EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Synthesis of epibatidine analogues by pyrrole Diels-Alder reactions: rapid access to azabicyclo[2.2.1]heptane and 3,8-diazabicyclo[3.2.1]-octane scaffolds for library synthesis

Authors: Alexander Murray; Emma Packard; Andrew Nortcliffe; William Lewis; Daniel Hamza; Geraint Jones; Christopher John Moody

To be cited as: Eur. J. Org. Chem. 10.1002/ejoc.201601177

Link to VoR: http://dx.doi.org/10.1002/ejoc.201601177

Supported by
ACES Asian Chemical Editorial Society

WILEY-VCH

Synthesis of epibatidine analogues by pyrrole Diels-Alder reactions: rapid access to azabicyclo[2.2.1]heptane and 3,8-diazabicyclo[3.2.1]-octane scaffolds for library synthesis

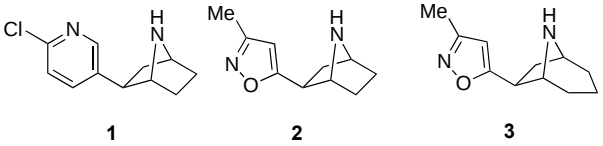
Alexander T. Murray,[a] Emma Packard,[a] Andrew Nortcliffe,[a] William Lewis,[a] Daniel Hamza,[b] Geraint Jones,[b] and Christopher J. Moody*[a]

Abstract: Analogues of the nicotinic acetylcholine antagonist epibatidine, suitable for diversification, were synthesized by application of a pyrrole Diels-Alder strategy, allowing rapid generation of azabicyclo[2.2.1]heptane bicyclic cores. Further molecular complexity could be accessed by use of intramolecular Diels-Alder reactions, or ring expansion by ozonolysis-reductive amination. Scaffolds were designed such that they could be orthogonally deprotected, yielding three points of diversity for library generation, exemplified by the synthesis of 24 compounds from four cores.

Introduction

The bicyclic alkaloid epibatidine **1** was discovered in 1974 from skin extracts of the frog Phyllobates anthonyi.[1] However, the structure and presence of the unusual 2-chloropyridyl motif was only unambiguously confirmed by 1H NMR and mass spectrometry in 1991,[2] and by several total syntheses one year later.[3] Several further synthetic approaches to epibatidine have since been published.[4] Epibatidine is considered an im-portant lead compound in the development of novel classes of analgesics via a non-narcotic mechanism of action, with its antagonist effect at nicotinic acetylcholine receptors (nAChRs) thought to be key to this action.[5] However, its non-specific activity as an agonist of both nicotinic and muscarinic acetylcholine receptors means that epibatidine possesses dangerous neurotoxic properties and thus possesses too low a therapeutic index for safe administration as an analgesic.[6] Additionally, very low quantities of this molecule are isolable from its natural source, with purification of the active alkaloid also proving problematic.[7]

One promising feature of the proposed structure-activity relationship of epibatidine in terms of scope for analogue synthesis is that the pendant 2-chloropyridyl motif appears not to be necessary for analgesic activity. Additionally, both enantiomers have similar nAChR agonist activity.[8] Several approaches to analogues have been published, many of them based on the key, less toxic isoxazolyl compound epiboxidine **2**, which has 10-fold lower analgesic activity than 1 but is at least 20 times less toxic (Figure 1).[9] Ring expansion of the six-membered carbocyclic ring has also been shown to be an effective strategy for synthesis of epibatidine-related analgesic lead compounds, with 8-azabicyclo[3.2.1]octane isoxazole **3** being still lower in toxicity than **2**.[10]



1 2 3

Figure 1. Structures of epibatidine (**1**), epiboxidine (**2**) and homoepiboxidine (**3**)

Among the total syntheses of epibatidine, one method of constructing the key azabicyclo[2.2.1]heptane core that was demonstrated in both Shen and Regan's routes to the natural product involved a Diels-Alder reaction of a pyrrole and an alkyne.[3d] N-Protected (activated) pyrroles can undergo a Diels-Alder reaction with a sufficiently electron deficient dienophile to form an azabicyclo[2.2.1]heptane scaffold. As well as the aforementioned epibatidine syntheses, this approach has been applied to the synthesis of the influenza antiviral drug, ostelamivir (Tamiflu®).[11] We thus considered the application of similar methodology, starting with commercially available N-Boc protected pyrroles in order to access a diverse library of epibatidine-like small nitrogenous saturated heterocycles as part of our work under the European Lead Factory.

Results and Discussion

Building on our previous work on Diels-Alder reactions as key transformations in natural product synthesis,[12] as well as rapid generation of sp^3-rich cores for library synthesis,[13] we chose to investigate the three scaffolds depicted in Figure 2 that could be synthesized *via* pyrrole Diels-Alder reactions as key C-C bond forming steps.

[a] School of Chemistry
University of Nottingham
University Park, Nottingham, NG7 2RD, U.K.
c.j.moody@nottingham.ac.uk
http://www.nottingham.ac.uk/~pczcm3/
[b] Sygnature Discovery
BioCity, Pennyfoot Street, Nottingham, NG1 1GF, U.K.

Supporting information for this article is given via a link at the end of the document.

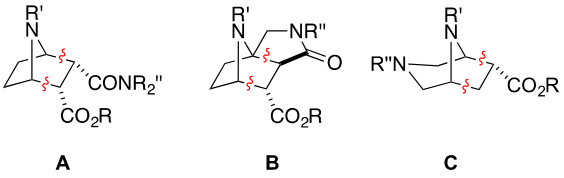
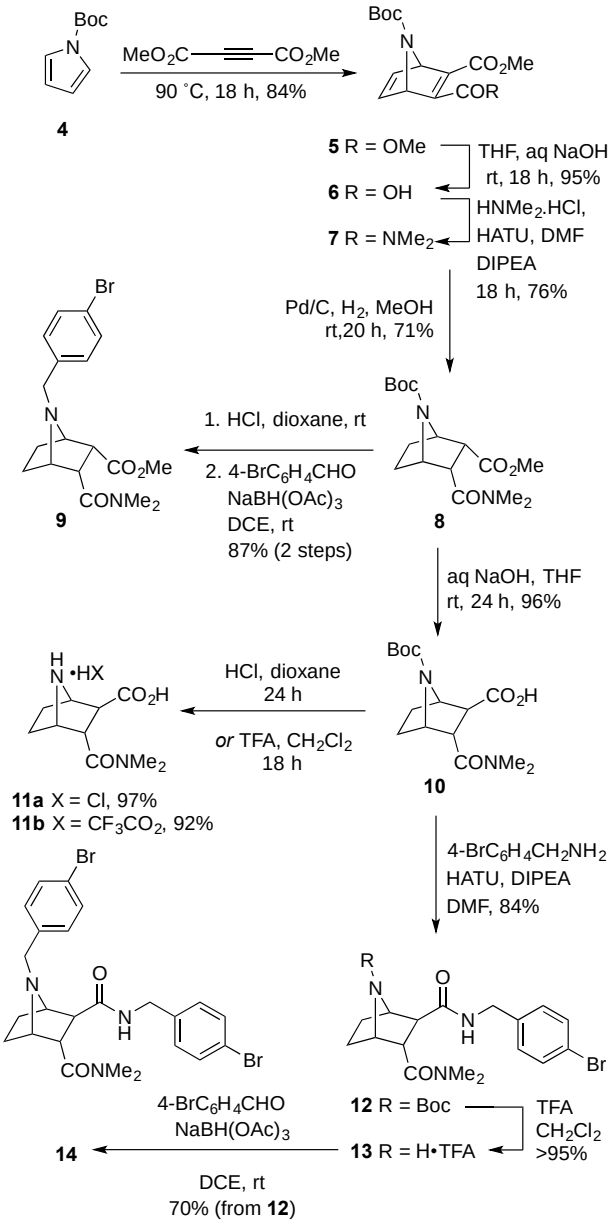


Figure 2. General scaffold structures **A, B** and **C**, showing key bonds to form *via* Diels-Alder cycloadditions.



Scheme 1. Synthesis of scaffold A and demonstration of ability to diversify in several vectors.

Firstly, scaffold A was synthesized starting with the Diels-Alder reaction of N-Boc pyrrole **4** with dimethyl acetylenedicarboxylate to give the key bicyclic system **5**.[14] Selective hydrolysis of one of the esters gave carboxylic acid **6**, which was condensed with dimethylamine under HATU coupling conditions. Hydrogenation gave the saturated *endo*-compound **8**, the structure of which was confirmed by X-ray crystallography (Figure 3), and the amine could be deprotected and subjected to reductive amination conditions to give **9**.

The scaffold could be further diversified by initial alkaline hydrolysis of the remaining ester to form carboxylic acid **10**, with concomitant epimerization. Further diversification was possible by acid-mediated Boc-deprotection to give amine salts **11**, or by amide formation to give **12**. Deprotection of the *N*-Boc compound **12** gave the trifluoroacetate salt **13**, the structure of which was established by X-ray crystallography (Figure 3) thereby confirming the earlier epimerization step. Finally reductive amination yielded compound **14** as example of a potential library compound (Scheme 1).[15]

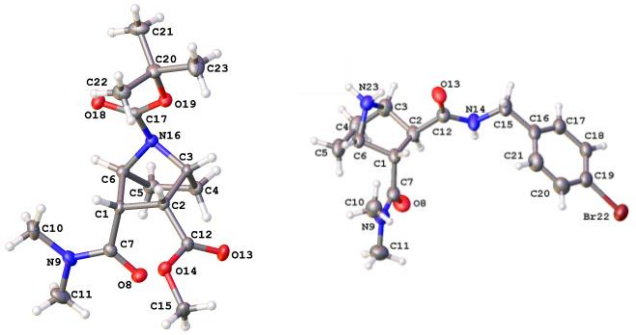
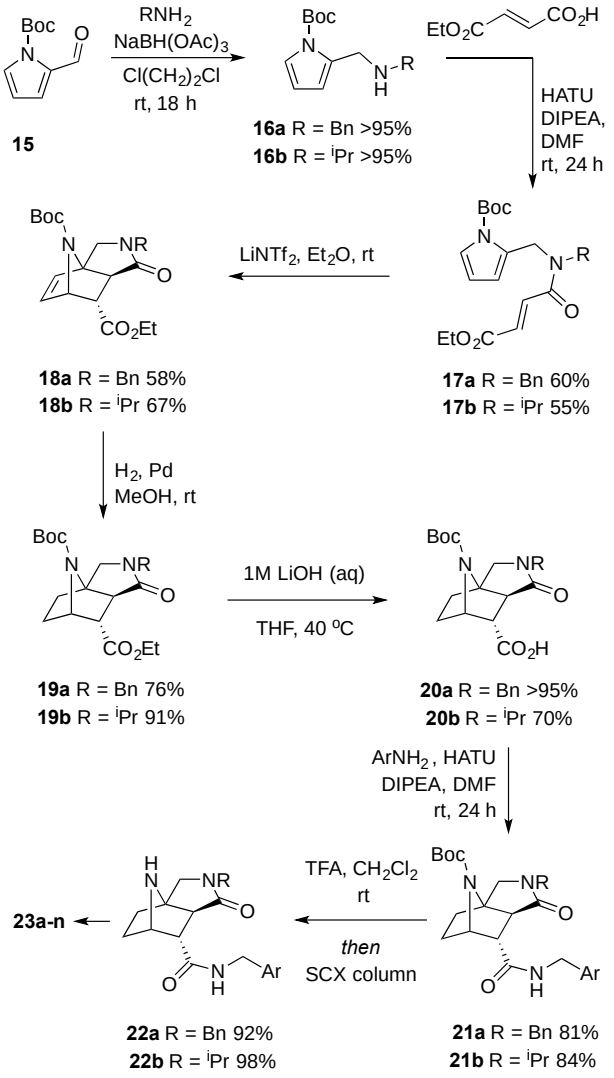
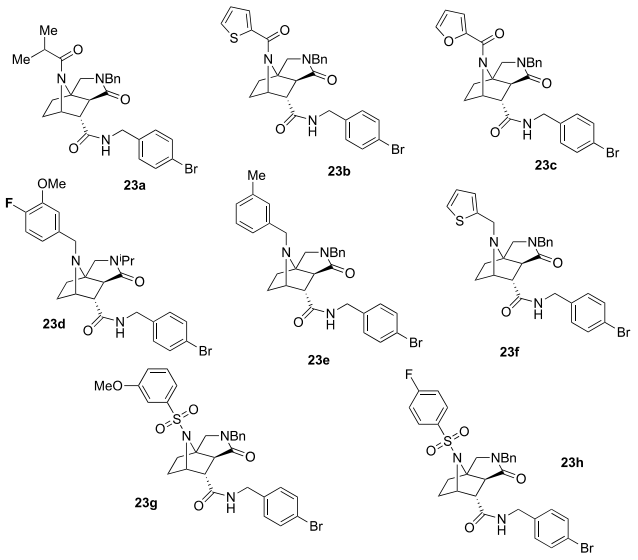


Figure 3. X-Ray crystal structures of azabicyclo[2.2.1]-heptanes **8** (CCDC 1511669) and **13** (CCDC 1511668). (TFA omitted for clarity)

Secondly, we examined the utilization of an *intra*molecular pyrrole Diels-Alder reaction in order to construct tricycle **B**. To append the internal dienophile, *N*-Boc-pyrrole-2-carboxaldehyde **15** was firstly subjected to reductive amination with either benzylamine or isopropylamine to give amines **16a/b**, followed by coupling with monoethyl fumarate to give Diels-Alder precursors **17a/b**. In this instance, use of lithium triflimide efficiently promoted the intramolecular cycloaddition to give **18a** and **18b** at ambient temperature.[16] Saturation of the double bond proceeded efficiently under hydrogenation conditions yielding **19a/b**, subsequently confirmed as the *trans* diastereomers by X-ray crystallography as described below. The ethyl esters were hydrolysed under basic conditions and the resulting acids **20** reacted with 4-bromobenzylamine as an example for a small amide library. The structures of acid **20a** and amide **21a** were both confirmed by X-ray crystallography (Figure 5).



Scheme 2. Synthesis of scaffold **B** (Ar = 4-bromophenyl).



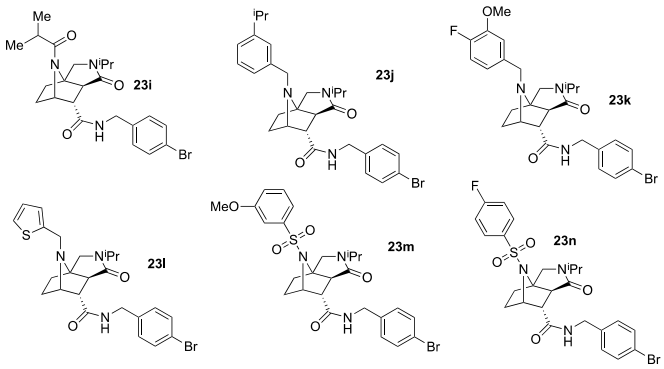
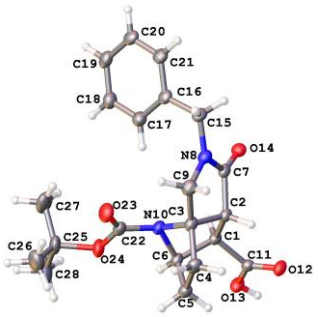


Figure 4. Library compounds **23a-n** synthesized *via* high-throughput methods.

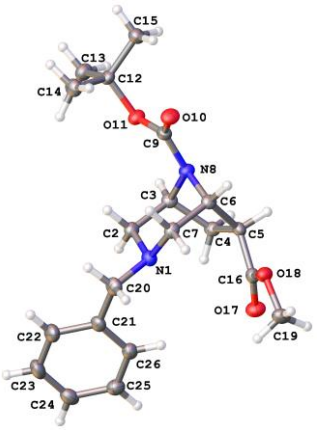
N-Deprotection under acidic conditions gave a pair of amines **22** that could be diversified into a small example library of 14 compounds **23a-n** (Figure 4) (see Supporting Information for details) of tertiary amines (by reductive amination), amides (by coupling mediated by HATU) and sulfonamides (by reaction with a sulfonyl chloride).

The final scaffold examined was the 3-aza analogue of homoepiboxidine **3**. This scaffold was proposed to be synthesized via a ring expansion reaction, and particularly interested us because it additionally bears similarities to the HIV entry inhibitor Maraviroc®.[17] The synthesis proceeded via an initial Diels-Alder reaction between N-Boc-pyrrole **4** and methyl 3-bromopropiolate **24**, followed by the reduction of the adduct **25** with $NaBH_4$ in acetonitrile to give ester **26** (Scheme 3). Although the analogous ethyl ester has been reported as a stable compound,[11] in our hands methyl ester **26** was prone to retro-Diels-Alder reaction upon concentration or storage. Direct ozonolysis of a CH_2Cl_2 solution of **26** was therefore necessary, without concentration of the unstable material. After reductive work-up with dimethyl sulfide, reductive amination of dialdehyde with benzylamine afforded 3,8-diazabicyclo[3.2.1]octane **27**. The yield was unfortunately lower on larger scales, but **27** could nevertheless be isolated in reasonable yield over three steps as a separable ca. 5:1 mixture of diastereomers. The major diastereomer was isolated and confirmed by X-ray crystallographic analysis to be *endo* compound **27a** (Figure 5).

20a



27a



21a

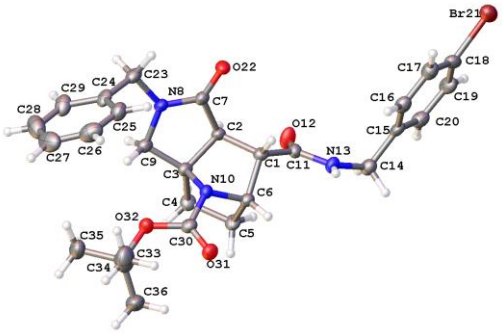
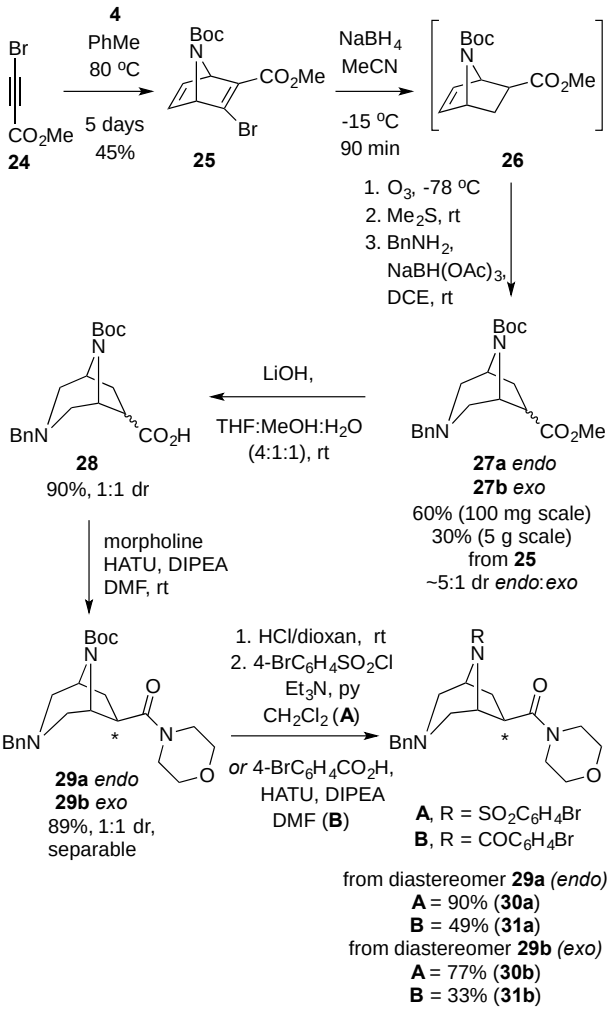


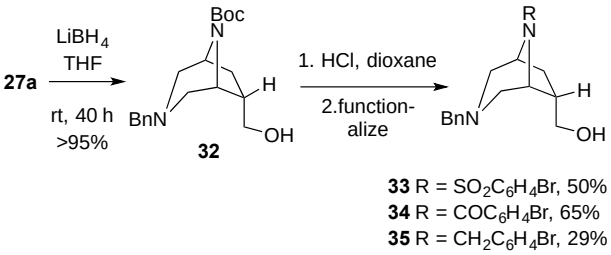
Figure 5. X-Ray crystal structures of azabicyclo[2.2.1] heptanes **20a** (CCDC 1511670) and **21a** (CCDC 1511667) and azadiazabicyclo[3.2.1]octane **27a** (CCDC 1511666).



Scheme 3. Synthesis of scaffold **C** and example library compound synthesis (**a**, *exo*-diastereomer; **b**, *endo*-diastereomer)

Upon saponification of ester **27a/b** with LiOH, a 1:1 mixture of epimers of acid **28** was obtained, which allowed access to both the separable diastereomers of key amide intermediates **29a** and **29b** upon coupling with morpholine using HATU. NOE analysis of the two diastereomers of amide **29** gave a characteristic cross-peak between the N-Boc group of **29b** and the morpholine protons, which was absent for **29a**. We therefore propose that **29b** is the *exo* isomer, and **29a** *endo*. N-Boc deprotection could be followed by direct sulfonamide formation or amide coupling to give sulfonamides **30a** and **30b** and amides **31a** and **31b** in order to demonstrate library synthesis potential from the free nitrogen, for either diastereomer.

As a variant on scaffold **C** that was more scalable and involved less arduous chromatographic separation of diastereomers, we decided to generate a homoepiboxidine-like scaffold that was not prone to epimerization. The major (*endo*) diastereomer **27a** was subjected to $LiBH_4$-mediated reduction, which proceeded in quantitative yield to give primary alcohol **32**. This was used to synthesize three example compounds; a sulfonamide, amine and amide (**33-35**) in reasonable yields over two steps.



Scheme 4. Reduction of **27a** and library synthesis examples

Conclusions

In conclusion, we have synthesized three new scaffolds suitable for library synthesis inspired by the analgesic alkaloid epibatidine, and based on pyrrole Diels-Alder reactions as key steps to rapidly build three-dimensional molecular complexity from simple, often commercially available, precursors. Library synthesis based on cores A and B has afforded 13 discrete scaffolds and delivered a total of 1233 compounds with an average molecular weight of 454 and average logP of 1.44.

Experimental Section

For general experimental procedures, see the supporting Information.

(1*R,4*S**)-7-*tert*-Butyl 2,3-dimethyl 7-azabicyclo[2.2.1]hepta-2,5-diene-2,3,7-tricarboxylate 5** *N*-Boc-pyrrole **4** (5.00 g, 30 mmol) and dimethyl acetylenedicarboxylate (31.0 mL, 250 mmol) were combined and heated at 90 °C for 18 h. The mixture became dark brown. The reaction mixture was cooled to rt and some excess alkyne was removed under high vacuum. The dark brown oil (37 g) was purified by flash column chromatography (10–25% ether in light petroleum, R_f 0.34 in 50% ether in light petroleum. The Diels-Alder adduct **5** was isolated as a pale yellow solid (7.82 g, 25.3 mmol, 84%). MP 71–72 °C (lit.,[14] MP 71 °C). HRMS *m/z* (ESI^+) Found 332.1111 $[M+Na]^+$, $C_{15}H_{19}NNaO_6$ requires

332.1105. ν_{max} ($CHCl_3$)/cm^{-1} 3776, 3685, 3606, 3012, 2413, 2245, 1884, 1714, 1522, 1477, 1424, 1334, 1239, 1017, 929, 850, 662, 627. ^1H NMR (400 MHz; $CDCl_3$) δ_H 7.14 (br s, 2H), 5.46 (br s, 2H), 3.83 (s, 6H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 163.3, 153.9, 143.4, 142.5, 81.5, 69.1, 52.3, 28.1.

(1*R,4*S**)-7-(*tert*-Butoxycarbonyl)-3-(methoxycarbonyl)-7-azabicyclo [2.2.1]hepta-2,5-diene-2-carboxylic acid 6** To a solution of **5** (7.80 g, 25.3 mmol) in THF (51 mL) was added NaOH (aq) (101 mL, 0.25 M, 25.3 mmol), and the solution gradually became pale yellow. The reaction mixture was stirred at rt for 18 h then acidified by 1 M HCl (50 mL) and extracted with ethyl acetate (2 × 50 mL). The organic phase was washed with water (70 mL), then with sat. $NaHCO_3$ (aq) (70 mL). The latter was extracted with ether (50 mL), separated and acidified to pH 1 with 1 M HCl. This was extracted with ethyl acetate (80 mL). The organic layer was dried over Na_2SO_4 and concentrated to give mono acid **6** as a bright yellow oil (7.10 g, 24.1 mmol, 95%) which required no further purification. HRMS *m/z* (ESI^+) Found 318.0943 $[M+Na]^+$, $C_{14}H_{17}NNaO_6$ requires 318.0948. ν_{max} ($CHCl_3$)/cm^{-1} 3012, 2983, 2772, 2668, 2361, 2342, 1729, 1714, 1682, 1617, 1441, 1413, 1371, 1337, 1240, 1120,1024, 927, 851. ^1H NMR (400 MHz; $CDCl_3$) δ_H 7.16 (br, s, 1H), 7.13 (br s, 1H), 5.65 (br s, 1H), 5.59 (br s, 1H), 3.98 (s, 3H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 166.4, 161.0, 160.7, 154.0, 153.9, 142.8 (2 C), 81.9, 69.7, 68.4, 54.2, 28.0. The data were in agreement with the literature.[18]

(1*S,4*R**)-7-*tert*-Butyl 2-methyl 3-(dimethylcarbamoyl)-7-azabicyclo-[2.2.1]hepta-2,5-diene-2,7-dicarboxylate 7** To a solution of **6** (7.10 g, 24.1 mmol), in dichloromethane (130 mL) and dimethylformamide (130 mL) was added dimethylamine hydrochloride (2.40 g, 28.9 mmol), followed by HATU (13.7 g, 36.2 mmol) then *N,N*-diisopropylethylamine (21 mL, 120.5 mmol). The solution gradually turned orange to dark green. This was stirred at rt for 18 h then diluted with ethyl acetate (200 mL) and extracted with sat. NH_4Cl (aq) (150 mL). The organic phase was washed with sat. $NaHCO_3$ (aq) (150 mL) followed by 5% aq LiCl solution (200 mL) then brine (150 mL). The organics were dried over Na_2SO_4 and concentrated to give a dark green oil (7.60 g). Purification by flash column chromatography (30–40% ethyl acetate in hexane with 1% NH_3 in H_2O, R_f 0.43 in 50% ethyl acetate in hexane with 0.1% NH_3 in H_2O) gave the desired compound **7** as a pale yellow oil (5.86 g, 18.2 mmol, 76%). HRMS *m/z* (ESI^+) Found 323.1590 $[M+H]^+$, $C_{16}H_{23}N_2O_5$ requires 323.1601.ν_{max} ($CHCl_3$)/cm^{-1} 3777, 3685, 3408, 3011, 2413, 2254, 1715, 1628, 1518, 1411, 1335, 1239, 1120, 1089, 1022, 928, 850, 662, 628. ^1H NMR (400 MHz; $CDCl_3$) δ_H 7.20 (br s, 1H), 7.03 (br s, 1H), 5.53 (br s, 1H), 5.19 (br s, 1H), 3.73 (s, 3H), 3.04 (s, 3H), 2.97 (s, 3H), 1.41 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 165.7, 162.6, 155.5, 151.5, 142.5 (2 C), 140.9, 95.6, 81.3, 70.2, 52.0, 34.1, 28.1.

(1*S,2*S**,3*R**,4*R**)-7-*tert*-Butyl 2-methyl 3-(dimethylcarbamoyl)-7-azabicyclo-[2.2.1]heptane-2,7-dicarboxylate 8** Adduct **7** (2.60 g, 8.1 mmol) was dissolved in methanol (150 mL) and palladium on activated carbon added (862 mg, 30% *w/w*). The solution was stirred under an atmosphere of hydrogen at rt for 20 h. Filtration through Celite and removal or methanol under reduced pressure gave the desired product **8** as a colorless solid (1.87 g, 5.7 mmol, 71%) that required no further purification. MP 105–106 °C. HRMS *m/z* (ESI^+) Found 349.1721 $[M+Na]^+$, $C_{16}H_{26}N_2NaO_5$ requires 349.1734. ν_{max} ($CHCl_3$)/cm^{-1} 3006, 2982, 2954, 2460, 1736, 1693, 1647, 1457, 1437, 1370, 1297, 1252, 1162, 1104, 1055, 906, 874. ^1H NMR (400 MHz; $CDCl_3$) δ_H 4.36 (br s, 2H), 3.66 (s, 3H), 3.62 (br s, 1H), 3.06 (s, 1H), 2.93 (s, 3H), 2.32 (br s, 1H), 1.89–1.71 (m, 1H), 1.71–1.55 (m, 1H), 1.46 (s, 9H).^{13}C NMR (100 MHz; $CDCl_3$) δ_C 171.6, 169.5, 155.2, 80.3, 60.3, 59.1, 51.3, 48.0, 45.8, 37.2, 35.6, 28.2, 25.7, 24.3.

(1*S,2*S**,3*R**,4*R**)-Methyl 3-(dimethylcarbamoyl) -7- azabicyclo [2.2.1]heptane-2-carboxylate hydrochloride 8a** Adduct **8** (205 mg, 0.63 mmol) was dissolved in 4 M HCl in dioxane (6 mL) and stirred at rt for 24 h. The volatiles were removed under reduced pressure to give **8a** as a colorless oil (160 mg, 0.61 mmol, quantitative) that required no further purification. HRMS *m/z* (ESI^+) Found 227.1383 $[M+H]^+$, $C_{11}H_{19}N_2O_3$ requires 227.1390. ν_{max} ($CHCl_3$)/cm^{-1} 3061, 2980, 2850, 2696, 2548, 2361, 1741, 1653, 1602, 1500, 1361, 1158, 1106.^1H NMR (400 MHz; $CDCl_3$) δ_H 9.90 (br s, 1H), 9.77 (br s, 1H), 4.47–4.34 (m, 2H), 4.07 (dd, *J* 11.2, 4.1, 1H), 3.66 (s, 3H), 3.60 (dd, *J* 11.2, 4.1, 1H), 3.07 (s, 3H), 2.95 (s, 3H), 2.20–1.99 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 169.3, 167.4, 61.0, 60.7, 51.8, 45.1, 42.4, 37.6, 35.9, 23.6, 22.4.

(1*S,2*S**,3*R**,4*R**)-Methyl 3-(dimethylcarbamoyl) -7- azabicyclo [2.2.1]heptane-2-carboxylate, 2,2,2-trifluoroacetate 8b** Adduct **8** (298 mg, 0.9 mmol) was dissolved in dichloromethane (1.5 mL), cooled to 0 ºC and TFA (0.8 mL) added dropwise over 30 sec. The reaction mixture was then stirred at rt for 1.5 h. The volatiles were removed under reduced pressure to give **8b** as a colorless oil (275 mg, 0.8 mmol, 88%) that required no further purification. HRMS *m/z* (ESI^+) Found 227.1380 $[M+H]^+$, $C_{11}H_{19}N_2O_3$ requires 227.1390. ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2955, 2720, 2564, 2362, 1741, 1676, 1654, 1438, 1192, 1065, 837. ^1H NMR (400 MHz; $CDCl_3$) δ_H 3.78 (dt, *J* 9.9, 4.6, 2 H), 3.58 (s, 3H), 3.38 (ddd, *J* 11.3, 4.8, 1.1, 1H), 2.98 (s, 3 H), 2.86 (s, 3H), 2.84 (dd, *J* 4.3, 1.8, 1H), 2.18 (ddd, *J* 12.4, 8.9, 4.3, 1H), 1.91 (br s, 1H), 1.76 (ddd, *J* 12.4, 8.9, 4.3, 1H), 1.60–1.46 (m, 1H), 1.45–1.32 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 172.2, 170.4, 59.6, 59.2, 51.1, 49.0, 46.6, 37.1, 35.5, 26.7, 24.9.

(1*S,2*S**,3*R**,4*R**)-Methyl 7-(4-bromobenzyl)-3-(dimethylcarbamoyl)-7-azabicyclo[2.2.1]heptane-2-carboxylate 9** Amine hydrochloride **8a** (53 mg, 0.23 mmol) and 4-bromobenzaldehyde (47 mg, 0.25 mmol), were dissolved in 1,2-dichloroethane (2 mL) and stirred for 30 min until complete dissolution occurred. Sodium triacetoxyborohydride (146 mg, 0.69 mmol) was added and the solution stirred at rt for 16 h. Following dilution with dichloromethane (10 mL), the solution was washed with water (2 × 10 mL). The organics were separated and dried over Na_2SO_4 and concentrated to give a colorless oil (93 mg). Purification by flash column chromatography (10–30% ethyl acetate in light petroleum with 1% NH_3 in H_2O, R_f 0.13 in 50% ethyl acetate in light petroleum with 0.1% NH_3 in H_2O) gave the desired compound **9** as a colorless oil (79 mg, 0.20 mmol, 87%). HRMS *m/z* (ESI^+) Found 395.0971 $[M+H]^+$, $C_{18}H_{24}{}^{79}BrN_2O_3$ requires 395.0965. ν_{max} ($CHCl_3$)/cm^{-1} 3010, 1735, 1645, 1488, 1352, 1192, 1071, 1013, 908, 870. ^1H NMR (400 MHz; $CDCl_3$) δ_H 7.42 (d, *J* 8.3, 2H), 7.22 (d, *J* 8.2 2H), 3.60 (s, 3H), 3.56 (s, 2H), 3.53 (dd, *J* 11.4, 4.0, 1H), 3.44 (dt, *J* 9.3, 4.3, 2H), 3.05 (dd, *J* 11.4, 4.0, 1H), 2.97 (s, 3H), 2.89 (s, 3H), 2.28–2.16 (m, 2H), 1.86–1.63 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 172.5, 170.5, 138.4, 131.3, 130.0, 120.7, 62.5, 61.9, 51.1, 50.5, 47.3, 45.8, 37.1, 35.5, 23.5, 22.4.

(1*S,2*S**,3*R**,4*R**)-7-(*tert*-Butoxycarbonyl)-3-(dimethylcarbamoyl)-7-azabicyclo[2.2.1]heptane-2-carboxylic acid 10** To a solution of **5b** (105.5 mg, 0.32 mmol) in THF (1.0 mL) was added NaOH (aq) (0.25 M, 0.32 mmol, 1.3 mL), the reaction mixture was stirred at rt for 18 h then acidified by 1 M HCl (1 mL) and extracted with ethyl acetate (2 × 5 mL). The organic phase was washed with water (10 mL) then with sat. $NaHCO_3$ (aq) (10 mL). The latter was extracted with ether (10 mL), separated and acidified to pH 1 with 1 M HCl. This was extracted with ethyl acetate (20 mL). The organic layer was dried over Na_2SO_4 and concentrated to give a colorless oil which was triturated with ether and hexanes, solvents were removed under reduced pressure to give acid **10** as a white foamy solid (96.8 mg, 0.31 mmol, 96%) that required no further purification. MP 113–114 °C. HRMS *m/z* (ESI^+) Found 335.1569 $[M+Na]^+$, $C_{15}H_{24}N_2NaO_5$ requires 335.1577. ν_{max} ($CHCl_3$)/cm^{-1} 3512, 2982, 2360, 1695, 1642, 1457, 1369, 1256, 1165, 1055, 904, 870. ^1H NMR (400 MHz; $CDCl_3$) δ_H 4.60 (br s, 1H), 4.44 (br s, 1H), 3.75–3.70 (m, 1H), 3.41 (d, *J* 4.9, 1h), 3.19 (s, 3H), 2.98 (s, 3H), 1.92–1.80 (m, 1H), 1.74–1.50 (m, 3H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 176.9, 169.8, 154.9, 80.5, 60.6, 57.6, 50.8, 47.9, 37.2, 36.0, 29.3, 28.0, 24.1.

(1*S,2*S**,3*R**,4*R**)-3-(Dimethylcarbamoyl)-7-azabicyclo[2.2.1]heptane-2-carboxylic acid hydrochloride 11a** Adduct **10** (96 mg, 0.3 mmol) was dissolved in 4 M HCl in dioxane (6 mL) and stirred at rt for 24 h over which time a white precipitate formed. The volatiles were removed under reduced pressure to give a turbid gummy solid that was triturated with ether, following evaporation **11a** was obtained as a colorless solid (72 mg, 0.3 mmol, 97%) that required no further purification. MP 160–162 °C. HRMS *m/z* (ESI$^+$) Found 213.1242 $[M+H]^+$, $C_{10}H_{17}N_2O_3$ requires 213.1234. ν_{max} ($CHCl_3$)/cm^{-1} 3776, 3685, 3607, 3012, 2413, 2245, 1885, 1735, 1646, 1522, 1424, 1239, 1015, 929, 850, 662, 627. ^{1}H NMR (400 MHz; D_2O) δ_H 4.59–4.53 (m, 2H), 3.77 (t, *J* 4.5, 1H), 3.47 (d, *J* 5.4, 1H), 3.11 (s, 3H), 2.93 (s, 3H), 2.06–1.92 (m, 1H), 1.92–1.74 (m, 2H), 1.72–1.60 (m,1H). ^{13}C NMR (100 MHz, D_2O) δ_C 175.1, 168.5, 61.7, 59.2, 48.0, 47.3, 37.3, 36.3, 25.7, 21.8.

(1*S,2*S**,3*R**,4*R**)-3- (Dimethylcarbamoyl)- 7-azabicyclo [2.2.1]heptane -2-carboxylic acid, 2,2,2-trifluoroacetate 11b** Adduct **10** (150 mg, 0.5 mmol) was dissolved in dichloromethane (2 mL), cooled to 0 ºC and TFA (418 μL) added dropwise over 15 sec. The reaction mixture was then stirred at rt for 18 h. The volatiles were removed under reduced pressure to give **11b** as a white foamy solid (143 mg, 0.4 mmol, 92%) that required no further purification. HRMS *m/z* (ESI$^+$) Found 213.1240 $[M+H]^+$, $C_{10}H_{17}N_2O_3$ requires 213.1234. ν_{max} ($CHCl_3$)/cm^{-1} 2927, 2854, 1716, 1652, 1587, 1406, 1142, 1109, 836. ^{1}H NMR (400 MHz; d_6-DMSO) δ_H 13.00 (br s, 1H), 9.11 (br s, 1H), 8.79 (br s, 1H), 4.47 (t, *J* 4.5, 1H), 4.43 (d, *J* 4.8, 1H), 3.64 (t, *J* 5.0, 1H), 3.31 (d, *J* 5.8, 1H), 3.07 (s, 3H), 2.89 (s, 3H), 1.92–1.78 (m, 1H), 1.77–1.61 (m, 2H), 1.58–1.47 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C 172.5, 166.8, 60.4, 58.4, 47.7, 46.5, 36.6, 35.6, 26.2, 21.4.

(1*S,2*S**,3*R**,4*R**)-*tert*-Butyl 2-((4-bromobenzyl)carbamoyl)-3-(dimethylcarbamoyl)-7-azabicyclo[2.2.1]heptane-7-carboxylate 12** To a solution of **10** (223 mg, 0.7 mmol), in dichloromethane (4 mL) and dimethylformamide (4 mL) was added 4-bromobenzylamine hydrochloride (191 mg, 0.9 mmol), followed by HATU (407 mg, 1.1 mmol) then *N,N*-diisopropylethylamine (622 μL, 3.6 mmol). The solution was stirred at rt for 18 h then diluted with ethyl acetate (10 mL) and extracted with sat. NH_4Cl (aq) (10 mL). The organic phase was then washed with sat. $NaHCO_3$ (aq) (10 mL) followed by 5% aq LiCl solution (10 mL) and finally brine (10 mL). The organics were dried over Na_2SO_4 and concentrated to give an orange oil (410 mg). Purification by flash column chromatography (1% methanol in dichloromethane with 1% NH_3 in H_2O, R_f 0.50 in 10% methanol in dichloromethane with 0.1% NH_3 in H_2O) gave the desired compound **12** as a colorless foamy solid (287 mg, 0.6 mmol, 84%). HRMS *m/z* (ESI$^+$) Found 502.1303 $[M+Na]^+$, $C_{22}H_{30}{}^{79}BrN_3NaO_4$ requires 502.1312. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 7.44 (*J* 8.5, 2H), 7.15 (d, *J* 8.5, 2H), 6.27 (br s, 1H), 4.50–4.30 (m, 4H), 3.77 (br s, 1H), 3.21 (d, *J* 5.0, 1H), 3.16 (s, 3H), 2.93 (s, 3H), 1.88–1.74 (m, 2H), 1.67–1.49 (m, 2H), 1.43 (s, 9H). ^{13}C NMR(100 MHz, $CDCl_3$) δ_C 172.3, 169.9, 154.8, 137.5, 131.7, 129.5, 129.4, 80.3, 51.7, 48.7 (2 C), 43.1, 38.6, 37.3, 35.9, 29.6, 28.2, 24.0.

(1*S,2*S**,3*R**,4*R**)-*N*^{2}-(4-Bromobenzyl)-*N*^{3},*N*^{3}-dimethyl-7-azabicyclo-[2.2.1]heptane-2,3-dicarboxamide 2,2,2-trifluoroacetate 13** Adduct **12** (287 mg, 0.6 mmol) was dissolved in dichloromethane (2 mL), cooled to 0 ºC and TFA (523 μL) added dropwise over 20 sec. The reaction mixture was then stirred at rt for 20 h. The volatiles were removed under reduced pressure to give **13** as an off-white solid (342 mg, 0.7 mmol, quantitative), which required no further purification. MP 150–152 °C. HRMS *m/z* (ESI$^+$) Found 380.0974 $[M+H]^+$, $C_{17}H_{23}{}^{79}BrN_3O_2$ requires 380.0968. ν_{max} ($CHCl_3$)/cm^{-1} 3440, 3012, 2931, 2717, 2542, 1778, 1673, 1648, 1524, 1490, 1407, 1173, 1073, 1013, 835. ^{1}H NMR (400 MHz; d_6-DMSO) δ_H 9.41 (br s, 1H), 8.84 (t, *J* 5.8, 1H), 8.29 (br s, 1H), 7.51 (d, *J* 8.3, 2H), 7.22 (*J* 8.3, 2H), 4.45 (t, *J* 4.6, 1H), 4.31 (d, *J* 4.6, 1H), 4.25 (t, *J* 5.3, 2H), 3.68 (td, *J* 4.1, 1.1, 1H), 3.27 (d, *J* 5.0, 1H), 3.06 (3 H, s, 3H), 2.88 (s, 3H), 1.93–1.80 (m, 1H), 1.80–1.68 (m, 1H), 1.68–1.49 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C 171.3, 169.2, 167.0, 158.3 (q, $J_{C,F}$ 35.3), 138.5, 131.2, 129.6, 119.9, 62.0, 58.3, 47.6, 46.2, 41.9, 36.7, 35.6, 26.3, 21.6.

(1*S*,2*S*,3*R*,4*R*)-*N*^{2},7-Bis(4-bromobenzyl)-*N*^{3},*N*^{3}-dimethyl-7-azabicyclo-[2.2.1]heptane-2,3-dicarboxamide 14 Amine **13** (50 mg, 0.13 mmol) and 4-bromobenzaldehyde (27 mg, 0.15 mmol), were dissolved in 1,2-dichloroethane (2 mL) and 3 Å molecular sieves (powdered, 50 mg) were added. The solution was stirred at rt for 17 h. Sodium triacetoxyborohydride (83 mg, 0.39 mmol) was added and the solution stirred at rt for 16 h. Following dilution with dichloromethane (5 mL), the solution was washed with water (2 × 5 mL). The organics were separated, dried over Na_2SO_4 and concentrated to give a pale yellow oil (103 mg). Purification by flash column chromatography (0.5–1% methanol in chloroform with 1% NH_3 in H_2O, R_f 0.23 in 2% methanol in chloroform with 0.1% NH_3 in H_2O) gave the desired compound **14** as a turbid oil (50 mg, 0.09 mmol, 70%). HRMS *m/z* (ESI$^+$) Found 548.0566 $[M+H]^+$, $C_{24}H_{28}{}^{79}Br_2N_3O_2$ requires 548.0543. ν_{max} ($CHCl_3$)/cm^{-1} 3445, 3293, 3011, 2967, 2930, 2856, 2361, 2342, 1647, 1515, 1489, 1403, 1240, 1107, 1072, 1013. ^{1}H NMR (400 MHz; d_6-DMSO) δ_H 8.30 (t, *J* 5.9, 1H), 7.44 (d, *J* 8.5, 2H), 7.40 (d, *J* 8.4, 2H), 7.20 (d, *J* 8.4, 2H), 7.10 (d, *J* 8.5, 2H), 4.30 (dd, *J* 15.2, 6.0, 1H), 4.10 (dd, *J* 15.2, 6.0 Hz, 1H), 3.73 (t, *J* 4.1, 1H), 3.61 (t, *J* 4.1, 1H), 3.56 (d, *J* 14.0, 1H), 3.44 (d, *J* 14.0, 1H), 3.38 (d, *J* 4.7, 1H), 3.06 (s, 3H), 2.95 (d, *J* 4.7, 1H), 2.83 (s, 3H), 1.83–1.72 (m, 1H), 1.66–1.54 (m, 1H), 1.37 (ddd, *J* 12.7, 9.0, 4.0, 1H), 1.28 (ddd, *J* 12.7, 9.0, 4.0, 1H).* ^{13}C NMR (100 MHz, DMSO-d_6) δ_C 172.7, 170.5, 142.0, 139.3, 131.0, 130.2, 129.4, 128.5, 119.7, 119.6, 63.6, 62.1, 61.5, 51.0, 49.5, 47.1, 41.7, 41.5, 36.7, 35.4. **With additional minor signals due to the presence of inseparable 4-bromobenzaldehyde.*

***tert*-Butyl 2-((benzylamino)methyl)-1*H*-pyrrole-1-carboxylate 16a** *N*-Boc-pyrrole-2-carboxaldehyde **15** (2.0 g, 10.25 mmol) and benzylamine (1.23 mL, 11.27 mmol) were dissolved in 1,2-dichloroethane (90 mL), sodium triacetoxyborohydride (6.9 g, 30.75 mmol) was added and the solution stirred at rt for 16 h. Following dilution with dichloromethane (90 mL), the solution was washed with sat. $NaHCO_3$ (aq) (60 mL). The organics were separated and the aqueous was re-extracted with dichloromethane (50 mL) the layers were separated and the combined organics dried over Na_2SO_4 and concentrated to give the desired amine **16a** as a pale orange oil (4.0 g, 14 mmol, quantitative) that required no further purification. HRMS *m/z* (ESI$^+$) Found 287.1747 $[M+H]^+$, $C_{17}H_{23}N_2O_2$ requires 287.1754. ν_{max} (ATR)/cm^{-1} 2979, 1738, 1494, 1455, 1409, 1370, 1336, 1256, 1168, 1133, 1061, 881, 848, 732. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 7.38–7.30 (m, 4H), 7.26–7.23 (1m, 1H), 7.22 (dd, *J* 3.3, 1.8, 1H), 6.15 (d, *J* 7.2, 1H), 6.12 (m, 1H), 3.97 (d, *J* 0.4, 1H), 3.80 (s, 2H), 1.60 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 149.4, 140.5, 133.7, 128.3, 128.1, 126.7, 121.6, 113.4, 110.0, 83.7, 52.4, 46.3, 28.0

(*E*)-*tert*-Butyl 2-((*N*-benzyl-4-ethoxy-4-oxobut-2-enamido)methyl)-1*H*-pyrrole-1-carboxylate 17a To a solution of **16a** (4.0 g, 14.00 mmol), in dichloromethane (70 mL) and dimethylformamide (70 mL) was added mono-ethyl fumarate (1.9 g, 12.17 mmol), followed by HATU (6.9 g, 18.26 mmol) and the mixture was cooled to 0 ºC. *N,N*-Diisopropylethylamine (8.5 mL, 48.68 mmol) was then added and the reaction was stirred at rt for 18 h. Following dilution with ethyl acetate (100 mL) the reaction mixture was extracted with sat. NH_4Cl (aq) (80 mL), the organic phase was then washed with sat. $NaHCO_3$ (aq) (80 mL) followed by 5% aq LiCl solution (100 mL) and finally brine (80 mL). The organics were dried over Na_2SO_4 and concentrated to give a deep red oil (5.9 g). Purification by flash column chromatography (50–70% ether in light petroleum with 1% NH_3 in H_2O) gave the desired amide **17a** as a pale yellow oil (3.0 g, 7.15 mmol, 59%). HRMS *m/z* (ESI$^+$) Found 413.2077 $[M+H]^+$, $C_{23}H_{29}N_2O_5$ requires 413.2071. ν_{max} (ATR)/cm^{-1} 2981, 1741, 1660, 1440, 1335, 1164, 1120, 1029, 973, 847, 755. ^{1}H NMR (400 MHz; DMSO-d_6) δ_H 7.47–7.14 (m, 7H), 6.69 (d, *J* 15.3, 2H), 6.16 (dt, *J* 6.5, 3.3, 1H), 5.97 (dd, *J* 3.1, 1.6, 1H), 4.80 (s, 1H), 4.75 (d, *J* 3.3, 2H),

4.62 (s, 1H), 4.16 (q, *J* 7.0, 2H), 1.49 (s, 9H), 1.21 (*J* 7.1, 3H), additional minor signals due to the presence of rotamers. ^{13}C NMR (100 MHz; DMSO-d_6, 70 ºC) δ_C 164.6, 164.5, 154.9, 148.4, 137.0, 134.3, 129.9, 128.1, 127.1, 126.8, 121.7, 111.9, 110.1, 83.9, 60.3, 50.4, 45.4, 27.2, 13.6, additional minor signals due to the presence of rotamers.

(3a*R,6*S**,7*S**,7a*S**)-8-*tert*-Butyl 7-ethyl 2-benzyl-1-oxo-1,2,3,6,7,7a-hexahydro-3a,6-epiminoisoindole-7,8-dicarboxylate 18a** To amide **17a** (2.9 g, 7.15 mmol) in dry ether (50 mL) was added lithium triflamide (50 g, 174.16 mmol; dried at 150 ºC under high vacuum immediately prior to use) and the mixture stirred at rt for 6 days. The reaction mixture was diluted with water (150 mL) and chloroform (100 mL). The phases were separated and the organic layer was washed with water (2 x 70 mL), the combined organics were washed with brine (150 mL) and dried over Na_2SO_4 to give a pale yellow oil (3.3 g). Purification by flash column chromatography (40–80% ethyl acetate in light petroleum with 1% NH_3 in H_2O) gave the Diels-Alder adduct **18a** as a colouless foamy oil (1.7 g, 4.17 mmol, 58%). HRMS *m/z* (ESI$^+$) Found 413.2096 $[M+H]^+$, $C_{23}H_{29}N_2O_5$ requires 413.2093.ν_{max} (ATR)/cm^{-1} 2979, 1720, 1630, 1425, 1369, 1331, 1159, 1117, 1062, 1028, 971, 843, 724, 698. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 7.40–7.18 (m, 5H), 6.51 (d, *J* 4.8, 1H), 6.28 (d, *J* 4.8, 1H), 5.05 (d, *J* 1.9, 1H), 4.78–4.66 (m, 1H), 4.55 (br s, 2H), 4.14 (q, *J* 7.1, 2H), 3.77 (d, *J* 11.5, 1H), 3.47 (t, *J* 4.0, 1H), 2.87 (d, *J* 4.0, 1H), 1.31 (br s, 9H), 1.26 (t, *J* 7.1, 3H), additional minor signals due to the presence of the retro Diels-Alder product (**17a**). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 172.0, 170.7, 155.8, 136.3, 133.7, 132.0, 128.6, 127.9, 127.5, 81.2, 74.2, 65.3, 61.1, 53.6, 47.4, 46.6, 43.4, 28.0, 14.1, additional minor signals due to the presence of the retro Diels-Alder product (**17a**).

(3a*R,6*S**,7*S**,7a*S**)-8-*tert*-Butyl 7-ethyl 2-benzyl-1-oxooctahydro-3a,6-epiminoisoindole-7,8-dicarboxylate 19a** Adduct **18a** (1.7 g, 4.17 mmol) was dissolved in methanol (85 mL) and palladium on activated carbon added (44 mg, 0.42 mmol, 10 mol%). The solution was stirred under an atmosphere of hydrogen at rt for 1.5 h. Filtration through Celite and removal of methanol under reduced pressure gave a colorless oily solid (1.5 g) that was purified by flash column chromatography (30–40% ethyl acetate in light petroleum with 1% NH_3 in H_2O) to give the desired product **19a** as a colorless oil (1.3 g, 3.15 mmol, 76%). HRMS *m/z* (ESI$^+$) Found 415.2232 $[M+H]^+$, $C_{23}H_{30}N_2O_5$ requires 415.2227. ν_{max} (ATR)/cm^{-1} 2981, 2933, 1739, 1654, 1494, 1414, 1372, 1335, 1165, 1120, 1062, 1016, 958, 891, 844, 755, 699, 666. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 7.30–7.17 (m, 5H), 4.49–4.38 (m, 4H), 4.16 (q, *J* 7.1, 2H), 3.40 (d, *J* 11.5, 1H), 3.26 (t, *J* 4.6, 1H), 3.01 (d, *J* 5.0, 1H), 1.88–1.72 (m, 2H), 1.71–1.61 (m, 1H), 1.60–1.53 (m, 1H), 1.32 (s, 9H), 1.25 (t, *J* 7.1, 3H). ^{13}C NMR (400 MHz; $CDCl_3$) δ_C 172.9, 170.9, 155.5, 136.1, 128.4, 127.7, 127.2, 80.5, 69.9, 61.0, 60.8, 53.7, 47.9, 47.2, 46.3, 28.4, 27.8, 25.2, 14.0.

(3a*R,6*S**,7*S**,7a*S**)-2-Benzyl-8-(*tert*-butoxycarbonyl)-1-oxooctahydro-3a,6-epiminoisoindole-7-carboxylic acid 20a** To a solution of ester **19a** (1.31 g, 3.15 mmol) in THF (16 mL) was added an aqueous solution of 1 M LiOH (5.1 mL) and the mixture was stirred at 40 ºC for 28 h. 1 M HCl was added until pH 3 and the mixture extracted with dichloromethane (3 x 20 mL). The organic phase was dried over Na_2SO_4 and concentrated to give acid **20a** (1.2 g, 3.13 mmol, 99%) as a colorless solid that required no further purification. MP 207–208 °C. HRMS *m/z* (ESI$^+$) Found 387.1914 $[M+H]^+$, $C_{21}H_{27}N_2O_5$ requires 387.1914. ν_{max} (ATR)/cm^{-1} 2928, 1730, 1697, 1637, 1486, 1453, 1329, 1241, 1151, 1122, 934, 874, 737, 701, 654, 632. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 11.64 (br s, 1H), 7.49–7.08 (m, 5H), 4.56 (m, 4H), 3.49 (d, *J* 11.8, 1H), 3.36 (t, *J* 4.6, 1H), 3.21 (d, *J* 5.1, 1H), 1.93–1.74 (m, 4H), 1.40 (br s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 175.3, 172.5, 155.6, 135.4, 128.6, 127.8, 127.6, 80.7, 70.0, 61.1, 54.3, 48.4, 47.8, 46.8, 28.5, 28.0, 25.1.

(3a*R,6*S**,7*S**,7a*S**)- *tert*-Butyl 2-benzyl-7 -((4-bromobenzyl) carbamoyl)-1-oxooctahydro-3a,6-epiminoisoindole-8-carboxylate 21a** To a solution of acid **20a** (1.2 g, 3.13 mmol), in dichloromethane (35 mL) and dimethylformamide (35 mL) was added 4-bromobenzylamine hydrochloride (852.0 mg, 3.75 mmol), followed by HATU (1.8 g, 4.70 mmol) and the mixture was cooled to 0 ºC. *N,N*-Diisopropylethylamine (2.7 mL, 15.65 mmol) was then added and the mixture was stirred at rt for 24 h. Following dilution with ethyl acetate (50 mL) the reaction mixture was extracted with sat. NH_4Cl (aq) (30 mL), the organic phase was then washed with sat. $NaHCO_3$ (aq) (30 mL) followed by 5% aq LiCl solution (60 mL) and finally brine (40 mL). The organics were dried over Na_2SO_4 and concentrated to give a foamy pale brown solid (1.9 g). Purification by flash column chromatography (30–50% ethyl acetate in light petroleum with 1% NH_3 in H_2O) gave the desired amide **21a** as a colorless oil (1.4 g, 2.54 mmol, 81%). HRMS *m/z* (ESI$^+$) Found 576.1457 $[M+Na]^+$, $C_{28}H_{32}{}^{79}BrN_3NaO_4$ requires 576.1468. ν_{max} (ATR)/cm^{-1} 3305, 3011, 2877, 2456, 1686, 1548, 1487, 1431, 1338, 1246, 1164, 1124, 1072, 1048, 1030, 1011, 925, 856, 754, 703, 667, 635. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 7.44 (d, *J* 8.4, 2H), 7.36–7.28 (m, 3H), 7.21 (m, 2H), 7.16 (d, *J* 8.5, 2H), 7.06 (t, *J* 5.6, 1H), 4.55–4.36 (m, 4H), 4.28 (dd, *J* 14.9, 5.6, 1H), 3.45 (d, *J* 11.8, 1H), 3.17–3.09 (m, 1H), 2.86 (d, *J* 6.0, 1H), 2.08–2.00 (m, 1H), 1.89–1.81 (m, 2H), 1.74–1.66 (m, 1H), 1.36 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 173.9, 170.3, 156.0, 137.4, 135.9, 131.7, 129.4, 128.7, 127.9, 127.6, 121.2, 80.7, 69.7, 61.3, 54.6, 49.0, 48.0, 46.6, 42.9, 29.5, 28.1, 24.9.

(3a*R,6*S**,7*S**,7a*S**)-2-Benzyl-*N*-(4-bromobenzyl)-1-oxooctahydro-3a,6-epiminoisoindole-7-carboxamide 22a** Adduct **21a** (688 mg, 0.91 mmol) was dissolved in dichloromethane (6 mL), cooled to 0 ºC and TFA (1.1 mL) added dropwise over 30 sec. The reaction mixture was then stirred at rt for 15 h. The volatiles were removed under reduced pressure to give **22a**.TFA as a pale pink foam (727 mg). Purification by ion-exchange chromatography (SCX*, 5% NH_3 in MeOH) gave free amine **22a** as a colorless solid (516 mg, 1.14 mmol, 92%). MP 221–223 °C. HRMS *m/z* (ESI$^+$) Found 456.1118 $[M+H]^+$, $C_{23}H_{25}{}^{81}BrN_3O_2$ requires 456.1119. ν_{max} (ATR)/cm^{-1} 3274, 2939, 2361, 1672, 1643, 1548, 1487, 1439, 1331, 1238, 1080, 1009, 832, 723, 692, 648. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 7.44 (d, *J* 8.3, 2H), 7.38–7.28 (m,3H), 7.22 (m, 2H), 7.17 (d, *J* 8.2, 2H), 7.00 (br s, 1H), 4.56 (d, *J* 14.8, 1H), 4.48 (dd, *J* 14.9, 6.1, 1H), 4.35 (d, *J* 14.9, 1H), 4.29 (dd, *J* 14.9, 9.8, 1H), 3.82 (t, *J* 3.7, 1H), 3.51 (d, *J* 11.1, 1H), 3.33 (d, *J* 11.0, 1H), 3.06 (t, *J* 4.4, 1H), 2.86 (d, *J* 5.4, 1H), 2.02–1.92 (m, 1H), 1.74–1.59 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 175.0, 170.7, 137.5, 136.0, 131.7, 129.5, 128.8, 128.0, 127.7, 121.2, 68.7, 60.1, 53.3, 52.7, 49.5, 46.9, 43.0, 30.5, 25.8.

***tert*-Butyl 2-((isopropylamino)methyl)-1*H*-pyrrole-1-carboxylate 16b** *N*-Boc-pyrrole-2-carboxaldehyde **15** (2.0 g, 10.25 mmol) and isoproylamine (0.97 mL, 11.27 mmol) were dissolved in 1,2-dichloroethane (90 mL), sodium triacetoxyborohydride (6.9 g, 30.75 mmol) was added and the solution stirred at rt for 16 h. Following dilution with dichloromethane (90 mL), the solution was washed with sat. $NaHCO_3$ (aq) (60 mL). The organics were separated and the aqueous was re-extracted with dichloromethane (50 mL) the layers were separated and the combined organics dried over Na_2SO_4 and concentrated to give the desired amine **16b** as a pale orange oil (3.0 g, 12.49 mmol, quantitative) that required no further purification. HRMS *m/z* (ESI$^+$) Found 239.1777 $[M+H]^+$, $C_{13}H_{23}N_2O_2$ requires 239.1754. ν_{max} (ATR)/cm^{-1} 2978, 2346, 1740, 1655, 1561, 1477, 1409, 1371, 1336, 1255, 1171, 1124, 1068, 1013, 882, 847, 730, 652. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 7.19 (dd, *J* 3.3, 1.8, 1H), 6.55 (br s, 1H), 6.21 (dd, *J* 3.1, 1.8, 1H), 6.10 (t, *J* 3.3, 1H), 4.04 (s, 2H), 2.94 (sep., *J* 6.4, 1H), 1.60 (s, 9H), 1.16 (d, *J* 6.4, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 149.6, 131.1, 122.0, 114.6, 110.2, 84.2, 47.4, 43.3, 28.0, 21.7.

(*E*)-*tert*-Butyl 2-((4-ethoxy-*N*-isopropyl-4-oxobut-2-enamido)methyl)-1*H*-pyrrole-1-carboxylate 17b To a solution of **16b** (3.0 g, 12.49 mmol), in dichloromethane (60 mL) and dimethylformamide (60 mL) was added mono-ethyl fumarate (1.7 g, 10.86 mmol), followed by HATU (6.2 g, 16.29 mmol) and the mixture was cooled to 0 ºC. *N,N*-

Diisopropylethylamine (7.6 mL, 43.44 mmol) was then added and the mixture was stirred at rt for 18 h. Following dilution with ethyl acetate (100 mL) the reaction mixture was extracted with sat. NH_4Cl (aq) (80 mL), the organic phase was then washed with sat. $NaHCO_3$ (aq) (80 mL) followed by 5% aq LiCl solution (100 mL) and finally brine (80 mL). The organics were dried over Na_2SO_4 and concentrated to give a deep red oil (4.7 g). Purification by flash column chromatography (50–70% ether in light petroleum with 1% NH_3 in H_2O) gave the desired amide **17b** as a yellow oil (2.2 g, 6.00 mmol, 55%). HRMS *m/z* (ESI^+) Found 365.2078 $[M+H]^+$, $C_{19}H_{29}N_2O_5$ requires 365.2071. ν_{max} (ATR)/cm^{-1} 2975, 1691, 1422, 1367, 1327, 1244, 1159, 1120, 1076, 1030, 709. ^1H NMR (400 MHz; $CDCl_3$) δ_H 7.18 (dd, *J* 3.1, 1.8, 1H), 7.14 (d, *J* 15.2, 1H), 6.88 (d, *J* 15.2, 1H), 6.08 (t, *J* 3.4, 1H), 5.99 (dd, *J* 3.3, 1.7, 1H), 4.85 (sep., *J* 6.8, 1H), 4.71 (s, 2H), 4.19 (q, *J* 7.1, 2H), 1.63 (s, 9H), 1.26 (t, *J* 7.2, 3H), 1.16 (d, *J* 6.8, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 165.9, 165.1, 149.4, 134.8, 132.4, 131.6, 121.7, 112.7, 110.5, 84.3, 60.9, 46.3, 41.9, 28.1, 20.1, 14.1.

(3a*R,6*S**,7*S**,7a*S**)-8-*tert*-Butyl 7-ethyl 2-isopropyl-1-oxo-1,2,3,6,7,7a-hexahydro-3a,6-epiminoisoindole-7,8-dicarboxylate 18b** To amide **17b** (2.2 g, 6.00 mmol) in dry ether (50 mL) was added lithium triflamide (50 g, 174.16 mmol; dried at 150 ºC under high vacuum immediately prior to use) and the mixture stirred at rt for 11 days. The reaction mixture was diluted with water (150 mL) and chloroform (100 mL). The phases were separated and the organic layer was washed with water (2 x 70 mL), the combined organics were washed with brine (150 mL) and dried over Na_2SO_4 to give a pale yellow oil (2.0 g). Purification by flash column chromatography (80%–neat ether in light petroleum with 1% NH_3 in H_2O) gave the Diels-Alder adduct **18b** as a colorless foamy solid (1.5 g, 4.03 mmol, 67%).MP 87–89 °C. HRMS *m/z* (ESI^+) Found 387.1895 $[M+Na]^+$, $C_{19}H_{28}N_2NaO_5$ requires 387.1890. ν_{max} (ATR)/cm^{-1} 3468, 2978, 2461, 1714, 1625, 1478, 1394, 1369, 1334, 1248, 1165, 1124, 1077, 1060, 1032, 968, 871, 842, 722, 666. ^1H NMR (400 MHz; $CDCl_3$) δ_H 6.47 (d, *J* 5.5, 1H), 6.19 (d, *J* 5.5, 1H), 4.92 (dd, *J* 3.8, 1.6, 1H), 4.61 (br s, 1H), 4.28 (sep., *J* 6.7, 1H), 4.02 (q, *J* 7.1, 2H), 3.65 (d, *J* 11.4, 1H), 3.28 (t, *J* 4.1, 1H), 2.71 (d, *J* 3.9, 1H), 1.30 (s, 9H), 1.15 (t, *J* 7.2, 3H), 1.07 (d, *J* 6.8, 3H), 1.02 (d, *J* 6.7, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 171.1, 170.5, 155.4, 136.2, 134.6, 80.8, 74.1, 64.7, 60.8, 53.8, 43.2, 42.3, 27.8, 19.7, 19.4, 13.9.

(3a*R,6*S**,7*S**,7a*S**)-8-*tert*-Butyl 7-ethyl 2-isopropyl-1-oxooctahydro-3a,6-epiminoisoindole-7,8-dicarboxylate 19b** Adduct **18b** (1.5 g, 4.03 mmol) was dissolved in methanol (82 mL) and palladium on activated carbon added (43.0 mg, 0.40 mmol, 10mol%). The solution was stirred under an atmosphere of hydrogen at rt for 1.5 h. Filtration through Celite and removal or methanol under reduced pressure desired tricycle **19b** as a turbid grey oil (1.4 g, 3.68 mmol, 91%), which crystallized on standing and required no further purification. MP 73–74 °C. HRMS *m/z* (ESI^+) Found 389.2053 $[M+Na]^+$, $C_{19}H_{30}N_2NaO_5$ requires 389.2047. ν_{max} (ATR)/cm^{-1} 2970, 1735, 1687, 1478, 1420, 1367, 1324, 1226, 1163, 1122, 1091, 1032, 1005, 858, 831, 684, 620. ^1H NMR (400 MHz; $CDCl_3$) δ_H 4.61 (d, *J* 11.8, 1H), 4.46 (t, *J* 4.7, 1H), 4.33 (sep., *J* 6.7, 1H), 4.17 (q, *J* 7.1, 2H), 3.40 (d, *J* 11.4, 1H), 3.21 (t, *J* 4.7, 1H), 2.97 (d, *J* 4.8, 1H), 1.91 (td, *J* 11.4, 4.0, 1H), 1.86–1.76 (m, 1H), 1.76–1.67 (m, 1H), 1.63–1.55 (m, 1H), 1.43 (s, 9H), 1.27 (t, *J* 7.2, 3H), 1.12 (d, *J* 6.9, 6H), 1.11 (d, *J* 6.7, 3H). ^{13}C NMR (400 MHz; $CDCl_3$) δ_C 172.4, 171.2, 155.5, 80.6, 70.2, 61.2, 60.8, 54.4, 47.9, 42.6, 42.5, 28.4, 28.2, 25.6, 19.9, 19.7, 14.2.

(3a*R,6*S**,7*S**,7a*S**)-8-(*tert*-Butoxycarbonyl)-2-isopropyl-1-oxooctahydro-3a,6-epiminoisoindole-7-carboxylic acid 20b** To a solution of ester **19b** (1.3 g, 3.48 mmol) in THF (18 mL) was added an aqueous solution of 1 M LiOH (6.0 mL) and the reaction was stirred at 40 ºC for 28 h. 1 M HCl was added until pH 3 and the mixture extracted with dichloromethane (3 x 20 mL). The organic phase was dried over Na_2SO_4 and concentrated to give acid **20b** (820.0 mg, 2.43 mmol, 70%), as a colorless solid which required no further purification. MP 220–221 °C. HRMS *m/z* (ESI^+) Found 361.1725 $[M+Na]^+$, $C_{17}H_{26}N_2NaO_5$ requires 361.1734. ν_{max} (neat)/cm^{-1} 2974, 2180, 1996, 1726, 1697, 1625, 1478, 1369, 1332, 1224, 1166, 1126, 1034, 1004, 857, 811, 775, 653, 620, 554. ^1H NMR (400 MHz; $CDCl_3$) δ_H 4.70 (1 H d, *J* 11.7, 1H), 4.47 (t, *J* 4.4, 1H), 4.34 (sep., *J* 6.8, 1H), 3.41 (d, *J* 11.7, 1H), 3.20 (t, *J* 4.4, 1H), 3.08 (d, *J* 5.0, 1H), 1.90–1.80 (m, 4H), 1.41 (s, 9H), 1.13 (d, *J* 6.7, 3H), 1.12 (d, *J* 6.9, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 174.5, 172.6, 155.5, 80.6, 70.1, 67.9, 61.0, 54.9, 48.4, 43.2, 28.5, 28.1, 25.5, 19.7, 19.6.

(3a*R,6*S**,7*S**,7a*S**)-*tert*-Butyl 7-((4-bromobenzyl)carbamoyl)-2-isopropyl-1-oxooctahydro-3a,6-epiminoisoindole-8-carboxylate 21b** To a solution of acid **20b** (820.0 mg, 2.42 mmol), in dichloromethane (27 mL) and dimethylformamide (27 mL) was added 4-bromobenzylamine hydrochloride (661.0 mg, 2.91 mmol), followed by HATU (1.4 g, 3.63 mmol) and the mixture was cooled to 0 ºC. *N,N*-Diisopropylethylamine (2.1 mL, 12.10 mmol) was then added and the reaction was stirred at rt for 24 h. Following dilution with ethyl acetate (50 mL) the reaction mixture was extracted with sat. NH_4Cl (aq) (30 mL), the organic phase was then washed with sat. $NaHCO_3$ (aq) (30 mL) followed by 5% aq LiCl solution (60 mL) and finally brine (40 mL). The organics were dried over Na_2SO_3 and concentrated to give a foamy pale brown solid (1.3 g). Purification by flash column chromatography (50–70% ethyl acetate in light petroleum with 1% NH_3 in H_2O) gave the desired amide **21b** as a foamy grey solid (1.0 g, 2.03 mmol, 84%). MP 156–157 ºC. HRMS *m/z* (ESI^+) Found 528.1475 $[M+Na]^+$, $C_{24}H_{32}{}^{79}BrN_3NaO_4$ requires 528.1468. ν_{max} (ATR)/cm^{-1} 3302, 2976, 1664, 1540, 1339, 1166, 1012, 755. ^1H NMR (400 MHz; $CDCl_3$) δ_H 7.43 (d, *J* 8.3, 2H), 7.14 (d, *J* 8.5, 2H), 7.03 (t, *J* 5.7, 1H), 4.63 (d, *J* 11.4, 1H), 4.46–4.41 (m, 2H), 4.32–4.22 (m, 2H), 3.43 (d, *J* 11.5, 1H), 3.04 (t, *J* 4.7, 1H), 2.75 (d, *J* 6.0, 1H), 2.10–1.99 (m, 1H), 1.98–1.79 (m, 2H), 1.74–1.69 (m, 1H), 1.44 (s, 9H), 1.15 (d, *J* 6.7, 3H), 1.14 (d, *J* 6.9, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 173.1, 170.5, 155.9, 137.4, 131.7, 129.4, 121.1, 80.7, 77.2, 61.0, 55.2, 48.9, 43.3, 42.9, 42.8, 29.5, 28.2, 25.1, 19.8, 19.7.

(3a*R,6*S**,7*S**,7a*S**)-*N*-(4-Bromobenzyl)-2-isopropyl-1-oxooctahydro-3a,6-epiminoisoindole-7-carboxamide 22b** Adduct **21b** (514.2 mg, 1.02 mmol) was dissolved in dichloromethane (5 mL), cooled to 0 ºC and TFA (890.0 μL) added dropwise over 20 sec. The reaction mixture was then stirred at rt for 15 h. The volatiles were removed under reduced pressure to give **22b**.TFA as a purple solid (410.0 mg). Purification by ion-exchange chromatography (SCX*, 5% NH_3 in MeOH) gave free amine **22b** as a brown solid (405 mg, 1.00 mmol, 98%). MP 200–201 ºC. HRMS *m/z* (ESI^+) Found 406.1123 $[M+H]^+$, $C_{19}H_{25}{}^{79}BrN_3O_2$ requires 406.1120. ν_{max} (ATR)/cm^{-1} 3250, 2971, 1650, 1545, 1487, 1428, 1331, 1228, 1071, 1011, 907, 794, 727, 646. ^1H NMR (400 MHz; $CDCl_3$) δ_H 7.44 (d, *J* 8.5, 2H), 7.16 (d, *J* 8.3, 2H), 6.94 (br s, 1H), 4.45 (dd, *J* 15.1, 6.1, 1H), 4.37–4.22 (m, 2H), 3.81 (t, *J* 4.2, 1H), 3.56–3.41 (m, 2H), 2.98 (t, *J* 4.5, 1H), 2.77 (d, *J* 5.6, 1H), 2.04–1.91 (m, 1H), 1.82–1.66 (m, 3H), 1.14 (d, *J* 6.7, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 174.2, 170.8, 137.5, 131.6, 129.5, 121.1, 68.6, 60.0, 54.0, 52.9, 44.6, 43.0, 42.7, 30.5, 25.7, 19.9, 19.6. *SCX* specifications:* SCX-2 pre-packed column, Isolute SPE column flash SCX-2 70 mL (Part no. 456-1000-F, Lot no. 4083405F1B).

Methyl 3-bromopropiolate 24 Methyl propiolate (29.4 g, 0.35 mol) was added to a solution of recrystallized *N*-bromosuccinimide (70 g, 0.40 mol) in acetone (1.1 L). Silver nitrate (6.0 g, 0.04 mol) was added and the reaction mixture was stirred under nitrogen at room temperature for 4 h. Volatiles were removed under reduced pressure to give a grey slurry. This was washed with hexane (2 × 1 L). Half the volume of hexane was removed under reduced pressure and the remainder removed by short path distillation at atmospheric pressure with heating at 90–93 ºC. Distillation under reduced pressure (33 mbar, 70–80 ºC external temperature, 60 ºC internal temperature) gave the desired product **24** as a colorless oil (41.9 g, 0.26 mol, 74%). ^1H NMR (400 MHz; $CDCl_3$) δ_H 3.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 152.8, 72.5, 53.0, 52.8. The data were in agreement with the literature.[19]

(1*S,4*R**)-7-*tert*-Butyl 2-methyl 3-bromo-7-azabicyclo[2.2.1]hepta-2,5-diene-2,7-dicarboxylate 25** Methyl 3-bromopropiolate **24** (41.9 g, 0.26 mol) and *N*-Boc pyrrole **4** (204 g, 1.22 mol) were dissolved in dry toluene (50 mL), the flask was well insulated with cotton and foil then heated at 80 ºC for 5 days. The mixture was reduced to a dark brown oil (183.11 g). Purification by flash column chromatography (10–30% ether in light petroleum) gave the desired Diels-Alder product **25** (37.6 g, 0.114 mmol, 45%) as a bright orange oil. HRMS *m/z* (ESI^+) Found 352.0140 $[M+Na]^+$, $C_{13}H_{16}{}^{79}BrNNaO_4$ requires 352.0115. ν_{max} (ATR) / cm^{-1} 2977, 1707, 1603, 1312,. 1254, 1207, 1158, 1032. ^1H NMR (400 MHz; $CDCl_3$) δ_H 7.13 (2 H, br s), 5.48 (s, 1 H), 5.13 (br s, 1H), 3.79 (s, 3H), 1.41 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 162.7, 154.0, 147.6, 143.2, 141.3, 140.4, 81.5, 74.7, 68.8, 51.8, 28.1. The data were in agreement with the literature.[20]

8-(*tert*-Butyl) 6-methyl (1*R,5*S**) -3-benzyl-3,8-diazabicyclo [3.2.1]octane-6,8-dicarboxylate 27a/27b** Carbamate **25** (3.03 g, 9.18 mmol) was dissolved in dry acetonitrile (100 mL) and cooled to -15 °C using a salt/ice bath. Sodium borohydride (870 mg, 23 mmol) was added portionwise over 15 min, and the suspension was stirred for 1.5 h. The reaction mixture was quenched using a saturated solution of ammonium chloride (20 mL) and CH_2Cl_2 (100 mL) was added. The organic layer was washed with water to remove acetonitrile (4 x 150 mL) and the dichloromethane solution of **26** was dried with $MgSO_4$, filtered, and used in the next step immediately. The dichloromethane solution of **26** was subjected to ozonolysis at -78 °C, until a blue colour was observed from remaining O_3. The solution was then warmed to 0 °C and dimethyl sulfide was added (3.37 mL, 45.9 mmol) and the mixture was allowed to warm to rt and stirred for 16 h. Volatiles were then removed *in vacuo* and the mixture was re-dissolved in dry 1,2-dichloroethane (50 mL) and cooled to 0 °C. Benzylamine (990 μL, 9 mmol) was added followed by sodium triacetoxyborohydride (9.54 g, 45 mmol) and the mixture was warmed to rt and stirred for 3 h. The reaction was slowly quenched with aqueous $NaHCO_3$ solution (saturated, 30 mL) and after gas evolution had ceased, the organics were extracted with CH_2Cl_2 (2 x 50 mL), dried with $MgSO_4$, and solvent was removed *in vacuo*. Purification by column chromatography (5 → 15% EtOAc in light petroleum) gave two separable diastereomers of **27**, the major being less polar and isolated as a colorless powder (823 mg, 25%). Recrystallization of the major diastereomer from CH_2Cl_2/hexane yielded crystals suitable for X-ray diffraction that confirmed the identity of the major diastereomer as *endo*. The minor diastereomer could not be isolated in sufficient purity to allow full characterization. Alternatively, both diastereomers taken together gave a total yield of 30%.Data for **27a** (*endo*): MP 119–120 ºC. HRMS *m/z* (ESI^+) Found 361.2121 $[M+H]^+$, $C_{20}H_{29}N_2O_4$ requires 361.2122. ν_{max} ($CHCl_3$)/cm^{-1} 3011, 1735, 1687. ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.44 – 7.10 (m, 5H), 4.50 – 4.15 (m, 2H), 3.60 (s, 3H), 3.49 (d, *J* 13.0 Hz, 1H), 3.37 (d, *J* 13.0 Hz, 1H), 3.10 (ddd, *J* 12.0, 6.9, 5.2 Hz, 1H), 2.99 – 2.87 (m, 1H), 2.69 (ddd, *J* 10.7, 2.8, 1.1 Hz, 1H), 2.44 (dd, *J* 12.3, 5.2 Hz, 1H), 2.16 (apparent td, *J* 12.0, 6.9 Hz, 1H), 1.50 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 172.6, 153.5, 138.5, 129.0, 128.3, 127.2, 79.9, 62.12, 60.5, 56.3, 54.6, 51.6, 46.0, 43.6, 30.3, 28.6.

(1*S,5*R**)-3-Benzyl-8-(tert-butoxycarbonyl)-3,8-diazabicyclo [3.2.1] octane-6-carboxylic acid 28a/b** Methyl ester **27** (900 mg, 2.5 mmol) was dissolved in THF (24 mL), MeOH (6 mL) and H_2O (6 mL) and cooled to 0 °C. Lithium hydroxide monohydrate (1.05 g, 25 mmol) was added and the mixture was warmed to r.t. and stirred for 20 h. The reaction was quenched with 1 M HCl, and acidified to a pH of ~2. Extraction with EtOAc (3 x 20 mL) followed by drying with $MgSO_4$ and removal of solvent *in vacuo* gave the carboxylic acid **28** (780 mg, 90%) as a 1:1 mixture of diastereomers **28a/b** that were used directly in the subsequent step without characterization.

***tert*-Butyl (1*S**,5*R**,6*R**/*S**) -3-benzyl-6-(morpholine-4-carbonyl)-3,8-diazabicyclo [3.2.1]octane-8-carboxylate 29a/b** Acid **28** (780 mg, 2.25 mmol, as a mixture of diastereomers **28a/28b**) was dissolved in DMF (30 mL) and cooled to 0 °C. *N,N*-Diisopropylethylamine (1.18 mL, 6.75 mmol) and morpholine (291 μL, 3.38 mmol) were added, and after 10 min HATU (1.28 g, 3.38 mmol) was also added. The mixture was allowed to warm to rt and stirred for 16 h. EtOAc (30 mL) was added and the mixture was washed with aqueous LiCl solution (10%, 50 mL), aqueous $NaHCO_3$ solution (saturated, 50 mL), water (50 mL) and brine (50 mL). The organic layer was dried with $MgSO_4$ and solvent was removed *in vacuo* to give the mixture of diastereomers (830 mg, 89%). Diastereomers could be separated by chromatography (5 → 30% Acetone in light petroleum). On 250 mg of mixed diastereomers this gave 86 mg of less polar diastereomer **29b** and 96 mg of more polar diastereomer **29a**, with the remainder being mixed fractions which could be resubjected to chromatography. Data for **29b** *(exo)* HRMS *m/z* (ESI^+) Found 416.2549 $[M+H]^+$, $C_{22}H_{33}N_3O_4$ requires 416.2544. ν_{max} ($CHCl_3$) / cm^{-1} 2977, 1688, 1647, 1056. ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.43 – 7.08 (m, 5H), 4.56 – 3.91 (m, 2H), 3.84 – 3.24 (m, 10H), 3.12 – 3.00 (m, 1H), 2.86 – 2.64 (m, 3H), 2.52 – 2.06 (m, 3H), 1.47 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 177.6, 150.4, 138.4, 129.1, 128.1, 127.0, 80.0, 67.0, 66.7, 62.1, 53.0, 46.1, 42.8, 31.0, 28.5, 24.0. Data for **29a** *(endo)* HRMS *m/z* (ESI^+) Found 416.2555 $[M+H]^+$, $C_{22}H_{33}N_3O_4$ requires 416.2544. ν_{max} ($CHCl_3$) / cm^{-1} 3006, 1687, 1644, 1115. ^1H NMR (400 MHz, $CDCl_3$) δ_H (*rotamers*) 7.41 – 7.20 (m, 5H), 4.54 – 4.14 (m, 2H), 3.89 – 3.38 (m, 10H), 3.33 – 3.18 (m, 1H), 2.76 – 2.59 (m, 1H), 2.60 – 1.88 (m, 4H), 1.47 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*two rotamers*) 172.5, 172.3, 153.5, 153.4, 138.3, 128.7, 128.7, 128.4, 127.2, 79.7, 67.0, 66.6, 66.5, 61.9, 57.5, 57.4, 57.4, 57.0, 56.8, 55.1, 54.0, 46.0, 44.4, 43.3, 42.5, 42.4, 38.7, 38.6, 32.9, 32.3, 28.5, 28.5.

***tert*-Butyl (1*S**,5*R**,6*S**)-3-Benzyl-6-(hydroxymethyl)-3,8-diazabicyclo [3.2.1]octane-8-carboxylate 32** Methyl ester **27a** (192 mg, 0.53 mmol) was dissolved in dry THF (10 mL), and cooled to 0 °C. Lithium borohydride (116 mg, 5.33 mmol) was added as a solid portionwise over 5 min, and the mixture was allowed to warm to rt and stirred for 40 h. Saturated NH_4Cl solution (5 mL) was added and the organics were extracted with EtOAc (3 x 10 mL). The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo* to give **32** as a colorless oil (169 mg, >95%) which could be used without further purification. HRMS *m/z* (ESI^+) Found 333.2177 $[M+H]^+$,$C_{19}H_{29}N_2O_3$ requires 333.2178. ν_{max} (ATR) /cm^{-1} 3427, 2976, 1689, 1476, 1173, 1108. ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.52 – 6.97 (m, 5H), 5.80 (br s, 1H), 4.27 – 3.97 (m, 2H), 3.93 – 3.74 (m, 2H), 3.67 (d, *J* 12.6, 1H), 3.28 (d, *J* 12.6, 1H), 2.97 (d, *J* 11.3, 1H), 2.62 (d, *J* 11.3, 1H), 2.57 – 2.36 (m, 2H), 2.36 – 2.12 (m, 1H), 2.12 – 1.77 (m, 2H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_c 153.5, 136.2, 129.6, 128.7, 127.8, 79.9, 62.3, 60.8, 57.1, 56.6, 54.1, 53.1, 42.5, 29.8, 28.6.

Experimental procedures for library compounds, X-Ray diffraction data and copies of ^1H and ^{13}C NMR spectra are given in the Supporting Information.

Acknowledgements

The research leading to these results was done within the European Lead Factory and has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no. 115489, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007–2013) and EFPIA companies' in-kind contribution.

Keywords: Nitrogen heterocycles • Diels-Alder reaction • Drug discovery • Medicinal chemistry • Library synthesis

[1] J. W. Daly, G. B. Brown, M. Mensah-Dwumah, C. W. Myers, *Toxicon* **1978**, *16*, 163-168.

[2] T. F. Spande, H. M. Garraffo, M. W. Edwards, H. J. C. Yeh, L. Pannell, J. W. Daly, *J. Am. Chem. Soc.* **1992**, *114*, 3475-3478.

[3] a) C. A. Broka, *Tetrahedron Lett.* **1993**, *34*, 3251-3254; b) D. F. Huang, T. Y. Shen, *Tetrahedron Lett.* **1993**, *34*, 4477-4480; c) S. R. Fletcher, R. Baker, M. S. Chambers, S. C. Hobbs, P. J. Mitchell, *J. Chem. Soc., Chem. Commun.* **1993**, 1216-1218; d) S. C. Clayton, A. C. Regan, *Tetrahedron Lett.* **1993**, *34*, 7493-7496; eE. J. Corey, T. P. Loh, S. AchyuthaRao, D. C. Daley, S. Sarshar, *J. Org. Chem.* **1993**, *58*, 5600-5602.

[4] a) D. A. Evans, K. A. Scheidt, C. W. Downey, *Org. Lett.* **2001**, *3*, 3009-3012; b) V. K. Aggarwal, B. Olofsson, *Angew. Chem. Int. Ed.* **2005**, *44*, 5516-5519; c) A. Armstrong, Y. Bhonoah, S. E. Shanahan, *J. Org. Chem.* **2007**, *72*, 8019-8024.

[5] B. Badio, J. W. Daly, *Mol. Pharmacol.* **1994**, *45*, 563-569.

[6] N. M. Rupniak, S. Patel, R. Marwood, J. Webb, J. R. Traynor, J. Elliott, S. B. Freedman, S. R. Fletcher, R. G. Hill, *Br. J. Pharmacol.* **1994**, *113*, 1487-1493.

[7] H. M. Garaffo, T. F. Spande, M. Williams, *Heterocycles* **2009**, *79*, 207-217.

[8] M. I. Damaj, K. R. Creasy, A. D. Grove, J. A. Rosecrans, B. R. Martin, *Brain Res.* **1994**, *664*, 34-40.

[9] B. Badio, H. M. Garraffo, C. V. Plummer, W. L. Padgett, J. W. Daly, *Eur. J. Pharmacol.* **1997**, *321*, 189-194.

[10] R. W. Fitch, X.-F. Pei, Y. Kaneko, T. Gupta, D. Shi, I. Federova, J. W. Daly, *Biorg. Med. Chem.* **2004**, *12*, 179-190.

[11] A. Kamimura, T. Nakano, *J. Org. Chem.* **2010**, *75*, 3133-3136.

[12] a) C. C. Nawrat, C. J. Moody, *Org. Lett.* **2012**, *14*, 1484-1487; b) C. E. Blunt, C. Torcuk, Y. Liu, W. Lewis, D. Siegel, D. Ross, C. J. Moody, *Angew. Chem. Int. Ed.* **2015**, *54*, 8740-8745.

[13] A. Nortcliffe, C. J. Moody, *Bioorg. Med. Chem.* **2015**, *23*, 2730-2735.

[14] A. Basso, L. Banfi, G. Guanti, R. Riva, *Org. Biomol. Chem.* **2009**, *7*, 253-258.

[15] 4-Bromophenyl substituted compounds were used as library molecule examples as they will not appear in the Joint European Compound Library

[16] S. T. Handy, P. A. Grieco, C. Mineur, L. Ghosez, *Synlett* **1995**, *1995*, 565-567.

[17] R. D. MacArthur, R. M. Novak, *Clin. Infect. Dis.* **2008**, *47*, 236-241.

[18] C. Traversa, K. Fégy, G. Balme, J. Goré, *Synth. Commun.* **1997**, *27*, 1087-1096.

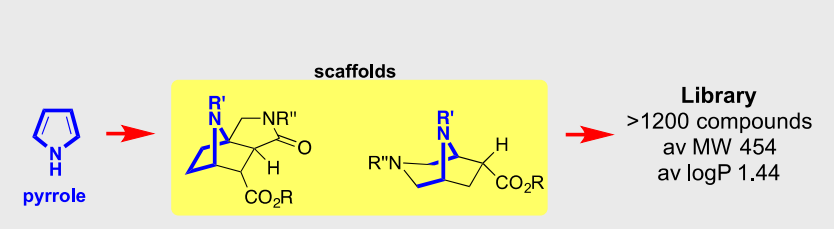
[19] J. Leroy, *Synth. Commun.* **1992**, *22*, 567-572.

[20] C. Zhang, M. L. Trudell, *J. Org. Chem.* **1996**, *61*, 7189-7191.

Entry for the Table of Contents (Please choose one layout)

Layout 2:

COMMUNICATION



Library synthesis

*A. T. Murray, E. Packard, A. Nortcliffe, W. Lewis, D. Hamza, G. Jones, and C. J. Moody**

Page No. – Page No.
Synthesis of epibatidine analogues by pyrrole Diels-Alder reactions: rapid access to azabicyclo[2.2.1]-heptane and 3,8-diazabicyclo[3.2.1]-octane scaffolds for library synthesis

Efficient access to *sp*^{3}-rich bicyclic amines using pyrrole Diels-Alder reactions: novel scaffolds for library synthesis in the European Lead Factory.