

## Regio- and Stereoselective Functionalisation of Monocyclic Medium Ring Lactams

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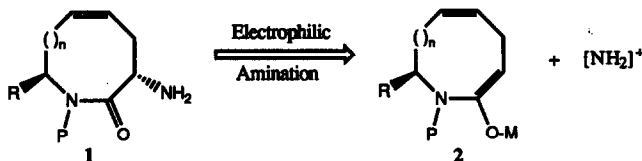
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**Abstract:** The functionalisation of the potassium enolates of a series of racemic 7-, 8-, and 9-membered unsaturated lactams with trisyl azide and phenylselenenyl chloride afforded the corresponding 3,*n*-disubstituted lactams with good stereoselectivities.

The regio- and stereoselective functionalisation of monocyclic medium ring lactams is an underdeveloped area,<sup>1</sup> although Hagen<sup>2</sup> has recently investigated the alkylation of the lithium enolates of *N*-tert-butyloxycarbonyl protected derivatives. However, the diastereoselectivity of these processes was not investigated, and recent work with medium ring lactones has shown that conformational control can profoundly influence the outcome.<sup>3</sup>

Figure 1



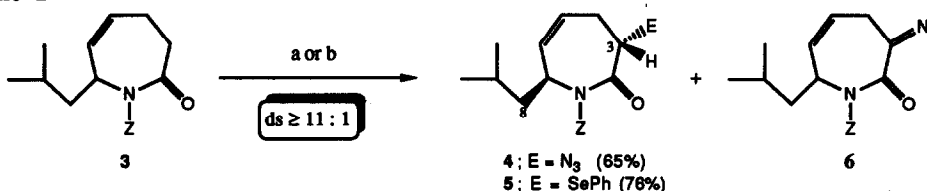
In this Letter we report the electrophilic amination of the enolates 2 as an approach to a family of conformationally rigid medium ring lactams 1 (Figure 1). An extensive literature on  $[NR_2]^+$  synthons exists, and has been comprehensively reviewed on several occasions,<sup>4</sup> with a notable contribution by Evans and co-workers in the development of the  $[N_3]^+$  synthon.<sup>5</sup> The *N*-benzyloxycarbonyl-protected medium ring unsaturated lactams which we have prepared<sup>6</sup> have a similar substructure to the imides used by Evans.<sup>5</sup> However, owing to the fact that the enolate double bond of 2 is endocyclic, the (*E*)-configuration will be preferred. We report here the outcome of the reactions of the enolates 2 with electrophilic azide and selenium reagents.

The racemic *N*-benzyloxycarbonyl azepin-2-one 3<sup>6</sup> was treated with potassium hexamethyldisilazide (KHMDS) to generate the enolate, followed by reaction with trisyl azide<sup>7</sup> for 5 minutes before being quenched by the rapid addition of glacial acetic acid.<sup>5</sup> The resulting azide 4 was obtained diastereoselectively (92 : 8 as detected by <sup>1</sup>H NMR) in 65% yield (Scheme 1). Molecular modelling of the enol derived from 3 shows that the preferred approach of electrophiles is likely to be from opposite the isobutyl substituent, thus favouring the *trans*-isomer.<sup>8</sup> This was supported by the observation in the <sup>1</sup>H NMR spectrum of 4 of a strong n.O.e between

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the methine proton at C-3 proton and the C-8 methylene protons of the isobutyl side chain. The n.o.e results also gave an indication of the solution conformation of **4**. The *trans* stereochemistry was supported by spectroscopic similarities ( $^1\text{H}$  NMR chemical shift and coupling constants of the proton at C-3)<sup>10</sup> to the corresponding phenylseleno derivative **5**, the X-ray crystal structure<sup>11</sup> of which also confirmed the *trans* relationship between the selenium substituent and the isobutyl side chain. It is of interest to note in passing that the diastereoselectivity (d.e. 84%) of the azide reaction with racemic lactam **4** was significantly less than with the previously described<sup>12</sup> enantiomerically pure material (d.e.  $\geq 90\%$ ).

#### Scheme 1

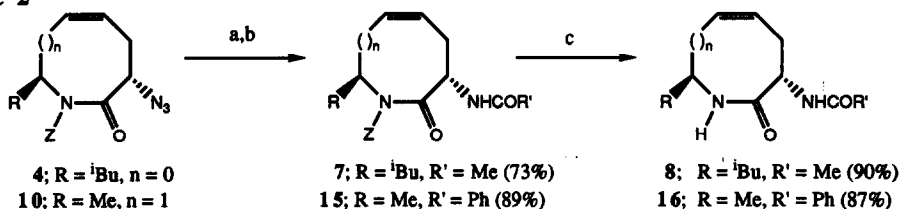


**Reagents and conditions**:- (a) KHMDS, THF,  $-78^\circ\text{C}$ , 1 h, followed by trisyl azide,  $-78^\circ\text{C}$ , 5 min, then by AcOH,  $-78^\circ\text{C}$  to RT, 30 min. (b) KHMDS, THF,  $-78^\circ\text{C}$ , 1 h; PhSeCl,  $-78^\circ\text{C}$ , 3 h, followed by AcOH,  $-78^\circ\text{C}$  to RT, 30 min.

The variability in yields of the azide transfer reaction was due to the formation of diazoketone **6** which was isolated in 14–42% yield. This problem had already been noted by Evans and co-workers,<sup>5</sup> who introduced the potassium acetate work-up specifically to eradicate diazoketone formation. However, it does appear that the yields of azidation of imide enolates can be quite substrate dependent as Evans has recently reported.<sup>13</sup>

The azide **4** was transformed into the differentially protected dipeptide unit **8** by a series of functional group manipulations (Scheme 2). Reduction with stannous chloride<sup>14</sup> in methanol, followed by *N*-acylation, furnished the *N*-benzyloxycarbonyl derivative **7** in 73% overall yield. Removal of the benzyloxycarbonyl protecting group with 45% hydrobromic acid in acetic acid<sup>15</sup> afforded the dipeptide **8** in 90% yield.

#### Scheme 2

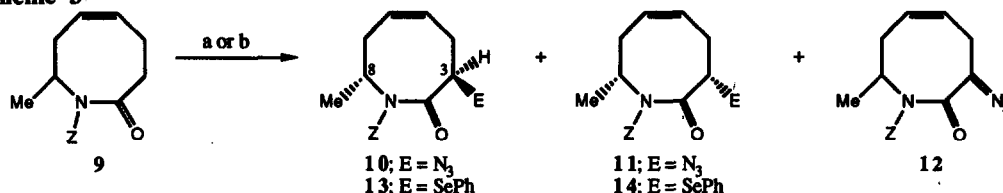


**Reagents and conditions**:- for n = 0, (a) SnCl<sub>2</sub>, MeOH, 0 °C to RT, 2.5 h; (b) AcCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to RT, 2.5 h; (c) 45% HBr in AcOH, RT, 1 h; for n = 1, (a) SnCl<sub>2</sub>, 0 °C to RT, 3 h; (b) BzCl, 4-dimethylaminopyridine, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to RT, 16 h; (c) BBr<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to RT, 1 h.

The eight-membered lactam **9** was similarly converted into a 4 : 1 mixture of the azides **10** and **11** in 80% yield (Scheme 3). The diazoketone **12** was also obtained, but unlike the previous example its formation was not as problematic. The observation in the  $^1\text{H}$  NMR of an n.o.e between the proton at C-3 and the protons of the C-8 methyl group in the major diastereoisomer again indicated *trans* stereochemistry.

Alkylation of the enolate derived from **9** with phenylselenenyl chloride furnished a 1 : 1 mixture of the phenylseleno-substituted lactams **13** and **14** in 62% yield (Scheme 3). The lack of diastereoselectivity was

### Scheme 3



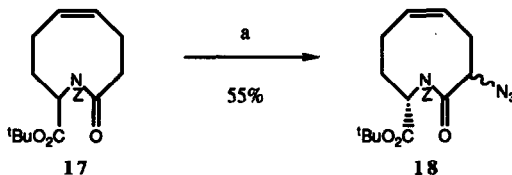
*Reagents and conditions*:- (a) KHMDS, THF,  $-78^{\circ}\text{C}$ , 1 h, followed by trisyl azide,  $-78^{\circ}\text{C}$ , 5 min, then AcOH,  $-78^{\circ}\text{C}$  to RT, 30 min (b) KHMDS, THF,  $-78^{\circ}\text{C}$ , 1 h, followed by PhSeCl,  $-78^{\circ}\text{C}$ , 3 h., then AcOH,  $-78^{\circ}\text{C}$  to RT, 30 min.

attributed to proton transfer during the alkylation since kinetic protonation with glacial acetic acid of the enolate derived from **14** gave a 3 : 1 mixture of the diastereoisomers **14** and **13** respectively.

Reduction<sup>14</sup> of the azide **10** as above, followed by *N*-benzyloxycarbonylation furnished the *N*-benzyloxycarbonyl dipeptide **15** in 89% overall yield (Scheme 2). Removal of the benzyloxycarbonyl protecting group with boron tribromide<sup>16</sup> afforded the dipeptide **16** in 87% yield.

The analogous azidation of the nine-membered lactam **17** gave the azides **18** as a 1.4 : 1 mixture of diastereoisomers in 55% yield (Scheme 4). The lower selectivity may be due to increased conformational flexibility in the enolate precursor.

### Scheme 4



*Reagents and conditions*:- (a) KHMDS, THF,  $-78^{\circ}\text{C}$ , 1 h, followed by trisyl azide,  $-78^{\circ}\text{C}$ , 5 min, then AcOH,  $-78^{\circ}\text{C}$  to RT, 30 min.

In summary we have shown that the introduction of amino substituents adjacent to the lactam carbonyl group using the Evans methodology can be achieved with good diastereocontrol in unsaturated medium ring lactam derivatives.<sup>17</sup> These compounds are well disposed to serve as potential constraints in sequences of bioactive peptides, and we are actively pursuing this area.

### Acknowledgements

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8. The enol corresponding to 3 was modelled using MacroModel<sup>®</sup> v 2.5 in the multiconformer mode<sup>9</sup> using torsion angles varied by 60° increments with a closure window of 1-3 Å. The lowest energy conformation (by 6 kJ mole<sup>-1</sup>) is shown in Figure 2.

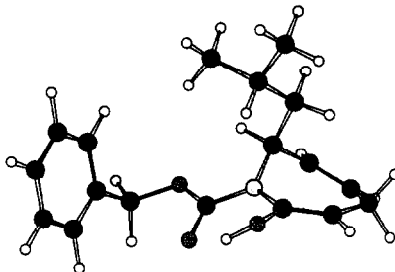


Figure 2: Minimum energy conformation of the enol form of 3

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10. Azide 4:  $\delta_{\text{H-3}}$  4.31 ( $J_{3,4}$  11.9,  $J_{3,4'}$  3.7); Phenylselenide 5:  $\delta_{\text{H-3}}$  4.52 ( $J_{3,4}$  12.4,  $J_{3,4'}$  3.4).
11. Compound 5 formed triclinic crystals, m.p. 101-103 °C, space group  $P\bar{1}$ ,  $a = 9.465(1)$ ,  $b = 9.739(1)$ ,  $c = 13.761(2)$  Å,  $\alpha = 97.73(1)^\circ$ ,  $\beta = 91.83(1)^\circ$ ,  $\gamma = 117.16(1)^\circ$  and revealed the structure shown in Figure 3. A full set of bond angles, bond lengths, atomic coordinates, and structure factors has been deposited with the Cambridge Crystallographic Data Centre.

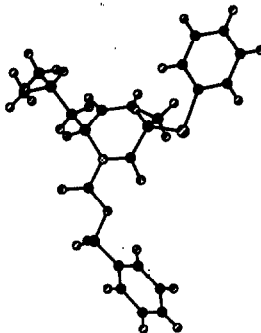


Figure 3: The X-ray crystal structure of the lactam 5

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13. Evans, D.A.; Lundy, K.M. *J. Am. Chem. Soc.*, 1992, 114, 1496-1496. Tc 3D TD 3 1Tc 0.0011 Tw (Tetrahedron:) T5e(
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17. All new compounds exhibited spectroscopic (IR and NMR) and analytical (combustion analysis and/or high resolution MS) data in accord with the assigned structure.