Tetrahedron 66 (2010) 7179–7191

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A double Mannich approach to the synthesis of substituted piperidones—application to the synthesis of substituted E-ring analogues of methyllycaconitine

Yinman Chan, Jared Balle, J. Kevin Sparrow, Peter D.W. Boyd, Margaret A. Brimble, David Barker *

Department of Chemistry, University of Auckland, 23 Symonds St, Auckland, New Zealand

ARTICLE INFO

Article history:
Received 22 April 2010
Received in revised form 14 June 2010
Accepted 28 June 2010
Available online 3 July 2010

Keywords:
Mannich reaction
4-Piperidones
Multicomponent reaction
Methyllycacontine

ABSTRACT

The double Mannich reaction of acyclic α,γ-substituted β-keto esters and bis(aminol) ethers gives substituted 3,5-substituted-4-piperidones with high levels of diastereoselectivity. These piperdiones can be easily transformed into substituted E-ring analogues of the delphinium alkaloid methyllycacotine.

1. Introduction

Methyllycaconitine **1** is the major toxic component in *Delphinium brownii* and was first discovered by Manske in 1938.[1] The methyllycaconitine **1** core structure contains a piperidine (E) ring and a 2-[2-(*S*)-methylsuccinimido]benzoate ester, which together are believed to form a homocholine motif, which mimics the endogenous ligand, acetylcholine.[2] The primary mode of action of methyllycaconitine **1** is via competitive blockade at the nicotinic acetylcholine receptors (nAChRs). Structure-activity studies on methyllycaconitine **1** have shown that both a tertiary amine in the piperidine E-ring and the *N*-substituted anthranilate ester moiety are essential for potent pharmacological activity.[2,3] Many groups,[4] including our own, have synthesised analogues of these alkaloids with some groups focussing specifically on the synthesis of piperidine E-ring analogues **2** (Fig. 1).[5] There are, however, very few examples of poly substituted piperidine E-ring analogues[5,6] with most focussing on altering the aromatic anthranilate moiety and the *N*-substituent on a mono-substituted piperidine ring. Functionalised piperidines and piperidones are also important intermediates in the synthesis of numerous other bioactive alkaloids and pharmaceuticals.[7]

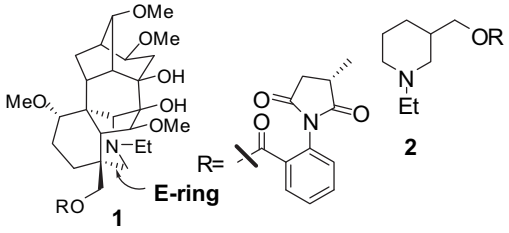


Figure 1. Methyllycaconitine (**1**) and typical E-ring analogue **2**.

There are few methods for the synthesis of 3,4,5-substituted piperidines,[8] with many recent strategies for the synthesis of substituted piperidines aimed particularly at the synthesis of 2-substitued[9] and 2,4- and 2,6-disubstitued[10] piperidines. We herein report the synthesis of substituted E-ring analogues of methyllycaconitine beginning with a double Mannich reaction of acyclic β-keto esters to form the substituted piperidine ring.

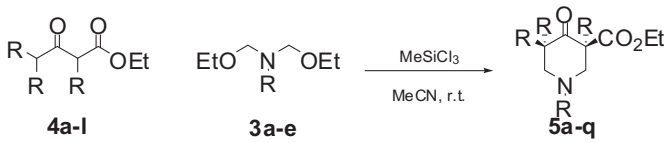
2. Results and discussion

The Lewis-acid catalysed double Mannich reaction of bis-aminol ethers **3** with cyclic β-keto esters[11] and cyclic ketones,[12] to give 3-azabicyclononanes, has been shown to give greatly improved yields when compared to classical double Mannich conditions. When classical, acidic or basic, double Mannich conditions are

* Corresponding author. E-mail address: d.barker@auckland.ac.nz (D. Barker).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.06.084

Table 1
Synthesis of substituted 4-piperidones



4a-l **3a-e** **5a-q**

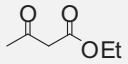
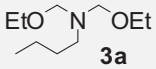
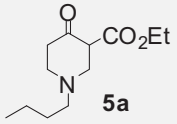
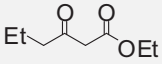
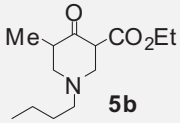
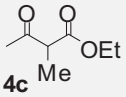
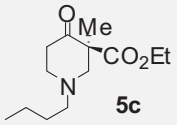
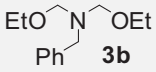
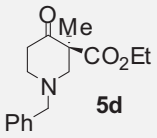
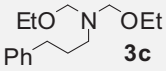
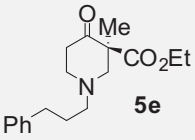
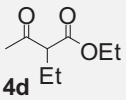
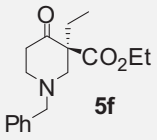
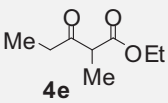
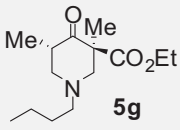
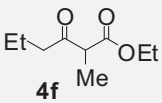
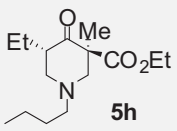
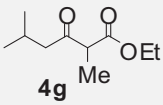
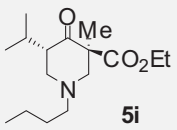
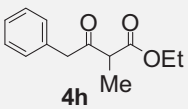
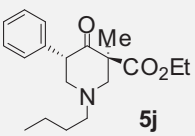
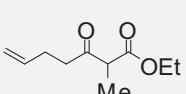
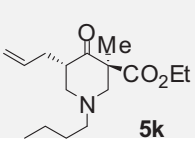
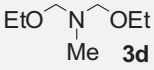
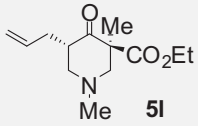
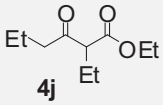
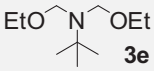
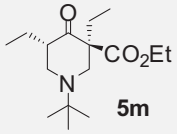
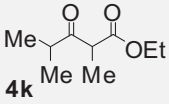
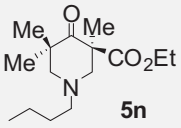
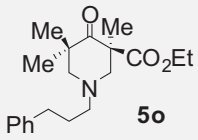
Entry	β-keto ester	Bis(aminol)ether	Product	Yield %
1	 **4a**	 **3a**	 **5a**	0
2	 **4b**	**3a**	 **5b**	0
3	 **4c**	**3a**	 **5c**	90
4	**4c**	 **3b**	 **5d**	82
5	**4c**	 **3c**	 **5e**	86
6	 **4d**	**3b**	 **5f**	85
7	 **4e**	**3a**	 **5g**	60
8	 **4f**	**3a**	 **5h**	63
9	 **4g**	**3a**	 **5i**	65
10	 **4h**	**3a**	 **5j**	88
11	 **4i**	**3a**	 **5k**	76

Table 1 (*continued*)

Entry	β-keto ester	Bis(aminol)ether	Product	Yield %
12	**4i**	 **3d**	 **5l**	80
13	 **4j**	 **3e**	 **5m**	79
14	 **4k**	**3a**	 **5n**	51
15	**4k**	**3c**	 **5o**	59

applied to form piperidones reactions only occur with β,β′-keto diesters and even then occur in low yields.[13] We previously reported[14] that the double Mannich of acyclic β-keto esters proceeds to give 4-piperidones only when there is a substituent at the α-position. When β-keto esters, such as **4a** and **4b**, with two acidic protons at the α-position are employed none of the desired piperidones **5a**/**b** are produced and only polymeric material is obtained (Table 1, entries 1 and 2). However, reaction of ethyl 2-methylacetoacetate **4c** and ethyl 2-ethylacetoacetate **4d** with bis(aminol) ethers **3a**–**c** gives 3,3-disubstituted 4-piperidones **5c**–**f** in 82—90% yields (Table 1, entries 3–6).

In order to prepare E-ring analogues with further substitution required synthesis of α,γ-substituted β-keto esters. Esters **4e** and **4j** were prepared from the Claisen condensation of ethyl propionate and ethyl butyrate, respectively,[15] whilst esters **4f**/**g**/**k** were prepared from the dianion alkylation[16] of **4c**. We found that 2-methyl-4-phenyl substituted ester **4h** was best prepared from the Blaise reaction[17] between benzyl cyanide and ethyl 2-bromopropionate as other methods[18] gave less satisfactory results. The α, γ,γ-trisubstituted β-keto ester **4k** was prepared from the titanium tetrachloride mediated cross-Claisen condensation[19] of isobutyryl chloride and ethyl propionate.

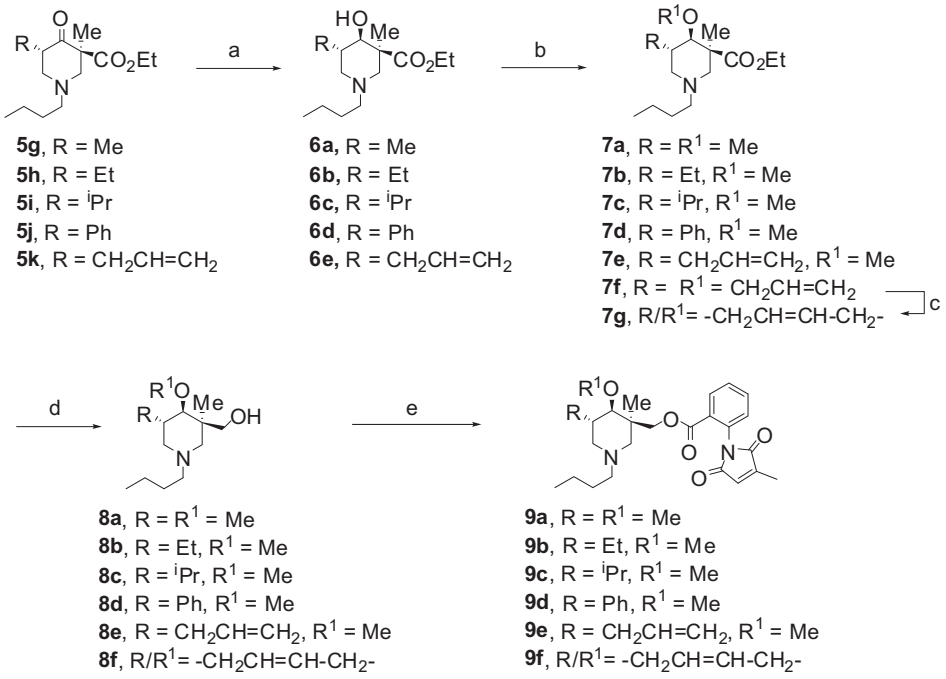
3,3,5-Trisubstituted-4-piperidones **5g**–**m** (Table 1, entries 7–13) were produced in good yields (60–88%) whilst 3,3,5,5-tetrasubstituted-4-piperidones **5n** and **5o** (Table 1, entries 14 and 15) were produced in 51% and 59% yields, respectively. The synthesis of 4-piperidones with a large variety of N-substitution can therefore be achieved by altering the bis(aminol) ethers, which are easily synthesised from a range of primary amines.[11,20] The reaction also accommodates varying sizes of alkyl or aryl substituents on the β-keto ester, with little difference in the yield of the piperidone **5** produced. In all cases trialled only a single diastereoisomer of piperidone **5** was formed and analysis of coupling constants and NOE interactions in the ^{1}H NMR indicated the conformation of these piperidones to have an axial 3-ester group.[14] In the case of 3,3,5-trisubstituted-4-piperidones **5g**–**m**, the 3- and 5- alkyl substituents were both in equatorial positions.[14] The relative stereochemistry of these piperidones was later confirmed when one of the subsequently modified compounds, **8f**, was found to be suitable for X-ray crystallographic analysis (see below).

For the synthesis of E-ring analogues of methyllycacontine we chose to functionalise piperidones **5c**, **5g**–**k** and **5n**, which all have the same *N*-butyl substituent, with altered substitution at the 5-position in the piperidine ring. Our route from piperidones to E-ring analogues of methyllycacontine began with reduction of the ketone with $NaBH_4$ to give piperidols **6**. In the case of 3,3,5-trisubstituted-4-piperidones **5g**–**k** the reduction was completely stereoselective giving piperidols **6a**–**e** in 93–98% yield (Scheme 1). The 4-hydroxy group in piperidols **6a**–**e** was *syn* to the 3-ethoxycarbonyl group, resulting from axial hydride attack, antiperiplanar to the axial ester group.[21] Reduction of the disubstituted piperidones **5c** and tetrasubstituted piperidones **5n** was not stereoselective, giving a 2:1 and 1:1 inseparable mixtures of diastereomers, respectively. We therefore decided to abandon working with these mixtures and carry on with only piperidols **6a**–**e**.[22]

With piperidols **6a**–**e** in hand, the next step was to methylate the 4-hydroxy group, using NaH and three equivalents of iodomethane in THF, to give methyl ethers **7a**–**e** in 68–94% yields. Extended reactions times of 3 days were required and we found the use of a sealed tube significantly increased the yield of the desired ether **7a**–**e**, whilst heating the reaction or adding further equivalents of iodomethane both led to reduced yields.

5-Allylpiperidol **6e** was also alkylated with allyl bromide, using the same conditions, to give allyl ether **7f** in 71% yield. Ring closing metathesis of diene **7f**, using the 10 mol % of first generation Grubbs' catalyst in DCM, gave piperidine **7g** in 64% yield. Piperidine **7g** contains an appended seven-membered ether ring, which also mimics sections of the B and F rings of methyllycacontine.

Lithium aluminium hydride reduction of ethyl esters **7a**–**e**,**g** afforded neopentyl-like alcohols **8a**–**f** in 92–98% yields. After purification bicyclic alcohol **8f** solidified to give crystals suitable for X-ray crystallographic analysis (Fig. 2). The crystal structure shows a trans-fused seven-membered ring and a *syn* arrangement between the 3-methyl and 5-substituent, thus confirming the



Scheme 1. Synthesis of substituted E-ring analogues of methyllycaconitine. Reagents: (a) $NaBH_4$, 1:1 THF/H_2O; **6a** 98%, **6b** 94%, **6c** 98%, **6d** 98%, **6e** 93%; (b) NaH, THF 1 h then, for **7a**–**7e** MeI and for **7f** CH_2=$CHCH_2Br$; **7a** 68%, **7b** 94%, **7c** 79%, **7d** 93%, **7e** 87%, **7f** 81%; (c) 10 mol % first generation Grubbs' catalyst, DCM, 64%; (d) $LiAlH_4$, THF, **8a** 98%, **8b** 95%, **8c** 92%, **8d** 94%, **8e** 96%, **8f** 98%; (e) 2-(2-methyl maleimido)benzoate acid, DCC, DMAP, MeCN, **9a** 57%, **9b** 62%, **9c** 55%, **9d** 74%, **9e** 77%, **9f** 64%.

stereoselectivity of both the double Mannich reaction and ketone reduction. Esterification of alcohols **8a**–**f** with 2-(2-methyl maleimido)benzoate acid using our previously reported conditions[23] afforded esters **9a**–**f** in 55–77% yields. Overall, use of this four-step sequence affords substituted E-ring analogues of MLA **9a**–**f** in good yields from piperidones **5i**–**m**.

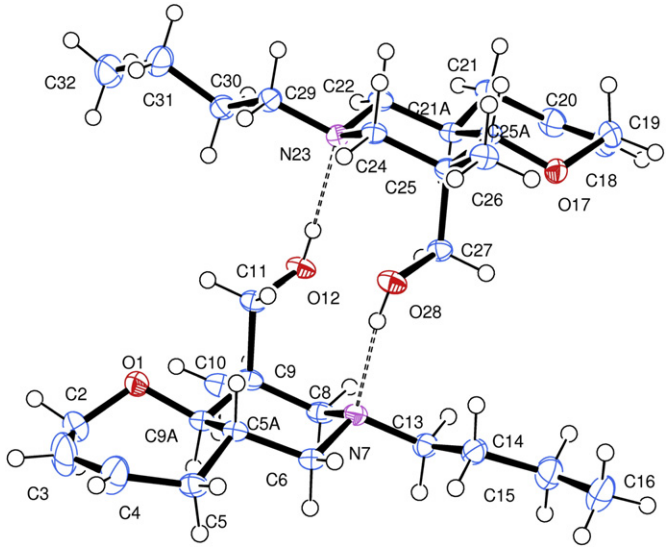


Figure 2. ORTEP diagram, with numbering (50% probability thermal ellipsoids) of **8f**. The major form of the disordered *n*-butyl group –C12 to C16 is shown. Dashed lined indicate the O–H···N hydrogen bonds between the two enantiomers in the asymmetric unit.

3. Conclusion

In summary, the successful syntheses of six substituted E-ring analogues **9a**–**f** of methyllycaconitine **1** have been achieved, with the key step being a stereoselective double Mannich reaction of α, γ-substituted β-keto esters **4** to give 3,3,5-trisubstituted-4-piperidones **5**. These synthetic analogues **9a**–**f** contain the key structural features of methyllycaconitine **1**, namely the presence of a homocholine motif derived from a tertiary amine, embedded within a piperidine ring, together with a benzoate ester side chain and may provide access to more effective inhibitors of nicotinic acetylcholine receptors.

4. Experimental section

4.1. General methods and materials

Reactions were monitored by TLC, using pre-coated silica gel TLC plates obtained from Merck. Flash chromatography was carried out on silica gel (Riedel-de Haën, particle size 0.032–0.063 mm). Retention times (R_f) were determined using the stated solvent mixture for column chromatography. Melting point determinations were performed on an Electrothermal® melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance DRX 300 MHz or 400 MHz spectrometers at ambient temperatures. Chemical shifts δ are expressed in parts per million and coupling constants J are reported in hertz. TMS served as internal standard (δ=0 ppm) for ^{1}H NMR, and $CDCl_3$ served as internal standard (δ=77.0 ppm) for ^{13}C NMR. In addition, ^{1}H–^{1}H-COSY and ^{1}H–^{13}C-HSQC correlation spectra were used for the complete assignment of the proton and carbon resonances. ^{1}H–^{1}H-NOESY NMR spectra were recorded in special cases. The NMR spectroscopic data for the benzoate esters analogues **9a**–**f** of methyllycaconitine were assigned using the following descriptors: piperidine ring system (two primes ″), anthranilate ring (no primes) and methyl maleimido ring (one prime ′). Infrared spectra were recorded on a Perkin–Elmer spectrum one FT-IR spectrometer either as a thin film between NaCl plates or neat on an ATR system and are reported as cm^{-1}. Ethyl acetoacetate **4a**, ethyl 2-methylacetoacetate **4c** and ethyl 2-ethylacetoacetate **4d** were purchased and used without additional purification. The previously reported compounds, ethyl

3-oxohexanoate **4b**, ethyl 2-methyl-3-oxohexanoate **4f** and ethyl 2-methyl-3-oxo-hept-6-enoate **4i** were prepared using general procedure A in 59, 61 and 91% yields, respectively. Ethyl 2-methyl-3-oxopentanoate **4e** and ethyl 2-ethyl-3-oxohexanoate **4j** were prepared using the method of Yoshizawa et.al.[15] Bis(aminol)ethers **3a**–**e**[11,20] and 2-(3-methyl-2,5-dioxo-2,5-dihydropyrrol-1-yl)benzoic acid[24] were prepared using reported methods.

4.2. General procedure A: synthesis of δ-substituted β-keto esters 4

A suspension of sodium hydride (0.44 g, 11 mmol, 60% w/w in oil) in dry THF (20 mL) was cooled to 0 °C and either ethyl acetoacetate or ethyl 2-methylacetoacetate (10 mmol) was added dropwise and the mixture stirred for 25 min. *n*-Butyllithium (1.4 M, 7.5 mL, 10.5 mmol) was added dropwise over a 15 min period then stirred at 0 °C for a further 25 min. A solution of alkylhalide (11 mmol) in dry THF (2 mL) was added dropwise and the resulting solution was stirred at room temperature overnight. The reaction was quenched with aqueous HCl (3.3 M, 6 mL) and diethyl ether (15 mL) added. The organic phase was separated and the aqueous phase was further extracted with diethyl ether (4×8 mL). The combined organic extracts were washed with water until neutral, dried ($MgSO_4$) and solvents were removed under reduced pressure to give the crude product, which was purified by distillation or flash chromatography (hexane, ethyl acetate) to afford the title compound.

*4.2.1. Ethyl 2,5-dimethyl-3-oxohexanoate **4g**.* Prepared using general procedure A from ethyl 2-methylacetoacetate **4c** (40 mmol, 5.77 g) and 2-iodopropane (44 mmol, 7.48 g) with purification by flash chromatography (9:1 hexane, ethyl acetate) to afford the title compound **4h** (4.17 g, 56%) as a pale yellow oil; R_f=0.4; IR (NaCl) ν_{max} 2960, 2874 (CH), 1746 (CO_2R), 1715 (C=O), 1469, 1455, 1367, 1248, 1195; δ_H (300 MHz; $CDCl_3$) 0.89 (6H, dd, J=6.6, 2.1 Hz, CH(CH_3)$_2$), 1.24 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.30 (3H, d, J=7.2 Hz, 2-CH_3), 2.11–2.20 (1H, m, 5-H), 2.39 (2H, d, J=8.7 Hz, 4-H), 3.46 (1H, q, J=7.1 Hz, 2-H), 4.15 (2H, q, J=7.3 Hz, OCH_2CH_3); δ_C (75 MHz; $CDCl_3$) 12.6 (2-CH_3), 14.0 (OCH_2CH_3), 22.4 (CH(CH_3)$_2$), 24.1 (C-5), 50.2 (C-4), 53.2 (C-2), 61.2 (OCH_2CH_3), 170.5 (C-1), 205.4 (C-3); m/z (EI^+) 186 (M^+, 5%), 141 (4), 129 (7), 102 (14), 85 (100), 74 (12), 57 (84), 41 (18); found [M^+] 186.12505. $C_{10}H_{18}O_3$ requires 186.12559.

*4.2.2. Ethyl 2-methyl-3-oxo-4-phenylbutanoate **4h**.* Zinc dust (8.17 g, 125 mmol) was activated by sequential addition, stirring for 5 min and removal, by syringe, of each of 3 M HCl (100 mL), deionised water (100 mL), ethanol (100 mL) and ether (2×100 mL), followed by drying in vacuo. The activated zinc dust was suspended in dry THF (120 mL) and heated under reflux with stirring, 20 drops of ethyl 2-bromopropanoate was added and the mixture heated further, developing a slight green colour upon successful initiation (ca. 60 min.). 2-Phenylacetonitrile (2.93 g, 25.0 mmol) was added in one portion then ethyl 2-bromopropanoate (10.0 g, 55.2 mmol) was added drop-wise over 1 h. The reaction mixture was heated for a further 10 min, cooled, diluted with THF (360 mL) and quenched with aqueous K_2CO_3 (50%, 52.0 mL). Rapid stirring for 10 min caused the mixture to separate into two layers, the organic layer was decanted and the aqueous layer was further extracted with THF (2×95 mL). The combined THF fractions were then stirred with 10% HCl (50 mL) at room temperature for 45 min before being concentrated in vacuo. The remaining aqueous mixture was diluted with dichloromethane (290 mL) and washed with satd $NaHCO_3$ (195 mL). The organic phase was separated before being dried over $MgSO_4$, filtered, evaporated in vacuo to give the crude product, which was purified by flash chromatography (9:1 hexane, ethyl acetate, 9:1) to afford the title compound **4i** (5.17 g, 94%) as a yellow oil. R_f=0.5; δ_H (300 MHz; $CDCl_3$) 1.23 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.30 (3H, d, J=7.2 Hz, 2-CH_3), 3.62 (1H, q, J=7.2 Hz, 2-H), 3.83 (2H, s, $PhCH_2CO$), 4.14 (2H, q, J=7.1 Hz, OCH_2CH_3), 7.18–7.34 (5H, m, Ph). The ^1H NMR data obtained was in agreement with that reported in the literature.[25]

*4.2.3. Ethyl 2,4-dimethyl-3-oxopentanoate **4k**.* Isobutyryl chloride (72 mmol, 7.67 g) was added to a stirred solution of ethyl propionate (40 mmol, 4.09 g) and 1-methylimidazole (48 mmol, 3.94 g) in dry toluene at −45 °C and stirred for 20 min. Titanium tetrachloride (132 mmol, 14.5 mL), followed by *N*,*N*-diisopropylethylamine (144 mmol, 25.1 mL) were added dropwise to the reaction mixture and stirred for 5 h at −45 °C. The reaction was quenched with deionised water 100 mL until and the aqueous layer extracted with diethyl ether (4×40 mL). The combined organic extracts were washed with satd $NaHCO_3$ and brine, dried ($MgSO_4$) and solvent removed under reduced pressure to give the crude product, which was purified by flash chromatography (14:1 hexane, ethyl acetate) to afford the title compound **4k** (2.90 g, 42%) as a pale yellow oil; R_f =0.7; IR (NaCl) ν_{max} 2977, 2939, 2877 (CH), 1745 (COO), 1715 (C=O), 1467, 1376, 1245, 1197, 1098, 1016; δ_H (300 MHz; $CDCl_3$) 1.10 (6H, dd, J=4.34, 1.55 Hz, CH(CH_3)$_2$), 1.23 (3H, t, J=7.13 Hz, OCH_2CH_3), 1.30 (3H, d, J=7.21 Hz, 2-CH_3), 2.76–2.86 (1H, m, 4-H), 3.66 (1H, q, J=7.09 Hz, 2-H), 4.15 (2H, q, J=7.14 Hz, OCH_2CH_3); δ_C (75 MHz; $CDCl_3$) 13.0 (OCH_2CH_3), 14.0 (2-CH_3), 18.1 (1×CH(CH_3)$_2$), 18.5 (1×CH(CH_3)$_2$), 40.1 (C-4), 50.8 (C-2), 61.2 (OCH_2CH_3), 170.6 (C-1), 209.8 (C-3); m/z (EI^+) 172 (M^+, 16%), 129 (22), 127 (10), 102 (11), 74 (25), 71 (90), 56 (17), 43 (100); found [M^+] 172.10981. $C_9H_{16}O_3$ requires 172.10994.

4.3. General procedure B: synthesis of 4-piperidones 5

Methyltrichlorosilane (2.24 g, 15 mmol) was added dropwise to a mixture of β-keto ester **4** (10 mmol) and bis-aminol ether **3** (12 mmol) in dry acetonitrile (30 mL) then stirred at room temperature for 20 h. The reaction was then quenched with aqueous satd $NaHCO_3$ until basic, extracted with ethyl acetate (3×30 mL), dried ($MgSO_4$), concentrated in vacuo to give the crude product, which was purified by flash chromatography (hexane, ethyl acetate) to afford the title compound.

*4.3.1. Ethyl 1-butyl-3-methyl-4-oxopiperidine-3-carboxylate **5c**.* Prepared using general procedure B from β-keto ester **4c** (6.3 mmol, 0.91 g) and bis(aminol)ether **3a** (7.5 mmol, 1.43 g) with purification by flash chromatography (3:1 hexane, ethyl acetate) to afford the title compound **5c** (1.37 g, 90%) as a yellow oil; R_f =0.25; IR (NaCl) ν_{max}, 2936, 2873 (CH), 1732 (COO), 1722 (C=O), 1458, 1378, 1129 (CN); δ_H (300 MHz; $CDCl_3$) 0.89 (3H, t, J=7.2 Hz, $NCH_2CH_2CH_2CH_3$), 1.20 (3H, s, 3-CH_3), 1.23 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.28–1.40 (2H, m, $NCH_2CH_2CH_2CH_3$), 1.41–1.50 (2H, m, $NCH_2CH_2CH_2CH_3$), 2.10 (1H, d, J=11.5 Hz, 2_A-H), 2.26–2.50 (4H, m, $NCH_2CH_2CH_2CH_3$ and 6-CH_2), 2.86–3.04 (2H, m, 5-CH_2), 3.45 (1H, dd, J=11.5, 2.9 Hz, 2_B-H), 4.12 (2H, m, OCH_2CH_3); δ_C (75 MHz; $CDCl_3$) 13.9 ($NCH_2CH_2CH_2CH_3$), 14.1 (OCH_2CH_3), 17.9 (3-CH_3), 20.2 ($NCH_2CH_2CH_2CH_3$), 29.2 ($NCH_2CH_2CH_2CH_3$), 40.4 (C-5), 56.5 ($NCH_2CH_2CH_2CH_3$), 60.8 (C-3), 61.4 (OCH_2CH_3), 62.2 (C-6), 62.8 (C-2), 173.0 (COO), 207.9 (C-4); m/z (ESI^+) 242 (MH^+, 100%); found [MH^+] 242.17597. $C_{13}H_{24}NO_3$ requires 242.17562.

*4.3.2. Ethyl 1-benzyl-3-methyl-4-oxopiperidine-3-carboxylate **5d**.* Prepared using general procedure B from β-keto ester **4c** (6.3 mmol, 0.91 g) and bis(aminol)ether **3b** (7.6 mmol, 1.69 g) with purification by flash chromatography (2:1 hexane, ethyl acetate) to afford the title compound **5d** (1.43 g, 82%) as a pale yellow oil; R_f =0.4; δ_H (300 MHz; $CDCl_3$) 1.21 (3H, s, 3-CH_3), 1.24 (3H, t, J=7.1 Hz, OCH_2CH_3), 2.15 (1H, d, J=11.4 Hz, 2_A-H), 2.35–2.45 (2H, m, 6-CH_2),

2.85–3.07 (2H, m, 5-CH_2), 3.47 (1H, dd, J=11.4, 2.7 Hz, 2_B-H), 3.59 (2H, m, NCH_2Ph), 4.19 (2H, m, OCH_2CH$_3$) and 7.20–7.34 (5H, m, Ph). The ^{1}H NMR data obtained was in agreement with that reported in the literature.[26]

4.3.3. Ethyl 5-methyl-4-oxo-1-(3-phenylpropyl)-piperidine-3-carboxylate ***5e****.* Prepared using general procedure B from β-keto ester **4c** (6.9 mmol, 1.00 g) and bis(aminol)ether **3c** (8.3 mmol, 2.10 g) with purification by flash chromatography (3:1 hexane, ethyl acetate) to afford the title compound **5e** (1.80 g, 86%) as a pale yellow oil; R_f =0.3; IR (NaCl) ν_{max} 2996, 2934, 2810 (CH), 1732 (COO), 1717 (C=O), 1378, 1251, 1136 (CN); δ_H (400 MHz; $CDCl_3$) 1.21 (3H, s, 3-CH_3), 1.22 (3H, t, J=7.0 Hz, OCH$_2$CH_3), 1.75 (2H, m, NCH$_2$CH_2CH$_2$Ph), 1.95 (1H, d, J=11.4 Hz, 2_A-H), 1.97 (1H, t, J=10.91 Hz, 6_A-H), 2.22 (2H, t, J=7.1 Hz, NCH_2CH$_2$CH$_2$Ph), 2.38–2.60 (4H, m, 6-CH_2 and NCH$_2$CH$_2$CH_2Ph), 2.86–3.03 (2H, m, 5-CH_2), 3.49 (1H, dd, J=11.4, 3.1 Hz, 2_B-H), 4.20 (2H, q, J=7.0 Hz, OCH_2CH$_3$), 7.14–7.29 (5H, m, Ph); δ_C (100 MHz; $CDCl_3$) 14.1 (OCH$_2$CH$_3$), 17.9 (3-CH_3), 28.8 (NCH$_2$CH$_2$CH$_2$Ph), 33.5 (NCH$_2$CH$_2$CH$_2$Ph), 40.2 (C-5), 56.9 (NCH$_2$CH$_2$CH$_2$Ph), 60.1 (C-3), 61.3 (OCH$_2$CH$_3$), 61.9 (C-6), 62.9 (C-2), 125.6 (Ar–C), 128.2 (Ar–C), 128.6 (Ar–C), 142.6 (Ar–C) 173.0 (COO), 207.8 (C-4); m/z (ESI$^+$) 326 (MNa$^+$, 100%); found [M$^+$] 303.18341. $C_{18}H_{25}NO_3$ requires 303.18344.

4.3.4. Ethyl 1-benzyl-3-ethyl-4-oxopiperidine-3-carboxylate ***5f****.* Prepared using general procedure B from β-keto ester **4d** (6.3 mmol, 1.00 g) and bis(aminol)ether **3b** (7.6 mmol, 1.70 g) with purification by flash chromatography (4:1 hexane, ethyl acetate) to afford the title compound **5f** (1.55 g, 85%) as a pale yellow oil; R_f=0.3. δ_H (300 MHz; $CDCl_3$) 0.82 (3H, t, J=7.1 Hz, 3-CH$_2$CH_3), 1.24 (3H, t, J=7.1 Hz, OCH$_2$CH_3), 1.75 (2H, q, J=7.1 Hz, 3-CH_2CH$_3$), 2.19 (1H, d, J=11.5 Hz, 2_A-H), 2.39–2.45 (2H, m, 6-CH_2), 2.86–3.09 (2H, m, 5-CH_2), 3.48 (1H, d, J=11.6 Hz, 2_B-H), 3.53 (2H, s, NCH_2Ph), 4.20 (2H, m, OCH_2CH$_3$) and 7.15–7.31 (5H, m, Ph). The ^{1}H NMR data obtained were in agreement with that reported in the literature.[27]

4.3.5. Ethyl 1-butyl-3,5-dimethyl-4-oxopiperidine-3-carboxylate ***5g****.* Prepared using general procedure B from β-keto ester **4e** (9.5 mmol, 1.51 g) and bis(aminol)ether **3a** (11.4 mmol, 2.16 g) with purification by flash chromatography (9:1 hexane, ethyl acetate) to afford the title compound **5g** (1.46 g, 60%) as a pale yellow oil; R_f =0.3; IR (NaCl) ν_{max} 2959, 2934, 2873, 2808 (CH), 1730 (COO), 1719 (C=O), 1457, 1378, 1251, 1135 (CN); δ_H (300 MHz; $CDCl_3$) 0.90 (3H, t, J=7.2 Hz, NCH$_2$CH$_2$CH$_2$CH_3), 1.00 (3H, d, J=6.5 Hz, 5-CH_3), 1.20 (3H, s, 3-CH_3), 1.23 (3H, t, J=7.1 Hz, OCH$_2$CH_3), 1.28–1.39 (2H, m, NCH$_2$CH$_2$CH_2CH$_3$), 1.41–1.51 (2H, m, NCH$_2$CH_2CH$_2$CH$_3$), 1.95 (1H, d, J=11.5 Hz, 2_A-H), 1.97 (1H, t, J=10.9 Hz, 6_A-H), 2.26–2.47 (2H, m, NCH_2CH$_2$CH$_2$CH$_3$), 2.89–3.01 (1H, m, 5-H), 3.03–3.10 (1H, m, 6_B-H), 3.54 (1H, dd, J=11.5, 3.1 Hz, 2_B-H), 4.17 (2H, q, J=7.1 Hz, OCH_2CH$_3$); δ_C (75 MHz; $CDCl_3$) 11.6 (5-CH_3), 13.9 (NCH$_2$CH$_2$CH$_2$CH_3), 14.0 (OCH$_2$CH_3), 17.9 (3-CH_3), 20.4 (NCH$_2$CH$_2$CH_2CH$_3$), 29.2 (NCH$_2$CH_2CH$_2$CH$_3$), 43.2 (C-5), 56.8 (NCH$_2$CH$_2$CH$_2$CH$_3$), 56.8 (C-3), 61.2 (OCH$_2$CH$_3$), 62.2 (C-6), 63.2 (C-2), 173.1 (COO), 208.1 (C-4); m/z (EI$^+$) 362 (M$^+$, 100%), 256 (16), 212 (65), 178 (23), 154 (11), 122 (4), 100 (12); found [M$^+$] 256.19112. $C_{14}H_{26}NO_3$ requires 256.19127.

4.3.6. Ethyl (3R,5R*)-1-butyl-5-ethyl-3-methyl-4-oxopiperidine-3-carboxylate* ***5h****.* Prepared using general procedure B from β-keto ester **4f** (29 mmol, 5 g) and bis(aminol)ether **3a** (35 mmol, 6.60 g) with purification by flash chromatography (9:1 hexane, ethyl acetate) to afford the title compound **5h** (4.93 g, 63%) as a pale yellow oil; R_f =0.4; IR (NaCl) ν_{max} 2960, 2935, 2874, 2807, 2773 (CH), 1720 (C=O and COO), 1457, 1377, 1246, 1203 (C–N), 1134, 1021; δ_H (400 MHz; $CDCl_3$) 0.88–0.95 (6H, m, 5-CH$_2$CH_3, NCH$_2$CH$_2$CH$_2$CH_3), 1.12–1.19 (1H, m, 1×5-CH_2CH$_3$), 1.21 (3H, s, 3-CH_3), 1.24–1.29 (3H, m, OCH$_2$CH_3), 1.31–1.38 (2H, m, NCH$_2$CH$_2$CH_2CH$_3$), 1.45–1.53 (2H, m, NCH$_2$CH_2CH$_2$CH$_3$), 1.86 (1H, p, J=5.4 Hz, 1×5-CH_2CH$_3$), 1.95 (1H, dd, J=8.6, 1.0 Hz, 2_A-H), 1.98 (1H, t, J=8.5 Hz, 6_A-H), 2.29–2.50 (2H, m, NCH_2CH$_2$CH$_2$CH$_3$), 2.73–2.81 (1H, m, 5-H), 3.10–3.15 (1H, m, 6_B-H), 3.57 (1H, dd, J=8.6, 2.2 Hz, 2_B-H), 4.15–4.25 (2H, m, OCH_2CH$_3$); δ_C (100 MHz; $CDCl_3$) 11.6 (5-CH$_2$CH_3), 13.9 (OCH$_2$CH_3 and NCH$_2$CH$_2$CH$_2$CH_3), 17.8 (3-CH_3), 19.7 (5-CH_2CH$_3$), 20.4 (NCH$_2$CH$_2$CH_2CH$_3$), 29.2 (NCH$_2$CH_2CH$_2$CH$_3$), 50.1 (C-5), 56.8 (C-3), 56.9 (NCH$_2$CH$_2$CH$_2$CH$_3$), 60.4 (C-6), 61.1 (OCH$_2$CH$_3$), 63.0 (C-2), 173.0 (COO), 207.62 (C-4); m/z (EI$^+$) 269 (M$^+$, 7%), 254 (1), 238 (3), 226 (100), 224 (8), 196 (16), 154 (7), 84 (18), 69 (29), 41 (57); found [M$^+$] 269.19918. $C_{15}H_{27}NO_3$ requires 269.19909.

4.3.7. Ethyl (3R,5R*)-1-butyl-5-isopropyl-3-methyl-4-oxopiperidine-3-carboxylate* ***5i****.* Prepared using general procedure B from β-keto ester **4g** (1.9 mmol, 0.35 g) and bis(aminol)ether **3a** (2.3 mmol, 0.43 g) in dry acetonitrile (20 mL) with purification by flash chromatography (9:1 hexane, ethyl acetate) to afford the title compound **5i** (0.33 g, 65%) as a pale yellow oil; R_f =0.4; IR (NaCl) ν_{max} 2958, 2935, 2873, 2809 (CH), 1721, 1721 (COO), 1715 (C=O), 1464, 1456, 1377, 1366, 1248, 1132, 1022 (C–N); δ_H (300 MHz; $CDCl_3$) 0.85 (3H, d, J=6.9 Hz, 1×CH(CH_3)$_2$), 0.91 (3H, t, J=7.2 Hz, NCH$_2$CH$_2$CH$_2$CH_3), 0.95 (3H, d, J=6.9 Hz, 1×CH(CH_3)$_2$), 1.19 (3H, s, 3-CH_3), 1.23 (3H, t, J=7.1 Hz, OCH$_2$CH_3), 1.27–1.37 (2H, m, NCH$_2$CH$_2$CH_2CH$_3$), 1.39–1.52 (2H, m, NCH$_2$CH_2CH$_2$CH$_3$), 1.91 (1H, d, J=11.5 Hz, 2_A-H), 2.05 (1H, t, J=11.34 Hz, 6_A-H), 2.15 (1H, sex, J=6.8 Hz, CH(CH$_3$)$_2$), 2.26–2.49 (2H, m, NCH_2CH$_2$CH$_2$CH$_3$), 2.67 (1H, p, J=6.0 Hz, 5-H), 3.05–3.12 (1H, m, 6_B-H), 3.54 (1H, dd, J=11.5, 4.0 Hz, 2_B-H), 4.10–4.23 (2H, m, OCH_2CH$_3$); δ_C (75 MHz; $CDCl_3$) 14.0 (NCH$_2$CH$_2$CH$_2$CH_3 and OCH$_2$CH_3), 17.9 (3-CH_3), 19.0 (CH(CH_3)$_2$), 20.5 (NCH$_2$CH$_2$CH_2CH$_3$), 21.3 (CH(CH_3)$_2$), 25.0 (CH(CH$_3$)$_2$), 29.3 (NCH$_2$CH_2CH$_2$CH$_3$), 54.6 (C-5), 57.0 (C-3), 57.2 (NCH$_2$CH$_2$CH$_2$CH$_3$), 57.5 (C-6), 61.2 (OCH$_2$CH$_3$), 62.9 (C-2), 173.1 (COO), 207.3 (C-4); m/z (EI$^+$) 284 (MH$^+$, 47%), 266 (6), 252 (4), 240 (100), 210 (15), 152 (4), 85 (18), 57 (32); found [MH$^+$] 284.22275. $C_{16}H_{30}NO_3$ requires 284.22257.

4.3.8. Ethyl (3R,5R*)-1-butyl-3-methyl-4-oxo-5-phenylpiperidine-3-carboxylate* ***5j****.* Prepared using general procedure B from β-keto ester **4h** (4.5 mmol, 1.0 g) and bis(aminol)ether **3a** (9.0 mmol, 1.70 g) with purification by flash chromatography (14:1 hexane, ethyl acetate) to afford the title compound **5j** (1.26 g, 88%) as a pale yellow oil. R_f =0.5; IR (neat) ν_{max} 3030 (C–H, Ph), 2958, 2933, 2871, 2809, 2775 (C–H), 1718 (COO, C=O), 1603 (C=C) 1498, 1456, 1377, 1302, 1245, 1208, 1192, 1175, 1125, 1107, 1046, 1018 (C–N); δ_H (300 MHz; $CDCl_3$) 0.92 (3H, t, J=7.3 Hz, NCH$_2$CH$_2$CH$_2$CH_3), 1.28 (3H, s, 3-CH_3), 1.31 (3H, t, J=7.1 Hz, OCH$_2$CH_3), 1.36 (2H, m, NCH$_2$CH$_2$CH_2CH$_3$), 1.50 (2H, p, J=7.3 Hz, NCH$_2$CH_2CH$_2$CH$_3$), 2.19 (1H, d, J=11.6 Hz, 2_A-H), 2..44 (2H, m, NCH_2CH$_2$CH$_2$CH$_3$), 2.57 (1H, dd, J=12.0, 11.0 Hz, 6_A-H), 3.25 (1H, m, 6_B-H), 3.66 (1H, dd, J=11.6, 3.2 Hz, 2_B-H), 4..25 (3H, m, 5-H, OCH_2CH$_3$), 7.13–7.16 (5H, m, Ph); δ_C (75 MHz; $CDCl_3$) 13.9 (NCH$_2$CH$_2$CH$_2$CH_3), 14.1 (OCH$_2$CH_3), 18.0 (3-CH_3), 20.4 (NCH$_2$CH$_2$CH_2CH$_3$), 29.2 (NCH$_2$CH_2CH$_2$CH$_3$), 55.6 (C-5), 56.8 (NCH$_2$CH$_2$CH$_2$CH$_3$), 57.0 (C-3), 61.3 (OCH$_2$CH$_3$), 61.5 (C-6), 63.3 (C-2), 127.2 (Ph), 128.3 (Ph), 129.1 (Ph), 136.3 (Ph), 173.0 (COO), 205.1 (C-4); m/z (EI$^+$, %) 318 (MH$^+$, 9%), 272 (100), 254 (16), 244 (28), 226 (11), 214 (1), 199 (2), 187 (16), 159 (7), 154 (8), 126 (9); found [MH$^+$] 318.2061. $C_{19}H_{28}NO_3$ requires 318.2069.

4.3.9. Ethyl (3R,5R*)-5-allyl-1-butyl-3-methyl-4-oxopiperidine-3-carboxylate* ***5k****.* Prepared using general procedure B from β-keto ester **4i** (2 g, 10.9 mmol) and bis(aminol)ether **3a** (21.8 mmol, 4.13 g) with purification by flash chromatography (14:1 hexane, ethyl acetate) to afford the title compound **5k** (2.33 g, 76%) as a pale yellow oil. R_f =0.4; IR (neat) ν_{max} 3076 (=CH$_2$, =CH–), 2979, 2957, 2933, 2872, 2807, 2773 (C–H), 1716 (COO, C=O), 1641 (C=C), 1466, 1455, 1377, 1366, 1300, 1270, 1241, 1173, 1110, 1097, 1020 (C–N); δ_H

(300 MHz; $CDCl_3$) 0.90 (3H, t, J=7.2 Hz, $NCH_2CH_2CH_2CH_3$), 1.20 (3H, s, 3-CH_3), 1.24 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.33 (2H, m, $NCH_2CH_2CH_2CH_3$), 1.46 (2H, m, $NCH_2CH_2CH_2CH_3$), 1.87–2.00 (3H, m, 2_A-H, 5-$CH_AH_BCH{=}CH_2$ and 6_A-H), 2.36 (2H, m, $NCH_2CH_2CH_2CH_3$), 2.59 (1H, dtt, J=14.7, 5.6, 1.5 Hz, 5-$CH_AH_BCH{=}CH_2$), 2.94 (1H, m, 5-H), 3.10 (1H, m, 6_B-H), 3.55 (1H, dd, J=11.5, 3.1 Hz, 2_B-H), 4.18 (2H, dq, J=7.1, 2.1 Hz, OCH_2CH_3), 5.02 (2H, m, 5-$CH_2CH{=}CH_2$), 5.76 (1H, m, 5-$CH_2CH{=}CH_2$); δ_C (75 MHz; $CDCl_3$) 13.9 ($CH_2CH_2CH_2CH_3$), 14.0 (OCH_2CH_3), 17.8 (3-CH_3), 20.4 ($NCH_2CH_2CH_2CH_3$), 29.2 ($NCH_2CH_2CH_2CH_3$), 31.1 (5-$CH_2CH{=}CH_2$), 47.8 (C-5), 56.8 ($NCH_2CH_2CH_2CH_3$), 56.9 (C-3), 60.2 (C-6), 61.2 (OCH_2CH_3), 63.0 (C-2), 116.3 (5-$CH_2CH{=}CH_2$), 135.9 (5-$CH_2CH{=}CH_2$), 173.0 (COO), 207.1 (C-4); m/z (EI^+, %) 282 (MH^+, 14%), 236 (100), 208 (86), 190 (8), 166 (7), 154 (12), 126 (28), 112 (1), 100 (6); found $[MH]^+$ 282.2069. $C_{16}H_{28}NO_3$ requires 282.2069.

4.3.10. Ethyl (3R,5R*)-5-allyl-1,5-dimethyl-4-oxopiperidine-3-carboxylate* ***5l***. Prepared using general procedure B from β-keto ester **4i** (1.0 g, 10.9 mmol) and bis(aminol)ether **3d** (6.83 mmol, 0.8 g) with purification by flash chromatography (2:1 hexane, ethyl acetate) to afford the title compound **5l** (1.0 g, 80%) as a pale yellow oil. R_f=0.2; IR (neat) ν_{max} 2936, 2774 (C–H), 1720 (COO, C=O), 1640 (C=C), 1466, 1455, 1248, 1195, 1097, 1021 (C–N); δ_H (300 MHz; $CDCl_3$) 1.21–1.26 (6H, m, 3-CH_3 and OCH_2CH_3), 1.90–2.03 (3H, m, 2_A-H, 5-$CH_AH_BCH{=}CH_2$ and 6_A-H), 2.31 (3H, s, NCH_3), 2.59 (1H, m, 5-$CH_AH_BCH{=}CH_2$), 2.93 (1H, m, 5-H), 3.08 (1H, m, 6_B-H), 3.47 (1H, dd, J=14.2, 4.0 Hz, 2_B-H), 4.20 (2H, m, OCH_2CH_3), 5.03 (2H, m, 5-$CH_2CH{=}CH_2$), 5.74 (1H, m, 5-$CH_2CH{=}CH_2$); δ_C (75 MHz; $CDCl_3$) 13.8 (OCH_2CH_3), 17.6 (3-CH_3), 31.2 (5-$CH_2CH{=}CH_2$), 46.8 (NCH_3), 47.9 (C-5), 57.0 (C-3), 59.3 (C-6), 61.5 (OCH_2CH_3), 62.8 (C-2), 116.4 (5-$CH_2CH{=}CH_2$), 136.2 (5-$CH_2CH{=}CH_2$), 173.7 (COO), 208.0 (C-4); m/z (ESI^+, %) 240 (MH^+, 100%), 208 (32), 115 (1), 100 (6); found $[MH]^+$ 240.15983. $C_{13}H_{21}NO_3$ requires 240.15996.

4.3.11. Ethyl (3R,5R*)-1-tert-butyl-3,5-diethyl-4-oxopiperidine-3-carboxylate* ***5m***. Prepared using general procedure B from β-keto ester **4j** (5.9 mmol, 1.1 g) and bis(aminol)ether **3e** (7.7 mmol, 1.22 g) with purification by flash chromatography (3:1 hexane, ethyl acetate) to afford the title compound **5m** (1.3 g, 79%) as a pale yellow oil; R_f =0.4; IR (NaCl) ν_{max} 2962, 2874, 2773 (CH), 1719 (C=O and COO), 1200 (C–N); δ_H (400 MHz; $CDCl_3$) 0.89 (3H, t, J=7.9 Hz, 5-CH_2CH_3), 0.93 (3H, t, J=8.0 Hz, 3-CH_2CH_3), 1.24 (9H, s, $NC(CH_3)_3$), 1.11–1.23 (1H, m, 1×5-CH_2CH_3), 1.27 (3H, m, OCH_2CH_3), 1.54 (2H, m, 3-CH_2CH_3), 1.87 (1H, m, 1×5-CH_2CH_3), 1.98 (1H, t, J=8.9 Hz, 6_A-H), 2.06 (1H, dd, J=8.7, 1.0 Hz, 2_A-H), 2.69 (1H, m, 5-H), 3.27–3.32 (1H, m, 6_B-H), 3.66 (1H, dd, J=8.7, 2.0 Hz, 2_B-H), 4.15–4.23 (2H, m, OCH_2CH_3); δ_C (100 MHz; $CDCl_3$) 9.30 (3-CH_2CH_3), 11.8 (5-CH_2CH_3), 14.2 (OCH_2CH_3), 19.8 (5-CH_2CH_3), 24.1 (3-CH_2CH_3), 26.4 ($NC(CH_3)_3$), 51.2 (C-5), 53.2 ($NC(CH_3)_3$), 56.3 (C-3), 60.7 (C-6), 60.9 (OCH_2CH_3), 61.6 (C-2), 174.9 (COO), 208.4 (C-4); m/z (ESI) 284 (M^+, 100%), 272 (50), 226 (M-C_4H_9, 15); found $[MH^+]$ 284.2220. $C_{16}H_{30}NO_3$ requires 269.2223.

4.3.12. Ethyl 1-butyl-3,5,5-trimethyl-4-oxopiperidine-3-carboxylate ***5n***. Prepared using general procedure B from β-keto ester **4k** (5.7 mmol, 0.96 g) and bis(aminol)ether **3a** (6.7 mmol, 1.27 g) with purification by flash chromatography (9:1 hexane, ethyl acetate) to afford the title compound **5n** (0.77 g, 51%) as a pale yellow oil; R_f =0.6; IR (NaCl) ν_{max} 2961, 2933, 2874 (CH), 1738, 1732 (COO), 1713 (C=O), 1470, 1463, 1456, 1380, 1242, 1109, 1015 (C–N); δ_H (300 MHz; $CDCl_3$) 0.85 (3H, t, J=7.2 Hz, $NCH_2CH_2CH_2CH_3$), 1.03 and 1.05 (2×3H, d, J=6.7 Hz, 5-$(CH_3)_2$), 1.24 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.22–1.40 (4H, m, $NCH_2CH_2CH_2CH_3$ and $NCH_2CH_2CH_2CH_3$), 1.38 (3H, s, 3-CH_3), 2.53 (2H, t, J=6.9 Hz, $NCH_2CH_2CH_2CH_3$), 2.86 (2H, t, J=6.7 Hz, 6-H), 2.91 (2H, d, J=1.5 Hz, 2-H), 4.16 (2H, q, J=10.7 Hz, OCH_2CH_3); δ_C (75 MHz; $CDCl_3$) 13.9 ($NCH_2CH_2CH_2CH_3$), 14.0 (OCH_2CH_3), 18.4 (3-CH_3), 19.9 (1×5-$(CH_3)_2$), 20.1 (C-3), 20.2 ($NCH_2CH_2CH_2CH_3$), 20.3 (1×5-$(CH_3)_2$), 32.0 ($NCH_2CH_2CH_2CH_3$), 37.0 (C-6), 50.2 ($NCH_2CH_2CH_2CH_3$), 54.2 (C-5), 54.2 (C-2), 61.1 (OCH_2CH_3), 172.7 (COO), 212.9 (C-4); m/z (EI^+, %) 270 (M^+, 100%), 198 (3), 139 (3), 98 (6), 86 (7), 84 (7), 71 (14), 43 (37); found $[M^+]$ 270.20699. $C_{15}H_{28}NO_3$ requires 270.20692.

4.3.13. Ethyl 1-(3-phenylpropyl)-3,5,5-trimethyl-4-oxopiperidine-3-carboxylate ***5o***. Prepared using general procedure B from β-keto ester **4k** (5.8 mmol, 1.00 g) and bis(aminol)ether **3c** (6.9 mmol, 1.75 g) with purification by flash chromatography (9:1 hexane, ethyl acetate) to afford the title compound **5o** (1.14 g, 59%) as a pale yellow oil; R_f=0.6; IR (NaCl) ν_{max} 2934, 2879 (CH), 1732 (COO), 1716 (C=O), 1470, 1380, 1242, 1015 (C–N); δ_H (300 MHz; $CDCl_3$) 1.02 and 1.05 (2×3H, d, J=6.8 Hz, 5-$(CH_3)_2$), 1.23 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.39 (3H, s, 3-CH_3), 1.75 (2H, m, $NCH_2CH_2CH_2Ph$), 2.23 (2H, t, J=7.1 Hz, $NCH_2CH_2CH_2Ph$), 2.68 (2H, t, J=7.3 Hz, $NCH_2CH_2CH_2Ph$), 2.86 (2H, m, 6-H), 2.91 (2H, m, 2-H), 4.16 (2H, m, OCH_2CH_3); δ_C (75 MHz; $CDCl_3$) 14.1 (OCH_2CH_3), 18.3 (3-CH_3), 19.8 (1×5-$(CH_3)_2$), 20.1 (C-3), 20.5 (1×5-$(CH_3)_2$), 28.9 ($NCH_2CH_2CH_2Ph$), 33.5 ($NCH_2CH_2CH_2Ph$), 37.1 (C-6), 54.6 (C-5), 54.7 (C-2), 56.9 ($NCH_2CH_2CH_2Ph$), 61.0 (OCH_2CH_3), 125.6 (Ar–C), 128.0 (Ar–C), 128.5 (Ar–C), 142.6 (Ar–C), 172.9 (COO), 213.0 (C-4); m/z (ESI^+, %) 332 (MH^+, 100%); found $[MH^+]$ 332.22249. $C_{20}H_{30}NO_3$ requires 332.22257.

4.4. General procedure C: synthesis of 4-hydroxypiperidines 6

A solution of piperidone **5** (10 mmol) in THF (40 mL) was added to a solution of sodium borohydride (0.19 g, 5 mmol) in THF (40 mL) and deionised water (40 mL). The mixture was stirred for 30 min at 0 °C, then stirred for 3 h at room temperature. The reaction was quenched with 2 M NaOH and extracted with diethyl ether (3×100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give the crude product, which was purified by flash chromatography (hexane, ethyl acetate) to afford the title compound.

4.4.1. Ethyl (3R,4S*,5R*)-1-butyl-3,5-dimethyl-4-hydroxypiperidine-3-carboxylate* ***6a***. Prepared using general procedure C from piperidone **5g** (5.6 mmol, 1.4 g) and sodium borohydride (2.8 mmol, 0.11 g) with purification by flash chromatography (4:1 hexane, ethyl acetate) to afford the title compound **6a** (1.41 g, 98%) as a pale yellow oil; R_f =0.5; IR (NaCl) ν_{max} 3519 (OH), 2956, 2932, 2873, 2805, 2765 (CH), 1708 (COO), 1466, 1376, 1327, 1252, 1216 (C–N), 1140, 1068 (C–O); δ_H (300 MHz; $CDCl_3$) 0.86 (3H, t, J=7.1 Hz, $NCH_2CH_2CH_2CH_3$), 0.97 (3H, d, J=6.5 Hz, 5-CH_3), 1.22–1.28 (8H, m, 3-CH_3, OCH_2CH_3, $NCH_2CH_2CH_2CH_3$), 1.30–1.44 (2H, m, $NCH_2CH_2CH_2CH_3$), 1.61 (1H, d, J=11.5 Hz, 2_A-H), 1.64 (1H, t, J=11.1, 6_A-H), 1.90–2.01 (1H, m, 5-H), 2.08–2.31 (2H, m, $NCH_2CH_2CH_2CH_3$), 2.69 (1H, t, J=11.2 Hz, 4-H), 2.73–2.79 (1H, m, 6_B-H), 3.26 (1H, dd, J=11.5, 5.2 Hz, 2_B-H), 3.36 (1H, d, J=11.2 Hz, OH), 4.14 (2H, q, J=7.1 Hz, OCH_2CH_3); δ_C (75 MHz; $CDCl_3$) 13.9 ($NCH_2CH_2CH_2CH_3$), 14.0 (OCH_2CH_3), 20.4 ($NCH_2CH_2CH_2CH_3$), 21.3 (3-CH_3), 29.2 ($NCH_2CH_2CH_2CH_3$), 36.3 (C-5), 47.9 (C-3), 57.4 ($NCH_2CH_2CH_2CH_3$), 60.4 (OCH_2CH_3), 61.7 (C-6), 62.1 (C-2), 81.9 (C-4), 177.4 (COO); m/z (CI^+) 258 (M^+, 64%), 240 (3), 214 (100), 168 (12), 140 (5), 84 (10); found $[M]^+$ 258.20681. $C_{14}H_{28}NO_3$ requires 258.20692.

4.4.2. Ethyl (3R,4S*,5R*)-1-butyl-5-ethyl-4-hydroxy-3-methylpiperidine-3-carboxylate* ***6b***. Prepared using general procedure C from piperidone **5h** (0.74 mmol, 0.2 g) and sodium borohydride (0.37 mmol, 140 mg) with purification by flash chromatography (4:1 hexane, ethyl acetate) to afford the title compound **6b** (0.19 g, 94%) as a pale yellow oil; R_f =0.4; IR (NaCl) ν_{max} 3518 (OH), 2960, 2933, 2874, 2804, 2765 (CH), 1708 (COO), 1465, 1378, 1324, 1248,

1238, 1215 (CN), 1139, 1067 (C–O); δ_H (300 MHz; $CDCl_3$) 0.87 (3H, t, J=7.1 Hz, $NCH_2CH_2CH_2CH_3$), 0.88 (3H, t, J=7.5 Hz, 5-CH_2CH_3), 1.06 (1H, p, J=7.5 Hz, 1×5-CH_ACH_3), 1.20–1.32 (7H, m, 3-CH_3, OCH_2CH_3, $NCH_2CH_2CH_2CH_3$), 1.35–1.42 (2H, m, $NCH_2CH_2CH_2CH_3$), 1.57 (1H, d, J=11.5 Hz, 2_A-H), 1.61 (1H, t, J=11.0 Hz, 6_A-H), 1.71–1.79 (1H, m, 5-H), 1.87–1.96 (1H, m, 1×5-CH_BCH_3), 2.09–2.36 (2H, m, $NCH_2CH_2CH_2CH_3$), 2.77 (1H, t, J=11.1 Hz, 4-H), 2.90 (1H, dt, J=11.0, 3.4 Hz, 6_B-H), 3.27 (1H, dd, J=11.5, 2.5, 2_B-H), 3.38 (1H, d, J=11.8 Hz, OH), 4.15 (2H, q, J=7.1 Hz, OCH_2CH_3); δ_C (100 MHz; $CDCl_3$) 11.4 (5-CH_2CH_3), 14.0 (OCH_2CH_3, $NCH_2CH_2CH_2CH_3$), 20.5 ($NCH_2CH_2CH_2CH_3$), 21.4 (3-CH_3), 23.14 (5-CH_2CH_3), 29.2 ($NCH_2CH_2CH_2CH_3$), 42.6 (C-5), 47.9 (C-3), 57.6 ($NCH_2CH_2CH_2CH_3$), 59.2 (C-6), 60.5 (OCH_2CH_3), 61.8 (C-2), 80.4 (C-4), 177.4 (COO); m/z (EI$^+$) 271 (M^+ 7%), 256 (3), 228 (100), 226 (6), 182 (12), 149 (20), 124 (11), 84 (21), 69 (29), 57 (47), 43 (46), 41 (61); found $[M]^+$ 271.21512. $C_{15}H_{29}NO_3$ requires 271.21474.

4.4.3. Ethyl (3R,4S*,5R*)-1-butyl-4-hydroxy-5-isopropyl-3-methylpiperidine-3-carboxylate* ***6c****.* Prepared using general procedure C using piperidone **5i** (3.9 mmol, 1.05 g) and sodium borohydride (1.9 mmol, 75 mg) with purification by flash chromatography (4:1 hexane, ethyl acetate) to afford the title compound **6c** (1.07 g, 98%) as a pale yellow oil; R_f =0.5; IR (NaCl) ν_{max} 3514 (OH), 2957, 2933, 2873, 2807 (CH), 1708 (COO), 1465, 1245, 1216, 1135 (C–O), 1068 (C–N); δ_H (300 MHz; $CDCl_3$) 0.83 (3H, d, J=7.1 Hz, 1× $CH(CH_3)_2$), 0.87 (3H, t, J=7.2 Hz, $NCH_2CH_2CH_2CH_3$), 0.88–0.97 (2H, m, $NCH_2CH_2CH_2CH_3$), 0.93 (3H, d, J=7.2 Hz, 1×$CH(CH_3)_2$), 1.25 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.26 (3H, s, 3-CH_3), 1.32–1.45 (2H, m, $NCH_2CH_2CH_2CH_3$), 1.54 (1H, d, J=11.5 Hz, 2_A-H), 1.70 (1H, d, J=11.3 Hz, 6_A-H), 1.79–1.88 (1H, m, 5-H), 2.03–2.34 (3H, m, $CH(CH_3)_2$, $NCH_2CH_2CH_2CH_3$), 2.70–2.75 (1H, m, 6_B-H), 3.00 (1H, d, J=10.5 Hz, 4-H), 3.26 (1H, dd, J=11.5, 3.4 Hz, 2_B-H), 3.72–3.74 (1H, m, OH), 4.14 (2H, qd, J=7.1, 1.7 Hz, OCH_2CH_3); δ_C (100 MHz; $CDCl_3$) 14.0 (OCH_2CH_3, $NCH_2CH_2CH_2CH_3$), 16.8 (1×$CH(CH_3)_2$), 20.5 ($NCH_2CH_2CH_2CH_3$), 20.9 (3-CH_3), 21.5 (1×$CH(CH_3)_2$), 25.6 ($CH(CH_3)_2$), 29.2 ($NCH_2CH_2CH_2CH_3$), 45.6 (C-5), 47.8 (C-3), 54.4 (C-6), 57.8 ($NCH_2CH_2CH_2CH_3$), 60.4 (OCH_2CH_3), 61.7 (C-2), 77.6 (C-4), 177.5 (COO); m/z (CI$^+$) 286 (MH$^+$, 15%), 242 (65), 200 (100), 100 (23), 86 (21), 58 (33); found $[MH]^+$ 286.23857. $C_{16}H_{32}NO_3$ requires 286.23822.

4.4.4. Ethyl (3R,4S*,5R*)-1-butyl-4-hydroxy-3-methyl-5-phenylpiperidine-3-carboxylate* ***6d****.* Prepared using general procedure C from piperidone **5j** (6.0 mmol, 1.90 g) and sodium borohydride (7.2 mmol, 0.272 g) with purification by flash chromatography (9:1 hexane, ethyl acetate) to afford the title compound **6d** (1.88 g, 98%) as a yellow oil. R_f =0.4; IR (neat) ν_{max} 3522 (O–H), 3028 (C–H, Ph), 2955, 2392, 2872, 2805, 2767 (C–H), 1705 (COO), 1603 (C=C), 1497, 1466, 1455, 1415, 1377, 1325, 1299, 1245, 1211 (C–N), 1145, 1132, 1093, 1068, 1023, 983 (C–O); δ_H (300 MHz; $CDCl_3$) 0.89 (3H, t, J=7.1 Hz, $NCH_2CH_2CH_2CH_3$), 1.26–1.47 (4H, m, $NCH_2CH_2CH_2CH_3$), 1.31 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.36 (3H, s, 3-CH_3), 1.83 (1H, d, J=11.6 Hz, 2_A-H), 2.10 (1H, t, J=11.4 Hz, 6_A-H), 2.28 (2H, m, $NCH_2CH_2CH_2CH_3$), 2.92 (1H, m, 6_B-H), 3.22 (1H, m, 5-H), 3.39 (1H, dd, J=11.6, 2.5 Hz, 2_B-H), 3.41 (1H, m, 4-OH), 3.45 (1H, m, 4-H), 4.22 (2H, q, J=7.1 Hz, OCH_2CH_3), 7.18–7.34 (5H, m, Ph); δ_C (75 MHz; $CDCl_3$) 13.9 ($NCH_2CH_2CH_2CH_3$), 14.0 (OCH_2CH_3), 20.4 ($NCH_2CH_2CH_2CH_3$), 21.3 (3-CH_3), 29.2 ($NCH_2CH_2CH_2CH_3$), 48.1 (C-3), 48.5 (C-5), 57.2 ($NCH_2CH_2CH_2CH_3$), 60.6 (OCH_2CH_3), 61.8 (C-6), 62.1 (C-2), 79.2 (C-4), 126.6 (Ph), 128.1 (Ph), 128.4 (Ph), 141.2 (Ph), 177.1 (COO); m/z (EI$^+$, %) 320 (MH$^+$, 7%), 302 (59), 292 (1), 274 (41), 256 (3), 246 (15), 228 (60), 217 (5), 204 (1), 189 (10), 171 (100), 161 (3), 143 (91), 128 (27); found $[MH^+]$ 320.2214. $C_{19}H_{30}NO_3$ requires 320.2226.

4.4.5. Ethyl (3R,4S*,5R*)-5-allyl-1-butyl-4-hydroxy-3-methylpiperidine-3-carboxylate* ***6e****.* Prepared using general procedure C from piperidone **5k** (5.3 mmol, 1.50 g) and sodium borohydride (6.4 mmol, 0.24 g) with purification by flash chromatography (9:1 hexane, ethyl acetate) to afford the title compound **6e** (1.41 g, 93%) as a yellow oil. R_f =0.35; IR (neat) ν_{max} 3511 (O–H), 3076 (=CH_2, =CH–), 2959, 2931, 2873, 2803, 2766 (C–H), 1705 (COO), 1640 (C=C), 1466, 1414, 1377, 1317, 1299, 1275, 1237, 1208 (C–N), 1145, 1112, 1095, 1069. 1038, 1024, 992 (C–O); δ_H (300 MHz; $CDCl_3$) 0.89 (3H, t, J=7.1 Hz, $NCH_2CH_2CH_2CH_3$), 1.27 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.27 (3H, s, 3-CH_3), 1.29–1.42 (4H, m, $NCH_2CH_2CH_2CH_3$), 1.62 (1H, d, J=11.7 Hz, 2_A-H), 1.64 (1H, t, J=11.2 Hz, 6_A-H), 1.79–2.04 (2H, m, 5-CH_AH_BCH=CH_2 and 5-H), 2.23 (2H, m, $NCH_2CH_2CH_2CH_3$), 2.67 (1H, m, 5-CH_AH_BCH=CH_2), 2.79–2.90 (2H, m, 4-H and 6_B-H), 3.29 (1H, dd, J=11.7, 2.6 Hz, 2_B-H), 3.46 (1H, d, J=10.7 Hz, 4-OH), 4.17 (2H, q, J=7.1 Hz, OCH_2CH_3), 5.02 (2H, m, 5-CH_2CH=CH_2), 5.79 (1H, m, 5-CH_2CH=CH_2); δ_C (75 MHz; $CDCl_3$) 14.0 ($NCH_2CH_2CH_2CH_3$, OCH_2CH_3), 20.5 ($NCH_2CH_2CH_2CH_3$), 21.3 (3-CH_3), 29.2 ($NCH_2CH_2CH_2CH_3$), 34.9 (5-CH_2CH=CH_2), 40.8 (C-5), 57.8 ($NCH_2CH_2CH_2CH_3$), 59.2 (C-6), 60.5 (OCH_2CH_3), 61.8 (C-2), 79.9 (C-4), 116.0 (5-CH_2CH=CH_2), 136.8 (5-CH_2CH=CH_2), 177.4 (COO); m/z (EI$^+$, %) 284 (MH$^+$, 53%), 266 (100), 238 (38), 224 (14), 210 (23), 194 (39), 181 (40), 153 (23), 135 (19), 107 (14); found $[MH^+]$ 284.2214. $C_{16}H_{30}NO_3$ requires 284.2226.

4.4.6. Reduction of piperidone ***5n*** *to give ethyl (3R*,4S*)-1-butyl-4-hydroxy-3,5,5-trimethylpiperidine-3-carboxylate and ethyl (3R*,4R*)-1-butyl-4-hydroxy-3,5,5-trimethylpiperidine-3-carboxylate.* Prepared using general procedure C from piperidone **5n** (0.33 mmol, 90 mg) and sodium borohydride (0.17 mmol, 6 mg) with purification by flash chromatography (4:1 hexane, ethyl acetate) to afford the title compounds (82 mg, 91%) as a pale yellow oil as a mixture of inseparable diastereomers, where * denotes signals from the second diastereomer; R_f =0.4; IR (NaCl) ν_{max} 3522 (OH), 2954, 2931, 2920, 2867, 2782, 2766 (CH), 1707 (COO), 1465, 1372, 1313, 1265, 1234, 1210 (CN), 1122, 1097 (C–O); δ_H (300 MHz; $CDCl_3$) 0.82–0.96 (2×9H, m, 2×$C(CH_3)_2$, 2×$C(CH_3)_2$*, $NCH_2CH_2CH_2CH_3$, $NCH_2CH_2CH_2CH_3$*), 1.08 (3H, s, 3-CH_3*), 1.20 (3H, s, 3-CH_3), 1.23 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.24 (3H, t, J=6.3 Hz, OCH_2CH_3*), 1.28–1.34 (2×2H, m, $NCH_2CH_2CH_2CH_3$, $NCH_2CH_2CH_2CH_3$*), 1.35–1.43 (2×2H, m, $NCH_2CH_2CH_2CH_3$, $NCH_2CH_2CH_2CH_3$*), 2.58–2.48 (2×2H, m, $NCH_2CH_2CH_2CH_3$, $NCH_2CH_2CH_2CH_3$*), 2.64 (1H, d, J=10.5 Hz, 6-H*), 2.78 (1H, d, J=12.4 Hz, 6-H), 2.97 (2H, d, J=4.8 Hz, 2-H*), 3.01 (2H, d, J=5.1 Hz, 2-H), 3.49 (1H, d, J=4.0 Hz, 4-H*), 3.81 (1H, d, J=5.5 Hz, 4-H), 4.06–4.16 (2×3H, m, OCH_2CH_3, OCH_2CH_3*, OH, OH*); δ_C (75 MHz; $CDCl_3$) 13.8–14.1 (OCH_2CH_3, OCH_2CH_3*, $NCH_2CH_2CH_2CH_3$, $NCH_2CH_2CH_2CH_3$*), 16.8 (3-CH_3*), 16.9 (1×5-$(CH_3)_2$*), 18.5 (1×5-$(CH_3)_2$), 20.2 ($NCH_2CH_2CH_2CH_3$*), 20.4 (3-CH_3), 21.3 (1×5-$(CH_3)_2$*), 22.0 (1×5-$(CH_3)_2$), 29.6 (C-3*), 30.9 (C-3), 31.8 ($NCH_2CH_2CH_2CH_3$*), 31.9 ($NCH_2CH_2CH_2CH_3$), 48.7 (C-5*), 49.7 ($NCH_2CH_2CH_2CH_3$*), 50.0 (C-5), 50.1 ($NCH_2CH_2CH_2CH_3$), 56.3 (C-2*, C-6*), 56.7 (C-2, C-6), 60.5 (OCH_2CH_3*), 60.6 (OCH_2CH_3), 81.0 (C-4*), 82.3 (C-4), 175.9 (COO*), 176.3 (COO); m/z (CI$^+$) 272 (M$^+$, 6%), 270 (13), 228 (12), 173 (42), 172 (41), 129 (24), 127 (30), 86 (81), 83 (51), 71 (100); found $[M]^+$ 272.22222. $C_{15}H_{30}NO_3$ requires 272.22257.

4.5. General procedure D: synthesis of 4-alkoxypiperidines 7

To a solution of 4-hydroxypiperidine **6** (1 mmol) in dry THF (10 mL) was added dropwise to a suspension of sodium hydride (80 mg, 2 mmol, 60% w/w in oil) in dry THF (10 mL) and stirred for 1 h at room temperature, iodomethane or allyl bromide (3 mmol) was added dropwise and the mixture stirred in a well sealed flask (preferably a Teflon sealed pressure tube) for 3 days at room temperature. The reaction was quenched with deionised water (30 mL) and the resulting aqueous mixture extracted with ethyl acetate (4×25 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), concentrated in vacuo to give the crude

product, which was purified by flash chromatography (hexane, ethyl acetate) to afford the title compound.

4.5.1. Ethyl (3R,4S*,5R*)-1-butyl-3,5-dimethyl-4-methoxypiperidine-3-carboxylate* ***7a****.* Prepared using general procedure D from alcohol **6a** (6.3 mmol, 1.62 g) and iodomethane (18.9 mmol, 1.19 mL) with purification by flash chromatography (9:1 hexane, ethyl acetate) to afford the title compound **7a** (1.71 g, 68%) as a pale yellow oil; R_f =0.4; IR (NaCl) ν_{max} 2956, 2928, 2872, 2825 (CH), 1744 (COO), 1465, 1375, 1260, 1237, 1188 (C–N), 1105, 1095 (C–O); δ_H (300 MHz; $CDCl_3$) 0.85 (3H, t, *J*=7.1 Hz, $NCH_2CH_2CH_2CH_3$), 0.97 (3H, d, *J*=6.4 Hz, 5-CH_3), 1.19–1.29 (8H, m, 3-CH_3, OCH_2CH_3, $NCH_2CH_2CH_2CH_3$), 1.31–1.41 (2H, m, $NCH_2CH_2CH_2CH_3$), 1.65–1.78 (3H, m, 2_A-H, 5-H, 6_A-H), 2.08–2.30 (2H, m, $NCH_2CH_2CH_2CH_3$), 2.42–2.47 (1H, m, 4-H), 2.67–2.73 (1H, m, 6_B-H), 3.04 (1H, dd, *J*=11.4, 2.2 Hz, 2_B-H), 3.47 (3H, s, OCH_3), 4.06–4.17 (2H, m, OCH_2CH_3); δ_C (75 MHz; $CDCl_3$) 13.9 ($NCH_2CH_2CH_2CH_3$), 14.2 (OCH_2CH_3), 16.6 (5-CH_3), 20.4 ($NCH_2CH_2CH_2CH_3$), 21.5 (3-CH_3), 29.2 ($NCH_2CH_2CH_2CH_3$), 34.0 (C-5), 48.9 (C-3), 57.3 ($NCH_2CH_2CH_2CH_3$), 59.7 (OCH_2CH_3), 60.9 (C-6), 62.2 (C-2), 62.3 (OCH_3), 91.8 (C-4), 173.9 (COO); *m*/*z* (Cl^+) 272 (M^+, 80%), 240 (4), 228 (100), 210 (2), 185 (5), 166 (6), 124 (3); found $[M]^+$ 272.22228. $C_{15}H_{30}NO_3$ requires 272.22257.

4.5.2. Ethyl (3R,4S*,5R*)-1-butyl-5-ethyl-4-methoxy-3-methylpiperidine-3-carboxylate* ***7b****.* Prepared using general procedure D from alcohol **6b** (3.3 mmol, 0.90 g) and iodomethane (10.0 mmol, 0.63 mL) with purification by flash chromatography (9:1 hexane, ethyl acetate) to afford the title compound **7b** (0.89 g, 94%) as a pale yellow oil; R_f =0.45; IR (NaCl) ν_{max} 2958, 2929, 2873, 2820 (CH), 1738 (COO), 1463, 1368, 1240 (C–N), 1108, 1094, 1027 (C–O); δ_H (400 MHz; $CDCl_3$) 0.86 (3H, t, *J*=7.2 Hz, $NCH_2CH_2CH_2CH_3$), 0.91 (3H, t, *J*=7.5 Hz, 5-CH_2CH_3), 1.10–1.19 (1H, m, 5-CH_ACH_3), 1.22 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 1.25–1.31 (2H, m, $NCH_2CH_2CH_2CH_3$), 1.27 (3H, s, 3-CH_3), 1.33–1.41 (2H, m, $NCH_2CH_2CH_2CH_3$), 1.64 (1H, s, 5-CH_BCH_3), 1.70–1.80 (1H, m, 6-H), 1.85 (1H, d, *J*=11.5 Hz, 2_A-H), 2.12–2.35 (3H, m, 5-H, $NCH_2CH_2CH_2CH_3$), 2.60 (1H, d, *J*=8.5 Hz, 4-H), 2.76 (1H, d, *J*=8.3 Hz, 6_B-H), 2.97 (1H, d, *J*=11.5 Hz, 2_B-H), 3.43 (3H, s, OCH_3), 4.07–4.17 (2H, m, OCH_2CH_3); δ_C (100 MHz; $CDCl_3$) 11.8 (5-CH_2CH_3), 14.0 ($NCH_2CH_2CH_2CH_3$), 14.2 (OCH_2CH_3), 20.5 ($NCH_2CH_2CH_2CH_3$), 21.6 (3-CH_3), 23.7 (5-CH_2CH_3), 29.2 ($NCH_2CH_2CH_2CH_3$), 40.4 (C-5), 48.7 (C-3), 57.5 ($NCH_2CH_2CH_2CH_3$), 57.7 (C-6), 59.8 (OCH_2CH_3), 61.3 (C-2), 61.4 (OCH_3), 90.0 (C-4), 174.2 (COO); *m*/*z* (Cl^+) 286 (M^+, 100%), 254 (5), 242 (72), 240 (6), 180 (4); found $[M]^+$ 286.23775. $C_{16}H_{32}NO_3$ requires 286.23822.

4.5.3. Ethyl (3R,4S*,5R*)-1-butyl-5-isopropyl-4-methoxy-3-methylpiperidine-3-carboxylate* ***7c****.* Prepared using general procedure D from alcohol **6c** (6.0 mmol, 1.70 g) and iodomethane (17.9 mmol, 1.14 mL) with purification by flash chromatography (9:1 hexane, ethyl acetate) to afford the title compound **7c** (1.47 g, 79%) as a pale yellow oil; R_f =0.5; IR (NaCl) ν_{max} 2957, 2928, 2871, 2818 (CH), 1738 (COO), 1464, 1367, 1268, 1239 (C–N), 1136, 1106, 1094 (C–O); δ_H (300 MHz; $CDCl_3$) 0.85 (3H, t, *J*=6.3 Hz, $NCH_2CH_2CH_2CH_3$), 0.87 (3H, d, *J*=7.2 Hz, 1×$CH(CH_3)_2$), 0.97 (3H, d, *J*=6.6 Hz, 1×$CH(CH_3)_2$), 1.19–1.28 (2H, m, $NCH_2CH_2CH_2CH_3$), 1.21 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 1.28 (3H, s, 3-CH_3), 1.31–1.42 (2H, m, $NCH_2CH_2CH_2CH_3$), 1.80 (1H, d, *J*=11.4 Hz, 2_A-H), 1.93 (1H, d, *J*=10.9 Hz, 6_A-H), 2.07–2.30 (4H, m, 5-H, $CH(CH_3)_2$, $NCH_2CH_2CH_2CH_3$), 2.60 (1H, d, *J*=10.9 Hz, 6_B-H), 2.85 (1H, d, *J*=8.4 Hz, 4-H), 2.95 (1H, dd, *J*=11.4, 1.6 Hz, 2_B-H), 3.43 (3H, s, OCH_3), 4.05–4.16 (2H, m, OCH_2CH_3); δ_C (75 MHz; $CDCl_3$) 14.0 ($NCH_2CH_2CH_2CH_3$), 14.2 (OCH_2CH_3), 20.5 ($NCH_2CH_2CH_2CH_3$), 21.6 (3-CH_3, $CH(CH_3)_2$), 21.8 ($CH(CH_3)_2$), 25.5 ($CH(CH_3)_2$), 29.3 ($NCH_2CH_2CH_2CH_3$), 43.9 (C-5), 48.8 (C-3), 53.3 (C-6), 57.9 ($NCH_2CH_2CH_2CH_3$), 59.8 (OCH_2CH_3), 61.3 (OCH_3), 61.4 (C-2), 86.4 (C-4), 174.2 (COO); *m*/*z* (Cl^+) 300 (MH^+, 34%), 256 (100), 254 (6), 85 (62), 83 (96); found $[MH]^+$ 300.25301. $C_{17}H_{34}NO_3$ requires 300.25387.

4.5.4. Ethyl (3R,4S*,5R*)-1-butyl-4-methoxy-3-methyl-5-phenylpiperidine-3-carboxylate* ***7d****.* Prepared using general procedure D from alcohol **6d** (5.1 mmol, 1.63 g) and iodomethane (15.3 mmol, 0.96 mL) with purification by flash chromatography (9:1 hexane, ethyl acetate) to afford the title compound **7d** (1.59 g, 93%) as a yellow oil. R_f =0.3; IR (neat) ν_{max} 3086, 3060, 3028 (C–H, Ph), 2955, 2931, 2873, 2818, 2767 (C–H), 1736 (COO), 1602 (C=C), 1494. 1465, 1454, 1365, 1311, 1276, 1249 (C–N), 1198, 1187, 1147, 1127, 1095, 1020 (C–O); δ_H (300 MHz; $CDCl_3$) 0.88 (3H, t, *J*=7.2 Hz, $NCH_2CH_2CH_2CH_3$), 1.24 (3H, s, 3-CH_3), 1.27 (3H, t, *J*=7.5 Hz, OCH_2CH_3), 1.30 (2H, sext, *J*=7.1 Hz, $NCH_2CH_2CH_2CH_3$), 1.41 (2H, p, *J*=6.7 Hz, $NCH_2CH_2CH_2CH_3$), 1.99 (1H, d, *J*=11.5 Hz, 2_A-H), 2.20–2.39 (3H, m, $NCH_2CH_2CH_2CH_3$ and 6_A-H), 2.88 (1H, ddd, *J*=11.4, 4.5, 2.1 Hz, 6_B-H), 2.97 (3H, s, 4-OCH_3), 3.03 (1H, d, *J*=9.5 Hz, 4-H), 3.13 (1H, dd, *J*=11.5, 2.1 Hz, 2_B-H), 3.66 (1H, td, *J*=9.5, 4.5 Hz, 5-H), 4.12–4.23 (2H, m, OCH_2CH_3), 7.18–7.41 (5H, m, Ph); δ_C (75 MHz; $CDCl_3$) 13.9 ($NCH_2CH_2CH_2CH_3$), 14.2 (OCH_2CH_3), 20.3 ($NCH_2CH_2CH_2CH_3$), 21.4 (3-CH_3), 29.2 ($NCH_2CH_2CH_2CH_3$), 44.9 (C-5), 48.9 (C-3), 57.3 ($NCH_2CH_2CH_2CH_3$), 59.3 (C-6), 59.8 (OCH_2CH_3), 61.4 (O–CH_3), 62.0 (C-2), 90.2 (C-4), 126.4 (Ph), 128.1 (Ph), 128.5 (Ph), 141.9 (Ph), 173.7 (COO); *m*/*z* (EI^+, %) 334 (MH^+, 13%), 302 (100), 288 (10), 274 (23), 256 (2), 228 (46), 217 (6), 189 (8), 171 (56), 143 (47), 128 (10); found $[MH^+]$ 334.2375. $C_{20}H_{32}NO_3$ requires 334.2382.

4.5.5. Ethyl (3R,4S*,5R*)-5-allyl-1-butyl-4-methoxy-3-methylpiperidine-3-carboxylate* ***7e****.* Prepared using general procedure D from alcohol **6e** (0.7 mmol, 0.20 g) and iodomethane (2.1 mmol, 0.12 mL) with purification by flash chromatography (9:1 hexane, ethyl acetate) to afford the title compound **7e** (0.184 g, 87%) as a yellow oil. R_f =0.4; IR (neat) ν_{max} 3076 (=CH_2, =CH–), 2956, 2931, 2874, 2821, 2760 (C–H), 1737 (COO), 1640 (C=C), 1466, 1366, 1312, 130, 1271, 1239 (C–N), 1187, 1151, 1133, 1107, 1090, 1053, 1027, 992, 971 (C–O); δ_H (300 MHz; $CDCl_3$) 0.87 (3H, t, *J*=7.1 Hz, $NCH_2CH_2CH_2CH_3$), 1.24 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 1.29 (3H, s, 3-CH_3), 1.29–1.43 (4H, m, $NCH_2CH_2CH_2CH_3$), 1.77–1.98 (3H, m, 6_A-H, 2_A-H and 5-CH_AH_BCH=CH_2), 2.12–2.43 (3H, m, $NCH_2CH_2CH_2CH_3$ and 5-H), 2.51 (1H, m, 5-CH_AH_BCH=CH_2), 2.65 (1H, d, *J*=8.5 Hz, 4-H), 2.72 (1H, ddd, *J*=11.2, 4.0, 1.5 Hz, 6_B-H), 2.99 (1H, dd, *J*=11.4, 1.5 Hz, 2_B-H), 2.45 (3H, s, 4-OCH_3), 4.14 (2H, m, OCH_2CH_3), 5.02 (2H, m, 5-CH_2CH=CH_2), 5.79 (1H, m, 5-CH_2CH=CH_2); δ_C (75 MHz; $CDCl_3$) 13.9 ($NCH_2CH_2CH_2CH_3$), 14.2 (OCH_2CH_3), 20.4 ($NCH_2CH_2CH_2CH_3$), 21.6 (3-CH_3), 29.2 ($NCH_2CH_2CH_2CH_3$), 35.6 (5-CH_2CH=CH_2), 38.3 (C-5), 48.8 (C-3), 57.5 ($NCH_2CH_2CH_2CH_3$ and C-6), 59.8 (OCH_2CH_3), 61.3 (C-2), 61.6 (4-OCH_3), 89.3 (C-4), 115.9 (5-CH_2CH=CH_2), 137.1 (5-CH_2CH=CH_2), 174.0 (COO); *m*/*z* (EI^+, %) 298 (MH^+, 29%), 266 (100), 252 (15), 238 (18), 224 (11), 211 (3), 192 (11), 181 (34), 168 (5), 153 (18), 135 (17), 117 (4), 100 (6); found $[MH^+]$ 298.2381. $C_{17}H_{32}NO_3$ requires 298.2382.

4.5.6. Ethyl (3R,4S*,5R*)-5-allyl-4-(allyloxy)-1-butyl-3-methylpiperidine-3-carboxylate* ***7f****.* Prepared using general procedure D using alcohol **6e** (3.5 mmol, 1.0 g) and allyl bromide (11 mmol, 1.85 g) with purification by flash chromatography (9:1 hexane, ethyl acetate) to afford the title compound **7f** (0.81 g, 71%) as a pale yellow oil. R_f =0.6; IR (neat) ν_{max} 3075 (=CH_2, =CH–), 2957, 2935, 2875, 2807, 2764 (C–H), 1736 (COO), 1639 (C=C), 1466, 1427, 1407, 1366, 1350, 1309, 1299 (C–N), 1272, 1238, 1202, 1172, 1154, 1131, 1106, 1081, 1052, 1026, 992 (C–O); δ_H (300 MHz; $CDCl_3$) 0.88 (3H, t, *J*=7.2 Hz, $NCH_2CH_2CH_2CH_3$), 1.24 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 1.24–1.44 (4H, m, $NCH_2CH_2CH_2CH_3$), 1.29 (3H, s, 3-CH_3), 1.85–2.04 (3H, m, 6_A-H, 2_A-H, 5-CH_AH_BCH=CH_2), 2.13–2.37 (3H, m, $NCH_2CH_2CH_2CH_3$ and 5-H), 2.47 (1H, m, 5-

$CH_AH_BCH{=}CH_2$), 2.68 (1H, dd, J=11.3, 2.9 Hz, 6_B-H), 2.89 (1H, d, J=7.7 Hz, 4-H), 2.95 (1H, dd, J=11.4, 1.3 Hz, 2_B-H), 4.06 (2H, m, 4-$OCH_2CH{=}CH_2$), 4.13 (2H, q, J=7.1 Hz, OCH_2CH_3), 5.02 (2H, m, 5-$CH_2CH{=}CH_2$), 5.10 (1H, dq, J=10.4, 1.5 Hz, 4-$OCH_2CH{=}CH_AH_B$), 5.23 (1H, dq, J=17.2, 1.5 Hz, 4-$OCH_2CH{=}CH_AH_B$), 5.78 (1H, m, 5-$CH_2CH{=}CH_2$), 5.91 (1H, m, 4-$OCH_2CH{=}CH_2$); δ_C (75 MHz; $CDCl_3$) 13.9 ($NCH_2CH_2CH_2CH_3$), 14.2 (OCH_2CH_3), 20.4 ($NCH_2CH_2CH_2CH_3$), 21.8 (3-CH_3), 29.2 ($NCH_2CH_2CH_2CH_3$), 35.8 (5-$CH_2CH{=}CH_2$), 38.4 (C-5), 48.6 (C-3), 56.9 (C-6), 57.6 ($NCH_2CH_2CH_2CH_3$), 59.8 (OCH_2CH_3), 60.8 (C-2), 74.2 (4-$OCH_2CH{=}CH_2$), 86.6 (C-4), 116.0 (4-$OCH_2CH{=}CH_2$), 116.1 (5-$CH_2CH{=}CH_2$), 135.2 (4-$OCH_2CH{=}CH_2$), 137.3 (5-$CH_2CH{=}CH_2$), 174.2 (COO); m/z (EI^+, %) 324 (MH^+, 21%), 296 (2), 278 (9), 266 (100), 238 (12), 224 (8), 192 (8), 181 (29), 153 (13), 135 (9), 121 (2); found [MH^+] 324.2535. $C_{19}H_{34}NO_3$ requires 298.2539.

4.5.7. Ethyl (5aR,9R*,9aS*)-7-butyl-9-methyl-2,5,5a,6,7,8,9,9a-octahydrooxepino[3,2-c]pyridine-9-carboxylate* ***7g***. To a dry, stirred suspension of bis(tricyclohexylphosphine)benzylideneruthenium (IV) chloride (51 mg, 0.062 mmol) in dry dichloromethane (40 mL) under an atmosphere of argon at room temperature, was added diene **7f** (200 mg, 0.62 mmol). After stirring for 1.5 h the solvent was removed in vacuo to give the crude product, which was purified by flash chromatography (9:1 hexane, ethyl acetate) afforded the title compound **7g** (0.12 g, 64%) as a yellow oil. R_f=0.5; IR (NaCl) ν_{max} 3017 (=CH_2, =CH−), 2957, 2932, 2871, 2821, 2764 (C−H), 1737, (COO), 1716 (C=C), 1464, 1393, 1374, 1322, 1299 (C−N), 1256, 1231, 1215, 1193, 1138, 1104, 1090, 1070, 1049, 1029 (C−O); δ_H (300 MHz; $CDCl_3$) 0.87 (3H, t, J=7.1 Hz, $NCH_2CH_2CH_2CH_3$), 1.23 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.23−1.43 (4H, m, $NCH_2CH_2CH_2CH_3$), 1.65 (1H, t, J=11.0 Hz, 6_A-H), 1.70 (1H, d, J=11.3 Hz, 8_A-H), 1.90 (1H, m, 5-H_A), 2.09−2.21 (2H, m, 5-H_B and $NCH_AH_BCH_2CH_2CH_3$), 2.28 (1H, m, $NCH_AH_BCH_2CH_2CH_3$), 2.67 (1H, m, 5a-H), 2.80 (1H, ddd, J=11.1, 4.6, 2.5 Hz, 6_B-H), 2.90 (1H, d, J=11.1 Hz, 6_B-H), 3.14 (1H, dd, J=11.3, 2.5 Hz, 8_B-H), 3.91 (1H, d, J=13.9 Hz, 2-H_A), 4.12 (2H, q, J=7.1 Hz, OCH_2CH_3), 4.48 (1H, m, 2-H_B), 5.86−5.87 (2H, m, 3-H and 4-H); δ_C (75 MHz; $CDCl_3$) 13.9 ($NCH_2CH_2CH_2CH_3$), 14.2 (OCH_2CH_3), 20.3 ($NCH_2CH_2CH_2CH_3$), 21.2 (9-CH_3), 29.2 ($NCH_2CH_2CH_2CH_3$), 33.3 (C-5), 36.6 (C-5a), 48.7 (C-9), 57.2 ($NCH_2CH_2CH_2CH_3$), 59.8 (OCH_2CH_3), 60.7 (C-6), 68.3 (C-2), 92.5 (C-9a), 130.9 and 131.33 (C-3 and C-4), 173.6 (COO); m/z (EI^+, %) 296 (MH^+, 36%), 278 (6), 242 (1), 222 (100), 196 (10), 180 (25), 164 (6), 150 (41), 135 (7), 126 (43), 119 (29), 100 (9), 91 (4); found [MH^+] 296.2213. $C_{17}H_{30}NO_3$ requires 296.2226.

4.6. General procedure E: synthesis of 3-hydroxymethylpiperidines 8

Lithium aluminium hydride (38 mg, 1 mmol) was added to a solution of piperidine 3-carboxylate ethyl ester **7** (0.5 mmol) in dry THF (10 mL) and the mixture stirred for 2 h at room temperature. The reaction was quenched with deionised water (5 mL), filtered through Celite and the aqueous mixture layer extracted with ethyl acetate (3×10 mL). The combined organic layers were dried ($MgSO_4$), concentrated in vacuo to give the crude product, which was purified by flash chromatography (hexane, ethyl acetate) to afford the title compound.

4.6.1. (3S,4S*,5R*)-(1-Butyl-3,5-dimethyl-4-methoxypiperidin-3-yl) methanol* ***8a***. Prepared using general procedure E from ester **7a** (5.9 mmol, 1.6 g) with purification by flash chromatography (4:1 hexane, ethyl acetate) to afford the title compound **8a** (1.32 g, 98%) as a colourless oil; R_f=0.4; IR (NaCl) ν_{max} 3439, 3291 (OH), 2958, 2926, 2858, 2828 (CH), 1463, 1455, 1376, 1177 (C−N), 1105, 1087, 1048 (C−O); δ_H (300 MHz; $CDCl_3$) 0.83 (3H, s, 3-CH_3), 0.87 (3H, t, J=8.6 Hz, 5-CH_3), 0.88 (3H, t, J=9.5 Hz, $NCH_2CH_2CH_2CH_3$), 1.23−1.31 (2H, m, $NCH_2CH_2CH_2CH_3$), 1.37−1.45 (2H, m, $NCH_2CH_2CH_2CH_3$), 1.52 (1H, t, J=11.3 Hz, 6_A-H), 1.88 (1H, dd, J=11.6, 2.0 Hz, 2_A-H), 2.15−2.25 (3H, m, 5-H, $NCH_2CH_2CH_2CH_3$), 2.54 (1H, d, J=10.6 Hz, 4-H), 2.81 (1H, dd, J=11.6, 2.5 Hz, 2_B-H), 2.93−2.99 (1H, m, 6_B-H), 3.49 (3H, s, OCH_3), 3.59 (1H, d, J=10.7 Hz, 1×OCH_AOH), 3.81 (1H, dd, J=10.7, 2.0 Hz, 1×CH_BOH), 5.49 (1H, s, OH); δ_C (75 MHz; $CDCl_3$) 11.2 ($NCH_2CH_2CH_2CH_3$), 13.9 (5-CH_3), 20.5 ($NCH_2CH_2CH_2CH_3$), 22.6 (3-CH_3), 29.1 ($NCH_2CH_2CH_2CH_3$), 39.7 (C-3), 41.4 (C-5), 57.7 ($NCH_2CH_2CH_2CH_3$), 57.9 (C-6), 62.5 (OCH_3), 64.4 (C-2), 68.9 (OCH_2OH), 91.4 (C-4); m/z (ESI) found [MNa]$^+$ 258.19383. $C_{13}H_{27}NO_2Na$ requires 252.19395.

4.6.2. (3S,4S*,5R*)-(1-Butyl-5-ethyl-4-methoxy-3-methylpiperidin-3-yl)methanol* ***8b***. Prepared using general procedure E from ester **7b** (0.56 mmol, 0.16 g) with purification by flash chromatography (4:1 hexane, ethyl acetate) to afford the title compound **8b** (0.13 g, 95%) as a colourless oil; R_f=0.2; IR (NaCl) ν_{max} 3443, 3289 (OH), 2955, 2872, 2828 (CH), 1463, 1455, 1372, 1180, 1106 (C−N), 1091, 1044 (C−O); δ_H (300 MHz; $CDCl_3$) 0.84 (3H, s, 3-CH_3), 0.87 (3H, t, J=7.2 Hz, 5-CH_2CH_3), 0.94 (3H, d, J=6.4 Hz, $NCH_2CH_2CH_2CH_3$), 1.22−1.34 (4H, m, 5-CH_2CH_3, $NCH_2CH_2CH_2CH_3$), 1.37−1.44 (2H, m, $NCH_2CH_2CH_2CH_3$), 1.57 (1H, t, J=11.4 Hz, 6_A-H), 1.91 (1H, dd, J=12.0, 1.9 Hz, 2_A-H), 2.20 (2H, td, J=14.4, 1.9 Hz, $NCH_2CH_2CH_2CH_3$), 2.28−2.40 (1H, m, 5-H), 2.48 (1H, d, J=10.6 Hz, 4-H), 2.79−2.84 (2H, m, 2_B-H, 6_B-H), 3.52 (3H, s, OCH_3), 3.60 (1H, d, J=10.8 Hz, 1×CH_AOH), 3.81 (1H, dd, J=10.8, 1.9 Hz, 1×CH_BOH), 5.48 (1H, s, OH); δ_C (75 MHz; $CDCl_3$) 13.9 ($NCH_2CH_2CH_2CH_3$), 16.8 (5-CH_2CH_3), 20.5 ($NCH_2CH_2CH_2CH_3$), 22.5 (3-CH_3), 29.1 ($NCH_2CH_2CH_2CH_3$), 29.7 (5-CH_2CH_3), 35.2 (C-5), 39.7 (C-3), 57.5 ($NCH_2CH_2CH_2CH_3$), 60.7 (C-6), 62.5 (OCH_3), 64.7 (C-2), 68.9 (CH_2OH), 93.0 (C-4). m/z (ESI) found [MNa]$^+$ 266.20901. $C_{14}H_{29}NO_2Na$ requires 266.20960.

4.6.3. (3S,4S*,5R*)-(1-Butyl-5-isopropyl-4-methoxy-3-methylpiperidin-3-yl)methanol* ***8c***. Prepared using general procedure E from ester **7c** (3.5 mmol, 1.04 g) with purification by flash chromatography (4:1 hexane, ethyl acetate) to afford the title compound **8c** (0.82 g, 92%) as a colourless oil; R_f=0.3; IR (NaCl) ν_{max} 3436 (OH), 2955, 2942, 2898, 2822 (CH), 1464, 1455, 1353, 1180, 1116 (C−N), 1086, 1077, 1065 (C−O); δ_H (400 MHz; $CDCl_3$) 0.82 (3H, d, J=7.9 Hz, 1×$CH(CH_3)_2$), 0.86 (3H, s, 3-CH_3), 0.87 (3H, t, J=7.1 Hz, $NCH_2CH_2CH_2CH_3$), 0.95 (3H, d, J=7.1 Hz, 1×$CH(CH_3)_2$), 1.21−1.31 (2H, m, $NCH_2CH_2CH_2CH_3$), 1.38−1.43 (2H, m, $NCH_2CH_2CH_2CH_3$), 1.64 (1H, t, J=11.6 Hz, 6_A-H), 7.61 (1H, dd, J=11.9, 1.6 Hz, 2_A-H), 2.16−2.25 (4H, m, 5-H, $CH(CH_3)_2$, $NCH_2CH_2CH_2CH_3$), 2.78−2.81 (3H, m, 2_B-H, 4-H, 6_B-H), 3.50 (3H, s, OCH_3), 3.59 (1H, d, J=10.7 Hz, 1×CH_AOH), 3.81 (1H, dd, J=10.7, 1.9 Hz, 1×CH_BOH), 6.01 (1H, s, OH); δ_C (100 MHz; $CDCl_3$) 13.9 ($NCH_2CH_2CH_2CH_3$), 16.0 (1×$CH(CH_3)_2$), 20.6 ($NCH_2CH_2CH_2CH_3$), 21.4 (1×$CH(CH_3)_2$), 22.9 (3-CH_3), 25.5 ($CH(CH_3)_2$), 29.2 ($NCH_2CH_2CH_2CH_3$), 39.6 (C-3), 44.4 (C-5), 52.9 ($NCH_2CH_2CH_2CH_3$), 57.9 (C-6), 62.1 (OCH_3), 64.4 (C-2), 68.9 (CH_2OH), 87.9 (C-4); m/z (Cl^+) 258 (MH^+, 87%), 226 (7), 214 (100), 196 (9), 182 (8), 88 (12); found [MH]$^+$ 258.24293. $C_{15}H_{32}NO_2$ requires 258.24330.

4.6.4. ((3S,4S*,5R*)-1-Butyl-4-methoxy-3-methyl-5-phenylpiperidin-3-yl)methanol* ***8d***. Prepared using general procedure E from ester **7d** (1.2 mmol, 0.4 g) with purification by flash chromatography (9:1 hexane, ethyl acetate) to afford the title compound **8d** (0.33 g, 94%) as a yellow oil. R_f=0.3; IR (NaCl) ν_{max} 3463, 3263 (O−H), 3030 (C−H, Ph), 2954, 2931, 2871, 2823, 2775 (C−H), 1601 (C=C), 1495, 1467, 1454, 1375, 1361, 1332, 1318, 1269, 1232 (C−N), 1174, 1127, 1102, 1080, 1044, 1019, 988, 967 (C−O); δ_H (300 MHz; $CDCl_3$) 0.89 (3H, t, J=7.3 Hz, $NCH_2CH_2CH_2CH_3$), 0.91 (3H, s, 3-CH_3), 1.31 (2H, sext, J=7.3 Hz, $NCH_2CH_2CH_2CH_3$), 1.45 (2H, p, J=7.3 Hz, $NCH_2CH_2CH_2CH_3$), 2.13 (1H, d, J=12.0 Hz, 2_A-H), 2.16 (1H, t, J=12.1 Hz, 6_A-H), 2.28 (2H, td, J=7.4, 1.6 Hz, $NCH_2CH_2CH_2CH_3$), 2.92

(3H, s, 4-OCH_3), 2.92–3.00 (2H, m, 2_B-H, 4-H), 3.10 (2H, d, J=10.8 Hz, 6_B-H), 3.53 (1H, m, 5-H), 3.72 (1H, d, J=10.9 Hz, 3-CH_AH$_B$OH), 3.93 (1H, dd, J=10.9 Hz, 2.12 Hz, 3-CH$_A$$H_B$OH), 7.20–7.36 (5H, m, Ph); δ_C (75 Hz; $CDCl_3$) 13.9 ($NCH_2CH_2CH_2CH_3$), 20.5 ($NCH_2CH_2CH_2CH_3$), 22.3 (3-CH_3), 29.1 ($NCH_2CH_2CH_2CH_3$), 39.7 (C-3), 46.9 (C-5), 57.5 ($NCH_2CH_2CH_2CH_3$), 59.8 (C-6), 61.3 (4-OCH_3), 64.8 (C-2), 69.0 (3-CH_2OH), 90.9 (C-4), 126.7 (Ph), 128.3 (Ph), 141.9 (Ph); m/z (EI$^+$, %) 292 (MH^+, 32%), 274 (1), 260 (100), 242 (2), 157 (3), 138 (4), 117 (7); found [MH^+] 292.2272. $C_{18}H_{30}NO_2$ requires 292.2277.

4.6.5. ((3S,4S*,5R*)-5-Allyl-1-butyl-4-methoxy-3-methylpiperidin-3-yl)methanol* ***8e***. Prepared using general procedure E from ester **7e** (2.7 mmol, 0.8 g) with purification by flash chromatography (9:1 hexane, ethyl acetate) to afford the title compound **8e** (0.67 g, 96%) as a yellow oil. R_f =0.25; IR (neat) ν_{max} 3419, 3277 (O–H), 3074 (=CH_2, =CH–), 2955, 2930, 2872, 2826, 2768 (C–H), 1639 (C=C), 1467, 1457, 1440, 1369, 1316, 1267, 1246 (C–N), 1176, 1154, 1132, 1102, 1083, 1043, 1020, 992, 965, 939 (C–O); δ_H (300 MHz; $CDCl_3$) 0.87 (3H, s, 3-CH_3), 0.89 (3H, t, J=7.3 Hz, $NCH_2CH_2CH_2CH_3$), 1.29 (2H, sext, J=7.3 Hz, $NCH_2CH_2CH_2CH_3$), 1.43 (2H, p, J=7.3 Hz, $NCH_2CH_2CH_2CH_3$), 1.57 (1H, t, J=11.4 Hz, 6_A-H), 1.79 (1H, dt, J=13.8, 8.9 Hz, 5-CH_AH$_B$CH=CH_2), 1.93 (1H, dd, J=11.6, 2.1 Hz, 2_A-H), 2.23 (2H, m, $NCH_2CH_2CH_2CH_3$), 2.38 (1H, m, 5-H), 2.56 (1H, m, 5-CH$_A$$H_B$CH=$CH_2$), 2.60 (1H, d, J=10.8 Hz, 4-H), 2.85 (1H, dd, J=11.6, 2.5 Hz, 2_B-H), 2.93 (1H, ddd, J=11.4, 4.4, 2.5 Hz, 6_B-H), 3.53 (3H, s, 4-OCH_3), 3.61 (1H, d, J=10.6 Hz, 3-CH_AH$_B$OH), 3.85 (1H, dd, J=10.6, 2.1 Hz, 3-CH$_A$$H_B$OH), 5.03 (2H, m, 5-$CH_2$CH=$CH_2$), 5.78 (1H, m, 5-$CH_2$CH=$CH_2$); δ_C (75 MHz; $CDCl_3$) 13.9 ($NCH_2CH_2CH_2CH_3$), 20.5 ($NCH_2CH_2CH_2CH_3$), 22.6 (3-CH_3), 29.1 ($NCH_2CH_2CH_2CH_3$), 35.8 (5-CH_2CH=CH_2), 39.6 (C-5), 57.6 ($NCH_2CH_2CH_2CH_3$), 58.1 (C-6), 62.5 (4-OCH_3), 64.5 (C-2), 68.8 (3-CH_2OH), 91.0 (C-4). 116.2 (5-CH_2CH=CH_2), 136.5 (5-CH_2CH=CH_2); m/z (EI$^+$, %) 256 (MH^+, 17%), 238 (2), 224 (100), 206 (11), 182 (12), 164 (18), 150 (3), 140 (22), 124 (4), 100 (3); found [MH^+] 256.2266. $C_{15}H_{30}NO_2$ requires 256.2277.

4.6.6. ((5aR,9S*,9aS*)-7-Butyl-9-methyl-2,5,5a,6,7,8,9,9a-octahydrooxepino[3,2-c]pyridin-9-yl)methanol* ***8f***. Prepared using general procedure E from ester **7g** (0.34 mmol, 0.10 g) with purification by flash chromatography (9:1 hexane, ethyl acetate) to afford the title compound **8f** (84 mg, 98%) as a pale yellow crystals. Mp 52–53 °C; R_f =0.3; IR (neat) ν_{max} 3175 (O–H), 3028 (=CH_2, =CH–), 2957, 2917, 2871, 2850, 2814, 2771, 2732, 2671 (C–H), 1470, 1461, 1447, 1398, 1370, 1341, 1315, 1275, 1261, 1242 (C–N), 1211, 1192, 1170, 1129, 1079, 1047, 1028, 1003 (C–O); δ_H (300 MHz; $CDCl_3$) 0.84 (3H, s, 9-CH_3), 0.90 (3H, t, J=7.5 Hz, $NCH_2CH_2CH_2CH_3$), 1.31 (2H, sext, J=7.5 Hz, $NCH_2CH_2CH_2CH_3$), 1.46 (2H, p, J=7.5 Hz, $NCH_2CH_2CH_2CH_3$), 1.64 (1H, t, J=11.4 Hz, 6_A-H), 1.93 (1H, m, 5-H_A), 1.97 (1H, dd, J=11.5, 1.0 Hz, 8_A-H), 2.16 (1H, m, 5-H_B), 2.24 (2H, m, $NCH_2CH_2CH_2CH_3$), 2.43–2.56 (1H, m, 5a-H), 2.81–2.92 (2H, m, 6_B-H and 8_B-H), 2.99 (1H, d, J=10.1 Hz, 9a-H), 3.60 (1H, d, J=10.8 Hz, 9-CH_AH$_B$OH), 3.85 (1H, dd, J=10.8, 2.36 Hz, 9-CH$_A$$H_B$OH), 3.98 (1H, d, J=14.6 Hz, 2-H_A), 4.40 (1H, m, 2-H_B), 5.84–5.86 (2H, m, 3-H and 4-H); δ_C (75 MHz; $CDCl_3$) 13.9 ($NCH_2CH_2CH_2CH_3$), 20.5 ($NCH_2CH_2CH_2CH_3$), 21.8 (9-CH_3), 29.1 ($NCH_2CH_2CH_2CH_3$), 34.0 (C-5), 37.9 (C-5a), 39.4 (C-9), 57.6 ($NCH_2CH_2CH_2CH_3$), 59.6 (C-6), 65.0 (C-8), 68.2 (9-CH_2OH), 92.3 (C-2), 130.9 and 131.2 (C-3 and C-4); m/z (EI$^+$, %) 254 (MH^+, 47%), 236 (22), 204 (12), 194 (8), 182 (34), 164 (100), 150 (26), 140 (89), 124 (91), 105 (48), 98 (21), 91 (24); found [MH^+] 254.2111. $C_{15}H_{28}NO_2$ requires 254.2120.

4.6.7. X-ray crystal structure of ((5aR,9S*,9aS*)-7-butyl-9-methyl-2,5,5a,6,7,8,9,9a-octahydrooxepino[3,2-c]pyridin-9-yl)methanol* ***8f***. The single crystal X-ray diffraction data were collected on a Bruker Smart APEX-2 CCD diffractometer using graphite monochromated Mo Kα radiation at 93 K. The structure was solved using direct methods (SHELXS-97). The asymmetric unit consisted of a hydrogen bonded pair of optical isomers of **8f**. Non-hydrogen atoms were refined anisotropically (SHELXL-97) and H atoms were refined using a riding model, with C–H =0.93–0.97 Å and $U_{iso}(H)$=1.2U_{eq}(C), 1.5U_{eq}(methyl C) or 1.5U_{eq}(O). The *n*-butyl group –C13–C14–C15–C16 is disordered with a minor component –C13a–C14a–C15a–C16a of 0.187. For this butyl group EADP constraints between corresponding atoms were applied. The deposition number for compound **8f** is CCDC-773732.

Crystallographic data for **8f**: $C_{30}H_{54}N_2O_4$ (MW=506.06), colourless fragment (0.45×0.29×0.12 mm^3), monoclinic, $P2_1/c$, a=9.2699 (3) Å, b=22.3936 (7) Å, c=14.2246 (5) Å, β=98.418 (2)°, V=2921.02 (17) Å^3, Z=4, D_{calcd}=1.152 Mg/m^3, μ(Mo Kα)=0.075 mm^{-1}. Measured reflections=36,883, independent reflections=6924 (R_{int}=0.0594), number of parameters=344. Final R indices [$I>2\sigma(I)$], $R1$=0.0470, $wR2$=0.1132, goodness-of-fit on F^2=1.032.

4.7. General procedure F: synthesis of anthranilate esters 9

To a solution of 3-hydroxymethyl-piperidine **8** (1 mmol) in dry acetonitrile (20 mL) were added 2-(3-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)benzoic acid[24] (462 mg, 2 mmol), DMAP (12 mg, 0.1 mmol) and DCC (412 mg, 2 mmol) and the resulting mixture stirred for 7 h at room temperature. The mixture was then filtered through Celite and solvent removed in vacuo and residue dissolved in ethyl acetate (30 mL), washed with satd $NaHCO_3$, washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give the crude product, which was purified by flash chromatography (hexane, ethyl acetate) to afford the title compound.

4.7.1. (3S,4S*,5R*)-(1-Butyl-3,5-dimethyl-4-methoxypiperidin-3-yl)methyl 2-(3-methyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoate* ***9a***. Prepared using general procedure F from alcohol **8a** (0.57 mmol, 0.13 g) with purification by flash chromatography (1:1 hexane, ethyl acetate) to afford the title compound **9a** (0.14 g, 57%) as a yellow oil; R_f =0.35; IR (NaCl) ν_{max} 2955, 2933, 2860, 2821 (CH), 2118, 1718 (COO, C=O), 1645 (C=C), 1602, 1494, 1452, 1394, 1261, (C–N), 1138, 1122, 1090 (C–O); δ_H (300 MHz; $CDCl_3$) 0.79 (3H, t, J=7.2 Hz, $NCH_2CH_2CH_2CH_3$), 0.88 (3H, d, J=6.4 Hz, 5″-CH_3), 1.01 (3H, s, 3″-CH_3), 1.15–1.29 (2H, m, $NCH_2CH_2CH_2CH_3$), 1.31–1.38 (2H, m, $NCH_2CH_2CH_2CH_3$), 1.53–1.56 (2H, m, 2″$_A$-H, 6″$_A$-H), 1.75–1.84 (1H, m, 5″-H), 2.12 (3H, d, J=1.4 Hz, 3′-CH_3), 2.41 (1H, d, J=10.6 Hz, 4″-H), 2.75 (1H, d, J=11.0 Hz, 2″$_B$-H), 2.83 (1H, d, J=11.7 Hz, 6″$_B$-H), 3.45 (3H, s, OCH_3), 4.26 (1H, d, J=10.4 Hz, CH_AO$_2$C), 4.54 (1H, d, J=10.4 Hz, CH_BO$_2$C), 6.45–6.48 (1H, m, 4′-H), 7.21–7.24 (1H, m, 6-H), 7.44–7.48 (1H, m, 5-H), 7.55–7.61 (1H, m, 4-H), 8.04 (1H, t, J=7.5 Hz, 3-H); δ_C (75 MHz; $CDCl_3$) 11.1 (3′-CH_3), 13.9 ($NCH_2CH_2CH_2CH_3$), 16.3 (5″-CH_3), 20.4 ($NCH_2CH_2CH_2CH_3$), 21.3 (3″-CH_3), 29.1 ($NCH_2CH_2CH_2CH_3$), 34.3 (C-5″), 40.5 (C-3″), 57.36 ($NCH_2CH_2CH_2CH_3$), 60.1 (C-6″), 61.0 (C-2″), 62.4 (OCH_3), 66.7 (CH_2O_2C), 92.7 (C-4″), 127.8 (C-4′), 128.4 (C-1), 128.7 (C-5), 130.3 (C-6), 131.1 (C-3), 131.7 (C-2), 132.8 (C-4), 146.0 (C-3′), 164.5 (COO), 169.7 (C-5′), 170.7 (C-2′); m/z (FAB$^+$) 443 (MH^+, 20%), 307 (21), 214 (16), 165 (3), 154 (100), 120 (11); found [MH^+] 443.25485. $C_{25}H_{35}N_2O_5$ requires 443.25460.

4.7.2. (3S,4S*,5R*)-(1-Butyl-5-ethyl-4-methoxy-3-methylpiperidin-3-yl)methyl 2-(3-methyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoate* ***9b***. Prepared using general procedure F from alcohol **8b** (0.58 mmol, 0.14 g) with purification by flash chromatography (1:1 hexane, ethyl acetate) to afford the title compound **9b** (0.16 g, 62%) as a yellow oil; R_f =0.6; IR (neat) ν_{max} 2959, 2932, 2860, 2828, 2806 (CH), 2118, 1715 (COO, C=O), 1645 (C=C), 1602, 1494, 1455, 1394, 1259, (C–N), 1138, 1091 (C–O); δ_H (400 MHz; $CDCl_3$) 0.82 (3H, t, J=7.3 Hz, $NCH_2CH_2CH_2CH_3$), 0.88 (3H, t, J=7.3 Hz, 5″-CH_3), 1.05 (3H,

s, 3″-CH_3), 1.22–1.32 (2H, m, $NCH_2CH_2CH_2CH_3$), 1.33–1.42 (2H, m, $NCH_2CH_2CH_2CH_3$), 1.53 (1H, d, J=11.7 Hz, 2″$_A$-H), 1.55 (1H, t, J=11.5 Hz, 6″$_A$-H), 1.66–1.77 (3H, m, 5″-H, 5″-CH_2CH_3), 2.14 (3H, s, 3′-CH_3), 2.14–2.30 (2H, m, $NCH_2CH_2CH_2CH_3$), 2.50 (1H, d, J=10.4 Hz, 4″-H), 2.84 (1H, dd, J=11.7, 1.7 Hz, 2″$_B$-H), 2.93 (1H, d, J=11.5 Hz, 6″$_B$-H), 3.47 (3H, s, OCH_3), 4.28 (1H, d, J=10.4 Hz, 1×CH_ACOO), 4.60 (1H, d, J=10.4 Hz, 1×CH_BCOO), 6.48 (1H, d, J=1.8 Hz, 4′-H), 7.28 (1H, dd, J=7.9, 1.0, 6-H), 7.47 (1H, td, J=7.6, 1.2 Hz, 5-H), 7.61 (1H, td, J=7.7, 1.6 Hz, 4-H), 8.06 (1H, dd, J=7.9, 1.3 Hz, 3-H); δ_C (100 MHz; $CDCl_3$) 11.0 (3′-CH_3), 11.2 (5″-CH_3), 13.8 ($NCH_2CH_2CH_2CH_3$), 20.3 ($NCH_2CH_2CH_2CH_3$), 21.32 (3″-CH_3), 23.2 (5″-CH_2CH_3), 29.2 ($NCH_2CH_2CH_2CH_3$), 40.4 (C-3″), 40.6 (C-5″), 57.5 ($NCH_2CH_2CH_2CH_3$), 58.2 (C-6″), 59.8 (C-2″), 66.8 (CH_2O_2C), 91.2 (C-4″), 127.8 (C-4′), 128.4 (C-1), 128.9 (C-5), 130.3 (C-6), 131.0 (C-3), 131.8 (C-2), 132.8 (C-4), 145.9 (C-3′), 164.4 (COO), 169.6 (C-5′), 170.6 (C-2′); m/z (FAB$^+$) 457 (MH^+, 100%), 413 (12), 314 (13), 286 (3), 214 (23), 120 (11); found [MH^+] 457.27109. $C_{26}H_{37}N_2O_5$ requires 457.27025.

4.7.3. (3S,4S*,5R*)-(1-Butyl-5-isopropyl-4-methoxy-3-methylpiperidin-3-yl)methyl 2-(3-methyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl) benzoate* ***9c***. Prepared using general procedure F from alcohol **8c** (0.54 mmol, 0.14 g) with purification by flash chromatography (1:1 hexane, ethyl acetate) to afford the title compound **9c** (0.14 g, 55%) as a yellow oil; R_f =0.4; IR (neat) ν_{max} 2958, 2932, 2873, 2825 (CH), 1716 (COO, C=O), 1645 (C=C), 1602, 1495, 1454, 1394, 1259 (C–N), 1107, 1095 (C–O); δ_H (400 MHz; $CDCl_3$) 0.79 (3H, t, J=9.6 Hz, $NCH_2CH_2CH_2CH_3$), 0.81 (3H, d, J=9.4 Hz, 1×$CH(CH_3)_2$), 0.92 (3H, d, J=9.4 Hz, 1×$CH(CH_3)_2$), 1.05 (3H, s, 3″-CH_3), 1.14–1.26 (2H, m, $NCH_2CH_2CH_2CH_3$), 1.27–1.39 (2H, m, $NCH_2CH_2CH_2CH_3$), 1.46 (1H, d, J=15.5 Hz, 2″$_A$-H), 1.55–1.74 (2H, m, 5-H, 6″$_A$-H), 1.93–2.27 (3H, m, $CH(CH_3)_2$, $NCH_2CH_2CH_2CH_3$), 2.12 (3H, d, J=2.5 Hz, 3′-CH_3), 2.72–2.82 (3H, m, 2″$_B$-H, 4″-H, 6″$_B$-H), 3.45 (3H, s, OCH_3), 4.25 (1H, d, J=13.9 Hz, CH_AO_2C), 4.59 (1H, d, J=13.9 Hz, CH_BO_2C), 6.46 (1H, d, J=2.4 Hz, 4′-H), 7.26 (1H, dd, J=10.4, 1.5 Hz, 6-H), 7.45 (1H, td, J=10.2, 1.7 Hz, 5-H), 7.59 (1H, td, J=10.2, 2.1 Hz, 4-H), 8.04 (1H, dd, J=10.4, 2.0 Hz, 3-H); δ_C (100 MHz; $CDCl_3$) 10.9 (3′-CH_3), 13.8 ($NCH_2CH_2CH_2CH_3$), 16.16 (1×$CH(CH_3)_2$), 20.4 ($NCH_2CH_2CH_2CH_3$), 21.3 (1×$CH(CH_3)_2$), 21.6 (3″-CH_3), 25.0 ($CH(CH_3)_2$), 29.2 ($NCH_2CH_2CH_2CH_3$), 40.4 (C-3″), 43.6 (C-5″), 53.1 (C-6″), 57.8 ($NCH_2CH_2CH_2CH_3$), 59.9 (C-2″), 61.9 (OCH_3), 66.83 (CH_2O_2C), 87.7 (C-4″), 127.8 (C-4′), 128.3 (C-1), 128.6 (C-5), 130.3 (C-6), 131.0 (C-3), 131.7 (C-2), 132.8 (C-4), 146.0 (C-3′), 164.6 (COO), 169.6 (C-5′), 170.64 (C-2′); m/z (FAB$^+$) 471 (MH^+, 100%), 439 (8), 427 (31), 328 (12), 240 (12), 214 (50), 196 (3); found [MH^+] 471.28601. $C_{27}H_{39}N_2O_5$ requires 471.28590.

4.7.4. ((3S,4S*,5R*)-1-Butyl-4-methoxy-3-methyl-5-phenylpiperidin-3-yl)methyl 2-(3-methyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoate* ***9d***. Prepared using general procedure F from alcohol **8d** (0.24 mmol, 70 mg) with purification by flash chromatography (9:1 hexane, ethyl acetate) to afford the title compound **9d** (89 mg, 74%) as a yellow foam. R_f =0.4; IR (neat) ν_{max} 3067 (=CH–), 3028 (CH, Ph), 2953, 2928, 2867, 2814, 2760 (C–H), 1784, 1711 (COO, C=O), 1643 (C=C), 1602, 1582, 1493, 1466, 1452, 1393, 1293, 1256 (C–N), 1209, 1176, 1136, 1102, 1083, 1042 (C–O); δ_H (300 MHz; $CDCl_3$) 0.81 (3H, t, J=7.2 Hz, $NCH_2CH_2CH_2CH_3$), 1.10 (3H, s, 3″-CH_3), 1.26 (2H, sext, J=7.2 Hz, $NCH_2CH_2CH_2CH_3$), 1.37 (2H, p, J=7.2 Hz, $NCH_2CH_2CH_2CH_3$), 1.74 (1H, d, J=11.6 Hz, 2″$_A$-H), 2.18 (4H, m, 3′-CH_3 and 6″$_A$-H), 2.28 (2H, m, $NCH_2CH_2CH_2CH_3$), 2.87 (3H, s, 4″-OCH_3), 2.91–4.04 (4H, m, 6$_B$″-H, 2$_B$″-H, 5″-H and 4″-H), 4.36 (1H, d, J=10.2 Hz, 3″-CH_AH_BO), 4.75 (1H, d, J=10.5 Hz, 3″-CH_AH_BO), 6.50 (1H, q, J=1.8 Hz, 4′-H), 7.19–7.33 (6H, m, 5″-Ph and 6-H), 7.49 (1H, td, J=7.6, 1.3 Hz, 5-H), 7.64 (1H, td, J=7.6, 1.5 Hz, 4-H), 8.09 (1H, dd, J=7.8, 1.5 Hz, 3-H); δ_C (75 MHz; $CDCl_3$) 11.2 (3′-CH_3), 13.9 ($NCH_2CH_2CH_2CH_3$), 20.4 ($NCH_2CH_2CH_2CH_3$), 21.3 (3″-CH_3), 29.3 ($NCH_2CH_2CH_2CH_3$), 40.6 (C-3″), 46.3 (C-5″), 57.4 ($NCH_2CH_2CH_2CH_3$), 60.2 (C-6″), 60.3 (C-2″), 61.7 (4″-OCH_3), 66.7 (3″-CH_2COO), 90.9 (C-4″), 126.7 (5″-Ph), 127.9 (C-4′), 128.2 (5″-Ph), 128.5 (C-1), 128.8 (C-5), 130.5 (C-6), 131.2 (C-3), 132.0 (C-2), 132.9 (C-4), 141.7 (5″-Ph), 146.1 (C-3′), 164.6 (COO), 169.8 (C-5′), 170.8 (C-2′); m/z (EI$^+$, %) 505 (MH^+, 14%), 473 (17), 274 (15), 242 (11), 214 (100), 186 (1), 157 (4), 138 (1); found [MH^+] 505.2691. $C_{31}H_{38}N_2O_5$ requires 505.2703.

4.7.5. ((3S,4S*,5R*)-5-Allyl-1-butyl-4-methoxy-3-methylpiperidin-3-yl)methyl 2-(3-methyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoate* ***9e***. Prepared using general procedure F from alcohol **8e** (0.78 mmol, 0.20 g) with purification by flash chromatography (9:1 hexane, ethyl acetate) to afford the title compound **9e** (0.252 g, 77%) as a viscous yellow oil. R_f =0.2; IR (neat) ν_{max} 3075 (=CH_2, =CH–), 2957. 2928, 2864, 2832, 2803, 2757 (C–H), 1785, 1709 (COO, C=O), 1643 (C=C), 1602, 1579, 1536, 1493, 1466, 1454, 1391, 1293, 1258 (C–N), 1209, 1195, 1177, 1165, 1136, 1106, 1085, 1045 (C–O); δ_H (300 MHz; $CDCl_3$) 0.82 (3H, t, J=7.2 Hz, $NCH_2CH_2CH_2CH_3$), 1.06 (3H, s, 3″-CH_3), 1.24 (2H, sext, J=7.2 Hz, $NCH_2CH_2CH_2CH_3$), 1.35 (2H, p, J=7.2 Hz, $NCH_2CH_2CH_2CH_3$), 1.55 (1H, d, J=1.7 Hz, 6″$_A$-H), 1.63 (1H, d, J=12.7 Hz, 2″$_A$-H), 1.72–1.89 (2H, m, 5″-CH_AH_BCH=CH_2, 5″-H), 2.11–2.31 (5H, m, $NCH_2CH_2CH_2CH_3$ and 3′-CH_3), 2.43–2.50 (1H, m, 5″-CH_AH_BCH=CH_2), 2.54 (1H, d, J=10.2 Hz, 4″-H), 2.81–2.89 (2H, m, 2″$_B$-H and 6″$_B$-H), 3.49 (3H, s, 4″-OCH_3), 4.30 (1H, d, J=10.3 Hz, 3″-CH_AH_BOOC), 4.58 (1H, d, J=10.4 Hz, 3″-CH_AH_BOOC), 5.01 (2H, m, 5″-CH_2CH=CH_2), 5.75 (1H, m, 5″-CH_2CH=CH_2), 6.49 (1H, q, J=1.8 Hz, 4′-H), 7.29 (1H, dd, J=7.9, 1.2 Hz, 6-H), 7.48 (1H, td, J=7.7, 1.4 Hz, 5-H), 7.62 (1H, td, J=7.7, 1.6 Hz, 4-H), 8.06 (1H, dd, J=7.8, 1.5 Hz, 3-H); δ_C (75 MHz; $CDCl_3$) 11.2 (3′-CH_3), 13.9 ($NCH_2CH_2CH_2CH_3$), 20.5 ($NCH_2CH_2CH_2CH_3$), 21.5 (3″-CH_3), 29.3 ($NCH_2CH_2CH_2CH_3$), (5″-CH_2CH=CH_2), 35.3 ($NCH_2CH_2CH_2CH_3$), 39.0 (C-5″), 57.6 ($NCH_2CH_2CH_2CH_3$), 58.5 (C-6″), 60.2 (C-2″), 62.5 (4″-OCH_3), 66.9 (3″-CH_2COO), 91.1 (C-4″), 116.1 (5″-CH_2CH=CH_2), 127.9 (C-4′), 128.5 (C-5), 130.5 (C-6), 131.2 (C-3), 131.9 (C-2), 132.9 (C-4), 136.6 (5″-CH_2CH=CH_2), 146.1 (C-3′), 164.6 (COO), 169.8 (C-5′), 170.8 (C-2′); m/z (EI$^+$, %) 469 (MH^+, 16%), 437 (21), 238 (15), 214 (100), 206 (16), 186 (1), 164 (3), 138 (2); found [MH^+] 469.2692. $C_{27}H_{37}N_2O_5$ requires 469.2703.

4.7.6. ((5aR,9S,9aS)-7-Butyl-9-methyl-2,5,5a,6,7,8,9,9a-octahydrooxepino[3,2-c]pyridin-9-yl)methyl 2-(3-methyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoate ***9f***. Prepared using general procedure F from alcohol **8f** (0.20 mmol, 50 mg) with purification by flash chromatography (9:1 hexane, ethyl acetate) to afford the title compound **9f** (59 mg, 64%) as a viscous yellow oil. R_f =0.3; IR (neat) ν_{max} 3096 (=CH), 2953, 2764 (C–H), 1785, 1707 (COO, C=O), 1645 (C=C), 1602, 1579, 1536, 1493, 1454, 1293, 1259 (C–N), 1209, 1177, 1135, 1106, 1085, 1044, 1033 (C–O); δ_H (300 MHz; $CDCl_3$) 0.81 (3H, t, J=7.2 Hz, $NCH_2CH_2CH_2CH_3$), 1.04 (3H, s, 9″-CH_3), 1.25 (2H, sext, J=7.2 Hz, $NCH_2CH_2CH_2CH_3$), 1.37 (2H, p, J=7.2 Hz, $NCH_2CH_2CH_2CH_3$), 1.55 (1H, d, J=11.6 Hz, 8$_A$″-H), 1.62 (1H, t, J=11.0, 6$_A$″-H), 1.78–1.99 (2H, m, 5a″-H and 5″-H$_A$), 2.04–2.30 (6H, m, 5″-H$_B$, 3′-CH_3 and $NCH_2CH_2CH_2CH_3$), 2.76 (1H, d, J=11.0 Hz, 6$_B$″-H), 2.91 (1H, dd, J=11.6, 2.8 Hz, 8$_B$″-H), 2.92 (1H, d, J=9.5 Hz, 9a″-H), 3.91 (1H, d, J=14.0 Hz, 2″-H$_A$), 4.25 (1H, m, 2″-H$_B$), 4.29 (1H, d, J=10.5 Hz, 9″-OCH_AH_BOOC), 4.61 (1H, d, J=10.5 Hz, 9″-OCH_AH_BOOC), 5.83–5.85 (2H, m, 3″-H and 4″-H), 6.51 (1H, q, J=1.8 Hz, 4′-H), 7.30 (1H, dd, J=8.0, 0.9 Hz, 6-H), 7.49 (1H, td, J=7.6, 1.2 Hz, 5-H), 7.64 (1H, td, J=7.6, 1.4 Hz, 4-H), 7.08 (1H, dd, J=7.6, 1.4 Hz, 3-H), δ_C (75 MHz; $CDCl_3$) 11.1 (3′-CH_3), 13.9 ($NCH_2CH_2CH_2CH_3$), 20.4 ($NCH_2CH_2CH_2CH_3$), 20.8 (9″-CH_3), 29.3 ($NCH_2CH_2CH_2CH_3$), 33.3 (C-5″), 37.3 (C-5a″), 57.5 ($NCH_2CH_2CH_2CH_3$), 60.1 (C-6″), 60.2 (C-8″), 66.9 (9″-CH_2OOC), 68.4 (C-2″), 93.0 (C-9a″), 127.8 (C-4′), 128.9 (C-5), 130.3 (C-6), 131.0 (C-3), 131.5 (C-3″ and C-4″), 133.2 (C-4), 146.2 (C-3′), 164.6 (COO), 169.7 (C-5′), 170.8 (C-2′); m/z (EI$^+$, %) 467 (MH^+,

6%), 236 (13), 214 (100), 186 (2), 158 (1); found [MH^+] 467.2543. $C_{27}H_{35}N_2O_5$ requires 467.2546.

Acknowledgements

We wish to thank the University of Auckland for supporting this research.

References and notes

1. Manske, R. H. *Can. J. Res.* **1938**, *16B*, 57.
2. (a) Kukel, C. F.; Jennings, K. R. *Can. J. Physiol. Pharmacol.* **1994**, *72*, 104; (b) Macallan, D. R. E.; Lunt, G. G.; Wonnacott, S.; Swanson, K. L.; Rapoport, H.; Albuquerque, E. X. *FEBS Lett.* **1988**, *226*, 357; (c) Reina, M.; González-Coloma, A. *Phytochem. Rev.* **2007**, *6*, 81.
3. (a) Jennings, K. R.; Brown, D. G.; Wright, D. P. *Experientia* **1986**, *42*, 611; (b) Wonnacott, S.; Alburquerque, E. X.; Bertrand, D. *Methods Neurosci.* **1993**, *12*, 263.
4. Goodall, K. J.; Barker, D.; Brimble, M. A. *Synlett* **2005**, 1809.
5. (a) Doisy, X.; Blagbrough, I. S.; Wonnacott, S.; Potter, B. V. L. *Pharm. Pharmacol. Commun.* **1998**, *4*, 313; (b) Bergmeier, S. C.; Lapinsky, D. J.; Free, R. B.; McKay, D. B. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2263; (c) Bryant, D. L.; Free, R. B.; Thomasy, S. M.; Lapinsky, D. J.; Ismail, K. A.; Arason, K. M.; Bergmeier, S. C.; McKay, D. B. *Ann. N.Y. Acad. Sci.* **2002**, *971*, 139; (d) 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; (e) Bergmeier, S. C.; Ismail, K. A.; Arason, K. M.; McKay, S.; Bryant, D. L.; McKay, D. B. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3739; (f) Ismail, K. A.; Bergmeier, S. C. *Eur. J. Med. Chem.* **2002**, *37*, 469; (g) Simoni, D.; Rossi, M.; Rondanin, R.; Baruchello, R.; Grisolia, G.; Eleopra, M.; Giovannini, R.; Bozzoli, A.; Davalli, S.; Di Fabio, R.; Donati, D. *Tetrahedron Lett.* **2005**, *46*, 759; (h) Huang, J.; Orac, C. M.; McKay, S.; McKay, D. B.; Bergmeier, S. C. *Bioorg. Med. Chem.* **2008**, *16*, 3816.
6. (a) Guthmann, H.; Conole, D.; Wright, E.; Koerber, K.; Barker, D.; Brimble, M. A. *Eur. J. Org. Chem.* **2009**, 1944; (b) Huang, J.; Bergmeier, S. C. *Tetrahedron* **2008**, *64*, 6434.
7. (a) Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679; (b) Danieli, B.; Lesma, G.; Passarella, D.; Silvani, A. *Tetrahedron Lett.* **2000**, *41*, 3489; (c) Danieli, B.; Lesma, G.; Passarella, D.; Silvani, A. *J. Org. Chem.* **1998**, *63*, 3492; (d) Davis, F. A.; Chao, B.; Rao, A. *Org. Lett.* **2001**, *3*, 3169; (e) Lagisetty, P.; Powell, D. R.; Awasthi, V. *J. Mol. Struct.* **2009**, *936*, 23; (f) Albrecht, B. K.; Berry, V.; Boezio, A. A.; Cao, L.; Clarkin, K.; Guo, W.; Harmange, J.-C.; Hierl, M.; Huang, L.; Janosky, B.; Knop, J.; Malmberg, A.; McDermott, J. S.; Nguyen, H. Q.; Springer, S. K.; Waldon, D.; Woodin, K.; McDonough, S. I. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5209.
8. (a) Wang, Y.; Yu, D.-F.; Liu, Y.-Z.; Wei, H.; Luo, Y.-C.; Dixon, D. J.; Xu, P.-F. *Chem.—Eur. J.* **2010**, *16*, 3922; (b) Clarke, P. A.; Zaytsev, A. V.; Whitwood, A. C. *Synthesis* **2008**, 3530; (c) Sales, M.; Charette, A. B. *Org. Lett.* **2005**, *7*, 5773.
9. (a) Coldham, I.; Raimbault, S.; Whittaker, D. T. E.; Chovatia, P. T.; Leonori, D.; Patel, J. J.; Sheikh, N. S. *Chem.—Eur. J.* **2010**, *16*, 4082; (b) Cheng, G.; Wang, X.; Su, D.; Liu, H.; Liu, F.; Hu, Y. *J. Org. Chem* **2010**, *75*, 1911; (c) Fustero, S.; Jimenez, D.; Moscardo, J.; Catalan, S.; del Pozo, C. *Org. Lett.* **2007**, *9*, 5283; (d) Rajender, R.; Leleti, D.; Sonia, G.; Liu, Y.; Prashad, M. *J. Org. Chem.* **2010**, *75*, 2236.
10. (a) Hande, S. M.; Kawai, N.; Uenishi, J. *J. Org. Chem.* **2009**, *74*, 244; (b) Murty, M. S. R.; Ram, R.; Yadav, J. S. *Tetrahedron Lett.* **2008**, *49*, 1141; (c) Dobbs, A. P.; Guesne, S. J. J. *Synlett* **2005**, 2101; (d) Carballo, R. M.; Ramirez, M. A.; Rodriguez, M. L.; Martin, V. S.; Padron, J. I. *Org. Lett.* **2006**, *8*, 3837.
11. Brimble, M. A.; Brocke, C. *Eur. J. Org. Chem.* **2005**, 2385.
12. (a) Halliday, J. I.; Chebib, M.; Turner, P.; McLeod, M. D. *Org. Lett.* **2006**, *8*, 3399; (b) Mityuk, A. P.; Denisenko, A. V.; Dacenko, O. P.; Grygorenko, O. O.; Mykhailiuk, P. K.; Volochnyuk, D. M.; Shishkin, O. V.; Tolmachev, A. A. *Synthesis* **2010**, 493.
13. (a) Kuthan, J.; Palecek, J. *Coll. Czech CC* **1963**, *28*, 2260; (b) Calabrese, A.A.; Fradet, D.S.; Hepworth, D.; Lansdell, M. U.S. Patent 20,050,176,772, 2005.
14. Chan, Y.; Guthmann, H.; Brimble, M. A.; Barker, D. *Synlett* **2008**, 2601.
15. Yoshizawa, K.; Toyota, S.; Toda, F. *Tetrahedron Lett.* **2001**, *42*, 7983.
16. Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.
17. Danel, K.; Larsen, E.; Pedersed, E. B. *Synthesis* **1995**, *8*, 934.
18. Base promoted methylation of ethyl 4-phenyl-2-oxobutanoate gave alkylation at both the α- and γ-positions, whilst the crossed Claisen method of Misaki et al. (Ref. 19) gave low and variable yields.
19. Misaki, T.; Nagase, R.; Matsumoto, K.; Tanabe, Y. *J. Am. Chem. Soc.* **2005**, *127*, 2854.
20. (a) Buckley, B. R.; Page, P. C. B.; Heaney, H.; Sampler, E. P.; Carley, S.; Brocke, C.; Brimble, M. A. *Tetrahedron* **2005**, *61*, 5876; (b) Brocke, C.; Brimble, M. A.; Lin, D. S.-H.; McLeod, M. D. *Synlett* **2004**, 2359; (c) Heaney, H.; Papageorgiou, G. *Tetrahedron* **1996**, *52*, 3473.
21. Beeson, C.; Pham, N.; Dix, T. A. *Tetrahedron Lett.* **1992**, *43*, 2925.
22. The diastereoisomers of these compounds were not separable even after formation of the methyl ether and reduction of the ester.
23. Lehmann, A.; Brocke, C.; Barker, D.; Brimble, M. A. *Eur. J. Org. Chem.* **2006**, 3205.
24. Barker, D.; Brimble, M. A.; McLeod, M. D. *Synthesis* **2003**, *5*, 656.
25. Nagao, K.; Chiba, M.; Kim, S. W. *Synthesis* **1983**, *3*, 197.
26. Dowd, P.; Choi, S. C. *Tetrahedron* **1991**, *47*, 4847.
27. Bonjoch, J.; Linares, A.; Guardia, M.; Bosch, J. *Heterocycles* **1987**, *26*, 2165.