Diastereoselective α-Alkylation of 2-Acyl-3-phenyl-*l*-menthopyrazoles

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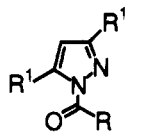
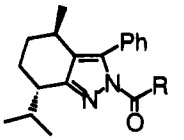
N-Acylpyrazoles were α-alkylated in good yields by the treatment with alkyl halides after metalation with LDA or LiHMDS. In the case of chiral *N*-acylpyrazoles, e.g., 2-acyl-3-phenyl-*l*-menthopyrazoles (**4**), the α-alkylation was highly diastereoselective. The subsequent α-alkylation products could be converted into esters in good yield in the presence of BF_3·OEt_2 without the loss of the optical purity.

Many methodologies are published at the basis of the utilization of various chiral auxiliaries,[1] in which two essential reaction steps are included. One is asymmetric induction on the substrate moiety by the activation according to the electronic and/or steric effects of the auxiliary compound. The other is the conversion of the substrate–auxiliary intermediate into the desired functionality accompanied by the recovery of the auxiliary compound. Since the many functionalization in these methodologies were carried out under a basic conditions, the retention of the subscequent chirality seemed to be difficult.

Recently we have investigated the utility of *N*-acylpyrazoles as the key intermediate compounds in this loop. The formation of auxiliary-substrate intermediate was accomplished through the acylation of pyrazoles with carboxylic acids or their acid chlorides.[2] In the case of an optically active pyrazole such as 3-phenyl-*l*-menthopyrazole [(4*R*,7*S*)-3-phenyl-4-methyl-7-isopropyl-4,5,6,7-tetrahydroindazole] (**3**), N-acylation proceeded regio- and stereoselectively to give the diastereomerically pure 2-acyl-3-phenyl-*l*-menthopyrazoles (**4**).[3] As the functionalization reactions, the nucleophilic reactions such as aminolysis,[4] alcoholysis[2] and the Grignard reactions[5] proceeded chemoselective under very mild conditions. In order to expand the usefulness of pyrazoles as auxiliary compounds, a wide variety of the stereoselective reactions of *N*-acylpyrazoles are highly desired. Here, we report the α-alkylation of the acyl moiety of *N*-acylpyrazoles, especially the diastereoselective α-alkylation using a new chiral auxiliary, 3-phenyl-*l*-menthopyrazole (**3**).



1: R^1=Me
2: R^1=t-Bu



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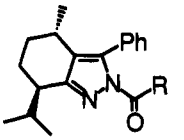

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a: R=Me	**i**: R=t-Bu-CH_2	**s**: R=Bn-CH(Me)
b: R=Et	**j**: R=Bn	**t**: R=1-Naph-CH(Me)
c: R=Pr	**k**: R=BnCH_2	**u**: R=Et-CH(Bn)
d: R=i-Pr	**m**: R=1-Naph-CH_2	**v**: R=Pr-CH(Bn)
e: R=Bu	**n**: R=Pr-CH(Me)	**w**: R=i-Pr-CH(Bn)
f: R=i-Bu	**p**: R=i-Pr-CH(Me)	**x**: R=t-Bu-CH(Bn)
g: R=s-Bu	**q**: R=t-Bu-CH(Me)	**y**: R=Ph-CH(Bn)
h: R=t-Bu	**r**: R=Ph-CH(Me)	

Result and Discussion

When 1-propanoyl-3,5-dimethylpyrazole (**1b**) was lithiated with lithium diisopropylamide (LDA) in THF and the subsequent lithium enolate was treated with methyl iodide, 1-(2′-methyl)propanoyl-3,5-dimethylpyrazole (**1d**) was obtained in moderate (65%) yield. The yield of **1d** was improved up to 95% by addition of hexamethylphosphoric triamide (HMPA), while the formation of **1d** could not be observed in less polar solvent such as ether and benzene. After the optimization of the reaction conditions, the formation of **1d** was carried out efficiently at room temperature using 2 equimolar amount of LDA. Similarly various N-acylpyrazoles were α–alkylated with alkyl halides to give the corresponding products as summarized in Table 1. Table 1 showed that 1-acetyl-3,5-dimethylpyrazole (**1a**) was α-alkylated in poor yield, while the desired methylated product was formed in moderate yield in the reaction of 1-acetyl-3,5-di(t-butyl)-pyrazole (**2a**) (Scheme 1). Further, the use of sterically more crowded lithium hexamethyldisilazide (LiHMDS) instead of LDA raised up to 69% yield in the reaction of **1a** with methyl iodide. Similar improvement of the yields was observed in the case of **1i.**

Next, we performed diastereoselective α-alkylation of N-acylpyrazoles using a new chiral auxiliary **3**, which was prepared in three steps from *l*-menthol.[3] When 2-butanoyl-3-phenyl-*l*-menthopyrazole (**4c**) was treated with LDA in the presence of HMPA followed by methyl iodide, 2-(2′-methyl)butanoyl-3-phenyl-*l*-menthopyrazole (**4g**) was obtained in 77% yield. ^{1}H NMR spectrum of **4g** showed two doublets appeared at δ 0.69 and 0.70 ppm, which were assigned to be the C-4 methyl protons of (2′S)- and (2′R)-(2′-methyl)butanoyl isomers respectively by the comparison to the authentic sample.[3] The major diastereomer was found to be (2′R)-**4g** with 60% de from the peak ratio of these doublets. The diastereomeric ratio was also evaluated to be 60% de by the ^{1}H NMR peak ratio of the (S)-1-(methoxycarbonyl)benzyl ester (**5g**)[6]

[⊗] Abstract published in *Advance ACS Abstracts,* November 1, 1994.

(1) For recent reviews, see: (a) *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press; New York, 1983–1985; Vol 1–5. (b) Kim, B. H.; Curran, D. P. *Tetrahedron* **1993**, *49*, 298. (c) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763. (d) Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297.

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(3) Kashima, C.; Fukuchi, I.; Takahashi, K.; Hosomi, A. *Tetrahedron Lett.* **1993**, *34*, 8305.

(4) Kashima, C.; Fukuchi, I.; Takahashi, K.; Hosomi, A. *Heterocycles* **1994**, *38*, 1407.

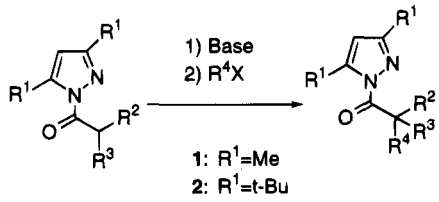
(5) Kashima, C.; Kita, I.; Takahashi, K.; Hosomi, A. *J. Heterocycl. Chem.*, in press.

0022-3263/94/1959-7821$04.50/0

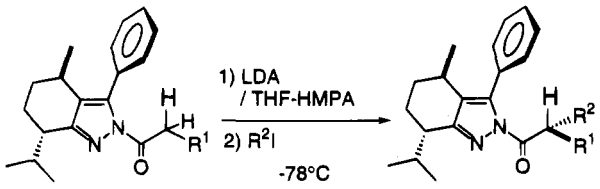
Table 1. The α-Alkylation of 1-Acyl-1,3,5-disubstituted Pyrazoles

substrate						yield (%) using LDA	yield (%) using LiHMDS
	R^1	R^2	R^3	R^4X	product		
1a	Me	H	H	MeI	**1b**	15	69
1b	Me	Me	H	MeI	**1d**	95	95
1c	Me	Et	H	MeI	**1g**	77	73
1d	Me	Me	Me	MeI	**1h**	48	28
1e	Me	Pr	H	MeI	**1n**	68	75
1f	Me	i-Pr	H	MeI	**1p**	51	77
1i	Me	t-Bu	H	MeI	**1q**	0	79
1j	Me	Ph	H	MeI	**1r**	48	80
1k	Me	$PhCH_2$	H	MeI	**1s**	50	80
1b	Me	Me	H	EtI	**1g**	11	
1b	Me	Me	H	EtBr	**1g**	13	
1a	Me	H	H	$PhCH_2Br$	**1k**	0	
1b	Me	Me	H	$PhCH_2Br$	**1s**	26	
1c	Me	Et	H	$PhCH_2Br$	**1u**	62	
1e	Me	Pr	H	$PhCH_2Br$	**1v**	52	
1f	Me	i-Pr	H	$PhCH_2Br$	**1w**	45	
1i	Me	t-Bu	H	$PhCH_2Br$	**1x**	0	
1j	Me	Ph	H	$PhCH_2Br$	**1y**	43	
2a	t-Bu	H	H	MeI	**2b**	73	
2b	t-Bu	Me	H	MeI	**2d**	78	
2a	t-Bu	H	H	$PhCH_2Br$	**2k**	7	
2b	t-Bu	Me	H	$PhCH_2Br$	**2s**	56	

Scheme 1



Scheme 2



derived from **4g** and methyl (S)-2-hydroxyphenylacetate in the presence of BF_3·OEt_2. From the accordance of the % de values by both methods, N-acylpyrazoles were suggested to be configurationally stable during the conversion into the corresponding esters even in the presence of acid.

When the reaction of **4c** with methyl iodide was carried out in the presence of HMPA after metalation using LiHMDS, **4g** was obtained in 88% yield with 73 % de (2′R). On the contrary, (2′S)-2-(2′-methyl)butanoyl-3-phenyl-*l*-menthopyrazole (**4g**) was preferably formed in 70% yield with 65% de in the reaction of 2-propanoyl-3-phenyl-*l*-menthopyrazole (**4b**) with ethyl iodide. This result showed that the steric factors on the intermediate reflected on the structure of the products. The asymmetric induction on α-alkylation may be reasonably explained by the following reaction mechanism. In the first step, *N*-acylpyrazoles would be deprotonated with LDA to lead to the stereoselective formation of lithium Z-enolate by the allylic strain interaction.[7] The subsequent lithium Z-enolate π plane was fixed to the pyrazole

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(7) Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. *Pure Chem.* **1981**, *53*, 1109.

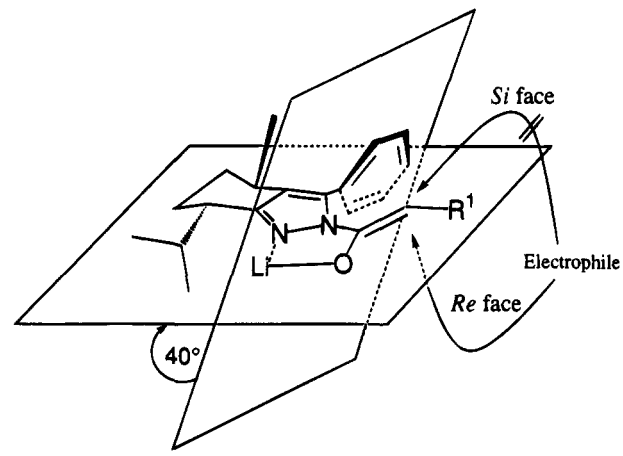


Figure 1.

Table 2. Diastereoselective α-Alkylation of 2-Acyl-3-phenyl-*l*-menthopyrazoles

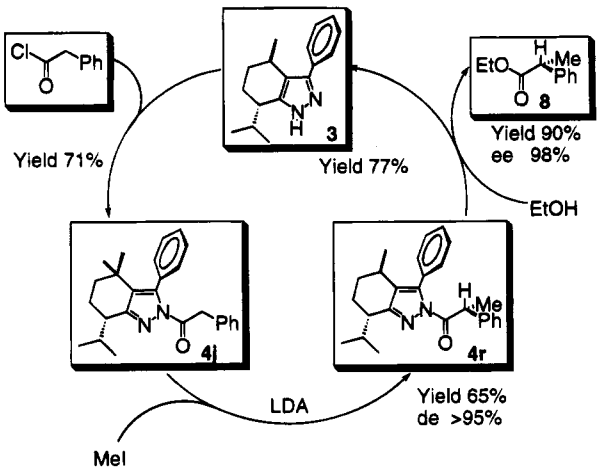
substrate		R^2X	base	product	yield (%)	de (%)	confign
4b	Me	EtI	LDA	**4g**	69	61	2′*S*
4c	Et	MeI	LDA	**4g**	77	60	2′*R*
4e	Pr	MeI	LDA	**4n**	72	70	2′*R*
4f	i-Pr	MeI	LDA	**4p**	42	>95	2′*R*
4j	Ph	MeI	LDA	**4r**	47	>95	2′*R*
4k	$PhCH_2$	MeI	LDA	**4s**	54	>95	2′*R*
4m	1-Naph	MeI	LDA	**4t**	44	>95	2′*R*
4c	Et	MeI	LiHMDS	**4g**	88	70	2′*R*
4e	Pr	MeI	LiHMDS	**4n**	73	74	2′*R*
4f	i-Pr	MeI	LiHMDS	**4p**	78	>95	2′*R*
4j	Ph	MeI	LiHMDS	**4r**	65	>95	2′*R*
4k	$PhCH_2$	MeI	LiHMDS	**4s**	72	>95	2′*R*
4m	1-Naph	MeI	LiHMDS	**4t**	48	>95	2′*R*
7b	Me	EtI	LDA	**7g**	58	63	2′*R*
7c	Et	MeI	LDA	**7g**	60	67	2′*S*

ring by the chelation between lithium and N-1 nitrogen atom of menthopyrazole as illustrated in Figure 1. On the basis of the X-ray structural analysis of 3-(4-chlorophenyl)-*l*-menthopyrazole,[3] the 3-phenyl ring was expected to be twisted about 40° against pyrazole ring in order to relax steric repulsions from the 4-methyl group. This twisted 3-phenyl ring would be somewhat overlaid on the lithium enolate plane. Through this atropic asymmetry of the 2-phenyl plane, the R-configuration on C-4 carbon would cause the preferential attack of electrophiles from Re-face of the Z-enolate plane. This could explain the high diastereoselectivities during the α−alkylation with preference of the R-configuration.

Similarly α-alkylation reactions of **4e−m** with alkyl halides were performed using LDA or LiHMDS summarized in Table 2. In the cases of **4f**, **4j**, **4k** and **4m**, the highest diastereoselectivities over 95% de were observed to give the corresponding **4p**, **4r**, **4s** and **4t**. Using of 3-phenyl-*d*-menthopyrazole (**6**) which was prepared from *d*-menthol, the stereo chemistry of α-alkylated product was found to be the S-configuration by the ^1H NMR spectrum of (S)-1-(methoxycarbonyl)benzyl ester derivative.

As a demonstration of the synthetic utility of the highly diastereoselective α-alkylation, the synthesis of ethyl (R)-2-phenylpropanoate (**8**) was undertaken (Scheme 3). 2-(Phenylacetyl)-3-phenyl-*l*-menthopyrazole (**4j**) was diastereoselectively α-alkylated with methyl iodide to give **4r** in 65% yield with over 95% de (2′R). Product **4r** was functionalized into **8** in 90% yield by treatment with ethanol in the presence of BF_3·OEt_2. The enantiomeric

Scheme 3



purity of **8** was found to be 98% by comparison of authentic $[\alpha]_D$ value.[8] Through these reactions constituting the loop, phenylacetyl chloride was converted into **8** in total yield 45% with 98% de (R), as well as the recovery of **3** in 77% yield with retention of its optical purity.

In conclusion, *N*-acylpyrazoles were α-alkylated in good yields by the treatment with alkyl halides after metalation with LDA or LiHMDS. In the case of 2-acyl-3-phenyl-*l*-menthopyrazole (**4**), α-alkylation was accomplished with excellently high diastereoselectivities, especially in the case of 2-(3′-methylbutanoyl)- (**4f**), 2-(phenylacetyl)- (**4j**), 2-(3′-phenylpropanoyl)- (**4k**), and 2-((1′-naphthyl)acetyl)-3-phenyl-*l*-menthopyrazole (**4m**) which proceeded with more than 95% de. Moreover, the diastereoselective α-alkylation products could be easily functionalized into esters in good yield by the alcoholysis in the presence of $BF_3{\cdot}OEt_2$ without the loss of the optical purity. During this functionalization, the chiral auxiliary **3** was recovered in good yield without racemization. Chiral pyrazoles are efficient chiral auxiliaries for the preparation of α-alkyl esters.

Experimental Section

Preparation of 2-Benzoyl-3-methyl-6-isopropylcyclohexanone. The THF solution (50 mL) of LDA was prepared from lithium wire (414 mg), chlorobutane (4.54 g), and diisopropylamine (3.05 g) according to the method of Einhorn.[9] To this LDA solution, the freshly prepared *l*-menthone (3.27 g) was added and stirred for 30 min at −78 °C. The reaction mixture was treated with benzoyl chloride (18 mmol) in THF (10 mL) at −78 °C, and warmed up to room temperature. After stirring for 1.5 h, the mixture was quenched with dilute hydrochloric acid and extracted with ether. The combined organic layer was washed with aqueous sodium hydrogen carbonate, water, and saturated sodium chloride, dried over anhydrous magnesium sulfate, and concentrated. The 2-benzoyl-3-methyl-6-isopropylcyclohexanone was purified by recrystallization from hexane: mp 136−8 °C (from hexane); yield 68%; $[\alpha]_D$ −16.4° (c 1.3, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.85 (3H, d, J = 7 Hz), 0.91 (3H, d, J = 7 Hz), 0.97 (3H, d, J = 7 Hz), 1.40−1.60 (2H, m), 1.98−2.14 (3H, m), 2.25−2.34 (1H, m), 2.51−2.55 (1H, m), 4.08 (1H, d, J = 12 Hz), 7.34−7.53 (3H, m), 7.82−7.85 (2H, m); ^{13}C NMR (270 MHz, $CDCl_3$) (DEPT) δ 18.5 (CH_3), 21.1 (CH_3), 21.1 (CH_3), 26.0 (CH_2), 28.0 (CH), 33.4 (CH), 37.6 (CH_2), 56.8 (CH), 66.0 (CH), 128.0 (CH), 128.6 (CH), 132.9 (CH), 138.1 (C), 198.1 (C), 209.0 (C). Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 78.98; H, 8.61.

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(9) Einhorn, J.; Luche, J. L. *J. Org. Chem.* **1987**, *52*, 4124.

Preparation of 3-Phenyl-*l*-menthopyrazole (3). The mixture of 2-benzoyl-3-methyl-6-isopropylcyclohexanone (8.5 mmol), hydrazine hydrate (3.02 g), and concd hydrochloric acid (0.1 mL) in methanol (20 mL) was reluxed for 16 h. The reaction mixture was acidified with hydrochloric acid, and extracted with dichloromethane. The organic layer was washed with water and saturated sodium chloride, dried over anhydrous magnesium sulfate, and concentrated. The reaction residue was purified by recrystallization from hexane or by silica gel column chromatography with benzene-ethyl acetate mixture: mp 122.5−124°C (from Hexane); yield 96% ; $[\alpha]_D$ −158.5° (c 4.6, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.81 (3H, d, J = 7 Hz), 0.97 (3H, d, J = 7 Hz), 0.98 (3H, d, J = 7 Hz), 1.18−1.37 (1H, m), 1.50−1.63 (1H, m), 1.77−1.88 (1H, m), 1.99−2.22 (2H, m), 2.55−2.65 (1H, m), 2.98−3.14 (1H, m), 7.27−7.39 (3H, m), 7.57−7.65 (2H, m), 11.25 (1H, broad d); ^{13}C NMR (270 MHz, $CDCl_3$) (DEPT) δ 18.3 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 21.9 (CH_2), 27.1 (CH), 30.3 (CH), 31.6 (CH_2), 39.7 (CH), 118.7 (C), 127.6 (CH), 127.7 (C), 128.4 (CH), 133.2 (CH), 145.4 (C), 146.7 (C); IR ($CHCl_3$ solution) 3395, 3175, 2930, 1450, 700. Anal. Calcd for $C_{17}H_{22}N_2$: C, 80.27; H, 8.72; N, 11.01. Found: C, 80.18; H, 8.56; N, 10.95.

Preparation of 3-Phenyl-*d*-menthopyrazole (6). Similarly **6** was prepared from *d*-menthol: yield 64% (from *d*-menthol); mp 122.5−124 °C (from hexane); $[\alpha]_D$ +130.5° (c 1.00, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.81 (3H, d, J = 7 Hz), 0.97 (3H, d, J = 7 Hz), 0.98 (3H, d, J = 7 Hz), 1.18−1.37 (1H, m), 1.50−1.63 (1H, m), 1.77−1.88 (1H, m), 1.99−2.22 (1H, m), 2.55−2.65 (1H, m), 2.98−3.14 (1H, m), 7.27−7.39 (3H, m), 7.57−7.65 (2H, m), 11.25 (1H, broad d); ^{13}C NMR (270 MHz, $CDCl_3$) δ (DEPT) 18.3 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 21.9 (CH_2), 27.1 (CH), 30.3 (CH), 31.6 (CH_2), 39.7 (CH), 118.7 (C), 127.6 (CH), 127.7 (C), 128.4 (CH), 133.2 (CH), 145.4 (C), 146.7 (C); IR ($CHCl_3$ solution) 3395, 3175, 2930, 1450, 700 cm^{-1}. Anal. Calcd for $C_{17}H_{22}N_2$: C, 80.27; H, 8.72; N, 11.01. Found: C, 80.24; H, 9.01; N, 11.04.

N-Acylation of 3. The mixture of **3** (1 mmol), acyl chloride (2.5 mmol), and triethylamine (3 mmol) in dry benzene was stirred for 3 h at 5 °C. The reaction mixture was washed with dil. hydrochloric acid, aqueous sodium hydroxide and saturated sodium chloride, dried over anhydrous magnesium sulfate, and concentrated. The product ratio was evaluated by HPLC of reaction residue. By the column chromatography on silica gel with benzene-hexane mixture, 1-acyl- and 2-acyl-3-phenyl-*l*-menthopyrazole (**4**) were isolated as the first and second fractions, respectively.

2-Propanoyl-3-phenyl-*l*-menthopyrazole (4b). yield 91%; ^1H NMR (270 MHz, $CDCl_3$) δ 0.69 (3H, d, J = 7 Hz), 0.94 (3H, d, J = 7 Hz), 1.08 (3H, d, J = 7 Hz), 1.16 (3H, t, J = 7 Hz), 1.20−1.31 (1H, m), 1.36−1.65 (1H, m), 1.76−2.06 (2H, m), 2.20−2.48 (1H, m), 2.54−2.68 (1H, m), 2.70−2.83 (1H, m), 3.04−3.24 (2H, m), 7.25−7.46 (5H, m). Anal. Calcd for $C_{20}H_{26}N_2O$: C, 77.38; H, 8.44; N, 9.02. Found: C, 77.43; H, 8.40; N, 9.10.

General α-Alkylation Procedure. To the solution of diisopropylamine (or hexamethyldisilazane, 1.2 mmol) in THF (10 mL), 1.1 mmol of butyllithium solution (1.6M in hexane) was added under nitrogen atmosphere at −78 °C. After stirring for 30 min at room temperature, HMPA (2 mL) and the *N*-acylpyrazole (1.1 mmol) were successively added at −78 °C with the continuous stirring for 30 min. The alkyl halide (1.1 mmol) was added at −78 °C, and then the reaction mixture was warmed to room temperature with stirring for 30 min. The reaction mixture was quenched with acetic acid and the products were extracted with dichloromethane. The organic layer was washed with water, aqueous sodium hydrogen carbonate, and aqueous sodium chloride. After dried over anhydrous magnesium sulfate, the solvent was removed under reduced pressure. The residue was chromatographed on silica gel using a hexane-benzene mixture.

2-(2′-Methylbutanoyl)-3-phenyl-*l*-menthopyrazole (4g): ^{13}C NMR (270 MHz, $CDCl_3$) (DEPT) δ 11.5 (CH_3), 16.5 (CH_3), 18.6 (CH_3), 20.2 (CH_3), 23.2 (CH_2), 27.1 (CH_2), 27.4 (CH), 30.0 (CH), 32.3 (CH_2), 39.4 (CH), 41.4 (CH), 126.0 (C), 127.8 (CH), 128.0 (CH), 129.2 (CH), 132.8 (C), 140.8 (C), 155.3 (C),

176.7 (C). Anal. Calcd for $C_{22}H_{30}N_2O$: C, 78.06; H, 8.93; N, 8.28. Found: C, 77.75; H, 8.83; N, 8.24.

***2S'-Diastereomer*:** ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.69 (3H, d, J = 7 Hz), 0.95 (3H, d, J = 7 Hz), 0.96 (3H, t, J = 7 Hz), 1.09 (3H, d, J = 7 Hz), 1.17 (3H, d, J=7 Hz), 1.20–1.31 (1H, m), 1.42–1.64 (2H, m), 1.66–2.04 (3H, m), 2.35–2.47 (1H, m), 2.60–2.67 (1H, m), 2.69–2.86 (1H, m), 3.60 (1H, sext, J = 7 Hz), 7.25–7.46 (5H, m).

***2R'-Diastereomer*:** ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.70 (3H, d, J = 7 Hz), 0.88 (3H, t, J = 7 Hz), 0.95 (3H, d, J = 7 Hz), 1.09 (3H, d, J = 7 Hz), 1.21 (3H, d, J = 7 Hz), 1.43–1.53 (2H, m), 1.58–1.81 (2H, m), 1.84–2.03 (2H, m), 2.35–2.48 (1H, m), 2.60–2.83 (2H, m), 3.86 (1H, sext, J = 7 Hz), 7.20–7.42 (5H, m).

2-(2'-Phenylpropanoyl)-3-phenyl-l-menthopyrazole (4r). ***2S'-Dastereomer*:** ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.62 (3H, d, J = 7 Hz), 1.00 (3H, d, J = 7 Hz), 1.12 (3H, d, J = 7 Hz), 1.48 (3H, d, J = 7 Hz), 1.1–1.7 (2H, m), 1.8–2.0 (2H, m), 2.3–2.5 (1H, m), 2.5–2.6 (1H, m), 2.6–2.8 (1H, m), 5.25 (1H, q, J = 7 Hz), 7.1–7.5 (10H, m). Anal. Calcd for $C_{26}H_{30}N_2O$: C, 80.79; H, 7.82; N, 7.25. Found: C, 80.64; H, 7.84; N, 7.34.

***2R'-Dastereomer*:** ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.68 (3H, d, J = 7 Hz), 0.76 (3H, d, J = 7 Hz), 1.01 (3H, d, J = 7 Hz), 1.51 (3H, d, J = 7 Hz), 1.1–1.7 (2H, m), 1.8–2.0 (2H, m), 2.3–2.5 (1H, m), 2.5–2.7 (2H, m), 5.22 (1H, q, J = 7 Hz), 7.1–7.5 (10H, m). Anal. Calcd for $C_{26}H_{30}N_2O$: C, 80.79; H, 7.82; N, 7.25. Found: C, 80.70; H, 7.84; N, 7.25.

Derivatization of 4g into (1'S)-1-(Methoxycarbonyl)-benzyl Ester (5g). Methyl (*S*)-2-hydroxyphenylacetate (1.1 mmol) and **4g** (1.0 mmol) was dissolved in THF (5 mL), and BF_3·OEt_2 (1.0 mmol) was added under nitrogen atmosphere. The mixture was refluxed for 6 h, and then extracted with dichloromethane. The organic layer was washed with water, aqueous sodium hydrogen carbonate, and aqueous sodium chloride and dried over anhydrous magnesium sulfate. After removal of the solvent, **3** and **5g** were isolated by chromatography on silica gel with hexane-benzene (2:1 v/v) mixture in 62 and 52% yield, respectively. The % de of **5g** was evaluated from the ^{1}H NMR peak intensity of α-proton of 1-(methoxycarbonyl)benzyl moiety at δ 5.93 and 5.92 ppm.

(1'S)-1-(Methoxycarbonyl)benzyl-2-methylbutanoate (5g): yield 52%; Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.07; H, 7.15.

***2S'-Dastereomer*:** ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.92 (3H, t, J = 7 Hz), 1.24 (3H, d, J = 7 Hz), 1.56 (1H, sept, J = 7 Hz), 1.78 (1H, m), 2.58 (1H, sext, J = 7 Hz), 3.71 (3H, s), 5.93 (1H, s), 7.39 (3H, m), 7.46 (2H, m).

***2R'-Dastereomer*:** ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.98 (3H, t, J = 7 Hz), 1.19 (3H, d, J = 7 Hz), 1.56 (1H, sept, J = 7 Hz), 1.78 (1H, m), 2.58 (1H, sext, J = 7 Hz), 3.71 (3H, s), 5.92 (1H, s), 7.39 (3H, m), 7.46 (2H, m).

Preparation of 8 from 4r. The mixture of **4r** (1.0 mmol) and BF_3·OEt_2 (1.0 mmol) in ethanol (10 mL) was refluxed for 6 h under nitrogen atmosphere. After being quenched with water, the mixture was worked up in the usual manner. The residue was chromatographed on silica gel with benzene to get **3** and **8** in 77 and 90% yield, respectively.

Ethyl (*R*)-2-phenylpropanoate (8): $[\alpha]_D$ −54° (c = 2.05, $CHCl_3$) [lit.[8] −54.82° (c = neat)]; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.30 (3H, t, J = 7 Hz), 1.59 (3H, d, J = 7 Hz), 3.81 (1H, q, J = 7 Hz), 4.23 (2H, m), 7.40 (5H, m).

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Supplementary Material Available: ^{1}H NMR and elemental analysis data for 1-acyl-3,5-dimethylpyrazoles (**1a–k**, **1n**, **1p–s**, **1u–y**), 1-acyl-3,5-di(t-butyl)pyrazoles (**2a–b**, **2d**, **2k**, **2s**), 2-acyl-3-phenyl-*l*-menthopyrazoles (**4c**, **4e–f**, **4j–k**, **4m–n**, **4p**, **4p–t**), and 2-acyl-3-phenyl-*d*-menthopyrazoles (**7b–c**, **7g**) (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.