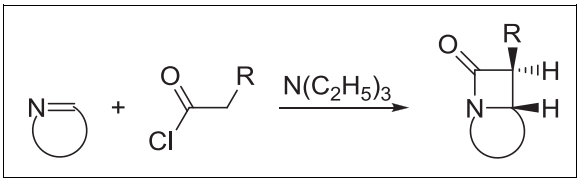
Stereospecific Synthesis of β-Lactams from Heterocyclic Imines Using the Staudinger Reaction

T. Stalling, K. Johannes, S. Polina, and J. Martens*

Carl von Ossietzky Universität Oldenburg, Carl-von-Ossietzky-Str. 9-11, 26129 Oldenburg, Germany
*E-mail: juergen.martens@uni-oldenburg.de

Received December 13, 2011
DOI 10.1002/jhet.1688
Published online in Wiley Online Library (wileyonlinelibrary.com).



The reactions of the heterocyclic imines 5,6-dihydro-2*H*-[1,3]oxazines and 2*H*-1,4-benzothiazines with different substituted acetyl chlorides in the presence of triethylamine forming β-lactams were examined focusing on the stereochemistry of the Staudinger reaction.

J. Heterocyclic Chem., **50**, 654 (2013).

INTRODUCTION

The β-lactam skeletal structure is the key component of the widespread antimicrobial agents mainly represented by the β-lactam antibiotics. The family of β-lactam antibiotics includes penicillins, cephalosporins, penems, carbapenems, and monolactams, amongst others [1].

As a consequence of the increased resistance against the common antibiotics [2,3], the interest in creating new β-lactam antibiotics characterized by a more specific antibacterial activity is rising. Besides the antibacterial activity, the β-lactam antibiotics are adequate for possible applications in inhibiting enzymes [4,5]. In addition, the β-lactam antibiotics take place as intermediates in the synthesis of other compounds of biological interest, for example, α-amino acids and β-amino acids [6].

As a result of the great interest in β-lactams, different ways of syntheses were developed. Among the most important of these methods is the Staudinger reaction [7]. It can be described as a stepwise [2 + 2]-cycloaddition reaction of an imine and a ketene to form a β-lactam showing two new stereocenters at the ring. Nowadays, the relative stereoselectivity of the Staudinger reaction is still in focus of many investigations [8].

A few years back, we performed the Staudinger reaction using a special type of heterocyclic imines, namely 5,6-dihydro-2*H*-[1,3]oxazines [9]. In the course of our interest in the synthesis of new heterocyclic imines [10], we developed a new method for the synthesis of various types of 2*H*-1,4-benzothiazines [11,12]. In the recent past, we focused our attention on reactions based on this substance class [11–13]. Thus, we were successful in the synthesis of different types of lactam structures offering opportunities for many functionalizations.

RESULTS AND DISCUSSION

In this article, we report on the Staudinger reaction of the 5,6-dihydro-2*H*-[1,3]oxazines **1a–c** and especially of the annulated 2*H*-1,4-benzothiazines **2a–d** and observed the stereoselectivity of the prepared β-lactams **4** in accordance with **3** (Scheme 1).

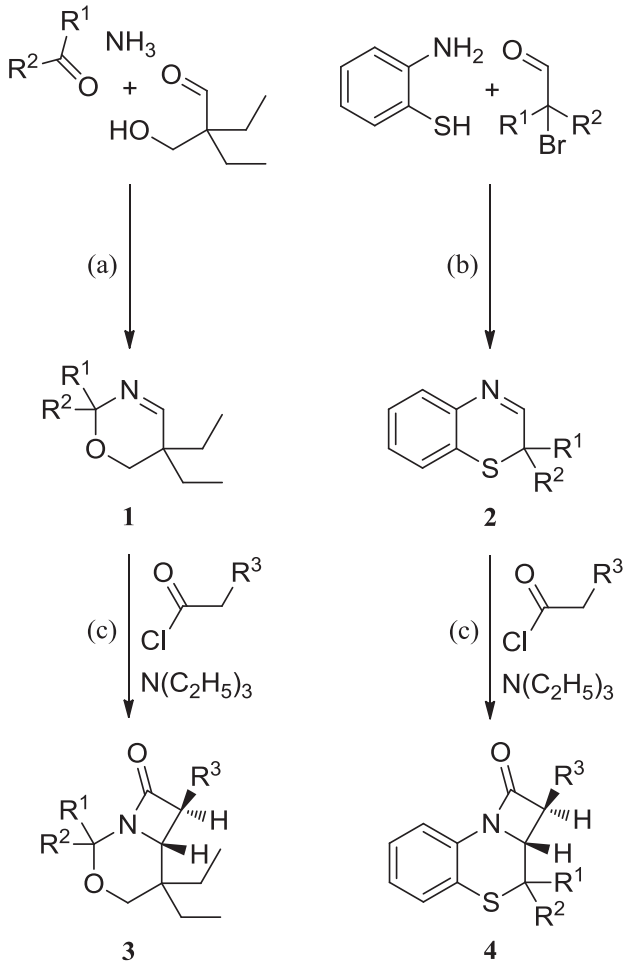
The oxazines **1** were achieved by a multicomponent reaction from the β-hydroxy aldehyde 2-ethyl-2-(hydroxymethyl)butanal, ammonia, and a variable carbonyl compound in dichloromethane. The benzothiazines **2** were synthesized from 2-aminothiophenol, an α-bromoaldehyde and sodium hydride in anhydrous tetrahydrofuran [11,12].

The imines **1** and **2** were treated with different ketenes, which were generated *in situ* from the respective substituted acetyl chloride with triethylamine in anhydrous dichloromethane, to prepare the new β-lactams **3a–c** and **4a–j**. The β-lactams were obtained in moderate yields (up to 82%) excepting the ones based on chiral starting materials (Table 1).

The structures of the products were confirmed by ^{1}H NMR, ^{13}C NMR, IR, MS, elemental analyses, and X-ray structures in certain cases. Particularly, the ^{1}H NMR spectra of the β-lactam oxazine derivatives **3** show a characteristic shift of the β-lactam ring proton H_A at 3.61–3.67 ppm and 5.05–5.10 ppm of the proton H_B (assignment see Scheme 2). The β-lactam benzothiazine derivatives **4** show a proton shift for H_A at 3.86–4.88 ppm and 3.95–5.39 ppm for H_B. Furthermore, the coupling constants, situated between 1.5 and 2.7 Hz, are characteristic for *trans* β-lactams [14].

According to the ^{1}H NMR spectra, only a single diastereomer was found in case of the products **3a**, **3b**, **4a**, **4b**, **4d**, **4e**, **4g**, and **4h** ($dr \geq 95{:}5$) starting from prochiral imines. We were able to obtain single crystals of **3b** and determined the proposed structure by X-ray analysis (Fig. 1).

Scheme 1. Diastereoselective synthesis of the β-lactams **3** and **4** starting from the heterocyclic imines **1** and **2** (only one enantiomer of the racemic β-lactams is shown). Reagents and conditions: (a) (i) CH_2Cl_2, 0°C, (ii) RT, overnight; (b) (i) NaH, THF, 0°C, (ii) RT, 2 h, (iii) THF, 0°C (iv) RT, overnight; (c) (i) CH_2Cl_2, 0°C, (ii) RT, overnight.



The structure documents the postulated *trans* configuration between the described protons H_A and H_B. This fact could be explicated by the proposed mechanism of the Staudinger reaction [16] of heterocyclic imines (Scheme 2).

The lone electron pair at the nitrogen atom of the C=N bond of the heterocyclic imine attacks nucleophilicly the carbonyl group of the ketene that is generated *in situ* from the respective substituted acetyl chloride by the use of triethylamine. A zwitterionic intermediate results from this process. The attack occurs on the unsubstituted side of the ketene directing the cyclic moiety of the imine and the voluminous substituent of the ketene in opposite orientations. Consequently, the steric hindrance is minimized.

The following ring closure is analog to an intramolecular nucleophilic addition of the enolate moiety to the iminium ion moiety. This step proceeds diastereoselectively forming only the *trans* β-lactam. The result is consistent with comparable synthetic results of the Staudinger reaction [17].

Starting from the chiral imines **1c** and **2c–d**, we obtained two diastereomers in some cases. For the β-lactam **4c** and **4f**, respectively, a *dr* = 62:38 and a *dr* = 83:17 were calculated in the crude product. In case of the racemic major diastereomer (2S*,2aR*,3R*)-**4c**, we were able to obtain single crystals and determined the proposed structure by X-ray analysis (Fig. 2).

The X-ray structure verifies the postulated *trans* configuration at the β-lactam ring once more. Furthermore, it is shown that the voluminous phenyl substituent and the lactam ring are in *trans* configuration because of steric hindrance. As a result, the minor racemic diastereomer (2S*,2aR*,3S*)-**4c** shows a *cis* configuration between the phenyl substituent and the β-lactam ring. Analogously, the relative configuration of the β-lactams **3c**, **4f**, **4i**, and **4j** according to chiral starting materials was assigned.

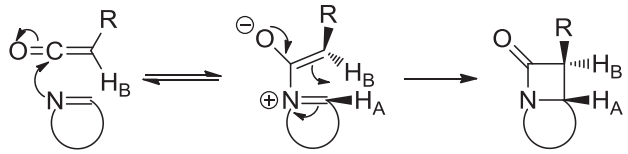
Table 1

β-Lactams **3** and **4**.

Imine	Lactam	R^1	R^2	R^3	Yield[a] (%)	*dr*[b]
1a	**3a**	CH_3	CH_3	OC_6H_5	64	≥95:5
1b	**3b**	-$(CH_2)_5$-		OC_6H_5	54	≥95:5
1c	**3c**	CH_3	H	OC_6H_5	19	≥95:5[c]
2a	**4a**	CH_3	CH_3	OCH_3	82	≥95:5
2b	**4b**	-$(CH_2)_5$-		OCH_3	74	≥95:5
2c	**4c**	CH_3	C_6H_5	OCH_3	28	62:38[c]
2a	**4d**	CH_3	CH_3	OC_6H_5	35	≥95:5
2b	**4e**	-$(CH_2)_5$-		OC_6H_5	40	≥95:5
2c	**4f**	CH_3	C_6H_5	OC_6H_5	18	83:17[c]
2a	**4g**	CH_3	CH_3	NPhth[d]	42	≥95:5
2b	**4h**	-$(CH_2)_5$-		NPhth[d]	37	≥95:5
2c	**4i**	CH_3	C_6H_5	NPhth[d]	23	≥95:5[c]
2d	**4j**	CH_3	*n*-C_3H_7	NPhth[d]	25	≥95:5[c]

[a]All yields are isolated yields.
[b]Diastereomeric ratio according to the ^{1}H NMR of the crude product.
[c]The diastereomeric ratio implies *trans* configuration at the β-lactam ring (see further discussion), so *dr* means the ratio between the β-lactam ring and the substituent at the six-membered imine ring.
[d]NPhth means phthalimido.

Scheme 2. Mechanism of the Staudinger reaction of heterocyclic imines [16].



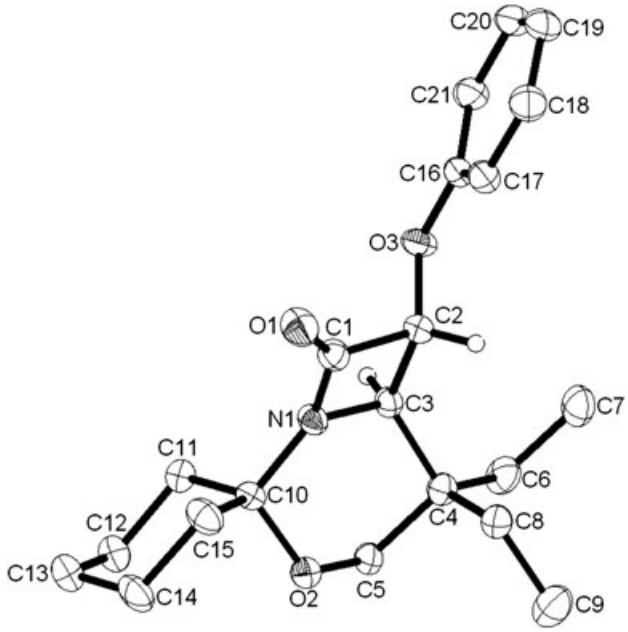


Figure 1. X-ray crystal structure of the racemic β-lactam **3b** (only one enantiomer is shown) [15]. The atom numbering in the X-ray structure does not follow the IUPAC nomenclature.

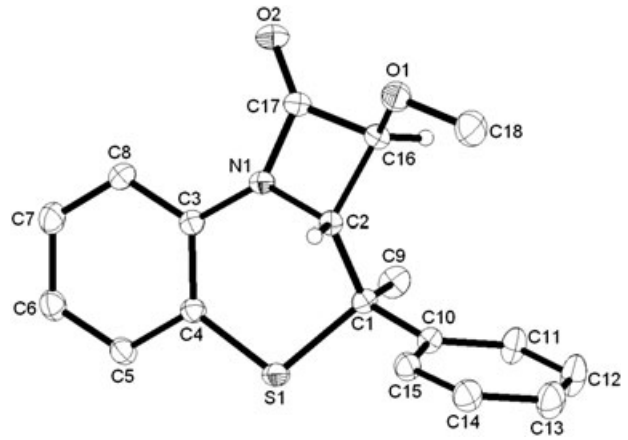


Figure 2. X-ray crystal structure of the racemic major diastereomer β-lactam (2S*,2aR*,3R*)-**4c** (only one enantiomer is shown) [15]. The atom numbering in the X-ray structure does not follow the IUPAC nomenclature.

CONCLUSIONS

Starting from the cyclic imines **1** und **2**, we succeeded in the stereoselective synthesis of the β-lactams **3** and **4** by the means of the Staudinger reaction. We observed the diastereoselectivity at the β-lactam ring in all cases. The *trans* configuration at the β-lactam ring was verified by X-ray structures and NMR data. In addition to the imines **1**, we applied the procedure successfully to the annulated benzothiazines **2**, a rarely investigated class of heterocyclic imines.

EXPERIMENTAL

Synthetic procedures, performed under argon atmosphere, were performed on a vacuum line using standard Schlenk techniques. Melting points were obtained on a melting point apparatus of laboratory devices and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AM 300 or a Bruker AMX R 500 spectrometer (Bruker AXS GmbH D-76187, Karlsruhe, Germany) with TMS as an internal standard in $CDCl_3$ solution. Assignments of the signals were supported by measurements applying DEPT and COSY techniques. Mass spectra were obtained on a Finnigan-MAT 212 mass spectrometer with isobutane as reagent gas. The IR spectra were recorded with a Bruker Vector 22 spectrometer as film between NaCl plats or in KBr or with a Bruker Tensor 27 spectrometer (Thermo Fisher Scientific, Waltham, MA) equipped with a "Golden Gate" diamond-ATR (attenuated total reflection) unit.

General procedure for the preparation of the 5,6-dihydro-2*H*-1,3-oxazines 1a–c (GP A). A solution of the oxocomponent (250.0 mmol in case of ketones or 50.0 mmol in case of aldehydes) and 25% solution of ammonia (3.8 mL, 50.0 mmol) was cooled down to 0°C. While constantly stirring, 2-ethyl-2-(hydroxymethyl) butanal (6.51 g, 50.0 mmol), dissolved in 50 mL dichloromethane, was added dropwise. After having been stirred overnight at room temperature, 50 mL water was added, and the phases were separated. The aqueous phase was extracted with dichloromethane (3×20 mL). The recombined organic phases were dried over magnesium sulfate, and the solvent was removed under reduced pressure. The crude product was purified by distillation.

5,5-Diethyl-2,2-dimethyl-5,6-dihydro-2H-1,3-oxazine (1a). Colorless oil; yield: 39%; bp: 70–81°C, 14 mbar; IR (film): ν 1650 (C═N) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, ^{3}J = 7.5 Hz, 6H, $2 \times CH_2CH_3$), 1.40 (2s, 6H, $(C(CH_3)_2)$, 1.46 (q, ^{3}J = 7.5 Hz, 2H, CH_2CH_3), 1.47 (q, ^{3}J = 7.5 Hz, 2H, CH_2CH_3,), 3.62 (s, 2H, CH_2O), 7.44 (s, 1H, N═CH); ^{13}C NMR (76 MHz, $CDCl_3$): δ = 8.06 ($2 \times CH_2CH_3$), 27.19 ($C(CH_3)_2$, $2 \times CH_2CH_3$), 38.08 ($C(CH_2CH_3)_2$), 63.96 (CH_2O), 86.33 ($C(CH_3)_2$), 164.39 (N═CH); MS (CI, isobutane): *m/z* (%): 170.2 (15) $[MH]^+$; HRMS (EI): *m/z* Calcd for $C_{10}H_{19}NO$ $[M]^+$: 169.1467; found: 169.1467.

3,3-Diethyl-1-oxa-5-azaspiro[5.5]undec-4-ene (1b). Colorless oil; yield: 65%; bp: 88–92°C, 0.06 mbar; IR (film): ν 1650 (C═N) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.66 (t, ^{3}J = 7.6 Hz, 6H, $2 \times CH_2CH_3$), 1.22 (q, ^{3}J = 7.6 Hz, 4H, $2 \times CH_2CH_3$), 1.32–1.50 (m, 10H, $5 \times CH_{2,Cy}$), 3.35 (s, 2H, CH_2O), 7.23 (s, 1H, N═CH); ^{13}C NMR (76 MHz, $CDCl_3$): δ = 8.63 ($2 \times CH_2CH_3$), 27.85 ($2 \times CH_2CH_3$), 22.55, 25.91, 36.22 ($5 \times CH_{2,Cy}$), 39.07 ($CH_2CH_3)_2$), 63.72 (CH_2O), 87.15 ($C(CH_{2,Cy})_5$), 165.09 (N═CH); MS (CI, isobutane): *m/z* (%): 210.2 (100) $[MH]^+$; HRMS (EI): *m/z* Calcd for $C_{13}H_{23}NO$ $[M]^+$: 209.1780; found: 209.1780.

(RS)-5,5-Diethyl-2-methyl-5,6-dihydro-2H-1,3-oxazine (1c). Colorless oil; yield: 60%; bp: 70–79°C, 15 mbar; IR (film): ν 1652 (C═N) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 0.87–0.89 (m, 3H, CH_2CH_3), 0.92–0.94 (m, 3H, CH_2CH_3), 1.38 (q, ^3J = 7.6 Hz, 2H, CH_2CH_3), 1.41 (d, ^3J = 5.8 Hz, 3H, CCH_3), 1.50–1.61 (m, 2H, CH_2CH_3), 3.55 (d, ^2J = 11.4 Hz, 1H, CH_2O), 3.73 (d, ^2J = 11.4 Hz, 1H, CH_2O), 4.82–4.86 (m, 1H, $CHCH_3$), 7.52 (s, 1H, N═CH); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 7.69, 8.43 (2 × CH_2CH_3), 22.27 (CCH_3), 26.51, 28.16 (2 × CH_2CH_3), 38.96 ($C(CH_2CH_3)_2$), 68.85 (CH_2O), 84.95 (CCH_3), 166.34 (N═CH); MS (CI, isobutane): *m/z* (%): 156.2 (100) $[MH]^+$; HRMS (EI): *m/z* Calcd for $C_9H_{17}NO$ $[M]^+$: 155.1310; found: 155.1311.

General procedure for the preparation of 2*H*-1,4-benzothiazines 2a–c (GP B). Under argon atmosphere, a solution of 2-aminothiophenol (6.00 g, 48.0 mmol) in anhydrous THF (20 mL) was added to a suspension of sodium hydride (2.00 g, 50.0 mmol, 60% in oil) in anhydrous THF (70 mL) at 0°C. The resulted foamy white/violet colored reaction mixture was stirred for 2 h at room temperature. The respective α-bromoaldehyde (50.5 mmol), dissolved in anhydrous THF (15 mL), was added dropwise. After having been stirred overnight at room temperature, molecular sieves were added, and the reaction mixture was stirred for 3 h. After filtration, the solvent was removed on a rotary evaporator. The crude product was purified by recrystallization from petroleum ether 40/60 or by distillation in certain cases.

2,2-Dimethyl-2H-1,4-benzothiazine (2a) [18]. After recrystallization, the product was obtained as a colorless solid. Yield: 57%; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.40 (2s, 6H, 2 × CH_3), 7.15 (ddd, ^3J = 7.5 Hz, ^3J = 9.1 Hz, ^4J = 1.4 Hz, 1H, Ar-H), 7.21 (ddd, ^3J = 7.8 Hz, ^3J = 9.1 Hz, ^4J = 1.4 Hz, 1H, Ar-H), 7.25 (dd, ^3J = 7.5 Hz, ^4J = 1.4 Hz, 1H, Ar-H), 7.43 (dd, ^3J = 7.8 Hz, ^4J = 1.4 Hz, 1H, Ar-H), 7.57 (s, 1H, N═CH); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 25.29 (2 × CH_3), 37.10 ($C(CH_3)_2$), 123.29, 126.25, 127.37, 127.60, 127.76, 140.94 (6 × Ar-C), 160.85 (N═CH).

Spiro[1,4-benzothiazine-2,1′-cyclohexane] (2b) [13]. After recrystallization, the product was obtained as red solid. Yield: 53%; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.38–1.44 (m, 1H, $CH_{2,Cy}$), 1.54–1.65 (m, 3H, 2 × $CH_{2,Cy}$), 1.68–1.80 (m, 6H, 3 × $CH_{2,Cy}$), 7.12 (ddd, ^3J = 7.5 Hz, ^3J = 9.0 Hz, ^4J = 1.4 Hz, 1H, Ar-H), 7.20 (ddd, ^3J = 7.7 Hz, ^3J = 9.2 Hz, ^4J = 1.4 Hz, 1H, Ar-H), 7.26 (dd, ^3J = 7.5 Hz, ^4J = 1.4 Hz, 1H, Ar-H), 7.41 (dd, ^3J = 7.8 Hz, ^4J = 1.4 Hz, 1H, Ar-H), 7.59 (s, 1H, N═CH); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.09, 25.58, 33.20 (5 × $CH_{2,Cy}$), 42.17 ($C(CH_{2,Cy})_5$), 122.98, 126.21, 127.70, 127.62, 127.78, 141.78 (6 × Ar-C), 160.73 (N═CH).

(RS)-2-Methyl-2-phenyl-2H-1,4-benzothiazine (2c) [18]. Purification was not necessary. The product was obtained as brown oil. Yield: 100%; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.78 (s, 3H, CH_3), 7.10–7.51 (m, 9H, 9 × Ar-H), 7.86 (s, 1H, N═CH); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 24.41 (CH_3), 43.76 (CCH_3), 122.97, 126.43, 126.88, 127.07, 127.73, 127.78, 127.84, 128.55, 140.42, 141.82 (12 × Ar-C), 159.48 (N═CH).

(RS)-2-Methyl-2-propyl-2H-1,4-benzothiazine (2d). After distillation, the product was obtained as yellow oil. Yield: 68%; bp: 152–154°C, 0.07 mbar; IR (film): ν 1595 (C═N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 0.89–0.91 (m, 3H, CH_2CH_3), 1.36 (s, 3H, CCH_3), 1.41–1.68 (m, 4H, 2 × CH_2), 7.10–7.43 (m, 4H, 4 × Ar-H), 7.54 (s, 1H, N═CH); ^{13}C NMR (76 MHz, $CDCl_3$): δ = 14.25 (CH_2CH_3), 17.39 (CH_2CH_3), 23.13 (CCH_3), 40.29 (CCH_2), 41.05 (CCH_3), 123.08, 125.98, 127.29, 127.43, 127.66, 140.74 (6 × Ar-C), 160.52 (N═CH); MS (CI, isobutane): *m/z* (%): 206.0 (100) $[MH]^+$; HRMS (CI, isobutane): *m/z* Calcd for $C_{12}H_{15}NS$ $[MH]^+$: 206.1003; found: 206.1003.

General procedure for the preparation of the β-lactams 3a–c and 4a–j (GP C). The heterocyclic imine **1** or **2** (5.0 mmol) and anhydrous triethylamine (1.01 g, 10.0 mmol) were dissolved in anhydrous dichloromethane (20 mL) and cooled down to 0°C. The respective acid chloride (5.0 mmol), dissolved in anhydrous dichloromethane (10 ml), was added dropwise. After having been stirred overnight at room temperature, aqueous saturated ammonium chloride solution (20 mL) was added. The organic phase was removed and washed with water. The aqueous phases were extracted with dichloromethane (3 × 20 mL). The recombined organic phases were dried over magnesium sulfate. After removal of the solvent on a rotary evaporator, the resulting residue was purified by recrystallization from dichloromethane/diethyl ether. The obtained solid compound was dried in vacuo.

(6S*,7S*)-5,5-Diethyl-2,2-dimethyl-7-phenoxy-3-oxa-1-azabicyclo[4.2.0]octan-8-one (3a). Analysis of the crude product by ^1H NMR spectroscopy showed a single diastereomer, indicating a *dr* ≥ 95:5. After recrystallization, the product was obtained as colorless crystals. Yield: 64%; mp: 144°C; IR (KBr): ν 1740 (C═O), 1235 (C-N) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 0.83–0.85 (m, 3H, CH_2CH_3), 0.88–0.90 (m, 3H, CH_2CH_3), 1.04–1.11, 1.34–1.44, 1.66–1.72 (3m, 4H, 2 × CH_2CH_3), 1.46, 1.76 (2s, 3H, $C(CH_3)_2$), 3.35 (d, ^2J = 12.5 Hz, 1H, CH_2O), 3.60 (d, ^2J = 12.5 Hz, 1H, CH_2O), 3.62 (d, ^3J = n.s., 1H, NCH), 5.07 (d, ^3J = n.s., 1H, $CHOC_6H_5$), 7.01–7.03, 7.14–7.16, 7.26–7.31 (3m, 5H, 5 × Ar-H); ^{13}C NMR (76 MHz, $CDCl_3$): δ = 7.27, 7.53 (2 × CH_2CH_3), 17.96, 22.06, 25.04, 26.30 ($C(CH_3)_2$, 2 × CH_2CH_3), 37.27 ($C(CH_2CH_3)_2$), 62.21 (NCH), 65.14 (CH_2O), 82.66 ($CHOC_6H_5$), 83.08 ($C(CH_3)_2$), 116.48, 122.42, 129.53, 157.81 (6 × Ar-C), 162.35 (C═O); MS (CI, isobutane): *m/z* (%): 304.3 (100) $[MH]^+$; HRMS (CI, isobutane): *m/z* Calcd for $C_{18}H_{26}NO_3$ $[MH]^+$: 304.1913; found: 304.1913.

(6S*,7S*)-5,5-Diethyl-7-phenoxy-3-oxa-1-azaspiro[bicyclo[4.2.0]octane-2,1′-cyclohexa-ne]-8-one (3b). Analysis of the crude product by ^1H NMR spectroscopy showed a single diastereomer, indicating a *dr* ≥ 95:5. After recrystallization, the product was obtained as colorless crystals. Yield: 54%; mp: 128°C; IR (KBr): ν 1739 (C═O), 1247 (C-N) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 0.82–0.84 (m, 3H, CH_3), 0.87–0.89 (m, 3H, CH_3), 1.02–1.09, 1.34–1.45, 1.48–1.55, 1.59–1.65, 1.69–1.75, 1.81–1.88, 2.05–2.08, 2.34–2.39 (8m, 14H, 5 × $CH_{2,Cy}$, 2 × CH_2CH_3), 3.32 (d, ^2J = 12.5 Hz, 1H, CH_2O), 3.58 (d, ^2J = 12.5 Hz, 1H, CH_2O), 3.61 (d, ^3J = n.s., 1H, NCH), 5.05 (d, ^3J = n.s., 1H, $CHOC_6H_5$), 7.00–7.03, 7.15–7.16, 7.27–7.30 (3m, 5H, 5 × Ar-H); ^{13}C NMR (76 MHz, $CDCl_3$): δ = 7.32, 7.55 (2 × CH_3), 18.07, 21.50, 21.73, 25.07, 25.15, 30.12, 34.84 (9 × CH_2), 37.35 ($C(CH_2CH_3)_2$), 61.72 (NCH), 64.31 (CH_2O), 82.46 ($CHOC_6H_5$), 84.51 ($C(CH_{2,Cy})_5$), 116.48, 122.35, 129.51, 157.84 (6 × Ar-C), 162.41 (C═O); MS (CI, isobutane): *m/z* (%): 344.3 (100) $[MH]^+$.

(2S*,6S*,7S*)-5,5-Diethyl-2-methyl-7-phenoxy-3-oxa-1-azabicyclo[4.2.0]octan-8-one (3c). Analysis of the crude product by ^1H NMR spectroscopy showed a single diastereomer, indicating a *dr* ≥ 95:5. After recrystallization, the product was obtained as colorless crystals. Yield: 19%; mp: 95–96°C; IR (KBr): ν 1744 (C═O), 1244 (C-N) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 0.83–0.85 (m, 3H, CH_2CH_3), 0.85–0.87 (m, 3H, CH_2CH_3,), 1.10–1.17, 1.39–1.44, 1.62–1.70 (3m, 4H, 2 × CH_2CH_3), 1.42 (d, ^3J = 6.2 Hz, 3H, CCH_3), 3.41 (d, ^2J = 12.4 Hz, 1H, CH_2O), 3.51 (d, ^2J = 12.4 Hz, 1H, CH_2O), 3.67 (d, ^3J = n.s., 1H, NC*H*CH), 5.10 (d, ^3J = n.s., 1H, $CHOC_6H_5$), 5.44 (q, ^3J = 6.2 Hz, 1H, $CHCH_3$),

7.00–7.03, 7.14–7.16, 7.28–7.31 (3m, 5H, 5 × Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 7.27, 7.47 (2 × CH_2CH_3), 17.54, 18.86 (2 × CH_2CH_3), 25.53 (CCH_3), 37.69 ($C(CH_2CH_3)_2$), 61.58 (NCHCH), 64.67 (CH_2O), 74.26 (CCH_3), 82.79 ($CHOC_6H_5$), 116.33, 122.44, 129.57, 157.71 (6 × Ar-C), 163.28 (C═O); MS (CI, isobutane): *m/z* (%): 290.2 (100) $[MH]^+$.

(2S*,2aR*)-2-Methoxy-3,3-dimethyl-2a,3-dihydroazeto[1,2-d]benzo[1,4]thiazin-1(2H)-one (4a). Analysis of the crude product by ^{1}H NMR spectroscopy showed a single diastereomer, indicating a *dr* ≥ 95:5. After recrystallization, the product was obtained as colorless crystals. Yield: 82%; mp: 107–108°C; IR (ATR): ν 1748 (C═O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.35, 1.53 (2s, 6H, $C(CH_3)_2$), 3.58 (s, 3H, OCH_3), 3.98 (d, ^3J = 1.5 Hz, 1H, NCH), 4.44 (d, ^3J = 1.5 Hz, 1H, $CHOCH_3$), 6.99 (ddd, ^3J = 8.0 Hz, ^3J = n.s., ^4J = 1.0 Hz, 1H, Ar-H), 7.12–7.15 (m, 2H, 2 × Ar-H), 7.78 (dd, ^3J = 8.5 Hz, ^4J = 1.0 Hz, 1H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 22.89, 24.87 ($C(CH_3)$), 40.11 ($C(CH_3)_2$), 57.98 (OCH_3), 64.27 (NCH), 85.49 ($CHOCH_3$), 118.91, 121.17, 124.24, 126.10, 127.62, 130.26 (6 × Ar-C), 162.97 (C═O); MS (CI, isobutane): *m/z* (%): 250.1 (100) $[MH]^+$; HRMS (CI, isobutane): *m/z* Calcd for $C_{13}H_{16}NO_2S$ $[MH]^+$: 250.0902; found: 250.0903.

(2S*,2aR*)-2-Methoxy-2,2a-dihydro-1H-spiro[azeto[1,2-d]benzo[1,4]thiazine-3,1′-cyclohexane]-1-one (4b). Analysis of the crude product by ^{1}H NMR spectroscopy showed a single diastereomer, indicating a *dr* ≥ 95:5. After recrystallization, the product was obtained as brown solid. Yield: 74%; mp: 127–131°C; IR (ATR): ν 1749 (C═O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.19–1.29 (m, 1H, $CH_{2,Cy}$), 1.39–1.44 (m, 1H, $CH_{2,Cy}$), 1.54–1.92 (m, 8H, 4 × $CH_{2,Cy}$), 3.58 (s, 3H, OCH_3), 3.98–3.99 (m, 1H, NCH), 4.60 (d, ^3J = 2.0 Hz, 1H, $CHOCH_3$), 6.96–6.99 (m, 1H, Ar-H), 7.11–7.14 (m, 1H, Ar-H), 7.16–7.17 (m, 1H, Ar-H), 7.75–7.77 (m, 1H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.48, 21.49, 25.95, 28.71, 33.95 (5 × $CH_{2,Cy}$), 46.12 ($C(CH_{2,Cy})_5$), 57.94 (OCH_3), 64.92 (NCH), 84.84 ($CHOCH_3$), 118.76, 120.48, 124.14, 126.05, 128.09, 130.94 (6 × Ar-C), 162.70 (C═O); MS (CI, isobutane): *m/z* (%): 290.1 (100) $[MH]^+$; HRMS (CI, isobutane): *m/z* Calcd for $C_{16}H_{20}NO_2S$ $[MH]^+$: 290.1215; found: 290.1214.

(2S*,2aR*,3R*)- and (2S*,2aR*,3S*)-2-Methoxy-3-methyl-3-phenyl-2a,3-dihydroazeto[1,2-d]benzo[1,4]thiazin-1(2H)-one (4c). Analysis of the crude product by ^{1}H NMR spectroscopy revealed a 62:38 mixture of diastereomers. The diastereomers were separated by recrystallization from dichloromethane/diethyl ether. The major diastereomer (2S*,2aR*,3R*)-**4c** was obtained as colorless crystals. Yield: 20%; mp: 114–116°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.69 (s, 3H, CCH_3), 3.35 (s, 3H, OCH_3), 4.48–4.49 (m, 2H, NCH, $CHOCH_3$), 7.02–7.05 (m, 1H, Ar-H), 7.18–7.22 (m, 2H, 2 × Ar-H), 7.36–7.39 (m, 1H, Ar-H), 7.44–7.47 (m, 2H, 2 × Ar-H), 7.58–7.59 (m, 2H, 2 × Ar-H), 7.86–7.88 (m, 1H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.85 (CCH_3), 46.65 (CCH_3), 57.91 (OCH_3), 63.54 ($CHOCH_3$), 85.83 (NCH), 118.98, 121.87, 124.25, 126.30, 126.37, 127.70, 128.43, 129.20, 130.40, 140.23 (12 × Ar-C), 163.12 (C═O). The minor diastereomer (2S*,2aR*,3S*)-**4c** was obtained as yellow solid. Yield: 8%; mp: 107–109°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.90 (s, 3H, CCH_3), 3.44 (s, 3H, OCH_3), 3.86 (d, ^3J = 2.0 Hz, 1H, NCH), 3.95 (d, ^3J = 2.0 Hz, 1H, $CHOCH_3$), 6.99 (ddd, ^3J = 7.5 Hz, ^3J = 8.5 Hz, ^4J = 1.0 Hz, 1H, Ar-H), 7.10 (ddd, ^3J = 7.5 Hz, ^3J = 8.0 Hz, ^4J = 1.5 Hz, 1H, Ar-H), 7.15–7.18 (m, 6H, 6 × Ar-H), 7.70 (dd, ^3J = 8.0 Hz, ^4J = 1.0 Hz, 1H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 25.44 (CCH_3), 46.62 (CCH_3), 58.02 (OCH_3), 62.85 ($CHOCH_3$), 86.77 (NCH), 119.19, 123.54, 124.43, 125.44, 125.81, 126.92, 127.97, 128.52, 130.31, 140.53 (12 × Ar-C), 162.38 (C═O). IR (ATR): ν 1748 (C═O) cm^{-1}; MS (CI, isobutane): *m/z* (%): 312.1 (100) $[MH]^+$; HRMS (CI, isobutane): *m/z* Calcd for $C_{18}H_{18}NO_2S$ $[MH]^+$: 312.1058; found: 312.1061.

(2S*,2aR*)-3,3-Dimethyl-2-phenoxy-2a,3-dihydroazeto[1,2-d]benzo[1,4]thiazin-1(2H)-one (4d). Analysis of the crude product by ^{1}H NMR spectroscopy showed a single diastereomer, indicating a *dr* ≥ 95:5. After recrystallization, the product was obtained as colorless crystals. Yield: 35%; mp: 120–122°C; IR (KBr): ν 1745 (C═O), 1301 (C-N) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.40, 1.49 (2s, 6H, 2 × CH_3), 4.21 (d, ^3J = 1.5 Hz, 1H, NCH), 5.09 (d, ^3J = 1.5 Hz, 1H, $CHOC_6H_5$), 6.97–7.82 (4m, 9H, 9 × Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 23.07, 24.87 (2 × CH_3), 40.19 ($C(CH_3)_2$), 64.98 (NCH), 83.01 ($CHOC_6H_5$), 116.71, 119.02, 121.29, 122.99, 124.41, 126.23, 127.65, 129.74, 130.42, 157.44 (12 × Ar-C), 162.21 (C═O); MS (CI, isobutane): *m/z* (%): 312.0 (100) $[MH]^+$; HRMS (CI, isobutane): *m/z* Calcd for $C_{18}H_{18}NO_2S$ $[MH]^+$: 312.1058; found: 312.1057.

(2S*,2aR*)-2-Phenoxy-2,2a-dihydro-1H-spiro[azeto[1,2-d]benzo[1,4]thiazine-3,1′-cyclohexane]-1-one (4e). Analysis of the crude product by ^{1}H NMR spectroscopy showed a single diastereomer, indicating a *dr* ≥ 95:5. After recrystallization, the product was obtained as colorless crystals. Yield: 40%; mp: 118–119°C; IR (KBr): ν 1733 (C═O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.19–1.89 (m, 10H, 5 × $CH_{2,Cy}$), 4.25 (d, ^3J = 1.5 Hz, 1H, NCH), 5.27 (d, ^3J = 1.5 Hz, 1H, $CHOC_6H_5$), 6.99–7.79 (5m, 9H, 9 × Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.43, 21.46, 25.88, 28.88, 33.74 (5 × $CH_{2,Cy}$), 46.10 ($C(CH_{2,Cy})_5$), 65.28 (NCH), 82.12 ($CHOC_6H_5$), 116.54, 118.81, 120.49, 122.81, 124.34, 126.13, 128.11, 129.69, 130.87, 157.38 (Ar-C), 162.03 (C═O); MS (CI, isobutane): *m/z* (%): 352.2 (100) $[MH]^+$.

(2S*,2aR*,3R*)- and (2S*,2aR*,3S*)-3-Methyl-2-phenoxy-3-phenyl-2a,3-dihydroazeto[1,2-d]benzo[1,4]thiazin-1(2H)-one (4f). Analysis of the crude product by ^{1}H NMR spectroscopy revealed an 83:17 mixture of diastereomers. The diastereomers were separated by recrystallization from dichloromethane/diethyl ether. The major diastereomer (2S*,2aR*,3R*)-**4f** was obtained as brown solid. Yield: 10%; mp: 141–143°C; IR (KBr): ν 1746 (C═O), 1239 (C-N) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.75 (s, 3H, CH_3), 4.74 (d, ^3J = 1.8 Hz, 1H, NCH), 5.11 (d, ^3J = 1.8 Hz, 1H, $CHOC_6H_5$), 6.90–7.92 (m, 14H, 14 × Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.83 (CH_3), 46.53 (CCH_3), 64.01 (NCH), 83.11 ($CHOC_6H_5$), 116.14, 119.04, 121.86, 122.62, 124.41, 126.30, 126.42, 127.54, 128.48, 129.15, 129.49, 130.22, 139.77, 157.08 (12 × Ar-C), 162.13 (C═O). The minor diastereomer (2S*,2aR*,3S*)-**4f** was obtained as colorless solid. Yield: 8%; mp: 107–109°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.90 (s, 3H, CH_3), 4.24 (d, ^3J = 1.9 Hz, 1H, NCH), 4.62 (d, ^3J = 1.9 Hz, 1H, $CHOC_6H_5$), 7.01–7.82 (m, 14H, 14 × Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 25.37 (CH_3), 46.60 ($C(CH_3)$), 63.47 (NCH), 83.77 ($CHOC_6H_5$), 116.33, 119.26, 122.82, 123.57, 124.62, 125.46, 125.89, 126.81, 128.13, 128.63, 129.67, 130.26, 140.53, 157.06 (18 × Ar-C), 161.40 (C═O). IR (KBr): ν 1746 (C═O), 1239 (C-N) cm^{-1}; MS (CI, isobutane): *m/z* (%): 374.0 (100) $[MH]^+$.

2-((2S*,2aR*)-3,3-Dimethyl-1-oxo-1,2,2a,3-tetrahydroazeto[1,2-d]benzo[1,4]thiazin-2-yl)isoindoline-1,3-dione (4g). Analysis of the crude product by ^{1}H NMR spectroscopy showed a single diastereomer, indicating a *dr* ≥ 95:5. After recrystallization, the product was obtained as colorless crystals. Yield: 42%; mp: 197–198°C; IR (KBr): ν 1788, 1729 (C═O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45, 1.51 (2s, 6H, 2 × CH_3), 4.36

(d, $^3J = 2.7$ Hz, 1H, NCH), 5.23 (d, $^3J = 2.7$ Hz, 1H, CHC═O), 7.00–7.90 (m, 8H, 8 × Ar-H); ^{13}C NMR (76 MHz, $CDCl_3$): δ = 22.38, 24.48 (2 × CH_3), 40.31 ($C(CH_3)_2$), 56.45 (*C*HC═O), 63.39 (NCH), 118.80, 120.96, 123.88, 124.26, 126.24, 127.65, 130.53, 131.62, 134.63 (12 × Ar-C), 160.17 (C═O), 166.68 (C═O); MS (CI, isobutane): *m/z* (%): 365.2 (100) $[MH]^+$; *Anal*. Calcd for $C_{20}H_{16}N_2O_3S$ (364.4): C, 65.92; H, 4.43; N, 7.69; S, 8.80; found: C, 65.56; H, 4.33; N, 7.55; S, 8.67.

2-((2S*,2aR*)-1-Oxo-2,2a-dihydro-1H-spiro[azeto[1,2-d]benzo[1,4]thiazine-3,1′-cyclohexane]-2-yl)isoindoline-1,3-dione (4h). Analysis of the crude product by ^{1}H NMR spectroscopy showed a single diastereomer, indicating a *dr* ≥ 95:5. After recrystallization, the product was obtained as colorless crystals. Yield: 37%; mp: 138–139°C; IR (KBr): ν 1766, 1728 (C═O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.30–1.92 (m, 10H, 5 × $CH_{2,Cy}$), 4.34 (d, $^3J = 2.7$ Hz, 1H, NCH), 5.39 (d, $^3J = 2.7$ Hz, 1H, CHC═O), 6.94–7.88 (m, 8H, 8 × Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.37, 21.44, 25.74, 28.00, 33.51 (5 × $CH_{2,Cy}$), 46.24 ($C(CH_{2,Cy})_5$), 55.66 (*C*HC═O), 63.95 (NCH), 118.58, 120.22, 123.82, 124.15, 126.17, 128.08, 131.09, 131.59, 134.59 (12 × Ar-C), 159.85 (C═O), 166.71 (C═O); MS (CI, isobutane): *m/z* (%): 405.2 (100) $[MH]^+$; *Anal*. Calcd for $C_{23}H_{20}N_2O_3S$ (404.5): C, 68.30; H, 4.98; N, 6.93; S, 7.93; found: C, 68.59; H, 5.14; N, 6.69; S, 7.52.

2-((2S*,2aR*,3R*)-3-Methyl-1-oxo-3-phenyl-1,2,2a,3-tetrahydroazeto[1,2-d]benzo[1,4]thiazin-2-yl)isoindoline-1,3-dione (4i). Analysis of the crude product by ^{1}H NMR spectroscopy showed a single diastereomer, indicating a *dr* ≥ 95:5. After recrystallization, the product was obtained as colorless crystals. Yield: 23%; mp: 192–193°C; IR (KBr): ν 1767, 1729 (C═O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.86 (s, 3H, CH_3), 4.88 (d, $^3J = 2.7$ Hz, 1H, NCH), 5.38 (d, $^3J = 2.7$ Hz, 1H, CHC═O), 7.07–7.96 (m, 13H, 13 × Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.27 (CH_3), 46.89 (*C*CH_3), 57.18 (*C*HC═O), 62.68 (NCH), 118.81, 121.43, 123.86, 124.28, 126.08, 126.38, 127.69, 128.32, 129.08, 130.47, 131.45, 134.56, 139.49 (18 × Ar-C), 160.44 (C═O), 166.51 (C═O); MS (CI, isobutane): *m/z* (%): 427.2 (100) $[MH]^+$; *Anal*. Calcd for $C_{25}H_{18}N_2O_3S$ (426.5): C, 70.40; H, 4.25; N, 6.57; S, 7.52; found: C, 70.82; H, 4.35; N, 6.55; S, 7.57.

2-((2S*,2aR*,3R*)-3-Methyl-1-oxo-3-propyl-1,2,2a,3-tetrahydroazeto[1,2-d]benzo[1,4]thiazin-2-yl)isoindoline-1,3-dione (4j). Analysis of the crude product by ^{1}H NMR spectroscopy showed a single diastereomer, indicating a *dr* ≥ 95:5. After recrystallization, the product was obtained as brown crystals. Yield: 25%; mp: 198–200°C; IR (KBr): ν 1755, 1728 (C═O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.92–0.94 (m, 3H, CH_2CH_3), 1.49 (s, 3H, CCH_3), 1.36–1.77 (m, 4H, 2 × CH_2), 4.43 (d, $^3J = 2.7$ Hz, 1H, NCH), 5.24 (d, $^3J = 2.7$ Hz, 1H, CHC═O), 6.99–7.92 (m, 8H, 8 × Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.50 (CH_2CH_3), 17.27 (CH_2CH_3), 19.71 (CH_3), 40.63 (C*C*H_3), 44.49 [*C*CH_3], 56.88 (*C*HC═O), 62.68 (NCH), 118.69, 120.51, 123.88, 124.22, 126.12, 127.72, 130.53, 131.60, 134.61 (12 × Ar-C), 160.36 (C═O), 166.69 (C═O); MS (CI, isobutane): *m/z* (%): 393.0 (100) $[MH]^+$; *Anal*. Calcd for $C_{22}H_{20}N_2O_3S$ (392.5): C, 67.33; H, 5.14; N, 7.14; S, 8.17; found: C, 67.35; H, 5.33; N, 7.00; S, 8.16.

Acknowledgments. T. S. and K. J. gratefully acknowledged the Heinz-Neumüller-Stiftung for a doctoral fellowship.

REFERENCES AND NOTES

[1] Dürckheimer, W.; Blumbach, J.; Lattrell, R.; Scheunemann, K. H. Angew Chem 1985, 97, 183; Angew Chem Int Ed Engl 1985, 24, 180.

[2] Chu, D. T. W.; Plattner, J. J.; Katz, L. J Med Chem 1996, 39, 3853.

[3] Niccolai, D.; Tarsi, L.; Thomas, R. J. Chem Commun 1997, 2333, DOI: 10.1039/A704497F.

[4] Wilmouth, R. C.; Kassamally, S.; Westwood, N. J.; Sheppard, R. J.; Claridge, T. D. W.; Aplin, R. T.; Wright, P. A.; Pritchard, G. J.; Schofield, C. J. Biochemistry 1999, 38, 7989.

[5] Burnett, D. A.; Caplen, M. A.; Davis, H. R., Jr.; Burrier, R. E.; Clader, J. W. J Med Chem 1994, 37, 1733.

[6] Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. Curr Med Chem 2004, 11, 1837.

[7] Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. Eur J Org Chem 1999, 12, 3223, DOI: 10.1002/(SICI)1099-0690.

[8] a) Wang, Y.; Liang, Y.; Jiao, L.; Du, D.-M.; Xu, J. J Org Chem 2006, 71, 6983; b) Qi, H.; Li, X.; Xu, J. Org Biomol Chem 2011, 9, 2702.

[9] Hatam, M.; Köpper, S.; Martens, J. Heterocycles 1996, 43, 675.

[10] Martens, J.; Offermanns, P.; Scherberich, P. Angew Chem 1981, 93, 680; Angew Chem Int Ed Engl 1981, 20, 668.

[11] Watzke, M.; Schulz, K.; Johannes, K.; Ullrich, P.; Martens, J. Eur J Org Chem 2008, 3859, DOI: 10.1002/ejoc.200800254.

[12] Schulz, K.; Watzke, M.; Johannes, K.; Ullrich, P.; Martens, J. Synthesis 2009, 665, DOI: 10.1055/s-0028-1083342.

[13] Schulz, K.; Ratjen, L.; Martens, J. Tetrahedron 2011, 67, 546.

[14] Hegedus, L. S.; Imwinkelried, R.; Alarid-Sargent, M.; Dvorak, D.; Satoh, Y. J Am Chem Soc 1990, 112, 1109.

[15] CCDC-857949 contains the supplementary crystallographic data for **3b** and CCDC-857950 for **4c**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[16] Jiao, L.; Liang, Y.; Xu, J. J Am Chem Soc 2006, 128, 6060.

[17] Li, B.; Wang, Y.; Du, D.-M.; Xu, J. J Org Chem 2007, 72, 990.

[18] Gröger, H.; Martens, J. Sulfur Lett 1996, 19, 197.