Synthesis of bridged azabicyclic compounds using radical translocation reactions of 1-(*o*-halogenobenzoyl)-2-(prop-2-enyl)- and -(prop-2-ynyl)-piperidines

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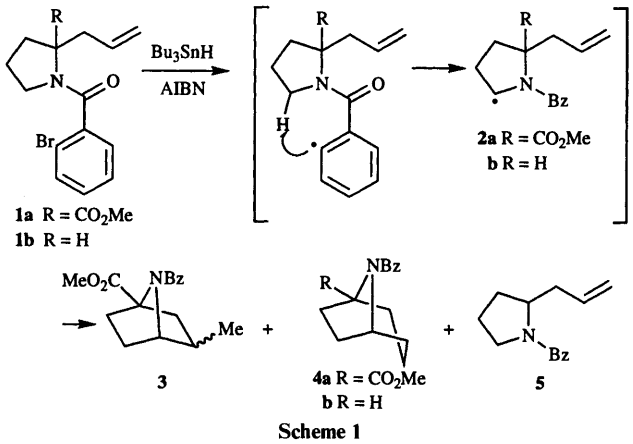
Methyl 1-(*o*-bromobenzoyl)-2-(prop-2-enyl)piperidine-2-carboxylate 8a, upon treatment with tributyltin hydride in the presence of azoisobutyronitrile in boiling toluene gave regioselectively the 8-azabicyclo[3.2.1]octane 14a (a 5-*exo* cyclisation product) in quantitative yield as a diastereomeric mixture (66:34). 1-(*o*-Bromobenzoyl)-2-(prop-2-enyl)piperidine 13 also gave the 8-azabicyclo[3.2.1]octane 16 (75% as a diastereomeric mixture), along with the pyrido[2,1-*a*]isoindolone 17 (10%) and the simple reduction product 18 (5%). 1-(*o*-Iodobenzoyl)-2-[3-(trimethylsilyl)prop-2-ynyl]piperidine 23 afforded, in addition to the pyrido[2,1-*a*]isoindolone 25 (18%), the 8-azabicyclo[3.2.1]octane 24 (75%) which was converted into the 6-oxo derivative 27. For comparison, the behaviour of the azetidine congener 31 was also examined.

The radical translocation reactions[1] of *N*-substituted *o*-halogenobenzamides are emerging as one of the methods for the generation of the synthetically useful α-acylamino radicals.[2,3] Previously we showed that methyl 1-(*o*-bromobenzoyl)-2-(prop-2-enyl)pyrrolidine-2-carboxylate **1a**, upon treatment with tributyltin hydride (Bu_3SnH) in the presence of azoisobutyronitrile (AIBN), gave the 7-azabicyclo[2.2.1]heptane **3** (42% as a diastereomeric mixture) and 8-azabicyclo[3.2.1]octane ring systems **4a** (30%) (Scheme 1).[4]

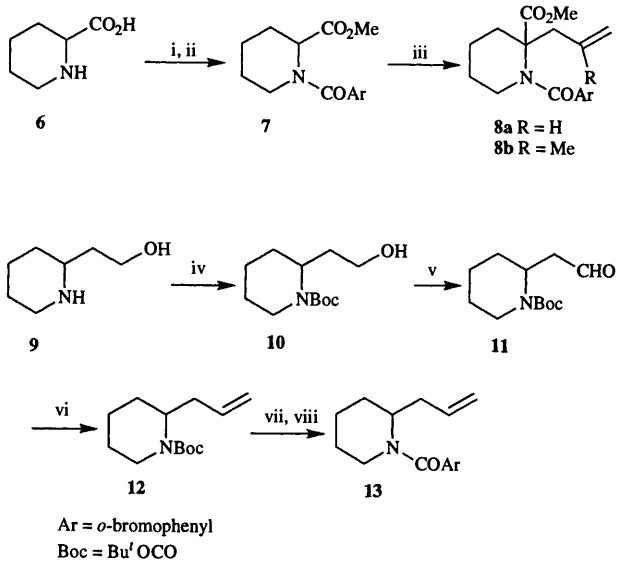


Scheme 1

The formation of **3** and **4a** was formulated as proceeding *via* the α-acylamino radical **2a** which is generated by 1,5-hydrogen transfer from the initially formed aryl radical. The radical **2a** then cyclises in either a 5-*exo-trig* or 6-*endo-trig* manner to give **3** and **4a**, respectively. This cyclisation is facilitated by the presence of the substituent at the 2-position of the pyrrolidine ring. As an extension of this reaction, we have now investigated the piperidine and azetidine derivatives,[5] and found that the 2-(prop-2-enyl)- and 2-(prop-2-ynyl)-piperidines give the 8-azabicyclo[3.2.1]octane ring system[6] with high regioselectivity.

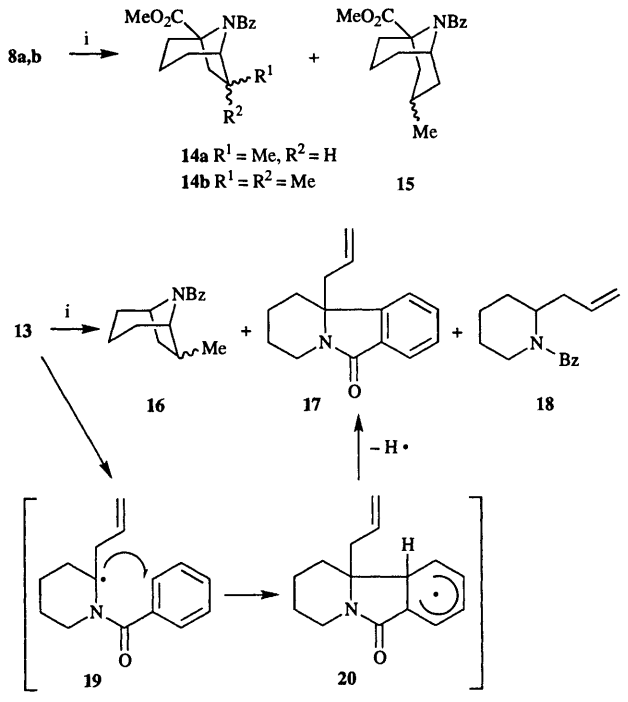
Results and discussion

The radical precursors **8a,b** were obtained readily by the alkylation[7] of methyl 1-(*o*-bromobenzoyl)piperidine-2-carboxylate **7** which, in turn, was prepared from pipecolinic acid **6** (Scheme 2). The 2-(prop-2-enyl)piperidine derivative **13** was prepared from commercially available piperidine-2-ethanol **9**. Thus, *N*-protection of **9** with a *tert*-butoxycarbonyl group followed by Swern oxidation of the resulting alcohol **10**[8] gave the aldehyde **11**. Wittig olefination of **11** followed by deprotection and *N*-acylation of **12** with *o*-bromobenzoyl chloride gave the desired **13**.



Scheme 2 *Reagents and conditions:* i, MeOH, $SOCl_2$, reflux; ii, *o*-bromobenzoyl chloride, Et_3N, CH_2Cl_2; iii, $(TMS)_2NLi$, THF, −78 °C, and then $CH_2{=}CRCH_2Br$; iv, $(Boc)_2O$, AcOEt; v, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; vi, $Ph_3P^+CH_3Br^-$, DMSO, NaH; vii, CF_3CO_2H; viii, *o*-bromobenzoyl chloride, Et_3N, DMAP, CH_2Cl_2

A toluene solution of Bu_3SnH (1.25 mol equiv.) and a small amount of AIBN (0.1 mol. equiv.) was added slowly to a boiling solution of **8a** in toluene over a period of 2 h, and the mixture was refluxed for 2 h. To complete the reaction, the procedure was repeated. The crude material was chromatographed on silica gel to give the 8-azabicyclo[3.2.1]octane **14a** (Scheme 3) (a 5-*exo* cyclisation product) in quantitative yield as a diastereomeric mixture in a ratio of 66:34 (determined by GLC). The structure of **14a** was deduced from a comparison of the spectroscopic data (the IR, ^1H and ^{13}C NMR spectra) with those of **5a** and the related compounds.[4] A similar treatment of the 2-(2-methylprop-2-enyl)piperidine **8b** gave the 8-azabicy-



Scheme 3 *Reagents and conditions:* i, Bu_3SnH, AIBN, toluene, reflux

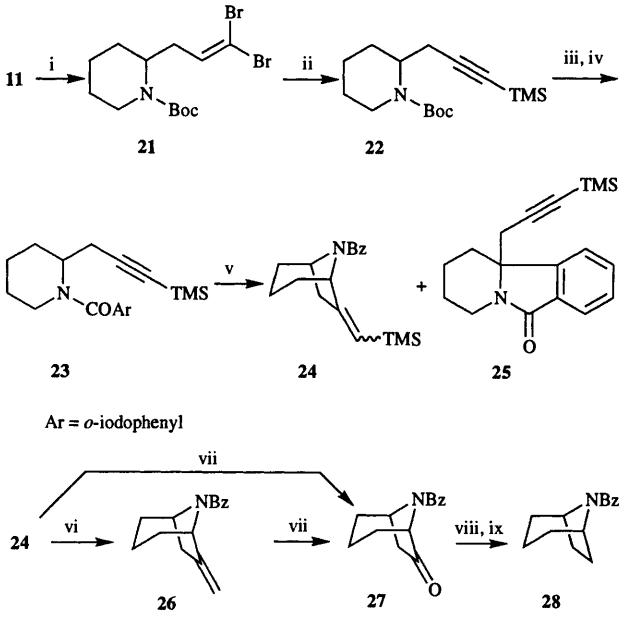
clo[3.2.1]octane **14b** (40%) and the 9-azabicyclo[3.3.1]nonane **15** (34% as a diastereomeric mixture in a ratio of 65:35).

The exclusive or predominant formation of the 5-*exo* cyclisation products **14a,b** from **8a,b** may reflect the closeness between the radical centre formed at the 2-position of the piperidine ring and the 2-position of the axial prop-2-enyl group. The increase of the 6-*endo* cyclisation product **15** in the product mixture obtained from **8b** may be a consequence of the steric hindrance and electronic stabilisation exerted by the methyl group on the radical intermediate formed after the cyclisation.

In contrast to the 2-unsubstituted pyrrolidine derivative **1b**, which gave predominantly the simple reduction product **5a** (81%) along with the 8-azabicyclo[3.2.1]octane **4b** (a 6-*endo* cyclisation product)(17%),[4] the 2-(prop-2-enyl)piperidine congener **13**, upon treatment with Bu_3SnH and AIBN, afforded the 8-azabicyclo[3.2.1]octane **16** (a 5-*exo*-cyclisation product) (75% as a diastereomeric mixture in a ratio of 63:37) as the major product. The other products were assigned the structures **17** (10%) and **18** (5%). The compound **17** showed an amide carbonyl absorption band at 1685 cm^{-1} in the IR spectrum. Its ^1H NMR spectrum revealed signals due to the prop-2-enyl group and four aromatic protons and the ^{13}C NMR spectrum indicated the presence of five methylene carbons and one quaternary carbon apart from the alkenic and aromatic carbons. The formation of **17** from **13** may proceed *via* the radical intermediate **19** which cyclises to form the radical intermediate **20**. This radical then loses hydrogen atom to give **17**.[2c]

The difference in behaviour between the piperidine **13** and the pyrrolidine **1b** may be rationalised by considering the preferred conformations of the radical intermediates *e.g.* **2b**. The prop-2-enyl group in the radical derived from **13** may occupy an axial position in order to minimise allylic 1,3-strain ($A^{1,3}$ strain) with the N=C double bond in the amide.[9] This causes the 2-position of the prop-2-enyl group to be brought into the correct position to react in the 5-*exo-trig* manner. The same argument may be applied to the pyrrolidine case, but close examination of the X-ray crystal structure of *N-tert*-butoxycarbonylproline[9] and related five-membered heterocycles,[9] as well as inspection of a molecular model of the radical derived from the pyrrolidine **1b**,[4] reveal that the 2-substituent adopts a quasi-axial position, so that the distance between either the 2- or 3-position of the prop-2-enyl group and the radical centre becomes longer than in the piperidine case. Consequently the reduction competes favourably with the cyclisation (since the 3-position of the two reactive sites is relatively closer to the radical centre, the observed 6-*endo* cyclisation is favoured over the 5-*exo* cyclisation). An intriguing alternative explanation is based on the fact that the five-membered ring is much more conformationally flexible than the six, so the former spends less time in the conformation favourable for cyclisation.

Since the 1,5-hydrogen transfer and cyclisation reactions were found to proceed cleanly in the 2-unsubstituted piperidine derivative, we then examined the cyclisation of the 2-(prop-2-ynyl)piperidine derivative **23**. Compound **23** was prepared as shown in Scheme 4. Thus, the aldehyde **11** was allowed to react



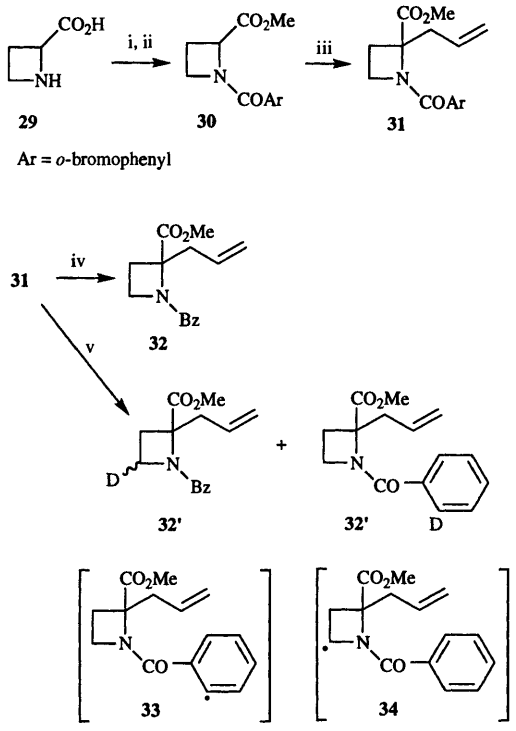
Scheme 4 *Reagents and conditions:* i, Ph_3P, CBr_4; ii, BuLi and then TMSCl; iii, TMSI, MeCN; iv, *o*-iodobenzoyl chloride, Et_3N, DMAP; v, Bu_3SnH, AIBN, toluene, reflux; vi, $TsOH{\cdot}H_2O$, MeCN, reflux; vii, OsO_4, $NaIO_4$; viii, NH_2NHTs; ix, $NaBH_3CN$, $TsOH{\cdot}H_2O$, DMF–sulfolane

with carbon tetrabromide and triphenylphosphine. Treatment of the resulting dibromide **21** with butyllithium[10] and then quenching with trimethylsilyl chloride gave **22**. Replacement of the *N*-Boc group of **22** by *o*-iodobenzoyl gave the radical precursor **23**.

Treatment of **23** with Bu_3SnH and AIBN† gave the 8-azabicyclo[3.2.1]octane **24** (75%) as a diastereomeric mixture along with the tricyclic compound **25** (18%). The structure of **24** was confirmed by chemical transformation to the known compound **28**. Thus, protodesilylation (93%) of **24** with toluene-*p*-sulfonic acid followed by oxidative cleavage of the resulting alkene **26** with osmium tetroxide and sodium metaperiodate (52%) gave the ketone **27**.[11] The same ketone **27** was also obtained in 53% yield directly from **24** by treatment with osmium tetroxide–sodium metaperiodate. Reduction of the tosylhydrazone of **27** with sodium cyanoborohydride in dimethylformamide–sulfolane[12] led to **28**.[4,13] The minor product **25** exhibited an amide carbonyl absorption at 1695 cm^{-1} in its IR spectrum, and the signals due to the 3-(trimethylsilyl)prop-2-ynyl group and four aromatic proton signals in its ^1H NMR spectrum. Its ^{13}C NMR spectrum was in good agreement with the assigned structure.

Finally, it was interesting to investigate the azetidine

† 1-(*o*-Bromobenzoyl)-2-(prop-2-ynyl)piperidine, upon treatment with Bu_3SnH and AIBN, gave only a complex mixture.



Scheme 5 *Reagents and conditions:* i, MeOH, $SOCl_2$, reflux; ii, *o*-bromobenzoyl chloride, Et_3N, CH_2Cl_2; iii, $(TMS)_2NLi$, THF, −78 °C, and then CH_2=$CHCH_2Br$; iv, Bu_3SnH, AIBN, toluene, reflux; v, Bu_3SnD, AIBN, toluene, reflux

derivative **31** in order to compare it with its pyrrolidine and piperidine counterparts **1a** and **8a**. Compound **31** was prepared from azetidine-2-carboxylic acid **29** by essentially the same procedure as that used for the synthesis of **8a** (see Experimental section). When **31** was treated with Bu_3SnH and AIBN, only the reduction product **32** was obtained in 63% yield. Treatment of **31** with Bu_3SnD and AIBN revealed that the deuterium atom was incorporated into the 4-position (71%) as well as the phenyl ring (29%) of **32**. Thus, in the azetidine case both the 1,5-hydrogen transfer and cyclisation steps are retarded. Examination of Dreiding models reveals that the distance between the radical centre formed on the phenyl ring and the 4-hydrogen atom in **33** is slightly longer than that in **1a** and the radical centre in **34** formed after the 1,5-hydrogen transfer is too far away from the alkenic double bond to permit the cyclisation.

In summary, we have shown that the 1-(*o*-halogenobenzoyl)-2-(prop-2-enyl)- and -(prop-2-ynyl)-piperidines smoothly undergo 1,5-hydrogen-transfer and cyclisation to give the 8-azabicyclo[3.2.1]octanes with high regioselectivity.

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. ^1H 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 (EI and FAB mass spectra) were obtained on a JEOL-SX 102A instrument. Column chromatography was performed on silica gel 60 PF_{254} (Nacalai Tesque) under pressure.

Methyl 1-(*o*-bromobenzoyl)piperidine-2-carboxylate 7

To a solution of pipecolinic acid **6** (piperidine-2-carboxylic acid; 5.0 g, 38.7 mmol) in absolute methanol (50 cm^3) was added dropwise thionyl chloride (5.07 g, 42.6 mmol) under a nitrogen atmosphere at 0 °C and the mixture was refluxed for 1 h. The solvent was evaporated off and the residue was dissolved in dichloromethane (60 cm^3) containing Et_3N (9.79 g, 96.8 mmol). A solution of *o*-bromobenzoyl chloride (8.92 g, 40.65 mmol) in dichloromethane (10 cm^3) was added to the above solution and the whole was stirred at room temperature overnight and the precipitated material was filtered off. After removal of the solvent, the residue was dissolved in diethyl ether (40 cm^3) and the solution was washed with 1 mol dm^{-3} HCl, saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (10:1)] to give **7** (12.6 g, quant.) as a colourless oil (Found: C, 51.1; H, 5.0; N, 4.2. $C_{14}H_{16}BrNO_3$ requires C, 51.55; H, 4.9; N, 4.3%); $\nu_{max}(CCl_4)/cm^{-1}$ 1740 and 1645; δ_H(60 MHz) 1.05–2.05 (6 H, m), 3.05–3.5 (2 H, m), 3.72, 3.78 (total 3 H, both s, OMe), 5.45–5.7 (1 H, m, 2-H) and 7.05–7.85 (4 H, m, ArH).

General procedure for the preparation of methyl 1-(*o*-bromobenzoyl)-2-(prop-2-enyl)piperidine-2-carboxylates 8a,b

To a solution of hexamethyldisilazane (1.09 g, 6.74 mmol) in THF (10 cm^3) at −78 °C under a nitrogen atmosphere was added a 1.6 mol dm^{-3} solution of butyllithium in hexane (4.2 cm^3, 6.74 mmol) and the mixture was stirred for 30 min. To this mixture was added **7** (2.0 g, 6.13 mmol) in THF (10 cm^3) at −78 °C and the whole was stirred for 15 min. After appropriate prop-2-enyl bromide (8.58 mmol) had been added at −78 °C to the mixture, it was stirred at room temperature for 5 h. The reaction mixture was acidified with 1 mol dm^{-3} HCl (5 cm^3) and concentrated under reduced pressure. The aqueous layer was extracted with diethyl ether and the extract was washed with 1 mol dm^{-3} HCl, saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (5:1)]. The following compounds were thus obtained.

Methyl 1-(*o*-bromobenzoyl)-2-(prop-2-enyl)piperidine-2-carboxylate 8a. Yield 57%, mp 69–70 °C (from hexane) (Found: C, 55.6; H, 5.5; N, 3.8. $C_{17}H_{20}BrNO_3$ requires C, 55.75; H, 5.5; N, 3.8%); $\nu_{max}(CCl_4)/cm^{-1}$ 1735 and 1640; δ_H(60 MHz) 1.3–2.15 (6 H, m), 2.45–3.4 (4 H, m), 3.76 (3 H, s, OMe), 4.9–5.35 (2 H, m, CH_2CH=CH_2), 5.65–6.5 (1 H, m, CH_2CH=CH_2), 6.95–7.35 (3 H, m, ArH) and 7.4–7.65 (1 H, m, ArH).

Methyl 1-(*o*-bromobenzoyl)-2-(2-methylprop-2-enyl)piperidine-2-carboxylate 8b. Yield 60%, mp 70–72.5 °C (from hexane) (Found: C, 57.1; H, 5.85; N, 3.9. $C_{18}H_{22}BrNO_3$ requires C, 56.85; H, 5.8; N, 3.7%); $\nu_{max}(CCl_4)/cm^{-1}$ 1740 and 1645; δ_H(60 MHz) 1.4–2.3 (6 H, m), 1.95 (3 H, s, CMe), 2.5–3.5 (4 H, m), 3.74 (3 H, s, OMe), 4.8–5.1 (2 H, m, CH_2CMe=CH_2), 7.0–7.4 (3 H, m, ArH) and 7.45–7.65 (1 H, m, ArH).

Radical cyclisation of compound 8a

General procedure. To a stirred and boiling solution of **8a** (600 mg, 1.6 mmol) in toluene (50 cm^3) was added a solution of Bu_3SnH (620 mg, 2.13 mmol) and AIBN (27 mg, 0.16 mmol) in toluene (60 cm^3) *via* a syringe over a period of 2 h, and the mixture was refluxed for 2 h. This procedure was repeated. After removal of the solvent, diethyl ether (15 cm^3) and 8% aqueous KF (15 cm^3) were added to the residue, and the whole was vigorously stirred 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 (20:1)] to give a mixture of *exo* and *endo* isomers (66:34 by GLC) of *methyl 8-benzoyl-6-methyl-8-azabicyclo*[3.2.1]*octane-1-carboxylate* **14a** (471 mg, quant.), mp 105–106 °C (from hexane) (Found: C, 71.0; H, 7.5; N, 4.8. $C_{17}H_{21}NO_3$ requires C, 71.1; H, 7.4; N, 4.9%); $\nu_{max}(CCl_4)/cm^{-1}$ 1740 and 1640; δ_H(300 MHz) (for the *exo* isomer) 1.29 (3 H, d, J 6.7, 6-Me), 1.35–1.42 (2 H, m), 1.60 (1 H, dd, J 12.7, 7.4), 1.70–1.98 (4 H, m), 2.15–2.45 (2 H, m), 3.754 (3 H, s, OMe), 3.88 (1 H, unresolved t, J 2.6, 5-H), 7.36–7.48 (3 H, m, ArH) and 7.50–7.59 (2 H, m, ArH); δ_H(300 MHz) (for the *endo* isomer) 1.09 (3 H, d, J 7.1, 6-Me), 1.35–1.98 (5 H, m), 2.15–2.45 (2 H, m), 2.55 (1 H, t, J

12.3), 2.72–2.88 (1 H, m), 3.749 (3 H, s, OMe), 3.99–4.04 (1 H, m, 5-H), 7.36–7.48 (3 H, m, ArH) and 7.50–7.59 (2 H, m, ArH); δ_C (for the *exo* isomer) 17.4 (CH_2), 22.6 (6-Me), 29.4 (CH_2), 31.6 (CH_2), 35.6 (6-C), 42.4 (CH_2), 52.3 (OMe), 66.0 (1-C), 66.6 (5-C), 127.7, 128.4, 130.3, 136.0, 170.4 (C=O) and 172.55 (C=O); δ_C (for the *endo* isomer) 14.0 (6-Me), 17.6 (CH_2), 26.95 (CH_2), 29.5 (CH_2), 35.05 (6-C), 40.9 (CH_2), 52.2 (OMe), 62.9 (5-C), 65.2 (1-C), 127.5, 128.4, 130.4, 136.0, 169.6 (C=O) and 172.8 (C=O).

Radical cyclisation of compound 8b

Following the general procedure, **8b** (500 mg, 1.31 mmol) was treated twice with Bu_3SnH (421 mg, 1.45 mmol) and AIBN (22 mg, 0.13 mmol) in toluene and the crude material was chromatographed on silica gel [hexane–AcOEt (7:1)]. The first fraction gave unchanged **8b** (130 mg, 26%). The second fraction gave a mixture of *exo* and *endo* isomers (65:35 by GLC) of *methyl 9-benzoyl-3-methyl-9-azabicyclo*[3.3.1]*nonane*-1-*carboxylate* **15** (134 mg, 34%), mp 134.5–136 °C (from hexane) (Found: C, 71.7; H, 7.8; N, 4.6. $C_{18}H_{23}NO_3$ requires C, 71.7; H, 7.7; N, 4.65%); $\nu_{max}(CCl_4)/cm^{-1}$ 1740 and 1640; δ_H(300 MHz) 0.95 (2/3 × 3 H, for the major isomer, d, *J* 6.3, 3-Me), 0.99–1.06 (1/3 × 3 H, for the minor isomer, br, 3-Me), 1.27–2.17 (10 H, m), 2.36–2.47 (1 H, m), 3.71 (3 H, s, OMe), 4.19–4.23, 4.08–4.12 (total 1 H, unresolved m, 5-H), 7.37–7.45 (3 H, m, ArH) and 7.50–7.58 (2 H, m, ArH). The third fraction gave *methyl 8-benzoyl-6,6-dimethyl-8-azabicyclo*[3.2.1]*octane*-1-*carboxylate* **14b** (156 mg, 40%), mp 96.5–98 °C (from hexane) (Found: C, 71.6; H, 7.7; N, 4.6); $\nu_{max}(CCl_4)/cm^{-1}$ 1740 and 1640; δ_H(300 MHz) 1.14 (3 H, s, 6-Me), 1.42 (3 H, s, 6-Me), 1.53–2.00 (5 H, m), 1.86, 2.06 (1 H each, ABq, *J* 12.6, 7-H_2), 2.33–2.45 (1 H, m), 3.65 (1 H, br s, 5-H), 3.76 (3 H, s, OMe), 7.36–7.45 (3 H, m, ArH) and 7.50–7.56 (2 H, m, ArH).

***tert*-Butyl 2-(formylmethyl)piperidine-1-carboxylate 11**

Di-*tert*-butyl dicarbonate (8.45 g, 38.7 mmol) was slowly added to a solution of **9** (5.0 g, 38.7 mmol) in ethyl acetate (20 cm^3) at 0 °C and the mixture was stirred at room temperature for 16 h. The reaction mixture was washed with 1 mol dm^{-3} HCl, saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated to give *tert*-butyl 2-(2-hydroxyethyl)piperidine-1-carboxylate **10**[8] (8.87 g, quant.) as an oil.

A solution of dimethyl sulfoxide (3.27 g, 41.9 mmol) in dry dichloromethane (20 cm^3) was added to a solution of oxalyl chloride (2.66 g, 20.9 mmol) in dry dichloromethane (20 cm^3) at −78 °C over the period of 10 min and the mixture was stirred for 10 min. After this, a solution of **10** (4.0 g, 20.9 mmol) in dry dichloromethane (40 cm^3) at −78 °C was added to the mixture which was then stirred at the same temperature for 20 min. After addition of triethylamine (8.8 g, 87.2 mmol) to the mixture, it was allowed to warm to room temperature. After 2 h, the mixture was diluted with water (40 cm^3) and the organic layer was separated and washed with 1 mol dm^{-3} HCl and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (7:1)] to give **11** (3.50 g, 88%) as a colourless oil (Found: C, 63.4; H, 9.5; N, 6.1. $C_{12}H_{21}NO_3$ requires C, 63.4; H, 9.3; N, 6.2%); $\nu_{max}(CCl_4)/cm^{-1}$ 2825, 2710, 1720 and 1685; δ_H(60 MHz) 1.3–1.8 (6 H, m), 1.45 (9 H, s), 2.5–3.05 (3 H, m), 3.8–4.25 (1 H, m), 4.6–5.05 (1 H, m) and 9.71 (1 H, t, *J* 2, CHO).

***tert*-Butyl 2-(prop-2-enyl)piperidine-1-carboxylate 12**

A solution of methyltriphenylphosphonium bromide (4.5 g, 12.6 mmol) in dimethyl sulfoxide (10 cm^3) was added to a solution of sodium methylsulfinylmethanide in dimethyl sulfoxide [prepared from sodium hydride (604 mg of 50% mineral oil dispersion, 12.6 mmol, freed of mineral oil by washing and decanting with pentane under a nitrogen atmosphere) and dimethyl sulfoxide (5 cm^3)] and the mixture was stirred at room temperature for 1 h. A solution of **11** (2.60 g, 11.4 mmol) in dimethyl sulfoxide (10 cm^3) at 0 °C was added to the mixture which was then stirred at room temperature for 2 h. The mixture was diluted with water (50 cm^3) and extracted with diethyl ether. The extract was dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (30:1)] to give **12** (1.51 g, 59%) as a colourless oil (Found: $[M + H]^+$, 226.1835. $C_{13}H_{23}NO_2$ requires [*M* + H], 226.1807); $\nu_{max}(CCl_4)/cm^{-1}$ 1685; δ_H(60 MHz) 1.46 (9 H, s), 1.4–1.7 (6 H, m), 2.15–3.1 (3 H, m), 3.8–4.5 (2 H, m), 4.8–5.2 (2 H, m, $CH_2CH{=}CH_2$) and 5.4–6.2 (1 H, m, $CH_2CH{=}CH_2$).

1-(*o*-Bromobenzoyl)-2-(prop-2-enyl)piperidine 13

Trifluoroacetic acid (2 cm^3) was added dropwise to a solution of **12** (900 mg, 3.99 mmol) in dichloromethane (1 cm^3) at 0 °C and the mixture was stirred at room temperature for 2 h. After removal of the solvent, the residue was dissolved in dichloromethane (10 cm^3). To this solution were added successively triethylamine (2.02 g, 19.95 mmol), DMAP (49 mg, 0.40 mmol) and a solution of *o*-bromobenzoyl chloride (1.14 g, 5.19 mmol) in dichloromethane (10 cm^3), and the whole was stirred at room temperature for 16 h. After water (10 cm^3) had been added to the reaction mixture, the organic layer was separated, washed with 1 mol dm^{-3} HCl, and saturated aq. $NaHCO_3$, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (7:1)] to give **13** (1.12 g, 91%) as a colourless oil (Found: C, 58.4; H, 6.0; N, 4.8. $C_{15}H_{18}BrNO$ requires C, 58.45; H, 5.9; N, 4.5%); $\nu_{max}(CCl_4)/cm^{-1}$ 1635; δ_H(60 MHz) 1.3–2.0 (6 H, br), 2.1–3.7 (4 H, m), 4.4–5.3 (3 H, m, 2-H, $CH_2CH{=}CH_2$), 5.35–6.5 (1 H, m, $CH_2CH{=}CH_2$), 6.9–7.4 (3 H, m, ArH) and 7.4–7.65 (1 H, m, ArH).

Radical cyclisation of compound 13

Following the general procedure, **13** (500 mg, 1.62 mmol) was treated twice with Bu_3SnH (614 mg, 2.11 mmol) and AIBN (27 mg, 0.16 mmol) in toluene and the crude material was chromatographed on silica gel [hexane–AcOEt (15:1)]. The first fraction gave 1-*benzoyl*-2-(*prop*-2-*enyl*)*piperidine* **18** (20 mg, 5%) as a colourless oil (Found: C, 78.1; H, 8.4; N, 6.25. $C_{15}H_{19}NO$ requires C, 78.6; H, 8.35; N, 6.1%); $\nu_{max}(CCl_4)/cm^{-1}$ 1625; δ_H(60 MHz) 1.64 (6 H, br s), 2.0–3.3 (3 H, m), 3.5–5.0 (2 H, br), 4.8–5.3 (2 H, m, $CH_2CH{=}CH_2$), 5.35–6.2 (1 H, m, $CH_2CH{=}CH_2$) and 7.33 (5 H, s, ArH). The second fraction gave a mixture of *exo* and *endo* isomers (63:37 by GLC) of 8-*benzoyl*-6-*methyl*-8-*azabicyclo*[3.2.1]*octane* **16** (278 mg, 75%) as a colourless oil (Found: C, 78.1; H, 8.2; N, 6.2. $C_{15}H_{19}NO$ requires C, 78.6; H, 8.35; N, 6.1%); $\nu_{max}(CCl_4)/cm^{-1}$ 1625; δ_H(300 MHz) (for a mixture of two isomers, each of which exists as two or more rotamers) 0.96, 1.06, 1.09, 1.16 (total 3 H, all d, *J* 7.0, 6-Me), 1.22–2.48 (9 H, m), 3.52–3.72, 4.01–4.09, 4.36–4.53, 4.78–4.90 (total 2 H, unresolved m, 1- and 5-H) and 7.36–7.50 (5 H, m, ArH). The third fraction gave 10*b*-(*prop*-2-*enyl*)-1,2,3,4,6,10*b*-*hexahydropyrido*[2,1-a]*isoindol*-6-*one* **17** (36 mg, 10%) as a colourless oil (Found: $[M + H]^+$, 228.1373. $C_{15}H_{17}NO$ requires [*M* + H], 228.1388); $\nu_{max}(CCl_4)/cm^{-1}$ 1685; δ_H(300 MHz) 1.21–1.97 (5 H, m), 2.15–2.24 (1 H, m), 2.60 (1 H, ddt, *J* 14.2, 6.5, 1.1, one of $CH_2CH{=}CH_2$), 2.86 (1 H, dd, *J* 14.2, 7.6, one of $CH_2CH{=}CH_2$), 2.91 (1 H, td, *J* 13.4, 3.2, one of 4-H_2), 4.43 (1 H, br dd, *J* 13.4, 4.9, one of 4-H_2), 4.88 (1 H, ddt, *J* 10.1, 2.1, 1.1, one of $CH_2CH{=}CH_2$), 4.94 (1 H, ddt, *J* 17.2, 2.1, 1.1, one of $CH_2CH{=}CH_2$), 5.15 (1 H, dddd, *J* 17.2, 10.1, 7.6, 6.5, $CH_2CH{=}CH_2$), 7.38 (1 H, br d, *J* 7.5, ArH), 7.44 (1 H, td, *J* 7.5, 1.2, ArH), 7.53 (1 H, td, *J* 7.5, 1.2, ArH) and 7.85 (1 H, br d, *J* 7.5, ArH); δ_C 20.2 (CH_2), 25.2 (CH_2), 35.1 (CH_2), 36.55 (CH_2), 37.2 (CH_2), 63.3 (10b-C), 118.8 ($CH_2{=}CHCH_2$), 120.8, 123.7, 128.0, 131.2, 131.3, 131.9, 150.2 and 166.3 (C=O).

***tert*-Butyl 2-(3,3-dibromoprop-2-enyl)piperidine-1-carboxylate 21**

A solution of **11** (412 mg, 1.18 mmol) in dichloromethane (10 cm^3) was added to a solution of triphenylphosphine (2.38 g,

9.06 mmol) and carbon tetrabromide (1.20 g, 3.63 mmol) in dichloromethane (20 cm^3) at 0 °C and the whole was stirred at room temperature for 30 min. To the reaction mixture was added saturated aq. $NaHCO_3$ (30 cm^3). The organic layer was separated and the aqueous layer was extracted with dichloromethane. The extracts were dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (20:1)] to give **21** (590 mg, 85%) as an oil (Found: C, 40.7; H, 5.6; N, 3.4. $C_{13}H_{21}Br_2NO_2$ requires C, 40.8; H, 5.5; N, 3.7%); $\nu_{max}(CCl_4)/cm^{-1}$ 1690; δ_H(300 MHz) 1.46, 1.47 (total 9 H, s), 1.5–1.7 (6 H, m), 2.16–2.85 (3 H, m), 3.93–4.06 (1 H, m), 4.32–4.42 (1 H, m) and 6.38 (1 H, t, *J* 7.1, $CH_2CH{=}CBr_2$).

tert-Butyl 2-[3-(trimethylsilyl)prop-2-ynyl]piperidine-1-carboxylate 22

A 1.6 mol dm^{-3} solution of butyllithium in hexane (4.57 cm^3, 7.31 mmol) was added to a solution of **21** (1.40 g, 3.65 mmol) in THF (20 cm^3) at −78 °C under a nitrogen atmosphere and the whole was stirred for 1 h. To the mixture was added trimethylsilyl chloride (595 mg, 5.48 mmol) at the same temperature and the reaction mixture was warmed to room temperature and stirred for 2 h. The mixture was diluted with ice–water and extracted with diethyl ether. The extract was washed with brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (4:1)] to give **22** (789 mg, 74%), mp 58–59 °C [from light petroleum (bp 30–60 °C)] (Found: C, 65.2; H, 10.1; N, 4.3. $C_{16}H_{29}NO_2Si$ requires C, 65.0; H, 9.9; N, 4.7%); $\nu_{max}(CCl_4)/cm^{-1}$ 2175 and 1690; δ_H(300 MHz) 0.20 (9 H, s), 1.54 (9 H, s), 1.55–1.70 (5 H, m), 1.91–1.98 (1 H, m), 2.44 (1 H, dd, *J* 16.6, 5.9, one of $CH_2C{\equiv}CTMS$), 2.61 (1 H, dd, *J* 16.6, 9.5, one of $CH_2C{\equiv}CTMS$), 2.77 (1 H, br t, *J* 13.2), 4.01 (1 H, m) and 4.37–4.47 (1 H, m).

1-(*o*-Iodobenzoyl)-2-[3-(trimethylsilyl)prop-2-ynyl]piperidine 23

Trimethylsilyl iodide (289 mg, 2.03 mmol) was added to a solution of **22** (400 mg, 1.36 mmol) in acetonitrile (2 cm^3) at room temperature and the whole was stirred for 10 min. Saturated aq. $NaHCO_3$ (5 cm^3) was added to the mixture and this was extracted with dichloromethane. The extract was dried ($MgSO_4$) and concentrated. The residue was dissolved in dichloromethane (10 cm^3). Triethylamine (572 mg, 4.08 mmol) and then a solution of *o*-iodobenzoyl chloride (544 mg, 2.04 mmol) in dichloromethane (10 cm^3) were added to this mixture and the whole was stirred at room temperature for 16 h. Water (10 cm^3) was added to the mixture and this was extracted with dichloromethane. The extract was dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (7:1)] to give **23** (490 mg, 85%) as a colourless oil (Found: C, 50.8; H, 5.7; N, 3.3. $C_{18}H_{24}INOSi$ requires C, 50.65; H, 5.9; N, 3.1%); $\nu_{max}(CCl_4)/cm^{-1}$ 2175 and 1625; δ_H(60 MHz) 0.15 (9 H, s), 1.3–2.0 (6 H, m), 2.4–3.3 (3 H, m), 3.4–3.9 (1 H, m), 4.5–5.2 (1 H, m), 6.8–7.5 (3 H, m) and 7.6–7.9 (1 H, m).

Radical cyclisation of 23

Following the general procedure, **23** (500 mg, 1.27 mmol) was treated with Bu_3SnH (480 mg, 1.65 mmol) and AIBN (22 mg, 0.13 mmol) in toluene and the crude material was chromatographed on silica gel [hexane–AcOEt (7:1)]. The first fraction gave a diastereomeric mixture of 8-*benzoyl*-6-(*trimethylsilylmethylene*)-8-*azabicyclo*[3.2.1]*octane* **24** (269 mg, 75%), mp 104.5–106 °C (from hexane) (Found: C, 72.2; H, 8.4; N, 4.7. $C_{18}H_{25}NOSi$ requires C, 71.85; H, 8.5; N, 4.6%); $\nu_{max}(CCl_4)/cm^{-1}$ 1625; its ^1H NMR spectrum was too complicated to be resolved. The structure was confirmed by conversion into the known compound **28**. The second fraction gave 10*b*-[3-(*trimethylsilyl*)*prop*-2-*ynyl*]-1,2,3,4,6,10*b*-*hexahydropyrido*[2,1-a]*isoindol*-6-*one* **25** (66 mg, 18%) as a colourless oil (Found: $[M + H]^+$, 298.1631. $C_{18}H_{23}NOSi$ requires [*M* + H], 298.1627); $\nu_{max}(CCl_4)/cm^{-1}$ 1695; δ_H(300 MHz) 0.09 (9 H, s), 1.40–1.82 (6 H, m), 2.52 (1 H, d, *J* 16.8, one of $CH_2C{\equiv}CTMS$), 2.91 (1 H, td, *J* 13.8, 3.0, one of 4-H_2), 2.99 (1 H, d, *J* 16.8, one of $CH_2C{\equiv}CTMS$), 4.44 (1 H, br dd, *J* 13.8, 5.1, one of 4-H_2), 7.47 (1 H, td, *J* 7.2, 1.2, ArH), 7.53 (1 H, td, *J* 7.2, 1.2, ArH), 7.64 (1 H, br d, *J* 7.2, ArH) and 7.85 (1 H, br d, *J* 7.2, ArH); δ_C −0.3 ($SiCH_3$), 20.1 (CH_2), 25.0 (CH_2), 25.7 (CH_2), 33.0 (CH_2), 36.4 (CH_2), 62.0 (10b-C), 88.5 ($CH_2C{\equiv}$CTMS), 101.4 ($CH_2C{\equiv}CTMS$), 121.3, 123.4, 128.2, 131.0, 131.4, 150.0 and 166.0 (C=O).

8-Benzoyl-6-methylene-8-azabicyclo[3.2.1]octane 26

A mixture of **24** (300 mg, 1.00 mmol) and toluene-*p*-sulfonic acid monohydrate (38 mg, 0.2 mmol) in wet acetonitrile (10 cm^3) was heated under reflux for 1.5 h. After removal of the solvent, the residue was dissolved in dichloromethane (5 cm^3). The solution was washed with 5% aq. Na_2CO_3 and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (7:1)] to give **26** (211 mg, 93%) as a colourless oil (Found: M^+, 227.1299. $C_{15}H_{17}NO$ requires *M*, 227.1310); $\nu_{max}(CCl_4)/cm^{-1}$ 1625; δ_H(300 MHz) 1.50–2.10 (6 H, m), 2.41 (1 H, t, *J* 14.4), 2.63–2.77 (1 H, m), 4.14–4.33 (1 H, unresolved m, 1- or 5-H), 4.84–5.10 (3 H, m, 1- or 5-H and $C{=}CH_2$) and 7.38–7.49 (5 H, m, ArH); δ_C(for a mixture of two rotamers) 16.8 (CH_2), 29.6, 31.6 (CH_2), 32.1, 33.9 (CH_2), 35.2, 36.2 (CH_2), 52.2, 57.1 (CH), 57.9, 62.5 (CH), 105.2, 105.7 ($C{=}CH_2$), 126.9, 127.0, 128.05, 128.1, 128.3, 129.7, 136.2, 148.1, 148.9 ($C{=}CH_2$) and 167.5, 167.7 (C=O).

8-Benzoyl-8-azabicyclo[3.2.1]octan-6-one 27

4% Aq. osmium tetroxide (0.05 cm^3, 2.54 mg as OsO_4, 0.01 mmol) was added to a solution of **26** (100 mg, 0.44 mmol) in THF–H_2O (4:1) (10 cm^3) at 0 °C and the whole was stirred for 5 min. To this mixture was added sodium metaperiodate (188 mg, 0.88 mmol) over a period of 30 min and the mixture was stirred at room temperature for 16 h. The whole was diluted with water and extracted with chloroform. The extract was dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (4:1)] to give **27** (53 mg, 52%), mp 78–78.5 °C (from hexane–AcOEt) (Found: C, 73.5; H, 6.7; N, 6.1. $C_{14}H_{15}NO_2$ requires C, 73.3; H, 6.6; N, 6.1%); $\nu_{max}(CCl_4)/cm^{-1}$ 1760 and 1625; δ_H(300 MHz) 1.62–2.34 (6 H, m), 2.31 (1 H, d, *J* 18, one of 7-H), 2.74 (1 H, dd, *J* 18, 7.5, one of 7-H), 3.98–4.05, 4.53–4.70, 5.23–5.30 (total 2 H, unresolved m, 1- and 5-H) and 7.40–7.49 (5 H, m, ArH).

The same ketone **27** (40 mg, 53%) was also obtained by direct oxidation of **24** (100 mg, 0.33 mmol) with osmium tetroxide–sodium metaperiodate, although much longer time (72 h) was required for completion of the reaction.

8-Benzoyl-8-azabicyclo[3.2.1]octane 28

A solution of **27** (80 mg, 0.35 mmol) and toluene-*p*-sulfonylhydrazine (78 mg, 0.42 mmol) in ethanol (3 cm^3) was heated under reflux overnight. After cooling, the precipitated crystalline solid was collected. The thus obtained crude tosylhydrazone was dissolved in DMF–sulfolane (a 1:1 mixture, 3 cm^3). To this solution were added sodium cyanoborohydride (88 mg, 1.40 mmol) and toluene-*p*-sulfonic acid monohydrate (30 mg), and the whole was heated at 110 °C for 2 h. This procedure was repeated with further sodium cyanoborohydride and toluene-*p*-sulfonic acid monohydrate. The mixture was diluted with water (5 cm^3) and extracted with diethyl ether. The extract was washed with brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (7:1)] to give **28** (27 mg, 36%), mp 91–92 °C (from hexane) (lit.,[4,13] 94–95 °C), whose IR and ^1H and ^{13}C NMR spectra were identical to those of an authentic sample.

Methyl 1-(*o*-bromobenzoyl)azetidine-2-carboxylate 30

Following the procedure described for the preparation of **7**, **30** (1.1 g, 76%) was obtained from azetidine-2-carboxylic acid **29** (500 mg, 4.9 mmol) as an oil (Found: C, 48.0; H, 4.0; N, 4.7. $C_{12}H_{12}BrNO_3$ requires C, 48.3; H, 4.1; N, 4.7%); $\nu_{max}(CCl_4)$/cm^{-1} 1740 and 1635; δ_H(60 MHz) 1.95–3.1 (2 H, m), 3.52, 3.82 (total 3 H, both s, OMe), 3.6–4.4 (2 H, m), 4.6–5.1 (1 H, m, 2-H) and 6.9–7.7 (4 H, m, ArH).

Methyl 1-(*o*-bromobenzoyl)-2-(prop-2-enyl)azetidine-2-carboxylate 31

Following the procedure described for the preparation of **8a**, **31** (288 mg, 51%) was obtained from **29** (500 mg, 1.7 mmol) and prop-2-enyl bromide (284 mg, 2.35 mmol) as colourless prisms, mp 72.5–73.5 °C (from hexane–AcOEt) (Found: C, 53.4; H, 4.7; N, 4.45. $C_{15}H_{16}BrNO_3$ requires C, 53.3; H, 4.8; N, 4.1%); $\nu_{max}(CCl_4)$/cm^{-1} 1740 and 1655; δ_H(60 MHz) 2.15–2.6 (2 H, m, 3-H_2), 2.80 (1 H, dd, *J* 14, 8, one of CH_2CH=CH_2), 3.20 (1 H, dd, *J* 14, 6.5, one of CH_2CH=CH_2), 3.6–4.0 (2 H, m, 4-H_2), 3.84 (3 H, s, OMe), 5.05–5.5 (2 H, m, CH$_2$CH=CH_2), 5.6–6.4 (1 H, m, CH$_2$C*H*=CH$_2$), 7.1–7.45 (3 H, m, ArH) and 7.5–7.75 (1 H, m, ArH).

Radical cyclisation of compound 31

Following the general procedure, **31** (416 mg, 1.23 mmol) was treated twice with Bu_3SnH (412 mg, 1.42 mmol) and AIBN (20 mg, 0.13 mmol) in toluene and the crude material was chromatographed on silica gel [hexane–AcOEt (5:1)] to give *methyl 1-benzoyl-2-(prop-2-enyl)azetidine-2-carboxylate* **32** (202 mg, 63%) as an oil (Found: C, 69.3; H, 6.8; N, 5.2. $C_{15}H_{17}NO_3$ requires C, 69.5; H, 6.6; N, 5.4%); $\nu_{max}(CCl_4)$/cm^{-1} 1740 and 1635; δ_H(300 MHz) 2.26–2.43 (2 H, m, 3-H_2), 2.72 (1 H, dd, *J* 14.4, 8.1, one of CH_2CH=CH$_2$), 3.16 (1 H, dd, *J* 14.4, 6.6, one of CH_2CH=CH$_2$), 3.81 (3 H, s, OMe), 4.10–4.19 (1 H, m, one of 4-H), 4.21–4.29 (1 H, m, one of 4-H), 5.23–5.29 (2 H, m, CH$_2$CH=CH_2), 5.91–6.05 (1 H, m, CH$_2$C*H*=CH$_2$), 7.37–7.46 (3 H, m, ArH) and 7.62–7.64 (2 H, m, ArH); δ_C 24.0 (CH$_2$), 37.4 (CH$_2$), 49.8 (CH$_2$), 52.4 (OMe), 70.2 (2-C), 119.8 (CH$_2$CH=*C*H$_2$), 127.5, 128.2, 130.9, 132.3, 133.2, 169.1 (C=O) and 172.4 (C=O).

Radical cyclisation of compound 31 with Bu_3SnD

Following the general procedure, **31** (150 mg, 0.44 mmol) was treated twice with Bu_3SnD (150 mg, 0.51 mmol) and AIBN (7 mg, 0.04 mmol) in toluene, and the crude material was chromatographed on silica gel [hexane–AcOEt (5:1)] to give **32′** (73 mg, 63%) as an oil. The ^{2}H NMR spectrum (in $CHCl_3$) of **32′** showed two signals due to a deuterium atom at the 4-position at δ 4.25 (deuterium distribution 71%) and a deuterium atom incorporated onto the phenyl ring at δ 7.67 (29%).

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