Pergamon

Tetrahedron 55 (1999) 14089–14096

TETRAHEDRON

Stereoselective Synthesis of β-Sultams using Chiral Tricarbonyl(η^6-Arene)Chromium(0) Complexes

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Received 2 July 1999; revised 9 September 1999; accepted 30 September 1999

Abstract. The reaction of (-)1*R* or (+)-1*S*-tricarbonyl(2-substituted benzaldehyde)chromium complexes with *tert*butylmethanesulfonamide dianion afforded, after decomplexation and intramolecular cyclization, the enantiomerically pure *N-tert*-butyl-3-(2-phenyl substituted)-1,2-thiazetidine 1,1 dioxide derivatives. The hydrolytic ring opening gave the corresponding enantiopure β-aminosulfonic acid.

Keywords: *β–sultam, 1,2.thiazetidine 1,1 dioxide, chiral tricarbonylarene chromium complexes, stereoselective synthesis*

Introduction

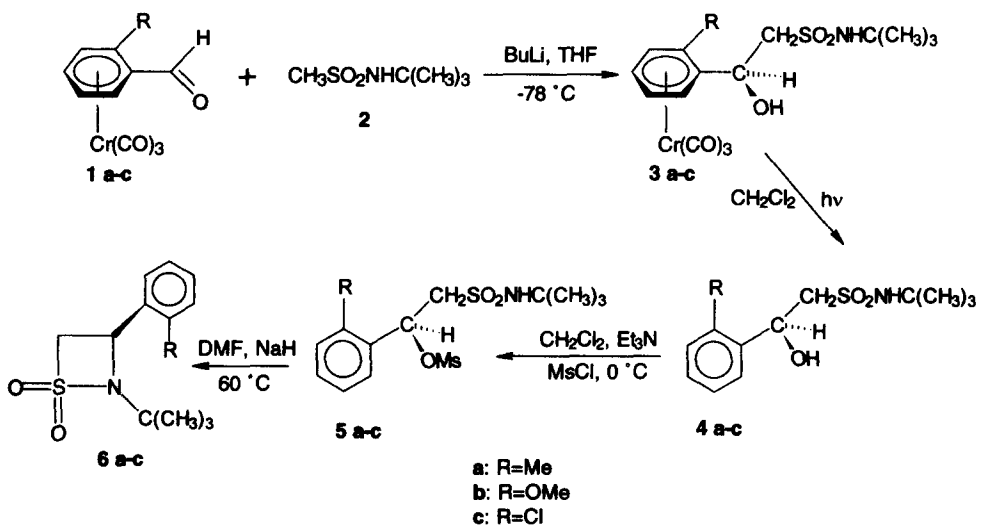
The chemical structures of many important antibiotics contain a β-lactam unit as a crucial moiety for their antimicrobial activity. Structurally, the 1,2-thiazetidine 1,1 dioxides (β-sultams) are S-analogues of β-lactam antibiotics and their highly strained and reactive ring makes them promising candidates for biological activity.[1-3] However, they have received much less attention. The solid-phase synthesis[4] of some β-sultams has recently been reported with the aim of producing libraries for the identification of new antibacterial agents. Through the breaking of their strained N-SO_2 bond, β-sultams are also the precursors of taurine analogues; over the last few years, many research groups have attempted to replace the peptide bond with mimetic groups, and the taurine analogues are promising substrates for the synthesis of sulfonamidopseudo peptides.[5,6] Furthermore, it has been found that the C-S[7] and C-N[8] bonds can be broken under different experimental conditions, thus making 1,2-thiazetidine 1,1 dioxides interesting building blocks for the construction of other heterocyclic systems. However, despite their widespread use and applicability in organic synthesis, no data for optically active β-sultams have yet been reported to the best of our knowledge.

The use of chiral tricarbonyl (η^6-arene) chromium complexes in stereoselective synthesis is well documented,[9] and we and others have recently reported that the enantiomerically pure tricarbonyl chromium complexes of benzaldehydes and benzaldimines are powerful auxiliaries in stereoselective

0040-4020/99/$ - see front matter
PII: S0040-4020(99)00875-3

cycloadditions[10-13] and in the synthesis of β-lactam rings.[14-17] With the aim of extending the use of these chiral complexes to the synthesis of different heterocyclic compounds, we studied the preparation of a series of *orho*-aryl-substituted 1,2-thiazetidine 1,1 dioxides. Among the β-sultam syntheses published in the literature, the method reported by Thompson[18] is considered to be the most suitable for chromium complexed substrates: an α,N-alkanesulfonamide dianion reacts with a large number of electrophiles to afford chemoselective C-alkylation, and particularly with aryl aldehydes to give more highly functionalized β–hydroxysulfonamides that are intermediates for the synthesis of β–styrilsulfonamides or 1,2-thiazetidine 1,1-dioxides. The reaction conditions were compatible with arene chromium derivatives, and the low reaction temperature was instrumental for high diastereoselection. The reaction sequence was first performed starting from racemic substrates and subsequentely repeated on the optically pure compunds.

We report here the synthesis of the enantiomerically pure N-*tert*-butyl-3-(2-phenyl substituted) 1,2-thiazetidine 1,1 dioxide derivatives **6a-c**, starting from optically pure tricarbonyl(2-substituted benzaldehyde)chromium(0) complexes **1a-c**.[19] (Scheme 1)



Scheme 1

Results and Discussion

The attack of the N-*tert*-butylmethansulfonamide dianion generated using BuLi in dry THF solution at -78 °C on *ortho* substituted optically pure benzaldehydes **1a-c** (the 1-(*R*) enantiomer is shown in the

scheme 1 for the sake of simplicity) afforded the corresponding complexed 2-hydroxysulfonamides **3a-c** in good yield. The diastereoselection evaluated by ^{1}H NMR on the crude reaction mixture was nearly complete in the case of **3b** and **3c**, whereas the 2-hydroxysulfonamide **3a** was obtained only in 60% d.e. However it is worth noting that the two diastereoisomers were easily separated by column chromatography and characterized.

The reaction of the N-*tert*-butylmethansulfonamide dianion on the pro-stereogenic formyl group is the key step for the diastereoselective formation of the new stereogenic center, and is controlled by means of the planar chirality produced by the $Cr(CO)_3$ unit. After this center was created in high enantiomeric purity, the organic ligand was therefore removed from the complex and the subsequent reactions were run in a stereoselective manner on the more easily handled substrates. The uncomplexed 2-hydroxysulfonamides **4a-c** were obtained in nearly quantitative yields by exposing a solution of complexed 2-hydroxysulfonamides **3a-c** in CH_2Cl_2 to air and sunlight.

In order to favour the intramolecular ring closure, the 2-hydroxyl group was transformed using mesyl chloride in the presence of Et_3N into the corresponding mesyl derivatives **5**, of which **5a** and **5c** were isolated in good yield; **5b** was used for the subsequent step without any purification.

As expected, the ring closure to form the β-sultam ring, which was performed in DMF solution at 60 °C using NaH as a base, underwent an S_N2 substitution with the complete inversion of the configuration and without any racemization. The β-sultams **6a-c** were recovered in good yield and with unchanged enantiopurity (e.e. ≥ 98%) with respect to the 2-hydroxysulfonamides **3a-c**.

It was possible to assign the absolute configuration to β-sultams **6a-c** on the basis of the following considerations: the accepted stereochemical model operating on *ortho* substituted benzaldehyde complexes predicts that the nucleophilic species attacks the formyl group from the opposite side to that of the $Cr(CO)_3$ unit and on the preferred conformation in which the C=O group is *anti* with respect to substituent in the *ortho* position. Therefore, starting from the (-)-(*1R*) tricarbonyl(2-chlorobenzaldehyde)chromium **1c** and (-)-(*1R*) tricarbonyl(2-methoxylbenzaldehyde)chromium **1b**, we assigned the (*2R*) configuration to the newly formed stereogenic center of the complexed 2-hydroxysulfonamides **3b,c** the (*2S*) configuration to the corresponding uncomplexed **4b,c**, and consequently, after the S_N2 intramolecular reaction, the (*3R*) absolute configuration to β-sultams **6b,c**.

This hypothesis was further confirmed by X-ray analysis of the optically pure β-sultam **6c**. As shown in the figure, the absolute configuration of C-3 (C1 in the figure) of β-sultam **6c** is (*R*).

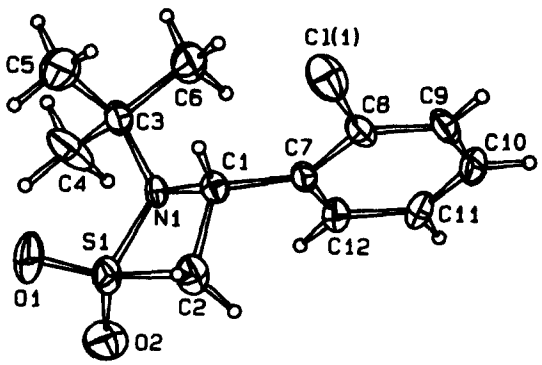
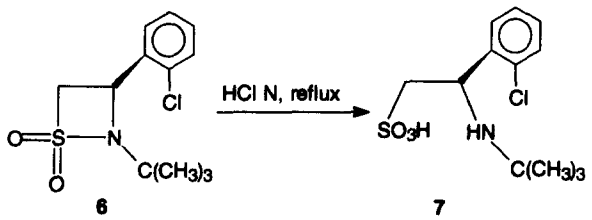


Figure: *ORTEP plot of (-)-(3R) N-tertbutyl-3(2-chlorophenyl) 1,2-thiazetidine 1,1 dioxide* **6c**; *heavy atom ellipsoids are at 20% probability level, H atoms not to scale.*

Finally as a probe for running further transformations of the above substrates, we hydrolysed the β-sultam **6c** with HCl $1N^{20}$ to the corresponding optically pure β-amino sulfonic acid in good yield. (Scheme 2)



Scheme 2

Conclusions

These results underline that chiral chromiumtricarbonyl arenes are extremely useful and versatile substrates for the enantioselective synthesis of optically pure β-sultams in excellent yields, and with predictable stereochemistry on the basis of the absolute configuration of the starting aldehydes. In addition, the possibility of transforming these monosubstituted β-sultams into the corresponding β-aminosulfonic acids opens the way to other interesting applications.

Experimental section

All of the reactions were performed under nitrogen. Thermolysis with hexacarbonylchromium(0) was carried out in a round-bottomed flask, equipped with a Liebig air condenser and a water condenser on top. All of the chemicals were used as obtained from commercial sources. Column chromatography and

TLC were carried out using silica gel 60 and silica gel 60 F_{254} pre-coated plates respectively. The melting points were measured using a Buchi apparatus and are uncorrected. The IR spectra were recorded using a 1725X FTIR spectrometer. NMR spectra were recorded in $CDCl_3$ using a Varian XL 300 spectrometer. Evaluation of enantiomeric excess was performed using Eu(hfc)$_3$ (tris [3-(heptafluoropropyl hydroxymethylene)–*d*-camphorato]europium(III) salt. The optical rotations were measured using a Perkin-Elmer 241 Polarimeter, with a 1 dm pathlengh at 25 °C. The racemic compounds were prepared as previously reported. The optically pure complexed benzaldehydes were obtained by resolution of the corresponding racemic substrate using a known procedure.[19]

Synthesis of complexed 2-hydroxysulfonamides* 3a-c *General procedure: *n*-BuLi (2.45 mmol, 1.6M solution in hexane) was added dropwise to a solution of of N-*tert*-butyl methanesulfonamide **2** (1.17 mmol) in 3.5 ml of dry THF at -78 °C. The resulting solution was warmed to -30 °C and maintained at this temperature for about 30 min. After re-cooling to -78 °C, a solution of complexed benzaldehyde **1a-c** 1.17 mmol in 7 ml of THF was slowly added. The hydroxysulfonamide **3a-c** was immediately formed and, after 10 min, the reaction was quenched by adding at -78 °C a 1:9 mixture of AcOH in THF until acidic pH (about 4 ml). The solution was warmed to room temperature and then the organic layer was washed with water (3 x 20 ml). After evaporation of the solvent under reduced pressure, the crude yellow oil was recrystallised by adding a 2:1 mixture of petroleum ether : diethylether, if no differently specified.

***N-tert-butyl-2-(2-methylphenyl tricarbonyl chromium)-2-hydroxyethansulfonamide* 3a:** Yield 95%; yellow solid, mp 140-160 °C; d.e. 60%, ν_{max}(Nujol) 3460, 3300, 1966, 1897, 1875, 1305, 1146; *Anal.* Calc. For $C_{16}H_{21}CrNSO_6$ (407.413); C, 47.16; H, 5.20; N, 3.44. Found C, 47.26; H, 5.19; N, 3.45. Starting from (+)-*1S* benzaldehyde **1a** $[\alpha]_D$= +627 ($CHCl_3$, *c* 0.1); The two diastereoisomers were separated by chromatography (SiO_2 eluent Et_2O:petroleum ether 3:1). *First diastereosomer:* yellow solid, mp 158-9 °C; yield 60%. ^{1}H NMR δ 1.25 (s, 9H, CMe_3); 2.1 (s, 3H, Me); 3.1 (AB part of ABX system, 2H, CH_2); 3.48 (s, 1H, OH); 4.3 (s, 1H, NH); 5.0 (d, 1H, aromCr(CO)$_3$, J=6.3 Hz); 5.05 (X part of ABX system, 1H, CH); 5.1 (dd, 1H, aromCr(CO)$_3$, J=6.3 and 6.4 Hz); 5.25 (dd, 1H, aromCr(CO)$_3$, J=6.4 and 6.3 Hz); 5.61 (d, 1H, aromCr(CO)$_3$, J=6.3 Hz); $[\alpha]_D$= +30.3 ($CHCl_3$, *c* 0.1); d.e. ≥98%. *Second diastereoisomer:* yellow solid, mp 149-50 °C; yield 15%. ^{1}H NMR δ 1.4 (s, 9H, CMe_3); 2.3 (s, 3H, Me); 3.45 (AB part of ABX system, 2H, CH_2); 3.85 (s, 1H, OH); 4.4 (s, 1H, NH); 5.05 (d, 1H, aromCr(CO)$_3$, J=6.6 Hz); 5.09 (X part of ABX system, 1H, CH); 5.12 (dd, 1H, aromCr(CO)$_3$, J=6.6 and 6.6 Hz); 4.51 (dd, 1H, aromCr(CO)$_3$, J=6.6 and 6.6 Hz); 5.7 (d, 1H, aromCr(CO)$_3$, J=6.6 Hz); $[\alpha]_D$= +40 ($CHCl_3$, *c* 0.1); d.e.≥98%.

***(2R)-N-tert-butyl-2-(2-methoxyphenyl tricarbonyl chromium)-2-hydroxyethansulfonamide* 3b:** Yield 88%; yellow solid, mp 109-110 °C; d.e.≥98% ν_{max}(Nujol) 3408, 3300, 1958, 1889, 1867, 1314, 1143; starting from (-)-(*1R*) benzaldehyde **1b**, $[\alpha]_D$= -1047 ($CHCl_3$, *c* 0.1).^{1}H NMR δ 1.4 (s, 9H, CMe_3); 3.21 (dd, 1H, CH_2, J=23.6 and 4.4 Hz); 3.36 (dd, 1H, CH_2 J=23.6 and 2.1 Hz); 3.46 (bs, 1H, OH); 3.76 (s, 3H, OMe); 4.4 (s, 1H, NH); 4.91 (dd, 1H, aromCr(CO)$_3$, J=6.2 and 6.6 Hz); 5.3 (d, 1H, aromCr(CO)$_3$, J=6.6); 5.27 (m, 1H, CH); 5.6 (dd, 1H, aromCr(CO)$_3$, J=6.6 and 6.2 Hz); 5.9 (d, 1H, aromCr(CO)$_3$, J=6.2 Hz). *Anal.* Calc. For $C_{16}H_{21}CrNSO_7$ (423.413); C, 45.39; H, 5.00; N, 3.31. Found C, 45.52; H, 4.99; N, 3.32; $[\alpha]_D$= +107 ($CHCl_3$, *c* 0.1).

***(2R)-N-tert-butyl-2-(2-chlorophenyl tricarbonyl chromium)-2-hydroxyethansulfonamide* 3c:** Yield 89%; yellow solid, m.p. 151 °C (diethyl ether/ petroleum ether 1/1) d.e. ≥98% ν_{max}(Nujol) 3450, 3300, 1983, 1920, 1897, 1330, 1150;Starting from (-)-(*1R*) benzaldehyde **1c** $[\alpha]_D$= -1015 (c= 0.1 $CHCl_3$). ^{1}H NMR δ 1.4 (m, 9H, CMe_3); 3.25 (dd, 1H, CH_2, J=14.2 Hz and 9.8 Hz); 3.49 (dd, 1H, CH_2, J=14.2 and 1.5 Hz); 3.84 (d, 1H, OH, J=2.7 Hz); 4.44 (bs, lH, NH); 5.1 (t, lH, aromCr(CO)$_3$, J=5.8 Hz); 5.27 (m, lH, CH); 5.4 (m, 2H, aromCr(CO)$_3$); 5.85 (d, lH, aromCr(CO)$_3$, J=7.3 Hz). *Anal.* Calc. For $C_{15}H_{18}ClCrNSO_6$

(427.831); C, 42.11; H, 4.24; N, 3.27. Found C, 42.23; H, 4.23; N, 3.26; $[\alpha]_D$= +31.1° (c= 0.1 $CHCl_3$).

Decomplexation of 2-hydroxymetansulfonamides* 3a-c *General procedure: The solution in CH_2Cl_2 of the appropriate complexed 2-hydroxysulfonamides **3a-c**, was exposed to air and sunlight for 3-5h. The solvent was evaporated and the residue treated with Et_2O and filtered over celite. After evaporation of the solvent, the residue was crystallised with petroleum ether.

***N-tert-butyl-2-(2-methylphenyl)-2-hydroxyethansulfonamide* 4a:** From the diastereomeric mixture: yield 97%; white solid, mp 98 °C; ν_{max}(Nujol) 3469, 3294, 1316, 1146; ^{1}H NMR δ 1.39 (s, 9H, CMe_3); 2.32 (s, 3H, Me); 3.23 (dd, 1H, CH_2, J=14.4 and 2.2 Hz); 3.33 (dd, 1H, CH_2, J=14.4 and 9.5 Hz); 3.52 (d, 1H, OH, J=2.2 Hz); 4.44 (s, 1H, NH); 5.50 (m, 1H, CH); 7.51-7.10 (m, 4H, arom). $[\alpha]_D$= -29.58 (c= 0.1 $CHCl_3$). *Anal.* Calc. For $C_{13}H_{21}NSO_3$ (271.384); C, 57.53; H, 7.80; N, 5.16. Found C, 57.60; H, 7.78; N, 5.17. The (-)-enantiomer **3a** $[\alpha]_D$= -48.1 (c= 0.1 $CHCl_3$) and the (+)-enantiomer $[\alpha]_D$= +45.8 (c= 0.1 $CHCl_3$)

***(2S)-N-tert-butyl-2-(2-methoxyphenyl)-2-hydroxyethansulfonamide* 4b:** Yield 94%; white solid, mp 100 °C; ν_{max}(Nujol) 3500, 3310, 1320, 1142; ^{1}H NMR δ 1.34 (s, 9H, CMe_3); 3.33 (dd, 1H, CH_2, J=14.4 and 9.1 Hz); 3.48 (dd, 1H, CH_2, J=14.4 and 2.5 Hz); 3.77 (d, 1H, OH, J=4.0 Hz); 3.84 (s, 1H, OMe); 4.30 (s, 1H, NH); 5.43 (m, 1H, CH); 7.42-7.20 (m, 4H, arom). *Anal.* Calc. For $C_{13}H_{21}NSO_4$ (287.384); C, 54.33; H, 7.36; N, 4.87. Found C, 54.40; H, 7.34; N, 4.88. $[\alpha]_D$= -44.3 (c= 0.1 $CHCl_3$)

***(2S)-N-tert-butyl-2-(2-chlorophenyl)-2-hydroxyethansulfonamide* 4c:** Yield 96%; white solid, mp 130-31 °C; ν_{max}(Nujol) 3500, 3310, 1330, 1140; ^{1}H NMR δ 1.25 (s, 9H, CMe_3); 3.10 (dd, 1H, CH_2, J=14.4 and 9.8 Hz); 3.34 (dd, 1H, CH_2, J=14.4 and 1.7 Hz); 3.08 (d, 1H, OH, J=2.4 Hz); 4.22 (s, 1H, NH); 5.44 (d, 1H, CH, J=9.8 Hz); 7.52-7.10 (m, 4H, arom). *Anal.* Calc. For $C_{12}H_{18}ClNSO_3$ (291.802); C, 49.39; H, 6.22; N, 4.80. Found C, 49.48; H, 6.21; N, 4.81. $[\alpha]_D$= +70.7 ($CHCl_3$ c= 0.1); e.e. ≥98%.

***Mesylation of* 4a-c:** To a solution of the appropriate **4a-c**, (1.1 mmol) and Et_3N (freshly distilled, 2.1 mmol), in 5.5 ml of dried CH_2Cl_2 under nitrogen atmosphere cooled to 0 °C, methanesulfonyl chloride (1.64 mmol) was added keepping the temperature under 2 °C. The reaction was immediately complete and was quenched at 0 °C by adding a solution of 5% HCl (about 5 ml) until acidic pH. The organic layer was washed several time with water, dried and evaporated in vacuo. The remaining pale yellow oil was crystallised as white crystals with Et_2O and petroleum ether in the case of **4a,c**. Compound **4b**, havever, was directly submitted to the following synthetic step without isolation of the product.

***N-tert-bytyl-2-(2-methylphenyl)-2-methansulfonyl ethansulfonamide* 5a:** Yield 98%; white solid, mp 98 °C. ν_{max}(Nujol) 3304, 1325, 1146; ^{1}H NMR δ 1.39 (s, 9H, CMe_3); 2.44 (s, 3H, Me); 2.80 (s, 3H, SO_3Me); 3.3 (dd, 1H, CH_2, J=15.1 and 2.9 Hz); 3.72 (dd, 1H, CH_2, J=15.1 and 9.0 Hz); 4.4 (s, 1H, NH); 6.27 (dd, 1H, CH, J=9.0 and 2.9 Hz); 7.42-7.20 (m, 4H, arom.). *Anal.* Calc. For $C_{14}H_{23}NS_2O_5$ (349.447); C, 48.11; H, 6.63; N, 4.01. Found C, 48.08; H, 6.61; N, 4.00. From the mixture of diastereoisomers $[\alpha]_D$= -29.58 ($CHCl_3$, *c* 0.1).

***(2S)-N-tert-bytyl-2-(2-chlorophenyl)-2-methansulfonyl ethansulfonamide* 5c:** Yield 96%; white solid, mp 130-1 °C. ν_{max}(Nujol) 3310, 1330, 1140; ^{1}H NMR δ 1.23 (s, 9H, CMe_3); 2.88 (s, 3H, SO_3Me); 3.30 (dd, 1H, CH_2, J=14.9 and 2.9 Hz); 3.48 (dd, 1H, CH_2, J=14.9 and 9.3 Hz); 4.5 (s, 1H, NH); 6.27 (dd, 1H, CH, J=9.3 and 2.9 Hz); 7.41-7.10 (m, 4H, arom.). *Anal.* Calc. For $C_{13}H_{20}ClNS_2O_5$ (368.895); C, 42.32; H, 5.46; N, 3.80. Found C, 42.29; H, 5.47; N, 3.79. $[\alpha]_D$= +53.48 ($CHCl_3$, *c* 0.1).

Synthesis of β-sultams* 6a-c. *General procedure: NaH (1.29 mmol, oil suspension) was added to a solution of **5a-c**, (0.86 mmol) in 12 ml of dry DMF. The solution was heated at 60 °C for about 15-20

min (monitored by TLC). The reaction mixture was cooled at room temperature and then diluted with water (30 ml). The aqueous layer was extracted with Et_2O (3x20 ml) and the organic solvent washed with water until neutral pH. After evaporation of the solvent in vacuo, the pale yellow oil was crystallised as white crystals by adding a 3:1 mixture of diethyl ether: petroleum ether.

***(+)-N-tert-butyl-3-(2-methylphenyl)-thiazetidine 1,1 dioxide* 6a:** Yield 90%; white solid, mp 100 °C; ν_{max}(Nujol) 1380, 1167; ^{1}H NMR δ 1.2 (s, 9H, CMe_3); 1.25 (s, 3H, Me); 3.72 (dd, 1H, CH_2, J=12.1 and 6.0 Hz); 4.34 (dd, 1H, CH_2, J=12.1 and 8.0); 4.77 (dd, 1H, CH, J=8.0 and 6.0 Hz); 7.3-7.05 (m, 4H, arom). *Anal.* Calc. For $C_{13}H_{19}NSO_2$ (253.368); C, 61.63; H, 7.56; N, 5.53. Found C, 61.58; H, 7.55; N, 5.54. From the first pure diastereoisomer of **3a**, $[\alpha]_D$= +58 ($CHCl_3$, *c* 0.2); e.e. ≥98%.

***(3R)-N-tert-butyl-3-(2-methoxyphenyl)-thiazetidine 1,1 dioxide* 6b:** Yield 90%; white solid, mp 87 °C; ν_{max}(Nujol) 1317, 1148; ^{1}H NMR δ 1.21 (s, 9H, CMe_3); 3.74 (dd, 1H, CH_2, J=12.2 and 5.4 Hz); 3.82 (s, 1H, OMe); 4.32 (dd, 1H, CH_2, J=12.2 and 8.3); 5.03 (dd, 1H, CH, J=8.3 and 5.4 Hz); 6.85-7.2 (m, 3H, arom); 7.7 (d, 1H, arom., J=7.8 Hz). *Anal.* Calc. For $C_{13}H_{19}NSO_3$ (269.368); C, 57.97; H, 7.11; N, 5.20. Found C, 57.95; H, 7.13; N, 5.19. $[\alpha]_D$ = +12.57 ($CHCl_3$ c=0.1); e.e. ≥98%.

***(3R)-N-tert-butyl-3-(2-chlorophenyl)-thiazetidine 1,1 dioxide* 6c:** Yield 94%; white solid, m.p. 74 °C ν_{max}(Nujol) 1313, 1143; ^{1}H NMR ($CDCl_3$) δ 1.2 (s, 9H, CMe_3); 3.75 (dd, 1H, J=5.2 Hz, J=12.4 Hz); 4.45 (dd, 1H, J=8.3 Hz, J=12.4 Hz); 5.06 (dd, 1H, J=8.3 Hz, J=5.2 Hz); 7.2-7.4 (m, 3H, arom.); 7.85 (d, 1H, arom., J=7.7 Hz); ^{13}C NMR ($CDCl_3$) δ 27.4 (Me_3); 42 (CH); 56.8 (CMe_3); 65.3 (CH_2); 127.6, 127.7, 129.8, 129.5 arom.: 132 (q-C): 137.3 (q-C). *Anal.* Calc. For $C_{12}H_{16}ClNSO_2$ (273.786); C, 52.64; H, 5.89; N, 5.12. Found C, 52.70; H, 5.90; N, 5.13. $[\alpha]_D$ = -107° ($CHCl_3$ c=0.2); e.e. ≥98%.

***Hydrolysis of* 6c *to* (3R)-N-tert-butyl-β -aminosulfonic acid 7:** 0.16 g (0.59 mmol) of **6c** was suspended in 12 ml of 1N HCl and heated under reflux for about 4h. The water was evaporated under reduced pressure and the remaining white solid was crystallized with ethanol/water giving the amino acid 7 in 50% yield. Mp >240 °C; $[\alpha]_D$= -49 ($CHCl_3$ *c* 0.3). ^{1}H NMR ($CDCl_3$ + DMSO) δ 1.2 (s, 9H, Me_3); 2.85 (dd, 1H, CH_2, J=14.2 and 2.3 Hz); 3.16 (dd, 1H, CH_2, J=10.5 and 14.2 Hz); 5.2 (m, 1H, CH); 7.4-8.1 (m,4H, arom.); 9.6 and 9.25 (2brs, 2H, NH and SO_3H).

***X-ray analysis of* (3R)-N-tert-butyl-3-(2-chlorophenyl)-thiazetidine 1,1 dioxide 6c:** $C_{12}H_{16}ClNO_2S$, F_w = 273.77, monoclinic, space group $P2_1$, *a* = 11.634(1), *b* = 10.203(1), *c* = 12.929(1) Å, β = 115.522(5) °, V = 1384.9(2) Å^{-3}, *Z* = 4, D_x = 1.313 Mg.m^{-3}, λ(Mo-*K*α) = 0.417 mm^{-1}; crystal dimensions 0.48x0.32x0.18 mm^3, λ = 0.71073 Å (Mo-*K*α radiation, graphite monochromator, Siemens P4 diffractometer). Data collection at room-temperature, ω-2θ scan mode, 4 < 2θ < 50°, *h* 0→13, *k* -12→12, *l* -15→13; 5125 collected reflections, 4873 unique reflections [3521 with $I_o > 2\sigma(I_o)$], merging R = 0.0144; no absorption correction. The structure was solved by SIR92 [21] and refined by SHELXL-93,[22] by full-matrix least-squares based on F_o^2, with weights w = $1/[\sigma^2(F_o)^2+(0.061P)^2]$, where P = $(Fo^2+2F_c^2)$. The final consistency index were R = 0.0414 and Rw = 0.0980 for the observed reflections (0.0603 and 0.1043 respectively for all reflections), goodness-of-fit = 0.977. The final map showed the maximum peak (0.51 e.Å^{-3}) near the SIB atom. The absolute configuration was determined by Flack [23] method [final Flack parameters 0.08(6)].

The structure has two independent molecules, whose main difference is the orientation of the phenyl group (the torsion N1-C1-C7-C8 is 146.8(3) and 131.7(4) ° for molecules A and B respectively).

Acknowledgement: We are grateful to MURST 40% and 60% grants and CNR for their financial support and to Dr. Arianna Ganzi for some preliminary experiments.

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