Diastereoselective Zinc-Mediated Barbier-Type Allylation and Propargylation of 3-Formylcephalosporins

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We describe the allylation and propargylation of 3-formylcephalosporins under zinc-mediated, aqueous Barbier conditions, from which the corresponding homoallylic alcohols are produced in good yields and with good-to-excellent diastereoselectivity.

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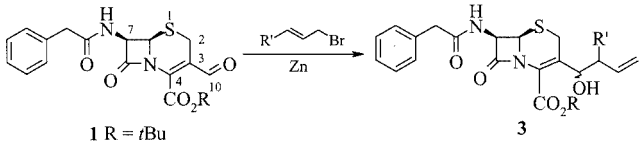
Introduction

The addition of carbon nucleophiles to carbonyl groups is one of the most frequently used methods for constructing carbon−carbon bonds.[1] A typical example is the allylation of aldehydes and ketones applying appropriate organometallic compounds.[2−5] The Grignard and Barbier-type organometallic additions are illustrative of these transformations. Allylic halides, which are difficult to transform into the corresponding Grignard reagents, frequently give excellent results in carbon−carbon bond formations when applying the Barbier procedure[6,7] in which the organometallic intermediate is generated in situ in the presence of the carbonyl group.[8] The possibility to conduct these Barbier-type reactions in aqueous media[9−13] has great practical advantage since no anhydrous organic solvents are needed. Moreover, this aqueous procedure does not require special safety precautions.[14−17]

So far, organometallic additions to 3-formylcephalosporins have been reported only for Grignard-type reactions, which afford the corresponding carbinols as mixtures of diastereoisomers without significant diastereoselectivity. The only examples reported have been additions with methyl, ethyl, and phenyl magnesium bromides,[18−23] and with vinyl-, ethynyl-, and propynylmagnesium bromides,[23−26] but no diastereoselectivity has been observed. So far, little attention has been paid to Barbier-type additions to 3-formylcephalosporins; aqueous conditions have not been investigated at all.

The allylation of 3-formylcephalosporins has attractive prospects for the synthesis of a variety of new 3-substituted cephalosporins (Scheme 1). Starting from the readily available aldehydes **1**[27] and **2**,[28] the resulting addition products **3** can be used as precursors for more complex cephalosporins.



1 R = *t*Bu
2 R = $CHPh_2$

3

Scheme 1

In this paper, the results of zinc-mediated allylation and propargylation of 3-formylcephalosporins using the Barbier methodology are described. The Zn-mediated addition of allylic halides to aldehydes and ketones in aqueous media was introduced by Luche et al.[11−13] Mechanistically, it is highly improbable that these reactions proceed via the intermediacy of organozinc compounds, since such species would react violently with water.[13] Although the details of the mechanism are still under debate,[13,29,30] there is considerable evidence for the involvement of allylic radicals,[29,30] which might be bound to the metal surface.[30,31] The Barbier reaction in organic solvents is also believed to follow a radical mechanism.[32]

Results and Discussion

We first investigated the zinc-mediated Barbier procedure for the allylation of 3-formylcephalosporin **1**. The reaction

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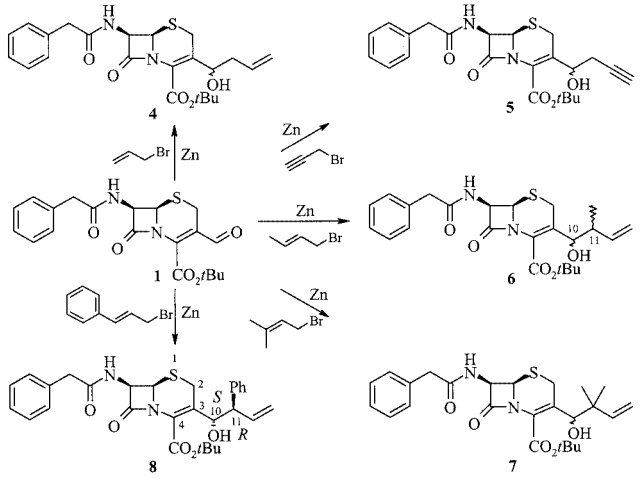
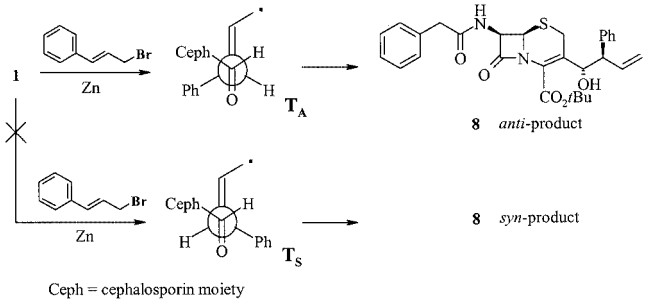
of **1**[27] with allyl bromide, nonactivated zinc, and saturated aqueous ammonium chloride, in THF at room temperature (Luche conditions[13]), resulted in homoallylic alcohol **4** in an excellent yield of 89% (Scheme 2). Ammonium chloride was added to activate the metal surface.[13] At ambient temperature, two diastereoisomers were formed in a 25:75 ratio (fast-moving:slow-moving diastereoisomer, respectively, on TLC). At 0 °C, however, the reaction appeared to be highly diastereoselective: the ratio of the homoallylic alcohols **4** was now 10:90. To establish the scope of the reaction, other allylic bromides, and also propargyl bromide, were applied under similar conditions. In all cases the corresponding carbinols were produced in satisfactory yields and with high diastereoselectivities (Table 1). For example, the reaction of **1** with propargyl bromide afforded the homopropargyl alcohols **5** in 85% yield (diastereoisomeric ratio of 17:83 at ambient temperature). Again, the selectivity was improved to 10:90 when the reaction was performed at 0 °C.



Scheme 2. General reaction conditions: 2 equiv. bromide, 5 equiv. Zn dust, aqueous NH_4Cl, THF, 0 °C or room temp.

The reaction of 3-formylcephalosporin **1** with crotyl bromide under Luche's Barbier conditions gave the methyl-substituted homoallyl alcohol **6** in 79% yield in a 1:1 diastereoisomeric ratio. This finding is in agreement with those of Luche et al.[13] and Wilson et al.[31] who observed that several allyl halides in the aqueous Barbier reaction invariably react at the more-highly substituted carbon atom.

The reaction of **1** with prenyl- and cinnamyl bromide resulted in the corresponding homoallylic alcohols with a good to excellent diastereoselectivity (Table 1), in which the couplings had also occurred at the more-highly substituted carbon atom. Usually, the reactions at ambient temperature resulted in lower yields and diastereoselectivities, and so the reactions were performed preferably at 0 °C. The reaction with cinnamyl bromide proceeded in a completely stereoselective manner and a single product was obtained. In-depth ^1H and ^{13}C NMR spectroscopic analysis of this product **8** (see Exp. Sect.) revealed that the hydroxy group and the phenyl group have an *anti* relationship. As will be shown below, the diastereoselective preference at the hydroxy-bearing carbon atom, as induced by the cephalosporin skeleton, leads to the alcohol with the (*S*) configuration. Thus, the absolute conformation of product **8** is as indicated (Scheme 2), viz. (10*S*,11*R*). The preferred formation of the *anti* product can be explained by considering the two possible transition states for the reaction of the radical derived from cinnamyl bromide with aldehyde **1**, viz. $\mathbf{T_A}$ and $\mathbf{T_S}$ (Scheme 3). The former transition state leads to the *anti* product, whereas the other will give the *syn* product. Apparently, the synclinal relationship of the phenyl group and the conjugated olefinic bond in $\mathbf{T_A}$ leads to a favorable π−π interaction,[33] producing the preferred *anti* product **8**. It should be noted that benzaldehyde reacts with cinnamyl chloride in a Barbier fashion to give also the *anti* isomer of 3,4-diphenylbut-1-en-ol as the main product.[30]



Scheme 3

To study the steric influence of a different ester group at C-4, aldehyde **2**, which contains a diphenylmethyl ester at C-4, was synthesized.[28] Surprisingly, the reaction of aldehyde **2** with allyl bromide did not afford the expected homoallyl alcohols, but instead gave the corresponding lactones **9** in a good yield of 76%, after purification. Even though TLC analysis showed the formation of the expected al-

Table 1. Barbier-type reactions of 3-formylcephalosporin **1**

Entry	Bromide	Product	Yield[a] [%]	Ratio[b] [0 °C]	Ratio[b] [20 °C]
1	allyl	**4**	89	10:90	25:75
2	propargyl	**5**	85	10:90	17:83
3	crotyl	**6**	79	50:50[c],[d]	—[e]
4	prenyl	**7**	80	33:67	—[e]
5	cinnamyl	**8**	71	0:100[c],[f]	10:90[c]

[a] Higher reaction temperature showed similar yield. [b] Ratio fast-moving : slow-moving (TLC; see text). [c] Ratio at C-10. [d] Inseparable *syn*/*anti* mixture. [e] Reaction not performed. [f] Single isomer.

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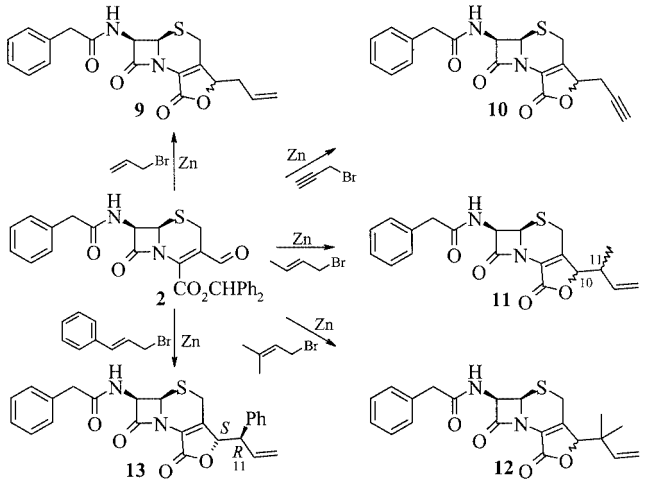
cohols, the only products obtained after column chromatography were the lactones **9** as a mixture of diastereoisomers (Scheme 4; Table 2).



Scheme 4. General reaction conditions: 2 equiv. bromide, 5 equiv. Zn dust, aqueous NH_4Cl, THF, 0 °C or room temp.

Table 2. Barbier-type reactions of 3-formylcephalosporin **2**

Entry	Bromide	Product	Yield[a] [%]	Ratio[b] [0 °C]	Ratio[b] [20 °C]
1	allyl	9	76	80:20	50:50
2	propargyl	10	95	98:02	67:33
3	crotyl	11	73	57:43[c]	–[d]
4	prenyl	12	87	70:30	–[d]
5	cinnamyl	13	70	100:0[e][f]	85:15

[a] Higher reaction temperature showed similar yield. [b] Ratio fast-moving : slow-moving (TLC; see text). [c] Inseparable mixture of 2 diastereoisomers (1:1) at C-11. [d] Reaction not performed. [e] Only trace amount of other isomer (TLC). [f] Single isomer at C-11.

The formation of the lactones **9** is the result of an intramolecular transesterification of the initially formed homoallylic alcohols. Apparently, such transesterification does not take place with the *tert*-butyl ester products **5**–**8**. This difference in chemical behavior of two related esters again points to the sensitivity of cephalosporin substrates to subtle structural differences. The lactonization of the initially formed diphenylmethyl esters could not be avoided, even under neutral conditions. A related facile lactonization has been reported for a cephalosporin diphenylmethyl ester containing an acetoxy methyl group at C-3.[25,26] Lactone formation clearly is an easy process.

The data in Table 2 reveal that in most cases the Barbier reaction with **2** is a highly diastereoselective process. These results are fully in line with those obtained for aldehyde **1** (*tert*-butyl ester) and those reported for 3-bromo-4-formylpyridine.[34] The relative configuration at C-10 in the lactones was established by X-ray crystal structure analyses of the minor diastereoisomers of lactones **9** and **12** (vide infra). Because the absolute configuration of the starting material **2** is known, the absolute configuration at the alcohol bearing carbon C-10 is also known. From these X-ray studies, and by comparison of the ^1H NMR spectral characteristics, the configuration at in other lactones **10**, **11**, and **13** was established.

The relative stereochemistry at the hydroxy-bearing carbon atom is governed by the facial selectivity of the reaction at the aldehyde function. In principle, the aldehyde (e.g., **1**) can react in four possible conformations (Figure 1). We assumed that the π-orbitals of the ester carbonyl group, the C^3-C^4 double bond, and the formyl carbonyl group have an optimal overlap (preferably a planar structure).

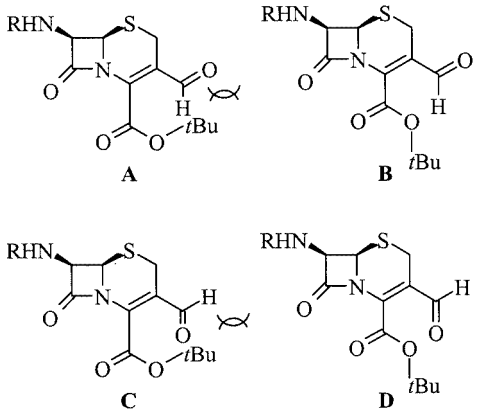


Figure 1. Possible conformations of 3-formylcephalosporin **1**

Initially, a space-filling model was used to differentiate between the possible conformations. It is obvious that the bulky *tert*-butyl ester will escape from steric hindrance, and therefore, the conformers **A** and **C** are energetically not very likely. Using this simple model, however, it is more difficult to discriminate between conformers **B** and **D**. Therefore, information from an X-ray structure of aldehyde **1** was examined in order to provide insight in this conformational preference. The result of this X-ray analysis is shown in Figure 2 and clearly reveals the s-trans conformation for the aldehyde moiety with respect to the olefinic bond, as in conformation **B**. It should be realized that this structural analysis refers to the solid state, but such evidence is commonly taken to be strongly suggestive for a preferred conformation in solution. To escape from steric hindrance, the bulky *tert*-butyl ester will be slightly tilted out of the plane.

Substantial structural information was provided by an X-ray analysis of two products. The two major isomers of products **9** and **12** did not give suitable crystalline material for X-ray diffraction analysis, but, fortunately, the minor diastereoisomers of these products did. The resulting structures are shown in Figure 3.

The stereochemistry at C-10 of the major isomers is opposite to that shown in Figure 3, and is depicted in Figure 4. In both compounds, the stereogenic center at the lactone ring has the (*S*) configuration. Assuming that conformation **B** predominates in solution, attack of the allylic reactant from the least-hindered face would be preferred. Such an attack would lead to the stereochemistry at C-10 opposite to that in the structures **8** and **13**. Apparently, the predominant conformation of the aldehyde in solution is

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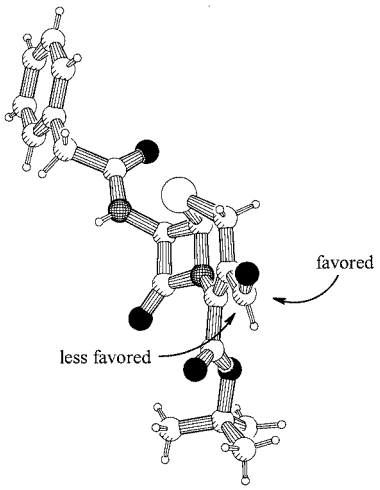

Figure 2. PLUTON drawing of the X-ray structure of aldehyde **1**

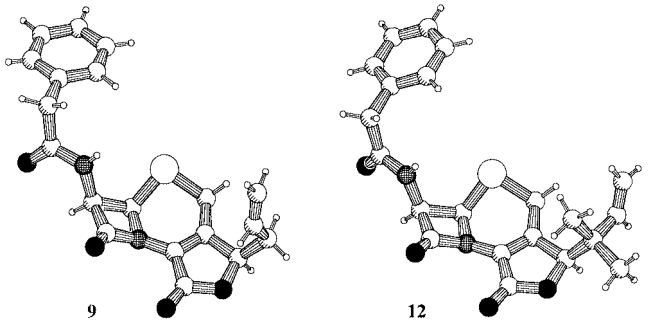

Figure 3. PLUTON drawings of the X-ray structures of allyl lactone **9** and prenyl lactone **12** (minor isomers)

conformation **D**. The information of the X-ray structure (Figure 2) regarding the preferred conformation of the substrate in solution in this case cannot be deduced from that in the solid state. Actually, it constitutes a pitfall! Thus, the obtained results are fully consistent with those derived from the face selectivity of the allylic reaction, when conformation **D** predominates in solution. This face selectivity is clearly the result of steric approach control, which is governed by the spatial encumbrance of the folded shape of the cephalosporin nucleus.

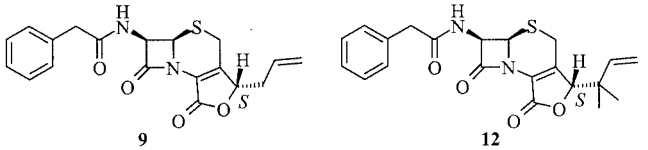

Figure 4. Structures of the major diastereoisomers of lactones **9** and **12**

It is reasonable to assume that the same diastereoselectivity, as induced by the cephalosporin moiety, will occur for the reaction with the *tert*-butyl ester aldehyde **1**, viz. the predominant isomer will have the (*S*) configuration at the hydroxy-bearing carbon atom. We also conclude that the high yields observed for the Barbier addition to the sensitive 3-formylcephalosporins demonstrate the relative mildness of this addition reaction, hence the Zn-mediated Barbier reaction offers unique opportunities for the selective functionalization of cephalosporins.

Experimental Section

General Remarks: 100-MHz ^{1}H NMR spectra were recorded with a Bruker AC 100 spectrometer and 300-MHz ^{1}H NMR spectra, and all ^{13}C NMR spectra, were recorded with a Bruker AC 300 using Me_4Si as the internal standard. All coupling constants are given as ^3J in Hz, unless indicated otherwise. Melting points were measured with a Reichert Thermopan microscope and are uncorrected. IR spectra were recorded with a Bio-Rad FTS-25 instrument. For mass spectra, a double-focusing VG7070E mass spectrometer was used. For some samples, High-Resolution FAB was carried out using a JEOL JMS SX/SX102A four-sector mass spectrometer (JEOL Ltd. 1−2 Musashino 3-chome, Akishima Tokyo), coupled to a MS-MP 9021D/UPD data system (University of Amsterdam). Elemental analyses were performed with a Carlo Erba Instruments CHNSO EA 1108 elemental analyzer. For the determination of optical rotations, a Perkin−Elmer 241MC polarimeter was used. Solvents were dried using the following methods: ethyl acetate was distilled from K_2CO_3; diethyl ether was distilled from NaH; hexane and heptane were distilled from CaH_2; tetrahydrofuran was distilled from sodium just before use. All other solvents were of analytical grade. Thin-layer chromatography (TLC) was carried out on Merck precoated silica gel 60 F254 plates (0.25 mm). Spots were visualized with UV or by using a molybdate spray. Flash chromatography was carried out at a pressure of ca. 1.5 bar, using Merck Kieselgel 60H. Column chromatography at atmospheric pressure was performed with ACROS silica gel (0.035−0.070 mm; pore diameter ca. 6 nm).

Systematic names were generated using the ACD/Name program provided by Advanced Chemistry Development Inc. (Toronto, Canada).

General Procedure for the Organozinc-Addition Reactions

Zinc dust (5 equiv.) and the corresponding bromide (2 equiv.) were added to a solution of aldehyde **1** or **2** in THF (10−20 mL), and then saturated aqueous ammonium chloride (5−10 mL) was added slowly at 0 °C. After completion of the reaction (TLC), the zinc salts were removed by filtration and ethyl acetate (50 mL) and 2 N HCl (25 mL) were added to the filtrate. The organic layer was washed with brine (25 mL), dried ($MgSO_4$) and concentrated in vacuo. The product was purified by column chromatography, followed by crystallization from ethyl acetate/heptane.

***tert*-Butyl (1*R*,7*R*,7a*R*)- and (1*S*,7*R*,7a*R*)-3-[1-Hydroxy-3-butenyl]-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*]-[1,3]thiazine-4-carboxylate (4):** The reaction was performed according to the general procedure, using aldehyde **1** (0.44 g, 1.10 mmol), allyl bromide (0.27 g, ca. 2 equiv.) and zinc dust (0.36 g, ca. 5 equiv.). After workup, the crude mixture was purified by column chromatography (SiO_2; ethyl acetate/heptane, 1:1) affording the allyl adducts **4** (0.43 g, 89%) as a mixture of diastereoisomers (ratio 10:90). Analytical samples were obtained by crystallization from ethyl acetate/heptane to give off-white plates (fast-moving isomer) and colorless needles (slow-moving isomer).

Fast-Moving Minor Isomer (1*R*)-4: M.p. 128−130 °C (dec.). $[\alpha]_D^{20}$ = +73.0 (*c* = 0.61, acetone). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48

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[s, 9 H, $C(CH_3)_3$], 2.17−2.27 (mAB, 1 H, $CH_2CH=CH_2$), 2.41−2.50 (mAB, 1 H, $CH_2CH=CH_2$), 3.32 and 3.64 (qAB, J_{AB} = 17.9 Hz, 2 H, SCH_2), 3.56 (s, 2 H, $PhCH_2$), 3.51 (br. s, 1 H, OH), 4.87 (d, J = 4.8 Hz, 1 H, NHCHCH), 4.90 [t, J = 7.5 Hz, 1 H, $C(OH)HCH_2$], 5.05−5.11 (m, 2 H, $CH=CH_2$), 5.57−5.69 (m, 1 H, $CH=CH_2$), 5.74 (dd, J = 4.8, 9.2 Hz, 1 H, NHCHCHS), 7.19−7.34 (m, 6 H, Ph-H and NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.6 (SCH_2), 27.7 [$C(CH_3)_3$], 38.0 ($CH_2CH=CH_2$), 43.3 ($PhCH_2$), 57.9 (CHNH), 58.8 (CHS), 68.4 (CHOH), 84.0 [$C(CH_3)_3$], 117.8 ($CH=CH_2$), 125.5 (=CCHOH), 127.3, 128.8, 129.4, and 134.0 (Ph-C), 129.6 (=CCO_2tBu), 133.4 ($CH=CH_2$), 161.2 (CO_2tBu), 165.1 (C=O, lactam), 171.4 [$PhCH_2C$(O)] ppm. IR (KBr): ṽ = 3435 (br., OH), 3272 (br., NH), 1786 (C=O, lactam), 17157 (C=O, ester), 1688 and 1514 (C=O, amide), 1391 (C−N), 1156 (C−O, ester) cm^{-1}. MS (CI^+): m/z (%) = 474 (1) [M + C_2H_5]$^+$, 445 (1) [M + H]$^+$, 404 (1), 377 (2), 174 (15), 136 (6), 91 (19) [$PhCH_2^+$], 57 (100) [$C_4H_9^+$]. HRMS (CI^+, m/z): 444.17183 (calcd. for $C_{23}H_{28}N_2O_5S$: 444.1719).

Slow-Moving Major Isomer (1*S*)-4: M.p. 221−223 °C (dec.). $[\alpha]_D^{20}$ = +10.0 (c = 0.13, acetone). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50 [s, 9 H, $C(CH_3)_3$], 2.25−2.35 (mAB, 1 H, $CH_2CH=CH_2$), 2.44−2.52 (mAB, 1 H, $CH_2CH=CH_2$), 2.80 (d, J = 3.6 Hz, 1 H, CHO*H*), 3.40 and 3.52 (qAB, J_{AB} = 18.6 Hz, 2 H, SCH_2), 3.62 (s, 2 H, $PhCH_2$), 4.81−4.87 (m, 1 H, CHOH), 4.88 (d, J = 4.8 Hz, 1 H, NHCHC*H*S), 5.14−5.19 (m, 2 H, $CH=CH_2$), 5.75 (dd, J = 4.8, 8.9 Hz, 1 H, NHC*H*CHS), 5.78−5.92 (m, 1 H, $CH=CH_2$), 6.58 (d, 8.9 Hz, 1 H, NH), 7.24−7.38 (m, 5 H, Ph-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.5 (SCH_2), 27.7 [$C(CH_3)_3$], 40.4 ($CH_2CH=CH_2$), 43.1 ($PhCH_2$), 57.7 (CHNH), 58.8 (CHS), 69.6 (CHOH), 83.3 [$C(CH_3)_3$], 118.7 ($CH=CH_2$), 123.8 (=CCHOH), 127.5, 129.0, 129.2, and 133.7 (Ph-C), 133.0 (=CCO_2tBu), 133.8 ($CH=CH_2$), 160.7 (CO_2tBu), 164.3 (C=O, lactam), 171.4 ($PhCH_2C$(O)) ppm.

***tert*-Butyl (1*R*,7*R*,7a*R*)- and (1*S*,7*R*,7a*R*)-3-[1-Hydroxy-3-butynyl]-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*]-[1,3]thiazine-4-carboxylate (5):** Aldehyde **1** (0.81 g, 2.0 mmol) was treated according to the general procedure (propargyl bromide) to give, after column chromatography (SiO_2; ethyl acetate/heptane, 1:1), both propargyl adducts **5** (0.71 g, 85%) as two separable diastereoisomers in a ratio of 10:90. Analytical samples were obtained by crystallization from ethyl acetate/heptane.

Fast-Moving Minor Isomer (1*R*)-5: M.p. 123−125 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50 [s, 9 H, $C(CH_3)_3$], 1.98 (t, ^4J = 2.6 Hz, 1 H, C≡CH), 2.41 (m, part of AB, J_{AB} = 17.7, 9.2, 2.6 Hz, 1 H, $CHCH_2C\equiv CH$), 2.58 (m, part of AB, J_{AB} = 17.7, 6.0, 2.6 Hz, 1 H, $CHCH_2C\equiv CH$), 3.43 and 3.63 (qAB, J_{AB} = 17.9 Hz, 2 H, SCH_2), 3.56 and 3.58 (qAB, J = 15.7 Hz, 2 H, $PhCH_2$), 3.72 (br. s, 1 H, OH), 4.91 (d, J = 4.8 Hz, 1 H, NHCHC*H*S), 5.04 [dd, J = 6.0, 9.2, 1 H, $CH(OH)CH_2$], 5.76 (dd, J = 4.8, 9.2 Hz, 1 H, NHC*H*CHS), 7.13 (d, J = 9.2 Hz, 1 H, NH), 7.20−7.34 (m, 5 H, Ph-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.2 ($CH_2C\equiv CH$), 23.8 (SCH_2), 27.8 [$C(CH_3)_3$], 43.4 ($PhCH_2$), 57.8 (CHNH), 58.9 (CHS), 67.5 (CHOH), 70.8 (C≡CH), 79.5 (C≡CH), 84.2 [$C(CH_3)_3$], 126.3 (=CCHOH), 127.3, 128.9, 129.4 and 133.9 (Ph-C), 128.5 (=CCO_2), 161.2 (CO_2tBu), 165.2 (C=O, lactam), 171.4 [$PhCH_2C$(O)] ppm. IR (KBr): ṽ = 3418 (br., OH), 3377 (br., NH), 1771 (C=O, lactam), 1692 (C=O, ester), 1667 and 1538 (C=O, amide), 1365 (C−N), 1155 (C−O, ester) cm^{-1}. MS (CI^+): m/z (%) = 443 (1), [M + H]$^+$, 425 (1) [M + H − H_2O]$^+$, 404 (1), 377(1) [M + H − C_4H_8]$^+$, 349 (1), 331 (1), 230 (8), 174 (15), 91 (16) [$PhCH_2^+$], 57 (100) [$C_4H_9^+$]. HRMS (CI^+, m/z): 442.15617 (calcd. for $C_{23}H_{26}N_2O_5S$: 442.1562).

Slow-Moving Major Isomer (1*S*)-5: M.p. 139−141 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50 [s, 9 H, $C(CH_3)_3$], 2.12 (t, ^4J = 2.6 Hz, 1 H, C≡CH), 2.55 (m, part of AB, J_{AB} = 16.7, 7.9, 2.6 Hz, 1 H, $CHCH_2C\equiv CH$), 2.66 (m, part of AB, J_{AB} = 16.7, 4.1, 2.6 Hz, 1 H, $CHCH_2C\equiv CH$), 3.13 (d, J = 3.9 Hz, 1 H, OH), 3.57 (s, 2 H, $PhCH_2$), 3.56 (s, 2 H, SCH_2), 4.89 (d, J = 4.9 Hz, 1 H, NHCHC*H*S), 4.88−4.95 [m, 1 H, $CH(OH)CH_2$], 5.78 (dd, J = 4.9, 8.9 Hz, 1 H, NHC*H*CHS), 6.41 (d, J = 8.9 Hz, 1 H, NH), 7.25−7.38 (m, 5 H, Ph-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.6 ($CH_2C\equiv CH$), 26.6 (SCH_2), 27.8 [$C(CH_3)_3$], 43.1 ($PhCH_2$), 57.5 (CHNH), 58.9 (CHS), 68.8 (CHOH), 71.7 (C≡CH), 80.1 (C≡CH), 83.6 [$C(CH_3)_3$], 124.4 (=CCHOH), 127.5, 129.0, 129.1 and 133.6 (Ph-C), 131.9 (=CCO_2), 160.6 (CO_2tBu), 164.4 (C=O, lactam), 171.3 [$PhCH_2C$(O)) ppm.

***tert*-Butyl (1*R*,2*R*,7*R*,7a*R*)-, (1*R*,2*S*,7*R*,7a*R*)-, (1*S*,2*R*,7*R*,7a*R*)-, and (1*S*,2S,7R,7a*R*)3-[-1-Hydroxy-2-methyl-3-butenyl]-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]-thiazine-4-carboxylate (6):** Aldehyde **1** (0.81 g, 2.0 mmol) was treated according to the general procedure (crotyl bromide) to give, after column chromatography (SiO_2; ethyl acetate/heptane, 1:1), the adducts **6** (0.73 g, 79%) as two separable diastereoisomers (50:50 ratio), both containing an inseparable mixture of *syn* and *anti* isomers. Analytical samples were obtained by crystallization from ethyl acetate/heptane.

Fast-Moving Minor Isomers (1*R*,2*R*)-6 and (1*R*,2*S*)-6 (ratio 5:2). (1*R*,2*R*)-6: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81 (d, J = 6.8 Hz, 1 H, CH_3), 1.48 [s, 9 H, $C(CH_3)_3$], 2.25−2.35 (m, 1 H, $CHCH_3$), 3.29 and 3.74 (qAB, J_{AB} = 17.8 Hz, 2 H, SCH_2), 3.56 (s, 2 H, $PhCH_2$), ≈3.5 (br. s, OH, 1 H), 4.64 (d, J = 9.7 Hz, 1 H, CHOH), 4.91 (d, J = 4.7 Hz, 1 H, NHCHC*H*S), 5.12 (d, J = 11.2 Hz, 1 H, $CH=CH_tH_c$), 5.13 (d, J = 16.2 Hz, 1 H, $CH=CH_tH_c$), 5.41−5.51 [m, 1 H, $CHOCH(CH_3)$], 5.68−5.76 (m, 1 H, NHC*H*CHS), 5.81 (d, J = 9.3 Hz, 1 H, NH), 7.20−7.33 (m, 5 H, Ph-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.7 ($CHCH_3$), 22.5 (SCH_2), 27.8 [$C(CH_3)_3$], 41.4 ($CHCH_3$), 43.4 ($PhCH_2$), 58.2 (CHNH), 58.8 (CHS), 72.5 (CHOH), 83.9 [$C(CH_3)_3$], 115.7 ($CH=CH_2$), 125.8 (=CCHOH), 127.3, 128.9, 129.4, and 133.9 (Ph-C), 139.4 (=CCO_2tBu), 140.9 ($CH=CH_2$), 162.5 (CO_2tBu), 165.0 (C=O, lactam), 171.6 [$PhCH_2C$(O)] ppm. IR (KBr): ṽ = 3449 (br., OH), 3326 (br., NH), 1757 (C=O, lactam), 1711 (C=O, ester), 1669 and 1536 (C=O, amide), 1368 (C−N), 1156 (C−O, ester) cm^{-1}. MS (CI^+): m/z (%) = 487 (1) [M + C_2H_5]$^+$, 459 (1), [M + H]$^+$, 403 (4) [M + H − C_4H_8]$^+$, 385 (16), 347 (12), 210 (27), 194 (15), 136 (10), 91 (60) [$PhCH_2^+$], 57 (100) [$C_4H_9^+$].

(1*R*,2*S*)-6: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.13 (d, J = 6.4 Hz, 1 H, CH_3), 1.48 [s, 9 H, $C(CH_3)_3$], 1.90−2.05 (m, 1 H, $CHCH_3$), 3.50−3.69 (qAB, J_{AB} = 18.0 Hz, 2 H, SCH_2), 3.56 (s, 2 H, $PhCH_2$), ≈3.5 (br. s, OH, 1 H), 4.59 (d, J = 9.7 Hz, 1 H, CHOH), 4.85 (d, J = 4.7 Hz, 1 H, NHCHC*H*S), 4.90−5.05 (m, $CH=CH_tH_c$), 5.41−5.51 [m, 1 H, $CHOCH(CH_3)$], 5.68−5.76 (m, 1 H, NHC*H*CHS), 5.87 (d, J = 9.3 Hz, 1 H, NH), 7.20−7.33 (m, 5 H, Ph-H) ppm.

Slow-Moving Major Isomers (1*S*,2*S*)-6 and (1*S*,2*R*)-6 (ratio 7:3). (1*S*,2*S*)-6: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.11 (d, J = 6.6 Hz, 1 H, CH_3), 1.50 [s, 9 H, $C(CH_3)_3$], 2.50−2.55 (m, 1 H, $CHCH_3$), 3.37 and 3.48 (qAB, J_{AB} = 18.5 Hz, 2 H, SCH_2), 3.62 (s, 2 H, $PhCH_2$), ≈3.6 (br. s, OH, 1 H), 4.46 (d, J = 7.3 Hz, 1 H, CHOH), 4.89 (d, J = 4.8 Hz, 1 H, NHCHC*H*S), 4.96−5.19 (m, 3 H, $CH=CH_2$), 5.71−5.80 (m, 2 H, $CHOCH(CH_3)$ and NHC*H*CHS), 6.31 (d, J = 9.0 Hz, 1 H, NH), 7.25−7.38 (m, 5 H, Ph−H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.1 ($CHCH_3$), 25.6 (SCH_2), 27.8

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[C(CH_3)$_3$], 43.3 ($CHCH_3$)*, 44.2 ($PhCH_2$)*, 57.7 (CHNH), 58.9 (CHS), 74.8 (CHOH), 83.4 [$C(CH_3)_3$], 115.7 (CH=CH_2), 125.1 (=CCHOH), 127.6, 129.1, 129.4, and 133.8 (Ph−C), 139.7 (CH=CH_2), 140.3 (=CCO_2tBu), 161.5 CO_2tBu), 164.4 (C=O, lactam), 171.3 [$PhCH_2C$(O)] ppm (*: signals may have interchanged).

(1*S*,2*R*)-6: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (d, J = 6.9 Hz, 1 H, CH_3), 1.50 [s, 9 H, C(CH_3)$_3$], 2.40−2.45 (m, 1 H, CHCH$_3$), 3.40−3.56 (qAB, J_{AB} = 18.3 Hz, 2 H, SCH_2), 3.62 (s, 2 H, $PhCH_2$), ≈3.6 (br. s, OH, 1 H), 4.67 (d, J = 7.6 Hz, 1 H, CHOH), 4.94 (d, J = 4.8 Hz, 1 H, NHCHCHS), 4.96−5.19 (m, 3 H, CH=CH_2), 5.71−5.80 [m, 2 H, CHOCH(CH_3) and NHCHCHS], 6.24 (d, J = 9.0 Hz, 1 H, NH), 7.25−7.38 (m, 5 H, Ph-H) ppm.

***tert*-Butyl (1*R*,7*R*,7a*R*)- and (1*S*,7*R*,7a*R*)-3-[1-Hydroxy-2,2-dimethyl-3-butenyl]-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (7):** Prenyl adducts **7** were synthesized from aldehyde **1** (0.75 g, 1.86 mmol) according to the general procedure (prenyl bromide). After column chromatography (SiO_2; ethyl acetate/heptane, 2:3), adducts **7** (0.70 g, 80%) were obtained in a diastereoisomeric ratio of 33:67. Analytical samples were obtained by crystallization from ethyl acetate/heptane, yielding colorless plates (fast-moving isomer) and colorless needles (slow-moving isomer).

Fast-Moving Minor Isomer (1*R*)-7: M.p. 170−172 °C (dec.). $[\alpha]_D^{20}$ = +52.0 (c = 0.46, acetone). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 (s, 3 H, CH_3), 1.08 (s, 3 H, CH_3), 1.49 [s, 9 H, C(CH_3)$_3$], 3.22 (d, J = 3.2 Hz, 1 H, OH), 3.29 and 3.67 (qAB, J_{AB} = 17.6 Hz, 2 H, SCH_2), 3.56 (s, 2 H, $PhCH_2$), 4.93 (d, J = 4.7 Hz, 1 H, NHCHCHS), 4.95−5.04 (m, 3 H, CH=CH_2 and CHOH), 5.71 (dd, J = 4.7, 9.2 Hz, 1 H, NHCHCHS), 6.02 (dd, J = 17.4, 11.0 Hz, 1 H, CH=CH$_t$H$_c$), 7.12 (d, J = 9.2 Hz, 1 H, NH), 7.20−7.34 (m, 5 H, Ph-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.9 (CH_3)*, 25.9 (CH_3)*, 23.8 (SCH_2)*, 27.8 [C(CH_3)$_3$], 42.0 ($CHCH_3$), 43.4 ($PhCH_2$), 58.7 (CHNH)$^{\#}$, 58.9 (CHS)$^{\#}$, 75.1 (CHOH), 83.8 [$C(CH_3)_3$], 112.7 (CH=CH_2), 125.8 (=CCHOH), 127.3, 128.9, 129.4, and 134.0 (Ph-C), 130.1 (=CCO_2tBu), 144.3 (CH=CH_2), 161.5 (CO_2tBu), 165.3 (C=O, lactam), 171.4 ($PhCH_2C$(O)) ppm (*,$^{\#}$: signals may have interchanged). IR (KBr): $\tilde{\nu}$ = 3415 (br., OH), 3292 (br., NH), 1775 (C=O, lactam), 1717 (C=O, ester), 1668 and 1539 (C=O, amide), 1368 (C−N), 1153 (C−O, ester) cm^{-1}. MS (FAB$^+$, NOBA): m/z (%) = 495 (2) [M + Na]$^+$, 473 (1) [M + H]$^+$, 439 (1) [M + Na − C_4H_8]$^+$, 413 (2) [M + H − C_4H_8]$^+$, 399 (5), 298 (7), 253 (20), 242 (39), 224 (55), 176 (93), 91 (100) [$PhCH_2^+$], 57 (95) [$C_4H_9^+$]. HRMS (FAB, m/z): 473.2141 (calcd. for $C_{25}H_{33}N_2O_5S$: 473.2110).

Slow-Moving Major Isomer (1*S*)-7: M.p. 213−215 °C (dec.). $[\alpha]_D^{20}$ = +69.4 (c = 0.89, acetone). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04 (s, 3 H, CH_3), 1.12 (s, 3 H, CH_3), 1.50 [s, 9 H, C(CH_3)$_3$], 3.24 (d, J = 5.6 Hz, 1 H, OH), 3.36 and 3.40 (qAB, J_{AB} = 17.1 Hz, 2 H, SCH_2), 3.61 (s, 2 H, $PhCH_2$), 4.81 (d, J = 5.6 Hz, 1 H, CHOH), 4.89 (d, J = 4.7 Hz, 1 H, NHCHCHS), 5.04 (d, J = 17.6 Hz, 1 H, CH=CH$_c$H$_t$), 5.08 (d, J = 10.8 Hz, 1 H, CH=CH$_c$H$_t$), 5.66 (dd, J = 4.7, 8.7 Hz, 1 H, NHCHCHS), 6.05 (dd, J = 17.6, 10.8 Hz, 1 H, CH=CH$_t$H$_c$), 6.55 (d, J = 8.7 Hz, 1 H, NH), 7.25−7.36 (m, 5 H, Ph-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.6 (CH_3)*, 25.9 (CH_3)*, 26.2 (SCH_2)*, 27.7 [C(CH_3)$_3$], 42.5 ($CHCH_3$), 43.1 ($PhCH_2$), 58.5 (CHNH)$^{\#}$, 59.2 (CHS)$^{\#}$, 76.6 (CHOH), 83.4 [$C(CH_3)_3$], 113.6 (CH=CH_2), 126.0 (=CCHOH), 127.4, 128.9, 129.3, and 133.8 (Ph-C), 136.9 (=CCO_2tBu), 144.3 (CH=CH_2), 161.2 (CO_2tBu), 164.6 (C=O, lactam), 171.3 [$PhCH_2C$(O)] ppm (*,$^{\#}$: signals may have interchanged).

***tert*-Butyl (1*S*,2*R*,7*R*,7a*R*)-3-[1-Hydroxy-2-phenyl-3-butenyl]-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]-thiazine-4-carboxylate (8):** Aldehyde **1** (0.81 g, 2.01 mmol) was reacted with cinnamyl bromide according to the general procedure to give, after column chromatography (SiO_2; ethyl acetate/heptane, 1:1), adduct **8** (0.74 g, 71%) as one single stereoisomer. An analytical sample was obtained by crystallization from ethyl acetate/heptane. M.p. 87−90 °C (dec.). $[\alpha]_D^{20}$ = +46.9 (c = 1.02, acetone). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 [s, 9 H, C(CH_3)$_3$], 3.18 and 3.68 (qAB, J_{AB} = 17.7 Hz, 2 H, SCH_2), 3.38−3.54 (m, 1 H, CHPh), 3.46 and 3.51 (qAB, J_{AB} = 15.6 Hz, 2 H, $PhCH_2$), 3.63 (d, J = 2.0 Hz, 1 H, OH), 4.47 (d, J = 4.8 Hz, 1 H, NHCHCHS), 5.03 (d, J = 17.0 Hz, 1 H, CH=CH$_t$H$_c$), 5.16 (d, J = 10.3 Hz, 1 H, CH=CH$_t$H$_c$), 5.27 (dd, J = 10.4, 1.6 Hz, 1 H, CHOH), 5.53 (dd, J = 4.8, 9.2 Hz, 1 H, NHCHCHS), 7.05 (d, J = 9.2 Hz, 1 H, NH), 6.99−7.36 (m, 10 H, Ph-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.7 (SCH_2), 27.8 [C(CH_3)$_3$], 43.4 ($PhCH_2$), 54.0 ($CHPh$), 57.8 (CHNH), 68.9 (CHS), 71.3 (CHOH), 83.7 [$C(CH_3)_3$], 116.9 (=CH_2), 126.1 (=CCHO), 125.9, 127.0, 127.3, 127.7, 128.0, 128.5, 128.7, 128.8, 128.9, 129.4, 133.8 (Ph-C, CHPhCH=CH_2, =CCO_2CH), 139.2 (CH=CH_2), 140.0 (=CCO_2tBu), 160.9 (CO_2tBu), 164.7 (C=O, lactam), 171.3 [$PhCH_2C$(O)] ppm. IR (KBr): $\tilde{\nu}$ = 3508 (br., OH), 3310 (br., NH), 1775 (C=O, lactam), 1713 (C=O, ester), 1665 and 1537 (C=O, amide), 1368 (C−N), 1154 (C−O, ester) cm^{-1}. MS (FAB$^+$, NOBA): m/z (%) = 543 (2) [M + Na]$^+$, 521 (2) [M + H]$^+$, 463 (3) [M + H − C_4H_8]$^+$, 447 (9) [M + H − C_4H_8 − H_2O]$^+$, 347 (10), 290 (18), 272 (39), 176 (100), 154 (45) [NOBA]*, 136 (54), 91 (67) [$PhCH_2^+$] (* defragmentation of NOBA matrix). HRMS (FAB, m/z): 543.1917 (calcd. for $C_{29}H_{32}O_5N_2SNa$: 543.1930). HRMS (FAB, m/z): 503.2037 (calcd. for $C_{29}H_{32}N_2O_5SNa$ [M − H_2O]: 503.2005).

(3*S*,5a*R*,6*R*)- and (3*R*,5a*R*,6*R*)-*N*-[3-Allyl-1,7-dioxo-1,4,6,7-tetrahydro-3*H*,5a*H*-azeto[2,1-*b*]furo[3,4-*d*][1,3]thiazin-6-yl]-2-phenylacetamide (9): Aldehyde **2** (0.77 g, 1.5 mmol) was converted in the corresponding allyl lactones **9** according to the general procedure (allyl bromide). After column chromatography (SiO_2; ethyl acetate/heptane, 2:3) and crystallization from ethyl acetate/heptane, lactones **9** (0.42 g, 76%) were obtained as a white solid (fast-moving isomer) and colorless needles (slow-moving isomer) in a ratio of 80:20.

Fast-Moving Major Isomer (3*S*)-9: M.p. 188−190 °C (dec.). $[\alpha]_D^{20}$ = +89.1 (c = 0.53, acetone). ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 2.49−2.59 (mAB, 1 H, CH_2CH=CH_2), 2.73−2.82 (mAB, 1 H, CH_2CH=CH_2), 3.68 and 3.73 (qAB, J_{AB} = 14.4 Hz, 2 H, $PhCH_2$), 3.77 and 3.90 (qAB, J_{AB} = 18.3 Hz, 2 H, SCH_2), 5.16 (d, J = 5.0 Hz, 1 H, NHCHCHS), 5.16−5.30 (m, 2 H, =CH_2), 5.33 (t, J = 5.2 Hz, 1 H, OCHCH$_2$), 5.74−5.86 (m, 1 H, CH=CH_2), 6.00 (dd, J = 5.0, 8.7 Hz, 1 H, NHCHCHS), 7.29−7.42 (m, 5 H, Ph-H), 8.13 (d, J = 8.7 Hz, 1 H, NH) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 23.3 (SCH_2), 37.1 (CH_2CH=CH_2), 42.9 ($PhCH_2$), 58.4 (CHNH), 60.9 (CHS), 82.2 (OCHCHCH$_3$), 119.8 (=CH_2), 125.4 (=CCHO), 127.5, 129.1, 130.0, and 136.4 (Ph-C), 132.1 (CH=CH_2), 143.2 (=CCO_2), 164.9 (C=O, lactam), 166.2 (CO_2CH_2), 171.6 [$PhCH_2C$(O)] ppm. IR (KBr): $\tilde{\nu}$ = 3258 (br., NH), 1787 (C=O, lactam), 1760 (C=O, lactone), 1667 and 1546 (C=O, amide), 1412 (C−N), 1156 (C−O, lactone) cm^{-1}. MS (FAB$^+$, NOBA): m/z (%) = 393 (65) [M + Na]$^+$, 371 (64) [M + H]$^+$, 196 (22), 176 (48), 154 (100) [NOBA]*, 91 (22) [$PhCH_2^+$] (* defragmentation of NOBA matrix). HRMS (FAB, m/z): 371.1096 (calcd. for $C_{19}H_{19}N_2O_4S$: 371.1066).

Slow-Moving Minor Isomer (3*R*)-9: M.p. 215−217 °C (dec.). $[\alpha]_D^{20}$ = +173.0 (c = 0.30, acetone). ^{1}H NMR (300 MHz, $CDCl_3$ and [D$_6$]-acetone): δ = 2.41−2.50 (mAB, 1 H, CH_2CH=CH_2), 2.70−2.79 (mAB, 1 H, CH_2CH=CH_2), 3.56 and 3.73 (qAB, J_{AB} = 18.5 Hz,

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2 H, SCH_2), 3.60 and 3.65 (qAB, J_{AB} = 14.5 Hz, 2 H, $PhCH_2$), 5.02 (d, J = 5.1 Hz, 1 H, NHCHC*H*S), 5.06−5.18 (m, 3 H, CH=CH_2 and OC*H*CH_2), 5.54−5.67 (m, 1 H, C*H*=CH_2), 5.88 (dd, J = 5.0, 8.7 Hz, 1 H, NHC*H*CHS), 7.16−7.31 (m, 5 H, Ph-H), 7.64 (d, J = 8.7 Hz, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ and [D_6]acetone): δ = 21.6 (SCH_2), 35.0 (CH_2CH=CH_2), 41.6 ($PhCH_2$), 56.8 (CHNH), 69.3 (CHS), 80.2 (O*C*HCHCH_3), 118.6 (=CH_2), 124.2 (=*C*CHO), 126.0, 127.6, 128.4, and 134.2 (Ph-C), 129.8 (*C*H=CH_2), 141.1 (=*C*CO_2), 163.0 (C=O, lactam), 164.7 (CO_2CH_2), 170.5 [$PhCH_2C$(O)] ppm. IR (KBr): $\tilde{\nu}$ = 3278 (br., NH), 1789 (C=O, lactam), 1764 (C=O, lactone), 1662 and 1536 (C=O, amide), 1422 (C−N), 1142 (C−O, lactone) cm^{-1}. MS (FAB^+, NOBA): *m*/*z* (%) = 393 (37) $[M + Na]^+$, 371 (28) $[M + H]^+$, 196 (9), 176 (31), 154 (100) [NOBA]*, 91 (18) $[PhCH_2^+]$ (* defragmentation of NOBA matrix).

(3*R*,5a*R*,6*R*)- and (3*S*,5a*R*,6*R*)-*N*-[1,7-Dioxo-3-(2-propynyl)-1,4,6,7-tetrahydro-3*H*,5a*H*-azeto[2,1-*b*]furo[3,4-*d*][1,3]thiazin-6-yl]-2-phenylacetamide (10): Aldehyde **2** (1.03 g, 2.0 mmol) was treated according to the general procedure (propargyl bromide) to give **10** (0.70 g, 95%) as colorless plates (fast-moving isomer) and traces of a yellowish solid (slow-moving isomer) after purification by column chromatography (SiO_2; ethyl acetate/heptane, 2:1), and subsequent crystallization from ethyl acetate/heptane.

Fast-Moving Major Isomer (3*S*)-10: M.p. 212−214 °C (dec.). $[\alpha]_D^{20}$ = +120.0 (*c* = 0.35, acetone). ^{1}H NMR (300 MHz, [D_6]acetone): δ = 2.67 (t, ^4J = 2.6 Hz, 1 H, C≡CH), 2.95 and 3.06 [q(dd)AB, J_{AB} = 17.3, 5.1, 2.6 Hz, 2 H, CHCH_2C≡CH), 3.77 and 3.82 (qAB, J_{AB} = 14.4 Hz, 2 H, $PhCH_2$), 3.91 and 3.98 (qAB, J_{AB} = 18.3 Hz, 2 H, SCH_2), 5.25 (d, J = 5.1 Hz, 1 H, NHCHC*H*S), 5.48 (t, J = 5.1 Hz, 1 H, OC*H*CH_2), 6.11 (dd, J = 5.1, 8.6 Hz, 1 H, NHC*H*CHS), 7.35−7.50 (m, 5 H, Ph-H), 8.22 (d, J = 8.6 Hz, 1 H, NH) ppm. ^{13}C NMR (75 MHz, [D_6]acetone): δ = 23.2 (SCH_2 and CH_2C≡CH), 42.9 ($PhCH_2$), 58.4 (CHNH), 60.9 (CHS), 73.5 (C≡*C*H), 77.9 (*C*≡CH), 80.2 (O*C*HCH_2), 127.5, 129.2, 130.0, and 136.4 (Ph-C and =*C*CHO), 142.3 (=*C*CO_2), 165.0 (C=O, lactam), 165.9 (CO_2CH_2), 171.6 [$PhCH_2C$(O)] ppm. MS (CI^+): *m*/*z* (%) = 369 (3) $[M + H]^+$, 337 (5), 203 (30), 136 (66), 91 (100) $[PhCH_2^+]$, 57 (52). HRMS (CI^+, *m*/*z*): 368.08238 (calcd. for $C_{19}H_{16}N_2O_4S$: 368.08310).

Slow-Moving Minor Isomer (3*R*)-10: M.p. > 150 °C (slow dec.). $[\alpha]_D^{20}$ = +145.3 (*c* = 0.17, acetone). ^{1}H NMR (300 MHz, [D_6]acetone): δ = 2.54 (t, ^4J = 2.6 Hz, 1 H, C≡CH), 2.92 and 3.05 [q(dd)AB, J_{AB} = 17.6, 4.9, 2.6 Hz, 2 H, CHCH_2C≡CH), 3.71 and 3.76 (qAB, J_{AB} = 14.2 Hz, 2 H, $PhCH_2$), 3.82 and 3.89 (qAB, J_{AB} = 18.6 Hz ^4J < 1.5 Hz, 2 H, SCH_2), 5.17 (d, J = 5.1 Hz, 1 H, NHCHC*H*S), 5.37 (t, J = 4.8 Hz, 1 H, OC*H*CH_2), 6.03 (dd, J = 5.1, 8.8 Hz, 1 H, NHC*H*CHS), 7.27−7.43 (m, 5 H, Ph-H), 8.17 (d, J = 8.8 Hz, 1 H, NH) ppm. ^{13}C NMR (75 MHz, [D_6]acetone): δ = 22.7 (CH_2C≡CH)*, 23.0 (SCH_2)*, 42.9 ($PhCH_2$), 58.2 (CHNH), 60.8 (CHS), 73.5 (C≡*C*H), 77.9 (*C*≡CH), 79.9 (O*C*HCH_2), 127.5, 129.1, 130.0, and 136.5 (Ph-C), 127.3 (=*C*CHO), 142.5 (=*C*CO_2), 164.9 (C=O, lactam), 166.0 (CO_2CH_2), 171.6 [$PhCH_2C$(O)] ppm (*: signals may have interchanged).

(1*R*,3*R*,5a*R*,6*R*)-, (1*R*,3*R*,5a*R*,6*R*)-, (1*S*,3*R*,5a*R*,6*R*)-, and (1*S*,3*S*,5a*R*,6*R*)-*N*-[3-(1-Methyl-2-propenyl)-1,7-dioxo-1,4,6,7-tetrahydro-3*H*,5a*H*-azeto[2,1-*b*]furo[3,4-*d*][1,3]thiazin-6-yl]-2-lxphenylacetamide (11): Aldehyde **2** (0.50 g, 0.98 mmol) was treated according to the general procedure (crotyl bromide) to give, after column chromatography (SiO_2; ethyl acetate/heptane, 2:1) and crystallization from heptane/ethyl acetate, lactones **11** (0.28 g, 73%) as an inseparable mixture consisting of two isomers (ratio 4:3).

Major Isomer 11: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (d, J = 6.9 Hz, 3 H, CH_3), 2.55 (m, 1 H, C*H*CH_3), 3.35 and 3.59 (qAB, J_{AB} = 18.3 Hz, 2 H, SCH_2), 3.61 and 3.65 (qAB, J_{AB} = 16.0 Hz, 2 H, $PhCH_2$), 4.92 (d, J = 5.0 Hz, 1 H, NHCHC*H*S), 4.96 (d, J = 5.1 Hz, 1 H, OC*H*CHCH_3), 5.14 (d, J = 17.3 Hz, 1 H, CH=C$H_t$$H_c$), 5.21 (d, J = 10.0 Hz, 1 H, CH=C$H_t$$H_c$), 5.69−5.80 (m, 1 H, C*H*=C$H_t$$H_c$), 5.90 (dd, J = 5.0, 8.9 Hz, 1 H, NHC*H*CHS), 6.44 (d, J = 8.9 Hz, 1 H, NH), 7.24−7.37 (m, 5 H, Ph-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.9 (CH_3), 23.7 (SCH_2), 41.3 (*C*HCH_3), 43.2 ($PhCH_2$), 57.7 (CHNH), 60.0 (CHS), 85.7 (O*C*HCHCH_3), 117.8 (=CH_2), 125.5 (=*C*CHO), 127.7, 129.1, 129.5, and 137.1 (Ph-C), 139.7 (=*C*CO_2), 163.8 (C=O, lactam), 165.5 (CO_2CH), 171.3 [$PhCH_2C$(O)] ppm. IR (both isomers, KBr): $\tilde{\nu}$ = 3385 (br., NH), 1765 (br., C=O, lactam and lactone), 1662, 1679 and 1505 (C=O, amide), 1423 (C−N), 1157 (C−O, lactone) cm^{-1}. MS (FAB^+, NOBA): *m*/*z* (%) = 407 (9) $[M + Na]^+$, 385 (36), 210 (62), 176 (100), 154 (54), [$NOBA^+$], 91 (58) $[PhCH_2^+]$. HRMS (FAB, *m*/*z*): 385.1237 (calcd. for $C_{20}H_{21}N_2O_4S$: 385.1222).

Minor Isomer 11: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16 (d, J = 6.9 Hz, 3 H, CH_3), 2.73 (m, 1 H, C*H*CH_3), 3.34 and 3.54 (qAB, J_{AB} = 18.3 Hz, 2 H, SCH_2), 3.61 and 3.65 (qAB, J_{AB} = 16.0 Hz, 2 H, $PhCH_2$), 4.92 (d, J = 5.0 Hz, 1 H, NHCHC*H*S), 4.96 (d, J = 5.1 Hz, 1 H, OC*H*CHCH_3), 5.14 (d, J = 17.3 Hz, 1 H, CH=C$H_t$$H_c$), 5.21 (d, J = 10.0 Hz, 1 H, CH=C$H_t$$H_c$), 5.53−5.65 (m, 1 H, C*H*=C$H_t$$H_c$), 5.90 (dd, J = 5.0, 8.9 Hz, 1 H, NHC*H*CHS), 6.44 (d, J = 8.9 Hz, 1 H, NH), 7.24−7.37 (m, 5 H, Ph-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.2 (CH_3), 23.3 (SCH_2), 40.0 (*C*HCH_3), 43.2 ($PhCH_2$), 57.5 (CHNH), 60.0 (CHS), 85.6 (O*C*HCHCH_3), 118.2 (=CH_2), 125.4 (=*C*CHO), 127.7, 129.1, 129.5, and 137.1 (Ph-C), 139.9 (=*C*CO_2), 163.8 (C=O, lactam), 165.7 (CO_2CH), 171.3 [$PhCH_2C$(O)] ppm.

(3*R*,5a*R*,6*R*)- and (3*S*,5a*R*,6*R*)-*N*-[-3-(1,1-Dimethylallyl)-1,7-dioxo-1,4,6,7-tetrahydro-3*H*,5a*H*-azeto[2,1-*b*]furo[3,4-*d*][1,3]thiazin-6-yl]-2-phenylacetamide (12): Aldehyde **2** (1.02 g, 2.0 mmol) was treated according to the general procedure (prenyl bromide) to give, after column chromatography (SiO_2; ethyl acetate/heptane, 2:1), lactones **12** (0.61 g, 87%) as a 70:30 mixture of two diastereoisomers. Analytical samples were obtained by crystallization from ethyl acetate/heptane to yield a white solid (fast-moving isomer) and transparent cubic crystals (slow-moving isomer).

Fast-Moving Major Isomer (3*S*)-12: M.p. 222−224 °C (dec.). $[\alpha]_D^{20}$ = +84.0 (*c* = 0.53, acetone). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 (s, 3 H, CH_3), 1.20 (s, 3 H, CH_3), 3.31 and 3.52 (qAB, J_{AB} = 18.3 Hz, 2 H, SCH_2), 3.59 (s, 2 H, $PhCH_2$), 4.80 (s, 1 H, CHOC), 4.92 (d, J = 5.0 Hz, 1 H, NHCHC*H*S), 5.16 (d, J = 17.3 Hz, 1 H, CH=C$H_t$$H_c$), 5.17 (d, J = 10.7 Hz, 1 H, CH=C$H_t$$H_c$), 5.80 (dd, J = 17.3, 10.7 Hz, 1 H, C*H*=C$H_t$$H_c$), 5.87 (dd, J = 5.0, 8.8 Hz, 1 H, NHC*H*CHS), 6.90 (d, J = 8.8 Hz, 1 H, NH), 7.23−7.34 (m, 5 H, Ph-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.8 (CH_3), 25.0 (CH_3)*, 25.1 (SCH_2)*, 41.3 [$C(CH_3)_2$], 42.9 ($PhCH_2$), 57.7 (CHNH), 59.9 (CHS), 88.9 [O*C*HC$(CH_3)_2$], 115.5 (=CH_2), 125.6 (=*C*CHO), 127.4, 128.9, 129.4, and 134.0 (Ph-C), 139.5 (=*C*CO_2), 141.4 (*C*H=CH_2), 163.8 (C=O, lactam), 166.0 (CO_2CH), 171.5 [$PhCH_2C$(O)] ppm (*: signals may have interchanged).

Slow-Moving Minor Isomer (3*R*)-12: M.p. 207−209 °C (dec.). $[\alpha]_D^{20}$ = +144.6 (*c* = 0.18, acetone). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3), 3.52 and 3.75 (qAB, J_{AB} = 18.3 Hz, J < 1.5 Hz, 2 H, SCH_2), 3.63 and 3.67 (qAB, J_{AB} = 16.1 Hz, 2 H, $PhCH_2$), 4.86 (s, 1 H, CHOC), 4.95 (d, J = 5.0 Hz, 1 H, NHCHC*H*S), 5.24 (d, J = 17.5 Hz, 1 H, CH=C$H_t$$H_c$), 5.28

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(d, J = 10.7 Hz, 1 H, CH=CH$_t$H$_c$), 5.91 (dd, J = 17.5, 10.7 Hz, 1 H, C*H*=CH$_t$H$_c$), 5.97 (dd, J = 5.0, 8.8 Hz, 1 H, NHC*H*CHS), 6.20 (d, J = 8.8 Hz, 1 H, NH), 7.30−7.41 (m, 5 H, Ph-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.8 (CH_3), 23.9 (CH_3)*, 27.2 (SCH_2)*, 41.3 [*C*(CH_3)$_2$], 43.3 ($PhCH_2$), 57.0 (CHNH), 60.3 (CHS), 87.8 [O*C*HC(CH_3)$_2$], 115.5 (=CH_2), 128.5 (=*C*CHO), 127.8, 129.2, 129.5, and 133.5 (Ph-C), 140.8 (=*C*CO_2), 142.8 (*C*H=CH_2), 163.7 (C=O, lactam), 166.0 (*C*O_2CH), 171.2 [$PhCH_2$*C*(O)] ppm (*: signals may have interchanged). IR (KBr): ṽ = 3248 (br., NH), 1770 (C=O (br), lactam and ester), 1654 and 1554 (C=O, amide), 1415 (C−N) cm^{-1}. MS (CI$^+$): *m*/*z* (%) = 399 (17) [M + H]$^+$, 367 (15), 224 (38), 176 (45), 136 (37), 91 (100) [$PhCH_2^+$]. HRMS (CI$^+$, *m*/*z*): 398.13026 (calcd. for $C_{21}H_{22}N_2O_4S$: 398.1300).

(1*R*,3*S*,5a*R*,6*R*)-*N*-{1,7-Dioxo-3-[1-(phenyl-2-propenyl)]-1,4,6,7-tetrahydro-3*H*,5a*H*-azeto[2,1-*b*]furo[3,4-*d*][1,3]thiazin-6-yl}-2-phenylacetamide (13): Aldehyde **2** (1.02 g, 2.0 mmol) was treated according to the general procedure (cinnamyl bromide) yielding, after column chromatography (SiO_2; ethyl acetate/heptane, 2:1) and crystallization from ethyl acetate/heptane, lactone **13** (0.63 g, 70%) as colorless plates. M.p. 101−103 °C (dec.). $[\alpha]_D^{20}$ = +200.7 (*c* = 0.28, acetone). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.00 and 3.44 (qAB, J_{AB} = 18.4 Hz, ^5J < 1.5 Hz, 2 H, SCH_2), 3.60 (m, 1 H, PhC*H*CH=), 3.63 and 3.65 (qAB, J_{AB} = 14.5 Hz, 2 H, $PhCH_2$), 4.93 (d, J = 5.0 Hz, 1 H, NHCHC*H*S), 5.07 (d, J = 17.1 Hz, 1 H, CH=C*H*$_t$H$_c$), 5.20 (d, J = 10.3 Hz, 1 H, CH=CH$_t$H$_c$), 5.29 (d, J = 4.5 Hz, 1 H, OC*H*CHPh), 5.92 (dd, J = 5.0, 8.7 Hz, 1 H, NHC*H*CHS), 5.90−6.00 (m, 1 H, C*H*=CH$_t$H$_c$), 6.11 (d, J = 8.7 Hz, 1 H, NH), 7.29−7.41 (m, 10 H, Ph-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.0 (SCH_2), 43.3 ($PhCH_2$), 52.4 (CHPh), 57.3 (CHNH), 60.2 (CHS), 84.3 (O*C*HCHPh), 119.2 (=CH_2), 126.1 (=*C*CHO), 127.8, 128.0, 128.3, 129.2, 129.3, 129.5, 133.5 134.3, 138.3 and 140.2 (Ph-C, CHPh*C*H=CH_2, =*C*CO_2CH), 163.7 (C=O, lactam), 165.5 (*C*O_2CH), 171.0 [$PhCH_2$*C*(O)] ppm. IR (KBr): ṽ = 3260 (br., NH), 1795 (br., C=O, lactam and lactone), 1670 and 1525 (C=O, amide), 1454 (C−N) cm^{-1}. MS (CI$^+$): *m*/*z* (%) = 447 (78) [M$^+$], 415 (71), 272 (100), 176 (76), 117 (44), 91 (45) [$PhCH_2^+$]. HRMS (CI$^+$, *m*/*z*): 446.13066 (calcd. for $C_{25}H_{22}N_2O_4S$: 446.13000).

X-ray Crystallographic Study

***tert*-Butyl (7*R*,7a*R*)-3-Formyl-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (1):** Crystals of aldehyde **1** suitable for X-ray diffraction studies were obtained from heptane/ethyl acetate. A single crystal was mounted in air on a glass fibre. Intensity data were collected at room temperature. An Enraf−Nonius CAD4 single-crystal diffractometer was used, Mo-K_α radiation, θ-2θ scan mode. Unit cell dimensions were determined from the angular setting of 25 reflections. Intensity data were corrected for Lorentz and polarization effects. Semi-empirical absorption correction (ψ-scans)[36] was applied. The structure was solved by the program CRUNCH[35] and was refined with standard methods (refinement against F^2 of all reflections with SHELXL-

Table 3. Crystal data and structure refinement for compound **1**

Empirical formula	$C_{20}H_{22}N_2O_5S$
M_w	402.46
Crystal system	monoclinic
Space group	*C*2
Crystal color	transparent colorless
Crystal shape	regular
Size [mm]	0.52 × 0.29 × 0.21
a [Å]	27.2202(11)
b [Å]	5.1944(4)
c [Å]	18.7846(7)
α [°]	90
β [°]	130.396(3)
γ [°]	90
Radiation/wavelength	Mo-K_α (graphite mon.)/ 0.71073 Å
Reflections for unit cell	25
θ range [°]for unit cell	18.431−21.309
V [Å^3]	2202.8(2)
Z	4
$D_{calcd.}$ [Mg·m^{-3}]	1.322
Abs. coeff. [mm^{-1}]	0.193
F(000)	848
θ range [°]for data collection	2.85−26.31
h range	−25 to 33
k range	0 to 6
l range	−23 to 0
Refl. coll./uniq.	2362/2293
R(int.)	0.0123
Refl. obsd. [$I_o > 2\sigma(I_o)$]	2112
Range of rel. transm. fact.	1.039/0.983
Data/restr./param.	2293/1/342
g.o.f. on F^2	1.023
SHELXL-97 weight parameters	0.036400, 0.560700
Final *R* indices [$I > 2\sigma(I)$]	R_1 = 0.0266 wR_2 = 0.0660
R indices (all data)	R_1 = 0.0304 wR_2 = 0.0682
$\Delta\rho_{max/min}$ [e·Å^{-3}]	0.162/−0.099

Table 4. Crystal data and structure refinement for compound **9** (slow-moving diastereoisomer)

Empirical formula	$C_{19}H_{18}N_2O_4S$
M_w	370.41
T [K]	293(2)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
Crystal color	transparent colorless
Crystal shape	regular
Size [mm]	0.53 × 0.29 × 0.21
a [Å]	9.6929(8)
b [Å]	11.8524(12)
c [Å]	15.5755(11)
α [°]	90
β [°]	90
γ [°]	90
Radiation/wavelength	Mo-K_α (graphite-mon.)/ 0.71073 Å
Reflections for unit cell	25
θ range [°]for unit cell	10.836 12.690
V [Å^3]	1789.4(3)
Z	4
$D_{calcd.}$ [Mg·m^{-3}]	1.375
Abs. coeff. [mm^{-1}]	0.208
F(000)	776
θ range [°] for data collection	2.62−27.48
h range	0 to 12
k range	0 to 15
l range	0 to 20
Refl. coll./uniq.	2337/2337
Refl. obsd. [$I_o > 2\sigma(I_o)$]	1830
Range of rel. transm. fact.	1.039/0.964
Data/restr./param.	2337/0/303
g.o.f. on F^2	1.054
SHELXL-97 weight parameters	0.091800 0.252700
Final *R* indices [$I > 2\sigma(I)$]	R_1 = 0.0517 wR_2 = 0.1303
R indices (all data)	R_1 = 0.0703 wR_2 = 0.1436
$\Delta\rho_{max/min}$ [e·Å^{-3}]	0.483/−0.325

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97[39] with anisotropic parameters for the non-hydrogen atoms. All hydrogen atoms were initially placed at calculated positions and were freely refined subsequently. A summary of the structure determination is given in Table 3.

A PLUTON[40] drawing is shown in Figure 2.

(3*R*,5a*R*,6*R*)-*N*-[3-Allyl-1,7-dioxo-1,4,6,7-tetrahydro-3*H*,5a*H*-azeto[2,1-*b*]furo[3,4-*d*][1,3]thiazin-6-yl]-2-phenylacetamide (9): Crystals of **9** (slow-moving diastereoisomer) suitable for X-ray diffraction studies were obtained from heptane/ethyl acetate by liquid diffusion. A single crystal was mounted in air on a glass fibre. Intensity data were collected at room temperature. An Enraf−Nonius CAD4 single-crystal diffractometer was used, Mo-K_α radiation, θ-2θ scan mode. Unit cell dimensions were determined from the angular setting of 25 reflections. Intensity data were corrected for Lorentz and polarization effects. Semi-empirical absorption correction (ψ-scans) was applied.[36] The structure was solved by the program system DIRDIF[37] by using the program PATTY[38] to locate the sulfur atom and was refined with standard methods (refinement against F^2 of all reflections with SHELXL-97[39] with anisotropic parameters for the non-hydrogen atoms. All hydrogen atoms, except the hydrogen atom attached to C(16), were initially placed at calculated positions and were freely refined subsequently. The hydrogen atoms attached to C(16) was refined riding on the parent atom. A summary of the structure determination is given in Table 4.

A PLUTON drawing[40] is shown in Figure 3.

Table 5. Crystal data and structure refinement for compound **12** (slow-moving diastereoisomer)

Emprical formula	$C_{21}H_{22}N_2O_4S$
M_w	398.47
T [K]	293(2)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
Crystal color	transparent colorless
Crystal shape	regular
Size [mm]	0.31 × 0.22 × 0.18
a [Å]	9.1629(13)
b [Å]	12.237(3)
c [Å]	18.108(3)
α [°]	90
β [°]	90
γ [°]	90
Radiation/wavelength	Mo-K_α (graphite-mon.)/0.71073 Å
Reflections for unit cell	25
θ range [°] for unit cell	10.228 14.261
V [Å^3]	2030.4(6)
Z	4
$D_{calcd.}$ [Mg·m^{-3}]	1.304
Abs. coeff. [mm^{-1}]	0.188
F(000)	840
θ range [°]for data collection	3.00−27.49
h range	0 to 11
k range	−15 to 0
l range	−23 to 0
Refl. coll./uniq.	2630/2630
Refl. obsd. [$I_o > 2\sigma(I_o)$]	1207
Range of rel. transm. fact.	1.005/0.991
Data/restr./param.	2260/0/255
g.o.f. on F^2	1.084
SHELXL-97 weight parameters	0.038000 0.942500
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0724$ $wR_2 = 0.1119$
R indices (all data)	$R_1 = 0.1865$ $wR_2 = 0.1425$
$\Delta\rho_{max/min}$ [e·Å^{-3}]	0.281/−0.240

(3*R*5a*R*,6*R*)-*N*-[3-(1,1-Dimethylallyl)-1,7-dioxo-1,4,6,7-tetrahydro-3*H*,5a*H*-azeto[2,1-*b*]furo[3,4-*d*][1,3]thiazin-6-yl]-2-phenylacetamide (12): Crystals of **12** (slow-moving diastereoisomer) suitable for X-ray diffraction studies were obtained from heptane/ethyl acetate by liquid diffusion. A single crystal was mounted in air on a glass fibre. Intensity data were collected at room temperature. An Enraf−Nonius CAD4 single-crystal diffractometer was used, Mo-K_α radiation, ω-scan mode. Unit cell dimensions were determined from the angular setting of 25 reflections. Intensity data were corrected for Lorentz and polarization effects. Semi-empirical absorption correction (ψ-scans)[36] was applied. The structure was solved by the program system DIRDIF[37] using the program PATTY[38] to locate the sulfur atom, and was refined with standard methods (refinement against F^2 of all reflections with SHELXL-97[39] with anisotropic parameters for the non-hydrogen atoms). All hydrogen atoms were placed at calculated positions and were refined riding on the parent atoms. A summary of the structure determination is given in Table 5.

A PLUTON drawing[40] is shown in Figure 3.

CCDC-186653−186655 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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