PERKIN 1

A new entry to 9-azabicyclo[3.3.1]nonanes using radical translocation/cyclisation reactions of 2-(but-3-ynyl)-1-(*o*-iodobenzoyl)piperidines †

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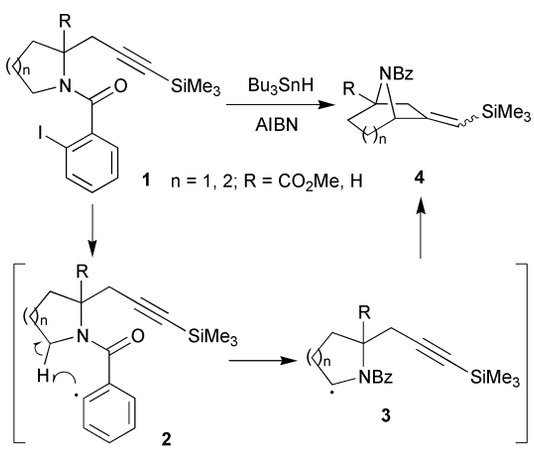
Received (in Cambridge, UK) 2nd April 2002, Accepted 22nd April 2002
First published as an Advance Article on the web 13th May 2002

The 2-[4-(trimethylsilyl)but-3-ynyl]piperidines **16a**–**c**, upon treatment with tributyltin hydride in the presence of azoisobutyronitrile in refluxing toluene, gave the 9-azabicyclo[3.3.1]nonanes **17a**–**c** in high yields, respectively. Compound **17c** was subjected to desilylation, ozonolysis, and subsequent 1,2-transposition of the resulting carbonyl group to give 9-benzoyl-1-methyl-9-azabicyclo[3.3.1]nonan-3-one, a potential precursor for the synthesis of (±)-euphococcinine.

Introduction

Bridged azabicyclic rings are widely found as the basic structural elements in biologically active alkaloids such as cocaine, atropine, and epibatidine. Recently we have developed a new synthetic method for the 7-azabicyclo[2.2.1]heptane and 8-azabicyclo[3.2.1]octane ring systems **4** which involves treatment of 1-(*o*-iodobenzoyl)-2-(prop-2-ynyl)-pyrrolidines and -piperidines **1** with tributyltin hydride (Bu_3SnH) in the presence of azoisobutyronitrile (AIBN) in boiling toluene.[1] The formation of **4** can be formulated as proceeding *via* the α-acylamino radicals **3** which are generated by a 1,5-hydrogen transfer (a radical translocation)[2] of the initially formed aryl radicals **2**. The radicals **3** then undergo a 5-*exo-dig* cyclisation to lead to **4** (Scheme 1). As a further extension of this reaction, we



Scheme 1

have now investigated the Bu_3SnH-mediated radical reaction of the 2-(but-3-ynyl)piperidines **16a**–**c** and found that the translocation and 6-*exo-dig* cyclisation reactions proceed in a regioselective manner to afford the expected 9-azabicyclo-[3.3.1]nonane ring system.[3] In this paper we also describe a transformation of the cyclised product **17c** into 9-benzoyl-1-methyl-9-azabicyclo[3.3.1]nonan-3-one **28**, a protected form of (±)-euphococcinine **29**.[4]

† Electronic supplementary information (ESI) available: Experimental details for **5**–**16**. See http://www.rsc.org/suppdata/p1/b2/b203243k/

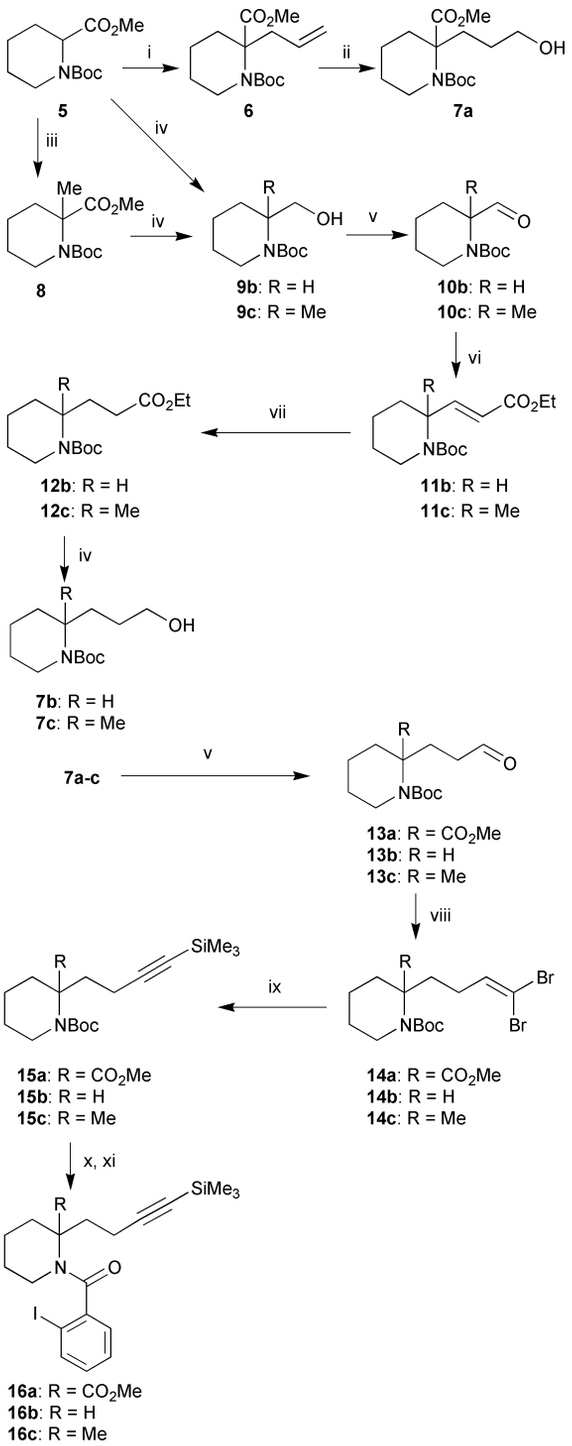
Results and discussion

The radical precursor **16a** was prepared starting from methyl *N*-Boc-pipecolinate **5**[5] according to the procedures previously described for the synthesis of the pyrrolidine congener[1d] (Scheme 2). Thus, **5** was subjected to allylation, and hydroboration of the resulting allylated ester **6** with bis(3-methylbutan-2-yl)borane (disiamylborane) followed by oxidation afforded the alcohol **7a**. Swern oxidation of **7a** gave the aldehyde **13a**, which was then allowed to react with bromoform and triphenylphosphine in the presence of potassium *tert*-butoxide to give the dibromoalkene **14a**. Treatment of **14a** with butyllithium and quenching with trimethylsilyl chloride gave the *N*-Boc-2-[4-(trimethylsilyl)but-3-ynyl]piperidine **15a**. Replacement of the *N*-Boc group by an *o*-iodobenzoyl group gave the radical precursor **16a**. The radical precursor **16b** was also prepared from **5**, which was subjected successively to $LiAlH_4$ reduction (**9b**), Swern oxidation (**10b**), the Horner–Emmons reaction with triethyl phosphonoacetate (**11b**), catalytic hydrogenation over Pd–C (**12b**), and $LiAlH_4$ reduction to afford the alcohol **7b**. This alcohol **7b** was converted into **16b** (*via* **13b**, **14b** and **15b**) in a similar manner to the reaction sequences used for the preparation of **16a**.

A toluene solution of Bu_3SnH (2.7 mol equiv.) and a small amount of AIBN (0.32 mol equiv.) was added by syringe pump to a refluxing solution of **16a** in toluene over a period of 1 h and the mixture was further refluxed for 2 h. The crude material was chromatographed on silica gel to give a *ca.* 1 : 1 diastereomeric mixture of the 9-azabicyclo[3.3.1]nonane **17a** in 98% combined yield. No simple reduction product was obtained. The structure of **17a** was confirmed by the following chemical transformation. Treatment of **17a** with trifluoroacetic acid in DCM gave the methylene derivative **18a** which was then oxidised with ozone to afford the ketone **19a** in 45% overall yield (Scheme 3). The ketone **19a** showed a strong carbonyl absorption at 1732 cm^{-1} (a ketone and an ester) in addition to an absorption due to the *N*-benzoyl group at 1646 cm^{-1} in the IR spectrum. The ^1H NMR spectrum revealed a doublet of doublets due to a bridgehead proton (5-H) at δ 4.32 (J 6.2 and 3.7 Hz).

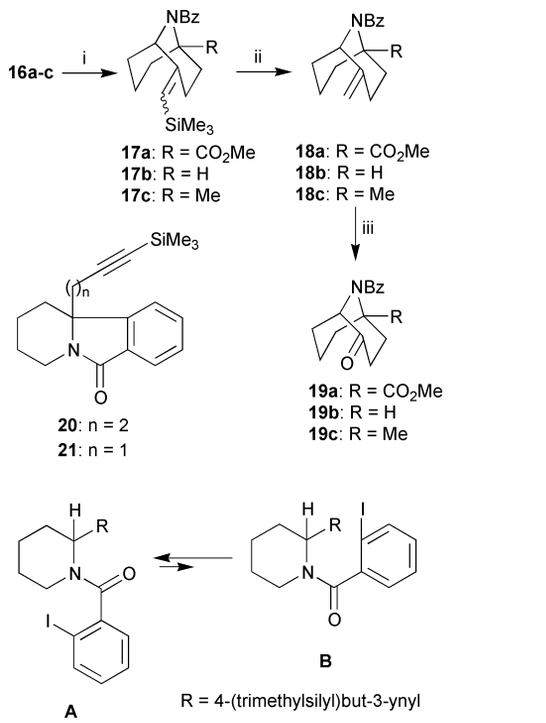
Similar treatment of **16b** with Bu_3SnH–AIBN gave the expected 9-azabicyclo[3.3.1]nonane **17b** in 67% yield as a *ca.* 1 : 1 diastereomeric mixture, along with the hexahydropyrido-[2,1-*a*]isoindolone **20** in 22% yield. The compound **17b** was again converted into the ketone **19b** *via* the methylene derivative **18b** in 55% overall yield, which showed a ketonic absorption at

 DOI: 10.1039/b203243k



Scheme 2 *Reagents and conditions*: i, $LiN(SiMe_3)_2$, THF, −78 °C; then $CH_2{=}CHCH_2Br$; ii, Sia_2BH, THF; then aq. NaOH, 30% H_2O_2; iii, $LiN(SiMe_3)_2$, THF, −78 °C; then MeI; iv, $LiAlH_4$, Et_2O; v, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; vi, $(EtO)_2P(O)CH_2CO_2Et$, BuLi, THF; vii, H_2 (5 kg cm^{-2}), 10% Pd–C, AcOEt; viii, $CHBr_3$, PPh_3, Bu^tOK, toluene; ix, BuLi, TMEDA, THF, −78 °C; then Me_3SiCl; x, Me_3SiI, MeCN; then MeOH; xi, *o*-iodobenzoyl chloride, DMAP, Et_3N, benzene.

1729 cm^{-1} in the IR spectrum. The structure of the minor product **20** was assigned by a comparison of the spectroscopic data with those of the closely related compound **21**.[1c] The product distribution of **17b** (65%) and **20** (23%) probably reflects the population of two conformers **A** and **B** of **16b**, which generate the α-acylamino radicals at the 6- (leading to **17b**) and 2-position of the piperidine ring (leading to **20**), respectively, through the corresponding short-lived aryl radicals. Conformer **A** is favoured over conformer **B** because the steric repulsion between the bulky *o*-iodophenyl and 2-[4-(trimethylsilyl)but-3-ynyl] groups may occur in the latter, in spite of the



Scheme 3 *Reagents and conditions*: i, Bu_3SnH, AIBN, toluene, reflux; ii, CF_3CO_2H, CH_2Cl_2; iii, O_3, CH_2Cl_2, −78 °C, then PPh_3.

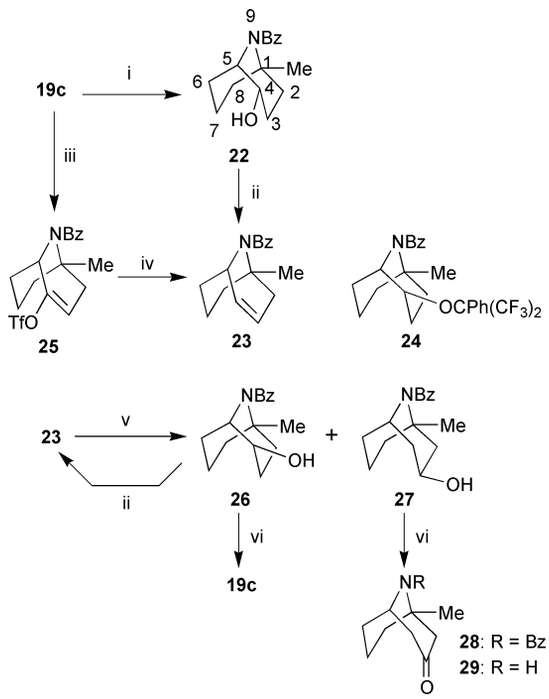
fact that the side chain at the 2-position mainly occupies an axial position in order to minimise allylic 1,3-strain [1c,6] with the N=C double bond in the amide.

Encouraged by the success of the synthesis of the 9-azabicyclo[3.3.1]nonane ring system, we then applied the present method to the synthesis of (±)-euphococcinine **29**, which is an alkaloid isolated from a small sea-coast plant, *Euphorbia atoto*[7] and also found in the defence secretion of the ladybugs *Cryptolaenus montrouzieri*[8a] and *Epilachna varivesti*.[8b] The radical precursor **16c** was prepared from methyl *N*-Boc-2-methylpiperidine-2-carboxylate **8** (*via* **9c**–**15c**) by the same reaction sequences as those used for the preparation of **16b**. The Bu_3SnH-mediated radical reaction of **16c** proceeded efficiently to give the 9-azabicyclo[3.3.1]nonane **17c** in 95% yield as a *ca.* 1 : 1 diastereomeric mixture, which was converted into the ketone **19c** *via* the methylene derivative **18c** in 63% overall yield (see Scheme 3).

The 1,2-transposition[9] of the carbonyl group of **19c** was then investigated. Considerable difficulty, however, was encountered in finding a route to the intermediate alkene **23**. Sodium borohydride reduction of **19c** gave the alcohol **22** in 81% yield. A variety of procedures for the dehydration of the alcohol **22**, employing the mesyl derivative in refluxing lutidine or collidine, the Burgess reagent,[10] and the xanthate in refluxing xylene were examined without success. In general, either unchanged material or uncharacterised products were obtained. Only when the alcohol **22** was treated with the Martin sulfurane dehydrating agent at 80 °C in benzene[11] the desired alkene **23** was obtained but in 5% yield; the major product (57% yield) was the bis(trifluoromethyl)phenylmethyl ether **24**, probably with inversion of configuration. The difficulty of attaining dehydration under the *E*2 elimination conditions may be ascribed to the rigidly fixed equatorial configuration of the hydroxy group of **22**. The *syn* elimination is also unfavourable because the location of the 7-methylene group blocks formation of the cyclic transition state involving the axial hydrogen at the 3-position‡ which is required for this elimination to take place.

‡ The numbering system of the 9-azabicyclo[3.3.1]nonane ring system may change depending upon the substituents. To avoid confusion in this discussion, we used the numbering system for compounds **22**–**28** as shown in formula **22**.

This view was supported later by isolation of the isomeric axial alcohol **26**, which underwent smooth dehydration with Martin sulfurane to give back the alkene **23**. An alternative synthesis of the alkene **23** was achieved by palladium-catalysed hydrogenolysis[12] of the alkenyl triflate **25**[13] in 61% overall yield in two steps from ketone **19c** (Scheme 4).



Scheme 4 *Reagents and conditions*: i, $NaBH_4$, MeOH; ii, Martin sulfurane, benzene, 80 °C; iii, LDA, THF, −78 °C; then Comins' reagent; iv, $Me_2NH{\cdot}BH_3$, cat. $Pd(PPh_3)_4$, K_2CO_3, MeCN, 40 °C; v, $BH_3{\cdot}$THF, THF; then aq. NaOH, H_2O_2; vi, TPAP, NMO, 4Å-MS, CH_2Cl_2.

Hydroboration of the alkene **23** with borane–THF complex and oxidation of the intermediate gave a mixture of two alcohols which were separated by silica gel chromatography to give the alcohols **26** and **27** in 31 and 39% yield, respectively. In an attempt to improve the regioselectivity, 9-BBN was used instead of borane–THF complex but the starting material was recovered unchanged. The structure and stereochemistry of the alcohol **26** were confirmed by oxidation with TPAP–NMO[14] to the ketone **19c** (95% yield) and the aforementioned smooth dehydration with Martin sulfurane to the alkene **23** (85% yield). The assigned stereochemistry of the alcohols **22** and **26** is consistent with the view that both hydride and borane approach from the less crowded convex face of the ketone **19c** and the alkene **23**, respectively. The structure and stereochemistry of the alcohol **27** were assigned on the basis of ^{1}H NMR spectroscopic evidence (the axial proton at the 3-position appeared at δ 4.62 as a triplet of triplets with coupling constants of 11.0 and 6.4 Hz) and oxidation with TPAP–NMO to the ketone **28** quantitatively. The ketone **28** is a potential precursor for the synthesis of (±)-euphococcinine **29**.

In summary, we have revealed that 2-(but-3-ynyl)-1-(*o*-iodobenzoyl)piperidines undergo radical translocation and 6-*exo*-*dig* cyclisation to give the 9-azabicyclo[3.3.1]nonane ring system in high yields.

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 or a JASCO-FT/IR-410 spectrophotometer. ^{1}H NMR (60, 300 and 400 MHz) and ^{13}C NMR (75.4 and 100.5 MHz) spectra were measured on a JEOL-JNM-PMX 60, a Varian XL-300 or a Varian UNITY INOVA 400NB spectrometer for solutions in $CDCl_3$. δ-Values quoted are relative to tetramethylsilane (δ_H 0) and $CDCl_3$ (δ_C 77.02) for ^{1}H and ^{13}C NMR, respectively, and *J*-values are given in Hz. Exact mass determinations (EI and FAB mass spectra) were obtained on a JEOL-GCmate or a JEOL-SX 102A instrument (3-NOBA as matrix), respectively. Column chromatography was performed on silica gel 60 PF_{254} (Nacalai Tesque) under pressure. The experimental details for the preparation of the radical precursors **16a**–**c** are described in the ESI.†

Radical cyclisation of compound 16a

General procedure. To a stirred, refluxing solution of **16a** (493 mg, 0.99 mmol) in toluene (100 cm^3) was added a solution of Bu_3SnH (780 mg, 2.68 mmol) and AIBN (53 mg, 0.32 mmol) in toluene (100 cm^3) *via* a syringe during 1 h, and the mixture was further refluxed for 2 h. After removal of the solvent *in vacuo*, diethyl ether (30 cm^3) and 8% aq. KF (50 cm^3) were added to the residue, and the whole was vigorously stirred at room temperature for 1 h. The organic phase was separated, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (10 : 1)] to give a mixture of the (*E*) and (*Z*) geometrical isomers (in a ratio of 58 : 42) of *methyl* 9-*benzoyl*-4-(*trimethylsilylmethylene*)-9-*azabicyclo*-[3.3.1]*nonane*-1-*carboxylate* **17a** (360 mg, 98%), mp 98.5–99 °C [from petroleum ether (distillation range 80–110 °C)] (Found: C, 67.80; H, 8.16; N, 3.80. $C_{21}H_{29}NO_3Si$ requires C, 67.89; H, 7.87; N, 3.77%); ν_{max} (CCl_4)/cm^{-1} 1745 and 1650; δ_H (300 MHz; $CDCl_3$) (the line-broadening of each signal occurred due to slow conformational exchange on the ^{1}H-NMR time scale) −0.28 (9 H × 58/100, br s), 0.09 (9 H × 42/100, br s), 1.60–2.05 (6 H, unresolved m), 2.15–2.88 (4 H, unresolved m), 3.707 (3 H × 42/100, s), 3.713 (3 H × 58/100, s), 4.47 (0.42 H, br s), 4.75 (0.58 H, br s), 4.88–5.18 (0.42 H, br), 5.20 (0.58 H, br s), 7.36–7.46 (3 H, m, ArH) and 7.47–7.55 (2 H, m, ArH).

Radical cyclisation of compound 16b

Following the general procedure, **16b** (202 mg, 0.46 mmol) was treated with Bu_3SnH (332 mg, 1.14 mmol) and AIBN (22 mg, 0.13 mmol) in toluene (45 cm^3) and the crude mixture was chromatographed on silica gel [hexane–AcOEt (20 : 1)]. The first fraction gave a mixture of (*E*) and (*Z*) geometrical isomers of 9-*benzoyl*-2-(*trimethylsilylmethylene*)-9-*azabicyclo*-[3.3.1]*nonane* **17b** (96 mg, 67%) as a colourless oil (Found: M$^+$, 313.1856. $C_{19}H_{27}NOSi$ requires *M*, 313.1862); ν_{max} (film)/cm^{-1} 1631; δ_H (400 MHz; $CDCl_3$) (because of the presence of mainly two rotamers for each geometrical isomer, the spectrum cannot be well analysed due to its complexity) −0.27, 0.10, 0.13 and 0.20 (total 9 H, all s, $SiMe_3$, in the proportions *ca.* 37 : 18 : 16 : 29, respectively), 1.22–2.26, 2.33–2.47, 2.56–2.64 and 2.74–2.90 (total 10 H, all m), 3.89–3.99 (m), 4.25 (br s), 4.53 (br s), 4.69–4.72 (m), 4.90–5.40 (m), 5.09–5.15 (br), 5.18 (br s), 5.30 (br s), 5.38 (br s), 5.43 (br s) and 5.55 (br s) (total 3 H) and 7.34–7.42 (5 H, m, ArH).

The second fraction gave 10b-[4-(*trimethylsilyl*)*but*-3-*ynyl*]-1,2,3,4,6,10b-*hexahydropyrido*[2,1-a]*isoindol*-6-*one* **20** (32 mg, 22%) as a colourless oil (Found: M$^+$, 311.1700. $C_{19}H_{25}NOSi$ requires *M*, 311.1705); ν_{max} (film)/cm^{-1} 2175 and 1693; δ_H (400 MHz; $CDCl_3$) (a mixture of mainly three rotamers in the proportions 75 : 21 : 4, for the major rotamer) 0.09 (9 H, s, $SiMe_3$), 1.25–1.39 (2 H, m), 1.47 (1 H, ddd, *J* 17.0, 11.2 and 5.1), 1.69–1.89 (5 H, m), 2.01 (1 H, ddd, *J* 14.3, 11.2 and 5.1), 2.15 (1 H, br d, *J* 13.4), 2.54 (1 H, ddd, *J* 14.3, 11.2 and 5.3), 2.89 (1 H, td, *J* 13.4 and 3.3), 4.42 (1 H, ddt, *J* 13.4, 5.1 and 1.3), 7.37 (1 H, dt, *J* 7.5 and 1.1, ArH), 7.44 (1 H, td, *J* 7.5 and 1.1, ArH), 7.54 (1 H, td, *J* 7.5 and 1.3, ArH) and 7.84 (1 H, dt, *J* 7.5 and 1.3, ArH).

Methyl 9-benzoyl-4-methylene-9-azabicyclo[3.3.1]nonane-1-carboxylate 18a

To a solution of **17a** (300 mg, 0.80 mmol) in DCM (5 cm_3) was added trifluoroacetic acid (226 mg, 1.98 mmol) at 0 °C and the whole was stirred for 15 min. The mixture was evaporated *in vacuo* and the residue was chromatographed on silica gel [hexane–AcOEt (20 : 1)] to give **18a** (172 mg, 72%), mp 113–114 °C (from hexane–AcOEt) (Found: C, 72.32; H, 7.05; N, 4.71. $C_{18}H_{21}NO_3$ requires C, 72.22; H, 7.07; N, 4.68%); ν_{max} (CCl_4)/cm^{-1} 1740 and 1650; δ_H (60 MHz; $CDCl_3$) 1.6–2.9 (10 H, m), 3.68 (3 H, s, OMe), 4.4–4.5 (1 H, m, 5-H), 4.50 and 4.78 (total 2 H, both br s, C=CH_2) and 7.2–7.7 (5 H, m, ArH).

Methyl 9-benzoyl-4-oxo-9-azabicyclo[3.3.1]nonane-1-carboxylate 19a

A stream of ozone-enriched oxygen was passed through a solution of **18a** (90 mg, 0.30 mmol) in DCM (5 cm^3) at −78 °C for 10 min. After purge of any unchanged excess of ozone by nitrogen flow, triphenylphosphine was added (87 mg, 0.33 mmol) to the reaction mixture, which was then stirred at room temperature for 15 min. The mixture was evaporated *in vacuo* and the residue was chromatographed on silica gel [hexane–AcOEt (10 : 1)] to give **19a** (54 mg, 60%), mp 149.5–150 °C (from hexane–AcOEt) (Found: C, 67.81; H, 6.16; N, 4.72. $C_{17}H_{19}NO_4$ requires C, 67.76; H, 6.36; N, 4.65%) (Found: M^+, 301.1309. $C_{17}H_{19}NO_4$ requires *M*, 301.1314); ν_{max} (film)/cm^{-1} 1732 and 1646; δ_H (400 MHz; $CDCl_3$) 1.45–1.59 (1 H, m), 1.76–1.93 (4 H, m), 2.01–2.09 (1 H, br), 2.26 (1 H, td, *J* 13.5 and 4.2), 2.43–2.62 (2 H, unresolved m), 3.13–3.39 (1 H, br), 3.76 (3 H, s, OMe), 4.32 (1 H, dd, *J* 6.2 and 3.7, 5-H), 7.39–7.44 (2 H, m, ArH) and 7.46–7.54 (3 H, m, ArH).

9-Benzoyl-2-methylene-9-azabicyclo[3.3.1]nonane 18b

Following the procedure described for the preparation of **18a**, **17b** (40 mg, 0.13 mmol) was treated with a solution of trifluoroacetic acid (41 mg, 0.36 mmol) in DCM (3 cm^3). The crude product was chromatographed on silica gel [hexane–AcOEt (7 : 1)] to give **18b** (22 mg, 70%) as a colourless oil (Found: M^+, 241.1465. $C_{16}H_{19}NO$ requires *M*, 241.1467); ν_{max} (film)/cm^{-1} 1628; δ_H (400 MHz; $CDCl_3$, for a mixture of two rotamers in a ratio of 1 : 1) 1.52–1.83 (5 H, m), 1.90–2.05 (2.5 H, m), 2.11–2.21 (0.5 H, m), 2.32–2.41 (1 H, m), 2.58–2.68 (1 H, m), 3.91–3.97 (0.5 H, unresolved m), 4.30 (0.5 H, br s), 4.54 (0.5 H, br s), 4.81 (0.5 H, br s), 4.92–4.99 (1.5 H, unresolved m), 5.35 (0.5 H, br s) and 7.37–7.42 (5 H, m, ArH).

9-Benzoyl-9-azabicyclo[3.3.1]nonan-2-one 19b

Following the procedure described for the preparation of **19a**, **18b** (22 mg, 0.09 mmol) was treated with ozone-enriched oxygen in DCM (5 cm^3) and then triphenylphosphine (20 mg, 0.08 mmol). The crude mixture was chromatographed on silica gel [hexane–AcOEt (10 : 1)] to give **19b** (17 mg, 78%), mp 87.5–88.5 °C (from hexane–AcOEt) (Found: M^+, 243.1256. $C_{15}H_{17}NO_2$ requires *M*, 243.1259); ν_{max} (KBr)/cm^{-1} 1729 and 1633; δ_H (400 MHz; $CDCl_3$) 1.49–1.84, 1.88–2.01 and 2.12–2.19 (total 7 H, all m), 2.35–2.69 (3 H, m), 4.17 (br s) and 4.25 (br d, *J* 9.5) (total 1 H), 5.14–5.21 (1 H, br) and 7.33–7.49 (5 H, m, ArH).

Radical cyclisation of compound 16c

Following the general procedure, **16c** (140 mg, 0.31 mmol) was treated with Bu_3SnH (203 mg, 0.70 mmol) and AIBN (14 mg, 0.09 mmol) in toluene (50 cm^3) and the crude mixture was chromatographed on silica gel [hexane–AcOEt (20 : 1)] to give a mixture of (*E*) and (*Z*) geometrical isomers (in a ratio of 1 : 1) of 9-*benzoyl*-1-*methyl*-4-(*trimethylsilylmethylene*)-9-*azabicyclo*-[3.3.1]*nonane* **17c** (96 mg, 95%) as a colourless oil (Found: M^+, 327.2021. $C_{20}H_{29}NOSi$ requires *M*, 327.2018); ν_{max} (film)/cm^{-1} 1651; δ_H (400 MHz; $CDCl_3$) −0.31 (9 H × 1/2, s), 0.08 (9 H × 1/2, s), 1.57–2.28 (8 H, m), 1.66 (3 H × 1/2, s), 1.70 (3 H × 1/2, s), 2.37–2.53 (1 H, m), 2.59–2.71 (0.5 H, m), 2.79–2.92 (0.5 H, m), 4.29 (0.5 H, br s), 4.61 (0.5 H, br s), 4.93 (0.5 H, br s), 5.14 (0.5 H, br s) and 7.32–7.53 (5 H, m, ArH).

9-Benzoyl-1-methyl-4-methylene-9-azabicyclo[3.3.1]nonane 18c

Following the procedure described for the preparation of **18a**, **17b** (310 mg, 0.95 mmol) was treated with trifluoroacetic acid (236 mg, 2.07 mmol) in DCM (5 cm^3) and the crude product was chromatographed on silica gel [hexane–AcOEt (20 : 1)] to give **18c** (215 mg, 89%) as a colourless oil (Found: M^+, 255.1630. $C_{17}H_{21}NO$ requires *M*, 255.1623); ν_{max} (film)/cm^{-1} 1648; δ_H (300 MHz; $CDCl_3$) 1.57–2.19 (7 H, m), 1.69 (3 H, s, 1-Me), 2.29–2.46 (2 H, m), 2.65–2.78 (1 H, m), 4.34–4.37 (1 H, unresolved m, 5-H), 4.47 (1 H, br s, alkenic), 4.73–4.76 (1 H, m, alkenic), 7.33–7.43 (3 H, m, ArH) and 7.47–7.51 (2 H, m, ArH); δ_C (75.5 MHz; $CDCl_3$) 19.7, 30.3, 31.1, 31.5, 37.0, 38.8, 55.2, 60.6, 109.2, 127.5, 128.3, 129.9, 138.5, 146.7 and 173.7.

9-Benzoyl-1-methyl-9-azabicyclo[3.3.1]nonan-4-one 19c

Following the procedure described for the preparation of **19a**, **18c** (263 mg, 1.03 mmol) was treated with ozone-enriched oxygen in DCM (5 cm^3) and then triphenylphosphine (278 mg, 1.06 mmol). The crude mixture was chromatographed on silica gel [hexane–AcOEt (10 : 1)] to give **19c** (189 mg, 71%), mp 56–57 °C (from hexane) (Found: M^+, 257.1414. $C_{16}H_{19}NO_2$ requires *M*, 257.1416); ν_{max} (KBr)/cm^{-1} 1724 and 1651; δ_H (300 MHz; $CDCl_3$) 1.44–2.05 (7 H, m), 1.83 (3 H, s, 1-Me), 2.38–2.52 (2 H, m), 2.61–2.73 (1 H, m), 4.19 (1 H, br t, *J* 4.0, 5-H) and 7.35–7.50 (5 H, m, ArH); δ_C (75.5 MHz; $CDCl_3$) 18.7, 28.1, 30.7, 31.6, 37.7, 40.9, 55.4, 65.8, 127.7, 128.7, 130.8, 136.9, 174.5 and 213.8.

9-Benzoyl-4α-hydroxy-1-methyl-9-azabicyclo[3.3.1]nonane 22

To a solution of **19c** (395 mg, 1.54 mmol) in methanol (7 cm^3) was added $NaBH_4$ (43 mg, 1.13 mmol) at room temperature and the whole was stirred for 5 min. 5% HCl (5 cm^3) was added to the mixture and the solution was extracted with AcOEt. The organic layer was dried and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (1 : 1)] to give **22** (324 mg, 81%), mp 155–156 °C (from AcOEt) (Found: M^+, 259.1565. $C_{16}H_{21}NO_2$ requires *M*, 259.1572); ν_{max} (film)/cm^{-1} 3388, 1645 and 1620; δ_H (300 MHz; $CDCl_3$) 1.54–1.80 (4 H, m), 1.61 (3 H, s, 1-Me), 1.85 (1 H, br s, OH), 1.92–2.15 (6 H, m), 3.81 (1 H, t, *J* 5.2), 3.95 (1 H, ddd, *J* 9.5, 7.5 and 5.2) and 7.33–7.50 (5 H, m, ArH); δ_C (75.5 MHz; $CDCl_3$) 20.5, 22.7, 30.1, 30.6, 36.9, 37.4, 54.8, 57.3, 69.9, 127.1, 128.5, 130.0, 138.4 and 173.9.

Dehydration of 22 with Martin sulfurane

To a solution of **22** (100 mg, 0.39 mmol) in benzene (10 cm^3) was added Martin sulfurane {bis[α,α-bis(trifluoromethyl)-phenylmethyloxy]diphenyl-λ^4-sulfane} (1.04 g, 1.54 mmol) and the solution was heated under reflux for 16 h. After cooling, the reaction mixture was diluted with saturated aq. $NaHCO_3$ and the organic phase was separated. The aqueous phase was extracted with diethyl ether, then the combined organic phase was washed with brine, dried ($MgSO_4$), and concentrated. The crude material was chromatographed on silica gel [hexane–AcOEt (15 : 1)]. The first fraction gave 9-*benzoyl*-1-*methyl*-9-*azabicyclo*[3.3.1]*non*-3-*ene* **23** (5 mg, 5%) as a colourless oil (Found: M^+, 241.1461. $C_{16}H_{19}NO$ requires *M*, 241.1467); ν_{max} (film)/cm^{-1} 1649; δ_H (400 MHz; $CDCl_3$) 1.39 (1 H, dtd, *J* 12.9, 4.3 and 2.4), 1.54–1.61 (2 H, m), 1.68 (3 H, s, 1-Me), 1.77 (1 H, dt, *J* 12.9 and 4.0), 1.83 (1 H, ddd, *J* 12.6, 4.3 and 1.6), 1.92 (1 H, tt, *J* 12.6 and 4.0), 2.03 (1 H, ddd, *J* 18.6, 4.3 and 1.9), 2.72

(1 H, br d, *J* 18.6), 4.33 (1 H, t like br s), 5.47 (1 H, dddd, *J* 9.8, 4.3, 2.4 and 1.9), 5.95 (1 H, dddd, *J* 9.8, 4.3, 3.1 and 0.7), 7.35–7.43 (3 H, m, ArH) and 7.51–7.54 (2 H, m, ArH); δ_C (100.5 MHz; $CDCl_3$) 17.4, 27.8, 30.5, 38.0, 41.6, 54.8 (CH), 55.0 (quaternary), 126.5, 127.5, 128.3, 129.1, 129.9, 138.4 and 173.7.

The second fraction gave 9-*benzoyl*-4β-[*bis*(*trifluoromethyl*)-*phenylmethoxy*]-1-*methyl*-9-*azabicyclo*[3.3.1]*nonane* **24** (106 mg, 57%) as a colourless oil (Found: M^+, 485.1787. $C_{25}H_{25}F_6NO_2$ requires *M*, 485.1789); ν_{max} (film)/cm^{-1} 1653; δ_H (300 MHz; $CDCl_3$) 1.50–1.82 (4 H, m), 1.57 (3 H, s, 1-Me), 1.92–2.32 (6 H, m), 3.89–4.01 (2 H, m) and 7.21–7.46 (10 H, m, ArH).

9-Benzoyl-4-(trifluoromethylsulfonyloxy)-1-methyl-9-azabicyclo[3.3.1]non-3-ene 25

To a solution of LDA [1.94 mmol, prepared from diisopropylamine (197 mg, 1.94 mmol) and a 1.6 mol dm^{-3} solution of butyllithium in hexane (1.25 cm^3, 1.94 mmol) at 0 °C] in THF (2 cm^3) was added dropwise a solution of **19c** (200 mg, 0.77 mmol) in THF (2 cm^3) and the whole was stirred at −78 °C for 1 h. To this mixture was added a solution of Comins' reagent {2-[*N,N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine} (458 mg, 1.17 mmol) at −20 °C and the reaction mixture was allowed to warm to room temperature overnight. After the mixture had been diluted with 5% HCl at 0 °C it was extracted with diethyl ether and the extract was washed successively with 5% aq. NaOH and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (15 : 1)]. The first fraction gave **25** (188 mg, 63%) as a colourless oil (Found: M^+, 389.0903. $C_{17}H_{18}F_3NO_4S$ requires *M*, 389.0908); [Found: $(M + H)^+$, 390.0983. $C_{17}H_{19}F_3NO_4S$ requires MH^+, 390.0987]; ν_{max} (film)/cm^{-1} 1660, 1419, 1211 and 1142; δ_H (400 MHz; $CDCl_3$) 1.61–1.75 (3 H, m), 1.69 (3 H, s, 1-Me), 1.77–1.92 (3 H, m), 2.21 (1 H, dd, *J* 18.5 and 4.9, one of 2-H_2), 2.94 (1 H, ddt, *J* 18.5, 3.1 and 1.5, one of 2-H_2), 4.37 (1 H, br s, 5-H), 5.98 (1 H, dd, *J* 4.9 and 3.1, 3-H), 7.34–7.49 (3 H, m, ArH) and 7.54–7.58 (2 H, m, ArH); δ_C (100.5 MHz; $CDCl_3$) 17.4 (CH_2), 25.3 (CH_2), 29.3 (1-Me), 35.8 (CH_2), 40.8 (CH_2), 54.1 (1-C), 56.2 (5-C), 119.2 (3-C), 127.9 (ArC), 128.5 (ArC), 131.0 (ArC), 136.6 (ArC), 145.5 (2-C) and 174.8 (C=O).

The second fraction gave the unchanged starting material **19c** (53mg, 27% recovery).

9-Benzoyl-1-methyl-9-azabicyclo[3.3.1]non-3-ene 23

To a solution of **25** (45 mg, 0.11 mmol) in acetonitrile (3 cm^3) were added borane–dimethylamine complex (7 mg, 0.11 mmol), tetrakis(triphenylphosphine)palladium(0) (7 mg, 5.8 μmol) and potassium carbonate (16 mg, 0.11 mmol) and the whole was heated at 40 °C for 1 h. After the solution had been diluted with diethyl ether (5 cm^3) and water (5 cm^3) the organic phase was separated and the aqueous phase was further extracted with diethyl ether. The combined organic phase was dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (15 : 1)] to give **23** (27 mg, 97%) as a colourless oil.

Hydroboration-oxidation of 23

To a solution of **23** (40 mg, 0.16 mmol) in THF (1 cm^3) was added a 0.9 mol dm^{-3} solution of borane–THF complex in THF (0.56 cm^3, 0.50 mmol) at 0 °C and the solution was stirred at room temperature for 2 h. After addition of 12% aq. NaOH and 30% H_2O_2 to it the whole was stirred at room temperature for 3 h. The mixture was diluted with diethyl ether (10 cm^3) and the organic phase was separated, washed successively with saturated aq. Na_2SO_3 and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (2 : 1)]. The first fraction gave 9-*benzoyl*-4β-*hydroxy*-1-*methyl*-9-*azabicyclo*[3.3.1]*nonane* **26** (13 mg, 31%), mp 136–137 °C (from hexane–AcOEt) (Found: C, 73.71; H, 8.30; N, 5.11. $C_{16}H_{21}NO_2$ requires C, 74.10; H, 8.16; N, 5.40); (Found: M^+, 259.1575. $C_{16}H_{21}NO_2$ requires *M*, 259.1572); ν_{max} (film)/cm^{-1} 3399, 1639 and 1624; δ_H (400 MHz; $CDCl_3$, OH was not observed) 1.48–2.10 (8 H, m), 1.58 (3 H, s, 1-Me), 2.25–2.38 (2 H, m), 3.75–3.78 (1 H, unresolved m), 3.99–4.03 (1 H, unresolved m), 7.33–7.41 (3 H, m, ArH) and 7.52–7.56 (2 H, m, ArH); δ_C (100.5 MHz; $CDCl_3$) 19.5, 25.9, 29.3, 31.3, 32.1, 38.5, 55.1, 58.9, 69.9, 127.7, 128.3, 129.8, 138.9 and 175.1.

The second fraction gave 9-*benzoyl*-3β-*hydroxy*-1-*methyl*-9-*azabicyclo*[3.3.1]*nonane* **27** (16 mg, 39%), mp 167–68 °C (from hexane–AcOEt) (Found: C, 73.91; H, 8.17; N, 5.29%) (Found: M^+, 259.1562); ν_{max} (film)/cm^{-1} 3399, 1645 and 1623; δ_H (400 MHz; $CDCl_3$, OH was not observed) 1.50–1.68 (3 H, m), 1.68 (3 H, s, 1-Me), 1.69–1.81 (3 H, m), 1.86 (1 H, ddd, *J* 13.3, 11.0 and 2.3), 1.94 (1 H, ddt, *J* 13.3, 6.4 and 1.8), 1.97–2.07 (1 H, m), 2.03 (1 H, ddd, *J* 13.3, 6.4 and 1.5), 4.04–4.08 (1 H, unresolved m), 4.62 (1 H, tt, *J* 11.0 and 6.4), 7.36–7.42 (3 H, m, ArH) and 7.49–7.53 (2 H, m, ArH); δ_C (100.5 MHz; $CDCl_3$) 21.1, 29.5, 31.0, 37.1, 39.9, 47.8, 54.0, 56.4, 64.8, 127.1, 128.5, 130.0, 138.4 and 173.5.

Dehydration of 26 with Martin sulfurane

Following the procedure described for the dehydration of **22**, **26** (9 mg, 34 μmol) was treated with a solution of Martin sulfurane (93 mg, 138 μmol) in benzene (5 cm^3) and the crude product was purified by column chromatography on silica gel [hexane–AcOEt (15 : 1)] to give **23** (7 mg, 85%).

9-Benzoyl-1-methyl-9-azabicyclo[3.3.1]nonan-3-one 28

To a solution of **27** (9 mg, 34 μmol) in DCM (3 cm^3) containing molecular sieves 4Å (10 mg) were added TPAP (2.4 mg, 6.8 μmol) and NMO (8.1 mg, 69 μmol) at room temperature and the whole was stirred for 15 min. After filtration of the insoluble material using AcOEt the filtrate was concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (2 : 1)] to give **28** (9 mg, quant.) as a colourless oil (Found: M^+, 257.1412. $C_{16}H_{19}NO_2$ requires *M*, 257.1416); ν_{max} (film)/cm^{-1} 1711 and 1650; δ_H (400 MHz; $CDCl_3$) 1.55–1.75 (4 H, m), 1.74 (3 H, s, 1-Me), 1.83–1.99 (2 H, m), 2.27 (1 H, dt, *J* 16.3 and 1.5), 2.42 (1 H, dd, *J* 16.3 and 1.8), 2.47 (1 H, dd, *J* 16.3 and 7.0), 2.96 (1 H, br d, *J* 16.3), 4.35–4.39 (1 H, unresolved m, 5-H), 7.40–7.51 (3 H, m, ArH) and 7.58–7.61 (2 H, m, ArH); δ_C (100.5 MHz; $CDCl_3$) 17.8, 29.6, 30.6, 39.4, 45.2, 51.8, 54.2, 57.2, 127.7, 128.7, 130.9, 137.3, 174.7 and 209.2.

Oxidation of alcohol 26 to 19c

Following the procedure described for the preparation of **28**, **26** (3.3 mg, 12.7 μmol) was treated with TPAP (1.3 mg, 3.60 μmol) and NMO (3.0 mg, 25.4 μmol) and the crude material was chromatographed on silica gel [hexane–AcOEt (10 : 1)] to give **19c** (3.1 mg, 95%).

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