Pergamon

Tetrahedron, Vol. 52, No. 31, pp. 10335-10346, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00550-9

Enantiomerically Enriched Preparation of Enolizable β-Keto Amides. Diastereoselective α-Acylation and Subsequent Aminolysis of 2-Acyl-3-phenyl-*l*-menthopyrazoles

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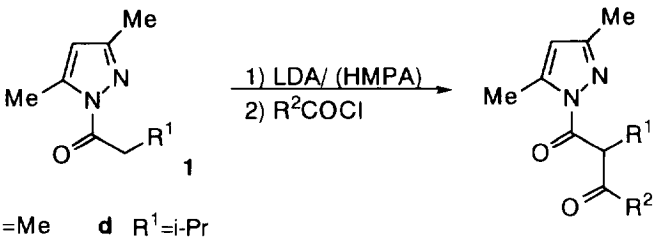
Abstract. After deprotonation with LDA, 2-acyl-3-phenyl-*l*-menthopyrazoles (**13**) were diastereomerically α-acylated to give N-(3-phenyl-*l*-menthopyrazolyl) β-keto amides (**14-19**). The subsequent amides were converted into the corresponding N-alkyl amides (**21-24**) retaining their enantiomeric enrichment on the α-position. These are the first examples of enolizable β-keto acid derivatives having only one chiral center at α-position. These chiral β-keto amides were surprisingly stable in dry benzene and their optical asymmetries were almost retained for two weeks at room temperature without any epimerization.

Recently we have been interested in the chemistry of N-acylpyrazoles, especially 2-acyl-3-phenyl-*l*-menthopyrazoles as chiral synthetic intermediates.[1] By 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 key intermediates for α-alkylation[6] and α-sulfenylation.[7] In the case of 2-acyl-3-phenyl-*l*-menthopyrazoles, highly diastereoselective α-alkylation was accomplished by diastereofacial attack of alkyl halides on the lithium enolate, which was rigidly fixed by intramolecular chelation between lithium and the N-1 atom.[6] For methodology using this auxiliary, the chemical behaviors of N-acylpyrazoles satisfy the requirements such as activation of the substrate moiety of substrate-auxiliary intermediate and the conversion of substrate-auxiliary intermediate into the desired functionalities. For the purpose of extension of the utility of N-acylpyrazoles as the substrate-auxiliary intermediate, a wide variety of the stereoselective reactions on the acyl moiety of N-acylpyrazoles are highly desired.

Since β-keto acid derivatives are easily enolized by intramolecular hydrogen bonding stabilization, the preparation of enantiomerically enriched α-monosubstituted β-keto acid derivative is generally very difficult. To the best of our knowledge, there is no report of any α-monosubstituted β-keto ester and amide having one asymmetric center at α-position, but the chiral imide type compounds were prepared with more than two asymmetric centers by α-acylation of N-acyloxazolidinones.[8] For the preparation of another type of enolizable β-keto acid derivatives, we report the α-acylation of N-acylpyrazoles, especially the diastereo-



a R^1=Me **d** R^1=i-Pr
b R^1=Et **e** R^1=Ph
c R^1=Pr **f** R^1=$PhCH_2$

2 R^2=Ph **8** R^2=t-Bu
3 R^2=Et **9** R^2=$PhCH_2$
4 R^2=Me **10** R^2=o-Tol
5 R^2=Pr **11** R^2=p-Tol
6 R^2=Bu **12** R^2=MeO
7 R^2=i-Bu

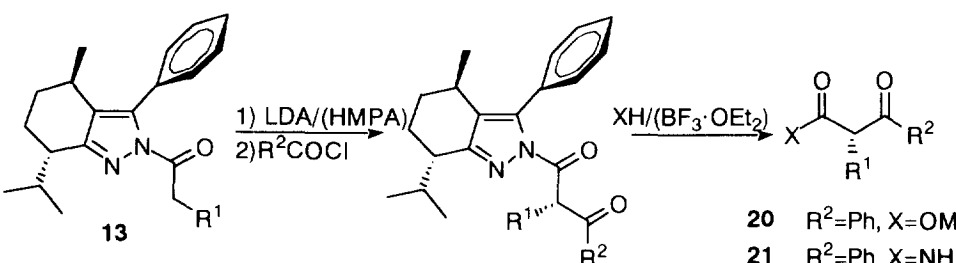
selective α-acylation using 3-phenyl-*l*-menthopyrazole as chiral auxiliary. Moreover, the chiral α-acylated products are converted into simple amides with retention of their chirality.

In order to determine optimal conditions and the limitations of the α-acylation reaction, 1-acyl-3,5-dimethylpyrazoles (**1**) were first treated with various acyl chlorides in the presence of LDA. When 1-propanoyl-3,5-dimethylpyrazole (**1a**) was treated with LDA and the resulting lithium enolate was treated with benzoyl chloride, 1-(2'-methyl-3'-phenyl-3'-oxo)propanoyl-3,5-dimethylpyrazole (**2a**) was obtained in 89 % yield. The addition of HMPA was not effective to the improvement of the yield of **2a**. On the contrary, the formation of 1-(2'-methyl-3'-oxo)butanoyl-3,5-dimethylpyrazole (**3a**) from **1a** and propanoyl chloride was depressed by the addition of HMPA and the O-acylated product was detected in the nmr spectrum of the crude product mixture. This deleterious effect upon the addition of HMPA was observed in every case using aliphatic acyl chlorides such as acetyl, propanoyl, and butanoyl chloride. Similar α-acylation on the acyl group of the 1-acyl-3,5-dimethylpyrazoles (**1**) is summarized in Table 1. Sterically hindered N-acylpyrazoles such as 2-methylpropanoyl and 3,3-dimethylbutanoyl derivatives did not give any β-keto acid derivatives. By using propanoic and benzoic anhydrides, the corresponding α-acylating products were also obtained in moderate yields.

Next, diastereoselective α-acylation of N-acylpyrazoles was undertaken using the 2-acyl-3-phenyl-*l*-menthopyrazoles (**13**). 2-Propanoyl-3-phenyl-*l*-menthopyrazole (**13a**) was treated with benzoyl chloride in the presence of 1.1 equimolar amount of LDA under the optimal conditions which were determined in the prior reactions using **1**. As a result, diastereomeric mixture of 2-(2'-methyl-3'-phenyl-3'-oxo)propanoyl-3-phenyl-*l*-menthopyrazole (**14a**) was obtained in 73 % yield with 79 % de, which was evaluated from a pair of nmr doublet peaks at δ 0.44 and 0.68 ppm assigned to the 4-Me protons of the menthopyrazole moiety.[9] The use of an excess amount of LDA did not show any remarkable change in either the yield or the de value. Similarly, the reactions of **13** with aliphatic and aromatic acyl chlorides were carried out as summarized in Table 2. The reaction of **13a** with 2,2-dimethylpropanoyl chloride was observed to be diastereoselective in nmr, while the de value was exceptionally low in the case using acetyl chloride. The resulting α-acylated products, which were the N-(3-phenyl-*l*-menthopyrazolyl) derivatives of β-keto amides, were quite stable to the epimerization, even with short contact with weak bases and acids such as dilute hydrochloric acid and

Table 1. α-Acylation of 1-Acyl-3,5-dimethylpyrazole (**1**)

	R^1	Acylating Agent	Additive	Product	Yield (%)
1a	Me	PhCOCl	none	**2a**	89
1a	Me	PhCOCl	HMPA	**2a**	91
1a	Me	$(PhCO)_2O$	none	**2a**	71
1b	Et	PhCOCl	HMPA	**2b**	86
1c	Pr	PhCOCl	HMPA	**2c**	85
1d	i-Pr	PhCOCl	HMPA	**2d**	43
1e	Ph	PhCOCl	HMPA	**2e**	63
1f	$PhCH_2$	PhCOCl	HMPA	**2f**	86
1a	Me	EtCOCl	none	**3a**	72
1a	Me	EtCOCl	HMPA	**3a**	59
1a	Me	$(EtCO)_2O$	none	**3a**	35
1b	Et	EtCOCl	none	**3b**	61
1c	Pr	EtCOCl	none	**3c**	61
1a	Me	MeCOCl	none	**4a**	86
1a	Me	PrCOCl	none	**5a**	93
1a	Me	BuCOCl	none	**6a**	95
1a	Me	i-BuCOCl	none	**7a**	82
1a	Me	t-BuCOCl	HMPA	**8a**	83
1a	Me	$PhCH_2COCl$	none	**9a**	28
1a	Me	o-TolCOCl	HMPA	**10a**	63
1a	Me	p-TolCOCl	HMPA	**11a**	90
1a	Me	MeOCOCl	HMPA	**12a**	47



13

a R^1=Me
b R^1=Et
d R^1=i-Pr
e R^1=Ph
f R^1=$PhCH_2$

14 R^2=Ph **17** R^2=i-Pr
15 R^2=Et **18** R^2=t-Bu
16 R^2=Me **19** R^2=p-Tol

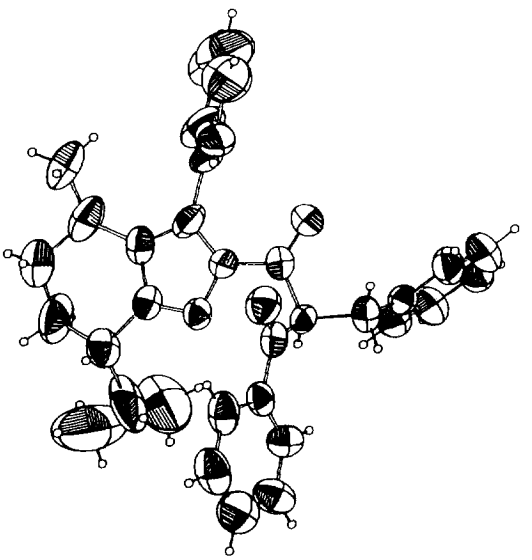
20 R^2=Ph, X=OMe
21 R^2=Ph, X=NHMe
22 R^2=i-Pr, X=NHMe
23 R^2=Ph, X=$NHCH_2Ph$
24 R^2=Ph, X=$N(CH_2)_4$

aqueous sodium hydrogen carbonate solution. Moreover, the separation of diastereomers was accomplished by silica gel column chromatography under ordinary conditions. These facts were reasonably explained by A(1,3) strain conformational effects like as the behaviors of N-(β-ketoacyl)oxazolidinones.[8b] The absolute configuration of the major α-acylated products was determined to be (2'S) by X-ray crystallographic analysis of **14f**, the ORTEP diagram of which is shown in Fig. 1.

Table 2. α-Acylation of 2-Acyl-3-phenyl-*l*-menthopyrazole (**13**)

	R^1	Acylating Agent	Additive	Product	Yield (%)	% De (Conf.)
13a	Me	PhCOCl	none	**14a**	96	84 (2'S)
13a	Me	PhCOCl	HMPA	**14a**	73	79 (2'S)
13b	Et	PhCOCl	HMPA	**14b**	82	80 (2'S)
13d	i-Pr	PhCOCl	HMPA	**14d**	81	80 (2'S)
13e	Ph	PhCOCl	HMPA	**14e**	85	54 (2'S)
13f	$PhCH_2$	PhCOCl	HMPA	**14f**	94	68 (2'S)
13a	Me	EtCOCl	none	**15a**	84	58 (2'S)
13b	Et	EtCOCl	none	**15b**	85	57 (2'S)
13a	Me	MeCOCl	none	**16a**	72	9 (2'S)
13a	Me	i-PrCOCl	none	**17a**	80	50 (2'S)
13a	Me	t-BuCOCl	none	**18a**	87	>95 (2'S)
13a	Me	p-TolCOCl	none	**19a**	75	87 (2'S)

Fig. 1 The ORTEP Diagram of
2-(2'-Benzyl-3'-phenyl-3'-oxo)propanoyl-3-phenyl-*l*-menthopyrazole (**14f**).



Finally, diastereomerically enriched **14** were converted into simple β−keto acid derivatives. Although ethyl 2-methyl-3-phenyl-3-oxopropanoate (**20a**) was obtained in good yield by the alcoholysis of **14a** with $BF_3{\cdot}OEt_2$, optical activity was completely lost. When methyl amine was passed into a toluene-hexane solution of **14a** at -78°C, the desired N-methyl amide (**21a**) precipitated. The $[\alpha]_D^{20}$ value of **21a** in dry benzene was measured to be -14.0°, while the ee was determined to be 15 % from the nmr spectrum using chiral europium shift reagent. On standing for 2 weeks at room temperature, about 90 % of this chirality in benzene was retained and the epimerization of **21a** was surprisingly slow. Also the chirality of **21a** was kept on silica gel chromatography. Similarly the enantiomerically enriched β-keto amides (**21b**, **21f**, **22a**, **23a** and **24a**) were obtained from **14a-b**, **14f**, and **17a** by treatment with methyl amine, benzyl amine and pyrrolidine, as listed in Table 3. However enantiomerically enriched N-unsubstituted β-keto amide could not be obtained from **14a** with liquid ammonia in toluene-hexane solution, and epimarization of **14a** was only observed. When **18a** was treated with methyl amine, N-methyl 2,2-dimethylproanamide and 3-phenyl-*l*-menthopyrazole were formed through retro condensation reaction and any desired β-keto amide could not be detected.

Table 3. The Preparation of Enantiomerically Enriched β-Keto Amides

Substrate	R^1	R^2	X	β-Keto Amide	Yield	Opt. Yield	$[\alpha]_D^{20}$ (% ee)[a]
14a	Me	Ph	NHMe	**21a**	84 %	20 %	-14.0° (17 %)
14b	Et	Ph	NHMe	**21b**	63 %	9 %	-22.4° (6 %)
14f	$PhCH_2$	Ph	NHMe	**21f**	55 %	51 %	-1.3° (41 %)
17a	Me	i-Pr	NHMe	**22a**	20 %	59 %	
14a	Me	Ph	NHBn	**23a**	51 %	10 %	-1.8° (8 %)
14a	Me	Ph	$N(CH_2)_4$	**24a**	75 %	4 %	-0.6° (3 %)

a: Enantiomer excess values of the solution in optical rotation measurement were represented in the parentheses.

In conclusion, 2-acyl-3-phenyl-*l*-menthopyrazoles (**13**) were diastereomerically α−acylated to give N-(3-phenyl-*l*-menthopyrazolyl) β−keto amides (**14-19**). By treatment with amines, amides **14-19** were converted into the corresponding amides (**21-24**) as enantiomerically enriched form on α−position. These are the first examples of enolizable β−keto acid derivatives having one chiral center at α−position. These chiral β−keto amides were surprisingly stable in dry benzene and their optical asymmetries were almost retained without any epimerization.

Experimental Section

Melting points are uncorrected. NMR spectra were obtained on JEOL JNM-EX270 (270 MHz) and Varian GEMINI 200 (200 MHz) spectrometers in $CDCl_3$ with TMS as an internal standard. Specific rotations were measured on a JASCO DIP-360 digital polarimeter.

Materials. N-acyl-3,5-dimethylpyrazoles (**1a-f**), and 2-acyl-3-phenyl-*l*-menthopyrazoles (**13a-b**, **13d-f**) were prepared from the corresponding pyrazoles according to the method reported in the previous paper.[1,3,6] The crude products were purified by the column chromatography on silica gel using benzene-hexane mixture as an eluent, and by recrystallization or distillation under reduced pressure by Kugelrohr.

General α-Acylation of N-Acylpyrazoles. To the solution of diisopropylamine (1.2 mmol) in THF (10 ml), 1.1 mmol of butyllithium solution (1.6 M in hexane) was added under nitrogen atmosphere at -78 °C. After stirring the solution for 30 min at rt, HMPA (2 ml) was added, and then N-acylpyrazole (1.1 mmol) were successively added at -78 °C with the continuous stirring for 30 min. The acylating reagent (1.1 mmol) was added and the mixture was kept for another 30 min at -78 °C. The reaction mixture was quenched with acetic acid and the products were extracted with CH_2Cl_2. The organic layer was washed with water, dilute HCl, aqueous $NaHCO_3$, and aqueous NaCl. After drying the solution over anhydrous $MgSO_4$, the solvent was removed under reduced pressure. The residue was chromatographed on silica gel using a hexane-benzene mixture.

1-(2'-Methyl-3'-phenyl-3'-oxo)propanoyl-3,5-dimethylpyrazole (2a).
^{1}H NMR (270 MHz); δ 1.52 (3H, d, J=7 Hz), 2.03 (3H, s), 2.52 (3H, d, J=1 Hz), 5.56 (1H, q, J=7 Hz), 5.90 (1H, d, J=1 Hz), 7.42-7.58 (3H, m), 8.00-8.04 (2H, d, J=8 Hz); Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.32; H, 6.28; N, 10.88.

1-(2'-Ethyl-3'-phenyl-3'-oxo)propanoyl-3,5-dimethylpyrazole (2b).
Yield 86 % ; bp 70°C/ 2 mmHg; ^{1}H NMR (270 MHz); δ 1.04 (3H, t, J=7 Hz), 2.06 (3H, s), 1.97-2.15 (2H, m), 2.55 (3H, d, J=1 Hz), 5.55 (1H, dd, J=8, 6 Hz), 5.91 (1H, d, J=1 Hz), 7.44-7.57 (3H, m), 8.03-8.07 (2H, d, J=8 Hz); Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36; Found: C, 71.13; H, 6.64; N, 9.99.

1-(2'-Propyl-3'-phenyl-3'-oxo)propanoyl-3,5-dimethylpyrazole (2c).
Yield 85 %; bp 70°C/ 2 mmHg; ^{1}H NMR (270 MHz); δ 0.95 (3H, t, J=7 Hz), 1.37-1.52 (2H, m J=7 Hz), 1.87-1.93 (1H, m), 2.06 (3H, s), 2.05-2.13 (1H, m), 2.54 (3H, d, J=1 Hz), 5.58 (1H, dd, J=8, 5 Hz), 5.91 (1H, s), 7.44-7.60 (3H, m), 8.03-8.07 (2H, d, J=8 Hz); Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85; Found: C, 71.63; H, 6.98; N, 9.86.

1-[2'-Isopropyl-3'-phenyl-3'-oxo]propanoyl-3,5-dimethylpyrazole (2d).
Yield 43 %; bp 67°C/ 2 mmHg; ^{1}H NMR (270 MHz); δ 0.96 (3H, d, J=7 Hz), 1.06 (3H, d, J=7 Hz), 2.10 (3H, s), 2.52 (3H, d, J=1 Hz), 2.71 (1H, m), 5.60 (1H, d, J=7 Hz), 5.90 (1H, s), 7.24-7.57 (3H, m), 8.13 (2H, d, J=8 Hz); Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85; Found: C, 71.71; H, 7.04; N, 9.78.

1-(2',3'-Diphenyl-3'-oxo)propanoyl-3,5-dimethylpyrazole (2e).
Yield 63 %; ^{1}H NMR (270 MHz); δ 2.08 (3H, s), 2.55 (3H, d, J=1 Hz), 5.93 (1H, d, J=1 Hz), 6.89 (1H, s), 7.25-7.57 (8H, m), 8.01 (2H, d, J=7 Hz); Anal. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80; Found: C, 75.47; H, 5.82; N, 8.69.

1-(2'-Benzyl-3'-phenyl-3'-oxo)propanoyl-3,5-dimethylpyrazole (2f).
Yield 86 %; ^{1}H NMR (270 MHz); δ 1.19 (3H, s), 2.48 (3H, s), 3.31 (2H, ABX, J=14, 8 Hz), 5.83 (1H, s), 5.91 (1H, t, J=8 Hz), 7.09-7.51 (8H, m), 7.99 (2H, d, J=8 Hz); Anal. Calcd for $C_{21}H_{20}N_2O_2$: C, 75.88; H, 6.06; N, 8.43; Found: C, 75.50; H, 6.14; N, 8.34.

1-(2'-Methyl-3'-oxo)pentanoyl-3,5-dimethylpyrazole (3a).
^{1}H NMR (270 MHz); δ 1.09 (3H, t, J=7 Hz), 1.40 (3H, d, J=7 Hz), 2.17 (3H, s), 2.53 (3H, d, J=1 Hz), 2.72 (2H, ABX_3, J=15, 7 Hz), 4.68 (1H, q, J=7 Hz), 5.94 (1H, d, J=1 Hz); Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.48; H, 7.80; N, 13.59.

1-(2'-Ethyl-3'-oxo)pentanoyl-3,5-dimethylpyrazole (3b).
Yield 61 %; bp 50°C/ 2 mmHg; ^{1}H NMR (270 MHz); δ 1.02 (3H, t, J=7 Hz), 1.08 (3H, t, J=7 Hz), 1.79-2.16 (2H, m), 2.19 (3H, s), 2.54 (3H, d, J=1 Hz), 2.70 (2H, ABX_3, J=18, 7 Hz), 4.62 (1H, dd, J=6, 8 Hz), 5.94 (1H, s); Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.6; Found: C, 64.65; H, 8.17; N, 12.58.

1-(2'-Propyl-3'-oxo)pentanoyl-3,5-dimethylpyrazole (3c).
Yield 61 %; bp 55°C/ 2 mmHg; ^{1}H NMR (270 MHz); δ 0.96 (3H, t, J=7 Hz), 1.07 (3H, t, J=7 Hz), 1.32-1.51 (1H, m), 1.69-1.83 (1H, m), 1.93-2.07 (1H, m), 2.19 (3H, s), 2.53 (3H, d, J=1 Hz), 2.70 (2H, ABX_3, J=18, 7 Hz), 4.70 (1H, dd, J=6, 9 Hz), 5.94 (1H, s); Anal. Calcd for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.85; Found: C, 65.97; H, 8.56; N, 12.04.

1-(2'-Methyl-3'-oxo)butanoyl-3,5-dimethylpyrazole (4a).
Yield 86 %; bp 30°C/ 2 mmHg; ^{1}H NMR (270 MHz); δ 1.23 (3H, t, J=7 Hz), 2.23 (3H, s), 2.54 (3H, d, J=1 Hz), 3.12 (2H, q, J=7 Hz), 5.94 (1H, s); Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.42; Found: C, 61.69; H, 7.34; N, 14.52.

1-(2'-Methyl-3'-oxo)hexanoyl-3,5-dimethylpyrazole (5a).
Yield 93 %; bp 47°C/ 2 mmHg; ^{1}H NMR (270 MHz); δ 0.93 (3H, t, J=7 Hz), 1.40 (3H, d, J=7 Hz), 1.64 (2H, sext, J=7 Hz), 2.18 (3H, s), 2.54 (3H, s), 2.65 (2H. ABX_2, J=18, 7 Hz), 4.67 (1H, q, J=7 Hz), 5.94 (1H, s); Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.6; Found: C, 66.06; H, 8.51; N, 11.88.

1-(2'-Methyl-3'-oxo)heptanoyl-3,5-dimethylpyrazole (6a).
Yield 95 %; bp 50°C/ 2 mmHg; ^{1}H NMR (270 MHz); δ 0.906 (3H, t, J=7 Hz), 1.22-1.37 (2H, m), 1.40 (3H, d, J=7 Hz), 1.54-1.65 (2H, m), 2.18 (3H, s), 2.53 (3H, d, J=1 Hz), 2.70 (2H, ABX_2, J=17, 7 Hz), 4.67 (1H, q, J=7 Hz), 5.93 (1H, d, J=1 Hz); Anal. Calcd for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.85; Found: C, 66.06; H, 8.51; N, 11.88.

1-(2',5'-Dimethyl-3'-oxo)hexanoyl-3,5-dimethylpyrazole (7a).
Yield 82 %; bp 35°C/ 2 mmHg; ^{1}H NMR (270 MHz); δ 0.92 (3H, d, J=7 Hz), 0.93 (3H, d, J=7 Hz), 1.39 (3H, d, J=7 Hz), 1.93-2.29 (1H, m), 2.18 (3H, s), 2.54 (3H, d, J=1 Hz), 2.55 (2H, ABX, J=17, 7 Hz), 4.65 (1H, q, J=7 Hz), 5.94 (1H, s); Anal. Calcd for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.85; Found: C, 66.19; H, 8.60; N, 12.06.

1-(2',4',4'-Trimethyl-3'-oxo)pentanoyl-3,5-dimethylpyrazole (8a).
Yield 83 % ; ^{1}H NMR (270 MHz); δ 1.27 (9H, s), 1.70 (3H, d, J=7 Hz), 2.20 (3H, s), 2.30 (3H, s), 5.34 (1H, q, J=7 Hz), 5.81 (1H, s); Anal. Calcd for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.85; Found: C, 65.97; H, 8.54; N, 11.82.

1-(2'-Methyl-4'-phenyl-3'-oxo)butanoyl-3,5-dimethylpyrazole (9a).
Yield 28 %; bp 64°C/ 2 mmHg; ^{1}H NMR (270 MHz); δ 1.35 (3H, d, J=7 Hz), 2.21 (3H, s), 2.51 (3H, d, J=1 Hz), 4.74 (2H, AB-q, J=14 Hz), 4.00 (1H, q, J=7 Hz), 5.94 (1H, s), 7.22-7.28 (5H, m); Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36; Found: C, 71.06; H, 6.71; N, 10.46.

1-(2'-Methyl-3'-*o*-toloyl-3'-oxo)propanoyl-3,5-dimethylpyrazole (10a).
Yield 63 %; ^{1}H NMR (270 MHz); δ 1.49 (3H, d, J=7 Hz), 2.09 (3H, s), 2.44 (3H, s), 2.51 (3H, s), 5.35 (1H, q, J=7 Hz), 5.88 (1H, s), 7.20-7.31 (3H, m), 7.95 (1H, d, J=7 Hz); Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36; Found: C, 71.33; H, 6.73; N, 10.40.

1-(2'-Methyl-3'-*p*-toloyl-3'-oxo)propanoyl-3,5-dimethylpyrazole (11a).
Yield 90 %; ^{1}H NMR (270 MHz); δ 1.51 (3H, d, J=7 Hz), 2.06 (3H, s), 2.41 (3H, s), 2.54 (3H, d, J=1 Hz), 5.55 (1H, q, J=7 Hz), 5.91 (1H, d, J=1 Hz), 7.26 (2H, d, J=8 Hz), 7.93 (2H, d, J=8 Hz); Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36; Found: C, 71.05; H, 6.69; N, 10.30.

1-(2'-Methoxycarbonyl)propanoyl-3,5-dimethylpyrazole (12a).
Yield 47 % ; ^{1}H NMR (270 MHz); δ 1.52 (3H, d, J=7 Hz), 2.20 (3H, s), 2.54 (3H, d, J=1 Hz), 3.71 (3H, s), 4.64 (1H, q, J=7 Hz), 5.97 (1H, s); Anal. Calcd for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.33; Found: C, 57.08; H, 6.71; N, 13.22.

2-(2'-Methyl-3'-phenyl-3'-oxo)propanoyl-3-phenyl-*l*-menthopyrazole (14a).
Anal. Calcd for $C_{28}H_{32}N_2O_2$: C, 78.47; H, 7.53; N, 6.54. Found: C, 78.18; H, 7.40; N, 6.63.
2'R-Diastereomer ^{1}H NMR (270 MHz); δ 0.43 (3H, d, J=7 Hz), 0.69 (3H, d, J=7 Hz), 0.76 (3H, d, J=7 Hz), 0.89 (3H, t, J=8 Hz), 0.95 (1H, m), 1.42 (1H, m), 1.77 (1H, m), 1.90 (2H, m), 2.06 (2H, m), 2.47 (1H, m), 2.74 (1H, m), 5.52 (1H, dd, J=6, 8 Hz), 7.23-7.55 (8H, m), 8.05 (2H, d, J=7 Hz).
2'S-Diastereomer ^{1}H NMR (270 MHz); δ 0.64 (3H, d, J=7 Hz), 0.82 (3H, d, J=7 Hz), 0.90 (3H, d, J=7 Hz), 0.97 (3H, t, J=8 Hz), 1.01 (1H, m), 1.41 (1H, m), 1.77 (1H, m), 1.90 (2H, m), 2.07 (2H, m), 2.36 (1H, m), 2.73 (1H, m), 5.42 (1H, dd, J=6, 8 Hz), 7.23-7.55 (8H, m), 8.05 (2H, d, J=7 Hz).

2-(2'-Ethyl-3'-phenyl-3'-oxo)propanoyl-3-phenyl-*l*-menthopyrazole (14b).
Anal. Calcd for $C_{28}H_{32}N_2O_2$: C, 78.47; H, 7.53; N, 6.54. Found: C, 78.32; H, 7.67; N, 6.51.
2'R-Diastereomer ^{1}H NMR (270 MHz); δ 0.42 (3H, d, J=7 Hz), 0.70 (3H, d, J=7 Hz), 0.76 (3H, d, J=7 Hz), 1.02 (3H, t, J=7 Hz), 1.20 (1H, m), 1.35 (1H, m), 1.78 (2H, m), 1.90 (2H, m), 2.10 (1H, m), 2.47 (1H, m), 2.69 (1H, m), 5.50 (1H, dd, J=6, 8 Hz), 7.40 (8H, m), 8.08 (2H, m).
2'S-Diastereomer ^{1}H NMR (270 MHz); δ 0.64 (3H, d, J=7 Hz), 0.80 (3H, d, J=7 Hz), 0.90 (3H, d, J=7 Hz), 0.97 (3H, t, J=7 Hz), 1.20 (1H, m), 1.40 (1H, m), 1.76 (1H, m), 1.91 (2H, m), 2.05 (2H, m), 2.35 (1H, m), 2.74 (1H, m), 5.40 (1H, dd, J=6, 8 Hz), 7.35 (5H, m), 7.48 (3H, m), 8.05 (2H, m).

2-(2'-Isopropyl-3'-phenyl-3'-oxo)propanoyl-3-phenyl-*l*-menthopyrazole (14d).
Anal. Calcd for $C_{29}H_{34}N_2O_2$: C, 78.7; H, 7.74; N, 6.33. Found: C, 78.55; H, 7.82; N, 6.35.
2'R-Diastereomer ^{1}H NMR (270 MHz); δ 0.63 (3H, d, J=7 Hz), 0.69 (3H, d, J=7 Hz), 0.77-0.87 (6H, m), 1.01 (3H, d, J=7 Hz), 1.23 (1H, m), 1.49 (1H, m), 1.85 (2H, m), 2.48 (2H, m), 2.63 (1H, m), 2.80 (1H, m), 5.53 (1H, d, J=8 Hz), 7.28-7.37 (5H, m), 7.46-7.54 (3H, m), 8.10 (2H, m).
2'S-Diastereomer ^{1}H NMR (270 MHz); δ 0.77-0.87 (12H, m), 1.01 (3H, d, J=7 Hz), 1.23 (1H, m), 1.49 (1H, m), 1.85 (2H, m), 2.48 (2H, m), 2.63 (1H, m), 2.80 (1H, m), 4.84 (1H, d, J=10 Hz), 7.28-7.37 (5H, m), 7.46-7.54 (3H, m), 7.95-7.99 (2H, m).

2-(2',3'-Diphenyl-3'-oxo)propanoyl-3-phenyl-*l*-menthopyrazole (14e).
Anal. Calcd for $C_{32}H_{32}N_2O_2$: C, 80.64; H, 6.77; N, 5.88. Found: C, 80.61; H, 6.73; N, 5.88.
2'R-Diastereomer ^{1}H NMR (270 MHz); δ 0.45 (3H, d, J=7 Hz), 0.70 (3H, d, J=7 Hz), 0.74 (3H, d, J=7 Hz), 1.19 (1H, m), 1.36 (1H, m), 1.45 (3H, d, J=7 Hz), 1.78 (1H, m), 1.87 (2H, m), 2.44 (1H, m), 2.69 (2H, m), 5.57 (1H, q, J=7 Hz), 7.38-7.60 (13H, m), 8.05 (2H, d, J=7 Hz).

2'S-Diastereomer ^{1}H NMR (270 MHz); δ 0.65 (3H, d, J=7 Hz), 0.76 (3H, d, J=7 Hz), 0.86 (3H, d, J=7 Hz), 1.20 (1H, m), 1.44 (1H, m), 1.44 (3H, d, J=7 Hz), 1.71-1.81 (1H, m), 1.84-2.03 (2H, m), 2.31-2.39 (1H, m), 2.69-2.80 (1H, m), 5.47 (1H, q, J=7 Hz), 7.33-7.59 (13H, m), 8.03 (2H, d, J=7 Hz).

2-(2'-Benzyl-3'-phenyl-3'-oxo)propanoyl-3-phenyl-*l*-menthopyrazole (14f).

Anal. Calcd for $C_{33}H_{34}N_2O_2$: C, 80.78; H, 6.99; N, 5.71. Found: C, 80.92; H, 6.96; N, 5.70.

2'R-Diastereomer ^{1}H NMR (270 MHz); δ 0.43 (3H, d, J=7 Hz), 0.65 (3H, d, J=8 Hz), 0.74 (3H, d, J=7 Hz), 1.07 (1H, m), 1.35 (1H, m), 1.70 (1H, m), 1.84 (1H, m), 2.00 (1H, m), 2.43 (1H, m), 2.68 (1H, m), 3.18 (1H, m), 3.44 (1H, m), 5.94 (1H, t, J=7 Hz), 7.01-7.45 (13H, m), 7.92 (2H, d, J=10 Hz).

2'S-Diastereomer ^{1}H NMR (270 MHz); δ 0.62 (3H, d, J=7 Hz), 0.78 (3H, d, J=7 Hz), 0.87 (3H, d, J=7 Hz), 1.07 (1H, m), 1.35 (1H, m), 1.70 (1H, m), 1.84 (1H, m), 2.00 (1H, m), 2.33 (1H, m), 2.68 (1H, m), 3.18 (1H, m), 3.44 (1H, m), 5.84 (1H, t, J=7 Hz), 7.01-7.45 (13H, m), 7.92 (2H, d, J=10 Hz).

2-(2'-Methyl-3'-oxo)pentanoyl-3-phenyl-*l*-menthopyrazole (15a).

Bp 110°C/ 5 mmHg; Anal. Calcd for $C_{23}H_{30}N_2O_2$: C, 75.37; H, 8.25; N, 7.64. Found: C, 75.09; H, 8.14; N, 7.97.

2'R-Diastereomer ^{1}H NMR (270 MHz); δ 0.68 (3H, d, J=7 Hz), 0.92 (3H, d, J=7 Hz), 1.05-1.14 (6H, m), 1.26 (1H, m), 1.33 (3H, d, J=7 Hz), 1.49 (1H, m), 1.80-1.99 (2H, m), 2.33 (1H, m), 2.52-2.89 (4H, m), 4.63 (1H, q, J=7 Hz), 7.34-7.42 (5H, m).

2'S-Diastereomer ^{1}H NMR (270 MHz); δ 0.74 (3H, d, J=7 Hz), 0.86 (3H, d, J=7 Hz), 1.02-1.07 (6H, m), 1.26 (1H, m), 1.49 (3H, d, J=7 Hz), 1.49 (1H, m), 1.80-1.99 (2H, m), 2.20 (2H, dq, J=0.1, 8 Hz), 2.48 (1H, m), 2.63 (1H, m), 2.79 (1H, m), 5.10 (1H, q, J=7 Hz), 7.34-7.42 (5H, m).

2-(2'-Ethyl-3'-oxo)pentanoyl-3-phenyl-*l*-menthopyrazole (15b).

Anal. Calcd for $C_{24}H_{32}N_2O_2$: C, 75.75; H, 8.48; N, 7.36. Found: C, 75.90; H, 8.78; N, 7.55.

2'R-Diastereomer ^{1}H NMR (270 MHz); δ 0.68 (3H, d, J=7 Hz), 0.92 (3H, d, J=7 Hz), 0.96 (3H, t, J=7 Hz), 1.07 (3H, d, J=7 Hz), 1.09 (3H, t, J=7 Hz), 1.26 (1H, m), 1.50 (1H, m), 1.89 (4H, m), 2.38 (2H, m), 2.58 (2H, m), 2.80 (1H, m), 4.55 (1H, dd, J=8, 7 Hz), 7.35 (5H, m).

2'S-Diastereomer ^{1}H NMR (270 MHz); δ 0.76 (3H, d, J=7 Hz), 0.79 (3H, t, J=7 Hz), 0.86 (3H, d, J=7 Hz), 1.06 (3H, d, J=7 Hz), 1.09 (3H, t, J=7 Hz), 1.26 (1H, m), 1.50 (1H, m), 1.88 (4H, m), 2.32 (2H, q, J=7 Hz), 2.46 (1H, m), 2.65 (1H, m), 2.78 (1H, m), 4.88 (1H, t, J=7 Hz), 7.40 (5H, m).

2-(2'-Methyl-3'-oxo)butanoyl-3-phenyl-*l*-menthopyrazole (16a).

Bp 106°C/ 5 mmHg; Anal. Calcd for $C_{22}H_{28}N_2O_2$: C, 74.97; H, 8.01; N, 7.95. Found: C, 75.09; H, 8.14; N, 7.97.

2'R-Diastereomer ^{1}H NMR (270 MHz); δ 0.68 (3H, d, J=7 Hz), 0.93 (3H, d, J=7 Hz), 1.06 (3H, d, J=7 Hz), 1.23 (1H, m), 1.35 (3H, d, J=7 Hz), 1.50 (1H, m), 1.90 (2H, m), 2.37 (1H, m), 2.36 (3H, s), 2.58 (1H, m), 2.76 (1H, m), 4.63 (1H, q, J=7 Hz), 7.37 (5H, m).

2'S-Diastereomer ^{1}H NMR (270 MHz); δ 0.74 (3H, d, J=7 Hz), 0.86 (3H, d, J=7 Hz), 1.06 (3H, d, J=7 Hz), 1.23 (1H, m), 1.35 (3H, d, J=7 Hz), 1.50 (1H, m), 1.90 (2H, m), 2.37 (1H, m), 2.36 (3H, s), 2.58 (1H, m), 2.76 (1H, m), 5.14 (1H, q, J=7 Hz), 7.37 (5H, m).

2-(2',4'-Dimethyl-3'-oxo)pentanoyl-3-phenyl-*l*-menthopyrazole (17a).

Bp 105°C/ 3 mmHg; Anal. Calcd for $C_{24}H_{32}N_2O_2$: C, 75.75; H, 8.48; N, 7.36. Found: C, 75.87; H, 8.64; N, 7.33.

2'R-Diastereomer ^{1}H NMR (270 MHz); δ 0.68 (3H, d, J=7 Hz), 0.89 (3H, d, J=7 Hz), 1.06 (3H, d, J=7 Hz), 1.17 (3H, d, J=7 Hz), 1.21 (3H, d, J=7 Hz), 1.20 (1H, m), 1.35 (3H, d, J=7 Hz), 1.50 (1H, m), 1.89 (2H, m), 2.37 (1H, m), 2.56 (1H, m), 2.75 (1H, m), 3.05 (1H, sept, J=7 Hz), 4.85 (1H, q, J=7 Hz), 7.35 (5H, m).

2'S-Diastereomer ^{1}H NMR (270 MHz); δ 0.75 (3H, d, J=7 Hz), 0.87 (3H, d, J=7 Hz), 1.05 (3H, d, J=7 Hz), 1.11 (6H, d, J=7 Hz), 1.26 (1H, m), 1.48 (3H, d, J=7 Hz), 1.48 (1H, m), 1.89 (2H, m), 2.50 (2H, m), 2.64 (1H, m), 2.80 (1H, m), 5.05 (1H, q, J=7 Hz), 7.40 (5H, m).

(2'S)-2-(2',4',4'-Trimethyl-3'-oxo)pentanoyl-3-phenyl-*l*-menthopyrazole (18a).

Bp 140°C/ 5 mmHg; ^{1}H NMR (270 MHz); δ 0.78 (3H, d, J=7 Hz), 0.86 (3H, d, J=7 Hz), 1.05 (3H, d, J=7 Hz), 1.12 (1H, m), 1.15 (9H, s), 1.49 (3H, d, J=7 Hz), 1.50 (1H, m), 1.85 (2H, m), 2.44 (1H, m), 2.61 (1H, m), 2.80 (1H, m), 5.03 (1H, q, J=7 Hz), 7.32-7.46 (5H, m); Anal. Calcd for $C_{25}H_{34}N_2O_2$: C, 76.10; H, 8.69; N, 7.10. Found: C, 76.39; H, 8.82; N, 7.39.

2-(2'-Methyl-3'-*p*-tolyl-3'-oxo)propanoyl-3-phenylmenthopyrazole (19a).

Anal. Calcd for $C_{28}H_{32}N_2O_2$: C, 78.47; H, 7.53; N, 6.54. Found: C, 78.22; H, 7.51; N, 6.58.

2'R-Diastereomer ^{1}H NMR (270 MHz); δ 0.47 (3H, d, J=7 Hz), 0.70 (3H, d, J=7 Hz), 0.87 (3H, d, J=7 Hz), 1.20 (1H, m), 1.42 (3H, d, J=7 Hz), 1.43 (1H, m), 1.75 (1H, m), 1.90 (1H, m), 2.00 (1H, m), 2.39 (1H, m), 2.43 (3H, s), 2.74 (1H, m), 5.57 (1H, q, J=7 Hz), 7.30 (2H, d, J=8 Hz), 7.36 (5H, m), 7.95 (2H, d, J=8 Hz).

2'S-Diastereomer ^{1}H NMR (270 MHz); δ 0.66 (3H, d, J=7 Hz), 0.77 (3H, d, J=7 Hz), 0.87 (3H, d, J=7 Hz), 1.20 (1H, m), 1.42 (3H, d, J=7 Hz), 1.43 (1H, m), 1.75 (1H, m), 1.90 (1H, m), 2.00 (1H, m), 2.39 (1H, m), 2.43 (3H, s), 2.74 (1H, m), 5.46 (1H, q, J=7 Hz), 7.30 (2H, d, J=8 Hz), 7.36 (5H, m), 7.95 (2H, d, J=8 Hz).

Conversion of 14a into 20a. The mixture of **14a** (134 mg, 0.326 mmol) and BF_3·OEt_2 (142 mg, 1.0 mmol) in ethanol (3 ml) was refluxed for 15 h. After quenched with water, products were extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$, and concentrated. The residue was chromatographed on silica gel with benzene to isolate **20a**, yield 40 %; $[\alpha]_D^{25}$ 0° (c=3.75, MeOH).

Conversion of 2-(β-Ketoacyl)-3-phenyl-*l*-menthopyrazoles into N-Methyl β-Keto Amides. Methyl amine, which was generated from aqueous methyl amine (40%, 2 ml) and solid sodium hydroxide, was passed into the solution of 2-acyl-3-phenyl-*l*-menthopyrazole (**14** or **17**, 0.67 mmol) in toluene (2 ml) and hexane (15 ml) at -78°C for 30 min. The precipitate was formed by warming up to room temperature. By the filtration, N-methyl amide was isolated as a pure form without any signal of the impurity in ^{1}H NMR and HPLC. The optical purity was evaluated from the ^{1}H NMR signals using the chiral Eu(tfc)3. The specific rotation of this precipitate was measured in dry benzene. In the case of **21a**, specific rotation was found to be $[\alpha]_D^{20}$ -14.0° (benzene, c=0.598), which was changed into $[\alpha]_D^{20}$ -11.8° (benzene, c=0.598) on standing for 2 weeks at room temperature.

N-Methyl 2-Methyl-3-phenyl-3-oxopropanamide (21a).

Yield 68 %; mp 136.5-137.5°C (from Hexane); $[\alpha]_D^{20}$: -14.0° (c 0.598, benzene, ee=17 %); ^{1}H NMR (270 MHz); δ 1.53 (3H, d, J=7 Hz), 2.80 (3H, d, J=5 Hz), 4.42 (1H, q, J=7 Hz), 6.51 (1H, broad s), 7.46-8.04 (5H, m).

N-Methyl 2-Ethyl-3-phenyl-3-oxopropanamide (21b).
Yield 63 %; mp 130-131°C (from Hexane); $[\alpha]_D^{20}$: -22.4° (c 0.449, benzene, ee=6 %); ^{1}H NMR (270 MHz); δ 0.96 (3H, t, J=8 Hz), 1.88-2.14 (2H, m), 2.80 (3H, d, J=5 Hz), 4.32 (1H, t, J=7 Hz), 6.61 (1H, broad s), 7.46-7.64 (3H, m), 8.01-8.05 (2H, dd, J=8, 1 Hz).

N-Methyl 2-Benzyl-3-phenyl-3-oxopropanamide (21f).
Yield 55 %; mp 107.5-108.5°C (from Hexane); $[\alpha]_D^{20}$: -1.3° (c 0.185, benzene, ee=41 %); ^{1}H NMR (270 MHz); δ 2.78 (3H, d, J=5 Hz), 3.22-3.41 (2H, ABX-oct, J=14, 6 Hz), 4.63 (1H, dd, J=9, 6 Hz), 6.39 (1H, broad s), 7.12-7.58 (8H, m), 7.88-7.92 (2H, m).

N-Methyl 2,4-Dimethyl-3-oxopentanamide (22a).
Yield 20 %; mp 58-59°C (from Hexane);^{1}H NMR (200 MHz); d 1.11 (6H, d, J=6.8 Hz), 1.38 (3H, d, J=7.2 Hz), 2.76-2.86 (1H, m), 2.80 (3H, d, J=4.8 Hz), 3.66 (1H, q, J=7.0 Hz), 6.50 (1H, broad s); ^{13}C NMR (50 MHz); d 15.8 (CH3), 17.4 (CH3), 17.5 (CH3), 25.8 (CH), 40.2 (CH), 51.7 (CH3), 170.0 (C).

Conversion 14a into N-Benzyl or Pyrrolidino β-Keto Amides. Benzyl amine or pyrrolidine (2.3 mmol) was stirred with **14a** (0.67 mmol) in hexane (4 ml) at -78°C for 30 min. After removal of the solvent, the residue was chromatographed on silica gel column with benzene-ethyl acetate mixture. The optical purity was evaluated from the ^{1}H NMR signals using the chiral Eu(tfc)3. The specific rotation was measured in dry benzene.

N-Benzyl 2-Methyl-3-phenyl-3-oxopropanamide (23a).
Yield 51 %; mp 114-115°C (from Hexane);^{1}H NMR (200 MHz); d 1.56 (3H, d, J=7.2 Hz), 4.32-4.54 (3H, m), 6.85 (1H, broad s), 7.16-7.65 (8H, m), 8.03 (2H, d, J=8.0 Hz); ^{13}C NMR (50 MHz); d 16.4 (CH3), 43.1 (CH2), 49.1 (CH), 127.1 (CH), 128.3 (CH), 128.5 (CH), 133.5 (CH).

Pyrrolidino 2-Methyl-3-phenyl-3-oxopropanamide (24a).
Yield 75 %; mp 90-91°C (from Hexane);^{1}H NMR (270 MHz); d 1.50 (3H, d, J=6.9 Hz), 1.78-1.99 (4H, m), 3.31-3.52 (4H, m), 4.34 (1H, q, J=6.9 Hz), 7.43-7.99 (5H, m).

Single-Crystal X-ray Diffraction Analysis of 14f. The crystal data for **14f** are as follows: Monoclinic; space group P21 with a=6.273 (2), b=20.454 (5), c=7.902 (4) Å, β=95.69 (2)°, V=1376.7 Å^3, and Z=2. The empirical formular is $C_{33}H_{34}N_2O_2$, molecular weight is 490.64, and calculated density is 1.18 g/cm^3. The three-dimensional X-ray data were collected by the use of graphite-monochromated Mo Kα radiation (λ=0.71073 Å) using the ω-2θ scan technique to a maximum 2θ of 46.0°. A total of 2099 reflections was collected, of which 2093 were unique and not systematically absent. Lorentz and polarization corrections were applied to the data. The linear absorption coefficient is 1.2 cm^{-1} for Mo K radiation. The structure was solved by direct methods. Using 502 reflections (minimum E of 1.200) a total of 40 phase sets was produced. The remaining atoms were located in succeeding difference Fourier syntheses. Hydrogen atoms were located. The structure was refined in full-matrix least-squares and converged to a conventional R factor of 0.084. Atomic coordinates, thermal parameters, and bond lengths and angles have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, upon request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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9. The method of determination of diastereomeric excess for α-acylation of **13** is described in Ref. 6.

(*Received in Japan* 14 *March* 1996; *accepted* 10 *June* 1996)