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Diastereoselective *5-exo-trig* Radical Cyclisation on N-Acryloyl-tetrahydro-1,3-oxazines. A Novel Approach to Enantiopure 3-Substituted Pyrrolidines

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Abstract: N-Acryloyl-2-(phenylselenomethyl)-tetrahydro-1,3-oxazine 1 generates a carbon-centred radical in the presence of tri-*n*-butyltin hydride and AIBN. This radical underwent diastereoselective 5-*exo*-trig cyclisation leading to a mixture of five-membered lactams 2a and 2b (d.e. 68%). Chromatographic separation of the diastereomers and elimination of the chiral auxiliary provided enantiopure (*R*)-3-methylpyrrolidine in good chemical yield. Copyright © 1996 Elsevier Science Ltd

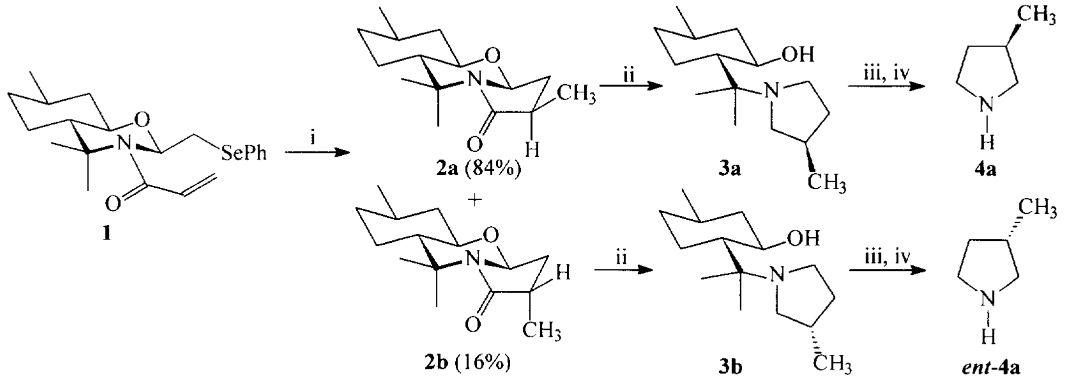
Radical cyclisations have become a powerful tool in the synthesis of heterocycles and nowadays are widely used in the preparation of many natural products.[1] Among these cyclisations, aza-5-hexenyl radicals leading to five-membered rings *via* 5-*exo* ring closure have been largely studied because of the great natural occurrence of pyrrolidine-like products.[2] On the other hand, successful asymmetric aza-*5-exo* cyclisations have also been reported.[3,4] The use of α,β-unsaturated amides as radical acceptors in radical cyclisations has received little attention probably due to the uncertainty of the radical attack site,[5] however, its intermolecular counterpart involving 1,4-addition of a carbon-centred radical to this system was investigated some years ago in the context of asymmetric induction, and it was found to be highly stereoselective.[6]

Based on the above precedents, we planned to explore the regio- and stereoselective cyclisation of an alkyl radical generated at the C-2 substituent of the N-acryloyl-tetrahydro-1,3-oxazine **1** derived from (−)-8-aminomenthol.[7] The starting amide **1** was prepared in high yield by condensation of (−)-8-aminomenthol and phenylselenoacetaldehyde[8] in dichloromethane at r. t., followed by N-acylation with acryloyl chloride in the presence of triethylamine at 0°C. The radical cyclisation in the acrylamide **1** was carried out following the tributyltin method.[9] After determination of the reaction parameters, the formation of the carbon-centred radical from the acrylamide **1** was promoted as follows: to a 0.02M solution of acrylamide in dry, refluxing benzene was slowly added a mixture of 1.3 equiv. of tri-n-butyltin hydride and 4% equiv. of AIBN in benzene for a period of 7-9 h, the heating was prolonged until all of the starting compound had been used (TLC).

After elimination of the solvent, ^{1}H-NMR analysis showed that the two diastereomeric five-membered lactams **2a** (84%) and **2b** (16%) were the only cyclisation products. These compounds result from the 5-*exo*-trigonal ring closure and no evidence for the 6-*endo* trig attack or reduction products was found.

Separation by flash chromatography (silica gel, CH_2Cl_2) afforded **2a** and **2b** as pure diastereomers with a 52% combined yield. The relative stereochemistry of each product was determined by NOESY experiments. The relative *cis* relationship for the protons at C-3 and C-5 in the lactam moiety for the major component **2a** allows assignment of the *R* configuration at the newly created stereocenter in this compound, whereas the contrary relationship was found for the minor isomer indicating the *S* configuration at C-3 for **2b**.

The transformation of these compounds into the 3-methyl pyrrolidines **4a** and ***ent*-4a** was carried out in three steps with a total yield of 80%. Treatment of **2a** or **2b** with aluminium hydride[10] led quantitatively to aminoalcohols **3a** or **3b** which by sequential PCC oxidation and treatment with 2.5 M aqueous KOH solution in THF-MeOH[11] afforded (*R*)-3-Methyl pyrrolidine **4a**[12] isolated as N-benzoyl derivative[13] or (*S*)-3-methyl pyrrolidine ***ent*-4a** characterized as hydrochloride[13] and (+)-pulegone.



Scheme. *Reagents*: (i) Bu_3SnH, AIBN, PhH; (ii) AlH_3 (7 equiv.), THF, -10 °C; (iii) PCC, 4Å mol. sieves; (iv) KOH, MeOH-THF.

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13. (*R*)-N-Benzoyl-3-methyl pyrrolidine: colourless solid, m.p. 64-65 °C (from hexanes), $[\alpha]_D^{20} = +70.2$ (c=1.03, CH_2Cl_2). (*S*)-3-Methyl pyrrolidine hydrochloride: very hygroscopic solid, $[\alpha]_D^{20} = -6.9$ (c=1.67, MeOH).

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