Synthesis of ABE tricyclic analogues of methyllycaconitine using a Wacker oxidation–aldol strategy to append the B ring to the AE fragment

David Barker,[a] Margaret A. Brimble,*[b] Malcolm McLeod,*[a] G. Paul Savage[c] and David J. Wong[a]

[a] *School of Chemistry, F11 University of Sydney, Camperdown, NSW 2006, Australia*
[b] *Department of Chemistry, University of Auckland, Private Bag 92019, Auckland, New Zealand. E-mail: m.brimble@auckland.ac.nz; Fax: +64 9 3737422*
[c] *CSIRO Molecular Science, Bag 10, Clayton South, Vic. 3169, Australia*

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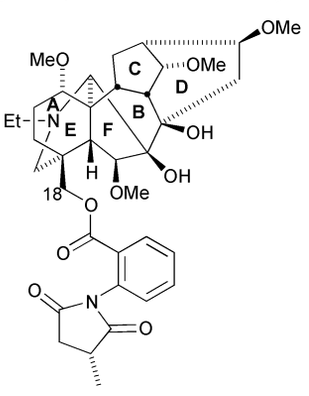
The synthesis of ABE tricyclic analogues **18** of the alkaloid methyllycaconitine **1** is described. The analogues contain the key pharmacophore reputed to be responsible for the biological activity of methyllycaconitine **1**, namely, a homocholine motif formed from a tertiary *N*-ethylamine in a 3-azabicyclo[3.3.1]nonane ring system and a 2-(3-methyl-2,5-dioxopyrrolin-1-yl)benzoate ester side chain. The 3-azabicyclo[3.3.1]nonane ring system **10** was assembled *via* a double Mannich reaction of ethyl 3-(but-3′-enyl)-2-oxocyclohexane-1-carboxylate **9** with ethylamine and formaldehyde. Attempts to append a B ring to this AE ring system *via* McMurray coupling of dialdehyde **5** were hampered by the inability to effect conversion of the C-9 ketone **10** to vinyl ether **6**. Wittig methylenation of ketone **10** afforded diene **7**, however, subsequent attempts to effect double hydroboration–oxidation of diene **7** failed to realise diol **11** *en route* to the key dialdehyde precursor **5** required for the McMurray coupling. Wacker oxidation of the homoallyl group of **10** afforded methyl ketone **12** which underwent intramolecular aldol condensation to form enone **13**. After selective reduction of the ketone and methylation, the resultant methyl ethers **15** underwent reduction of the ester sidechain affording neopentyl substituted alcohols **16**. Finally, the 2-(3-methyl-2,5-dioxopyrrolin-1-yl)benzoate ester sidechain was appended by treatment of alcohols **16** with *N*-(trifluoroacetyl)anthranilic acid followed by fusion of the resultant anthranilates **17** with methylsuccinic anhydride.

Introduction

Methyllycaconitine **1** is the principle toxin in *Delphinium brownii*,[1] a cattle-stock poison in Western Canada, and is also found in at least 30 *Delphinium* species as well as in *Consolida ambigua* and *Inaularoyaleana*.[2,3] Both its toxicity and insecticidal activity have been attributed to its ability to act as a potent inhibitor of the nicotinic acetylcholine receptor (nAChR) binding in mammalian and insect neural membranes.[4] At the α-7 subtype of nAChR, methyllycaconitine **1** is among the most potent, small molecule competitive antagonists yet reported.[5]



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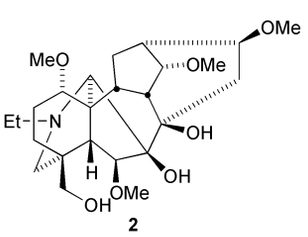

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Methyllycaconitine **1** is the 2-[2-(*S*)-methylsuccinimido]-benzoate ester of the norditerpenoid alkaloid lycoctonine **2**.[6] Lycoctonine **2**, however, exhibits 2000 times less affinity for rat neuronal α7 subtype nAChRs than its substituted anthranilate ester methyllycaconitine **1**.[5] The high toxicity of methyllycaconitine **1** to mammals prevents its use as an agrochemical, however, if the inhibitory action of methyllycaconitine **1** is localised in a small toxophoric section of the molecule, a subunit of methyllycaconitine **1** based on this section, may have the desired toxophoric properties yet be significantly lower in toxicity towards mammals. Therefore interest in synthesizing analogues of methyllycaconitine **1** as lead compounds for the development of new insecticides continues.

The *N*-substituted anthranilate ester moiety is considered 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 AF rings of methyllycaconitine **1** is protonated and therefore mimics acetylcholine, and that the (*S*)-methylsuccinimido ring may help to maintain the correct geometry between the tertiary nitrogen atom of the F ring in the alkaloid and the carbonyl oxygen of the ester bond.[7] We therefore herein report the synthesis of tricyclic analogues of methyllycaconitine **18** containing the key 2-(3-methyl-2,5-dioxopyrrolin-1-yl)benzoate ester in which an additional six membered ring (a B ring) is appended to a 3-azabicyclo[3.3.1]nonane framework (the AE rings). It was envisaged that incorporation of the *N*-substituted anthranilate ester and the *N*-ethyl group embedded in the homocholine motif, into a conformationally restricted framework may enhance the biostability, selectivity and potency of simpler bicyclic AE analogues of methyllycaconitine **1** that had been prepared previously.

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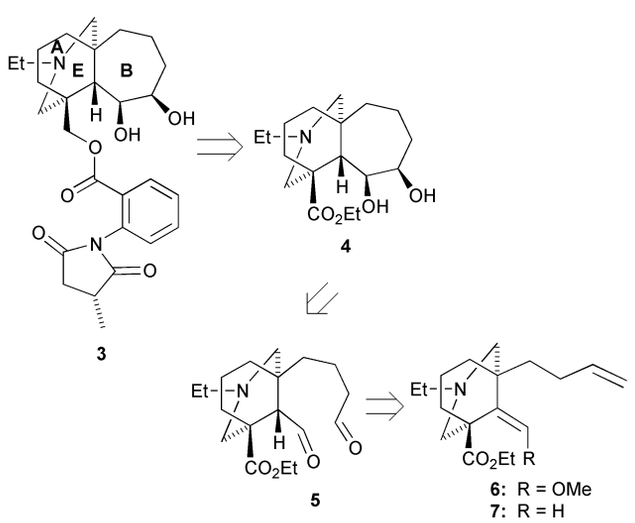
Methyllycaconitine **1** has not succumbed to total synthesis, however, a semi-synthesis of methyllycaconitine **1** from its parent alkaloid lycoctonine **2** has been reported by Blagbrough and co-workers[8] which established the absolute configuration of the methylsuccinimide moiety to be *S*. Alternative semi-syntheses of methyllycaconitine **1** from lycoctonine **2** used a 2-(*N*-succinimido)benzoic acid to append the anthranilate ester moiety to a neopentyl alcohol.[9]

Simple E ring analogues of methyllycaconitine **1** containing the homocholine motif have been prepared by Bergmeier *et al.*[10] containing a piperidine ring substituted at C-3 with a 2-(3-methyl-2,5-dioxopyrrolin-1-yl)benzoate ester. AE bicyclic analogues of methyllycaconitine **1** have been prepared by Blagbrough and co-workers[11] in which the 3-azabicyclo[3.3.1]-nonane framework was assembled *via* a double Mannich reaction using 2-oxocyclohexane-1-carboxylate, ethylamine and formaldehyde. The azabicyclo[3.3.1]nonane bicyclic skeleton was then extended from the ketone at C-5 by the addition of Grignard, Wittig and alkyllithium reagents.[12]

To date the main attention for the synthesis of tricyclic analogues of methyllycaconitine **1** has been focused on assembly of AEF analogues. One approach by Kraus and Dneprovskaia[13] involved carrying out a similar Mannich reaction on a spirocyclic enone whereas Whiting and co-workers[14] formed the azabicyclic system *via* condensation of an ester with an amine formed by reduction of a nitrone that in turn had been formed by oxidative cleavage of an isoxazolidine. The work reported herein provides methodology for the synthesis of the first examples of tricyclic analogues of methyllycaconitine **1** that contain an ABE framework. The synthetic work reported herein was prompted by a report that an ABE tricyclic analogue of methyllycaconitine **1** was more potent than an AE bicyclic analogue, however, the synthesis and characterisation of the ABE tricyclic analogue was not described.[15]

Results and discussion

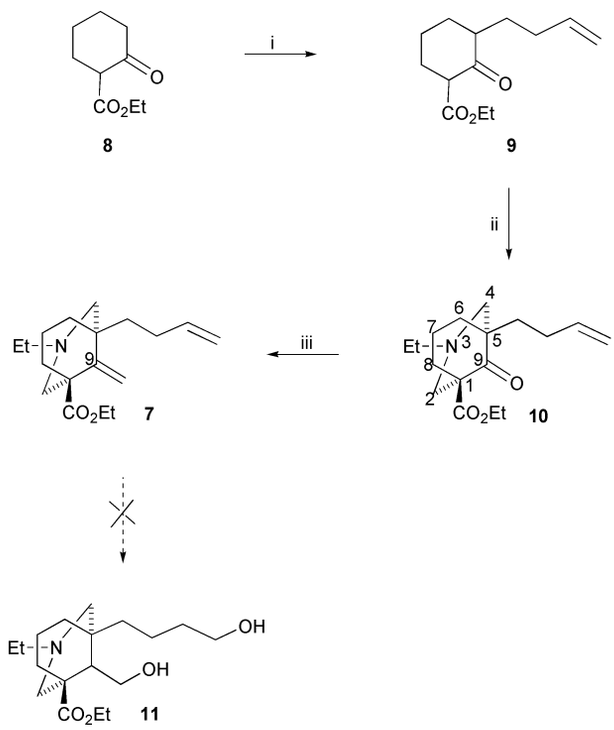
Initial synthetic effort was directed towards the synthesis of ABE tricyclic analogue **3** which contains a dihydroxylated seven membered B ring (Scheme 1). Our synthetic strategy to prepare



Scheme 1

analogue **3** hinged on the use of a McMurray coupling to assemble diol **4** from dialdehyde **5**. It was envisaged that the butyraldehyde side chain in dialdehyde **5** would be formed *via* hydroboration of an alkene and that the second aldehyde group could be generated *via* hydrolysis of enol ether **6**. In turn enol ether **6** was available *via* Wittig olefination of ketone **10**.

Homoallylation of β-keto ester **8** was performed efficiently using the method reported by Huckin and Weiler.[16] Thus β-keto ester **8** was treated with NaH to generate the sodium enolate followed by the addition of butyllithium at 0 °C in dry THF to generate the dianion. Subsequent addition of 4-bromobut-1-ene and warming the reaction mixture to room temperature afforded the desired butenyl-substituted keto ester **9** in 83% yield (Scheme 2). The ^{1}H NMR spectrum of the product **9** was in agreement with the literature.[17]



Scheme 2 *Reagents, conditions and yields*: (i) NaH, THF (2.0 equiv.), 0 °C, 10 min, then BuLi (1.6 equiv.), 0 °C, 25 min, 4-bromobut-1-ene, 0 °C, 2 h then room temp., 20 h (83%) (ii) $EtNH_2$, H_2CO, EtOH, reflux, 24 h (41%) (iii) $Ph_3P^+CH_3Br^-$ (4.0 equiv.), BuLi (3.0 equiv.), THF, refux, 24 h (85%).

With butenyl-substituted keto ester **9** in hand, attention then turned to the formation of the azabicyclic ring system present in the AE rings of methyllycaconitine **1**. Keto ester **9** was heated under reflux with one equivalent of ethylamine and two equivalents of formaldehyde in ethanol for 24 h to afford Mannich product **10** in 41% yield. The moderate yield obtained for this step is consistent with reports in the literature that state that double Mannich reactions using cyclohexanones that are substituted with only one carboxylate group at the α position such as keto ester **9**, proceed in much lower yield than analogous reactions carried out using more highly activated cyclohexanones that are substituted with esters at both the α and α′ positions.[18] This is due to the low reactivity of the alternative α′ carbon in β keto ester **9** (*i.e.* C-6) relative to the highly acidic α-position (C-2).

Elemental analysis of **10** was consistent with the required formula $C_{17}H_{27}NO_3$. In the ^{1}H NMR spectrum 7A-H characteristically resonated at δ_H 2.86–2.98 further downfield than 7B-H due to the deshielding influence of the nearby nitrogen lone pair. This feature of the spectrum together with the long range W-coupling observed between 2A-H and 4A-H ($J_{2A,4A}$ 2.2 Hz) were consistent with formation of the 3-azabicyclo[3.3.1]-nonane ring system (Fig. 1).[19] The large upfield shift of 2B-H (δ_H 2.86–2.98) and 4B-H (δ_H 2.55) compared to their geminal protons 2A-H and 4A-H respectively, is attributed to the overlap of the nitrogen lone pair with the adjacent *trans*-coplanar C–H anti-bonding orbitals.

The proposed conversion of azabicyclo[3.3.1]nonane **10** to ABE analogue **4** required initial preparation of dialdehyde **5** proceeding by way of methyl vinyl ether **6**. Unfortunately,

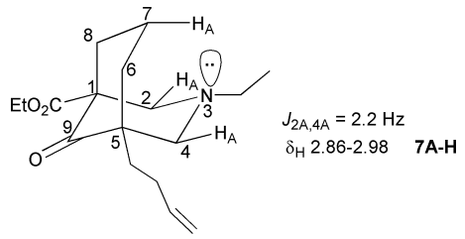


Fig. 1 Characteristic features in the ^{1}H NMR spectrum of **10**.

attempts to effect Wittig olefination of ketone **10** with methoxymethyltriphenylphosphonium chloride using either butyllithium, LDA or NaH–DMSO as base were disappointing despite the successful use of these reagents to effect a similar conversion on a simpler keto ester which lacked a butenyl side chain at C-5.[11] Use of methoxymethyldiphenylphosphine oxide was also unsuccessful.

Due to the inaccessibility of dialdehyde **5** from methyl vinyl ether **6**, it was decided to alter the synthesis of **6** in light of our observation that the Wittig reaction of a keto ester analogous to **10** which lacked the butenyl group at C-5, proceeded in much higher yield using methyltriphenylphosphonium bromide rather than methoxymethyltriphenylphosphonium chloride. It was therefore envisaged that dialdehyde **5** could also be synthesised by the double oxidation of diol **11** which in turn could be synthesised by effecting a double hydroboration of diene **7**. Treatment of keto ester **10** with methyltriphenylphosphonium bromide (4 equiv.) using butyllithium as base afforded the desired diene **7** in 85% yield after heating the reaction mixture under reflux for 24 h. With diene **7** in hand, attention then turned to its conversion to diol **11**.

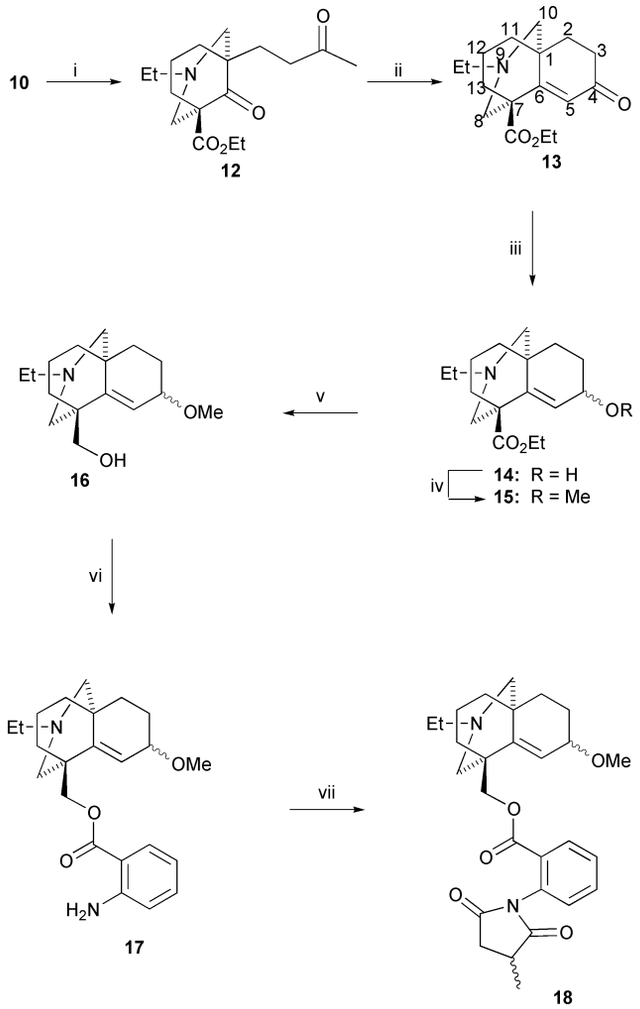
Treatment of diene **7** with excess dicyclohexylborane[20] only effected hydroboration of the less hindered olefin in the butenyl side chain as evidenced by the disappearance of only the resonances due to the butenyl vinylic protons in the ^{1}H NMR spectrum of the crude product. Use of a large excess of borane–dimethyl sulfide for 24 h similarly did not result in hydroboration of the more hindered olefin at C-9 and neither did the use of borane generated *in situ* from sodium borohydride and boron trifluoride–diethyl ether and 9-borabicyclo[3.3.1]nonane.

The unsuccessful attempts to prepare dialdehyde **5** from diene **7** meant that efforts to synthesize the B ring of ABE tricyclic methyllycaconitine analogues derived from diol **4** using a pinacol coupling were abandoned. It was therefore decided to explore alternative avenues to produce tricyclic ABE analogues of methyllycaconitine.

In an alternative approach for the synthesis of ABE tricyclic analogues of methylycaconitine **1** it was envisaged that appendage of a B ring to the AE bicyclic system could be achieved by intramolecular ring-closure of a suitably appended nucleophile at C-5 of the azabicyclic system onto the carbonyl group at C-9. The nucleophile could be generated at this position by forming the enolate of methyl ketone **12** which in turn can be formed by Wacker oxidation of alkene **10** (Scheme 3).

Alkene **10** was treated with palladium(II) chloride (0.2 equivalents) and copper(I) chloride (1.2 equivalents) and the mixture stirred overnight whilst bubbling oxygen through the reaction vessel. After purification of the reaction mixture the desired product **12** was isolated in 39% yield after purification by flash chromatography. Use of DMF as solvent maximised the formation of methyl ketone **12** and minimised the competing double isomerization reaction.[21] Copper(I) chloride was also used rather than copper(II) chloride in order to reduce competing chlorination of the carbonyl group[22] and to increase the rate of the reaction.[23]

With a reliable synthesis of methyl ketone **12** in hand, attention turned to the use of an intramolecular aldol cyclisation to convert **12** into enone **13**. Treatment of methyl ketone **12** with potassium hexamethyldisilazanide, sodium hexamethyldisilazanide or lithium hexamethyldisilazanide only returned starting material as did use of potassium *tert*-butoxide in THF and the amino acids phenylalanine and proline. Finally success was realised when ketone **12** was treated with ethanolic potassium hydroxide[24] for 2 h affording the desired enone **13** in 96% yield after work up and purification by flash chromatography.



Scheme 3 *Reagents, conditions and yields*: (i) $PdCl_2$, CuCl, O_2, 8 : 1 DMF–H_2O, room temp., 24 h (39%) (ii) KOH (4.0 equiv.), EtOH, room temp., 2 h (96%) (iii) $NaBH_4$, THF, H_2O (81%) (iv) NaH, THF, 1 h then MeI, 20 h (86%) (v) $LiAlH_4$, THF, 0 °C, 30 min (86%) (vi) *N*-(trifluoroacetyl)anthranilic acid, DMAP, DCC, MeCN, 40 °C, 24 h then $NaBH_4$, EtOH, room temp., 2 h (77%) (vii) 2-methylsuccinic anhydride, 125 °C, 36 h (50%).

The high resolution mass spectrum recorded for enone **13** exhibited a molecular ion at *m*/*z* 291.1827, corresponding to the molecular formula $C_{17}H_{25}NO_3$ and consistent with loss of water during the intramolecular aldol condensation of methyl ketone **12**. The ^{1}H NMR spectrum exhibited a vinylic proton at δ_H 5.55 and the infrared spectrum exhibited two carbonyl absorbances due to the ester and α,β unsaturated ketone at 1727 cm^{-1} and 1676 cm^{-1}, respectively. The ^{13}C NMR spectrum showed the lack of resonances due to C-4′ at δ_C 29.7 and C-9 at δ_C 212.9 in methyl ketone **12**. A new protonated vinylic carbon at δ_C 120.3 was assigned to C-5 and a quaternary vinylic carbon at δ_C 167.7 was assigned to C-6.

With the tricyclic framework in place it was then required to convert the ester in **13** into an alcohol in preparation for attachment of the *N*-(methylsuccinimido)anthranilate ester sidechain. Direct reduction of ester **13** with lithium aluminium hydride would also introduce a secondary alcohol at C-4. Thus, in order to prevent complication of the subsequent esterification of the C-7 alcohol it was decided to convert the C-4 ketone into a methoxy group, before reduction of the ester. The

ketone at C-4 was therefore selectively reduced with sodium borohydride to give alcohol **14** which then underwent methylation to give methyl ether **15**. Finally reduction of the ethyl ester gave the desired primary alcohol **16**.

The initial selective reduction of ketone **13** proceeded readily in 81% yield using sodium borohydride in THF affording alcohols **14** as an inseparable 2.3 : 1 mixture of diastereomers for which the stereochemistry was not assigned. The high resolution mass spectrum for the mixture of alcohols **14** exhibited a molecular ion at *m/z* 293.1993, consistent with the molecular formula $C_{17}H_{27}NO_3$. The infrared spectrum of the product showed an absorbance at 3354 cm^{-1} indicating a hydroxy group whilst an absorbance at 1726 cm^{-1} showed that the ethyl ester was still present. In the ^1H NMR spectrum a two proton multiplet at δ_H 4.07–4.11 simplified to a single proton multiplet upon addition of D_2O indicating a hydroxy proton was now present. The vinylic proton, 5-H, which resonated as a singlet at δ_H 5.55 in the starting material was observed as two doublets at δ_H 5.22 ($J_{5,4}$ 2.2 Hz) and δ_H 5.31 ($J_{5,4}$ 3.9 Hz) indicating the presence of two isomeric allylic alcohols. Integration of the two resonances showed the ratio of isomers to be 2.3 : 1, with the resonance at δ_H 5.22 arising from the major isomer and that at δ_H 5.31 from the minor isomer.

The ^{13}C NMR spectrum indicated that the C-4 carbonyl resonance present in the starting material **13** at δ_C 198.7 had disappeared and had been replaced by two new resonances for C-4 at δ_C 67.1 for the major isomer and at δ_C 67.3 for the minor isomer. The vinylic carbon, C-5, resonated at δ_C 120.9 for the major isomer and at δ_C 119.6 for the minor isomer. All other carbon resonances were coincidental.

The next step in the synthesis involved the conversion of alcohols **14** to methyl ethers **15** and was achieved using sodium hydride and excess methyl iodide in THF. After purification by flash chromatography methyl ethers **15** were isolated in 86% yield. The ^1H NMR spectrum exhibited two new singlets at δ_H 3.16 and δ_H 3.17, which had a combined integration for three protons, in a ratio of 2.3 : 1. The larger singlet at δ_H 3.16 was assigned to the methoxy group of the major isomer whilst the singlet at δ_H 3.17 was assigned to the minor isomer. The vinylic proton, 5-H resonated at δ_H 5.15 for the major isomer and δ_H 5.21 for the minor isomer. The ^{13}C NMR spectrum exhibited distinct resonances for the methoxy group, C-4 and C-5.

Reduction of the ethyl esters **15** to neopentyl alcohols **16** was achieved using lithium aluminium hydride in THF for 2 hours at room temperature. After workup, purification by flash chromatography afforded alcohols **16** as an inseparable 2.3 : 1 mixture of diastereomers in 86% yield. The high resolution mass spectrum for alcohols **16** exhibited a molecular ion at *m/z* 265.1974, consistent with the molecular formula $C_{16}H_{26}NO_2$. The infrared spectrum exhibited a broad absorbance at 3445 cm^{-1} due to the hydroxy group and no carbonyl absorbances, confirming reduction of the ester had taken place. The ^1H NMR spectrum showed the absence of resonances from the ethyl ester, whilst two doublets at δ_H 3.37 (J_{gem} 11.1 Hz) and δ_H 3.44 (J_{gem} 11.1 Hz) were assigned to the C-7 hydroxymethyl protons. The ^{13}C NMR spectrum showed the absence of resonances due to the ethyl ester and a new methylene resonance at δ_C 74.4 was assigned to the C-7 hydroxymethyl group. The spectrum exhibited individual resonances, for both diastereomers, for the methoxy group, C-4, C-5 and C-6 whilst all the other carbons were coincidental.

With the successful synthesis of tricyclic ABE analogues **16** in hand, it next remained to append the key *N*-(methylsuccinimido)anthranilate ester group. Addition of the 2-(3-methyl-2,5-dioxopyrrolin-1-yl)benzoate ester to alcohols **16** in a single synthetic step *via* esterification using 2-(3-methyl-2,5-dioxopyrrolin-1-yl)benzoic acid using methods reported by Kraus and Dneprovskaia[13] were unsuccessful. Whiting *et al.*[14] have also reported the inability to effect direct esterification of benzyl alcohol with 2-(3-methyl-2,5-dioxopyrrolin-1-yl)benzoic acid using DCC as a coupling agent and attributed this to complications arising from the presence of nucleophilic imide carbonyl groups which can react with the activated acid leading to the formation of 1,3-oxazines.

An alternative two step procedure for attaching the 2-(3-methyl-2,5-dioxopyrrolin-1-yl)benzoate ester to alcohols **16** was more fruitful and consisted of conversion of alcohols **16** to anthranilates **17** followed by reaction with 2-methylsuccinic acid to afford the 2-(3-methyl-2,5-dioxopyrrolin-1-yl)benzoates **18**. The most common method for conversion of alcohols to anthranilate esters involves reaction of the alcohol with isatoic anhydride and catalytic base[25] at high temperature, however, this method only proceeds in low yields when using hindered alcohols.[8,11,14] We therefore developed[26] a high yielding and operationally simple method for the conversion of hindered alcohols to anthranilate esters which was applied to the conversion of alcohols **16** to anthranilates **17** in the present work.

Treatment of alcohols **16** with *N*-(trifluoroacetyl)anthranilic acid[27] and 1,3-dicyclohexylcarbodiimide in acetonitrile using 4-dimethylaminopyridine as acylation catalyst afforded the *N*-(trifluoroacetyl)anthranilates which were then on work up treated directly with sodium borohydride to effect cleavage of the trifluoroacetyl group affording anthranilates **17** in 77% yield. Finally fusion of anthranilates **17** with 2-methylsuccinic anhydride effected conversion to 2-(3-methyl-2,5-dioxopyrrolin-1-yl)benzoate esters **18** in 50% yield.

In summary the successful synthesis of esters **18** which are ABE tricyclic analogues of the alkaloid methyllycaconitine **1** has been achieved. The analogues contain the key pharmacophore reputed to be responsible for the biological activity of **1**, namely: a homocholine motif formed from a tertiary *N*-ethylamine in a 3-azabicyclo[3.3.1]nonane ring system and a 2-(3-methyl-2,5-dioxopyrrolin-1-yl)benzoate ester side chain. The key steps in the synthesis involved the use of a double Mannich reaction to assemble the 3-azabicyclo[3.3.1]nonane AE ring system in combination with the use of a Wacker oxidation–aldol reaction to append a six membered B ring to the AE framework. Appendage of the 2-(3-methyl-2,5-dioxopyrrolin-1-yl)benzoate ester was effected by treatment of alcohols **16** with *N*-(trifluoroacetyl)anthranilic acid followed by fusion of the resultant anthranilates with 2-methylsuccinic anhydride.

Experimental

Mps were determined on a Koffler hot-stage apparatus and are uncorrected. IR spectra were recorded using a Perkin-Elmer 1600 Fourier Transform IR spectrophotometer as thin films between sodium chloride plates. Absorption spectra are expressed in wavenumbers (cm^{-1}) with the following abbreviations: s = strong, m = medium, w = weak and br = broad. ^1H NMR spectra were recorded on a Bruker AC 200 (200 MHz) or a Bruker DRX 400 (400 MHz) spectrometer at ambient temperature. All *J*-values are given in Hz. Chemical shifts are expressed in parts per million downfield shift from tetramethylsilane as an internal standard, and reported as position (δ_H), relative integral, multiplicity (s = singlet, br s = broad singlet, d = doublet, dd = double doublet, ddd = double double doublet, t = triplet, q = quartet, m = multiplet) and assignment. ^{13}C NMR spectra were recorded on a Bruker AC 200 (50.3 MHz) or a Bruker DRX 400 (100.5 MHz) spectrometer at ambient temperature with complete proton decoupling. Chemical shifts are expressed in parts per million downfield shift from tetramethylsilane as an internal standard and reported as position (δ_C), multiplicity (aided by DEPT 135, DEPT 90, COSY and HETCOR experiments) and assignment. When NMR data are reported for isomeric mixtures, resonances for the minor isomer are denoted by an asterisk (*). Low resolution mass spectra were recorded on a VG70-250S, a VG70-SD or a AEI model MS902 double focusing magnetic sector mass spectrometer

operating with an ionisation potential of 70 eV. High resolution mass spectra were recorded at nominal resolution of 5000 to 10 000 as appropriate. Major fragments are given as percentages relative to the base peak and assigned where possible. Ionisation methods employed were either electron impact or chemical ionisation with ammonia or methane as reagent gas (CI). Low resolution chemical ionisation mass spectra were also recorded on a Hewlett Packard 5989A mass spectrometer using ammonia as reagent gas with the sample dissolved in methanol. Elemental analyses were carried out by the Microanalytical Unit at the Research School of Chemistry, Australian National University, Canberra. Flash chromatography was performed using Merck Kieselgel 60 (230–400 mesh) with the indicated solvents. Thin layer chromatography (tlc) was performed using 0.2 mm thick precoated silica gel plates (Merck Kieselgel 60 F_{254} or Riedel-de Haen Kieselgel S F_{254}). Compounds were visualised by ultraviolet fluorescence or by staining with iodine or vanillin in methanolic sulfuric acid.

Ethyl 3-(but-3′-enyl)-2-oxocyclohexane-1-carboxylate 9

A solution of ethyl 2-oxocyclohexane-1-carboxylate **8** (5.58 g, 32.8 mmol) in dry THF (10 mL) was added dropwise to a suspension of sodium hydride (1.56 g, 65.0 mmol) in dry THF (100 mL) at 0 °C. *n*-BuLi (21.0 mL, 52.5 mmol, 2.5 M solution in hexane) was added dropwise to the reaction mixture which was stirred for 25 min followed by the addition of a solution of 4-bromobut-1-ene (4.43 g, 32.8 mmol) in dry THF (5 mL). Stirring was continued at 0 °C for 2 h then at room temperature for 20 h. The reaction mixture was quenched with distilled water (20 mL) and the solvent removed at reduced pressure to afford an orange oil. Saturated ammonium chloride solution (150 mL) was added to the resulting crude oil and the organic material extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were dried over anhydrous sodium sulfate and the solvent was removed at reduced pressure to afford a dark orange oil. Purification by flash chromatography (19 : 1 hexane–ethyl acetate) afforded the title compound **9** (6.10 g, 83%) as a yellow oil for which the ^{1}H NMR data were in agreement with the literature.[17]

Ethyl (1*R**,5*S**)-5-(but-3′-enyl)-3-ethyl-9-oxo-3-azabicyclo-[3.3.1]nonane-1-carboxylate 10

A mixture of ethyl 3-(but-3′-enyl)-2-oxocyclohexane-1-carboxylate **9** (1.01 g, 4.50 mmol), ethylamine (674 mg, 4.48 mmol, 30% aq. v/v) and formaldehyde (750 mg, 8.99 mmol, 36% aq. v/v) in ethanol (60 mL) was heated under reflux for 24 h. After removal of the solvent at reduced pressure, the dark yellow oil was dissolved in ether (70 mL) and extracted with 2 M hydrochloric acid (3 × 80 mL). The aqueous extract was made basic with 10% sodium hydroxide solution (250 mL) whilst cooling with ice then extracted with ether (3 × 150 mL) and dried over anhydrous sodium sulfate. The solvent was removed at reduced pressure and the resultant yellow oil purified by flash chromatography (9 : 1 hexane–ethyl acetate) to afford the *title compound* **10** (546 mg, 41%) as a pale yellow oil (Found: C, 69.4; H, 9.2; N, 4.8. $C_{17}H_{27}NO_3$ requires C, 69.6; H, 9.3; N, 4.8%); ν_{max} (NaCl)/cm^{-1} 1736 (C=O, ester) and 1718 (C=O, ketone), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.09 (3H, t, *J* 7.2, NCH_2CH_3), 1.28 (3H, t, *J* 7.2, OCH_2CH_3), 1.41–2.22 (6H, m, 6-CH_2, 7B-H, 8B-H, 1′-CH_2), 2.26–2.29 (1H, m, 2′B-H), 2.39 (2H, q, *J* 7.2, NCH_2CH_3), 2.48–2.56 (2H, m, 8A-H, 2′A-H), 2.55 (1H, dd, $J_{4B,2B}$ 1.7, J_{gem} 11.0, 4B-H), 2.86–2.98 (2H, m, 2B-H, 7A-H), 3.05 (1H, dd, $J_{4A,2A}$ 2.2, J_{gem} 11.0, 4A-H), 3.18 (1H, dd, $J_{2A,4A}$ 2.2, J_{gem} 11.3, 2A-H), 4.20 (2H, q, *J* 7.2, OCH_2CH_3), 4.92 (1H, dd, J_{gem} 1.4, $J_{4′B,3′}$ 10.1, 4′B-H), 5.01 (1H, dd, J_{gem} 1.4, $J_{4′A,3′}$ 17.1, 4′A-H), 5.74–5.85 (1H, m, 3′-H); δ_C (100 MHz, $CDCl_3$) 13.3 (CH_3, NCH_2CH_3), 14.8 (CH_3, OCH_2CH_3), 21.2 (CH_2, C-7), 28.4 (CH_2, C-1′), 34.7 (CH_2, C-6), 37.7 (CH_2, C-8), 39.8 (CH_2, C-2′), 49.8 (quat., C-5), 51.2 (CH_2, NCH_2CH_3), 59.7 (quat., C-1), 61.7 (CH_2, OCH_2CH_3), 62.5 (CH_2, C-4), 65.4 (CH_2, C-2), 114.9 (CH_2, C-4′), 139.6 (CH, C-3′), 172.1 (quat., OC=O), 213.7 (quat., C-9); *m*/*z* (EI) 293 (M^+, 4), 278 (M − CH_3, 5), 252 (100), 238 (M − C_4H_7, 6). Found M^+, 293.1979. $C_{17}H_{27}NO_3$ requires M^+, 293.1991.

Ethyl (1*S**,5*S**)-5-(but-3′-enyl)-3-ethyl-9-methylidene-3-aza-bicyclo[3.3.1]nonane-1-carboxylate 7

n-BuLi (3.0 mL, 5.13 mmol, 1.7 M solution in hexane) was added dropwise to a suspension of methyltriphenylphosphonium bromide (2.44 g, 6.83 mmol) in dry THF (40 mL) at −78 °C. The reaction mixture was stirred at 0 °C for 10 min then cooled to −78 °C followed by the dropwise addition of a solution of ethyl (1*R**,5*S**)-5-(but-3′-enyl)-3-ethyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate **10** (500 mg, 1.70 mmol) in dry THF (10 mL). The reaction mixture was allowed to warm to room temperature then heated under reflux for 24 h. The reaction was quenched with distilled water (5 mL) and the solvent removed at reduced pressure. The residue was dissolved in dry ether (40 mL) and extracted with 2 M hydrochloric acid (3 × 80 mL). The aqueous extract was made basic with 10% sodium hydroxide solution then extracted with ether (3 × 100 mL) and dried over anhydrous sodium sulfate. The solvent was removed at reduced pressure and the resultant dark yellow oil purified by flash chromatography (19 : 1 hexane–ethyl acetate) to afford the *title compound* **7** (420 mg, 85%) as a pale yellow oil. ν_{max}(NaCl)/cm^{-1} 1727 (C=O, ester), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.08 (3H, t, *J* 7.1, NCH_2CH_3), 1.32 (3H, t, *J* 7.1, OCH_2CH_3), 1.40–1.53 (5H, m, 7B-H, 6-CH_2 and 8B-H), 1.88–1.98 (3H, m, 1′-CH_2 and 2′-CH_2), 2.07–2.26 (2H, m, 4B-H and 8A-H), 2.31 (2H, q, *J* 7.1, NCH_2CH_3) 2.59 (1H, dd, $J_{2B,4B}$ 2.1, J_{gem} 10.7, 2B-H), 2.85–2.91 (1H, m, 7A-H), 2.93 (1H, d, J_{gem} 11.2, 4A-H), 3.05 (1H, d, J_{gem} 10.7, 2A-H), 4.22 (2H, q, *J* 7.1, OCH_2CH_3), 4.61 (1H, br s, 10A-H), 4.75 (1H, br s, 10B-H), 4.98 (1H, dd, $J_{4′B,3′}$ 10.1, J_{gem} 1.7, 4′B-H), 5.06 (1H, dd, $J_{4′A,3′}$ 17.1, J_{gem} 1.7, 4′A-H), 5.80–5.90 (1H, m, 3′-H); δ_C (100 MHz, $CDCl_3$) 13.2 (CH_3, NCH_2CH_3), 14.9 (CH_3, OCH_2CH_3), 21.7 (CH_2, C-7), 28.4 (CH_2, C-1′), 36.7 (CH_2, C-6), 38.4 (CH_2, C-8), 38.7 (CH_2, C-2′), 40.7 (quat., C-5), 52.6 (quat., C-1), 52.8 (CH_2, NCH_2CH_3), 61.1 (CH_2, OCH_2CH_3), 62.9 (CH_2, C-4), 65.3 (CH_2, C-2), 103.7 (CH_2, C-10), 114.8 (CH_2, C-4′), 140.0 (CH, C-3′), 155.4 (quat., C-9) and 175.5 (quat., OC=O); *m*/*z* (EI) 291 (M^+, 5), 276 (M − CH_3, 9), 262 (M − C_2H_5, 10), 218 (M − $C_2H_5CO_2$, 19) and 58 (100). Found M^+, 291.2217. $C_{18}H_{29}NO_2$ requires M^+, 291.2198.

Ethyl (1*R**,5*S**)-3-ethyl-9-oxo-5-(3′-oxobutyl)-3-azabicyclo-[3.3.1]nonane-1-carboxylate 12

A mixture of copper(I) chloride (445 mg, 4.50 mmol) and palladium(II) chloride (133 mg, 0.750 mmol) in DMF (10 mL) and water (2 mL) was stirred vigorously until the initially brownish solution became green (approximately 2 h). A solution of ethyl (1*R**,5*S**)-5-(but-3′-enyl)-3-ethyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate **10** (1.10 g, 3.75 mmol) in DMF (5 mL) was then added and oxygen was bubbled through the mixture with stirring for 18 h. After this time water (100 mL) was added and the mixture extracted with ethyl acetate (5 × 100 mL). The combined organic extracts were washed with brine (3 × 100 mL) then dried ($MgSO_4$) and the solvent removed *in vacuo* to leave the crude product. Purification by flash chromatography (4 : 1 hexane–ethyl acetate) afforded the *title compound* **12** (449 mg, 39%) as an orange oil. ν_{max}(NaCl)/cm^{-1} 1732 (C=O, ester) and 1715 (C=O, ketones); δ_H (200 MHz, $CDCl_3$) 1.04 (3H, t, *J* 7.1, NCH_2CH_3), 1.23 (3H, t, *J* 7.1, OCH_2CH_3), 1.37–1.82 (5H, m, 1′-CH_2, 6-CH_2 and 7B-H), 1.94–2.06 (1H, m, 8B-H), 2.09 (3H, s, $COCH_3$), 2.12–2.27 (2H, m, 2′-CH_2), 2.35 (2H, q, *J* 7.1, NCH_2CH_3), 2.40–2.55 (2H, m, 4B-H and 8A-H), 2.75–2.90 (2H, m, 2B-H and 7A-H), 2.94 (1H, dd, $J_{4A,2A}$ 2.1, J_{gem}, 11.3, 4A-H), 3.21 (1H, dd, $J_{2A,4A}$ 2.1, J_{gem}, 11.3, 2A-H) and

4.15 (2H, q, *J* 7.1, OCH_2CH$_3$); δ_C (50 MHz, $CDCl_3$) 12.5 (CH_3, NCH$_2$CH_3), 14.0 (CH_3, OCH$_2$CH_3), 20.2 (CH_2, C-7), 28.4 (CH_2, C-1′), 29.7 (CH_3, C-4′), 36.7 (CH_2, C-6), 38.3 (CH_2, C-8), 39.4 (CH_2, C-2′), 48.7 (quat., C-5), 51.0 (CH_2, NCH_2CH$_3$), 58.8 (quat., C-1), 61.0 (CH_2, OCH_2CH$_3$), 61.6 (CH_2, C-4), 64.7 (CH_2, C-2), 171.1 (quat., OC=O), 208.5 (quat., C-3′) and 212.9 (quat., C-9); *m*/*z* (EI) 309 (M^+, 23%), 266 (M − CH_3CO, 21), 252 (M − C_3H_5O, 98), 238 (M − C_4H_7O, 13) and 43 (CH_3CO, 100). Found M^+, 309.1958. $C_{17}H_{27}NO_4$ requires M^+, 309.1940.

Ethyl (1*R**,7*S**)-9-ethyl-4-oxo-9-azatricyclo[5.3.3.0^{1,6}]tridec-5-ene-7-carboxylate 13

To a solution of potassium hydroxide (0.524 g, 9.33 mmol) in ethanol (25 mL) was added a solution of ethyl (1*R**,5*S**)-3-ethyl-9-oxo-5-(3′-oxobutyl)-3-azabicyclo[3.3.1]nonane-1-carboxylate **12** (0.723 g, 2.33 mmol) in ethanol (25 mL) and the mixture stirred for 1.5 h at room temperature. After this time brine (20 mL) was added and the solution diluted with water (100 mL). The aqueous solution was extracted with diethyl ether (3 × 50 mL), the combined organic layers washed with brine (50 mL) then dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. Further purification by flash chromatography (7 : 3 hexane–ethyl acetate) afforded the *title compound* **13** (0.657 g, 96%) as a clear oil. ν_{max}(NaCl)/cm^{-1} 2924 (C–H), 1727 (C=O, ester), 1676 (C=C–C=O), 1617 (C=C), 1457 and 1251; δ_H (200 MHz, $CDCl_3$) 0.98 (3H, t, *J* 7.2, NCH$_2$CH_3), 1.18 (3H, t, *J* 7.1, OCH$_2$CH_3), 1.41–1.49 (1H, m, 12B-H), 1.60–1.95 (5H, m, 2-CH_2, 11-CH_2 and 13B-H), 2.00–2.35 (6H, m, 3-CH_2, 10B-H, 13A-H and NCH_2CH$_3$), 2.55 (1H, dd, $J_{8B,10B}$ 1.9, J_{gem}, 11.0, 8B-H), 2.81 (1H, dd, $J_{10A,8A}$ 1.1, J_{gem}, 11.8, 10A-H), 2.82–2.97 (1H, m, 12A-H), 3.00 (1H, dd, $J_{8A,10A}$ 1.1, J_{gem}, 11.0, 8A-H), 4.09 (2H, q, *J* 7.1, OCH_2CH$_3$) and 5.55 (1H, br s, 5-H); δ_C (50 MHz, $CDCl_3$) 12.2 (CH_3, NCH$_2$CH_3), 13.9 (CH_3, OCH$_2$CH_3), 20.3 (CH_2, C-12), 32.8 (CH_2, C-2), 33.1 (CH_2, C-11), 36.5 (CH_2, C-3), 37.3 (quat., C-1), 38.1 (CH_2, C-13), 51.3 (CH_2, NCH_2CH$_3$), 51.8 (quat., C-7), 60.8 (CH_2, OCH_2CH$_3$), 61.1 (CH_2, C-10), 66.0 (CH_2, C-8), 120.3 (CH, C-5), 167.7 (quat., C-6), 172.4 (quat., OC=O) and 198.7 (quat., C-4); *m*/*z* (EI) 291 (M^+, 65%), 276 (M − CH_3, 60), 262 (M − CH_2CH_3, 61), 218 (M − $CO_2C_2H_5$, 44) and 58 (100). Found M^+, 291.1827. $C_{17}H_{25}NO_3$ requires M^+, 291.1834.

Ethyl (1*R**,7*S**)-9-ethyl-4-hydroxy-9-azatricyclo[5.3.3.0^{1,6}]-tridec-5-ene-7-carboxylate 14

To a solution of sodium borohydride (86 mg, 2.27 mmol) in THF (3 mL) and water (7 mL) was added a solution of ethyl (1*R**,7*S**)-9-ethyl-4-oxo-9-azatricyclo[5.3.3.0^{1,6}]tridec-5-ene-7-carboxylate **13** (0.657 g, 2.25 mmol) in THF (4 mL) and the mixture stirred for 8 h. After this time the reaction was quenched by the addition of water (20 mL) and the volatiles were removed *in vacuo*. The remaining aqueous solution was extracted with ethyl acetate (3 × 30 mL), the combined organic layers washed with brine (50 mL) then dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography (7 : 3 hexane–ethyl acetate) to give the *title compound* **14** (0.535 g, 81%) as a clear oil and as a 2.3 : 1 inseparable mixture of isomers. ν_{max}(NaCl)/cm^{-1} 3354 (O–H), 2931 (C–H), 1726 (C=O, ester), 1661 (C=C), 1451 and 1253; δ_H (200 MHz, $CDCl_3$) 1.02 (3H, t, *J* 7.2, NCH$_2$CH_3), 1.26 (3H, t, *J* 7.1, OCH$_2$CH_3), 1.38–1.59 (5H, m, 2-CH_2, 11B-H, 12B-H and 13B-H), 1.64–1.96 (4H, m, 3-CH_2, 11A-H and 13A-H), 2.13 (1H, dd, $J_{10B,8B}$ 2.0, J_{gem}, 10.3, 10B-H), 2.24 (2H, q, *J* 7.2, NCH_2CH$_3$), 2.51 (1H, dd, $J_{8B,10B}$ 2.0, J_{gem}, 10.8, 8B-H), 2.74 (1H, d, J_{gem}, 10.3, 10A-H), 2.79–2.92 (1H, m, 12A-H), 2.99 (1H, d, J_{gem}, 10.8, 8A-H), 4.07–4.11 (2H, m, 4-H and OH), 4.16 (2H, q, *J* 7.1, OCH_2CH$_3$), 5.22 (0.7H, d, $J_{5,4}$ 2.2, 5-H) and 5.31* (0.3H, d, $J_{5,4}$ 3.9, 5-H); δ_C (50 MHz, $CDCl_3$) 12.4 (CH_3, NCH$_2$CH_3), 14.1 (CH_3, OCH$_2$CH_3), 20.9 (CH_2, C-12), 28.3 (CH_2, C-2), 32.4 (CH_2, C-11), 34.2 (CH_2, C-3), 36.2 (quat., C-1), 38.8 (CH_2, C-13), 38.9 (quat., C-7), 51.8 (CH_2, NCH_2CH$_3$), 60.5 (CH_2, OCH_2CH$_3$), 61.9 (CH_2, C-10), 66.9 (CH_2, C-8), 67.1 (CH, C-4), 67.3* (CH, C-4), 119.6* (CH, C-5), 120.9 (CH, C-5), 145.2 (quat., C-6) and 179.6 (quat., OC=O); *m*/*z* (EI) 293 (M^+, 40%), 278 (M − CH_3, 78), 264 (M − CH_2CH_3, 14), 220 (M − $COOC_2H_5$, 42) and 42 (100). Found M^+, 293.1993. $C_{17}H_{27}NO_3$ requires M^+, 293.1991.

Ethyl (1*R**,7*S**)-9-ethyl-4-methoxy-9-azatricyclo[5.3.3.0^{1,6}]-tridec-5-ene-7-carboxylate 15

To a suspension of sodium hydride (219 mg, 60% in oil, 5.48 mmol) in dry THF (20 mL) at 0 °C was added a solution of ethyl (1*R**,7*S**)-9-ethyl-4-hydroxy-9-azatricyclo[5.3.3.0^{1,6}]tridec-5-ene-7-carboxylate **14** (535 mg, 1.82 mmol) in dry THF (5 mL). The mixture was then stirred for 1 h after which time iodomethane (776 mg, 0.34 mL, 5.47 mmol) was added and the mixture stirred at room temperature for 20 h. The reaction was quenched by the careful addition of sat. ammonium chloride solution (20 mL). The volatile solvents were removed *in vacuo* and the remaining aqueous mixture was diluted with water (50 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (50 mL) then dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product which was purified by flash chromatography (7 : 3 hexane–ethyl acetate) to give the *title compound* **15** (484 mg, 86%) as a clear oil and as a 2.3 : 1 inseparable mixture of isomers. ν_{max}(NaCl)/cm^{-1} 2932 (C–H), 1727 (C=O, ester), 1661 (C=C), 1453 and 1252; δ_H (200 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.1, NCH$_2$CH_3), 1.12 (3H, t, *J* 7.0, OCH$_2$CH_3), 1.27–1.48 (5H, m, 2-CH_2, 11B-H, 12B-H and 13B-H), 1.56–1.88 (4H, m, 3-CH_2, 11A-H and 13A-H), 2.09 (2H, q, *J* 7.1, NCH_2CH$_3$), 2.28 (1H, d, J_{gem}, 10.5, 10B-H), 2.43 (1H, d, J_{gem}, 10.8, 8B-H), 2.60 (1H, d, J_{gem}, 10.5, 10A-H), 2.63–2.79 (1H, m, 12A-H), 2.84 (1H, d, J_{gem}, 10.8, 8A-H), 3.16 (2.1H, s, OCH_3), 3.17* (0.9H, s, OCH_3), 3.54–3.58 (1H, m, 4-H), 4.01 (2H, q, *J* 7.0, OCH_2CH$_3$), 5.15 (0.7H, br s, 5-H) and 5.21* (0.3H, d, $J_{5,4}$ 3.6, 5-H); δ_C (50 MHz, $CDCl_3$) 12.2 (CH_3, NCH$_2$CH_3), 13.9 (CH_3, OCH$_2$CH_3), 20.7 (CH_2, C-12), 23.9 (CH_2, C-2), 32.1 (CH_2, C-11), 35.1 (quat., C-1), 35.6 (CH_2, C-3), 38.7 (CH_2, C-13), 39.0 (quat., C-7), 51.6 (CH_2, NCH_2CH$_3$), 55.2 (CH_3, OCH_3), 55.6* (CH_3, OCH_3), 60.0 (CH_2, OCH_2CH$_3$), 61.8 (CH_2, C-10), 66.7 (CH_2, C-8), 73.9 and 75.4* (CH, C-4), 117.0* (CH, C-5), 117.9 (CH, C-5), 145.1 (quat., C-6) and 173.7 (quat., OC=O); *m*/*z* (EI) 307 (M^+, 29%), 292 (M − CH_3, 44), 278 (M − CH_2CH_3, 22), 276 (M − OCH_3, 34), 234 (M − $COOC_2H_5$, 42) and 29 (CH_3CH_2, 100). Found M^+, 307.2143. $C_{18}H_{29}NO_3$ requires M^+, 307.2147.

(1*R**,7*S**)-(9-Ethyl-4-methoxy-9-azatricyclo[5.3.3.0^{1,6}]tridec-5-en-7-yl)methanol 16

To a slurry of lithium aluminium hydride (109 mg, 2.87 mmol) in dry THF (20 mL) at 0 °C, was slowly added a solution of ethyl (1*R**,7*S**)-9-ethyl-4-methoxy-9-azatricyclo[5.3.3.0^{1,6}]tridec-5-ene-7-carboxylate **15** (442 mg, 1.44 mmol) in dry THF (20 mL) and the mixture stirred under an atmosphere of nitrogen for 30 min. The reaction was quenched by the slow addition of water (30 mL) and the volatiles removed *in vacuo*. The remaining aqueous mixture was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers washed with brine (40 mL) then dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. Further purification by flash chromatography (1 : 1 hexane–ethyl acetate) afforded the *title compound* **16** (329 mg, 86%) as a clear oil and as a 2.3 : 1 inseparable mixture of isomers. ν_{max}(NaCl)/cm^{-1} 3445 (O–H), 2929 (C–H), 1654 (C=C), 1452 and 1084; δ_H (200 MHz, $CDCl_3$) 0.92 (3H, t, *J* 7.1, NCH$_2$CH_3), 1.28–1.64 (7H, m, 2-CH_2, 11-CH_2, 12B-H and 13-CH_2), 1.70–1.82 (3H, m, 3-CH_2, 10B-H), 2.11 (2H, q, *J* 7.2, NCH_2CH$_3$), 2.64 (1H, d, J_{gem}, 10.4, 8B-H), 2.71–2.82 (2H, m, 10A-H and 12A-H), 2.89 (1H, d, J_{gem}, 10.4, 8A-H), 3.11 (1H,

brs, OH), 3.22 (2.1H, s, OCH_3), 3.24* (0.9H, s, OCH_3), 3.37 (1H, d, J_{gem} 11.1, CH_AH$_B$OH), 3.44 (1H, d, J_{gem}, 11.1, CH$_A$-H_BOH), 3.57–3.70 (1H, m, 4-H), 5.20 (0.7H, d, $J_{5,4}$ 1.5, 5-H) and 5.28* (0.3H, d, $J_{5,4}$ 3.8, 5-H); δ_C (50 MHz, $CDCl_3$) 12.5 (CH_3, NCH$_2$*C*H$_3$), 20.7 (CH_2, C-12), 23.9 (CH_2, C-2), 31.5 (CH_2, C-11), 35.6 (quat., C-1), 36.2 (CH_2, C-3), 39.0 (quat., C-7), 41.3 (CH_2, C-13), 51.8 (CH_2, N*C*H$_2$CH$_3$), 55.3 (CH_3, OCH_3), 55.4* (CH_3, OCH_3), 62.1 (CH_2, C-10), 67.9 (CH_2, C-8), 74.4 (CH_2, OCH_2), 75.9 (CH, C-4), 76.3* (CH, C-4), 114.5* (CH, C-5), 115.7 (CH, C-5), 147.8 (quat., C-6) and 149.3* (quat., C-6); *m*/*z* (EI) 265 (M^+, 1%), 250 (M − CH_3, 9), 234 (M − OCH_3, 10) and 72 (100). Found M^+, 265.1974. $C_{16}H_{26}NO_2$ requires M^+, 265.1964.

(1′*R**,7′*S**)-(9-Ethyl-4-methoxy-9-azatricyclo[5.3.3.0^{1,6}]tridec-5-en-7-yl)methyl 2-aminobenzoate 17

To a mixture of alcohol **16** (70 mg, 0.264 mmol), *N*-(trifluoroacetyl)anthranilic acid[26,27] (246 mg, 1.06 mmol) and 4-(dimethylamino)pyridine (32 mg, 0.262 mmol) in acetonitrile (5 mL) was added 1,3-dicyclohexylcarbodiimide (217 mg, 1.05 mmol) and the mixture stirred, under an atmosphere of nitrogen, at 40 °C for 24 h. After this time the mixture was cooled, filtered and the filtrate evaporated to dryness. The crude mixture was then dissolved in dichloromethane (20 mL), washed with aq. sodium bicarbonate (20 mL) and brine (20 mL) then dried ($MgSO_4$) and concentrated *in vacuo* to leave the crude *N*-(trifluoroacetyl)anthranilate ester. This residue was suspended in absolute ethanol (10 mL), sodium borohydride (50 mg, 1.32 mmol) added, and the mixture stirred for 2 h. The reaction was quenched by the addition of water and the volatile solvent removed *in vacuo*. The remaining aqueous solution was extracted with ethyl acetate (2 × 30 mL) and the combined organic layers washed with brine (50 mL) then dried ($MgSO_4$) and concentrated *in vacuo* to leave the crude product, which was purified by flash chromatography using 7 : 3 hexane–ethyl acetate as eluent to afford the *title compound* **17** (78 mg, 77%) as a yellow oil and as a 2.3 : 1 inseparable mixture of isomers. ν_{max}(NaCl)/cm^{-1} 3474 and 3370 (N–H), 2929 (C–H), 1689 (C=O), 1617, 1589, 1453, 1244 and 1099; δ_H (200 MHz, $CDCl_3$) 1.04 (3H, t, *J* 7.2, NCH$_2$C*H*$_3$), 1.28–1.69 (8H, m, 2′-CH_2, 3′-CH_2, 11′-CH_2, 12′B-H and 13′B-H), 1.81 (1H, d, J_{gem} 11.2, 10′B-H), 2.00 (2H, q, *J* 7.2, NC*H*$_2$CH$_3$), 2.10–2.28 (2H, m, 10′A-H and 13′A-H), 2.80 (1H, d, J_{gem}, 10.4, 8′B-H), 2.84–3.04 (1H, m, 12′A-H), 3.06 (1H, d, J_{gem}, 10.4, 8′A-H), 3.34 (2.1H, s, OCH_3), 3.37* (0.9H, s, OCH_3), 3.70–3.85 (1H, m, 4′-H), 4.21 (2H, br s, OCH_2), 5.42 (0.7H, d, $J_{5',4'}$ 1.9, 5′-H), 5.50* (0.3H, d, $J_{5',4'}$ 3.9, 5′-H), 5.73 (2H, brs, NH_2), 6.60–6.68 (2H, m, 3-H and 5-H), 7.26 (1H, td, *J* 7.4, 1.9, 4-H) and 7.84 (1H, dd, *J* 1.4, 8.1, 6-H); δ_C (50 MHz, $CDCl_3$) 12.5 (CH_3, NCH$_2$*C*H$_3$), 21.0 (CH_2, C-12′), 24.3 (CH_2, C-2′), 32.3 (CH_2, C-11′), 36.4 (CH_2, C-3′), 36.5 (quat., C-1′), 39.2 (CH_2, C-13′), 40.7 (quat., C-7′), 52.0 (CH_2, N*C*H$_2$CH$_3$), 55.7 (CH_3, OCH_3), 55.8* (CH_3, OCH_3), 62.8 (CH_2, C-10′), 67.3 (CH_2, C-8′), 67.7 (CH_2, OCH_2), 74.4* (CH, C-4′), 76.0 (CH, C-4′), 110.2 (quat., C-1), 115.3* (CH, C-5′), 116.2 (CH, C-5′), 116.4 (CH, C-3), 116.6 (CH, C-5), 131.1 (CH, C-6), 134.0 (CH, C-4), 149.3 (quat., C-6′), 150.5 (quat., C-2) and 166.9 (quat., OC=O); *m*/*z* (EI) 384 (M^+, 37%), 369 (M − CH_3, 29), 353 (M − OCH_3, 27), 264 (M − $NH_2C_6H_4CO$, 56), 248 (M − $NH_2C_6H_4CO_2$, 57), 120 (C_7H_6NO, 69) and 72 (100). Found M^+, 384.2419. $C_{23}H_{32}N_2O_3$ requires M^+, 384.2413.

(1″*R**,7″*S**,3′*R**)- and (1″*R**,7″*S**,3′*S**)-(9-Ethyl-4-methoxy-9-aza-tricyclo[5.3.3.0^{1,6}]tridec-5-en-7-yl)methyl 2-(3-methyl-2,5-dioxopyrrolidin-1-yl)benzoate 18

Anthranilate ester **17** (72 mg, 0.187 mmol) and 2-methylsuccinic anhydride (64 mg, 0.561 mmol) were heated together at 125 °C for 36 h. After this time the crude mixture was dissolved in warm ethyl acetate (10 mL), washed with sat. sodium bicarbonate solution (30 mL) and brine (30 mL) then dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography using 3 : 2 hexane–ethyl acetate as eluent to afford the *title compound* **18** (45 mg, 50%) as a yellow oil and as a mixture of isomers. ν_{max}(NaCl)/cm^{-1} 2931 (C–H), 1781 (N–C=O), 1716 (C=O), 1602, 1493, 1454, 1391, 1259 and 1186; δ_H (200 MHz, $CDCl_3$) 1.03 (3H, t, *J* 7.1, NCH$_2$C*H*$_3$), 1.20–1.35 (2H, m, 11″B-H and 12″B-H), 1.35–1.74 (9H, m, 3′-CH_3, 2″-CH_2, 3″-CH_2, 11″A-H and 13″-H), 1.79 (1H, d, J_{gem} 11.2, 10″B-H), 1.96 (2H, q, *J* 7.2, NC*H*$_2$CH$_3$), 2.13–2.29 (2H, m, 10″A-H and 13″A-H), 2.45–2.68 (1H, m, 3′-H), 2.79 (1H, d, J_{gem} 10.3, 8″B-H), 2.83–3.09 (4H, br m, 4′-CH_2, 8″A-H and 12″A-H), 3.33 (2.1H, s, OCH_3), 3.36* (0.9H, s, OCH_3), 3.68–3.81 (1H, m, 4″-H), 4.12 (2H, br s, OCH_2), 5.36 (0.7H, d, $J_{5'',4''}$ 2.0, 5″-H), 5.43* (0.3H, d, $J_{5'',4''}$ 3.9, 5″-H), 7.24 (1H, dd, *J* 1.1, 7.7, 3-H), 7.51 (1H, td, *J* 7.8, 1.4, 5-H), 7.65 (1H, td, *J* 7.7, 1.7, 4-H) and 8.08 (1H, dd, *J* 1.6, 7.8, 6-H); δ_C (50 MHz, $CDCl_3$) 12.5 (CH_3, NCH$_2$*C*H$_3$), 16.3 (CH_3, 3′-*C*H$_3$), 20.9 (CH_2, C-12″), 24.3 (CH_2, C-2″), 32.2 (CH_2, C-11″), 35.2 (CH, C-3′), 36.2 (quat., C-1″), 36.5 (quat., C-3″), 36.9 (CH_2, C-4′), 39.1 (CH_2, C-13″), 40.7 (quat., C-7″), 52.0 (CH_2, N*C*H$_2$CH$_3$), 55.7 (CH_3, OCH_3), 55.9* (CH_3, OCH_3), 62.6 (CH_2, C-10″), 67.2 (CH_2, C-8″), 70.5 (CH_2, OCH_2), 74.3* (CH, C-4″), 75.9 (CH, C-4″), 115.4* (CH, C-5″), 116.5 (CH, C-5″), 127.2 (quat., C-1), 129.3 (CH, C-5), 129.8 (CH, C-3), 131.4 (CH, C-6), 132.8 (quat., C-2), 133.3 (CH, C-4), 147.0 (quat., C-6″), 148.5* (quat., C-6″), 164.2 (quat., OC=O), 175.8 (quat., C-5′) and 179.9 (quat., C-2′); *m*/*z* (EI) 480 (M^+, 26%), 449 (M − OCH_3, 26), 264 (M − $C_{12}H_{10}O_3N$, 67), 248 (M − $C_{12}H_{10}O_4N$, 61) and 72 (100). Found M^+, 480.2619. $C_{28}H_{36}N_2O_5$ requires M^+, 480.2624.

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