Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 61 (2005) 5876–5888

Use of bis-(aminol) ethers derived from *N*-(*S*)-(−)-α-methylbenzylamine in reactions with resorcinarenes and double Mannich reactions

Benjamin R. Buckley,[a] Philip C. Bulman Page,[a] Harry Heaney,[a,*] Edward P. Sampler,[a] Sarah Carley,[b] Constanze Brocke[b] and Margaret A. Brimble[b,*]

[a]*Department of Chemistry, Loughborough University, Loughborough, Leicestershire LE11 3TU, UK*
[b]*Department of Chemistry, University of Auckland, 23 Symonds St., Auckland, New Zealand*

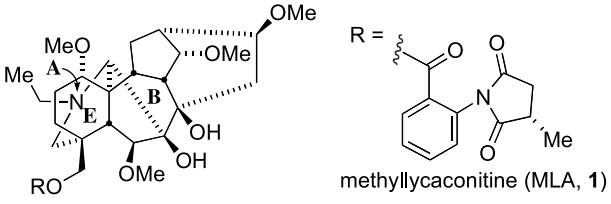
Received 19 January 2005; revised 16 March 2005; accepted 31 March 2005

Available online 10 May 2005

Abstract—The synthesis of some chiral bis-(aminol)ethers are described. Reaction of a solution of the resorcin[4]arene derived from propanal with *N*,*N*-bis(methoxymethyl)-*N*-(*S*)-(−)-α-methylbenzylamine in toluene at 85 °C initially afforded a 1:1 mixture of two diastereoisomeric tetrakis(benzoxazines). Further, heating of this mixture under reflux in ethanol for 24 h afforded the crystalline (α*S*),(*S*)-diastereoisomer in 77% yield. *N*,*N*-bis(ethoxymethyl)-*N*-(*S*)-(−)-α-methylbenzylamine and *N*,*N*-bis(ethoxymethyl)-*N*-(*R*)-(+)-α-methylbenzylamine were reacted with β keto esters to afford a 1:1 mixture of the diastereoisomeric double Mannich adducts. Two of the double Mannich adducts were converted into tricyclic ABE analogues of the alkaloid methyllycaconitine **1**.

1. Introduction

Bis-(aminol) ethers derived from primary amines are efficient *bis*-aminoalkylating agents used for the synthesis of tertiary amines upon reaction with a nucleophilic source. Our synthetic work in this area has focused on their use for the efficient preparation of secondary and tertiary amines using aromatic nucleophiles[1] and for the construction of the azabicyclo[3.3.1]nonane ring system present in the alkaloid methyllycaconitine **1**[2] via use of ethyl 2-oxocyclohexane1-carboxylate as the nucleophile in a double Mannich



methyllycaconitine (MLA, **1**)

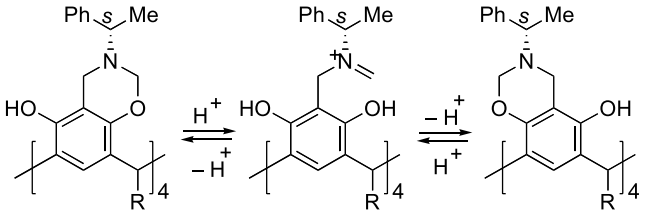
reaction.[3] We herein report our studies on the use of chiral bis-(aminol) ether *N*,*N*-bis(methoxymethyl)-*N*-(*S*)-(−)-α-methylbenzylamine **2** as a bis-aminoalkylating agent in an effort to exert diastereocontrol in reactions to prepare tetrakis(benzoxazines) and the double Mannich reaction.

2. Results and discussion

Some time ago we[4] and others[5,6] showed that the reactions of formaldehyde and either (*R*)-(+)-α-methylbenzylamine or (*S*)-(−)-α-methylbenzylamine with a number of resorcin-[4]arenes in ethanol led to the formation of crystalline tetrakis(benzoxazines) with high diastereoselectivity and in high yield, also that the ^{1}H and ^{13}C NMR spectroscopic data for the two sets of diastereoisomers were identical and their optical rotation values were of opposite signs. These data established that the two sets of diastereoisomers were enantiomers. Further, we also showed that the bis-(aminol) ethers derived from either (*R*)-(+)-α-methylbenzylamine or (*S*)-(−)-α-methylbenzylamine together with methanol and paraformaldehyde gave the same diastereoisomeric tetrakis(benzoxazines) in high yield in ethanol.[7] The diastereoisomerization of the tetrakis(benzoxazines) in, for example, carefully purified and acid-free deuteriochloroform, must proceed via a series of iminium ions that are generated intramolecularly as a result of hydrogen bonding between the residual phenolic hydroxyl groups and the adjacent benzoxazine oxygen atoms and led to an approximately 2:1

Keywords: Chiral bis-(aminol) ether; Mannich reaction; Resorcinarenes; Methyllycaconitine.
* Corresponding authors. Tel.: +64 9 3737599x88259; fax: +64 9 3737422 (H.A.); e-mail: m.brimble@auckland.ac.nz

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.03.130



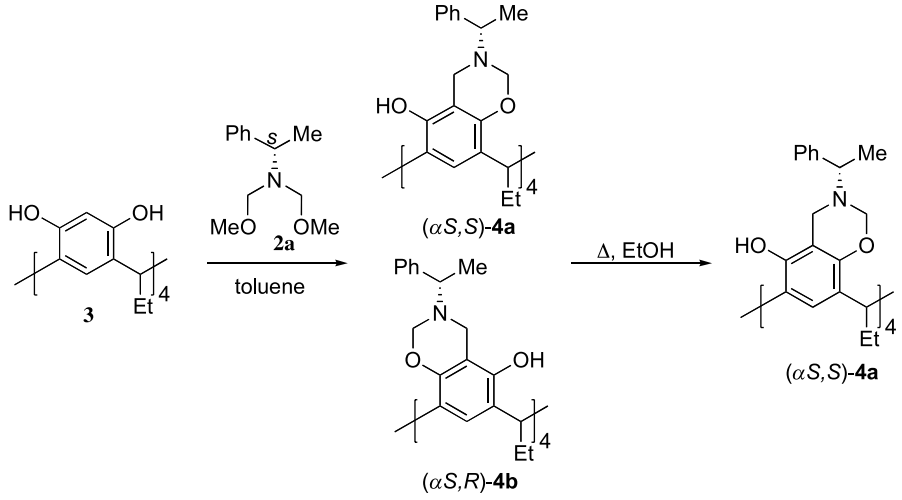
Scheme 1.

mixture of the previously isolated product together with its diastereoisomer (Scheme 1).[4]

We presumed that the reason for the diastereoselectivity in ethanol was related to the isolated products being the most thermodynamically stable stereoisomers as a result of intramolecular hydrogen bonding and gearing of the phenyl groups that are evident in the X-ray structure that we had obtained.[4] Böhmer[8] carried out an experiment of the dodecanal derived resorcin[4]arene with formaldehyde and (*R*)-(+)-α-methylbenzylamine in ethanol in which an aliquot was taken and quenched just as precipitation had started, that reaction established that the initial reaction involved the random formation of benzoxazines in equilibrium and that the observed diastereoselectivity resulted from the lower solubility of one of the two diastereoisomers. We had also carried out experiments that were designed to establish the reason for the preferred isolation of a single diastereoisomer in related reactions.[9]

We now present details of our experiments using *N*,*N*-bis(methoxymethyl)-*N*-(*S*)-(−)-α-methylbenzylamine **2a** (Scheme 2). When a solution of the resorcin[4]arene **3** derived from propanal was heated in toluene at 85 °C with *N*,*N*-bis(methoxymethyl)-*N*-(*S*)-(−)-α-methylbenzylamine **2a** the reaction mixture remained homogeneous and a ^{1}H NMR spectrum of an aliquot taken after a few hours showed that a complex mixture of products was present. The solvent was removed after 24 h and a portion of the residue was examined by ^{1}H NMR spectroscopy. The spectrum showed that the product was made up of an approximately 1:1 mixture of two diastereoisomers **4a**, **4b** related to those that had been observed in the diastereoisomerization reactions reported earlier,[4] together with a small amount of other regioisomers. The AB quartets for the methylene group(s) between the oxygen and nitrogen atoms are the diagnostic resonances and were observed for one diastereoisomer at δ_H 5.16 and 4.96 and for the second diastereoisomer at δ_H 5.02 and 4.74 ppm. Ethanol was then added to the oily mixture of products and the mixture was heated under reflux for a further, 24 h, after which time the cooled solution gave a crystalline product in 77% yield which was shown to be the (α*S*),(*S*)-diastereoisomer **4a** δ_H 5.16 and 4.96 for the O–CH_2–N AB quartet, by comparison with data from related compounds. These results establish that the tetrakis-(3,4-dihydro-2*H*−1,3-benzoxazines) are initially formed as a random mixture of regio- and diastereo-isomers and that isomerization under equilibrium reaction conditions leads eventually to the two thermodynamically favoured diastereoisomers, one of which crystallizes from ethanolic solution. We were interested to establish whether the equilibrium position for the two major diastereoisomers was solvent dependent, particularly in view of the observed ratios in deuteriochloroform (2:1) and toluene (1:1). A sample of the 1:1 mixture of diastereoisomers, obtained from the reaction carried out in toluene, was dissolved in [$^2H_4$]methanol and its ^{1}H NMR spectrum was taken after ca. 1.5 h. The ^{1}H NMR spectrum showed that the diastereoisomer that crystallized from ethanol was the major isomer present in solution, the second diastereoisomer was only present in a trace amount. These results support the view that, in solution, the position of the equilibrium between the two major diastereoisomers is dependent on the polarity of the solvent and that the isolation of a single diastereoisomer from an ethanolic solution results from a solvent–solute interaction that results in the equilibrium favouring its preferential formation both as a result of the hydrogen bonding between the residual phenolic hydroxyl groups and the adjacent benzoxazine oxygen atoms and the gearing of the phenyl residues, as observed previously in the X-ray crystal structures.

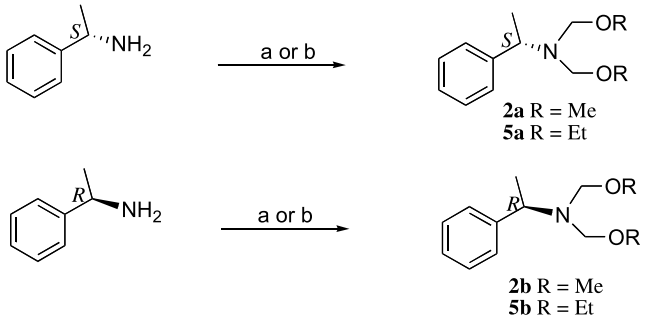
In light of the ability of *N*,*N*-bis(methoxymethyl)-*N*-(*S*)-(−)-α-methylbenzylamine **2a** to influence diastereocontrol in the above reaction with resorcinarene **3**, it was decided to investigate the ability of chiral bis-(aminol) ether **5** to exert



Scheme 2.

diastereocontrol in double Mannich reactions with cyclic β-keto esters. Use of ethyl 2-oxocyclohexane-1-carboxylate **6** in this latter reaction provides an efficient entry to the AE bicyclic ring system present in methyllycaconitine **1**, an alkaloid that binds with high affinity to the α7 nicotinic acetylcholine receptor.[10] A number of approaches to the synthesis of small molecule analogues of methyllycaconitine have been reported, including the synthesis of E,[11] AE[12] and AEF[13] ring systems, some of which display significant biological activity.[11,14] The present investigation provided an opportunity to construct the AE azabicyclo[3.3.1]nonane ring system in enantiopure form through implementation of an asymmetric variant of the key double Mannich reaction we had previously developed using bis-(aminol) ethers derived from achiral amines.

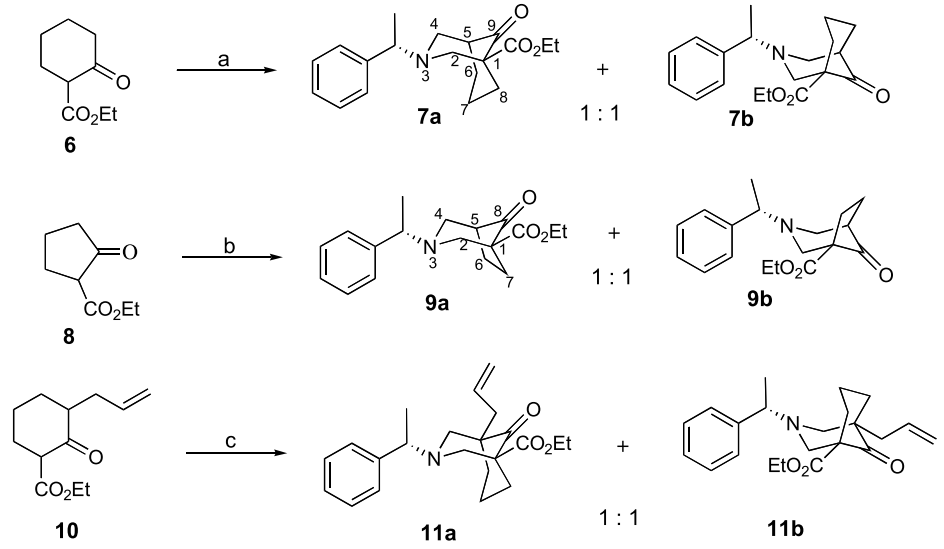
Chiral bis-(aminol)ethers **2a**, **2b** and **5a**, **5b** were prepared by reaction of (*S*)-(−)-α-methylbenzylamine or (*R*)-(+)-α-methylbenzylamine with potassium carbonate (1.0 equiv) and paraformaldehyde (2.0 equiv) in either methanol or ethanol for 48 h followed by purification by vacuum distillation (Scheme 3). The double Mannich reaction of chiral bis-(aminol) ether **5a** with keto ester **6** was carried out in an analogous manner to the racemic work.[3] Thus, a mixture of β-keto ester **6** and bis-(aminol)ether **5a** (2.0 equiv) in acetonitrile was treated with trichloromethylsilane (2.0 equiv) with stirring for 20 h (Scheme 4). It was envisaged that the reaction would result in the formation of a mixture of two diastereomeric bicyclic ketones **7a**, **7b** which would then be separated by flash chromatography and further, elaborated to provide the azabicyclo[3.3.1]nonane ring system in enantiopure AE analogue of MLA after removal of the chiral amine group. Disappointingly the two diastereomeric double Mannich products **7a**, **7b** only appeared as a single spot upon analysis by TLC using several solvent systems. Numerous attempts to separate the diastereomers by flash chromatography and HPLC were fruitless. The double Mannich product albeit as a 1:1 mixture of diastereomers **7a**, **7b** was afforded as a colourless oil in 76% yield.



Scheme 3. Reagents, conditions and yields: (a) K_2CO_3, CH_2O, MeOH, 48 h, **2a**, 65%; **2b**, 66%. (b) K_2CO_3, CH_2O, EtOH, 48 h, **5a**, 40%; **5b**, 22%.

A similar reaction of the five membered β-keto ester **8** with bis-(aminol) ether **5a** afforded an inseparable 1:1 mixture of the diastereoisomeric adducts **9a**, **9b** in 74% yield. It was next, decided to investigate the use of allylated keto ester **10** in the double Mannich reaction with bis-(aminol) ether **2a** hoping that the presence of an allyl side chain would afford separable diastereomeric adducts **11a**, **11b**. As it transpired the adducts **11a**, **11b** were afforded in 77% yield also as an inseparable 1:1 mixture. Similar yields were obtained for the analogous reaction of the enantiomeric chiral bis-(aminol) ether **5b** with β-keto esters **6**, **8** and **10**.

The structures of the adducts **7a**, **7b** were supported by a molecular ion at *m/z* 315.1830 (M^+) in the high resolution mass spectrum, corresponding to the molecular formula $C_{19}H_{25}NO_3$. The ^1H NMR spectrum of a basic 3-azabicyclo[3.3.1]nonane ring system is complex yet distinct due to the non-equivalence of the methylene protons in the bicyclic ring system. The ^1H NMR spectrum of bicyclic ketones **7a**, **7b** was further, complicated due to the doubling of signals resulting from the presence of a 1:1 diastereomeric mixture of products. Using 2D COSY and heteronuclear ^1H-^{13}C correlated NMR spectra it was possible to completely assign all protons and carbons relating to either diasteromeric adduct **7a** or **7b**. Using data obtained through structural studies performed by Arias-Pérez



Scheme 4. Reagents, conditions and yields: (a) **5a**, $SiCl_3Me$, acetonitrile, 20 h, **7a**:**7b** (1:1), 76%; (b) **5a**, $SiCl_3Me$, acetonitrile, 20 h, **9a**:**9b** (1:1), 74%; (c) **5a**, $SiCl_3Me$, acetonitrile, 20 h, **11a**:**11b** (1:1), 77%.

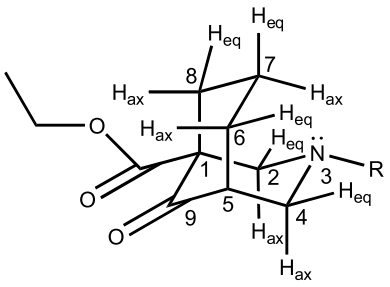


Figure 1. Conformation of the 3-azabicyclo[3.3.1]nonane-1-carboxylate ring system.

et al[15] it was possible to assign the protons on the bicyclic ring to axial or equatorial positions (Fig. 1).

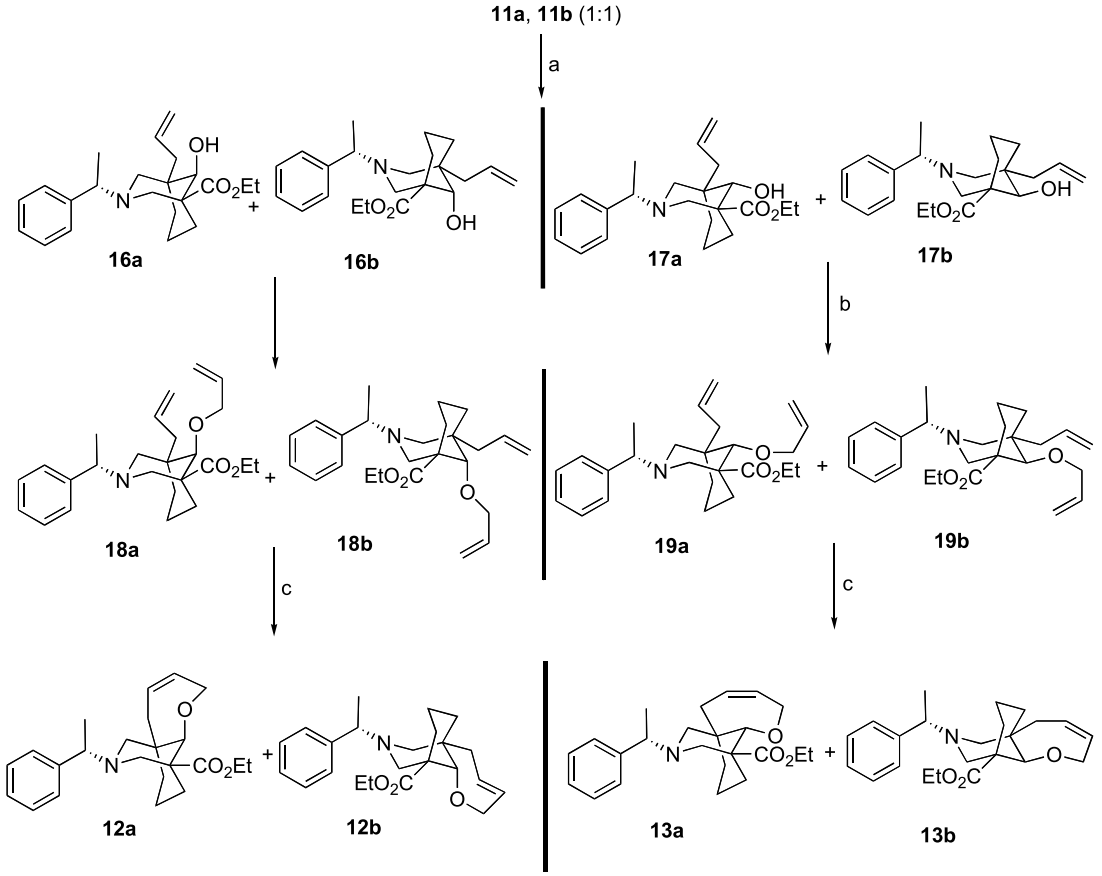
The axial proton attached to C-7 at δ_H 2.83–3.00 resonates further, downfield than the equatorial proton positioned on the same carbon that resonates at δ_H 1.51–1.69, due to the intense deshielding effect by the nitrogen lone pair that lies in close proximity to the axial proton.[15] A doublet of doublets at δ_H 2.88 (J=1.6, 11.7 Hz) was assigned to 2-H_{ax} and a multiplet at δ_H 2.98–3.02 was assigned to 4-H_{eq} and 2-H_{ax}*. The deshielded doublet of doublets at δ_H 3.10 (J= 2.3, 11.7 Hz) was assigned to 2-H_{eq}, while the doublet of doublets of doublets at δ_H 3.30 (J=2.3, 2.3, 11.0 Hz) was assigned to 4-H_{eq}*. The doublet of doublets at δ_H 3.36 (J= 2.7, 11.3 Hz) was assigned to the more deshielded 2-H_{eq}*.

The axial protons of 2-H_{ax} and 4-H_{ax} are more shielded than the equatorial protons 2-H_{eq} and 4-H_{eq} due to delocalisation of the nitrogen lone pair electrons into the *trans*-coplanar C–H bond[15] (Fig. 1). The assignment of the 4-H and 2-H protons is usually derived from the four-bond coupling constants; however, the presence of a diastereomeric mixture in this case complicated the assignment.

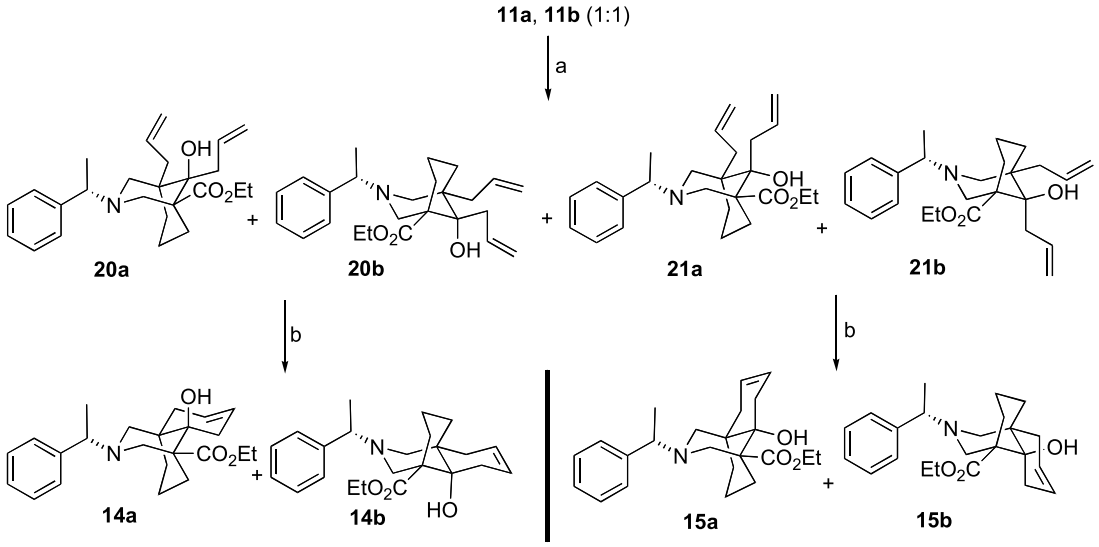
Given that the two diastereomers of the double Mannich adduct **11a**, **11b** were also not separable by flash chromatography, it was decided to pursue the synthesis of the oxygen containing tricyclic analogues of methyllycaconitine **12a/12b** and **13a/13b** (Scheme 5) and the all carbon tricyclic analogues of methyllycaconitine **14a/14b**, **15a/15b** (Scheme 6) with the hope that separation of the individual diastereoisomers would be possible at a later stage in the synthesis.

The next, step in the synthesis of the ABE tricyclic analogues **12a/12b** and **13a/13b** involved reduction of the allyl substituted bicyclic ketones **11a**, **11b** using sodium borohydride in aqueous THF. After careful purification by flash chromatography the major alcohols **16a**, **16b**, were afforded in 39% yield as an inseparable 1:1 mixture of the two diastereomers together with a 1:1 mixture of the minor alcohols **17a**, **17b** isolated in 32% yield.

The ^{1}H NMR spectra of the major **16a**, **16b** and minor alcohols **17a**, **17b** displayed a broad singlet at δ_H 3.61



Scheme 5. Reagents, conditions and yields: (a) $NaBH_4$, 1:1 THF–H_2O, 2 h, **16a**:**16b** (1:1), 39%; **17a**:**17b** (1:1), 32%; (b) NaH, 0 °C to room temperature, THF, 30 min, allyl bromide, THF, 48 h, **18a**:**8b** (1:1), 68%; **19a**:**19b** (1:1), 67%; (c) $Cl_2(PCy_3)_3Ru$=CHPh (5 mol %), CH_2Cl_2, 48 h, **12a**:**12b** (1:1), 95%; **13a**:**13b** (1:1), 95%.



Scheme 6. Reagents, conditions and yields: (a) allyl magnesium bromide, 0 °C to room temperature, 30 min, THF, **20a**:**20b**: **21a**:**21b** (1:1:1:1), 74%; (b) $Cl_2(PCy_3)_3Ru{=}CHPh$ (10 mol %), CH_2Cl_2, 48 h, **14a**:**14b** (1:1), 41%; **15a**:**15b** (1:1), 36%.

(major) and δ_H 2.72 (minor), assigned to the hydroxyl protons. Doublets at δ_H 3.10 (major) and δ_H 3.69 (minor) were assigned to the methine C*H*OH proton. The ^{13}C NMR data was used to assign the stereochemistry of the 9-OH group. The γ-gauche effect establishes that the alcohols with a *syn* hydroxyl group experiences an upfield shift of the neighbouring bicyclic ring carbons in the ^{13}C NMR spectrum.[16] Using this analysis the stereochemistry of alcohols **16a**, **16b** was established to be (1*R**, 5*R**, 9*R**) and hence the stereochemistry of alcohols **17a**, **17b** was established to be (1*R**, 5*R**, 9*S**).

The next, step in the synthesis of tricyclic methyllycaconitine analogues **12a**, **12b** required the allylation of alcohols **16a**, **16b** by treatment with sodium hydride and allyl bromide to afford the allyl ethers **18a**, **18b** in 67% yield as a 1:1 mixture of diastereomers. Allylation of the 1:1 mixture of the minor alcohols **17a**, **17b** in a similar fashion afforded the desired allyl ethers **19a**, **19b**, in 68% yield.

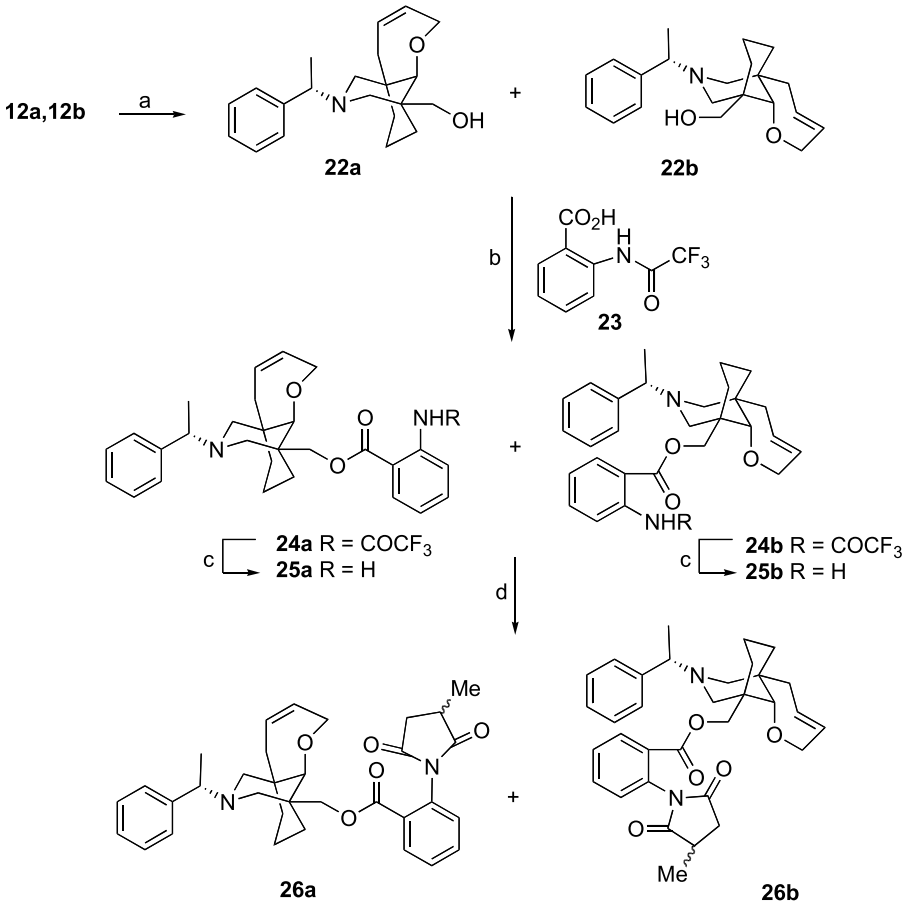
With the necessary diene functionality installed in the AE bicyclic dienes **18a**, **18b** and **19a**, **19b**, subsequent ring closing metathesis using Grubbs' first, generation catalyst was undertaken. Dienes **18a**, **18b** (1:1 mixture) were treated with 5 mol % Grubbs' catalyst in dichloromethane at room temperature for 22 h. Work-up and chromatography afforded the tricyclic ethers **12a**, **12b** in 95% yield as a 1:1 mixture of diastereomers. Subsequent treatment of dienes **19a**, **19b** with 5 mol % Grubbs' catalyst afforded tricyclic ethers **13a**, **13b** in 95% yield also as a 1:1 mixture of diastereomers.

It was hoped that the diastereomeric adducts of the azabicyclic ring system could be separated during one of the steps in the conversion of the allyl keto esters **11a**, **11b** to the tricyclic compounds **12a**, **12b** and **13a**, **13b**. Disappointingly, no separation of the individual isomers by flash chromatography was possible in any of the synthetic steps undertaken. Attempts to separate the diastereomeric mixture of tricyclic ethers **12a**, **12b** by HPLC were also unsuccessful. At this stage it was therefore, decided to investigate the synthesis of the six-membered all carbon tricyclic analogues of methyllycaconitine **14a**, **14b** and **15a**, **15b** as outlined in Scheme 6.

The first, step involved treatment of bicyclic ketones **11a**, **11b** with allyl magnesium bromide in THF to afford an inseparable 1:1:1:1 mixture of the four possible isomeric alcohols **20a**, **20b** and **21a**, **21b** in 74% yield. Ring closing metathesis of the 1:1:1:1 mixture of isomeric dienes **20a/20b**, **21a/21b** was next, carried out by treatment with 10 mol % Grubbs' catalyst under reflux in dichloromethane for 24 h to afford the ABE tricyclic carbon analogues of methyllycaconitine **14a**, **14b** and **15a**, **15b**. After work-up of the reaction mixture careful separation by flash chromatography afforded the tricyclic ABE analogues **14a**, **14b** and **15a**, **15b** in 41% and 36% yield respectively, both as a 1:1 mixture of diastereomers.

It was next, decided to continue with the attachment of the methylsuccinimido anthranilate ester pharmacophore to the ether containing ABE analogues **12a**, **12b** with the hope that later separation of the individual diastereomers would be possible when further, functionality had been added to the molecule (Scheme 7).

Reduction of the ethyl esters **12a**, **12b** was performed by treatment with lithium aluminium hydride in THF affording alcohols **22a**, **22b** in 85% yield. The next, step involved the attachment of the pharmacophore, using *N*-(trifluoroacetyl)-anthranilic acid **23** following a well established protocol.[3] Alcohols **22a**, **22b** were treated with *N*-(trifluoroacetyl)-anthranilic acid **23**, DMAP and DCC in acetonitrile to afford trifluoroacetyl anthranilate esters **24a**, **24b** that were subsequently treated with sodium borohydride to afford anthranilates **25a**, **25b**. Finally fusion with methylsuccinimide afforded the substituted methyllycaconitine analogues **26a**, **26b**. Disappointingly the individual diastereomers were not able to be separated during any of the steps in the further, conversion of esters **12a**, **12b** to methylsuccinimido anthranilate esters **26a**, **26b**.



Scheme 7. Reagents, conditions and yields: (a) $LiAlH_4$, THF, 24 h, **22a**:**22b** (1:1), 86%; (b) **23**, DCC, DMAP, CH_3CN, **24a**:**24b** (1:1), 53%; (c) $NaBH_4$, EtOH, **25a**: **25b** (1:1), 82%; (d) methylsuccinic anhydride, 125 °C, **26a**:**26b** (1:1), 55%.

In summary, the synthesis of four analogues of the alkaloid methyllycaconitine albeit as a 1:1 mixture of diastereomers was successfully completed. Tricyclic ABE analogues **12a**, **12b** and **13a**, **13b** contained a seven membered ether B ring whereas tricyclic analogues **14a**, **14b** and **15a**, **15b** contained a six membered all carbon B ring. The AE azabicyclo[3.3.1]nonane ring system was constructed using a key double Mannich reaction starting from a chiral bis(aminol)ether. The attempted asymmetric variant of the double Mannich reaction was the first, example of the use of a chiral bis(aminol)ether as an electrophile in a reaction with a cyclic β-keto ester, however, disappointingly no diastereomeric excess was observed.

3. Experimental

3.1. General details

All reactions were conducted in flame-dried or oven-dried glassware under a dry nitrogen atmosphere unless otherwise noted. Tetrahydrofuran was dried over sodium/benzophenone and distilled prior to use. Flash chromatography was performed using Merck Kieselgel 60 (230–400 mesh) with the indicated solvents. Thin layer chromatography (TLC) was carried out on precoated silica plates (Merck Kieselgel $60F_{254}$) and compounds were visualized by UV fluorescence or by staining with vanillin in methanolic sulfuric acid and heating. Infrared spectra were recorded with a Perkin–Elmer 1600 series Fourier-transform infrared spectrometer as thin films between sodium chloride plates. Absorption maxima are expressed in wavenumbers (cm^{-1}) with the following abbreviations: s=strong, m=medium, w=weak and br=broad. ^1H and ^{13}C NMR spectra were obtained using Bruker AC 200B, AM 400, and DPX400 spectrometers and a JEOL EX400 spectrometer. All chemical shifts are given in parts per million (ppm) downfield from tetramethylsilane as internal standard (^1H) or relative to $CDCl_3$ (^{13}C) and *J* values are given in Hz. ^1H NMR data are tabulated as s, singlet; d, doublet; t, triplet; q, quartet: m, multiplet, br, broad. High resolution mass spectra were recorded using a VG70-SE spectrometer operating at nominal accelerating voltage of 70 eV. Chemical ionisation (CI) mass spectra were obtained with ammonia as the reagent gas.

3.2. Standard procedure for the formation of *N*,*N*-bis(alkoxymethyl)amines

Dry potassium carbonate (1 mol equiv) was added to a mixture of dry amine (1 mol equiv) and anhydrous ethanol or methanol (4 mol equiv). Dry paraformaldehyde (2 mol equiv) was added and the resulting mixture stirred for 48 h. The suspension was filtered to remove all solids. Excess ethanol or methanol was removed by distillation at ambient pressure. The crude product was purified by vacuum

distillation to afford the *N*,*N*-bis(alkoxymethyl)amine as a colourless oil.

3.2.1. *N*,*N*-Bis(methoxymethyl)-*N*-(*R*)-α-methylbenzylamine 2b. The reaction was carried out according to the standard procedure using dry (*R*)-α-methylbenzylamine (5.32 mL, 41.3 mmol), anhydrous methanol (6.7 mL, 165 mmol), potassium carbonate (5.70 g, 41.26 mmol) and paraformaldehyde (2.47 g, 82.5 mmol). The crude product was purified by Kugelrohr distillation to afford the title compound **2b** (5.69 g, 66%) as a colourless oil; $[\alpha]_D+4.5$ (*c* 1.32, $CHCl_3$); (Found: M^+, 209.1412, $C_{12}H_{19}NO_2$ requires 209.1416); ν_{max} (neat)/cm^{-1} 3509 (C=H), 2924, 1492 (C=C, Ar), 1382 (C=H), 1066 (C=O, ether); δ_H (400 MHz, $CDCl_3$), 1.54 (3H, d, $J=6.7$ Hz, CH_3), 3.08 (6H, s, OCH_3) 4.20 (2H, d, $J=9.8$ Hz, NCH_2O), 4.28 (2H, d, $J=9.8$ Hz, NCH_2O), 4.29 (1H, q, $J=6.7$ Hz, CHN), 7.24–7.28 (5H, m, PhH); δ_C (100 MHz, $CDCl_3$), 20.3 (CH_3, CH*C*H$_3$), 54.7 (OCH_3), 57.7 (CH, Ph*C*H), 84.6 (NCH_2O), 126.6 (CH, C-4), 127.5 (CH, C-3, C-5), 128.3 (CH, C-2, C-6), 144.2 (quat., C-1); *m*/*z* (EI, %) 209 (M^+, 1).

3.2.2. *N*,*N*-Bis(ethoxymethyl)-*N*-(*S*)-α-methylbenzylamine 5a. The reaction was carried out according to the standard procedure using dry (*S*)-α-methylbenzylamine (15.0 g, 123.8 mmol), anhydrous ethanol (27.9 mL, 22.8 g, 495.1 mmol), potassium carbonate (17.1 g, 123.8 mmol) and paraformaldehyde (7.4 g, 247.6 mmol). The crude product was purified by vacuum distillation to afford the title compound **5a** (11.7 g, 40%) as a colourless oil (bp 95–105 °C at 0.75 mmHg); $[\alpha]_D^{22}-15.8$ (*c* 2.08, $CHCl_3$); (Found: M^+, 237.1727, $C_{14}H_{23}NO_2$ requires 237.1729); ν_{max} (NaCl)/cm^{-1} 2973 (C=H), 1453 (C=C, Ar), 1376 (C=H), 1072 (C–O, ether); δ_H (400 MHz, $CDCl_3$) 1.15 (6H, t, $J=7.0$ Hz, 2×CH_2CH_3), 1.48 (3H, q, 6.9 Hz, CHCH_3), 3.34–3.40 (4H, m, 2×OCH_2CH$_3$), 4.25 (1H, q, $J=7.0$ Hz, CH*N*), 4.29 (4H, s, 2×NCH_2O), 7.24–7.38 (5H, m, PhH); δ_C (100 MHz, $CDCl_3$) 15.2 (2×CH_3, CH_2CH_3), 20.2 (CH_3, CH*C*H$_3$), 57.0 (CH, Ph*C*H), 62.3 (2×CH_2, O*C*H$_2$CH$_3$), 82.3 (NCH_2O), 126.8 (CH, C-4), 127.5 (CH, C-3, C-5), 128.1 (CH, C-2, C-6), 144.5 (quat., C-1); *m*/*z* (EI, %) 237 (M^+, 1), 192 (10), 118 (11), 105 (100), 91 (11), 79 (12), 77 (12).

3.2.3. Synthesis of tetrakis-(3,4-dihydro-2*H*-1,3-benzoxazine) 4a. A solution of *C*-ethylcalix[4]resorcinarene **3** (500 mg, 0.83 mmol) and *N*,*N*-bis(methoxymethyl)-*N*-(*S*)-α-methylbenzylamine **2a** (710 mg, 3.4 mmol) in toluene (20 mL) was heated at 85 °C for 24 h. After this time the reaction mixture was allowed to cool to room temperature and the solvent removed under reduced pressure to give a pale brown oil. A sample was submitted for analysis by ^1H NMR spectroscopy and showed the presence of resonances at δ_H 5.16 and 4.96 and at δ_H 5.02 and 4.74 ppm in a 1:1 ratio. Ethanol (20 mL) was added to the mixture which was then heated under reflux for a further, 24 h. After this time the reaction mixture was cooled using an ice-bath and the resulting off-white precipatate was collected by filtration and washed with cold anhydrous ethanol to give the tetrakis(3-[1*S*)-1-phenylethyl]-3,4-dihydro-2H-1,3-benzoxazine) derivative **4a** (720 mg, 77%); $[\alpha]_D^{22}$ −102.2 (*c* 1.19, $CHCl_3$); (Found: C=76.86, H=7.16, N=4.77% $C_{76}H_{84}N_4O_8$ requires C=77.26, H=7.17, N=4.74%); ν_{max} (thinfilm) 3355, 3034, 2962, 2928, 2870, 1601, 1468, 885; δ_H (400 MHz, $CDCl_3$) 0.95 (12H, t, $J=6.8$ Hz, –CH_2CH_3), 1.33 (12H, d, $J=6.4$ Hz, ArCHCH_3), 2.24 (8H, m, CHCH_2CH$_3$), 3.75 (4H, d, $J_{AB}=17.6$ Hz, NCH_A-H$_B$Ar), 3.83 (4H, q, $J=6.0$ Hz, C*H*CH$_3$), 4.01 (4H, d, $J_{AB}=17.6$ Hz, NCH_AH_BAr), 4.14 (4H, t, $J=7.6$ Hz, C*H*CH$_2$), 4.96 (4H, d, $J_{AB}=10.0$ Hz, NCH_AH_BO), 5.16 (4H, d, $J_{AB}=10.0$ Hz, NCH_AH_BO), 6.96–7.21 (24H, m, ArH) and 7.71 (4H, s, ArOH); δ_C (100 MHz, $CDCl_3$) 12.73 (CH_3), 21.47 (CH_3), 26.76 (CH), 34.85 (CH_2), 44.58 (CH), 58.06 (CH_2), 80.93 (CH_2), 108.98 (C), 121.00 (CH), 123.38 (C), 124.14 (C), 127.04 (CH), 127.07 (CH), 128.25 (CH), 144.55 (C), 148.84 (C) 149.70 (C).

3.3. General procedure for the double mannich reaction

To a mixture of β-ketoester (1 mol equiv) and *N*,*N*-bis(ethoxymethyl)amine (2 mol equiv) in acetonitrile (2 mL) was added trichloromethylsilane (2 mol equiv). The mixture was stirred under an atmosphere of nitrogen at room temperature for 20 h. The reaction was quenched by the addition of sat. $NaHCO_3$ (20 mL) and the aqueous layer extracted with ethyl acetate (3×20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography to afford the double Mannich adduct.

3.3.1. Ethyl (1*R,5*R**)-3-((*S*)-1-methylbenzyl)-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate 7a, 7b.** The reaction was carried out according to the standard procedure using ethyl 2-oxo-cyclohexane-1-carboxylate **6** (100 mg, 0.59 mmol), *N*,*N*-bis(ethoxymethyl)-(*S*)-α-methylbenzylamine **5a** (280 mg, 1.17 mmol) and trichloromethylsilane (140 mL, 1.17 mmol). Use of 19:1 hexane–ethyl acetate as eluent for flash chromatography afforded the title compounds **7a**, **7b** (141 mg, 76%) as a colourless oil and as a 1:1 mixture of diastereomers; (Found: M^+, 315.1830, $C_{19}H_{25}NO_3$ requires 315.1834); ν_{max} (NaCl)/cm^{-1} 1732 (C=O, ester), 1716 (C=O, ketone), 1453 (C=C, Ar), 1257 (*tert*-N, amine); δ_H (300 MHz, $CDCl_3$) 1.22–1.33 (3H, m, OCH_2CH_3 and OCH_2CH_3*), 1.39–1.42 (3H, m, CHCH_3Ph and CHCH_3Ph*), 1.51–1.69 (1H, m, 7-H_{eq}, 7-H_{eq}*), 2.01–2.14 (1H, m, 6-H_{ax}, 6-H_{eq}), 2.15–2.26 (1.5H, m, 6-H_{ax}*, 6-H_{eq}*, 8-H_{eq}), 2.27–2.32 (0.5H, m, 8-H_{eq}*), 2.34–2.41 (0.5H, m, 5-H), 2.44–2.60 (2H, m, 8-H_{ax}, 8-H_{ax}*, 5-H*, 4-H_{ax}), 2.64 (0.5H, dd, $J=2.3$, 11.0 Hz, 4-H_{ax}*), 2.83–3.00 (1H, m, 7-H_{ax},7-H_{ax}*), 2.88 (0.5H, dd, $J=1.6$, 11.7 Hz, 2-H_{ax}), 2.98–3.03 (1H, m, 4-H_{eq}, 2-H_{ax}*), 3.10 (0.5H, dd, $J=2.3$, 11.7 Hz, 2-H_{eq}), 3.30 (0.5H, ddd, $J=2.3$, 2.3, 11.0 Hz, 4-H_{eq}*), 3.36 (0.5H, dd, $J=2.7$, 11.3 Hz, 2-H_{eq}*), 3.42 (1H, q, $J=6.7$ Hz, C*H*CH$_3$Ph), 4.10–4.20 (1H, m, OCH_2CH$_3$), 4.18–4.25 (1H, m, OCH_2CH$_3$*), 7.23–7.34 (5H, m, Ar-H, Ar-H*); δ_C (75 MHz, $CDCl_3$), 14.0 (CH_3, OCH_2CH_3), 14.1 (CH_3, OCH_2CH_3*), 19.7 (CH_3, CH*C*H$_3$-Ph), 19.9 (CH_3, CH*C*H$_3$Ph*), 20.6 (CH_2, C-7), 20.7 (CH_2, C-7*), 33.7 (CH_2, C-6), 34.1 (CH_2, C-6*), 36.3 (CH_2, C-8), 36.7 (CH_2, C-8*), 47.1 (2×CH, C-5, C-5*), 56.9 (CH_2, C-4), 58.3 (CH_2, C-4*), 58.8 (CH_2, C-2), 60.0 (CH_2, C-2*), 61.0 (CH_2, O*C*H$_2$CH$_3$), 61.1 (CH_2, O*C*H$_2$CH$_3$*), 64.2 (2×CH, *C*HCH$_3$Ph, *C*HCH$_3$Ph*), 127.1, 127.2, 127.3, 128.4, 128.5 (10×CH, Ar, Ar*), 143.8 (quat., Ar), 143.9 (quat., Ar*), 171.1 (quat., OC=O), 171.2 (quat., OC=O*), 212.7

(quat., C-9), 212.8 (quat., C-9*); *m/z* (EI, %) 315 (M^+,10), 300 (22), 298 (27), 272 (21), 105 (100), 79 (13), 44 (22).

3.3.2. Ethyl (1*R,5*R**)-3-((*S*)-1-methylbenzyl)-9-oxo-3-azabicyclo[3.2.1]octane-1-carboxylate 9a, 9b.** The reaction was carried out according to the standard procedure using ethyl 2-oxo-cyclopentane-1-carboxylate **8** (100 mg, 0.64 mmol), *N*,*N*-bis(ethoxymethyl)-(*S*)-α-methylbenzylamine **5a** (300 mg, 1.28 mmol) and trichloromethylsilane (150 μL, 1.28 mmol). Use of 19:1 hexane–ethyl acetate as eluent for flash chromatography afforded the title compounds **9a**, **9b** (131 mg, 74%) as a colourless oil and as a 1:1 mixture of diastereomers; (Found: M^+, 301.1679, $C_{18}H_{23}NO_3$ requires 301.1678); ν_{max} (NaCl)/cm^{-1} 1759 (C=O, ester), 1726 (C=O, ketone), 1453 (C=C, Ar), 1262 (*tert*-N, amine); δ_H (400 MHz, $CDCl_3$) 1.22–1.28 (3H, m, OCH_2CH_3 and OCH_2CH_3*), 1.37–1.41 (3H, m, $CHCH_3Ph$ and $CHCH_3Ph$*), 1.88–2.01 (2H, m, 7-H_A, 7-H_A*, 7-H_B, 7-H_B*), 2.23–2.31 (1.5H, m, 5-H, 6-H_B, 6-H_B*), 2.33–2.42 (1.5H, m, 5-H*, 6-H_A, 6-H_A*), 2.51 (0.5H, d, J=11.0 Hz, 4-H_{ax}), 2.58 (0.5H, d, J=11.0 Hz, 4-H_{ax}*), 2.74–2.79 (1H, m, 2-H_A, 2-H_{ax}*), 2.99 (0.5H, ddd, J=3.5, 3.5, 11.0 Hz, 4-H_{eq}), 3.01 (0.5H, ddd, J=2.8, 2.8, 11.0 Hz, 4-H_{eq}*), 3.08 (0.5H, dd, J=2.8, 11.0 Hz, 2-H_{eq}), 3.21 (0.5H, dd, J=2.8, 11.0 Hz, 2-H_{eq}*), 3.68 (1H, dq, J=2.7, 11.0 Hz, C*H*CH_3-Ph), 4.15–4.22 (2H, m, OCH_2CH_3, OCH_2CH_3*), 7.23–7.36 (5H, m, Ar-H, Ar-H*); δ_C (100 MHz, $CDCl_3$), 14.2 (2×CH_3, OCH_2CH_3*), 18.7 (CH_3, $CHCH_3Ph$), 19.1 (CH_3, $CHCH_3Ph$*), 21.7 (2×CH_2, C-7, C-7*), 27.4 (CH_2, C-6), 27.5 (CH_2, C-6*), 46.6 (2×CH, C-5, C-5*), 57.3 (CH_2, C-4), 58.8 (CH_2, C-2), 59.6 (CH_2, C-4*), 60.6 (CH_2, C-2*), 60.9 (CH_2, OCH_2CH_3), 61.9 (CH, $CHCH_3Ph$), 62.2 (CH, $CHCH_3Ph$*), 127.1, 127.2, 127.3, 128.3, 128.4 (10×CH, Ar, Ar*), 143.5 (quat., Ar), 143.6 (quat., Ar*), 170.2 (quat., OC=O), 170.4 (quat., OC=O*), 213.5 (quat., C-8, C-8*); *m/z* (EI, %) 301 (M^+, 12), 286 (17), 105 (100), 79 (13), 77 (12), 57 (15), 44 (30).

3.3.3. Ethyl (1*R,5*R**)-3-((*S*)-1-methylbenzyl)-9-oxo-5-(2′-propenyl)-3-azabicyclo[3.3.1]nonane-1-carboxylate 11a, 11b.** The reaction was carried out according to the standard procedure using ethyl 2-oxo-3-(2′-propenyl)cyclohexane-1-carboxylate **10**[17] (100 mg, 0.51 mmol), *N*,*N*-bis(ethoxymethyl)-(*S*)-α-methylbenzylamine **5a** (240 mg, 1.02 mmol), and trichloromethylsilane (110 μL, 1.02 mmol). Use of 19:1 hexane–ethyl acetate as eluent for flash chromatography afforded the title compounds **11a**, **11b** (0.14 g, 77%) as a colourless oil and as a 1:1 mixture of diastereomers; (Found: M^+, 355.2148, $C_{22}H_{29}NO_3$ requires 355.2147); ν_{max} (NaCl)/cm^{-1} 1732 (C=O, ester), 1714 (C=O, ketone), 1639 (C=C), 1454 (C=C, Ar), 1259 (*tert*-N, amine); δ_H (300 MHz, $CDCl_3$) 1.26 (3H, m, OCH_2CH_3 and OCH_2CH_3*), 1.39 (3H, dq, J=1.9, 6.7 Hz, $CHCH_3Ph$ and $CHCH_3Ph$*), 1.48–1.62 (1H, m, 7-H_{eq}, 7-H_{eq}*), 1.71–1.89 (1H, m, 6-H_{eq}, 6-H_{eq}*), 1.95–2.07 (1H, m, 6-H_{ax}, 6-H_{ax}*), 2.09–2.20 (3H, m, 1′-CH_2, 1′-CH_2*, 8-H_{eq}, 8-H_{eq}*), 2.22–2.30 (0.5H, dd, J=1.6, 11.0 Hz, 4-H_{ax}), 2.35 (0.5H, dd, J=1.4, 11.0 Hz, 4-H_{ax}*), 2.44–2.58 (1H, m, 8-H_{ax}, 8-H_{ax}*), 2.84–2.92 (1H, m, 2-H_{ax}, 4-H_{eq}), 2.92–3.02 (1H, m, 7-H_{ax}, 7-H_{ax}*), 2.99–3.04 (0.5H, m, 2-H_{ax}*), 3.08 (0.5H, dd, J=2.5, 11.0 Hz, 2-H_{eq}), 3.18 (0.5H, dd, J=2.5, 11.0 Hz, 4-H_{eq}*), 3.28 (0.5H, dd, J=2.4, 11.0 Hz, 2-H_{eq}*), 3.38 (0.5H, q, J=6.7 Hz, C*H*CH_3Ph), 3.47 (0.5H, q, J=6.7 Hz, C*H*CH_3Ph*), 4.17 (2H, m, OCH_2CH_3, OCH_2CH_3*), 4.95–4.98 (1H, m, 3′-H_B, 3′-H_B*), 5.03–5.06 (1H, m, 3′-H_A, 3′-H_A*), 5.62–5.86 (1H, m, 2′-H, 2′-H*), 7.23–7.34 (5H, m, Ar-H, Ar-H*); δ_C (75 MHz, $CDCl_3$), 14.0 (CH_3, OCH_2CH_3), 14.1 (CH_3, OCH_2CH_3*), 18.9 (CH_3, $CHCH_3Ph$), 20.1 (CH_3, $CHCH_3Ph$*), 20.5 (2×CH_2, C-7, C-7*), 36.3 (CH_2, C-8), 36.6 (CH_2, C-8*), 38.7 (CH_2, C-6), 39.1 (quat., C-5), 39.3 (CH_2, C-1′), 39.4 (CH_2, C-1′*), 48.8 (quat., C-1), 48.9 (quat., C-1*), 58.6 (CH_2, C-2), 59.0 (CH_2, C-2*), 60.9 (CH_2, OCH_2CH_3), 61.0 (CH_2, OCH_2CH_3*), 61.7 (CH_2, C-4), 62.8 (CH_2, C-4*), 63.9 (CH, $CHCH_3Ph$), 64.3 (CH, $CHCH_3Ph$*), 117.8 (CH_2, C-3′), 118.0 (CH_2, C-3′*), 127.0, 127.2, 127.3, 128.3, 128.4 (10×CH, Ar, Ar*), 133.7 (2×CH, C-2′, C-2′*), 143.4 (quat., Ar), 143.7 (quat., Ar*), 171.1 (quat., OC=O), 171.3 (quat., OC=O*), 212.7 (2×quat., C-9, C-9*); *m/z* (EI, %) 355 (M^+, 6), 340 (33), 312 (14), 209 (12), 105 (100), 79 (14), 42 (16).

3.3.4. Ethyl (1*R,5*R**,9*R**)-9-hydroxy-3-((*S*)-1-methylbenzyl)-5-(2′-propenyl)-3-azabicyclo[3.3.1]nonane-1-carboxylate 16a,16b and ethyl (1*R**, 5*R**, 9*S**)-9-hydroxy-3-((*S*)-1-methylbenzyl)-5-(2′-propenyl)-3-azabicyclo[3.3.1]nonane-1-carboxylate 17a, 17b.** To a solution of sodium borohydride (43 mg, 1.125 mmol) in THF (7 mL) and distilled water (14 mL) at 0 °C was added dropwise a solution of ketones **11a**, **11b** (0.80 g, 2.25 mmol) in THF (7 mL). The reaction mixture was stirred for 2 h then quenched with water (14 mL) and the volatile solvents were removed in vacuo. The residual aqueous layer was then extracted with ethyl acetate (3×25 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography using 32:1 hexane–ethyl acetate as eluent to afford: (i) *alcohols* **16a**, **16b** (0.31 g, 39%) as a colourless oil and as a 1:1 mixture of diastereomers; (Found: M^+, 357.2298, $C_{22}H_{31}NO_3$ requires 357.2304); ν_{max} (NaCl)/cm^{-1} 3535 (O=H), 1710 (C=O, ester), 1638 (C=C), 1452 (C=C, Ar), 1259 (*tert*-N, amine); δ_H (400 MHz, $CDCl_3$) 1.26 (3H, t, J=7.1 Hz, OCH_2CH_3 and OCH_2CH_3*), 1.30–1.33 (3H, m, $CHCH_3Ph$ and $CHCH_3Ph$*), 1.51–1.59 (1H, m, 7-H_{eq}, 7-H_{eq}*), 1.63–1.71 (1H, m, 6-H_{eq}, 6-H_{eq}*), 1.78–1.85 (1H, m, 6-H_{ax}, 6-H_{ax}*), 1.86 (0.5H, dd, J=1.8, 11.4 Hz, 4-H_{ax}), 1.96–2.13 (3.5H, m, 1′-CH_2, 1′-CH_2*, 4-H_{ax}*, 8-H_{eq}, 8-H_{eq}*), 2.20 (0.5H, dd, J=1.8, 11.4 Hz, 2-H_{ax}), 2.58 (0.5H, dd, J=1.8, 11.4 Hz, 4-H_{eq}), 2.78–2.86 (1H, m, 7-H_{ax}, 7-H_{ax}*), 2.89 (0.5H, dd, J=1.8, 11.4 Hz, 2-H_{ax}*), 2.96 (0.5H, dd, J=1.8, 11.4 Hz, 2-H_{eq}), 3.03 (0.5H, d, J=7.3 Hz, 9-H), 3.10 (0.5H, d, J=7.3 Hz, 9-H*), 3.17–3.22 (1.5H, m, C*H*CH_3Ph, C*H*CH_3Ph*, 4-H_{eq}*), 3.29 (0.5H, dd, J=1.8, 11.0 Hz, 2-H_{eq}*), 3.61 (1H, br s, O–H), 4.01–4.19 (2H, m, OCH_2CH_3, OCH_2CH_3*), 4.92–4.96 (1H, m, 3′-H_B, 3′-H_B*), 5.02–5.06 (1H, m, 3′-H_A, 3′-H_A*), 5.68–5.88 (1H, m, 2′-H, 2′-H*), 7.21–7.33 (5H, m, Ar-H, Ar-H*); δ_C (100 MHz, $CDCl_3$), 14.0 (2×CH_3, OCH_2CH_3, OCH_2CH_3*), 20.1 (2×CH_3, $CHCH_3Ph$, $CHCH_3Ph$*), 20.9 (CH_2, C-7), 21.0 (CH_2, C-7*), 26.8 (CH_2, C-8), 27.2 (CH_2, C-8*), 29.5 (CH_2, C-6), 37.5 (quat., C-5), 37.6 (quat., C-5*), 42.5 (CH_2, C-1′), 42.9 (CH_2, C-1′*), 48.0 (quat., C-1), 57.7 (CH_2, C-2), 59.3 (CH_2, C-2*), 60.3 (CH_2, OCH_2CH_3), 60.7 (CH_2, C-4), 60.8 (CH_2, C-4*), 65.1 (CH, $CHCH_3Ph$), 74.0 (CH, C-9), 74.4 (CH, C-9*), 117.3 (CH_2, C-3′), 117.4 (CH_2,

C-3′*), 126.7, 127.3, 128.3 (10×CH, Ar, Ar*), 134.3 (CH, C-2′), 134.4 (CH, C-2′*), 144.2 (quat., Ar), 144.3 (quat., Ar*), 176.7 (quat., OC=O), 176.9 (quat., OC=O*); *m/z* (EI, %) 357 (M^+, 10), 342 (46), 315 (15), 242 (28), 105 (100), 91 (23), 79 (18).

(ii) *Alcohols* **17a**, **17b** (0.25 g, 32%) as a colourless oil and as a 1:1 mixture of diastereomers; (Found: M^+, 357.2298, $C_{22}H_{31}NO_3$ requires 357.2304); ν_{max} (NaCl)/cm^{-1} 3536 (O=H), 1710 (C=O, ester), 1638 (C=C), 1452 (C=C), 1259 (*tert*-N, amine); δ_H (400 MHz, $CDCl_3$) 1.26 (3H, t, J= 7.1 Hz, OCH_2CH_3 and OCH_2CH_3*), 1.30–1.33 (3H, m, $CHCH_3Ph$ and $CHCH_3Ph$*), 1.41–1.61 (2H, m, 6-H_{eq}, 6-H_{eq}*, 7-H_{eq}, 7-H_{eq}*), 1.73–1.91 (1H, m, 6-H_{ax}, 6-H_{ax}*), 1.96–2.07 (3.5H, m, 1′-CH_2, 1′-CH_2*, 4-H_{ax}, 8-H_{eq}, 8-H_{eq}*), 2.11–2.31 (1.5H, m, 4-H_{ax}*, 8-H_{ax}, 8-H_{ax}*), 2.62 (0.5H, dd, J=1.8, 11.0 Hz, 2-H_{ax}), 2.72 (1H, br s, OH), 2.74–2.87 (2H, m, 2-H_{ax}, 4-H_{eq}, 7-H_{ax}, 7-H_{ax}*), 2.89 (0.5H, dd, J=1.8, 11.4 Hz, 2-H_{eq}), 2.96 (0.5H, dd, J=1.8, 11.4 Hz, 4-H_{eq}*), 3.19–3.31 (1.5H, m, $CHCH_3Ph$, $CHCH_3$-Ph*, 2-H_{eq}*), 3.69 (1H, d, J=7.5 Hz, 9-H), 4.01–4.18 (2H, m, OCH_2CH_3, OCH_2CH_3*), 4.96–5.01 (1H, m, 3′-H_B, 3′-H_B*), 5.02–5.07 (1H, m, 3′-H_A, 3′-H_A*), 5.76–5.86 (1H, m, 2′-H, 2′-H*), 7.21–7.33 (5H, m, Ar-H, Ar-H*); δ_C (100 MHz, $CDCl_3$), 14.1 (CH_3, OCH_2CH_3) 14.2 (CH_3, OCH_2CH_3*), 20.1 (CH_3, $CHCH_3Ph$), 20.2 (CH_3, $CHCH_3$-Ph*), 20.8 (CH_2, C-7), 20.9 (CH_2, C-7*), 34.3 (CH_2, C-8), 34.7 (CH_2, C-8*), 34.9 (CH_2, C-6), 35.2 (CH_2, C-6*), 38.1 (quat., C-5), 41.6 (CH_2, C-1′), 42.0 (CH_2, C-1′*), 48.9 (quat., C-1), 51.6 (CH_2, C-2), 54.1 (CH_2, C-2*), 60.6 (CH_2, OCH_2CH_3), 60.7 (CH_2, C-4), 65.1 (CH, $CHCH_3Ph$), 65.2 (CH, $CHCH_3Ph$*), 74.0 (CH, C-9), 74.4 (CH, C-9*), 117.6 (CH_2, C-3′), 117.7 (CH_2, C-3′*), 126.6, 126.8, 127.3, 127.4, 128.3 (10×CH, Ar, Ar*), 134.2 (CH, C-2′), 134.3 (CH, C-2′*), 145.1 (quat., Ar), 176.5 (quat., OC=O); *m/z* (EI, %) 357 (M^+, 11), 342 (100), 252 (33), 242 (27), 105 (90), 91 (16), 79 (14).

3.3.5. Ethyl (1*R,5*R**,9*R**)-3-((*S*)-1-methylbenzyl)-5-(2′-propenyl)-9-(2′-propenyloxy)-3-azabicyclo[3.3.1]-nonane-1-carboxylate 18a, 18b.** To a suspension of sodium hydride (78 mg, 3.25 mmol), in dry THF (15 mL) at 0 °C was added a solution of alcohols **16a**, **16b** (290 mg, 0.81 mmol) in dry THF (1.5 mL) and the mixture was stirred for 30 mins. Allyl bromide (393 mg, 280 mL, 3.25 mmol) was then added and the reaction mixture stirred for 48 h at room temperature. The reaction was quenched by the addition of distilled water (15 mL) and the volatile solvents were removed in vacuo. The residual aqueous layer was then extracted with ethyl acetate (2×20 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography using 19:1 hexane–ethyl acetate as eluent to afford the title compounds **18a**, **18b** (220 mg, 67%) as a colourless oil and as a 1:1 mixture of diastereomers; (Found: M^+, 397.2603, $C_{25}H_{35}NO_3$ requires 397.2617); ν_{max} (NaCl)/cm^{-1} 2924 (C=H), 1731 (C=O, ester), 1638 (C=C), 1452 (C=C, Ar), 1258 (*tert*-N, amine); δ_H (400 MHz, $CDCl_3$) 1.22–1.28 (3H, m, OCH_2CH_3, OCH_2CH_3*), 1.30–1.33 (3H, m, $CHCH_3Ph$ and $CHCH_3Ph$*), 1.51–1.57 (1H, m, 6-H_{eq}, 6-H_{eq}*), 1.61–1.72 (2H, m, 7-H_{eq}, 7-H_{eq}*, 8-H_{eq}, 8-H_{eq}*), 1.79–1.84 (1H, m, 6-H_{ax}, 6-H_{ax}*), 1.90–2.02 (2H, m, 4-H_{ax}, 4-H_{ax}*, 8-H_{ax}, 8-H_{ax}*), 2.09–2.21 (2H, m, 1′-CH_2, 1′-CH_2*), 2.19 (0.5H, dd, J=1.8, 11.0 Hz, 2-H_{ax}), 2.39 (0.5H, dd, J=1.8, 11.0 Hz, 4-H_{eq}), 2.62 (0.5H, dd, J=1.8, 11.0 Hz, 2-H_{ax}*), 2.73 (0.5H, dd, J=1.8, 11.0 Hz, 2-H_{eq}), 2.69–2.83 (1H, m, 7-H_{ax}, 7-H_{ax}*), 2.99 (0.5H, dd, J=1.8, 11.0 Hz, 4-H_{eq}*), 3.04 (0.5H, dd, J=1.8, 11.0 Hz, 2-H_{eq}*), 3.11 (0.5H, q, J=6.7 Hz, $CHCH_3Ph$), 3.21 (0.5H, q, J= 6.7 Hz, $CHCH_3Ph$*), 3.43 (1H, br s, 9-H), 3.94–4.14 (4H, m, OCH_2CH_3, OCH_2CH_3*, 1″-CH_2, 1″-CH_2*), 4.89–4.94 (1H, m, 3′-H_B, 3′-H_B*), 4.98–5.08 (2H, m, 3″-H_B, 3″-H_B*, 3′-H_A, 3′-H_A*), 5.19–5.24 (1H, m, 3″-H_A, 3″-H_A*), 5.62–5.72 (0.5H, m, 2′-H), 5.78–5.87 (1.5H, m, 2′-H*, 2″-H, 2″-H*), 7.21–7.30 (5H, m, Ar-H, Ar-H*); δ_C (100 MHz, $CDCl_3$), 14.1 (CH_3, OCH_2CH_3), 14.2 (CH_3, OCH_2CH_3*), 19.6 (2×CH_3, $CHCH_3Ph$, $CHCH_3Ph$*), 20.7 (CH_2, C-7), 21.0 (CH_2, C-7*), 26.2 (CH_2, C-8), 26.6 (CH_2, C-8*), 30.0 (CH_2, C-6), 30.1 (CH_2, C-6*), 39.0 (quat., C-5), 39.1 (quat., C-5*), 43.0 (CH_2, C-1′), 43.3 (CH_2, C-1′*), 48.0 (quat., C-1), 58.5 (2×CH_2, C-2, C-2*), 59.8 (CH_2 C-4), 59.9 (CH_2, C-4*), 60.5 (CH_2, OCH_2CH_3), 60.6 (CH_2, OCH_2CH_3*), 64.9 (CH, $CHCH_3Ph$), 65.5 (CH, $CHCH_3Ph$*), 73.7 (CH_2, C-1″), 84.3 (CH, C-9), 84.7 (CH, C-9*), 115.2 (CH_2, C-3″), 117.2 (CH_2, C-3′), 117.4 (CH_2, C-3′*), 126.7, 127.2, 127.3, 128.2, 128.3 (10×CH, Ar, Ar*), 134.1 (CH, C-2′), 134.2 (CH, C-2′*), 135.4 (CH, C-2″), 135.5 (CH, C-2″*), 144.3 (quat., Ar), 144.7 (quat., Ar*), 175.6 (quat., OC=O), 175.8 (quat., OC=O*); *m/z* (EI, %) 397 (M^+, 7) 382 (50), 356 (18), 206 (16), 105 (100), 91 (15), 41 (15).

3.3.6. Ethyl (1*R,5*R**,9*S**)-3-((*S*)-1-methylbenzyl)-5-(2′-propenyl)-9-(2′-propenyloxy)-3-azabicyclo[3.3.1]-nonane-1-carboxylate 19a, 19b.** To a suspension of sodium hydride (33 mg, 1.38 mmol) in dry THF (9 mL) at 0 °C was added a solution of alco hols **17a**, **17b** (123 mg, 0.34 mmol) in dry THF (1.0 mL) and the mixture was stirred for 30 mins. Allyl bromide (167 mg, 120 mL, 1.38 mmol) was then added and the reaction mixture stirred for 48 h at room temperature. The reaction was quenched by the addition of distilled water (10 mL) and the volatile solvents were removed in vacuo. The residual aqueous layer was extracted with ethyl acetate (2×15 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography (19:1 hexane–ethyl acetate) to afford the title compounds **19a**, **19b** (90 mg, 68%) as a colourless oil and as a 1:1 mixture of diastereomers; (Found: M^+, 397.2606, $C_{25}H_{35}NO_3$ requires 397.2617); ν_{max} (NaCl)/cm^{-1} 2924 (C=H), 1731 (C=O, ester), 1639 (C=C), 1452 (C=C, Ar), 1258 (*tert*-N, amine);*)*; δ_H (400 MHz, $CDCl_3$) 1.22–1.28 (3H, m, OCH_2CH_3, OCH_2CH_3*), 1.30–1.33 (3H, m, $CHCH_3Ph$ and $CHCH_3Ph$*), 1.46–1.63 (2H, m, 6-H_{eq}, 6-H_{eq}*, 7-H_{eq}, 7-H_{eq}*), 1.62–1.83 (2H, m, 8-H_{eq}, 8-H_{eq}*, 6-H_{ax}, 6-H_{ax}*), 1.81–2.23 (3H, m, 1′-CH_2, 1-CH_2*, 8-H_{ax}, 8-H_{ax}*), 2.69–2.91 (1H, m, 7-H_{ax}, 7-H_{ax}*), 2.58–2.82 (2H, m, 2-H_{ax}, 2-H_{eq}, 2-H_{ax}*, 4-H_{eq}), 3.01 (0.5H, dd, J=1.8, 11.0 Hz, 4-H_{eq}*), 3.08–3.31 (1.5H, m, $CHCH_3Ph$, $CHCH_3$-Ph*, 2-H_{eq}*), 3.42–3.44 (1H, m, 9-H, 9-H*), 3.97–4.13 (4H, m, OCH_2CH_3, OCH_2CH_3*, 1″-CH_2, 1″-CH_2*), 4.85–4.97 (1H, m, 3′-H_B, 3′-H_B*), 4.98–5.08 (2H, m, 3″-H_B, 3″-H_B*, 3′-H_A, 3′-H_A*), 5.16–5.26 (1H, m, 3″-H_A, 3″-H_A*), 5.62–5.75 (0.5H, m, 2′-H), 5.77–5.91 (1.5H, m, 2″-H, 2″-H*, 2′-H*), 7.21–7.30 (5H, m, Ar-H, Ar-H*); δ_C (100 MHz,

$CDCl_3$), 14.1 (2×CH_3, OCH_2CH_3, OCH_2CH_3*), 20.3 (CH_3, $CHCH_3Ph$), 20.5 (CH_3, $CHCH_3Ph$*), 20.9 (CH_2, C-7), 26.4 (CH_2, C-8), 30.0 (CH_2, C-6), 39.4 (quat., C-5), 41.7 (CH_2, C-1′), 42.2 (CH_2, C-1′*), 48.9 (quat., C-1), 50.6 (CH_2, C-2) 52.4 (CH_2, C-2*), 59.8 (CH_2, C-4), 59.9 (CH_2, C-4*), 60.2 (CH_2, OCH_2CH_3), 65.6 (CH, $CHCH_3Ph$), 65.7 (CH, $CHCH_3Ph$*), 73.7 (CH_2, C-1″), 73.8 (CH_2, C-1″*), 83.2 (CH, C-9), 83.5 (CH, C-9*), 114.8 (CH_2, C-3″), 114.9 (CH_2, C-3″*), 117.4 (CH_2, C-3′), 117.6 (CH_2, C-3′*), 126.4, 126.5, 127.2, 127.3, 128.2, 128.3 (10×CH, Ar, Ar*), 134.2 (CH, C-2′), 135.4 (2×CH, C-2″, C-2″*), 145.9 (2×quat., Ar, Ar*), 175.7 (quat., OC=O), 175.9 (quat., OC=O*); *m/z* (EI, %) 397 (M^+, 3) 382 (33), 156 (35), 141 (51), 105 (84), 71 (61), 57 (100).

3.3.7. Ethyl (1*R,7*R**,8*R**)-10-((*S*)-1-methylbenzyl)-6-oxa-10-azatricyclo[6.3.3.0]tetradec-3-ene-8-carboxylate 12a, 12b.** To a solution of bis(tricyclohexylphosphine)-benzylidene ruthenium(IV) dichloride (7 mg, 0.009 mmol) in dry dichloromethane (2.5 mL) was added dropwise a solution of dienes **18a**, **18b** (70 mg, 0.176 mmol) in dry dichloromethane (1 mL). The mixture was stirred for 22 h, concentrated in vacuo and the crude product purified by flash chromatography using 19:1 hexane–ethyl acetate as eluent to afford the title compounds **12a**, **12b** (62 mg, 95%) as a colourless oil and as a 1:1 mixture of diastereomers; (Found: M^+, 369.2301, $C_{23}H_{31}NO_3$ requires 369.2304); ν_{max} (NaCl)/cm^{-1} 2974 (C=H), 1734 (C=O, ester), 1654 (C=C), 1451 (C=C, Ar), 1255 (*tert*-N, amine); δ_H (400 MHz, $CDCl_3$) 1.17–1.20 (3H, m, OCH_2CH_3, OCH_2CH_3*), 1.23–1.32 (5H, m, 12-H_{eq}, 12-H_{eq}*, 14-H_{eq}, 14-H_{eq}*, $CHCH_3Ph$, $CHCH_3Ph$*), 1.53–1.60 (1H, m, 13-H_{eq}, 13-H_{eq}*), 1.68–1.84 (1.5H, m, 2-H_B, 11-H_{ax}, 11-H_{ax}*), 1.87–2.16 (4H, m, 2-H_A, 2-H_A*, 2-H_B*, 9-H_{ax}, 12-H_{ax}, 12-H_{ax}*, 14-H_{ax}, 14-H_{ax}*), 2.25 (0.5H, dd, J=1.8, 11.0 Hz, 11-H_{ax}), 2.42 (0.5H, dd, J=1.8, 11.0 Hz, 9-H_{ax}), 2.53 (0.5H, dd, J=1.8, 11.0 Hz, 9-H_{eq}), 2.75 (0.5H, dd, J=1.8, 11.0 Hz, 11-H_{eq}), 2.77–2.91 (1H, m, 13-H_{ax}, 13-H_{ax}*), 2.89 (0.5H, dd, J=1.8, 11.0 Hz, 9-H_{eq}), 3.09–3.17 (1H, m, $CHCH_3Ph$, $CHCH_3Ph$*), 3.61 (1H, br s, 7-H, 7-H*), 3.96–4.23 (4H, m, 5-CH_2, 5-CH_2*, OCH_2CH_3, OCH_2CH_3*), 5.61–5.89 (2H, m, 3-H, 3-H*, 4-H, 4-H*), 7.21–7.32 (5H, m, Ar-H, Ar-H*); δ_C (100 MHz, $CDCl_3$), 14.2 (2×CH_3, OCH_2CH_3, OCH_2CH_3*), 20.5 (CH_3, $CHCH_3Ph$), 20.6 (CH_2, C-13), 20.7 (CH_2, C-13*), 26.0 (CH_2, C-14), 26.4 (CH_2, C-14*), 28.8 (CH_2, C-12), 29.2 (CH_2, C-12*), 37.0 (quat., C-1), 37.1 (quat., C-1*), 40.0 (CH_2, C-2), 40.3 (CH_2, C-2*), 49.0 (quat., C-8), 49.1 (quat., C-8*), 58.8 (CH_2, C-9), 59.8 (CH_2, C-9*), 60.2 (CH_2, C-11), 60.3 (CH_2, C-11*), 62.2 (CH_2, OCH_2CH_3), 65.1 (CH, $CHCH_3Ph$), 65.3 (CH, $CHCH_3Ph$*), 68.4 (CH_2, C-5), 88.5 (CH, C-7), 88.6 (CH, C-7*), 126.8, 127.2, 128.3 (10×CH, Ar, Ar*), 130.2 (CH, C-3), 130.3 (CH, C-3*), 130.7 (CH, C-4), 130.8 (CH, C-4*), 144.4 (quat., Ar), 144.7 (quat., Ar*), 175.1 (quat., OC=O), 175.3 (quat., OC=O*); *m/z* (EI, %) 369 (M^+, 20), 354 (59), 264 (25), 134 (28), 105 (100), 91 (26), 44 (28).

3.3.8. Ethyl (1*R,7*S**,8*R**)-10-((*S*)-1-methylbenzyl)-6-oxa-10-azatricyclo[6.3.3.0]tetradec-3-ene-8-carboxylate 13a, 13b.** To a solution of bis(tricyclohexylphosphine)-benzylidene ruthenium(IV) dichloride (6 mg, 0.007 mmol) in dry dichloromethane (2.5 mL) was added dropwise a solution of dienes **19a**, **19b** (60 mg, 0.151 mmol) in dry dichloromethane (1 mL). The mixture was stirred for 22 h, concentrated in vacuo and the crude product purified by flash chromatography using 19:1 hexane–ethyl acetate as eluent to afford the title compounds **13a**, **13b** (53 mg, 95%) as a colourless oil and as a 1:1 mixture of diastereomers; (Found: M^+, 369.2297, $C_{23}H_{31}NO_3$ requires 369.2304); ν_{max} (NaCl)/cm^{-1} 2975 (C=H), 1731 (C=O, ester), 1652 (C=C), 1452 (C=C, Ar), 1257 (*tert*-N, amine); δ_H (400 MHz, $CDCl_3$) 1.17–1.21 (3H, m, OCH_2CH_3, OCH_2CH_3*), 1.17–1.34 (5H, m, 12-H_{eq}, 12-H_{eq}*, 14-H_{eq}, 14-H_{eq}*, $CHCH_3Ph$, $CHCH_3Ph$*), 1.41–1.57 (1H, m, 13-H_{eq}, 13-H_{eq}*), 1.81–2.16 (4H, m, 2-H_A, 2-H_B, 9-H_{ax}, 11-H_{ax}, 12-H_{ax}, 12-H_{ax}*,14-H_{ax}, 14-H_{ax}*), 1.61–1.77 (1.5H, m, 2-H_B*, 9-H_{ax}*, 11-H_{ax}*), 2.24–2.33 (0.5H, m, 2-H_A*), 2.50–2.53 (0.5H, m, 9-H_{eq}), 2.54–2.56 (0.5H, m, 11-H_{eq}), 2.72–2.74 (0.5H, m, 9-H_{eq}*), 2.75–2.77 (0.5H, m, 11_{eq}*), 2.83–3.01 (1H, m, 13-H_{ax}, 13-H_{ax}*), 3.13–3.18 (1H, m, $CHCH_3Ph$, $CHCH_3Ph$*), 3.69 (1H, s, 7-H, 7-H*), 3.96–4.26 (4H, m, 5-CH_2, 5-CH_2*, OCH_2CH_3, OCH_2CH_3*), 5.69–5.75 (2H, m, 3-H, 3-H*, 4-H, 4-H*), 7.19–7.32 (5H, m, Ar-H, Ar-H*); δ_C (100 MHz, $CDCl_3$), 14.2 (CH_3, OCH_2CH_3) 14.3 (CH_3, OCH_2CH_3*), 20.6 (CH_3, $CHCH_3Ph$), 20.7 (CH_3, $CHCH_3Ph$*), 21.2 (CH_2, C-13), 21.3 (CH_2, C-13*), 26.0 (CH_2, C-14), 29.2 (CH_2, C-12), 38.2 (quat., C-1), 39.2 (CH_2, C-2), 39.5 (CH_2, C-2*), 48.8 (quat., C-8), 49.1 (quat., C-8*), 59.8 (CH_2, C-9), 60.0 (CH_2, C-9*), 60.2 (CH_2, C-11), 60.4 (CH_2, C-11*), 62.2 (CH_2, OCH_2CH_3), 65.1 (CH, $CHCH_3$-Ph), 65.3 (CH, $CHCH_3Ph$*), 68.3 (CH_2, C-5), 68.8 (CH_2, C-5*), 85.5 (CH, C-7), 85.6 (CH, C-7*), 126.4, 126.8, 127.3, 127.4, 128.2, 128.3 (10×CH, Ar, Ar*), 129.1 (CH, C-3), 130.3 (CH, C-4), 130.5 (CH, C-4*), 145.6 (quat., Ar), 146.2 (quat., Ar*), 175.1 (quat., OC=O), 175.4 (quat., OC=O*); *m/z* (EI, %) 369 (M^+, 19), 354 (76), 264 (32), 105 (100), 91 (35), 79 (25), 41 (29).

3.3.9. Ethyl (1*R,5*R**,9*R**)-9-hydroxy-3-((*S*)-1-methylbenzyl)-5-(2′-propenyl)-9-(2′-propenyl)-3-azabicyclo-[3.3.1]nonane-1-carboxylate 20a, 20b and ethyl (1*R**, 5*R**, 9*S**)-9-hydroxy-3-((*S*)-1-methylbenzyl)-5-(2′-propenyl)-9-(2′-propenyl)-3-azabicyclo[3.3.1]nonane-1-carboxylate 21a, 21b.** To a solution of ketones **11a**, **11b** (330 mg, 0.928 mmol) in THF (10 mL) at 0 °C was added dropwise allyl magnesium bromide (1.4 mL, 1 M in diethyl ether, 1.4 mmol) under an atmosphere of nitrogen. The reaction was stirred for 1 h then warmed to room temperature and stirred for a further, 48 h. The reaction was quenched by the addition of sat. NH_4Cl (10 mL) and the residual aqueous layer was extracted with diethyl ether (1× 20 mL, 2×10 mL). The aqueous mixture was further, extracted with diethyl ether (2×10 mL) and the combined organic extracts washed with brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography using 19:1 hexane–ethyl acetate as eluent to afford the title compounds **20a/20b**, **21a/21b** (265 mg, 74%) as a colourless oil and as a 1:1:1:1 mixture of four diastereomers; (Found: M^+, 397.2621, $C_{25}H_{35}NO_3$ requires 397.2617); ν_{max} (NaCl)/cm^{-1} 3463 (O=H), 2984 (C=H), 1741 (C=O, ester), 1639 (C=C), 1447 (C=C, Ar), 1373 (*tert*-N, amine), 1241 (*tert*-N, amine); δ_H (400 MHz, $CDCl_3$) 1.18–1.23 (3H, m, $CHCH_3Ph$, $CHCH_3Ph$*, $CHCH_3Ph$*′, $CHCH_3Ph$*″), 1.27–1.34 (1.5H, m, $CHCH_3Ph$, $CHCH_3Ph$*), 1.34–1.41 (1.5H, m, $CHCH_3Ph$*′, $CHCH_3Ph$*″), 1.43–2.99 (11.5H, m, 1′-H_A,

1′-H_B, 1′-H_A*, 1′-H_B*, 1″-H_A, 1″-H_B, 1″-H_A*, 1″-H_B*, 2-H_{ax}, 2-H_{ax}*, 2-H_{eq}, 2-H_{eq}*, 2-H_{eq}*′, 2-H_{eq}*″, 4-H_{eq}, 4-H_{eq}*, 4-H_{eq}*′, 4-H_{eq}*″, 4-H_{ax}, 4-H_{ax}*, 4-H_{ax}*′, 4-H_{ax}*″,6-H_{eq}, 6-H_{eq}*, 6-H_{eq}*′, 6-H_{eq}*″, 6-H_{ax}, 6-H_{ax}*, 6-H_{ax}*′,6-H_{ax}*″, 7-H_{eq}, 7-H_{eq}*, 7-H_{eq}*′, 7-H_{eq}*″, 7-H_{ax}, 7-H_{ax}*, 7-H_{ax}*′, 7-H_{ax}*″, 8-H_{eq}, 8-H_{eq}*, 8-H_{eq}*′, 8-H_{eq}*″, 8-H_{ax}, 8-H_{ax}*, 8-H_{ax}*′, 8-H_{ax}*″), 3.12–3.36 (1.5H, m, 2-H_{ax}*′, 2-H_{ax}*″, C*H*CH_3Ph, C*H*CH_3Ph*,C*H*CH_3Ph*′, C*H*CH_3Ph*″), 3.97–4.14 (2.5H, m, OCH_2CH_3, OCH_2CH_3*, OCH_2CH_3*′, OCH_2CH_3*″, OH, OH*), 4.54 (0.25, s, OH*′), 4.59 (0.25, s, OH*″), 4.87–5.07 (4H, m, 3′-H_A, 3′-H_A*, 3′-H_A*′, 3′-H_A*″, 3′-H_B, 3′-H_B*, 3′-H_B*′, 3′-H_B*″, 3″-H_A, 3″-H_A*, 3″-H_A*′, 3″-H_A*″, 3″-H_B, 3″-H_B*, 3″-H_B*′, 3″-H_B*″), 5.65–5.91 (2H, m, 2′-H_A, 2′-H_A*, 2′-H_A*′, 2′-H_A*″, 2″-H_B, 2″-H_B*, 2″-H_B*′, 2″-H_B*″); δ_C (100 MHz, $CDCl_3$), 13.6 (CH_3, OCH_2*C*H_3), 13.8 (CH_3, OCH_2*C*H_3*), 13.9 (CH_3, OCH_2*C*H_3*′), 14.1 (CH_3, OCH_2*C*H_3*″), 18.8, 19.7, 20.0, 20.1, 20.2, 20.4, 21.2 (4×CH_3, CH*C*H_3Ph, CH*C*H_3Ph*, CH*C*H_3Ph*′, CH*C*H_3Ph*″ and 4×CH_2, C-7, C-7*, C-7*′, C-7*″), 29.5, 29.8, 30.5, 30.7, 31.8, 32.4, 32.6, 32.8 (8×CH_2, C-6, C-6*, C-6*′, C-6*″, C-8, C-8*, C-8*′, C-8*″), 37.8, 37.9, 38.0 (4×CH_2, C-1″, C-1″*, C-1″*′, C-1″*″), 39.0, 39.1, 39.4, 39.5 (4×CH_2, C-1′, C-1′*, C-1′*′, C-1′*″), 50.3, 50.6, 50.7 (4×quat., C-1, C-1*, C-1*′, C-1*″), 53.1, 54.0, 55.1, 55.3, 56.6, 57.1, 57.2 (8×CH_2, C-2, C-2*, C-2*′, C-2*″, C-4, C-4*, C-4*′, C-4*″), 60.6, 60.7, 60.9, 61.0 (4×CH_2, O*C*H_2CH$_3$, O*C*H_2CH$_3$*, O*C*H_2CH$_3$*′, O*C*H_2CH$_3$*″), 64.8, 65.1, 65.2, 65.8 (4×CH, *C*HCH$_3$Ph, *C*HCH$_3$Ph*, *C*HCH$_3$Ph*′, *C*HCH$_3$Ph*″), 74.0, 74.1, 74.4, 74.5 (4× quat., C-9, C-9*, C-9*′, C-9*″), 116.7, 116.8, 117.0, 117.2 (8×CH_2, C-3′, C-3′*, C-3′*′, C-3′*″, C-3″, C-3″*, C-3″*′, C-3″*″), 126.6, 126.7, 127.2, 127.3, 128.1, 128.2, 128.3 (10×CH, Ar, Ar*, Ar*′, Ar*″), 134.6, 134.7, 134.8, 134.9, 135.0, 135.1, 135.2 (8×CH, C-2′, C-2′*, C-2′*′, C-2′*″, C-2″, C-2″*, C-2″*′, C-2″*″), 144.2, 144.3, 144.8, 145.6 (4×quat., Ar, Ar*, Ar*′, Ar*″), 177.0, 177.2, 177.4 (4× OC=O, OC=O*, OC=O*′, OC=O*″); *m/z* (EI, %) 397 (M^+, 13), 382 (36), 292 (18), 206 (9), 105 (100), 79 (13), 41 (13).

3.3.10. Ethyl (1*R, 6*R**, 7*R**)-6-hydroxy-9-((*S*)-1-methylbenzyl)-9-azatricyclo[5.3.3.0^{1,6}]tridec-3-ene-7-carboxylate 14a, 14b and ethyl (1*R**, 6*S**, 7*R**)-6-Hydroxy-9-((*S*)-1-methylbenzyl)-9-azatricyclo[5.3.3.0^{1,6}]tridec-3-ene-7-carboxylate 15a, 15b.** To a solution of bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride (46 mg, 0.06 mmol) in dry dichloromethane (7 mL) was added dropwise a solution of dienes **20a/20b**, **21a/21b** (0.22 g, 0.6 mmol) in dry dichloromethane (3 mL). The mixture was heated under reflux for 48 h, concentrated in vacuo and the crude product purified by flash chromatography using 19:1 hexane–ethyl acetate as eluent to afford:

(i) *alkenes* **14a**, **14b** (91 mg, 41%) as a colourless oil and as a 1:1 mixture of diastereomers; (Found: M^+, 369.2305, $C_{23}H_{31}NO_3$ requires 369.2304); ν_{max} (NaCl)/cm^{-1} 3518 (O–H), 2976 (C–H), 1731 (C=O, ester), 1698 (C=C), 1453 (C=C,Ar), 1261 (*tert*-N, amine); δ_H (400 MHz, $CDCl_3$) 1.22–1.45 (7H, m, 11-H_{eq}, 11-H_{eq}*, CHC*H*$_3$Ph, CHC*H*$_3$Ph*, OCH$_2$C*H*$_3$, OCH$_2$C*H*$_3$*), 1.57–1.64 (1.5H, m, 12-H_{eq}, 12-H_{eq}*, 5-H_B), 1.73–1.78 (0.5H, m, 5-H_B*), 1.82–2.19 (3.5H, m, 2-H_A, 2-H_B, 2-H_A*, 2-H_B*, 5-H_A, 13-H_{eq}, 13-H_{eq}*), 2.23 (0.5H, dd, *J*=1.8, 11.0 Hz, 10-H_{ax}), 2.36 (0.5H, d, *J*=11.0 Hz, 5-H_A*), 2.47 (0.5H, dd, *J*=1.8, 11.0 Hz, 10-H_{eq}), 2.52–2.68 (2.5H, m, 8-H_{ax}, 8-H_{ax}*, 10-H_{ax}*, 13-H_{ax}, 13-H_{ax}*), 2.72 (0.5H, dd, *J*=1.8, 11.0 Hz, 8-H_{eq}), 2.94–3.06 (2H, m, 12-H_{ax}, 12-H_{ax}*, 8-H_{eq}*, 10-H_{eq}*), 3.21 (0.5H, q, *J*=6.7 Hz, C*H*CH$_3$Ph) 3.33 (0.5H, q, *J*=6.7 Hz, C*H*CH$_3$Ph*), 3.41 (0.5H, d, *J*=11.0 Hz, OH), 3.67 (0.5H, d, *J*=11.0 Hz, OH*), 4.13 (1H, q, *J*=7.1 Hz, OC*H*$_2$CH$_3$), 4.23 (1H, q, *J*=7.1 Hz, OC*H*$_2$CH$_3$*), 5.53–5.69 (2H, m, 3-H, 4-H), 7.25–7.36 (5H, m, Ar-H, Ar-H*); δ_C (100 MHz, $CDCl_3$), 14.1 (CH_3, OCH_2C*H*$_3$), 14.2 (CH_3, OCH_2C*H*$_3$*), 19.4 (CH_2, C-12), 20.9 (CH_3, CHC*H*$_3$Ph), 20.1 (CH_3, CHC*H*$_3$Ph*), 31.4 (CH_2, C-2), 31.8 (CH_2, C-13), 33.9 (CH_2, C-11), 34.2 (CH_2, C-11*), 35.0 (CH_2, C-5), 35.4 (CH_2, C-5*), 49.6 (quat., C-7), 49.7 (quat., C-7*), 54.8 (CH_2, C-8), 56.0 (CH_2, C-8*), 57.4 (CH_2, C-10), 59.4 (CH_2, C-10*), 60.7 (CH_2, O*C*H$_2$CH$_3$), 60.8 (CH_2, O*C*H$_2$CH$_3$*), 65.1 (CH, *C*HCH$_3$Ph), 65.7 (CH, *C*HCH$_3$Ph*), 71.3 (quat., C-6), 71.4 (quat., C-6*), 121.7 (CH, C-4), 121.9 (CH, C-4*), 125.4 (CH, C-3), 125.5 (CH, C-3*), 126.7, 127.2, 127.3, 128.2, 128.3 (10×CH, Ar, Ar*), 144.7 (quat., Ar), 145.3 (quat., Ar*), 176.4 (quat., OC=O), 176.6 (quat., OC=O*); *m/z* (EI, %) 369 (M^+, 37), 354 (100), 296 (14), 264 (26), 105 (81), 91 (15), 79 (13).

(ii) *Alkenes* **15a**, **15b** (80 mg, 36%) as a colourless oil and as a 1:1 mixture of diastereomers; (Found: M^+, 369.2297, $C_{23}H_{31}NO_3$ requires 369.2304); ν_{max} (NaCl)/cm^{-1}3507 (O–H), 2911 (C–H), 1731 (C=O),1698 (C=C), 1452 (C=C, Ar), 1262 (*tert*-N, amine); δ_H (400 MHz, $CDCl_3$) 1.21–1.49 (7.5H, m, 5-H_B, 11-H_{eq}, 11-H_{eq}*, CHC*H*$_3$Ph, CHC*H*$_3$Ph*, OCH$_2$C*H*$_3$, OCH$_2$C*H*$_3$*), 1.51–1.63 (1.5H, m, 12-H_{eq}, 12-H_{eq}*, 5-H_B*), 1.72–2.24 (6H, m, 2-H_A, 2-H_B, 2-H_A*, 2-H_B*, 5-H_A, 10-H_{ax}, 10-H_{ax}*, 13-H_{eq}, 13-H_{eq}*, 11-H_{ax}, 11-H_{ax}*), 2.28 (0.5H, d, *J*=11.0 Hz, 5-H_A*), 2.52 (0.5H, dd, *J*=1.8, 11.0 Hz, 10-H_{eq}), 2.58–2.65 (1.5H, m, 10-H_{ax}*, 13-H_{ax}, 13-H_{ax}*), 2.96 (0.5H, dd, *J*=1.8, 11.0 Hz, 10-H_{eq}*), 2.94–3.11 (3H, m, 8-H_{ax}, 8-H_{ax}*, 8-H_{eq}, 8-H_{eq}*, 12-H_{ax}, 12-H_{ax}*), 3.24–3.31 (1H, m, C*H*CH$_3$Ph, C*H*CH$_3$Ph*), 3.63–3.68 (1H, m, OC*H*$_2$CH$_3$), 4.19–4.24 (1H, m, OC*H*$_2$CH$_3$*), 5.57–5.70 (2H, m, 3-H, 3-H*, 4-H, 4-H*), 7.24–7.37 (5H, m, Ar-H, Ar-H*); δ_C (100 MHz, $CDCl_3$), 14.1 (CH_3, OCH_2C*H*$_3$), 14.2 (CH_3, OCH_2C*H*$_3$*), 19.4 (CH_2, C-12), 20.0 (CH_2, C-12*), 20.7 (CH_3, CHC*H*$_3$Ph), 20.9 (CH_3, CHC*H*$_3$Ph*), 31.2 (CH_2, C-2), 31.6 (CH_2, C-2*), 31.7 (CH_2, C-13), 31.8 (CH_2, C-13*), 33.9 (CH_2, C-11), 34.0 (CH_2, C-11*), 34.2 (CH_2, C-5), 34.5 (CH_2, C-5*), 50.3 (quat., C-7), 50.4 (quat., C-7*), 54.5 (CH_2, C-8), 54.8 (CH_2, C-8*), 56.1 (CH_2, C-10), 59.0 (CH_2, C-10*), 60.8 (CH_2, O*C*H$_2$CH$_3$), 60.9 (CH_2, O*C*H$_2$CH$_3$*), 65.1 (CH, *C*HCH$_3$Ph), 65.5 (CH, *C*HCH$_3$Ph*), 71.4 (quat., C-6), 71.5 (quat., C-6*), 122.6 (CH, C-4), 122.7 (CH, C-4*), 125.4 (CH, C-3), 125.5 (CH, C-3*), 126.6, 126.7, 127.2, 127.3, 128.3 (10×CH, Ar, Ar*), 145.5 (quat., Ar), 145.6 (quat., Ar*), 175.9 (quat., OC=O), 176.2 (quat., OC=O*); *m/z* (EI, %) 369 (M^+, 40), 354 (100), 292 (11), 164 (62), 105 (73), 91 (14), 44 (20).

3.3.11. (1*R,7*S**,8*R**)-10-((*S*)-1-Methylbenzyl)-6-oxa-10-azatricyclo[6.3.3.0]tetradec-3-en-8-yl)methanol 22a, 22b.** To a slurry of lithium aluminium hydride (17 mg, 0.44 mmol) in dry THF (5 mL) was slowly added a solution

of esters **12a**, **12b** (33 mg, 0.088 mmol) in dry THF (2 mL) and the mixture stirred under an atmosphere of nitrogen for 24 h. The reaction was quenched on the addition of $Na_2SO_4 \cdot 10H_2O$ and stirring was continued for 1 h. The mixture was filtered through Celite® and the filtrate concentrated in vacuo. The residue was dissolved in ethyl acetate (50 mL) washed with sat. $NaHCO_3$ (20 mL), brine (20 mL) then dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography using 19:1 hexane–ethyl acetate as eluent to afford the title compounds **22a**, **22b** (25 mg, 85%) as a colourless oil and as a 1:1 mixture of diastereomers; (Found: M^+, 327.2199, $C_{21}H_{29}NO_2$ requires 327.2198); ν_{max} (NaCl)/cm^{-1} 3429 (O–H), 2921 (C–H), 1451 (C=C, Ar), 1105 (C=O, ether), 1255 (*tert*-N, amine); δ_H (400 MHz, $CDCl_3$) 0.82–1.23 (1H, m, 12-H_{eq}, 14-H_{eq}) 1.26–1.33 (4H, m, 12-H_{eq}*, 14-H_{eq}*, CHCH_3Ph, CHCH_3Ph*), 1.54–1.59 (1H, m, 13-H_{eq}, 13-H_{eq}*), 1.64–1.71 (1H, m, 2-H_B, 11-H_{ax}), 1.76 (0.5H, dd, J= 1.8, 11.0 Hz, 9-H_{ax}), 1.85–2.01 (4H, m, 2-H_A*, 2-H_B*, 9-H_{ax}*, 11-H_{ax}*, 12-H_{ax}, 12-H_{ax}*, 14-H_{ax}, 14-H_{ax}*), 2.10–2.17 (0.5H, m, 2-H_A), 2.44 (0.5H, dd, J=1.8, 11.0 Hz, 9-H_{eq}), 2.49 (0.5H, dd, J=1.8, 11.0 Hz, 11-H_{eq}), 2.68–2.93 (2H, m, 9-H_{eq}*, 11-H_{eq}*, 13-H_{ax}, 13-H_{ax}*), 3.06–3.11 (1H, m, CHCH$_3$Ph, CHCH$_3$Ph*), 3.12–3.19 (0.5H, m, CH_AH$_B$OH), 3.27–3.28 (1H, m, 7-H, 7-H*), 3.27–3.34 (0.5H, m, CH$_A$$H_B$OH), 3.32 (0.5H, d, J=11.0 Hz, CH_AH$_B$OH*), 3.48 (0.5H, d, J=11.0 Hz, CH$_A$$H_B$OH*), 4.00–4.07 (1H, m, 5-H_B), 4.23–4.30 (1H, m, 5-H_A), 5.69–5.93 (2H, m, 3-H, 4-H), 7.22–7.30 (5H, m, Ar-H, Ar-H*); δ_C (100 MHz, $CDCl_3$) 20.5 (CH$_3$, CHCH$_3$Ph), 20.7 (CH$_2$, C-13), 20.8 (CH$_2$, C-13*), 26.6 (CH$_2$, C-14), 27.0 (CH$_2$, C-14*), 29.1 (CH$_2$, C-12), 29.5 (CH$_2$, C-12*), 36.9 (quat., C-1), 37.0 (quat., C-1*), 39.7 (quat., C-8), 39.9 (CH$_2$, C-2), 40.0 (CH$_2$, C-2*), 58.6 (CH$_2$, C-9), 59.5 (CH$_2$, C-9*), 62.4 (CH$_2$, C-11), 63.7 (CH$_2$, C-11*), 65.4 (CH, CHCH$_3$Ph), 65.6 (CH, CHCH$_3$Ph*), 67.9 (CH$_2$, C-5), 70.8 (CH$_2$, CH$_2$OH), 71.0 (CH$_2$, CH$_2$OH*), 92.8 (CH, C-7), 92.9 (CH, C-7*), 126.7, 127.2, 127.3, 128.3 (10×CH, Ar, Ar*), 129.7 (CH, C-3), 129.8 (CH, C-3*), 132.1 (CH, C-4), 132.3 (CH, C-4*), 144.6 (quat., Ar), 145.0 (quat., Ar*); *m/z* (EI, %) 327 (M^+, 34), 312 (78), 222 (23), 134 (39), 105 (100), 91 (23), 44 (25).

3.3.12. (1*S*,7*R*,8*S*)-(10-((1*S*)-1-Phenylethyl)-6-oxa-10-azatricyclo[6.3.3.0^{1,7}]tetra-dec-3-en-8-yl)methyl 2-(*N*-trifluoroacetyl)aminobenzoate 24a and (1*R*,7*S*,8*R*)-(10-((1*S*)-1-phenylethyl)-6-oxa-10-azatricyclo[6.3.3.0^{1,7}]-tetradec-3-en-8-yl)methyl 2-(*N*-trifluoroacetyl)amino-benzoate 24b. To a mixture of alcohols **22a**, **22b** (32 mg, 0.098 mmol), *N* (trifluoroacetyl)anthranilic acid **23**[18] (69 mg, 0.294 mmol) and 4 (dimethylamino)pyridine (6 mg, 0.049 mmol) in acetonitrile (10 mL) was added 1,3-dicyclohexyl-carbodiimide (61 mg, 0.294 mmol), and the reaction mixture was stirred for 20 h at 40 °C. The reaction mixture was cooled, filtered, and the filtrate evaporated to dryness. The residue was purified by flash chromatography (10% EtOAc in hexane) to afford the title compounds **24a**, **24b** (28 mg, 53%) as a colourless oil and as a 1:1 mixture of diasteromers; (Found: M^+, 542.2391, $C_{30}H_{33}F_3N_2O_4$ requires 542.2392); δ_H (400 MHz, $CDCl_3$) 1.08–1.17 (0.5H, m, 14-H_{ax}*), 1.23–1.43 (4H, m, 12-H_{ax}*, 14-H_{ax}, NCH(CH_3)Ph, NCH(CH_3)Ph*), 1.48–1.77 (3.5H, m, 2-H_b*, 9H_{ax}, 12-H_{ax}, 12-H_{eq}, 12-H_{eq}*, 13H_{eq}, 13H_{eq}*), 1.88–2.28 (4H, m, 2-H_a, 2-H_a*, 2-H_b, 9H_{ax}*, 11H_{ax}, 11H_{ax}*, 14H_{eq}, 14H_{eq}*), 2.56 (0.5H, d, $^2J_{gem}$=12.8 Hz, 9H_{eq}), 2.80–2.98 (2H, m, 9H_{eq}*, 11-H_{eq}, 13H_{ax}, 13H_{ax}*), 3.07–3.19 (2.5H, m, 7H, 7H*, 11-H_{eq}*, NCH(CH$_3$)Ph, NCH(CH$_3$)-Ph*), 3.86–4.28 (m, 4H, 5H_a, 5H_a*, 5-H_b, 5-H_b*, CH$_2$O, CH$_2$O*), 5.67 5.96 (2H, m, 3-H, 3-H*, 4-H, 4-H*), 7.13–7.31 (6H, m, 4′-H, 4′-H*, H(Ph), H*(Ph*)), 7.59–7.72 (1.5H, m, 3′-H*, 5′-H, 5′ H*), 8.05 (0.5H, dd, $^3J_{3',4'}$= 8.0 Hz, $^4J_{3',5'}$=1.5 Hz, 3′-H), 8.64 (0.5H, d, $^3J_{5'*,6'*}$= 8.4 Hz 6′-H*), 8.69 (0.5H, d, $^3J_{5',6'}$=8.4 Hz 6′-H), 12.33 (0.5H, s, NH*), 12.40 (0.5H, s, NH); δ_C (75 MHz, $CDCl_3$) 20.4 (NCH(CH_3)Ph*), 20.6 (C-13, C 13*), 20.7 (NCH(CH_3)Ph), 27.5 (C 12*), 27.8 (C 12), 29.3 (C-14*), 29.7 (C-14), 36.7 (C-1*), 36.9 (C-1), 39.9 (C-8, C-8*), 40.0 (C-2*), 40.2 (C-2), 58.6 (C-11*), 59.8 (C-11), 62.7 (C-9*), 63.7 (C-9), 65.4 (NCH(CH$_3$)Ph*), 65.5 (NCH(CH$_3$)Ph), 68.4 (C-5, C-5*), 71.0 (CH$_2$O*), 71.3 (CH$_2$O), 88.2 (C 7*), 88.6 (C 7), 116.4 (C-1′*), 116.5 (C-1′), 120.7 (C 6′*), 120.8 (C 6′), 124.7 (C-4′*), 124.8 (C-4′), 126.7 (C-4*), 126.8 (C-4), 127.3 (C-2, C-2*, C 6, C 6*), 128.3 (C 3, C 3*, C-5, C-5*), 130.2 (C-3*), 130.3 (C-3), 130.7 (C-3′, C 3′*), 131.2 (C-4*), 131.3 (C-4), 134.7 (C 5′*), 134.9 (C 5′), 139.1 (C-2′*), 139.2 (C-2′), 144.6 (C-1*), 144.8 (C-1), 168.0 (C=O* (ester)), 168.2 (C=O (ester)).

3.3.13. (1*S*,7*R*,8*S*)-(10-((1*S*)-1-phenylethyl)-6-oxa-10-azatricyclo[6.3.3.0^{1,7}]-tetradec-3-en-8-yl)methyl 2-amino-benzoate 25a and (1*R*,7*S*,8*R*)-(10-((1*S*)-1-phenylethyl)-6-oxa-10-azatricyclo[6.3.3.0^{1,7}]tetradec-3-en-8-yl)methyl 2-aminobenzoate 25b. To a mixture of trifluoroaceates **24a**, **24b** (24 mg, 0.044 mmol) in dry ethanol (5 mL) was added sodium borohydride (7 mg, 0.176 mmol) and the reaction mixture was stirred for 20 h at room temperature. The reaction was quenched with water (5 mL) and the volatiles were removed at reduced pressure. The residue was dissolved in ethyl acetate (30 mL), washed with aq. $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography (10% EtOAc in hexane) to afford the title compounds **25a**,**25b** (16 mg, 82%) as a colourless oil and as a 1:1 mixture of diastereomers; (Found: M^+, 446.2573, $C_{28}H_{34}N_2O_3$ requires 446.2569); δ_H (400 MHz, $CDCl_3$) 1.07–1.16 (0.5H, m,14-H_{ax}*), 1.22–1.44 (4H, m, 12-H_{ax}*, 14-H_{ax}, NCH(CH_3)Ph, NCH(CH_3)Ph*), 1.47–1.76 (3.5H, m, 2-H_b*, 9H_{ax}, 12H_{ax}, 12-H_{eq}, 12-H_{eq}*, 13H_{eq}, 13H_{eq}*), 1.87 2.17 (3.5H, m, 2-H_a, 2H_a*, 2-H_b, 9H_{ax}*, 11H_{ax}, 14H_{eq}, 14H_{eq}*), 2.25 (0.5H, dd, $^2J_{gem}$=10.7 Hz, $^4J_{11ax*,12ax*}$=1.8 Hz, 11H_{ax}*), 2.53 (0.5H, d, $^2J_{gem}$= 11.4 Hz, 9H_{eq}), 2.78–2.95 (2H, m, 9H_{eq}*, 11-H_{eq}, 13H_{ax}, 13H_{ax}*), 3.05–3.17 (1.5H, m, 11-H_{eq}*, NCH(CH$_3$)Ph, NCH(CH$_3$)Ph*), 3.21 (0.5H, s, 7H*), 3.22 (0.5H, s, 7H), 3.86–4.27 (4H, m, 5H_a, 5H_a*, 5-H_b, 5-H_b*, CH$_2$O, CH$_2$O*), 5.62 5.91 (4H, m, 3-H, 3-H*, 4-H, 4-H*, NH$_2$, NH$_2$*), 6.56–6.69 (2H, m, 3′-H, 3′ H*, 5′-H, 5′ H*), 7.20–7.34 (6H, m, 4′-H, 4′-H*, H(Ph), H*(Ph*)), 7.56 (0.5H, dd, $^3J_{5'*,6'*}$= 8.0 Hz, $^4J_{4'*,6'*}$=1.4 Hz, 6′-H*), 7.84 (0.5H, dd, $^3J_{5',6'}$= 8.3 Hz, $^4J_{4',6'}$=1.5 Hz, 6′-H); δ_C (75 MHz, $CDCl_3$) 20.5 (NCH(CH_3)Ph*), 20.7 (C-13, C 13*), 20.8 (NCH(CH_3)Ph), 27.6 (C 12*), 27.9 (C 12), 29.5 (C-14*), 29.9 (C-14), 36.7 (C-1*), 36.9 (C-1), 39.8, 39.9, 40.0, 40.3 (C-2, C-2*, C-8, C-8*), 58.8 (C 11*), 59.8 (C-11), 62.6 (C-9*), 64.0 (C-9), 65.4 (NCH(CH$_3$)Ph*), 65.6 (NCH(CH$_3$)Ph), 68.4 (C-5, C-5*), 69.2 (CH$_2$O*), 69.4 (CH$_2$O), 88.1 (C 7*), 88.4 (C 7),

111.1 (C-1′, C-1′*), 116.2 (C-3′*), 116.3 (C-3′), 116.6 (C 5′*), 116.7 (C 5′), 126.7 (C-4, C-4*), 127.3 (C-2*, C-6*), 127.4 (C-2, C-6), 128.3 (C 3, C 3*, C-5, C-5*), 130.2 (C-3*), 130.4 (C-3), 131.0 (C 6′, C 6′*), 131.1 (C-4*), 131.2 (C-4), 133.9 (C-4′*), 134.0 (C-4′), 144.9 (C-1*), 145.1 (C-1), 150.4 (C-2′*), 150.5 (C-2′), 167.9 (C═O* (ester)), 168.1 (C═O (ester)).

3.3.14. (1*S*,7*R*,8*S*)-(10-((1*S*)-1-Phenylethyl)-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 26a and (1*R*,7*S*,8*R*)-(10-((1*S*)-1-phenylethyl)-6-oxa-10-azatricyclo-[6.3.3.0^{1,7}]tetra-dec-3-en-8-yl)-methyl 2-(3-methyl-2,5-dioxopyrrolidin-1-yl)benzoate 26b. A mixture of amines **25a**, **25b** (14 mg, 0.031 mmol) and methylsuccinic anhydride (11 mg, 0.093 mmol) was heated at 125 °C for 4 h. The reaction mixture was dissolved in warm ethyl acetate (20 mL), washed with aq. $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (100% $CHCl_3$) to afford the title compounds **26a**, **26b** (9 mg, 55%) as a colourless oil and as a 1:1 mixture of diastereomers; (Found: M^+, 542.2776, $C_{33}H_{38}N_2O_5$ requires 542.2781); δ_H (400 MHz, $CDCl_3$) 1.06–1.14 (0.5H, m, 12-H_{ax}*), 1.40–1.62 (4.5H, m, 12H_{ax}, 14-H_{ax}, 14H_{ax}*, NCH(CH_3)Ph, NCH(CH_3)Ph*), 1.55–1.62 (4H, m, 13H_{eq}, 13H_{eq}*, 3″-CH_3, 3″-CH_3*), 1.60–1.74 (1.5H, m, 9H_{ax}, 12-H_{eq}, 12-H_{eq}*), 1.85–2.23 (4.5H, m, 2-H_a, 2H_a*, 2-H_b, 2-H_b*, 9H_{ax}*, 11H_{ax}, 11H_{ax}*, 14H_{eq}, 14H_{eq}*), 2.45–2.62 (1.5H, m, 9H_{eq}, 4″ H_b, 4″-H_b*), 2.76 2.93 (2H, m, 9H_{eq}*, 11-H_{eq}, 13H_{ax}, 13H_{ax}*), 3.00–3.18 (4.5H, m, 3″ H, 3″-H*, 4″-H_a, 4″-H_a*, 7H, 7H*, 11-H_{eq}*, NC*H*(CH_3)Ph, NC*H*(CH_3)Ph*), 3.87 4.26 (4H, m, 5H_a, 5H_a*, 5-H_b, 5-H_b*, CH_2O, CH_2O*), 5.63 5.92 (2H, m, 3-H, 3-H*, 4-H, 4-H*), 7.21–7.36 (6H, m, 3′-H, 3′ H*, H(Ph), H(Ph*)), 7.44 (0.5H, ddd, $^3J_{4'*,5'*}$= 7.7 Hz, $^3J_{5'*,6'*}$=7.7 Hz, $^4J_{3'*,5'*}$=1.1 Hz, 5′ H*), 7.54 (0.5H, ddd, $^3J_{4',5'}$=7.7 Hz, $^3J_{5',6'}$=7.7 Hz, $^4J_{3',5'}$=1.1 Hz, 5′-H), 7.61–7.70 (1H, m, 4′-H, 4′-H*), 7.75 (0.5H, d, $^3J_{5'*,6'*}$=7.9 Hz, 6′-H*), 8.08 (0.5H, d, $^3J_{5',6'}$=7.8 Hz, 6′-H,); δ_C (75 MHz, $CDCl_3$) 16.3 (3″ CH_3*), 16.5 (3″-CH_3), 20.6 (C-13, C-13*, NCH(*C*H_3)Ph, NCH(*C*H_3)Ph*), 27.5 (C-12*), 27.8 (C-12), 29.4 (C-14*), 29.8 (C-14), 35.2 (C-3″*), 35.4 (C-3″), 36.6 (C-1*), 36.8 (C-1), 37.0 (C-4″, C-4″*), 39.8, 39.9, 40.3 (C-2, C-2*, C-8, C-8*), 58.6 (C-11*), 59.7 (C-11), 62.6 (C-9*), 63.8 (C-9), 65.4 (N*C*H(CH_3)Ph*), 65.5 (N*C*H(CH_3)Ph), 68.4 (C-5, C-5*), 70.1 (CH_2O, CH_2O*), 88.0 (C 7*), 88.4 (C 7), 126.6 (C-4*), 126.7 (C-4), 127.3 (C-2*, C-6*, C-1′, C-1′*), 127.4 (C 2, C-6), 128.3 (C 3, C 3*, C-5, C-5*), 129.4 (C 5′*), 129.5 (C 5′), 129.9 (C-3′*), 130.0 (C-3′), 130.3 (C-3, C-3*), 130.4 (C-4, C-4*), 131.2 (C 6′*), 131.4 (C 6′), 132.9 (C-2′*), 133.0 (C-2′), 133.3 (C-4′*), 133.4 (C-4′), 144.9 (C-1, C-1*), 164.0 (C═O, C═O* (ester)), 176.1 (C 5″, C 5″*), 180.0 (C-2″, C-2″*).

References and notes

1. (a) Earle, M. J.; Fairhurst, R. A.; Heaney, H.; Papageorgiou, G.; Wilkins, R. F. *Tetrahedron Lett.* **1990**, *31*, 4229. (b) Cooper, M. S.; Earle, M. J.; Fairhurst, R. A.; Heaney, H.; Papageorgiou, G.; Wilkins, R. F. *Synlett* **1990**, 617. (c) Heaney, H.; Papageorgiou, G.; Wilkins, R. F. *Tetrahedron* **1995**, *51*, 10737.
2. (a) Manske, R. H. *Can. J. Res.* **1938**, *16B*, 57. (b) Pelletier, S. W.; Joshi, B. S. In Pelletier, S. W., Ed.; Alkaloids: Chemical and Biological Perspectives; Springer: New York, 1991; 7, p 297.
3. Brocke, C.; Brimble, M. A.; Lin, D. S.; McLeod, M. D. *Synlett* **2004**, 2359.
4. El Gihani, M. T.; Heaney, H.; Slawin, A. M. Z. *Tetrahedron Lett.* **1995**, *36*, 4905.
5. Iwanek, W.; Mattay, J. *Liebigs Ann. Chem.* **1995**, 1463.
6. Arnecke, R.; Böhmer, V.; Friebe, S.; Gebauer, S.; Krauss, G. J.; Thondorf, I.; Vogt, W. *Tetrahedron Lett.* **1995**, *36*, 6221.
7. Page, P. C. B.; Heaney, H.; Sampler, E. P. *J. Am. Chem. Soc.* **1999**, *121*, 6751.
8. Schmidt, C.; Paulus, E. F.; Böhmer, V.; Vogt, W. *New J. Chem.* **2001**, *25*, 374.
9. Sampler, E. P. PhD Thesis, Loughborough University, 2001.
10. Davies, A. R. L.; Hardick, D. J.; Blagbrough, I. S.; Potter, B. V. L.; Wolstenholme, A. J.; Wonnacott, S. *Neuropharmacology* **1999**, *38*, 679.
11. (a) Bergmeier, S. C.; Lapinsky, D. J.; Free, R. B.; McKay, D. B. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2263. (b) Doisy, X.; Blagbrough, I. S.; Wonnacott, S.; Potter, B. V. L. *Pharm. Pharmacol. Commun.* **1998**, *4*, 313.
12. Trigg, W. J.; Hardick, D. J.; Grangier, G.; Wonnacott, S.; Lewis, T.; Rowan, M. G.; Potter, B. V. L.; Blagbrough, I. S. *ACS Symp. Ser.* **1998**, *686*, 194.
13. (a) Baillie, L. C.; Bearder, J. R.; Li, W.-S.; Sherringham, J. A.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4047. (b) Kraus, G. A.; Dneprovskaia, E. *Tetrahedron Lett.* **1998**, *39*, 2451.
14. (a) Davies, A. R. L.; Hardick, D. J.; Blagbrough, I. S.; Potter, B. V. L.; Wolstenholme, A. J.; Wonnacott, S. *Biochem. Soc. Trans.* **1997**, *25*, 545S. (b) Bryant, D. L.; Free, R. B.; Thomasy, S. M.; Lapinsky, D. J.; Ismail, K. A.; McKay, S. B.; Bergmeier, S. C.; McKay, D. B. *Neurosci. Res.* **2002**, *42*, 57.
15. Arias-Pérez, M. S.; Alejo, A.; Gálvez, E.; Pérez, S. M.; Santos, M. J. *J. Mol. Struct.* **1995**, *349*, 169.
16. Jeyaraman, R.; Jawaharsingh, C. B.; Avila, S.; Eliel, E. L.; Ganapathy, K.; Manoharan, M.; Morris-Natschke, S. *J. Heterocycl. Chem.* **1982**, *19*, 449.
17. Gravel, D.; Labelle, M. *Can. J. Chem.* **1985**, *63*, 1874.
18. Schepartz, A.; Breslow, R. *J. Am. Chem. Soc.* **1987**, *109*, 1814.