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Synthesis of *N*-(3-Phenylpropyl)-Substituted Tricyclic ABE Ring Analogues of the Alkaloid Methyllycaconitine

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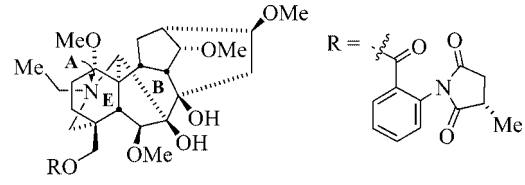
The synthesis of several ABE tricyclic analogues **5**, **31** and **32** of the alkaloid methyllycaconitine (**1**) is reported. The analogues contain two key pharmacophores: a tertiary *N*-(3-phenylpropyl) substituent attached to a 3-azabicyclo-[3.3.1]nonane ring system and a 2-(3-methyl-2,5-dioxopyrrolidin-1-yl)benzoate ester. Double Mannich reaction of the cyclic β-keto esters **6** and **17** with the bis(aminol) ether **7** using methyltrichlorosilane as an activating agent provided an efficient method for the construction of the 3-azabicyclo[3.3.1]nonanes **8** and **18**. Ring-closing metathesis of the derived dienes **11**, **19**, and **20** afforded the tricyclic ethers **12**, **21**, and **22**, respectively, the C-8 ester of which was reduced to a hydroxymethyl group to form the ABE tricyclic analogues **13**, **23**, and **24**. Conversion of the alcohol **13** to the anthranilate ester **14** using *N*-(trifluoroacetyl)anthranilic acid followed by fusion with methylsuccinic anhydride afforded the analogue **5** containing the key *N*-(methylsuccinimido)anthranilate pharmacophore. In the case of the alcohols **23** and **24** the 2-(3-methyl-2,5-dioxopyrrolidin-1-yl)benzoate ester pharmacophore was appended by direct esterification with unsaturated acid **28** followed by hydrogenation to the ABE tricyclic compounds **33** and **34**.

Introduction

Methyllycaconitine (MLA, **1**) (Figure 1) is the principle toxin in *Delphinium brownii* and is found in at least 30 *Delphinium* species as well as in *Consolida ambigua* and *Inaula-royaleana*.[1,2] MLA is the 2-[2-(*S*)-methylsuccinimido]benzoate ester of the norditerpenoid alkaloid lycoctonine and contains a piperidine (E) and cyclohexane (A) ring in a 3-azabicyclo[3.3.1]nonane motif. MLA's primary mode of action is by competitive blockade at nicotinic acetylcholine receptors (nAChRs). The neuromuscular action of MLA is almost completely destroyed if the aromatic ester functionality is cleaved. Comparison of the neuromuscular activity of MLA with its parent alkaloid lycoctonine (**2**) established that **2** has approximately 2000 times less affinity for rat neuronal α7 subtype nAChRs than its *N*-substituted anthranilate ester **1**.[3] MLA displays specific reversible, competitive antagonistic activity towards α-bungarotoxin-sensitive nAChRs, rendering it a unique probe for discrimination of these particular nAChRs. MLA also has a much higher affinity for α-bungarotoxin-sensitive insect nAChRs than for α-bungarotoxin-sensitive rat neuronal tissue preparations[4–6] thus establishing MLA as a possible lead target for the development of insecticides. The high toxicity of MLA to mammals prevents its use as an agrochemical; however, if the inhibitory action of MLA is localised in a small toxophoric section of the molecule, a subunit of MLA based on this section may have the desired toxophoric properties, yet be significantly lower in toxicity to mammals. The synthesis of analogues of MLA 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.



methyllycaconitine (MLA) **1**
lycoctonine R = H **2**

Figure 1. Structure of the alkaloid methyllycaconitine (MLA) illustrating the ABE rings.

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 **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.[7] A total synthesis of **1** has not been achieved to date. A number of approaches to the preparation of small molecule analogues of MLA incorporating the putative pharmacophore have been reported, including the synthesis of E,[8–10] AE,[11] AEF,[12,13] ABE,[14,15] and

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ABEF[16] ring systems, and some of these analogues display significant biological activity.[17,18] Bergmeier and coworkers[8,10,18] have reported that simple E ring analogues of MLA act as antagonists ($IC_{50} > 11.4$ μM) of bovine adrenal α3β4* nAChRs. However, competition binding assays at the α3β4* nAChR suggested a noncompetitive mode of inhibition in contrast to the competitive binding observed for MLA at this receptor.[18] Studies on rat brain α7 nAChR showed little inhibition of [^{125}I]α-bungarotoxin binding by these analogues ($IC_{50} > 177$ μM).[18] Furthermore, the binding affinity at both α3 and α7 receptors was found to be independent of analogue stereochemistry.[10]

A simple E ring analogue **3** of MLA containing a *N*-(3-phenylpropyl) substituent (Figure 2) has been tested in an inhibition assay of nicotine-stimulated catecholamine release by multiple nicotinic acetylcholine receptor subtypes derived from adrenal chromaffin cells.[8] In this assay, the *N*-(3-phenylpropyl) analogue **3** was found to be much more efficient (86.3% inhibition compared to 95.2% inhibition for **1**) than the corresponding *N*-ethyl analogue **4** (33.5% inhibition). Furthermore, the four different diastereomers of **3** have been synthesized and evaluated in competitive ligand-binding assays.[10] All four diastereomers showed the same potency at both the α3 and α7 nicotinic acetylcholine receptors as the racemic compound.

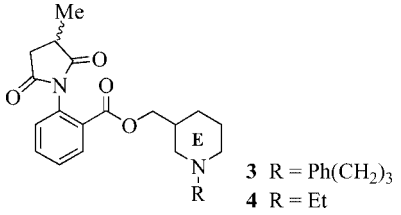
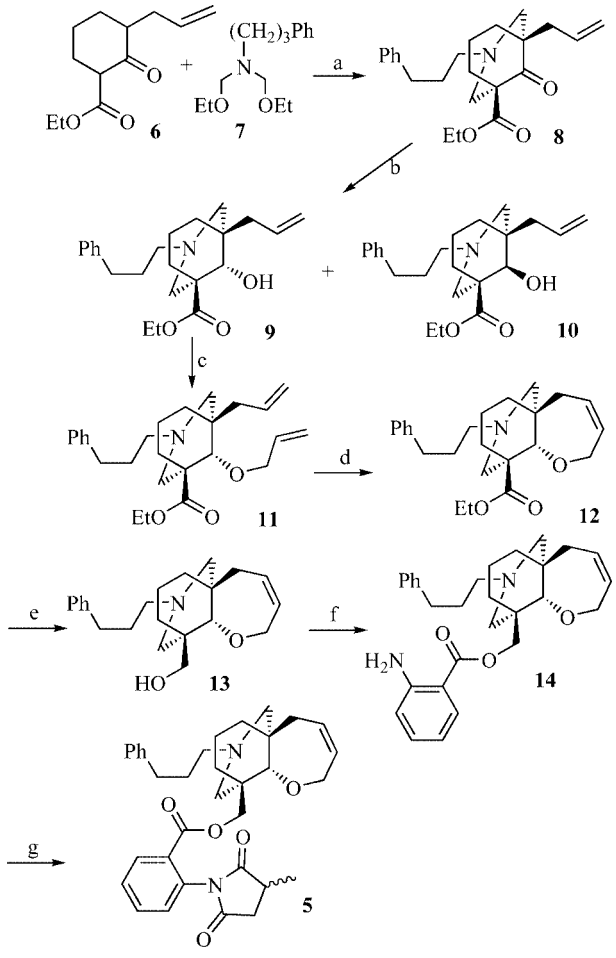


Figure 2. Structure of the E ring analogues **3**,**4** of MLA **1** tested for inhibition of nicotinic acetylcholine receptor sub-types.

We have previously reported[14] the synthesis of several tricyclic analogues of **1** containing the key 2-(3-methyl-2,5-dioxopyrrolin-1-yl)benzoate ester in which an additional seven-membered ring (a B ring) was appended to a 3-azabicyclo[3.3.1]nonane framework (the AE rings) envisaging that incorporation of the *N*-substituted anthranilate ester into a conformationally restricted framework might enhance the biostability, selectivity and potency of previously prepared simpler bicyclic AE analogues. We have also recently reported that bis-aminoalkylation of cyclic β-keto esters using bis(aminol) ethers provides an efficient entry to azabicyclo[3.3.1]nonanes.[19] Previous use of a classical double Mannich reaction to construct the azabicyclo[3.3.1]-nonane AE ring system[14,15,20] only proceeded in low yield, and could not be readily extended to the use of alternative primary amines thus limiting our analogue development programme. We therefore herein report the synthesis of several rigid tricyclic analogues of MLA combining the use of our ring-closing metathesis strategy with our bis-aminoalkylation strategy to introduce the desired *N*-(3-phenylpropyl) substituent into the E ring.

Results and Discussion

Initial attention focussed on the synthesis of the ABE analogue **5** of **1** bearing a *N*-(3-phenylpropyl) substituent with a seven-membered cyclic ether B ring appended to the AE bicyclic system (Scheme 1). The synthesis started from allylated β-keto ester **6**[14] that underwent facile double Mannich reaction with bis(aminol) ether **7**[19] using methyltrichlorosilane as the activator in acetonitrile at ambient temperature providing an efficient method for construction of the *N*-(3-phenylpropyl)-substituted azabicyclo[3.3.1]-nonane **8**.[19] Sodium borohydride reduction of the ketone **8** then afforded the secondary alcohol **9** in 46% yield together with the alcohol **10** in 33% yield, which were readily separated by flash chromatography. The 9-OH has a γ-shielding effect on the chemical shift of the carbon atoms in the bicyclic ring structure that are *syn* to the hydroxy group thus the resonances assigned to C-2 and C-4 of the azabicyclo[3.3.1]nonane ring resonate further upfield in **9** relative to **10**.[21–23]

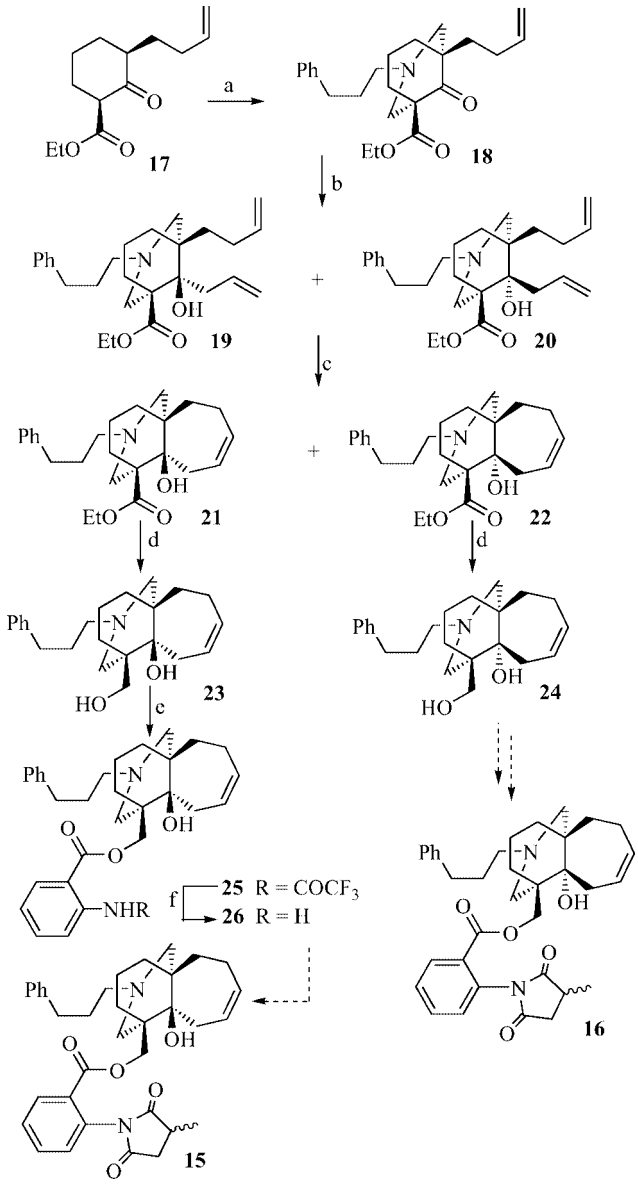


Scheme 1. (a) $MeSiCl_3$, CH_3CN, 20 h, 77%; (b) $NaBH_4$, THF, H_2O, 0 °C, **9**, 46%, **10**, 33%; (c) NaH, allyl bromide, THF, room temp., 48 h, 33%; (d) 5% Grubbs' 1st generation RCM catalyst, room temp., 20 h, **12**, 99%; (e) $LiAlH_4$, THF, room temp., 2 h, **13**, 79%; (f) *N*-(trifluoroacetyl)anthranilic acid, DCC, DMAP, CH_3CN, 40 °C, 16 h then $NaBH_4$, EtOH, room temp., 20 h, 80%; (g) methylsuccinic anhydride, 125 °C, 4 h, 97%.

Allylation of the major alcohol **9** using sodium hydride and allyl iodide proceeded in low yield affording the diene **11**, the low yield was presumably due to the slow reaction at the sterically hindered C-9 hydroxy group thus allowing competing decomposition reactions to occur. The diene **11** then underwent smooth ring-closing metathesis using Grubbs' first-generation metathesis to give the ABE tricyclic ester **12**. Reduction of the ester **12** using lithium aluminium hydride then provided the alcohol **13** in preparation for appendage of the key *N*-(methylsuccinimido)anthranilate pharmacophore. The anthranilate ester **14** was prepared in 80% yield from *N*-(trifluoroacetyl)anthranilic acid following our two-step protocol.[24] Finally, fusion of the anthranilate ester **14** with methylsuccinic anhydride afforded the tricyclic analogue **5** containing a seven-membered ether B ring with the same *trans* AB ring fusion as present in **1** together with the desired *N*-(3-phenylpropyl) substituent in the E ring.

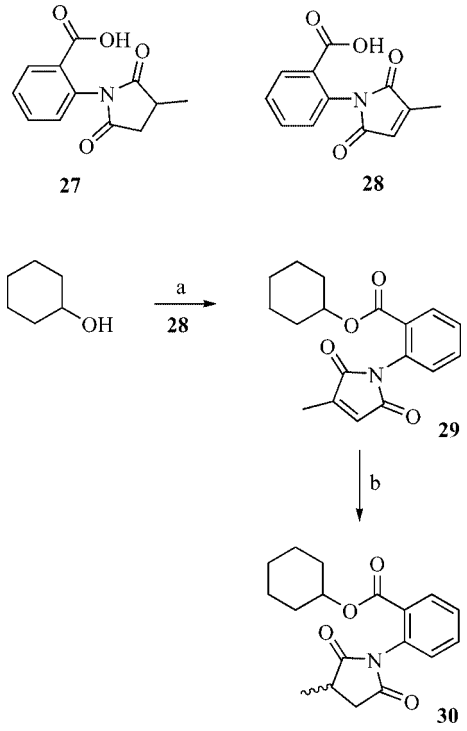
The synthesis of a second series of ABE analogues containing a carbocyclic B ring, namely analogues **15** and **16**, was next initiated adopting a separate synthetic sequence starting from the butenyl-substituted ketone **17**[14] (Scheme 2). Double Mannich reaction with bis(aminol) ether **7** afforded the azabicyclo[3.3.1]nonane **18**. Careful addition of allylmagnesium bromide to **18** at 0 °C followed by stirring at room temperature for 24 h afforded the allylated products **19** and **20** in 76% combined yield as a 1.7:1 ratio of diastereomers, which were separable by flash chromatography. Ring-closing metathesis of the dienes **19** and **20** afforded the respective carbocyclic products **21** and **22** in excellent yield which were then reduced with lithium aluminium hydride to give the diols **23** and **24** (89% and 87% yield, respectively). Selective esterification of the *trans*-fused neopentyl alcohol in **23** using *N*-(trifluoroacetyl)anthranilic acid afforded the anthranilate ester **25** in 95% yield, however subsequent attempts to remove the trifluoroacetyl group using sodium borohydride surprisingly only proceeded in low yield (12%), thus limiting access to the desired analogue **15**. The major product of the reaction was the alcohol **23**, which results from reductive cleavage of the anthranilate ester. The use of the milder reagent sodium cyanoborohydride or use of methanolic potassium carbonate to remove the trifluoroacetyl group only resulted in the formation of the alcohol **23** or decomposition. Moreover, similar conversion of *cis*-fused neopentyl alcohol **24** to the desired *cis*-fused tricyclic analogue **16** was thwarted by the inability to affect initial esterification using *N*-(trifluoroacetyl)anthranilic acid in this case. These later difficulties thus prompted investigation of an alternative method to append the substituted anthranilate pharmacophore to the basic tricyclic framework in alcohols **23** and **24**.

We previously reported[24] an efficient two-step procedure for the introduction of the key 2-(2′-methylsuccinimido)-benzoate ester pharmacophore by esterification of the alcohol precursors with *N*-(trifluoroacetyl)anthranilic acid under Steglich conditions, followed by sodium borohydride mediated cleavage of the trifluoroacetyl group to afford an anthranilate ester. Subsequent fusion with methylsuccinic anhydride affords the key *N*-substituted anthranilate pharmacophore. This method proved more efficient than earlier methods developed by Kraus and Dneprovskaia[13] and by Bergmeier and co-workers,[8,9] which involved direct esterification using 2-(3-methyl-2,5-dioxopyrrolidin-1-yl)benzoic acid (**27**). The use of isatoic anhydride also developed by Blagbrough[20] has been adopted by others to append the anthranilate ester group to MLA analogues;[12,13] however, in general low yields (typically 40–65%) of the desired anthranilate esters are obtained, which is attributed to the hindered neopentyl environment of the hydroxy group present in **2** and many of the simpler analogues.



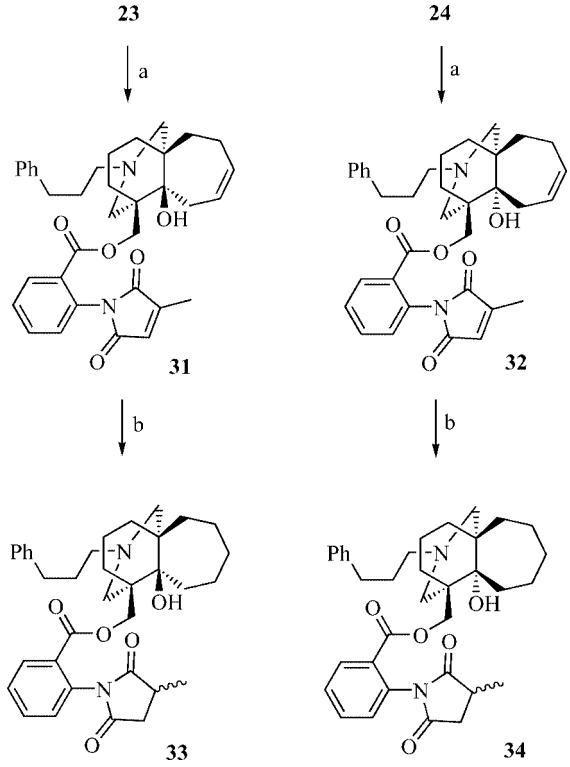
Scheme 2. (a) **7**, $MeSiCl_3$, CH_3CN, 20 h, 55%; (b) allylmagnesium bromide, THF, 0 °C to room temp., 24 h, **19**, 48%, **20**, 28%; (c) 5% Grubbs' 1st generation RCM catalyst, room temp., 20 h, **21**, 52%, **22**, 33%; (d) $LiAlH_4$, THF, room temp., 2 h, **23**, 89%, **24**, 87%; (e) *N*-(trifluoroacetyl)anthranilic acid, DCC, DMAP, CH_3CN, 40 °C, 20 h, 95%; (f) $NaBH_4$, EtOH, room temp., 18 h, 12%.

In light of our inability to effect introduction of the substituted anthranilate pharmacophore onto the neopentyl alcohols **23** and **24** we decided to investigate an alternative method for the introduction of this key functionality using cyclohexanol as a model system (Scheme 3). It was envisaged that the readily prepared[25] unsaturated 2-[3-methyl-2,5-dihydro-2,5-dioxo-1*H*-pyrrol-1-yl]benzoic acid (**28**) would prove to be a more reactive esterification partner than the corresponding saturated acid **27**. Hydrogenation of the olefin after esterification would then provide the methylsuccinimido anthranilate pharmacophore. When the carboxylic acid of **27** is activated, it is known that it can undergo competing intramolecular attack by one of the succinimido carbonyl groups.[12] It was hoped that this competing reaction would be disfavored by the altered electronic nature of the unsaturated succinimido ring. This hypothesis proved fruitful in a model system in that cyclohexanol underwent facile DCC-mediated esterification with the unsaturated acid **28** to give the 2-[3-methyl-2,5-dihydro-2,5-dioxo-1*H*-pyrrol-1-yl]anthranilate **29**. Subsequent hydrogenation over 10% palladium on charcoal afforded the *N*-(methylsuccinimido)anthranilate **30** in almost quantitative yield.



Scheme 3. (a) DCC, DMAP, room temp., 10 h, 98%; (b) H_2, 10% Pd/C, EtOAc, 99%.

Encouraged by the improved method for appendage of the key *N*-(methylsuccinimdo)anthraniliate ester pharmacophore to cyclohexanol using the unsaturated acid **28** we then proceeded to apply this new method for the more problematic esterification of the hindered neopentyl alcohols **23** and **24** (Scheme 4). Pleasingly, DCC-mediated coupling of the tricyclic alcohols **23** and **24** with the unsaturated acid **28** resulted in selective esterification of the neopentyl alcohol affording the unsaturated anthranilates **31** and **32** in excellent yield (83% and 85%, respectively). Finally, hydrogenation over 10% palladium on charcoal afforded the desired tricyclic analogues **33** and **34** of **1** in which concomitant hydrogenation of the internal olefin had also taken place.



Scheme 4. (a) **28**, DCC, DMAP, room temp., 6 h, **31**, 83%, **32**, 85%; (b) H_2, 10% Pd/C, EtOAc, **33**, 92%, **34**, 90%.

Conclusions

In summary, the successful synthesis of three ABE tricyclic analogues **5**, **31** and **32** of methyllycaconitine (**1**) has been reported using a double Mannich cyclisation followed by a Grubbs' ring-closing metathesis to introduce the seven-membered B ring. These analogues also contain an *N*-(3-phenylpropyl) substituent, which when incorporated into a tricyclic ABE framework may prove more effective as inhibitors of the α7 nAChR sub-type.

Experimental Section

General Methods: Analytical thin-layer chromatography (TLC) was performed using 0.2 mm thick precoated silica gel plates (Merck Kieselgel 60 F_{254}). Compounds were visualized by ultraviolet fluorescence or by staining with potassium permanganate in aqueous sodium hydroxide. Flash chromatography was performed using Riedel de Haen silica gel (0.032–0.063 mm) with the indicated solvents. ^{1}H NMR spectra were recorded with a Bruker DRX 300 (300 MHz), a Bruker DRX 400 (400 MHz) or a Bruker DRX 600 (600 MHz) spectrometer at ambient temperature using $CDCl_3$ as a solvent. Chemical shifts are given in parts per million downfield

shift from tetramethylsilane as an internal standard, and reported as position (δ), multiplicity (s = singlet, br. s = broad singlet, d = doublet, dd = double doublet, ddd = double double doublet, dddd = double double double doublet, t = triplet, dt = double triplet, tt = triple triplet, q = quartet, quint = quintet, sept = septet, m = multiplet), relative integral, assignment and coupling constant (J in Hz). ^{13}C NMR spectra were recorded with a Bruker DRX 300 (75 MHz), a Bruker DRX 400 (100 MHz) or a Bruker DRX 600 (150 MHz) spectrometer at ambient temperature with complete proton decoupling. Chemical shifts are expressed in parts per million referenced to the residual chloroform peak (δ = 77.0 ppm), and reported as position (δ) and assignment, aided by DEPT 135 experiments. In addition, ^{1}H-^{1}H-COSY and ^{1}H-^{13}C-HSQC correlation spectra were used for the complete assignment of the proton and carbon resonances. ^{1}H-^{1}H-NOESY NMR spectra were recorded in special cases to determine the constitution of diastereomers. The NMR spectroscopic data for the bicyclic analogues of methyllycaconitine were assigned using the following descriptors: bicyclic ring system (no prime), 3-phenylpropyl (arom), anthranilate ester (′) and methylsuccinimide (′′). High-resolution mass spectra were recorded with a VG-70SE mass spectrometer operating with an ionisation potential of 70 eV at nominal resolutions of 5000 to 10000 as appropriate. Ionisation methods employed were either electron impact (EI) or fast-atom bombardment (FAB) using *m*-nitrobenzyl alcohol as matrix. Major fragments are given as mass to charge ratios. Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. β-Keto esters **6** and **17** were prepared as described in our previous paper.[14] *N*-(Trifluoroacetyl)anthranilic acid was prepared as reported.[26] In compounds **33** and **34** the stereochemistry of the C3′′–CH_3 is undefined and is presumable a 1:1 mixture of diastereomers at this position.

Ethyl 9-Oxo-3-(3-phenylpropyl)-5-(2-propenyl)-3-azabicyclo[3.3.1]-nonane-1-carboxylate (8): The title compound was prepared from the β-keto ester **6**[20] (650 mg, 3.09 mmol), *N*,*N*-bis(ethoxymethyl)-3-phenylpropylamine **7**[19] (1.55 g, 6.18 mmol) and methyltrichlorosilane (726 μL, 6.18 mmol) in acetonitrile (15 mL) following the reported procedure.[19] Yield 882 mg (2.39 mmol, 77%) of a clear oil.

Ethyl (1*R,5*S**,9*S**)-9-Hydroxy-3-(3-phenylpropyl)-5-(2-propenyl)-3-azabicyclo[3.3.1]nonane-1-carboxylate (9) and Ethyl (1*R**,5*S**,9*R**)-9-Hydroxy-3-(3-phenylpropyl)-5-(2-propenyl)-3-azabicyclo[3.3.1]nonane-1-carboxylate (10):** To a suspension of sodium borohydride (28 mg, 0.75 mmol) in THF (5 mL) and water (10 mL) was added dropwise a solution of the β-keto ester **8** (550 mg, 1.49 mmol) in THF (5 mL) at 0 °C. The mixture was stirred for 20 h at room temperature and then diluted with water (30 mL). The volatiles were removed at reduced pressure and the remaining aqueous solution was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The alcohols **9** and **10** were separated by flash chromatography (5% EtOAc in hexane). **Alcohol 9:** 255 mg (0.69 mmol, 46%) of a clear oil; R_f = 0.40 (10% EtOAc in hexane); HRMS (EI): *m*/*z* calcd. for $C_{23}H_{33}NO_3$: 371.2460, found: 371.2462 [M^+]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.16 [m, 5 H, H_{arom} (Ph)], 5.91–5.81 (m, 1 H, CH_2CH=CH_2), 5.08–5.04 (m, 2 H, CH_2CH=CH_2), 4.15 [q, ^3J = 7.1 Hz, 2 H, CH_2 (Et)], 3.72 (s, 1 H, 9-H), 2.86 (d, $^2J_{gem}$ = 11.1 Hz, 1 H, 4-H_{eq}), 2.77–2.71 (m, 1 H, 7-H_{ax}), 2.74 (br. s, 1 H, 9-OH), 2.65–2.63 (m, 1 H, 4-H_{ax}), 2.63 [t, ^3J = 7.7 Hz, 2 H, N(CH_2)$_2$CH_2Ph], 2.43 (d, $^2J_{gem}$ = 11.0 Hz, 1 H, 2-H_{eq}), 2.30–2.28 (m, 1 H, 2-H_{ax}), 2.28 [t, ^3J = 7.4 Hz, 2 H, NCH_2(CH_2)$_2$Ph], 2.14 (dd, $^2J_{gem}$ = 13.6, ^3J = 7.2 Hz, 1 H, C$H_a$$H_b$CH=$CH_2$), 2.05–1.96 (m, 2 H, $CH_a$$H_b$CH=$CH_2$, 6-$H_{eq}$), 1.80 (quint, $^3J_{gem}$ = 7.7 Hz, 2 H, $NCH_2CH_2CH_2$Ph), 1.73–1.60 (m, 2 H, 6-H_{ax}, 8-H_{eq}), 1.53–1.43 (m, 2 H, 7-H_{eq}, 8-H_{ax}), 1.25 [t, ^3J = 7.1 Hz, 3 H, CH_3 (Et)] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.3 [C=O (ester)], 142.5 (C-1$_{arom}$), 134.2 (CH_2*C*H=CH_2), 128.4 (C-3$_{arom}$, C-5$_{arom}$), 128.3 (C-2$_{arom}$, C-6$_{arom}$), 125.7 (C-4$_{arom}$), 117.7 (CH_2CH=*C*H_2), 73.6 (C-9), 60.7 [CH_2 (Et)], 57.8 (C-2), 57.6 [N*C*H_2(CH_2)$_2$Ph], 53.6 (C-4), 48.9 (C-1), 41.9 (*C*H_2CH=CH_2), 38.2 (C-5), 35.2 (C-8), 34.7 (C-6), 33.6 [N(CH_2)$_2$*C*H_2Ph], 28.9 (NCH_2*C*H_2CH_2Ph), 20.8 (C-7), 14.1 [CH_3 (Et)] ppm. The ^{1}H-^{1}H-NOESY NMR spectra (400 MHz, $CDCl_3$, T_{mix} = 800 ms) exhibited NOEs between 9-H and 6-H_{ax} and between 9-H and 8-H_{ax}. Couplings between 9-H and 2-H_{ax} or 4-H_{ax} were not detected.

Alcohol 10: Yield 182 mg (0.49 mmol, 33%) of a clear oil; R_f = 0.49 (10% EtOAc in hexane); HRMS (EI): *m*/*z* calcd. for $C_{23}H_{33}NO_3$: 371.2460, found: 371.2460 [M^+]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.17 [m, 5 H, H_{arom} (Ph)], 5.89–5.78 (m, 1 H, CH_2*C*H=CH_2), 5.05–5.01 (m, 2 H, CH_2CH=CH_2), 4.14 [dq, ^3J = 7.1 Hz, 2 H, CH_2 (Et)], 3.64 (s, 1 H, 9-H), 3.23 (d, $^3J_{9,OH}$ = 2.2 Hz, 1 H, 9-OH), 3.12 (dd, $^2J_{gem}$ = 11.1, $^4J_{2eq,4eq}$ = 1.3 Hz, 1 H, 4-H_{eq}), 2.75–2.66 (m, 1 H, 7-H_{ax}), 2.71 (dd, $^2J_{gem}$ = 10.9, $^4J_{2eq,4eq}$ = 1.4 Hz, 1 H, 2-H_{eq}), 2.63 [t, ^3J = 7.5 Hz, 2 H, N(CH_2)$_2$CH_2Ph], 2.19 [t, ^3J = 6.9 Hz, 2 H, NCH_2(CH_2)$_2$Ph], 2.14–2.02 (m, 4 H, 4-H_{ax}, 6-H_{eq}, CH_2CH=CH_2), 1.91 (dd, $^2J_{gem}$ = 11.2, $^4J_{2ax,8ax}$ = 2.2 Hz, 1 H, 2-H_{ax}), 1.81–1.73 (m, 4 H, 6-H_{ax}, 8-H_{eq}, NCH_2CH_2CH_2Ph), 1.55–1.51 (m, 1 H, 7-H_{eq}), 1.41 (dd, $^2J_{gem}$ = 13.5, $^3J_{7eq,8ax}$ = 6.2 Hz, 1 H, 8-H_{ax}), 1.25 [t, ^3J = 7.1 Hz, 3 H, CH_3 (Et)] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.9 [C=O (ester)], 142.4 (C-1$_{arom}$), 134.3 (CH_2*C*H=CH_2), 128.4 (C-3$_{arom}$, C-5$_{arom}$), 128.3 (C-2$_{arom}$, C-6$_{arom}$), 125.7 (C-4$_{arom}$), 117.4 (CH_2CH=*C*H_2), 74.3 (C-9), 62.7 (C-2), 60.8 [CH_2 (Et)], 59.9 (C-4), 57.4 [N*C*H_2(CH_2)$_2$Ph], 47.9 (C-1), 42.7 (*C*H_2CH=CH_2), 37.6 (C-5), 33.5 [N(CH_2)$_2$*C*H_2Ph], 29.6 (C-8), 29.0 (NCH_2*C*H_2CH_2Ph), 27.3 (C-6), 20.9 (C-7), 14.1 [CH_3 (Et)]. The ^{1}H-^{1}H-NOESY NMR spectra (400 MHz, $CDCl_3$, T_{mix} = 800 ms) exhibited NOEs between 9-H and 2-H_{ax} and between 9-H and 4-H_{ax}. In addition, NOEs between 9-OH and 6-H_{ax} were observed. Couplings between 9-H and 6-H_{ax} or 8-H_{ax} were not detected.

Ethyl (1*R,5*S**,9*S**)-3-(3-Phenylpropyl)-5-(2-propenyl)-9-(2-propenyloxy)-3-azabicyclo[3.3.1]nonane-1-carboxylate (11):** To a suspension of sodium hydride (95%, 40 mg, 1.60 mmol) in dry THF (8 mL) was added a solution of alcohol **9** (150 mg, 0.40 mmol) in dry THF (2 mL) at 0 °C, and the mixture was stirred for 30 min. Allyl bromide (138 μL, 1.60 mmol) was then added and the reaction mixture was stirred for 4 days at room temperature. The reaction mixture was quenched by the addition of water (5 mL) and the volatiles were removed at reduced pressure. The residue was diluted with brine (10 mL), extracted with ethyl acetate (3 × 20 mL), and the combined organic layers dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (5% EtOAc in hexane). Yield 55 mg (0.13 mmol, 33%) of a clear oil; R_f = 0.60 (5% EtOAc in hexane). HRMS (EI): m/z calcd. for $C_{26}H_{37}NO_3$: 411.2773, found: 411.2772 [M^+]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.15 [m, 5 H, H_{arom} (Ph)], 5.86–5.77 (m, 2 H, OCH_2C*H*=CH_2, CH_2C*H*=CH_2), 5.22 (dd, $^2J_{gem}$ = 1.8, $^3J_{trans}$ = 17.2 Hz, 1 H, OCH_2CH=C$H_a$$H_b$), 5.07–5.00 (m, 3 H, OCH_2CH=C$H_a$$H_b$, CH_2CH=CH_2), 4.17–4.05 [m, 4 H, CH_2 (Et), O*C*H_2CH=CH_2], 3.45 (s, 1 H, 9-H), 2.90 (d, $^2J_{gem}$ = 11.2 Hz, 1 H, 4-H_{eq}), 2.83–2.71 (m, 1 H, 7-H_{ax}), 2.67–2.60 [m, 3 H, 4-H_{ax}, N(CH_2)$_2$CH_2Ph], 2.44 (d, $^2J_{gem}$ = 10.7 Hz, 1 H, 2-H_{eq}), 2.29–2.21 [m, 3 H, 2-H_{ax}, NCH_2(CH_2)$_2$Ph], 2.11–1.99 (m, 2 H, CH_2CH=CH_2), 1.88–1.85 (m, 2 H, 6-H_{ax}, 6-H_{eq}), 1.78 (quint, ^3J = 7.3 Hz, 2 H, NCH_2CH_2CH_2Ph), 1.77–1.71 (m, 1 H, 8-H_{eq}), 1.49–1.37 (m, 2 H, 7-H_{eq}, 8-H_{ax}), 1.25 [t, ^3J = 7.1 Hz, 3 H, CH_3 (Et)] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.8 [C=O (ester)], 142.6 (C-1$_{arom}$), 135.4 (OCH_2*C*H=CH_2), 134.1 (CH_2*C*H=CH_2), 128.4 (C-

3_{arom}, C-5_{arom}), 128.2 (C-2_{arom}, C-6_{arom}), 125.6 (C-4_{arom}), 117.6 ($CH_2CH{=}CH_2$), 114.9 ($OCH_2CH{=}CH_2$), 83.8 (C-9), 74.0 ($OCH_2CH{=}CH_2$), 60.3 [CH_2 (Et)], 58.0 (C-2), 57.7 [$NCH_2(CH_2)_2$-Ph], 54.1 (C-4), 48.9 (C-1), 42.1 ($CH_2CH{=}CH_2$), 39.5 (C-5), 35.8 (C-8), 35.6 (C-6), 33.6 [$N(CH_2)_2CH_2Ph$], 28.9 ($NCH_2CH_2CH_2Ph$), 20.8 (C-7), 14.2 [CH_3 (Et)] ppm.

Ethyl (1*S,7*S**,8*R**)-10-(3-Phenylpropyl)-6-oxa-10-azatricyclo-[6.3.3.0^{1,7}]tetradec-3-ene-8-carboxylate (12):** To a solution of bis-(tricyclohexylphosphane)benzylideneruthenium(IV) dichloride (Grubbs' catalyst, 3 mg, 0.004 mmol) in dry dichloromethane (3 mL) was added dropwise a solution of diene **11** (30 mg, 0.073 mmol) in dry dichloromethane (2 mL) and the reaction mixture stirred for 2 days at room temperature. After concentration in vacuo, the residue was purified by flash chromatography (5% EtOAc in hexane). Yield 28 mg (0.073 mmol, >99%) of a clear oil; R_f = 0.25 (5% EtOAc in hexane). HRMS (EI): *m*/*z* calcd. for $C_{24}H_{33}NO_3$: 383.2460, found: 383.2457 [M^+]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.15 [m, 5 H, H_{arom} (Ph)], 5.79–5.66 (m, 2 H, 3-H, 4-H), 4.27–4.05 [m, 4 H, CH_2 (Et), 5-CH_2], 3.72 (s, 1 H, 7-H), 2.88 (d, $^2J_{gem}$ = 11.3 Hz, 1 H, 11-H_{eq}), 2.87–2.77 (m, 1 H, 13-H_{ax}), 2.63 [t, ^3J = 7.5 Hz, 2 H, $N(CH_2)_2CH_2Ph$], 2.56 (dd, $^4J_{11ax,12ax}$ = 1.8, $^2J_{gem}$ = 11.3 Hz, 1 H, 11-H_{ax}), 2.42 (dd, $^2J_{gem}$ = 10.7, $^4J_{9eq,11eq}$ = 1.6 Hz, 1 H, 9-H_{eq}), 2.34 (d, $^2J_{gem}$ = 10.6 Hz, 1 H, 9-H_{ax}), 2.33–2.21 [m, 2 H, $NCH_2(CH_2)_2Ph$], 2.04 (d, ^3J = 6.0 Hz, 2 H, 2-CH_2), 1.96–1.85 (m, 2 H, 12-CH_2), 1.79 (quint, ^3J = 7.5 Hz, 2 H, $NCH_2CH_2CH_2Ph$), 1.66–1.60 (m, 1 H, 14-H_{eq}), 1.52–1.40 (m, 2 H, 13-H_{eq}, 14-H_{ax}), 1.25 [t, ^3J = 7.1 Hz, 3 H, CH_3 (Et)] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.5 [C=O (ester)], 142.6 (C-1_{arom}), 130.5 (C-4), 129.1 (C-3), 128.4 (C-3_{arom}, C-5_{arom}), 128.2 (C-2_{arom}, C-6_{arom}), 125.6 (C-4_{arom}), 85.8 (C-7), 68.8 (C-5), 60.1 [CH_2 (Et)], 58.3 (C-9), 57.6 [$NCH_2(CH_2)_2Ph$], 54.1 (C-11), 48.7 (C-8), 39.4 (C-2), 39.1 (C-14), 38.1 (C-1), 35.7 (C-12), 33.6 [$N(CH_2)_2$-CH_2Ph], 28.9 ($NCH_2CH_2CH_2Ph$), 21.2 (C-13), 14.3 [CH_3 (Et)] ppm.

(1*S,7*S**,8*S**)-{10-(3-Phenylpropyl)-6-oxa-10-azatricyclo[6.3.3.0^{1,7}]-tetradec-3-en-8-yl}methanol (13):** To a slurry of lithium aluminium hydride (13 mg, 0.344 mmol) in dry THF (5 mL) was added dropwise a solution of the ester **12** (66 mg, 0.172 mmol) in dry THF (5 mL) at 0 °C. The reaction mixture was stirred for 3 h at room temperature, then quenched by the addition of water (20 mL) and the volatiles were removed at reduced pressure. The remaining aqueous solution was diluted with brine (20 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (30% EtOAc in hexane). Yield 46 mg (0.135 mmol, 79%) of a clear oil; R_f = 0.23 (30% EtOAc in hexane). HRMS (EI): *m*/*z* calcd. for $C_{22}H_{31}NO_2$: 341.2355, found: 341.2357 [M^+]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.15 [m, 5 H, H_{arom} (Ph)], 5.85–5.74 (m, 2 H, 3-H, 4-H), 4.32 (dd, $^2J_{gem}$ = 14.8, $^3J_{5a,4}$ = 5.2 Hz, 1 H, 5-H_a), 4.12 (dd, $^2J_{gem}$ = 14.8, $^3J_{5b,4}$ = 3.3 Hz, 1 H, 5-H_b), 3.52 (d, $^2J_{gem}$ = 11.1 Hz, 1 H, CH_aH_bOH), 3.40 (s, 1 H, 7-H), 3.34 (d, $^2J_{gem}$ = 11.0 Hz, 1 H, CH_aH_bOH), 3.02 (s, 1 H, OH), 2.85–2.78 (m, 1 H, 13-H_{ax}), 2.63 [t, ^3J = 7.5 Hz, 2 H, $N(CH_2)_2CH_2Ph$], 2.54 (dd, $^2J_{gem}$ = 11.0, $^4J_{9eq,11eq}$ = 2.0 Hz, 1 H, 11-H_{eq}), 2.46 (d, $^2J_{gem}$ = 11.0 Hz, 1 H, 11-H_{ax}), 2.41 (dd, $^2J_{gem}$ = 10.8, $^4J_{9eq,11eq}$ = 1.6 Hz, 1 H, 9-H_{eq}), 2.36 (d, $^2J_{gem}$ = 10.8 Hz, 1 H, 9-H_{ax}), 2.24 [t, ^3J = 6.9 Hz, 2 H, $NCH_2(CH_2)_2Ph$], 2.09 (dd, $^2J_{gem}$ = 15.2, $^3J_{2a,3}$ = 4.4 Hz, 1 H, 2-H_a), 1.99 (dd, $^2J_{gem}$ = 15.0, $^3J_{2b,3}$ = 6.5 Hz, 1 H, 2-H_b), 1.77 (quint, ^3J = 7.2 Hz, 2 H, $NCH_2CH_2CH_2Ph$), 1.62–1.57 (m, 1 H, 12-H_{eq}), 1.48 (dd, $^2J_{gem}$ = 13.3, $^3J_{12ax,13eq}$ = 6.3 Hz, 1 H, 12-H_{ax}), 1.43–1.26 (m, 3 H, 13-H_{eq}, 14-CH_2) ppm. ^{13}C NMR (100 MHz, BB, DEPT, $CDCl_3$): δ = 142.7 (C-1_{arom}), 130.8 (C-4), 129.8 (C-3), 128.4 (C-3_{arom}, C-5_{arom}), 128.2 (C-2_{arom}, C-6_{arom}), 125.6 (C-4_{arom}), 91.3 (C-7), 71.6 (CH_2OH), 68.2 (C-5), 58.4 (C-9), 57.9 [$NCH_2(CH_2)_2Ph$], 55.2 (C-11), 40.0 (C-8), 39.3 (C-2, C-14), 38.4 (C-1), 34.8 (C-12), 33.5 [$N(CH_2)_2CH_2Ph$], 28.9 ($NCH_2CH_2CH_2Ph$), 21.0 (C-13) ppm.

(1*S,7*S**,8*S**)-{10-(3-Phenylpropyl)-6-oxa-10-azatricyclo[6.3.3.0^{1,7}]-tetradec-3-en-8-yl}methyl 2-Aminobenzoate (14):** To a solution of the alcohol **13** (40 mg, 0.117 mmol), *N*-(trifluoroacetyl)anthranilic acid[26] (82 mg, 0.351 mmol) and 4-(dimethylamino)pyridine (7 mg, 0.059 mmol) in acetonitrile (6 mL) was added 1,3-dicyclohexylcarbodiimide (72 mg, 0.351 mmol), and the reaction mixture was stirred for 16 h at 40 °C. The mixture was then cooled, filtered, and the filtrate was evaporated to dryness. The residue was dissolved in dichloromethane (25 mL), washed with aq. $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude ester was dissolved in dry ethanol (5 mL), treated with sodium borohydride (18 mg, 0.468 mmol) and stirred for 20 h at room temperature. The reaction was quenched with water (10 mL), and the volatiles were removed at reduced pressure. The residue was dissolved in ethyl acetate (30 mL), washed with brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography (15% EtOAc in hexane). Yield 43 mg (0.093 mmol, 80%) of a yellow oil; R_f = 0.55 (20% EtOAc in hexane). HRMS (EI): *m*/*z* calcd. for $C_{29}H_{36}N_2O_3$: 460.2726, found: 460.2730 [M^+]. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (dd, $^3J_{5',6'}$ = 8.3, $^4J_{4',6'}$ = 1.6 Hz, 1 H, 6′-H), 7.22–7.09 [m, 6 H, 4′-H, H_{arom} (Ph)], 6.62–6.57 (m, 2 H, 3′-H, 5′-H), 5.69–5.63 (m, 4 H, 3-H, 4-H, NH_2), 4.22 (dd, $^2J_{gem}$ = 14.8, $^3J_{4,5a}$ = 4.2 Hz, 1 H, 5-H_a), 4.09 (d, $^2J_{gem}$ = 10.6 Hz, 1 H, CH_aH_bO), 3.99 (d, $^2J_{gem}$ = 10.6 Hz, 1 H, CH_aH_bO), 3.98–3.91 (m, 1 H, 5-H_b), 3.30 (s, 1 H, 7-H), 2.86–2.72 (m, 1 H, 13-H_{ax}), 2.59–2.54 (m, 1 H, 11-H_{eq}), 2.57 [t, ^3J = 7.0 Hz, 2 H, $N(CH_2)_2CH_2Ph$], 2.39 (d, $^2J_{gem}$ = 10.9 Hz, 1 H, 9-H_{eq}), 2.34 (d, $^2J_{gem}$ = 10.8 Hz, 1 H, 9-H_{ax}), 2.25–2.15 [m, 3 H, 11-H_{ax}, $NCH_2(CH_2)_2Ph$], 1.97 (d, $^3J_{2,3}$ = 5.2 Hz, 2 H, 2-CH_2), 1.83–1.48 (m, 5 H, 12-CH_2, 14-H_{eq}, $NCH_2CH_2CH_2Ph$), 1.46–1.32 (m, 2 H, 13-H_{eq}, 14-H_{ax}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.0 [C=O (ester)], 150.5 (C-2′), 142.6 (C-1_{arom}), 133.9 (C-4′), 131.0 (C-6′), 130.3 (C-4), 129.4 (C-3), 128.4 (C-3_{arom}, C-5_{arom}), 128.2 (C-2_{arom}, C-6_{arom}), 125.6 (C-4_{arom}), 116.7 (C-5′), 116.2 (C-3′), 111.1 (C-1′), 85.8 (C-7), 69.1 (CH_2O), 68.9 (C-5), 59.0 (C-9), 57.7 [NCH_2-$(CH_2)_2Ph$], 55.9 (C-11), 40.2 (C-8), 39.3 (C-2, C-14), 38.3 (C-1), 34.6 (C-12), 33.5 [$N(CH_2)_2CH_2Ph$], 28.9 ($NCH_2CH_2CH_2Ph$), 21.0 (C-13) ppm.

(1*S,7*S**,8*S**)-{10-(3-Phenylpropyl)-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 (5):** A mixture of the the amine **14** (30 mg, 0.065 mmol) and Methylsuccinic anhydride (22 mg, 0.195 mmol) was heated at 125 °C for 4 h. The reaction mixture was then dissolved in warm ethyl acetate (20 mL), washed with aq. $NaHCO_3$ (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (100% $CHCl_3$). Yield 35 mg (0.063 mmol, 97%) of a clear oil; R_f = 0.21 (100% $CHCl_3$). HRMS (EI): *m*/*z* calcd. for $C_{34}H_{40}N_2O_5$: 556.2937, found: 556.2937 [M^+]. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11 (d, $^3J_{5',6'}$ = 7.0 Hz, 1 H, 6′-H), 7.66 (dt, $^3J_{3',4'}$ = $^3J_{4',5'}$ = 7.7, $^4J_{4',6'}$ = 1.5 Hz, 1 H, 4′-H), 7.53 (dt, $^3J_{4',5'}$ = $^3J_{5',6'}$ = 7.7, $^4J_{3',5'}$ = 1.3 Hz, 1 H, 5′-H), 7.30–7.17 [m, 6 H, 3′-H, H_{arom} (Ph)], 5.76–5.73 (m, 2 H, 3-H, 4-H), 4.27 (dd, $^2J_{gem}$ = 14.9, $^3J_{4,5a}$ = 4.3 Hz, 1 H, 5-H_a), 4.14 (d, $^2J_{gem}$ = 10.6 Hz, 1 H, CH_aH_bO), 4.04–3.93 (m, 2 H, 5-H_b, CH_aH_bO), 3.32 (s, 1 H, 7-H), 3.18–2.99 (m, 2 H, 3′′-H, 4′′-H_a), 2.95–2.78 (m, 1 H, 13-H_{ax}), 2.66–2.56 (m, 1 H, 4′′-H_b), 2.64 [t, ^3J = 7.4 Hz, 2 H, $N(CH_2)$ $_2CH_2Ph$], 2.58 (d, $^2J_{gem}$ = 10.7 Hz, 1 H, 11-H_{eq}), 2.45 (d, $^2J_{gem}$ = 10.5 Hz, 1 H, 9-H_{eq}), 2.40 (d, $^2J_{gem}$ = 10.7 Hz, 1 H, 9-H_{ax}), 2.29–2.21 [m, 3 H, 11-H_{ax}, $NCH_2(CH_2)_2Ph$], 2.04–2.02 (m, 2 H, 2-CH_2),

1.88–1.73 (m, 3 H, 12-H_{eq}, $NCH_2CH_2CH_2Ph$), 1.66–1.60 (m, 2 H, 12-H_{ax}, 14-H_{eq}), 1.50–1.40 (m, 5 H, 14-H_{ax}, 13-H_{eq}, 3′′-CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.9 (C-2′′), 175.8 (C-5′′), 164.0 [C=O (ester)], 142.6 (C-1_{arom}), 133.3 (C-4′), 132.9 (C-2′), 131.3 (C-6′), 130.4 (C-4), 129.9 (C-3′), 129.6 (C-3), 129.3 (C-5′), 128.4 (C-3_{arom}, C-5_{arom}), 128.2 (C-2_{arom}, C-6_{arom}), 127.6 (C-1′), 125.6 (C-4_{arom}), 85.9 (C-7), 70.1 (CH_2O), 68.8 (C-5), 58.8 (C-9), 57.7 [$NCH_2(CH_2)_2Ph$], 55.9 (C-11), 40.2 (C-8), 39.4 (C-2, C-14), 38.2 (C-1), 37.0 (C-4′′), 35.3 (C-3′′), 34.4 (C-12), 33.5 [$N(CH_2)_2CH_2Ph$], 28.9 ($NCH_2CH_2CH_2Ph$), 21.0 (C-13), 16.3 (3′′-CH_3) ppm.

Ethyl 5-(3-Butenyl)-3-(3-phenylpropyl)-9-oxo-3-azabicyclo[3.3.1]-nonane-1-carboxylate (18): To a mixture of β-keto ester **17**[20] (4.50 g, 20.06 mmol) and the *N*,*N*-bis(ethoxymethyl)amine **7** (6.05 g, 24.07 mmol) in acetonitrile (100 mL) was added methyltrichlorosilane (2.83 mL, 24.07 mmol). The reaction mixture was stirred for 20 h at room temperature, then quenched with aq. $NaHCO_3$ and extracted with ethyl acetate (3× 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (EtOAc/hexane). Yield 4.22 g (11.00 mmol, 55%) of a clear oil; R_f = 0.46 (10% EtOAc in hexane). HRMS (EI): *m*/*z* calcd. for $C_{24}H_{33}NO_3$: 383.2460, found: 383.2460 [M^+]. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.17 [m, 5 H, H_{arom} (Ph)], 5.84–5.74 (m, 1 H, CH_2CH_2CH=CH_2), 5.01 (dd, $^2J_{gem}$ = 1.7, $^3J_{trans}$ = 17.1 Hz, 1 H, CH_2CH_2CH=CH_aH_b), 4.93 (dd, $^2J_{gem}$ = 1.4, $^3J_{cis}$ = 10.2 Hz, 1 H, CH_2CH_2CH=CH_aH_b), 4.20 [q, ^3J = 7.1 Hz, 2 H, CH_2 (Et)], 3.17 (dd, $^2J_{gem}$ = 11.4, $^4J_{2eq,4eq}$ = 2.1 Hz, 1 H, 4-H_{eq}), 3.04 (dd, $^2J_{gem}$ = 11.0, $^4J_{2eq,4eq}$ = 2.1 Hz, 1 H, 2-H_{eq}), 3.02–2.91 (m, 1 H, 7-H_{ax}), 2.94 (dd, $^2J_{gem}$ = 11.2, $^4J_{4ax,6ax}$ = 1.6 Hz, 1 H, 4-H_{ax}), 2.69 [t, ^3J = 7.4 Hz, 2 H, $N(CH_2)_2CH_2Ph$], 2.59–2.50 (m, 1 H, 6-H_{eq}), 2.34 [t, ^3J = 7.0 Hz, 2 H, $NCH_2(CH_2)_2Ph$], 2.28 (dd, $^2J_{gem}$ = 11.0, $^4J_{2ax,8ax}$ = 1.5 Hz, 1 H, 2-H_{ax}), 2.24–2.19 (m, 1 H, 6-H_{ax}), 2.15–2.10 (m, 1 H, 8-H_{eq}), 2.08–1.96 (m, 2 H, CH_2CH_2CH=CH_2), 1.86–1.76 (m, 3 H, 8-H_{ax}, $NCH_2CH_2CH_2Ph$), 1.58–1.41 (m, 3 H, 7-H_{eq}, CH_2CH_2CH=CH_2), 1.28 [t, ^3J = 7.1 Hz, 3 H, CH_3 (Et)] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.8 (C-9), 171.2 [C=O (ester)], 141.9 (C-1_{arom}), 138.7 (CH_2CH_2CH=CH_2), 128.3 (C-3_{arom}, C-5_{arom}), 128.2 (C-2_{arom}, C-6_{arom}), 125.8 (C-4_{arom}), 114.3 (CH_2CH_2CH=CH_2), 65.0 (C-2), 62.1 (C-4), 61.0 [CH_2 (Et)], 58.9 (C-1), 56.4 [$NCH_2(CH_2)_2Ph$], 49.0 (C-5), 39.2 (C-8), 36.8 (C-6), 33.9 (CH_2CH_2CH=CH_2), 33.4 [$N(CH_2)_2CH_2Ph$], 29.0 ($NCH_2CH_2CH_2Ph$), 27.7 (CH_2CH_2CH=CH_2), 20.4 (C-7), 14.1 [CH_3 (Et)] ppm.

Ethyl (1*R,5*S**,9*R**)-5-(3-Butenyl)-9-hydroxy-3-(3-phenylpropyl)-9-(2-propenyl)-3-azabicyclo[3.3.1]nonane-1-carboxylate (19) and Ethyl (1*R**,5*S**,9*S**)-5-(3-Butenyl)-9-hydroxy-3-(3-phenylpropyl)-9-(2-propenyl)-3-azabicyclo[3.3.1]nonane-1-carboxylate (20):** To a solution of the β-keto ester **18** (2.30 g, 6.00 mmol) in dry THF (120 mL) was added dropwise allylmagnesium bromide (9.00 mL of a 1.0 M solution in diethyl ether, 9.00 mmol) under nitrogen at 0 °C. The mixture was stirred for 1 h at 0 °C then for 2 days at room temperature. The reaction mixture was quenched by the addition of aq. NH_4Cl (100 mL) and extracted with diethyl ether (100 mL). The remaining aqueous phase was further extracted with diethyl ether (2× 100 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The alcohols **19** and **20** were separated by flash chromatography (3% Et_2O in hexane). **Alcohol 19:** Yield 1.23 g (2.89 mmol, 48%) of a clear oil; R_f = 0.45 (10% Et_2O in hexane). HRMS (EI): *m*/*z* calcd. for $C_{27}H_{39}NO_3$: 425.2930, found: 425.2923 [M^+], calcd. for $C_{27}H_{38}NO_3$: 424.2852, found: 424.2850 ([M–H]$^+$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.17 [m, 5 H, H_{arom} (Ph)], 5.87–5.75 (m, 2 H, CH_2CH=CH_2, CH_2CH_2CH=CH_2), 5.01–4.90 (m, 4 H, CH_2CH=CH_2, CH_2CH_2CH=CH_2), 4.08 [q, ^3J = 7.2 Hz, 2 H, CH_2 (Et)], 3.07 (d, $^2J_{gem}$ = 11.9 Hz, 1 H, 2-H_{eq}), 2.84–2.74 (m, 1 H, 7-H_{ax}), 2.76 (d, $^2J_{gem}$ = 11.9 Hz, 1 H, 4-H_{eq}), 2.69–2.60 [m, 3 H, $N(CH_2)_2CH_2Ph$, $CH_2CH_aH_bCH$=CH_2], 2.56–2.52 (m, 1 H, $CH_2CH_aH_bCH$=CH_2), 2.38–2.26 [m, 4 H, 2-H_{ax}, $NCH_2(CH_2)_2Ph$, OH], 2.24–1.87 (m, 5 H, 4-H_{ax}, CH_2CH=CH_2, CH_2CH_2CH=CH_2), 1.84–1.74 (m, 2 H, $NCH_2CH_2CH_2Ph$), 1.70–1.43 (m, 4 H, 6-CH_2, 7-H_{eq}, 8-H_{eq}), 1.27–1.17 (m, 1 H, 8-H_{ax}), 1.25 [t, ^3J = 7.1 Hz, 3 H, CH_3 (Et)] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.3 [C=O (ester)], 142.4 (C-1_{arom}), 139.7 (CH_2CH_2CH=CH_2), 135.0 (CH_2CH=CH_2), 128.4 (C-3_{arom}, C-5_{arom}), 128.3 (C-2_{arom}, C-6_{arom}), 125.7 (C-4_{arom}), 116.9 (CH_2CH=CH_2), 113.9 (CH_2CH_2CH=CH_2), 74.5 (C-9), 60.8 [C-2, CH_2 (Et)], 57.5 (C-4), 56.4 [$NCH_2(CH_2)_2Ph$], 50.6 (C-1), 40.7 (C-5), 38.2 (CH_2CH_2CH=CH_2), 34.2 (CH_2CH=CH_2), 33.5 [$N(CH_2)_2CH_2Ph$], 33.8 (CH_2CH_2CH=CH_2), 30.1 (C-8), 28.9 ($NCH_2CH_2CH_2Ph$), 28.1 (C-6), 20.3 (C-7), 13.9 [CH_3 (Et)] ppm.

Alcohol 20: Yield 715 mg (1.68 mmol, 28%) of a clear oil; R_f = 0.40 (10% Et_2O in hexane). HRMS (EI): *m*/*z* calcd. for $C_{27}H_{39}NO_3$: 425.2930, found: 425.2918 [M^+], calcd. for $C_{27}H_{38}NO_3$: 424.2852, found: 424.2851 ([M–H]$^+$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.17 [m, 5 H, H_{arom} (Ph)], 5.89–5.74 (m, 2 H, CH_2CH=CH_2, CH_2CH_2CH=CH_2), 5.06–4.90 (m, 4 H, CH_2CH=CH_2, CH_2CH_2CH=CH_2), 4.53 (s, 1 H, OH), 4.09–4.01 [m, 2 H, CH_2 (Et)], 2.84–2.75 (m, 1 H, 7-H_{ax}), 2.83 (d, $^2J_{gem}$ = 10.3 Hz, 1 H, 2-H_{eq}), 2.66–2.59 [m, 5 H, 2-H_{ax}, 4-H_{eq}, $N(CH_2)_2CH_2Ph$, $CH_2CH_aH_bCH$=CH_2], 2.54–2.48 (m, 1 H, $CH_2CH_aH_bCH$=CH_2), 2.53 (d, $^2J_{gem}$ = 10.6 Hz, 1 H, 4-H_{ax}), 2.31–2.19 [m, 2 H, $NCH_2(CH_2)_2Ph$], 2.05–1.95 (m, 4 H, CH_2CH=CH_2, CH_2CH_2CH=CH_2), 1.80–1.71 (m, 4 H, 6-H_{eq}, 8-H_{eq}, $NCH_2CH_2CH_2Ph$), 1.60–1.52 (m, 2 H, 6-H_{ax}, 7-H_{eq}), 1.33–1.24 (m, 1 H, 8-H_{ax}), 1.25 [t, ^3J = 7.1 Hz, 3 H, CH_3 (Et)] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.3 [C=O (ester)], 142.5 (C-1_{arom}), 139.7 (CH_2CH_2CH=CH_2), 134.8 (CH_2CH=CH_2), 128.4 (C-3_{arom}, C-5_{arom}), 128.3 (C-2_{arom}, C-6_{arom}), 125.7 (C-4_{arom}), 117.2 (CH_2CH=CH_2), 113.9 (CH_2CH_2CH=CH_2), 74.9 (C-9), 61.0 [CH_2 (Et)], 58.9 (C-2), 58.1 (C-4), 57.5 [$NCH_2(CH_2)_2Ph$], 50.3 (C-1), 41.1 (C-5), 37.9 (CH_2CH_2CH=CH_2), 33.8 (C-8), 33.5 [$N(CH_2)_2CH_2Ph$], 32.8 (C-6), 29.8 (CH_2CH=CH_2), 28.8 ($NCH_2CH_2CH_2Ph$), 28.0 (CH_2CH_2CH=CH_2), 20.1 (C-7), 13.8 [CH_3 (Et)] ppm.

Ethyl (1*S,7*R**,8*R**)-7-Hydroxy-10-(3-phenylpropyl)-10-azatricyclo[6.3.3.0^{1,7}]tetradec-4-ene-8-carboxylate (21) and Ethyl (1*S**,7*S**,8*R**)-7-Hydroxy-10-(3-phenylpropyl)-10-azatricyclo-[6.3.3.0^{1,7}]tetradec-4-ene-8-carboxylate (22):** To a mixture of the dienes **19** and **20** (1.40 g, 3.29 mmol) in dry dichloromethane (100 mL) was added bis(tricyclohexylphosphane)benzylideneruthenium(IV) dichloride (Grubbs' catalyst, 131 mg, 0.16 mmol), and the reaction mixture was stirred for 20 h at room temperature. The mixture was then concentrated in vacuo, and the tricyclic products **21** and **22** were separated by flash chromatography (5% EtOAc in hexane). **Olefin 21:** Yield 678 mg (1.71 mmol, 52%) of a clear oil; R_f = 0.35 (5% EtOAc in hexane). HRMS (EI): *m*/*z* calcd. for $C_{25}H_{35}NO_3$: 397.2617, found: 397.2610 [M^+], calcd. for $C_{25}H_{34}NO_3$: 396.2539, found: 396.2539 ([M–H]$^+$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.17 [m, 5 H, H_{arom} (Ph)], 5.95–5.89 (m, 1 H, 4-H), 5.59–5.53 (m, 1 H, 5-H), 4.18 [dq, ^3J = 7.1 Hz, 2 H, CH_2 (Et)], 3.67 (s, 1 H, OH), 3.08 (d, $^2J_{gem}$ = 11.9 Hz, 1 H, 11-H_{eq}), 2.99 (d, $^2J_{gem}$ = 15.4 Hz, 1 H, 6-H_a), 2.86–2.76 (m, 1 H, 13-H_{ax}), 2.78 (dd, $^2J_{gem}$ = 11.9, $^4J_{9eq,11eq}$ = 2.5 Hz, 1 H, 9-H_{eq}), 2.66 [t, ^3J = 8.0 Hz, 2 H, $N(CH_2)_2CH_2Ph$], 2.53 (dd, $^2J_{gem}$ = 11.9, $^4J_{11ax,12ax}$ = 2.4 Hz, 1 H, 11-H_{ax}), 2.47 (d, $^2J_{gem}$ = 11.5 Hz, 1 H, 9-H_{ax}), 2.44–2.38 (m, 1 H, 2-H_a), 2.37–2.20 [m, 3 H, 3-H_a, $NCH_2(CH_2)_2Ph$]) , 2.17–2.08 (m, 1 H, 14-H_{eq}), 2.04–1.97 (m, 1 H, 3-H_b), 1.85–1.77 (m, 3 H, 6-H_b, $NCH_2CH_2CH_2Ph$), 1.71–1.61 (m,

2 H, 2-H_b, 12-H_{eq}), 1.55–1.49 (m, 1 H, 13-H_{eq}), 1.28 [t, ^3J = 7.1 Hz, 3 H, CH_3 (Et)], 1.17 (dd, $^2J_{gem}$ = 13.3, $^3J_{13eq,14ax}$ = 6.7 H, 1 H, 14-H_{ax}z), 1.10–1.06 (m, 1 H, 12-H_{ax}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.4 [C=O (ester)], 142.4 (C-1_{arom}), 133.0 (C-4), 128.4 (C-3_{arom}, C-5_{arom}), 128.3 (C-2_{arom}, C-6_{arom}), 127.2 (C-5), 125.7 (C-4_{arom}), 73.1 (C-7), 60.8 [CH_2 (Et)], 60.7 (C-9), 57.6 [N*C*H_2(CH_2)$_2$-Ph], 57.2 (C-11), 51.8 (C-8), 40.8 (C-1), 36.1 (C-14), 34.4 (C-12), 33.5 [N(CH_2)$_2$*C*H_2Ph], 33.0 (C-6), 32.4 (C-2), 28.9 (NCH_2*C*H_2CH_2Ph), 23.7 (C-3), 20.6 (C-13), 14.2 [CH_3 (Et)] ppm.

Olefin 22: Yield 438 mg (1.10 mmol, 33%) of a clear oil; R_f = 0.31 (5% EtOAc in hexane). HRMS (EI): *m*/*z* calcd. for $C_{25}H_{35}NO_3$: 397.2617, found: 397.2618 [M^+]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.15 [m, 5 H, H_{arom} (Ph)], 5.91–5.86 (m, 1 H, 4-H), 5.57–5.52 (m, 1 H, 5-H), 4.16 [q, ^3J = 7.1 Hz, 2 H, CH_2 (Et)], 3.74 (s, 1 H, OH), 2.95–2.88 (m, 3 H, 6-H_a, 11-H_{eq}, 13-H_{ax}), 2.67 (d, $^2J_{gem}$ = 10.7 Hz, 1 H, 11-H_{ax}), 2.63 [t, ^3J = 8.1 Hz, 2 H, N(CH_2)$_2$C*H*$_2$Ph], 2.57 (dd, $^2J_{gem}$ = 10.6, $^4J_{9eq,11eq}$ = 2.1 Hz, 1 H, 9-H_{eq}), 2.32–2.21 [m, 5 H, 3-H_a, 14-H_{eq}, 9-H_{ax}, NC*H*$_2$(CH$_2$)$_2$Ph], 2.03–1.96 (m, 4 H, 2-CH_2, 3-H_b, 6-H_b), 1.83–1.72 (m, 3 H, 12-H_{eq}, NCH$_2$C*H*$_2$CH$_2$Ph), 1.62–1.57 (m, 1 H, 13-H_{eq}), 1.33–1.25 (m, 1 H, 14-H_{ax}), 1.27 [t, ^3J = 7.1 Hz, 3 H, CH_3 (Et)], 0.89–0.84 (m, 1 H, 12-H_{ax}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.8 [C=O (ester)], 142.5 (C-1_{arom}), 132.5 (C-4), 128.4 (C-3_{arom}, C-5_{arom}), 128.2 (C-2_{arom}, C-6_{arom}), 127.1 (C-5), 125.6 (C-4_{arom}), 73.0 (C-7), 62.4 (C-9), 60.9 [CH_2 (Et)], 58.0 (C-11), 57.2 [N*C*H$_2$(CH$_2$)$_2$Ph], 52.2 (C-8), 41.4 (C-1), 33.5 [N(CH$_2$)$_2$-*C*H$_2$Ph], 33.2 (C-6), 32.1 (C-14), 31.6 (C-12), 30.8 (C-2), 28.8 (NCH$_2$*C*H$_2$CH$_2$Ph), 23.4 (C-3), 20.0 (C-13), 14.1 [CH_3 (Et)] ppm.

(1*S,7*R**,8*S**)-8-(Hydroxymethyl)-10-(3-phenylpropyl)-10-azatricyclo[6.3.3.0^{1,7}]tetradec-3-en-7-ol (23):** To a solution of the ester **21** (70 mg, 0.18 mmol) in dry THF (10 mL) was added lithium aluminium hydride (14 mg, 0.36 mmol), and the mixture was stirred for 2 h at room temperature. Sodium sulfate decahydrate (excess, 100 mg) was added, and stirring was continued for 1 h. The mixture was filtered through celite, and the solvent was removed from the filtrate at reduced pressure. The residue was dissolved in ethyl acetate (50 mL), washed with aq. $NaHCO_3$ (20 mL), brine (20 mL) then dried ($MgSO_4$) and concentrated in vacuo. The alcohol **23** was purified by flash chromatography (25% EtOAc in hexane). Yield 56 mg (0.16 mmol, 89%) of a clear oil; R_f = 0.47 (30% EtOAc in hexane). HRMS (EI): *m*/*z* calcd. for $C_{23}H_{33}NO_2$: 355.2511, found: 355.2507 [M^+], calcd. for $C_{23}H_{32}NO_2$: 354.2433, found: 354.2432 ([M–H]$^+$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.18 [m, 5 H, H_{arom} (Ph)], 6.13–6.07 (m, 1 H, 4-H), 5.65–5.61 (m, 1 H, 5-H), 3.85 (d, $^2J_{gem}$ = 10.9 Hz, 1 H, C*H*$_a$H$_b$OH), 3.74 (s, 1 H, OH), 3.15 (d, $^2J_{gem}$ = 10.8 Hz, 1 H, CH$_a$*H*$_b$OH), 2.92–2.82 (m, 2 H, 6-H_a, 13-H_{ax}), 2.66–2.61 [m, 4 H, 9-H_{eq}, N(CH$_2$)$_2$C*H*$_2$Ph, OH], 2.57–2.42 (m, 4 H, 2-H_a, 6-H_b, 9-H_{ax}, 11-H_{eq}), 2.32–2.21 [m, 3 H, 3-H_a, NC*H*$_2$(CH$_2$)$_2$Ph]) , 2.07–1.98 (m, 3 H, 3-H_b, 11-H_{ax}, 14-H_{eq}), 1.77 (quint, ^3J = 7.6 Hz, 2 H, NCH$_2$C*H*$_2$CH$_2$Ph), 1.59–1.53 (m, 1 H, 13-H_{eq}), 1.43–1.32 (m, 2 H, 2-H_b, 12-H_{eq}), 1.26–1.13 (m, 2 H, 12-H_{ax}, 14-H_{ax}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.4 (C-1_{arom}), 136.6 (C-4), 128.4 (C-3_{arom}, C-5_{arom}), 128.3 (C-2_{arom}, C-6_{arom}), 126.6 (C-5), 125.7 (C-4_{arom}), 76.4 (C-7), 68.9 (CH_2OH), 61.4 (C-9), 59.0 (C-11), 57.7 [N*C*H$_2$(CH$_2$)$_2$Ph], 42.1 (C-8), 41.6 (C-1), 36.4 (C-14), 34.8 (C-12), 33.4 [N(CH$_2$)$_2$*C*H$_2$Ph], 30.6 (C-2), 29.3 (C-6), 28.8 (NCH$_2$*C*H$_2$CH$_2$Ph), 23.7 (C-3), 20.6 (C-13) ppm.

(1*S,7*S**,8*S**)-8-(Hydroxymethyl)-10-(3-phenylpropyl)-10-azatricyclo[6.3.3.0^{1,7}]tetradec-4-en-7-ol (24):** To a solution of the ester **22** (100 mg, 0.25 mmol) in dry THF (10 mL) was added lithium aluminium hydride (20 mg, 0.51 mmol), and the mixture was stirred for 2 h at room temperature. Sodium sulfate decahydrate (excess, 100 mg) was added, and stirring was continued for 1 h. The mixture was filtered through celite, and the solvent was removed from the filtrate at reduced pressure. The residue was dissolved in ethyl acetate (50 mL), washed with aq. $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo. The alcohol **24** was purified by flash chromatography (25% EtOAc in hexane). Yield 78 mg (0.22 mmol, 87%) of a clear oil. IR (NaCl): $\tilde{\nu}_{max}$ = 3238, 2900, 1452, 1295 and 1073. HRMS (EI): *m*/*z* calcd. for $C_{23}H_{33}NO_2$: 355.2511, found: 355.2510 [M^+]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.18 [m, 5 H, H_{arom} (Ph)], 6.04–5.96 (m, 1 H, 4-H), 5.65–5.54 (m, 1 H, 5-H), 3.83 (d, $^2J_{gem}$ = 10.8 Hz, 1 H, C*H*$_a$H$_b$-OH), 3.71 (br. s, 1 H, OH), 3.09 (d, $^2J_{gem}$ = 10.8 Hz, 1 H, CH$_a$*H*$_b$-OH), 2.95–2.80 (m, 2 H, 6-H_a, 13-H_{ax}), 2.67–2.60 [m, 4 H, 9-H_{eq}, N(CH$_2$)$_2$C*H*$_2$Ph, OH], 2.51–2.40 (m, 4 H, 2-H_a, 6-H_b, 9-H_{ax}, 11-H_{eq}), 2.36–2.30 [m, 3 H, 3-H_a, NC*H*$_2$(CH$_2$)$_2$Ph]) , 2.10–1.98 (m, 3 H, 3-H_b, 11-H_{ax}, 14-H_{eq}), 1.79 (quint, ^3J = 7.6 Hz, 2 H, NCH$_2$C*H*$_2$CH$_2$Ph), 1.52–1.32 (m, 3 H, 13-H_{eq}, 2-H_b, 12-H_{eq}), 1.10–0.99 (m, 2 H, 12-H_{ax}, 14-H_{ax}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.3 (C-1_{arom}), 135.6 (C-4), 128.5 (C-3_{arom}, C-5_{arom}), 128.1 (C-2_{arom}, C-6_{arom}), 126.5 (C-5), 125.9 (C-4_{arom}), 76.0 (C-7), 69.4 (CH_2OH), 62.0 (C-9), 57.5 (C-11), 57.9 [N*C*H$_2$(CH$_2$)$_2$Ph], 42.1 (C-8), 41.5 (C-1), 32.4 (C-6), 32.4 (C-14), 31.6 (C-2), 29.5 (C-12), 33.23 [N(CH$_2$)$_2$*C*H$_2$Ph], 28.8 (NCH$_2$*C*H$_2$CH$_2$Ph), 22.8 (C-3) and 20.0 (C-13) ppm. MS (FAB): *m*/*z* (%) = 355 (100) [M^+], 354 (23) [M – H], 264 (15) [M – C_7H_7].

(1*S,7*R**,8*S**)-{7-Hydroxy-10-(3-phenylpropyl)-10-azatricyclo[6.3.3.0^{1,7}]tetradec-4-en-8-yl}methyl 2-(Trifluoroacetylamino)benzoate (25):** To a solution of the alcohol **23** (40 mg, 0.113 mmol), *N*-(trifluoroacetyl)anthranilic acid[26] (79 mg, 0.339 mmol) and 4-(dimethylamino)pyridine (7 mg, 0.057 mmol) in acetonitrile (10 mL) was added 1,3-dicyclohexylcarbodiimide (70 mg, 0.339 mmol), and the reaction mixture was stirred for 20 h at 40 °C. The mixture was then cooled, filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (10% EtOAc in hexane). Yield 61 mg (0.107 mmol, 95%) of a yellow oil; R_f = 0.73 (20% EtOAc in hexane). HRMS (EI): *m*/*z* calcd. for $C_{32}H_{37}F_3N_2O_4$: 570.2705, found: 570.2696 [M^+], calcd. for $C_{32}H_{36}F_3N_2O_4$: 569.2627, found: 569.2607 ([M–H]$^+$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.35 (s, 1 H, NH), 8.67 (d, $^3J_{5',6'}$ = 8.3 Hz, 1 H, 6′-H), 8.08 (dd, $^3J_{3',4'}$ = 8.0, $^4J_{3',5'}$ = 1.5 Hz, 1 H, 3′-H), 7.64 (ddd, $^3J_{4',5'}$ = $^3J_{5',6'}$ = 7.2, $^4J_{3',5'}$ = 1.5 Hz, 1 H, 5′-H), 7.29–7.16 [m, 6 H, 4′-H, H_{arom} (Ph)], 6.12–6.06 (m, 1 H, 4-H), 5.58–5.54 (m, 1 H, 5-H), 4.41 (d, $^2J_{gem}$ = 11.0 Hz, 1 H, C*H*$_a$H$_b$O), 4.37 (d, $^2J_{gem}$ = 11.0 H, 1 H, CH$_a$*H*$_b$Oz), 2.98–2.79 (m, 3 H, 6-H_a, 9-H_{eq}, 13-H_{ax}), 2.68–2.57 [m, 4 H, N(CH$_2$)$_2$C*H*$_2$Ph, 9-H_{ax}, 11-H_{eq}], 2.38–2.21 [m, 5 H, 2-H_a, 3-H_a, 6-H_b, NC*H*$_2$(CH$_2$)$_2$Ph], 2.17 (s, 1 H, OH), 2.15–2.02 (m, 2 H, 3-H_b, 11-H_{ax}), 1.79 (quint, ^3J = 7.4 Hz, 2 H, NCH$_2$C*H*$_2$CH$_2$Ph), 1.71 (dd, $^2J_{gem}$ = 13.3, $^3J_{13ax,14eq}$ = 6.9 Hz, 1 H, 14-H_{eq}), 1.60–1.53 (m, 2 H, 2-H_b, 13-H_{eq}), 1.45–1.39 (m, 1 H, 12-H_{eq}), 1.29–1.24 (m, 1 H, 12-H_{ax}), 1.17 (dd, $^2J_{gem}$ = 13.2, $^3J_{13eq,14ax}$ = 6.7 Hz, 1 H, 14-H_{ax}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4 [C=O (ester)], 142.5 (C-1_{arom}), 139.1 (C-2′), 136.7 (C-4), 134.9 (C-5′), 130.9 (C-3′), 128.4 (C-3_{arom}, C-5_{arom}), 128.3 (C-2_{arom}, C-6_{arom}), 126.2 (C-5), 125.7 (C-4_{arom}), 124.8 (C-4′), 120.8 (C-6′), 116.5 (C-1′), 74.0 (C-7), 69.7 (CH_2O), 62.2 (C-9), 59.1 (C-11), 57.7 [N*C*H$_2$(CH$_2$)$_2$Ph], 42.4 (C-8), 41.9 (C-1), 35.9 (C-14), 35.5 (C-12), 33.5 [N(CH$_2$)$_2$*C*H$_2$Ph], 30.3 (C-2), 29.9 (C-6), 29.0 (NCH$_2$*C*H$_2$CH$_2$Ph), 24.0 (C-3), 20.5 (C-13) ppm.

(1*S,7*R**,8*S**)-{7-Hydroxy-10-(3-phenylpropyl)-10-azatricyclo[6.3.3.0^{1,7}]tetradec-4-en-8-yl}methyl 2-Aminobenzoate (26):** The trifluoroacetamide **25** (61 mg, 0.107 mmol) was dissolved in dry ethanol (5 mL), treated with sodium borohydride (16 mg, 0.428 mmol) and stirred for 20 h at room temperature. The reaction mixture was quenched with water (10 mL) and the volatiles removed at reduced

pressure. The residue was dissolved in ethyl acetate (30 mL), washed with aq. $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography (20% EtOAc in hexane). Yield 6 mg (0.013 mmol, 12%) of a yellow oil; R_f = 0.32 (20% EtOAc in hexane). HRMS (FAB): *m*/*z* calcd. for $C_{30}H_{39}N_2O_3$: 475, found: 475 ([M + H]$^+$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (dd, $^3J_{5',6'}$ = 8.3, $^4J_{4',6'}$ = 1.5 Hz, 1 H, 6′-H), 7.29–7.16 [m, 6 H, 4′-H, H_{arom} (Ph)], 6.68–6.64 (m, 2 H, 3′-H, 5′-H), 6.12–6.04 (m, 1 H, 4-H), 5.73 (s, 2 H, NH_2), 5.60–5.52 (m, 1 H, 5-H), 4.30 (d, $^2J_{gem}$ = 11.1 Hz, 1 H, CH_aH$_b$O), 4.25 (d, $^2J_{gem}$ = 11.0 Hz, 1 H, CH$_a$$H_b$O), 2.97–2.75 (m, 2 H, 6-H$_a$, 13-H$_{ax}$), 2.86 (d, $^2J_{gem}$ = 11.0 Hz, 1 H, 9-H$_{eq}$), 2.68–2.55 [m, 4 H, N(CH$_2$)$_2$CH_2Ph, 9-H$_{ax}$, 11-H$_{eq}$], 2.42–2.19 [m, 5 H, 2-H$_a$, 3-H$_a$, 6-H$_b$, NCH_2(CH$_2$)$_2$Ph], 2.17 (s, 1 H, OH), 2.15–2.03 (m, 2 H, 3-H$_b$, 11-H$_{ax}$), 1.83–1.74 (m, 2 H, NCH$_2$CH_2CH$_2$Ph), 1.68 (dd, $^2J_{gem}$ = 13.4, $^3J_{13ax,14eq}$ = 7.0 Hz, 1 H, 14-H$_{eq}$), 1.62–1.40 (m, 3 H, 2-H$_b$, 12-H$_{eq}$, 13-H$_{eq}$), 1.29–1.21 (m, 1 H, 12-H$_{ax}$), 1.16 (dd, $^2J_{gem}$ = 13.3, $^3J_{13eq,14ax}$ = 7.0 Hz, 1 H, 14-H$_{ax}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.5 (C-2′), 142.6 (C-1$_{arom}$), 136.3 (C-4), 134.0 (C-4′), 131.0 (C-6′), 128.5 (C-3$_{arom}$, C-5$_{arom}$), 128.3 (C-2$_{arom}$, C-6$_{arom}$), 126.5 (C-5), 125.7 (C-4$_{arom}$), 116.7 (C-5′), 116.4 (C-3′), 111.0 (C-1′), 74.2 (C-7), 68.1 (CH$_2$O), 62.2 (C-9), 59.2 (C-11), 57.7 [N*C*H$_2$(CH$_2$)$_2$Ph], 42.3 (C-8), 41.9 (C-1), 35.9 (C-14), 35.7 (C-12), 33.5 [N(CH$_2$)$_2$*C*H$_2$Ph], 30.5 (C-2), 29.9 (C-6), 29.0 (NCH$_2$*C*H$_2$CH$_2$Ph), 24.0 (C-3), 20.6 (C-13) ppm. The signal for the ester carbon was unresolved.

Cyclohexyl 2-(3-Methyl-2,5-dihydro-2,5-dioxo-1*H*-pyrrol-1-yl)benzoate (29): To a solution of cyclohexanol (62 mg, 0.62 mmol) in acetonitrile (8 mL) was added 2-[3-methyl-2,5-dihydro-2,5-dioxo-1*H*-pyrrol-1-yl]benzoic acid (**28**)[25] (385 mg, 1.23 mmol) and 4-(dimethylamino)pyridine (7 mg, 0.06 mmol) and the solution placed under nitrogen. Dicyclohexylcarbodiimide (253 mg, 1.23 mmol) was added, and the mixture stirred under nitrogen at room temperature for 6 h. After this time, the mixture was filtered through celite and the solvent removed in vacuo. The residue was dissolved in ethyl acetate (25 mL), washed with saturated sodium hydrogencarbonate (25 mL) and brine (25 mL), dried (Na_2SO_4), filtered and the solvent removed in vacuo. The crude product was purified by flash chromatography (9:1 hexane/ethyl acetate). Yield 190 mg (98%) of a pale yellow oil. HRMS (EI): *m*/*z* calcd. for $C_{18}H_{19}NO_4$: 313.3478, found: 313.3477 [M$^+$]. IR (NaCl): $\tilde{\nu}_{max}$ = 2923(C–H), 1714 (C=O), 1646 (C=C) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (dd, $^3J_{3',4'}$ = 7.8, $^4J_{3',5'}$ = 1.5 Hz, 1 H, 3′-H), 7.63 (dt, $^3J_{3',4'}$ = $^3J_{4',5'}$ = 7.6, $^4J_{4',6'}$ = 1.2 Hz, 1 H, 4′-H), 7.50 (dt, $^3J_{4',5'}$ = $^3J_{5',6'}$ = 7.7, $^4J_{4',6'}$ = 1.2 Hz, 1 H, 5′-H), 7.29 (dd, $^3J_{5',6'}$ = 7.9, $^4J_{4',6'}$ = 1.2 Hz, 6′-H, 1 H), 6.52 (q, $^4J_{3''\text{-}CH_3,4''}$ = 1.8 Hz, 1 H, 4′′-H), 4.91–4.88 (m, 1 H, HC–O), 2.18 (d, $^4J_{3''\text{-}CH_3,4''}$ = 1.8 Hz, 3 H, 3′′-CH$_3$), 1.76–1.73 (m, 2 H, Cy), 1.92–1.89 (m, 2 H, Cy), 1.55–1.25 (m, 6 H, Cy) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7 (C-2′′), 169.6 (*C*=O, ester), 164.3 (C-5′′), 146.1 (C-2′), 132.8 (C-4′′), 131.5 (C-4′) 130.1 (C-6′), 131.3 (C-3′) 128.8(C-3′), 127.8 (C-5′ and C-1′), 73.6 (*C*HO), 41.5, 25.2 and 21.4 (3×CH$_2$, Cy), 11.1 (C3′′-*C*H$_3$) ppm.

Cyclohexyl 2-(3-Methyl-2,5-dioxopyrrolidin-1-yl)benzoate (30): To a solution of cyclohexyl 2-[3-methyl-2,5-dihydro-2,5-dioxo-1*H*-pyrrol-1-yl]benzoate (**29**) (100 mg, 0.32 mmol) in ethyl acetate (10 mL) was added 10% palladium on carbon (15 mg), and the mixture stirred under hydrogen for 3 h. After this time the solution was filtered through a 1:1 mixture of celite and silica and the solvent removed in vacuo. The crude product was purified by flash chromatography (5:1 hexane/ethyl acetate). Yield 100 mg (99%) of a clear oil. HRMS (EI): *m*/*z* calcd. for $C_{18}H_{21}NO_4$: 315.3636, found: 315.3636 [M$^+$]. IR (NaCl): $\tilde{\nu}_{max}$ = 2928, 1714, 1392, 1261 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12–8.07 (m, 1 H, 5′-H), 7.61 (t, $^3J_{3',4'}$ = 7.5, 1 H, 3′-H), 7.49 (t, $^3J_{3',4'}$ = $^3J_{4',5'}$ = 7.6 Hz, 1 H, 4′-H), 7.23 (d, $^3J_{5',6'}$ = 7.5 Hz, 1 H, 6′-H), 4.90 (br. s, 1 H, OCH), 3.12–3.02 (m, 2 H, 3′′-H, 4′′-H$_a$), 2.57–2.47 (m, 1 H, 4′′-H$_b$), 1.79–1.70 (m, 2 H, Cy), 1.95–1.85 (m, 2 H, Cy), 1.60–1.25 (m, 9 H, 3′′-CH$_3$, Cy) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.8 (C-2′), 175.9/175.7 (C-5′), 163.8 (C=O, ester), 133.4 (C-5′), 132.8 (C-1′), 131.0 (C-3′), 130.1 (C-6′), 129.4 (C-4′), 73.4/73.6 (CHO), 36.9 (C-4′′), 35.1/35.3 (C-3′′), 31.4, 25.9/25.3 and 24.2/23.6 (Cy) and 16.1/16.5 (C3′′-*C*H$_3$) ppm.

(1*S,7*S**,8*S**)-{7-Hydroxy-10-(3-phenylpropyl)-10-azatricyclo-[6.3.3.0^{1,7}]tetradec-4-en-8-yl}methyl 2-(3-Methyl-2,5-dihydro-2,5-dioxo-1*H*-pyrrol-1-yl)benzoate (31):** To a solution of the alcohol **23** (276 mg, 0.78 mmol) in acetonitrile (8 mL) was added 2-[3-methyl-2,5-dihydro-2,5-dioxo-1*H*-pyrrol-1-yl]benzoic acid (**28**)[25] (360 mg, 1.55 mmol) and 4-(dimethylamino)pyridine (10 mg, 0.08 mmol) and the solution placed under nitrogen. Dicyclohexylcarbodiimide (311 mg, 1.55 mmol) was added, and the mixture stirred under nitrogen at room temperature for 6 h. After this time, the mixture was filtered through celite and the solvent removed in vacuo. The residue was dissolved in ethyl acetate (25 mL), washed with saturated sodium hydrogencarbonate (25 mL) and brine (25 mL), dried (Na_2SO_4), filtered and the solvent removed in vacuo. The crude product was purified by flash chromatography (20% ethyl acetate in hexane). Yield 365 mg (83%) of a pale yellow solid; m.p. (from dichloromethane) 57.5–58.5 °C. HRMS (EI): *m*/*z* calcd. for $C_{35}H_{41}N_2O_5$: 569.3016, found: 569.3017 [MH$^+$]. IR (NaCl): $\tilde{\nu}_{max}$ = 3559, 2923, 1714, 1395, 1259 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, $^3J_{5',6'}$ = 7.8 Hz, 1 H, 6′-H), 7.64 (t, $^3J_{3',4'}$ = $^3J_{4',5'}$ = 7.7 Hz, 1 H, 4′-H), 7.49 (t, $^3J_{4',5'}$ = $^3J_{5',6'}$ = 7.6 Hz, 1 H, 5′-H), 7.31–7.25 (m, 3 H, 3′-H, H$_{arom}$), 7.20–7.16 (m, 3 H, H$_{arom}$), 6.49–6.46 (m, 1 H, 4′′-H), 6.11–6.03 (m, 1 H, 4-H), 5.59–5.51 (m, 1 H, 5-H), 4.32–4.23 (m, 2 H, OCH$_2$), 2.94–2.88 (m, 1 H, 13-H$_a$), 2.82 (d, $^2J_{gem}$ = 11.0 Hz, 1 H, 9-H$_a$), 2.70 (d, $^2J_{gem}$ = 10.7 Hz, 1 H, 11-H$_a$), 2.65 [m, 2 H, N(CH$_2$)$_2$CH_2Ph], 2.57 (d, $^2J_{gem}$ = 11.0 Hz, 1 H, 9-H$_b$), 2.41 (d, $^2J_{gem}$ = 10.7 Hz, 1 H, 11-H$_b$), 2.42–2.18 [m, 7 H, NCH_2(CH$_2$)$_2$Ph, 2-H$_a$, 3-H$_a$, 6-CH$_2$, 7-OH], 2.17 (d, $^3J_{3'',\ 3''\text{-}CH_3}$ = 1.8 Hz, 3 H, 3′′-CH_3), 2.00–1.94 (m, 1 H, 3-H$_b$), 1.81–1.77 (m, 2 H, NCH$_2$CH_2CH$_2$Ph), 1.69–1.47 (m, 4 H, 2-H$_b$, 12-H$_a$, 13-H$_b$, 14-H$_a$), 1.39–1.31 (m, 1 H, 12-H$_b$), 0.98–0.93 (m, 1 H, 14-H$_b$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8 (C-2′′), 169.8 (C-5′′), 164.9 (C=O, ester), 146.2 (C-3′′), 142.7 (C-1$_{arom}$), 136.4 (CH, C-4), 133.2 (C-4′′), 131.8 (C-2′), 131.3 (C-4′), 130.5 (C-6′), 129.0 (CH, C-5′), 128.4 (C-3$_{arom}$, C-5$_{arom}$), 128.3 (C-2$_{arom}$, C-6$_{arom}$), 128.1 (C-1′), 127.9 (C-3′), 126.7 (C-5), 125.6 (C-4$_{arom}$), 73.0 (C-7), 69.3 (CH$_2$O), 62.9 (C-9), 57.7 (C-11), 57.5 (NCH$_2$CH$_2$*C*H$_2$Ph), 42.3 (C-1), 42.5 (C-8), 33.5 (N*C*H$_2$CH$_2$CH$_2$Ph), 32.3 (C-14), 32.8 (C-6), 30.1 (C-2), 31.3 (C-12), 28.8 (NCH$_2$*C*H$_2$CH$_2$Ph), 19.8 (C-13), 23.1 (C-3), 11.2 (C3′′-*C*H$_3$) ppm.

(1*S,7*R**,8*S**)-{7-Hydroxy-10-(3-phenylpropyl)-10-azatricyclo-[6.3.3.0^{1,7}]tetradec-4-en-8-yl}methyl 2-(3-Methyl-2,5-dihydro-2,5-dioxo-1*H*-pyrrol-1-yl)benzoate (32):** To a solution of the alcohol **24** (125 mg, 0.35 mmol) in acetonitrile (4 mL) was added **28** (163 mg, 0.70 mmol) and 4-(dimethylamino)pyridine (5 mg, 0.04 mmol), and the solution placed under nitrogen. Dicyclohexylcarbodiimide (141 mg, 0.70 mmol) was added, and the mixture stirred under nitrogen at room temperature for 5 h. After this time, the mixture filtered through celite and the solvent removed in vacuo. The residue was dissolved in ethyl acetate (20 mL), washed with saturated sodium hydrogencarbonate (20 mL) and brine (20 mL), dried (Na_2SO_4), filtered and the solvent removed in vacuo. The crude product was purified by flash chromatography (20% ethyl acetate in hexane). Yield 170 mg (85%) of a pale yellow solid; m.p. (from

dichloromethane) 57–58 °C. HRMS (EI): *m*/*z* calcd. for $C_{35}H_{41}N_2O_5$: 569.3016, found: 569.3015 [MH^+]. IR (NaCl): $\tilde{\nu}_{max}$ = 3561, 2926, 1714, 1395, 1259 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.06 (dd, $^3J_{5',6'}$ = 7.8, $^3J_{4',6'}$ = 1.5 Hz, 1 H, 6′-H), 7.65 (t, $^3J_{3',4'}$ = $^3J_{4',5'}$ = 7.7, $^3J_{4',6'}$ = 1.6 Hz, 1 H, 4′-H), 7.49 (td, $^3J_{4',5'}$ = $^3J_{5',6'}$ = 7.7, $^3J_{3',5'}$ = 1.2 Hz, 1 H, 3′-H), 7.32–7.26 (m, 3 H, 3′-H, H_{arom}), 7.20–7.16 (m, 3 H, H_{arom}), 6.47–6.45 (m, 1 H, 4′′-H), 6.08–6.03 (m, 1 H, 4-H), 5.55–5.51 (m, 1 H, 5-H), 4.27–4.19 (m, 2 H, OCH_2), 2.91 (d, $^2J_{gem}$ = 15.0 Hz, 1 H, 9-H_a), 2.83–2.80 (m, 2 H, 6-H_a 13-H_a), 2.66 [m, 2 H, $N(CH_2)_2CH_2Ph$], 2.60–53 (m, 2 H, 9-H_a,11-H_a), 2.34–2.20 [m, 5 H, 2-H_a, 3-H_a, 6-H_b, $NCH_2(CH_2)_2Ph$], 2.16 (d, $^3J_{3'',3''\text{-}CH_3}$ = 1.8 H, 3 H, 3′′-CH_3z), 2.12 (s, 1 H, 7-OH), 2.11–2.03 (m, 2 H, 3-H_b, 11-H_b), 1.80–1.76 (m, 2 H, $NCH_2CH_2CH_2Ph$), 1.63 (dd, $^2J_{gem}$ = 13.3, $^3J_{13,14}$ = 6.9 Hz, 1 H, 14-H_a), 1.54–1.51 (m, 1 H, 2-H_b), 1.40–1.37 (m, 1 H, 13-H_b), 1.24–1.21 (m, 1 H, 12-H_a), 1.16–1.13 (m, 1 H, 12-H_b), 0.88–0.85 (m, 1 H, 14-H_b) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8 (C-2′′), 169.8 (C-5′′), 164.9 (C=O, ester), 146.2 (C-3′′), 142.5 (C-1_{arom}), 136.4 (C-4), 133.2 (C-4′′), 131.9 (C-2′), 131.3 (C-4′), 130.5 (C-6′), 129.0 (C-5′), 128.5 (C-3_{arom}, C-5_{arom}), 128.3 (C-2_{arom}, C-6_{arom}), 127.9 (C-3′), 128.1 (C-1′), 125.6 (C-4_{arom}), 126.4 (C-5), 74.0 (C-7), 69.0 (OCH_2), 62.1 (C-9), 59.0 (C-11), 57.6 ($NCH_2CH_2CH_2Ph$), 42.3 (C-8), 41.8 (C-1), 35.8 (C-14), 35.6 (C-12), 33.5 ($NCH_2CH_2CH_2Ph$), 30.3 (C-2), 29.8 (C-6), 28.9 ($NCH_2CH_2CH_2Ph$), 23.9 (C-3), 20.5 (C-13), 11.2 (C3′′-CH_3) ppm.

(1*S,7*S**,8*S**)-{7-Hydroxy-10-(3-phenylpropyl)-10-azatricyclo-[6.3.3.0^{1,7}]tetradecane-8-yl}methyl 2-(3-Methyl-2,5-dioxopyrrolidin-1-yl)benzoate (33):** To a solution of the olefin **31** (100 mg, 0.18 mmol) in ethyl acetate (10 mL) was added 10% palladium on carbon (15 mg) and the mixture stirred under hydrogen for 3 h. After this time the solution was filtered through a 1:1 mixture of celite and silica, and the solvent removed in vacuo. The crude product was purified by flash chromatography (2:1 hexane/ethyl acetate). Yield 92 mg (92%) of a colourless solid; m.p. (from dichloromethane) 53.5–54.5 °C. HRMS (EI): *m*/*z* calcd. for $C_{35}H_{44}N_2O_5$: 572.3250, found: 572.3238 [M^+]. IR (NACl): $\tilde{\nu}_{max}$ = 3543, 2928, 1714, 1392, 1261 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 8.06 (d, $^3J_{3',4'}$ = 5.2 Hz, 1 H, 3′-H), 7.66 (td, $^3J_{4',5'}$ = $^3J_{5',6'}$ = 7.7, $^3J_{3',5'}$ = 1.5 Hz, 1 H, 5′-H), 7.52 (td, $^3J_{3',4'}$ = $^3J_{4',5'}$ = 7.7, $^3J_{4',6'}$ = 1.5 Hz, 1 H, 4′-H), 7.29–7.25 (m, 3 H, 6′-H, H_{arom}), 7.20–7.17, (m, 3 H, H_{arom}), 4.17 (d, $^2J_{gem}$ = 11.0 Hz, 1 H, C$H_a$$H_b$O), 4.03 (d, $^2J_{gem}$ = 11.0 Hz, 1 H, C$H_a$$H_b$O), 3.07 (m, 2 H, 4′′-$H_a$, 3′′-H), 2.87–2.81 (m, 1 H, 5-H_a), 2.75 (d, $^2J_{gem}$ = 11.1 Hz, 1 H, 9-H_a), 2.65 [t, ^3J = 7.1 Hz, 2 H, $N(CH_2)_2CH_2Ph$], 2.57–2.50 (m, 2 H, 4′′-H_b, 11-H_a), 2.40 (d, $^2J_{gem}$ = 11.2 Hz, 1 H, 11-H_b), 2.28–2.21 [m, 3 H, 9-H_b, $NCH_2(CH_2)_2Ph$], 2.09 (s, 1 H, 6-H_a), 1.98 (t, $^2J_{gem}$ = 13 Hz, 1 H, 12-H_a), 1.86–1.83 (m, 2 H, 2-H_a, 14-H_a), 1.80–1.70 (m, 5 H, 4-H_a, 12-H_b, 13-H_a, $NCH_2CH_2CH_2Ph$), 1.58–1.42 (m, 9 H, 3-CH_2, 4-H_b, 6-H_b, 5-H_b, 13-H_b, 3′′-CH_3), 1.29–1.26 (m, 1 H, 2-H_b), 1.01–0.96 (m, 1 H, 14-H_b) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 179.7/179.8 (C-2′′), 175.8/176.0 (C-5′′), 164.2/164.3 (C=O, ester), 142.5 (C-2′), 133.4 (C-5′), 132.7 (C-1′), 131.0/131.2 (C-3′), 129.8 (C-6′), 129.4 (C-4′), 128.4 (C-3_{arom}, C-5_{arom}), 128.2 (C-2_{arom}, C-6_{arom}), 127.3 (C-4_{arom}), 125.6 (C-1_{arom}), 75.7 (C-7), 69.7 (OCH_2), 60.9 (C-11), 59.3 (C-9), 57.7 ($NCH_2CH_2CH_2Ph$), 42.2 (C-8), 41.2 (C-1), 36.9 (C-4′′), 36.9 (C-2), 35.3/35.1 (C-3′′), 34.0 (C-14), 33.4 ($NCH_2CH_2CH_2Ph$), 33.0 (C-12), 29.7 (C-6), 28.9 ($NCH_2CH_2CH_2Ph$), 21.0 (C-4), 20.3 (C-5), 20.3 (C-13) and 16.3/16.5 (C3′′-CH_3) ppm.

(1*S,7*R**,8*S**)-{7-Hydroxy-10-(3-phenylpropyl)-10-azatricyclo-[6.3.3.0^{1,7}]tetradecane-8-yl}methyl 2-(3-Methyl-2,5-dioxopyrrolidin-1-yl)benzoate (34):** To a solution of the olefin **32** (50 mg, 0.088 mmol) in ethyl acetate (5 mL) was added 10% palladium on carbon (10 mg) and the mixture stirred under hydrogen for 3 h. After this time the solution was filtered through a 1:1 mixture of celite and silica, and the solvent removed in vacuo. The crude product, was purified by flash chromatography (2:1 hexane/ethyl acetate). Yield 45 mg (90%) of a colourless solid; m.p. (from dichloromethane) 53–54 °C. HRMS (EI): *m*/*z* calcd. for $C_{35}H_{44}N_2O_5$: 572.3250, found: 572.3255 [M^+]. IR (NaCl): $\tilde{\nu}_{max}$ = 3545, 2926, 1714, 1392, 1262 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 8.04 (d, $^3J_{3',4'}$ = 7.6 Hz, 1 H, 3′-H), 7.66 (td, $^3J_{4',5'}$ = $^3J_{5',6'}$ = 7.6, $^3J_{3',5'}$ = 1.1 Hz, 1 H, 5′-H), 7.52 (td, $^3J_{3',4'}$ = $^3J_{4',5'}$ = 7.6, $^3J_{4',6'}$ = 1.1 H, 1 H, 4′-Hz), 7.29–7.27 (m, 3 H, 6′-H, H_{arom}), 7.19–7.16 (m, 3 H, H_{arom}), 4.26 (d, $^2J_{gem}$ = 11.1 Hz, 1 H, OC$H_a$$H_b$), 4.12 (d, $^2J_{gem}$ = 11.1 Hz, 1 H, $OCH_a$$H_b$), 3.11–3.02 (m, 2 H, 4′′-H_a, 3′′-H), 2.76–2.71 (m, 2 H, 9-H_a, 13-H_a), 2.65 [t, ^3J = 7.5 Hz, 2 H, $N(CH_2)_2$-CH_2Ph], 2.59–2.49 (m, 2 H, 4′′-H_b, 9-H_b), 2.39 (d, $^2J_{gem}$ = 11.2 Hz, 1 H, 11-H_a), 2.32 (d, $^2J_{gem}$ = 11.0 Hz, 1 H, 11-H_b), 2.26 [t, ^3J = 6.8 Hz, 2 H, $NCH_2(CH_2)_2Ph$], 1.94–1.87 (m, 2 H,12-H_a, 6-H_a), 1.80–1.76 (m, 3 H, 6-H_B, $NCH_2CH_2CH_2Ph$), 1.72 (m, 2 H,4-H_a, 5-H_a), 1.66 (m, 2 H, 14-CH_2), 1.58–1.51 (m, 5 H, 3-CH_2, 4-H_b, 5-H_b, 13-H_b), 1.49–1.42 (m, 3 H, 3′′-CH_3), 1.39 (dd, $^2J_{gem}$ = 13.2, $^3J_{12,13}$ = 6.3 H, 1 H, 12-H_bz), 0.90–0.87 (m, 2 H, m,2-CH_2) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 179.9 (C-2′′), 176.0/174.8 (C-5′′), 164.4/164.1 (C=O, ester), 142.5 (C-2′), 133.4 (C-5′), 132.8 (C1′), 131.2/131.1 (C-3′), 129.9 (C-6′), 129.5 (CH, C-4′), 128.4 (C-3_{arom}, C-5_{arom}), 128.3 (C-2_{arom}, C-6_{arom}), 127.3 (C-1_{arom}), 125.6 (C-4_{arom}), 75.8 (C-7), 70.1 (OCH_2), 62.8 (C-11), 57.2 ($NCH_2CH_2CH_2Ph$), 57.1 (C-9), 42.6 (C-8), 41.2 (C-1), 37.0 (C-4′′), 35.4/35.2 (C-3′′), 33.5 ($NCH_2CH_2CH_2Ph$), 33.4 (C-2), 32.9 (C-12), 32.4 (C-6), 31.8 (C-14), 28.8 ($NCH_2CH_2CH_2Ph$), 26.5 (C-4), 21.1 (C-3), 20.5 (C-5), 19.8 (C-13) and 16.5/16.3 (C3′′-CH_3) ppm.

Acknowledgments

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