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Enantioselective synthesis of functionalized α-amino acids via a chiral guanidine catalyzed Michael addition reaction

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Abstract

Several chiral guanidines were evaluated as catalysts for the Michael reaction of glycine derivatives **7** with acrylic esters **8**. The best result (30.4% ee) was obtained when **7b** was reacted with **8b** under the catalysis of guanidine **1** in THF. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

As a strong organic base, tetramethylguanidine (TMG) has been used as a catalyst for carbon–carbon bond formation,[1–3] and known reactions catalyzed by TMG include Michael additions[2] and aldol condensations.[3] Thus, the use of chiral guanidines as catalysts could open a new avenue for the asymmetric formation of a carbon–carbon bond. Recently, successful asymmetric inductions have been achieved in the nitroaldol reaction[4] and Strecker reaction[5] by using enantiomerically pure guanidines as catalysts. The chiral guanidines have also shown the ability to induce enantioselective alkylative esterification.[6] Herein, we wish to report the first example of an asymmetric Michael addition reaction catalyzed by a chiral guanidine.

2. Results and discussion

Two methods were used for preparation of our chiral guanidine catalysts, which are illustrated by the syntheses of catalysts **1**, **2** and **3**. The catalyst **1** ($[\alpha]_D^{25}=-57.6$ (*c* 0.65, H_2O)) was synthesized from (*S*)-α-methylbenzylamine by the reaction sequence shown in Scheme 1 according to a similar procedure reported by Poss and coworkers.[7]

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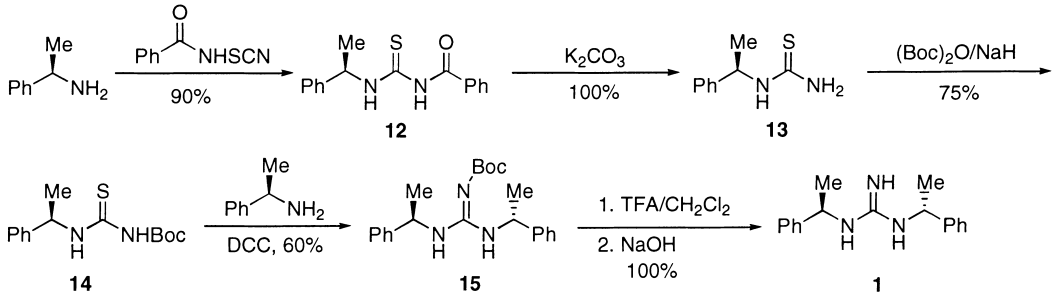
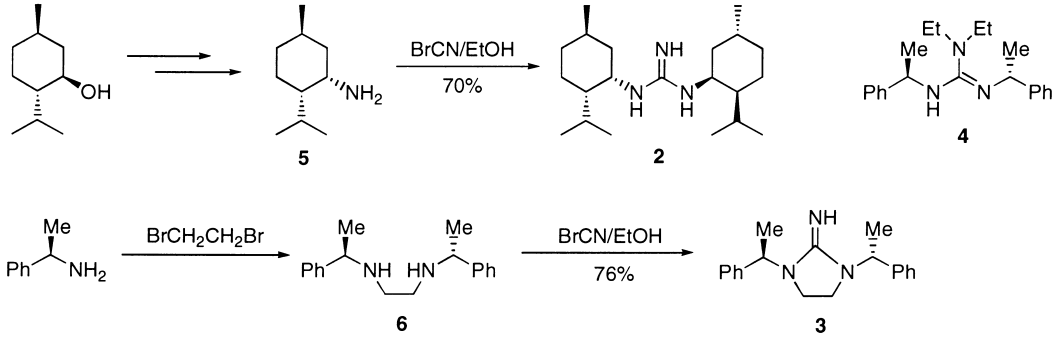


Scheme 1.

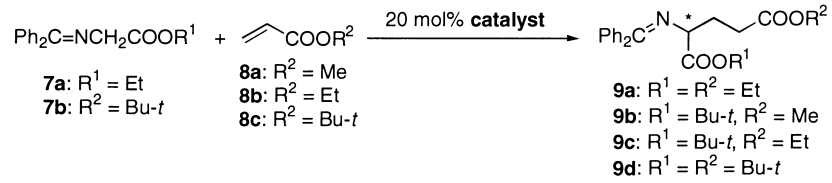
As outlined in Scheme 2, the other two catalysts were prepared by treatment of the corresponding amine with cyanogen bromide in ethanol.[8] From the secondary amine **5** prepared from (1*R*,2*S*,5*R*)-menthol the catalyst **2** ($[\alpha]_D^{25}$=+56.9 (*c* 1, $CHCl_3$)) was obtained, while the cyclic guanidine **3** ($[\alpha]_D^{25}$=+78.5 (*c* 1, $CHCl_3$)) was synthesized by the reaction of diamine **6** with cyanogen bromide. In addition, the known guanidine **4**[4] was also prepared for comparison.



Scheme 2.

The Michael addition reaction of glycine derivatives[9] to acrylic esters was chosen as our model reaction to check the asymmetric induction of guanidines **1**–**4** as chiral catalysts. It is obvious that success in this reaction will lead to a new methodology for preparing synthetically useful α-amino acid derivatives. The reaction was carried out simply by stirring a mixture of imine **7**, excess acrylic ester **8** and a catalytic amount of chiral guanidine in a suitable solvent at room temperature. The enantiomeric purity of the resultant α-amino acid derivative was determined by chiral HPLC analysis using a Chiralpak AD column with 1% isopropyl alcohol in hexane for elution at 25°C. The configuration of each product was assigned by its transformation to glutamic acid and determination of the sign of its optical rotation. As shown in Table 1, the reaction proceeded with high chemical yield and modest enantioselectivity. Among the glycine derivatives examined, *tert*-butyl glycinate benzophenone imine **7b** gave higher enantioselectivity than ethyl glycinate benzophenone imine **7a** (compare entries 1 and 3), which implied that an imine–guanidine complex might form in the course of the reaction thereby determining the outcome of the enantioselectivity. As in many other asymmetric catalytic reactions, the enantioselectivity of the present reaction was highly dependent on the nature of solvent. Among the solvents examined, THF was the best solvent for this reaction (compare entries 3 and 5–7). As catalysts, guanidines derived from (*S*)-α-methylbenzylamine gave better results than those of (1*R*,2*S*,5*R*)-menthol-derived guanidines (compare entries 3 and 9–11), while the cyclic guanidine delivered poorer enantioselectivity in comparison with acyclic guanidine (entries 3 and 11). In addition, lowering the reaction temperatures was found not to improve the enantioselectivity of this reaction (entries 3 and 12).

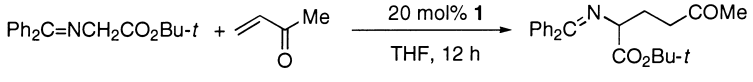
Table 1
Chiral guanidine catalyzed Michael addition reaction of glycine derivatives to acrylic esters[a]



Entry	Catalyst	R^1	R^2	Solvent	Yield (%)[b]	$[\alpha]_D^{20}$	ee (%)	Configuration
1	**1**	Et	Et	THF	99	+8.3	6.4	R
2	**1**	*t*-Bu	Me	THF	95	+14.6	15.7	R
3	**1**	*t*-Bu	Et	THF	99	+28.5	30.4	R
4	**1**	*t*-Bu	*t*-Bu	THF	98	+20.2	30.1	R
5	**1**	*t*-Bu	Et	CH_2Cl_2	95	-6.3	6.7	S
6	**1**	*t*-Bu	Et	toluene	99	-5.2	5.6	S
7	**1**	*t*-Bu	Et	CH_3CN	95	+7.3	7.8	R
8	**1**	*t*-Bu	Et	ether	98	+4.2	4.5	R
9	**4**	*t*-Bu	Et	THF	85	+24.0	25.6	R
10	**2**	*t*-Bu	Et	THF	95	+5.8	6.2	R
11	**3**	*t*-Bu	Et	THF	97	+16.1	17.2	R
12[c]	**1**	*t*-Bu	Et	THF	90[d]	+27	28.8	R

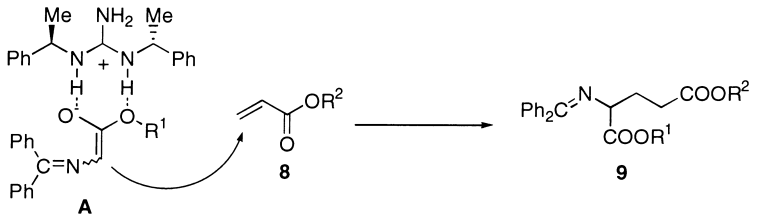
[a]Reaction conditions: Imine **7** (0.13 mmol), acrylic ester **8** (0.46 mmol), chiral guanidine (0.025 mmol), solvent (0.5 mL), -78 °C - -10 °C, 48 h. [b]Isolated yield. [c]Reaction was carried out at -78 °C - -50 °C, 72 h. [d]Based on 51% recovery of the starting material.

To check if enones could be suitable Michael addition acceptors under the present reaction conditions we attempted the reaction of **7b** with vinyl methyl ketone using catalyst **1**. It was found that the reaction was complete in 12 h to give the addition product **10** in 98% yield. However, the enantioselectivity (16.5% ee) was poor.



10

It is known that guanidines could be used for molecular recognition of carboxylate anions because of their ability to form strong zwitterionic hydrogen bonds.[10] Based on these results we propose the possible mechanism of the present reaction as follows. After deprotonation of **7** under the action of the chiral guanidine **1**, a complex A might form, which could react with acrylic ester **8** to deliver the addition product **9**. It might be possible to obtain better enantioselectivity by using a bulkier R^1 group or by replacement of the phenyl group in the guanidine **1** with a larger group.



In conclusion, we have found that some chiral guanidines can catalyze the Michael addition of glycine derivatives to acrylic esters or enones to provide the addition products with low enantioselectivity.[11] Although the enantioselectivity was poor, these results demonstrate the ability of chiral guanidines as asymmetric catalysts in the Michael addition reaction. Optimization of the reaction conditions together with the application of these chiral guanidines to other systems are presently under study in our laboratory.

3. Experimental

*3.1. (*R*)-*N*-*Benzoyl*-N′-(1-phenylethyl)thiourea **12***

To a solution of ammonium thiocyanate (3.80 g, 50 mmol) in 20 mL of anhydrous acetone under a nitrogen atmosphere, was added dropwise benzoyl chloride (7.10 g, 50 mmol) at 60°C. The mixture was stirred for 15 min and then a solution of (*R*)-α-methylbenzylamine (6.05 g, 50 mmol) in 10 mL of acetone was added dropwise. After the reaction mixture was stirred for 2 h at 65°C, it was poured into 100 mL of water and extracted with methylene chloride (3×50 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to dryness under reduced pressure. Purification of the residue by column chromatography (using 1:10 ethyl acetate:petroleum ether as an eluent) afforded 12.8 g (90%) of **12** as a light-yellow oil. $[\alpha]_D^{20}$=+8.9 (*c* 1, $CHCl_3$); IR (KBr) 1671, 1539, 1376 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.65 (d, *J*=7.2 Hz, 3H), 1.85 (s, 1H), 5.65 (q, *J*=7.2 Hz, 1H), 7.41–7.92 (m, 10H), 9.10 (s, 1H); MS *m/z* 284 (M^+), 120, 105, 77; HRMS calcd for $C_{16}H_{16}N_2OS$: 284.0983; found: 284.0976.

*3.2. (*R*)-*N*-*(1-Phenylethyl)thiourea **13***

A solution of **12** (10.99 g, 38.7 mmol), potassium carbonate (10.68 g, 77.0 mmol) and water (10 mL) in methanol (100 mL) was stirred at rt for 3 h. The mixture was evaporated and the residue was extracted with ethyl ether (2×50 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to dryness. The residual oil was purified by column chromatography (using 1:1 ethyl acetate:petroleum ether as an eluent) afforded 6.97 g (90%) of **13** as colorless prisms. $[\alpha]_D^{20}$=−51.3 (*c* 1.0, $CHCl_3$); IR (KBr): 3274, 1538, 1274 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.50 (d, *J*=7.1 Hz, 3H), 2.05 (s, 1H), 4.50 (q, *J*=7.2 Hz, 1H), 6.10 (br s, 2H), 7.20–7.50 (m, 5H); MS *m/z* 180 (M^+), 120, 105, 77; HRMS calcd for $C_9H_{12}N_2S$: 180.0721; found: 108.0706.

*3.3. (*R*)-*N*′-(*tert*-Butoxycarboxyl)-*N*-(1-phenylethyl)thiourea **14***

To a suspension of NaH (65% in mineral oil, 1.80 g, 47 mmol) and **13** (5.96 g, 33 mmol) in THF (150 mL) under a nitrogen atmosphere, was added portionwise a solution of di-*tert*-butyl dicarbonate (7.22 g, 33 mmol) in THF (10 mL) which was then stirred at room temperature overnight. After evaporation of THF, the mixture was poured into water, and then extracted with ethyl acetate (2×100 mL). The

organic solution was washed with water and brine, respectively, dried over $MgSO_4$, and evaporated to dryness. The residue was purified by column chromatography (using 1:7 ethyl acetate:petroleum ether as an eluent) affording 6.95 g (75%) of **14** as colorless prisms. $[\alpha]_D^{21}$=+33.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (s, 9H), 1.60 (d, *J*=7.2 Hz, 3H), 5.60 (q, *J*=7.2 Hz, 1H), 7.20–7.40 (m, 5H), 7.90 (s, 1H), 10.0 (br s, 1H); MS *m/z* 280 (M^+), 224, 120, 105, 77. Anal. calcd for $C_{14}H_{20}N_2O_2S$: C, 59.63; H, 7.19; N, 9.90; found: C, 59.97; H, 7.19; N, 9.99.

3.4. (R,R)-N,N′-*Bis(1-phenylethyl)*-N″-tert-*butoxycarbonyl guanidine* ***15***

To a solution of **14** (0.28 g, 1.0 mmol), Et_3N (0.12 mL) and DCC (0.21 g, 1.0 mmol) in DMF (4 mL) under a nitrogen atmosphere, was added dropwise (*R*)-α-methylbenzylamine (0.13 g, 1.1 mmol) at 40°C. After the mixture had been stirred at 70°C overnight, 10 mL of water was added. The resultant mixture was extracted with ethyl acetate (2×20 mL), and dried over Na_2SO_4. After removal of solvent, the residual oil was purified by column chromatography (using 1:7 ethyl acetate:petroleum ether as an eluent) affording 0.22 g (66%) of **15** as colorless prisms. $[\alpha]_D^{23}$=−143.9 (*c* 1.0, $CHCl_3$); IR (KBr) 3268, 1598 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (s, 9H), 1.60 (d, *J*=7.2 Hz, 6H), 4.60 (q, *J*=7.2 Hz, 2H), 7.10 (br s, 2H), 7.20–7.40 (m, 10H); MS *m/z*: 367 (M^+), 267, 206, 120, 105, 77; HRMS calcd for $C_{22}H_{29}N_3O_2$: 367.2260; found: 367.2297.

3.5. (R,R)-N,N′-*Bis(1-phenylethyl)guanidine* ***1***

A solution of **15** (0.58 g, 1.58 mmol) and TFA (5 mL) in methylene chloride (5 mL) was stirred at rt for 1 h. After the excess of TFA was evaporated, the residue was basified with 5 mL of 50% aqueous NaOH, and extracted with methylene chloride (3×10 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to dryness to yield 0.42 g (100%) of **1** as a light-yellow solid. $[\alpha]_D^{23}$=−54.8 (*c* 1.0, $CHCl_3$); IR (KBr) 3294, 3028, 1621 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (d, *J*=7.0 Hz, 6H), 4.50 (q, *J*=7.1 Hz, 2H), 7.00–7.20 (br s, 3H), 7.20–7.40 (m, 10H); MS *m/z* 267 (M^+), 252, 162, 120, 105, 77; HRMS calcd for $C_{17}H_{21}N_3$: 267.1735; found: 267.1744.

3.6. N,N′-*Bis(2-isopropyl-5-methylcyclohexyl)guanidine* ***2***

To a stirring solution of **5** (1.55 g, 10 mmol) in 3 mL of ethanol was carefully added a solution of cyanogen bromide (1.16 g, 11 mmol) in 1 mL of ethanol at 0°C. After the addition, the reaction mixture was allowed to warm to 25°C in 10 min and then heated at 150°C for 30 min, while N_2 was swept through the flask to completely remove the boiling solvent. The fused reaction mixture was allowed to cool to rt, and the resulting glassy solid was taken up in hot EtOH (15 mL). The resultant solution was treated with decolorizing charcoal (60 mg) and filtered through Celite. The filtrate was diluted with aqueous 1 N NaOH (20 mL), and the precipitate guanidine free base was filtered off to afford 1.17 g (35%) of **2** as colorless prisms in 35% yield. $[\alpha]_D^{28}$=+56.9 (*c* 1.0, $CHCl_3$); IR (KBr): 3288, 3171, 2952, 1629, 1556 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, *J*=7.2 Hz, 6H), 0.90 (d, *J*=7.1 Hz, 12H), 0.95–1.10 (m, 10H), 1.50 (m, 4H), 1.80 (m, 4H), 3.30 (m, 1H), 7.30 (br s, 3H); MS *m/z* 335 (M^+), 320, 292, 250, 224, 154, 70; HRMS calcd for $C_{21}H_{41}N_3$: 335.3300; found: 335.3275.

3.7. (R,R)-N,N′-(1-Phenylethyl)-ethylenediamine **6**

A mixture of (*R*)-α-methylbenzylamine (2.42 g, 20 mmol), 1,2-dibromoethane (1.88 g, 10 mmol) and sodium hydroxide (0.16 g, 40 mmol) in 5 mL of DMSO was stirred at 70°C for 24 h. The mixture was poured into water (20 mL) and then extracted with ethyl ether (2×20 mL). The combined organic layers were washed with water and brine, respectively, dried over $MgSO_4$, and concentrated via rotavapor. The residual oil was chromatographed (using 0.05:1:3 triethyl amine:ethyl acetate:petroleum ether as an eluent) to afford 1.88 g (70%) of **6** as a colorless oil. $[\alpha]_D^{23}$=+73.3 (*c* 1.0, $CHCl_3$); IR (KBr) 3311, 1452, 1124 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (d, *J*=7.1 Hz, 6H), 2.30 (br s, 2H), 2.55 (t, *J*=6.9 Hz, 4H), 3.70 (q, *J*=7.1 Hz, 2H), 7.20–7.40 (m, 10H); MS *m/z* 269 (M^++H^+), 163, 149, 134, 120, 105, 91, 77; HRMS calcd for $C_{18}H_{24}N_2$: 268.1939; found: 268.1911.

3.8. (R,R)-N,N′-Bis(1-phenylethyl)-2-imidazolidine **3**

Following the procedure for preparing **2** from **5**, the cyclic guanidine **3** was prepared from **6** in 40% yield as colorless prisms. $[\alpha]_D^{25}$=+78.5 (*c* 1.0, $CHCl_3$); IR (KBr) 3344, 3030, 1618, 1289 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.55 (d, *J*=7.0 Hz, 6H), 2.95 (m, 2H), 3.15 (m, 2H), 5.15 (q, *J*=7.0 Hz, 2H), 7.25 (br s, 1H), 7.30–7.40 (m, 10H); MS 292 (M^+−H^+), 278, 188, 148, 105, 84; HRMS calcd for $C_{19}H_{22}N_3$: 292.1814; found: 292.1798.

3.9. Typical procedure for asymmetric Michael addition reactions catalyzed by chiral guanidine

To a mixture of glycine derivative **7** (0.125 mmol) and guanidine **1** (7 mg, 0.025 mmol) in THF (0.5 mL) was added a suitable acrylic ester (or vinyl methyl ketone) (0.46 mmol) dropwise at −78°C. The resulting reaction mixture was stirred for 2 h at −78°C and then warmed to −10°C. The stirring was continued until no more **7** existed as monitored by TLC. The mixture was concentrated under reduced pressure followed by purification by column chromatography (using 1:10 ethyl acetate:petroleum ether as an eluent) to afford the corresponding addition product.

3.9.1. 2-Benzhydrylideneamino-1,5-pentanedioic acid diethyl ester **9a**

98% yield, 6.4% ee. $[\alpha]_D^{25}$=+8.3 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, *J*=7.1 Hz, 3H), 1.20 (t, *J*=7.1 Hz, 3H), 2.10–2.20 (m, 4H), 3.90 (dd, *J*=7.0, 5.8 Hz, 1H), 4.05 (q, *J*=7.1 Hz, 2H), 4.10 (q, *J*=7.1 Hz, 2H), 7.10–7.60 (m, 10H); MS *m/z* 367 (M^+−H^+), 338, 294, 220, 206, 165, 117; HRMS calcd for $C_{22}H_{25}NO_4$: 367.1784 [M^+−H^+]; found: 367.1681.

3.9.2. 2-Benzhydrylideneamino-1,5-pentanedioic acid, 1-tert-butylester 5-methyl ester **9b**

95% yield, 15.7% ee. $[\alpha]_D^{25}$=+14.6 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.10–2.20 (m, 2H), 2.30–2.40 (m, 2H), 3.50 (s, 3H), 3.95 (dd, *J*=7.1, 5.8 Hz, 1H), 7.10–7.60 (m, 10H); MS *m/z* 381 (M^+), 366, 326, 294, 280, 248, 165, 57; HRMS calcd for $C_{23}H_{27}NO_4$: 381.1940; found: 381.1941.

3.9.3. 2-Benzhydrylideneamino-1,5-pentanedioic acid 1-tert-butylester 5-ethyl ester **9c**

99% yield, 30.4% ee. $[\alpha]_D^{25}$=+28.5 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, *J*=7.1 Hz, 3H), 1.45 (s, 9H), 2.00–2.10 (m, 2H), 2.10–2.20 (m, 2H), 3.85 (dd, *J*=7.0, 5.8 Hz, 1H), 4.10 (q, *J*=7.1 Hz, 2H), 7.05–7.60 (m, 10H); MS *m/z* 396 (M^++H^+), 338, 294, 220, 165, 57; HRMS calcd for $C_{24}H_{29}NO_4$: 395.2097; found: 395.2104.

3.9.4. 2-Benzhydrylideneamino-1,5-pentanedioic acid di-tert-*butylester* ***9d***

99% yield, 30.1% ee. $[\alpha]_D^{25}$=+20.2 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 9H), 1.45 (s, 9H), 2.05–2.10 (m, 2H), 2.10–2.20 (m, 2H), 3.90 (dd, *J*=6.4, 5.8 Hz, 1H), 7.10–7.60 (m, 10H); MS *m/z* 424 (M^++H^+), 368, 350, 294, 266, 194, 165, 91, 57; HRMS calcd for $C_{26}H_{33}NO_4$: 423.2410; found: 423.2416.

3.9.5. 2-Benzhydrylideneamino-5-oxo-1-hexanoic acid tert-*butylester* ***10***

99% yield, 16.5% ee. $[\alpha]_D^{25}$=+17.1 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.40 (s, 9H), 2.00–2.10 (m, 2H), 2.10–2.20 (m, 2H), 2.25 (s, 3H), 3.90 (dd, *J*=7.0, *J*=5.8 Hz, 1H), 7.10–7.60 (m, 10H); MS 365 (M^++H^+), 308, 264, 206, 182, 165, 57; HRMS calcd for $C_{24}H_{29}NO_4$: 365.1991; found: 365.1993.

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