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Synthesis of Enantiopure 3-Alkyl-perhydroazepines by Diastereoselective 7-*endo*-Radical Cyclisation on a Chiral 1,3-Perhydrobenzoxazine Derivative

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Abstract: Competitive alkyl radical 6-*exo*/ 7-*endo* cyclisation on α,β-unsaturated amides derived from chiral perhydrobenzoxazines are controlled by the alkene substitution pattern. Stereocontrol leading to 7-*endo* regioisomers is considerably higher and allows to prepare enantiopure hexahydroazepine derivatives.

Keywords: *Asymmetric Synthesis, Radical cyclisations, Perhydroazepines, Stereoselective synthesis*

The use of α,β-unsaturated amides as acceptors in radical cyclisation has received limited attention hitherto.[1] One of the advantages offered by this type of reaction is easy access to lactams of different sizes which are biologically potent molecules or valuable synthetic intermediaries,[2] although there is an important drawback of such reactions related to the competition between cyclisation modes. Typically mixtures of *exo*/*endo* regioisomers are frequently encountered with amide acceptors when using aryl radicals,[3] and in most cases the known neophyl rearrangement is responsible for *exo* to *endo* product interconversion.[4] However as alkyl radical cyclisations onto α,β-unsaturated amides are essentially irreversible processes the *exo*-*endo* ratio must be kinetically controlled. Nevertheless, mixtures of products have been found with alkyl radicals although the number of reported examples is too scarce for predicting results.[5]

Herein we describe an intramolecular radical addition onto chiral α,β-unsaturated amides with 6-*exo* vs 7-*endo* competition using alkyl radicals generated by homolysis of C-Se bonds. This stereoselective version was performed on perhydro-1,3-benzoxazines **3a-c** which were synthesised in two steps and excellent yield from (-) 8-aminomenthol **1** (Scheme 1). Condensation of **1** with 3-phenylselenyl propionaldehyde yielded the *N*-unsubstituted perhydro-1,3-benzoxazine **2** which was acylated at 0°C in CH_2Cl_2 with acryloyl chloride/ triethylamine, crotonyl chloride/ pyridine and methacryloyl chloride/ TMEDA, leading to **3a-c** respectively. Each benzoxazine **3a-c** could be purified by either recrystallisation or chromatography, with 78-83% yield.[6]

Radical cyclisations were promoted by the tributyltin method (Scheme 1). A solution of tributyltin hydride (1.2 equiv) and catalytic amounts of AIBN was slowly added (syringe pump, 6-8 h) to a solution of perhydro-1,3-benzoxazines **3a-c** in boiling benzene. Once complete (TLC) the crude reaction was analyzed by ^1H NMR and the products isolated by flash chromatography. The results are summarized in Table 1.

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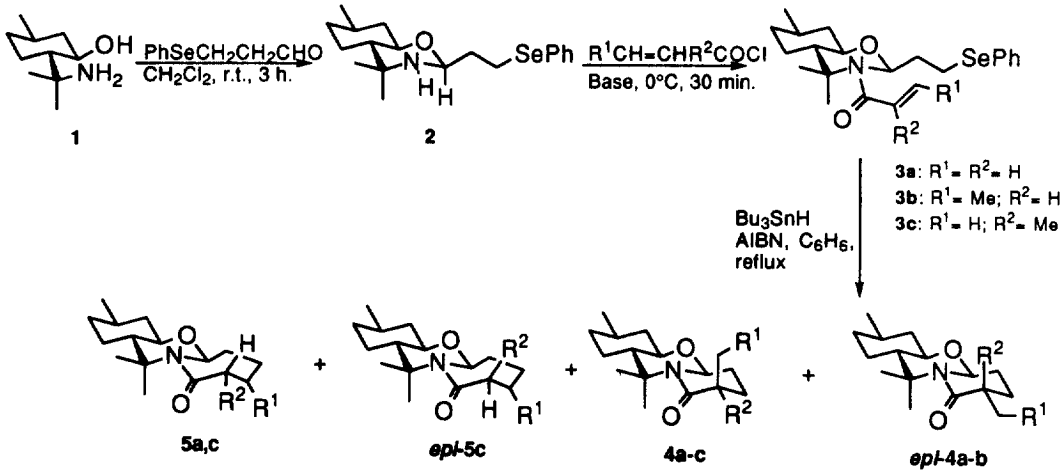
Table 1. Radical Cyclisation of Perhydro-1,3-benzoxazines **3a-c**

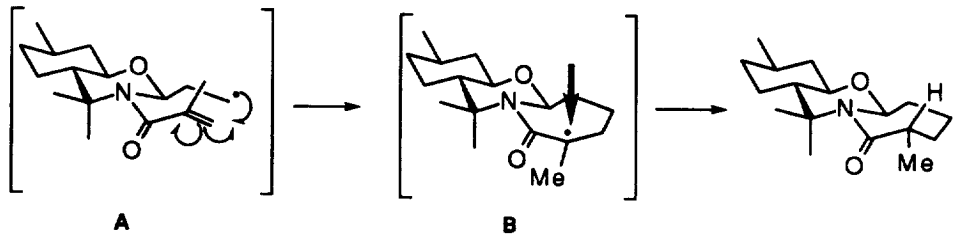
Entry	Amide	R^1	R^2	Products (ratio)	Yield (%)
1	**3a**	H	H	**4a** (42), *epi*-**4a** (23), **5a** (35)	88
2	**3b**	Me	H	**4b** (66), *epi*-**4b** (34)	93
3	**3c**	H	Me	**4c** (13), **5c** (75), *epi*-**5c** (12)	99

Cyclisation of the parent acrylamide **3a** occurs with low regioselectivity (6-*exo*/ 7-*endo* ratio 65/35) and poor stereoselectivity (**4a**: *epi*-**4b** 42:23). The presence of a substituent at the β carbon in the crotylamide **3b** (R^1 = Me) disfavours the 7-*endo* cyclisation process[7] giving 6-membered lactams, although the stereoselectivity remains practically constant with respect to the acrylamide derivative (**4b**: *epi*-**4b** 66:34). Much better results were obtained in the cyclisation of methacrylamide **3c** (R^2 = Me). The presence of the substituent at the α-position of the double bond causes a retardation of the 6-*exo* attack in favour of the 7-*endo* cyclisation product. As a result, a mixture of caprolactams **5c** and *epi*-**5c**, and the 6-membered lactam **4c** were obtained in a ratio 87:13.



Scheme 1

This improvement in the 7-*endo* cyclisation mode in the 6-heptenyl radical can be explained by the presence of steric congestion[8] at the normally favoured bond-forming site in **A**, and formation of the highly stabilized radical **B** (Scheme 2).

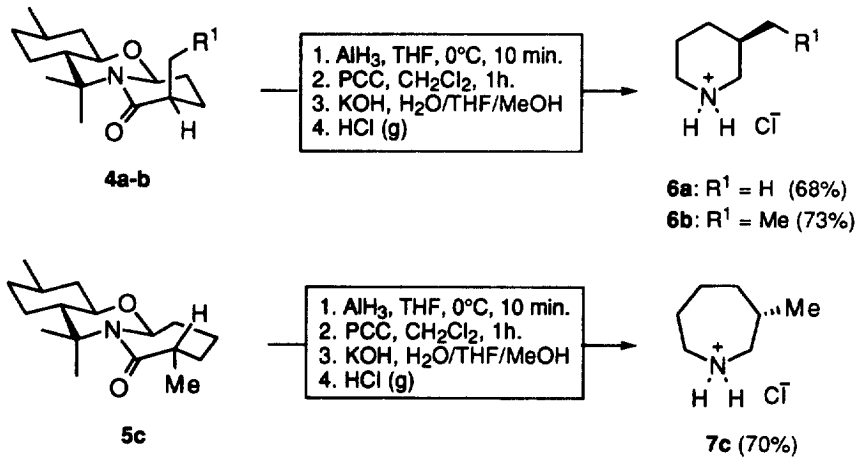


Scheme 2

The efficient production of the 7-membered ring is also interesting from the stereochemical point of view. The origin of the stereoselection observed (**5c**: *epi*-**5c** 86:14; 72% d.e.) is different from that of the 6-*exo* cyclisation process. In this case, the configuration of the newly created stereocenter is dictated by hydrogen transfer to the postcyclisation radical. This hydrogen transfer is probably sterically controlled, and it occurs axially, from the less hindered face of the quasi-planar intermediate radical **B** (Scheme 2).

The cyclisation products from each reaction were isolated by flash chromatography, and the stereochemistry for **4a**, *epi*-**4a**, **4b**, *epi*-**4b**, **5c** and *epi*-**5c** was determined by NOESY experiments. In addition, the major 6-membered lactams **4a** and **4b** were transformed into the known enantiopure (*R*)-3-methylpiperidine[9] and (*R*)-3-ethylpiperidine[10], and characterized as their hydrochlorides **6a** and **6b** respectively (Scheme 3).

In the same way, the major component **5c** of the 7-*endo* cyclisation reaction of methacrylamide **3c** was transformed into the enantiopure (*S*)-3-methylperhydroazepine **7c** (Scheme 3). Treatment of **5c** with excess of aluminum hydride (7 equiv) in THF at 0°C for 10 min leads to 8-perhydroazepinylmenthol resulting from the reduction of the amide group and the reductive ring opening of the 1,3-perhydrobenzoxazine moiety. After isolation, the menthol derivative was subjected to oxidation with PCC, and the crude reaction product was treated, without isolation, with 2.5 N solution of KOH in THF-MeOH-H_2O giving enantiopure (*S*)-3-methylperhydroazepine, isolated as hydrochloride **7c**,[11] in 70% total yield.



Scheme 3.

These preliminary results open a way to the synthesis of enantiopure perhydroazepine derivatives by uncommon stereoselective 7-*endo* radical cyclisation. We are now working to extend this method to the synthesis of other nitrogen-containing 7-membered rings, and the results will be published in due course.

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11. (S)-*3-Methylhexahydroazepine, hydrochloride* **7c**: Colorless solid, mp 111-113°C (from CH_2Cl_2/Et_2O); $[\alpha]_D^{23}$ = -7.0 (c 0.9, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.0 (d, 3H, *J* = 6.8 Hz), 1.32-1.38 (m, 1H), 1.55-1.70 (m, 1H), 1.72-1.90 (m, 3H), 1.92-2.10 (m, 1H), 2.10-2.25 (m, 1H), 2.60-2.82 (m, 1H), 3.10-3.30 (m, 3H), 9.40 (br. s, 1H), 9.60 (br. s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ = 20.4, 24.7, 24.8, 31.3, 35.5, 45.7, 51.4. IR (cm^{-1}, nujol): 3400, 1500. Anal Calcd for $C_7H_{16}ClN$: C, 56.34; H, 10.81; N, 9.39. Found: C, 56.65; H, 10.55; N, 9.72.