Supplementary Material (ESI) for Organic and Biomolecular Chemistry

Reactivity and selectivity in the inhibition of elastase by 3-oxo-β-sultams and in their hydrolysis

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Supplementary information

Synthesis

Benzyl 2'-(4,4-dimethyl-1,1-dioxido-3-oxo-1,2-thiazetidin-2-yl) phenylacetate (S3)
2-(Chlorosulfonyl)-2-methylpropionyl chloride **(S2)** (1 g, 4.88 mmol) was dissolved in dry ether (200 ml) and the mixture was cooled to –78 ^{o}C. A solution of DL-phenyl glycine benzyl ester (1.18 g, 4.87 mmol) in ether (10ml) was added dropwise over 30 minutes at –78^{o}C with stirring. The mixture was stirred for 10 minutes before triethylamine (1.35 ml, 14.7 mmol) in ether (10 ml) was added at –78^{o}C. The reaction mixture was filtered (to remove $Et_3N.HCl$) and the solvent was removed using reduced pressure rotary evaporation at 30 ^{o}C to yield a yellow oil, which was purified twice by column chromatography. 1st purification: 3:2 hexane : EtOAc. 2nd purification: 7:3 $CHCl_3$: ether. A white solid (0.98 g, 54 %), m.p. 84 – 85 ^{o}C was obtained. IR ν_{max} (cm^{-1}) (Neat) 3385, 1777, 1748, 1690, 1498, 1456, 1344, 1306, 1246, 1207, 1183, 1123. ^{1}H NMR: δ ($CDCl_3$): 7.48 – 7.42 (5H, m, **Ph**), 7.34 – 7.26 (5H, m, **Ph**), 5.6 (1H, s, **CH**), 5.2 (2H, s, **CH_2**), 1.69 (3H, s, **CH_3**), 1.68 (3H, s, **CH_3**). ^{13}C NMR: δ ($CDCl_3$): 166.43 (**C=O**), 164.52 (**C=O**), 134.5 (quaternary carbon), 133.19 (quaternary carbon), 129.69 (**CH** (Ph)), 129.21 (**CH** (Ph)), 128.61 (**CH** (Ph)), 128.55 (**CH** (Ph)), 128.44 (**CH** (Ph)), 128.34 (**CH** (Ph)), 83.07 (quaternary carbon), 68.32 (**CH_2**), 61.02 (**CH**), 18.48 (**CH_3**), 18.31 (**CH_3**).

(DL)-2'-(4,4-Dimethyl-1,1-dioxido-3-oxo-1,2-thiazetidin-2-yl) phenylacetic acid (9)
Palladium (0.1 g, 10% Pd/C) was added to dry ethyl acetate (2 ml) and then to a solution of benzyl (DL)-2'-(4,4-dimethyl-1,1-dioxido-3-oxo-1,2-thiazetidin-2-yl) phenyl acetate **(S3)** (0.1 g, 0.268 mmol) in dry ethyl acetate (11 ml). The reaction vessel was flushed with nitrogen for 2 minutes followed by hydrogen for 1 minute. The solution was hydrogenated at atmospheric pressure for 2 hours before filtering through celite. The solvent was removed by reduced pressure rotary evaporation at 30 ^{o}C to yield a white solid (74 mg, 98 %) m.p.195-197 ^{o}C (decomposes to a dark oil). IR ν_{max} (cm^{-1}) ($CHCl_3$) 3020, 2956, 1776, 1732, 1354, 1337, 1216, 1181, 1124. ^{1}H NMR: δ ($CDCl_3$): 7.47 – 7.37 (5H, m, **Ph**), 5.76 (1H, s, **CH**), 1.62 (3H, s, **CH_3**), 1.58 (3H, s, **CH_3**). ^{13}C NMR: δ ($CDCl_3$): 167.98 (**C=O**), 164.58 (**C=O**), 134.3 (quaternary carbon), 129.06 (**CH** (Ph)), 128.84 (**CH** (Ph)), 128.45 (**CH** (Ph)), 82.71 (quaternary carbon), 60.15 (**CH**), 17.8 (**CH_3**), 17.68 (**CH_3**). HREI-MS $[M+NH_4]^+$ for $C_{12}H_{13}NO_5S$ calc. 301.0853 measured 301.0855.

(L)-Benzyl 2'-(4,4-dimethyl-1,1-dioxido-3-oxo-1,2-thiazetidin-2-yl)-3'-methylbutanoate (S4)
2-(Chlorosulfonyl)-2-methylpropionyl chloride **(S2)** (1 g, 4.88 mmol) was dissolved in dry ether (150 ml,) and stirred at –78^{o}C. A solution of L-valine benzyl ester (1 g, 4.85 mmol) in ether (10 ml) was added dropwise over 30 minutes at –78 ^{o}C. After 10 minutes of stirring at -78^{o}C, triethylamine (2 ml, 14.63 mmol) in ether (10ml) was added dropwise over 10 minutes to the mixture. The reaction mixture was stirred at -78^{o}C for 1 hour and for a further 5 hours at ambient temperature, before the mixture was filtered (to remove $Et_3N.HCl$) and the solvent was removed using reduced pressure rotary evaporation at 30^{o}C to yield a yellow oil, which was purified by column chromatography (50g silica) (3:2 hexane : EtOAc R_f = 0.46) to yield a white solid (0.63 g, 38 %), m.p. 39-40^{o}C. IR ν_{max} (cm^{-1}) ($CHCl_3$) 3065, 3032, 2969, 2936, 2880, 1773, 1744, 1456, 1343, 1298, 1270, 1182, 1122. ^{1}H NMR: δ ($CDCl_3$): 7.39 – 7.36 (5H, m, **Ph**), 5.22 (2H, d, J 2.2, **CH_2**Ph), 4.26 (1H, d, J 7.3, N**CH**CO), 2.52 (1H, oct, J 6.8, CH_3**CH**CH_3) 1.69 (3H, s, **CH_3**CSO_2), 1.68 (3H, s, **CH_3**CSO_2), 1.06 (3H, d, J 6.7, **CH_3**$CHCH_3$), 1.01 (3H, d, J 6.8, CH_3CH**CH_3**). ^{13}C NMR: δ ($CDCl_3$): 166.99 (**C=O**), 164.83 (**C=O**), 134.65 (quaternary carbon), 128.69 (**CH** (Ph)), 128.64 (**CH** (Ph)), 128.58 (**CH** (Ph)), 82.62 (quaternary carbon), 67.9 (**CH_2**), 62.93 (N**CH**CO), 29.64 (CH_3**CH**CH_3), 18.92 (**CH_3**CSO_2), 18.92 (**CH_3**CSO_2) 18.6 (**CH_3**$CHCH_3$), 17.41 (CH_3CH**CH_3**). HREI-MS $[M+NH_4]^+$ for $C_{16}H_{21}NO_5S$ calc. 357.1479 measured 357.1482.

(L)-2'-(4,4-Dimethyl-1,1-dioxido-3-oxo-1,2-thiazetidin-2-yl)-3'-methylbutanoic acid (7)
Palladium (0.1 g, 10% Pd/C) was added to dry ethyl acetate (5 ml) and then to a solution of (L)-benzyl 2'-(4,4-dimethyl-1,1-dioxido-3-oxo-1,2-thiazetidin-2-yl)-3'-methylbutanoate **(S4)** (0.1 g, 0.295 mmol) in dry ethyl acetate (10 ml). The reaction vessel was flushed with nitrogen for 2 minutes followed by hydrogen for 1 minute. The solution was hydrogenated at atmospheric pressure for 2.5 hours before filtering through

celite. The solvent was removed by reduced pressure rotary evaporation at 30°C to yield a white solid (70 mg, 95 %). m.p. 102-104 °C. IR ν_{max} (cm^{-1}) ($CHCl_3$) 3021, 2974 (broad OH), 1776, 1726, 1346, 1216, 1185, 1123. ^{1}H NMR: δ ($CDCl_3$): 4.29 (1H, d, J 6.8, **CH**CO), 2.56 (1H, oct., J 6.8, CH_3**CH**CH_3), 1.76 (3H, s, **CH$_3$**CSO_2), 1.75 (3H, s, **CH$_3$**CSO_2), 1.13 (3H, d, J 6.8, **CH$_3$**$CHCH_3$), 1.11 (3H, d, J 6.9, CH_3CH**CH$_3$**). ^{13}C NMR: δ ($CDCl_3$): 167.56 (**C=O**), 164.85 (**C=O**), 82.75 (quaternary carbon), 62.57 (**CH**CO), 29.44 (CH_3**CH**CH_3), 19.24 (**CH$_3$**CSO_2), 18.95 (**CH$_3$**CSO_2), 18.65 (**CH$_3$**CH CH_3), 18.54 (CH_3CH**CH$_3$**). HREI-MS $[M+NH_4]^+$ for $C_9H_{15}NO_5S$ calc. 267.1009 measured 267.1012.

(D)-Benzyl 2'-(4,4-dimethyl-1,1-dioxido-3-oxo-1,2-thiazetidin-2-yl)-3'-methylbutanoate (S5)
S5 was synthesized by following the same procedure as that for **S4** except that the reaction was carried out using a more dilute 2-(chlorosulfonyl)-2-methylpropionyl chloride **(S2)** solution (1 g in 225 ml of ether), to give 0.51 g, 30 %. The analytical data for **S5** follows: m.p. 45-47 °C. IR ν_{max} (cm^{-1}) ($CHCl_3$) 3019, 2971, 2938, 1777, 1747, 1457, 1342, 1298, 1265, 1184, 1123. ^{1}H NMR: δ ($CDCl_3$): 7.41 – 7.36 (5H, m, **Ph**), 5.24 (2H, d, J 2.0, **CH$_2$**Ph), 4.29 (1H, d, J 7.1, N**CH**CO), 2.55 (1H, oct, J 6.8, CH_3**CH**CH_3) 1.72 (3H, s, **CH$_3$**CSO_2), 1.71 (3H, s, **CH$_3$**CSO_2), 1.09 (3H, d, J 6.8, **CH$_3$**$CHCH_3$), 1.03 (3H, d, J 6.9, CH_3CH**CH$_3$**). ^{13}C NMR: δ ($CDCl_3$): 166.99 (**C=O**), 164.83 (**C=O**), 134.64 (quaternary carbon), 128.69 (**CH** (Ph)), 128.64 (**CH** (Ph)), 128.58 (**CH** (Ph)), 82.62 (quaternary carbon), 67.91 (**CH$_2$**), 62.94 (N**CH**CO), 29.64 (CH_3**CH**CH_3), 19.14 (**CH$_3$**CSO_2), 18.92 (**CH$_3$CSO$_2$**) 18.61 (**CH$_3$**$CHCH_3$), 18.41 (CH_3CH**CH$_3$**).

(D)-2'-(4,4-Dimethyl-1,1-dioxido-3-oxo-1,2-thiazetidin-2-yl)-3'-methylbutanoic acid (8)
8 was synthesized by following the same procedure for **7** to give 71.2 mg, 97 %. The analytical data for **8** follows: m.p. 109-110 °C. IR ν_{max} (cm^{-1}) ($CHCl_3$) 3020, 2973, 2938, 1774, 1726, 1402, 1393, 1345, 1299, 1266, 1215, 1185, 1123. ^{1}H NMR: δ ($CDCl_3$): 8.0 (1H, bs, **OH**), 4.32 (1H, d, J 6.8, **CH**CO), 2.58 (1H, oct., J 6.9, CH_3**CH**CH_3), 1.79 (3H, s, **CH$_3$**CSO_2), 1.78 (3H, s, **CH$_3$**CSO_2), 1.16 (3H, d, J 6.8, **CH$_3$**$CHCH_3$), 1.13 (3H, d, J 6.9, CH_3CH**CH$_3$**). ^{13}C NMR: δ ($CDCl_3$): 167.52 (**C=O**), 164.9 (**C=O**), 82.80 (quaternary carbon), 62.61 (**CH**CO), 29.46 (CH_3**CH**CH_3), 19.24 (**CH$_3$**CSO_2), 18.97 (**CH$_3$**CSO_2), 18.66 (**CH$_3$**$CHCH_3$), 18.54 (CH_3CH**CH$_3$**). HREI-MS [M-H] for $C_9H_{15}NO_5S$ calc. 248.0598 measured 248.0596.

(L)-Benzyl 2'-(4,4-dimethyl-1,1-dioxido-3-oxo-1,2-thiazetidin-2-yl)-4'-methylpentanoate (S6)
2-(Chlorosulfonyl)-2-methylpropionyl chloride **(S2)** (1 g, 4.88 mmol) was dissolved in dry ether (200 ml) and stirred at –78 °C. A solution of L-leucine benzyl ester (1.07 g, 4.83 mmol) in ether (10 ml) was added dropwise over 30 minutes at –78 °C. After 10 minutes of stirring at -78 °C, triethylamine (2 ml, 14.63 mmol) in ether (10 ml) was added dropwise over 10 minutes to the mixture. The reaction mixture was stirred at -78 °C for 1 hour and for a further 7 hours at ambient temperature, before the mixture was filtered (to remove $Et_3N.HCl$) and the solvent was removed using reduced pressure rotary evaporation at 30 °C to yield a yellow oil, which was purified by column chromatography. (55 g silica) (1:8:1 ether : hexane : EtOAc R_f = 0.27) to yield a white solid (0.65 g, 38 %), m.p. 52-53 °C. IR ν_{max} (cm^{-1}) ($CHCl_3$) 3032, 2963, 2874, 1778, 1747, 1457, 1391, 1342, 1310, 1216, 1185, 1123. ^{1}H NMR: δ ($CDCl_3$): 7.42 – 7.35 (5H, m, **Ph**), 5.23 (2H, s, **CH$_2$**Ph), 4.46 (1H, dd, J 4.8 and 10.7, N**CH**CO), 2.08 (1H, m, CH_3**CH**CH_3) 1.82 (2H, m, CH**CH$_2$**CH), 1.71 (3H, s, **CH$_3$**CSO_2), 1.69 (3H, s, **CH$_3$**CSO_2), 1.0 (3H, d, J 12.1, **CH$_3$**$CHCH_3$), 0.97 (3H, d, J 12.2, CH_3CH**CH$_3$**). ^{13}C NMR: δ ($CDCl_3$): 167.97 (**C=O**), 164.58 (**C=O**), 134.67 (quaternary carbon), 128.6 (**CH** (Ph)), 128.51 (**CH** (Ph)), 128.45 (**CH** (Ph)), 83.12 (quaternary carbon), 68.1 (**CH$_2$Ph**), 54.73 (N**CH**CO), 37.78 (CH**CH$_2$**CH), 25.08 (CH_3**CH**CH_3), 22.59 (**CH$_3$**CSO_2), 21.07 (**CH$_3$**CCO) 18.34 (**CH$_3$**$CHCH_3$), 18.30 (CH_3CH**CH$_3$**).

(L)-2'-(4,4-Dimethyl-1,1-dioxido-3-oxo-1,2-thiazetidin-2-yl)-4'-methylpentanoic acid (10)
Palladium (0.1 g, 10% Pd/C) was added to dry ethyl acetate (2 ml) which was then added to a solution of (L)-benzyl 2'-(4,4-dimethyl-1,1-dioxido-3-oxo-1,2-thiazetidin-2-yl)-4'-methylpentanoate **(S6)** (0.1 g, 0.283 mmol) in dry ethyl acetate (12 ml). The reaction vessel was flushed with nitrogen for 2 minutes followed by hydrogen for 1 minute. The solution was hydrogenated at atmospheric pressure for 2.5 hours before filtering through celite. The solvent was removed by reduced pressure rotary evaporation 30 °C to yield a white solid (64.4 mgs, 86 %), m.p. 110-111 °C. IR ν_{max} (cm^{-1}) ($CHCl_3$) 3417, 3020, 2963, 1779, 1727, 1460, 1392, 1342, 1216, 1186, 1122. ^{1}H NMR: δ ($CDCl_3$): 4.47 (1H, dd, J 4.4 and 10.7, N**CH**CO), 2.15 (1H, m, CH_3**CH**CH_3) 1.87 (2H, m, CH**CH$_2$**CH), 1.79 (3H, s, **CH$_3$**CSO_2), 1.78 (3H, s, **CH$_3$**CCO), 1.03 (3H, d, J 9.2, **CH$_3$**$CHCH_3$), 1.02 (3H, d, J 9.2, CH_3CH**CH$_3$**). ^{13}C NMR: δ ($CDCl_3$): 172.4 (**C=O**), 164.63 (**C=O**), 83.32 (quaternary carbon), 54.31 (N**CH**CO), 37.69 (CH**CH$_2$**CH), 25.17 (CH_3**CH**CH_3), 22.6 (**CH$_3$**CSO_2), 21.06 (**CH$_3$**CCO) 18.47 (**CH$_3$**$CHCH_3$), 18.44 (CH_3CH**CH$_3$**). HREI-MS [M-H] for $C_{10}H_{17}NO_5S$ calc. 262.0755 measured 262.0759.

Sodium 2-ethylbutanoate (S7)
2-Ethylbutanoic acid (10 ml, 86.1 mmol) was added dropwise to a solution of sodium ethoxide in ethanol, prepared by reacting sodium (1.98 g, 86.2 mmol) with ethanol (32 ml) at room temperature. The reaction mixture was stirred for 1 hour before the solvent was removed by reduced pressure rotary evaporation at 50 ^{o}C. The residue was washed with toluene (2 x 10 ml) to yield a white solid (10.34 g, 85 %). IR ν_{max} (cm^{-1}) ($CHCl_3$) 3019, 2963, 2934, 1558, 1464, 1417, 1216. ^{1}H NMR: δ ($CDCl_3$): 4.7 (H_2O), 1.94 (1H, quintet, J 7.3, **CH**), 1.33 (4H, dq, J 7.4, **CH_2 x2**), 0.75 (6H, t, J 7.4, **CH_3 x2**). ^{13}C NMR: δ ($CDCl_3$): 186.78 (**C=O**), 53.39 (**CH**), 26.18 (**CH_2**), 12.14 (**CH_3**).

2-Ethylbutanoic anhydride (S8)
Sodium 2-ethylbutanoate **(S7)** (5 g, 36.4 mmol) was added to toluene (25 ml) at room temperature. To the solution, 2-ethylbutanoyl chloride (5.53 ml, 38.8 mmol) was added dropwise over 15 minutes, during which an exotherm was observed and the temperature rose to 40 ^{o}C. The mixture was heated at reflux for 1.25 hours, and allowed to cool to room temperature. Ice (20 g) was added to the reaction mixture which was stirred until the ice was melted. The two layers were separated and the organic layer was dried over sodium sulfate, the solvent was removed by reduced pressure rotary evaporation to yield an oily residue, which was purified by vacuum distillation to give the desired anhydride (2.33 g, 60 %), b.p. 85 – 86 ^{o}C at 0.7 mbar Hg. IR ν_{max} (cm^{-1}) 2967, 2880, 1810, 1744, 1461, 1008. ^{1}H NMR: δ ($CDCl_3$): 2.34 (1H, t, J 5.6, **CH**), 2.32 (2H, t, J 5.6, **CH x2**), 2.30 (1H, t, J 5.6, **CH**), 1.71 (2H, dq, J 7.6 and 14.0, **CH_2**), 1.70 (2H, dq, J 7.6 and 14.1, **CH_2**), 1.60 (2H, dq, J 7.6 and 14.4, **CH_2**), 1.59 (2H, dq, J 7.5 and 15.4, **CH_2**), 0.98 (12H, t, J 7.5, **CH_3 x4**). ^{13}C NMR: δ ($CDCl_3$): 171 (**C=O**), 49.2 (**CH**), 24.3 (**CH_2**), 11.5 (**CH_3**).

Disodium 2-ethyl-2-sulfonatobutanoate (S9)
Concentrated H_2SO_4 (2.7 g, 27.5 mmol) was added dropwise to 2-ethylbutanoic anhydride **(S8)** (10 ml, 46.7 mmol) and the solution stirred for 30 minutes at 20-35 ^{o}C. The reaction mixture was gently heated to 90 ^{o}C and stirred for approximately 7 hours. The hot reaction mixture was poured into ice-cold water and then extracted with ether (3 x 20 ml). (Ether extracts contain the diethyl butyric acid from the sulfonation). To the aqueous phase, a solution of NaOH (3.00 g) in water (10 ml) was added in small portions to adjust the pH to around pH 8. The solution was evaporated to dryness using reduced pressure rotary evaporation at 40 ^{o}C. The residue was dissolved in hot water (10 ml) and precipitated by the addition of ethanol (30 ml) and the resulting precipitate isolated by vacuum filtration. A second crop was isolated by adding ethanol to the mother liquor. The product isolated (6.44 g, 57 %) was carried through to the next step without any purification. IR ν_{max} (cm^{-1})(nujol) 2923, 2853, 1580, 1457, 1387, 1240, 1162, 1037. ^{1}H NMR: δ (D_2O): 1.91 (4H, q, J 7.4, **CH_2**), 1.90 (4H, q, J 7.4, **CH_2**), 0.89 (6H, t, J 7.49, **CH_3 x2**). ^{13}C NMR: δ ($CDCl_3$): 176.59 (**C=O**), 74.17 (quaternary carbon), 25.73 (**CH_2**), 9.41 (**CH_3**).

2-(Chlorosulfonyl)-2-ethylbutanoyl chloride (S10)
Disodium 2-ethyl-2-sulfonatobutanoate **(S9)** (5.0 g, 20.8 mmol) was added to thionyl chloride (18.5 ml, 153 mmol) in small portions over 10 minutes at 0 ^{o}C with stirring. DMF (0.34 ml) was added dropwise over 2 minutes and the mixture was heated to 70 ^{o}C. After gas production was complete the mixture was heated for a further 5 hours at 70 ^{o}C. Excess thionyl chloride was evaporated using reduced pressure rotary evaporation at 40 ^{o}C, yielding a pale yellow residue, which was dissolved in ether. The resultant NaCl was filtered and the solvent was removed by reduced pressure rotary evaporation at 30 ^{o}C to yield a yellow oil (3.13 g, 81 %). IR ν_{max} (cm^{-1}) 2984, 2950, 2890 1792, 1459, 1376, 1175, 974, 813. ^{1}H NMR: δ ($CDCl_3$): 2.47 (4H, q, J 7.4, **CH_2 x2**), 1.21 (6H, t, J 7.4, **CH_3 x2**). ^{13}C NMR: δ ($CDCl_3$): 169.07 (**C=O**), 94.11 (quaternary carbon), 26.99 (**CH_2**), 8.81 (**CH_3**).

4,4-Diethyl-1,2-thiazetidin-3-one-1,1-dioxide (S11)
2-(Chlorosulfonyl)-2-ethylbutanoyl chloride **(S10)** (0.7 g, 3.0 mmol) was dissolved in ether (10 ml) and added dropwise over 10 minutes (VERY SLOWLY) to liquid NH_3 (3.74 ml) in ether (10 ml) at –78^{o}C. The mixture was warmed to room temperature and stirred until all the solvent had evaporated. The residue was dissolved in $CHCl_3$ (5 ml) and water (5 ml) at 0-4 ^{o}C, and the pH of the solution was adjusted to pH 1 using dilute HCl. The aqueous layer was extracted into $CHCl_3$ (3 x 5 ml). The organic layers were combined and dried over sodium sulfate, and the solvent was removed by reduced pressure rotary evaporation at 30^{o}C to yield a white solid (0.40 g, 65 %) m.p. 53-55^{o}C. IR ν_{max} (cm^{-1}) 3261, 2980, 1773, 1458, 1341, 1233, 1145, 1110. ^{1}H NMR: δ ($CDCl_3$): 8.6 (1H, bs, **N-H**), 2.21 (4H, q, J 7.4, **CH_2 x2**), 1.16 (6H, t, J 7.5, **CH_3 x2**). ^{13}C NMR: δ ($CDCl_3$): 163.58 (**C=O**), 89.75 (quaternary carbon), 22.58 (**CH_2**), 8.21 (**CH_3**). HREI-MS $[M-H]^+$ for $C_6H_{11}NO_3S$ calc. 176.0376 measured 176.0378.

2-Benzyl-4,4-diethyl-1,2-thiazetidin-3-one 1,1-dioxide (5)

At 0 ^{o}C under an atmosphere of dry nitrogen, 4,4-diethyl-3-oxo-β-sultam **(S11)** (0.36 g, 2.05 mmol) in anhydrous THF (10 ml) was added to a suspension of sodium hydride (0.05 g, 2.08 mmol) (pre-washed 2-3 times with petroleum ether) in DMF (10 ml). The mixture was stirred for 15 minutes and benzyl bromide (0.35 g, 2.046 mmol) was injected through a septum dropwise over 5 minutes. The mixture was allowed to warm to room temperature and was stirred for 24 hours. The mixture was cooled to 0 ^{o}C, ether (10 ml) and brine (10 ml) were added to the solution, and the pH was adjusted to 4-5 using dilute HCl. The organic layer was separated and the aqueous layer was extracted with ether (2 x 10 ml). The organic layers were combined, washed with brine (2 x 10 ml) and dried over Na_2SO_4. The solvent was removed by rotary evaporation at 30 ^{o}C. The product was purified using column chromatography (1:8:1, EtOAc: hexane: ether, R_f 0.43), (0.26 g 48 %). m.p. 58-59 ^{o}C. IR ν_{max} (cm^{-1}) 2977, 2944, 1770, 1497, 1456, 1339, 1167, 1111. ^{1}H NMR: δ ($CDCl_3$): 7.41 – 7.34 (5H, m, **Ph**), 4.6 (2H, s, **CH_2**Ph), 2.15 (4H, dq, J 3.0 and 15.0, **CH_2 x2**), 1.15 (6H, t, J 7.5 **CH_3 x2**). ^{13}C NMR: δ ($CDCl_3$): 164.12 (**C=O**), 133.89 (quaternary carbon), 129.37 (**CH** (Ph)), 128.88 (**CH** (Ph)), 128.53 (**CH** (Ph)), 91.05 (quaternary carbon), 44.59 (**CH_2**Ph), 23.07 (**CH_2**CH_3), 8.85 (CH_2**CH_3**).

(D)-Benzyl 2'-(4,4-diethyl-1,1-dioxido-3-oxo-1,2-thiazetidin-2-yl)-3'-methylbutanoate (S12)

2-(Chlorosulfonyl)-2-ethylbutanoyl chloride **(S10)** (1 g, 4.33 mmol) was dissolved in dry ether (200 ml) and stirred at –78 ^{o}C. A solution of D-valine benzyl ester (1 g, 4.29 mmol) in ether (20 ml) was added dropwise over 30 minutes at –78 ^{o}C. After 10 minutes of stirring at -78 ^{o}C, triethylamine (1.81 ml, 12.95 mmol) in ether (20 ml) was added dropwise over 10 minutes to the mixture. The reaction mixture was stirred at -78 ^{o}C for 1 hour and overnight at ambient temperature, before the mixture was filtered (to remove Et_3N.HCl) and the solvent was removed using reduced pressure rotary evaporation at 30 ^{o}C to yield a yellow oil, which was purified by column chromatography. (55 g silica) (1:8:1 ether : hexane : EtOAc R_f = 0.29) to yield a colourless oil (0.5 g, 31 %). IR ν_{max} (cm^{-1}) ($CHCl_3$) 3032, 2976, 2944, 1774, 1744, 1458, 1342, 1297, 1242, 1170. ^{1}H NMR: δ ($CDCl_3$): 7.41 – 7.35 (5H, m, **Ph**), 5.24 (2H, s, **CH_2**Ph), 4.28 (1H, d, J 7.28, N**CH**CO), 2.55 (1H, oct, J 6.88, CH_3**CH**CH_3), 2.13 (4H, m, **CH_2** (ethyl)) 1.12 (3H, t, J 7.45, **CH_3** (ethyl)), 1.11 (3H, t, J 7.45, **CH_3** (ethyl)), 1.09 (3H, d, J 6.9, **CH_3**$CHCH_3$), 1.03 (3H, d, J 6.87, CH_3CH**CH_3**). ^{13}C NMR: δ ($CDCl_3$): 167.06 (**C=O**), 164.01 (**C=O**), 134.89 (quaternary carbon), 128.73 (**CH** (Ph)), 128.61 (**CH** (Ph)), 128.57 (**CH** (Ph)), 90.08 (quaternary carbon), 67.87 (**CH_2**Ph), 62.67 (N**CH**CO), 29.42 (CH_3**CH**CH_3), 22.76 (**CH_2** (ethyl)), 22.59 (**CH_2** (ethyl)), 19.23 (**CH_3**$CHCH_3$), 18.96 (CH_3CH**CH_3**), 8.42 (**CH_3** (ethyl)), 8.39 (**CH_3** (ethyl)).

(D)-2'-(4,4-Diethyl-1,1-dioxido-3-oxo-1,2-thiazetidin-2-yl)-3'-methylbutanoic acid (11)

Palladium (0.1 g, 10% Pd/C) was added to dry ethyl acetate (2 ml) and was added to a solution of benzyl (D)-benzyl 2'-(4,4-diethyl-1,1-dioxido-3-oxo-1,2-thiazetidin-2-yl)-3'-methylbutanoate **(S12)** (0.1 g, 0.227 mmol) in dry EtOAc (12 ml). The reaction vessel was flushed with nitrogen for 2 minutes followed by hydrogen for 1 minute. The solution was hydrogenated at atmospheric pressure for 2 hours before filtering through celite. The solvent was removed by reduced pressure rotary evaporation at 30 ^{o}C to yield a white solid (70.5 mg, 99 %), m.p. 115-116 ^{o}C. IR ν_{max} (cm^{-1}) 2976, 2944, 2884, 1771, 1729, 1462, 1374, 1343, 1281, 1169, 1112, 1046. ^{1}H NMR: δ ($CDCl_3$): 6.53 (1H, bs, **OH**), 4.31 (1H, d, J 6.92, N**CH**CO), 2.43 (1H, oct, J 6.8, CH_3**CH**CH_3), 2.17 (4H, m, **CH_2** (ethyl)) 1.15 (3H, t, J 7.45, **CH_3** (ethyl)), 1.13 (3H, t, J 7.46, **CH_3** (ethyl)), 1.1 (3H, d, J 6.99, **CH_3**$CHCH_3$), 1.07 (3H, d, J 6.81, CH_3CH**CH_3**). ^{13}C NMR: δ ($CDCl_3$): 171.59 (**C=O**), 164.2 (**C=O**), 89.76 (quaternary carbon), 64.35 (N**CH**CO), 30.38 (CH_3**CH**CH_3), 22.82 (**CH_2** (ethyl)), 22.45 (**CH_2** (ethyl)), 19.01 (**CH_3**$CHCH_3$), 18.97 (CH_3CH**CH_3**), 8.46 (**CH_3** (ethyl)), 8.38 (**CH_3** (ethyl)). HREI-MS $[M\text{-}NH_4]^+$ for $C_{11}H_{19}NO_5S$ calc. 295.1322 measured 295.1326.

Cyclohexanecarbonyl chloride (S13)

Cyclohexanecarboxylic acid (10 g, 78.02 mmol) was added to a flask and heated gently on a water bath at 30 ^{o}C. Thionyl chloride (10.5 g, 88.2 mmol) was added dropwise over a period of about 30 minutes, during which the mixture was stirred occasionally to ensure mixing. The reaction mixture was then heated at reflux for 30 minutes and the product was isolated by vacuum distillation, b.p. 44-45 ^{o}C at 1.0 mm Hg. (5.06 g, 44 %). IR ν_{max} (cm^{-1}) 2936, 2858, 1798, 1451, 1292, 1138, 1091, 1045, 925. ^{1}H NMR: δ ($CDCl_3$) 2.75 (1H, m, cyclohexyl **H**), 2.11 (2H, m, cyclohexyl **H**), 1.83 (2H, m, cyclohexyl **H**), 1.69 (1H, m, cyclohexyl **H**), 1.55 (2H, cyclohexyl **H**), 1.3 (3H, m, cyclohexyl **H**). ^{13}C NMR: δ ($CDCl_3$): 176.92 (**C=O**), 54.97 (**CH**), 29.15 (**C_1/C_5 CH_2**), 25.4 (**C_3 CH_2**), 24.97 (**C_2/C_4 CH_2**).

Cyclohexanecarboxylic anhydride (S14)

Sodium cyclohexanecarboxylate (5 g, 33.3 mmol) was added to toluene (40 ml) at room temperature with

stirring. To the solution cyclohexanecarbonyl chloride **(S13)** (4.8 g, 32.7 mmol) was added dropwise over 10 minutes, during which an exotherm was observed and the temperature rose up to 35 ^{o}C. The mixture was heated to reflux and stirred for 11 hours. The mixture was cooled to room temperature and ice (15 g) was added to the reaction mixture with stirring until the ice had melted. The two layers were separated and the organic layers dried over sodium sulfate, the solvent was removed under reduced pressure rotary evaporation to yield an oily residue, which was purified by vacuum distillation to give pure anhydride (4.29 g, 57 %), b.p. 155 - 156 ^{o}C at 0.7 mm Hg. IR ν_{max} (cm^{-1}) (neat) 2934, 2856, 1809, 1741, 1451, 1372, 1309, 1239.1, 1186, 1139, 1122, 1066, 990, 922, 895, 839. ^{1}H NMR: δ ($CDCl_3$) 2.41 (1H, m, cyclohexyl **H**), 1.97 (2H, m, cyclohexyl **H**), 1.78 (2H, m, cyclohexyl **H**), 1.65 (1H, m, cyclohexyl **H**), 1.5 (2H, m, cyclohexyl **H**) 1.33 (1H, m, cyclohexyl **H**) 1.29 (2H, m, cyclohexyl **H**). ^{13}C NMR: δ ($CDCl_3$): 171.8 (**C=O**), 43.9 (**CH**), 28.35 (C_1/C_5 **CH_2**), 25.5 (C_3 **CH_2**), 25.1 (C_2/C_4 **CH_2**).

Disodium 1-sulfonylcyclohexanecarboxylate (S15)
Concentrated H_2SO_4 (2.7 g, 27.5 mmol) was added dropwise to cyclohexanecarboxylic anhydride **(S14)** (4 g, 16.93 mmol) and the mixture stirred for 30 minutes at 20-35 ^{o}C. The reaction mixture was gently heated to 90 ^{o}C and stirred for approximately 5 hours. The hot reaction mixture was poured into ice-cold water and extracted with ether (3 x 20 ml). (Ether extracts contain the cyclohexanecarboxylic acid from the sulfonation). To the aqueous phase, a solution of NaOH (1.2 g) in water (4 ml) was added in small portions to adjust the pH to around pH 8. The solution was evaporated to dryness using reduced pressure rotary evaporation at 40 ^{o}C. The residue was dissolved in hot water (10 ml) and precipitated by addition of ethanol (30 ml) and the resulting precipitate was isolated by vacuum filtration. A second crop was isolated by adding ethanol to the mother liquor. The product isolated (2.83 g, 66 %) was carried through to the next step without any purification. IR ν_{max} (cm^{-1}) 3422, 2924, 2854, 1582, 1445, 1431, 1387, 1237, 1171, 1069, 1016. ^{1}H NMR: δ ($CDCl_3$) 2.3 (2H, m, cyclohexyl **H**), 1.65 (2H, m, cyclohexyl **H**), 1.5 (1H, m, cyclohexyl **H**), 1.15 (5H, m, cyclohexyl **H**). ^{13}C NMR: δ ($CDCl_3$): 175.66 (**C=O**), 71.28 (quaternary carbon), 30.96 (**C_1/C_5 CH_2**), 25.28 (**C_3 CH_2**), 23.83 (**C_2/C_4 CH_2**).

1-(Chlororsulfonyl)cyclohexane carbonyl chloride (S16)
Disodium 1-sulfonylcyclohexanecarboxylate **(S15)** (2.5 g, 9.91 mmol) was added to thionyl chloride (8.5 ml) at 0 ^{o}C with stirring. DMF (0.2 ml) was added dropwise over 2 minutes and the mixture was heated to 70 ^{o}C. After gas production was complete the mixture was heated for 5 hours at 70 ^{o}C. Excess thionyl chloride was removed by reduced pressure rotary evaporation yielding a pale yellow residue which was dissolved in ether. The sodium chloride formed was filtered off and the solvent was removed by reduced pressure rotary evaporation at 30 ^{o}C, to yield a pale yellow oil (1.77 g, 73 %). IR ν_{max} (cm^{-1}) 2948, 2867, 1769, 1455, 1379, 1346, 1171, 975, 853, 773. ^{1}H NMR: δ ($CDCl_3$) 2.86 (2H, m, cyclohexyl **H**), 2.14 (2H, m, cyclohexyl **H**), 2.02 (2H, m, cyclohexyl **H**), 1.79 (1H, m, cyclohexyl **H**), 1.4 (3H, m, cyclohexyl **H**). ^{13}C NMR: δ (CDCl3): 169.6 (**C=O**), 90.33 (quaternary carbon), 30.73 (**C_1/C_5 CH_2**), 23.88 (**C_3 CH_2**), 22.94 (**C_2/C_4 CH_2**).

4-*Spiro*-cyclohexyl-3-oxo-β-sultam (S17)
1-(Chlororsulfonyl)cyclohexane carbonyl chloride **(S16)** (1 g, 4.33 mmol) was dissolved in ether (10 ml) and added dropwise over 20 minutes (VERY SLOWLY) to liquid NH_3 (5.3 ml) in ether (10 ml) at –78 ^{o}C. The mixture was warmed to room temperature and stirred until all the solvent had evaporated. The residue was dissolved using $CHCl_3$ (5 ml) and water (5 ml) at 0-4 ^{o}C, and the pH of the solution was adjusted to pH 1 using dilute HCl. The organic layer was separated and the aqueous layer extracted with $CHCl_3$ (3 x 5 ml). The organic layers were combined and dried over sodium sulfate, and then the solvent was removed by reduced pressure rotary evaporation 30 ^{o}C to give a white solid (0.50 g, 65 %) m.p. 61-62 ^{o}C. IR ν_{max} (cm^{-1}) 3241, 2946, 2864, 1778, 1452, 1356, 1338, 1215 1161 1132 754. ^{1}H NMR: δ ($CDCl_3$): 8.27 (1H, bs, **NH**), 2.41 (2H, m, cyclohexyl **H**), 2.01 (2H, m, cyclohexyl **H**), 1.91 (2H, m, cyclohexyl **H**) 1.71 (1H, m, cyclohexyl **H**), 1.6 (2H, m**,** cyclohexyl **H**), 1.44 (1H, m, cyclohexyl **H**. ^{13}C NMR: δ ($CDCl_3$): 163.29 (**C=O**), 86.75 (quaternary carbon), 28.11 (**C_1/C_5 CH_2**), 24.05 (**C_3 CH_2**), 22.62 (**C_2/C_4 CH_2**). HREI-MS [M-H] for $C_7H_{11}NO_3S$ calculated 188.0376 measured 188.0379.

***N*-Benzyl-4-*spiro*-cyclohexyl-3-oxo-β-sultam (6)**
At 0 ^{o}C under nitrogen, 4-*spiro*-cyclohexyl-3-oxo-β-sultam **(S17)** (0.1 g, 0.53 mmol) in anhydrous THF (5 ml) was added to a suspension of NaH (0.015 g, 0.6 mmol) (pre-washed 2-3 times with petroleum ether) in DMF (2 ml). The mixture was stirred for 15 minutes and benzyl bromide (0.09 g, 0.526 mmol) was injected through a septum dropwise over 5 minutes. The mixture was allowed to warm up to room temperature and stirred for 24 hours. The mixture was then cooled to 0 ^{o}C, ether (10 ml) was added, the solution was hydrolysed with brine, and the pH was adjusted to 4-5 using dilute HCl. The organic layer was separated and

the aqueous layer was extracted with ether (2 x 10 ml). The organic layers were combined, washed with saturated brine (2 x 10 ml) and dried over Na_2SO_4. The solvent was removed by rotary evaporation at 30 ^oC and the resulting pale yellow oil was purified using column chromatography (silica 3 g) (1:8:1 Ether: Hexane: EtOAc) R_f = 0.58 (0.082 g 53 %) m.p. 73-74 ^oC. IR ν_{max} (cm^{-1}) ($CHCl_3$) 3020.6, 2944.8, 1768.8, 1335.8, 1215.9, 1168.4, 668. ^1H NMR: δ ($CDCl_3$): 7.40 – 7.36 (5H, m, **Ph**), 4.6 (2H, s, C**H$_2$**Ph), 2.37 (2H, m, cyclohexyl **H**), 1.99 (2H, m, cyclohexyl **H**), 1.89 (2H, m, cyclohexyl **H**) 1.7 (1H, m, cyclohexyl **H**), 1.59 (2H, m**,** cyclohexyl **H**), 1.42 (1H, m, cyclohexyl **H**). ^{13}C NMR: δ ($CDCl_3$): 163.71 (**C=O**), 133.4 (quaternary carbon), 128.84 (**CH** (Ph)), 128.34 (**CH** (Ph)), 127.97 (**CH** (Ph)), 87.53 (quaternary carbon), 44.09 (**CH$_2$**Ph), 27.91 (**C$_1$/C$_5$ CH$_2$**), 23.99 (**C$_3$ CH$_2$**), 22.75 (**C$_2$/C$_4$ CH$_2$**).