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Stereoselective synthesis of homochiral annulated sultams via intramolecular cycloaddition reactions

Ugo Chiacchio,[a,*] Antonino Corsaro,[a] Antonio Rescifina,[a] Majdi Bkaithan,[b] Giovanni Grassi,[b] Anna Piperno,[b] Tindara Privitera[b] and Giovanni Romeo[b]

[a]*Dipartimento di Scienze Chimiche, Università di Catania, 95125 Catania, Italy*
[b]*Dipartimento Farmaco-Chimico, Università di Messina, Messina, Italy*

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Abstract—Different homochiral dipoles containing a sulfonamido group have been synthesized, starting from L-amino acids, and used for the construction of functionalized and enantiomerically pure annulated sultams.

1. Introduction

The synthetic versatility of the intramolecular cycloaddition of nitrones, containing additional oxygen, nitrogen or sulfur atoms in a tether connecting the dipole to the dipolarophile moiety, has been widely exploited.[1] Applications of this methodology are seen in the synthetic routes towards functionalized furan, pyrrole and thiophene nuclei, some of which occur in natural and biologically active compounds. In some cases these syntheses start from homochiral educts.[2]

Factors controlling the stereochemical outcome of the reaction have been elucidated on the basis of a kinetic control of the process and the stability of the different transition states leading to different diastereoisomers.[3] A chiral center in the starting nitrone could cause asymmetric induction giving rise to the formation of new chiral centers with definite configuration in the obtained cycloadducts, so extending the synthetic potential of the reaction.

In this context, we have previously reported the intramolecular 1,3-dipolar cycloaddition of suitably substituted α- and β-sulfonamides, which leads to isoxazole and pyrazole annulated γ- and δ-sultams: the obtained isothiazole 1,1-dioxide derivatives belong to a class of heterocycles which exhibit interesting pharmacological properties;[4] in particular, the 2-methyl-5,6-diphenylperhydro-1λ^6-pyrazolo[3,4-d]isothiazole-1,1-dioxide shows antimicotic activity.[5]

In this paper we have investigated the intramolecular cycloaddition process of different dipoles, where the sulfonamido group is located in α-position with respect to the reactive center, i.e. the aldehydic moiety on which different dipoles have been built.

The presence of a stereocenter at C_2 furnishes a valid tool for the diastereoselective synthesis of isoxazole-, pyrazole-, pyrrolo-fused isothiazole-1,1-dioxides, some of which have also been accessible in enantiopure forms (Scheme 1).

The synthetic potential of this kind of sulfonamido-based dipoles has not been fully exploited; moreover, sultams have acquired good interest for the biological activity of some members of this class of compounds[6] and as chiral auxiliaries in asymmetric syntheses.[7]

2. Results and discussion

The different synthetic approaches which lead to the target molecules are based on the sulfonamido aldehydes **4**, which have been obtained as reported in Scheme 2.

Starting from L-amino acids **1**, aminoalcohols **2** have been obtained according to standard procedures.[8] Compounds **2** have been treated with *trans* 2-phenylethenesulfonyl chloride to give the corresponding sulfonamido alcohols **3**, which have been converted into the α-sulfonamido aldehydes **4a–d** by oxidation with Dess–Martin periodinane (DMP).[9] Subsequent treatment with *N*-substituted hydroxylamines **5** (R=Me or $PhCH_2$) furnished nitrones **6a**, **b**, **d**, **e**, which immediately underwent intramolecular cycloaddition to bicyclo compounds **7a**, **b**, **d**, **e** in good yields (Scheme 3).

Similar treatment of **4a**, **c** with hydroxylamine produces the

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* Corresponding author. Tel.: +39-095-738-5014; fax: +39-095-580138; e-mail: uchiacchio@dipchi.unict.it

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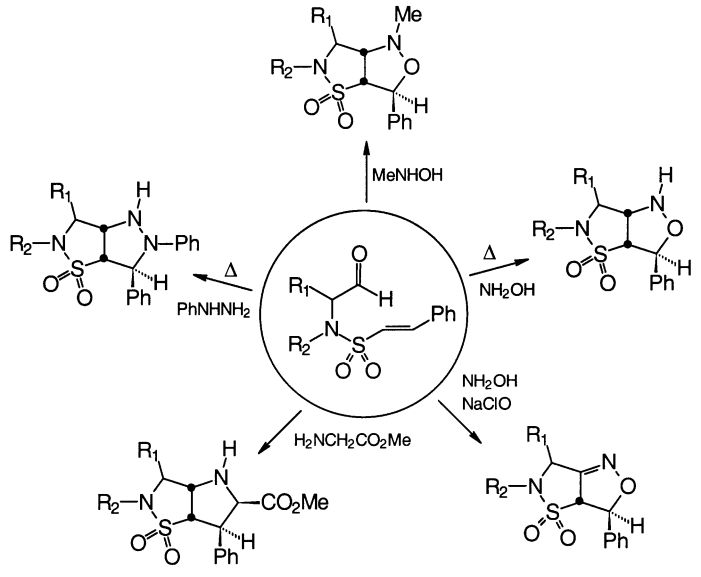
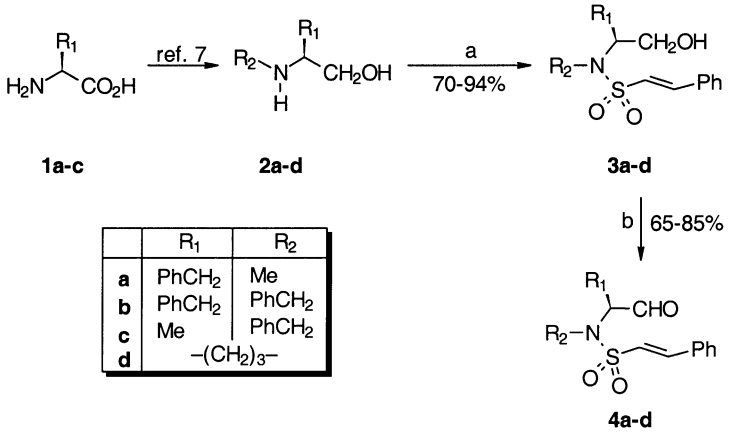


Scheme 1.

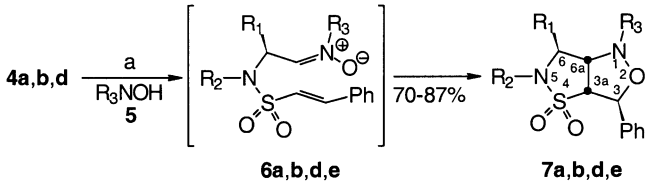


	R_1	R_2
a	$PhCH_2$	Me
b	$PhCH_2$	$PhCH_2$
c	Me	$PhCH_2$
d	$-(CH_2)_3-$	

a) *trans* 2-phenylethenesulfonyl chloride, Et_3N, CH_2Cl_2, $0 \rightarrow 25°C$, 6 h
b) Dess-Martin Periodinane, CH_2Cl_2, r.t., 30 min

Scheme 2.

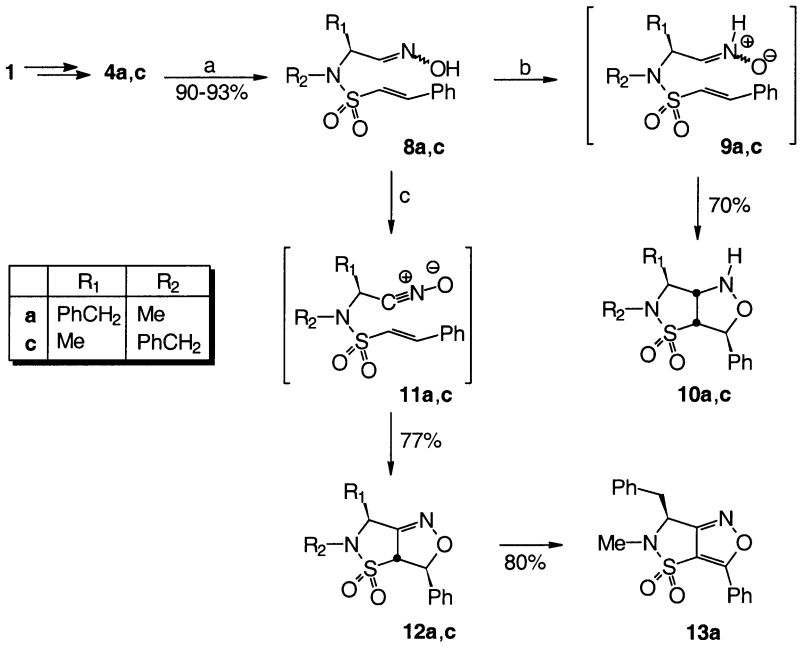
bicyclo compounds **10a**, **c** which result from the thermally induced oxime-nitrone **8→9** isomerization, followed by subsequent intramolecular cyloaddition (Scheme 4). Moreover, the oxime **8a** is converted by NaOCl oxidation to nitrile oxide **11a**, which gives rise to intramolecular cycloaddition at the styryl group to afford intermediate **12a**, which spontaneously aromatizes into isoxazole derivative **13a**. On the contrary, compound **8c** is converted into



	R_1	R_2	R_3
a	$PhCH_2$	Me	Me
b	$PhCH_2$	$PhCH_2$	Me
d	$-(CH_2)_3-$		Me
e	$PhCH_2$	Me	$PhCH_2$

a) Et_3N, EtOH, reflux, 24 h

Scheme 3.



	R_1	R_2
a	$PhCH_2$	Me
c	Me	$PhCH_2$

Scheme 4.

compound **12c**, which does not aromatize in our reaction conditions.

Structures of obtained cycloadducts were assigned on the basis of analytical and spectroscopic data. High-resolution mass spectra gave the correct molecular ions for all the examined compounds. The ^{1}H NMR spectra of compounds **7a**, **b**, **d**, **e**, **10a**, **c** and **12c** showed the diagnostic resonances of H_3 protons in the range 5.34–5.95 ppm, while H_{3a} protons appear at 3.98–4.76 ppm; H_{6a} protons, for compounds **7a**, **b**, **e** and **10a**, **c**, resonate in the range 3.39–4.14 ppm; for compound **7d** the H_{8b} proton results at 3.56 ppm. For compound **13a** the diagnostic resonance of H_6 proton is at 4.64 ppm.

The investigated 1,3-dipolar cycloadditions showed high regioselectivity; according to similar intramolecular processes, no bridged adducts have been detected in the crude reaction mixture.

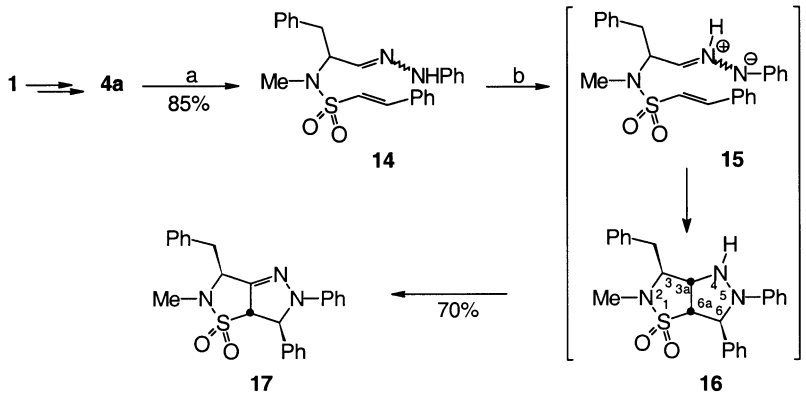
The cycloaddition process has also been found to proceed with complete diasteroselectivity: the NMR spectra or tlc of crude products do not show evidence of any diastereoisomers. The chiral center at C_2 induces a complete asymmetric induction furnishing homochiral compounds **7**, **10**, **12** and **13** from homochiral starting material. In fact, the ^{1}H NMR spectra of the above reported compounds, recorded in the presence of increasing amounts of the chiral shift reagent [Eu(tfc)$_3$], do not show any change of the single resonances, apart from the expected shifts induced by the paramagnetic reagent.

The absolute stereochemistry of the cycloadducts **7**, **10** and **12** was elucidated by ^{1}H NMR. The stereochemical information present in the dipolarophile moiety is completely retained in the cycloadducts and the relative stereochemistry at C_3 and C_{3a} in the formed isoxazolidine and isoxazoline ring is predetermined by the alkene geometry. Furthermore, the ring junction between the two fused rings in compounds **7** and **10** is always *cis*, as confirmed by coupling constants and NOE measurements. For instance, in compound **7a**, the coupling constant for the *cis* ring junction protons ($J_{3a,6a}$) is 8.4 Hz, indicative of a nearly eclipsed dihedral angle between H_{3a} and H_{6a}. Irradiation of H_{3a} gives rise to a positive NOE effect for H_{6a} (9.43%), for aromatic protons at C_3 (3.54%) and for benzylic protons at C_6, so indicating a *cis* relationship between these protons. By considering that the C_6 configuration is *S*, the obtained data are only compatible with a (3*S*,3a*R*,6*S*,6a*S*) stereochemistry.

The stereocenter at the α-position effectively controls the formation of the three new contiguous stereocenters and one of the eight possible stereoisomers is produced in a highly stereoselective process.

The syntheses of pyrazolo-fused γ-sultams have also been investigated, starting from sulfonamido aldehyde **1** (Scheme 5). Thus, reaction of **4a** with phenylhydrazine afforded the racemic phenylhydrazone **14** (see Section 3); thermal hydrazone–azomethine imine isomerization, performed in ethanol at reflux temperature, generates the 1,3-dipole **15**, which spontaneously underwent intramolecular cycloaddition to cycloadduct **16**, as evidenced in the ^{1}H NMR spectrum of the crude reaction mixture. The attempts to isolate this compound by flash chromatography led to the isolation of compound **17**, which originates from a rapid air oxidation of **16**.

Compound **17** was obtained as a racemic mixture: this result is the consequence of the racemization process, occurring in the hydrazone formation.



Scheme 5.

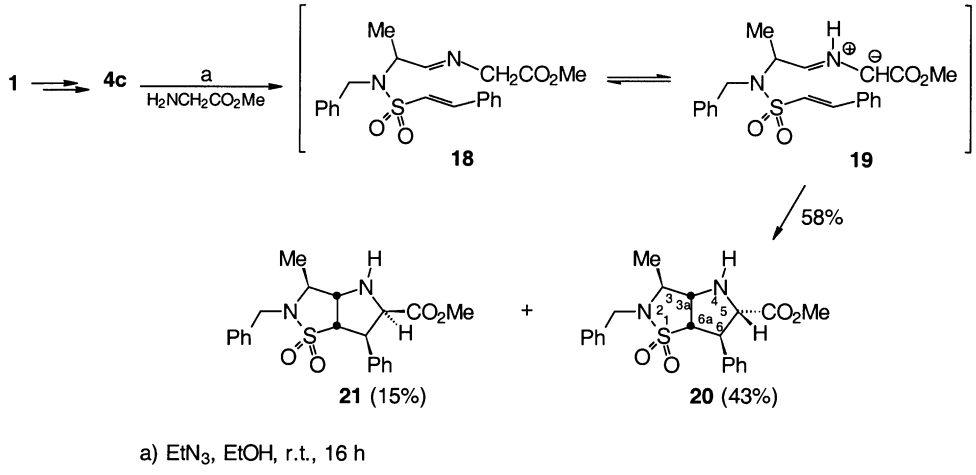
In the attempt to establish the scope and limitations of the investigated approach towards bicyclic sultams, we have also examined the synthesis of pyrrolidino-isothiazole dioxide fused systems, starting from the sulfonamido aldehyde **4c** (Scheme 6).

Reaction with glycine methyl ester hydrochloride in the presence of 6 equiv. of triethylamine afforded compounds **20** and **21** as racemic mixtures, in a 3:1 relative ratio.

The reaction pathway is rationalized on the basis of the initial formation of imino derivative **18**, which undergoes a thermal imine–azomethine ylide **19** isomerization by 1,2 prototropic shift.[10]

The stereochemical assignments have been performed on the basis of NOE measurements; thus, irradiation of H_{3a} in **20** resulted in NOE enhancements for H_5, H_{6a} and the methyl group at C_3, so indicating a *cis* spatial relationship between these protons.

Conversely, in compound **21**, no NOE effect has been detected between H_{3a} and H_5: irradiation of H_{3a} gives rise only to enhancement of H_{6a} and the methyl group at C_3.



Scheme 6.

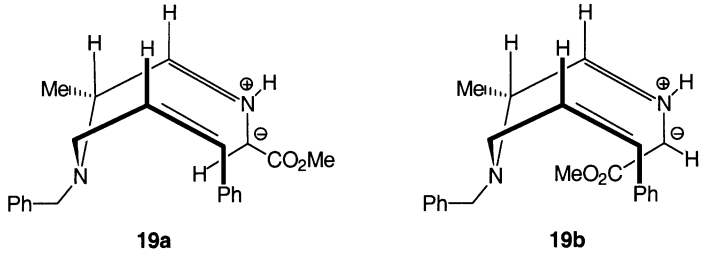


Figure 1.

The absence of any diastereomeric control in the examined process could be ascribed to the existence of two stereoisomeric azomethine ylides **19a** and **19b**, which independently undergo the cycloaddition reaction (Fig. 1).

The possible alternative, i.e. that compound **21** originates from **20** by epimerization, can be ruled out: in fact, when **20** was treated with triethylamine for several hours at reflux temperature, starting material was recovered unaltered.

Moreover, formation of **20** and **21** as racemic mixtures is explainable on the basis of a racemization process occurring in the initial step leading to the imino derivative, promoted by the basic reaction medium.

In conclusion, the homochiral aldehyde **4** has been used as a valid source of different homochiral dipoles for the construction of functionalized isothiazoloisoxazole-4,4-dioxides, pyrazoloisothiazole-1,1-dioxides and pyrroloisothiazole-1,1-dioxides by exploiting the intramolecular 1,3-dipolar cycloaddition. In particular, enantiomerically pure annulated sultams **7**, **10**, **12** and **13** with specific absolute stereochemistry have been obtained. These ring closures offer the possibility of usefully synthetic manipulations directed towards the synthesis of biologically active compounds.

3. Experimental

Melting points were measured on a Kofler apparatus and are uncorrected. Elemental analyses were performed with a Perkin–Elmer elemental analyzer. Infrared spectra were recorded on a Perkin–Elmer 377 instrument. ^{1}H NMR spectra were measured on a 500 MHz Varian Unity Inova instrument in $CDCl_3$ as solvent. Chemical shifts are in ppm (δ) from TMS as internal standard. NOE difference spectra were obtained by subtracting alternatively right-off-resonance free induction decays (FIDS) from right-on-resonance-induced FIDS. Merck silica gel 60H was used for preparative short-column chromatography. Optical rotations were measured on a PF 241 MC Polarimeter (Perkin–Elmer). Compounds **2a–d** have already been reported.[2a,11]

3.1. Preparation of *trans* sulfonamido alcohols 3a–d—general procedure

A solution (11.14 g, 55 mmol) of *trans* 2-phenylethenesulfonyl chloride in anhydrous dichloromethane (50 mL) was added dropwise, at 0°C, to a stirred solution containing compounds **2** (50 mmol) and triethylamine (5.44 g, 7.5 mL, 53.8 mmol). The reaction mixture was stirred at 0°C for 30 min and then at 25°C for 6 h. At the end of this time the mixture was extracted with dichloromethane, washed with 10% aqueous $NaHCO_3$ and dried (Na_2SO_4). The solvent was removed and the crude residue was purified by silica gel flash chromatography (2% methanol/chloroform).

3.1.1. Reaction of 2a with *trans* 2-phenylethenesulfonyl chloride. First elution gave *N*-[(1*S*)-1-benzyl-2-hydroxyethyl]-*N*-methyl-(*E*)-2-phenyleth-1-ene-1-sulfonamide **3a** (15.56 g, 94%) as a yellow solid, mp 89–91°C; $[\alpha]_D^{25}=-38.6$ (*c* 1.20, $CHCl_3$); ν_{max} (KBr) 3380, 3030, 2995, 1600, 1330, 1060, 920, 750, 700 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 2.40 (bs, 1H), 2.70 (dd, 1H, *J*=9.6 and 14.1 Hz), 2.80 (s, 3H), 2.83 (dd, 1H, *J*=6.0 and 14.1 Hz), 3.69 (d, 2H, *J*=5.7 Hz), 4.35 (m, 1H), 5.74 (d, 1H, *J*=15.6 Hz), 7.19–7.37 (m, 11H); δ_C (125 MHz, $CDCl_3$) 27.74, 35.16, 60.81, 62.25, 123.88, 126.85, 128.27, 128.41, 128.66, 129.17, 130.46, 132.58, 137.62, 141.24. Exact mass calculated for $C_{18}H_{21}NO_3S$: 331.1242. Found: 331.1240.

3.1.2. Reaction of 2b with *trans* 2-phenylethenesulfonyl chloride. First elution gave *N*-benzyl-*N*-[(1*S*)-1-benzyl-2-hydroxyethyl]-(*E*)-2-phenyleth-1-ene-1-sulfonamide **3b** (18.32 g, 90%) as a yellow solid, mp 110–113°C; ν_{max} (KBr) 3380, 3035, 2995, 1650,1620, 1600, 1330, 1060, 920, 750, 700 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 2.75 (bs, 1H), 2.65 (dd, 1H, *J*=7.2 and 14.1 Hz), 2.85 (dd, 1H, *J*=7.2 and 14.1 Hz), 3.47 (m, 1H), 4.17 (q, 2H, *J*=6.0 and 7.2 Hz), 4.31 (d, 1H, *J*=15.4 Hz), 4.45 (d, 1H, *J*=15.4 Hz) 6.17 (d, 1H, *J*=15.5 Hz), 7.19–7.55 (m, 16H); δ_C (125 MHz, $CDCl_3$) 36.39, 48.32, 62.52, 62.98, 125.05, 126.79, 126.82, 127.96, 128.20, 128.26, 128.37, 128.56, 128.59, 128.65, 128.68, 128.73, 128.84, 128.95, 129.11, 129.25, 132.64, 137.68, 137.81, 141.19. Exact mass calculated for $C_{24}H_{25}NO_3S$: 407.1555. Found: 407.1550.

3.1.3. Reaction of 2c with *trans* 2-phenylethenesulfonyl chloride. First elution gave *N*-benzyl-*N*-[(1*S*)-2-hydroxy-1-methylethyl]-(*E*)-2-phenyleth-1-ene-1-sulfonamide **3c** (13.08 g, 79%) as a white solid, mp 90–92°C; $[\alpha]_D^{25}=+22.1$ (*c* 1.99, $CHCl_3$); ν_{max} (KBr) 3524, 3062, 3029, 2978, 2940, 1615, 1496, 1450, 1324, 1140, 1063, 1021, 863, 817, 747 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.13 (d, 3H, *J*=6.9 Hz), 2.23 (bs, 1H, OH), 3.41 (dd, 1H, *J*=5.6 and 11.6 Hz), 3.47 (dd, 1H, *J*=8.2 and 11.6 Hz), 4.03 (ddd, 1H, *J*=5.6, 6.9 and 8.2 Hz), 4.30 (d, 1H, *J*=15.8 Hz), 4.45 (d, 1H, *J*=15.8 Hz), 6.79 (d, 1H, *J*=15.4 Hz), 6.75–7.48 (m, 11H); δ_C (125 MHz, $CDCl_3$) 15.66, 47.41, 56.10, 64.25, 124.99, 127.63, 127.78, 128.08, 128.57, 128.94, 130.59, 132.62, 137.94, 140.97. Exact mass calculated for $C_{18}H_{21}NO_3S$: 331.1242. Found: 331.1245.

3.1.4. Reaction of 2d with *trans* 2-phenylethenesulfonyl chloride. First elution gave ((2*S*)-1-{[(*E*)-2-phenyleth-1-enyl]sulfonyl}tetrahydro-1*H*-pyrrol-2-yl)methanol **3d**, (9.35 g, 70%) as a yellow oil; ν_{max} (neat) 3375, 3058, 3030, 2960, 1600, 1490, 1320, 1060, 980, 760 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.81 (m, 2H), 1.96 (m, 2H), 2.71 (t, 1H, *J*=6.0 Hz, OH), 3.46 (m, 1H), 3.48 (m, 1H), 3.71 (m, 3H), 6.75 (d, 1H, *J*=15.3 Hz), 7.42–7.57 (m, 6H); δ_C (125 MHz, $CDCl_3$) 29.80, 29.09, 49.82, 61.80, 65.77, 128.15, 128.27, 129.00, 130.99, 137.61, 143.95. Exact mass calculated for $C_{13}H_{17}NO_3S$: 267.0929. Found: 267.0932.

3.2. Preparation of *trans* sulfonamido aldehydes 4a–d—general procedure

Wet CH_2Cl_2 (20 mL; 20 μL H_2O in 20 mL CH_2Cl_2) was added slowly to a vigorously stirring solution of

sulfonamido alcohol **4** (1 mmol) and DMP[9] (640 mg, 1 mmol) in dry CH_2Cl_2 (6 mL) and allowed to stir for 30 min. The mixture was then diluted with ether, and concentrated into a few milliliters of solvent by rotary evaporator. The residue was taken up in ether (50 mL) and then washed with a 1:1 solution of 10% aqueous $Na_2S_2O_3$ in saturated aqueous $NaHCO_3$ (30 mL), followed by H_2O (10 mL) and brine (10 mL). The aqueous washings were back-extracted with ether (20 mL), and this organic layer was washed with H_2O and brine. The combined organic layers were dried (Na_2SO_4) and the solvent removed under reduced pressure. The residue was then subjected to silica gel flash chromatography (2% methanol/chloroform).

3.2.1. Oxidation of 3a with DMP. First elution gave *N*-[(1*S*)-1-benzyl-2-oxoethyl]-*N*-methyl-(*E*)-2-phenyleth-1-ene-1-sulfonamide **4a** (280 mg, 85%) as a white sticky oil; ν_{max} (neat) 3060, 3020, 2980, 2850, 2730, 1740, 1600, 1500, 1315, 1030, 980, 920, 760 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 2.69 (s, 3H), 2.74 (dd, 1H, *J*=9.9 and 15.1 Hz), 3.28 (dd, 1H, *J*=7.3 and 15.1 Hz), 4.73 (dd, 1H, *J*=7.3 and 9.9 Hz), 5.54 (d, 1H, *J*=15.3 Hz), 7.08–7.27 (m, 11H), 9.60 (s, 1H); δ_C (125 MHz, $CDCl_3$) 29.95, 31.99, 67.23, 126.61, 126.99, 128.38, 128.50, 128.98, 130.19, 130.54, 132.32, 136.39, 141.84, 198.95. Exact mass calculated for $C_{18}H_{19}NO_3S$: 329.1086. Found: 329.1085.

3.2.2. Oxidation of 3b with DMP. First elution gave *N*-benzyl-*N*-[(1*S*)-1-benzyl-2-oxoethyl]-(*E*)-2-phenyleth-1-ene-1-sulfonamide **4b** (324 mg, 80%) as a yellow sticky oil; ν_{max} (neat) 3035, 2995, 2850, 2750, 1740, 1650,1620, 1600, 1330, 1060, 920, 750, 700 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 2.87 (dd, 1H, *J*=10.0 and 15.0 Hz), 3.35 (dd, 1H, *J*=5.0 and 15.0 Hz), 4.18 (m, 2H), 4.42 (dd, 1H, *J*=5.0 and 10.0 Hz), 5.95 (d, 1H, *J*=15.3 Hz), 7.19–7.55 (m, 16H), 9.28 (s, 1H); δ_C (125 MHz, $CDCl_3$) 32.92, 49.56, 67.66, 124.67, 127.10, 128.40, 128.63, 128.88, 129.08, 129.16, 129.19, 130.88, 132.33, 135.29, 137.13, 142.11, 142.14, 198.17. Exact mass calculated for $C_{24}H_{23}NO_3S$: 405.1399. Found: 405.1396.

3.2.3. Oxidation of 3c with DMP. First elution gave *N*-benzyl-*N*-[(1*S*)-1-methyl-2-oxoethyl]-(*E*)-2-phenyleth-1-ene-1-sulfonamide **4c** (263 mg, 80%) as a white solid, mp 78–80°C; $[\alpha]_D^{25}$=−7.1 (*c* 5.62, $CHCl_3$); ν_{max} (KBr) 3058, 2982, 2833, 2755, 1735, 1615, 1449, 1239, 1143, 977, 934, 830, 750, 700 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.39 (d, 1H, *J*=7.2 Hz), 4.09 (q, 1H, *J*=7.2 Hz), 4.33 (d, 1H, *J*=15.2 Hz), 4.44 (d, 1H, *J*=15.2 Hz), 6.75 (d, 1H, *J*=15.4 Hz), 7.25–7.58 (m, 11H), 9.43 (s, 1H); δ_C (125 MHz, $CDCl_3$) 12.33, 49.74, 61.75, 124.62, 128.26, 128.36, 128.51, 128.82, 129.10, 131.04, 132.34, 135.74, 142.42, 198.83. Exact mass calculated for $C_{18}H_{19}NO_3S$: 329.1086. Found: 329.1090.

3.2.4. Oxidation of 3d with DMP. First elution gave (2*S*)-1-{[(*E*)-2-phenyleth-1-enyl]sulfonyl}tetrahydro-1*H*-pyrrole-2-carbaldehyde **4d** (172 mg, 65%) as a yellow oil; ν_{max} (neat) 3050, 3030, 2960, 2750, 1760, 1600, 1490,1350, 1060, 980, 760 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 2.05 (m, 4H), 3.47 (m, 2H), 4.05 (m, 1H), 6.79 (d, 1H, *J*=17.1 Hz), 7.42–7.56 (m, 6H), 9.65 (s, 1H); δ_C (125 MHz, $CDCl_3$) 24.94, 27.61, 48.84, 66.45, 120.80, 128.53, 129.10, 131.11, 132.34, 143.83, 199.85. Exact mass calculated for $C_{13}H_{15}NO_3S$: 265.0773. Found: 265.0777.

3.3. Preparation of isothiazolo[4,5-*c*]isoxazole-4,4-dioxides 7a, b, d, e—general procedure

A mixture containing compound **4** (**a**, **b** or **d**) (50 mmol), triethylamine (5.56 g, 7.66 mL, 55 mmol) and *N*-substituted hydroxylamine hydrochloride (55 mmol) in absolute ethanol (50 mL) was refluxed for 24 h. At the end of this time the solvent was removed and the residue extracted with dichloromethane, washed with water and dried (Na_2SO_4). The residue was then subjected to silica gel flash chromatography (2% methanol/chloroform).

3.3.1. Reaction of 4a with *N*-methyl hydroxylamine. First elution gave (3*S*,3a*R*,6*S*,6a*S*)-6-benzyl-1,5-dimethyl-3-phenylperhydro-4λ^6-isothiazolo[4,5-*c*]isoxazole-4,4-dioxide **7a** (13.43 g, 75%) as a white solid, mp 152–153°C; $[\alpha]_D^{25}$=+29.5 (*c* 1.15, $CHCl_3$); ν_{max} (KBr) 3075, 3025, 2980, 1490, 1315, 1050, 980, 760 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 2.38 (s, 3H), 2.81 (dd, 1H, H_{7a}, *J*=10.5 and 12.6 Hz), 2.88 (s, 3H), 3.23 (dd, 1H, H_{7b}, *J*=5.4 and 12.6 Hz), 3.37 (dd, 1H, H_6, *J*=5.4 and 10.5 Hz), 3.42 (d, 1H, H_{6a}, *J*=8.4 Hz), 3.98 (dd, 1H, H_{3a}, *J*=7.2 and 8.4 Hz), 5.34 (d, 1H, H_3, *J*=7.2 Hz), 7.23–7.44 (m, 10H); δ_C (125 MHz, $CDCl_3$) 29.44, 36.18, 42.69, 63.45, 70.10, 70.67, 81.36, 126.43, 127.31, 128.76, 128.93, 129.36, 130.51, 132.05, 136,28. Exact mass calculated for $C_{19}H_{22}N_2O_3S$: 358.1351. Found: 358.1350.

3.3.2. Reaction of 4b with *N*-methyl hydroxylamine. First elution gave (3*S*,3a*R*,6*S*,6a*S*)-5,6-dibenzyl-1-methyl-3-phenylperhydro-4λ^6-isothiazolo[4,5-*c*]isoxazole-4,4-dioxide **7b** (18.45 g, 85%); $[\alpha]_D^{25}$=+8.8 (*c* 0.75, $CHCl_3$); ν_{max} (KBr) 3070, 3050, 3020, 2980, 1490, 1350, 1320, 1050, 980, 760 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 2.24 (s, 3H), 2.78 (dd, 1H, H_{7a}, *J*=10.8 and 13.3 Hz), 3.10 (dd, 1H, H_{7b}, *J*=4.9 and 13.3 Hz), 3.25 (dd, 1H, H_6, *J*=4.9 and 10.8 Hz), 3.39 (d, 1H, H_{6a}, *J*=8.5 Hz), 4.06 (dd, 1H, H_{3a}, *J*=7.4 and 8.5 Hz), 4.24 (d, 1H, H_{8a}, *J*=14.6 Hz), 4.63 (d, 1H, H_{8b}, *J*=14.6 Hz), 5.41 (d, 1H, H_3, *J*=7.4 Hz), 6.97–7.47 (m, 15H); δ_C (125 MHz, $CDCl_3$) 36.70, 46.92, 52.03, 59.88, 70.96, 73.20, 81.50, 126.03, 126.49, 127.06, 127.54, 128.07, 128.55, 128.76, 128.81, 129.23, 129.35, 134.99, 136.55. Exact mass calculated for $C_{25}H_{26}N_2O_3S$: 434.1664. Found: 434.1663.

3.3.3. Reaction of 4d with *N*-methyl hydroxylamine. First elution gave (3*S*,3a*R*,8a*S*,8b*S*)-1-methyl-3-phenylperhydro-4λ^6-pyrrolo[1′,2′:2,3]isothiazolo[4,5-*c*]isoxazole-4,4-dioxide **7d** (10.29 g, 70%) as a yellow solid, mp 142–144°C; $[\alpha]_D^{25}$=−7.3 (*c* 0.83, $CHCl_3$); ν_{max} (KBr) 3050, 3020, 2970, 1500, 1350, 1320, 1050, 980, 760 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.79 (m, 1H), 1.97 (m, 2H), 2.17 (m, 1H), 2.80 (s, 3H), 3.23 (dt, 1H, H_{6a}, *J*=7.5 and 11.7 Hz), 3.56 (dd, 1H, H_{8b}, *J*=2.5 and 9.0 Hz), 3.74 (m, 2H, H_{6b} and H_{8a}), 4.05 (dd, 1H, H_{3a}, *J*=6.3 and 9.0 Hz), 5.68 (d, 1H, H_3, *J*=6.3 Hz), 7.33–7.45 (m, 5H); δ_C (125 MHz, $CDCl_3$) 25.26, 31.51, 44.14, 47.40, 59.35, 63.97, 72.62, 80.90, 126.18, 128.57, 128.80, 134.15.

Exact mass calculated for $C_{14}H_{18}N_2O_3S$: 294.1038. Found: 294.1039.

3.3.4. Reaction of 4a with *N*-benzyl hydroxylamine. First elution gave (3*S*,3a*R*,6*S*,6a*S*)-1,6-dibenzyl-5-methyl-3-phenylperhydro-4λ^6-isothiazolo[4,5-*c*]isoxazole-4,4-dioxide **7e** (18.88 g, 87%) as a white solid, mp 157–158°C; $[\alpha]_D^{25}=+18.2$ (*c* 1.65, $CHCl_3$); ν_{max} (KBr) 3080, 3040, 3025, 2980, 1490, 1320, 1050, 980, 760 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 2.70 (dd, 1H, H_{7a}, *J*=4.5 and 13.5 Hz), 2.78 (s, 3H), 3.13 (dd, 1H, H_{7b}, *J*=6.9 and 13.5 Hz), 3.31 (ddd, 1H, H_6, *J*=4.5, 6.9 and 8.4 Hz), 3.66 (d, 1H, H_{8a}, *J*=13.8 Hz), 3.72 (dd, 1H, H_{6a}, *J*=8.4 and 8.7 Hz), 3.89 (d, 1H, H_{8b}, *J*=13.8 Hz), 3.98 (dd, 1H, H_{3a}, *J*=7.2 and 8.7 Hz), 5.34 (d, 1H, H_3, *J*=7.2 Hz), 7.12–7.48 (m, 15H); δ_C (125 MHz, $CDCl_3$) 30.62, 36.57, 59.98, 64.09, 69.97, 70.03, 81.04, 125.99, 126.34, 126.92, 127.67, 128.27, 128.53, 128.72, 129.23, 129.27, 135.04, 136.39, 136.49. Exact mass calculated for $C_{25}H_{26}N_2O_3S$: 434.1664. Found: 434.1665.

3.4. Preparation of sulfonamido oximes 8a,c—general procedure

A mixture containing compound **4a**, **c** (3.3 mmol), 95% aqueous ethanol (30 mL), hydroxylamine hydrochloride (330 mg, 4.8 mmol) and sodium acetate (390 mg, 4.8 mmol) was stirred at 0°C for 6 h. At the end of this time the solvent was evaporated at reduced pressure and the residue was extracted with dichloromethane, washed with 10% aqueous $NaHCO_3$ and dried (Na_2SO_4). The solvent was removed and the crude residue was purified by silica gel flash chromatography (70% CCl_4/ethyl acetate).

3.4.1. Reaction of 4a with hydroxylamine hydrochloride. First eluted product was a *syn–anti* mixture (1:3) of *N*-[(1*S*)-1-benzyl-2-hydroxyiminoethyl]-*N*-methyl-(*E*)-2-phenyleth-1-ene-1-sulfonamide **8a** (1.02 g, 90%) as a sticky oil; $[\alpha]_D^{25}=-4.82$ (*c* 0.41, $CHCl_3$). Major isomer: δ_H (500 MHz, $CDCl_3$) 2.78 (s, 3H), 2.94 (dd, 1H, *J*=10.2 and 14.6 Hz), 3.15 (dd, 1H, *J*=5.7 and 14.6 Hz), 4.99 (ddd, 1H, *J*=4.3, 5.7 and 10.2 Hz), 5.65 (d, 1H, *J*=15.3 Hz), 7.24–7.39 (m, 11H), 7.52 (d, 1H, *J*=4.3 Hz), 8.15 (bs, 1H, OH); δ_C (125 MHz, $CDCl_3$) 29.74, 35.54, 57.71, 123.75, 127.06, 128.33, 128.78, 128.91, 129.354, 130.61, 132.55, 137.12, 141.64, 149.63. Exact mass calculated for $C_{18}H_{20}N_2O_3S$: 344.1194. Found: 344.1190.

3.4.2. Reaction of 4c with hydroxylamine hydrochloride. First eluted product gave a *syn–anti* mixture (1:3) of *N*-benzyl-*N*-[(1*S*)-2-hydroxyimino-1-methylethyl]-(*E*)-2-phenyleth-1-ene-1-sulfonamide **8c** (1.05 g, 93%) as a white solid, mp 132–135°C; $[\alpha]_D^{25}=-1.20$ (*c* 8.36, $CHCl_3$). Major isomer: δ_H (500 MHz, $CDCl_3$) 1.27 (d, 3H, *J*=7.0 Hz), 4.27 (d, 1H, *J*=16.0 Hz), 4.30 (d, 1H, *J*=16.0 Hz), 4.55 (dq, 1H, *J*=4.5 and 7.0 Hz), 6.57 (d, 1H, *J*=15.0 Hz), 7.16–7.39 (m, 12H), 7.52 (bs, 1H, OH); δ_C (125 MHz, $CDCl_3$) 16.97, 48.39, 53.08, 125.13, 127.71, 128.12, 128.16, 128.29, 128.62, 129.03, 129.05, 130.81, 132.60, 132.61, 141.53, 151.06. Exact mass calculated for $C_{18}H_{20}N_2O_3S$: 344.1194. Found: 344.1192.

3.5. Preparation of 1-*N*-unsubstituted isothiazolo[4,5-*c*]-isoxazole-4,4-dioxides 10a,c—general procedure

A solution containing sulfonamido oxime **8a**, **c** (2.24 mmol) in absolute ethanol (100 mL) was refluxed for 60 h. The reaction mixture was evaporated under reduced pressure and the residue purified by silica gel flash chromatography (3% MeOH/$CHCl_3$).

3.5.1. Reaction of oxime 8a. (3*S*,3a*R*,6*S*,6a*S*)-6-Benzyl-5-methyl-3-phenylperhydro-4λ^6-isothiazolo[4,5-*c*]isoxazole-4,4-dioxide **10a** (539 mg. 70%); sticky oil; $[\alpha]_D^{25}=-22.4$ (*c* 0.62, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 2.77 (s, 3H), 2.99 (dd, 1H, H_{7a}, *J*=9.3 and 13.8 Hz), 3.20 (dd, 1H, H_{7b}, *J*=6.3 and 13.8 Hz), 3.49 (dd, 1H, H_6, *J*=6.3, and 9.3 Hz), 4.14 (dd, 1H, H_{6a}, *J*=7.2 and 7.3 Hz), 4.19 (dd, 1H, H_{3a}, *J*=6.0 and 7.3 Hz), 5.31 (d, 1H, NH, *J*=7.2 Hz), 5.57 (d, 1H, H_3, *J*=6.0 Hz), 7.23–7.42 (m, 10H); δ_C (125 MHz, $CDCl_3$) 33.15, 37.81, 65.92, 69.46, 70.83, 82.97, 125.97, 127.14, 128.36, 128.86, 129.09, 129.33, 135.92, 136.33. Exact mass calculated for $C_{18}H_{20}N_2O_3S$: 344.1194. Found: 344.1195.

3.5.2. Reaction of oxime 8c. (3*S*,3a*R*,6*S*,6a*S*)-5-Benzyl-6-methyl-3-phenylperhydro-4λ^6-isothiazolo[4,5-*c*]isoxazole-4,4-dioxide **10c** (539 mg, 70%); sticky oil; $[\alpha]_D^{25}=-15.6$ (*c* 0.52, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.11 (bs, 1H, NH), 1.26 (d, 1H, *J*=6.7 Hz), 3.20 (dq, 1H, H_6, *J*=1.7 and 6.7 Hz), 4.01 (dd, 1H, H_{6a}, *J*=1.7, and 8.3 Hz), 4.03 (dd, 1H, H_{3a}, *J*=1.2 and 8.3 Hz), 4.06 (d, 1H, $H_{5'a}$, *J*=14.6 Hz), 4.41 (d, 1H, $H_{5'b}$, *J*=14.6 Hz), 5.53 (d, 1H, H_3, *J*=1.2 Hz), 7.23–7.35 (m, 10H); δ_C (125 MHz, $CDCl_3$) 16.38, 44.61, 68.65, 68.66, 70.21, 86.75, 126.14, 128.20, 128.36, 128.91, 129.09, 135.00, 136.32. Exact mass calculated for $C_{18}H_{20}N_2O_3S$: 344.1194. Found: 344.1189.

3.6. Preparation of sultams 12c and 13a—general procedure

To a solution containing sulfonamido oxime **8a**,**c** (2.24 mmol) in dichloromethane (250 mL) was added dropwise sodium hypochlorite (6 mL, 7% solution) at 0°C with vigorous stirring. After 3 h the reaction mixture was evaporated and the residue subjected to silica gel flash chromatography (40% CCl_4/ethyl ether).

3.6.1. Reaction of oxime 8c. (3*S*,3a*R*,6*S*)-5-Benzyl-6-methyl-3-phenyl-3a,4,5,6-tetrahydro-3*H*-4λ^6-isothiazolo-[4,5-*c*]isoxazole-4,4-dioxide **12c** (590 mg, 77%); $[\alpha]_D^{25}=-7.14$ (*c* 1.08, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.37 (d, 3H, *J*=6.4 Hz), 4.07 (d, 1H, *J*=15.2 Hz), 4.09 (q, 1H, H_6, *J*=6.4 Hz), 4.56 (d, 1H, *J*=15.2 Hz), 4.76 (dd, 1H, H_{3a}, *J*=2.2 and 10.8 Hz), 5.95 (d, 1H, H_3, *J*=10.8 Hz), 7.05–7.49 (m, 10H); δ_C (125 MHz, $CDCl_3$) 16.94, 46.16, 52.38, 74.28, 85.34, 126.36, 128.16, 128.26, 128.31, 128.37, 128.95, 134.40, 135.17, 158.53. Exact mass calculated for $C_{18}H_{18}N_2O_3S$: 342.1038. Found: 342.1041.

3.6.2. Reaction of oxime 8a. (6*S*)-6-Benzyl-5-methyl-3-phenyl-5,6-dihydro-4*H*-4λ^6-isothiazolo[4,5-*c*]isoxazole-4,4-dioxide **13a** (609 mg, 80%); white solid, mp 109–112°C; $[\alpha]_D^{25}=-2.41$ (*c* 2.49, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 2.83 (s, 3H), 3.30 (d, 2H, H_7, *J*=6.3 Hz), 4.64 (t,

1H, H_6, J=6.3 Hz), 7.25–7.93 (m, 10H); δ_C (125 MHz, $CDCl_3$) 29.67, 38.59, 61.01, 113.59, 124.33, 127.50, 127.70, 128.70, 129.57, 129.66, 132.68, 134.84, 156.39, 165.41. Exact mass calculated for $C_{18}H_{16}N_2O_3S$: 340.0881. Found: 340.0877.

3.7. Preparation of sultam 17

A mixture containing compound **4a** (2.04 g, 6.20 mmol), 95% aqueous ethanol (30 mL), phenylhydrazine (670 mg, 6.20 mmol) and *p*-toluenesulfonic acid (10 mg) was stirred at 0°C for 6 h, under nitrogen. At the end of this time the solvent was evaporated at reduced pressure and the residue was extracted with dichloromethane, washed with 10% aqueous $NaHCO_3$ and dried (Na_2SO_4). Evaporation of the solvent and silica gel flash chromatography (70% CCl_4/ethyl acetate) gave *N*-(1*SR*)-1-benzyl-2-(2-phenylhydrazono)ethyl-*N*-methyl-(*E*)-2-phenyleth-1-ene-1-sulfonamide **14** (2.21 g, 85%) as a white solid, mp 118–121°C; δ_H (500 MHz, $CDCl_3$) 1.47 (bs, 1H, NH), 2.73 (s, 3H), 2.98 (dd, 1H, J=9.6 and 14.2 Hz), 3.26 (dd, 1H, J=6.0 and 14.2 Hz), 4.98 (ddd, 1H, J=3.6, 6.0 and 9.6 Hz), 5.67 (d, 1H, J= 15.3 Hz), 7.29–7.46 (m, 12H); δ_C (125 MHz, $CDCl_3$) 31.21, 36.98, 62.43, 112.57, 116.69, 125.13, 125.93, 126.51, 127.83, 128.59, 130.01, 135.99, 144.18, 144.81, 151.46, 163.12. Exact mass calculated for $C_{24}H_{25}N_3O_2S$: 419.1667. Found: 419.1669.

A solution of **14** (914 mg, 2.18 mmol) in ethanol (100 mL) was heated under nitrogen at reflux temperature for 72 h. The solution was cooled off, evaporated and the residue subjected to flash chromatography (40% CCl_4/ethyl ether), giving (3*SR*,6*SR*,6a*SR*)-3-benzyl-2-methyl-5,6-diphenyl-1,2,3,5,6,6a-hexahydro-1λ^6-pyrazolo[3,4-*d*]isothiazole-1,1-dioxide **17** (636 mg, 70%) as a white solid, mp 180–182°C; δ_H (500 MHz, $CDCl_3$) 2.89 (s, 3H), 3.14 (d, 2H, J=4.2 Hz), 3.50 (dd, 1H, H_{6a}, J=1.8 and 7.6 Hz), 4.30 (dt, 1H, H_3, J=1.8 and 4.2 Hz), 5.41 (d, 1H, H_6, J=7.6 Hz), 6.84–7.40 (m, 15H); δ_C (125 MHz, $CDCl_3$) 37.06, 56.25, 61.74, 67.92, 73.02, 114.76, 121.29, 125.21, 126.37, 127.40, 128.56, 128.83, 129.37, 129.84, 134.79, 138.74, 143.81, 145.06. Exact mass calculated for $C_{24}H_{23}N_3O_2S$: 417.1511. Found: 417.1507.

3.8. Preparation of sultams 20 and 21

A mixture containing **4c** (16.45 g, 50 mmol), triethylamine (33.39 g, 46 mL, 330 mmol) and glycine methyl ester hydrochloride (6.90 g, 55 mmol) in absolute ethanol (50 mL) was stirred at rt for 16 h. At the end of this time the solvent was removed and the residue extracted with dichloromethane, washed with water and dried (Na_2SO_4). The residue, subjected to silica gel flash chromatography (2% methanol/chloroform), gave, as first eluted product, methyl (3*SR*,3a*SR*,5*SR*,6*RS*,6a*SR*)-2-benzyl-3-methyl-1,1-dioxo-6-phenylperhydro-1λ^6-pyrrolo[2,3-*d*]isothiazole-5-carboxylate **20** (8.60 g, 43%) as a white solid, mp 110–111°C; ν_{max} (KBr): 3337, 3026, 2990, 2900, 1741, 1600, 1495, 1450, 1280, 1218, 1130, 910, 855, 748, 697 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.31 (d, 3H, J=7.0 Hz), 2.28 (bs, 1H, NH), 3.28 (dq, 1H, H_3, J=1.5 and 7.0 Hz), 3.70 (s, 3H), 3.83 (dd, 1H, H_{6a}, J=6.0 and 7.5 Hz), 3.86 (d, 1H, H_5, J=8.5 Hz), 3.96 (dd, 1H, H_{3a}, J=1.5 and 7.5 Hz), 4.01 (dd, 1H, H_6, J=6.0 and 8.5 Hz), 4.08 (d, 1H, J=14.5 Hz), 4.50 (d, 1H, J=14.5 Hz), 7.28–7.42 (m, 10H); δ_C (125 MHz, $CDCl_3$) 16.19, 44.54, 52.46, 53.83, 55.34, 66.57, 68.74, 69.05, 127.53, 127.68, 128.04, 128.39, 128.83, 129.04, 135.24, 138.94, 171.56. Exact mass calculated for $C_{21}H_{24}N_2O_4S$: 400.1457. Found: 400.1459. Further eluted product was methyl (3*SR*,3a*SR*,5*RS*,6*RS*,6a*SR*)-2-benzyl-3-methyl-1,1-dioxo-6-phenylperhydro-1λ^6-pyrrolo-[2,3-*d*]isothiazole-5-carboxylate **21** (3.00 g, 15%); white solid, mp 120–122°C; ν_{max} (KBr): 3350, 3020, 3015, 2960, 1730, 1600, 1450, 1350, 1310, 1140, 860, 800, 750 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.27 (d, 3H, J=6.5 Hz), 2.42 (bs, 1H, NH), 3.16 (dq, 1H, H_3, J=4.3 and 6.5 Hz), 3.69 (s, 3H), 4.02 (dd, 1H, H_{6a}, J=2.6 and 8.6 Hz), 4.21 (dd, 1H, H_{3a}, J=4.3 and 8.6 Hz), 4.26 (d, 1H, J=15.2 Hz), 4.28 (dd, 1H, H_6, J=2.6 and 6.8 Hz), 4.29 (d, 1H, J=15.2 Hz), 4.33 (d, 1H, H_5, J=6.8 Hz), 7.05–7.39 (m, 10H); δ_C (125 MHz, $CDCl_3$) 17.34, 44.99, 51.47, 51.74, 56.77, 65.74, 66.20, 66.42, 127.51, 127.77, 128.26, 128.32, 128.61, 128.71, 135.86, 137.13, 170.50. Exact mass calculated for $C_{21}H_{24}N_2O_4S$: 400.1457. Found: 400.1456.

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