Synthetic approaches to the polycyclic alkaloid stemofoline†‡

Alison M. Baylis, Michael. P. H. Davies and Eric J. Thomas*

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Preliminary studies of a synthetic approach to the alkaloid stemofoline **1** are reported. Stereoselective cyclisation of the ketoester **14** gave the 1-butyl-2,8-bis(methoxycarbonyl)-8-azabicyclo[3.2.1]octane **21** in which the 2-methoxycarbonyl group is in the axial position. The analogous ketones **15**, **18** and **19** were also cyclised to give the 8-azabicyclo[3.2.1]octanes **22–24** with axial electron-withdrawing 2-substituents. The structure of the bicyclic ketosulfone **22** was confirmed by X-ray diffraction. Conversion of ester **21** into the tricyclic lactams **31** and **39**, in which the amide fragments are significantly distorted from planarity, was achieved by treatment of the iodides **29** and **38** with *tert*-butyllithium. The structure of the deprotected tricyclic hydroxylactam **40** was confirmed by X-ray diffraction, which showed the non-planar geometry of the lactam fragment and the distortion induced into the bicyclo[3.2.1]octane by the additional two-carbon bridge. This meant that the *endo* hydrogen at C9 was significantly closer to the 5-hydroxyl group than the *endo* hydrogen at C8. This structural feature was utilised to direct a regioselective remote oxidation of the hydroxylactam **40** using lead tetraacetate, which was accompanied by selective insertion into the closer *endo* C–H bond to give the tetracyclic ether **41**. Lactam **39** was converted into the tricyclic aminoketone **49** by reduction to the aminol **44** using lithium aluminium hydride and reduction of the intermediate, possibly the chloride **46**, formed from aminol **44** using thionyl chloride, with more lithium aluminium hydride, followed by *O*-deprotection and oxidation. The bicyclic ketoester **21** was also protected as its ketal **50**, which was taken through *via* the tricyclic lactam **54** into the ketoamine **49**. Finally, allylation of the tricyclic lactam **42** and amine **49** gave the axial allylated products **60** and **58**, but further elaboration for incorporation of C10 and C11 (of stemofoline) was not straightforward. Alkylation of the protected hydroxyketone **64**, which was prepared from the bicyclic ketoester **21**, gave the axial alkylated products **65** and **69**, and the ketoester **69** was converted into the tricyclic hydroxylactone **73**. However, the formation of a tetracyclic lactam by treatment of the iodide **75** with *tert*-butyllithium was not successful.

Introduction

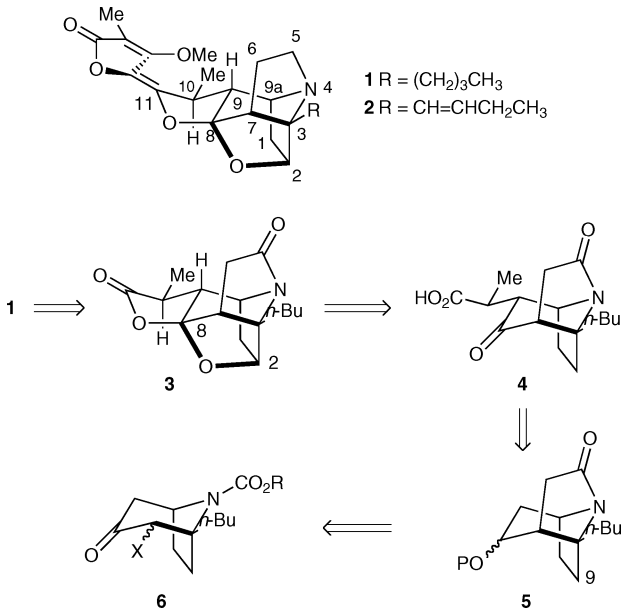
Extracts of the roots and leaves of several *Stemonacea* have been widely used in traditional Chinese, Japanese and Thai medicine to treat respiratory complaints and parasitic infections, and as insecticides. More than twenty alkaloids have been isolated from these species of which the most complex are stemofoline **1** and its dehydro analogue, asparagamine A **2**, which has also been isolated from *Asparagus racemosus*.[1] Because of their biological activities, many synthetic studies have been carried out on the synthesis of the stemona alkaloids including a synthesis of (±)-isostemofoline [the (*E*)-isomer of stemofoline],[2] and a synthesis of (±)-asparagamine and its (*E*)-isomer,[3] together with total syntheses of stenine,[4] tuberostemonine,[5] croomine,[6] stemospironine,[7] stemonamide[8] and stemoamide.[9] Several other synthetic approaches to these alkaloids have been reported,[10] and simplified analogues of stemofoline have also been prepared for evaluation of their biological activity.[11] No biosynthetic studies have been carried out on Stemona alkaloids but, on the basis of their structures, a biogenetic route from spermidine and isoprenoid fragments, has been proposed.[12]

A possible strategy for the synthesis of stemofoline is outlined in Scheme 1. 8-Azabicyclo[3.2.1]octanes, *e.g.* **6**, should be available *via* iminium ion cyclisations, such reactions having been widely used for the synthesis of alkaloids.[13] Construction of the third ring of the stemofoline nucleus by regioselective alkylation would provide a tricyclic intermediate, *e.g.* **5**, and addition of the remaining three-carbon fragment would deliver the ketolactam **4**. At some point it will be necessary to introduce the oxygen functionality which is to become the ethereal bridge between C2 and C8 (stemofoline numbering). It may be necessary to introduce this additional functionality earlier in the synthesis, but an attractive strategy would be to use the ketoacid present in **4** to effect a regioselective remote oxidation generating an intermediate such as the pentacyclic acetal **3**. Reduction of the lactam and addition of the tetronic acid would then complete a synthesis of stemofoline **1**. We now report details of a synthesis of the tricyclic hydroxylactam **40**, which is analogous to **5**, together with studies of its regioselective remote oxidation and other functional group interconversions that will underpin future attempts to complete a synthesis of stemofoline.[14,15]

The School of Chemistry, The University of Manchester, Manchester, UK M13 9PL. E-mail: e.j.thomas@manchester.ac.uk

† Electronic supplementary information (ESI) available: full experimental details for the preparation of compounds **8–19** and **50–57**. See DOI: 10.1039/b708910d

‡ CCDC reference number 650400. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b708910d

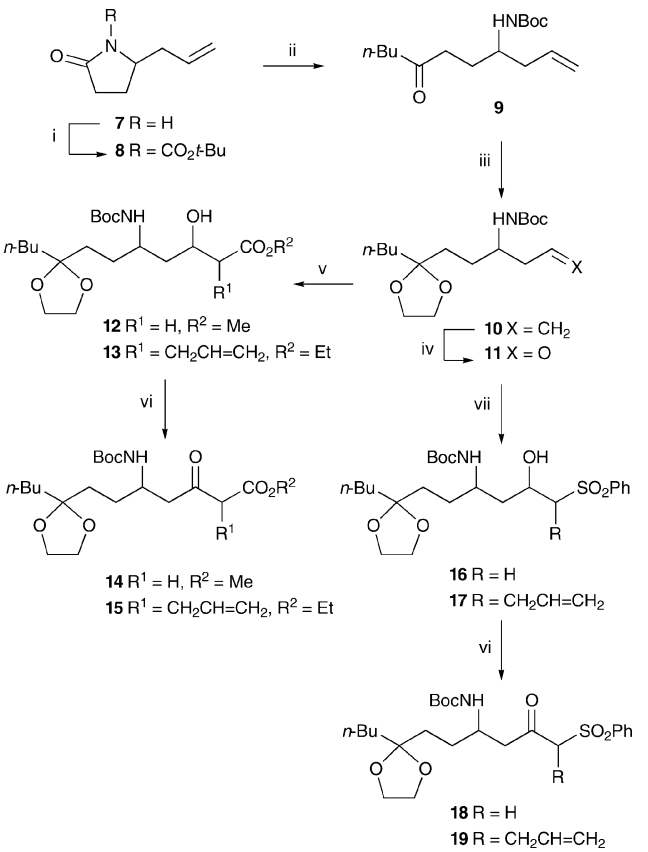


Scheme 1 Outline of a possible synthesis of stemofoline.

Results and discussion

Assembly of the tropanone

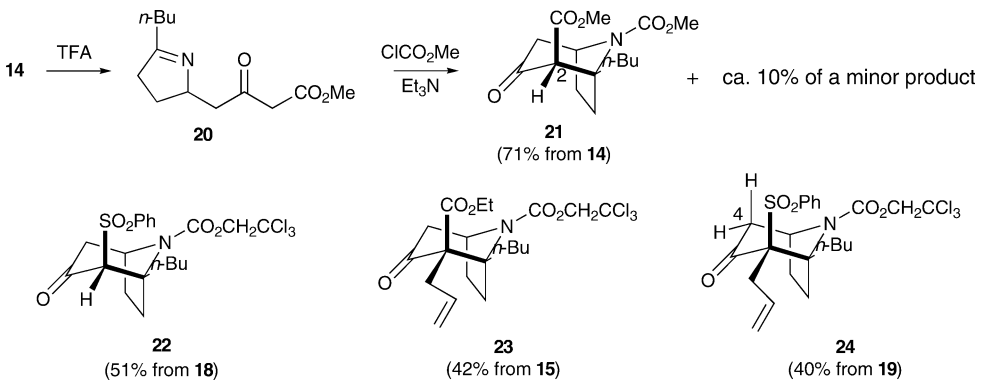
Cyclisation precursors were prepared from 5-prop-2-enylpyrrolidinone **7**, as outlined in Scheme 2. Reaction of the racemic§ pyrrolidinone *N*-*tert*-butoxycarbonyl derivative **8**[16] with butylmagnesium bromide[17] gave ketone **9**, which was protected as its acetal **10**. Ozonolysis gave the aldehyde **11**, which was converted into the ketoester **14** *via* an aldol condensation followed by oxidation, and into the ketosulfone **18** by addition of lithiated methyl phenyl sulfone followed by oxidation. The allylated analogues **15** and **19** were similarly prepared. In the nucleophilic additions to aldehyde **11**, it was found not to be necessary to allow for complete deprotonation of the *N*-*tert*-butoxycarbonyl group, the use of *ca.* 25% of an excess of the lithiated esters and sulfones was generally found to be sufficient.



Scheme 2 Synthesis of cyclisation precursors. *Reagents and conditions*: i) (t-$BuCO_2$)$_2$O, DMAP, Et_3N (76%); ii) *n*-BuMgBr, THF (91%); iii) $(CH_2OH)_2$, pyH·OTs, benzene (81%); iv) O_3, MeOH, then Ph_3P (90%); v) $MeCO_2Me$, LDA, −78 °C (**12**, 95%) or ethyl pent-4-enoate, LDA, −78 °C (**13**, 92%); vi) PDC (**14**, 73%) or Dess Martin (**15**, 59%; **18**, 72%; **19**, 66%); vii) $PhSO_2Me$, LDA, −78 °C (**16**, 58%) or but-3-enyl phenyl sulfone, LDA, −78 °C (**17**, 80%).

Treatment of the ketoester **14** with trifluoroacetic acid in dichloromethane gave the imine **20**, which was characterised by a peak at υ_{max} 1642 cm^{-1} in its IR spectrum corresponding to the C=N stretch, and by ^{1}H NMR, see Scheme 3.[18,19] The imine was unstable to chromatography, and so the crude imine was treated with methyl chloroformate followed by an excess of triethylamine at −78 °C, which gave a mixture of two products in the ratio 85 : 15. The major product was isolated (71% from **14**) and identified

§ All of the work in this paper was carried out using racemic compounds. However, the use of (*S*)-5-prop-2-enylpyrrolidinone would lead to an asymmetric synthesis of stemofoline.



Scheme 3 Cyclisations of ketoesters.

as the 8-azabicyclo[3.2.1]octane **21**. The minor product could not be isolated free of the major product and was not formally identified, but may have been the C2-epimer of **21**. The structure of the tropanone **21** was consistent with its spectroscopic data, but the configuration at C2 was not unequivocally assigned at this point. The structure shown was assigned by analogy with the stereoselectivities of analogous cyclisations and was subsequently confirmed by later transformations, *vide infra*.

Cyclisation of the sulfone **18** was carried out in a similar manner except using 2,2,2-trichloroethyl chloroformate to form the iminium ion. This gave a 51% yield of a single crystalline product shown to be the azabicyclooctane **22** with a chair conformation for the six-membered ring and the phenylsulfonyl group in the axial position, by X-ray crystallography, see Fig. 1. Of interest was the broadening of the ^{1}H NMR peaks assigned to the diastereotopic methylene protons of the trichloroethyl ester, which indicated hindered rotation about this fragment. On warming to 100 °C, these broad peaks were replaced by two doublets at δ 5.24 and 5.02, each with J 11.5 Hz.

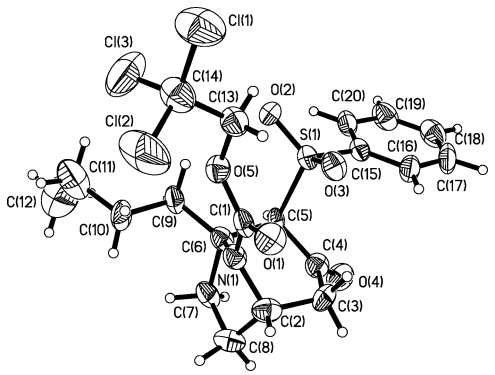


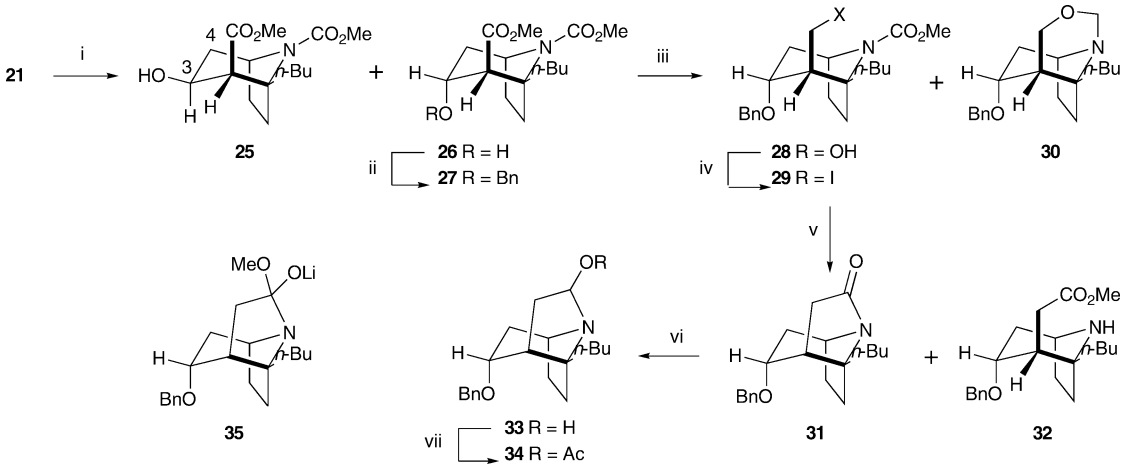
Fig. 1 ORTEP projection of the sulfone **22** as determined by X-ray crystallography, ellipsoids shown at 30% probability.

The ester **15** and sulfone **19** had been prepared with a view to using the allyl groups to introduce the third ring of the stemofoline nucleus, *cf.* the conversion of **6** into **5**. In the event, on cyclisation of these using trichloroethyl chloroformate each gave a single product identified as the corresponding 8-azabicyclooctane **23** (42%) and **24** (40%). Neither of these cyclised products was crystalline. However, the observation of an NOE enhancement of H-4$_{ax}$ on irradiation of the phenyl *ortho* protons for the product from cyclisation of the sulfone **19** indicated that the sulfone was axial, as shown in structure **24**. The ester **23** was identified by analogy.

In these cyclisations, which are likely to be under thermodynamic control, the electron-withdrawing group α to the ketone seems to prefer the axial position in all cases, perhaps to avoid unfavourable dipolar interactions with the ketone at C3. This means that the allyl group at C2 in the bicyclic products **23** and **24** is unfavourably disposed for elaboration to form the third ring of the stemofoline nucleus. Moreover, the hydrogen at C2 in products **21** and **22** is in the plane of the carbonyl group and so is not particularly acidic. For these reasons, it was decided to study the chemistry of the ketoester **21** with a view to modifying the axial 2-methoxycarbonyl group to introduce the third ring of stemofoline.

Synthesis of a tetracyclic ether corresponding to the nucleus of stemofoline

Reduction of the ketone **21** using sodium borohydride gave a 50 : 50 mixture of the epimeric alcohols **25** and **26**. With zinc borohydride, the reaction was 60 : 40 in favour of the axial alcohol **26**, and with zinc cyanoborohydride, the selectivity improved to 75 : 25 in favour of alcohol **26**, see Scheme 4. The configurations of these alcohols were assigned on the basis of the diaxial 3,4-coupling of 13 Hz observed for the equatorial alcohol **25**. As this equatorial alcohol could be re-oxidised back to the ketone **21** using pyridinium dichromate (87%), procedures with improved stereoselectivity were not investigated at this stage for the reduction of ketone **21**. Attempts to protect alcohol **26** using benzyl chloride and sodium hydride led to mixtures of products, perhaps due to a competing reverse aldol reaction, but the benzyl ether **27** was obtained in excellent yield using benzyl trichloroacetimidate under acidic conditions. Reduction of the ester **27** into the primary alcohol **28** using diisobutylaluminium hydride at 0 °C gave the

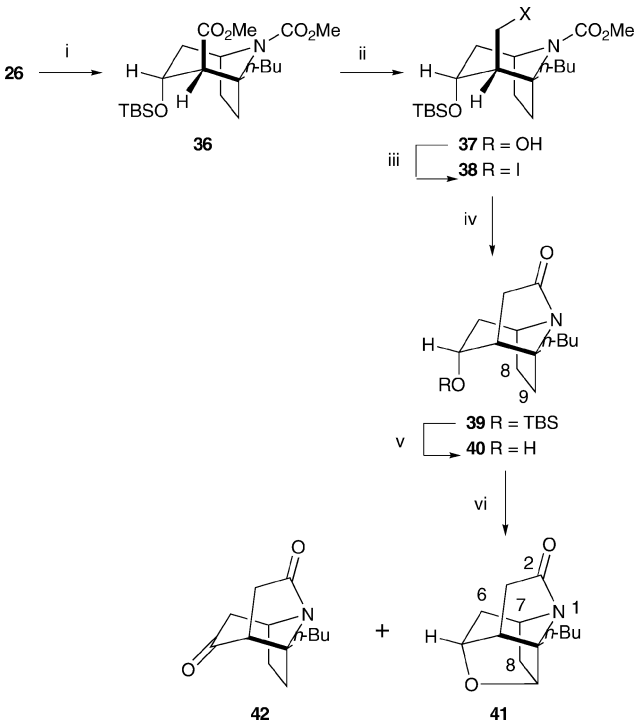


Scheme 4 Synthesis of tricyclic lactam **31**. *Reagents and conditions*: i) $ZnCl_2$, $NaBH_3CN$, Et_2O (**25** : **26** = 25 : 75, 91%); ii) benzyl trichloroacetimidate, TfOH (99%); iii) DIBAL-H, hexane, 0 °C (**28**, 59%; **30**, 18%) or DIBAL-H, hexane, −78 °C to rt (**28**, 75%); iv) I_2, PPh_3, imid. (81%); v) *t*-BuLi, −78 °C to rt (**31**, 71%) or *t*-BuLi, −78 °C (**31**, 20%; **32**, 65%); vi) $LiAlH_4$, ether, 0 °C (99%); vii) Ac_2O, DMAP (cat.), Et_3N (72%).

tricyclic aminoacetal **30** as a side product, but the formation of this aminoacetal, which confirmed the axial stereochemistry assigned to the ester **21**, could be avoided by carrying out the reduction at a lower temperature. Aminoacetal **30** was of interest, however, since its formation must have involved capture of an iminium ion derived from the methyl carbamate by the primary alkoxide formed on reduction of the ester. This observation suggested that the carbonyl carbon of the carbamate could be incorporated into the third ring of stemofoline. To investigate this possibility, the alcohol **28** was converted into the iodide **29**, and cyclisation of the corresponding organolithium species formed by treatment of **29** with *tert*-butyllithium was investigated. It was found that reaction of the iodide **29** with an excess of *tert*-butyllithium with an immediate quench gave a mixture of the aminoester **32** (65%) and the tricyclic lactam **31** (20%). However, if after the addition of the *tert*-butyllithium at −78 °C, the cooling bath was removed and the reaction mixture stirred for 15 min, the aminoester **32** was not formed and the tricyclic lactam **31** was isolated on work-up in a good yield. These results were interpreted in terms of protonation of the carbamate adduct **35** during an immediate quench or loss of lithium methoxide on standing.

The geometry of the lactam **31** was determined by its tricyclic structure, which required the lone-pair on nitrogen to be more or less orthogonal to the Π-orbitals of the carbonyl group.[20] This distortion from the usually planar amide geometry was reflected in the IR spectrum of **31**, which showed a carbonyl stretching absorption at υ_{max} 1747 cm^{-1}, and in its chemistry. For example, reduction using lithium aluminium hydride gave the aminol **33** as a single diastereoisomer, characterised as its acetate **34**, although the configuration of the hydroxyl bearing carbon was not established.

The benzyl-protected hydroxylactam **31** was an oil, but the corresponding *tert*-butyldimethylsilyloxylactam **39** was crystalline. This was prepared from the bicyclic aminoester **26** in a similar fashion by *O*-silylation, reduction of the ester **36**, conversion of the alcohol **37** into the primary iodide **38**, and treatment of the iodide with *tert*-butyllithium, see Scheme 5. Lactam **39** was deprotected to give the crystalline alcohol **40**, the structure of which was confirmed by X-ray crystallography, see Fig. 2.[21] The N–C2 bond length of 1.432 Å in the X-ray crystal structure of **40** confirmed the single-bond character of this bond due to the non-planarity of the lactam. It also revealed a twist in the azabicyclo[3.2.1]octane fragment induced by the additional two-carbon bridge, which positioned the *endo* hydrogens at C8 and C9 2.97 and 2.32 Å, respectively, from the oxygen atom of the hydroxyl group. This



Scheme 5 Synthesis of the pentacyclic lactam **41**. *Reagents and conditions*: i) TBSOTf, 2,6-lutidine (86%); ii) DIBAL-H, hexane, −78 °C to rt (78%); iii) I_2, PPh_3, imid. (83%); iv) *t*-BuLi, −78 °C to rt (81%); v) TBAF, THF, rt (99%); vi) $Pb(OAc)_4$, benzene, reflux (**40**, 12%; **41**, 35%; **42**, 16%).

suggested that the hydroxyl oxygen could be used to discriminate between these two *endo* hydrogens, providing a model for the regioselective remote oxidation proposed for the conversion of ketone **4** into acetal **3**. Indeed, this was found to be the case, in that oxidation of the alcohol **40** using an excess of lead(IV) acetate gave the tetracyclic ether **41** as the major product (35%) together with ketone **42** (16%) and unchanged starting material **40** (12%). The structure of ether **41** was confirmed by 2D COSY ^{1}H NMR studies. In particular, H-7 showed vicinal couplings with the methylene protons at both C6 and at C8 confirming the regioselectivity of the oxidation.

The structure of ether **41** corresponds to the tetracyclic nucleus of stemofoline. Indeed it has been suggested that an oxidation akin to the conversion of alcohol **40** into ether **41** is involved in the biosynthesis of stemofoline *via* protostemonine **43**, another alkaloid isolated from *Stemonacea*.[12] Fig. 3 shows a comparison of the structures of stemofoline **1** and protostemonine **43**. It can be

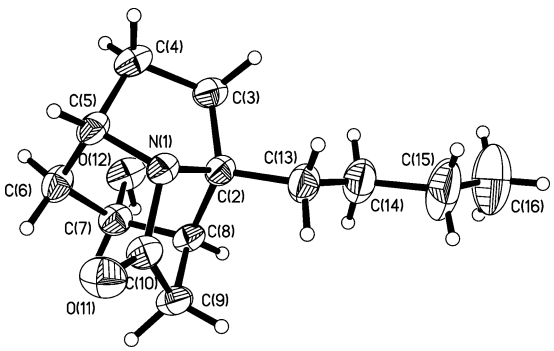


Fig. 2 ORTEP projection of the tricyclic lactam **40** as determined by X-ray crystallography, ellipsoids shown at 30% probability.

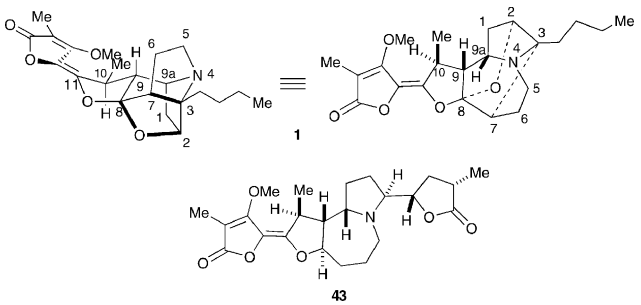
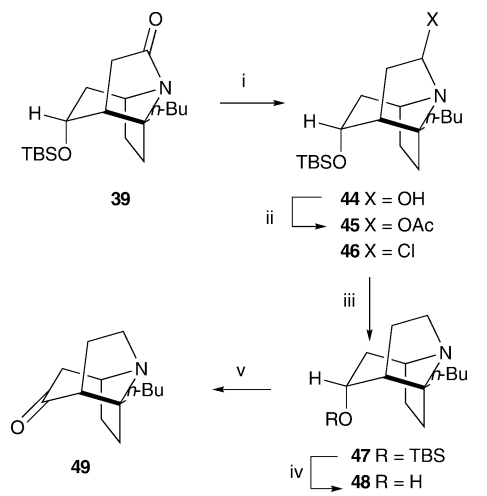


Fig. 3 A comparison of the structures of stemofoline and protostemonine.

seen that the polycyclic core components of these two structures differ only by the extra oxygen in stemofoline between C2 and C8, and the C–C bond between C3 and C7. The regioselective introduction of the C5–C9 oxygen bridge in **41** could therefore be regarded as mimicking the biosynthetic introduction of the oxygen between C3 and C8 into stemofoline **1** albeit using very different chemistry.

At this point, a procedure was developed to convert lactam **39** into the tricyclic ketoamine **49**, see Scheme 6, since this conversion will have to be carried out at some point in the synthesis of stemofoline. As observed for the benzyl-protected lactam **31**, reduction of lactam **39** using lithium aluminium hydride gave the aminol **44** (97%) as a single epimer, characterised as its acetate **45**. After unsuccessful attempts to deoxygenate the aminol **44** using free-radical chemistry,[22] it was converted into the amine **47** by treatment with thionyl chloride followed by reduction of the intermediate so formed, possibly the chloride **46**, with lithium aluminium hydride (92% overall). Desilylation of the silyl ether **47** to the corresponding alcohol **48** was more efficient using boron trifluoride diethyl etherate than with either aqueous acid or TBAF, and the hydroxyamine **48** was oxidised to give the aminoketone **49** using Swern conditions.

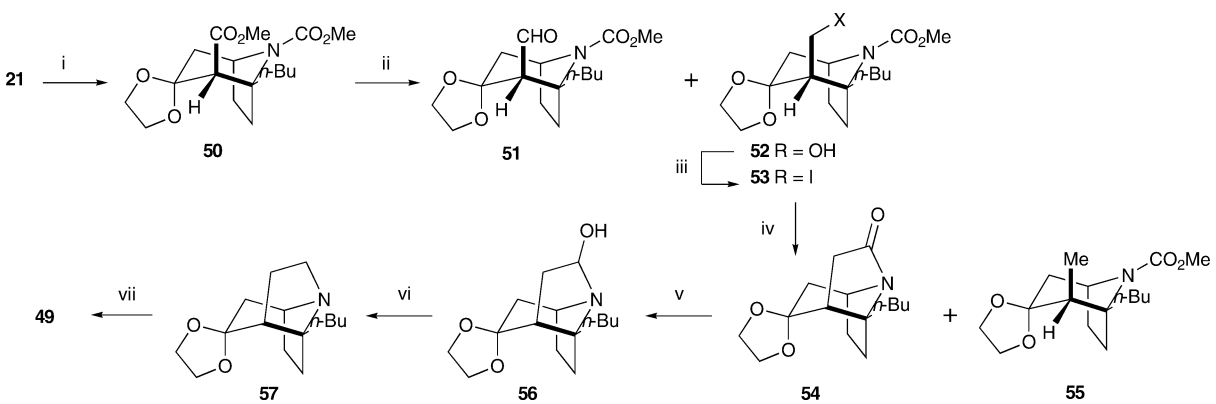


Scheme 6 Synthesis of the tricyclic aminoketone **49**. *Reagents and conditions*: i) $LiAlH_4$, ether (97%); ii) Ac_2O, py, DMAP (93%); iii) $SOCl_2$, then $LiAlH_4$, ether (92%); iv) $BF_3{\cdot}Et_2O$ (85%); v) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2 (85%).

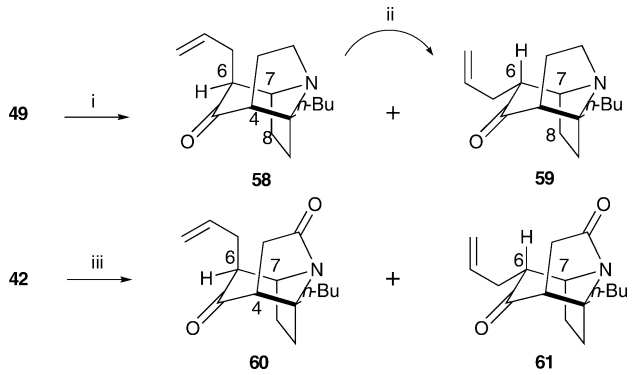
This preparation of the aminoketone **49** had involved reduction of the ketoester **21**, protection of the alcohol as its *tert*-butyldimethylsilyl ether **36** and, following introduction of the third ring, desilylation and reoxidation of alcohol **48** to the ketone. To avoid the unnecessary steps of ketone reduction and alcohol oxidation, an alternative sequence was investigated with protection, rather than reduction, of the ketone **21**, see Scheme 7. Protection of the ketone **21** as its acetal **50** was best achieved using 2-methoxy-1,3-dioxolane and toluene *p*-sulfonic acid (cat.) in methanol–toluene. Reduction of the ester **50** into the primary alcohol **52** required rather forceful conditions and gave the aldehyde **51** as a side product, even with a large excess of diisobutylaluminium hydride. Following conversion to the iodide **53**, cyclisation using *tert*-butyllithium gave the tricyclic lactam **54** accompanied by small amounts of the bicyclic carbamate **55**. The lactam **54** was taken through *via* the aminol **56** to the acetal **57**, which was hydrolysed to the aminoketone **49** using dilute aqueous acid. This second synthesis of the aminoketone **49** is slightly shorter than the first but is, if anything, less efficient with a *ca.* 15% overall yield from the bicyclic ketone **21** as compared to a *ca.* 20% overall yield for the first route.

Alkylation of bi- and tricyclic ketones

It was now necessary to develop procedures for the incorporation of the fragment corresponding to C10 and C11 of stemofoline to complete an assembly of the intact pentacyclic nucleus of stemofoline. Initial studies were based on alkylation of the advanced tricyclic ketoamine **49** and ketolactam **42** since the configuration at C-4 in these compounds is fixed, see Scheme 8. Alkylation of the amine using allyl iodide and potassium hexamethyldisilazide gave a mixture of the axial and equatorial allylated products **58** and **59**, ratio 80 : 20, combined yield 56%. With lithium diisopropylamide, a slightly lower yield, 42%, was obtained but only the axial product **58** was isolated. Treatment of **58** with potassium *tert*-butoxide led to clean epimerisation to the equatorial product **59**. Allylation of the ketolactam **42** took place regioselectively α to the ketone, with a mixture of the axial and equatorial products **60** and **61**, ratio 65 : 35, being obtained in modest yield using lithium diisopropylamide and allyl bromide.



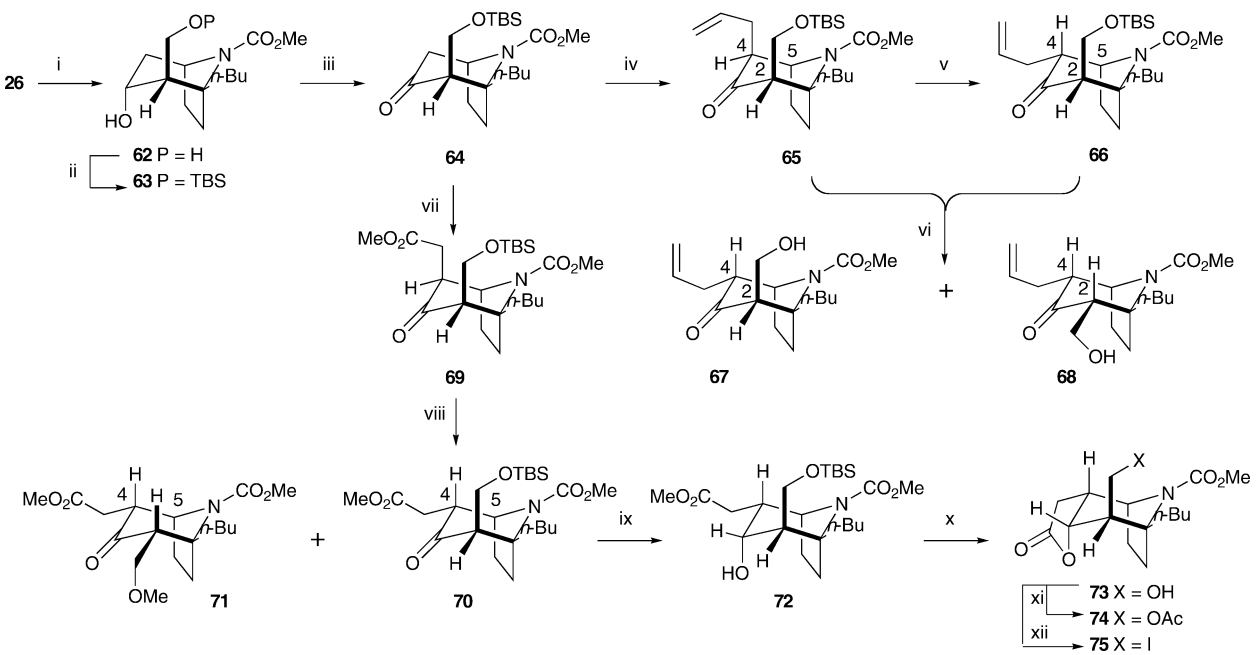
Scheme 7 A second synthesis of aminoketone **49**. *Reagents and conditions*: i) 2-methoxy-1,3-dioxolane, TsOH, MeOH, toluene, 50 °C (87%); ii) DIBAL-H (**51**, 9%; **52**, 55%); iii) I_2, PPh_3, imid. (78%); iv) *t*-BuLi, THF, −78 °C (**54**, 74%; **55**, 4%); v) $LiAlH_4$, Et_2O (83%); vi) $SOCl_2$ then $LiAlH_4$ (75%); vii) 1% aq. H_2SO_4 (90%).



Scheme 8 Allylation of tricyclic intermediates. *Reagents and conditions*: i) KHMDS, allyl iodide, −78 °C (**58** : **59** = 80 : 20, 56%) or LDA, allyl iodide, −78 to rt (**60**, 42%); ii) KO*t*-Bu, CH_2Cl_2, methanol, rt (88%); iii) LDA, allyl bromide, −78 °C to rt (**60** : **61** = 65 : 35, 39%).

The structures of these allylated products were assigned on the basis of spectroscopic data. Vicinal bond angles between the C–H bond at C-7 and the methylene C–H bonds at C-6 and C-8 in the X-ray structure of the tricyclic hydroxylactam **40** were 71° and 49° for the equatorial and axial hydrogens at C-6 and 85° and 28° for the *endo* and *exo*-hydrogens at C-8, respectively. For the major products from the alkylation reactions, H-7 was observed as a doublet with a coupling constant of *ca.* 7 Hz due to the coupling with 8-H_{exo}, no coupling being observed between H-6_{eq} and H-7, and so these products were identified as the axially alkylated products **58** and **60**. For the epimeric products, H-7 was a triplet with *J ca.* 7 Hz, due to coupling with both H-8_{exo} and H-6_{axial} consistent with the structures assigned to **59** and **61**. The equilibration of the axial isomer **58** into its equatorial epimer **59** is also consistent with these structural assignments. However, oxidative cleavage of the terminal double bond of the equatorial allylated ketoamine **59** by ozonolysis or hydroxylation – periodate oxidation was unsuccessful in our hands and alkylation of the aminoketone **49** using methyl bromoacetate was also unsuccessful. As the allylation of the ketolactam **42** was less efficient than allylation of the ketoamine **49**, it was decided not to investigate alkylation of the ketolactam **42** using methyl bromoacetate, but instead to investigate alkylation of more accessible bicyclic ketones earlier in the synthesis.

Reduction of the bicyclic ester **26** using diisobutylaluminium hydride gave the diol **62**, which was converted into the ketone **64** by regioselective monoprotection and oxidation of the mono-*tert*-butyldimethylsilyl ether **63**, see Scheme 9. Allylation of the ketone **64** using lithium hexamethyldisilazide and allyl iodide gave the axially allylated product **65** in a moderate 55% yield, and epimerisation to the equatorial epimer **66** was achieved using potassium *tert*-butoxide in dichloromethane. The configuration of epimers **65** and **66** at C4 was assigned on the basis of $J_{4,5}$ in their ^{1}H NMR spectra with H-5 being observed as a doublet (*J* 7 Hz) for the axially alkylated product **65**, and as a double doublet (*J* 4, 7.5 Hz) for the equatorially alkylated product **66** (*cf.* the ^{1}H NMR data for **58–61**). Their retained configuration at C2 was provisionally assigned on the basis of unchanged ^{1}H NMR chemical shifts and coupling constants for H-2 and 2-CH_2. However, partial epimerisation at C2 was observed during desilylation using tetrabutylammonium fluoride of both **65** and **66**, which gave mixtures of the C2 epimers **67** and **68**. For both **67** and **68**, H-5 was a double doublet consistent with the allyl group



Scheme 9 Alkylation and further modification of bicyclic intermediates. *Reagents and conditions*: i) DIBAL-H, CH_2Cl_2, −78 °C, then $NaBH_4$ (63%); ii) TBSOTf, 2,6-lutidine, CH_2Cl_2 (94%); iii) PDC, CH_2Cl_2 (98%); iv) KHMDS, allyl iodide, −78 °C (63%); v) KO*t*-Bu, CH_2Cl_2, methanol (56%); vi) TBAF, THF (**67** : **68** = 60 : 40, 56% from **65**; **67** : **68** = 50 : 50, 36%, from **66**); vii) KHMDS, $BrCH_2CO_2Me$, −78 °C to rt (58%); viii) KO*t*-Bu, CH_2Cl_2, methanol (**70**, 66%; **71**, 9%); ix) $ZnCl_2$, $NaCNBH_3$, (74%); x) TBAF, THF (84%); xi) Ac_2O, DMAP, Et_3N (69%); xii) I_2, PPh_3, imid. (80%).

being in the equatorial position at C4, *i.e.* **67** and **68** had to be epimers at C2.

In the case of the bicyclic ketone **64**, alkylation using methyl bromoacetate and potassium hexamethyldisilylazide was successful, albeit only in a moderate 58% yield, and gave the diaxial product **69**. Epimerisation using potassium *tert*-butoxide in dichloromethane–methanol gave the C4 epimer **70** (66%) together with the doubly epimerised methyl ether **71** (9%). The configuration of this methyl ether was established by ^{1}H NMR with an enhancement of H-4 on irradiation of H-2 and *vice versa*. It may have been formed by elimination of *tert*-butyldimethylsilanol from the β-silyloxyketone **69** followed by conjugate addition of methanol with axial protonation at C2. For the silyl ether **70**, an NOE enhancement of H-4 was observed on irradiation of one of the 2-CH protons and *vice versa*. For the compounds **69–71**, the configurations at C4 were also consistent with the coupling between H-4 and H-5 observed for the equatorially alkylated epimers **70** and **71** but not for the axially alkylated product **69**. Reduction of the silyloxyketone **70** using zinc borohydride gave the alcohol **72**. As observed for the reduction of ketone **21**, the reduction of ketone **70** was stereoselective in favour of the axial alcohol, as shown by the ^{1}H NMR spectrum of **72** in which $J_{2,3} = J_{3,4} = 4$, *i.e.* H-3 must be equatorial. Desilylation of **72** using either amberlite resin or tetrabutylammonium fluoride in tetrahydrofuran was accompanied by cyclisation and gave the hydroxylactone **73**, the structure of which was confirmed by conversion to its acetate **74**. In particular the axial configuration at C2 was confirmed by NOE. Finally, the iodide **75** was prepared from the hydroxylactone **73**, but attempts to cyclise this *via* halogen–metal exchange using *tert*-butyllithium were unsuccessful, complex mixtures of products being obtained.

Summary and conclusions

This work has provided a useful basis for a synthesis of stemofoline **1**. Several 2-substituted-1-butyl-8-azabicyclo[3.2.1]octanes, including the ester **21**, in which the 2-substituents are in the axial position ready for incorporation into the second pyrrolidine ring of stemofoline, have been prepared stereoselectively. The tricyclic lactams **31** and **39**, in which the amides are significantly distorted from planar geometry, have been prepared by cyclisation of the iodides **29** and **38** using *tert*-butyllithium, and lactam **39** was taken through to the tetracyclic ether **41** by regioselective remote oxidation of the alcohol **40**, and to the tricyclic ketoamine **49** by reduction of the lactam. However, although allylation of the tricyclic amide **42** and amine **49** *en route* to appending the final ring of stemofoline was successful, further elaboration of the products **59** and **61** proved difficult. Although the bicyclic ester **21** could be converted into the tricyclic lactone **73**, this sequence was rather inefficient, and preliminary studies on the conversion of the tricyclic iodide **75** into a tetracyclic lactam were unsuccessful. At this point, rather than incorporate the C(10)–C(11) fragment of stemofoline by alkylation of cyclic intermediates, it was decided to study the synthesis and cyclisation of more complex precursors analogous to the ketoester **14**, which already contain this additional fragment, and which could lead to an asymmetric synthesis of stemofoline. This work is on-going.

Experimental

Melting points were recorded on a Koffler heated stage microscope. Proton NMR spectra were recorded in deuterated chloroform, unless otherwise indicated, on Bruker AC300, Varian XL300 and Varian Unity 500 spectrometers; coupling constants are given in Hz and chemical shifts relative to Me_4Si. IR spectra were recorded on a Perkin Elmer 1710FT spectrometer and were run as evaporated films. Mass spectra were measured on a Kratos MS20 and MS25 spectrometers.

Chromatography refers to flash chromatography using Merck silica gel 60 H (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.

2-Butyl-5-(3-methoxycarbonyl-2-oxopropyl)pyrroline 20

Trifluoroacetic acid (36.0 cm^3, 462 mmol) was added dropwise to the ketoester **14** (12.4 g, 30.8 mmol) in dichloromethane (250 cm^3) at 0 °C, and the mixture allowed to warm to ambient temperature, stirred for 5 h, then concentrated under reduced pressure. The residue in ethyl acetate was washed with saturated aqueous sodium hydrogen carbonate, water and brine, then dried ($MgSO_4$). Concentration under reduced pressure afforded the title compound **20** as a bright yellow oil (7.36 g, *ca.*100%) used without further purification. A small quantity was chromatographed using dichloromethane–methanol–triethylamine (89 : 10 : 1) for characterisation. Found: M$^+$, 239.1521. $C_{13}H_{21}NO_3$ requires *M*, 239.1521; υ_{max} 1747, 1714, 1642, 1551, 1367, 1245, 1199 and 1169 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.93 (3 H, t, *J* 9.5 Hz, CH_3), 1.28–1.48 (3 H, m, 3′-H_2 and 4-H), 1.50–1.62 (2 H, m, 2′-H_2), 2.15 (1 H, m, 4-H′), 2.30 (2 H, m, 1′-H_2), 2.44–2.58 (2 H, m, 3-H_2), 2.61 and 2.87 (each 1 H, dd, *J* 17 Hz, 9.5 Hz, 1′-H), 3.56 (2 H, s, 3′-H_2), 3.73 (3 H, s, OCH_3) and 4.28 (1 H, m, 5-H); δ_C (50 MHz, $CDCl_3$) 15.87, 24.62, 30.32, 30.54, 30.68, 35.22, 39.32, 50.72, 51.46, 54.42, 68.96, 169.51 and 184.14; *m*/*z* CI(NH_3) 241 (15%), 240 (M$^+$ + 1, 100).

(1*RS*,2*RS*,5*SR*)-1-Butyl-2,8-dimethoxycarbonyl-8-azabicyclo[3.2.1]octan-3-one 21

Methyl chloroformate (3.58 cm^3, 46.2 mmol) was added dropwise to the imine **20** (7.36 g, 30.8 mmol) in dichloromethane (250 cm^3) at −78 °C and the mixture stirred for 15 min. Triethylamine (26.0 cm^3, 185 mmol) was added dropwise, maintaining the reaction mixture below −70 °C, then the mixture was stirred at −78 °C for 9 h and allowed to warm to ambient temperature over 3 h. Saturated aqueous ammonium chloride was added, and the organic phase washed with water and brine, then dried ($MgSO_4$). After concentration under reduced pressure, chromatography using light petroleum–ethyl acetate (80 : 20) as eluent gave the title compound **21** as a colourless oil (6.51 g, 71% from **14**). Found: M$^+$, 297.1574. $C_{15}H_{23}NO_5$ requires *M*, 297.1576; υ_{max} 1740, 1713, 1369, 1279, 1235, 1195, 1157, 1126 and 1098 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.97 (3 H, t, *J* 7.5, CH_3), 1.20–1.75 (6 H, m, 2 × CH_2, 6-H and

7-H), 1.88–2.24 (4 H, m, CH_2, 6-H′ and 7-H′), 2.35 (1 H, d, *J* 17.5 Hz, 4-H_{eq}), 3.24 (1 H, dd, *J* 17.5 Hz, 4 Hz, 4-H_{ax}), 3.33 (1 H, s, 2-H), 3.69 and 3.71 (each 3 H, s, OCH_3) and 4.66 (1 H, m, 5-H); *m*/*z* CI(NH_3) 298 (M^+ + 1, 100%).

(1*RS*,2*RS*,5*SR*)-l-Butyl-2-phenylsulfonyl-8-(2,2,2-trichloroethoxycarbonyl)-8-azabicyclo[3.2.1]-octan-3-one 22

Following the procedure outlined for the synthesis of pyrroline **20**, trifluoroacetic acid (0.536 cm^3, 7.35 mmol) and ketosulfone **18** (237 mg, 0.49 mmol) in dichloromethane (5.0 cm^3) gave the corresponding pyrroline as a yellow oil (156 mg, 99%) used without further purification. Found: M^+, 321.1398. $C_{17}H_{23}NO_3S$ requires *M*, 321.1399; υ_{max} 1719, 1641, 1448, 1323 and 1154 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.92 (3 H, t, *J* 9.5 Hz, CH_3) 1.23–1.42 (2 H, m, 3′-H_2), 1.40 (1 H, m, 4-H), 1.47–1.60 (2 H, m, 2′-H_2), 2.14 (1 H, m, 4-H′), 2.25–2.36 (2 H, br t, *J* 7.5 Hz, 1′-H_2), 2.37–2.62 (2 H, m, 3-H_2), 2.83 (1 H, dd, *J* 17 Hz, 7.5 Hz, 1″-H), 3.03 (1 H, dd, *J* 17 Hz, 6.5 Hz, 1″-H′), 4.29 (1 H, m, 5-H), 4.25 and 4.32 (each 1 H, d, *J* 15 Hz, 3″-H), 7.58 (2 H, m, ArH), 7.67 (1 H, ArH) and 7.90 (2 H, m, ArH); *m*/*z* CI(NH_3) 322 (M^+ + 1, 12%) and 182 (100).

Following the procedure outlined for the synthesis of azabicyclooctane **21**, 2,2,2-trichloroethyl chloroformate (0.1 cm^3, 0.98 mmol) and the pyrroline (156 mg, 0.49 mmol) in dichloromethane (10.0 cm^3), after chromatography using light petroleum–ethyl acetate (85 : 15) as eluent, gave the title compound **22** as a white solid (124 mg, 51% from **18**), recrystallised from ethyl acetate–hexane to give colourless crystals, m.p. 144–145 °C. Found: C, 48.4; H, 4.8; Cl, 21.2; N, 2.9; S, 6.6%. $C_{20}H_{24}Cl_3NO_5S$ requires C, 48.35; H, 4.85; Cl, 21.45; N, 2.8; S, 6.45%; υ_{max} 1714, 1402, 1326, 1205 and 1145 cm^{-1}; δ_H (300 MHz, C_6D_6) 0.80–1.84 (11 H, m, $CH_2CH_2CH_2CH_3$, 6-H_{exo} and 7-H_{exo}), 2.13 (1 H, d, *J* 17 Hz, 4-H_{eq}), 2.44 (1 H, m, 6-H_{endo}), 3.28 (1 H, td, *J* 15 Hz, 5.5 Hz, 7-H_{endo}), 3.58 (1 H, dd, *J* 17 Hz, 5 Hz, 4-H_{ax}), 3.87 (1 H, s, 2-H), 4.79 (1 H, m, 5-H), 4.90 and 5.67 (each 1 H, br s, OHC*H*CCl_3), 6.92–7.08 (3 H, m, ArH) and 7.67–7.86 (2 H, m, ArH); *m*/*z* CI(NH_3) 500 (27%), 498 (74) and 496 (M^+, 100).

(1*RS*,2*RS*,5*SR*)-1-Butyl-2-ethoxycarbonyl-2-prop-2-enyl-8-(2,2,2-trichloroethoxycarbonyl)-8-azabicyclo[3.2.1]octan-3-one 23

Following the procedure outlined for the synthesis of the pyrroline **20**, trifluoroacetic acid (1.6 cm^3, 22.4 mmol) and the ketoester **15** (1.02 g, 2.24 mmol) in dichloromethane (20.0 cm^3) gave the corresponding pyrroline (644 mg, 99%) used without further purification. Found: M^+, 293.1986. $C_{17}H_{27}NO_3$ requires *M*, 293.1991; υ_{max} 1740, 1715, 1640, 1370, 1182 and 1030; δ_H (300 MHz, $CDCl_3$) 0.85 (3 H, t, *J* 7.5 Hz, CH_3), 1.18 (3 H, t, *J* 8 Hz, CH_3), 1.21–1.37 (3 H, m, 4-H and CH_2), 1.40–1.58 (2 H, m, CH_2), 2.10 (1 H, m, 4-H′), 2.20–2.32 (2 H, m, CH_2), 2.32–2.58 (5 H, m, 1″-H, 3-H_2, 4″-H_2), 2.97 and 3.06 (each 0.5 H, dd, *J* 17 Hz, 7.5 Hz, 1″-H), 3.52 and 3.55 (each 0.5 H, t, *J* 7.5 Hz, 3″-H), 4.11 (2 H, q, *J* 8 Hz, OCH_2), 4.28 (1 H, m, 5-H), 4.93–5.09 (2 H, m, 6″-H_2) and 5.68 (1 H, m, 5″-H); δ_C (75 MHz, $CDCl_3$) 13.68, 13.96, 22.41, 28.42, 28.75, 31.87, 33.36, 37.09, 48.53, 48.82, 58.59, 61.24, 67.76, 117.26, 134.14, 169.31, 178.67 and 203.11; *m*/*z* (FAB) 402 (50%), 294 (M^+ + 1, 34) and 124 (100).

Following the procedure outlined for the preparation of the azabicyclooctane **21**, 2,2,2-trichloroethyl chloroformate (0.5 cm^3, 8.8 mmol) and the imine (644 mg) with triethylamine (1.85 cm^3, 13.2 mmol) in dichloromethane (15 cm^3), after chromatography using light petroleum–ethyl acetate (98 : 2) as eluent, gave the title compound **23** (436 mg, 42% from the ketoester **15**), as a colourless oil. Found: M^+ + H, 467.1015. $C_{20}H_{28}{}^{35}Cl_3NO_5$ requires *M*, 467.1033; υ_{max} 1717, 1639, 1397 and 1114 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.96 (3 H, t, *J* 7.5 Hz, CH_3), 1.13–2.08 (9 H, m, 3 × CH_2, 6-H_2 and 7-H), 1.28 (3 H, t, *J* 8 Hz, OCH_2CH_3), 2.37 (1 H, d, *J* 17 Hz, 4-H_{eq}), 2.49 (1 H, dd, *J* 13.5 Hz, 5.5 Hz, l′-H), 2.60 (1 H, dd, *J* 13.5 Hz, 9.5 Hz, l′-H′), 2.99 (1 H, m, 7-H′), 3.50 (1 H, dd, *J* 17 Hz, 5.5 Hz, 4-H_{ax}), 3.97–4.19 (2 H, m, OCH_2), 4.58 (1 H, d, *J* 13 Hz, HC*H*CCl_3), 4.73 (1 H, m, 5-H), 4.79 (1 H, d, *J* 13 Hz, HC*H*CCl_3), 4.99–5.17 (2 H, m, 3′-H_2) and 5.87–6.03 (1 H, m, 2′-H); δ_H (75 MHz, $CDCl_3$) 13.84, 14.16, 23.13, 25.73, 28.36, 30.56, 30.84, 34.61, 48.37, 56.69, 61.58, 69.82, 71.13, 74.66, 95.50, 118.19, 134.48, 151.10 and 169.51; *m*/*z* (+FAB) 472 (2%), 470 (6) and 468 (M^+ + 1, 8).

(1*RS*,2*RS*,5*SR*)-l-Butyl-8-(2,2,2-trichloroethoxycarbonyl)-2-phenylsulfonyl-2-prop-2′-enyl-8-azabicyclo[3.2.l]octan-3-one 24

Trifluoroacetic acid (0.428 cm^3, 5.60 mmol) was added to a mixture of the ketosulfones **19** (195 mg, 0.37 mmol) in dichloromethane (5.0 cm^3) at 0 °C. The mixture was stirred at ambient temperature for 3 h then concentrated under reduced pressure. A solution of the residue in ethyl acetate was washed with saturated aqueous sodium hydrogen carbonate, water and brine, then dried ($MgSO_4$). Concentration under reduced pressure afforded a mixture of diastereoisomers of the corresponding pyrroline (132 mg, 98%), a mobile yellow oil used without further purification. Found: M^+ + H, 362.1788, $C_{20}H_{28}NO_3S$ requires *M*, 362.1790; υ_{max} 1719, 1641, 1586, 1448, 1323, 1153 and 1086 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.90 (3 H, t, *J* 8 Hz, CH_3), 1.1–2.75 (12 H, m), 2.83 (0.5 H, dd, *J* 18.5 Hz, 9.5, 1′-H), 2.93 (0.5 H, dd, *J* 18.5 Hz, 11.5 Hz, 1′-H), 3.21 (0.5 H, dd, *J* 18.5 Hz, 7.5 Hz, 1′-H), 3.30 (0.5 H, dd, *J* 18.5 Hz, 5.5 Hz, 1′-H), 4.21–4.44 (2 H, m, 5-H and 3′-H), 4.96–5.02 (2 H, m, 6′-H), 5.50–5.18 (1 H, m, 5′-H), 7.49–7.65 (2 H, m, ArH), 7.65–7.76 (1 H, m, ArH) and 7.76–7.90 (2 H, m, ArH); *m*/*z* CI(NH_3) 362 (M^+ + 1, 100%) and 222 (95).

2,2,2-Trichloroethyl chloroformate (0.103 cm^3, 0.75 mmol) was added to the pyrroline (132 mg, 0.37 mmol) in dichloromethane (5.0 cm^3) at −78 °C. The mixture was stirred for 20 min then triethylamine (0.314 cm^3, 2.22 mmol) was added. After stirring for 9 h, the mixture was allowed over 3 h to warm to ambient temperature. Saturated aqueous ammonium chloride was added and the mixture was stirred for 30 min. The organic phase was washed with water and brine then dried ($MgSO_4$). Concentration under reduced pressure and flash chromatography of the residue, using light petroleum–ethyl acetate (90 : 10) as eluent, gave the title compound **24** (80 mg, 40%) as a colourless oil. Found: M^+ + H, 536.0860. $C_{23}H_{29}{}^{35}Cl_3NO_5S$ requires *M*, 536.0832; υ_{max} 1737, 1611, 1387, 1307, 1286, 1152 and 1127 cm^{-1}; δ_H (200 MHz, C_6D_6) 0.95 (3 H, m, CH_3), 1.16–1.87 (8 H, m), 2.28–2.47 (2 H, m), 2.92 (1 H, br dd, *J* 17.5 Hz, 5, 4-H_{eq}), 3.26 (1 H, ddd, *J* 15 Hz, 6.5 Hz, 2, l′-H), 3.40 (1 H, ddd, *J* 15 Hz, 7.5 Hz, 2.0 Hz, l′-H′), 3.73 (1 H, dd, *J* 17.5 Hz, 2.5 Hz, 4-H_{ax}), 4.30 (1 H, m, 5-H), 4.30 and 4.59

(each 1 H, d, *J* 12.5 Hz, HC*H*CCl_3), 5.00 (1 H, dq, *J* 10 Hz, 2 Hz, 3′-H), 5.16 (1 H, dq, *J* 17 Hz, 2 Hz, 3′-H′), 5.98 (1 H, dddd, *J* 17 Hz, 10 Hz, 7.5 Hz, 6.5 Hz, 2′-H), 6.93–7.04 (3 H, m, ArH) and 7.82–7.94 (2 H, m, ArH); *m*/*z* (+FAB) 536 (M^+ + 1, 24%), 394 (10) and 298 (15).

Dimethyl (1*RS*,2*RS*,3*SR*,5*SR*)- and (1*RS*,2*RS*,3*RS*,5*SR*)-1-butyl-3-hydroxy-8-azabicyclo[3.2.1]-octane-2,8-dicarboxylates 25 and 26

Zinc chloride (940 mg, 6.87 mmol) and sodium cyanoborohydride (840 mg, 13.38 mmol) were added to the β-ketoester **21** (810 mg, 2.73 mmol) in ether (50 cm^3) at ambient temperature. After 15 h, aqueous potassium iodate (80 cm^3, 0.1 M) was added, and the mixture extracted with ethyl acetate. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (13 : 7) as eluent gave first the title compound **26** (555 mg, 68%), as a colourless oil. Found: M^+, 299.1742. $C_{15}H_{25}NO_5$ requires *M*, 299.1733; υ_{max} 3450, 1733, 1712, 1687, 1451, 1383 and 1193 cm^{-1}; δ_H (500 MHz, CD_2Cl_2) 0.96 (3 H, t, *J* 7 Hz, 4′-H_3), 1.20–1.40 (4 H, m, 2′-H_2 and 3′-H_2), 1.45 (1 H, m, 1′-H), 1.59 (1 H, br d, *J* 14.5 Hz, 4-H_{eq}), 1.72–2.05 (4 H, m, 1′-H′, 6-H_2 and 7-H), 2.20 (1 H, br s, OH), 2.35–2.46 (2 H, m, 4-H_{ax} and 7-H), 2.72 (1 H, s, 2-H), 3.57 and 3.61 (each 3 H, s, OCH_3), 4.15 (1 H, d, *J* 6 Hz, 3-H) and 4.64 (1 H, m, 5-H); *m*/*z* CI(NH_3) 300 (M^+ + 1, 100%). The second eluted product was the title compound **25** (188 mg, 23%). Found: M^+, 299.1734, $C_{15}H_{25}NO_5$ requires *M*, 299.1733; υ_{max} 3437, 1740, 1713, 1695, 1448, 1381 and 1169 cm^{-1}; δ_H (500 MHz, CD_2Cl_2) 0.92 (3 H, t, *J* 7 Hz, 4′-H_3), 1.17–1.53 (6 H, m), 1.67–1.98 (5 H, m), 2.08 (1 H, s, OH), 2.21 (1 H, m, 4-H_{ax}), 2.95 (1 H, d, *J* 6.5 Hz, 2-H), 3.57 and 3.64 (each 3 H, s, OCH_3), 4.06 (1 H, dt, *J* 13 Hz, 6.5 Hz, 3-H) and 4.39 (1 H, m, 5-H); *m*/*z* (EI) 300 (M^+ + 1, 28%), 299 (M^+, 56), 282 (13), 268 (15), 257 (34), 240 (76), 197 (23) and 183 (100).

The equatorial hydroxyketone **25** (2.45 g, 8.36 mmol) was stirred with pyridinium dichromate (4.36 g, 12.5 mmol) and powdered 4 Å molecular sieves (2.5 g) in dichloromethane (40 cm^3) at ambient temperature for 12 h to give the ketone **21** (1.96 g, 87%) after chromatography.

Dimethyl (1*RS*,2*RS*,3*RS*,5*SR*)-3-benzyloxy-l-butyl-8-azabicyclo[3.2.1]octane-2,8-dicarboxylate 27

Benzyl-2,2,2-trichloroacetimidate (0.09 cm^3, 0.13 mmol) was added to the alcohol **26** (121 mg, 0.11 mmol) in cyclohexane and dichloromethane (3.0 cm^3, 65:35) at ambient temperature. Trifluoromethane sulfonic acid (0.006 cm^3, 0.02 mmol) was added and the mixture stirred for 12 h. The precipitate was removed by filtration and the filtrate washed with saturated aqueous sodium hydrogen carbonate, water and brine then dried (Na_2SO_4). Concentration under reduced pressure and chromatography of the residue using light petroleum–ethyl acetate (80 : 20) as eluent afforded the title compound **27** (160 mg, 99%), as a colourless oil. Found: M^+ + H, 390.2269. $C_{22}H_{32}NO_5$ requires *M*, 390.2280; υ_{max} 1733, 1709, 1444, 1377 and 1099 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.94 (3 H, t, *J* 7.5 Hz, 4′-H_3), 1.16–1.58 (5 H, m), 1.74–2.03 (5 H, m), 2.30–2.50 (2 H, m), 2.91 (1 H, s, 2-H), 3.62 and 3.68 (each 3 H, s, OCH_3), 3.83 (1 H, d, *J* 6.5 Hz, 3-H), 4.40 (1 H, m, 5-H), 4.47 and 4.55 (each 1 H, d, *J* 11.5 Hz, HC*H*Ph) and 7.22–7.42 (5 H, m, ArH); *m*/*z* CI(NH_3) 390 (M^+ + 1, 100%), 300 (46) and 298 (37).

(1*RS*,2*SR*,3*RS*,5*SR*)-3-Benzyloxy-1-butyl-2-hydroxymethyl-8-methoxycarbonyl-8-azabicyclo-[3.2.1]octane 28

Diisobutylaluminium hydride (0.55 cm^3, 1 M in hexane, 0.55 mmol) was added to the ester **27** (69 mg, 0.18 mmol) in hexane (3.0 cm^3) at −78 °C. After 1 h, the mixture was allowed to warm to ambient temperature, and celite (250 mg) and water (0.25 cm^3) were added. The slurry was diluted with ether (3.0 cm^3), and after 30 min, magnesium sulfate was added in small portions until the mixture became granular. After a further 30 min, the mixture was filtered and the filtrate washed with ethyl acetate and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (70 : 30) as eluent gave the title compound **28** (48 mg, 75%) as a colourless oil. Found: M^+, 361.2265. $C_{21}H_{31}NO_4$ requires *M*, 361.2253; υ_{max} 3442, 1705, 1684, 1453, 1382, 1098, 1066, 755 and 698 cm^{-1}; δ_H (300 MHz, C_6D_6) 0.98 (3 H, t, *J* 8 Hz, 4′-H_3), 1.25–1.50 (5 H, m), 1.63–1.87 (3 H, m), 1.95–2.22 (4 H, m), 2.37–2.60 (2 H, m, 7-H and 2-H), 3.48 (3 H, s, OCH_3), 3.65–3.86 (2 H, m, 2-CH_2), 3.86 (1 H, d, *J* 6 Hz, 3-H), 4.31 (2 H, s, CH_2Ph), 4.43 (1 H, m, 5-H) and 7.12–7.38 (5 H, m, ArH); *m*/*z* CI(NH_3) 362 (M^+ + 1, 35%), 331 (27) and 330 (100).

Reduction of the benzyloxyester **27** using diisobutylaluminium hydride in hexane at 0 °C following the above procedure gave the alcohol **28** (59%) and (5*SR*,6*RS*,8*SR*,11*RS*)-6-benzyloxy-11-butyl-l-aza-3-oxatricyclo[6.3.0.$0^{5,11}$]undecane **30** (18%). Found: M^+, 315.2195. $C_{20}H_{29}NO_2$ requires *M*, 315.2198; υ_{max} 3029, 1384, 1210, 1145, 1092, 1070, 1043, 840, 734 and 697 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.94 (3 H, t, *J* 7.5 Hz, 4′-H_3), 1.16–1.50 (5 H, m), 1.57 (1 H, dt, *J* 4 Hz, 12.5 Hz, 9-H), 1.69–2.05 (4 H, m, 7-H_{eq}, 9-H, 10-H and 5-H), 2.21 (1 H, m, 1′-H), 2.46–2.66 (2 H, m, 10-H and 7-H_{ax}), 3.53–3.70 (2 H, m, 8-H and 4-H), 3.92 (1 H, d, *J* 6.3 Hz, 6-H), 4.19 (1 H, dd, *J* 11.5 Hz, 2.5 Hz, 4-H), 4.50 and 4.59 (each 1 H, d, *J* 12.5 Hz, HC*H*Ph), 4.63 and 4.89 (each 1 H, d, *J* 11.5 Hz, 2-H) and 7.21–7.43 (5 H, m, ArH); *m*/*z* Cl(NH_3) 316 (M^+ + 1, 100%) and 208 (37).

(1*RS*,2*RS*,3*RS*,5*SR*)-3-Benzyloxy-1-butyl-2-iodomethyl-8-methoxycarbonyl-8-azabicyclo[3.2.1]-octane 29

The alcohol **28** (49 mg, 0.14 mmol), iodine (26 mg, 0.21 mmol), imidazole (14 mg, 0.21 mmol) and triphenylphosphine (54 mg, 0.21 mmol) were stirred in dichloromethane (3.0 cm^3) at ambient temperature for 3 h. Saturated aqueous sodium thiosulfate was added until the yellow colour disappeared then saturated aqueous sodium hydrogen carbonate was added until the solids had dissolved. The organic phase was washed with water and brine, then dried ($MgSO_4$) and concentrated under reduced pressure. The residue was triturated with light petroleum–ethyl acetate (90 : 10) and the mixture filtered. Concentration of the filtrate under reduced pressure and chromatography of the residue using light petroleum–ethyl acetate (94 : 6) as eluent gave the title compound **29** (52 mg, 81%) as a colourless oil. Found: M^+ − I, 344.2230. $C_{21}H_{30}NO_3$ requires *M*, 344.2226; υ_{max} 1703, 1443, 1377 and 1098 cm^{-1}; δ_H (200 MHz, C_6D_6) 0.92 (3 H, t, *J* 7.5 Hz, 4′-H_3), 1.19–1.44 (4 H, m, 2′-H_2 and 3′-H_2), 1.50–2.10 (6 H, m,

2-H, 4-H_{eq}, 6-H, 7-H and 1′-H_2), 2.32–2.50 (3 H, m, 6-H, 7-H and 4-H_{ax}), 2.88 (1 H, t, *J* 11.5 Hz, 2-CH), 3.44 (3 H, s, OCH_3), 3.91 (1 H, d, *J* 6.5 Hz, 3-H), 4.06 (1 H, dd, *J* 11.5 Hz, 2.5 Hz, 2-CH′), 4.10 (1 H, m, 5-H), 4.40 and 4.51 (each 1 H, d, *J* 12.5 Hz, HC*H*Ph) and 7.13–7.40 (5 H, m, ArH); *m*/*z* (EI) 344 ($M^+ - 127$, 13%) and 182 (22).

(4*RS*,5*RS*,7*SR*,l0*RS*)-5-Benzyloxy-10-butyl-1-azatricyclo[5.3.0.0^{4,10}]decan-2-one 31

tert-Butyllithium (0.195 cm^3,1.6 M in hexanes, 0.31 mmol) was added to the iodide **29** (52 mg, 0.11 mmol) in tetrahydrofuran (1.5 cm^3) at −78 °C. The cooling bath was removed and the reaction mixture stirred for 5 min before the addition of water (3 drops). The organic phase was diluted with ethyl acetate, washed with saturated aqueous ammonium chloride and brine, then dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue using light petroleum–ethyl acetate (80 : 20) as eluent gave the title compound **31** (25 mg, 71%) as a colourless oil. Found: M^+, 313.2034. $C_{20}H_{27}NO_2$ requires *M*, 313.2042; υ_{rnax} 1747, 1255, 1133, 1092, 1066, 736 and 697 cm^{-1}; δ_H (500 MHz, C_6D_6) 0.94 (3 H, t, *J* 8 Hz, 4′-H_3), 1.18–1.30 (4 H, m, 2′-H_2 and 3′-H_2), 1.31 (1 H, d, *J* 16 Hz, 6-H), 1.36 and 1.47 (each 1 H, m, 1′-H), 1.65 (1 H, dt, *J* 3 Hz, 12.5 Hz, 9-H_{exo}), 1.75 (1 H, d, *J* 18 Hz, 3-H), 1.79 (1 H, ddd, *J* 2.5 Hz, 9.5 Hz, 3 Hz, 8-H_{exo}), 2.10 (2 H, m, 6-H_{ax} and 8-H_{endo}), 2.40 (1 H, dd, *J* 3 Hz, 2.5 Hz, 4-H), 2.66 (1 H, dd, *J* 18 Hz, 6.5 Hz, 3-H′), 3.03 (1 H, ddd, *J* 12.5 Hz, 9.5 Hz, 6.5 Hz, 9-H_{endo}), 3.20 (1 H, dd, *J* 5.5 Hz, 2.5 Hz, 5-H), 4.10 (1 H, m, 7-H), 4.23 (2 H, s, CH_2Ph) and 7.17–7.35 (5 H, m, ArH); δ_C (50 MHz, C_6D_6) 14.13, 23.41, 26.90, 30.23, 30.88, 31.42, 39.15, 41.56, 45.36, 65.76, 70.18, 71.02, 79.34 and 194.16; *m*/*z* CI(NH_3) 314 (M^+ + 1, 100%) and 206 (10).

Addition of water immediately after the *tert*-butyllithium gave rise to reduced yields of lactam **31** (*ca.* 20%). Filtration of the residue after extraction into ethyl acetate through silica gel eluting with methanol gave (1*RS*,2*RS*,3*RS*,5*SR*)-3-benzyloxy-1-butyl-2-methoxycarbonylmethyl-8-azabicyclo-[3.2.1]octane **32** (65%); υ_{max} 1736, 1563, 1455, 1435, 1403, 1198, 1175, 1095, 1065, 736 and 699 cm^{-1}; δ_H (200 MHz, C_6D_6) 0.87 (3 H, t, *J* 7.5, 4′-H_3), 1.04–1.76 (11 H, m), 1.89–2.28 (3 H, m), 2.52 (l H, m, 7-H), 3.35 (3 H, s, OCH_3), 3.45 (1 H, d, *J* 5 Hz, 3-H), 3.68 (1 H, m, 5-H), 4.40 and 4.57 (each 1 H, d, *J* 13 Hz, HC*H*Ph), 5.05 (1 H, br s, NH) and 7.08–7.39 (5 H, m, ArH); *m*/*z* CI(NH_3) 346 (M^+ + 1, 93%) and 100 (100).

(4*RS*,5*RS*,7*SR*,10*RS*)-5-Benzyloxy-l0-butyl-l-azatricyclo[5.3.0.0^{4,10}]decan-2-ol 33

Lithium aluminium hydride (6 mg, 0.16 mmol) was added to the lactam **31** (25 mg, 0.08 mmol) in ether (1.0 cm^3) at 0 °C. The mixture was stirred for 30 min, then celite (25 mg) was added, followed by water (2 drops). Stirring was continued for 15 min, then small portions of magnesium sulfate were added until the solid material became granular. Filtration and concentration under reduced pressure afforded the title compound **33** (25 mg, 99%), apparently a single diastereoisomer, as a colourless oil. Found: M^+, 315.2223. $C_{20}H_{29}NO_2$ requires *M*, 315.2198; υ_{max} 3120, 1455, 1096, 1069, 733 and 697 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.92 (3 H, m, 4′-H_3), 1.13–2.30 (13 H, m), 2.55 (1 H, m, 4-H), 2.80 (1 H, m, 9-H), 3.34–3.60 (3 H, m, 5-H, 7-H and OH), 4.44 and 4.55 (each 1 H, d, *J* 16.5 Hz, HC*H*Ph), 5.15 (1 H, m, 2-H) and 7.24–7.42 (5 H, m, ArH); *m*/*z* CI(NH_3) 316 (M^+ + 1, 9%).

(4*RS*,5*RS*,7*SR*,10*RS*)-2-Acetoxy-5-benzyloxy-l0-butyl-l-azatricyclo[5.3.0.0^{4,10}]decane 34

Triethylamine (0.045 cm^3, 0.324 mmol) was added to the aminol **33** (8.5 mg, 0.027 mmol.), 4-*N*,*N*-dimethylaminopyridine (1 mg, 0.008 mmol) and acetic anhydride (0.016 cm^3, 0.162 mmol) in dichloromethane (1.5 cm^3) at 0 °C, and the mixture was stirred at ambient temperature for 12 h. Concentration under reduced pressure and chromatography of the residue using light petroleum–ethyl acetate (60 : 40) as eluent gave the title compound **34** (6.9 mg, 72%) as a colourless oil. Found: M^+, 357.2284. $C_{22}H_{31}NO_3$ requires *M*, 357.2304; υ_{max} 1736, 1650, 1366, 1244, 1122, 1099, 1021, 735 and 698 cm^{-1}; δ_H (300 MHz, C_6D_6) 1.00 (3 H, t, *J* 7.5 Hz, 4′-H_3), 1.25–1.88 (10 H, m, 3 × CH_2, 3-H, 6-H_{eq}, 8-H_{exo} and 9-H_{exo}), l.82 (3 H, s, CH_3CO), 2.07–2.29 (3 H, m, 8-H_{endo}, 3-H′, 6-H_{ax}), 2.35 (1 H, dd, *J* 7.5 Hz, 2.5 Hz, 4-H), 2.97 (1 H, ddd, *J* 13 Hz, 9 Hz and 6 Hz, 9-H_{endo}), 3.18 (1 H, dd, *J* 5 Hz, 2.5 Hz, 5-H), 3.55 (1 H, m, 7-H), 4.22 and 4.28 (each 1 H, d, *J* 14 Hz, HC*H*Ph), 6.14 (1 H, dd, *J* 7.5 Hz, 4 Hz, 2-H) and 7.15–7.48 (5 H, m, ArH); δ_C (50 MHz, $CDCl_3$), 14.42, 21.77, 23.73, 27.14, 29.25, 30.14, 31.26, 38.58, 39.55, 45.71, 53.64, 61.67, 71.15, 79.61, 88.28, 127.25, 127.54, 128.51, 138.91 and 170.76; *m*/*z* CI(NH_3) 358 (M^+ + 1, 100%) and 298 (26).

(1*RS*,2*RS*,3*RS*,5*SR*)-1-Butyl-3-*tert*-butyldimethylsilyloxy-2,8-dimethoxycarbonyl-8-azabicyclo-[3.2.1]octane 36

tert-Butyldimethylsilyl triflate (5.0 cm^3, 22.3 mmol) was added to the hydroxyester **26** (3.90 g, 13.1 mmol) and 2,6-lutidine (6.0 cm^3, 52.5 mmol) in dichloromethane (39 cm^3) at 0 °C. After 1 h, the reaction mixture was washed with saturated aqueous ammonium chloride and water. The aqueous phase was washed with ethyl acetate, and the combined organic phase was washed with brine and dried ($MgSO_4$). Concentration under reduced pressure and chromatography of the residue using light petroleum–ethyl acetate (90 : 10) as eluent gave the title compound **36** (4.7 g, 86%) as a colourless oil. Found: M^+, 413.2591. $C_{21}H_{39}NO_5Si$ requires *M*, 413.2597; υ_{max} 1734, 1713, 1443, 1376, 1257, 1191, 1159, 1130, 1098, 1081, 836 and 776 cm^{-1}; δ_H (300 MHz, C_6D_6) 0.00 and 0.02 (each 3 H, s, $SiCH_3$), 0.96 (9 H, s, $C(CH_3)_3$), 1.03 (3 H, t, *J* 7 Hz, 4′-H_3), 1.42–1.60 (5 H, m, 2′-H_2, 3′-H_2 and 4-H_{eq}), 1.60–1.82 (2 H, m, 6-H_{endo} and 4-H_{ax}), 1.90 (1 H, dt, *J* 3 Hz, 12 Hz, 7-H_{exo}), 2.02 (1 H, dt, *J* 3 Hz, 9.5 Hz, 6-H_{exo}), 2.24 (1 H, m, 1′-H), 2.55 (1 H, ddd, *J* 12 Hz, 9.5 Hz, 5 Hz, 7-H_{endo}), 2.80 (1 H, m, 1′-H′), 2.91 (1 H, s, 2-H), 3.55 (3 H, br s, OCH_3), 3.60 (3 H, s, OCH_3), 4.33 (l H, d, *J* 5 Hz, 3-H) and 4.53 (1 H, m, 5-H); δ_C (75 MHz, C_6D_6) −5.35, −5.24, 14.22, 17.89, 23.69. 25.80, 26.01, 26.67, 35.4, 36.28, 37.32, 51.26, 51.52, 56.44, 56.63, 64.64, 68.20, 156.12 and 172.20; *m*/*z* CI(NH_3) 415 (100%) and 414 (M^+ + 1, 99.5).

(1*RS*,2*SR*,3*RS*,5*SR*)-1-Butyl-3-*tert*-butyldimethylsilyloxy-2-hydroxymethyl-8-methoxycarbonyl-8-azabicyclo[3.2.1]octane 37

Diisobutylaluminium hydride (25.0 cm^3,1 M in pentane, 25 mmol) was added to the ester **36** (4.7 g, 11.4 mmol) in hexane (90 cm^3) at −78 °C. The mixture was stirred for 1 h then allowed to warm to ambient temperature over 1 h. Celite (5.0 g) was added, followed

by water (3.0 cm^3) and stirring was continued for 2 h. Magnesium sulfate was added in small portions until the solid material became granular. The solid material was removed by filtration and washed with ethyl acetate. The combined organic phases were concentrated under reduced pressure and chromatography of the residue using light petroleum–ethyl acetate (75 : 25) as eluent gave the title compound **37** (3.40 g, 78%) as a colourless oil. Found: $M^+ + H$, 386.2722. $C_{20}H_{40}NO_4Si$ requires *M*, 386.2726); υ_{max} 3463, 1710, 1685, 1451, 1382, 1255, 1098, 1056, 837 and 776 cm^{-1}; δ_H (300 MHz, C_6D_6) 0.10 and 0.14 (each 3 H, s, $SiCH_3$), 0.98 (3 H, t, *J* 7.5 Hz, 4′-H_3), 1.03 (9 H, s, $C(CH_3)_3$), 1.33–1.51 (4 H, m), 1.59 (1 H, m, 4-H_{eq}), 1.67–1.92 (3 H, m), 2.05–2.26 (4 H, m), 2.44–2.61 (2H, m), 3.51 (3 H, s, OCH_3), 3.69 (1 H, dd, *J* 13 Hz, 7.5, 2-CH), 3.90 (1 H, dd, *J* 13 Hz, 3 Hz, 2-CH′), 4.30 (1 H, d, *J* 4.8 Hz, 3-H) and 4.41–4.49 (1 H, m, 5-H); δ_C (75 MHz, C_6D_6) −5.04, −4.89, 14.22, 17.93, 23.71, 25.88, 25.94, 26.61, 35.77, 36.40, 37.67, 51.62, 54.79, 56.62, 61.88, 64.81, 69.33 and 155.33; *m*/*z* CI(NH_3) 386 ($M^+ + 1$, 7%), 355 (23) and 354 (100).

(1*RS*,2*SR*,3*RS*,5*SR*)-1-Butyl-3-*tert*-butyldimethylsilyloxy-2-iodomethyl-5-methoxycarbonyl-8-azabicyclo[3.2.1]octane 38

The alcohol **37** (3.40 g, 8.83 mmol), imidazole (0.89 g, 13.3 mmol), triphenylphosphine (3.48 g, 13.3 mmol) and iodine (3.36 g, 13.7 mmol) were stirred in dichloromethane (100 cm^3) for 12 h. Saturated aqueous sodium thiosulfate and saturated aqueous sodium hydrogen carbonate were added and the reaction mixture stirred for 30 min. The organic phase was washed with water and brine then dried. Concentration under reduced pressure and chromatography of the residue using light petroleum–ethyl acetate (95 : 5) as eluent gave the title compound **38** (3.64 g, 83%) as a white amorphous, hygroscopic solid. Found: C, 48.4; H, 8.1; I, 25.7; N, 2.8. M^+, 495.1634. $C_{20}H_{38}INO_3Si$ requires C, 48.5; H, 7.7; I, 25.7; N, 2.8%; *M*, 495.1667; υ_{max} 1707, 1444, 1376, 1256, 1150, 1098, 1050, 836 and 776 cm^{-1}; δ_H (300 MHz, C_6D_6) 0.19 and 0.31 (each 3 H, s, $SiCH_3$), 1.94 (3 H, t, *J* 7.5 Hz, 4′-H_3), 1.02 [9 H, s, $C(CH_3)_3$], 1.29–1.49 (5 H, m), 1.58–1.80 (2 H, m), 1.85–2.10 (3 H, m), 2.36 (1 H, d, *J* 11.5 Hz, 4-H_{ax}), 2.44–2.65 (2 H, m), 2.82 (1 H, t, *J* 11 Hz, 2-CH), 3.46 (3 H, s, OCH_3), 4.03 (1 H, dd, *J* 11 Hz, 2, 2-CH′), 4.31 (1 H, d, *J* 4.5 Hz, 3-H) and 4.31–4.40 (1 H, m, 5-H); δ_C (75 MHz, C_6D_6) −4.69, −3.99, 6.64, 14.16, 17.88, 23.54, 25.92, 26.03, 26.78, 35.36, 35.44, 36.11, 51.54, 56.00, 56.52, 66.49, 70.60 and 154.59; *m*/*z* CI(NH_3) 496 ($M^+ + 1$, 36%), 495 (M^+, 100) and 370 (71).

(4*RS*,5*RS*,7*SR*,10*RS*)-10-Butyl-5-*tert*-butyldimethylsilyloxy-1-azabicyclo[5.3.0.$0^{4,10}$]decan-2-one 39

tert-Butyllithium (12.65 cm^3,1.6 M in hexanes, 20.24 mmol) was added to the iodide **38** (3.55 g, 7.17 mmol) in tetrahydrofuran (100 cm^3) at −78 °C. The mixture was stirred at −78 °C for 30 min, then at ambient temperature for 3 h. Saturated aqueous ammonium chloride was added, and the organic phase diluted with ether and washed with water. The combined aqueous phase was washed with ethyl acetate, and the combined organic phase washed with brine and dried ($MgSO_4$). Concentration under reduced pressure and chromatography of the residue using light petroleum–ethyl acetate (85 : 15) as eluent gave the title compound **39** (1.94 g, 81%) as a white microcrystalline solid, m.p. 70–71 °C. Found: C, 67.9; H, 10.2; N, 4.3; M^+, 337.2446. $C_{19}H_{35}NO_2Si$ requires C, 67.7; H, 10.4; N, 4.15%; *M*, 337.2437; υ_{max} 1749, 1254, 1192, 1133, 1091, 1060, 834 and 776 cm^{-1}; δ_H (300 MHz, C_6D_6) −0.02 and 0.01 (each 3 H, s, $SiCH_3$), 0.89 (3 H, t, *J* 7.5 Hz, 4′-H_3), 0.97 (9 H, s, $C(CH_3)_3$), 1.09 (1 H, d, *J* 15.5 Hz, 6-H_{eq}), 1.17–1.54 (6 H, m), 1.65 (1 H, dt, *J* 3 Hz, 12.5 Hz), 1.80 (1 H, m), 1.78 (1 H, d, *J* 17.5 Hz, 3-H), 2.03–2.24 (2 H, m), 2.24 (1 H, dd, *J* 5.5 Hz, 2.5 Hz, 4-H), 2.64 (1 H, dd, *J* 17.5 Hz, 5.5 Hz, 3-H), 3.10 (1 H, ddd, *J* 12.5 Hz. 9.5 Hz, 6.5 Hz, 9-H_{endo}), 3.61 (1 H, dd, *J* 5.5 Hz, 2.5 Hz, 5-H) and 4.08 (1 H, m, 7-H); δ_C (75 MHz, C_6D_6) −5.12, −5.07, 14.07, 17.96, 23.41, 25.83, 26.92, 30.17, 30.89, 35.40, 39.29, 41.51, 48.73, 66.22, 70.41, 72.72 and 194.16; *m*/*z* CI(NH_3) 338 ($M^+ + 1$, 100%).

(4*RS*,5*RS*,7*SR*,10*RS*)-10-Butyl-5-hydroxy-1-azatricyclo[5.3.0.$0^{4,10}$]decan-2-one 40

Tetrabutylammonium fluoride (0.40 cm^3, 1 M in tetrahydrofuran, 0.40 mmol) was added to the silyl ether **39** (68 mg, 0.2 mmol) in tetrahydrofuran (2.0 cm^3) at ambient temperature. The reaction mixture was stirred for 12 h, then diluted with ethyl acetate and washed with saturated aqueous ammonium chloride and water. The combined aqueous phase was washed with ethyl acetate, and the organic phase washed with brine and dried ($MgSO_4$). Concentration under reduced pressure and chromatography of the residue using light petroleum–ethyl acetate (60 : 40) gave the title compound **40** (45 mg, 99%) as a white solid recrystallised from hexane–ethyl acetate to give colourless prismatic crystals, m.p. 86–88 °C. Found: M^+, 223.1576. $C_{13}H_{21}NO_2$ requires *M*, 223.1572; υ_{max} 3426, 1746, 1724, 1460, 1133, 1017 and 941 cm^{-1}; δ_H (200 MHz, C_6D_6) 0.90 (3 H, t, *J* 8.7 Hz, 4′-H_3), 0.96 (1 H, d, *J* 19 Hz, 6-H_{eq}), 1.06–1.50 (7 H, m, 3 × CH_2 and OH), 1.50–1.84 (3 H, m, 3-H, 8-H_{exo} and 9-H_{exo}), 2.06–2.24 (3 H, m, 4-H, 8-H_{endo} and 6-H_{ax}), 2.60 (1 H, dd, *J* 17.5 Hz, 6.5 Hz, 3-H′), 3.04 (1 H, ddd, *J* 12.5 Hz, 10 Hz and 7 Hz, 9-H_{endo}), 3.32 (1 H, dd, *J* 6.5 Hz, 4 Hz, 5-H) and 3.95–4.09 (1 H, m, 7-H); δ_C (75 MHz, C_6D_6) 14.25, 23.63, 27.25, 30.25, 31.10, 35.13, 39.50, 41.88, 48.50, 66.25, 70.25, 71.88 and 194.50; *m*/*z* CI(NH_3) 225 (13%) and 224 ($M^+ + 1$, 100).

(4*RS*,5*RS*,7*SR*,9*SR*,10*SR*)-10-Butyl-1-aza-11-oxatetracyclo-[5.3.0.$0^{4,10}$.$1^{5,9}$]undecan-2-one 41 and (4*RS*,7*SR*,10*RS*)-l0-butyl-1-azatricyclo[5.3.0.$0^{4,10}$]decane-2,5-dione 42

The hydroxylactam **40** (17 mg, 0.08 mmo1) and lead(IV) acetate (38 mg, 0.08 mmol) were heated under reflux in benzene (2.0 cm^3) for 12 h, more lead(IV) acetate (10 mg, 0.02 mmol) was added, and the mixture heated for a further 6 h before being concentrated under reduced pressure and diluted with ethyl acetate. The solution was washed with saturated aqueous sodium thiosulfate, water, and brine, then dried ($MgSO_4$). Concentration under reduced pressure and chromatography of the residue using hexane–ethyl acetate (75 : 25) as eluent gave the title compound **41** (6 mg, 35%), as an oil. Found: M^+, 221.1414. $C_{13}H_{19}NO_2$ requires *M*, 221.1416); υ_{max} 1747, 1188, 1148, 1082, 1044, 1022, 993, 943, 864 and 848 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.88 (3 H, t, *J* 7.5 Hz, 4′-H_3), 1.21 (1 H, m, 1′-H), 1.32 (2 H, dq, *J* 9 Hz, 7.5 Hz, 3′-H_2), 1.45 (1 H, m, 1′-H′), 1.55–1.63 (2 H, m, 2′-H_2), 1.72 (1 H, dd, *J* 15 Hz, 3.5 Hz, 6-H), 1.84 (1 H, ddt, *J* 15 Hz, 4 Hz, 2 Hz, 6-H), 1.98 (1 H, dddt, *J* 12.5 Hz,

5.5 Hz, 3.5 Hz, 1.2 Hz, 8-H), 2.23 (1 H, dd, *J* 12.5 Hz, 1 Hz, 8-H′), 2.47 (1 H, dd, *J* 19 Hz, 1 Hz, 3-H_{endo}), 2.76 (1 H, t, *J* 6 Hz, 4-H), 2.87 (1 H, dd, *J* 19 Hz, 6 Hz, 3-H_{exo}), 4.02 (1 H, m, 7-H), 4.35 (1 H, m, 5-H) and 4.46 (1 H, m, 9-H); δ_C (75 MHz, $CDCl_3$) 13.96, 23.12, 27.15, 30.70, 33.54, 38.28, 40.01, 52.04, 63.42, 79.44, 80.00, 83.08 and 194.53; *m*/*z* (EI) 221 (M^+, 57%), 192 (20), 179 (44) and 164 (22). The next product eluted was the title compound **42** (3 mg, 16%). Found: M^+, 221.1421. $C_{13}H_{19}NO_2$ requires *M*, 221.1416; υ_{max} 1752, 1718 and 1132 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.82 (3 H, t, *J* 7.5 Hz, 4′-H_3), 0.82–1.78 (10 H, m), 1.78 (1 H, d, *J* 16.5 Hz, 6-H), 1.87 (1 H, d, *J* 17.5 Hz, 3-H_{endo}), 2.45 (1 H, dd, *J* 16.5 Hz, 2 Hz, 6-H′), 2.47 (1 H, dd, *J* 17.5 Hz, 5 Hz, 3-H_{exo}), 2.74 (1 H, d, *J* 5 Hz, 4-H) and 3.75 (1 H, t, *J* 4.5 Hz, 7-H); δ_C (75 MHz, $CDCl_3$) 13.9, 23.0, 26.6, 30.7, 32.4, 36.3, 40.9, 43.7, 61.0, 62.0, 72.2, 192.5, 208.5; *m*/*z* (EI) 221 (M^+, 30%), 193 (47), 164 (31), 151 (26), 136 (37) and 123 (100). Finally, starting material **40** (2 mg, 12%) was recovered.

Following the procedure outlined for the preparation of ketone **49**, the alcohol **40** (160 mg, 0.717 mmol), after chromatography using light petroleum–ethyl acetate (75 : 25) as eluent, gave the ketone **42** (155 mg, 98%).

(4*RS*,5*RS*,7*SR*,10*RS*)-10-Butyl-5-*tert*-butyldimethylsilyloxy-1-azatricyclo[5.3.0.$0^{4,10}$]decan-2-ol 44

Lithium aluminium hydride (18 mg, 0.474 mmol) was added to the lactam **39** (80 mg, 0.237 mmol) in ether (1.0 cm^3) at 0 °C. The mixture was stirred at ambient temperature for 30 min, then celite (70 mg) was added, followed by 10 drops of water. Stirring was continued for 45 min, then small portions of magnesium sulfate were added until the solid material became granular. Filtration and concentration under reduced pressure afforded the title compound **44** (78 mg, 97%) as a white solid, m.p. 148–149 °C. Found: M^+ + H, 340.2677. $C_{19}H_{38}NO_2Si$ requires *M*, 340.2672; υ_{max} 3115, 1256, 1096, 1061, 1026, 861, 836 and 776 cm^{-1}; δ_H (300 MHz, C_6D_6) 0.03 and 0.07 (each 3 H, s, $SiCH_3$), 0.89–1.10 (12 H, m, 4′-H_3 and $C(CH_3)_3$), 1.15 (1 H, d, *J* 15.5 Hz, 6-H_{eq}), 1.29–1.68 (5 H, m), 1.68–1.98 (4 H, m), 2.16–2.45 (4 H, m), 3.15 (1 H, m, 9-H), 3.47 (1 H, m, 7-H), 3.65 (1 H, m, 5-H) and 5.26 (1 H, m, 2-H); *m*/*z* CI(NH_3) 341 (27%) and 340 (M^+ + 1, 100).

(4*RS*,5*RS*,7*SR*,10*RS*)-2-Acetoxy-10-butyl-5-*tert*-butyldimethylsilyloxy-1-azatricyclo[5.3.0.$0^{4,10}$]-decane 45

Triethylamine (5 μl, 0.359 mmol) was added to the aminol **44** (10 mg, 0.029 mmol), DMAP (1 mg, 0.008 mmol) and acetic anhydride (15 μl, 0.159 mmol) in dichloromethane (1.0 cm^3) at 0 °C. The mixture was stirred at ambient temperature for 15 h. Concentration under reduced pressure and chromatography of the residue using light petroleum–ethyl acetate (60 : 40) as eluent gave the title compound **45** (10.5 mg, 93%) as a white solid, m.p. 40.5–42.5 °C. Found: M^+, 381.2693. $C_{21}H_{39}NO_3Si$ requires *M*, 381.2699); υ_{max} 1737, 1250, 1112, 1065, 1021, 835 and 776 cm^{-1}; δ_H (300 MHz, C_6D_6) 0.01 and 0.05 (each 3 H, s, $SiCH_3$), 0.94–1.04 (12 H, m, 4′-H_3 and $C(CH_3)_3$), 1.08 (1 H, d, *J* 15.5 Hz, 6-H_{eq}), 1.35–1.49 (3 H, m), 1.49–1.89 (7 H, m), 1.81 (3 H, s, CH_3CO), 2.08–2.29 (3 H, m), 3.08 (1 H, m, 9-H), 3.53–3.63 (2 H, m, 5-H and 7-H), 6.14 (1 H, dd, *J* 7 Hz, 4 Hz, 2-H); *m*/*z* (EI) 382 (M^+ + 1, 12%) and 381 (34).

(4*RS*,5*RS*,7*SR*,10*RS*)-10-Butyl-5-*tert*-butyldimethylsilyloxy-1-azatricyclo[5.3.0.$0^{4,10}$]decane 47

Thionyl chloride (0.38 cm^3, 5.21 mmol) was added dropwise to a stirred solution of hydroxyamine **45** (515 mg, 1.52 mmol) in ether (14.0 cm^3). After 90 min, the solvent was removed under reduced pressure, the residue was dissolved in ether (15 cm^3), and the solution added dropwise to lithium aluminium hydride (450 mg, 11.8 mmol) in ether (2 cm^3) at 0 °C. The mixture was stirred at ambient temperature for 3 h, then cooled to 0 °C, and water (2 cm^3) and celite (500 mg) were added. Stirring was continued for 30 min, then small portions of magnesium sulfate were added until the solid material became granular. Filtration and concentration under reduced pressure, after chromatography using ethyl acetate–triethylamine (96 : 4) as eluent, gave the title compound **47** (450 mg, 92%), as a yellow oil. Found: M^+, 323.2650. $C_{19}H_{37}NOSi$ requires *M*, 323.2644; υ_{max} 1254, 1096, 1058, 863, 834 and 774 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.03 and 0.05 (each 3 H, s, $SiCH_3$), 0.87–0.93 (12 H, m, 4′-H_3 and $C(CH_3)_3$), 1.20–1.48 (8 H, m), 1.64 (1 H, td, *J* 14 Hz, 3 Hz), 1.90 (1 H, ddd, *J* 13 Hz, 10 Hz, 5.5 Hz), 1.95–2.14 (4 H, m), 2.90 (1 H, ddd, *J* 14 Hz, 10 Hz and 5.5 Hz, 9-H), 2.95–3.03 (2 H, m, 2-H_2), 3.31 (1 H, t, *J* 5.5 Hz, 7-H) and 3.76 (1 H, br s, 5-H); *m*/*z* (EI) 324 (22%), 323 (M^+, 72), 24 (45), 281 (29), 280 (37), 266 (27), 224 (38) and 192 (100).

(4*RS*,5*RS*,7*SR*,10*RS*)-10-Butyl-1-azatricyclo-[5.3.0.$0^{4,10}$]decan-5-ol 48

Boron trifluoride diethyletherate (0.60 cm^3, 4.78 mmol) was added to the silyl ether **47** (450 mg, 1.39 mmol) in chloroform (15 cm^3) at ambient temperature. After 20 h, the solvent and excess boron trifluoride diethyletherate were removed completely under reduced pressure, and the mixture was taken up in aqueous sodium hydroxide (10%) and extracted with chloroform. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate–triethylamine (90 : 10) as eluent gave the title compound **48** (248 mg, 85%) as a white solid, m.p. 113–115 °C. Found: M^+, 209.1778. $C_{13}H_{23}NO$ requires *M*, 209.1780; υ_{max} 3300, 1461, 1096, 1027 and 954 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.87 (3 H, t, *J* 6.5 Hz, 4′-H_3), 1.10 (1 H, m, 2′-H), 1.20–1.43 (5 H, m), 1.36–1.43 (2 H, m), 1.61 (1 H, td, *J* 13 Hz, 3 Hz), 1.81 (1 H, ddd, *J* 13 Hz, 10 Hz, 3 Hz), 1.95 (1 H, m, 3-H), 1.98–2.07 (4 H, m), 2.78 (1 H, ddd, *J* 15.5 Hz, 10 Hz, 6 Hz, 9-H), 2.88 (1 H, ddd, *J* 17 Hz, 10 Hz, 4.5 Hz, 2-H), 2.94 (1 H, ddd, *J* 17 Hz, 9 Hz, 5.5 Hz, 2-H′), 3.20 (1 H, t, *J* 5.5 Hz, 7-H) and 3.83 (1 H, t, *J* 3.5 Hz, 5-H); δ_C (75 MHz, $CDCl_3$) 14.09, 23.49, 27.06, 28.89, 29.76, 30.23, 32.37, 37.46, 44.87, 45.92, 61.89, 72.13 and 73.06; *m*/*z* (EI) 209 (M^+, 3%) and 192 (11).

(4*RS*,7*SR*,10*RS*)-10-Butyl-1-azatricyclo[5.3.0.$0^{4,10}$]decan-5-one 49

Dimethyl sulfoxide (1.50 cm^3, 21.16 mmol) was added dropwise to oxalyl chloride (1.08 cm^3, 12.38 mmol) in dichloromethane (15.0 cm^3) at −50 °C. After 2 min, the aminol **48** (800 mg, 3.83 mmol) in dichloromethane (40 cm^3) was added, and the reaction stirred at −50 °C for 30 min. Triethylamine (5.60 cm^3, 40.18 mmol) was added, and the mixture was allowed to warm to ambient temperature. After concentration under reduced pressure, the residue was dissolved in water and extracted with ethyl acetate. The organic phase was dried ($MgSO_4$) and concentrated

under reduced pressure. Chromatography of the residue using ethyl acetate–pyridine (99 : 1) as eluent gave the title compound **49** (670 mg, 85%) as a pale yellow oil. Found: M^+, 207.1631. $C_{13}H_{21}NO$ requires *M*, 207.1623; υ_{max} 1715 and 1103 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.86 (3 H, t, *J* 6.5 Hz, 4′-H_3), 1.09–1.34 (5 H, m, 1′-H, 2′-H_2 and 3′-H_2), 1.40–1.47 (1 H, m, 1′-H′), 1.57 (1 H, ddd, *J* 3.5 Hz, 8 Hz, 11.5 Hz), 1.72 (1 H, ddd, *J* 3.5 Hz, 8.5 Hz, 13 Hz, 3-H), 1.76–1.80 (2 H, m), 1.97 (1 H, d, *J* 16 Hz, 6-H_{eq}), 2.07 (1 H, m, 8-H), 2.11 (1 H, m, 3-H), 2.50 (1 H, br dd, *J* 16 Hz, 5.5 Hz, 6-H_{ax}), 2.58 (1 H, d, *J* 6 Hz, 4-H), 3.08 (1 H, ddd, *J* 14 Hz, 8.5 Hz, 5, 2-H), 3.16 (1 H, ddd, *J* 14 Hz, 9 Hz, 3.5 Hz, 2-H′) and 3.50 (1 H, t, *J* 5.5 Hz, 7-H); δ_C (75 MHz, C_6D_6) 14.75, 24.03, 27.14, 29.50, 31.25, 31.50, 35.50, 42.85, 46.52, 60.22, 64.23, 76.70 and 209.81; *m*/*z* (EI) 207 (M^+, 11%).

(4*RS*,6*SR*,7*SR*,10*RS*)- and (4*RS*,6*RS*,7*SR*,10*RS*)-10-Butyl-6-prop-2′-enyl-1-azatricyclo[5.3.0.0^{4,10}]-decan-5-one 58 and 59

Potassium bis(trimethylsilyl)amide (0.7 cm^3, 0.5 M in toluene, 0.35 mmol) was added to the ketone **49** (24 mg, 0.116 mmol) in tetrahydrofuran (0.75 cm^3) at −78 °C. After 30 min, allyl iodide (86 µl, 0.94 mmol) was added, and the mixture was stirred for 75 min. Water was added, and the mixture was allowed to warm to ambient temperature and extracted with chloroform. The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using 1% pyridine in light petroleum–ethyl acetate (50 : 50) as eluent gave a mixture of the title compounds **58** and **59** (16 mg, 56%), **58** : **59** = 80 : 20, as a pale yellow oil.

n-Butyllithium (0.45 cm^3, 1.6 M in hexane, 0.72 mmol) was added to diisopropylamine (92 µl, 0.656 mmol) in tetrahydrofuran (3.5 cm^3) at 0 °C, and the solution was stirred for 30 min. An aliquot (1.7 cm^3, 0.276 mmol) was added to the ketone **49** (20 mg, 0.097 mmol) in tetrahydrofuran (1.0 cm^3) at −78 °C. After 1 h, allyl iodide (70 µl, 0.766 mmol) was added and the mixture was allowed to warm to ambient temperature. Water was added and the mixture extracted with chloroform. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using 1% pyridine in light petroleum–ethyl acetate (50 : 50) as eluent gave the title compound **58** (10 mg, 42%) as a pale yellow oil. Found: M^+, 247.1944. $C_{16}H_{25}NO$ requires *M*, 247.1936; υ_{max} 1706, 1466, 1097 and 913 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.87 (3 H, t, *J* 7 Hz, 4″-H_3), 1.18–1.36 (5 H, m), 1.41–1.52 (2 H, m), 1.71–1.86 (3 H, m), 2.04 (1 H, m, 8-H), 2.11 (1 H, dd, *J* 10.5 Hz, 7 Hz, 6-H_{eq}), 2.19 (1 H, m, 3-H), 2.34 and 2.48 (each 1 H, m, 1′-H), 2.66 (1 H, d, *J* 7 Hz, 4-H), 3.15 (1 H, ddd, *J* 14 Hz, 10 Hz, 4.5 Hz, 2-H), 3.27 (1 H, ddd, *J* 14 Hz, 9 Hz, 5.5 Hz, 2-H′), 3.47 (1 H, d, *J* 5.5 Hz, 7-H), 5.12–5.09 (2 H, m, 3′-H_2) and 5.70 (1 H, m, 2′-H); δ_C (75 MHz, C_6D_6) 14.25, 23.54, 26.54, 29.16, 30.16, 34.15, 34.63, 38.37, 45.57, 54.24, 60.10, 64.17, 74.53, 116.43, 136.95 and 211.47; *m*/*z* (CI) 249 (19%) and 248 (M^+ + 1, 100).

Potassium *t*-butoxide (3.0 mg, 0.027 mmol) was added to ketone **58** (8 mg, 0.032 mmol) in a mixture of dichloromethane (1.0 cm^3) and methanol (0.5 cm^3) at ambient temperature. After 15 h, water was added and the mixture extracted with dichloromethane. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to yield the title compound **59** (7 mg, 88%) as a pale yellow oil. Found: M^+ + H, 248.2012. $C_{16}H_{26}NO$ requires *M*, 248.2012; υ_{max} 1707, 1467, 1091 and 911 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.88 (3 H, t, *J* 7 Hz, 4′-H_3), 1.18–1.41 (5 H, m), 1.47 (1 H, m), 1.52–1.87 (6 H, m), 2.13 (1 H, m, 3-H), 2.49 (1 H, q, *J* 6.5 Hz, 8-H), 2.57 (1 H, m), 2.62 (1 H, d, *J* 6.5 Hz, 4-H), 3.11–3.25 (2 H, m, 2-CH_2), 3.43 (1 H, t, *J* 5 Hz, 7-H), 4.96–5.05 (2 H, m, 3′-H_2) and 5.73 (1 H, m, 2′-H); δ_C (75 MHz, $CDCl_3$) 14.00, 23.21, 25.02, 26.83, 28.85, 29.83, 30.99, 34.87, 45.71, 47.20, 58.20, 67.97, 77.02, 116.38, 135.98 and 211.06; *m*/*z* (CI) 265 (M^+ + 18, 2%), 264 (11), 249 (22) and 248 (100).

(4*RS*,6*SR*,7*SR*,10*RS*)- and (4*RS*,6*RS*,7*SR*,10*RS*)-10-Butyl-6-prop-2′-enyl-1-azatricyclo[5.3.0.0^{4,10}]decane-2,5-dione 60 and 61

n-Butyllithium (0.30 cm^3, 1.6 M in hexanes, 0.48 mmol) was added to diisopropylamine (70 µl, 0.50 mmol) in tetrahydrofuran (1.0 cm^3) at 0 °C. The solution was stirred for 20 min, cooled to −78 °C and the ketolactam **42** (50 mg, 0.226 mmol) was added. After 30 min, the mixture was allowed to warm to −35 °C, then recooled to −78 °C, and allyl bromide (82 µl, 0.969 mmol) was added. The mixture was allowed to warm to ambient temperature over 2 h, then saturated aqueous ammonium chloride was added and the mixture extracted with ethyl acetate. The organic phase was washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (65 : 35) as eluent gave a mixture of the title compounds **60** and **61** (23 mg, 39%) as a colourless oil, along with some recovered ketoamide **42** (19 mg, 38%). HPLC using acetonitrile–water (45 : 55) as eluent gave the title compound **60** (15 mg, 25%). Found: M^+, 261.1725. $C_{16}H_{23}NO_2$ requires *M*, 261.1729; υ_{max} 1748, 1708 and 1136 cm^{-1}; δ_H (300 MHz, C_6D_6) 0.84 (3 H, t, *J* 7 Hz, 4″-H_3), 0.86–1.24 (7 H, m), 1.40–1.48 (2 H, m), 1.76 (1 H, m), 2.03 (1 H, dd, *J* 10.5 Hz, 6, 6-H_{eq}), 2.09 (1 H, d, *J* 18.5 Hz, 3-H), 2.36–2.57 (2 H, m, 1′-H_2), 2.57 (1 H, dd, *J* 18.5 Hz, 5.5 Hz, 3-H′), 2.86 (1 H, d, *J* 5.5 Hz, 4-H), 4.08 (1 H, d, *J* 5 Hz, 7-H), 5.05 and 5.20 (each 1 H, m, 3′-H) and 5.58 (1 H, m, 2′-H); *m*/*z* (EI) 262 (M^+ + 1, 4%), 261 (19), 125 (38) and 124 (100). The next eluted product was the title compound **61** (8 mg, 14%). Found: M^+, 261.1720. $C_{16}H_{23}NO_2$ requires *M*, 261.1729); υ_{max} 1751, 1713 and 1132 cm^{-1}; δ_H (300 MHz, C_6D_6) 0.84 (3 H, t, *J* 7 Hz, 4′-H_3), 0.87–1.18 (4 H, m), 1.18–1.31, 1.36–1.46, and 1.46–1.65 (each 2 H, m), 1.66–1.79 (1 H, m, 6-H_{ax}), 1.89 (1 H, d, *J* 18.5 Hz, 3-H), 2.49 (1 H, dd, *J* 18.5 Hz, 5.5 Hz, 3-H′), 2.55–2.74 (2 H, m, 1′-H_2), 2.77 (1 H, d, *J* 5.5 Hz, 4-H), 3.98 (1 H, t, *J* 5.5 Hz, 7-H), 4.91–5.01 (2 H, m, 3′-H_2) and 5.55 (1 H, m, 2′-H); *m*/*z* (EI) 262 (M^+ + 1, 3%), 261 (11), 125 (36) and 124 (100).

Methyl (1*RS*,2*SR*,3*RS*,5*SR*)-1-butyl-3-hydroxy-2-hydroxymethyl-8-azabicyclo[3.2.1]octane-8-carboxylate 62

Diisobutylaluminium hydride (8.5 cm^3, 1 M in dichloromethane, 8.5 mmol) was added to the β-hydroxyester **26** (695 mg, 2.32 mmol) in dichloromethane (40 cm^3) at −78 °C. After 90 min, water (1 cm^3) and celite (1.0 g) were added, and the mixture was stirred at ambient temperature for 1 h. Magnesium sulfate was added until the solid material became granular. The solid was removed by filtration and washed with dichloromethane. The organic phase was concentrated under reduced pressure, and the residue was dissolved in ethanol (30 cm^3). Sodium borohydride (230 mg, 6.08 mmol) was added, and the mixture was stirred

at ambient temperature for 2 h, then water (10 cm^3) was added and the mixture extracted with ethyl acetate. The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (65 : 35) as eluent, yielded the title compound **62** (397 mg, 63%) as a white solid, m.p. 121–122 °C. Found: C, 62.0; H, 9.4; N, 5.2; M^+, 271.1789. $C_{14}H_{25}NO_4$ requires C, 61.95; H, 9.3; N, 5.15%; *M*, 271.1783); υ_{max} 3401, 1679, 1452, 1385, 1096 and 1048 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.90 (3 H, t, *J* 7.5 Hz, 4′-H_3), 1.17–1.38 (4 H, m, 2′-H_2 and 3′-H_2), 1.59–1.67 (2 H, m, 4-H_{eq} and 3-OH), 1.75 (1 H, ddd, *J* 16 Hz, 11.5 Hz, 4.5 Hz, 1′-H), 1.80–1.91 (3 H, m), 1.97 (1 H, m), 2.12 (1 H, dt, *J* 14.5 Hz, 4.5 Hz, 4-H_{ax}), 2.35–2.47 (3 H, m, 7-H, 1′-H′ and OH), 3.61 (3 H, s, OCH_3), 3.68 and 3.76 (each 1 H, m, 2-CH), 4.19 (1 H, d, *J* 4.5 Hz, 3-H) and 4.35 (1 H, m, 5-H); δ_C (50 MHz, $CDCl_3$) 14.63, 23.88, 26.26, 27.04, 36.04, 37.26, 37.71, 52.55, 53.87, 56.42, 62.36, 64.98, 68.97 and 155.84; *m*/*z* (EI) 271 (M^+, 7%), 254 (23), 212 (84), 196 (26), 184 (30), 183 (100), 182 (68), 155 (32), 140 (66) and 126 (46).

Methyl (1*RS*,2*SR*,3*RS*,5*SR*)-1-butyl-2-*tert*-butyldimethylsilyloxymethyl-3-hydroxy-8-azabicyclo-[3.2.1]octane-8-carboxylate 63

tert-Butyldimethylsilyl triflate (0.35 cm^3, 1.52 mmol) was added to the diol **62** (397 mg, 1.46 mmol) and 2,6-lutidine (0.21 cm^3, 1.80 mmol) in dichloromethane (40 cm^3) at ambient temperature. After 3 h, saturated aqueous ammonium chloride solution was added, and the organic phase separated. The aqueous phase was extracted with dichloromethane and the combined organic phase dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (90 : 10) as eluent gave the title compound **63** (530 mg, 94%) as a colourless oil. Found: M^+, 385.2651. $C_{20}H_{39}NO_4Si$ requires *M*, 385.2648; υ_{max} 3470, 1710, 1683, 1452, 1385, 1256, 1094 and 836 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.04 and 0.05 (each 3 H, s, $SiCH_3$), 0.86 (9 H, s, $C(CH_3)_3$), 0.90 (3 H, t, *J* 7 Hz, 4′-H_3), 1.19–1.40 (4 H, m, 2′-H_2 and 3′-H_2), 1.59 (1 H, d, *J* 15 Hz, 4-H_{eq}), 1.65–1.98 (5 H, m), 2.11 (1 H, dt, *J* 14.5 Hz, 4.5 Hz, 4-H_{ax}), 2.30–2.48 (2 H, m), 3.26 (1 H, t, *J* 10.5 Hz, 2-CH), 3.59 (3 H, s, OCH_3), 3.94 (1 H, dd, *J* 10.5 Hz, 4 Hz, 2-CH′), 4.24 (1 H, d, *J* 5 Hz, 3-H) and 4.32 (1 H, m, 5-H); δ_C (75 MHz, $CDCl_3$), −5.24, 14.24, 18.35, 23.48, 26.02, 26.26, 26.80, 35.51, 35.62, 36.61, 51.72, 54.72, 55.79, 61.73, 64.48, 67.27 and 154.47; *m*/*z* (EI) 386 (M^+ + 1, 6,%), 328 (79), 326 (43), 184 (55), 183 (100) and 182 (94).

Methyl (1*RS*,2*SR*,5*SR*)-1-butyl-2-*tert*-butyldimethylsilyloxymethyl-3-oxo-8-azabicyclo[3.2.1]-octane-8-carboxylate 64

Following the procedure outlined for the oxidation of alcohol **12**, alcohol **63** (330 mg, 0.857 mmol), after chromatography using light petroleum–ethyl acetate (93 : 7) gave the title compound **64** (322 mg, 98%) as a colourless oil. Found: M^+ + H, 384.2570. $C_{20}H_{37}NO_4Si$ requires *M*, 384.2570); υ_{max} 1711, 1444, 1375, 1098 and 838 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.01 and 0.03 (each 3 H, s, $SiCH_3$), 0.86 (9 H, s, $C(CH_3)_3$), 0.93 (3 H, t, *J* 7 Hz, 4′-H_3), 1.19–1.45 (4 H, m, 2′-H_2 and 3′-H_2), 1.52 and 1.74 (each 1 H, m), 1.84–2.09 (3 H, m), 2.22 (1 H, m), 2.27 (1 H, d, *J* 15 Hz, 4-H_{eq}), 2.60 (1 H, t, *J* 6.5 Hz, 2-H), 2.74 (1 H, dd, *J* 15 Hz, 4, 4-H_{ax}), 3.71 (3 H, s, OCH_3), 3.79 (1 H, dd, *J* 10.5 Hz, 7.5 Hz, 2-CH), 3.96 (1 H, dd, *J* 10.5 Hz, 6 Hz, 2-CH′) and 4.64 (1 H, m, 5-H); δ_C (75 MHz, $CDCl_3$) −5.69, −5.59, 14.04, 18.20, 23.18, 25.78, 26.41, 26.50, 34.39, 36.10, 47.77, 52.05, 55.85, 60.95, 64.98, 66.03, 154.56 and 209.26; *m*/*z* (CI) 384 (M^+ + 1, 100%) and 326 (14).

Methyl (1*RS*,2*SR*,4*SR*,5*SR*)-1-butyl-4-prop-2′-enyl-2-*tert*-butyldimethylsilyloxymethyl-3-oxo-8-azabicyclo[3.2.1]-octane-8-carboxylate 65

Potassium bis(trimethylsilyl)amide (0.16 cm^3, 15% in tetrahydrofuran, 0.12 mmol) was added to the ketone **64** (23 mg, 0.06 mmol) in tetrahydrofuran (1.0 cm^3) at −78 °C. The mixture was allowed to warm to −25 °C over 1 h, then recooled to −78 °C. Allyl iodide (35 μl, 0.382 mmol) was added, and the mixture was warmed to ambient temperature over 2 h. Saturated aqueous ammonium chloride was added and the mixture extracted with ethyl acetate, and the extracts dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (30 : 1) gave the title compound **65** (16 mg, 63%) as a colourless oil. Found: M^+ + H, 424.2870. $C_{23}H_{42}NO_4Si$ requires *M*, 424.2883; υ_{max} 1705, 1446, 1382, 1256, 1099, 839 and 778 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.00 and 0.03 (each 3 H, s, $SiCH_3$), 0.84 (9 H, s, $C(CH_3)_3$), 0.89 (3 H, t, *J* 7 Hz, 4′-H_3), 1.17 (1 H, m, 2′-H), 1.21–1.39 (3 H, m, 2′-H′ and 3′-H_2), 1.45–1.52 (1 H, m), 1.71 (1 H, m), 1.87–2.00 (3 H, m), 2.14 (1 H, m, 1″-H), 2.19–2.28 (2 H, m, 4-H_{eq} and 1″-H′), 2.39 (1 H, td, *J* 13, 3, 1′-H), 2.63 (1 H, t, *J* 7 Hz, 2-H), 3.67 (3 H, s, OCH_3), 3.72 and 3.98 (each 1 H, dd, *J* 10.5 Hz, 7 Hz, 2-CH), 4.59 (1 H, d, *J* 7 Hz, 5-H), 5.02–5.09 (2 H, m, 3″-H_2) and 5.76 (1 H, m, 2″-H); δ_C (75 MHz, $CDCl_3$) −5.50, 14.12, 18.20, 23.31, 25.85, 26.89, 27.76, 34.08, 34.60, 36.46, 51.94, 57.39, 59.52, 61.67, 65.20, 66.29, 117.25, 135.37, 154.78 and 211.39; *m*/*z* (CI) 424 (M^++1, 100%) and 366 (13). Further elution yielded recovered starting material **64** (6 mg, 26%).

Methyl (1*RS*,2*SR*,4*RS*,5*SR*)-1-butyl-4-prop-2′-enyl-2-*tert*-butyldimethylsilyloxymethyl-3-oxo-8-azabicyclo[3.2.1]-octane-8-carboxylate 66

Potassium *tert*-butoxide (28 mg, 0.25 mmol) was added to the tropanone **65** (32 mg, 0.076 mmol) in dichloromethane (1.5 cm^3) and methanol (0.75 cm^3) at ambient temperature. After 36 h, saturated aqueous ammonium chloride was added, and the mixture extracted with dichloromethane. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (95 : 5) gave the title compound **66** (18 mg, 56%) as a colourless oil. Found: M^+ + H, 424.2884. $C_{23}H_{42}NO_4Si$ requires *M*, 424.2883); υ_{max} 1708, 1443, 1377, 1257, 1096, 839 and 779 cm^{-1}; δ_H (500 MHz, $CDCl_3$) −0.03 and −0.01 (each 3H, s, $SiCH_3$), 0.81 (9 H, s, $C(CH_3)_3$), 0.89 (3 H, t, *J* 7 Hz, 4′-H_3), 1.15–1.39 (4 H, m, 2′-H_2 and 3′-H_2), 1.46 (1 H, m), 1.61–1.73 (2 H, m), 1.81–1.91 (2 H, m), 1.95 and 2.12 (each 1 H, m, 1′-H), 2.55–2.66 (2 H, m, 2-H and 1″-H), 2.74 (1 H, dt, *J* 8.5 Hz, 4.5 Hz, 4-H_{ax}), 3.70 (3 H, s, OCH_3), 3.77 (1 H, t, *J* 9.5 Hz, 2-CH), 3.92 (1 H, dd, *J* 10.5 Hz, 6.5 Hz, 2-CH′), 4.46 (1 H, dd, *J* 7.5 Hz, 4 Hz, 5-H), 5.00–5.09 (2 H, m, 3″-H_2) and 5.78 (1 H, m, 2″-H); *m*/*z* (CI) 424 (M^+ + 1, 100%).

Methyl (1*RS*,2*SR*,4*RS*,5*SR*)- and (1*RS*,2*RS*,4*RS*,5*SR*)-1-butyl-2-hydroxymethyl-4-prop-2′-enyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylates 67 and 68

Following the procedure outlined for the synthesis of alcohol **40**, *tert*-butyldimethylsilyl ether **65** (17 mg, 0.040 mmol), after chromatography using light petroleum–ethyl acetate (75 : 25) as eluent gave the title compound **68** (3 mg, 24%), as a colourless oil. Found: $M^+ + H$, 310.2015. $C_{17}H_{28}NO_4$ requires *M*, 310.2018); υ_{max} 3477, 1700, 1443, 1358, 1193 and 1103 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.86 (3 H, t, *J* 7.5 Hz, 4′-H_3), 1.08–1.45 (5 H, m), 1.47–1.61 (2 H, m), 1.68–1.94 (3 H, m), 2.29 (1 H, m), 2.58–2.69 (2 H, m), 2.88 (1 H, m, 2-H), 3.74 (3 H, s, OCH_3), 3.63–3.81 (2 H, m, 2-CH_2), 4.41 (1 H, dd, *J* 4.5 Hz, 6 Hz, 5-H), 5.01–5.12 (2 H, m, 3″-H_2) and 5.75 (1 H, m, 2″-H); *m*/*z* (CI) 327 (M^+ + 18, 21%), 311 (20) and 310 (100). The second eluted product was the title compound **67** (4 mg, 32%), a colourless oil. Found: $M^+ + H$, 310.2021. $C_{17}H_{28}NO_4$ requires *M*, 310.2018); υ_{max} 3460, 1704, 1446 and 1379 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.91 (3 H, t, *J* 7, 4′-H_3), 1.10–1.43 (4 H, m), 1.51 (1 H, m), 1.62–1.93 (3 H, m), 1.94–2.06 (2 H, m), 2.30 (1 H, m), 2.45 (1 H, t, *J* 5 Hz, 2-H), 2.66–2.78 (2 H, m), 3.71 (3 H, s, OCH_3), 3.82 (1 H, dd, *J* 12 Hz, 4, 2-CH), 3.94 (1 H, dd, *J* 12 Hz, 5.5 Hz, 2-CH′), 4.50 (1 H, dd *J* 7.5 Hz, 3.5 Hz, 5-H), 5.02–5.11 (2 H, m, 3″-H_2) and 5.76 (1 H, m, 2″-H); δ_C (75 MHz, $CDCl_3$) 14.04, 21.74, 23.23, 26.47, 29.78, 33.95, 37.17, 52.54, 54.74, 58.38, 61.21, 63.57, 66.00, 116.72, 128.35, 135.26 and 156.53; *m*/*z* (CI) 327 (M^++18, 3%), 311 (20) and 310 (100).

Following this procedure, *tert*-butyldimethylsilyl ether **66** (15 mg, 0.035 mmol) gave the alcohol **68** (2 mg, 18%) then the more polar alcohol **67** (2 mg, 18%).

Methyl (1*RS*,2*SR*,4*SR*,5*SR*)-1-butyl-2-*tert*-butyldimethylsilyloxymethyl-4-methoxycarbonyl-methyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate 69

Potassium bis(trimethylsilyl)amide (6.5 cm^3,15% in tetrahydrofuran, 4.89 mmol) was added to the ketone **64** (350 mg, 0.914 mmol) in tetrahydrofuran (11 cm^3) at −78 °C. The mixture was allowed to warm to 5 °C over 90 min, then recooled to −78 °C. Methyl bromoacetate (1.4 cm^3, 15.15 mmol) was added and the mixture warmed to ambient temperature over 2 h. Saturated aqueous ammonium chloride was added and the mixture extracted with ethyl acetate. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (95 : 5) gave first recovered starting material **64** (136 mg, 39%) and then the title compound **69** (244 mg, 58%), as a colourless oil. Found: $M^+ + H$, 456.2774. $C_{23}H_{42}NO_6Si$ requires *M*, 456.2781); υ_{max} 1743, 1706, 1444, 1381, 1256, 1098 and 838 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.01 and 0.04 (each 3 H, s, $SiCH_3$), 0.84 (9 H, s, $C(CH_3)_3$), 0.90 (3 H, t, *J* 7.5 Hz, 4′-H_3), 1.14–1.40 (4 H, m, 2′-C_2 and 3′-C_2), 1.54 and 1.72 (each 1 H, m), 1.88–2.05 (3 H, m), 2.32 (1 H, dd, *J* 17.5 Hz, 4 Hz, 4-CH), 2.35 (1 H, m, 1′-H), 2.56–2.63 (2 H, m, 2-H, 4-CH′), 2.77 (1 H, dd, *J* 11 Hz, 4 Hz, 4-H_{eq}), 3.61 and 3.69 (each 3 H, s, OCH_3), 3.79 (1 H, dd, *J* 10.5 Hz, 7 Hz, 2-CH), 3.94 (1 H, dd, *J* 10.5 Hz, 6.5 Hz, 2-CH′) and 4.65 (1 H, d, *J* 7 Hz, 5-H); δ_C (75 MHz, $CDCl_3$) −5.59, −5.51, 14.10, 18.25, 23.28, 25.89, 26.87, 27.34, 33.19, 34.37, 36.50, 51.84, 54.63, 57.25, 61.76, 64.48, 66.14, 154.46, 171.57 and 210.87; *m*/*z* (CI) 473 (M^+ + 18, 4%), 457 (36) and 456 (100).

Methyl (1*RS*,2*SR*,4*RS*,5*SR*)-1-butyl-2-*tert*-butyldimethylsilyloxymethyl-4-methoxycarbonyl-methyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate 70 and methyl (1*RS*,2*RS*,4*RS*,5*SR*)-1-butyl-4-methoxycarbonylmethyl-2-methoxymethyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate 71

Potassium *tert*-butoxide (5 mg, 0.045 mmol) was added to the ketoester **69** (29 mg, 0.064 mmol) in a mixture of dichloromethane (1.0 cm^3) and methanol (0.5 cm^3) at ambient temperature. After 24 h, saturated aqueous ammonium chloride was added and the mixture extracted with dichloromethane. The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography using light petroleum–ethyl acetate (90 : 10) gave the title compound **70** (19 mg, 66%), as a colourless oil. Found: $M^+ + H$, 456.2784. $C_{23}H_{42}NO_6Si$ requires *M*, 456.2781); υ_{max} 1744, 1709, 1442, 1371, 1256, 1101, 839 and 778 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.04 and 0.06 (each 3 H, s, $SiCH_3$), 0.87 (9 H, s, $C(CH_3)_3$), 0.93 (3 H, t, *J* 7 Hz, 4′-H_3), 1.15–1.50 (5 H, m), 1.61–1.84 and 1.87–2.10 (each 2 H, m), 2.13 (1 H, dd, *J* 16 Hz, 6.5 Hz, 4-CH), 2.31 (1 H, m, 1′-H), 2.66 (1 H, t, *J* 7 Hz, 2-H), 2.80 (1 H, dd, *J* 16.5 Hz, 7 Hz, 4-CH′), 3.25 (1 H, m, 4-H_{ax}), 3.69 and 3.73 (each 3 H, s, OCH_3), 3.82 (1 H, dd, *J* 10.5 Hz, 8 Hz, 2-CH), 3.98 (1 H, dd, *J* 10.5 Hz, 6 Hz, 2-CH′) and 4.49 (1 H, dd, *J* 7 Hz, 4.5 Hz, 5-H); δ_C (75 MHz, $CDCl_3$) −5.58, −5.69, 14.09, 18.21, 22.27, 23.23, 25.82, 26.71, 30.82, 34.33, 36.17, 50.73, 51.83, 52.30, 59.50, 61.06, 64.49, 66.94, 154.57, 172.09 and 208.40; *m*/*z* (CI) 473 (M^+ + 18, 3%) and 456 (100). The second eluted product was the title compound **71** (2 mg, 9%), a colourless oil. Found: $M^+ + H$, 356.2076. $C_{18}H_{30}NO_6$ requires *M*, 356.2073; υ_{max} 1740, 1706, 1441, 1359 and 1119 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.96 (3 H, t, *J* 7 Hz, 4′-H_3), 1.23–1.61 (6 H, m), 1.76–1.96 (3 H, m), 2.13 (1 H, dd, *J* 16.5 Hz, 5.5 Hz, 4-CH), 2.46 (1 H, m, 1′-H), 2.81 (1 H, dd, *J* 16.5 Hz, 8 Hz, 4-CH′), 2.95 (1 H, m, 2-H), 3.14–3.24 (1 H, m, 4-H), 3.34 (3 H, s, OCH_3), 3.63 (1 H, dd, *J* 10 Hz, 3.5 Hz, 2-CH), 3.72 (1 H, m, 2-CH′), 3.74 and 3.81 (each 3 H, s, CO_2CH_3) and 4.44 (1 H, t, *J* 5.5 Hz, 5-H); δ_C (75 MHz, $CDCl_3$) 14.20, 23.12, 23.50, 25.27, 30.97, 31.12, 34.26, 51.22, 51.92, 52.59, 59.09, 60.78, 67.21, 67.84, 77.24, 155.11, 172.23 and 206.68; *m*/*z* (CI) 355 (M^+, 1.5%), 182 (82) and 181 (100).

Methyl (1*RS*,2*SR*,3*RS*,4*RS*,5*SR*)-1-butyl-2-*tert*-butyldimethylsilyloxymethyl-3-hydroxy-4-methoxy-carbonylmethyl-8-azabicyclo[3.2.1]octane-8-carboxylate 72

Following the procedure outlined for the reduction of ketone **21**, ketone **70** (65 mg, 0.143 mmol), after chromatography using light petroleum–ethyl acetate (90:10) as eluent gave the title compound **72** (48 mg, 74%), as a colourless oil. Found: $M^+ + H$, 458.2934. $C_{23}H_{44}NO_6Si$ requires *M*, 458.2938; υ_{max} 3471, 1741, 1710, 1684, 1448, 1385, 1254, 1100 and 838 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.00 and 0.02 (each 3 H, s, $SiCH_3$), 0.85 (9 H, s, $C(CH_3)_3$), 0.90 (3 H, t, *J* 7 Hz, 4′-H_3), 1.17–1.39 (4 H, m, 2′-H_2 and 3′-H_2), 1.61 (1 H, m, 6-H), 1.70 (1 H, m, 1′-H), 1.76 (1 H, td, *J* 12.5 Hz, 3.5 Hz), 1.95–2.04 (2 H, m), 2.10 (1 H, d, *J* 4 Hz, OH), 2.27 (1 H, m, 4-H), 2.32–2.48 (3 H, m, 7-H, 1′-H′ and 4-CH), 2.54 (1 H, dd, *J* 15, 11, 4-CH′), 3.26 (1 H, t, *J* 10.5 Hz, 2-CH), 3.60 and 3.67 (each 3 H, s, OCH_3), 3.91 (1 H, dd, *J* 11 Hz, 4 Hz, 2-CH′), 4.07 (1 H, dd, *J* 7.5 Hz, 2.5 Hz, 5-H) and 4.18 (1 H, t, *J* 4 Hz, 3-H); δ_C (75 MHz, $CDCl_3$) −5.42, −5.39, 14.14, 18.25, 21.82, 23.43, 25.92,

26.93, 33.87, 35.44, 36.22, 38.14, 51.81, 53.44, 53.98, 59.61, 61.15, 64.67, 67.89, 154.49 and 173.27; *m/z* (CI) 475 (M^+ + 18, 3%), 460 (7), 459 (26) and 458 (100).

Methyl (1*RS*,2*SR*,3*RS*,7*RS*,8*RS*)-1-butyl-2-hydroxymethyl-5-oxo-4-oxa-11-azatricyclo[6.2.1.0^{3,7}]-undecane-11-carboxylate 73

Following the procedure outlined for deprotection of the silyl ether **39**, silyl ether **72** (7 mg, 0.015 mmol), after chromatography using light petroleum–ethyl acetate (50 : 50) as eluent, gave the title compound **73** (4 mg, 84%) as a colourless oil. Found: M^+ + H, 312.1808. $C_{16}H_{26}NO_5$ requires *M*, 312.1811; υ_{max} 3472, 1778, 1760, 1705, 1686, 1448, 1383, 1190, 1160 and 1042 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.92 (3 H, t, *J* 7.5 Hz, 4′-H_3), 1.15–1.43 (4 H, m, 2′-H_2 and 3′-H_2), 1.54 (1 H, ddd, *J* 13.5 Hz, 10 Hz, 3.5 Hz), 1.75–1.89 (2 H, m), 1.94–2.10 (2 H, m), 2.16 (1 H, t, *J* 3.5 Hz, 2-H), 2.25 (1 H, d, *J* 18 Hz, 6-H), 2.40 (1 H, m, 1′-H′), 2.69–2.82 (3 H, m), 3.64 (3 H, s, OCH_3), 3.69 (1 H, m, 2-CH), 3.95 (1 H, dt, *J* 12.5 Hz, 4.5 Hz, 2-CH′), 4.28 (1 H, dd, *J* 8 Hz, 5.5 Hz, 8-H) and 4.73 (1 H, d, *J* 5.5 Hz, 3-H); δ_C (75 MHz, $CDCl_3$) 14.08, 21.24, 23.28, 26.31, 33.41, 34.90, 36.22, 37.67, 47.51, 52.43, 58.09, 61.74, 63.78, 81.65, 155.30 and 176.23; *m/z* (EI) 311 (M^+, 17%), 269 (45) and 182 (100).

Methyl (1*RS*,2*SR*,3*RS*,7*RS*,8*RS*)-2-acetoxymethyl-1-butyl-5-oxo-4-oxa-11-azatricyclo[6.2.1.0^{3,7}]-undecane-11-carboxylate 74

Following the procedure outlined for the acetylation of alcohol **44**, the alcohol **73** (4.5 mg, 0.014 mmol), after chromatography using light petroleum–ethyl acetate (65 : 35) as eluent, gave the title compound **74** (3.5 mg, 69%) as a colourless oil. Found: M^+, 353.1829. $C_{18}H_{27}NO_6$ requires *M*, 353.1838; υ_{max} 1782, 1741, 1705, 1446, 1380, 1238, 1189, 1163 and 1038 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.91 (3 H, t, *J* 7 Hz, 4′-H_3), 1.21 (1 H, m, 2′-H), 1.30–1.39 (3 H, m, 2′-H and 3′-H_2), 1.54 (1 H, m), 1.73–1.87 (2 H, m, 9-H and 1′-H), 1.95 (1 H, td, *J* 13 Hz, 3 Hz), 2.04 (3 H, s, CH_3CO), 2.13 (1 H, ddd, *J* 16 Hz, 9.5 Hz, 6.5 Hz), 2.29 (1 H, d, *J* 18 Hz, 6-H), 2.44 (1 H, dd, *J* 9 Hz, 3.5 Hz, 2-H), 2.43 (1 H, m, 1′-H), 2.72 (1 H, dd, *J* 18 Hz, 8 Hz, 6-H′), 2.86 (1 H, m, 7-H), 3.63 (3 H, s, OCH_3), 3.93 (1 H, dd, *J* 12 Hz, 9 Hz, 2-CH), 4.30 (1 H, t, *J* 6 Hz, 8-H), 4.43 (1 H, dd, *J* 12 Hz, 4 Hz, 2-CH′) and 4.57 (1 H, d, *J* 5.5 Hz, 3-H); *m/z* (EI) 354 (M^+ + 1, 5%), 353 (9), 311 (17), 183 (19), 182 (100) and 181 (85).

Methyl (1*RS*,2*SR*,3*RS*,7*RS*,8*RS*)-1-butyl-2-iodomethyl-5-oxo-4-oxa-11-azatricyclo[6.2.1.0^{3,7}]undecane-11-carboxylate 75

Following the procedure outlined for the preparation of iodide **38**, the alcohol **73** (12 mg, 0.039 mmol), after chromatography using light petroleum–ethyl acetate (85 : 15) as eluent gave the title compound **75** (13 mg, 80%) as colourless oil. Found: M^+ + H, 422.0824. $C_{16}H_{25}INO_4$ requires *M*, 422.0828); υ_{max} 1782, 1701, 1443, 1379, 1188, 1162 and 985 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.93 (3 H, t, *J* 7.2 Hz, 4′-H_3), 1.16–1.42 (4 H, m, 2′-H_2 and 3′-H_2), 1.52 (1 H, m), 1.72–1.87 (2 H, m, 9-H and 1′-H), 1.94 (1 H, td, *J* 13 Hz, 3 Hz), 2.13 (1 H, ddd, *J* 16 Hz, 9.5 Hz, 6.5 Hz), 2.29 (1 H, d, *J* 18 Hz, 6-H), 2.43–2.55 (1 H, m), 2.48 (1 H, dd, *J* 11.5 Hz, 2 Hz), 2.68–2.77 (2 H, m, 2-CH and 6-H), 2.85 (1 H, m 7-H), 3.63 (3 H, s, OCH_3), 3.74 (1 H, dd, *J* 10.5 Hz, 2 Hz, 2-CH′), 4.29 (1 H, t, *J* 6.5 Hz, 8-H) and 4.75 (1 H, d, *J* 5.5 Hz, 3-H); *m/z* (EI) 422 (M^+ + 1, 1%), 294 (80) and 182 (100).

Crystal data for 22‡

$C_{20}H_{24}Cl_3NO_5S$, colourless, acicular, m.p. 144–145 °C, crystal dimensions 0.550 × 0.150 × 0.010 mm, monoclinic, $a = 10.716(1)$, $b = 20.066(2)$, $c = 10.835(1)$ Å, $\beta = 91.767(9)°$, $U = 2328.8(4)$ Å^3, space group $P2_1/c$ (No. 14), $Z = 4$, F(000) = 1032. $\omega/2\theta$ scans of (1.21 + 0.30 tanθ)° were made at a speed of 16.0° min^{-1} at 296 ± 1 K; 2963 reflections were collected with $0° < 2\theta < 120.2°$; of these 2804 were unique and had $I > 3.0\sigma(I)$, and were used in the analysis. The data were collected on a Rigaku AFC5R diffractometer using graphite monochromated Cu Kα radiation. Lorentz, polarisation and linear intensity drift (maximum 13.0%) corrections were applied. The structure was solved by direct methods. The refinement converged with $R = 0.077$, $R_\omega = 0.078$. All calculations were performed using the TEXSAN crystallographic software package of the Molecular Structure Corporation (1985). Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the CCDC‡.

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21 Details of the X-ray structure of the tricyclic hydroxyamide **40** have already been described (see ref. 14), and the data deposited with the CCDC.

22 Attempts to reduce the corresponding *S*-methyl xanthate or iodide under free-radical conditions led to complex mixtures of products.