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Synthesis of tricyclic analogues of methyllycaconitine using ring closing metathesis to append a B ring to an AE azabicyclic fragment

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The synthesis of several ABE tricyclic analogues of the alkaloid methyllycaconitine **1** is reported. The analogues contain two key pharmacophores: a homocholine motif formed from a tertiary *N*-ethyl amine in a 3-azabicyclo-[3.3.1]nonane ring system and a 2-(3-methyl-2,5-dioxopyrrolidin-1-ly)benzoate ester. The synthesis of the ABE tricyclic analogues of MLA **1** began with selective allylation at C-3 of **3** to produce allyl β-keto ester **4**. Double Mannich reaction of **4** with ethylamine and formaldehyde produced bicyclic amine **5**. The C-9 ketone of bicyclic amine **5** was selectively reduced to form bicyclic alcohols **6** and **7** which were subsequently allylated to form dienes **8** and **9**. Ring closing metathesis of dienes **8** and **9** afforded tricyclic ethers **11** and **12**, respectively, the C-8 ester of which was reduced to a hydroxymethyl group to form ABE tricyclic analogues **13** and **14**. Addition of allylmagnesium bromide to the C-9 ketone of **20** afforded dienes **21** and **22**, which underwent ring closing metathesis to form tricyclic esters **23** and **24**, respectively. Reduction of the C-8 ethyl ester of **23** and **24** to a hydroxymethyl group afforded diols **25** and **26** respectively. The 2-(3-methyl-2,5-dioxopyrrolin-1-ly)benzoate ester was introduced by conversion of alcohols **13**, **14**, **25** and **26**, to the anthranilate esters **16**, **17**, **27** and **28** using *N*-(trifluoroacetyl)-anthranilic acid **15** followed by fusion with methylsuccinic anhydride to afford the substituted anthranilates **18**, **19**, **29** and **30** containing the key 2-(3-methyl-2,5-dioxopyrrolidin-1-ly)benzoate ester pharmacophore.

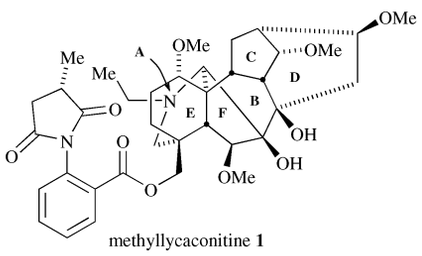
Introduction

Methyllycaconitine **1** is the principle toxin in *Delphinium brownii* and is found in at least 30 *Delphinium* species as well as in *Consolida ambigua* and *Inaularoyaleana*.[1,2] First discovered from *Delphinium brownii* by Manske[3] in 1938 and its formula correctly determined by Goodson[4] in 1943, it is the 2-[2-(*S*)-methylsuccinimido]benzoate ester of the norditerpenoid alkaloid lycoctonine **2**. Methyllycaconitine **1** contains a piperidine (E) and cyclohexane (A) ring in a 3-azabicyclo[3.3.1]nonane motif. Methyllycaconitine's primary mode of action is by competitive blockade at nicotinic acetylcholine receptors (nAchRs). The neuromuscular action of methyllycaconitine **1** is almost completely destroyed if the aromatic ester functionality is cleaved. Comparison of the neuromuscular activity of methyllycaconitine **1** with its parent alkaloid lycoctonine **2** established that lycoctonine **2** has approximately 2000 times less affinity for rat neuronal α7 subtype nAChRs than its *N*-substituted anthranilate ester methyllycaconitine **1**.[5]

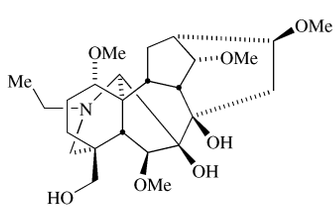
Methyllycaconitine **1** displays specific reversible, competitive antagonistic activity towards α-bungarotoxin-sensitive nAChRs.[5] The exceptional potency of methyllycaconitine **1** for α-bungarotoxin-sensitive neuronal nAChRs renders methyllycaconitine **1** a unique probe for discrimination of these particular nAChRs. Most nonpeptide nAChR antagonists act noncompetitively at the level of the nicotinic channel, however, competitive antagonists offer two distinct advantages over channel-blocking, noncompetitive antagonists: they tend to be more specific and they provide excellent correlation between binding data and functional potency.[5] The reversibility of the effects of methyllycaconitine **1**, along with its relatively high selectivity for neuronal nAChRs over muscular nAChRs, make it an invaluable tool, especially in the elucidation of α-bungarotoxin-sensitive nAChRs in mammalian systems.[5]

Methyllycaconitine **1** also has a much higher affinity for α-bungarotoxin-sensitive insect nAChRs than for α-bungarotoxin-sensitive rat neuronal tissue preparations[5–8] thus establishing methyllycaconitine **1** as a possible lead target for the development of insecticides. The high toxicity of methyllycaconitine **1** to mammals prevents its use an agrochemical, however, if the inhibitory action of methyllycaconitine is localised in a small toxophoric section of the molecule, a subunit of methyllycaconitine **1** based on this section may have the desired toxophoric properties, yet be significantly lower in toxicity to mammals. The synthesis of analogues of methyllycaconitine **1** as lead compounds for the development of insecticides and as pharmacological agents to probe the subtype selectivity of nAChRs continues to attract attention from synthetic chemists.

The *N*-substituted anthranilate ester moiety is an essential structural feature for insecticidal and pharmacological activity. It has also been proposed that at physiological pH the tertiary amine in the homocholine motif embedded in the AE rings of



methyllycaconitine **1**



lycoctonine **2**

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methyllycaconitine **1** is protonated and therefore mimics acetylcholine and that the (*S*)-methylsuccinimido ring may help to maintain the correct geometry between the tertiary nitrogen atom of the E ring in the alkaloid with the carbonyl oxygen of the ester bond.[9] We therefore herein report the full details[10] of the synthesis of several tricyclic analogues of methyllycaconitine **1** containing the key 2-(3-methyl-2,5-dioxopyrrolin-1-yl)benzoate ester in which an additional seven membered ring (a B ring) is appended to a 3-azabicyclo[3.3.1]nonane framework (the AE rings). Incorporation of the *N*-substituted anthranilate ester and the *N*-ethyl group embedded in the homocholine motif, into a conformationally restricted framework was envisaged to enhance the biostability, selectivity and potency of previously prepared simpler bicyclic AE analogues. Encouragement for our synthetic work is provided by a report that an ABE tricyclic analogue of methyllycaconitine **1** was more potent than an AE bicyclic analogue, however, the synthesis and characterisation of the ABE tricyclic analogue was not described.[11]

A total synthesis of methyllycaconitine **1** has not been reported to date, however, several semi-syntheses of methyllycaconitine **1** from its parent alkaloid lycoctonine **2** have been reported by Blagbrough and co-workers[12] and others.[13]

Simple E ring analogues of methyllycaconitine **1** containing the homocholine motif have been prepared by Bergmeier *et al*.[14] containing a piperidine ring substituted at C-3 with a 2-(3-methyl-2,5-dioxopyrrolin-1-yl)benzoate ester. AE bicyclic analogues of methyllycaconitine **1** have also been prepared by Blagbrough and co-workers[15] in which the 3-azabicyclo-[3.3.1]nonane framework was assembled *via* a double Mannich reaction using 2-oxo-cyclohexane-1-carboxylate, ethylamine and formaldehyde. The azabicyclo[3.3.1]nonane bicyclic skeleton was then extended from the ketone at C-5 by the addition of Grignard, Wittig and alkyllithium reagents.[16]

Attention for the synthesis of tricyclic analogues of methyllycaconitine **1** has mainly concentrated on assembly of AEF analogues. One approach by Kraus and Dneprovskaia[17] involved carrying out a similar Mannich reaction on a spirocyclic enone whereas Whiting and co-workers[18] made use of an isoxazolidine intermediate. Our research group reported[19] the first examples of tricyclic analogues of methyllycaconitine **1** containing an ABE framework by using a Wacker oxidation–aldol strategy to append a six membered B ring to a 3-azabicyclo[3.3.1]framework (the AE rings). We therefore herein report the synthesis of ABE tricyclic analogues of the alkaloid methyllycaconitine **1** using Grubbs ring closing metathesis to construct the key seven membered B ring.

Results and discussion

The first series of analogues, prepared from ethyl 2-oxocyclohexanecarboxylate **3** (Scheme 1), contained a seven membered ether ring appended to the AE fragment. Treatment of **3** with LDA (two equivalents) in THF at 0 °C followed by the addition of allyl bromide afforded the allylated product **4**[20] in 93% yield providing a significantly better yield than that obtained using the procedure reported by Huckin and Weiler.[21] Heating allyl keto ester **4** with ethylamine and formaldehyde then effected a double Mannich reaction[22] affording azabicyclic compound **5** in 22% yield. Sodium borohydride reduction of ketone **5** then afforded a 1 : 1.2 mixture of the secondary alcohols **6** and **7** in 93% combined yield that were readily separated by flash chromatography.

Comparison of the ^{13}C NMR data for alcohols **6** and **7** can be used to determine the stereochemistry of the 9-OH. The 9-OH has a shielding effect on the chemical shift of the carbons in the bicyclic ring structure that are *syn* to the hydroxyl group. This γ-gauche effect has been extensively studied in 3-azabicyclo[3.3.1]nonane ring systems.[23–26] The chemical shift of the ring carbons that are *syn* to the hydroxyl group are shifted upfield when compared to the chemical shift of the non-hydroxyl ring system. Both diastereomers **6** and **7** exhibited similar C-7 shifts consistent with a chair–chair conformation of the azabicyclo[3.3.1]nonane ring system as depicted in Fig. 1.[24,26] The resonances assigned to C-2 and C-4 of the azabicyclo[3.3.1]nonane ring are shifted 4.9 and 6.3 ppm upfield respectively in **6** relative to **7** due to the shielding γ-effect of the C-9 hydroxyl group. Consistent with this analysis, the chemical shifts of C-6 and C-8 appear upfield in **7** relative to **6**.

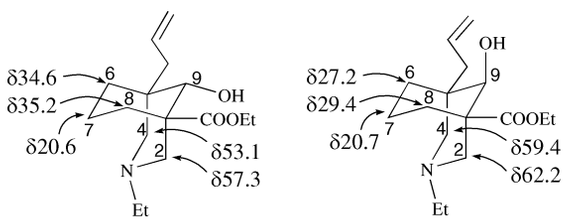
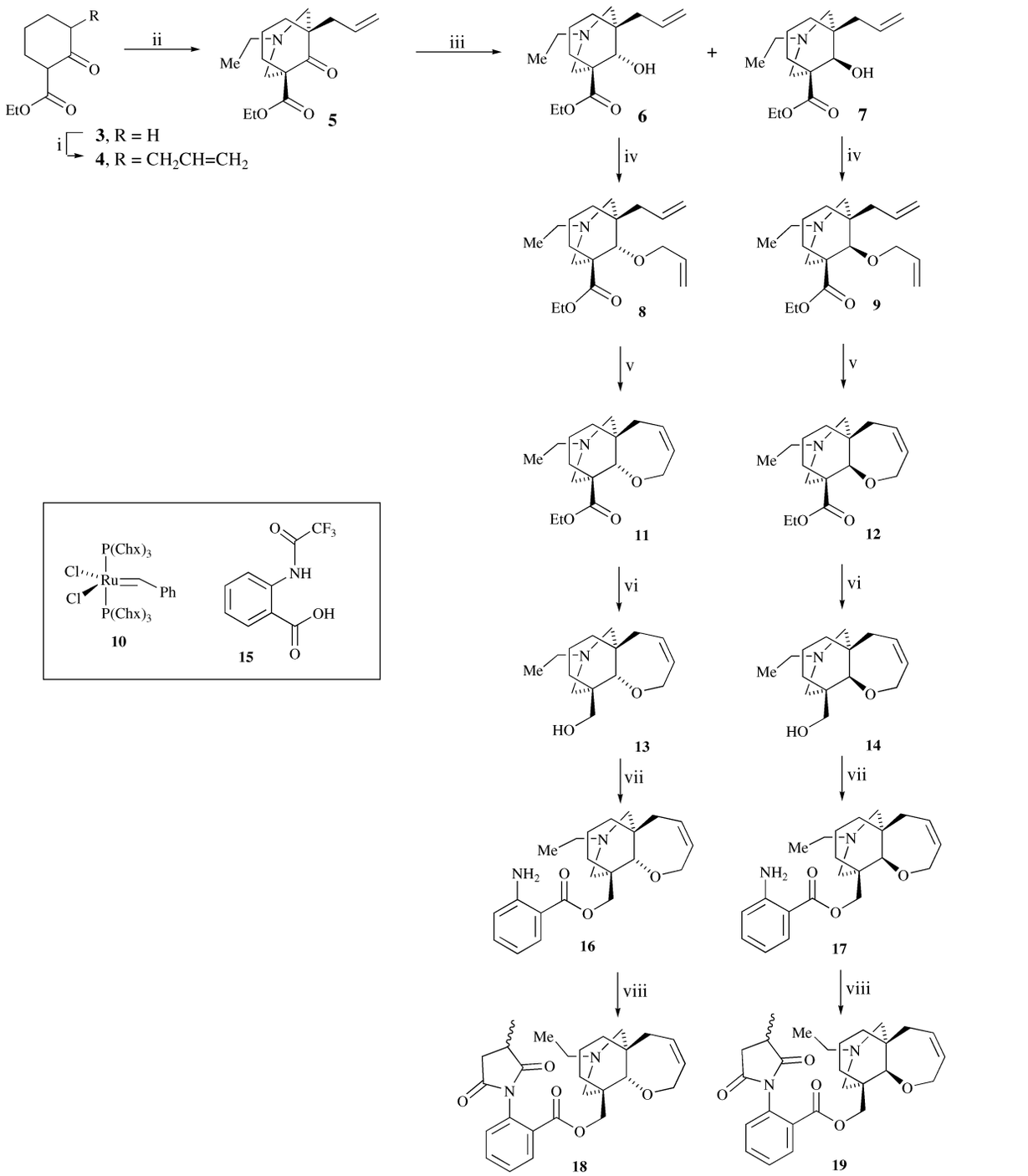


Fig. 1 Selected ^{13}C NMR chemical shifts of 9-hydroxyazabicyclo-[3.3.1]nonane diastereomers **6** and **7**.

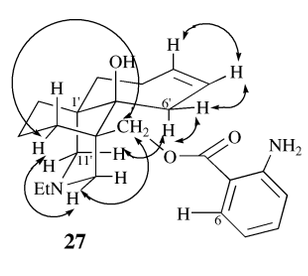
With alcohols **6** and **7** in hand, the next step of the synthesis involved allylation of the free hydroxyl groups. Alcohols **6** and **7** were individually allylated using four equivalents of both sodium hydride and allyl bromide to afford the desired allyl ethers **8** and **9** in 72% and 73% yield respectively for which the high resolution mass spectra, IR, ^{1}H and ^{13}C NMR data supported the assigned structures. Subjecting diene **8** to ring closing metathesis[27] using 5% Grubbs' catalyst **10**[28] in dichloromethane at room temperature for 22 h afforded the 7-membered ether **11** in an excellent 90% yield. A molecular ion at *m*/*z* 293.2008 in the high resolution mass spectrum corresponded to the molecular formula $C_{17}H_{27}NO_3$ clearly establishing that ring closing metathesis had taken place by the loss of one equivalent of ethylene from the starting diene **8**. In the ^{1}H NMR spectrum, the vinylic protons for diene **8** were absent and had been replaced by a two proton multiplet at δ_H 5.66–5.82 assigned to the olefinic protons 3-H and 4-H. The ^{13}C NMR spectrum of **11** only exhibited two olefinic methine carbons at δ_C 129.1 and 130.4 assigned to C-3 and C-4 respectively. Similar treatment of diene **9** with Grubbs' catalyst afforded tricyclic ether **12** in 96% yield.

Reduction of the esters **11** and **12** with lithium aluminium hydride smoothly afforded the primary alcohols **13** and **14** of known relative stereochemistry. Use of *N*-(trifluoroacetyl)-anthranilic acid **15** to prepare the anthranilate esters **16** and **17** following our two-step protocol[29] proceeded in good yield (62% and 67% respectively). Finally fusion of the anthranilate ester **16** with methylsuccinic anhydride[15] afforded the tricyclic analogue **18** containing a 7-membered ether B-ring with the same *trans* AB ring fusion as present in methyllycaconitine **1**. Diastereomeric anthranilate ester **17** underwent similar conversion to analogue **19** containing *cis* AB ring fusion.

A second series of ABE-analogues containing a carbocyclic B-ring were afforded by a separate sequence starting from butenyl substituted ketone **20**[19] (Scheme 2). Careful addition of 1.05 equivalents of allylmagnesium bromide to **20** at 0 °C over 30 min followed by stirring at room temperature for 40 h afforded the allylated products **21** and **22** in 80% combined yield as a 2.2 : 1 ratio of diastereomers, which were separable by flash chromatography. Ring closing metathesis[27] of dienes **21** and **22** afforded the respective carbocyclic products **23** and **24** in excellent yield that were then reduced with lithium aluminium hydride to give diols **25** and **26** (69% and 75% yield respectively). Selective esterification of the neo-pentyl alcohols in **25** and **26** using *N*-(trifluoroacetyl)anthranilic acid **15**[29] afforded the anthranilate esters **27** and **28** in 78% and 72% yield respectively. The NOESY spectrum of ester **27** clearly displayed a strong reciprocal NOE between C6′ and C11′ protons consistent with the *trans* AB ring junction (Fig. 2). Reaction of **27** with methylsuccinic anhydride afforded analogue **29** in 90% yield



Scheme 1 *Reagents, conditions and yields*: (i) LDA, allyl bromide, THF, 0 °C, 93%; (ii) $EtNH_2$, CH_2O, EtOH, reflux, 22%; (iii) $NaBH_4$, THF, H_2O, 0 °C, **6**, 42%, **7**, 51%; (iv) NaH, allyl bromide, THF, room temp., 48 h, **8**, 72%, **9**, 73%; (v) 5% **10**, room temp., 22 h, **11**, 90%, 18 h, **12**, 96%; (vi) $LiAlH_4$, THF, 0 °C, **13**, 83%, **14**, 91%; (vii) **15**, DCC, DMAP, CH_3CN, 40 °C, 24 h then $NaBH_4$, EtOH, room temp., 2 h, **16**, 62%, **17**, 67%; (viii) methylsuccinic anhydride, 125 °C, 8 h, **18**, 60%, 3 h, **19**, 62%.



NOEs

Fig. 2 Selected NOEs observed for tricyclic ester **27**.

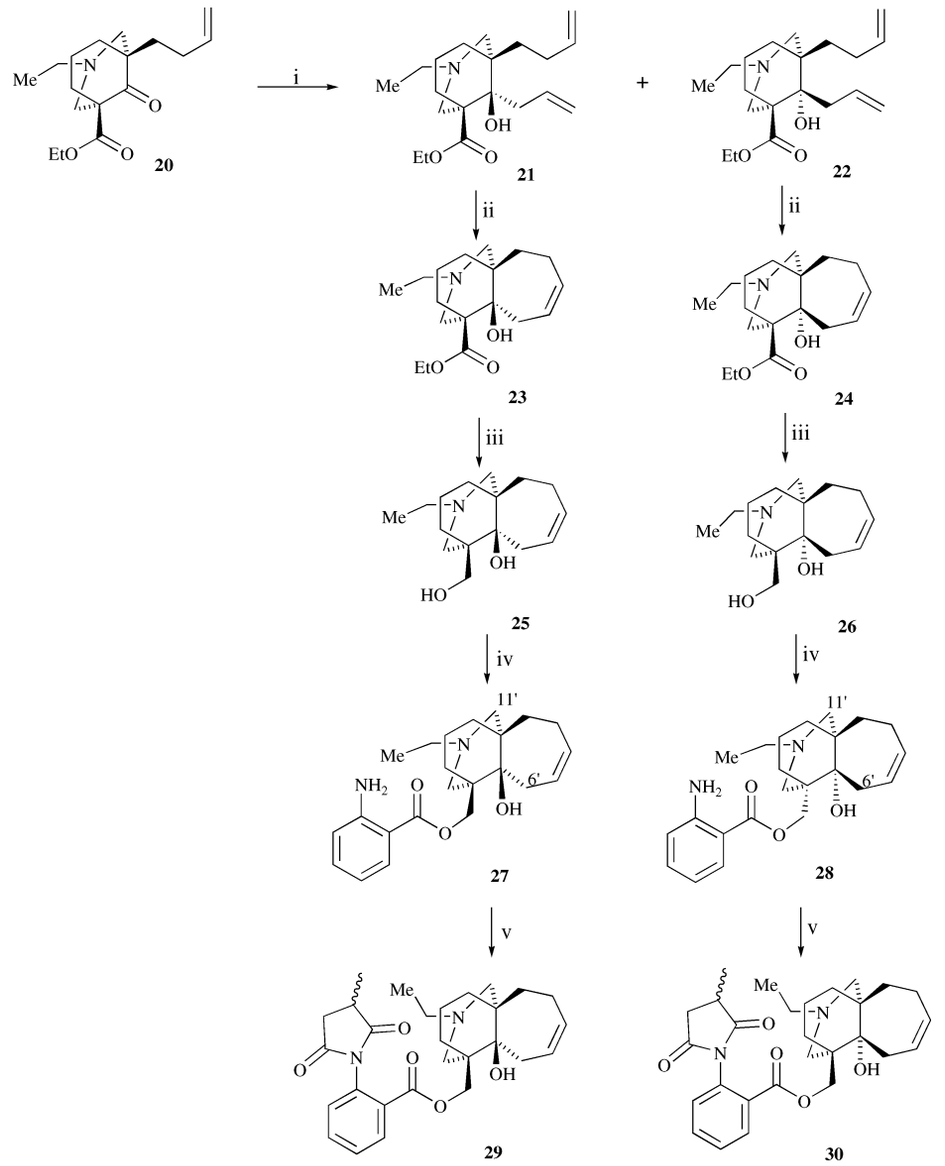
exhibiting *trans* AB ring fusion present in methyllycaconitine **1**. Similar conversion of anthranilate **28** to tricyclic analogue **30** containing *cis* AB ring fusion proceeded in 82% yield.

In summary, the successful synthesis of four stereochemically divergent ABE tricyclic analogues **18**, **19**, **29** and **30** of methyllycaconitine **1** has been reported using a double Mannich cyclisation followed by the Grubbs ring closing metathesis to introduce the 7-membered B-ring. The evaluation of these compounds and intermediates at the α7 nAChR subtype for binding affinity in competitive ligand binding assays and functional potency against recombinant protein expressed in *Xenopus* oocytes will be reported elsewhere.

Experimental

General

Mps were determined on a Koffler hot-stage apparatus and are uncorrected. IR spectra were recorded using a Perkin-Elmer



Scheme 2 *Reagents, conditions and yields*: (i) allylmagnesium bromide, THF, 0 °C, **21**, 55%, **22**, 25%; (ii) 10% **10**, room temp., 24 h, **23**, 97%, 18 h, **24**, 99%; (iii) $LiAlH_4$, THF, 0 °C, 20 h, **25**, 69%, 24 h, **26**, 75%; (iv) **15**, DCC, DMAP, CH_3CN, 40 °C, 24 h then $NaBH_4$, EtOH, room temp., 2 h, **27**, 78%, **28**, 72%; (v) methylsuccinic anhydride, 125 °C, 12 h, **29**, 90%, 3 h, **30**, 82%.

1600 Fourier Transform IR spectrophotometer as thin films between sodium chloride plates. Absorption spectra are expressed in wavenumbers (cm^{-1}) with the following abbreviations: s = strong, m = medium, w = weak and br = broad. ^1H NMR spectra were recorded on a Bruker AC 200 (200 MHz) or a Bruker DRX 400 (400 MHz) spectrometer at ambient temperature. All *J*-values are given in Hz. Chemical shifts are expressed in parts per million downfield shift from tetramethylsilane as an internal standard, and reported as position (δ_H), relative integral, multiplicity (s = singlet, br s = broad singlet, d = doublet, dd = double doublet, ddd = double double doublet, t = triplet, q = quartet, m = multiplet) and assignment. ^{13}C NMR spectra were recorded on a Bruker AC 200 (50.3 MHz) or a Bruker DRX 400 (100.5 MHz) spectrometer at ambient temperature with complete proton decoupling. Chemical shifts are expressed in parts per million downfield shift from tetramethylsilane as an internal standard and reported as position (δ_C), multiplicity (aided by DEPT 135, DEPT 90, COSY and HETCOR experiments) and assignment. Low resolution mass spectra were recorded on a VG70-250S, a VG70-SD or an AEI model MS902 double focusing magnetic sector mass spectrometer operating with an ionisation potential of 70 eV. High resolution mass spectra were recorded at nominal resolutions of 5000 to 10000 as appropriate. Major fragments are given as percentages relative to the base peak and assigned where possible. Ionisation methods employed were either electron impact or chemical ionisation with ammonia or methane as reagent gas (CI). Low resolution chemical ionisation mass spectra were also recorded on a Hewlett Packard 5989A mass spectrometer using ammonia as reagent gas with the sample dissolved in methanol. Elemental analyses were carried out by the Microanalytical Unit at the Research School of Chemistry, Australian National University, Canberra. Flash chromatography was performed using Merck Kieselgel 60 (230–400 mesh) with the indicated solvents. Thin layer chromatography (TLC) was performed using 0.2 mm thick precoated silica gel plates (Merck Kieselgel 60 F_{254} or Riedel-de Haen Kieselgel S F_{254}). Compounds were visualised by ultraviolet fluorescence or by staining with iodine or vanillin in methanolic sulfuric acid.

Ethyl 2-oxo-3-(2′-propenyl)cyclohexane-1-carboxylate (4)

n-BuLi (4.7 mL, 11.8 mmol, 2.5 M solution in hexane) was added dropwise to a solution of diisopropylamine (1.8 mL, 13 mmol) in dry THF (30 mL) at −78 °C. The reaction mixture was stirred at −20 °C for 0.5 h. A solution of ethyl 2-oxo-cyclohexane-1-carboxylate **3** (1.0 g, 5.9 mmol) in dry THF (5 mL)

was added dropwise and stirring was continued at 0 °C for 1 h. Allyl bromide (0.71 g, 5.9 mmol) was added and the mixture stirred at room temperature for 20 h. The reaction was quenched with distilled water (5 mL) followed by saturated ammonium chloride solution (20 mL), then extracted with ether (3 × 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate and the solvent removed at reduced pressure to afford an orange oil. Purification by flash chromatography (9 : 1 hexane : ethyl acetate) afforded the title compound **4** (1.15 g, 93%) as a pale yellow oil for which the ^{1}H NMR data were in agreement with the literature.[20]

Ethyl (1*R**,5*S**)-3-ethyl-9-oxo-5-(2′-propenyl)-3-azabicyclo-[3.3.1]nonane-1-carboxylate (5)

A mixture of ethyl 2-oxo-3-(2′-propenyl)cyclohexane-1-carboxylate **4** (500 mg, 2.4 mmol), ethylamine (359 mg, 2.4 mmol, 30% aq. v/v), and formaldehyde (398 mg, 4.8 mmol, 36% aq. v/v) in ethanol (40 mL) was heated under reflux for 30 h. After removal of the solvent at reduced pressure, the viscous dark yellow oil was dissolved in ether (50 mL) and extracted with 2 M hydrochloric acid (3 × 60 mL). The aqueous layer was made basic with 10% sodium hydroxide solution (150 mL) whilst cooling with ice, then extracted with ether (3 × 100 mL) and dried over anhydrous sodium sulfate. The solvent was removed at reduced pressure and the orange oil purified by flash chromatography using (9 : 1 hexane : ethyl acetate) to afford the *title compound* **5** (R_f 0.7) (150 mg, 22%) as a pale yellow oil [Found: C, 68.8; H, 9.0; N, 5.1. $C_{16}H_{25}NO_3$ requires C, 68.8; H 9.0; N, 5.0%]; ν_{max}(NaCl)/cm^{-1} 1738 (C=O, ester) and 1714 (C=O, ketone), 1640 (C=C); δ_H (400 MHz; $CDCl_3$) 1.10 (3H, t, *J* 7.1, NCH_2CH_3), 1.29 (3H, t, *J* 7.1, OCH_2CH_3), 1.48–1.56 (1H, m, 7B-H), 2.11–2.65 (6H, m, 6-CH_2, 8-CH_2, 1′-CH_2), 2.53 (2H, q, *J* 7.1, NCH_2CH_3), 2.86–3.04 (3H, m, 2-CH_2, 7A-H), 3.19–3.22 (2H, m, 4-CH_2), 4.20 (2H, q, *J* 7.1, OCH_2CH_3), 4.99–5.07 (2H, m, 3′-CH_2), 5.74–5.84 (1H, m, 2′-H); δ_C (100 MHz; $CDCl_3$) 17.6 (CH_3, NCH_2CH_3), 19.2 (CH_3, OCH_2CH_3), 25.4 (CH_2, C-7), 27.4 (CH_2, C-6), 32.6 (CH_2, C-8), 38.7 (CH_2, C-1′), 46.2 (quat., C-5), 53.9 (CH_2, NCH_2CH_3), 56.2 (quat., C-1), 64.0 (CH_2, OCH_2CH_3), 65.2 (CH_2, C-4), 66.7 (CH_2, C-2), 123.1 (CH_2, C-3′), 139.8 (CH, C-2′), 176.2 (quat., OC=O), 217.8 (quat., C-9); *m*/*z* (EI) 279 (M^+, 43%), 264 (M − CH_3, 54), 250 (M − CH_2CH_3, 12), 238 (M − C_3H_5, 83), 237 (M − C_3H_6, 15), 136 (100).

Ethyl (1*R**,5*S**,9*S**)-3-ethyl-9-hydroxy-5-(2′-propenyl)-3-aza-bicyclo[3.3.1]nonane-1-carboxylate (6) and ethyl (1*R**,5*S**,9*R**)-3-ethyl-9-hydroxy-5-(2′-propenyl)-3-azabicyclo[3.3.1]nonane-1-carboxylate (7)

To a solution of sodium borohydride (135 mg, 3.58 mmol) in THF (15 mL) and water (30 mL), at 0 °C, was added dropwise a solution of ethyl (1*R**, 5*S**)-3-ethyl-9-oxo-5-(2′-propenyl)-3-azabicyclo[3.3.1]nonane-1-carboxylate **5** (2 g, 7.16 mmol) in THF (15 mL). After 2 h water (30 mL) was added and the volatiles removed *in vacuo*. The remaining aqueous solution was extracted with ethyl acetate (3 × 50 mL) and the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and the solvent removed *in vacuo* to leave the crude mixture which was purified by flash chromatography (9 : 1 hexane–ethyl acetate) to give the title compounds **6** and **7**.

(i) The *title compound* **6** (R_f 0.25) (847 mg, 42%) was a clear oil [Found: C, 68.1; H, 9.4; N, 5.0. $C_{16}H_{27}NO_3$ requires C, 68.3; H, 9.7; N, 5.0%; Found (EI): M^+, 281.1983; $C_{16}H_{27}NO_3$ requires M^+ 281.1991]; ν_{max}(NaCl)/cm^{-1} 3532 (OH), 2917, 1728 (C=O, ester), 1638 (C=C) and 1453; δ_H (200 MHz; $CDCl_3$) 1.05 (3H, t, *J* 7.1, NCH_2CH_3), 1.25 (3H, t, *J* 7.1, OCH_2CH_3), 1.35–1.85 (4H, m, 1′-CH_2, 6B-H and 7B-H), 1.90–2.22 (3H, m, 6A-H and 8-CH_2), 2.24–2.49 (4H, m, 2B-H, 4B-H, and NCH_2CH_3), 2.54–2.75 (2H, m, 4A-H and 7A-H), 2.87 (1H, d, J_{gem} 11.0, 2A-H), 2.91 (1H, s, OH), 3.70 (1H, d, *J* 2.4, 9-H), 4.12 (2H, q, *J* 7.1, OCH_2CH_3), 4.98–5.12 (2H, m, 3′-CH_2) and 5.76–6.00 (1H, m, 2′-H); δ_C (50 MHz; $CDCl_3$) 12.5 (CH_3, NCH_2CH_3), 14.0 (CH_3, OCH_2CH_3), 20.6 (CH_2, C-7), 34.6 (CH_2, C-6), 35.2 (CH_2, C-8), 38.0 (quat., C-5), 41.9 (CH_2, C-1′), 48.8 (quat., C-1), 52.1 (CH_2, NCH_2CH_3), 53.1 (CH_2, C-4), 57.3 (CH_2, C-2), 60.6 (CH_2, OCH_2CH_3), 73.6 (CH, C-9), 117.5 (CH_2, C-3′), 134.2 (CH, C-2′) and 176.2 (quat., OC=O); *m*/*z* (EI) 281 (M^+, 15%), 280 (M − H, 22), 266 (M − CH_3, 43), 264 (M − OH, 15), 252 (M − CH_3CH_2, 38), 208 (M − CH_3CH_2OCO, 15) and 58 (100).

(ii) The *title compound* **7** (R_f 0.4) (1.017 g, 51%) was a clear oil [Found (EI): M^+, 281.1992; $C_{16}H_{27}NO_3$ requires M^+ 281.1991]; ν_{max}(NaCl)/cm^{-1} 3532 (OH), 1713 (C=O, ester), 1637 (C=C) and 1454; δ_H (200 MHz; $CDCl_3$) 1.01 (3H, t, *J* 7.2, NCH_2CH_3), 1.24 (3H, t, *J* 7.1, OCH_2CH_3), 1.33–1.51 (2H, m, 6B-H and 7B-H), 1.60–1.94 (5H, m, 1′-CH_2, 6A-H and 8-CH_2), 1.96–2.10 (2H, m, 2B-H and 4B-H), 2.20 (2H, q, *J* 7.2, NCH_2CH_3), 2.57–2.61 (1H, m, 7A-H), 2.70 (1H, d, J_{gem} 11.2, 4A-H), 3.15 (1H, d, J_{gem} 11.1, 2A-H), 3.23 (1H, d, *J* 2.5, 9-H), 3.60 (1H, br s, OH), 4.12 (2H, q, *J* 7.1, OCH_2CH_3), 4.97–5.05 (2H, m, 3′-CH_2) and 5.72–5.93 (1H, m, 2′-H); δ_C (50 MHz; $CDCl_3$) 12.6 (CH_3, NCH_2CH_3), 14.0 (CH_3, OCH_2CH_3), 20.7 (CH_2, C-7), 27.2 (CH_2, C-6), 29.4 (CH_2, C-8), 37.4 (quat., C-5), 42.6 (CH_2, C-1′), 47.7 (quat., C-1), 51.9 (CH_2, NCH_2CH_3), 59.4 (CH_2, C-4), 60.4 (CH_2, OCH_2CH_3), 62.2 (CH_2, C-2), 74.2 (CH, C-9), 117.3 (CH_2, C-3′), 134.0 (CH, C-2′) and 176.8 (quat., OC=O); *m*/*z* (EI) 281 (M^+, 11%), 266 (M − CH_3, 12), 264 (M − OH, 16), 252 (M − CH_2CH_3, 25) and 44 (100).

Ethyl (1*R**,5*S**,9*S**)-3-ethyl-5-(2′-propenyl)-9-(2″-propenyloxy)-3-azabicyclo[3.3.1]nonane-1-carboxylate (8)

To a suspension of sodium hydride (163 mg, 60% in oil, 4.07 mmol) in dry THF (20 mL) at 0 °C was added a solution of ethyl (1*R**,5*S**,9*S**)-3-ethyl-9-hydroxy-5-(2′-propenyl)-3-azabicyclo[3.3.1]nonane-1-carboxylate **6** (286 mg, 1.02 mmol) in dry THF (5 mL). The mixture was then stirred for 30 min after which time allyl bromide (490 mg, 4.07 mmol) was added and the mixture was stirred at room temperature for 72 h. The reaction was then quenched by the addition of water (30 mL). The volatile solvents were removed *in vacuo* and the remaining aqueous mixture extracted with ethyl acetate (2 × 25 mL). The combined organic layers were washed with brine (50 mL) then dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product which was purified by flash chromatography (19 : 1 hexane–ethyl acetate) to give the *title compound* **8** (234 mg, 72%) as a clear oil [Found (EI): M^+, 321.2309; $C_{19}H_{31}NO_3$ requires M^+, 321.2304]; ν_{max}(NaCl)/cm^{-1} 2921 (C–H), 1730 (C=O, ester), 1638 (C=C), 1453 and 1258; δ_H (200 MHz; $CDCl_3$) 1.04 (3H, t, *J* 7.2, NCH_2CH_3), 1.25 (3H, t, *J* 7.1, OCH_2CH_3), 1.30–1.55 (2H, m, 6B-H and 7B-H), 1.59–1.87 (3H, m, 6A-H and 8-CH_2), 2.01–2.08 (2H, m, 1′-CH_2), 2.20 (1H, d, J_{gem} 10.7, 4B-H), 2.24 (2H, q, *J* 7.2, NCH_2CH_3), 2.46 (1H, d, J_{gem} 10.7, 4A-H), 2.62 (1H, d, J_{gem} 11.3, 2B-H), 2.64–2.83 (1H, m, 7A-H), 2.91 (1H, d, J_{gem} 11.3, 2A-H), 3.44 (1H, s, 9-H), 4.02–4.18 (4H, m, 1″-CH_2 and OCH_2CH_3), 4.98–5.27 (4H, m, 3′-CH_2 and 3″-CH_2) and 5.75–5.89 (2H, m, 2′-H and 2″-H); δ_C (50 MHz; $CDCl_3$) 12.7 (CH_3, NCH_2CH_3), 14.2 (CH_3, OCH_2CH_3), 20.8 (CH_2, C-7), 35.6 (CH_2, C-6), 36.0 (CH_2, C-8), 39.5 (quat., C-5), 42.2 (CH_2, C-1′), 48.8 (quat., C-1), 52.3 (CH_2, NCH_2CH_3), 53.7 (CH_2, C-4), 57.6 (CH_2, C-2), 60.3 (CH_2, OCH_2CH_3), 74.0 (CH_2, C-1″), 83.9 (CH, C-9), 114.9 (CH_2, C-3″), 117.5 (CH_2, C-3′), 134.2 (CH, C-2′), 135.4 (CH, C-2″) and 173.3 (quat., OC=O); *m*/*z* (EI) 321 (M^+, 44%), 306 (M − CH_3, 55), 292 (M − C_2H_5, 44), 280 (M − CH_2=$CHCH_2$, 47) and 41 (100).

Ethyl(1*R**,5*S**,9*R**)-3-ethyl-5-(2′-propenyl)-9-(2″-propenyloxy)-3-azabicyclo[3.3.1]nonane-1-carboxylate (9)

To a suspension of sodium hydride (113 mg, 60% in oil, 2.84 mmol) in dry THF (9 mL) at 0 °C was added a solution of ethyl (1*R**,5*S**,9*R**)-3-ethyl-9-hydroxy-5-(2-propenyl)-3-azabicyclo-

[3.3.1]nonane-1-carboxylate **7** (200 mg, 0.71 mmol) in dry THF (1 mL). The mixture was then stirred for 30 min after which time allyl bromide (340 mg, 2.84 mmol) was added and the mixture was stirred at room temperature for 48 h. The reaction was then quenched by the addition of water (10 mL). The volatile solvents were removed *in vacuo* and the remaining aqueous mixture extracted with ethyl acetate (2 × 15 mL). The combined organic layers were washed with brine (20 mL) then dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product which was purified by flash chromatography (9 : 1 hexane–ethyl acetate) to give the *title compound* **9** (168 mg, 73%) as a clear oil [Found (EI): M^+, 321.2299: $C_{19}H_{31}NO_3$ requires M^+, 321.2304]; ν_{max}(NaCl)/cm^{-1} 2924 (C–H), 1732 (C=O, ester), 1638 (C=C), 1456 and 1243; δ_H (200 MHz; $CDCl_3$) 1.04 (3H, t, *J* 7.0, NCH_2CH_3), 1.26 (3H, t, *J* 7.2, OCH_2CH_3), 1.34–1.47 (3H, m, 6-CH_2 and 7B-H), 1.58–1.87 (2H, m, 8-CH_2), 2.01–2.08 (2H, m, 1′-CH_2), 2.12–2.19 (4H, m, 2B-H, 4B-H and NCH_2CH_3), 2.52–2.71 (1H, m, 7A-H), 2.75 (1H, dd, $J_{4A,2A}$ 2.0, J_{gem} 11.2, 4A-H), 2.89 (1H, dd, $J_{2A,4A}$ 2.0, J_{gem} 10.6, 2A-H), 3.45 (1H, s, 9-H), 4.05–4.16 (4H, m, 1″-CH_2 and OCH_2CH_3), 4.97–5.28 (4H, m, 3′-CH_2 and 3″-CH_2) and 5.75–5.89 (2H, m, 2′-H and 2″-H); δ_C (50 MHz; $CDCl_3$) 12.7 (CH_3, NCH_2CH_3), 14.2 (CH_3, OCH_2CH_3), 20.6 (CH_2, C-7), 26.6 (CH_2, C-6), 30.0 (CH_2, C-8), 39.0 (quat., C-5), 43.2 (CH_2, C-1′), 48.6 (quat., C-1), 52.0 (CH_2, NCH_2CH_3), 60.5 (CH_2, OCH_2CH_3), 61.5 (CH_2, C-4), 62.7 (CH_2, C-2), 73.8 (CH_2, C-1″), 84.7 (CH, C-9), 115.2 (CH_2, C-3″), 117.3 (CH_2, C-3′), 134.2 (CH, C-2′), 135.4 (CH, C-2″) and 175.7 (quat., OC=O); *m*/*z* (EI) 321 (M^+, 20%), 306 (M − CH_3, 26), 292 (M − C_2H_5, 25), 280 (M − $CH_2CH{=}CH_2$, 57) and 43 (100).

Ethyl (1*S**,7*S**,8*R**)-10-ethyl-6-oxa-10-azatricyclo[6.3.3.0^{1,7}]-tetradec-3-ene-8-carboxylate (11)

To a dry two-neck flask, under an atmosphere of nitrogen, was added a recently prepared solution of bis(tricyclohexylphosphine)benzylideneruthenium(IV) dichloride **10** (62 mg, 0.075 mmol) in dichloromethane (1 mL). The catalyst was diluted by addition of dry dichloromethane (20 mL) and a solution of ethyl (1*R**,5*S**,9*S**)-3-ethyl-5-(2′-propenyl)-9-(2″-propenyloxy)-3-azabicyclo[3.3.1]nonane-1-carboxylate **8** (485 mg, 1.51 mmol) in dry dichloromethane (4 mL) added dropwise over 2 min. The mixture was stirred for 22 h, concentrated *in vacuo* and the crude mixture purified by flash chromatography (19 : 1 hexane–ethyl acetate) to give the *title compound* **11** (398 mg, 90%) as a clear oil [Found (EI): M^+, 293.2008. $C_{17}H_{27}NO_3$ requires M^+, 293.1991]; ν_{max}(NaCl)/cm^{-1} 2919 (C–H), 1732 (C=O, ester), 1654 (C=C), 1451 and 1258; δ_H (200 MHz; $CDCl_3$) 0.98 (3H, t, *J* 7.1, NCH_2CH_3), 1.24 (3H, t, *J* 7.2, OCH_2CH_3), 1.28–1.64 (5H, m, 12-CH_2, 13B-H and 14-CH_2), 1.83–1.92 (3H, m, 2-CH_2 and 11B-H), 2.26–2.37 (3H, m, 11A-H and NCH_2CH_3), 2.52 (1H, d, J_{gem} 11.3, 9B-H), 2.65–2.84 (1H, m, 13A-H), 2.88 (1H, d, J_{gem} 11.3, 9A-H), 3.71 (1H, s, 7-H), 4.01–4.29 (4H, m, 5-CH_2 and OCH_2CH_3) and 5.66–5.82 (2H, m, 3-H and 4-H); δ_C (50 MHz; $CDCl_3$) 12.7 (CH_3, NCH_2CH_3), 14.2 (CH_3, OCH_2CH_3), 21.1 (CH_2, C-13), 35.8 (CH_2, C-12), 38.0 (quat., C-1), 39.1 (CH_2, C-2), 39.4 (CH_2, C-14), 48.6 (quat., C-8), 52.2 (CH_2, NCH_2CH_3), 53.7 (CH_2, C-11), 58.0 (CH_2, C-9), 60.1 (CH_2, OCH_2CH_3), 68.8 (CH_2, C-5), 85.9 (CH, C-7), 129.1 (CH, C-3), 130.4 (CH, C-4) and 175.6 (quat., OC=O); *m*/*z* (EI) 293 (M^+, 75%), 278 (M − CH_3, 57), 264 (M − C_2H_5, 63), 220 (M − $CO_2CH_2CH_3$, 73) and 58 (100).

Ethyl (1*S**,7*R**,8*R**)-10-ethyl-6-oxa-10-azatricyclo[6.3.3.0^{1,7}]-tetradec-3-ene-8-carboxylate (12)

To a dry two-neck flask, under an atmosphere of nitrogen, was added a recently prepared solution of bis(tricyclohexylphosphine)benzylideneruthenium(IV) dichloride **10** (38 mg, 0.046 mmol) in dichloromethane (1 mL). The catalyst was diluted by addition of dry dichloromethane (10 mL) and a solution of ethyl (1*R**,5*S**,9*R**)-3-ethyl-5-(2′-propenyl)-9-(2″-propenyloxy)-3-azabicyclo[3.3.1]nonane-1-carboxylate **9** (300 mg, 0.93 mmol) in dry dichloromethane (4 mL) added dropwise over 2 min. The mixture was stirred for 18 h, concentrated *in vacuo* and the crude mixture purified by flash chromatography (19 : 1 hexane–ethyl acetate) to give the *title compound* **12** (263 mg, 96%) as a clear oil [Found (EI): M^+, 293.1961; $C_{17}H_{27}NO_3$ requires M^+, 293.1991]; ν_{max}(NaCl)/cm^{-1} 2971 (C–H), 1732 (C=O, ester), 1654 (C=C), 1453 and 1254; δ_H (200 MHz; $CDCl_3$) 0.98 (3H, t, *J* 7.1, NCH_2CH_3), 1.04–1.16 (1H, m, 12B-H), 1.20 (3H, t, *J* 7.3, OCH_2CH_3), 1.38–1.59 (1H, m, 13B-H), 1.66–2.03 (6H, m, 2-CH_2, 11B-H, 12A-H and 14-CH_2), 2.17 (2H, q, *J* 7.1, NCH_2CH_3), 2.27 (1H, d, J_{gem} 10.5, 9B-H), 2.51–2.64 (1H, m, 13A-H), 2.66 (1H, dd, $J_{11A,9A}$ 1.1, J_{gem} 10.2, 11A-H), 2.85 (1H, dd, $J_{9A,11A}$ 1.1, J_{gem} 10.5, 9A-H), 3.60 (1H, s, 7-H), 3.99–4.24 (4H, m, 5-CH_2 and OCH_2CH_3) and 5.68–5.85 (2H, m, 3-H and 4-H); δ_C (50 MHz; $CDCl_3$) 12.6 (CH_3, NCH_2CH_3), 14.2 (CH_3, OCH_2CH_3), 20.4 (CH_2, C-13), 26.3 (CH_2, C-12), 29.0 (CH_2, C-14), 36.9 (quat., C-1), 40.0 (CH_2, C-2), 48.9 (quat., C-8), 51.8 (CH_2, NCH_2CH_3), 60.2 (CH_2, OCH_2CH_3), 61.5 (CH_2, C-11), 65.2 (CH_2, C-9), 68.3 (CH_2, C-5), 88.5 (CH, C-7), 130.2 (CH, C-3), 130.7 (CH, C-4) and 175.1 (quat., OC=O); *m*/*z* (EI) 293 (M^+, 20%), 278 (M − CH_3, 13), 264 (M − C_2H_5, 21), 220 (M − $CO_2CH_2CH_3$, 30) and 72 (100).

(1*S**,7*S**,8*S**)-(10-Ethyl-6-oxa-10-azatricyclo[6.3.3.0^{1,7}]-tetradec-3-en-8-yl)methanol (13)

To a slurry of lithium aluminium hydride (153 mg, 4.03 mmol) in dry THF (40 mL) at 0 °C, a solution of ethyl (1*S**,7*S**,8*R**)-10-ethyl-6-oxa-10-azatricyclo[6.3.3.0^{1,7}]tetradec-3-ene-8-carboxylate **11** (394 mg, 1.34 mmol) in dry THF (10 mL) was slowly added and the mixture stirred under an atmosphere of nitrogen for 2.5 h. The reaction was then quenched by dropwise addition of water (30 mL) and the volatiles removed *in vacuo*. The remaining aqueous solution was extracted with diethyl ether (3 × 50 mL) and the combined organic layers washed with brine (50 mL) then dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product which was purified by flash chromatography (1 : 1 hexane–ethyl acetate) to give the *title compound* **13** (283 mg, 83%) as a clear oil [Found (EI): M^+, 251.1887; $C_{15}H_{25}NO_2$ requires M^+, 251.1885]; ν_{max}(NaCl)/cm^{-1} 3388 (O–H), 2917 (C–H), 1652 (C=C) and 1453; δ_H (400 MHz; $CDCl_3$) 1.03 (3H, t, *J* 7.1, NCH_2CH_3), 1.23–1.29 (1H, m, 12A-H), 1.31–1.38 (2H, m, 13B-H and 14B-H), 1.45 (1H, dd, $J_{14A,13A}$ 6.0, J_{gem} 11.9, 14A-H), 1.57 (1H, dd, $J_{12B,13A}$ 6.0, J_{gem} 12.1, 12B-H), 1.96–2.09 (2H, m, 2-CH_2), 2.20–2.31 (2H, m, NCH_2CH_3), 2.35–2.42 (2H, m, 11-CH_2), 2.45–2.53 (2H, m, 9-CH_2), 2.70–2.84 (1H, m, 13A-H), 3.02 (1H, br, OH), 3.32 (1H, d, J_{gem} 11.0, CH_AH_BOH), 3.38 (1H, s, 7-H), 3.53 (1H, d, J_{gem} 11.0, CH_AH_BOH), 4.10 (1H, br d, J_{gem} 14.5, 5A-H or 5B-H), 4.31 (1H, br d, J_{gem} 14.5, 11A-H or 11B-H) and 5.73–5.83 (2H, m, 3-H and 4-H); δ_C (100 MHz; $CDCl_3$) 12.7 (CH_3, NCH_2CH_3), 21.0 (CH_2, C-13), 34.8 (CH_2, C-14), 38.3 (quat., C-1), 39.3 (CH_2, C-2 and C-12), 40.0 (quat., C-8), 52.5 (CH_2, NCH_2CH_3), 54.9 (CH_2, C-11), 58.1 (CH_2, C-9), 68.2 (CH_2, C-5), 71.5 (CH_2, CH_2OH), 91.2 (CH, C-7), 129.8 (CH, C-3) and 130.8 (CH, C-4); *m*/*z* (EI) 251 (M^+, 23%), 234 (M − OH, 10), 220 (M − CH_2OH, 22) and 58 (100).

(1*S**,7*R**,8*S**)-(10-Ethyl-6-oxa-10-azatricyclo[6.3.3.0^{1,7}]-tetradec-3-en-8-yl)methanol (14)

To a slurry of lithium aluminium hydride (58 mg, 1.53 mmol) in dry THF (25 mL) at 0 °C, a solution of ethyl (1*S**,7*R**,8*R**)-10-ethyl-6-oxa-10-azatricyclo[6.3.3.0^{1,7}]tetradec-3-ene-8-carboxylate **12** (150 mg, 0.511 mmol) in dry THF (5 mL) was slowly added and the mixture stirred under an atmosphere of nitrogen for 2 h. The reaction was then quenched by dropwise addition of water (15 mL) and sat. ammonium chloride solution (10 mL) and the volatiles removed *in vacuo*. The remaining aqueous

solution was extracted with ethyl acetate (2 × 20 mL) and the combined organic layers washed with brine (30 mL) then dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product which was purified by flash chromatography (1 : 1 hexane–ethyl acetate) to give the *title compound* **14** (116 mg, 91%) as a clear oil [Found (EI): M^+, 251.1895; $C_{15}H_{25}NO_2$ requires M^+, 251.1885]; ν_{max}(NaCl)/cm^{-1} 3405 (O–H), 2912 (C–H), 1654 (C=C), 1453 and 1100; δ_H (200 MHz; $CDCl_3$) 0.97 (3H, t, *J* 7.1, NCH_2CH_3), 1.07–1.26 (1H, m, 12B-H), 1.37–1.48 (1H, m, 13B-H), 1.66–1.96 (5H, m, 2-CH_2, 12A-H and 14-CH_2), 1.98–2.06 (2H, m, 9B-H and 11B-H), 2.12 (2H, q, *J* 7.1, NCH_2CH_3), 2.59 (1H, dd, $J_{11A,9A}$ 1.4, J_{gem} 10.6, 11A-H), 2.61 (1H, dd, $J_{9A,11A}$ 1.4, J_{gem} 11.0, 9A-H), 2.66–2.78 (1H, m, 13A-H), 2.89 (1H, br, OH), 3.24 (1H, s, 7-H), 3.26 (1H, d, J_{gem} 11.3, CH_AH_BOH), 3.38 (1H, d, J_{gem} 11.3, CH_AH_BOH), 3.94–4.28 (2H, m, 5-CH_2) and 5.73–5.88 (2H, m, 3-H and 4-H); δ_C (50 MHz; $CDCl_3$) 12.5 (CH_3, NCH_2CH_3), 20.4 (CH_2, C-13), 26.9 (CH_2, C-12), 29.4 (CH_2, C-14), 36.8 (quat., C-1), 39.7 (quat., C-8), 39.8 (CH_2, C-2), 52.1 (CH_2, NCH_2CH_3), 61.2 (CH_2, C-11), 65.4 (CH_2, C-9), 67.8 (CH_2, C-5), 70.4 (CH_2, CH_2OH), 92.4 (CH, C-7), 129.7 (CH, C-3) and 132.0 (CH, C-4); *m*/*z* (EI) 251 (M^+, 5%), 234 (M − OH, 4), 220 (M − CH_2OH, 10) and 58 (100).

Standard procedure for the formation of anthranilate esters using *N*-(trifluoroacetyl)anthranilic acid (15)

To a solution of alcohol (1 mmol), *N*-(trifluoroacetyl)anthranilic acid **15** (2 mmol) and 4-(dimethylamino)pyridine (0.1 mmol) in acetonitrile (5 mL) was added 1,3-dicyclohexylcarbodiimide (2 mmol) and the mixture stirred under an atmosphere of nitrogen at 40 °C for 24 h. After this time the mixture was cooled, filtered and the filtrate evaporated to dryness. The crude mixture was then dissolved in dichloromethane (20 mL), washed with aq. sodium bicarbonate (20 mL) and brine (20 mL) then dried ($MgSO_4$) and concentrated *in vacuo* to leave the crude *N*-(trifluoroacetyl)anthranilate ester. This residue was suspended in absolute ethanol (10 mL), sodium borohydride (2 mmol) added, and the mixture stirred for 2 h. The reaction was quenched by the addition of water and the volatile solvent removed *in vacuo*. The remaining aqueous solution was extracted with ethyl acetate (2 × 30 mL) and the combined organic layers washed with brine (50 mL) then dried ($MgSO_4$) and concentrated *in vacuo* to leave the crude product, which was purified by flash chromatography to afford the anthranilate ester.

(1′*R**,7′*S**,8′*S**)-(10-Ethyl-6-oxa-10-azatricyclo[6.3.3.0^{1,7}]-tetradec-3-en-8-yl)methyl 2-aminobenzoate (16)

The reaction was carried out according to the standard procedure using (1*R**,7*S**,8*S**)-(10-ethyl-6-oxa-10-azatricyclo[6.3.3.0^{1,7}]tetradec-3-en-8-yl)methanol **13** (100 mg, 0.398 mmol), *N*-(trifluoroacetyl)anthranilic acid **15** (278 mg, 1.19 mmol), 4-(dimethylamino)pyridine (24 mg, 0.2 mmol), 1,3-dicyclohexylcarbodiimide (245 mg, 1.19 mmol) and sodium borohydride (39 mg, 0.80 mmol) with 3 : 2 hexane–ethyl acetate as eluent for flash chromatography to afford the *title compound* **16** (93 mg, 62%) as a yellow oil [Found (EI): M^+, 370.2262; $C_{22}H_{30}N_2O_3$ requires M^+,370.2257]; ν_{max}(NaCl)/cm^{-1} 3481 and 3370 (N–H), 2918 (C–H), 1689 (C=O), 1616, 1588, 1561 and 1454; δ_H (200 MHz; $CDCl_3$) 1.04 (3H, t, *J* 7.1, NCH_2CH_3), 1.20–1.51 (2H, m, 12′A-H and 13′B-H), 1.56–1.71 (2H, m, 12′B-H and 14′B-H), 1.85 (1H, dd, $J_{14'A,13'A}$ 6.7, J_{gem} 13.4, 14′A-H), 2.03–2.05 (2H, m, 2′-CH_2), 2.21–2.35 (3H, m, 11′B-H and NCH_2CH_3), 2.38–2.45 (2H, m, 9′B-H and 11′A-H), 2.66 (1H, d, J_{gem} 10.6, 9′A-H), 2.75–2.88 (1H, m, 13′A-H), 3.36 (1H, s, 7′-H), 3.97–4.34 (4H, m, OCH_2 and 5′-CH_2), 5.71–5.80 (4H, m, 3′-H, 4′-H and NH_2), 6.62–6.69 (2H, m, 3-H and 5-H), 7.26 (1H, td, *J* 7.6, 1.4, 4-H) and 7.87 (1H, dd, *J* 1.2, 8.2, 6-H); δ_C (50 MHz; $CDCl_3$) 12.6 (CH_3, NCH_2CH_3), 20.9 (CH_2, C-13′), 34.5 (CH_2, C-12′), 38.2 (quat., C-1′), 39.3 (CH_2, C-14′), 39.4 (CH_2, C-2′), 40.1 (quat., C-8′), 52.3 (CH_2, NCH_2CH_3), 55.6 (CH_2, C-11′), 58.6 (CH_2, C-9′), 68.8 (CH_2, C-5′), 69.1 (CH_2, OCH_2), 85.8 (CH, C-7′), 110.9 (quat., C-1), 116.1 (CH, C-3), 116.6 (CH, C-5), 129.3 (CH, C-3′), 130.2 (CH, C-6), 130.9 (CH, C-4′), 133.9 (CH, C-4), 150.5 (quat., C-2) and 168.0 (quat., OC=O); *m*/*z* (EI) 370 (M^+, 20%), 355 (M − CH_3, 15), 250 (M − $NH_2C_6H_4CO$, 17), 234 (M − $NH_2C_6H_4CO_2$, 32) and 120 ($NH_2C_6H_4CO$, 100).

(1′*R**,7′*R**,8′*S**)-(10-Ethyl-6-oxa-10-azatricyclo[6.3.3.0^{1,7}]-tetradec-3-en-8-yl)methyl 2-aminobenzoate (17)

The reaction was carried out according to the standard procedure using (1*R**,7*R**,8*S**)-(10-ethyl-6-oxa-10-azatricyclo[6.3.3.0^{1,7}]tetradec-3-en-8-yl)methanol **14** (100 mg, 0.398 mmol), *N*-(trifluoroacetyl)anthranilic acid **15** (278 mg, 1.19 mmol), 4-(dimethylamino)pyridine (24 mg, 0.2 mmol), 1,3-dicyclohexylcarbodiimide (245 mg, 1.19 mmol) and sodium borohydride (39 mg, 0.80 mmol) with 3 : 2 hexane–ethyl acetate as eluent for flash chromatography to afford the *title compound* **17** (100 mg, 67%) as a pale yellow oil [Found (EI): M^+, 370.2254; $C_{22}H_{30}N_2O_3$ requires M^+, 370.2257]; ν_{max}(NaCl)/cm^{-1} 3477 and 3370 (N–H), 2931 (C–H), 1688 (C=O), 1619, 1588, 1454 and 1245; δ_H (200 MHz; $CDCl_3$) 1.03 (3H, t, *J* 7.1, NCH_2CH_3), 1.16–1.29 (1H, m, 12′A-H), 1.44–1.53 (2H, m, 12′B-H and 13′B-H), 1.59–1.89 (4H, m, 2′-CH_2 and 14′-CH_2), 1.94–2.26 (4H, m, 9′B-H, 11′B-H and NCH_2CH_3), 2.64–2.83 (2H, m, 11′A-H and 13′A-H), 2.93 (1H, d, J_{gem} 10.9, 9′A-H), 3.25 (1H, s, 7′-H), 3.90–4.33 (4H, m, OCH_2 and 5′-CH_2), 5.69–5.93 (4H, m, 3′-H, 4′-H and NH_2), 6.63–6.71 (2H, m, 3-H and 5-H), 7.27 (1H, td, *J* 7.2, 1.6, 4-H) and 7.86 (1H, dd, *J* 1.6, 8.4, 6-H); δ_C (50 MHz; $CDCl_3$) 12.6 (CH_3, NCH_2CH_3), 20.4 (CH_2, C-13′), 26.9 (CH_2, C-12′), 29.8 (CH_2, C-14′), 36.6 (quat., C-1′), 39.8 (quat., C-8′), 40.0 (CH_2, C-2′), 52.2 (CH_2, NCH_2CH_3), 61.6 (CH_2, C-11′), 65.6 (CH_2, C-9′), 68.4 (CH_2, OCH_2), 69.2 (CH_2, C-5′), 88.2 (CH, C-7′), 109.2 (quat., C-1), 116.2 (CH, C-3), 116.7 (CH, C-5), 130.3 (CH, C-3′), 130.9 (CH, C-6), 131.1 (CH, C-4′), 133.9 (CH, C-4), 150.5 (quat., C-2) and 167.8 (quat., OC=O); *m*/*z* (EI) 370 (M^+, 30%), 355 (M − CH_3, 9), 250 (M − $NH_2C_6H_4CO$, 9), 234 (M − $NH_2C_6H_4CO_2$, 77), 120 ($NH_2C_6H_4CO$, 79) and 72 (100).

(1″*R**,7″*S**,8″*S**,3′*R**)- and (1″*R**,7″*S**,8″*S**,3′*S**)-(10-Ethyl-6-oxa-10-azatricyclo[6.3.3.0^{1,7}]tetradec-3-en-8-yl)methyl 2-(3-methyl-2,5-dioxopyrrolidin-1-yl)benzoate (18)

(1*R**,7*S**,8*S**)-(10-Ethyl-6-oxa-10-azatricyclo[6.3.3.0^{1,7}]tetradec-3-en-8-yl)methyl 2-aminobenzoate **16** (70 mg, 0.19 mmol) and methylsuccinic anhydride (86 mg, 0.76 mmol) were heated together at 125 °C for 8 h. After this time the crude mixture was dissolved in warm ethyl acetate (10 mL), washed with sat. sodium bicarbonate (30 mL), brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography using 3 : 2 hexane–ethyl acetate as eluent afforded the *title compound* **18** (52 mg, 60%) as a pale orange oil [Found (EI): M^+, 466.2466; $C_{27}H_{34}N_2O_5$ requires M^+, 466.2468]; ν_{max}(NaCl)/cm^{-1} 2933 (C–H), 1787 (N-C=O), 1715 (C=O), 1602, 1492 and 1260; δ_H (200 MHz; $CDCl_3$) 1.02 (3H, t, *J* 7.1, NCH_2CH_3), 1.10–1.28 (1H, m, 12″A-H), 1.42–1.48 (4H, m, 3′-CH_3 and 13″B-H), 1.57–2.10 (7H, m, 2″-CH_2, 9″B-H, 11″B-H, 12″B-H and 14″-CH_2), 2.19 (2H, q, *J* 7.1, NCH_2CH_3), 2.45–2.69 (2H, m, 3′-H and 13″A-H), 2.70 (1H, d, J_{gem} 10.8, 11″A-H), 2.88 (1H, d, J_{gem} 11.0, 9″A-H), 3.03–3.15 (2H, m, 4′-CH_2), 3.19 (1H, s, 7″-H), 3.88–4.30 (4H, m, OCH_2 and 5″-CH_2), 5.70–5.91 (2H, m, 3″-H and 4″-H), 7.25 (1H, dd, *J* 1.4, 7.6, 3-H), 7.53 (1H, td, *J* 7.7, 1.4, 5-H), 7.66 (1H, td, *J* 7.4, 1.5, 4-H) and 8.10 (1H, dd, *J* 1.2, 7.7, 6-H); δ_C (50 MHz; $CDCl_3$) 12.7 (CH_3, NCH_2CH_3), 16.3 (CH_3, 3′-CH_3), 20.4 (CH_2, C-13″), 27.8 (CH_2, C-12″), 30.0 (CH_2, C-14″), 35.3 (quat., C-1″), 36.6 (CH_2, C-4′), 37.0 (CH, C-3′), 39.8 (quat., C-8″), 40.0 (CH_2, C-2″), 52.2 (CH_2, NCH_2CH_3), 61.5 (CH_2, C-11″), 65.6 (CH_2,

C-9″), 68.4 (CH_2, OCH_2), 70.0 (CH_2, C-5″), 88.1 (CH, C-7″), 129.4 (CH, C-5), 129.7 (quat., C-1), 129.9 (CH, C-3), 130.3 (CH, C-3″), 131.1 (CH, C-4″), 131.4 (CH, C-6), 132.9 (quat., C-2), 133.3 (CH, C-4), 164.1 (quat., OC=O), 175.9 (quat., C-5′) and 179.9 (quat., C-2′); *m/z* (EI) 466 (M^+, 7%), 451 (M − CH_3, 10), 250 (M − $C_{12}H_{10}O_3N$, 5), 234 (M − $C_{12}H_{10}O_4N$, 20) and 72 (100).

(1*R,7*R**,8*S**,3′*R**)- and (1*R**,7*R**,8*S**,3′*S**)-(10-Ethyl-6-oxa-10-azatricyclo[6.3.3.0^{1,7}]tetradec-3-en-8-yl)methyl 2-(3-methyl-2,5-dioxopyrrolidin-1-yl)benzoate (19)**

(1′*R**,7′*R**,8′*S**)-(10-Ethyl-6-oxa-10-azatricyclo[6.3.3.0^{1,7}]-tetradec-3-en-8-yl)methyl 2-aminobenzoate **17** (60 mg, 0.16 mmol) and methylsuccinic anhydride (55 mg, 0.49 mmol) were heated together at 125 °C for 3 h. After this time the crude mixture was dissolved in warm ethyl acetate (10 mL), washed with sat. sodium bicarbonate (30 mL), brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography using 3 : 2 hexane–ethyl acetate as eluent afforded the *title compound* **19** (47 mg, 62%) as a yellow oil [Found (EI): M^+, 466.2475; $C_{27}H_{34}N_2O_5$ requires M^+, 466.2468]; ν_{max}(NaCl)/cm^{-1} 2925 (C–H), 1781 (N-C=O), 1715 (C=O), 1602, 1492, 1453 and 1263; δ_H (200 MHz; $CDCl_3$) 1.03 (3H, t, *J* 7.1, NCH$_2$C*H*$_3$), 1.20–1.67 (5H, m, 3′-C*H*$_3$, 12″A-H and 13″B-H), 1.82 (1H, dd, $J_{14''B,13''B}$ 6.3, J_{gem} 13.3, 14″B-H), 2.01–2.05 (4H, m, 2″-CH_2, 12″A-H and 14″A-H), 2.28 (2H, q, *J* 7.1, NC*H*$_2$CH$_3$), 2.43–2.52 (4H, m, 3′-H, 9″B-H and 11″-CH_2), 2.63 (1H, d, J_{gem} 10.6, 9″A-H), 2.71–2.81 (1H, m, 13″A-H), 3.00–3.15 (2H, m, 4′-CH_2), 3.30 (1H, s, 7″-H), 3.94–4.32 (4H, m, 5″-CH_2 and OCH_2), 5.68–5.83 (2H, m, 3″-H and 4″-H), 7.24 (1H, d, *J* 6.9, 3-H) 7.53 (1H, td, *J* 7.6, 1.0, 5-H), 7.66 (1H, td, *J* 7.6, 1.3, 4-H) and 8.11 (1H, d, *J* 7.4, 6-H); δ_C (50 MHz; $CDCl_3$) 12.5 (CH_3, NCH$_2$*C*H$_3$), 16.3 (CH_3, 3′-*C*H$_3$), 20.8 (CH_2, C-13″), 34.3 (CH_2, C-12″), 35.2 (quat., C-1″), 36.9 (CH_2, C-4′), 38.1 (CH, C-3′), 39.2 (CH_2, C-14″), 39.4 (CH_2, C-2″), 40.1 (quat., C-8″), 52.4 (CH_2, N*C*H$_2$CH$_3$), 55.3 (CH_2, C-11″), 58.2 (CH_2, C-9″), 68.7 (CH_2, C-5″), 70.0 (CH_2, OCH_2), 85.8 (CH, C-7″), 127.5 (quat., C-1), 129.3 (CH, C-5), 129.5 (CH, C-3), 129.9 (CH, C-3″), 130.3 (CH, C-4″), 131.3 (CH, C-6), 132.9 (quat., C-2), 133.3 (CH, C-4), 164.1 (quat., OC=O), 175.8 (quat., C-5′) and 179.8 (quat., C-2′); *m/z* (EI) 466 (M^+, 10%), 451 (M − CH_3, 5), 234 (M − $C_{12}H_{10}O_4N$, 23) and 44 (100).

Ethyl (1*R,5*S**,9*R**)-5-(3′-butenyl)-3-ethyl-9-hydroxy-9-(2′-propenyl)-3-azabicyclo[3.3.1]nonane-1-carboxylate (21) and ethyl (1*R**,5*S**,9*S**)-5-(3′-butenyl)-3-ethyl-9-hydroxy-9-(2′-propenyl)-3-azabicyclo[3.3.1]nonane-1-carboxylate (22)**

To a solution of ethyl (1*R**,5*S**)-5-(3′-butenyl)-3-ethyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate **20**[19] (2 g, 6.82 mmol) in THF (60 mL) at 0 °C, under an atmosphere of nitrogen, allylmagnesium bromide (7.20 mL, 1 M in diethyl ether, 7.20 mmol) was added dropwise over 25 min. The reaction was stirred for a further 1 h and then allowed to warm to room temperature and stirred for 48 h. The reaction was quenched by the addition of sat. ammonium chloride solution (50 mL), diethyl ether (100 mL) was added and the organic layer separated. The remaining aqueous mixture was further extracted with diethyl ether (2 × 50 mL) and the combined ethereal layers were washed with brine (100 mL) then dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. Further purification by flash chromatography afforded the *title compounds* **21** and **22**.

(i) *Ethyl (1R*,5S*,9R*)-5-(3′-butenyl)-3-ethyl-9-hydroxy-9-(2′-propenyl)-3-azabicyclo[3.3.1]nonane-1-carboxylate* **21** (1.25 g, 55%) was a clear oil [Found (EI): M^+, 335.2459; $C_{20}H_{33}NO_3$ requires M^+, 335.2460]; ν_{max} (NaCl)/cm^{-1} 3482 (O–H), 2975 (C–H), 1730 (C=O, ester), 1697, 1638, 1455, 1367 and 1258; δ_H (200 MHz; $CDCl_3$) 1.05 (3H, t, *J* 7.0, NCH$_2$C*H*$_3$), 1.24 (3H, t, *J* 7.1, OCH$_2$C*H*$_3$), 1.37–1.72 (4H, m, 1′-CH_2, 6B-H and 7B-H), 1.82–2.07 (7H, m, 1″-CH_2, 2′-CH_2, 6B-H and 8-CH_2), 2.15 (1H, dd, $J_{4B,2B}$ 2.4 J_{gem} 11.6, 4B-H), 2.30 (2H, q, *J* 7.0, NC*H*$_2$CH$_3$), 2.50 (1H, dd, $J_{2B,4B}$ 2.4, J_{gem} 11.9, 2B-H), 2.60–2.71 (2H, m, 7A-H and OH), 2.75 (1H, d, J_{gem} 11.6, 4A-H), 3.06 (1H, d, J_{gem} 11.9, 2A-H), 4.06 (2H, q, *J* 7.1, OC*H*$_2$CH$_3$), 4.86–5.01 (4H, m, 3″-CH_2 and 4′-CH_2) and 5.67–5.93 (2H, m, 3′-H and 2″-H); δ_C (50 MHz; $CDCl_3$) 12.5 (CH_3, NCH$_2$*C*H$_3$), 13.8 (CH_3, OCH$_2$*C*H$_3$), 20.3 (CH_2, C-7), 28.1 (CH_2, C-6), 30.1 (CH_2, C-8), 32.8 (CH_2, C-1′), 34.2 (CH_2, C-1″), 38.2 (CH_2, C-2′), 40.6 (quat., C-5), 50.5 (quat., C-1), 52.0 (CH_2, N*C*H$_2$CH$_3$), 56.0 (CH_2, C-4), 60.3 (CH_2, O*C*H$_2$CH$_3$), 60.7 (CH_2, C-2), 74.5 (quat., C-9), 113.8 (CH_2, C-4′), 116.9 (CH_2, C-3″), 135.1 (CH, C-2″), 139.8 (CH, C-3′) and 177.4 (quat., OC=O); *m/z* (EI) 335 (M^+, 7%), 320 (M − CH_3, 5), 306 (M − CH_2CH_3, 6), 262 (M − $CO_2C_2H_5$, 7) and 58 (100).

(ii) *Ethyl (1R*,5S*,9S*)-5-(3′-butenyl)-3-ethyl-9-hydroxy-9-(2′-propenyl)-3-azabicyclo[3.3.1]nonane-1-carboxylate* **22** (0.58 g, 25%) was a clear oil [Found (EI): M^+, 335.2463; $C_{20}H_{33}NO_3$ requires M^+, 335.2460]; ν_{max} (NaCl)/cm^{-1} 3462 (O–H), 2934 (C–H), 1732 (C=O, ester), 1691, 1639, 1464, 1381 and 1262; δ_H (200 MHz; $CDCl_3$) 1.01 (3H, t, *J* 7.2, NCH$_2$C*H*$_3$), 1.23 (3H, t, *J* 7.2, OCH$_2$C*H*$_3$), 1.25–1.33 (1H, m, 6B-H), 1.46–1.57 (2H, m, 6A-H and 7B-H), 1.66–1.81 (3H, m, 1′-CH_2 and 8B-H), 1.90–2.01 (5H, m, 1″-CH_2, 2′-CH_2 and 8A-H), 2.17–2.35 (3H, m, 4B-H and NC*H*$_2$CH$_3$), 2.52 (1H, d, J_{gem} 10.3, 2B-H), 2.75 (1H, d, J_{gem} 10.7, 4A-H), 2.61–2.78 (1H, m, 7A-H), 2.80 (1H, d, J_{gem} 10.3, 2A-H), 4.03 (2H, q, *J* 7.1, OC*H*$_2$CH$_3$), 4.55 (1H, s, O*H*), 4.86–5.06 (4H, m, 3″-CH_2 and 4′-CH_2) and 5.67–5.92 (2H, m, 3′-H and 2″-H); δ_C (50 MHz; $CDCl_3$) 12.4 (CH_3, NCH$_2$*C*H$_3$), 13.7 (CH_3, OCH$_2$*C*H$_3$), 20.1 (CH_2, C-7), 27.9 (CH_2, C-1′), 29.7 (CH_2, C-1″), 32.8 (CH_2, C-6), 33.8 (CH_2, C-2′), 37.8 (CH_2, C-8), 40.0 (quat., C-5), 50.3 (quat., C-1), 52.0 (CH_2, N*C*H$_2$CH$_3$), 53.7 (CH_2, C-4), 58.5 (CH_2, C-2), 60.8 (CH_2, O*C*H$_2$CH$_3$), 74.8 (quat., C-9), 113.8 (CH_2, C-4′), 117.0 (CH_2, C-3″), 134.8 (CH, C-2″), 139.7 (CH, C-3′) and 177.3 (quat., OC=O); *m/z* (EI) 335 (M^+, 7%), 320 (M − CH_3, 25), 306 (M − CH_2CH_3, 30), 294 (M − $CH_2CH{=}CH_2$, 29) and 41 (C_3H_5, 100).

Ethyl (1*S,7*R**,8*R**)-10-ethyl-7-hydroxy-10-azatricyclo-[6.3.3.0^{1,7}]tetradec-4-ene-8-carboxylate (23)**

To a dry two-neck flask, under an atmosphere of nitrogen, was added a recently prepared solution of bis(tricyclohexylphosphine)benzylideneruthenium(IV) dichloride **10** (269 mg, 0.326 mmol) in dichloromethane (5 mL). The catalyst was diluted by the addition of dry dichloromethane (25 mL) and a solution of ethyl (1*R**,5*S**,9*R**)-5-(3′-butenyl)-3-ethyl-9-hydroxy-9-(2′-propenyl)-3-azabicyclo[3.3.1]nonane-1-carboxylate **21** (1.10 g, 3.26 mmol) in dry dichloromethane (10 mL) was added. The mixture was stirred for 24 h, concentrated *in vacuo* and the crude mixture purified by flash chromatography (4 : 1 hexane–ethyl acetate) to give the *title compound* **23** (1.00 g, 97%) as a clear oil [Found (EI): M^+, 307.2138; $C_{18}H_{29}NO_3$ requires M^+, 307.2147]; ν_{max}(NaCl)/cm^{-1} 3505 (O–H), 2930 (C–H), 1731 (C=O, ester), 1696 (C=C), 1444, 1383 and 1269; δ_H (200 MHz; $CDCl_3$) 1.07 (3H, t, *J* 7.2, NCH$_2$C*H*$_3$), 1.10–1.20 (2H, m, 12-CH_2), 1.27 (3H, t, *J* 7.1, OCH$_2$C*H*$_3$), 1.39–1.55 (1H, m, 13B-H), 1.59–1.86 (2H, m, 2A-H or 2B-H and 14B-H), 1.90–2.19 (3H, m, 2A-H or 2B-H, 3A-H or 3B-H and 14A-H), 2.27–2.57 (6H, m, 3A-H or 3B-H, 6A-H or 6B-H, 9B-H, 11B-H and NC*H*$_2$CH$_3$), 2.65–2.81 (2H, 11A-H and 13A-H), 2.99 (1H, d, J_{gem} 15.4, 6A-H or 6B-H), 3.08 (1H, d, J_{gem} 11.9, 9A-H), 3.68 (1H, s, OH), 4.18 (2H, q, *J* 7.1, OC*H*$_2$CH$_3$), 5.52–5.63 (1H, m, 5-H) and 5.86–5.96 (1H, m, 4-H); δ_C (50 MHz; $CDCl_3$) 12.6 (CH_3, NCH$_2$*C*H$_3$), 14.1 (CH_3, OCH$_2$*C*H$_3$), 20.6 (CH_2, C-13), 23.7 (CH_2, C-3), 32.4 (CH_2, C-12), 33.0 (CH_2, C-2), 34.5 (CH_2, C-14), 36.1 (CH_2, C-6), 40.7 (quat., C-1), 51.7 (quat., C-8), 52.2 (CH_2, N*C*H$_2$CH$_3$), 56.8 (CH_2, C-11), 60.3 (CH_2, O*C*H$_2$CH$_3$), 60.8 (CH_2, C-9), 73.1 (quat., C-7), 127.3

(CH, C-5), 133.0 (CH, C-4) and 177.4 (quat., OC=O); *m/z* (EI) 307 (M^+, 28%), 292 (M − CH_3, 100), 290 (M − OH, 31), 278 (M − C_2H_5, 49) and 234 (M − $CO_2CH_2CH_3$, 34).

Ethyl (1*S,7*S**,8*R**)-10-ethyl-7-hydroxy-10-azatricyclo-[6.3.3.0^{1,7}]tetradec-4-ene-8-carboxylate (24)**

To a dry two-neck flask, under an atmosphere of nitrogen, was added a recently prepared solution of bis(tricyclohexylphosphine)benzylideneruthenium(IV) dichloride **10** (123 mg, 0.149 mmol) in dichloromethane (3 mL). The catalyst was diluted by the addition of dry dichloromethane (15 mL) and a solution of ethyl (1*R**,5*S**,9*S**)-5-(3′-butenyl)-3-ethyl-9-hydroxy-9-(2′-propenyl)-3-azabicyclo[3.3.1]nonane-1-carboxylate **22** (500 mg, 1.49 mmol) in dry dichloromethane (7 mL) added dropwise over 2 min. The mixture was stirred for 18 h, concentrated *in vacuo* and the crude mixture purified by flash chromatography (4 : 1 hexane–ethyl acetate) to give the *title compound* **24** (457 mg, 99%) as a clear oil [Found (EI): M^+, 307.2156; $C_{18}H_{29}NO_3$ requires M^+ 307.2148]; ν_{max}(NaCl)/cm^{-1} 3494 (O–H), 2931 (C–H), 1732 (C=O, ester), 1696 (C=C), 1463 and 1259; δ_H (200 MHz; $CDCl_3$) 0.80 (1H, ddd, $J_{12A,13B}$ 2.5, $J_{12A,13A}$ 5.7, J_{gem} 13.4, 12A-H), 0.97 (3H, t, *J* 7.2, NCH_2CH_3), 1.22 (3H, t, *J* 7.1, OCH_2CH_3), 1.24–1.27 (1H, m, 12B-H), 1.41–1.51 (2H, m, 2A-H or 2B-H and 13B-H), 1.71 (1H, ddd, J_{gem} 13.7, $J_{14B,13A}$ 13.7 $J_{14B,13B}$ 2.4, 14B-H), 1.87–1.99 (3H, m, 2A-H or 2B-H, 3A-H or 3B-H and 14A-H), 2.17 (1H, dd, $J_{11B,9B}$ 2.4, J_{gem} 10.3, 11B-H), 2.20 (2H, q, *J* 7.2, NCH_2CH_3), 2.26–2.34 (2H, m, 6A-H or 6B-H and 3A-H or 3B-H), 2.50 (1H, dd, $J_{9B,11B}$ 2.4, J_{gem} 10.4, 9B-H), 2.62 (1H, d, J_{gem} 10.3, 11A-H), 2.75–2.93 (3H, m, 6A-H or 6B-H, 9A-H and 13A-H), 3.70 (1H, s, OH), 4.10 (2H, q, *J* 7.1, OCH_2CH_3), 5.41–5.54 (1H, m, 5-H) and 5.76–5.88 (1H, m, 4-H); δ_C (50 MHz; $CDCl_3$) 12.3 (CH_3, NCH_2CH_3), 13.9 (CH_3, OCH_2CH_3), 19.9 (CH_2, C-13), 23.3 (CH_2, C-3), 30.7 (CH_2, C-12), 31.5 (CH_2, C-2), 32.0 (CH_2, C-14), 33.1 (CH_2, C-6), 41.2 (quat., C-1), 51.7 (CH_2, NCH_2CH_3), 52.0 (quat., C-8), 57.5 (CH_2, C-11), 60.7 (CH_2, OCH_2CH_3), 62.0 (CH_2, C-9), 72.8 (quat., C-7), 126.9 (CH, C-5), 132.2 (CH, C-4) and 176.7 (quat., OC=O); *m/z* (EI) 307 (M^+, 36%), 292 (M − CH_3, 25), 290 (M − OH, 10), 278 (M − C_2H_5, 42), 262 (M − OCH_2CH_3, 18), 234 (M − $CO_2CH_2CH_3$, 11) and 58 (100).

(1*S,7*R**,8*S**)-10-Ethyl-8-(hydroxymethyl)-10-azatricyclo-[6.3.3.0^{1,7}]tetradec-4-en-7-ol (25)**

To a slurry of lithium aluminium hydride (111 mg, 2.93 mmol) in dry THF (25 mL) at 0 °C, was slowly added a solution of ethyl (1*S**,7*R**,8*R**)-10-ethyl-7-hydroxy-10-azatricyclo-[6.3.3.0^{1,7}]tetradec-4-ene-8-carboxylate **23** (300 mg, 0.98 mmol) in dry THF (5 mL) and the mixture stirred under an atmosphere of nitrogen for 20 h. The reaction was then quenched by slow addition of water (25 mL) and the volatiles removed *in vacuo*. The remaining aqueous mixture was extracted with ethyl acetate (3 × 30 mL) and the combined organic layers washed with brine (50 mL) then dried ($MgSO_4$) and concentrated *in vacuo.* The crude product was then purified by flash chromatography (1 : 1 hexane–ethyl acetate) to give the *title compound* **25** (179 mg, 69%) as a clear oil [Found (EI): M^+, 265.2036: $C_{16}H_{27}NO_2$ requires M^+, 265.2042]; ν_{max}(NaCl)/cm^{-1} 3361 (O–H), 2907 (C–H), 1661, 1445, 1298 and 1076; δ_H (200 MHz; $CDCl_3$) 1.02 (3H, t, *J* 7.2, NCH_2CH_3), 1.10–1.38 (4H, m, 2A-H or 2B-H, 12-CH_2 and 13B-H), 1.48 (1H, dd, $J_{14A,13A}$ 6.8, J_{gem} 12.8, 14A-H), 1.89–2.04 (3H, m, 2A-H or 2B-H, 3A-H or 3B-H and 14A-H), 2.24 (2H, q, *J* 7.2, NCH_2CH_3), 2.43–2.69 (6H, m, 3A-H or 3B-H, 6A-H or 6B-H, 7-OH, 11-CH_2 and 9B-H), 2.72–2.94 (4H, m, 6A-H or 6B-H, 9A-H, 13A-H and CH_2OH), 3.11 (1H, d, J_{gem} 10.8, CH_AH_BOH), 3.84 (1H, d, J_{gem} 10.8, CH_AH_BOH), 5.57–5.65 (1H, m, 5-H) and 6.05–6.10 (1H, m, 4-H); δ_C (50 MHz; $CDCl_3$) 12.3 (CH_3, NCH_2CH_3), 20.2 (CH_2, C-13), 23.4 (CH_2, C-3), 28.9 (CH_2, C-12), 30.2 (CH_2, C-2), 34.4 (CH_2, C-14), 36.1 (CH_2, C-6), 41.1 (quat., C-1), 41.6 (quat., C-8), 51.9 (CH_2, NCH_2CH_3), 58.3 (CH_2, C-11), 60.7 (CH_2, C-9), 68.6 (CH_2, CH_2OH), 76.3 (quat., C-7), 126.3 (CH, C-5) and 136.1 (CH, C-4); *m/z* (EI) 265 (M^+, 30%), 264 (M − H, 27), 250 (M − CH_3, 100), 248 (M − OH, 45) and 234 (M − CH_2OH, 23).

(1*S,7*S**,8*S**)-10-Ethyl-8-(hydroxymethyl)-10-azatricyclo-[6.3.3.0^{1,7}]tetradec-4-en-7-ol (26)**

To a slurry of lithium aluminium hydride (92 mg, 2.44 mmol) in dry THF (30 mL) a solution of ethyl (1*S**,7*S**,8*R**)-10-ethyl-7-hydroxy-10-azatricyclo[6.3.3.0^{1,7}]tetradec-4-ene-8-carboxylate **24** (250 mg, 0.81 mmol) in dry THF (10 mL) was slowly added and the mixture stirred under an atmosphere of nitrogen for 24 h. The reaction was then quenched by dropwise addition of water (20 mL) and the volatiles removed *in vacuo*. The remaining aqueous solution was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers washed with brine (50 mL) then dried ($MgSO_4$) and concentrated *in vacuo.* The crude product was then purified by flash chromatography (1 : 1 hexane–ethyl acetate) to give the *title compound* **26** (162 mg, 75%) as a clear oil [Found (EI): M^+, 265.2036; $C_{16}H_{27}NO_2$ requires M^+, 265.2042]; ν_{max}(NaCl)/cm^{-1} 3242 (OH), 2901 (C–H), 1452, 1295 and 1073; δ_H (200 MHz; $CDCl_3$) 0.90 (1H, ddd, $J_{12A,13B}$ 1.8, $J_{12A,13A}$ 5.7, J_{gem} 14.4, 12A-H), 0.99 (3H, t, *J* 7.2, NCH_2CH_3), 1.13–1.31 (2H, m, 12B-H and 13B-H), 1.41–1.50 (1H, m, 2A-H or 2B-H), 1.52 (1H, td, J_{gem} 14.2, $J_{14B,13A}$ 14.2, $J_{14B,13B}$ 1.8, 14B-H), 1.84–2.00 (2H, m, 2A-H or 2B-H and 14A-H), 2.06–2.25 (4H, m, 3-CH_2 and NCH_2CH_3), 2.31 (1H, dd, $J_{11B,9B}$ 1.8, J_{gem} 11.3, 11B-H), 2.37–2.47 (2H, m, 6A-H or 6B-H and 9B-H), 2.58–2.80 (4H, m, 6A-H or 6B-H, 11A-H, 13A-H and 7-OH), 2.97 (1H, d, J_{gem} 11.0. 9A-H), 3.08 (1H, d, J_{gem} 11.4, CH_AH_BOH), 3.40 (1H, br, CH_2OH), 3.83 (1H, d, J_{gem} 11.4, CH_AH_BOH), 5.53–5.62 (1H, m, 5-H) and 5.96–6.03 (1H, m, 4-H); δ_C (50 MHz; $CDCl_3$) 12.4 (CH_3, NCH_2CH_3), 19.4 (CH_2, C-13), 22.9 (CH_2, C-3), 29.4 (CH_2, C-12), 31.8 (CH_2, C-2), 31.9 (CH_2, C-14), 32.3 (CH_2, C-6), 41.3 (quat., C-1), 42.3 (quat., C-8), 52.0 (CH_2, NCH_2CH_3), 57.4 (CH_2, C-11), 62.9 (CH_2, C-9), 69.5 (CH_2, CH_2OH), 76.0 (quat., C-7), 126.6 (CH, C-5) and 135.7 (CH, C-4); *m/z* (EI) 265 (M^+, 52%), 264 (M − H, 50), 250 (M − CH_3, 55), 248 (M − OH, 48), 236 (M − C_2H_5, 17) and 58 (100).

(1′*S,7′*R**,8′*S**)-(10-Ethyl-7-hydroxy-10-azatricyclo-[6.3.3.0^{1,7}]tetradec-4-en-8-yl)methyl 2-aminobenzoate (27)**

The reaction was carried out according to the standard procedure, with the esterification step being left for 40 h, using (1*S**,7*R**,8*S**)-10-ethyl-8-(hydroxymethyl)-10-azatricyclo[6.3.3.0^{1,7}]tetradec-4-en-7-ol **25** (180 mg, 0.68 mmol), *N*-(trifluoroacetyl)anthranilic acid **15** (474 mg, 2.04 mmol), 4-(dimethylamino)pyridine (41 mg, 0.34 mmol), 1,3-dicyclohexylcarbodiimide (420 mg, 2.04 mmol) and sodium borohydride (51 mg, 1.36 mmol). Flash chromatography with 4 : 1 hexane–ethyl acetate as eluent afforded the *title compound* **27** (204 mg, 78%) as a pale orange oil [Found (EI): M^+, 384.2410: $C_{23}H_{32}N_2O_3$ requires M^+, 384.2413]; ν_{max}(NaCl)/cm^{-1} 3480 and 3370 (N–H), 2927 (C–H), 1687 (C=O), 1616, 1588, 1455 and 1248; δ_H (400 MHz; $CDCl_3$) 1.05 (3H, t, *J* 7.2, NCH_2CH_3), 1.13 (1H, ddd, $J_{12'B,13'B}$ 6.8, $J_{12'B,13'A}$ 13.2, J_{gem} 13.2, 12′B-H), 1.25 (1H, ddd, $J_{12'A,13'B}$ 1.7, $J_{12'A,13'A}$ 6.9, J_{gem} 13.2, 12′A-H), 1.39–1.50 (2H, m, 2′A-H or 2′B-H and 13′B-H), 1.65 (1H, ddd, $J_{14'B,13'B}$ 6.8, $J_{14'B,13'A}$ 12.8, J_{gem} 12.8, 14′B-H), 2.01–2.15 (3H, m, 2′A-H or 2′B-H, 3′A-H or 3′B-H and 14′A-H), 2.18–2.40 (5H, m, 3′A-H or 3′B-H, 6′A-H or 6′B-H, 7′-OH, 9′B-H and NCH_2CH_3), 2.56–2.60 (2H, m, 11′-CH_2), 2.79–2.82 (1H, m, 13′A-H), 2.87 (1H, d, J_{gem} 11.2, 9′A-H), 2.94 (1H, br d, J_{gem} 15.4, 6′A-H or 6′B-H), 4.24 (1H, d, J_{gem} 11.1, OCH_AH_B), 4.28 (1H, d, J_{gem} 11.1, OCH_AH_B), 5.53–5.57 (1H, m, 5′-H), 5.75 (2H, br, NH_2), 6.02–6.08 (1H, m, 4′-H), 6.63–6.66 (2H, m, 3-H

and 5-H), 7.25 (1H, td, *J* 7.7, 1.5, 4-H) and 7.82 (1H, dd, *J* 1.6, 8.3, 6-H); δ_C (100 MHz; $CDCl_3$) 12.6 (CH_3, NCH_2CH_3), 20.5 (CH_2, C-13′), 23.9 (CH_2, C-3′), 29.8 (CH_2, C-2′), 30.4 (CH_2, C-12′), 35.7 (CH_2, C-6′), 35.8 (CH_2, C-14′), 41.7 (quat., C-1′), 42.2 (quat., C-8′), 52.4 (CH_2, NCH_2CH_3), 58.8 (CH_2, C-11′), 61.7 (CH_2, C-9′), 68.0 (CH_2, OCH_2), 74.1 (quat., C-7′), 110.9 (quat., C-1), 116.2 (CH, C-3), 116.7 (CH, C-5), 126.5 (CH, C-5′), 131.0 (CH, C-6), 133.9 (CH, C-4), 136.1 (CH, C-4′), 150.4 (quat., C-2) and 168.1 (quat., OC=O); *m*/*z* (EI) 384 (M^+, 17%), 369 (M − CH_3, 49), 367 (M − OH, 9), 264 (M − $NH_2C_6H_4CO$, 10) and 120 ($NH_2C_6H_4CO$, 100).

(1′*S,7′*S**,8′*S**)-(10-Ethyl-7-hydroxy-10-azatricyclo-[6.3.3.0^{1,7}]tetradec-4-en-8-yl)methyl 2-aminobenzoate (28)**

The reaction was carried out according to the standard procedure, with the esterification step being left for 48 h, using (1*S**,7*S**,8*S**)-10-ethyl-8-(hydroxymethyl)-10-azatricyclo[6.3.3.01,7]tetradec-4-en-7-ol **26** (173 mg, 0.652 mmol), *N*-(trifluoroacetyl)anthranilic acid **15** (456 mg, 1.96 mmol), 4-(dimethylamino)pyridine (39 mg, 0.33 mmol), 1,3-dicyclohexylcarbodiimide (404 mg, 1.96 mmol) and sodium borohydride (49 mg, 1.30 mmol). Flash chromatography with 4 : 1 hexane–ethyl acetate as eluent afforded the *title compound* **28** (181 mg, 72%) as a pale yellow oil [Found (EI): M^+; 384.2405; $C_{23}H_{32}N_2O_3$ requires M^+, 384.2413]; ν_{max}(NaCl)/cm^{-1} 3501 (O–H), 3474 and 3368 (N–H), 2917 (C–H), 1686 (C=O), 1616, 1587, 1560, 1453 and 1245; δ_H (200 MHz; $CDCl_3$) 0.97 (1H, ddd, $J_{12A,13B}$ 2.0, $J_{12A,13A}$ 5.9, J_{gem} 14.5, 12A-H), 1.04 (3H, t, *J* 7.2, NCH_2CH_3), 1.22–1.41 (2H, m, 12′B-H and 13′B-H), 1.47–2.05 (5H, m, 3′A-H or 3′B-H, 2′-CH_2 and 14′-CH_2), 2.21–2.39 (4H, m, 3′A-H or 3′B-H, 6′A-H or 6′B-H, 11′B-H and NCH_2CH_3), 2.42 (1H, d, J_{gem} 11.2, 11′A-H), 2.62 (1H, dd, $J_{9'B,11'B}$ 1.5, J_{gem} 10.8, 9′B-H), 2.77 (1H, d, J_{gem} 10.8, 9′A-H), 2.81–2.93 (3H, m, 6′A-H or 6′B-H, 13′A-H and OH), 4.27 (1H, d, J_{gem} 11.2, OCH_AH_B), 4.27 (1H, d, J_{gem} 11.4, OCH_AH_B), 5.52–5.64 (1H, m, 5′-H), 5.74 (2H, br, NH_2), 6.00–6.13 (1H, m, 4′-H), 6.61–6.68 (2H, m, 3-H and 5-H), 7.25 (1H, td, *J* 7.6, 1.5, 4-H) and 7.82 (1H, dd, *J* 1.6, 8.2, 6-H); δ_C (50 MHz; $CDCl_3$) 12.5 (CH_3, NCH_2CH_3), 19.8 (CH_2, C-13′), 23.1 (CH_2, C-3′), 30.2 (CH_2, C-12′), 31.4 (CH_2, C-6′), 32.5 (CH_2, C-14′), 32.8 (CH_2, C-2′), 42.3 (quat., C-1′), 42.4 (quat., C-8′), 52.1 (CH_2, NCH_2CH_3), 57.5 (CH_2, C-11′), 62.6 (CH_2, C-9′), 68.2 (CH_2, OCH_2), 73.2 (quat., C-7′), 111.0 (quat., C-1), 116.3 (CH, C-3), 116.7 (CH, C-5), 126.8 (CH, C-5′), 131.0 (CH, C-6), 134.0 (CH, C-4), 136.1 (CH, C-4′), 150.4 (quat., C-2) and 168.1 (quat., OC=O); *m*/*z* (EI) 384 (M^+, 18%), 367 (M − OH, 5), 264 (M − $NH_2C_6H_4CO$, 17), 120 ($NH_2C_6H_4CO$, 73) and 72 (100).

(1″*S,7″*R**,8″*S**,3′*R**)- and (1″*S**,7″*R**,8″*S**,3′*S**)-(10-Ethyl-7-hydroxy-10-azatricyclo[6.3.3.0^{1,7}]tetradec-4-en-8-yl)methyl 2-(3-methyl-2,5-dioxopyrrolidin-1-yl)benzoate (29)**

(1′*S**,7′*R**,8′*S**)-(10-Ethyl-7-hydroxy-10-azatricyclo-[6.3.3.0^{1,7}]tetradec-4-en-8-yl)methyl 2-aminobenzoate **27** (73 mg, 0.189 mmol) and methylsuccinic anhydride (65 mg, 0.569 mmol) were heated together at 125 °C for 12 h. After this time the crude mixture was dissolved in warm ethyl acetate (10 mL), washed with sat. sodium bicarbonate (30 mL), brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography using 49 : 1 dichloromethane–methanol as eluent afforded the *title compound* **29** (82 mg, 90%) as an orange oil [Found (EI): M^+ 480.2627; $C_{28}H_{36}N_2O_5$ requires M^+, 480.2624]; ν_{max}(NaCl)/cm^{-1} 3310 (O–H), 2924 (C–H), 1783 (N-C=O), 1715 (C=O), 1603, 1492, 1453, 1391 and 1260; δ_H (200 MHz; $CDCl_3$) 1.00 (1H, dd, $J_{12''A,13''A}$ 5.8, J_{gem} 14.3, 12″A-H), 1.10 (3H, t, *J* 7.1, NCH_2CH_3), 1.21–1.36 (2H, m, 12″B-H and 13″B-H), 1.45 (3H, br d, *J* 5.6, 3′-CH_3), 1.53–2.03 (5H, m, 2″-CH_2, 3″A-H or 3″B-H and 14″-CH_2), 2.26–2.53 (6H, m, 6″A-H or 6″B-H, 3″A-H or 3″B-H, 11″-CH_2 and NCH_2CH_3), 2.68 (1H, d, J_{gem} 11.4, 9″B-H), 2.71–2.86 (3H, m, 6″A-H or 6″B-H, 3′-H and 13″A-H), 2.89 (1H, d, J_{gem} 11.4, 9″A-H), 3.04–3.18 (2H, m, 4′-CH_2), 3.32 (1H, s, OH), 4.28 (2H, br s, OCH_2), 5.46–5.61 (1H, m, 5″-H), 6.00–6.16 (1H, m, 4″-H), 7.24 (1H, d, *J* 7.3, 3-H), 7.53 (1H, t, *J* 7.6, 5-H), 7.65 (1H, t, *J* 7.5, 4-H) and 8.08 (1H, d, *J* 7.7, 6-H); δ_C (50 MHz; $CDCl_3$) 11.8 (CH_3, NCH_2CH_3), 19.4 (CH_2, C-13″), 23.0 (CH_2, C-3″), 29.9 (CH_2, C-12″), 31.4 (CH_2, C-6″), 32.4 (CH_2, C-2″ and C-14″), 35.3 (CH, C-3′), 37.0 (CH_2, C-4′), 42.3 (quat., C-1″), 42.4 (quat., C-8″), 53.0 (CH_2, NCH_2CH_3), 56.7 (CH_2, C-11″), 61.2 (CH_2, C-9″), 69.0 (CH_2, OCH_2), 72.7 (quat., C-7″), 126.4 (CH, C-5″), 127.2 (quat., C-1), 129.5 (CH, C-3), 130.0 (CH, C-5), 131.3 (CH, C-4), 132.8.4 (quat., C-2), 133.4 (CH, C-6), 136.5 (CH, C-4″), 164.2 (quat., OC=O), 175.9 (quat., C-5′) and 179.9 (quat., C-2′); *m*/*z* (EI) 480 (M^+, 25%), 465 (M − CH_3, 100) and 188 ($C_{11}H_{10}NO_2$, 10).

(1″*S,7″*S**,8″*S**,3′*R**)- and (1″*S**,7″*S**,8″*S**,3′*R**)-(10-Ethyl-7-hydroxy-10-azatricyclo[6.3.3.0^{1,7}]tetradec-4-en-8-yl)methyl 2-(3-methyl-2,5-dioxopyrrolidin-1-yl)benzoate (30)**

(1′*S**,7′*S**,8′*S**)-(10-Ethyl-7-hydroxy-10-azatricyclo-[6.3.3.0^{1,7}]tetradec-4-en-8-yl)methyl 2-aminobenzoate **28** (117 mg, 0.304 mmol) and methylsuccinic anhydride (104 mg, 0.913 mmol) were heated together at 125 °C for 3 h. After this time the crude mixture was dissolved in warm ethyl acetate (10 mL), washed with sat. sodium bicarbonate (30 mL), brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography using 100% ethyl acetate as eluent afforded the *title compound* **30** (120 mg, 82%) as a yellow oil [Found (EI): M^+, 480.2618; $C_{28}H_{36}N_2O_5$ requires M^+, 480.2624]; ν_{max}(NaCl)/cm^{-1} 3301 (O–H), 2929 (C–H), 1777 (N-C=O), 1714 (C=O), 1602, 1493, 1454 and 1260; δ_H (200 MHz; $CDCl_3$) 1.06 (3H, t, *J* 7.1, NCH_2CH_3), 1.13–1.70 (8H, m, 3′-CH_3, 2″A-H or 2″B-H, 12″-CH_2, 13″B-H and 14″B-H), 1.90–2.38 (9H, m, 2″A-H or 2″B-H, 3″-CH_2, 6″A-H or 6″B-H, 7″-OH, 9″B-H, 14″A-H and NCH_2CH_3), 2.41–2.68 (4H, 3′-H, 6″A-H or 6″B-H and 11″-CH_2), 2.70–2.94 (2H, m, 9″A-H and 13″A-H), 3.04–3.15 (2H, m, 4′-CH_2), 4.15–4.29 (2H, m, OCH_2), 5.49–5.54 (1H, m, 5″-H), 6.01–6.11 (1H, m, 4″-H), 7.23 (1H, dd, *J* 1.9, 6.5, 3-H), 7.52 (1H, td, *J* 7.7, 1.3, 5-H), 7.65 (1H, td, *J* 7.4, 1.4, 4-H) and 8.09 (1H, d, *J* 6.6, 6-H); δ_C (50 MHz; $CDCl_3$) 12.5 (CH_3, NCH_2CH_3), 16.3 (CH_3, 3′-CH_3), 20.4 (CH_2, C-13″), 23.8 (CH_2, C-3″), 29.6 (CH_2, C-2″), 29.8 (CH_2, C-12″), 35.2 (CH_2, C-6″), 35.3 (CH_2, C-14″), 35.9 (CH, C-3′), 36.9 (CH_2, C-4′), 41.7 (quat., C-1″), 42.1 (quat., C-8″), 52.3 (CH_2, NCH_2CH_3), 58.6 (CH_2, C-11″), 61.6 (CH_2, C-9″), 68.8 (CH_2, OCH_2), 73.9 (quat., C-7″), 126.2 (CH, C-5″), 127.2 (quat., C-1), 129.3 (CH, C-3), 129.7 (CH, C-5), 131.2 (CH, C-4), 132.7 (quat., C-2) 133.3 (CH, C-6), 136.3 (CH, C-4″), 164.2 (quat., OC=O), 175.8 (quat., C-5′) and 179.8 (quat., C-2′); *m*/*z* (EI) 480 (M^+, 6%), 465 (M − CH_3, 20), 188 ($C_{11}H_{10}NO_2$, 2) and 146 (100).

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