Rearrangement of 2-Azabicyclo[2.2.1]hept-5-en-3-ones: Synthesis of *cis*-3-Aminocyclopentane Carboxylic Acid Derivatives

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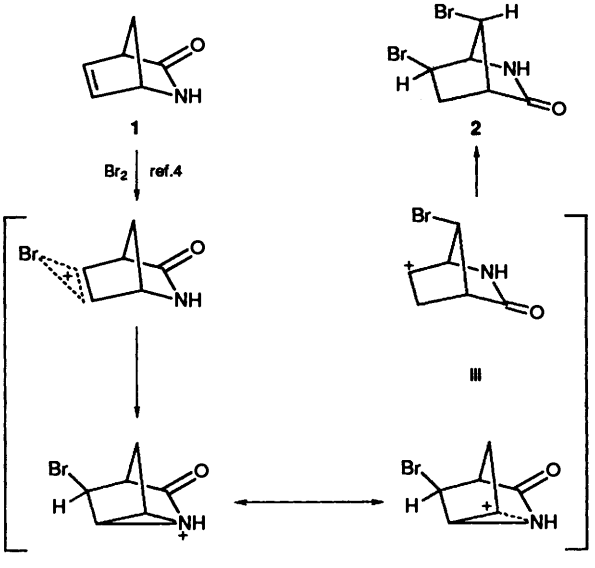
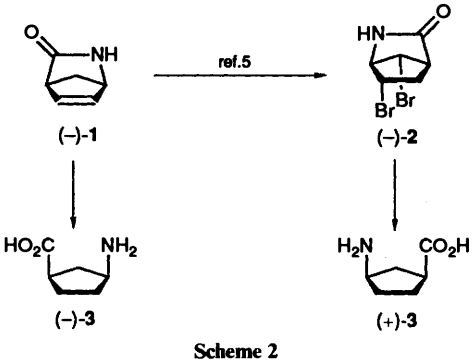
The γ-lactam **4** was converted into the bromo ester **6** and the latter compound was transformed in five steps into the diester **10**. Similarly the lactam **4** was converted into the hydroxy amide **17** *via* the intermediacy of the dihalogeno compound **11**. Compounds **10** and **17** are potential precursors of deoxycarbocyclic nucleosides. Unexpectedly, the lactam **4** furnished the addition product **25** on reaction with benzeneselenenyl bromide and a tentative rationale for the preferred reaction pathway is proposed

2-Azabicyclo[2.2.1]hept-5-en-3-one (±)-**1** is readily available by reaction of cyclopentadiene with either chlorosulfonyl isocyanate[1] or toluene-*p*-sulfonyl cyanide[2] followed by a simple workup procedure. Furthermore, both enantiomers of the lactam **1** can be obtained in optically pure form by enzyme-catalysed enantiospecific hydrolysis procedures.[3]

Bromination of the lactam (±)-**1** has been shown to give the dihalogeno compound (±)-**2** by way of an elegant 'molecular somersault' (Scheme 1).[4] In an extension of this work (Scheme 2) we have shown[5] that bromination of (−)-**1** afforded the dibromo compound (−)-**2** and this compound, after hydrodebromination, was hydrolysed to give (+)-*cis*-3-aminocyclopentanecarboxylic acid (+)-**3**. Hydrogenation and hydrolysis of the lactam (−)-**1** gave the laevorotatory amino acid (−)-**3**. Thus by using the deep-seated rearrangement originally reported by Snider *et al.*, the lactam (−)-**1** can be converted, very simply, into either enantiomer of *cis*-3-aminocyclopentanecarboxylic acid, a compound that has been shown to act as an agonist at the γ-aminobutyric acid (GABA) receptor.[6] Now we report that closely related rearrangements provide access to potentially important novel derivatives of the amino acid **3**, but that the rearrangement is not observed when such lactams are treated with the benzeneselenenyl electrophile.



Scheme 1



Scheme 2

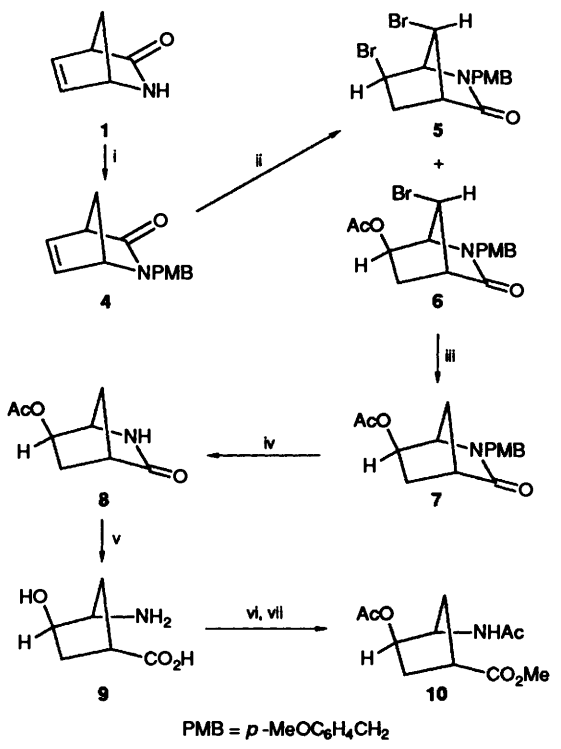
Results and Discussion

Treatment of the racemic lactam **1** with 1,3-dibromo-5,5-dimethylhydantoin† (DBDMH) either in acetone–water or in glacial acetic acid gave rise to complex mixtures of products. Similarly, treatment of (±)-**1** with *N*-bromosuccinimide‡ (NBS) in the presence of triethylamine tris(hydrogen fluoride) (TEA·3HF)[6] gave no identifiable products. However, more success was obtained by employing the *N*-*para*-methoxybenzylated lactam as the starting material (Scheme 3). Thus, reaction of the protected lactam **4** with DBDMH in glacial acetic acid at room temperature afforded the dibromo compound **5** (4%) and the required bromo acetate **6** (70%). The ^{1}H NMR spectrum of **6** in [$^2H_6$]benzene shows 6-H (δ 4.53) as a doublet of doublets with $J_{6,5endo}$ 8 Hz and $J_{6,5exo}$ 4 Hz. 5-H*endo* (δ 1.94) exhibited a small ω-coupling to 7-H. Furthermore irradiation of the signal due to 6-H produced enhancements of the signals due to 5-H*endo*, 1-H and, significantly, N-CH_2-Ar confirming that the acetoxy group is in the *exo*-configuration.

Hydrodebromination of **6** [tributyltin hydride, azoisobutyronitrile (AIBN), benzene] furnished the ester **7** (86% yield) and this compound was deprotected with ceric ammonium nitrate[8] (CAN) to give the required lactam **8** (83% yield). This lactam was hydrolysed readily in hot hydrochloric acid to afford the amino acid **9** which was fully characterised as the diester **10** (65% overall yield). It is noteworthy that the latter compound is a useful intermediate for the synthesis of 3′-deoxycarbocyclic nucleosides.[2,9]

Treatment of the *N*-(4-methoxybenzyl) lactam **4** with NBS and TEA·3HF in dichloromethane at 4 °C for 4 days gave the dibromide **5** (22%) and the bromo fluoride **11** (43%) (Scheme 4). The structure proposed for compound **11** was supported by the

† 1,3-Dibromo-5,5-dimethyl-1,3-diazolidine-2,4-dione.
‡ 1-Bromopyrrolidine-2,4-dione.

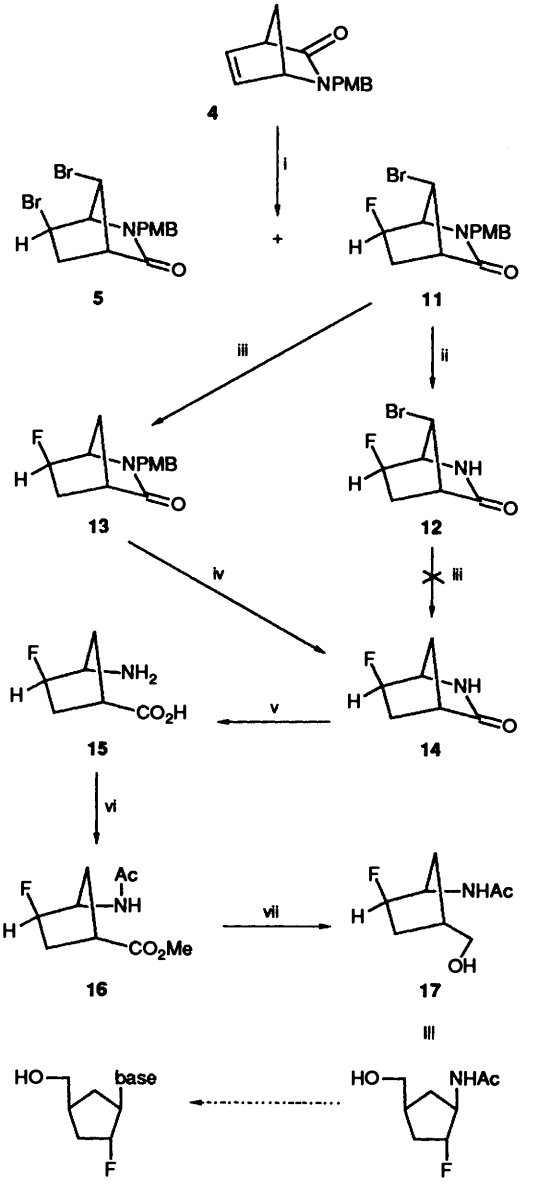


Scheme 3 *Reagents and conditions:* i, 4-$MeOC_6H_4CH_2Cl$, $LiN(SiMe_3)_2$, Bu_4NI, THF, dimethylformamide (DMF) (66%); ii, DBDMH, HOAc, room temp.; iii, Bu_3SnH, AIBN, benzene, heat (86%); iv, $(NH_4)_2Ce(NO_3)_6$, H_2O, MeCN, room temp. (83%); v, HCl (1 mol dm^{-3}), heat, 1 h; vi, $(MeO)_2CMe_2$, MeOH, H^+ (cat.); vii, Ac_2O, pyridine (65% for steps v–vii)

^{13}C NMR spectrum which showed a large $^1J_{C\text{-}6,F}$ coupling (200 Hz) as well as two other diagnostic coupling constants $^2J_{C\text{-}1,F}$ 22.9 and $^2J_{C\text{-}5,F}$ 21.5 Hz. The magnitude of these couplings is in agreement with those reported for 7-*anti*-bromo-2-*exo*-fluorobicyclo[2.2.1]heptane.[10] Deprotection of the lactam **11** using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[11] in dioxane under reflux gave the dihalogeno compound **12** (61%). Disappointingly, the attempted hydrodebromination[12] of **12** using tributyltin hydride and AIBN in hot benzene was unsuccessful. Fortunately, the same reaction conditions smoothly converted the lactam **11** into the fluoro compound **13** (90%) and this compound was deprotected using ceric ammonium nitrate (CAN) in acetonitrile–water[8] to give the lactam **14** (86%). Acid hydrolysis of the latter compound gave the amino acid **15** which was esterified and acetylated to afford the amide **16**. The overall yield **14** ⟶ **16** was 85%. The amido ester **16** is a potentially useful intermediate for the synthesis of 2′-fluoro-2′,3′-dideoxycarbocyclic ribonucleosides. In this connection we can report that the ester **16** is readily reduced to the hydroxy amide **17** using calcium borohydride in tetrahydrofuran under sonication.[9]

In an attempt to extend this chemistry so as to provide useful intermediates for the synthesis of analogues of the carbocyclic nucleoside neplanocin we investigated the reaction of the 2-azabicyclo[2.2.1]hept-5-en-3-one system with sulfur and selenium based electrophiles.

Treatment of the lactam **4** with benzenesulfenyl chloride (PhSCl)[13] in acetonitrile or tetrahydrofuran (THF) gave the chloro compound **18** in 44% and 45% respectively. The structure of **18** was established by NMR spectroscopy: the coupling constants $J_{6.5endo}$ 8 Hz and $J_{6,5exo}$ 4 Hz were informative and the NOE observed between 6-H and one of the benzylic protons (NCH_2Ar) was in accord with the proposed structure. Similarly reaction of the lactam **20** with PhSCl in

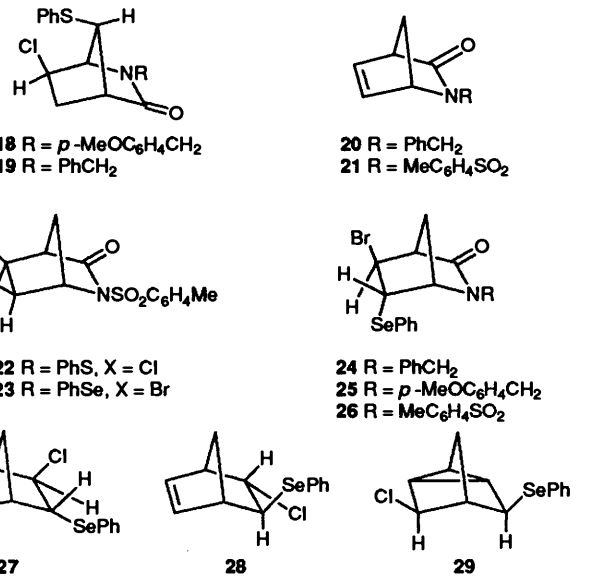


Scheme 4 *Reagents and conditions:* i, NBS, $Et_3N{\cdot}3HF$, CH_2Cl_2, 4 °C, 4 days; ii, DDQ, dioxane, heat, 24 h (61%); iii, Bu_3SnH, AIBN, benzene, heat (90%); iv, $(NH_4)_2Ce(NO_3)_6$, MeCN, H_2O (86%); v, HCl (1 mol dm^{-3}), heat; vi, $(MeO)_2CMe_2$, MeOH, H^+ cat., then Ac_2O, pyridine (85% for v and vi); vii, $CaBH_4$, THF, ultrasound (93%)

acetonitrile gave the rearranged compound **19** as the only identifiable product.

Not surprisingly, the *N*-tosyl lactam **21**[14] reacted with PhSCl in acetonitrile to give the non-rearranged product **22**. The same result occurred in THF indicating that the reaction course was independent of the solvent used. The stereochemical assignments of the chloro and phenylsulfenyl substituents were made, once again, on the basis of ^1H NMR spectroscopy. Obviously the electron-withdrawing tosyl group decreases electron density on the nitrogen atom, which, then, cannot intercept the transannular carbonium ion.* *anti*-1,2-Addition to the double bond takes place: the inductive effect of the *N*-tosyl group militates

* The extent and availability of electron density on the ring nitrogen atom can be qualitatively assessed, indirectly, by observing the IR adsorption band due to the neighbouring carbonyl group for the *N*-*para*-methoxybenzyl lactam (ν_{max}/cm^{-1} 1690) and the *N*-tosyl lactam (ν_{max}/cm^{-1} 1742).



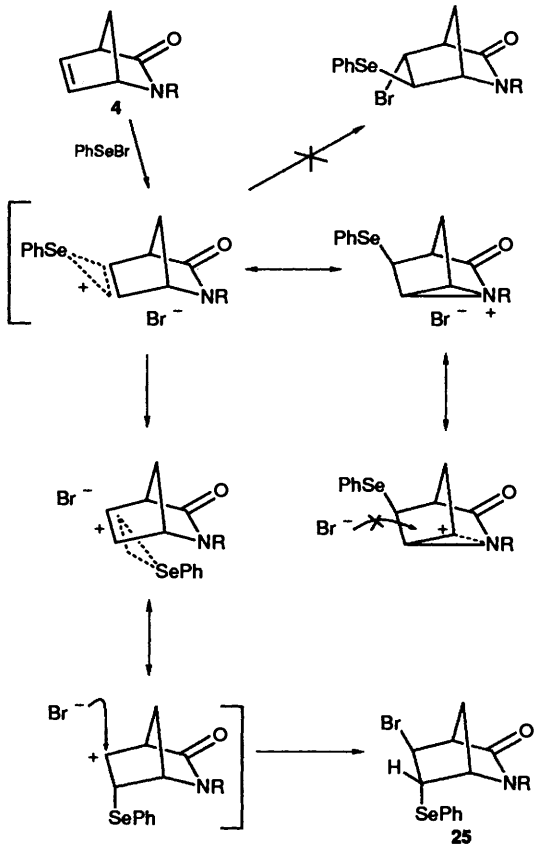
against a significant build up of positive charge at C-6 and attack by chloride ion takes place at C-5.

Unexpectedly, reaction of the *N*-benzyl lactam **20** with benzeneselenenyl bromide[15] in THF gave the compound **24** (55%), the product of *anti*-addition to the double bond with the attacking electrophile attached to the *endo* face. The NOE observed for 7-H (3.6%) on irradiation of 6-H was particularly noteworthy and informative as were the C-6–^{77}Se satellite signals (J_{C-Se} 77 Hz). In exactly the same fashion the *N*-protected lactam **4** produced the bromo lactam **25** (42%) on reaction with PhSeBr in THF.

We explain these latter results by assuming that the phenylselenenyl moiety present at C-7 is simply too bulky to allow access of the bromide ion to C-5 from the *exo*-face (Scheme 5). Instead the *endo*-phenylselenenyl cation is the reactive intermediate that provides a manifold to the reaction product.

This postulate was tested by reaction of *N*-tosyl-γ-lactam **21** with PhSeBr in THF. Since the nitrogen atom in this compound is deactivated towards attack by electrophiles it is not expected to participate in the reaction. Approach of the electrophile to the *exo*-face of the double bond can then give rise to the product of 1,2-addition by attack of the attendant nucleophile from the unguarded *endo*-face, at the position remote from the *N*-tosyl substituent. The expected compound **23** *was* formed (31% yield) but the *major* product was identified as the isomer **26** (43%). Once again NOE studies proved to be crucial in elucidating the structures of the compounds **23** and **26**. Most significantly, for compound **26** enhancement of the signal due to 7-H was observed on irradiation of the signal due to 6-H, while for compound **23** enhancement of the signal due to 7-H was effected by irradiation at the field strength corresponding to that of the signal due to 5-H.

Thus the proposal outlined in Scheme 5 is probably still valid, *i.e.* formation of the *exo*-phenylselenenyl cation does not lead to reaction product(s) when the neighbouring nitrogen atom participates; *i.e.* the molecular somersault originally observed by Snider *et al.* does not take place. In addition to this stereochemical factor which affects the reaction pathway it seems that the phenylselenenyl cation does have a proclivity to approach the alkene unit from the ostensibly more hindered *endo*-face. This situation is reminiscent to that pertaining on reaction of norbornadiene with benzeneselenenyl chloride in dichloromethane whereupon the *endo*-seleno compound **27** and the *exo*-seleno products **28**, **29** are formed in the ratio 69:31.[16]



Scheme 5

Perhaps for both norbornadiene and the unsaturated lactams the *exo*- and *endo*-phenylselenenyl cations (designated A and B for the lactam system in Scheme 5) are loose transition states and are very similar in energy. As a result it is the relative ease of access of the nucleophile to C-5 (*exo versus endo* approach) which dictates the product ratio. With nucleophilic attack from the *exo*-face being favoured, the major products formed are **26** in the case of the lactam and **27** in the case of norbornadiene.

Conclusions

The rearrangement **1** ⟶ **2** observed by Snider *et al.* has been developed to provide a small range of novel 5,(7)-substituted 2-azabicycloheptan-3-ones. Some of the lactams were readily converted into carbocyclic δ-substituted γ-amino acids and derivatives which are potentially useful, *inter alia*, for the synthesis of 3′-deoxycarbocyclic nucleosides. The rearrangement does not take place when PhSeBr is used as the attacking reagent so that a simple access to 3′-deoxyneplanocins was thwarted.

Experimental

THF was dried over, and distilled from, lithium aluminium hydride and stored over sodium–benzophenone in a recycling still. Benzene was distilled from lithium aluminium hydride and stored over 4Å molecular sieves. Pyridine was distilled from CaH_2 and stored over 4Å molecular sieves. Ethyl acetate and dichloromethane were distilled from CaH_2. Light petroleum (b.p. 40–60 °C) [referred to as LP (40–60)] was distilled prior to use and light petroleum (b.p. 60–80 °C) [referred to as LP (60–80)] was distilled from P_2O_5. All other

reagents were used as commercially supplied. Reactions requiring anhydrous conditions were carried out using oven dried glassware under a static argon atmosphere unless otherwise stated.

Analytical thin layer chromatography was performed on commercially available glass backed plates coated with Kieselgel 60-F_{254}, visualizing with UV light, *p*-anisaldehyde, basic $KMnO_4$, iodine or ninhydrin. Preparative flash column chromatography[17] was carried out using Merck Kieselgel 60 (230–400 mesh). Solvent compositions are quoted as v/v. M.p.s were determined in open capillary tubes using an Electrothermal melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 881 spectrometer. Solutions and films were recorded using sodium chloride cells. ^1H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker AM250 spectrometer operating at 250, 62.9 and 235 MHz. ^1H and ^{13}C NMR spectra are reported in ppm relative to tetramethylsilane. ^{19}F NMR spectra were obtained using hexafluorobenzene as an external standard. ^{13}C NMR spectra were obtained fully decoupled and multiplicities were determined using DEPT. Coupling constants are in Hz. High resolution mass spectra were obtained *via* the SERC Mass Spectrometry Centre, Swansea. Low resolution mass spectra were obtained from the CDC group, ICI Agrochemicals, Jealott's Hill. Elemental analysis were obtained from Butterworths and ICI Agrochemicals.

2-(4′-Methoxybenzyl)-2-azabicyclo[2.2.1]*hept-5-en-3-one* **4**.—Lithium bis(trimethylsilyl)amide (prepared according to the literature procedure)[18] in dry THF (50 cm^3) was added dropwise to a stirred solution of 2-azabicyclo[2.2.1]hept-5-en-3-one (**1**) (2.949 g, 27.06 mmol) in dry THF (50 cm^3) at −78 °C. Stirring was continued at −78 °C for 30 min. A solution of 4-methoxybenzyl chloride (4.33 cm^3, 31.90 mmol) and tetrabutylammonium iodide (TBAI) (170 mg) in dry DMF (10 cm^3) was added dropwise over 15 min. The resulting solution was allowed to warm to room temperature and stirring was continued for a further 24 h. Ethanol (20 cm^3) was added dropwise and the solution filtered through Celite. The solvent was removed under reduced pressure and the residue purified by column chromatography [silica, 2:1 ether–LP (40–60)] to give the title compound **4** (4.057 g, 66%) as a clear oil (Found: $[M + H]^+$ 230.1181. $C_{14}H_{15}NO_2$ requires $[M + H]^+$ 230.1181); ν_{max}(film)/cm^{-1} 2994, 2839 (CH), 1685 (CO), 1559 and 1507 (C=CAr); δ_H($CDCl_3$) 7.10 (2 H, m, 3′-H, 5′-H), 6.90 (2 H, m, 2′-H, 6′-H), 6.50 (2 H, m, 5-H, 6-H), 4.32 (H, d, *J* 14, CH_2Ar), 3.96 (2 H, m containing d, *J* 14, CH_2Ar, 1-H), 3.77 (3 H, s, $ArOCH_3$), 3.34 (H, m, 4-H), 2.25 (H, ddd, *J* 8, 2, 2, 7-H) and 2.05 (H, ddd, *J* 8, 2, 2, 7-H); δ_C($CDCl_3$) 179.8 (CON), 159.1 (C-4′), 139.6, 137.0 (C-5, C-6), 129.7 (C-1′), 128.4 (C-2′, C-6′), 113.9 (C-3′, C-5′), 62.5 (C-1), 58.3 (C-7), 55.2 ($ArOCH_3$), 53.8 (C-4) and 47.3 ($ArCH_2$).

Bromoacetoxylation of 2-(4′-*Methoxybenzyl*)-2-*azabicyclo*-[2.2.1]*hept-5-en-3-one* **4**.—1,3-Dibromo-5,5-dimethylhydantoin (0.965 g, 3.38 mmol) was added portionwise to a stirred solution of compound **4** (1.539 g, 6.72 mmol) in glacial acetic acid (15 cm^3) and the resulting solution stirred at room temperature for 18 h. The solution was diluted with dichloromethane (250 cm^3) and washed with water (3 × 50 cm^3), 10% aqueous sodium sulfite (3 × 50 cm^3) and saturated aqueous sodium hydrogen carbonate (3 × 50 cm^3). The aqueous layers were combined, extracted with dichloromethane (2 × 100 cm^3) and the combined organic extracts were washed with brine (50 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography [silica, 3:1 LP (60–80)–ethyl acetate] to give 6-*exo*-7-*anti*-dibromo-2-(4′-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one **5** (0.095 g, 4%) as a white solid, m.p. 117–118 °C (dichloromethane–hexane); (Found: C, 42.9; H, 3.7; N, 3.6. $C_{14}H_{15}Br_2NO_2$ requires C, 43.2; H, 3.9; N, 3.6%); *m/z* (CI) 389 (< 10%, M^+, ^{79}Br, ^{81}Br), 308 (50, [M − Br] and 121 (100, $C_8H_9O^+$); ν_{max}($CHCl_3$)/cm^{-1} 2997, 2956, 2840 (CH), 1706 (CO), 1609 and 1507 (C=CAr); δ_H-($CDCl_3$) 7.10 (2 H, m, ArH), 6.90 (2 H, m, ArH), 4.56 (H, d, *J* 14.8, CH_2Ar), 4.21 (H, m, 7-H), 4.00 (H, d, *J* 14.8, CH_2Ar), 3.87 (H, dd, *J* 1.7, 1.7, 1-H), 3.80 (4 H, m, CH_3O, 6-H), 2.94 (H, m, 4-H), 2.64 (H, dd, *J* 13.9, 4.9, 3.8, 5-H_{exo}) and 2.50 (H, dddd, *J* 13.9, 8.1, 1.2, 0.9, 5-H_{endo}); δ_C($CDCl_3$) 172.0 (CON), 157.7 (C-4′), 129.6 (C-2′, C-6′), 127.5 (C-1′), 114.6 (C-3′, C-5′), 66.9 (C-1), 55.3 (CH_3O), 52.4 (C-4), 48.1 (C-7), 44.0 (CH_2Ar), 40.6 (C-6) and 33.7 (C-5). Further elution gave 6-*exo*-acetoxy-7-*anti*-bromo-2-(4′-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one **6** (1.723 g, 70%) as a clear oil (Found: $[M + H]^+$ 368.0497. $C_{16}H_{18}{}^{79}BrNO_4$ requires $[M + H]^+$ 368.0497); *m/z* (CI) 370 (100%, $[M + 1]^+$, ^{81}Br), 368 (100, $[M + 1]^+$, ^{79}Br), 290 (10, $[M - Br]^+$) and 121 (35, $C_8H_9O^+$); ν_{max}($CHCl_3$)/cm^{-1} 2997, 2839 (CH), 1706 (CO), 1609 and 1507 (C=CAr); δ_H($CDCl_3$) 7.20 (2 H, m, ArH), 6.90 (2 H, m, ArH), 4.69 (2 H, m, including d, *J* 15, 6-H, CH_2Ar), 4.15 (H, m, 7-H), 3.93 (H, d, *J* 15, CH_2Ar), 3.79 (3 H, s, CH_3O), 2.90 (H, m, 4-H), 2.32 (2 H, m, 5-H) and 2.03 (3 H, s, CH_3C); δ_C($CDCl_3$) 172.8 (CON), 170.6 (COMe), 159.5 (C-4′), 129.8 (C-2′, C-6′), 127.8 (C-1′), 114.4 (C-3′, C-5′), 72.7 (C-6), 63.8 (C-1), 55.3 (CH_3O), 50.6 (C-4), 48.4 (C-7), 44.0 CH_2Ar), 29.9 (C-5) and 20.9 (CH_3CO).

6-exo-*Acetoxy*-2-(4′-*methoxybenzyl*)-2-*azabicyclo*[2.2.1]-*heptan*-3-*one* **7**.—A solution of compound **6** (1.723 g, 4.68 mmol), AIBN (11 mg) and tributyltin hydride (1.9 cm^3, 7.06 mmol) in dry benzene (25 cm^3) was stirred at reflux under argon for 18 h. The solvent was removed under reduced pressure and the residue partitioned between acetonitrile (200 cm^3) and hexane (50 cm^3). The acetonitrile layer was separated and extracted with hexane (4 × 50 cm^3). The solvent was removed under reduced pressure and the residue purified by column chromatography [silica, 2:1 ethyl acetate–LP (60–80)] to give the title compound **7** (1.167 g, 86%) as an oil (Found: $[M^+]$ 289.1314. $C_{16}H_{19}NO_4$ requires $[M^+]$ 289.1314); ν_{max}-($CHCl_3$)/cm^{-1} 2993, 2839 (CH), 1725, 1687 (CO), 1609 and 1506 (C=CAr); δ_H($CDCl_3$) 7.20 (2 H, m, ArH), 6.90 (2 H, m, ArH), 4.75 (H, m, 6-H), 4.56 (H, d, *J* 15, CH_2Ar), 3.95 (H, d, *J* 15, CH_2Ar), 3.79 (3 H, s, CH_3O), 3.66 (H, br s, 1-H), 2.77 (H, m, 4-H), 2.14 (H, ddd, *J* 13, 7, 2, 5-H_{endo}), 2.01 (3 H, s, CH_3CO), 1.86 (H, m, 7-H_{anti}) and 1.70 (2 H, m, 5-H_{exo}, 7-H_{syn}); δ_C($CDCl_3$) 177.2 (CON), 170.2 ($COCH_3$), 159.2 (C-4′), 129.5 (C-2′, C-6′), 128.8 (C-1′), 114.1 (C-3′, C-5′), 72.6 (C-6), 60.8 (C-1), 55.2 (CH_3O), 44.1 (CH_2Ar), 43.9 (C-4), 37.2 (C-7), 33.3 (C-5) and 20.9 (CH_3CO).

6-exo-*Acetoxy*-2-*azabicyclo*[2.2.1]*heptan*-3-*one* **8**.—A solution of ceric ammonium nitrate (2.676 g, 4.58 mmol) in water (5 cm^3) was added dropwise to a stirred solution of compound **7** (416 mg, 1.44 mmol) in acetonitrile (20 cm^3) and the resulting solution stirred at room temperature for 6 h. The solution was diluted with ethyl acetate (200 cm^3) and washed (water, 4 × 10 cm^3). The aqueous phases were combined, saturated with sodium chloride and extracted with ethyl acetate (3 × 50 cm^3). The organic layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (silica, ethyl acetate) to give the title compound **8** (202 mg, 83%) as a white solid, m.p. 130.5–132 °C. (Found: $[M + H^+]$ 170.0817. $C_8H_{11}NO_3$ requires $[M + H]^+$ 170.0817); ν_{max}(KBr)/cm^{-1} 3197 (NH) and 1729 (CO); δ_H($CDCl_3$) 6.00 (H, br s, NH), 4.87 (H, m, 6-H), 3.83 (H, s, 1-H), 2.74 (H, m, 4-H), 2.16 (H, ddd, *J* 14, 8, 3, 5-H_{exo}), 2.02 (4 H, m, CH_3CO, 7-H_{anti}) and 1.76 (2 H, m, 5-H_{endo}, 7-H_{syn}); δ_C($CDCl_3$) 180.7, 170.3 (CO), 74.4 (C-6), 57.4 (C-1), 43.1 (C-4), 38.2 (C-5), 32.4 (C-7) and 20.9 (CH_3CO).

Methyl 3β-*Acetamido*-4α-*acetoxycyclopentane*-1β-*carboxylate* **10**.—A solution of compound **8** (86 mg, 0.51 mmol) in HCl (10 cm^3 1 mol dm^{-3}) was heated under gentle reflux for 1 h. The solution was concentrated under reduced pressure and the residue azeotroped with toluene (3 × 5 cm^3). The resulting solid was taken up in methanol (1 cm^3) and 2,2-dimethoxypropane (5 cm^3). Concentrated hydrochloric acid (3 drops) was added and the solution stirred at room temperature for 8 h. The solution was concentrated under reduced pressure and the residue taken up in dichloromethane (10 cm^3). Acetic anhydride (2.43 mmol) and pyridine (2.44 mmol) were added and the resulting solution stirred at room temperature for 24 h. The solution was partitioned between water (10 cm^3) and ethyl acetate (20 cm^3). The aqueous phase was separated and extracted with ethyl acetate (3 × 20 cm^3). The organic layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure. Toluene (3 × 5 cm^3) was evaporated from the residue to remove final traces of pyridine. The residue was purified by column chromatography (silica, ethyl acetate) to give the title compound **10** (80 mg, 65%) (Found: $[M + H]^+$ 244.1189. $C_{11}H_{17}NO_5$ requires $[M + H]^+$ 244.1185); ν_{max}($CHCl_3$)/cm^{-1} 3439 (NH), 2999, 2957 (CH), 1720 and 1666 (2 × CO); δ_H($CDCl_3$) 6.49 (H, br d, *J* 6, NH), 5.03 (H, ddd, *J* 8, 3.5, 3, 3-H), 4.23 (H, br m, 4-H), 3.66 (3 H, s, CH_3O), 2.99 (H, m, 1-H), 2.42 (H, ddd, *J* 14, 9, 8, 5-H), 2.20 (H, m, 2-H), 2.00 (7 H, br m, 2 × CH_3CO, 2-H) and 1.70 (H, m, 5-H); δ_C($CDCl_3$) 177.0 (CONH), 170.5, 169.8 (2 × $COCH_3$), 78.5 (C-3), 55.4 (C-4), 52.1 (CH_3O), 39.7 (C-1), 34.0, 33.8 (C-2, C-5), 23.2 and 21.0 (2 × CH_3CO).

Bromofluorination of 2-(4′-*Methoxybenzyl*)-2-*azabicyclo*-[2.2.1]*hept*-5-*en*-3-*one* **4**.—Triethylamine tris(hydrogen fluoride) (12 cm^3) was added dropwise to a stirred solution of compound **4** (3.40 g, 14.80 mmol) and *N*-bromosuccinimide (4.22 g, 23.7 mmol, 1.6 equiv.) in dichloromethane (150 cm^3) in the dark at 0 °C and the resulting solution stirred at 4 °C for 4 d. The solution was diluted with dichloromethane (500 cm^3), washed with water (2 × 50 cm^3), 10% aqueous sodium sulfite (4 × 50 cm^3) and saturated aqueous sodium hydrogen carbonate (4 × 50 cm^3). The aqueous layers were combined and extracted with dichloromethane (2 × 100 cm^3) and the organic extracts combined, washed (brine), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography [silica, 3:1 LP (60–80) ethyl acetate] to give 2-(4′-methoxybenzyl)-6-*exo*-7-*anti*-dibromo-2-azabicyclo[2.2.1]heptan-3-one **5** (1.26 g, 22%). The physical data for this compound were as previously described. Further elution gave 7-*anti*-bromo-6-*exo*-fluoro-2-(4′-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one **11** (2.09 g, 43%), m.p. 95–97 °C (ethanol–water) (Found: C, 51.1; H, 4.9, N, 4.1. $C_{14}H_{15}BrFNO_2$ requires C, 51.2; H, 4.6; N, 4.3%); *m*/*z* (CI) 330 (95%, M + 1, ^{81}Br), 328 (100, M + 1, ^{79}Br) and 250 (20, M − Br); ν_{max}($CHCl_3$)/cm^{-1} 2958, 2840 (CH), 1706 (CO), 1610 and 1507 (C=CAr); δ_H($CDCl_3$) 7.20 (2 H, m, ArH), 6.80 (2 H, m, ArH), 4.62 (2 H, dm, J_{H-F} 54, including d, *J* 14.5, 6-H, CH_2Ar), 4.21 (H, br s, 7-H), 4.07 (H, d, *J* 14.5, CH_2Ar), 3.90 (H, br s, 1-H), 3.81 (3 H, s, CH_3O), 2.93 (H, m, 4-H) and 2.40 (2 H, m, 2 × 5-H); δ_C($CDCl_3$) 172.6 (CON), 159.6 (C-4′), 129.6 (C-2′, C-6′), 127.7 (C-1′), 114.5 (C-3′, C-5′), 90.6 (d, J_{C-F} 200.1, C-6), 64.4 (d, J_{C-F} 22.9, C-1), 55.3 (CH_3O), 50.4, 47.9 (C-4, C-7), 44.3 (CH_2Ar) and 30.9 (d, J_{C-F} 21.5, C-5); δ_F($CDCl_3$) −11.3 (ddd, J_{H-F} 54, 27, 12, 6-F).

7-anti-*Bromo*-6-exo-*fluoro*-2-*azabicyclo*[2.2.1]*heptan*-3-*one*-**12**.—A solution of 7-*anti*-bromo-6-*exo*-fluoro-2-(4′-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one **11** (50 mg, 0.15 mmol) and DDQ (85 mg, 0.37 mmol) in dioxane (2 cm^3) was heated under reflux under argon for 24 h. The solution was partitioned between dichloromethane (10 cm^3) and saturated aqueous sodium hydrogen carbonate (5 cm^3). The aqueous layer was separated and extracted with dichloromethane (3 × 5 cm^3). The organic layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography [silica, 1:1 LP (60–80)–ethyl acetate] to give the title compound **12** (19 mg, 61%) as an off-white solid, m.p. 134–136.5 °C (Found: $[M + NH_4]^+$ 225.0039. C_6H_7-BrFNO requires $[M + NH_4]^+$ 225.0038); *m*/*z* (CI) 227 (95%, $[M + NH_4]^+$, ^{81}Br), 225 (100, $[M + NH_4]^+$, ^{79}Br), 210 (< 10, $[M + H]^+$, ^{81}Br), 208 (< 10, $[M + H]^+$, ^{79}Br) and 147 (60, $[M - Br]^+$); ν_{max}(KBr)/cm^{-1} 3180 (NH), 3087, 2979, 2833 (CH) and 1702 (CO); δ_H[$^2H_6$]acetone) 7.10 (H, br s, NH), 4.94 (H, dm, J_{H-F} 54, 6-H), 4.50 (H, br s, 7-H), 4.16 (H, br s, 1-H), 2.72 (H, m, 4-H) and 2.30 (2 H, br m, 2 × 5-H); δ_F([$^2H_6$]acetone) 6.57 (ddd, J_{H-F} 54, 27, 13, 7-F).

6-exo-*Fluoro*-2-(4′-*methoxybenzyl*)-2-*azabicyclo*[2.2.1]-*heptan*-3-*one* **13**.—A solution of 7-*anti*-bromo-6-*exo*-fluoro-2-(4′methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one **11** (2.210 g, 6.74 mmol), AIBN (24 mg, 0.15 mmol) and tributyltin hydride (2.7 cm^3, 10.04 mmol) in dry benzene (25 cm^3) was heated at reflux under an argon atmosphere for 18 h. The solvent was removed under reduced pressure and the residue partitioned between acetonitrile (200 cm^3) and hexane (50 cm^3). The acetonitrile layer was separated and washed with hexane (4 × 50 cm^3). The solvent was removed under reduced pressure and the residue purified by column chromatography [silica, 1:1 LP (60–80)–ethyl acetate] to give the title compound **13** (1.502 g, 90%) as an oil which solidified with time at room temperature, m.p. 51–52 °C (Found: $[M^+]$ 249.1165. $C_{14}H_{16}FNO_2$ requires $[M^+]$ 249.1165); ν_{max}($CHCl_3$)/cm^{-1} 1689 (CO), 1609 and 1506 (C=CAr); δ_H($CDCl_3$) 7.20 (2 H, m, ArH), 6.90 (2 H, m, ArH), 4.57 (H, dddd, J_{H-F} 54, *J* 7, 2, 2, 6-H), 4.36 (H, d, *J* 15, CH_2Ar), 4.10 (H, d, *J* 15, CH_2Ar), 3.78 (3 H, s, CH_3O), 3.73 (H, br s, 1-H), 2.75 (H, m, 4-H), 2.07 (H, ddddd, J_{H-F} 17, *J* 14, 6.5, 3.3, 5-H_{exo}) and 1.86 (3 H, m, 5-H, 2 × 7-H); δ_C($CDCl_3$) 177.2 (CONPMB), 159.4 (C-4′), 129.4 (C-2′, C-6′), 128.9 (C-1′), 114.3 (C-3′, C-5′), 90.8 (d, J_{C-F} 191.8, C-6), 61.2 (d, J_{C-F} 26.8, C-1), 55.3 (CH_3O), 44.4 (CH_2Ar), 43.5 (C-4), 37.1 (C-7) and 33.9 (d, J_{C-F} 20.9, C-5); δ_F($CDCl_3$) −9.95 (dddd, J_{H-F} 54, 34, 17, 3, 6-F).

6-exo-*Fluoro*-2-*azabicyclo*[2.2.1]*heptan*-3-*one* **14**.—A solution of ceric ammonium nitrate (3.259 g, 5.58 mmol) in water was added dropwise to a stirred solution of compound **13** (417 mg, 1.67 mmol) in acetonitrile (20 cm^3) and the resulting solution stirred at room temperature for 6 h. The solution was diluted with ethyl acetate (200 cm^3), washed with water (4 × 10 cm^3) and the aqueous phase back extracted with ethyl acetate (3 × 50 cm^3). The organic layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (silica, ethyl acetate) to give the title compound **14** (188 mg, 87%), m.p. 134–136.5 °C (Found: $[M^+]$ 129.0590. C_6H_8FNO requires $[M^+]$ 129.0590); ν_{max}($CHCl_3$/cm^{-1} 3443, 3234 (NH), 2999 (CH) and 1704 (CO); δ_H($CDCl_3$) 6.20 (H, br s, NH), 4.87 (H, dm, J_{H-F} 54, 6-H), 3.93 (H, s, 1-H), 2.66 (H, br d, *J* 3, 4-H) and 2.20–1.72 (4 H, m, 2 × 5-H, 2 × 7-H); δ_C($CDCl_3$) 180.9 (CONH), 92.1 (d, J_{C-F} 191.9, C-6), 57.5 (d, J_{C-F} 27.1, C-1), 42.5 (C-4), 37.9 (C-7) and 33.0 (d, J_{C-F} 20.9, C-5); δ_F($CDCl_3$) −7.85 (ddd, J_{H-F} 54, 35, 20, 6-F).

Methyl 3β-*Acetamido*-4α-*fluorocyclopentane*-1β-*carboxylate* **16**.—A solution of 6-*exo*-fluoro-2-azabicyclo[2.2.1]heptan-3-one **15** (158 mg, 1.22 mmol) in HCl (1 mol dm^{-3}; 10 cm^3) was heated under gentle reflux for 1 h. The solution was concentrated under reduced pressure and the residue azeotroped with toluene (3 × 5 cm^3). The resulting solid was taken up in methanol (1 cm^3) and 2,2-dimethoxypropane (5 cm^3). Concen-

trated hydrochloric acid (3 drops) was added and the solution stirred at room temp. for 14 h. The solution was concentrated under reduced pressure and the residue taken up in dichloromethane (10 cm^3). Acetic anhydride (2.43 mmol) and pyridine (2.44 mmol) were added and the resulting solution stirred at room temperature for 24 h. The solution was diluted with water (10 cm^3) and extracted with ethyl acetate (4 × 20 cm^3). The organic layers were combined, dried ($MgSO_4$), and concentrated under reduced pressure. Toluene (3 × 5 cm^3) was evaporated from the residue to remove final traces of pyridine. The residue was purified by column chromatography (silica, ethyl acetate) to give the title compound **16** (211 mg, 85%) as a white solid, m.p. 86–87 °C. (Found: $[M + H]^+$ 204.1036. $C_9H_{14}FNO_3$ requires $[M + H]^+$ 204.1036); $\nu_{max}(CHCl_3)/cm^{-1}$ 3374 (NH), 2984 (CH), 1714 (CO_2Me) and 1665 (NHAc); $\delta_H(CDCl_3)$ 6.50 (H, br s, NH), 4.95 (H, dm, J_{H-F} 51.5, 4-H), 4.38 (H, m, 3-H), 3.69 (3 H, s, CH_3O), 3.11 (H, m, 1-H), 2.47–1.90 (6 H, m including d 1.96, s, CH_3CO, 2-H, 2 × 5-H) and 1.78 (H, ddd, J 14, 4, 4, 2-H); $\delta_C(CDCl_3)$ 178.3 (CONH), 169.6 (CO_2Me), 97.4 (d, J_{C-F} 179.8, C-3), 55.6 (d, J_{C-F} 28.5, C-4), 52.3 (CH_3O), 40.1 (C-1), 35.3 (d, J_{C-F} 22.4, C-5), 33.0 (C-2) and 23.2 (CH_3CO); $\delta_F(CDCl_3)$ −13.77 (dddd, J_{H-F} 51.5, 36, 23, 13, 2-F).

1β-*Acetamido*-2α-*fluoro*-4β-*hydroxymethylcyclopentane* **17**.—Calcium chloride (183 mg, 1.65 mmol) and sodium borohydride (112 mg, 2.96 mmol) in dry THF (5 cm^3) were sonicated for 30 min. A solution of compound **16** (162 mg, 0.82 mmol) in dry THF (5 cm^3) was added and the resulting suspension sonicated for a further 5 h. The suspension was cooled (ice bath), and saturated aqueous ammonium chloride (10 cm^3) was added carefully. Ethyl acetate (50 cm^3) was added, the organic phase separated and the aqueous layer extracted with ethyl acetate (3 × 50 cm^3). The organic layers were combined, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography (silica, 19:1 ethyl acetate–methanol) to give the title compound **17** (130 mg, 93%) (Found: $[M + H]^+$ 176.1087. $C_8H_{14}FNO_2$ requires $[M + H]^+$ 176.1087); $\nu_{max}(CHCl_3)/cm^{-1}$ 3361 (OH, NH), 2973, 2860 (CH) and 1767 (CO); $\delta_H(CDCl_3)$ 7.25 (H, d, J 5, NH), 4.81 (H, d m, J_{H-F} 52, 2-H), 4.22 (H, m, 1-H), 4.10 (H, br s, OH), 3.60 (2 H, m, CH_2O), 2.45 (H, m, 3-H), 2.30 (H, m, 5-H), 1.90 (5 H, m, CH_3, 3-H, 4-H) and 1.44 (H, ddd, J 14, 4, 4, 5-H); $\delta_C(CDCl_3)$ 170.1 (CONH), 98.6 (d, J_{C-F} 177.9, C-2), 64.9 (CH_2OH), 55.0 (d, J_{C-F} 78.1, C-1), 37.1 (C-4), 32.6 (d, J_{C-F} 21.4, C-3), 32.4 (C-5) and 23.1 (CH_3CO).

2-*Benzyl*-2-*azabicyclo*[2.2.1]*hept*-5-*en*-3-*one* **20**.—A solution of 2-azabicyclo[2.2.1]hept-5-en-3-one **1** (6.01 g, 55.1 mmol) in dry THF (50 cm^3) was added dropwise to a stirred suspension of sodium hydride [4.81 g of a 60% dispersion in oil, washed with dry hexane (50 cm^3), 120 mmol] in dry THF (50 cm^3) at 0 °C. Stirring was continued at room temperature for 30 min and then the suspension was cooled to 0 °C. A solution of benzyl bromide (10 cm^3, 84.1 mmol) and TBAI (134 mg) in dry DMF (10 cm^3) was added dropwise and the resulting solution stirred at room temperature for 18 h. The reaction was quenched by cautiously pouring onto saturated ammonium chloride–ice (200 cm^3). The solution was extracted with dichloromethane (5 × 100 cm^3). The organic layers were combined, washed with brine (100 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (silica, 3:2 hexane–ethyl acetate) to give 2-benzyl-2-azabicyclo[2.2.1]hept-5-en-3-one **20** (9.49 g, 87%). The physical properties were as previously described.[4]

2-(p-*Tolylsulfonyl*)-2-*azabicyclo*[2.2.1]*hept*-5-*en*-3-*one* **21**.[14]—A solution of 2-azabicyclo[2.2.1]hept-5-en-3-one **1** (3.08 g, 28.2 mmol) in dry THF (25 cm^3) was added to a stirred suspension of sodium hydride [60% suspension in oil, washed with hexane (20 cm^3); 1.83 g, 45.8 mmol] in dry THF (50 cm^3) at 0 °C and the resulting suspension stirred at room temperature for 30 min. A solution of toluene-*p*-sulfonyl chloride (8.07 g, 42.3 mmol) in dry THF (50 cm^3) was added and the resulting solution stirred at room temperature for 24 h. The reaction was quenched by the dropwise addition of saturated aqueous sodium hydrogen carbonate (30 cm^3) at 0 °C. The solution was partitioned between ether (500 cm^3) and saturated aqueous sodium hydrogen carbonate (100 cm^3). The organic layer was separated and the aqueous layer extracted with diethyl ether (2 × 200 cm^3). The organic layers were combined, washed with saturated sodium hydrogen carbonate (2 × 100 cm^3), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography [silica, 3:2 LP (40–60)–ether] to give the title compound **21** (1.57 g, 21%), m.p. 110–112 °C (dichloromethane–hexane) (lit[14] 110–112 °C) (Found: C, 59.5; H, 4.9; N, 5.45. $C_{13}H_{13}NO_3S$ requires C, 59.3; H, 5.0; N, 5.3%); *m*/*z* (CI) 263 (<10%, M^+) and 197 (20, $M - C_5H_6$); ν(KBr)/cm^{-1} 2977 (CH), 1742 (CO), 1596 (C=CAr), 1357 and 1141 (SO_2); $\delta_H(CDCl_3)$ 7.70 (2 H, d, J 8.5, ArH), 7.27 (2 H, d, J 8.5, ArH), 6.64 (H, dd, J 5.3, 2, 6-H), 6.36 (H, ddd, J 5.3, 3.5, 1.5, 5-H), 5.20 (H, m, 1-H), 3.35 (H, m, 4-H), 2.40 (4 H, m, CH_3, 7-H) and 2.18 (H, ddd, J 9, 2, 2, 7-H).

2-*Benzyl*-6-exo-*chloro*-7-anti-*phenylsulfenyl*-2-*azabicyclo*-[2.2.1]*heptan*-3-*one* **19**.—A solution of benzenesulfenyl chloride (272 mg, 1.88 mmol) in acetonitrile (2 cm^3) was added dropwise to a stirred solution of compound **20** (375 mg, 1.88 mmol) in acetonitrile (6 cm^2) at room temperature and the resulting solution stirred at room temp. for 24 h. The solvent was removed under reduced pressure and the residue purified by column chromatography [silica, 4:1 LP (60–80)–ethyl acetate] to give the title compound **19** (320 mg, 50%), m.p. 136–137 °C (dichloromethane–hexane) (Found: C, 66.3; H, 5.2 N, 4.1. $C_{19}H_{18}ClNOS$ requires C, 66.4 H, 5.3; N, 4.1%); *m*/*z* (CI) 346 (35%, M + 1, ^{37}Cl), 344 (100, M + 1, ^{35}Cl) and 308 (<10, M − Cl); ν_{max}(KBr)/cm^{-1} 3061, 3012, 2931 (CH), 1679 (CO), 1578 and 1493 (C=CAr); $\delta_H(CDCl_3)$ 7.30 (10 H, m, ArH), 4.64 (H, d, J 15, CH_2Ph), 4.08 (H, d, J 15, CH_2Ph), 3.86 (2 H, m, 1-H, 6-H), 3.67 (H, m, 7-H_{syn}), 2.95 (H, m, 4-H), 2.64 (H, ddd, J 14, 4, 4, 5-H_{exo}) and 2.46 (H, m, 5-H_{endo}); $\delta_C(CDCl_3)$ 174.6 (CONBn), 136.0, 135.0 (ArC), 131.2, 129.3, 129.1, 128.2, 127.6 (ArCH), 67.2 (C-1), 57.1 (C-7), 54.3 (C-6), 50.8 (C-4), 44.8 (CH_2Ph) and 33.9 (C-5).

Phenylsulfenylation of compounds **4** *and* **21** *in Acetonitrile*.—General procedure. A solution of benzesulfenyl chloride in acetonitrile (1 cm^3) was added dropwise to a stirred solution of the lactam in acetonitrile (1 cm^3) at 0 °C and the resulting solution stirred for 24 h whilst warming to room temperature. The solvent was removed under reduced pressure and the residue purified by column chromatography over silica to give the corresponding chloro sulfides.

Compound **4** (104 mg, 0.45 mmol) and benzenesulfenyl chloride (65 mg, 0.45 mmol) gave after chromatography [3:1 LP (bp. 60–80)–ethyl acetate] 6-*exo*-chloro-2-(4′-methoxybenzyl)-7-*anti*-phenylsulfenyl-2-azabicyclo[2.2.1]heptan-3-one **18** (73 mg, 44%), m.p. 131–132 °C (Found: $[M + H]^+$ 374.0982. $C_{20}H_{20}{}^{35}ClNO_2S$ requires $[M + H]^+$ 374.0981); $\nu_{max}(CHCl_3)/cm^{-1}$ 3008 (CH), 1700 (CO), 1585 and 1510 (C=CAr); $\delta_H(CDCl_3)$ 7.40 (5 H, m, ArH), 7.20 (2 H, m, 2′-H, 6′-H), 6.90 (2 H, m, 3′-H, 5′-H), 4.53 (H, d, J 15, $ArCH_2$), 4.06 (H, d, J 15, $ArCH_2$), 3.83 (5 H, m, CH_3, 1-H, 6-H), 3.63 (H, dd, J 2, 1.5, 7-H), 2.92 (H, dd, J 2, 1.5, 4-H), 2.62 (H, dd, J 14, 4, 5-H_{exo}) and 2.44 (H, br dd, J 14, 8, 5-H_{endo}); $\delta_C(CDCl_3)$ 174.5 (CON), 159.6 (C-4′), 135.0 (ArCS), 128.0 (C-1′), 131.2, 129.5, 129.3 (ArCH), 127.5 (C-2′, C-6′), 114.5 (C-3′, C-5′), 67.1 (C-1), 57.1 (C-7),

55.3 (CH_3O), 54.3 (C-6), 50.9 (C-4), 44.3 ($ArCH_2$) and 33.9 (C-5).

Compound **21** (121 mg, 0.46 mmol) and benzenesulfenyl chloride (65 mg, 0.45 mmol) gave after chromatography [3:1 LP (60–80)–ethyl acetate] 5-*endo*-chloro-6-*exo*-phenylsulfenyl-2-(*p*-tolylsulfonyl)-2-azabicyclo[2.2.1]heptan-3-one **22** (93 mg, 50%), m.p. 103–105 °C (Found: $[M^+]$ 407.0417. $C_{19}H_{18}{}^{35}ClNO_3S_2$ requires $[M^+]$ 407.0417); ν_{max}(KBr)/cm^{-1} 2966 (CH), 1768 (CO), 1592 (C=CAr), 1363, 1167 (SO_2); δ_H($CDCl_3$) 7.50 (10 H, m, ArCH), 4.58 (H, br s, 1-H), 4.11 (H, dd, *J* 4, 4, 5-H), 3.40 (H, dd, *J* 4, 4, 6-H), 3.07 (H, m, 4-H), 2.42 (3 H, s, CH_3) and 2.26 (2 H, m, 7-H); δ_C($CDCl_3$) 168.9 (CON), 145.5 (C-1′), 136.1, 133.2 (ArC), 129.8, 129.5, 129.1, 127.5, 127.6 (ArCH), 64.6 (C-1), 58.7 (C-5), 57.4 (C-6), 53.8 (C-4), 36.8 (C-7) and 21.7 (CH_3).

Phenylsulfenylation of Compounds **4** and **21** in THF.—*General procedure.* A solution of benzenesulfenyl chloride (0.18 g, 1.25 mmol) in dry THF (5 cm^3) was added dropwise to a stirred solution of the lactam in dry THF (5 cm^3) at room temperature and the resulting solution stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the residue purified by column chromatography over silica to give the corresponding chloro sulfides.

Compound **4** (131 mg, 0.50 mmol) gave after chromatography [3:1 LP (60–80)–ethyl acetate] 6-*endo*-chloro-7-*exo*-phenylsulfenyl-2-(4′-methoxybenzyl)-2-azabicyclo[2.2.1]-heptan-3-one **18** (129 mg, 63%). The physical properties were as previously described.

Compound **21** (124 mg, 0.54 mmol) gave after chromatography [3:1 LP (60–80)–ethyl acetate] 5-*endo*-chloro-6-*exo*-phenylsulfenyl-2-(*p*-tolylsulfonyl)-2-azabicyclo[2.2.1]heptan-3-one **22** (90 mg, 45). The physical properties were as previously described.

Phenylselenenylation of Compounds **4**, **20** *and* **21** *in THF.*—*General procedure.* A solution of benzeneselenenyl bromide in THF (5 cm^3) was added dropwise to a stirred solution of the lactam in dry THF (5 cm^3) at −78 °C and the resulting solution was stirred for 24 h whilst warming to room temperature. The solvent was removed under reduced pressure and the residue purified by column chromatography over silica to give the corresponding bromo selenides.

Compound **20** (102 mg, 0.51 mmol) and benzeneselenenyl bromide (0.17 g, 0.51 mmol) gave after chromatography [4:1 LP (60–80)–ethyl acetate] 2-benzyl-5-*exo*-bromo-6-*endo*-phenylselenenyl-2-azabicyclo[2.2.1]heptan-3-one **24** (121 mg, 55%), m.p. 91–92 °C (dichloromethane–hexane) (Found: C, 52.3; H, 3.9; Br, 18.5; N, 3.3. $C_{19}H_{18}BrNOSe$ requires C, 52.4; H, 4.2; Br, 18.4; N, 3.2%); *m*/*z* (CI) 436 (95%, $[M + 1]^+$), 356 (10, $[M - Br]^+$) and 200 (100, $[M - PhSeBr + H_2]^+$); ν_{max}($CHCl_3$)/cm^{-1} 2998 (CH), 1697 (CO), 1579 and 1477 (C=CAr); δ_H($CDCl_3$) 7.60 (2 H, m, ArCH), 7.40 (6 H, m, ArH), 7.20 (2 H, m, ArH), 5.14 (H, d, *J* 15, CH_2Ph), 4.22 (H, dd, *J* 3.5, 1.8, 5-H), 4.10 (H, d, *J* 15, CH_2Ph), 3.95 (H, dd, *J* 3.5, 2.5, 6-H), 3.80 (H, dd, *J* 2.5, 1.8, 1-H), 3.11 (H, apparent d, *J* 1.8, 4-H) and 2.14 (2 H, m, 7-H); δ_C($CDCl_3$) 172.7 (CONBn), 133.7, 129.5, 128.8, 128.7, 128.2, 128.1, 127.8, (ArC, 6 × ArCH), 62.9 (C-1), 56.6 (C-^{77}Se satellites, J_{C-Se} 76, C-6), 55.7 (C-4), 51.1 (J_{C-Se} 16, C-5), 47.0 (CH_2Ph) and 40.8 (C-7).

2-(4′-Methoxybenzyl)-2-azabicyclo[2.2.1]hept-5-en-3-one **4** (115 mg, 0.5 mmol) and benzeneselenenyl bromide (0.16 g, 0.68 mmol) gave after chromatography [3:1 LP (60–80)–ethyl acetate]-5-*exo*-bromo-2-(4′-methoxybenzyl)-6-*endo*-phenylselenenyl-2-azabicyclo[2.2.1]heptan-3-one **25** (98 mg, 42%), m.p. 89–90 °C (Found: $[M + H]^+$ 465.9921. $C_{20}H_{20}{}^{79}BrNO_2{}^{80}Se$ requires $[M + H]^+$ 465.9920); ν_{max}($CHCl_3$)/cm^{-1} 2831 (CH), 1699 (CO), 1606 and 1509 (C=CAr); δ_H($CDCl_3$) 7.70 (2 H, m, ArCH), 7.40 (3 H, m, ArH), 7.10 (2 H, d, *J* 8.5, 2′-H, 6′-H), 6.90 (2 H, d, *J* 8.5, 3′-H, 5′-H), 5.05 (H, d, *J* 15, CH_2Ar), 4.20 (H, apparent dd, *J* 3.5, 2, 5-H), 4.02 (H, d, *J* 15, CH_2Ar), 3.93 (H, dd, *J* 3.5, 2.5, 6-H), 3.74 (4 H, br s, CH_3O, 1-H), 3.09 (H, br d, *J* < 2, 4-H) and 2.10 (H, br m, 7-H); δ_C($CDCl_3$) 172.6 (CONAr), 159.3 (ArC–OMe), 133.8, 129.5 (ArCH), 128.9, 128.4 (ArC, ArCSe), 128.1, 114.3 (ArCH), 62.4 (C-1), 58.8 (C-^{77}Se satellites, J_{C-Se} 77, C-6), 55.8 (C-4), 55.3 (CH_3O), 51.2 (C-5), 46.4 (CH_2Ar) and 40.8 (C-7).

Compound **21** (127 mg, 0.48 mmol) and benzeneselenenyl bromide (0.16 g, 0.68 mmol) gave after chromatography [3:1 LP (60–80)–ethyl acetate] 5-*exo*-bromo-6-*endo*-phenylselenenyl-2-(*p*-tolylsulfonyl)-2-azabicyclo[2.2.1]heptan-3-one **26** (102 mg, 43%), m.p. 125–127 °C (Found: $[M + NH_4]^+$ 516.9700. $C_{19}H_{18}{}^{79}BrNO_3S^{80}Se$ requires $[M + NH_4]^+$ 516.9699); ν_{max}(KBr)/cm^{-1} 3033, 2960 (CH), 1746 (CO), 1598 (C=CAr) and 1358 (SO_2); δ_H($CDCl_3$) 7.90 (2 H, m, ArH), 7.70 (2 H, m, ArH), 7.40 (5 H, m, ArH), 4.90 (H, dddd, *J* 2.5, 2, 1.8, 1.2, 1-H), 4.11 (H, ddd, *J* 3.5, 1.8, 0.6, 5-H), 3.87 (H, dd, *J* 3.5, 2.5, 6-H), 3.04 (H, m, 4-H), 2.44 (3 H, s, CH_3), 2.33 (H, ddd, *J* 10.8, 1.2, 1.2, 7-H_{anti}) and 2.20 (H, dddd, *J* 10.8, 1.8, 1.8, 1.8, 7-H_{syn}); δ_C($CDCl_3$) 170.1 (CONTs), 145.3, 136.1 (ArC), 135.2, 129.6, 129.4, 128.6, 128.3 (ArCH), 128.1 (ArC), 67.0 (C-1), 57.0 (C-4), 55.8 (C-6), 49.1 (C-5), 40.5 (C-7) and 21.7 (CH_3).

Further elution gave 5-*endo*-bromo-6-*exo*-phenylselenenyl-2-(*p*-tolylsulfonyl)-2-azabicyclo[2.2.1]heptan-3-one **23** (73 mg, 31%), m.p. 149–150 °C (Found: $[M + NH_4]^+$ 516.9700. $C_{19}H_{18}{}^{79}BrNO_3S^{80}Se$ requires $[M + NH_4]^+$ 516.9699); ν_{max}(KBr)/cm^{-1} 2962, 2923 (CH), 1766 (CO), 1594 (C=CAr) and 1363 (SO_2); δ_H($CDCl_3$) 7.70 (2 H, m, ArH), 7.60 (2 H, m, ArH), 7.40 (3 H, m, ArH), 7.30 (2 H, m, ArH), 4.67 (H, m, 1-H), 4.10 (H, ddd, *J* 4.3, 4.3, 0.8, 5-H), 3.41 (H, dd, *J* 4.3, 4.3, 6-H), 3.05 (H, m, 4-H), 2.42 (3 H, s, CH_3) and 2.15 (2 H, m, 7-H); δ_C($CDCl_3$) 169.0 (CONTs), 145.4, 136.0 (ArC), 134.4, 129.8, 129.7, 128.7 (ArCH), 128.1 (ArC), 127.8 (ArCH), 65.6 (C-1), 54.2 (C-4), 51.0 (C-6), 46.2 (C-5), 37.6 (C-7) and 21.7 (CH_3).

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