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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-*exol* 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. © 1999 Elsevier Science Ltd. All rights reserved.

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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 *exolendo* 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 7endo 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 CH₂Cl₂ 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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| Entry | Amide | R ¹ | R ² | Products (ratio) | Yield (%) | |
|-------|-----------|----------------|----------------|---|-----------|--|
| 1 | 3a | Н | H | 4a (42), epi-4a (23), 5a (35) | 88 | |
| 2 | 3b | Me | н | 4b (66), <i>epi</i> - 4b (34) | 93 | |
| 3 | <u>3c</u> | <u>H</u> | Me | 4c (13), 5c (75), epi-5c (12) | 99 | |

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

Cyclisation of the parent acrylamide 3a occurs with low regioselectivity (6-exol 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 (R¹ = Me) disfavours the 7-endo cyclisation process⁷ 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 (R² = 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 congestion⁸ 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-methylpiperidine⁹ and (R)-3-ethylpiperidine¹⁰, 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-H₂O giving enantiopure (S)-3-methylperhydroazepine, isolated as hydrochloride **7c**,¹¹ in 70% total yield.





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 CH₂Cl₂/Et₂O); $[\alpha]_D^{23} = -7.0$ (c 0.9, MeOH); ¹H NMR (CDCl₃, 300 MHz): $\delta = 1.0$ (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). ¹³C NMR (CDCl₃, 75 MHz), $\delta = 20.4$, 24.7, 24.8, 31.3, 35.5, 45.7, 51.4. IR (cm⁻¹, nujol): 3400, 1500. Anal Calcd for C₇H₁₆ClN: C, 56.34; H, 10.81; N, 9.39. Found: C, 56.65; H, 10.55; N, 9.72.