Regiochemistry in radical cyclisations (4-*exo-trig versus* 5-*endo-trig*) of 2-halo-*N*-(3,4-dihydro-2-naphthyl)acetamides

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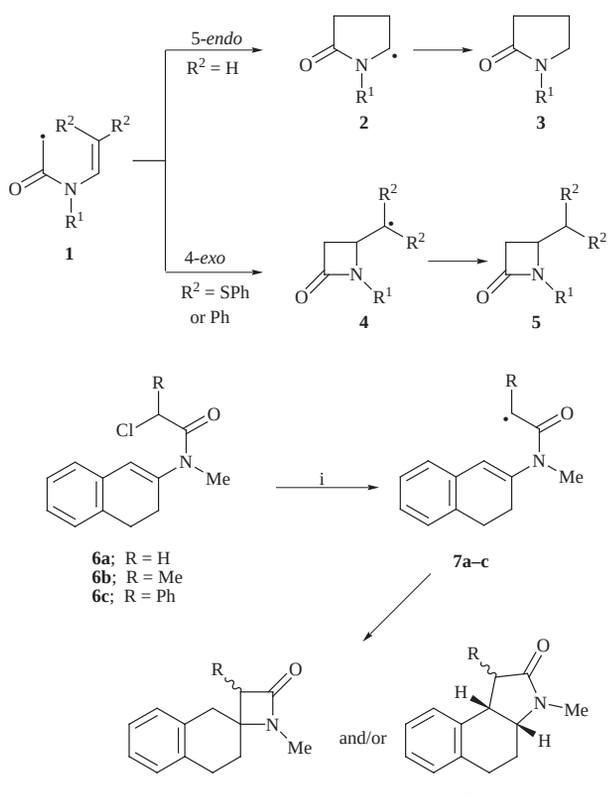
The regioselectivity in Bu_3SnH-mediated radical cyclisations (4-*exo-trig versus* 5-*endo-trig*) of a range of 2-halo-*N*-(3,4-dihydro-2-naphthyl)acetamides has been examined from the standpoint of the effects of substituents on the radical centre and on the nitrogen atom as well as the reaction temperature. When the substituent on the radical centre is a hydrogen or chlorine atom, 4-*exo-trig* cyclisation (β-lactam formation) is favoured in boiling toluene, while radical stabilising substituents such as methyl, phenyl, phenylthio, dimethyl and dichloro groups bring about 5-*endo-trig* cyclisation (γ-lactam formation) predominantly or exclusively. In boiling benzene, however, the predominant formation of β-lactam is observed for the methyl-substituent. On the other hand, no remarkable difference in the product distributions between the methyl and benzyl substituents on the nitrogen atom is observed. These results are discussed in terms of kinetic or thermodynamic considerations.

Introduction

The control of the regiochemistry of radical cyclisations is a subject of intense investigation.[1] We and others have demonstrated that the *N*-vinylic carbamoylmethyl radicals **1**, generated from the corresponding α-halo amides, cyclise generally in a 5-*endo-trig* manner yielding γ-lactams **3** through the intermediates **2**,[2,3] while introduction of radical stabilising group(s) such as phenylthio or phenyl at the terminus of the *N*-vinyl group leads to the formation of β-lactams **5** (Scheme 1).[4,5] These results suggest that the high stability of the radical intermediates **4** plays a crucial role in the switch of regioselectivity from the 5-*endo-trig* mode to the 4-*exo-trig* mode in the ring closure of **1**. On the other hand, Bu_3SnH-mediated radical cyclisation of 2-chloro-*N*-(3,4-dihydro-2-naphthyl)-*N*-methylacetamides **6a**–**c** in boiling toluene gave β-lactams **8** and/or γ-lactams **9**, depending upon the nature of the substituents on the radical centre of the initially formed carbamoylmethyl radicals **7**.[2b] The 2-chloroacetamide **6a** afforded exclusively the β-lactam **8a**, while the 2-chloro-2-phenylacetamide **6c** gave solely the γ-lactam **9c**. The 2-chloropropanamide **6b** showed an intermediate behaviour to give a mixture of the β-lactam **8b** (29%) and the γ-lactam **9b** (40%). These observations indicate that the substituents on the radical centre of the carbamoylmethyl radicals **7** also affect the regiochemistry of cyclisation. In order to obtain more information on the factors determining the regiochemistry of the radical cyclisation of **6**, we now examined in detail the effects of the substituents on the radical centre and on the nitrogen atom of **7** as well as the reaction temperature.



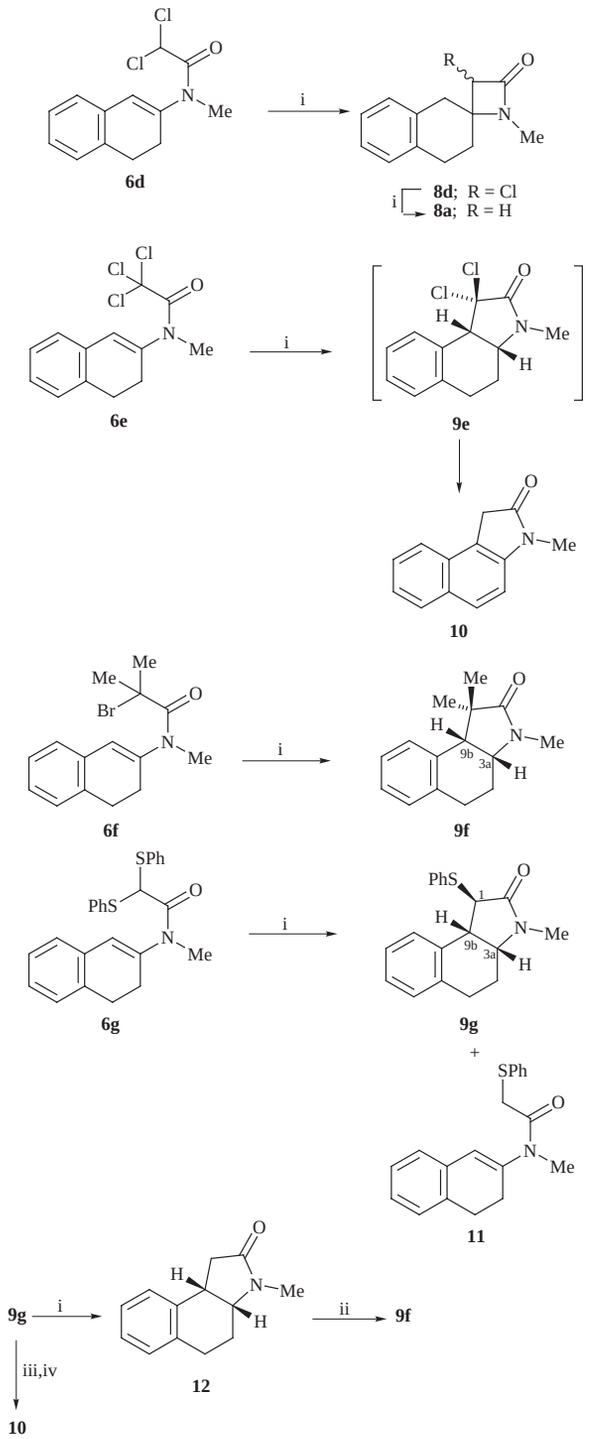
Scheme 1 *Reagents and conditions*: i, Bu_3SnH, AIBN, toluene, reflux

Results and discussion

The *N*-methyl substituted radical precursors **6d**–**f** were readily prepared by acylation of the imines derived from β-tetralone and methylamine. The 2,2-bis(phenylthio)acetamide **6g** was prepared by a nucleophilic substitution reaction of the 2,2-dichloroacetamide **6d** with benzenethiolate ion.

When the dichloroacetamide **6d** was treated with Bu_3SnH (3.6 equiv.) and a small amount of azoisobutyronitrile (AIBN) in boiling toluene, the β-lactam **8a** was obtained in 52% yield through reduction of the corresponding chloro lactam **8d** (Scheme 2). Interestingly, the trichloroacetamide **6e**, upon treatment with Bu_3SnH (1.2 equiv.) and AIBN, gave the aromatised product **10** in 40% yield. Since only 1.2 equiv. of Bu_3SnH was used, it was assumed that the aromatisation took place by a non-radical process which involved dehydrochlorination from the initially formed dichloro γ-lactam **9e**.

Treatment of 2-bromo-2-methylpropanamide **6f** with Bu_3SnH (1.2 equiv.) and AIBN in boiling toluene gave the γ-lactam **9f** as the sole product in 68% yield. The *cis*-stereochemistry of

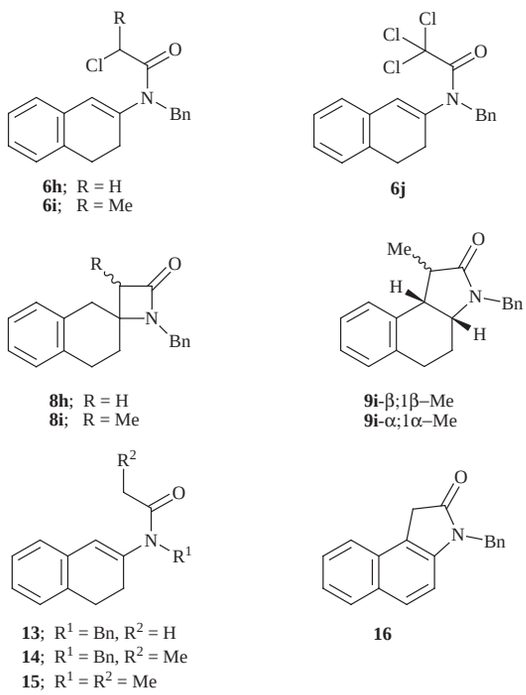


Scheme 2 *Reagents and conditions*: i, Bu_3SnH, AIBN, toluene, reflux; ii, LDA, MeI, THF, −78 °C; iii, $NaIO_4$, H_2O–acetone, room temp.; iv, toluene, reflux

the ring-junction was assigned on the basis of the coupling constant (*J* 8.6 Hz) between 3a-H and 9b-H, which closely resembled that (*J* 7.8 Hz) for **9b** obtained as the major product of the cyclisation of **6b**.

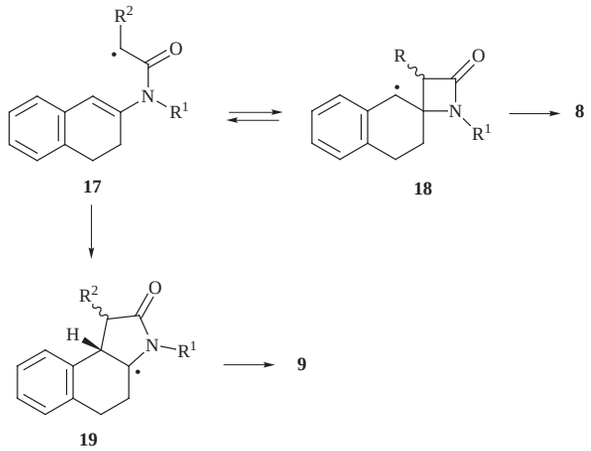
Treatment of the bis(phenylthio)acetamide **6g** with Bu_3SnH (1.2 equiv.) and AIBN in boiling toluene gave the γ-lactam **9g** in 52% yield as a single stereoisomer along with the reduction product **11** (13%). The *cis* ring-junction of **9g** was determined by transformation to compound **9f** through desulfurisation followed by dimethylation of the resulting lactam **12**. The *anti*-relationship between 1-H and 9b-H of **9g** was confirmed by an epimerisation experiment: treatment of **9g** with potassium *tert*-butoxide in boiling 2-methylpropan-2-ol resulted in recovery of the starting material, indicating that **9g** is the thermodynamically more stable 1β(*exo*)-PhS isomer. Thermal elimination of benzenesulfenic acid from the corresponding sulfoxide gave the aromatised product **10** in 38% yield. The formation of **10** may be rationalised by assuming that migration of the double bond from the initially formed C-1–C-9b position to the C-3a–C-9b position is followed by subsequent dehydrogenation. Apparently, aromatisation is the driving force of this reaction.

Next, in order to see the steric effects of the substituent on the nitrogen atom, we prepared the *N*-benzyl congeners **6h–j**



and subjected them to the radical cyclisation conditions. Treatment of the 2-chloroacetamide **6h** with Bu_3SnH and AIBN in boiling toluene gave the β-lactam **8h** (44%), along with the reduction product **13** (23%). The propanamide **6i** gave a mixture of the β-lactam **8i** and the γ-lactams **9i**-β (1β-Me) and **9i**-α (1α-Me) in 21, 45 and 6% yields, respectively, in addition to the reduction product **14** (12%). The ^1H NMR spectrum of **8i** showed it to be a mixture of two diastereoisomers in a ratio of *ca.* 1.8 : 1. Stereochemistries of **9i**-β and **9i**-α were confirmed by a comparison of the chemical shifts of their C-1-methyl protons with those of the *N*-methyl congeners **9b**. Thus, the signal due to the 1β-methyl protons of **9b** appeared at δ 1.41, whereas the signal due to the 1α-methyl protons shifted upfield to δ 0.90. In the cases of **9i**-β and **9i**-α, the corresponding signals appeared at δ 1.46 and 0.97, respectively, indicating the C-1-methyl groups of **9i**-β and **9i**-α to have the β- and α-configurations, respectively. The trichloroacetamide **6j** gave the aromatised compound **16** in 53% yield. Thus, no remarkable difference was observed in the behaviour of cyclisations between the *N*-methyl and *N*-benzyl derivatives.

The above results revealed that the substituent(s) on the initially formed carbamoylmethyl radical **17** play(s) a crucial role in determining the regiochemistry. When R^2 = H or Cl in **17**, then β-lactam formation is favoured, while radical stabilising substituents such as methyl, phenyl, phenylthio, dimethyl or dichloro groups lead to γ-lactams predominantly or exclusively. One possible explanation for these results is based on a consideration of the reversibility of the 4-*exo-trig* cyclisation and ring-opening between **17** and **18**.[6] The 4-*exo-trig* cyclisation might be a kinetically favoured process compared to the 5-*endo-trig* one, so that the carbamoylmethyl radicals **17** would give initially the benzylic radicals **18** (see Scheme 3). In the former case (R^2 = H or Cl), the subsequent reduction step is faster than the ring-opening step, and hence β-lactam form-



Scheme 3

ation takes place. On the other hand, in the latter case having the radical-stabilising substituent(s), the ring-opening of **18** occurs rapidly to give the relatively stable initial radicals **17**, and the reduction step takes place after the thermodynamically more stable radicals **19** have been formed by the 5-*endo-trig* cyclisation of **17** to lead to the formation of the γ-lactams **9**.

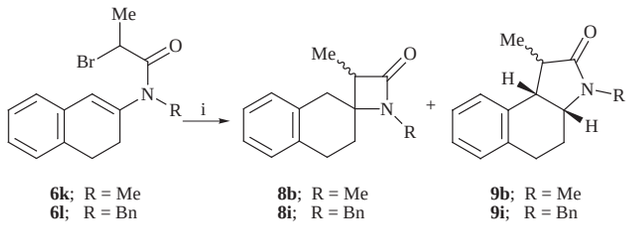
Support for the proposed mechanistic scheme was derived from an examination of the effects of the reaction temperature[7] using the 2-bromopropanamides **6k** and **6l** as radical precursors instead of the corresponding chloro amides **6b** and **6i**. Thus, a solution of the *N*-methyl derivative **6k** in boiling benzene (at 80 °C) was treated slowly with a mixture of Bu_3SnH and AIBN during 3 h to give the β-lactam **8b** as the major product (see entry 1 in Table 1), whereas in boiling toluene (at 110 °C) the γ-lactam **9b** was obtained as the major product (see entry 2). This was also the case for the *N*-benzyl congener **6l** (see entries 3 and 4). These results clearly indicate that the 4-*exo* cyclisation is a kinetically favoured process, whereas at higher temperature (in boiling toluene), the ring-opening of the radicals **18** formed by 4-*exo* cyclisation rapidly occurs, and the resulting radicals **17** cyclise in a 5-*endo-trig* manner to give the thermodynamically stable radicals **19**. If Bu_3SnH was added rapidly to a solution of these radical precursors, the kinetically favoured radicals **18** might be immediately trapped by Bu_3SnH to result in an increase in the amount of the β-lactams. This was realised by adding a mixture of Bu_3SnH and AIBN to a boiling toluene solution of **6k** within 30 min; these conditions gave an approximately equal amount (54:46) of the β-lactam **8b** and the γ-lactam **9b** (compare with entry 2).

Experimental

Mps were measured on a Yanaco MP-J3 micro melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO-IR-A-100 spectrophotometer. ^{1}H NMR (60 and 300 MHz) and ^{13}C NMR (75.4 MHz) spectra were measured on a JEOL-JNM-PMX 60 or a Varian XL-300 spectrometer for solutions in $CDCl_3$. δ Values quoted are relative to tetramethylsilane, and *J* values are given in Hz. Exact mass determinations (FAB and EI mass spectra) were obtained on a JEOL-SX 102A instrument. Column chromatography was performed on Silica gel 60 PF_{254} (Nacalai Tesque) under pressure.

General procedure for the preparation of 2-halo-*N*-(3,4-dihydro-2-naphthyl)-*N*-methylacetamides 6d–f

β-Tetralone (3.0 g, 21 mmol) was added to anhydrous methylamine (10 cm^3) at −78 °C and the mixture was heated in a sealed tube at 100 °C for 2 h. The reaction vessel was cooled to −78 °C, the stopper was removed, and the reaction mixture was allowed to warm to room temperature to remove any excess of methylamine. To the residue cooled to 0 °C were successively added diethyl ether (30 cm^3), triethylamine (2.5 g, 25 mmol),



6k; R = Me
6l; R = Bn

8b; R = Me
8i; R = Bn

9b; R = Me
9i; R = Bn

Scheme 4 *Reagents and conditions*: i, Bu_3SnH, AIBN, benzene or toluene, reflux

Table 1 Effects of the reaction temperature on the regioselectivity in radical cyclisations of **6k** and **6l**[a]

			Products[b]		
Entry	Compound	Solvent		Yield (%)[c]	**8b**:**9b** or **8i**:**9i**
1	**6k**	benzene	**8b** + **9b**	56	73:27
2	**6k**	toluene	**8b** + **9b**	60	38:62
3	**6l**	benzene	**8i** + **9i**	49	69:31
4	**6l**	toluene	**8i** + **9i**	63	30:70

[a] For the reaction conditions, see the text. [b] Simple reduction product **15** (19 and 13% yields for entries 1 and 2, respectively) or **14** (16 and 13% yields for entries 3 and 4, respectively) was also obtained. [c] Combined yield of **8b** and **9b**, or **8i** and **9i**.

and a solution of an appropriate acyl chloride (bromide for **6f**) (25 mmol) in diethyl ether (10 cm^3). The mixture was stirred at room temperature for 30 min and water (10 cm^3) was added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with diethyl ether. The combined organic layer and extracts were dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (4:1)] to give an enamide. The following compounds were thus obtained.

2,2-Dichloro-*N*-(3,4-dihydro-2-naphthyl)-*N*-methylacetamide 6d. Yield 73%, *crystals*, mp 104–104.5 °C (from hexane–AcOEt) (Found: C, 57.6; H, 4.8; N, 5.2. $C_{13}H_{13}Cl_2NO$ requires C, 57.8; H, 4.85; N, 5.2%); $\nu_{max}(CCl_4)$/cm^{-1} 1695; δ_H(300 MHz, $CDCl_3$) 2.53 (2 H, t like, *J ca.* 8), 3.04 (2 H, t like, *J ca.* 8), 3.18 (3 H, s, NMe), 6.52 (2 H, s, 1-H, COCH) and 7.07–7.27 (4 H, m, ArH).

2,2,2-Trichloro-*N*-(3,4-dihydro-2-naphthyl)-*N*-methylacetamide 6e. Yield 43%, an *oil* (Found: C, 51.2; H, 4.0; N, 4.3. $C_{13}H_{12}Cl_3NO$ requires C, 51.3; H, 4.0; N, 4.6%), $\nu_{max}(CCl_4)$/cm^{-1} 1695; δ_H(60 MHz, $CDCl_3$) 2.35–3.2 (4 H, m), 3.33 (3 H, s, NMe), 6.54 (1 H, br s, 1-H) and 7.05–7.3 (4 H, m, ArH).

2-Bromo-*N*-(3,4-dihydro-2-naphthyl)-2,*N*-dimethylpropanamide 6f. Yield 80%, an *oil* (Found: C, 58.5; H, 5.9; N, 4.4. $C_{15}H_{18}BrNO$ requires C, 58.45; H, 5.9; N, 4.5%); $\nu_{max}(CCl_4)$/cm^{-1} 1630; δ_H(60 MHz, $CDCl_3$) 2.04 (6 H, s, 2 × Me), 2.4–3.1 (4 H, m), 3.24 (3 H, s, NMe), 6.50 (1 H, br s, 1-H) and 6.85–7.4 (4 H, m, ArH).

N-(3,4-Dihydro-2-naphthyl)-*N*-methyl-2,2-bis(phenylthio)-acetamide 6g

Benzenethiol (897 mg, 8.14 mmol) was added to a solution of sodium ethoxide (558 mg, 8.14 mmol) in ethanol (10 cm^3) at 0 °C, and the mixture was stirred at room temperature for 10 min. To this was added a solution of **6d** (1.0 g, 3.7 mmol) in ethanol (3 cm^3) and the mixture was stirred at room temperature overnight. The solvent was evaporated off, dichloromethane (15 cm^3) was added to the residue, and the whole was washed with water, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (7:1)] to give **6g** (1.39 g, 90%), mp 106–106.5 °C (from hexane–AcOEt) (Found: C, 72.1; H, 6.0; N, 3.1. $C_{25}H_{23}NOS_2$ requires C, 71.9; H, 5.5; N, 3.35%); $\nu_{max}(CCl_4)$/cm^{-1} 1640; δ_H(60 MHz, $CDCl_3$) 1.75–2.85 (4 H, m), 3.04 (3 H, s, NMe), 5.38 (1 H, s, COCH), 6.01 (1 H, br s, 1-H) and 6.6–7.7 (14 H, m, ArH).

Radical cyclisation of 6d

General procedure. A solution of Bu_3SnH (1.36 g, 4.66 mmol) and AIBN (129 mg, 0.79 mmol) in toluene (100 cm^3) was added to a boiling solution of compound **6d** (350 mg, 1.30 mmol) in toluene (100 cm^3) by using a syringe pump over a period of 1 h and the mixture was heated under reflux overnight. After removal of the solvent, diethyl ether (20 cm^3) and 8% aq. KF (20 cm^3) were added to the residue, and the mixture was stirred vigorously at room temperature for 30 min. The organic layer was separated, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (5:1)] to give 1-methylspiro[azetidine-4,2′-1′,2′,3′,4′-tetrahydronaphthalen]-2-one **8a** (137 mg, 52%), mp 96.5–97.5 °C (from hexane) (lit.,[2b] 93.5–94.5 °C); $\nu_{max}(CCl_4)/cm^{-1}$ 1755; δ_H(300 MHz, $CDCl_3$) 1.85–1.94 (1 H, m), 2.12 (1 H, ddd, *J* 12.4, 10.3, 6.8), 2.69 (1 H, d, *J* 14.5), 2.76 (3 H, s), 2.76 (1 H, d, *J* 14.5), 2.82 (1 H, d, *J* 16.3), 2.88–3.08 (2 H, m), 3.20 (1 H, d, *J* 16.3) and 7.06–7.18 (4 H, m).

Radical cyclisation of 6e

Following the general procedure, compound **6e** (500 mg, 1.64 mmol) was treated with Bu_3SnH (573 mg, 1.97 mmol) and AIBN (80 mg, 0.33 mmol). After work-up, the crude material was chromatographed on silica gel [hexane–AcOEt (10:1)] to give 3-*methyl*-2,3-*dihydro*-1H-*benz*[e]*indol*-2-*one* **10** (129 mg, 40%), mp 143–144 °C (from hexane–AcOEt) (Found: C, 78.9; H, 5.65; N, 7.1. $C_{13}H_{11}NO$ requires C, 79.7; H, 5.6; N, 7.1%); $\nu_{max}(CCl_4)/cm^{-1}$ 1705; δ_H(300 MHz, $CDCl_3$) 3.31 (3 H, s, NMe), 3.78 (2 H, s, 1-H_2), 7.16 (1 H, d, *J* 8.5), 7.34–7.39 (1 H, m), 7.48–7.53 (1 H, m), 7.65 (1 H, d, *J* 8.5) and 7.84 (2 H, dd, *J* 8.2, 3.1); δ_C(75 MHz, $CDCl_3$) 26.5 (CH_2), 34.9 (CH_3), 109.6, 117.8, 122.6, 123.9, 127.3, 128.9, 129.1, 129.6, 130.0, 142.6 and 175.7 (C=O).

Radical cyclisation of 6f

Following the general procedure, compound **6f** (650 mg, 2.11 mmol) was treated with Bu_3SnH (737 mg, 2.53 mmol) and AIBN (69 mg, 0.42 mmol). After work-up, the crude material was chromatographed on silica gel [hexane–AcOEt (4:1)] to give (3aR*,9aR*)-2,3,3a,4,5,9b-*hexahydro*-1H-1,1,3-*trimethylbenz*[e]*indol*-2-*one* **9f** (326 mg, 68%), mp 85–86 °C (from hexane–AcOEt) (Found: C, 78.75; H, 8.4; N, 6.15. $C_{15}H_{19}NO$ requires C, 78.6; H, 8.35; N, 6.1%); $\nu_{max}(CCl_4)/cm^{-1}$ 1680; δ_H(300 MHz, $CDCl_3$) 0.79, 1.47 (3 H each, both s, 1-Me_2), 1.65–1.77 (1 H, m), 2.05–2.15 (1 H, m), 2.61–2.81 (2 H, m), 2.95 (3 H, s, NMe), 3.40 (1 H, d, *J* 8.6, 9b-H), 3.79 (1 H, td, *J* 8.6, 4.4, 3a-H) and 7.10–7.23 (4 H, m, ArH); δ_C(75 MHz, $CDCl_3$) 23.2 (CH_3), 25.8 (CH_2), 26.8 (CH_2), 28.0 (CH_3), 28.6 (CH_3), 44.6 (quaternary C), 45.8 (CH), 57.4 (CH), 126.1, 126.3, 128.6, 129.1, 134.7, 137.2 and 178.9 (C=O).

Radical cyclisation of 6g

Following the general procedure, compound **6g** (700 mg, 1.56 mmol) was treated with Bu_3SnH (544 mg, 1.87 mmol) and AIBN (51 mg, 0.31 mmol). After work-up, the crude material was chromatographed on silica gel [hexane–AcOEt (9:2)]. The first fraction gave N-(3,4-*dihydro*-2-*naphthyl*)-N-*methyl*-2-(*phenylthio*)*acetamide* **11** (64 mg, 13%) as an oil (Found: C, 73.6; H, 6.4; N, 4.4. $C_{19}H_{19}NOS$ requires C, 73.75; H, 6.2; N, 4.5%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1635; δ_H(60 MHz, $CDCl_3$) 2.2–3.2 (4 H, m), 3.09 (3 H, s, NMe), 3.80 (2 H, s, $COCH_2$), 6.28 (1 H, br s, 1-H) and 6.9–7.6 (9 H, m, ArH).

The second fraction gave (1R*,3aS*,9bR*)-2,3,3a,4,5,9b-*hexahydro*-1H-1-*phenylthio*-3-*methylbenz*[e]*indol*-2-*one* **9g** (252 mg, 52%), mp 91.5–92.5 °C (from hexane–AcOEt) (Found: C, 73.5; H, 6.5; N, 4.8%); $\nu_{max}(CCl_4)/cm^{-1}$ 1680; δ_H(300 MHz, $CDCl_3$) 1.82–1.93 (2 H, m), 2.54–2.71 (2 H, m), 2.87 (3 H, s, NMe), 3.50–3.55 (1 H, m), 3.59–3.67 (2 H, m), 7.05–7.46 (7 H, m, ArH) and 7.63–7.70 (2 H, m, ArH).

Base treatment of 9g

A mixture of **9g** (69 mg, 0.2 mmol) and potassium *tert*-butoxide (46 mg, 0.41 mmol) in 2-methylpropan-2-ol (5 cm^3) was heated under reflux for 1 h. Water (10 cm^3) was added to the reaction mixture and the whole was extracted with diethyl ether. The organic phase was washed with brine and dried ($MgSO_4$). The solvent was evaporated off and the residue was chromatographed on silica gel [hexane–AcOEt (2:1)] to give crystals whose ^1H NMR spectrum was identical to that of the starting material **9g**.

(3a*R**,9a*S**)-2,3,3a,4,5,9b-Hexahydro-1*H*-3-methylbenz[*e*]-indol-2-one 12

A solution of Bu_3SnH (259 mg, 0.89 mmol) and AIBN (23 mg, 0.14 mmol) in toluene (2 cm^3) was added all at once to a boiling solution of compound **9g** (232 mg, 0.69 mmol) in toluene (5 cm^3) and the mixture was heated under reflux for 2 h. After removal of the solvent, diethyl ether (10 cm^3) and 8% aq. KF (10 cm^3) were added to the residue, and the mixture was stirred vigorously at room temperature for 30 min. The organic layer was separated, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (1:1)] to give **12** (119 mg, 84%), mp 88–89 °C (from hexane–AcOEt) (Found: C, 77.3; H, 7.7; N, 7.2. $C_{13}H_{15}NO$ requires C, 77.6; H, 7.5; N, 7.0%); $\nu_{max}(CCl_4)/cm^{-1}$ 1695; δ_H(300 MHz, $CDCl_3$) 1.69–1.82 (1 H, m), 2.02–2.12 (1 H, m), 2.40 (1 H, dd, *J* 16.7, 8.1, one of 1-H_2), 2.61–2.80 (2 H, m), 2.90 (1 H, dd, *J* 16.7, 9.8, one of 1-H_2), 2.91 (3 H, s, NMe), 3.65 (1 H, q, *J* 8.7, 9b-H), 3.84 (1 H, td, *J* 8.1, 4.0, 3a-H) and 7.09–7.23 (4 H, m, ArH).

Preparation of 9f from 12

A solution of **12** (119 mg, 0.59 mmol) in THF (2 cm^3) was added to a solution of LDA in THF [prepared from diisopropylamine (573 mg, 5.67 mmol) in THF (2 cm^3) and butyllithium (1.6 M in hexane solution, 1.47 cm^3, 2.36 mmol) at −78 °C] and the whole was stirred for 1 h at the same temperature. To this was added a solution of methyl iodide (1.79 g, 12.6 mmol) and hexamethylphosphoramide (2 cm^3) in THF (2 cm^3) at −78 °C and the mixture was stirred for 1.5 h at the same temperature. After quenching with sat. aq. ammonium chloride (10 cm^3), the mixture was extracted with diethyl ether and the extract was washed with 5% HCl and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (1:1)] to give a mixture of the monomethylated and dimethylated derivatives. This mixture was again treated with LDA and methyl iodide to give **9f** (129 mg, 96%), whose mp (84–85.5 °C) and spectroscopic data were identical to those of the compound obtained by cyclisation of **6f**.

Preparation of 10 from 9g

A solution of sodium metaperiodate (192 mg, 0.9 mmol) in water (3 cm^3) was added dropwise to a solution of compound **9g** (252 mg, 0.81 mmol) in acetone (3 cm^3) at 0 °C, and the mixture was stirred at room temperature overnight. The precipitated salts were removed by filtration and the filtrate was concentrated under reduced pressure. Water was added and the whole was extracted with ethyl acetate. The extract was dried ($MgSO_4$) and concentrated, and the residue was purified by column chromatography on silica gel [hexane–AcOEt (2:1)] to give the corresponding sulfoxide (105 mg, 40%). This sulfoxide (105 mg, 0.32 mmol) was dissolved in toluene (5 cm^3) and the mixture was heated under reflux in the presence of $NaHCO_3$ (30 mg, 0.36 mmol) overnight. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (4:1)] to give **10** (24 mg, 38%), whose spectroscopic data were identical to those of the compound obtained by cyclisation of **6e**.

General procedure for the preparation of *N*-benzyl-2-halo-*N*-(3,4-dihydro-2-naphthyl)acetamides 6h–j

A solution of β-tetralone (1.02 g, 7.0 mmol) and benzylamine

(897 mg, 8.4 mmol) in benzene (30 cm^3) was heated under reflux with azeotropic removal of water for 3 h. The solvent was evaporated to give the crude imine which was dissolved in dichloromethane (30 cm^3). To this was added an appropriate acyl chloride (9.1 mmol) at 0 °C and the mixture was stirred at room temperature overnight. After saturated aq. $NaHCO_3$ (30 cm^3) had been added at 0 °C, the whole was stirred for 10 min. The organic layer was separated, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (3:1)] to give an enamide. The following compounds were thus obtained.

***N*-Benzyl-2-chloro-*N*-(3,4-dihydro-2-naphthyl)acetamide 6h.** Yield 99%, an *oil* (Found: C, 73.6; H, 6.1; N, 4.2. $C_{19}H_{18}ClNO$ requires C, 73.2; H, 5.8; N, 4.5%); $\nu_{max}(CCl_4)/cm^{-1}$ 1665; δ_H(60 MHz, $CDCl_3$) 2.1–2.6 (2 H, m), 2.7–3.1 (2 H, m), 4.19 (2 H, s, $COCH_2$), 4.76 (2 H, CH_2Ph), 6.20 (1 H, br s, 1-H) and 6.8–7.5 (9 H, m, ArH).

***N*-Benzyl-2-chloro-*N*-(3,4-dihydro-2-naphthyl)propanamide 6i.** Yield 82%, an *oil* (Found: C, 73.5; H, 6.2; N, 4.0. $C_{20}H_{20}ClNO$ requires C, 73.7; H, 6.2; N, 4.3%); $\nu_{max}(CCl_4)/cm^{-1}$ 1670; δ_H(60 MHz, $CDCl_3$) 1.65 (3 H, d, *J* 7, Me), 2.15–2.6 (2 H, m), 2.7–3.2 (2 H, m), 4.73 (2 H, br s, CH_2Ph), 4.82 (1 H, q, *J* 7, COCH), 6.21 (1 H, br s, 1-H) and 6.8–7.5 (9 H, m, ArH).

***N*-Benzyl-2,2,2-trichloro-*N*-(3,4-dihydro-2-naphthyl)acetamide 6j.** Yield 25%, a *glass* [Found: $(M + H)^+$, 380.0362. $C_{19}H_{17}{}^{35}Cl_3NO$ requires MH^+, 380.0376]; $\nu_{max}(CCl_4)/cm^{-1}$ 1675; δ_H(60 MHz, $CDCl_3$) 2.3–3.2 (4 H, m), 4.83 (2 H, br s, CH_2Ph), 6.27 (1 H, br s, 1-H) and 6.7–7.6 (9 H, m, ArH).

Radical cyclisation of 6h

Following the general procedure, compound **6h** (1.29 g, 4.15 mmol) was treated with Bu_3SnH (1.45 g, 4.98 mmol) and AIBN (145 mg, 0.88 mmol). After work-up, the crude material was chromatographed on silica gel [hexane–AcOEt (5:1)]. The first fraction gave N-*benzyl*-N-(3,4-*dihydro*-2-*naphthyl*)*acetamide* **13** (260 mg, 23%) as an oil (Found: C, 82.2; H, 6.9; N, 4.8. $C_{19}H_{19}NO$ requires C, 82.3; H, 6.9; N, 5.05%); $\nu_{max}(CCl_4)/cm^{-1}$ 1640; δ_H(300 MHz, $CDCl_3$) 2.16 (3 H, s, COMe), 2.32 (2 H, br t, *J* 8.0), 2.86 (2 H, br t, *J* 8.2), 4.76 (2 H, s, CH_2Ph), 6.15 (1 H, s, 1-H), 6.92–6.98 (1 H, m, ArH), 7.08–7.19 (3 H, m, ArH) and 7.20–7.32 (5 H, m, ArH).

The second fraction gave 1-*benzylspiro*[*azetidine*-4,2′-1′,2′,3′,4′-*tetrahydronaphthalen*]-2-*one* **8h** (502 mg, 44%) as an oil (Found: C, 81.8; H, 7.1; N, 5.0%); $\nu_{max}(CCl_4)/cm^{-1}$ 1735; δ_H(300 MHz, $CDCl_3$) 1.71–1.81 (1 H, m), 1.89 (1 H, dt, *J* 12.5, 8.5), 2.68–2.88 (5 H, m), 3.06 (1 H, d, *J* 16.4), 4.30, 4.44 (1 H, each, ABq, *J* 15.4, CH_2Ph), 6.96–7.15 (4 H, m) and 7.24–7.35 (5 H, m).

Radical cyclisation of 6i

A solution of Bu_3SnH (683 mg, 2.35 mmol) and AIBN (59 mg, 0.36 mmol) in toluene (70 cm^3) was added to a solution of compound **6i** (590 mg, 1.81 mmol) in boiling toluene (150 cm^3) over a period of 4 h and the mixture was heated under reflux overnight. After work-up as described in the general procedure, the crude material was chromatographed on silica gel [hexane–AcOEt (9:1)]. The first fraction gave N-*benzyl*-N-(3,4-*dihydro*-2-*naphthyl*)*propanamide* **14** (63 mg, 12%) as an oil (Found: C, 82.4; H, 7.2; N, 4.75. $C_{20}H_{21}NO$ requires C, 82.4; H, 7.3; N, 4.8%); $\nu_{max}(CCl_4)/cm^{-1}$ 1660; δ_H(300 MHz, $CDCl_3$) 1.17 (3 H, t, *J* 7.5, CH_2CH_3), 2.32 (2 H, br t, *J* 8.1), 2.43 (2 H, q, *J* 7.5, CH_2CH_3), 2.87 (2 H, br t, *J* 8.3), 4.75 (2 H, s, CH_2Ph), 6.14 (1 H, s, 1-H), 6.92–6.97 (1 H, m, ArH), 7.07–7.19 (3 H, m, ArH) and 7.20–7.34 (5 H, m, ArH).

The second fraction gave (1R*,3aR*,9bR*)-2,3,3a,4,5,9b-*hexahydro*-1H-1-*methyl*-3-*benzylbenz*[e]*indol*-2-*one* **9i**-β (235 mg, 45%) as a glass, mp 100–100.5 °C (from hexane–AcOEt) (Found: C, 82.6; H, 7.3; N, 5.1%); $\nu_{max}(CCl_4)/cm^{-1}$ 1690; δ_H(300 MHz, $CDCl_3$) 1.46 (3 H, d, *J* 7.1, 1-Me), 1.71–1.95 (2 H, m, 4-H_2), 2.41–2.52 (1 H, m, 1-H), 2.61 (1 H, ddd, *J* 16.0, 9.0, 4.6, one of 5-H_2), 2.73 (1 H, ddd, *J* 16.0, 6.6, 4.6, one of 5-H_2), 3.07 (1 H, br t, *J* 8.6, 9b-H), 3.70 (1 H, td, *J* 8.0, 4.6, 3a-H), 4.11 (1 H, d, *J* 15.0, one of CH_2Ph), 5.05 (1 H, d, *J* 15.0, one of CH_2Ph), 7.09–7.24 (4 H, m, ArH) and 7.25–7.39 (5 H, m, ArH).

The third fraction gave a mixture of 1-*benzyl*-3-*methylspiro*[*azetidine*-4,2′-1′,2′,3′,4′-*tetrahydronaphthalen*]-2-*one* **8i** and (1S*,3aR*,9bR*)-2,3,3a,4,5,9b-*hexahydro*-1H-1-*methyl*-3-*benzylbenz*[e]*indol*-2-*one* **9i**-α (total 146 mg, total 27%) as an oil. The ^1H NMR spectrum of the mixture showed the compound **8i** to be a mixture of two diastereoisomers in a ratio of *ca.* 1.8:1 and the ratio of **8i**:**9i**-α to be 3.4:1, thereby indicating the yields of **8i** and **9i**-α to be 21 and 6%, respectively. A careful separation of the mixture by chromatography on silica gel afforded a small quantity of an analytical sample of **8i** (Found: C, 82.5; H, 7.8; N, 5.0%); $\nu_{max}(CCl_4)/cm^{-1}$ 1745; δ_H(300 MHz, $CDCl_3$) for the major isomer 1.27 (3 H, d, *J* 7.5), 1.88 (2 H, br t, *J* 7.2), 2.70–3.02 (5 H, m), 4.19 (1 H, d, *J* 15.6), 4.37 (1 H, d, *J* 15.6) and 6.93–7.36 (9 H, m); δ_H(300 MHz, $CDCl_3$) for the minor isomer (diagnostic data only) 1.06 (3 H, d, *J* 7.5), 4.26 (1 H, d, *J* 15.4) and 4.41 (1 H, d, *J* 15.4); for **9i-α**: $\nu_{max}(CCl_4)/cm^{-1}$ 1690; δ_H(300 MHz, $CDCl_3$) 0.97 (3 H, d, *J* 7.7), 1.57–1.79 (2 H, m), 2.61–2.80 (3 H, m), 3.68–3.79 (2 H, m), 4.15 (1 H, d, *J* 15.1), 5.04 (1 H, d, *J* 15.1) and 7.1–7.4 (9 H, m).

Radical cyclisation of 6j

Following the general procedure, compound **6j** (497 mg, 1.30 mmol) was treated with Bu_3SnH (468 mg, 1.61 mmol) and AIBN (42 mg, 0.26 mmol). After work-up, the crude material was chromatographed on silica gel [hexane–AcOEt (7:1)] to give 3-*benzyl*-2,3-*dihydro*-1H-*benz*[e]*indol*-2-*one* **16**[8] (188 mg, 53%), mp 160–160.5 °C (from hexane–AcOEt) (Found: C, 83.5; H, 5.5; N, 5.0. $C_{19}H_{15}NO$ requires C, 83.5; H, 5.5; N, 5.1%); $\nu_{max}(CCl_4)/cm^{-1}$ 1715; δ_H(300 MHz, $CDCl_3$) 3.86 (2 H, s, 1-H_2), 5.00 (2 H, s, CH_2Ph), 7.01 (1 H, d, *J* 8.6, ArH), 7.21–7.37 (6 H, m, ArH), 7.48 (1 H, td, *J* 8.3, 1.2, ArH), 7.63 (1 H, d, *J* 8.3, ArH), 7.69 (1 H, d, *J* 8.5, ArH) and 7.76 (1 H, d, *J* 8.3, ArH).

2-Bromo-*N*-(3,4-dihydro-2-naphthyl)-*N*-methylpropanamide 6k
Following the general procedure, the imine prepared from β-tetralone (1.55 g, 10.6 mmol) and a large excess of methylamine was treated with 2-bromopropanoyl bromide (2.74 g, 12.7 mmol) in the presence of triethylamine (1.3 g, 12.7 mmol), and the crude material was chromatographed on silica gel [hexane–AcOEt (4:1)] to give **6k** (2.39 g, 76%) as an oil (Found: M^+, 293.0402. $C_{14}H_{16}{}^{79}BrNO$ requires M^+, 293.0415); $\nu_{max}(CCl_4)/cm^{-1}$ 1670; δ_H(60 MHz, $CDCl_3$) 1.80 (3 H, d, *J* 7), 2.3–2.7 (2 H, m), 2.8–3.2 (2 H, m), 3.10 (3 H, s), 4.83 (1 H, q, *J* 7), 6.40 (1 H, br s) and 7.10 (4 H, br s).

***N*-Benzyl-2-bromo-*N*-(3,4-dihydro-2-naphthyl)propanamide 6l**
Following the general procedure, the imine prepared from β-tetralone (1.17 g, 8.0 mmol) and benzylamine (943 mg, 8.8 mmol) was treated with 2-bromopropanoyl bromide (2.25 g, 10.4 mmol), and the crude material was chromatographed on silica gel [hexane–AcOEt (5:1)] to give **6l** (2.83 g, 95%) as an oil (Found: M^+, 369.0725. $C_{20}H_{20}{}^{79}BrNO$ requires M^+, 369.0728); $\nu_{max}(CCl_4)/cm^{-1}$ 1665; δ_H(60 MHz, $CDCl_3$) 1.80 (3 H, d, *J* 7), 2.15–2.6 (2 H, m), 2.7–3.1 (2 H, m), 4.70 (2 H, s), 4.82 (1 H, q, *J* 7), 6.17 (1 H, br s) and 6.8–7.4 (9 H, m, ArH).

Studies on the effect of temperature on the regioselectivity in radical cyclisations of 6k and 6l

A mixture of Bu_3SnH (348 mg, 1.2 mmol) and AIBN (33 mg, 0.2 mmol) in benzene or toluene (50 cm^3) was added to a boiling solution of **6k** (293 mg, 1 mmol) or **6l** (369 mg, 1 mmol) in the same solvent (100 cm^3) as that described above by using a syringe pump over a period of 3 h. For the reactions in benzene, heating was continued for a further hour. After usual work-up, the crude material was chromatographed on silica gel [hexane–

AcOEt (9:1)]. The first fraction gave the simple reduction product **15** (from **6k**) or **14** (from **6l**).

The second fraction gave a mixture of the radical cyclisation products **8b** and **9b** (from **6k**) or **8i** and **9i** (from **6l**), whose ratios were estimated by the integrated intensities of the peak height of the *C*-methyl protons at δ 1.02 and 1.20 (for the two diastereoisomers of **8b**), δ 0.90 and 1.41 (for the two diastereoisomers of **9b**), δ 1.06 and 1.27 (for the two diastereoisomers of **8i**) and δ 0.97 and 1.46 (for the two diastereoisomers of **9i**). These results are summarised in Table 1.

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