.26-3.51 (2H, m), 3.63-3.70 (1H, m), 7.14-7.46 (10H, m).

Minor Diastereomer. ^{1}H-Nmr ($CDCl_3$) δ 0.68 (3H, d, J = 6.6 Hz), 0.92 (3H, d, J = 6.6 Hz), 1.00-1.10 (6H, m), 1.16-1.28 (1H, m), 1.43-1.72 (3H, m), 1.82-1.97 (2H, m), 2.36-2.45 (1H, m), 2.57-2.65 (1H, m), 2.70-2.78 (1H, m), 3.26-3.51 (2H, m), 3.63-3.70 (1H, m), 7.14-7.46 (10H, m).

2-(3-Phenylthio-4-methyl)pentanoyl-3-phenyl-l-menthopyrazole (**9d**). Oil;, yield 84%. Anal. Calcd for $C_{29}H_{36}N_2OS$: C, 75.61; H, 7.88; N, 6.08. Found. C, 75.34; H, 7.88; N, 6.01.

Major Diastereomer. ^{1}H-Nmr ($CDCl_3$) δ 0.68 (3H, d, J = 6.6 Hz), 0.93 (3H, d, J = 6.6 Hz), 1.00-1.10 (9H, m), 1.17-1.30 (1H, m), 1.44-1.56 (1H, m), 1.83-2.03 (3H, m), 2.38-2.48 (1H, m), 2.58-2.66 (1H, m), 2.70-2.78 (1H, m), 3.28-3.59 (2H, m), 3.72-3.82 (1H, m), 7.12-7.43 (10H, m).

Minor Diastereomer. ^{1}H-Nmr ($CDCl_3$) δ 0.68 (3H, d, J = 6.6 Hz), 0.91 (3H, d, J = 6.9 Hz), 1.00-1.10 (9H, m), 1.17-1.30 (1H, m), 1.44-1.56 (1H, m), 1.83-2.03 (3H, m), 2.38-2.48 (1H, m), 2.58-2.66 (1H, m), 2.70-2.78 (1H, m), 3.28-3.59 (2H, m), 3.72-3.82 (1H, m), 7.12-7.43 (10H, m).

2-(3-Phenylthio-4,4-dimethyl)pentanoyl-3-phenyl-l-menthopyrazole (**9e**). Oil; yield 76%. Anal. Calcd for $C_{30}H_{38}N_2OS$: C, 75.91; H, 8.07; N, 5.9. Found. C, 75.37; H, 8.03; N, 5.60.

Major Diastereomer. ^{1}H-Nmr ($CDCl_3$) δ 0.67 (3H, d, J = 6.9 Hz), 0.95 (3H, d, J = 6.9 Hz), 1.06 (9H, s), 1.09 (3H, d, J = 6.9 Hz), 1.13-1.29 (1H, m), 1.44-1.57 (1H, m), 1.84-1.96 (2H, m), 2.34-2.46 (1H, m), 2.58-2.73 (2H, m), 3.33-3.81(3H, ddd, J = 5.6, 8.6, 16.2 Hz), 7.04-7.50 (10H, m).

Minor Diastereomer. ^{1}H-Nmr ($CDCl_3$) δ 0.67 (3H, d, J = 6.9 Hz), 0.93 (3H, d, J = 6.9 Hz), 1.03 (9H, s), 1.09 (3H, d, J = 6.9 Hz), 1.13-1.29 (1H, m), 1.44-1.57 (1H, m), 1.84-1.96 (2H, m), 2.34-2.46 (1H, m), 2.58-2.73 (2H, m), 2.86-3.15 (2H, ddd, J = 5.0, 8.6, 16.2 Hz), 3.67-3.76 (1H, dd, J = 5.0, 8.6 Hz), 7.04-7.50 (10H, m).

2-(3-Phenylthio-2-methyl)propanoyl-3-phenyl-l-menthopyrzole (**9f**). Oil; yield 85%. Anal. Calcd for $C_{27}H_{32}N_2OS$: C, 74.96; H, 7.46; N, 6.48. Found: C, 74.79; H, 7.35; N, 6.56.

Major Diastereomer. ^{1}H-Nmr ($CDCl_3$) δ 0.69 (3H, d, J = 6.9 Hz), 0.90 (3H, d, J = 6.9 Hz), 1.07 (3H, d, J = 6.9 Hz), 1.16-1.28 (1H, m), 1.29 (3H, d, J = 6.9 Hz), 1.43-1.55 (1H, m), 1.83-1.98 (2H, m), 2.37-2.44 (1H, m), 2.57-2.64 (1H, m), 2.70-2.79 (1H, m), 2.99 (1H, dd, J = 7.6, 13.2 Hz), 3.44 (1H, dd, J = 6.9, 13.2 Hz), 4.14-4.25 (1H, m), 7.11-7.41 (10H, m).

Minor Diastereomer. ^{1}H-Nmr ($CDCl_3$) δ 0.69 (3H, d, J = 6.9 Hz), 0.89 (3H, d, J = 6.6 Hz), 1.05 (3H, d, J = 6.9 Hz), 1.16-1.28 (1H, m), 1.35 (3H, d, J = 6.9 Hz), 1.43-1.55 (1H, m), 1.83-1.98 (2H, m), 2.37-2.44 (1H, m), 2.57-2.64 (1H, m), 2.70-2.79 (1H, m), 2.89 (1H, dd, J = 7.6, 13.2 Hz), 3.39 (1H, dd, J = 6.9, 13.2 Hz), 4.14-4.25 (1H, m), 7.11-7.41 (10H, m).

2-(3-Phenylthio-2-methyl)butanoyl-3-phenyl-l-menthopyrazole (**9g**). Oil; yield 78 %. Anal. Calcd for $C_{28}H_{34}N_2OS$: C, 75.29; H, 7.67; N, 6.27. Obsd: C, 75.23; H, 7.72; N, 6.28.

syn-Major Diastereomer. ^{1}H-Nmr ($CDCl_3$) δ 0.69 (3H, d, J = 6.6 Hz), 0.94 (3H, d, J = 6.9 Hz), 1.07 (3H, d, J = 6.9 Hz), 1.13-1.31 (1H, m), 1.36 (3H, d, J = 6.9 Hz), 1.38 (3H, d, J = 6.6 Hz), 1.41-1.58 (1H, m), 1.83-2.00 (2H, m), 2.31-2.46 (1H, m), 2.57-2.68 (1H, m), 2.71-2.87 (1H, m), 3.71 (1H, dq, J = 6.9, 8.3 Hz), 4.08 (1H, dq, J = 6.9, 8.3 Hz), 7.14-7.55 (10H, m).

syn-Minor Diastereomer. ^{1}H-Nmr ($CDCl_3$) δ 0.70 (3H, d, J = 6.6 Hz), 0.87 (3H, d, J = 6.6 Hz), 1.05 (3H, d, J = 6.9 Hz), 1.08-1.27 (1H, m), 1.26 (3H, d, J = 6.9 Hz), 1.42 (3H, d, J = 6.9 Hz), 1.41-1.55 (1H, m), 1.84-1.98 (2H, m), 2.30-2.42 (1H, m), 2.58-2.68 (1H, m), 2.70-2.76 (1H, m), 3.53 (1H, dq, J = 6.9, 8.6 Hz), 4.14 (1H, dq, J = 6.9, 8.6 Hz), 7.17-7.50 (10H, m).

anti-Major Diastereomer. ^{1}H-Nmr ($CDCl_3$) δ 0.69 (3H, d, J = 6.9 Hz), 0.88 (3H, d, J = 6.6 Hz), 1.09 (3H, d, J = 6.9 Hz), 1.13-1.31 (1H, m), 1.22 (3H, d, J = 6.9 Hz), 1.29 (3H, d, J = 6.9 Hz), 1.41-1.58 (1H, m), 1.83-2.00 (2H, m), 2.31-2.46 (1H, m), 2.57-2.68 (1H, m), 2.71-2.87 (1H, m), 3.88 (1H, quint, J = 6.9 Hz), 4.14 (1H, quint, J = 6.9 Hz), 7.14-7.55 (10H, m).

anti-Minor Diastereomer. ^{1}H-Nmr ($CDCl_3$) δ 0.68 (3H, d, J = 6.6 Hz), 0.92 (3H, d, J = 6.6 Hz), 1.08-1.27 (1H, m), 1.11 (3H, d, J = 6.9 Hz), 1.19 (3H, d, J = 6.9 Hz), 1.42 (3H, d, J = 6.9 Hz), 1.41-1.55 (1H, m), 1.84-1.98 (2H, m), 2.30-2.42 (1H, m), 2.58-2.68 (1H, m), 2.70-2.76 (1H, m), 3.79 (1H, quint, J = 6.9 Hz), 4.14 (1H, quint, J = 6.9 Hz), 7.17-7.50 (10H, m).

The Formation of 7a.

The mixture of thiophenol (500 µl, 5.0 mmol) and butyllithium (1.6M in hexane, 30 µl, 0.05 mmol) in THF (5 ml) was added to the THF (2 ml) solution of **6a** (170 mg, 0.5 mmol) and stirred for 8 h at room temperature under nitrogen atmosphere. The reaction was quenched with water and extracted with CH_2Cl_2. The organic layer was washed with saturated aq-NaCl and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel column with the eluting solvent of benzene-hexane mixture. Oil; yield 86%; ^{1}H-nmr ($CDCl_3$) δ 3.25 (2H, d, J = 7.6 Hz), 4.73 (1H, t, J = 7.6 Hz), 7.21-7.39 (15H, m). Anal. Calcd for $C_{21}H_{18}OS_2$: C, 71.96; H, 5.18. Found: C, 72.06; H, 5.15.

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Received, 1st February, 1995