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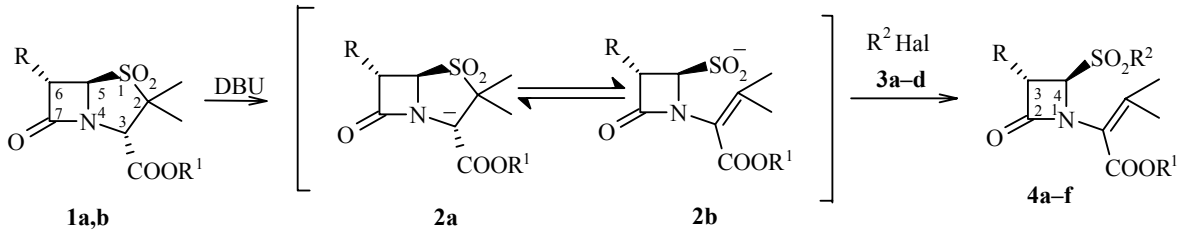
SYNTHESIS OF CYTOTOXIC 4-SULFONYL-, 4-SULFONYLTHIO- AND 4-SULFOTHIOAZETIDINONES-2*

G. Veinberg, M. Vorona, D. Musel, R. Bokaldere, I. Shestakova, I. Kanepe, and E. Lukevics

4-Sulfonylazetidinones-2 were synthesized by the reaction of DBU and organic halides with the esters of penicillin sulfones. 4-Sulfonylthio- and 4-sulfothioazetidinones-2 were synthesized by nucleophilic substitution of the 2-benzothiazolylthio groups in 4-(benzothiazolylthio)azetidinones-2 using sodium sulfinates or sodium hydrogen sulfite. A study of their cytotoxic activities revealed the anticancer effect of compounds containing methylsulfonylthio-, 4-tolylsulfonylthio-, and 4-methoxycarbonylamino-phenylsulfonylthio-substituents at position 4 of the β-lactam ring relative to a wide range of monolayer cultures of cancer cells in vitro.

Keywords: 2-[4-sulfonyl-2-oxoazetidinyl-1]-2-(isopropyliden)acetic acid esters, 2-[4-sulfonylthio-2-oxoazetidinyl-1]-, and 2-[4-sulfothio-2-oxoazetidinyl-1]-2-(isopropenyl)acetic acid esters, cytotoxic activity.

In a continuation of a study connected with the synthesis of 1,3,4-trisubstituted β-lactams and the analysis of the relationship between their structure and cytotoxic activities [1, 2], we have chosen as new objects azetidinones-2 formed as result of scission of the S(1)–C(2) bond in the thiazolidine ring of penicillin sulfones.



1 a R = H; $R^1 = CHPh_2$; **b** R = Cl, $R^1 = CH_2Ph$; **3 a** R^2 = Me, Hal = I; **b** $R^2 = CH_2Ph$, Hal = Br; **c** $R^2 = CH_2CH{=}CH_2$, Hal = Br; **d** $R^2 = CH_2SiMe_3$, Hal = I; **4 a** R = H; $R^1 = CHPh_2$, R^2 = Me; **b** R = H; $R^1 = CHPh_2$, $R^2 = CH_2Ph$; **c** R = Cl, $R^1 = CH_2Ph$, R^2 = Me; **d** R = Cl, $R^2 = CH_2Ph$; **e** R = Cl, $R^1 = CH_2Ph$, $R^2 = CH_2CH{=}CH_2$; **f** R = Cl, $R^1 = CH_2Ph$, $R^2 = CH{=}CHMe$-*trans*

* Dedicated to Academician A. Strakovs on his jubilee.

Latvian Institute of Organic Synthesis, Riga LV-1006; e-mail: veinberg@osi.lv. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, 949-956, June 2004. Original article submitted December 7, 2002.

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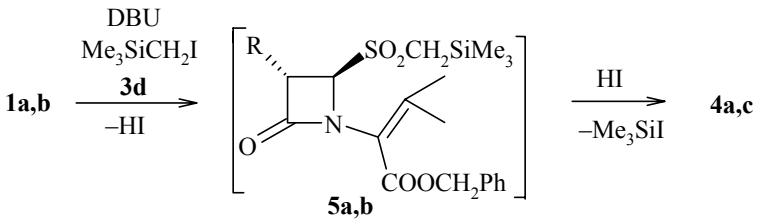
The synthesis of the target 4-sulfonyl-substituted azetidinones **4a-i** was carried out using the reactions, studied in [3,4], which includes: deprotonation of atom C(3) in the penicillin sulfone **1** with the help of DBU, leading to an equilibrium mixture of anions in which the thiazolidine ring is retained (**2a**) and the product of its opening (**2b**); and alkylation of the anion **2b** with organic halides **3**.

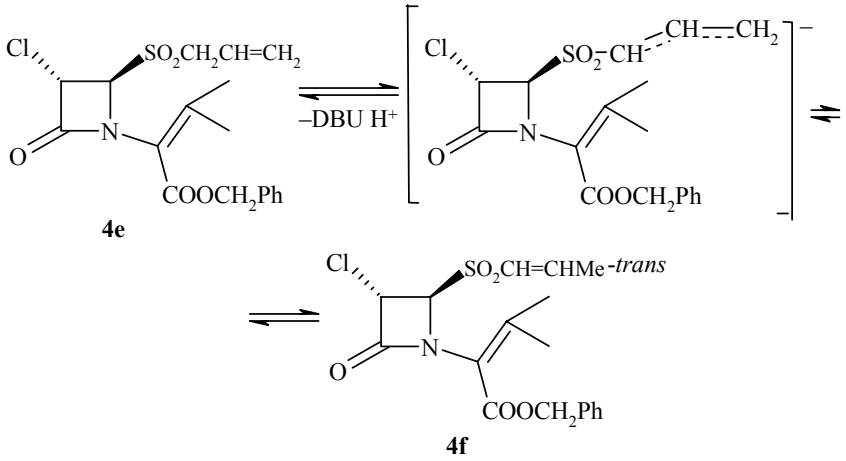
In contrast to the alternative method , based on the desulfuration of 4-dithiosubstituted azetidinones-2 by triphenylphosphine with subsequent oxidation of the 4-thioazetidinone-2 to the corresponding sulfone [5], the reaction with the use of DBU and organic halides occurs with retention of configuration at C(4), which is indicated by the characteristic coupling constant J = 1-2 Hz of the *trans*-orientated vicinal protons on C(3) and C(4) in compounds **4a-f**.

When iodomethyltrimethylsilane (**3d**) was used as the alkylating agent, in place of the expected 4-trimethylsilylmethylsulfonylazetidinones-2 (**5a,b**), 4-methylsulfonylazetidinones-2 (**4a,c**) were isolated which indicates that the trimethylsilyl groups in the intermediate 4-trimethylsilylmethylsulfonylazetidinones-2 (**5a,b**) underwent electrophilic displacement by a proton.

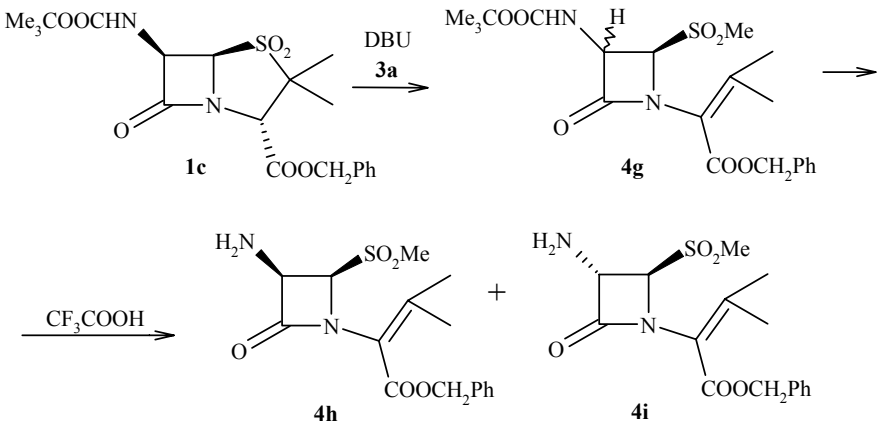


5 a R = H; **b** R = Me

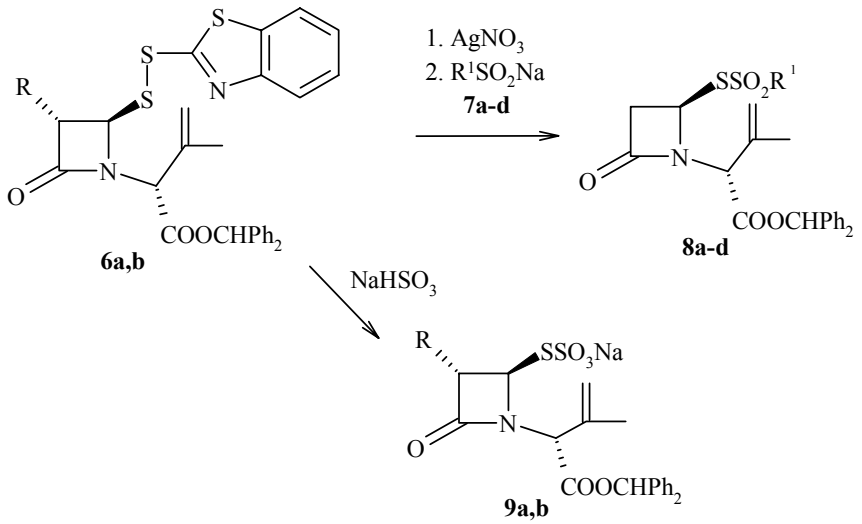
The formation of the mixture of isomers **4e** and **4f** from the reaction of penicillin **1b** with allyl bromide **3c** indicates the deprotonation of the methylene group in the 4-alkylsulfonyl substituent under the influence of DBU with subsequent migration of the double bond.



Interaction of DBU with the sulfone of 6β-(*tert*-butoxycarbonyl)aminopenicillanate **1c** gives deprotonation at C(3) and opening of the thiazolidine ring but also reversal of the configuration at C(6) with formation of a mixture of 3*R*- and 3*S*-isomers of azetidinones-2 (**4g**). The isomeric 3-amino-4-methylsulfonylazetidinones **4h** and **4i**, formed by treatment of compound **4g** with trifluoroacetic acid were successfully isolated by preparative column chromatography.



Nucleophilic substitution of the 2-thiobenzothiazolyl groups in the 4-dithio-substituted azetidinones-2 **6** with sodium sulfinates **7** or sodium hydrogen sulfite according the patented methods [6, 7] led to the previously unknown 4-sulfonylthio- and 4-sulfothioazetidinones-2 , **8a-d** and **9a,b.**



6, **9 a** R = H, **b** R = Cl; **7**, **8 a** R^1 = Me, **b** R^1 = 4-MeC_6H_4, **c** R^1 = 4-$MeOCONHC_6H_4$, **d** R^1= 2-naphthyl

The biological part of the study *in vitro* included the determination of the cytotoxic properties of the compounds synthesized in monolayer cancer cells and the ability to initiate the biosynthesis of the nitric oxide radical (TG_{100}), the high reactivity of which is an important ingredient of the cytotoxic effect [8, 9].

The TD_{50} concentrations of the substrates were determined by the standard method on four lines of cancer cells: HT-1080 (human fibrosarcoma), MG-22A (mouse hepatoma), B 16 (mouse melanoma) and Neuro 2A (mouse neuroblastoma) [9].

The compounds synthesized can be divided into three groups according to their biological effects. In the first group are compounds which possess no cytotoxic effects at concentrations up to 100 μg/ml. This group includes esters of the sulfones of penicillanic acids **1a-c**, 4-sulfonyl-3,3-dihydroazetidinones-2 **4a,b**, and 4-methylsulfonyl-3-aminoazetidinones-2 with free and substituted amino groups, **4g-i** (Table 1, No:1-5, 10-12).

TABLE 1. Biological Properties of Derivatives of 1,3,4-Trisubstituted Azetidinones-2

No.	Compound	Cytotoxic effect (μg/ml) and specific NO generating effect with respect to tumour cells *					
		HT-1080			MG-22A		
		TD_{50} (CV)	TD_{50} (MTT)	TG_{100}	TD_{50} (CV)	TD_{50} (MTT)	TG_{100}
1	**1a**	>100	100	36	>100	100	43
2	**1b**	>100	>100	8	>100	>100	7
3	**1c**	>100	>100	6	>100	>100	9
4	**4a**	>100	>100	3	>100	>100	5
5	**4b**	>100	>100	2	>100	>100	6
6	**4c**	57	54	200	24	28	200
7	**4d**	43	93	67	13	16	44
8	**4e**, **4f**	6	4.9	250	8.2	9.5	250
10	**4g**	>100	>100	20	22	21.3	40
11	**4h**	>100	>100	15	27	10	50
12	**4i**	>100	>100	21	37	>100	59
13	**8a**	2.8	30	400	0.8	9.0	450
14	**8b**	8.7	10	500	6.8	4.5	450
15	**8c**	4	35.7	200	5.6	5	250
16	**8d**	26.8	39.2	150	34.3	46.4	100
17	**9a**	53	52	500	52	48	600
18	**9b**	56	60	286	48	50	750

* TD_{50} – concentration causing 50% death of the cells; CV – crystal violet; MTT – staining 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; TG_{100} – specific NO generating ability [9].

The second group, characterized by small cytotoxic effects, includes 3-chloro-4-sulfonylazetidinones-2 **4c,d** and the sodium salts of 4-sulfothioazetidinones-2 **9a,b** (Table 1, No: 6, 7, 17, 18).

The third group includes the most active substances with cytotoxic effects over a wide range of cancer cells: the isomeric mixture of 4-(prop-2-enylsulfonyl)- and 4-(*trans*-prop-1-enylsulfonyl)azetidinones-2 **4e,f** and the whole group of 4-sulfonylthioazetidinones-2 **8a-c** (Tables 1 and 2). As in previous papers [1, 2], for all three groups there is an excellent correlation between cytotoxic concentrations and the intensity of intracellular generation of the nitric oxide radicals, which indicates the interrelation of these two biological effects.

TABLE 2. Biological Properties of Derivatives of 1,3,4-Trisubstituted Azetidinones-2

No.	Compound	Cytotoxic effect (μg/ml) and specific NO generating ability with respect to cancer cells					
		B 16			Neuro 2A		
		TD_{50} (CV)	TD_{50} (MTT)	TG_{100}	TD_{50} (CV)	TD_{50} (MTT)	TG_{100}
1	**4e**, **4f**	6.2	8.8	200	4.1	4.5	150
2	**8a**	3.0	38	450	5.3	58	400
3	**8b**	7.8	10.4	450	47	58	400
4	**8c**	<1	<1	200	59	53	100

EXPERIMENTAL

^{1}H NMR spectra of DMSO-d_6 solutions with TMS as internal standard were recorded on a Bruker WH-90/DS (90 MHz) machine. Microanalytical data were determined using a Carlo Erba 1108 analyzer. The course of reactions was monitored by TLC on Merck Kieselgel plates with spots revealed by UV radiation. Merck Kieselgel (0.063-0.230 mm) was used for preparative column chromatography. Reagents and materials from Aldrich, Acros, and Sigma were used in the experiments.

Benzyl Ester of the Sulfone of 6β-(*tert*-Butoxycarbonyl)aminopenicillanic Acid (1c). 3-Chloroperbenzoic acid (75%) (3.30 g, 14.28 mmol) was added to a solution of the benzyl ester of 6β-(*tert*-butoxycarbonyl)aminopenicillanic acid (2.0 g, 4.92 mmol) in dichloromethane (40 ml) at 0°C. The mixture was stirred at room temperature for 1 h, diluted with dichloromethane (20 ml), washed with 5% Na_2SO_3 solution (50 ml), 5% Na_2CO_3 solution (2 × 50 ml), and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was fractionated by column chromatography with 1:3 ethyl acetate-hexane as eluent. The fraction with R_f 0.30 was collected and evaporated to give compound **1c** (1.5 g, 69%); mp 70-73°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.44 (12H, br. s, *t* -Bu, CH_3); 1.51 (3H, s, CH_3); 4.44 (1H, s, 3-H); 4.71 (1H, d, *J* = 4, 5-H); 5.11 and 5.26 (2H, AB-system, *J* = 12, CH_2); 5.71-5.93 (2H, m, 6-H, NH); 7.33 (5H, s, C_6H_5). Found, %: C 59.29; H 6.49; N 6.92. $C_{20}H_{26}N_2O_5S$. Calculated, %: C 59.09; H 6.45; N 6.89.

4-Sulfonyl-substituted Azetidinones-2, 4a-g. DBU (0.6 mmol) was added to a sulfone ester of penicillanic acid **1a-c** (0.5 mmol) in dichloromethane (7 ml) at 0°C. The mixture was kept at room temperature for 5 min and then an organic halide **3a-d** (0.5 mmol) was added. The mixture was stirred at room temperature for 1 h, then dichloromethane (15 ml) was added, and the mixture was washed with 0.5 N HCl (10 ml), 5% NaCl solution (2 × 10 ml), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was fractionated by silicagel column chromatography with 1:3 ethyl acetate–hexane as eluent. The fraction containing the desired product was collected and evaporated.

Benzhydryl 2-[4(*R*)-Methylsulfonyl-2-oxoazetidinyl-1]-2-(isopropyliden)acetate (4a). A. The compound was obtained as an amorphous substance from the reaction of penicillin **1a** with **3a** in a yield of 72%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.11 (3H, s, CH_3); 2.28 (3H, s, CH_3); 2.53 (3H, s, SO_2CH_3); 3.17 (1H, dd, *J* = 16, *J* = 6, 3-H *cis*); 3.41(1H, dd, *J* = 16, *J* = 3, 3,3-H *trans*); 4.88 (1H, dd, *J* = 6, *J* = 3, 4-H); 6.93 (1H, s, C<u>H</u>Ph_2); 7.31 (10H, s, C_6H_5). Found, %: 64.12; H 5.75; N 3.48. $C_{22}H_{23}NO_5S$. Calculated, %: C 63.90; H 5.61; N 3.39.

B. The identical compound was obtained from the interaction of penicillin **1a** and iodide **3d**. Yield 52%.

Benzhydryl 2-[4(*R*)-Benzylsulfonyl-2-oxoazetidinyl-1]-2-(isopropyliden)acetate (4b) was obtained as an oil from the reaction of penicillin **1a** and **3b**. Yield 15%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.13 (3H, s, CH_3); 2.31 (3H, s, CH_3); 2.98 (1H, dd, *J* = 16, *J* =5, 3-H *cis*); 3.19 (1H, dd, *J* = 16, *J* =5, 3-H *trans*); 3.86 and 4.11 (2H, AB-system, *J* = 15, SO_2CH_2); 4.80 (1H, dd, *J* = 2, *J* = 5, 4-H); 6.91 (1H, s, C<u>H</u>Ph_2); 7.22-7.56 (15H, m, $3C_6H_5$). Found, %: C 68.74; H 5.66; N 2.73. $C_{28}H_{27}NO_5S$. Calculated, %: 68.69; H 5.56; N 2.86.

Benzyl 2-[3(*S*)-Chloro-4(*R*)-methylsulfonyl-2-oxoazetidinyl-1]-2-(isopropyliden)acetate (4c). A. The compound was obtained as an amorphous solid from the reaction of **1b** and **3a** in 23% yield. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.07 (3H, s, CH_3); 2.31 (3H, s , CH_3); 2.71 (3H, s, SO_2CH_3); 5.02 (1H, br. s, 4-H); 5.09 (1H, br. s, 3-H); 5.15 and 5.40 (2H, AB-system, *J* = 12, C<u>H</u>$_2$Ph); 7.40 (5H, s, C_6H_5). Found %: C 51.76; H 4.97; N 3.86. $C_{16}H_{18}ClNO_5S$. Calculated, %: C 51.68; H 4.88; N 3.77.

B. The identical compound was obtained from the reaction of **1b** and **3d** in 19% yield.

Benzyl 2-[4(*R*)-Benzylsulfonyl-3(*S*)-chloro-2-oxoazetidinyl-1]-2-(isopropyliden)acetate (4d) was obtained as an amorphous solid from the reaction of **1b** and **3b** in 32% yield. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.09 (3H, s, CH_3); 2.31 (3H, s, CH_3); 4.06 and 4.26 (2H, AB-system, *J* = 15, SO_2C<u>H</u>$_2$); 4.82 (1H, d, *J* = 1, 4-H); 4.93 (1H, d, *J* = 1, 3-H); 5.06 and 5.24 (2H, AB-system, *J* = 12, C<u>H</u>$_2$Ph); 7.40 (10H, s, $2C_6H_5$). Found, %: C 59.13; H 5.07; N 3.26. $C_{22}H_{22}ClNO_5S$. Calculated, %: C 58.99; H 4.95; N 3.13.

Benzyl 2-[4(*R*)-(Prop-2-enylsulfonyl-3(*S*)-chloro-2-oxoazetidinyl-1]-2(isopropyliden)acetate (4e) and Benzyl 2-[4(*R*)-(*trans*-Prop-1-enylsulfonyl-3(*S*)-chloro-2-oxoazetidinyl-1]-2(isopropyliden)acetate (4f). The mixture of isomers was obtained by the interaction of **1b** and **3c** in 23% yield. According to HPLC (Ultrasphere Si, 20:80 chloroform–hexane) the ratio of **4e** to **4f** is 1:3, their overall content in the substance isolated was >97%. Found, %: C 54.54; H 4.99; N 3.76. $C_{18}H_{20}NO_5S$. Calculated, %: C 54.34; H 5.07; N 3.52. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): **4e**: 2.09 (3H, s, CH_3); 2.31 (3H, s, CH_3); 3.42-3.74 (2H, m, CH_2-allyl); 4.88 (1H, d, *J* = 2, 4-H); 5.01 (1H, d, *J* = 2, 3-H); 5.24-5.44 (4H, m, C<u>H</u>$_2$Ph, =CH_2); 5.44-5.80 (1H, m, CH-allyl); 7.33 (5H, s, C_6H_5). **4f**: 1.84 (3H, dd, *J* = 7, *J* = 1.6, CH_3 propenyl); 2.06 (3H, s, CH_3); 2.27 (3H, s, CH_3); 4.88 (1H, d, *J* = 2, 4-H); 5.01 (1H, d, *J* = 2, 3-H); 5.11 and 5.33 (2H, AB-system, *J* = 12, C<u>H</u>$_2$Ph); 5.90 (1H, dd, *J* = 14, *J* = 1.6, 1-H propenyl); 6.82 (1H, dd, *J* = 14, *J* = 7, 2-H propenyl); 7.33 (5H, s, C_6H_5).

Benzyl 2-[3-*tert*-Butoxycarbonylamino-4(*R*)-(methylsulfonyl)-2-oxoazetidinyl-1]-2-(isopropyliden)-acetate (4g) was obtained as an amorphous substance from the reaction of **1b** and **3a** in 40% yield. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.46 (9H, s, *t* -Bu); 2.07 (3H, s, CH_3); 2.31 (3H, s, CH_3); 2.71 (3H, s, SO_2CH_3); 5.02 (1H, br. s, 4-H); 5.09 (1H, br. s, 3-H); 5.15 and 5.40 (2H, AB-system, *J* = 12, C<u>H</u>$_2$Ph); 5.65-5.75 (1H, m, NH); 7.40 (5H, s, C_6H_5). Found, %: C 55.87; H 6.32; N 6.30. $C_{28}H_{20}N_2O_7S$. Calculated, %: C 55.74; H 6.24; N 6.19.

Benzyl 2-[3(*R*)-Amino-4(*R*)-methylsulfonyl-2-oxazetidinyl-1]-2-(isopropyliden)acetate (4h) and Benzyl 2-[3(*S*)-Amino-4(*R*)-methylsulfonyl-2-oxazetidinyl-1]-2-(isopropyliden)acetate (4i). Compound **4g** (650 mg, 1.43 mmol) was dissolved at 0°C in dichloromethane (2 ml) and trifluoroacetic acid (3 ml). The solution was stirred for 2 h at 0°C and for 1 h at room temperature, diluted with dichloromethane (70 ml), washed with 5% potassium carbonate (50 ml) until neutral, with water, and then dried over anhydrous Na_2SO_4. The solvent was removed at reduced pressure and the residue was fractionated by column chromatography with ethyl acetate as eluent. The fraction with R_f 0.48 contained ester **4h** (100 mg, 20%); mp 90-92°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.06 (2H, br. s, NH_2); 2.15 (3H, s, CH_3); 2.26 (3H, s, CH_3); 2.88 (3H, s, SO_2CH_3); 4.53 (1H, d, *J* = 5, 4-H); 4.95 (1H, d, *J* = 5, 3-H); 5.11, 5.31 (2H, AB-system, *J* = 13, C<u>H</u>$_2$Ph); 7.37 (5H, s, C_6H_5). Found, %: C 54.81; H 5.62; N 7.60. $C_{16}H_{20}N_2O_5S$. Calculated, %: C 54.53; H 5.72; N 7.95.

The fractions with R_f 0.31 contained ester **4i** (51 mg, 10%) as an oily substance, 98% pure according to HPLC (Zorbax RxC_{18}, mobile phase 45:55 acetonitrile-water). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.69 (2H, br. s, NH_2); 2.04 (3H, s, CH_3); 2.26 (3H, s, CH_3); 2.66 (3H, s, SO_2CH_3); 4.57 (1H, d, *J* = 2, 4-H); 4.66 (1H, d, *J* = 2, 3-H); 5.11 and 5.33 (2H, AB-system, *J* = 13, C<u>H</u>$_2$Ph); 7.37 (5H, s, C_6H_5).

4-Sulfonylthio-substituted Azetidinones-2 8a-d. Silver nitrate (105 mg, 0.5 mmol) was added to benzhydryl 2-[4-(2-benzothiazolyldithio)-2-oxoazetidinyl-1]-2-(isopropenyl)acetate (0.5 mmol) (**6a**) in 9:1 acetone–water (5 ml), the mixture was stirred for 30 min at room temperature and then a sodium sulfinate **7a-d** (0.5 mmol) in 9:1 acetone–water (5 ml) was added. The mixture was stirred for 2 h at room temperature and then filtered through of Celite. The filtrate was dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was fractionated on a silica gel column with 3:2 ethyl acetate–hexane as eluent. The fractions containing the desired product were collected and evaporated.

Benzhydryl 2-(4-Methylsulfonylthio-2-oxoazetidinyl-1]-2-(isopropenyl)acetate (8a) was obtained as an amorphous substance from the interaction of compounds **6a** and **7a** in 21% yield. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.88 (3H, s, CH_3); 3.24 (1H, dd, *J* = 16, *J* = 2, 3-H, *trans*); 3.31 (3H, s, SO_2CH_3); 3.71 (1H, dd, *J* = 16, *J* = 5, 3-H *cis*); 4.93 (2H, d, *J* = 7, =CH_2); 5.11 (1H, d, *J* = 1, NCHCOO); 5.68 (1H, dd, *J* = 5, *J* = 2, 4-H); 7.00 (1H, s, C<u>H</u>Ph_2); 7.35 (10H, s, $2C_6H_5$). Found, %: C 59.46; H 5.37; N 3.16. $C_{22}H_{23}NO_5S_2$. Calculated, %: C 59.30; H 5.20; N 3.14.

Benzhydryl 2-[4-(4-Tolylsulfonylthio-2-oxoazetidinyl-1]-2-(isopropenyl)acetate (8b) was obtained as an amorphous substance from the interaction of compounds **6a** and **7b** in 35% yield. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.62 (3H, s, CH_3); 2.31 (3H, s, CH_3Ph); 2.91 (1H, dd, *J* = 2, *J* = 16, 3-H *trans*); 3.53 (1H, dd, *J* =16, *J* = 5, 3-H *cis*); 4.66 (2H, d, *J* = 7, =CH_2); 4.89 (1H, d, *J* = 1, NCHCOO); 5.37 (1H, dd, *J* = 5,

J = 2, 4-H); 7.04 (1H, s,C<u>H</u>Ph$_2$); 7.17 and 7.67 (4H, two d, *J* = 8, C$_6$H$_4$); 7.42 (10H, s, 2C$_6$H$_5$). Found, %: C 63.91; H 5.26; N 2.66. $C_{28}H_{27}NO_5S_2 \cdot 0.25H_2O$. Calculated, %: C 63.85; H 5.35; N 2.62.

Benzhydryl 2-[4-(4-Methoxycarbonylaminophenyl)sulfonylthio-2-oxoazetidinyl-1]-2-(isopropenyl)-acetate (8c) was obtained from the interaction of compounds **6a** and **7c** in 31% yield; mp 60-63°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.77 (3H, s, CH_3); 2.99 (1H, dd, *J* = 17, *J* = 2, 3-H *trans*); 3.52 (1H, dd, *J* = 17, *J* = 6, 3-H *cis*); 3.80 (3H, s, OCH_3); 4.75 (2H, d, *J* = 7, =CH_2); 4.97 (1H, d, *J* = 1, NCHCOO); 5.46 (1H, dd, *J* = 6, *J* = 2, 4-H); 6.82 (1H, br. s, NH); 6.91 (1H, br. s, C<u>H</u>Ph$_2$); 7.35 (10H, s, 2C$_6$H$_5$); 7.79 and 7.82 (4H, two d, C$_6$H$_4$). Found, %: C 59.99; H 4.86; N 4.82. $C_{29}H_{28}N_2O_7S_2$. Calculated, %: C 60.29; H 4.89; N 4.64.

Benzhydryl 2-[4-(2-Naphthyl)sulfonylthio-2-oxoazetidinyl-1]-2-(isopropenyl)acetate (8d) was obtained as an amorphous substance from the interaction of compounds **6a** and **7d** in 36% yield; mp 45-48°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.73 (3H, s, CH_3); 2.97 (1H, dd, *J* =15, *J* = 3, 3-H *trans*); 3.50 (1H, dd, *J* = 15, *J* = 6, 3-H *cis*); 4.71 (2H, d, *J* = 12, =CH_2); 4.89 (1H, d, *J* = 1, NCHCOO); 5.53 (1H, dd, *J* = 6, *J* = 3, 4-H); 6.82 (1H, s, C<u>H</u>Ph$_2$); 7.26 (10H, s, 2C$_6$H$_5$); 7.57-8.04 (6H, m, 3-H-8-H naphthyl); 8.42 (1H, s, 1-H naphthyl). Found, %: C 66.7; H 4.88; N 2.51. $C_{31}H_{27}NO_5S_2$. Calculated, %: C 66.15; H 4.82; N 2.57.

Sodium 2-[Sulfothio-2-oxoazetidinyl-1]-2-(isopropenyl)acetate (9a). $NaHSO_3$ (40 mg, 0.38 mmol) was added to compound **6a** (209 mg, 0.37 mmol) in a mixture of THF (10 ml) and water (3ml). The mixture was stirred at room temperature for 30 min and evaporated. The residue was dissolved in water and filtered. The filtrate was evaporated, the residue was dissolved in absolute ethanol, filtered, and evaporated to give compound **9a** (150 mg, 80%); mp 86-88°C. ^{1}H NMR spectrum (DMSO-d$_6$), δ, ppm (*J*, Hz): 1.75 (3H, s, CH_3), , 2.86 (1H, dd, *J* = 16, *J* = 3, 3-H *trans*); 3.53 (1H, dd, *J* =16, *J* = 6, 3-H *cis*); 5.00 (2H, br. s, =CH_2); 5.15 (1H, s, NCHCOO); 5.24 (1H, q, *J* = 6, *J* = 3, 4-H); 6.82 (1H, s, C<u>H</u>Ph$_2$); 7.42 (10H, s, C$_6$H$_5$). Found, %: C 50.86; H 4.33; N 2.82. $C_{21}H_{20}NNaO_6S_2 \cdot 1.5H_2O$. Calculated, %: C 50.80; H 4.66; N 2.96.

Sodium 2-[4(*R*)-Sulfothio-3(*S*)-chloro-2-oxazetidinyl-1]-2-(isopropenyl)acetate (9b) was obtained in 75% yield as an amorphous substance analogously to **9a,** starting from compound **6b**. ^{1}H NMR spectrum (DMSO-d$_6$), δ, ppm (*J*, Hz): 1.77 (3H, s, CH_3); 5.02 (2H, br. s, =CH_2); 5.11 (1H, s, NCHCOO); 5.20 (1H, d, *J* = 1, 4-H); 5.26 (1H, d, *J* =1, 3-H); 6.89 (1H, s, C<u>H</u>Ph$_2$); 7.40 (10H, s, 2C$_6$H$_5$). Found, %: C 48.34; H 3.90; N 2.71. $C_{21}H_{19}ClNNaO_6S_2 \cdot H_2O$. Calculated, %: C 48.32; H 4.05; N 2.68.

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