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Functional Derivatives of 4-Oxoazetidine-2-sulfinic Acids in Asymmetric Synthesis of 2-Azacepham Sulfoxides and Their Transformation

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Abstract: The enantiomerically pure 2-azacepham sulfoxide **2a** was synthesized by stereocontrolled intramolecular cyclization of sulfinates **3** or sulfinamides **8** in the presence of dry hydrogen chloride followed by triethylamine. The cyclization accrued *via* equilibrated mixtures of sulfinyl chlorides **10a/10b**, which presence was confirmed by chemical transformations. The absolute configuration of the sulfinic acid **9a** as a product of their hydrolysis was determinate by a single crystal X-ray analysis.

INTRODUCTION

In a series of recent publications Wills *et al.*¹ described the preparation and synthetic applications of the chiral, non-racemic, cyclic sulfinamides, which may be converted into chiral sulfoxides in the reactions with nucleophiles such as Grignard reagents or the enolates of esters or ketones. In all cases the inversion of configuration at sulfur is observed.

On the other hand, in connection with our program directed towards the search of derivatives of 4-oxoazetidine-2-sulfinic acids we described the course of the stereochemical transformation of sulfinamides **1** *via* bicyclic 2-azacephams **2** into sulfinates **3** which involved the migration of an amino group from sulfur to carbon. The nucleophilic opening of **2a** with methanol takes place with stereocontrolled transformation to furnish the single stereoisomer **3b** in high yield.²

This excellent regio and stereoselectivity proved to be very useful for preparation of the new functionalized well-defined chiral monobactams or precursors for novel bicyclic β -lactams.

In this context we have studied other aspects of the behaviour of 2-azacephams **2** as well as possible methods for their efficient preparation.

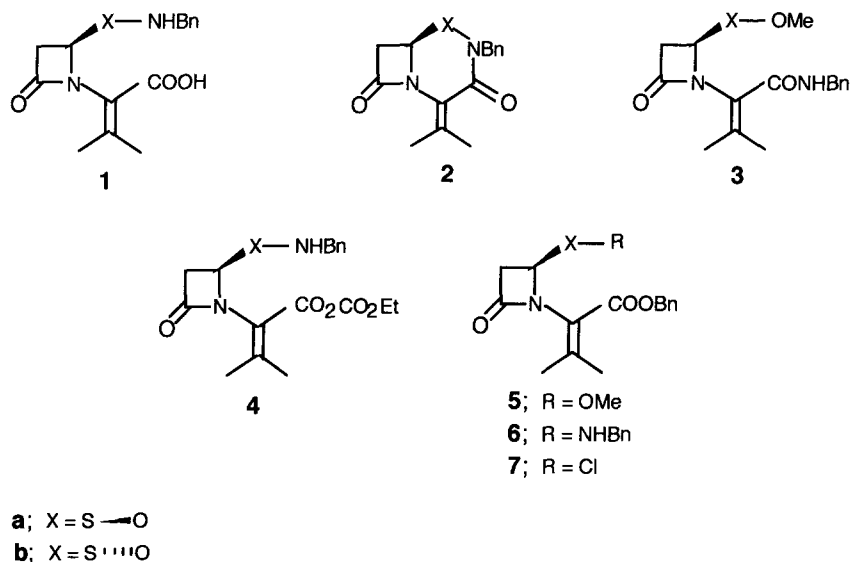
RESULTS AND DISCUSSION

Chemistry

Two routes for the preparation of 2-azacephams **2** were explored, depending on the substitution type in the starting material.

The first one was cyclization of 4-oxoazetidine-2-sulfinamide **1**, accomplished by stirring the diastereoisomerically pure mixed anhydride **4a** or **4b** in dichloromethane at room temperature in the presence

of triethylamine.² It was shown that in either case a single diastereoisomer **2a** or **2b** was formed as a result of retention of the configuration at both asymmetric centers. Although diastereoisomerically pure products were obtained this procedure has several disadvantages. The preparation of the mixed anhydrides **4a** and **4b** requires several steps and obtained products are unstable in the presence of silica gel and polar solvents. In addition, during the synthetic sequence, the cleavage of S-N bond causes destruction of the chiral sulfinamide group and the final overall yields are very poor.



Directed at the solution to these problems we envisaged the preparation and the use of carbamoyl-sulfinyl chlorides as a crucial step, which could lead directly to azacephams **2**.

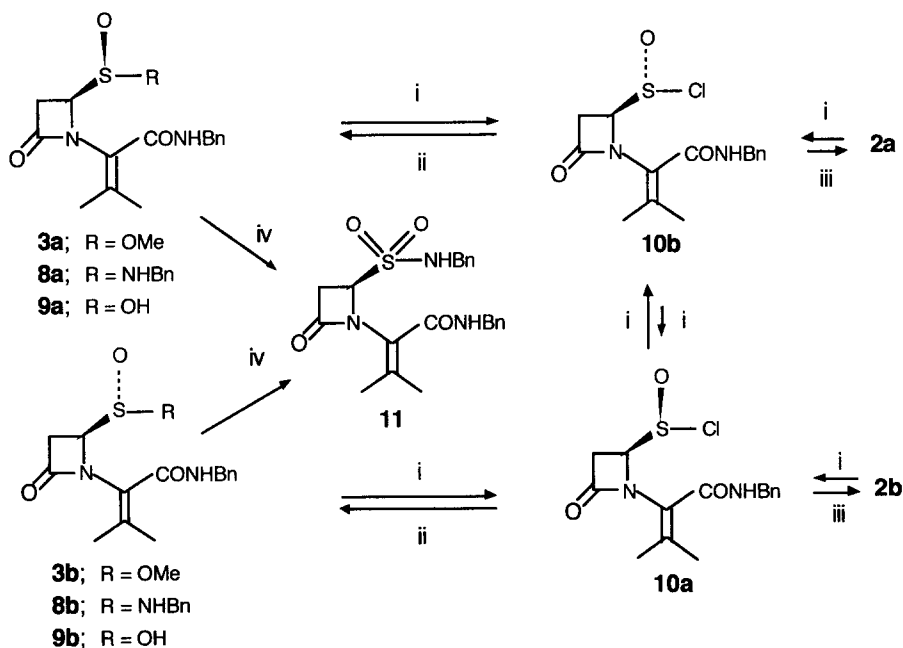
Following our results³ in the sulfinate (**5**) \leftrightarrow sulfinamide (**6**) interconversion in which sulfinyl chlorides **7** were found to be intermediates we investigated the sulfinates **3** as possible precursor for cyclization.

It was found that sulfinate **3a** in the reaction with hydrogen chloride in dry dichloromethane gave a reaction mixture which upon evaporation of the solvent and treatment with triethylamine, resulted in the formation of azacepham **2a** (Scheme 1), which was contaminated by a small amount of diastereoisomer **2b** (detectable in the reaction mixture by TLC). From the reaction mixture the diastereoisomerically pure azacepham **2a** (40%) and starting non-racemic **3a** (30%) were isolated by column chromatography.

Similar results were obtained by changing the starting diastereoisomer. The diastereoisomerically pure **3b** under the same reaction conditions gave the same azacepham **2a** and starting sulfinate **3b** in approximate the same yields as earlier described. It should be noted that in each case some non- β -lactam products were also isolated (15-20%). In an attempt to complete the chemical reaction starting sulfinates were subjected to longer treatment with dry hydrogen chloride. Unfortunately, the yields of β -lactam products were lower and the quantity of non- β -lactam products was increased.

We then turned to examining the sulfinamides **8** (Scheme 1) as better precursors for generation of sulfinyl chlorides **10**. The compounds **8a** and **8b** were prepared from the corresponding mixed anhydrides **4a** and **4b** on treatment with benzylamine in dry dichloromethane. The stereochemical assignments for novel sulfinamides were deduced from ^1H NMR data⁴ and were additionally confirmed by their oxidation to the corresponding sulfonamide **11**. The reaction of **8a** or **8b** in a manner analogous to that of **3a** or **3b** under the previously described conditions led to the formation of **2a** in 60% yield as a single β -lactam product.

By analogy to earlier observation,³ these facts are the result of equilibrated mixture of sulfinyl chlorides **10a/10b** formed as actual intermediates. Although the isolation and characterization of these very reactive intermediates from the reaction mixture failed, their presence was confirmed by chemical transformations. Thus, after addition of methanol or benzylamine they were transformed into the diastereoisomeric mixture of sulfinates **3a/3b** or sulfinamides **8a/8b** in high yields, with predominant diastereoisomers **a**.



Scheme 1. Reagents and conditions: i, HCl (g)/CH₂Cl₂, r.t., 15 min.; ii, RH/CH₂Cl₂, r.t., 30 min; iii, Et₃N/CH₂Cl₂, r.t., 1 hr.; iv, *m*-CPBA/CH₂Cl₂, r.t., 2 hrs.

Several attempts to isolate azacepham **2b** were unsuccessful. The failure was rationalized by the observed instability of the final azacepham **2b**, leading to the numerous non- β -lactam compounds under reaction conditions used for the intramolecular cyclization. In any case the azacepham **2b** is rather less stable than **2a**. A similar distinction in the stability between two sulfur diastereoisomers of some other bicyclic sulfinates was reported earlier.⁵

Therefore, we investigated the stability of the azacepham system **2** in the presence of hydrogen chloride. The azacepham **2a** in reaction with hydrogen chloride in a dry dichloromethane solution followed by treatment of non-volatile residue with methanol or benzylamine also gave a diastereoisomeric mixture of sulfinates **3a/3b** or sulfinamides **8a/8b**, with predominant diastereoisomers **a**. The diastereoisomeric ratio (**a/b**) in the mixtures was approximately 3/2 for both species. It was almost identical to that obtained earlier.³ This suggested that the identical equilibrated mixture of sulfinyl chlorides **10a/10b** was probably formed as a result of opening of thiadiazine ring *via* nucleophilic attack on sulfur atom by chloride anion.

Under the same reaction conditions **2b** gave only non- β -lactam products.

On the other hand, the azacepham **2a** when treated with anhydrous hydrogen chloride and then with water or strong aqueous hydrochloric acid offered the corresponding sulfinic acid **9** in a moderate yield, characterized by its physical and spectroscopic properties. Sulfinic acid **9** was also obtained starting from sulfinates **3** or sulfinamides **8** under the same reaction conditions (Scheme 1).

Although ¹H NMR spectra of sulfinic acid **9** in CDCl₃ solution showed achiral behavior around the sulfur atom, we managed to prepare a single crystal of chiral sulfinic acid by crystallization from diethyl ether. Its X-ray crystallographic analysis (Figure 1; Selected atomic coordinates are listed in Table 1) firmly established 2*R*,5*S*⁶ absolute configuration (**9a**). This behavior implies that the tetrahedral like configuration around the sulfur atom in sulfinic acid is stable enough in the solid state and that two diastereoisomeric structures **9a** and **9b** should be present. On the other hand, sulfinic acids in solutions are effectively achiral. This is due to a fast proton exchange between two chiral forms *via* the achiral sulfinic acid anion.⁷

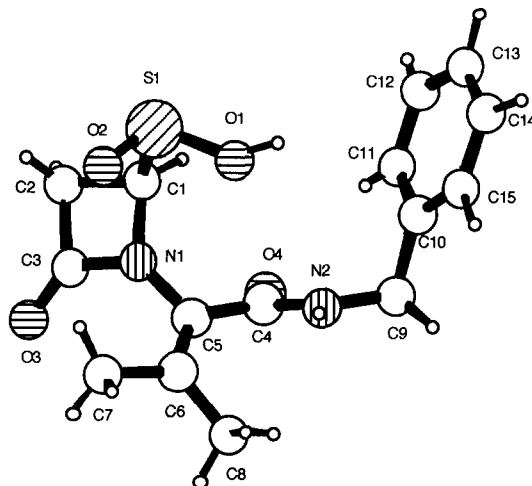
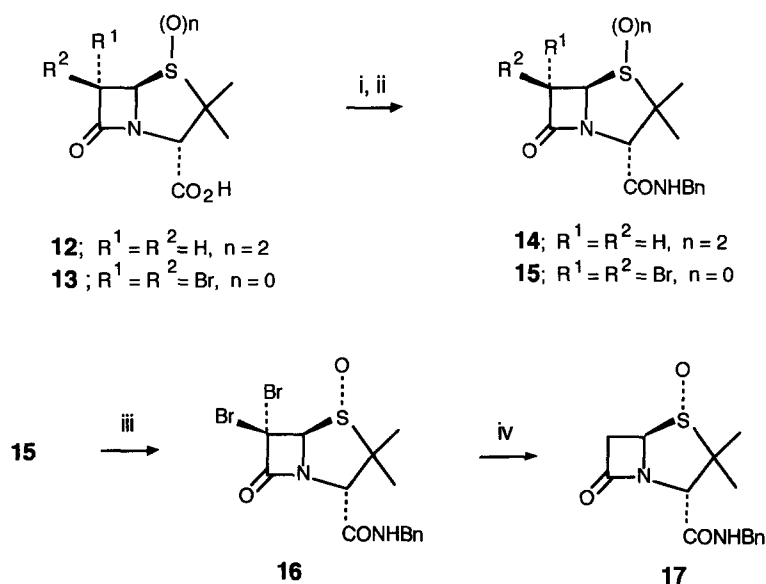


Figure 1. X-Ray molecular structure of (2*R*,5*S*)-1-(1-benzylcarbamoyl-2-methylprop-1-enyl)-4-oxoazetidine-2-sulfinic acid **9a**, showing crystallographic numbering scheme

We also wanted to prepare sulfinic acid **9** or its functional derivatives suitable for cyclization, such as sulfinyl chloride **10**, directly from bicyclic penicillanic structure, for which purpose we prepared penicillamides **14-17** (Scheme 2). The penicillamides **14** and **15** were obtained from the corresponding carboxylic acids **12**

and **13** by reaction with ethyl chloroformate followed by benzylamine. The sulfide **15** by oxidation with *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane produced sulfoxide **16**,⁸ which after hydrogenolysis in the presence of 10 % Pd/C catalyst gave sulfoxide **17**. Using the convenient and efficient method for preparation of 4-oxoazetidine-2-sulfinic acids,⁹ the starting sulfone **14** in the reaction with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) remained unchanged, or after longer reaction time gave sulfinic acid **9** only in traces. On the other hand, sulfoxide **17** in the reaction with *N*-chlorosuccinimide by well-established methodology for preparation of sulfinyl chlorides¹⁰ gave numerous non- β -lactam products. These failures were obtained with a minimum of developmental work and only few experimental observations were made in adjusting of the reaction conditions.



Scheme 2. Reagents and conditions: i, EtOCOCI/Et₃N/CH₂Cl₂, r.t., 1 hr; ii, BnNH₂/CH₂Cl₂, r.t., 1 hrs; iii, *m*-CPBA/CH₂Cl₂, r.t., 2 hrs.; iv, H₂/Pd-C/C₂H₅OH, r.t., 2 hrs.

Other approaches to find abbreviated synthesis of 4-oxoazetidine-2-sulfinic acid derivatives and their cyclization to novel β -lactams are in progress and will be described in next communication.

X-Ray Crystal Analysis

(2*R*,*S*₅)-1-(1-Benzylcarbamoyl-2-methylprop-1-enyl)-4-oxoazetidine-2-sulfinic acid **9a**; Molecular formula C₁₅H₁₈N₂O₄S; Formula weight 322.37; Tetragonal P4₁2₁2; $a = 12.479(2)$, $c = 21.269(4)$ Å, $V = 3312.1(10)$ Å³; $Z = 8$; $D_c = 1.29$ g cm⁻³; $F_{000} = 1360$; Mo-K α radiation; structure refined on F^2 to final $wR2 = 0.113$; $R1 = 0.054$ for 1706 reflections with $I > 4\sigma(I)$.

A suitable crystal of the dimension 0.6 x 0.3 x 0.2 mm was obtained by slow evaporation of diethyl ether solution at room temperature. Data collection was performed with a four circle diffractometer Philips

PW1100/20 modified by Stoe&Cie. A total of 5442 reflections was collected between 2–30° Θ . Lorentz and polarization effects were corrected.¹¹ The structure was solved by direct methods using the program SHELXS86¹² and refined on F^2 by SHELXL93¹³ to final $wR2 = 0.113$ ($R1 = 0.054$) and Flack parameter¹⁴ $x = 0.00(14)$. The hydrogen atoms were placed geometrically. All the non-hydrogen temperature factors were refined anisotropically. Atomic coordinates for the compound were deposited at the Cambridge Crystallographic Data Centre¹⁵

The β -lactam ring is nearly planar. The N1 atom is 0.025(3) Å out of plane defined by the other three atoms within β -lactam ring (C1, C2 and C3). Atoms in carbamoyl-propenyl group define two planes containing C=C and O=C—N π -systems. The planes make an angle of 50.1(1)°, most probably due to intermolecular H-bonds O1(H)···O4' of 2.575(4) Å.

Generally, there are numbers of salts, complexes and other derivatives of sulfinic acids which crystal structures have been solved for some time, but the crystal structure of the acids themselves is known in two cases only.^{16,17} In one of them¹⁶ the methanesulfinic acid molecules are joined to one another by hydrogen bonds in infinite spiral chains along a 2₁ screw axis parallel to c . Similar molecular linking in a helix along a 4₁ screw axis is noticed in sulfinic acid **9a**.

Table 1. Fractional atomic coordinates and equivalent isotropic temperature factors [$\times 10^4$] U_{eq} with standard deviation (in parenthesis) for non-hydrogen atoms of (2*R*,*S*_S)-1-(1-benzylcarbamoyl-2-methylprop-1-enyl)-4-oxoazetidine-2-sulfinic acid (**9a**)

Atom	x/a	y/b	z/c	U _{eq}
S1	0.50677(9)	0.88651(8)	0.09785(4)	0.0489(3)
O1	0.5691(2)	0.9882(2)	0.07180(11)	0.0572(7)
O2	0.3967(2)	0.8883(2)	0.07279(11)	0.0620(8)
O3	0.2728(2)	1.0150(2)	0.24743(12)	0.0602(8)
O4	0.5801(2)	1.1773(2)	0.22682(11)	0.0590(8)
N1	0.4224(2)	1.0331(2)	0.18142(13)	0.0398(8)
N2	0.5882(3)	1.2385(2)	0.12777(14)	0.0491(9)
C1	0.4951(3)	0.9418(3)	0.1764(2)	0.0408(9)
C2	0.4184(3)	0.8806(3)	0.2200(2)	0.0513(11)
C3	0.3536(3)	0.9820(3)	0.2211(2)	0.0466(10)
C4	0.5390(3)	1.1882(3)	0.1744(2)	0.0426(10)
C5	0.4320(3)	1.1411(3)	0.1598(2)	0.0366(8)
C6	0.3490(3)	1.1915(3)	0.1333(2)	0.0452(10)
C7	0.2447(3)	1.1373(4)	0.1193(2)	0.0592(11)
C8	0.3500(3)	1.3085(3)	0.1174(2)	0.0616(13)
C9	0.6947(3)	1.2865(4)	0.1344(2)	0.0584(12)
C10	0.7827(3)	1.2098(4)	0.1152(2)	0.0580(12)
C11	0.8227(4)	1.1371(4)	0.1570(2)	0.079(2)
C12	0.9061(5)	1.0673(5)	0.1395(4)	0.107(2)
C13	0.9495(6)	1.0764(7)	0.0811(4)	0.134(3)
C14	0.9082(5)	1.1462(7)	0.0387(3)	0.117(2)
C15	0.8254(4)	1.2116(5)	0.0558(2)	0.080(2)

EXPERIMENTAL

M.p.s were determined by a Fisher-Johns apparatus and were uncorrected. IR spectra were recorded by using a Perkin-Elmer Model 257 G spectrometer. ^1H NMR spectra were recorded by a Jeol FX 90Q and Varian XL-GEM 300 spectrometers. Chemical shifts δ_{H} were in ppm downfield from Me_4Si , and J -values were given in Hz. Specific rotations were recorded at 589 nm [sodium D line] on a Jasco DIP-360 polarimeter using a 1 dm cell. TLC was run on a Merck Kieselgel HF₂₅₄ plates and visualized under UV light or I_2 vapor adsorption. Column chromatography was performed on a Merck Kieselgel 60 (70-230 mesh ASTM) activated at 105 °C. 4-Oxoazetidine-2-sulfinates **3a** and **3b**, sulfinamides **4a** and **4b** and 2-azacepham sulfoxides **2a** and **2b** were prepared previously.²

Benzyl (2*R*,*R*_S)-1-(1-benzylcarbamoyl-2-methylprop-1-enyl)-4-oxoazetidine-2-sulfonamide (8a): To a cooled solution (0 °C) of mixed anhydride **4a** (786 mg, 2.0 mmol) in dry dichloromethane (20 mL), a solution of benzylamine (5%) in dry dichloromethane (5 mL) was added dropwise until the pH was adjusted to 7.5. The mixture was allowed to warm to room temperature. After stirring for 1 hour, the mixture was washed with water and then with diluted hydrochloric acid (10 mL). The organic phase was washed with water once again and dried (Na_2SO_4). Evaporation of the organic layer under reduced pressure and purification of the residue by silica gel chromatography with dichloromethane-ethyl acetate (gradient elution) gave sulfonamide **8a** (364 mg, 44.3%) as yellowish foam: R_f 0.67 (ethyl acetate); $[\alpha]_{\text{D}}^{20} = +110.4$ (c 1, CH_2Cl_2); IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3250s, 1765vs, 1650s, 1520m, 1450m, 1350m, 1070m, 1050m; ^1H NMR (300 MHz, CDCl_3) δ 1.88 and 1.92(each 3 H, s, CMe_2), 3.03(1 H, dd, J 2.4 and 15.4, $3\beta\text{-H}$), 3.18(1 H, dd, J 5.4 and 15.4, $3\alpha\text{-H}$), 4.15 and 4.20(each 1 H, dd, J 5.4, 6.3 and 14.1, SONHCH_2), 4.42 and 4.51(each 1 H, dd, J 5.7, 6.3 and 14.7, CONHCH_2), 4.72(1 H, dd, J 2.4 and 5.4, 2-H), 4.80(1 H, dd, J 5.4 and 6.3, SONH), 7.26-7.36(10 H, m, 2 C_6H_5), 7.48(1 H, dd, J 5.7 and 6.3, CONH).

Benzyl (2*R*,*S*_S)-1-(1-benzylcarbamoyl-2-methylprop-1-enyl)-4-oxoazetidine-2-sulfonamide (8b): The same treatment of mixed anhydride **4b** as described for the preparation of **8a**, gave sulfonamide **8b** (42%) as yellowish oil: R_f 0.61 (ethyl acetate) $[\alpha]_{\text{D}}^{20} = -1.6$ (c 1, CH_2Cl_2); IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3350s, 1770vs, 1660s, 1515m, 1450m, 1340m, 1050s; ^1H NMR (300 MHz, CDCl_3) δ 1.87 and 1.97(each 3 H, s, CMe_2), 3.13(1 H, dd, J 5.1 and 15.3, $3\alpha\text{-H}$), 3.32(1 H, dd, J 2.2 and 15.3, $3\beta\text{-H}$), 4.24(2 H, d, J 6.0, SONHCH_2), 4.45(2 H, d, J 5.7, CONHCH_2), 4.73(1 H, dd, J 2.2 and 5.1, 2-H), 4.76(1 H, t, J 6.0, SONH), 6.58(1 H, t, J 5.7, CONH), 7.22-7.36(10 H, m, 2 C_6H_5).

Benzyl (2*R*)-1-(1-benzylcarbamoyl-2-methylprop-1-enyl)-4-oxoazetidine-2-sulfonamide 11 (a): A solution of sulfonamide **8a** (205 mg, 0.5 mmol) and *m*-chloroperbenzoic acid (55%, 251 mg, 0.80 mmol) in dichloromethane (20 mL) was stirred at room temperature for 2 hours. The reaction mixture was then washed with 5% aqueous $\text{Na}_2\text{S}_2\text{O}_5$ (20 mL), saturated aqueous NaHCO_3 (20 mL) and water. The dried (Na_2SO_4) organic layer was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane-ethyl acetate 2:1) to give sulfonamide **11** (138 mg, 65 %) as white foam: R_f 0.6 [dichloromethane-ethyl acetate (2:1 v/v)]; IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3340m, 1775vs, 1640s, 1530m, 1505m, 1355m, 1330s, 1150s, 1060s; ^1H NMR (90 MHz, CDCl_3) δ 1.68 and 1.91(each 3 H, s, CMe_2), 3.18(2 H, d, J

3.8, 3-H₂), 4.25(2 H, d, *J* 6.2, SONHCH₂), 4.48(2 H, d, *J* 5.8, CONHCH₂), 4.57(1 H, t, *J* 3.8, 2-H), 6.16(1 H, t, *J* 6.2, SONH), 6.55(1 H, t, *J* 5.8, CONH), 7.30(10 H, s, 2 C₆H₅).

(*b*): The same treatment of sulfinate **8b** with *m*-CPBA as reported for **8a** afforded **11** in 70% yield.

(5*R*,6*R*)-4-Benzyl-2-isopropylidene-5-oxo-5-thia-1,4-diazabicyclo[4.2.0]octane-3,8-dione (2a)

Starting from methylsulfinates 3 (a): Hydrogen chloride was bubbled through a stirred solution of methylsulfinate **3a** (1 mmol) in dry dichloromethane (15 mL) for 15 minutes. The reaction mixture was then stirred for further 15 minutes and dichloromethane was removed by evaporation under reduced pressure to give yellowish syrup. To a cooled solution (0 °C) of evaporated residue in dichloromethane (50 mL) triethylamine was added dropwise until the pH was adjusted to 7.5. The resulting mixture was allowed to warm to room temperature. After being stirring 30 minutes, the mixture was washed with water and with diluted hydrochloric acid (20 mL). The organic phase was washed with water once again and dried (Na₂SO₄). Evaporation of the organic layer under reduced pressure and purification of the residue by silica gel chromatography with dichloromethane-ethyl acetate (gradient elution) gave azacepham **2a** (40%) and starting sulfinate **3a** (30%), which showed spectroscopic properties identical to those described earlier.²

(*b*): The same treatment of diastereoisomerically pure methylsulfinate **3b** with hydrogen chloride as previously reported for **3a** afforded **2a** and **3b** in 40% and 28% yields, respectively.

Starting from benzylsulfinamides 8 (a): Hydrogen chloride was bubbled through an ice-cooled solution of benzylsulfinamide **8a** (4.5 mmol) in dry dichloromethane (40 mL) for 15 minutes. The reaction mixtures was stirred at the same temperature. TLC analysis after 15 minutes showed that the starting sulfonamide was not present in the reaction mixture. The white precipitate of benzylamine hydrochloride was filtered off. The filtrate was concentrated and after the work-up earlier described gave **2a** (60%).

(*b*): The same treatment of diastereoisomerically pure benzylsulfinamide **8b** with hydrogen chloride as previously reported for **8a** afforded **2a** (62%).

(2*R*)-1-(1-Benzylcarbamoyl-2-methylprop-1-enyl)-4-oxoazetidine-2-sulfinic acid (9)

Starting from 2-azacepham 2a (a): Hydrogen chloride was bubbled through a stirred solution of 2-azacepham **2a** (200 mg, 0.66 mmol) in dry dichloromethane (40 mL) for 15 minutes. The reaction mixture was stirred at the same temperature for 15 minutes, and dichloromethane was removed by evaporation under reduced pressure. The non-volatile residue was dissolved into dichloromethane (10 mL) and water (10 mL) and stirred for 15 minutes. The solution was extracted with aq. sodium hydrogen carbonate (5%) and the layers were separated. Ethyl acetate (10 mL) was added to the aq. layer and the mixture was acidified with diluted hydrochloric acid until the pH was adjusted at 2. The mixture was saturated with sodium chloride and layers separated. The aq. layer was extracted several times with ethyl acetate. Evaporation of the dry (Na₂SO₄) organic layer under reduced pressure and after trituration in diethyl ether and filtration gave sulfinic acid **9** (133 mg, 63%) as white solid: m.p. 131–132 °C; *R*_f 0.70 [*n*-butanol-acetic acid-water (4:1:1 v/v)]; [α]_D²⁰ = +1.8 (c 1, MeOH); IR (KBr) ν_{max}/cm⁻¹ 3300m, 1755vs, 1595vs, 1370m, 1245m, 1115s; ¹H NMR (300 MHz,

DMSO- d_6) δ 1.77 and 1.93(each 3 H, s, CMe₂), 3.12(2 H, d, J 3.5, 3-H₂), 4.35 (2 H, d, J 5.8, NHCH₂), 4.47(1H, t, J 3.5, 2-H), 7.28(5 H, s, C₆H₅), 9.10(1 H, t, J 5.8, NHCH₂); Found: C, 56.00; H, 5.50; N, 8.55; S, 9.60%; C₁₅H₁₈N₂O₄S requires C, 55.88; H, 5.63; N, 8.69; S, 9.95%.

(b): A solution of 2-azacepham **2a** (0.66 mmol) in conc. hydrochloric acid (10 mL) was stirred at room temperature for 15 minutes and concentrated by evaporation under reduced pressure and after previously described work-up it gave **2a** (65%).

Sulfinic acid **9** was also obtained by treatment of sulfinates **3** or sulfinamides **8** according to the above method (a) or (b).

(2S,5R)-2-Benzylcarbamoyl-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-4,4-dioxide (14): To a cooled solution (0 °C) of carboxylic acid **12** (1165 mg, 5 mmol), triethylamine (616 mg, 6.1 mmol) and dichloromethane (15 mL), the solution of ethyl chloroformate (620 mg, 5.7 mmol) in dichloromethane (5 mL) was added dropwise. After stirring for 30 minutes a solution of benzylamine (5%) in dry dichloromethane was added dropwise until the pH was adjusted to 7.5. The mixture was allowed to warm to room temperature and stirred for another hour, then washed with water and with diluted hydrochloric acid (10 mL). The organic phase was washed with water once again and dried (Na₂SO₄). Evaporation of the organic layer under reduced pressure gave an amorphous residue which after trituration with diethyl ether and filtration gave amide **14** (1075 mg, 66.7%) as white crystalline solid: m.p. 160-162 °C (diethyl ether), R_f 0.75 [dichloromethane-ethyl acetate (2:1 v/v)]; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 3380s, 1790vs, 1680vs, 1530s, 1325vs, 1275m, 1195m, 1115m; ¹H NMR (300 MHz, CDCl₃) δ 1.43 and 1.70(each 3 H, s, CMe₂), 3.48(2 H, br, 6-H₂), 4.25(1 H, s, 2-H), 3.36 and 4.65(each 1 H, dd, J 5.2, 6.3 and 14.8, NHCH₂), 4.55(1 H, br, 5-H), 6.85(1 H, dd, J 5.2 and 6.3, NH), 7.20-7.50(5 H, m, C₆H₅); Found: C, 55.36; H, 5.30; N, 8.45; S, 9.20%; C₁₅H₁₈N₂O₄S requires C, 55.88; H, 5.63; N, 8.69; S, 9.95%.

Attempted preparation of sulfinic acid 9 from sulfone 14 using 1,5-diazabicyclo[4.3.0]non-5-ene (DBN):⁹ To a stirred solution of sulfone **14** (515 mg, 1.6 mmol) in dry dichloromethane (3 mL), DBN (0.3 mL, 2.4 mmol) was added in one portion. After 30 minutes the solution was diluted with dichloromethane (20 mL) and washed with water. Evaporation of the dried (Na₂SO₄) organic layer left unchanged sulfone **14** (480 mg, 93 %) as judged by ¹H NMR and TLC.

(2S,5R)-2-Benzylcarbamoyl-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-4-oxide (17): The suspension of penicillamide **16**⁸ (1000 mg, 2.15 mmol), sodium hydrogen carbonate (5% aq. solution, 15 mL) and 10% Pd-C catalyst (500 mg) was stirred at room temperature for 2 hours under 2 atm until no further uptake of hydrogen was observed. The suspension was filtered through Celite, acidified to pH 2 and extracted with ethyl acetate. The organic extract was washed with brine, dried (Na₂SO₄) and evaporated under reduced pressure. The residue was purified by silica gel column chromatography with dichloromethane-ethyl acetate (gradient elution) to gave amide **17** (520 mg, 79 %) as yellowish foam: R_f 0.12 [dichloromethane-ethyl acetate (2:1 v/v)]; IR (film) $\nu_{\max}/\text{cm}^{-1}$ 3300m, 1785vs, 1665s, 1530m, 1300m, 1195m, 1050s; ¹H NMR (300 MHz, CDCl₃) δ 1.36 and 1.71(each 3 H, s, CMe₂), 3.39(1 H, dd, J 2.1 and 16.8, 6 β -H), 3.56(1 H, dd, J 4.5 and 16.8, 6 α -H), 4.25(1 H, s, 2-H), 4.43(1 H, dd, J 2.1 and 4.5, 5-H), 4.37 and 4.54(each 1 H, dd, J 5.5, 6.2 and 14.7 CH₂), 6.87(1 H, br, NH), 7.26-7.38(5 H, m, C₆H₅).

Attempted cleavage of sulfoxide 17 using *N*-chlorosuccinimide (NCS):¹⁰ A mixture of sulfoxide 17 (306 mg, 1 mmol) and dry toluene (50 mL) was refluxed for 10 minutes by using a Dean-Stark trap for removing a trace amount of water. Then NCS (146 mg, 1.1 mmol) was added and the mixture was refluxed under nitrogen for 1.5 hours and cooled to 5 °C. Dry methanol was added to dark reaction mixture, stirred at 5 °C for 2 hours and washed successively with aqueous sodium bicarbonate, water and brine. Evaporation of the organic layer under reduced pressure yielded 280 mg of decomposed non- β -lactam products as judged by IR.

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REFERENCES AND NOTES

1. Hose, D. R. J.; Wills, M.; Raynham, T. *Tetrahedron Lett.*, **1994**, 5303-5306 and references cited therein.
2. Herak, J. J.; Vinković, M.; Mandić, Z.; Lukić, I.; Tomić, M.; Kovačević, M. *Tetrahedron: Asymmetry*, **1994**, 5, 1605-1612.
3. Herak J. J. *Croat. Chem. Acta*, **1995**, in the press.
4. Herak, J. J.; Vinković, M.; Kojić-Prodić, B. *J. Chem. Res.*, (S), **1994**, 214-215; (M), 1201-1226.
5. Butlin, R. J.; Linney, I. D.; Critcher, D. J.; Mahon, M. F.; Molloy, K. C.; Wills, M. *J. Chem. Soc., Perkin Trans. I*, **1993**, 1581-1589.
6. The symbol (*S*_S) given in this text indicates that the chirality of the sulfur is *S*.
7. Drabowicz, J.; Kielbasicki, P.; Mikołajczyk, M. in *The Chemistry of Sulfinic Acids, Esters and their Derivatives*, ed. S. Patai, Wiley, Sussex, 1990, 352.
8. Belinzoni, D. U.; Setti, E. L.; Mascaretti, O. A. *J. Chem. Res.*, (S) **1988**, 176-177; (M) 1501-1536
9. Pant, C. M.; Steele, J.; Stoodley, R. J. *J. Chem. Soc., Perkin Trans. I*, **1982**, 595-602.
10. Kukulja, S.; Lammert, S. R.; Gleissner, M. R. B. Ellis, A. J. *J. Am. Chem. Soc.*, **1976**, 98, 5040-5041; Kukulja, S; *US pat* 4052387 (1977), *Chem. Abstr.* **1977**, 86, 43714d.
11. Stoe&Cie REDU4S. Data Reduction Program. Stoe&Cie, Darmstadt, Germany, 1992.
12. Sheldrick, G. M. *Program for the Solution of Crystal Structures*, 1985, Univ. of Göttingen, Germany.
13. Sheldrick, G. M. *J. Appl. Cryst.*, in the press.
14. Flack, H. D. *Acta Cryst.*, **1983**, A39, 876-881.
15. The tables of bond angles, bond distances, torsion angles, anisotropic thermal parameters, atomic coordinates and list of structure factors are available on request from the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW.
16. Berthon, J.; Laurent, A.; Rimsky, A. *C. R. Acad. Sci., Ser. C*, **1972**, 274, 157.
17. Seff, K.; Heidner, G.; Meyers, M.; Treublood, K. N. *Acta Crystallogr., Sect. B*, **1969**, 25, 350-354.

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