Synthesis of β-Lactams via Ring Opening of a Serine Derived Aziridine

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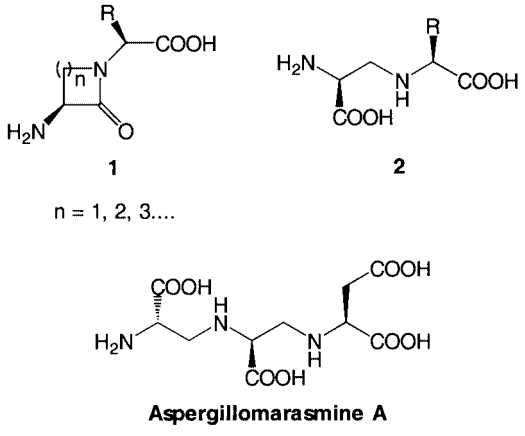
Abstract: Serine derived aziridine **15** was successfully ring-opened with amino acid esters to give diaminopropionic acid derivatives in excellent yield and regioselectivity. These compounds were cyclised to form the corresponding β-lactams in good overall yield. One example was fully deprotected to give target compound **1** (n = 1, R = Me) in excellent yield.

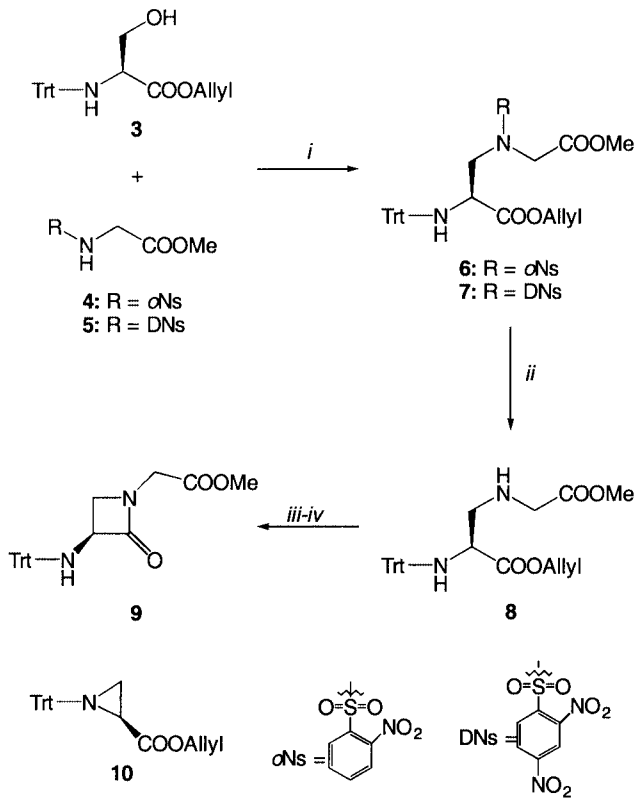
Key words: Freidinger lactams, Mitsunobu reaction, nitrobenzenesulfonamides, aziridine, stereoselective synthesis

Over the last twenty years, there has been increasing use of modified peptides in the rational design and synthesis of pharmaceuticals. Of the various modifications known, the employment of conformationally restricted peptide analogues has received considerable attention especially concerning the development of enzyme inhibitors and receptor ligands.[1] In this respect, Freidinger lactams[2] **1** (see Figure), due to their close resemblance to the parent dipeptide sequence, have been used as tools to limit the amount of conformers of biologically active oligopeptides either in efforts directed towards enhancing potency or for structure activity relationship (SAR) studies.[3] There are many reports on the syntheses of these compounds,[2–4] however, there is a notable lack of stereoselective synthetic routes to Freidinger β-lactams (**1**, n = 1). It occurred to us that such compounds should be accessible in a stereoselective manner by cyclisation of their linear counterparts **2**. The latter compounds can be considered either as modified side chain monomers or as dipeptide isosteres with enhanced resistance towards proteolytic cleavage. In addition, their structural motif in repeated form is present (Figure) in biologically active substrates such as aspergillomarasmine A.[5] The synthesis of compounds of type **2** has been previously reported albeit as a mixture of diastereoisomers.[6] We here present our investigations into the stereoselective synthesis of diaminopropionic acid derivatives **2** (R = H, Me, CH_2Ph) and their conversion into the corresponding β-lactams **1** (n = 1).



Figure

In the first instance, *N*-2-nitrobenzenesulfonamide-glycine methyl ester **4** was condensed (Scheme 1) with *N*-trityl-L-serine allyl ester[7] **3** (1.3 equivalents) under Mitsunobu conditions to give amino acid–amino acid hybrid **6** in an unacceptable 34% yield. It was reasoned, based on related observations concerning the inversion of sterically congested alcohols with carboxylic acids,[8] that



Scheme 1 Reagents and conditions: (i) Ph_3P (1.5 equiv), DEAD (1.5 equiv), THF, –5 °C to r.t., 16 h, **6:** 34%, **7:** 68%. (ii) *n*$PrNH_2$ (10 equiv), DCM, r.t., 5 min., 96%. (iii) $Pd(Ph_3)Cl_2$ (cat.), HOBt (2 equiv), Bu_3SnH (2 equiv), DCM, r.t., 30 min. (iv) EDC (1.5 equiv), DIPEA (2 equiv), DCM, r.t., 16 h, 85% (2 steps from **8**).

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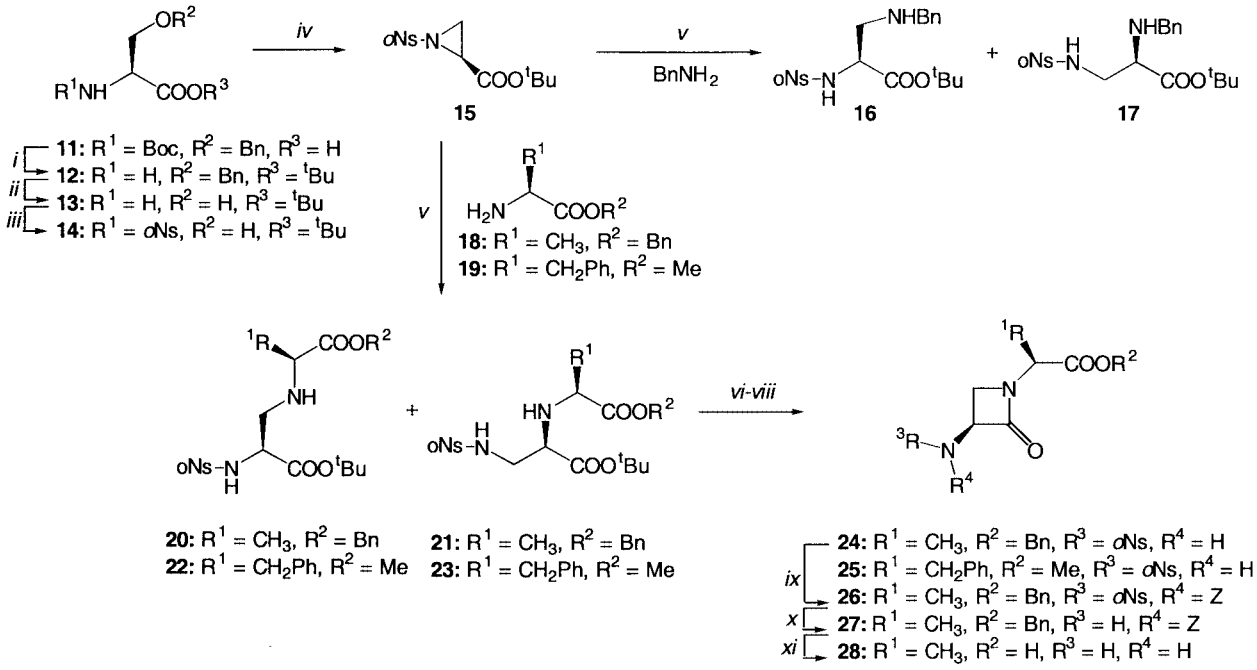
replacing the 2-nitrobenzenesulfonyl (*o*Ns) group with the more electron withdrawing 2,4-dinitrobenzenesulfonyl (DNs) group might result in a more efficient reaction. Accordingly, glycine derivative **5** was reacted with **3** under the same Mitsunobu conditions to give dipeptide isostere **7** in an improved 68% yield. However, the condensation of **3** with more functionalised amino acid (e.g. alanine, phenylalanine) esters bearing the DNs group furnished no desired product. Instead, intramolecular cyclisation of **3** was observed giving aziridine **10** typically in 40% yield.[9] Nevertheless, Freidinger β-lactam **9** could be readily obtained in good overall yield via dinitrosulfonyl cleavage of **7** furnishing **8**, followed by cleavage[10] of the allyl ester and intramolecular condensation under the agency of EDC.

The inability to form Freidinger β-lactams possessing side chain functionality on the exocyclic amino acid (e.g. **1**, n = 1, R = Me, CH_2Ph) led us to explore the ring opening of a suitably protected serine derived aziridine with α-amino acid esters. The ring opening of *(S)*-1-tosyl-aziridine-2-carboxylic acid *tert*-butyl ester with simple, primary alkyl amines has been shown to proceed with good regioselectivity and high yield[11] but the need for a large excess of amine and the harsh conditions required for cleavage of the tosyl group are notable disadvantages. Furthermore, *N*-nosyl aziridines are significantly more reactive[12] than their tosyl counterparts and the conditions for the removal of the nosyl group are comparatively mild.[13]

The required *(S)*-1-(2-nitrobenzenesulfonyl)-aziridine-2-carboxylic acid *tert*-butyl ester **15** was synthesised as shown in Scheme 2 from commercially available *N*-Boc-*O*-benzyl-L-serine **11**. Thus, protective group manipulation of **11** involving simultaneous removal of the Boc group and *tert*-butyl ester formation gave *O*-benzyl-L-serine *tert*-butyl ester **12** in 65% yield. Hydrogenation of **12** followed by sulfonamide formation under Schotten–Baumann conditions furnished aziridine precursor *N*-(*ortho*-nitrobenzenesulfonyl)-serine *tert*-butyl ester **14** in 96% yield over the two steps. Ring closure of **14** under Mitsunobu conditions provided aziridine **15** in 92% yield.[14] Although the synthetic route described above could be conducted on a multi gram scale, due to the observation that the target aziridine started to decompose upon prolonged storage, conversion of **14** to **15** was subsequently performed on a scale equal to immediate requirement.[15]

Having aziridine **15** in hand, a test reaction with benzylamine (2 equivalents) was carried out (Scheme 2) at ambient temperature in THF with a catalytic amount of triethylamine[12] resulting in a mixture of **16** and **17** in favour of ring opening at the less hindered β-carbon in an overall yield of 96%. Ring opening of **15** with both L-alanine benzyl ester **18** and L-phenylalanine methyl ester **19**, gave **20** and **22** respectively in excellent yield. In this respect it is worthwhile mentioning that the latter products were accompanied by only traces of the corresponding α-attack products **21** and **23**. In contrast to the ring opening



Scheme 2 Reagents and conditions: (i) *t*BuOAc, $HClO_4$, 65%. (ii) Pd/C, H_2, 1 M HCl aq (1 equiv), dioxane/H_2O 1/1 (v/v), r.t., 16 h. (iii) *o*NsCl (1.2 equiv), Na_2CO_3 (1.3 equiv), dioxane/H_2O 1/1 (v/v), r.t., 3 h, 96% (2 steps from **12**). (iv) Ph_3P (1.2 equiv), DEAD (1.2 equiv), THF, –5 °C, 1 h, 92%. (v) Et_3N (0.2 equiv), THF, r.t., 16 h, **16:** 74%, **17:** 22%, **20/21:** 94% (17/1), **22/23:** 88% (15/1). (vi) TFA, r.t., 30 min. (vii) 1 M HCl aq/dioxane 1/1 (v/v), r.t., 5 min. (viii) EDC (1.5 equiv), DIPEA (2 equiv), DCM, r.t., 16 h, **24:** 73% (from **15**), **25:** 75% (from **15**). (ix) Z-Cl (2 equiv), pyridine (1.5 equiv), DCM, 0 °C, 6 h, 90%. (x) PhSH (5 equiv), DIPEA (4 equiv), DMF, r.t., 4 h, 99%. (xi) Pd/C, H_2, AcOH (1.5 equiv), dioxane/H_2O 1/1 (v/v), r.t., 16 h, 100%.

of **15** with benzylamine, the aforementioned α-attack products observed from the reaction of amino acid esters **18** and **19** with **15** could not be separated from the major products **20** and **22** by column chromatography.[16] Nonetheless, treatment of the crude mixtures with trifluoroacetic acid (TFA) to cleave the *tert*-butyl ester, followed by their transformation to the corresponding HCl salts and cyclisation under the agency of EDC, gave the β-lactams **24** and **25** which could be isolated in a pure form and in good yield.[17]

Although it is possible to deprotect primary nitrobenzenesulfonamides,[12] the reaction conditions required are potentially detrimental to the integrity of the lactam ring.[18] However, the *o*Ns protecting group can be activated for conventional, mild deprotection by conversion of the primary sulfonamide to the corresponding urethane protected nitrobenzenesulfonylimide.[12] In order to confirm this, β-lactam **24** was reacted with benzyl chloroformate[19] to give **26**. Treatment of **26** with thiophenol (5 equivalents) in the presence of DIPEA (4 equivalents),[20] gave the benzyloxy carbonyl protected Freidinger β-lactam **27** in excellent yield. Deprotection of **27** by palladium assisted hydrogenation in the presence of acetic acid (1.5 equivalents) afforded **28** in quantitative yield.

In summary, the Mitsunobu condensation of amino acids onto the side chain of serine to form dipeptide isosteres of type **2** could only be realised with glycine derivatives **4** and **5**. However, further examples were obtained by ring opening serine-derived aziridine **15** with α-amino acid esters **18** and **19**. Compounds of type **2** made in either way were readily cyclised to form the target Freidinger β-lactams (**1**, n = 1) in good overall yield. Furthermore, the ability to fully deprotect these compounds was demonstrated by the conversion of **24** to **28** in excellent yield. The efficient and facile synthesis of aziridine **15** in conjunction with its regioselective and high yielding ring opening with amino acid esters represents an attractive route to the synthesis of both target compounds **1** (n = 1) and **2**.

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(7) All new compounds were fully characterised by ^{1}H and ^{13}C NMR spectroscopy as well as mass spectrometry. Data for selected examples is as follows. ***(S)*-1-(2-Nitrobenzenesulfonyl)-aziridine-2-carboxylic Acid *tert*-Butyl Ester(15)**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.30–8.25 (m, 1 H, 1 × H_{arom} *o*Ns), 7.81–7.74 (m, 3 H, 1 × H_{arom} *o*Ns), 3.52 (dd, 1 H, H_2, $J_{2,3}$ = 7.3 Hz, $J_{2,3'}$ = 4.4 Hz), 3.02 (d, 1 H, H_3), 2.72 (d, 1 H, $H_{3'}$), 1.49 (s, 9 H, CH_3 *t*-Bu); ^{13}C NMR (50 MHz, $CDCl_3$): δ 164.8 (C_1), 147.8 (C-NO_2), 134.6, 132.0, 130.6, 124.1 (CH_{arom} *o*Ns), 82.4 (C_q *t*-Bu), 38.0 (C_2), 33.1 (C_3), 27.1 (CH_3 *t*-Bu); MS (ESI): *m/z* (%) = 351.0 $[M + Na]^+$. ***(S)*-3-Benzylamino-2-(2-nitro-benzenesulfonylamino)-propionic Acid *tert*-Butyl Ester(16)**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.11–8.08 (m, 1 H, 1 × H_{arom} *o*Ns), 7.94–7.90 (m, 1 H, 1 × H_{arom} *o*Ns), 7.73–7.68 (m, 2 H, 1 × H_{arom} *o*Ns), 7.30 (m, 5 H, H_{arom} Bn), 6.35 (bs, 1 H, NH-*o*Ns), 4.19 (t, 1 H, H_2, $J_{2,3}$ = 4.8 Hz), 3.82 (AB, 2 H, CH_2 Bn), 2.99 (d, 2 H, H_3), 1.25 (CH_3 *t*-Bu); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.9 (C_1), 133.5, 132.8, 130.4 (3 × CH_{arom} *o*Ns), 128.4, 128.0, 127.1 (CH_{arom} Bn), 126.5 (C_q Bn), 125.5 (1 × CH_{arom} *o*Ns), 82.7 (C_q *t*-Bu), 57.0 (C_2), 53.1, 50.7 (C_3 and CH_2 Bn), 27.6 (CH_3 *t*-Bu); MS (ESI): *m/z* (%) = 436.2 $[M + H]^+$. ***(R)*-2-Benzylamino-3-(2-nitro-benzenesulfonylamino)-propionic Acid *tert*-Butyl Ester(17)**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16–8.08 (m, 1 H, 1 × H_{arom} *o*Ns), 7.92–7.83 (m, 1 H, 1 × H_{arom} *o*Ns), 7.78–7.70 (m, 2 H, 1 × H_{arom} *o*Ns), 7.35–7.23 (m, 5 H, H_{arom} Bn), 6.12 (bs, 1 H, NH-*o*Ns), 3.70 (AB, 2 H, CH_2 Bn), 3.39–3.27 (m, 2 H, H_2 and 1 × H_3), 3.13–3.07 (m, 1 H, 1 × H_3), 1.49 (CH_3 *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4 (C_1), 148.1 (C-NO_2), 139.0 (C_q Bn), 135.1, 132.7, 131.0 (3 × CH_{arom} *o*Ns), 128.4, 128.2, 127.3 (CH_{arom} Bn), 126.5 (C_q Bn), 125.3 (1 × CH_{arom} *o*Ns), 82.7 (C_q *t*-Bu), 59.9 (C_2), 52.0 (CH_2 Bn), 45.0 (C_3), 28.0 (CH_3 *t*-Bu);); MS (ESI): *m/z* (%) = 436.2 $[M + H]^+$. ***(S)*-3-(*(S)*-1-Methoxycarbonyl-2-phenyl-ethylamino)-2-(2-nitrobenzenesulfonylamino)-propionic Acid *tert*-Butyl Ester(22)**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08–8.03 (m, 1 H, 1 × H_{arom} *o*Ns), 7.94–7.90 (m, 1 H, 1 × H_{arom} *o*Ns), 7.75–7.67 (m, 2 H, 1 × H_{arom} *o*Ns), 7.31–7.13 (m, 5 H, H_{arom} Ph), 6.46 (bd, 1 H, NH *o*Ns, $J_{NH,2}$ = 8.7 Hz), 4.12 (m, 1 H, H_2), 3.66 (s, 3 H, OMe), 3.46 (m, 1 H, $H_{1'}$), 3.12 (dd, 1 H, H_{3a}, $J_{3a,3b}$ = 12.3 Hz, $J_{3a,2}$ = 4.4 Hz), 2.92–2.74 (m, 2 H, $H_{2'}$), 2.72 (dd, 1 H, H_{3b}, $J_{3b,2}$ = 4.5 Hz), 1.22 (s, 9 H, CH_3 *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.2, 168.7 (C_1, COOMe), 147.6 (C-NO_2), 136.6 (C_q, Ph), 134.5 (C-SO_2), 133.4, 132.7, 130.4 (3 × CH_{arom} *o*Ns), 129.1, 128.4, 126.7 (CH_{arom} Ph), 125.4 (1 × CH_{arom} *o*Ns), 82.6 (C_q, *t*-Bu), 62.5 ($C_{1'}$), 57.2 (C_2), 51.7 (COOMe), 49.8 (C_3), 39.6 ($C_{2'}$), 27.5 (CH_3, *t*-Bu); MS (ESI): *m/z* (%) = 508.3 $[M + H]^+$. ***(S)*-2-[*(S)*-3-(2-Nitrobenzenesulfonylamino)-2-oxo-azetidin-1-yl]-propionic Acid Benzyl Ester(24)**: ^{1}H NMR ($CDCl_3$): δ 8.16–8.13 (m, 1 H, 1 × H_{arom} *o*Ns), 7.92–7.89 (m, 1 H, 1 × H_{arom} *o*Ns), 7.78–7.72 (m, 2 H, 1 × H_{arom} *o*Ns), 7.41–7.32 (m, 5 H, H_{arom} Bn), 6.28 (bs, 1 H, NH), 5.17 (s, 2 H, CH_2 Bn), 4.70 (dd, 1 H, $H_{3'}$ ser, $J_{3',4a'}$ = 5.2 Hz, $J_{3',4b'}$ = 2.5 Hz), 4.45 (q, 1 H, H_2 ala, $J_{2,3}$ = 7.4 Hz), 3.65 (app. t, 1 H, $H_{4a'}$ ser), 3.42 (dd, 1 H,

$H_{4b'}$ ser, $J_{4b',4a'}$ = 5.9 Hz), 1.41 (d, 3 H, H_3). ^{13}C NMR ($CDCl_3$): δ 170.2, 164.7 (2 × C=O), 147.8 (C-NO_2), 135.0 (C_q Bn), 134.0, 133.0, 130.9 (3 × CH_{arom} *o*Ns), 128.7, 128.7, 128.3 (CH_{arom} Bn), 125.6 (1 × CH_{arom} *o*Ns), 67.5 (CH_2 Bn), 58.6 ($C_{3'}$), 49.7 (C_2), 47.0 ($C_{4'}$), 15.0 (C_3); MS (ESI): *m/z* (%) = 434.0 $[M + H]^+$, 456.1 $[M + Na]^+$. ***(S)*-2-(*(S)*-3-Amino-2-oxo-azetidin-1-yl)-propionic Acid(28)**: ^1H NMR (600 MHz, D_2O): δ 4.26 (dd, 1 H, $H_{3'}$, $J_{3',4a'}$ = 5.0 Hz, $J_{3',4b'}$ = 10.0 Hz), 4.01 (q, 1 H, H_2, $J_{2,3}$ = 7.2 Hz), 3.79 (dd, 1 H, $H_{4a'}$, $J_{4a',4b'}$ = 13.1 Hz), 3.30 (dd, 1 H, $H_{4b'}$), 1.52 (d, 3 H, H_3); MS (ESI): *m/z* (%) = 158.9 $[M + H]^+$.

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(14) ***N*-(2-Nitrobenzenesulfonyl)-l-serine *tert*-Butyl Ester 14** was coevaporated with 1,2-dichloroethane (3 × 10 mL), dissolved in THF (10 mL/mmol), cooled to –5 °C and PPh_3 (1.2 eq) was added. After stirring for 5 min, DEAD (1.2 eq) was added dropwise over a period of 30 min and the reaction was maintained at low temperature for a further 30 min whereupon the reaction mixture was diluted with toluene (10 mL/mmol) and concentrated in vacuo at 30 °C to give an orange oil. The residue was purified by column chromatography on silica gel (toluene/acetone) to give **15** as a colourless oil in 92% yield.

(15) It should be noted that aziridine **15** had to be purified directly, to prevent its decomposition presumably by attack from byproducts of the Mitsunobu reaction.

(16) The ratios of **20**:**21** and **22**:**23** were obtained by NMR spectroscopy and further confirmed with reverse phase LCMS where the products were clearly separable.

(17) The enantiomer of aziridine **15** was subjected to ring opening with **18** and cyclised to the β-lactam. Comparison of this compound to **24** as well as comparing the major ring opened product to **20** (^1H NMR) showed that the reaction sequence proceeds without detectable racemisation (> 95% diastereomeric purity).

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