Synthesis of Optically Active β-Lactams by the Reaction of 2-Acyl-3-phenyl-*l*-menthopyrazoles with C=N Compounds

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The reaction of 1-acyl-3,5-dimethylpyrazoles **1** with C=N compounds was kinetically controlled with *syn* stereoselectivity through a lithium enolate intermediate using lithium diisopropylamide. In contrast, the *anti* stereoselective reaction of **1** was caused by the action of diisopropylethylamine in the presence of magnesium bromide under the thermodynamic control. Reaction of 2-acyl-3-phenyl-*l*-menthopyrazoles **12** with C=N compounds was observed in higher chemical and optical yields with the predominant 2'*S* configuration. An especially diastereomerically pure product was isolated in the reaction of 2-propanoyl-3-phenyl-*l*-menthopyrazole (**12a**) with *N*-benzylidene-4-toluenesulfonamide (**2**). The products from *N*-acylpyrazoles and C=N compounds were further cyclized into β-lactams directly or with short conversion steps.

Recently we have been very interested in the chemistry of *N*-acylpyrazoles, especially 2-acyl-3-phenyl-*l*-menthopyrazoles as chiral synthetic intermediates [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 lithium diisopropylamide or lithium hexamethyldisilazide 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, α-acylation, and aldol condensation [9] were accomplished by diastereofacial attack on the lithium enolate, which was rigidly fixed by the intramolecular chelation between lithium and the N-1 atom [6]. Otherwise, *N*-acylpyrazoles formed the 5-membered C=O•••Mg•••N-2 chelate complexes with magnesium bromide which afforded the Claisen condensation products by the action of a tertiary amine through the corresponding enolate [10]. These Mg chelate complexes were allowed to react with aldehydes to give aldol products in the presence of tertiary amines [9]. For a further extension of the utilization of *N*-acylpyrazoles as synthetic intermediates, a wide variety of the stereoselective reactions on the acyl moiety of *N*-acylpyrazoles is highly desired. We report the reactions of *N*-acylpyrazoles with C=N compounds, especially the diastereoselective reactions using a new chiral auxiliary, 3-phenyl-*l*-menthopyrazole. Moreover, the conversion of the resulting *N*(β-amino)acylpyrazoles into β-lactams will be described with the retention of their chirality.

Results and Discussion.

As analogs to aldehydes [9], C=N compounds were expected to react with *N*-acylpyrazoles to afford *N*-(β-amino)acylpyrazoles, which should be a good precursor for β-lactams through an intramolecular cyclization [2]. When 1-propanoyl-3,5-dimethylpyrazole (**1a**) was treated with *N*-benzylidene-4-toluenesulfonamide (**2**) in the presence of lithium diisopropylamide and hexamethylphosphoramide, 1-[2-methyl-3-phenyl-3-(4-toluene)sulfonamido]propanoyl-3,5-dimethylpyrazole (**3a**) was formed in good yield as the *syn/anti* mixture in a ratio of 58:42. The *syn* and *anti* isomers were easily separated by silica gel column chromatography, and their stereo structures and ratios were deduced from ¹H-nmr data [11]. The stereoselectivity of this reaction was slightly in favor of the *anti* form at lower reaction temperatures. By the use of diisopropylethylamine in the presence of magnesium bromide, *anti*-**3a** was predominantly formed from **1a** and **2**. Similarly β-(4-toluene)sulfonamidoacylpyrazoles **3** were obtained in good yields from various **1** and **2** using either lithium diisopropylamide or magnesium bromide-diisopropylethylamine summarized in Table 1.

Since *N*-methyl-*N*-(4-toluene)sulfonyl-3-phenylpropanamide was obtained in 66% yield by treatment of *N*-methyl-4-toluenesulfonamide with **1e** in the presence of boron trifluoride etherate, the conversion of **3** into β-lactams was attempted intramolecularly. However the desired β-lactam could not be detected from **3a** using boron trifluoride etherate. A retro aldol type reaction occurred to give **1a** and **2**. As an alternative conversion, the *syn* and *anti* isomers of **3a** were quantitatively hydrolyzed by the action of dilute sulfuric acid into 2-methyl-3-phenyl-3-(4-toluene)sulfonamidopropanoic acids (**4a**) with the retention of their stereo structures, which were assigned by comparison with authentic data [12]. Further **4a** was converted into 3-methyl-4-phenyl-1-(4-toluene)sulfonylazetidin-2-one (**5a**) under the condition of Abrahams [12].

When *N*-benzylidene aniline (**6**) was treated with **1a** under the condition of diisopropylethylamine-magnesium bromide, neither *N*-(β-amino)acylpyrazoles nor β-lactams could be detected but 1-(2-methyl-3-oxo)pentanoyl-3,5-dimethylpyrazole was obtained. The use of lithium diiso-

Table 1

The Reaction of 1-Acyl-3,5-dimethylpyrazoles with C=N Compounds

Substrate		C=N Compound		Product	with Lithium Diisopropylamide [a]		with Diisopropyllethylamine-Magnesium Bromide	
	R^1		R^2		Yield (%)	Syn:Anti	Yield (%)	Syn:Anti
1a	Me	2	Ts	3a	90	58:42	89	5:95
1a	Me	2	Ts	3a	85 [b]	48:52		
1b	H	2	Ts	3b			89	
1c	Et	2	Ts	3c	85	34:66	84	10:90
1d	Pr	2	Ts	3d	80	36:64	95	9:91
1e	PhCH$_2$	2	Ts	3e	87	30:70	93	1:99
1a	Me	6	Ph	8a	98	69:31	0	
1c	Et	6	Ph	8c	66	82:18		
1d	Pr	6	Ph	8d	68	84:16		
1e	PhCH$_2$	6	Ph	8e	66	92:8		
1a	Me	9	PhCH$_2$	none	0			
1a	Me	10	t-Bu	none	0			
1a	Me	11	TMS	none	0			

[a] The reaction was carried out at 0°; [b] The reaction was carried out at -78°.

Scheme 1
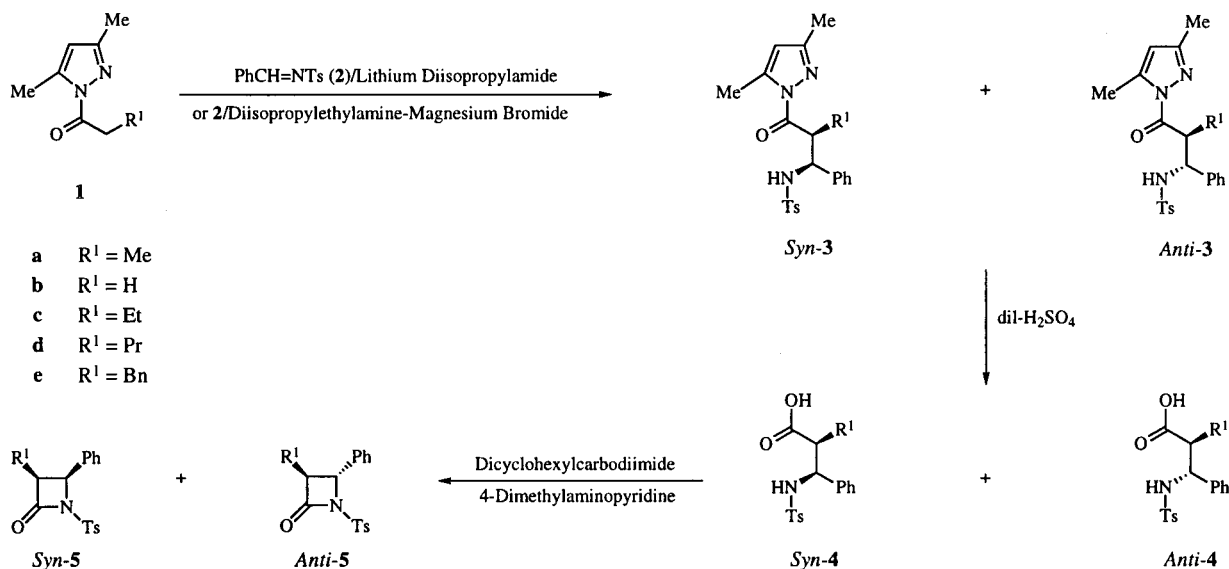

propylamide in the presence of hexamethylphosphor-amide allowed the reaction of 1a with 6 to give 1,4-di-phenyl-3-methylazetidin-2-one (8a) [13], while 1a was completely recovered in the reaction of 6 without hexa-methylphosphoramide. As illustrated in Scheme 2, 1-(3-anilino-3-phenyl-2-methyl)propanoyl-3,5-dimethyl-pyrazole (7a) was first afforded and spontaneous cycliza-tion followed to form 8a by an intramolecular aminolysis. Analogous formation of β-lactams by the treatment of 1b and 1e-f with 6 are listed in Table 1, where syn isomers were predominant and the syn/anti ratios were dependent on the bulkiness of the acyl moiety of 1. In the case of

C=N compounds having electron donating substituents such as 9~11, 1a was recovered even under the forcing conditions using hexamethylphosphoramide; the reaction did not occur at all due to their low reactivity.

In an attempt to prepare diastereomerically enriched β-lactams, 2-acyl-3-phenyl-l-menthopyrazoles 12 were first treated with 6. By the use of lithium diisopropyl-amide-hexamethylphosphoramide at 0°, syn-8a was pref-erentially obtained in moderate yield from 12a and 6. By lowering the reaction temperature, the stereoselectivity to syn isomer was improved with a drop in the yield of 8a. Therefore, the reaction temperature was optimized at -20°

Scheme 2

a   R¹ = Me
b   R¹ = H
c   R¹ = Et
d   R¹ = Pr
e   R¹ = Bn
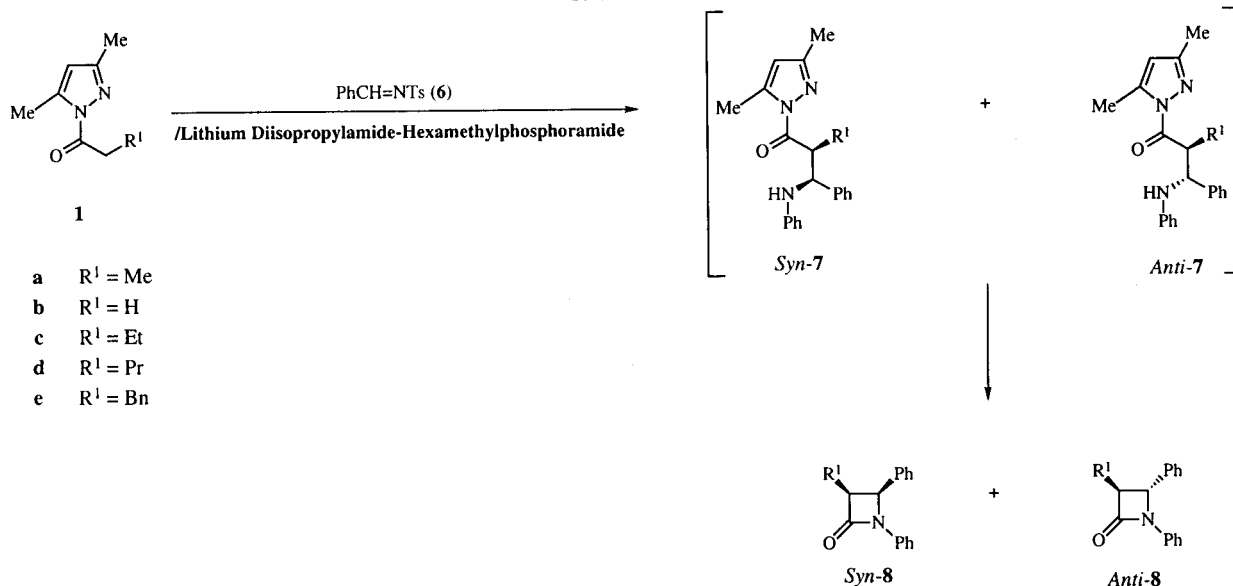
with high *syn* preference in moderate yield of β-lactam. The yield was slightly improved by the use of lithium hexamethyldisilazide with hexamethylphosphoramide instead of lithium diisopropylamide-hexamethylphosphoramide. During this reaction, 3-phenyl-*l*-menthopyrazole was recovered in about 50% yield. The prefered structure of *syn*-**8a** was the 3*R*,4*S* configuration from comparison of the specific rotation [14]. From the nmr spectrum using a chiral europium shift reagent, the optical yield was shown to be relatively low, less than 10% ee. Analogous results were obtained from various compounds **12** and **6** summarized in Table 2.

When **12a** was treated with **2** using lithium diisopropyl-amide-hexamethylphosphoramide at 0°, *syn*-2-[2-methyl-3-phenyl-3-(4-toluene)sulfonamido]propanoyl-3-phenyl-*l*-menthopyrazole (*syn*-**13a**) was formed in high yield with high diastereoselectivity over 90% de. Reaction at lower temperatures caused lower *syn/anti* stereo-selectivity but higher diastereoselectivity. After separation of the *syn* and *anti* isomers by column chromatography, both isomers were converted into the corresponding β-lac-tams, *syn*-**5a** and *anti*-**5a**. From comparison of the specific rotation of **5a**, the absolute configurations of *syn*-**13a** and *anti*-**13a** were shown to be the 2'*S*,3'*S* and 2'*S*,3'*R* configu-rations, respectively [12]. This diastereoselectivity using 3-phenyl-*l*-menthopyrazole as a chiral auxiliary was con-sistent with those in the previous reported reactions such as α-alkylation [6], α-sulfenylation [7], α-acylation [8],

Table 2

The Reaction of 2-Acyl-3-phenyl-*l*-menthopyrazoles **12** with Benzylidene Aniline (**6**)

	R¹	Base [a]	Product	Yield (%)	Syn (% de)		Anti
12a	Me	Lithium Diisopropylamide-Hexamethylphosphoramide	**8a**	45	>98	(8)	2
12a	Me	Lithium Diisopropylamide-Hexamethylphosphoramide [b]	**8a**	66	87	(3)	13
12a	Me	Lithium Hexamethyldisilazide-Hexamethylphoramide	**8a**	53	>98	(3)	2
12a	Me	Lithium Hexamethyldisilazide-Hexamethylphoramide [b]	**8a**	44	>98	(4)	2
12c	Et	Lithium Diisopropylamide-Hexamethylphosphoramide	**8c**	18	>98	(14)	2
12d	Pr	Lithium Diisopropylamide-Hexamethylphosphoramide	**8d**	19	>98	(14)	2
12e	PhCH₂	Lithium Diisopropylamide-Hexamethylphosphoramide	**8e**	20	>98	(26)	2

[a] The reaction was carried out at -20°; [b] The reaction was carried out at 0°.

and aldol condensation [9]. Similarly the reaction of 2-acyl-3-phenyl-*l*-menthopyrazoles **12** with **2** was carried out using lithium diisopropylamide-hexamethyl-phosphoramide at -78° summarized in Table 3, where high chemical and optical yields were observed and *syn/anti* stereoselectivities were dependent on the bulkiness of the acyl moiety.

also observed in every case of the various compounds **12** listed in Table 3. These reaction tendencies are proposed to be caused by an equilibration through the retro reaction.

In conclusion, the reaction of 1-acyl-3,5-dimethylpyrazoles (**1**) with C=N compounds was kinetically controlled with *syn* stereoselectivity through the lithium enolate
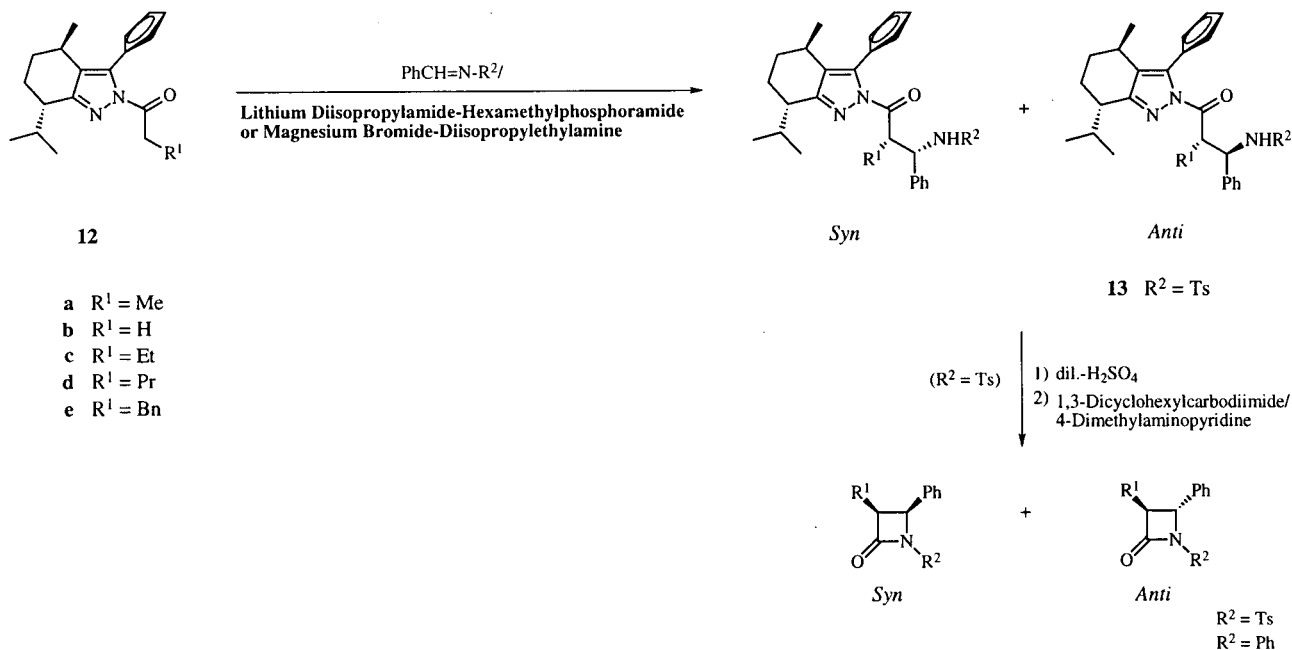
Scheme 3

12

a R¹ = Me
b R¹ = H
c R¹ = Et
d R¹ = Pr
e R¹ = Bn

Syn   *Anti*

13 R² = Ts

(R² = Ts) | 1) dil.-H₂SO₄
2) 1,3-Dicyclohexylcarbodiimide/ 4-Dimethylaminopyridine

Syn   *Anti*

R² = Ts
R² = Ph

Table 3

The Reaction of 2-Acyl-3-phenyl-*l*-menthopyrazoles **12** with *N*-Benzylidene 4-Toluenesulfonamide (**2**)

Substrate	R¹	Product	With Lithium Diisopropylamide-Hexamethylphosphoramide (-78°)			With Diisopropylethylamine-Magnesium Bromide (0°)		
			Yield (%)	Syn (% de)	Anti (% de)	Yield (%)	Syn (% de)	Anti (% de)
12a	Me	**13a**	92	80 (91)	20 (76)	94	4 (91)	96 (15)
12a	Me	**13a**	90 [a]	95 (95)	5 (32)			
12b	H	**13b**				98 [b]		
12c	Et	**13c**	85	64 (95)	36 (85)	93	3 (15)	97 (12)
12d	Pr	**13d**	77	57 (93)	43 (91)	97	4 (7)	96 (17)
12e	PhCH₂	**13e**	79	53 (85)	47 (76)	98	4 (21)	96 (8)

[a] The reaction was carried out at 0°; [b] Diastereomer excess at the β-position was 13% de.

The diisopropylethylamine catalyzed reaction of **2** in the presence of magnesium bromide, **12a** gave *anti*-**13a** predominantly with an 2'*S*,3'*R* configuration in a low diastereomer excess. Otherwise, the diastereomerically enriched *syn*-**13a** was isomerized into *anti*-**13a** with the loss of diastereomer enrichment by the action of diisopropylethylamine in the presence of magnesium bromide. The higher *anti*- and the poor diastereoselectivities were

intermediate using lithium diisopropylamide. In contrast, the *anti* stereoselective reaction of **1** was caused by the action of diisopropylethylamine in the presence of magnesium bromide under the thermodynamic control. Reaction of 2-acyl-3-phenyl-*l*-menthopyrazoles **12** with C=N compounds was observed in higher chemical and optical yields with the 2'*S* configuration predominating. Especially diastereomerically pure product was isolated in

the reaction of 2-propanoyl-3-phenyl-*l*-menthopyrazole (**12a**) with *N*-benzylidene-4-toluenesulfonamide (**2**). The products from *N*-acylpyrazoles and C=N compounds were further cyclized into β-lactams directly or with short conversion steps.

EXPERIMENTAL

Melting points are uncorrected. The nmr spectra were obtained on JEOL JNM-EX270 (270 MHz) spectrometer in deuteriochloroform with tetramethylsilane as an internal standard. Tetrahydrofuran and dichloromethane were dried over the benzophenone ketyl radical and calcium hydride, respectively. 1-Acyl-3,5-dimethylpyrazoles (**1**) and 2-acyl-3-phenyl-*l*-menthopyrazoles **12** were prepared from the corresponding pyrazoles by the method used in previous papers [1,3,7]. The C=N compounds **2** and **9~11** were prepared by ordinary methods [15-18].

Reaction of *N*-Acylpyrazoles with **2**.

With Lithium Diisopropylamide.

To a lithium diisopropylamide solution, which was prepared from diisopropylamine (1.5 mmoles) and butyllithium (1.6*M* in hexane, 1.4 mmoles) in tetrahydrofuran, *N*-acylpyrazole (1 mmole) was added at -78° under a nitrogen atmosphere. After stirring for 30 minutes at -78°, **2** (1.1 mmoles) in tetrahydrofuran (2 ml) was added with continuous stirring at 0° during 3 hours. The mixture was quenched with acetic acid and extracted with dichloromethane. The organic layer was washed with dilute hydrochloric acid, water, aqueous sodium hydrogen carbonate and aqueous sodium chloride, dried over anhydrous magnesium sulfate, and concentrated. The residue was chromatographed on silica gel with benzene-ethyl acetate mixture as an eluent.

With Diisopropylethylamine-Magnesium Bromide.

To a mixture of *N*-acylpyrazole (1 mmole), magnesium bromide-diethyl ether (1 mmole), and **2** (1.4 mmoles) in dichloromethane (4 ml), diisopropylethylamine (2 mmoles) in dichloromethane (1 ml) was added at -5° under nitrogen atmosphere. After stirring for 1 hour, the mixture was worked up as described above.

1-[2,3-*syn*-2-Methyl-3-phenyl-3-(4-toluene)sulfonamido]propanoyl-3,5-dimethylpyrazole (*syn*-**3a**).

This compound had ^{1}H nmr (deuteriochloroform): δ 1.09 (3H, d, J = 6.9 Hz), 2.24 (3H, s), 2.33 (3H, s), 2.38 (3H, d, J = 0.7 Hz), 4.20-4.31 (1H, m), 4.46-4.52 (1H, m), 5.94 (1H, s), 6.38 (1H, d, J = 8.3 Hz), 7.03-7.42 (9H, m).
Anal. Calcd. for $C_{22}H_{25}N_3O_3S$: C, 64.21; H, 6.12; N, 10.21. Found: C, 64.26; H, 5.90; N, 9.99.

1-[2,3-*anti*-2-Methyl-3-phenyl-3-(4-toluene)sulfonamido]propanoyl-3,5-dimethylpyrazole (*anti*-**3a**).

This compound had ^{1}H nmr (deuteriochloroform): δ 1.12 (3H, d, J = 6.9 Hz), 2.26 (3H, s), 2.28 (3H, d, J = 0.7 Hz), 2.33 (3H, s), 4.12-4.21 (1H, m), 4.82-4.86 (1H, m), 5.70 (1H, d, J = 7.3 Hz), 5.88 (1H, s), 7.03-7.53 (9H, m).
Anal. Calcd. for $C_{22}H_{25}N_3O_3S$: C, 64.21; H, 6.12; N, 10.21. Found: C, 64.38; H, 6.06; N, 10.21.

1-[3-Phenyl-2-phenylmethyl-3-(4-toluene)sulfonamido]propanoyl-3,5-dimethylpyrazole (**3b**).

The yield was 89%; ^{1}H nmr (deuteriochloroform): δ 2.25 (3H, s), 2.36 (3H, s), 2.37 (3H, d, J = 0.7 Hz), 3.29 (1H, dd, J = 15.5, 5.0 Hz), 3.67 (1H, dd, J = 15.5, 8.3 Hz), 4.81-4.88 (1H, m), 5.94 (1H, s), 6.16 (1H, d, J = 6.9 Hz), 7.11-7.53 (9H, m).
Anal. Calcd. for $C_{21}H_{23}N_3O_3S$: C, 63.45; H, 5.83; N, 10.57. Found: C, 63.26; H, 5.75; N, 10.40.

1-[2,3-*syn*-2-Ethyl-3-phenyl-3-(4-toluene)sulfonamido]propanoyl-3,5-dimethylpyrazole (*syn*-**3c**).

This compound had ^{1}H nmr (deuteriochloroform): δ 0.79 (3H, t, J = 7.6 Hz), 1.61-1.86 (2H, m), 2.20 (3H, s), 2.31 (3H, s), 2.37 (3H, d, J = 0.7 Hz), 4.11-4.19 (1H, m), 4.54-4.60 (1H, m), 5.91 (1H, s), 6.41 (1H, d, J = 8.3 Hz), 7.03-7.52 (9H, m)
Anal. Calcd. for $C_{23}H_{27}N_3O_3S$: C, 64.92; H, 6.40; N, 9.87. Found: C, 64.87; H, 6.48; N, 9.78.

1-[2,3-*anti*-2-Ethyl-3-phenyl-3-(4-toluene)sulfonamido]propanoyl-3,5-dimethylpyrazole (*anti*-**3c**).

This compound had ^{1}H nmr (deuteriochloroform): δ 0.76 (3H, t, J = 7.6 Hz), 1.24-1.41 (2H, m), 2.25 (3H, s), 2.26 (3H, s), 2.37 (3H, d, J = 0.7 Hz), 4.00-4.19 (1H, m), 4.76-4.81 (1H, m), 5.87 (1H, s), 6.03 (1H, d, J = 7.3 Hz), 7.03-7.52 (9H, m).
Anal. Calcd. for $C_{23}H_{27}N_3O_3S$: C, 64.92; H, 6.40; N, 9.87. Found: C, 64.86; H, 6.38; N, 9.63.

1-[2,3-*syn*-3-Phenyl-2-propyl-3-(4-toluene)sulfonamido]propanoyl-3,5-dimethylpyrazole (*syn*-**3d**).

This compound had ^{1}H nmr (deuteriochloroform): δ 0.71-0.78 (3H, m), 1.14-1.79 (4H, m), 2.20 (3H, s), 2.32 (3H, s), 2.36 (3H, s), 4.20-4.29 (1H, m), 4.51-4.58 (1H, m), 5.91 (1H, s), 6.37 (1H, d, J = 8.3 Hz), 7.03-7.53 (9H, m).
Anal. Calcd. for $C_{24}H_{29}N_3O_3S$: C, 65.58; H, 6.65; N, 9.56. Found: C, 65.51; H, 6.63; N, 9.37.

1-[2,3-*anti*-3-Phenyl-2-propyl-3-(4-toluene)sulfonamido]propanoyl-3,5-dimethylpyrazole (*anti*-**3d**).

This compound had ^{1}H nmr (deuteriochloroform): δ 0.71-0.78 (3H, m), 1.14-1.79 (4H, m), 2.26 (3H, s), 2.32 (3H, s), 2.36 (3H, s), 4.06-4.13 (1H, m), 4.74-4.79 (1H, m), 5.87 (1H, s), 5.93 (1H, d, J = 6.9 Hz), 7.03-7.53 (9H, m).
Anal. Calcd. for $C_{24}H_{29}N_3O_3S$: C, 65.58; H, 6.65; N, 9.56. Found: C, 65.40; H, 6.61; N, 9.43.

1-[2,3-*syn*-3-Phenyl-2-phenylmethyl-3-(4-toluene)sulfonamido]propanoyl-3,5-dimethylpyrazole (*syn*-**3e**).

This compound had ^{1}H nmr (deuteriochloroform): δ 2.17 (3H, s), 2.27 (3H, s), 2.32 (3H, s), 2.66-2.78 (2H, m), 4.48-4.60 (2H, m), 5.84 (1H, s), 6.67 (1H, d, J = 7.9 Hz), 6.95-7.54 (14H, m).
Anal. Calcd. for $C_{28}H_{29}N_3O_3S$: C, 68.97; H, 5.99; N, 8.62. Found: C, 68.85; H, 5.94; N, 8.58.

1-[2,3-*anti*-3-Phenyl-2-phenylmethyl-3-(4-toluene)sulfonamido]propanoyl-3,5-dimethylpyrazole (*anti*-**3e**).

This compound had ^{1}H nmr (deuteriochloroform): δ 2.24 (3H, s), 2.32 (3H, s), 2.34 (3H, s), 2.98-3.06 (2H, m), 4.36-4.46 (1H, m), 4.87-4.91 (1H, m), 5.84 (1H, s), 6.18 (1H, d, J = 6.9 Hz), 6.95-7.54 (14H, m).
Anal. Calcd. for $C_{28}H_{29}N_3O_3S$: C, 68.97; H, 5.99; N, 8.62. Found: C, 68.77; H, 5.92; N, 8.49.

2-[2,3-*syn*-2-Methyl-3-phenyl-3-(4-toluene)sulfonamido]propanoyl-3-phenyl-*l*-menthopyrazole (*syn*-**13a**).

This compound had ^{1}H nmr (deuteriochloroform): δ 0.63 (3H, d, J = 6.9 Hz), 0.95 (3H, d, J = 6.6 Hz), 1.10-1.26 (7H, m), 1.49-1.61 (1H, m), 1.85-1.99 (2H, m), 2.34 (3H, s), 2.38-2.47 (1H, m), 2.62-2.78 (2H, m), 4.13-4.23 (1H, m), 4.75-4.80 (1H, m), 5.68 (1H, d, J = 7.9 Hz), 6.86-7.56 (14H, m).

Anal. Calcd. for $C_{34}H_{39}N_3O_3S$: C, 71.67; H, 6.90; N, 7.38. Found: C, 71.37; H, 6.84; N, 7.27.

2-[2,3-*anti*-2-Methyl-3-phenyl-3-(4-toluene)sulfonamido]propanoyl-3-phenyl-*l*-menthopyrazole (*anti*-**13a**).

This compound had ^{1}H nmr (deuteriochloroform): δ 0.62 (3H, d, J = 6.6 Hz), 0.92 (3H, d, J = 6.9 Hz), 1.07 (3H, d, J = 6.9 Hz), 1.17-1.25 (1H, m), 1.20 (3H, d, J = 6.9 Hz), 1.46-1.62 (1H, m), 1.81-1.97 (2H, m), 2.31 (3H, s), 2.34-2.44 (1H, m), 2.54-2.62 (1H, m), 2.69-2.77 (1H, m), 4.24-4.29 (1H, m), 4.57-4.62 (1H, m), 6.51 (1H, d, J = 8.9 Hz), 7.01-7.45 (14H, m).

Anal. Calcd. for $C_{34}H_{39}N_3O_3S$: C, 71.67; H, 6.90; N, 7.38. Found: C, 71.27; H, 6.94; N, 7.27.

2-[3-Phenyl-3-(4-toluene)sulfonamido]propanoyl-3-phenyl-*l*-menthopyrazole (**13b**).

This compound had ^{1}H nmr (deuteriochloroform): δ 0.64 (3H, d, J = 6.8 Hz), 0.84-0.99 (3H, m), 1.09 (3H, d, J = 6.8 Hz), 1.07-1.52 (2H, m), 1.65-2.00 (2H, m), 2.29 (3H, s), 2.30-2.43 (1H, m), 2.58-2.71 (2H, m), 3.25-3.70 (2H, m), 4.87-4.93 (1H, m), 6.47 (1H, d, J = 7.2 Hz), 6.85-7.53 (14H, m).

Anal. Calcd. for $C_{33}H_{37}N_3O_3S$: C, 71.32; H, 6.71; N, 7.56. Found: C, 71.55; H, 6.98; N, 7.37.

2-[2,3-*syn*-2-Ethyl-3-phenyl-3-(4-toluene)sulfonamido]propanoyl-3-phenyl-*l*-menthopyrazole (*syn*-**13c**).

This compound had ^{1}H nmr (deuteriochloroform): δ 0.59 (3H, d, J = 6.6 Hz), 0.77 (3H, t, J = 7.3 Hz), 0.93 (3H, d, J = 6.6 Hz), 1.10 (3H, d, J = 6.6 Hz), 1.14-1.26 (1H, m), 1.46-1.50 (1H, m), 1.73-1.95 (4H, m), 2.32 (3H, s), 2.41-2.49 (1H, m), 2.62-2.71 (2H, m), 4.16-4.23 (1H, m), 4.62-4.68 (1H, m), 5.87 (1H, d, J = 8.3 Hz), 6.75-7.53 (14H, m).

Anal. Calcd. for $C_{35}H_{41}N_3O_3S$: C, 72.01; H, 7.08; N, 7.20. Found: C, 71.88; H, 7.16; N, 7.15.

2-[2,3-*anti*-2-Ethyl-3-phenyl-3-(4-toluene)sulfonamido]propanoyl-3-phenyl-*l*-menthopyrazole (*anti*-**13c**).

This compound had ^{1}H nmr (deuteriochloroform): δ 0.61 (3H, d, J = 6.6 Hz), 0.83-0.94 (6H, m), 1.06 (3H, d, J = 6.6 Hz), 1.12-1.25 (1H, m), 1.39-1.56 (1H, m), 1.67-1.95 (4H, m), 2.29 (3H, s), 2.29-2.42 (1H, m), 2.52-2.59 (1H, m), 2.65-2.70 (1H, m), 4.14-4.19 (1H, m), 4.68-4.74 (1H, m), 6.42 (1H, d, J = 8.9 Hz), 6.99-7.44 (14H, m).

Anal. Calcd. for $C_{35}H_{41}N_3O_3S$: C, 72.01; H, 7.08; N, 7.20. Found: C, 71.69; H, 7.16; N, 7.16.

2-[2,3-*syn*-3-Phenyl-2-propyl-3-(4-toluene)sulfonamido]propanoyl-3-phenyl-*l*-menthopyrazole (*syn*-**13d**).

This compound had ^{1}H nmr (deuteriochloroform): δ 0.59 (3H, d, J = 6.6 Hz), 0.66-0.85 (3H, m), 0.92 (3H, d, J = 0.7 Hz), 1.01-1.27 (6H, m), 1.42-1.72 (3H, m), 1.86-1.96 (2H, m), 2.30-2.33 (1H, m), 2.33 (3H, s), 2.43-2.52 (1H, m), 2.61-2.74

(1H, m), 4.20-4.28 (1H, m), 4.61-4.71 (1H, m), 5.73 (1H, d, J = 5.6 Hz), 6.76-7.55 (14H, m).

Anal. Calcd. for $C_{36}H_{43}N_3O_3S$: C, 72.33; H, 7.25; N, 7.03. Found: C, 72.46; H, 7.45; N, 6.99.

2-[2,3-*anti*-3-Phenyl-2-propyl-3-(4-toluene)sulfonamido]propanoyl-3-phenyl-*l*-menthopyrazole (*anti*-**13d**).

This compound had ^{1}H nmr (deuteriochloroform): δ 0.60 (3H, d, J = 6.6 Hz), 0.66-0.95 (6H, m), 1.05 (3H, d, J = 6.9 Hz), 1.01-1.51 (4H, m), 1.58-1.66 (2H, m), 1.82-1.93 (2H, m), 2.30 (3H, s), 2.28-2.42 (1H, m), 2.53-2.58 (1H, m), 2.65-2.70 (1H, m), 4.26-4.31 (1H, m), 4.66-4.71 (1H, m), 6.42 (1H, d, J = 8.3 Hz), 7.01-7.46 (14H, m).

Anal. Calcd. for $C_{36}H_{43}N_3O_3S$: C, 72.33; H, 7.25; N, 7.03. Found: C, 72.26; H, 7.37; N, 7.05.

2-[2,3-*syn*-3-Phenyl-2-phenylmethyl-3-(4-toluene)sulfonamido]propanoyl-3-phenyl-*l*-menthopyrazole (*syn*-**13e**).

This compound had ^{1}H nmr (deuteriochloroform): δ 0.60 (3H, d, J = 6.6 Hz), 0.88 (3H, d, J = 6.6 Hz), 1.07 (3H, d, J = 6.9 Hz), 1.06-1.25 (1H, m), 1.38-1.50 (2H, m), 1.84-1.90 (2H, m), 2.34 (3H, s), 2.34-2.43 (1H, m), 2.58-2.66 (2H, m), 2.82-3.05 (1H, m), 4.47-4.62 (1H, m), 4.76-4.84 (1H, m), 6.09 (1H, m), 6.76-7.53 (19H, m).

Anal. Calcd. for $C_{40}H_{43}N_3O_3S$: C, 74.39; H, 6.71; N, 6.51. Found: C, 74.11; H, 6.85; N, 6.45.

2-[2,3-*anti*-3-Phenyl-2-phenylmethyl-3-(4-toluene)sulfonamido]propanoyl-3-phenyl-*l*-menthopyrazole (*anti*-**13e**).

This compound had ^{1}H nmr (deuteriochloroform): δ 0.61 (3H, d, J = 6.9 Hz), 0.89 (3H, d, J = 6.6 Hz), 1.07 (3H, d, J = 6.9 Hz), 1.08-1.23 (1H, m), 1.37-1.49 (2H, m), 1.81-1.92 (2H, m), 2.28 (3H, s), 2.42-2.64 (2H, m), 2.79-2.87 (1H, m), 3.01-3.08 (1H, m), 4.50-4.61 (2H, m), 6.69 (1H, d, J = 8.6 Hz), 6.94-7.38 (19H, m).

Anal Calcd. for $C_{40}H_{43}N_3O_3S$: C, 74.39; H, 6.71; N, 6.51. Found: C, 74.10; H, 6.81; N, 6.44.

Reaction of *N*-Acylpyrazoles with **6**.

With Lithium Diisopropylamide.

To a lithium diisopropylamide solution, which was prepared from diisopropylamine (1.5 mmoles) and butyllithium (1.6*M* in hexane, 1.4 mmoles) in tetrahydrofuran, *N*-acylpyrazole (1 mmole) was added at -78° under a nitrogen atmosphere. After stirring for 30 minutes at -78°, **6** (1.1 mmoles) in tetrahydrofuran (2 ml) was added with 30 minutes stirring at -78°. The mixture was quenched with acetic acid and extracted with dichloromethane. The organic layer was washed with dilute hydrochloric acid, water, aqueous sodium hydrogen carbonate and aqueous sodium chloride, dried over anhydrous magnesium sulfate, and concentrated. The residue was chromatographed on silica gel with benzene-hexane mixture as an eluent, and further purified by recrystallization from hexane.

With Diisopropylethylamine-Magnesium Bromide.

To a mixture of *N*-acylpyrazole (1 mmole), magnesium bromide-diethyl ether (1 mmole), and **6** (1.4 mmoles) in dichloromethane (4 ml), diisopropylethylamine (2 mmoles) in dichloromethane (1 ml) was added at -5° under a nitrogen atmosphere. After stirring for 1 hour, the mixture was worked up as described above.

3,4-*trans*-3-Methyl-1,4-diphenylazetidin-2-one (*trans*-**8a**).

The product was identified from authentic data [14], mp 101.0-104.5° (from hexane); ^{1}H nmr (deuteriochloroform): δ 1.48 (3H, d, J = 7.3 Hz), 3.13 (1H, m, J = 5.0 Hz), 4.58 (1H, d, J = 2.3 Hz), 7.00-7.06 (1H, m), 7.21-7.38 (9H, m).

3,4-*trans*-3-Ethyl-1,4-diphenylazetidin-2-one (*trans*-**8c**).

The product was identified from authentic data [14], mp 106.0-117.0° (from hexane); ^{1}H nmr (deuteriochloroform): δ 1.11 (3H, t, J = 7.4 Hz), 1.92-1.99 (2H, m), 3.02-3.08 (1H, m), 4.67 (1H, d, J = 2.3 Hz), 7.00-7.37 (10H, m).

3,4-*trans*-1,4-Diphenyl-3-propylazetidin-2-one (*trans*-**8d**).

This compound had ^{1}H nmr (deuteriochloroform): δ 0.94 (3H, t, J = 7.4 Hz), 1.50-1.58 (2H, m), 1.74-2.00 (2H, m), 3.07-3.13 (1H, m), 4.66 (1H, d, J = 2.3 Hz), 6.99-7.46 (10H, m).

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.24; H, 7.19; N, 5.44.

3,4-*trans*-1,4-Diphenyl-3-(phenylmethyl)azetidin-2-one (*trans*-**8e**).

This compound had mp 141-150.5° (from hexane); ^{1}H nmr (deuteriochloroform): δ 3.03-3.13 (1H, m), 3.30-3.42 (2H, m), 4.71 (1H, d, J = 2.0 Hz), 7.23-7.28 (15H, m).

Anal. Calcd. for $C_{22}H_{19}NO$: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.27; H, 6.21; N, 4.51.

The Reaction of **1e** with *N*-Methyl 4-toluenesulfonamide.

A mixture of **1e** (1.0 mmole), *N*-methyl 4-toluenesulfonamide (1.0 mmole) and boron trifluoride etherate (1.6 mmoles) in dry benzene (5 ml) was refluxed for 20 hours under a nitrogen atmosphere. After quenching with water, the mixture was extracted with benzene. The organic layer was washed with aqueous sodium hydrogen carbonate, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel with benzene-ethyl acetate (30:1 v/v) mixture to isolate *N*-methyl-*N*-(4-toluene)sulfonyl-3-phenylpropanamide, yield 66%; ^{1}H nmr (deuteriochloroform): δ 2.43 (3H, s), 2.88-3.03 (4H, m), 3.26 (3H, s), 7.09-7.35 (7H, m), 7.20 (2H, d, J = 8.4 Hz).

Hydrolysis of **3** and **13**.

N-(4-Toluene)sulfonamidoacylpyrazole **3** or **13**, (0.5 mmole) was dissolved in 20 ml of a mixture of water and tetrahydrofuran (1:2 v/v), and acidified with concentrated sulfuric acid (2 ml). After heating for 20 hours at 60°, the mixture was extracted with dichloromethane. The organic layer was washed with aqueous sodium chloride, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by recrystallization or by silica gel column chromatography with chloroform-acetone-methanol mixture (100:20:4 v/v) as an eluent.

2,3-*syn*-[2-Methyl-3-phenyl-3-(4-toluene)sulfonamido]propanoic Acid (*syn*-**4a**).

The product was identified from authentic data [13];, ^{1}H nmr (deuteriochloroform): δ 1.09 (3H, d, J = 6.9 Hz), 2.28 (3H, s), 2.79-2.90 (1H, m), 4.48-4.58 (1H, m), 6.46 (1H, d, J = 8.9 Hz), 6.98-7.10 (7H, m), 7.45-7.50 (2H, m).

2,3-*anti*-[2-Methyl-3-phenyl-3-(4-toluene)sulfoneamido]propanoic Acid (*anti*-**4a**).

The product was identified from authentic data [13]; ^{1}H nmr

(deuteriochloroform): δ 1.17 (3H, d, J = 6.9 Hz), 2.29 (3H, s), 2.79-2.90 (1H, m), 4.48-4.58 (1H, m), 6.31 (1H, d, J = 9.6 Hz), 6.98-7.10 (7H, m), 7.45-7.50 (2H, m).

Cyclization into **5**.

By the method of Abrahams *et al.* [13], **4** (1 mmole) was dissolved in dichloromethane (10 ml), and dicyclohexylcarbodiimide (1.30 mmoles) and 4-dimethylaminopyridine (0.11 mmole) were added. The mixture was stirred for 15 hours at room temperature. The precipitate was filtered and the solution was washed with dilute acetic acid and water, dried over anhydrous magnesium sulfate, and concentrated. The residue was chromatographed on silica gel with a dichloromethane-hexane mixture (1:1 v/v) as the eluent.

3,4-*cis*-3-Methyl-4-phenyl-1-(4-toluene)sulfonylazetidin-2-one (*cis*-**5a**).

The product was identified from authentic data [13], yield 67%; ^{1}H nmr (deuteriochloroform): δ 0.81 (3H, d, J = 7.6 Hz), 2.46 (3H, s), 3.54-3.65 (1H, m), 5.21 (1H, d, J = 6.6 Hz), 7.11-7.82 (9H, m).

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