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Radical deoxygenation of 3-azatricyclo[2.2.1.0^{2,6}]heptan-5-ols to 2-azabicyclo[2.2.1]hept-5-enes and 1,2-dihydropyridines

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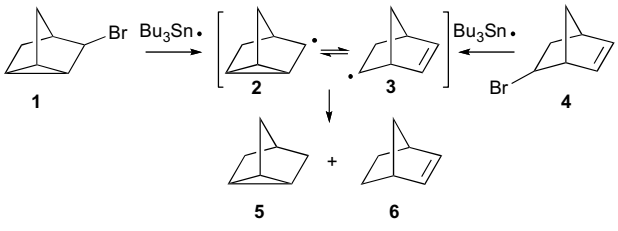
ABSTRACT

Additions of alkyl or aryl Grignard reagents, or pyridin-3-yl-lithiums or lithium alkoxides, to *exo*-5,6-epoxy-7-(*tert*-butoxycarbonyl)-2-tosyl-7-azabicyclo[2.2.1]hept-2-ene lead to 7-substituted-1-tosyl-3-azatricyclo[2.2.1.0^{2,6}]heptan-5-ols. Radical deoxygenations of 7-alkyl-1-tosyl-3-azatricyclo[2.2.1.0^{2,6}]heptan-5-ols give 7-alkyl-4-tosyl-2-azabicyclo[2.2.1]hept-5-enes, whereas 7-aryl-1-tosyl-3-azatricyclo[2.2.1.0^{2,6}]heptan-5-ols give 2-(arylmethyl)-5-tosyl-1,2-dihydropyridines.

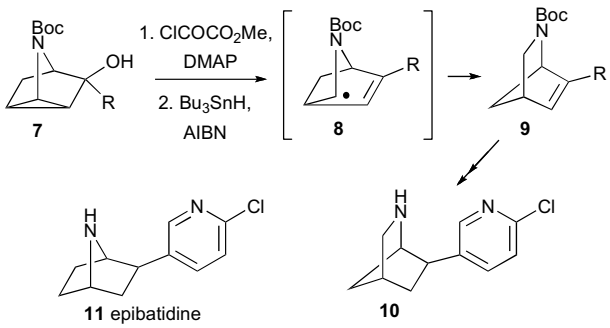
1. Introduction

Radical cyclisations and rearrangements are versatile processes for the synthesis of ring systems.[1] An important radical process is the cyclopropylmethyl–homoallyl rearrangement.[2] Bridged nortricyclyl (tricyclo[2.2.1.0^{2,6}]heptanyl)–norbornenyl (bicyclo[2.2.1]heptenyl) examples were well-studied in the 1950s and 1960s. For example, starting from nortricyclyl bromide **1** or norbornenyl bromide **4**, reaction with Bu_3SnH and AIBN at low concentration of H-atom donor led to the same (approximately equal) mixture of nortricyclane **5** and norbornene **6** (Scheme 1), whereas varying the concentration led to varying proportions of nortricyclane **5** and norbornene **6**, from which it was concluded that the process involves classical radicals **2** and **3**, rather than a single non-classical species.[3] Formation of significant quantities of nortricyclane **5** is partly a reflection of strain in the norbornenyl system. Note also that, in this degenerate/symmetrical system, homoallylic radical **3** (*ent*-**3**) forms regardless of which cyclopropyl bond cleaves from radical **2**.

In contrast to the generation of a mixture of nortricyclane **5** and norbornene **6** from radical reduction of nortricyclyl bromide **1** (Scheme 1), we previously showed during the development of novel analgesics (e.g., **10**) related to epibatidine **11** (Scheme 2) that radical deoxygenation of 7-azanortricyclanols **7** selectively gave 6-substituted 2-azabicyclo[2.2.1]hept-5-enes **9**, even when R is potentially radical stabilising (e.g., aryl).[4] The potential dative stabilising effect of an α-nitrogen in the product-producing radical[5] likely directs this homoallylic radical rearrangement.[6] An earlier example of the influence of nitrogen on a homoallylic radical rearrangement was observed by Rigby and Pigge in an 8-azabicyclo[3.2.1] system.[7] We have subsequently used this concept in the synthesis of other azacycles,[8] including kainic acid,[9] ibogamine[10] and fused aromatic systems.[11] In the present paper we detail studies originally designed to



Scheme 1.



Scheme 2.

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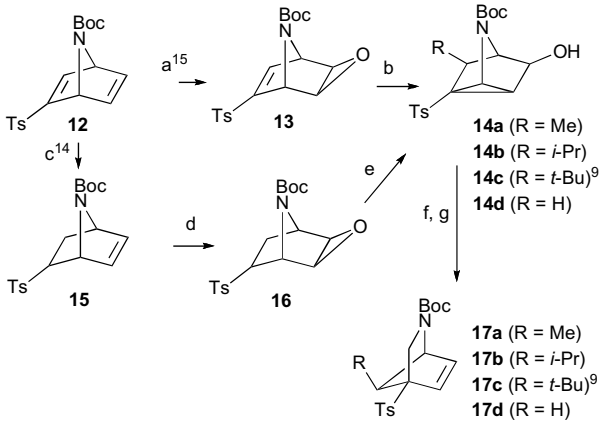
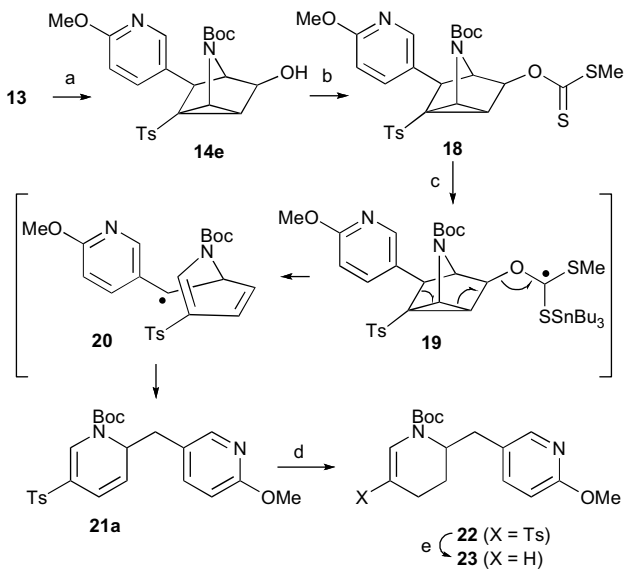
broaden the scope of the above strategy to give differently substituted 2-azabicyclo[2.2.1]hept-5-enes,[12] but, which have also led to finding an extended radical rearrangement process to give 1,2-dihydropyridines,[13] as well as alternative fragmentation–rearrangement modes in heterosubstituted systems.

2. Results and discussion

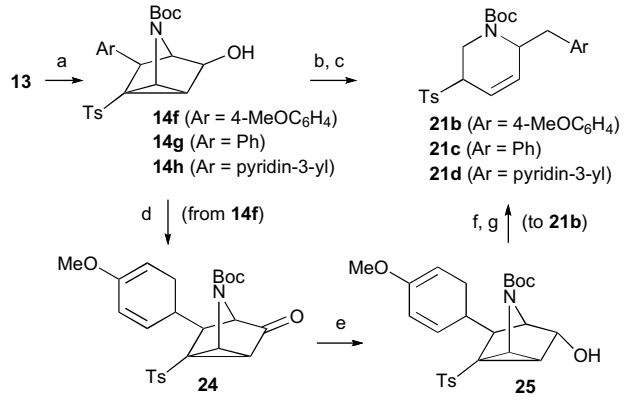
Epoxide **13** (readily available from cycloaddition of the commercial materials *N*-Boc pyrrole and tosyl ethyne,[14] followed by epoxidation of the resulting bicyclic diene **12**)[15] underwent *exo*-selective attack at the α,β-unsaturated sulfone functionality with alkyl Grignard reagents, to give the corresponding substituted 7-azanortricyclanols **14a–c** in excellent yields (90–96%, Scheme 3). While conjugate reduction–transannular cyclisation using $LiAlH_4$ gave the parent 7-azanortricyclanol **14d** (42%), the latter was more reproducibly accessed by base-induced transannular cyclisation[16] of sulfone epoxide **16** (available from bicyclic diene **12** by conjugate reduction using $NaBH_4$ to give known alkene **15**,[14] followed by epoxidation with MCPBA). Subsequent radical deoxygenation (via the xanthates)[17] of 7-azanortricyclanols **14a–d** using Bu_3SnH (2 equiv) gave the anticipated 2-azabicyclo[2.2.1]heptenes **17a–d** (45–65%).[18]



Scheme 3. (a) MCPBA, CH_2Cl_2, reflux, 62%; (b) RMgBr, THF, −78 °C (R=Me, 96%; *i*-Pr, 90%; *t*-Bu, 92%), or (R=H) $LiAlH_4$, THF, 42%; (c) $NaBH_4$, MeOH, 73%; (d) MCPBA, CH_2Cl_2, reflux, 40%; (e) MeLi, THF, 0 °C, 67%; (f) KH, CS_2, MeI, THF [R=Me (57%), *t*-Bu (92%), H (59%)], or 1,1′-thiocarbonyldiimidazole, CH_2Cl_2 [R=*i*-Pr (92%)]; (g) Bu_3SnH, AIBN, toluene, reflux [R=Me (65%), *i*-Pr (52%), *t*-Bu (45%), H (59%)].



Scheme 4. (a) 6-Methoxypyridin-3-ylLi, THF, −78 °C, 78%); (b) KH, CS_2, MeI, THF, 80%; (b) Bu_3SnH, AIBN, toluene, reflux, 78%; (c) H_2 (2 atm), 10% Pd/C, toluene, 87%; (d) 6% Na-Hg, MeOH, 55%.



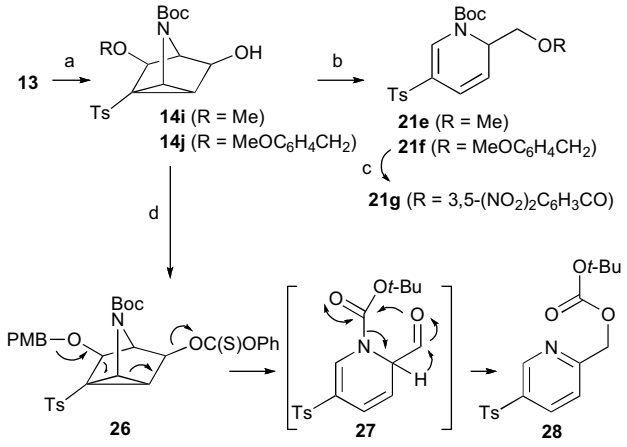
Scheme 5. (a) ArMgBr, THF, 0 °C (Ar=4-$MeOC_6H_4$, 72%; Ph, 82%), or pyridin-3-ylLi, TMEDA, THF, −78 °C, 74%, (b) KH, CS_2, MeI, THF (Ar=4-$MeOC_6H_4$, 84%; Ph, 95%; pyridin-3-yl, 77%); (c) Bu_3SnH, AIBN, toluene, reflux (R=4-$MeOC_6H_4$, 62%; Ph, 65%; pyridin-3-yl, 52%); (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 98%; (e) *i*-PrMgCl, THF, 77%; (f) KH, CS_2, MeI, THF, 72%; (g) Bu_3SnH, AIBN, toluene, reflux, 33%.

In attempting to apply the above chemistry towards new epibatidine analogues, Bu_3SnH (2 equiv)-induced deoxygenation of the xanthate **18** (0.02 M in toluene) of 6-methoxypyridin-3-yl lithium-derived 7-azanortricyclanol **14e** (78%) was examined (Scheme 4). However, none of the expected 2-azabicyclo[2.2.1]-hept-5-ene **17** (R=6-methoxypyridin-3-yl) was detected, but rather the reaction proceeded cleanly to give 1,2-dihydropyridine **21a** (78%). All spectroscopic data (including ^1H–^1H and ^1H–^{13}C correlation spectra) were fully in accord with the structural assignment. Use of Bu_3SnD instead of Bu_3SnH in the deoxygenation resulted in deuterium incorporation in the methylene group of 1,2-dihydropyridine **21a**; the latter is what would be expected from the **19** to **20** fragmentation pathway indicated in Scheme 4. Further supporting evidence for the product of deoxygenation was obtained by partial hydrogenation and desulfonylation; the resulting tetrahydropyridines **22** and **23** both exhibited analytical data consistent[19] with the proposed structures.

Presuming that dihydropyridine formation might be favoured by R in **14** (Scheme 3) being an electron donating and/or aryl substituent, we examined additional 7-azanortricyclanols **14** bearing such functionality (Scheme 5). However, the xanthate of 7-azanortricyclanol **14f** (R=4-$MeOC_6H_4$; the structural assignment was supported by X-ray crystallographic analysis[20]) initially gave a modest yield (31%) of the corresponding dihydropyridine **21b** (R=4-$MeOC_6H_4$). This might be due to stannyl radical attack on the product, since subjecting dihydropyridine **21b** (R=4-$MeOC_6H_4$) to the reaction conditions resulted in 60% decomposition, whereas simply boiling dihydropyridine **21b** (R=4-$MeOC_6H_4$) in toluene for 2 h resulted in no discernible decomposition (^1H NMR analysis). With these observations in mind, we reduced the quantity of Bu_3SnH to 1.1 equiv and increased the time over which it was added from 20 min to 2.25 h. These latter conditions gave the desired dihydropyridine **21b** (R=4-$MeOC_6H_4$) in satisfactory and reproducible yields (62%). Variation of the thiocarbonyl moiety (thiocarbonylimidazolyl or CSOPh) gave 1,2-dihydropyridine **21b** (R=4-$MeOC_6H_4$) in 43% and 59% yields, respectively. Similar yields of 1,2-dihydropyridines **21c,d** were observed with phenyl and pyridin-3-yl substituents. The influence of the relative configuration at the radical progenitor on the viability of the deoxygenation/rearrangement chemistry was explored using *endo*-alcohol **25**,[21] prepared by Swern oxidation of 7-azanortricyclanol **14f** (R=4-$MeOC_6H_4$) to the ketone **24** (98%), followed by reduction using *i*-PrMgBr (77%). In the event, *endo*-alcohol **25**

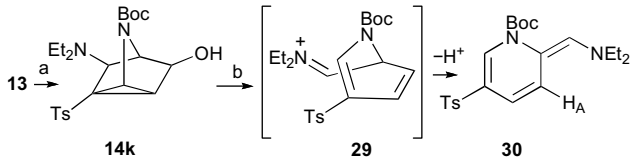
underwent deoxygenation to give dihydropyridine **21b** (R=4-$MeOC_6H_4$), but in reduced yield (33%) compared to when using *exo*-alcohol **14f** (R=4-$MeOC_6H_4$).

Investigation of the effect on the deoxygenation/rearrangement of a heteroatom directly bonded to the azanortricyclanol was examined by the addition of alkoxides and a lithium amide to epoxide **13**. With methoxy and *p*-methoxybenzyloxy substituents, the yields of the corresponding 1,2-dihydropyridines **21e,f** were considerably reduced (37–10%, Scheme 6), however in the latter case removal of the PMB group using DDQ and X-ray crystallographic analysis of the dinitrobenzoate derivative **21g** of the resulting alcohol provided confirmation of the presence of the 1,2-dihydropyridine motif (Scheme 6).[22] The origins of the lower deoxygenation yields with 7-azanortricyclanols **14i,j** are not clear. In the deoxygenation of the methoxy-substituted azanortricyclanol **14i**, partial recovery (20%) of the corresponding unreacted xanthate (which also, unusually, required heating for it to be formed in good yield) could be indicative of a less efficient radical chain process. Also, attempted deoxygenation of the thiocarbonate **26** of 7-azanortricyclanol **14j** (R=4-$MeOC_6H_4CH_2$) caused elimination to give pyridine carbonate **28** (72%).[23] The electron rich PMB ether in the thiocarbonate **26** likely induces bond cleavages in the azatricyclic nucleus similar to those shown in **19**, but in a heterolytic manner as shown in **26** below, to give 1,2-dihydropyridine aldehyde **27** from which rearrangement provides the aromatic product **28**.[24]



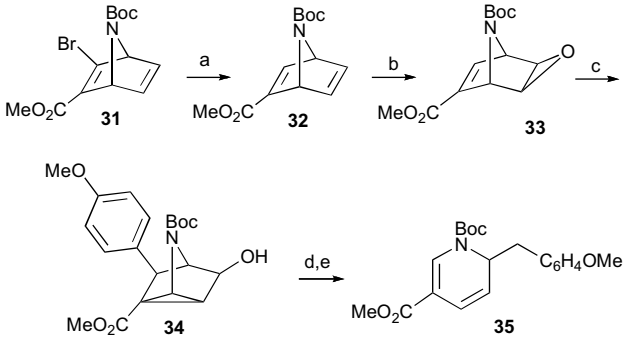
Scheme 6. (a) R=Me: MeOLi, MeOH, reflux, 90%; R=4-$MeOC_6H_4CH_2$: 4-$MeOC_6H_4CH_2ONa$, THF, 58%; (b) R=Me: NaH, CS_2, MeI, THF, reflux, 77%, then Bu_3SnH, AIBN, toluene, reflux, 37%; R=4-$MeOC_6H_4CH_2$: KH, CS_2, MeI, THF, then Bu_3SnH, AIBN, toluene, reflux, 10%; (c) DDQ, H_2O, CH_2Cl_2, then 3,5-$(NO_2)_2C_6H_3COCl$, Et_3N, CH_2Cl_2, 10%; (d) PhOC(S)Cl, DMAP, MeCN, 56%, then Bu_3SnH, AIBN, reflux, 72%.

In the case of the diethylamino system **14k**, attempted deoxygenation of the corresponding xanthate with Bu_3SnH returned only starting material. In contrast, the corresponding phenyl thiocarbonate gave no dihydropyridine, with only the enamine **30** (Scheme 7) being isolated (likely formed via iminium **29**) from reflux in cumene under either free radical deoxygenation conditions (27%, no reaction was observed in refluxing toluene), or simple thermal conditions (38%). NOESY correlation between the proton marked H_A and the ethyl groups supports the *E*-geometry of the enamine **30** shown.



Scheme 7. (a) Et_2NH, CH_2Cl_2, then MeLi, THF, 74%; (b) PhOC(S)Cl, DMAP, CH_2Cl_2, 78%, then cumene, reflux, 38%.

The effect of an alternative electron withdrawing group to the sulfone substituent was also investigated, with ester-substituted 7-azanortricyclanol **34** (Scheme 8). This alcohol was prepared by debromination[25] of the known diene **31**,[26] followed by epoxidation and subsequent addition of 4-$MeOC_6H_4MgBr$. Reaction of the corresponding thiocarbonylimidazole with Bu_3SnH gave 1,2-dihydropyridine **35** as the only isolable product (46%).



Scheme 8. (a) Zn/Ag, MeOH, 80%; (b) MCPBA, $NaHCO_3$, CH_2Cl_2, 44%; (c) 4-$MeOC_6H_4MgBr$, THF, 0 °C, 46%; (d) 1,1′-thiocarbonyldiimidazole, CH_2Cl_2, quant.; (e) Bu_3SnH, AIBN, toluene, reflux, 46%.

3. Conclusion

The present study shows that the outcome of deoxygenation of (1-tosyl)-3-azatricyclo[2.2.1.$0^{2,6}$]heptan-5-ols (7-azanortricyclanols) is significantly influenced by the nature of the substituent at the 7-position. Alkyl (or no) substitution at the 7-position as in **14a–d** (and similarly, from our earlier study,[4] 5-alkyl or 5-(hetero)aryl substitution in systems **7** lacking the tosyl group) leads to 2-azabicyclo[2.2.1]hept-5-enes (e.g., **17**). In certain cases, the 7-alkyl-4-tosyl-2-azabicyclo[2.2.1]hept-5-ene products **17** may be more concisely obtained by direct (*n*)-alkyl radical addition–homoallylic radical rearrangement from diene **12**. In all these examples, α-N stabilisation of the product-forming radical likely plays a significant role. 7-Aryl substitution of (1-tosyl)-3-azatricyclo[2.2.1.$0^{2,6}$]-heptan-5-ols leads on radical deoxygenation to a more extended rearrangement to generate 1,2-dihydropyridines **21**, with the overriding driving forces likely being a combination of benzylic radical stabilisation and full relief of ring strain. The latter extended rearrangement is of interest as a new method for accessing dihydropyridines, which are important as biologically active agents.[27] One common method to prepare dihydropyridines is by nucleophilic addition of organometallics to *N*-acylpyridinium salts, although the regioselectivity of addition (C-2/C-4) can sometimes be problematic.[28] For example, regioisomeric mixtures were obtained in the addition of Grignard reagents to the *N*-benzoylpyridinium salt of a pyridin-3-yl sulfonamide.[29] In the present study, reductive deoxygenation of 3-azatricyclo[2.2.1.$0^{2,6}$]heptan-5-ols **14**/**34** [bearing an aryl or methoxy substitutent in the 7-position and an electron withdrawing group (sulfone or ester) at C-1] is shown to provide a regiospecific route to 2,5-disubstituted 1,2-dihydropyridines **21**/**35**. More mesomerically electron donating substituents at the 7-position (e.g., alkoxy, dialkylamino) reduce the efficiency of dihydropyridine formation and lead to alternative fragmentation–rearrangement modes.

4. Experimental section

4.1. Materials and methods

All reactions requiring anhydrous conditions were conducted in flame-dried apparatus under an atmosphere of argon. Syringes and

needles for the transfer of reagents were oven-dried and allowed to cool in a desiccator over P_2O_5 before use. Ethers were distilled from benzophenone ketyl, hydrocarbons from CaH_2 and alcohols from their magnesium alkoxides. All reactions were monitored by TLC, using commercially available (Merck or Camlab) plates pre-coated with a 0.25 mm layer of silica containing a fluorescent indicator. Visualisation of reaction components was achieved with 254 nm light, and with vanillin or $KMnO_4$ dips. Unless stated otherwise organic layers were dried using $MgSO_4$, evaporated with a Buchi rotary evaporator, followed by drying on a high vacuum oil pump (~1 mmHg). Column chromatography was carried out on Kieselgel 60 (40–63 μm). Petrol refers to the fraction with bp 40–60 °C. Unless otherwise stated, IR spectra were recorded using a Perkin–Elmer 1750 FTIR spectrophotometer. Peak intensities are specified as strong (s), medium (m) or weak (w). Only selected absorbancies are reported. ^{1}H NMR spectra of compounds were recorded in $CDCl_3$ unless otherwise stated, using a Varian Gemini 200 (200 MHz), Bruker DPX400 (400 MHz) or AMX500 spectrometer (500 MHz). Chemical shifts (δ) are reported relative to $CHCl_3$ (δ 7.27). Coupling constants (J) are given in hertz and multiplicities are given as multiplet (m), doublet (d), triplet (t) or quartet (q). ^{13}C NMR spectra were recorded on the Bruker DPX400 (100 MHz) or AMX500 (125 MHz). Chemical shifts are reported relative to $CDCl_3$ (central line of triplet δ 77.0) unless stated otherwise. ^{1}H–^{1}H and ^{1}H–^{13}C COSY spectra were used to aid peak assignments. Mass spectra were obtained from the EPSRC Mass Spectrometry Service Centre, Swansea with a Micromass, ZAB-E instrument or 900 XLT high resolution double focussing mass spectrometer with tandem ion trap. Alternatively they were recorded in-house using a VG mass Lab. TRIO1 (GCMS) or Micromass platform APCI spectrometer. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoKα radiation, λ=0.71073 Å) and intensity data were integrated and scaled using the DENZO-SMN package.[30] The structures were all solved using the direct-methods program SIR92,[31] which located all non-hydrogen atoms. Subsequent full-matrix least-squares refinement was carried out using the CRYSTALS program suite[32] and coordinates and anisotropic thermal parameters of all non-hydrogen atoms were refined. Hydrogen atoms were visible in the difference map and initially refined with soft-restraints before refinement with a riding model.

4.2. 3-(*tert*-Butoxycarbonyl)-7-methyl-1-tosyl-3-azatricyclo[2.2.1.0^{2,6}]heptan-5-ol (14a)

MeMgBr (3.0 M in THF; 138 μL, 0.413 mmol) was added to a solution of epoxide **13**[15] (100 mg, 0.275 mmol) in THF (7 mL) at −78 °C. The solution was then allowed to warm to rt over 9 h. Saturated aq NH_4Cl (3 mL) was then added and the mixture extracted with Et_2O (3×10 mL). The combined organic layers were washed with brine, dried and evaporated under reduced pressure. Purification of the residue by recrystallisation (EtOAc–petrol) gave a white solid, *7-azanortricyclanol* **14a** (100 mg, 96%); R_f 0.1 (60% Et_2O in petrol); mp 175–176 °C (dec). Found: C, 60.3; H, 6.6; N, 3.7. $C_{19}H_{25}O_5NS$ requires C, 60.1; H, 6.6; N, 3.7%. IR (KBr) 3456br, 2977m, 2930m, 1698s, 1597m, 1393m, 1302m, 1146m and 1089m cm^{-1}; δ_H (400 MHz) 7.75 (2H, d, J 8, 2×CH of Ts), 7.35 (2H, d, J 8, 2×CH of Ts), 4.78 (1H, br s, NCHCTs), 3.87–3.68 (2H, m, NC*H*CHMe, C*H*OH), 2.46 (3H, s, CH_3 of Ts), 2.34 (1H, d, J 5, TsCC*H*CHOH), 2.20 (1H, br s, OH), 1.91 (1H, q, J 6.5, C*H*CH_3), 1.47 (9H, s, 3×CH_3) and 0.89 (3H, d, J 6.5, C*H*$_3$CH); δ_C (100 MHz) 155.8 (C=O), 144.8 (C_{quat} of Ts), 136.9 (C_{quat} of Ts), 130.0 (2×CH of Ts), 127.8 (2×CH of Ts), 81.3 (*C*Me_3), 72.1 (COH), 62.7 (NCH), 49.5 (TsC), 38.0 (NC*H*CTs, Me*C*H), 28.2 (3×CH_3), 27.5 (TsC*C*HCHOH), 21.6 (CH_3 of Ts) and 12.0 (CH_3); m/z (CI, NH_3) 397 (38%, M+NH_4^+), 341 (73) and 124 (100) (Found: M+NH_4^+, 397.1802. $C_{19}H_{29}O_5N_2S$ requires M, 397.1797.).

4.3. 3-(*tert*-Butoxycarbonyl)-7-isopropyl-1-tosyl-3-azatricyclo[2.2.1.0^{2,6}]heptan-5-ol (14b)

i-PrMgCl (2.0 M in THF; 0.62 mL, 1.2 mmol) was added to a solution of epoxide **13**[15] (300 mg, 0.83 mmol) in THF (20 mL) at −78 °C. The solution was warmed to rt over 2.5 h and then saturated aq NH_4Cl (10 mL) added and the mixture extracted with Et_2O (3×25 mL). The combined organic layers were washed with brine, dried and evaporated under reduced pressure to give an oil, which crystallised slowly. Trituration with Et_2O gave a white solid, *7-azanortricyclanol* **14b** (302 mg 90%); R_f 0.5 (Et_2O); mp 169 °C. Found: C, 61.6; H, 7.4; N, 3.4. $C_{21}H_{29}O_5NS$ requires C, 61.9; H, 7.2; N, 3.4%. IR (KBr) 3310br, 2969w, 1677s, 1453s, 1314m, 1170m, 1138s and 1090m cm^{-1}; δ_H (400 MHz) 7.74 (2H, d, J 8, 2×CH of Ts), 7.33 (2H, d, J 8, 2×CH of Ts), 4.53 (1H, d, J 5, NCHCTs), 3.99 (1H, s, NCHCH*i*-Pr), 3.75 (1H, s, C*H*OH), 3.30 (1H, br s, C*Hi*-Pr), 2.43 (3H, s, CH_3 of Ts), 2.28 (1H, s, TsCC*H*CHOH), 2.01 (1H, br s, C*H*CH_3), 1.44 (9H, s, 3×CH_3), 0.91 (3H, d, J 7, CHC*H*$_3$) and 0.85 (3H, d, J 7, CHC*H*$_3$); δ_C (100 MHz) 154.1 (C=O), 144.8 (C_{quat} of Ts), 136.6 (C_{quat} of Ts), 129.9 (2×CH of Ts), 127.7 (2×CH of Ts), 81.0 (*C*Me_3), 72.6 (COH), 65.8 (NCH), 57.8 (*CH*i-Pr), 48.3 (CTs), 47.9 (*C*HCH_3), 38.2 (NCHCTs), 28.3 (3×CH_3), 27.3 (TsCCHCHOH), 26.0 (CH_3 of *i*-Pr), 22.3 (CH_3 of *i*-Pr) and 21.6 (CH_3 of Ts); m/z (CI, NH_3) 425 (M+NH_4^+, 38%), 369 (100), 308 (26), 215 (14) and 154 (24) (Found: M+NH_4^+, 425.2112. $C_{21}H_{33}O_5N_2S$ requires M, 425.2110.).

4.4. 8-(*tert*-Butoxycarbonyl)-6-tosyl-8-aza-3-oxatricyclo[3.2.1.0^{2,4}]octane (16)

To a solution of alkene **15**[14] (3.6 g, 10 mmol) in CH_2Cl_2 (70 mL) was added *m*-CPBA (55% w/w remainder water; 4.5 g, 15 mmol) in one portion. The reaction mixture was heated to reflux for 2 days, then cooled to rt. The mixture was washed with 10% aq sodium bisulphite (100 mL), saturated $NaHCO_3$ (100 mL) and brine (100 mL). The organic phase was dried and evaporated under reduced pressure. Purification of the residue by column chromatography (50→80% Et_2O in petrol) gave a white crystalline solid, *epoxide* **16** (929 mg, 40%); R_f 0.6 (Et_2O); mp 180 °C (sharp). Found: C, 58.9; H, 6.5; N, 3.7. $C_{18}H_{23}O_5NS$ requires C, 59.2, H, 6.3, N, 3.8%.; IR (KBr) 2985w, 2938w, 1706s, 1399m, 1365m, 1320m, 1287m, 1250m, 1149s, 1090m, 664m and 590m cm^{-1}; δ_H (500 MHz; DMSO; 370 K) 7.84 (2H, d, J 8, 2×CH of Ts), 7.49 (2H, d, J 8, 2×CH of Ts), 4.30 (1H, s, NCHCTs), 4.26 (1H, d, J 4, NCH), 4.03 (1H, ddd, J 9.7, 5, 4.8, TsCH), 3.79 (1H, d, J 3.5, OCH), 3.61 (1H, d, J 3.5, OCH), 2.46 (3H, s, CH_3 of Ts), 2.08 (1H, br, CH_aH$_b$), 1.79 (1H, dd, J 12.7, 5, CH$_a$H$_b$) and 1.38 (9H, s, 3×CH_3); δ_C (125 MHz; DMSO; 370 K) 156.5 (C=O), 145.7 (C_{quat} of Ts), 137.6 (C_{quat} of Ts), 131.0 (2×CH of Ts) 128.5 (2×CH of Ts), 80.5 (*C*Me_3), 65.7 (TsC), 59.4 (NCH), 58.2 (NCH), 50.0 (CHO), 47.9 (CHO), 28.8 (3×CH_3), 28.0 (CH_2) and 21.9 (CH_3 of Ts); m/z (CI, NH_3) 383.2 (M+NH_4^+, 23%), 366.2 (M+H^+, 19), 327.2 (50), 266.1 (54), 229.2 (26), 200.1 (51), 173.1 (30), 129.1 (19) and 112.3 (100) (Found: M+H^+, 366.1380. $C_{18}H_{24}O_5NS$ requires M, 366.1375.).

4.5. 3-(*tert*-Butoxycarbonyl)-1-tosyl-3-azatricyclo[2.2.1.0^{2,6}]heptan-5-ol (14d)

To a cooled (0 °C) solution of epoxide **16** (100 mg, 0.27 mmol) in THF (5 mL) was added MeLi (1.2 M in THF; 0.34 mL, 0.41 mmol) dropwise. The orange solution was stirred at 0 °C for 2 h, then saturated aq NH_4Cl (2 mL) added. The aqueous phase was separated and extracted with Et_2O (3×10 mL). The combined organic extracts were washed (brine), dried and evaporated under reduced pressure. Purification of the residue by column chromatography (Et_2O) gave a white solid foam, *7-azanortricyclanol* **14d** (67 mg, 67%); R_f 0.5 (Et_2O); mp 156–157 °C. Found: C, 59.1; H, 6.5; N, 3.7. $C_{18}H_{23}NO_5S$

requires C, 59.2; H, 6.3; N, 3.8%. IR (KBr) 3469br, 3200br, 2979m, 2933m, 1705s, 1598m, 1453m, 1369s, 1316s, 1302s, 1167s, 1146s, 1091s and 670s cm^{-1}; δ_H (400 MHz) 7.69 (2H, d, *J* 8, 2×CH of Ts), 7.29 (2H, d, *J* 8, 2×CH of Ts), 4.20 (1H, d, *J* 5, NCHCTs), 4.00–3.92 (2H, m, NCH and CHO), 2.48 (1H, d, *J* 5, TsCC*H*CHOH), 2.38 (3H, s, CH_3 of Ts), 1.82 (1H, d, *J* 9, OH, removed with D_2O shake), 1.65 (1H, d, *J* 11, CH_aH_b), 1.39 (1H, m, CH_aH_b) and 1.32 (9H, s, 3×CH_3); δ_C (100 MHz) 156.5 (C=O), 143.3 (C_{quat} of Ts), 136.1 (C_{quat} of Ts), 130.4 (2×CH of Ts), 128.5 (2×CH of Ts), 82.0 (CMe_3), 74.7 (COH), 66.3 (NCH), 58.8 (TsC), 47.3 (NCHCTs), 39.4 (CH_2), 31.3 (TsC*C*HCHOH), 28.5 (3×CH_3 of Boc), 22.0 (CH_3 of Ts); *m*/*z* (CI, NH_3) 383.3 ($M+NH_4^+$, 80%), 366.2 ($M+H^+$, 15), 327.2 (100) (Found: $M+H^+$, 366.1379. $C_{18}H_{24}NO_5S$ requires M, 366.1375.).

4.6. 2-(*tert*-Butoxycarbonyl)-7-methyl-4-tosyl-2-azabicyclo[2.2.1]hept-5-ene (17a)

A solution of 7-azanortricyclanol **14a** (240 mg, 0.63 mmol) in THF (3 mL) was added dropwise to a slurry of KH (30% dispersion in mineral oil; 108 mg, 0.95 mmol) in THF (3 mL) at 0 °C. The solution was then warmed to rt and stirred for 20 min, then cooled to 0 °C and CS_2 (47 μL, 0.76 mmol) added. The mixture was stirred for a further 10 min before addition of MeI (47 μL, 0.76 mmol). The solution was then warmed to rt and stirred for 20 min before water (5 mL) was added dropwise. The aqueous layer was extracted with Et_2O (3×20 mL) and the combined organic layers were washed with brine, dried and evaporated under reduced pressure. Purification of the residue by column chromatography (40% Et_2O in petrol) gave an off-white solid, the corresponding *xanthate* (168 mg; 57%). Diagnostic data: δ_H (200 MHz) 5.25 (0.5H, s, C*H*O), 5.17 (0.5H, s, C*H*O) and 2.43 (3H, s, SCH_3). The above xanthate (165 mg, 0.35 mmol) was dissolved in toluene (16 mL), AIBN (10 mg, 0.06 mmol) was added and the mixture heated to reflux. Bu_3SnH (217 μL, 0.81 mmol) was added over 5 min. After 2 h, the reaction mixture was cooled and evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL) and stirred vigorously with aq NaOH (1 M; 10 mL) for 1 h. The organic layer was washed with aq NaOH (1 M; 10 mL), then brine, dried and evaporated under reduced pressure. Purification of the residue by column chromatography (40% Et_2O in petrol) gave a colourless oil, *2-azabicyclo-[2.2.1]heptene* **17a** (83 mg, 65%); R_f 0.4 (50% Et_2O in petrol); IR (film) 2975m, 1699s, 1597w, 1478w, 1456m, 1393s, 1317m, 1303m, 1168s, 1139s and 1088m cm^{-1}; δ_H (400 MHz) (split by rotamers 1:1 ratio) 7.80 (2H, d, *J* 8, 2×CH of Ts), 7.37 (2H, d, *J* 8, 2×CH of Ts), 6.45 (0.5H, dd, *J* 5.5, 2, CHC*H*=), 6.36 (0.5H, dd, *J* 5.5, 2, CHC*H*=), 6.31 (0.5H, d, *J* 5.5, CHCH=C*H*), 6.23 (0.5H, d, *J* 5.5, CHCH=C*H*), 4.37 (0.5H, br s, C*H*CH=), 4.25 (0.5H, br s, C*H*CH=), 3.92 (0.5H, d, *J* 9, NCH_2), 3.86 (0.5H, d, *J* 9, NCH_2), 2.91 (0.5H, d, *J* 9, NCH_2), 2.83 (0.5H, d, *J* 9, NCH_2), 2.45 (3H, s, CH_3 of Ts), 2.14 (0.5H, q, *J* 6.5, C*H*CH_3), 1.86 (0.5H, q, *J* 6.5, C*H*CH_3), 1.41, 1.43 (9H, 2×s, Bu^t), 1.20 (1.5H, d, *J* 6.5, CH_3CH) and 1.17 (1.5H, d, *J* 6.5, CH_3CH); δ_C (100 MHz, split by rotamers) 155.9, 155.5 (C=O), 145.4, 145.3 (C_{quat} of Ts), 136.8, 136.1 (CHCH=), 135.6, 135.5 (CHCH=CH), 134.8, 134.6 (C_{quat} of Ts), 130.0, 129.8 (2×CH of Ts), 128.7, 128.6 (2×CH of Ts), 80.3, 80.2 (CMe_3), 76.0, 75.4 (TsC), 66.1, 64.6 (NCH), 55.7, 53.4 ($CHCH_3$), 44.0, 43.4 (NCH_2), 28.3 (3×Me), 21.6 (CH_3 of Ts) and 12.3 and 11.9 (CH_3CH); *m*/*z* (CI, NH_3) 381 (55%, $M+NH_4^+$), 364 (100, $M+H^+$) and 342 (33) (Found: $M+H^+$, 364.1583. $C_{19}H_{26}O_4NS$ requires M, 364.1582.).

4.7. 2-(*tert*-Butoxycarbonyl)-7-isopropyl-4-tosyl-2-azabicyclo[2.2.1]hept-5-ene (17b)

1,1′-Thiocarbonyldiimidazole (177 mg, 0.99 mmol) was added to a solution of 7-azanortricyclanol **14b** (90 mg, 0.22 mmol) in CH_2Cl_2 (1.5 mL) at rt. After 14 h, the reaction mixture was poured onto the top of a silica gel column and eluted with 80% Et_2O in petrol to give the corresponding *thiocarbamate* (105 mg, 92%). Diagnostic data: δ_H (200 MHz) 8.28 (1H, d, *J* 4, NCH=), 7.56 (1H, s, NCH=), 7.07–6.98 (1H, m, NCH=), 5.21 (0.5H, s, C*H*O) and 5.19 (0.5H, s, C*H*O). The above thiocarbamate (100 mg, 0.19 mmol) was dissolved in toluene (20 mL), AIBN (10 mg, 0.06 mmol) was added and the mixture heated to reflux. Bu_3SnH (104 μL, 0.39 mmol) was then added over 15 min. After 1 h, the reaction mixture was cooled and evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL) and stirred vigorously with aq NaOH (1 M; 10 mL) for 1 h. The organic layer was washed with aq NaOH (1 M; 10 mL), then brine, dried and evaporated under reduced pressure. Purification of the residue by column chromatography (50% Et_2O in petrol) gave a colourless oil, *2-azabicyclo[2.2.1]heptene* **17b** (39 mg, 52%); R_f 0.8 (Et_2O); IR (film) 2963m, 2873w, 1698s, 1598w, 1477w, 1456w, 1392s, 1367s, 1320m, 1304m and 1256w cm^{-1}; δ_H (400 MHz) (split by rotamers 3:7 ratio) 7.82–7.80 (2H, m, 2×CH of Ts), 7.41–7.28 (2H, m, 2×CH of Ts), 6.44 (0.3H, dd, *J* 5.5, 2, CHC*H*=), 6.32 (0.7H, dd, *J* 5.5, 2.5, CHC*H*=), 6.09 (0.3H, d, *J* 5.5, CHCH=C*H*), 6.23 (0.7H, d, *J* 5.5, CHCH=C*H*), 4.65 (0.3H, br s, C*H*CH=), 4.49 (0.7H, br s, C*H*CH=), 4.00–3.95 (1H, m, NCH_2), 2.68 (1H, d, *J* 9, NCH_2), 2.67 (0.9H, s, CH_3 of Ts), 2.47 (2.1H, s, CH_3 of Ts), 2.13 (0.7H, d, *J* 8, C*H*i-Pr), 2.02 (0.3H, d, *J* 8, C*H*i-Pr), 1.94–1.81 (1H, m, CH of *i*-Pr), 1.40 (9H, s, *t*-Bu), 1.26–1.18 (3H, m, CH_3 of *i*-Pr) and 0.98 (3H, d, *J* 7, CH_3 of *i*-Pr); δ_C (100 MHz, some signals split by rotamers) 155.2 (C=O), 145.2 (C_{quat} of Ts), 137.2 (CHCH=), 136.2 (C_{quat} of Ts), 135.5 (CHCH=CH), 130.0 (2×CH of Ts), 128.9 (2×CH of Ts), 80.1 (CMe_3), 75.6 (TsC), 69.6, 69.2 (NCH), 63.8, 62.4 (CHi-Pr), 46.0, 45.6 (NCH_2), 28.3 (3×Me), 25.8 (CH of *i*-Pr), 23.4 (CH_3 of *i*-Pr), 21.6 (CH_3 of *i*-Pr) and 21.6 (CH_3 of Ts); *m*/*z* (Found: $M+H^+$, 392.1902. $C_{21}H_{30}O_4NS$ requires M, 392.1895.).

4.8. 2-(*tert*-Butoxycarbonyl)-4-tosyl-2-azabicyclo[2.2.1]-hept-5-ene (17d)

To a cooled (0 °C) stirred slurry of KH (164 mg, 1.23 mmol; 30% w/w dispersion in mineral oil) in THF (3 mL) was added a solution of alcohol **14d** (150 mg, 0.41 mmol) in THF (2 mL). The reaction mixture was warmed to rt and stirred for 20 min. CS_2 (128 μl, 2.05 mmol) was added then after 15 min MeI (128 μl, 2.05 mmol). After 30 min the reaction mixture was quenched with water (5 mL), the aqueous layer was separated and extracted with Et_2O (3×10 mL). The combined organic layers were washed (brine), dried and evaporated under reduced pressure. Purification of the residue by column chromatography (40% Et_2O in light petroleum) gave a light brown oil, the corresponding *xanthate* (110 mg, 59%). Diagnostic data: δ_H (200 MHz) 2.50 (3H, s, SCH_3). The above xanthate (110 mg, 0.24 mmol) and AIBN (8 mg) were dissolved in toluene (9 mL) and the mixture heated to reflux. Bu_3SnH (97 μl, 0.36 mmol) was added dropwise over 10 min. After 2 h, the reaction mixture was cooled and evaporated under reduced pressure. Purification of the residue by column chromatography (40% Et_2O in petrol) gave a clear colourless oil, *2-azabicyclo[2.2.1]heptene* **17d** (49 mg, 59%); R_f 0.2 (40% Et_2O in petrol); IR (film) 2925m, 1697s, 1400m, 1364m, 1306m, 1173m, 1139s, 1087m, 868w, 811w and 664s cm^{-1}; δ_H (400 MHz) (spectrum broad due to rotamers) 7.81 (2H, d, *J* 8, 2×CH of Ts), 7.38 (2H, d, *J* 8, 2×CH of Ts), 6.53–6.30 (2H, m, 2×CH=), 4.77–4.67 (1H, m, NCH), 3.73–3.65 (1H, m, NCH_aH_b), 2.88–2.84 (1H, m, NCH_aH_b), 2.46 (3H, s, CH_3 of Ts), 2.08–1.80 (2H, m, CH_2) and 1.41 (9H, s, *t*-Bu); δ_C (100 MHz) (spectrum broadened/split by rotamers) 161.0 (C=O), 145.4 (C_{quat} of Ts), 137.0, 136.3 (C_{quat} of Ts), 132.8 (CH=), 132.4 (CH=), 130.0 (2×CH of Ts), 128.9 (2×CH of Ts), 80.3 (CMe_3), 75.5 (TsC), 61.3, 60.1 (NCH), 49.6 (CH_2), 47.1, 46.6 (NCH_2), 28.3 (3×CH_3) and 21.7 (CH_3 of Ts); *m*/*z* (CI, NH_3) 367.3 ($M+NH_4^+$, 60%), 350.2 ($M+H^+$, 100) (Found: $M+H^+$, 350.1432. $C_{18}H_{24}NO_4S$ requires M, 350.1426).

4.9. 3-(*tert*-Butoxycarbonyl)-7-(6-methoxypyridin-3-yl)-1-tosyl-3-azatricyclo[2.2.1.0^{2,6}]heptan-5-ol (14e)

n-BuLi (2.1 M in hexanes; 5.90 mL, 12.4 mmol) was added dropwise over 15 min to a stirred solution of 5-bromo-2-methoxypyridine[33] (3.11 g, 16.5 mmol) in THF (125 mL) at −78 °C. After 0.5 h, epoxide **13** (3.0 g, 8.3 mmol) in THF (100 mL) was added via cannula. The reaction mixture was stirred for 2 h at −78 °C. Saturated aq NH_4Cl (50 mL) was then added and the mixture extracted with Et_2O (3×80 mL). The combined organic layers were washed with brine, dried and evaporated under reduced pressure to give a brown oil. Purification of the residue by column chromatography (Et_2O) gave a white foam, *7-azanortricyclanol* **14e** (3.07 g, 78%); R_f (Et_2O) 0.19. Found: C, 61.0; H, 5.9; N, 5.8. Calcd for $C_{24}H_{28}N_2O_6S$: C, 61.0; H, 6.0; N, 5.9%.; IR (film) 3428br m, 2980s, 1704s, 1608m, 1496s, 1394s, 1259s, 1147s and 1091s cm^{-1}; δ_H (500 MHz) 7.78 (1H, d, *J* 2.0, C(2 of pyridine)H), 7.42 (2H, d, *J* 8.0, 2×CH of Ar), 7.25–7.11 (3H, m, C(4 of pyridine)H and 2×CH of Ar), 6.42 (1H, br s, C(5 of pyridine)H), 4.67 (1H, br s, C(2)H), 4.09 (1H, br s, C*H*OH), 3.93–3.87 (1H, m, C(4)H), 3.88 (3H, s, OMe), 2.98 (1H, br s, C(7)H), 2.62 (1H, br s, C(6)H), 2.40 (3H, s, $ArCH_3$), 1.88 (1H, br s, OH) and 1.59–1.20 (9H, br s, *t*-Bu); ^{1}H NMR NOE experiments: irradiation at δ 4.09 saw enhancement at 2.98 (7.6%), 2.62 (3.6%) and 1.88 (3%); δ_C (125 MHz) ($C6_{quat}$ of pyridine), 154.9 (C=O), 146.3 (C2 of pyridine), 144.9 (C_{quat} of Ar), 138.1 (C4 of pyridine), 136.0 (C_{quat} of Ar), 129.7 (2×CH of Ar), 128.1 (2×CH of Ar), 122.4 ($C3_{quat}$ of pyridine), 110.2 (C5 of pyridine), 81.6 (*C*Me$_3$), 72.9 (CHOH), 63.8 (C4), 53.4 (OMe), 49.8 ($C1_{quat}$), 44.3 (C7), 38.5 (C2), 28.1 (3×Me), 26.5 (C6) and 21.6 ($ArCH_3$); *m*/*z* (Found: M+H$^+$, 473.1746. $C_{24}H_{29}N_2O_6S$ requires M, 473.1746.).

4.10. 1-(*tert*-Butoxycarbonyl)-2-(6-methoxypyridin-3-yl)methyl-5-tosyl-1,2-dihydropyridine (21a)

A solution of alcohol **14e** (535 mg, 1.13 mmol) in THF (5 mL) was added dropwise to a suspension of KH (30% dispersion in mineral oil; 226 mg, 1.70 mmol) in THF (10 mL) at 0 °C. After stirring for 20 min at 25 °C, the solution was re-cooled to 0 °C and CS_2 (211 μL, 3.40 mmol) was added. The mixture was stirred for 15 min at 0 °C, then MeI (211 μL, 3.40 mmol) was added and the reaction mixture was stirred for 20 min at 25 °C. Water (20 mL) was added and the aqueous layer was extracted with Et_2O (3×25 mL). The combined organic layers were washed with brine, dried and evaporated under reduced pressure. Purification of the residue by column chromatography (60% Et_2O in petrol) gave a white solid foam, the corresponding *xanthate* **18** (509 mg, 80%). Diagnostic data: δ_H (400 MHz) 5.60 (0.5H, s, C*H*O), 5.56 (0.5H, s, C*H*O), 2.47 (1.5H, s, SCH_3) and 2.45 (1.5H, s, SCH_3). The above xanthate (169 mg, 0.31 mmol) and AIBN (10 mg, 0.061 mmol) were dissolved in degassed toluene (13 mL) and the mixture heated to 110 °C, then Bu_3SnH (190 μL, 0.71 mmol) was added over 20 min. After 2 h, the reaction mixture was allowed to cool and evaporated under reduced pressure to give a yellow oil, which was treated exactly according to the procedure of Curran and Chang[34] to remove tin by-products. Final purification by column chromatography (60% Et_2O in petrol) gave a clear colourless oil, *1,2-dihydropyridine* **21a** (107 mg, 78%); R_f (60% Et_2O–petrol) 0.31; IR (film) 2980m, 2946w, 1724s, 1608m, 1494s, 1394s, 1290s, 1259s and 1144s cm^{-1}; δ_H (400 MHz) 7.80–7.76 (1H, m, C(2 of pyridine)H), 7.69–7.63 (3H, m, 2×CH of Ar and C(6)H), 7.31–7.27 (3H, m, 2×CH of Ar and C(4 of pyridine)H), 6.67 and 6.55 (1H, 2×d, *J* 8.5, C(5 of pyridine)H), 6.13 (1H, d, *J* 10.0, C4), 5.48 (1H, dd, *J* 10.0, 5.5, C3), 4.90 (1H, br s, NCH), 3.89 (3H, s, OMe), 2.71 (1H, dd, *J* 13.5, 7.5, H of CH_2), 2.55 (1H, dd, *J* 13.5, 5.0, H of CH_2), 2.43 (3H, s, $ArCH_3$) and 1.50 and 1.43 (9H, 2×s, *t*-Bu); δ_C (100 MHz) 163.2 ($C6_{quat}$ of pyridine), 151.6 (C=O), 147.2 (C2 of pyridine), 143.8 (C_{quat} of Ar), 139.7 (C4 of pyridine), 138.2 ($C5_{quat}$), 133.7 (C_{quat} of Ar), 129.8 (2×CH of Ar), 128.9 (C6), 127.2 (2×CH of Ar), 123.7 ($C3_{quat}$ of pyridine), 121.7 (C5), 118.3 (C4), 110.5 (C5 of pyridine), 84.0 (*C*Me$_3$), 53.4 and 53.3 (OMe and CHN), 37.0 (ArCH_2), 28.3 and 27.9 (3×Me) and 21.6 ($ArCH_3$); *m*/*z* (CI) 457 (M+H$^+$, 100%), 401 (40) and 357 (M−Boc, 20) (Found: M+H$^+$, 457.1789. $C_{24}H_{29}N_2O_5S$ requires M, 457.1797.).

4.11. 1-(*tert*-Butoxycarbonyl)-2-(6-methoxypyridin-3-yl)methyl-5-tosyl-1,2,3,4-tetrahydropyridine (22)

Pd/C (10%, 55 mg) was added to a solution of 1,2-dihydropyridine **21a** (90 mg, 0.20 mmol) in toluene (15 mL) and the reaction mixture was stirred under H_2 (2.0 atm) for 14 h. The catalyst was filtered off and the solvent evaporated under reduced pressure. Purification of the residue by column chromatography (50% Et_2O–petrol) gave a clear colourless oil, *tetrahydropyridine-sulfone* **22** (80 mg, 87%); R_f (60% Et_2O–petrol) 0.31; IR (film) 2978m, 1721s, 1639s, 1494s, 1392s, 1290s, 1143s and 1090s cm^{-1}; δ_H (400 MHz) 8.23–7.96 (1H, m, C=CH), 7.88–7.81 (1H, m, C(2 of pyridine)H), 7.76 (2H, app. d, *J* 8.5, 2×CH of Ar), 7.39–7.33 (1H, m, C(4 of pyridine)H), 7.30 (2H, app. d, *J* 8.5, 2×CH of Ar), 6.67 (1H, d, *J* 8.5, C(5 of pyridine)H), 4.44–4.25 (1H, m, NCH), 3.88 (3H, s, OMe), 2.68–2.63 (1H, m, H of $C(2)H_2$), 2.45–2.40 (4H, m, $ArCH_3$ and H of $ArCH_2$), 2.26–2.19 (2H, m, CH_2), 1.81–1.77 (1H, m, H of $ArCH_2$) and 1.58–1.44 (10H, m, H of CH_2, *t*-Bu); δ_C (100 MHz) ($C6_{quat}$ not observed) 163.3 ($C6_{quat}$ of pyridine), 151.1 (C=O), 146.9 (C2 of pyridine), 143.6 (C_{quat} of Ar), 139.4 (C4 of pyridine), 137.8 ($C3_{quat}$ of pyridine), 133.5 (C=*CH*), 129.7 (2×CH of Ar), 127.6 (2×CH of Ar), 125.4 (C_{quat} of Ar), 110.8 (C5 of pyridine), 83.2 (*C*Me$_3$), 53.3 (OMe), 51.6 (CHN), 33.8 (ArCH_2), 28.0 (3×Me), 22.3 (CH_2), 21.5 ($ArCH_3$) and 16.4 (CH_2); *m*/*z* (EI) 458 (M$^+$, 45%), 402 (60), 358 (M−Boc, 90) and 280 (100) (Found: M$^+$, 458.1868. $C_{24}H_{30}N_2O_5S$ requires M, 458.1875.).

4.12. 1-(*tert*-Butoxycarbonyl)-2-(6-methoxypyridin-3-yl)methyl-1,2,3,4-tetrahydropyridine (23)

Na–Hg[35] (6%, 0.7 g) and Na_2HPO_4 (300 mg, 0.028 mol) were added to a stirred solution of tetrahydropyridine-sulfone **22** (X=Ts) (70 mg, 0.15 mmol) in anhydrous MeOH (4 mL) at −20 °C. The reaction mixture was warmed to 25 °C over 4 h, then water (10 mL) was added and the reaction mixture filtered. The filtrate was extracted with CH_2Cl_2 (4×5 mL) and the combined organic layers washed with brine, dried and evaporated under reduced pressure. Purification of the residue by column chromatography (50% Et_2O–petrol) gave a clear colourless oil, *tetrahydropyridine* **23** (25 mg, 55%); R_f (75% Et_2O–petrol) 0.73; IR (film) 2931m, 1693s, 1650s, 1610s, 1494s, 1360s, 1289s, 1162s and 1060m cm^{-1}; δ_H (500 MHz) (3:2 mixture of rotational isomers observed) 8.00–7.92 (1H, m, C(2 of pyridine)H), 7.52 and 7.37 (1H, 2×d, *J* 8.5, C(4 of pyridine)H), 6.87 and 6.70 (1H, 2×d, *J* 8.5, C(6)H), 6.70–6.64 (1H, m, C(5 of pyridine)H), 4.99 and 4.85 (1H, 2×br s, C(5)H), 4.45 and 4.27 (1H, 2×br s, C(2)H), 3.92 (3H, s, OMe), 2.94–2.53 (2H, m, ArCH_2), 2.21–2.12 (1H, m, H of CH_2), 2.07–1.96 (1H, m, CH_2), 1.76–1.61 (2H, m, CH_2) and 1.43–1.31 (9H, m, *t*-Bu); δ_C (125 MHz) (3:2 mixture of rotational isomers observed) 163.0 ($C6_{quat}$ of pyridine), 151.9 (C=O), 146.9 and 146.7 (C2 of pyridine), 139.8 and 139.6 (C4 of pyridine), 129.6 ($C3_{quat}$ of pyridine), 124.2 and 123.7 (C6), 110.6 (C5 of pyridine), 105.1 and 104.5 (C5), 80.5 (*C*Me$_3$), 53.3 (OMe), 52.2 and 50.5 (NCH), 33.2 and 32.8 (ArCH_2), 28.3 and 28.2 (3×Me), 23.4 and 22.8 (CH_2) and 17.5 (CH_2); *m*/*z* (EI) 304 (M$^+$, 20%), 233 (30) and 204 (M−Boc, 100) (Found: M$^+$, 304.1784. $C_{17}H_{24}N_2O_3$ requires M, 304.1784.).

4.13. 3-(*tert*-Butoxycarbonyl)-7-(4-methoxyphenyl)-1-tosyl-3-azatricyclo[2.2.1.0^{2,6}]heptan-5-ol (14f)

4-Methoxyphenylmagnesium bromide (0.50 M in THF; 8.25 mL, 4.13 mmol) was added to solution of epoxide **13** (1.00 g, 2.75 mmol) in THF (10 mL) at 0 °C. The reaction mixture was allowed to warm to

rt over 2 h. After this time the reaction mixture was poured into saturated aq NH_4Cl (20 mL) and extracted with Et_2O (3×50 mL). The combined organic layers were washed with brine, dried and evaporated under reduced pressure. Purification of the residue by column chromatography (80→100% Et_2O in petrol) gave a white crystalline solid, *7-azanortricyclanol* **14f** (930 mg, 72%); R_f 0.5 (Et_2O); mp 196–197 °C (dec) (Et_2O). Found: C, 64.01; H, 6.39; N, 3.00. $C_{25}H_{29}O_6NS$ requires C, 63.68; H, 6.20; N, 2.97%. IR 3737br, 2978m, 2932m, 1704s, 1614m, 1515s, 1427m, 1368m, 1312m, 1304m, 1250s, 1144s and 676m cm^{-1}; δ_H (400 MHz) 7.37 (2H, br s, 2×CH_2 of Ts), 7.11 (2H, br s, 2×CH_2 of Ts), 6.87 (2H, br s, 2×CH_2 of MeOAr), 6.58 (2H, br s, 2×CH_2 of MeOAr), 4.65 (1H, br s, NCHCTs), 4.02 (1H, br s, NCH), 3.86 (1H, br s, C*H*OH), 3.72 (3H, s, OMe), 3.01–2.59 (3H, m, C*H*ArOMe, TsCC*H*CHOH, O*H*), 2.37 (3H, s, CH_3 of Ts) and 1.47–1.18 (9H, m, 3×CH_3 of Boc); δ_C (100 MHz) 155.2 (C_{quat} of MeOAr), (carbonyl not observed), 144.4 (C_{quat} of Ts), 136.3 (C_{quat} of Ts), 129.5 (2×CH_2 of Ts), 129.3 (2×CH_2 of Ts), 128.1 (2×CH of MeOAr), 125.6 (C_{quat} of MeOAr), 113.4 (2×CH_2 of MeOAr), 81.1 (*C*Me_3), 72.7 (CHOH), 65.1 (NCH), 55.1 (OMe), 50.1 (TsC), 46.8 (CHArOMe), 38.6 (NCHCTs), 28.1 (3×CH_3 of Boc), 26.6 (TsCCHCHOH) and 21.5 (CH_3 of Ts); *m*/*z* (CI, NH_3) 489 ($M+NH_4^+$, 48%), 433 (75), 216 (28), 200 (72), 186 (46) and 108 (100) (Found: $M+H^+$, 472.1783. $C_{25}H_{30}O_6NS$ requires M, 472.1794.).

4.14. 3-(*tert*-Butoxycarbonyl)-7-phenyl-1-tosyl-3-azatricyclo[2.2.1.0^{2,6}]heptan-5-ol (14g)

PhMgBr (1.0 M in THF; 4.13 mL, 4.13 mmol) was added to a solution of epoxide **13** (1.00 g, 2.75 mmol) in THF (50 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 3 h. After this time the reaction mixture was poured into saturated aq NH_4Cl (100 mL) and extracted with Et_2O (3×100 mL). The combined organic layers were washed with brine, dried and evaporated under reduced pressure. Purification of the residue by column chromatography (80→100% Et_2O in petrol) gave a white crystalline solid, *7-azanortricyclanol* **14g** (1.00 g, 82%); R_f 0.5 (Et_2O); mp 191 °C (Et_2O). Found: C, 65.4; H, 5.8; N, 3.1. $C_{24}H_{27}O_5SN$ requires C, 65.3; H, 6.2; N, 3.2%. IR (KBr) 3431br, 2977m, 2930w, 1703s, 1426m, 1368m, 1316s, 1303s, 1126m, 1089m, 865m, 705m, 674m, 593m and 565m cm^{-1}; δ_H (400 MHz) 7.38 (2H, br s, 2×CH of Ts), 7.12–6.95 (7H, m, 2×CH of Ts, 5×CH of Ph), 4.69 (1H, s, NCHCTs), 4.05 (1H, s, NCH), 3.92–3.88 (1H, m, C*H*OH), 3.07–2.95 (1H, m, PhC*H*), 2.46 (1H, br s, TsCC*H*CHOH), 2.37 (3H, s, CH_3 of Ts) and 1.47–1.17 (10H, m, 3×CH_3 of Boc, OH); δ_C (100 MHz) 154.6 (C=O), 144.5 (C_{quat} of Ts), 136.2 (C_{quat} of Ts), 133.6 (CH of Ph), 129.5 (2×CH of Ts), 128.2 (2×CH of Ph), 128.1 (2×CH of Ph), 128.0 (2×CH of Ts), 127.2 (C_{quat} of Ph), 80.9 (*C*Me_3), 72.9 (CHOH), 65.1 (NCH), 50.0 (TsC), 47.6 (PhCH), 38.2 (NCHCTs), 28.0 (3×CH_3 of Boc), 26.4 (TsCCHCHOH) and 21.5 (CH_3 of Ts); *m*/*z* (CI, NH_3) 459 ($M+NH_4^+$, 43%), 403 (100), 186 (60), 170 (72), 156 (39) and 108 (71) (Found: $M+H^+$, 442.1679. $C_{24}H_{28}O_5SN$ requires M, 442.1688.).

4.15. 3-(*tert*-Butoxycarbonyl)-7-(pyridin-3-yl)-1-tosyl-3-azatricyclo[2.2.1.0^{2,6}]heptan-5-ol (14h)

To a cooled (−78 °C) solution of *n*-BuLi (1.6 M in hexanes; 2.6 mL, 4.2 mmol) in Et_2O (30 mL) was added dropwise a solution of 3-bromopyridine (440 μl, 4.6 mmol) in Et_2O (10 mL), followed by TMEDA (0.70 mL, 4.6 mmol). The mixture was allowed to stir for 30 min, then a solution of epoxide **13** (1.0 g, 2.75 mmol) in THF (5 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 1 h, then allowed to warm slowly to rt overnight. Saturated aq NH_4Cl (40 mL) was added and the mixture was extracted with EtOAc (3×80 mL). The combined organic layers were dried and evaporated under reduced pressure. Purification of the residue by column chromatography (EtOAc) gave a white crystalline solid, *7-azanortricyclanol* **14h** (900 mg, 74%); R_f 0.2 (EtOAc); mp 199 °C (dec); IR (KBr) 3084w, 2967w, 1708s, 1431s, 1305s, 1148s, 1133m, 1092m, 874m and 674m cm^{-1}; δ_H (400 MHz) 8.43 (1H, s, CH of Py), 8.26 (1H, s, CH of Py), 7.47–7.32 (3H, m, 2×CH of Ts, CH of Py), 7.19 (2H, d, *J* 7, 2×CH of Ts), 7.04 (1H, s, CH of Py), 4.76 (1H, s, NCHCTs), 4.12 (1H, s, NC*H*CHPy), 4.02–3.89 (1H, m, C*H*OH), 3.11–2.93 (1H, m, PyC*H*), 2.63 (1H, s, TsCC*H*CHO), 2.41 (3H, s, CH_3 of Ts), 2.15–1.92 (1H, br, OH) and 1.63–1.05 (9H, m, *t*-Bu); δ_C (100 MHz) 154.7 (C=O), 149.3 (C2 of Py), 148.5 (C6 of Py), 145.1 (C_{quat} of Ts), 135.9 (C_{quat} of Ts), 135.8 (C4 of Py), 129.9 (2×CH of Ts), 128.0 (2×CH of Ts), (C_{quat} of Py not observed), 123.1 (C5 of Py), 81.7 (*C*Me_3), 73.0 (CHOH), 68.0 (NCH), 49.8 (TsC), 44.96 (CHPy), 39.0 (NCHCTs), 28.1 (3×CH_3 of Boc), 26.6 (TsCCHCHOH) and 21.6 (CH_3 of Ts); *m*/*z* (CI, NH_3) 443 ($M+H^+$, 12%), 259 (10) and 90 (100) (Found: $M+H^+$, 443.1638, $C_{23}H_{26}O_5N_2S$ requires M, 443.1640.).

4.16. 1-(*tert*-Butoxycarbonyl)-2-(4-methoxyphenyl)methyl-5-(*p*-tolylsulfonyl)-1,2-dihydropyridine (21b)

A solution of 7-azanortricyclanol **14f** (350 mg, 0.74 mmol) in THF (4 mL) was added dropwise to a slurry of KH (30% dispersion in mineral oil; 148 mg, 1.11 mmol) in THF (4 mL) at 0 °C. After 20 min, CS_2 (55 μL, 0.88 mmol) was added and the mixture stirred for a further 15 min before addition of MeI (55 μL, 0.88 mmol). The solution was then warmed to rt for 20 min, after which time water (20 mL) was added dropwise. The aqueous layer was extracted with Et_2O (3×20 mL) and the combined organic layers were dried and evaporated under reduced pressure. Purification of the residue by column chromatography (40% Et_2O in petrol) gave a white solid foam, the corresponding *xanthate* (350 mg, 84%); R_f 0.5 (50% Et_2O in petrol); IR (film) 3103w, 2978m, 2931m, 2837w, 2253w, 1709s, 1613m, 1514s, 1392s, 1319s, 1304s, 1251s, 1211s, 1161s, 1119s, 1078s, 1035m, 913m, 863m, 831m, 732s, 678s and 598s cm^{-1}; δ_H (400 MHz) (shows rotamers 4:6 ratio) 7.42 (0.8H, d, *J* 8, 2×CH of Ts), 7.33 (1.2H, d, *J* 8, 2×CH of Ts), 7.17 (0.8H, d, *J* 8, 2×CH of Ts), 7.01 (1.2H, d, *J* 8, 2×CH of Ts), 6.95 (0.8H, d, *J* 9, 2×CH of MeOAr), 6.89 (1.2H, d, *J* 9, 2×CH of MeOAr), 6.64 (0.8H, d, *J* 9, 2×CH of MeOAr), 6.55 (1.2H, d, *J* 9, 2×CH of MeOAr), 5.51 (0.4H, t, *J* 1, CHO), 5.50 (0.6H, t, *J* 1, CHO), 4.75 (0.6H, dd, *J* 4.5, 0.5, NCHCTs), 4.73 (0.4H, dd, *J* 4.4, 0.5, NCHCTs), 4.36–4.34 (1H, m, NCH), 3.75 (1.2H, s, OMe), 3.74 (1.8H, s, OMe), 3.21 (0.6H, s, CHArOMe), 3.05 (0.4H, s, CHArOMe), 2.98–2.95 (0.6H, m, C*H*CHO), 2.88–2.85 (0.4H, m, C*H*CHO), 2.53 (1.8H, s, CH_3S), 2.52 (1.2H, s, CH_3S), 2.41 (1.2H, s, CH_3 of Ts), 2.37 (1.8H, s, CH_3 of Ts), 1.51 (3.6H, s, 3×CH_3 of Boc) and 1.30 (5.4H, s, 3×CH_3 of Boc); δ_C (100 MHz) (shows rotamers) 215.3, 215.0 (C=S), 159.2, 159.1 (C_{quat} of MeOAr), 154.5, 153.7 (C=O), 144.8, 144.5 (C_{quat} of Ts), 136.0 (C_{quat} of Ts), 129.64, 129.60 (2×CH of Ts), 129.4 (2×CH of MeOAr), 128.3, 128.2 (2×CH of Ts), 125.2, 125.0 (C_{quat} of MeOAr), 113.5, 113.4 (2×CH of MeOAr), 81.9, 81.4 (*C*HO), 81.3, 81.2 (*C*Me_3), 62.0, 61.2 (NCH), 55.2, 55.1 (OMe), 50.1, 50.0 (CTs), 46.6, 46.4 (*C*HArOMe), 39.5, 39.0 (NCHCTs), 28.4, 28.1 (3×CH_3 of Boc), 25.0, 24.5 (TsCCHCHO), 21.6, 21.5 (CH_3 of Ts) and 19.4, 19.2 (CH_3S); *m*/*z* (ES^+) 579 ($M+NH_4^+$, 82%), 54 (60), 462 (50), 398 (85), 395 (43) and 354 (100) (Found: $M+NH_4^+$, 579.1670. $C_{27}H_{35}O_6N_2S_3$ requires M, 579.1657). A solution of Bu_3SnH (211 μL, 0.78 mmol, 1.1 equiv) and AIBN (23 mg, 0.14 mmol, 0.2 equiv) in toluene (5 mL) was added via syringe pump over 2.25 h to a solution of the above xanthate (400 mg, 0.71 mmol) in toluene (25 mL) at reflux. The mixture was then stirred for an additional 45 min before being cooled and worked-up by the method of Curran and Chang.[34] Purification of the residue by column chromatography (30→50% Et_2O in petrol) gave a colourless oil, *1,2-dihydropyridine* **21b** (202 mg, 62%); R_f 0.5 (60% Et_2O in petrol); IR (film) 2979m, 2933m, 1723s, 1633m, 1596m, 1513s, 1393m, 1370m, 1288s, 1250s, 1176m, 1144s, 1088s, 814m, 732m, 715m, 662s and 579s cm^{-1}; δ_H (500 MHz) 8.01–7.75 (1H, m, =CHN), 7.70 (2H, d, *J* 8, 2×CH of Ts), 7.30 (2H, d, *J* 8, 2×CH of Ts), 6.97 (2H, d, *J* 8, 2×CH of

MeOAr), 6.76 (2H, d, *J* 8, 2×CH of MeOAr), 5.90–6.10 (1H, m, CCH=), 5.41 (1H, dd, *J* 10, 5.5, CHCH=), 5.01–4.89 (1H, m, CHN), 3.77 (3H, s, OMe), 2.69 (1H, dd, *J* 13 and 8, H of CH_2), 2.59 (1H, dd, *J* 13 and 5, H of CH_2), 2.43 (3H, s, Me of Ts) and 1.48 (9H, s, *t*-Bu); δ_C (100 MHz) 158.4 (C_{quat} of MeOAr), 151.3 (C=O) 143.7 (C_{quat} of Ts), 138.3 (C_{quat} of Ts), 133.7 (=CHN), 130.5 (2×CH of Ts), 130.0 (2×CH of MeOAr), 127.6 (C_{quat} of MeOAr), 127.2, (2×CH of Ts), 122.5 (CHCH=), (TsC_{quat} not observed), 118.2 (CCH=, br), 114.3 (2×CH of MeOAr), 83.6 (CMe_3), 55.2 (OMe), 53.8 (CHN, br), 39.9 ($ArCH_2$), 28.5 (3×Me of Boc) and 22.2 (Me of Ts); δ_C (100 MHz; DMSO; 373 K) 159.3 (C_{quat} of MeOAr), 152.0 (C=O) 144.5 (C_{quat} of Ts), 139.4 (C_{quat} of Ts), 134.1 (=CHN), 131.3 (2×CH of Ts), 130.7 (2×CH of MeOAr), 128.7 (C_{quat} of MeOAr), 127.6, (2×CH of Ts), 124.3 (CHCH=), 119.9 (TsC_{quat}), 118.0 (CCH=, br), 114.9 (2×CH of MeOAr), 84.3 (CMe_3), 56.1 (OMe), 54.9 (CHN, br), 40.2 ($ArCH_2$), 28.4 (3×Me of Boc) and 21.7 (Me of Ts); *m*/*z* (CI, NH_3) 473 ($M+NH_4^+$, 100%) and 354 (30) (Found $M+NH_4$, 473.2098. $C_{25}H_{33}O_5N_2S$ requires M, 473.2110.).

4.17. 1-(*tert*-Butoxycarbonyl)-2-benzyl-5-tosyl-1,2-dihydropyridine (21c)

A solution of 7-azanortricyclanol **14g** (600 mg, 1.36 mmol) in THF (5 mL) was added dropwise to a slurry of KH (30% dispersion in mineral oil; 272 mg, 2.04 mmol) in THF (10 mL) at 0 °C. After 1 h, CS_2 (254 μL, 4.08 mmol) was added and the mixture stirred for a further 15 min before addition of MeI (254 μL, 4.08 mmol). The solution was then warmed to rt for 20 min, after which time water (10 mL) was added dropwise. The mixture was extracted with Et_2O (3×20 mL) and the combined organic layers dried and evaporated under reduced pressure. Purification of the residue by column chromatography (40% Et_2O in petrol) gave an off-white solid foam, the corresponding *xanthate* (689 mg; 95%). Diagnostic data: δ_H (400 MHz) 5.55 (1H, s, CHO) and 2.50 (3H, s, SCH_3). Reaction of the above xanthate (335 mg, 0.63 mmol), Bu_3SnH (187 μL, 0.69 mmol) and AIBN (21 mg, 0.13 mmol) as described in the preparation of **21b** gave, after purification by column chromatography (40% Et_2O in petrol) a colourless oil, *1,2-dihydropyridine* **21c** (174 mg, 65%); R_f 0.3 (20% Et_2O in petrol); IR (film) 2984 m, 1722s, 1287s, 1144s and 1087s cm^{-1}; δ_H (400 MHz) 7.93–7.79 (1H, m, NCH=), 7.72 (2H, d, *J* 8, 2×CH of Ts), 7.32 (2H, d, *J* 8, 2×CH of Ts), 7.24–7.19 (3H, m, CH of Ph), 7.06 (2H, d, *J* 8, 2×CH of Ph), 6.12 (1H, d, *J* 9.5, TsCCH=), 5.47 (1H, dd, *J* 9.5, 5.5, PhCHCH), 4.94 (1H, br s, NCH), 2.75 (1H, dd, *J* 13, 8, H of $PhCH_2$), 2.68 (1H, dd, *J* 13, 6, H of $PhCH_2$), 2.44 (3H, s, CH_3 of Ts) and 1.50, 1.48 (9H, 2×s, 3×CH_3 of Boc); δ_C (100 MHz) (C=O and NCH not observed), 143.7 (C_{quat} of Ts), 138.3 (C_{quat} of Ts), 135.7 (CH of Ph), 133.7 (NCH=), 129.8 (2×CH of Ts), 129.6 (2×CH of Ph), 128.3 (2×CH of Ph), 127.3 (2×CH of Ts), 126.7 (TsCCH=), 122.4 (PhCHCH=), 121.4 (TsC_{quat}), 83.7 (CMe_3), 39.3 ($PhCH_2$), 27.9 (3×CH_3 of Boc) and 21.6 (CH_3 of Ts); *m*/*z* (CI, NH_3) 443 ($M+NH_4^+$, 100%) (Found: $M+NH_4^+$, 443.2003. $C_{24}H_{31}O_4N_2S$ requires M, 443.2005.).

4.18. 1-(*tert*-Butoxycarbonyl)-2-(pyridin-3-yl)methyl-5-tosyl-1,2-dihydropyridine (21d)

A solution of 7-azanortricyclanol **14h** (500 mg, 1.13 mmol) in THF (2 mL) was added dropwise to a slurry of KH (30% dispersion in mineral oil; 226 mg, 1.69 mmol) in THF (10 mL) at 0 °C. After 30 min, CS_2 (107 μL, 1.69 mmol) was added and the mixture stirred for a further 15 min before addition of MeI (86 μL, 1.36 mmol). The solution was then warmed to rt for 20 min, after which time water (5 mL) was added dropwise. The mixture was extracted with Et_2O (3×10 mL) and the combined organic layers were dried and evaporated under reduced pressure. Purification of the residue by column chromatography (80% Et_2O in petrol) gave an off-white solid foam, the corresponding *xanthate* (461 mg, 77%). Diagnostic data: δ_H (200 MHz) 5.56 (0.5H, s, CHO), 5.51 (0.5H, s, CHO), 2.43 (1.5H, s, SCH_3) and 2.40 (1.5H, s, SCH_3). Reaction of the above xanthate (350 mg, 0.66 mmol), Bu_3SnH (194 μL, 0.72 mmol) and AIBN (21 mg, 0.13 mmol) as described in the preparation of **21b** gave, after purification by column chromatography (80% Et_2O in petrol) a colourless oil, *1,2-dihydropyridine* **21d** (146 mg, 52%); R_f 0.3 (Et_2O); IR (film) 2979m, 2929m, 1723s, 1634m, 1595m, 1394m, 1370m, 1287s, 1144s and 1088s cm^{-1}; δ_H (500 MHz) 8.41 (1H, s, Py), 8.30 (1H, s, Py), 7.83–7.61 (3H, m, NCH=, 2×CH of Ts), 7.39 (1H, s, Py), 7.32 (2H, d, *J* 7.5, 2×CH of Ts), 7.11 (1H, s, Py), 6.16 (1H, d, *J* 9, TsCCH=), 5.47 (1H, dd, *J* 9, 5, CHCH=), 5.02 (1H, br, NCH), 2.84 (1H, dd, *J* 13, 7.5, CH_aH_b), 2.70 (1H, dd, *J* 13, 5.5, CH_aH_b), 2.45 (3H, s, CH_3 of Ts) and 1.63–1.05 (9H, br, 3×CH_3 of Boc); δ_C (125 MHz) 151.5 (C=O), 150.6 (C2 of Py), 148.0 (C6 of Py), 143.8 (C_{quat} of Ts), 138.1 (C4 Py), 136.9 (C_{quat} of Ts), 133.5 (NCH=), 131.1 (C3 of Py), 129.8 (2×CH of Ts), 127.2 (2×CH of Ts), 125.4 (CTs), 123.0 (C5 of Py), 121.1 (PyCHCH=), 118.5 (TsCCH=), 84.0 (CMe_3), 53.4 (NCH), 37.8 (CH_2), 27.9 (3×CH_3 of Boc) and 21.5 (CH_3 of Ts); *m*/*z* (CI, NH_3) 427 ($M+H^+$, 100%), 352 (20) and 273 (80) (Found: $M+H^+$, 427.1696. $C_{23}H_{27}N_2O_4S$ requires M, 427.1691.).

4.19. 3-*tert*-Butoxycarbonyl-7-(4-methoxyphenyl)-1-tosyl-3-azatricyclo[2.2.1.0^{2,6}]heptan-5-one (24)

DMSO (336 μL, 4.73 mmol) was added to a solution of $(COCl)_2$ (216 μL, 2.47 mmol) in CH_2Cl_2 (12 mL) at −78 °C. After 10 min, alcohol **14f** (968 mg, 2.05 mmol) in CH_2Cl_2 (5 mL) was added dropwise. After a further 20 min Et_3N (1.7 mL, 6.98 mmol) was added and the reaction mixture allowed to warm to rt. The reaction mixture was then poured into water (10 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine, dried and evaporated under reduced pressure. Purification of the residue by column chromatography (Et_2O) and recrystallisation (EtOAc) gave a white solid, *ketone* **24** (947 mg, 98%); R_f 0.5 (Et_2O); mp 205 °C (dec); IR (film) 3106m, 2982w, 1784s, 1689s, 1516s, 1420s, 1318m, 1255s, 1148s, 847m, 671s and 587s cm^{-1}; δ_H (400 MHz) 7.45 (2H, d, *J* 8, CH of Ts), 7.20 (2H, d, *J* 8, CH of Ts), 7.00 (2H, d, *J* 8.5, CH of MeOAr), 6.70 (2H, d, *J* 8.5, CH of MeOAr), 5.30 (1H, dd, *J* 5, 1, NCH), 3.8 (1H, s, NCH), 3.77 (3H, s, OMe), 3.31 (1H, s, TsCCHCHOH), 2.67 (1H, dd, *J* 5.1, 1.0, CHArOMe), 2.42 (3H, s, CH_3 of Ts) and 1.31 (9H, s, *t*-Bu); δ_C (100 MHz) 198.4 (C=O), 159.5 (C_{quat} of ArOMe), 153.0 (C=O), 145.3 (C_{quat} of Ts), 135.7 (C_{quat} of Ts), 129.9 (2×CH of Ts), 129.5 (2×CH of Ts), 128.3 (2×CH of ArOMe), 124.2 (C_{quat} of ArOMe), 113.8 (2×CH of ArOMe), 82.0 (CMe_3), 64.0 (NCH), 55.2 (OMe), 54.7 (TsC), 48.5 (CHArOMe), 44.1 (NCH), 28.1 (3×CH_3 of Boc), 27.6 (TsCCHCHOH) and 21.6 (CH_3 of Ts); *m*/*z* (CI, NH_3) 487.2 ($M+NH_4^+$, 5%), 431.1 (100), 370.1 (80), 216.1 (25) and 167.1 (20) (Found: $M+NH_4^+$, 487.1884. $C_{25}H_{31}O_6N_2S$ requires M, 487.1903.).

4.20. *endo* 3-(*tert*-Butoxycarbonyl)-7-(4-methoxyphenyl)-1-tosyl-3-azatricyclo[2.2.1.0^{2,6}]heptan-5-ol (25)

i-PrMgCl (2.0 M in Et_2O; 0.42 mL, 0.85 mmol) was added to a solution of ketone **24** (255 mg, 0.54 mmol) in THF (25 mL) at 0 °C. The reaction mixture was warmed to rt and stirred for 3 h, then saturated aq NH_4Cl (25 mL) added. The aqueous layer was extracted with Et_2O (3×50 mL) and the combined organic layers were dried and evaporated under reduced pressure. Purification of the residue by column chromatography (80→100% Et_2O in petrol) gave *endo-alcohol* **25** (197 mg, 77%); R_f 0.6 (Et_2O); IR (film) 3460br, 2977w, 2932w, 1705s, 1515s, 1421m, 1251s, 1145s, 1089s, 671s and 582m cm^{-1}; δ_H (400 MHz) (spectrum split by rotamers 1:1 ratio) 7.48 (1H, d, *J* 7.5, 2×CH of Ts), 7.41 (1H, d, *J* 7.5, 2×CH of Ts), 7.17 (1H, d, *J* 7.5, 2×CH of Ts), 7.08 (1H, d, *J* 7.5, 2×CH of Ts), 6.95 (1H, d, *J* 7.5, 2×CH of MeOAr), 6.84 (1H, d, *J* 7.5, 2×CH of MeOAr), 6.65 (1H, d, *J* 7.5, 2×CH of MeOAr), 6.55 (1H, d, *J* 7.5, 2×CH of MeOAr), 4.64 (1H, d, *J* 5.5, NCHCTs), 4.01 (1H, s, CHOH), 3.83–3.55 (5H, m, OMe, NCHCHAr and CHAr), 2.57 (0.5H, s, TsCCHCHOH), 2.50 (0.5H, s, TsCCHCHOH), 2.38

(1.5H, s, CH_3 of Ts), 2.36 (1.5H, s, CH_3 of Ts), 1.78 (1H, s, OH), 1.46 (4.5H, s, Boc) and 1.16 (4.5H, s, Boc); δ_C (100 MHz) (spectrum split by rotamers) 158.8, 158.6 (C_{quat} of MeOAr), 153.9, 153.2 (C=O), 144.3 (C_{quat} of Ts), 136.2 (C_{quat} of Ts), 129.6 (2×CH of Ts), 128.2 (2×CH of Ts), 128.0 (2×CH of MeOAr), 125.8 (C_{quat} of MeOAr), 113.4 (2×CH of MeOAr), 81.2, 80.6 (*C*Me_3), 73.5, 73.3 (CHO), 63.9, 62.8 (NCH), 55.1 (OMe), 49.0 (TsC), 46.8, 46.5 (MeOAr*C*H), 41.9, 41.6 (NCH), 28.4, 28.0 (3×CH_3 of Boc), 27.8 (TsCCHCHOH), 21.6 (CH_3 of Ts); *m*/*z* (ES^+) 494.2 (M+Na^+, 27%), 489.2 (M+NH_4^+, 30), 472.2 (M+H^+, 10), 457.1 (100), 448.1 (90) (Found: M+NH_4^+, 489.2049. $C_{25}H_{33}O_6N_2S$ requires M, 489.2059.).

4.21. 3-(*tert*-Butoxycarbonyl)-7-methoxy-1-tosyl-3-azatricyclo[2.2.1.0^{2,6}]heptan-5-ol (14i)

Lithium ribbon (17 mg, 2.5 mmol) was carefully added to dry MeOH (20 mL). The solution was allowed to return to rt and epoxide **13** (300 mg, 0.83 mmol) was added in one portion. The mixture was heated to reflux for 3 days. Water (10 mL) and Et_2O (10 mL) were then added and the aqueous layer separated and extracted with Et_2O (2×20 mL). The combined organic layers were washed with brine, dried and evaporated under reduced pressure. Purification of the residue by column chromatography gave a white solid foam, *7-azanortricyclanol* **14i** (294 mg, 90%); R_f 0.3 (Et_2O). Found: C, 57.8; H, 6.5; N, 3.5. $C_{19}H_{25}O_6NS$ requires C, 57.7; H, 6.4; N, 3.5%. IR (KBr) 3425br, 2979m, 2931m, 1699s, 1598m, 1386s, 1317s, 1145s, 1089s, 1006m, 868m and 680m cm^{-1}; δ_H (400 MHz) 7.79 (2H, d, *J* 8, 2×CH of Ts), 7.31 (2H, d, *J* 8, 2×CH of Ts), 4.22 (1H, s, NC*H*), 4.11 (1H, d, *J* 5, NC*H*CTs), 3.97 (1H, s, MeOC*H*), 3.76 (1H, s, C*H*OH), 3.09 (3H, s, OMe), 2.70 (1H, d, *J* 5, TsCC*H*CHOH), 2.43 (4H, s, CH_3 of Ts, OH) and 1.37–1.26 (9H, m, *t*-Bu); δ_C (100 MHz) 157.0 (C=O), 144.3 (C_{quat} of Ts), 137.7 (C_{quat} of Ts), 129.2 (2×CH of Ts), 128.6 (2×CH of Ts), 81.1 (*C*Me_3), 79.8 (COH), 68.4 (*C*OMe), 59.9 (NCH), 56.6 (MeO), 49.7 (TsC), 39.4 (NCHCTs), 29.4 (TsC*C*HCHOH), 27.6 (3×CH_3 of Boc) and 21.5 (CH_3 of Ts); *m*/*z* (CI, NH_3) 413 (M+NH_4^+, 68%), 357 (28), 296 (20) and 108 (100) (Found: M+NH_4^+, 413.1751. $C_{19}H_{29}O_6N_2S$ requires M, 413.1746.).

4.22. 3-(*tert*-Butoxycarbonyl)-7-(4-methoxybenzyloxy)-1-tosyl-3-azatricyclo[2.2.1.0^{2,6}]heptan-5-ol (14j)

4-Methoxybenzyl alcohol (243 mg, 1.76 mmol) in THF (5 mL) was added to a stirred slurry of NaH (66 mg, 1.65 mmol; 60% w/w dispersion in mineral oil) at 0 °C. After 0.5 h, epoxide **13** (400 mg, 1.10 mmol) in THF (5 mL) was added. The reaction mixture was warmed to rt and stirred for 22 h. Water (10 mL) was then added and the aqueous layer extracted with Et_2O (3×20 mL). The combined organic layers were washed with brine, dried and evaporated under reduced pressure. Purification of the residue by column chromatography (60→100% Et_2O in light petroleum) gave a white crystalline solid, *alcohol* **14j** (319 mg, 58%); R_f 0.4 (Et_2O); mp 150–151 °C (Et_2O). Found: C, 62.3; H, 6.4; N, 2.8. $C_{26}H_{31}NO_7S$ requires C, 62.3; H, 6.2; N, 2.8%. IR (film) 3278br, 2978m, 2932m, 1681s, 1612m, 1515s, 1465m, 1396s, 1302s, 1252s, 1175s, 1090s, 1036m, 1019m and 680m cm^{-1}; δ_H (400 MHz; $CDCl_3$) (shows rotamers 1:4 ratio) 7.74 (0.4H, d, *J* 7.5, 2×CH of Ts), 7.69 (1.6H, d, *J* 8, 2×CH of Ts), 7.20 (0.4H, d, *J* 7.5, 2×CH of Ts), 7.08 (1.6H, d, *J* 8, 2×CH of Ts), 6.99 (1.6H, d, *J* 8.5, 2×CH of MeOAr), 6.95–6.80 (0.8H, m, 4×CH of MeOAr), 6.77 (1.6H, d, *J* 8.5, 2×CH of MeOAr), 4.56 (0.2H, d, *J* 4, NCHTs), 4.34 (0.2H, d, *J* 14, C*H*OH) 4.34–4.28 (1.6H, m, CH_2), 4.18 (0.8H, d, *J* 5, NCHTs), 4.16–4.06 (1.2H, m, C*H*OH, CH_2), 3.99 (1H, d, *J* 10, NCH), 3.94 (1H, s, C*H*OCH_2), 3.80 (3H, s, OMe), 3.82–3.68 (2H, m, TsCC*H*CHOH, OH), 2.39 (0.6H, s, CH_3 of Ts), 2.33 (2.4H, s, CH_3 of Ts) and 1.26 (9H, s, 3×CH_3 of Boc); δ_C (100 MHz; $CDCl_3$) 159.2 (C_{quat} of MeOAr), 156.7 (C=O), 144.1 (C_{quat} of Ts), 137.5 (C_{quat} of Ts), 130.0 (2×CH of Ts), 129.1 (2×MeOAr), 128.7 (C_{quat} of MeOAr), 128.4 (2×CH of Ts), 113.3 (2×CH of MeOAr), 81.25 (*C*Me_3), 77.5 (CHOH), 71.2 (CH_2O*C*H), 68.4 (CH_2), 60.0 (NCH), 55.2 (OMe), 49.4 (TsC), 39.6 (NCHCTs), 28.9 (TsCCHCHOH), 27.8 (3×CH_3 of Boc) and 21.5 (CH_3 of Ts); *m*/*z* (CI, NH_3) 519.3 (M+NH_4^+, 100%), 463.2 (17), 402.2 (30) and 343.2 (17) (Found: M+NH_4^+, 519.2173. $C_{26}H_{35}N_2O_7S$ requires M, 519.2165.).

4.23. 1-(*tert*-Butoxycarbonyl)-2-methoxymethyl-5-tosyl-1,2-dihydropyridine (21e)

A solution of 7-azanortricyclanol **14i** (220 mg, 0.56 mmol) in THF (3 mL) was added dropwise to a slurry of NaH (60% dispersion in mineral oil; 72 mg, 1.8 mmol) in THF (2 mL). The mixture was heated to reflux for 1 h, then CS_2 (186 μL, 3.0 mmol) in THF (1 mL) was added and heating continued for 30 min. MeI (186 μL, 3.0 mmol) was then added and the mixture heated for a further 30 min. After this time, the mixture was cooled and water (1 mL) cautiously added, followed by saturated aq NH_4Cl (15 mL). The aqueous phase was extracted with Et_2O (2×30 mL), and the combined organic layers washed with brine, dried and evaporated under reduced pressure. Purification of the residue by column chromatography (40% Et_2O in petrol) gave a pale cream foam, the corresponding *xanthate* (209 mg, 77%). Diagnostic data: δ_H (200 MHz) 5.54 (0.7H, s, C*H*O), 5.46 (0.3H, s, C*H*O), 2.52 (2.1H, s, SCH_3) and 2.50 (0.9H, s, SCH_3). Reaction of the above xanthate (209 mg, 0.43 mmol), Bu_3SnH (128 μL, 0.47 mmol) and AIBN (14 mg, 0.09 mmol) as described in the preparation of **21b** gave, after purification by column chromatography (20→30% Et_2O in petrol) a colourless oil, *1,2-dihydropyridine* **21e** (61 mg, 37%, 46% based on recovered xanthate); R_f 0.4 (50% Et_2O in petrol); IR (film) 2980m, 2931m, 1725s, 1634m, 1596m, 1456m, 1393m, 1370m, 1321s, 1289s, 1259m, 1144s, 1089s, 1057m, 1019m, 814m, 731m, 716m and 661s cm^{-1}; δ_H (400 MHz) 7.85 (1H, br s, NCH=), 7.75 (2H, d, *J* 8, 2×CH of Ts), 7.30 (2H, d, *J* 8, 2×CH of Ts), 6.19 (1H, d, *J* 10, TsCC*H*=), 5.55 (1H, dd, *J* 10, 5.5, CHC*H*=), 4.97 (1H, br s, NCH), 3.30–3.21 (5H, m, CH_2, OMe), 2.42 (3H, s, CH_3 of Ts) and 1.54 (9H, s, 3×CH_3 of Boc); δ_C (100 MHz) (C=O not observed), 143.7 (C_{quat}Me of Ts), 138.4 (C_{quat} of Ts), 134.3 (NCH=), 129.7 (2×CH of Ts), 127.2 (2×CH of Ts), (TsC_{quat} not observed), 120.0 (CHCH=), 119.3 (TsC*C*H=), 83.8 (*C*Me_3), 73.1 (CH_2OMe), 59.1 (OMe), 51.9 (NCH), 28.0 (3×CH_3 of Boc) and 21.5 (CH_3 of Ts); *m*/*z* (CI, NH_3) 397 (M+NH_4^+, 35%), 278 (72), 248 (97), 234 (100) and 124 (45) (Found: M+NH_4^+, 397.1791. $C_{19}H_{29}O_5N_2S$ requires M, 397.1797.).

4.24. *tert*-Butyl 2-[(4-methoxybenzyloxy)methyl]-5-tosylpyridine-1(2*H*)-carboxylate (21f)

A solution of 7-azanortricyclanol **14j** (210 mg, 0.42 mmol) in THF (2 mL) was added dropwise to a slurry of KH (30% dispersion in mineral oil; 168 mg, 1.26 mmol) in THF (3 mL) at 0 °C. The reaction mixture was warmed to rt, stirred for 20 min and CS_2 (131 μL, 2.1 mmol) was added. After a further 10 min, MeI (131 μL, 2.10 mmol) was added and the mixture stirred for 30 min. Water (10 mL) was then added, the aqueous layer extracted with Et_2O (3×20 mL) and the combined organic layers washed with brine, dried and evaporated under reduced pressure to give the corresponding *xanthate* as a yellow oil. Diagnostic data: δ_H (400 MHz) 5.47 (0.8H, s, C*H*O), 5.37 (0.2H, s, C*H*O), 2.41 (0.6H, s, SCH_3) and 2.45 (2.4H, s, SCH_3). The above crude xanthate was dissolved in toluene (15 mL), AIBN (14 mg, 0.08 mmol) was added and the mixture heated to reflux. Bu_3SnH (169 μL, 0.63 mmol) was then added and the heating continued for 2 h. Workup by the method of Curran and Chang[34] and purification of the residue by column chromatography (50% Et_2O in petrol) gave *1,2-dihydropyridine* **21f** as a colourless oil (21 mg, 10%); R_f 0.25 (50% Et_2O in petrol); IR (film) 2977m, 1723s, 1613m, 1514m, 1455m, 1393m, 1370m, 1289s, 1257s, 1144s, 1089s, 1033m, 814m, 732m and 661s cm^{-1}; δ_H (500 MHz) 7.85 (1H, br s,

NCH=), 7.72 (2H, d, *J* 8, 2×CH of Ts), 7.27 (2H, d, *J* 8, 2×CH of Ts), 7.15 (2H, d, *J* 8.5, 2×CH of MeOAr), 6.85 (2H, d, *J* 8.5, 2×CH of MeOAr), 6.19 (1H, d, *J* 10, TsCC*H*=), 5.55 (1H, dd, *J* 10, 5.5, CHC*H*=), 5.04 (1H, br s, NCH), 4.40 (1H, d, *J* 11.5, H of ArCH_2O), 4.32 (1H, d, *J* 11.5, H of ArCH_2O), 3.81 (3H, s, OMe), 3.34 (1H, dd, *J* 10 and 5, H of CHCH_2O), 3.28 (1H, dd, *J* 10 and 6, H of CHCH_2O), 2.41 (3H, s, CH_3 of Ts) and 1.51 (9H, s, 3×CH_3 of Boc); δ_C (125 MHz) (C=O not observed), 159.1 (C_{quat} of MeOAr), 143.5 (C_{quat} of Ts), 138.3 (C_{quat} of Ts), 134.2 (=CHN), 130.1 (C_{quat} of MeOAr), 129.7 (2×CH of Ts), 129.1 (2×CH of MeOAr), 127.7 (=CSO_2), 127.1 (2×CH of Ts), 119.9 (CHCH=), 119.2 (CCH=, br), 113.6 (2×CH of MeOAr), 83.6 (*C*Me_3), 72.6 (ArCH_2), 70.0 (CHCH_2O), 55.2 (OMe), 52.0 (NCH, br), 27.9 (3×CH_3 of Boc) and 21.4 (CH_3 of Ts); *m*/*z* (CI, NH_3) 503 (M+NH_4^+, 100%), 486 (15), 447 (20), 430 (20) and 386 (50) (Found: M+NH_4^+, 503.2212. $C_{26}H_{35}O_6N_2S$ requires M, 503.2216.).

4.25. *tert*-Butyl 2-[(3,5-dinitrobenzoyloxy)methyl]-5-tosylpyridine-1(2*H*)-carboxylate (21g)

To a solution of dihydropyridine **21f** (21 mg, 0.043 mmol) in CH_2Cl_2 (1 mL) was added water (59 μL, 0.0033 mmol) and DDQ (14.7 mg, 0.065 mmol). The mixture was stirred for 3 h at rt, then CH_2Cl_2 (4 mL) was added and the organic layer washed with saturated $NaHCO_3$ (2×5 mL), brine, then dried and evaporated under reduced pressure. Purification of the residue by column chromatography (70% Et_2O in petrol) gave a colourless oil, the corresponding alcohol (3.9 mg, 24%). This labile alcohol (3.9 mg, 10.7 μmol) was dissolved in CH_2Cl_2 (2 mL), NEt_3 (30 μL, 214 μmol) and 3,5-dinitrobenzoyl chloride (25 mg, 108 μmol) were added and the mixture stirred at rt for 14 h. The reaction mixture was absorbed onto silica and purified by column chromatography (40% Et_2O in petrol) to give dihydropyridine **21g** as a white micro-crystalline solid (2.4 mg, 42%); R_f 0.3 (50% Et_2O in petrol); IR (KBr) 2977m, 1722s, 1613s, 1513s, 1370s, 1513s, 1455m, 1370m, 1288m, 1257m, 1144s, 1034m, 814m and 732m cm^{-1}; δ_H (500 MHz) 9.23 (1H, t, *J* 2, C4 of $ArCO_2$), 9.11 (2H, d, *J* 2, C2 and C6 of $ArCO_2$), 7.82 (1H, br s, NCH=), 7.72 (2H, d, *J* 8, 2×CH of Ts), 7.29 (2H, d, *J* 8, 2×CH of Ts), 6.29 (1H, d, *J* 10, TsCCH=), 5.58 (1H, dd, *J* 10, 5.5, CHC*H*=), 5.31 (1H, br s, NCH), 4.45 (1H, d, *J* 11, C$H_a$$H_b$), 4.30–4.13 (1H, m, C$H_a$$H_b$), 2.42 ($CH_3$Ar), 1.49 (9H, s, 3×$CH_3$ of Boc); δ_C (125 MHz) 162.4 (C=O), 151.2 (C=O), 148.5 (C3 and C5 of Ar), 144.0 (C4 of Ar), 137.7 (C2 and C6 of Ar), 129.8 (2×CH_2 of Ts), 129.5 (NCH=), 129.3 (C1 of Ar), 127.3 (2×CH of Ts), 122.5 (CH=), 120.9 (CH=), 84.6 (*C*Me_3), 27.8 (3×CH_3 of Boc), 21.5 (CH_3 of Ts); *m*/*z* (ES^+) 582.0 (M+Na^+, 55%), 577.1 (M+NH_4^+, 35) and 102.1 (100) (Found: M+NH_4^+, 577.1602. $C_{25}H_{29}N_4O_{10}S$ requires M, 577.1604.).

4.26. *tert*-Butyl (5-tosylpyridin-2-yl)methyl carbonate (28)

To a solution of 7-azanortricyclanol **14j** (899 mg, 1.79 mmol) in MeCN (20 mL) was added DMAP (657 mg, 5.38 mmol) and PhOC(S)Cl (496 μL, 3.58 mmol) and the mixture was stirred at rt for 14 h. Purification of the mixture by column chromatography (10→60% Et_2O in petrol) gave a white foam, the corresponding thiocarbonate (623 mg, 56%). The thiocarbonate was dissolved in toluene (39 mL), AIBN (32 mg, 0.2 mmol) was added and the mixture heated to reflux. Bu_3SnH (289 μL, 1.1 mmol) was then added and the heating continued for 2 h. Workup by the method of Curran and Chang[34] and purification of the residue by column chromatography (50% Et_2O in petrol) gave a clear colourless oil, *pyridine carbonate* **28** (260 mg, 72%); R_f 0.3 (50% Et_2O in petrol); IR (film) 2980w, 2932w, 1747s, 1585m, 1370m, 1326m, 1282s, 1255m, 1160s, 1108m, 1017w, 867w, 814w, 708m and 686s cm^{-1}; δ_H (400 MHz) 9.05 (1H, d, *J* 2, pyC6-H), 8.19 (1H, dd, *J* 8, 2, pyC4-H), 7.83 (2H, d, *J* 8, 2×CH of Ts), 7.49 (1H, d, *J* 8, pyC3-H), 7.32 (2H, d, *J* 8, 2×CH of Ts), 5.23 (2H, s, OCH_2), 2.40 (3H, s, CH_3 of Ts) and 1.49 (9H, s, Boc); δ_C (100 MHz) 160.6 (pyC2), 152.9 (C=O), 148.2 (pyC6), 144.9 (C_{quat} of Ts), 137.8 (pyC5), 137.6 (C_{quat} of Ts), 135.9 (pyC4), 130.2 (2×CH of Ts), 127.8 (2×CH of Ts), 120.9 (pyC3), 83.1 (*C*Me_3), 68.0 (OCH_2), 27.7 (3×CH_3 of Boc) and 21.6 (CH_3 of Ts); *m*/*z* (ES^+) 364.1 (M+H^+, 37%) and 308.1 (100) (Found: M+H^+, 364.1211. $C_{18}H_{22}O_5NS$ requires M, 364.1219.).

4.27. 3-*tert*-Butoxycarbonyl-7-diethylamino-1-tosyl-3-azatricyclo[2.2.1.$0^{2,6}$]heptan-5-ol (14k)

To a solution of epoxide **13** (500 mg, 1.37 mmol) in CH_2Cl_2 (5 mL) was added $HNEt_2$ (2.5 mL, 0.024 mol) and the mixture stirred at rt. After 14 h, the mixture was evaporated to dryness under reduced pressure to reveal a brown foam, the corresponding amino epoxide. The crude amino epoxide was dissolved in THF (10 mL) then cooled to 0 °C, MeLi (1.0 M in THF; 2.75 mL, 2.75 mmol) was added and the mixture stirred for 3 h. Water (10 mL) was added followed by EtOAc (20 mL). The aqueous layer was separated and washed with EtOAc (20 mL), then the combined organic layers washed with brine, dried and evaporated under reduced pressure. Purification of the residue by column chromatography gave a white solid, *tricyclanol* **14k** (444 mg, 74%); R_f 0.4 (Et_2O); IR (film) 3453br, 2974m, 2931m, 2872w, 2816w, 1694s, 1433m, 1316m, 1294m, 1162s, 1142s, 865m, 676m and 577m cm^{-1}; δ_H (400 MHz) (spectrum broadened by rotamers) 7.82 (2H, d, *J* 7.5, 2×CH of Ts), 7.30 (2H, d, *J* 7.5, 2×CH of Ts), 4.60 (1H, d, *J* 5, NC*H*CTs), 4.05 (1H, s, NC*H*CHN), 3.68 (1H, s, C*H*OH), 3.08 (1H, s, Et_2NCH), 2.95–2.05 (8H, m, CH_3 of Ts, 2×CH_2 of Et, and TsCC*H*CHOH), 1.44 (9H, s, 3×CH_3 of Boc), 0.85 (6H, s, 2×CH_3 of Et); δ_C (100 MHz) (spectrum broadened by rotamers) 154.1 (C=O), 144.6 (C_{quat} of Ts), 136.3 (C_{quat} of Ts), 129.5 (2×CH of Ts), 128.4 (2×CH of Ts), 81.2 (*C*Me_3), 70.2 (CHO), 62.2 (Et_2N*C*), 57.7 (NCH), 46.7 (TsC), 42.9 (2×CH_2 of Et), 38.2 (NCHCTs), 28.3 (3×CH_3 of Boc), 26.6 (TsCCHCHOH), 21.6 (CH_3 of Ts), 13.5 (2×CH_3 of Et); *m*/*z* (ES^+) 437.2 (M+H^+, 100%) 409.2 (20) (Found: M+H^+, 437.2103. $C_{22}H_{33}O_5N_2S$ requires M, 437.2110.).

4.28. 1-*tert*-Butoxycarbonyl-2-[(diethylamino)methylene]-5-tosyl-1,2-dihydropyridine (30)

To a solution of tricyclanol **14k** (440 mg, 1.0 mmol) in CH_2Cl_2 (15 mL) was added DMAP (247 mg, 2.02 mmol) then PhOC(S)Cl (153 μL, 1.11 mmol). The mixture was stirred at rt for 14 h. Dry SiO_2 was added and the solvent evaporated. Purification of the residue by column chromatography (10→50% Et_2O in petrol) gave the corresponding *thiocarbonate* as a white foam (451 mg, 78%); R_f 0.7 (Et_2O); IR (film) 2976m, 2933m, 1710s, 1596m, 1490s, 1392s, 1306s, 1278s, 1215s, 1090m, 864m, 773m, 733m and 581m cm^{-1}; δ_H (400 MHz) (spectrum split by rotamers 4:6) 7.90 (0.8H, d, *J* 8.5, 2×CH of Ts), 7.87 (1.2H, d, *J* 8, 2×CH of Ts), 7.42–7.18 (5H, m, 2×CH of Ts and 3×CH of OPh), 7.10–7.05 (2H, m, 2×CH of OPh), 5.03 (0.4H, dd, *J* 1.5 and 1.5, CHO), 4.94 (0.6H, dd, *J* 1.5 and 1.5, CHO), 4.81 (0.4H, d, *J* 4.5, NCHCTs), 4.77 (0.6H, d, *J* 4.5, NCHCTs), 4.68 (0.6H, s, NCHCO), 4.50 (0.4H, s, NCHCO), 3.13 (0.4H, s, C*H*NEt_2), 2.93 (0.6H, s, C*H*NEt_2), 2.81 (0.4H, ddd, *J* 4.4, 1.2 and 1.2, TsCC*H*CHO), 2.75–2.34 (7.6H, m, 0.6×TsCC*H*CHO, 3×CH_3 of Ts and 4×CH_2 of NEt_2), 1.51 (5.4H, s, 3×CH_3 of Boc), 1.48 (3.6H, s, 3×CH_3 of Boc) and 0.93 (3.6H, t, *J* 7.0, 6×CH_3 of NEt_2); δ_C (100 MHz) (spectrum split by rotamers) 194.0 (C=S), 154.0 (C=O), 153.3, 153.2 (C_{quat} of OPh), 145.0, 144.9 (C_{quat} of Ts), 136.2, 135.9 (C_{quat} of Ts), 129.63, 129.58 (2×CH of Ts), 129.54, 129.50 (2×CH of OPh), 128.8, 128.6 (2×CH of Ts), 126.8, 126.7 (CH of OPh), 121.8, 121.7 (2×CH of OPh), 81.4, 81.0 (*C*Me_3), 80.5, 80.0 (CHO), 62.6, 61.1 (NCHCHO), 57.2, 55.6 (CHNEt_2), 46.9, 46.3 (TsC_{quat}), 43.1, 43.0 (2×CH_2 of NEt_2), 39.5, 38.9 (NCHCTs), 28.3 (3×CH_3 of Boc), 24.3, 23.9 (TsC*C*HCHO), 21.7 (CH_3 of Ts) and 13.5, 13.2 (2×CH_3 of NEt_2); *m*/*z* (CI, NH_3) 573.3 (M+H^+, 30%), 419.3 (85), 319.2 (30), 74.2 (100) (Found: M+H^+, 573.2091. $C_{29}H_{37}O_6N_2S_2$ requires M, 573.2093.). The above thiocarbonate (50 mg, 0.087 mmol) was

dissolved in cumene (5 mL) and heated to reflux for 2 h. The reaction mixture was cooled and the solvent removed under reduced pressure. Purification of the residue by column chromatography (30→50% Et_2O in petrol) gave a clear colourless oil, *enamine* **30** (14 mg, 38%); R_f 0.4 (50% Et_2O in petrol); IR (film) 2978m, 2934w, 1736s, 1628s, 1558w, 1400m, 1370m, 1332s, 1295m, 1140s, 1107m, 1085m and 733w cm^{-1}; δ_H (400 MHz; C_6D_6) 7.85 (2H, d, *J* 8, 2×CH of Ts), 7.79 (1H, s, NCH=), 7.70 (1H, dd, *J* 3.5 and 2, TsCC*H*), 6.86 (2H, d, *J* 8, 2×CH of Ts), 6.06 (1H, t, *J* 3.5, TsCCH=C*H*), 6.01 (1H, dd, *J* 3.5 and 2, =C*H*NEt_2), 2.65 (4H, q, *J* 7, 2×CH_2 of NEt_2), 2.00 (3H, s, CH_3 of Ts), 1.60 (9H, s, 3×CH_3 of Boc) and 0.72 (6H, br, s, 2×CH_3 of NEt_2); δ_C (100 MHz) 148.8 (C=O), 146.7 (CHNBoc), 141.7 (C_{quat} of Ts), 140.0 (C_{quat}NBoc), 128.9 (2×CH of Ts), 127.2 (2×CH of Ts), 123.3 (TsCC*H*), 122.3 (C_{quat} of Ts), 119.5 (TsCCH=*C*H), 110.0 (*C*HNEt), 97.5 (TsC_{quat}) 83.7 (*C*Me_3), 27.7 (3×CH_3 of Boc) and 21.4 (CH_3 of Ts) (note: CH_2 and CH_3 of NEt_2 not observed—very broad); *m*/*z* (ES^+) 859.0 (2 M+Na^+, 70%), 441.0 (M+Na^+, 50), 419.1 (M+H^+, 100), 264.1 (80) and 162.9 (40) (Found: M+H^+, 419.2005. $C_{22}H_{31}O_4N_2S$ requires M, 419.2005.).

4.29. 7-*tert*-Butyl 2-methyl 7-azabicyclo[2.2.1]hepta-2,5-diene-2,7-dicarboxylate (32)

Zinc/silver couple was prepared as follows:[25] 10% HCl (5 mL) was added to Zn dust (710 mg, 11.0 mmol) and the reaction mixture stirred for 5 min. The liquid was decanted and the Zn was washed with acetone (2×5 mL) and Et_2O (5 mL). A suspension of AgOAc (25 mg, 0.15 mmol) in AcOH (2 mL) was added with stirring to the digested Zn. After 1 min, the supernatant was decanted and the black Zn/Ag was washed with AcOH (3 mL), Et_2O (4×5 mL) and MeOH (5 mL). The moist Zn/Ag was added to a stirred solution of bromodiene **31**[26] (500 mg, 1.50 mmol) in MeOH (5 mL) and the reaction mixture was stirred for 2 h. The solid was filtered off and the solvent evaporated under reduced pressure. Purification by column chromatography (25% Et_2O–hexane) gave a pale yellow oil, *debrominated diene* **32** (300 mg, 80%); R_f (25% Et_2O–hexane) 0.16; IR (film) 2978s, 1712s, 1460m, 1368s, 1324s, 1168s and 790m cm^{-1}; δ_H (270 MHz) 7.70 (1H, br s, C(3)H), 7.13 (1H, br s, *H*C=CH), 6.98 (1H, br s, HC=C*H*), 5.42 (1H, br s, CH), 5.33 (1H, br s, CH), 3.76 (3H, s, OMe) and 1.41 (9H, s, *t*-Bu); δ_C(100 MHz) (broadening due to rotational isomers, C2 not observed) 163.8 (C=O), 155.0 (C=O), 154.4 and 153.8 (C3), 145.0, 144.0, 143.3 and 142.3 (C=C), 81.0 (*C*Me_3), 67.9 and 67.5 (C1), 66.8 and 66.3 (C4), 51.9 and 51.7 (OMe) and 28.4, 28.3, 28.1 and 28.0 (3×Me); *m*/*z* (CI) 252 (M+H^+, 10%), 182 (90), 154 (95) and 113 (100) (Found: M+H^+, 252.1235. $C_{13}H_{18}NO_4$ requires M, 252.1236.).

4.30. 8-(*tert*-Butoxycarbonyl)-6-(methoxycarbonyl)-8-aza-3-oxatricyclo [3.2.1.$0^{2,4}$]octane (33)

To a solution of debrominated diene **32** (1.52 g, 6.05 mmol) in CH_2Cl_2 (60 mL) was added aqueous $NaHCO_3$ (0.5 M; 20 mL) then MCPBA (70% remainder water; 2.24 g, 9.08 mmol). The mixture was stirred at rt for 24 h. Saturated Na_2SO_3 was added until a negative starch iodide test was obtained. The aqueous phase was extracted with CH_2Cl_2 (60 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (2×50 mL) then brine (50 mL) and dried. Purification of the residue by column chromatography (50→60% Et_2O in petrol) gave a clear colourless oil, *epoxide* **33** (711 mg, 44%); R_f 0.3 (40% Et_2O in petrol); IR (film) 2927m, 1714s, 1369s, 1335m, 1271m, 1227m, 1169m and 1072m cm^{-1}; δ_H (400 MHz) (shows rotamers at 300 K) 7.29–7.27 (1H, m, CH=), 5.03 (0.4H, s, NC*H*CO_2Me), 4.90 (0.6H, s, NC*H*CO_2Me), 4.85 (0.6H, d, *J* 2.8, NCH), 4.72 (0.4H, d, *J* 2.7, NCH), 3.79 (1.8H, s, OMe), 3.78 (1.2H, s, OMe), 3.65 (0.4H, d, *J* 3.65, CHO), 3.62 (0.6H, d, *J* 3.65, CHO), 3.57 (0.6H, d, *J* 3.65, CHO), 3.54 (0.4H, d, *J* 3.65, CHO), 1.48 (1.8H, s, 3×CH_3 of Ts) and 1.47 (1.2H, s, 3×CH_3 of Ts); δ_C (100 MHz) (split by rotamers), 181.3 (C=O), 162.8 (C=O), 155.8, 155.6 (C=), 147.1, 146.8 (CH=), 80.7, 80.6 (*C*Me_3), 62.6, 61.9 (CHN), 61.6, 60.8 (CHN), 56.8, 56.5 (CHO), 56.4, 56.2 (CHO), 52.1 (OMe) and 28.2, 28.1 (3×CH_3 of Boc); *m*/*z* (CI, NH_3) 285 (M+NH_4^+, 15%), 268 (M+H^+, 95), 256 (12), 247 (11), 243 (22) and 229 (100) (Found: M+H^+, 268.1187. $C_{13}H_{18}NO_5$ requires M, 268.1185.).

4.31. 3-(*tert*-Butoxycarbonyl)-1-(methoxycarbonyl)-7-(4-methoxyphenyl)-3-azatricyclo [2.2.1.$0^{2,6}$]heptan-5-ol (34)

To a cooled (0 °C) solution of epoxide **33** (690 mg, 2.58 mmol) in THF (50 mL) was added 4-methoxyphenylmagnesium bromide (0.5 M in THF; 10.3 mL, 5.17 mmol). The reaction mixture was stirred for 2 h at 0 °C, then saturated aq NH_4Cl (50 mL) was added and the mixture extracted with Et_2O (3×50 mL). The combined organic layers were washed with brine, dried and evaporated under reduced pressure. Purification of the residue by column chromatography (50→100% Et_2O in petrol) gave a white foam, 7-azanortricyclanol **34** (443 mg, 46%); R_f 0.2 (80% Et_2O in petrol); IR (film) 3423br, 2977w, 1698s, 1515s, 1440m, 1368m, 1307m, 1250s, 1180m, 1135m, 1070w, 1035w and 732w cm^{-1}; δ_H (400 MHz) (spectrum split by rotamers 6:4 ratio) 7.04 (2H, d, *J* 8.4, 2×MeOAr), 6.81 (2H, d, *J* 8.4, 2×MeOAr), 4.54 (0.6H, br s, NCHTs), 4.40 (0.4H, br s, NCHTs), 4.20–4.11 (1H, m, C*H*OH), 3.98 (0.4H, br s, NCH), 3.87 (0.6H, br s, NCH), 3.76 (3H, s, OMe), 3.61 (3H, s, CO_2Me), 3.27 (1H, s, ArCH), 2.29 (1H, br s, C*H*CHOH), 2.08–1.86 (1H, m, br, OH) 1.40 (3.6H, br s, 3×CH_3 of Boc) and 1.06 (5.4H, br s, 3×CH_3 of Boc); δ_C (100 MHz) 169.7 (C=O), 158.6 (C_{quat} of MeOAr), C=O not observed, 128.8 (2×CH of MeOAr), 128.2 (C_{quat} of MeOAr), 113.8 (2×CH of MeOAr), 80.3 (*C*Me_3), 73.9 (*C*HOH), 64.4 (NCH), 55.2 (OMe), 52.0 (CO_2*Me*), 45.3 (*C*HAr), 38.4 (NCHCTs), 32.7 (*C*CO_2Me) and 27.8 (3×CH_3); *m*/*z* (EI) 375 (M^+, 100%), 319 (79), 302 (70) and 288 (40) (Found: M^+, 375.1678. $C_{20}H_{25}O_6N$ requires M, 375.1682.).

4.32. 1-(*tert*-Butoxycarbonyl)-5-(methoxycarbonyl)-2-(4-methoxyphenyl)methyl-1,2-dihydropyridine (35)

1,1′-Thiocarbonyldiimidazole (631 mg, 3.54 mmol) was added to a solution of 7-azanortricyclanol **34** (443 mg, 1.18 mmol) in CH_2Cl_2 (5 mL). After 14 h the mixture was evaporated under reduced pressure. Purification of the residue by column chromatography (80→100% Et_2O in petrol) gave a white foam, the corresponding *thiocarbamate* (572 mg, 100%). Diagnostic data: δ_H (400 MHz) 8.29 (1H, s, NCH=), 7.57 (1H, s, NCH=), 7.02 (0.5H, s, NCH=), 6.99 (0.5H, s, NCH=) and 5.56 (1H, s, C*H*O). Reaction of the above thiocarbamate (535 mg, 1.10 mmol), Bu_3SnH (363 μL, 1.35 mmol) and AIBN (40.0 mg, 0.24 mmol) as described in the preparation of **21b** gave, after purification by column chromatography (10→20% Et_2O in petrol) a clear colourless oil, *1,2-dihydropyridine* **35** (181 mg, 46%); R_f 0.4 (20% Et_2O in petrol); IR (KBr) 2952m, 2837w, 1713s, 1640m, 1584m, 1513s, 1441m, 1394m, 1369m, 1340m, 1246s, 1150s, 1084m, 1036m, 981m, 852m and 731m cm^{-1}; δ_H (400 MHz) 8.00–7.71 (1H, m, br, NCH=), 7.06 (2H, br s, 2×CH of MeOAr), 6.82 (2H, d, *J* 8.5, 2×CH of MeOAr), 6.43 (1H, d, *J* 9.5, CH=), 5.45 (1H, dd, *J* 9.5, 5.5, CHCH=), 4.88 (1H, br s, NCH), 3.77 (6H, s, 2×OMe), 2.72 (2H, d, *J* 7, CH_2) and 1.47 (9H, br s, Boc); δ_C (100 MHz) (C=O of Boc not seen) 166.3 (CO_2), 158.4 (C_{quat} of MeOAr), 135.1 (NCH=), 130.6 (2×CH of MeOAr), 128.3 (C_{quat} of MeOAr), 120.7 (CH=), 120.3 (CHCH=), 113.7 (2×CH of MeOAr), 82.9 (CMe_3), 55.2 ($ArOCH_3$), 53.6 (br, NCH), 51.4 (CO_2CH_3), 39.9 (CH_2) and 27.9 (3×CH_3 of Boc); *m*/*z* (CI, NH_3) 377.2 (M+NH_4^+, 10%), 360 (80), 321 (20), 304 (15), 258 (25), 138 (100) and 121 (25) (Found: M+H^+, 360.1809. $C_{20}H_{26}O_5N$ requires M, 360.1811.).

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Supplementary data

ORTEP drawings of **14f**, **21g** and **25** (Figs. S1–S3). Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre, CCDC nos. 237474, 735974 and 735975 for **14f**, **21g** and **25**, respectively. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk). Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.07.022.

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20. Single crystal diffraction data for **14f**: $C_{25}H_{29}NO_6S$, M_r=471.57, monoclinic ($P2_1/c$), a=18.5776(6) Å, b=6.0148(2) Å, c=20.7897(7) Å, β=91.9711(16)°, V=2321.7 Å^3, D_c=1.349 Mg/m^3, Z=4, μ=0.181 mm^{-1}, 18,822 data collected, 5253 unique data [R(int)=0.063], $R1$=0.0408, $wR2$=0.0464, CCDC 237474.
21. Single crystal diffraction data for **25**: $C_{25}H_{29}NO_6S$, M_r=471.57, triclinic ($P\bar{1}$), a=6.1488(2) Å, b=9.6920(2) Å, c=19.4435(4) Å, α=85.9004(9)°, β=84.7239(9)°, γ=84.3066(9)°, V=1145.84(5) Å^3, D_c=1.367 Mg/m^3, Z=2, μ=0.184 mm^{-1}, 17,784 data collected, 5161 unique data [R(int)=0.041], $R1$=0.0384, $wR2$=0.0391, CCDC 735975.
22. Single crystal diffraction data for **21g**: $C_{25}H_{25}N_3O_{10}S$, M_r=559.55, triclinic ($P\bar{1}$), a=8.5894(2) Å, b=13.0366(2) Å, c=13.4603(3) Å, α=117.4440(9)°, β=96.5625(9)°, γ=98.9757(9)°, V=1291.09(5) Å^3, D_c=1.439 Mg/m^3, Z=2, μ=0.189 mm^{-1}, 15,245 data collected, 5877 unique data [R(int)=0.030], $R1$=0.0424, $wR2$=0.0385, CCDC 735974.
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