Properties and Reactions of Substituted 1,2-Thiazetidine 1,1-Dioxides: Aldol Additions of Ketones and Aldehydes

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Aldol reactions between *N*-silylated or 2,3-disubstituted β-sultams and ketones or aldehydes result in the C-4 aldol derivatives **2** and **6**. Desilylation of **2** with TBAF yields the *N*-unsubstituted compounds **3**. Mixtures of diastereomers obtained from reactions with aldehydes are separated by CC, and their structures are elucidated by spectroscopic data.

Eigenschaften und Reaktionen substituierter 1,2-Thiazetidin-1,1-dioxide: Aldol-Addition von Ketonen und Aldehyden

Aldolreaktionen von *N*-silylierten bzw. 2,3-disubstituierten β-Sultamen mit Ketonen oder Aldehyden geben die C-4-Aldol-Derivate **2** und **6**. Die Desilylierung von **2** mit TBAF ermöglicht die Darstellung der *N*-unsubstituierten β-Sultame **3**. Diastereomere aus den Reaktionen mit Aldehyden werden se getrennt, ihre Konfigurationen können mit spektroskopischen Methoden geklärt werden.

Carbapenems, as thienamycin, differ from penicillins and cephalosporins by their characteristic α-hydroxyethyl side chain, which is believed to be responsible for their great antibacterial activity and their stability against β-lactamases[1]. As 1,2-thiazetidine 1,1-dioxides (β-sultams) are highly reactive sulfon analogues of β-lactams, it is of special interest to introduce the hydroxyalkyl side chain into position 4 of the β-sultam ring. Here, we wish to report about our results using *N*-substituted β-sultams as model compounds for the introduction of the α-hydroxyalkyl function by aldol reactions with ketones and aldehydes.

Refering to a procedure from *Durst*[2], the *N*-substituted β-sultams **1a,b** were allowed to react at -78°C with the secondfold amount of LDA, and acetone or benzophenone. We isolated the aldols **2a**[3], **2b**, and **2c** as stable, colorless, crystalline compounds. The highest yields were obtained, when the freshly prepared LDA reacts not longer than 30 sec with the β-sultam, and the overall reaction time does not exceed 5 min.

The structure of **2** is confirmed by their IR- and ^{1}H-NMR spectra, which show a strong absorption of the hydroxy group around 3500 cm^{-1}, the two absorptions of the SO_2 group at 1290-1275 and 1140 cm^{-1}, and the typical ABX pattern of 4-monosubstituted β-sultams.

Desilylation of **2b,c** was easily done by treatment with TBAF on silica gel in ethanol at room temp. yielding the desilylated products **3b** and **3c** with yields >80%, which can be stored *in vacuo* for some weeks without decomposition.

The reaction with aromatic aldehydes was first studied with benzaldehyde, which was reacted with equimolar amounts of **1b** and BuLi. After work-up, we found a compound, $C_{17}H_{28}N_2O_4S_2Si$, m/z = 416 (M^+), m.p. 128°C (methanol), which obviously was not the expected aldol. From the analytical and spectral data the structure **4** results, which might be formed by dimerisation[4] of the anion of **1b** and reaction of the *N,N'*-bis-silylated intermediate with benzaldehyde followed by protonation during work-up. To avoid this reaction, we used 2 equivalents of LDA and a slight excess of the aromatic aldehyde. By this procedure, the aldols **2d-g** were obtained from **1b**. All aldols were isolated as diastereomeric mixtures, which were separated by CC (silica gel). The (αR^*, $4S^*$)-isomers[5] (**A**) were first eluated with dichloromethane, the (αS^*, $4S^*$)-isomers (**B**) we obtained by subsequent extraction with ethyl acetate. The ratio of isomers was always around 1:1. The yield of the aldol **2g** from acetaldehyde was maximal 15%[6]. When the α,β-unsaturated mesityl oxide was used as an electrophil, only the 1,2-addition products **2h** were isolated. We did not find any 1,4-addition product, which is in agreement with other experiments, in which α,β-unsaturated carbonyl compounds reacted with α-sulfonyl carbanions forming exclusively 1,2-addition products[7].

The differentiation between (αR^*, $4S^*$) and (αS^*, $4S^*$) isomers is mainly based on their ^{1}H-NMR spectroscopic data (Table 1).

2b and **2c**, even **2d-g** are easily desilylated with high yields by treatment with TBAF on silica gel in ethanol at room temp. forming the desired α-hydroxybenzyl β-sultams **3d-g** as stable, crystalline products, which can be recrystallized and stored *in vacuo* for some weeks without decomposition. The only exception was the (αR^*, $4S^*$) isomer of **3g**, which was purified by distillation.

Similiar results were obtained, when the 2,3-disubstituted[8] β-sultam **5** reacted with the appropriate carbonyl compounds. The aldols **6a-d** are stable crystalline compounds. As **5** has a chiral center at C-3, **6a** may exist either as the *trans*- or the *cis*-form, or as a mixture of both. We isolated only one compound. From the coupling constant J = 6 Hz (H-3/H-4) we deduce the *trans*-form. As a second chiral center is formed in **6b-d**, these products exist as mixtures of diastereomers, which were separated by CC[9]. Their spectroscopic data are summarized in table 2.

The reaction between **5** and benzaldehyde gave **7** as a by-product (8%, mp. 154°C, $C_{17}H_{19}NO_5S_2$, 381.5). The formation of **7** is best explained by a base catalyzed rearrange-

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Table 1. Selected ^{1}H-NMR data of β-sultams **2** and **3** (spectra in $CDCl_3$)

Nr.	Chemical shift δ ppm				Coupling constants J Hz			
	H-3'	H-3	H-4	H-α	gem3/3'	cis3'/4	trans3/4	4/α
2b	3.32	3.43	4.47	-	-4.5	8	5.5	-
2c	3.11	3.45	5.54	-	-5.5	8	5.5	-
2dA	3.18	3.53	4.73	5.46	-5.0	8	5.0	3
2dB	3.22	3.00	4.80	5.16	-5.5	8	5.5	9
2eA	3.16	3.49	4.67	5.38	-5.0	8	5.0	3
2eB	3.18	2.93	4.74	5.08	-5.5	8	5.5	9
2fA	3.13	3.43	4.72	5.57	-5.5	8	5.5	2.5
2fB	3.32	3.16	4.78	5.25	-6.0	8	5.5	8
2gA	3.33	3.47	4.44	4.50	-5.0	8	5.0	3
2gB	3.38	3.18	4.43	4.14	-5.0	8	5.0	6.5
3b	3.35	3.49	4.52	-	-6	8	6	-
3c	3.08	3.53	5.58	-	-6.5	8.5	6.5	-
3dA	3.42	3.42	4.79	5.23	x	x	x	8.5
3dB	3.08	2.78	4.82	5.17	-6.5	8	6.5	10
3eA	3.40	3.40	4.79	5.17	x	x	x	9
3eB	3.10	2.85	4.87	5.15	-6	8	6	10
3fA	3.46	3.46	4.86	5.45	x	x	x	8.5
3fB	3.19	2.99	4.90	5.38	-6	8	6	10
3gA	3.42	3.19	4.02	4.52	-6	8	6	x
3gB	3.40	3.02	4.10	4.65	-6	8	6	x

Table 2. Selected ^{1}H-NMR data of β-sultams **6** (spectra in $CDCl_3$/* spectra in $[D_6]$-DMSO)

Nr.	Chemical shift δ ppm			Coupling constants J Hz	
	H-3	H-4	H-α	trans3/4	4/α
6a	4.32	4.15	-	6	-
6bA	4.28	4.45	5.48	x	3
*	4.28	4.48	5.15	6	9
6bB	3.78	4.46	5.23	6.5	8.5
*	3.81	4.41	5.08	6.5	10
6cA	4.28	4.45	5.41	x	4
*	4.23	4.43	5.06	6	9.5
6cB	3.76	4.41	5.15	6	8
*	3.77	4.40	5.02	6	10
6dA*	4.32	4.59	5.30	6	9
6dB*	3.93	4.57	5.27	6.5	10

ment[4] of **5** to the dithiazine tetroxide derivative, followed by an aldol addition of benzaldehyde at C-6. The intermediate is stabilized by a retro *Michael*-type reaction yielding structure **7** after protonation.

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Experimental Part

M.p. (uncorrected): Linström apparatus.- IR (KBr, cm^{-1}): Perkin-Elmer IR 1310, Beckman IR 4240.- ^{1}H-NMR: Varian T60, Bruker WP80, or Bruker WP250; δ (ppm), δ_{TMS} = 0.00; temp. of the probe 37°C; δ values from 80 MHz spectra, if not otherwise noted, solvent $CDCl_3$.- ^{13}C-NMR: Bruker WP80 (20.15 MHz); δ (ppm), δ_{TMS} = 0.00, solvent $CDCl_3$.- MS: Finnigan GC MS 4000.- Elementary analyses: Pharmazeutisches Institut or Chemisches Laboratorium der Universität Freiburg.- Solvents were dried according to literature procedures.- Abbreviations: TBAF = Tetrabutylammonium fluoride, either on silicagel (Fluka No. 86876) or in THF solution (Aldrich No. 21,614-3); BuLi = n-Butyl lithium, 15% in hexane; LDA = Lithium diisopropylamide, freshly prepared by mixing equimolar amounts of BuLi and diisopropylamine; THF = Tetrahydrofuran, dried with $CaCl_2$ and distilled over $LiAlH_4$ before use; DMF = Dimethylformamide; DMSO = Dimethyl sulfoxide; CC = column chromatography on silicagel (Kieselgel 60, Merck, Darmstadt No. 7734); ar = aromatic.

2-Piperidinomethyl-1,2-thiazetidine 1,1-dioxide (**1a**):[10]

2-(tert-Butyldimethylsilyl)-1,2-thiazetidine 1,1-dioxide (**1b**):[11]

Aldol reaction with β-sultams. **1** *and* **5** *General Procedure*

5 mmol of **1** (or **5**) are dissolved in 40 ml of THF and cooled to -78°C. At the same temp., this solution is added to a freshly prepared solution of 10 mmol of LDA in THF, and after 30 sec, the carbonyl compound is added. The mixture is stirred for another 5 min (20 min) at -78°C, and then immediately hydrolyzed with saturated NH_4Cl (NaCl) solution. The org. layer is separated, dried with Na_2SO_4, and evaporated *in vacuo*. Work-up of the residue either by recrystallisation or by bulb-to-bulb distillation.

To purify the residue of reactions with aromatic aldehydes, the residue is dissolved in 40 ml of ether, 40 ml of 40% $NaHSO_3$ solution is added, and the mixture is vigorously stirred for 2 h. The org. layer is separated, once washed with water, dried with Na_2SO_4, concentrated *in vacuo*, and purified by CC on silica gel. First, isomers A are separated by elution with dichloromethane, secondly isomers B are obtained by elution with ethyl acetate.

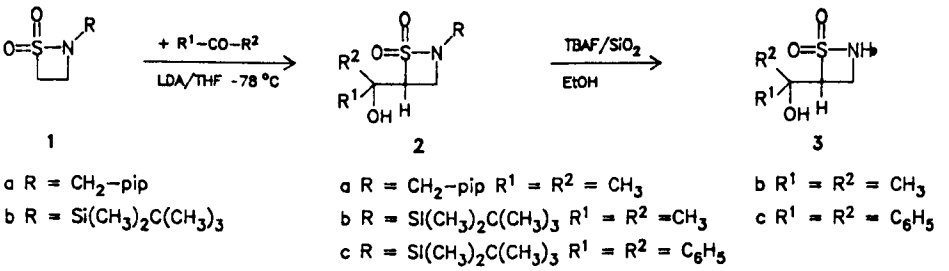
4-(1-Hydroxy-1-methylethyl)-2-piperidinomethyl-1,2-thiazetidine 1,1-dioxide (**2a**):[12]

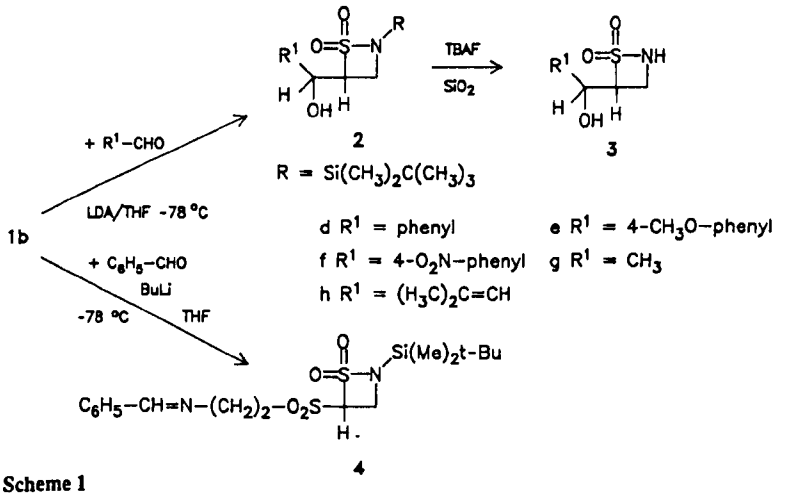
2-(tert-Butyldimethylsilyl)-4-(1-hydroxy-1-methylethyl)-1,2-thiazetidine 1,1-dioxide (**2b**)

From 3.6 ml (50 mmol) acetone; the residue is dissolved in chloroform, petroleum ether is added, the precipitate is removed, and the solvent is evaporated. The residue is dissolved in a few ml of pentane and stored at -10°C until crystallisation is complete; yield 950 mg (68%), colorless crystals, m.p. 63°C (pentane).- IR: 3515 (OH); 2960; 2930; 2900; 2880; 2860 (CH); 1470; 1390; 1375; 1360 (CH_3); 1275; 1145 (SO_2).- ^{1}H-NMR: δ = 0.27 (s, 6H, Si-CH_3), 0.97 (s, 9H, Si-tert Bu), 1.17 (s, 3H, CH_3), 1,53 (s, 3H, CH_3), 3.32 (dd, J = 8 and -4.5 Hz, 1H, H-3'), 3.38 (s, 1H, OH), 3.43 [t(dd), J = 5.5 and -4.5 Hz, 1H, H-3], 4.47 (dd, J = 8 and 5.5 Hz, 1H, H-4).- $C_{11}H_{25}NO_3SSi$ (279.5) Calcd. C 47.3 H 9.02 H 5.0 S 11.5 Found C 47.0 H 8.95 N 5.1 S 11.6.

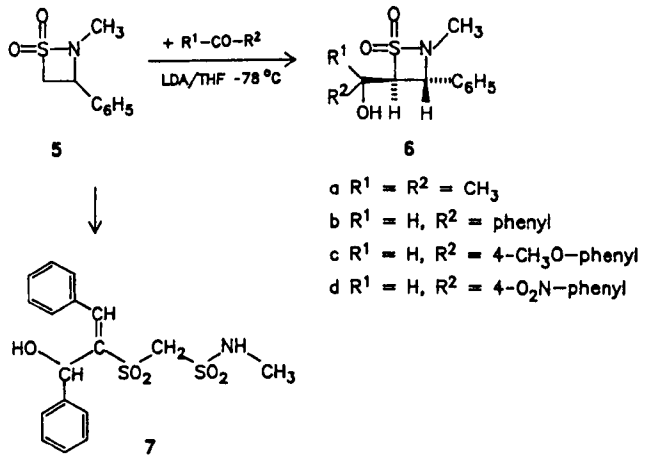
2-(tert-Butyldimethylsilyl)-4-(hydroxydiphenylmethyl)-1,2-thiazetidine 1,1-dioxide (**2c**)

From 3.6 g (20 mmol) of benzophenone; yield 1.3 g (65%), colorless crystals, m.p. 160°C (methanol).- IR: 3500 (OH); 3080; 3050; 3020 (arCH); 2980; 2929; 2890; 2850 (CH); 1590; 1485; 1445 (arC-C); 1465; 1385; 1360 (CH_3); 1285; 1140 (SO_2).- ^{1}H-NMR: δ = 0.25 (s, 3H, Si-CH_3), 0.28 (s, 3H, Si-CH_3), 0.95 (s, 9H, Si-tert Bu), 3.11 (dd, J = 8 and -5.5 Hz, 1H, H-3'), 3.45 [t(dd), J = 5.5 and -5.5 Hz, 1H, H-3], 4.36 (s, 1H, OH), 5.54 (dd, J = 8 and 5.5 Hz, 1H, H-4), 7.1-7.6 (m, 10H, arom. H).- $C_{21}H_{29}NO_3SSi$ (403.6) Calcd. C 62.5 H 7.24 N 3.5 S 7.9 Found C 62.4 H 7.21 N 3.6 S 7.8.





Scheme 1



Scheme 2

2-(tert-Butyldimethylsilyl)-4-(α-hydroxybenzyl)-1,2-thiazetidine 1,1-dioxide (**2d**)

From 2.6 ml (25 mmol) of benzaldehyde, CC (dichloromethane, ethyl acetate).- ($\alpha R^*,4S^*$)-Isomer (A): Yield 458 mg (28%), colorless crystals, m.p. 88°C (cyclohexane).- IR: 3515 (OH); 3090; 3060; 3030 (arCH); 2960; 2940; 2900; 2860 (CH); 1605; 1500; 1455 (arC-C); 1475; 1395, 1365 (CH_3); 1290; 1185 (SO_2).- ^{1}H-NMR: δ = 0.28 (s, 3H, Si-CH_3), 0.32 (s, 3H, Si-CH_3), 1.00 (s, 9H, Si-tert Bu), 3.18 (dd, J = 8 and -5 Hz, 1H, H-3'), 3.53 [t(dd), J = -5 and 5 Hz, 1H, H-3], 3.72 (d, J = 2.5 Hz, 1H, OH), 4.73 (ddd, J = 8, 5, and 3 Hz, 1H, H-4), 5.46 (dd, J = 3 and 2.5 Hz, 1H, H-α), 7.46 [s(mc), 5H, arom. H].- $C_{15}H_{25}NO_3SSi$ (327.5) Calcd. C 55.0 H 7.69 N 4.28 S 9.8 Found C 55.3 H 7.55 N 4.18 S 10.0.

($\alpha S^*,4S^*$)-Isomer (B): Yield 508 mg (31%), colorless crystals, m.p. 92°C (cyclohexane).- IR: 3460 (OH); 3050; 3030 (arCH); 2940; 2920; 2889; 2845 (CH); 1485; 1450 (arC-C); 1465; 1390; 1355 (CH_3); 1290; 1180; 1130 (SO_2).- ^{1}H-NMR: δ = 0.27 (s, 6H, Si-CH_3), 0.80 (s, 9H, Si-tert Bu), 3.00 [t(dd), J = -5.5 and 5.5 Hz, 1H, H-3], 3.22 (dd, J = 8 and -5.5 Hz, 1H, H-3'), 3.44 (d, J = 5 Hz, 1H, OH), 4.80 (ddd, J = 9, 8, and 5.5 Hz, 1H, H-4), 5.16 (dd, J = 9 and 5 Hz, 1H, H-α), 7.39 [s(mc), 5H, arom. H].- $C_{15}H_{25}NO_3SSi$ (327.5) Calcd. C 55.0 H 7.69 N 4.3 S 9.8 Found C 54.8 H 7.60 N 4.3 S 9.9.

2-(tert-Butyldimethylsilyl)-4-(α-hydroxy-4-methoxybenzyl)-1,2-thiazetidine 1,1-dioxide (**2e**)

From 2.7 g (20 mmol) of 4-methoxybenzaldehyde, CC.- ($\alpha R^*,4S^*$)-Isomer (A): Yield 305 mg (17%), colorless crystals, m.p. 96°C (cyclohexane).- IR: 3530 (OH); 2960; 2940; 2910; 2865 (CH); 1615; 1590; 1520; 1450 (arC-C); 1475; 1395; 1365 (CH_3); 1300; 1185; 1140 (SO_2).- ^{1}H-NMR: δ = 0.25 (s, 3H, Si-CH_3), 0.28 (s, 3H, Si-CH_3), 0.95 (s, 9H, Si-tert Bu), 3.16 (dd, J = 8 and -5 Hz, 1H, H-3'), 3.49 [t(dd), J = 5 and -5 Hz, 1H, H-3], 3.56 (d, J = 3 Hz, 1H, OH), 3.77 (s, 3H, OCH_3), 4.67 (ddd, J = 8, 5, and 3 Hz, 1H, H-4), 5.38 [t(dd), J = 3 Hz, 1H, H-α], 6.82-7.32 (AA'BB', 4H, arom. H).- $C_{16}H_{27}NO_4SSi$ (357.5) Calcd. C 53.8 H 7.61 N 3.9 S 9.0 Found C 54.0 H 7.53 N 3.8 S 8.9.

($\alpha S^*,4S^*$)-Isomer (B): Yield 310 mg (17%), colorless crystals, m.p. 89°C (cyclohexane).- IR: 3490 (OH); 3075 (arCH); 2955; 2930; 2900; 2860 (CH); 1615; 1590; 1515; 1465 (arC-C); 1475; 1395; 1365 (CH_3); 1300; 1170 (SO_2).- ^{1}H-NMR: δ = 0.23 (s, 6H, Si-CH_3), 0.93 (s, 9H, Si-tert Bu), 2.93 [t(dd), J = 5.5 and -5.5 Hz, 1H, H-3], 3.18 (dd, J = 8 and -5.5 Hz, 1H, H-3'), 3.19 (d, J = 5 Hz, 1H, OH), 3.77 (s, 3H, OCH_3), 4.74 (ddd, J = 9, 8, and 5.5 Hz, 1H, H-4), 5.08 (dd, J = 9 and 5 Hz, 1H, H-α), 6.83-7.34 (AA'BB', 4H, arom. H).- $C_{16}H_{27}NO_4SSi$ (357.5) Calcd. C 53.8 H 7.61 N 3.9 S 9.0 Found C 54.0 H 7.60 N 3.7 S 8.8.

2-(tert-Butyldimethylsilyl)-4-(α-hydroxy-4-nitrobenzyl)-1,2-thiazetidine 1,1-dioxide (**2f**)

From 2.2 g (15 mol) of 4-nitrobenzaldehyde, CC.- ($\alpha R^*,4S^*$)-Isomer (A): Yield 450 mg (24%), colorless crystals, m.p. 180°C (methanol).- IR: 3450

(OH); 2955; 2930; 2900; 2860 (CH); 1605 (arC-C); 1515; 1350 (NO_2); 1470 (CH_3); 1290; 1155 (SO_2).- ^{1}H-NMR: δ = 0.23 (s, 3H, Si-CH_3), 0.26 (s, 3H, Si-CH_3), 0.97 (s, 9H, Si-tert Bu), 3.13 (dd, J = 8 and -5.5 Hz, 1H, H-3'), 3.43 [t(dd), J = 5.5 and -5.5 Hz, 1H, H-3], 3.88 (d, J = 2.5 Hz, 1H, OH), 4.72 (ddd, J = 8, 5.5, and 2.5 Hz, 1H, H-4), 5.57 [t(dd), J = 2.5 Hz, 1H, H-α], 7.50-8.32 (AA'BB', 4H, arom. H).- $C_{15}H_{24}N_2O_5SSi$ (372.5) Calcd. C 48.4 H 6.49 N 7.5 S 8.6 Found C 48.5 H 6.48 N 7.6 S 8.7.

(α*S**,4*S**)-Isomer (B): Yield 412 mg (22%), colorless crystals, m.p. 144°C (chloroform/petroleum ether 1:1).- IR: 3460 (OH); 2960; 2930; 2900; 2860 (CH); 1610; 1600 (arC-C); 1520; 1350 (NO_2); 1470 (CH_3); 1300; 1150 (SO_2).- ^{1}H-NMR: δ = 0.29 (s, 6H, Si-CH_3), 0.96 (s, 9H, Si-tert Bu), 3.16 [t(dd), J = 6 and 5.5 Hz, 1H, H-3], 3.32 (dd, J = 8 and -6 Hz, 1H, H-3'), 3.67 (d, J = 7 Hz, 1H, OH), 4.78 [dt(ddd), J = 8 and 5.5 Hz, 1H, H-4], 5.25 (dd, J = 8 and 7 Hz, 1H, H-α), 7.55-8.32 (AA'BB', 4 H, arom. H).- $C_{15}H_{24}N_2O_5SSi$ (372.5) Calcd. C 48.4 H 6.49 N 7.5 S 8.6 Found C 48.6 H 6.42 N 7.6 S 8.5.

2-(tert-Butyldimethylsilyl)-4-(1-hydroxyethyl)-1,2-thiazetidine 1,1-dioxide (2g)

From 0.28 ml (25 mmol) of acetaldehyde, CC cyclohexane/ethyl acetate 2:1.- (α*R**,4*S**)-Isomer (A): R_f = 0.17.- IR (film): 3500 (OH); 2960; 2930; 2900; 2860 (CH); 1465; 1395; 1365 (CH_3); 1300; 1140 (SO_2).- ^{1}H-NMR (250 MHz): δ = 0.27 (s, 3H, Si-CH_3), 0.29 (s, 3H, Si-CH_3), 0.97 (s, 9H, Si-tert Bu), 1.22 (d, J = 6 Hz, 3H, αC-CH_3), 3.23 (d, J = 3 Hz, 1H, OH), 3.33 (dd, J = 8 and -5 Hz, 1H, H-3'), 3.47 [t(dd), J = 5 and -5 Hz, 1H, H-3], 4.44 (ddd, J = 8, 5, and 3 Hz, 1H, H-4), 4.5 (mc, J = 6 and 3 Hz, 1H, H-α).- $C_{10}H_{23}NO_3SSi$ (265.4) Calcd. C 45.3 H 8.73 N 5.3 Found C 45.3 H 8.65 N 5.4.

(α*S**,4*S**)-Isomer (B): R_f = 0.14.- IR: 3475 (OH); 2955; 2940; 2925; 2890; 2855 (CH); 1465; 1395; 1365 (CH_3); 1290; 1140 (SO_2).- ^{1}H-NMR (250 MHz): δ = 0.26 (s, 3H, Si-CH_3), 0.28 (s, 3H, Si-CH_3), 0.97 (s, 9H, Si-tert-Bu), 1.40 (d, J = 6.5 Hz, αC-CH_3), 2.98 (d, J = 8 Hz, 1H, OH), 3.18 [t(dd), J = 5 and -5 Hz, 1H, H-3], 3.38 (dd, J = 8 and -5 Hz, 1H, H-3'), 4.14 (mc, J = 8 and 6.5 Hz, 1H, H-α), 4.43 (ddd, J = 8, 6.5, and 5 Hz, 1H, H-4).- $C_{10}H_{23}NO_3SSi$ (265.4) Calcd. C 45.3 H 8.73 N 5.3 S 12.1 Found C 45.3 H 8.70 N 5.4 S 12.2.

2-(tert-Butyldimethylsilyl)-4-(1-hydroxy-1,3-dimethyl-2-butenyl)-1,2-thiazetidine 1,1-dioxide (2h)

From 981 mg (5 mmol) of mesityl oxide, CC with cyclohexane/ethyl acetate 9:1 and subsequent bulb-to-bulb distillation.- (α*R**,4*S**)-Isomer (A): R_f = 0.18, yield 217 mg (14%), b.p. 127°C/0.01 Torr.- IR (film): 3520 (OH); 2970; 2940; 2910; 2870 (CH); 1480; 1470; 1390; 1380; 1370 (CH_3); 1300; 1160 (SO_2).- ^{1}H-NMR (60 MHz): δ = 0.27 (s, 6H, Si-CH_3), 0.95 (s, 9H, Si-tert Bu), 1.64 (s, 3H, αC-CH_3), 1.70 (d, J = 1.5 Hz, 3H, C=C-CH_3), 1.87 (d, J = 1.5 Hz, 3H, C=C-CH_3), 3.14-3.51 (m, 3H, H-3, H-3', and OH), 4.57 (dd, J = 8 and 5.5 Hz, 1H, H-4), 4.92 (mc, 1H, C=CH).- $C_{11}H_{29}NO_3SSi$ (319.5) Calcd. C 52.6 H 9.15 N 4.4 S 10.0 Found C 52.6 H 9.06 N 4.5 S 9.8.

(α*S**,4*S**)-Isomer (B): R_f = 0.10, yield 305 mg (19%), b.p. 127°C/0.01 Torr.- IR (film): 3520 (OH); 2950; 2920; 2890; 2860 (CH); 1655 (C=C); 1465; 1375; 1360 (CH_3); 1295; 1140 (SO_2).- ^{1}H-NMR (60 MHz): δ = 0.19 (s, 6H, Si-CH_3), 0.90 (s, 9H, Si-tert Bu), 1.19 (s, 3H, αC-CH_3), 1.68 (d, J = 1.5 Hz, 3H, C=C-CH_3), 1.84 (d, J = 1.5 Hz, 3H, C=C-CH_3), 3.14-3.47 (m, 3H, H-3', H-3, and OH), 4.56 (dd, J = 8 and 5.5 Hz, 1H, H-4), 5.36 (mc, 1H, C=CH).- $C_{11}H_{29}NO_3SSi$ (319.5) Calcd. C 52.6 H 9.15 N 4.4 S 10.0 Found C 52.3 H 9.00 N 4.6 S 10.2.

Desilylation with TBAF on silica gel: see ref.[13]

4-(1-Hydroxy-1-methylethyl)-1,2-thiazetidine 1,1-dioxide (3b)

From 839 mg (3 mmol) of **2b** and 84 mg TBAF/silica gel (10%); yield 431 mg (87%), colorless crystals, m.p. 99°C (chloroform).- IR: 3480 (OH); 3240 (NH); 2980; 2970; 2935 (CH); 1480, 1380; 1370 (CH_3); 1305; 1160 (SO_2).- ^{1}H-NMR: δ = 1.17 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 3.35 (dd, J = 8 and -6 Hz, 1H, H-3'), 3.49 [t(dd), J = 6 and -6 Hz, 1H, H-3], 3.92 (bs, 2H, NH and OH), 4.52 (dd, J = 8 and 6 Hz, 1H, H-4).- $C_5H_{11}NO_3S$ (165.2) Calcd. C 36.4 H 6.71 N 8.5 S 19.4 Found C 36.1 H 6.60 N 8.3 S 19.3.

4-(Hydroxydiphenylmethyl)-1,2-thiazetidine 1,1-dioxide (3c)

From 1.21 g (3 mmol) of **2c** and 121 mg TBAF/silica gel (10%); yield 713 mg (82%), colorless crystals, m.p. 78° (chloroform/petroleum ether 1:1).- IR: 3500 (OH); 3300 (NH); 3060; 3030 (arCH); 2980 (CH); 1495; 1450 (arC-C); 1310; 1155 (SO_2).- ^{1}H-NMR: δ = 3.08 (mc, 1H, H-3'), 3.53 (mc, 1H, H-3), 4.15 (s, 1H, OH), 5.58 (dd, J = 8.5 and 6.5 Hz, 1H, H-4), 5.60 (bs, 1H, NH), 7.1-7.6 (m, 10H, arom. H).- $C_{15}H_{15}NO_3S$ (289.3) Calcd. C 62.3 H 5.22 N 4.8 S 11.1 Found C 62.3 H 5.32 N 5.0 S 10.9.

4-(α-Hydroxybenzyl)-1,2-thiazetidine 1,1-dioxide (3d)

(α*R**,4*S**)-Isomer (A): From 328 mg (1 mmol) of **2dA** and 65 mg TBAF/silica gel (20%); yield 200 mg (94%), colorless crystals, m.p. 105°C (chloroform).- IR: 3455; 3420 (OH); 3190; 3170 (NH); 3030 (arCH); 2985; 2970; 2900 (CH); 1495; 1450 (arC-C); 1310; 1140 (SO_2).- ^{1}H-NMR ([D_6]-acetone): δ = 3.42 (mc, 2H, H-3' and H-3), 4.79 (mc, 1H, H-4), 4.80 (d, J = 4.5 Hz, 1H, OH), 5.23 (dd, J = 8.5 and 4.5 Hz, 1H, H-α), 6.67 (bs, 1H, NH), 7.2-7.6 (m, 5H, arom. H).- $C_9H_{11}NO_3S$ (213.3) Calcd. C 50.7 H 5.20 N 6.6 S 15.0 Found C 50.8 H 5.12 N 6.4 S 15.2.

(α*S**,4*S**)-Isomer (B): From 328 mg (1 mmol) of **2dB** and 65 mg TBAF/silica gel (20%); yield 193 mg (91%), colorless crystals, m.p. 143°C (chloroform).- IR: 3460 (OH); 3310 (NH); 3070 (arCH); 2980; 2910 (CH); 1500; 1460 (arC-C), 1310; 1150 (SO_2).- ^{1}H-NMR ([D_6]-acetone): δ = 2.87 (mc, J = 6.5, -6.5, and 5 Hz, 1H, H-3), 3.08 (mc, J = 8, -6.5, and 3 Hz, 1H, H-3'), 4.82 (ddd, J = 10, 8, and 6.5 Hz, 1H, H-4), 4.96 (d, J = 4.5 Hz, 1H, OH), 5.17 (dd, J = 10 and 4.5 Hz, 1H, H-α), 6.62 (bs, 1H, NH), 7.23-7.65 (m, 5H, arom. H).- $C_9H_{11}NO_3S$ (213.3) Calcd. C 50.7 H 5.20 N 6.6 S 15.0 Found C 50.7 H 5.21 N 6.7 S 15.1.

4-(α-Hydroxy-4-methoxybenzyl)-1,2-thiazetidine 1,1-dioxide (3e)

(α*R**,4*S**)-Isomer (A): From 358 mg (1 mmol) of **2eA** and 70 mg TBAF/silica gel (20%); yield 200 mg (82%), colorless crystals, m.p. 111°C (chloroform).- IR: 3505 (OH); 3240 (NH); 3010 (arCH); 2975; 2960; 2900; 2835 (CH); 1610; 1585; 1510; 1465 (arC-C); 1310; 1295; 1275; 1175; 1145 (SO_2).- ^{1}H-NMR ([D_6]-acetone): δ = 2.78 (s, 3H, OCH_3), 3.40 (mc, 2H, H-3 and H-3'), 4.73 (d, J = 4.5 Hz, 1H, OH), 4.79 (mc, 1H, H-4), 5.17 (dd, J = 9 and 4.5 Hz, 1H, H-α), 6.73 (bs, 1H, NH), 6.83-7.44 (AA'BB', 4H, arom. H).- $C_{10}H_{13}NO_4S$ (243.3) Calcd. C 49.4 H 5.38 N 5.8 S 13.2 Found C 49.4 H 5.30 N 5.7 S 13.0.

(α*S**,4*S**)-Isomer (B): From 358 mg (1 mmol) of **2eB** and 70 mg TBAF/silica gel (20%); yield 178 mg (73%), colorless crystals, m.p. 127°C (chloroform).- IR: 3500 (OH); 3310 (NH); 2980; 2940; 2920; 2845 (CH); 1610; 1590; 1515; 1460 (arC-C); 1305; 1145 (SO_2).- ^{1}H-NMR ([D_6]-acetone): δ = 2.85 (mc, 1H, H-3), 3.10 (mc, 1H, H-3'), 3.80 (s, 3H, OCH_3), 4.84 (d, J = 4 Hz, 1H, OH), 4.87 (mc, 1H, H-4), 5.15 (dd, J = 10 and 4 Hz, 1H, H-α), 6.60 (bs, 1H, NH), 6.87-7.47 (AA'BB', 4H, arom. H).- $C_{10}H_{13}NO_4S$ (243.3) Calcd. C 49.4 H 5.38 N 5.8 S 13.2 Found C 49.4 H 5.40 N 5.7 S 13.3.

4-(α-Hydroxy-4-nitrobenzyl)-1,2-thiazetidine 1,1-dioxide (3f)

(α*R**,4*S**)-Isomer (A): From 373 mg (1 mmol) of **2fA** and 56 mg TBAF/silica gel (15%); yield 144 mg (56%), light yellow crystals, m.p. 167°C (acetone/petroleum ether 1:1).- IR: 3510 (OH), 3350; 3280 (NH); 3120; 3080 (arCH); 2980; 2910 (CH); 1610; 1600; 1490 (arC-C); 1520; 1350 (NO_2); 1310; 1295; 1170; 1155 (SO_2).- ^{1}H-NMR ([D_6]-acetone): δ = 3.46 (mc, 2H, H-3 and H-3'), 4.86 (mc, 1H, H-4), 5.45 (dd, J = 8.5 and 4

4Hz, 1H, H-α), 5.95 (bs, 2H, OH and NH), 7.75-8.32 (AA'BB', 4H, arom. H).- $C_9H_{10}N_2O_5S$ (258.2) Calcd. C 41.9 H 3.90 N 10.9 S 12.4 Found C 42.0 H 3.98 N 10.7 S 12.6.

(α*S**,4*S**)-Isomer (B): From 373 mg (1 mmol) of **2fB** and 56 mg TBAF/silicagel (15%); yield 200 mg (78%), light yellow crystals; m.p. 158°C (dichloromethane).- IR: 3510 (OH); 3300 (NH); 3120; 3090 (arCH); 2980; 2920 (CH); 1610; 1600; 1485 (arC-C); 1510; 1355 (NO_2); 1305; 1140 (SO_2).- ^{1}H-NMR ([D$_6$]-acetone): δ = 2.99 (mc, 1H, H-3), 3.19 (mc, 1H, H-3'), 4.90 (ddd, J = 10, 8, and 6 Hz, 1H, H-4), 5.38 (dd, J = 10 and 5 Hz, 1H, H-α), 6.0 (bs, 2H, OH and NH), 7.75-8.30 (AA'BB', 4H, arom. H).- $C_9H_{10}N_2O_5S$ (258.2) Calcd. C 41.9 H 3.90 N 10.9 S 12.4 Found C 41.8 H 3.91 N 10.8 S 12.5.

4-(1-Hydroxyethyl)-1,2-thiazetidine 1,1-dioxide (**3g**)

(α*R**,4*S**)-Isomer (A): From 531 mg (2 mmol) of **2gA** and 105 mg TBAF/silica gel (20%); yield 233 mg (77%), colorless liquid, b.p. 192°C/0.02 Torr.- IR (film): 3500 (OH); 3300 (NH); 2980; 2940; 2920 (CH); 1460; 1380 (CH_3); 1305; 1155 (SO_2).- ^{1}H-NMR ([D$_6$]-acetone): δ = 1.25 (d, J = 6 Hz, 3H, CH_3), 3.19 (mc, 1H, H-3), 3.42 (mc, 1H, H-3'), 4.02-4.52 (m, 3H, H-4, H-α, and OH), 6.70 (bs, 1H, NH).- $C_4H_9NO_3S$ (151.2) Calcd. C 31.8 H 6.00 N 9.3 S 21.2 Found C 31.6 H 6.04 N 9.1 S 21.0.

(α*S**,4*S**)-Isomer (B): From 531 mg (2 mmol) of **2gB** and 105 mg TBAF/silicagel (20%); yield 260 mg (86%), colorless crystals, m.p. 81°C (chloroform).- IR: 3450 (OH); 3300 (NH); 2980; 2940 (CH); 1360 (CH_3); 1315; 1155 (SO_2).- ^{1}H-NMR ([D$_6$]-acetone): δ = 1.25 (d, J = 6 Hz, 3H, CH_3), 3.02 (mc, 1H, H-3), 3.40 (mc, 1H, H-3'), 4.1-4.65 (m, 3H, H-4, H-α, and OH), 6.60 (bs, 1H, NH).- $C_4H_9NO_3S$ (151.2) Calcd. C 31.8 H 6.00 N 9.3 S 21.2 Found C 31.7 H 5.93 N 9.1 S 21.3.

4-[2-(Benzylideneamino)ethylsulfonyl]-2-(tert-butyldimethylsilyl)-1,2-thiazetidine 1,1-dioxide (**4**)

A solution of 1.1 g (5 mmol) of **1b** in 40 ml of THF is added at -78°C to a solution of 3.2 ml (5 mmol) of BuLi in 10 ml of THF. After 1 min, 0.53 ml (5 mmol) of benzaldehyde are added, the mixture is stirred for 10 min at -78°C, hydrolyzed with saturated NH_4Cl solution, the org. layer is separated, dried with Na_2SO_4, and evaporated *in vacuo*; yield 555 mg (27%), colorless crystals, m.p. 128°C (methanol).- IR: 3005 (arCH); 2955; 2930; 2860 (CH); 1645 (C=N); 1580; 1455 (arC-C); 1465; 1385; 1365 (CH_3); 1325; 1310; 1180; 1135 (SO_2).- ^{1}H-NMR: δ = 0.27 (s, 3H, Si-CH_3), 0.30 (s, 3H, Si-CH_3), 0.97 (s, 9H, Si-tert Bu), 3.25-4.20 (m, 6H, H-3, H-3', CH_2-CH_2), 5.75 (dd, J = 7 and 5 Hz, 1H, H-4), 7.2-7.9 (m, 5H, arom. H), 8.33 (s, 1H, CH=N).- MS (70eV): m/z = 416 (4%, M^+), 132 (100); other characteristic fragments at m/z = 417 (30%, M+1)$^+$, 359 (24%, M-tert Bu)$^+$, 140 (19), 133 (16), 105 (16).- $C_{17}H_{28}N_2O_4S_2Si$ (416.6) Calcd. C 49.0 H 6.77 N 6.7 S 15.4 Found C 49.3 H 6.70 N 6.6 S 15.5.

(RS)-2-Methyl-3-phenyl-1,2-thiazetidine 1,1-dioxide (**5**):[8]

(3R,4S*)-4-(1-Hydroxy-1-methylethyl)-2-methyl-3-phenyl-1,2-thiazetidine 1,1-dioxide* (**6a**):[12]

4-(α-Hydroxybenzyl)-2-methyl-3-phenyl-1,2-thiazetidine 1,1-dioxide (**6b**)

From 2 ml (20 mmol) of benzaldehyde, and separation by CC.- (α*R**,3*R**,4*S**)-Isomer (A): Elution with dichloromethane, R_f = 0.10; yield 376 mg (25%), colorless crystals, m.p. 151°C (methanol).- IR: 3525 (OH); 3060; 3025 (arCH); 2980; 2930 (CH); 1600; 1495; 1450 (arC-C); 1305; 1170 (SO_2).- ^{1}H-NMR: δ = 2.69 (s, 3H, N-CH_3), 3.37 (d, J = 3 Hz, 1H, OH), 4.28-4.45 (m, 2H, H-3, H-4), 5.48 (t, J = 3 Hz, 1H, H-α), 7.0-7.5 (m, 1OH, arom. H).- ^{1}H-NMR ([D$_6$]-DMSO, 80 MHz): δ = 2.58 (s, 3H, N-CH_3), 4.28 (d, J = 6 Hz, 1H, H-3), 4.48 (dd, J = 9 and 6 Hz, 1H, H-4), 5.15 (dd, J = 9 and 5.5 Hz, 1H, H-α), 6.02 (d, J = 5.5 Hz, 1H, OH), 7.22-7.60 (m, 10H, arom. H).- $C_{16}H_{17}NO_3S$ (303.4) Calcd. C 63.3 H 5.65 N 4.6 S 10.6 Found C 63.5 H 5.62 N 4.5 S 10.7.

(α*S**,3*R**,4*S**)-Isomer (B): After separation of isomer A the column is eluated with ethyl acetate, the eluate is concentrated *in vacuo*, the residue is dissolved in a few ml of dichloromethane, and pentane is added until opacness. After 24 h the precipitate (7) is separated, the filtrate is evaporated *in vacuo* to dryness, dissolved in chloroform, pentane is added, and after 24 h at -10°C the crystals are collected; yield 170 mg (11%), colorless crystals, m.p. 143 °C (chloroform/pentane 1:1).- IR: 3480 (OH); 3060; 3035 (arCH); 2965; 2925; 2850 (CH); 1495; 1455 (arC-C); 1310; 1160 (SO_2).- ^{1}H-NMR: δ = 2.66 (s, 3H, N-CH_3), 3.32 (d, J = 6 Hz, 1H, OH), 3.78 (d, J = 6.5 Hz, 1H, H-3), 4.46 (dd, J = 8.5 and 6.5 Hz, 1H, H-4), 5.23 (dd, J = 8.5 and 6 Hz, 1H, H-α), 6.83-7.33 (m, 10 H, arom. H).- ^{1}H-NMR ([D$_6$]-DMSO, 80 MHz): δ = 2.52 (s, 3H, N-CH_3), 3.81 (d, J = 6.5 Hz, 1H, H-3), 4.41 (dd, J = 10 and 6.5 Hz, 1H, H-4), 5.08 (dd, J = 10 and 5 Hz, 1H, H-α), 6.12 (d, J = 5 Hz, 1H, OH), 6.7-7.5 (m, 10 H, aromat. H).- $C_{16}H_{17}NO_3S$ (303.4) Calcd. C 63.3 H 5.65 N 4.6 S 10.6 Found C 63.1 H 5.55 N 4.8 S 10.5.

4-(α-Hydroxy-4-methoxybenzyl)-2-methyl-3-phenyl-1,2-thiazetidine 1,1-dioxide (**6c**)

From 2.43 ml (20 mmol) of 4-methoxybenzaldehyde as described for **6b**.- (α*R**,3*R**,4*S**)-Isomer (A): Yield 390 mg (23%), colorless crystals, m.p. 148°C (chloroform/petroleum ether 1:1).- IR: 3480 (OH); 3040; 3010 (arCH); 2980; 2960; 2840 (CH); 1610; 1590; 1515; 1455 (arC-C); 1305; 1180 (SO_2).- ^{1}H-NMR: δ = 2.68 (s, 3H, N-CH_3), 3.15 (d, J = 3.5 Hz, 1H, OH), 3.75 (s, 3H, OCH_3), 4.28-4.45 (m, 2H, H-3, H-4), 5.41 (dd, J = 4 and 3.5 Hz, 1H, H-α), 6.8-7.5 (m, 9H, arom. H).- ^{1}H-NMR ([D$_6$]-DMSO, 80 MHz): δ = 2.58 (s, 3H, N-CH_3), 3.72 (s, 3H, OCH_3), 4.23 (d, J = 6 Hz, 1H, H-3), 4.43 (dd, J = 9.5 and 6 Hz, 1H, H-4), 5.06 (dd, J = 9.5 and 5.5 Hz, 1H, H-α), 5.87 (d, J = 5 Hz, 1H, OH), 6.8-7.6 (m, 9H, arom. H).- $C_{17}H_{19}NO_4S$ (333.4) Calcd. C 61.2 H 5.74 N 4.2 S 9.6 Found C 61.0 H 5.60 N 4.1 S 9.7.

(α*S**,3*R**,4*S**)-Isomer (B): Yield 235 mg (14%), colorless crystals, m.p. 163°C (dichloromethane/petroleum ether 1:1).- IR: 3490 (OH); 3070; 3040; 3010 (arCH); 2960; 2935; 2840 (CH); 1615; 1590; 1515; 1460 (arC-C); 1300; 1150 (SO_2).- ^{1}H-NMR: δ = 2.64 (s, 3H, N-CH_3), 2.94 (d, J = 6 Hz, 1H, OH), 3.73 (s, 3H, OCH_3), 3.76 (d, J = 6 Hz, 1H, H-3), 4.41 (dd, J = 8 and 6 Hz, 1H, H-4), 5.15 (dd, J = 8 and 6 Hz, 1H, H-α), 6.7-7.3 (m, 9H, arom. H).- ^{1}H-NMR ([D$_6$]-DMSO, 80 MHz): δ = 2.52 (s, 3H, N-CH_3), 3.67 (s, 3H, OCH_3), 3.77 (d, J = 6.5 Hz, 1H, H-3), 4.40 (dd, J = 10 and 6.5 Hz, 1H, H-4), 5.02 (dd, J = 10 and 5 Hz, 1H, H-α), 5.97 (d, J = 5 Hz, 1H, OH), 6.7-7.3 (m, 9H, arom. H).- $C_{17}H_{19}NO_4S$ (333.4) Calcd. C 61.2 H 5.74 N 4.2 S 9.6 Found C 61.2 H 5.77 N 4.1 S 9.5.

4-(α-Hydroxy-4-nitrobenzyl)-2-methyl-3-phenyl-1,2-thiazetidine 1,1-dioxide (**6d**)

From 3.02 g (20 mmol) of 4-nitrobenzaldehyde as described for **6b**.- (α*R**,3*R**,4*S**)-Isomer (A): Yield 380 mg (22%); light yellow crystals, m.p. 206°C (methanol).- IR: 3510 (OH); 3110; 3080; 3060; 3040 (arCH); 2960; 2920; 2900 (CH); 1600; 1490; 1450 (arC-C); 1515; 1350 (NO_2); 1315; 1160 (SO_2).- ^{1}H-NMR ([D$_6$]-DMSO, 80 MHz): δ = 2.60 (s, 3H, N-CH_3), 4.32 (d, J = 6 Hz, 1H, H-3), 4.59 (dd, J = 9 and 6 Hz, 1H, H-4), 5.30 (dd, J = 9 and 5.5 Hz, 1H, H-α), 6.36 (d, J = 5.5 Hz, 1H, OH), 7.5-7.6 (m, 5H, arom. H), 7.65-8.26 (AA'BB', 4H, arom. H).- $C_{16}H_{16}N_2O_5S$ (348.4) Calcd. C 55.2 H 4.63 N 8.0 S 9.2 Found C 55.3 H 4.65 N 8.1 S 9.1.

(α*S**,3*R**,*S**)-Isomer (B): Yield 285 mg (16%), yellow crystals, m.p. 200°C (methanol).- IR: 3460 (OH); 3110; 3080; 3060; 3030 (arCH); 2960; 2920; 2890 (CH); 1605; 1490; 1450 (arC-C), 1520; 1345 (NO_2), 1305; 1160 (SO_2).- ^{1}H-NMR ([D$_6$]-DMSO, 80 MHz): δ = 2.53 (s, 3H, N-CH_3), 3.93 (d, J = 6.5 Hz, 1H, H-3), 4.57 (dd, J = 10 and 6.5 Hz, 1H, H-4), 5.27 (dd, J = 10 and 4.5 Hz, 1H, H-α), 6.45 (d, J = 4.5 Hz, 1H, OH), 6.8-7.2 (m, 5H, arom. H), 7.62-8.11 (AA'BB', 4H, arom. H).- $C_{16}H_{16}N_2O_5S$ (348.4) Calcd. C 55.2 H 4.63 N 8.0 S 9.2 Found C 55.3 H 4.73 N 8.1 S 9.1.

N-Methyl-1-[1-(α-hydroxybenzyl)-2-phenylvinylsulfonyl]methansulfonamide (7)

For the isolation see at **6b**, isomer B; yield 80 mg (8%), colorless crystals, m.p. 154°C (dichloromethane/pentane 1:1).- IR: 3460 (OH); 3340 (NH); 3060; 3030; 3000 (arCH); 2940 (CH); 1620 (C=C); 1500; 1450 (arC-C); 1340; 1320; 1170; 1145 (SO_2).- ^{1}H-NMR ([D_6]-DMSO, 80 MHz): δ = 2.67 (bs, 3H, N-CH_3), 4.9-5.3 (AB, J = -16 Hz, 2H, -CH_2-), 6.03 (d, J = 5 Hz, 1H, -CH-OH), 6.60 (d, J = 5 Hz, 1H, -CH-OH-), 7.1-7.6 (m, 10 H, arom. H), 7.89 (s, 1H, C=CH), 9.90 (bs, 1H, NH).- $C_{17}H_{19}NO_5S_2$ (381.5).

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