Turk J Chem
24 (2000) , 59 – 66.

Auxiliary Controlled Intramolecular 1,3-Dipolar Cycloaddition Reactions of Chiral Azomethine Ylides

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Received 29.06.1999

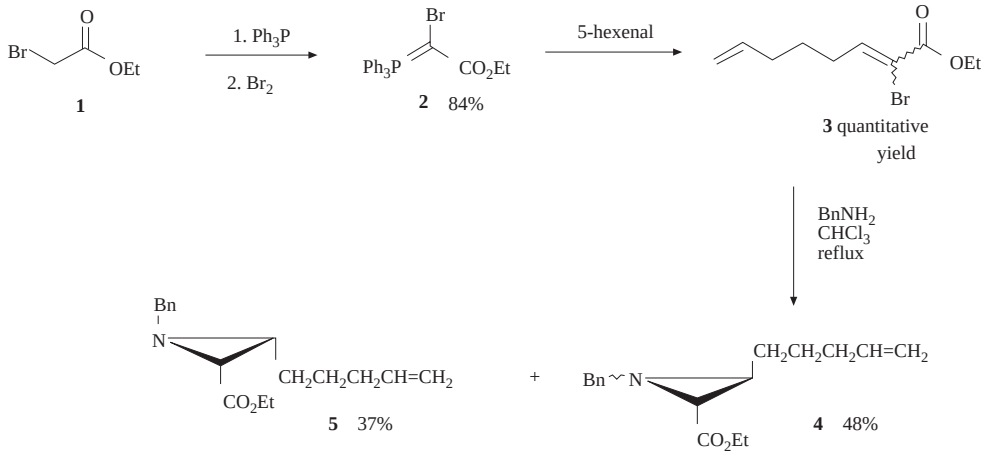
Intramolecular 1,3-dipolar cycloaddition reactions of chiral azomethine ylides obtained by thermal ring opening of chiral aziridines **7a, b** and **8a, b** are investigated. Synthesis of these aziridines **7a, b** and **8a, b** is described.

Introduction

1,3-Dipolar cycloaddition reactions of azomethine ylides[1] play an important role in the synthesis of highly substituted pyrollidines which are found in the structures of many important natural products and pharmaceuticals[2]. Using this chemistry, four chiral centers can be created in a single step. The asymmetric version of this reaction[3] has been tried both with achiral azomethine ylides and chiral dipolarophiles[4] as well as chiral azomethine ylides[5] and achiral dipolarophiles. In the former case, different chiral auxiliaries were attached to the dipolarophiles and very good results (in terms of yield and stereoselectivity) were obtained. In the case of chiral azomethine ylides, although different chiral auxiliaries were attached to the precursors of the azomethine ylides, a truly general solution to this problem remains to be found. For this purpose, we used Oppolzer's sultam[6] as a recoverable chiral auxiliary and developed a very good method for the synthesis of stereodefined aziridine-2-carboxylic acid derivatives[7]. We used these aziridines in intermolecular 1,3-dipolar cycloaddition reactions of chiral stabilized azomethine yields with electron deficient dipolarophiles for the synthesis of highly substituted pyrrolidines[5a]. We extended our method and synthesized aziridines that could be used in intramolecular 1,3-dipolar cycloaddition reactions of chiral stabilized azomethine ylides. These types of reaction are commonly used in the literature especially in relation to total synthesis[8]. In this paper, the synthesis of these aziridines and the results of the intramolecular 1,3-dipolar cycloaddition reactions of azomethine ylides derived from their thermal ring opening are reported.

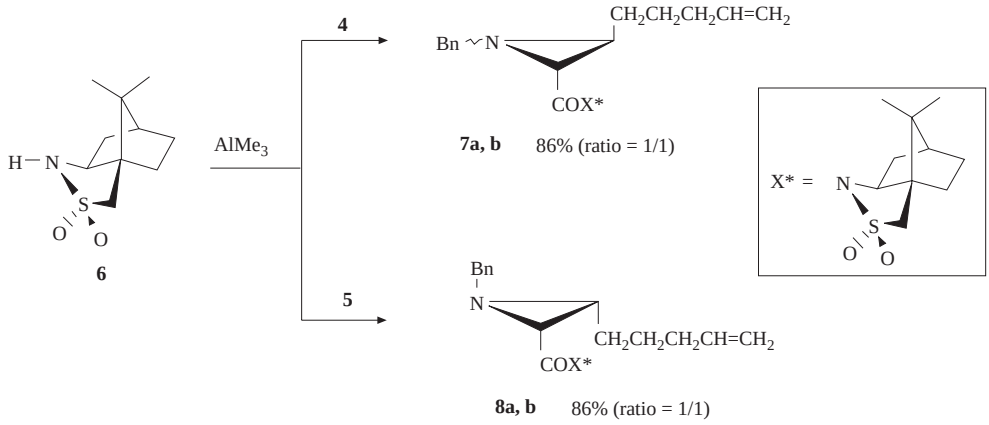
Results and Discussion

For the synthesis of aziridines used in intramolecular 1,3-dipolar cycloaddition reactions of azomethine ylides, bromophosphorene **2** was synthesized from α-bromoester **1** using the procedure described in the literature.[9] Reaction of this bromophosphorene **2** with 5-hexenal obtained from 5-hexenol by the Swern oxidation gave the desired long chain α-bromoester **3** as a mixture of E and Z isomers in quantitative yield. Aziridine formation reaction was easily carried out by refluxing ester **3** with benzyl amine in chloroform. Desired racemic aziridines **4** and **5** were obtained in 85% yield in a ratio of 1.3/1 respectively **(Scheme 1)**. These aziridines were easily separated by flash column chromatography on silica gel. *Trans* and *cis* stereochemical assignments were based on the coupling constants between H-2 and H-3. Thus, the *trans* aziridine **4** showed $J_{2,3}$=2.8 Hz and the *cis* isomer showed $J_{2,3}$=6.8 Hz.



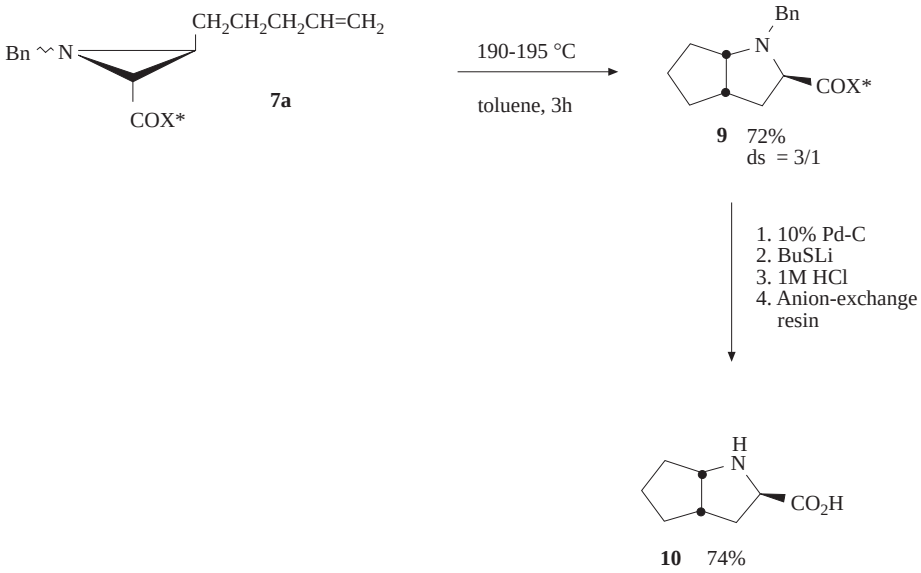
Scheme 1. Formation of aziridines **4** and **5**..

Aziridines **4** and **5** were coupled with sultam **6** separately in the presence of Me_3Al[10]. Both coupling reactions gave the desired auxiliary attched aziridines **7a, b** and **8a, b** as 1/1 mixtures of diastereomers in 86% yield **(Scheme 2).** In each case, the diastereomeric mixture was easily separated by flash column chromatography on silica gel. The *cis* and *trans* stereochemical assignments were also based on the coupling constants of H-2 hydrogens. *Trans* disubstituted aziridines **7a, b** remained mixtures of N-invertomers, even upon heating the NMR sample up to 150°C in DMSO-d_6.



Scheme 2. Coupling of sultam **6** with **4** and **5** to give aziridines **7a,b** and **8a,b**.

The next step in this study was the trial of these aziridines in intramolecular 1,3-dipolar cycloaddition reactions. For this purpose, the starting aziridine **7a** was sealed in a glass tube with toluene and heated at 190-195 °C for three hours. As a result of this process cycloadduct **9** was obtained as the major product in 72% yield in a 3/1 diastereomeric ratio **(Scheme 3)**. These cycloadducts could not be separated by flash column chromatography on silica gel but most of the major cycloadduct was separated by fractional crystallization from ethanol.



Scheme 3. Synthesis of bicyclic amino acid **10** from aziridine **7a**.

The absolute stereochemistry of this cycloadduct **9** was determined by converting it to a known compound **10** (mp= 117-119 °C; $[\alpha]_D^{24}$=+35.2°, c=0.25 H_2O; lit.[11] mp=120 °C; $[\alpha]_D^{29}$=+47.5°, c=0.4 H_2O) after removing the benzyl group and the auxiliary **(Scheme 3)**. Formation of the cycloadduct **9** can be explained by the transition state as shown in **Figure 1.** In this transition state, the dipolarophile (double bond) approach the ylide from the *re-face* (referring to the α-carbon), as expected according to the Oppolzer-Curran model[6] which explains the selectivity of the sultam.

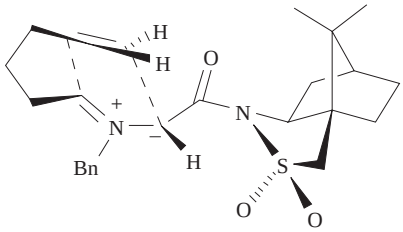


Figure 1. Transition state leading to the product **9**.

Carrying out the intramolecular 1,3-dipolar cycloaddition reaction under the same conditions with any one of these aziridines **7a, 7b, 8a,** and **8b** or a mixture of all, did not change the results, the yield and the diasteroselectivity were the same. This is because of the isomerization between *syn* and *anti* azomethine ylides **11 (Figure 2)** as is often observed even with reactive dipolarophiles[12].

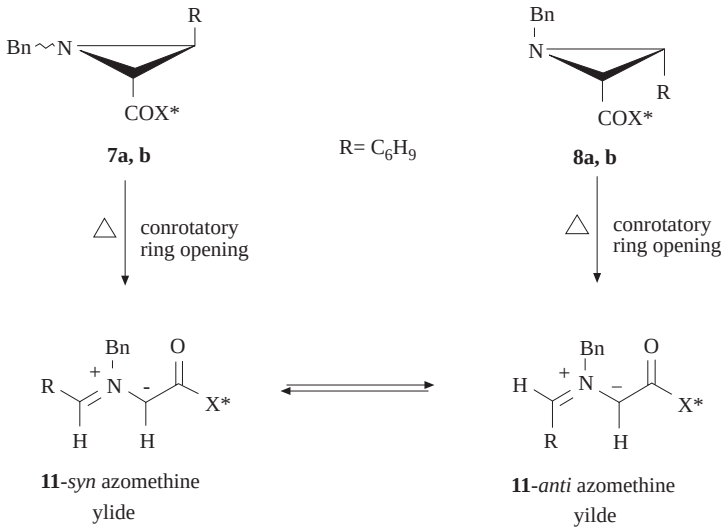


Figure 2. Isomerization of *syn* and *and* azomethine ylides.

Experimental

General Experimental: Melting points were determined on a Mel-Temp Capillary melting point apparatus and were uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at λ=589 nm (Na D line) at room temperature and were reported as follows: $[\alpha]_D^T$, concentration (c=g/100 mL), and solvent. IR spectra were obtained on a Perkin-Elmer 1420 spectrophotometer. ^{1}H NMR spectra were recorded at 200 MHz (Varian XL-200), and 300 MHz (Varian Gemini-300) and are reported in parts per million (ppm) on the δ scale relative to residual $CHCl_3$ (δ 7.25), TMS (δ 0.00) or HDO (δ 4.63). ^{13}C NMR spectra were acquired at 75 MHz (Varian Gemini-300) and are reported in parts per million (ppm) on the δ scale relative to $CHCl_3$ (δ 77.00). The NMR experiments were performed at room temperature unless otherwise indicated. ^{1}H-NMR signal assignments were based on the selective homonuclear decoupling experiments. Mass spectra were measured on a Kratos/AE1 MS-25A mass spectrometer and all samples were direct probe injected. High resolution mass spectra (HRMS) data were reported for M^+ or the highest mass fragment derived from M^+ in electron impact (EI) mode.

All reactions were carried out in oven-or flame-dried glassware under an argon or nitrogen atmosphere unless otherwise stated. Air sensitive liquids were transferred via syringe or cannula through rubber septa. Cooling was achieved with the following baths: ice/water (0 °C) and dry ice/acetone (-78 °C). Degassing was performed under vacuum.

Reagent grade solvents were used for all extractions and chromatography. Solvents used for HPLC were HPLC grade and degassed prior to use.

Thin layer chromatography (TLC) analysis was performed on E. Merck 0.25 mm precoated silica gel 60 F-254 and visualized with UV ilumination followed by charring with either 5% anisaldehyde in (95:5:1) EtOH-AcOH-H_2SO_4 (char A) or 0.3% ninhydrin in (97:3) n-BuOH-AcOH (char B). Flash column chromatography[13] was carried out using E. Merck silica gel 60 (230-400 mesh).

Ethyl 2-bromoocta-2,7-dienoate (3). To a stirring solution of bromophosphorane **2** (918 mg, 2.00 mmol) was added 5-hexenal (220 mg, 2.23 mmol). After stirring the reaction mixture at 75 °C for 6 h, it was judged complete by TLC. The solution was concentrated and purified by flash chromatography (SiO_2,

2:1 hexanes/EtOAc) to give the desired product **3** in quantitative yield as a light yellow oil. *Rf* 0.72 (5:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$) δ 7.29 (t, J=7.2 Hz, 1 H, H-3), 5.80 (1 H), 5.03 (2 H), 4.27 (q, J=14.2 & 7.1 Hz, 2 H, OCH_2), 2.36 (q, J=14.9 & 7.4 Hz, 2 H), 2.13 (2 H), 1.60 (2 H), 1.33 (t, J=7.1, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 162.6, 145.8, 137.8, 116.6, 115.3, 62.43, 33.32, 31.58, 26.80, 14.23; IR ($CHCl_3$) cm^{-1} 2950 (w), 2380 (w), 1700 (s), 1250 (s), 900 (m); HRMS calcd for $C_{10}H_{15}O_2Br$ (M^+) 246.0255, found 246.0251.

trans-1-Benzyl-3-pent-4-enylaziridine-2-carboxylic acid ethyl ester (4).

Bromoester **3** (1 mol eq) was dissolved in $CHCl_3$ (spectroscopic grade, concentration approx. 0.3 M) under an Ar atmosphere. To this solution was added benzyl amine (1.5 mol eq) and the resulting reaction mixture was stirred judged complete by TLC. The cooled reaction mixture was diluted with $CHCl_3$ and washed successively with 0.1 N HCl, sat. $NaHCO_3$ soln., brine, and dried ($MgSO_4$). Evaporation of the solvent gave the crude product as a1.3:1 mixture of *trans* and *cis* aziridines which were separated by flash chromatography (SiO_2, 2:1 hexanes/EtOAc) to give **4** in 48% yield; *Rf* 0.53 (5:1 hexanes-EtOAc); ^{1}H NMR (major conformer, $CDCl_3$) δ 7.30 (5 H, Ph), 5.74 (1 H), 4.95 (2 H), 4.12 (q, J=14.3 & 7.2 Hz, 2 H, OCH_2), 3.99 (d, J= 13.6 Hz, 1 H, 1/2 CH_2Ph), 3.89 (d, J=13.5 Hz, 1 H, 1/2 CH_2Ph), 2.48 (d, J=2.8 Hz, 1 H, H-2), 2.28 (1 H), 2.15-1.95 (2 H), 1.55-1.30 (4 H), 1.21 (t, J=7.1 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 191.4, 138.8, 128.4 (2C), 128.7, 127.6 (2C), 114.5, 61.02, 55.33, 47.36, 40.80, 33.67, 32.41, 28.52, 27.61, 15.40; IR ($CHCl_3$) cm^{-1} 2900 (m), 2240 (w), 1720 (s), 1450 (s), 1350 (m), 1180 (s), 900 (s); HRMS calcd for $C_{17}H_{23}NO_2$ (M^+) 273.1729, found 273.1730.

cis-1-benzyl-3-pent-4-enylaziridine-2-carboxylic acid ethyl ester (5). Yield 37%; *Rf* 0.42 (5:1 hexanes/etOAc); ^{1}H NMR ($CDCl_3$) δ 7.30 (5 H, Ph), 5.72 (1 H), 4.93 (2 H), 4.19 (q, J=14.3 & 7.1 Hz, 2 H, OCH_2), 3.58 (s, 2 H, CH_2Ph), 2.24 (d, J= 6.8 Hz, 1 H, H-2), 2.05-1.88 (3 H), 1.70-1.30 (4 H), 1.26 (t, J=7.1 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 169.8, 138.5, 137.9, 128.4, 127.3, 114.6, 63.98, 60.94, 46.54, 42.74, 33.36, 27.30, 26.68, 14.37; IR ($CHCl_3$) cm^{-1} 2900 (m), 2220 (w), 1730 (s), 1450 (s), 1370 (m), 1180 (s), 900 (s); HRMS calcd for $C_{17}H_{23}NO_2$ (M^+) 273.1729, found 273.1731.

[trans-1-Benzyl-3-pent-4-enyl-aziridin-2-yl][(3aR)-(3aα,7aβ)- 3H-3a,6-methano-2,1-benzisothiazolehexahydro-8,8-dimethyl-2,2-dioxo-1-yl] methanone (7a,b). To a stirring solution of sultam **6** (426 mg, 1.98 mmol) in benzene (3 mL) was added $AlMe_3$ (1.10 mL, 2.00 mmol, 20 % solution in toluene) at RT. After 30 min stirring, a solution of aziridine **4** (180 mg, 0.66 mmol) in benzene (1.00 mL) was added. The reaction mixture was stirred overnight at 85 °C, cooled in an ice-bath, diluted with benzene, and the $AlMe_3$ hydrolyzed by slow addition of 0.10 N HCl. The aluminum salts were removed by suction filtration and the organic phase was separated. The aqueous layer was extracted with $CHCl_3$ (2×5 mL) and the combined organic extracts were washed with sat. $NaHCO_3$ (5 mL) and brine (5 mL). The organic layer was dried ($MgSO_4$), concentrated, and purified by flash chromatography (SiO_2, 3:1 hexanes/EtOAc) to give the desired aziridines **7a** (126 mg, 43% yield) and **7b** (126 mg, 43%). Data for **7a**: *Rf* 0.59 (2:1 hexanes/EtOAc); mp=84-85 °C; $[\alpha]^{22}$D=+44.8° (c= 2.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.40-7.21 (5 H, Ph), 5.75 (1 H), 4.95 (2 H), 4.05 (d, J=14.2, Hz, 1 H, 1/2 CH_2SO_2), 3.93 (d, J==14.3 Hz, 1 H, 1/2 CH_2SO_2), 3.81 (dd, J= 7.7 & 4.4 Hz, 1 H, H-7a), 3.47 (d, J=13.8 Hz, 1 H, 1/2 CH_2Ph), 3.40 (d, J=13.8 Hz, 1 H, 1/2 CH_2Ph), 3.13 (d, J=2.6 Hz, 1 H, H-2), 2.40 (1 H, H-3), 2.10-1.20 (13 H), 0.91 (s, 3 H, CH_3), 0.84 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 167.5, 138.5, 138.2, 128.2 (2C), 127.8 (2C), 126.8, 114.7, 65.50, 55.07, 53.13, 48.27, 47.15, 4.83, 40.91, 38.48, 33.42, 33.34, 31.99, 26.99, 26.46, 26.15, 20.79, 19.87; IR ($CHCl_3$) cm^{-1} 3000 (s), 1680 (s), 1330 (s), 1260 (s), (1210 (s); HRMS calcd for $C_{25}H_{34}N_2O_3S$ (M^+) 442.2290, found 442.2292.

7b. *Rf* 0.50 (2:1 hexanes/EtOAc); $[\alpha]^{22}$D=+47.4° (c=2.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.40-7.22, (5 H, Ph), 5.70 (1 H), 4.90 (2 H), 3.93 (d, J=13.1 Hz, 1 H, 1/2 CH_2Ph), 3.92 (dd, J=7.0 & 5.0 Hz, 1 H, H-7a), 3.54 (d, J=13.7, Hz, 1 H, 1/2 CH_2SO_2), 3.52 (d, J=13.1 Hz, 1 H, 1/2 CH_2Ph), 3.44 (d, J=13.7 Hz

1 H, 1/2 CH_2SO_2), 3.12 (1 H, H-2), 2.41 (1 H, H-3), 2.10 (2 H), 1.91 (4 H), 1.60-1.20 (6 H), 1.19 (s, 3 H, CH_3), 0.98 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 167.4, 139.2, 138.5, 128.5 (2C), 128.3 (2C), 127.1, 114.6, 65.42, 55.48, 53.18, 48.51, 47.83, 47.48, 44.87, 41.72, 38.55, 33.19, 32.99, 31.88, 26.45, 26.19, 21.06, 19.94; IR ($CHCl_3$) cm^{-1} 3000 (s), 1680 (s), 1330 (s), 1260 (s), 1210 (s); HRMS calcd for $C_{25}H_{34}N_2O_3S$ (M^+) 442.2290, found 442.2293.

cis-1-Benzyl-3-pent-4-enyl-aziridin-2-yl][3aR)-(3aα,6α,7a β)-3H-3a,6-methano-2,1-benzi sothiazolehexahydro-8,8-dimethyl-2,2-dioxo -1-yl]methanone (8a,b). Following an analogous procedure as that used for the synthesis of aziridines **7a&b, 8a&b** were obtained as a 1/1 mixture and separated by flash chromatography (SiO_2, 3:1 hexanes/EtOAc) to give **8a** in 43% yield; *Rf* 0.72 (2:1 hexanes/EtOAc); mp=120-121°C; $[\alpha]^{22}$D=-16.4°(c=0.80, $CHCl_3$); ^{1}H NMR ($CDCl_3$)δ 7.30 (5 H, Ph), 5.70 (1 H), 4.88 (2 H), 3.87 (dd, J=7.0& 5.1 Hz, 1 H, H-7a), 3.86 (d, J=13.1 Hz, 1 H, 1/2 CH_2Ph), 3.52 (d, J=13.7, Hz, 1 H, 1/2 CH_2SO_2), 3.42 (d, J=13.8 Hz 1 H, 1/2 CH_2SO_2), 3.34 (d, J=13.2 Hz, 1 H, 1/2 CH_2Ph), 2.91 (d, J=6.7 Hz, 1 H, H-2), 2.11 (2 H), 1.90 (5 H), 1.70-1.50 (2 H), 1.45-1.20 (5 H), 1.16 (s, 3 H, CH_3), 0.97 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$)δ 167.8, 138.7, 138.1 (2 C), 128.4 (2C), 128.3 (2C), 127.3, 114.4, 65.36, 64.16, 53.17, 48.78, 47.88, 44.70, 43.55, 38.48, 33.37, 32.84, 26.90, 26.52, 20.90, 19.94; IR ($CHCl_3$) cm^{-1} 3000 (s), 1720 (s), 1450 (m), 1350 (s), 1280 (s), 1230 (s), 1150 (s), 1080 (m); HRMS calcd for $C_{25}H_{34}N_2O_3S$ (M^+) 442.2290, found 442.2265.

8b. 43% yield; *Rf* 0.59 (2:1 hexanes/EtOAc); $[\alpha]$ ^{22}D=+131.2° (c=0.60, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.30 (5 H, Ph), 5.70 (1 H), 4.88 (2 H), 3.91 (t, J=5.6 Hz, 1 H, H-7a), 3.72 (d, J=13.3 Hz, 1 H, 1/2 CH_2Ph), 3.50 (d, J=13.7, Hz, 1 H, 1/2 CH_2SO_2), 3.49 (d, J=13.3 Hz, 1 H, 1/2 CH_2Ph), 3.45 (d, J=13.7 Hz 1 H, 1/2 CH_2SO_2), 2.94 (d, J=6.8 Hz, 1 H, H-2), 2.12-1.82 (7 H), 1.62-1.20 (7 H), 1.12 (s, 3 H, CH_3), 0.96 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 167.2, 138.4, 137.9, 128.3 (2 C), 127.2 (2C), 114.6, 65.52, 63.85, 53.10, 48.82, 47.82, 47.59, 44.69, 44.07, 38.59, 33.45, 32.92, 27.42, 26.68, 26.42, 20.87, 19.94; IR ($CHCl_3$) cm^{-1} 3000 (s), 1720 (s), 1450 (m), 1350 (s), 1280 (s), 1230 (s), 1150 (s), 1080 (m); HRMS calcd for $C_{25}H_{34}N_2O_3S$ (M^+) 442.2290, found 442.2276.

[(2R, 3aS, 6aS)-1-Benzyloctahydrocyclopenta[b]-pyrrol-2-yl][(3aR)-(3aα, 6α, 7aβ)-3H-3a,6-methano-2,1-benzisothiazolehexahydro-8,8-dimethyl-2,2- dioxo-1-yl]methanone (9). Starting aziridine **(7a, 7b, 8c,** or **8b)** was dissolved in toluene (concentration ~0.3 M) in a Pyrex tube (1.5 mm thickness, 5×1.5 cm outside diameter), frozen at -78°C, degassed three times and sealed from the open-end using a toch. The sealed tube was warmed up to RT and heated for 3 h with an oil bath which was initially set to 190-195 °C. The solution was cooled, concentrated and purified by flash chromatography (SiO_2, 5:1 hexanes/EtOAc); 72% yield (ds=3:1); *Rf* 0.61 (2:1 hexanes-EtOAc, char A or B); mp: 145-146°C; $[\alpha]^{22}$D=+147° (c=0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.30 (5 H, Ph), 5.70 (1 H), 4.88 (2 H), 3.87 (dd, J=7.0 & 5.1 Hz, 1 H, H-7a), 3.86 (d, J=13.1 Hz, 1 H, 1/2 CH_2Ph), 3.52 (d, J=13.7, Hz, 1 H, 1/2 CH_2SO_2), 3.42 (d, J=13.8 Hz 1 H, 1/2 CH_2SO_2), 3.34 (d, J=13.2 Hz, 1 H, 1/2 CH_2Ph), 2.91 (d, J=6.7 Hz, 1 H, H-2), 2.11 (2 H), 1.90 (5 H), 1.70-1.50 (2 H), 1.45-1.20 (5 H), 1.16 (s, 3 H, CH_3), 0.97 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 174.0, 140.2, 128.8 (2C), 128.1 (2C), 126.7, 68.33, 65.39, 64.77, 53.78, 52.88, 48.70, 44.77, 44.63, 40.97, 38.41, 37.44, 33.05, 32.77, 32.22, 24.05, 20.85, 19.92; IR ($CHCl_3$) cm^{-1} 3010 (m), 2950 (w), 1710 (s), 1330 (s), 1260 (m), 1200 (s), 1160 (m); HRMS calcd for $C_{14}H_{18}NO$ ([M-$C_{11}H_{16}NO_3S$]$^+$]200.1439, found 200.1445.

(2R, 3aS, 6aS)-Octahydrocyclopenta[b]pyrrole-2-carboxylic acid (10). A solution of **9** (130 mg, 0.29 mmol) in MeOH (2 mL) was stirred at RT in the presence of 10% Pd-C (130 mg) under a H_2-atmosphere. The reaction mixture was stirred at this temperature until judged complete by TLC (usually 2 h), filtered through a pad of celite, and the filtrate concentrated to give crude debenzylated product in

quantitative yield. This crude product **9** was dissolved in THF (concentration approx. 0.2 M) and added to a stirring solution of 2 eq. BnSH and 1.5 eq. n-BuLi (2.5 M in hexanes) at 0°C. After confirming by TLC that the starting material was consumed, the reaction mixture was diluted with ether and quenched with 1 N HCI soln. The organic phase was separated and the aqueous layer was extracted with $3 \times$ EtOAc. The solids obtained from the water layer were dissolved in a minimum of water and loaded onto an ion-exchange column containing 2 g (wet weight) of Bio Rad Ag-1-X2 anion exchange resin. The column was washed with five bad volumes of water, and the crude product was eluted with 1% aqueous acetic acid. The ninhydrin (char B) active fractions were collected and freeze-dried to afford bicyclic amino acid **10** in 74% yield (35 mg, 0.21 mmol); mp=117-119°C; $[\alpha]^{24}$D=+35.2° (c=0.25, H_2O) [lit.[11] mp=120°, $[\alpha]^{29}$D=+47.2° (c=0.4, H_2O); ^{1} H NMR (D_2O) δ 4.05 (ddd J=3.4 & 7.7 Hz, 1 H, H-3), 3.92 (t, J=7.7 Hz, 1 H-2), 2.70 (1 H), 2.08 (1 H), 1.90-1.30 (7 H) these data were the same as in the literature; HRMS calcd for $C_7H_{12}N$ ([M-COOH]$^+$) 110.0970, found 110.0966. To recover sultam **6** the combined organic layers were dried ($MgSO_4$), concentrated, and purified by flash chromatography (SiO_2, 2:1 hexanes/EtOAc) to give 78% of **6** (49 mg, 0.23 mmol).

Acknowledgment

This work was supported by the National Institute of General Medical Science and the Turkish of Education (doctoral fellowship to Ö.D.).

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