Organic & Biomolecular Chemistry

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Cite this: *Org. Biomol. Chem.*, 2012, **10**, 575

www.rsc.org/obc

PAPER

Synthesis of thiazolidine-fused heterocycles *via exo*-mode cyclizations of vinylogous *N*-acyliminium ions†

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Received 24th August 2011, Accepted 6th October 2011
DOI: 10.1039/c1ob06451g

Syntheses of thiazolidine-fused heterocycles *via exo*-mode cyclizations of vinylogous *N*-acyliminium ions incorporating heteroatom-based nucleophiles have been examined and discussed. The formation of (5,6)-membered systems was feasible with all nucleophiles tried (O, S and N), while the closing of the five-membered ring was restricted to O- and S-nucleophiles. The closure of a four-membered ring failed. Instead, the bicyclic (5,6)-membered acetal derivative and the tricyclic system with an eight-membered central ring were obtained from the substrates containing O and S nucleophilic moieties, respectively. The reaction outcome and stereochemistry are rationalized using quantum chemical calculations at B3LYP/6-31G(d) level. The exclusive *cis*-stereoselectivity in the formation of (5,6)- and (5,5)-membered systems results from thermodynamic control, whereas the formation of the eight-membered ring was kinetically controlled.

Introduction

Carbocations, owing to their electron deficiency and high reactivity, are widely employed for the formation of carbon–carbon and carbon–heteroatom bonds. A notable example is the well-known Mannich reaction,[1] which plays an important role in organic synthesis. It is based on the addition of enols and enolates onto *N*-alkyliminium ions (Fig. 1a) as electrophilic species and is broadly used by chemists to form carbon–carbon bonds. An intramolecular variant of the Mannich reaction involving a cyclization process, the Pictet–Spengler reaction,[2] has long been used for the synthesis of indole and isoquinoline alkaloids. Iminium ion-based cyclizations are widely employed for the formation of a variety of nitrogen-containing heterocycles.[3] A large range of nucleophiles, such as π-nucleophiles (aromatic rings, carbon–carbon double and triple bonds), σ-nucleophiles and heteroatom-based nucleophiles, have been used to react with various acyclic and cyclic iminium ions, usually generated prior to use. For less reactive nucleophiles, iminium ions activated by *N*-acyl groups (Fig. 1b) are employed. These *N*-acyl iminium ions[4] are much more reactive because of the electron-attracting properties of the carbonyl group on nitrogen, which makes the iminium carbon more electron-deficient. A subtype of *N*-acyliminium ions with a carbon–carbon double bond conjugated to an acyl group on nitrogen are referred to as *vinylogous N-acyliminium ions* (Fig. 1c). Despite the rich chemistry of iminium ions, just a few reports on the reactivity of this type of iminium ions are published thus far. It has been shown that vinylogous *N*-acyliminium ions react with added nucleophiles,[5] or that they can initiate a ring-closing reaction with a π-nucleophile, such as an olefin[6] or aromatic ring.[7]

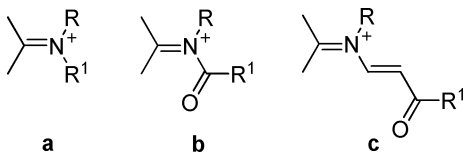

Fig. 1 a) *N*-Alkyliminium ions, b) *N*-acyliminium ions, c) vinylogous *N*-acyliminium ions.

Heterocycles produced *via* the addition of heteroatoms as nucleophiles onto the iminium ions are not only well-known and important compounds, particularly in the field of medicinal chemistry, but also represent stable potential iminium ion equivalents due to the reversibility of the addition process. Suitable structural variations in the iminium ion precursor, like the introduction of a second heteroatom, enlarges the scope of the iminium ion methodology. For example, cyclizations involving thiazolidine-based iminium ions can result in the formation of a variety of derivatives of interesting pharmacological structures.[8] In addition, further desulfurization of thiazolidine-containing polycycles is a valuable method for synthesis of various ring structures, some of which are not easily accessible by other routes.[8c,9]

In 1976, Baldwin formulated rules that allow chemists to predict the ease of ring-closing reactions involving nucleophilic attack on

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† Electronic supplementary information (ESI) available: *X*, *Y*, *Z* Coordinates for the optimized structures of products, intermediates, ground states and transition states. Copies of ^{1}H NMR, ^{13}C NMR and NOESY NMR spectra for the synthesized compounds. See DOI: 10.1039/c1ob06451g

tetrahedral, trigonal and digonal atoms.[10] The rules are based on the possibility of reacting atoms to achieve the required geometry of the transition states. Despite the fact that, according to Baldwin's rules, all *exo*-trig cyclizations are favoured processes, this type of cyclization of iminium ions is far less described than its *endo*-trig counterpart (Fig. 2).[3a]

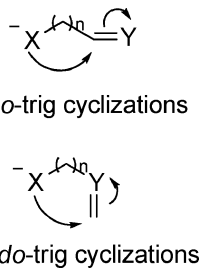


Fig. 2 *Exo*- and *endo*-trig cyclizations.

In the course of our studies on the physico-chemical properties of 2-alkylidene-4-oxothiazolidines we treated compound **1** with $NaBH_4$, aiming to reduce the benzoyl group to the corresponding hydroxy function. The reduction did not occur, but unexpectedly, bicyclic derivative **5** was isolated (21%) along with the thiazoline **6** (18%) and thiazolidine **7** (2%) (Scheme 1).[11] We postulated the *vinylogous N-acyliminium ion* **3** as a key intermediate. It is formed from the hydroxy derivative **2**, produced by the regioselective reduction of one carbonyl of the vinylogous imide function. The resistance of another carbonyl to reduction is considered to reside in its deactivation due to the push–pull effect of the carbon–carbon double bond.[12] The isolation of compounds **6** and **7** supports the existence of **3** as the intermediate. Thus, an abstraction of the C(5)-hydrogen affords **6** and addition of EtOH leads to the traces of **7**. The formation of the iminium ion enhances the electrophilicity of the ester function in **3**, allowing its reduction to **4**, even at room temperature.[13] Subsequent 5-*exo*-trig cyclization affords the *cis*-fused tetrahydrofurothiazolidine **5**, though in low yield. This finding prompted us to further explore the ability of this new vinylogous *N*-acyliminium ion to participate in cyclization reactions with suitably positioned nucleophiles. Herein, we present the results of *exo*-mode cyclizations with a range of heteroatom-based nucleophiles.

Results and discussion

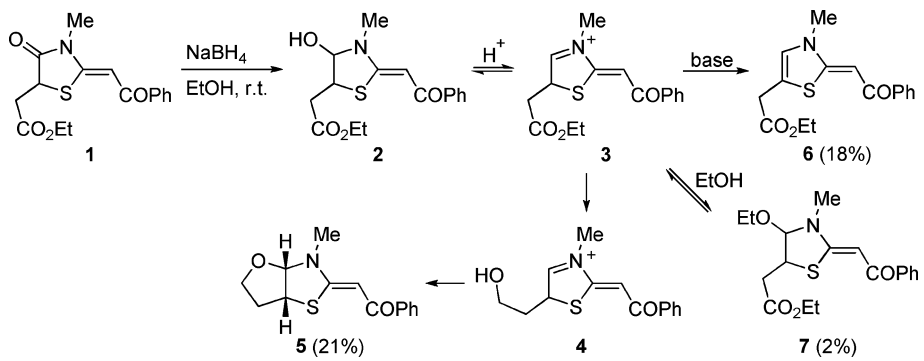
Synthesis of 4-oxothiazolidines

Starting 4-oxothiazolidines **9** were prepared by the base-catalyzed reaction of ethyl cyanoacetate and α-mercapto esters **8** (Table 1), with a slight modification of our published procedure;[14] the syntheses were run without solvent, which resulted in significant shortening of the reaction time and increase in the yields of products. Both products were obtained exclusively as *Z* isomers.[15]

Cyclization Reactions

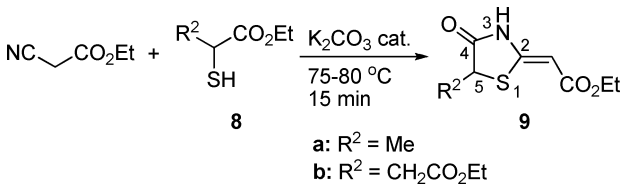
6-*exo* Cyclizations. Substrates, incorporating O, S and N nucleophilic moieties required for 6-*exo*-trig cyclizations, were prepared as presented in Scheme 2. The most acidic position of **9a**, the lactam function, was alkylated first to give the *N*-methyl derivative **10** in high yield. Subsequent alkylation at the activated ring C(5) position with α,β-unsaturated carbonyl compounds, acrolein and methyl vinyl ketone, afforded 5,5-dialkyl products **11** in good yields.[16] This step was followed by regioselective reduction of only the aldehyde/keto group, yielding alcohols **12** as iminium ion precursors containing an O-nucleophile, in high yields. The regioselectivity could be achieved at low temperature using one molar equivalent of reducing agent, $NaBH_4$. With an excess of $NaBH_4$ or at room temperature the lactam carbonyl function was reduced too. Compound **12b** was obtained as a 1 : 1 mixture of diastereomers. The lack of stereoselectivity comes from the distance of the reactive site from the stereogenic C(5) of the thiazolidine ring. The OH group of **12a** was next activated towards nucleophilic substitution by its conversion into mesylate **13**.[17] Substitution with a thioacetyl group yielded the *S*-acyl derivative **14** in almost quantitative yield. It was deprotected with NaOEt/EtOH[18] prior to cyclization. Reaction of **13** with NaN_3 gave azide **15** in quantitative yield, which was subsequently reduced to amino derivative **16** with Ph_3P in refluxing EtOH[19] in high yield.

Vinylogous *N*-acyl iminium ions **18** were generated from substrates **12**, **14**[20] and **16** according to the procedure of Speckamp[8b,21] (Scheme 3). Thus, the ring carbonyl group was reduced to the hydroxy derivatives **17** with $NaBH_4$ in EtOH at 0 °C, in the presence of a catalytic amount of HCl. They were used without isolation for the subsequent dehydration to the iminium ions **18**, which was achieved by the addition of 1 M HCl in EtOH. All



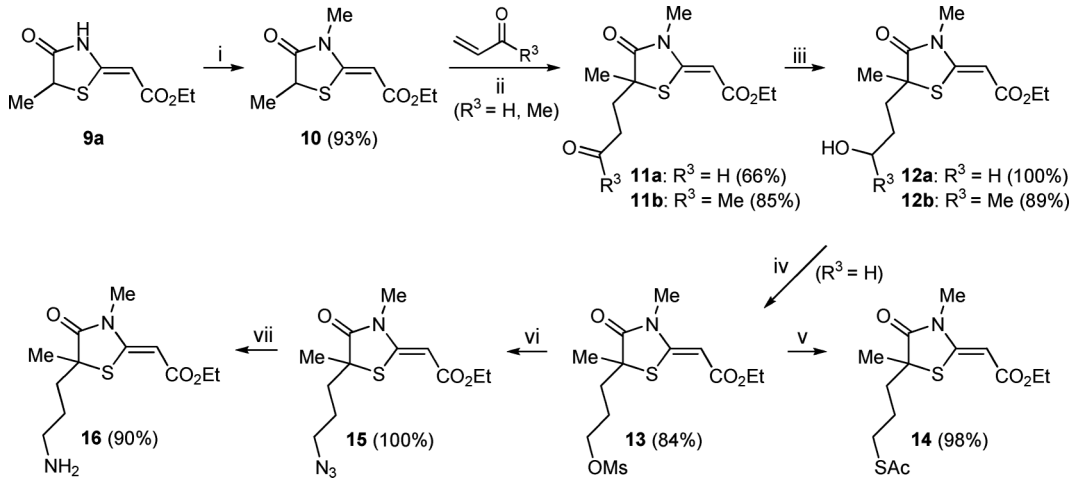
Scheme 1 The reaction of compound **1** upon treatment with $NaBH_4$.

Table 1 Comparison of the synthesis of 4-oxothiazolidines **9** with[14] and without solvent

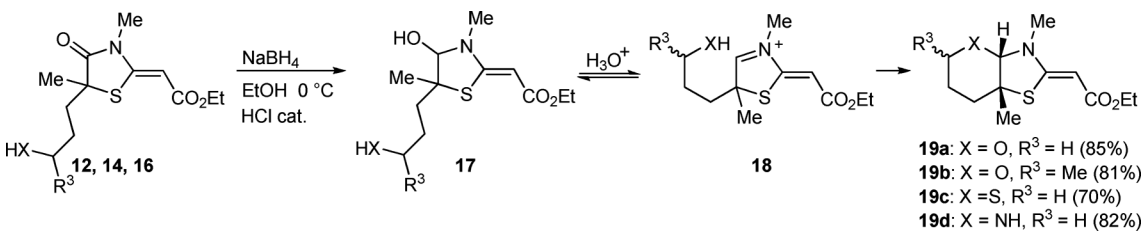


Product	Reaction conditions and yield (%)[a]	
9a-***Z*** (R^2 = Me)	EtOH, reflux, 6 h (42)	no solvent, 75–80 °C, 15 min (76)
9b-***Z*** (R^2 = CH_2CO_2Et)	EtOH, reflux, 9 h (70)	no solvent, 75–80 °C, 15 min (86)

[a] Yield of isolated products.



Scheme 2 Reagents and conditions: (i) MeI (1.2 equiv), K_2CO_3 (1.1 equiv), DMF, rt, 45 min; (ii) K_2CO_3, DMF, rt, 45 min; (iii) $NaBH_4$ (1 equiv), abs EtOH, 0 °C; 15–75 min; (iv) MsCl (2 equiv), Et_3N (2 equiv), CH_2Cl_2, rt, 1.5 h; (v) KSAc (3 equiv), DMF, rt, 1 h; (vi) NaN_3 (3.1 equiv), DMF, rt, 18 h; (vii) Ph_3P (1.5 equiv), MeOH, reflux, 1.5 h.



Scheme 3 6-*exo* Cyclizations of vinylogous *N*-acyliminium ions **18**.

iminium ions cyclized with excellent diastereoselectivity to give single, *cis*-fused bicyclic products **19** in good yields (70–85%). The stereochemistry of the ring junction was assigned on the basis of NOESY NMR experiments, where distinct NOEs were observed between the H(4) and C(5)–C<u>H</u>$_3$ protons.

Table 2 lists the energies of *cis* and *trans* isomers of **19** obtained by DFT calculations at the B3LYP/6-31G(d) level[22] together with their differences ΔE. As can be seen, the *cis* isomers are much more stable than the *trans* isomers, suggesting that the cyclization is thermodynamically controlled. Compound **19b** was obtained as a mixture of two diastereomers (*cis*/*trans* 1 : 1.1, Fig. 3), implying that the rate of ring-closing of two diastereomeric alcohols **12b** was almost the same, due to the distance of the nucleophilic oxygen from the stereogenic C(5) of the thiazolidine ring.

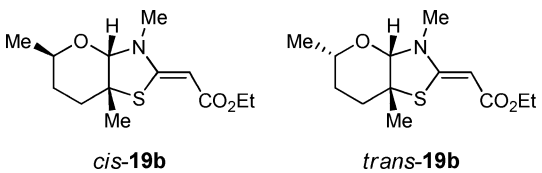
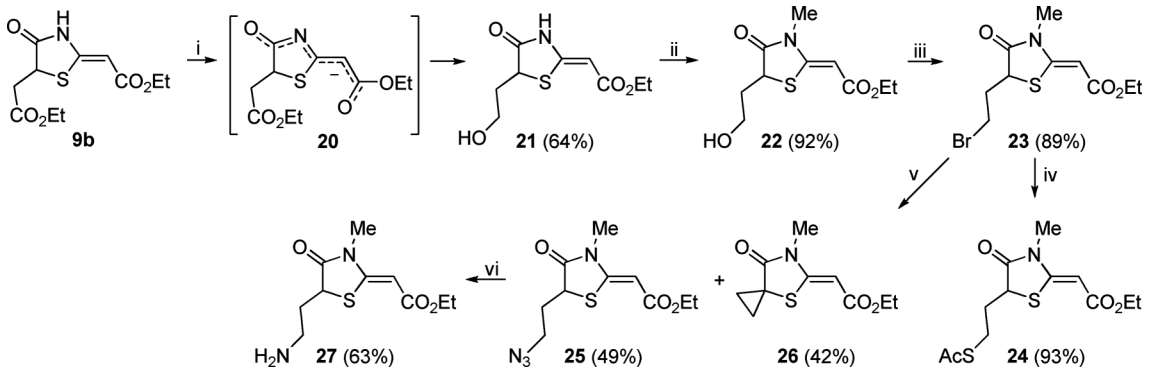


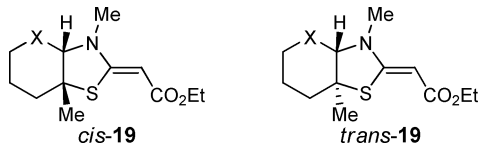
Fig. 3 *Cis* and *trans* isomers of **19b**.

5-*exo* Cyclizations. Substrates for 5-*exo* cyclizations were prepared as shown in Scheme 4. In order to achieve regioselective reduction of the ester group connected to the C(5) position of the ring *via* a methylene group, we started from *N*-unsubstituted 4-oxothiazolidine **9b**. The reduction was performed in EtOH under reflux[13] with a large excess of reducing agent, $NaBH_4$. The first



Scheme 4 Reagents and conditions: (i) $NaBH_4$ (10 equiv), EtOH, reflux, 3 h; (ii) MeI (1.1 equiv), K_2CO_3 (1 equiv), acetone, reflux, 2.5 h; (iii) Ph_3P (5 equiv), Br_2 (4.8 equiv), MeCN, rt, 5 min; (iv) KSAc (1.1 equiv), acetone, rt, 20 min; (v) NaN_3 (1.5 equiv), DMF, rt, 0.5 h; (vi) Ph_3P (1.6 equiv), MeOH, reflux, 1 h.

Table 2 Energies[a] (kcal mol^{-1}) of *cis* and *trans* isomers of **19** and their differences

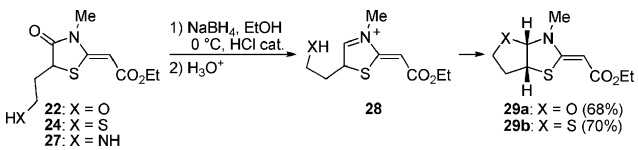


cis-**19** *trans*-**19**

Compound	X	E_{cis}	E_{trans}	ΔE
19a	O	−719965.79	−719959.91	5.88
19c	S	−922632.39	−922629.54	2.85
19d	NH	−707498.15	−707490.40	7.75

[a] Obtained at the B3LYP/6-31G(d) level.

The vinylogous *N*-acyliminium ion **28**, generated from **22**, **24**[20] and **27** in a standard fashion, was trapped only by O- and S-nucleophiles to give energetically preferred[26] *cis*-fused bicyclic derivatives **29** (Scheme 5). In the case of **27**, having a nucleophilic amino group, a complex mixture was formed in which neither bicyclic product nor thiazoline derivative (see below) were detected.

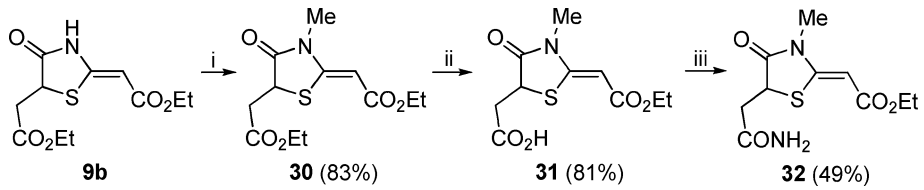


Scheme 5 5-*exo* Cyclizations of vinylogous *N*-acyliminium ions **28**.

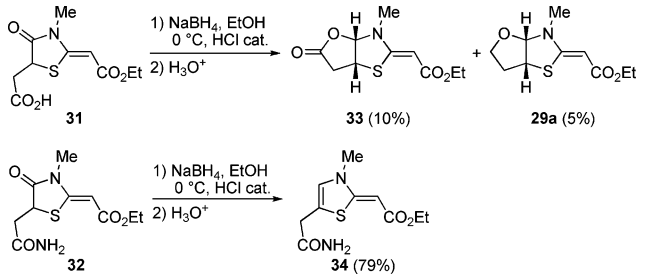
step was the abstraction of the acidic lactam hydrogen, evidenced by the vigorous evolution of H_2. Thus formed, highly stabilized anion **20** inhibited the reduction of the ring carbonyl, so that in the next step $NaBH_4$ selectively reduced the side-chain ester group, in moderate yield.[11b] *N*-Methylation of alcohol **21** was performed under standard alkylating conditions to give **22**, possessing oxygen as an internal nucleophile, in high yield.[11a] It was converted into bromide **23** by the action of Br_2 and Ph_3P.[23] The iminium ion precursor with a sulfur nucleophile **24** was obtained from **23** by the reaction with KSAc in acetone, at room temperature.[24] Substrate **27**, possessing NH_2 as a nucleophilic group, was prepared in two steps. First, bromide **23** was allowed to react with NaN_3 in DMF at room temperature.[25] The azido derivative **25**, obtained in reduced yield due to the formation of spiro-compound **26** as a side product, was then subjected to reduction using Ph_3P in refluxing MeOH[19] to give **27** in moderate yield.

We also investigated whether cyclization of a carboxylate anion and an amide group could be realized in 5-*exo*-mode. The requisite substrates **31** and **32** were prepared according to Scheme 6. Thus, *N*-methylation of **9b** to **30** was followed by hydrolysis[27] to carboxylic acid derivative **31** in good yield. The amide containing compound was synthesized from carboxylic acid **31** by the conversion of COOH into an acid chloride,[28] which was treated *in situ* with ammonium acetate[29] to give **32** in moderate yield.

Upon treatment with $NaBH_4$ substrate **31** cyclized to a γ-lacton only in a small yield of 10% (Scheme 7). Another product, which was isolated in even lower yield (5%), was the bicyclic compound **29a**, obviously formed by the reduction of both lactam carbonyl and carboxy groups. The carboxy group/carboxylate anion was probably activated toward reduction in the same way as the ester group of **3** (Scheme 1), already discussed in the introduction.



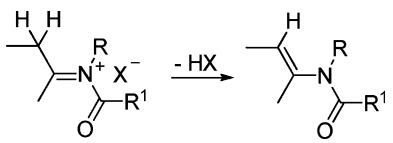
Scheme 6 Reagents and conditions: (i) MeI (1.2 equiv), K_2CO_3 (1.1 equiv), DMF, rt, 45 min; (ii) Na_2CO_3 (2.1 equiv), MeOH–H_2O, rt, 24 h; (iii) 1) $SOCl_2$ (1.5 equiv), Et_3N (2.1 equiv), CH_2Cl_2, rt, 1h, 2) NH_4OAc (18.2 equiv), acetone, reflux, 45 min.



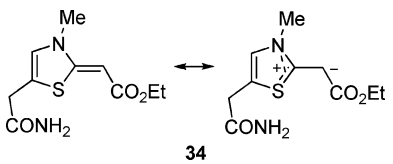
Scheme 7 Reactions of **31** and **32** upon treatment with $NaBH_4$.

Amide **32** did not cyclize, but underwent C(5) deprotonation to give thiazoline **34**, in good yield (Scheme 7).

In general, cyclizations involving *N*-acyliminium ions can be accompanied by an elimination process, resulting in the formation of an enamide[4a] (Scheme 8). This is especially true if cyclizations are relatively sluggish, because of a less reactive nucleophile or steric hindrance. In many instances, particularly under protic acid conditions, this side reaction can be reversed. However, cyclizations involving *N*-acyliminium ions based on imidazolidin-2-ones and thiazolidin-2-ones can be slowed down or completely blocked by this side reaction, leading to the formation of imidazolin-2-one and thiazolin-2-one, respectively.[8b,8c,30] The reluctance of **34** to participate in cyclization can be accounted for by its stabilization due to the development of a partial aromaticity in the thiazoline ring[31] (Scheme 9).



Scheme 8 The elimination reaction of an *N*-acyliminium ion.



Scheme 9 Resonance structures of thiazoline derivative **34**.

Next, we used computational methods to rationalize the difference in chemical behavior between the amide-containing substrate **32**, which underwent elimination reactions, and other substrates undergoing cyclization. Using DFT calculations we estimated the activation free energy for the cyclization and elimination processes. As we envisioned these reaction steps to be initiated by proton abstraction from the reactive site with the solvent molecule, the supramolecular structures **35–37** (Fig. 4) were optimized at the B3LYP/6-31G(d) level[22] and transition state geometries were found by the "reaction coordinate method".[32] In this method, one parameter, chosen as a reaction coordinate, is limited for the appropriate degree of freedom while all other variables are freely optimized. In the studied reactions, the reaction coordinate was taken to be the distance between the hydrogen and heteroatom in **35** and **36** (H–X), leading to cyclization, and hydrogen and C(5) of the thiazolidine ring in **37** (H–C(5)), leading to elimination. The reaction path was calculated by the successive increase in this distance. In the case of substrates containing an amino group as a nucleophile the reaction path was calculated by the successive decrease in the distance between the nitrogen and the iminium carbon, without the added solvent molecule.

The activation free energies (ΔG_{act}), presented in Table 3, were calculated from the difference in energies of the transition states and starting supramolecular geometries. The highest barrier was found for the amide-containing structure **36b** (Entry 8), the only precursor that did not cyclize, but yielded the thiazoline **34** (Scheme 7). It is interesting to note that the calculated cyclization path for this substrate is a multistep process beginning with the formation of imino derivative **38** (ΔG_{act} = 16.73 kcal mol^{-1}) from the most stable structure **36b**, with the carbonyl oxygen pointing toward the iminium carbon (Scheme 10). The next step is the protonation followed by the ring opening to the iminium ion **39**. Rotation around the C–C bond, occurring with the activation free energy of 4.28 kcal mol^{-1}, places the imino group next to the iminium carbon, yielding structure **40**, which cyclizes rapidly, without activation barrier, to the expected product **41**. Thus, in this case, the more favorable elimination pathway, with an activation energy of 5.57 kcal mol^{-1} (Table 3, Entry 9), took place. Noticeable in this process is the increase in the ethanolic oxygen nucleophilicity by the hydrogen bond formation between the carbonyl oxygen and ethanolic hydrogen, as shown in structure **37** (Fig. 4). In the absence of such an interaction, the barrier for the thiazoline formation was estimated to be as high as 24.08 kcal mol^{-1}.

The activation energies for the cyclization step of structures **35a–f** and **36a** are much lower, thus explaining the formation of cyclic products in good yields. A favorable chair-like conformation adopted by the C(5)-side chain in the transition state for the closure of a six-membered ring (Fig. 5) can account for the smaller

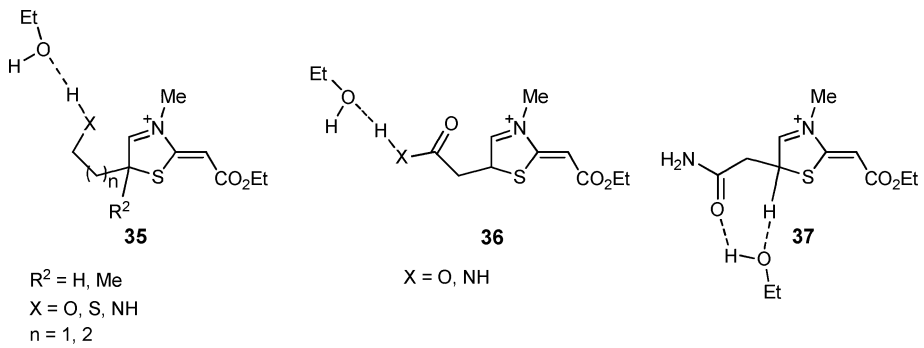


Fig. 4 Initial supramolecular structures used for the calculation of activation parameters.

Table 3 The activation free energy for the cyclization and elimination processes, calculated from structures **35–37**

Entry	Starting structure	R^2	*n*	X	ΔG_{act}[a,b]
1	**35a**	H	1	O	9.47
2	**35b**	H	1	S	6.80
3	**35c**	H	1	NH	0.00[c]
4	**35d**	Me	2	O	6.20
5	**35e**	Me	2	S	1.38
6	**35f**	Me	2	NH	0.00[c]
7	**36a**			O	4.50
8	**36b**			NH	21.01[d]
9	**37**				5.57

[a] Obtained at the B3LYP/6-31G(d) level in the gas phase. [b] Values are in kcal mol^{-1}. [c] Optimization of iminium ion structures **35c** and **35f**, without the added EtOH, resulted in cyclic products. [d] Total barrier including barriers for all steps leading to the expected, final product.

barriers in comparison with those found for the formation of five-membered rings (barriers for **35d** and **35e**, 6.20 and 1.38 kcal mol^{-1}, *versus* barriers for **35a** and **35b**, 9.47 and 6.80 kcal mol^{-1}, respectively, Table 3, Entries 1, 2, 4 and 5).

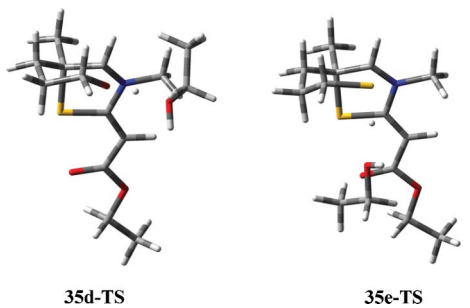


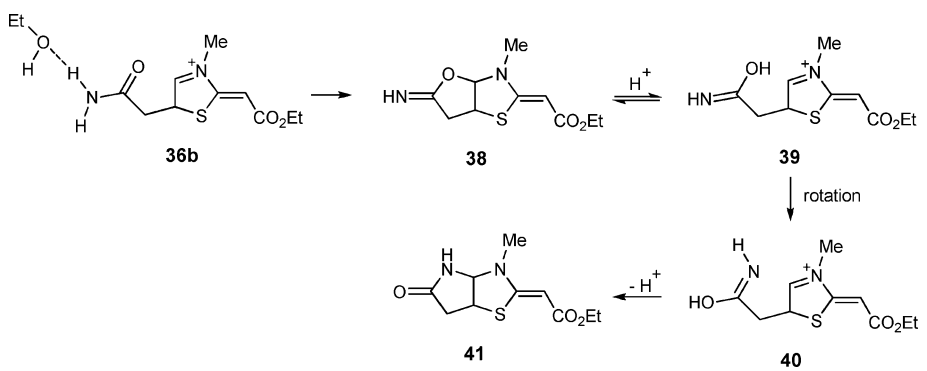
Fig. 5 Transition state geometries for structures **35d** and **35e**.

As can be seen from Table 3, there is no barrier for the formation of C–N bond from precursors **35c** and **35f**, incorporating amino group (Entries 3 and 6). However, only the (5,6)-membered system **19d** was obtained from precursor **16** (Scheme 3). Obviously, in the case of another substrate **27** (Scheme 5), with the nucleophilic amino group, decomposition prevailed. Probably, this is also the reason for the low yield of the isolated lactone **33** (10%), despite the favorable activation energy of 4.50 kcal mol^{-1} (Table 3, Entry 7) found for the cyclization step.

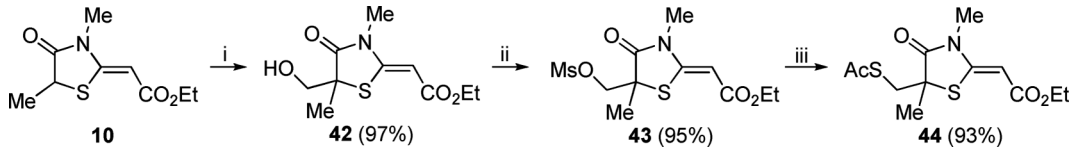
Attempted 4-*exo* cyclizations. The application of iminium ion chemistry to the formation of four-membered rings is limited to the construction of β-lactams from an imine and a ketene, known as the Staudinger reaction.[33] No examples of heteroatom-based cyclizations have been reported. Thus, we were intrigued to see if such cyclizations could occur with the investigated vinylogous *N*-acyliminium ions. Two substrates, **42** and **44**, were prepared, as outlined in Scheme 11. Hydroxymethylation[34] of the C(5) position of 3,5-dimethyl derivative **10** was accomplished in high yield to afford **42**, which was used as an O-nucleophilic precursor.[16] Activation of OH in **42** by its conversion into OMs **43** and subsequent substitution with AcS afforded precursor **44**, containing sulfur as an internal nucleophile, in high yield.

When the reaction of **42** was carried out under standard conditions (EtOH as a solvent)[8b,21] it stopped with the formation of the 4-ethoxy derivative, which failed to react further. It is known that iminium ions exist in equilibrium with a covalent adduct, the structure of which depends on the type of nucleophiles present in solution (Scheme 12). This type of equilibrium has been experimentally proved by Yamamoto *et al.* in their studies of the reaction of α-alkoxy carbamates with Lewis acids.[35] A possible reason for the reaction failure in EtOH can be a complete shifting of equilibrium, shown in Scheme 12, toward the covalent adduct due to the low propensity of the iminium ion generated from **42** to initiate the four-membered ring closure. Hence, in this case, the solvent EtOH was replaced by CH_2Cl_2 prior to the generation of the iminium ion (Scheme 13). The reaction resulted in the formation of two products, thiazoline **47** and bicyclic compound **48**, with the total conversion of 48%. This unexpected reaction outcome is explained by retro aldol reaction of iminium ion **46** leading to the formation of **47** and liberation of formaldehyde, which was trapped by **45** or **46** to give the bicyclic derivative **48**, albeit in low yield.

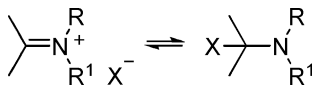
The suggested mechanism has been supported by theoretical calculations. Thus, the supramolecular structure **49** (Fig. 6) was optimized at the B3LYP/6-31G(d) level[22] and the reaction followed by the "reaction coordinate method".[32] The reaction path was calculated by the successive increase in the distance between the oxygen and hydrogen from the reactive hydroxy group of the substrate, which was taken to be the reaction coordinate. When the transition state was reached (Fig. 7) the C–C bond was broken, leading, in the following steps, to the formation of thiazoline and formaldehyde. The activation free energy was estimated to be 12.74 kcal mol^{-1}. Obviously, this reaction path



Scheme 10 Calculated reaction path for the cyclization of amide-containing structure **36b**.



Scheme 11 Reagents and conditions: (i) HCHO (2 equiv), K_2CO_3 (2 equiv), THF-H_2O, rt, 1 h; (ii) MsCl (1.3 equiv), Et_3N (1.5 equiv), CH_2Cl_2, rt, 15 min; (iii) KSAc (3 equiv), DMF, 100 °C, 2 h.



Scheme 12 The equilibrium between an iminium ion and a covalent adduct in solution.

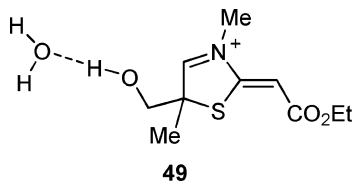


Fig. 6 The initial supramolecular structure used for the calculation of the reaction path of iminium ion **46**.

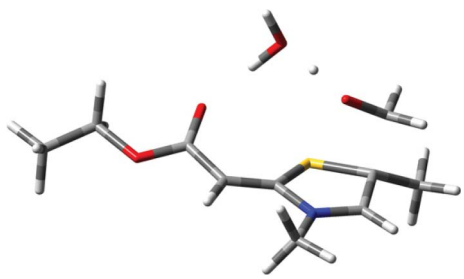


Fig. 7 The transition state for the retro aldol reaction of iminium ion **46**.

was energetically preferable over the closing of a four-membered ring.

Similarly, as in the case of **42**, reduction of deprotected **44** resulted in the formation of a 4-ethoxy derivative when the reaction was run in EtOH as a solvent. Upon shifting to a non-nucleophilic solvent, CH_2Cl_2, a tricyclic system with an eight-membered central ring **51** was formed as a mixture of diastereomers (Scheme 14). Apparently, dimerization to the energetically more stable eight-membered ring was preferred over the formation of the expected four-membered ring (the enthalpy difference between the (4,5)-membered system and the obtained **51** was estimated to be 8.21 kcal mol^{-1}, on the basis of DFT calculations at the B3LYP/6-31G(d) level[22]). It is assumed that the iminium ion exists in equilibrium with the 4-hydroxy derivative **50** and that the attacking nucleophile approaches the iminium carbon opposite to the hydroxy group. As the computed energy difference between the **50**-*cis* and **50**-*trans* (Fig. 8) is small ($\Delta\Delta G_{cis/trans} = -0.15$ kcal mol^{-1}; $\Delta G_{cis} = -921068.37$ kcal mol^{-1}, $\Delta G_{trans} = -921068.22$ kcal mol^{-1}), the stereochemical outcome for the formation of eight-membered ring is the result of kinetic control. Indeed, after keeping the isolated product in a freezer for several weeks, it became enriched in one stereoisomer. Based on DFT calculated energies of all possible

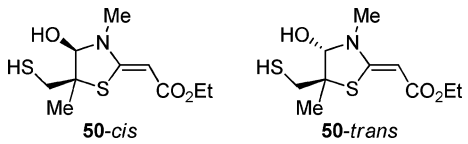


Fig. 8 *Cis* and *trans* isomers of intermediate **50**.

stereoisomers of **51**, the most stable one is the isomer presented in Fig. 9.

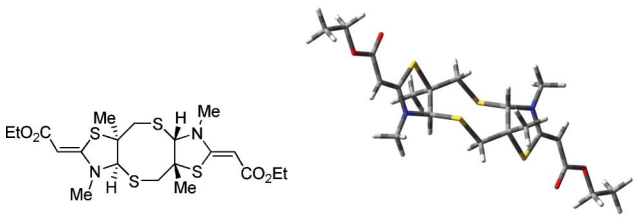


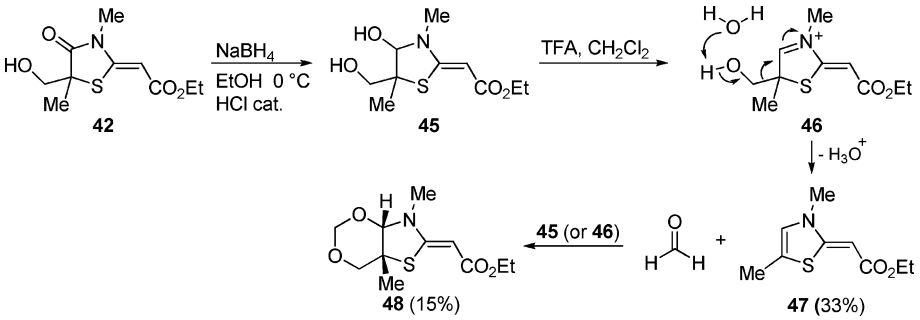
Fig. 9 The most stable stereoisomer of **51**, predicted on the basis of DFT calculations at the B3LYP/6-31G(d) level.

Conclusions

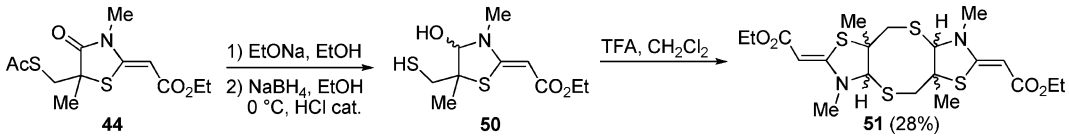
In summary, we have shown that vinylogous *N*-acyliminium ions, possessing heteroatoms as internal nucleophiles, can cyclize in an *exo*-mode fashion yielding thiazolidine-fused (5,6)- and (5,5)-membered heterocycles. While the formation of (5,6)-membered systems was feasible with all nucleophiles tried (O, S and N), the closing of five-membered ring was restricted to O- and S-nucleophiles, and failed with amino and aminocarbonyl groups, where β-elimination took place. Quantum chemical calculations predicted a much higher activation energy (ΔG_{act} = 21.01 kcal mol^{-1}) for trapping of the aminocarbonyl group by the iminium carbon than the energy required for the elimination (ΔG_{act} = 5.57 kcal mol^{-1}), thus explaining the reaction outcome. The activation free energies for the cyclization step range from 0.00–9.47 kcal mol^{-1}.

The closure of a four-membered ring was not achieved. Instead, the precursor incorporating a nucleophilic hydroxy function gave the bicyclic acetal derivative **48** along with the thiazoline **47**. The suggested mechanism was proved by DFT calculations. In the case of the precursor containing a sulfhydryl group, the tricyclic system **51** with an eight-membered central ring was obtained, *i.e.* dimerization was the preferred pathway.

The exclusive *cis*-stereoselectivity in the formation of (5,6)- and (5,5)-membered systems arises from thermodynamic control, as proved by the computation of the energy difference between the two isomers. By contrast, the formation of the eight-membered ring was kinetically controlled.



Scheme 13 The reaction of precursor **42** upon treatment with $NaBH_4$.



Scheme 14 The reaction of precursor **44** upon treatment with $NaBH_4$.

Computational details

All calculations were done using the Gaussian 03 program package.[36] The geometries were fully optimized at the B3LYP/6-31G(d) level[22] and the minimum energy structures confirmed by all positive vibrational force constants. The reaction path was calculated by the "reaction coordinate method".[32] In this method, one parameter, chosen as a reaction coordinate, is limited for the appropriate degree of freedom while all other variables are freely optimized. Initial supramolecular structures, consisting of an optimized iminium ion and suitably placed solvent molecule, were fully optimized at the same level of theory. The reaction coordinate was taken to be the distance between the hydrogen and heteroatom/C(5) of the reactive group of a substrate. The reaction path was calculated by the successive increase in this distance (by 0.1 and 0.02 Å). In the case of substrates containing an amino group as a nucleophile the reaction path was calculated by the successive decrease in the distance between nitrogen and the iminium carbon, without the added solvent molecule. The transition state structures were verified by having only one negative frequency. The activation energies were calculated from the difference in energies of the transition state structures and the initial supramolecules.

Experimental

Melting points were determined on a Stuart SMP10 apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer FT-IR 1725X spectrophotometer and are reported as wave numbers (cm^{-1}). The NMR spectra were recorded on a Varian Gemini 2000 spectrometer (^1H at 200 MHz, ^{13}C at 50.3 MHz) and on a Bruker Ultrashield Advance III (^1H at 500.26 MHz, ^{13}C at 125.79 MHz) in DMSO-d_6 or $CDCl_3$. Chemical shifts are reported in parts per milion (ppm) on the δ scale from TMS as an internal standard. Elemental analyses were performed at the microanalysis laboratory at the Centre for Chemistry ICTM. HRMS was carried out on 6210 TOF LC/MS coupled with HPLC 1200 Series Agilent Technologies. Thin-layer chromatography (TLC) was carried out on Kieselgel G nach Stahl and spots were visualized by iodine or by 50% H_2SO_4. Column chromatography was carried out on SiO_2 (silica gel 60 Å, 12–26, ICN Biomedicals). All solvents were distilled before use. DMF was distilled over CaH_2 and THF over $LiAlH_4$.

General procedure for synthesis of 4-oxothiazolidines 9

A mixture of ethyl cyanoacetate (1 equiv), α-mercapto ester **8** (1.05 equiv) and K_2CO_3 (0.05 equiv) was heated with stirring at the temperature of an oil bath of 75–80 °C for 15 min and then cooled to rt. After adding water/EtOH 7/3 (v/v) to the solidified reaction mixture, stirring was continued for 1 h at rt. Filtration of the solid gave pure products **9**.

(*Z*)-Ethyl 2-(5-methyl-4-oxothiazolidin-2-ylidene)acetate (9a). Compound **9a** was obtained from ethyl cyanoacetate (1.59 g, 14.10 mmol), ethyl 2-mercaptopropionate (1.99 g, 14.85 mmol) and K_2CO_3 (94.5 mg; 0.68 mmol) according to the general procedure, as a white solid (2.17 g; 76%), mp 120–121 °C (lit.[37] 123 °C); IR (KBr): ν_{max} = 3156, 1726, 1657, 1164 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.28 (t, J = 7.0 Hz, 3H, CH_3CH_2), 1.63 (d, J = 7.0 Hz, 3H, CH_3CH), 3.97 (q, J = 7.0 Hz, 1H, CHS), 4.20 (q, J = 7.0 Hz, 2H, CH_2O), 5.64 (s, 1H, =CH), 9.62 (br s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 (CH_3CH_2), 18.8 (CH_3CH), 41.8 (CHS), 60.1 (CH_2O), 91.3 (=CH), 154.6 (C=), 167.9 (CO_{ester}), 178.2 (CO_{lactam}).

(*Z*)-Ethyl 2-(5-ethoxycarbonylmethyl-4-oxothiazolidin-2-ylidene)acetate (9b)[14]. Compound **9b** was obtained from ethyl cyanoacetate (1.28 g, 11.28 mmol), ethyl mercaptosuccinate (2.42 g, 11.73 mmol) and K_2CO_3 (78.4 mg; 0.57 mmol) according to the general procedure, as a white solid (2.66 g; 86%), mp 109–110 °C.

General procedure for synthesis of *N*-methyl derivatives 10, 22 and 30

Methyl iodide was added to a stirred mixture of 4-oxothiazolidine **9** and K_2CO_3 in DMF/acetone, and stirring was continued at rt until the disappearance of the starting material (TLC). The reaction mixture was then diluted with CH_2Cl_2, washed with water, saturated aq NaCl, and dried over Na_2SO_4. After evaporation of

the solvent, the crude product was purified by stirring with *n*-hexane for 2 h at rt.

(*Z*)-Ethyl 2-(3,5-dimethyl-4-oxothiazolidin-2-ylidene)acetate (10). Compound **10** was obtained from **9a** (282.6 mg; 1.40 mmol), K_2CO_3 (212.8 mg; 1.54 mmol; 1.1 equiv), MeI (239.4 mg; 1.69 mmol; 1.2 equiv) in DMF (3.5 mL) according to the general procedure (reaction time 45 min, TLC: toluene/ethyl acetate 3 : 2), as a white solid (281.3 mg; 93%), mp 100–101 °C; IR (KBr): ν_{max} = 1718, 1679, 1586, 1361, 1174, 1034 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, J = 7.0 Hz, 3H, CH_3CH$_2$), 1.61 (d, J = 7.3 Hz, 3H, CH_3CH), 3.17 (s, 3H, NCH_3), 3.90 (q, J = 7.3 Hz, 1H, CHS), 4.22 (q, J = 7.0 Hz, 2H, CH_2O), 5.48 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 (*C*H$_3$CH$_2$), 19.0 (*C*H$_3$CH), 30.0 (NCH_3), 40.5 (CHS), 60.0 (CH_2O), 90.2 (=CH), 157.3 (C=), 167.5 (CO_{ester}), 175.5 (CO_{lactam}). HRMS: Calcd for $C_9H_{14}NO_3S$ $[M+H]^+$ 216.0689, found 216.0692.

(*Z*)-Ethyl 2-(5-(2-hydroxyethyl)-3-methyl-4-oxothiazolidin-2-ilidene)acetate (22). Compound **22** was synthesized according to the published procedure,[11a] in which acetone was used as a solvent.

(*Z*)-Ethyl 2-(5-ethoxycarbonylmethyl-3-methyl-4-oxothiazolidin-2-ylidene)acetate (30). Compound **30** was obtained from **9b** (427.7 mg; 1.56 mmol), K_2CO_3 (238.0 mg; 1.72 mmol; 1.1 equiv), MeI (250.1 mg; 1.71 mmol; 1.2 equiv) in DMF (5.0 mL) according to the general procedure (reaction time 45 min, TLC: toluene/ethyl acetate 7 : 3), as a white solid (369.3 mg; 83%), mp 78–79 °C; IR (KBr): ν_{max} = 1724, 1687, 1370, 1179 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.26 (t, J = 7.4 Hz, 3H, CH_3), 1.29 (t, J = 7.2 Hz, 3H, CH_3), 2.81–3.21 (m, 2H, CH_2CO$_2$Et), 3.19 (s, 3H, NCH_3), 4.12–4.26 (m, 5H, 2 × CH_2O and CHS), 5.50 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0 (CH_3), 14.1 (CH_3), 30.0 (NCH_3), 37.6 (*C*H$_2$CHS), 41.8 (CHS), 60.0 (CH_2O), 61.4 (CH_2O), 90.7 (=CH), 157.4 (C=), 167.5 (CO_{ester}), 169.8 (CO_{ester}), 173.8 (CO_{lactam}); HRMS: Calcd for $C_{12}H_{18}NO_5S$ $[M+H]^+$ 288.0900, found 288.0890.

General procedure for C(5)-alkylation of 3,5-dimethyl-4-oxothiazolidine 10

An alkylating agent was added to a stirred mixture of 3,5-dimethyl-4-oxothiazolidine **10** and K_2CO_3 in DMF (or THF–H_2O, see below), and stirring continued at rt until the disappearance of the starting material (TLC). The reaction mixture was then diluted with $CHCl_3$, washed with water, saturated aq NaCl, and dried over Na_2SO_4. After evaporation of the solvent, the product was purified by stirring with *n*-hexane for 2 h at rt, or by column chromatography.

(*Z*)-Ethyl 2-(3,5-dimethyl-4-oxo-5-(3-oxopropyl)thiazolidin-2-ylidene)acetate (11a). Compound **11a** was obtained from **10** (88.0 mg; 0.41 mmol), K_2CO_3 (5.6 mg; 0.04 mmol; 0.1 equiv), acrolein (25.2 mg; 0.45 mmol; 1.1 equiv) in DMF (2.0 mL) according to the general procedure (reaction time 45 min, TLC: toluene/ethyl acetate 4 : 1). Column chromatography (eluent: gradient petroleum ether (40–60 °C)/ethyl acetate 100 : 0 to 60 : 40) gave pure **11a**, as a white solid (72.8 mg; 66%), mp 95–96 °C; IR (KBr): ν_{max} = 1713, 1678, 1575, 1181, 1084, 1038 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.30 (t, J = 7.0 Hz, 3H, CH_3CH$_2$), 1.63 (s, 3H, CH_3C), 2.13 (ddd, J_1 = 14.5 Hz, J_2 = 10.5 Hz, J_3 = 5.0 Hz, 1H, C*H*HCH$_2$CHO), 2.25 (ddd, J_1 = 14.5 Hz, J_2 = 10.0 Hz, J_3 = 5.0 Hz, 1H, CH*H*CH$_2$CHO), 2.38 (dddd, J_1 = 18.0 Hz, J_2 = 10.5 Hz, J_3 = 5.5 Hz, J_4 = 1.5 Hz,1H, C*H*HCHO), 2.64 (dddd, J_1 = 18.0 Hz, J_2 = 10.0 Hz, J_3 = 5.0 Hz, J_4 = 1.0 Hz, 1H, CH*H*CHO), 3.18 (s, 3H, NCH_3), 4.22 (q, J = 7.0 Hz, 2H, CH_2O), 5.51 (s, 1H, =CH), 9.73 (dd, J_1 = 1.5 Hz, J_2 = 1.0 Hz, 1H, CHO); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.4 (*C*H$_3$CH$_2$), 27.0 (*C*H$_3$C), 30.1 (NCH_3), 32.3 (*C*H$_2$CH$_2$CHO), 39.6 (*C*H$_2$CHO), 53.0 (CH_3*C*), 60.2 (CH_2O), 90.7 (=CH), 155.5 (C=), 167.5 (CO_{ester}), 176.8 (CO_{lactam}), 199.9 (CHO); Anal. Calcd for $C_{12}H_{17}NO_4S$: C, 53.12; H, 6.32; N, 5.16; S, 11.82, found: C, 53.43; H, 6.45; N, 5.14; S, 11.58.

(*Z*)-Ethyl 2-(3,5-dimethyl-4-oxo-5-(3-oxobutyl)thiazolidin-2-ylidene)acetate (11b). Compound **11b** was obtained from **10** (84.0 mg; 0.39 mmol), K_2CO_3 (80.0 mg; 0.58 mmol; 1.5 equiv), methyl vinyl ketone (55.9 mg; 0.8 mmol; 2 equiv) in DMF (4.0 mL) according to the general procedure (reaction time 45 min TLC: toluene/ethyl acetate 4 : 1). Column chromatography (eluent: gradient petroleum ether/ethyl acetate 100 : 0 to 70 : 30) gave pure **11b**, as a pale yellow oil (94.6 mg; 85%); R_f 0.46 (toluene/ethyl acetate 4 : 1); IR (KBr): ν_{max} = 1712, 1685, 1568, 1172, 1078 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, J = 7.4 Hz, 3H, CH_3CH$_2$), 1.61 (s, 3H, CH_3C), 2.13 (s, 3H, CH_3CO), 2.06–2.25 (m, 2H, CH_2CH$_2$CO), 2.33 (ddd, J_1 = 16.8 Hz, J_2 = 10.6 Hz, J_3 = 5.0 Hz, 1H, C*H*HCO), 2.63 (ddd, 1H, J_1 = 16.8 Hz, J_2 = 10.0 Hz, J_3 = 5.6 Hz, C*H*HCO), 3.19 (s, 3H, NCH_3), 4.22 (q, J = 7.4 Hz, 2H, CH_2O), 5.51 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4 (*C*H$_3$CH$_2$), 27.0 (*C*H$_3$C), 29.9 (*C*H$_3$CO), 30.1 (NCH_3), 33.6 (*C*H$_2$CH$_2$CO), 38.9 (CH$_2$*C*H$_2$CO), 53.0 (CH_3*C*), 60.1 (CH_2O), 90.5 (=CH), 155.8 (C=), 167.6 (CO_{ester}), 177.0 (CO_{lactam}), 206.6 (CO_{ketone}); HRMS: Calcd for $C_{13}H_{20}NO_4S$ $[M+H]^+$ 286.1108, found 286.1108.

(*Z*)-Ethyl 2-(5-hydroxymethyl-3,5-dimethyl-4-oxothiazolidin-2-ylidene)acetate (42). Compound **42** was obtained from **10** (293.8 mg; 1.36 mmol), K_2CO_3 (378.0 mg; 2.73 mmol; 2 equiv), formaldehyde (82.0 mg; 2.73 mmol; 2 equiv) in THF–H_2O 1 : 1 (v/v) (5.0 mL) according to the general procedure (reaction time 1h; TLC: toluene/ethyl acetate 3 : 2). The crude product was purified by stirring with *n*-hexane. Filtration gave pure **42**, as a white solid (323.2 mg; 97%), mp 99–100 °C; IR (KBr): ν_{max} = 3441, 1706, 1663, 1577, 1335, 1190, 1072 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 1.20 (t, J = 7.0 Hz, 3H, CH_3CH$_2$), 1.40 (s, 3H, CH_3C), 3.09 (s, 3H, NCH_3), 3.48 (dd, J_1 = 11.0 Hz, J_2 = 5.6 Hz, 1H, C*H*HOH), 3.64 (dd, J_1 = 11.0 Hz, J_2 = 5.6 Hz, 1H, CH*H*OH), 4.09 (q, J = 7.0 Hz, 2H, CH_2O), 5.47 (t, J = 5.6 Hz, 1H, OH), 5.58 (s, 1H, =CH); ^{13}C NMR (50 MHz, DMSO-d_6): δ 14.6 (*C*H$_3$CH$_2$), 22.1 (*C*H$_3$C), 30.1 (NCH_3), 56.5 (CH_3*C*), 59.4 (CH_2O), 67.0 (CH_2OH), 89.5 (=CH), 157.5 (C=), 167.1 (CO_{ester}), 176.3 (CO_{lactam}); HRMS: Calcd for $C_{10}H_{16}NO_4S$ $[M+H]^+$ 246.0795, found 246.0788; Anal. Calcd for $C_{10}H_{15}NO_4S$: C, 48.96; H, 6.16; N, 5.71; S, 13.07, found: C, 48.61; H, 5.88; N, 5.61; S, 13.49.

Regioselective reduction of compounds 11a and 11b to alcohols 12a and 12b

To a stirred solution of **11** in absolute EtOH, cooled in an ice bath, $NaBH_4$ was added at once and stirring was continued at 0–5 °C

until the disappearance of the starting material (TLC). Water was then added followed by a few drops of concentrated HCl, until the evolution of H_2 had ceased. The reaction mixture was extracted with $CHCl_3$, organic layer was washed with saturated aq NaCl and dried over Na_2SO_4. Evaporation of the solvent gave pure products **12**.

(*Z*)-Ethyl 2-(5-(3-hydroxypropyl)-3,5-dimethyl-4-oxothiazolidin-2-ylidene)acetate (12a). Compound **12a** was prepared from **11a** (79.2 mg; 0.29 mmol), $NaBH_4$ (11.0 mg; 0.29 mmol) in absolute EtOH (4.0 mL) according to the general procedure (reaction time 15 min, TLC: toluene/ethyl acetate 7 : 3) as a colorless oil (79.4 mg; 100%); R_f 0.28 (toluene/ethyl acetate 7 : 3); IR (KBr): ν_{max} = 3472, 1713, 1687, 1568, 1174, 1081, 1042 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, J = 7.2 Hz, 3H, CH_3CH$_2$), 1.34–1.52 (m, 1H, CH$_2$CHHCH$_2$) 1.61 (s, 3H, CH$_3$C), 1.66–2.08 (m, 3H, CH_2CHHCH$_2$OH), 3.18 (s, 3H, NCH$_3$), 3.62 (t, J = 6.2 Hz, 2H, CH_2OH), 4.21 (q, J = 7.2 Hz, 2H, CH$_2$O), 5.48 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4 (*C*H$_3$CH$_2$), 26.9 (*C*H$_3$C), 28.0 (CH$_2$*C*H$_2$CH$_2$), 30.0 (NCH$_3$), 36.5 (*C*H$_2$CH$_2$CH$_2$OH), 53.9 (CH$_3$*C*), 60.0 (CH$_2$O), 62.1 (CH$_2$OH), 90.2 (=CH), 156.4 (C=), 167.6 (CO$_{ester}$), 177.6 (CO$_{lactam}$); HRMS: Calcd for $C_{12}H_{20}NO_4S$ $[M+H]^+$ 274.1108, found 274.1095.

(*Z*)-Ethyl 2-(5-(3-hydroxybutyl)-3,5-dimethyl-4-oxothiazolidin-2-ylidene)acetate (12b). Compound **12b** was prepared from **11b** (40.0 mg; 0.14 mmol), $NaBH_4$ (4.8 mg; 0.14 mmol) in abs EtOH (5.0 mL) according to general procedure (reaction time 75 min, TLC: toluene/ethyl acetate 4 : 1) as a white solid (36.0 mg; 89%; 1 : 1 mixture of two diastereomers), mp 57–58 °C; IR (KBr): ν_{max} = 3480, 1715, 1689, 1572, 1365, 1176, 1041 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.16 and 1.19 (s, 6H, 2 × CH_3CHOH), 1.30 (t, J = 7.2 Hz, 6H, 2 × CH_3CH$_2$), 1.61 (s, 6H, 2 × CH$_3$C), 1.65–2.17 (m, 8H, 2 × CH_2CH_2CH(CH$_3$)OH), 3.18 (s, 6H, 2 × NCH$_3$), 3.68–3.84 (m, 2H, 2 × CH$_3$CHOH), 4.21 (q, J = 7.2 Hz, 4H, 2 × CH$_2$O), 5.48 (s, 2H, 2 × =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 (*C*H$_3$CH$_2$), 23.4 (*C*H$_3$CHOH), 26.9 and 27.0 (*C*H$_3$C), 30.0 (NCH$_3$), 34.1 (CH$_2$*C*H$_2$CH(CH$_3$)OH), 36.2 and 36.4 (*C*H$_2$CH$_2$CH(CH$_3$)OH), 53.9 (CH$_3$*C*), 60.0 (CH$_2$O), 67.4 and 67.6 (CHOH), 90.0 and 90.1 (=CH), 156.4 (C=), 167.6 (CO$_{ester}$), 177.5 and 177.6 (CO$_{lactam}$); HRMS: Calcd for $C_{13}H_{22}NO_4S$ $[M+H]^+$ 288. 1264, found 288. 1260.

General procedure for conversion of alcohols 12a and 42 into mesylates 13 and 43

A solution of an alcohol, MsCl and Et_3N in CH_2Cl_2 was stirred at rt until the disappearance of the starting material (TLC). The reaction mixture was then diluted with CH_2Cl_2, washed with 0.35% aq HCl, water, 5% aq $NaHCO_3$, water and dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by stirring with *n*-hexane for 2 h at rt, or by column chromatography.

(*Z*)-Ethyl 2-(3,5-dimethyl-5-(3-(methylsulfonyloxy)propyl)-4-oxothiazolidin-2-ylidine)acetate (13). Compound **13** was obtained from **12a** (82.2 mg; 0.29 mmol), MsCl (66.7 mg; 0.58 mmol; 2 equiv) and Et_3N (57.6 mg; 0.57 mmol; 2 equiv) in CH_2Cl_2 (5.0 mL) according to the general procedure (reaction time 1.5 h; TLC: toluene/ethyl acetate 7 : 3). Column chromatography (eluent: gradient petroleum ether/ethyl acetate 100 : 0 to 50 : 50) gave pure **13**, as a colorless oil (86.5 mg; 84%); R_f 0.62 (toluene/ethyl acetate 1 : 1); IR (KBr): ν_{max} = 1711, 1682, 1565, 1331, 1167 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, J = 7.4 Hz, 3H, CH_3CH$_2$), 1.62 (s, 3H, CH$_3$C), 1.83–2.07 (m, 4H, CH_2CH_2CH$_2$OMs), 3.01 (s, 3H, CH$_3$SO$_3$) 3.19 (s, 3H, NCH$_3$), 4.20 (t, J = 5.6 Hz, 2H, CH$_2$OMs), 4.21 (q, J = 7.4 Hz, 2H, CH$_2$O), 5.50 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4 (*C*H$_3$CH$_2$), 24.7 (CH$_2$*C*H$_2$CH$_2$), 26.9 (*C*H$_3$C), 30.1 (NCH$_3$), 36.2 (*C*H$_2$CH$_2$CH$_2$OMs), 37.44 (CH$_3$SO$_3$), 53.3 (CH$_3$*C*), 60.1 (CH$_2$O), 68.8 (CH$_2$OMs), 90.5 (=CH), 155.7 (C=), 167.5 (CO$_{ester}$), 177.0 (CO$_{lactam}$); HRMS: Calcd for $C_{13}H_{22}NO_6S_2$ $[M+H]^+$ 352.0883, found 352.0880.

(*Z*)-Ethyl 2-(5-((methylsulfonyloxy)methyl)-3,5-dimethyl-4-oxothiazolidin-2-ylidene)acetate (43). Compound **43** was obtained from **42** (76.5 mg; 0.31 mmol), MsCl (46.4 mg; 0.4 mmol; 1.3 equiv) and Et_3N (47.2 mg; 0.47 mmol; 1.5 equiv) in CH_2Cl_2 (4.0 mL) according to the general procedure (reaction time 15 min; TLC: toluene/ethyl acetate 7 : 3). The crude product was purified by stirring with *n*-hexane. Filtration gave pure **43** as a white solid (96.0 mg; 95%), mp 128–129 °C; IR (KBr): ν_{max} = 1711, 1671, 1563, 1356, 1174, 1149 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, J = 7.0 Hz, 3H, CH_3CH$_2$), 1.64 (s, 3H, CH$_3$C), 3.04 (s, 3H, CH$_3$SO$_3$), 3.10 (s, 3H, NCH$_3$), 4.22 (q, J = 7.0 Hz, 2H, CH$_2$O), 4.29 (d, J = 10.0 Hz, 1H, CHHOMs), 4.43 (d, J = 10.0 Hz, 1H, CHHOMs), 5.55 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 (*C*H$_3$CH$_2$), 22.8 (*C*H$_3$C), 30.3 (NCH$_3$), 37.2 (CH$_3$SO$_3$), 52.6 (CH$_3$*C*), 60.2 (CH$_2$O), 72.5 (CH$_2$OSO$_2$), 91.4 (=CH), 154.8 (C=), 167.4 (CO$_{ester}$), 174.1 (CO$_{lactam}$); HRMS: Calcd for $C_{11}H_{18}NO_6S_2$ $[M+H]^+$ 324.0570, found 324.0572; Anal. Calcd for $C_{11}H_{17}NO_6S_2$×0.5H_2O: C, 39.75; H, 5.46; N, 4.21; S, 19.29, found: C, 40.17; H, 5.62; N, 4.16; S, 19.17.

Regioselective reduction of 9b to alcohol 21

A solution of 4-oxothiazolidine **9b** (990 mg; 3.62 mmol) in absolute EtOH (20 mL) was added dropwise into a solution of $NaBH_4$ (1.37 g; 36.21 mmol; 10 equiv) in absolute EtOH (20 mL) over a period of 15 min, at rt. The resulting suspension was then heated under reflux for 3 h, cooled to rt and concentrated to a smaller volume. An aq 10% NH_4Cl (70 mL) was added (pH of the solution was 8–8.5), the mixture stirred at rt for 30 min and extracted with EtOAc. The organic layer was washed with concentrated aq NaCl and dried over Na_2SO_4. Column chromatography (eluent: gradient toluene/ethyl acetate 100 : 0 to 50 : 50) gave **21** (536 mg; 64%) as a colorless needles, mp 110–111 °C; IR (KBr): ν_{max} = 3392, 3217, 1712, 1673, 1582, 1192, 1164, 1031 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 1.18 (t, J = 7.2 Hz, 3H, CH$_3$), 1.70–1.91 (m,1H, CHHCH$_2$OH), 2.10–2.27 (m,1H, CHHCH$_2$OH), 3.54 (m, 2H, CH_2OH), 4.07 (dd, J_1 = 9.6 J_2 = 4.4 Hz, 1H, CHS), 4.05 (q, J = 7.2 Hz, 2H, CH$_2$O), 4.77 (br s, 1H, OH), 5.43 (s, 1H, =CH), 11.54 (br s, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): δ 14.6 (CH$_3$), 36.0 (*C*H$_2$CH$_2$OH), 44.5 (CHS), 58.6 (CH$_2$OH), 59.2 (CH$_2$O), 88.6 (=CH), 157.9 (C=), 167.2 (CO$_{ester}$), 176.8 (CO$_{lactam}$); Anal. Calcd for $C_9H_{13}NO_4S$: C, 46.74; H, 5.67; N, 6.06; S, 13.87, found: C, 46.36; H, 5.53; N, 6.05; S, 13.65.

Conversion of alcohol 22 into bromide 23

A solution of Br_2 (466.5 mg; 2.92 mmol; 4.8 equiv) in MeCN (2 mL) was added dropwise to a solution of Ph_3P (800.0 mg;

3.05 mmol; 5 equiv) in MeCN (7.0 mL), followed by the dropwise addition of a solution of alcohol **22** (150.1 mg; 0.61 mmol) in MeCN (2.0 mL). The reaction mixture was stirred at rt for 5 min (TLC: toluene/ethyl acetate 4 : 1), then diluted with water, neutralized with $NaHCO_3$, extracted with $CHCl_3$ and dried over Na_2SO_4. Column chromatography (eluent: gradient petrolether/ethyl acetate 100 : 0 to 70 : 30) gave pure **23**, as a white solid (167.5 mg; 89%), mp 95–96 °C; IR (KBr): ν_{max} = 1708, 1678, 1570, 1177 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, J = 7.0 Hz, 3H, CH_3), 2.19–2.36 (m, 1H, C*H*HCH$_2$Br), 2.58–2.75 (m, 1H, CH*H*CH$_2$Br), 3.18 (s, 3H, NCH_3), 3.47–3.70 (m, 2H, CH_2Br), 4.13 (dd, J_1 = 8.8, J_2 = 5.0 Hz, 1H, CHS), 4.22 (q, J = 7.0 Hz, 2H, CH_2O), 5.51 (s, 1H, ═CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 (CH_3), 29.5 (CH_2Br), 30.0 (NCH_3), 36.2 (*C*H$_2$CH$_2$Br), 44.6 (CHS), 60.2 (CH_2O), 90.9 (═CH), 156.5 (C═), 167.5 (CO_{ester}), 174.1 (CO_{lactam}); HRMS: Calcd for $C_{10}H_{15}BrNO_3S$ $[M+H]^+$ 307.9950, found 307.9928; Anal. Calcd for $C_{10}H_{14}BrNO_3S$: C, 38.97; H, 4.58; N, 4,54; S, 10.40, found: C, 38.54; H, 4.42; N, 4.44; S, 10.58.

General procedure for synthesis of *S*-acyl derivatives 14, 24 and 44

A solution of bromide **23**/mesylate **13**, **43** and KSAc in dry acetone/DMF was stirred at rt/100 °C until the disappearance of the starting material (TLC). The reaction mixture was then diluted with CH_2Cl_2, washed with water, saturated aq NaCl, and dried over Na_2SO_4. Evaporation of the solvent gave either pure or crude product, which was purified by stirring with *n*-hexane for 2 h at rt.

(*Z*)-Ethyl 2-(5-(3-(acetylthio)propyl)-3,5-dimethyl-4-oxothiazolidin-2-ylidene)acetate (14). Compound **14** was obtained from **13** (43.0 mg; 0.12 mmol) and KSAc (42.0 mg; 0.37 mmol; 3 equiv) in DMF (3.0 mL) according to the general procedure (rt, reaction time 1 h, TLC: toluene/ethyl acetate 7 : 3) as a pale yellow oil (39.5 mg; 98%); R_f 0.75 (toluene/ethyl acetate 7 : 3); IR (KBr): ν_{max} = 1712, 1682, 1565, 1168, 1072 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, J = 7.4 Hz, 3H, C*H*$_3$CH$_2$), 1.59 (s, 3H, CH_3C), 1.67–2.02 (m, 4H, C*H*$_2$C*H*$_2$CH$_2$SAc), 2.32 (s, 3H, CH_3COS), 2.86 (t, J = 6.8 Hz, 2H, CH_2S), 3.19 (s, 3H, NCH_3), 4.21 (q, J = 7.4 Hz, 2H, CH_2O), 5.48 (s, 1H, ═CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4 (*C*H$_3$CH$_2$), 25.0 (CH$_2$*C*H$_2$CH$_2$), 26.9 (*C*H$_3$C), 28.5 (CH_2S), 30.0 (NCH_3), 30.6 (*C*H$_3$COS), 39.1 (*C*H$_2$CH$_2$CH$_2$SAc), 53.7 (CH$_3$*C*), 60.0 (CH_2O), 90.2 (═CH), 156.2 (C═), 167.6 (CO_{ester}), 177.3 (CO_{lactam}), 195.5 (COS); HRMS: Calcd for $C_{14}H_{22}NO_4S_2$ $[M+H]^+$ 332.0985, found 332.0986.

(*Z*)-Ethyl 2-(5-(2-(acetylthio)ethyl)-3-methyl-4-oxothiazolidin-2-ylidene)acetate (24). Compound **24** was obtained from **23** (59.5 mg; 0.19 mmol) and KSAc (24.0 mg; 0.21 mmol; 1.1 equiv) in acetone (5.0 mL) according to general procedure (rt, reaction time 20 min, TLC: toluene/ethyl acetate 9 : 1). The crude product was purified by stirring with *n*-hexane. Filtration gave pure **24**, as a white solid (54.5 mg; 93%), mp 67–69 °C; IR (KBr): ν_{max} = 1717, 1690, 1577, 1364, 1177 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, J = 7.0 Hz, 3H, CH_3), 1.98–2.16 (m, 1H, C*H*HCH$_2$SAc), 2.30–2.47 (m, 1H, CH*H*CH$_2$SAc), 2.35 (s, 3H, CH_3COS), 3.02–3.10 (m, 2H, CH_2SAc), 3.17 (s, 3H, NCH_3), 3.95 (dd, J_1 = 8.6, J_2 = 5.0 Hz, 1H, CHS), 4.22 (q, J = 7.0 Hz, 2H, CH_2O), 5.49 (s, 1H, ═CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4 (CH_3), 26.3 (CH_2SAc), 30.0 (NCH_3), 30.6 (*C*H$_3$COS), 33.4 (*C*H$_2$CH$_2$SAc), 45.1 (CHS), 60.1 (CH_2O), 90.7 (═CH), 157.0 (C═), 167.53 (CO_{ester}), 174.2 (CO_{lactam}), 195.0 (COS); Anal. Calcd for $C_{12}H_{17}NO_4S_2$: C, 47.50; H, 5.65; N, 4.62; S, 21.14, found: C, 47.29; H, 5.68; N, 4.60; S, 20.99.

(*Z*)-Ethyl 2-(5-(acetylthiomethyl)-3,5-dimethyl-4-oxothiazolidin-2-ylidene)acetate (44). Compound **44** was obtained from **43** (101.1 mg; 0.31 mmol) and KSAc (107.0 mg; 0.94 mmol; 3 equiv) in DMF (4.0 mL) according to general procedure (reaction temperature 100 °C, reaction time 2 h, TLC: toluene/ethyl acetate 7 : 3) as a light yellow solid (89.7 mg; 93%), mp 79–80 °C; IR (KBr): ν_{max} = 1712, 1686, 1568, 1175, 1068 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.29 (t, J = 7.2 Hz, 3H, C*H*$_3$CH$_2$), 1.66 (s, 3H, CH_3C), 2.35 (s, 3H, *C*H$_3$COS), 3.18 (s, 3H, NCH_3), 3.42 (s, 2H, CH_2SCO) 4.21 (q, J = 7.2 Hz, 2H, CH_2O), 5.49 (s, 1H, ═CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4 (*C*H$_3$CH$_2$), 26.0 (*C*H$_3$C), 30.2 (NCH_3), 30.5 (*C*H$_3$COS), 38.3 (CH_2S), 54.0 (CH$_3$*C*), 60.1 (CH_2O), 90.6 (═CH), 155.7 (C═), 167.4 (CO_{ester}), 175.8 (CO_{lactam}), 193.5 (COS); Anal. Calcd for $C_{12}H_{17}NO_4S_2$: C, 47.50; H, 5.65; N, 4.62; S, 21.14, found: C, 47.41; H, 5.72; N, 4.69; S, 20.81.

General procedure for synthesis of azides 15 and 25

A solution of mesylate **13**/bromide **23** and NaN_3 in DMF was stirred at rt until the disappearance of the starting material (TLC). The reaction mixture was then diluted with $CHCl_3$, washed with water, saturated aq NaCl, and dried over Na_2SO_4. Evaporation of the solvent gave pure product **15**. In the case of **25**, which was obtained in a mixture with the spiro compound **26**, column chromatography was used to separate the products.

(*Z*)-Ethyl 2-(5-(3-azidopropyl)-3,5-dimethyl-4-oxothiazolidin-2-ylidene)acetate (15). Compound **15** was obtained from **13** (43.0 mg; 0.12 mmol) and NaN_3 (24.0 mg; 0.37 mmol; 3.1 equiv) in DMF (3.0 mL) according to general procedure (reaction time 18 h, TLC: toluene/ethyl acetate 7 : 3) as a colorless oil (36.4 mg; 100%); R_f 0.71 (toluene/ethyl acetate 7 : 3); IR (KBr): ν_{max} = 2096, 1714, 1687, 1572, 1175, 1082 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, J = 7.4 Hz, 3H, C*H*$_3$CH$_2$), 1.36–1.53 (m, 1H, CH$_2$C*H*HCH$_2$N$_3$), 1.61 (s, 3H, CH_3C), 1.69–2.06 (m, 3H, C*H*$_2$CH*H*CH$_2$N$_3$), 3.19 (s, 3H, NCH_3), 3.29 (t, J = 6.8 Hz, 2H, CH_2N_3) 4.21 (q, J = 7.4 Hz, 2H, CH_2O), 5.50 (s, 1H, ═CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4 (*C*H$_3$CH$_2$), 24.5 (CH$_2$*C*H$_2$CH$_2$), 26.9 (*C*H$_3$C), 30.0 (NCH_3), 37.3 (*C*H$_2$CH$_2$CH$_2$N$_3$), 51.0 (CH_2N_3), 53.6 (CH$_3$*C*), 60.0 (CH_2O), 90.4 (═CH), 156.0 (C═), 167.6 (CO_{ester}), 177.2 (CO_{lactam}); HRMS: Calcd for $C_{12}H_{19}N_4O_3S$ $[M+H]^+$ 299.1172, found 299.1177.

(*Z*)-Ethyl 2-(5-(2-azidoethyl)-3-methyl-4-oxothiazolidin-2-ylidene)acetate (25). Compound **25** was obtained from **23** (42.6 mg; 0.14 mmol) and NaN_3 (13.8 mg; 0.21 mmol; 1.5 equiv) in DMF (3.0 mL) according to the general procedure (reaction time 0.5 h, TLC: petroleum ether/ethyl acetate 4 : 1). Column chromatography (eluent: gradient petroleum ether/ethyl acetate 100 : 0 to 70 : 30) gave pure **25** (18.5 mg; 49%) as a white solid, mp 74–75 °C; IR (KBr): ν_{max} = 2104, 1715, 1686, 1578, 1178 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, J = 7.2 Hz, 3H, CH_3), 1.98–2.16 (m, 1H, C*H*HCH$_2$N$_3$), 2.29–2.45 (m, 1H, CH*H*CH$_2$N$_3$), 3.18 (s, 3H, NCH_3), 3.45–3.67 (m, 2H, CH_2N_3), 3.99 (dd, J_1 = 8.2, J_2 = 4.6 Hz, 1H, CHS), 4.22 (q, J = 7.2 Hz, 2H, CH_2O), 5.50 (s, 1H, ═CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 (CH_3), 30.0 (NCH_3), 32.5 (*C*H$_2$CH$_2$N$_3$), 43.4 (CHS),

48.4 (CH_2N_3), 60.1 (CH_2O), 90.9 (=CH), 156.8 (C=), 167,54 (CO_{ester}), 174.2 (CO_{lactam}); HRMS: Calcd for $C_{10}H_{15}N_4O_3S$ $[M+H]^+$ 271.0859, found 271.0854.

(*Z*)-Ethyl 2-(6-methyl-7-oxo-4-thia-6-azaspiro[2.4]heptan-5-ylidene)acetate (26). Compound **26** was obtained as a by-product in the synthesis of **25**. Pure **26** (13.4 mg; 42%) is a white solid, mp 158–160 °C; IR (KBr): ν_{max} = 1714, 1668, 1581, 1177 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.27–1.35 (m, 2H, CH_2CH_2), 1.30 (t, J = 7.2 Hz, 3H, CH_3), 1.60–1.66 (m, 2H, CH_2CH_2), 3.21 (s, 3H, NCH_3), 4.22 (q, J = 7.2 Hz, 2H, CH_2O), 5.57 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4 (CH_3), 17.4 (CH_2CH_2), 27.2 (C(5)S), 30.3 (NCH_3), 60.0 (CH_2O), 90.0 (=CH), 157.7 (C=), 167.9 (CO_{ester}), 174.9 (CO_{lactam}); Anal. Calcd for $C_{10}H_{13}NO_3S$: C, 52.85; H, 5.77; N, 6.16; S, 14.11, found: C, 52.58; H, 5.72; N, 6.19; S, 13.83.

General procedure for synthesis of amines 16 and 27

A solution of azide and Ph_3P in MeOH was refluxed until the disappearance of the starting material (TLC). The reaction mixture was then diluted with CH_2Cl_2, a few drops of concentrated HCl were added and it was extracted with water. The water layer was neutralized with Na_2CO_3, extracted with CH_2Cl_2 and dried over Na_2SO_4. Evaporation of the solvent gave pure products.

(*Z*)-Ethyl 2-(5-(3-aminopropyl)-3,5-dimethyl-4-oxothiazolidin-2-ylidene)acetate (16). Compound **16** was obtained from **15** (36.4 mg; 0.12 mmol) and Ph_3P (48.0 mg; 0.18 mmol; 1.5 equiv) in MeOH (5.0 mL) according to the general procedure (reaction time 1.5 h, TLC: toluene/ethyl acetate 4 : 1) as a colorless oil (30.1 mg; 90%); R_f 0.19 (MeOH); IR (KBr): ν_{max} = 3385, 1711, 1683, 1563, 1169, 1039 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, J = 7.2 Hz, 3H, CH_3CH_2), 1.60 (s, 3H, CH_3C), 1.65–2.02 (m, 4H, $CH_2CH_2CH_2NH_2$), 2.68 (t, J = 7.0 Hz, 2H, CH_2NH_2), 3.18 (s, 3H, NCH_3), 4.21 (q, J = 7.2 Hz, 2H, CH_2O), 5.48 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4 (CH_3CH_2), 26.8 (CH_3C), 28.9 ($CH_2CH_2CH_2$), 29.6 (NCH_3), 37.6 ($CH_2CH_2CH_2NH_2$), 41.7 (CH_2NH_2), 54.0 (CH_3C), 60.0 (CH_2O), 90.1 (=CH), 155.4 (C=), 167.6 (CO_{ester}), 177.6 (CO_{lactam}); HRMS: Calcd for $C_{12}H_{21}N_2O_3S$ $[M+H]^+$ 273.1267, found 273.1268.

(*Z*)-Ethyl 2-(5-(2-aminoethyl)-3-methyl-4-oxothiazolidin-2-ylidene)acetate (27). Compound **27** was obtained from **25** (28.0 mg; 0.1 mmol) and Ph_3P (41.0 mg; 0.16 mmol; 1.6 equiv) in MeOH (3.0 mL) according to the general procedure (reaction time 1 h, TLC: toluene/ethyl acetate 3 : 2) as a colorless oil (20.1 mg; 63%); R_f 0.24 (ethyl acetate/MeOH 1 : 1); IR (KBr): ν_{max} = 3438, 1713, 1685, 1631, 1574, 1179 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, J = 7.0 Hz, 3H, CH_3), 1.83–2.01 (m, 1H, $CHHCH_2NH_2$), 2.20–2.36 (m, 1H, $CHHCH_2NH_2$), 2.89–2.97 (m, 2H, CH_2NH_2), 3.16 (s, 3H, NCH_3), 4.03 (dd, J_1 = 9.0 J_2 = 4.2 Hz, 1H, CHS), 4.22 (q, J = 7.0 Hz, 2H, CH_2O), 5.47 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4 (CH_3), 29.9 (NCH_3), 36.6 ($CH_2CH_2NH_2$), 39.4 (CH_2NH_2), 44.1 (CHS), 60.0 (CH_2O), 90.3 (=CH), 157.8 (C=), 167.6 (CO_{ester}), 175.2 (CO_{lactam}); HRMS: Calcd for $C_{10}H_{17}N_2O_3S$ $[M+H]^+$ 245.0954, found 245.0947.

Synthesis of (*Z*)-Ethyl 2-(5-hydroxycarbonylmethyl-3-methyl-4-oxothiazolidin-2-ylidene)acetate (31). A solution of **30** (89.5 mg; 0.31 mmol) and Na_2CO_3 (70.5 mg; 0.66 mmol; 2.1 equiv) in MeOH–H_2O (9.0 mL; 2 : 1 v/v) was stirred at rt for 24 h. The reaction mixture was then diluted with water and extracted with CH_2Cl_2. The water layer was acidified with concentrated HCl and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and evaporated to give **31** (65.1 mg; 81%) as a white solid, mp 135–137 °C; IR (KBr): ν_{max} = 3495, 1718, 1686, 1573, 1182, 1124 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, J = 7.2 Hz, 3H, CH_3), 2.92 (dd, J_1 = 18.0 Hz, J_2 = 9.0 Hz, 1H, $CHHCO_2H$), 3.19 (s, 3H, NCH_3), 3.26 (dd, J_1 = 18.0 Hz, J_2 = 4.0 Hz, 1H, $CHHCO_2H$), 4.19 (dd, J_1 = 9.0 Hz, J_2 = 4.0 Hz, 1H, CHS), 4.22 (q, J = 7.2 Hz, 2H, CH_2O), 5.51 (s, 1H, =CH), 9.44 (br s, 1H, CO_2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 (CH_3), 30.1 (NCH_3), 37.4 (CH_2CO_2Et), 41.5 (CHS), 60.2 (CH_2O), 91.0 (=CH), 157.3 (C=), 167.6 (CO_{ester}), 173.6 (CO_{acid}), 175.1 (CO_{lactam}); HRMS: Calcd for $C_{10}H_{14}NO_5S$ $[M+H]^+$ 260.0587, found 260.0596.

Synthesis of (*Z*)-Ethyl 2-(5-aminocarbonylmethyl-3-methyl-4-oxothiazolidin-2-ylidene)acetate (32). A solution of **31** (47.9 mg; 0.18 mmol) and Et_3N (39.6 mg; 0.39 mmol; 2.1 equiv) in CH_2Cl_2 (3.5 mL) was stirred at rt for 15 min and then $SOCl_2$ (32.6 mg; 0.27 mmol; 1.52 equiv) was added. Stirring was continued for 1 h and the reaction mixture was evaporated. The residue was dissolved in acetone (4.0 mL), NH_4OAc (252.0 mg; 3.27 mmol; 18.2 equiv) was added and the mixture was refluxed for 45 min. After cooling, the reaction mixture was diluted with water, extracted with $CHCl_3$ and dried over Na_2SO_4. Column chromatography (eluent: ethyl acetate) gave pure **32** (23.5 mg; 49%) as a white solid, mp 203–204 °C; IR (KBr): ν_{max} = 3421, 1712, 1666, 1616, 1574, 1186 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 1.19 (t, J = 7.0 Hz, 3H, CH_3), 2.57 (dd, J_1 = 16.2 Hz, J_2 = 10.0 Hz, 1H, $CHHCONH_2$), 2.94 (dd, J_1 = 16.2 Hz, J_2 = 3.4 Hz, 1H, $CHHCONH_2$), 3.07 (s, 3H, NCH_3), 4.08 (q, J = 7.0 Hz, 2H, CH_2O), 4.19 (dd, J_1 = 10.0 Hz, J_2 = 3.4 Hz, 1H, CHS), 5.53 (s, 1H, =CH), 7.07 (br s, 1H, NHH), 7.53 (br s, 1H, NHH); ^{13}C NMR (50 MHz, DMSO-d_6): δ 14.6 (CH_3), 30.0 (NCH_3), 38.1 (CH_2CONH_2), 42.0 (CHS), 59.4 (CH_2O), 89.4 (=CH), 159.3 (C=), 167.2 (CO_{ester}), 171.2 (CO_{amide}), 174.6 (CO_{lactam}); HRMS: Calcd for $C_{10}H_{15}N_2O_4S$ $[M+H]^+$ 259.0747, found 259.0744.

Deprotection of *S*-acyl derivatives prior to the generation of an iminium ion

All *S*-acyl derivatives were deprotected by 0.2 M NaOEt/EtOH (1 equiv of NaOEt) at rt for 15 min (TLC: toluene/ethyl acetate 4 : 1) and used without isolation for the formation of an iminium ion.

General procedure for generation of an iminium ion and work-up of reaction mixture

To a mixture of a substrate and $NaBH_4$ in absolute EtOH at 0 °C three drops of 0.4 M aq HCl were added every 10–15 min until the completion of the reduction (TLC). The reaction mixture was then acidified by the dropwise addition of 1 M ethanolic HCl (until H_2 evolution had ceased) and stirring was continued for 30 min at 0 °C. After dilution with water, stirring was continued at rt for an additional 30 min. The reaction mixture was then neutralized with $NaHCO_3$, extracted with CH_2Cl_2 and dried over Na_2SO_4. Evaporation of the solvent gave pure or crude product, which was purified by column chromatography.

(*Z*)-Ethyl (3,7a-dimethylhexahydro-2*H*-pyrano[2,3-*d*]thiazol-2-ylidene)acetate (19a). Compound **19a** was obtained from **12a** (39.2 mg; 0.14 mmol) and $NaBH_4$ (88.4 mg; 2.2 mmol; 16.3 equiv) in EtOH (8.0 mL) according to the general procedure (reduction time 2 h, TLC: toluene/ethyl acetate 1 : 1). Evaporation of the solvent after the extraction gave pure **19a** (31.2 mg; 85%) as a colorless oil; R_f 0.76 (toluene/ethyl acetate 1 : 1); IR (KBr): ν_{max} = 1672, 1558, 1432, 1372, 1161, 1054 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.26 (t, J = 7.0 Hz, 3H, CH_3CH$_2$), 1.44 (s, 3H, CH$_3$C), 1.52–1.56 (m, 1H, CH$_2$CHHCH$_2$O), 1.72–1.78 (m, 1H, CHHCH$_2$CH$_2$O), 1.86–1.93 (m, 1H, CH$_2$CHHCH$_2$O), 2.05–2.10 (m, 1H, CHHCH$_2$CH$_2$O), 2.91 (s, 3H, NCH$_3$), 3.40–3.45 (m, 1H, CH$_2$CH$_2$CHHO), 3.80–3.84 (m, 1H, CH$_2$CH$_2$CHHO), 4.15 (q, J = 7.0 Hz, 2H, CH$_2$O), 4.47 (s, 1H, OCHN), 4.95 (s, 1H, ═CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.6 (*C*H$_3$CH$_2$), 21.2 (*C*H$_3$C), 28.2 (CH$_2$*C*H$_2$CH$_2$O), 32.0 (NCH$_3$), 33.5 (*C*H$_2$CH$_2$CH$_2$O), 48.8 (CH$_3$*C*), 59.1 (CH$_2$O), 63.3 (CH$_2$CH$_2$*C*H$_2$O), 82.8 (═CH), 97.2 (OCHN), 163.6 (C═), 168.9 (CO); HRMS: Calcd for $C_{12}H_{20}NO_3S$ $[M+H]^+$ 258.1158, found 258.1154.

(*Z*)-Ethyl (3,5,7a-trimethylhexahydro-2*H*-pyrano[2,3-*d*]thiazol-2-ylidene)acetate (19b). Compound **19b** was obtained from **12b** (45.0 mg; 0.16 mmol) and $NaBH_4$ (91.7 mg; 2.4 mmol; 15.2 equiv) in EtOH (5.0 mL) according to the general procedure (reduction time 3.5 h, TLC: toluene/ethyl acetate 1 : 1). Column chromatography (eluent: gradient petroleum ether/ethyl acetate 100 : 0 to 80 : 20) gave pure **19b** (30.2 mg; 81%; *trans*/*cis* 1.1 : 1, separated by column chromatography) as a colorless oil; R_f 0.57 (toluene/ethyl acetate 4 : 1); IR (KBr): *cis* isomer ν_{max} = 1676, 1562, 1452, 1386, 1150, 1051 cm^{-1}, *trans* isomer ν_{max} = 1674, 1557, 1449, 1372, 1148, 1052 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *cis* isomer δ 1.21 (d, J = 6.5 Hz, 3H, CH_3CH), 1.26 (t, J = 7.0 Hz, 3H, CH_3CH$_2$), 1.37–1.44 (m, 1H, CH$_2$CHHCH(CH$_3$)O), 1.50 (s, 3H, CH_3C), 1.61–1.66 (m, 1H, CH$_2$CHHCH(CH$_3$)O), 1.85–1.90 (m, 1H, CHHCH$_2$CH(CH$_3$)O), 1.99–2.05 (m, 1H, CHHCH$_2$CH(CH$_3$)O), 2.80 (s, 3H, NCH$_3$), 3.68–3.74 (m, 1H, CH$_3$CH), 4.15 (q, J = 7.0 Hz, 2H, CH$_2$O), 4.65 (s, 1H, OCHN), 4.93 (s, 1H, ═CH), *trans* isomer δ 1.17 (d, J = 6.5 Hz, 3H, CH_3CH), 1.26 (t, J = 7.0 Hz, 3H, CH_3CH$_2$), 1.40 (s, 3H, CH_3C), 1.44–1.48 (m, 1H, CH$_2$CHHCH(CH$_3$)O), 1.61–1.76 (m, 2H, CHHCHHCH(CH$_3$)O), 2.06–2.10 (m, 1H, CHHCH$_2$CH(CH$_3$)O), 2.95 (s, 3H, NCH$_3$), 3.37–3.43 (m, 1H, CH$_3$CH), 4.14 (q, J = 7.0 Hz, 2H, CH$_2$O), 4.46 (s, 1H, OCHN), 4.93 (s, 1H, ═CH); ^{13}C NMR (50 MHz, $CDCl_3$): *cis* isomer δ 14.6 (*C*H$_3$CH$_2$), 21.0 (*C*H$_3$C), 23.5 (*C*H$_3$CH), 28.4 (CH$_2$*C*H$_2$CH(CH$_3$)O), 32.0 (NCH$_3$), 33.7 (*C*H$_2$CH$_2$CH(CH$_3$)O), 45.4 (CH$_3$*C*), 59.1 (CH$_2$O), 65.7 (CH$_3$*C*H), 81.4 (═CH), 96.4 (OCHN), 161.5 (C═), 167.0 (CO), *trans* isomer δ 14.6 (*C*H$_3$CH$_2$), 21.2 (*C*H$_3$C), 28.4 (*C*H$_3$CH) 29.6 (CH$_2$*C*H$_2$CH(CH$_3$)O), 31.9 (NCH$_3$), 34.0 (*C*H$_2$CH$_2$CH(CH$_3$)O), 49.0 (CH$_3$*C*), 59.1 (CH$_2$O), 70.4 (CH$_3$*C*H), 82.8 (═CH), 98.0 (OCHN), 164.5 (C═), 169.1 (CO); HRMS: Calcd for $C_{13}H_{22}NO_3S$ $[M+H]^+$ 272.1315, found 272.1312.

(*Z*)-Ethyl (3,7a-dimethylhexahydro-2*H*-thiopyrano[2,3-d]thiazol-ylidene)acetate (19c). Compound **19c** was obtained from **14** (39.0 mg; 0.12 mmol), deprotected prior to the addition of a reducing agent, and $NaBH_4$ (80.1 mg; 2.1 mmol; 18.1 equiv) in EtOH (3.0 mL) according to general procedure (reduction time 1.5 h, TLC: toluene/ethyl acetate 4 : 1). Column chromatography (eluent: gradient petroleum ether/ethyl acetate 100 : 0 to 80 : 20) gave pure **19c** (16.5 mg; 70%) as a colorless oil; R_f 0.67 (toluene/ethyl acetate 4 : 1); IR (KBr): ν_{max} = 1673, 1552, 1369, 1159, 1135, 1051 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.27 (t, J = 7.0 Hz, 3H, CH_3CH$_2$), 1.68 (s, 3H, CH$_3$C), 1.75–1.90 (m, 4H, CH_2CH_2CH$_2$S), 2.27–2.36 (m, 1H, CHHS), 2.51–2.64 (m, 1H, CHHS), 3.01 (s, 3H, NCH$_3$), 4.10 (s, 1H, SCHN), 4.15 (q, J = 7.0 Hz, 2H, CH$_2$O), 5.00 (s, 1H, ═CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.6 (*C*H$_3$CH$_2$), 23.2 (*C*H$_3$C), 23.2 (CH$_2$*C*H$_2$CH$_2$S), 23.6 (CH$_2$S), 33.6 (NCH$_3$), 35.9 (*C*H$_2$CH$_2$CH$_2$S), 48.5 (CH$_3$*C*), 59.1 (CH$_2$O), 73.3 (SCHN), 82.7 (═CH), 163.4 (C═), 168.8 (CO); HRMS: Calcd for $C_{12}H_{20}NO_2S_2$ $[M+H]^+$ 274.0930, found 274.0935.

(*Z*)-Ethyl (3,7a-dimethylhexahydrothiazolo[4,5-b]pyridin-2-(3*H*)-ylidene)acetate (19d). Compound **19d** was obtained from **16** (40.1 mg; 0.15 mmol) and $NaBH_4$ (160.0 mg; 4.2 mmol; 28.0 equiv) in EtOH (4.0 mL) according to the general procedure (reduction time 4 h, TLC: MeOH). Column chromatography (eluent: gradient petroleum ether/ethyl acetate 100 : 0 to 80 : 20) gave pure **19d** (31.0 mg; 82%) as a colorless oil; R_f 0.30 (toluene/ethyl acetate 3 : 2); IR (KBr): ν_{max} = 1671, 1556, 1375, 1141, 1051 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.26 (t, J = 7.0 Hz, 3H, CH_3CH$_2$), 1.47 (s, 3H, CH$_3$C), 1.51–1.59 (m, 2H, CH$_2$CH_2CH$_2$NH), 1.70–1.83 (m, 1H, CHHCH$_2$CH$_2$NH), 1.87 (s, 1H, NH), 1.96–2.10 (m, 1H, CHHCH$_2$CH$_2$NH), 2.55–2.66 (m, 1H, CH$_2$CH$_2$CHHNH), 2.75–2.84 (m, 1H, CH$_2$CH$_2$CHHNH), 2.86 (s, 3H, NCH$_3$), 3.98 (s, 1H, NHCHNMe), 4.15 (q, J = 7.0 Hz, 2H, CH$_2$O), 4.90 (s, 1H, ═CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.6 (*C*H$_3$CH$_2$), 22.5 (*C*H$_3$C), 25.6 (CH$_2$*C*H$_2$CH$_2$NH), 32.6 (NCH$_3$), 34.2 (*C*H$_2$CH$_2$CH$_2$NH), 40.4 (CH$_2$NH), 48.0 (CH$_3$*C*), 59.0 (CH$_2$O), 81.4 (═CH), 83.3 (NHCHN), 164.4 (C═), 168.9 (CO); HRMS: Calcd for $C_{12}H_{21}N_2O_2S$ $[M+H]^+$ 257.1318, found 257.1317.

(*Z*)-Ethyl (3-methyltetrahydrofuro[2,3-*d*]thiazol-2(3*H*)-ylidene)-acetate (29a). Compound **29a** was obtained from **22** (35.0 mg; 0.14 mmol) and $NaBH_4$ (70.0 mg; 1.85 mmol; 13.2 equiv) in EtOH (5.0 mL) according to general procedure (reduction time 2 h, TLC: toluene/ethyl acetate 1 : 1). Column chromatography (eluent: gradient toluene/ethyl acetate 100 : 0 to 70 : 30) gave pure **29a** (22.1 mg; 68%) as a white solid, mp 48–49 °C.[11a]

(*Z*)-Ethyl (3-methyltetrahydrothieno[2,3-*d*]thiazol-2(3*H*)-ylidene)acetate (29b). Compound **29b** was obtained from **24** (55.2 mg; 0.18 mmol), deprotected prior to the addition of a reducing agent, and $NaBH_4$ (112.4 mg; 3.0 mmol; 16.5 equiv) in EtOH (5.0 mL) according to general procedure (reduction time 2 h, TLC: toluene/ethyl acetate 4 : 1). Column chromatography (eluent: gradient petroleum ether/ethyl acetate 100 : 0 to 80 : 20) gave pure **29b** (31.2 mg; 70%) as a white solid, mp 107–108 °C; IR (KBr): ν_{max} = 1668, 1551, 1442, 1363, 1154, 1043 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.26 (t, J = 7.2 Hz, 3H, CH$_3$), 2.25–2.53 (m, 2H, CH_2CH$_2$S), 2.84 (s, 3H, NCH$_3$), 2.86–2.95 (m, 1H, CHHS), 3.32–3.46 (m, 1H, CHHS), 4.15 (q, J = 7.2 Hz, 2H, CH$_2$O), 4.34–4.41 (m, 1H, CHS), 4.89 (s, 1H, ═CH), 5.59 (d, 1H, J = 6.8 Hz, SCHN); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.6 (CH$_3$), 31.2 (NCH$_3$), 35.0 (CH$_2$S), 37.5 (*C*H$_2$CH$_2$S), 49.6 (CHS), 59.2 (CH$_2$O), 80.6 (SCHN), 81.8 (═CH), 162.5 (C═), 169.0 (CO); Anal. Calcd for $C_{10}H_{15}NO_2S_2$: C, 48.95; H, 6.16; N, 5.71; S, 13.04, found: C, 48.58; H, 5.88; N, 5.56; S, 13.62.

(*Z*)-Ethyl (3-methyl-5-oxotetrahydrofuro[2,3-*d*]thiazol-2(3*H*)-ylidene)acetate (33). Compound **33** was obtained from **31** (55.3 mg; 0.21 mmol) and $NaBH_4$ (123.1 mg; 3.2 mmol; 15.5 equiv) in EtOH (5.0 mL) according to the general procedure (reduction time 75 min, TLC: toluene/ethyl acetate 7 : 3). Column chromatography (eluent: gradient petroleum ether/ethyl acetate 100 : 0 to 0 : 100) gave pure **33** (5.3 mg; 10%) as a white solid, decomposes when heated; R_f 0.27 (toluene/ethyl acetate 7 : 3); IR (KBr): ν_{max} = 1784, 1674, 1567, 1440, 1160 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.27 (t, J = 7.0 Hz, 3H, CH_3), 2.90 (d, J = 18.0 Hz, 1H, C*H*HCO$_2$), 3.06 (s, 3H, NCH_3), 3.08 (dd, J_1 = 18.0 Hz, J_2 = 7.5 Hz, 1H, CH*H*CO$_2$), 4.14–4.21 (m, 2H, CH_2O), 4.25–4.28 (m, 1H, CHS), 5.05 (s, 1H, =CH), 5.91 (d, J = 6.0 Hz, 1H, OCHN); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.5 (CH_3), 34.4 (NCH_3), 36.7 (CHS), 41.4 (*C*H$_2$CO$_2$), 59.8 (CH_2O), 84.6 (=CH), 98.5 (OCHN), 161.2 (C=), 168.6 (*C*O$_2$Et), 172.2 (*C*O$_2$CH); HRMS: Calcd for $C_{10}H_{14}NO_4S$ $[M+H]^+$ 244.0638, found 244.0629.

(*Z*)-Ethyl 2-(5-aminocarbonylmethyl-3-methylthiazol-2(3*H*)-ylidene)acetate (34). Compound **34** was obtained from **32** (22.0 mg; 0.09 mmol) and $NaBH_4$ (45.0 mg; 1.19 mmol; 14.0 equiv) in EtOH (5.0 mL) according to the general procedure (reduction time 2 h, TLC: ethyl acetate). Crude product was purified by stirring with toluene at rt for 2 h. Filtration gave pure **34** (16.4 mg; 79%) as a white solid, mp 163–164 °C; IR (KBr): ν_{max} = 3449, 1631, 1525, 1430, 1380, 1166, 1054 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 1.16 (t, J = 7.0 Hz, 3H, CH_3), 3.29 (s, 3H, NCH_3), 3.31 (s, 2H, C*H*$_2$CONH$_2$), 4.00 (q, J = 7.0 Hz, 2H, CH_2O), 4.89 (s, 1H, =CHCO$_2$Et), 7.03 (br s, 1H, N*H*H), 7.50 (br s, 1H, NH*H*), 6.89 (s, 1H, =CHN); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.8 (CH_3), 29.7 (NCH_3), 35.6 (*C*H$_2$C=), 59.1 (CH_2O), 76.2 (=CHCO$_2$Et), 113.6 (=CS), 127.9 (=CHN), 162.4 (C=), 170.9 (CO_{amide}); HRMS: Calcd for $C_{10}H_{15}N_2O_3S$ $[M+H]^+$ 243.0798, found 243.0796.

Reaction of precursor 42

Compound **42** (115.4 mg; 0.47 mmol) was reduced according to the general procedure with $NaBH_4$ (230.0 mg; 6.08 mmol; 12.9 equiv) in EtOH (5.0 mL) (reduction time 1 h, TLC: toluene/ethyl acetate 7 : 3). The reaction mixture was then diluted with water, stirred at rt for 30 min, extracted with $CHCl_3$, dried over Na_2SO_4 and evaporated. The crude 4-hydroxy derivative was dissolved in CH_2Cl_2 (10 mL), TFA (0.1 mL) was added and the reaction mixture was stirred at rt for 18 h. The reaction mixture was then diluted with CH_2Cl_2, washed with 10% aq $NaHCO_3$, water and dried over Na_2SO_4. Column chromatography (eluent: gradient petroleum ether/ethyl acetate 100 : 0 to 50 : 50) gave a mixture (24.6 mg) of **47** and **48** (1 : 2). The yields of products (**47**, 33% and **48**, 15%) are based on the integration of the corresponding signals in the ^1H NMR spectrum.

(*Z*)-Ethyl (3,5-dimethylthiazol-2(3*H*)-ilidene)acetate (47). Compound **47** was separated from the mixture by stirring with *n*-hexane and filtration. White solid, mp 106–107 °C; IR (KBr): ν_{max} = 1635, 1526, 1381, 1167, 1141, 1088, 1055 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.29 (t, J = 7.0 Hz, 3H, C*H*$_3$CH$_2$), 2.16 (d, J = 1.2 Hz, 3H, CH$_3$C=), 3.26 (s, 3H, NCH_3), 4.19 (q, J = 7.0 Hz, 2H, CH_2O), 4.92 (br s, 1H, =CHCO$_2$Et), 6.29 (d, J = 1.2 Hz, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): 11.7 (*C*H$_3$C), 14.7 (*C*H$_3$CH$_2$), 35.3 (NCH_3), 58.7 (CH_2O), 74.6 (=CHCO$_2$Et), 117.1 (=*C*(CH$_3$)S), 125.1 (=CHN), 163.0 (C=), 168.8 (CO_{ester}); HRMS: Calcd for $C_9H_{14}NO_2S$ $[M+H]^+$ 200.0740, found 200.0749; Anal. Calcd for $C_9H_{13}NO_2S$: C, 54.25; H, 6.58; N, 7.03; S, 16.09, found: C, 53.81; H, 6.43; N, 6.81; S, 16.08.

(*Z*)-Ethyl (3,7a-dimethyltetrahydro-2*H*-[1,3]dioxino[4,5-*d*]-thiazol-2-ylidene)acetate (48). ^1H NMR (200 MHz, $CDCl_3$): δ 1.29 (t, J = 7.0 Hz, 3H, C*H*$_3$CH$_2$), 1.50 (s, 3H, CH$_3$C), 2.89 (s, 3H, NCH_3), 3.74 (d, J = 12.4 Hz, 1H, OC*H*HC), 3.98 (d, J = 12.4 Hz, 1H, OCH*H*C), 4.16 (q, J = 7.0 Hz, 2H, CH_2O), 4.71 (s, 1H, OCHN), 4.75 (d, 1H, J = 6.4 Hz, OC*H*HO), 4.96 (d, J = 6.4 Hz, 1H, OCH*H*O), 5.02 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.5 (*C*H$_3$CH$_2$), 22.3 (*C*H$_3$C), 32.8 (NCH_3), 45.9 (CH$_3$*C*), 59.3 (CH_2O), 71.6 (O*C*H$_2$C), 84.0 (=CH), 88.6 (OCH_2O), 95.4 (OCHN), 161.7 (C=), 168.6 (CO_{ester}); HRMS: Calcd for $C_{11}H_{18}NO_4S$ $[M+H]^+$ 260.0951, found 260.0956.

(2*Z*,2′*Z*)-Diethyl 2,2′-(3,8,5a,10a-tetramethyloctahydro-2*H*,7*H*-thiazolo[4′,5′:6,7][1,5]dithiocino[2,3-*d*]thiazol-2,7-diylidene)-diacetate (51). Compound **44** (89.7 mg; 0.29 mmol) was first deprotected and then reduced with $NaBH_4$ (320.0 mg; 8.4 mmol; 30.8 equiv) in EtOH (3.5 mL) according to the general procedure (reduction time 4 h, TLC: toluene/ethyl acetate 7 : 3). The reaction mixture was then diluted with water, stirred at rt for 30 min, extracted with $CHCl_3$, dried over Na_2SO_4 and evaporated. The crude 4-hydroxy derivative was dissolved in CH_2Cl_2 (15 mL), TFA (0.2 mL) and Na_2SO_4 (2 g) were added and the reaction mixture was stirred at rt for 3 h. The reaction mixture was then filtrated, washed with 10% aq $NaHCO_3$, saturated aq NaCl and dried over Na_2SO_4. Column chromatography (eluent: gradient petroleum ether/ethyl acetate 100 : 0 to 70 : 30) gave pure **51** (20.4 mg; 28%; mixture of diastereomers) as a colorless oil; R_f 0.56 (toluene/ethyl acetate 4 : 1); the spectral data refer to the main diastereomer after equilibration of the isolated product in a freezer; IR (KBr): ν_{max} = 1671, 1558, 1373, 1163, 1102 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.25 (t, J = 7.0 Hz, 6H, 2 × C*H*$_3$CH$_2$), 1.60 (s, 6H, 2 × CH$_3$C), 2.97 (s, 6H, 2 × NCH_3), 3.28 (d, J = 13.5 Hz, 2H, 2 × C*H*HS), 3.49 (d, 2H, J = 13.5 Hz, 2 × CH*H*S), 4.14 (q, J = 7.0 Hz, 4H, 2 × CH_2O), 4.71 (s, 2H, 2 × SCHN), 4.86 (s, 2H, 2 × =CH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.6 (*C*H$_3$CH$_2$), 28.5 (*C*H$_3$C), 35.0 (NCH_3), 43.2 (CH_2S), 57.2 (CH$_3$*C*), 59.4 (CH_2O), 82.1 (=CH), 90.0 (SCHN), 160.7 (C=), 168.7 (CO_{ester}); HRMS: Calcd for $C_{20}H_{31}N_2O_4S_4$ $[M+H]^+$ 491.1161, found 491.1195.

Acknowledgements

This work was supported by the Ministry of Science of the Republic of Serbia, Grant No. 142007 (to R.M.), and Deutscher Akademischer Austauschdienst (DAAD)-project ID: 504 252 70.

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