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Bicyclic Sultams with a Nitrogen at the Bridgehead and a Sulfur Atom in the Apex Position: Facile Preparation and Conformational Properties

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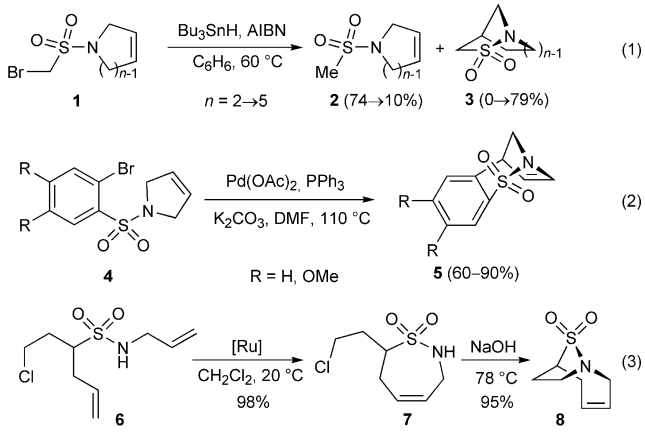
A practical synthesis of bicyclic sultams with a pyramidal bridgehead nitrogen atom and a sulfur atom in the apex position has been elaborated. Compounds with 1-azathiabicyclo[2.2.1]heptane (**12a**), -bicyclo[3.2.1]octane (**12b**, **12d**), and -bicyclo[3.3.1]nonane (**13b**) skeletons were obtained by direct twofold inter/intramolecular alkylation of corresponding monocyclic sultams **9** and **10** with α,ω-dihalides **11** in K_2CO_3/DMF in 56, 68, 52 and 52 % yield, respectively. On the other hand, a 1-aza-9-thiabicyclo[4.2.1]nonane derivative (**12c**) could be prepared only by stepwise dialkylation in 24 % overall yield. Structural and conformational properties of four of the newly prepared bicyclic sultams in solution as well as in the solid state are discussed.

Introduction

The sulfonamide functional group stands out as one of the most important pharmacophores and thus is a constituent of many commonly used therapeutic agents. Cyclic sulfonamides (sultams) have also received significant attention due to their biological activities and medicinal uses.[1] For example, it has been shown recently that the rates of hydrolytic ring opening of β-sultams are 10^2 to 10^3 fold higher than those for the corresponding β-lactams[2] – compounds, which inhibit serine transpeptidases by acylation via ring opening.[3] While the acyclic sulfonamides can easily be prepared by reaction of sulfonyl chlorides with amines, the synthesis of their cyclic analogues (sultams) in many cases appears to be a problem, which needs further development of convenient synthetic methods. No wonder that only a few bridged sultams have been reported up to now.[4–7] The first compounds of this type were synthesized in 1999 applying a radical-initiated cyclization [Scheme 1, see Equation (1)].[6] However, this method has two major disadvantages in that it does not provide access to azathiabicyclo[2.2.1]heptanes (**3**, $n = 2$), and in other cases ($n \geq 3$) always yields mixtures of **2** and **3**, as simple reductive dehalogenation to furnish **2** competes with intramolecular cyclization.[4,6]



Scheme 1. Known approaches to bicyclic sultams.[4–7]

Another known approach to bicyclic sultams of the type **5** is based on an intramolecular Heck-type reaction [Scheme 1, Equation (2)].[7] Although this method provides such bicyclic sultams in good yields, it cannot be considered as being general, since it furnishes only benzannelated compounds of type **5**. The third method, by which only the single bicyclic sultam **8** with a pyramidal nitrogen at the bridgehead and a sulfur atom at the apex position was prepared [Scheme 1, see Equation (3)],[5] relies on a ring-closing metathesis reaction (RCM) of the precursor **6**, followed by an intramolecular cycloalkylation in the seven-membered sultam **7**.

Recently, our group has reported intermolecular alkylation reactions of secondary sulfonamides, containing an additional nucleophilic center, with a wide range of alkylating agents.[8] As was found during that study, twofold inter/intramolecular alkylation of such sulfonamides with α,ω-

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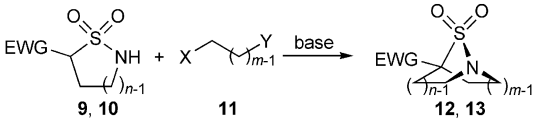
dibromides provides a rather simple and efficient route to five-, six- and seven-membered sultams with an α-methoxycarbonyl group. Analogous intramolecular cyclodialkylations occurring in *N*-(ω–1,ω-dibromoalkyl)(methoxycarbonyl)methanesulfanilides led to a wide range of bicyclic sultams with 1-methoxycarbonyl-1-sulfonylcyclopropane moieties in good yields.[9] Here we report our results concerning sequential inter/intramolecular dialkylations of sultams of type **9**, **10** with a free NH group and an additional nucleophilic center with different bifunctional alkylating agents **11** (Scheme 2). The resulting bridged bicyclic sultams **12** and **13** may constitute potential serine protease inhibitors.



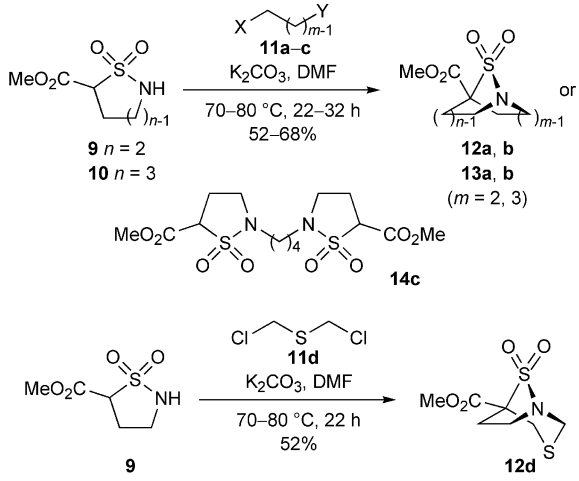
Scheme 2. Concept for a sequential inter/intramolecular dialkylation of sultams **9**, **10**.

Results and Discussion

The monocyclic sultams methyl 1,2-thiazolidine-5-carboxylate 1,1-dioxide (**9**) and methyl 1,2-thiazinane-6-carboxylate 1,1-dioxide (**10**) were prepared in three steps from methyl 2-(chlorosulfonyl)acetate and *p*-anisidine according to previously published protocols.[8,9] Alkylation of compound **9** with different α,ω-dihalides (**11**) was performed under the conditions of White (K_2CO_3/DMF),[10] which had turned out to be the most efficient ones for the intermolecular cyclodialkylation of the sulfonamides.[8] Thus, treatment **9** with 1,2-dibromoethane (**11a**) led to methyl 1-aza-7-thiabicyclo[2.2.1]heptane-4-carboxylate 7,7-dioxide (**12a**) in 56% yield (Scheme 3, Table 1). Cyclodialkylations of the six-membered sultam **10** required an excess of the bifunctional alkylating agent and prolonged heating (see Exp. Sect.). However, the corresponding bicyclic sultam **13a** was isolated in a similarly good yield (59%).

To test the scope and limitations of this method with respect to the preparation of substituted azathiabicyclo[3.2.1]octane and azathiabicyclo[4.2.1]nonane skeletons, the alkylations of **9** and **10** were carried out with 1-bromo-3-chloropropane (**11b**), 1,4-dibromobutane (**11c**) and bis(chloromethyl) sulfide (**11d**). In the case of **11b** and **11d**, the corresponding azathiabicyclooctanes **12b** and **12d** were isolated in acceptable yields (Table 2). However, in the case of **11c** only the product **14c** of a twofold intermolecular nucleophilic substitution linking two molecules of **9** by a C_4 chain was obtained in 53% yield (Scheme 3). This result is due to the kinetically disfavored formation of a seven-membered ring by intramolecular *C*-alkylation in the initially formed monoalkylation product.[11]

To circumvent this difficulty, the *N*-(*p*-methoxyphenyl)-protected monocyclic sultam **9**-PMP was first *C*-alkylated with 1,4-dibromobutane (**11c**) and the resulting product **15**-PMP deprotected by oxidation with ceric ammonium nitrate (Scheme 4).[9] Subsequent treatment of the deprotected **15**-H with potassium carbonate in DMF gave the 1-aza-9-thiabicyclo[4.2.1]nonane derivative **12c** in 56% yield (24% over three steps).



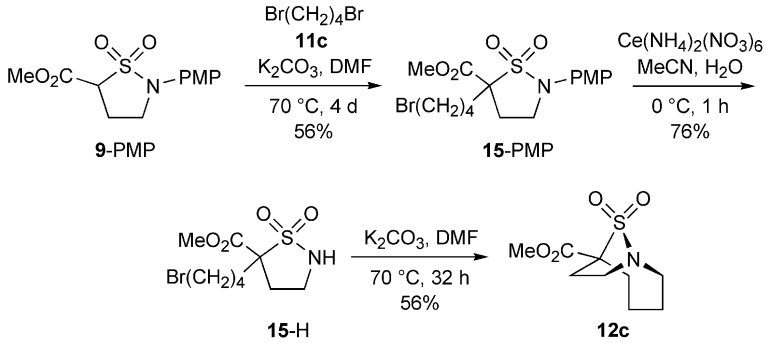
Scheme 3. Synthesis of 1-aza-7-thiabicyclo[2.2.1]heptane, 1-aza-8-thiabicyclo[3.2.1]octane and 1-aza-9-thiabicyclo[3.3.1]nonane derivatives **12**, **13**. For details see Table 1.

Table 1. Synthesis of 1-aza-7-thiabicyclo[2.2.1]heptane, 1-aza-8-thiabicyclo[3.2.1]octane and 1-aza-9-thiabicyclo[3.3.1]nonane derivatives **12**, **13** (see Scheme 3).

Starting materials		11	Product	*n*	*m*	Yield (%)
9	**a**	$Br(CH_2)_2Br$	**12a**	2	2	56
9	**b**	$Br(CH_2)_3Cl$	**12b**	2	3	68
9	**c**	$Br(CH_2)_4Br$	**14c**	–	–	53
9	**d**	$(ClCH_2)_2S$	**12d**	2	–	52
10	**a**	$Br(CH_2)_2Br$	**13a≡12b**	3	2	59
10	**b**	$Br(CH_2)_3Cl$	**13b**	3	3	52

Table 2. Crystal and data collection parameters for compounds **12a**–**c**, and **13b**.

Compound	**12a**	**12b**	**12c**	**13b**
Formula	$C_7H_{11}NO_4S$	$C_8H_{13}NO_4S$	$C_9H_{15}NO_4S$	$C_9H_{15}NO_4S$
Molecular mass	205.23	219.25	233.28	233.28
Crystal system	monoclinic	orthorhombic	orthorhombic	monoclinic
Space group	$P2_1/n$	$P2_12_12_1$	$Pna2_1$	$P2_1/n$
a (Å)	6.4352(3)	7.1099(3)	12.9261(3)	6.3040(2)
b (Å)	13.8165(6)	10.2973(5)	10.1607(2)	16.2543(6)
c (Å)	10.0096(5)	13.0695(6)	7.7015(2)	10.0908(4)
β (°)	97.44(2)	90.00	90.00	99.51(2)
V (Å^3)	882.47(7)	956.85(8)	1011.50(4)	1019.78(6)
Z	4	4	4	4
F(000)	432	464	496	496
D [g cm^{-3}]	1.545	1.522	1.532	1.519
μ [mm^{-1}]	0.349	0.327	0.314	0.312
Refl. collected	9703	12011	12610	11193
Refl. independent	2557	2660	2943	2968
R_{int}	0.0475	0.1038	0.0269	0.0475
R_1 [$I \geq 2\sigma(I)$]	0.0299	0.0339	0.0311	0.0297
wR_2 (all data)	0.0881	0.0807	0.0838	0.0663
Number of parameters refined	162	179	196	196
GOOF	1.174	1.007	0.999	1.047



Scheme 4. Synthesis of methyl 1-aza-9-thiabicyclo[4.2.1]nonane-6-carboxylate 9,9-dioxide (**12c**). PMP = 4-$MeOC_6H_4$.

The structures of the sultams **12a**,**b**,**c** and **13b** were unequivocally proved by X-ray crystallography (Figure 1).

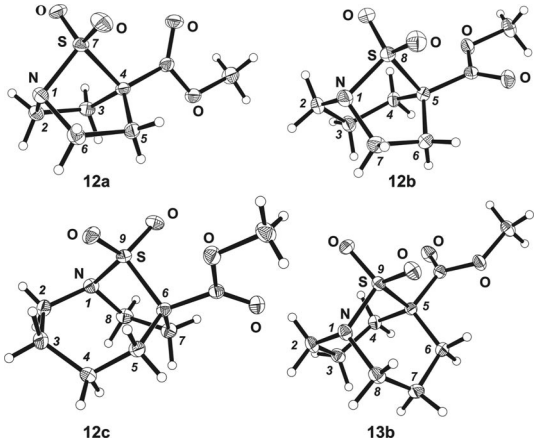


Figure 1. Molecular structures of methyl 1-aza-7-thiabicyclo[2.2.1]-heptane-4-carboxylate 7,7-dioxide (**12a**), of methyl 1-aza-8-thiabicyclo[3.2.1]octane-5-carboxylate 8,8-dioxide (**12b**), of methyl 1-aza-9-thiabicyclo[4.2.1]nonane-6-carboxylate 9,9-dioxide (**12c**) and of methyl 1-aza-9-thiabicyclo[3.3.1]nonane-5-carboxylate 9,9-dioxide (**13b**) in the crystals.[12]

The Cambridge Crystallographic Database[13] contains only thirteen structures of norbornane derivatives with a substituent at the bridgehead carbon, the same number of 1-substituted bicyclo[3.3.1]nonanes (nine of which are part of bulky triphenylene-based inclusion compounds[14]), and only one 1-substituted bicyclo[3.2.1]octane derivative.[15] Even fewer heterocyclic analogues with these skeletons have been studied, so the synthesis and structural characterization of the sultams **12a**–**c** and **13b** provided an opportunity to analyze the influence of ring size changes on the geometry of the skeleton and the orientation of the substituents. This effect is demonstrated in Figure 2, where the molecules **12a**–**c** and **13b** are viewed along the N···C_{quat} direction.

Several features of the molecular geometries have to be noticed. The relative orientation of the methoxycarbonyl substituent is different in all four compounds: whereas in the molecule **12a** the S–C_{quat} and C=O bonds are eclipsed, in the other three molecules these bonds are almost perpendicular to each other; the corresponding torsional angles S–C–C–O are equal to –3.2, 88.8, 129.3 and 102.3° in **12a**–**c** and **13b**, respectively. Such a difference in the orientation

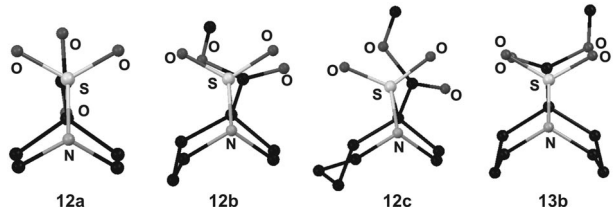


Figure 2. Views of the molecules **12a**–**c** and **13b** along the N···C_{quat} direction.

comes along with a different extent of interaction between the carbonyl group and the sultam framework, causing the bridgehead to carbonyl C–C bond in **12a** to be significantly shorter than the equivalent bonds in the three other compounds [1.506(1) vs. 1.526–1.537Å]. Interestingly enough, the other bond lengths are not affected. The ring strain energy decreases with the increase of bridge lengths in compounds **12a**–**c**, **13b**, which can be easily derived from a comparison of the sums of bond angles at the nitrogen atoms in these compounds. Indeed, these sums are equal to 310.2, 325.3, 341.6 and 340.0° in **12a**–**c**, **13b**, respectively, i.e. the nitrogen atom in molecule **12a** is the most pyramidalized one. Figure 2 also demonstrates the effect of the oligomethylene spacer on the orientation of the methoxycarbonyl group: in molecules **12a** and **13b** with symmetrical core skeletons, the (SO_2)C–C(OO) bonds are in the NSC plane, whereas in **12b** and **12c** they are bent significantly into the direction of the less bulky dimethylene bridges. The packing of molecules **12a**–**c**, **13b** can be described as a three-dimensional network of various CH···O contacts. Short CH···N contacts are present only in the crystal of **12a**. This probably reflects a higher basicity of the nitrogen atom in **12a** due to its more pyramidalized configuration (see above).

Molecules of heteroanalogues of bicyclo[3.3.1]nonane are known to adopt chair-chair as well as chair-boat conformations in solution as well as in the solid state depending on their substitution pattern.[16] As expected, the heterosubstituted bicyclo[3.3.1]nonane moiety in **13b** adopts a flattened chair-chair conformation in the solid phase with torsional angles C8–C7–C6–C5 and N–C6–C7–C6 equal to –44.6 and 43.8°, respectively. An alternative chair-boat conformer in this specific case should be additionally destabilized by van der Waals interactions be-

tween the SO_2 moiety and the C-3 (C-7) methylene groups. In the case of the sultam **12b**, the six-membered fragment also prefers a flattened chair conformation with torsional angles C2–C3–C4–C5 and N–C2–C3–C4 equal to 48.9 and –46.7°, respectively. It should be noted that the conformations of the six-membered fragments in sultams **12b** and **13b** are essentially the same.

In their ^{1}H-NMR spectra, the sultams with a six-membered fragment exhibit a long-range spin-spin coupling between H-4′/H-6′ (in sultam **12b**) and H-2/H-4 (in sultam **12d**) protons, with coupling constants of ^4J = 1.2 and 2.8 Hz, respectively. Such couplings should be associated with a W-type mutual arrangement of these hydrogen atoms in solution. In the case of the sultam **12b**, this phenomenon undoubtedly indicates the chair conformation for the six-membered ring moiety. In the case of **12d**, however, no definite conclusion can be derived from this fact, as both, the possible chair and boat conformers of the 2-aza-1,4-dithiane 1,1-dioxide moiety[16] should possess such a mutual arrangement of protons. The conformations of sultams **12b**, **13b** can be unambiguously determined based on the difference in signal width for the two protons at the same carbon atom. The corresponding values of these differences for H-2 protons of sultams **12b** and **13b** are approximately the same and equal to 10 Hz. This clearly indicates the chair conformation of the 2-azathiane 1,1-dioxide fragments for both of these compounds in their solutions.

Conclusions

The cyclodialkylation of *N*-unprotected sultams **9**, **10** with an additional nucleophilic center appears to be a new general and efficient method for the synthesis of bicyclic sultams **12**, **13** with a pyramidal nitrogen atom at the bridgehead and a sulfur atom at the apex position. Variation of the starting materials **9**, **10** and the bifunctional alkylating agents **11** allows the preparation of a range of heterosubstituted bicyclo[*n.m.*1]alkanes **12**, **13** with potential biological activity. Further applications of the new synthetic method towards this interesting family of heterocycles are currently in progress.

Experimental Section

General Aspects: Compounds **9**, **9**-PMP and **10** were prepared according to previously published procedures.[8,9] All other chemicals were used as commercially available. IR spectra were recorded with a Bruker IFS 66 spectrometer as KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded at ambient temperature with a Bruker DPX 300 instrument at 300.13 (^{1}H) and 75.54 (^{13}C and DEPT) MHz, Varian VXR Inova 500 S instrument at 125.71 (^{13}C and APT) MHz and Varian Inova 600 at 599.74 (^{1}H) MHz. Chemical shifts (δ) are given in ppm relative to resonances of solvents (^{1}H: δ = 7.26 for $CHCl_3$ and δ = 2.50 for [D_5]DMSO; ^{13}C: δ = 77.0 for $CDCl_3$ and δ = 39.5 for [D_6]DMSO). Coupling constants (J) are given in Hz. Multiplicities of signals are described as follows: s = singlet, d = doublet, t = triplet, m = multiplet. The multiplicities of signals in ^{13}C NMR spectra were determined by the DEPT and APT technique. Assignment of signals for the bicyclic sultams **12**, **13** were performed on the basis of 2D NMR experiments (NOESY, HSQS, gCOSY, TOCSY). Mass spectra were recorded with a Finnigan MAT 95 spectrometer. TLC analyses were performed on precoated sheets, 0.25 mm Sil G/UV_{254} (Macherey–Nagel). Silica gel grade 60 (230–400 mesh) (Merck) was used for column chromatography. Melting points were determined with a Büchi 510 capillary melting point apparatus, values are uncorrected. Elemental analyses of solid compounds: Analytical Laboratory of the Department of Organic Chemistry, Chemical Faculty, Saint-Petersburg State University and Mikroanalytisches Laboratorium des Instituts für Anorganische Chemie der Georg-August-Universität Göttingen.

Crystal Structure Analyses: Crystals suitable for X-ray diffractometry of compounds **12a**–**c**, and **13b** were obtained by slow evaporation of their solutions in octane/EtOAc (**12a**, **12b**), octane/$CHCl_3$ (**12c**) and octane/CH_2Cl_2 (**13b**). The single-crystal X-ray data were collected on a Bruker SMART-CCD 6000 diffractometer at 120.0(2) K using graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å). All structures were solved by direct methods and refined by full-matrix least-squares on F^2 for all data. All non-hydrogen atoms were refined with anisotropic displacement parameters, H-atoms were located on the difference map and refined isotropically.[12] Crystal and data collection parameters are summarized in Table 2.

General Procedure for the Dialkylation of the Sultams 9, 10 (GP1): To a mixture of the respective sultam **9**, **10** (3 mmol) and anhydrous K_2CO_3 (1.38 g, 10 mmol) in DMF (100 mL), a solution of the respective bifunctional alkylating agent **11** (3.2 mmol) in DMF (20 mL) was added at 70 °C during 10 h, and the reaction mixture was stirred at this temperature for an additional 12 h. [In the case of sultam **10**, an additional quantity of the bifunctional alkylating agent (1 mmol) was added in one portion, and the reaction mixture was stirred for an additional 10 h]. The reaction mixture was concentrated on a rotary evaporator, the residue taken up with CH_2Cl_2 (150 mL) and washed successively with water (2 × 70 mL), 10% aq. HCl solution (3 × 75 mL), water (50 mL) and brine (50 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by recrystallization from EtOAc/hexane or by column chromatography to give the corresponding bicyclic sultam **12**, **13**.

Methyl 1-Aza-7-thiabicyclo[2.2.1]heptane-4-carboxylate 7,7-Dioxide (12a): From **9** (537 mg, 3 mmol) and **11a** (602 mg, 3.2 mmol), compound **12a** (344 mg, 56%) was obtained according to GP1 as a slightly grey solid, m.p. 102–104 °C. IR (KBr): $\tilde{\nu}$ = 3022, 2981, 1729, 1440, 1345, 1260, 1167, 1083, 1015, 926, 812, 759, 647 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.08–2.16 (m, 2 H), 2.81–2.96 (m, 4 H), 3.60–3.69 (m, 2 H), 3.88 (s, 3 H, OCH_3) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 30.6 (2 C, C-3, 5), 47.8 (2 C, C-2, 6), 52.6 (OCH_3), 62.7 (C-4), 166.1 (CO) ppm. MS (EI, 70 eV): *m*/*z* (%) = 205 (1) [M]$^+$, 174 (16), 126 (60), 110 (12), 82 (100), 42 (80). $C_7H_{11}NO_4S$ (205.2): calcd. C 40.97, H 5.40, N 6.82; found C 40.95, H 5.41, N 6.96.

Methyl 1-Aza-8-thiabicyclo[3.2.1]octane-5-carboxylate 8,8-Dioxide (12b): From **9** (537 mg, 3 mmol) and **11b** (504 mg, 3.2 mmol), compound **12b** (447 mg, 68%) was obtained according to GP1 as a slightly grey solid, m.p. 104–105 °C. IR (KBr): $\tilde{\nu}$ = 2955, 1742, 1440, 1339, 1288, 1254, 1156, 899, 851, 747, 657 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.64 (m, 1 H, H-3/3′), 1.82–1.91 (m, 1 H, H-3′/3), 2.04 (ddt, J = 1.8, 6.0, 14.0 Hz, 1 H, H-4), 2.41 (ddd, J = 4.6, 10.7, 13.3 Hz, 1 H, H-6), 2.76 (ddt, J = 1.2, 5.4, 14.0 Hz, 1 H, H-4′), 2.85–2.89 (m, 1 H, H-6′), 3.07 (ddd, J = 4.6, 10.7, 13.3 Hz, 1 H, H-7), 3.19 (ddd, J = 1.9, 5.9, 14.2 Hz, 1 H, H-2), 3.50 (dddd,

J = 0.7, 4.8, 10.2, 13.3 Hz, 1 H, H-7′), 3.82 (s, 3 H, OCH_3), 3.99 (br. dt, J = 4.8, 14.2 Hz, 1 H, H-2′) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.5 (C-3), 30.0 (C-6), 32.9 (C-4), 43.9 (C-7), 53.5 (OCH_3), 54.0 (C-2), 64.6 (C-5), 167.6 (CO) ppm. MS (ESI): m/z = 220 $[M + H]^+$, 242 $[M + Na]^+$. $C_8H_{13}NO_4S$ (219.1): calcd. C 43.82, H 5.98, N 6.39; found C 43.85, H 5.90, N 6.44.

Dimethyl 2,2′-(Butane-1,4-diyl)bis(1,2-thiazolidine-5-carboxylate) 1,1,1′,1′-Tetraoxide (14c): From **9** (537 mg, 3 mmol) and **11c** (691 mg, 3.2 mmol), compound **14c** (328 mg, 53%) was obtained as a mixture of two diastereomers according to GP1 as a colorless solid, m.p. 59–60 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.62–1.73 (m, 4 H), 2.43–2.58 (m, 2 H), 2.64–2.80 (m, 2 H), 3.06–3.16 (m, 4 H), 3.19–3.30 (m, 2 H), 3.33–3.40 (m, 2 H), 3.86 (s, 6 H, OCH_3), 4.05–4.12 (m, 2 H), ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.49 (CH_2), 22.52 (CH_2), 24.97 (CH_2), 25.01 (CH_2), 45.04 (CH_2), 45.10 (CH_2), 45.27 (CH_2), 45.35 (CH_2), 53.64 (OCH_3), 60.68 (CH), 165.61 (CO) ppm. MS (ESI): m/z = 413 $[M + H]^+$, 435 $[M + Na]^+$, 451 $[M + K]^+$, 847 $[2M + Na]^+$, 863 $[2M + K]^+$. $C_{14}H_{24}N_2O_8S_2$ (412.5): calcd. C 40.77, H 5.86, N 6.79; found C 40.77, H 5.84, N 6.76.

Methyl 1-Aza-9-thiabicyclo[3.3.1]nonane-5-carboxylate 9,9-Dioxide (13b): From **9** (579 mg, 3 mmol) and **11b** (662 mg, 4.2 mmol), compound **13b** (363 mg, 52%) was obtained according to GP1 as a colorless solid, m.p. 109–110 °C. IR (KBr): $\tilde{\nu}$ = 3438, 2964, 1738, 1487, 1452, 1427, 1324, 1251, 1138, 927, 768, 720 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 1.66 (br. dt, J = 6.8, 14.6 Hz, 2 H, H-3, 7), 2.15–2.25 (m, 2 H, H-3′,7′), 2.35 (ddt, J = 1.5, 6.8, 14.4 Hz, 2 H, H-4, 6), 2.87 (ddt, J = 2.3, 6.8, 14.2 Hz, 2 H, H-4′,6′), 3.33 (ddd, J = 1.3, 6.8, 14.8 Hz, 2 H, H-2, 8), 3.79 (s, 3 H, OCH_3), 4.09 (br. dt, J = 5.9, 13.9 Hz, 2 H, H-2′,8′) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.1 (2 C, C-3, 7), 32.5 (2 C, C-4, 6), 52.0 (2 C, C-2, 8), 53.3 (OCH_3), 62.6 (C-5), 169.2 (CO) ppm. MS (ESI): m/z = 256 $[M + Na]^+$, 489 $[2M + Na]^+$, 505 $[2M + K]^+$. $C_9H_{15}NO_4S$ (233.3): calcd. C 46.34, H 6.48, N 6.00, S 13.75; found C 46.00, H 6.53, N 5.88, S 13.74.

Methyl 1-Aza-3,8-dithiabicyclo[3.2.1]octane-5-carboxylate 8,8-Dioxide (12d): From **9** (537 mg, 3 mmol) and **11e** (419 mg, 3.2 mmol), compound **12d** (370 mg, 52%) was obtained according to GP1 as a colorless solid, m.p. 94–96 °C. IR (KBr): $\tilde{\nu}$ = 3004, 2979, 1740, 1343, 1269, 1231, 1156, 1087, 764, 726 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 2.76 (ddd, J = 4.8, 10.7, 13.0 Hz, 1 H, H-6), 2.77 (dd, J = 2.8, 14.0 Hz, 1 H, H-4), 2.88 (dddd, J = 0.8, 4.3, 9.9, 13.0 Hz, 1 H, H-6′), 3.36 (ddd, J = 4.3, 10.7, 12.6 Hz, 1 H, H-7), 3.47 (ddd, J = 4.8, 9.9, 12.6 Hz, 1 H, H-7′), 3.83 (s, 3 H, OCH_3), 3.96 (dd, J = 2.8, 13.5 Hz, 1 H, H-2), 4.00 (br. d, J = 14.0 Hz, 1 H, H-4′), 5.29 (d, J = 13.5 Hz, 1 H, H-2′) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 30.4 (C-6), 36.7 (C-4), 43.7 (C-7), 53.8 (OCH_3), 57.4 (C-2), 64.5 (C-5), 166.3 (CO) ppm. MS (ESI): m/z = 260 $[M + Na]^+$, 276 $[M + K]^+$, 497 $[2M + Na]^+$, 513 $[2M + K]^+$. $C_7H_{11}NO_4S_2$ (237.3): calcd. C 35.43, H 4.67, N 5.90; found C 35.20, H 4.62, N 5.92.

Methyl 5-(4-Bromobutyl)-2-(4-methoxyphenyl)-1,2-thiazolidine-5-carboxylate 1,1-Dioxide (15-PMP): To a mixture of 1,4-dibromobutane (**11c**) (75.6 g, 350 mmol), K_2CO_3 (6.9 g, 50 mmol) in DMF (200 mL), a solution of methyl 2-(4-methoxyphenyl)-1,2-thiazolidine-5-carboxylate 1,1-dioxide (**9**-PMP) (9.98 g, 35 mmol) in DMF (50 mL) was added at 70 °C over a period of 5 h, and the reaction mixture was stirred at this temperature for an additional 3 d. Then the solvent was removed in vacuo, the residue was dissolved in CH_2Cl_2 (250 mL) and the solution washed successively with water (75 mL), 5% aq. HCl solution (5 × 75 mL), water (50 mL) and brine (50 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography to give **15**-PMP (8.29 g, 56%) as a colorless solid, R_f = 0.26 (EtOAc/hexane, 1:2), m.p. 64–65 °C. IR (KBr): $\tilde{\nu}$ = 3255, 2961, 2837, 1741, 1430, 1391, 1337, 1276, 1167, 1042, 925, 742, 707 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.31–1.45 (m, 1 H), 1.52–1.66 (m, 1 H), 1.53–2.00 (m, 3 H), 2.32 (ddd, J = 6.9, 8.0, 13.5 Hz, 1 H), 2.47 (dt, J = 4.4, 12.9 Hz, 1 H), 3.03 (ddd, J = 4.8, 7.7, 13.4 Hz, 1 H), 3.45 (dt, J = 0.9, 6.4 Hz, 2 H), 3.57 (dt, J = 4.7, 8.5 Hz, 1 H), 3.73–3.81 (m, 1 H), 3.81 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 6.88–6.93 (m, 2 H, H-Ar), 7.22–7.27 (m, 2 H, H-Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.1 (CH_2), 26.9 (CH_2), 32.1 (CH_2), 32.2 (CH_2), 33.0 (CH_2), 45.1 (CH_2), 53.7 (OCH_3), 53.7 (OCH_3), 69.0 (SC), 114.7 (2 C, CH-Ar), 125.3 (2 C, CH-Ar), 129.6 (C-Ar), 158.3 (C-Ar), 167.4 (CO) ppm. MS (ESI): m/z = 419 $[M(^{79}Br)]^+$, 421 $[M(^{81}Br)]^+$, 442 $[M(^{79}Br) + Na]^+$, 444 $[M(^{81}Br) + Na]^+$, 458 $[M(^{79}Br) + K]^+$, 460 $[M(^{81}Br) + K]^+$, 861 $[2M (^{79}Br/^{79}Br) + Na]^+$, 863 $[2M (^{79}Br/^{81}Br) + Na]^+$, 865 $[2M (^{81}Br/^{81}Br) + Na]^+$, 877 $[2M (^{79}Br/^{79}Br) + K]^+$, 879 $[2M (^{79}Br/^{81}Br) + K]^+$, 881 $[2M (^{81}Br/^{81}Br) + K]^+$. $C_{16}H_{22}BrNO_5S$ (420.3): calcd. C 45.72, H 5.28, N 3.33; found C 45.74, H 5.31, N 3.14.

Methyl 5-(4-Bromobutyl)-1,2-thiazolidine-5-carboxylate 1,1-Dioxide (15-H): To a stirred solution of methyl 5-(4-bromobutyl)-2-(4-methoxyphenyl)-1,2-thiazolidine-5-carboxylate 1,1-dioxide (**15**-PMP) (4.20 g, 10 mmol) in MeCN (100 mL), a solution of CAN (17.26 g, 31.5 mmol) in water (80 mL) was slowly added at 0 °C. The reaction mixture was stirred for an additional 1 h, concentrated under reduced pressure, to the residue was added water (100 mL), and the mixture was extracted with EtOAc (5 × 50 mL). The combined organic phases were successively washed with aq. 10% Na_2SO_3 solution (3 × 75 mL), water (50 mL), brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash column chromatography followed by recrystallization from EtOAc/hexane to afford **15**-H (2.39 g, 76%) as a colorless solid, m.p. 69–70 °C. IR (KBr): $\tilde{\nu}$ = 3952, 2876, 2835, 1735, 1513, 1311, 1234, 835, 809, 659 cm^{-1}. ^1H NMR (300 MHz, [D_6]-DMSO): δ = 1.19–1.32 (m, 1 H), 1.38–1.52 (m, 1 H), 1.65 (dt, J = 4.4, 12.8 Hz, 1 H), 1.83–1.84 (m, 2 H), 2.13–2.24 (m, 2 H), 2.73–2.82 (m, 1 H), 3.08–3.17 (m, 2 H), 3.48 (t, J = 6.6 Hz, 2 H), 3.77 (s, 3 H, OCH_3), 7.11 (t, J = 6.8 Hz, 1 H, NH) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 22.8 (CH_2), 30.9 (CH_2), 31.3 (CH_2), 31.8 (CH_2), 33.1 (CH_2), 37.6 (CH_2), 52.5 (OCH_3), 67.8 (SC), 167.2 (CO) ppm. MS (ESI): m/z = 314 $[M(^{79}Br) + H]^+$, 316 $[M(^{81}Br) + H]^+$, 336 $[M(^{79}Br) + Na]^+$, 338 $[M(^{81}Br) + Na]^+$, 352 $[M(^{79}Br) + K]^+$, 354 $[M(^{81}Br) + K]^+$, 649 $[2M (^{79}Br/^{79}Br) + Na]^+$, 651 $[2M (^{79}Br/^{81}Br) + Na]^+$, 653 $[2M (^{81}Br/^{81}Br) + Na]^+$, 665 $[2M (^{79}Br/^{79}Br) + K]^+$, 667 $[2M (^{79}Br/^{81}Br) + K]^+$, 669 $[2M (^{81}Br/^{81}Br) + K]^+$. $C_9H_{16}BrNO_4S$ (314.2): calcd. C 34.40, H 5.13, N 4.46; found C 34.53, H 5.11, N 4.36.

Methyl 1-Aza-9-thiabicyclo[4.2.1]nonane-6-carboxylate 9,9-Dioxide (12c): To a suspension of K_2CO_3 (690 mg, 5 mmol) in DMF (100 mL), a solution of the (bromobutyl)sultam **15**-H (471 mg, 1.5 mmol) in DMF (20 mL) was added at 70 °C over a period of 20 h. The reaction mixture was stirred at this temperature for an additional 12 h and then concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (150 mL) and the solution washed successively with water (75 mL), aq. 10% HCl solution (3 × 75 mL), water (50 mL) and brine (50 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was recrystallized from EtOAc/hexane/CH_2Cl_2 to give **12c** (196 mg, 56%) as a colorless solid, m.p. 114–115 °C. IR (KBr): $\tilde{\nu}$ = 3472, 2953, 1744, 1430, 1325, 1264, 1212, 1138, 1079, 700, 643 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 1.53–1.59 (m, 1 H, H-4), 1.77–1.85 (m, 2 H, H-3, H-5), 1.95–2.03 (m, 1 H, H-4′), 2.14–2.24 (m, 2 H, H-3′, H-7), 2.34 (ddd, J = 3.2, 11.3, 14.5 Hz, 1

H, H-5′), 2.77 (ddd, J = 6.2, 10.0, 15.0 Hz, 1 H, H-2), 2.98–3.03 (m, 2 H, H-7′, H-8), 3.55 (ddd, J = 2.9, 6.6, 14.9 Hz, 1 H, H-2′), 3.65–3.70 (m, 1 H, H-8′), 3.82 (s, 3 H, OCH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.4 (C-4), 27.2 (C-3), 29.2 (C-7), 33.5 (C-5), 46.9 (C-8), 51.0 (C-2), 53.4 (OCH_3), 69.1 (C), 167.9 (CO) ppm. MS (ESI): m/z = 234 $[M + H]^+$, 256 $[M + Na]^+$, 489 $[2M + Na]^+$, 722 $[3M + Na]^+$. $C_9H_{15}NO_4S$ (233.3): calcd. C 46.34, H 6.48, N 6.00; found C 46.31, H 6.65, N 5.91.

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