Synthesis of δ-lactam (2-oxopiperazine) inhibitors of elastase

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Different routes for the synthesis of N-sulfonyl derivatives of δ-lactam (2-oxopiperazine) inhibitors of the serine protease elastase were evaluated.

Keywords: acylation, elastase, δ-lactam, serine protease.

Elastases and other serine proteases, including those involved in blood clotting and infection, are targets for medicinal chemistry.[1] Amongst those forming a covalent link are acylating agents, including both monocyclic and bicyclic β-and γ-lactams.[2-4] Bicyclic γ-lactam templates are potent inhibitors of elastase and thrombin.[3] In contrast the potency of reported monocyclic γ-lactam inhibitiors is weaker,[4] both in comparison with β-analogues and the bicyclic γ-lactams.[3]

Imming *et al.*[5] have reported analyses on the hydrolytic lability of a series of lactams, revealing that analogous δ- and β-lactams have a similar reactivity. Factors other than a threshold level of chemical reactivity are required for efficient and selective acylation of a target protease such as elastase, by a small-molecule.[6] If an acyl-enzyme complex is formed it must be sufficiently stable both with respect to hydrolysis and, in the case of cyclic lactam or lactone inhibitors, reversible recyclisation.[4] Given the observations of Imming *et al.*,[5] it was of interest to examine the potential of δ-lactams to inhibit serine proteases.

Various strategies have been employed for the synthesis of 2-oxopiperazines including the ring closure of acyclic precursors to form the amine[7-9] or amide[10,11] bonds in 2-oxo-piperazines. There are also reports of 2-oxopiperazine synthesis via solid phase methodology.[12-15]

We synthesised of a series of N-arylsulfonylated δ-lactams/2-oxopiperazines, some of which are inhibitors of porcine pancreatic and human neutrophil elastase. The choices of group α- to the lactam carbonyl and the N-substituent took into account previous structure-activity work on β and γ-lactams as serine protease inhibitors.[1-4]

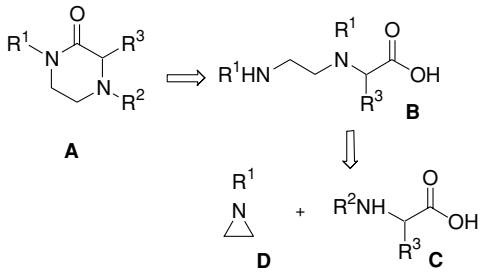
Results and discussion

An initial potential route to N-sulfonyl δ-lactams was based on that shown in Scheme 1, *i.e.* alkylation of a monoprotected amino acid by a toluenesulfonylaziridine, followed by late stage lactam formation. The N-sulfonyl lactams were targeted due to precedent for activity with this functional group with β- and γ-lactam inhibitors of elastase. (See ref. 4 and refs therein.)

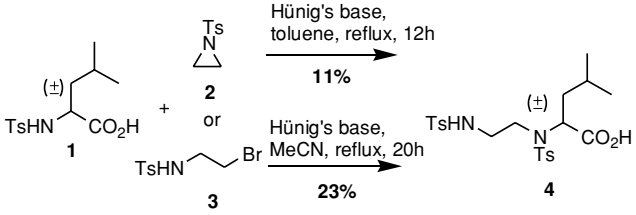
Alkylation of racemic-*N*-(*p*-toluenesulfonyl)-leucine **1**[17] with aziridine **2**[18] or bromide **3**,[19] provided the cyclisation precursor **4** in low (unoptimised) yields (Scheme 2).

The yields of alkylation were increased by use of the *tert*-butyl ester of (*S,S*)-*N*-(*p*-toluenesulfonyl)-isoleucine **5**. The resultant *N*-alkylated product *tert*-butyl ester **6** underwent near-quantitative acid mediated deprotection to the cyclisation precursor **7**, enabling attempts at δ-lactam formation.

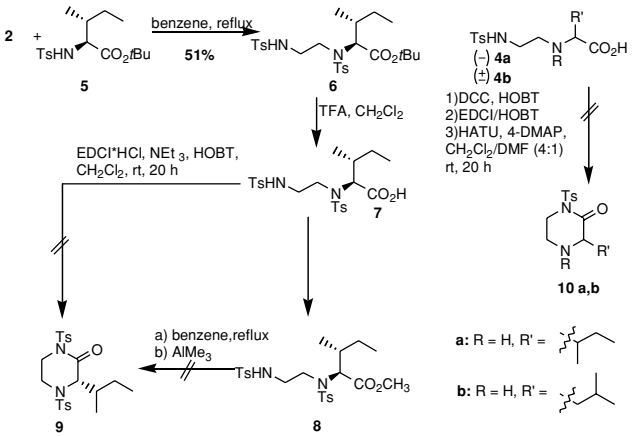
Unfortunately, neither 1,3-dicyclohexylcarbodiimide (DCCI) with or without (N-hydroxybenzotriazole) (HOBT), 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide (EDCI),



Scheme 1



Scheme 2



Scheme 3

nor *O*-7-(azabenzotriazol-1-yl)-N, N, N'', N'-tetramethyl-uronium-hexafluorophosphate (HATU) effected useful levels of cyclisation of **7** to the δ-lactam **9,** nor of **4a**,**b** to **10a**,**b** (Scheme 3). In the case of **7,** initial activation of the carboxyl group with EDCI/HOBT was observed by mass spectrometry, indicating that cyclisation rather than activation was problematic. The ester **8** did not cyclise under reflux conditions, nor in the presence of a Lewis acid catalyst ($AlMe_3$). Thus it appears that electron-withdrawing groups, such as *p*-toluenesulfonyl, hinder the desired cyclisation.

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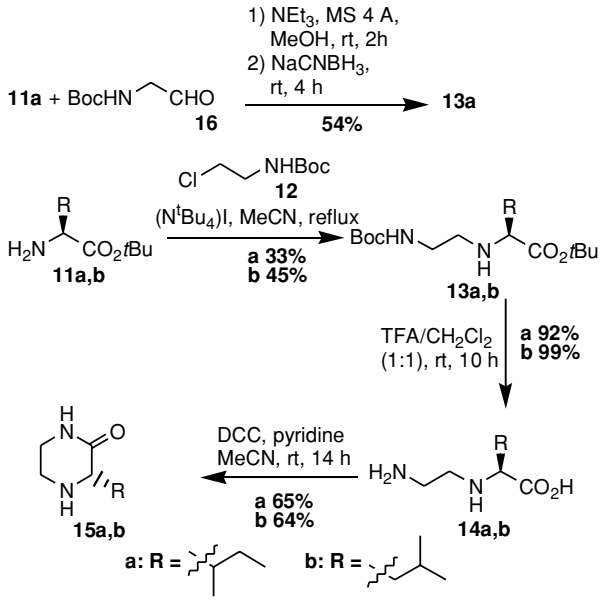
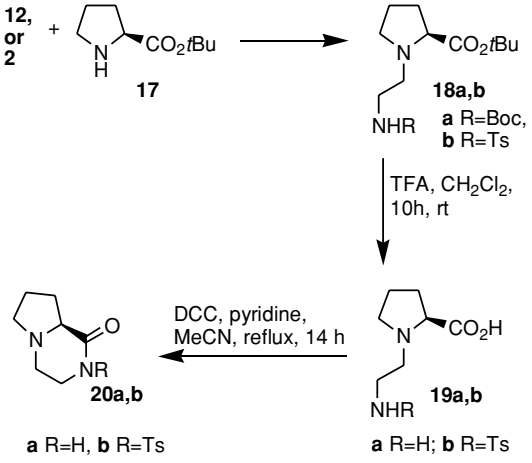


Scheme 4

A modified approach involving cyclisation of a primary amine, rather than a sulfonamide in order to increase the nucleophilicity of the amine in the intramolecular lactamisation, was then examined. Prior work has achieved lactamisation from a primary amine and an ester[20] or primary amine and the carboxylic acid under acid conditions and reflux. With regard to maintaining the integrity of the chiral centre we examined milder conditions. Alkylation of *tert*-butylesters **11a,b**[21] with chloride **12,**[22] followed by deprotection of secondary amine **13** with CF_3CO_2H yielded the cyclisation precursor **14** (Scheme 4). Lactamisation was achieved with DCCI and pyridine in moderate yields to give the δ-lactams **15a,b** (Scheme 4). Sulfamylation of both amide and amine nitrogens of **15a** was achieved by reaction with *n*-BuLi in THF at 0°C followed by TsCl to provide **9**. Yields were improved by employing a reductive alkylation protocol for the preparation of **13**, *e.g.* reaction of amine **11a**[21] and aldehyde **16**[23] gave **13a** in moderate yield.

Following from the work on γ-lactam serine protease inhibitors, bicyclic δ-lactams were prepared from *L*-proline *tert*-butylester by this strategy (Scheme 5). These compounds



Scheme 5

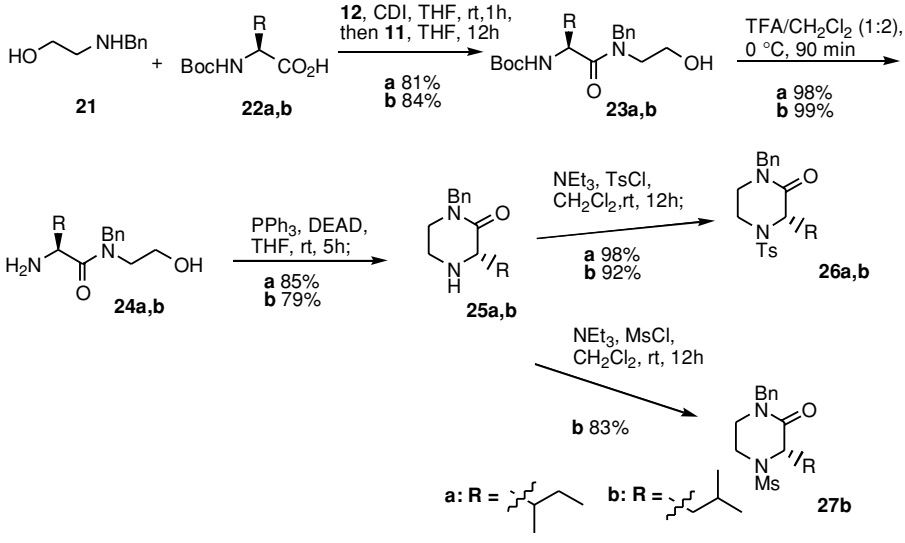
are related to a series of thrombin inhibitors, containing a bicyclic δ-lactam core.[24]

Although this approach (Scheme 4) could be improved by differential *N*-protection, it is limited since lactam formation could not be achieved (in sufficiently high yield if at all) when electron-withdrawing groups (*e.g. para*-toluenesulfonyl) were present on the primary amine of the cyclisation precursor. A second, straightforward and flexible, strategy was based on a Mitsunobu cyclisation[25] (Scheme 6).

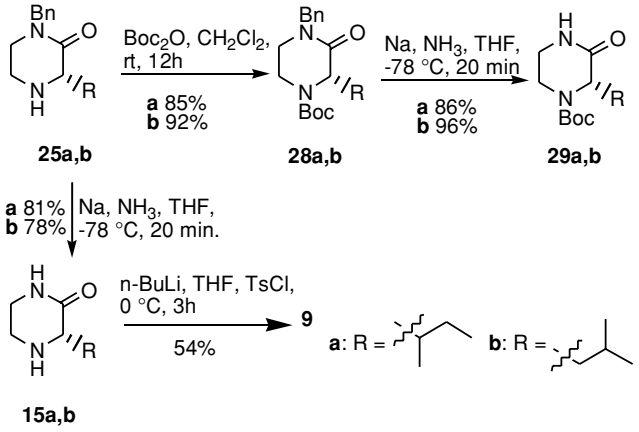
Coupling of N-Boc amino acids **22a,b** with *N*-benzylethanolamine **21** mediated by 1,1'-carbonyldiimidazole (CDI) gave **23a,b**.[26] Deprotection followed by cyclisation using the Mitsunobu protocol gave 2-oxopiperazines **25a,b** in 66 to 68 % overall from **22a,b**. Diversity at the nitrogen amide was introduced by Boc protection and removal of the benzyl group by Birch reduction (Schemes 6 and 7).

p-Toluenesulfonyl and methanesulfonyl groups were introduced by reaction of the nitrogen amine **29a,b** to give **30** and **31**, respectively (Scheme 8).

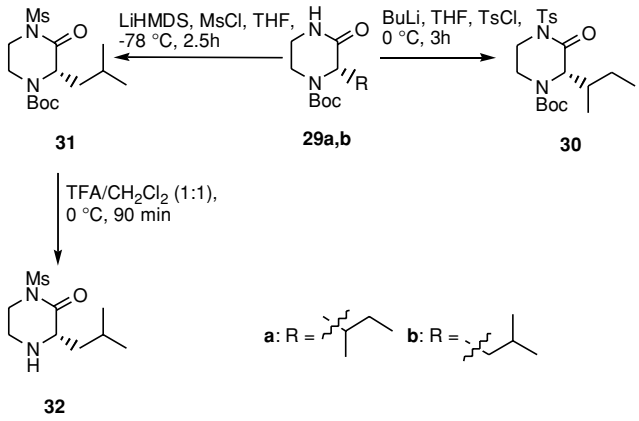
Results for the inhibition of human neutrophil elastase by some of the compounds are shown in Table 1. At this stage the mechanism of action of the δ-lactam inhibitors is uncertain, but there are some points of interest that emerged from the data. δ-Lactam **26b** was found to be an inhibitor of human neutrophil elastase (HNE) (Table 1), but close structural analogues (*e.g.* **26a**, **27b**) were not. Further two acyclic



Scheme 6



Scheme 7

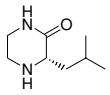
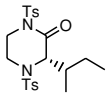
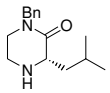
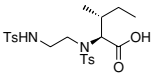
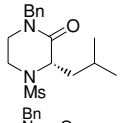
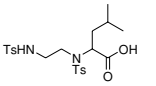
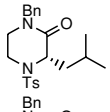
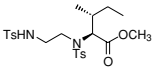
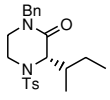
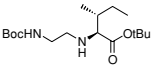
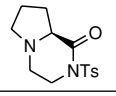


Scheme 8

compounds were found to be inhibitors (**4b** and **8**). In itself this is not surprising as peptides can inhibit elastase via reversible acyl-enzyme formation, but, as with the δ-lactams, close structural analogues of the acyclic inhibitors (e.g. **7**) did not display activity. Some of the apparent discrepancy may have been explained by solubility factors, e.g. the low solubility of **9.** However, this is unlikely to explain the difference in potency between isomers (**26a** *vs* **26b** and **7** *vs* **4b**). It is notable that in both cases the more sterically hindered (at least with respect to the lactam carbonyl) sec-butyl compound was significantly less potent than its *iso*-butyl analogue.

In summary the synthetic strategy to the monocyclic δ-lactams that proceeds via lactam ring-closure is readily amenable to the production of large numbers of piperaz-2-ones via variation of the starting materials and/or the *N*-substituents, in an analogous manner to that and for the preparation of diketopiperazones in a combinatorial manner.

Table 1 *In vitro* human neutrophil elastase (HNE) activities

		HNE IC_{50} (μM)[a]			HNE IC_{50} (μM)[a]
15b		>323	**9**		>323
25b		>323	**7**		>323
27b		>323	**4b**		22
26b		28	**8**		51
26a		>323	**13a**		>323
20b		>323			

[a]IC_{50} values were used for ranking only. Values are mean of three experiments. 50 mM Tris/HCl (pH 8.6), 150 mM NaCl, 11.8 nM purified HNE and water dilutions of inhibitor from 10 mM stock solution in DMSO are incubated for 15 min at 30 °C. After the addition of 0.6 mM MeO-Succ-Ala-Ala-Pro-Val-p-nitroanilide the residual elastase activity is measured. See refs 4,16 for experimental details.

Experimental

General

All reactions requiring anhydrous conditions were conducted in flame- or oven-dried apparatus under an argon atmosphere. Syringes and needles for the transfer of reagents were dried at 140 °C and allowed to cool in a desiccator over P_2O_5 before use. Ethers were distilled from sodium benzophenone ketyl under Ar; CH_2Cl_2, pentane and Et_3N from CaH_2 under Ar. External reaction temperatures are reported unless stated otherwise. Reactions were monitored by TLC using glass-backed plates, precoated with a 0.25 mm layer of silica containing a fluorescent indicator (Merck). Organic layers were dried over $MgSO_4$ unless stated otherwise. Column chromatography was carried out on Kieselgel 60 (40–63 μm). Petroleum ether refers to the fraction with b.p. 40–60 °C. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ unless stated otherwise using a Varian Gemini 200, Bruker AC200, Bruker WM250, Bruker WH300, JEOL EX400, Bruker AM500 or Bruker AMX500 spectrometers. Chemical shifts are reported relative to $CHCl_3$ [δ_H 7.26, δ_C (central of triplet) 77.0] or CH_3OH [δ_H 3.35, δ_C (central of septet) 49.0]. Conformational isomers (rotamers) were apparent in some of the ^{13}C NMR spectra leading to the excess of signals relative to carbons in some cases. Experimental details of the action of the δ-lactam potential as elastase inhibitors have been reported elsewhere.[16]

Synthesis of cyclisation precursors **4, 7**

(±)-4-Methyl-2-{(toluene-4-sulfonyl)-[2-(toluene-4-sulfonylamino)-ethyl]-amino}-pentanoic acid **4**: **1**[17] (568 mg, 2 mmol) and *N*-(*p*-toluenesulfonyl)aziridine **2**[18] (364 mg, 2 mmol) were suspended in toluene (10 ml) and stirred at 110 °C for 12 h. Solvent was evaporated *in vacuo*, and the residue chromatographed (MeOH/CH_2Cl_2 10:1) to afford the product **4** (101 mg, 11%) as a yellow oil. IR (film) ν_{max} 3275, 2959, 1734, 1465, 1332, 1092, 815, 668 cm^{-1}.^1H NMR (200 MHz, $CDCl_3$) δ 0.75 (d, *J* = 7.5 Hz, 3H), 0.80 (d, *J* = 7.5 Hz, 3H), 1.38–1.46 (m, 2H), 1.56–1.78 (m, 1H), 2.37 (s, 3H), 2.40 (s, 3H), 2.97–3.11 (m, 2H), 3.77–4.01 (m, 3H), 5.50–5.65 (m, 2H), 7.21–7.37 (m, 4H), 7.68–7.80 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.9, 21.3, 22.5, 24.1, 41.5, 54.5, 63.9, 127.3, 127.3, 129.8, 129.9, 136.8, 137.0, 143.8, 143.9, 172.0. MS AP$^-$: *m/z* (%) = 480 (76, [M - H$^+$]). HRMS: *m/z* calcd for $C_{22}H_{30}N_2O_6NaS_2$ [M+Na$^+$], 505.1443; found 505.1442.

(S,S)-3-Methyl-2-{(toluene-4-sulfonyl)[2-(toluene-4-sulfonylamino) ethyl]amino}pentanoic acid **7**: To a solution of **5** (188mg, 0.55 mmol) in benzene (5 ml) was added *N*-(*p*-toluenesulfonyl) aziridine **2** (100 mg, 0.55 mmol) and the reaction refluxed for 12 h. The solvents were removed *in vacuo* and the residue purified by column chromatography (CH_2Cl_2/MeOH 15:1) to afford **6** (151 mg) as a yellow oil. The *tert*-butyl ester **6** was dissolved in CH_2Cl_2 (3 ml) and treated with CF_3CO_2H(1 ml). The reaction mixture was stirred for 3 h at room temperature and the solvents evaporated *in vacuo* to yield 166 mg (51%, 0.28 mmol) of **7** as a yellow oil. $[\alpha]_D$ = –8.5 (c 0.2, CH_3OH). IR (film) ν_{max} 3281, 2968, 1716, 1335, 1159, 1091, 815, 660 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.75 (d, *J* = 6.5 Hz, 3H), 0.80 (d, *J* = 7.5 Hz, 3H), 0.91–0.94 (m, 2H), 1.41–1.52 (m, 1H), 2.39 (s, 3H), 2.45 (s, 3H), 3.11–3.30 (m, 3H), 3.51–3.59 (m, 1H), 4.05 (t, *J* = 9.0 Hz, 1H), 4.83 (d, *J* = 14.5 Hz, 1H), 5.41 (t, *J* = 6.0 Hz, 1H), 7.22–7.32 (m, 4H), 7.68 (d, *J* = 7.5 Hz, 2H), 7.78 (d, *J* = 7.5 Hz, 2H). MS AP$^+$: *m/z* (%) = 482 (100, [M + H$^+$ - CHO_2]). HRMS: *m/z* calcd for $C_{22}H_{30}N_2O_6NaS_2$ [M+Na$^+$], 505.1443; found 505.1435.

Alkylation route to piperazones **15a**,**b**

(S,S)-2-(2-tert-Butoxycarbonylaminoethylamino)-3-methylpentanoic acid tert-butyl ester **13a**: *(a)* To a solution of *L*-isoleucine *tert*-butyl ester hydrochloride salt **11a**[20] (500 mg, 2.23 mmol) in CH_3CN (10 ml) and diisopropylethylamine (556 mg, 4.46 mmol, 763 µl) was added **12**[21] (397mg, 2.23 mmol) in CH_3CN (1 ml) dropwise by room temperature, following by NBu_4I (826 mg, 2.23 mmol). The reaction was refluxed for 12 h, diluted with water, and extracted with EtOAc (3 × 30 ml). The combined organic extracts were washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was chromatographed (MeOH/CH_2Cl_2 1:10) to afford 243 mg (0.74 mmol, 0.74 mmol, 33%) of **13a**.

(b) To a solution of *L*-isoleucine *tert*-butyl ester hydrochloride salt **11a** (223 mg, 1 mmol) in MeOH (10 ml) was added dropwise NEt_3 (140 µl, 1.00 mmol) at room temperature, followed by slow addition of Boc-glycinal **16** (176 mg, 1.1 mmol) in methanol (1 ml) and 2g of molecular sieve. After 2 h, $NaCNBH_3$ (70 mg, 1.1 mmol) was added. The mixture was stirred for 4 h, diluted with water, and extracted with EtOAc (3 × 10 ml). The organic extract was dried over $MgSO_4$, evaporated *in vacuo*, and the residue was chromatographed (CH_2Cl_2/MeOH 15:1) to afford **13a** (178 mg, 0.54 mmol, 54%) as a yellow oil. R_f = 0.35 (silica gel, CH_2Cl_2/MeOH, 40:1); $[\alpha]_D$ = –2.5 (c 1.0, CH_3OH). IR (film) ν_{max} 3362, 2973, 2934, 2877, 1723, 1514, 1366, 1251, 1170 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.85–0.92 (m, 6H), 1.01–1.30 (m, 2H), 1.44 (s, 9H), 1.46 (s, 9H), 1.50–1.70 (m, 1H), 2.40–2.58 (m 1H), 2.68–2.82 (m, 1H), 2.86 (d, *J* = 6.0 Hz, 1H), 3.00–3.30 (m, 2H), 5.00 (s, 1H), 5.14 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.5,15.5,25.6, 28.1, 28.3, 38.4, 40.3, 47.7, 66.1, 79.0, 80.9, 156.0, 174.4. MS AP$^+$: *m/z* (%) = 331 (22, [M + H$^+$]), 275 (49, [M-C_4H_9 + H$^+$]), 219 (100, [M-C_8H_{17}]). HRMS: *m/z* calcd for $C_{17}H_{35}N_2O_4$ [M+1], 331.2597; found 331.2599.

(S)-2-(2-tert-Butoxycarbonylamino-ethyl-amino)-4-methylpentanoic acid tert-butyl ester **13b**: To a solution of *L*-leucine *tert*-butyl ester hydrochloride salt **11b**[20] (200 mg, 0.90 mmol) in CH_3CN (4 ml) and diisopropylethylamine (222 mg, 1.8 mmol, 306 µl) was added **12** (160mg, 0.90 mmol) in CH_3CN (1 ml) dropwise by room temperature, followed by nBu_4NI (330 mg, 0.90 mmol). The reaction was refluxed for 12 h, diluted with water, and extracted with EtOAc (3 × 10 ml). The organic extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was chromatographed (MeOH/CH_2Cl_2 1:10) to afford 134 mg (0.41 mmol, 45%) of the desired product. R_f = 0.30 (silica gel, CH_2Cl_2/MeOH, 40:1). $[\alpha]_D$ = –3.5 (c 0.2, CH_3OH). IR (film) ν_{max} 3295, 2968, 1722, 1336, 1170, cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (t, *J* = 6.0 Hz, 6H), 1.37 (m, 1H), 1.42 (s, 9H), 1.43 (s, 9H), 1.56–1.80 (m, 2H), 2.44–2.60 (m, 1H), 2.67–2.80 (m, 1H), 3.11 (t, *J* = 7.5 Hz, 1H), 3.00–3.28 (m, 2H), 5.02 (s, 1H).^{13}C NMR (50 MHz, $CDCl_3$) δ 22.4, 22.6, 24.9, 28.0, 28.4, 40.4, 42.8, 47.2, 60.2, 79.0, 81.0, 156.0, 175.3. MS AP$^+$: *m/z* (%) = 331 (22, [M + H$^+$]), 275 (49, [M-C_4H_9 + H$^+$]), 219 (100, [M-C_8H_{17} + H$^+$M+H$^+$]). HRMS: *m/z* calcd for $C_{17}H_{35}N_2O_4$ [M+1], 331.2597; found 331.2599.

(S,S)-3-sec-Butylpiperazin-2-one **15a**: The *tert*-butyl ester **13a** (82 mg, 0.25 mmol) was dissolved in CH_2Cl_2 (4 ml) and treated with CF_3CO_2H (2 ml). The reaction mixture was stirred for 3 h at room temperature and the solvents evaporated *in vacuo* to yield 71 mg (99%, apparent) of a yellow oil, to give **14a** which was used without further purification. $[\alpha]_D$ = –4.2 (c 1.0, CH_3OH). IR (film) ν_{max} 3316, 2978, 1674, 1434, 1203, 1135 cm^{-1}. ^1H NMR (200 MHz, MeOD) δ 1.00–1.09 (m, 6H), 1.40–1.80 (m, 2H), 2.00–2.20 (m, 1H), 3.35–3.47 (m, 4H), 4.00–4.10 (m, 1H).^{13}C NMR (50 MHz, MeOD) δ 12.5, 14.8, 28.0, 37.3, 38.0, 46.2, 66.7, 168.4. MS AP$^+$: *m/z* (%) = 175 (100, [M + H$^+$]), 157 (22, [M-H_2O]). To a solution of *N*,*N*′-dicyclohexylcarbodiimide (59 mg, 0.21 mmol) in CH_3CN (3 ml) was added a mixture the crude **14a** (50 mg, 0.29 mmol) and pyridine (0.58 mmol, 48 µl). The mixture was stirred at room temperature for 6 h. The solid was filtered of and the solvent was evaporated *in vacuo*; then CH_2Cl_2 (1 ml) added. The solution was cooled to 0 °C for 2h. The resultant solid was filtrated and the filtrate was concentrated *in vacuo* to yield the crude product (18 mg, 0.16 mmol, 54%).

15a was also prepared from **25a**. Na was added to NH_3(l) until a blue colour persisted. (*S*,*S*)-1-Benzyl-3-*sec*-butyl-piperazin-2-one **25a** (100 mg, 406 µmol) was then added in THF (5 ml). After 20 min, H_2O (5 ml) and a small amount of NH_4Cl (0.20 ml) were added. The pH of the mixture was then adjusted to pH 11 with 6N HCl. The mixture was extracted with EtOAc (5 × 5 ml) and washed with brine. The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated *in vacuo* to afford 51 mg (329 µmol, 81%) of a colourless oil, which was used for the next step without further purification. Data for **15a**. $[\alpha]_D$ = –41.4 (c 0.5, CH_3OH).IR (film) ν_{max} 3300, 2966, 2879, 1731, 1434, 1322, 1150 cm^{-1}. ^1H NMR (200 MHz, MeOD) δ 0.95 (t, *J* = 7.5 Hz, 3H), 1.06 (d, *J* = 7.0 Hz, 3H), 1.21–1.51 (m, 2H), 2.00–2.22 (m, 1H), 2.80–3.30 (m, 1H), 3.08–3.42 (m, 4H), 4.00–4.10 (m, 1H). ^{13}C NMR (50 MHz, MeOD) δ 13.3, 15.0, 26.3, 38.5, 43.4, 43.8, 65.1, 174.6. MS AP$^+$: *m/z* (%) = 156 (100, [M + H$^+$]). HRMS: *m/z* calcd for $C_8H_{17}N_2O$ [M+1], 157.1341; found 157.1341.

3(S)-3-Isobutyl-piperazin-2-one **15b**: Crude **14b** was prepared in >95% apparent yield as a yellow oil, according to the procedure used for the synthesis of **14a** and used without further purification [^1H NMR (200 MHz, MeOD): δ = 0.91–1.12 (m, 6H), 1.60–1.75 (m, 3H), 3.24–3.56 (m, 4H), 4.00 (t, *J* = 7.4 Hz, 1H)]. Compound **15b** was prepared in 64% yield as a yellow oil, according to the procedure used for the synthesis of **15a**. $[\alpha]_D$ = –38.5 (c 0.2, CH_3OH). IR (film) ν_{max} 3296, 2968, 1738, 1320, 1120 cm^{-1}. ^1H NMR (200 MHz, MeOD) δ 0.95 (t, *J* = 7.5 Hz, 3H), 1.06 (d, *J* = 7.0 Hz, 3H), 1.21–1.51 (m, 2H), 2.00–2.22 (m, 1H), 2.80–3.30 (m, 1H), 3.08–3.42 (m, 4H), 2.00–2.20 (m, 1H), 3.35–3.47 (m, 4H), 4.00–4.10 (m, 1H). ^{13}C NMR (50 MHz, MeOD) δ 13.3, 15.0, 26.3, 38.5, 43.4, 43.8, 65.1, 174.6. HRMS: *m/z* calcd for $C_8H_{17}N_2O$ [M+1], 157.1341; found 157.1343.

Mitsunobu route to 2-oxopiperazines

(S,S)-[1-(2-Hydroxyethyl-N-benzyl-carbamoyl)-2-methyl-butyl]-carbamic acid tert-butyl ester **23a**: To a solution of N-Boc-*L*-isoleucine **22a** (1.00 g, 4.01 mmol) in THF (15 ml) was added 1,1'-carbonyldiimidazole (0.65 g, 4.00 mmol) and stirred for 1h at room temperature. A solution of *N*-benzylethanolamine **21** (0.60 g, 4.00 mmol) in THF (2 ml) was then added dropwise and stirred for 12 h at room temperature. The reaction mixture was evaporated *in vacuo* and the residue chromatographed (MeOH/CH_2Cl_2 1:4) to afford 1.18 g (3.25 mmol, 81 %) of the desired product as a yellow oil. $[\alpha]_D$ = 38.8 (c 0.8, CH_3OH). IR (film) ν_{max} 3312, 2967, 2933, 2877, 1705, 1634, 1497, 1452, 1366, 1251, 1169, 1081, 1044, 1019, 753, 699 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.85–0.93 (m, 6H), 1.02–1.18 (m, 1H), 1.42 (s, 9H), 1.70–1.92 (m, 2H), 2.87 (t, *J* = 5.0 Hz, 2H), 3.80 (s, 2H), 4.25 (t, *J* = 5.0 Hz, 2H), 5.08–5.12 (m, 1H), 7.10–7.40 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.6, 15.6, 25.1, 28.3, 38.0, 47.4, 52.6, 58.0, 64.5, 79.8, 127.1, 128.5, 128.6, 137.4, 155.6, 172.4. MS AP$^+$: *m/z* (%) = 365 (97, [M + H$^+$]), 309 (100, [M-C_4H_9 + H$^+$]), 265 (24, [M-$C_6H_{12}O$]).

(S)-[1-(2-Hydroxyethyl-N-benzylcarbamoyl)-3-methyl-butyl]-carbamic acid tert-butyl ester **23b**: Compound **23b** was prepared from *N*-Boc-L-leucine **22b** in 84% yield as a yellow oil, according to the procedure used for the synthesis of **23a**. R_f = 0.60 (silica gel, CH_2Cl_2/MeOH, 10:1); $[\alpha]_D$ = –33.0 (c 0.2, CH_3OH). IR (film) ν_{max} 3311, 2958, 1699, 1634, 1497, 1452, 1366, 1251, 1168, 1048, 731, 699 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.74 (d, *J* = 6.5 Hz, 1.5H, rotamer), 0.82 (d, *J* = 6.5 Hz, 1.5H, rotamer), 0.94 (t, *J* = 6.0 Hz, 3H, rotamer), 1.20–1.40 (m, 1H), 1.41 (s, 9H), 1.40–1.78 (m, 2H), 3.28–3.80 (m, 5H), 4.30 (apparent, d, *J* = 16.0 Hz, 0.5 H, rotamer), 4.60–4.78 (m, 2H), 4.96 (apparent, d, *J* = 16.0 Hz, rotamer), 5.20–5.40 (m, 1H), 7.10–7.40 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.4, 21.7, 23.3, 23.4, 24.5, 24.6, 28.3, 41.8, 42.3, 49.2, 49.8, 52.2, 60.2, 61.1, 65.8, 79.7, 80.0, 126.8, 127.3, 127.8, 128.6, 128.9, 136.3, 137.3, 155.7, 156.5, 174.1, 175.3. MS AP$^+$: *m/z* (%) = 365 (20, [M + H$^+$]), 309 (35, [M-C_4H_9 + H$^+$]), 265 (100, [M-$C_6H_{12}O$]).

(S,S)-2-Amino-3-methyl-pentanoic acid (2-hydroxyethyl)-(N-benzyl)-amide **24a:** To a solution of **23a** (0.70g, 1.92 mmol) in CH_2Cl_2 (5 ml) was added trifluoroacetic acid (3 ml) at 0°C. The reaction mixture was stirred for 90 min at the same temperature, concentrated *in vacuo* and portioned between CH_2Cl_2 (10 ml) and 25% NaOH (10 ml) The aqueous layer was further extracted with CH_2Cl_2 and the combined organic fractions were dried over $MgSO_4$. The solvent was evaporated *in vacuo* to provide **24a** (495 mg, >95 %) as a colourless oil, which was carried on as a crude amino alcohol. R_f = 0.25 (silica gel, CH_2Cl_2/MeOH, 10:1); $[\alpha]_D$ = –5.1 (c 1, CH_3OH). IR (film) ν_{max} 3363, 2969, 1682, 1454, 1204, 1140, 1029, 840, 801, 777, 701 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.70–1.00 (m, 6H, rotamer), 1.00–1.22 (m, 1H, rotamer), 1.32–1.70 (m, 1H, rotamer), 1.71–2.00 (m, 1H, rotamer), 3.00 (d, *J* = 11.0 Hz, 1H, rotamer), 3.50–3.90 (m, 3H), 4.40 (m, 1H), 4.61 (m, 1H, rotamer), 5.38 (m, 1H), 7.10–7.45 (m, 5H).^{13}C NMR (50 MHz, $CDCl_3$) δ 10.9, 14.9, 21.1, 23.8, 37.2, 48.4, 55.4, 58.2, 60.5, 113.6, 119.3, 126.5, 128.1, 128.8, 136.1, 161.8, 162.5.

(S)- 2-Amino-4-methylpentanoic acid(2-hydroxy-ethyl)-(N-benzyl)-amide **24b**: **24b** was prepared in >95% (apparent) yield as a colourless oil, according to the procedure used for the synthesis of **24a**. $[\alpha]_D$ = –24.3 (c 1.0, CH_3OH). IR (film) ν_{max} 3352, 2956, 1634, 1468, 1452, 1365, 1202, 1075, 131, 699 cm^{-1}.^1H NMR (200 MHz, $CDCl_3$)

δ 0.75–0.96 (m, 6H, rotamer), 1.32–1.44 (m, 2H, rotamer), 1.60–1.80 (m, 1H, rotamer), 2.90–3.20 (m, 4H), 3.50–3.80 (m, 3H), 7.10–7.40 (m, 5H).^{13}C NMR (50 MHz, $CDCl_3$) δ 21.4, 21.9, 23.3, 23.4, 24.5, 24.7, 44.3, 44.7, 48.3, 48.7, 49.0, 49.7, 52.0, 59.1, 60.7, 126.2, 127.4, 127.8, 128.6, 129.0, 136.6, 137.2, 176.4, 177.9. MS AP$^+$: *m/z* (%) = 265 (36, [M + H$^+$]).

(S,S)-1-Benzyl-3-sec-butyl-piperazin-2-one **25a**: To a solution of the amino alcohol **24a** (700mg, 2.6 mmol) and triphenylphosphine (1.31g, 5.00 mmol) in THF (25 ml) was added diethyl azodicarboxylate (755 µl, 4.80 mmol). The solution was stirred at room temperature for 5h. Then the solvent was evaporated *in vacuo* and the residue was chromatographed (EtOAc/MeOH 4:1) to afford 545mg (2.21 mmol, 85%) of a yellow oil. R_f = 0.15 (silica gel, CH_2Cl_2/MeOH, 10:1); $[\alpha]_D$ = +56.0 (c 0.2, CH_3OH). IR (film) 3314, 2962, 1633, 1453, 1203, 701 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.81 (t, *J* = 7.5 Hz, 3H), 0.90 (d, *J* = 7.0 Hz, 3H), 1.05–1.42 (m, 2H), 2.01–2.31 (m, 1H), 2.68–3.08 (m, 3H), 3.10–3.40 (m, 2H), 3.48–3.53 (m, 1), 4.43 (d, *J* = 14.5 Hz, 1H), 4.58 (d, *J* = 14.5 Hz, 1H), 7.08–7.30 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.4, 16.4, 24.6, 36.9, 42.4, 47.5, 50.2, 64.4, 127.4, 128.1, 136.8, 170.2. HRMS: *m/z* calcd for $C_{15}H_{23}N_2O$ [M+1], 247.1810; found 247.1810.

(S)-1-Benzyl-3-isobutyl-piperazin-2-one **25b**: Compound **25b** was prepared from **24b** in 79% yield as a yellow oil, according to the procedure used for the synthesis of **25a**. R_f = 0.10 (silica gel, CH_2Cl_2/MeOH, 40:1); $[\alpha]_D$ = –37.0 (c 0.1, CH_3OH). IR (film) ν_{max} 3315, 2955, 1633, 1488, 1433, 1343, 1312, 1234, 1168, 936, 799 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.96 (t, *J* = 6.5 Hz, 6H), 1.50–2.00 (m, 3H), 2.90–3.05 (m, 1H), 3.10–3.20 (m, 2H), 3.24–3.40 (m, 1H), 3.48–3.53 (m, 1), 4.50 (d, *J* = 14.5 Hz, 1H), 4.70 (d, *J* = 14.5 Hz, 1H), 7.10–7.40 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.0, 23.6, 24.6, 41.2, 41.6, 47.6, 50.1, 57.3, 127.4, 128.1, 128.6, 137.0, 170.9. MS AP$^+$: *m/z* (%) = 247 (65, [M + H$^+$]).

(S)-1-Benzyl-3-isobutyl-4-(toluene-4-sulfonyl)piperazin-2-one **26b**: To the 2-oxopiperazine **25b** (70mg, 291 µmol) in CH_2Cl_2 (7 ml) and NEt_3 (55 µl, 459 µmol) was added *p*-toluenesulfonylchloride (76 mg, 399 µmol) and stirred at room temperature for 12 h. The solvent was evaporated *in vacuo* and the residue was chromatographed (diethylether/petrolether 2:1) to afford 107 mg (268 µmol, 92 %) as a colourless oil. R_f = 0.45 (silica gel, diethylether / petrolether 2:1); $[\alpha]_D$ = 56.0 (c 0.2, CH_3OH). IR (film) ν_{max} 2958, 1649, 1495, 1452, 1338, 1163 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.91–0.99 (m, 6H), 1.57–1.92 (m, 3H), 2.39 (s, 3H), 2.79–3.01 (m, 2H), 3.33–3.52 (m, 1H), 3.72–3.89 (m, 1H), 4.22 (d, *J* = 14.5 Hz, 1H), 4.38 (d, *J* = 14.5 Hz, 1H), 4.48 (d, *J* = 8.0 Hz, 1H), 7.00 (m, 2H), 7.13–7.28 (m, 5H), 7.68 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.2, 21.7, 23.4, 24.4, 38.1, 41.2, 44.0, 50.1, 56.8, 127.1, 127.6, 128.1, 128.6, 130.0, 135.9, 137.1, 143.9, 168.1. MS AP$^+$: *m/z* (%) = 401 (100, [M + H$^+$]).HRMS: *m/z* calcd for for $C_{22}H_{29}N_2O_3S$ [M+1], 401.1899; found 401.1892.

(S)-1-Benzyl-3-isobutyl-4-methanesulfonyl-piperazin-2-one **29b**: To the 2-oxopiperazine **25b** (100mg, 0.41 mmol) in CH_2Cl_2 (7 ml) and NEt_3 (55 µl, 0.46 mmol) was added methanesulfonylchloride (41 µl, 0.46 mmol) and stirred at room temperature for 12 h. The solvent was evaporated *in vacuo* and the residue was chromatographed (diethylether) to afford 111mg (0.34 mmol, 83 %) as a white solid (m.p. 88–89 °C). $[\alpha]_D$ = 26.8 (c 1.0, CH_3OH). IR (film) ν_{max} 2965, 1678, 1455, 1163 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.00 (t, *J* = 5.0 Hz, 6H), 1.69–1.84 (m, 3H), 2.79 (s, 3H), 3.06–3.20 (m, 1H), 3.30–3.58 (m, 2H), 3.70–3.84 (m, 1H), 4.30–4.40 (m, 1H), 4.52 (d, *J* = 14.5 Hz, 1H), 4.65 (d, *J* = 14.5 Hz, 1H), 7.13–7.30 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.3, 23.3, 23.4, 24.6, 38.2, 40.0, 40.9, 45.0, 50.2, 56.5, 128.0, 128.3, 128.9, 136.1, 168.0.6, 128.1, 128.6, 130.0, 135.9, 137.1, 143.9, 168.0. MS AP$^+$: *m/z* (%) = 325 (100, [M + H$^+$]). HRMS: *m/z* calcd for $C_{16}H_{25}N_2O_3S$ [M +1], 325.1586; found 325.1580.

(S,S)-4-Benzyl-2-sec-butyl-3-oxopiperazine-1-carboxylic acid tert-butyl ester **28a**: To a stirred suspension of the 2-oxopiperazine **25a** (40 mg, 0.17 mmol) in CH_2Cl_2 (5 ml) was added dropwise a solution of di-*tert*-butyl dicarbonate (46 mg, 0.21 mmol) in CH_2Cl_2 (5 ml). After stirring for 12 h, the solution was diluted with Et_2O (5 ml) and washed with phosphate buffer (0.5 M, pH 5.0, 2 × 5 ml), saturated aqueous $NaHCO_3$ (5 ml), and brine. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed (diethylether/petrolether 2:1) to afford 50 mg (0.14 mmol, 85 %) as a white solid. R_f = 0.70 (silica gel, diethylether/petrolether 2:1); $[\alpha]_D$ = +57.0 (c 0.2, CH_3OH). IR (film) ν_{max} 2911, 1696, 1646, 1179 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.96 (t, *J* = 7.4 Hz, 6H), 1.07 (d, *J* =6.8 Hz, 3H), 1.20–1.29 (m, 1H), 1.48 (s, 9H), 1.57–1.62 (m, 1H), 2.02–2.09 (m, 1H), 3.28–3.40 (m, 3H), 4.00 (m, 1H), 4.43 (d, *J* = 14.5 Hz, 1H), 4.83 (d, *J* = 14.5 Hz, 1H), 7.20–7.43 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.2, 13.5, 26.6, 27.6, 39.0, 45.4, 50.0, 61.4, 81.2, 127.8, 128.1, 128.3, 128.8, 136.9, 155.2, 169,2. MS AP$^+$: *m/z* (%) = 347 (54, [M + H$^+$]), 290 (59, [M + H$^+$-CO]), 247 (100, [M- $C_5H_8O_2$]). HRMS: *m/z* calcd for $C_{20}H_{31}N_2O_3$ [M$^+$], 347.2335; found 347.2336.

(S)-4-Benzyl-2-isobutyl-3-oxopiperazine-1-carboxylic acid tert-butyl ester **28b**: Compound **28b** was prepared in 92% yield as a white solid, according to the procedure used for the synthesis of **28a**. R_f = 0.65 (silica gel, diethylether/petrolether 2:1) $[\alpha]_D$ = 56.1 (c 0.2, CH_3OH). IR (film) ν_{max} 2959, 2870, 1696, 1697, 1650, 1416, 1169 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.93 (d, *J* = 6.0 Hz, 3H), 1.00 (d, *J* = 6.0 Hz, 1H), 1.43 (s, 9H), 1.60–1.80 (m, 3H), 2.95–3.48 (m, 3H), 4.00–4.32 (m, 2H), 4.58–4.92 (m, 2H), 7.13–7.37 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.0, 23.3, 24.7, 28.3, 36.3, 41.2, 45.5, 50.0, 55.9, 80.7, 127.6, 128.1, 128.7, 136.6, 154.0, 169.2. MS AP$^+$: *m/z* (%) = 347 (10, [M + H$^+$]), 291 (100, [M-C_4H_8 + H$^+$]).

(S,S)-2-sec-Butyl-3-oxopiperazine-1-carboxylic acid tert-butyl ester **29a**: Compound **29a** was prepared from **28a** in 96% yield as a colourless oil, according to the procedure b) used for the synthesis of **15a**. R_f = 0.2 (silica gel, CH_2Cl_2/MeOH, 40:1); $[\alpha]_D$ = 54.6 (c 0.7, CH_3OH). IR (film) ν_{max} 3330, 2972, 1744, 1682, 1456, 1369, 1145 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.00 (d, *J* = 7.0 Hz, 3H), 1.02–1.27 (m, 1H), 1.42 (s, 9H), 1.40–1.61 (m, 1H), 1.92–2.10 (m, 1H), 3.00–3.50 (m, 3H), 3.74–3.80 (m, 1H), 4.10–4.20 (m, 1H), 4.38–4.44 (m, 1H), 7.56 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.8, 15.8, 26.1, 28.2, 37.8, 38.7, 40.9, 61.4 , 80.7, 154.9, 171.5. MS AP$^+$: *m/z* (%) = 257 (13, [M + H$^+$]), 201 (40, [M- C_4H_8 + H$^+$]). HMRS: *m/z* calc for $C_{13}H_{25}N_2O_3$ [M+1], 257.1865; found 257.1869.

(S)-2-Isobutyl-3-oxopiperazine-1-carboxylic acid tert-butyl ester **29b**: Compound **29b** was prepared from **28b** in 86% yield as a colourless oil, according to the procedure b) used for the synthesis of **29a**. $[\alpha]_D$ = +77.0 (c 1.0, CH_3OH). IR (film) ν_{max} 3210, 2957, 1668, 1674, 1415, 1366, 1329, 1249, 1170, 1135, 1026, 977, 766 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.94 (d, *J* = 6.0 Hz, 3H), 1.00 (d, *J* =6.0 Hz, 3H), 1.46 (s, 9H), 1.67 (d, *J* = 6.0 Hz, 3H), 3.10–3.17 (m, 1H), 3.20–3.23 (m, 1H), 3.43–3.48 (m, 1H), 4.17 (d, *J* = 12.5 Hz, 1H), 4.72 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.8, 23.3, 24.4, 28.3, 35.6, 37.9, 40.8, 41.1, 55.7, 80.9, 154.2, 171.9. MS AP$^+$: *m/z* (%) = 257 (6, [M + H$^+$]), 201 (100, [M- C_4H_8 + H$^+$]). HRMS: *m/z* calcd for $C_{13}H_{25}N_2O_3$ [M+1], 257.1865; found 257.1865.

(S,S)-2-sec-Butyl-3-oxo-4-(toluene-4-sulfonyl)-piperazine-1-carboxylic acid tert-butyl ester **30**: **29a** (55mg, 215 µmol) was dissolved in THF (5 ml) and cooled to 0°C. A hexane solution of nBuLi (1.5 M, 186 µl, 1.3 eq) was then added dropwise. After 5 min, *p*-toluenesulfonylchloride (62 mg, 1.5 eq) in THF (2 ml) was added dropwise. After 3 h, H_2O (1 ml) and NH_4Cl (1 ml) was added, and the aq. layer was extracted with EtOAc (5 × 50 ml) and washed with brine. The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated *in vacuo*. Purification of the yellow oil by chromatography yielded a pure sample as colorless oil 67 mg (163 µmol, 76%) of a colourless oil. R_f = 0.40 (silica gel, CH_2Cl_2/MeOH, 40:1); $[\alpha]_D$ = +8.0 (c 0.1, CH_3OH). IR (film) ν_{max} 2971, 1697, 1366, 1293, 1172, 1146, 902, 756, 688, 545 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.84–0.89 (m, 6H), 1.10–1.20 (m, 1H), 1.44 (s, 9H), 1.60–1.68 (m, 1H), 2.44 (s, 3H), 3.34–3.42 (m, 1H), 3.87–3.91 (m, 1H), 4.00–4.40 (m, 3H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.91 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.5, 15.3, 21.6, 25.8, 28.1, 38.7, 39.3, 44.7, 61.5, 80.1, 128.6, 129.3, 135.3, 145.1, 154.0, 167.8. MS AP$^+$: *m/z* (%) = 331 (22, [M + H$^+$]), 275 (49, [M-C_4H_9 + H$^+$]), 219 (100, [M-C_8H_{17}]).HRMS: *m/z* calcd for $C_{20}H_{31}N_2O_5S$ [M+1], 411.1954; found 411.1950.

(S)-2-Isobutyl-4-methanesulfonyl-3-oxopiperazine-1-carboxylic acid tert-butyl ester **31**: To a solution of **25b** (70 mg, 276 µmol) in THF (5 ml) stirred at –78°C, was added dropwise a THF solution of lithium bis(trimethylsilyl)amide (1M, 280 µl). The solution was stirred for 10 min, then methanesulfonylchloride (32 µl, 420 µmol) was added. The reaction mixture was stirred for 30 min then slowly warmed up to room temperature. After 2h, EtOAc (2 ml) was added, immediately followed by a saturated solution of NH_4Cl (1 ml). The aqueous layer was extracted with EtOAc (3 × 5 ml), and the combined organic layers were washed with brine, dried over $MgSO_4$ under concentrated under reduced pressure. Purification of the yellow oil by chromatography on silica gel (diethylether/petrolether 2:1) yielded a pure sample (75 mg, 224 µmol, 82%) of a colourless oil. $[\alpha]_D$ = +7.7 (c 0.2, CH_3OH). IR (film) ν_{max} 2968, 1733, 1329,1150 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.97 (d, *J* = 6.0 Hz, 3H), 1.00 (d, *J* = 6.0 Hz, 3H), 1.40–1.68 (m, 3H), 2.36 (s, 9H), 3.15–3.25 (m, 1H),

3.37 (s, 3H), 3.66–3.72 (m, 1H), 3.85–3.90 (m, 1H), 4.08–4.14 (m, 1H), 4.72–4.77 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.0, 22.9, 24.5, 28.4, 37.00, 41.3, 41.8, 44.8,57.0, 81.6, 153.5, 170.4. MS AP$^+$: *m/z* (%) = 279 (25, [M + H$^+$ -C_4H_8]), 235 (71, [M-$C_5H_9O_2$ + H$^+$]), 207 (100, [M+H$^+$-$C_7H_{12}O_2$]). HRMS: *m/z* calcd for $C_{14}H_{26}N_2O_5NaS$ [M+Na$^+$], 357.1460; found 357.1461

(S)-3-Isobutyl-1-methanesulfonylpiperazin-2-one **32:** Compound **32** was prepared from **31** in >95% yield as a white solid, according to the procedure used for the synthesis of **24a**. R_f = 0.35 (silica gel, CH_2Cl_2/MeOH, 40:1); $[\alpha]_D$ = –99.5 (c 0.4, CH_3OH). IR (film) ν_{max} 3312, 2967, 1642, 1164 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ0.94 (d, *J* = 6.5 Hz, 3H), 0.97 (d, *J* = 6.5 Hz, 3H), 1.58–1.65 (m, 1H), 1.76–1.92 (m, 2H), 3.06–3.13 (m, 1H), 3.36 (s, 3H), 3.54–3.62 (m, 1H), 3.71–3.77 (m, 1H), 3.88–3.95 (m, 1H).^{13}C NMR (50 MHz, $CDCl_3$) δ 21.1, 23.1, 24.5, 40.5, 41.6, 41.8, 46.4, 58.7, 171.3. MS AP$^+$: *m/z* (%) = 235 (80, [M + H$^+$]), 207 (100, [M-C_2H_3 + H$^+$]). HRMS: *m/z* calcd for $C_9H_{19}N_2O_3S$ [M+1], 235.1116; found 235.1116.

(S,S)-3-sec-Butyl-1,4-bis-(toluene-4-sulfonyl)piperazin-2-one **9**: **15a** (10 mg, 64 μmol) was dissolved in THF (1 ml) and cooled to 0°C. A hexane solution of nBuLi (1.5 M, 90 μl, 2.1 eq) was then added dropwise. After 5 min, *p*-toluenesulfonylchloride (27 mg, 2.2 eq) in THF (1 ml) was added dropwise. After 3 h, H_2O (1 ml) and NH_4Cl (1 ml) was added, and the aq. layer was extracted with EtOAc (5 × 20 ml) and washed with brine. The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated *in vacuo*. Purification by chromatography yielded a white solid 17 mg (35 μmol, 54%). m.p. 118–119 °C. R_f = 0.80 (silica gel, CH_2Cl_2/MeOH, 40:1); $[\alpha]_D$ = +6.8 (c 0.6, $CHCl_3$). IR (film) ν_{max} 2966, 1697, 1597, 1360, 1171, 1088, 1024, 908, 874, 812, 735, 688 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.82–1.07 (m, 6H), 1.10–1.20 (m, 2H), 1.90–2.00 (m, 1H), 2.43 (s, 3H), 2.47 (s, 3H), 3.48–3.65 (m, 2H), 3.70–3.92 (m, 2H), 4.04 (dd, *J* = 7.5 Hz, 0.5 H), 4.10 (d, *J* = 7.5 Hz, 0.5 H), 7.21 (d, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.74 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.2, 15.3, 21.6, 21.7, 25.9, 38.1, 41.1, 43.6, 63.9, 127.2, 127.3, 128.6, 129.3, 130.1, 144.1, 144.8, 159.4 . MS AP$^+$: *m/z* (%) = 465 (8, [M + H$^+$]), 437 (100, [M-C_2H_5+ H$^+$]). HRMS: *m/z* calcd for $C_{22}H_{29}N_2O_5S_2$ [M+1], 465.1518; found 465.1517.

Synthesis of bicyclic δ*-lactams*

(S)-1-(2-tert-Butoxycarbonylamino-ethyl)pyrrolidine-2-carboxylic acid tert-butyl ester **18a**: To a solution of *L*-proline tert-butylester dibenezenesulfimide salt **17** (120 mg, 0.25 mmol) in DMF (5 ml) and diisopropylethylamine (0.42 mmol, 70 μl) was added **12** (53 mg, 0.30 mmol) in DMF (1 ml) dropwise by room temperature, following by NBu_4I (20 mg). The reaction mixture was stirred at 110 °C for 24 h. The solvent was then removed at oil-pump vacuum and room temperature, and the residue chromatographed (MeOH/CH_2Cl_2 1:10). The desired product **18a** was eluted as colourless oil (68 mg, 87 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.39 (s, 9H), 1.42 (s, 9H), 1.65–2.10 (m, 4H), 2.20–2.80 (m, 4H), 2.95–3.18 (m, 3H), 5.30 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.4, 28.0, 28.4, 29.4, 39.2, 53.4, 54.0, 66.4, 78.7, 80.7, 156.0, 173.6. MS AP$^+$: *m/z* (%) = 315 (20, [M + H$^+$]), 259 (26, [M-C_4H_8]), 203 (35, [M+H$^+$-C_8H_{15}]).

(S)-1-[2-(Toluene-4-sulfonylamino)ethyl]-pyrrolidine-2-carboxylic acid tert-butyl ester **18b**: To a solution of *L*-proline *tert*-butylester dibenezenesulfimide salt **17**[27] (400mg, 0.85 mmol) in THF was added *N*-tosyl aziridine **2** (155 mg, 0.85 mmol) in THF (2 ml) dropwise by room temperature. Then NEt_3 (300 μl) was added and the reaction mixture was stirred at 67 °C for 14 h. The solvents evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 (20 ml) and aqueous $NaHCO_3$ (20 ml). The aqueous wash was extracted with CH_2Cl_2 (3 × 20 ml), the combined organic phase dried over $MgSO_4$, evaporated *in vacuo*, and chromatographed (CH_2Cl_2/MeOH 40:1) to afford **18b** (368 mg, 76%) of a yellow oil. R_f = 0.25 (silica gel, CH_2Cl_2/MeOH, 40:1);$[\alpha]_D$ = –32.5 (c 0.3, CH_3OH). IR (film) ν_{max} 3276, 2979, 1732, 1320, 1149, 975, 760 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.33 (s, 9H), 1.52–1.70 (m, 2H), 1.85–2,20 (m, 2H), 2.30 (s, 3H), 2.40–2.98 (m, 7H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.3, 23.3, 27.9, 29.6, 41.5, 52.9, 53.0, 65.9, 81.0, 127.1, 129.4, 136.8, 142.9, 173.9. MS AP$^+$: *m/z* (%) = 369 (30, M + H$^+$) 313 (100, [M + H$^+$]), 267 (52, [M-CO_2H]).

(S)-Hexahydro-pyrrolo[1,2-a]pyrazin-1-one **20a**: Initially **19a** was prepared in >95% yield as a yellow oil, according to the procedure used for the synthesis of **14a**. [^{1}H NMR (200 MHz, MeOD) δ 1.90–2.28 (m, 3H), 2.30–2.60 (m, 1H), 2.95–3.95 (m, 7H). MS AP$^+$: *m/z* (%) = 157 (100, [M + H$^+$]).] To a solution of *N,N'*-dicyclohexylcarbodiimide (78 mg, 0.38 mmol) in CH_3CN (5 ml) was then added a mixture of the carboxylic acid CF_3CO_2H salt **19a** (40 mg, 0.150 mmol) and pyridine (0.76 mmol, 60 μl). The mixture was stirred at room temperature for 6 h. The solid was filtered of and the solvent was evaporated *in vacuo* and CH_2Cl_2 (1 ml) added. The solution was cooled to 0 °C for 2h. The solid was filtrated and the filtrate was concentrated under reduced pressure to yield **20a** (15 mg, 0.107 mmol, 71%) as an oil. The spectroscopic data corresponded to literature values.[28] $[\alpha]_D$ = 62.5 (c 0.4, CH_3OH). IR (film) ν_{max} 3250, 2970, 1670, 1150 cm^{-1}. ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.2, 27.7, 38.6, 46.5, 53.3, 62.1, 170.3; MS AP$^+$ (*m/z*; relative intensity): M+H$^+$ (141,100).

(S)-2-(Toluene-4-sulfonyl)hexahydropyrrolo[1,2-a]pyrazin-1-one **20b**: Initially compound **19b** was prepared in >95% yield as a yellow oil, according to the procedure for the synthesis of **14a**. R_f = 0.30 (silica gel, CH_2Cl_2/MeOH, 10:1); $[\alpha]_D$ = –16.5 (c 0.2, CH_3OH). IR (film) ν_{max} 3068, 2868, 1673, 1329, 1159, 720 cm^{-1}. ^{1}H NMR (200 MHz, MeOD) δ 1.90–2.28 (m, 4H), 2.36 (s, 3H), 2.40–2.60 (m, 1H), 3.05–3.70 (m, 5H), 4.35 (m, 1H), 7.34 (d, *J* = 7.5 Hz, 2H), 7.73 (d, *J* = 7.5 Hz, 2H). ^{13}C NMR (50 MHz, MeOD) δ 22.0, 24.0, 29.0, 40.6, 56.4, 56.5, 128.7, 131.5, 138.0, 145.8. MS AP$^+$: *m/z* (%) = 313 (100, [M + H$^+$]), 267 (52, [M-CO_2H]). HMRS: *m/z* calcd for $C_{14}H_{21}N_2O_4S$ [M+1], 313.1222; found 313.1225. To a solution of *N,N'*-dicyclohexylcarbodiimide (198 mg, 0.960 mmol) in CH_3CN (50 ml) was dropwise added a mixture of the carboxylic acid CF_3CO_2H salt **19b** (300 mg, 0.705 mmol) and pyridine (1.50 mmol, 124 μl). The mixture was stirred at room temperature for 6 h. The solvent was evaporated *in vacuo* and the residue was chromatographed (petrolether/ diethylether 2:1) to afford 162 mg (78%) of the product as colourless oil. R_f = 0.15 (silica gel, CH_2Cl_2/MeOH, 40:1); $[\alpha]_D$ = –30.0 (c 0.1, CH_3OH). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.70–2.20 (m, 4H), 2.43 (s, 3H), 2.56–2.70 (m, 2H), 2.80–2.98 (m, 2H), 3.05–3.24 (m, 2H), 4.00 (dd, *J* = 4.5 Hz, 1H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.73 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.7, 22.5, 26.7, 45.3, 48.0, 53.0, 65.3, 128.6, 129.4, 135.7, 144.9, 170.5. MS AP$^+$: *m/z* (%) = 295 (8, [M + H$^+$]), 267 (8, [M-CO]), 225 (100, [M+H$^+$-C_4H_5O]). HMRS: *m/z* calcd for $C_{14}H_{19}N_2O_3S$ [M+1], 295.1116; found 295.1119.

Received 31 March 2005; accepted 5 August 2005
Paper 05/3139

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