Tetrahedron 66 (2010) 242–250

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# Synthesis of different types of valerolactams starting from 2,5-dihydrooxazoles

Katharina Johannes, Jürgen Martens *

*Institute of Pure and Applied Chemistry, University of Oldenburg, Carl-von-Ossietzky-Str. 9-11, 26129 Oldenburg, Germany*

ARTICLE INFO

*Article history:*
Received 16 September 2009
Received in revised form 22 October 2009
Accepted 29 October 2009
Available online 1 November 2009

*Keywords:*
Heterocycles
Imines
Valerolactams
Addition reactions
Diastereoselectivity

ABSTRACT

Tricyclic valerolactams characterized by a variable heteroatom in γ-position, for example, sulfur, oxygen or nitrogen, were synthesized starting from 2,5-dihydrooxazoles. The chosen synthetic procedures included the addition of thiosalicylic acid as well as the addition of salicyl chloride. The nitrogen containing lactams were prepared in a cycloaddition and subsequent oxidation.



## 1. Introduction

Valerolactam substructures containing variable heteroatoms in γ-position are numerously represented in heterocyclic compounds. Heteroatoms taken into consideration are sulfur and oxygen as well as nitrogen leading to the substructures **I**–**III** shown in Figure 1. In literature, different ways to synthesize compounds including the pointed substructures were described.[1]

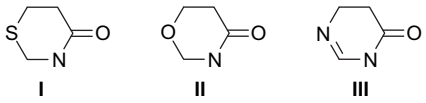


**Figure 1.** Valerolactam substructures **I**–**III**.

We focused our attention to the synthesis of tricyclic valerolactams **2**–**4** characterized by the emphasized substructures **I**–**III** (Fig. 1). For this purpose, rarely used heterocyclic imines, the 2,5-dihydrooxazoles **1**, were chosen as starting material (Fig. 2). Due to their aldiminic C=N-double bond, these reactive species **1** were suited for addition reactions.[2] Thus, we concentrated on different addition reactions as preferred synthetic procedures leading to the aspired target structures **2**–**4** (Fig. 2).

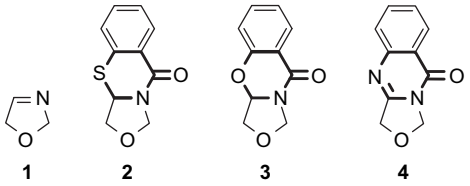


**Figure 2.** 2,5-Dihydrooxazole **1** and the target structures **2**–**4**.

Besides, some valerolactams show interesting characteristics as biological active substances. Thiavalerolactams were reported, for example, as anti-inflammatory agents[3] and sodium channel blockers[4] used for the treatment of neurodegenerative conditions. Oxavalerolactams structurally comparable to the aspired lactams **3** were described as modulators of neurotransmitters in the human brain[5] being useful for the treatment of mental disorders and diseases of the nervous system.[6] The aspired azavalerolactams **4** show structural similarity with alkaloids, which are known for their anti-inflammatory, antimicrobial and antidepressant activities[7] as well as their cytotoxicity.[8] Furthermore, the *N*-heterocyclus of 2,5-dihydrooxazoles **1** represents an interesting synthetic fragment because the oxazolidin substructure is, for example, found in the strong β-lactamase inhibitor clavulanic acid.[9]

In addition, the 2,5-dihydrooxazoles **1** as well as comparable compounds proved themselves in the synthesis of different lactam systems, which were in the focus of our group in the recent past (Fig. 3). For example, five-membered β-oxabutyrolactams **IV** were prepared by addition of acid chloride followed by oxidation in the presence of pyridinium chloro chromate.[10] Five- or six-membered lactams V (n=1, 2) containing a sulfur in β-, respectively, γ-position

* Corresponding author. Tel.: +49 441 7983837; fax: +49 441 7983757.
*E-mail address:* juergen.martens@uni-oldenburg.de (J. Martens).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.10.107

were synthesized by addition of thiocarboxylic acids to 2,5-dihydrothiazoles.[11] Furthermore, α,β-unsaturated valerolactams **VI** were obtained in a three-step synthesis comprising acid chloride addition, Hosomi–Sakurai reaction and a ring-closing metathesis.[12] In a comparable synthetic procedure α,β-unsaturated δ-oxacaprolactams **VII** were formed.[13]

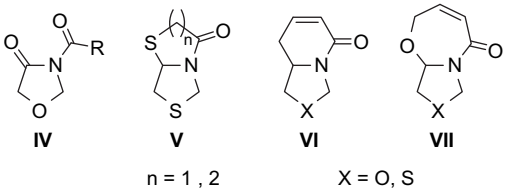
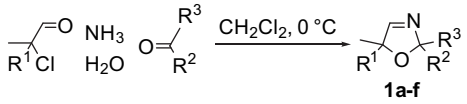



**Figure 3.** Lactam systems **IV–VII** prepared from 2,5-dihydrooxazoles and thiazoles.

## 2. Results and discussion

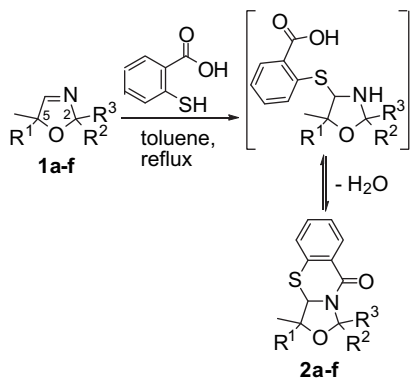
According to a procedure established in our group, the 2,5-dihydrooxazoles **1a–f** were synthesized in an one-pot reaction using an α-halogen aldehyde, aqueous ammonia and a carbonyl compound (aldehyde or ketone) (Scheme 1).[14]




**Scheme 1.** Synthesis of 2,5-dihydrooxazoles **1a–f**.

Due to the great number of useable α-halogen aldehydes and carbonyl compounds, a high diversity of precursors was available without high effort. By this way, some examples of chiral imines **1c–f** were synthesized. Thus, the subsequent reactions were investigated concerning the aspect of diastereoselectivity.

First, we presented the synthesis of tricyclic γ-thiavalerolactams **2a–f** starting from 2,5-dihydrooxazoles **1a–f** via addition of thiosalicylic acid (Scheme 2). This type of reaction went back to investigations of Erlenmeyer and Oberlin, respectively, Surrey who independently reported the addition of thioglycolic acid to acyclic imines.[15] Modifying the used thiocarboxylic acids as well as imines caused a broad expansion of this type of reaction.[16] However, only a few examples for addition of thiosalicylic acid are known.[17]




**Scheme 2.** Addition of thiosalicylic acid to 2,5-dihydrooxazoles **1a–f**.

The γ-thiavalerolactams **2a–f** were prepared from 2,5-dihydrooxazoles **1a–f** and thiosalicylic acid by heating the reaction mixture for several hours in toluene using a Dean–Stark apparatus. Removing the formed water, the reaction was accelerated by displacing the equilibrium between the intermediate proposed by Tierney[18] and the desired products **2a–f**. The lactams **2a–f** were obtained in yields up to 74% (Table 1).

**Table 1**
γ-Thiavalerolactams **2a–f**

| Imine | Lactam | $R^1$ | $R^2$ | $R^3$ | Yield (%) | dr[a] (*trans*:*cis*) |
|---|---|---|---|---|---|---|
| **1a** | **2a** | $CH_3$ | $CH_3$ | $CH_3$ | 27 | — |
| **1b** | **2b** | $CH_3$ | $-(CH_2)_5-$ | | 43 | — |
| **1c** | **2c** | $C_6H_5$ | $CH_3$ | $CH_3$ | 50 | 71:29 |
| **1d** | **2d** | $C_6H_5$ | $-(CH_2)_5-$ | | 74 | 74:26 |
| **1e** | **2e** | $CH_3$ | $CH(CH_3)_2$ | H | 57 | 79:21 |
| **1f** | **2f** | $CH_3$ | $C(CH_3)_3$ | H | 40 | 72:28 |

[a] Diastereomeric ratio determined from $^1$H NMR spectra of the crude product.

Starting from C5-chiral 2,5-dihydrooxazoles **1c**,**d** as well as C2-chiral 2,5-dihydrooxazoles **1e**,**f**, we received two diastereomers of the reaction products **2c–f** in a ratio about dr=75:25 as determined from $^1$H NMR spectra of the crude product. According to ROE experiments, the major diastereomers of **2c–f** showed trans-configuration concerning the substituents of the lowest priority, the proton at C4 and the methyl moiety at C5 in the case of the lactams **2c**,**d**, respectively, the proton at C4 and the proton at C2 in the case of the products **2e**,**f**. These results were based on strong NOEs observed in the ROE experiments as illustrated in Figure 4 for the lactams **2c** and **2f**. In contrast, the ROE experiments of the minor diastereomers of **2c–f** showed cis-configuration between the concerned moieties.

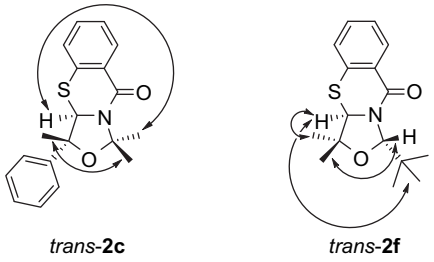
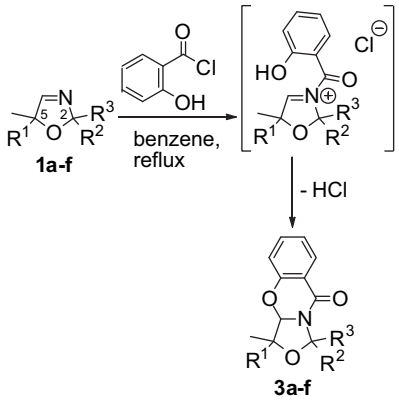



**Figure 4.** Observed NOEs for the major diastereomers of the lactams **2c** and **2f**.

The achieved results concerning the diastereoselectivity were attributed to the use of the bulky thiosalicylic acid, which attacked the imines **1a–f** preferentially from the less shielded side. Consequently, the sterically demanding substituents took the biggest distance possible, that is, trans-configuration.

Subsequently, the synthesis of γ-oxavalerolactams **3a–f** was considered by addition of salicylic acid in analogous way to the preparation of γ-thiavalerolactams **2a–f**. However, exploratory experiments were not successful. Thus, we chose a synthesis according to investigations of Ziegler.[19] Starting from heterocyclic imines **1a–f**, salicyl chloride[20] prepared from salicylic acid and oxalyl chloride was added. Thus, an *N*-acyliminium ion stabilized by resonance was generated.[21] Without isolation, the intermediate closed the ring under elimination of hydrogen chloride and led to the desired γ-oxavalerolactams **3a–f** (Scheme 3).




**Scheme 3.** Addition of salicyl chloride to 2,5-dihydrooxazoles **1a**–**f**.

The treatment of salicyl chloride and 2,5-dihydrooxazoles **1a**–**f** in anhydrous benzene at reflux for several hours followed by column chromatography afforded the γ-oxavalerolactams **3a**–**f** in yields up to 60% (Table 2).

**Table 2**
γ-Oxavalerolactams **3a**–**f**

| Imine | Lactam | $R^1$ | $R^2$ | $R^3$ | Yield (%) | dr[a] (*trans*:*cis*) |
|---|---|---|---|---|---|---|
| **1a** | **3a** | $CH_3$ | $CH_3$ | $CH_3$ | 60 | — |
| **1b** | **3b** | $CH_3$ | $-(CH_2)_5-$ | | 42 | — |
| **1c** | **3c** | $C_6H_5$ | $CH_3$ | $CH_3$ | 44 | 83:17 |
| **1d** | **3d** | $C_6H_5$ | $-(CH_2)_5-$ | | 48 | 85:15 |
| **1e** | **3e** | $CH_3$ | $CH(CH_3)_2$ | H | 29 | 33:67 |
| **1f** | **3f** | $CH_3$ | $C(CH_3)_3$ | H | 25 | 39:61 |

[a] Diastereomeric ratio determined from $^1$H NMR spectra of the crude product.

Starting from C5-chiral 2,5-dihydrooxazoles **1c**,**d**, two diastereomers of the γ-oxavalerolactams **3c**,**d** were received in a diastereomeric ratio about 85:15 as determined from the $^1$H NMR spectra of the crude products. According to ROE experiments, the proton at C4 and the methyl moiety at C5 in the major diastereomers of **3c**,**d** showed trans-configuration based on the observed NOEs described in Figure 5 for lactam **3c**. The results were confirmed by comparison to ROE experiments of the minor diastereomers of **3c**,**d** showing cis-configuration.

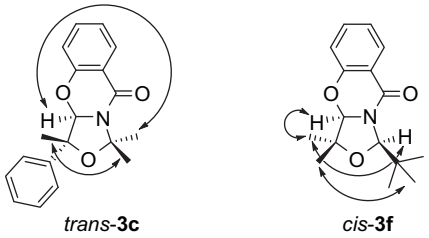



**Figure 5.** Observed NOEs for the major diastereomers of the lactams **3c** and **3f**.

When C2-chiral imines **1e**,**f** were used, two diastereomers of the products **3e**,**f** were received in a diastereomeric ratio about 65:35. The ROE experiments of the major diastereomers of **3e**,**f** indicated cis-configuration between the proton at C4 and the proton at C2. These results were founded on the observed NOEs shown in Figure 5 for lactam **3f**.

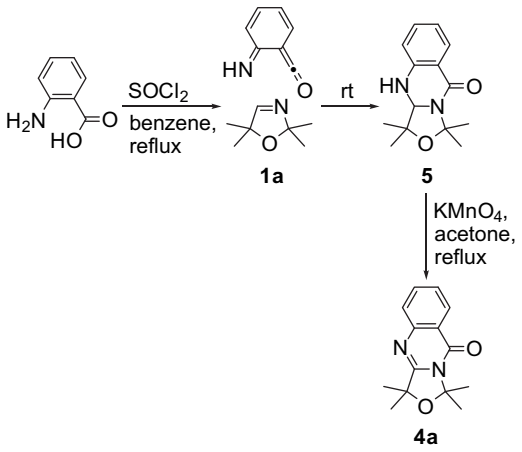
In the case of the *N*-acyliminium ions leading to the lactams **3c**,**d** (Scheme 3), the bulky substituent at the carbon C5 ($R^1$=$C_6H_5$) and the acyl moiety strove for the biggest distance possible. Thus, the ring closure took place from the less hindered side resulting predominantly in *trans*-configurated lactams **3c**,**d**. In the *N*-acyliminium ions forming the lactams **3e**,**f** (Scheme 3), the bulky substituents at the carbon C2 ($R^2$=$CH(CH_3)_2$, $C(CH_3)_3$) displaced the acyl moiety the way, that the reactive centre at the carbon C4 was blocked from one side. Consequently, the attack was observed from the less hindered side and *cis*-configurated lactams **3e**,**f** were obtained.

The achieved diastereoselectivities in the synthesis of γ-thiavalerolactams **2a**–**f** compared to the results of γ-oxavalerolactams **3a**–**f** showed obvious differences induced by divergent courses of the reactions. More precisely, the obtained diastereoselectivities were influenced by the new bond formed in the first step of the addition reaction. Whereas the reaction of C5-chiral imines **1c**,**d** led to *trans*-configurated products in the case of sulfur as well as oxygen containing lactams **2c**,**d** and **3c**,**d**, starting from C2-chiral imines **1e**,**f** the formation of *trans*-configurated lactams **2e**,**f**, respectively, *cis*-configurated lactams **3e**,**f** was observed.

The diastereomers **2c**–**f**, **3c**–**f** show a stable configuration under the chosen reaction conditions as known for other cyclic *N*-acyl 1,3-heterocycles.[22]

Inspired by works of Kametani, we aimed to synthesize γ-azavalerolactams **4a**–**f** starting from 2,5-dihydrooxazoles **1a**–**f**.[23] In comparison to previously prepared lactams **2** and **3**, the γ-azavalerolactams **4** were characterized by insertion of nitrogen as part of a C=N-double bond.

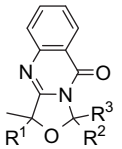
On heating anthranilic acid in the presence of thionyl chloride an unstable sulfinamide anhydride was formed and dissociated to an iminoketene. In a cycloaddition, this reactive species and the heterocyclic imines **1a**–**f** should generate the γ-azavalerolactams **4a**–**f** under elimination of hydrogen according to the results of Kametani.[24] But instead we obtained the dihydroquinazoline **5** starting from 2,5-dihydrooxazole **1a** in a first exploratory experiment (Scheme 4). Subsequent oxidation with potassium permanganate led to the desired γ-azavalerolactam **4a**.




**Scheme 4.** Generation of the γ-azavalerolactams **4a**.

In order to develop a general procedure for the synthesis of γ-azavalerolactams **4a**–**f**, we optimized the known reaction sequence by integration of an oxidation as final step. We passed on the purification of the dihydroquinazolines and joined the oxidation to the lactams **4a**–**f** directly. The desired products **4a**–**f** were obtained in satisfactory yields up to 50% (Table 3).

**Table 3**
γ-Azavalerolactams **4a–f**



**4a-f**

| Imine | Lactam | $R^1$ | $R^2$ | $R^3$ | Yield (%) |
|---|---|---|---|---|---|
| **1a** | **4a** | $CH_3$ | $CH_3$ | $CH_3$ | 48 |
| **1b** | **4b** | $CH_3$ | $-(CH_2)_5-$ | | 36 |
| **1c** | **4c** | $C_6H_5$ | $CH_3$ | $CH_3$ | 50 |
| **1d** | **4d** | $C_6H_5$ | $-(CH_2)_5-$ | | 49 |
| **1e** | **4e** | $CH_3$ | $CH(CH_3)_2$ | H | 38 |
| **1f** | **4f** | $CH_3$ | $C(CH_3)_3$ | H | 22 |

The γ-azavalerolactams **4a–f** were characterized by their amidine substructure offering the possibility for further functionalisations as well as for use as synthetic reagent.[25]

## 3. Conclusions

In conclusion, we were able to prepare tricyclic valerolactams **2a–f**, **3a–f** and **4a–f** containing variable heteroatoms in γ-position. The 2,5-dihydrooxazoles **1a–f** used as precursors in the respective reactions showed their high reactivity. The γ-thiavalerolactams **2a–f** were received by addition of thiosalicylic acid whereas the γ-oxavalerolactams **3a–f** were synthesized by adding salicyl chloride. Both, the lactams **2a–f** and **3a–f** were prepared focussing on the aspect of diastereoselectivity. The γ-azavalerolactams **4a–f** were generated in a synthetic procedure starting from anthranilic acid and thionyl chloride, following cycloaddition and final oxidation.

## 4. Experimental

### 4.1. General methods

Synthetic procedures were performed on a vacuum line using standard Schlenk techniques under argon. All reagents and solvents were of commercial grade and purified prior to use when necessary. Preparative column chromatography was carried out using Grace $SiO_2$ (0.040–0.063 mm, type KG 60). TLC was performed on Merck $SiO_2$ $F_{254}$ plates on aluminium sheets. IR spectra were recorded on a Bruker Tensor 27 spectrometer equipped with a GoldenGate diamond-ATR unit. $^1H$ and $^{13}C$ NMR spectra were recorded with Bruker AMX R 500 and AM 300 spectrometers. NMR chemical shifts are reported in parts per million using TMS as internal standard. Assignments of the signals in the $^{13}C$ NMR spectrum were supported by measurements applying COSY and *J* modulated techniques. CI–MS and HRMS spectra were recorded on a Finnigan MAT 212 spectrometer.

### 4.2. General procedure for synthesis of γ-thiavalerolactams 2 (GP 1)

Under exclusion of moisture, 1 equiv of 2,5-dihydrooxazole and 5 equiv of thiosalicylic acid were refluxed in toluene (30 mL) for 48 h using a Dean–Stark apparatus. After cooling down to room temperature, the organic phase was washed with saturated sodium bicarbonate solution (3×20 mL) and water (3×20 mL) and dried with magnesium sulfate. After filtration, the solvent was removed under reduced pressure and the crude product was purified as described below.

*4.2.1. (RS)-1,1,3,3-Tetramethyl-3,3a-dihydrooxazolo[4,3-b][1,3]benzothiazin-9-one **2a**.* Following **GP 1**, 2,5-dihydrooxazole **1a** (0.64 g, 5.0 mmol) and thiosalicylic acid (3.85 g, 25.0 mmol) were used. The product was purified by column chromatography on silica gel (solvent: *n*-hexane/ethyl acetate, 1:1) and obtained as yellow oil (0.35 g, 27%); $R_f$=0.89 (*n*-hexane/ethyl acetate, 1:1); IR: ν 2981, 2934, 1647, 1590, 1443, 1391, 1370, 744 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 1.45 (s, 3H, $CH_3$), 1.51 (s, 3H, $CH_3$), 1.69 (s, 3H, $CH_3$), 1.79 (s, 3H, $CH_3$), 5.15 (s, 1H, SCH), 7.25–7.29 (m, 2H, ArH), 7.35–7.39 (m, 1H, ArH), 8.09–8.11 (m, 1H, ArH); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 25.7 ($CH_3$), 27.3 ($CH_3$), 27.8 ($CH_3$), 28.0 ($CH_3$), 68.2 (SCH), 81.0 ($OC(CH_3)_2CH$), 96.9 ($OC(CH_3)_2N$), 126.2 (ArCH), 127.5 (ArCH), 130.0 (ArCH), 130.3 (ArC), 132.0 (ArCH), 134.7 (ArC), 161.6 (CO); MS (CI, isobutane): *m*/*z* (%)=264.1 (100) $[MH]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{14}H_{18}NO_2S]^+$: 264.1058; found: 264.1060.

*4.2.2. (RS)-Spiro[3,3-dimethyl-3,3a-dihydrooxazolo[4,3-b][1,3]benzothiazin-9-one-1,1′-cyclohexane] **2b**.* Following **GP 1**, 2,5-dihydrooxazole **1b** (0.84 g, 5.0 mmol) and thiosalicylic acid (3.85 g, 25.0 mmol) were used. The product was crystallized from petrol ether (40/60) and obtained as yellow solid (0.65 g, 43%); mp 112–115 °C; IR: ν 2936, 2863, 1650, 1591, 1445, 1383, 1152, 745 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 1.44 (s, 3H, $CH_3$), 1.49 (s, 3H, $CH_3$), 1.51–1.55 (m, 1H, $-(CH_2)_5-$), 1.59–1.75 (m, 7H, $-(CH_2)_5-$), 2.58–2.66 (m, 2H, $-(CH_2)_5-$), 5.12 (s, 1H, SCH), 7.24–7.28 (m, 2H, ArH), 7.34–7.37 (m, 1H, ArH), 8.07–8.09 (m, 1H, ArH); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 23.1 ($-(CH_2)_5-$), 23.3 ($-(CH_2)_5-$), 24.7 ($-(CH_2)_5-$), 25.9 ($CH_3$), 28.4 ($CH_3$), 35.2 ($-(CH_2)_5-$), 35.5 ($-(CH_2)_5-$), 68.5 (SCH), 80.7 ($OC(CH_3)_2CH$), 98.7 (OCN), 126.2 (ArCH), 127.4 (ArCH), 130.1 (ArCH), 130.7 (ArC), 131.9 (ArCH), 134.7 (ArC), 161.7 (CO); MS (CI, isobutane): *m*/*z* (%)=304.2 (100) $[MH]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{17}H_{22}NO_2S]^+$: 304.1371; found: 304.1372.

*4.2.3. 1,1,3-Trimethyl-3-phenyl-3,3a-dihydrooxazolo[4,3-b][1,3]benzothiazin-9-one (3R*,3aR*)-**2c** and (3R*,3aS*)-**2c**.* Following **GP 1**, 2,5-dihydrooxazole **1c** (0.95 g, 5.0 mmol) and thiosalicylic acid (3.85 g, 25.0 mmol) were used. After column chromatography on silica gel (solvent: *n*-hexane/ethyl acetate, 4:1) two diastereomers were isolated (3*R**,3a*R**)-**2c** and (3*R**,3a*S**)-**2c**, ratio of diastereomers 71:29 (determined from $^1H$ NMR spectra of crude product); total yield: 0.83 g, 51%.

*4.2.3.1. Major diastereomer (3R*,3aR*)-**2c**.* Yellow solid (0.69 g, 42%); $R_f$=0.68 (*n*-hexane/ethyl acetate, 4:1); mp 101–103 °C; IR: ν 2977, 2931, 2854, 1646, 1591, 1440, 1387, 1371, 769, 734, 698 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 1.65 (s, 3H, $OC(CH_3)_2N$), 1.73 (s, 3H, $OC(CH_3)CH$), 1.87 (s, 3H, $OC(CH_3)_2N$), 5.35 (s, 1H, SCH), 7.17–7.32 (m, 6H, ArH), 7.45–7.47 (m, 2H, ArH), 8.02–8.04 (m, 1H, ArH); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 26.7 ($OC(CH_3)_2N$), 27.4 ($OC(CH_3)CH$), 28.0 ($OC(CH_3)_2N$), 68.9 (SCH), 84.2 ($OC(CH_3)CH$), 97.4 ($OC(CH_3)_2N$), 124.3 (ArCH), 126.3 (ArCH), 127.5 (ArCH), 127.7 (ArCH), 128.5 (ArCH), 130.0 (ArC), 130.1 (ArCH), 132.1 (ArCH), 134.6 (ArC), 144.7 (ArC), 161.4 (CO); MS (CI, isobutane): *m*/*z* (%)=326.0 (100) $[MH]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{19}H_{20}NO_2S]^+$: 326.1209; found: 326.1208.

*4.2.3.2. Minor diastereomer (3R*,3aS*)-**2c**.* Yellow oil (0.14 g, 8%); $R_f$=0.56 (*n*-hexane/ethyl acetate, 4:1); IR: ν 2984, 2928, 2855, 1652, 1589, 1443, 1371, 771, 745, 698 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 1.89 (s, 3H, $OC(CH_3)CH$), 1.92 (s, 3H, $OC(CH_3)_2N$), 1.95 (s, 3H, $OC(CH_3)_2N$), 5.56 (s, 1H, SCH), 7.15–7.17 (m, 1H, ArH), 7.22–7.25 (m, 1H, ArH), 7.29–7.32 (m, 1H, ArH), 7.37–7.44 (m, 3H, ArH), 7.57–7.59 (m, 2H, ArH), 8.04–8.06 (m, 1H, ArH); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 27.8 ($OC(CH_3)CH$), 28.2 ($OC(CH_3)_2N$), 29.9 ($OC(CH_3)_2N$), 72.3 (SCH), 84.6 ($OC(CH_3)CH$), 98.2 ($OC(CH_3)_2N$), 122.0 (ArCH), 125.9 (ArCH), 126.1 (ArCH), 127.7 (ArCH), 128.0 (ArCH), 128.3 (ArC), 129.9 (ArCH), 131.9 (ArCH), 137.0 (ArC), 141.8 (ArC), 162.3 (CO); MS

(CI, isobutane): *m*/*z* (%)=326.2 (100) $[MH]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{19}H_{20}NO_2S]^+$: 326.1215; found: 326.1214.

*4.2.4. Spiro[3-methyl-3-phenyl-3,3a-dihydrooxazolo[4,3-b][1,3]benzothiazin-9-one-1,1′-cyclohexane] (3R*,3aR*)-**2d** and (3R*,3aS*)-**2d**.* Following **GP 1**, 2,5-dihydrooxazole **1d** (1.15 g, 5.0 mmol) and thiosalicylic acid (3.85 g, 25.0 mmol) were used. After column chromatography on silica gel (solvent: *n*-hexane/ethyl acetate, 5:1) two diastereomers were isolated (3*R**,3a*R**)-**2d** and (3*R**,3a*S**)-**2d**, ratio of diastereomers 74:26 (determined from $^1$H NMR spectra of crude product); total yield: 1.35 g, 74%.

*4.2.4.1. Major diastereomer (3R*,3aR*)-**2d**.* Yellow solid (0.98 g, 54%); $R_f$=0.88 (*n*-hexane/ethyl acetate, 5:1); mp 118–120 °C; IR: *ν* 2931, 2858, 1653, 1590, 1441, 1381, 1362, 771, 735, 698 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$): *δ* 1.24–1.34 (m, 1H, –$(CH_2)_5$–), 1.46–1.49 (m, 1H, –$(CH_2)_5$–), 1.64–1.84 (m, 6H, –$(CH_2)_5$–), 1.72 (s, 3H, $CH_3$), 2.51–2.57 (m, 1H, –$(CH_2)_5$–), 2.66–2.72 (m, 1H, –$(CH_2)_5$–), 5.31 (s, 1H, SCH), 7.15–7.23 (m, 3H, ArH), 7.26–7.29 (m, 3H, ArH), 7.47–7.49 (m, 2H, ArH), 7.99–8.00 (m, 1H, ArH); $^{13}$C NMR (125 MHz, $CDCl_3$): *δ* 23.3 (–$(CH_2)_5$–), 23.4 (–$(CH_2)_5$–), 24.7 (–$(CH_2)_5$–), 27.5 ($CH_3$), 34.4 (–$(CH_2)_5$–), 35.8 (–$(CH_2)_5$–), 69.0 (SCH), 84.0 (O*C*$(CH_3)$CH), 99.0 (OCN), 124.2 (ArCH), 126.2 (ArCH), 127.4 (ArCH), 127.7 (ArCH), 128.4 (ArCH), 130.1 (ArCH), 130.5 (ArC), 132.0 (ArCH), 134.4 (ArC), 145.0 (ArC), 161.6 (CO); MS (CI, isobutane): *m*/*z* (%)=365.9 (100) $[M]^+$; HRMS (ESI): *m*/*z* calcd for $[C_{22}H_{22}NO_2S]^+$: 364.1366; found: 364.1375.

*4.2.4.2. Minor diastereomer (3R*,3aS*)-**2d**.* Yellow solid (0.37 g, 20%); $R_f$=0.76 (*n*-hexane/ethyl acetate, 5:1); mp 117–118 °C; IR: *ν* 2961, 2935, 2859, 1656, 1590, 1443, 1370, 1361, 750, 773, 696 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$): *δ* 1.60–1.78 (m, 6H, –$(CH_2)_5$–), 1.81 (s, 3H, $CH_3$), 1.83–1.91 (m, 2H, –$(CH_2)_5$–), 2.58–2.67 (m, 2H, –$(CH_2)_5$–), 5.46 (s, 1H, SCH), 7.07–7.09 (m, 1H, ArH), 7.15–7.18 (m, 1H, ArH), 7.21–7.24 (m, 1H, ArH),7.30–7.37 (m, 3H, ArH), 7.51–7.53 (m, 2H, ArH), 7.96–7.98 (m, 1H, ArH); $^{13}$C NMR (125 MHz, $CDCl_3$): *δ* 23.3 (–$(CH_2)_5$–), 23.6 (–$(CH_2)_5$–), 24.7 (–$(CH_2)_5$–), 30.1 ($CH_3$), 36.0 (–$(CH_2)_5$–), 36.3 (–$(CH_2)_5$–), 72.6 (SCH), 84.4 (O*C*$(CH_3)$CH), 99.8 (OCN), 126.0 (ArCH), 126.1 (ArCH), 127.6 (ArCH), 128.0 (ArCH), 128.3 (ArCH), 130.0 (ArCH), 130.3 (ArC), 131.8 (ArCH), 137.1 (ArC), 142.1 (ArC), 162.4 (CO); MS (CI, isobutane): *m*/*z* (%)=366.4 (100) $[MH]^+$; HRMS (ESI): *m*/*z* calcd for $[C_{22}H_{22}NO_2S]^+$: 364.1366; found: 364.1378.

*4.2.5. 1-Isopropyl-3,3-dimethyl-3,3a-dihydrooxazolo[4,3-b][1,3]benzothiazin-9-one (1R*,3aS*)-**2e** and (1R*,3aR*)-**2e**.* Following **GP 1**, 2, 5-dihydrooxazole **1e** (0.71 g, 5.0 mmol) and thiosalicylic acid (3.85 g, 25.0 mmol) were used. After column chromatography on silica gel (solvent: *n*-hexane/ethyl acetate, 6:1) two diastereomers were isolated (1*R**,3a*S**)-**2e** and (1*R**,3a*R**)-**2e**, ratio of diastereomers 79:21 (determined from $^1$H NMR spectra of crude product); total yield: 0.79 g, 57%.

*4.2.5.1. Major diastereomer (1R*,3aS*)-**2e**.* Colourless solid (0.64 g, 46%); $R_f$=0.71 (*n*-hexane/ethyl acetate, 6:1); mp 87–91 °C; IR: *ν* 2976, 2962, 2933, 2875, 1641, 1590, 1444, 1416, 1385, 1157, 741 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$): *δ* 0.76 (d, $^3J$=7.0 Hz, 3H, CH(C*H*$_3$)$_2$), 1.02 (d, $^3J$=7.1 Hz, 3H, CH(C*H*$_3$)$_2$), 1.39 (s, 3H, OC(C*H*$_3$)$_2$CH), 1.43 (s, 3H, OC(C*H*$_3$)$_2$CH), 2.91 (dsept, $^3J$=2.1 Hz, $^3J$=7.0 Hz, 1H, C*H*$(CH_3)_2$), 4.94 (s, 1H, SCH), 5.39 (d, $^3J$=2.1 Hz, 1H, OCHN), 7.24–7.27 (m, 2H, ArH), 7.35–7.38 (m, 1H, ArH), 8.01–8.03 (m, 1H, ArH); $^{13}$C NMR (125 MHz, $CDCl_3$): *δ* 13.7 (CH(*C*H$_3$)$_2$), 17.8 (CH(*C*H$_3$)$_2$), 22.3 (OC(*C*H$_3$)$_2$CH), 25.0 (OC(*C*H$_3$)$_2$CH), 28.4 (*C*H$(CH_3)_2$), 66.1 (SCH), 81.5 (O*C*$(CH_3)_2$CH), 92.7 (OCHN), 126.4 (ArCH), 127.4 (ArCH), 129.6 (ArCH), 130.7 (ArC), 132.1 (ArCH), 133.3 (ArC), 161.1 (CO); MS (CI, isobutane): *m*/*z* (%)=278.2 (100) $[MH]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{15}H_{20}NO_2S]^+$: 278.1215; found: 278.1214.

*4.2.5.2. Minor diastereomer (1R*,3aR*)-**2e**.* Colourless solid (0.15 g, 11%); $R_f$=0.54 (*n*-hexane/ethyl acetate, 6:1); mp 63–65 °C; IR: *ν* 2970, 2931, 2853, 1644, 1592, 1402, 1386, 1149, 744 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$): *δ* 0.83 (d, $^3J$=7.0 Hz, 3H, CH(C*H*$_3$)$_2$), 1.03 (d, $^3J$=7.1 Hz, 3H, CH(C*H*$_3$)$_2$), 1.40 (s, 3H, OC(C*H*$_3$)$_2$CH), 1.49 (s, 3H, OC(C*H*$_3$)$_2$CH), 2.87 (dsept, $^3J$=2.3 Hz, $^3J$=7.0 Hz, 1H, C*H*$(CH_3)_2$), 5.12 (s, 1H, SCH), 5.33 (d, $^3J$=2.3 Hz, 1H, OCHN), 7.25–7.28 (m, 1H, ArH), 7.32–7.38 (m, 2H, ArH), 8.11–8.13 (m, 1H, ArH); $^{13}$C NMR (125 MHz, $CDCl_3$): *δ* 14.1 (CH(*C*H$_3$)$_2$), 18.2 (CH(*C*H$_3$)$_2$), 23.8 (OC(*C*H$_3$)$_2$CH), 26.6 (OC(*C*H$_3$)$_2$CH), 27.2 (*C*H$(CH_3)_2$), 70.8 (SCH), 80.5 (O*C*$(CH_3)_2$CH), 93.3 (OCHN), 126.0 (ArCH), 128.0 (ArCH), 129.6 (ArC), 130.2 (ArCH), 132.0 (ArCH), 137.0 (ArC), 162.1 (CO); MS (CI, isobutane): *m*/*z* (%): 278.2 (100) $[MH]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{15}H_{20}NO_2S]^+$: 278.1215; found: 278.1214.

*4.2.6. 1-tert-Butyl-3,3-dimethyl-3,3a-dihydrooxazolo[4,3-b][1,3]benzothiazin-9-one (1R*,3aS*)-**2f** and (1R*,3aR*)-**2f**.* Following **GP 1**, 2,5-dihydrooxazole **1f** (0.78 g, 5.0 mmol) and thiosalicylic acid (3.85 g, 25.0 mmol) were used. After column chromatography on silica gel (solvent: *n*-hexane/ethyl acetate, 5:1) two diastereomers were isolated (1*R**,3a*S**)-**2f** and (1*R**,3a*R**)-**2f**, ratio of diastereomers 72:28 (determined from $^1$H NMR spectra of crude product); total yield: 0.59 g, 40%.

*4.2.6.1. Major diastereomer (1R*,3aS*)-**2f**.* Yellow oil (0.50 g, 34%); $R_f$=0.81 (*n*-hexane/ethyl acetate, 5:1); IR: *ν* 2974, 2905, 1651, 1590, 1443, 1394, 1156, 740 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$): *δ* 0.99 (s, 9H, C$(CH_3)_3$), 1.28 (s, 3H, OC(C*H*$_3$)$_2$CH), 1.38 (s, 3H, OC(C*H*$_3$)$_2$CH), 4.90 (s, 1H, SCH), 5.50 (s, 1H, OCHN), 7.19–7.23 (m, 2H, ArH), 7.33–7.37 (m, 1H, ArH), 7.97–7.99 (m, 1H, ArH); $^{13}$C NMR (125 MHz, $CDCl_3$): *δ* 22.1 (OC(*C*H$_3$)$_2$CH), 24.1 (OC(*C*H$_3$)$_2$CH), 25.9 (C(*C*H$_3$)$_3$), 38.2 (*C*$(CH_3)_3$), 64.5 (SCH), 82.4 (O*C*$(CH_3)_2$CH), 95.1 (OCHN), 126.1 (ArCH), 126.3 (ArCH), 129.7 (ArCH), 129.8 (ArC), 131.8 (ArC), 132.1 (ArCH), 162.5 (CO); MS (CI, isobutane): *m*/*z* (%)=292.2 (100) $[MH]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{16}H_{22}NO_2S]^+$: 292.1371; found: 292.1370.

*4.2.6.2. Minor diastereomer (1R*,3aR*)-**2f**.* Yellow oil (0.09 g, 6%); $R_f$=0.71 (*n*-hexane/ethyl acetate, 5:1); IR: *ν* 2964, 2931, 1668, 1591, 1442, 1389, 1370, 742 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$): *δ* 1.07 (s, 9H, C$(CH_3)_3$), 1.40 (s, 3H, OC(C*H*$_3$)$_2$CH), 1.51 (s, 3H, OC(C*H*$_3$)$_2$CH), 5.09 (s, 1H, SCH), 5.37 (s, 1H, OCHN), 7.34–7.40 (m, 2H, ArH), 7.45–7.48 (m, 1H, ArH), 8.15–8.17 (m, 1H, ArH); $^{13}$C NMR (125 MHz, $CDCl_3$): *δ* 24.3 (OC(*C*H$_3$)$_2$CH), 26.1 (OC(*C*H$_3$)$_2$CH), 26.7 (C(*C*H$_3$)$_3$), 36.7 (*C*$(CH_3)_3$), 72.9 (SCH), 88.7 (O*C*$(CH_3)_2$CH), 97.3 (OCHN), 127.9 (ArCH), 128.0 (ArCH), 129.7 (ArC), 130.7 (ArCH), 133.3 (ArC), 133.4 (ArCH), 163.6 (CO); MS (CI, isobutane): *m*/*z* (%)=292.2 (100) $[MH]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{16}H_{22}NO_2S]^+$: 292.1371; found: 292.1370.

### 4.3. General procedure for synthesis of γ-oxavalerolactams 3 (GP 2)

Under exclusion of moisture, 1 equiv of 2,5-dihydrooxazole and 1.2 equiv of salicyl chloride in benzene (20 mL) were refluxed for several hours. After cooling down to room temperature, the reaction mixture was washed with saturated sodium bicarbonate solution (3×20 mL) and water (3×20 mL) and dried with magnesium sulfate. After filtration, the solvent was removed under reduced pressure and the crude product was purified as described below.

*4.3.1. (RS)-1,1,3,3-Tetramethyl-3,3a-dihydrooxazolo[4,3-b][1,3]benzoxazin-9-one **3a**.* Following **GP 2**, 2,5-dihydrooxazole **1a** (0.64 g,

5.0 mmol) and salicyl chloride (0.94 g, 6.0 mmol) were used. The product was purified by column chromatography on silica gel (solvent: *n*-hexane/ethyl acetate, 1:1) and obtained as yellow solid (0.74 g, 60%); $R_f$=0.91 (*n*-hexane/ethyl acetate, 1:1); mp 51–54 °C; IR: $\nu$ 3067, 2985, 2937, 1672, 1610, 1464, 1420, 1374, 760 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 1.44 (s, 3H, OC($CH_3$)$_2$CH), 1.47 (s, 3H, OC($CH_3$)$_2$CH), 1.65 (s, 3H, OC($CH_3$)$_2$N), 1.76 (s, 3H, OC($CH_3$)$_2$N), 5.28 (s, 1H, OC($CH_3$)$_2$C*H*), 6.98 (dd, $^3J$=8.2 Hz, $^4J$=0.9 Hz, 1H, ArH), 7.12 (ddd, $^3J$=7.1 Hz, $^3J$=7.8 Hz, $^4J$=0.9 Hz, 1H, ArH), 7.45 (ddd, $^3J$=7.1 Hz, $^3J$=8.2 Hz, $^4J$=1.6 Hz, 1H, ArH), 7.94 (dd, $^3J$=7.8 Hz, $^4J$=1.6 Hz, 1H, ArH); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 23.2 (OC($CH_3$)$_2$CH), 26.7 (OC($CH_3$)$_2$CH), 27.3 (OC($CH_3$)$_2$N), 27.9 (OC($CH_3$)$_2$N), 80.1 (O*C*($CH_3$)$_2$CH), 91.5 (OC($CH_3$)$_2$*C*H), 93.4 (O*C*($CH_3$)$_2$N), 116.6 (ArCH), 119.2 (ArC), 122.8 (ArCH), 127.8 (ArCH), 134.1 (ArCH), 156.9 (ArC), 159.4 (CO); MS (CI, isobutane): *m*/*z* (%)=248.2 (100) $[MH]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{14}H_{18}NO_3]^+$: 248.1287; found: 248.1286.

*4.3.2. (RS)-Spiro[3,3-dimethyl-3,3a-dihydrooxazolo[4,3-b][1,3]benzoxazin-9-one-1,1′-cyclohexane]* ***3b***. Following **GP 2**, 2,5-dihydrooxazole **1b** (0.84 g, 5.0 mmol) and salicyl chloride (0.94 g, 6.0 mmol) were used. The product was purified by column chromatography on silica gel (solvent: *n*-hexane/ethyl acetate, 2:1) and obtained as colourless solid (0.61 g, 42%); $R_f$=0.89 (*n*-hexane/ethyl acetate, 2:1); mp 115–119 °C; IR: $\nu$ 2983, 2929, 2861, 1663, 1610, 1464, 1421, 749 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 1.26–1.32 (m, 1H, –($CH_2$)$_5$–), 1.41 (s, 3H, $CH_3$), 1.46 (s, 3H, $CH_3$), 1.53–1.73 (m, 7H, –($CH_2$)$_5$–), 2.43–2.56 (m, 2H, –($CH_2$)$_5$–), 5.25 (s, 1H, OC($CH_3$)$_2$C*H*), 6.96 (dd, $^3J$=8.2 Hz, $^4J$=0.9 Hz, 1H, ArH), 7.10 (ddd, $^3J$=6.8 Hz, $^3J$=7.8 Hz, $^4J$=0.9 Hz, 1H, ArH), 7.42 (ddd, $^3J$=6.8 Hz, $^3J$=8.2 Hz, $^4J$=1.6 Hz, 1H, ArH), 7.93 (dd, $^3J$=7.8 Hz, $^4J$=1.6 Hz, 1H, ArH); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 22.6 (–($CH_2$)$_5$–), 23.0 (–($CH_2$)$_5$–), 23.4 ($CH_3$), 24.6 (–($CH_2$)$_5$–), 27.0 ($CH_3$), 35.0 (–($CH_2$)$_5$–), 36.2 (–($CH_2$)$_5$–), 79.7 (O*C*($CH_3$)$_2$CH), 91.5 (OC($CH_3$)$_2$*C*H), 94.8 (OCN), 116.5 (ArCH), 119.5 (ArC), 122.7 (ArCH), 127.8 (ArCH), 134.0 (ArCH), 156.7 (ArC), 159.4 (CO); MS (CI, isobutane): *m*/*z* (%)=288.2 (100) $[MH]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{17}H_{22}NO_3]^+$: 288.1600; found: 288.1601.

*4.3.3. 1,1,3-Trimethyl-3-phenyl-3,3a-dihydrooxazolo[4,3-b][1,3]benzoxazin-9-one (3R*,3aR*)-* ***3c*** *and (3R*,3aS*)-* ***3c***. Following **GP 2**, 2,5-dihydrooxazole **1c** (0.95 g, 5.0 mmol) and salicyl chloride (0.94 g, 6.0 mmol) were used. After column chromatography on silica gel (solvent: *n*-hexane/ethyl acetate, 3:1) two diastereomers were isolated (3*R**,3a*R**)-**3c** and (3*R**,3a*S**)-**3c**, ratio of diastereomers 83:17 (determined from $^1H$ NMR spectra of crude product); total yield: 0.69 g, 45%.

*4.3.3.1. Major diastereomer (3R*,3aR*)-* ***3c***. Yellow oil (0.61 g, 39%); $R_f$=0.74 (*n*-hexane/ethyl acetate, 3:1); IR: $\nu$ 2990, 2936, 1675, 1612, 1466, 1415, 755, 700 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 1.70 (s, 3H, OC($CH_3$)$_2$N), 1.74 (s, 3H, OC($CH_3$)CH), 1.91 (s, 3H, OC($CH_3$)$_2$N), 5.53 (s, 1H, OC($CH_3$)C*H*), 7.07 (d, $^3J$=8.2 Hz, 1H, ArH), 7.13 (ddd, $^3J$=6.9 Hz, $^3J$=7.8 Hz, $^4J$=0.8 Hz, 1H, ArH), 7.29–7.32 (m, 1H, ArH), 7.37–7.40 (m, 2H, ArH), 7.47 (ddd, $^3J$=6.9 Hz, $^3J$=8.2 Hz, $^4J$=1.6 Hz, 1H, ArH), 7.54–7.56 (m, 2H, ArH), 7.96 (dd, $^3J$=7.8 Hz, $^4J$=1.6 Hz, 1H, ArH); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 25.1 (OC($CH_3$)CH), 27.5 (OC($CH_3$)$_2$N), 27.5 (OC($CH_3$)$_2$N), 83.2 (O*C*($CH_3$)CH), 91.8 (OC($CH_3$)*C*H), 94.0 (O*C*($CH_3$)$_2$N), 116.8 (ArCH), 119.2 (ArC), 122.9 (ArCH), 124.5 (ArCH), 127.6 (ArCH), 127.8 (ArCH), 128.4 (ArCH), 134.2 (ArCH), 144.1 (ArC), 156.8 (ArC), 159.4 (CO); MS (CI, isobutane): *m*/*z* (%)=310.4 (100) $[MH]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{19}H_{20}NO_3]^+$: 310.1443; found: 310.1443.

*4.3.3.2. Minor diastereomer (3R*,3aS*)-* ***3c***. Yellow oil (0.08 g, 5%); $R_f$=0.63 (*n*-hexane/ethyl acetate, 3:1); IR: $\nu$ 2985, 2934, 1674, 1611, 1467, 1415, 758, 700 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 1.82 (s, 6H, OC($CH_3$)$_2$N, OC($CH_3$)CH), 1.89 (s, 3H, OC($CH_3$)$_2$N), 5.63 (s, 1H, OC($CH_3$)C*H*), 6.89 (d, $^3J$=8.2 Hz, 1H, ArH), 7.07 (ddd, $^3J$=6.9 Hz, $^3J$=7.8 Hz, $^4J$=0.9 Hz, 1H, ArH), 7.29–7.33 (m, 1H, ArH), 7.37–7.40 (m, 3H, ArH), 7.59–7.62 (m, 2H, ArH), 7.91 (dd, $^3J$=7.8 Hz, $^4J$=1.6 Hz, 1H, ArH); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 27.1 (OC($CH_3$)$_2$N), 28.1 (OC($CH_3$)$_2$N), 29.8 (OC($CH_3$)CH), 83.8 (O*C*($CH_3$)CH), 93.0 (OC($CH_3$)*C*H), 95.1 (O*C*($CH_3$)$_2$N), 116.9 (ArCH), 119.2 (ArC), 122.8 (ArCH), 126.7 (ArCH), 127.4 (ArCH), 127.6 (ArCH), 127.7 (ArCH), 134.1 (ArCH), 141.1 (ArC), 156.8 (ArC), 159.8 (CO); MS (CI, isobutane): *m*/*z* (%)=310.4 (73) $[MH]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{19}H_{20}NO_3]^+$: 310.1443; found: 310.1443.

*4.3.4. Spiro[3-methyl-3-phenyl-3,3a-dihydrooxazolo[4,3-b][1,3]benzoxazin-9-one-1,1′-cyclohexane] (3R*,3aR*)-* ***3d*** *and (3R*,3aS*)-* ***3d***. Following **GP 2**, 2,5-dihydrooxazole **1d** (1.15 g, 5.0 mmol) and salicyl chloride (0.94 g, 6.0 mmol) were used. After column chromatography on silica gel (solvent: *n*-hexane/ethyl acetate, 5:1) two diastereomers were isolated (3*R**,3a*R**)-**3d** and (3*R**,3a*S**)-**3d**, ratio of diastereomers 85:15 (determined from $^1H$ NMR spectra of crude product); total yield: 0.84 g, 48%.

*4.3.4.1. Major diastereomer (3R*,3aR*)-* ***3d***. Colourless oil (0.72 g, 41%); $R_f$=0.63 (*n*-hexane/ethyl acetate, 5:1); IR: $\nu$ 2932, 2860, 1673, 1611, 1465, 1413, 754, 699 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 1.33–1.42 (m, 1H, –($CH_2$)$_5$–), 1.59–1.63 (m, 1H, –($CH_2$)$_5$–), 1.73 (s, 3H, $CH_3$), 1.75–1.89 (m, 6H, –($CH_2$)$_5$–), 2.44–2.51 (m, 1H, –($CH_2$)$_5$–), 2.66–2.72 (m, 1H, –($CH_2$)$_5$–), 5.52 (s, 1H, OC($CH_3$)C*H*), 7.07 (dd, $^3J$=8.2 Hz, $^4J$=0.8 Hz, 1H, ArH), 7.13 (ddd, $^3J$=7.0 Hz, $^3J$=7.8 Hz, $^4J$=0.8 Hz, 1H, ArH), 7.30–7.33 (m, 1H, ArH), 7.38–7.42 (m, 2H, ArH), 7.47 (ddd, $^3J$=7.0 Hz, $^3J$=8.2 Hz, $^4J$=1.6 Hz, 1H, ArH), 7.58–7.60 (m, 2H, ArH), 7.96 (dd, $^3J$=7.8 Hz, $^4J$=1.6 Hz, 1H, ArH); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 22.8 (–($CH_2$)$_5$–), 23.2 (–($CH_2$)$_5$–), 24.7 (–($CH_2$)$_5$–), 25.3 ($CH_3$), 35.5 (–($CH_2$)$_5$–), 35.7 (–($CH_2$)$_5$–), 83.0 (O*C*($CH_3$)CH), 91.7 (OC($CH_3$)*C*H), 95.3 (OCN), 116.7 (ArCH), 119.4 (ArC), 122.9 (ArCH), 124.5 (ArCH), 127.6 (ArCH), 127.9 (ArCH), 128.4 (ArCH), 134.1 (ArCH), 144.5 (ArC), 156.7 (ArC), 159.5 (CO); MS (CI, isobutane): *m*/*z* (%)=350.3 (100) $[MH]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{22}H_{24}NO_3]^+$: 350.1756; found: 350.1756.

*4.3.4.2. Minor diastereomer (3R*,3aS*)-* ***3d***. Yellow oil (0.12 g, 7%); $R_f$=0.54 (*n*-hexane/ethyl acetate, 5:1); IR: $\nu$ 2933, 2861, 1672, 1611, 1466, 1414, 758, 700 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 1.36–1.41 (m, 1H, –($CH_2$)$_5$–), 1.73–1.95 (m, 7H, –($CH_2$)$_5$–), 1.82 (s, 3H, $CH_3$), 2.45–2.51 (m, 1H, –($CH_2$)$_5$–), 2.60–2.66 (m, 1H, –($CH_2$)$_5$–), 5.62 (s, 1H, OC($CH_3$)C*H*), 6.87 (dd, $^3J$=8.2 Hz, $^4J$=0.9 Hz, 1H, ArH), 7.08 (ddd, $^3J$=7.7 Hz, $^3J$=8.5 Hz, $^4J$=0.9 Hz, 1H, ArH), 7.29–7.33 (m, 1H, ArH), 7.37–7.40 (m, 3H, ArH), 7.59–7.61 (m, 2H, ArH), 7.91 (dd, $^3J$=7.7 Hz, $^4J$=1.6 Hz, 1H, ArH); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 22.8 (–($CH_2$)$_5$–), 23.2 (–($CH_2$)$_5$–), 24.7 (–($CH_2$)$_5$–), 30.1 ($CH_3$), 34.8 (–($CH_2$)$_5$–), 36.6 (–($CH_2$)$_5$–), 83.8 (OC($CH_3$)CH), 93.1 (OC($CH_3$)CH), 96.6 (OCN), 116.9 (ArCH), 119.5 (ArC), 122.7 (ArCH), 126.6 (ArCH), 127.4 (ArCH), 127.7 (ArCH), 127.8 (ArCH), 134.1 (ArCH), 141.5 (ArC), 156.7 (ArC), 160.0 (CO); MS (CI, isobutane): *m*/*z* (%)=350.3 (100) $[MH]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{22}H_{24}NO_3]^+$: 350.1756; found: 350.1755.

*4.3.5. 1-Isopropyl-3,3-dimethyl-3,3a-dihydrooxazolo[4,3-b][1,3]benzoxazin-9-one (1R*,3aR*)-* ***3e*** *and (1R*,3aS*)-* ***3e***. Following **GP 2**, 2,5-dihydrooxazole **1e** (0.71 g, 5.0 mmol) and salicyl chloride (0.94 g, 6.0 mmol) were used. After column chromatography on silica gel (solvent: *n*-hexane/ethyl acetate, 6:1) two diastereomers were isolated (1*R**,3a*R**)-**3e** and (1*R**,3a*S**)-**3e**, ratio of diastereomers 67:33 (determined from $^1H$ NMR spectra of crude product); total yield: 0.40 g, 31%.

*4.3.5.1. Major diastereomer (1R*,3aR*)-* ***3e***. Colourless solid (0.29 g, 22%); $R_f$=0.33 (*n*-hexane/ethyl acetate, 6:1); mp 94–95 °C;

IR: $\nu$ 2962, 2933, 2877, 1681, 1610, 1467, 1428, 764 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 0.73 (d, $^3J$=6.9 Hz, 3H, CH($CH_3$)$_2$), 1.01 (d, $^3J$=6.9 Hz, 3H, CH($CH_3$)$_2$), 1.36 (s, 3H, OC($CH_3$)$_2$CH), 1.47 (s, 3H, OC($CH_3$)$_2$CH), 2.86 (dsept, $^3J$=1.8 Hz, $^3J$=6.9 Hz, 1H, C*H*($CH_3$)$_2$), 5.11 (s, 1H, OC($CH_3$)$_2$C*H*), 5.16 (d, $^3J$=1.8 Hz, 1H, OCHN), 6.99 (d, $^3J$=8.2 Hz, 1H, ArH), 7.09 (dd, $^3J$=7.4 Hz, $^3J$=7.8 Hz, 1H, ArH), 7.43 (ddd, $^3J$=7.4 Hz, $^3J$=8.2 Hz, $^4J$=1.2 Hz, 1H, ArH), 7.93 (dd, $^3J$=7.8 Hz, $^4J$=1.2 Hz, 1H, ArH); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 13.5 (CH(*C*H$_3$)$_2$), 18.2 (CH(*C*H$_3$)$_2$), 22.1 (OC(*C*H$_3$)$_2$CH), 25.0 (OC(*C*H$_3$)$_2$CH), 27.4 (*C*H(CH$_3$)$_2$), 80.3 (O*C*(CH$_3$)$_2$CH), 91.5 (OCHN), 92.8 (OC(CH$_3$)$_2$CH), 116.8 (ArCH), 119.4 (ArC), 122.5 (ArCH), 128.1 (ArCH), 134.2 (ArCH), 157.2 (ArC), 160.6 (CO); MS (CI, isobutane): $m/z$ (%)=262.4 (100) $[MH]^+$; HRMS (CI, isobutane): $m/z$ calcd for $[C_{15}H_{20}NO_3]^+$: 262.1443; found: 262.1443.

*4.3.5.2. Minor diastereomer (1R*,3aS*)-**3e**.* Colourless solid (0.11 g, 8%); $R_f$=0.47 (*n*-hexane/ethyl acetate, 6:1); mp 79–81 °C; IR: $\nu$ 2962, 2932, 2875, 1673, 1612, 1468, 1431, 755 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 0.83 (d, $^3J$=6.8 Hz, 3H, CH($CH_3$)$_2$), 1.02 (d, $^3J$=6.8 Hz, 3H, CH($CH_3$)$_2$), 1.32 (s, 3H, OC($CH_3$)$_2$CH), 1.47 (s, 3H, OC($CH_3$)$_2$CH), 2.73 (dsept, $^3J$=1.8 Hz, $^3J$=6.8 Hz, 1H, C*H*($CH_3$)$_2$), 5.16 (s, 1H, OC($CH_3$)$_2$C*H*), 5.35 (d, $^3J$=1.8 Hz, 1H, OCHN), 6.97 (d, $^3J$=8.2 Hz, 1H, ArH), 7.11 (dd, $^3J$=7.0 Hz, $^3J$=7.8 Hz, 1H, ArH), 7.43 (ddd, $^3J$=7.0 Hz, $^3J$=8.2 Hz, $^4J$=1.0 Hz, 1H, ArH), 7.90 (dd, $^3J$=7.8 Hz, $^4J$=1.0 Hz, 1H, ArH); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 13.9 (CH(*C*H$_3$)$_2$), 17.3 (CH(*C*H$_3$)$_2$), 19.7 (OC(*C*H$_3$)$_2$CH), 24.3 (OC(*C*H$_3$)$_2$CH), 29.8 (*C*H(CH$_3$)$_2$), 80.3 (O*C*(CH$_3$)$_2$CH), 90.5 (OC(CH$_3$)$_2$CH), 90.6 (OCHN), 116.5 (ArCH), 119.2 (ArC), 122.9 (ArCH), 127.6 (ArCH), 134.0 (ArCH), 156.3 (ArC), 158.5 (CO); MS (CI, isobutane): $m/z$ (%)=262.3 (100) $[MH]^+$; HRMS (CI, isobutane): $m/z$ calcd for $[C_{15}H_{20}NO_3]^+$: 262.1443; found: 262.1444.

*4.3.6. 1-tert-Butyl-3,3-dimethyl-3,3a-dihydrooxazolo[4,3-b][1,3]benzoxazin-9-one (1R*,3aR*)-**3f** and (1R*,3aS*)-**3f**.* Following **GP 2**, 2,5-dihydrooxazole **1f** (0.78 g, 5.0 mmol) and salicyl chloride (0.94 g, 6.0 mmol) were used. After column chromatography on silica gel (solvent: dichloromethane) two diastereomers were isolated (1*R**,3a*R**)-**3f** and (1*R**,3a*S**)-**3f**, ratio of diastereomers 61:39 (determined from $^1H$ NMR spectra of crude product); total yield: 0.34 g, 25%.

*4.3.6.1. Major diastereomer (1R*,3aR*)-**3f**.* Colourless solid (0.22 g, 16%); $R_f$=0.69 (dichloromethane); mp 78–80 °C; IR: $\nu$ 2987, 2898, 1685, 1611, 1470, 760 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 1.07 (s, 9H, C(CH$_3$)$_3$), 1.37 (s, 3H, OC(C*H*$_3$)$_2$CH), 1.49 (s, 3H, OC(C*H*$_3$)$_2$CH), 5.08 (s, 1H, OCHN), 5.11 (s, 1H, OC(CH$_3$)$_2$C*H*), 7.02 (dd, $^3J$=8.2 Hz, $^4J$=0.8 Hz, 1H, ArH), 7.11 (ddd, $^3J$=7.0 Hz, $^3J$=7.8 Hz, $^4J$=0.8 Hz, 1H, ArH), 7.45 (ddd, $^3J$=7.0 Hz, $^3J$=8.2 Hz, $^4J$=1.6 Hz, 1H, ArH), 7.98 (dd, $^3J$=7.8 Hz, $^4J$=1.6 Hz, 1H, ArH); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 22.6 (OC(*C*H$_3$)$_2$CH), 25.7 (OC(*C*H$_3$)$_2$CH), 26.3 (C(*C*H$_3$)$_3$), 36.1 (*C*(CH$_3$)$_3$), 78.9 (O*C*(CH$_3$)$_2$CH), 94.5 (OC(CH$_3$)$_2$*C*H), 95.6 (OCHN), 116.7 (ArCH), 119.8 (ArC), 122.4 (ArCH), 128.5 (ArCH), 134.3 (ArCH), 157.6 (ArC), 162.4 (CO); MS (CI, isobutane): $m/z$ (%)=276.3 (100) $[MH]^+$, 218.2 (20) $[M-C_4H_9]^+$; HRMS (CI, isobutane): $m/z$ calcd for $[C_{16}H_{22}NO_3]^+$: 276.1600; found: 276.1598.

*4.3.6.2. Minor diastereomer (1R*,3aS*)-**3f**.* Colourless oil (0.12 g, 9%); $R_f$=0.60 (dichloromethane); IR: $\nu$ 2976, 2874, 1675, 1613, 1468, 1418, 755 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 1.00 (s, 9H, C(CH$_3$)$_3$), 1.20 (s, 3H, OC(C*H*$_3$)$_2$CH), 1.46 (s, 3H, OC(C*H*$_3$)$_2$CH), 5.28 (s, 1H, OCHN), 5.34 (s, 1H, OC(CH$_3$)$_2$C*H*), 6.92 (dd, $^3J$=8.2 Hz, $^4J$=0.9 Hz, 1H, ArH), 7.08 (ddd, $^3J$=7.6 Hz, $^3J$=7.7 Hz, $^4J$=0.9 Hz, 1H, ArH), 7.41 (ddd, $^3J$=7.6 Hz, $^3J$=8.2 Hz, $^4J$=1.7 Hz, 1H, ArH), 7.85 (dd, $^3J$=7.7 Hz, $^4J$=1.7 Hz, 1H, ArH); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 20.1 (OC(*C*H$_3$)$_2$CH), 23.9 (OC(*C*H$_3$)$_2$CH), 25.5 (C(*C*H$_3$)$_3$), 37.8 (*C*(CH$_3$)$_3$), 80.7 (O*C*(CH$_3$)$_2$CH), 90.7 (OCHN), 93.4 (OC(CH$_3$)$_2$*C*H), 115.9 (ArCH), 118.2 (ArC), 122.6 (ArCH), 127.6 (ArCH), 133.9 (ArCH), 155.3 (ArC), 159.1 (CO); MS (CI, isobutane): $m/z$ (%)=276.3 (100) $[MH]^+$; HRMS (CI, isobutane): $m/z$ calcd for $[C_{16}H_{22}NO_3]^+$: 276.1600; found: 276.1599.

### 4.4. General procedure for synthesis of γ-azavalerolactams 4 (GP 3)

Under argon atmosphere, 1 equiv of anthranilic acid and 5 equiv of thionyl chloride were refluxed in anhydrous benzene (30 mL) for 2–3 h. After cooling the reaction mixture to room temperature, the excess of thionyl chloride and the solvent were removed under reduced pressure at room temperature. Under exclusion of moisture, the remaining yellow oil was resolved in anhydrous benzene (10 mL) before 1 equiv of 2,5-dihydrooxazole dissolved in anhydrous benzene (10 mL) was added. After stirring overnight at room temperature, the solvent was removed under reduced pressure. The obtained crude product dissolved in acetone (15 mL) and 2.5 equiv of potassium permanganate were refluxed for 2 h. After cooling to room temperature, the solid was filtered off and the solvent was removed under reduced pressure. The crude product was purified as described below.

*4.4.1. 1,1,3,3-Tetramethyl-3H-oxazolo[4,3-b]chinazolin-9-one **4a**.* Following **GP 3**, anthranilic acid (0.34 g, 2.5 mmol), thionyl chloride (0.9 mL, 12.5 mmol), 2,5-dihydrooxazole **1a** (0.32 g, 2.5 mmol) and potassium permanganate (0.99 g, 6.25 mmol) were used. The product was purified by column chromatography on silica gel (solvent: *n*-hexane/ethyl acetate, 2:1) and obtained as colourless solid (0.29 g, 48%); $R_f$=0.69 (*n*-hexane/ethyl acetate, 2:1); mp 114–116 °C; IR: $\nu$ 3068, 2987, 2936, 1670, 1634, 1606, 1469, 1378, 777 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 1.65 (s, 6H, OC(CH$_3$)$_2$N), 1.85 (s, 6H, OC(C*H*$_3$)$_2$C), 7.46 (ddd, $^3J$=7.0 Hz, $^3J$=8.1 Hz, $^4J$=1.1 Hz, 1H, ArH), 7.69 (dd, $^3J$=8.1 Hz, $^4J$=1.1 Hz, 1H, ArH), 7.74 (ddd, $^3J$=7.0 Hz, $^3J$=8.1 Hz, $^3J$=1.3 Hz, 1H, ArH), 8.29 (dd, $^3J$=8.1 Hz, $^4J$=1.3 Hz, 1H, ArH); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 27.4 (OC(*C*H$_3$)$_2$C), 28.2 (OC(*C*H$_3$)$_2$N), 81.2 (O*C*(CH$_3$)$_2$C), 97.1 (O*C*(CH$_3$)$_2$N), 121.3 (ArC), 126.4 (ArCH), 126.5 (ArCH), 127.1 (ArCH), 134.3 (ArCH), 149.6 (ArC), 159.3 (CO), 159.5 (CN); MS (CI, isobutane): $m/z$ (%)=245.1 (100) $[MH]^+$; HRMS (CI, isobutane): $m/z$ calcd for $[C_{14}H_{17}N_2O_2]^+$: 245.1290; found: 245.1294.

*4.4.2. Spiro[3,3-dimethyl-3H-oxazolo[4,3-b]chinazolin-9-one-1,1′-cyclohexane] **4b**.* Following **GP 3**, anthranilic acid (0.34 g, 2.5 mmol), thionyl chloride (0.9 mL, 12.5 mmol), 2,5-dihydrooxazole **1b** (0.42 g, 2.5 mmol) and potassium permanganate (0.99 g, 6.25 mmol) were used. The product was purified by column chromatography on silica gel (solvent: *n*-hexane/ethyl acetate, 2:1) and obtained as yellow solid (0.24 g, 36%); $R_f$=0.79 (*n*-hexane/ethyl acetate, 2:1); mp 161–163 °C; IR: $\nu$ 2939, 2855, 1680, 1632, 1607, 1469, 1381, 775 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 1.31–1.42 (m, 1H, –(CH$_2$)$_5$–), 1.65 (s, 6H, OC(CH$_3$)$_2$C), 1.66–1.79 (m, 7H, –(CH$_2$)$_5$–), 2.70–2.76 (m, 2H, –(CH$_2$)$_5$–), 7.45 (ddd, $^3J$=6.8 Hz, $^3J$=8.0 Hz, $^4J$=1.1 Hz, 1H, ArH), 7.69 (dd, $^3J$=8.3 Hz, $^4J$=1.1 Hz, 1H, ArH), 7.73 (ddd, $^3J$=6.8 Hz, $^3J$=8.3 Hz, $^4J$=1.4 Hz, 1H, ArH), 8.29 (dd, $^3J$=8.0 Hz, $^4J$=1.4 Hz, 1H, ArH); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 22.5 (–(CH$_2$)$_5$–), 24.3 (–(CH$_2$)$_5$–), 28.5 (OC(*C*H$_3$)$_2$C), 35.2 (–(CH$_2$)$_5$–), 80.9 (O*C*(CH$_3$)$_2$C), 98.7 (OCN), 121.4 (ArC), 126.3 (ArCH), 126.6 (ArCH), 127.0 (ArCH), 134.2 (ArCH), 149.3 (ArC), 159.4 (CO), 159.9 (CN); MS (CI, isobutane): $m/z$ (%)=285.2 (100) $[MH]^+$; HRMS (CI, isobutane): $m/z$ calcd for $[C_{17}H_{21}N_2O_2]^+$: 285.1603; found: 285.1601.

*4.4.3. (RS)-1,1,3-Trimethyl-3-phenyl-3H-oxazolo[4,3-b]chinazolin-9-one **4c**.* Following **GP 3**, anthranilic acid (0.34 g, 2.5 mmol), thionyl chloride (0.9 mL, 12.5 mmol), 2,5-dihydrooxazole **1c** (0.47 g, 2.5 mmol) and potassium permanganate (0.99 g, 6.25 mmol) were

used. The product was purified by column chromatography on silica gel (solvent: *n*-hexane/ethyl acetate, 3:1) and obtained as colourless solid (0.37 g, 50%); $R_f$=0.69 (*n*-hexane/ethyl acetate, 3:1); mp 85–87 °C; IR: $\nu$ 3064, 2984, 2931, 1674, 1635, 1609, 1472, 1370, 767, 696 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 1.73 (s, 3H, $OC(CH_3)_2N$), 1.95 (s, 3H, $OC(CH_3)CH$), 1.99 (s, 3H, $OC(CH_3)_2N$), 7.27–7.30 (m, 1H, ArH), 7.34–7.38 (m, 2H, ArH), 7.48 (ddd, $^3J$=6.8 Hz, $^3J$=7.9 Hz, $^4J$=1.0 Hz, 1H, ArH), 7.77 (ddd, $^3J$=6.8 Hz, $^3J$=8.1 Hz, $^4J$=1.2 Hz, 1H, ArH), 7.80–7.82 (m, 3H, ArH), 8.30 (dd, $^3J$=7.9 Hz, $^4J$=1.2 Hz, 1H, ArH); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 26.4 ($OC(CH_3)_2N$), 27.5 ($OC(CH_3)_2N$), 30.6 ($OC(CH_3)_2C$), 83.4 ($OC(CH_3)_2C$), 97.7 ($OC(CH_3)_2N$), 121.4 (ArC), 125.1 (ArCH), 126.4 (ArCH), 126.6 (ArCH), 127.6 (ArCH), 127.8 (ArCH), 128.2 (ArCH), 134.3 (ArCH), 143.0 (ArC), 149.4 (ArC), 157.6 (CO), 159.2 (CN); MS (CI, isobutane): *m*/*z* (%)=307.1 (100) $[MH]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{19}H_{19}N_2O_2]^+$: 307.1447; found: 307.1448.

*4.4.4. (RS)-Spiro[3-methyl-3-phenyl-3H-oxazolo[4,3-b]chinazolin-9-one-1,1′-cyclohexane]* ***4d***. Following **GP 3**, anthranilic acid (0.34 g, 2.5 mmol), thionyl chloride (0.9 mL, 12.5 mmol), 2,5-dihydrooxazole **1d** (0.57 g, 2.5 mmol) and potassium permanganate (0.99 g, 6.25 mmol) were used. The product was purified by column chromatography on silica gel (solvent: *n*-hexane/ethyl acetate, 2:1) and obtained as yellow solid (0.41 g, 49%); $R_f$=0.82 (*n*-hexane/ethyl acetate, 2:1); mp 151–152 °C; IR: $\nu$ 3067, 2934, 2853, 1676, 1629, 1601, 1470, 1444, 1375, 778, 767, 696 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 1.36–1.45 (m, 1H, $-(CH_2)_5-$), 1.51–1.56 (m, 1H, $-(CH_2)_5-$), 1.72–1.93 (m, 6H, $-(CH_2)_5-$), 1.95 (s, 3H, $CH_3$), 2.48–2.54 (m, 1H, $-(CH_2)_5-$), 2.87–2.93 (m, 1H, $-(CH_2)_5-$), 7.26–7.30 (m, 1H, ArH), 7.34–7.37 (m, 2H, ArH), 7.47 (ddd, $^3J$=6.9 Hz, $^3J$=8.0 Hz, $^4J$=1.1 Hz, 1H, ArH), 7.76 (ddd, $^3J$=6.9 Hz, $^3J$=8.3 Hz, $^4J$=1.3 Hz, 1H, ArH), 7.80 (dd, $^3J$=8.3 Hz, $^4J$=1.1 Hz, 1H, ArH), 7.82–7.84 (m, 2H, ArH), 8.29 (dd, $^3J$=8.0 Hz, $^4J$=1.3 Hz, 1H, ArH); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 22.5 ($-(CH_2)_5-$), 22.7 ($-(CH_2)_5-$), 24.4 ($-(CH_2)_5-$), 30.9 ($CH_3$), 33.5 ($-(CH_2)_5-$), 35.4 ($-(CH_2)_5-$), 83.3 ($OC(CH_3)C$), 99.2 (OCN), 121.5 (ArC), 124.9 (ArCH), 126.5 (2×ArCH), 127.5 (ArCH), 127.7 (ArCH), 128.2 (ArCH), 134.2 (ArCH), 143.5 (ArC), 149.1 (ArC), 157.7 (CO), 159.4 (CN); MS (CI, isobutane): *m*/*z* (%)=347.0 (100) $[MH]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{22}H_{23}N_2O_2]^+$: 347.1760; found: 347.1759.

*4.4.5. (RS)-1-Isopropyl-3,3-dimethyl-3H-oxazolo[4,3-b]chinazolin-9-one* ***4e***. Following **GP 3**, anthranilic acid (0.34 g, 2.5 mmol), thionyl chloride (0.9 mL, 12.5 mmol), 2,5-dihydrooxazole **1e** (0.35 g, 2.5 mmol) and potassium permanganate (0.99 g, 6.25 mmol) were used. The product was purified by column chromatography on silica gel (solvent: *n*-hexane/ethyl acetate, 2:1) and obtained as yellow solid (0.23 g, 38%); $R_f$=0.78 (*n*-hexane/ethyl acetate, 2:1); mp 114–115 °C; IR: $\nu$ 3065, 2972, 2935, 2879, 1675, 1640, 1610, 1475, 1398, 774 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 0.74 (d, $^3J$=6.9 Hz, 3H, $CH(CH_3)_2$), 1.12 (d, $^3J$=6.9 Hz, 3H, $CH(CH_3)_2$), 1.54 (s, 3H, $OC(CH_3)_2C$), 1.70 (s, 3H, $OC(CH_3)_2C$), 3.06 (dsept, $^3J$=2.1 Hz, $^3J$=6.9 Hz, 1H, $CH(CH_3)_2$), 5.81 (d, $^3J$=2.1 Hz, 1H, OCHN), 7.46 (ddd, $^3J$=6.9 Hz, $^3J$=7.9 Hz, $^4J$=1.1 Hz, 1H, ArH), 7.70 (dd, $^3J$=8.3 Hz, $^4J$=1.1 Hz, 1H, ArH), 7.75 (ddd, $^3J$=6.9 Hz, $^3J$=8.3 Hz, $^4J$=1.3 Hz, 1H, ArH), 8.29 (dd, $^3J$=7.9 Hz, $^4J$=1.3 Hz, 1H, ArH); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 13.3 ($CH(CH_3)_2$), 17.6 ($CH(CH_3)_2$), 25.6 ($OC(CH_3)_2C$), 26.1 ($OC(CH_3)_2C$), 28.6 ($CH(CH_3)_2$), 81.6 ($OC(CH_3)_2C$), 93.2 (OCHN), 120.9 (ArC), 126.5 (ArCH), 126.6 (ArCH), 127.1 (ArCH), 134.4 (ArCH), 149.5 (ArC), 159.7 (CO), 160.0 (CN); MS (CI, isobutane): *m*/*z* (%)=259.3 (100) $[MH]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{15}H_{19}N_2O_2]^+$: 259.1447; found: 259.1448.

*4.4.6. (RS)-1-tert-Butyl-3,3-dimethyl-3H-oxazolo[4,3-b]chinazolin-9-one* ***4f***. Following **GP 3**, anthranilic acid (0.34 g, 2.5 mmol), thionyl chloride (0.9 mL, 12.5 mmol), 2,5-dihydrooxazole **1f** (0.39 g, 2.5 mmol) and potassium permanganate (0.99 g, 6.25 mmol) were used. The product was purified by column chromatography on silica gel (solvent: *n*-hexane/ethyl acetate, 4:1) and obtained as yellow solid (0.14 g, 22%); $R_f$=0.52 (*n*-hexane/ethyl acetate, 4:1); mp 68–73 °C; IR: $\nu$ 2957, 2902, 2856, 1685, 1644, 1607, 1470, 1381, 772 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 1.08 (s, 9H, $C(CH_3)_3$), 1.49 (s, 3H, $OC(CH_3)_2C$), 1.74 (s, 3H, $OC(CH_3)_2C$), 5.84 (s, 1H, OCHN), 7.46 (ddd, $^3J$=7.2 Hz, $^3J$=8.0 Hz, $^4J$=1.0 Hz, 1H, ArH), 7.69 (dd, $^3J$=8.4 Hz, $^4J$=1.0 Hz, 1H, ArH), 7.74 (ddd, $^3J$=7.2 Hz, $^3J$=8.4 Hz, $^4J$=1.4 Hz, 1H, ArH), 8.27 (dd, $^3J$=8.0 Hz, $^4J$=1.4 Hz, 1H, ArH); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 25.6 ($OC(CH_3)_2C$), 26.0 ($C(CH_3)_3$), 28.2 ($OC(CH_3)_2C$), 38.0 ($C(CH_3)_3$), 81.5 ($OC(CH_3)_2C$), 97.1 (OCHN), 121.3 (ArC), 126.4 (ArCH), 126.8 (2×ArCH), 134.4 (ArCH), 149.1 (ArC), 160.6 (CO), 160.8 (CN);MS (CI, isobutane): *m*/*z* (%)=273.3 (100) $[MH]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{16}H_{21}N_2O_2]^+$: 273.1603; found: 273.1606.

### 4.5. Preparation of (*RS*)-1,1,3,3-tetramethyl-3a,4-dihydro-3*H*-oxazolo[4,3-*b*]chinazolin-9-one 5

Under argon atmosphere, anthranilic acid (0.34 g, 2.5 mmol) and thionyl chloride (0.9 mL, 12.5 mmol) were refluxed in anhydrous benzene (30 mL) for 2–3 h. After cooling the reaction mixture to room temperature, the excess of thionyl chloride and solvent were removed under reduced pressure at room temperature. Under exclusion of moisture, the remaining yellow oil was resolved in anhydrous benzene (10 mL) before 2,5-dihydrooxazole **1a** (0.32 g, 2.5 mmol) dissolved in anhydrous benzene (10 mL) was added. After stirring overnight at room temperature, the solvent was removed under reduced pressure. The product was purified by column chromatography on silica gel (solvent: *n*-hexane/ethyl acetate, 2:1) and obtained as colourless solid (0.17 g, 28%); $R_f$=0.43 (*n*-hexane/ethyl acetate, 2:1); mp 202–205 °C; IR: $\nu$ 3293, 2980, 2937, 1631, 1612, 1423, 1373, 752 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 1.39 (s, 3H, $OC(CH_3)_2CH$), 1.40 (s, 3H, $OC(CH_3)_2CH$), 1.64 (s, 3H, $OC(CH_3)_2N$), 1.77 (s, 3H, $OC(CH_3)_2N$), 4.12 (br s, 1H, NH), 4.94 (d, $^3J$=1.9 Hz, 1H, $OC(CH_3)_2CH$), 6.70 (dd, $^3J$=8.1 Hz, $^4J$=0.9 Hz, 1H, ArH), 6.89 (ddd, $^3J$=7.0 Hz, $^3J$=7.8 Hz, $^4J$=0.9 Hz, 1H, ArH), 7.30 (ddd, $^3J$=7.0 Hz, $^3J$=8.1 Hz, $^4J$=1.4 Hz, 1H, ArH), 7.91 (dd, $^3J$=7.8 Hz, $^4J$=1.4 Hz, 1H, ArH); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 23.4 ($OC(CH_3)_2CH$), 26.4 ($OC(CH_3)_2CH$), 26.9 ($OC(CH_3)_2N$), 27.4 ($OC(CH_3)_2N$), 75.4 ($OC(CH_3)_2CH$), 80.4 ($OC(CH_3)_2CH$), 93.7 ($OC(CH_3)_2N$), 115.0 (ArCH), 117.6 (ArC), 120.0 (ArCH), 128.2 (ArCH), 133.4 (ArCH), 146.7 (ArC), 160.7 (CO); MS (CI, isobutane): *m*/*z* (%)=247.1 (100) $[MH]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{14}H_{19}N_2O_2]^+$: 247.1447; found: 247.1442.

### Acknowledgements

The silica gel was generously supplied by Grace GmbH & Co. KG. K.J. gratefully acknowledges the Heinz Neumüller-Stiftung for a doctoral fellowship.

### References and notes

1. Thiavalerolactams: (a) Nagakura, I.; Oka, H.; Nitta, Y. *Heterocycles* **1975**, *3*, 453; (b) Nyitrai, J.; Fetter, J.; Hornyák, G.; Zauer, K.; Lempert, K.; Koczka, I.; Sági, I.; Rétháti, C. *Tetrahedron* **1978**, *34*, 1031; (c) Shimizu, H.; Ueda, N.; Kataoka, T.; Hori, M. *Chem. Pharm. Bull.* **1984**, *32*, 2571; (d) Couture, A.; Grandclaudon, P.; Huguerre, E. *Tetrahedron* **1989**, *45*, 4153; (e) Mizutani, N.; Chiou, W.-H.; Ojima, I. *Org. Lett.* **2002**, *4*, 4575; Oxavalerolactams: (f) Takacs, J. M.; Helle, M. A.; Takusagawa, F. *Tetrahedron Lett.* **1989**, *30*, 7321; (g) Bandini, E.; Martelli, G.; Spunta, G.; Bongini, A.; Panunzio, M. *Synlett* **1999**, 1735; (h) Reid, M.; Taylor, R. J. K. *Tetrahedron Lett.* **2004**, *45*, 4181; (i) Chiou, W.-H.; Mizutani, N.; Ojima, I. *J. Org. Chem.* **2007**, *72*, 1871; Azavalerolactams: (j) Veale, C. A.; Steelman, G. B.; Chow, M. M. *J. Org. Chem.* **1993**, *58*, 4490; (k) Rossi, E.; Abbiati, G.; Pini, E. *Tetrahedron* **1997**, *53*, 14107; (l) Fülöp, F.; Palkó, M.; Bernáth, G.; Sohár, P. *Synth. Commun.* **1997**, *27*, 195; (m) Servais, A.; Azzous, M.; Lopes, D.; Courillon, C.; Malacria, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 576.

2. Harada, K. Additions to the azomethine group. In *The Chemistry of the Carbon–Nitrogen Double Bond*; Patai, S., Ed.; John Wiley & Sons: London, 1970; pp 255–298.
3. Hamley, P.; Tinker, A. PCT Int. Appl. WO 0006576, 2000; *Chem. Abstr.* **2000**, *132*, 137406.
4. Sun, Q.; Kyle, D. J.; Victory, S. F. PCT Int. Appl. WO 2004013111, 2004; *Chem. Abstr.* **2004**, *140*, 181460.
5. (a) Jin, R.; Clark, S.; Weeks, A. M.; Dudman, J. T.; Gouaux, E.; Partin, K. M. *J. Neurosci.* **2005**, *25*, 9027; (b) Kessler, M.; Arai, A. C. *Brain Res.* **2006**, *1076*, 25.
6. Rogers, G. A.; Allan, M.; Harris, C.; Huang, J.; Marrs, C. M.; Müller, R.; Rachwal, S. PCT Int. Appl. WO 03045315, 2003; *Chem. Abstr.* **2003**, *139*, 22217.
7. (a) Mhaske, S. B.; Argade, N. P. *J. Org. Chem.* **2001**, *66*, 9038; (b) Liu, J.-F.; Ye, P.; Sprague, K.; Sargent, K.; Yohannes, D.; Baldino, C. M.; Wilson, C. J.; Ng, S.-C. *Org. Lett.* **2005**, *7*, 3363.
8. Cagir, A.; Jones, S. H.; Gao, R.; Eisenhauer, B. M.; Hecht, S. M. *J. Am. Chem. Soc.* **2003**, *125*, 13628.
9. (a) Holzgrabe, U. *Pharm. Unserer Zeit* **2006**, *35*, 410; (b) Elander, R. P. *Appl. Microbiol. Biotechnol.* **2003**, *61*, 385.
10. Johannes, K.; Jakob, J.; Hatam, M.; Martens, J. *Synthesis* **2009**, 3279.
11. Köpper, S.; Lindner, K.; Martens, J. *Tetrahedron* **1992**, *48*, 10277.
12. Schulz, K.; Watzke, M.; Johannes, K.; Ullrich, P.; Martens, J. *Synthesis* **2009**, 665.
13. Watzke, M.; Schulz, K.; Johannes, K.; Ullrich, P.; Martens, J. *Eur. J. Org. Chem.* **2008**, 3859.
14. Weber, M.; Jakob, J.; Martens, J. *Liebigs Ann. Chem.* **1992**, 1.
15. (a) Erlenmeyer, H.; Oberlin, V. *Helv. Chim. Acta* **1947**, *30*, 1329; (b) Surrey, A. R. *J. Am. Chem. Soc.* **1947**, *69*, 2911.
16. (a) Asinger, F.; Diem, H.; Schäfer, W. *Monatsh. Chem.* **1964**, *95*, 1391; (b) Kessar, S. V.; Jit, P.; Mundra, K. P.; Lumb, A. K. *J. Chem. Soc. C* **1971**, 266; (c) Ottenheijm, H. C. J.; Vermeulen, N. P. E.; Breuer, L. F. J. M. *Liebigs Ann. Chem.* **1974**, 206; (d) Rozwadowska, M. D.; Sulima, A. *Tetrahedron* **2001**, *57*, 3499; (e) Srivastava, T.; Haq, W.; Katti, S. B. *Tetrahedron* **2002**, *58*, 7619.
17. (a) Jain, R.; Vajpei, S. *Phosphorus, Sulfur, and Silicon* **1992**, *70*, 63; (b) Bajpai, S. N.; Joshi, K. C.; Jain, R. *Heterocycl. Commun.* **1997**, *3*, 41; (c) Solomon, V. R.; Haq, W.; Srivastava, K.; Puri, S. K.; Katti, S. B. *J. Med. Chem.* **2007**, *50*, 394.
18. Tierney, J. *J. Heterocycl. Chem.* **1989**, *26*, 997.
19. (a) Ziegler, E.; Hanus, H. D. *Monatsh. Chem.* **1965**, *96*, 411; (b) Ziegler, E.; Kappe, T.; Kollenz, G. *Monatsh. Chem.* **1968**, *99*, 2024.
20. Kametani, T.; Van Loc, C.; Ihara, M.; Fukumoto, K. *Heterocycles* **1978**, *9*, 673.
21. Ziegler, E.; Kollenz, G.; Kappe, T. *Monatsh. Chem.* **1968**, *99*, 804.
22. Lázár, L.; Fülöp, F. *Eur. J. Org. Chem.* **2003**, 3025.
23. (a) Kametani, T.; Higa, T.; Fukumoto, K.; Koizumi, M. *Heterocycles* **1976**, *4*, 23; (b) Kametani, T.; Van Loc, C.; Higa, T.; Koizumi, M.; Ihara, M.; Fukumoto, K. *Heterocycles* **1976**, *4*, 1487.
24. (a) Kametani, T.; Higa, T.; Van Loc, C.; Ihara, M.; Koizumi, M.; Fukumoto, K. *J. Am. Chem. Soc.* **1976**, *98*, 6186; (b) Kametani, T.; Van Loc, C.; Higa, T.; Koizumi, M.; Ihara, M.; Fukumoto, K. *J. Am. Chem. Soc.* **1977**, *99*, 2306.
25. Boyd, G. V. Reactions and synthetic use of amidines. In *The Chemistry of Amidines and Imidates*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: Chichester, UK, 1991; Vol. 2, pp 367–424.