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Synthesis of simple analogues of methyllycaconitine—an efficient method for the preparation of the *N*-substituted anthranilate pharmacophore

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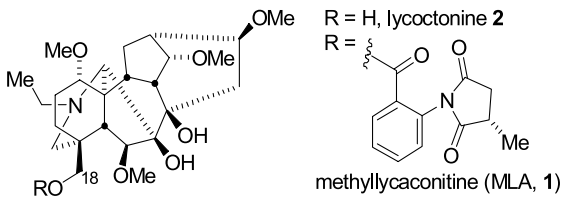
Abstract—The synthesis of several A and AE ring analogues of the alkaloid methyllycaconitine is reported. The key 2-(2″-methylsuccinimido)benzoate ester pharmacophore is introduced using an efficient two step procedure. Esterification of the alcohol precursors with *N*-(trifluoroacetyl)anthranilic acid under Steglich conditions followed by sodium borohydride mediated cleavage of the trifluoroacetyl group affords the anthranilate esters. Subsequent fusion with methylsuccinic anhydride affords the *N*-substituted anthranilate derivatives containing the key pharmacophore present in a range of commonly occurring *Delphinium* and *Aconitum* alkaloids.

Nicotinic acetylcholine receptors (nAchRs) are a family of ligand gated ion channels that are widely distributed in the human brain.[1,2] These receptors have numerous receptor subtypes composed of combinations of α2-7, α9-10 and β2-4 subunits.[3] nAchRs are involved in a number of physiological and behavioural conditions hence there is a pressing need for subtype selective agonists and antagonists to elucidate the biological roles of these receptors and to provide candidates for drug discovery. The α7 nAChR subtype is amongst the most prevalent in the brain and has been implicated as playing a key role in conditions such as schizophrenia, Alzheimer's disease and epilepsy.[4] Methyllycaconitine (MLA) **1**[5] is one of only a few compounds (including the peptide toxins α-bungarotoxin[6] and α-conotoxin ImI[7]) that binds with high affinity and selectivity to the α7 nAChR. MLA **1** is therefore a prime lead compound for development of new therapies targeting the α7 nAChR. We have therefore embarked on a programme to provide novel compounds that may help elucidate the key structural features of nAChR ligands that give rise to binding affinity, subtype selectivity and agonist/antagonist activity.



MLA **1** is the major toxic component of *Delphinium brownii*[8] and is a potent antagonist of the α7 nAChR in mammalian neuronal membranes. Furthermore, it exhibits very high selectivity for this subtype over other neuronal nAChRs rendering it a prime lead for the development of new therapeutic agents targeting the α7 nAChR. Structure activity studies on MLA have shown the *N*-substituted anthranilate ester moiety is an essential structural feature for pharmacological activity[9] and competitive ligand binding studies revealed that MLA **1** containing the 2-(2′-methylsuccinimido)benzoate ester sidechain displays ca. 10^3 times more potent inhibition that the parent alkaloid lycoctonine **2**.[10] It has also been proposed that the tertiary amine and ester sidechain of MLA form an acylated homocholine pharmacophore at physiological pH that gives rise to the high affinity nicotinic acetylcholine receptor binding.

A number of approaches to the synthesis of small molecule analogues of MLA incorporating the putative pharmacophore have been reported, including the synthesis of E,[11] AE[12] and AEF[13] ring systems, some of which display

Keywords: Methyllycaconitine; Anthranilate esters; Nicotinic acetylcholine receptors; Alkaloids.
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significant biological activity.[11,14] Given the demonstrated importance of the *N*-substituted anthranilate sidechain to the pharmacology of MLA analogues, we herein report[15] the full synthetic details for several analogues of MLA prepared using our recently developed efficient procedure for the introduction of this key structural unit.

Previous syntheses of *Delphinium* alkaloids and their analogues that contain a 2-(2′-methylsuccinimido)benzoate ester sidechain have made use of one of two methods (Scheme 1). The first method involves a two-step process using isatoic anhydride **3** to convert the alcohol into an anthranilate[16] then adding methylsuccinic anhydride **4** to form the desired cyclic imide. The second more convergent method involves direct addition of the entire 2-(3-methyl-2,5-dioxopyrrolidin-1-yl)benzoate group to the alcohol in a single step by esterification of the alcohol with acid **5**.

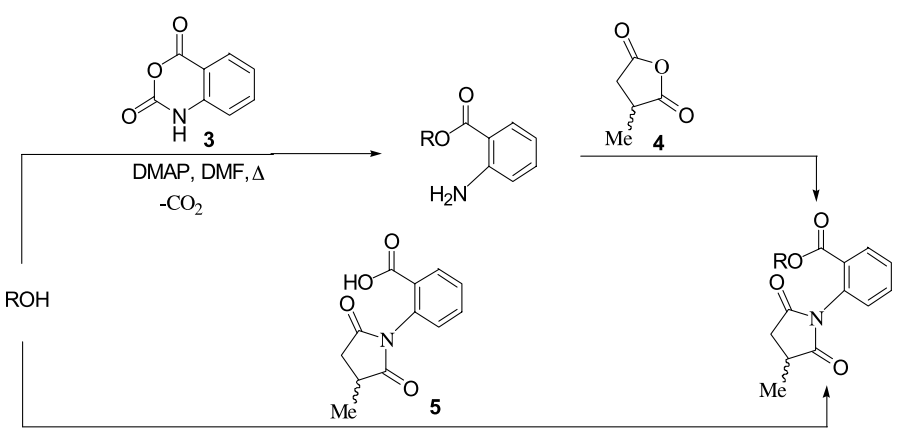
Kraus and Dneprovskaia[13b] reported the esterification of 2-(3-methyl-2,5-dioxopyrrolidin-1-yl)benzoic acid **5** by formation of the sodium salt of acid **5** followed by treatment with oxalyl chloride to generate the acid chloride, however our attempts to repeat this procedure met with little success. The same authors also reported that this high yielding esterification procedure failed to work using more hindered neopentyl-type alcohols giving mixtures of the desired ester and undesired isomeric carbamate by-product, and the procedure failed completely when using tertiary alcohols. They overcame this problem by effecting an S_N2 displacement of the neopentyl mesylate by the sodium salt of acid **5**. In our hands this procedure failed to give significant quantities of the anthranilate ester of the model compound, 1-methyl-3-piperidinemethanol **7** (Table 1). Bergmeier and co-workers[11a] reported that esterification of acid **5** using the coupling agent, 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) was inconsistent with yields ranging from 6 to 60%.

Use of isatoic anhydride **3** as developed by Blagbrough[17] has been adopted by others to append the anthranilate ester group to MLA analogues.[13] In general, low yields (typically 40–65%) of the desired anthranilate esters are obtained which can be attributed to the hindered neopentyl environment of the C-18 hydroxyl group present in lycoctonine and many simpler analogues. The low yields of ester formation by these methods have prompted investigations into the introduction of this sidechain by alternative procedures,[13,18] however none of these methods has offered a general and high yielding solution to the problem of sidechain introduction.

In connection with our studies towards MLA analogues we turned our attention to the use of *N*-(trifluoroacetyl)anthranilic acid **6**[19] and the coupling procedure developed by Breslow[19] as an alternative to the isatoic anhydride mediated synthesis. Initial attempts to repeat this coupling procedure on stoichiometric quantities of the alkoxide salt derived from 1-methyl-3-piperidinemethanol (**7**, Table 1) did not result in practical yields of the coupled product. However, reaction of **7** with 3 equiv. of *N*-(trifluoroacetyl)-anthranilic acid **6** under Steglich conditions[11] (DCC/DMAP) followed directly by sodium borohydride mediated cleavage of the crude amide gave a gratifying 81% yield of the anthranilate ester. This compares favourably with the base catalysed reaction of isatoic anhydride, which in our hands proceeded in 72% yield (Table 1, entry 1).[16b] This high yielding and operationally simple anthranilate ester synthesis prompted us to explore the scope of this coupling reaction as an alternative approach.

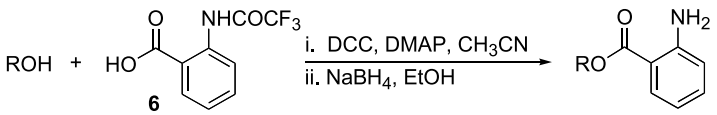
This two step coupling procedure was studied using a range of primary, neopentyl, secondary and tertiary alcohols together with the azabicyclic neopentyl alcohols **8**, **9** (Table 1) and diol **10** (Scheme 3). Heating ethyl 2-oxocyclohexane carboxylate with ethylamine and formaldehyde, according to the method of Iwai et al.[21] afforded the double Mannich adduct **11** (Scheme 2) that underwent Wittig reaction with the ylide derived from methyltriphenylphosphonium bromide to afford alkene **12** and thence alcohol **8** upon reduction of the ester with $LiAlH_4$. Reduction of keto ester **11** afforded a 1:1.25 mixture of the alcohols **13** and **14** and the major isomer **14** underwent smooth methylation to methyl ether **15**, followed by reduction of the ester to alcohol **9**. Direct reduction of **11** with $LiAlH_4$ afforded diol **10** that was used to probe the selective esterification of the neopentyl alcohol using this coupling procedure.

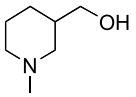
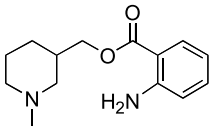
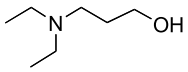
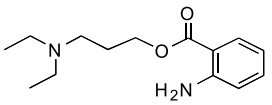
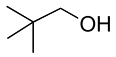
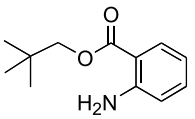
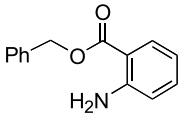
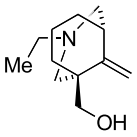
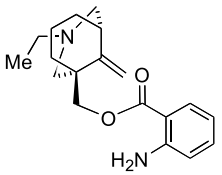
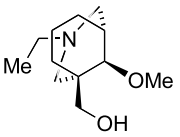
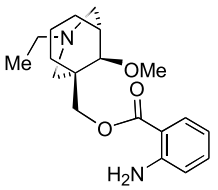
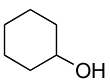
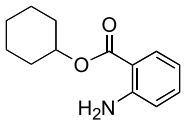
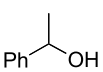
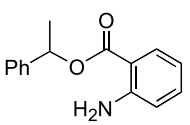
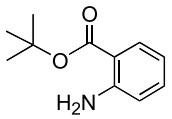
The reaction of a range of simple primary alcohols with *N*-(trifluoroacetyl)anthranilic acid **6** afforded good yields of the anthranilate esters in comparison with the isatoic anhydride mediated synthesis (Table 1, entries 2, 3 and 4).



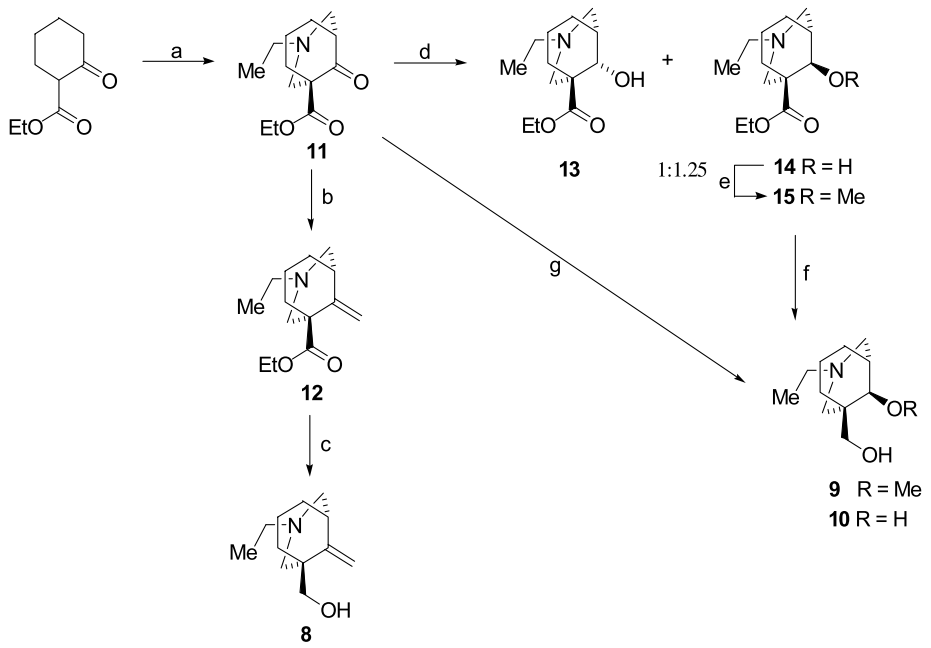
Scheme 1.

Table 1. Synthesis of anthranilate esters with *N*-(trifluoroacetyl)anthranilic acid **6**



Entry	Alcohol	Product	Yield of ester (%)[a]
1	 **7**	 **16**	81 (72)[b,c]
2		 **17**	85 (75)[b,c]
3		 **18**	94 (64)[b,d]
4		 **19**	85 (90)[b,e]
5	 **8**	 **20**	75 (40)[b,c]
6	 **9**	 **21**	78 (65)[b,d]
7		 **22**	97 (16)[b,c]
8		 **23**	91
9		 **24**	39 (77)[f]

[a] Yield of anthranilate ester prepared by alternative literature based methods in parentheses.
[b] Prepared by reaction with isatoic anhydride.
[c] Prepared according to Ref. 16b.
[d] See Ref. 17c.
[e] See Ref. 16b.
[f] See Ref. 19.



Scheme 2. Reagents and conditions: (a) $EtNH_2$, CH_2O, EtOH, reflux, 30 h, 27%; (b) *n*-BuLi, $MePPh_3Br$, THF, 92%; (c) $LiAlH_4$, THF, room temperature, 10 min, 94%; (d) $NaBH_4$, 1:1 THF/H_2O, 0 °C, 30 min, 81%; (e) NaH, MeI, THF, 0 °C, 70%; (f) $LiAlH_4$, THF, room temperature, 2 h, 91%; (g) $LiAlH_4$, THF, room temperature, 1 h, 54%.

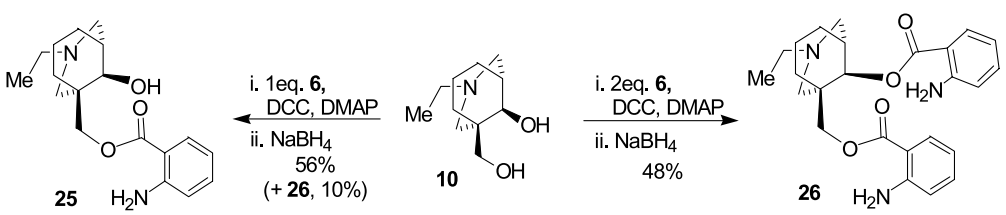
Extension of this procedure to AE bicyclic analogues of MLA, **8** and **9**[17d] (Table 1, entries 5 and 6) containing neopentyl substituted alcohols, also afforded coupled product in improved yield.

Secondary alcohols were observed to react readily with **6** to afford high yields of the anthranilate ester (Table 1, entries 7 and 8) providing the first direct, high yielding synthesis of anthranilate esters derived from secondary alcohols reported in the literature.[16] Attempts to promote the esterification of tertiary alcohols however, afforded lower yields of the coupled product, in line with the synthesis of *t*-butyl benzoate ester derivatives initially reported by Steglich.[20] The use of di-2-pyridyl thiocarbonate, recommended[22] for the synthesis of esters derived from tertiary alcohols, failed to give the desired product.

The extreme conditions associated with the isatoic anhydride mediated synthesis of anthranilate esters have been reported to lead to poor regioselectivity or possibly transesterification during reactions with diol substrates.[5a] We therefore investigated the new procedure to assess its potential for kinetic discrimination leading to the selective esterification of diol substrates (Scheme 3). To this end the reaction of bicyclic diol **10** with 1 equiv. of acid **6** favoured reaction at the primary hydroxyl to give mono-anthranilate ester **25** in 56%, together with a small quantity of the diester **26** (10%). Reaction of **10** with 2 equiv. of acid **6** gave the di-ester **26** in a moderate 48% yield.

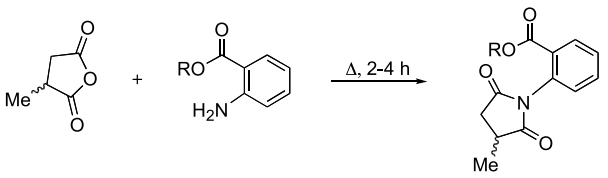
Finally, heating the anthranilate esters with 2 equiv. of 2-methylsuccinic acid at 125 °C according to the procedure of Blagbrough[17c] cleanly afforded the succinimide derivatives in good yield (Table 2). This procedure therefore offers a simple two step synthesis of the 2-(2′-methylsuccinimido)benzoate ester sidechain present in methyllycaconitine **1** and other *Delphinium* alkaloids.

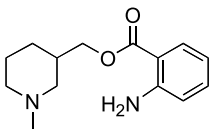
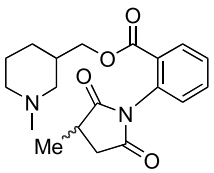
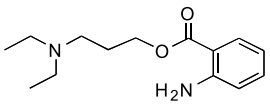
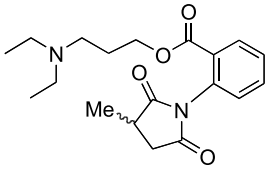
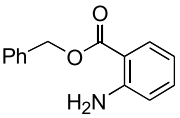
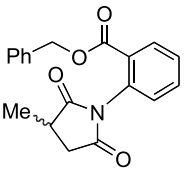
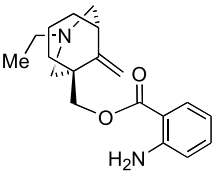
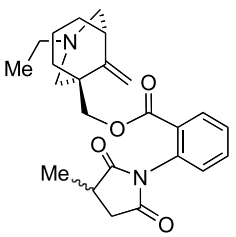
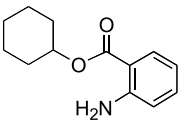
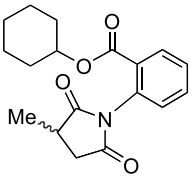
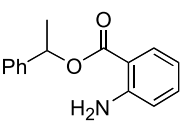
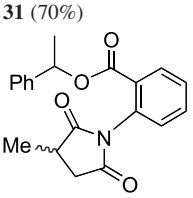
In conclusion, we have developed a practical, high yielding synthesis of anthranilate esters from primary and secondary alcohols using *N*-(trifluoroacetyl)anthranilic acid **6**. The reactions proceed under mild conditions and offer a practical alternative to existing procedures. The method has wide applicability for the synthesis of diterpenoid alkaloids such as methyllycaconitine **1** and their analogues and has been readily adopted by us for the synthesis of more complex tricyclic analogues of MLA.



Scheme 3.

Table 2. Reaction of anthranilate esters with methyl succinic anhydride



Entry	Anthranilate ester	Succinimide (yield %)
1	 **16**	 **27** (96%)
2	 **17**	 **28** (91%)
3	 **19**	 **29**[a] (73%)
4	 **20**	 **30** (84%)
5	 **22**	 **31** (70%)
6	 **23**	 **32** (70%)

[a] See Ref. 13a.

1. Experimental

1.1. General details

tert-Butyl 2-aminobenzoate **24** was synthesised using standard procedure given in Section 1.2 to give data which is in agreement literature values.[19] Benzyl 2-(3-methyl-2,5-dioxopyrrolidin-1-yl)benzoate **29** was synthesised using standard procedure given in Section 1.3 to give data which is in agreement literature values.[13a] All reactions were conducted in flame-dried or oven-dried glassware under a dry nitrogen atmosphere unless otherwise noted. Tetrahydrofuran was dried over sodium/benzophenone and distilled prior to use. Flash chromatography was performed using Merck Kieselgel 60 (230–400 mesh) with the indicated solvents. Thin layer chromatography (TLC) was carried out on precoated silica plates (Merck Kieselgel $60F_{254}$) and compounds were visualized by UV fluorescence or by staining with vanillin in methanolic sulfuric acid and heating. Infrared spectra were recorded with a Perkin Elmer 1600 series Fourier-transform infrared spectrometer as thin films between sodium chloride plates. Absorption maxima are expressed in wavenumbers (cm^{-1}) with the following abbreviations: s=strong, m=medium, w=weak and br=broad. ^1H and ^{13}C NMR spectra were obtained using a Bruker AC 200B or a Bruker AM 400 spectrometer. All chemical shifts are given in parts per million (ppm) downfield from tetramethylsilane as internal standard (^1H) or relative to $CDCl_3$ (^{13}C) and J values are given in Hz. ^1H NMR data are tabulated as s, singlet; d, doublet; t, triplet; q, quartet, m, multiplet, br, broad. High-resolution mass spectra were recorded using a VG70-SE spectrometer operating at nominal accelerating voltage of 70 eV. Chemical ionisation (CI) mass spectra were obtained with ammonia as the reagent gas.

1.1.1. Ethyl (1*R* *,5*R* *)-3-ethyl-9-oxo-3-azabicyclo-[3.3.1]nonane-1-carboxylate 11.[17d] A mixture of ethyl 2-oxo-cyclohexane-1-carboxylate (5.60 g, 32.9 mmol), ethylamine (1.48 g, 32.9 mmol, 40% aq. v/v) and formaldehyde (1.97 g, 65.8 mmol, 36% aq. v/v) in ethanol (500 ml) was heated under reflux for 30 h. After removal of the solvent at reduced pressure, the oily orange residue was dissolved in ether (200 ml) and extracted with 2 M hydrochloric acid (3×80 ml). The aqueous extract was made basic with 10% sodium hydroxide then extracted with ether (3×150 ml) and dried over anhydrous sodium sulfate. The solvent was removed at reduced pressure and the resultant dark orange oil was purified by flash chromatography (19:1 hexane–ethyl acetate) to afford the title compound **11** (2.10 g, 27%) as a bright yellow oil. $\nu_{max}(NaCl)/cm^{-1}$ 1738 (C=O, ester), 1718 (C=O, ketone); δ_H (400 MHz; $CDCl_3$) 1.07 (3H, t, J=7.2 Hz, NCH_2CH_3), 1.25 (3H, t, J=7.2 Hz, OCH_2CH_3), 1.45–1.53 (1H, m, 7B-H), 1.98–2.29 (3H, m, 6-CH_2, 8A-H), 2.35–2.54 (5H, m, 4B-H, 5-H, 8B-H, NCH_2CH_3), 2.76–2.87 (1H, m, 7A-H), 2.89 (1H, d, J_{gem}=11.4 Hz, 2B-H), 3.11 (1H, ddd, $J_{4A,5}$=2.2 Hz, $J_{4A,2A}$=2.2 Hz, J_{gem}=11.0 Hz, 4A-H), 3.18 (1H, dd, $J_{2A,4A}$=2.2 Hz, J_{gem}=11.4 Hz, 2A-H), 4.17 (2H, q, J=7.2 Hz, OCH_2CH_3); δ_C (100 MHz; $CDCl_3$) 12.6 (CH_3, NCH_2CH_3), 14.0 (CH_3, OCH_2CH_3), 20.4 (CH_2, C-7), 34.0 (CH_2, C-6), 36.7 (CH_2, C-8), 47.1 (CH, C-5), 51.0 (CH_2, NCH_2CH_3), 58.7 (quat., C-1), 59.8 (CH_2, C-4), 60.9 (CH_2, OCH_2CH_3), 61.5 (CH_2, C-2), 171.1 (quat., OC=O), 212.6 (quat., C-9); m/z (EI) 239 (M^+, 13), 224 ($M-CH_3$, 17), 222 (100), 210 ($M-C_2H_5$, 7), 196 (64), 194 ($M-OC_2H_5$, 32).

1.1.2. Ethyl (1*S* *,5*S* *)-3-ethyl-9-methylidene-3-aza-bicyclo[3.3.1]nonane-1-carboxylate 12. *n*-BuLi (5.3 ml,

8.48 mmol, 1.6 M solution in hexane) was added dropwise to a suspension of methyltriphenylphosphonium bromide (4.06 g, 11.37 mmol) in dry THF (40 ml) at −78 °C. The reaction mixture was stirred at 0 °C for 10 min then cooled to −78 °C and ethyl (1*R**,5*R**)-3-ethyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate **11** (680 mg, 2.84 mmol) in dry THF (10 ml) added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction was quenched with distilled water (10 ml) and the solvent removed at reduced pressure. The residue was dissolved in dry ether (40 ml) and extracted with 2 M hydrochloric acid (3×80 ml). The aqueous extract was made basic with 10% sodium hydroxide solution (250 ml) then extracted with ether (3×100 ml) then dried ($MgSO_4$) and concentrated in vacuo to leave the crude product which was purified by flash chromatography (19:1 hexane–ethyl acetate) to give the title compound **12** (624 mg, 92%) as a pale yellow oil. ν_{max}(NaCl)/cm^{-1} 2915 (CH), 1728 (C═O), 1651 (C═C), 1452, and 1252; δ_H (200 MHz; $CDCl_3$) 1.00 (3H, t, *J*=7.2 Hz, NCH_2CH_3), 1.19 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 1.36–1.82 (1H, m, 7B-H), 1.66–1.89 (3H, m, 6-CH_2 and 8A-H), 2.03–2.26 (4H, m, 5-H, 8B-H and NCH_2), 2.31–2.34 (1H, m, 4B-H), 2.42–2.49 (1H, dd, $J_{2B,4B}$=1.7 Hz, J_{gem}=10.7 Hz, 2B-H), 2.59–2.74 (1H, m, 7A-H), 2.87–2.99 (2H, m, 2A-H and 4A-H), 4.09 (2H, q, *J*=7.1 Hz, OCH_2), 4.38 (1H, d, *J*=0.8 Hz, 10A-H) and 4.65 (1H, br s, 10B-H); δ_C (100 MHz; $CDCl_3$) 12.4 (CH_3, NCH_2CH_3), 14.0 (CH_3, OCH_2CH_3), 21.2 (CH_2, C-7), 33.3 (CH_2, C-6), 35.6 (CH_2, C-8), 40.8 (CH, C-5), 50.3 (quat., C-1), 51.8 (CH_2, NCH_2CH_3), 60.1 (CH_2, OCH_2CH_3), 60.4 (CH_2, C-4), 61.8 (CH_2, C-2), 103.2 (CH_2, C-10), 152.0 (quat., C-9) and 174.1 (quat., OC═O); *m*/*z* (EI) 237 (M^+, 50%), 222 (M−CH_3, 73), 208 (M−CH_3CH_2, 50), 164 (M−CH_3CH_2OCO, 69) and 58 (100). Found: M^+ 237.1743. $C_{14}H_{23}NO_2$ requires M^+ 237.1743.

1.1.3. (1*S,5*S**)-(3-Ethyl-9-methylidene-3-azabicyclo-[3.3.1]non-1-yl)methanol 8.** To a solution of ethyl (1*S**,5*S**)-3-ethyl-9-methyidene-3-azabicyclo[3.3.1]nonane-1-carboxylate **12** (250 mg, 1.05 mmol) in dry THF (25 ml) was added lithium aluminium hydride (80 mg, 2.11 mmol) and the mixture stirred, under an atmosphere of nitrogen, for 10 min. The reaction was then quenched by dropwise addition of water (10 ml), the volatiles removed in vacuo. The remaining aqueous mixture was extracted with ethyl acetate (2×30 ml) and the combined organic layers washed with brine (50 ml) then dried ($MgSO_4$) and concentrated in vacuo to give the crude product which was purified by flash chromatography (1:1 hexane–ethyl acetate) to give the title compound **8** (191 mg, 94%) as a clear oil. ν_{max}(NaCl)/cm^{-1} 3356 (OH), 2914 (CH), 1649 (C═C), 1471, 1451, and 1239; δ_H (200 MHz; $CDCl_3$) 1.05 (3H, t, *J*=7.2 Hz, NCH_2CH_3), 1.22–1.48 (2H, m, 6B-H and 7B-H), 1.59–1.74 (1H, m, 8A-H), 1.82–1.99 (3H, m, 5-H, 6A-H, 8B-H), 2.12–2.17 (1H, m, 4B-H), 2.26 (2H, q, *J*=7.2 Hz, NCH_2CH_3), 2.34–2.35 (1H, m, 2B-H), 2.56–2.78 (2H, m, 7A-H and 11-OH), 2.92–2.97 (2H, m, 2A-H and 4A-H), 3.44 (2H, m, OCH_2), 4.43 (1H, br s, 10A-H) and 4.68 (1H, br s, 10B-H); δ_C (50 MHz; $CDCl_3$) 12.5 (CH_3, NCH_2CH_3), 21.3 (CH_2, C-7), 34.1 (CH_2, C-6), 36.1 (CH_2, C-8), 41.8 (quat., C-1), 41.9 (CH, C-5), 52.1 (CH_2, NCH_2CH_3), 60.5 (CH_2, C-4), 62.3 (CH_2, C-2), 68.8 (CH_2, OCH_2), 101.0 (CH_2, C-10) and 155.0 (quat., C-9); *m*/*z* (EI) 195 (M^+, 13%), 180 (M−CH_3, 62), 178 (M−OH, 34), 164 (M−CH_2OH, 18) and 72 (100). Found: M^+ 195.1634. $C_{12}H_{21}NO$ requires M^+ 195.1623.

1.1.4. Ethyl (1*R,5*R**,9*R**)-3-ethyl-9-hydroxy-3-azabicyclo[3.3.1]nonane-1-carboxylate 14 and ethyl (1*R**,5*R**,9*S**)-3-ethyl-9-hydroxy-3-azabicyclo[3.3.1]-nonane-1-carboxylate 13.** A solution of ethyl (1*R**,5*R**) 3-ethyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate **11** (3.00 g, 12.54 mmol) in THF (15 ml) was added dropwise to a solution of sodium borohydride (0.24 g, 6.27 mmol) in THF (15 ml) and water (15 ml) at 0 °C and the mixture stirred for 30 min. The reaction mixture was then allowed to warm to room temperature and stirred for a further 2 h. After this time the reaction was quenched by the addition of 2.5 M NaOH (20 ml) and the volatile solvents removed in vacuo. The remaining aqueous mixture was extracted with diethyl ether (3×50 ml), the combined ether layers washed with brine (100 ml) then dried (Na_2SO_4) and concentrated in vacuo to give a residue which was purified by flash chromatography (4:1 hexane–ethyl acetate) to give: (i) ethyl (1*R**,5*R**,9*R**)-3-ethyl-9-hydroxy-3-azabicyclo-[3.3.1]nonane-1-carboxylate **14** (R_f 0.4) (1.36 g, 45%). ν_{max}(NaCl)/cm^{-1} 3527 (OH) and 1707 (C═O, ester); δ_H (400 MHz; $CDCl_3$) 1.03 (3H, t, *J*=6.9 Hz, NCH_2CH_3), 1.25 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 1.45–1.46 (2H, m, 6B-H and 7B-H), 1.74–1.79 (1H, m, 8B-H), 1.94–2.09 (4H, m, 4B-H, 5-H, 6A-H and 8A-H), 2.20 (2H, q, *J*=7.1 Hz, NCH_2CH_3), 2.22–2.25 (1H, m, 2B-H), 2.57–2.61 (1H, m, 7A-H), 2.93 (1H, d, J_{gem}=11.0 Hz, 4A-H), 3.15 (1H, d, J_{gem}=11.0 Hz, 2A-H), 3.47 (1H, br s, OH), 3.87 (1H, s, 9-H) and 4.15 (2H, q, *J*=7.1 Hz, OCH_2CH_3); δ_C (100 MHz; $CDCl_3$) 12.7 (CH_3, NCH_2CH_3), 14.0 (CH_3, OCH_2CH_3), 20.8 (CH_2, C-7), 23.5 (CH_2, C-6), 27.5 (CH_2, C-8), 34.6 (CH, C-5), 46.7 (quat., C-1), 51.9 (CH_2, NCH_2CH_3), 58.2 (CH_2, C-4), 59.1 (CH_2, C-2), 60.7 (CH_2, OCH_2CH_3), 71.8 (CH, C-9) and 177.0 (quat., OC═O); *m*/*z* (EI) 241 (M^+, 40%), 224 (M−CH_3, 40), 224 (M−OH, 14), and 72 (100). Found: M^+ 241.16743. $C_{13}H_{23}NO_3$ requires M^+ 241.16780; (ii) ethyl (1*R**,5*R**, 9*S**)-3-ethyl-9-hydroxy-3-azabicyclo[3.3.1]nonane-1-carboxylate **13** (R_f 0.28) (1.09 g, 36%). ν_{max}(NaCl)/cm^{-1} 3508 (OH) and 1728 (C═O, ester); δ_H (400 MHz; $CDCl_3$) 1.04 (3H, t, *J*=7.1 Hz, NCH_2CH_3), 1.25 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 1.40–1.46 (1H, m 7B-H), 1.74–1.79 (1H, m, 6B-H), 1.93–2.09 (3H, m, 6A-H and 8-CH_2), 2.17–2.24 (1H, m, 5-H), 2.25 (2H, q, *J*=7.1 Hz, NCH_2CH_3), 2.30–2.66 (3H, m, 2B-H, 4B-H and 7A-H), 2.94 (1H, d, J_{gem}=11.0 Hz, 4A-H), 3.15 (1H, d, J_{gem}=11.0 Hz, 2A-H), 3.47 (1H, br, OH), 3.87 (1H, br s, 9-H) and 4.13 (2H, q, *J*=7.1 Hz, OCH_2CH_3); δ_C (100 MHz; $CDCl_3$) 12.5 (CH_3, NCH_2CH_3), 14.1 (CH_3, OCH_2CH_3), 20.7 (CH_2, C-7), 31.0 (CH_2, C-6), 34.4 (CH_2, C-8), 35.2 (CH, C-5), 48.1 (quat., C-1), 51.6 (CH_2, NCH_2CH_3), 52.2 (CH_2, C-4), 53.4 (CH_2, C-2), 60.6 (CH_2, OCH_2CH_3), 71.6 (CH, C-9) and 176.4 (quat., OC═O); *m*/*z* (EI) 241 (M^+, 27%), 224 (M−CH_3, 100), 224 (M−OH, 8), 212 (M−C_2H_5, 38) and 196 (M−OC_2H_5, 60. Found: M^+ 241.1672. $C_{13}H_{23}NO_3$ requires M^+ 241.1678.

1.1.5. (1*S,5*R**,9*R**)-3-Ethyl-1-hydroxymethyl-3-azabicyclo[3.3.1]nonan-9-ol 10.** To a solution of (1*R**,5*R**)-ethyl 3-ethyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate **11** (200 mg, 0.836 mmol) in dry THF (20 ml) was added lithium aluminium hydride (63 mg, 1.67 mmol) and

the mixture stirred, under an atmosphere of nitrogen, for 1 h. The reaction was then quenched by the dropwise addition of water (10 ml) and the volatiles removed in vacuo. The remaining aqueous solution was extracted with ethyl acetate (2×30 ml) and the combined organic layers washed with brine (50 ml) then dried (Na_2SO_4) and concentrated in vacuo. The crude product was then purified by flash chromatography (9:1 dichloromethane–methanol) to give the title compound **10** (90 mg, 54%) as a clear oil. ν_{max}(NaCl)/cm^{-1} 3355 (OH), 2912 (CH), 1472, 1453, 1069 and 1037; δ_H (200 MHz; $CDCl_3$) 1.00 (3H, t, J=7.2 Hz, NCH_2CH_3), 1.19–1.28 (2H, m, 6-CH_2), 1.38–1.53 (2H, m, 7B-H and 8A-H), 1.75–2.05 (4H, m, 2B-H, 4B-H, 5-H and 8B-H), 2.16 (2H, q, J=7.2 Hz, NCH_2CH_3), 2.48–2.54 (1H, m, 7A-H), 2.61 (1H, d, J_{gem}=12.2 Hz, 4A-H), 2.96 (1H, d, J_{gem}=11.1 Hz, 2A-H), 3.29–3.45 (3H, m, OCH_2 and OH), 3.68 (1H, d, J=3.2 Hz, 9-H) and 3.71 (1H, br, 9-OH); δ_C (50 MHz; $CDCl_3$) 12.7 (CH_3, NCH_2CH_3), 20.6 (CH_2, C-7), 23.9 (CH_2, C-6), 26.6 (CH_2, C-8), 36.0 (CH, C-5), 37.9 (quat., C-1), 52.3 (CH_2, NCH_2CH_3), 58.4 (CH_2, C-4), 60.5 (CH_2, C-2), 70.6 (CH_2, OCH_2), and 74.9 (CH, C-9); m/z (EI) 199 (M^+, 28%), 184 (M−CH_3, 47), 182 (M−OH, 18) and 72 (100). Found: M^+ 199.1571. $C_{11}H_{21}NO_2$ requires M^+ 199.1572.

1.1.6. Ethyl (1*R,5*R**,9*R**)-3-ethyl-9-methoxy-3-azabicyclo[3.3.1]nonane-1-carboxylate 15.** To a suspension of sodium hydride (132 mg, 60% in oil, 3.32 mmol) in dry THF (10 ml) at 0 °C was added a solution of ethyl (1*R**,5*R**,9*R**)-3-ethyl-9-hydroxy-3-azabicyclo[3.3.1]-nonane-1-carboxylate **14** (200 mg, 0.83 mmol) in dry THF (10 ml). The mixture was then stirred for 1 h after which time iodomethane (0.70 g, 0.32 ml, 5.00 mmol) was added and the mixture was stirred at room temperature for 72 h. The reaction was then quenched by the careful addition of water (25 ml). The volatile solvents were removed in vacuo and the remaining aqueous solution extracted with ethyl acetate (3×20 ml). The combined organic layers were washed with brine (50 ml) then dried ($MgSO_4$) and concentrated in vacuo to give the crude product which was purified by flash chromatography (7:3 hexane–ethyl acetate) to give ethyl (1*R**,5*R**,9*R**)-3-ethyl-9-methoxy-3-azabicyclo[3.3.1]nonane-1-carboxylate **15** (R_f 0.4) (148 mg, 70%) as a clear oil. ν_{max}(NaCl)/cm^{-1} 2927 (C–H), 1731 (C=O, ester) and 1259 (C–O); δ_H (200 MHz; $CDCl_3$) 0.97 (3H, t, J=7.1 Hz, NCH_2CH_3), 1.19 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.35–1.51 (2H, m, 6B-H and 7B-H), 1.70–1.80 (2H, m, 6A-H and 8B-H), 1.98–2.04 (2H, m, 5-H and 8A-H), 2.13–2.25 (4H, m, 2B-H, 4B-H and NCH_2CH_3), 2.44–2.54 (1H, m, 7A-H), 2.85 (1H, d, J_{gem}=10.8 Hz, 4A-H), 2.96 (1H, d, J_{gem}=11.1 Hz, 2A-H), 3.26 (3H, s, OCH_3), 3.47 (1H, d, J=3.6 Hz, 9-H) and 4.01–4.12 (2H, m, OCH_2CH_3); δ_C (50 MHz; $CDCl_3$) 12.6 (CH_3, NCH_2CH_3), 14.0 (CH_3, OCH_2CH_3), 20.5 (CH_2, C-7), 23.6 (CH_2, C-6), 26.5 (CH_2, C-8), 30.8 (CH, C-5), 46.9 (quat., C-1), 51.8 (CH_2, NCH_2CH_3), 55.9 (CH_3, OCH_3), 58.1 (CH_2, C-4), 60.1 (CH_2, C-2), 61.3 (CH_2, OCH_2CH_3), 81.4 (CH, C-9) and 175.2 (quat., OC=O); m/z (EI) 255 (M^+, 32%), 240 (M−CH_3, 44), 226 (M−C_2H_5, 30) and 224 (M−OCH_3, 100). Found: M^+ 255.1845. $C_{14}H_{25}NO_3$ requires M^+ 255.1834.

1.1.7. (1*R,5*S**,9*R**)-(3-Ethyl-9-methoxy-3-azabicyclo[3.3.1]non-1-yl)methanol 9.**[17d] A solution of ethyl (1*R**,5*R**,9*R**)-3-ethyl-9-methoxy-3-azabicyclo[3.3.1]-nonane-1-carboxylate **15** (546 mg, 2.14 mmol) in dry THF (10 ml) was added dropwise to a solution of lithium aluminium hydride (162 mg, 4.26 mmol) in THF (20 ml) and the mixture stirred, under an atmosphere of nitrogen, for 2 h. The reaction was then quenched by dropwise addition of water (20 ml), the volatiles removed in vacuo. The remaining aqueous mixture was extracted with ethyl acetate (2×20 ml). The combined organic layers were washed with brine (50 ml) then dried ($MgSO_4$) and concentrated in vacuo to give the crude product which was purified by flash chromatography (1:1 hexane–ethyl acetate) to give the title compound **9** (413 mg, 91%) as a clear oil. ν_{max}(NaCl)/cm^{-1} 3435 (OH) and 2947 (C–H); δ_H (200 MHz; $CDCl_3$) 0.99 (3H, t, J=7.1 Hz, NCH_2CH_3), 1.22–1.34 (2H, m, 6B-H and 7B-H), 1.37–1.45 (2H, m, 6A-H and 8B-H), 1.64–1.80 (2H, m, 5-H and 8A-H), 1.85–2.03 (2H, m, 2B-H and 4B-H) 2.13 (2H, q, J=7.1 Hz, NCH_2CH_3), 2.42–2.67 (1H, m, 7A-H), 2.61 (1H, d, J_{gem}=10.3 Hz, 4A-H), 2.97 (1H, d, J_{gem}=8.4 Hz, 2A-H), 3.14 (1H, d, J=3.1 Hz, 9-H), 3.29 (3H, s, OCH_3) and 3.24–3.28 (3H, m, OH and CH_2OH); δ_C (50 MHz; $CDCl_3$) 12.6 (CH_3, NCH_2CH_3), 20.4 (CH_2, C-7), 23.9 (CH_2, C-6), 27.1 (CH_2, C-8), 30.6 (CH, C-5), 38.1 (quat., C-1), 52.1 (CH_2, NCH_2CH_3), 55.0 (CH_3, OCH_3), 58.0 (CH_2, C-4), 60.9 (CH_2, C-2), 70.6 (CH_2, OCH_2OH) and 84.5 (CH, C-9); m/z (EI) 213 (M^+, 28%), 198 (M−CH_3, 59), 224 (M−OCH_3, 38) and 72 (100). Found: M^+ 213.1729. $C_{12}H_{23}NO_2$ requires M^+ 213.1729.

1.1.8. *N*-(Trifluoroacetyl)anthranilic acid 6. Anthranilic acid (15.13 g, 0.11 mol) was carefully added in portions over 15 min to a 250 ml round bottom flask containing vigourously stirred trifluoroacetic anhydride (30.7 ml, 0.22 mol). After 1 h the mixture was cooled to 0 °C and carefully quenched by the addition of water (100 ml). The mixture was then filtered and the crude product recystallised from ethanol/water to give the title compound **6** (18.77 g, 73%) as colourless crystals, mp 178–180 °C (lit.[19] mp 179–182 °C).

1.2. Standard procedure for the formation of 2-aminobenzoate esters using *N*-(trifluoroacetyl)anthranilic acid 6

To a solution of alcohol (1 mmol), *N*-(trifluoroacetyl)-anthranilic acid **179** (2 mmol) and 4-(dimethylamino)-pyridine (0.1 mmol) in acetonitrile (5 ml) was added 1,3-dicyclohexylcarbodiimide (2 mmol) and the mixture stirred, under an atmosphere of nitrogen, at 40 °C for 24 h. After this time the mixture was cooled, filtered and the filtrate evaporated to dryness. The crude mixture was then dissolved in dichloromethane (20 ml), washed with aq. sodium bicarbonate (20 ml) and brine (20 ml) then dried ($MgSO_4$) and concentrated in vacuo to leave the crude *N*-(trifluoroacetyl)anthranilate ester. This residue was suspended in absolute ethanol (10 ml), sodium borohydride (2 mmol) added, and the mixture stirred for 2 h. The reaction was quenched by the addition of water and the volatile solvent removed in vacuo. The remaining aqueous solution was extracted with ethyl acetate (2×30 ml) and the combined organic layers washed with brine (50 ml) then dried ($MgSO_4$) and concentrated in vacuo to leave the crude product, which was purified by flash chromatography to afford the anthranilate ester.

1.2.1. 1-Methyl-piperidin-3-ylmethyl 2-aminobenzoate 16. This reaction was carried out according to the standard procedure using 1-methyl-3-piperidinemethanol **7** (50 mg, 0.39 mmol), *N*-(trifluoroacetyl)anthranilic acid **6** (180 mg, 0.77 mmol), 4-(dimethylamino)pyridine (5 mg, 0.04 mmol), 1,3-dicyclohexylcarbodiimide (160 mg, 0.77 mmol) and sodium borohydride (29 mg, 0.77 mmol) using 5:1 dichloromethane–methanol as solvent for flash chromatography to afford the title compound **16** (78 mg, 81%) as a cream solid, mp 51–52 °C. ν_{max}(NaCl)/cm^{-1} 3480 and 3369 (NH_2), 1686 (C═O), 1618, 1589, 1560, 1456, 1296 and 1245; δ_H (400 MHz; $CDCl_3$) 1.07 (1H, ddd, $J_{4'A,5'A\text{-}H}$=4.5 Hz, $J_{4'A,5'B}$=4.5 Hz, J_{gem}=11.4 Hz, 4′A-H), 1.55–1.82 (4H, m, 2′A-H, 4′B-H and 5′-CH_2), 1.91 (1H, td, J_{gem}=11.2 Hz, $J_{6'A,5'A}$=11.2 Hz, $J_{6'A,5'B}$=3.0 Hz, 6′A-H), 2.03–2.17 (1H, br m, 3′-CH), 2.27 (3H, s, N-CH_3), 2.78 (1H, br d, J_{gem}=11.2 Hz, 6′B-H), 2.93 (1H, dt, J_{gem}=10.8 Hz, $J_{2'B,3'A}$=1.6 Hz, $J_{2'B,6'B}$=1.6 Hz, 2′B-H), 4.06–4.17 (2H, m, OCH_2), 5.72 (2H, br, NH_2), 6.60–6.64 (2H, m, 3-H and 5-H), 7.24 (1H, t, *J*=7.7 Hz, 4-H) and 7.82 (1H, d, *J*=7.5 Hz, 6-H); δ_C (100 MHz; $CDCl_3$) 24.7 (CH_2, C-5′), 26.7 (CH_2, C-4′), 35.9 (CH, C-3′), 46.5 (CH_3, N-*C*H_3), 55.9 (CH_2, C-6′), 59.1 (CH_2, C-2′), 66.9 (CH_2, OCH_2), 110.7 (quat., C-1), 116.2 (CH, C-3), 116.6 (CH, C-5), 131.0 (CH, C-6), 133.9 (CH, C-4), 150.5 (quat., C-2) and 167.9 (quat., C═O); *m*/*z* (EI) 248 (M^+, 82%), 233 (M−CH_3, 2), 128 (M−C_7H_6NO, 65), 120 (C_7H_6NO, 35), 112 (M−$C_7H_6NO_2$, 59) and 111 ($C_7H_{13}N$, 100). Found: M^+ 248.1536. $C_{14}H_{20}N_2O_2$ requires M^+ 248.1536.

1.2.2. 3-(Diethylamino)propyl 2-aminobenzoate 17. This reaction was carried out according to the standard procedure using 3-(diethylamino)-1-propanol (28 mg, 0.21 mmol), *N*-(trifluoroacetyl)anthranilic acid **6** (100 mg, 0.43 mmol), 4-(dimethylamino)pyridine (3 mg, 0.02 mmol), 1,3-dicyclohexylcarbodiimide (89 mg, 0.43 mmol) and sodium borohydride (16 mg, 0.43 mmol) using 5:1 dichloromethane–methanol as solvent for flash chromatography to afford the title compound **17** (45 mg, 85%) as a pale yellow oil. ν_{max}(NaCl)/cm^{-1} 3477 and 3370 (NH_2), 1689 (C═O), 1617, 1588, 1562, 1467 and 1245; δ_H (400 MHz; $CDCl_3$) 1.07 (6H, t, *J*=7.2 Hz, 2×NCH_2CH_3), 2.00 (2H, quin, *J*=6.3 Hz, 2′-CH_2), 2.65–2.73 (6H, m, 2×NCH_2CH_3 and 3′-CH_2), 4.33 (2H, t, *J*=6.3 Hz, 1′-CH_2), 5.73 (2H, br, NH_2), 6.61–6.67 (2H, m, 3-H and 5-H), 7.26 (1H, td, *J*=7.1 Hz, 1.6, 4-H) and 7.83 (1H, dd, *J*=8.0 Hz, 1.6, 6-H); δ_C (50 MHz; $CDCl_3$) 11.2 (CH_3, NCH_2CH_3), 22.9 (CH_2, C-2′), 46.7 (CH_2, NCH_2CH_3), 49.1 (CH_2, C-3′), 62.6 (CH_2, C-1′), 110.7 (quat., C-1), 116.1 (CH, C-3), 116.5 (CH, C-5), 131.0 (CH, C-6), 134.0 (CH, C-4), 150.4 (quat., C-2) and 167.9 (quat., C═O); *m*/*z* (EI) 250 (M^+, 46%), 235 (M−CH_3, 31), 221 (M−CH_2CH_3, 6), 178 (M−$N(CH_2CH_3)_2$, 11), 120 (M−$C_7H_{16}NO$, 62) and 86 ($(CH_3CH_2)_2NCH_2$, 100). Found: M^+ 250.1699. $C_{14}H_{22}N_2O_2$ requires M^+ 250.1681.

1.2.3. 2,2-Dimethylpropyl 2-aminobenzoate 18. The reaction was carried out according to the standard procedure using neopentyl alcohol (90 mg, 1.02 mmol), *N*-(trifluoroacetyl)anthranilic acid **6** (529 mg, 2.27 mmol), 4-(dimethylamino)pyridine (14 mg, 0.113 mmol), 1,3-dicyclohexylcarbodiimide (468 mg, 2.27 mmol) and sodium borohydride (85 mg, 2.27 mmol) using 6:4 hexane–ethyl acetate as the solvent for flash chromatography to afford the title compound **18**[17d] (198 mg, 94%) as a pale yellow oil. ν_{max}(NaCl)/cm^{-1} 3483 and 3372 (NH_2), 2957 (C–H), 1690 (C═O), 1617, 1589, 1560, 1371, 1293, 1245, 1161 and 1105; δ_H (200 MHz; $CDCl_3$) 1.03 (9H, br s, 3×2′-CH_3), 3.96 (2H, s, 1′-CH_2), 5.55 (2H, br, NH_2), 6.62–6.70 (2H, m, 3-H and 5-H), 7.26 (1H, t, *J*=7.7 Hz, 4-H) and 7.89 (1H, d, *J*=8.3 Hz, 6-H); δ_C (50 MHz; $CDCl_3$) 26.6 (CH_3, 2′-CH_3), 31.5 (quat., C-2′), 73.6 (CH_2, C-1′), 111.4 (quat., C-1), 116.6 (CH, C-3), 116.9 (CH, C-5), 131.0 (CH, C-6), 133.9 (CH, C-4), 149.9 (quat., C-2) and 168.0 (quat., OC═O); *m*/*z* (EI) 207 (M^+, 71%), 120 (M−$C_5H_{11}O$, 98), 119 (M−$C_5H_{12}O$, 98), 92 (M−$C_6H_{11}O_2$, 100). Found: M^+ 207.1261. $C_{12}H_{17}NO_2$ requires M^+ 207.1259.

1.2.4. Benzyl 2-aminobenzoate 19.[16b] The reaction was carried out according to the standard procedure using benzyl alcohol (500 mg, 4.62 mmol), *N*-(trifluoroacetyl)anthranilic acid **6** (2.15 g, 9.23 mmol), 4-(dimethylamino)pyridine (56 mg, 0.46 mmol), 1,3-dicyclohexylcarbodiimide (1.9 g, 9.25 mmol) and sodium borohydride (350 mg, 9.25 mmol) using 5:1 hexane–ethyl acetate as the solvent for flash chromatography to afford the title compound **19** (893 mg, 85%) as a pale oil. ν_{max}(NaCl)/cm^{-1} 3482 and 3373 (NH_2), 3031, 1690 (C═O), 1615, 1587, 1560, 1292 and 1242; δ_H (200 MHz; $CDCl_3$) 5.32 (2H, s, 1′-CH_2), 5.72 (2H, br, NH_2), 6.60–6.67 (2H, m, 3-H and 5-H), 7.21 (1H, td, *J*=7.7 Hz, 1.4, 4-H), 7.32–7.47 (5H, m, 5×Ar-H) and 7.94 (1H, dd, *J*=8.2 Hz, 1.4, 6-H); δ_C (50 MHz; $CDCl_3$) 65.8 (CH_2, 1′-CH_2), 110.3 (quat., C-1), 116.0 (CH, C-3), 116.5 (CH, C-5), 127.8 (CH, Ar), 127.9 (CH, Ar), 128.4 (CH, Ar), 131.1 (CH, C-6), 134.0 (CH, C-4), 136.1 (quat., Ar), 150.4 (quat., C-2) and 167.6 (quat., C═O); *m*/*z* (EI) 227 (M^+, 65%), 150 (M−C_6H_5, 5), 120 (M−C_7H_7O, 28) and 91 (C_7H_7, 100). Found: M^+ 227.0943. $C_{14}H_{13}NO_2$ requires M^+ 227.0946.

1.2.5. (1′*S,5′*S**)-(3-Ethyl-9-methyidene-3-azabicyclo-[3.3.1]non-1-yl)methyl 2-aminobenzoate 20.** The reaction was carried out according to the standard procedure using (1*S**,5*S**)-(3-ethyl-9-methyidene-3-azabicyclo[3.3.1]non-1-yl)methanol **8** (50 mg, 0.257 mmol), *N*-(trifluoroacetyl)-anthranilic acid **6** (120 mg, 0.515 mmol), 4-(dimethylamino)pyridine (3 mg, 0.026 mmol), 1,3-dicyclohexylcarbodiimide (107 mg, 0.518 mmol) and sodium borohydride (49 mg, 1.29 mmol) using 1:1 hexane–ethyl acetate as solvent for flash chromatography to afford the title compound **20** (60 mg, 75%) as a pale yellow oil. ν_{max}(NaCl)/cm^{-1} 3482 and 3373 (NH_2), 2919 (CH), 1688 (C═O), 1652 (C═C), 1616, 1589, 1456, 1293 and 1244; δ_H (200 MHz; $CDCl_3$) 1.06 (3H, t, *J*=7.1 Hz, NCH_2CH_3), 1.46–2.09 (6H, m, 5′-H, 6′-CH_2, 7′B-H and 8′-CH_2), 2.19–2.33 (3H, m, 4′B-H and NCH_2CH_3), 2.43–2.44 (1H, m, 2′B-H), 2.74–2.83 (1H, m, 7′A-H), 3.00–3.11 (2H, m, 2′A-H and 4′A-H), 4.21 (2H, s, OCH_2), 4.56 (1H, br s, 10′A-H) and 4.78 (1H, br s, 10′B-H), 5.72 (2H, br, NH_2), 6.61–6.69 (2H, m, 3-H and 5-H), 7.22–7.30 (1H, m, 4-H) and 7.85 (1H, dd, *J*=1.6 Hz, 7.5, 6-H); δ_C (50 MHz; $CDCl_3$) 12.5 (CH_3, NCH_2CH_3), 21.4 (CH_2, C-7′), 33.9 (CH_2, C-6′), 36.4 (CH_2, C-8′), 40.9 (quat., C-1′), 41.7 (CH, C-5′), 52.1 (CH_2, NCH_2CH_3), 60.4 (CH_2, C-4′), 62.8 (CH_2, C-2′), 69.9 (CH_2, OCH_2), 101.7 (CH_2, C-10′), 110.9 (quat., C-1), 116.3 (CH, C-3), 116.7 (CH, C-5), 131.1 (CH, C-6), 134.0 (CH, C-4), 150.4 (quat., C-2), 155.9 (quat., C-9′) and 168.0 (quat., C═O); *m*/*z* (EI) 314 (M^+, 31%), 299 (M−CH_3, 19), 178

(M−$NH_2C_6H_4CO_2$, 100) and 120 ($NH_2C_6H_4CO$, 60). Found: M^+ 314.1979. $C_{19}H_{26}N_2O_2$ requires M^+ 314.1994.

1.2.6. (1′*S* *,5′*R* *,9′*R* *)-(3-Ethyl-9-methoxy-3-azabicyclo[3.3.1]non-1-yl)methyl 2-aminobenzoate 21.[17d] The reaction was carried out according to the standard procedure using (1*R* *,5*S* *,9*R* *)-(3-ethyl-9-methoxy-1-3-azabicyclo[3.3.1]non-1-yl)methanol **9** (258 mg, 1.19 mmol), *N*-(trifluoroacetyl)anthranilic acid **6** (556 mg, 2.39 mmol), 4-(dimethylamino)pyridine (72 mg, 0.60 mmol), 1,3-dicyclohexylcarbodiimide (492 mg, 2.39 mmol) and sodium borohydride (135 mg, 3.58 mmol) using 1:1 hexane–ethyl acetate as solvent for flash chromatography to afford the title compound **21** (312 mg, 78%) as a clear oil. ν_{max} (NaCl)/cm^{-1} 3481 and 3371 (NH_2), 2969 and 2971 (C–H), 1689 (C═O), 1617, 1588, 1561, 1487, 1455, 1379, 1294 and 1244; δ_H (200 MHz; $CDCl_3$) 1.04 (3H, t, *J*=7.1 Hz, NCH_2CH_3), 1.21–1.57 (3H, m, 7′B-H and 6′-CH_2), 1.62–1.95 (2H, m, 8′-CH_2), 2.05–2.30 (5H, m, 2′B-H, 4′B-H, 5′-H and NCH_2CH_3), 2.54–2.67 (1H, m, 7′A-H), 2.94 (1H, d, J_{gem}=11.0 Hz, 4′A-H), 3.06 (1H, d, J_{gem}=10.2 Hz, 2′A-H), 3.16 (1H, br s, 9-H), 3.31 (3H, s, OCH_3), 4.05 (2H, m, OCH_2), 5.75 (2H, br, NH_2), 6.62–6.69 (2H, m, 3-H and 5-H), 7.26 (1H, td, *J*=7.2 Hz, 0.8. 4-H) and 7.85 (1H, dd, *J*=1.4 Hz, 8.3, 6-H); δ_C (50 MHz; $CDCl_3$) 12.7 (CH_3, NCH_2CH_3), 20.4 (CH_2, C-7′), 24.3 (CH_2, C-6′), 28.0 (CH_2, C-8′), 30.7 (CH, C-5′), 38.2 (quat., C-1′), 52.3 (CH_2, NCH_2CH_3), 56.0 (CH_3, OCH_3), 58.3 (CH_2, C-4′), 61.4 (CH_2, C-2′), 69.3 (CH_2, OCH_2), 81.1 (CH, C-9′), 110.9 (quat., C-1), 116.2 (CH, C-3), 116.7 (CH, C-5), 130.9 (CH, C-6), 133.9 (CH, C-4), 150.5 (quat., C-2) and 168.0 (quat., OC═O); *m*/*z* (EI) 332 (M^+, 50%), 317 (M−CH_3, 35), 301 (M−OCH_3, 30), 196 (M−$NH_2C_6H_4CO_2$, 25), 165 (M−$C_8H_9NO_2$, 64), 120 ($NH_2C_6H_4CO$, 59) and 72 (100). Found: M^+ 332.2094. $C_{19}H_{28}N_2O_3$ requires M^+ 332.2099.

1.2.7. Cyclohexyl 2-aminobenzoate 22.[23] The reaction was carried out according to the standard procedure, with the esterification step being left for 48 h, using cyclohexanol (200 mg, 2.0 mmol), *N*-(trifluoroacetyl)anthranilic acid **6** (920 mg, 3.94 mmol), 4-(dimethylamino)pyridine (24.0 mg, 0.196 mmol), 1,3-dicyclohexylcarbodiimide (812 mg, 3.94 mmol) and sodium borohydride (75 mg, 1.98 mmol) using 1:1 hexane–ethyl acetate as solvent for flash chromatography to afford the title compound **22** (426 mg, 97%) as a clear oil. ν_{max} (NaCl)/cm^{-1} 3479 and 3369 (NH_2), 2935 and 2858 (C–H), 1686 (C═O), 1615; δ_H (200 MHz; $CDCl_3$) 1.28–1.93 (10H, m, 5×CH_2), 4.98–5.06 (1H, m, 1′-H), 5.61 (2H, br, NH_2), 6.62–6.70 (2H, m, 3-H and 5-H), 7.26 (1H, t, *J*=7.7 Hz, 4-H), 7.91 (1H, d, *J*=8.2 Hz, 6-H); δ_C (50 MHz; $CDCl_3$) 23.5 (CH_2, C-3′), 25.3 (CH_2, C-4′), 31.5 (CH_2, C-2′), 72.1 (CH, C-1′), 111.3 (quat., C-1), 116.0 (CH, C-3), 116.5 (CH, C-5), 131.0 (CH, C-6), 133.7 (CH, C-4), 150.2 (CH, C-2), 167.4 (quat., OC═O); *m*/*z* (EI) 219 (M^+, 43%), 137 (M−C_6H_{10}, 94) and 119 (M−$C_6H_{12}O$, 100). Found: M^+ 219.1259. $C_{13}H_{17}NO_2$ requires M^+ 219.1259.

1.2.8. 1-Phenylethyl 2-aminobenzoate 23. The reaction was carried out according to the standard procedure, with the esterification step being left for 48 h, using 1-phenylethanol (200 mg, 1.63 mmol), *N*-(trifluoroacetyl)anthranilic acid **6** (763 mg, 3.27 mmol), 4-(dimethylamino)pyridine (20 mg, 0.163 mmol), 1,3-dicyclohexylcarbodiimide (675 mg, 3.27 mmol) and sodium borohydride (123 mg, 3.23 mmol) using 7:3 hexane–ethyl acetate as solvent for flash chromatography to afford the title compound **23** (335 mg, 85%) as a pale yellow oil. ν_{max}(NaCl)/cm^{-1} 3485 and 3373 (NH_2), 3031, 2980, 1687 (C═O), 1616, 1560, 1487, 1292 and 1240; δ_H (200 MHz; $CDCl_3$) 1.65 (3H, d, *J*=6.7 Hz, 2′-CH_3), 5.44 (2H, br, NH_2), 6.07 (1H, q, *J*=6.7 Hz, 1′-CH), 6.62–6.70 (2H, m, 3-H and 5-H), 7.22–7.46 (6H, m, 5×Ar-H and 4-H) and 7.98 (1H, dd, *J*=8.4 Hz, 1.8, 6-H); δ_C (50 MHz; $CDCl_3$) 22.6 (CH_3, C-2′), 72.1 (CH, C-1′), 110.7 (quat., C-1), 116.2 (CH, C-3), 116.6 (CH, C-5), 125.9 (CH, Ar), 127.7 (CH, Ar), 128.5 (CH, Ar), 131.2 (CH, C-6), 134.1 (CH, C-4), 142.0 (quat., Ar), 150.4 (quat., C-2) and 167.2 (quat., C═O); *m*/*z* (EI) 241 (M^+, 50%), 150 (M−C_7H_7, 73), 120 (C_7H_6NO, 41) and 105 (C_6H_5CO, 33). Found: M^+ 241.1102. $C_{15}H_{15}NO_2$ requires M^+ 241.1103.

1.2.9. (1′*S* *,5′*S* *,9′*R* *)-3-Ethyl-9-hydroxy-3-azabicyclo[3.3.1]non-1-ylmethyl 2-aminobenzoate 25. The reaction was carried out according to the standard pro cedure using (1*S* *,5*R* *,9*R* *)-3-ethyl-1-hydroxymethyl-3-azabicyclo[3.3.1]nonan-9-ol **10** (200 mg, 1.00 mmol), *N*-(trifluoroacetyl)anthranilic acid **6** (234 mg, 1.00 mmol), 4-(dimethylamino)pyridine (61 mg, 0.50 mmol), 1,3-dicyclohexylcarbodiimide (207 mg, 1.00 mmol) and sodium borohydride (76 mg, 2.01 mmol) using 1:1 hexane–ethyl acetate as solvent for flash chromatography to afford the title compound **25** (178 mg, 56%) as a pale yellow oil. ν_{max} (NaCl)/cm^{-1} 3481 (NH) and 3371 (NH and OH), 2969 and 2971 (C–H), 1689 (C═O), 1617, 1588, 1561, 1487, 1455, 1379, 1294 and 1244; δ_H (200 MHz; $CDCl_3$) 1.09 (3H, t, *J*=6.9 Hz, NCH_2CH_3), 1.34–1.59 (4H, m, 6′-CH_2, 7′B-H and 8′A-H), 1.71–2.31 (6H, m, 2′B-H, 4′B-H, 5′-H, 8′B-H and NCH_2CH_3), 2.57–2.66 (1H, m, 7′A-H), 2.92–3.05 (3H, m, 2′A-H, 4′A-H and 9′-OH), 3.51 (1H, br s, 9′-H), 3.66 (1H, d, J_{gem}=11.5 Hz, OCH_AH_B), 4.47 (1H, d, J_{gem}=11.5 Hz, OCH_AH_B), 5.72 (2H, br, NH_2), 6.62–6.69 (2H, m, 3-H and 5-H), 7.28 (1H, t, *J*=7.3 Hz, 4-H) and 7.85 (1H, d, *J*=8.3 Hz, 6-H); δ_C (50 MHz; $CDCl_3$) 12.8 (CH_3, NCH_2CH_3), 20.6 (CH_2, C-7′), 24.1 (CH_2, C-6′), 27.2 (CH_2, C-8′), 35.3 (CH, C-5′), 38.8 (quat., C-1′), 52.2 (CH_2, NCH_2CH_3), 58.7 (CH_2, C-4′), 60.7 (CH_2, C-2′), 68.9 (CH_2, OCH_2), 71.0 (CH, C-9′), 110.2 (quat., C-1), 116.2 (CH, C-3), 116.7 (CH, C-5), 131.1 (CH, C-6), 134.3 (CH, C-4), 150.7 (quat., C-2) and 168.6 (quat., C═O); *m*/*z* (EI) 318 (M^+, 35%), 303 (M−CH_3, 9), 198 (M−$NH_2C_6H_4CO$, 22), 182 (M−$NH_2C_6H_4CO_2$, 55), 120 ($NH_2C_6H_4CO$, 35) and 72 (100). Found: M^+ 318.1940. $C_{18}H_{26}N_2O_3$ requires M^+ 318.1943. A second fraction afforded (1*S* *,5*R* *,9*R* *)-9-(2-aminobenzoyl)-3-ethyl-3-azabicyclo[3.3.1]non-1-ylmethyl 2-aminobenzoate **26** (44 mg, 10%) as a yellow oil, for which the spectroscopic data was in agreement with that reported in the procedure described below.

1.2.10. (1′*S* *,5′*R* *,9*R* *)-9-(2-Aminobenzoyl)-3-ethyl-3-azabicyclo[3.3.1]non-1-lymethyl 2-aminobenzoate 26. The reaction was carried out according to the standard procedure using (1*S* *,5*R* *,9*R* *) 3-ethyl-1-hydroxymethyl-3-azabicyclo[3.3.1]nonan-9-ol **10** (50 mg, 0.250 mmol), *N*-(trifluoroacetyl)anthranilic acid **6** (120 mg, 0.515 mmol), 4-(dimethylamino)pyridine (3 mg, 0.026 mmol), 1,3-dicyclohexylcarbodiimide (107 mg, 0.519 mmol) and sodium

borohydride (49 mg, 1.29 mmol) using 1:1 hexane–ethyl acetate as solvent for flash chromatography to afford the title compound **26** (52 mg, 48%) as a yellow oil. ν_{max} (NaCl)/cm^{-1} 3483 and 3373 (NH_2), 2924 and 2779 (C–H), 1687 (C=O), 1616, 1588, 1561, 1487, 1454, 1383, 1294 and 1242; δ_H (200 MHz; $CDCl_3$) 1.07 (3H, t, J=7.1 Hz, NCH_2CH_3), 1.57–2.05 (5H, m, 6′-CH_2, 7′B-H and 8′-CH_2), 2.15–2.42 (5H, m, 2′B-H, 4′B-H, 5′-H and NCH_2CH_3), 2.65–2.86 (1H, m, 7′A-H), 3.05 (2H, m, 2′A-H and 4′A-H), 3.99–4.12 (2H, m, OCH_2), 5.11 (1H, d, J=3.5 Hz, 9′-H), 5.60–5.80 (4H, br, NH_2), 6.61–6.70 (4H, m, 2×3-H and 2×5-H), 7.21–7.31 (2H, m, 2×4-H) and 7.85–7.96 (2H, m, 2×6-H); δ_C (50 MHz; $CDCl_3$) 12.7 (CH_3, NCH_2CH_3), 20.5 (CH_2, C-7′), 25.0 (CH_2, C-6′), 28.5 (CH_2, C-8′), 33.2 (CH, C-5′), 37.7 (quat., C-1′), 52.0 (CH_2, NCH_2CH_3), 57.9 (CH_2, C-4′), 61.1 (CH_2, C-2′), 68.7 (CH_2, OCH_2), 74.3 (CH, C-9′), 110.6 and 110.8 (quat., 2×C-1), 116.2 (CH, 2×C-3), 116.5 and 116.6 (CH, 2×C-5), 130.9 and 131.0 (CH, 2×C-6), 133.9 and 134.0 (CH, 2×C-4), 150.4 and 150.6 (quat., 2×C-2) and 167.1 and 167.7 (quat., 2×OC=O); m/z (EI) 437 (M^+, 11%), 317 (M−$NH_2C_6H_4CO$, 5), 300 (M−$NH_2C_6H_4CO_2$, 58), 164 [M−2×($NH_2C_6H_4CO_2$), 100] and 120 ($NH_2C_6H_4CO_2$, 92). Found: M^+ 437.2315. $C_{25}H_{31}N_3O_4$ requires M^+ 437.2315.

1.3. Standard procedure for the formation of 2-(3-methyl-2,5-dioxopyrrolidin-1-yl)benzoate esters using methylsuccinic anhydride

2-Aminobenzoate ester (1 mmol) and methylsuccinic anhydride (3 mmol) were heated together at 125 °C for 3 h. After this time the crude mixture was dissolved in warm ethyl acetate (10 ml), washed with sat. sodium bicarbonate solution (30 ml) and brine (30 ml) then dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography to afford the 2-(3-methyl-2,5-dioxopyrrolidin-1-yl)benzoate ester.

1.3.1. 1-Methyl-piperidin-3-ylmethyl 2-(3-methyl-2,5-dioxopyrrolidin-1-yl)benzoate 27. The reaction was carried out according to the standard procedure using 1-methyl-piperidin-3-ylmethyl 2-aminobenzoate **16** (200 mg, 0.81 mmol) and methylsuccinic anhydride **28** (276 mg, 2.41 mmol) using 4:1 dichloromethane–methanol as solvent for flash chromatography to afford the title compound **27** (266 mg, 96%) as a clear oil. ν_{max} (NaCl)/cm^{-1} 2938 (C–H), 1776 (O=C–N–C=O), 1712 (C=O), 1578, 1492, 1393 and 1263; δ_H (400 MHz; $CDCl_3$) 1.01–1.04 (1H, m, 4″A-H), 1.44 (3H, br d, 3′-CH_3), 1.58–1.80 (4H, m, 2″ A-H, 4″ B-H and 5″ –CH_2), 1.93 (1H, d, J_{gem}=10.3 Hz, 6″ A-H), 2.07–2.13 (1H, br m, 3″-H), 2.28 (3H, s, N-CH_3), 2.43–2.56 (1H, br m, 3′-H), 2.77 (1H, d, J_{gem}=10.9 Hz, 6″ B-H), 2.87 (1H, d, J_{gem}=10.7 Hz, 2″ B-H), 3.02–3.08 (2H, br m, 4′-CH_2), 4.01–4.12 (2H, m, OCH_2), 7.22 (1H, d, J=7.8 Hz, 3-H), 7.49 (1H, td, J=7.6 Hz, 1.4, 5-H), 7.63 (1H, td, J=7.2 Hz, 1.8, 4-H) and 8.08 (1H, dd, J=1.2 Hz, 6.9, 6-H); δ_C (100 MHz; $CDCl_3$) 17.1 (CH_3, 3′-CH_3), 25.2 (CH_2, C-5″), 27.2 (CH_2, C-4″), 35.8 (CH, C-3″), 36.4 (CH, C-3′), 37.6 (CH_2, C-4′), 47.1 (CH_3, NCH_3), 56.6 (CH_2, C-6″), 59.5 (CH_2, C-2″), 68.4 (CH_2, OCH_2), 127.9 (quat., C-1), 129.9 (CH, C-5), 130.4 (CH, C-3), 131.1 (CH, C-6), 133.4 (quat., C-2), 133.9 (CH, C-4), 164.9 (quat., OC=O), 176.5 (quat., C-5′) and 180.5 (quat., C-2′); m/z (EI) 344 (M^+, 45%), 329 (M−CH_3, 5), 216 (M−$C_7H_{14}NO$, 36), 188 (M−$C_8H_{14}NO_2$, 40), 128 ($C_8H_{14}NO_2$, 81) and 41 (100). Found: M^+ 344.1734. $C_{19}H_{24}N_2O_4$ requires M^+ 344.1736.

1.3.2. 3-(Diethylamino)propyl 2-(3-methyl-2,5,dioxopyrrolidin-1-yl)benzoate 28. The reaction was carried out according to the standard procedure using 3-(diethylamino)propyl 2-aminobenzoate **17** (300 mg, 1.198 mmol) and methylsuccinic anhydride (410 mg, 3.595 mmol) using 4:1 dichloromethane–methanol as solvent for flash chromatography to afford the title compound **28** (377 mg, 91%) as a yellow oil. ν_{max} (NaCl)/cm^{-1} 1777 (N–C=O), 1713 (C=O) and 1573; δ_H (200 MHz; $CDCl_3$) 1.11 (6H, br t, 2×NCH_2CH_3), 1.30 (3H, br d, 3′-CH_3), 1.94 (2H, m, 2″-CH_2), 2.31–2.46 (2H, m, 4′-CH_2), 2.55–2.64 (1H, m, 3′-H), 2.90–3.01 (6H, m, 2×NCH_2CH_3 and 3″-CH_2), 4.19 (2H, br t, 1″-CH_2), 7.14 (1H, dd, J=1.0 Hz, 7.8, 3-H), 7.40 (1H, td, J=7.6 Hz, 1.3, 5-H), 7.54 (1H, td, J=7.6 Hz, 1.6, 4-H) and 7.92 (1H, dd, J=1.4 Hz, 7.7, 6-H); δ_C (50 MHz; $CDCl_3$) 8.1 (CH_3, 2×NCH_2CH_3), 16.9 (CH_3, 3′-CH_3), 23.0 (CH_2, C-2″), 36.4 (CH_2, C-4′), 36.7 (CH, C-3′), 45.9 (CH_2, 2×NCH_2CH_3), 48.2 (CH_2, C-3″), 61.8 (CH_2, C-1″), 126.6 (quat., C-1), 129.0 (CH, C-5), 129.2 (CH, C-3), 130.7 (CH, C-6), 132.1 (quat., C-2), 133.2 (CH, C-4), 164.0 (quat., OC=O), 177.3 (quat., C-5″) and 179.6 (quat., C-2′); m/z (EI) 346 (M^+, 5%), 331 (M−CH_3, 30), 274 (M−$(C_2H_5)_2N$, 4), 188 (M−$C_8H_{16}NO_2$, 27) and 86 ($C_5H_{12}N$, 100). Found: M^+ 346.1882. $C_{19}H_{26}N_2O_4$ requires M^+ 346.1893.

1.3.3. (1″*S,5″*S**,3′*R**)- and (1″ *S**,5″ *S**,3″*S**)-(3-Ethyl-9-methyidene-3-azabicyclo[3.3.1]non-1-yl)methyl 2-(3-methyl-2,5-dioxopyrrolidin-1-yl)benzoate 30.** The reaction was carried out according to the standard procedure using (1′*S**,5′*S**)-(3-ethyl-9-methyidene-3-azabicyclo-[3.3.1]non-1-yl)methyl 2-aminobenzoate **20** (45 mg, 0.143 mmol) and methylsuccinic anhydride (48 mg, 0.429 mmol) using 7:3 hexane–ethyl acetate as solvent for flash chromatography to afford the title compound 30 (49 mg, 84%) as a clear oil. ν_{max}(NaCl)/cm^{-1} 2920 (C–H), 1779 (N–C=O), 1715 (C=O), 1602, 1492, 1262 and 1186; δ_H (200 MHz; $CDCl_3$) 1.21 (3H, t, J=7.2 Hz, NCH_2CH_3), 1.38–1.62 (4H, m, 3′-CH_3 and 6″ B-H), 1.68–2.10 (4H, m, 6″ A-H, 7″ B-H and 8″-CH_2), 2.15–2.16 (1H, m, 5″-H), 2.20–2.30 (4H, m, 2″ B-H, 4″ B-H and NCH_2CH_3), 2.42–2.79 (3H, br m, 3′-H, 4″ A-H and 7″ A-H), 3.00–3.09 (3H, br m, 2″ A-H and 4′-CH_2), 4.15 (2H, s, OCH_2), 4.49 (1H, br s, 10″ A-H), 4.75 (1H, br s, 10″ B-H), 7.24 (1H, dd, J=0.9 Hz, 7.7, 3-H) 7.51 (1H, td, J=7.7 Hz, 1.3, 5-H), 7.64 (1H, td, J=7.7 Hz, 1.5, 4-H) and 8.10 (1H, dd, J=1.0 Hz, 7.7, 6-H); δ_C (50 MHz; $CDCl_3$) 12.5 (CH_3, NCH_2CH_3), 16.3 (CH_3, 3′-CH_3), 21.4 (CH_2, C-7″), 33.9 (CH_2, C-6″), 35.2 (CH_2, C-4′), 36.8 (CH_2, C-8″), 36.9 (CH, C-3′), 40.9 (quat., C-1″), 41.7 (CH, C-5″), 52.0 (CH_2, NCH_2CH_3), 60.4 (CH_2, C-4″), 62.8 (CH_2, C-2″), 70.7 (CH_2, OCH_2), 101.6 (CH_2, C-10″), 126.3 (quat., C-1), 129.2 (CH, C-5), 129.3 (CH, C-3), 129.8 (CH, C-6), 131.4 (quat., C-2), 133.4 (CH, C-4), 156.9 (quat., C-9″), 164.5 (quat., OC=O), 176.0 (quat., C-5′) and 179.4 (quat., C-2′); m/z (EI) 410 (M^+, 4%), 439 (M−CH_3, 14), 194 (M−$C_{12}H_{10}O_3N$, 27) and 178 (M−$C_{12}H_{10}O_4N$, 100). Found: M^+ 410.2229. $C_{24}H_{30}N_2O_4$ requires M^+ 410.2206.

1.3.4. Cyclohexyl 2-(3-methyl-2,5-dioxopyrrolidin-1-yl)benzoate 31. The reaction was carried out according to

the standard procedure using cyclohexyl 2-aminobenzoate **22** (100 mg, 0.456 mmol) and methylsuccinic anhydride (156 mg, 1.37 mmol) using 1:1 hexane–ethyl acetate as solvent for flash chromatography to afford the title compound **31** (101 mg, 70%) as a yellow oil. ν_{max} (NaCl)/cm^{-1} 2937 and 2859 (C–H), 1781 (O═C–N–C═O), 1715 (C═O), 1602, 1492, 1453, 1390 and 1259; δ_H (200 MHz; $CDCl_3$) 1.25–1.94 (13H, m, 5×CH_2 and 3′-CH_3), 2.46–2.61 (1H, m, 3′-H), 3.05–3.15 (2H, m, 4′-CH_2), 4.85–4.94 (1H, m, 1″-H), 7.23 (1H, dd, *J*=1.4 Hz, 7.8, 3-H), 7.50 (1H, td, *J*=7.5 Hz, 1.1, 5-H), 7.63 (1H, td, *J*=7.6 Hz, 1.5, 4-H) and 8.10 (1H, d, *J*=6.9 Hz, 6-H); δ_C (50 MHz; $CDCl_3$) 16.3 (CH_3, 3′-CH_3), 23.6 (CH_2, C-3″), 25.2 (CH_2, C-4″), 31.4 (CH_2, C-2″), 35.1 (CH_2, C-4′), 36.8 (CH, C-3′), 73.4 (CH, C-1″), 126.2 (quat., C-1), 129.1 (CH, C-5), 129.5 (CH, C-3), 131.2 (CH, C-6), 131.3 (quat., C-2), 132.9 (CH, C-4), 164.3 (quat., OC═O), 175.8 (quat., C-5′) and 179.7 (quat., C-2′); *m/z* (EI) 315 (M^+, 2%), 216 (M−$C_6H_{11}O$, 100) and 188 (M−$C_7H_{11}O_2$, 40). Found: M^+ 315.1466. $C_{18}H_{21}NO_4$ requires M^+ 315.1470.

1.3.5. 1.1.1-Phenylethyl 2-(3-methyl-2,5-dioxopyrrolidin-1-yl)benzoate 32. The reaction was carried out according to the standard procedure using 1-phenylethyl 2-aminobenzoate **23** (70 mg, 0.29 mmol) and methylsuccinic anhydride (132 mg, 1.16 mmol) using 1:1 hexane–ethyl acetate as solvent for flash chromatography to afford the title compound **32** (49 mg, 50%) as an orange oil. ν_{max} (NaCl)/cm^{-1} 2979, 1775 (O═C–N–C═O), 1713 (C═O), 1602, 1493, 1454, 1390 and 1259; δ_H (400 MHz; $CDCl_3$) 1.24–1.39 (3H, m, 3′-CH_3), 1.62 (3H, d, *J*=6.5 Hz, 2″-CH_3), 2.37–2.43 (1H, m, 3′-H), 2.86–3.04 (2H, m, 4′-H), 6.01 (1H, q, *J*=6.5 Hz, 1″-CH), 2.23–7.40 (6H, m, 3-H and 5×Ar-H), 7.50 (1H, td, *J*=7.7 Hz, 1.1, 5-H), 7.64 (1H, td, *J*=7.5 Hz, 1.5, 4-H) and 8.14 (1H, d, *J*=7.5 Hz, 6-H); δ_C (100 MHz; $CDCl_3$) 16.7 (CH_3, 3′-CH_3), 22.5 (CH_3, C-2″), 35.8 (CH_2, C-4′), 37.4 (CH, C-3′), 74.1 (CH, C-1″), 126.9 (quat., C-1), 128.7 (CH, Ar), 128.7 (CH, Ar), 128.9 (CH, Ar), 129.2 (CH, C-5), 129.9 (CH, C-3), 130.2 (CH, Ar), 132.1 (CH, C-6), 132.5 (CH, Ar), 132.9 (quat., C-2), 133.8 (CH, C-4), 141.7 (quat., Ar), 164.5 (quat., OC═O), 176.3 (quat., C-5′) and 180.5 (quat., C-2′); *m/z* (EI) 337 (M^+, 6%), 322 (M−CH_3, 8) and 188 (M−C_8H_9O, 100). Found: M^+ 337.1313. $C_{20}H_{19}NO_4$ requires M^+ 337.1314.

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