Synthesis of 3-Carbamoyl β-Lactams *via* Manganese(III)-Promoted Cyclization of *N*-Alkenylmalonamides

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Manganese(III)-promoted cyclization of *N*-alkenylmalonamides (= *N*-alkenylpropanediamides) gave 3-(aryl/(alkylamino)carbonyl) β-lactams as well as 3-(aryl/(alkylamino)thiocarbonyl) β-lactams. The relative configuration of the obtained products was unambiguously determined by X-ray crystallography. The proposed method is very useful for the one-pot synthesis of a number of 3-(aryl/(alkylamino)carbonyl) β-lactams, especially those containing an amino(thiocarbonyl) moiety, which are not selectively accessible by other methods.

Introduction. – For the period of almost seven decades, after the first documented use of penicillin had begun, the β-lactam system has been at the center of interest of organic chemistry. Of course, the main stream of research is related to the potential applications of β-lactams as effective antimicrobial chemotherapeutics. However, purely synthetic studies are also known, for example, the '*Ojima* β-Lactam Synthon Method' for the preparation of peptides [1], amino acids [2], and hydroxy acids [3].

So far, several methods for the preparation of the azetidine-2-one system have been developed, *e.g.*, carbodiimide coupling of β-amino acids [4], condensation with PPh_3 pyridine disulfide developed by *Ohno* and co-workers [5], *Grignard* reagent-mediated cyclization of silyl esters of amino acids [6], cyclizations using an epoxide system and anion-stabilizing group [7], intramoleular electrophilic addition to olefins [8], or radical cyclization of 3-oxoenamides [9]. However, it should be noted that the first method used for the preparation of β-lactams *via* the cycloaddition of ketenes to imines, proposed by *Staudinger* at the beginning of the 19th century [10], after several modification and improvements, is still one of the most popular methods for the preparation of these compounds.

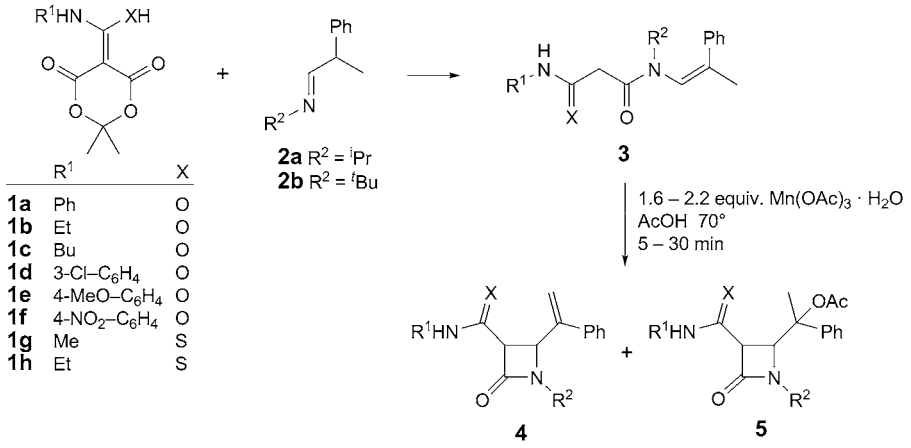
Recently, we have reported a variation of the *Staudinger* method for the preparation of 3-carbamoyl β-lactams by addition of aldimines to carbamoyl ketenes, generated from 5-[hydroxy(arylamino)methylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione [11]. Despite many advantages, mainly due to the simplicity of this method, we were not able to obtain models of 3-carbamoyl β-lactams with alkyl groups or S in the carbamoyl fragment.

As mentioned already, an alternative way of forming β-lactams may be the cyclization of enamides, which was demonstrated by *Trogolo* and co-workers [9] in the oxidative cyclization of 3-oxo enamides. On the other hand, we have recently developed a method for the preparation of *N*-alkenylmalonamides (= *N*-alkenylpropanediamides) and *N*-alkenylthiomalonamides **3** from carbamoyl and thiocarbamoyl *Meldrum*'s acids **1**, respectively [12].

Considering the above mentioned findings, we decided to check if oxidative cyclization of **3** allows avoiding the limitations, which we encountered in our previous method of preparing 3-carbamoyl β-lactams. Radical cyclization of carbonyl derivatives containing an active α-position promoted by transition metals is a well-known and broadly applied method [13]; however, to the best of our knowledge, this method has not been used so far for the cyclization of malonamides, and particularly for their thio derivatives.

Results and Discussion. – In this article, we present the synthesis of β-lactams **4** and **5** with a *retro*-amide and *retro*-thioamide side chain based on the Mn^{III}-promoted oxidative cyclization of suitable malonamides (= propanediamides) (*Scheme*).

Scheme. *Synthesis of 3-Carbamoyl and 3-Thiocarbamoyl β-Lactams*



First, we performed the reaction of *N*-isopropyl-*N*′-phenyl-*N*-[(1*Z*)-2-phenylprop-1-enyl]malonamide (**3a**) with 2 equiv. of $Mn(OAc)_3 \cdot H_2O$ under typical conditions for radical cyclization reactions with Mn^{III}, *i.e.*, 70° and AcOH as a solvent [13]. After purification, we obtained two main products, the first, **4a**, containing a vinyl moiety, in 30% yield, and the second, **5a**, without elimination of AcOH, in 41% yield (*Table*, *Entry 1*), accompanied by traces of unreacted starting material. Then, we tried to optimize the conditions used, first by checking the optimal temperature, and we observed that, while gradually increasing the temperature up to 50°, no reaction occurred even for an extended reaction time, whereas at the threshold of 65 – 70°, the reaction proceeded with noticeable rate, and consumption of Mn^{III} required *ca.* 0.5 h. On the other hand, conducting the reaction in boiling AcOH caused a very fast reaction; Mn^{III} was consumed just after addition, but the yield of **4a** and **5a** remained in the same range (*Entry 2*). Moreover, portionwise addition of $Mn(OAc)_3 \cdot H_2O$ to the hot reaction mixture allowed us to determine the moment, when an additional amount of oxidizer was no longer consumed at a fast rate. In the case of **1**, the optimal amount of $Mn(OAc)_3 \cdot H_2O$ was *ca.* 1.6 equiv.

Table. *Synthesis of 3-(Thio)carbamoyl β-Lactams* **4** *and* **5** *by Oxidation of* N*-Alkenyl(thio)malonamides* **3**

Entry	R^1	R^2	X	**3**–**5**	Temp. [°]	Time [min]	$Mn(OAc)_3 \cdot H_2O$ [equiv.]	Yield of **4**/**5** [%]
1	Ph	^{i}Pr	O	**a**	70	30	1.6	30 : 41
2	Ph	^{i}Pr	O	**a**	120	5	1.9	29 : 40
3	Ph	^{i}Pr	O	**a**	70	240	4.0	16 : 17
4[a])	Ph	^{i}Pr	O	**a**	65	30	2.0	16 : 34
5[a])	Et	^{t}Bu	O	**b**	65	30	2.0	9 : 0
6	Et	^{t}Bu	O	**b**	70	30	2.0	42 : 0
7	Et	^{i}Pr	O	**c**	70	30	1.6	42 : 0
8	Bu	^{t}Bu	O	**d**	70	30	2.3	42 : 0
9	Bu	^{i}Pr	O	**e**	70	30	1.7	45 : 0
10	3-Cl–C_6H_4	^{t}Bu	O	**f**	70	30	1.6	37 : 0
11	4-MeO–C_6H_4	^{t}Bu	O	**g**	70	30	1.6	42 : (15 : 20)[b])
12	4-NO_2–C_6H_4	^{t}Bu	O	**h**	70	30	1.6	42 : 15[c])
13[d])	Et	^{t}Bu	O	**b**	70	26 h	0	0 : 0
14[d])	Ph	^{i}Pr	O	**a**	70	19 h	0	0 : 0
15[e])	Ph	^{i}Pr	O	**a**	90	5	1.6	26 : 39
16[f])	Et	^{t}Bu	O	**b**	70	60	0	15 : 0
17[g])	Ph	^{i}Pr	O	**a**	70	30	2.0	25 : 48
18[g])	Et	^{t}Bu	O	**b**	70	30	2.0	45 : 0
19[h])	Et	^{t}Bu	O	**b**	70	30	2.0	25 : 0
20	Me	^{t}Bu	S	**i**	70	30	2.2	40 : 0
21	Me	^{i}Pr	S	**j**	70	30	2.2	42 : 0
22	Et	^{t}Bu	S	**k**	70	30	2.2	37 : 8
23	Et	^{i}Pr	S	**l**	70	30	2.2	42 : 10

[a]) MeOH was used as a solvent. [b]) Compound **5** was isolated as two pairs of diastereoisomers. [c]) Additional 10% of **6h** with free OH group was isolated. [d]) Two equiv. of $Cu(OAc)_2$ was used. [e]) One equiv. of $Cu(OAc)_2$ was used. [f]) Two equiv. of $Co(OAc)_2$ was used. [g]) Three equiv. of pyridine was used. [h]) Two equiv. of AcONa was used.

In all these experiments, after quenching the reaction, a small amount of unreacted **3** was detected by TLC. Therefore, in the next experiment, we checked whether using an excess of oxidizing reagent might improve the yield: the use of 4 equiv. of $Mn(OAc)_3 \cdot H_2O$ required an extended time of 4 h for complete consumption of oxidant, and the yield of **4a**/**5a** was significantly reduced (*Entry 3*), indicating that the already obtained β-lactams underwent subsequent oxidation, leading to a decrease in yield. Solvents have an important influence on the oxidation with $Mn(OAc)_3 \cdot H_2O$; usually highly polar protic solvents were used, and in most cases AcOH was the solvent of choice; however, sometimes alcohols were used [13]. Therefore, we conducted two experiments in which **3a** and **3e**, respectively, were oxidized with 2 equiv. of $Mn(OAc)_3 \cdot H_2O$ in boiling MeOH for 0.5 h. After purification, we obtained products **4**/**5** in much lower yields than in the reactions carried out in AcOH (*Entries 4* and *5 vs. Entries 1* and *6*).

Results obtained on a series of *N*-alkenylmalonamides are compiled in the *Table*. When R^1 was an alkyl group, only the product after elimination, **4**, was obtained, whereas introduction of any aryl group as R^1 led to the formation of both **4** and **5**. Probably, if R^1 is an alkyl group, the higher basicity of the amide O-atom leads to a fast

intramolecular deprotonation. For the higher overall yield of β-lactams in the case of cyclization of **3** with R^1 = aryl, the π-interaction between two aromatic rings during radical ring closure may be responsible.

The ^{1}H-NMR spectra of the prepared β-lactams **4** and **5** showed coupling constants for H–C(3) and H–C(4) in the range of 2.0–2.5 Hz in all cases, indicating exclusive formation of *trans*-products. Moreover, the X-ray crystal structures obtained for selected compounds **4** and **5** established the *trans*-configurations of the products (*Fig. 1*).

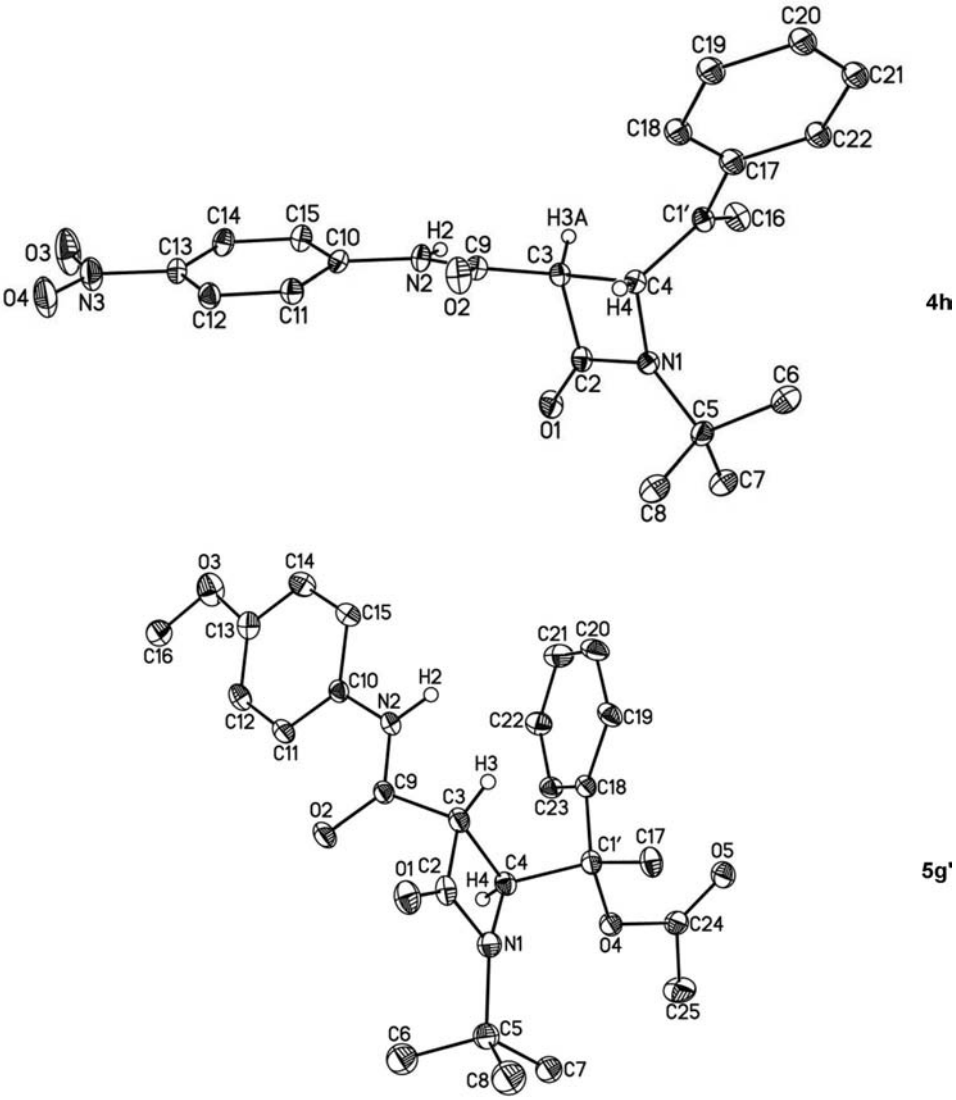


Fig. 1. *Molecular structures of* **4h** *and* **5g′** (ellipsoids represent 10% probability levels; H-atoms are omitted for clarity, except those at C(2), C(3), and N(2))

The β-lactam **5** possesses an additional stereogenic center; hence, considering that only *trans*-β-lactams were obtained, **5** should exist as four diastereoisomers, (1′*R*,3*R*,4*R*), (1′*S*,3*S*,4*S*), (1′*R*,3*S*,4*S*), and (1′*S*,3*R*,4*R*). Indeed, in one case (*Entry 11*), it was possible to separate the two pairs of enantiomers. To assigne an absolute configuration for each pair, first we performed NOESY experiments as well as conformational analysis with HyperChem software using OPLS force field. In the NOESY spectrum of the pair of enatiomers eluted from column chromatography as a first pair, **5g′**, we observed interactions between both β-lactam-ring H-atoms and the Me group of the side chain, whereas the spectrum for the second pair of diastereoisomers, **5g″**, showed interactions between the β-lactam H–C(3) and the Me group, as well as between the H–C(3) and the amide NH. The calculated lowest-energy conformations revealed that one diasteroisomer has short interatomic distances of *ca.* 0.24 nm between β-lactam-ring H-atoms and the Me group, while the second diasteroisomer has short interatomic distances of 0.22 and 0.24 nm, between H–C(3) H-atom and the Me group, and between the H–C(3) and the amide NH respectively (*Fig. 2*). Comparing distances between H-atoms in the lowest-energy conformation with the results of the NOESY experiments strongly suggested that **5g′** has to be the pair of (1′*R*,3*R*,4*R*)- and (1′*S*,3*S*,4*S*)-isomers, and **5g″** of (1′*R*,3*S*,4*S*)- and (1′*S*,3*R*,4*R*)-isomers. Fortunately, **5g′** provided crystals suitable for X-ray crystallography, and the X-ray data confirmed our assumption (*Fig. 1*). In the cases of **5a** and **5h**, it was not possible to separate the diastereoisomers chromatographically, however, slow crystallization allowed to obtain good-enough crystals for X-ray crystallography of one pair of less soluble enantiomers from each mixture. Furthermore, in the case of model **h** (*Entry 12*), besides two main products **4h** and **5h**, also the unexpected product **6h** with free OH group in the side chain was isolated.

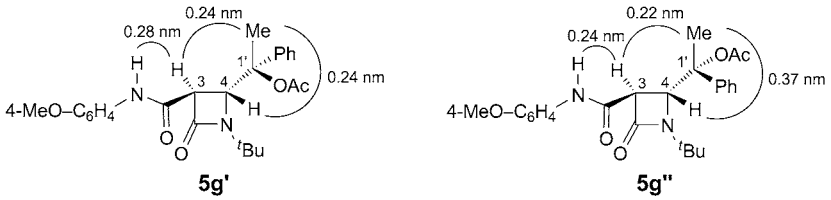


Fig. 2. *Distances between the H-atoms in the lowest-energy conformations for diastereoisomers* **5g′** *and* **5g″**

Another question we decided to resolve was whether other salts of transition metals could be used in this oxidative cyclization. For this purpose, we checked two systems, the first being $Cu(OAc)_2$ in AcOH as a solvent at 70° or at boiling point. In both cases, even using an extended reaction time, no trace of β-lactams was obtained (*Entries 13* and *14*). When we used a mixture of 1 equiv. of $Cu(OAc)_2$ together with 1.6 equiv. of $Mn(OAc)_3$, β-lactams **4a** and **5a** were obtained in a yield slightly lower than in the experiment when only $Mn(OAc)_3$ was used (*Entry 15 vs. Entry 1*). As the second oxidative system, we used $Co(OAc)_2$ in hot AcOH. In this case, we obtained the required β-lactam, however, in a significantly reduced yield (*Entry 16*).

Overall yields of the prepared 3-carbamoyl β-lactams range from 37 to 71%, and may be considered as modest. However, it should be emphasized that, in the present synthesis, *N*-alkenyl malonamides were used which are least prone to enolization, while it is known that radical formation occurs from the enolic form of malonic acid derivatives [9b][14]. Therefore, three experiments were carried out with the addition of a base (pyridine or MeONa) to the reaction mixture (*Entries 17–19*). Only the introduction of pyridine as a base for the enolization did not disrupt the oxidation–cyclization process. However, enhancement of the yield is minimal (*Entries 17 vs. 1*, and *18 vs. 6*).

The most interesting question that arose during our experiments was whether the *N*-alkenyl-thiomalonoenamides can be also radically cyclized to give 3-thiocarbamoyl β-lactams. To the best of our knowledge, a general selective method for the preparation of 3-thiocarbamoyl β-lactams is not known. Moreover, for this class of compounds only one example is known [15].

The main problem during oxidative cyclization of *N*-alkenyl-thiomalonoenamides **3** may arise from the possible desulfurization, which for thioamides is easily feasible with various oxidating agents like, for example, oxone, Ag^I [16] salts, or Na_2O_2 [17]. Fortunately, the experiments have shown that radical cyclization of **3** (X = S) with $Mn(OAc)_3 \cdot H_2O$ occurs with good yield in a short time to furnish of 3-thiocarbamoyl β-lactams **4** and **5** (X = S; *Entries 20–23*). However, slightly higher amounts of oxidant are required to complete the reaction, most probably due to some desulfurization side reactions.

In summary, we have developed a new method for the preparation of 3-carbamoyl β-lactams and 3-thiocarbamoyl β-lactams, which are not available by other approaches. The method is fast and selective, and the products are obtained in moderate yields. The structure of the prepared compounds was confirmed by X-ray crystallography.

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Experimental Part

General. All solvents used were dried over appropriate drying agents and distilled prior to use. Commercially available reagents were purchased from *Sigma-Aldrich.* Commercially unavailable reagents were prepared according to literature procedures: *5-[(hydroxy)(phenylamino)methylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione* (**1a**) [18], *5-[(hydroxy)(ethylamino)methylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione* (**1b**) [11], *5-[(hydroxy)[(3-chlorophenyl)amino]methylidene}-2,2-dimethyl-1,3-dioxane-4,6-dione* (**1d**) [11], *5-{(hydroxy)[(4-nitrophenyl)amino]methylidene}-2,2-dimethyl-1,3-dioxane-4,6-dione* (**1f**) [19], *5-[(methylamino)(sulfanyl)methylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione* (**1g**) [20], (*isopropyl)(2-phenylpropylidene)amine* (**2a**) and *(*tert*-butyl)(2-phenylpropylidene)amine* (**2b**) [21], and N-*alkenylmalonamides* and N-*alkenylthiomalonamides*, **3a**–**3c**, **3f**, **3i**, and **3j** [12]. TLC: *Merck Kieselgel 60* F_{254}. Flash column chromatography (FC): *Zeochem ZEOprep 60/40–63*. M.p.: *Warsztat Elektromechaniczny W-wa*; uncorrected. NMR Spectra: *Varian Unity Plus 500* (^{1}H: 500 and ^{13}C: 125 MHz) or *Varian Gemini 200* (^{1}H: 200 and ^{13}C: 50 MHz); δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. HR-ESI-MS: *MicroMas Quattro LCT* mass spectrometer; in *m*/*z*.

5-[(Butylamino)(hydroxy)methylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**1c**). Prepared as described in [18][11] for **1a** and **1b**, using *Meldrum*'s acid (0.72 g, 5 mmol), anh. DMF (5 ml), Et_3N (1.4 ml, 10 mmol), and butyl isocyanate (0.495 g, 5 mmol) Yield: 0.729 g (60%). M.p. 69–71°. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.96 (*t*, *J* = 7.1, 3 H); 1.25–1.46 (*m*, 2 H); 1.49–1.70 (*m*, 2 H); 1.71 (*s*, 6 H); 3.41 (*q*,

$J = 6.2$, 2 H); 9.27 (br. *s*, 1 H); 13.80 (br. *s*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 14.0; 20.4; 26.7; 31.6; 40.6; 73.3; 105.0; 121.7; 164.8; 170.7; 170.8. HR-ESI-MS: 266.1007 ($[M+Na]^+$, $C_{11}H_{17}NNaO_5^+$; calc. 266.1004).

5-[(Hydroxy)[(4-methoxyphenyl)amino]methylidene}-2,2-dimethyl-1,3-dioxane-4,6-dione (**1e**). Prepared as described in [18][11] for **1a** and **1b**, using *Meldrum*'s acid (0.72 g, 5 mmol), anh. DMF (5 ml), Et_3N (1.4 ml, 10 mmol), and 4-methoxyphenyl isocyanate (0.745 g, 5 mmol). Yield: 0.646 g (44%). M.p. 130–132°. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.77 (*s*, 6 H); 3.83 (*s*, 3 H); 6.92 (*d*, $J = 9.3$, 2 H); 7.35 (*d*, $J = 9.3$, 2 H); 11.02 (br. *s*, 1 H); 15.55 (br. *s*, 1 H).

5-[(Ethylamino)(sulfanyl)methylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**1h**). Prepared as described in [20] for **1g**, using *Meldrum*'s acid (0.72 g, 5 mmol), anh. DMF (5 ml), Et_3N (1.4 ml, 10 mmol), and ethyl isothiocyanate (0.435 g, 5 mmol). Yield: 0.196 g (17%). M.p. 58–60°. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.36 (*t*, $J = 7.3$, 3 H); 1.72 (*s*, 6 H); 3.48–3.62 (*m*, 2 H); 11.30 (br. *s*, 1 H); 14.20 (br. *s*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 13.4; 26.0; 40.0; 82.2; 103.6; 164.6; 170.1; 179.7. HR-ESI-MS: 254.0464 ($[M+Na]^+$, $C_9H_{13}NNaO_4S^+$; calc. 254.0463).

N^3-*Butyl*-N^1-*(1,1-dimethylethyl)*-N^1-*[(1Z)-2-phenylprop-1-en-1-yl]propanediamide* (**3d**). Prepared as described in [12] for **3a**–**3c**, **3f**, **3i**, and **3j**, using **1c** (0.486 g, 2 mmol), anh. toluene (10 ml), and **2b** (0.756 g, 4 mmol). Yield: 0.455 g (69%). ^{1}H-NMR (200 MHz, $CDCl_3$): (*t*, $J = 7.2$, 3 H); 1.30–1.69 (*m*, 4 H); 1.46 (*s*, 9 H); 2.01 (*s*, 2 H); 3.21–3.35 (*m*, 4 H); 6.30 (*s*, 1 H); 7.34–7.39 (*m*, 5 H); 7.81 (br. *s*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 13.7; 15.7; 20.1; 28.4; 31.5; 39.1; 42.7; 59.5; 125.3; 126.1; 128.3; 128.6; 139.5; 140.1; 166.5; 169.5. HR-ESI-MS: 353.2191 ($[M+Na]^+$, $C_{20}H_{30}N_2NaO_2^+$; calc. 353.2205).

N^3-*Butyl*-N^1-*(1-methylethyl)*-N^1-*[(1Z)-2-phenylprop-1-en-1-yl]propanediamide* (**3e**). Prepared as described in [12], using **1c** (0.486 g, 2 mmol), anh. toluene (10 ml), and **2a** (0.7 g, 4 mmol). Yield: 0.480 g (76%). ^{1}H-NMR (200 MHz, $CDCl_3$): 0.92 (*t*, $J = 7.1$, 3 H); 1.15 (*d*, $J = 6.8$, 6 H); 1.30–1.56 (*m*, 4 H); 1.98 (*d*, $J = 1.3$, 3 H); 3.22–3.31 (*q*, $J = 6.8$, 2 H); 3.28, (*s*, 3 H); 4.90 (*quint.*, $J = 6.8$, 1 H); 6.23 (*s*, 1 H); 7.33–7.44 (*m*, 5 H); 7.93 (br. *s*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 13.7; 15.9; 19.8; 20.1; 31.5; 39.1; 40.6; 46.8; 121.0; 126.1; 128.4; 128.6; 139.4; 142.0; 166.2; 168.4. HR-ESI-MS: 359.2051 ($[M+Na]^+$, $C_{19}H_{28}N_2NaO_2^+$; calc. 339.2048).

N^1-*(1,1-Dimethylethyl)*-N^3-*(4-methoxyphenyl)*-N^1-*[(1Z)-2-phenylprop-1-en-1-yl]propanediamide* (**3g**). Prepared as described in [12], using **1e** (0.586 g, 2 mmol), anh. toluene (10 ml), and **2b** (0.756 g, 4 mmol). Yield: 0.311 g (41%). ^{1}H-NMR (500 MHz, $CDCl_3$): 1.50 (*s*, 9 H); 2.04 (*s*, 3 H); 3.36 (*d*, $J = 17.1$, 1 H); 3.40 (*d*, $J = 17.1$, 1 H); 3.78, (*s*, 3 H); 6.33 (*s*, 1 H); 6.85 (*d*, $J = 8.7$, 2 H); 7.26–7.50 (*m*, 7 H); 9.99 (br. *s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 16.0; 28.6; 43.0; 55.7; 60.4; 114.2; 121.9; 125.2; 126.3; 128.6; 128.8; 131.4; 139.5; 140.6; 156.5; 164.7; 169.7. HR-ESI-MS: 403.1994 ($[M+Na]^+$, $C_{23}H_{28}N_2NaO_3^+$; calc. 403.1998).

N^1-*(1,1-Dimethylethyl)*-N^3-*(4-nitrophenyl)*-N^1-*[(1Z)-2-phenylprop-1-en-1-yl]propanediamide* (**3h**). Prepared as described in [12], for using **1f** (0.616 g, 2 mmol), anh. toluene (10 ml), and **2b** (0.756 g, 4 mmol). Yield: 0.150 g (19%). ^{1}H-NMR (200 MHz, $CDCl_3$): 1.51 (*s*, 9 H); 2.04 (*d*, $J = 1.4$, 3 H); 3.43 (*d*, $J = 1.6$, 2 H); 6.33 (*d*, $J = 1.4$, 1 H); 7.38–7.44 (*m*, 5 H); 7.77 (*d*, $J = 9.1$, 2 H); 8.20 (*d*, $J = 9.1$, 2 H); 10.95 (br. *s*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 16.3; 28.9; 42.8; 60.7; 119.9; 125.1; 125.5; 126.5; 129.1; 129.2; 139.5; 141.2; 144.2; 165.8; 169.5. HR-ESI-MS: 418.1741 ($[M+Na]^+$, $C_{22}H_{25}N_3NaO_4^+$; calc. 418.1743).

N-*(1,1-Dimethylethyl)-3-(ethylamino)*-N-*[(1Z)-2-phenylprop-1-en-1-yl]-3-thioxopropanamide* (**3k**). Prepared as described in [12], using **1h** (0.462 g, 2 mmol), anh. toluene (10 ml), and **2b** (0.756 g, 4 mmol). Yield: 0.387 g (61%). ^{1}H-NMR (200 MHz, $CDCl_3$): 1.29 (*t*, $J = 7.4$, 3 H); 1.46 (*s*, 9 H); 2.03 (*d*, $J = 1.4$, 3 H); 3.68–3.80 (*m*, 4 H); 6.30 (*d*, $J = 1.4$, 1 H); 7.34–7.42 (*m*, 5 H); 10.12 (br. *s*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 13.0; 16.0; 28.4; 40.8; 49.8; 59.7; 124.9; 126.2; 128.3; 128.6; 139.4; 140.5; 169.7; 194.8. HR-ESI-MS: 341.1672 ($[M+Na]^+$, $C_{18}H_{26}N_2NaOS^+$; calc. 341.1664).

3-(Ethylamino)-N-*(1-methylethyl)*-N-*[(1Z)-2-phenylprop-1-en-1-yl]-3-thioxopropanamide* (**3l**). Prepared as described in [12], using **1h** (0.462 g, 2 mmol), anh. toluene (10 ml), and **2a** (0.700 g, 4 mmol). Yield: 0.320 g (51%). ^{1}H-NMR (200 MHz, $CDCl_3$): 1.16 (*d*, $J = 6.6$, 6 H); 1.30 (*t*, $J = 7.3$, 3 H); 2.00 (*s*, 3 H); 3.64–3.78 (*m*, 2 H); 3.81 (*s*, 2 H); 4.87 (*quint.*, $J = 6.8$, 1 H); 6.23 (*s*, 1 H); 7.36–7.48 (*m*, 5 H); 10.20 (br. *s*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 13.4; 16.7; 20.2; 41.4; 47.5; 48.3; 121.1; 126.7; 128.9; 129.1; 139.8; 143.0; 169.1; 194.8. HR-ESI-MS: 327.1514 ($[M+Na]^+$, $C_{17}H_{24}N_2NaOS^+$; calc. 327.1507).

Radical Cyclization of N-*Alkenylmalonamides and* N-*Alkenylthiomalonamides* **3**. *General Procedure.* A soln. of **3** (1 mmol) in AcOH (10 ml) was heated to 70°. Then, $Mn(OAc)_3 \cdot H_2O$ (1.6–2.3 mmol; amount specified in the *Table*) was added. The mixture was stirred and heated to 70° for 30 min. The hot mixture was poured into 50 ml of cold H_2O, and extracted with CH_2Cl_2 (5 × 20 ml). The combined org. layer was washed with 5% aq. $NaHCO_3$ (2 × 10 ml) and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified.

*1-(1-Methylethyl)-2-oxo-*N-*phenyl-4-(1-phenylethenyl)azetidine-3-carboxamide* (**4a**). Purification by FC (AcOEt/hexane 1:3). ^{1}H-NMR (200 MHz, $CDCl_3$):1.27 (*d*, *J* = 6.6, 3 H); 1.44 (*d*, *J* = 6.8, 3 H); 3.69–3.77 (*m*, 1 H); 3.79 (*d*, *J* = 2.1, 1 H); 4.90 (*d*, *J* = 2.1, 1 H); 5.49 (*s*, 1 H); 5.65 (*s*, 1 H); 7.10–7.63 (*m*, 10 H); 8.25 (br. *s*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 20.8; 21.4; 47.1; 56.4; 62.5; 115.1; 120.5; 125.0; 126.7; 128.8; 129.2; 129.4; 137.8; 138.6; 146.1; 163.9; 165.5. HR-ESI-MS: 357.1575 ($[M+Na]^+$, $C_{21}H_{22}N_2NaO_2^+$; calc. 357.1579).

*2-[1-(Acetyloxy)-1-phenylethyl]-1-(1-methylethyl)-4-oxo-*N-*phenylazetidine-3-carboxamide* (**5a**; mixture of diastereoisomers). Purification by FC (AcOEt/hexane 3:5). M.p. 152–160°. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.22 (*d*, *J* = 6.8, 3 H); 1.41 (*d*, *J* = 6.8, 3 H); 1.99 (*s*, 3 H); 2.14 (*s*, 3 H); 3.41 (*quint.*, *J* = 6.8, 1 H); 3.60 (*d*, *J* = 2.0, 1 H), 4.20 (*d*, *J* = 2.0, 1 H); 7.05 (*t*, *J* = 7.3, 1 H); 7.22–7.31 (*m*, 2 H); 7.32–7.42 (*m*, 7 H); 7.60 (br. *s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 19.7; 20.7; 21.4; 22.5; 47.8; 56.3; 63.1; 83.2; 120.3; 124.9; 125.1 (minor); 125.4 (major); 128.7; 129.1 (minor); 129.2 (major); 129.3 (major); 129.4 (minor); 137.7; 140.5; 163.3; 165.0; 169.2. HR-ESI-MS: 417.1802 ($[M+Na]^+$, $C_{23}H_{26}N_2NaO_4^+$; calc. 417.1790).

*1-(1,1-Dimethylethyl)-*N-*ethyl-2-oxo-4-(1-phenylethenyl)azetidine-3-carboxamide* (**4b**). Purification by FC (AcOEt/hexane 3:5). ^{1}H-NMR (200 MHz, $CDCl_3$): 1.14 (*t*, *J* = 7.3, 3 H); 1.35 (*s*, 9 H); 3.26–3.37 (*m*, 2 H); 3.50 (*d*, *J* = 2.1, 1 H); 4.81 (*d*, *J* = 2.1, 1 H); 5.56 (*s*, 1 H); 5.59 (*s*, 1 H); 6.30 (br. *s*. 1 H); 7.30–7.40 (*m*, 3 H); 7.57–7.62 (*m*, 2 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 14.6; 27.9; 34.4; 55.2; 55.8; 61.7; 114.2; 126.2; 128.2; 128.6; 138.6; 147.5; 165.3; 165.7. HR-ESI-MS: 323.1732 ($[M+Na]^+$, $C_{18}H_{24}N_2NaO_2^+$; calc. 323.1735).

N-*Ethyl-1-(1-methylethyl)-2-oxo-4-(1-phenylethenyl)azetidine-3-carboxamide* (**4c**). Purification by FC (AcOEt/hexane 1:2). ^{1}H-NMR (500 MHz, $CDCl_3$): 1.15 (*t*, *J* = 7.3, 3 H); 1.23 (*d*, *J* = 6.3, 3 H); 1.39 (*d*, *J* = 6.8, 3 H); 3.23–3.31 (*m*, 1 H); 3.33–3.39 (*m*, 1 H); 3.56 (*d*, *J* = 2.0, 1 H); 3.68 (*quint.*, *J* = 6.3, 1 H); 4.80 (*d*, *J* = 2.0, 1 H); 5.45 (*s*, 1 H); 5.61 (*s*, 1 H); 6.28 (br. *s*, 1 H); 7.30–7.41 (*m*, 3 H); 7.58–7.60 (*m*, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.8; 20.6; 21.2; 34.7; 46.6; 56.1; 61.8; 114.4; 126.4; 128.5; 128.8; 138.4; 146.0; 165.5. HR-ESI-MS: 309.1572 ($[M+Na]^+$, $C_{17}H_{22}N_2NaO_2^+$; calc. 309.1579).

N-*Butyl-1-(1,1-dimethylethyl)-2-oxo-4-(1-phenylethenyl)azetidine-3-carboxamide* (**4d**). Purification by FC (AcOEt/hexane 1:2). ^{1}H-NMR (200 MHz, $CDCl_3$): 0.90 (*t*, *J* = 7.0, 3 H); 1.34 (*s*, 9 H); 1.27–1.53 (*m*, 4 H); 3.24–3.30 (*m*, 1 H); 3.49 (*d*, *J* = 2.1, 1 H); 4.80 (*d*, *J* = 2.1, 1 H); 5.45 (*s*, 1 H); 5.61 (*s*, 1 H); 6.35 (br. *s*, 1 H); 7.30–7.39 (*m*, 3 H); 7.57–7.61 (*m*, 2 H). ^{13}C-NMR (50 MHz, CDCl3): 13.7; 19.9; 27.9; 31.4; 39.2; 55.1; 55.8; 61.7; 114.1; 126.2; 128.2; 128.6; 138.6; 147.5; 165.4; 165.8. HR-ESI-MS: 351.2041 ($[M+Na]^+$, $C_{20}H_{28}N_2NaO_2^+$; calc. 351.2048).

N-*Butyl-1-(1-methylethyl)-2-oxo-4-(1-phenylethenyl)azetidine-3-carboxamide* (**4e**). Purification by FC (AcOEt/hexane 1:2). ^{1}H-NMR (200 MHz, $CDCl_3$): 0.91 (*t*, *J* = 7.2, 3 H); 1.21 (*d*, *J* = 6.7, 3 H); 1.40 (*d*, *J* = 6.8, 3 H); 1.20–1.54 (*m*, 4 H); 3.22–3.35 (*m*, 2 H); 3.56 (*d*, *J* = 2.2, 1 H); 3.68 (*quint.*, *J* = 6.7, 1 H); 4.80 (*d*, *J* = 2.2, 1 H); 5.45 (*s*, 1 H); 5.61 (*s*, 1 H); 6.27 (br. *s*, 1 H); 7.26–7.42 (*m*, 3 H); 7.56–7.63 (*m*, 2 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 13.7; 20.0; 20.3; 20.9; 31.4; 39.3; 46.4; 55.9; 61.6; 114.1; 126.2; 128.2; 128.6; 138.2; 145.8; 165.3; 165.4. HR-ESI-MS: 337.1902 ($[M+Na]^+$, $C_{19}H_{26}N_2NaO_2^+$; calc. 337.1892).

N-*(3-Chlorophenyl)-1-(1,1-dimethylethyl)-2-oxo-4-(1-phenylethenyl)azetidine-3-carboxamide* (**4f**). Purification by FC (AcOEt/hexane 1:2). ^{1}H-NMR (200 MHz, $CDCl_3$): 1.40 (*s*, 9 H); 3.75 (*d*, *J* = 2.1, 1 H); 5.00 (*d*, *J* = 2.1, 1 H); 5.61 (*s*, 1 H); 5.65 (*s*, 1 H); 7.00–7.30 (*m*, 3 H); 7.36–7.52 (*m*, 3 H); 7.53–7.65 (*m*, 3 H); 8.70 (br. *s*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 28.4; 56.0; 56.1; 62.6; 115.1; 118.1; 120.3; 124.9; 126.6; 128.8; 129.2; 130.2; 135.0; 138.8; 139.0; 147.5; 163.9; 166.0. HR-ESI-MS: 405.1351 ($[M+Na]^+$, $C_{22}H_{23}ClN_2NaO_2^+$; calc. 405.1346).

*1-(1,1-Dimethylethyl)-*N-*(4-methoxyphenyl)-2-oxo-4-(1-phenylethenyl)azetidine-3-carboxamide* (**4g**). Purification by FC (AcOEt/hexane 1:3). ^{1}H-NMR (200 MHz, $CDCl_3$): 1.40 (*s*, 9 H); 3.69 (*d*, *J* = 2.3, 1 H); 3.76 (*s*, 3 H); 4.99 (*d*, *J* = 2.3, 1 H); 5.62 (*s*, 1 H); 5.65 (*s*, 1 H); 6.85–6.89 (*m*, 2 H); 7.35–7.41 (*m*,

3 H); 7.50–7.60 (*m*, 4 H); 9.14 (br. *s*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 28.4; 55.8; 55.9; 56.4; 62.5; 114.5; 115.0; 122.1; 126.7; 128.7; 129.1; 129.6; 131.0; 139.0; 147.8; 157.0; 163.7. HR-ESI-MS: 401.1827 ($[M+Na]^+$, $C_{23}H_{26}N_2NaO_3^+$; calc. 401.1841).

*(2*RS*,3*RS*)-2-[(1*RS*)-1-(Acetyloxy)-1-phenylethyl]-1-(1,1-dimethylethyl)*-N*-(4-methoxyphenyl)-4-oxoazetidine-3-carboxamide* (**5g′**). Purification by FC (AcOEt/hexane 2:3). ^{1}H-NMR (500 MHz, $CDCl_3$): 1.40 (*s*, 9 H); 2.06 (*s*, 3 H); 2.07 (*s*, 3 H); 3.34 (*d*, *J* = 2.0, 1 H); 3.77 (*s*, 3 H); 4.45 (*d*, *J* = 2.0, 1 H); 6.78–6.83 (*m*, 2 H); 7.30–7.48 (*m*, 7 H); 7.91 (br. *s*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 21.5; 22.7; 29.1; 55.8; 55.9; 56.3; 62.8; 83.3; 114.5; 121.9; 125.4; 126.9; 128.6; 131.0; 139.2; 156.9; 163.3; 166.6; 169.1. HR-ESI-MS: 461.2069 ($[M+Na]^+$, $C_{25}H_{30}N_2NaO_5^+$; calc. 461.2052).

*(2*RS*,3*RS*)-2-[(1*SR*)-1-(Acetyloxy)-1-phenylethyl]-1-(1,1-dimethylethyl)*-N*-(4-methoxyphenyl)-4-oxoazetidine-3-carboxamide* (**5g″**). Purification by FC (AcOEt/hexane 2:3). ^{1}H-NMR (500 MHz, $CDCl_3$): 1.51 (*s*, 9 H); 1.96 (*s*, 3 H); 2.07 (*s*, 3 H); 3.40 (*d*, *J* = 2.4, 1 H); 3.72 (*s*, 3 H); 4.45 (*d*, *J* = 2.4, 1 H); 6.77–6.79 (*m*, 2 H); 7.19–7.22 (*t*, *J* = 7.3, 1 H); 7.27–7.33 (*m*, 4 H); 7.44–7.46 (*m*, 2 H); 8.44 (br. *s*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 17.8; 22.4; 29.4; 55.9; 56.1; 58.5; 63.4; 83.9; 114.8; 122.0; 122.1; 126.5; 128.8; 129.6; 142.5; 157.5; 164.1; 165.2; 169.7. HR-ESI-MS: 461.2069 ($[M+Na]^+$, $C_{25}H_{30}N_2NaO_5^+$; calc. 461.2052).

1-(1,1-Dimethylethyl)-N*-(4-nitrophenyl)-2-oxo-4-(1-phenylethenyl)azetidine-3-carboxamide* (**4h**). Purification by FC (AcOEt/hexane 1:2). ^{1}H-NMR (200 MHz, $CDCl_3$): 1.42 (*s*, 9 H); 3.80 (*d*, *J* = 2.2, 1 H); 5.01 (*d*, *J* = 2.2, 1 H); 5.63 (*s*, 1 H); 5.68 (*s*, 1 H); 7.38–7.54 (*m*, 3 H); 7.56–7.64 (*m*, 4 H); 8.08–8.13 (*m*, 2 H); 9.09 (br. *s*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 28.4; 56.0; 56.3; 62.7; 115.4; 119.6; 125.3; 126.6; 129.0; 129.3; 138.6; 143.7; 144.1; 147.2; 164.4; 165.8. HR-ESI-MS: 416.1594 ($[M+Na]^+$, $C_{22}H_{23}N_3NaO_4^+$; calc. 416.1586).

2-[1-(Acetyloxy)-1-phenylethyl]-1-(1,1-dimethylethyl)-N*-(4-nitrophenyl)-4-oxoazetidine-3-carboxamide* (**5h**; mixture of diastereoisomers). Purification by FC (AcOEt/hexane 1:2). ^{1}H-NMR (200 MHz, $CDCl_3$): 1.38 (*s*, 9 H); 2.01 (*s*, 3 H); 2.05 (*s*, 3 H); 3.66 (*d*, *J* = 2.4, 1 H); 4.56 (*d*, *J* = 2.4, 1 H); 7.31–7.41 (*m*, 3 H); 7.42–7.54 (*m*, 2 H); 7.89–7.95 (*m*, 2 H); 8.19–8.25 (*m*, 2 H); 9.80 (br. *s*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 21.5; 22.5; 29.3; 56.2; 59.1; 62.5; 83.9; 120.3 (major); 120.2 (minor); 126.0; 128.0; 128.9; 129.1; 140.9; 144.5; 145.9; 164.7; 166.2; 169.4. HR-ESI-MS: 476.1783 ($[M+Na]^+$, $C_{24}H_{27}N_3NaO_6^+$; calc. 476.1798).

1-(1,1-Dimethylethyl)-2-(1-hydroxy-1-phenylethyl)-N*-(4-nitrophenyl)-4-oxoazetidine-3-carboxamide* (**6h**; mixture of diastereoisomers). Purification by FC (AcOEt/hexane 1:2). ^{1}H-NMR (200 MHz, $CDCl_3$): 1.34 (*s*, 9 H); 1.79 (*s*, 3 H); 2.89 (br. *s*, 1 H); 3.74 (*d*, *J* = 2.4, 1 H); 4.54 (*d*, *J* = 2.4, 1 H); 7.30–7.45 (*m*, 3 H); 7.59–7.64 (*m*, 2 H); 7.88–7.94 (*m*, 2 H); 8.20–8.26 (*m*, 2 H); 9.81 (br. *s*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 21.0; 29.1; 56.0; 59.4; 60.0; 86.6; 120.2; 120.3; 126.0; 127.1; 129.0; 141.0; 144.3; 145.9; 164.6; 166.3.

1-(1,1-Dimethylethyl)-N*-methyl-2-oxo-4-(1-phenylethenyl)azetidine-3-carbothioamide* (**4i**). Purification by FC (AcOEt/hexane 3:5). ^{1}H-NMR (200 MHz, $CDCl_3$): 1.36 (*s*, 9 H); 3.16 (*d*, *J* = 4.8, 3 H); 3.77 (*d*, *J* = 2.0, 1 H); 5.14 (*d*, *J* = 2.0, 1 H); 5.59 (*s*, 1 H); 5.62 (*s*, 1 H); 7.33–7.37 (*m*, 3 H); 7.51–7.56 (*m*, 2 H); 8.50 (br. *s*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 28.5; 33.1; 55.8; 60.1; 67.5; 116.3; 127.1; 128.7; 129.0; 139.0; 147.7; 166.5; 196.0. HR-ESI-MS: 325.1343 ($[M+Na]^+$, $C_{17}H_{22}N_2NaOS^+$; calc. 325.1351).

N*-Methyl-1-(1-methylethyl)-2-oxo-4-(1-phenylethenyl)azetidine-3-carbothioamide* (**4j**). Purification by FC (AcOEt/hexane 1:2). ^{1}H-NMR (200 MHz, $CDCl_3$): 1.25 (*d*, *J* = 6.6, 3 H); 1.40 (*d*, *J* = 6.8, 3 H); 3.16 (*d*, *J* = 4.8, 3 H); 3.66–3.80 (*m*, 1 H); 3.81 (*d*, *J* = 2.3, 1 H); 5.09 (*d*, *J* = 2.3, 1 H); 5.51 (*s*, 1 H); 5.61 (*s*, 1 H); 7.26–7.38 (*m*, 3 H); 7.39–7.53 (*m*, 2 H); 8.38 (br. *s*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 20.4; 20.9; 32.6; 46.4; 59.7; 66.8; 116.1; 126.6; 128.2; 128.5; 138.2; 145.6; 165.6; 195.6. HR-ESI-MS: 311.1188 ($[M+Na]^+$, $C_{16}H_{20}N_2NaOS^+$; calc. 311.1194).

1-(1,1-Dimethylethyl)-N*-ethyl-2-oxo-4-(1-phenylethenyl)azetidine-3-carbothioamide* (**4k**). Purification by FC (AcOEt/hexane 1:3). ^{1}H-NMR (200 MHz, $CDCl_3$): 1.24 (*t*, *J* = 7.3, 3 H); 1.37 (*s*, 9 H); 3.50–3.82 (*m*, 2 H); 3.74 (*d*, *J* = 1.7, 1 H); 5.17 (*d*, *J* = 1.7, 1 H); 5.58 (*s*, 1 H); 5.62 (*s*, 1 H); 7.33–7.37 (*m*, 3 H); 7.51–7.56 (*m*, 2 H); 8.43 (br. *s*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 12.8; 27.9; 40.7; 55.3; 59.5; 67.2; 115.6; 126.5; 128.2; 128.5; 138.5; 147.1; 166.0; 194.2. HR-ESI-MS: 339.1520 ($[M+Na]^+$, $C_{18}H_{24}N_2NaOS^+$; calc. 339.1507).

2-[1-(Acetyloxy)-1-phenylethyl]-1-(1,1-dimethylethyl)-N-*ethyl-2-oxoazetidine-3-carbothioamide* (**5k**; mixture of diastereoisomers). Purification by FC (AcOEt/hexane 2:3). ^{1}H-NMR (200 MHz, $CDCl_3$): 0.90 (*t*, *J* = 7.3, 3 H); 1.51 (*s*, 9 H); 1.93 (*s*, 3 H); 2.06 (*s*, 3 H); 3.12–3.45 (*m*, 2 H); 3.53 (*d*, *J* = 2.5, 3 H); 4.67 (*d*, *J* = 2.5, 1 H); 7.26–7.42 (*m*, 5 H); 8.33 (br. *s*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 13.2; 18.0; 22.4; 29.4; 41.0; 64.2; 64.3; 67.2; 83.9; 126.6; 128.7; 129.4; 142.1; 164.5; 169.4; 186.3. HR-ESI-MS: 399.1704 ($[M+Na]^+$, $C_{20}H_{28}N_2NaO_3S^+$; calc. 399.1718).

N-*Ethyl-1-(1-methylethyl)-2-oxo-4-(1-phenylethenyl)azetidine-3-carbothioamide* (**4l**). Purification by FC (AcOEt/hexane 1:3). ^{1}H-NMR (200 MHz, $CDCl_3$): 1.24 (*dt*, *J* = 1.0, *J* = 6.6, 3 H); 1.26 (*dd*, *J* = 1.0, *J* = 6.7, 3 H); 1.39 (*dd*, *J* = 1.0 *J* = 6.7, 3 H); 3.58–3.68 (*m*, 2 H); 3.70–3.78 (*m*, 1 H); 3.79 (*d*, *J* = 2.3, 1 H); 5.11 (*d*, *J* = 2.3, 1 H); 7.30–7.40 (*m*, 3 H); 7.41–7.52 (*m*, 2 H); 8.38 (br. *s*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 12.9; 20.4; 20.9; 40.6; 46.3; 59.7; 66.9; 116.1; 126.7; 128.2; 128.4; 128.5; 145.7; 165.6; 194.4. HR-ESI-MS: 325.1341 ($[M+Na]^+$, $C_{17}H_{22}N_2NaOS^+$; calc. 325.1350).

2-[1-(Acetyloxy)-1-phenylethyl]-N-*ethyl-1-(1-methylethyl)-2-oxoazetidine-3-carbothioamide* (**5l**; mixture of diasteroisomers). Purification by FC (AcOEt/hexane 2:3). ^{1}H-NMR (200 MHz, $CDCl_3$): 0.97 (*t*, *J* = 7.3, 3 H); 1.28 (*d*, *J* = 6.7, 3 H); 1.42 (*d*, *J* = 6.8, 3 H); 1.93 (*s*, 3 H); 2.10 (*s*, 3 H); 3.25–3.48 (*m*, 2 H); 3.50–3.70 (*m*, 1 H); 3.84 (*d*, *J* = 2.7, 1 H); 4.57 (*d*, *J* = 2.7, 1 H); 7.24–7.41 (*m*, 5 H); 8.60 (br. *s*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 13.2; 19.1; 21.1; 21.8; 22.4; 40.9 (minor); 41.1 (major); 47.7; 63.9 (minor); 64.0 (major); 66.7; 84.0; 126.4; 128.7; 129.4; 142.2; 164.8; 169.5; 196.2. HR-ESI-MS: 385.1564 ($[M+Na]^+$, $C_{19}H_{26}N_2NaO_3S^+$; calc. 385.1562).

Crystal-Structure Determination[1]). Diffraction data were collected on *KUMA KM4* diffractometer with graphite-monochromated MoK_α using a *Sapphire-2 CCD* detector (*Agilent Ltd.*). The structures were solved with direct methods and refined with the SHELX97 program package [22] with the full-matrix least-squares refinement based on F^2. The data were corrected for absorption with the CrysAlis RED program [23]. All non-H-atoms were refined anisotropically. All H-atoms were positioned with idealized geometry and were refined isotropically with $U_{iso}(H) = 1.2\ U_{eq}$(C and N) for aromatic, CH_2, CH, and amine H-atoms (1.5 for Me H-atoms) using a riding model with C–H = 0.93 (arom. H-atoms), 0.96 (Me H-atoms), 0.97 (CH_2 H-atoms) 0.98 (CH H-atoms), and 0.86 Å (N–H bonds).

Crystal Data of **5a**: $C_{23}H_{26}N_2O_4$, M_r 394.46; colorless block, size 0.23 × 0.18 × 0.15 mm; monoclinic, space group *C*2/*c*; *a* = 19.6870(17), *b* = 8.8802(4), *c* = 25.6299(13) Å, *β* = 98.177(5)°, *V* = 4435.2(5) Å^3; *T* = 20°, *Z* = 8, $\rho_{calc.}$ = 1.181 g cm^{-3}, μ(MoK_α) = 0.081 mm^{-1}; *F*(000) = 1680, 13677 reflections in *h* (−23/24), *k* (−10/10), *l* (−21/31), measured in the range 2.40 ≤ *Θ* ≤ 28.72°, completeness Θ_{max} = 99.9%, 4354 independent reflections, R_{int} = 0.0437, 2209 reflections with $F_o > 4\sigma(F_o)$, 262 parameters, 0 restraint, R^1_{obs} = 0.0466, wR^2_{obs} = 0.1104, R^1_{all} = 0.0971, wR^2_{all} = 0.1245, goodness-of-fit = 0.841, largest difference peak and hole: 0.233/−0.134 e Å^{-3}.

Crystal Data of **5g′**: $C_{25}H_{27}N_2O_5$, M_r 435.49; colorless block, size 0.31 × 0.27 × 0.24 mm; orthorhombic, space group $P2_12_12_1$; *a* = 8.9667(3), *b* = 12.2729(5), *c* = 21.6290(11) Å, *V* = 2380.22(17) Å^3; *T* = 25°, *Z* = 4, $\rho_{calc.}$ = 1.215 g cm^{-3}, μ(MoK_α) = 0.085 mm^{-1}; *F*(000) = 924, 15467 reflections in *h* (−11/10), *k* (−15/14), *l* (−26/26), measured in the range 2.50 ≤ *Θ* ≤ 28.55°, completeness Θ_{max} = 99.9%, 4676 independent reflections, R_{int} = 0.0269, 3226 reflections with $F_o > 4\sigma(F_o)$, 298 parameters, 1 restraint, R^1_{obs} = 0.0571, wR^2_{obs} = 0.1616, R^1_{all} = 0.0779, wR^2_{all} = 0.1749, goodness-of-fit = 0.962, largest difference peak and hole: 0.330/−0.183 e Å^{-3}.

Crystal Data of **4h**: $C_{22}H_{24}N_3O_4$, M_r 394.44; colorless block, size 0.10 × 0.05 × 0.4 mm; monoclinic, space group $P2_1/c$; *a* = 13.3919(13), *b* = 20.346(2), *c* = 7.9436(11) Å, *β* = 92.995(9)°, *V* = 2161.4(4) Å^3; *T* = 25°, *Z* = 4, $\rho_{calc.}$ = 1.212 g cm^{-3}, μ(MoK_α) = 0.085 mm^{-1}; *F*(000) = 836, 13437 reflections in *h* (−16/16), *k* (−25/12), *l* (−9/9), measured in the range 2.51 ≤ *Θ* ≤ 28.63°, completeness Θ_{max} = 99.9%, 4234 independent reflections, R_{int} = 0.0649, 2013 reflections with $F_o > 4\sigma(F_o)$, 243 parameters, 0 restraints, R^1_{obs} = 0.0933, wR^2_{obs} = 0.2603, R^1_{all} = 0.1707, wR^2_{all} = 0.3243, goodness-of-fit = 1.073, largest difference peak and hole: 0.728/−0.313 e Å^{-3}.

Crystal Data of **5h**: $C_{25.25}H_{30}N_3O_6$, M_r 471.52; colorless block, size 0.27 × 0.19 × 0.14 mm; triclinic, space group *P*1; *a* = 9.7291(3), *b* = 15.6542(6), *c* = 18.4054(6) Å, *α* = 73.740(3), *β* = 80.503(3), *γ* =

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[1]) CCDC-903076–903079 contain the supplementary crystallographic data for **5a**, **5g′**, **4h**, and **5h**, resp. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request/cif.

82.990(3)°, $V = 2645.63(16)$ Å^3; $T = 20°$, $Z = 4$, $\rho_{calc.} = 1.184$ g cm^{-3}, $\mu(\mathrm{Mo}K_\alpha) = 0.085$ mm^{-1}; $F(000) =$ 1002, 26020 reflections in h (−11/11), k (−18/19), l (−22/22), measured in the range $2.32 \leq \Theta \leq$ 28.51°, completeness $\Theta_{max} = 99.9\%$, 10385 independent reflections, $R_{int} = 0.0209$, 6247 reflections with $F_o > 4\sigma(F_o)$, 676 parameters, 8 restraints, $R^1_{obs} = 0.0693$, $wR^2_{obs} = 0.1965$, $R^1_{all} = 0.1067$, $wR^2_{all} = 0.2373$, goodness-of-fit = 1.022, largest difference peak and hole: 0.501/ − 0.187 e Å^{-3}.

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