STEREOCONTROLLED ALDOL REACTION OF *N*-ACYLPYRAZOLES WITH ALDEHYDES USING LDA OR $MgBr_2$-DIEA†

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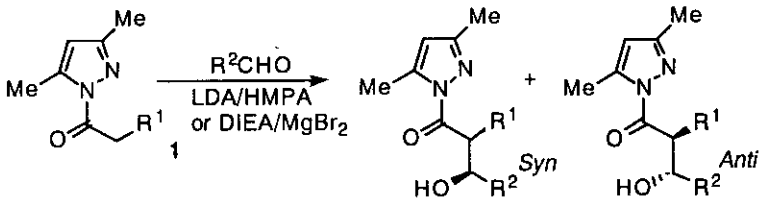
Abstract—The aldol reaction of 1-acyl-3,5-dimethylpyrazoles (**1**) was kinetically controlled with *syn* stereoselectivity through lithium enolate intermediate using LDA. On the contrary, the *anti* stereoselective aldol reaction of **1** was caused by the action of DIEA in the presence of $MgBr_2$ under the thermodynamic control. In the formation of *syn*-aldol products using 3-phenyl-*l*-menthopyrazole as a chiral auxiliary, the diastereoselectivity was observed up to 81% de with the predominant configuration of 2'*S* form.

Recently we have been much interesting in the chemistry of *N*-acylpyrazoles, especially 2-acyl-3-phenyl-*l*-menthopyrazoles as the chiral synthetic intermediate.[1] By the treatment with various nucleophiles, *N*-acylpyrazoles were converted into the corresponding amides,[2] esters,[3] ketones[4] and β-keto esters.[5] Moreover, *N*-acylpyrazoles were allowed to react with LDA or LiHMDS to generate lithium enolates, which were the key intermediates for α-alkylation,[6] α-sulfenylation[7] and α-acylation.[8] In the case of using 2-acyl-3-phenyl-*l*-menthopyrazoles, the highly diastereoselective α-alkylation and α-acylation were accomplished by the diastereofacial attack of alkyl halides and acyl halides respectively on the lithium enolate, which was rigidly fixed by the intramolecular chelation between lithium and N-1 atom.[6,9] The subsequent α-acylated products were easily converted into the chiral *N*-methyl β-keto amides in spite of the enolizable compounds. For the further extension of the utilities of *N*-acylpyrazoles as the synthetic intermediate, a wide variety of the stereoselective reactions on the acyl moiety of *N*-acylpyrazoles are highly desired. Also we are longing to improve the reactions of *N*-acylpyrazoles under the more mild, efficient and convenient conditions. Here, we report the aldol reactions on the acyl moiety of N-acylpyrazoles with aldehydes, especially the diastereoselective aldol reactions using a new chiral auxiliary, 3-phenyl-l-menthopyrazole.

When 1-propanoyl-3,5-dimethylpyrazole (1a) was treated with LDA followed by benzaldehyde, 1-(3'-hydroxy-2'-methyl-3'-phenyl)propanoyl-3,5-dimethylpyrazole (2a) was obtained in good yield as the syn/anti isomeric mixture. From the NMR spectrum, the syn/anti ratio was found to be 85 : 15. The

† This paper is dedicated to Professor Koji Nakanishi on the occasion of his 75th birthday for his brilliant achievment in the field of natural product chemistry and heterocyclic chemistry.



a R^1=Me
b R^1=H
c R^1=Et
d R^1=*i*-Pr
e R^1=Bn

2 R^2=Ph **6** R^2=*p*-Tol
3 R^2=Et **7** R^2=*o*-Tol
4 R^2=*i*-Pr **8** R^2=*p*-Anis
5 R^2=*t*-Bu

Scheme 1

structures of *syn* (*syn*-**2a**) and *anti* isomers (*anti*-**2a**) were deduced by the derivatization into methyl 3-hydroxy-2-methyl-3-phenyl-propanoate.[8] Similarly the aldol reactions of **1a** were carried out in good yields with aromatic aldehydes, as listed in Table 1. The yields were still poor in the aldol condensation of **1a** with aliphatic aldehydes because of the competitive self-condensation of aldehydes, and a large excess amount of aldehydes was required for the improvement of their yields. The Table 1 showed that every aldol reaction proceeded with the *syn* stereoselectivity, especially bulky aldehydes such as isobutyraldehyde and pivalaldehyde gave predominantly *syn* isomers. The *syn* selectivity of this reaction was speculated by the formation of *Z*-lithium enolate and following aldehyde attack through the chair like cyclic transition structure with R^2 group on pseudo equatorial position.[10]

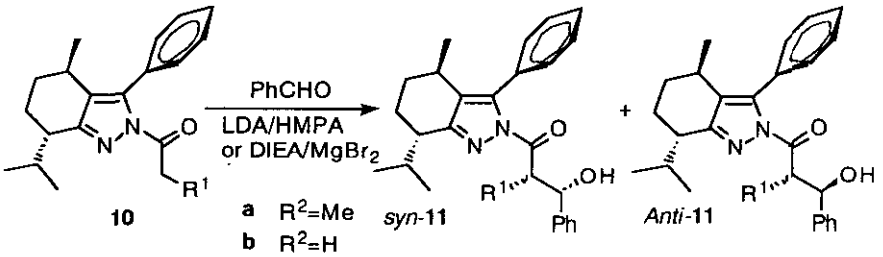
Mukaiyama reported that the cross aldol reaction was regio- and stereoselectively controlled by the corresponding boron enolate using dialkylboron triflate.[11] Therefore, the reaction of **1a** lithium enolate with dialkylboron compound was carried out, and subsequent boron enolate was treated with aldehydes.

Table 1. The Aldol Reaction of 1-Propanoyl-3,5-dimethylpyrazole (**1a**)

Substrate		Aldehyde	With LDA		With LDA-Bu_2BBr		With $MgBr_2$-*i*Pr_2NEt	
	R^1	R^2CHO	Yield (%)	*syn/anti*	yield (%)	*syn/anti*	Yield (%)	*syn/anti*
1a	Me	Ph-CHO	69	85:15	78	72:28	91	31:69
1a	Me	Et-CHO	27	67:33	64	60:40	37	32:68
1a	Me	*i*-Pr-CHO	37	90:10	56	75:25	47	32:68
1a	Me	*t*-Bu-CHO	13	>95:5			37	13:87
1a	Me	*p*-Tol-CHO	76	78:22			76	28:72
1a	Me	*o*-Tol-CHO	71	55:45			74	29:71
1a	Me	*p*-Anis-CHO	65	78:22			70	28:72
1b	H	Ph-CHO					64	——
1b	H	Et-CHO					51	——
1b	H	*t*-Bu-CHO					57	——
1c	Et	Ph-CHO	50	69:31			83	14:86
1d	*i*-Pr	Ph-CHO	78	16:84			50	0:100
1e	Bn	Ph-CHO	68	63:37			57	23:77

Dibutylboron triflate exhibits no effect in the promotion of the yield and the stereoselectivity. Although less stereoselective effect was observed, the addition of dibutylboron bromide promoted the yields of the aldol products even in the use of small excess of aldehydes.

Otherwise, *N*-Acylpyrazoles formed the 5-membered C=O···Mg···N-2 chelate complexes with $MgBr_2$ which afforded the Claisen condensation products, 1-(2'-methyl-3'-oxo)pentanoyl-3,5-dimethylpyrazole (**9**), by the action of tertiary amine through the corresponding enolate.[12] This fact suggested that the aldol condensation reaction of *N*-acylpyrazole was expected with aldehydes by the use of tertiary amines in the presence of $MgBr_2$. Actually **2a** and **9** were formed from the mixture of **1a**, $MgBr_2$, and diisopropylethylamine (DIEA) in CH_2Cl_2 by the action of benzaldehyde at room temperature. After the optimizing the reaction temperature and the order of addition of reagents, the formation of **9** was depressed and **2a** was formed predominantly. Similarly the aldol reaction of various 1-acyl-3,5-dimethylpyrazoles (**1**) was carried out with either aromatic or aliphatic aldehydes as summarized in Table 1. The *syn/anti* ratios in this reaction of **1a** were found to be about 30 : 70 independent from the structures of aldehyde, except the reaction with pivalaldehyde. Further, the structure of acyl moiety of **1** was much effected to the *syn/anti* ratios. When *syn*-**2a** was treated with $MgBr_2$ and DIEA in CH_2Cl_2, isomerization into *anti*-**2a** was observed with the *syn-anti* ratio of 35 : 65 accompanying with small amount of **1a**. By the treatment of **2a** with $MgBr_2$ and DIEA in the presence of **1b**, the formation of **1a** and **2b** was detected as well as the *syn-anti* isomerization. These facts suggested that the aldol reaction using $MgBr_2$ and DIEA was equilibrated with retro aldol reaction, and that the product ratio was dependent on the stabilities of the products.



Scheme 2

Finally, the reaction of 2-acyl-3-phenyl-*l*-menthopyrazoles (**10**) with benzaldehyde was performed under the conditions using either LDA to form lithium enolate or DIEA in the presence of $MgBr_2$. Under the conditions using LDA, 2-propanoyl-3-phenyl-*l*-menthopyrazole (**10a**) gave the aldol mixture of 4 isomers. From the NMR spectrum, these isomers were assigned to be the diastereomeric pairs of *syn* (*syn*-**11a**) and *anti* isomers (*anti*-**11a**) with the *syn/anti* ratio of 69 : 31. The diastereomer ratios of *syn*-**11a** and *anti*-**11a** were found to be 51 and 24% de, respectively. The predominance of *syn*-**11a** and *anti*-**11a** was determined to be 2'*S* configuration by the hydride reduction of (2'*S*)-2-(2'-methyl-3'-oxo-3'-phenyl)propanoyl-3-phenyl-*l*-menthopyrazole[9] with K-selectride. On the contrary, *anti*-**11a** was the major aldol product from **10a** and benzaldehyde with the *syn/anti* ratio of 32 : 68 by the action of DIEA in the

presence of $MgBr_2$. The diastereomer ratios of *syn*-**11a** and *anti*-**11a** were found to be 30 and 43% de with the predominance of 2'*S* configuration, respectively. In the case of **10b**, the asymmetric induction on 3'-position was observed with poor diastereoselectivity. The results of another reaction of **10** were summarized in Table 2.

Table 2. Aldol Reaction of 2-Acyl-3-phenyl-*l*-menthopyrazoles (**10**) with Benzaldehyde

Substrate		With LDA			with $MgBr_2$-iPr_2NEt		
	R^1	Yield	*syn* (% de)[a]	*anti* (% de)[a]	Yield	*syn* (% de)[a]	*anti* (% de)[a]
10a	Me	38%	69% (51)	31% (24)	80%	32% (30)	68% (43)
10b	H				70%[b]	—	—
10c	Et	53%	65% (52)	35% (55)	80%	11% (28)	89% (29)
10d	*i*-Pr	0%	—	—	69%	0% (—)	100% (15)
10e	Bn	58%	32% (81)	68% (52)	67%	7% (c)	93% (8)

a: *syn/anti* Ratios and diastereomer ratios were evaluated by NMR spectra.
b: Diastereoselectivity on 3'-position was 6.9% de.
c: Diastereomer ratio is unmeasurable.

In conclusion, the aldol reaction of 1-acyl-3,5-dimethylpyrazoles (**1**) was kinetically controlled with *syn* stereoselectivity under the conditions using LDA. On the contrary, the *anti* stereoselective aldol reaction of **1** was caused by the action of DIEA in the presence of $MgBr_2$ under the thermodynamic control. In the formation of *syn*-aldol products using 3-phenyl-*l*-menthopyrazole as a chiral auxiliary, the diastereoselectivity was observed up to 81% de with the predominant configuration of 2'*S* form.

EXPERIMENTAL

Melting points are uncorrected. NMR spectra were obtained on JEOL JNM-EX270 (270 MHz) spectrometers in $CDCl_3$ with TMS as an internal standard. THF and CH_2Cl_2 were dried over benzophenone ketyl radical and calcium hydride, respectively. *N*-Acyl-3,5-dimethylpyrazoles (**1**) and 2-acyl-3-phenyl-*l*-menthopyrazoles (**10**) were prepared from the corresponding pyrazoles according to the method reported in the previous paper.[1,3,6]

General Procedures. *With LDA* To the LDA solution, which was prepared from diisopropylamine (1.2 mmol) and butyllithium (1.6 M in hexane, 680 μL) in THF (8 mL), *N*-acylpyrazole (1 mmol) was added at -78 °C under nitrogen atmosphere. After stirring for 30 min at -78 °C, aromatic aldehyde (1.1 mmol) or aliphatic aldehyde (5 mmol) in THF (2 mL) was added with a continuous 30 min stirring at -78 °C. The mixture was quenched with acetic acid and extracted with CH_2Cl_2. The organic layer was washed with 6N hydrochloric acid, water, aqueous sodium hydrogen carbonate (saturated) and aqueous sodium chloride (saturated), dried over anhydrous magnesium sulfate, and concentrated. The residue was

chromatographed on silica gel with benzene-ethyl acetate mixture (hexane-ethyl acetate mixture in the cases of **11**) as an eluent, and by recrystallization or distillation under reduced pressure by Kugelrohr.

With LDA followed by Dibutylboron Bromide To the LDA solution, which was prepared from diisopropylamine (1.2 mmol) and butyllithium (1.6 M in hexane, 680 μL) in THF (8 mL), *N*-acylpyrazole (1 mmol) was added at -78 °C under nitrogen atmosphere. After stirring for 30 min at -78 °C, dibutylboron bromide (1.1 mmol) in THF (1 mL) was added with 30 min stirring. Aldehyde (1.2 mmol) in THF (2 mL) was added to the mixture and stirred for another 30 min at -78 °C. The mixture was quenched with acetic acid and worked up as described above.

With DIEA in the Presence of $MgBr_2$. To the mixture of *N*-acylpyrazole (1 mmol), $MgBr_2 \cdot OEt_2$ (284 mg), aldehyde (1.4 mmol) in CH_2Cl_2 (4 mL), DIEA (258 mg) in CH_2Cl_2 (1 mL) was added at -5 °C under nitrogen atmosphere. After stirring for 1 h, the mixture was worked up as described above.

1-(3'-Hydroxy-2'-methyl-3'-phenyl)propanonyl-3,5-dimethylpyrazole (**2a**). Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.42; H, 7.04; N, 10.98.

Anti Isomer: δ_H ($CDCl_3$); 1.10 (3H, d, J=7.3 Hz), 2.25 (3H, s), 2.55 (3H, s), 4.27 (1H, dq, J=7.3, 8.9 Hz), 4.85 (1H, d, J=8.9 Hz), 5.98 (1H, s), 7.24-7.40 (5H, m).

Syn Isomer: δ_H ($CDCl_3$); 1.21 (3H, d, J=6.9 Hz), 2.25 (3H, s), 2.51 (3H, s), 4.16 (1H, dq, J=3.0, 7.3 Hz), 5.21 (1H, d, J=3.0 Hz), 5.98 (1H, s), 7.24-7.40 (5H, m).

1-(3'-Hydroxy-3'-phenyl)propanoyl-3,5-dimethylpyrazole (**2b**). bp 130-140 °C/ 5 mmHg; yield 60%; δ_H ($CDCl_3$); 2.22 (3H, s), 2.55 (3H, s), 3.51 (2H, ABX, J=3.3, 17.2, 8.9 Hz), 3.91 (1H, br s), 5.27 (1H, dd, J=8.9, 3.6 Hz), 5.98 (1H, s), 7.26-7.46 (5H, m). Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.6; N, 11.47. Found: C, 68.81; H, 6.71; N, 11.43.

1-(2'-Ethyl-3'-hydroxy-3'-phenyl)propanoyl-3,5-dimethylpyrazole (**2c**). bp 145-150 °C/ 5 mmHg; yield 83%; Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.4; N, 10.29. Found: C, 70.50; H, 7.45; N, 10.16.

Anti Isomer: δ_H ($CDCl_3$); 0.81 (3H, t, J=7.4 Hz), 1.41-1.82 (2H, m), 2.24 (3H, s), 2.53 (3H, d, J=0.7 Hz), 3.37 (1H, br s), 4.20-4.29 (1H, m), 4.89 (1H, d, J=8.6 Hz), 5.96 (1H, d, J=0.7 Hz), 7.25-7.42 (5H, m).

Syn Isomer: δ_H ($CDCl_3$); 0.81 (3H, t, J=7.4 Hz), 1.41-1.82 (2H, m), 2.26 (3H, s), 2.48 (3H, d, J=1.0 Hz), 3.37 (1H, br s), 4.10-19 (1H, m), 5.12 (1H, d, J=3.6 Hz), 5.97 (1H, s), 7.25-7.42 (5H, m).

1-(3'-Hydroxy-2'-isopropyl-3'-phenyl)propanoyl-3,5-dimethylpyrazole (**2d**). bp 135-140 °C/ 4 mmHg; 50%. Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.3; H, 7.74; N, 9.78. Found: C, 71.22; H, 7.93; N, 10.15.

Anti Isomer: δ_H ($CDCl_3$); 0.94 (3H, d, J=6.9 Hz), 1.12 (3H, d, J=6.9 Hz), 2.18 (3H, s), 2.06-2.36 (1H, m), 2.40 (3H, d, J=1.0 Hz), 4.06 (1H, dd, J=8.6, 5.9 Hz), 4.25 (1H, br s), 5.11 (1H, dd, J=8.6, 5.9 Hz), 5.85 (1H, d, J=0.7 Hz), 7.13-7.36 (5H, m).

Syn Isomer: δ_H ($CDCl_3$); 1.00 (3H, d, J=6.9 Hz), 1.01 (3H, d, J=6.6 Hz), 2.24 (3H, s), 2.06-2.36 (1H, m), 2.40 (3H, s), 4.22 (1H, dd, J=7.3, 5.6 Hz), 4.24 (1H, br s), 5.19 (1H, d, J=5.3 Hz), 5.92 (1H, s), 7.13-7.36 (5H, m).

1-(2'-Benzyl-3'-hydroxy-3'-phenyl)propanoyl-3,5-dimethylpyrazole (**2e**). mp 111-112 °C (from Hexane); yield 57%; Anal. Calcd for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.65; H, 6.64; N, 8.39.

Anti Isomer: δ_H ($CDCl_3$); 2.20 (3H, s), 2.40 (3H, d, J=0.7 Hz), 2.83-3.15 (2H, m), 4.07-4.13 (1H, m), 4.52-4.63 (1H, m), 4.85 (1H, t, J=6.9 Hz), 5.87 (1H, s), 7.07-7.42 (10H, m).

Syn Isomer: δ_H ($CDCl_3$); 2.21 (3H, s), 2.40 (3H, d, J=0.7 Hz), 3.20 (2H, dd, J=14.2, 10.2 Hz), 4.24 (1H, br s), 4.52-4.63 (1H, m), 5.24 (1H, m), 5.90 (1H, s), 7.07-7.42 (10H, m).

1-(3'-Hydroxy-2'-methyl)pentanoyl-3,5-dimethylpyrazole (**3a**). Anal. Calcd for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 62.82; H, 8.73; N, 13.09.

Anti Isomer: δ_H ($CDCl_3$); 1.01 (3H, t, J=7 Hz), 1.30 (3H, d, J=7 Hz), 1.64 (2H, m), 2.23 (3H, s), 2.54 (3H, s), 3.35 (1H, br s), 3.70 (1H, m), 3.90 (1H, m), 5.98 (1H, s).

Syn Isomer: δ_H ($CDCl_3$); 1.00 (3H, t, J=7 Hz), 1.27 (3H, d, J=7 Hz), 1.48 (2H, m), 2.23 (3H, s), 2.54 (3H, s), 3.35 (1H, br s), 3.90 (2H, m), 5.98 (1H, s).

1-(3'-Hydroxy)pentanoyl-3,5-dimethylpyrazole (**3b**). bp 100 °C/ 5 mmHg; yield 51%; δ_H ($CDCl_3$); 1.02 (3H, t, J=7.6 Hz), 1.55-1.70 (2H, m), 2.24 (3H, s), 2.55 (3H, s), 3.24 (2H, ABX, J=16.8, 8.9, 3.0 Hz), 4.02-4.11 (1H, m), 5.98 (1H, s). Anal. Calcd for $C_{10}H_{16}N_2O_2$: C, 61.2; H, 8.22; N, 14.0. Found: C, 60.96; H, 8.52; N, 13.64.

1-(2',4'-Dimethyl-3'-hydroxy)pentanoyl-3,5-dimethylpyrazole (**4a**). bp 60 °C/ 2 mmHg. Anal. Calcd for $C_{12}H_{20}N_2O_2$: C, 64.26; H, 8.99; N, 12.49. Found: C, 64.30; H, 9.09; N, 12.21.

Anti Isomer. δ_H ($CDCl_3$); 0.97 (3H, d, J=7 Hz), 0.98 (3H, d, J=7 Hz), 1.76 (1H, sept, J=7 Hz), 2.23 (3H, s), 2.53 (3H, s), 1.30 (3H, d, J=7 Hz), 3.20 (1H, br s), 3.44-3.53 (1H, m), 4.01-4.14 (1H, m), 5.97 (1H, s).

Syn Isomer. δ_H ($CDCl_3$); 0.96 (3H, d, J=6.6 Hz), 1.00 (3H, d, J=6.6 Hz), 1.28 (3H, d, J=7.3 Hz), 1.75 (1H, oct, J=6.6 Hz), 2.23 (3H, s), 2.53 (3H, d, J=0.7 Hz), 3.21 (1H, s), 3.64 (1H, dd, J=3.0, 7.6 Hz), 4.06 (1H, dq, J=3.0, 7.3 Hz), 5.97 (1H, s).

1-(3'-Hydroxy-2',4',4'-trimethyl)pentanoyl-3,5-dimethylpyrazole (**5a**). Yield 38%. Anal. Calcd for $C_{13}H_{22}N_2O_2$: C, 65.52; H, 9.3; N, 11.75. Found: C, 65.41; H, 9.38; N, 11.48.

Anti Isomer. δ_H ($CDCl_3$); 0.88 (9H, s), 1.47 (3H, d, J=7.3 Hz), 2.24 (3H, s), 2.51 (3H, d, J=1 Hz), 3.34 (1H, dd, J=9.3 , 2.3 Hz), 4.25 (2H, m), 5.99 (1H, s).

Syn Isomer. δ_H ($CDCl_3$); 0.98 (9H, s), 1.33 (3H, d, J=7.3 Hz), 2.24 (3H, s), 2.53 (3H, d, J=1 Hz), 3.28 (1H, br d, J=4.0 Hz), 3.69 (1H, br t, J=3.6 Hz), 3.98 (1H, dq, J=3.3, 6.9 Hz), 5.97 (1H, s).

1-(3'-Hydroxy-2'-methyl-3'-p-tolyl)propanonyl)-3,5-dimethylpyrazole (**6a**). Yield 76%. Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.4; N, 10.29. Found: C, 70.63; H, 7.48; N, 10.22.

Anti Isomer. δ_H ($CDCl_3$); 1.07 (3H, d, J=6.9 Hz), 2.24 (3H, s), 2.34 (3H, s), 2.55 (3H, s), 3.36 (1H, br s), 4.26 (1H, dq, J=6.9, 8.9 Hz), 4.82 (1H, d, J=8.9 Hz), 5.97 (1H, m), 7.15 (2H, d, J=8.6 Hz), 7.27 (2H, d, J=8.6 Hz).

Syn Isomer. δ_H ($CDCl_3$); 1.20 (3H, d, J=7.3 Hz), 2.24 (3H, s), 2.32 (3H, s), 2.50 (3H, s), 3.94 (1H, br s), 4.13 (1H, dq, J=3.3, 7.3 Hz), 5.15 (1H, d, J=3.3 Hz), 5.97 (1H, s), 7.12 (2H, d, J=8.3 Hz), 7.24 (2H, d, J=8.3 Hz).

1-(3'-Hydroxy-2'-methyl-3'-o-tolyl)propanonyl-3,5-dimethylpyrazole (**7a**). Yield 71%. Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.4; N, 10.29. Found: C, 70.63; H, 7.44; N, 10.01.

Anti Isomer. δ_H ($CDCl_3$); 1.10 (3H, d, J=7.3 Hz), 2.23 (3H, s), 2.42 (3H, s), 2.56 (3H, s), 3.28 (1H, br s), 4.36 (1H, dq, J=6.9, 9.2 Hz), 5.20 (1H, d, J=9.2 Hz), 5.97 (1H, s), 7.12-7.25 (3H, m), 7.47-7.56 (1H, dd, J=6.9, 15.2 Hz).

Syn Isomer. δ_H ($CDCl_3$); 1.20 (3H, d, J=7.3 Hz), 2.22 (3H, s), 2.39 (3H, s), 2.54 (3H, s), 3.42 (1H, br s), 4.10 (1H, dq, J=2.6, 6.9 Hz), 5.43 (1H, d, J=2.6 Hz), 5.98 (1H, s), 7.12-7.25 (3H, m), 7.47-7.56 (1H, dd, J=6.9, 15.2 Hz).

1-(3'-Hydroxy-2'-methyl-3'-p-anisyl)propanonyl-3,5-dimethylpyrazole (**8a**). bp 80 °C/ 2 mmHg; yield 65%. Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.65; H, 7.05; N, 9.60.

Anti Isomer. δ_H ($CDCl_3$); 1.06 (3H, d, J=7.3 Hz), 2.25 (3H, s), 2.55 (3H, s), 3.33 (1H, br s), 3.80 (1H, s), 4.25 (1H, dq, J=7.3, 9.1 Hz), 4.80 (1H, d, J=9.1 Hz), 5.97 (1H, s), 6.89 (2H, d, J=8.6 Hz).

Syn Isomer. δ_H ($CDCl_3$); 1.21 (3H, d, J=7.3 Hz), 2.25 (3H, s), 2.50 (3H, s), 3.79 (3H, s), 3.93 (1H, br s), 4.13 (1H, dq, J=3.6, 7.3 Hz), 5.12 (1H, d, J=3.6 Hz), 5.97 (1H, s), 6.84 (2H, d, J=8.6 Hz), 7.28 (2H, d, J=8.6 Hz).

2-(3'-Hydroxy-2'-methyl-3'-phenyl)propanoyl-3-phenylmenthopyrazole (**11a**). Yield 80%. Anal. Calcd for $C_{27}H_{32}N_2O_2$: C, 77.85; H, 7.74; N, 6.73. Found: C, 77.77; H, 7.77; N, 6.61.

(2'S)-Anti Isomer. δ_H ($CDCl_3$); 0.67-0.71 (3H, m), 0.86-0.97 (6H, m), 1.06-1.31 (5H, m), 142-1.58 (1H, m), 1.86-2.04 (2H, m), 2.37-2.50 (1H, m), 2.61-2.78 (2H, m), 3.52 (1H, br s), 4.22-4.35 (1H, m), 4.81 (1H, d, J=8.3 Hz), 7.22-7.57 (10H, m).

(2'R)-Anti Isomer. δ_H ($CDCl_3$); 0.67-0.71 (3H, m), 0.86-0.97 (6H, m), 1.06-1.31 (5H, m), 142-1.58 (1H, m), 1.86-2.04 (2H, m), 2.37-2.50 (1H, m), 2.61-2.78 (2H, m), 3.52 (1H, br s), 4.22-4.35 (1H, m), 4.73 (1H, d, J=8.3 Hz), 7.22-7.57 (10H, m).

(2'S)-Syn Isomer. δ_H ($CDCl_3$); 0.67-0.71 (3H, m), 0.86-0.97 (6H, m), 1.06-1.31 (5H, m), 142-1.58 (1H, m), 1.86-2.04 (2H, m), 2.37-2.50 (1H, m), 2.61-2.78 (2H, m), 3.87 (1H, br s), 4.10-4.18 (1H, m), 5.15 (1H, d, J=3.0 Hz), 7.22-7.57 (10H, m).

(2'R)-Syn Isomer. δ_H ($CDCl_3$); 0.67-0.71 (3H, m), 0.86-0.97 (6H, m), 1.06-1.31 (5H, m), 142-1.58 (1H, m), 1.86-2.04 (2H, m), 2.37-2.50 (1H, m), 2.61-2.78 (2H, m), 3.87 (1H, br s), 4.10-4.18 (1H, m), 5.22 (1H, d, J=2.6 Hz), 7.22-7.57 (10H, m).

2-(3'-Hydroxy-3'-phenyl)propanoyl-3-phenyl-l-menthopyrazole (**11b**). Yield 70%. Anal. Calcd for $C_{26}H_{30}N_2O_2$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.21; H, 7.57; N, 6.82.

Major Isomer. δ_H ($CDCl_3$); 0.70 (3H, d, J=6.9 Hz), 0.90 (3H, d, J=6.6 Hz), 1.07 (3H, d, J=6.9 Hz), 1.18-1.31 (1H, m), 1.44-1.59 (1H, m), 1.83-2.00 (2H, m), 2.36-2.48 (1H, m), 2.59-2.68 (1H, m), 2.71-2.80 (1H, m), 3.42-3.63 (2H, m), 4.01 (1H, br s), 5.19 (1H, t, J=5.6 Hz), 7.24-7.43 (10H, m).

Minor Isomer. δ_H ($CDCl_3$); 0.69 (3H, d, J=6.9 Hz), 0.90 (3H, d, J=6.6 Hz), 1.07 (3H, d, J=6.9 Hz), 1.18-1.31 (1H, m), 1.44-1.59 (1H, m), 1.83-2.00 (2H, m), 2.36-2.48 (1H, m), 2.59-2.68 (1H, m), 2.71-2.80 (1H, m), 3.42-3.63 (2H, m), 3.93 (1H, br s), 5.21 (1H, dd, J=5.3, 3.3 Hz), 7.24-7.43 (10H, m).

2-(2'-Ethyl-3'-hydroxy-3'-phenyl)propanoyl-3-phenylmenthopyrazole (**11c**). Yield 80%. Anal. Calcd for $C_{28}H_{34}N_2O_2$: C, 78.1; H, 7.96; N, 6.51. Found: C, 77.81; H, 8.06; N, 6.63.

(2'S)-Anti Isomer. δ_H ($CDCl_3$); 0.67-0.71 (3H, m), 0.78-1.01 (6H, m), 1.05-1.19 (3H, m), 1.43-2.04 (5H, m), 2.40-2.53 (1H, m), 2.63-2.79 (2H, m), 4.06 (1H, br s), 4.18-4.31 (2H, m), 4.88 (1H, d, J=7.9 Hz), 7.07-7.60 (10H, m).

(2'R)-Anti Isomer. δ_H ($CDCl_3$); 0.67-0.71 (3H, m), 0.78-1.01 (6H, m), 1.05-1.19 (3H, m), 1.43-2.04 (5H, m), 2.40-2.53 (1H, m), 2.63-2.79 (2H, m), 4.06 (1H, br s), 4.18-4.31 (2H, m), 4.76 (1H, m), 7.07-7.60 (10H, m).

(2'S)-Syn Isomer. δ_H ($CDCl_3$); 0.67-0.71 (3H, m), 0.78-1.01 (6H, m), 1.05-1.19 (3H, m), 1.43-2.04 (5H, m), 2.40-2.53 (1H, m), 2.63-2.79 (2H, m), 3.40 (1H, br s), 4.08-4.16 (1H, m), 5.14 (1H, d, J=4.0 Hz), 7.07-7.60 (10H, m).

(2'R)-Syn Isomer. δ_H ($CDCl_3$); 0.67-0.71 (3H, m), 0.78-1.01 (6H, m), 1.05-1.19 (3H, m), 1.43-2.04 (5H, m), 2.40-2.53 (1H, m), 2.63-2.79 (2H, m), 3.40 (1H, br s), 4.08-4.16 (1H, m), 5.08 (1H, d, J=3.3 Hz), 7.07-7.60 (10H, m).

2-(3'-Hydroxy-2'-isopropyl-3'-phenyl)Propanoyl-3-phenylmenthopyrazole (**11d**). Yield 69%. Anal. Calcd for $C_{29}H_{36}N_2O_2$: C, 78.34; H, 8.16; N, 6.3. Found: C, 77.83; H, 8.21; N, 6.17.

Anti Isomer. δ_H ($CDCl_3$); 0.64 (3H, d, J=6.6 Hz), 0.84-0.92 (6H, m), 0.95-1.17 (6H, m), 1.19-1.27 (5H, m), 1.36-1.59 (2H, m), 1.81-1.95 (2H, m), 2.17-2.28 (1H, m), 2.33-2.73 (3H, m), 4.08-4.13 (1H, m), 4.41-4.45 (1H, m), 5.01-5.13 (1H, m), 6.89-7.02 (2H, m), 7.14-7.54 (8H, m).

Syn Isomer. δ_H ($CDCl_3$); 0.60 (3H, d, J=6.9 Hz), 0.84-0.92 (6H, m), 0.95-1.17 (6H, m), 1.19-1.27 (5H, m), 1.36-1.59 (2H, m), 1.81-1.95 (2H, m), 2.17-2.28 (1H, m), 2.33-2.73 (3H, m), 3.82-3.96 (1H, m), 4.17-4.22 (1H, m), 5.01-5.13 (1H, m), 6.89-7.02 (2H, m), 7.14-7.54 (8H, m).

2-(2'-Benzyl-3'-hydroxy-3'-phenyl)propanoyl-3-phenylmenthopyrazole (**11e**). Yield 67%. Anal. Calcd for $C_{33}H_{38}N_2O_2$: C, 80.13; H, 7.74; N, 5.66. Found: C, 80.08; H, 7.36; N, 5.55.

(2'S)-Anti Isomer. δ_H ($CDCl_3$); 0.63-0.66 (3H, m), 0.86-0.97 (6H, m), 1.05-1.59 (6H, m), 1.83-1.97 (2H, m), 2.42-3.17 (5H, m), 4.11-4.13 (1H, m), 4.53-4.67 (2H, m), 5.22 (1H, m), 6.89-7.45 (15H, m).

(2'R)-Anti Isomer. δ_H ($CDCl_3$); 0.63-0.66 (3H, m), 0.86-0.97 (6H, m), 1.05-1.59 (6H, m), 1.83-1.97 (2H, m), 2.42-3.17 (5H, m), 4.11-4.13 (1H, m), 4.70-4.81 (2H, m), 5.22 (1H, m), 6.89-7.45 (15H, m).

Isomerization of *syn*-2a into *anti*-2a. To the mixture of *syn*-**2a** (76 mg, 0.3 mmol) and $MgBr_2 \cdot OEt_2$ (90 mg, 0.35 mmol) in CH_2Cl_2 (1.5 mL), DIEA (78 mg, 0.6 mmol) in CH_2Cl_2 (1 mL) was added at -5 °C under nitrogen atmosphere. After stirring for 2 h, the mixture was worked up as described above. The ratio of *syn*-**2a** and *anti*-**2a** in the residue (48 mg) was measured to be 38 : 62 by ^1H NMR.

Isomerization of 2a in the Presence of 1b. To the mixture of **2a** (124 mg, 0.48 mmol), $MgBr_2 \cdot OEt_2$ (286 mg, 1.1 mmol) and **1b** (69 mg, 0.5 mmol) in CH_2Cl_2 (1.8 mL), DIEA (103 mg, 0.81 mmol) in CH_2Cl_2 (0.3 mL) was added at -5 °C under nitrogen atmosphere. After stirring for 1 h, the mixture was worked up as described above. The product ratio of the residue was measured by ^1H NMR. From *syn*-**2a**, the ratio of *syn*-**2a**, *anti*-**2a** and **2b** was 52 : 22 : 26, while that from *anti*-**2a** was 17 : 59 : 25.

Conversion of 2a into Methyl 3-Hydroxy-2-methyl-3-phenylpropanoate. The methanol (2 mL) solution of **2a** (86 mg, 0.33 mmol) and $BF_3 \cdot OEt_2$ (67 mg, 0.47 mmol) was refluxed for 1 h. After being quenched with water, products were extracted with CH_2Cl_2, and the organic layer was washed with

aqueous sodium hydrogen carbonate (saturated) and aqueous sodium chloride (saturated), dried over anhydrous magnesium sulfate, and concentrated. The residue was chromatographed on silica gel column with hexane-ethyl acetate (v/v 7 : 1) mixture. The products were identified with *syn* and *anti* forms of methyl 3-hydroxy-2-methyl-3-phenylpropanoate in 62% yield by the comparison of the ^{1}H NMR spectral data.[10]

Anti Isomer. δ_H ($CDCl_3$); 1.00 (3H, d, J=7.3 Hz), 2.74-2.87 (1H, m), 2.98 (1H, s), 3.73 (3H, s), 4.75 (1H, d, J=8.6 Hz), 7.23-7.36 (5H, m).

Syn Isomer. δ_H ($CDCl_3$); 1.13 (3H, d, J=6.9 Hz), 2.74-2.87 (1H, m), 2.98 (1H, s), 3.67 (3H, s), 5.10 (1H, d, J=3.6 Hz), 7.23-7.36 (5H, m).

Reduction of (2'*S*)-2-(2'-Methyl-3'-oxo-3'-phenyl)propanoyl-3-phenyl-l-menthopyrazole with K-Selectride. (2'*S*)-2-(2'-Methyl-3'-oxo-3'-phenyl)propanoyl-3-phenyl-*l*-menthopyrazole (76% de, 101 mg, 0.24 mmol), which was prepared from **10a** and benzoyl chloride,[9] was reduced in THF (5 mL) for 1 h in the presence of $MgBr_2{\cdot}OEt_2$ (119 mg, 0.46 mmol) with K-selectride (Aldrich, 1.0 M in THF, 360 μL, 0.36 mmol) at -78 °C. The reaction mixture was quenched with acetic acid, diluted with water and acidified with 6N hydrochloric acid. The products were extracted with CH_2Cl_2, and the organic layer was washed with aqueous sodium hydrogen carbonate (saturated) and aqueous sodium chloride solution (saturated), dried over anhydrous magnesium sulfate, and concentrated. The fraction of **11a** was collected on the silica gel column chromatography of the residue with hexane-ethyl acetate (v/v 7 : 1) mixture. In the NMR spectrum of the mixture, (2'*S*)-*anti*-**11a**, (2'*R*)-*anti*-**11a**, (2'*S*)-*syn*-**11a** and (2'*R*)-*syn*-**11a** was assigned by the peaks at δ 4.81 (d, J=8.3 Hz), 4.72 (d, J=8.3 Hz), 5.22 (d, J=3.0 Hz), 5.15 (d, J=3.0 Hz) with the ratio of 72 : 14 : 14 : <1 in total yield of 29%, respectively.

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