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Camphoric acid derived sulfur containing bicyclic carboxylic acids as chiral auxiliaries in *N*-acyliminium ion chemistry

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ABSTRACT

Three novel sulfur containing chiral bicyclic carboxylic acids were synthesized from D-camphoric acid. Two of these compounds were briefly evaluated for their potency as chiral auxiliaries in Asymmetric Electrophilic α-Amidoalkylation (AEαA) reactions.

1. Introduction

The development of methodologies that allow efficient and variable access to common and potentially bioactive structural units is a challenging and ongoing task in modern organic chemistry. The number of general synthetic tools for the construction of such chiral core structures is still rather limited. *N*-Heterocycles are an important structural motif frequently found for bioactive substances. Among these, substituted and often chiral piperidines are of particular interest in both academia and industry. A common approach, which is widely applied and of high flexibility to construct this type of compounds is based on trapping reactions of *N*-acyliminium salts,[1] which can often be prepared in situ from readily available starting materials, such as pyridine and carboxylic acid derivatives. Especially the use of pyridines as precursors for the generation of *N*-acyliminium salts[2] appears to be very attractive since the repertoire for the synthesis of functionalized pyridines is well established in the literature, giving rapid access to almost all kinds of substituted piperidine derivatives.

We and others have previously reported efficient protocols for the in situ formation of *N*-acyliminium salts derived from activated carboxylic acid moieties, such as acyl chlorides and pyridines in the presence of trimethylsilyl triflate (TMS-OTf).[3–7] Especially the generation of chiral *N*-acyliminium salts with the potential to give rise to high levels of asymmetric induction in trapping reactions with appropriate nucleophiles has attracted our attention. As part of our studies, we have developed the bicyclic lactone carboxylic acid **1** (Fig. 1) derived from camphoric acid as an easily accessible auxiliary for asymmetric electrophilic α-amidoalkylation (AEαA)[8] reactions in the past. The asymmetric induction observed in

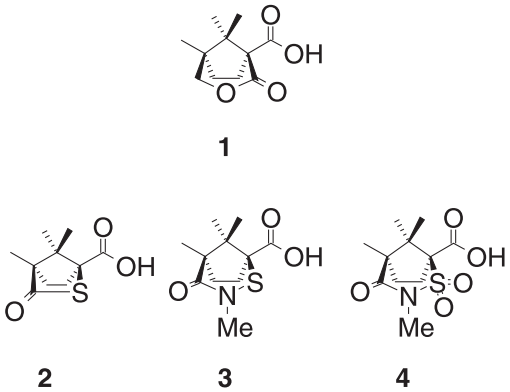

Figure 1.

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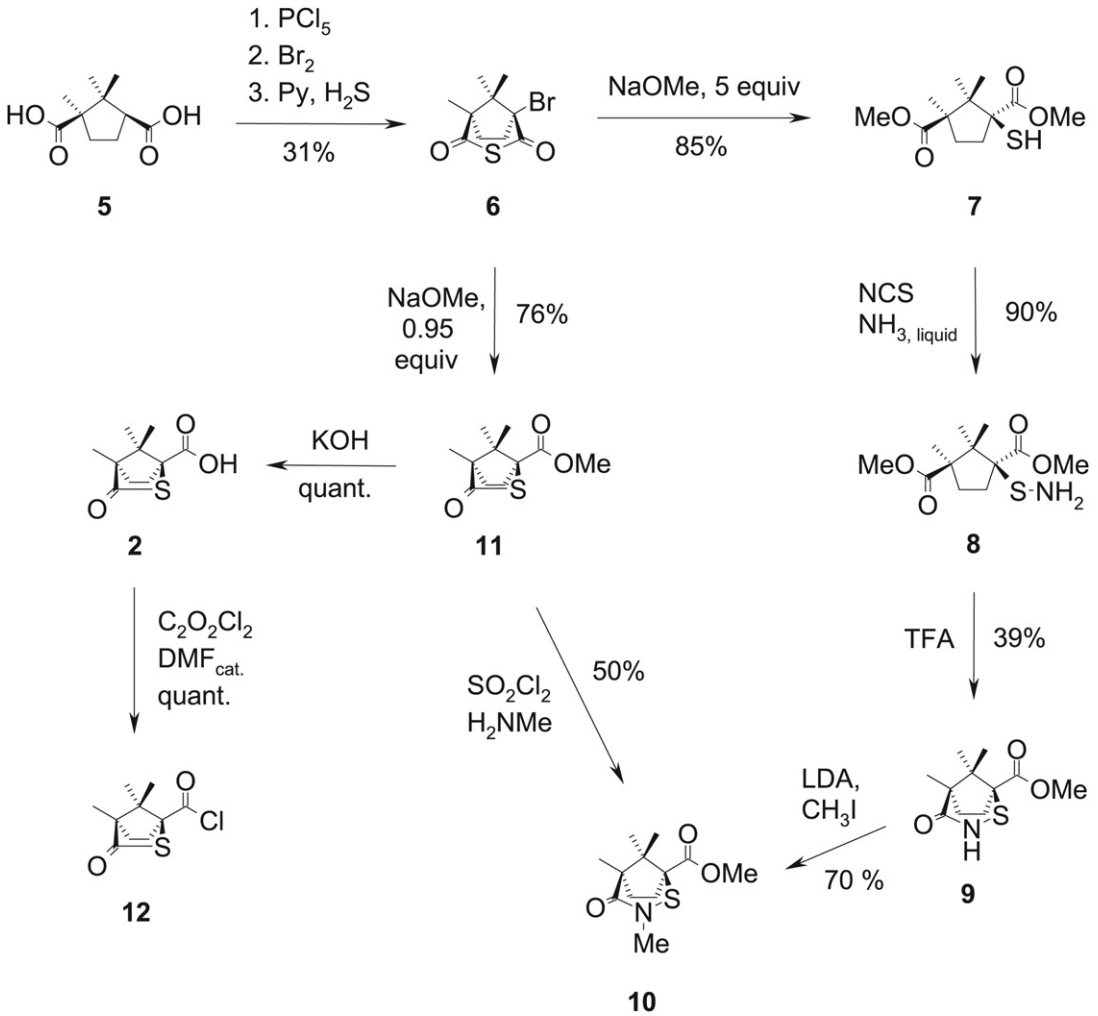
trapping reactions of *N*-acyliminium ions derived from **1** with amphiphilic nucleophiles is assumed to be the result of a coordination complex that might form between the organometallic reagent and the lactone function of the chiral auxiliary **1**.[9] The auxiliary allows excellent stereocontrol in many examples.[10–13] In continuation of our efforts to develop new and efficient chiral auxiliaries for AEαA reactions, we became interested in thiocamphanic acid **2**, sulfenamide **3** and sultame **4**. In this paper we present the successful syntheses of these so far unknown compounds as well as preliminary results regarding the use of carboxylic acid **2** and **4** as chiral auxiliaries in asymmetric electrophilic α-amidoalkylation (AEαA) reactions.

2. Results and discussion

For the synthesis of thiocamphanic acid **2**, a thio analogue of camphanic acid, a long known and widely used chiral derivatizing reagent, a procedure published by Gerlach and Kappes[14] and Müller and Boléa[15] for the preparation of this compound was followed. Accordingly, D-camphoric acid **5** was subjected to a Hell–Volhard–Zelinsky reaction for α-bromination and subsequently treated with hydrogen sulfide in the presence of pyridine as a base to give thioanhydride **6**. The yield for **6** still amounted to 31%, though the synthetic sequence consisted of three steps and for the purification of the crude product in addition to column chromatography, crystallization from *tert*-butyl methyl ether had been required. Similar to the oxo analogue[14] and the corresponding *N*-phenylimide[16,17] of **6**, treatment of **6** with base, a substoichiometric amount of sodium methanolate, resulted in a ring contraction yielding thiocamphanic acid methyl ester **11**. Interestingly, in line with the results observed for rearrangement reactions of the aforementioned compounds, the nucleophile had exclusively added to the α-bromo substituted carbonyl group resulting in the formation of thiolactone **11**. The lactone that would form upon attack on the opposite carbonyl group in **6**, could not be detected. Finally, saponification of **11** with potassium hydroxide in THF/H_2O provided thiolactone **2**, a thio analogue of camphanic acid. The yield for this step was quantitative, as for the subsequent transformation of **2** into the acid chloride **12** by treatment with oxalyl chloride/$DMF_{cat.}$ (Scheme 1).

Thioanhydride **6** appeared to be a suitable starting material for the preparation of sulfenamide derivative **10**, as well. When thioanhydride **6** was treated with an excess of sodium methoxide, in contrast to the reaction with substoichiometric amounts of base, which had led to **11**, the mercapto carboxylic acid ester **7** was obtained (85%). Presumably, in this case the thiolactone **11** is formed as well, but cleaved to **7** by the excess of base now present in the reaction mixture. To bring along the transformation of **7** into the sulfenamide derivative **8**, compound **7** was treated with *N*-chlorosuccinimide in liquid ammonia providing **8** in a clean reaction in 90% yield.[18,19] Acid catalyzed cyclization of **8** led to the



Scheme 1.

bicyclic sulfenamide derivative **9**, which represents a rare example of this class of compounds. However, extensive side reactions had reduced the yield to 39%. Finally, N-methylation employing LDA and methyl iodide completed the synthesis of the bicyclic ester **10** (yield 70%). Interestingly, sulfenamide **10** is also accessible from thiolactone **11**, a transformation that can be performed in a single synthetic step only. Thus, treatment of thiolactone **11** with sulfuryl chloride and methylamine gives rise to sulfenamide **10** in 50% yield. To the best of our knowledge, this type of reaction representing a formal nitrogen insertion into the sulfur–carbon bond of a thiolactone moiety is unprecedented so far. This transformation may be rationalized by an oxidative cleavage reaction of the thiolactone unit by sulfuryl chloride leading to an intermediate with an activated thiol and carboxylic acid moiety. Aminolysis of these functions should establish the final *N*-acyl sulfenamide group.

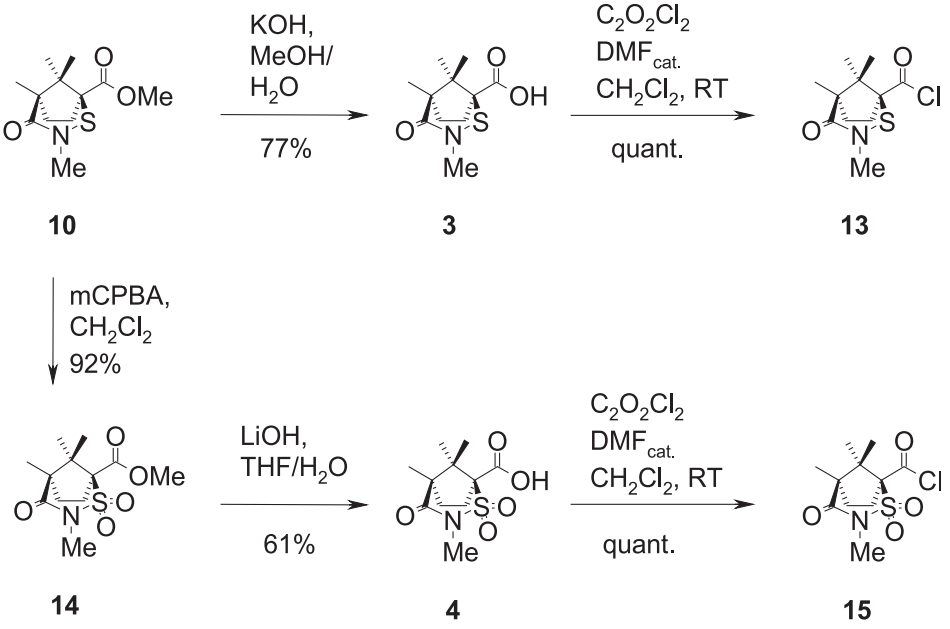
The sulfenamide derivative **10** was finally used for the preparation of the carboxylic acid derivative **15** exhibiting a sultame moiety, the compound to be tested as chiral auxiliary in Asymmetric Electrophilic α-Amidoalkylation reactions. Fortunately, the sulfenamide derivative **10** underwent a clean oxidation reaction to give sultame derivative **14** when treated with *m*-chloroperbenzoic acid in dichloromethane, the yield for this step amounting to 92% (Scheme 2). The subsequent saponification of ester **14** with LiOH in aqueous THF provided carboxylic acid **4**, but in reduced yield, as decomposition reactions occurred (62%). Finally, when **4** was treated with oxalyl chloride/$DMF_{cat.}$ the desired carboxylic acid halide **15** was obtained in quantitative yield.

The sulfenamide derivative **10** was, in addition, used for the preparation of the carboxylic acid **3** and the carboxylic acid chloride **13**. Saponification of **10** with potassium hydroxide in aqueous MeOH gave carboxylic acid **3** (77%) and treatment with oxalyl chloride/$DMF_{cat.}$ provided acid chloride **13**.

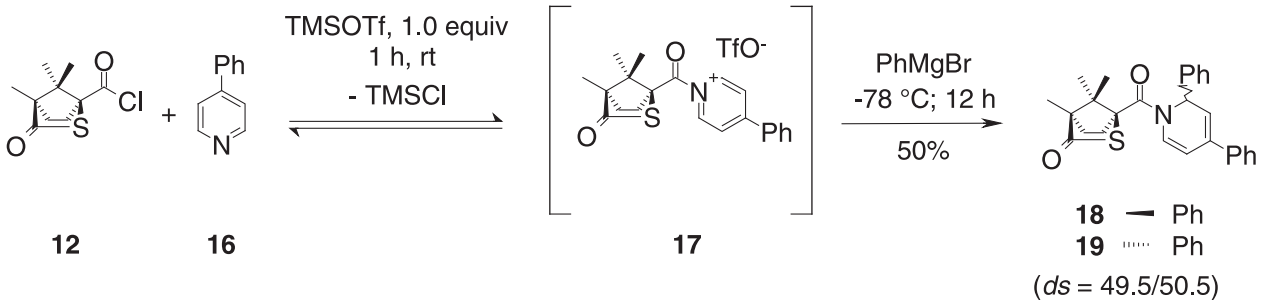
To evaluate the potency of the acid chlorides **12** and **15** as chiral auxiliaries in Asymmetric Electrophilic α-Amidoalkylation reactions, some trapping reactions of *N*-acylpyridinium ions generated from these compounds were performed.

N-Acyliminium ions derived from pyridine derivatives are commonly generated in an equilibrium reaction by treating the pyridine derivative with an appropriate acid chloride. Trapping reactions, however, may fail when the equilibrium is too far on the left side, which is often the case for reactants in which the reaction centres are sterically hindered. But, in general, the situation is distinctly improved when 1 equiv of a silyl triflate, like TMS-OTf, is added as this effects a shift of the equilibrium towards the side of the products as reported by us.[7]

Based on this result, 1 equiv of TMS-OTf was employed for the generation of the *N*-acyliminium ion **17** from **16** and the carboxylic acid chloride **12** whose potency as a chiral auxiliary should be studied. For the asymmetric amidoalkylation reaction, 4-phenylpyridine (**16**), acid chloride **12** and TMS-OTf were mixed at room temperature and after 1 h cooled to −78 °C before PhMgBr (3.0 equiv) was added to trap the thus generated *N*-acyliminium ion **17**. As expected, the diastereomeric dihydropyridines **18** and **19** were obtained, but though the yield was still acceptable (50%), the reaction was practically devoid of any diastereoselection (Scheme 3). For



Scheme 2.



Scheme 3.

compound **18**, for which suitable crystals had been obtained, an X-ray analysis was performed, which revealed that compound **18** possesses (*R*)-configuration at the newly created stereocentre (see Fig. 2). As any significant asymmetric induction was lacking, further experiments with chiral auxiliary **12** were abandoned.

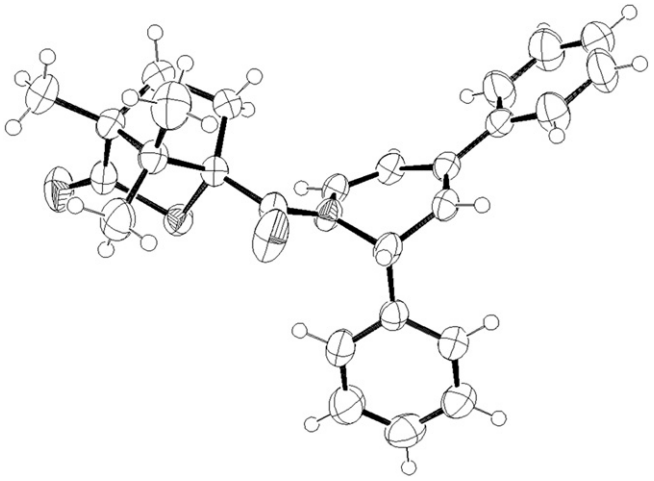


Figure 2. Crystal structure of the dihydropyridine **18**.

Further experiments were performed to test the potency of the sultame derivative **15** as a chiral auxiliary. This time 4-methoxypyridine was used as a precursor for the generation of the *N*-acyliminium ion. Under common conditions similar to those described above and unaffected whether TMS-OTf had been employed or not, either no addition products or only very small quantities were formed. A reasonable conversion was finally effected when the *N*-acyliminium ion **21** (Scheme 4) was generated by employing a large excess of 4-methoxypyridine (**20**, 10 equiv). Then upon addition of EtMgI (at −78 °C), the desired diastereomeric dihydropyridones **22** and **23** were formed in reasonable yield (74%) (Scheme 4). With a diastereomeric ratio of 91/9 (**22**/**23**), also the diastereoselectivity had been quite pleasing, but significantly dropped to 61/39 (**24** and **25**), when PhMgBr was used for the trapping reaction of the *N*-acyliminium ion **21**, though the yield remained almost unchanged (74%). The major diastereomer resulting from the EtMgBr addition, **22**, was found by X-ray analysis to be (*S*)-configured at the newly created stereocenter (Fig. 3). For diastereomers **24** and **25** no efforts to determine the configuration were made.

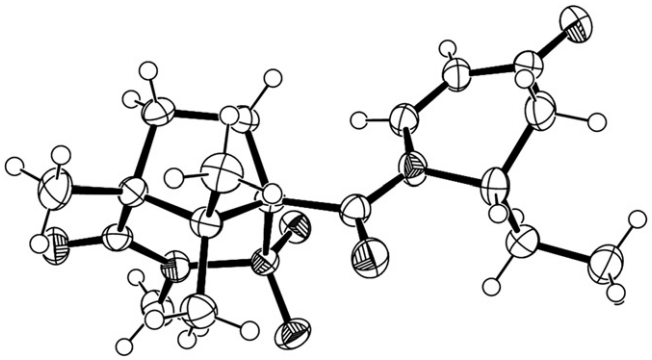
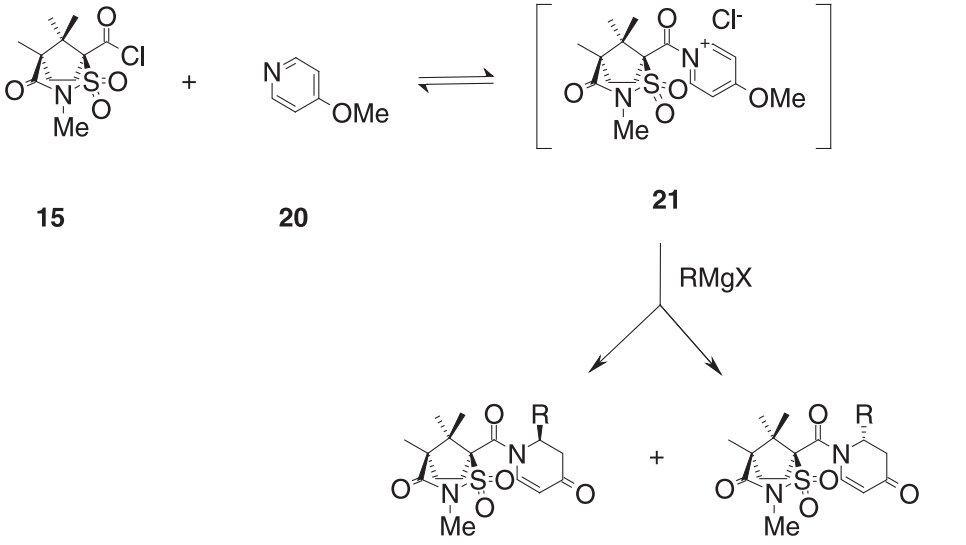


Figure 3. Crystal structure of the dihydropyridine **22**.

3. Conclusion

In summary, we have performed the synthesis of the new sulfur containing chiral bicyclic carboxylic acids **2**, **3** and **4** and their carboxylic acid chlorides. The acid chlorides **12** and **15** were evaluated for their potency as chiral auxiliaries in Asymmetric Electrophilic α-Amidoalkylation (AEαA) reactions. But though these were only



Scheme 4.

preliminary studies, the potency for asymmetric induction of these compounds appears to be low.

4. Experimental section

4.1. General experimental

All reactions were performed using flame-dried glassware under argon atmosphere. All solvents were freshly dried using standard procedures.[20] As petroleum ether (PE) the fraction 40–80 °C was used. ^{1}H and ^{13}C NMR spectra were recorded on a JNMR-GX 400 (Joel, 400 MHz) or a JNMR-GX 500 (Joel, 500 MHz) spectrometer, respectively. The nature of the carbon substitution deduced from DEPT and HMQC spectra are expressed as multiplicity that would have been observed in a proton coupled carbon NMR spectrum. Infrared spectra were obtained on a Perkin–Elmer Model 1600 FT-IR spectrometer. Microanalytical data for carbon, hydrogen and nitrogen were determined on a Heraeus Rapid Analyser and on an Elementar Vario EL Analyser. Flash chromatography (CC) was performed with 40–63 mesh silica gel.

4.2. General procedure for the synthesis of carboxylic acid halides (GP 1)

The carboxylic acid was dissolved in 2 mL of anhyd CH_2Cl_2. After addition of one drop anhyd DMF (1:10 in CH_2Cl_2), it was treated with stated quantity of $C_2O_2Cl_2$. The solvent was removed in high vacuum after 2 h, and a solution was generated from residue in specified concentration.

4.3. (1*R*,5*R*)-1-Bromo-5,8,8-trimethyl-3-thiabicyclo[3.2.1] octane-2,4-dione (6)

PCl_5 (20.5 g, 100 mmol) in petroleum ether (40 mL) was suspended in a dry Schlenk flask. Camphoric acid (10.0 g, 50 mmol) was added to this suspension while cooling with ice. The mixture was stirred for 2 h at 0 °C, and for 3 h at room temperature. After the solvent was removed in high vacuum, a reflux condenser was added to the Schlenk flask. Bromine (1.71 mL, 33 mmol) was added dropwise and the resulting mixture was heated to 55 °C. Further bromine was added after 2 h (1.50 mL, 29 mmol) and 8 h (1.00 mL, 20 mmol). Excess bromine was removed in high vacuum after 16 h, and the product was distilled in vacuo (4.2×10^{-1} mbar, 130 °C). The resulting, pale yellow coloured oil was immediately used without further purification.

Hydrogen sulfide gas was introduced into a solution of pyridine (38.6 mL, 10 equiv) in anhyd THF (80 mL) at −78 °C and the crude product from the first step dissolved in anhyd THF (10 mL) was slowly added dropwise. The mixture was warmed to room temperature over night. The resulting, colourless precipitation was filtrated and washed with THF. The filtrate was treated with 2 M HCl (saturated with NaCl). The aqueous layer was extracted with THF (3×300 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed in vacuum. The resulting residue was purified from pyridine and other polar side products by CC with a short column (PE/EtOAc=9:1). Crystallization from *tert*-butyl methyl ether resulted **6**.

Yield 4.30 g (31%), colourless crystals, mp 249–253 °C. TLC R_f=0.42 (PE/EtOAc=8:2). $[\alpha]_D^{20}$ −2.0 (*c* 1.01, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ=1.16 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 2.11 (ddd, *J*=14.8/11.8/5.0 Hz, 1H, CH_2), 2.25 (ddd, *J*=14.8/9.6/5.7 Hz, 1H, CH_2), 2.66 (ddd, *J*=15.1./9.6/5.0 Hz, 1H, CH_2), 2.74 (ddd, *J*=15.1/11.8/5.7 Hz, 1H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$) δ=17.4 (q, CH_3), 17.5 (q, CH_3), 25.0 (q, CH_3), 33.8 (t, CH_2), 37.5 (t, CH_2), 51.8 (s), 61.8 (s), 83.7 (s), 192.2 (s, CO), 199.6 (s, CO). MS (CI, CH_5^+): *m*/*z* (%)= 279 (98) $[M+1]^+$, 277 (100) $[M+1]^+$, 199 (10), 197 (17). IR: ν=2970 cm^{-1}, 1709, 1681. $C_{10}H_{13}BrO_2S$ (277.18): calcd. C 43.33, H 4.73; S 11.57; found C 43.58, H 4.73, S 11.72.

4.4. Methyl (1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-thiabicyclo[2.2.1] heptane-1-carboxylate (11)

To a solution of **6** (2.76 g, 9.97 mmol) in anhyd THF (5 mL) at −50 °C a NaOMe solution (5.4 M in MeOH, 1.75 mL, 9.45 mmol) was carefully added. The mixture was warmed to 0 °C over night (at −33 °C a precipitate is formed). After removing the solvent, the residue was dissolved in 2 M HCl and extracted with CH_2Cl_2 (4×20 mL). After drying over $MgSO_4$, the solvent was removed in vacuo and the resulting residue purified by CC (PE/EtOAc=8:2).

Yield 1.72 g (76%), colourless crystals, mp 72–75 °C. TLC R_f=0.38 (PE/EtOAc=8:2). $[\alpha]_D^{20}$ +80.5 (*c* 1.01, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ=1.09 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 1.75–1.87 (m, 2H, CH_3CCH_2), 2.30 (ddd, *J*=13.4/9.2/4.1 Hz, 1H, CH_2), 2.75 (ddd, *J*=13.4/10.5/5.5 Hz, 1H, CH_2), 3.81 (s, 3H, OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ=11.7 (q, CH_3), 18.7 (q, CH_3), 18.7 (q, CH_3), 30.1 (t, CH_2), 34.8 (t, CH_2), 52.7 (q, OCH_3), 55.6 (s), 62.8 (s), 69.9 (s), 169.5 (s, *C*OOCH$_3$), 207.4 (s, COSR). MS (CI, CH_5^+): *m*/*z* (%)=229 (32) $[M+1]^+$, 223 (35), 187 (876), 167 (39), 159 (100). IR: ν=2977 cm^{-1}, 2363, 1734. HRMS (70 eV): $[M]^+$ calcd for $C_{11}H_{16}O_3S$ (228.0820), found 228.0833.

4.5. (1*S*,4*R*)-4,7,7-Trimethyl-3-oxo-2-thiabicyclo[2.2.1] heptane-1-carboxylic acid (2)

A solution of **11** (124.8 mg, 0.547 mmol) and KOH (92.0 mg, 1.64 mmol) in a THF/H_2O (5:1) mixture (1.0 mL) was stirred at room temperature for 12 h. After removing the solvent in vacuo 2 M HCl was added to the resulting residue and the aqueous layer was extracted with CH_2Cl_2 (5×). The combined organic layers were dried over $MgSO_4$, and the solvent was removed in vacuo. The free carboxylic acid **2** was obtained as colourless crystals.

Yield 117.3 mg (quant.), colourless crystals, mp 238–240 °C. TLC R_f=0.31 (PE/EtOAc/HOAc=69:30:1). $[\alpha]_D^{20}$ +93.9 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ=1.11 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 1.61 (m, 2H, CH_2), 2.37 (ddd, *J*=13.3/9.1/4.2 Hz, 1H, CH_2), 2.78 (ddd, *J*=13.3/10.6/5.2 Hz, 1H, CH_2), 2.51 (ddd, *J*=13.6/10.6/4.2 Hz, 1H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ=11.7 (q, CH_3), 16.7 (q, CH_3), 16.7 (q, CH_3), 30.4 (t, CH_2), 34.7 (t, CH_2), 55.8 (s), 63.0 (s), 69.7 (s), 174.2 (C=O), 207.0 (C=O). MS (FAB^+): *m*/*z* (%)= 215 $[M+1]^+$. HRMS (FAB^+): $[M+H]^+$ calcd for $C_{10}H_{15}O_3S$ (215.0742), found 215.0781. IR: ν=2970 cm^{-1}, 2682, 1707. Anal. Calcd for $C_{10}H_{14}O_3S$ (214.29): C 56.05, H 6.59, S 14.96. Found C 55.80, H 6.45, S 14.81.

4.6. (1*S*,4*R*)-4,7,7-Trimethyl-3-oxo-2-thiabicyclo[2.2.1] heptane-1-carbonyl chloride (12)

According to GP 1 from oxalyl chloride (8.9 mg, 71 μmol, 6.0 μl) and **2** (10 mg, 47 μmol). The residue was dissolved in anhyd $CDCl_3$ (0.7 mL), transferred in a NMR sample tube under inert gas and employed for NMR-experiments. The carboxylic acid chloride was obtained in quantitative yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ=1.00 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.65 (ddd, *J*=13.2/9.4/4.1 Hz, 1H, CH_2), 2.01 (ddd, *J*=13.2/10.8/4.7 Hz, 1H, CH_2), 2.22 (ddd, *J*=13.7/9.4/4.7 Hz, 1H, CH_2), 2.66 (ddd, *J*=13.7/10.8/4.1 Hz, 1H, CH_2).

4.7. Dimethyl (1*S*,3*R*)-1-mercapto-2,2,3-trimethylcyclopentane-1,3-dicarboxylate (7)

Compound **6** (4.11 g, 14.8 mmol) in anhyd THF (10 mL) was cooled to −50 °C and a NaOMe solution (5.4 M in MeOH,

74.0 mmol, 13.7 mL) was added. The reaction mixture was warmed to room temperature. After16 h, it was acidified with 30 mL 2 M HCl and the aqueous layer was extracted with CH_2Cl_2 (5×100 ml). Rests of methanol in the aqueous layer were removed in vacuo and the resulting aqueous layer was saturated with NaCl. After extracting with CH_2Cl_2 (2×) the combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. The raw product was purified by CC (PE/EtOAc=9:1).

Yield 3.29 g (85%), colourless oil. TLC R_f=0.36 (PE/EtOAc=8:2). $[\alpha]_D^{20}$ +18.2 (*c* 0.87, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.97 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.57 (ddd, *J*=13.7/10.4/7.3 Hz, 1H, $H_3CCC$$H_2$), 1.90 (dddd, *J*=14.8/9.5/7.3/1.4 Hz, 1H, HSCCH_2), 2.43 (t, *J*=1.4 Hz, 1H, S*H*), 2.65 (ddd, *J*=13.7/9.5/4.4 Hz, 1H, $H_3CCC$$H_2$), 2.89 (dddd, *J*=14.8/10.4/4.4/1.4 Hz, 1H, HSCCH_2), 3.68 (s, 3H, $HSCCO_2C$$H_3$), 3.74 (s, 3H, $CO_2C$$H_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ=21.9 (q, CH_3), 22.1 (q, CH_3), 22.5 (q, CH_3), 32.2 (t, CH_2), 34.1 (t, CH_2), 50.8 (s), 51.7 (q, OCH_3), 52.5 (q, OCH_3), 54.9 (s), 62.2 (s), 173.6 (s, *C*$OOCH_3$), 177.0 (s, *C*$OOCH_3$). MS (CI, CH_5^+): *m*/*z* (%)=261 (8) $[M+1]^+$, 229 (100), 201 (13), 197 (12). IR: ν=3449 cm^{-1}, 2969, 2361, 2341. Anal. Calcd for $C_{12}H_{20}O_4S$ (260.35): C 55.36, H 7.74; S 12.32. Found. C 55.71, H 7.58, 12.39.

4.8. Dimethyl (1*S*,3*R*)-1-aminosulfanyl-2,2,3-trimethylcyclopentane-1,3-dicarboxylate (8)

N-Chlorosuccinimide (3.29 g, 24.6 mmol) in anhyd THF (10 mL) was filled in a flame-dried two-neck Schlenk flask with dry ice cooler. Ammonia was condensed at −78 °C (150 mL). Compound **7** (3.21 g, 12.3 mmol) in anhyd THF (10 mL) was dropped to this mixture. The mixture was slowly warmed to −30 °C and stirred until the ammonia was completely vaporized (8 h). Phosphate buffer (*c*=1.0 M, pH 7, 30 mL) was added to the residue and the aqueous phase extracted with CH_2Cl_2 (5×). The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. The resulting raw product was purified by CC (PE/EtOAc=8:2).

Yield 3.05 g (90%), pale yellow oil. TLC R_f=0.15 (PE/EtOAc=8:2). $[\alpha]_D^{20}$ +2.0 (*c* 1.16, CH_2Cl_2). ^{1}H NMR (400 MHz, CD_2Cl_2) δ=1.02 (s, 3H, CH_3), 1.13 (s, 3H, $CH_3O_2CCC$$H_3$), 1.22 (s, 3H, C$H_3$), 1.54 (ddd, *J*=13.8/10.6/6.1 Hz, 1H, $SCCH_2C$$H_2$), 1.86 (ddd, *J*=16.0/9.6/6.1 Hz, 1H, SCCH_2), 2.44–2.56 (m, 2H, CH_2), 2.60 (br s, 2H, NH_2), 3.62 (s, 3H, $H_3CCCO_2C$$H_3$), 3.70 (s, 3H, $SCCO_2C$$H_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ=20.7 (q, CH_3), 21.3 (q, CH_3), 22.9 (q, CH_3), 27.7 (t, *C*H_2CSNH_2), 32.0 (t, CH_2), 51.2 (s), 51.5 (q, $H_3CCCOOC$$H_3$), 51.9 ($OCH_3$), 55.6 (s), 69.2 (s, $CSNH_2$), 172.7 (s, $H_2NSCCOOCH_3$), 176.8 (s, $H_3CCCOOC$$H_3$). MS (EI, 70 eV): *m*/*z* (%)=275 (12) [M^+], 195 (19), 167 (62), 94 (100). IR: ν=3405 cm^{-1}, 2950, 1718, 1204. Anal. Calcd for $C_{12}H_{21}NO_4S$ (275.37): C 52.34, H 7.69, N 5.09, S 11.64. Found C 52.19, H 7.51, N 5.20, S 11.92.

4.9. Methyl (1*S*,5*R*)-5,8,8-trimethyl-4-oxo-2-thia-3-azabicyclo[3.2.1]octane-1-carboxylate (9)

A mixture of **8** (3.01 g, 10.9 mmol) in anhyd CH_3CN (40 mL) and TFA (1.37 g, 12.0 mmol, 0.92 mL) was heated under reflux for 12 h. After removing the solvent, crude **8** was purified by CC on silica gel (PE/EtOAc/HOAc=68:30:2).

Yield 1.02 g (39%), yellow crystal, mp 131–133 °C. TLC R_f=0.15 (PE/EtOAc=8:2). $[\alpha]_D^{20}$ −206.6 (*c* 1.04, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ=1.05 (s, 3H, CH_3), 1.20 (s, 3H, NOCCH_3), 1.38 (s, 3H, CH_3), 1.92 (ddd, *J*=13.8/12.4/5.8 Hz, 1H, $CH_2CH_2CCO_2CH_3$), 2.26 (ddd, *J*=13.8/10.1/4.4 Hz, 1H, $CH_2CH_2CCO_2CH_3$), 2.64 (ddd, *J*=15.1/10.1/5.8 Hz, 1H, $CH_2CCO_2CH_3$), 3.15 (ddd, *J*=15.1/12.4/4.4 Hz, 1H, $CH_2CCO_2CH_3$), 3.78 (s, 3H, OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ=14.7 (q, CH_3), 20.5 (q, CH_3), 21.5 (q, CH_3), 37.1 (t, CH_2), 37.6 (t, CH_2), 48.1 (s), 53.0 (q, OCH_3), 55.2 (s), 67.1 (s, CS), 169.5 (s, CO_2CH_3), 177.4 (s, CONS). MS (CI, CH_5^+): *m*/*z* (%)=244 (100) $[M+1]^+$, 212 (6). IR: ν=3110 cm^{-1}, 2976, 2810, 1719, 1638. Anal. Calcd for $C_{11}H_{17}NO_3S$ (243.33): C 54.30, H 7.04, N 5.76, S 13.18. Found C 54.22, H 6.87, N 5.62, S 13.30.

4.10. Methyl (1*S*,5*R*)-3,5,8,8-tetramethyl-4-oxo-2-thia-3-azabicyclo[3.2.1]octane-1-carboxylate (10)

Procedure A: At −78 °C a lithium diisopropylamide solution (2.0 M THF/*n*-heptane, 950 mmol, 475 µl) was added to **9** (0.19 g, 0.79 mmol) in anhyd THF (5 mL). The mixture was allowed to warm to room temperature for some minutes, then again cooled to −78 °C, and treated with CH_3I (561 mg, 3.95 mmol, 246 µL). After stirring over night at room temperature, 5 mL of 2 M HCl were added. The aqueous layer was extracted with CH_2Cl_2 (5×20 mL). The combined organic layers were washed with a Na_2SO_3 solution, dried over $MgSO_4$ and the solvent was removed in vacuo. Purification was effected by CC (PE/EtOAc=8:2).

Yield 142.1 mg (70%), colourless crystals, mp 82–85 °C. TLC R_f=0.25 (PE/EtOAc=8:2). $[\alpha]_D^{20}$ −180.1 (*c* 0.455, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ=1.04 (s, 3H, CH_3), 1.22 (s, 3H, NCOCH_3), 1.28 (s, 3H, CH_3), 1.87 (ddd, *J*=14.2/12.3/5.2 Hz, 1H, $CH_2CH_2CCO_2CH_3$), 2.17 (ddd, *J*=14.2/9.8/5.0 Hz, 1H, $CH_2CH_2CCO_2CH_3$), 2.58 (ddd, *J*=14.8/9.8/5.2 Hz, 1H, $CH_2CCO_2CH_3$), 2.90 (s, 3H, NCH_3), 3.09 (ddd, *J*=14.8/12.3/5.0 Hz, 1H, $CH_2CCO_2CH_3$), 3.78 (s, 3H, OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ=15.6 (q, CH_3), 20.2 (q, CH_3), 21.7 (q, CH_3), 34.9 (q, NCH_3), 36.8 (t, CH_2), 37.7 (t, CH_2), 48.4 (s), 52.9 (q, OCH_3), 54.8 (s), 68.2 (s, CS), 169.2 (s, *C*$OOCH_3$), 175.0 (s, CONS). MS (CI, CH_5^+): *m*/*z* (%)=258 (100) $[M+1]^+$. IR: ν=2980 cm^{-1}, 1709, 1630, 1290. Anal. Calcd for $C_{12}H_{19}NO_3S$ (257.35): C 56.01, H 7.44, N 5.44, S 12.46. Found C 56.10, H 7.28, N 5.28, S 12.68.

Procedure B: At −20 °C **11** (20 mg, 0.089 mmol) in anhyd CH_2Cl_2 (2 mL) was treated with SO_2Cl_2 (74 mg, 0.44 mmol, 36 µL). The mixture was warmed to room temperature and the solvent was removed in high vacuo. The residue was dissolved in anhyd CH_2Cl_2 (2 mL) and the solution was treated with methylamine (2.0 M in THF, 0.444 mmol, 222 µl) at −20 °C. The mixture was allowed to warm to room temperature and the reaction was interrupted after 12 h adding phosphate buffer (*c*=1.0, pH 7). CC on silica gel (PE/EtOAc=8:2) yielded 11.4 mg (50%) of **10**.

4.11. (1*S*,5*R*)-3,5,8,8-Tetramethyl-2,2,4-trioxo-2λ^6-thia-3-azabicyclo[3.2.1]octane-1-carbonyl chloride (15)

According to GP 1 from **4** (4.0 mg, 15 µmol) and oxalyl chloride (22 mg, 0.18 mmol, 15 µl). The obtained residue was dissolved in anhyd $CDCl_3$ (0.7 mL), transferred in a NMR sample tube under inert gas and employed for NMR-experiments. The carboxylic acid chloride was obtained in quantitative yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ=1.17 (s, 3H, CH_3), 1.28 (s, 3H, NCOCCH_3), 1.42 (s, 3H, CH_3), 1.91 (ddd, *J*=14.8/12.1/4.4 Hz, 1H, CH_2CH_2CCOCl), 2.03 (ddd, *J*=14.8/9.6/5.6 Hz, 1H, CH_2CH_2CCOCl), 2.82 (ddd, *J*=15.7/12.1/5.6 Hz, 1H, CH_2CCOCl), 3.10–3.18 (m, 1H, CH_2CCOCl), 3.16 (s, 3H, NCH_3). IR: ν=2989 cm^{-1}, 1782, 1698.

4.12. (1*S*,5*R*)-3,5,8,8-Tetramethyl-2,2,4-trioxo-2λ^6-thia-3-azabicyclo[3.2.1]octane-1-carboxylic acid (4)

A solution of **14** (215 mg, 0.744 mmol) in THF/H_2O 4:1 (10 mL) was treated with LiOH (156 mg, 3.71 mmol). The mixture was stirred over night and 5 mL of 2 M HCl were added. The aqueous layer was extracted with CH_2Cl_2 (5×30 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed in vacuo. CC (PE/EtOAc/HOAc=67:30:3) yielded **4**.

Yield 125.7 mg (61%), colourless crystals, mp 149 °C decomp. TLC R_f=0.1 (PE/EtOAc/HOAc=67:30:3). $[\alpha]_D^{20}$ −6.8 (*c* 0.65, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$) δ=1.17 (s, 3H, CH_3), 1.28 (s, 3H, NCOCCH_3), 1.42 (s, 3H, CH_3), 1.91 (ddd, J=14.6/12.0/5.0 Hz, 1H, CH_2CH$_2$CCO$_2$H), 2.03 (ddd, J=14.6/9.8/5.4 Hz, 1H, CH_2CH$_2$CCO$_2$H), 2.81 (ddd, J=16.2/12.0/5.4 Hz, 1H, CH_2CCO$_2$H), 2.96 (ddd, J=16.2/9.8/5.0 Hz, 1H, CH_2CCO$_2$H), 3.14 (s, 3H, NCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ=15.8 (q, COCCH_3), 19.4 (q, CH_3), 21.7 (q, CH_3), 25.2 (q, NCH_3), 28.8 (t, CH_2), 32.1 (t, CH_2), 48.0 (s), 55.1 (s), 80.7 (s, CS), 167.8 (s, COOH), 172.8 (s, CONCH$_3$). MS (ESI): m/z (%)=276 [M+1]$^+$, 298 (M+Na$^+$). IR: ν=3543 cm^{-1}, 3474, 2973, 2783, 2623, 1742, 1683. Anal. Calcd for $C_{11}H_{17}NO_5S$ (275.33): C 47.99, H 6.22, N 5.09, S 11.65. Found C 47.72, H 6.08, N 4.97, S 11.61.

4.13. (1*S*,5*R*)-1-[((*S*)-2-Ethyl-4-oxo-3,4-dihydropyridin- 1(2*H*)-yl)carbonyl]-3,5,8,8-tetramethyl-2,2-dioxo-2λ^6-thia-3-azabicyclo[3.2.1]octane-4-on (22) and (1*S*,5*R*)-1-[((*R*)-2-Ethyl-4-oxo-3,4-dihydropyridin-1(2*H*)-yl)carbonyl]-3,5,8,8-tetramethyl-2,2-dioxo-2λ^6-thia-3-azabicyclo[3.2.1]octane-4-on (23)

According to GP 1 from **4** (14 mg, 0.05 mmol) and oxalyl chloride (22 mg, 0.18 mmol) under DMF-catalysis acid chloride **15** was prepared. The residue was dissolved in CH_2Cl_2 (2 mL) and 4-methoxypyridine (55 mg, 0.50 mmol) was added. To the resulting mixture EtMgI (2.74 M in Et_2O, 0.052 mmol, 19 µl,) was added at −78 °C. After 12 h the mixture was stirred for further 15 min at room temperature and quenched with 2 M HCl (2 mL). After extracting with CH_2Cl_2 the combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. CC (^{i}Pr$_2$O/EtOAc=6:4) yielded 14.2 mg (74%) of a diastereomeric mixture of **22** and **23**. The separation of isomers occurred by prep. HPLC (^{i}Pr$_2$O/EtOAc=70:30): t_R=17.3 min; t_R=24.0 min. HPLC analysis of the raw product (Si 60, ^{i}Pr$_2$O/EtOAc=6:4, 1 mL/min): **23** t_R=9.6 min, 8.6%; **22** t_R=13.3 min, 91.4%. The relative configuration of **22** was determined by X-ray structure analysis.

*4.13.1. Compound **22**.* Yield 10.0 mg (52%), colourless crystals, mp 218 °C (decomp.). TLC R_f=0.14 (^{i}Pr$_2$O/EtOAc=6:4). $[\alpha]_D^{20}$ +352.0 (*c* 0.29, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ=0.95 (t, J=7.5 Hz, 3H, CH$_2$CH_3), 1.16 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 1.66−1.82 (m, 2H, CH_2), 1.94−2.02 (m, 1H, CH_2), 2.07−2.14 (m, 1H, CH_2), 2.59−2.64 (m, 2H, CH_2, CH$_2$CO), 2.76 (dd, J=16.9/6.0 Hz, 1H, CH_2C=O), 3.04 (ddd, J=15.0/9.9/5.0 Hz, 1H, CH$_2$), 3.17 (s, 3H, NCH_3), 4.75−4.82 (m, 1H, NC*H*Et), 5.45 (dd, J=8.4/1.3 Hz, 1H, NCH=C*H*), 8.10 (dd, J=8.4/1.5 Hz, 1H, NC*H*=CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ=10.2 (q, CH$_2$CH_3), 16.1 (q, CH$_3$NCOCCH_3), 20.5 (q, CH_3), 21.4 (q, CH_3), 22.9 (t, CH$_2$), 25.4 (q, NCH_3), 30.7 (t, CH$_2$), 33.0 (t, CH$_3$NCOCCH$_2$), 40.3 (t, *C*H$_2$CO), 51.9 (s), 54.0 (s), 56.8 (d, NCHEt), 80.7 (s), 109.5 (d, NCH=*C*H), 141.0 (d, N*C*H=CH), 163.0 (s, NCO), 172.3 (CH$_3$N*C*O), 192.7 (CH$_2$*C*O). MS (CI, CH$_5^+$): m/z (%)=383 (100) [M+1]$^+$, 319 (37). IR: ν=2925 cm^{-1}, 1697, 1664, 1598, 1319. HRMS (70 eV): [M]$^+$ calcd for $C_{18}H_{26}N_2O_5S$ (382.1562), found 382.1575.

*4.13.2. Compound **23**.* Yield 1.4 mg (7%), colourless crystals. TLC R_f=0.12 (^{i}Pr$_2$O/EtOAc=6:4). ^{1}H NMR (500 MHz, $CDCl_3$) δ=0.89 (t, J=7.4 Hz, 3H), 1.20 (s, 3H), 1.29 (s, 3H), 1.49−1.72 (m, 5H), 1.91−2.02 (m, 1H), 2.11 (ddd, J=14.3/9.9/4.7 Hz, 1H), 2.48−2.61 (m, 2H), 2.82 (dd, J=16.6/6.5 Hz, 1H), 3.08 (ddd, J=14.8/10.0/4.9 Hz, 1H), 3.14 (s, 3H), 5.03 (q, J=6.7 Hz, 1H), 5.34 (dd, J=8.5/1.4 Hz, 1H), 7.90 (dd, J=8.5/1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=10.4 (q, CH$_2$CH_3), 16.2 (q, CH$_3$NCOCCH_3), 20.2 (q, CH_3), 21.6 (q, CH_3), 24.6 (t, CH$_2$), 25.6 (q, NCH_3), 30.1 (t, CH$_2$), 32.9 (t, CH$_3$NCOCCH$_2$), 39.1 (t, *C*H$_2$CO), 51.9 (s), 53.8 (s), 54.9 (d, NCHEt), 80.1 (s), 107.8 (d, NCH=*C*H), 140.3 (d, N*C*H=CH), 162.1 (s, NCO), 172.2 (s, CH$_3$N*C*O), 192.9 (s, CH$_2$*C*O). MS (CI, CH$_5^+$): m/z (%)=383 (100) [M+1]$^+$, 319 (32), 242 (18). IR: ν=2928 cm^{-1}, 1669, 1598. HRMS (70 eV): [M]$^+$ calcd for $C_{18}H_{26}N_2O_5S$ (382.1562), found 382.1553.

4.14. (1*S*,5*R*)-3,5,8,8-Tetramethyl-2,2-dioxo-1-[((*R*)-4-oxo-2-phenyl-3,4-dihydropyridin-1(2*H*)-yl)carbonyl]-2λ^6-thia-3-azabicyclo[3.2.1]octane-4-on (24) and (1*S*,5*R*)-3,5,8,8-Tetramethyl-2,2-dioxo-1-[((*S*)-4-oxo-2-phenyl-3,4-dihydropyridin-1(2*H*)-yl)carbonyl]-2λ^6-thia-3-azabicyclo [3.2.1]octane-4-on (25)

According to GP 1 from **4** (12 mg, 0.043 mmol) and Oxalyl chloride (30 mg, 0.23 mmol) under DMF-catalysis **15** was prepared. The residue was dissolved in CH_2Cl_2 (2 mL) and 4-methoxypyridine (46 mg, 0.42 mmol) was added. To the resulting mixture PhMgBr (3 M in Et_2O, 0.051 mmol, 17 µl,) was added at −78 °C. After 12 h the mixture was stirred for further 15 min at room temperature and quenched with 2 M HCl (2 mL). After extracting with CH_2Cl_2 the combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. The two diastereomers could be separated by CC (^{i}Pr$_2$O/EtOAc=7:3). The relative stereochemistry of the two diastereomeres could not be assigned (selectivity according their order of elution: 39/61; determined from the raw product).

Minor isomer: Yield 4.4 mg (24%), colourless crystals, mp 118 °C (decomp.). TLC R_f=0.27 (^{i}Pr$_2$O/EtOAc=7:3). $[\alpha]_D^{20}$ +65.4 (*c* 0.15, CH_2Cl_2). ^{1}H NMR (500 MHz, CD_2Cl_2): δ=0.85 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.94 (ddd, J=14.3/11.8/5.0 Hz, 1H, CH_2), 2.10 (ddd, J=14.3/9.9/5.0 Hz, 1H, CH_2), 2.58 (ddd, J=14.8/11.8/4.7 Hz, 1H, CH_2), 2.78 (ddd, J=16.5/2.8/1.1 Hz, 1H, CH_2=O), 3.08−3.14 (m, 2H, CH_2; CH$_2$CO), 3.12 (s, 3H, NCH_3), 5.41 (dd, J=8.8/1.1 Hz, 1H, NCH=C*H*), 6.08 (dd, J=7.4/2.5 Hz, 1H, NC*H*Ph), 7.23−7.42 (m, 2H, H$_{ar}$), 7.27−7.34 (m, 3H, H$_{ar}$), 8.15 (d, J=8.8 Hz, 1H, NC*H*=CH). ^{13}C NMR (100 MHz, CD_2Cl_2): δ=15.9 (q, CH$_3$), 20.1 (q, CH$_3$), 21.0 (q, CH$_3$), 25.4 (q, NCH$_3$), 30.0 (t, CH$_2$), 32.8 (t, CH$_2$), 42.0 (*C*H$_2$CO), 52.0 (s), 54.0 (s), 56.6 (d, NCHPh), 81.0 (s), 108.0 (NCH=*C*H), 126.1 (d, C$_{ar.}$), 128.2 (d, C$_{ar.}$), 129.0 (d, C$_{ar.}$), 139.3 (d, NCH=CH), 141.5 (s, C$_{ar.}$), 163.0 (s, NCO), 172.2 (s, CH$_3$NCO), 191.3 (s, CH$_2$*C*O). MS (CI, CH$_5^+$): m/z (%)=431 (33) [M+1]$^+$, 367 (100). IR: ν=2950 cm^{-1}, 1672, 1600, 1320, 1294, 1209. HRMS (70 eV): [M]$^+$ calcd for $C_{22}H_{26}N_2O_5S$ (430.1562), found 430.1529.

Major isomer: Yield 9.0 mg (50%), colourless crystals, mp 249−253 °C. TLC R_f=0.06 (^{i}Pr$_2$O/EtOAc=7:3). $[\alpha]_D^{20}$ +277.3 (*c* 0.29, CH_2Cl_2). ^{1}H NMR (500 MHz, $C_2D_2Cl_4$, 80 °C): δ=1.22 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.95−2.03 (m, 1H, CH_2), 2.09−2.16 (m, 1H, CH_2), 2.60−2.68 (m, 1H, CH_2), 3.01−3.17 (m, 3H, CH_2C=O, CH_2), 3.21 (s, 3H, NCH_3), 5.49 (d, J=8.4 Hz, 1H, NCH=C*H*), 6.12 (br s, 1H, NC*H*Ph), 7.19−7.22 (m, 2H, H$_{ar}$), 7.29−7.40 (m, 3H, H$_{ar}$), 8.31 (d, J=8.4 Hz, 1H, NC*H*=CH). ^{13}C NMR (125 MHz, $C_2D_2Cl_4$, 80 °C): δ=16.1 (q, CH$_3$), 20.5 (q, CH$_3$), 21.6 (q, CH$_3$), 25.4 (q, NCH$_3$), 30.6 (t, CH$_2$), 33.2 (t, CH$_2$), 42.9 (*C*H$_2$CO), 52.0 (s), 54.2 (s), 57.7 (d, NCHPh), 81.3 (s), 111.1 (NCH=*C*H), 126.1 (d, C$_{ar.}$), 128.0 (d, C$_{ar.}$), 129.0 (d, C$_{ar.}$), 136.5 (d, N*C*H=CH), 141.5 (s, C$_{ar.}$), 163.3 (s, NCO), 172.3 (s, CH$_3$N*C*O), 191.3 (s, CH$_2$*C*O). MS (CI, CH$_5^+$): m/z (%)=431 (92) [M+1]$^+$, 367 (100), 327 (53). IR: ν=2977 cm^{-1}, 1697, 1667, 1602, 1320, 1292, 1207, 1158. HRMS (70 eV): [M]$^+$ calcd for $C_{22}H_{26}N_2O_5S$ (430.1562), found 430.1532.

4.15. (1*S*, 4*R*)-1-[(*R*)-2,4-Diphenyl-1,2-dihydropyridylcarbonyl]-4,7,7-trimethyl-2-thiabicyclo[2.2.1] heptane-3-on (18) and (1*S*,4*R*)-1-[(*S*)-2,4-diphenyl-1,2-dihydropyridylcarbonyl]-4,7,7-trimethyl-2-thiabicyclo[2.2.1] heptane-3-on (19)

To a solution of **12** (70 mg, 0.30 mmol) and **16** (47 mg, 0.30 mmol) in CH_2Cl_2 (3 mL) TMS-OTf (67 mg, 0.30 mmol, 54 µl) was added. The resulting solution was cooled to −78 °C and PhMgBr (3.0 M in Et_2O, 0.9 mmol, 0.3 ml) was added. The mixture was stirred for 12 h and quenched with phosphate buffer (c=1.0 M, pH 7, 2 mL). After extracting with CH_2Cl_2 the combined organic

layers were dried over $MgSO_4$ and the solvent was removed in vacuo. CC (PE/EtOAc=9:1) yielded a diastereomeric mixture of **18** and **19**. The separation of isomers occurred by prep. HPLC (*n*-heptane/EtOAc=92:8) **18**: t_R=17.3 min; **19**: t_R=24.0 min. HPLC analysis of the raw product (Si 60, *n*-heptane/EtOAc=95:5): **18** t_R=19.3 min, 50.5%; **19** t_R=23.4 min, 49.5%. The relative configuration of **18** was determined through X-ray structure analysis.

*4.15.1. Compound **18**.* Yield 19.2 mg (15%), colourless crystals, mp 83 °C (decomp.). TLC R_f=0.45 (PE/EtOAc=8:2). ^{1}H NMR (500 MHz, CD_2Cl_2) δ=1.07 (s, 3H, C*H*$_3$), 1.19 (s, 3H, C*H*$_3$), 1.27 (s, 3H, C*H*$_3$), 1.87 (br s, 2H, C*H*$_2$), 2.63 (br s, 2H, C*H*$_2$), 5.84 (m, 1H, NCH=C*H*), 6.16 (m, 1H, NCHPhC*H*), 6.33 (m, 1H, NC*H*PhCH), 7.22–7.40 (m, 9H, H$_{ar}$, NC*H*=CH), 7.44–7.47 (m, 2H, H$_{ar}$). ^{13}C NMR (125 MHz, $CDCl_3$) δ=11.7 (q, *C*H$_3$), 18.5 (q, *C*H$_3$), 19.0 (q, *C*H$_3$), 31.0 (q, *C*H$_2$), 34.2 (t, *C*H$_2$), 54.8 (d, NCHPhCH), 56.8 (s), 61.6 (s), 67.8 (s), 108.5 (d, NCH=*C*H), 120.2 (d, NCHPh*C*H), 125.6 (d, *C*H), 126.7 (d, *C*H), 126.8 (d, *C*H), 127.8 (d, *C*H), 128.0 (d, *C*H), 128.6 (d, *C*H), 128.7 (d, *C*H), 132.8 (s), 138.0 (s), 140.6 (s), 167.5 (*C*=O), 206.6 (s, S*C*=O). MS (CI, CH_5^+): *m*/*z* (%)=291 (2) [M+1]$^+$, 197 (100), 169 (29). IR: ν=2977 cm^{-1}, 1701, 1654, 1651, 1334. HRMS (70 eV): [M]$^+$ calcd for $C_{27}H_{27}NO_2S$ (429.1762), found 429.1757.

*4.15.2. Compound **19**.* Yield 10.2 mg (8%), yellow crystals, mp 83 °C (decomp.). TLC: R_f=0.42 (PE/EtOAc=8:2). ^{1}H NMR (500 MHz, $CDCl_3$) δ=1.08 (s, 3H, C*H*$_3$), 1.23 (s, 3H, C*H*$_3$), 1.27 (s, 3H, C*H*$_3$), 1.81–1.93 (m, 2H, C*H*$_2$), 2.44–2.45 (m, 2H, C*H*$_2$), 5.84 (m, 1H, NCH=C*H*), 6.06 (m, 1H, NCHPhC*H*), 6.35 (m, 1H, NC*H*PhCH), 7.08 (m, 1H, NC*H*=CH), 7.25–7.45 (m, 8H, H$_{ar}$), 7.58–7.60 (m, 2H, H$_{ar}$). ^{13}C NMR (125 MHz, CD_2Cl_2) δ=11.1 (q, *C*H$_3$), 18.1 (q, *C*H$_3$), 18.8 (q, *C*H$_3$), 30.9 (q, *C*H$_2$), 33.4 (t, *C*H$_2$), 54.7 (d, NCHPhCH), 57.0 (s), 61.2 (s), 67.9 (s), 108.0 (d, NCH=*C*H), 119.7 (d, NCHPh*C*H), 125.1 (d, *C*H), 125.4 (d, *C*H), 126.3 (d, *C*H), 127.4 (d, *C*H), 127.5 (d, *C*H), 128.2 (d, *C*H), 128.4 (d, *C*H), 132.1 (s), 137.6 (s), 140.4 (s), 166.0 (*C*=O), 206.5 (s, S*C*=O). IR: ν=2959 cm^{-1}, 1717, 1653, 1329. HRMS (FAB$^+$): [M]$^+$ calcd for $C_{27}H_{28}NO_3S$ (430.1850), found 430.1864.

4.16. (1*S*,5*R*)-3,5,8,8-Tetramethyl-4-oxo-2-thia-3-aza-bicyclo[3.2.1]octane-1-carboxylic acid (3)

KOH (279 mg, 4.98 mmol) was added to a solution of **10** (428 mg, 1.66 mmol) in MeOH/water (4:1) (10 mL) and the mixture was stirred for 28 h at room temperature. After removing of MeOH in vacuo CH_2Cl_2 (10 mL) was added and the aqueous layer was acidified with 2 M HCl. The aqueous layer was extracted with CH_2Cl_2 (5×), the combined organic layers were dried over $MgSO_4$ and after removing the solvent the remaining residue was purified by CC (PE/EtOAc/HOAc=78:2:2).

Yield 310 mg (77%), colourless crystals, mp 224 °C. TLC R_f=0.12 (PE/EtOAc/HOAc=78:20:2). $[\alpha]_D^{20}$ −187.8 (*c* 1.03, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.10 (s, 3H, C*H*$_3$), 1.22 (s, 3H, NCOC*H*$_3$), 1.30 (s, 3H, C*H*$_3$), 1.87 (ddd, *J*=14.0/12.4/5.2 Hz, 1H, C*H*$_2$CH$_2$CCO$_2$CH$_3$), 2.19 (ddd, *J*=14.0/9.9/5.0 Hz, 1H, C*H*$_2$CH$_2$CCO$_2$CH$_3$), 2.60 (ddd, *J*=14.8/9.9/5.2 Hz, 1H, C*H*$_2$CCO$_2$CH$_3$), 2.91 (s, 3H, NC*H*$_3$), 3.07 (ddd, *J*=14.8/12.4/5.0 Hz, 1H, C*H*$_2$CCO$_2$CH$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ=15.6 (q, CH$_3$), 20.1 (q, CH$_3$), 21.7 (q, CH$_3$), 35.2 (q, NCH$_3$), 36.8 (t, CH$_2$), 37.6 (t, CH$_2$), 48.4 (s), 54.8 (s), 68.2 (s, CS), 173.0 (s, CO$_2$H), 175.2 (s, CONS). MS (CI, CH_5^+): *m*/*z* (%)=244 (100) [M+1]$^+$, 212 (10), 200 (10). IR: ν=2971 cm^{-1}, 1726, 1594, 1206. Anal. Calcd for $C_{11}H_{17}NO_3S$ (243.33): C 54.30, H 7.04, N 5.76, S 13.18. Found C 54.11, H 7.02, N 5.68, S 12.83.

4.17. (1*S*,5*R*)-3,5,8,8-Tetramethyl-4-oxo-2-thia-3-aza-bicyclo[3.2.1]octane-1-carbonyl chloride (13)

According to GP1 from **3** (4.3 mg, 0.018 mmol, 22 μmol) and oxalyl chloride (5 mg, 0.06 mmol, 5 μL). The solvent was removed in high vacuum after 2 h. The residue was dissolved in anhyd $CDCl_3$ (1.0 mL), transferred in a NMR sample tube under inert gas, and employed for NMR experiments. The carboxylic acid chloride was obtained in quantitative yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ=1.15 (s, 3H, C*H*$_3$), 1.23 (s, 3H, C*H*$_3$), 1.31 (s, 3H, C*H*$_3$), 1.87 (ddd, *J*=14.2/12.0/4.5 Hz, 1H, C*H*$_2$CH$_2$CCO$_2$CH$_3$), 2.25 (ddd, *J*=14.2/9.8/5.7 Hz, 1H, C*H*$_2$CH$_2$CCO$_2$CH$_3$), 2.72 (ddd, *J*=14.3/9.8/4.5 Hz, 1H, C*H*$_2$CCO$_2$CH$_3$), 2.96 (s, 3H, NC*H*$_3$), 3.04 (ddd, *J*=14.3/12.0/5.7 Hz, 1H, C*H*$_2$CCO$_2$CH$_3$). IR: ν=2972 cm^{-1}, 1727, 1601.

4.18. Methyl (1*S*,5*R*)-3,5,8,8-tetramethyl-2,2,4-trioxo-2λ^6-thia-3-aza-bicyclo[3.2.1]octane-1-carboxylate (14)

To a solution of **10** (362 mg, 1.40 mmol) in $CHCl_3$ (15 mL) MCPBA (517.1 mg, 3.0 mmol) was added at 0 °C. The mixture was slowly warmed to room temperature and stirred for 24 h. The organic layer was diluted with CH_2Cl_2 (100 mL) and extracted with $NaHCO_3$ (2×). The organic layer was dried over $MgSO_4$ and the solvent was removed. Purification was effected by CC (PE/EtOAc=8:2).

Yield 373.4 mg (92%), colourless crystal, mp 127–128 °C. TLC R_f=0.18 (PE/EtOAc=8:2). $[\alpha]_D^{20}$ −9.6 (*c* 0.56, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ=1.10 (s, 3H, C*H*$_3$), 1.27 (s, 3H, NCOCC*H*$_3$), 1.42 (s, 3H, C*H*$_3$), 1.87 (ddd, *J*=14.2/12.0/4.8 Hz, 1H, C*H*$_2$CH$_2$CCO$_2$CH$_3$), 2.02 (ddd, *J*=14.2/9.8/5.4 Hz, 1H, C*H*$_2$CH$_2$CCO$_2$CH$_3$), 2.73 (ddd, *J*=16.0/12.0/5.4 Hz, 1H, C*H*$_2$CCO$_2$CH$_3$), 2.95 (ddd, *J*=16.0/9.8/4.8 Hz, 1H, C*H*$_2$CCO$_2$CH$_3$), 3.13 (s, 3H, NC*H*$_3$), 3.91 (s, 3H, OC*H*$_3$). ^{13}C NMR (125 MHz, $CDCl_3$) δ=15.8 (q, COCCH$_3$), 19.4 (q, CH$_3$), 21.6 (q, CH$_3$), 25.2 (q, NCH$_3$), 28.9 (t, CH$_2$), 32.1 (t, CH$_2$), 47.8 (s), 53.8 (q, OCH$_3$), 55.1 (s), 80.8 (s, CS), 164.3 (s, COOCH$_3$), 172.8 (s, CONCH$_3$). MS (CI, CH_5^+): *m*/*z* (%)=290 (100) [M+1]$^+$, 232 (63). IR: ν=2980 cm^{-1}, 2956, 1743, 1696. Anal. Calcd for $C_{12}H_{19}NO_5S$ (289.35): C 49.81, H 6.62, N 4.84, S 11.08. Found C 49.80, H 6.22, N 4.80, S 11.13.

4.19. X-ray crystallographic data

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 769427 and nos. CCDC 743814. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223336033 or e-mail: deposit@ccdc.cam.ac.uk).

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.07.009.

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