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Aspects of the chemistry of 8-azabicyclo[3.2.1]octanes

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Abstract—Mesylation and elimination from dimethyl 3-hydroxy-8-azabicyclo[3.2.1]octane-2,8-dicarboxylate gave a conjugated alkenyl ester. Reduction of the mesyloxy ester by di-isobutylaluminium hydride was also accompanied by elimination giving an unsaturated aldehyde. Treatment of the mesylate of the corresponding monoprotected diol with potassium *tert*-butoxide gave a 2-unsubstituted alkene via a Grob fragmentation but a different alkene was obtained using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile. Epoxidation of both the protected hydroxy-alkene and the free hydroxy-alkene was stereoselective in favour of epoxidation from the *exo*-face, and ring-opening of the hydroxy-epoxide using hydrogen bromide gave the diaxial bromohydrin. Treatment of a 2-iodomethyl-3-oxo-8-azabicyclo[3.2.1]octane with *tert*-butyllithium gave a cyclopropane, whereas the corresponding iodo-alcohol gave the 1-azatricyclo[5.3.0.0^{4,10}]decan-2-one as the major product.

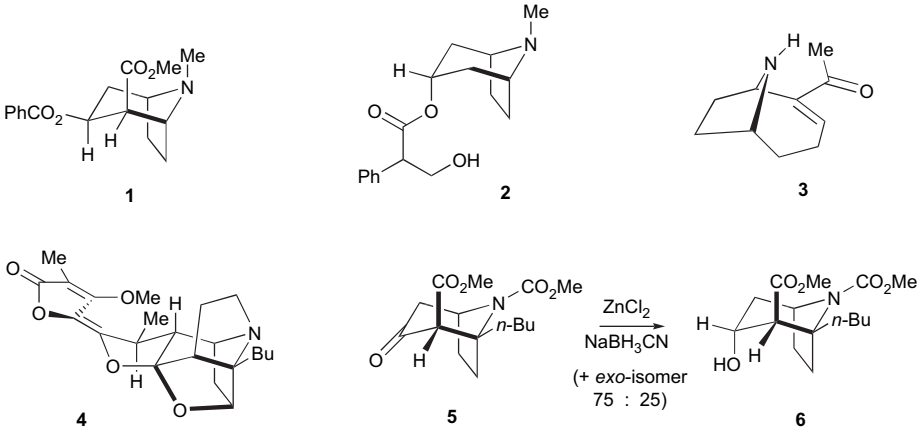
1. Introduction

Many 8-azabicyclo[3.2.1]octanes and related compounds show pronounced biological activity. Examples include the tropane alkaloids, e.g., cocaine **1** and atropine **2**, and the related anatoxin *a* **3**, which has the 9-azabicyclo[4.2.1]nonane skeleton.[1,2] Recently during studies of an approach to a synthesis of stemofoline **4**,[3–5] the 8-azabicyclo[3.2.1]octane-8-carboxylate **5** was prepared by a Mannich reaction and reduced to give the axial alcohol **6**.[6,7] In view of the interest in 8-azabicyclo[3.2.1]octanes, we report further aspects of the chemistry of the alcohol **6** and related compounds, including regioselective dehydration and the synthesis of tricyclic derivatives.

2. Results and discussion

An anti-dehydration of the hydroxy-ester **6** would be expected to give the corresponding non-conjugated unsaturated ester, but conversion to the mesylate **7** and treatment of the mesylate with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave the conjugated alkenyl ester **8**. Indeed reduction of the mesylate **7** with di-isobutylaluminium hydride (DIBAL–H) was also accompanied by elimination and gave the conjugated unsaturated aldehyde **9**, see Scheme 1.

Regioselective elimination from a 2-substituted 3-mesyloxy-8-azabicyclo[3.2.0]octane-8-carboxylate to give an 8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate with a disubstituted



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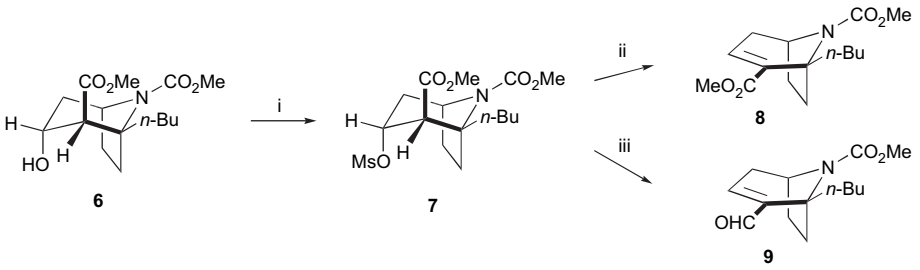
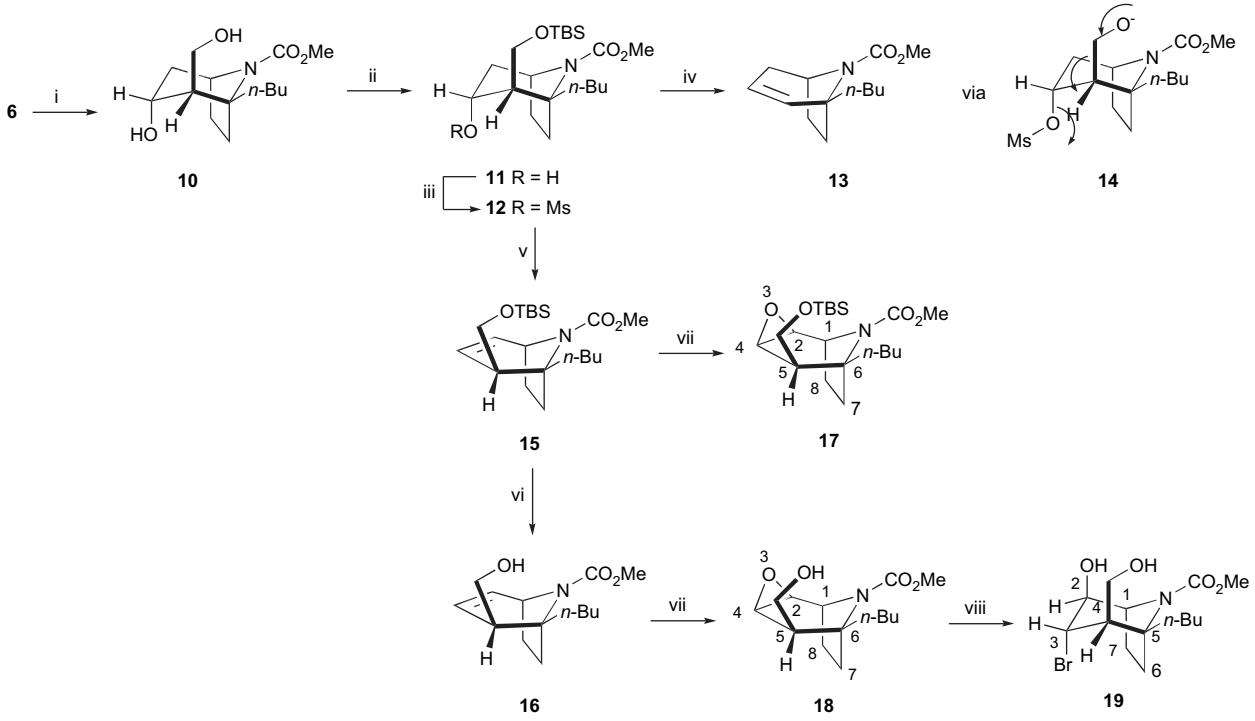


Scheme 1. Reagents and conditions: (i) MsCl, Et_3N, CH_2Cl_2 (87%); (ii) DBU, THF, heat (67%); (iii) DIBAL–H, hexane, −78 °C (68%).

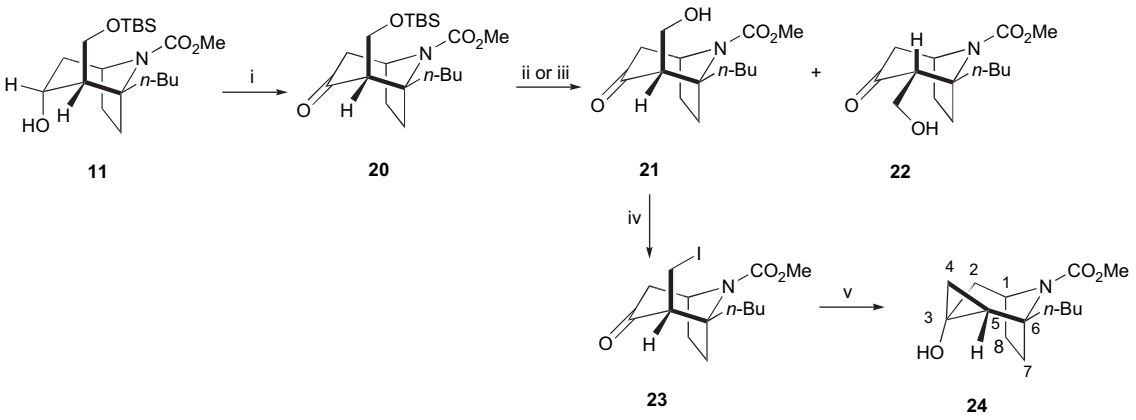
double-bond, was achieved as outlined in Scheme 2. Following reduction of the ester **6**, the diol **10** so obtained was selectively monoprotected to give the silyl ether **11**, which was converted into the mesylate **12**. Attempts to eliminate the mesylate using DBU in tetrahydrofuran, alumina, sodium methoxide or potasium *tert*-butoxide in tetrahydrofuran gave recovered starting material, and the use of potassium *tert*-butoxide in dimethyl sulfoxide gave the 2-unsubstituted 1-butyl-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate **13**, presumably by a base-induced, Grob-type of fragmentation,[8] see **14**. However, elimination of the mesylate from **12** was achieved using DBU in acetonitrile at 100 °C and gave the disubstituted alkene **15**, which on desilylation, using tetra-*n*-butylammonium fluoride (TBAF), was converted into the alkenol **16**.

Epoxidation of both of the alkenes **15** and **16** using *meta*-chloroperoxybenzoic acid took place from the *exo*-face to give the epoxides **17** and **18** with the epoxidation of the 4-hydroxymethyl alkene **16** being significantly faster perhaps because of hydrogen bonding to the incoming per-acid.[9] The stereoselectivity of epoxidation of the silyl ether **15** was confirmed by ^1H NMR spectroscopy with strong NOEs being observed for the epoxide **17**, for H-2 and H-5 on irradiation of H-4, and for H-1 and H-4 on irradiation of H-2, but not for the 5-CH_2 in either case. Ring-opening of the epoxide **18** on reaction with hydrogen bromide was regioselective with the diaxial ring-opened product **19** being obtained. In the bromohydrin **19**, the hydroxyl group at C2 was assigned the axial stereochemistry as shown because H-1 was observed as a doublet, coupling only to H-7$_{exo}$, and H-3 was observed as a broadened singlet.[10]

In our approach to stemofoline **4**, alkyllithium intermediates generated from 2-iodomethyl-8-azabicyclo[3.2.1]octane-8-carboxylates, were shown to react with the 8-methoxycarbonyl substituents to form tricyclo[5.3.0.0^{4,10}]decan-2-ones.[6,7] It was of interest to investigate the compatibility of this chemistry with other functionality in the 8-azabicyclo[3.2.1]octane. Oxidation of the monoprotected diol **11** gave ketone **20** (Scheme 3). Desilylation of this using TBAF gave a mixture of the axial and equatorial hydroxymethylketones **21** and **22**, ratio ca. 2:1, but the use of acidic amberlite resin avoided epimerisation and gave the axial 2-hydroxymethyl ketone **21** with little epimerisation. The

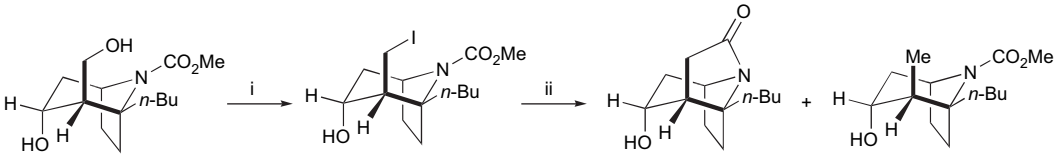


Scheme 2. Reagents and conditions: (i) DIBAL–H, CH_2Cl_2, −78 °C, then $NaBH_4$, EtOH (63%); (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2 (94%); (iii) MsCl, Et_3N, CH_2Cl_2 (71%); (iv) KO*t*-Bu, DMSO (78%); (v) DBU, CH_3CN, 100 °C (84%); (vi) TBAF, THF (100%); (vii) MCPBA, K_2CO_3, CH_2Cl_2 (**17**, 47%; **18**, 75%); (viii) HBr (83%).



11 20 21 22 23 24

Scheme 3. Reagents and conditions: (I) PDC, CH_2Cl_2 (98%); (ii) TBAF, THF (60%; **21**/**22**=2:1); (iii) Amberlite IR-120 (**21**, 79%); (iv) I_2, PPh_3, imid. (76%); (v) *t*-BuLi (3 equiv.), THF, −78 °C (67%).



10 25 26 27

Scheme 4. Reagents and conditions: (i) I_2, PPh_3, imid. (82%); (ii) *t*-BuLi (4 equiv), THF, −78 °C (**26**, 47%; **27**, 20%).

alcohol **21** was converted into the iodide **23** using iodine, triphenylphosphine and imidazole and treatment of the iodide with *tert*-butyllithum effected halogen metal exchange. This generated the corresponding alkyllithium reagent, which underwent addition to the adjacent ketonic carbonyl group to give the hydroxycyclopropane **24** rather than reaction with the 8-methoxycarbonyl group. The structure of cyclopropane **24** was established spectroscopically, in particular on the basis of the shielding observed for 4-H_2 and 5-H, which is characteristic of hydrogens attached to cyclopropyl rings.

However, it was found that the reaction of an alkyllithium intermediate with an 8-methoxycarbonyl group can be carried out in the presence of an unprotected, albeit trans-disposed, 3-hydroxyl group (Scheme 4). Thus, the diol **10** was reacted selectively with iodine, triphenylphosphine and imidazole to give the primary iodide **25**, which on treatment with *tert*-butyllithium gave the tricyclic lactam **26**, by addition of the alkyllithium generated from the iodide by iodine–lithium exchange into the methyl carbamate, together with the 2-methyl compound **27** formed by alkyllithium protonation. The yield of lactam **26** was not optimised, but its formation shows that protection of the hydroxyl group in this system is not essential.

3. Conclusion

This work has developed several selective sequences for the modification of 8-azabicyclo[3.2.1]octanes. Of interest are the regioselective syntheses of the alkenes **8/9** and **15/16** together with the fragmenation of the mesylate **12**, which gave alkene **13** and the alkyllithium additions, which gave the hydroxycyclopropane **2** from the ketone **23**, and the 1-azatricyclo[5.3.0.$0^{4,10}$]decan-2-one **26** from the hydroxy-iodide **25** without the hydroxyl group being protected.

4. Experimental

4.1. General

Melting points were recorded on a Koffler heated stage microscope. Proton NMR spectra were recorded in deuteriated chloroform, unless otherwise indicated, on Bruker AC300, Varian XL300 and Varian Unity 500 spectrometers. Coupling constants are given in hertz and chemical shifts are relative to Me_4Si. IR spectra were recorded on a Perkin Elmer 1710FT spectrometer and were run as evaporated films unless otherwise stated. Mass spectra were measured on a Kratos MS20 and MS25 spectrometers. Chromatography refers to flash chromatography using Merck silica gel 60H (40–63 mm^3, 230–400 mesh). Light petroleum refers to the fraction boiling at 40–60 °C and ether to diethyl ether. All solvents and reagents were purified by standard techniques before use. All non-aqueous reactions were performed under an atmosphere of dry argon or nitrogen.

4.1.1. Dimethyl (1*RS*,2*RS*,3*RS*,5*SR*)-1-butyl-3-mesyloxy-8-azabicyclo[3.2.1]octane-2,8-dicarboxylate 7. Mesyl chloride (70 μL, 0.903 mmol) was added to a solution of the alcohol **6**[7] (100 mg, 0.334 mmol) and triethylamine (140 μL, 1.004 mmol) in dichloromethane (2.0 ml). After 1 h, aqueous sodium bicarbonate (3 ml; 10%) was added and the organic phase separated. The aqueous phase was extracted with dichloromethane and the organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue, using light petroleum/ethyl acetate (60:40) as eluent, gave the *title compound* **7** (110 mg, 87%) as a colourless oil. (Found: M^+, 377.1508. $C_{16}H_{27}NO_7S$ requires *M*, 377.1508.) ν_{max} 1733, 1707, 1446, 1380, 1357, 1340, 1175, 1099 and 918 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.93 (3H, t, *J* 7, 4′-H3), 1.19–1.54 (4H,

m), 1.76–2.08 (5H, m), 2.19–2.40 (2H, m), 2.65 (1H, dt, *J* 14.5, 4, 4-H_{ax}), 3.00 (1H, s, 2-H), 3.04 (3H, s, CH_3SO_2), 3.63 (3H, s, CO_2CH_3), 3.71 (3H, s, CO_2CH_3), 4.45 (1H, br s, 5-H) and 5.07 (1H, d, *J* 5, 3-H); *m*/*z* (EI) 377 (M+, 6%), 282 (100), 182 (74), 181 (29), 140 (27), 96 (29) and 79 (38).

4.1.2. Dimethyl (1*RS*,5*SR*)-1-butyl-8-azabicyclo-[3.2.1]oct-2-ene-2,8-dicarboxylate 8. 1,8-Diazabicyclo-[5.4.0]undec-7-ene (30 μL, 0.201 mmol) was added to the mesylate **7** (16 mg, 0.042 mmol) in THF (1.5 ml), and the solution heated under reflux for 40 h. When cool, saturated aqueous ammonium chloride solution was added and the reaction mixture extracted with dichloromethane. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue, using light petroleum/ether (80:20) as eluent, afforded the *title compound* **8** (8 mg, 67%) as a colourless oil. (Found: M^+, 281.1620. $C_{15}H_{23}NO_4$ requires *M*, 281.1627) ν_{max} 1716, 1439, 1355, 1312, 1249, 1189, 1125, 1095 and 1062 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.92 (3H, t, *J* 6.5, 4′-H3), 1.20–1.43 (5H, m), 1.55 (1H, m), 1.93 (1H, dd, *J* 19, 4.5, 4-H_{eq}), 2.08–2.27 (4H, m), 2.87 (1H, br d, *J* 19, 4-H_{ax}), 3.67 (3H, s, CO_2CH_3), 3.72 (3H, s, CO_2CH_3), 4.41 (1H, t, *J* 6, 5-H) and 6.46 (1H, m, 3-H); *m*/*z* (EI) 281 (M+, 16%), 239 (100), 182 (74), 180 (38), 126 (27), 105 (22).

4.1.3. Methyl (1*RS*,5*SR*)-1-butyl-2-formyl-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate 9. Di-isobutylaluminium hydride (0.07 ml, 1 M in pentane, 0.07 mmol) was added dropwise to the ester **7** (11 mg, 0.029 mmol) in hexane (0.5 ml) at −78 °C. The mixture was stirred for 1 h at −78 °C then allowed to warm to room temperature over 90 min. Magnesium sulfate was added, the mixture filtered and the filtrate concentrated under reduced presure. Chromatography of the residue, using light petroleum/ether (80:20) as eluent, afforded the *title compound* **9** (5 mg, 68%) as a colourless oil. (Found: M^+, 251.1519. $C_{14}H_{21}NO_3$ requires *M*, 251.1521.) ν_{max} 1716, 1688, 1441, 1354, 1314, 1257, 1176, 1118 and 1096 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.92 (3H, t, *J* 7, 4′-H3), 1.25–1.45 (4H, m), 1.52 (1H, m), 1.92 (1H, m, 4-H_{eq}), 2.07–2.51 (5H, m), 3.03 (1H, dt, *J* 20, 1.5, 4-H_{ax}), 3.66 (3H, s, CO_2CH_3), 4.46 (1H, t, *J* 6, 5-H), 6.57 (1H, m, 3-H) and 9.34 (1H, s, CHO); *m*/*z* (EI) 251 (M+, 19%), 234 (25), 222 (45), 209 (32), 192 (23), 182 (100), 181 (84), 152 (27), 134 (28) and 126 (38).

4.1.4. Methyl (1*RS*,2*SR*,3*RS*,5*SR*)-1-butyl-2-*tert*-butyldimethylsilyoxymethyl-3-mesyloxy-8-azabicyclo[3.2.1]-octane-8-carboxylate 12. Triethylamine (150 μL, 1.078 mmol) and mesyl chloride (80 μL, 1.032 mmol) were added to the monoprotected diol **11**[7] (140 mg, 0.364 mmol) in dichloromethane (5 ml). After 1 h, aqueous sodium carbonate (10%) was added. The mixture extracted with dichloromethane, and the organic phase dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue, using light petroleum/ethyl acetate (8:1) as eluent, gave the *title compound* **12** (120 mg, 71%) as a colourless oil. (Found: M^+, 463.2424. $C_{21}H_{41}NO_6SiS$ requires *M*, 463.2424) ν_{max} 1708, 1446, 1380, 1364, 1257, 1178, 1095, 905, 858, 837 and 778 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.07 (6H, s, $Si(CH_3)_2$), 0.87–0.98 (12H, m, $C(CH_3)_3$ and 4′-H3), 1.21–1.43 (4H, m, 2′-H2 and 3′-H2), 1.75 (1H, m, 1′-H), 1.83–2.06 (4H, m), 2.09–2.50 (4H, m), 3.00 (3H, s, CH_3SO_2), 3.27 (1H, t, *J* 11, 2-CH), 3.63 (3H, s, CO_2CH_3), 4.00 (1H, dd, *J* 11, 4, 2-CH′), 4.39 (1H, m, 5-H) and 5.17 (1H, d, *J* 4.5, 3-H); δ_C (75 MHz, $CDCl_3$) −5.48, −5.40, 14.11, 18.31, 23.33, 25.31, 25.93, 26.65, 33.87, 35.26, 36.11, 37.96, 51.92, 52.52, 55.30, 60.40, 64.10, 78.44 and 154.48; *m*/*z* (EI) 464 (M^++1, 1%), 406 (100), 368 (52), 310 (63), 236 (32) and 182 (66).

4.1.5. Methyl (1*RS*,5*SR*)-1-butyl-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate 13. Potassium *tert*-butoxide (64 mg, 0.570 mmol) was added to the mesylate **12** (40 mg, 0.086 mmol) in dimethylsulfoxide (1.0 ml). After 30 min, hexane (2 ml) and water (2 ml) were added and the mixture extracted with hexane. The organic phase was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue, using light petroleum/ethyl acetate (9:1) as eluent, afforded the *title compound* **13** (15 mg, 78%) as a colourless oil. (Found: M^++H, 224.1639. $C_{13}H_{22}NO_2$ requires *M*, 224.1651.) ν_{max}, 1717, 1700, 1443, 1359, 1296, 1259, 1187, 1120 and 1095 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7 , 4′-H3), 1.22–1.40 (4H, m, 2′-H2 and 3′-H2), 1.54 (1H, m), 1.74 (1H, dd, *J* 18, 4, 4-H_{eq}), 1.85–1.98 (3H, m), 2.01–2.10 (2H, m), 2.50 (1H, dd, *J* 18, 2.5, 4-H_{ax}), 3.63 (3H, s, CO_2CH_3), 4.38 (1H, dd, *J* 6.5, 4.5, 5-H), 5.48 (1H, m, 3-H) and 5.88 (1H, dt, *J* 10, 2, 2-H); *m*/*z* (CI) 224 (M^++1, 100%), 194 (5), 182 (6), 181 (24), 166 (5) and 149 (6).

4.1.6. Methyl (1*SR*,4*SR*,5*RS*)-5-butyl-4-*tert*-butyldimethylsilyoxymethyl-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate 15. 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.2 ml, 1.34 mmol) was added to the mesylate **12** (33 mg, 0.071 mmol) in acetonitrile (1.5 ml) and the mixture heated at 100 °C for 17 h. After cooling, the solvent was removed under reduced pressure. Chromatography of the residue, using light petroleum/ethyl acetate (25:1) as eluent, afforded the *title compound* **15** (22 mg, 84%) as a colourless oil. (Found: M^+, 367.2538. $C_{20}H_{37}NO_3Si$ requires *M*, 367.2543) ν_{max} 1706, 1444, 1387, 1362, 1319, 1097, 838 and 777 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.03 (3H, s, $SiCH_3$), 0.04 (3H, s, $SiCH_3$), 0.89 (9H, s, $C(CH_3)_3$), 0.93 (3H, t, *J* 6.5, 4′-H3), 1.20–1.45 (4H, m, 2′-H2 and 3′-H2), 1.65–1.88 (3H, m), 1.91–2.08 (2H, m), 2.08–2.26 (2H, m), 3.49 (1H, t, *J* 9, 4-CH), 3.61 (3H, s, CO_2CH_3), 3.92 (1H, dd, *J* 9, 5.5, 4-CH′), 4.52 (1H, m, 1-H), 5.71 (1H, dd, *J* 9.5, 4, 3-H) and 6.01 (1H, ddd, *J* 9.5, 5, 1.5, 2-H); δ_C (75 MHz, $CDCl_3$) −5.27, 14.25, 18.34, 23.38, 25.92, 26.50, 32.22, 34.66, 37.73, 51.75, 52.76, 56.67, 63.92, 65.03, 127.52, 132.00 and 154.68; *m*/*z* (EI) 367 (M^+, 15%), 311 (21), 310 (100), 266 (12), 194 (12), 119 (14), 89 (72) and 73 (63).

4.1.7. Methyl (1*SR*,4*SR*,5*RS*)-5-butyl-4-hydroxymethyl-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate 16. Tetra-*n*-butylammonium fluoride (0.24 ml, 1 M in THF, 0.24 mmol) was added to the *tert*-butyldimethylsilyl ether **15** (43 mg, 0.117 mol) at ambient temperature and the mixture stirred for 15 h. Ethyl acetate was added and the solution washed with saturated aqueous ammonium chloride and water then dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue, using ether/light petroleum (40:60) as eluent, afforded the *title compound*

16 (30 mg, 100%) as a colourless oil. (Found: M^++, 253.1680. $C_{14}H_{23}NO_3$ requires *M*, 253.1678) ν_{max} 3442, 1705, 1684, 1449, 1391, 1364, 1320, 1097 and 951 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.93 (3H, t, *J* 7, 4′-H3), 1.24–1.44 (4H, m, 2′-H2 and 3′-H2), 1.71–1.83 (2H, m), 1.88 (1H, m), 1.96–2.21 (4H, m), 2.86 (1H, s, OH), 3.57 (1H, dd, *J* 12.5, 3.5, 4-CH), 3.62 (3H, s, CO_2CH_3), 3.87 (1H, dd, *J* 12.5, 3.5, 4-CH′), 4.55 (1H, t, *J* 5.5, 1-H), 5.58 (1H, dd, *J* 9.5, 3.5, 3-H) and 6.13 (1H, ddd, *J* 9, 4.5, 1.5, 2-H); δ_C (50 MHz, $CDCl_3$) 14.63, 23.77, 26.69, 32.71, 34.91, 38.87, 52.74, 52.87, 56.95, 61.87, 65.17, 127.81, 134.12 and 157.50; *m/z* (CI) 254 (M^++1, 100%), 253 (11), 236 (4), 222 (9), 194 (2) and 178 (2).

4.1.8. Methyl (1*SR*,2*SR*,4*RS*,5*SR*,6*RS*)-6-butyl-5-*tert*-butyldimethylsilyloxymethyl-3-oxa-9-azatricyclo[4.2.1.$0^{2,4}$]-nonane-9-carboxylate 17. 3-Chloroperoxybenzoic acid (132 mg, 55%, 0.421 mmol) was added to the alkene **15** (67 mg, 0.183 mmol) and potassium carbonate (177 mg, 1.281 mmol) in dichloromethane (1.0 ml) at ambient temperature. After 20 h, saturated aqueous sodium sulfite was added and the mixture extracted with dichloromethane. The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue, using light petroleum/ethyl acetate (30:1) as eluent, gave the *title compound* **17** (33 mg, 47%) as a colourless oil. (Found: M^++H, 384.2572. $C_{20}H_{38}NO_4Si$ requires *M*, 384.2570.) ν_{max} 1710, 1444, 1377, 1320, 1102, 1074, 837 and 778 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.08 (6H, s, $Si(CH_3)_2$), 0.87–0.94 (12H, m, $Si(CH_3)_3$ and 4′-H3), 1.17–1.39 (4H, m, 2′-H2 and 3′-H2), 1.70–1.94 (4H, m), 1.94–1.29 (3H, m), 3.08 (1H, m, 2-H), 3.25 (1H, t, *J* 4, 4-H), 3.63 (3H, s, CO_2CH_3), 3.87–4.05 (2H, m, 5-CH_2) and 4.52 (1H, m, 1-H); δ_C (75 MHz, $CDCl_3$) −5.43, 14.11, 18.31, 23.21, 24.17, 25.96, 26.32, 34.26, 38.10, 48.06, 50.42, 51.86, 53.95, 55.64, 60.88, 62.81 and 156.27; *m/z* (CI) 384 (M^++1, 100%), 326 (11), 252 (20), 196 (18) and 183 (11). Further elution recovered starting alkene **15** (32 mg, 48%).

4.1.9. Methyl (1*SR*,2*SR*,4*RS*,5*SR*,6*RS*)-6-butyl-5-hydroxymethyl-3-oxa-9-azatricyclo[4.2.1.$0^{2,4}$]-nonane-9-carboxylate 18. 3-Chloroperoxybenzoic acid (10 mg, 55%, 0.032 mmol) was added to the alkene **16** (5 mg, 0.020 mmol) and potassium carbonate (9 mg, 0.065 mmol) in dichloromethane (0.5 ml) at ambient temperature. After 8 h, saturated aqueous sodium sulfite was added and the mixture extracted with dichloromethane. The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressue. Chromatography of the residue, using light petroleum/ethyl acetate (50:50) as eluent, gave the *title compound* **18** (4 mg, 75%) as a colourless oil. (Found: M^+, 269.1624. $C_{14}H_{23}NO_4$ requires *M*, 269.1627.) ν_{max} 3437, 1707, 1690, 1447, 1380, 1321, 1241 and 1100 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.87 (3H, t, *J* 7, 4′-H3), 1.15–1.36 (4H, m, 2′-H2 and 3′-H2), 1.70–1.82 (3H, m), 1.82–1.95 (2H, m), 1.99–2.16 (3H, m), 3.09 (1H, br s, 2-H), 3.26 (1H, t, *J* 4, 4-H), 3.61 (3H, s, CO_2CH_3), 3.89 (1H, dd, *J* 4.5, 10, 5-CH), 4.05 (1H, m, 5-CH′) and 4.53 (1H, m, 1-H); δ_C (75 MHz, $CDCl_3$) 14.09, 23.20, 24.14, 26.31, 34.21, 38.22, 47.22, 50.35, 51.99, 53.83, 55.60, 60.65, 62.85 and 156.37; *m/z* (EI) 270 (M^++1, 10%), 196 (17), 183 (82), 140 (100) and 126 (58).

4.1.10. Methyl (1*SR*,2*SR*,3*SR*,4*SR*,5*RS*)-3-bromo-5-butyl-2-hydroxy-4-hydroxymethyl-8-azabicyclo-[3.2.1]octane-8-carboxylate 19. Hydrobromic acid (48%, 250 μL, 2.21 mmol) was added to the epoxide **18** (12 mg, 0.045 mmol) and the mixture stirred for 5 min. Water (1.5 ml) was added and the mixture extracted with dichloromethane. The organic extracts were dried (Na_2SO_4) and concentrated under reduced presssure. Chromatography, using light petroleum/ethyl acetate (50:50) as eluent, gave the *title compound* **19** (13 mg, 83%) as a white solid, mp 96–97 °C. (Found: M^++H, 350.0941. $C_{14}H_{24}{}^{79}BrNO_4$ requires *M*, 350.0967.) ν_{max} 3390, 1680, 1455, 1391, 1328, 1236, 1192, 1140, 1104, 1027 and 978 cm^{-1}; δ_H (500 MHz, C_6D_6) 0.93 (3H, t, *J* 7, 4′-H3), 0.99 (1H, m, 2′-H), 1.10 (1H, m, 2′-H′), 1.23–1.37 (2H, m, 3′-H2), 1.59–1.75 (3H, m), 2.01–2.10 (2H, m), 2.29–2.38 (2H, m), 3.23 (1H, ddd, *J* 12.5, 10, 2.5, 4-CH), 3.45 (3H, s, CO_2CH_3), 3.79 (1H, dt, *J* 12.5, 3.5, 4-CH′), 4.11 (1H, d, *J* 9.5, 2-H), 4.28 (1H, s, 3-H), 4.40 (1H, br s, OH), 4.54 (1H, d, *J* 7, 1-H) and 4.80 (1H, d, *J* 9.5, 2-OH); δ_C (75 MHz, $CDCl_3$) 14.07, 23.29, 26.55, 35.07, 36.72, 48.48, 51.65, 52.54, 62.16, 62.50, 64.37, 74.12, 77.24 and 156.82; *m/z* (CI) 352 (100%), 350 (M+, 100), 338 (22) and 270 (63).

4.1.11. Methyl (1*RS*,2*SR*,5*SR*)- and (1*RS*,2*RS*,5*SR*)-1-butyl-2-hydroxymethyl-3-oxo-8-azabicyclo-[3.2.1]octane-8-carboxylates 21 and 22. Tetra-*n*-butylammonium fluoride (0.22 ml, 1 M in THF, 0.22 mmol) was added to the *tert*-butyldimethylsilyloxytropanone **20**[7] (43 mg, 0.112 mmol) at ambient temperature and the mixture stirred for 15 h. Ethyl acetate was added and the solution washed with saturated aqueous ammonium chloride and water then dried ($MgSO_4$). Chromatography of the residue, using light petroleum/ethyl acetate (2:1) as eluent, gave first the *title compound* **22** (6 mg, 20%), as a colourless oil. (Found: M^+, 269.1626. $C_{14}H_{23}NO_4$ requires *M*, 269.1627.) ν_{max} 3487, 1701, 1444, 1364, 1345 and 1098 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.96 (3H, t, *J* 7, 4′-H3), 1.24–1.53 (5H, m), 1.55–1.69 (2H, m), 1.85–2.10 (3H, m), 2.36 (1H, m), 2.37 (1H, dd, *J* 15.5, 1.5, 4-H_{eq}), 2.76 (1H, dd, *J* 15.5, 5, 4-H_{ax}), 2.91 (1H, m, 2-H), 3.79 (3H, s, CO_2CH_3), 3.83–3.91 (2H, m, 2-CH_2) and 4.58 (1H, br t, *J* 5.5, 5-H); δ_C (75 MHz, $CDCl_3$) 14.12, 23.04, 25.28, 27.56, 31.00, 34.48, 48.22, 52.53, 56.86, 58.95, 61.41, 66.55, 155.20 and 212.17; *m/z* (EI) 270 (M^++1, 2%), 269 (3), 182 (74), 181 (100), 139 (52) and 138 (40). The second product off the column was the *title compound* **21** (12 mg, 40%) as a colourless oil. (Found: M^++H, 270.1702. $C_{14}H_{24}NO_4$ requires *M*, 270.1705.) ν_{max} 3454, 1708, 1446, 1377, 1345, 1099 and 1048 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.91 (3H, t, *J* 7, 4′-H3), 1.18–1.44 (4H, m, 2′-H2 and 3′-H2), 1.54 (1H, m), 1.75 (1H, m), 1.91–2.12 (3H, m), 2.12–3.31 (2H, m), 2.36 (1H, dt, *J* 16, 1.5, 4-H_{eq}), 2.44 (1H, t, *J* 4.5, 2-H), 2.70 (1H, ddd, *J* 16, 4.5, 1, 4-H_{ax}), 3.70 (3H, s, CO_2CH_3), 3.84 (1H, dd, *J* 12, 4.5, 2-CH), 3.92 (1H, dd, *J* 12, 5.5, 2-CH′) and 4.63 (1H, br t, *J* 5, 5-H); δ_C (75 MHz, $CDCl_3$) 14.05, 23.20, 26.33, 26.55, 34.01, 37.13, 48.64, 52.51, 55.55, 61.18, 64.08, 65.12, 156.57 and 211.05; *m/z* (EI) 270 (M^++1, 4%), 269 (3), 182 (81), 181 (100), 139 (38) and 138 (39).

Acidic amberlite resin IR-120 (20 mg) was added to the *tert*-butyldimethylsilyloxy ether **20** (9 mg, 0.023 mmol) in methanol (1.0 ml). After 6 h, the resin was removed by filtration

and washed with ethyl acetate. The organic extract was concentrated under reduced pressure and chromatography of the residue, using light petroleum/ethyl acetate (2:1) as eluent, gave the 2-axial 2-hydroxymethyl ketone **21** (5 mg, 79%), as a colourless oil.

4.1.12. Methyl (1*RS*,2*RS*,5*SR*)-1-butyl-2-iodomethyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate 23. The alcohol **21** (14 mg, 0.052 mmol), imidazole (5 mg, 0.075 mmol), triphenylphosphine (20 mg, 0.075 mmol) and iodine (20 mg, 0.075 mmol) were stirred in dichloromethane (0.5 ml) for 12 h. Saturated aqueous sodium thiosulfate (0.25 ml) and saturated sodium bicarbonate (0.25 ml) were added and the mixture stirred for 30 min. The aqueous phase was extracted with dichloromethane and the organic extracts were washed with water and dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue, using light petroleum/ethyl acetate (8:1), afforded the *title compound* **23** (15 mg, 76%) as a colourless oil. (Found: M^++H, 380.0725. $C_{14}H_{23}INO_3$ requires *M*, 380.0723.) ν_{max} 1703, 1444, 1376, 1343, 1276, 1103 and 992 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.93 (3H, t, *J* 7, 4′-H3), 1.18–1.46 (4H, m, 2′-H2 and 3′-H2), 1.59 (1H, m), 1.71–1.97 (2H, m), 1.98–2.13 (2H, m), 2.20–2.33 (2H, m, 4-H_{eq} and 1′-H), 2.70–2.82 (2H, m, 4-H_{ax} and 2-H), 3.03 (1H, t, *J* 11, 2-CH), 3.62 (1H, dd, *J* 11, 4, 2-CH′), 3.73 (3H, s, CO_2CH_3) and 4.70 (1H, m, 5-H); δ_C (75 MHz, $CDCl_3$) −1.05, 14.04, 23.15, 26.30, 26.32, 33.98, 35.77, 45.93, 52.50, 56.63, 65.10, 68.25 and 154.91; *m*/*z* (CI) 397 (M^++18, 15%), 380 (43), 336 (25), 271 (98), 269 (28), 254 (100), 252 (45) and 182 (14).

4.1.13. Methyl (1*SR*,3*RS*,5*RS*,6*RS*)-6-butyl-3-hydroxy-9-azatricyclo[4.2.1.0^{3,5}]nonane-9-carboxylate 24. *tert*-Butyllithium (65 μL, 1.7 M in pentane, 0.111 mmol) was added to the iodide **23** (14 mg, 0.037 mmol) in THF (0.5 ml) at −78 °C and the mixture stirred at −78 °C for 40 min and then at ambient temperature for 3 h. Saturated aqueous ammonium chloride was added and the mixture diluted with ether. The aqueous phase was extracted with ethyl acetate and the organic extracts washed with water and dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue, using light petroleum/ethyl acetate (75:25) as eluent, gave the *title compound* **24** (6 mg, 67%) as a colourless oil. (Found: M^++H, 254.1752. $C_{14}H_{24}NO_3$ requires *M*, 254.1756.) ν_{max} 3358, 1703, 1685, 1451, 1384, 1308, 1275, 1192, 1166, 1121 and 1100 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.24 (1H, t, *J* 6, 5-H), 0.85 (1H, m, 4-H), 0.93 (3H, t, *J* 7, 4′-H3), 1.23 (1H, dd, *J* 10, 6, 4-H′), 1.22–1.48 (4H, m, 2′-H2 and 3′-H2), 1.67 (1H, m), 1.73–1.88 (3H, m), 1.90–2.13 (4H, m), 2.57 (1H, dd, *J* 14, 5, 2-H_{ax}), 3.60 (3H, s, CO_2CH_3) and 4.17 (1H, m, 1-H); *m*/*z* (CI) 271 (M^++18, 18%), 255 (19), 254 (100), 196 (5) and 182 (7).

4.1.14. Methyl (1*RS*,2*RS*,3*RS*,5*SR*)-1-butyl-3-hydroxy-2-iodomethyl-8-azabicyclo[3.2.1]octane-8-carboxylate 25. Following the procedure outlined for the preparation of the iodide **23**, the diol **10**[7] (39 mg, 0.144 mmol) gave, after chromatography using light petroleum/ethyl acetate (10:1) the *title compound* **25** (45 mg, 82%) as white solid, mp 133 °C. (Found: C, 44.35; H, 6.65; N, 3.7; I, 33.4%. $C_{14}H_{24}INO_3$ requires C, 44.0; H, 6.6; N, 3.65; I, 33.2%. Found: M^++H, 382.0884. $C_{14}H_{25}INO_3$ requires *M*, 382.0879.) ν_{max} 3446, 1677, 1452, 1384, 1189, 1150, 1097 and 1032 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.91 (3H, t, *J* 7, 4′-H3), 1.20–1.40 (4H, m, 2′-H2 and 3′-H2), 1.64 (1H, d, *J* 14, 4-H_{eq}), 1.71–1.85 (4H, m), 1.95 (1H, m), 2.04–2.14 (2H, m), 2.43–2.54 (2H, m), 2.65 (1H, t, *J* 11.5, 2-CH), 3.60 (3H, s, CO_2CH_3), 3.72 (1H, dd, *J* 11, 1.5, 2-CH′), 4.29 (1H, m, 3-H) and 4.35 (1H, m, 5-H); *m*/*z* (CI) 399 (M^++18, 5%), 383 (15), 382 (100), 257 (17), 256 (77) and 254 (21).

4.1.15. (4*RS*,5*RS*,7*SR*,10*RS*)-10-Butyl-5-hydroxy-1-azatricyclo[5.3.0.0^{4,10}]decan-2-one 26[7] and methyl (1*RS*,2*RS*,3*RS*,5*SR*)-1-butyl-3-hydroxy-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate 27. Following the procedure outlined for the synthesis of cyclopropane **24**, the iodide **25** (22 mg, 0.058 mmol) was treated with *tert*-butyllithium (145 μL, 1.7 M in pentane, 0.247 mmol) to give, after chromatography using light petroleum/ethyl acetate (8:1) as eluent, the tricyclic amide **26**[7] (6 mg, 47%) as a white solid, followed by the *title compound* **27** (3 mg, 20%) as a colourless oil. (Found: M^+, 255.1839, $C_{14}H_{25}NO_3$ requires *M*, 255.1834.); ν_{max} 3437, 1705, 1683, 1452, 1384 and 1098 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7, 4′-H3), 0.94 (3H, d, *J* 7.5, 2-CH_3), 1.19–1.37 (4H, m, 2′-H2 and 3′-H2), 1.39–1.44 (1H, m, OH), 1.55 (1H, d, *J* 15.5, 4-H_{eq}), 1.72 (1H, td, *J* 15, 4.5), 1.76–1.83 (2H, m), 1.86 (1H, m, 2-H), 1.94 (1H, m), 2.12 (1H, m, 4-H_{ax}), 2.34–2.44 (2H, m), 3.61 (3H, s, CO_2CH_3), 3.81 (1H, d, *J* 4.5, 3-H) and 4.34 (1H, m, 5-H); *m*/*z* (EI) 256 (M^++1, 13%), 255 (12), 238 (21), 196 (100), 183 (43) and 140 (35).

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References and notes

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10. For a discussion, based on X-ray crystal data, of the use of coupling constants involving the bridgehead hydrogens to establish stereochemistry in these 8-azabicyclo[3.2.1]octanes and related systems, see Ref. 7.