

# 1,3-Dipolar Cycloaddition of Schiff Bases and Electron-Deficient Alkenes, Catalyzed by $\alpha$ -Amino Acids

K. V. Kudryavtsev and A. A. Zagulyaeva

Faculty of Chemistry, Moscow State University, Vorob'evy gory 1, Moscow, 119992 Russia  
e-mail: kudr@org.chem.msu.ru

Received April 6, 2007

**Abstract**—L- $\alpha$ -Amino acids catalyze 1,3-dipolar cycloaddition of methyl  $\alpha$ -benzylideneamino acids to electron-deficient olefins in different solvents at room temperature. L- $\alpha$ -Amino acids ensure stereoselective formation of the corresponding *syn,syn*-azomethine ylides. The subsequent reaction with an active dipolarophile is stereospecific; it occurs as *endo*-cycloaddition with low asymmetric induction (up to ee 12%). 3,4-Substituted 5-arylprolines were obtained in preparative yields using L-pyroglyutamic acid or L-proline as catalyst.

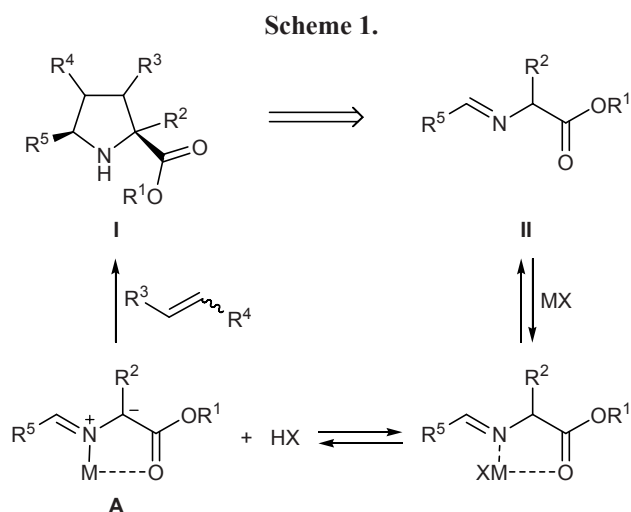
DOI: 10.1134/S1070428008030123

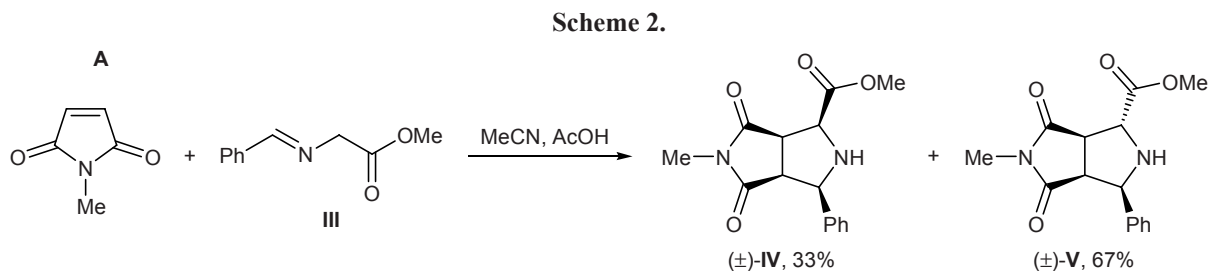
[3+2]-Cycloaddition reactions provide an effective and extensively used method for the synthesis of proline derivatives **I** which are widespread in nature [1] and are physiologically active toward some biological targets [2]. As a rule, this procedure utilizes Schiff bases **II** as synthetic precursors of compounds **I**. Compounds **II** are readily available from the corresponding aldehydes and  $\alpha$ -amino acid esters having a primary amino group (Scheme 1). Prototropic tautomerization catalyzed by Brønsted or Lewis acids gives rise to a 1,3-dipole, azomethine ylide **A**, which possesses 4 $\pi$ -electron system; it reacts with electron-deficient alkenes  $R^3CH=CHR^4$  with formation of pyrrolidine ring [3, 4]. Each elementary step of the process shown in Scheme 1 is characterized by high stereo- and regioselectivity, and this procedure was used by us previ-

ously to synthesize new functional derivatives of pyrrolidine-2-carboxylic acids [5, 6]. Dipole **A** (Scheme 1) has *syn,syn* configuration due to coordination of the carbonyl oxygen atom with acid; the latter in turn interacts with lone electron pair on the azomethine nitrogen atom; *cis* arrangement of the ester group in position 2 and substituent in position 5 of the pyrrolidine ring in molecule **I** is also favored by steric factors. Cycloaddition of unsymmetrical alkenes  $R^3CH=CHR^4$  ( $R^3 \neq R^4$ ) to dipole **A** occurs with a good regioselectivity and with *endo*- [7] or *exo*-stereoselectivity [8], depending on the reaction conditions. The use of Co(II), Mn(II), Ag(I), Cu(II), and Zn(II) salts as Lewis acids to generate metal-containing dipole **A** (where M is a metal) and of chiral ligands ensures asymmetric synthesis of pyrrolidines **I** with an optical purity reaching 99% [9, 10].

1,3-Dipolar cycloaddition of alkenes to azomethine ylides in the presence of Brønsted acids has been studied to a lesser extent. The main reasons are a limited set of dipolarophiles capable of reacting in the presence of a protic acid and poor stereoselectivity of the process. For example, methyl (benzylideneamino)acetate (**III**) reacted with *N*-methylmaleimide in acetonitrile in the presence of 10 mol % of acetic acid to give a mixture of isomeric cycloadducts **IV** and **V** at a ratio of 1:2 in quantitative yield (Scheme 2) [11]. The temperature conditions given in [11] in the text and Experimental section are contradictory; therefore, the reaction conditions remain unclear.

Generation of 1,3-dipole from imino esters **VI** and the subsequent cycloaddition of *N*-phenylmaleimide





occur in a stereoselective fashion in the presence of Brønsted acids on heating or in acetic anhydride containing 6% of acetic acid at room temperature; as a result, bicyclic compounds **VII** are formed (Scheme 3) [12]. Maleic anhydride was also brought into analogous reaction as dipolarophile, whereas dimethyl maleate and dimethyl fumarate failed to react, presumably due to their lower reactivity [12].

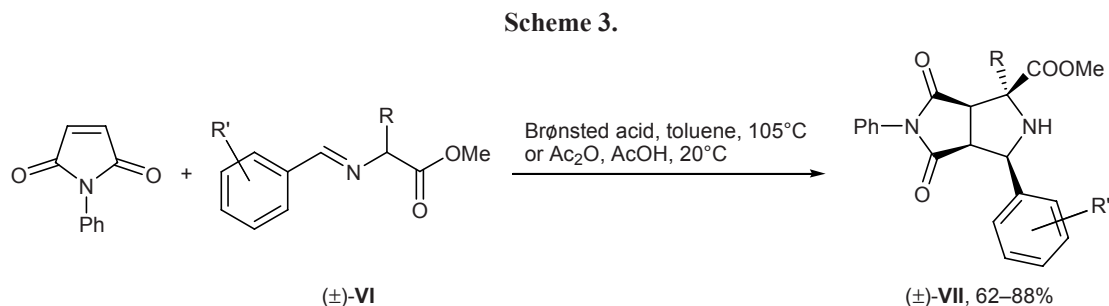
As noted above, the use of transition metal salts in combination with enantiomerically pure phosphine and nitrogen-containing ligands makes it possible to accomplish a catalytic version of asymmetric 1,3-dipolar cycloaddition of azomethines with high enantioselectivity [9, 10, 13]. Chiral Brønsted acids were not reported as catalysts in such reactions. In the present work we were the first to examine L- $\alpha$ -amino acids as catalysts in asymmetric 1,3-dipolar cycloaddition of imino esters **II** to dipolarophiles. Catalysis by substoichiometric amounts of organic compounds having a low molecular weight (so-called organocatalysis) is widely used to perform various asymmetric organic reactions (for review, see [14]). Asymmetric organocatalytic 1,3-dipolar cycloaddition of azomethine ylides was not reported previously.

$\alpha$ -Amino acids are cheap difunctional compounds containing amino and carboxy groups and are available as two individual enantiomers. Both these functional groups are amphoteric. Reaction of an  $\alpha$ -amino acid with Schiff base **III** could initiate the following transformation sequence generating azomethine ylide: (1) protonation of the imino nitrogen atom and (2) deprotonation at the  $\alpha$ -position with respect to the nitro-

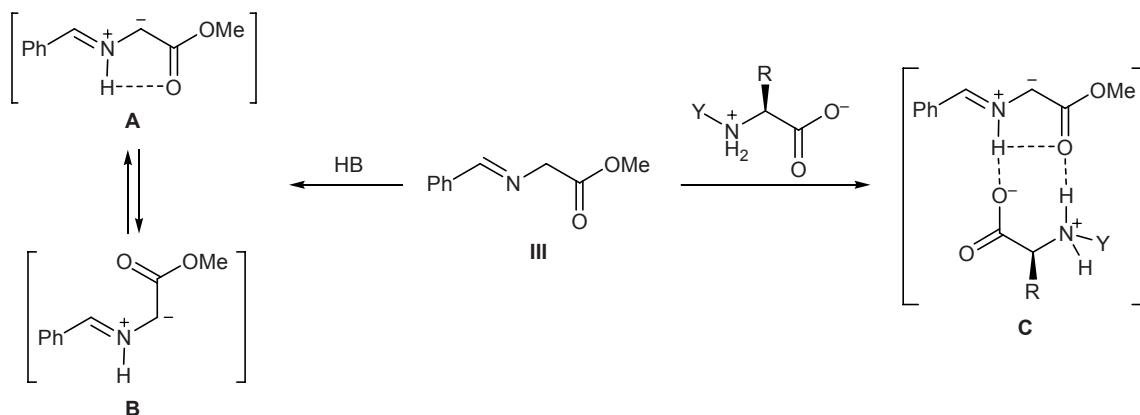
gen atom (Scheme 4). Hydrogen bond in azomethine ylide **A** derived from Schiff bases **II** ( $R^2 = H$ ) and **III**, which contain no substituent in the  $\alpha$ -position, is a weak stabilizing factor, and dipole **B** becomes thermodynamically more stable (Scheme 4). As a result, the stereoselectivity of cycloaddition decreases [11]. Electrostatic and other interactions between the conjugate base of enantiomerically pure Brønsted acid and azomethine ylide **A** could give rise to asymmetric induction in the subsequent 1,3-dipolar cycloaddition. Zwitterionic form of enantiomerically pure  $\alpha$ -amino acid is a bidentate chiral ligand which is capable of reacting with azomethine ylide **A** to give hydrogen bond-stabilized associate **C**, providing additional activation and stabilization of *syn,syn*-dipole **A** (Scheme 4).

As model process we examined the reaction of methyl (benzylideneamino)acetate (**III**) with *N*-methylmaleimide in various solvents at room temperature in the presence of L-proline (L-Pro, 20 mol %; Scheme 5; Table 1, run nos. 1–6). Proline is a cyclic amino acid having a secondary amino group; it effectively catalyzes reactions involving iminium and enamine intermediates and is an effective organocatalyst in various processes [15]. In our case, the acidity of amino acids and their subsequent association with 1,3-dipole are important.

L-Proline was added to a mixture of the reactants in appropriate solvent, and the mixture was stirred at room temperature over a period indicated in Table 1. The reaction mixtures were generally heterogeneous (run nos. 1, 2, 4–6); an exception was the reaction in



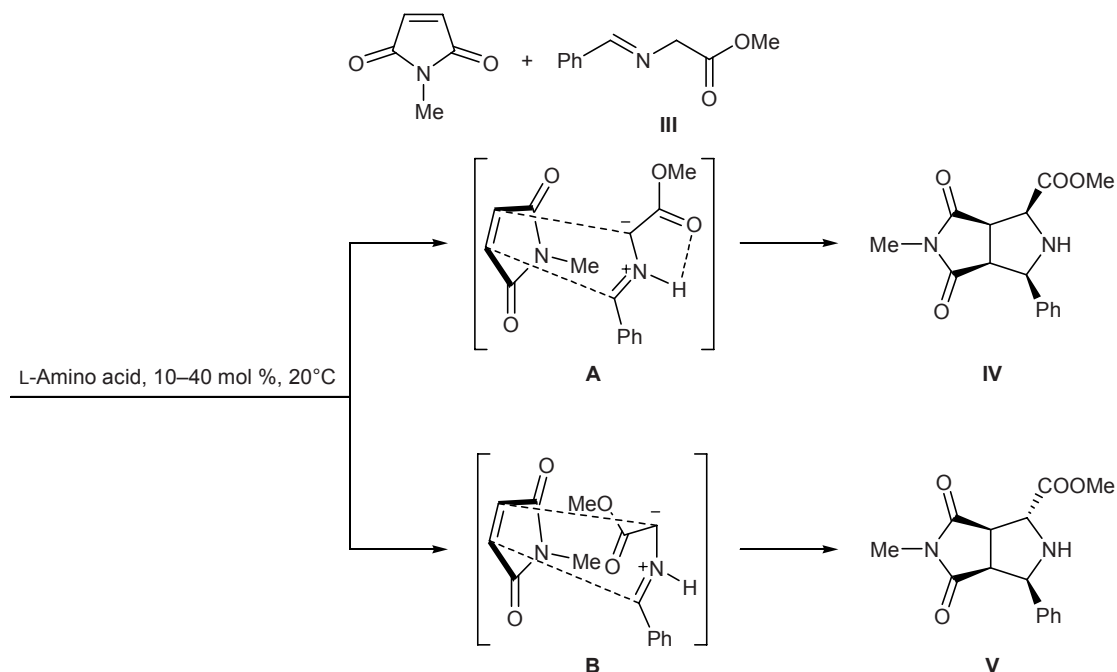
Scheme 4.



aqueous acetonitrile (run no. 3). In all cases, the conversion of the initial reactants was not complete. All reactions performed in the presence of L-proline, except for the process in water, gave the corresponding cycloaddition products. The structure of the major product was determined by comparing its physical constants and spectral parameters with those reported in the literature [8, 11, 13]; it was identified as cycloadduct **IV** formed via *endo*-addition of *N*-methylmaleimide to *syn,syn*-dipole **A** (Scheme 5). The minor product was assigned structure **V** on the basis of its IR and NMR spectral parameters and those given in [11]. Taking into account that the NMR spectra of isomeric *exo*-addition product formed through intermediate *syn,syn* dipole **A** differ only slightly from the corre-

sponding parameters of *endo*-adduct **IV** [8], the structure of racemate **IV** was finally proved by X-ray analysis (Fig. 1, Table 2). A unit cell of compound **IV** in crystal includes two enantiomeric molecules linked by two hydrogen bonds (Fig. 2). The asymmetric induction in reactions catalyzed by L-proline was low (run nos. 1–5, Table 1). The optical purity of pyrrolidine **IV** was determined by comparing its specific rotation with published data [8, 13]. The highest optical purity of compound **IV** was 12% (Table 1, run no. 5), when the reaction was carried out in THF. The major enantiomer **IV** is characterized by a positive optical rotation; in keeping with published data, its absolute configuration corresponds to that shown in Scheme 5. Imide **VIII** was the only product in the reaction performed in

Scheme 5.



**Table 1.** Reaction of methyl (benzylideneamino)acetate (**III**) with *N*-methylmaleimide in the presence of amino acids

Run no.	Amino acid, mol %	Solvent	Reaction time, day	Yield of <b>IV</b> , %	Optical purity of <b>IV</b> , <sup>a</sup> %	Other products, yield, %
1	L-Pro, 20	CH <sub>2</sub> Cl <sub>2</sub>	3	46	<1	–
2	L-Pro, 20	MeCN	3	30	6	<b>V</b> , 4
3	L-Pro, 20 <sup>b</sup>	MeCN/ H <sub>2</sub> O	3	7	<1	–
4	L-Pro, 20	MeOH	3	24	<1	–
5	L-Pro, 20	THF	3	15	12	–
6	L-Pro, 20	H <sub>2</sub> O	1	0	–	<b>VIII</b> , 21
7	L-Pro, 40 <sup>c</sup>	CH <sub>2</sub> Cl <sub>2</sub>	4	62	3	<b>V</b> , 3
8	L-Pro, 40 <sup>c</sup>	MeCN	4	26	–	–
9	L-Glu, 20	CH <sub>2</sub> Cl <sub>2</sub>	4	17	–	<b>V</b> , 3
10	L-Trp, 20	CH <sub>2</sub> Cl <sub>2</sub>	4	23	–	<b>V</b> , 3
11	L-Hyp, 20	CH <sub>2</sub> Cl <sub>2</sub>	4	20	–	<b>V</b> , 5
12	L-Pyr, 20	CH <sub>2</sub> Cl <sub>2</sub>	1	63	<1	<b>V</b> , 4
13	β-Ala	CH <sub>2</sub> Cl <sub>2</sub>	3	24	–	<b>V</b> , 3
14	GlyGly, 20	CH <sub>2</sub> Cl <sub>2</sub>	3	33	–	<b>V</b> , 2
15	L-Pyr, 20	MeOH	1	18	<1	–
16	L-Pyr, 20	MeCN	1.5	45	<1	<b>V</b> , 21
17	L-Pyr, 20	THF	3	48	<1	–
18	L-Pyr, 20 <sup>b</sup>	MeCN/ H <sub>2</sub> O	3	11	–	–
19	L-Pyr, 30	CH <sub>2</sub> Cl <sub>2</sub>	2	68	5	<b>V</b> , 8
20	L-Pyr, 40 <sup>c</sup>	CH <sub>2</sub> Cl <sub>2</sub>	4	60	<1	<b>V</b> , 3
21	L-Pyr, 40 <sup>c</sup> , argon	CH <sub>2</sub> Cl <sub>2</sub>	4	70	3	<b>V</b> , 4
22	L-Pyr, 40 <sup>c</sup>	MeCN	4	53	–	<b>V</b> , 20

<sup>a</sup> Calculated from the optical rotation of the isolated product and published data for compound **IV** with known optical purity [8, 13].

<sup>b</sup> The amino acid was added as an aqueous solution to a solution of Schiff base **III** and *N*-methylmaleimide in acetonitrile.

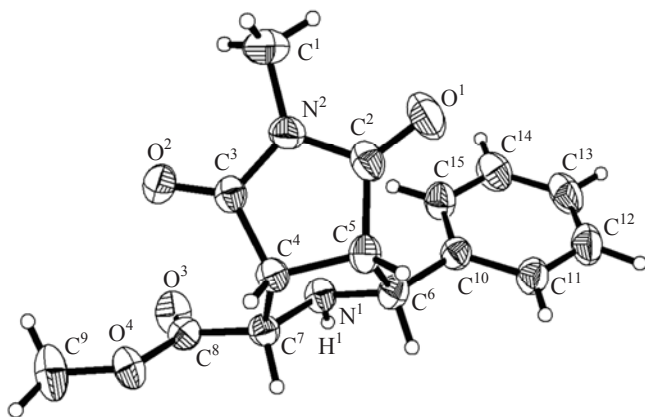
<sup>c</sup> The amino acid was added in portions (4 × 10 mol %) at 24-h intervals.

water (Table 1, run no. 6); compound **VIII** was formed via Michael addition of glycine methyl ester to *N*-methylmaleimide. Presumably, glycine methyl ester appeared in the reaction mixture as a result of hydrolysis of Schiff base **III**.

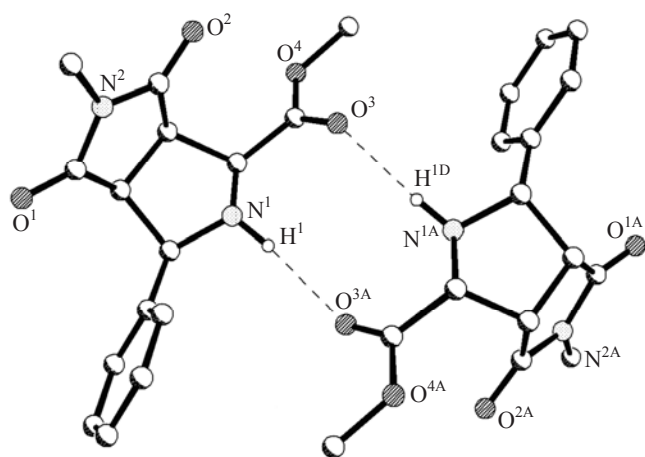
Probable factors responsible for incomplete conversion of the reactants in run nos. 1–5 (Table 1) are the following: (1) conjugate addition of L-proline to *N*-methylmaleimide and (2) accumulation in the reaction medium of a mixture of pyrrolidines **IV** and **V** which are likely to be stronger bases than Schiff base **III** and are capable of competing with the latter for proton. In order to maintain a required amount of the amino acid catalyst in the reaction mixture, L-proline was added in portions (10 mol % each) every 24 h (run nos. 7, 8; Table 1). In the reaction performed in methylene chloride (run no. 7) the yield and optical purity

of cycloadduct **IV** were higher; these findings may be regarded as an indirect support for the above assumptions.

We also examined how the structure of amino acid affects the enantioselectivity of 1,3-dipolar cycloaddition and the yields of products. For this purpose, we performed 1,3-dipolar cycloadditions of Schiff base **III** to *N*-methylmaleimide using 20 mol % of L-glutamic acid (L-Glu), L-tryptophane (L-Trp), *trans*-4-hydroxy-L-proline (L-Hyp), L-pyrroglutamic acid (L-Pyr), β-alanine (β-Ala), and glycylglycine (GlyGly) as catalyst (Scheme 5; Table 1, run nos. 9–14). The reactions were carried out in methylene chloride, taking into account that the maximal yields of the target products in the reactions catalyzed by L-proline were obtained just in that solvent. In all cases, except for L-Pyr, the yields of cycloadduct **IV** were poor, and the isolated product



**Fig. 1.** Structure of the molecule of methyl ( $1S^*,3R^*,3aS^*,6aR^*$ )-5-methyl-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (**IV**) according to the X-ray diffraction data.



**Fig. 2.** Intermolecular interactions in crystal of methyl ( $1S^*,3R^*,3aS^*,6aR^*$ )-5-methyl-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (**IV**) according to the X-ray diffraction data:  $N^1-H^1$  0.92(2),  $H^1-O^{3A}$  2.24(2),  $N^1-O^{3A}$  3.122(2) Å;  $N^1H^1O^{3A}$  159.9(19)°.

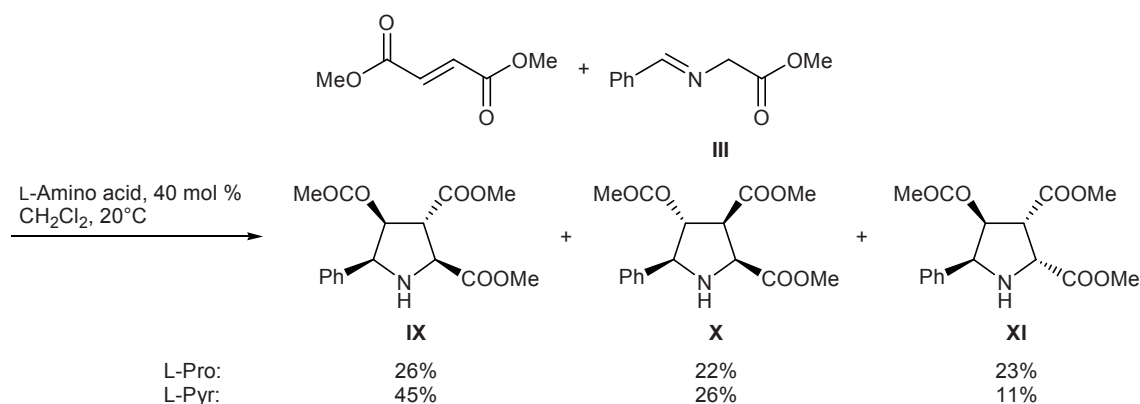
contained an impurity of isomer **V**; therefore, it was sometimes impossible to determine the optical purity of individual stereoisomers. Cycloadduct **V** is formed via 1,3-dipolar cycloaddition of *N*-methylmaleimide to *syn,anti*-azomethine ylide **B** (Scheme 5). In all the examined reactions pyrrolidine **V** was formed as minor product, while the reaction in acetonitrile in the presence of acetic acid gave compound **V** as the major product [11] (Scheme 2). Samples of **V** isolated in the present work were optically inactive. Thus the presence of an  $\alpha$ -amino acid in the reaction mixture stabilizes conformation **A** of azomethine ylide derived from Schiff base **III**; as a result, the observed stereoselectivity is the reversed as compared to 1,3-dipolar cycloaddition of **III** to *N*-methylmaleimide on heating or in

the presence of acetic acid, where intermediate azomethine ylide preferentially adopts conformation **B** (Scheme 4) [11]. The reaction catalyzed by L-Pyr occurred at a higher rate, and the yield of diazabicyclooctane **IV** was greater. No appreciable increase in the yield and enantioselectivity was observed when the reactions catalyzed by L-Pyr were carried out in other solvents (Table 1, run nos. 15–18). Raising the amount of L-Pyr to 30 mol % increased the yield of cycloadduct **IV** to 68% and the optical purity to 5% (solvent  $CH_2Cl_2$ ). The addition of L-Pyr in 10-mol % portions at 24-h intervals did not affect the yield and asymmetric induction to a considerable extent. These parameters were improved by carrying out the process in an inert atmosphere with gradual addition of L-Pyr; on the other hand, they did not exceed those obtained upon addition of a smaller amount of the amino acid catalyst in one portion.

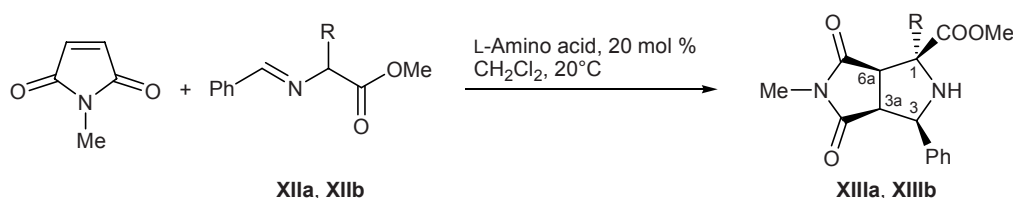
Dimethyl fumarate and dimethyl maleate also reacted with Schiff base **III** in the presence of L-Pro or L-Pyr in  $CH_2Cl_2$  at room temperature. However, the stereoselectivity was poor. The cycloaddition of dimethyl fumarate to Schiff base **III** catalyzed by L-Pro gave a mixture of approximately equimolar amounts of three isomeric pyrrolidinetricarboxylic esters **IX–XI** (Scheme 6). In the presence of L-Pyr as catalyst, the yield of isomer **IX** (product of *endo*-addition of dimethyl fumarate to *syn, syn*-dipole **A**) increased almost twofold, while the amount of pyrrolidine **XI** (*endo*-addition to *syn, anti*-dipole **B**) decreased (Schemes 5, 6). The yields of compounds **IX–XI** were calculated from the  $^1H$  NMR spectra of fractions containing the corresponding isomers; we failed to separate the isomers completely because of their similar chromatographic mobilities.

The structures of pyrrolidines **IX** and **X** were assigned by comparing their spectral parameters with those given in [7, 8] for individual stereoisomers. The *cis* arrangement of the methoxycarbonyl group in position 4 of the pyrrolidine ring and phenyl substituent on  $C^5$  in **XI** follows from the observed shielding of the methoxy protons due to magnetically anisotropic properties of the aromatic ring, which is typical of pyrrolidines [6, 7]. In the  $^1H$  NMR spectra of **XI** and **IX**, protons of the 4-COOMe group give signals at  $\delta$  3.17 and 3.21 ppm, respectively, while signals from the other ester moieties in molecules **XI** and **IX**, as well as analogous signals in the spectrum of stereoisomer **X**, appear as singlets in the  $\delta$  range 3.65–3.85 ppm. Insofar as the dipolarophile structure implies *trans* orientation of the methoxycarbonyl groups on  $C^3$  and  $C^4$ ,

Scheme 6.



Scheme 7.



R = Me (a), Et (b).

compound **XI** should have a structure shown in Scheme 6, which corresponds to *endo*-addition of dimethyl fumarate to *syn,anti*-dipole **B**, in keeping with the results of the reaction of Schiff base **III** with *N*-methylmaleimide (Scheme 5). Isolated samples of individual stereoisomers **X** and **XI** were optically inactive. Dimethyl maleate reacted with compound **III** in the presence of L-Pro or L-Pyr to give more than four stereoisomers. Presumably, the process is accompanied by isomerization of the dipolarophile into thermodynamically more stable dimethyl fumarate.

Introduction of a substituent into the  $\alpha$ -position of Schiff base improves the stereoselectivity of cycloaddition.

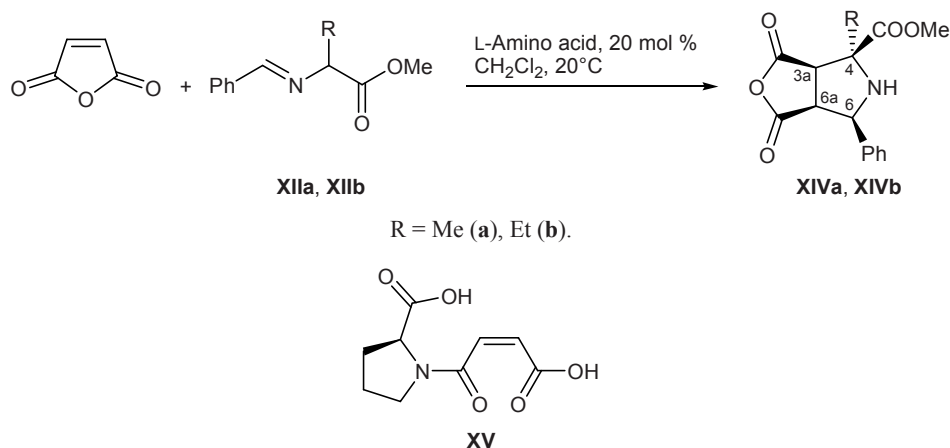
Schiff bases **XIIIa** and **XIIIb** obtained from racemic  $\alpha$ -alanine methyl ester and methyl 2-aminobutanoate reacted with *N*-methylmaleimide and maleic anhydride in methylene chloride in the presence of amino acids to give the corresponding pyrrolidines **XIII** and **XIV** with high stereoselectivity (Schemes 7, 8).

In the reaction with maleic anhydride, catalyzed by L-proline, the amino acid quickly dissolves in methylene chloride, presumably due to formation of compound **XV** which is the true catalyst in these reactions (Scheme 8). Despite relatively small size, the methyl or ethyl group in the  $\alpha$ -position with respect to the ester group in molecules **XIIIa** and **XIIIb** effectively

**Table 2.** Selected bond lengths and bond angles in the molecule of methyl (1*S*\*,3*R*\*,3*aS*\*,6*aR*\*)-5-methyl-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (**IV**)

Bond	<i>d</i> , Å	Bond	<i>d</i> , Å	Angle	$\omega$ , deg	Angle	$\omega$ , deg
N <sup>1</sup> -C <sup>7</sup>	1.452(2)	O <sup>4</sup> -C <sup>8</sup>	1.336(2)	C <sup>7</sup> N <sup>1</sup> C <sup>6</sup>	103.21(15)	C <sup>3</sup> C <sup>4</sup> C <sup>5</sup>	104.31(16)
N <sup>1</sup> -C <sup>6</sup>	1.473(2)	O <sup>4</sup> -C <sup>9</sup>	1.447(2)	C <sup>3</sup> N <sup>2</sup> C <sup>2</sup>	112.64(18)	C <sup>3</sup> C <sup>4</sup> C <sup>7</sup>	111.76(16)
N <sup>1</sup> -H <sup>1</sup>	0.92(2)	C <sup>2</sup> -C <sup>5</sup>	1.507(3)	C <sup>3</sup> N <sup>2</sup> C <sup>1</sup>	123.34(18)	C <sup>5</sup> C <sup>4</sup> C <sup>7</sup>	103.99(15)
N <sup>2</sup> -C <sup>3</sup>	1.374(2)	C <sup>3</sup> -C <sup>4</sup>	1.507(3)	C <sup>2</sup> N <sup>2</sup> C <sup>1</sup>	124.00(19)	C <sup>2</sup> C <sup>5</sup> C <sup>4</sup>	104.69(16)
N <sup>2</sup> -C <sup>2</sup>	1.396(2)	C <sup>4</sup> -C <sup>5</sup>	1.536(3)	O <sup>1</sup> C <sup>2</sup> C <sup>5</sup>	128.9(2)	C <sup>2</sup> C <sup>5</sup> C <sup>6</sup>	115.08(18)
N <sup>2</sup> -C <sup>1</sup>	1.458(3)	C <sup>4</sup> -C <sup>7</sup>	1.539(3)	N <sup>2</sup> C <sup>2</sup> C <sup>5</sup>	108.26(17)	C <sup>4</sup> C <sup>5</sup> C <sup>6</sup>	104.03(15)
O <sup>1</sup> -C <sup>2</sup>	1.205(2)	C <sup>5</sup> -C <sup>6</sup>	1.562(3)	O <sup>2</sup> C <sup>3</sup> N <sup>2</sup>	123.8(2)	C <sup>10</sup> C <sup>6</sup> C <sup>5</sup>	118.50(18)
O <sup>2</sup> -C <sup>3</sup>	1.213(2)	C <sup>6</sup> -C <sup>10</sup>	1.509(3)	O <sup>2</sup> C <sup>3</sup> C <sup>4</sup>	127.12(19)	N <sup>1</sup> C <sup>7</sup> C <sup>4</sup>	100.77(16)
O <sup>3</sup> -C <sup>8</sup>	1.196(2)	C <sup>7</sup> -C <sup>8</sup>	1.508(3)	N <sup>2</sup> C <sup>3</sup> C <sup>4</sup>	109.06(16)	C <sup>8</sup> C <sup>7</sup> C <sup>4</sup>	116.14(16)

## Scheme 8.



hinders intramolecular rotation in intermediate *syn,syn*-dipole like **A**. This factor together with *endo*-cycloaddition of active dipolarophiles ensures stereoselectivity of the process on the whole. Under analogous conditions Schiff base **III** reacts with maleic anhydride to produce a complex mixture of products.

The  $^1\text{H}$  NMR spectra of methyl-substituted cycloadducts **XIIIa** and **XIVa** were consistent with published data [7, 16]. Bicyclic compounds **IV**, **XIII**, and **XIV** are characterized by comparable chemical shifts and coupling constants of protons in the pyrrolidine ring, which confirm their steric structure shown in Schemes 7 and 8. On the other hand, asymmetric induction in the reactions catalyzed by L-Pro or L-Pyr remains fairly poor: all the isolated samples of **XIII** and **XIV** had optical rotations comparable in absolute values with those found for cycloadduct **IV**. As follows from published data on the optical rotations of structurally related diazabicyclooctanes, introduction of an alkyl group into the 2-position of the pyrrolidine fragment does not affect  $[\alpha]_D$  to an appreciable extent [8]. Development of a chromatographic procedure for the determination of optical purity of compounds **XIII** and **XIV** is now in progress.

To conclude, we were the first to propose a procedure for asymmetric organocatalytic 1,3-dipolar cycloaddition of azomethine ylides using chiral Brønsted acids as catalysts and to examine the catalytic activity of some L- $\alpha$ -amino acids in this process. Despite low asymmetric induction, L-pyroglutamic acid and L-proline ensure stereoselective syntheses of functionalized pyrrolidines with preparative yields under mild conditions. Modification of the catalyst structure and reaction conditions with a view to improve the optical purity of the products and their analogs is the subject of our current studies.

## EXPERIMENTAL

The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded at 293 K from solutions in  $\text{CDCl}_3$  or  $\text{DMSO}-d_6$  on a Bruker DRX-400 instrument at 400 MHz for  $^1\text{H}$  and 100 MHz for  $^{13}\text{C}$ ; the chemical shifts were measured relative to the residual solvent signals. The optical rotations were determined on a VNIEKIProd mash EPO 1A polarimeter using 10-cm cells. The optical purities were calculated as described in [17]. The X-ray diffraction data for a single crystal of compound **IV** were acquired on an Enraf-Nonius CAD-4 diffractometer at 293 K.

**$\alpha$ -(Benzylideneamino) acid methyl esters III, XIIa, and XIIb (general procedure).** Triethylamine, 8.5 ml (61 mmol), was added to a suspension of 70.5 mmol of the corresponding  $\alpha$ -amino acid methyl ester hydrochloride and 11.28 g (94 mmol) of anhydrous  $\text{MgSO}_4$  in 150 ml of methylene chloride. The mixture was stirred for 1 h at room temperature in an inert atmosphere, 4.8 ml (47 mmol) of benzaldehyde was added, and the mixture was stirred for 24 h. Water, 150 ml, was then added, the mixture was stirred for 30 min, and the organic phase was separated, washed in succession with a saturated solution of  $\text{NaHCO}_3$ , water, and a saturated solution of  $\text{NaCl}$ , dried over  $\text{Na}_2\text{SO}_4$ , and evaporated. The product was brought into further syntheses without additional purification.

**Methyl (benzylideneamino)acetate (III)** was synthesized from glycine methyl ester hydrochloride. Yield 86%, oily substance.  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm: 3.79 s (3H,  $\text{OCH}_3$ ), 4.43 s (2H,  $\text{CH}_2$ ), 7.41–7.46 m (3H,  $\text{H}_{\text{arom}}$ ), 7.79 d.d (2H,  $\text{H}_{\text{arom}}$ ,  $J = 7.6, 1.8$  Hz), 8.31 s (1H,  $\text{CH}=\text{O}$ ).

**Methyl 2-(benzylideneamino)propionate (XIIa)** was synthesized from DL-alanine methyl ester hydrochloride. Yield 92%, oily substance.  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm: 1.54 d (3H,  $\text{CH}_3$ ,  $J = 6.8$  Hz), 3.75 s (3H,  $\text{OCH}_3$ ), 4.17 q (1H, CH,  $J = 6.8$  Hz), 7.40–7.45 m (3H,  $\text{H}_{\text{arom}}$ ), 7.79 d.d (2H,  $\text{H}_{\text{arom}}$ ,  $J = 7.6$ , 1.8 Hz), 8.32 s (1H, CH=).

**Methyl 2-(benzylideneamino)butanoate (XIIb)** was synthesized from DL- $\alpha$ -aminobutanoic acid methyl ester hydrochloride. Yield 97%, oily substance.  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm: 0.94 t (3H,  $\text{CH}_2\text{CH}_3$ ,  $J = 7.6$  Hz), 1.87–1.98 m (1H,  $\text{CH}_2\text{CH}_3$ ), 2.01–2.12 m (1H,  $\text{CH}_2\text{CH}_3$ ), 3.76 s (3H,  $\text{OCH}_3$ ), 3.91 d.d (1H, CH,  $J = 8.0$ , 5.6 Hz), 7.39–7.46 m (3H,  $\text{H}_{\text{arom}}$ ), 7.80 d.d (2H,  $\text{H}_{\text{arom}}$ ,  $J = 7.6$ , 1.8 Hz), 8.29 s (1H, CH=).

**Reaction of Schiff bases III, XIIa, and XIIb with electron-deficient olefins in the presence of L- $\alpha$ -amino acids (general procedure).** The corresponding dipolarophile, 1 equiv, was added at room temperature to a solution of 500 mg of Schiff base III, XIIa, or XIIb in 5 ml of a solvent indicated in Table 1, and 0.2–0.4 equiv of L- $\alpha$ -amino acid was added. The mixture was stirred at room temperature until the initial reactants no longer changed, the precipitate was filtered off, and the products were separated from the amino acid by repeated washing of the precipitate with methylene chloride and/or isolated from the filtrate by chromatography on silica gel.

**Methyl (1S,3R,3aS,6aR)-5-methyl-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (IV).** Colorless crystals, mp 216–218°C; published data [11]: mp 215–216°C;  $[\alpha]_{\text{D}}^{20} = +16.7^\circ$  ( $c = 0.42$ ,  $\text{CH}_2\text{Cl}_2$ ), optical purity 12%; published data [8]:  $[\alpha]_{\text{D}}^{20} = +34.3^\circ$  ( $c = 0.45$ ,  $\text{CH}_2\text{Cl}_2$ ), optical purity 25%.  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm: 2.44 br.s (1H, NH), 2.88 s (3H,  $\text{NCH}_3$ ), 3.44 d.d (1H, 3a-H,  $J = 8.4$ , 8.0 Hz), 3.58 d.d (1H, 6a-H,  $J = 8.0$ , 6.8 Hz), 3.89 s (3H,  $\text{OCH}_3$ ), 4.07 d (1H, 1-H,  $J = 6.8$  Hz), 4.51 d (1H, 3-H,  $J = 8.4$  Hz), 7.30–7.40 m (5H,  $\text{H}_{\text{arom}}$ ).  $^{13}\text{C}$  NMR spectrum ( $\text{DMSO}-d_6$ ),  $\delta_{\text{C}}$ , ppm: 24.35, 47.78, 48.89, 51.34, 60.86, 62.78, 127.14, 127.24 (2C), 127.70 (2C), 138.52, 170.24, 175.05, 176.40. Found, %: C 62.75; H 5.66; N 9.58.  $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_4$ . Calculated, %: C 62.49; H 5.59; N 9.72. X-Ray diffraction data: triclinic crystals, racemate,  $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_4$ ,  $M$  288.31, space group  $P-1$ ; unit cell parameters:  $a = 6.382(1)$ ,  $b = 10.583(1)$ ,  $c = 11.064(2)$  Å;  $\alpha = 88.13(1)$ ,  $\beta = 76.89(1)$ ,  $\gamma = 76.57(1)^\circ$ ;  $V = 707.7(2)$  Å $^3$ ;  $Z = 2$ ;  $d_{\text{calc}} = 1.353$  g/cm $^3$ ;  $\text{CuK}\alpha$ -irradiation ( $\lambda = 1.54178$  Å, graphite monochromator),  $F(000) = 304$ . Intensities of 4027 reflections,

2723 of which were independent ( $R_{\text{int}} = 0.0526$ ), were measured by  $\omega$ -scanning in the range  $4.10 < \theta < 70.89^\circ$  ( $-7 \leq h \leq 7$ ,  $-12 \leq k \leq 12$ ,  $-4 \leq l \leq 13$ ). The structure was solved by the direct method [18]. All non-hydrogen atoms were refined in full-matrix anisotropic approximation with respect to  $F^2$  using SHELXL-97 program [19]. The final divergence factors were  $R_1 = 0.0344$ ,  $wR_2 = 0.0836$  [for 1263 reflections with  $I > 2\sigma(I)$ ]. The complete set of crystallographic data for compound IV is available from the authors.

**Methyl (1R\*,3R\*,3aS\*,6aR\*)-5-methyl-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (V).** Colorless crystals, mp 141–143°C [11].  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm: 2.61 br.s (1H, NH), 2.92 s (3H,  $\text{NCH}_3$ ), 3.38 d.d (1H, 3a-H,  $J = 8.6$ , 7.8 Hz), 3.69 d (1H, 6a-H,  $J = 7.8$  Hz), 3.84 s (3H,  $\text{OCH}_3$ ), 4.42 s (1H, 1-H), 4.63 d (1H, 3-H,  $J = 8.6$  Hz), 7.29–7.37 m (5H,  $\text{H}_{\text{arom}}$ ).  $^{13}\text{C}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta_{\text{C}}$ , ppm: 25.11, 48.48, 48.68, 52.74, 61.51, 63.13, 127.08 (2C), 128.23, 128.36 (2C), 137.56, 172.95, 175.05, 177.48.

**Methyl (1-methyl-2,5-dioxopyrrolidin-3-yl-amino)acetate (VIII).** Oily substance.  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm: 2.41 d.d (1H,  $\text{CH}_2$ ,  $J = 17.7$ , 4.6 Hz), 2.80 s (3H,  $\text{NCH}_3$ ), 2.87 d.d (1H,  $\text{CH}_2$ ,  $J = 17.7$ , 8.5 Hz), 3.49–3.59 m (2H,  $\text{CH}_2\text{COOCH}_3$ ), 3.63 s (3H,  $\text{OCH}_3$ ), 3.75 d.d (1H, CH,  $J = 8.5$ , 4.6 Hz). Mass spectrum,  $m/z$ : 200  $[M]^+$ , 112, 88, 56.

**Trimethyl (2S\*,3R\*,4R\*,5R\*)-5-phenylpyrrolidine-2,3,4-tricarboxylate (X).** Colorless crystals, mp 95–97°C.  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm: 2.57 br.s (1H, NH), 3.43 d.d (1H, 4-H,  $J = 8.8$ , 8.4 Hz), 3.66 s (3H,  $\text{OCH}_3$ ), 3.72 s (3H,  $\text{OCH}_3$ ), 3.77 s (3H,  $\text{OCH}_3$ ), 3.79 d (1H, 3-H,  $J = 8.4$  Hz), 4.24 d (1H, 2-H,  $J = 8.4$  Hz), 4.34 d (1H, 5-H,  $J = 8.8$  Hz), 7.30–7.39 m (3H,  $\text{H}_{\text{arom}}$ ), 7.46–7.48 m (2H,  $\text{H}_{\text{arom}}$ ). Found, %: C 60.00; H 5.94; N 4.59.  $\text{C}_{16}\text{H}_{19}\text{NO}_6$ . Calculated, %: C 59.81; H 5.96; N 4.36.

**Trimethyl (2R\*,3S\*,4S\*,5R\*)-5-phenylpyrrolidine-2,3,4-tricarboxylate (XI).** Colorless crystals, mp 105–107°C.  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm: 2.53 br.s (1H, NH), 3.17 s (3H, 4-COOCH $_3$ ), 3.71 s (3H,  $\text{OCH}_3$ ), 3.74 s (3H,  $\text{OCH}_3$ ), 3.79 t (1H, 4-H,  $J = 9.2$  Hz), 3.91 d.d (1H, 3-H,  $J = 9.2$ , 7.6 Hz), 4.51 d (1H, 2-H,  $J = 7.6$  Hz), 4.97 d (1H, 5-H,  $J = 9.2$  Hz), 7.23–7.26 m (1H,  $\text{H}_{\text{arom}}$ ), 7.28–7.32 m (4H,  $\text{H}_{\text{arom}}$ ). Found, %: C 59.93; H 5.99; N 4.49.  $\text{C}_{16}\text{H}_{19}\text{NO}_6$ . Calculated, %: C 59.81; H 5.96; N 4.36.

**Methyl (1S,3R,3aS,6aR)-1,5-dimethyl-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carbox-**



**ylate (XIIIa).** Yield 83% (catalyst L-Pyr). Colorless crystals, mp 217–218°C; published data [20]: mp 217–219°C;  $[\alpha]_D^{20} = +3^\circ$  ( $c = 0.57$ ,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm: 1.63 s (3H,  $\text{CH}_3$ ), 2.57 br.s (1H, NH), 2.83 s (3H,  $\text{NCH}_3$ ), 3.30 d (1H, 6a-H,  $J = 7.2$  Hz), 3.56 d.d (1H, 3a-H,  $J = 9.2, 7.2$  Hz), 3.90 s (3H,  $\text{COOCH}_3$ ), 4.79 d (1H, 3-H,  $J = 9.2$  Hz), 7.29–7.39 m (5H,  $\text{H}_{\text{arom}}$ ).  $^{13}\text{C}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta_{\text{C}}$ , ppm: 23.77, 24.84, 50.36, 52.65, 55.69, 62.13, 67.27, 126.96 (2C), 128.33, 128.46 (2C), 136.96, 172.78, 174.64, 175.79. Found, %: C 63.45; H 6.13; N 9.24.  $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_4$ . Calculated, %: C 63.57; H 6.00; N 9.27.

In the presence of L-Pro as catalyst, racemic product with the same spectral parameters was obtained in 75% yield.

**Methyl (1S\*,3R\*,3aS\*,6aR\*)-1-ethyl-5-methyl-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (XIIIb).** Yield 32 (L-Pro), 79% (L-Pyr). Colorless crystals, mp 170°C.  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm: 0.90 t (3H,  $\text{CH}_2\text{CH}_3$ ,  $J = 7.6$  Hz), 1.79–1.89 m (1H,  $\text{CH}_2\text{CH}_3$ ), 2.08–2.18 m (1H,  $\text{CH}_2\text{CH}_3$ ), 2.65 br.s (1H, NH), 2.82 s (3H,  $\text{NCH}_3$ ), 3.28 d (1H, 6a-H,  $J = 7.2$  Hz), 3.50 d.d (1H, 3a-H,  $J = 9.2, 7.2$  Hz), 3.90 s (3H,  $\text{OCH}_3$ ), 4.63 d (1H, 3-H,  $J = 9.2$  Hz), 7.31–7.38 m (5H,  $\text{H}_{\text{arom}}$ ).  $^{13}\text{C}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta_{\text{C}}$ , ppm: 7.94, 24.80, 27.91, 50.29, 52.48, 55.31, 61.40, 71.20, 126.99 (2C), 128.37, 128.48 (2C), 137.26, 172.03, 174.81, 175.87. Found, %: C 64.63; H 6.48; N 8.93.  $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_4$ . Calculated, %: C 64.54; H 6.37; N 8.85.

**Methyl (3aR,4S,6R,6aS)-4-methyl-1,3-dioxo-6-phenylhexahydrofuro[3,4-c]pyrrole-4-carboxylate (XIVa).** L-Pro: yield 48%,  $[\alpha]_D^{20} = -4.0^\circ$  ( $c = 0.56$ ,  $\text{CH}_2\text{Cl}_2$ ); L-Pyr: yield 42%,  $[\alpha]_D^{20} = -7.0^\circ$  ( $c = 0.52$ ,  $\text{CH}_2\text{Cl}_2$ ). Colorless crystals, mp 183–185°C.  $^1\text{H}$  NMR spectrum ( $\text{DMSO}-d_6$ ),  $\delta$ , ppm: 1.50 s (3H,  $\text{CH}_3$ ), 3.48 br.s (1H, NH), 3.65 d (1H, 3a-H,  $J = 8.0$  Hz), 3.71 s (3H,  $\text{OCH}_3$ ), 3.92 d.d (1H, 6a-H,  $J = 8.8, 8.0$  Hz), 4.78 d (1H, 6-H,  $J = 8.8$  Hz), 7.23–7.28 m (1H,  $\text{H}_{\text{arom}}$ ), 7.31–7.38 m (4H,  $\text{H}_{\text{arom}}$ ).  $^{13}\text{C}$  NMR spectrum ( $\text{DMSO}-d_6$ ),  $\delta_{\text{C}}$ , ppm: 22.92, 50.50, 52.38, 55.85, 61.10, 67.47, 127.65 (2C), 128.14, 128.51 (2C), 139.07, 170.29, 172.17, 172.68. Found, %: C 62.00; H 5.34; N 4.99.  $\text{C}_{15}\text{H}_{15}\text{NO}_5$ . Calculated, %: C 62.28; H 5.23; N 4.84.

**Methyl (3aR,4S,6R,6aS)-4-ethyl-1,3-dioxo-6-phenylhexahydrofuro[3,4-c]pyrrole-4-carboxylate (XIVb).** Yield 79% (L-Pyr),  $[\alpha]_D^{20} = +3.0^\circ$  ( $c = 0.50$ ,  $\text{CH}_2\text{Cl}_2$ ). Colorless crystals, mp 164°C.  $^1\text{H}$  NMR spectrum ( $\text{DMSO}-d_6$ ),  $\delta$ , ppm: 0.79 t (3H,  $\text{CH}_2\text{CH}_3$ ,  $J = 7.2$  Hz), 1.88 q (2H,  $\text{CH}_2\text{CH}_3$ ,  $J = 7.2$  Hz), 3.58 d (1H,

NH,  $J = 4.0$  Hz), 3.69 d (1H, 3a-H,  $J = 8.0$  Hz), 3.73 s (3H,  $\text{OCH}_3$ ), 3.89 d.d (1H, 6a-H,  $J = 9.2, 8.0$  Hz), 4.65 d.d (1H, 6-H,  $J = 9.2, 4.0$  Hz), 7.26–7.28 m (1H,  $\text{H}_{\text{arom}}$ ), 7.32–7.39 m (4H,  $\text{H}_{\text{arom}}$ ).  $^{13}\text{C}$  NMR spectrum ( $\text{DMSO}-d_6$ ),  $\delta_{\text{C}}$ , ppm: 8.11, 27.32, 50.55, 52.35, 55.69, 60.45, 71.54, 127.66 (2C), 128.18, 128.52 (2C), 139.10, 170.32, 171.68, 172.23. Found, %: C 63.28; H 5.66; N 4.84.  $\text{C}_{16}\text{H}_{17}\text{NO}_5$ . Calculated, %: C 63.36; H 5.65; N 4.62.

In the presence of L-Pro as catalyst, racemic product with the same spectral parameters was obtained in 75% yield.

## REFERENCES

1. Mauger, A.B., *J. Nat. Prod.*, 1996, vol. 59, p. 1205.
2. Burton, G., Ku, T.W., Carr, T.J., Kiesow, T., Sarisky, R.T., Lin-Goerke, J., Baker, A., Earnshaw, D.L., Hofmann, G.A., Keenan, R.M., and Dhanak, D., *Bioorg. Med. Chem. Lett.*, 2005, vol. 15, p. 1553; Zubia, A., Mendoza, L., Vivanco, S., Aldaba, E., Carrascal, T., Lecea, B., Arrieta, A., Zimmerman, T., Vidal-Vanaclocha, F., and Cossio, F.P., *Angew. Chem., Int. Ed.*, 2005, vol. 44, p. 2903; Fournie-Zaluski, M., Coric, P., Thery, V., Gonzalez, W., Meudal, H., Turcaud, S., Michel, J., and Roques, B.P., *J. Med. Chem.*, 1996, vol. 39, p. 2594; Murphy, M.M., Schullek, J.R., Gordon, E.M., and Gallop, M.A., *J. Am. Chem. Soc.*, 1995, vol. 117, p. 7029.
3. Grigg, R., *Chem. Soc. Rev.*, 1987, vol. 16, p. 89.
4. Tsuge, O. and Kanemasa, S., *Advances in Heterocyclic Chemistry*, Katritzky, A.R., Ed., San Diego: Academic, 1989, p. 231.
5. Kudryavtsev, K.V., Nukolova, N.V., Kokoreva, O.V., and Smolin, E.S., *Russ. J. Org. Chem.*, 2006, vol. 42, p. 412.
6. Kudryavtsev, K.V., Tsentelovich, M.Yu., Yegorov, A.S., and Kolychev, E.L., *J. Heterocycl. Chem.*, 2006, vol. 43, p. 1461.
7. Cabrera, S., Arrayas, R.G., and Carretero, J.C., *J. Am. Chem. Soc.*, 2005, vol. 127, p. 16394.
8. Oderaotoshi, Y., Cheng, W., Fujitomi, S., Kasano, Y., Minakata, S., and Komatsu, M., *Org. Lett.*, 2003, vol. 5, p. 5043.
9. Husinec, S. and Savic, V., *Tetrahedron: Asymmetry*, 2005, vol. 16, p. 2047.
10. Najera, C. and Sansano, J.M., *Angew. Chem., Int. Ed.*, 2005, vol. 44, p. 6272.
11. Tsuge, O., Kanemasa, S., Ohe, M., Yorozu, K., Takenaka, S., and Ueno, K., *Bull. Chem. Soc. Jpn.*, 1987, vol. 60, p. 4067.
12. Grigg, R., Gunaratne, H.Q.N., and Sridharan, V., *Tetrahedron*, 1987, vol. 43, p. 5887.

13. Dogan, O., Koyuncu, H., Garner, P., Bulut, A., Youngs, W.J., and Panzner, M., *Org. Lett.*, 2006, vol. 8, p. 4687.
14. Marigo, M. and Jorgensen, K.A., *Chem. Commun.*, 2006, p. 2001; List, B., *Chem. Commun.*, 2006, p. 819; Lelais, G. and MacMillan, D.W.C., *Aldrichim. Acta*, 2006, vol. 39, p. 79; Berkessel, A. and Groger, H., *Asymmetric Organocatalysis*, Weinheim: Wiley, 2005; Seayad, J. and List, B., *Org. Biomol. Chem.*, 2005, vol. 3, p. 719; Dalko, P.I. and Moisan, L., *Angew. Chem., Int. Ed.*, 2004, vol. 43, p. 5138; *Acc. Chem. Res.*, 2004, vol. 37 (special issue on organocatalysis).
15. List, B., *Tetrahedron*, 2002, vol. 58, p. 5573.
16. Amornraksa, K., Grigg, R., Gunaratne, H.Q.N., Kemp, J., and Sridharan, V., *J. Chem. Soc., Perkin Trans. 1*, 1987, p. 2285.
17. Potapov, V.M., *Stereokhimiya* (Stereochemistry), Moscow: Khimiya, 1988, p. 143.
18. Sheldrick, G.M., *Acta Crystallogr., Sect. A*, 1990, vol. 46, p. 467.
19. SHELXL-97, *Program for the Refinement of Crystal Structures*, Gottingen: Univ. of Gottingen, 1997.
20. Tsuge, O., Kanemasa, S., and Yoshioka, M., *J. Org. Chem.*, 1988, vol. 53, p. 1384.