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Synthesis Of Homochiral Unsaturated Seven-Membered Lactams

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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 **2**[4] 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 **3**[5] which was *N*-protected, using benzyl chloroformate and sodium hydroxide, to furnish the vinyl Z-protected amino alcohol **4a**[5] in 61% overall yield. Benzyloxycarbonyl-protected amino-alcohols form stable aminals.[6] Treatment of **4a** with *p*-toluenesulphonic acid and phenylseleno-acetaldehyde diethyl acetal[7] under Dean-Stark conditions furnished the the aminal **5a**[5] 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 **7a**[5] {$[\alpha]_D^{20}$ = +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 acid[9] afforded the 7-substituted azepin-2-one **8**[5] {$[\alpha]_D^{20}$ = +15.3 (*c* 1.38, MeOH)} in 98% yield.

A similar sequence was carried out on the *N*-tosyl analogue **4b**,[5] prepared by tosylation of **3** with *p*-toluenesulphonyl chloride and triethylamine in 82% yield. It was expected that the *N*-tosyl aminal, **5b**[5] 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 **7b**[5] {$[\alpha]_D^{20}$ = +128.1 (*c* 1.65, MeOH)} was obtained in a

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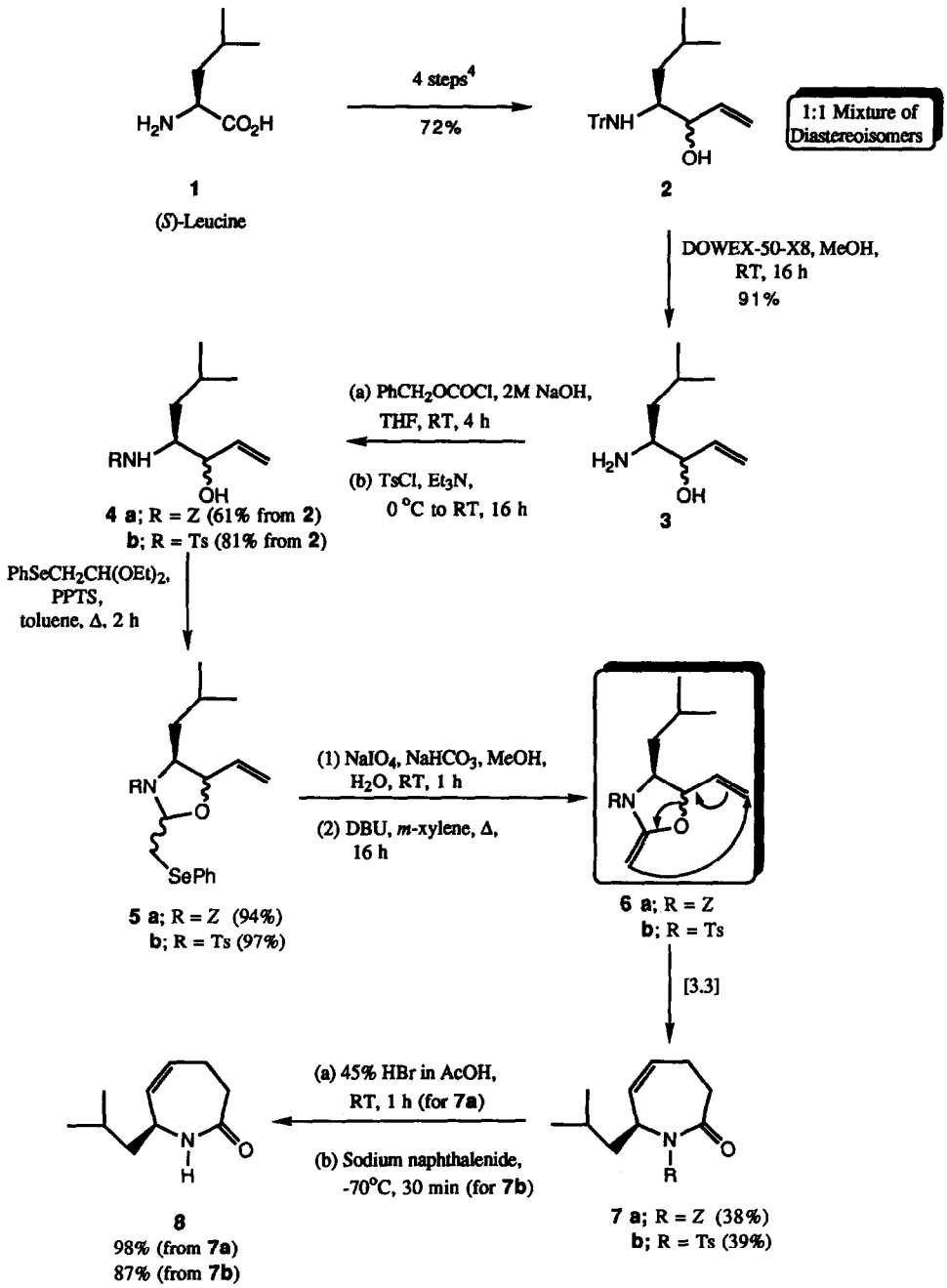
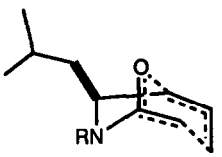

4 steps[4]
72%
1:1 Mixture of Diastereoisomers
1
(S)-Leucine
2
DOWEX-50-X8, MeOH, RT, 16 h
91%
(a) PhCH2OCOCl, 2M NaOH, THF, RT, 4 h
(b) TsCl, Et3N, 0 °C to RT, 16 h
3
4 a; R = Z (61% from 2)
b; R = Ts (81% from 2)
PhSeCH2CH(OEt)2, PPTS, toluene, Δ, 2 h
5 a; R = Z (94%)
b; R = Ts (97%)
(1) NaIO4, NaHCO3, MeOH, H2O, RT, 1 h
(2) DBU, m-xylene, Δ, 16 h
6 a; R = Z
b; R = Ts
[3.3]
7 a; R = Z (38%)
b; R = Ts (39%)
(a) 45% HBr in AcOH, RT, 1 h (for 7a)
(b) Sodium naphthalenide, -70°C, 30 min (for 7b)
8
98% (from 7a)
87% (from 7b)

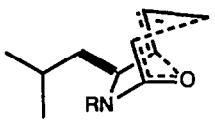
SCHEME 1

comparable (39%) yield to **7a**. Deprotection of the *p*-toluenesulphonyl protecting group with sodium naphthalenide[10] at −70 °C gave the 7-substituted azepin-2-one **8**[5] {$[\alpha]_D^{20}$ = +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.

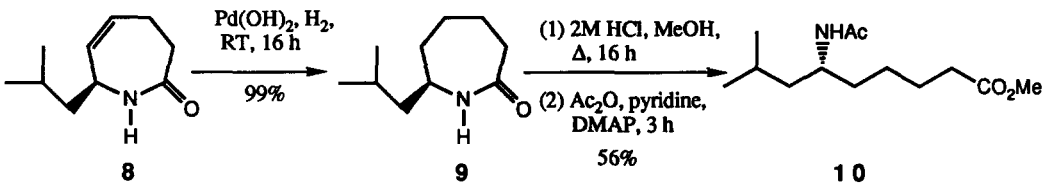


6-*anti*



6-*syn*

Catalytic reduction of the lactam **8** gave **9**[5] {$[\alpha]_D^{20}$ = −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] {$[\alpha]_D^{20}$ = −24.9} *c* 1.02, MeOH). ^{1}H N.M.R. chiral shift studies on **10** using (+)-Eu(hfc)$_3$ indicated an enantiomeric excess (e.e.) ≥ 95%.



8 **9** **10**

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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