Reactions of ethyl 2-acetyl-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate and 4-acetylamino-2-oxabicyclo[3.3.0]oct-7-en-3-one with some electrophiles

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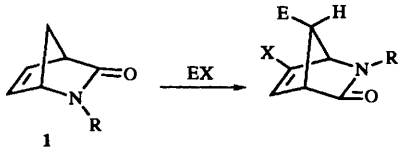
The amide **3** reacted with various electrophilic reagents to give the addition products **5–9**; reaction of **3** with *m*-chloroperoxybenzoic acid (MCPBA) gave the epoxide **10**; similarly, the lactone **4** (an isomer of **3**) reacted extremely selectively with a variety of electrophiles to give a range of polyfunctionalised bicyclic systems **12–15**: reaction with MCPBA gave the epoxide **16** as the major product.

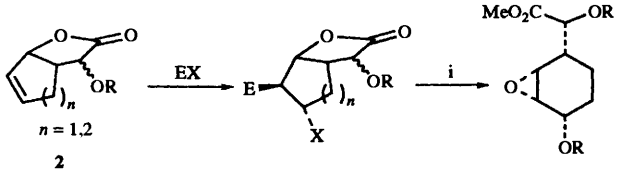
Introduction and background information

We have described the reactions of *N*-protected γ-lactams **1** with electrophilic reagents E^+X^- (Scheme 1).[1]



Scheme 1

In addition, the products obtained on treating the lactones **2** with EX (*e.g.* BrOH) and further transformation of the initially formed adducts (Scheme 2) have been reported.[2]



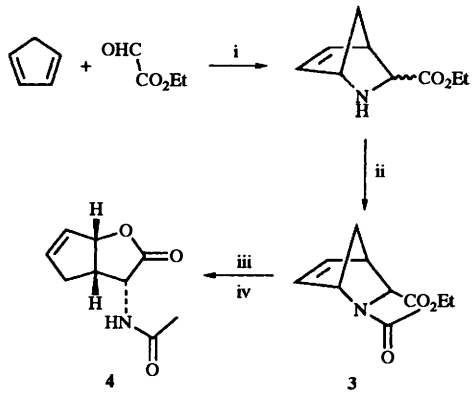
Scheme 2 *Reagents and conditions:* i, OMe^- on compound E = Br, X = OR, *n* = 2

Given the ready availability of the amide **3** and the lactone **4** by the pre-recorded chemistry outlined in Scheme 3,[3] we felt that it would be interesting to further functionalise these potentially useful synthons through controlled reactions at the alkene units.

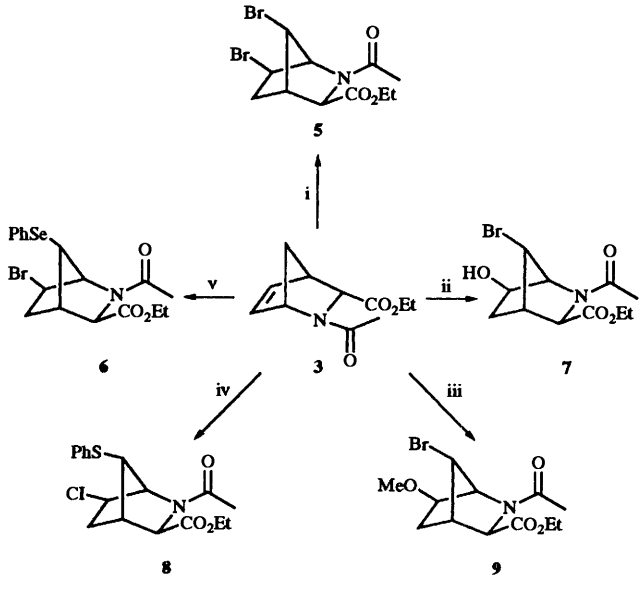
Results and discussion

The lactam **3** undergoes rearrangement on treatment with a range of electrophilic reagents (Scheme 4). Thus, bromination of the bicyclic compound **3** afforded the dihalogeno compound **5** which proved to be unstable to chromatography. The structure of the product was elucidated by NMR spectroscopy, including NOE measurements (see Experimental section). The mechanism of the rearrangement is detailed in Scheme 5 and closely resembles the pathway proposed by Snider[4] for similar transformations involving the lactam **1**.

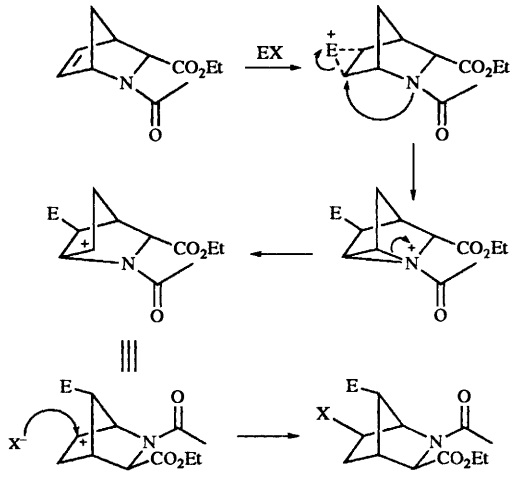
It is interesting to note that the ethoxycarbonyl group, initially on the *endo*-face of the bicyclic lactam, assumes an *exo*-configuration in the product.



Scheme 3 *Reagents and conditions:* i, NH_4Cl, 7 h, room temp.; ii, NEt_3, Ac_2O, CH_2Cl_2, room temp., 12 h, chromatography; iii, NaOH, EtOH–H_2O (2:1), 12 h, room temp.; iv, CF_3CO_2H, 0 °C, 10 min

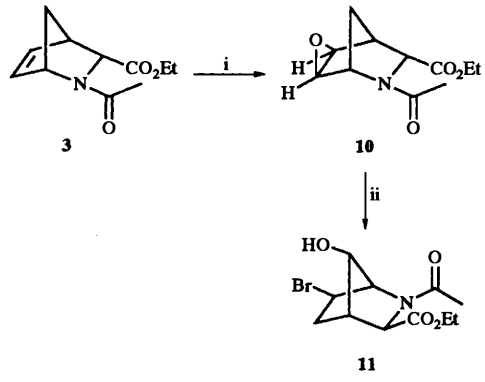


Scheme 4 *Reagents and conditions:* i, Br_2, CH_2Cl_2, room temp., 16 h (40%); ii, *N*-bromoacetamide, acetone, water, room temp., 16 h (75%); iii, 1,3-dibromo-5,5-dimethylhydantoin, MeOH, 0 °C→room temp., 16 h (70%); iv, PhSCl, MeCN, 0 °C→room temp. (100%); v, PhSeBr, tetrahydrofuran, −78 °C→room temp. (60%)



Scheme 5

Reaction of the azabicycloheptane **3** with *N*-bromoacetamide in aqueous acetone furnished a good yield of the bromohydrin **7**. Note that an isomeric bromohydrin was produced by a two-step process *via* treatment of **3** with *m*-chloroperoxybenzoic acid to give the epoxide **10** (Scheme 6) which on subsequent reaction with hydrobromic acid in water gave the expected product **11** (Scheme 6).



Scheme 6 *Reagents and conditions:* i, *m*-chloroperoxybenzoic acid, CH_2Cl_2, 0 °C→35 °C, 16 h (57%); ii, 48% HBr, water, room temp., 16 h (50%)

Bromination of the lactam **3** in the presence of methanol gave the halogeno ether **9** which was characterised by X-ray crystallography. The molecular structure of **9** together with the crystallographic numbering scheme is shown in Fig. 1. The geometry parameters are as expected for this type of compound, with the nitrogen atom showing only small pyramidal distortion [sum of the inter-bond angles = 358.2(2)°]. Of the two C=O bond distances, one [C(7)–O(1) = 1.227(4) Å] is slightly longer than the other [C(10)–O(3) = 1.195(4) Å], probably caused by the involvement of O(1) in the intermolecular hydrogen bonding [C(5)–H(5)···O(1) at $(-0.5 + x, 0.5 - y, 1 - z)$, C–H = 0.91, H···O = 2.29, C···O = 3.18 Å, <C–H–O = 170.1°; C(12)–H(12)···O(1) at $(1.5 - x, 0.5 + y, z)$, C–H = 1.01, H···O = 2.32, C···O = 3.19 Å, <C–H–O = 142.9°].

Electrophiles other than Br^+ can be employed to promote these rearrangements as exemplified by reaction of the amide **3** with benzenesulfenyl chloride and benzeneselenenyl bromide which gave the halides **8** and **6**, respectively, in good to excellent yield.

A complementary selection of reactions was carried out on

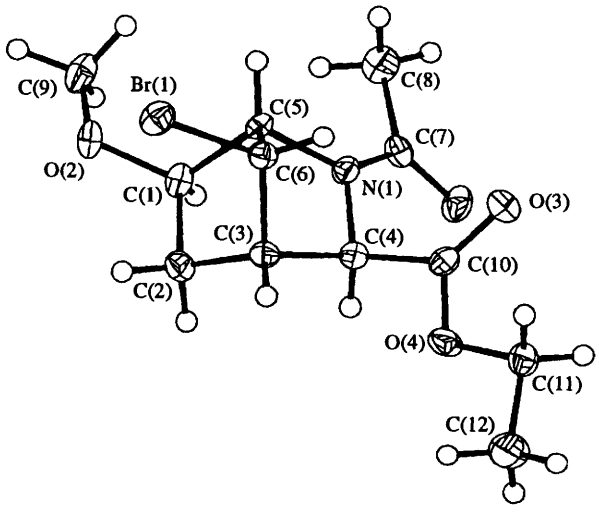
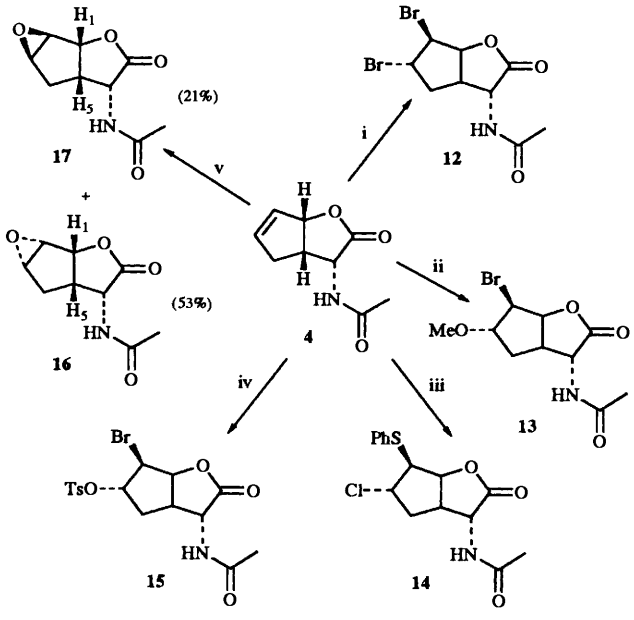


Fig. 1. The X-ray structure of compound **9** showing the numbering of the non-hydrogen atoms



Scheme 7 *Reagents and conditions:* i, Br_2, CH_2Cl_2, 0 °C→room temp. (90%); ii, 1,3-dibromo-5,5-dimethylhydantoin, MeOH, 0 °C→room temp. (66%); iii, PhSCl, MeCN, room temp., 16 h (100%); iv, NBS, *p*-TsOH, CH_2Cl_2, 0 °C room temp. (68%); v, *m*-chloroperbenzoic acid, CH_2Cl_2, 0 °C→35 °C, 16 h

the lactone **4** (Scheme 7). Thus, bromination of **4** in an inert solvent gave the dibromide **12** while treatment of the lactone with dibromodimethylhydantoin in methanol gave the bromomethoxy compound **13** clearly showing bromonium ion formation on the *exo*-face of the molecule and attack by the attendant nucleophile at the less-hindered position (Fig. 2).

The reactions of benzenesulfenyl chloride and *N*-bromosuccinimide–toluene-*p*-sulfonic acid with the lactone **4** proceed as expected to give the addition compounds **14** and **15**, respectively.

Oxidation of the lactone **4** with *m*-chloroperoxybenzoic acid gave a mixture of two compounds in the ratio 5:2 which were separated by chromatography. The structure of the major compound was elucidated by X-ray crystallography and proved to be the *endo*-epoxide **16**. The molecular structure of **16** together with the crystallographic numbering scheme is shown in Fig. 3. The bond lengths and angles are as expected and, as in

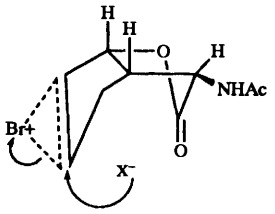


Fig. 2

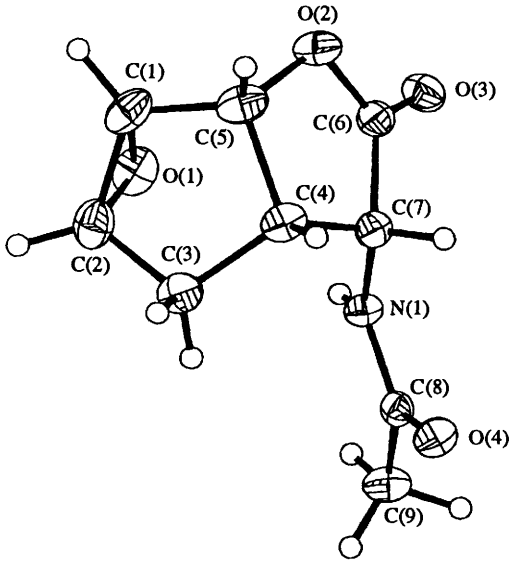


Fig. 3 The X-ray structure of **16** showing the numbering of the non-hydrogen atoms

9, the carbonyl bond [C(8)–O(4) = 1.233(2) Å] involved in the intermolecular hydrogen bonding [N(1)–H(1)···O(4) at (0.5 − *x*, −0.5 + *y*, *z*), N–H = 0.84, H···O = 2.04, N···O = 2.87 Å, N–H···O = 172.4°] shows a slight lengthening compared with the other carbonyl bond [C(6)–O(3) = 1.206(2) Å].

This result was surprising since the lactone **2** (*n* = 1, R = H) gave the *exo*-epoxide as the major product (72%) with the *endo*-isomer as a side product (13%) under very similar reaction conditions. Obviously for compound **4** the peracid is led to the hindered face of the bicyclic system by favourable interactions with the lactone and/or the amide moiety.

In general, the amide **3** and the lactone **4** react with electrophilic reagents in a highly selective manner to give polysubstituted and polyfunctional bicyclic systems.

Experimental

General

All starting materials were obtained from commercial suppliers (Aldrich, Lancaster) and were used without further purification unless otherwise stated. All deuteriated solvents were obtained from Nuclear Magnetic Resonance Limited. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl prior to use. Dry dichloromethane (CH_2Cl_2) was obtained by distillation from calcium hydride. Ethyl acetate and light petroleum (bp 40–60 °C LP) were distilled prior to use. Dry 1,2-dichloroethane and dry dioxane were obtained dry from Aldrich and stored over 4 Å molecular sieves. Dry pyridine was obtained by distillation from barium oxide and stored over 4 Å molecular sieves. Methanol was dried over magnesium and iodine and stored over 4 Å molecular sieves. Triethylamine was dried and stored over potassium hydroxide. Ether refers to diethyl ether. All aqueous inorganic reagents were previously prepared to the stated concentration or as a saturated aqueous (satd., aq.) solution. Brine is saturated aqueous sodium chloride. The only drying agent used was magnesium sulfate. All filtrations were carried out through Celite. Flash chromatography was carried out using silica gel 60H (Merck 7385). Thin layer chromatography (TLC) was performed on Merck 60F-254 (0.25 mm thickness, Art. 5715) glass backed plates with visualisation by UV light (254 nm) and *p*-anisaldehyde unless otherwise stated. All mps are uncorrected. IR spectra were recorded on a Perkin-Elmer 880 Grating spectrophotometer or a Nicolet 550 FT Magna-IR spectrometer. The spectra were recorded as solutions in chloroform, as films on sodium chloride plates or as solids in potassium bromide discs. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC300 spectrometer at 300 MHz for ^1H and 75.5 MHz for ^{13}C. Chemical shifts are reported in ppm relative to trimethylsilane as the internal standard. All spectra are recorded as solutions in deuteriochloroform, deuterium oxide, [$^2H_6$]dimethyl sulfoxide or [$^2H_6$]benzene. Coupling constants (*J*) are reported in Hz. The numbering system used in all cyclic compounds is applied to the assignment of positions around the ring in the NMR spectra, in accordance with the literature. Mass spectra and high-resolution mass spectra were obtained from a Kratos Profile HV3 instrument and were recorded under electron-impact (EI) or chemical-ionisation (CI) conditions. X-Ray crystallographic studies were performed at the SERC School of Chemistry and Applied Chemistry at Cardiff.

Preparation of ethyl glyoxylate

A solution of diethyl L-(+)-tartrate (82.5 g) in water (400 cm^3) was stirred at 0 °C whilst sodium metaperiodate (112.2 g) was added to it over a period of 15 min to give a white precipitate. The reaction mixture was filtered, washed with water (30 cm^3) and concentrated under reduced pressure. The residue was washed with CH_2Cl_2 (~200 cm^3) and the white precipitate again filtered off. The filtrate was dried $MgSO_4$, filtered and concentrated under reduced pressure to give ethyl glyoxylate in 66% yield.

Preparation of ethyl 2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate

A solution of cyclopenta-1,3-diene (92.2 cm^3) and ethyl glyoxylate (63.79 g) in saturated aqueous ammonium chloride (310 cm^3) was stirred at room temperature under an atmosphere of nitrogen (N_2) for 7 h after which it was extracted with ether to remove excess of starting material. The ether layer was discarded and the aqueous layer was adjusted to pH 9 with sodium hydrogen carbonate ($NaHCO_3$) (satd., aq.) and 4 mol dm^{-3} aq. NaOH and extracted with CH_2Cl_2. The extract was dried, filtered and concentrated under reduced pressure to give the title compound as a crude, unstable orange-coloured oil (60.86 g, 69%); ν_{max}(NaCl)/cm^{-1} 3000 (NH) and 1730 (CO_2Et); δ_H(300 MHz; $CDCl_3$) 6.40–6.32 (1 H, m, 6-H), 5.92–5.82 (1 H, m, 5-H), 4.12 (2 H, q, *J* 7.2, CH_2 ester), 4.01 (1 H, br s, 1-H), 3.95 (1 H, d, *J* 3.5, 3-H), 3.50 (1 H, br s, 4-H), 1.72 (1 H, br s, NH), 1.65 (1 H, d, *J* 8.8, *anti*-7-H), 1.45 (1 H, d, *J* 8.8, *syn*-7-H) and 1.25 (3 H, t, *J* 7.2, CH_3 ester); δ_C(75.5 MHz; $CDCl_3$) 173.87 (C=O), 136.60, 129.85 (2 × CH, C-6 and C-5), 61.05 (CH, C-1) 60.89 (CH_2 ester), 57.38 (CH, C-3), 49.58 (CH_2, C-7), 48.08 (CH, C-4) and 14.24 (CH_3 ester).

Preparation of ethyl 2-acetyl-2-azabicyclo[2.2.1]hept-5-ene-3-*endo*-carboxylate 3

The above ester (60.86 g) was dissolved in CH_2Cl_2 (375 cm^3) at room temperature and triethylamine (55.81 cm^3) was added to

the solution which was then cooled to 0 °C. After slow addition of acetic anhydride (41.23 cm^3) to the reaction mixture it was stirred for 24 h at room temperature, after which time all the starting material had been consumed. The mixture was partitioned between CH_2Cl_2 and water and the organic layer was separated, washed with aqueous $NaHCO_3$, dried, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography [ethyl acetate–LP (2:1 ⟶ 7:1)] to give two products as dark red oils in the ratio 13:2. The products were assigned to be ethyl 2-acetyl-2-azabicyclo[2.2.1]hept-5-ene-3-*exo*-carboxylate (7.93 g, 10%) and ethyl 2-acetyl-2-azabicyclo[2.2.1]hept-5-ene-3-*endo*-carboxylate **3** (49.98 g, 66%).

3-*exo*-Carboxylate. R_F [EtOAc–LP (2:1) SiO_2] 0.185; ν_{max}($CHCl_3$)/cm^{-1} 1744 (CO_2Et), 1647 and 1413 (C=O); δ_H(300 MHz; $CDCl_3$) 6.40 (2 H, m, 5-H and 6-H), 4.70 (1 H, br s, 1-H), 4.20 (2 H, q, *J* 7.9, CH_2 ester), 3.70 (1 H, s, 3-H), 3.30 (1 H, br s, 4-H), 2.15 (1 H, d, *J* 9.5, *anti*-7-H), 1.60 (1 H, d, *J* 9.5, *syn*-7-H) and 2.25 (3 H, t, *J* 7.9, CH_3 ester); δ_C(75.5 MHz; $CDCl_3$) 170.82, 169.49 (2 × C=O), 138.15 (CH, C-6), 135.25 (CH, C-5), 62.78 (CH, C-3), 61.24 (CH_2 ester), 58.25 (CH, C-1), 47.81 (CH, C-4), 46.11 (CH_2, C-7), 21.83, (CH_3 amide) and 14.17 (CH_3 ester) (Found: $[M]^+$, 209.104 99. $C_{11}H_{15}NO_2$ requires *m*/*z*, 209.105 19).

3-*endo*-Carboxylate. R_F [EtOAc–LP (7:1) SiO_2] 0.09. ν_{max}($CHCl_3$)/cm^{-1} 1750 (CO_2Et), 1647 and 1421 (C=O); δ_H[300 MHz; $(CD_3)_2SO$] 6.42–6.36 (1 H, m, 6-H), 6.10–6.00 (1 H, m, 5-H), 4.76 (1 H, br s, 1-H), 4.28 (1 H, d, *J* 2.4, 3-H), 4.12–3.97 (2 H, m, CH_2 ester), 3.40 (1 H, br s, 4-H), 2.0 (3 H, br s, CH_3 amide), 1.66 (1 H, q, *J* 9.5, *anti*-7-H), 1.57 (1 H, q, *J* 7.2, *syn*-7-H) and 1.15 (3 H, t, *J* 7.5, CH_3 ester); δ_C[75.5 MHz; $(CD_3)_2SO$] 169.21, 167.38 (2 × C=O), 135.32, (CH, C-6), 134.70 (CH, C-5), 63.62 (CH, C-3), 61.02 (CH_2 ester), 57.36 (CH, C-1), 49.88 (CH_2, C-7), 46.73 (CH, C-4), 21.79 (CH_3 amide) and 14.04 (CH_3 ester) (Found: $[M]^+$, 209.104 99. $C_{11}H_{15}NO_3$ requires *m*/*z*, 209.105 19).

Preparation of sodium 2-acetyl-2-azabicyclo[2.2.1]hept-5-ene-3-*endo*-carboxylate

Sodium hydroxide (0.97 g) was added to a solution of the ester **3** (5.0 g) dissolved in ethanol–water (2:1; 60 cm^3) at room temperature; the reaction mixture was stirred at room temperature for 24 h. It was then concentrated under reduced pressure and the product partitioned between water (50 cm^3) and Et_2O (50 cm^3). The aqueous layer was separated and evaporated under reduced pressure to give crude title compound (5.70 g, quant); ν_{max}(KBr)/cm^{-1} 1610 and 1466–1404 (CO_2^-); δ_H(300 MHz; D_2O) 6.47 (1 H, d, *J* 3.0, 6-H), 6.30 (1 H, 2dd, $J_{5,6}$ 3.0, $J_{5,4}$ 1.0, 5-H), 4.30 (1 H, br s, 1-H), 3.95 (1 H, d, *J* 3.2, 3-H), 3.60 (1 H, br s, 4-H), 2.05 (3 H, br s, CH_3 amide) and 1.72 (2 H, m, *anti*- and *syn*-7-H) (Found: $[M - 23]^+$, 180.066 032. $C_9H_{10}NO_3$ requires *m*/*z*, 180.066 068).

Preparation of 4-*endo*-acetylamino-2-oxabicyclo[3.3.0]oct-7-en-3-one 4

The crude sodium carboxylate (above) (100 mg) was cooled to 0 °C and trifluoracetic acid (TFA) (2.0 ml) also cooled to 0 °C was added dropwise to it over a 5 min period. The reaction mixture was stirred for 10 min at 0 °C after which the TFA was removed under reduced pressure. The residue was then partitioned between CH_2Cl_2 and aqueous $NaHCO_3$, and the organic layer separated, washed with water, dried and concentrated under reduced pressure. The residue, a crude mixture of *endo*:*exo* isomers (20:1) was separated by flash chromatography [ethyl acetate–LP (7:1)]. Compound **4** (55 mg, 64%) was obtained as a pale-yellow fluffy solid mp 166.5–167 °C, R_F [EtOAc–LP (7:1) SiO_2] 0.26; ν_{max}(KBr)/cm^{-1} 3282 (NH amide), 1759 (lactone), 1639 and 1543; δ_H(300 MHz; $CDCl_3$) 6.22 (1 H, 2 t, *J* 2.5, 8-H) 6.11 (1 H, br s, NH), 6.00–5.90 (1 H, m, 7-H), 5.40 (1 H, 2 t, *J* 2.0, 4-H), 4.78 (1 H, 2d, *J* 4.8, 1-H), 3.52 (1 H, m, 5-H), 2.47 and 2.31 (2 × 1 H, m, *exo*- and *endo*-6-H) and 2.08 (3 H, br s, CH_3 amide); δ_C(75.5 MHz; $CDCl_3$) 170.48 (O–C=O), 140.57, (CH, C-8), 127.70 (CH, C-7), 87.30 (CH, C-4), 52.87 (CH, C-1), 40.51 (CH, C-5), 32.04 (CH_2, C-6) and 22.71 (CH_3 amide) (Found: $[M]^+$, 181.074 44. $C_9H_{11}NO_3$ requires *m*/*z*, 181.073 89).

Preparation of ethyl 2-acetyl-6-*exo*,7-*anti*-dibromo-2-azabicyclo[2.2.1]heptane-3-*endo*-carboxylate 5

A solution of bromine (0.08 cm^3) in dry CH_2Cl_2 (1.5 cm^3) was added dropwise over a 3 min period to a stirred solution of the ester **3** (200 mg) in dry CH_2Cl_2 (2.0 cm^3) and acetic acid (0.5 cm^3). The reaction mixture was stirred for 24 h at room temperature, after which time all starting material had been consumed. The solution was diluted with CH_2Cl_2 and washed with 10% aq. Na_2SO_3, $NaHCO_3$ (satd. aq.) and brine. The organic layer was dried, filtered and concentrated, and the residue purified by flash chromatography [ethyl acetate–LP (7:3)] to give a brown solid. This was recrystallised from C_6D_6 to give yellow–brown crystals of compound **5** (140 mg, 40 %), mp 150–151 °C, R_F [EtOAc–LP (7:3), SiO_2] 0.5; ν_{max}(NaCl)/cm^{-1} 1733 (CO_2Et), 1655 (lactam) and 1411 (C=O amide); δ_H(300 MHz; $CDCl_3$) 4.62–4.59 (1 H, m, *syn*-7-H), 3.96–3.86 (3 H, m, 1-H and CH_2 ester), 3.68 (1 H, br s, 3-H), 3.25–3.19 (1 H, m, 6-H), 2.44–2.36 (1 H, m, *exo*-5-H), 2.36–2.30 (1 H, m, 4-H), 1.71–1.61 (1 H, m, *endo*-5-H), 1.51 (3 H, br s, CH_3 amide) and 0.85 (3 H, t, *J* 7.5, CH_3 ester); δ_C(75.5 MHz; $CDCl_3$) 169.44, 166.84 (2 × C=O), 65.38 (CH, C-1), 61.61 (CH_2 ester), 60.85 (CH, C-3), 48.83 (CH, C-4), 45.52 (CH, C-7), 42.95 (CH, C-6), 39.21 (CH_2, C-5), 21.48 (CH_3 amide) and 14.09 (CH_3 ester); major NOE enhancements: 7-H! [H-1 (4.9 %), 4-H (4.9 %)], 4.8 6-H! [*exo*-5-H (4.8 %), 1-H (4.0 %)] and 3-H! [*exo*-5-H (3.6%)] (Found: $[M]^+$, 366.942 20, 368.940 17, 370.937 93. $C_{11}H_{15}Br_2NO_3$ requires *m*/*z*, 366.941 87, 368.939 95, 370.938 03).

Preparation of ethyl 2-acetyl-7-*anti*-bromo-6-*exo*-hydroxy-2-azabicyclo[2.2.1]heptane-3-*endo*-carboxylate 7

N-Bromoacetamide (NBA) (188 mg) was added in small portions to a stirred solution of the ester **3** (200 mg) in acetone–water (4:1; 5 cm^3). The reaction mixture was stirred at this temperature for 24 h, after which time all starting material had been consumed. The solution was diluted with brine and extracted with EtOAc and the extract was washed with 10% aqueous Na_2SO_3 and brine, dried, filtered, and concentrated under reduced pressure. No further purification was necessary. The product was identified as compound **7** (220 mg, 75%), mp 184.5–188 °C, R_F [EtOAc–LP (1:1), SiO_2] 0.37; ν_{max}(NaCl)/cm^{-1} 3450 (OH), 2975, 1760 (CO_2Et) and 1640; δ_H(300 MHz; $CDCl_3$) 4.55 (1 H, br s, 7-H), 4.25 (1 H, d, *J* 1.2, 1-H), 4.20 (2 H, q, *J* 7.5, CH_2 ester), 4.0–3.90 (1 H, m, 6-H), 3.87 (1 H, s, 3-H), 2.87 (1 H, br d, *J* 2.5, 4-H, 2.30–2.20 (1 H, m, *endo*-5-H), 2.12 (3 H, s, CH_3 amide), 2.12–1.98 (1 H, m, *exo*-5-H) and 1.30 (3 H, t, *J* 7.5, CH_3 ester); δ_C(75.5 MHz; $CDCl_3$) 169.47, 168.24 (2 × C=O), 74.47 (CH, C-6), 64.75 (CH, C-1), 61.73 (CH_2 ester), 60.87 (CH, C-3), 46.94 (CH, C-4), 46.25 (CH, C-7), 38.80 (CH_2, C-5), 21.87 (CH_3 amide) and 14.03 (CH_3 ester) (Found: $[M]^+$, 305.026 74, 307.022 62. $C_{11}H_{16}BrNO_4$ requires *m*/*z*, 305.026 27, 307.024 35).

Preparation of ethyl 2-acetyl-5,6-*exo*-epoxy-2-azabicyclo-[2.2.1]heptane-3-*endo*-carboxylate 10

Chloroperoxybenzoic acid (346 mg) and the ester **3** (200 mg) were dissolved in dry CH_2Cl_2 (5.0 cm^3) at 0 °C under an atmosphere of N_2. The reaction mixture was allowed to warm to room temperature and stirred at this temperature for 24 h, after which time all starting material had been consumed. The

solution was diluted with CH_2Cl_2 and washed with 10% aqueous Na_2SO_3 and water. The aqueous layers were combined and washed with CH_2Cl_2; the combined organic layers were dried, filtered and concentrated under reduced pressure. The residue was diluted with CH_2Cl_2 and shaken with solid $NaHCO_3$ in order to remove aromatic acid by-products. Filtration and evaporation of the solvent gave the product which was identified as compound **10** (123 mg, 57%); R_F [EtOAc–LP (10:1), SiO_2] 0.68; ν_{max}(NaCl)/cm^{-1} 2975, 1745 (CO_2Et) and 1660; δ_H(300 MHz; C_6D_6) 4.17 (1 H, d, *J* 3.5, 3-H), 3.96 (2 H, q, *J* 7.0, CH_2 ester), 3.41 (1 H, br s, 1-H), 3.12 (1 H, br d, *J* 3.9, 6-H), 3.00 (1 H, br d, *J* 3.6, 5-H), 2.44 (1 H, br d, *J* 3.5, 4-H), 1.60 (3 H, s, CH_3 amide), 1.36 (1 H, br d, *J* 10.1, *anti*-7-H), 0.95 (3 H, t, *J* 7.0, CH_3 ester) and 0.42 (1 H, d, *J* 10.1, *syn*-7-H); δ_C(75.5 MHz; C_6D_6), 168.65, 167.48 (2 × C=O), 61.05 (CH_2 ester), 60.42 and 60.03 (2 × CH, C-5 and C-6), 49.54 (CH, C-1), 47.98 (CH, C-3), 40.55 (CH, C-4), 27.33 (CH_2, C-7), 21.36 (CH_3 amide) and 14.22 (CH_3 ester). Major NOE enhancements: *syn*-7-H! [2-H (3.2%), 1-H (2.2%), 4-H (1.9%)], *anti*-7-H-[H-1 (2.0%) and 4-H (1.5%)] (Found: $[M]^+$, 225.101 29. $C_{11}H_{15}NO_4$ requires *m/z*, 225.100 11).

Preparation of ethyl 2-acetyl-6-*exo*-bromo-7-*anti*-hydroxy-2-azabicyclo[2.2.1]heptane-3-*endo*-carboxylate 11

Hydrogen bromide (48% in water, 41 cm^3) was cooled to 0 °C in an ice–salt bath and then added very slowly in small portions to the epoxy ester **7** (50 mg). The reaction mixture was allowed to warm to room temperature and then stirred at this temperature for 1 h. The solution was diluted with Et_2O and solid anhydrous Na_2CO_3 (~8 g) was added to it. After being swirled the solution was saturated with solid Na_2SO_3 (~8 g) and further swirled. It was then filtered and the filter cake washed with Et_2O. The aqueous layer was then extracted with Et_2O and the extract washed with Na_2SO_3 (satd., aq.), dried, filtered and concentrated under reduced pressure. The residue was flash chromatographed [ethyl acetate–LP (10:1)] to give compound **11** (10 mg, 50%); R_F [EtOAc–LP (10:1), SiO_2] 0.20; ν_{max}(NaCl)/cm^{-1} 3450 (OH), 1760 (CO_2Et) and 1640 (3° amide); δ_H(300 MHz; $CDCl_3$) 4.65 (1 H, br s, 7-H), 4.40–4.30 (1 H, m, 1-H), 4.30–4.15 (2 H, m, CH_2 ester), 4.0–3.90 (1 H, m, 6-H), 3.90 (1 H, s, 3-H), 2.70 (1 H, br d, *J* 3.0, 4-H), 2.65–2.50 (1 H, m, *endo*-5-H), 2.50–2.45 (1 H, m, *exo*-5-H), 2.15 (3 H, s, CH_3 amide) and 0.95 (3 H, t, *J* 8, CH_3 ester); δ_C(75.5 MHz; $CDCl_3$) 169.46, 167.95 (2 × C=O), 73.98 (CH, C-6), 64.24 (CH, C-1), 61.02 (CH_2 ester), 60.85 (CH, C-3), 47.85 (CH, C-7), 46.85 (CH, C-4), 38.79 (CH_2, C-5), 21.87 (CH_3 amide) and 14.05 (CH_3 ester) (Found: $[M]^+$, 305.026 58. $C_{11}H_{16}BrNO_4$ requires *m/z*, 305.026 27).

Preparation of ethyl 2-acetyl-7-*anti*-bromo-6-*exo*-methoxy-2-azabicyclo[2.2.1]heptane-3-*endo*-carboxylate 9

1,3-Dibromo-5,5-dimethylhydantoin (683 mg) was added in small portions to a stirred solution of the ester **3** (500 mg) in methanol (15 cm^3) at 0 °C. The reaction mixture was allowed to warm to room temperature and then stirred at this temperature for 24 h after which all the starting material had been consumed. The solution was concentrated under reduced pressure and the residue diluted with CH_2Cl_2 and washed with 10% aqueous Na_2SO_3, $NaHCO_3$ (satd., aq.) and brine. The combined aqueous layers were washed with CH_2Cl_2; the combined organic extracts were then dried, filtered and concentrated under reduced pressure. The product was flash chromatographed [ethyl acetate–LP (1:1)] to give a brown solid, which after recrystallisation from ethyl acetate–hexane afforded crystals of compound **9** (534 mg, 70%), mp 95–96 °C; R_F [EtOAc–LP (1:1), SiO_2] 0.35; ν_{max}(NaCl)/cm^{-1} 2950, 1760 (CO_2Et) and 1660; δ_H(300 MHz; $CDCl_3$) 4.38 (1 H, br s, 7-H), 4.23 (1 H, br s, 1-H), 4.10 (2 H, q, *J* 7.5, CH_2 ester), 3.72 (1 H, s, 3-H), 3.51–3.42 (1 H, m, 6-H), 3.30 (3 H, s, CH_3 methoxy), 2.72 (1 H, br d, *J* 4.5, 4-H), 2.18 (1 H, t, *J* 4.0, *endo*-5-H), 2.04 (3 H, s, CH_3 amide), 2.05–1.96 (1 H, m, *exo*-5-H) and 1.20 (3 H, t, *J* 7.5, CH_3 ester); δ_C(75.5 MHz; $CDCl_3$) 169.37, 167.52 (2 × C=O), 82.88 (CH, C-6), 61.67 (CH, C-1), 61.56 (CH_2 ester), 61.10 (CH, C-3), 57.03 (CH_3 methoxy), 46.71 (CH, C-4), 44.78 (CH, C-7), 35.67 (CH_2, C-5), 21.82 (CH_3 amide) and 14.01 (CH_3 ester). Major NOE enhancements: *exo*-5-H! [6-H (8.1%), 3-H (7.9%)], 7-H! [1-H (4.9%), 4-H (4.5%)] and 6-H! [1-H (3.5%)] (Found: $[M]^+$, 319.040 27. $C_{12}H_{18}BrNO_4$ requires *m/z*, 319.041 92).

Preparation of benzenesulfenyl chloride

To a stirred mixture of diphenyl disulfide (4.37 g) and triethylamine (3 drops) at 0 °C in CCl_4 (35 cm^3) was added dropwise sulfuryl chloride (1.7 cm^3) in CCl_4 (35 cm^3). After the addition the mixture was stirred at 0 °C for 1 h and then evaporated under reduced pressure to give a sticky yellow semisolid which was distilled at 0.35 mmHg to afford benzenesulfenyl chloride (5.04 g, 87%) as a dark red distillate. This was used immediately.

Preparation of ethyl 2-acetyl-6-*exo*-chloro-7-*anti*-phenylsulfenyl-2-azabicyclo[2.2.1]heptane-3-*endo*-carboxylate 8

A solution of benzenesulfenyl chloride (346 mg) in acetonitrile (5.0 cm^3) was added dropwise to a stirred solution of the ester **3** (500 mg) in acetonitrile (5.0 cm^3) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred at this temperature for 24 h, after which time all the starting material had been consumed. The solution was concentrated under reduced pressure and the product was identified after as compound **8** (864 mg, quant.); mp 69–70 °C, R_F [EtOAc–LP (7:1) SiO_2] 0.34; ν_{max}(KBr)/cm^{-1} 3400 (PhH), 1740 (CO_2Et), 1640 and 700; δ_H(300 MHz; $CDCl_3$) 7.35–7.25 (5 H, m, Ph), 4.28 (1 H, br s, 1-H), 4.10 (2 H, q, *J* 7.2, CH_2 ester), 4.03 (1 H, br s, 7-H), 4.00–3.91 (1 H, m, 6-H), 3.91 (1 H, s, 3-H), 2.77 (1 H, br d, *J* 4.0, 4-H), 2.62–2.52 (1 H, m, *endo*-5-H), 2.40–2.28 (1 H, m, *exo*-5-H), 2.10 (3 H, s, CH_3 amide) and 1.15 (3 H, t, *J* 7.2, CH_3 ester); δ_C(75.5 MHz; $CDCl_3$) 169.28, 167.91 (2 × C=O), 135.35 (C, Ph), 130.49, 130.31, 129.24, 129.18, 127.14 (5 × CH, Ph), 65.91 (CH, C-1), 61.58 (CH, C-3), 61.49 (CH_2 ester), 56.20 (CH, C-6), 51.78 (CH, C-7), 46.83 (CH, C-4), 38.91 (CH_2, C-5), 22.00 (CH_3 amide) and 14.09 (CH_3 ester). Major NOE enhancements: 7-H! [4-H (2.6%), 1-H (2.1%)], 6-H! [1-H (1.2%)] and *exo*-5-H! [3-H (0.9%)] (Found: $[M]^+$, 353.084 22. $C_{17}H_{20}ClNO_3S$ requires *m/z*, 353.085 24).

Preparation of ethyl 2-acetyl-6-*exo*-bromo-7-*anti*-phenylselenenyl-2-azabicyclo[2.2.1]heptane-3-*endo*-carboxylate 6

A solution of benzeneselenenyl bromide (400 mg) in dry THF (15 cm^3) was added dropwise to a stirred solution of the ester **3** (250 mg) in dry THF (10 cm^3) at −78 °C. The reaction mixture was allowed to warm to room temperature and stirred at this temperature for 24 h, after which time all the starting material had been consumed. The solution was concentrated under reduced pressure and the residue purified by flash chromatography (1:1 ethyl acetate–LP). The product was identified as compound **6** (312 mg, 60%); R_F [EtOAc–LP (1:1) SiO_2] 0.33; ν_{max}(NaCl)/cm^{-1} 2981 (PhH), 1738 (CO_2Et) and 1655; δ_H(300 MHz; C_6D_6) 7.50–7.40 (2 H, m, Ph), 7.10–6.90 (3 H, m, Ph), 4.22 (1 H, br s, 7-H), 4.09 (1 H, br s, 1-H), 3.92–3.80 (3 H, m, 3-H and CH_2 ester), 3.34–3.28 (1 H, m, 6-H), 2.58–2.48 (1 H, m, *endo*-5-H). 2.48–2.43 (1 H, m, 4-H), 1.77–1.66 (1 H, m, *exo*-5-H), 1.54 (3 H, s, CH_3 amide) and 0.80 (3 H, t, *J* 8.0, CH_3 ester); δ_C(75.5 MHz; $CDCl_3$) 169.24, 168.01 (2 × C=O), 133.03, 132.75 (2 × CH, Ph), 131.23 (C, Ph), 129.36, 129.30, 127.69 (3 × CH, Ph), 66.60 (CH, C-1), 61.68 (CH, C-3), 61.49 (CH_2

ester), 48.27 (CH, C-4), 45.79 (CH, C-7), 45.02 (CH, C-6), 39.40 (CH_2, C-5), 22.06 (CH_3 amide) and 14.02 (CH_3 ester). Major NOE enhancements: 7-H! [4-H (2.6%), 1-H (2.1%)], 6-H! [1-H (1.2%)] and *exo*-5-H! [3-H (0.9%)] (Found: $[M]^+$, 444.980 48. $C_{17}H_{20}BrNO_3Se$ requires *m/z* 444.979 16).

Preparation of 4-*endo*-acetylamino-7-*endo*,8-*exo*-dibromo-2-oxabicyclo[3.3.0]octan-3-one 12

A solution of bromine (137 mg) in dry CH_2Cl_2 (2.0 cm^3) was added dropwise to a stirred solution of the lactone **4** (100 mg) and acetic acid (0.5 cm^3) in dry CH_2Cl_2 (3.0 cm^3) at room temperature. The reaction mixture was stirred for 24 h, after which time the starting material had been consumed. The solution was diluted with CH_2Cl_2 and washed with 10% aqueous Na_2SO_3, $NaHCO_3$ (satd., aq.) and brine. The organic layer was dried, filtered and concentrated under reduced pressure to give compound **12** (168 mg, 90%) mp 111.5–112.5 °C; R_F [EtOAc–LP (10:1), SiO_2] 0.56; ν_{max}(KBr)/cm^{-1} 3277 (NH), 1780 (lactone), 1660 and 1500 (C=O amide); δ_H(300 MHz; $CDCl_3$) 6.64 (1 H, br d, *J* 5.8, NH), 5.26 (1 H, d, *J* 6.6, 1-H), 4.87 (1 H, dd, $J_{4,5}$ 10.3, $J_{4,NH}$ 5.8, 4-H), 4.68 (1 H, br s, 8-H), 4.48 (1 H, br d, *J* 5.9, 7-H), 3.74 (1 H, ddd, $J_{5,6endo}$ $J_{5,4}$ 10.3, $J_{5,1}$ 6.6, $J_{5,6exo}$ 3.5, 5-H), 2.86 (1 H, ddd, $J_{6endo,6exo}$ 16.2, $J_{6endo,5}$ 10.3, $J_{6endo,7}$ 5.9, *endo*-6-H), 2.24 (1 H, br d, $J_{6exo,6endo}$ 16.2, *exo*-6-H), and 2.10 (3 H, s, CH_3 amide); δ_C(75.5 MHz; $CDCl_3$) 173.76, 170.69 (2 × C=O), 88.67 (CH, C-1), 55.35 (CH, C-8), 51.86 (CH, C-4), 50.41 (CH, C-7), 40.66 (CH, C-5), 34.66 (CH_2, C-6) and 22.66 (CH_3 amide) (Found: $[M]^+$, 338.913 68, 340.907 38, 342.906 57. $C_9H_{12}Br_2NO_3$ requires *m/z*, 338.910 57, 340.908 65, 342.906 73).

Preparation of 4-*endo*-acetylamino-8-*exo*-bromo-7-*endo*-methoxy-2-oxabicyclo[3.3.0]octan-3-one 13

1,3-Dibromo-5,5-dimethylhydantoin (80 mg) was added in small portions to a stirred solution of the lactone **4** (50 mg) in methanol (5.0 cm^3) at 0 °C. The reaction mixture was allowed to warm to room temperature and then stirred for 24 h at this temperature. The reaction mixture was concentrated under reduced pressure after which the residue was diluted with CH_2Cl_2, washed with Na_2SO_3 (satd., aq.), $NaHCO_3$ (sat, aq) and brine, dried ($MgSO_4$) filtered and concentrated under reduced pressure. The product was identified as compound **13** (54 mg, 66%); mp 136–140.5 °C; R_F [EtOAc–LP (10:1) SiO_2] 0.82; ν_{max}(KBr)/cm^{-1} 3300 (NH), 2900–2850, 1780 (lactone), 1660 and 1520 (C=O amide); δ_H(300 MHz; $CDCl_3$) 6.07 (1 H, d, *J* 7.7, NH), 5.17 (1 H, dd, $J_{1,5}$ 7.0, $J_{1,7}$ 1.0, 1-H), 4.95 (1 H, dd, $J_{4,5}$ 11.0, $J_{4,NH}$ 7.7, 4-H), 4.43 (1 H, d, *J* 2.0, 8-H), 3.94 (1 H, dd, $J_{7,6endo}$ 4.0, $J_{7,1}$ 1.0, 7-H), 3.56–3.42 (1 H, m, 5-H), 3.30 (3 H, s, methoxy), 2.38 (1 H, ddd, $J_{6endo,6exo}$ 14.9, $J_{6endo,5}$ 9.9, $J_{6endo,7}$ 4.0, *endo*-6-H), 1.95 (1 H, br d, $J_{6exo,6endo}$ 14.9, *exo*-6-H) and 2.08 (3 H, s, CH_3 amide); δ_C(75.5 MHz; $CDCl_3$) 174.18, 170.10 (2 × C=O), 87.90 (CH, C-1), 87.02 (CH, C-7), 56.40 (CH_3, methoxy), 50.97 (CH, C-4), 50.14 (CH, C-8), 38.59 (CH, C-5), 30.91 (CH_2, C-6) and 22.82 (CH_3 amide) (Found: $[M]^+$, 291.010 90, 293.008 61. $C_{10}H_{15}BrNO_4$ requires *m/z*, 291.010 62, 293.008 70).

Preparation of 4-*endo*-acetylamino-7-*endo*-chloro-8-*exo*-phenylsulfenyl-2-oxabicyclo[3.3.0]octan-3-one 14

A solution of benzenesulfenyl chloride (100 mg) in acetonitrile (1.0 cm^3) was added dropwise to a stirred solution of the lactone **4** (100 mg) in acetonitrile (2.0 cm^3) at 0 °C. The reaction mixture was allowed to warm to room temperature and then stirred for 24 h. The solution was concentrated under reduced pressure to give a white fluffy solid which was identified as compound **14** (190 mg, quant.), mp 145–146 °C, R_F [EtOAc–LP (10:1) SiO_2] 0.48; ν_{max}(KBr)/cm^{-1} 3250 (NH and PhH), 1790 (lactone), 1660 (C=O amide), 1530 and 700 (strong); δ_H(300 MHz; $CDCl_3$) 7.65–7.15 (5 H, m, Ph), 6.60 (1 H, br d, *J* 3.5, NH), 4.94 (1 H, br d, *J* 5.3, 1-H), 4.90–4.80 (1 H, m, 4-H), 4.18 (1 H, br s, 7-H), 3.98 (1 H, d, *J* 2.5, 8-H), 3.52 (1 H, br s, 5-H), 2.60–2.48 (1 H, m, *endo*-6-H), 2.07 (3 H, s, CH_3 amide) and 2.02 (1 H, br s, *exo*-6-H); δ_C(75.5 MHz; $CDCl_3$) 173.87, 170.76 (2 × C=O), 132.17 (C, Ph), 131.70, 129.60, 129.07, 128.23, 127.56 (5 × CH, Ph), 87.11 (CH, C-1), 60.96 (CH, C-7), 60.10 (CH, C-8), 52.21 (CH, C-4), 41.04 (CH, C-5), 35.25 (CH_2, C-6) and 22.65 (CH_3 amide). Major NOE enhancements: 6-H! [*exo*-5-H (4.9%), 3-H (4.7%)] 7-H! [1-H (4.3%), 4-H (3.2%)] and 6-H! [1-H (4.1%)] (Found: $[M]^+$, 325.055 33. $C_{15}H_{16}ClSNO_3$ requires *m/z*, 325.053 94).

Preparation of 4-*endo*-acetylamino-8-*exo*-bromo-7-*endo*-methylphenylsulfonyl-2-oxabicyclo[3.3.0]octan-3-one 15

N-Bromosuccinimide (NBS) (106 mg) was added in small portions over a 5 min period to a stirred solution of the *endo*-lactone **4** (100 mg) and toluene-*p*-sulfonic acid (126 mg) in CH_2Cl_2 (3.0 cm^3) at 0 °C. The reaction mixture was stirred at room temperature for 24 h after which it was washed with 2 mol dm^{-3} HCl and extracted with CH_2Cl_2. The organic layer was washed with $NaHCO_3$ (satd. aq.) dried and concentrated under reduced pressure. No further purification was deemed necessary. The product was identified as compound **15** (125 mg, 68%), mp 126–127 °C, R_F [EtOAc–LP (10:1) SiO_2] 0.38; ν_{max}(KBr)/cm^{-1} 3400 br (NH), 2960, 1780 (lactone), 1670 (C=O amide), 1540, 1350 (SO_2) and 860; δ_H(300 MHz; $CDCl_3$) 7.75 (2 H, d, *J* 9.6, Ph), 7.35 (2 H, d, *J* 9.6, Ph), 6.72 (1 H, d, *J* 6.8, NH), 5.12 (1 H, s, 7-H), 5.10 (1 H, s, 1-H), 4.95 (1 H, dd, $J_{4,5}$ 10.5, $J_{NH,4}$ 6.8, 4-H), 4.19 (1 H, br s, 8-H), 3.69–3.57 (1 H, m, 5-H), 2.61–2.50 (1 H, 2dd, $J_{6endo,6exo}$ 15.8, $J_{6endo,5}$ 10.5, $J_{6endo,7}$ 4.4, *endo*-6-H), 2.44 (3 H, s, CH_3 tosyl), 2.23 (1 H, br d, *J* 15.8, *exo*-6-H) and 2.07 (3 H, s, CH_3 amide); δ_C(75.5 MHz; $CDCl_3$) 173.38, 170.80 (2 × C=O), 145.75, 133.04 (2 × C, Ph), 130.14, 127.72 (2 × 2 CH, Ph), 87.16 (CH, C-7), 86.34 (CH, C-1), 51.28 (CH, C-4), 50.95 (CH, C-8), 39.24 (CH, C-5), 30.86 (CH_2, C-6), 22.60 (CH_3 tosyl) and 21.70 (CH_3 amide) (Found: $[M]^+$, 431.002 59. $C_{16}H_{18}BrSNO_7$ requires *m/z*, 431.003 82).

Preparation of 4-*endo*-acetylamino-7,8-*exo*-epoxy-2-oxabicyclo[3.3.0]octan-3-one 17 & 4-*endo*-acetylamino-7,8-*endo*-epoxy-2-oxabicyclo[3.3.0]octan-3-one 16

The lactone **4** (300 mg) was dissolved with 90% MCPBA (400 mg) in dry CH_2Cl_2 (10 cm^3) at 0 °C under N_2. The reaction was allowed to warm to room temperature and then heated to 35 °C and refluxed gently for 24 h. The reaction mixture was then allowed to cool and diluted with 10% aqueous Na_2SO_3, before being extracted with CH_2Cl_2. The extract was washed with water, dried, filtered and concentrated. Purification of the residue by flash chromatography [ethyl acetate–LP (10:1)] gave two compounds, ratio 5:2, as off-white solids, both of which were recrystallised from ethyl acetate–hexane. The major product was compound **16** (174 mg, 53% yield) and the minor product compound **17** (65.5 mg, 20% yield). The prominent signals in the IR spectra were essentially the same for both compounds: ν_{max}(KBr)/cm^{-1} 3331 (NH), 3048 (CH epoxide), 1773 (lactone), 1667 and 1518 (C=O amide). Compound **17**; mp 201–202 °C, R_F [EtOAc–LP (10:1) SiO_2] 0.31; δ_H(300 MHz; C_6D_6) 6.24 (1 H, br s, NH), 4.97 (1 H, d, *J* 5.3, 1-H), 4.75 (1 H, dd, $J_{4,NH}$ 4.8, $J_{4,5}$ 8.2, 4-H), 3.74 (1 H, d, *J* 2.4, 8-H), 3.59 (1 H, br s, 7-H) 3.22–3.10 (1 H, m, 5-H), 2.14 (1 H, dd, $J_{6endo,5}$ 8.4, $J_{6endo,6exo}$ 14.8, *endo*-6-H), 2.05 (3 H, br s, CH_3 amide) and 1.60 (1 H, ddd, $J_{6exo,7}$ 1.5, $J_{6exo,5}$ 7.9, $J_{6exo,6endo}$ 14.8, *exo*-6-H); δ_C(75.5 MHz; C_6D_6) 174.20, 170.65 (2 × C=O), 81.23 (CH, C-1), 57.86 (CH, C-8), 56.22 (CH, C-7), 52.26 (CH, C-4), 39.03 (CH, C-5), 26.63 (CH_2, C-6) and 22.63 (CH_3 amide). Major NOE enhancements: 5-H! [*endo*-6-H (4.3%)], 7-H! [*exo*-6-H (3.1%), *endo*-6-H (1.9%)], 1-H! [8-H (2.9%)], *exo*-6-H! [NH

Table 1 Crystal data and details of data collection and refinement for $C_{12}H_{18}BrNO_4$ **9** and $C_9H_{11}NO_4$ **16**[a]

Compound	**9**	**16**
Formula	$C_{12}H_{18}BrNO_4$	$C_9H_{11}NO_4$
M	320.18	197.19
a/Å	10.361(1)	13.183(1)
b/Å	14.801(2)	9.260(1)
c/Å	17.712(2)	15.180(2)
V/Å^3	2716.2(5)	1853.1(3)
D_c/g cm^{-3}	1.566	1.414
$F(000)$	1312	832
μ(Mo-Kα)/cm^{-1}	30.3	1.12
Crystal size/mm^3	0.25 × 0.12 × 0.10	0.30 × 0.18 × 0.15
θ range for cell and data collection/°	2.30–24.96	3.00–24.95
h_{min}, h_{max}	−11,7	−15,15
k_{min}, k_{max}	−16,16	−10,7
l_{min}, l_{max}	−19,17	−17,17
Total data measured	9814	7114
Total unique (R_{int})	2113 (0.0563)	1479 (0.0532)
Absorption correction factors, min, max	0.894, 1.042	none
Refinement method	Full-matrix least-squares on F_o^2	
No. of parameters/data	235/2113	171/1479
ρ_{min}, ρ_{max}/e Å^{-3}	−0.367, +0.952	−0.176, +0.254
$(\Delta/\sigma)_{max}$	0.001	0.001
Goodness-of-fit	0.972	1.015
R_1	0.0447 (0.0322)[b]	0.0461 (0.0361)
wR_2	0.0745 (0.0730)[b]	0.0926 (0.0903)

[a] Details in common: cell parameters from 250 reflections, orthorhombic, space group *Pbca* (No. 61), $Z = 8$, 120 K, Mo-Kα radiation, $\lambda = 0.710\,69$ Å. [b] The R_1 and wR_2 values for data with $F_o^2 > 2\sigma(F_o^2)$ are given in parentheses. $R_1 = \Sigma(F_o - F_c)/\Sigma(F_o)$; $wR_2 = [\Sigma\{w(F_o^2 - F_c^2)^2\}/\Sigma\{w(F_o^2)^2\}]^{\frac{1}{2}}$; $w = 1/[\sigma^2(F_o^2) + (aP)^2]$, where $P = [F_o^2 + 2F_c^2]/3$ and $a = 0.0422$ for **9** and 0.0617 for **16**.

(2.7%)]. Compound **16**, mp 124–125.5 °C; R_F [EtOAc–LP (10:1), SiO_2] 0.28; δ_H(300 MHz; C_6D_6) 6.22 (1 H, br d, J 9.2, NH), 5.12 (1 H, dd, $J_{1,8}$ 1.5, $J_{1,5}$ 8.6, 1-H), 4.83 (1 H, dd, $J_{4,NH}$ 9.2, $J_{4,5}$ 12.0, 4-H), 3.66–3.61 (2 H, m, 7-H and 8-H), 3.08–2.96 (1 H, m, 5-H), 2.11–2.03 (4 H, m, *exo*-6-H and CH_3 amide), 2.03–1.93 (1 H, m, *endo*-6-H); δ_C(75.5 MHz; C_6D_6) 174.98, 170.11 (2 × C=O), 82.50 (CH, C-1), 59.65 (CH, C-8), 57.42, (CH, C-7), 48.99 (CH, C-4), 37.72 (CH, C-5), 27.48 (CH_2, C-6) and 22.83 (CH_3 amide). Major NOE enhancements: *exo*-6-H! [NH (5.4%)], 1-H! [8-H (5.1%)], 7-H! [*endo*-6-H (3.3%), *exo*-6-H (2.4%)], 5-H! [*endo*-6-H (3.0%)] (**16** + **17** Found: $[M]^+$, 197.068 77. $C_9H_{11}NO_4$ requires m/z, 197.068 81).

X-Ray crystallography

Crystals of compounds **9** and **16** suitable for X-ray work were obtained from mixed solvent systems of ethyl acetate–hexane. All measurements were made at 120 K using a Delft Instruments FAST TV area detector diffractometer positioned at the window of a rotating anode generator using Mo-Kα radiation ($\lambda = 0.710\,69$ Å) by following procedures described elsewhere.[5] The structures were solved by direct methods (SHELX-S)[6] and refined by full matrix least-squares (SHELXL-93)[7] using all unique F_o^2 data corrected for Lorentz and polarisation factors, and in the case of **9** also for absorption effects (DIFABS).[8] In both cases, the non-hydrogen atoms were refined anisotropically; the hydrogen atoms were located from different maps and refined isotropically. Sources of scattering factors as in ref. 7. The diagrams were drawn with SNOOPI.[9] The calculations were done on a 486DX2/66 personal computer. The crystal data and details of data collection and structure refinement are presented in Table 1. The atomic coordinates, anisotropic displacement coefficients, hydrogen atom parameters, bond lengths and angles and structure factor tables have been deposited with the Cambridge Crystallographic Data Centre.†

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† For details see Instructions for Authors (1995), *J. Chem. Soc., Perkin Trans. 1*, 1995, Issue 1.

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