Regioselective synthesis of bridged azabicyclic compounds using radical translocations/cyclisations of methyl 2-alkynyl-1-(*o*-iodobenzoyl)pyrrolidine-2-carboxylates: a formal total synthesis of (±)-epibatidine

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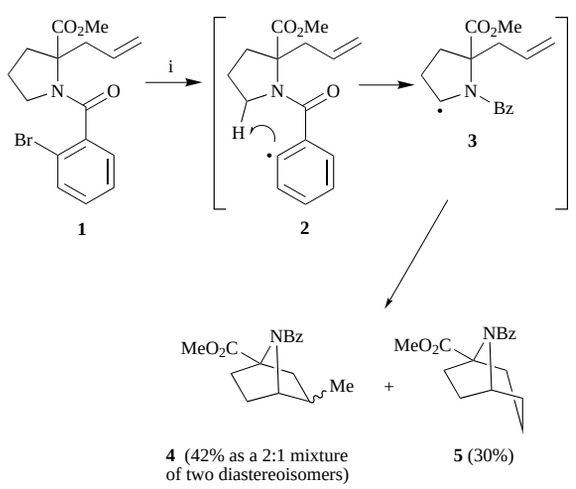
Bu_3SnH-mediated radical translocations/cyclisations of methyl 2-alkynyl-1-(*o*-iodobenzoyl)pyrrolidine-2-carboxylates have been examined. The 2-[3-(trimethylsilyl)prop-2-ynyl]-8,2-[4-(trimethylsilyl)but-3-ynyl]- 14, and 2-[5-(trimethylsilyl)pent-4-ynyl]-pyrrolidine derivatives 18, upon treatment with tributyltin hydride in the presence of azoisobutyronitrile in boiling toluene gave, regioselectively, the 7-azabicyclo-[2.2.1]heptane 19, 8-azabicyclo[3.2.1]octane 23, and 9-azabicyclo[4.2.1]nonane 26, respectively. The method has been applied to a formal total synthesis of (±)-epibatidine.

Introduction

Earlier we showed that methyl 1-(*o*-bromobenzoyl)-2-(prop-2-enyl)pyrrolidine-2-carboxylate **1**, upon treatment with tributyltin hydride (Bu_3SnH) in the presence of azoisobutyronitrile (AIBN), gave a mixture of the 7-azabicyclo[2.2.1]heptane **4** (42% as a 2:1 diastereoisomeric mixture) and 8-azabicyclo-[3.2.1]octane **5** (30%).[1] A mechanistic rationalisation for the formation of **4** and **5** would involve a 1,5-hydrogen transfer[2] of the initially formed aryl radical **2** to form the α-acylamino radical **3**, followed by either a 5-*exo*-*trig* or 6-*endo*-*trig* cyclisation of this to give **4** and **5**, respectively. The main disadvantage of

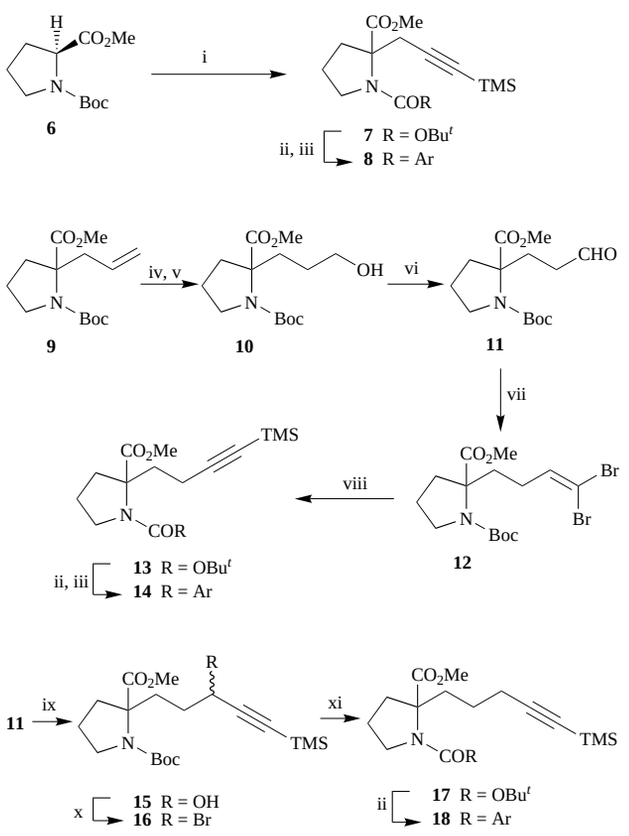


Scheme 1 *Reagents*: i, Bu_3SnH, AIBN, toluene, reflux

this reaction is the lack of regioselectivity. In an effort to circumvent this problem we have now examined the behaviour of the 2-alkynylpyrrolidine-2-carboxylates **8**, **14** and **18**, and found that they undergo *exo*-selective cyclisation to give the 7-azabicyclo[2.2.1]heptane **19**,[3] 8-azabicyclo[3.2.1]octane **23**[4] and 9-azabicyclo[4.2.1]nonane **26**,[5] respectively. In this paper we also describe a formal total synthesis of (±)-epibatidine **33**.

Results and discussion

The radical precursor, 2-[3-(trimethylsilyl)prop-2-ynyl]pyrrolidine-2-carboxylate **8** was readily obtained by direct alkylation of methyl 1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylate **6**[6] with 3-iodo-1-(trimethylsilyl)prop-1-yne[7] followed by deprotection and *N*-acylation of the resulting compound **7** with *o*-iodobenzoyl chloride. The 2-[4-(trimethylsilyl)but-3-ynyl]pyrrolidine-2-carboxylate **14** was prepared from methyl 1-(*tert*-butoxycarbonyl)-2-(prop-2-enyl)pyrrolidine-2-carboxylate **9**[6] as shown in Scheme 2. Thus, hydroboration of **9** with 3-methyl-



Ar = *o*-iodophenyl

Scheme 2 *Reagents and conditions*: i, $(TMS)_2NLi$, THF, −78 °C and then $TMSC{\equiv}CCH_2I$, 62%; ii, TMSI; iii, *o*-Iodobenzoyl chloride, Et_2NPh, DMAP, 77% for **8**, **14** and **18**; iv, Sia_2BH; v, H_2O_2, NaOH, 91%; vi, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 95%; vii, PPh_3, $CHBr_3$, *tert*-BuOK, toluene, 76%; viii; BuLi, THF, −78 °C, and then TMSCl, 86%; ix, $TMSC{\equiv}CH$, EtMgBr, 93%; x, PPh_3, CBr_4, CH_2Cl_2, 88%; xi, Bu_3SnH, AIBN, toluene, reflux, 94%

butan-2-ylborane and subsequent Swern oxidation of the resulting alcohol **10** gave the aldehyde **11**, which was allowed to react with bromoform and triphenylphosphine in the presence of potassium *tert*-butoxide to give the dibromide **12**. Treatment of **12** with butyllithium[8] and quenching with trimethylsilyl chloride gave the 2-[4-(trimethylsilyl)but-3-ynyl]pyrrolidine **13**. Replacement of the *N*-*tert*-butoxycarbonyl group of **13** by an *o*-iodobenzoyl group gave the radical precursor **14**. The 2-[5-(trimethylsilyl)pent-4-ynyl]pyrrolidine-2-carboxylate **18** was prepared from the aldehyde **11**. Grignard reaction of **11** with trimethylsilylethynylmagnesium bromide gave the ethynic alcohol **15**. Treatment of **15** with carbon tetrabromide and triphenylphosphine followed by reduction of the resulting bromide **16** with Bu_3SnH in the presence of a small amount of AIBN gave the 2-[5-(trimethylsilyl)pent-4-ynyl]pyrrolidine **17**, which was converted into **18**.

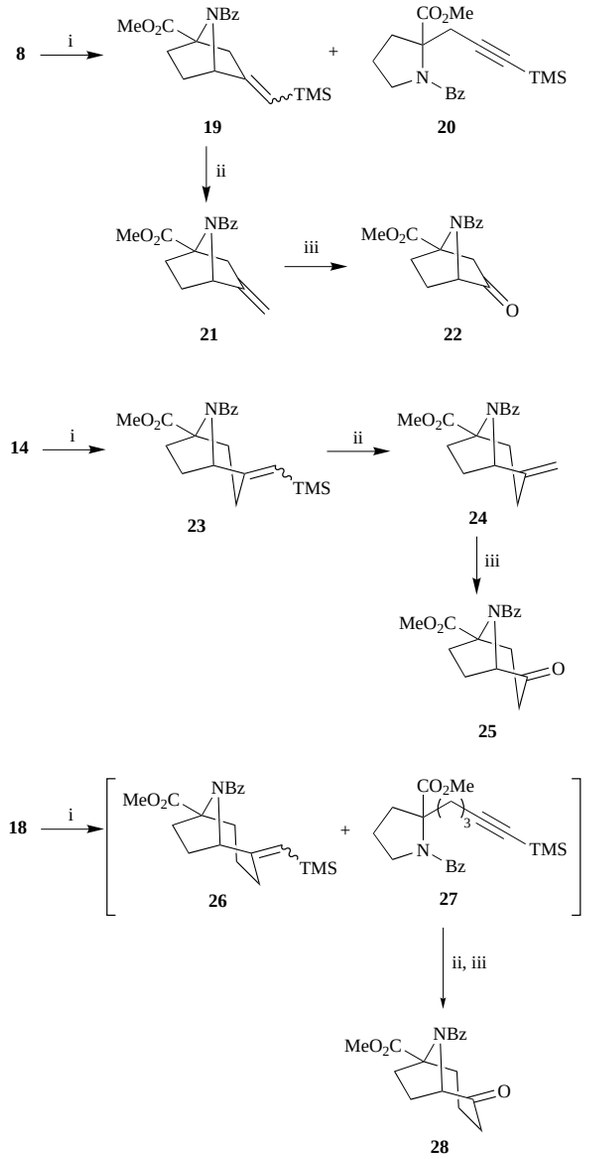
A toluene solution of Bu_3SnH (1.25 mol equiv.) and a small amount of AIBN (0.1 mol equiv.) was added slowly to a boiling solution of **8** in toluene over a period of 2 h, and the mixture was refluxed for 2 h. The crude material was chromatographed on silica gel to give the 7-azabicyclo[2.2.1]heptane **19** (a 5-*exo* cyclisation product) in a 78% combined yield as a diastereoisomeric mixture along with the reduction product **20** (18%). The structure of compound **19** was confirmed by the following chemical transformation. Treatment of **19** with toluene-*p*-sulfonic acid in acetonitrile gave the methylene derivative **21** (69%) which was then oxidised with OsO_4 and $NaIO_4$ to afford the ketone **22** (55%). The ketone **22** showed strong carbonyl absorptions at 1760 (a five-membered ketone) and 1750 cm^{-1} (an ester) in addition to an absorption due to an *N*-benzoyl group at 1660 cm^{-1} in the IR spectrum. The ^1H NMR spectrum revealed a doublet due to a bridgehead proton (4-H) at δ 4.36 (J 5.1) and the ^{13}C NMR spectrum was in good agreement with the assigned structure.

Cyclisation of compound **14** proceeded more smoothly to give exclusively the 8-azabicyclo[3.2.1]octane **23** (a 6-*exo* cyclisation product) in a 83% combined yield as a diastereoisomeric mixture: no reduction product was detected. Compound **23** was again converted into the ketone **25** *via* the methylene derivative **24**. The ^1H NMR spectrum of **25** showed a doublet due to a bridgehead proton (5-H) at δ 4.42 (J 7.0).

Compound **18** upon treatment with Bu_3SnH–AIBN, gave an inseparable mixture of the 9-azabicyclo[4.2.1]nonane **26** (as a diastereoisomeric mixture) and the reduction product **27** in 86% total yield and in a ratio of 48 : 52 (the ratio was determined by HPLC). The yield of **26** was estimated to be approximately 40%. The mixture was treated with toluene-*p*-sulfonic acid followed by oxidation with OsO_4 and $NaIO_4$ to give the ketone **28** in 17% overall yield. The signal of the bridgehead proton (6-H) of **28** in the ^1H NMR spectrum appeared as a doublet at δ 4.48 (J 9.2).

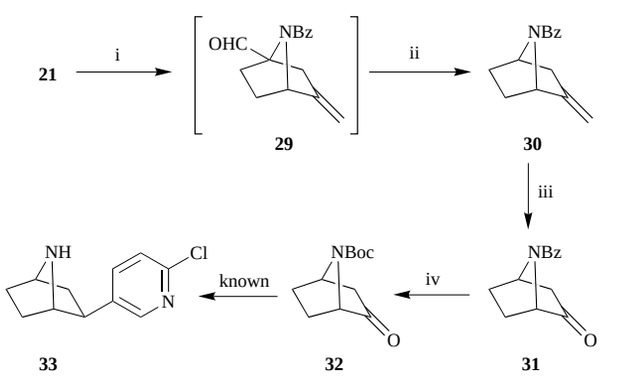
The exclusive formation of the *exo* cyclisation products **19**, **23** and **26** may reflect the closeness of the radical centre formed at the 5-position of the pyrrolidine ring and the internal position of the alkynic bond. Of the possibilities, 5- and 6-membered ring formation is favoured over that of a larger ring.

Our interest was then focused on the application of the present method to the synthesis of the 7-azabicyclo[2.2.1]heptan-3-one **32**, a key intermediate in the total synthesis of (±)-epibatidine **33**. Epibatidine is an alkaloid isolated from the skin of an Ecuadoran frog *Epipedobates tricolor*[9] and the first alkaloid containing a 7-azabicyclo[2.2.1]heptane ring system. This structural feature together with its potent analgesic properties rendered this alkaloid an attractive synthetic target and a number of total syntheses of it have already been reported.[10] Thus, compound **21** was reduced with DIBAL-H followed by decarbonylation of the resulting aldehyde **29** with Wilkinson's catalyst[11] to give the 3-methylene-7-azabicyclo[2.2.1]heptane **30** in 49% overall yield. Oxidation of **30** with OsO_4 and $NaIO_4$ yielded the *N*-benzoyl ketone **31** in 65% yield. Compound **31**



Scheme 3 *Reagents and conditions*: i, Bu_3SnH, AIBN, toluene, reflux; ii, TsOH, CH_3CN; iii, OsO_4, $NaIO_4$

was then converted into **32** (54%) by acid hydrolysis and reprotection with di-*tert*-butyl dicarbonate. Since compound **32** has previously been converted into (±)-epibatidine **33** by Fletcher and co-workers,[10e] the present preparation of **32** constitutes, in a formal sense, a total synthesis of (±)-epibatidine.



Scheme 4 *Reagents and conditions*: i, DIBAL-H, Et_2O, −50 °C; ii, $Rh(PPh_3)_3Cl$, xylene, 49% overall yield; iii, OsO_4, $NaIO_4$, 65%; iv, 5% HCl, dioxane, reflux; Et_3N, $(Boc)_2O$, CH_2Cl_2, 54%

In summary, we have shown that the 2-alkynyl-1-(*o*-iodobenzoyl)pyrrolidine-2-carboxylates undergo smoothly a 1,5-hydrogen-transfer followed by an *exo*-selective cyclisation of

the resulting α-acylamino radicals to give the azabicyclic compounds.

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 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-(*tert*-butoxycarbonyl)-2-[3-(trimethylsilyl)prop-2-ynyl]pyrrolidine-2-carboxylate 7

To a solution of hexamethyldisilazane (1.58 g, 9.81 mmol) and hexamethylphosphoramide (HMPA) (1.76 g, 9.81 mmol) in THF (10 cm^3) at −78 °C under a nitrogen atmosphere was added dropwise a 1.6 mol dm^{-3} solution of butyllithium in hexane (9.13 cm^3, 9.81 mmol). The mixture was stirred for 15 min after which it was treated with a solution of **6**[6] (1.50 g, 6.54 mmol) in THF (10 cm^3) at −78 °C and then stirred for 15 min. After a solution of 3-iodo-1-(trimethylsilyl)prop-1-yne[7] (4.78 g, 13.1 mmol) in THF (10 cm^3) had been added at −78 °C to the mixture, it was stirred at room temperature for 2 days. The reaction mixture was then acidified with 10% aq. HCl (20 cm^3) and concentrated under reduced pressure. The aqueous layer was extracted with diethyl ether and the extract was washed with saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (7:1)] to give **7** (1.38 g, 62%) as a colourless oil (Found: C, 60.6; H, 8.8; N, 4.05. $C_{17}H_{29}NO_4Si$ requires C, 60.1; H, 8.6; N, 4.1%) [Found: (M + H)$^+$, 340.1933. $C_{17}H_{30}NO_4Si$ requires m/z 340.1944]; $\nu_{max}(CCl_4)$/cm^{-1} 2170, 1740 and 1695; δ_H(60 MHz) 0.20 (9 H, s, $SiMe_3$), 1.44 (9 H, s, Bu^t), 1.7–2.5 (4 H, m), 2.77 (1 H, d, J 18, C*H*HC≡CTMS), 3.0–3.8 (3 H, m, 5-H_2 and one of CH*H*C≡CTMS) and 3.70 (3 H, s, OMe).

Methyl 1-(*o*-iodobenzoyl)-2-[3-(trimethylsilyl)prop-2-ynyl]-pyrrolidine-2-carboxylate 8

Trimethylsilyl iodide (1.91 g, 13.4 mmol) was added to a solution of **7** (3.80 g, 11.9 mmol) in acetonitrile (5 cm^3) at room temperature and after the mixture had been stirred for 10 min, methanol (2.1 cm^3) and saturated aq. $NaHCO_3$ (10 cm^3) were added to it; the mixture was then extracted with dichloromethane. The extract was dried ($MgSO_4$) and concentrated and the residue was dissolved in benzene (30 cm^3). This solution was then treated with *N*,*N*-diethylaniline (3.20 g, 22.4 mmol) and a solution of *o*-iodobenzoyl chloride (4.46 g, 16.8 mmol) in benzene (20 cm^3) at 0 °C, after which the whole was stirred at room temperature overnight. The mixture was then diluted with water (30 cm^3) and the organic layer was separated. The aqueous layer was extracted with diethyl ether. The combined organic layer and extracts were washed with 10% aq. 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 **8** (4.06 g, 77%), mp 73.5–74 °C (from hexane) (Found: C, 48.4; H, 5.1; N, 2.9. $C_{19}H_{24}INO_3Si$ requires C, 48.6; H, 5.15; N, 3.0%); $\nu_{max}(CCl_4)$/cm^{-1} 2175, 1740 and 1640; δ_H(60 MHz) 0.18 (9 H, s, $SiMe_3$), 1.8–2.5 (4 H, m), 2.89 (1 H, d, J 18, CH*H*C≡CTMS), 3.2–3.6 (2 H, m, 5-H_2), 3.69 (1 H, d, J 18, C*H*HC≡CTMS), 3.78 (3 H, s, OMe), 6.85–7.4 (3 H, m, ArH) and 7.80 (1 H, br d, J 8, ArH).

Methyl 1-(*tert*-butoxycarbonyl)-2-(3-hydroxypropyl)pyrrolidine-2-carboxylate 10

A 2 mol dm^{-3} solution of 2-methylbut-2-ene in THF (9.28 cm^3, 18.56 mmol) was added to a solution of borane–THF complex (1 mol dm^{-3} solution in THF; 9.28 cm^3, 9.28 mmol) at −15 °C and the mixture was stirred at 0 °C for 1 h. To the resulting solution of 3-methylbutan-2-ylborane was added dropwise a solution of **9**[6] (1.00 g, 3.71 mmol) in THF (10 cm^3). The mixture was stirred at room temperature for 1 h after which a 30% H_2O_2 solution (7.5 cm^3), water (1.5 cm^3) and 20% aqueous NaOH (3 cm^3) were added to the mixture at 0 °C. After the mixture had been stirred for 1 h it was extracted with diethyl ether. The extract was washed with brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (1:1)] to give **10** (974 mg, 91%) as a colourless oil [Found: (M + H)$^+$, 288.1821. $C_{14}H_{26}NO_5$ requires m/z 288.1811]; $\nu_{max}(CCl_4)$/cm^{-1} 3450, 1730 and 1680; δ_H(60 MHz) 1.41 (9 H, s, Bu^t), 1.3–2.5 (9 H, m), 3.4–3.8 (4 H, m) and 3.68 (3 H, s, OMe).

Methyl 1-(*tert*-butoxycarbonyl)-2-(2-formylethyl)pyrrolidine-2-carboxylate 11

A solution of dimethyl sulfoxide (870 mg, 11.1 mmol) in dry dichloromethane (5 cm^3) was added to a solution of oxalyl chloride (706 mg, 5.56 mmol) in dry dichloromethane (5 cm^3) at −78 °C over a period of 10 min after which the mixture was stirred for 10 min. After this, a solution of **10** (1.07 g, 18.6 mmol) in dry dichloromethane (10 cm^3) at −78 °C was added to the mixture which was then stirred at the same temperature for 1 h. After addition of triethylamine (1.88 g, 18.5 mmol) to the mixture, it was allowed to warm to room temperature. After 30 h, the mixture was diluted with water (10 cm^3) and the organic layer was separated and washed with 10% aq. HCl and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (4:1)] to give **11** (925 mg, 95%) as a colourless oil [Found: (M + H)$^+$, 286.1667. $C_{14}H_{24}NO_5$ requires m/z 286.1655]; $\nu_{max}(CCl_4)$/cm^{-1} 1725 and 1690; δ_H(60 MHz) 1.45 (9 H, s, Bu^t), 1.7–2.2 (5 H, m), 2.3–2.6 (3 H, m), 3.2–3.9 (2 H, m, 5-H_2), 3.70 (3 H, s, OMe) and 9.65–9.85 (1 H, unresolved m, CHO).

Methyl *N*-(*tert*-butoxycarbonyl)-2-(4,4-dibromobut-3-enyl)-pyrrolidine-2-carboxylate 12

Bromoform (2.83 g, 11.2 mmol) was added to a solution of triphenylphosphine (2.94 g, 11.2 mmol) and potassium *tert*-butoxide (1.26 g, 11.2 mmol) in toluene (10 cm^3) at −20 °C and the mixture was stirred at the same temperature for 15 min. A solution of **11** (800 mg, 2.80 mmol) in toluene (10 cm^3) was added to the mixture after which it was stirred for 1 h at the same temperature. The mixture was then diluted with pentane (80 cm^3) and the resulting precipitate was filtered off. The filtrate was concentrated and the residue was chromatographed on silica gel [hexane–AcOEt (6:1)] to give **12** (942 mg, 76%) as a colourless oil (Found: C, 40.8; H, 5.2; N, 3.0. $C_{15}H_{23}Br_2NO_4$ requires C, 40.8; H, 5.25; N, 3.2%); $\nu_{max}(CCl_4)$/cm^{-1} 1735 and 1690; δ_H(60 MHz) 1.46 (9 H, s, Bu^t), 1.7–2.5 (8 H, m), 3.1–3.8 (2 H, m, 5-H_2), 3.71 (3 H, s, OMe) and 6.25–6.5 (1 H, m, olefinic H).

Methyl *N*-(*tert*-butoxycarbonyl)-2-[4-(trimethylsilyl)but-3-ynyl]-pyrrolidine-2-carboxylate 13

TMEDA (1.5 cm^3) and a 1.6 mol dm^{-3} solution of butyllithium in hexane (3.89 cm^3, 6.22 mmol) were added to a solution of **12** (1.10 g, 2.49 mmol) in THF (10 cm^3) at −78 °C under a nitrogen atmosphere and the whole was stirred for 1 h. Trimethylsilyl chloride (406 mg, 3.73 mmol) was added to the reaction mixture at the same temperature after which it was stirred at room temperature overnight. The mixture was diluted with saturated aq. NH_4Cl 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 (5:1)] to give **13** (766 mg, 86%) as a colourless oil [Found: (M + H)$^+$, 354.2089. $C_{18}H_{32}NO_4Si$ requires m/z 354.2100]; $\nu_{max}(CCl_4)$/cm^{-1}

2180, 1740 and 1695; δ_H(60 MHz) 0.15 (9 H, s, $SiMe_3$), 1.44 (9 H, s, Bu^t), 1.7–2.6 (8 H, m), 3.2–3.8 (2 H, m, 5-H_2) and 3.67 (3 H, s, OMe).

Methyl 1-(*o*-iodobenzoyl)-2-[4-(trimethylsilyl)but-3-ynyl]-pyrrolidine-2-carboxylate 14

Following the procedure described for the preparation of **8**, **14** (1.68 g, 77%) was obtained from **13** (1.60 g, 4.53 mmol) and *o*-iodobenzoyl chloride (2.42 g, 9.06 mmol) as an oil [Found: $(M + H)^+$, 484.0794. $C_{20}H_{27}INO_3Si$ requires *m*/*z* 484.0805]; $\nu_{max}(CCl_4)/cm^{-1}$ 2180, 1740 and 1645; δ_H(60 MHz) 0.16 (9 H, s, $SiMe_3$), 1.7–2.9 (8 H, m), 3.36 (2 H, t, *J* 6.0, 5-H_2), 3.78 (3 H, s), 6.9–7.5 (3 H, m, ArH) and 7.78 (1 H, br d, *J* 8.0, ArH).

Methyl 1-(*tert*-butoxycarbonyl)-2-[3-hydroxy-5-(trimethylsilyl)-pent-4-ynyl]pyrrolidine-2-carboxylate 15

A solution of ethynyltrimethylsilane (258 mg, 2.63 mmol) in THF (2 cm^3) was added to a 1 mol dm^{-3} solution of ethylmagnesium bromide in THF (2.63 cm^3, 2.63 mmol) at −78 °C under a nitrogen atmosphere and the mixture was stirred at −78 °C for 30 min. After being stirred for 2 h at room temperature, the mixture was treated with a solution of **11** (500 mg, 1.75 mmol) in THF (10 cm^3), added at 0 °C. After the mixture had been stirred at 0 °C for 1 h, it was diluted with saturated aq. NH_4Cl and extracted with diethyl ether. The extract was dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (4:1)] to give **15** (621 mg, 93%) as an oily diastereoisomeric mixture [Found: $(M + H)^+$, 384.2203. $C_{19}H_{34}NO_5Si$ requires *m*/*z* 384.2206]; $\nu_{max}(CCl_4)/cm^{-1}$ 3660, 3450, 2175, 1740 and 1700; δ_H(60 MHz) 0.16 (9 H, s, $SiMe_3$), 1.42 (9 H, s, Bu^t), 1.55–2.5 (9 H, m), 3.2–3.8 (2 H, m), 3.71 (3 H, s, OMe) and 4.2–4.5 (1 H, m, C*H*OH).

Methyl 1-(*tert*-butoxycarbonyl)-2-[3-bromo-5-(trimethylsilyl)-pent-4-ynyl]pyrrolidine-2-carboxylate 16

Carbon tetrabromide (779 mg, 2.35 mmol) and triphenylphosphine (615 mg, 2.35 mmol) were added to a solution of **15** (600 mg, 1.57 mmol) in dichloromethane (10 cm^3) at 0 °C and the whole was stirred at room temperature for 1 h. The mixture was evaporated and the residue was chromatographed on silica gel [hexane–AcOEt (4:1)] to give **16** (616 mg, 88%) as an oily diastereoisomeric mixture [Found: $(M + H)^+$, 446.1374. $C_{19}H_{33}{}^{79}BrNO_4Si$ requires *m*/*z* 446.1362]; $\nu_{max}(CCl_4)/cm^{-1}$ 2175, 1740 and 1700; δ_H(300 MHz) 0.18 (9 H, s, $SiMe_3$) 1.43, 1.45 (total 9 H, both s, Bu^t), 1.80–2.18, 2.32–2.42 (total 8 H, both m), 3.37–3.79 (2 H, m, 5-H_2), 3.71, 3.72 (total 3 H, both s, OMe) and 4.46–4.59 (1 H, m, CHBr).

Methyl 1-(*tert*-butoxycarbonyl)-2-[5-(trimethylsilyl)pent-4-ynyl]-pyrrolidine-2-carboxylate 17

Bu_3SnH (862 mg, 2.96 mmol) and AIBN (45 mg, 0.27 mmol) were added to a solution of **16** (1.20 g, 2.69 mmol) in benzene (20 cm^3) and the mixture was refluxed for 1 h. After evaporation of the mixture, the residue was chromatographed on silica gel [hexane–AcOEt (4:1)] to give **17** (924 mg, 94%) as a colourless oil [Found: $(M + H)^+$, 368.2267. $C_{19}H_{34}NO_4Si$ requires *m*/*z* 368.2258]; $\nu_{max}(CCl_4)/cm^{-1}$ 2180, 1745 and 1700; δ_H(300 MHz) 0.15, 0.18 (total 9 H, both s, $SiMe_3$), 1.41, 1.43, 1.45 (total 9 H, s each, Bu^t), 1.30–2.29 (8 H, m), 2.26 (2 H, t, *J* 7.1), 3.35–3.77 (2 H, m, 5-H_2) and 3.71, 3.72 (total 3 H, both s, OMe).

Methyl 1-(*o*-iodobenzoyl)-2-[5-(trimethylsilyl)pent-4-ynyl]-pyrrolidine-2-carboxylate 18

Following the procedure described for the preparation of **8**, **18** (681 mg, 77%) was obtained from **17** (630 mg, 1.72 mmol) and *o*-iodobenzoyl chloride (687 mg, 2.58 mmol) as a colourless oil [Found: $(M + H)^+$, 498.0974. $C_{21}H_{29}INO_3Si$ requires *m*/*z* 498.0962]; $\nu_{max}(CCl_4)/cm^{-1}$ 2180, 1745 and 1650; δ_H(300 MHz) 0.15 (9 H, s, $SiMe_3$), 1.65–2.04 (4 H, m), 2.13–2.40 (1 H, m), 2.16 (2 H, t, *J* 6.9), 2.30 (2 H, q, *J* 6.9), 2.47–2.58 (1 H, m), 3.30–3.40 (2 H, br, 5-H_2), 3.79 (3 H, s, OMe), 7.07 (1 H, td, *J* 7.8, 1.8, ArH), 7.21 (1 H, dd, *J* 7.8, 1.8, ArH), 7.39 (1 H, td, *J* 7.8, 0.9, ArH) and 7.82 (1 H, d, *J* 7.8, ArH).

Radical cyclisation of compound 8

General procedure. To a stirred and boiling solution of **8** (405 mg, 0.86 mmol) in toluene (40 cm^3) was added a solution of Bu_3SnH (326 mg, 1.12 mmol) and AIBN (14 mg, 0.09 mmol) in toluene (40 cm^3) *via* a syringe during 2 h, and the mixture was refluxed for 2 h. The same procedure was repeated. After evaporation of the mixture, diethyl ether (20 cm^3) and 8% aqueous KF (20 cm^3) were added to the residue, and the whole was vigorously stirred at room temperature for 1 h. The organic layer was separated, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (10:1)]. The first fraction gave a mixture of *E* and *Z* isomers (*ca.* 1:1 ratio) of *methyl* 7-*benzoyl*-3-(*trimethylsilylmethylene*)-7-*azabicyclo*[2.2.1]*heptane*-1-*carboxylate* **19** (230 mg, 78%) as a colourless oil [Found: $(M + H)^+$, 344.1691. $C_{19}H_{26}NO_3Si$ requires *m*/*z* 344.1682]; $\nu_{max}(CCl_4)/cm^{-1}$ 1740 and 1650; δ_H(300 MHz) (for a mixture of two isomers) −0.15, 0.07 (total 9 H, both s, $SiMe_3$), 1.56–1.68 (1 H, m), 1.80–1.91 (1 H, m), 2.03–2.22 (1 H, m), 2.37 (1 H, dt, *J* 11.9, 3.6), 2.46 (1 H, dt, *J* 16.2, 2.7), 2.98–3.11 (1 H, m), 3.827, 3.834 (total 3 H, both s, OMe), 4.40 (1/2 H, d, *J* 4.6, 4-H), 4.63 (1/2 H, d, *J* 4.9, 4-H), 5.25 (1/2 H, t, *J* 2.25, olefinic H), 5.28 (1/2 H, br s, olefinic H), 7.38–7.52 (3 H, m, ArH) and 7.65–7.68 (2 H, m, ArH).

The second fraction gave *methyl* 1-*benzoyl*-2-[3-(*trimethylsilyl*)*prop*-2-*ynyl*]*pyrrolidine*-2-*carboxylate* **20** (53 mg, 18%), mp 60–61.5 °C (from pentane) (Found: C, 66.7; H, 7.5; N, 4.0. $C_{19}H_{25}NO_3Si$ requires C, 66.4; H, 7.3; N, 4.1%); $\nu_{max}(CCl_4)/cm^{-1}$ 2175, 1740 and 1635; δ_H(60 MHz) 0.20 (9 H, s, $SiMe_3$), 1.8–2.5 (4 H, m), 2.80 (1 H, d, *J* 17, C*H*HC≡CTMS), 3.4–3.8 (2 H, m, 5-H_2), 3.66 (1 H, d, *J* 17, CH*H*C≡CTMS), 3.74 (3 H, s, OMe) and 7.2–7.6 (5 H, m, ArH).

Methyl 7-benzoyl-3-methylene-7-azabicyclo[2.2.1]heptane-1-carboxylate 21

A mixture of **19** (200 mg, 0.58 mmol) and toluene-*p*-sulfonic acid monohydrate (55 mg, 0.29 mmol) in wet acetonitrile (10 cm^3) was heated under reflux for 3.5 h. After evaporation of the mixture, the residue was dissolved in diethyl ether (10 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 **21** (109 mg, 69%) as a colourless oil [Found: $(M + H)^+$, 272.1275. $C_{16}H_{18}NO_3$ requires *m*/*z* 272.1287]; $\nu_{max}(CCl_4)/cm^{-1}$ 1740 and 1650; δ_H(300 MHz) 1.65 (1 H, ddd, *J* 11.5, 9.3, 3.9), 1.87 (1 H, ddd, *J* 11.8, 9.3, 4.8), 2.13 (1 H, tt, *J* 11.9, 4.8), 2.40 (1 H, tt, *J* 11.9, 3.6), 2.47 (1 H, br d, *J* 15.9, 2-*H*H), 3.05 (1 H, dq, *J* 15.9, 2.7, 2-H*H*), 3.82 (3 H, s, OMe), 4.51 (1 H, d, *J* 4.8, 4-H), 4.78 (1 H, br s, C=C*H*H), 4.82 (1 H, t, *J* 2.7, C=CH*H*), 7.37–7.53 (3 H, m, ArH) and 7.65–7.70 (2 H, m, ArH).

Methyl 7-benzoyl-3-oxo-7-azabicyclo[2.2.1]heptane-1-carboxylate 22

4% Aq. osmium tetroxide (0.05 cm^3, 2.54 mg as OsO_4, 0.01 mmol) was added to a solution of **21** (100 mg, 0.37 mmol) in THF–H_2O (4:1) (5 cm^3) at 0 °C and the whole was stirred for 5 min. To this mixture was added $NaIO_4$ (237 mg, 1.11 mmol) over a period of 30 min and the mixture was stirred at room temperature overnight after which it was diluted with water and extracted with diethyl ether. The extract was dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (3:1)] to give **22** (55 mg, 55%), mp 109–110 °C (from hexane–AcOEt) (Found: C, 65.5; H, 5.5; N, 4.9. $C_{15}H_{15}NO_4$ requires C, 65.9; H, 5.5; N, 5.1%); $\nu_{max}(CCl_4)/cm^{-1}$ 1760, 1750 and 1660; δ_H(300 MHz) 1.77 (1 H, ddd, *J* 12.9, 9.3, 4.3), 1.97 (1 H, ddd, *J* 12.2, 9.3, 4.3), 2.24 (1 H, tt, *J* 12.2, 5.1), 2.43 (1 H, d, *J* 17.6, 2-*H*H), 2.53 (1 H, tt, *J* 12.2, 3.9), 3.08 (1 H,

dd, *J* 17.6, 2.6, 2-H*H*), 3.87 (3 H, s, OMe), 4.36 (1 H, d, *J* 5.1, 4-H), 7.39–7.57 (3 H, m, ArH) and 7.63–7.70 (2 H, m, ArH); δ_C 25.0 (CH_2), 30.7 (CH_2), 47.0 (CH_2), 52.8 (OMe), 67.6 (1-C), 69.1 (4-C), 128.65, 128.7, 132.35, 133.05, 169.2 (C=O), 172.1 (C=O) and 206.3 (C=O).

Radical cyclisation of compound 14

Following the general procedure, **14** (500 mg, 1.04 mmol) was treated with Bu_3SnH (393 mg, 1.35 mmol) and AIBN (17 mg, 0.10 mmol) in toluene and the crude material was chromatographed on silica gel [hexane–AcOEt (7:1)] to give a mixture of *E* and *Z* isomers (1:1 ratio) of *methyl* 8-*benzoyl*-4-(*trimethylsilylmethylene*)-8-*azabicyclo*[3.2.1]*octane*-1-*carboxylate* **23** (318 mg, 86%) as a colourless oil [Found: $(M + H)^+$, 358.1829. $C_{20}H_{28}NO_3Si$ requires *m*/*z* 358.1838]; $\nu_{max}(CCl_4)/cm^{-1}$ 1735 and 1630; δ_H(300 MHz, for a mixture of two isomers) −0.37, 0.14 (total 9 H, both s, $SiMe_3$), 1.76–1.87 (1 H, m), 1.99–2.17 (2 H, m), 2.24–2.79 (5 H, m), 3.74, 3.77 (total 3 H, both s, OMe), 4.33–4.37 (1/2 H, m, 5-H), 4.42 (1/2 H, d, *J* 1.8, olefinic H), 4.89 (1/2 H, d, *J* 6.6, 5-H), 4.97 (1/2 H, d, *J* 2.1, olefinic H), 7.33–7.48 (3 H, m, ArH) and 7.50–7.56 (2 H, m, ArH).

Methyl 8-benzoyl-4-methylene-8-azabicyclo[3.2.1]octane-1-carboxylate 24

Following the procedure described for the preparation of **21**, **24** (103 mg, 86%) was obtained from **23** (150 mg, 0.42 mmol) as a colourless oil [Found: $(M + H)^+$, 286.1447. $C_{17}H_{20}NO_3$ requires *m*/*z* 286.1443]; $\nu_{max}(CCl_4)/cm^{-1}$ 1740 and 1640; δ_H(300 MHz) 1.72–1.90 (1 H, m), 2.00–2.18 (2 H, m), 2.23–2.54 (5 H, m), 3.76 (3 H, s, OMe), 4.08 (1 H, br s, C=C*H*H), 4.46 (1 H, br s, C=CH*H*), 4.50 (1 H, d, *J* 6.1, 5-H), 7.35–7.48 (3 H, m, ArH) and 7.48–7.55 (2 H, m, ArH).

Methyl 8-benzoyl-4-oxo-8-azabicyclo[3.2.1]octane-1-carboxylate 25

Following the procedure described for the preparation of **22**, **25** (43 mg, 43%) was obtained from **24** (100 mg, 0.35 mmol), mp 146–147 °C (from AcOEt) [Found: $(M + H)^+$, 288.1227. $C_{16}H_{18}NO_4$ requires *m*/*z* 288.1236]; $\nu_{max}(CCl_4)/cm^{-1}$ 1745, 1730 and 1655; δ_H(300 MHz) 1.92–2.00 (1 H, m), 2.15–2.33 (2 H, m), 2.40–2.65 (4 H, m), 2.86–2.98 (1 H, m), 3.80 (3 H, s, OMe), 4.42 (1 H, d, *J* 7.0, 5-H) and 7.36–7.51 (5 H, m, ArH); δ_C 27.25 (CH_2), 29.7 (CH_2), 32.7 (CH_2), 33.4 (CH_2), 52.7 (OMe), 64.2 (1-C), 68.5 (5-C), 127.5, 128.7, 131.2, 134.3, 170.1 (C=O), 171.15 (C=O) and 205.2 (C=O).

Radical cyclisation of compound 18

Following the general procedure, **18** (700 mg, 1.37 mmol) was treated twice with Bu_3SnH (518 mg, 1.78 mmol) and AIBN (23 mg, 0.14 mmol) in toluene and the crude material was chromatographed on silica gel [hexane–AcOEt (6:1)] to give an inseparable mixture of methyl 9-benzoyl-5-(trimethylsilylmethylene)-9-azabicyclo[4.2.1]nonane-1-carboxylate **26** (*E*:*Z* = 9:7 by HPLC) and methyl 1-benzoyl-2-[5-(trimethylsilyl)pent-4-ynyl]pyrrolidine-2-carboxylate **27** (455 mg, 86%) in a ratio of 48:52 (by HPLC) as a colourless oil. The ^1H NMR spectrum of the mixture could not be analysed due to its complexity.

Methyl 9-benzoyl-5-oxo-9-azabicyclo[4.2.1]nonane-1-carboxylate 28

Following the procedure described for the preparation of **21**, a mixture of **26** and **27** (220 mg, 0.57 mmol) was treated with toluene-*p*-sulfonic acid (33 mg, 0.17 mmol) in acetonitrile to give again an inseparable 1:1 mixture of methyl 9-benzoyl-5-methylene-9-azabicyclo[4.2.1]nonane-1-carboxylate and methyl 1-benzoyl-2-(pent-4-ynyl)pyrrolidine-2-carboxylate (total 118 mg, 66% combined yield), which was used for the next step without further purification.

Following the procedure described for the preparation of **22**, the mixture obtained above (200 mg, 0.64 mmol) was oxidised with OsO_4 and $NaIO_4$. The crude material was chromatographed on silica gel [hexane–AcOEt (1:1)] to give **28** (53 mg, 26%), mp 175–176 °C (from AcOEt) (Found: C, 67.5; H, 6.4; N, 4.6. $C_{17}H_{19}NO_4$ requires C, 67.8; H, 6.35; N, 4.65%); $\nu_{max}(CCl_4)/cm^{-1}$ 1745, 1715 and 1640; δ_H(300 MHz) 1.63–1.80 (1 H, m), 1.96–2.16 (3 H, m), 2.20–2.36 (2 H, m), 2.37–2.58 (2 H, m), 2.69–2.83 (2 H, m), 3.79 (3 H, s, OMe), 4.48 (1 H, d, *J* 9.2, 6-H) and 7.33–7.47 (5 H, m, ArH); δ_C 19.3 (CH_2), 30.4 (CH_2), 31.4 (CH_2), 32.1 (CH_2), 41.7 (CH_2), 52.6 (OMe), 68.2 (1-C or 6-C), 68.3 (6-C or 1-C), 126.5, 128.8, 130.4, 135.5, 168.8 (C=O), 172.7 (C=O) and 214.2 (C=O).

7-Benzoyl-2-methylene-7-azabicyclo[2.2.1]heptane 29

A 0.95 mol dm^{-3} solution of DIBAL-H in hexane (2.24 cm^3, 2.13 mmol) was added to a solution of **21** (480 mg, 1.77 mmol) in diethyl ether (20 cm^3) at −50 °C under a nitrogen atmosphere and the mixture was stirred for 30 min. Methanol (1 cm^3) and then 10% NaOH solution (15 cm^3) were added to this mixture and the organic layer was separated. The aqueous layer was extracted with diethyl ether and the combined organic layer and extracts were washed with brine, dried ($MgSO_4$) and concentrated to give 7-benzoyl-3-methylene-7-azabicyclo[2.2.1]-heptane-1-carbaldehyde **29** (382 mg), which was used for the next step without further purification.

A solution of the crude aldehyde (382 mg, 1.58 mmol) and Wilkinson's complex $Rh(PPh_3)_3Cl$ (1.61 g, 1.74 mmol) in xylene (5 cm^3) was refluxed for 3 h under a nitrogen atmosphere. The mixture was concentrated and the residue was chromatographed on silica gel [hexane–AcOEt (5:1)] to give **30** (184 mg, 49% overall yield from **21**), mp 46–47 °C (from pentane) [Found: $(M + H)^+$, 214.1239. $C_{14}H_{16}NO$ requires *m*/*z* 214.1232]; $\nu_{max}(CCl_4)/cm^{-1}$ 1640; δ_H(300 MHz) 1.50–1.66 (2 H, m), 1.80–2.20 (2 H, br), 2.17 (1 H, d, *J* 15.7), 2.48–2.70 (1 H, br), 4.20–5.15 (1 H, br), 4.70–5.15 (3 H, br), 7.36–7.50 (3 H, m, ArH) and 7.51–7.58 (2 H, m, ArH).

7-Benzoyl-7-azabicyclo[2.2.1]heptan-2-one 31

Following the procedure described for the preparation of **22**, **31** (118 mg, 65%) was obtained from **30** (180 mg, 0.85 mmol) as an oil [Found: $(M + H)^+$, 216.1033. $C_{13}H_{14}NO_2$ requires *m*/*z* 216.1025]; $\nu_{max}(CCl_4)/cm^{-1}$ 1760 and 1645; δ_H(300 MHz) 1.63–1.79 (2 H, m), 2.00–2.21 (3 H, m), 2.64 (1 H, dd, *J* 17.5, 5.3), 4.30–4.62 (1 H, br, 1- or 4-H), 4.69–5.05 (1 H, br, 4- or 1-H) and 7.38–7.60 (5 H, m, ArH).

***tert*-Butyl 2-oxo-7-azabicyclo[2.2.1]heptane-7-carboxylate 32**

A solution of **31** (30 mg, 0.14 mmol) in 5% aq. HCl (1.5 cm^3) and dioxane (2 cm^3) was heated under reflux for 15 h. The mixture was concentrated *in vacuo* and a trace of water was removed by azeotropic distillation with ethanol. The residue was dissolved in dichloromethane (5 cm^3), and triethylamine (70 mg, 0.69 mmol) and di-*tert*-butyl dicarbonate (76 mg, 0.35 mmol) were added to the mixture. The whole was stirred at room temperature for 16 h, washed with 5% aq. HCl and saturated aq. $NaHCO_3$, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (5:1)] to give **32** (16 mg, 54%) as a colourless oil which solidified with time, mp 50–52 °C [from light petroleum (bp 30–70 °C)] (lit.,[10e] 60–62 °C); $\nu_{max}(CCl_4)/cm^{-1}$ 1765 and 1705; δ_H(300 MHz) 1.46 (9 H, s, Bu^t), 1.53–1.69 (2 H, m), 1.91–2.09 (2 H, m), 2.00 (1 H, d, *J* 17.6, 3-*H*H), 2.42–2.52 (1 H, dd like m, 3-H*H*), 4.25 (1 H, d, *J* 4.9, 1- or 4-H) and 4.56 (1 H, t, *J* 4.8, 4- or 1-H); δ_C 24.4 (CH_2), 27.5 (CH_2), 28.2 (Bu^t), 45.2 (3-C), 56.0 (4-C), 63.9 (1-C), 80.8 (*C*Me_3), 155.0 (C=O) and 209.6 (C=O).

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