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Synthesis of Monocyclic Medium Ring Lactams

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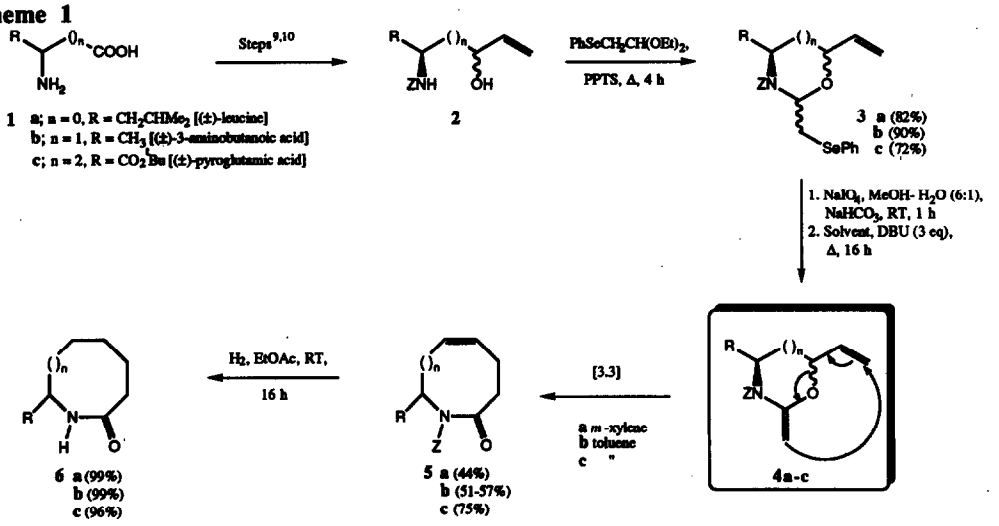
Abstract: The Claisen rearrangement of the vinyl substituted ketene aminals **4a-c** which were generated *in situ* by selenoxide elimination of the aminal precursors **3a-c** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene gave the monocyclic unsaturated medium ring lactams **5a-c**.

Monocyclic medium ring nitrogen heterocycles are particularly challenging targets owing to the difficulties associated with their construction, and they constitute an important class of compounds both in terms of natural and unnatural products.[1,2] The medium sized rings, in particular, the eight- and nine-membered rings are generally the most difficult to prepare by methods involving conventional cyclisation of acyclic precursors.[3] Current synthetic methodology for the preparation of this class of compounds still remains very specific, with limited attention given to stereocontrol,[1-5] and the search for synthetic methods for the preparation of a various ring sizes still continues to attract attention.[6] In this respect the Claisen rearrangement[7,8] of vinyl-substituted ketene acetals and aminals is expected to serve as a rather general approach to medium ring unsaturated heterocycles.[9] In this Letter we report its application to the synthesis of the racemic 7-, 8- and 9-membered unsaturated lactams **5** (Scheme 1).

Scheme 1



The α-, β- and γ-amino acids **1a-c** were converted respectively to the corresponding vinyl-substituted 1,2-, 1,3- and 1,4-amino alcohols[9,10] **2a-c** as mixtures of diastereoisomers using standard procedures.

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Cyclisation of the amino alcohols with pyridinium *p*-toluenesulphonate (PPTS) and phenylselenoacetaldehyde diethyl acetal[8c,11] under Dean-Stark conditions furnished the corresponding aminals **3a-c**. These were oxidised to the selenoxides in quantitative yields using sodium periodate. When heated under reflux in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) the selenoxides were presumed to form the ketene aminals **4a-c** which then underwent *in situ* [3.3] sigmatropic rearrangement to furnish the *cis*-unsaturated lactams **5a-c** respectively in yields of 44%, 51-57%, and 75%.

The above results indicate that the Claisen methodology is more efficient for the larger rings, presumably owing to the relative ease of formation of the (presumed) chair-like transition-state required for Claisen rearrangement. The fully reduced and *N*-deprotected lactams **6a-c** were obtained by catalytic hydrogenation of the unsaturated *N*-benzyloxycarbonyl lactams **5a-c** in the presence of Pearlman's catalyst. In summary these studies have demonstrated the development of a *new and general method* for the preparation of the 7-, 8- and 9-membered lactams.[12] These structures have traditionally been rather inaccessible by the currently available methods. In the adjacent Letter we describe ring functionalisation with electrophiles.

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12. All new compounds exhibited spectroscopic (IR and NMR) and analytical (combustion analysis and/or high resolution MS) data in accord with the assigned structure.

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