

Synthesis Of Homochiral Unsaturated Seven-Membered Lactams

P. Andrew Evans and Andrew B. Holmes*

University Chemical Laboratory, Lensfield Road, CAMBRIDGE CB2 1EW, U.K.

Keith Russell†

I.C.I. Pharmaceuticals, Mereside, Alderley Park, MACCLESFIELD, SK10 4TG, U.K.

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Abstract: The Claisen rearrangement of the vinyl substituted ketene aminals **6** which were generated *in situ* by selenoxide elimination of the aminal precursors **5** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave the homochiral unsaturated seven-membered lactams **7**.

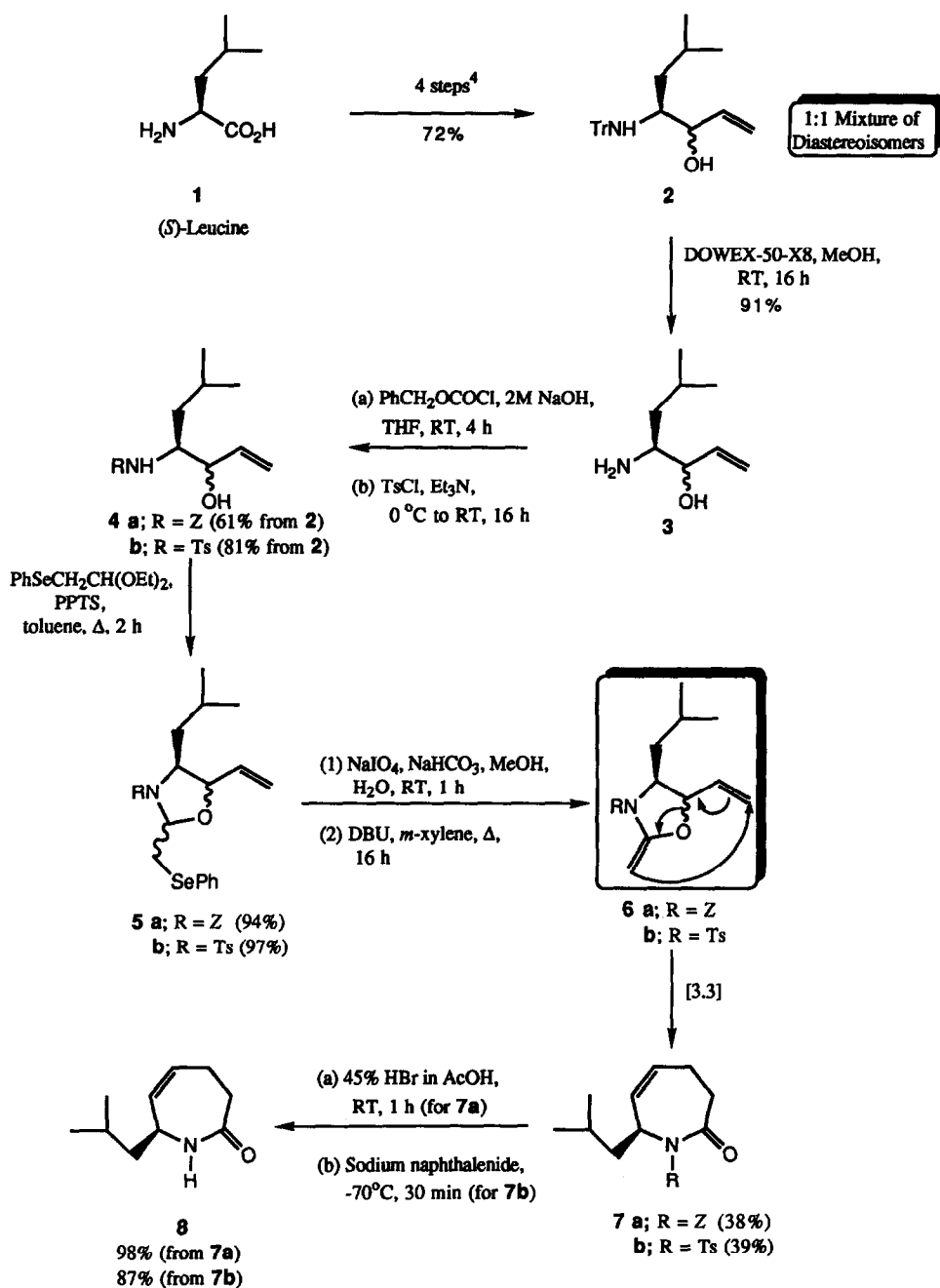
Monocyclic medium ring nitrogen heterocycles are an extremely important class of compounds which occur in a range of natural products. The methods so far employed to synthesise such compounds are often not very versatile, and limited attention has been given to stereocontrol.¹ In this Letter we report the first phase of an approach to monocyclic medium ring lactams which employs the Claisen rearrangement^{2,3} in a ring expansion of a vinyl ketene aminal **6** to afford homochiral 7-substituted tetrahydro-azepin-2-ones **7**.

Scheme 1 illustrates the conversion of (*S*)-leucine **1** into the *N*-trityl vinyl amino alcohol **2⁴** as a 1:1 mixture of diastereoisomers in an overall yield of 72%. Deprotection of the trityl group was achieved using Dowex-50-X8 resin (H⁺ form) to afford the required vinyl amino alcohol **3⁵** which was *N*-protected, using benzyl chloroformate and sodium hydroxide, to furnish the vinyl *Z*-protected amino alcohol **4a⁵** in 61% overall yield. Benzyloxycarbonyl-protected amino-alcohols form stable aminals.⁶ Treatment of **4a** with *p*-toluenesulphonic acid and phenylseleno-acetaldehyde diethyl acetal⁷ under Dean-Stark conditions furnished the aminal **5a⁵** in 51% yield. The moderate yield was improved to 94% by using the milder catalyst pyridinium *p*-toluenesulphonate.

The aminal **5a** was oxidised with sodium periodate to the corresponding selenoxides quantitatively,^{3a,b} which on treatment with DBU in refluxing *m*-xylene generated the ketene aminals **6a** which underwent [3,3] sigmatropic rearrangement^{3,8} *in situ* to give the required *Z*-protected-7-substituted azepin-2-one **7a⁵** $[\alpha]_{\text{D}}^{20} = +223.9$ (*c* 1.64, MeOH) in 38% yield. The moderate yield was attributed to the instability of the aminal. Deprotection of the benzyloxycarbonyl protecting group with 45% hydrobromic acid in acetic acid⁹ afforded the 7-substituted azepin-2-one **8⁵** $[\alpha]_{\text{D}}^{20} = +15.3$ (*c* 1.38, MeOH) in 98% yield.

A similar sequence was carried out on the *N*-tosyl analogue **4b⁵**, prepared by tosylation of **3** with *p*-toluenesulphonyl chloride and triethylamine in 82% yield. It was expected that the *N*-tosyl aminal, **5b⁵** would better survive the vigorous rearrangement conditions. However, when it was heated in refluxing *m*-xylene with DBU the *N*-tosyl-7-substituted azepin-2-one **7b⁵** $[\alpha]_{\text{D}}^{20} = +128.1$ (*c* 1.65, MeOH) was obtained in a

† Present address: Stuart Pharmaceuticals, I.C.I. Americas, Wilmington, DE 19897, USA.



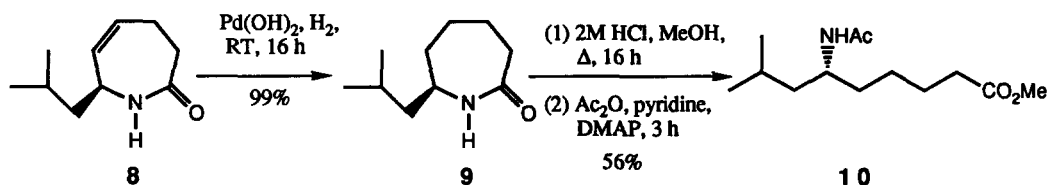
SCHEME 1

comparable (39%) yield to **7a**. Deprotection of the *p*-toluenesulphonyl protecting group with sodium naphthalenide¹⁰ at -70°C gave the 7-substituted azepin-2-one **8**⁵ $\{[\alpha]_{\text{D}}^{20} = +15.8$ (*c* 1.41, MeOH) $\}$ in 87% yield.

The moderate yields in the cyclisations may be due to steric effects. Assuming a chair-like conformation for the components of the Claisen rearrangement,^{3c} the *anti*-diastereomer, **6-anti**, is clearly favoured over the *syn*-diastereoisomer, **6-syn**. The latter has severe 1,2-eclipsing interactions in the chair conformation; the boat-like conformation (see **6-syn**) is disfavoured since it would produce the high energy (*E*)-alkene. Further studies on this problem are in progress.



Catalytic reduction of the lactam **8** gave **9**⁵ $\{[\alpha]_{\text{D}}^{20} = -9.3$ (*c* 0.53, MeOH) $\}$. This was hydrolysed with hydrochloric acid in methanol and then acylated to afford the *N*-acyl amino ester **10**⁵ $\{[\alpha]_{\text{D}}^{20} = -24.9$ *c* 1.02, MeOH) $\}$. ¹H N.M.R. chiral shift studies on **10** using (+)-Eu(hfc)₃ indicated an enantiomeric excess (e.e.) $\geq 95\%$.



SCHEME 2

This assay confirms the faithful transformation of (*S*)-leucine **1** into the lactams **8** and **9** without loss of stereochemical integrity at the original stereocentre of the amino acid, and should enable a wide range of homochiral substituted seven-membered lactams to be prepared.

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