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Multicomponent reaction for the first synthesis of 2,2-dialkyl- and 2-alkyl-2-aryl-5,6-diaryl-2*H*-1,3-thiazines as scaffolds for various 3,4-dihydro-2*H*-1,3-thiazine derivatives†

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A two-step sequence for the synthesis of various 3,4-dihydro-2*H*-1,3-thiazines is presented. In the first step, 2*H*-1,3-thiazines were prepared by a new multicomponent reaction (MCR). Starting from β -chloro-vinyl aldehydes, this MCR offers an efficient and facile access to 2,2-dialkyl- and 2-alkyl-2-aryl-5,6-diaryl-2*H*-1,3-thiazines. The potential of these products in subsequent reactions was verified by the conversion to 3,4-dihydro-2*H*-1,3-thiazine-containing bisamides, β -lactams, and methoxy amides.

Introduction

Heterocyclic compounds containing sulfur and nitrogen are omnipresent in natural products and play a vital role in pharmaceutical applications and materials science.¹ Consequently, there is ongoing interest in drug discovery and other fields of application of organic chemistry in the development of efficient synthesis routes to new and relevant heterocyclic scaffolds containing sulfur and nitrogen.²

Well-known through the famous and widely applied penicillin, the substructure of 1,3-thiazolidine is one of the most important heterocyclic skeletons.^{3,4} 2,5-Dihydro-1,3-thiazole, one of the iminic unsaturated forms of the 1,3-thiazolidine, can also be found in several natural products and applicable compounds.⁵ Additionally, their use as scaffolds in the synthesis of derivatives of 1,3-thiazolidines is prevalent.⁶ The preparation of 2,5-dihydro-1,3-thiazoles can be realized by a four-component reaction (4-CR) known as the Asinger reaction, using an α -chloro aldehyde, a second carbonyl compound, ammonia and sodium hydrosulfide.^{6*b-d,7*} In addition the Asinger reaction provided the basis for the synthesis of several further heterocyclic structures.⁸ Combination of a multicomponent reaction (MCR) employed to synthesize relatively complex heterocyclic scaffolds with a subsequent post-transformation has been abundantly highlighted as an

advantageous method for the synthesis of heterocyclic compounds. This synthesis strategy is characterized by a high diversity.⁹

1,4-Thiazine, an unsaturated six-membered ring containing sulfur and nitrogen, and its hydrogenated structures dihydro-1,4-thiazine and tetrahydro-1,4-thiazine (thiomorpholine) are other well explored heterocycles. They can be found as substructures in natural products extracted from plants like seaweeds¹⁰ and in pharmaceuticals used as antipsychotic,¹¹ soporific,¹² analgesic,¹³ anticonvulsant,¹⁴ and antimycobacterial¹⁵ drugs or as TACE inhibitors.¹⁶ In contrast, 1,3-thiazines and compounds containing the dihydro-1,3-thiazine and tetrahydro-1,3-thiazine substructure have not been sufficiently investigated. Most notably the iminic 2,2,5,6-tetrasubstituted 2*H*-1,3-thiazines and their derived forms, *i.e.* 2,2,5,6-tetrasubstituted 3,4-dihydro-2*H*-1,3-thiazines, are interesting substructures and building blocks in the synthesis of novel potentially beneficial compounds.

Ceftazidime,¹⁷ one of the dihydro-1,3-thiazine based structural analogues of penicillin utilized as an antibacterial agent, and xylazine,¹⁸ a widely used drug in veterinary medicine, are two of the few examples of known compounds containing a dihydro-1,3-thiazine substructure.

The main reason for the lack of known beneficial dihydro-1,3-thiazine-containing compounds lies in the fact that only a few synthesis routes to 1,3-thiazines and different types of dihydro-1,3-thiazine, first of all 3,4-dihydro-2*H*-1,3-thiazine, containing structures are developed.¹⁹ As a consequence, we developed a MCR for the synthesis of 2,2-dialkyl- and 2-alkyl-2-aryl-5,6-diaryl-2*H*-1,3-thiazines (**2**), which have not been accessible yet. According to the method mentioned above, these cyclic imines serve as scaffolds for the preparation of several 3,4-dihydro-2*H*-1,3-thiazines (**5–7**) (Fig. 1).

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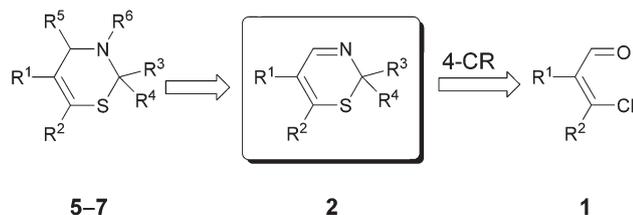


Fig. 1 Retrosynthetic consideration of the target structures.

In consideration of our experience^{6b-d,7} in the synthesis of 2,5-dihydro-1,3-thiazoles, we envisioned that the formation of 2H-1,3-thiazines **2** could be realized on the lines of the Asinger reaction by modifying the structure of the chloro aldehyde.

Results and discussion

Synthesis of the substrates

To obtain 2H-1,3-thiazines **2** via a procedure analogous to the Asinger reaction β -chlorovinyl aldehydes instead of α -chloro aldehydes have to be converted with a second carbonyl compound, ammonia and sodium hydrosulfide. β -Chlorovinyl aldehydes are easily accessible by treatment of α -methylene ketones with DMF and POCl₃.²⁰ We were able to synthesize (*E*)-, (*Z*)-, (*EZ*)-2-chloro-2,3-diphenylacrylaldehyde²¹ (**1a**), (*EZ*)-3-chloro-3-(4-chlorophenyl)-2-phenylacrylaldehyde²² (**1b**), (*E*)-3-chloro-2,3-bis(4-methoxyphenyl)acrylaldehyde²³ (**1d**), 2-chloro-1-cyclopentene-1-carboxaldehyde²⁴ (**1e**), and the previously unknown (*EZ*)-3-chloro-3-(4-hydroxyphenyl)-2-phenylacrylaldehyde (**1c**) and (*E*)-, (*EZ*)-3-chloro-2,3-bis(4-nitrophenyl)acrylaldehyde (**1f**).

Screening of reaction conditions

In an initial attempt to synthesize the 2H-1,3-thiazines **2**, we selected (*Z*)-**1a** and acetone as model substrates to probe the reaction conditions (Table 1). In the first experiment, we adopted our standard reaction conditions^{6b-d} used in the Asinger reactions, but no 2H-1,3-thiazine **2a** was formed. A change of the solvent to the polar protic methanol resulted in the formation of the intended product 2H-1,3-thiazine **2a** (Table 1, entry 1). But the known isothiazole **3a** was formed simultaneously. Starting from β -chlorovinyl aldehydes, the preparation of isothiazoles is usually realized by treatment of the aldehydes with ammonium cyanide.²⁵ The observed formation of isothiazole **3a** is likely to proceed via a hitherto unknown oxidation of the respective β -mercaptovinyl imine.

To improve the efficiency of the reaction, we examined classical conditions of the Asinger reaction based on α -chloro aldehydes.²⁶ Stirring of the β -chlorovinyl aldehyde and NaSH in methanol before addition of all the other reactants and the usage of gaseous ammonia led to a better ratio **2a** : **3a** (Table 1, entry 2). However, according to ¹H NMR of the crude product the quantity of other byproducts was likewise increased. Due to the expectable low yield the isolation of the products was consciously abandoned. The use of DMF as the solvent did not lead to the formation of the desired products **2a** or **3a**. Upon combining the pre-reaction time (aldehyde and NaSH) in methanol and the use of an aqueous ammonia solution (Table 1, entry 3) the yield of **2a** was slightly increased, but the ratio **2a** : **3a** was as unsatisfying as in the first successful experiment (Table 1, entry 1). According to the observation that the slower addition of ammonia using the gaseous one compared to the all-at-once addition of an aqueous ammonia solution had led to an increased formation of the thiazine **2a** in com-

Table 1 Optimization of the multicomponent reaction to prepare 2H-1,3-thiazine **2a**

Entry	Solvent	1a	1a : NaSH : acetone : NH ₃	Method ^a	Addition of ammonia	Ratio ^b 2a : 3a	Yield ^c [%]	
							2a	3a
1	MeOH	(<i>Z</i>)	1 : 1.5 : 2 : 2	A	aq	63 : 37	30	29
2	MeOH	(<i>Z</i>)	1 : 1.5 : 1.5	B, 2 h, r.t.	g, 4 h	75 : 25	— ^f	— ^e
3	MeOH	(<i>Z</i>)	1 : 1.5 : 1.5 : 2	B, 3 h, r.t.	aq	66 : 34	36	— ^e
4	MeOH	(<i>Z</i>)	1 : 1.5 : 1.5 : 2	B, 3 h, 60 °C	aq	—	— ^d	— ^d
5	MeOH	(<i>Z</i>)	1 : 1.5 : 1.5 : 2	B, 3 h, r.t.	aq, in MeOH, 1 h	77 : 23	49	— ^e
6	MeOH	(<i>EZ</i>)	1 : 1.5 : 1.5 : 2	B, 3 h, r.t.	aq, in MeOH, 1 h	81 : 19	48	— ^e
7	MeOH	(<i>EZ</i>)	1 : 1.5 : 1.5 : 2	B, 4 h, r.t.	aq, in MeOH, 1 h	82 : 18	46	— ^e
8	MeOH	(<i>EZ</i>)	1 : 1.5 : 2 : 2	B, 3 h, r.t.	aq, in MeOH, 1 h	81 : 19	57	— ^e
9	MeOH	(<i>EZ</i>)	1 : 1.5 : 3 : 2	B, 3 h, r.t.	aq, in MeOH, 1 h	80 : 20	63	14

^a (i) Method A: NaSH, NH₃ in solvent, then acetone and **1a** at 0 °C, for 18 h at r.t. (ii) Method B: **1a** and NaSH under given conditions, then acetone, and ammonia at once unless specified otherwise, for 18 h r.t. ^b The ratio according to ¹H NMR of the crude product. ^c All yields are isolated yields. ^d No product was formed. ^e The isolation of the byproduct was consciously abandoned. ^f Due to the excess undefined byproducts according to the ¹H NMR of the crude product the isolation of the thiazine was consciously abandoned.

parison with the isothiazole **3a**, we next added a more diluted solution of aqueous ammonia to the reaction mixture within one hour. Under these conditions the product was obtained in a comparatively higher yield and a good ratio **2a**:**3a** (49%, Table 1, entry 5).

It is noteworthy that the reaction could be performed using a (*EZ*)-mixture of **1a** without a significant decrease of yield (Table 1, entry 6). Due to the formation of a small amount of (*Z*)-**1**, if at all, compared to (*E*)-**1**, by converting the respective ketone and the complex isolation of (*Z*)-**1**, the feasibility of using both isomers simplifies the synthesis of the thiazines **2** tremendously. In addition, the efficiency of the synthesis route to the *2H*-1,3-thiazines **2** starting from the ketone is increased.

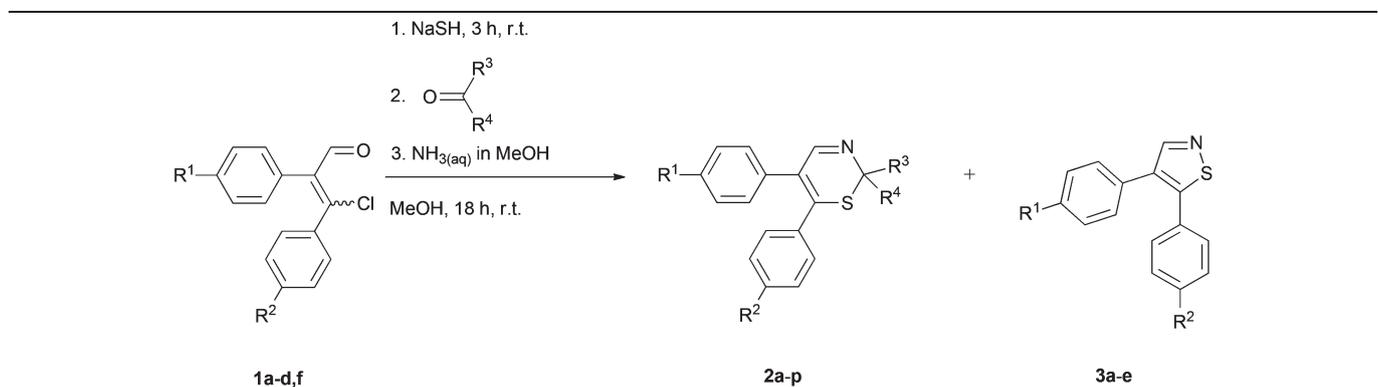
Finally, by raising the molar equivalents of acetone to 3.0 relative to the aldehyde, the yield of isolated **2a** was improved to 63% (Table 1, entry 9).

Reaction scope

Under these optimized conditions (Table 1, entry 9), we next studied the influence of the substituents on the aldehydes **1** and the second carbonyl compound on the formation of the products **2**.

The results are summarized in Table 2. Thus, we expanded the scope of the second carbonyl compound. Cyclic ketones such as cyclohexanone (Table 2, entries 2, 9, 12, and 18) as well as aldehydes like isopentanal (Table 2, entries 6 and 17) or 3-phenylpropanal (Table 2, entries 7 and 10) were all feasible substrates in the reaction. Although the yields of the *2H*-1,3-thiazines **2b** and **2d** were slightly lower, we were pleased to find that in both cases the ratio **2**:**3** was enhanced. Aromatic ketones such as acetophenone cannot be converted to the desired product **2** (Table 2, entry 4). Carbonyl compounds containing aromatic groups in the α - or β -position, however, are usable substrates for the synthesis of thiazines **2** (Table 2, entries 6, 7, 8, 10, 14, and 15). Moreover, the reaction tolerates several functional groups on the carbonyl compound, such as sulfide (Table 2, entry 3), ether (Table 2, entry 14), ester (Table 2, entry 16) and hydroxy (Table 2, entry 15) groups. Although the yield was a little lower compared to other carbonyl compounds, it is noteworthy that even the use of a substrate bearing a carbamate moiety led to the formation of the perspective product **2** (Table 2, entry 8). Conversion of an amine to thiazine **2k** (Table 2, entry 13) revealed the best ratio **2**:**3** (99:01) and the highest yield (90%).

Table 2 Preparation of *2H*-1,3-thiazines **2** and isothiazoles **3**



Entry	Aldehyde	R ¹	R ²	R ³	R ⁴	Ratio ^a 2 : 3	Yield ^b [%]
1	(<i>EZ</i>)- 1a	H	H	Me	Me	79:21	2a : 63
2	(<i>EZ</i>)- 1a	H	H	-(CH ₂) ₅ -		95:05	2b : 58
3	(<i>EZ</i>)- 1a	H	H	-(CH ₂) ₂ S(CH ₂) ₂ -		96:04	2c : 66
4	(<i>EZ</i>)- 1a	H	H	Me	Ph	— ^d	—
5	(<i>EZ</i>)- 1a	H	H	Me	CF ₃	— ^d	—
6	(<i>EZ</i>)- 1a	H	H	H	iBu	98:02	2d : 56
7	(<i>EZ</i>)- 1a	H	H	H	CH ₂ CH ₂ Ph	95:05	2e : 59
8	(<i>EZ</i>)- 1a	H	H	H	CH ₂ CH ₂ N(H)Cbz	86:14	2f : 47
9	(<i>EZ</i>)- 1b	H	Cl	-(CH ₂) ₅ -		97:03	2g : 72
10	(<i>EZ</i>)- 1c	H	OH	H	CH ₂ CH ₂ Ph	94:04	2h : 77
11	(<i>E</i>)- 1d	OCH ₃	OCH ₃	Me	Me	86:14	2i : 79
12	(<i>E</i>)- 1d	OCH ₃	OCH ₃	-(CH ₂) ₅ -		97:03	2j : 79
13	(<i>E</i>)- 1d	OCH ₃	OCH ₃	-(CH ₂) ₂ N(CH ₃)(CH ₂) ₂ -		99:01	2k : 90
14	(<i>E</i>)- 1d	OCH ₃	OCH ₃	Me	CH ₂ (4-OMe-Ph)	98:02	2l : 83
15	(<i>E</i>)- 1d	OCH ₃	OCH ₃	Me	CH ₂ CH ₂ (4-OH-Ph)	94:06	2m : 88
16	(<i>E</i>)- 1d	OCH ₃	OCH ₃	Me	CH ₂ CH ₂ COOEt	83:17	2n : 72
17	(<i>E</i>)- 1d	OCH ₃	OCH ₃	H	iBu	97:03	2o : 70
18	(<i>E</i>)- 1f	NO ₂	NO ₂	-(CH ₂) ₅ -		82:18	2p : 17

^a The ratio according to ¹H NMR of the crude product. ^b All yields are isolated yields. ^c The isolation of the byproduct was consciously abandoned.

^d No products (**2** or **3**) were formed.

Besides the model substrate **1a**, other β -chlorovinyl aldehydes were examined likewise. Both substrates with electron-donating (Table 2, entries 9–17) and electron-withdrawing (Table 2, entry 18) groups in the *para*-position afforded the target *2H*-1,3-thiazines **2**. Comparison of the reactions forming products **2b**, **2g**, **2j**, and **2p** (Table 2, entries 2, 9, 12 and 18) as well as products **2e** and **2h** (Table 2, entries 7 and 10) shows that the more electron-rich the β -chlorovinyl aldehydes **1**, the better the ratio **2**:**3** and as a consequence the yield of the desired product **2**. By the use of the electron-rich aldehyde **1d** the desired *2H*-1,3-thiazines (**2i–o**) are obtained in good to very good yields.

The formation of *2H*-1,3-thiazines **2** is limited to 2,3-diaryl- β -chlorovinyl aldehydes **1**. Under identical reaction conditions β -chlorovinyl aldehyde **1e** is converted to 1-chloro-2-(dimethoxymethyl)cyclopent-1-ene (**4**).²⁷ Even a change of the solvent (acetonitrile, DMF, 1,4-dioxane) did not lead to the desired *2H*-1,3-thiazine **2**.

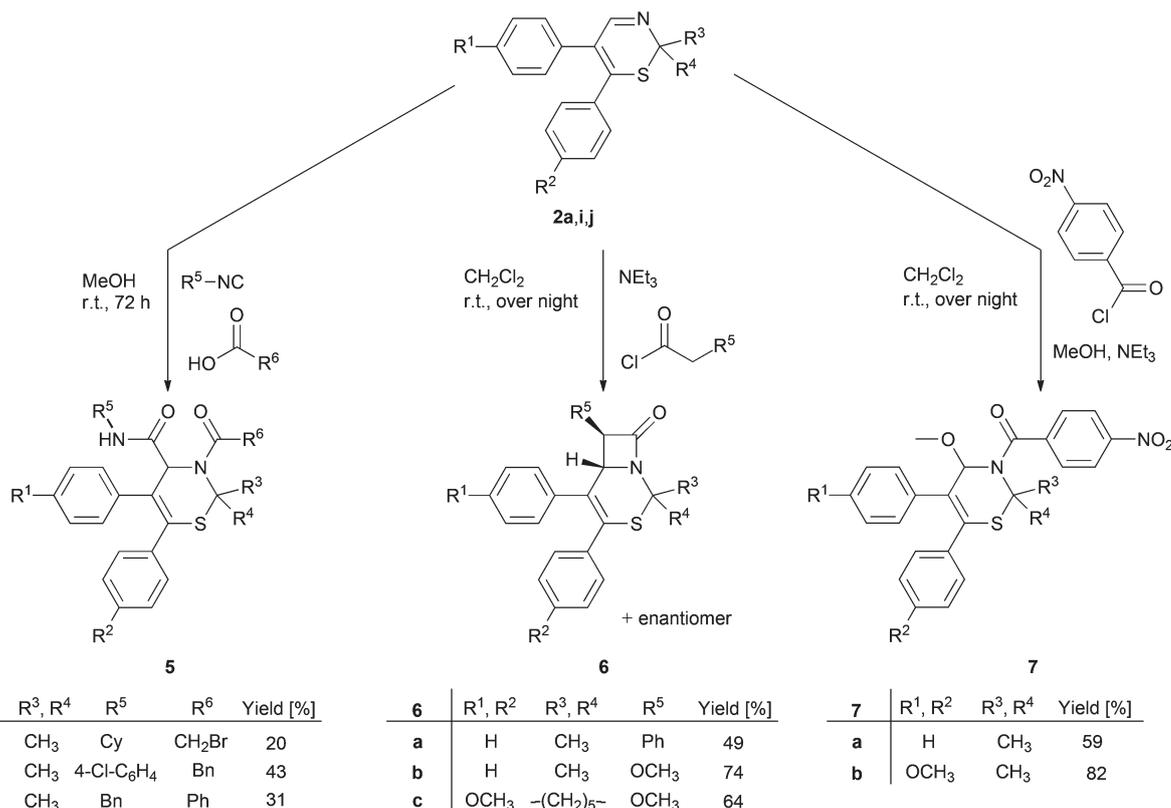
Nevertheless, the depicted results documented that the novel MCR (Table 2) allows the preparation of various *2H*-1,3-thiazines **2** in moderate to excellent yields starting from readily accessible substrates. The synthesis of 2,2-dialkyl- and 2-alkyl-2-aryl-5,6-diaryl-*2H*-1,3-thiazines is reported for the first time.

Derivatization

As mentioned in the Introduction, the *2H*-1,3-thiazines **2** can serve as precursors in subsequent reactions to gain sundry 3,4-dihydro-*2H*-1,3-thiazines.

To investigate the reactivity of the synthesized *2H*-1,3-thiazines **2**, we examined several subsequent reactions, which are typical for imines, *i.e.* Ugi-3CR,²⁸ the Staudinger reaction,²⁹ and addition of acyl chloride^{6b,c} (Scheme 1). By treatment of the imine with an isocyanide and an acid, the Ugi-3CR enables the preparation of bisamides.²⁸ Starting from *2H*-1,3-thiazines **2**, the bisamides **5** were obtained in all cases in moderate yields.

By means of the Staudinger reaction, imines could be converted to β -lactams.²⁹ The *2H*-1,3-thiazines **2** were therefore treated with triethylamine and an acyl chloride. The desired β -lactams **6** were obtained in moderate to good yields. As expected, the ¹H NMR of the crude product revealed the formation of only one racemic diastereomer. We were able to obtain single crystals of **6b** to verify the proposed structure of the β -lactams **6** and as a consequence thereof the constitution of the *2H*-1,3-thiazines **2** by X-ray crystal structure analysis (Fig. 2) in addition to NMR, IR, and mass analysis. Furthermore, the relative configuration between the two stereocenters was determined. Analogously, the relative configuration of the β -lactams **6a** and **6c** was appointed congruent to the configuration documented for the X-ray crystal structure of **6b**. The basis for this conclusion by analogy was the comparison of the coupling constants between the protons at the stereocenters of **6a–c**. Coupling constants of all three β -lactams **6**, situated between 1.5 and 1.8 Hz, are in the same range and are characteristic³⁰ of *trans* β -lactams.



Scheme 1 Subsequent reactions to various 3,4-dihydro-*2H*-1,3-thiazine derivatives: bisamides **5**, β -lactams **6**, methoxy amides **7**.

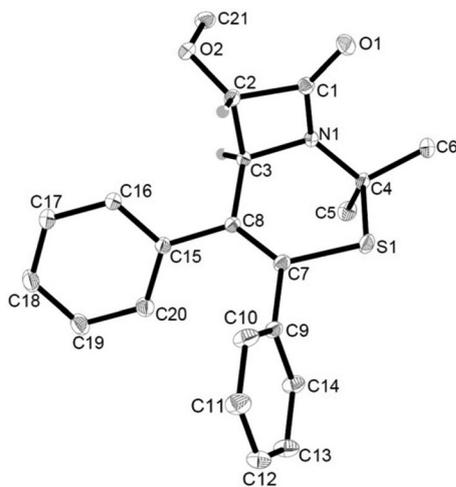


Fig. 2 X-ray crystal structure of the racemic β -lactam **6b** (only one enantiomer is shown).³¹ The atom numbering does not follow the IUPAC nomenclature.

Treatment of imines with acyl chlorides led to the formation of chloro amides. Substitution of the chloride with methanol affords methoxy amides.^{6b,c}

When using alkyl acyl chlorides like pivaloyl chloride to convert the *2H*-1,3-thiazines **2** no reaction was observed. However, treatment of *2H*-1,3-thiazines **2** with more reactive 4-nitrobenzoyl chloride led to the attainment of the desired methoxy amides **7**. Starting from **2a**, the methoxy amide **7a** was obtained in 59% yield. The use of *2H*-1,3-thiazine (**2i**) bearing electron-donating groups results expectably in an appreciable higher yield (82%).

Thus, several compounds containing the 3,4-dihydro-*2H*-1,3-thiazine substructures in addition to another biologically active structure (*i.e.* β -lactam) could be formed based on the synthesized *2H*-1,3-thiazines **2**.

These examples underline the feasibility to create plenty of 3,4-dihydro-*2H*-1,3-thiazine-containing compounds starting from *2H*-1,3-thiazines **2** using diverse subsequent reactions.

Conclusions

Starting from readily accessible β -chlorovinyl aldehydes, we developed a two-step sequence to synthesize various 3,4-dihydro-*2H*-1,3-thiazines. First, *2H*-1,3-thiazines were generated by a new four-component reaction. Characterized by easily accessible substrates, mild conditions, high yields and the toleration of many functional groups this MCR allows the preparation of various previously unknown 2,2-dialkyl- and 2-alkyl-2-aralkyl-5,6-diaryl-*2H*-1,3-thiazines. The shown potential of these *2H*-1,3-thiazines in subsequent reactions gives access to 3,4-dihydro-*2H*-1,3-thiazines. In line with this fact several bisamides, β -lactams and methoxy amides with a *S,N*-heterocyclic ring were synthesized. Exploiting the developed MCR and following the new two-step synthesis route, it is poss-

ible to prepare a great number of products with high diversity, which could be useful in pharmaceutical research.

Experimental

General methods

Synthetic procedures, performed under an argon atmosphere, were performed on a vacuum line using standard Schlenk techniques. Preparative column chromatography was carried out using Grace SiO₂ (0.035–0.070 mm, type KG 60). TLC was performed on Machery–Nagel SiO₂ F254 plates on aluminum sheets. Melting points were obtained on melting point apparatus of Laboratory Devices and are uncorrected. ¹H and ¹³C NMR spectra were recorded with a Bruker AM 300 (measuring frequency: ¹H NMR = 300.1 MHz), a Bruker AMX R 500 (measuring frequency: ¹H NMR = 500.1 MHz, ¹³C NMR = 125.8 MHz) or a Bruker Avance III 500 (measuring frequency: ¹H NMR = 499.9 MHz, ¹³C NMR = 125.7 MHz) spectrometer in CDCl₃ or DMSO-*d*₆ solution. Chemical shifts are referenced to the residual peaks of the solvent [CDCl₃: 7.26 ppm (¹H NMR), 77.16 ppm (¹³C NMR); DMSO-*d*₆: 2.50 ppm (¹H NMR), 39.53 ppm (¹³C NMR)].³² Assignments of the signals were supported by measurements applying DEPT and COSY techniques. Mass spectra were obtained on a Waters Q-TOF Premier (ESI) and a Finnigan MAT 95 (EI) spectrometer. The IR spectra were recorded with a Bruker Tensor 27 spectrometer equipped with a “Golden Gate” diamond-ATR (attenuated total reflection) unit. Elemental analyses were performed with a Eurovector EA3000.

(*E*)-, (*Z*)-, (*EZ*)-2-Chloro-2,3-diphenylacrylaldehyde²¹ (**1a**), (*EZ*)-3-chloro-3-(4-chlorophenyl)-2-phenylacrylaldehyde²² (**1b**), (*E*)-3-chloro-2,3-bis(4-methoxyphenyl)acrylaldehyde²¹ (**1d**), 2-chloro-1-cyclopentene-1-carboxaldehyde²³ (**1e**), and 1,2-bis-(4-nitrophenyl)ethan-1-one³³ were prepared according to published procedures. CH₂Cl₂ was refluxed with CaH and freshly distilled prior to use. MeOH was refluxed with Mg and freshly distilled prior to use. Et₃N was dried over molecular sieves (3 Å) and freshly distilled prior to use.

(*EZ*)-3-Chloro-3-(4-hydroxyphenyl)-2-phenylacrylaldehyde (**1c**). Under an argon atmosphere, POCl₃ (8.670 g, 56.55 mmol) and DMF (4.133 g, 56.55 mmol), dissolved in 15 mL anhydrous CH₂Cl₂, were cooled down to 0–5 °C. 1-(4-Hydroxyphenyl)-2-phenylethan-1-one (4.000 g, 18.85 mmol) was added dropwise. After stirring for 40 h at r.t., the reaction mixture was brought to pH 7 by addition of saturated aqueous Na₂CO₃ solution and extracted with EtOAc (3 × 150 mL). The combined organic phases were washed with a saturated aqueous NaCl solution (2 × 150 mL), dried (MgSO₄) and the solvent was removed on a rotary evaporator. Analysis of the crude product by ¹H NMR spectroscopy revealed the formation of both isomers in a ratio of 76:24 ((*E*)-**1c**:(*Z*)-**1c**). Column chromatography (*n*-hexane–EtOAc, 5:1; *R*_f = 0.06) afforded the desired (*EZ*)- β -chlorovinyl aldehyde (*EZ*)-**1c** as a mixture of both isomers (3.507 mg, 72%; (*E*)-/(*Z*)-isomer 75:25) as a yellow solid, mp 160–161 °C (from CH₂Cl₂–*n*-hexane); IR (ATR)

$\tilde{\nu}$ 3392, 3063, 2892, 1648, 1602, 1576, 1507, 1489, 1433, 1373, 1271, 1232, 1212, 1173, 1083, 902, 828, 766, 707, 635 cm^{-1} ; ^1H NMR (500.1 MHz, CDCl_3): δ 5.26 (1 H, br s, OH^Z), 5.71 (1 H, br s, OH^E), 6.61–6.64 [2 H, m, 2 $m\text{-CH}_{\text{Ar}}(\text{CCl})^Z$], 6.90–6.93 [2 H, m, 2 $m\text{-CH}_{\text{Ar}}(\text{CCl})^E$], 7.00–7.01 [2 H, m, 2 $m\text{-CH}_{\text{Ar}}(\text{CCHO})^Z$], 7.17–7.20 [2 H, m, 2 $o\text{-CH}_{\text{Ar}}(\text{CCl})^Z$], 7.25–7.30 [5 H, m, 2 $m\text{-CH}_{\text{Ar}}(\text{CCHO})^E$, 2 $o\text{-CH}_{\text{Ar}}(\text{CCHO})^Z$, $p\text{-CH}_{\text{Ar}}(\text{CCHO})^Z$], 7.38–7.41 [1 H, m, $p\text{-CH}_{\text{Ar}}(\text{CCHO})^E$], 7.44–7.49 [4 H, m, 2 $o\text{-CH}_{\text{Ar}}(\text{CCHO})^E$, 2 $o\text{-CH}_{\text{Ar}}(\text{CCl})^E$], 9.67 (1 H, s, CHO^E), 10.57 (1 H, s, CHO^Z) ppm; ^{13}C NMR (125.8 MHz, CDCl_3): δ 115.10 [2 $m\text{-CH}_{\text{Ar}}(\text{CCl})^Z$], 115.68 [2 $m\text{-CH}_{\text{Ar}}(\text{CCl})^E$], 128.09 [$p\text{-CH}_{\text{Ar}}(\text{CCHO})^Z$], 128.16 ($\text{C}_{\text{Ar}}\text{CCl}^E$), 128.43 [2 $o\text{-CH}_{\text{Ar}}(\text{CCHO})^E$], 128.51, 128.53 [2 $o\text{-CH}_{\text{Ar}}(\text{CCHO})^Z$, $p\text{-CH}_{\text{Ar}}(\text{CCHO})^E$], 129.67 ($\text{C}_{\text{Ar}}\text{CCl}^Z$), 129.98 [2 $m\text{-CH}_{\text{Ar}}(\text{CCHO})^E$], 130.76 [2 $m\text{-CH}_{\text{Ar}}(\text{CCHO})^Z$], 132.00 [2 $o\text{-CH}_{\text{Ar}}(\text{CCl})^Z$], 132.56 [2 $o\text{-CH}_{\text{Ar}}(\text{CCl})^E$], 134.32 ($\text{C}_{\text{Ar}}\text{CCHO}^Z$), 134.35 ($\text{C}_{\text{Ar}}\text{CCHO}^E$), 136.60 (CCHO^Z), 140.13 (CCHO^E), 155.99 (CCl^E), 156.02 (CCl^Z), 157.30 ($\text{C}_{\text{Ar}}\text{OH}^Z$), 158.54 ($\text{C}_{\text{Ar}}\text{OH}^E$), 190.53 (CHO^E), 191.84 (CHO^Z) ppm; MS (ESI): m/z 281.1 ($\text{M} + \text{Na}^+$, 100%); HRMS (ESI): Found 281.0342; Calc. for $\text{C}_{15}\text{H}_{11}\text{NaO}_2\text{Cl}$ [$\text{M} + \text{Na}$] $^+$ 281.0345.

(E)-3-Chloro-2,3-bis(4-nitrophenyl)acrylaldehyde and (E)-3-chloro-2,3-bis(4-nitrophenyl)acrylaldehyde (1f). Under an argon atmosphere, 1,2-bis(4-nitrophenyl)ethan-1-one (4.500 g, 15.72 mmol) and DMF (2.298 g, 31.44 mmol), dissolved in 9 mL anhydrous CH_2Cl_2 , were cooled down to 0–5 °C. POCl_3 (4.821 g, 31.44 mmol) was added dropwise. After stirring for 20 h at 45 °C, the reaction mixture was brought to pH 7 by addition of saturated aqueous Na_2CO_3 solution and extracted with EtOAc (3 \times 90 mL). The combined organic phases were washed with a saturated aqueous NaCl solution (2 \times 90 mL), dried (MgSO_4) and the solvent was removed on a rotary evaporator. Analysis of the crude product by ^1H NMR spectroscopy revealed the formation of both isomers in a ratio of 59:41 ((E)-**1f**:**(Z)-1f**). Column chromatography (*n*-hexane–EtOAc, 7:3; (E)-**1f**, R_f = 0.44; (Z)-**1f**, R_f = 0.43) afforded the desired (E)- β -chlorovinyl aldehyde (E)-**1f** (406 mg, 8%) as a yellow solid, mp 232 °C (from CH_2Cl_2 -*n*-hexane); IR (ATR) $\tilde{\nu}$ 3107, 3071, 1685, 1601, 1510, 1408, 1343, 1295, 1220, 857, 849, 812, 727, 695 cm^{-1} ; ^1H NMR (500.1 MHz, $\text{DMSO}-d_6$): δ 7.65–7.68 [2 H, m, 2 $o\text{-CH}_{\text{Ar}}(\text{C})$], 8.04–8.07 [2 H, m, 2 $o\text{-CH}_{\text{Ar}}(\text{C})$], 8.34–8.36 [2 H, m, 2 $m\text{-CH}_{\text{Ar}}(\text{C})$], 8.40–8.43 [2 H, m, 2 $m\text{-CH}_{\text{Ar}}(\text{C})$], 9.50 (1 H, s, CHO) ppm; ^{13}C NMR (125.8 MHz, $\text{DMSO}-d_6$): δ 123.31, 123.90 [4 $m\text{-CH}_{\text{Ar}}(\text{C})$], 131.38, 131.59 [4 $o\text{-CH}_{\text{Ar}}(\text{C})$], 139.86 (CCHO), 140.55, 140.82 (2 C_{Ar}), 147.36, 148.67 (2 NC_{Ar}), 150.85 (CCl), 188.04 (CHO) ppm; MS (EI, 70 eV): m/z 231.7 (M^+ , 20%); HRMS (EI): Found 332.0196; Calc. for $\text{C}_{15}\text{H}_9\text{ClN}_2\text{O}_5$ [$\text{M} + \text{H}$] $^+$ 332.0195. The (Z)- β -chlorovinyl aldehyde (Z)-**1e** was obtained as a mixture of both isomers (576 mg, 11%; (E)-/(Z)-isomer 74:26) as a yellow solid; ^1H NMR (500.1 MHz, CDCl_3): δ 7.16–7.18 [m, 2 H, 2 $o\text{-CH}_{\text{Ar}}(\text{C})$], 7.43–7.44 [m, 2 H, 2 $o\text{-CH}_{\text{Ar}}(\text{C})$], 8.11–8.13 [m, 4 H, 4 $m\text{-CH}_{\text{Ar}}(\text{C})$], 10.58 (s, 1 H, CHO) ppm; ^{13}C NMR (125.8 MHz, CDCl_3): δ 123.82, 123.93 [4 $m\text{-CH}_{\text{Ar}}(\text{C})$], 130.57, 131.75 [4 $o\text{-CH}_{\text{Ar}}(\text{C})$], 137.56 (CCHO), 139.49, 142.60 (2 C_{Ar}), 147.83, 148.57 (2 NC_{Ar}), 148.95 (CCl), 188.79 (CHO) ppm.

General procedure (GP A)

The respective β -chlorovinyl aldehyde (1.0 equiv.) was dissolved in MeOH (5 mL per mmol β -chlorovinyl aldehyde). $\text{NaSH}\cdot\text{H}_2\text{O}$ (1.5 equiv.) was added and the solution was stirred for 3 h at r.t. After addition of the respective carbonyl compound (3.0 equiv.), a mixture of aqueous ammonia solution (2.0 equiv., 25%) and MeOH (5 mL per mmol β -chlorovinyl aldehyde) was added dropwise within 1 h. After stirring overnight at r.t., the reaction mixture was poured into water (10 mL per mmol β -chlorovinyl aldehyde) and extracted with CH_2Cl_2 (3 \times 10 mL per mmol β -chlorovinyl aldehyde). The combined organic phases were dried (MgSO_4), the solvent was removed on a rotary evaporator and the crude product was purified by column chromatography on silica gel or by recrystallization.

2,2-Dimethyl-5,6-diphenyl-2H-1,3-thiazine (2a) and 4,5-diphenylisothiazole.³⁴ (3a). Following GP A, aldehyde (E)-**1a** (485 mg, 2.00 mmol), $\text{NaSH}\cdot\text{H}_2\text{O}$ (222 mg, 3.00 mmol), acetone (348 mg, 6.00 mmol) and 25% aqueous ammonia solution (272 mg, 4.00 mmol) were used. Analysis of the crude product by ^1H NMR spectroscopy revealed the formation of both title compounds in a ratio of 79:21 (**2a**:**3a**). Column chromatography (*n*-hexane–EtOAc, 7:3; thiazine **2a**, R_f = 0.43; isothiazole **3a**, R_f = 0.34) afforded the desired thiazine **2a** (352 mg, 63%) as a greenish-yellow solid, mp 70 °C (from CH_2Cl_2 -*n*-hexane); IR (ATR) $\tilde{\nu}$ 3076, 3057, 3019, 2970, 2928, 1622, 1599, 1531, 1484, 1459, 1442, 1361, 1196, 1175, 875, 767, 756, 695, 665 cm^{-1} ; ^1H NMR (500.1 MHz, CDCl_3): δ 1.72 [6 H, s, $\text{C}(\text{CH}_3)_2$], 7.11–7.13 (2 H, m, 2 CH_{Ar}), 7.16–7.26 (8 H, m, 8 CH_{Ar}), 8.01 (1 H, s, NCH) ppm; ^{13}C NMR (125.8 MHz, CDCl_3): δ 28.99 [$\text{C}(\text{CH}_3)_2$], 63.59 [$\text{C}(\text{CH}_3)_2$], 126.46 ($\text{CHC}=\text{C}$), 126.94 ($p\text{-CH}_{\text{Ar}}$), 128.19, 128.66, 128.84 (4 $m\text{-CH}_{\text{Ar}}$, 2 $o\text{-CH}_{\text{Ar}}$), 129.10 ($p\text{-CH}_{\text{Ar}}$), 130.67 (2 $o\text{-CH}_{\text{Ar}}$), 136.67 ($\text{C}_{\text{Ar}}\text{CS}$), 137.39 ($\text{C}_{\text{Ar}}\text{CCH}$), 143.98 ($\text{CHC}=\text{C}$), 158.22 ($\text{C}=\text{N}$) ppm; MS (ESI): m/z 280.2 ($\text{M} + \text{H}^+$, 100%); HRMS (ESI): Found 280.1152; Calc. for $\text{C}_{18}\text{H}_{18}\text{NS}$ [$\text{M} + \text{H}$] $^+$ 280.1160. The isothiazole³⁴ **3a** (66 mg, 14%) was obtained as a brown oil; ^1H NMR (500.1 MHz, CDCl_3): δ 7.31–7.33 (10 H, m, 10 CH_{Ar}), 8.52 (1 H, s, NCH) ppm; ^{13}C NMR (125.8 MHz, CDCl_3): δ 128.75, 128.79, 128.95, 128.97 (4 $o\text{-CH}_{\text{Ar}}$, 4 $m\text{-CH}_{\text{Ar}}$), 129.06 (2 $p\text{-CH}_{\text{Ar}}$), 130.55 ($\text{CHC}=\text{C}$), 132.87, 135.65 (C_{Ar}), 159.18 ($\text{C}=\text{N}$), 161.57 ($\text{CHC}=\text{C}$) ppm.

2,3-Diphenyl-1-thia-5-azaspiro[5.5]undeca-2,4-diene (2b) and 4,5-diphenylisothiazole.³⁴ (3a). Following GP A, aldehyde (E)-**1a** (485 mg, 2.00 mmol), $\text{NaSH}\cdot\text{H}_2\text{O}$ (222 mg, 3.00 mmol), cyclohexanone (589 mg, 6.00 mmol) and 25% aqueous ammonia solution (272 mg, 4.00 mmol) were used. Analysis of the crude product by ^1H NMR spectroscopy revealed the formation of both title compounds in a ratio of 95:05 (**2b**:**3a**). Column chromatography (*n*-hexane–EtOAc, 9:1; thiazine **2b**, R_f = 0.29; isothiazole **3a**, R_f = 0.16) afforded the desired thiazine **2b** (368 mg, 58%) as a yellow solid, mp 116 °C (from CH_2Cl_2 -*n*-hexane); IR (ATR) $\tilde{\nu}$ 3078, 3060, 3025, 2926, 2855, 1623, 1600, 1539, 1485, 1459, 1445, 757, 716, 694, 662 cm^{-1} ; ^1H NMR (500.1 MHz, CDCl_3): δ 1.43–1.51 (1 H, m, CH_2 ,_{Cy}), 1.67–1.72 (1 H, m, CH_2 ,_{Cy}), 1.76–1.80 (4 H, m, 3 CH_2 ,_{Cy}), 1.97–2.03 (2 H, m, 2 CH_2 ,_{Cy}), 2.12–2.16 (2 H, m, 2 CH_2 ,_{Cy}),

7.11–7.12 (2 H, m, 2 CH_{Ar}), 7.16–7.26 (8 H, m, 8 CH_{Ar}), 8.06 (1 H, s, NCH) ppm; ¹³C NMR (125.8 MHz, CDCl₃): δ 22.24, 25.85, 37.28 (5 CH_{2,Cy}), 67.99 [C(CH₂)₂], 126.87 (*p*-CH_{Ar}), 126.91 (CHC=C), 128.14, 128.63, 128.79 (4 *m*-CH_{Ar}, 2 *o*-CH_{Ar}), 129.03 (*p*-CH_{Ar}), 130.84 (2 *o*-CH_{Ar}), 136.84 (C_{Ar}CS), 137.42 (C_{Ar}CCH), 143.11 (CHC=C), 158.10 (C=N) ppm; MS (ESI): *m/z* 320.3 (M + H⁺, 100%); HRMS (ESI): Found 320.1468; Calc. for C₂₁H₂₂NS [M + H]⁺ 320.1473. The isothiazole³⁴ **3a** (14 mg, 3%) was obtained as a brown oil.

2,3-Diphenyl-1,9-dithia-5-azaspiro[5.5]undeca-2,4-diene (2c) and 4,5-diphenylisothiazole.³⁴ (**3a**). Following GP A, aldehyde (*EZ*)-**1a** (485 mg, 2.00 mmol), NaSH·H₂O (222 mg, 3.00 mmol), tetrahydro-4*H*-thiopyran-4-one (697 mg, 6.00 mmol) and 25% aqueous ammonia solution (272 mg, 4.00 mmol) were used. Analysis of the crude product by ¹H NMR spectroscopy revealed the formation of both title compounds in a ratio of 96:04 (**2c**:**3a**). Recrystallization from MeOH-*n*-hexane afforded the desired thiazine **2c** (445 mg, 66%) as a yellow solid, mp 123–124 °C; IR (ATR) $\tilde{\nu}$ 3059, 3014, 2938, 2906, 1621, 1574, 1533, 1482, 1442, 1425, 1414, 1271, 1237, 1195, 1094, 1037, 920, 876, 816, 760, 691, 662 cm⁻¹; ¹H NMR (500.1 MHz, CDCl₃): δ 2.39–2.41 [4 H, m, C(CH₂)₂], 2.87–2.97 [4 H, m, S(CH₂)₂], 7.10–7.13 (2 H, m, 2 CH_{Ar}), 7.18–7.25 (8 H, m, 8 CH_{Ar}), 8.09 (1 H, s, NCH) ppm; ¹³C NMR (125.8 MHz, CDCl₃): δ 24.35 [S(CH₂)₂], 38.28 [C(CH₂)₂], 66.75 [C(CH₂)₂], 126.86 (CHC=C), 127.09 (*p*-CH_{Ar}), 128.26, 128.74 (6 CH_{Ar}), 129.30 (*p*-CH_{Ar}), 130.80 (2 CH_{Ar}), 136.36 (C_{Ar}CS), 137.01 (C_{Ar}CCH), 142.29 (CHC=C), 158.45 (C=N) ppm; MS (ESI): *m/z* 338.0 (M + H⁺, 100%); HRMS (ESI): Found 338.1037; Calc. for C₂₀H₂₀NS₂ [M + H]⁺ 338.1037. The isolation of the isothiazole³⁴ **3a** was consciously abandoned.

(RS)-2-Isobutyl-5,6-diphenyl-2*H*-1,3-thiazine (2d) and 4,5-diphenylisothiazole.³⁴ (**3a**). Following GP A, aldehyde (*EZ*)-**1a** (485 mg, 2.00 mmol), NaSH·H₂O (222 mg, 3.00 mmol), isopentanal (517 mg, 6.00 mmol) and 25% aqueous ammonia solution (272 mg, 4.00 mmol) were used. Analysis of the crude product by ¹H NMR spectroscopy revealed the formation of both title compounds in a ratio of 98:02 (**2d**:**3a**). Column chromatography (*n*-hexane–EtOAc, 9:1; thiazine **2d**, R_f = 0.29) afforded the desired thiazine **2c** (345 mg, 56%) as an orange oil; IR (ATR) $\tilde{\nu}$ 3057, 3025, 2955, 2930, 1683, 1598, 1525, 1484, 1466, 1444, 1367, 1197, 1172, 759, 694, 664 cm⁻¹; ¹H NMR (500.1 MHz, CDCl₃): δ 1.04 [6 H, d, ³J = 6.5 Hz, CH(CH₃)₂], 1.86–1.92, 2.01–2.07 (2 H, 2 m, CH₂), 2.09–2.14 [1 H, m, CH(CH₃)₂], 4.73 (1 H, ddd, ³J = 7.1 Hz, ³J = 7.1 Hz, ⁴J = 1.9 Hz, SCH), 7.13–7.28 (10 H, m, 10 CH_{Ar}), 8.12 (1 H, d, ⁴J = 1.9 Hz, NCH) ppm; ¹³C NMR (125.8 MHz, CDCl₃): δ 22.26, 22.81 [CH(CH₃)₂], 25.12 [CH(CH₃)₂], 43.87 (CH₂), 60.47 (SCH), 126.99 (*p*-CH_{Ar}), 128.17 (2 CH_{Ar}), 128.64 (CHC=C), 128.65, 128.77 (4 CH_{Ar}), 129.23 (*p*-CH_{Ar}), 131.04 (2 *o*-CH_{Ar}), 136.36 (C_{Ar}CS), 137.06 (C_{Ar}CCH), 145.75 (CHC=C), 160.28 (C=N) ppm; MS (ESI): *m/z* 308.2 (M + H⁺, 100%); HRMS (ESI): Found 308.1465; Calc. for C₂₀H₂₂NS [M + H]⁺ 308.1473. The isolation of the isothiazole³⁴ **3a** was consciously abandoned.

(RS)-2-Phenethyl-5,6-diphenyl-2*H*-1,3-thiazine (2e) and 4,5-diphenylisothiazole.³⁴ (**3a**). Following GP A, aldehyde (*EZ*)-**1a**

(485 mg, 2.00 mmol), NaSH·H₂O (222 mg, 3.00 mmol), 3-phenylpropanal (805 mg, 6.00 mmol) and 25% aqueous ammonia solution (272 mg, 4.00 mmol) were used. Analysis of the crude product by ¹H NMR spectroscopy revealed the formation of both title compounds in a ratio of 95:05 (**2e**:**3a**). Recrystallization from MeOH-*n*-hexane afforded the desired thiazine **2e** (421 mg, 59%) as a yellow solid, mp 91–92 °C; IR (ATR) $\tilde{\nu}$ 3050, 3029, 2994, 2917, 2859, 1607, 1511, 1480, 1450, 1441, 1281, 1154, 1095, 1026, 883, 768, 745, 699 cm⁻¹; ¹H NMR (500.1 MHz, CDCl₃): δ 2.34–2.49 (2 H, m, CHCH₂), 2.96–3.05 (2 H, m, C_{Ar}CH₂), 4.71 (1 H, ddd, ³J = 6.5 Hz, ³J = 6.5 Hz, ⁴J = 1.8 Hz, SCH), 7.14–7.35 (15 H, m, 15 CH_{Ar}), 8.16 (1 H, d, ⁴J = 1.8 Hz, NCH) ppm; ¹³C NMR (125.8 MHz, CDCl₃): δ 32.23 (CHCH₂), 36.30 (C_{Ar}CH₂), 61.41 (SCH), 126.19, 127.03 (2 *p*-CH_{Ar}), 128.20 (2 CH_{Ar}), 128.62 (CHC=C), 128.64, 128.67, 128.74, 128.78 (8 CH_{Ar}), 129.28 (*p*-CH_{Ar}), 131.03 (2 CH_{Ar}), 136.32 (C_{Ar}CS), 137.01 (C_{Ar}CCH), 141.34 (C_{Ar}CH₂), 145.49 (CHC=C), 160.45 (C=N) ppm; MS (ESI): *m/z* 356.1 (M + H⁺, 100%); HRMS (ESI): Found 356.1462; Calc. for C₂₄H₂₂NOS [M + H]⁺ 356.1473. The isolation of the isothiazole³⁴ **3a** was consciously abandoned.

(RS)-2-{2-[(Benzyloxycarbonyl)amino]ethyl}-5,6-diphenyl-2*H*-1,3-thiazine (2f) and 4,5-diphenylisothiazole.³⁴ (**3a**). Following GP A, aldehyde (*EZ*)-**1a** (243 mg, 1.00 mmol), NaSH·H₂O (111 mg, 1.50 mmol), 3-[(benzyloxycarbonyl)amino]propanal (622 mg, 3.00 mmol) and 25% aqueous ammonia solution (136 mg, 2.00 mmol) were used. Analysis of the crude product by ¹H NMR spectroscopy revealed the formation of both title compounds in a ratio of 86:14 (**2f**:**3a**). Column chromatography (*n*-hexane–acetone–toluene, 4:3:3; thiazine **2f**, R_f = 0.43) afforded the desired thiazine **2f** (201 mg, 47%) as a yellow oil; IR (ATR) $\tilde{\nu}$ 3326, 3265, 3059, 3032, 2941, 1700, 1599, 1512, 1443, 1244, 1136, 1027, 759, 694 cm⁻¹; ¹H NMR (500.1 MHz, CDCl₃): δ 2.26–2.36 (2 H, m, CHCH₂), 3.52–3.59, 3.60–3.67 (2 H, 2 m, NCH₂), 4.76 (1 H, ddd, ³J = 6.7 Hz, ³J = 6.7 Hz, ⁴J = 1.4 Hz, SCH), 5.14 (2 H, s, C_{Ar}CH₂), 5.66 (1 H, dd, ³J = 5.3 Hz, ³J = 5.3 Hz, NH), 7.13–7.40 (15 H, m, 15 CH_{Ar}), 8.13 (1 H, d, ⁴J = 1.4 Hz, NCH) ppm; ¹³C NMR (125.8 MHz, CDCl₃): δ 34.24 (CHCH₂), 38.51 (NCH₂), 60.40 (SCH), 66.71 (C_{Ar}CH₂), 127.06, 128.14, 128.18, 128.22 (5 CH_{Ar}, CHC=C), 128.57, 128.66, 128.69, 129.37, 131.01 (10 CH_{Ar}), 135.94 (C_{Ar}CS), 136.71 (C_{Ar}CCH, C_{Ar}CH₂), 146.03 (CHC=C), 156.51 (C=O), 160.75 (C=N) ppm; MS (ESI): *m/z* 429.2 (M + H⁺, 100%); HRMS (ESI): Found 429.1626; Calc. for C₂₆H₂₄N₂O₂S [M + H]⁺ 429.1637. The isolation of the isothiazole³⁴ **3a** was consciously abandoned.

2-(4-Chlorophenyl)-3-phenyl-1-thia-5-azaspiro[5.5]undeca-2,4-diene (2g) and 5-(4-chlorophenyl)-4-diphenylisothiazole (3b). Following GP A, aldehyde (*EZ*)-**1b** (275 mg, 0.99 mmol), NaSH·H₂O (110 mg, 1.49 mmol), acetone (172 mg, 2.97 mmol) and 25% aqueous ammonia solution (135 mg, 1.98 mmol) were used. Analysis of the crude product by ¹H NMR spectroscopy revealed the formation of both title compounds in a ratio of 97:03 (**2g**:**3b**). Column chromatography (*n*-hexane–MTBE, 9:1; thiazine **2g**, R_f = 0.13) afforded the desired thiazine **2g** (223 mg, 72%) as a yellow solid, mp 101 °C (from

CH₂Cl₂-*n*-hexane); IR (ATR) $\tilde{\nu}$ 2932, 2894, 2855, 1672, 1619, 1595, 1586, 1532, 1480, 1443, 1369, 1266, 1244, 1087, 1055, 1014, 884, 830, 821, 765, 737 cm⁻¹; ¹H NMR (500.1 MHz, CDCl₃): δ 1.42–1.50 (1 H, m, CH_{2,Cy}), 1.66–1.72 (1 H, m, CH_{2,Cy}), 1.74–1.79 (4 H, m, 2 CH_{2,Cy}), 1.96–2.01 (2 H, m, 2 CH_{2,Cy}), 2.09–2.13 (2 H, m, 2 CH_{2,Cy}), 7.09–7.11 (2 H, m, CH_{Ar}), 7.15–7.25 (7 H, m, CH_{Ar}), 8.04 (1H, s, NCH) ppm; ¹³C NMR (125.8 MHz, CDCl₃): δ 22.23, 25.81, 37.28 (5 CH_{2,Cy}), 68.17 [C(CH₂)₂], 127.12 (*p*-CH_{Ar}), 127.19 (CHC=C), 128.46, 128.73, 128.83, 132.14 (4 *o*-CH_{Ar}, 4 *m*-CH_{Ar}), 135.07, 135.36 (C_{Ar}CS, C_{Ar}Cl), 137.06 (C_{Ar}CCH), 141.66 (CHC=C), 157.99 (C=N) ppm; MS (ESI): *m/z* 354.1 (M + H⁺, 100%); HRMS (ESI): Found 354.1075, Calc. for C₂₁H₂₁ClNS [M + H]⁺ 354.1083. The isothiazole **3b** was further purified by a second column chromatography (*n*-hexane–CH₂Cl₂–toluene–EtOH, 6 : 2 : 1 : 1; R_f = 0.62). The isothiazole was obtained (8 mg, 3%) as a colorless solid, mp 115 °C; IR (ATR) $\tilde{\nu}$ 3082, 3060, 3036, 3029, 2959, 1594, 1576, 1495, 1481, 1397, 1261, 1208, 1089, 1015, 894, 825, 793, 758, 736, 700, 629, 542 cm⁻¹; ¹H NMR (499.9 MHz, CDCl₃): δ 7.25–7.38 (9 H, m, 9 CH_{Ar}), 8.51 (1 H, s, NCH) ppm; ¹³C NMR (125.7 MHz, CDCl₃): δ 128.02 [*p*-CH_{Ar}(C)], 129.00, 129.04 (4 CH_{Ar}), 129.18 (CHC=C), 129.33, 130.09 (4 CH_{Ar}), 132.67 (C_{Ar}CS), 135.31 (C_{Ar}Cl), 136.12 (C_{Ar}CCH), 159.33 (C=N), 160.24 (CHC=C) ppm; MS (ESI): *m/z* 272.1 (M + H⁺, 100%); HRMS (ESI): Found 272.0302, Calc. for C₁₅H₁₁ClNS [M + H]⁺ 272.0301.

(RS)-6-(4-Hydroxyphenyl)-2-phenethyl-5-phenyl-2H-1,3-thiazine (2h) and 5-(4-hydroxyphenyl)-4-phenylisothiazole (3c). Following GP A, aldehyde (*EZ*)-**1c** (388 mg, 1.50 mmol), NaSH·H₂O (167 mg, 2.25 mmol), 3-phenylpropanal (604 mg, 4.50 mmol) and 25% aqueous ammonia solution (204 mg, 3.00 mmol) were used. Analysis of the crude product by ¹H NMR spectroscopy revealed the formation of both title compounds in a ratio of 94 : 4 (**2h** : **3c**). Column chromatography (*n*-hexane–EtOAc–CH₂Cl₂, 6 : 2 : 2; thiazine **2h**, R_f = 0.29; isothiazole **3c**, R_f = 0.47) afforded the desired thiazine **2h** (429 mg, 77%) as a yellow solid, mp 198–200 °C (decomp.; from CH₂Cl₂–*n*-hexane); IR (ATR) $\tilde{\nu}$ 3029, 3990, 2917, 2854, 2661, 1598, 1574, 1495, 1475, 1438, 1289, 1217, 1171, 1090, 958, 840, 767, 744, 700 cm⁻¹; ¹H NMR (500.1 MHz, DMSO-*d*₆): δ 2.19–2.31 (2 H, m, CHCH₂), 2.89–2.92 (2 H, m, C_{Ar}CH₂), 4.62 (1 H, ddd, ³J = 6.4 Hz, ³J = 6.4 Hz, ⁴J = 1.7 Hz, SCH), 6.60–6.62 [2 H, m, 2 *m*-CH_{Ar}(CS)], 7.06–7.08 [2 H, m, 2 *o*-CH_{Ar}(CS)], 7.17–7.32 (10 H, m, 10 CH_{Ar}), 8.13 (1 H, d, ⁴J = 1.7 Hz, NCH), 9.86 (1 H, s, OH) ppm; ¹³C NMR (125.8 MHz, DMSO-*d*₆): δ 31.53 (CHCH₂), 35.77 (C_{Ar}CH₂), 60.97 (SCH), 115.10 [2 *m*-CH_{Ar}(CS)], 125.94 (*p*-CH_{Ar}), 126.15 (C_{Ar}CS), 126.61 (*p*-CH_{Ar}), 127.12 (CHC=C), 128.40, 128.43, 128.47, 128.55 (8 CH_{Ar}), 132.31 [2 *o*-CH_{Ar}(CS)], 136.99 (C_{Ar}CCH), 141.22 (C_{Ar}CH₂), 144.06 (CHC=C), 158.61 (C_{Ar}OH), 159.91 (C=N) ppm; MS (ESI): *m/z* 372.1 (M + H⁺, 100%); HRMS (ESI): Found 372.1417, Calc. for C₂₄H₂₂NOS [M + H]⁺ 372.1422. The isothiazole³⁴ **3c** (15 mg, 4%) was obtained as a colorless solid, mp 220–221 °C; IR (ATR) $\tilde{\nu}$ 3114, 2801, 2730, 2667, 1612, 1586, 1542, 1510, 1402, 1280, 1209, 1173, 827, 762, 695, 657 cm⁻¹; ¹H NMR (499.9 MHz, DMSO-*d*₆): δ 6.77–6.80 [2 H, m, 2 *o*-CH_{Ar}(OH)], 7.12–7.15 [2 H, m, 2 *m*-CH_{Ar}(OH)], 7.32–7.39 (5 H, m, 5 CH_{Ar}),

8.63 (1 H, s, NCH), 9.90 (1 H, br s, OH) ppm; ¹³C NMR (125.7 MHz, DMSO-*d*₆): δ 115.97 [2 *o*-CH_{Ar}(OH)], 120.28 (C_{Ar}CS), 127.67 [*p*-CH_{Ar}(CCH)], 128.69, 128.78 [2 *o*-CH_{Ar}(CCH), 2 *m*-CH_{Ar}(CCH)], 129.78 [2 *m*-CH_{Ar}(OH)], 132.61 (CHC=C), 134.42 (C_{Ar}CCH), 158.50 (C_{Ar}OH), 159.72 (C=N), 161.33 (CHC=C) ppm; MS (ESI): *m/z* 276.0 (M + Na⁺, 100%); HRMS (ESI): Found 276.0455, Calc. for C₁₅H₁₁NNaOS [M + Na]⁺ 276.0459.

5,6-Bis(4-methoxyphenyl)-2,2-dimethyl-2H-1,3-thiazine (2i) and 4,5-bis(4-methoxyphenyl)isothiazole.^{25a} (3d). Following GP A, aldehyde (*E*)-**1d** (303 mg, 1.00 mmol), NaSH·H₂O (111 mg, 1.50 mmol), acetone (174 mg, 3.00 mmol) and 25% aqueous ammonia solution (136 mg, 2.00 mmol) were used. Analysis of the crude product by ¹H NMR spectroscopy revealed the formation of both title compounds in a ratio of 86 : 14 (**2i** : **3d**). Column chromatography (*n*-hexane–EtOAc, 9 : 1; thiazine **2i**, R_f = 0.11, isothiazole **3d**, R_f = 0.22) afforded the desired thiazine **2i** (267 mg, 79%) as an orange oil; IR (ATR) $\tilde{\nu}$ 3031, 2999, 2966, 2929, 2835, 1666, 1621, 1573, 1508, 1495, 1460, 1440, 1291, 1243, 1197, 1172, 828, 805, 787 cm⁻¹; ¹H NMR (500.1 MHz, CDCl₃): δ 1.67 [6 H, s, C(CH₃)₂], 3.76, 3.76 (6 H, 2 s, 2 OCH₃), 6.70–6.73 [2 H, m, 2 *m*-CH_{Ar}(CS)], 6.76–6.79 [2 H, m, 2 *m*-CH_{Ar}(CCH)], 7.03–7.06 [2 H, m, 2 *o*-CH_{Ar}(CCH)], 7.18–7.21 [2 H, m, 2 *o*-CH_{Ar}(CS)], 7.96 (1 H, s, NCH) ppm; ¹³C NMR (125.8 MHz, CDCl₃): δ 28.96 [C(CH₃)₂], 55.34 (2 OCH₃), 63.54 [C(CH₃)₂], 113.62 [2 *m*-CH_{Ar}(CS)], 114.24 [2 *m*-CH_{Ar}(CCH)], 125.12 (CHC=C), 128.99 (C_{Ar}CS), 129.82 [2 *o*-CH_{Ar}(CCH)], 129.87 (C_{Ar}CCH), 132.12 [2 *o*-CH_{Ar}(CS)], 142.46 (CHC=C), 158.51 [*p*-C_{Ar}(CCH)], 158.62 (C=N), 160.15 [*p*-C_{Ar}(CS)] ppm; MS (ESI): *m/z* 340.2 (M + H⁺, 100%); HRMS (ESI): Found 340.1368, Calc. for C₂₀H₂₁NO₂S [M + H]⁺ 340.1371. The isothiazole^{25a} **3d** (33 mg, 11%) was obtained as a yellow oil; ¹H NMR (500.1 MHz, CDCl₃): δ 3.81, 3.82 (6 H, 2s, 2 OCH₃), 6.85–6.89 [4 H, m, 4 *m*-CH_{Ar}(C)], 7.22–7.26 [4 H, m, 4 *o*-CH_{Ar}(C)], 8.45 (1 H, s, NCH) ppm; ¹³C NMR (125.8 MHz, CDCl₃): δ 55.34, 55.38 (2 CH₃), 114.29, 114.43 [4 *m*-CH_{Ar}(C)], 123.08, 125.46 (2 C_{Ar}C), 130.03, 130.16 [4 *o*-CH_{Ar}(C)], 134.75 (CHC=C), 159.18 [*p*-C_{Ar}(C)], 159.33 (C=N), 160.21 (CHC=C), 160.67 [*p*-C_{Ar}(C)] ppm.

2,3-Bis(4-methoxyphenyl)-1-thia-5-azaspiro[5.5]undeca-2,4-diene (2j) and 4,5-bis(4-methoxyphenyl)isothiazole.^{25a} (3d). Following GP A, aldehyde (*EZ*)-**1d** (303 mg, 1.00 mmol), NaSH·H₂O (111 mg, 1.50 mmol), cyclohexanone (294 mg, 3.00 mmol) and 25% aqueous ammonia solution (136 mg, 2.00 mmol) were used. Analysis of the crude product by ¹H NMR spectroscopy revealed the formation of both title compounds in a ratio of 97 : 03 (**2j** : **3d**). Column chromatography (*n*-hexane–EtOAc, 7 : 3; thiazine **2j**, R_f = 0.29, isothiazole **3c**, R_f = 0.65) afforded the desired thiazine **2j** (301 mg, 79%) as a yellowish-orange solid, mp 162 °C (from CH₂Cl₂–*n*-hexane); IR (ATR) $\tilde{\nu}$ 3070, 3040, 3024, 2931, 2855, 2835, 1623, 1603, 1571, 1538, 1497, 1459, 1441, 1295, 1256, 1243, 1172, 846, 828, 802, 786 cm⁻¹; ¹H NMR (500.1 MHz, CDCl₃): δ 1.41–1.49 (1 H, m, CH_{2,Cy}), 1.65–1.70 (1 H, m, CH_{2,Cy}), 1.74–1.79 (4 H, m, 3 CH_{2,Cy}), 1.93–1.99 (2 H, m, 2 CH_{2,Cy}), 2.08–2.12 (2 H, m, 2 CH_{2,Cy}), 3.75 (3 H, s, SCPhOCH₃), 3.76 (3 H, s, CHCPhOCH₃), 6.70–6.73 [2 H, m, 2 *m*-CH_{Ar}(CS)], 6.75–6.78 [2 H, m, 2 *m*-CH_{Ar}(CCH)],

7.02–7.05 [2 H, m, 2 *o*-CH_{Ar}(CCH)], 7.19–7.22 [2 H, m, 2 *o*-CH_{Ar}(CS)], 8.02 (1H, s, NCH) ppm; ¹³C NMR (125.8 MHz, CDCl₃): δ 22.27, 25.86, 37.23 (5 CH_{2,Cy}), 55.31 (2 OCH₃), 67.93 [C(CH₂)₂], 113.55 [2 *m*-CH_{Ar}(CS)], 114.19 [2 *m*-CH_{Ar}(CCH)], 125.51 (CHC=C), 129.14 (C_{Ar}CS), 129.75 [2 *o*-CH_{Ar}(CCH)], 129.90 (C_{Ar}CCH), 132.24 [2 *o*-CH_{Ar}(CS)], 141.25 (CHC=C), 158.43 [*p*-C_{Ar}(CCH)], 158.46 (C=N), 160.07 [*p*-C_{Ar}(CS)] ppm; MS (ESI): *m/z* 380.3 (M + H⁺, 100%); HRMS (ESI): Found 380.1671, Calc. for C₂₃H₂₅NO₂S [M + H]⁺ 380.1684. The isothiazole^{25a} **3d** (9 mg, 3%) was obtained as a yellow oil.

2,3-Bis(4-methoxyphenyl)-9-methyl-1-thia-5,9-diazaspiro[5.5]-undeca-2,4-diene (2k) and 4,5-bis(4-methoxyphenyl)isothiazole.^{25a} (3d). Following GP A, aldehyde (*E*)-**1d** (606 mg, 2.00 mmol), NaSH·H₂O (222 mg, 3.00 mmol), *N*-methylpiperidin-4-one (678 mg, 6.00 mmol) and 25% aqueous ammonia solution (272 mg, 4.00 mmol) were used. Analysis of the crude product by ¹H NMR spectroscopy revealed the formation of both title compounds in a ratio of 99:1 (**2k**:**3d**). Column chromatography (acetone–EtOH, 9:1; thiazine **2k**, R_f = 0.06) afforded the desired thiazine **2k** (705 mg, 90%) as a yellow solid, mp 125–127 °C (from CH₂Cl₂–*n*-hexane); IR (ATR) $\tilde{\nu}$ 3001, 2938, 2836, 2792, 2739, 1602, 1509, 1495, 1463, 1440, 1377, 1292, 1244, 1174, 1144, 1030, 881, 826, 729, 540 cm⁻¹; ¹H NMR (500.1 MHz, CDCl₃): δ 2.06–2.18 [4 H, m, C(CH₂)₂], 2.28 (3 H, s, NCH₃), 2.49–2.54 [2 H, m, N(CH₂)₂], 2.62–2.66 [2 H, m, N(CH₂)₂], 3.63 (3 H, s, SCPhOCH₃), 3.64 (3 H, s, CHCPhOCH₃), 6.61–6.64 [2 H, m, 2 *m*-CH_{Ar}(CS)], 6.66–6.69 [2 H, m, 2 *m*-CH_{Ar}(CCH)], 6.94–6.97 [2 H, m, 2 *o*-CH_{Ar}(CCH)], 7.11–7.14 [2 H, m, 2 *o*-CH_{Ar}(CS)], 7.98 (1H, s, NCH) ppm; ¹³C NMR (125.8 MHz, CDCl₃): δ 36.71 [C(CH₂)₂], 46.04 (NCH₃), 51.37 [S(CH₂)₂], 54.99 (2 OCH₃), 64.95 [C(CH₂)₂], 113.34 [2 *m*-CH_{Ar}(CS)], 113.98 [2 *m*-CH_{Ar}(CCH)], 125.46 (CHC=C), 128.53 (C_{Ar}CS), 129.43 [2 *o*-CH_{Ar}(CCH)], 129.30 (C_{Ar}CCH), 131.99 [2 *o*-CH_{Ar}(CS)], 140.83 (CHC=C), 158.24 [*p*-C_{Ar}(CCH)], 158.69 (C=N), 159.91 [*p*-C_{Ar}(CS)] ppm; MS (ESI): *m/z* 395.2 (M + H⁺, 100%); HRMS (ESI): Found 395.1782, Calc. for C₂₃H₂₇N₂O₂S [M + H]⁺ 395.1793. The isolation of the isothiazole^{25a} **3d** was consciously abandoned.

(RS)-2-(4-Methoxybenzyl)-5,6-bis(4-methoxyphenyl)-2-methyl-2H-1,3-thiazine (2l) and 4,5-bis(4-methoxyphenyl)isothiazole.^{25a} (3d). Following GP A, aldehyde (*E*)-**1d** (606 mg, 2.00 mmol), NaSH·H₂O (222 mg, 3.00 mmol), 1-(4-methoxyphenyl)propan-2-one (985 mg, 6.00 mmol) and 25% aqueous ammonia solution (272 mg, 4.00 mmol) were used. Analysis of the crude product by ¹H NMR spectroscopy revealed the formation of both title compounds in a ratio of 98:02 (**2l**:**3d**). Column chromatography (*n*-hexane–CH₂Cl₂–EtOAc, 10:4:1; thiazine **2l**, R_f = 0.06) afforded the desired thiazine **2l** (738 mg, 83%) as an orange solid, mp 136–137 °C (from CH₂Cl₂–*n*-hexane); IR (ATR) $\tilde{\nu}$ 3036, 3015, 2973, 2955, 2923, 2838, 1604, 1574, 1509, 1498, 1455, 1300, 1293, 1246, 1171, 1113, 1078, 1027, 830, 821, 806, 755 cm⁻¹; ¹H NMR (500.1 MHz, CDCl₃): δ 1.67 (3 H, s, CCH₃), 3.08 (1 H, d, ²J = 13.9 Hz, CH₂), 3.20 (1 H, d, ²J = 13.8 Hz, CH₂), 3.75, 3.76, 3.78 (9 H, 3 s, 3 OCH₃), 6.69–6.72 (2 H, m, CH_{Ar}), 6.74–6.77 (2 H, m, CH_{Ar}), 6.83–6.86 (2 H, m, CH_{Ar}), 6.93–6.96 (2 H, m, CH_{Ar}), 7.16–7.19 (2 H, m,

CH_{Ar}), 7.23–7.26 (2 H, m, CH_{Ar}) ppm; ¹³C NMR (125.8 MHz, CDCl₃): δ 28.02 (CCH₃), 46.44 (CH₂), 55.27 (3 OCH₃), 67.89 (CCH₃), 113.35, 113.56, 114.07 [6 *o*-CH_{Ar}(O)], 124.83 (CHC=C), 128.58, 128.91, 129.87 (3 C_{Ar}C), 129.87, 131.92, 132.12 [6 *m*-CH_{Ar}(O)], 142.02 (CHC=C), 158.43, 158.60 [2 C_{Ar}O], 158.78 (C=N), 160.08 [C_{Ar}O] ppm; MS (ESI): *m/z* 446.0 (M + H⁺, 100%); HRMS (ESI): Found 446.1779, Calc. for C₂₇H₂₈NO₃S [M + H]⁺ 446.1790. The isolation of the isothiazole^{25a} **3d** was consciously abandoned.

(RS)-2-(4-Hydroxyphenethyl)-5,6-bis(4-methoxyphenyl)-2-methyl-2H-1,3-thiazine (2m) and 4,5-bis(4-methoxyphenyl)isothiazole.^{25a} (3d). Following GP A, aldehyde (*E*)-**1d** (606 mg, 2.00 mmol), NaSH·H₂O (222 mg, 3.00 mmol), 4-(4-hydroxyphenyl)butan-2-one (985 mg, 6.00 mmol) and 25% aqueous ammonia solution (272 mg, 4.00 mmol) were used. Analysis of the crude product by ¹H NMR spectroscopy revealed the formation of both title compounds in a ratio of 94:6 (**2m**:**3d**). Column chromatography (*n*-hexane–EtOAc–CH₂Cl₂, 6:2:2; thiazine **2m**, R_f = 0.26) afforded the desired thiazine **2m** (780 mg, 88%) as a yellow solid, mp 161–162 °C (from CH₂Cl₂–*n*-hexane); IR (ATR) $\tilde{\nu}$ 3101, 3004, 2931, 2836, 2679, 2607, 1601, 1510, 1494, 1441, 1372, 1293, 1244, 1173, 1077, 1029, 825 cm⁻¹; ¹H NMR (500.1 MHz, CDCl₃): δ 1.71 (CCH₃), 2.15–2.22, 2.27–2.33 [2 H, 2 m, C(CH₃)CH₂], 2.72–2.87 (2 H, m, C_{Ar}CH₂), 3.77 (6 H, 2 s, OCH₃), 6.73–6.76 [2 H, m, 2 *m*-CH_{Ar}(CS)], 6.77–6.80 [4 H, m, 2 *m*-CH_{Ar}(CCH), 2 *o*-CH_{Ar}(OH)], 7.02–7.07 [4 H, m, 2 *o*-CH_{Ar}(CCH), 2 *m*-CH_{Ar}(OH)], 7.21–7.24 [2 H, m, 2 *o*-CH_{Ar}(CS)], 7.61 (1H, br s, OH), 8.07 (1H, s, NCH) ppm; ¹³C NMR (125.8 MHz, CDCl₃): δ 27.11 (CCH₃), 30.74 (C_{Ar}CH₂), 43.89 [C(CH₃)CH₂], 55.35 (2 OCH₃), 67.05 (CCH₃), 113.69 [2 *m*-CH_{Ar}(CS)], 114.13 [2 *m*-CH_{Ar}(CCH)], 115.67 [*o*-CH_{Ar}(OH)], 124.87 (CHC=C), 128.82 (C_{Ar}CS), 129.56 [C_{Ar}CCH, 2 *m*-CH_{Ar}(OH)], 129.85 [2 *o*-CH_{Ar}(CCH)], 132.12 [2 *o*-CH_{Ar}(CS)], 133.31 (C_{Ar}CH₂), 143.20 (CHC=C), 154.74 (C_{Ar}OH), 158.56 [*p*-C_{Ar}(CCH)], 159.26 (C=N), 160.30 [*p*-C_{Ar}(CS)] ppm; MS (ESI): *m/z* 446.2 (M + H⁺, 100%); HRMS (ESI): Found 446.1786, Calc. for C₂₇H₂₈NO₃S [M + H]⁺ 446.1790. The isolation of the isothiazole^{25a} **3d** was consciously abandoned.

(RS)-2-(3-Ethoxy-3-oxopropyl)-5,6-bis(4-methoxyphenyl)-2-methyl-2H-1,3-thiazine (2n) and 4,5-bis(4-methoxyphenyl)isothiazole.^{25a} (3d). Following GP A, aldehyde (*E*)-**1d** (606 mg, 2.00 mmol), NaSH·H₂O (222 mg, 3.00 mmol), ethyl oxopentanoate (865 mg, 6.00 mmol) and 25% aqueous ammonia solution (272 mg, 4.00 mmol) were used. Analysis of the crude product by ¹H NMR spectroscopy revealed the formation of both title compounds in a ratio of 83:17 (**2n**:**3d**). Column chromatography (*n*-hexane–EtOAc–CH₂Cl₂, 6:2:2; thiazine **2n**, R_f = 0.27) afforded the desired thiazine **2n** (525 mg, 72%) as an orange oil; IR (ATR) $\tilde{\nu}$ 3032, 2972, 2930, 2836, 1730, 1602, 1509, 1496, 1441, 1374, 1291, 1244, 1173, 1077, 1030, 828, 615 cm⁻¹; ¹H NMR (500.1 MHz, CDCl₃): δ 1.24 (3 H, t, ³J = 7.1 Hz, CH₂CH₃), 1.63 (3 H, s, CCH₃), 2.22–2.28 [1 H, m, C(CH₃)CH₂], 2.31–2.37 [1 H, m, C(CH₃)CH₂], 2.54–2.65 (2 H, m, CH₂C=O), 3.75 (3 H, s, SCPhOCH₃), 3.76 (3 H, s, CHCPhOCH₃), 4.13 (2 H, q, ³J = 7.1 Hz, CH₂CH₃), 6.69–6.72 [2 H, m, 2 *m*-CH_{Ar}(CS)], 6.76–6.79 [2 H, m, 2 *m*-CH_{Ar}(CCH)], 7.02–7.05 [2 H, m, 2

o-CH_{Ar}(CCH)], 7.17–7.20 [2 H, m, 2 *o*-CH_{Ar}(CS)], 7.98 (1H, s, NCH) ppm; ¹³C NMR (125.8 MHz, CDCl₃): δ 14.34 (CH₂CH₃), 27.06 (CCH₃), 30.40 (CH₂C=O), 36.42 (CH₂CH₂C=O), 55.32 (2 OCH₃), 60.57 (CH₂CH₃), 66.53 (CCH₃), 113.62 [2 *m*-CH_{Ar}(CS)], 114.24 [2 *m*-CH_{Ar}(CCH)], 124.76 (CHC=C), 128.91 (C_{Ar}CS), 129.75 (C_{Ar}CCH), 129.84 [2 *o*-CH_{Ar}(CCH)], 132.05 [2 *o*-CH_{Ar}(CS)], 141.95 (CHC=C), 158.53 [*p*-C_{Ar}(CCH)], 158.94 (C=N), 160.18 [*p*-C_{Ar}(CS)] ppm; MS (ESI): *m/z* 426.2 (M + H⁺, 100%); HRMS (ESI): Found 426.1729, Calc. for C₂₄H₂₈NO₄S [M + H]⁺ 426.1739. The isolation of the isothiazole^{25a} **3d** was consciously abandoned.

(RS)-2-Isobutyl-5,6-bis(4-methoxyphenyl)-2H-1,3-thiazine (2o) and 4,5-bis(4-methoxyphenyl)isothiazole.^{25a} (3d). Following GP A, aldehyde (*EZ*)-**1d** (303 mg, 1.00 mmol), NaSH·H₂O (111 mg, 1.50 mmol), isopentanal (258 mg, 3.00 mmol) and 25% aqueous ammonia solution (136 mg, 2.00 mmol) were used. Analysis of the crude product by ¹H NMR spectroscopy revealed the formation of both title compounds in a ratio of 97:03 (**2o**:**3d**). Column chromatography (*n*-hexane–EtOAc, 9:1; thiazine **2o**, R_f = 0.17) afforded the desired thiazine **2o** (257 mg, 70%) as an orange oil; IR (ATR) $\tilde{\nu}$ 3036, 3002, 2956, 2935, 2910, 2870, 2838, 1656, 1603, 1575, 1529, 1511, 1496, 1465, 1443, 1294, 1246, 1176, 829, 799 cm⁻¹; ¹H NMR (500.1 MHz, CDCl₃): δ 1.02, 1.02 [6 H, 2 d, ³J = 6.5 Hz, CH(CH₃)₂], 1.84–1.89, 2.00–2.06 (2 H, 2 m, CH₂), 2.07–2.13 [1 H, m, CH(CH₃)₂], 3.75 (3 H, s, SCPhOCH₃), 3.76 (3 H, s, CHCPhOCH₃), 4.65 (1 H, ddd, ³J = 7.2 Hz, ³J = 7.2 Hz, ⁴J = 1.9 Hz, SCH), 6.70–6.73 [2 H, m, 2 *m*-CH_{Ar}(CS)], 6.76–6.79 [2 H, m, 2 *m*-CH_{Ar}(CCH)], 7.06–7.09 [2 H, m, 2 *o*-CH_{Ar}(CCH)], 7.21–7.24 [2 H, m, 2 *o*-CH_{Ar}(CS)] 8.09 (1 H, d, ⁴J = 1.9 Hz, NCH) ppm; ¹³C NMR (125.8 MHz, CDCl₃): δ 22.63, 22.80 [CH(CH₃)₂], 25.17 [CH(CH₃)₂], 43.95 (CH₂), 55.33 (2 OCH₃), 60.52 (SCH), 113.59 [2 *m*-CH_{Ar}(CS)], 114.24 [2 *m*-CH_{Ar}(CCH)], 127.27 [CHC=C], 128.70 (C_{Ar}CS), 129.57 (C_{Ar}CCH), 129.74 [2 *o*-CH_{Ar}(CCH)], 132.54 [2 *o*-CH_{Ar}(CS)], 144.31 [CHC=C], 158.54 [*p*-C_{Ar}(CCH)], 160.27 [*p*-C_{Ar}(CS)], 160.71 (C=N) ppm; MS (ESI): *m/z* 368.3 (M + H⁺, 100%); HRMS (ESI): Found 368.1678, Calc. for C₂₂H₂₆NO₂S [M + H]⁺ 368.1684. The isolation of the isothiazole^{25a} **3d** was consciously abandoned.

2,3-Bis(4-nitrophenyl)-1-thia-5-azaspiro[5.5]undeca-2,4-diene (2p) and 4,5-bis(4-nitrophenyl)isothiazole (3e). Following GP A, aldehyde (*E*)-**1f** (318 mg, 0.96 mmol), NaSH·H₂O (107 mg, 1.44 mmol), cyclohexanone (283 mg, 2.88 mmol) and 25% aqueous ammonia solution (107 mg, 1.44 mmol) were used. Analysis of the crude product by ¹H NMR spectroscopy revealed the formation of both title compounds in a ratio of 82:18 (**2p**:**3e**). Column chromatography (*n*-hexane–EtOAc, 8:2; thiazine **2p**, R_f = 0.16) afforded the desired thiazine **2p** (65 mg, 17%) as an orange solid, mp 138 °C; IR (ATR) $\tilde{\nu}$ 3107, 3032, 2921, 2856, 1624, 1594, 1516, 1481, 1451, 1340, 1294, 1252, 1209, 905, 890, 856, 843, 751, 728, 707, 694, 633 cm⁻¹; ¹H NMR (500.1 MHz, CDCl₃): δ 1.46–1.52 (1 H, m, CH₂,_{Cy}), 1.66–1.88 (5 H, m, 3 CH₂,_{Cy}), 2.01–2.06 (2 H, m, 2 CH₂,_{Cy}), 2.09–2.13 (2 H, m, 2 CH₂,_{Cy}), 7.25–7.26 [2 H, m, 2 *o*-CH_{Ar}(CCH)], 7.38–7.41 [2 H, m, 2 *o*-CH_{Ar}(CS)], 8.04 (1 H, s, NCH), 8.07–8.09 [2 H, m, 2 *m*-CH_{Ar}(CS)], 8.08–8.11 [2 H, m, 2

m-CH_{Ar}(CCH)] ppm; ¹³C NMR (125.8 MHz, CDCl₃): δ 22.07, 25.59, 37.45 (5 CH₂,_{Cy}), 68.99 [C_q(CH₂)₂], 123.78 [2 *o*-CH_{Ar}(CS)], 124.26 [2 *o*-CH_{Ar}(CCH)], 126.67 (CHC=C), 129.38 [2 *m*-CH_{Ar}(CCH)], 131.70 [2 *m*-CH_{Ar}(CS)], 142.69, 143.36 [2 C_{Ar}C], 144.21 (CHC=C), 146.92 [*p*-C_{Ar}(CCH)], 148.22 [*p*-C_{Ar}(CS)], 155.82 (C=N) ppm; MS (ESI): *m/z* 410.1 (M + H⁺, 100%); HRMS (ESI): Found 410.1164, Calc. for C₂₁H₂₀N₃O₄S [M + H]⁺ 410.1160. The isothiazole **3e** was further purified by a second column chromatography (CH₂Cl₂–*n*-hexane–EtOAc, 15:4:1; R_f = 0.71). The isothiazole was obtained (9 mg, 3%) as a yellow solid, mp 226 °C; IR (ATR) $\tilde{\nu}$ 3113, 3062, 3040, 1595, 1537, 1506, 1479, 1408, 1346, 1314, 1287, 898, 848, 795, 750, 734, 693, 673, 523 cm⁻¹; ¹H NMR (500.1 MHz, CDCl₃): δ 7.44–7.48 [4 H, m, 4 *o*-CH_{Ar}(C)], 8.23–8.26 [4 H, m, 4 *m*-CH_{Ar}(C)], 8.61 (1 H, s, NCH) ppm; ¹³C NMR (125.8 MHz, CDCl₃): δ 124.55, 124.68 [4 *m*-CH_{Ar}(C)], 129.83, 129.88 [4 *o*-CH_{Ar}(C)], 135.03 (CHC=C), 136.30, 138.68 (2 C_{Ar}C), 147.69 148.44 (C_{Ar}N), 158.70 (C=N), 160.86 (CHC=C) ppm; MS (EI, 70 eV): *m/z* 326.8 (M⁺, 20%); HRMS (EI): Found 327.0300, Calc. for C₁₅H₉N₃O₄S [M + H]⁺ 327.0308.

1-Chloro-2-(dimethoxymethyl)cyclopent-1-ene (4). Following GP A, 2-chloro-1-cyclopentene-1-carboxaldehyde (652 mg, 4.99 mmol), NaSH·H₂O (555 mg, 7.49 mmol), acetone (869 mg, 14.97 mmol) and 25% aqueous ammonia solution (680 mg, 9.98 mmol) were used. Column chromatography (*n*-hexane–MTBE–CH₂Cl₂, 6:3:1; R_f = 0.56) afforded the dimethyl acetal **4** instead of the desired thiazine (352 mg, 40%) as a dark brown oil; IR (ATR) $\tilde{\nu}$ 2956, 2932, 2910, 2857, 2828, 1663, 1443, 1363, 1184, 1111, 1090, 1069, 961, 917, 905 cm⁻¹; ¹H NMR (500.1 MHz, CDCl₃): δ 1.92–1.98 (2 H, m, CH₂CH₂CH₂), 2.45–2.49 (2 H, m, CHCCH₂), 2.59–2.63 (2 H, m, ClCCH₂), 3.38 (6 H, s, 2 OCH₃), 5.05 (1 H, s, CH) ppm; ¹³C NMR (125.8 MHz, CDCl₃): δ 20.96 (CH₂CH₂CH₂), 29.67 (CHCCH₂), 38.39 (ClCCH₂), 54.80 (2 OCH₃), 100.83 (CH), 131.05 (CHC=C), 134.50 (CHC=C) ppm; MS (ESI): *m/z* 199.1 (M + Na⁺, 100%); HRMS (ESI): Found 199.0496, Calc. for C₈H₁₃NNaO₂Cl [M + Na]⁺ 199.0502.

General procedure (GP B)

The respective imine (1.0 equiv.), dissolved in anhydrous MeOH (2 mL per mmol imine), was treated with the respective isocyanide (1.0 equiv.), dissolved in anhydrous MeOH (2 mL per mmol imine), and the respective acid (1.0 equiv.), dissolved in anhydrous MeOH (2 mL per mmol imine). After stirring for 72 h at r.t., the solvent was removed on a rotary evaporator. The crude product was purified by column chromatography on silica gel.

(RS)-3-(2-Bromoacetyl)-4-(N-cyclohexylcarbamoyl)-2,2-dimethyl-5,6-diphenyl-3,4-dihydro-2H-1,3-thiazine (5a). Following GP B, 2H-1,3-thiazine **2a** (279 mg, 1.00 mmol), bromoacetic acid (139 mg, 1.00 mmol) and isocyanocyclohexane (109 mg, 1.00 mmol) were used. Column chromatography (*n*-hexane–EtOAc, 7:3; R_f = 0.57) afforded the desired bisamide **5a** (105 mg, 20%) as a colourless solid, mp 75 °C (from CH₂Cl₂–*n*-hexane); IR (ATR) $\tilde{\nu}$ 3058, 3037, 3021, 2974, 2941, 2931, 2854, 1678, 1651, 1599, 1497, 1462, 1444, 1393, 1377, 1359, 1337,

1205, 1162, 787, 763, 695 cm^{-1} ; ^1H NMR (500.1 MHz, CDCl_3): δ 1.09–1.28 (3 H, m, 3 CH_2 ,_{Cy}), 1.31–1.46 (2 H, m, 2 CH_2 ,_{Cy}), 1.55–1.63 (2 H, m, 2 CH_2 ,_{Cy}), 1.68–1.70 (1 H, m, CH_2 ,_{Cy}), 1.90–1.93 (1 H, m, CH_2 ,_{Cy}), 1.97–2.01 (1 H, m, CH_2 ,_{Cy}), 1.98, 2.05 [6 H, s, $\text{C}(\text{CH}_3)_2$], 3.77 (1 H, d, $^2J = 10.9$ Hz, $\text{C}=\text{OCH}_2$), 3.82–3.91 (1 H, m, CH_2 ,_{Cy}), 3.95 (1 H, d, $^2J = 10.9$ Hz, $\text{C}=\text{OCH}_2$), 5.24 (1 H, s, $\text{NCHC}=\text{O}$), 6.12 (1 H, d, $^3J = 8.3$ Hz, NH), 7.16–7.24 (8 H, m, 8 CH_Ar), 7.29–7.31 (2 H, m, 2 CH_Ar) ppm; ^{13}C NMR (125.8 MHz, CDCl_3): δ 24.48, 24.66, 25.49 (3 CH_2 ,_{Cy}), 26.26, 28.62 [$\text{C}(\text{CH}_3)_2$], 29.44 ($\text{C}=\text{OCH}_2$), 32.47, 33.02 (2 CH_2 ,_{Cy}), 48.83 (NHCH_2 ,_{Cy}), 67.38 ($\text{NCHC}=\text{O}$), 69.37 [$\text{C}(\text{CH}_3)_2$], 127.77 ($p\text{-CH}_\text{Ar}$), 128.53, 128.60, 128.82 (6 CH_Ar), 128.86 ($p\text{-CH}_\text{Ar}$), 129.96 (2 CH_Ar), 135.10 ($\text{CHC}=\text{C}$), 136.83 (C_ArCS), 139.26 (C_ArCCH), 141.04 ($\text{CHC}=\text{C}$), 166.65 ($\text{C}=\text{OCH}_2$), 168.03 ($\text{C}=\text{OCH}$) ppm; MS (ESI): m/z 549.3 ($\text{M} + \text{Na}^+$, 100%); HRMS (ESI): Found 549.1176, Calc. for $\text{C}_{27}\text{H}_{31}\text{BrN}_2\text{NaO}_2\text{S}$ [$\text{M} + \text{Na}^+$] 549.1187.

(RS)-4-(N-(4-Chlorophenyl)carbamoyl)-2,2-dimethyl-5,6-diphenyl-3-(2-phenylacetyl)-3,4-dihydro-2H-1,3-thiazine (5b). Following GP B, 2H-1,3-thiazine **2a** (10 mg, 0.07 mmol), phenylacetic acid (10 mg, 0.07 mmol) and *p*-chloroisocyanobenzene (10 mg, 0.07 mmol) were used. Column chromatography (*n*-hexane–EtOAc, 7 : 3; $R_f = 0.44$) afforded the desired bisamide **5b** (18 mg, 43%) as a yellow solid, mp 96 °C; IR (ATR) $\tilde{\nu}$ 3407, 3059, 3027, 2977, 2930, 1693, 1650, 1492, 1444, 1375, 1304, 1163, 1090, 1030, 1013, 826, 757, 721, 693, 627, 579 cm^{-1} ; ^1H NMR (500.1 MHz, CDCl_3): δ 2.09, 2.16 [6 H, 2 s, $\text{C}(\text{CH}_3)_2$], 3.78 (2 H, s, CH_2), 5.44 (1 H, s, NCH), 6.98–7.01 (3 H, m, 3 CH_Ar), 7.02–7.07 (4 H, m, 4 CH_Ar), 7.09–7.15 (3 H, m, 3 CH_Ar), 7.18–7.22 (3 H, m, 3 CH_Ar), 7.27–7.31 (4 H, m, 4 CH_Ar), 7.40–7.42 (2 H, m, 2 $\text{NC}_\text{ArCH}_\text{Ar}$), 7.84 (1 H, s, NH) ppm; ^{13}C NMR (125.8 MHz, CDCl_3): δ 26.96, 28.88 [$\text{C}(\text{CH}_3)_2$], 44.36 (CH_2), 67.44 (NCH), 69.47 [$\text{C}(\text{CH}_3)_2$], 121.35 (2 $\text{NC}_\text{ArCH}_\text{Ar}$), 127.25, 127.65, 128.17, 128.49, 128.84, 128.92, 128.98, 129.27, 130.08 (17 CH_Ar), 134.04 ($\text{CH}_2\text{C}_\text{Ar}$), 135.80 ($\text{CHC}=\text{C}$), 136.10 (NC_Ar), 136.94 (C_ArCS), 139.24 (C_ArCCH), 140.57 ($\text{CHC}=\text{C}$), 168.05 ($\text{CHC}=\text{O}$), 171.47 ($\text{CH}_2\text{C}=\text{O}$) ppm; MS (ESI): m/z 575.0 ($\text{M} + \text{Na}^+$, 100%); HRMS (ESI): Found 575.1522; Calc. for $\text{C}_{33}\text{H}_{29}\text{ClN}_2\text{NaO}_2\text{S}$ [$\text{M} + \text{Na}^+$] 575.1536.

(RS)-3-Benzoyl-4-(N-benzylcarbamoyl)-2,2-dimethyl-5,6-diphenyl-3,4-dihydro-2H-1,3-thiazine (5c). Following GP B, 2H-1,3-thiazine **2a** (100 mg, 0.36 mmol), benzoic acid (44 mg, 0.36 mmol) and (isocyanomethyl)benzene (42 mg, 0.36 mmol) were used. Column chromatography (*n*-hexane–EtOAc, 7 : 3; $R_f = 0.35$) afforded the desired bisamide **5c** (55 mg, 31%) as an orange oil; IR (ATR) $\tilde{\nu}$ 3353, 3059, 3028, 2974, 2929, 1718, 1676, 1638, 1600, 1492, 1444, 1377, 1360, 1298, 1169, 754, 729, 694 cm^{-1} ; ^1H NMR (500.1 MHz, CDCl_3): δ 2.16, 2.22 [6 H, s, $\text{C}(\text{CH}_3)_2$], 4.47 (1 H, dd, $^2J = 14.8$ Hz, $^3J = 5.2$ Hz, CH_2), 4.57 (1 H, dd, $^2J = 14.8$ Hz, $^3J = 5.9$ Hz, CH_2), 5.29 (1 H, s, NCH), 6.26–6.29 (1 H, m, NH), 6.97–6.98 (2 H, m, 2 CH_Ar), 7.05–7.07 (2 H, m, 2 CH_Ar), 7.11–7.32 (16 H, m, 16 CH_Ar) ppm; ^{13}C NMR (125.8 MHz, CDCl_3): δ 26.76, 29.55 [$\text{C}(\text{CH}_3)_2$], 44.64 (CH_2), 68.87 (CH), 69.39 [$\text{C}(\text{CH}_3)_2$], 125.89 (2 CH_Ar), 127.62 ($p\text{-CH}_\text{Ar}$), 127.82, 128.48, 128.49 (6 CH_Ar), 128.52 ($p\text{-CH}_\text{Ar}$), 128.56 (2 CH_Ar), 128.75 ($p\text{-CH}_\text{Ar}$), 128.79, 128.86 (4 CH_Ar), 129.32

($p\text{-CH}_\text{Ar}$), 130.10 (2 CH_Ar), 136.33 ($\text{CHC}=\text{C}$), 137.06 (C_ArCS), 137.62 ($\text{C}=\text{OC}_\text{Ar}$), 137.93 ($\text{CH}_2\text{C}_\text{Ar}$), 138.97 (C_ArCCH), 140.37 ($\text{CHC}=\text{C}$), 169.55 ($\text{C}=\text{OCH}$), 172.08 ($\text{C}=\text{OC}_\text{Ar}$) ppm; MS (ESI): m/z 541.1 ($\text{M} + \text{Na}^+$, 100%); HRMS (ESI): Found 541.1918, Calc. for $\text{C}_{33}\text{H}_{30}\text{N}_2\text{NaO}_2\text{S}$ [$\text{M} + \text{Na}^+$] 541.1926.

General procedure (GP C)

Under an argon atmosphere, the respective 2H-1,3-thiazine (1.0 equiv.), dissolved in anhydrous CH_2Cl_2 (5 mL per mmol thiazine), was cooled down to 0–5 °C. After addition of anhydrous Et_3N (2.0 equiv.), the respective acyl chloride (1.0 equiv.), dissolved in anhydrous CH_2Cl_2 (5 mL per mmol thiazine), was added dropwise. After stirring overnight at r.t., the reaction mixture was poured into saturated aqueous NH_4Cl solution (20 mL per mmol thiazine). The layers were separated and the organic phase was washed with water (20 mL per mmol thiazine). The combined aqueous phases were extracted with CH_2Cl_2 (2 \times 20 mL per mmol thiazine). The combined organic phases were dried (MgSO_4) and the solvent was removed on a rotary evaporator. The crude product was purified by column chromatography on silica gel.

(6R*,7R*)-2,2-Dimethyl-4,5,7-triphenyl-3-thia-1-azabicyclo[4.2.0]oct-4-en-8-one (6a). Following GP C, 2H-1,3-thiazine **2a** (138 mg, 0.49 mmol), Et_3N (99 mg, 0.98 mmol) and phenylacetyl chloride (77 mg, 0.49 mmol) were used. Column chromatography (CHCl_3 –*n*-hexane–toluene–MTBE, 4 : 3 : 2 : 1; $R_f = 0.41$) afforded the desired β -lactam **6a** (95 mg, 49%) as a yellow solid, mp 142 °C (from CH_2Cl_2 –*n*-hexane); IR (ATR) $\tilde{\nu}$ 3057, 3027, 3007, 2972, 2934, 1751, 1599, 1494, 1454, 1442, 1155, 1136, 1117, 766, 754, 729, 702, 682 cm^{-1} ; ^1H NMR (499.9 MHz, CDCl_3): δ 1.83, 2.14 [6 H, 2 s, $\text{C}(\text{CH}_3)_2$], 4.21–4.22 (1 H, m, CHC_Ar), 4.44 (1 H, d, $^3J = 1.8$ Hz, NCH), 7.00–7.02 (2 H, m, 2 \times CH_Ar), 7.04–7.06 [2 H, m, 2 *o*- $\text{CH}_\text{Ar}(\text{CH})$], 7.11–7.18 (8 H, m, 8 CH_Ar), 7.21–7.27 (3 H, m, 3 CH_Ar) ppm; ^{13}C NMR (125.7 MHz, CDCl_3): δ 26.28, 29.73 [$\text{C}(\text{CH}_3)_2$], 58.80 (NCH), 60.66 (CHC_Ar), 61.68 [$\text{C}(\text{CH}_3)_2$], 127.24 ($p\text{-CH}_\text{Ar}$), 127.46 (*o*- $\text{CH}_\text{Ar}(\text{CH})$), 127.68 ($p\text{-CH}_\text{Ar}$), 127.76 ($\text{CHC}=\text{C}$), 127.94 ($p\text{-CH}_\text{Ar}$), 128.24, 128.46, 128.90, 129.56, 129.76 (10 CH_Ar), 133.66 ($\text{CHC}=\text{C}$), 134.99 (C_ArCH), 138.22, 138.76 (2 C_Ar), 166.50 ($\text{C}=\text{O}$) ppm; MS (ESI): m/z 398.2 ($\text{M} + \text{H}^+$, 100%); HRMS (ESI): Found 398.2388; Calc. for $\text{C}_{26}\text{H}_{24}\text{NOS}$ [$\text{M} + \text{H}^+$] 398.2394.

(6R*,7R*)-7-Methoxy-2,2-dimethyl-4,5-diphenyl-3-thia-1-azabicyclo[4.2.0]oct-4-en-8-one (6b). Following GP C, 2H-1,3-thiazine **2a** (200 mg, 0.72 mmol), Et_3N (146 mg, 1.44 mmol) and 2-methoxyacetyl chloride (78 mg, 0.72 mmol) were used. Column chromatography (CHCl_3 –toluene–*n*-hexane–MTBE, 6 : 2 : 1 : 1; $R_f = 0.41$) afforded the desired β -lactam **6b** (187 mg, 74%) as a yellow solid, mp 81 °C (from CH_2Cl_2 –*n*-hexane); IR (ATR) $\tilde{\nu}$ 3086, 3058, 3033, 3006, 2970, 2943, 2924, 2841, 1741, 1595, 1586, 1493, 1457, 1440, 1392, 1372, 1324, 1220, 1206, 1131, 1122, 936, 913, 893, 851, 732, 705, 692, 666 cm^{-1} ; ^1H NMR (500.1 MHz, CDCl_3): δ 1.80, 2.06 [6 H, 2 s, $\text{C}(\text{CH}_3)_2$], 3.21 (3 H, s, OCH_3), 4.42 (1 H, d, $^3J = 1.5$ Hz, NCH), 4.44 (1 H, d, $^3J = 1.5$ Hz, CHOCH_3), 7.04–7.06 (2 H, m, 2 CH_Ar), 7.11–7.19 (8 H, m, 8 CH_Ar) ppm; ^{13}C NMR (125.8 MHz, CDCl_3): δ 25.84, 29.14 [$\text{C}(\text{CH}_3)_2$], 57.67 (OCH_3), 58.63 (NCH), 61.39 [$\text{C}(\text{CH}_3)_2$],

87.65 (CHOCH₃), 125.73 (CHC=C), 127.15, 127.91 (2 *p*-CH_{Ar}), 128.15, 128.35, 129.23, 129.54 (8 CH_{Ar}), 134.03 (CHC=C), 137.72, 138.49 (2 C_{Ar}), 164.02 (C=O) ppm; MS (ESI): *m/z* 374.1 (M + Na⁺, 100%); HRMS (ESI): Found 374.1183, Calc. for C₂₁H₂₁NNaO₂S [M + Na]⁺ 374.1191.

Crystal structure determination of β-lactam 6b

Crystal data. C₂₁H₂₁NO₂S, *M* = 351.45, monoclinic, *a* = 15.9577(7), *b* = 6.3713(3), *c* = 17.8868(8) Å, *U* = 1804.89(14) Å³, *T* = 120 K, space group *P*2₁/*c*, *Z* = 4, 75519 reflection measured, 7935 unique (*R*_{int} = 0.0291) which were used in all calculations. The final *wR*(*F*₂) was 0.1351 (all data).

(6R*,7R*)-7-Methoxy-4,5-bis(4-methoxyphenyl)-3-thia-1-azaspiro[bicyclo[4.2.0]octane-2,1'-cyclohexan]-4-en-8-one (6c). Following GP C, 2*H*-1,3-thiazine 2j (85 mg, 0.22 mmol), Et₃N (45 mg, 0.44 mmol) and 2-methoxyacetyl chloride (24 mg, 0.22 mmol) were used. Column chromatography (CH₂Cl₂-*n*-hexane-toluene-MTBE, 4 : 3 : 2 : 1; *R*_f = 0.39) afforded the desired β-lactam 6c (64 mg, 64%) as a yellow oil; IR (ATR) $\tilde{\nu}$ 2998, 2934, 2855, 2836, 1753, 1604, 1507, 1462, 1442, 1291, 1245, 1219, 1174, 1123, 1031, 1014, 909, 827, 800, 793, 728 cm⁻¹; ¹H NMR (500.1 MHz, CDCl₃): δ 1.42–1.48 (1 H, m, CH_{2,Cy}), 1.56–1.63 (2 H, m, 2 CH_{2,Cy}), 1.68–1.73 (2 H, m, 2 CH_{2,Cy}), 1.85–1.94 (2 H, m, 2 CH_{2,Cy}), 2.04–2.09 (1 H, m, CH_{2,Cy}), 2.25–2.29 (1 H, m, CH_{2,Cy}), 2.73–2.77 (1 H, m, CH_{2,Cy}), 3.30 (3 H, s, CHOCH₃), 3.73 [3 H, s, CHCPhOCH₃], 3.74 [3 H, s, SCPhOCH₃], 4.30 (1 H, d, ³*J* = 1.5 Hz, NCH), 4.44 (1 H, d, ³*J* = 1.5 Hz, CHOCH₃), 6.68–6.72 [4 H, m, 2 *m*-CH_{Ar}(CS)], 2 *m*-CH_{Ar}(CCH)], 6.93–6.96 [2 H, m, 2 *o*-CH_{Ar}(CCH)], 7.06–7.08 [2 H, m, 2 *o*-CH_{Ar}(CS)] ppm; ¹³C NMR (125.8 MHz, CDCl₃): δ 22.64, 22.70, 25.23, 34.44, 36.67 (5 CH_{2,Cy}), 55.24, 55.28 (2 C_{Ar}OCH₃), 57.59 (CHOCH₃), 58.04 (NCH), 65.69 [C(CH₂)₂], 87.63 (CHOCH₃), 113.69 [2 *m*-CH_{Ar}(CCH)], 113.83 [2 *m*-CH_{Ar}(CS)], 124.71 (CHC=C), 130.39 [C_{Ar}CS, 2 *o*-CH_{Ar}(CCH)], 131.03 [2 *o*-CH_{Ar}(CS)], 131.18 (C_{Ar}CCH), 132.43 (CHC=C), 158.39 [*p*-C_{Ar}(CCH)], 159.16 [*p*-C_{Ar}(CS)], 164.81 (C=O) ppm; MS (ESI): *m/z* 474.1 (M + Na⁺, 100%); HRMS (ESI): Found 474.1717, Calc. for C₂₆H₂₉NNaO₄S [M + Na]⁺ 474.1715.

General procedure (GP D)

Under an argon atmosphere, the respective 2*H*-1,3-thiazine (1.0 equiv.), dissolved in anhydrous CH₂Cl₂ (5 mL per mmol thiazine), was cooled down to 0–5 °C. A solution of the respective acyl chloride (1.1 equiv.) in anhydrous CH₂Cl₂ (5 mL per mmol thiazine) was added dropwise. After stirring overnight at r.t., a solution of anhydrous MeOH (3.7 equiv.) and anhydrous Et₃N (1.75 equiv.) in anhydrous CH₂Cl₂ (5 mL per mmol thiazine) was added dropwise at 0–5 °C. After stirring overnight at r.t., the reaction mixture was poured into ice-water (20 mL per mmol thiazine). The layers were separated and the aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL per mmol thiazine). The combined organic phases were washed with saturated aqueous NaHCO₃ solution (20 mL per mmol thiazine) and water (20 mL per mmol thiazine) and dried (MgSO₄). The solvent was removed on a rotary evaporator and the crude product was purified by column chromatography on silica gel.

(RS)-2,2-Dimethyl-5,6-diphenyl-4-methoxy-3-(4-nitrobenzoyl)-2*H*-1,3-thiazine (7a). Following GP D, 2*H*-1,3-thiazine 2a (1.321 g, 4.73 mmol), 4-nitrobenzoyl chloride (798 mg, 5.20 mmol), Et₃N (689 mg, 8.28 mmol) and MeOH (661 mg, 17.50 mmol) were used. Column chromatography (*n*-hexane-diethyl ether-CH₂Cl₂, 7 : 2 : 1; *R*_f = 0.43) afforded the desired methoxy amide 7a (1.294 g, 59%) as a yellow solid, mp 107 °C (from CH₂Cl₂-*n*-hexane); Anal. Found: C, 68.12; H, 5.62; N, 6.10; O, 13.62; S, 6.53. Calc. for C₂₆H₂₄N₂O₄S: C, 67.81; H, 5.25; N, 6.08; O, 13.90; S, 6.96%; IR (ATR) $\tilde{\nu}$ 3189, 3103, 3078, 3056, 3026, 2975, 2928, 2858, 1661, 1599, 1524, 1498, 1462, 1443, 1389, 1344, 1332, 1197, 1174, 1121, 908, 862, 756, 730, 713, 694 cm⁻¹; ¹H NMR (500.1 MHz, CDCl₃): δ 2.17, 2.17 [6 H, 2 s, C(CH₃)₂], 3.33 (3 H, s, OCH₃), 5.36 (1 H, s, NCH), 6.93–6.95 (2 H, m, 2 CH_{Ar}), 7.11–7.23 (6 H, m, 6 CH_{Ar}), 7.32–7.34 (2 H, m, 2 CH_{Ar}), 7.42–7.44 [2 H, m, 2 *m*-CH_{Ar}(NO₂)], 8.07–8.09 [2 H, m, 2 *o*-CH_{Ar}(NO₂)] ppm; ¹³C NMR (125.8 MHz, CDCl₃): δ 27.81, 29.48 [C(CH₃)₂], 54.97 (OCH₃), 66.43 [C(CH₃)₂], 90.27 (NCH), 123.67 [2 *o*-CH_{Ar}(NO₂)], 127.50 (*p*-CH_{Ar}), 128.18 [2 *m*-CH_{Ar}(NO₂)], 128.35 (2 CH_{Ar}), 128.71 (2 CH_{Ar}), 128.73 (*p*-CH_{Ar}), 128.78 (2 CH_{Ar}), 130.19 (2 CH_{Ar}), 132.73 (CHC=C), 137.26 (C_{Ar}CS), 138.69 (CHC=C), 138.92 (C_{Ar}CCH), 143.01 (C_{Ar}C=O), 148.54 (C_{Ar}NO₂), 170.03 (C=O) ppm.

(RS)-2,2-Dimethyl-4-methoxy-5,6-bis(4-methoxyphenyl)-3-(4-nitrobenzoyl)-2*H*-1,3-thiazine (7b). Following GP D, 2*H*-1,3-thiazine 2i (1.500 g, 4.42 mmol), 4-nitrobenzoyl chloride (798 mg, 4.86 mmol), Et₃N (689 mg, 7.74 mmol) and MeOH (661 mg, 16.35 mmol) were used. Column chromatography (*n*-hexane-diethyl ether-CH₂Cl₂, 5 : 3 : 2; *R*_f = 0.37) afforded the desired methoxy amide 7b (1.885 g, 82%) as a yellow solid, mp 112 °C (from CH₂Cl₂-*n*-hexane); Anal. Found: C, 64.56; H, 5.68; N, 5.36; O, 18.51; S, 5.89. Calc. for C₂₈H₂₈N₂O₆S: C, 64.60; H, 5.42; N, 5.38; O, 18.44; S, 6.16%; IR (ATR) $\tilde{\nu}$ 3034, 2933, 2837, 1660, 1602, 1524, 1508, 1462, 1442, 1393, 1345, 1292, 1246, 1174, 1030, 910, 860, 834, 731, 633 cm⁻¹; ¹H NMR (500.1 MHz, CDCl₃): δ 2.13, 2.15 [6 H, 2 s, C(CH₃)₂], 3.32 (3 H, s, CHOCH₃), 3.75, 3.77 (6 H, 2 s, 2 C_{Ar}OCH₃), 5.29 (1 H, s, NCH), 6.65–6.68 [2 H, m, 2 *m*-CH_{Ar}(CS)], 6.72–6.75 [2 H, m, 2 *m*-CH_{Ar}(CCH)], 6.86–6.89 [2 H, m, 2 *o*-CH_{Ar}(CCH)], 7.26–7.29 [2 H, m, 2 *o*-CH_{Ar}(CS)], 7.45–7.47 [2 H, m, 2 *m*-CH_{Ar}(NO₂)], 8.10–8.12 [2 H, m, 2 *o*-CH_{Ar}(NO₂)] ppm; ¹³C NMR (125.8 MHz, CDCl₃): δ 27.59, 29.28 [C(CH₃)₂], 54.83 (CHOCH₃), 55.33, 55.34 (2 C_{Ar}OCH₃), 66.44 [C(CH₃)₂], 90.38 (NCH), 113.81 [2 *m*-CH_{Ar}(CCH)], 114.16 [2 *m*-CH_{Ar}(CS)], 123.65 [2 *o*-CH_{Ar}(NO₂)], 128.18 [2 *m*-CH_{Ar}(NO₂)], 129.66 (C_{Ar}CCH), 130.03 [2 *o*-CH_{Ar}(CCH)], 130.94 (CHC=C), 131.26 (C_{Ar}CS), 131.48 [2 *o*-CH_{Ar}(CS)], 137.36 (CHC=C), 143.17, 148.51 (C_{Ar}NO₂, C_{Ar}C=O), 158.73 [*p*-C_{Ar}(CS)], 159.84 [*p*-C_{Ar}(CCH)], 169.94 (C=O) ppm.

Notes and references

- For several examples, see: (a) R. A. Hughes and C. J. Moody, *Angew. Chem.*, 2007, **119**, 8076, (*Angew. Chem., Int. Ed.*, 2007, **46**, 7930); (b) O. G. Vitzthum, P. Werkhoff

- and P. Hubert, *J. Agric. Food Chem.*, 1975, **23**, 999;
- (c) R. M. Seifert and A. D. King, *J. Agric. Food Chem.*, 1982, **30**, 786; (d) P. Sensi, P. Margalith and M. T. Timbal, *Farmaco Sci.*, 1959, **14**, 146; (e) A. A. Stierle, J. H. Cardellina and F. L. Singleton, *Tetrahedron Lett.*, 1991, **32**, 4847; (f) A. K. Gadad, C. S. Mahajanshetti, S. Nimbalkar and A. Raichurkar, *Eur. J. Med. Chem.*, 2000, **35**, 853; (g) A. Andreani, M. Rambaldi, A. Locatelli and A. M. Isetta, *Eur. J. Med. Chem.*, 1991, **26**, 335; (h) E. W. Thomas, E. E. Nishizawa, D. D. Zimmermann and C. J. Williams, *J. Med. Chem.*, 1985, **28**, 442.
- 2 R. Dua, S. Shrivastava, S. K. Sonwane and S. K. Srivastava, *Adv. Biol. Res.*, 2011, **5**, 120.
- 3 For representative examples dealing with penicillin, see: (a) R. Bentley, *J. Chem. Educ.*, 2004, **81**, 1462; (b) J. C. Sheehan, in *Molecular Modification in Drug Design, Advances in Chemistry Series*, ed. F. W. Schueler, Am. Chem. Soc., Washington, 1964, vol. 45, ch. 2; (c) W. Dürckheimer, J. Blumbach, R. Lauttrell and K. H. Scheunemann, *Angew. Chem.*, 1985, **97**, 183, (*Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 180).
- 4 For an example of 2,5-dihydro-1,3-thiazole-containing compound except for penicillin, see: (a) P. S. Gillies and C. J. Dunn, *Drugs*, 2000, **60**, 333; (b) B. B. Lohray, V. Bhusan, B. P. Rao, G. R. Medhavan, N. Murali, K. N. Rao, A. K. Reddy, B. M. Rajesh, P. G. Reddy, R. Chakrabarti, R. K. Vikramadithyan, R. Rajagopalan, R. N. V. S. Mamidi, H. K. Jajoo and S. Subramanian, *J. Med. Chem.*, 1998, **41**, 1619.
- 5 (a) A. Chatterjee, F. C. Schroeder, C. T. Jurgenson, S. E. Ealick and T. P. Begley, *J. Am. Chem. Soc.*, 2008, **130**, 11394; (b) J. N. Seiber, C. N. Roeske and J. M. Benson, *Phytochemistry*, 1978, **17**, 967; (c) M. C. Roy, F.-R. Chang, H.-C. Huang, M. Y.-N. Chiang and Y.-C. Wu, *J. Nat. Prod.*, 2005, **68**, 1494; (d) K. Kobayakawa and R. Kobayakawa, *US Patent*, US0005715, 2013; (e) C. Boule, *US Patent*, US20070059265, 2007; (f) N. Mani, P. Sanchet, Z.-D. Jiang, C. Mcnane, M. Decenzo, B. Knight, M. Stankis, M. Kuranda and D. M. Rothstein, *J. Antibiot.*, 1998, **51**, 471; (g) T. Ginman, J. Viklund, J. Malmstroem, J. Blid, R. Emond, E. Forsblom, A. Johansson, A. Kers, F. Lake, F. Sehgelmeble, K. J. Sterky, M. Bergh, A. Lindgren, P. Johansson, F. Jeppsson, J. Faelting, Y. Gravenfors and F. Rahm, *J. Med. Chem.*, 2013, **56**, 4181; (h) C. J. Mussinan, B. D. Mookherjee, D. A. Withycombe, J. Kiwala and J. F. Vinals, *US Patent*, US04067344, 1978.
- 6 (a) H. Gröger, Y. Saida, H. Sasai, K. Yamaguchi, J. Martens and M. Shibusaki, *J. Am. Chem. Soc.*, 1998, **120**, 3089; (b) K. Johannes, M. Watzke and J. Martens, *J. Heterocycl. Chem.*, 2010, **47**, 697; (c) F. Brockmeyer, T. Stalling and J. Martens, *Synthesis*, 2012, 2947; (d) F. Brockmeyer, D. Kröger, T. Stalling, P. Ullrich and J. Martens, *Helv. Chim. Acta*, 2012, **95**, 1857; (e) I. Hoppe, U. Schöllkopf, M. Nieger and E. Egert, *Angew. Chem.*, 1985, **97**, 1066, (*Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 1067); (f) I. Ugi and E. Wischhöfer, *Chem. Ber.*, 1962, **95**, 136; (g) Y. Y.- Tong, J. J. R. F. da Silva, A. J. L. Pombeiro, G. Wagner and R. Herrmann, *J. Organomet. Chem.*, 1998, **552**, 17; (h) A. Dömling and I. Ugi, *Angew. Chem.*, 1993, **105**, 634, (*Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 563).
- 7 J. Martens, H. Offermanns and P. Scherberich, *Angew. Chem.*, 1981, **93**, 680, (*Angew. Chem., Int. Ed. Engl.*, 1981, **20**, 668).
- 8 (a) A. Dömling and I. Ugi, *Tetrahedron*, 1993, **49**, 9495; (b) A. Dömling, A. Bayler and I. Ugi, *Tetrahedron*, 1995, **51**, 755.
- 9 For recent examples, see: (a) S. Marcaccini and T. Torroba, in *Multicomponent Reactions*, ed. J. Zhu and H. Bienaymé, Wiley-VCH, Weinheim, 2005, ch. 2; (b) J. D. Sunderhaus and S. F. Martin, *Chem. – Eur. J.*, 2009, **15**, 1300.
- 10 J. K. Landquist, in *Heterocyclic compounds, Comprehensive Organic Chemistry*, ed. D. Barton, D. W. Ollis and P. G. Sammes, Pergamon Press, Oxford, New York, 1979, vol. 4, ch. 20.2.
- 11 (a) P. Charpentier, *US Patent*, US2645640, 1953; (b) J. M. Kane, A. Rifkin, D. Quitkin, D. Nayak and J. Ramos-Lorenzi, *Arch. Gen. Psychiatry*, 1982, **39**, 70.
- 12 S. Chater, R. Viola, J. Paterson and V. Jarvis, *J. Palliat. Med.*, 1998, **12**, 255.
- 13 (a) S. Bloomfiel, S. Simard-Savoie, J. Bernier and L. Tetreault, *Can. Med. Assoc. J.*, 1964, **90**, 1156; (b) O. Davidsen, O. Lindeneg and M. Walsh, *Acta Med. Scand.*, 1979, **205**, 191.
- 14 E. Sianesi, R. Redaelli, M. J. Magistretti and E. Massarani, *J. Med. Chem.*, 1973, **16**, 1133.
- 15 J. Nyitrai, J. Fetterm, G. Hornyak, K. Zauer, K. Lempert, I. Koczka, I. Sagi and C. Rethati, *Tetrahedron*, 1987, **34**, 1031.
- 16 J. M. Chen, D. C. Cole and J. I. Levin, *European Patent*, EP1144368, 2004.
- 17 S. A. Greene and J. C. Thurmon, *J. Vet. Pharmacol. Ther.*, 1988, **11**, 295.
- 18 Q. Lu, J. Yang, Z. Liu, C. Gutierrez, G. Aymard and J.-J. Rouby, *Am. J. Respir. Crit. Care Med.*, 2011, **184**, 106.
- 19 For examples, see: (a) B. Vigante, J. Ozols, A. Mishnev, G. Duburs and B. Chekavichus, *Chem. Heterocycl. Compd.*, 2000, **36**, 862; (b) S. Shibuya, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 3767; (c) L. Hu, A.-N. T. Kong, L. Chen, S. Magesh and C. L. Saw, *World Patent*, WO145420, 2012; (d) T. W. Glotova, M. Y. Dvorko and A. I. Albanov, *Russ. J. Org. Chem.*, 2005, **41**, 629.
- 20 (a) F. Barth, J.-P. Ducoux, M. Rinaldi-Carmona and C. Congy, *US Patent*, US264470, 2006; (b) T. Inouw, M. Tanaka, H. Uno and N. Ono, *Synthesis*, 1999, 471.
- 21 D. Prim, A. Fuss, G. Kirsch and A. M. S. Silva, *J. Chem. Soc., Perkin Trans. 2*, 1999, 1175.
- 22 M. Weiffenfels and M. Pulst, *Tetrahedron Lett.*, 1968, **9**, 3045.
- 23 B. J. Stokes, C. V. Vogel, L. K. Urnezis, M. Pan and T. G. Driver, *Org. Lett.*, 2010, **12**, 2884.
- 24 A. Chakraborty and J. K. Ray, *Synth. Commun.*, 1995, **25**, 1869.

- 25 (a) B. Schulze, K. Gisela, S. Kirrbach, A. Rahm and H. Heimgartner, *Helv. Chim. Acta*, 1991, **74**, 1059; (b) D. Greif, U. Eilitz, M. Pulst, D. Riedel and M. Wecks, *J. Fluorine Chem.*, 1999, **94**, 91; (c) M. Scholz, H. K. Ulbrich, O. Soehnlein, L. Lindbom, A. Mattern and G. Dannhardt, *Bioorg. Med. Chem.*, 2009, **17**, 558; (d) J. Y. Gauthier, Y. Leblanc, W. C. Black, C.-C. Chan, W. A. Cromlish, R. Gordon, B. P. Kennedy, C. K. Lau, S. Léger, Z. Wang, D. Ethier, J. Guay, J. Mancini, D. Riendeau, P. Tagari, P. Vickers, W. Wong, L. Xu and P. Prasit, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 87.
- 26 F. Asinger, W. Schäfer, M. Baumann and H. Römgens, *Liebigs Ann. Chem.*, 1964, **672**, 103.
- 27 The conversion of β -chlorovinyl aldehydes to the dimethyl acetals under comparable conditions was described once before K. Bodendorf and R. Mayer, *Chem. Ber.*, 1965, **98**, 3554.
- 28 (a) I. Ugi and E. Wischhöfer, *Chem. Ber.*, 1962, **95**, 136; (b) I. Ugi, *Angew. Chem.*, 1962, **74**, 9, (*Angew. Chem., Int. Ed. Engl.*, 1962, 1–8); (c) J. Kintscher and J. Martens, *Synthesis*, 1991, 837.
- 29 T. Stalling, K. Johannes, S. Polina and J. Martens, *J. Heterocycl. Chem.*, 2013, **50**, 654.
- 30 L. S. Hegedus, R. Imwinkelried, M. Alarid-Sargent, D. Dvorak and Y. Satoh, *J. Am. Chem. Soc.*, 1990, **112**, 1109.
- 31 CCDC-976016 contains the supplementary crystallographic data for this paper.
- 32 G. R. Fulmer, A. J. M. Miller, N. H. Sherden, H. E. Gottlieb, A. Nudelman, B. M. Stoltz, J. E. Bercaw and K. I. Goldberg, *Organometallics*, 2010, **29**, 2176.
- 33 E. W. Thomas and R. H. Rynbrandt, *US Patent*, US5098918, 1992.
- 34 N. Plavac, I. W. J. Still, M. S. Chauhan and D. M. McKinnon, *Can. J. Chem.*, 1975, **53**, 836.