SYNTHESIS OF A BICYCLIC γ-LACTAM DIPEPTIDE ANALOGUE

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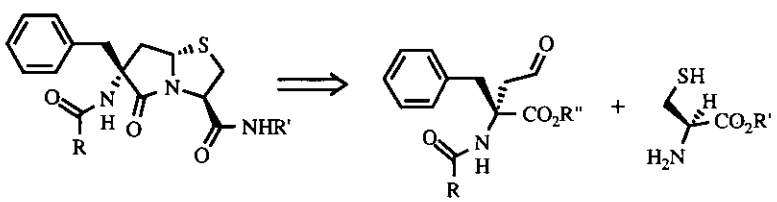
Abstract - The asymmetric synthesis of a bicyclic γ-lactam analogue of a dipeptide, in which the key step was the bis-alkylation of an optically active diphenyloxazinone chiral glycine anion equivalent is described.

In recent years both ourselves[1] and others[2] have synthesised γ-lactams designed to act as antibacterials by the inhibition of transpeptidases. Some of these compounds have displayed interesting biological activities.[3] As a result of a desire to extend the use of γ-lactams for the inhibition of therapeutically important proteases we wished to synthesise conformationally restricted analogues of Phe-Pro or Tyr-Pro, which are cleavage sites for the HIV protease.[4] In this communication we describe the asymmetric synthesis of a bicyclic analogue of Phe-Pro (**1**), in which the key step was the dialkylation of a chiral diphenyloxazinone glycine anion equivalent.[5]



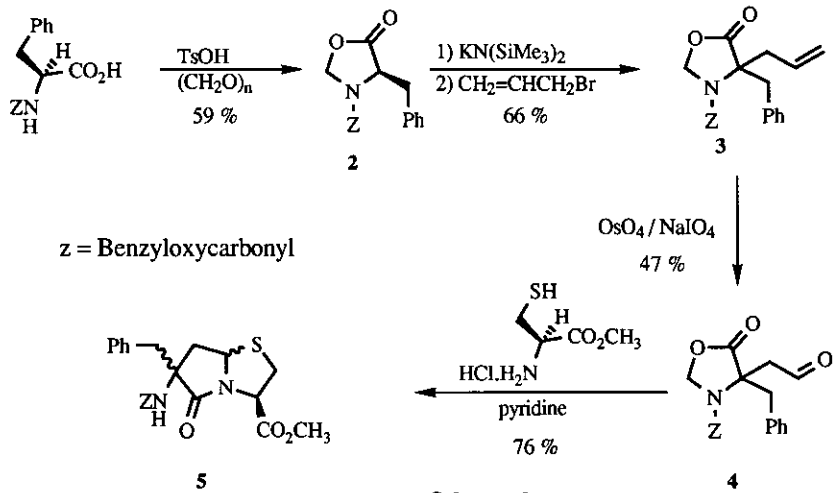
1

Scheme 1

We envisaged that the desired ring system could be obtained from amino acid derived precursors (Scheme 1) and the literature contains several methods for the synthesis of monocyclic lactams containing quaternary substituted centres, adjacent to the lactam carbonyl.[6,7] There was, however, no precedent for the synthesis of bicyclic γ-lactams by lactamisation of α-alkylated amino acid precursors such as we plannned to do. Hence, in order to test the feasibility of the cyclisation reactions, a model study was undertaken using readily available racemic materials.

The oxazolidinone (**2**), synthesised from (*S*)-N-CBz-Phe, paraformaldehyde, *p*-toluenesulphonic acid, was deprotonated with potassium bis(trimethylsilyl)amide and quenched with allyl bromide to give the quaternary substituted oxazolidinone (**3**)[6] (Scheme 2). Oxidation of the double bond with sodium periodiate/osmium tetroxide (cat.) gave the aldehyde (**4**), which was condensed with *R*-cysteine methyl ester hydrochloride in refluxing pyridine to give the desired bicylic γ-lactam (**5**), as a mixture of diastereomers (76 %).

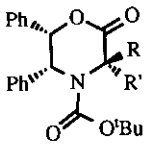
The next objective was to synthesise (**1**) in a chiral form. Methods for the asymmetric syntheses of α-substituted amino acids are extensively documented.[8] Williams has pioneered the use of optically active oxazinone derivatives as chiral glycine anion equivalents for the synthesis of mono- and dialkylated amino acids[5] and it was anticipated that this method would allow the synthesis of the desired α–alkylated amino acid[9] for the synthesis of chiral **1**.



2 **3** **4** **5**

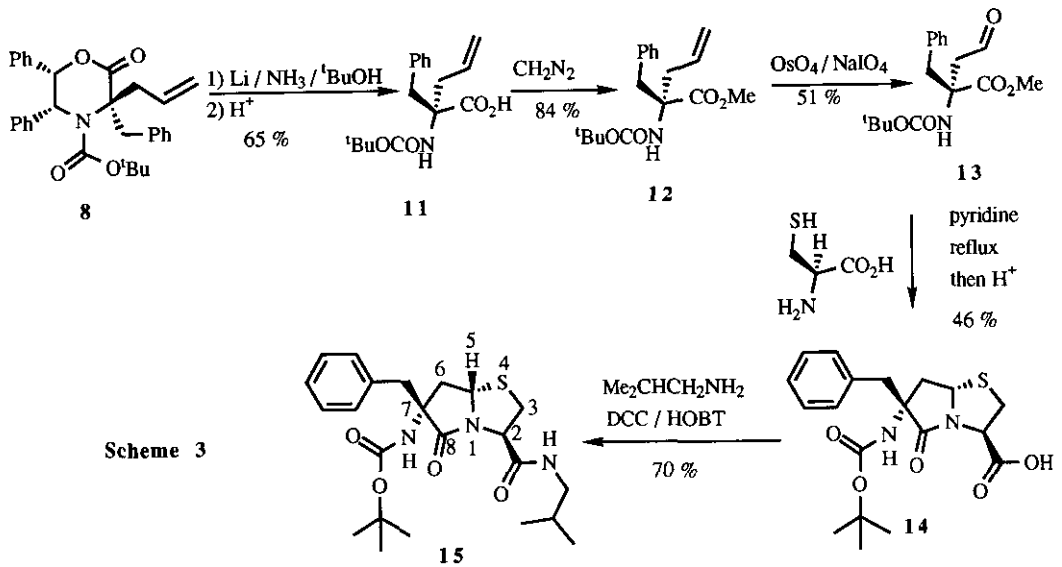
Scheme 2

Deprotonation of (**6**) with sodium bis(trimethylsilyl)amide followed by quenching with benzyl bromide gave the α-benzylated heterocycle (**7**) {mp 158-159°C, $[\alpha]_D^{20}$ -45.4° (*c* 1.09 in $CHCl_3$)} (93%), which was subsequently deprotonated with the same base and quenched with allyl bromide to give the dialkylated compound (**8**) {$[\alpha]_D^{20}$ -13.5° (*c* 1.03 in $CHCl_3$)}(96%). Reversal of the order of alkylations gave (**10**) {$[\alpha]_D^{20}$ -92.3° (*c* 0.66 in $CHCl_3$)} [*via* (**9**) {mp 176-177°C, $[\alpha]_D^{20}$ +63.4° (*c* 0.70 in $CHCl_3$)}] [57 % overall from (**6**)]. We were unable to detect any cross contamination between the samples of (**8**) [in $(CD_3)_2SO$ at 353 K] and (**10**) (in $(CD_3)_2SO$ at 383 K) by ^1H nmr (500 MHz).



6, R = R' = H
7, R = Bn, R' = H
8, R = $CH_2CH=CH_2$, R' = Bn
9, R = $CH_2CH=CH_2$, R' = H
10, R = Bn, R' = $CH_2CH=CH_2$

The heterocycle (**8**) was subjected to Birch reduction cleavage to give N-BOC amino acid (**11**) {mp 121-122°C, $[\alpha]_D^{20}$ +20.1° (*c* 0.78 in $CHCl_3$)}after acidic workup (Scheme 3) which was esterified with diazomethane to give methyl ester (**12**) {$[\alpha]_D^{20}$ +55.0° (*c* 0.59 in $CHCl_3$)}. Subsequent oxidation [sodium periodiate/osmium tetroxide (cat.)] gave aldehyde (**13**) which was condensed with *R*-cysteine in refluxing pyridine to give a single isolated bicylic γ-lactam free acid (**14**) {mp 181-184°C, $[\alpha]_D^{20}$ -107.4° (*c* 0.61 in $CHCl_3$)}. Acid (**14**) was coupled to isobutylamine (dicyclohexylcarbodiimide / 1-hydroxybenzotriazole) to give the corresponding isobutyl amide (**15**) {$[\alpha]_D^{20}$ -96.0° (*c* 0.62 in $CHCl_3$). The stereochemistry of γ-lactam isobutyl amide (**15**) was provisionally assigned by NOE difference studies.[10]



Scheme 3

ACKNOWLEDGEMENT

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10. Selected NOE data (% enhancements in parentheses): irradiation of 5-H caused enhancement of Ar-H (5) and N<u>H</u>-^{i}Bu (4); irradiation of β3-H caused enhancement of 5-H (2); 2-H (2) and α3-H (26); irradiation of α3-H caused enhancement of β3-H (37) and 2-H (12); irradiation of N<u>H</u>-^{i}Bu caused enhancement of 2-H (7) and 5-H (5); irradiation of Ar-H caused enhancement of 5-H (5) and C<u>H</u>Me$_2$ (5).

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