Synthesis of bridged azabicyclic compounds using radical translocation reactions of 1-(*o*-bromobenzoyl)-2-(prop-2-enyl)pyrrolidines

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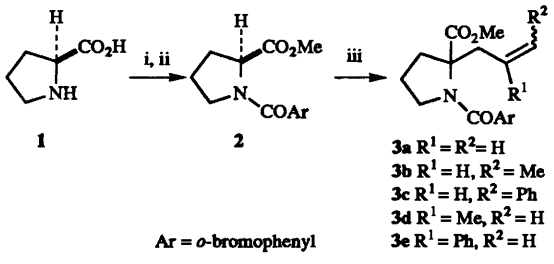
A new synthesis of the 7-azabicyclo[2.2.1]heptane and 8-azabicyclo[3.2.1]octane systems is described in which α-acylamino radicals generated from 1-(*o*-bromobenzoyl)-2-(prop-2-enyl)pyrrolidines by a Bu_3SnH-mediated radical translocation reaction are cyclised. Treatment of methyl 1-(*o*-bromobenzoyl)-2-(prop-2-enyl)pyrrolidine-2-carboxylate **3a** with Bu_3SnH in the presence of a catalytic amount of azoisobutyronitrile in boiling toluene gave the 7-azabicyclo[2.2.1]heptane **4a** (a 5-*exo* cyclisation product) [42% yield as a diastereoisomeric mixture (66:34)] and the 8-azabicyclo[3.2.1]octane **5a** (a 6-*endo* product) (30%), together with the reduction product **6a** (12%). The regiochemistry (5-*exo*/6-*endo*) of this cyclisation could be controlled by the introduction of a substituent on the prop-2-enyl group. The substituent(s) at the 2- and/or 4-position(s) of the pyrrolidine ring were found to play an important role in this cyclisation.

α-Acylamino radicals have been widely used for the construction of a variety of the nitrogen-containing heterocycles.[1,2] In general, the radicals can be generated either by the tin hydride method from functionalised acylamino derivatives[1] or by a radical translocation reaction of aryl radicals generated from *o*-halogenobenzamides[2] and related compounds.[3,4] We report here a new route to the 7-azabicyclo[2.2.1]heptane and 8-azabicyclo[3.2.1]octane systems by cyclisation of α-acylamino radicals[5] generated from 1-(*o*-bromobenzoyl)-2-(prop-2-enyl)pyrrolidines **3** by the latter method.[6]

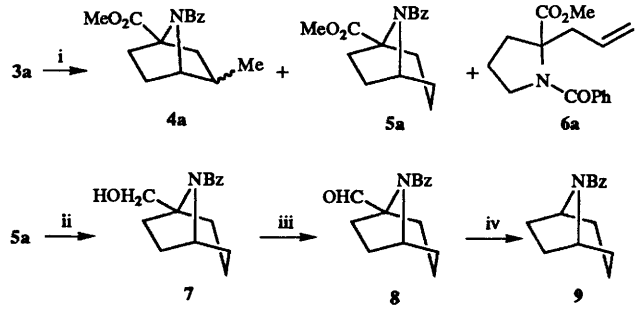
Results and discussion

The radical precursors **3a–e** were prepared by the alkylation of methyl 1-(*o*-bromobenzoyl)pyrrolidine-2-carboxylate **2** which, in turn, was prepared from L-proline **1** in two steps in quantitative yield.[7]



Scheme 1 *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 $R^2CH{=}CR^1CH_2X$

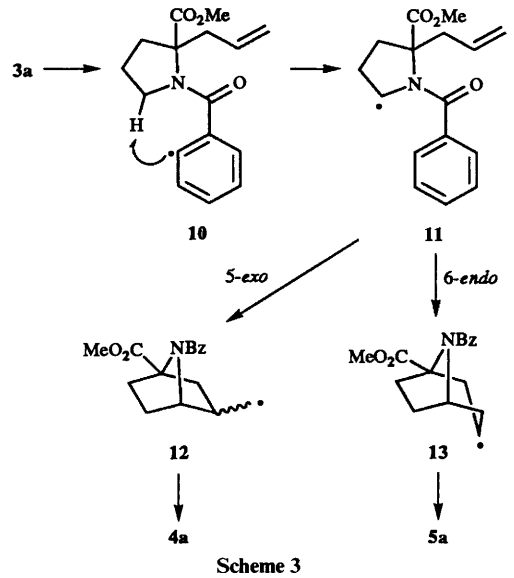
A toluene solution of tributyltin hydride (Bu_3SnH) (1.3 mol equiv.) and a catalytic amount of azoisobutyronitrile (AIBN) (0.1 mol equiv.) was added slowly to a boiling solution of **3a** in toluene over a period of 2 h, and the mixture was refluxed for 5 h. To complete the reaction, the same procedure was repeated. The crude material was chromatographed on silica gel to give 7-azabicyclo[2.2.1]heptane **4a** (a 5-*exo* cyclisation product) (42% yield) as a mixture of *exo* and *endo* isomers in a ratio of 66:34 (determined by GLC), from which only the major *exo* isomer was obtained as a pure compound, 8-azabicyclo-[3.2.1]octane **5a** (a 6-*endo* cyclisation product) (30%), and the reduction product **6a** (12%). The structures of **4a** and **5a** were deduced from the spectroscopic evidence [**4a**: ν_{max} 1740, 1650 cm^{-1}; $\delta_H(CDCl_3)$ 3.91 (d, *J* 4.8 Hz, 4-H) for the *exo* isomer and 4.05 (t, *J* 4.5 Hz, 4-H) for the *endo* isomer. **5a**: ν_{max} 1740, 1640 cm^{-1}; $\delta_H(CDCl_3)$ 4.33 (quintet, *J* 3.2 Hz, 5-H)].[8] The structure of **5a** was confirmed by chemical transformation of the compound to the known compound **9**.[9] Thus, reduction of **5a** with sodium boranuide in methanol–THF[10] followed by Swern oxidation of the resulting alcohol **7** gave the aldehyde **8** in 65% overall yield. Treatment of **8** with Wilkinson's catalyst in refluxing xylene[11] gave **9** in 91% yield.



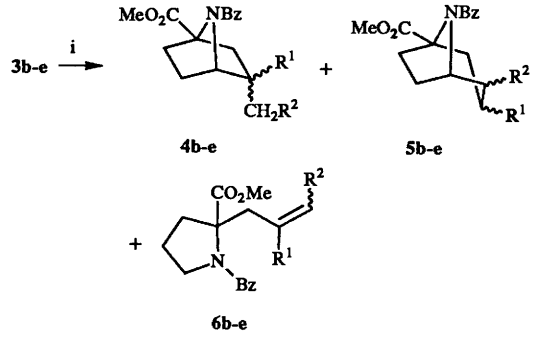
Scheme 2 *Reagents and conditions:* i, Bu_3SnH, AIBN, toluene, reflux; ii, $NaBH_4$, MeOH, THF; iii, $(COCl)_2$, DMSO, Et_3N; iv, $Rh(PPh_3)_3Cl$

A mechanistic rationalisation for the formation of **4a** and **5a** would involve a [1,5] hydrogen atom transfer of the initially formed phenyl radical **10** to form the α-acylamino radical **11**. This step is followed by either a 5-*exo-trig* or 6-*exo-trig* cyclisation, leading to the new radical intermediates **12** and **13** which are then reduced to **4a** and **5a**, respectively. Support for this mechanistic scheme was derived from a deuterium labelling experiment. Thus, treatment of **3a** with Bu_3SnD (in this experiment a higher concentration of the reagent was used in order to increase the yield of the reduction product) gave the corresponding deuteriated derivatives of **4a** (42% as a 2:1 diastereoisomeric mixture), **5a** (29%) and **6a** (24%). The ^2H NMR spectrum of the deuteriated **6a** showed that a deuterium atom was found only at the 5-position and not at all on the phenyl ring. This observation also indicates that the [1,5] hydrogen atom transfer is very fast.

We next examined the effect of a substituent on the prop-2-enyl group in the hope of directing the regiochemistry (5-*exo*/6-*endo*) of this cyclisation. The results are summarised in Table 1. The pyrrolidines **3b** and **3c**, when treated with Bu_3SnH and AIBN, gave the corresponding 7-azabicyclo[2.2.1]heptanes **4b, c** predominantly or exclusively. On the other hand, **3d** and **3e**



Scheme 3



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

Table 1 Product distributions on radical cyclisation of **3a–e**

Entry	Starting material	Products (%) 4[a]	5	6
1	**3a**	42 (66:34)[b]	30	12
2	**3b**	63 (68:32)[b]	29 (a single isomer)	8
3	**3c**	81 (72:28)[b]	trace	NI[c]
4	**3d**	0	75 (78:22)[b,d]	15
5	**3e**	0	72 (54:46)[d,e]	NI[c]

[a] The values in parentheses refer to the ratio of the *exo*:*endo* isomers. [b] Determined by GLC. [c] NI = not isolated. [d] The stereochemistry is not known. [e] Determined by HPLC.

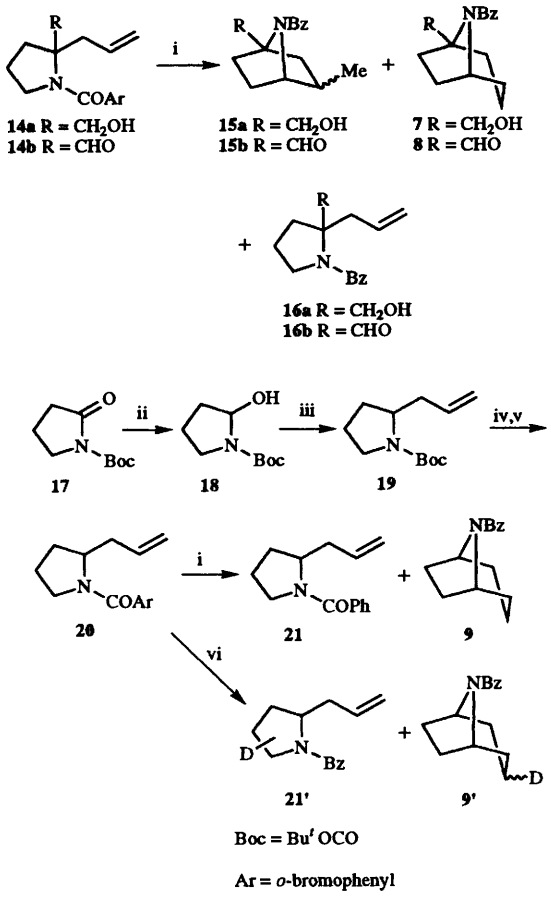
afforded only the 8-azabicyclo[3.2.1]octanes **5d, e**, respectively. The observed high regioselectivity could be explained in terms of the combined effects of (1) the electronic stabilisation of the developing radical by the methyl or phenyl group in the transition state leading to either the radical **12** or **13** and (2) the decreased rate of reaction for sterically hindered 6-*endo* (for **3b, c**) or 5-*exo* (for **3d, e**) cyclisation modes brought about by the methyl or phenyl group. Thus, the regiochemical course of the cyclisation could be controlled by placing an appropriate substituent on the alkenic double bond.

In order to see if the methoxycarbonyl group is essential for this cyclisation to take place, we prepared the 2-hydroxymethyl **14a**, 2-formyl **14b**, and 2-unsubstituted 1-(*o*-bromobenzoyl)-2-(prop-2-enyl)pyrrolidines **20** and treated them with Bu_3SnH. The precursors **14a, b** were prepared in a straightforward manner from **3a** (see Experimental section). The compound **20** was prepared as outlined in Scheme 5. Thus, reduction of 1-*tert*-butoxycarbonylpyrrolidin-2-one **17**[12] with lithium triethylboranuide[13] (1.5 mol equiv.) in THF at room temperature followed by treatment of the resulting 2-hydroxypyrrolidine **18** with allyltrimethylsilane (1.5 mol equiv.) in the presence of titanium(IV) chloride in dichloromethane[14] to give the 2-(prop-2-enyl)pyrrolidine **19** in 49% overall yield. Deprotection of **19** and acylation with *o*-bromobenzoyl chloride gave the desired compound **20** in 96% yield.

The alcohol **14a**, when treated with Bu_3SnH and AIBN, gave a mixture of the 7-azabicyclo[2.2.1]heptane **15a** (84%), the 8-azabicyclo[3.2.1]octane **7** (12%), and the reduction product **16a** (4%). The high combined yield (96%) of the cyclisation products as well as the high *exo*/*endo* selectivity (7:1) are somewhat surprising when compared to those of **3a** (70% and 1.3:1). The aldehyde **14b** also afforded a mixture of three products, **15b** (22%), **8** (20%), and **16b** (15%), but in much lower yields. The low yields of the products are attributed, at least in part, to the instability of the aldehyde **14b** under the reaction conditions.

In sharp contrast, the 2-unsubstituted substrate **20** gave the reduction product **21** as the major product (81%) and the 8-azabicyclo[3.2.1]octane **9** as the minor product (17%). It should be noted that the corresponding 5-*exo* product was not isolated. In order to get more information concerning the formation of **21**, the reaction was repeated with Bu_3SnD instead of Bu_3SnH to give the corresponding deuteriated compounds **21'** (62%) and **9'** (31%). The ^2H NMR spectrum of **21'** showed that the deuterium atom was incorporated into the 5-C, 2-C and 3-C/4-C positions[15] in a ratio of 42:22:36, but no deuterium was found on the phenyl ring. Taking into account the 31% conversion into the cyclised product **9'**, the yields of the radicals formed as a result of the hydrogen-abstraction by the phenyl radical from the 5-C, 2-C and 3-C/4-C positions were 57, 14 and 22%, respectively. These results indicate that, although the initially formed phenyl radical **10** (H instead of 2-CO_2Me) rapidly undergoes the [1,5] hydrogen abstraction mainly from the 5-C to form the radical **11** (H instead of 2-CO_2Me) (57%), the cyclisation of this radical to **9'** (31%) seems to be only slightly favoured over the reduction (26%). Considering an isotope effect would lower the rate of the reduction, the cyclisation process under the normal conditions may be much less favoured. Thus, it is apparent that the 2-substituent facilitates this cyclisation. One possible explanation for this would involve a higher population of the reactive conformer in the 2-substituted derivatives.[16] In order for the cyclisation to take place, the alkenic double bond and the radical centre must first be brought closer together. The radicals derived from the 2-substituted derivatives **3a** and **14a, b** can take the conformation required for the cyclisation more readily than the radical derived from the 2-unsubstituted derivative **20**. This is because the reactive conformer **A** derived from **3a** is almost energetically equivalent to the conformer **B** (although it depends on the sizes of the substituent at the 2-position), whereas the conformation of the reactive conformer **C** derived from **20** is less stable than that of **D** (Fig. 1). An alternative explanation is based on angle compression at the 2-position caused by the 2-substituent ('geminal dialkyl effect').[16] This effect may lead to a decrease of the angle θ_A ($\theta_A < \theta_B$), which causes the prop-2-enyl group to be moved closer to the radical centre. Probably both the factors are responsible for the increase in rate of cyclisation in the 2-substituted derivatives.

Further support for such an argument was obtained from a comparison of the behaviour between two isomeric 4-(*tert*-butyldimethylsilyloxy)pyrrolidines **24a, b**. Compounds **24a, b** were easily prepared starting from L-4-hydroxyproline methyl ester hydrochloride **22**[17] as illustrated in Scheme 6. Acylation of **22** with *o*-bromobenzoyl chloride followed by silylation of the



Scheme 5 *Reagents and conditions:* i, Bu_3SnH, AIBN, toluene, reflux; ii, $LiEt_3BH$, THF; iii, $CH_2{=}CHCH_2SiMe_3$, $TiCl_4$, CH_2Cl_2; iv, CF_3CO_2H, CH_2Cl_2; v, *o*-bromobenzoyl chloride, Et_3N, DMAP, CH_2Cl_2; vi, Bu_3SnD, AIBN, toluene, reflux

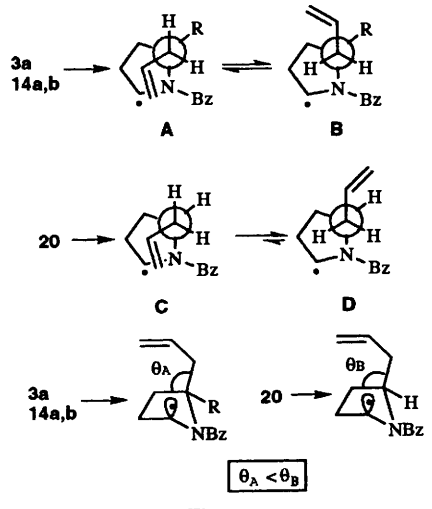
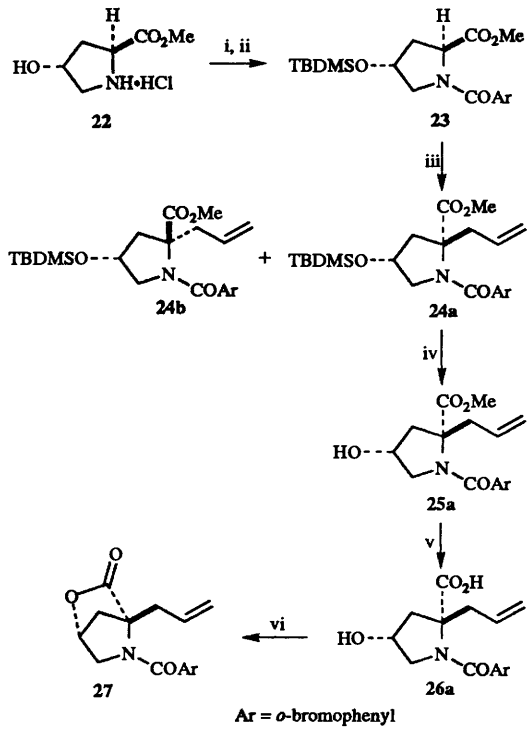


Fig. 1

hydroxy group with *tert*-butyldimethylsilyl chloride in the presence of imidazole in dimethylformamide gave the silyl ether **23** in 82% overall yield. Alkylation of **23** with prop-2-enyl bromide gave a diastereoisomeric mixture of the 2-(prop-2-enyl)pyrrolidine-2-carboxylates **24** in a ratio of 46 : 54 which was separated by silica gel chromatography to give the silyl ethers **24a** and **24b**. The stereochemistry of the silyl ethers **24a**, **b** was determined by conversion of one of the isomers into the lactone

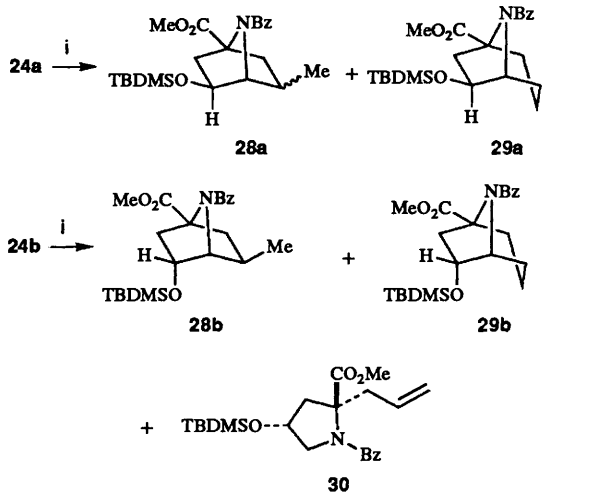


Scheme 6 *Reagents and conditions:* i, *o*-bromobenzoyl chloride, Et_3N, DMAP, CH_2Cl_2; ii, TBDMSCl, imidazole, DMF; iii, $(TMS)_2NLi$, THF, −78 °C, and then $CH_2{=}CHCH_2Br$; iv, $BF_3{-}OEt_2$, MeCN; v, Bu^tOK, DMSO; vi, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, reflux

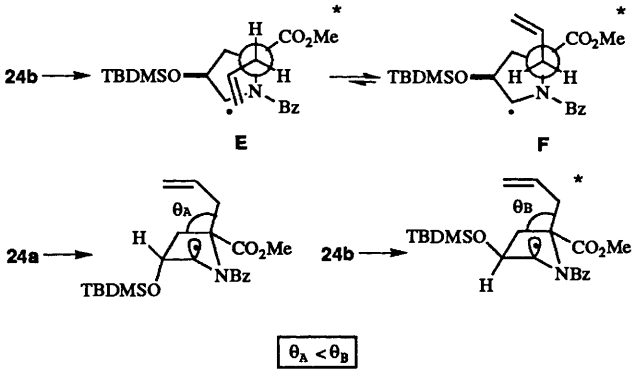
27. Thus, the silyl ether **24a** was deprotected with boron trifluoride followed by hydrolysis of the ester **25a** with potassium *tert*-butoxide in dimethyl sulfoxide at room temperature[18] to give the hydroxy carboxylic acid **26a**. Treatment of **26a** with 2,4,6-trichlorobenzoyl chloride in the presence of triethylamine and 4-dimethylaminopyridine (DMAP) in boiling toluene[19] gave the lactone **27** in 63% overall yield (from **24a**). A similar sequence of the reactions of the other isomer **24b** failed to give the lactone. This result indicates that the silyl ethers **24a**, **b** are assigned as (2*R*,4*R*) and (2*S*,4*R*), respectively.

Treatment of **24a** with Bu_3SnH and AIBN gave 7-azabicyclo[2.2.1]heptane **28a** in an 80% yield (as a 2 : 1 diastereoisomeric mixture) and 8-azabicyclo[3.2.1]octane **29a** (18%). No reduction product was detected. On the other hand, similar treatment of **24b** gave 7-azabicyclo[2.2.1]heptane **28b** in a 41% yield (as an essentially single stereoisomer), 8-azabicyclo[3.2.1]octane **29b** (5%) along with the reduction product **30** (32%). The increase of the total yield of the cyclised products and enhancement of the regioselectivity in the cyclisation of **24a** as compared to those of **3a** and **24b** could be attributed to the steric repulsion between the bulky *tert*-butyldimethylsilyloxy and methoxycarbonyl groups which causes the prop-2-enyl group to be brought closer to the radical centre (a decrease of θ_A) (Fig. 2). On the other hand, in the isomeric compound **24b** the steric repulsion occurs between the silyloxy and prop-2-enyl groups and this may result in not only destabilisation of the reactive conformer **E**, but also an increase of θ_B. Consequently, the rate of the cyclisation is expected to decrease.

In summary, we found that the 1-(*o*-bromobenzoyl)-2-(prop-2-enyl)pyrrolidines **3**, on treating with Bu_3SnH and AIBN in boiling toluene, gave the azabicyclic compounds **4** and/or **5**. Applications of this method of radical cyclisation to the synthesis of biologically active compounds are now in progress.



Scheme 7 *Reagents and conditions:* i, Bu_3SnH, AIBN, toluene, reflux



* For comparison, the enantiomeric structures are shown

Fig. 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. ^1H (60 or 300 MHz), ^2H (46 MHz) and ^{13}C NMR spectra (75.4 MHz) were measured on a JEOL-JNM-PMX 60 or on a Varian XL-300 spectrometer for solutions in $CDCl_3$, unless otherwise stated. δ Values quoted are relative to tetramethylsilane, and J values are given in Hz. Exact mass (MS) determinations were obtained on a Hitachi M-80 instrument operating at 20 eV. Column chromatography was performed under pressure on silica gel 60 PF_{254} for preparative TLC (Nacalai Tesque, Inc.). $[\alpha]_D$ values are expressed in units of 10^{-1} deg cm^2 g^{-1}.

Methyl 1-(*o*-bromobenzoyl)pyrrolidine-2-carboxylate 2

To a stirred solution of L-proline **1** (5.0 g, 43.4 mmol) in absolute methanol (60 cm^3) under a nitrogen atmosphere at 0 °C was added dropwise thionyl chloride (5.68 g, 47.7 mmol) and the mixture was refluxed for 1 h. The solvent was evaporated off and the residue dissolved in dichloromethane (60 cm^3) containing Et_3N (11.0 g, 108.5 mmol). A solution of *o*-bromobenzoyl chloride (10.0 g, 45.6 mmol) in dichloromethane (10 cm^3) was added to the above solution which was then stirred at room temperature overnight. After this, precipitated material was filtered off and the filtrate evaporated. 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 to give **2** (13.5 g, quant.) as colourless prisms, mp 76–78 °C (from hexane–AcOEt) (Found: C, 49.8; H, 4.3; N, 4.15. $C_{13}H_{14}BrNO_3$ requires C, 50.0; H, 4.5; N, 4.5%); $\nu_{max}(CCl_4)$/cm^{-1} 1745 and 1650; δ_H(60 MHz) (for the major rotamer) 1.7–2.5 (4 H, m), 3.0–3.9 (2 H, m), 3.74 (3 H, s, OMe), 4.64 (1 H, dd, J 7 and 5, 2-H) and 6.9–7.7 (4 H, m); (for the minor rotamer) 1.7–2.5 (4 H, m), 3.0–3.9 (2 H, m), 3.49 (3 H, s, OMe), 4.13 (1 H, dd, J 6.5 and 4, 2-H) and 6.9–7.7 (4 H, m).

General procedure for the preparation of methyl 1-(*o*-bromobenzoyl)-2-(prop-2-enyl)pyrrolidine-2-carboxylates 3a–e

To a solution of hexamethyldisilazane (284 mg, 1.76 mmol) in THF (5 cm^3) at −78 °C under a nitrogen atmosphere was added a 1.6 mol dm^{-3} solution of butyllithium in hexane (1.1 cm^3, 1.76 mmol) and the mixture was stirred for 30 min. To this mixture was added the ester **2** (1.6 mmol) in THF (5 cm^3) at −78 °C and the whole was stirred for 15 min. After appropriate prop-2-enyl bromide (for **3a–c**, **e**) or chloride (for **3d**) (2.24 mmol) had been added at −78 °C to the mixture it was stirred at room temperature for 5 h. After this 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)pyrrolidine-2-carboxylate 3a. Yield 93%, mp 77–79 °C (from hexane) (Found: C, 54.3; H, 5.1; N, 4.0. $C_{16}H_{18}BrNO_3$ requires C, 54.6; H, 5.15; N, 4.0%); $\nu_{max}(CCl_4)$/cm^{-1} 1740 and 1650; δ_H(60 MHz) 1.6–2.35 (4 H, m), 2.74 (1 H, dd, J 14 and 8), 3.1–3.55 (3 H, m), 3.77 (3 H, s, OMe), 5.0–5.4 (2 H, m), 5.55–6.3 (1 H, m) and 7.0–7.65 (4 H, m).

Methyl 1-(*o*-bromobenzoyl)-2-(but-2-enyl)pyrrolidine-2-carboxylate 3b. Yield 96%, an oil (Found: M$^+$, 365.0649. $C_{17}H_{20}BrNO_3$ requires M, 365.0626); $\nu_{max}(CCl_4)$/cm^{-1} 1740 and 1650; δ_H(60 MHz) 1.55–2.35 (7 H, m), 2.45–3.55 (4 H, m), 3.77 (3 H, s, OMe), 5.4–5.75 (2 H, m) and 7.0–7.65 (4 H, m).

Methyl 1-(*o*-bromobenzoyl)-2-(3-phenylprop-2-enyl)pyrrolidine-2-carboxylate 3c. Yield 89%, an oil (Found: C, 61.2; H, 5.5; N, 3.1. $C_{22}H_{22}BrNO_3$ requires C, 61.7; H, 5.2; N, 3.3%); $\nu_{max}(CCl_4)$/cm^{-1} 1740 and 1645; δ_H(60 MHz) 1.5–2.4 (4 H, m), 2.7–3.9 (4 H, m), 3.80 (3 H, s, OMe), 6.05–6.75 (2 H, m) and 6.95–7.65 (9 H, m).

Methyl 1-(*o*-bromobenzoyl)-2-(2-methylprop-2-enyl)pyrrolidine-2-carboxylate 3d. Yield 45%, an oil (Found: M$^+$, 365.0634. $C_{17}H_{20}BrNO_3$ requires M, 365.0626); $\nu_{max}(CCl_4)$/cm^{-1} 1740 and 1650; δ_H(60 MHz) 1.6–2.4 (4 H, m), 1.90 (3 H, s, CMe), 2.86, 3.29 (1 H each, ABq, J 14), 3.15–3.9 (2 H, m), 3.76 (3 H, s, OMe), 4.8–5.05 (2 H, m) and 6.9–7.7 (4 H, m).

Methyl 1-(*o*-bromobenzoyl)-2-(2-phenylprop-2-enyl)pyrrolidine-2-carboxylate 3e. Yield 47%, mp 85–86.5 °C (from hexane–AcOEt) (Found: C, 61.7; H, 5.2; N, 3.3. $C_{22}H_{22}BrNO_3$ requires C, 61.7; H, 5.2; N, 3.3%); $\nu_{max}(CCl_4)$/cm^{-1} 1740 and 1645; δ_H(300 MHz) 1.64–2.06 (3 H, m), 2.21–2.34 (1 H, m), 2.85–2.96 (1 H, m), 3.15 (1 H, d, J 14.2, one of $CH_2CPh{=}CH_2$), 3.21 (1 H, ddd, J 10.3, 7.4 and 5.1), 3.78 (3 H, s, OMe), 4.02 (1 H, d, J 14.2, one of $CH_2CPh{=}CH_2$), 5.29 (1 H, br s), 5.42 (1 H, d, J 1.8), 5.7–6.0 (1 H, br), 7.03–7.15 (2 H, m), 7.27–7.38 (3 H, m) and 7.43–7.50 (3 H, m).

Radical cyclisation of compound 3a

General procedure. To a stirred and boiling solution of **3a** (600 mg, 1.70 mmol) in toluene (50 cm^3) was added a solution of Bu_3SnH (643 mg, 2.21 mmol) and AIBN (28 mg, 0.17 mmol) in toluene (60 cm^3) *via* a syringe during 2 h, and the mixture was

heated under reflux for 2 h. This procedure was repeated. After removal of the solvent, diethyl ether (15 cm^3) and 8% aq. 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)]. The first fraction gave a mixture of *exo* and *endo* isomers (66:34 by GLC) of *methyl 7-benzoyl-3-methyl-7-azabicyclo*[2.2.1]*heptane-1-carboxylate* **4a** (196 mg, 42%), from which the major *exo*-isomer was obtained pure by recrystallisation from hexane, mp 88–92 °C (Found: C, 70.3; H, 7.1; N, 5.1. $C_{16}H_{19}NO_3$ requires C, 70.3; H, 7.0; N, 5.1%); $\nu_{max}(CCl_4)/cm^{-1}$ 1740 and 1650; δ_H(300 MHz) 1.06 (3 H, d, *J* 6.7, 3-Me), 1.54 (1 H, ddd, *J* 11.4, 8.2 and 4.2), 1.71–2.02 (4 H, m), 2.04 (1 H, dd, *J* 11.2 and 8.3), 2.34 (1 H, dt, *J* 11.4 and 4.0), 3.84 (3 H, s, OMe), 3.91 (1 H, d, *J* 4.8, 4-H), 7.37–7.52 (3 H, m, ArH) and 7.67–7.72 (2 H, m, ArH); δ_C 21.1 (3-Me), 30.3 (CH_2), 30.8 (CH_2), 38.1 (3-C), 41.7 (CH_2), 52.3 (OMe), 67.6 (C-4), 68.0 (C-1), 128.3, 128.7, 131.3, 134.8, 171.4 and 172.3. The second fraction gave *methyl 1-benzoyl-2-(prop-2-enyl)pyrrolidine-2-carboxylate* **6a** (54 mg, 12%) as an oil (Found: M^+, 273.1380. $C_{16}H_{19}BrNO_3$ requires *M*, 273.1363); $\nu_{max}(CCl_4)/cm^{-1}$ 1740 and 1635; δ_H(300 MHz) 1.77–2.11 (3 H, m), 2.13–2.25 (1 H, m), 2.71 (1 H, dd, *J* 14.2 and 7.9, one of $CH_2CH{=}CH_2$), 3.34 (1 H, dd, *J* 14.2 and 7.0, one of $CH_2CH{=}CH_2$), 3.42–3.62 (2 H, m), 3.78 (3 H, s, OMe), 5.15–5.20 (1 H, m, one of $CH_2CH{=}CH_2$), 5.20–5.24 (1 H, m, one of $CH_2CH{=}CH_2$), 5.77–5.93 (1 H, m, $CH_2CH{=}CH_2$), 7.35–7.45 (3 H, m) and 7.45–7.52 (2 H, m); δ_C 24.1, 35.15, 37.25, 51.85, 52.4, 68.0, 119.5, 127.0, 128.2, 128.3, 130.0, 133.1, 136.8, 169.2 and 174.15. The third fraction gave *methyl 8-benzoyl-8-azabicyclo*[3.2.1]*octane-1-carboxylate* **5a** (141 mg, 30%), mp 111–114 °C (from hexane–AcOEt) (Found: C, 70.3; H, 7.1; N, 5.1. $C_{16}H_{19}NO_3$ requires C, 70.3; H, 7.0; N, 5.1%); $\nu_{max}(CCl_4)/cm^{-1}$ 1740 and 1640; δ_H(300 MHz) 1.29–1.51 (2 H, m), 1.68–1.90 (3 H, m), 1.96 (1 H, ddd, *J* 13.8, 5.2 and 2.0), 2.04 (1 H, dd, *J* 9.5 and 7.8), 2.27–2.42 (3 H, m), 3.75 (3 H, s, OMe), 4.33 (1 H, quintet, *J* 3.2, 5-H), 7.36–7.48 (3 H, m, ArH) and 7.54–7.59 (2 H, m, ArH); δ_C 17.2 (CH_2), 27.7 (CH_2), 29.9 (CH_2), 32.2 (CH_2), 33.7 (CH_2), 52.3 (OMe), 59.7 (C-5), 65.0 (C-1), 127.7, 128.4, 130.5, 136.0, 170.0 and 172.6.

Radical cyclisation of compound 3a with Bu_3SnD

Following the general procedure, **3a** (500 mg, 1.42 mmol) was treated twice with Bu_3SnD (539 mg, 1.85 mmol) and AIBN (23 mg, 0.14 mmol) in toluene and the crude material was chromatographed on silica gel [hexane–AcOEt (20:1)] to give the deuteriated derivatives of **4a** (165 mg, 42%), **6a** (92 mg, 24%) and **5a** (113 mg, 29%) in that order. The ^2H NMR spectrum (in $CHCl_3$) of the deuteriated **6a** showed a signal due to a deuterium at the 5-position at δ 3.48 as a broad singlet.

8-Benzoyl-8-azabicyclo[3.2.1]octane-1-methanol 7

To a stirred solution of **5a** (100 mg, 0.37 mmol) in THF (10 cm^3) was added portionwise sodium boranuide (207 mg, 5.5 mmol). To the boiling mixture was added dropwise absolute methanol (5 cm^3) over 1 h and the whole was refluxed for 30 min and concentrated. After the residue had been dissolved in 1 mol dm^{-3} HCl (10 cm^3), the aqueous layer was extracted with dichloromethane. The extract was dried ($MgSO_4$) and concentrated to give **7** (90 mg, quant.), mp 127–128.5 °C (from hexane) (Found: C, 73.5; H, 7.9; N, 5.9. $C_{15}H_{19}NO_2$ requires C, 73.4; H, 7.8; N, 5.7%); $\nu_{max}(CCl_4)/cm^{-1}$ 3380 and 1615; δ_H(300 MHz) 1.35–1.44 (1 H, m), 1.45–1.69 (3 H, m), 1.72–2.09 (5 H, m), 2.26 (1 H, td, *J* 13.2 and 6.1), 3.66 (1 H, dd, *J* 12.7 and 10.9, one of OCH_2), 3.86 (1 H, dd, *J* 12.7 and 2.7, one of OCH_2), 4.12 (1 H, dt, *J* 7.1 and 2.7, 5-H), 5.77 (1 H, dd, *J* 10.9 and 2.7, OH) and 7.41 (5 H, s, ArH); δ_C 17.5 (CH_2), 25.9 (CH_2), 32.1 (CH_2), 32.6 (CH_2), 32.7 (CH_2), 61.2 (C-5), 66.35 (OCH_2), 68.3 (C-1), 126.4, 128.6, 129.7, 137.6 and 169.6.

8-Benzoyl-8-azabicyclo[3.2.1]octane-1-carbaldehyde 8

A solution of dimethyl sulfoxide (86 mg, 1.1 mmol) in dry dichloromethane (5 cm^3) was added to a solution of oxalyl chloride (70 mg, 0.55 mmol) in dry dichloromethane (5 cm^3) at −78 °C over a period of 10 min and the mixture was stirred for 15 min. After this, a solution of **7** (85 mg, 0.35 mmol) in dry dichloromethane (5 cm^3) at −78 °C was added to the mixture which was then stirred at the same temperature for 30 min. After addition of triethylamine (185 mg, 1.8 mmol) to the mixture it was allowed to warm to room temperature. After 2 h, the mixture was diluted with water (10 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 (10:1)] to give **8** (55 mg, 65%), mp 122–124 °C (from hexane–AcOEt) (Found: C, 74.0; H, 6.8; N, 5.55. $C_{15}H_{17}NO_2$ requires C, 74.0; H, 7.0; N, 5.75%); $\nu_{max}(CCl_4)/cm^{-1}$ 1730 and 1635; δ_H(300 MHz) 1.34–1.58 (2 H, m), 1.70–2.48 (8 H, m), 4.32 (1 H, dt, *J* 7.0 and 2.8, 5-H), 7.36–7.48 (3 H, m, ArH), 7.52–7.58 (2 H, m, ArH) and 9.60 (1 H, s, CHO); δ_C 16.85 (CH_2), 27.5 (CH_2), 28.0 (CH_2), 29.4 (CH_2), 32.4 (CH_2), 59.4, 69.2, 127.4, 128.5, 130.7, 135.2, 170.1 and 195.95.

8-Benzoyl-8-azabicyclo[3.2.1]octane 9

A solution of **8** (80 mg, 0.33 mmol) and Wilkinson's complex $Rh(PPh_3)_3Cl$ (305 mg, 0.33 mmol) in xylene (5 cm^3) was refluxed under a nitrogen atmosphere for 3 h. The mixture was concentrated and the residue was chromatographed on silica gel [hexane–AcOEt (7:1)] to give **9** (64 mg, 91%) as colourless plates, mp 94–95 °C (from hexane) (lit.,[9] 94–95 °C) (Found: C, 78.05; H, 7.75; N, 6.6. Calc. for $C_{14}H_{17}NO$: C, 78.1; H, 8.0; N, 6.5%); $\nu_{max}(CCl_4)/cm^{-1}$ 1625; δ_H(300 MHz) 1.46 (1 H, br d, *J ca.* 11), 1.53–1.87 (6 H, m), 1.87–2.10 (3 H, m), 4.00–4.08 (1 H, m), 4.79–4.87 (1 H, m), 7.35–7.45 (3 H, m) and 7.45–7.51 (2 H, m); δ_C 16.9, 27.05, 28.35, 30.9, 32.6, 52.1, 57.0, 127.0, 128.3, 129.65, 136.8 and 167.6.

Radical cyclisation of compound 3b

Following the general procedure, **3b** (700 mg, 1.91 mmol) was treated twice with Bu_3SnH (0.61 g, 2.1 mmol) and AIBN (31 mg, 0.19 mmol) in toluene and the crude material was chromatographed on silica gel [hexane–AcOEt (7:1)]. The first fraction gave a mixture of *exo* and *endo* isomers (68:32 by GLC) of *methyl 7-benzoyl-3-ethyl-7-azabicyclo*[2.2.1]*heptane-1-carboxylate* **4b** (345 mg, 63%) as an oil (Found: M^+, 287.1533. $C_{17}H_{21}NO_3$ requires *M*, 287.1520); $\nu_{max}(CCl_4)/cm^{-1}$ 1745 and 1655; δ_H(300 MHz) 0.80 (2/3 × 3 H, t, *J* 7.3, CH_2CH_3 for the *exo* isomer), 0.85 (1/3 × 3 H, t, *J* 7.3, CH_2CH_3 for the *endo* isomer), 1.23–1.50 (2 H, m, CH_2CH_3), 1.48–1.58 (1 H, m), 1.64–1.95 (4 H, m), 2.00 (2/3 H, dd, *J* 12.2 and 8.4), 2.29–2.41 (1 H, m), 2.59 (1/3 H, td, *J* 12.0 and 3.6), 3.80 (1/3 H, s, OMe for the *endo* isomer), 3.81 (2/3 H, s, OMe for the *exo* isomer), 4.03 (2/3 H, d, *J* 4.8, 4-H for the *exo* isomer), 4.11 (1/3 H, t, *J* 4.3, 4-H for the *endo* isomer), 7.34–7.53 (3 H, m) and 7.64–7.73 (2 H, m). The second fraction gave *methyl 1-benzoyl-2-(3-methylprop-2-enyl)pyrrolidine-2-carboxylate* **6b** (44 mg, 8%) as an oil (Found: M^+, 287.1534. $C_{17}H_{21}NO_3$ requires *M*, 287.1520); $\nu_{max}(CCl_4)/cm^{-1}$ 1740 and 1635; δ_H(60 MHz) 1.2–3.9 (11 H, m), 3.74 (3 H, s, OMe), 5.1–5.9 (2 H, m, $CH{=}CH$) and 7.37 (5 H, br s). The third fraction gave *methyl 8-benzoyl-4-methyl-8-azabicyclo*[3.2.1]*octane-1-carboxylate* **5b** (161 mg, 29%) as a single isomer (the stereochemistry is unknown), mp 94.5–96 °C (from hexane) (Found: C, 70.9; H, 7.5; N, 4.9. $C_{17}H_{21}NO_3$ requires C, 71.1; H, 7.4; N, 4.9%); $\nu_{max}(CCl_4)/cm^{-1}$ 1740 and 1640; δ_H(300 MHz) 0.66 (3 H, d, *J* 6.6, 4-Me), 1.23–1.43 (2 H,

m), 1.58–1.77 (2 H, m), 1.78–1.98 (3 H, m), 2.09–2.22 (1 H, m), 2.29–2.42 (1 H, m), 3.75 (3 H, s, OMe), 4.02 (1 H, dd, *J* 7.0 and 2.5, 5-H), 7.36–7.52 (3 H, m, ArH) and 7.52–7.59 (2 H, m, ArH); δ_C 17.95 (4-Me), 22.8 (CH_2), 26.0 (CH_2), 29.7 (CH_2), 33.6 (CH_2), 36.3 (C-4), 52.2 (OMe), 64.5 (C-1 and C-5), 127.7, 128.4, 130.5, 135.8, 170.0 and 172.6.

Radical cyclisation of compound 3c

Following the general procedure, **3c** (880 mg, 2.05 mmol) was treated twice with Bu_3SnH (0.66 g, 2.26 mmol) and AIBN (34 mg, 0.20 mmol) in toluene and the crude material was chromatographed on silica gel [hexane–AcOEt (9:2)] to give a mixture of *exo* and *endo* isomers (72:28 by GLC) of *methyl 7-benzoyl-3-benzyl-7-azabicyclo*[2.2.1]*heptane-1-carboxylate* **4c** (582 mg, 81%) as colourless rods, mp 117–119 °C (from hexane–AcOEt) (Found: C, 75.3; H, 6.8; N, 4.3. $C_{22}H_{23}NO_3$ requires C, 75.6; H, 6.6; N, 4.0%); $\nu_{max}(CCl_4)/cm^{-1}$ 1740 and 1650; δ_H(300 MHz) 1.48 (1 H, ddd, *J* 12.0, 8.8 and 4.1), 1.73–2.09 (4 H, m), 2.15 (1 H, ddt, *J* 9.3, 7.0 and 6.2), 2.35 (1 H, dt, *J* 12.0 and 2.9), 2.50 (1 H, dd, *J* 13.9 and 9.2), 2.57–2.70 (1 H, m), 3.83 (3 H, s, OMe), 4.04 (1 H, d, *J* 4.7, 4-H), 6.78–6.82 (2 H, m, ArH), 7.09–7.20 (3 H, m, ArH), 7.35–7.56 (3 H, m, ArH) and 7.72–7.77 (2 H, m, ArH); δ_C (for the major isomer) 30.3 (CH_2), 31.7 (CH_2), 39.4 (CH_2), 40.9 (CH_2), 45.75 (C-3), 52.4 (OMe), 64.7 (C-4), 67.9 (C-1), 126.1, 128.38, 128.41, 128.6, 128.9, 131.5, 134.6, 139.7, 171.2 and 172.0.

Radical cyclisation of compound 3d

Following the general procedure, **3d** (500 mg, 1.37 mmol) was treated twice with Bu_3SnH (438 mg, 1.50 mmol) and AIBN (34 mg, 0.20 mmol) in toluene and the crude material was chromatographed on silica gel [hexane–AcOEt (10:1)]. The first fraction gave a mixture of methyl 1-benzoyl-2-(2-methylprop-2-enyl)pyrrolidine-2-carboxylate **6d** and *methyl 8-benzoyl-3-methyl-8-azabicyclo*[3.2.1]*octane-1-carboxylate* **5d** (200 mg, 7:3 by GLC). The second fraction gave **5d** (153 mg, 39%) as a diastereoisomeric mixture (78:22 by GLC), mp 113–116 °C (from hexane–AcOEt) (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) 0.89–2.48 (9 H, m), 0.94 (3 H for the major isomer, d, *J* 5.7, 3-Me), 1.14 (3 H for the minor isomer, d, *J* 7.3, 3-Me), 3.75 (3 H, s, OMe), 4.29–4.35 (1 H, m, 5-H), 7.36–7.48 (3 H, m, ArH) and 7.53–7.59 (2 H, m, ArH); δ_C (for the major isomer) 21.4 (3-Me), 24.1 (3-C), 28.0 (CH_2), 34.0 (CH_2), 38.6 (CH_2), 41.0 (CH_2), 52.3 (OMe), 59.4 (5-C), 64.9 (1-C), 127.7, 128.4, 130.5, 135.9, 170.1 and 172.6.

Radical cyclisation of compound 3e

Following the general procedure, **3e** (480 mg, 1.12 mmol) was treated with Bu_3SnH (489 mg, 1.68 mmol) and AIBN (18 mg, 0.11 mmol) in toluene and the crude material was chromatographed on silica gel [hexane–AcOEt (3:1)] to give a diastereoisomeric mixture (54:46 by GLC) of *methyl 8-benzoyl-3-phenyl-8-azabicyclo*[3.2.1]*octane-1-carboxylate* **5e** (283 mg, 72%), mp 172–173 °C (from hexane–AcOEt) (Found: C, 75.9; H, 6.7; N, 4.0. $C_{22}H_{23}NO_3$ requires C, 75.6; H, 6.6; N, 4.0%); $\nu_{max}(CCl_4)/cm^{-1}$ 1730 and 1625; δ_H(300 MHz) 1.50–2.53 (7 H, m), 2.55 (1/2 × 1 H, t, *J* 13.0), 2.85 (1/2 × 1 H, dt, *J* 9.3 and 7.7), 3.15 (1/2 × 1 H, ddd, *J* 17.9, 12.3 and 5.7), 3.29 (1/2 × 1 H, dd, *J* 14.1 and 7.7), 3.77 (3 H, s, OMe), 4.37–4.48 (1 H, m, 5-H), 7.16–7.24 (2 H, m, ArH), 7.25–7.34 (3 H, m, ArH), 7.38–7.51 (3 H, m, ArH) and 7.59–7.65 (2 H, m, ArH).

1-(*o*-Bromobenzoyl)-2-(prop-2-enyl)pyrrolidine-2-methanol 14a

Following a procedure similar to that described for the preparation of **7** from **5a**, the ester **3a** (1.40 g, 3.97 mmol) was reduced with sodium boranuide (1.50 g, 39.8 mmol). The crude material was chromatographed on silica gel [hexane–AcOEt (4:1)] to give **14a** (978 mg, 76%) as an oil (Found: C, 55.3; H, 5.7; N, 4.2. $C_{15}H_{18}BrNO_2$ requires C, 55.6; H, 5.6; N, 4.3%); $\nu_{max}(CCl_4)/cm^{-1}$ 3370 and 1625; δ_H(60 MHz) 1.5–2.2 (4 H, m), 2.5–3.0 (2 H, m), 3.0–3.4 (2 H, m), 3.80 (2 H, d, *J* 5.5), 4.95–6.45 (4 H, m) and 7.0–7.7 (4 H, m).

1-(*o*-Bromobenzoyl)-2-(prop-2-enyl)pyrrolidine-2-carbaldehyde 14b

Following a procedure similar to that described for the preparation of **8** from **7**, Swern oxidation of the alcohol **14a** (595 mg, 1.84 mmol) with oxalyl chloride (419 mg, 3.30 mmol) and dimethyl sulfoxide (430 mg, 5.51 mmol) followed by chromatography of the crude product on silica gel [hexane–AcOEt (4:1)] gave **14b** (550 mg, 93%), mp 89–89.5 °C (from hexane–AcOEt) (Found: C, 55.7; H, 5.0; N, 4.3. $C_{15}H_{16}BrNO_2$ requires C, 55.9; H, 5.0; N, 4.35%); $\nu_{max}(CCl_4)/cm^{-1}$ 1730 and 1635; δ_H(60 MHz) 1.7–2.2 (4 H, m), 2.74 (1 H, dd, *J* 14 and 7.8), 3.14 (1 H, dd, *J* 14 and 7.3), 3.2–3.5 (2 H, m), 5.0–5.4 (2 H, m), 5.6–6.4 (1 H, m), 7.1–7.7 (4 H, m) and 9.70 (1 H, s, CHO).

Radical cyclisation of 14a

Following the general procedure, **14a** (500 mg, 1.54 mmol) was treated twice with Bu_3SnH (0.52 g, 1.78 mmol) and AIBN (25 mg, 0.16 mmol) in toluene and the crude product was chromatographed on silica gel [hexane–AcOEt (10:1)]. The first fraction gave a mixture of *exo* and *endo* isomers (61:39 by GLC) of *7-benzoyl-3-methyl-7-azabicyclo*[2.2.1]*heptane-1-methanol* **15a** (273 mg, 72%) as an oil (Found: C, 73.1; H, 8.0; N, 5.9. $C_{15}H_{19}NO_2$ requires C, 73.4; H, 7.8; N, 5.7%); $\nu_{max}(CCl_4)/cm^{-1}$ 3360 and 1610; δ_H(300 MHz) (for the *exo* isomer) 0.88 (3 H, d, *J* 6.9, 3-Me), 1.39–1.76 (3 H, m), 1.80–2.10 (3 H, m), 2.18–2.37 (1 H, m), 3.70 (1 H, d, *J* 4.6, 4-H), 3.94 (1 H, dd, *J* 13.1 and 7.9, one of OCH_2), 4.02 (1 H, dd, *J* 13.1 and 6.6, one of OCH_2), 5.65 (1 H, dd, *J* 7.9 and 6.6, OH) and 7.36–7.50 (5 H, m, ArH); (for the *endo* isomer) 1.00 (3 H, d, *J* 6.7, 3-Me), 1.39–1.76 (3 H, m), 1.80–2.10 (3 H, m), 2.18–2.37 (1 H, m), 3.87 (1 H, t, *J* 4.5, 4-H), 3.93 (2 H, d, *J* 7.2, OCH_2), 5.61 (1 H, t, *J* 7.2, OH) and 7.36–7.50 (5 H, m, ArH). The second fraction gave a mixture of **7** and 1-benzoyl-2-(prop-2-enyl)pyrrolidine-2-methanol **16a** (49 mg, 10:3 by GLC), from which only **7**, mp 127–128.5 °C, was isolated as a pure compound by recrystallisation from hexane.

Radical cyclisation of 14b

Following the general procedure, **14b** (500 mg, 1.55 mmol) was treated with Bu_3SnH (404 mg, 1.56 mmol) and AIBN (26 mg, 0.16 mmol) in toluene and the crude product was chromatographed on silica gel [hexane–AcOEt (15:1)]. The first fraction gave a diastereoisomeric mixture (57:43 by ^1H NMR) of *7-benzoyl-3-methyl-7-azabicyclo*[2.2.1]*heptane-1-carbaldehyde* **15b** (82 mg, 22%), mp 84–85 °C (from hexane–AcOEt) (Found: C, 74.1; H, 6.95; N, 5.7. $C_{15}H_{17}NO_2$ requires C, 74.05; H, 7.0; N, 5.8%); $\nu_{max}(CCl_4)/cm^{-1}$ 1725 and 1640; δ_H(300 MHz) (for the *exo* isomer) 1.06 (3 H, d, *J* 6.8, 3-Me), 1.25–2.26 (6 H, m), 2.29–2.41 (1 H, m), 3.95 (1 H, d, *J* 4.8, 4-H), 7.34–7.68 (5 H, m, ArH) and 10.05 (1 H, s, CHO); (for the *endo* isomer) 1.02 (3 H, d, *J* 6.8, 3-Me), 1.25–2.26 (6 H, m), 2.48 (1 H, td, *J* 11.6 and 3.4), 4.09 (1 H, t, *J* 4.5, 4-H), 7.34–7.68 (5 H, m, ArH) and 9.99 (1 H, s, CHO). The second fraction gave *1-benzoyl-2-(prop-2-enyl)pyrrolidine-2-carbaldehyde* **16b** (56 mg, 15%) as an oil (Found: C, 73.6; H, 7.4; N, 5.8. $C_{15}H_{17}NO_2$ requires C, 74.05; H, 7.0; N, 5.8%); $\nu_{max}(CCl_4)/cm^{-1}$ 1735 and 1630; δ_H(60 MHz) 1.7–2.2 (4 H, m), 2.68 (1 H, dd, *J* 14 and 7.5), 3.13 (1 H, dd, *J* 14 and 6.7), 3.4–3.7 (2 H, m), 4.95–5.4 (2 H, m), 5.6–6.3 (1 H, m), 7.44 (5 H, s) and 9.68 (1 H, s). The third fraction gave **8** (76 mg, 20%), mp 122–124 °C.

1-(*o*-Bromobenzoyl)-2-(prop-2-enyl)pyrrolidine 20

To a solution of 1-(*tert*-butoxycarbonyl)pyrrolidin-2-one **17**[12] (1.50 g, 8.10 mmol) in anhydrous THF (20 cm^3) at −78 °C under a nitrogen atmosphere was added a 1.0 mol dm^{-3} solution of $LiEt_3BH$ in THF (12.2 cm^3, 12.2 mmol) and the mixture was stirred at the same temperature for 40 min. The reaction was quenched by adding saturated aq. $NaHCO_3$. 30% H_2O_2 (5 drops) was then added to the reaction mixture at 0 °C and the whole was stirred for 20 min. After removal of the solvent by evaporation, the residue was dissolved in dichloromethane (30 cm^3), and the solution was dried ($MgSO_4$) and concentrated to give the crude 1-(*tert*-butoxycarbonyl)pyrrolidin-2-ol **18** (1.52 g, quant.) as an oil, which was used directly for the next step.

To a solution of **18** (1.52 g, 8.10 mmol) and allyltrimethylsilane (1.44 g, 12.6 mmol) in dichloromethane (25 cm^3) at −78 °C under a nitrogen atmosphere was added dropwise $TiCl_4$ (2.40 g, 12.6 mmol) and the mixture was stirred at the same temperature for 1 h. After water (10 cm^3) had been added to the mixture, the organic layer was separated, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (15:1)] to give 1-(*tert*-butoxycarbonyl)-2-(prop-2-enyl)pyrrolidine **19** (765 mg, 43%) as an oil; δ_H(60 MHz) 1.45 (9 H, s), 1.65–2.6 (6 H, m), 3.2–3.5 (2 H, m), 3.5–4.0 (1 H, m), 4.8–5.2 (2 H, m) and 5.4–6.05 (1 H, m).

Trifluoroacetic acid (35 cm^3) was added to a solution of **19** (765 mg, 3.62 mmol) in dichloromethane (3.5 cm^3) and the mixture was stirred at room temperature for 1 h. The solvent was evaporated off and the residue was dissolved in dichloromethane (20 cm^3). To this solution were added successively Et_3N (1.83 g, 18.1 mmol), DMAP (42 mg, 0.36 mmol) and *o*-bromobenzoyl chloride (1.19 g, 5.43 mmol) and the whole was stirred at room temperature for 1 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, saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (5:1)] to give **20** (1.02 g, 96%) as an oil (Found: C, 57.0; H, 5.5; N, 4.9. $C_{14}H_{16}BrNO$ requires C, 57.2; H, 5.5; N, 4.8%); $\nu_{max}(CCl_4)/cm^{-1}$ 1635; δ_H(60 MHz) 1.6–3.4 (7 H, m), 3.4–3.9 (1 H, m), 4.1–4.6 (1 H, m), 4.6–5.3 (2 H, m), 5.3–6.2 (1 H, m) and 7.0–7.7 (4 H, m).

Radical cyclisation of 20

Following the general procedure, **20** (600 mg, 2.04 mmol) was treated twice with Bu_3SnH (772 mg, 2.65 mmol) and AIBN (33 mg, 0.20 mmol) in toluene and the crude material was chromatographed on silica gel [hexane–AcOEt (10:1)]. The first fraction gave 1-*benzoyl*-2-(*prop*-2-*enyl*)*pyrrolidine* **21** (356 mg, 81%) as an oil (Found: M^+, 215.1288. $C_{14}H_{17}NO$ requires *M*, 215.1308); $\nu_{max}(CCl_4)/cm^{-1}$ 1630; δ_H(60 MHz) 1.5–2.9 (6 H, m), 3.3–3.7 (2 H, br), 4.05–4.6 (1 H, br), 4.8–5.4 (2 H, m), 5.4–6.25 (1 H, m) and 7.2–7.7 (5 H, m); δ_C 24.9, 29.4, 37.4, 50.35 (5-C), 56.5 (2-C), 117.4, 127.1, 128.1, 129.7, 134.5, 137.4 and 169.7. The second fraction gave **9** (74 mg, 17%), mp 94–95 °C.

Radical cyclisation of 20 with Bu_3SnD

Following the general procedure, **20** (400 mg, 1.36 mmol) was treated twice with Bu_3SnD (478 mg, 1.64 mmol) and AIBN (23 mg, 0.14 mmol) in toluene and the crude material was chromatographed on silica gel [hexane–AcOEt (10:1)]. The first fraction gave the deuteriated 1-*benzoyl*-2-(*prop*-2-*enyl*)-*pyrrolidine* **21′** (181 mg, 62%) as an oil. The ^2H NMR spectrum (in $CHCl_3$) showed three signals at δ 0.99 (deuterium distribution, 36%), 3.42 (42%) and 4.33 (22%) due to deuteriums at the 3- and/or 4-, 5- and 2-positions, respectively. The second fraction gave [3-$^2H_1$]-8-*benzoyl*-8-*azabicyclo*[3.2.1]*octane* **9′** (93 mg, 31%) as colourless crystals, whose ^2H NMR spectrum (in $CHCl_3$) showed signals at δ 1.63 (for the major isomer) and 1.78 (for the minor isomer).

Methyl (2*S*,4*R*)-1-(*o*-bromobenzoyl)-4-(*tert*-butyldimethylsilyloxy)pyrrolidine-2-carboxylate 23

Following a procedure similar to that for the preparation of **2**, methyl (2*S*,4*R*)-1-(2-bromobenzoyl)-4-hydroxypyrrolidine-2-carboxylate (3.56 g, 97%) was obtained from *trans*-4-hydroxy-L-proline methyl ester hydrochloride **22**[17] (2.04 g, 11.2 mmol) and *o*-bromobenzoyl chloride (2.71 g, 12.4 mmol) as an oil, which was used for the next step without further purification.

tert-Butyldimethylsilyl chloride (110 mg, 0.73 mmol) and imidazole (104 mg, 1.52 mmol) were added to a solution of the thus obtained amido ester (200 mg, 0.61 mmol) in DMF (2 cm^3) and the mixture was stirred at room temperature for 4 h. Dichloromethane (10 cm^3) and water (5 cm^3) were added to the reaction mixture and the organic layer was separated, washed with saturated aq. NH_4Cl (5 cm^3), dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (4:1)] to give **23** (220 mg, 82%), mp 93.5–94.5 °C (from hexane) (Found: C, 51.4; H, 6.4; N, 3.4. $C_{19}H_{28}BrNO_4Si$ requires C, 51.6; H, 6.4; N, 3.2%); $[\alpha]_D^{24}$ −65.4 (*c* 0.81, EtOH); $\nu_{max}(CCl_4)/cm^{-1}$ 1745 and 1650; δ_H(60 MHz) (as a mixture of two rotamers) 0.00, 0.05, 0.10 (total 6 H, s each), 0.85, 0.90 (total 9 H, both s), 2.0–2.4 (2 H, m), 3.0–3.3 (1 H, m), 3.4–3.7 (1 H, m), 3.46, 3.80 (total 3 H, both s, OMe), 4.2–4.9 (2 H, m) and 7.15–7.75 (4 H, m).

Methyl (2*R*,4*R*)- and (2*S*,4*R*)-1-(*o*-bromobenzoyl)-4-(*tert*-butyldimethylsilyloxy)-2-(prop-2-enyl)pyrrolidine-2-carboxylates 24a and 24b

Following a procedure similar to that for the preparation of **3a**, the ester **23** (1.00 g, 2.26 mmol) was treated with lithium hexamethyldisilazide [prepared from hexamethyldisilazane (474 mg, 2.94 mmol) and a 1.6 mol dm^{-3} solution of butyllithium in hexane (1.84 cm^3, 2.94 mmol)] and prop-2-enyl bromide (383 mg, 3.16 mmol). The crude material was chromatographed on silica gel [hexane–AcOEt (5:1)]. The first fraction gave **24a** (482 mg, 44%) as an oil (Found: C, 55.1; H, 6.8; N, 3.2. $C_{22}H_{32}BrNO_4Si$ requires C, 54.8; H, 6.7; N, 2.9%); $[\alpha]_D^{23}$ −48.9 (*c* 2.60, EtOH); $\nu_{max}(CCl_4)/cm^{-1}$ 1740 and 1650; δ_H (300 MHz) −0.04 (3 H, s), −0.01 (3 H, s), 0.82 (9 H, s), 2.14 (1 H, br dd, *J* 12.9 and 6.1, one of 3-H_2), 2.31 (1 H, dd, *J* 12.9 and 6.1, one of 3-H_2), 2.70 (1 H, dd, *J* 14.0 and 8.8, one of CH_2CH=CH_2), 3.10–3.27 (1 H, br, one of CH_2CH=CH_2), 3.41 (2 H, br dd, *J* 13.9 and 6.1, 5-H_2), 3.80 (3 H, s, OMe), 4.36 (1 H, quintet, *J* 6.1, 4-H), 5.17–5.27 (2 H, m, CH_2CH=CH_2), 5.83–6.02 (1 H, br, CH_2CH=CH_2), 7.20–7.31 (2 H, m, ArH), 7.36 (1 H, br t, *J ca.* 7.5, ArH) and 7.57 (1 H, br d, *J ca.* 7.5, ArH); δ_C −5.0, −4.95, 17.9, 25.6, 38.6, 44.2, 52.5, 57.15, 68.1, 68.7, 119.5, 127.7, 130.3, 132.85, 133.5, 139.1, 167.3 and 173.2. The second fraction gave **24b** (564 mg, 52%) as an oil (Found: C, 54.85; H, 6.95; N, 3.2. $C_{22}H_{32}BrNO_4Si$ requires C, 54.8; H, 6.7; N, 2.9%); $[\alpha]_D^{24}$ +24.4 (*c* 1.24, EtOH); $\nu_{max}(CCl_4)/cm^{-1}$ 1740 and 1645; δ_H(300 MHz) −0.01 (3 H, s), 0.03 (3 H, s), 0.85 (9 H, s), 2.12–2.28 (2 H, m), 2.86–2.97 (1 H, m), 3.03–3.18 (1 H, br), 3.23 (1 H, dd, *J* 14.3 and 7.2), 3.41–3.53 (1 H, m), 3.80 (3 H, s, OMe), 4.46 (1 H, quintet, *J* 7.2), 5.20–5.28 (2 H, m, CH_2CH=CH_2), 5.93–6.12 (1 H, m, CH_2CH=CH_2), 7.21–7.29 (2 H, m, ArH), 7.36 (1 H, td, *J* 7.4 and 1.2, ArH) and 7.56–7.60 (1 H, m, ArH).

Methyl (2*R*,4*R*)-1-(*o*-bromobenzoyl)-4-hydroxy-2-(prop-2-enyl)pyrrolidine-2-carboxylate 25a

To a solution of **24a** (206 mg, 0.43 mmol) in acetonitrile (5 cm^3) at 0 °C was added BF_3·OEt_2 (273 mg, 1.92 mmol) and the mixture was stirred at the same temperature for 30 min. The reaction mixture was made alkaline with saturated aq. $NaHCO_3$ (20 cm^3) and extracted with AcOEt. The extract

was dried ($MgSO_4$) and concentrated and the residue was chromatographed on silica gel [hexane–AcOEt (1:1)] to give **25a** (150 mg, 95%), mp 97–98 °C (from hexane–AcOEt) (Found: C, 52.1; H, 4.7; N, 4.1. $C_{16}H_{18}BrNO_4$ requires C, 52.2; H, 4.9; N, 3.8%); $[\alpha]_D^{25}$ −68.6 (*c* 0.21, EtOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 3430, 1740, 1705 and 1630; δ_H(60 MHz) 2.1–2.4 (2 H, m), 2.68 (1 H, dd, *J* 14 and 8), 3.1–3.55 (3 H, m), 3.86 (3 H, s), 4.1–4.4 (2 H, m), 5.0–5.4 (2 H, m), 5.55–6.3 (1 H, m) and 7.0–7.7 (4 H, m).

(1*R*,4*R*)-5-(*o*-Bromobenzoyl)-4-(prop-2-enyl)-2-oxa-5-azabicyclo[2.2.1]heptan-3-one 27

To a solution of **25a** (86 mg, 0.23 mmol) in dimethyl sulfoxide (1 cm^3) was added Bu^{t}OK (39 mg, 0.35 mmol) and the mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with water (10 cm^3), acidified with conc. HCl, and extracted with dichloromethane. The extract was dried ($MgSO_4$) and concentrated to give the carboxylic acid **26a** (82 mg, quant.). To a solution of **26a** (82 mg, 0.23 mmol) in toluene (3 cm^3) were added successively Et_3N (116 mg, 1.15 mmol), DMAP (3 mg, 0.02 mmol) and a solution of 2,4,6-trichlorobenzoyl chloride (280 mg, 1.15 mmol) in toluene (5 cm^3), and the whole was refluxed for 5 h. The reaction mixture was diluted with water (5 cm^3) and the organic layer was separated. The aqueous layer was extracted with toluene and the combined extracts were 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 (2:1)] to give **27** (49 mg, 63% from **25a**), mp 163–164 °C (from hexane–AcOEt) (Found: C, 53.7; H, 4.1; N, 4.1. $C_{15}H_{14}BrNO_3$ requires C, 53.4; H, 4.2; N, 4.2%); $[\alpha]_D^{24}$ −164.3 (*c* 0.23, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1795 and 1660; δ_H(300 MHz) 2.16, 2.20 (1 H each, ABq, *J* 11.3, 7-H_2), 2.99 (1 H, br dd, *J* 13.5 and 7.5), 3.24 (1 H, br d, *J* 10), 3.54 (1 H, br d, *J* 10), 3.61–3.74 (1 H, br), 4.90–6.05 (4 H, m), 7.24–7.33 (2 H, m), 7.38 (1 H, br t, *J* 7.2) and 7.58 (1 H, d, *J* 7.8); δ_C 31.5 (CH_2), 42.8 (CH_2), 54.3 (CH_2), 69.0, 74.9, 119.5, 127.9, 128.0, 131.0, 132.4, 133.1, 138.3, 169.0 and 170.75.

Radical cyclisation of compound 24a

Following the general procedure, **24a** (500 mg, 1.04 mmol) was treated twice with Bu_3SnH (390 mg, 1.35 mmol) and AIBN (17 mg, 0.10 mmol) in toluene and the crude material was chromatographed on silica gel [hexane–AcOEt (10:1)]. The first fraction gave a mixture of *exo* and *endo* isomers (77:23 by GLC) of *methyl* (1R,3R,4S)-7-*benzoyl*-3-(tert-*butyldimethylsilyloxy*)-5-*methyl*-7-*azabicyclo*[2.2.1]*heptane*-1-*carboxylate* **28a** (333 mg, 79%), mp 135–136 °C (from hexane–AcOEt) (Found: C, 64.95; H, 7.9; N, 3.8. $C_{22}H_{33}NO_4Si$ requires C, 65.5; H, 8.2; N, 3.5%); $\nu_{max}(CCl_4)/cm^{-1}$ 1740 and 1650; δ_H(300 MHz) (for the *exo* isomer) −0.14 (3 H, s), −0.03 (3 H, s), 0.75 (9 H, s), 1.19 (3 H, d, *J* 6.5, 5-Me), 1.68–1.92 (2 H, m), 1.71 (1 H, dt, *J* 10.6 and 3.3), 2.10 (1 H, dd, *J* 12.9 and 6.6), 2.21 (1 H, dt, *J* 12.9 and 2.5), 3.76 (1 H, s, 4-H), 3.82 (3 H, s, OMe), 3.97 (1 H, dd, *J* 6.5 and 2.3, 3-H), 7.32–7.48 (3 H, m, ArH) and 7.71–7.77 (2 H, m, ArH); (for the *endo* isomer) −0.15 (3 H, s), −0.03 (3 H, s), 0.74 (9 H, s), 1.03 (3 H, d, *J* 6.8, 5-Me), 1.13 (1 H, dd, *J* 10.7 and 3.9), 1.68–1.92 (1 H, m), 2.13 (1 H, dd, *J* 12.9 and 6.7), 2.27 (1 H, dt, *J* 12.9 and 2.5), 2.41–2.57 (1 H, m), 3.81 (3 H, s, OMe), 3.94–3.99 (1 H, m, 4-H), 4.31 (1 H, dd, *J* 6.7 and 2.2, 3-H), 7.32–7.48 (3 H, m, ArH) and 7.71–7.77 (2 H, m, ArH); δ_C (for the *exo* isomer) −4.7, 18.0, 20.55, 25.7, 32.4, 41.4, 43.25, 52.4, 67.5, 74.8, 75.1, 128.0, 129.15, 131.0, 145.05, 170.8 and 172.6. The second fraction gave *methyl* (1R,5S,6S)-8-*benzoyl*-6-(tert-*butyldimethylsilyloxy*)-8-*azabicyclo*[3.2.1]*octane*-1-*carboxylate* **29a** (86 mg, 21%) as an oil (Found: C, 65.6; H, 8.4; N, 3.3. $C_{22}H_{33}NO_4Si$ requires C, 65.5; H, 8.2; N, 3.5%); $[\alpha]_D^{23}$ +2.1 (*c* 0.28, EtOH); $\nu_{max}(CCl_4)/cm^{-1}$ 1740 and 1640; δ_H(300 MHz) 0.06 (3 H, s), 0.09 (3 H, s), 0.94 (9 H, s), 1.20–1.94 (4 H, m), 1.38 (1 H, dd, *J* 5.5 and 1.0), 2.21–2.37 (2 H, m), 2.38 (1 H, dd, *J* 13.8 and 6.6), 3.78 (3 H, s, OMe), 4.10 (1 H, br t, *J* 3.0), 4.25 (1 H, dd, *J* 6.6 and 2.7), 7.35–7.48 (3 H, m, ArH) and 7.65–7.70 (2 H, m, ArH); δ_C −4.8, −4.7, 17.75, 18.0, 25.7, 29.2, 45.8, 52.4, 65.7, 68.45, 74.15, 128.3, 128.4, 130.6, 135.4, 169.9 and 172.1.

Radical cyclisation of compound 24b

Following the general procedure, **24b** (307 mg, 0.64 mmol) was treated twice with Bu_3SnH (242 mg, 0.83 mmol) and AIBN (11 mg, 0.06 mmol) in toluene and the crude material was chromatographed on silica gel [hexane–AcOEt (10:1)]. The first fraction gave *methyl* (1S,3R,4R,5R)-7-*benzoyl*-3-(tert-*butyldimethylsilyloxy*)-5-*methyl*-7-*azabicyclo*[2.2.1]*heptane*-1-*carboxylate* **28b** (105 mg, 41%) as an essentially single isomer, mp 82–83 °C (from hexane–AcOEt) (Found: C, 65.5; H, 8.3; N, 3.7. $C_{22}H_{33}NO_4Si$ requires C, 65.5; H, 8.2; N, 3.5%); $[\alpha]_D^{24}$ −11.2 (*c* 0.28, EtOH); $\nu_{max}(CCl_4)/cm^{-1}$ 1740 and 1650; δ_H(300 MHz) −0.02 (3 H, s), 0.01 (3 H, s), 0.84 (9 H, s), 1.05 (3 H, d, *J* 7.1, 5-Me), 1.40 (1 H, dd, *J* 12.5 and 3.5), 1.83 (1 H, ddd, *J* 12.0, 4.7 and 3.2), 2.09 (1 H, dd, *J* 12.0 and 8.6), 2.63–2.78 (2 H, m), 3.74 (1 H, d, *J* 4.7, 4-H), 3.79 (3 H, s, OMe), 4.26 (1 H, ddd, *J* 9.9, 4.7 and 3.5, 3-H), 7.38–7.52 (3 H, m, ArH) and 7.62–7.69 (2 H, m, ArH) [the spectrum also exhibited a small doublet at δ 0.97 (*J* 7.0) due to the 5-methyl group of the (5*S*)-isomer of **28b**]; δ_C −5.0, −4.8, 17.9, 20.4, 25.7, 28.7, 40.9, 41.5, 52.35, 68.7, 70.5, 71.4, 128.4, 128.6, 131.4, 134.5, 171.0 and 172.2. The second fraction gave methyl (2S,4R)-1-*benzoyl*-4-(tert-*butyldimethylsilyloxy*)-2-(*prop*-2-*enyl*)*pyrrolidine*-2-*carboxylate* **30** (81 mg, 32%) as an oil (Found: M^+, 403.2151. $C_{22}H_{33}NO_3Si$ requires *M*, 403.2178); $\nu_{max}(CCl_4)/cm^{-1}$ 1735 and 1635; δ_H(60 MHz) 0.00, 0.10 (total 6 H, both s), 0.86 (9 H, s), 2.05–2.3 (2 H, m), 2.73 (1 H, dd, *J* 14 and 6.5), 3.0–3.9 (3 H, m), 3.77 (3 H, s, OMe), 4.50 (1 H, quintet, *J* 7), 5.0–5.4 (2 H, m), 5.5–6.3 (1 H, m) and 7.2–7.6 (5 H, m). The third fraction gave *methyl* (1S,5R,6R)-8-*benzoyl*-6-(tert-*butyldimethylsilyloxy*)-8-*azabicyclo*[3.2.1]*octane*-1-*carboxylate* **29b** (14 mg, 5%) as an oil (Found: M^+, 403.2195. $C_{22}H_{33}NO_3Si$ requires *M*, 403.2178); $\nu_{max}(CCl_4)/cm^{-1}$ 1740 and 1640; δ_H(300 MHz) (as a mixture of two rotamers) 0.04, 0.09 (total 6 H, both s), 0.84 (9 H, s, for the minor rotamer), 0.88 (9 H, s, for the major rotamer), 1.20–2.75 (8 H, m), 1.78 (1 H, dd, *J* 13.0 and 4.4, for the major rotamer), 2.70 (1 H, ddd, *J* 13.0, 10.5 and 1.0, for the major rotamer), 3.70 (3 H, s, OMe for the minor rotamer), 3.75 (3 H, s, OMe for the major rotamer), 4.06–4.11 (1 H, m, 5-H), 4.74 (1 H, ddd, *J* 10.5, 6.3 and 4.4, 6-H), 7.37–7.55 (5 H for the major rotamer and 3 H for the minor rotamer, m, ArH) and 7.72–7.78 (2 H, for the minor rotamer, m, ArH); δ_C −5.1, −4.7, 17.5, 17.9, 25.7, 26.7, 29.4, 43.25, 52.3, 62.5, 64.8, 70.3, 127.6, 128.5, 130.5, 135.7, 170.3 and 172.6.

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