The Synthesis and Transformations of 2-[2-Ethoxycarbonyl-2-(2-pyridinyl)ethenyl]amino-3-dimethylaminopropenoates. The Synthesis of Substituted β-Amino-α,β-didehydro-α-amino Acid Derivatives

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Alkyl (*Z*)-2-[(*E*)-2-ethoxycarbonyl-2-(2-pyridinyl)ethenyl]amino-3-dimethylaminopropenoates **7** and **8** were prepared from ethyl 2-pyridinylacetate (**1**) in two steps. Substitution of the dimethylamino group with alkyl-, aryl-, or heteroarylamines afforded the corresponding β-alkyl- **22-24**, β-aryl- **25-35**, and β-herteroaryl-amino-α,β-didehydro-α-amino acid **36** and **37** derivatives, intermediates for further preparation of various heterocyclic systems. The orientation around both double bonds were determined by various nmr techniques.

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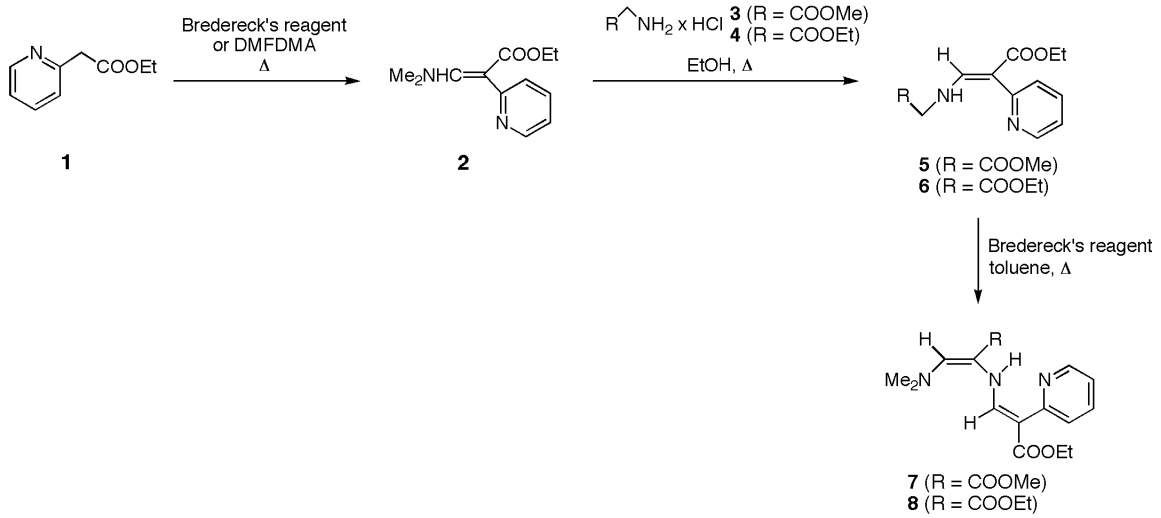
Recently, substituted 2-acylamino- or 2-hydroxy-3-(dimethylamino)propenoates as masked α-formyl-α-amino- or α-formyl-α-hydroxy acid derivatives, and 2-[(2,2-disubstituted ethenyl)amino]-3-(dimethylamino)-propenoates and related compounds have been prepared in our laboratory and used as reagents for preparation of various heterocyclic systems, such as 2*H*-pyran-2-ones and fused pyran-2-ones, fused pyridinones, pyrimidinones [1-10], imidazole-4-carboxylates [11], alkyl 1-acyl-3,4-disubstituted pyrrole-2-carboxylates [12,13], dialkyl 3-amino-pyrrole-2,4-dicarboxylates and 5*H*-pyrrolo[3,2-*d*]-pyrimidine derivatives [14], and (*Z*)-aplysinopsin analogs in a simple and stereoselektive manner [15]. Alkyl 2-[2-cyano-2-(2-pyridinyl)ethenyl]amino-3-dimethylamino-propenoates have been transformed into alkyl 2-[2-cyano-2-(2-pyridinyl)ethenyl]amino-3-[2-methoxycarbonyl-4-(2-pyridinyl)-1*H*-pyrrol-3-yl]aminopropenoates [16]. Chiral 3-(dimethylamino)propenoate analogs derived from L-glutamic and L-pyroglutamic acid have been used for the preparation of (*S*)-3-(heteroaryl)alanine and (*S*)-3-(heteroaryl)lactic acid derivatives, as well as for the preparation of heterocyclic systems with an α-amino acid structural element incorporated into the cyclic system [17-23].

In continuation of our studies in this area, we report the synthesis of alkyl (*Z*)-2-[(*E*)-2-alkoxycarbonyl-2-(2-pyridinyl)ethenyl]amino-3-dimethylaminopropenoates **7** and **8**, and their further transformations with alkyl-, aryl-, and heteroarylamines into β-alkyl (aryl and heteroaryl)amino-α,β-didehydro-α-amino acid derivatives **22-37** as intermediates for preparation of various heterocyclic systems.

Alkyl (*E*)-*N*-[2-ethoxycarbonyl-2-(2-pyridinyl)ethenyl]-glycinates **5** and **6** were prepared by heating a mixture of ethyl 2-pyridinylacetate (**1**) and *N*,*N*-dimethylformamid dimethylacetal (DMFDMA) or (*t*-butyloxy)bis(dimethyl-amino)methane (Bredereck's reagent) at 85 °C for 1.5 hours in an argon atmosphere to give ethyl 3-(dimethylamino-2-(2-pyridinyl)propenoate (**2**) followed, without purification, by treatment with an alkyl glycinate hydrochloride **3**, **4** in ethanol by heating at reflux temperature for 1.5 hours in 80-86% yield. They were transformed with (*t*-butyloxy)-

Scheme 1



1 **2** **5** (R = COOMe) **6** (R = COOEt) **7** (R = COOMe) **8** (R = COOEt)

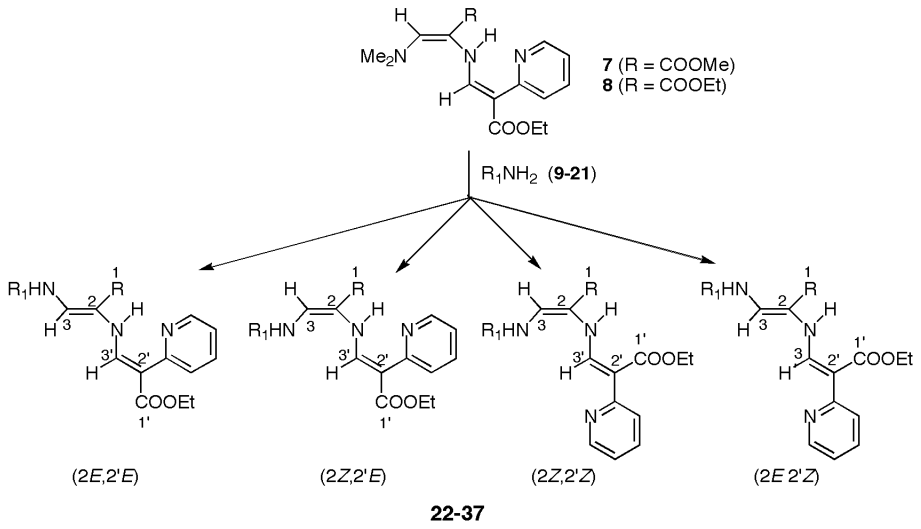
bis(dimethylamino)methane (Bredereck's reagent) in dry toluene by heating under reflux for several hours into alkyl (*Z*)-2-[(*E*)-2-ethoxycarbonyl-2-(2-pyridinyl)ethenyl]-amino-3-dimethylamino-propenoates **7** and **8** in 91% and 62% yield, respectively. (Scheme 1).

The dimethylamino group in compounds **7** and **8** can be easily substituted with benzyl amines **9-11**, aromatic amines **12-20**, and heteroaromatic amines, such as 2-amino-5-chloropyridine (**21**) in acetic acid at room temperature to form β-alkylamino-α,β-didehydro-α-amino acid derivatives **22-24** in 15-43% yield, β-arylamino-α,β-didehydro-α-amino acid derivatives **25-35** in 13-78% yield, and β-heteroarylamino-α,β-didehydro-α-amino acid derivatives **36** and **37** in 62 and 73% yield, respectively. (Scheme 2). Experimental and analytical data are given in Tables 1, 2, 3, and 4.

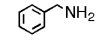
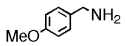
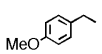
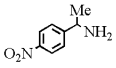
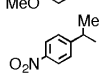
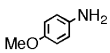
Structure Determination.

The structures of the new compounds were determined by ^{1}H nmr spectra and Heteronuclear Multiple Bond Correlation

Scheme 2



22-37

amines (R_1NH_2)		products					
			R	R_1-		R	R_1-
9		**22**	COOMe		**30**	COOMe	
10		**23**	COOMe		**31**	COOMe	
11		**24**	COOMe		**32**	COOMe	
12		**25**	COOMe		**33**	COOMe	
13		**26**	COOMe		**34**	COOEt	
14		**27**	COOMe		**35**	COOEt	
15		**28**	COOMe		**36**	COOMe	
16		**29**	COOMe		**37**	COOEt	
17							
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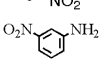
19							
20							
21							

Table 1
Experimental and Analytical Data

Compound	Yield (%)	mp (°C)	Molecular formula Analyses	Number of isomers (ratio)
5	86	95-97 from ethyl acetate/n-heptane (1:6)	$C_{13}H_{16}N_2O_4$ Calcd: C, 59.08; H, 6.10; N, 10.60 Found: C, 58.85; H, 5.86; N, 10.40	1
6	80	57-61 from ethyl acetate/n-heptane (1:6)	$C_{14}H_{18}N_2O_4$ Calcd: C, 60.42; H, 6.52; N, 10.07 Found:C, 60.43; H, 6.72; N, 10.00	1
7	91	115-117 from ethyl acetate/n-heptane (1:3)	$C_{16}H_{21}N_3O_4$ Calcd: C, 60.18; H, 6.63; N, 13.16 Found:C, 60.11; H, 6.88; N, 13.05	1
8	62	63-69 from ethyl acetate/n-heptane (1:3)	$C_{17}H_{23}N_3O_4$ Calcd: C, 61.25; H, 6.95; N, 12.60 Found:C, 61.23; H, 7.23; N, 12.57	1
22	36	106-108 from ethanol/water	$C_{21}H_{23}N_3O_4$ Calcd: C, 66.13; H, 6.08; N, 11.02 Found:C, 66.31; H, 6.17; N, 10.98	1 [a]
23	43	105-108 from ethanol/water	$C_{22}H_{25}N_3O_5$ Calcd: C, 64.22; H, 6.12; N, 10.21 Found:C, 64.43; H, 6.24; N, 10.23	1 [a]
24	15	103-107 from acetone	$C_{22}H_{24}N_4O_6$ Calcd: C, 59.99; H, 5.49; N, 12.72 Found:C, 59.63; H, 5.82; N, 11.80	1 [a]
25	23	132-144 from methanol	$C_{20}H_{21}N_3O_4$ Calcd: C, 65.38; H, 5.76; N, 11.44 Found:C, 65.31; H, 5.96; N, 11.43	4 [b] (11:9:2:1)
26	17	128-130 from methanol	$C_{21}H_{23}N_3O_5$ Calcd: C, 63.47; H, 5.83; N, 10.57 Found:C, 63.75; H, 5.90; N, 10.55	1 [a]
27	78	129-155 from methanol	$C_{21}H_{23}N_3O_5$ Calcd: C, 63.47; H, 5.83; N, 10.57 Found:C, 63.54; H, 6.09; N, 10.49	4 [b, c]
28	60	163-178 from methanol/toluene	$C_{20}H_{20}FN_3O_4$ Calcd: C, 62.33; H, 5.23; N, 10.90 Found:C, 62.60; H, 5.33; N, 10.96	4 [b] (11:6:1:1)
29	66	144-169 from methanol	$C_{20}H_{19}ClFN_3O_4$ Calcd: C, 57.22; H, 4.56; N, 10.01 Found:C, 57.25; H, 4.64; N, 10.02	4 [b] (13:9:2:1)
30	53	156-162 from methanol	$C_{20}H_{20}BrN_3O_4$ Calcd: C, 53.82; H, 4.52; N, 9.42 Found:C, 53.75; H, 4.48; N, 9.37	2 [d] (6:1)
31	13	129-132 from methanol/toluene	$C_{20}H_{20}BrN_3O_4$ Calcd: C, 53.82; H, 4.52; N, 9.42 Found:C, 54.37; H, 4.56; N, 9.42	2 [d] (7:1)
32	31	138-160 from methanol	$C_{20}H_{20}N_4O_6$ Calcd: C, 58.25; H, 4.89; N, 13.58 Found:C, 58.01; H, 4.87; N, 13.52	2 [d] (10:1)
33	45	158-162 from methanol	$C_{20}H_{20}N_4O_6$ Calcd: C, 58.25; H, 4.89; N, 13.58 Found:C, 58.19; H, 4.86; N, 13.59	2 [d] (8:1)
34	67	121-135 from ethanol	$C_{22}H_{25}N_3O_5$ Calcd: C, 64.22; H, 6.12; N, 10.21 Found:C, 64.20; H, 6.22; N, 10.34	2 [c, d]
35	37	159-165 from ethanol	$C_{21}H_{21}ClFN_3O_4$ Calcd: C, 58.14; H, 4.88; N, 9.68 Found:C, 58.07; H, 5.01; N, 9.54	1 [a]
36	62	192-194 from ethanol	$C_{19}H_{19}ClN_4O_4$ Calcd: C, 56.65; H, 4.75; N, 13.91 Found:C, 56.67; H, 4.72; N, 13.97	1 [a]
37	73	193-196 from ethanol/water	$C_{20}H_{21}ClN_4O_4$ Calcd: C, 57.63; H, 5.08; N, 13.44 Found:C, 57.77; H, 5.10; N, 13.55	1 [a]

[a] (2*E*, 2'*E*). [b] (2*E*, 2'*E*) : (2*Z*, 2'*E*) : (2*Z*, 2'*Z*) : (2*E*, 2'*Z*). [c] The ratio was not determined. [d] (2*E*, 2'*E*) : (2*Z*, 2'*E*).

Table 2

^{1}H nmr Data

Compound	MHz Solvent	δ (tetramethylsilane)
5	300 $CDCl_3$	1.33 (3H, t, $COOCH_2CH_3$), 3.79 (3H, s, COOMe), 4.12 (2H, d, CH_2), 4.24 (2H, q, $COOCH_2CH_3$), 6.97 (1H, ddd, H_5), 7.62 (1H, ddd, H_4), 7.92 (1H, d, C*H*NH), 8.31 (1H, ddd, H_3), 8.42 (1H, ddd, H_6), 11.02 (1H, br.s, CHN*H*), J_{H3H4} = 8.5 Hz, J_{H3H5} = 1.1 Hz, J_{H3H6} = 1.0 Hz, J_{H4H5} = 7.4 Hz, J_{H4H6} = 2.0 Hz, J_{H5H6} = 5.0 Hz, J_{CHNH} = 12.8 Hz, J_{CH2NH} = 6.0 Hz, J_{CH2CH3} = 7.1 Hz.
6	300 $CDCl_3$	1.30 (3H, t, $COOCH_2CH_3$), 1.33 (3H, t, $COOCH_2CH_3$), 4.10 (2H, d, CH_2), 4.24 (2H, q, $COOCH_2CH_3$), 4.25 (2H, q, $COOCH_2CH_3$), 6.96 (1H, ddd, H_5), 7.61 (1H, ddd, H_4), 7.93 (1H, d, C*H*NH), 8.31 (1H, ddd, H_3), 8.41 (1H, ddd, H_6), 11.02 (1H, br.s, CHN*H*), J_{H3H4} = 8.5 Hz, J_{H3H5} = 1.1 Hz, J_{H3H6} = 1.0 Hz, J_{H4H5} = 7.4 Hz, J_{H4H6} = 2.0 Hz, J_{H5H6} = 5.0 Hz, J_{CHNH} = 12.4 Hz, J_{CH2NH} = 6.0 Hz, J_{CH2CH3} = 7.1 Hz.
7	300 $CDCl_3$	1.32 (3H, t, $COOCH_2CH_3$), 3.03 (6H, s, $CHNMe_2$), 3.71 (3H, s, COOMe), 4.23 (2H, q, $COOCH_2CH_3$), 6.94 (1H, ddd, H_5), 7.27 (1H, s, C*H*NMe_2), 7.60 (1H, ddd, H_4), 7.90 (1H, d, C*H*NH), 8.34-8.38 (2H, m, H_3, H_6), 11.52 (1H, br.s, CHN*H*), J_{H3H4} = 8.6 Hz, J_{H3H5} = 1.1 Hz, J_{H3H6} = 0.7 Hz, J_{H4H5} = 7.2 Hz, J_{H4H6} = 1.7 Hz, J_{H5H6} = 5.0 Hz, J_{CHNH} = 12.5 Hz, J_{CH2CH3} = 7.1 Hz.
	DMSO-d_6	1.24 (3H, t, $COOCH_2CH_3$), 3.00 (6H, s, $CHNMe_2$), 3.59 (3H, s, COOMe), 4.14 (2H, q, $COOCH_2CH_3$), 7.07 (1H, ddd, H_5), 7.30 (1H, s, C*H*NMe_2), 7.71 (1H, ddd, H_4), 7.77 (1H, d, C*H*NH), 8.28 (1H, d, H_3), 8.46 (1H, ddd, H_6), 11.40 (1H, d, CHN*H*), J_{H3H4} = 8.4 Hz, J_{H3H5} = 1.1 Hz, J_{H3H6} = 1.0 Hz, J_{H4H5} = 7.3 Hz, J_{H4H6} = 1.9 Hz, J_{H5H6} = 5.0 Hz, J_{CHNH} = 13.0 Hz, J_{CH2CH3} = 7.0 Hz.
8	300 $CDCl_3$	1.26 (3H, t, $COOCH_2CH_3$), 1.31 (3H, t, $COOCH_2CH_3$), 3.03 (6H, s, $CHNMe_2$), 4.18 (2H, q, $COOCH_2CH_3$), 4.25 (2H, q, $COOCH_2CH_3$), 6.94 (1H, ddd, H_5), 7.24 (1H, s, C*H*NMe_2), 7.60 (1H, ddd, H_4), 7.93 (1H, d, C*H*NH), 8.36 (1H, ddd, H_3), 8.37 (1H, ddd, H_6), 11.58 (1H, d, CHN*H*), J_{H3H4} = 8.5 Hz, J_{H3H5} = 1.1 Hz, J_{H3H6} = 1.0 Hz, J_{H4H5} = 7.4 Hz, J_{H4H6} = 1.9 Hz, J_{H5H6} = 4.6 Hz, J_{CHNH} = 12.6 Hz, J_{CH2CH3} = 7.1 Hz.
22	300 $CDCl_3$	(2*E*, 2'*E*): 1.30 (3H, t, $COOCH_2CH_3$), 3.72 (3H, s, COOMe), 4.22 (2H, q, $COOCH_2CH_3$), 4.40 (2H, d, R_1CH_2NHCH), 5.09 (1H, m, R_1CH_2NHCH), 6.94-6.97 (1H, m, H_5'), 7.26-7.39 (5H, m, 5H(Ph)), 7.44 (1H, d, R_1CH_2NHCH), 7.59-7.64 (1H, m, H_4'), 7.95 (1H, d, C*H*NH), 8.30-8.41 (2H, m, H_3', H_6'), 11.27 (1H, br.s, CHN*H*), $J_{R1CH2NHCH}$ = 5.6 Hz, $J_{R1CH2NHCH}$ = 13.8 Hz, J_{CHNH} = 9.0 Hz, J_{CH2CH3} = 7.2 Hz.
23	300 $CDCl_3$	(2*E*, 2'*E*): 1.30 (3H, t, $COOCH_2CH_3$), 3.72, 3.80 (2x 3H, 2x s, COOMe, OMe), 4.22 (2H, q, $COOCH_2CH_3$), 4.33 (2H, d, R_1CH_2NHCH), 5.03 (1H, br.s, R_1CH_2NHCH), 6.89 (2H, d, H_3, H_5), 6.95 (1H, dd, H_5'), 7.19 (2H, d, H_2, H_6), 7.44 (1H, d, R_1CH_2NHCH), 7.62 (1H, dd, H_4'), 7.93 (1H, br.s, C*H*NH), 8.31 (1H, d, H_3'), 8.37 (1H, d, H_6'), 11.28 (1H, br.s, CHN*H*), $J_{H3'H4'}$ = 8.8 Hz, $J_{H4'H5'}$ = 6.6 Hz, J_{H2H3} = J_{H5H6} = 8.3 Hz, $J_{R1CH2NHCH}$ = 4.9 Hz, $J_{R1CH2NHCH}$ = 13.9 Hz, J_{CH2CH3} = 7.2 Hz.
24	300 $CDCl_3$	(2*E*, 2'*E*): 1.32 (3H, t, $COOCH_2CH_3$), 1.59 (3H, d, R_1(*Me*)CHNHCH), 3.69 (3H, s, COOMe), 4.24 (2H, q, $COOCH_2CH_3$), 4.60 (1H, qd, R_1(Me)C*H*NHCH), 5.07 (1H, dd, R_1(Me)CHN*H*CH), 7.00 (1H, ddd, H_5'), 7.26 (1H, d, R_1(Me)CHNHC*H*), 7.46 (2H, dd, H_2, H_6), 7.65 (1H, ddd, H_4'), 7.96 (1H, d, C*H*NH), 8.23 (2H, dd, H_3, H_5), 8.33 (1H, ddd, H_3'), 8.41 (1H, ddd, H_6'), 11.31 (1H, d, CHN*H*), $J_{H3'H4'}$ = 8.5 Hz, $J_{H3'H5'}$ = 1.1 Hz, $J_{H3'H6'}$ = 1.0 Hz, $J_{H4'H5'}$ = 7.4 Hz, $J_{H4'H6'}$ = 2.0 Hz, $J_{H5'H6'}$ = 5.0 Hz, J_{H2H3} = J_{H5H6} = 6.6 Hz, J_{H2H6} = J_{H3H5} = 2.0 Hz, $J_{R1(Me)CHNHCH}$ = 7.0 Hz, $J_{R1(Me)CHNHCH}$ = 13.7 Hz, $J_{R1(Me)CHNHCH}$ = 13.6 Hz, J_{CHNH} = 12.7 Hz, J_{CH2CH3} = 7.1 Hz.

(2*E*,2'*E*) and (2*Z*,2'*E*) isomers of **25** were separated by radial chromatography (petrolether/ethyl acetate = 5:1):

25	300 $CDCl_3$	(2*E*, 2'*E*): 1.31 (3H, t, $COOCH_2CH_3$), 3.79 (3H, s, COOMe), 4.24 (2H, q, $COOCH_2CH_3$), 6.78 (1H, br.d, R_1NHCH), 6.96-7.06 (4H, m, H_5', 3H(Ph)), 7.29-7.35 (2H, m, 2H(Ph)), 7.66 (1H, ddd, H_4'), 7.92 (1H, br.d, R_1NHCH), 8.01 (1H, br.d, C*H*NH), 8.36 (1H, ddd, H_3'), 8.45 (1H, ddd, H_6'), 11.53 (1H, br.s, CHN*H*), $J_{H3'H4'}$ = 8.5 Hz, $J_{H3'H5'}$ = 1.0 Hz, $J_{H3'H6'}$ = 1.0 Hz, $J_{H4'H5'}$ = 7.4 Hz, $J_{H4'H6'}$ = 2.1 Hz, $J_{H5'H6'}$ = 4.9 Hz, J_{R1NHCH} = 12.8 Hz, J_{CHNH} = 12.1 Hz, J_{CH2CH3} = 7.1 Hz. By addition of D_2O the doublet at δ = 6.78 ppm and the broad singlet at δ = 11.53 ppm disappear; the doublets at δ = 7.92 ppm and δ = 8.01 change into singlets.
		(2*Z*, 2'*E*): 1.33 (3H, t, $COOCH_2CH_3$), 3.86 (3H, s, COOMe), 4.26 (2H, q, $COOCH_2CH_3$), 7.41 (1H, br.d, R_1NHCH), 7.63 (1H, ddd, H_4'), 8.35 (1H, ddd, H_3'), 8.43 (1H, ddd, H_6'), 9.62 (1H, br.d, R_1NHCH), 12.01 (1H, br.d, CHN*H*). By addition of D_2O the doublet at δ = 9.62 ppm and the broad singlet at δ = 12.01 ppm disappear; the doublet at δ = 7.41 ppm changes into singlet.
		(2*Z*, 2'*Z*) and (2*E*, 2'*Z*): 1.36 (6H, t, 2x $COOCH_2CH_3$), 3.76, 3.83 (6H, 2x s, 2x COOMe), 4.32 (4H, q, 2x $COOCH_2CH_3$).
25 (2*E*, 2'*E*)	$CDCl_3$	1.31 (3H, t, $COOCH_2CH_3$), 3.79 (3H, s, COOMe), 4.23 (2H, q, $COOCH_2CH_3$), 6.83 (1H, d, R_1NHCH), 6.98-7.06 (4H, m, H_5', 3H(Ph)), 7.29-7.35 (2H, m, 2H(Ph)), 7.66 (1H, ddd, H_4'), 7.92 (1H, d, R_1NHCH), 7.99 (1H, d, C*H*NH), 8.36 (1H, ddd, H_3'), 8.45 (1H, ddd, H_6'), 11.49 (1H, d, CHN*H*), $J_{H3'H4'}$ = 8.5 Hz, $J_{H3'H5'}$ = 1.0 Hz, $J_{H3'H6'}$ = 1.0 Hz, $J_{H4'H5'}$ = 7.4 Hz, $J_{H4'H6'}$ = 2.1 Hz, $J_{H5'H6'}$ = 4.9 Hz, J_{R1NHCH} = 13.2 Hz, J_{CHNH} = 12.2 Hz, J_{CH2CH3} = 7.1 Hz. By addition of D_2O the doublets at δ = 6.83 ppm and δ = 11.49 ppm disappear; the doublets at δ = 7.92 ppm and δ = 7.99 change into broad singlets.
25 (2*Z*, 2'*E*)	$CDCl_3$	1.33 (3H, t, $COOCH_2CH_3$), 3.86 (3H, s, COOMe), 4.27, (2H, q, $COOCH_2CH_3$), 6.96-7.05 (4H, m, H_5', 3H(Ph)), 7.30-7.35 (2H, m, 2H(Ph)), 7.41 (1H, d, R_1NHCH), 7.63 (1H, ddd, H_4'), 8.01 (1H, d, C*H*NH), 8.35 (1H, ddd, H_3'), 8.44 (1H, ddd, H_6'), 9.62 (1H, d, R_1NHCH), 12.02 (1H, d, CHN*H*), $J_{H3'H4'}$ = 8.5 Hz, $J_{H3'H5'}$ = 1.0 Hz, $J_{H3'H6'}$ = 1.0 Hz, $J_{H4'H5'}$ = 7.4 Hz, $J_{H4'H6'}$ = 2.1 Hz, $J_{H5'H6'}$ = 4.9 Hz, J_{R1NHCH} = 12.5 Hz, J_{CHNH} = 12.2 Hz, J_{CH2CH3} = 7.1 Hz. By addition of D_2O the doublets at δ = 9.62 ppm and δ = 12.02 ppm disappear; the doublets at δ = 7.41 ppm and δ = 8.01 change into singlets.
26	300 DMSO-d_6	(2*E*, 2'*E*): 1.25 (3H, t, $COOCH_2CH_3$), 3.79 (3H, s, OMe), 3.90 (3H, s, COOMe), 4.16, (2H, q, $COOCH_2CH_3$), 6.95-7.11 (4H, m, 4H(Ph)), 7.51 (1H, ddd, H_5'), 7.73 (1H, ddd, H_4'), 7.80 (2H, d, R_1NHCH, C*H*NH), 8.26 (1H, ddd, H_3'), 8.48 (1H, ddd, H_6'), 9.93 (1H, d, R_1NHCH), 12.00 (1H, d, CHN*H*), $J_{H3'H4'}$ = 8.3 Hz, $J_{H4'H5'}$ = 7.5 Hz, J_{R1CHNH} = 12.6 Hz, J_{CHNH} = 12.3 Hz, J_{CH2CH3} = 7.1 Hz.

Table 2 (continued)

Compound	MHz Solvent	δ (tetramethylsilane)
27	300 $CDCl_3$	(2*E*, 2'*E*): 1.31 (3H, t, $COOCH_2CH_3$), 3.79 (6H, s, OMe, COOMe), 4.24 (2H, q, $COOCH_2CH_3$), 6.69 (1H, br.d, R_1NHCH), 6.85-7.03 (5H, m, H_5', 4H(Ph)), 7.66 (1H, ddd, H_4'), 7.84 (1H, br.d, R_1NHCH), 8.00 (1H, br.d, CHNH), 8.36 (1H, ddd, H_3'), 8.44 (1H, ddd, H_6'), 11.42 (1H, br.s, CHNH), $J_{H3'H4'}$ = 8.5 Hz, $J_{H3'H5'}$ = 1.1 Hz, $J_{H3'H6'}$ = 1.0 Hz, $J_{H4'H5'}$ = 7.4 Hz, $J_{H4'H6'}$ = 2.0 Hz, $J_{H5'H6'}$ = 5.0 Hz, J_{R1NHCH} = 13.0 Hz, J_{CHNH} = 12.5 Hz, J_{CH2CH3} = 7.1 Hz. (2*Z*, 2'*E*): 1.33 (3H, t, $COOCH_2CH_3$), 3.77, 3.84 (6H, 2x s, OMe, COOMe), 4.26 (2H, q, $COOCH_2CH_3$), 7.33 (1H, d, R_1NHCH), 7.63 (1H, ddd, H_4'), 8.34 (1H, ddd, H_3'), 8.43 (1H, ddd, H_6'), 9.54 (1H, br.d, R_1NHCH), 11.93 (1H, br.d, CHNH). The signals for (2*Z*, 2'*Z*) and (2*E*, 2'*Z*) isomers are overlapped.
28	300 $CDCl_3$	(2*E*, 2'*E*): 1.31 (3H, t, $COOCH_2CH_3$), 3.78 (3H, s, COOMe), 4.24 (2H, q, $COOCH_2CH_3$), 6.78 (1H, br.d, R_1NHCH), 6.93-7.06 (5H, m, H_5', 4H(Ph)), 7.66 (1H, ddd, H_4'), 7.82 (1H, br.d, R_1NHCH), 7.99 (1H, br.d, CHNH), 8.34 (1H, ddd, H_3'), 8.43 1H, ddd, H_6'), 11.43 (1H, br.s, CHNH), $J_{H3'H4'}$ = 8.5 Hz, $J_{H3'H5'}$ = 1.0 Hz, $J_{H3'H6'}$ = 0.9 Hz, $J_{H4'H5'}$ = 7.4 Hz, $J_{H4'H6'}$ = 2.0 Hz, $J_{H5'H6'}$ = 5.0 Hz, J_{R1NHCH} = 13.3 Hz, J_{CHNH} = 12.5 Hz, J_{CH2CH3} = 7.1 Hz. (2*Z*, 2'*E*): 1.33 (3H, t, $COOCH_2CH_3$), 3.85 (3H, s, COOMe), 4.26 (2H, q, $COOCH_2CH_3$), 7.31 (1H, d, R_1NHCH), 7.63 (1H, ddd, H_4'), 8.33 (1H, ddd, H_3'), 8.43 (1H, ddd, H_6'), 9.59 (1H, br.d, R_1NHCH), 12.00 (1H, br.d, CHNH). (2*Z*, 2'*Z*) and (2*E*, 2'*Z*): 3.76, 3.83 (6H, 2x s, 2x COOMe).
29	300 $DMSO-d_6$	(2*E*, 2'*E*): 1.22 (3H, t, $COOCH_2CH_3$), 3.69 (3H, s, COOMe), 4.14 (2H, q, $COOCH_2CH_3$), 7.11 (1H, ddd, H_5'), 7.20-7.71 (3H, m, 3H (Ph)), 7.76 (1H, ddd, H_4'), 7.85 (1H, br.d, R_1NHCH), 7.89 (1H, br.d, CHNH), 8.28 (1H, ddd, H_3'), 8.50 (1H, ddd, H_6'), 9.53 (1H, br.d, R_1NHCH), 11.57 (1H, br.d, CHNH), $J_{H3'H4'}$ = 8.5 Hz, $J_{H3'H5'}$ = 1.1 Hz, $J_{H3'H6'}$ = 1.0 Hz, $J_{H4'H5'}$ = 7.3 Hz, $J_{H4'H6'}$ = 2.0 Hz, $J_{H5'H6'}$ = 4.9 Hz, J_{R1NHCH} = 12.6 Hz, J_{CHNH} = 12.5 Hz, J_{CH2CH3} = 7.1 Hz. (2*Z*, 2'*E*): 1.25 (3H, t, $COOCH_2CH_3$), 3.80 (3H, s, COOMe), 4.16 (2H, q, $COOCH_2CH_3$), 7.09 (1H, ddd, H_5'), 7.75 (1H, ddd, H_4'), 7.76 (1H, br.d, R_1NHCH), 7.99 (1H, br.d, CHNH), 8.25 (1H, ddd, H_3'), 8.48 (1H, ddd, H_6'), 9.29 (1H, br.d, R_1NHCH), 12.02 (1H, br.d, CHNH). (2*Z*, 2'*Z*) and (2*E*, 2'*Z*): 3.68, 3.79 (6H, 2x s, 2x COOMe).
30	300 $CDCl_3$	(2*E*, 2'*E*): 1.34 (3H, t, $COOCH_2CH_3$), 3.89 (3H, s, COOMe), 4.27 (2H, q, $COOCH_2CH_3$), 6.88 (1H, ddd, H_5(Ph)), 7.00 (1H, ddd, H_5'), 7.11 (1H, ddd, H_3(Ph)), 7.30 (1H, ddd, H_4(Ph)), 7.38 (1H, br.d, R_1NHCH), 7.56 (1H, dd, H_6(Ph)), 7.64 (1H, ddd, H_4'), 8.03 (1H, br.d, CHNH), 8.34 (1H, ddd, H_3'), 8.45 (1H, ddd, H_6'), 10.04 (1H, br.d, R_1NHCH), 12.13 (1H, br.d, CHNH), $J_{H3'H4'}$ = 8.5 Hz, $J_{H3'H5'}$ = 1.1 Hz, $J_{H3'H6'}$ = 1.0 Hz, $J_{H4'H5'}$ = 7.4 Hz, $J_{H4'H6'}$ = 2.0 Hz, $J_{H5'H6'}$ = 5.0 Hz, J_{H3H4} = 8.2 Hz, J_{H3H5} = 1.5 Hz, J_{H4H5} = 7.4 Hz, J_{H4H6} = 1.5 Hz, J_{H5H6} = 8.0 Hz, J_{R1NHCH} = 12.2 Hz, J_{CHNH} = 11.9 Hz, J_{CH2CH3} = 7.1 Hz. (2*Z*, 2'*E*): 3.91 (3H, s, COOMe), 7.31 (1H, ddd, H_4(Ph)).
31	300 $CDCl_3$	(2*E*, 2'*E*): 1.34 (3H, t, $COOCH_2CH_3$), 3.84 (3H, s, COOMe), 4.28 (2H, q, $COOCH_2CH_3$), 6.89-6.92 (1H, ddd, 1H(Ph)), 6.99 (1H, ddd, H_5'), 7.12-7.23 (3H, m, 3H(Ph)), 7.32 (1H, br.d, R_1NHCH), 7.64 (1H, ddd, H_4'), 8.00 (1H, br.d, CHNH), 8.34 (1H, ddd, H_3'), 8.43 (1H, ddd, H_6'), 9.61 (1H, br.d, R_1NHCH), 12.08 (1H, br.d, CHNH), $J_{H3'H4'}$ = 8.7 Hz, $J_{H3'H5'}$ = 1.1 Hz, $J_{H3'H6'}$ = 1.0 Hz, $J_{H4'H5'}$ = 7.4 Hz, $J_{H4'H6'}$ = 1.9 Hz, $J_{H5'H6'}$ = 5.1 Hz, J_{R1NHCH} = 12.4 Hz, J_{CHNH} = 12.2 Hz, J_{CH2CH3} = 7.2 Hz. By addition of D_2O the doublets at δ = 9.61 ppm and δ = 12.08 ppm disappear; the doublets at δ = 7.32 ppm and δ = 8.00 ppm change into singlets. (2*Z*, 2'*E*): 3.86 (3H, s, COOMe).
32	300 $CDCl_3$	(2*E*, 2'*E*): 1.30 (3H, t, $COOCH_2CH_3$), 3.87 (3H, s, COOMe), 4.26 (2H, q, $COOCH_2CH_3$), 6.99-7.06 (2H, m, H_5', 1H(Ph)), 7.31-7.40 (1H, m, 1H(Ph)), 7.65 (1H, d, R_1NHCH), 7.67 (1H, ddd, H_4'), 7.78 (1H, d, CHNH), 8.22-8.32 (2H, m, 2H(Ph)), 8.40 (1H, ddd, H_3'), 8.47 (1H, ddd, H_6'), 10.23 (1H, br.d, R_1NHCH), 12.60 (1H, br.d, CHNH), $J_{H3'H4'}$ = 8.5 Hz, $J_{H3'H5'}$ = 1.1 Hz, $J_{H3'H6'}$ = 1.1 Hz, $J_{H4'H5'}$ = 7.4 Hz, $J_{H4'H6'}$ = 1.9 Hz, $J_{H5'H6'}$ = 6.0 Hz, J_{R1NHCH} = 12.2 Hz, J_{CHNH} = 12.6 Hz, J_{CH2CH3} = 7.2 Hz. (2*Z*, 2'*E*): 1.35 (3H, t, $COOCH_2CH_3$), 3.99 (3H, s, COOMe), 4.31 (2H, q, $COOCH_2CH_3$), 7.62 (1H, d, R_1NHCH), 7.63 (1H, ddd, H_4'), 7.90 (1H, d, CHNH).
33	300 $CDCl_3$	(2*E*, 2'*E*): 1.30 (3H, t, $COOCH_2CH_3$), 3.82 (3H, s, COOMe), 4.22 (2H, q, $COOCH_2CH_3$), 7.03 (1H, ddd, H_5'), 7.21 (1H, br.d, R_1NHCH), 7.29-7.32 (1H, m, 1H(Ph)), 7.45-7.50 (1H, m, 1H(Ph)), 7.67 (1H, ddd, H_4'), 7.83-7.88 (2H, m, 2H(Ph)), 7.86 (1H, br.d, CHNH), 7.95 (1H, br.s, R_1NHCH), 8.32 (1H, ddd, H_3'), 8.45 (1H, ddd, H_6'), 11.51 (1H, br.s, CHNH), $J_{H3'H4'}$ = 8.5 Hz, $J_{H3'H5'}$ = 1.1 Hz, $J_{H3'H6'}$ = 1.0 Hz, $J_{H4'H5'}$ = 7.4 Hz, $J_{H4'H6'}$ = 1.9 Hz, $J_{H5'H6'}$ = 5.0 Hz, J_{R1NHCH} = 12.9 Hz, J_{CHNH} = 12.9 Hz, J_{CH2CH3} = 7.2 Hz. (2*Z*, 2'*E*): 3.89 (3H, s, COOMe).
34	300 $CDCl_3$	(2*E*, 2'*E*): 1.30, 1.31 (6H, 2x t, 2x $COOCH_2CH_3$), 3.79 (3H, s, OMe), 4.20-4.34 (4H, m, 2x $COOCH_2CH_3$), 6.69 (1H, d, R_1NHCH), 6.86-7.03 (5H, m, H_5', 4H(Ph)), 7.66 (1H, ddd, H_4'), 7.81 (1H, d, R_1NHCH), 8.02 (1H, d, CHNH), 8.36 (1H, ddd, H_3'), 8.44 (1H, ddd, H_6'), 11.44 (1H, d, CHNH), $J_{H3'H4'}$ = 8.5 Hz, $J_{H3'H5'}$ = 1.0 Hz, $J_{H3'H6'}$ = 0.9 Hz, $J_{H4'H5'}$ = 7.3 Hz, $J_{H4'H6'}$ = 2.0 Hz, $J_{H5'H6'}$ = 5.0 Hz, J_{R1NHCH} = 13.4 Hz, J_{CHNH} = 12.3 Hz, J_{CH2CH3} = 7.1 Hz. (2*Z*, 2'*E*): 1.33, 1.37 (6H, 2x t, 2x $COOCH_2CH_3$), 7.31 (1H, d, R_1NHCH), 7.63 (1H, ddd, H_4'), 8.04 (1H, d, CHNH), 8.35 (1H, ddd, H_3'), 8.42 (1H, ddd, H_6'), 9.52 (1H, d, R_1NHCH), 12.16 (1H, d, CHNH).
35	300 $CDCl_3$	(2*E*, 2'*E*): 1.35, 1.39 (6H, 2x t, 2x $COOCH_2CH_3$), 4.28, 4.32 (4H, 2x q, 2x $COOCH_2CH_3$), 6.80-6.85 (1H, m, 1H(Ph)), 6.99 (1H, ddd, H_5'), 7.02-7.12 (2H, m, 2H (Ph)), 7.22 (1H, d, R_1NHCH), 7.64 (1H, ddd, H_4'), 8.03 (1H, d, CHNH), 8.34 (1H, ddd, H_3'), 8.42 (1H, ddd, H_6'), 9.57 (1H, d, R_1NHCH), 12.26 (1H, d, CHNH), $J_{H3'H4'}$ = 8.5 Hz, $J_{H3'H5'}$ = 1.1 Hz, $J_{H3'H6'}$ = 1.0 Hz, $J_{H4'H5'}$ = 7.4 Hz, $J_{H4'H6'}$ = 2.0 Hz, $J_{H5'H6'}$ = 5.0 Hz, J_{R1NHCH} = 12.2 Hz, J_{CHNH} = 12.2 Hz, J_{CH2CH3} = 7.1 Hz.
36	300 $CDCl_3$	(2*E*, 2'*E*): 1.30 (3H, t, $COOCH_2CH_3$), 3.80 (3H, s, COOMe), 4.22 (2H, q, $COOCH_2CH_3$), 6.77 (1H, dd, H_3), 7.02 (1H, ddd, H_5'), 7.46 (1H, d, R_1NHCH), 7.55 (1H, dd, H_4), 7.66 (1H, ddd, H_4'), 7.97 (1H, br.s, R_1NHCH), 8.22 (1H, d, H_6), 8.32 (1H, ddd, H_3'), 8.33 (1H, d, CHNH), 8.44 (1H, ddd, H_6'), 11.48 (1H, br.s, CHNH), J_{H3H4} = 8.7 Hz, J_{H3H6} = 0.6 Hz, J_{H4H6} = 2.5 Hz, $J_{H3'H4'}$ = 8.5 Hz, $J_{H3'H5'}$ = 1.0 Hz, $J_{H3'H6'}$ = 0.9 Hz, $J_{H4'H5'}$ = 7.3 Hz, $J_{H4'H6'}$ = 2.0 Hz, $J_{H5'H6'}$ = 5.0 Hz, J_{R1NHCH} = 13.4 Hz, J_{CHNH} = 12.5 Hz, J_{CH2CH3} = 7.2 Hz.

Table 2 (continued)

Compound	MHz Solvent	δ (tetramethylsilane)
37	300 $CDCl_3$	(2*E*, 2'*E*): 1.29 (3H, t, $COOCH_2CH_3$), 1.33 (3H, t, $COOCH_2CH_3$), 4.22 (2H, q, $COOCH_2CH_3$), 4.27 (2H, q, $COOCH_2CH_3$), 6.77 (1H, d, H_3), 7.01 (1H, ddd, H_5'), 7.45 (1H, d, R_1NHCH), 7.55 (1H, dd, H_4), 7.66 (1H, ddd, H_4'), 8.00 (1H, br.s, R_1NHCH), 8.22 (1H, dd, H_6), 8.29 (1H, d, $CHNH$), 8.32 (1H, ddd, H_3'), 8.44 (1H, ddd, H_6'), 11.56 (1H, br.s, $CHNH$), J_{H3H4} = 8.7 Hz, J_{H3H6} = 0.6 Hz, J_{H4H6} = 2.5 Hz, $J_{H3'H4'}$ = 8.6 Hz, $J_{H3'H5'}$ = 1.0 Hz, $J_{H3'H6'}$ = 0.8 Hz, $J_{H4'H5'}$ = 7.4 Hz, $J_{H4'H6'}$ = 1.9 Hz, $J_{H5'H6'}$ = 5.0 Hz, J_{R1NHCH} = 12.7 Hz, J_{CHNH} = 12.6 Hz, J_{CH2CH3} = 7.2 Hz.

Table 3

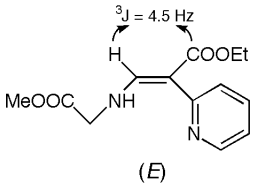
^1H nmr ($CDCl_3$) [a] (δ in ppm, J in Hz)

	d_{R1NHCH}	d_{R1NHCH}	d_{CHNH}	d_{CHNH}	J_{R1NHCH}	J_{CHNH}
22 (2*E*, 2'*E*)	7.44	5.09	7.95	11.27	13.8	9.0
23 (2*E*, 2'*E*)	7.44	5.03	7.93	11.28	13.9	-
24 (2*E*, 2'*E*)	7.26	5.07	7.96	11.31	13.6	12.7
26 (2*E*, 2'*E*)	7.80	9.93	7.80	12.00	12.6	12.3
35 (2*E*, 2'*E*)	7.22	9.57	8.03	12.26	12.2	12.2
36 (2*E*, 2'*E*)	7.46	7.97	8.33	11.48	13.4	12.5
37 (2*E*, 2'*E*)	7.45	8.00	8.29	11.56	12.7	12.6
30 [b] (2*E*, 2'*E*)	7.38	10.04	8.03	12.13	12.2	11.9
(2*Z*, 2'*E*)	7.38	10.04	8.03	12.13	12.2	11.9
31 [b] (2*E*, 2'*E*)	7.32	9.61	8.00	12.08	12.4	12.2
(2*Z*, 2'*E*)	7.32	9.61	8.00	12.08	12.4	12.2
32 [b] (2*E*, 2'*E*)	7.65	10.23	7.78	12.60	12.2	12.6
(2*Z*, 2'*E*)	7.62	10.23	7.90	12.60	12.2	12.6
33 [b] (2*E*, 2'*E*)	7.21	7.95	7.86	11.51	12.9	12.9
(2*Z*, 2'*E*)	7.21	7.95	7.86	11.51	12.9	12.9
34 (2*E*, 2'*E*)	7.81	6.69	8.02	11.44	13.4	12.3
(2*Z*, 2'*E*)	7.31	9.52	8.04	12.16	13.4	12.3
25 [b] (2*E*, 2'*E*)	7.92	6.78	8.01	11.53	12.8	12.1
(2*Z*, 2'*E*)	7.41,	9.62	8.01	12.01	12.8	12.1
(2*Z*, 2'*Z*) and (2*E*, 2'*Z*)	7.41, 7.92	6.78, 9.62	2X 8.01	11.53, 12.01	12.8	12.1
27 [b] (2*E*, 2'*E*)	7.84	6.69	8.00	11.42	13.0	12.5
(2*Z*, 2'*E*)	7.33	9.54	8.00	11.93	13.0	12.5
(2*Z*, 2'*Z*) and (2*E*, 2'*Z*)	2X 7.84	6.69, 9.54	2X 8.00	11.42, 11.93	13.0	12.5
28 [b] (2*E*, 2'*E*)	7.82	6.78	7.99	11.43	13.3	12.5
(2*Z*, 2'*E*)	7.31	9.59	7.99	12.00	13.3	12.5
(2*Z*, 2'*Z*) and (2*E*, 2'*Z*)	2X 7.82	6.78, 9.59	2X 7.99	11.43, 12.00	13.3	12.5
29 [b] (2*E*, 2'*E*)	7.85	9.53	7.89	11.57	12.6	12.5
(2*Z*, 2'*E*)	7.76	9.29	7.99	12.02	12.6	12.5
(2*Z*, 2'*Z*) and (2*E*, 2'*Z*)	7.76, 7.85	9.29, 9.53	7.89, 7.99	11.57, 12.02	12.6	12.5

[a] Spectra of compounds **26** and **29** were obtained in dimethyl sulfoxide-d_6 as solvent. [b] The similar chemical shifts and coupling constants for R_1NHCH, R_1NHCH, $CHNH$, and $CHNH$ for (2*E*, 2'*E*) and (2*Z*, 2'*E*) isomers in ^1H nmr spectra of compounds **30**-**33** and for some isomers in ^1H nmr spectra of compounds **25**, **27**-**29** result in broad singlets and broad doublets due to overlapping.

(HMBC) experiments. The HMBC nmr experiment of compound **5** in deuteriochloroform solution at room temperature shows that the compound exists in one isomeric form. The orientation around the C=C double bond was deduced from the coupling constant $^3J^{13}_{C=O,}{}^1_H$ = 4.5 Hz, which indicates the (*E*) orientation (Figure 1). The ^1H nmr chemical shifts and coupling constants for compound **5** [δ($CHNH$) = 7.92 ppm, δ($CHNH$) = 11.02 ppm, J_{CH-NH} = 12.8 Hz] are of similar values as those for compound **6** [δ($CHNH$) = 7.93 ppm, δ($CHNH$) = 11.02 ppm, J_{CH-NH} = 12.4 Hz].

The ^1H nmr spectra of compounds **7** and **8** in deuteriochloroform exhibit besides the signals characteristic for pyridine ring, ethyl and methyl groups in esters, and dimethylaminomethylene group, a doublet at δ = 7.90-7.93 ppm for $CHNH$ and δ = 11.52-11.58 ppm for $CHNH$ with the coupling constant J_{CHNH} = 12.5-12.6 Hz, thus indicating



(*E*)

5

Figure 1

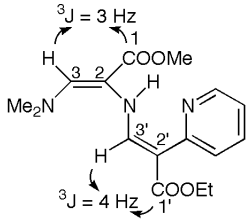
Table 4

^{13}C nmr Data

Compound	MHz Solvent	δ (tetramethylsilane)
5	75.5 $CDCl_3$	14.70 ($COOCH_2CH_3$), 50.16 ($COOCH_3$), 52.51 (CH_2NH), 59.48 ($COOCH_2CH_3$), 97.04, 118.73, 122.34, 135.95, 146.19, 153.21, 157.58, 167.92, 170.23.
7	75.5 $CDCl_3$	15.00 ($COOCH_2CH_3$), 43.12 ($N(CH_3)_2$), 51.75 ($COOCH_3$), 59.64 ($COOCH_2CH_3$), 96.66, 101.11, 118.75, 122.51, 136.16, 144.81, 146.42, 155.66, 158.28, 168.46, 168.55.
8	75.5 $CDCl_3$	14.96, 15.00 (2x $COOCH_2CH_3$), 43.07 ($N(CH_3)_2$), 59.61, 60.36 (2x $COOCH_2CH_3$), 96.49, 101.50, 118.72, 122.47, 136.16, 144.27, 146.40, 155.58, 158.34, 167.98, 168.49.
26	75.5 DMSO-d_6	15.05 ($COOCH_2CH_3$), 52.20 ($COOCH_3$), 56.52 (OMe), 59.37 ($COOCH_2CH_3$), 96.15, 106.11, 111.83, 113.43, 119.18, 121.69, 121.99, 122.76, 129.91, 136.61, 136.94, 146.89, 147.80, 151.48, 157.62, 166.84, 167.59.
29 [a]	75.5 DMSO-d_6	15.01, 15.05 (2X $COOCH_2CH_3$), 52.01, 52.21 (2X $COOCH_3$), 59.41, 59.66 (2X $COOCH_2CH_3$), 96.22, 97.37, 106.86, 107.33, 116.57, 116.66, 116.95, 117.04, 117.75, 117.82, 118.05, 118.16, 119.20, 119.36, 120.39, 120.55, 120.64, 120.80, 122.02, 122.11, 135.03, 136.61, 136.68, 137.04, 138.81, 139.40, 139.43, 146.86, 147.01, 148.84, 151.20, 151.62, 154.07, 154.81, 157.59, 157.68, 166.16, 166.31, 167.47, 167.60.

[a] The assigments of two major isomers in ^{13}C nmr spectrum are based on the signals of aliphatic groups. The assigments of other signals were not possible due to overlapping and ^{13}C-^{19}F couplings.

that the orientation of protons in NHCH structural element is *trans* (*antiperiplanar*). The orientation around the C=C double bonds was determined on the basis of HMBC nmr experiment for compound **7**, indicating that compound exists in one isomeric form. Both coupling constants, $^3J^{13}_{CO,}{}^1_H$ are 3 Hz and 4 Hz, respectively, indicating that the orientation around C(2)=C(3) is (*Z*), while the orientation around the C(2')=C(3') is (*E*). (Figure 2).



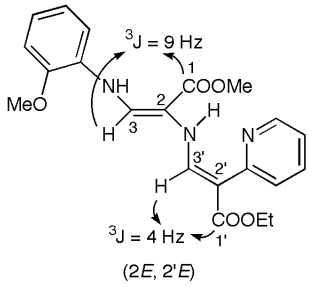
(2*Z*, 2'*E*)

7

Figure 2

The ^{1}H nmr spectra of crude compounds **22-37** [24] exhibit one, two or four sets of signals, indicating that these compounds exist in one, two or four isomeric forms. The ratio of isomers was determined on the basis of peaks for methyl and ethyl groups in esters, except for compounds **27** and **34**, due to overlapping of signals.

Compound **26** exists as a single isomer. The HMBC nmr experiment in dimethyl sulfoxide-d_6 (at 302 K), shows on the basis of the coupling constants $^3J^{13}_{CO,}{}^1_H$ = 9 Hz for ^{1}H-C(3)=C(2)-^{13}COOMe and $^3J^{13}_{CO,}{}^1_H$ = 4 Hz for ^{1}H-C(3')=C(2')-^{13}COOEt, that the compound exists in the (2*E*,2'*E*) form. (Figure 3). In ^{1}H nmr spectrum, compound **29** shows four sets of signals in the ratio of 13:9:2:1. The HMBC nmr experiment in dimethyl sulfoxide-d_6 (at 302

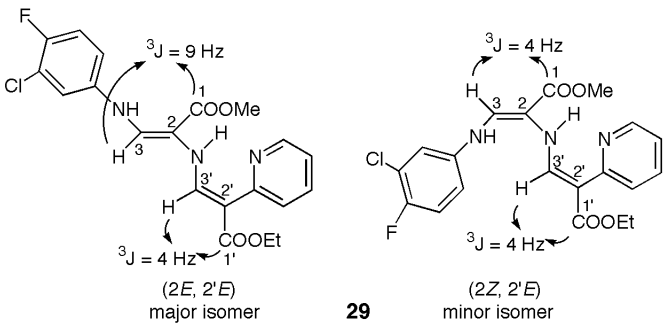


(2*E*, 2'*E*)

26

Figure 3

K) indicates (2*E*,2'*E*) orientation ($^3J^{13}_{CO,}{}^1_H$ = 9 Hz for ^{1}H-C(3)=C(2)-^{13}COOMe, and $^3J^{13}_{CO,}{}^1_H$ = 4 Hz for ^{1}H-C(3')=C(2')-^{13}COOEt) and (2*Z*, 2'*E*) orientation ($^3J^{13}_{CO,}{}^1_H$ = 4 Hz for ^{1}H-C(3)=C(2)-^{13}COOMe, and $^3J^{13}_{CO,}{}^1_H$ = 4 Hz for ^{1}H-C(3')=C(2')-^{13}COOEt) for two major isomers, respectively. (Figure 4). The determination of orientations around the double bonds for two minor isomers was not possible due to low ratios and overlapping with the signals of major isomers.



(2*E*, 2'*E*) major isomer **29** (2*Z*, 2'*E*) minor isomer

Figure 4

The orientation around the double bonds for all other compounds were determined on the basis of analogous chemical shifts for C*H*NH and CHN*H*, and J_{CH-NH} coupling constants in ^{1}H nmr spectra. In all cases the orientation in major isomer is (*E*) for C(2)=C(3) and (*E*) for C(2')=C(3') and in the second major isomer (or in the minor isomer for compounds which exist in two isomeric forms, respectively) is (*Z*) around the C(2)=C(3) and (*E*) around the C(2')=C(3') double bonds. Assignments of signals for the two minor isomers, (2*Z*, 2'*Z*) and (2*E*, 2'*Z*), for those compounds, which exist as four isomeric forms, were not possible. (Table 5).

Table 5

HMBC nmr Data

Compound	Solvent Temp.	
5	$CDCl_3$ 302 K	One isomer (*E*): $^3J^{13}_{CO,}{}^1_H$ = 4.5 Hz
7	$CDCl_3$ 302 K	One isomer (2*Z*, 2'*E*): $^3J^{13}_{CO,}{}^1_H$ = 3 Hz for ^{1}H-C(3)=C(2)-^{13}COOMe $^3J^{13}_{CO,}{}^1_H$ = 4 Hz for ^{1}H-C(3')=C(2')-^{13}COOEt
26	DMSO-d_6 302 K	One isomer (2*E*, 2'*E*): $^3J^{13}_{CO,}{}^1_H$ = 9 Hz for ^{1}H-C(3)=C(2)-^{13}COOMe $^3J^{13}_{CO,}{}^1_H$ = 4 Hz for ^{1}H-C(3')=C(2')-^{13}COOEt
29	DMSO-d_6 302 K	Four isomers (13:9:2:1) Major isomer (2*E*, 2'*E*): $^3J^{13}_{CO,}{}^1_H$ = 9 Hz for ^{1}H-C(3)=C(2)-^{13}COOMe $^3J^{13}_{CO,}{}^1_H$ = 4 Hz for ^{1}H-C(3')=C(2')-^{13}COOEt Minor isomer (2*Z*,2'*E*): $^3J^{13}_{CO,}{}^1_H$ = 4 Hz for ^{1}H-C(3)=C(2)-^{13}COOMe $^3J^{13}_{CO,}{}^1_H$ = 4 Hz for ^{1}H-C(3')=C(2')-^{13}COOEt

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^{1}H nmr spectra were obtained on a Bruker Avance DPX 300 (300 MHz) spectrometer in such solvent as dimethyl sulfoxide-d_6 and deuteriochloroform with tetramethylsilane as internal standard. The elemental analyses for C, H and N were obtained on a Perkin-Elmer CHN Analyser 2400.

General Procedure for the Preparation of Alkyl (*E*)-*N*-[2-Ethoxycarbonyl-2-(2-pyridinyl)ethenyl]glycinates **5**, **6**.

The mixture of ethyl 2-pyridinylacetate (**1**) (20 mmol, 3 ml) and Bredereck's reagent (25 mmol, 5 ml) was stirred in the oil bath at 85 °C in an argon atmosphere for 1.5 hours. Then ethanol (10 ml) was added and the volatile compounds were evaporated *in vacuo*. The obtained oily residue, ethyl 3-dimethylamino-2-(2-pyridinyl)propenoate (**2**), was without further purification dissolved in ethanol (25 ml), glycine alkyl ester hydrochloride **3** or **4** (20 mmol) was added, and the mixture was heated under reflux for 1.5 hours. The volatile compounds were evaporated *in vacuo* and water (30 ml) was added. The precipitate, which had been formed in refrigerator, was collected by filtration and washed with ether (5 ml). The following compounds were prepared in this manner: methyl (*E*)-*N*-[2-ethoxycarbonyl-2-(2-pyridinyl)-ethenyl]glycinate (**5**) from glycine methyl ester hydrochloride (**3**) (20 mmol, 2.5 g) and ethyl (*E*)-*N*-[2-ethoxycarbonyl-2-(2-pyridinyl)ethenyl]glycinate (**6**) from glycine ethyl ester hydrochloride (**4**) (20 mmol, 2.8 g). Experimental and analytical data are given in Tables 1, 2, and 5.

General Procedure for the Preparation of Alkyl (*Z*)-2-[(*E*)-2-Ethoxycarbonyl-2-(2-pyridinyl)ethenyl]amino-3-dimethylaminopropenoates **7**, **8**.

To compound **5** or **6** (10 mmol) suspended in dry toluene (10 ml), Bredereck's reagent (20 mmol) was added and the mixture was heated under reflux for several hours. The volatile compounds were evaporated *in vacuo* and the mixture of ethyl acetate (5 ml)/*n*-heptane (15 ml) was added. The precipitate was collected by filtration and washed with ether. The following compounds were prepared in this manner: methyl (*Z*)-2-[(*E*)-2-ethoxycarbonyl-2-(2-pyridinyl)ethenyl]amino-3-dimethylaminopropenoate (**7**) and ethyl (*Z*)-2-[(*E*)-2-ethoxycarbonyl-2-(2-pyridinyl)ethenyl]amino-3-dimethylamino-propenoate (**8**). Experimental and analytical data are given in Tables 1, 2, 4, and 5.

General Procedure for the Preparation of β-Alkylamino-α,β-didehydro-α-amino Acid Derivatives **22-24**.

To compound **7** (0.5 mmol, 160 mg) the corresponding aliphatic amine **9-11** (0.5 mmol) and acetic acid (2 ml) were added and stirred at room temperature for 24 hours. The volatile compounds were evaporated *in vacuo*, the appropriate solvent (3 ml) was added and the precipitate was collected by filtration.

Methyl (*E*)-2-[(*E*)-2-Ethoxycarbonyl-2-(2-pyridinyl)ethenyl]–amino-3-benzylaminopropenoate (**22**).

This compound was prepared from bezylamine hydrochloride (**9**) (0.5 mmol, 54 mg). The mixture of ethanol (1 ml) and water (1 ml) was used for crystallization. Experimental and analytical data are given in Tables 1,2 , and 3.

Methyl (*E*)-2-[(*E*)-2-Ethoxycarbonyl-2-(2-pyridinyl)ethenyl]–amino-3-(4-methoxybenzyl)aminopropenoate (**23**).

This compound was prepared from 4-methoxybezylamine (**10**) (0.5 mmol, 63 mg). The mixture of ethanol (1 ml) and water (1 ml) was used for crystallization. Experimental and analytical data are given in Tables 1, 2, and 3.

Methyl (*E*)-2-[(*E*)-2-Ethoxycarbonyl-2-(2-pyridinyl)ethenyl]–amino-3-(4-nitro-α-methylbenzyl)aminopropenoate (**24**).

This compound was prepared from 4-nitro-α-methylbezyl-amine hydrochloride (**11**) (0.5 mmol, 101 mg). Acetone (2 ml)

was used for crystallization. Experimental and analytical data are given in Tables 1, 2, and 3.

General Procedure for the Preparation of β-Arylamino-α,β-didehydro-α-amino Acid Derivatives **25-35**.

To compound **7** (0.5 mmol, 160 mg) or **8** (0.5 mmol, 167 mg) the corresponding aromatic amine **12-20** (0.5 mmol) and acetic acid (2 ml) were added and stirred at room temperature for a few minutes to 24 hours. The volatile compounds were evaporated *in vacuo*, the appropriate solvent (3 ml) was added and the precipitate was collected by filtration.

Methyl (*E*)-2-[(*E*)-2-Ethoxycarbonyl-2-(2-pyridinyl)ethenyl]–amino-3-phenylaminopropenoate (**25**) and (*Z*)-2-[(*E*)-, (*Z*)-2-[(*Z*)-, and (*E*)-2-[(*Z*)- Isomers.

This compound was prepared from compound **7** (0.5 mmol, 160 mg) and alanine (**12**) (0.5 mmol, 47 mg), 24 hours, in 11:9:2:1 ratio. The mixture of methanol (1 ml) and water (1 ml) was used for crystallization. Two isomers, (*E*)-2-[(*E*)- and (*Z*)-2-[(*E*)-, were separated with radial chromatography (petrol-ether/ethyl acetate = 5:1). Experimental and analytical data are given in Tables 1, 2, and 3.

Methyl (*E*)-2-[(*E*)-2-Ethoxycarbonyl-2-(2-pyridinyl)ethenyl]–amino-3-(2-methoxyphenyl)aminopropenoate (**26**).

This compound was prepared from compound **7** (0.5 mmol, 160 mg) and 2-methoxyaniline (**13**) (0.5 mmol, 62 mg), 24 hours. The mixture of methanol (1 ml) and water (1 ml) was used for crystallization. Experimental and analytical data are given in Tables 1, 2, 3, and 5.

Methyl (*E*)-2-[(*E*)-2-Ethoxycarbonyl-2-(2-pyridinyl)ethenyl]–amino-3-(4-methoxyphenyl)aminopropenoate (**27**) and (*Z*)-2-[(*E*)-, (*Z*)-2-[(*Z*)-, and (*E*)-2-[(*Z*)- Isomers.

This compound was prepared from compound **7** (0.5 mmol, 160 mg) and 4-methoxyaniline (**14**) (0.5 mmol, 61 mg), 24 hours. The ratio was not defined. Methanol (2 ml) was used for crystallization. Experimental and analytical data are given in Tables 1, 2, and 3.

Methyl (*E*)-2-[(*E*)-2-Ethoxycarbonyl-2-(2-pyridinyl)ethenyl]–amino-3-(4-flourophenyl)aminopropenoate (**28**) and (*Z*)-2-[(*E*)-, (*Z*)-2-[(*Z*)-, and (*E*)-2-[(*Z*)- Isomers.

This compound was prepared from compound **7** (0.5 mmol, 160 mg) and 4-fluoroaniline (**15**) (0.5 mmol, 56 mg), 24 hours, in 11:6:1:1 ratio. Methanol (2 ml) was used for crystallization. Experimental and analytical data are given in Tables 1, 2, and 3.

Methyl (*E*)-2-[(*E*)-2-Ethoxycarbonyl-2-(2-pyridinyl)ethenyl]–amino-3-(3-chloro-4-flourophenyl)aminopropenoate (**29**) and (*Z*)-2-[(*E*)-, (*Z*)-2-[(*Z*)-, and (*E*)-2-[(*Z*)- Isomers.

This compound was prepared from compound **7** (0.5 mmol, 160 mg) and 3-chloro-4-fluoroaniline (**16**) (0.5 mmol, 74 mg), 24 hours, in 13:9:2:1 ratio. Methanol (2 ml) was used for crystallization. Experimental and analytical data are given in Tables 1,2, 3, and 5.

Methyl (*E*)-2-[(*E*)-2-[2-Ethoxycarbonyl-2-(2-pyridinyl)-ethenyl]amino-3-(2-bromophenyl)aminopropenoate (**30**) and (*Z*)-2-[(*E*)- Isomer.

This compound was prepared from compound **7** (0.5 mmol, 160 mg) and 2-bromoaniline (**17**) (0.5 mmol, 83 mg), 24 hours, in 6:1 ratio. Methanol (2 ml) was used for crystallization. Experimental and analytical data are given in Tables 1, 2, and 3.

Methyl (*E*)-2-[(*E*)-2-[2-Ethoxycarbonyl-2-(2-pyridinyl)-ethenyl]amino-3-(3-bromophenyl)aminopropenoate (**31**) and (*Z*)-2-[(*E*)- Isomer.

This compound was prepared from compound **7** (0.5 mmol, 160 mg) and 3-bromoaniline (**18**) (0.5 mmol, 83 mg), 24 hours, in 7:1 ratio. Methanol (2 ml) was used for crystallization. Experimental and analytical data are given in Tables 1, 2, and 3.

Methyl (*E*)-2-[(*E*)-2-Ethoxycarbonyl-2-(2-pyridinyl)ethenyl]–amino-3-(2-nitrophenyl)aminopropenoate (**32**) and (*Z*)-2-[(*E*)-Isomer.

This compound was prepared from compound **7** (0.5 mmol, 160 mg) and 2-nitroaniline (**19**) (0.5 mmol, 70 mg), 10 minutes, in 10:1 ratio. Methanol (2 ml) was used for crystallization. Experimental and analytical data are given in Tables 1, 2, and 3.

Methyl (*E*)-2-[(*E*)-2-Ethoxycarbonyl-2-(2-pyridinyl)ethenyl]–amino-3-(3-nitrophenyl)aminopropenoate (**33**) and (*Z*)-2-[(*E*)-Isomer.

This compound was prepared from compound **7** (0.5 mmol, 160 mg) and 3-nitroaniline (**20**) (0.5 mmol, 70 mg), 24 hours, in 8:1 ratio. Methanol (2 ml) was used for crystallization. Experimental and analytical data are given in Tables 1, 2, and 3.

Ethyl (*E*)-2-[(*E*)-2-Ethoxycarbonyl-2-(2-pyridinyl)ethenyl]–amino-3-(4-methpxyphenyl)aminopropenoate (**34**) and (*Z*)-2-[(*E*)- Isomer.

This compound was prepared from compound **8** (0.5 mmol, 167 mg) and 4-methoxyaniline (**14**) (0.5 mmol, 61 mg), 24 hours. The ratio was not defined. Ethanol (2 ml) was used for crystallization. Experimental and analytical data are given in Tables 1, 2, and 3.

Ethyl (*E*)-2-[(*E*)-2-Ethoxycarbonyl-2-(2-pyridinyl)ethenyl]–amino-3-(4-fluoro-3-chlorophenyl)aminopropenoate (**35**).

This compound was prepared from compound **8** (0.5 mmol, 167 mg) and 4-fluoro-3-chloroaniline (**16**) (0.5 mmol, 74 mg), 24 hours. Ethanol (2 ml) was used for crystallization. Experimental and analytical data are given in Tables 1, 2, and 3.

The Preparation of β-Heteroarylamino-α,β-didehydro-α-amino Acid Derivatives **36, 37**.

Methyl (*E*)-2-[(*E*)-2-Ethoxycarbonyl-2-(2-pyridinyl)ethenyl]–amino-3-(5-chloro-2-pyridinyl)aminopropenoate (**36**).

To compound **7** (0.5 mmol, 160 mg) 2-amino-5-chloropyridine (**21**) (0.5 mmol, 64 mg) and acetic acid (2 ml) were added and stirred at room temperature for 4 days. The volatile compounds were evaporated *in vacuo* and ethanol (2 ml) was added. The precipitate was collected by filtration and washed with ethanol. Experimental and analytical data are given in Tables 1, 2, and 3.

Ethyl (*E*)-2-[(*E*)-2-Ethoxycarbonyl-2-(2-pyridinyl)ethenyl]–amino-3-(5-chloro-2-pyridinyl)aminopropenoate (**37**).

To compound **8** (0.5 mmol, 167 mg) 2-amino-5-chloropyridine (**21**) (0.5 mmol, 64 mg) and acetic acid (2 ml) were added and stirred at room temperature for 24 hours. The volatile compounds were evaporated *in vacuo* and ethanol (2 ml) was added. The precipitate was collected by filtration and washed with ethanol. Experimental and analytical data are given in Tables 1, 2, and 3.

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REFERENCES AND NOTES

[1] L. Selič, S. Golič Grdadolnik, and B. Stanovnik, *Helv. Chim. Acta*, **80**, 2418 (1997).

[2] R. Toplak, L. Selič, G. Soršak, and B. Stanovnik, *Heterocycles*, **45**, 555 (1997).

[3] L. Pizzioli, B. Ornik, J. Svete, and B. Stanovnik, *Helv. Chim. Acta*, **81**, 231 (1998).

[4] J. Smodiš and B. Stanovnik, *Tetrahedron*, **54**, 9799 (1998).

[5] R. Toplak, J. Svete, B. Stanovnik, and S. Golič Grdadolnik, *J. Heterocyclic Chem.*, **36**, 225 (1999).

[6] R. Toplak, J. Svete, S. Golič Grdadolnik, and B. Stanovnik, *Collect. Czech. Chem. Commun.*, **64**, 177 (1999).

[7] L. Selič, S. Golič Grdadolnik, and B. Stanovnik, *Heterocycles*, **49,** 133 (1998).

[8] R. Toplak, M. Zucchiati, S. Golič Grdadolnik, and B. Stanovnik, *Heterocycles*, **50**, 853 (1999).

[9] U. Bratušek, A. Hvala, and B. Stanovnik, *J. Heterocyclic Chem.*, **35**, 1281 (1998).

[10] S. Rečnik, R. Toplak, J. Svete, L. Pizzioli, and B. Stanovnik, *J. Heterocyclic Chem.*, **37**, 783 (2000).

[11] L. Selič and B. Stanovnik, *J. Heterocyclic Chem.*, **35**, 1527 (1999).

[12] M. Malešič, A. Krbavčič, A. Golobič, L. Golič, and B. Stanovnik, *J. Heterocyclic Chem.*, **34**, 1757 (1997).

[13] L. Selič and B. Stanovnik, *Synthesis*, 1999, 479.

[14] L. Selič and B. Stanovnik, *Helv. Chim. Acta*, **81**, 1634 (1998).

[15] L. Selič, R. Jakše, K. Lampič, L. Golič, S. Golič Grdadolnik, and B. Stanovnik, *Helv. Chim. Acta*, **83**, 2802 (2000).

[16] L. Jukić, J. Svete, A. Golobič, L. Golič, and B. Stanovnik, *Heterocycles*, **53**, 805 (2000).

[17] M. Škof, J. Svete, B. Stanovnik, L. Golič, S. Golič Grdadolnik, and L. Selič, *Helv. Chim. Acta*, **81**, 2332 (1998).

[18] M. Škof, J. Svete, M. Kmetič, S. Golič Grdadolnik, and B. Stanovnik, *Eur. J. Org. Chem.*, 1999, 1581.

[19] M. Škof, J. Svete, and B. Stanovnik, *Heterocycles*, **51**, 1051 (1999).

[20] M. Škof, J. Svete, and B. Stanovnik, *Heterocycles*, **52**, 845 (2000).

[21] M. Škof, J. Svete, and B. Stanovnik, *Heterocycles*, **53**, 339 (2000).

[22] M. Škof, J. Svete, and B. Stanovnik, *J. Heterocyclic Chem.*, **37**, 703 (2000).

[23] For reviews see: [a] B. Stanovnik, *J. Heterocyclic Chem.*, **36,** 1581 (1999); [b] B. Stanovnik and J. Svete, *Synlett*, 2000, 1077; [c] B. Stanovnik and J. Svete, "Alkyl 3-(Dimethylamino)propenoates and Related Compounds as Useful Building Blocks in the Synthesis of Heterocyclic Systems – Approaches Towards the Synthesis of Natural Products and their Close Analogs" in "Targets in Heterocyclic Systems. Chemistry and Properties", O. A. Attanasi, D. Spinelli, eds., Vol. 4, Reviews and Accounts on Heterocyclic Chemistry, Italian Society of Chemistry, Rome 2000, pp. 105-137.

[24] The samples of crude products **22-37**, isolated from the reaction mixtures were used without further purification for determination of isomer ratios by ^{1}H nmr techniques.