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SYNTHESIS OF CYTOTOXIC 1,3,4-TRISUBSTITUTED 2-AZETIDINONES*

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A series of 1,3,4-trisubstituted and 3,4-disubstituted 2-azetidinones were synthesized in order to study the relation between their structure and biological characteristics. Study of the cytotoxic activity of these compounds revealed an anticancer effect in (3S,4S)- 1-(4-methoxyphenyl)-3-methyl-2-azetidinones containing 2-acetoxybenzoyloxymethyl and 2,2-dicyanovinyl substituents at position 4 in vitro with respect to a wide range of monolayer cultures of cancer cells.

Keywords: 4-substituted (3*S*,4*S*)-1-(4-methoxyphenyl)-3-methyl-2-azetidinones, cytotoxic activity.

Investigations of the last 15 years have demonstrated convincingly the prospects of structural modification of the substituents in monocyclic β-lactams as an effective procedure for the detection and enhancement of pharmacological effects not related to antibacterial characteristics. Various 1,3,4-trisubstituted 2-azetidinones having anti-inflammatory, anticoagulation, anticancer, and antiviral characteristics due to the ability of these compounds to inhibit serine-containing proteases (elastase [1-3], thrombine [4], the specific antigen of the prostate [5], and protease of human cytomegalovirus [6,7]) were produced.

Earlier we presented data on the presence of anticancer characteristics in 4-heteryldithio-substituted 2-azetidinones, produced by the reaction of heterocyclic thiols with the sulfoxides of 6,6-dihydro- and 6α-chloropenicillanates [8]. In a continuation of the research into the relation between the structure and cytotoxic characteristics of monocyclic β-lactams as subject for structural modification in the present work we chose *cis*-4-formyl-1-(4-methoxyphenyl)-3-methyl-2-azetidinone (**1**), produced [9] by the cyclocondensation of glyoxaldimine (**2**) with propionyl chloride (**3**) (Scheme 1).

By oxidative and reductive transformation of the formyl group in this compound it was possible to obtain its carboxyl and hydroxymethyl analogs **4** and **5**. The corresponding ester **7** was synthesized by the action of 2-acetoxybenzoic acid **6** on **5** in the presence of a base. The substituted 4-vinyl-1-(4-methoxyphenyl)-3-methyl-2-azetidinones **9**, **12a**,**b**, and **14a**,**b** were synthesized by the condensation of **1** with malononitrile **8** or with the phosphoranes **11** and **13**.

4-(2,2-Dicyanoethyl)-2-azetidinone (**10**) was obtained by the catalytic hydrogenation of the double bond in compound **9**.

* Dedicated to Prof. A. A. Potekhin on his 65th birthday.

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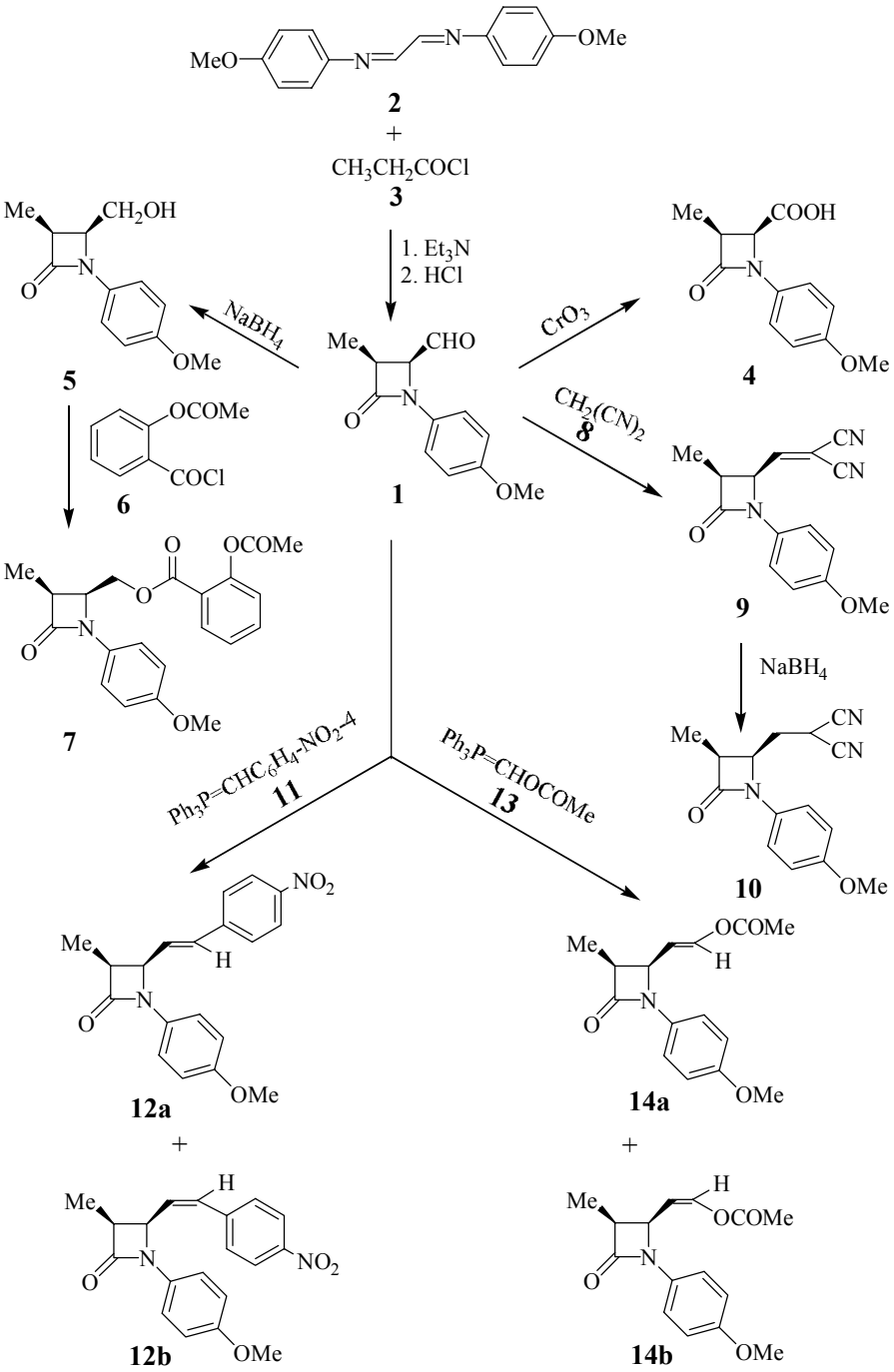
Scheme 1



In order to study the effect of the nature of the substituents, their size, and their configuration on the biological characteristics of the monocyclic β-lactams the following compounds were also synthesized (Scheme 2): a) 4-Acetoxy-1-(1-methoxycarbonyl-2-methyl-1-propenyl)-3-phthalimido-2-azetidinone (**16**) and *trans*-4-acetoxy-3-phthalimido-2-azetidinone (**17**) [10]; b) 3-benzoyloxycarbonylamino-2-azetidinone (**19**) [11] was obtained by an original cyclization of 3-amino-2-benzyloxycarbonylaminopropionic acid (**18**).

Scheme 2

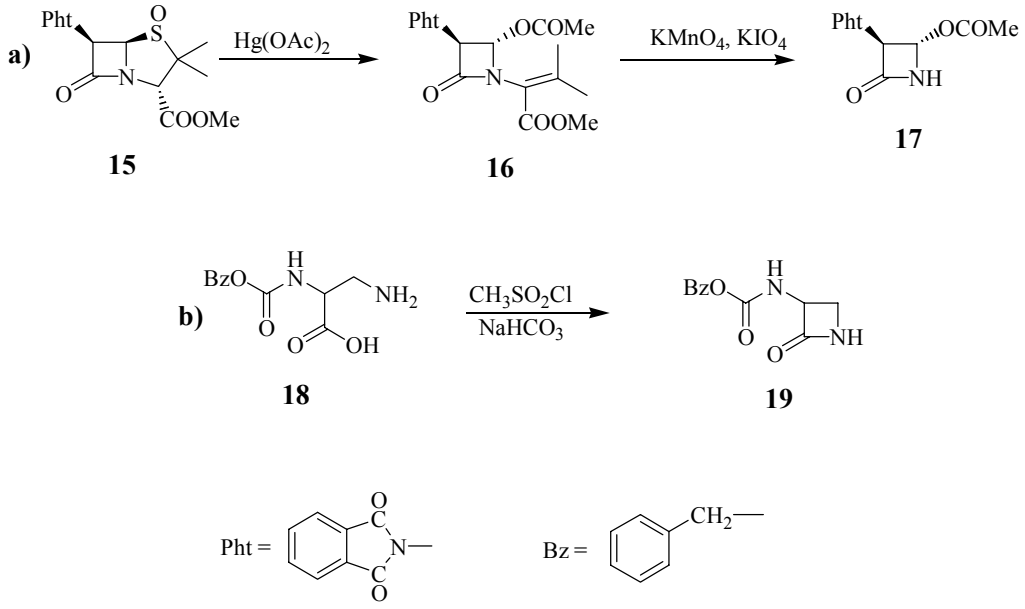


TABLE 1. The Biological Activity of Derivatives of 1,3,4-Trisubstituted 2-Azetidinones *in vitro* toward Tumor Cells of Human Fibrosarcoma and Mouse Hepatoma

No.	Com-pound	Cytotoxic effect (μg/ml) and specific NO-generating ability					
		HT-1080			MG-22A		
		TD_{50} (CV)*	TD_{50} (MTT)*[2]	TG_{100}*[3]	TD_{50} (CV)	TD_{50} (MTT)	TG_{100}
1	**4**	>100	100	2	>100	100	6
2	**5**	>100	>100	8	>100	>100	7
3	**12b**	>100	>100	4	>100	>100	8
4	**14a**	>100	>100	7	>100	>100	9
5	**14b**	>100	>100	2	>100	>100	6
6	**16**	>100	>100	13	>100	>100	12
7	**17**	>100	>100	5	>100	>100	4
8	**19**	>100	>100	7	>100	>100	7
9	**1**	7	9.6	100	42	60	42
10	**10**	5	5	200	5.3	4.4	200
11	**12a**	51	41	18	46	53	12
12	**7**	1	2	250	13	27	250
13	**9**	1.5	8.4	150	0.5	4	200

* The concentration securing 50% destruction of the cells (dye CV – crystal violet).

*[2] The concentration securing 50% destruction of the cells [dye MTT – 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyltetrazolium bromide].

*[3] Specific $NO^{\cdot}$ generating ability [13].

TABLE 2. The Biological Activity of Derivatives of 1,3,4-Trisubstituted 2-Azetidinones *in vitro* toward the Tumor Cells of Mouse Melanoma and Mouse Neuroblastoma

No.	Compound	Cytotoxic effect (μg/ml) and specific NO-generating ability					
		B 16			Neuro 2A		
		TD_{50} (CV)	TD_{50} (MTT)	TG_{100}	TD_{50} (CV)	TD_{50} (MTT)	TG_{100}
1	**7**	64	60	250	6.6	9	67
2	**9**	<1	<1	200	25	10	57

The individuality and structure of the new and resynthesized compounds were confirmed by elemental analysis, HPLC, and ^{1}H NMR spectra.

The biological part of the *in vitro* investigations included determination of the cytotoxic characteristics of the synthesized substances toward monolayer cancer cells and also their ability to initiate the biosynthesis of nitric oxide radicals (TG_{100}), the high reactivity of which is an important component of the cytotoxic effect [12, 13].

The concentrations of the substances leading to 50% destruction of the cells (TD_{50}) were determined by the standard procedure on four lines of tumor cells: HT-1080 (human fibrosarcoma), MG-22A (mouse hepatoma), B 16 (mouse melanoma), and Neuro 2A (mouse neuroblastoma) [13].

The synthesized compounds can be divided into three groups according to the biological effect. The first contains substances not having cytotoxic characteristics at concentrations up to 100 μg/ml (Table 1, Nos. 1-8). They include compounds **4** and **5**, formed as a result of oxidation and reduction of the formyl group in **1** and also the azetidinones **12b** and **14**, containing *cis*-4-nitrophenylvinyl and methoxycarbonylvinyl substituents at position 4. The absence of a cytotoxic effect was also demonstrated by the azetidinones **16** and **17**, having a bulky substituent at position 3, and also by the N-protected 3-amino-2-azetidinone (**19**).

The second group, characterized by a moderate cytotoxic effect (see Table 1, Nos. 9-11), is represented by the β-lactams **1**, **10**, and **12a**, containing polar formyl, dicyanoethyl, and (4-nitrophenyl)vinyl groups at position 4.

The third group of most active compounds, the cytotoxic action of which extends to a wide range of tumor cells (see Tables 1 and 2), included compounds **7** and **9**, containing 2-acetoxybenzoyloxymethyl and 2,2-dicyanovinyl substituents at position 4 of the β-lactam ring. Here, as in the previous investigation [8], for all three groups of substances good correlation was observed between the cytotoxic concentrations and the intensity of the intracellular generation of nitric oxide radicals, indicating mutual interaction of these two biological effects.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker WH-90/DS spectrometer (90 Mhz) in deuterochloroform or DMSO-d_6 with TMS as internal standard. The microanalytical data were obtained by means of a Carlo Erba 1108 analyzer. The reaction was monitored by TLC on Merck Kieselgel plates with UV development. Merck Kieselgel silica gel (0.063-0.230 mm) was used for preparative column chromatography. Reagents and materials from Aldrich, Acros, and Sigma were used in the experiments.

(3*S*,4*S*)-4-Formyl-1-(4-methoxyphenyl)-3-methyl-2-azetidinone (1). This compound was synthesized according to the method in [9]. ^{1}H NMR spectrum (deuterochloroform), ppm: 1.33 (3H, d, J = 6, CH_3); 3.66 (1H, d, J = 6, 3-H); 3.77 (3H, s, OCH_3); 4.46 (1H, q, J = 3, J = 6, 4-H); 6.84 and 7.24 (4H, dd, J = 7, C_6H_4); 9.78 (1H, d, J = 3, CHO).

(3*S*,4*S*)-4-Carboxy-1-(4-methoxyphenyl)-3-methyl-2-azetidinone (4). The compound was synthesized by the oxidation of compound **1** (110 mg, 0.5 mmol) with Jones' reagent (0.53 mmol of CrO_3) in acetone (5 ml) at 0°C for 10 min (TLC). The reaction mixture was diluted with 2-propanol (0.25 ml) and filtered through a layer of celite, and the filtrate was evaporated. The residue was dissolved in chloroform (10 ml). The obtained solution was washed with a 5% solution of sodium chloride (2 × 10 ml) and evaporated at reduced pressure. The residue was fractionated on a chromatographic column of silica gel in a mixture of ethyl acetate, chloroform, methanol, and acetic acid (100:60:20:1). The fractions with R_f 0.33 were combined and evaporated. We obtained 45 mg of a crystalline substance (38%); mp 120-122°C. ^{1}H NMR spectrum (deuterochloroform), ppm: 1.31 (3H, d, J = 7, CH_3); 3.55-3.93 (1H, m, 3-H); 3.77 (3H, s, OCH_3); 4.84 (1H, d, J = 7, 4-H); 6.84 and 7.26 (4H, dd, J = 7, C_6H_4); 8.73 (1H, s, COOH). Found, %: C 59.77; H 5.83; N 5.57. $C_{12}H_{13}NO_4 \cdot 0.3H_2O$. Calculated, %: C 59.89; H 5.70; N 5.82.

(3*S*,4*S*)-4-Hydroxymethyl-1-(4-methoxyphenyl)-3-methyl-2-azetidinone (5). The compound was obtained by the reduction of compound **1** (55 mg, 0.25 mmol) with sodium borohydride (9.5 mg, 0.25 mmol) in a mixture consisting of chloroform (0.6 ml) and ethanol (0.6 ml) for 15 min at room temperature (TLC). The residue was dissolved in 10 ml of ethyl acetate. The obtained solution was washed (2 × 10 ml) with a 5% solution of sodium chloride and evaporated at reduced pressure. The residue was fractionated on a chromatographic column of silica gel in the 2:3 ethyl acetate–hexane system. The fractions with R_f 0.73 were combined and evaporated. We obtained 40 mg of a crystalline substance (72%); mp 75-76°C. ^{1}H NMR spectrum (deuterochloroform), ppm: 1.37 (3H, d, J = 7, CH_3); 1.93 (1H, s, OH); 3.08-3.66 (1H, m 3-H); 3.77 (3H, s, OCH_3); 3.91-4.33 (3H, m, CH_2, 4-H); 6.86 and 7.24 (4H, dd, J = 7, C_6H_4). Found, %: C 65.26; H 6.87; N 6.26. $C_{12}H_{15}NO_3$. Calculated, %: C 65.14; H 6.83; N 6.33.

(3*S*,4*S*)-4-(2-Acetoxybenzoyloxymethyl)-1-(4-methoxyphenyl)-3-methyl-2-azetidinone (7). The compound was synthesized by the reaction of compound **5** (88 mg, 0.4 mmol) with 2-acetoxybenzoic acid **6** (100 mg, 0.5 mmol) in dichloromethane (3 ml) and triethylamine (0.1 ml, 0.75 mmol) for six days at room temperature. The reaction mixture was evaporated at reduced pressure. The residue was dissolved in 10 ml of ethyl acetate. The obtained solution was washed with 10 ml of a 5% solution of hydrochloric acid and 10 ml of a 5% solution of sodium chloride and evaporated at reduced pressure. The residue was fractionated on a chromatographic column of silica gel in the 2:3 ethyl acetate–hexane system. The fractions with R_f 0.43 were combined and evaporated. We obtained 100 mg of a crystalline substance (65%) with mp 91-92°C. ^{1}H NMR spectrum (deuterochloroform), ppm: 1.37 (3H, d, J = 7, CH_3); 2.33 (3H, s, $OCOCH_3$); 3.35-3.71 (1H, m, 3-H); 3.77 (3H, s, OCH_3); 4,26-4.84 (3H, m, CH_2, 4-HG); 6.66-8.04 (8H, m, $2C_6H_4$). Found, %: C 65.80; H 5.60; N 3.59. $C_{21}H_{21}NO_6$. Calculated, %: C 65.79; H 5.52; N 3.65.

(3*S*,4*S*)-4-(2,2-Dicyanovinyl)-1-(4-methoxyphenyl)-3-methyl-2-azetidinone (9). The compound was obtained by the reaction of compound **1** (44 mg, 0.20 mmol) with malononitrile **8** (15 mg, 0.22 mmol) in a 1:4 mixture of water and ethanol (1 ml) in the presence of diisopropylamine (0.05 ml) at ~20°C for 1 h. The crystals that separated were filtered off and crystallized from a 1:2 mixture of ethyl acetate and hexane. We obtained 35 mg of a crystalline substance (65%); mp 134-135°C (R_f 0.43, 2:3 ethyl acetate–hexane). ^{1}H NMR spectrum (deuterochloroform), ppm: 1.33 (3H, d, J = 9, CH_3); 3.73-4.07 (1H, m, 3-H); 3.80 (3H, s, OCH_3); 5.04 (1H, q, J = 6, J = 9, 4-H); 6.86, 7.20 (4H, dd, J = 9, C_6H_4); 7.40 (1H, d, J = 9, –CH=). Found, %: C 67.55; H 4.81; N 15.72. $C_{15}H_{13}NO_2$. Calculated, %: C 67.41; H 4.90; N 15.72.

(3*S*,4*R*)-4-(2,2-Dicyanovinyl)-1-(4-methoxyphenyl)-3-methyl-2-azetidinone (10). The compound was synthesized by the reaction of compound **9** (210 mg, 0.78 mmol) with sodium borohydride (35 mg, 0.92 mmol) in a mixture consisting of chloroform (1 ml) and ethanol (1 ml) for 30 min at room temperature (TLC). The reaction mixture was diluted with water and evaporated. The residue was dissolved in ethyl acetate (10 ml). The obtained solution was washed with 2 × 10 ml of a 5% solution of sodium chloride and evaporated at reduced pressure. The residue was fractionated on a chromatographic column of silica gel in the 2:3 ethyl acetate–hexane system. The fractions with R_f 0.65 were combined and evaporated. We obtained 40 mg of a crystalline substance (40%); mp 96-97°C. ^{1}H NMR spectrum (deuterochloroform), ppm: 1.33 (3H, d, J = 9, CH_3);

2.26-2.55 (2H, m, 4-CH_2); 3.40-3.93 (2H, m, $CH(CN)_2$, 3-H); 3.77 (3H, s, OCH_3); 4.20-4.88 (1H, m, 4-H); 6.88 and 7.22 (4H, dd, J = 9, C_6H_4). Found, %: C 67.22; H 5.69; N 15.45. $C_{15}H_{15}NO_2$. Calculated, %: C 66.90; H 5.61; N 15.60.

(3*S*,4*S*)-1-(4-Methoxyphenyl)-3-methyl-4-*trans*-[2-(4-nitrophenyl)vinyl]-2-azetidinone (12a) and (3*S*,4*S*)-1-(4-Methoxyphenyl)-3-methyl-4-*cis*-[2-(4-nitrophenyl)vinyl]-2-azetidinone (12b). The compounds were synthesized by the reaction of compound **1** (66 mg, 0.30 mmol) with 4-nitrobenzyltriphenylphosphonium bromide (144 mg, 0.30 mmol) and potassium carbonate (42 mg, 0.30 mmol) in dichloromethane (4 ml) in the presence of 18-crown-6 (3 mg) at ~20°C for 24 h. The reaction mixture was evaporated at reduced pressure. The residue was dissolved in ethyl acetate (10 ml). The obtained solution was washed with a 5% solution of hydrochloric acid (10 ml) and a 5% solution of sodium chloride (10 ml) and evaporated at reduced pressure. The residue was fractionated on a chromatographic column of silica gel in the 2:3 ethyl acetate–hexane system.

The fractions with R_f 0.33 were combined and evaporated. We obtained 56 mg of **12a** in the form of a crystalline substance (55%); mp 144-146°C. ^{1}H NMR spectrum (deuterochloroform), ppm: 1.28 (3H, d, J = 7, CH_3); 3.49-3.82 (1H, m, 3-H); 3.77 (3H, s, OCH_3); 4.66 (1H, q, J = 6, J = 8, 4-H); 6.48 and 6.80 (2H, dd, J = 15, CH=CH *trans*); 6.86 and 7.40 (4H, dd, J = 9, $C_6H_4OCH_3$); 7.53 and 8.22 (4H, dd, J = 9, $C_6H_4NO_2$). Found, %: C 67.31; H 5.45; N 8.32. $C_{19}H_{18}N_2O_4$. Calculated, %: C 67.45; H 5.36; N 8.28.

The fractions with R_f 0.50 were combined and evaporated. We obtained 30 mg of **12b** in the form of a crystalline substance (20%); mp 141-143°C. ^{1}H NMR spectrum (deuterochloroform), ppm: 1.33 (3H, d, J = 7, CH_3); 3.48-3.75 (1H, m, 3-H); 3.75 (3H, s, OCH_3); 4.77-5.04 (1H, m, 4-H); 6.91 and 7.04 (2H, dd, J = 9, CH=CH *cis*); 6.82 and 7.22 (4H, dd, J = 9, $C_6H_4OCH_3$); 7.44 and 8.31 (4H, dd, J = 9, $C_6H_4NO_2$). Found, %: C 67.28; H 5.49; N 8.22. $C_{19}H_{18}N_2O_4$. Calculated, %: C 67.45; H 5.36; N 8.28.

(3*S*,4*S*)-4-*trans*-[2-(Methoxycarbonyl)vinyl]-1-(4-methoxyphenyl)-3-methyl-2-azetidinone (14a) and (3*S*,4*S*)-4-*cis*-[2-(Methoxycarbonyl)vinyl]-1-(4-methoxyphenyl)-3-methyl-2-azetidinone (14b). The compounds were synthesized by the reaction of compound **1** (70 mg, 0.32 mmol) with methoxycarbonylmethyltriphenylphosphorane **13** (110 mg, 0.32 mmol) in methylene chloride (5 ml) (1 h, ~20°C). The reaction mixture was evaporated at reduced pressure. The residue was dissolved in 10 ml of ethyl acetate. The obtained solution was washed with a 5% solution of sodium chloride (10 ml) and evaporated at reduced pressure. The residue was fractionated on a chromatographic column of silica gel in the 2:3 ethyl acetate–hexane system.

The fractions with R_f 0.20 were combined and evaporated. We obtained 65 mg of **14a** in the form of a crystalline substance (74%); mp 78-79°C. ^{1}H NMR spectrum (deuterochloroform), ppm: 1.20 (3H, d, J = 7, CH_3); 3.37-3.80 (1H, m, 3-H); 3.72 and 3.73 (6H, s, 2OCH_3); 4.69 (1H, q, J = 6, J = 8, 4-H); 6.04 (1H, d, J = 16, =CHCO *trans*); 6.93 (1H, q, J = 7, J = 16, 4-CH=); 6.82 and 7.24 (4H, dd, J = 9, C_6H_4). Found, %: C 65.50; H 6.27; N 5.06. $C_{15}H_{17}NO_4$. Calculated, %: C 65.44; H 6.22; N 5.09.

The fractions with R_f 0.60 were combined and evaporated. We obtained 10 mg (11%) of **14b** in the form of an oil. ^{1}H NMR spectrum (deuterochloroform), ppm: 1.20 (3H, d, J = 7, CH_3); 3.44-3.86 (1H, m, 3-H); 3.77 (6H, s, 2OCH_3); 5.57 (1H, q, J = 6, J = 8, 4-H); 6.08 (1H, d, J = 12, =CHCO *cis*); 6.30 (1H, q, J = 7, J = 12, 4-CH=); 6.84 and 7.26 (4H, dd, J = 9 , C_6H_4). Found, %: C 65.25; H 6.37; N 5.16. $C_{15}H_{17}NO_4$. Calculated, %: C 65.44; H 6.22; N 5.09.

(3*S*,4*S*)-4-Acetoxy-1-(2-methyl-1-methoxycarbonyl-1-propenyl)-3-phthalimido-2-azetidinone (16). The compound was synthesized according to the method described in [10]. ^{1}H NMR spectrum (deuterochloroform), ppm: 2.11 (6H, s, CH_3, $COCH_3$); 2.22 (3H, s, CH_3); 3.84 (3H, s, OCH_3); 5.40 (1H, d, J = 1, 3-H); 6.53 (1H, d, J = 1, 4-H); 6.66-7.95 (4H, m, C_6H_4).

(3*S*,4*S*)-4-Acetoxy-3-phthalimido-2-azetidinone (17). The compound was synthesized by the method described in [10]; mp 183-185°C. ^{1}H NMR spectrum (DMSO-d_6), ppm: 2.04 (3H, s, $COCH_3$); 5.20 (1H, d, J = 1, 3-H); 6.04 (1H, d, J = 1, 4-H); 8.11 (4H, s, C_6H_4); 9.55 (1H, s, NH).

3-(Benzyloxycarbonylamino)-2-azetidinone (19). In contrast to the method described in [11], the compound was synthesized by the cyclization of 3-amino-2-(benzyloxycarbonylamino)propionic acid **18** (300 mg, 1.2 mmol) by addition of the latter over 2 h with vigorous stirring to a suspension of methanesulfonyl

chloride (0.1 ml, 1.3 mmol) and sodium bicarbonate (0.63 g, 7.5 mmol) in acetonitrile (12 ml) previously heated to 80°C. The mixture was further stirred at the indicated temperature for 2 h, cooled, and filtered, and the precipitate was washed with acetonitrile (12 ml). The filtrate was evaporated at reduced pressure. The residue was fractionated on a chromatographic column of silica gel in the 3:1 chloroform–acetone system. The fractions with R_f 0.35 were combined and evaporated. We obtained 40 mg of a crystalline substance (15%); mp 163-164°C. ^{1}H NMR spectrum (DMSO-d_6), ppm: 2.04 (3H, s, $COCH_3$); 3.02-3.51 (2H, m, 4-H_2); 4.55-4.82 (1H, m, 3-H); 5.88 (2H, s, CH_2); 7.40 (5H, s, C_6H_5); 7.80-8.08 (2H, m, NH, NHOCO). Found, %: C 59.83; H 5.63; N 12.34. $C_{11}H_{12}N_2O_3$. Calculated, %: C 59.99; H 5.49; N 12.72. IR spectrum (nujol), cm^{-1}: 3300, 1730, 1700.

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