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Generation of a Heteropolycyclic and sp^3 -Rich Scaffold for Library Synthesis from a Highly Diastereoselective Petasis/Diels-Alder and ROM-RCM Reaction Sequence

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Abstract: Efficient access to diverse screening compounds with desirable, lead-like properties can be a bottleneck in early drug discovery and chemical biology. Here we present an efficient, rapid route to three structurally distinct classes of compounds (A–C) from a single precursor, which in turn is available through a one-pot Petasis 3-component-reaction–Diels-Alder cascade reaction. We demonstrate the versatility of the approach through the synthesis of 35 exemplary compounds from the three classes, as well as by the production of 2188 final compounds, which have been included in the Joint European Compound Library of the European Lead Factory.

Introduction

Accessing new drug candidates through high-throughput screening (HTS) has become an increasingly difficult challenge primarily due to the lack of investigatory efforts into compounds inhabiting a different chemical space.^[1] The libraries typically generated for screening often bear similar chemical topology, flat in structure possessing mostly sp^2 -hybridized carbon atoms making it more challenging to discover new biological activity.^[2] Thus, it has become necessary to increase efforts towards screening simple natural product like and sp^3 -rich cores through diversity-oriented synthesis.^[3] However, routine syntheses of such sp^3 -rich molecules with stereochemical control for use in screening library productions remains a significant challenge.^[4] The European Lead Factory initiative addresses this developing issue by targeting natural product-like libraries,^[5] while providing production feasible routes from cheap and commercially available building blocks in order to access scaffolds that are sp^3 -rich with 3–5 functional group handles.^[6] These handles can be further functionalized to provide a large library of compounds to be screened for biological activity. We recently published the synthesis of a sp^3 -rich library based on a 3-component Petasis/Diels-Alder strategy.^[7] This sequence in

combination with two ring opening/ring closing metathesis (ROM/RCM) cascade reactions enabled us to access different, diverse and sp^3 -rich scaffolds. Herein we present the synthesis of a new library that has led to the production of 2188 HTS compounds.

Results and Discussion

In order to rapidly build a compact functionalized core system, we focused on a synthetic route which includes a highly diastereoselective 3-component Petasis/Diels-Alder tandem reaction from allylic amines (**1a**), furylboronic acids (**1b**), and α -hydroxylated aldehydes (**1c**) (Scheme 1). This reaction manifold was first reported by Norsikian, Beau, and co-workers and later further explored by us.^[8] We envisioned that this strategy would allow us to access different libraries depending on the N -substituent on the boronic acid building block **1b** and the R^3 substituent on the aldehyde **1c** as a single diastereomer. Based on this scaffold **1**, we wish to report the generation of three different sub-libraries (library A–C) using robust and scalable chemistry.

Scheme 1: Synthetic strategy for the generation of libraries A–C from tandem Petasis 3-CR/Diels-Alder product **1**.

The Petasis 3-component reaction^[9] followed by an intramolecular Diels-Alder reaction^[10] was introduced early in the scaffold synthesis to provide the core skeleton with the stereocenters pre-set for the library generation. The benzyl group, used in lieu of R^1 during scaffold construction, was strategically employed to serve as an orthogonal protecting group to the Boc-protected amine tethered to the furylboronic acid **1b**. This would allow for selective late stage deprotection and functionalization. Boronic acids **3** and **4** were obtained through a reductive

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amination of commercially available 5-formyl-2-furanylboronic acid (**2**) and a primary amine followed by a subsequent Boc protection (Scheme 2). The boronic acid obtained could not easily be purified using conventional methods, so it was directly employed in the Petasis/Diels-Alder reaction after extraction to afford key intermediates **5** (library A), **6** (library B), and **7** (library C) in 75%, 31%, and 44% isolated yields, respectively - each as a racemic mixture of a single diastereomer.

Scheme 2: Petasis 3-component reaction accessing key intermediates **5-7**.

Library A was constructed from scaffold **5** through a series of deprotection and derivatisation steps of the three available handles as depicted in Scheme 3. The primary alcohol of **5** could be functionalized using Mitsunobu conditions^[11] to provide aryl ether **8**. *N*-Functionalization of the two amines was then performed, first by Boc-deprotection of the exocyclic amine followed by either acylation or sulfonylation, and then benzyl deprotection of the pyrrolidine amine followed by reductive alkylation over four steps. Alternatively, subjecting **5** to reductive conditions followed by reductive alkylation of the resulting amine provided 2-fluorobenzyl amine **15** in 84% isolated yield over two steps. Subsequently, arylation of the primary alcohol, like described above, followed by Boc-deprotection of the exocyclic amine and either alkylation or acylation gave **16** and **17** in excellent yields over three steps.

The synthesis of library B core scaffold **18** relied on a metathesis cascade reaction^[12] from **6** (Scheme 4). Upon subjecting to Grubbs' 2nd generation catalyst (Grubbs II) under acidic conditions, the 7-oxabicyclo[2.2.1]hept-2-ene underwent a ROM/RCM cascade reaction with the distal monosubstituted alkene to provide core **18** in 86% yield. Olefin reduction and pyrrolidine amine benzyl deprotection was performed using palladium on carbon and ammonium formate. The pyrrolidine amine could then be selectively alkylated over the exocyclic secondary amine using reductive alkylation conditions. Finally, the exocyclic secondary amine was derivatised by reaction with an acid chloride or an isocyanate to provide **19** and **20**, respectively, in high yields over three steps.

Scheme 3: Synthesis of library A through *N*-functionalization of the pyrrolidine amine, arylation of the primary alcohol using Mitsunobu conditions, and exocyclic amine functionalisation. Reagents and conditions: (a) 2-methoxyphenol, PPh₃, DEAD, THF, 0→20 °C, 18 h. (b) TFA, CH₂Cl₂, 20 °C, 1 h. (c) AcCl, DIPEA, DMF, 20 °C, 18 h. (d) 5% Pd/C, HCOONH₄, MeOH, reflux, 1.5 h. (e) CyCHO, NaBH₃CN, HOAc, MeOH, 20 °C, 18 h. (f) thiophene-2-carbonyl chloride, DIPEA, DMF, 20 °C, 18 h. (g) MsCl, DIPEA, DMF, 0 °C, 1 h. (h) cyclopentyl isocyanate, DMF, 20 °C, 18 h. (i) nicotinaldehyde, NaBH₃CN, HOAc, MeOH, 20 °C, 18 h. (j) *n*-HexNCO, DMF, 20 °C, 18 h. (k) 2-fluorobenzaldehyde, NaBH₃CN, HOAc, MeOH, 20 °C, 18 h. (l) 5-hydroxy-2-methylpyridine, PPh₃, DEAD, THF, 0→20 °C, 18 h. (m) valeraldehyde, NaBH₃CN, HOAc, MeOH, 20 °C, 18 h. (n) *i*-PrNCO, DMF, 20 °C, 18 h.

Scheme 4: Library B scaffold synthesis and diversification.

By switching the methyl substituent to an allyl group on the exocyclic amine, library C core scaffold **21** was accessed after treatment of the HCl salt of **7** with 2 mol% of Grubbs II (Scheme 5). Ring opening of the internal olefin followed by ring closing metathesis with the tethered allyl amine provided spirocycle **21** in 83% isolated yield as a single diastereomer, the stereochemistry being determined in the preceding tandem Petasis/Diels-Alder reaction. Based on **21**, library C scaffold diversification was achieved through *N*-functionalization of both the pyrrolidine and piperidine rings and amidations of the ester. The orthogonal protecting groups allowed for the selective deprotection of either the methyl ester, pyrrolidine amine, or piperidine amine and their subsequent functionalisations.

Scheme 5: Library C scaffold synthesis.

Hydrolysis of the methyl ester using LiOH followed by TBTU mediated amidation provided **22** and **23** in high yields (Scheme 5). Based on compounds **21**, **22**, and **23**, one of three different derivatisation pathways were used to access final screening compounds. Scheme 6 shows one example of each reaction sequence. To further demonstrate functional group tolerability, additional compounds were synthesised using these three routes with varying *N*-functionalisations. An overview of these compounds are shown in Scheme 7.

From compound **21**, both *N*-functionalisations were performed in the same reaction sequence (Scheme 6). First, piperidine derivatisation was achieved by removal of the Boc-group with TFA followed by reductive alkylation. Then, benzyl deprotection and

global reduction using hydrogenation and subsequent acylation of the pyrrolidine afforded **24** in 77% yield over four steps. Ester hydrolysis and amidation provided morpholine amide **25** in 60% yield over two steps. Using this procedure, an additional three compounds, **30**, **31**, and **32**, were likewise synthesised from **24** to give examples of both primary, secondary, and tertiary amides in the R¹ handle (Scheme 7).

Starting from **22**, deprotection of the pyrrolidine ring and global reduction was performed first followed by reductive alkylation to provide **26** in quantitative yield. Subsequent Boc deprotection of the piperidine with TFA followed by sulfonylation afforded **27** in 93% over two steps (Scheme 6). Using this deprotection and derivatisation sequence, compounds **33–38** were synthesised to provide examples of acylation and reductive alkylation on both heterocyclic amines (Scheme 7).

The order of functionalization of the two saturated heterocycles can also be reversed. Boc deprotection of the piperidine in **23** followed by acylation provided **28** in 85% yield over two steps. Subsequent hydrogenation deprotected the pyrrolidine amine and globally reduced the olefins. The pyrrolidine amine was then functionalized by sulfonylation to afford **29** in 75% yield over two steps (Scheme 6). Five additional compounds, **39–44**, were synthesised in this fashion using acylation or reductive alkylation (Scheme 7).

The developed strategy was subsequently used to produce 2,188 high-throughput screening compounds for the European Lead Factory. The library showed a high degree of three-dimensionality with an average Fsp³ of 0.72 and good distributions of cLogP, molecular weight, and polar surface area (PSA) (Figure 1). Figure 2 shows a comparison of cLogP vs. molecular weight.

Figure 1: Analysis of the 2,188 synthesised high-throughput screening compounds for the European Lead Factory. Average Fsp³ = 0.72, average MW = 486 Da, average cLogP = 1.98, and average PSA = 83.5 Å².

Scheme 6: Library C scaffold diversification through ester amidation and *N*-functionalization of pyrrolidine and piperidine rings. Orthogonal protecting groups allowed for variation in the order of functionalizations which is exemplified by three different routes. All compounds in library C were synthesised using one of these three overall derivatisation pathways.

Figure 2: Physical chemical property analysis of the compounds reported here (red) compared to entire library of 2,188 high-throughput screening compounds synthesised for the European Lead Factory (blue).

Conclusions

In conclusion, we were able to construct a compact functionalized scaffold as a single diastereomer in one step from allylic amines, furylboronic acids, and α -hydroxylated aldehydes by employing a highly diastereoselective 3-component Petasis/Diels-Alder tandem reaction. By simply varying the *N*-substituent on the

boronic acid building block or the R³ substituent on the aldehyde, we could access the core structures for libraries A–C. By judicious selection of the protecting group strategy in the initial step, we executed the synthesis of the libraries with a wide variety of different functional groups, thus providing a method to access an expansive set of natural product-like and sp³-rich compounds for biological testing. 2,188 of these have been included in the ELF Joint European Compounds Library.

Experimental Section

All reagents and solvents were purchased from commercial suppliers and used without further purification. All solvents used were of HPLC-grade, which predominantly were used without further drying. Unless otherwise stated, reactions were run as open-system reactions, using only a loosely fitted plastic plug in order to avoid contamination of the reaction mixture. Reaction products have been purified using flash column chromatography or preparative high-performance liquid chromatography (prep-HPLC). Reactions were routinely monitored using thin layer chromatography (TLC), ultra-performance liquid-chromatography mass-spectrometry (UPLC-MS) and/or high performance liquid-chromatography with UV detection (HPLC-UV). Analytical TLC was performed using Merck aluminum sheets covered with silica (C60). The plates were visualized using UV light and/or a KMnO₄ staining solution (3 g in water (300 mL), K₂CO₃ (20 g) and 5% aq NaOH (5 mL)) followed by heating. Analytical UPLC-MS (ESI)

was performed on a S2 Waters ACQUITY RPUPLC system equipped with a diode array detector using an ACQUITY UPLC BEH C18 column (d 1.7 μ m, 2.1 x 50mm; column temp: 65 $^{\circ}$ C; flow: 0.6 mL/min), as well as a SQD ESI MS detector. Eluents A1 (0.1% HCOOH in H₂O), A2 (0.1% NH₄COOCH₃), B1 (0.1% HCOOH in MeCN) and B2 (0.1% NH₄COOCH₃ in MeCN) were used in a linear gradient 5% B1/B2 to 100% B1/B2 in a total run time of 2.6 min. Analytical LC-HRMS (ESI) analysis was performed on an Agilent 1100 RP-LC system equipped with a diode array detector using a Phenomenex Luna C18 column (d 3 μ m, 2.1 x 50 mm; column temp: 40 $^{\circ}$ C; flow: 0.4 mL/min).

Eluents A (0.1% HCOOH in H₂O) and B (0.1% HCOOH in MeCN) were used in a linear gradient (20% B to 100% B) in a total run time of 15 min. The LC system was coupled to a Micromass LCT orthogonal time-of-flight mass spectrometer equipped with a Lock Mass probe operating in positive electrospray mode. Flash column chromatography was achieved using a glass column packed with Merck Geduran® 60 silica gel (40–63 μ m particles) as stationary phase, and liquid phase as specified in the individual experimental.

Scheme 7: Functional group tolerability in functionalization of library C. From 21, 23 screening compounds were synthesised with varying R¹-R⁵ substituents. Compounds were synthesised using one of the three derivatisation pathways depicted in Scheme 6. Yields of final compounds were 41–93% over 2 steps. See appendix for reagents and conditions. ^a synthesised from 21; ^b synthesised from 24; ^c synthesised from 22; ^d synthesised from 22; ^e synthesised from 35; ^f synthesised from 23; ^g synthesised from 28; ^h synthesised from 41.

All purified compounds have been routinely characterized by ^1H NMR, ^{13}C NMR, RP-UPLC-MS, and RP-HPLC-UV. Novel compounds were further characterized via HRMS. NMR spectra were recorded on a Bruker Ascend spectrometer with a Prodigy cryoprobe (operating at 400 MHz for ^1H NMR and at 101 MHz for ^{13}C NMR), and analyzed via the NMR software MestReNova (version 6.2.1-7569) released by Mestrelab Research S.L. The chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (J) in Hz. The majority of the spectra have been recorded in CDCl_3 , and the signals were adjusted relative to this position (δ 7.26 ppm for ^1H NMR and δ 77.2 ppm for ^{13}C NMR). For spectra recorded in $\text{DMSO}-d_6$, the signals were adjusted relative to the DMSO signal (δ 2.5 ppm for ^1H NMR and δ 39.5 ppm for ^{13}C NMR). For spectra recorded in CD_3OD , signal were adjusted relative to this position (δ 3.31 ppm for ^1H NMR and δ 49.00 ppm for ^{13}C NMR). Compounds have been drawn and named through use of the visualization software ChemDraw Ultra 14.0 released by PerkinElmer Informatics. Molecular- and exact masses have been calculated via this program as well.

General Method A. Mitsunobu conditions for arylation of alcohols

Alcohol (0.19 mmol), 5-hydroxy-2-methylpyridine (25 mg, 0.23 mmol) and triphenylphosphine (60 mg, 0.23 mmol) was dissolved in dry THF (2 mL, 0.1 M) under nitrogen atmosphere and cooled to 0 °C. DEAD (131 μL of a 40% toluene solution, 0.29 mmol) was added dropwise and then warmed slowly to 20 °C where it was stirred for 16 hours. The reaction was concentrated, and the crude was purified by flash column chromatography.

General Method B. Hydrogenation conditions for deprotection of benzyl groups and/or for the reduction of olefins

Benzylamine or olefin (2.56 mmol) was dissolved in MeOH (9 mL, 0.3 M) and added Pd/C (5 wt% Pd/C (10%), 0.13 mmol) and HCOONH_4 (12.8 mmol, 5 equiv.) and the mixture was stirred 1.5 h at reflux. The reaction mixture was then filtered using celite and the filtrate was concentrated *in vacuo*. The residue was added CH_2Cl_2 (30 mL), H_2O (20 mL) and sat. NaHCO_3 (aq.) (10 mL) and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2x 30 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give the reduced compound.

General Method C. Hydrogenation conditions for deprotection of benzyl groups and/or for the reduction of olefins

Benzyl amine or olefin (2.05 mmol) was dissolved in $\text{EtOH}:\text{H}_2\text{O}$ (10:1, 20 mL, 0.1 M). Pd/C (109 mg of 10% Pd/C, 0.103 mmol) was added and stirred at 60 °C under a hydrogen gas atmosphere for 28 hours. The reaction mixture was filtered through a celite pad and the filtrate was concentrated.

General Method D. Reductive amination conditions

Amine (0.53 mmol) was dissolved in MeOH (5 mL, 0.1 M). Aldehyde (0.79 mmol), AcOH (45 μL , 0.79 mmol), and sodium cyanoborohydride (50 mg, 0.79 mmol) were added to the solution. The reaction was stirred for 16 hours at 20 °C. The reaction was concentrated and partitioned between sat. aq. NaHCO_3 (25 mL) and CH_2Cl_2 (25 mL). The two phases were separated and the aqueous phase extracted with CH_2Cl_2 (2 x 25 mL). The combined organic phases were dried over sodium sulfate anhydrous, filtered and concentrated. The crude was purified by flash column chromatography to provide the alkylated amine.

General Method E. Reductive amination conditions

Amine (1.39 mmol) was dissolved in CH_2Cl_2 (7 mL). Aldehyde (1.74 mmol, 1.25 equiv.) was added followed by $\text{NaBH}(\text{OAc})_3$ (426 mg, 2.01 mmol, 1.5 equiv.). The mixture was stirred 1 h at 20 °C and then purified directly using flash column chromatography.

General Method F. Boc deprotection of amines

Boc protected amine (0.19 mmol) was dissolved in a 3:1 mixture of DCM and TFA (0.1 M, 1.5 mL). The reaction was stirred for 1 h at 20 °C and then concentrated under reduced pressure. The crude was solubilized in ethyl acetate (20 mL) and washed with sat. aq. NaHCO_3 (2 x 15 mL), dried over sodium sulfate anhydrous, filtered and concentrated. The crude was used directly in the next step without further purification.

General Method G. Acylation of amines using isocyanate

Amine (0.05 mmol) was dissolved in 1 mL of DMF. Isopropyl isocyanate (0.06 mmol) was added and stirred 18 h at 20 °C. The reaction mixture was diluted with 1 mL of DMF and purified by preparative HPLC to give the desired acylated amine.

General Method H. Acylation of amines using acid chlorides

Amine (0.07 mmol) was dissolved in 1 mL of DMF. DIPEA (36 μL , 0.21 mmol) and acid chloride (0.077 mmol) was added, and the reaction stirred 18 h at 20 °C. The reaction mixture was diluted with 1 mL of DMF and purified by preparative HPLC to give the desired compound.

General Method I. Acylation of amines using acid chlorides

Methyl ester (6.96 mmol) was dissolved in $\text{MeOH}:\text{H}_2\text{O}$ (24 mL, 2:1) and added LiOH (500 mg, 20.9 mmol, 3 equiv.) and the mixture was stirred 5 h at 80 °C. The mixture was cooled to 20 °C and added H_2O (40 mL) and ether (30 mL) and the layers were separated. The organic layer was extracted with 1 M NaOH (20 mL) and the combined aqueous phases were combined and acidified (pH = 6). The aqueous phase was then extracted with CH_2Cl_2 (3 x 60 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude extract was used in the next step without further purification.

General Method J. Amide formation from carboxylic acids

Carboxylic acid (3.47 mmol) was dissolved in CH_2Cl_2 (11 mL, 0.3 M) and added DIPEA (0.91 mL, 5.21 mmol, 1.5 equiv.) followed by TBTU (1.23 g, 3.82 mmol, 1.1 equiv.) and the mixture was stirred at 20 °C. After 5 min, amine (6.96 mmol, 2 equiv) was added and the mixture was stirred for another 30 min. The mixture

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was then concentrated and purified by flash column chromatography to provide the desired amide product.

General Method K. Sulfonylation of amines

Amine (1.49 mmol) was dissolved in CH_2Cl_2 (8 mL), added Et_3N (312 μL , 2.24 mmol, 1.5 equiv.) and cooled to 0 °C. The mixture was added sulfonyl chloride (1.79 mmol, 1.2 equiv.), and the mixture was stirred 1 h at 0 °C and then purified directly using flash column chromatography to give the desired sulfonylated amine.

Synthesis of building blocks for library A-C

Synthesis of *N*-benzylprop-2-en-1-amine

N-Benzylprop-2-en-1-amine (**S1**). Benzaldehyde (40 g, 38.5 mL, 0.377 mol) was dissolved in MeOH (300 mL, 1.2 M) and allyl amine was added (43 g, 57 mL, 0.753 mol) (**Warning**: Exothermic reaction). After stirring for 5 min, MgSO_4 (40 g) was added and the mixture was stirred 1 h at 20 °C. The mixture was then cooled to 0 °C and added NaBH_4 (15.7 g, 0.415 mmol) portion wise over 30 min (**Warning**: Very exothermic reaction) and after the last addition the mixture was stirred for another 30 min. The ice bath was then removed and the mixture was stirred 1 h at 20 °C. where upon sat. aq. NaHCO_3 (100 mL) was added and the mixture stirred for more 30 min. The mixture was then filtered and the volatiles were removed under reduced pressure. The residue was partitioned between water (100 mL) and EtOAc (200 mL) and the layers separated. The aqueous phase was extracted with EtOAc (100 mL) and the combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to give the title compound as a colorless oil (49 g, 88%) that was used directly in the next step without further purification.

Synthesis of boronic acid building blocks

(5-(((*Tert*-butoxycarbonyl)(methyl)amino)methyl)furan-2-yl)boronic acid (**3**). (5-Formylfuran-2-yl)boronic acid (**2**) (2.04 g, 14.6 mmol) and methyl amine (33% in ethanol) (3.6 mL, 29.0 mmol) were dissolved in MeOH (36 mL, 0.4 M) and 3 Å molecular sieves (3 g) were added. The mixture was stirred 1.5 h at 20 °C, where after the mixture was cooled to 0 °C in an ice bath and added NaBH_4 (0.607 g, 16 mmol) portion wise. After the addition, the mixture was stirred for 10 min at 0 °C followed by 1 h at 20 °C. The reaction mixture was concentrated *in vacuo* and the crude mixture used directly in the next step. The crude was dissolved in CH_2Cl_2 (36 mL, 0.4 M), added Et_3N (6 mL, 43.7 mmol, 3 equiv.) followed by Boc_2O (3.2 g, 14.6 mmol) dissolved in CH_2Cl_2 (8 mL) and the mixture was stirred 30 min at 20 °C. Then sat. aq. NaHCO_3 (50 mL) was added and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (2x50 mL) and the combined organic layers were dried over sodium sulfate anhydrous, filtered and concentrated. The crude was used directly in without further purification.

(5-((Allyl(*tert*-butoxycarbonyl)amino)methyl)furan-2-yl)boronic acid (**4**). (5-Formylfuran-2-yl)boronic acid (10 g, 71 mmol) and allyl amine (16 mL, 214 mmol) were dissolved in MeOH (180 mL, 0.4 M) and 3 Å molecular sieves were added, and the mixture stirred 1 h at 20 °C. Then, the mixture was cooled to 0 °C in an ice bath and added NaBH_4 (3.0 g, 79 mmol) portion wise. The mixture was dissolved in CH_2Cl_2 (50 mL) and Et_3N (5 mL) and the

mixture was again concentrated *in vacuo*. (**NOTE**: done to ensure full removal of allyl amine before step 2).

The crude was dissolved in CH_2Cl_2 (150 mL, 0.4 M), added Et_3N (20 mL, 143 mmol, 2 equiv.) followed by Boc_2O (15.6 g, 71 mmol) dissolved in CH_2Cl_2 (30 mL) and the mixture was stirred 1 h at 20 °C. Then sat. aq. NaHCO_3 (200 mL) was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2x100 mL) and the combined organic layers were dried over sodium sulfate anhydrous, concentrated to 100 mL and used directly in the next step without further purification.

Synthesis of aldehyde building block

2-Hydroxypent-4-enoic acid (**S2**). To a solution of allyl bromide (11.3 mL, 131 mmol) in THF:H₂O (2:1) (300 mL) at 0 °C was added glyoxylic acid (8 g, 87 mmol). Then, indium (11 g, 96 mmol) was added in one portion and the suspension stirred vigorously, and allowed to reach 20 °C, where it was stirred for more 19 h. The reaction was quenched by the addition of HCl 1M (350 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 350 mL). The combined organic layers were dried over sodium sulfate anhydrous, filtered and concentrated. The crude was distilled under reduced pressure (2.7 mbar, 120-130 °C), to give the title compound as a colorless oil (4.85 g, 48 %). ¹H NMR (400 MHz, CDCl_3) δ 6.12 (broad s, 1H), 5.88 – 5.76 (m, 1H), 5.25 – 5.13 (m, 2H), 4.36 (dd, J = 6.7, 4.5 Hz, 1H), 2.70 – 2.58 (m, 1H), 2.56 – 2.43 (m, 1H). ¹³C NMR (101 MHz, CDCl_3) δ 178.7, 132.1, 119.6, 69.9, 38.5. The data is in accordance with the literature [ACS Comb. Sci. 2012, 14, 253–257].

5-Allyl-2,2-dimethyl-1,3-dioxolan-4-one (**S3**). To a solution of 2-hydroxypent-4-enoic acid (**S4**) (4.85 g, 41.8 mmol) in acetone (84 mL) was added 2,2-dimethoxypropane (41.1 mL, 334 mmol) and pyridinium *p*-toluenesulfonate (5.25 g, 20.9 mmol) and the reaction stirred at reflux for 2½ h. The reaction was allowed to cool to 20 °C and filtered through a pad of celite, and the solid washed with EtOAc (2 x 100 mL). The filtrate was concentrated and the crude distilled (3-4 mbar, 80 °C), to give the title compound as colorless oil (5.3 g/33.9 mmol). ¹H NMR (400 MHz, CDCl_3) δ 5.79 (ddt, J = 17.1, 10.2, 6.9 Hz, 1H), 5.22 – 5.12 (m, 2H), 4.45 (dd, J = 6.7, 4.4 Hz, 1H), 2.62 (dddt, J = 14.8, 6.9, 4.4, 1.4 Hz, 1H), 2.46 (ddt, J = 14.9, 6.9, 1.3 Hz, 1H), 1.58 (d, J = 0.8 Hz, 3H), 1.52 (d, J = 0.8 Hz, 3H). ¹³C NMR (101 MHz, CDCl_3) δ 172.6, 131.9, 119.2, 110.7, 73.8, 35.8, 27.2, 26.0. The data is in accordance with the literature [ACS Comb. Sci. 2012, 14, 253–257].

5-Allyl-2,2-dimethyl-1,3-dioxolan-4-ol (**S4**). To a solution of 5-allyl-2,2-dimethyl-1,3-dioxolan-4-one (2.55 g, 16.3 mmol) (**S3**) in dry toluene (25 mL) at -78 °C was added dropwise DIBAL-H (24.4 mL of a 1M DIBAL-H toluene solution, 24.4 mmol) and after 30 min, the reaction was quenched with aqueous 1M HCl (30 mL). The reaction was allowed to warm to 20 °C and stirred for another 30 min, whereupon the reaction mixture was diluted with H₂O (100 mL) and extracted with CH_2Cl_2 (3x 100 mL). The combined organic layers were dried over sodium sulfate anhydrous and concentrated to give the title compound as colorless oil which was used directly in the next step without any purification.

Petasis/Diels-Alder Tandem Reaction in the Synthesis of Library A-C Scaffold and Library Production

Tert-butyl (((3*S*',3*aR*',6*R*',7*aR*')-2-benzyl-3-(hydroxymethyl)2,3,7,7*a*-tetrahydro-3*a*,6-epoxyisoindol-6(1*H*)-

yl)methyl)(methyl)carbamate (**5**). To a solution containing glycolaldehyde dimer (700 mg, 5.85 mmol) and *N*-allylbenzylamine (**S1**) (2.15 mL, 14.6 mmol) dissolved in CH₂Cl₂ (36 mL, 0.4 M) was added the crude 5-(((*tert*-butoxycarbonyl)(methyl)amino)methyl)furan-2-yl)boronic acid (**3**) (dissolved in 10 mL CH₂Cl₂) and the mixture was stirred 1 h at 20 °C. Then, sat. aq. NaHCO₃ (50 mL) was added and the layers were separated. The aqueous phase was extracted with CH₂Cl₂ (2x 50 mL) and the combined organic layers were dried over sodium sulfate anhydrous, filtered and concentrated. The crude was taken in MeCN (36 mL, 0.4 M) and the mixture was stirred at reflux for 24 h. The mixture was then concentrated and purified by flash column chromatography (EtOAc:heptane 1:1, *R_f* = 0.2) to give the title compound as a yellow oil (3.502 g, 75%). ¹H NMR (400 MHz, CDCl₃) δ 7.31 – 7.12 (m, 5H), 6.49 (d, *J* = 5.8 Hz, 1H), 6.18 (d, *J* = 5.8 Hz, 1H), 3.93 (d, *J* = 13.7 Hz, 2H, major rotamer), 3.74 (d, *J* = 11.4 Hz, 1H), 3.70 – 3.54 (m, 3H), 3.48 (d, *J* = 13.7 Hz, 2H, minor rotamer), 3.17 (t, *J* = 7.7 Hz, 1H), 2.96 (s, 1H), 2.86 (s, 3H), 2.17 (dd, *J* = 10.6, 8.7 Hz, 1H), 1.91 (dtd, *J* = 10.3, 6.9, 6.5, 2.9 Hz, 1H), 1.41 (s, 9H), 1.40 – 1.22 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 156.4 (major rotamer), 155.7 (minor rotamer), 138.4 (major rotamer), 138.4 (minor rotamer), 136.9 (major rotamer), 136.6 (minor rotamer), 136.4 (major rotamer), 136.1 (minor rotamer), 129.0, 128.6 (2 carbons), 127.5 (2 carbons), 98.9, 92.4 (major rotamer), 91.8 (minor rotamer), 79.9 (minor rotamer), 79.6 (major rotamer), 65.8 (major rotamer), 65.7 (minor rotamer), 59.7, 58.7, 58.5, 50.6 (major rotamer), 49.8 (major rotamer), 45.2, 36.0 (major rotamer), 35.9 (minor rotamer), 32.6 (major rotamer), 32.5 (minor rotamer), 28.5 (3C). HRMS (ESI) calcd for C₂₃H₃₃N₂O₄ [M+H]⁺ 401.2435, found 401.2468.

Tert-butyl (((3*S**,3*aR**,6*R**,7*aR**)-2-benzyl-3-((*S**)-1-hydroxybut-3-en-1-yl)-2,3,7,7a-tetrahydro-3*a*,6-epoxyisoindol-6(1*H*)-yl)methyl)(methyl)carbamate (**6**). To a solution of 5-allyl-2,2-dimethyl-1,3-dioxolan-4-ol (**S4**) (1.1g, 7.0 mmol) and *N*-allylbenzylamine (**S1**) (0.93 g, 6.3 mmol) in CH₂Cl₂ (36 mL, 0.4 M) was added 5-(((*tert*-butoxycarbonyl)(methyl)amino)methyl)furan-2-yl)boronic acid (**3**) (1.86 g, 7.3 mmol), dissolved in 10 mL CH₂Cl₂ and the mixture was stirred 1 h at 20 °C. Sat. aq. NaHCO₃ (50 mL) was then added and the layers were separated. The aqueous phase was extracted with CH₂Cl₂ (2x 50 mL) and the combined organic layers were dried over sodium sulfate anhydrous, filtered and concentrated. The crude was taken in acetonitrile (18 mL, 0.4 M) and the mixture was stirred at reflux for 24 h. The mixture was then concentrated and purified by flash column chromatography (EtOAc/heptane, 1:3, *R_f* = 0.25) to give the desired compound as a clear yellow oil (0.68 g, 31%). ¹H NMR (400 MHz, CDCl₃) δ 7.37 – 7.25 (m, 5H), 6.76 (dd, *J* = 10.2, 5.7 Hz, 1H), 6.13 (dd, *J* = 11.8, 5.7 Hz, 1H), 5.97 – 5.79 (m, 1H), 5.19 – 5.06 (m, 2H), 4.07 – 3.38 (m, 5H), 3.16 (br. s, 1H), 3.07 – 2.77 (m, 5H, two rotamers), 2.68 – 2.52 (m, 1H), 2.51 – 2.32 (m, 1H), 2.11 (t, *J* = 9.6 Hz, 1H), 1.92 (br. s, 1H), 1.47 (s, 9H), 1.41 – 1.30 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 156.4 (major rotamer), 155.8 (minor rotamer), 138.9, 137.4 (minor rotamer), 137.2 (major rotamer), 135.0, 134.8, 128.9, 128.6 (2C), 127.4 (2C), 117.6, 97.6, 91.6 (major rotamer), 91.1 (minor rotamer), 79.8 (major rotamer), 79.6 (minor rotamer), 69.7, 69.3, 58.7, 58.3, 50.5 (minor rotamer), 49.6 (major rotamer), 45.7, 37.0, 35.9, 32.5, 28.6 (3C). HRMS (ESI) calcd for C₂₆H₃₇N₂O₄ [M+H]⁺ 441.2748, found 441.2770.

Methyl ((3*R**,3*aR**,6*R**,7*aR**)-6-((allyl(*tert*-butoxycarbonyl)amino)methyl)-2-benzyl-1,2,3,6,7,7a-hexahydro-3*a*,6-epoxyisoindole-3-carboxylate (**7**). Glyoxylic acid monohydrate (6.6 g, 71 mmol) and *N*-allylbenzylamine (8.42 mL, 57 mmol) was dissolved in CH₂Cl₂ (100 mL). 5-(((allyl(*tert*-butoxycarbonyl)amino)methyl)furan-2-yl)boronic acid (**4**) was

added, and the mixture was stirred 18 h at 20 °C. (**NOTE**: the reaction usually takes around 1 h). Water (200 mL) was added and the layers were separated. The aqueous phase was extracted with CH₂Cl₂ (2 x 100 mL), and the combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. The crude was dissolved in acetone (180 mL, 0.4 M), and K₂CO₃ (11.9 g, 86 mmol) was added followed by MeI (4.45 mL, 71 mmol). The mixture was stirred for 4 h at 20 °C. Additional K₂CO₃ (5.5 g, 40 mmol) and MeI (2.3 mL, 37 mmol) were added, and the mixture was stirred 16 h at 20 °C. Then EtOAc (200 mL) was added and was washed with water. The aqueous phase was extracted with CH₂Cl₂ (2 x 100 mL), and the combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica plug (EtOAc:heptane 1 : 4) to give the methyl ester as a yellow oil. (**NOTE**: It is a lot easier to purify the final compound if some of the impurities are removed using the silica plug before the Diels-Alder reaction. **Step 5**: The compound from step 4 was taken in MeCN (180 mL) and the mixture was stirred at reflux for 24 h. The mixture was then concentrated *in vacuo* and purified by flash column chromatography (EtOAc:heptane 3:7, *R_f* = 0.2) to give the title compound as a yellow oil (11.5 g, 44% over 5 steps, based on allylbenzylamine). ¹H NMR (400 MHz, CDCl₃) δ 7.36 – 7.10 (m, 5H), 6.27 – 6.02 (m, 2H), 5.79 – 5.58 (m, 1H), 5.11 – 4.94 (m, 2H), 3.95 – 3.80 (m, 2H), 3.81 – 3.61 (m, 4H), 3.56 (s, 3H), 3.49 (s, 1H), 3.51 – 3.42 (m, 1H), 3.26 (t, *J* = 7.0 Hz, 1H), 2.24 – 2.08 (m, 2H), 1.38 (s, 9H), 1.35 – 1.27 (m, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 172.3, 156.2, 138.0, 137.3, 135.3, 134.0, 129.5, 128.3 (2C), 127.4 (2C), 116.0, 98.3, 92.8, 79.8, 67.7, 59.5, 58.6, 52.1, 50.5, 47.4, 45.3, 32.2, 28.5 (major rotamer, 3C). HRMS (ESI) calcd for C₂₆H₃₅N₂O₅ [M+H]⁺ 455.2540, found 455.2575.

Tert-butyl (((3*S**,3*aR**,6*R**,7*aR**)-2-benzyl-3-((2-methoxyphenoxy)methyl)-2,3,7,7a-tetrahydro-3*a*,6-epoxyisoindol-6(1*H*)-yl)methyl)(methyl)carbamate (**8**). **General Method A** was applied to *tert*-butyl (((3*S**,3*aR**,6*R**,7*aR**)-2-benzyl-3-(hydroxymethyl)-2,3,7,7a-tetrahydro-3*a*,6-epoxyisoindol-6(1*H*)-yl)methyl)(methyl)carbamate (**5**) (1.00 g, 2.49 mmol) and 2-methoxyphenol (335 µL, 3mmol). The reaction was concentrated and the crude was purified by flash column chromatography (EtOAc/heptane 4:1, *R_f* = 0.2) to give the desired compound as a colorless oil (762 mg, 60 %). ¹H NMR (400 MHz, CDCl₃) δ 7.43 – 7.36 (m, 2H), 7.36 – 7.29 (m, 2H), 7.29 – 7.23 (m, 1H), 7.00 – 6.88 (m, 4H), 6.61 (dd, *J* = 10.0, 5.7 Hz, 1H), 6.26 (dd, *J* = 18.8, 5.8 Hz, 1H), 4.20 – 4.06 (m, 3H), 3.83 (s, 3H), 3.81 – 3.70 (m, 2H), 3.36 (dd, *J* = 6.6, 4.9 Hz, 1H), 3.25 (dd, *J* = 7.8, 6.2 Hz, 1H), 2.99 (d, *J* = 7.7 Hz, 3H), 2.32 – 2.13 (m, 2H), 1.58 – 1.28 (m, 12H). ¹³C NMR (101 MHz, CDCl₃) δ 156.3 (major rotamer), 155.7 (minor rotamer), 150.2, 148.6, 139.6 (major rotamer), 139.4 (minor rotamer), 136.4 (major rotamer), 136.1 (minor rotamer), 136.0 (major rotamer), 135.7 (minor rotamer), 129.0 (minor rotamer), 128.9 (major rotamer), 128.3 (2C), 127.0 (2C), 121.8, 121.0, 115.1 (major rotamer), 115.0 (minor rotamer), 112.64 (major rotamer), 112.59 (minor rotamer), 98.4, 92.0 (major rotamer), 91.5 (minor rotamer), 79.7 (major rotamer), 79.4 (minor rotamer), 70.4 (major rotamer), 70.2 (minor rotamer), 63.7 (major rotamer), 63.6 (minor rotamer), 59.9 (major rotamer), 59.1 (minor rotamer), 56.1, 50.5, 49.7, 44.2, 35.9 (major rotamer), 35.8 (minor rotamer), 32.4, 28.53 (minor rotamer, 3C), 28.48 (major rotamer, 3C). HRMS (ESI) calcd for C₃₀H₃₉N₂O₅ [M+H]⁺ 507.2853, found 507.2858.

1-(((3*S**,3*aR**,6*S**,7*aR**)-2-benzyl-3-((2-methoxyphenoxy)methyl)hexahydro-3*a*,6-epoxyisoindol-6(1*H*)-yl)-*N*-methylmethanamine (**S5**). **General Method F** was applied to *tert*-butyl (((3*S**,3*aR**,6*R**,7*aR**)-2-benzyl-3-((2-

methoxyphenoxy)methyl)-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-6(1*H*)-yl)methyl)carbamate (**8**) (418 mg, 0.825 mmol). The crude mixture was purified by flash column chromatography (CH₂Cl₂/MeOH with 5 % of NH₄OH (25 % aq.) 95:5, *R_f* = 0.25) to give the desired compound as a white solid (241 mg, 72 %). ¹H NMR (400 MHz, CDCl₃) δ 7.40–7.36 (m, 2H), 7.34–7.20 (m, 3H), 7.02–6.86 (m, 4H), 6.60 (d, *J* = 5.8 Hz, 1H), 6.30 (d, *J* = 5.8 Hz, 1H), 4.16 (d, *J* = 13.0 Hz, 1H), 4.13–4.05 (m, 2H), 3.82 (s, 3H), 3.73 (d, *J* = 12.9 Hz, 1H), 3.36 (dd, *J* = 6.5, 4.8 Hz, 1H), 3.24 (dd, *J* = 7.7, 6.1 Hz, 1H), 3.15 (d, *J* = 12.6 Hz, 1H), 3.06 (d, *J* = 12.5 Hz, 1H), 2.53 (s, 3H), 2.34–2.18 (m, 2H), 1.69–1.63 (br. s, 1H), 1.59 (dd, *J* = 11.3, 2.6 Hz, 1H), 1.40 (dd, *J* = 11.3, 7.1 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 150.2, 148.6, 139.7, 136.7, 135.5, 129.0, 128.3 (2C), 127.0 (2C), 121.7, 121.0, 114.9, 112.6, 98.4, 90.7, 70.3, 63.7, 60.0, 59.0, 56.1, 54.4, 44.4, 37.2, 32.8. HRMS (ESI) calcd for C₂₅H₃₁N₂O₃ [M+H]⁺ 407.2329, found 407.2328.

N-(((3*S**,3*aR**,6*S**,7*aR**)-2-(Cyclohexylmethyl)-3-((2-methoxyphenoxy)methyl)hexahydro-3a,6-epoxyisoindol-6(1*H*)-yl)methyl)-*N*-methylacetamide (**9**). **General Method H** was applied to 1-(((3*S**,3*aR**,6*S**,7*aR**)-2-benzyl-3-((2-methoxyphenoxy)methyl)hexahydro-3a,6-epoxyisoindol-6(1*H*)-yl)-*N*-methylmethanamine (**S5**) (131 mg, 0.32 mmol) and acetyl chloride (28 μL, 0.39 mmol) then the crude (145 mg, 0.32 mmol) was subjected to conditions in **General Method B**. **General Method D** was then applied to the crude (38 mg, 0.09 mmol) and cyclohexanecarbaldehyde (14 μL, 0.11 mmol). The reaction mixture was purified directly by preparative HPLC to give the desired compound as a colorless oil (28.2 mg, 66% over three steps). ¹H NMR (400 MHz, CDCl₃) δ 6.94–6.85 (m, 4H), 4.02–3.84 (m, 3H), 3.83 (s, 3H), 3.62–3.49 (m, 1H), 3.23–3.14 (m, 2H), 3.13 (s, 2H, major rotamer), 3.03 (s, 1H, minor rotamer), 2.59 (td, *J* = 11.8, 9.3 Hz, 1H), 2.45–2.31 (m, 2H), 2.12 (s, 2H, major rotamer), 2.11 (s, 1H, minor rotamer), 2.02–1.34 (m, 13H), 1.30–1.04 (m, 3H), 0.95–0.67 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 171.4 (minor rotamer), 171.2 (major rotamer), 149.8, 148.7 (major rotamer), 148.6 (minor rotamer), 121.34 (minor rotamer), 121.31 (major rotamer), 120.97 (major rotamer), 120.95 (minor rotamer), 113.83 (major rotamer), 113.77 (minor rotamer), 112.3, 96.0 (minor rotamer), 95.8 (major rotamer), 88.1 (major rotamer), 87.6 (minor rotamer), 70.0 (major rotamer), 69.8 (minor rotamer), 65.7 (major rotamer), 65.5 (minor rotamer), 63.3 (major rotamer), 63.1 (minor rotamer), 59.9 (major rotamer), 59.7 (minor rotamer), 56.1 (major rotamer), 53.6 (minor rotamer), 49.3, 47.01 (major rotamer), 46.96 (minor rotamer), 37.7 (major rotamer), 37.62 (major rotamer), 37.59 (minor rotamer), 36.98 (major rotamer), 36.95 (minor rotamer), 35.5 (minor rotamer), 32.9 (major rotamer), 32.7 (minor rotamer), 32.22 (major rotamer), 32.17 (minor rotamer), 31.60 (minor rotamer), 31.58 (major rotamer), 28.80 (minor rotamer), 28.78 (major rotamer), 26.95 (major rotamer), 26.94 (minor rotamer), 26.28 (major rotamer), 26.25 (minor rotamer), 26.1, 21.84 (minor rotamer), 21.82 (major rotamer). HRMS (ESI) calcd for C₂₇H₄₁N₂O₄ [M+H]⁺ 457.3061, found 457.3071.

N-(((3*S**,3*aR**,6*S**,7*aR**)-3-((2-Methoxyphenoxy)methyl)-2-(thiophene-2-carbonyl)hexahydro-3a,6-epoxyisoindol-6(1*H*)-yl)methyl)-*N*-methylacetamide (**10**). **General Method H** was applied to 1-(((3*S**,3*aR**,6*S**,7*aR**)-2-benzyl-3-((2-methoxyphenoxy)methyl)hexahydro-3a,6-epoxyisoindol-6(1*H*)-yl)-*N*-methylmethanamine (**S5**) (131 mg, 0.32 mmol) and acetyl chloride (28 μL, 0.39 mmol) then the crude (145 mg, 0.32 mmol) was subjected to conditions in **General Method B**. **General Method H** was then applied to the crude (28.3 mg, 0.08 mmol) and thiophene-2-carbonyl chloride (10 μL, 0.09 mmol). The

reaction mixture was purified by preparative HPLC to give the desired compound as an amorphous white solid (24 mg, 65 % over three steps). ¹H NMR (400 MHz, CDCl₃) δ 7.61–7.51 (m, 1H), 7.48 (d, *J* = 5.0 Hz, 1H), 7.12–7.01 (m, 1H), 6.96–6.78 (m, 4H), 4.88 (s, 1H), 4.64 (td, *J* = 10.2, 9.7, 3.2 Hz, 1H), 4.31 (t, *J* = 9.5 Hz, 1H), 4.09 (dd, *J* = 10.0, 2.0 Hz, 1H), 3.86–3.63 (m, 5H), 3.37 (q, *J* = 8.9 Hz, 1H), 3.27–3.11 (m, 1H), 3.07 (s, 2.3H, major rotamer), 2.98 (s, 0.7H, minor rotamer), 2.11 (s, 2.3H, major rotamer), 2.10 (s, 0.7H, minor rotamer), 2.06–1.86 (m, 3H), 1.74–1.46 (m, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 171.30 (major rotamer), 171.28 (minor rotamer), 161.9, 149.6, 148.3, 139.5, 130.3, 130.2, 127.4, 121.5, 121.1, 113.5, 112.1, 93.4 (minor rotamer), 93.3 (major rotamer), 88.3 (major rotamer), 87.9 (minor rotamer), 66.9, 61.3 (major rotamer), 61.1 (minor rotamer), 56.9 (major rotamer), 56.7 (minor rotamer), 56.0 (major rotamer), 53.4 (minor rotamer), 49.3, 46.9 (minor rotamer), 46.8 (major rotamer), 42.1 (major rotamer), 41.6 (minor rotamer), 37.9 (major rotamer), 35.5 (minor rotamer), 32.3 (minor rotamer), 31.9 (major rotamer), 28.6, 21.9 (minor rotamer), 21.8 (major rotamer). HRMS (ESI) calcd for C₂₅H₃₁N₂O₅S [M+H]⁺ 471.1948, found 471.1948.

N-(((3*S**,3*aR**,6*S**,7*aR**)-3-((2-Methoxyphenoxy)methyl)-2-(methylsulfonyl)hexahydro-3a,6-epoxyisoindol-6(1*H*)-yl)methyl)-*N*-methylacetamide (**11**). **General Method H** was applied to 1-(((3*S**,3*aR**,6*S**,7*aR**)-2-benzyl-3-((2-methoxyphenoxy)methyl)hexahydro-3a,6-epoxyisoindol-6(1*H*)-yl)-*N*-methylmethanamine (**S5**) (131 mg, 0.32 mmol) and acetyl chloride (28 μL, 0.39 mmol) then the crude (145 mg, 0.32 mmol) was subjected to conditions in **General Method B**. **General Method K** was then applied to the crude (32.3 mg, 0.09 mmol) and methanesulfonyl chloride (8 μL, 0.11 mol). The reaction mixture was purified by preparative HPLC to give the desired compound as an amorphous white solid (24 mg, 61 % over three steps). ¹H NMR (400 MHz, CDCl₃) δ 6.97–6.83 (m, 4H), 4.26–4.08 (m, 3H), 3.89–3.63 (m, 6H), 3.09 (s, 2.2H, major rotamer), 3.00 (s, 0.8H, minor rotamer), 2.99–2.88 (m, 1H), 2.84 (d, *J* = 8.4 Hz, 4H), 2.12 (s, 2.2H, major rotamer), 2.10 (s, 0.8H, minor rotamer), 1.93 (tdd, *J* = 15.3, 10.2, 6.5 Hz, 3H), 1.73–1.45 (m, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 171.2, 149.64 (major rotamer), 149.60 (minor rotamer), 148.05 (major rotamer), 148.03 (minor rotamer), 121.7, 121.11 (minor rotamer), 121.05 (major rotamer), 113.5, 112.22 (minor rotamer), 112.19 (major rotamer), 95.3 (minor rotamer), 95.1 (major rotamer), 88.7 (major rotamer), 88.2 (minor rotamer), 69.7 (minor rotamer), 69.5 (major rotamer), 62.0 (major rotamer), 61.9 (minor rotamer), 56.07 (major rotamer), 56.05 (minor rotamer), 55.98 (major rotamer), 55.8 (minor rotamer), 53.4 (minor rotamer), 49.4 (major rotamer), 46.40 (minor rotamer), 46.35 (major rotamer), 40.9 (major rotamer), 40.7 (minor rotamer), 37.8 (major rotamer), 35.8 (minor rotamer), 34.5 (major rotamer), 33.9 (minor rotamer), 32.5 (minor rotamer), 32.4 (major rotamer), 28.2, 21.8. HRMS (ESI) calcd for C₂₁H₃₁N₂O₆S [M+H]⁺ 439.1897, found 439.1899.

(3*S**,3*aR**,6*S**,7*aR**)-*N*-Cyclopentyl-3-((2-methoxyphenoxy)methyl)-6-((*N*-methylacetamido)methyl)hexahydro-3a,6-epoxyisoindole-2(3*H*)-carboxamide (**12**). **General Method H** was applied to 1-(((3*S**,3*aR**,6*S**,7*aR**)-2-benzyl-3-((2-methoxyphenoxy)methyl)hexahydro-3a,6-epoxyisoindol-6(1*H*)-yl)-*N*-methylmethanamine (**S5**) (131 mg, 0.32 mmol) and acetyl chloride (28 μL, 0.39 mmol) then the crude (145 mg, 0.32 mmol) was subjected to conditions in **General Method B**. **General Method G** was then applied to the crude (40.6 mg, 0.11 mmol) and cyclopentyl isocyanate (15 μL, 0.135 mmol). The reaction mixture was purified by preparative HPLC to give the desired compound as an amorphous white solid (32 mg, 60 % over three

steps). ^1H NMR (400 MHz, CDCl_3) δ 6.96 – 6.79 (m, 4H), 4.78 – 4.19 (m, 3H), 4.12 – 4.01 (m, 1H), 3.98 (ddd, $J = 9.7, 5.3, 3.6$ Hz, 1H), 3.81 (s, 3H), 3.79 – 3.55 (m, 3H), 3.07 (s, 2.2H, major rotamer), 2.98 (s, 0.8H, minor rotamer), 2.96 – 2.68 (m, 2H), 2.10 (s, 2.2H, major rotamer), 2.08 (s, 0.8H, minor rotamer), 2.02 – 1.78 (m, 5H), 1.69 – 1.51 (m, 6H), 1.46 (dt, $J = 12.0, 3.1$ Hz, 1H), 1.40 – 1.25 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 171.24 (minor rotamer), 171.17 (major rotamer), 157.1 (major rotamer), 156.8 (minor rotamer), 149.5 (major rotamer), 149.4 (minor rotamer), 148.23 (minor rotamer), 148.19 (major rotamer), 121.5 (major rotamer), 121.4 (minor rotamer), 121.1 (minor rotamer), 121.1 (major rotamer), 113.6 (major rotamer), 113.4 (minor rotamer), 112.0, 94.3 (minor rotamer), 94.1 (major rotamer), 88.3 (major rotamer), 87.8 (minor rotamer), 60.0 (major rotamer), 59.8 (minor rotamer), 56.0 (minor rotamer), 55.9 (major rotamer), 53.7 (major rotamer), 53.4 (minor rotamer), 53.3, 52.4 (major rotamer), 52.3 (minor rotamer), 49.2, 46.0 (minor rotamer), 45.7 (major rotamer), 41.0 (major rotamer), 40.7 (minor rotamer), 37.8, 35.5, 33.7 (minor rotamer), 33.6 (major rotamer), 32.3 (minor rotamer), 32.0 (major rotamer), 28.7 (major rotamer), 28.6 (minor rotamer), 23.8 (major rotamer), 23.71 (minor rotamer), 23.69, 21.83 (minor rotamer), 21.79 (major rotamer). HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{38}\text{N}_3\text{O}_5$ [$\text{M}+\text{H}^+$] 472.2806, found 472.2809.

N-(((3*S**,3*aR**,6*S**,7*aR**)-3-((2-Methoxyphenoxy)methyl)-2-(pyridin-3-ylmethyl)hexahydro-3*a*,6-epoxyisoindol-6(1*H*)-yl)methyl)-*N*-methylmethanesulfonamide (**13**). **General Method K** was applied to 1-(((3*S**,3*aR**,6*S**,7*aR**)-2-benzyl-3-((2-methoxyphenoxy)methyl)hexahydro-3*a*,6-epoxyisoindol-6(1*H*)-yl)-*N*-methylmethanamine (**S5**) (105 mg, 0.258 mmol) and methanesulfonyl chloride (24 μL , 0.310 mmol) then the crude (125 mg, 0.25832 mmol) was subjected to conditions in **General Method B**. **General Method D** was then applied to the crude (26 mg, 0.066 mmol) and nicotinaldehyde (6 μL , 0.066 mmol). The reaction mixture was purified by preparative HPLC to give the desired compound as a colorless oil solid (21 mg, 65 % over three steps). ^1H NMR (400 MHz, CDCl_3) δ 8.54 (d, $J = 2.0$ Hz, 1H), 8.47 (dd, $J = 4.8, 1.6$ Hz, 1H), 7.65 (dt, $J = 7.8, 2.0$ Hz, 1H), 7.21 (dd, $J = 7.8, 4.8$ Hz, 1H), 6.98 – 6.84 (m, 4H), 4.22 (d, $J = 13.4$ Hz, 1H), 4.04 (dd, $J = 9.7, 6.1$ Hz, 1H), 3.96 (dd, $J = 9.6, 5.5$ Hz, 1H), 3.80 (s, 3H), 3.66 (d, $J = 13.4$ Hz, 1H), 3.51 (d, $J = 14.6$ Hz, 1H), 3.42 (t, $J = 5.8$ Hz, 1H), 3.36 (d, $J = 14.6$ Hz, 1H), 3.04 – 2.95 (m, 4H), 2.81 (s, 3H), 2.40 (dtd, $J = 11.0, 7.2, 4.0$ Hz, 1H), 2.17 – 1.96 (m, 2H), 1.84 – 1.68 (m, 2H), 1.71 – 1.62 (m, 2H), 1.65 – 1.55 (m, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 150.3, 149.9, 148.5, 148.4, 136.8, 134.8, 123.4, 121.6, 121.0, 113.9, 112.2, 96.1, 87.6, 70.5, 64.3, 59.1, 56.9, 56.0, 52.4, 46.8, 37.6, 36.8, 35.4, 32.6, 29.0. HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{34}\text{N}_3\text{O}_5\text{S}$ [$\text{M}+\text{H}^+$] 488.2214, found 488.2217.

(3*S**,3*aR**,6*S**,7*aR**)-*N*-Hexyl-3-((2-methoxyphenoxy)methyl)-6-((*N*-methylmethylsulfonamido)methyl)hexahydro-3*a*,6-epoxyisoindole-2(3*H*)-carboxamide (**14**). **General Method K** was applied to 1-(((3*S**,3*aR**,6*S**,7*aR**)-2-benzyl-3-((2-methoxyphenoxy)methyl)hexahydro-3*a*,6-epoxyisoindol-6(1*H*)-yl)-*N*-methylmethanamine (**S5**) (105 mg, 0.258 mmol) and methanesulfonyl chloride (24 μL , 0.310 mmol) then the crude (125 mg, 0.25832 mmol) was subjected to conditions in **General Method B**. **General Method G** was then applied to the crude (32 mg, 0.081 mmol) and hexyl isocyanate (14 μL , 0.098 mmol). The reaction mixture was purified by preparative HPLC to give the desired compound as a colorless oil solid (15 mg, 35 % over three steps). ^1H NMR (400 MHz, CDCl_3) δ 6.96 – 6.83 (m, 4H), 4.76 (br. s, 1H), 4.46 (t, $J = 3.9$ Hz, 1H), 4.36 (dd, $J = 9.9, 3.5$ Hz, 1H), 3.99 (dd, $J = 9.8, 4.2$ Hz, 1H), 3.82 (s, 3H), 3.65 (t, $J = 8.9$ Hz, 1H), 3.48 (d, $J = 14.6$ Hz, 1H), 3.41 (d, $J = 14.6$ Hz, 1H), 3.30 – 3.10

(m, 2H), 3.03 – 2.96 (m, 1H), 2.98 (s, 3H), 2.90 – 2.79 (m, 4H), 1.98 – 1.82 (m, 3H), 1.85 – 1.71 (m, 2H), 1.70 – 1.58 (m, 1H), 1.55 – 1.40 (m, 2H), 1.36 – 1.17 (m, 6H), 0.90 – 0.81 (m, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 157.5, 149.4, 148.2, 121.5, 121.1, 113.1, 111.9, 94.5, 87.7, 68.8, 60.0, 56.0, 53.6, 52.3, 45.8, 40.9, 40.7, 36.9, 35.3, 32.3, 31.7, 30.4, 28.7, 26.8, 22.7, 14.2. HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{42}\text{N}_3\text{O}_5\text{S}$ [$\text{M}+\text{H}^+$] 524.2789, found 524.2792.

Tert-butyl (((3*S**,3*aR**,6*S**,7*aR**)-2-(2-fluorobenzyl)-3-(hydroxymethyl)hexahydro-3*a*,6-epoxyisoindol-6(1*H*)-yl)methyl)(methyl)carbamate (**15**). **General Method B** was applied to *tert*-butyl (((3*S**,3*aR**,6*R**,7*aR**)-2-benzyl-3-(hydroxymethyl)-2,3,7,7a-tetrahydro-3*a*,6-epoxyisoindol-6(1*H*)-yl)methyl)(methyl)carbamate (**5**) (1.03g, 2.56 mmol) and then the crude (165 mg, 0.53 mmol) and 2-fluorobenzaldehyde (83 μL , 0.79 mmol) were subjected to **General Method D**. The benzylated compound was purified by flash column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ with 5 % of NH_4OH (25 % aq) 98:2, $R_f = 0.25$) to give the title compound as a colorless oil (196 mg, 88 %). ^1H NMR (400 MHz, CDCl_3) δ 7.33 – 7.21 (m, 2H), 7.10 (t, $J = 7.4$ Hz, 1H), 7.07 – 7.00 (m, 1H), 3.98 (d, $J = 13.0$ Hz, 1H), 3.67 (td, $J = 11.7, 9.9, 6.0$ Hz, 3H), 3.59 – 3.54 (m, 1H), 3.44 (dd, $J = 24.0, 15.1$ Hz, 1H), 3.04 (dd, $J = 13.7, 5.4$ Hz, 2H), 2.95 (s, 3H), 2.28 – 2.13 (m, 2H), 1.89 (dt, $J = 12.8, 6.3$ Hz, 1H), 1.80 (dt, $J = 11.9, 8.9$ Hz, 1H), 1.71 – 1.55 (m, 3H), 1.46–1.37 (m, 10H). ^{13}C NMR (101 MHz, CDCl_3) δ 161.4 (d, $J = 246.6$ Hz), 156.3 (minor rotamer), 155.8 (major rotamer), 131.3 (d, $J = 6.9$ Hz), 129.2 (d, $J = 8.2$ Hz), 125.6 (d, $J = 14.4$ Hz), 124.0 (d, $J = 3.6$ Hz), 115.6 (d, $J = 22.0$ Hz), 95.9, 88.6 (minor rotamer), 88.4 (major rotamer), 79.6 (major rotamer), 79.4 (minor rotamer), 66.4 (minor rotamer), 66.3 (major rotamer), 59.5, 58.8 (minor rotamer), 58.7 (major rotamer), 51.6 (major rotamer), 51.5 (d, $J = 1.7$ Hz), 50.7 (minor rotamer), 47.3, 37.5, 35.8 (minor rotamer), 35.7 (major rotamer), 32.7 (major rotamer), 32.4 (minor rotamer), 29.9, 28.5 (3C). HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{34}\text{FN}_2\text{O}_4$ [$\text{M}+\text{H}^+$] 421.2497, found 421.2498.

Tert-butyl (((3*S**,3*aR**,6*S**,7*aR**)-2-(2-fluorobenzyl)-3-(((6-methylpyridin-3-yl)oxy)methyl)hexahydro-3*a*,6-epoxyisoindol-6(1*H*)-yl)methyl)(methyl)carbamate (**S6**). **General Method A** was applied to *tert*-butyl (((3*S**,3*aR**,6*S**,7*aR**)-2-(2-fluorobenzyl)-3-(hydroxymethyl)hexahydro-3*a*,6-epoxyisoindol-6(1*H*)-yl)methyl)(methyl)carbamate (**9**) (80 mg, 0.19 mmol) and 5-hydroxy-2-methylpyridine (25 mg, 0.23 mmol). The crude was purified by flash column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ with 5 % of NH_4OH (25 % aq.) 98:2, $R_f = 0.2$) to give an impure compound which was used in the next step without further purification.

N-(((3*S**,3*aR**,6*S**,7*aR**)-2-(2-Fluorobenzyl)-3-(((6-methylpyridin-3-yl)oxy)methyl)hexahydro-3*a*,6-epoxyisoindol-6(1*H*)-yl)methyl)-*N*-methylpentan-1-amine (**16**). **General Method F** was applied to (((3*S**,3*aR**,6*S**,7*aR**)-2-(2-fluorobenzyl)-3-(((6-methylpyridin-3-yl)oxy)methyl)hexahydro-3*a*,6-epoxyisoindol-6(1*H*)-yl)methyl)(methyl)carbamate (**S6**) (95 mg, 0.19 mmol). The crude (20 mg, 0.05 mmol) was then directly subjected to **General Method D** and valeraldehyde (6 μL , 0.058 mmol) and purified directly by preparative HPLC to give the desired compound as a colorless oil (21 mg, 90% over three steps). ^1H NMR (400 MHz, CDCl_3) δ 8.18 (d, $J = 2.9$ Hz, 1H), 7.33 (td, $J = 7.5, 1.8$ Hz, 1H), 7.21 (tdd, $J = 7.5, 5.2, 1.8$ Hz, 1H), 7.09 (dd, $J = 8.5, 2.9$ Hz, 1H), 7.07 – 6.97 (m, 3H), 4.06 (dd, $J = 13.4, 1.4$ Hz, 1H), 4.01 – 3.89 (m, 2H), 3.79 (dd, $J = 13.3, 1.2$ Hz, 1H), 3.35 (dd, $J = 6.1, 4.5$ Hz, 1H), 3.06 (dd, $J = 8.3, 6.9$ Hz, 1H), 2.69 (d, $J = 13.9$ Hz, 1H), 2.62 (d, $J = 13.9$ Hz, 1H), 2.52 – 2.43 (m, 4H), 2.41 – 2.31 (m, 2H), 2.29 (s, 3H), 2.27 – 2.19 (m, 1H), 1.92 (td, $J = 12.3, 11.6, 4.8$ Hz, 1H), 1.76 – 1.53 (m, 5H), 1.52 – 1.39 (m, 2H), 1.39 – 1.19 (m, 4H),

0.90 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 161.3 (d, $J = 246.2$ Hz), 153.2, 150.6, 136.9, 131.5 (d, $J = 4.6$ Hz), 128.9 (d, $J = 8.2$ Hz), 125.8 (d, $J = 14.7$ Hz), 124.0 (d, $J = 3.6$ Hz), 123.4, 122.2, 115.5 (d, $J = 22.1$ Hz), 95.5, 88.4, 69.1, 64.7, 60.5, 59.2, 59.1, 52.1 (d, $J = 2.2$ Hz), 47.1, 44.0, 38.1, 33.9, 29.8, 29.3, 27.1, 23.5, 22.8, 14.3. HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{41}\text{FN}_3\text{O}_2$ [$\text{M}+\text{H}^+$] 482.3177, found 482.3176.

1-(((3*S**,3*aR**,6*S**,7*aR**)-2-(2-Fluorobenzyl)-3-(((6-methylpyridin-3-yl)oxy)methyl)hexahydro-3*a*,6-epoxyisoindol-6(1*H*)-yl)methyl)-3-isopropyl-1-methylurea (**17**). **General Method F** was applied to (((3*S**,3*aR**,6*S**,7*aR**)-2-(2-fluorobenzyl)-3-(((6-methylpyridin-3-yl)oxy)methyl)hexahydro-3*a*,6-epoxyisoindol-6(1*H*)-yl)methyl)(methyl)carbamate (**S6**) (95 mg, 0.19 mmol). The crude (20 mg, 0.05 mmol) and isopropyl isocyanate (5.7 μL , 0.06 mmol) was then subjected to **General Method G** to give the desired compound as an amorphous white solid (79 mg, 86% over three steps). ^1H NMR (400 MHz, CDCl_3) δ 8.18 (d, $J = 2.8$ Hz, 1H), 7.30 (td, $J = 7.5$, 1.8 Hz, 1H), 7.22 (tdd, $J = 7.3$, 5.2, 1.8 Hz, 1H), 7.12 – 6.98 (m, 4H), 5.43 (broad s, 1H), 4.04 (dd, $J = 13.3$, 1.4 Hz, 1H), 3.97 – 3.86 (m, 3H), 3.73 (d, $J = 13.3$ Hz, 1H), 3.49 (d, $J = 16.1$ Hz, 1H), 3.44 (d, $J = 17.0$ Hz, 1H), 3.28 (t, $J = 5.3$ Hz, 1H), 3.06 (d, $J = 7.6$ Hz, 1H), 2.92 (s, 3H), 2.48 (s, 3H), 2.44 – 2.35 (m, 1H), 2.23 – 2.12 (m, 1H), 2.02 – 1.82 (m, 1H), 1.74 (ddd, $J = 12.0$, 8.8, 4.1 Hz, 1H), 1.69 – 1.46 (m, 4H), 1.15 (d, $J = 6.2$ Hz, 3H), 1.13 (d, $J = 6.1$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 161.3 (d, $J = 246.2$ Hz), 159.2, 153.1, 150.6, 136.5, 131.6 (d, $J = 4.4$ Hz), 129.2 (d, $J = 8.1$ Hz), 125.3 (d, $J = 14.8$ Hz), 124.1 (d, $J = 3.6$ Hz), 123.6, 122.5, 115.6 (d, $J = 22.1$ Hz), 96.5, 89.0, 68.7, 64.7, 59.0, 52.2, 52.1 (d, $J = 1.9$ Hz), 47.0, 42.7, 37.0, 36.8, 32.1, 29.3, 23.8, 23.7, 23.3. HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{38}\text{FN}_4\text{O}_3$ [$\text{M}+\text{H}^+$] 497.2922, found 497.2922.

Tert-butyl (((2*R**,3*aR**,5*aS**,6*S**,9*aR**)-5-benzyl-6-hydroxy-2-vinyl-2,3,3*a*,4,5,5*a*,6,7-octahydrofuro[3,2-*c*]indol-2-yl)methyl)(methyl)carbamate (**18**). A stirred solution of *tert*-butyl (((3*S**,3*aR**,6*R**,7*aR**)-2-benzyl-3-(((*S*)-1-hydroxybut-3-en-1-yl)-2,3,7,7*a*-tetrahydro-3*a*,6-epoxyisoindol-6(1*H*)-yl)methyl)(methyl)carbamate (**6**) (180 mg, 0.41 mmol) in CH_2Cl_2 (25 mL) was added 1M HCl in Et_2O (450 μL , 1.1 equiv) followed by the Grubbs II catalyst (18 mg, 0.021 mmol). The reaction mixture was heated to reflux for 16 h, whereupon it was cooled to 20 °C and saturated aqueous NaHCO_3 (20 mL) was added under stirring. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over sodium sulfate and the volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc /heptane, 1:4 and 3:4, $R_f = 0.15$ in EtOAc /heptane, 1:4) to give compound **18** as a clear yellow oil (155 mg, 86%). ^1H NMR (400 MHz, CDCl_3) δ 7.41 – 7.23 (m, 5H), 5.88 (td, $J = 17.3$, 10.7 Hz, 1H), 5.75 – 5.60 (m, 2H), 5.23 (dd, $J = 17.3$, 1.4 Hz, 1H), 5.07 (dd, $J = 10.9$, 3.0 Hz, 1H), 4.17 (dd, $J = 13.3$, 6.2 Hz, 1H), 3.99 (q, $J = 3.9$ Hz, 1H), 3.68 – 3.20 (m, 4H), 3.19 – 3.00 (m, 2H), 2.94 (s, 3H), 2.52 – 2.29 (m, 3H), 2.28 – 1.92 (m, 3H), 1.47 – 1.42 (m, 9H, two rotamers). ^{13}C NMR (101 MHz, CDCl_3) δ 156.8 (major rotamer), 155.9 (minor rotamer), 144.0 (major rotamer), 143.5 (minor rotamer), 138.7, 129.5 (major rotamer), 129.3 (minor rotamer), 128.9 (2C), 128.5 (2C), 127.4, 124.6 (minor rotamer), 124.4 (major rotamer), 113.8 (minor rotamer), 113.6 (major rotamer), 91.3 (major rotamer), 91.2 (minor rotamer), 88.6 (major rotamer), 88.1 (minor rotamer), 79.8 (minor rotamer), 79.5 (major rotamer), 70.7 (major rotamer), 70.6 (minor rotamer), 65.9 (minor rotamer), 65.6 (major rotamer), 59.2, 57.7 (minor rotamer), 57.2, 56.9 (major rotamer), 47.3 (major rotamer), 47.2 (minor rotamer), 37.8 (minor rotamer), 37.4 (major rotamer), 37.3 (major rotamer), 36.9 (minor rotamer), 28.7, 28.5

(3C). HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{37}\text{N}_2\text{O}_4$ [$\text{M}+\text{H}^+$] 441.2748, found 441.2783.

Tert-butyl (((2*S**,3*aR**,5*aS**,6*S**,9*aR**)-2-ethyl-6-hydroxydecahydrofuro[3,2-*c*]indol-2-yl)methyl)(methyl)carbamate (**S7**). **General Method C** was applied to *tert*-butyl (((2*R**,3*aR**,5*aS**,6*S**,9*aR**)-5-benzyl-6-hydroxy-2-vinyl-2,3,3*a*,4,5,5*a*,6,7-octahydrofuro[3,2-*c*]indol-2-yl)methyl)(methyl)carbamate (**18**) (905 mg, 2.05 mmol). The crude was purified by flash column chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ with 5 % of NH_4OH (25 % aq) 9:1, $R_f = 0.1$) and the desired compound **S7** was isolated a colorless oil (340 mg, 78%) which was not completely pure but used in the next step without further purification.

(2*S**,3*aR**,5*aS**,6*S**,9*aR**)-2-ethyl-2-((methylamino)methyl)-5-(pyridin-3-ylmethyl)decahydrofuro[3,2-*c*]indol-6-ol (**S8**). **General Method D** was applied to *tert*-butyl (((2*S**,3*aR**,5*aS**,6*S**,9*aR**)-2-ethyl-6-hydroxydecahydrofuro[3,2-*c*]indol-2-yl)methyl)(methyl)carbamate (**S7**) (143 mg, 0.4 mmol) and nicotinaldehyde (45 μL , 0.48 mmol). The crude was then solubilized in a 3:1 mixture of CH_2Cl_2 and TFA (0.1 M) and stirred for 1 h at 20 °C. Then, it was concentrated under reduced pressure and used directly in the next step without further purification.

3-(3-Chlorophenyl)-1-(((2*S**,3*aR**,5*aS**,6*S**,9*aR**)-2-ethyl-6-hydroxy-5-(pyridin-3-ylmethyl)decahydrofuro[3,2-*c*]indol-2-yl)methyl)-1-methylurea (**19**). **General Method G** was applied to (2*S**,3*aR**,5*aS**,6*S**,9*aR**)-2-ethyl-2-((methylamino)methyl)-5-(pyridin-3-ylmethyl)decahydrofuro[3,2-*c*]indol-6-ol (**S8**) (22.6 mg, 0.06 mmol) and 3-chlorophenyl isocyanate (10 μL , 0.065 mmol) to give the desired compound as an amorphous white solid (19.8 mg, 61 % over three steps). ^1H NMR (400 MHz, CDCl_3) δ 8.70 – 8.25 (m, 3H), 7.79 – 7.55 (m, 1H), 7.50 (t, $J = 2.1$ Hz, 1H), 7.30 – 7.13 (m, 3H), 7.01 – 6.89 (m, 1H), 5.23 – 4.50 (m, 2H), 4.46 – 4.11 (m, 1H), 4.11 – 3.78 (m, 1H), 3.75 – 3.30 (m, 2H), 3.30 – 3.09 (m, 1H), 3.05 (s, 3H), 2.88 – 2.69 (m, 1H), 2.50 (br. s, 1H), 2.32 (br. s, 1H), 2.08 – 1.86 (m, 3H), 1.86 – 1.43 (m, 7H), 0.95 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 165.1, 157.7, 149.5, 141.1, 137.4, 134.7, 130.1, 123.8, 122.6, 122.8, 119.2, 117.0, 93.5, 90.6, 77.4, 70.5, 63.9, 58.1, 46.6, 46.4, 38.8, 38.6, 33.7, 32.7, 27.0, 18.5, 8.9. HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{36}\text{ClN}_4\text{O}_3$ [$\text{M}+\text{H}^+$] 499.2476, found 499.2485.

(2*S**,3*aR**,5*aS**,6*S**,9*aR**)-2-Ethyl-2-((methylamino)methyl)-5-pentyldecahydrofuro[3,2-*c*]indol-6-ol (**S9**). **General Method E** was applied to *tert*-butyl (((2*S**,3*aR**,5*aS**,6*S**,9*aR**)-2-ethyl-6-hydroxydecahydrofuro[3,2-*c*]indol-2-yl)methyl)(methyl)carbamate (**S7**) (134 mg, 0.38 mmol) and valeraldehyde (48 μL , 0.45 mmol). After the reaction, the crude mixture was dissolved in a 3:1 mixture of CH_2Cl_2 and TFA (0.1 M) and stirred for 1 h at 20 °C. The reaction mixture was concentrated under reduced pressure and used directly in the next step without further purification.

N-(((2*S**,3*aR**,5*aS**,6*S**,9*aR**)-2-Ethyl-6-hydroxy-5-pentyldecahydrofuro[3,2-*c*]indol-2-yl)methyl)-*N*-methylthiophene-2-carboxamide (**20**). **General Method H** was applied to (2*S**,3*aR**,5*aS**,6*S**,9*aR**)-2-Ethyl-2-((methylamino)methyl)-5-pentyldecahydrofuro[3,2-*c*]indol-6-ol (**S9**) (22.6 mg, 0.07 mmol) and thiophene-2-carbonyl chloride (8 μL , 0.077 mmol) to give the desired compound as an amorphous white solid (18.1 mg, 60% over three steps). ^1H NMR (400 MHz, CDCl_3) δ 8.52 (s, 1H), 7.52 (d, $J = 5.0$ Hz, 1H), 7.46 (d, $J = 3.7$ Hz, 1H), 7.09 (dd, $J = 5.1$, 3.8 Hz, 1H), 6.92 (br. s, 1H), 4.25 (br. s, 1H), 4.13 – 3.51 (m, 2H),

3.51 – 3.31 (m, 4H), 3.30 – 2.58 (m, 4H), 2.13 (dd, $J = 13.8, 7.3$ Hz, 1H), 2.08 – 1.11 (m, 15H), 0.97 (t, $J = 7.5$ Hz, 3H), 0.93 – 0.84 (m, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 167.8, 166.0, 137.7, 130.5, 127.3, 92.2, 88.2, 77.4, 64.9, 59.0, 54.2, 45.4, 41.2, 39.8, 33.4, 33.1, 29.6, 29.0, 25.6, 22.3, 17.3, 14.0, 9.2, 1.1. HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{39}\text{N}_2\text{O}_3\text{S}$ [$\text{M}+\text{H}^+$] 435.2676, found 435.2702.

1'-(*Tert*-butyl) 6-methyl (2*R,3*aR**,6*R**,6*aR**)-5-benzyl-6*a*-vinyl-3,3*a*,4,5,6,6*a*-hexahydro-2'*H*-spiro[furo[2,3-*c*]pyrrole-2,3'-pyridine]-1',6(6'*H*)-dicarboxylate (21).** Methyl (3*R**,3*aR**,6*R**,7*aR**)-6-((allyl(*tert*-butoxycarbonyl)amino)methyl)-2-benzyl-1,2,3,6,7,7*a*-hexahydro-3*a*,6-epoxyisoindole-3-carboxylate (**7**) (5.0 g, 11 mmol) was dissolved in CH_2Cl_2 (40 mL) and added 4 M HCl in dioxane (3.3 mL, 13.2 mmol) whereupon the mixture was concentrated *in vacuo* followed by 30 min under vacuum using an oil pump which gave a white HCl-salt. The salt was then added dry CH_2Cl_2 (55 mL) followed by Grubbs II (93 mg, 1%) and the atmosphere was exchanged to ethylene and the mixture was stirred at 20 °C. After 16 h Grubbs II (93 mg, 1%) was added and the mixture was stirred 5 h at reflux under an ethylene atmosphere. The reaction was allowed to cool to 20 °C, added sat. NaHCO_3 (aq.) (100 mL, pH > 7) and CH_2Cl_2 (50 mL) and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc:heptane 1:4, $R_f = 0.2$) to give the title compound as a white solid (4.14 g, 83%). ^1H NMR (400 MHz, CDCl_3) δ 7.42 – 7.13 (m, 5H), 5.88 (dd, $J = 16.9, 10.6$ Hz, 1H), 5.71 (s, 2H), 5.44 (d, $J = 16.9$ Hz, 1H), 5.11 (d, $J = 10.6$ Hz, 1H), 4.37 (d, $J = 13.1$ Hz, 1H), 4.18 (d, $J = 18.5$ Hz, 1H), 3.81 (d, $J = 13.1$ Hz, 1H), 3.72 – 3.49 (m, 6H), 3.44 (t, $J = 9.9$ Hz, 1H), 3.28 – 3.05 (m, 1H), 3.05 – 2.79 (m, 2H), 2.01 (d, $J = 13.4$ Hz, 1H), 1.88 (dd, $J = 13.4, 8.0$ Hz, 1H), 1.52 – 1.36 (m, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 171.6, 154.6, 138.4, 133.1, 128.9 (2C), 128.5 (2C), 127.4, 127.2, 125.1, 114.9, 96.3, 83.0, 80.1, 76.1, 58.6, 56.2, 51.4, 50.6, 47.9, 42.7, 39.3, 28.6 (major rotamer, 3C). HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{35}\text{N}_2\text{O}_5$ [$\text{M}+\text{H}^+$] 455.2540, found 455.2572.

***Tert*-butyl (2*R**,3*aR**,6*R**,6*aR**)-5-benzyl-6-(pyrrolidine-1-carbonyl)-6*a*-vinyl-3,3*a*,4,5,6,6*a*-hexahydro-2'*H*-spiro[furo[2,3-*c*]pyrrole-2,3'-pyridine]-1'(6'*H*)-carboxylate (22).** General Method I was applied to 1'-(*tert*-butyl) 6-methyl (2*R**,3*aR**,6*R**,6*aR**)-5-benzyl-6*a*-vinyl-3,3*a*,4,5,6,6*a*-hexahydro-2'*H*-spiro[furo[2,3-*c*]pyrrole-2,3'-pyridine]-1',6(6'*H*)-dicarboxylate (**21**) (3.17 g, 6.96 mmol). General Method J was applied to the crude carboxylic acid (1.53 g, 3.47 mmol) and pyrrolidine (0.57 mL, 6.96 mmol). The crude mixture was purified by flash column chromatography (EtOAc:heptane 1:1, $R_f = 0.2$) to give the title compound as a white solid (1.476 g, 86%). ^1H NMR (400 MHz, CDCl_3) δ 7.41 – 7.16 (m, 5H), 5.93 (dd, $J = 16.9, 10.6$ Hz, 1H), 5.80 – 5.66 (m, 2H), 5.47 (d, $J = 16.7$ Hz, 1H), 5.05 (d, $J = 10.5$ Hz, 1H), 4.70 – 3.69 (m, 4H), 3.69 – 3.30 (m, 5H), 3.21 – 2.86 (m, 4H), 2.47 – 2.20 (m, 1H), 2.11 – 1.97 (m, 1H), 1.88 (dd, $J = 13.3, 8.4$ Hz, 1H), 1.76 – 1.54 (m, 4H), 1.47 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 169.5, 154.8, 139.3, 139.1, 133.2, 129.0, 128.4 (2C), 127.2 (2C), 125.1, 114.4, 96.8, 82.5, 80.1, 72.3, 60.3, 55.1, 50.2, 48.7, 46.4, 45.4, 42.7, 39.8, 28.7 (3C), 26.1, 24.2. HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{40}\text{N}_3\text{O}_4$ [$\text{M}+\text{H}^+$] 494.3013, found 494.3051.

***Tert*-butyl (2*R**,3*aR**,6*R**,6*aR**)-5-benzyl-6-(isopropylcarbamoyl)-6*a*-vinyl-3,3*a*,4,5,6,6*a*-hexahydro-2'*H*-spiro[furo[2,3-*c*]pyrrole-2,3'-pyridine]-1'(6'*H*)-carboxylate (23).** General Method I was applied to 1'-(*tert*-butyl) 6-methyl (2*R**,3*aR**,6*R**,6*aR**)-5-benzyl-6*a*-vinyl-3,3*a*,4,5,6,6*a*-hexahydro-2'*H*-spiro[furo[2,3-*c*]pyrrole-2,3'-pyridine]-1',6(6'*H*)-

dicarboxylate (**21**) (3.166 g, 6.96 mmol). General Method J was applied to the crude carboxylic acid (1.53 g, 3.47 mmol) and *i*-PrNH₂ (0.60 mL, 6.96 mmol). The crude mixture was purified via flash column chromatography (EtOAc:heptane 2:3, $R_f = 0.2$) and the title compound was afforded as a white solid (1.515 g, 91%). ^1H NMR (400 MHz, CDCl_3) δ 7.39 – 7.16 (m, 5H), 6.68 – 6.49 (m, 1H), 6.03 – 5.87 (m, 1H), 5.84 – 5.68 (m, 1H), 5.68 – 5.49 (m, 1H), 5.37 – 5.17 (m, 1H), 5.08 (d, $J = 10.9$ Hz, 1H), 4.24 – 3.80 (m, 4H), 3.80 – 3.47 (m, 1H), 3.43 – 3.31 (m, 2H), 3.25 (t, $J = 8.4$ Hz, 1H), 3.16 (d, $J = 12.8$ Hz, 1H), 2.81 (q, $J = 8.2$ Hz, 1H), 2.63 (t, $J = 9.1$ Hz, 1H), 2.07 – 1.90 (m, 1H), 1.90 – 1.76 (m, 1H), 1.46 (s, 9H), 1.14 – 1.06 (m, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 169.0, 154.4, 138.6, 138.1, 133.4, 128.8, 128.6 (2C), 127.5 (2C), 124.1, 114.0, 96.3, 82.5, 80.0, 79.0, 58.5, 57.9, 51.3, 47.1, 42.5, 40.6, 37.5, 28.6 (2C), 22.9 (major rotamer, 3C). HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{40}\text{N}_3\text{O}_4$ [$\text{M}+\text{H}^+$] 482.3013, found 482.3044.

Methyl (2*S,3*aR**,6*R**,6*aR**)-6*a*-ethyl-1'-pentyl-5-(thiophene-2-carbonyl)hexahydrospiro[furo[2,3-*c*]pyrrole-2,3'-piperidine]-6-carboxylate (24).** General Method F was applied to 1'-(*tert*-butyl) 6-methyl (2*R**,3*aR**,6*R**,6*aR**)-5-benzyl-6*a*-vinyl-3,3*a*,4,5,6,6*a*-hexahydro-2'*H*-spiro[furo[2,3-*c*]pyrrole-2,3'-pyridine]-1',6(6'*H*)-dicarboxylate (**21**) (207 mg, 0.445 mmol) followed by General Method E with valeraldehyde (63 μL , 0.592 mmol), General Method B, and General Method H with thiophene-2-carbonyl chloride (58 μL , 0.456 mmol), respectively. The crude mixture was purified directly using flash column chromatography (EtOAc:heptane 9:1 + 1% Et₃N, $R_f = 0.2$) to give the title compound as a yellow oil (158 mg, 77%). ^1H NMR (400 MHz, CDCl_3) δ 7.48 (d, $J = 3.4$ Hz, 1H), 7.43 (d, $J = 4.8$ Hz, 1H), 7.04 – 6.98 (m, 1H), 4.85 (s, 1H), 4.22 – 3.85 (m, 2H), 3.67 (s, 3H), 2.80 (d, $J = 4.6$ Hz, 1H), 2.43 (t, $J = 11.4$ Hz, 2H), 2.32 – 2.04 (m, 3H), 2.04 – 1.96 (m, 2H), 1.69 – 1.59 (m, 1H), 1.60 – 1.31 (m, 5H), 1.32 – 1.07 (m, 6H), 0.95 (t, $J = 7.3$ Hz, 3H), 0.85 – 0.72 (m, 4H) (two rotamers). ^{13}C NMR (101 MHz, CDCl_3) δ 170.9, 162.2, 137.8, 130.5, 130.3, 127.1, 92.7, 83.5, 71.0, 64.0, 58.6, 54.4, 53.7, 52.0, 46.0, 41.2, 37.6, 29.7, 27.2, 26.3, 23.4, 22.4, 14.1, 8.3 (major rotamer). HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{37}\text{N}_2\text{O}_4\text{S}$ [$\text{M}+\text{H}^+$] 449.2469, found 449.2525.

((2*S,3*aR**,6*R**,6*aR**)-6*a*-Ethyl-1'-pentyl-5-(thiophene-2-carbonyl)hexahydrospiro[furo[2,3-*c*]pyrrole-2,3'-piperidine]-6-yl)(morpholino)methanone (25).** General Method I was applied to methyl (2*S**,3*aR**,6*R**,6*aR**)-6*a*-ethyl-1'-pentyl-5-(thiophene-2-carbonyl)hexahydrospiro[furo[2,3-*c*]pyrrole-2,3'-piperidine]-6-carboxylate (**24**) (158 mg, 0.352 mmol). The carboxylic acid (20 mg, 0.046 mmol) and morpholine (8 μL , 0.092) was used following General Method J. The mixture was purified directly using preparative HPLC to give the title compound as a white solid (14 mg, 60%). ^1H NMR (400 MHz, CDCl_3) δ 7.55 (d, $J = 3.8$ Hz, 1H), 7.49 (dd, $J = 5.0, 0.8$ Hz, 1H), 7.08 (dd, $J = 5.0, 3.9$ Hz, 1H), 5.33 (s, 1H), 4.37 (dd, $J = 10.5, 8.9$ Hz, 1H), 3.95 (dd, $J = 10.7, 3.0$ Hz, 2H), 3.87 – 3.76 (m, 1H), 3.77 – 3.65 (m, 5H), 3.50 (ddd, $J = 13.0, 6.7, 3.5$ Hz, 1H), 3.10 – 2.99 (m, 1H), 2.85 – 2.76 (m, 1H), 2.64 (d, $J = 11.3$ Hz, 1H), 2.51 – 2.32 (m, 4H), 2.26 (d, $J = 11.9$ Hz, 1H), 2.05 (dd, $J = 13.6, 8.1$ Hz, 1H), 1.92 – 1.81 (m, 1H), 1.78 – 1.67 (m, 1H), 1.67 – 1.56 (m, 4H), 1.33 (dt, $J = 14.1, 7.1$ Hz, 2H), 1.22 – 1.10 (m, 4H), 0.97 (t, $J = 7.4$ Hz, 3H), 0.82 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 168.9, 167.3, 138.0, 130.8, 130.5, 127.5, 94.7, 82.4, 67.1, 67.0, 66.7, 61.7, 58.0, 55.7, 53.1, 47.3, 47.1, 42.5, 41.8, 37.5, 29.5, 27.5, 25.0, 22.3, 22.1, 14.1, 9.0. HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{42}\text{N}_3\text{O}_4\text{S}$ [$\text{M}+\text{H}^+$] 504.2891, found 504.2955.

Tert-butyl ($2S^*,3aR^*,6R^*,6aR^*$)-6a-ethyl-5-(pyridin-2-ylmethyl)-6-(pyrrolidine-1-carbonyl)hexahydrospiro[furo[2,3-c]pyrrole-2,3'-piperidine]-1'-carboxylate (**26**). **General Method B** was applied to *tert*-butyl ($2R^*,3aR^*,6R^*,6aR^*$)-5-benzyl-6-(pyrrolidine-1-carbonyl)-6a-vinyl-3,3a,4,5,6,6a-hexahydro-2'H-spiro[furo[2,3-c]pyrrole-2,3'-pyridine]-1'(6'H)-carboxylate (**22**) (1.32 g, 2.65 mmol). Following this reaction, **General Method E** was applied to the amine (567 mg, 1.39 mmol) and 2-pyridinecarboxaldehyde (164 μ L, 1.74 mmol). The crude mixture was purified directly using flash column chromatography (EtOAc:MeOH 9:2, R_f = 0.2) to give the title compound as a yellow solid (697 mg, 95%). ^1H NMR (400 MHz, CDCl_3) δ 8.46 (d, J = 4.9 Hz, 1H), 7.75 – 7.53 (m, 2H), 7.16 – 7.09 (m, 1H), 4.48 – 3.90 (m, 2H), 3.85 – 3.56 (m, 3H), 3.56 – 3.23 (m, 4H), 3.10 – 2.82 (m, 2H), 2.81 – 2.59 (m, 2H), 2.04 – 1.89 (m, 1H), 1.81 – 1.50 (m, 11H), 1.43 (s, 10H), 0.84 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 174.4, 169.3, 159.6, 154.9, 148.6, 136.8, 122.1, 97.8, 83.7, 79.9, 73.4, 61.2, 57.8, 53.5, 46.5, 45.6, 43.2, 40.2, 39.1, 29.3 (3C), 28.7, 26.4, 24.1, 23.7, 21.6, 8.7. HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{43}\text{N}_4\text{O}_4$ [$\text{M}+\text{H}^+$] 499.3279, found 499.3376.

($2S^*,3aR^*,6R^*,6aR^*$)-1'-(Butylsulfonyl)-6a-ethyl-5-(pyridin-2-ylmethyl)hexahydrospiro[furo[2,3-c]pyrrole-2,3'-piperidine]-6-yl(pyrrolidin-1-yl)methanone (**27**). **General Method F** was applied to *tert*-butyl ($2S^*,3aR^*,6R^*,6aR^*$)-6a-ethyl-5-(pyridin-2-ylmethyl)-6-(pyrrolidine-1-carbonyl)hexahydrospiro[furo[2,3-c]pyrrole-2,3'-piperidine]-1'-carboxylate (**26**) (85 mg, 0.17 mmol). Following this reaction, **General Method K** was applied to TFA amine salt (32 mg, 0.051 mmol) and 1-butanefulfonyl chloride (6 mg, 0.038 mmol) to give after preparative HPLC, the title compound as a white foam (25 mg, 93%). ^1H NMR (400 MHz, CDCl_3) δ 8.49 (dd, J = 4.9, 0.9 Hz, 1H), 7.64 (td, J = 7.6, 1.8 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.13 (ddd, J = 7.3, 4.9, 1.0 Hz, 1H), 3.97 (d, J = 13.8 Hz, 1H), 3.82 (d, J = 11.0 Hz, 1H), 3.81 (s, 1H), 3.73 (d, J = 13.8 Hz, 1H), 3.62 – 3.51 (m, 2H), 3.46 – 3.36 (m, 3H), 3.14 – 3.04 (m, 2H), 3.03 – 2.94 (m, 1H), 2.93 – 2.86 (m, 2H), 2.83 (dd, J = 9.0, 4.7 Hz, 1H), 2.79 – 2.72 (m, 1H), 2.12 (d, J = 13.4 Hz, 1H), 1.88 – 1.73 (m, 8H), 1.68 – 1.54 (m, 5H), 1.49 – 1.38 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H), 0.87 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 169.4, 159.1, 148.8, 136.7, 123.9, 122.1, 98.2, 83.0, 73.6, 60.5, 57.7, 54.8, 49.6, 46.9, 46.3, 45.9, 45.7, 41.2, 38.1, 29.1, 26.4, 25.3, 24.2, 23.8, 22.0, 13.8, 8.8. HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{43}\text{N}_4\text{O}_4\text{S}$ [$\text{M}+\text{H}^+$] 519.3000, found 519.3035.

($2R^*,3aR^*,6R^*,6aR^*$)-1'-Benzoyl-5-benzyl-*N*-isopropyl-6a-vinyl-1',3,3a,4,5,6,6a,6'-octahydro-2'H-spiro[furo[2,3-c]pyrrole-2,3'-pyridine]-6-carboxamide (**28**). **General Method F** was applied to *tert*-butyl ($2R^*,3aR^*,6R^*,6aR^*$)-5-benzyl-6-(isopropylcarbamoyl)-6a-vinyl-3,3a,4,5,6,6a-hexahydro-2'H-spiro[furo[2,3-c]pyrrole-2,3'-pyridine]-1'(6'H)-carboxylate (**23**) (1.439 g, 2.99 mmol). **General Method H** was applied to amine (570 mg, 1.49 mmol) and benzoyl chloride (208 μ L, 1.79 mmol). The mixture was purified using flash column chromatography (gradient from EtOAc:heptane 3:2 to 100% EtOAc, R_f = 0.3 in 100% EtOAc) to give the title compound as a white solid (616 mg, 85%). ^1H NMR (400 MHz, CDCl_3) δ 7.64 – 7.35 (m, 5H), 7.37 – 7.20 (m, 4H), 7.18 – 6.99 (m, 1H), 6.72 (s, 0.5H), 6.42 (d, J = 6.5 Hz, 0.5H), 6.07 – 5.46 (m, 3H), 5.25 (d, J = 16.9 Hz, 1H), 5.08 (d, J = 10.9 Hz, 1H), 4.65 (d, J = 11.0 Hz, 0.5H), 4.32 – 3.76 (m, 4H), 3.80 – 3.59 (m, 2H), 3.55 – 3.07 (m, 2H), 3.12 – 2.62 (m, 2.5H), 1.95 – 1.77 (m, 1H), 1.79 – 1.54 (m, 1H), 1.19 – 0.96 (m, 6H) (two rotamers). ^{13}C NMR (101 MHz, CDCl_3) δ 171.1, 168.9, 138.6, 138.1, 136.2, 134.3, 132.6, 129.7, 128.7 (2C), 128.6 (2C), 127.8 (2C), 127.5 (2C), 124.6, 114.1, 96.4, 79.0, 60.5, 58.8, 58.2, 54.9, 46.7, 41.5,

40.6, 38.1, 22.9, 14.3 (major rotamer). HRMS (ESI) calcd for $\text{C}_{30}\text{H}_{36}\text{N}_3\text{O}_3$ [$\text{M}+\text{H}^+$] 486.2751, found 486.2754.

($2S^*,3aR^*,6R^*,6aR^*$)-1'-Benzoyl-6a-ethyl-*N*-isopropylhexahydrospiro[furo[2,3-c]pyrrole-2,3'-piperidine]-6-carboxamide (**S10**). ($2R^*,3aR^*,6R^*,6aR^*$)-1'-benzoyl-5-benzyl-*N*-isopropyl-6a-vinyl-1',3,3a,4,5,6,6a,6'-octahydro-2'H-spiro[furo[2,3-c]pyrrole-2,3'-pyridine]-6-carboxamide (**28**) (318 mg, 0.65 mmol) was hydrogenated following **General Method B** to give the title compound as a white solid (245 mg, 95%). The amine was used directly without further purification.

($2S^*,3aR^*,6R^*,6aR^*$)-1'-Benzoyl-5-(cyclopropylsulfonyl)-6a-ethyl-*N*-isopropylhexahydrospiro[furo[2,3-c]pyrrole-2,3'-piperidine]-6-carboxamide (**29**). **General Method K** was applied to ($2S^*,3aR^*,6R^*,6aR^*$)-1'-benzoyl-6a-ethyl-*N*-isopropylhexahydrospiro[furo[2,3-c]pyrrole-2,3'-piperidine]-6-carboxamide (**S10**) (18 mg, 0.045 mmol) and cyclopropanesulfonyl chloride (7.6 mg, 0.054 mmol) gave after preparative HPLC the title compound as a white foam (17 mg, 75%). ^1H NMR (400 MHz, CDCl_3) δ 7.43 – 7.39 (m, 3H), 7.36 (d, J = 4.6 Hz, 2H), 6.94 (d, J = 7.2 Hz, 1H), 4.44 (s, 1H), 4.41 (s, 1H), 4.07 (dq, J = 13.3, 6.6 Hz, 1H), 3.75 (d, J = 10.3 Hz, 1H), 3.58 (dd, J = 10.4, 6.3 Hz, 1H), 3.52 (d, J = 13.5 Hz, 1H), 3.22 (d, J = 13.1 Hz, 1H), 3.14 (t, J = 11.9 Hz, 1H), 2.91 – 2.83 (m, 1H), 2.76 (dd, J = 14.7, 6.8 Hz, 1H), 2.19 – 1.94 (m, 2H), 1.93 – 1.73 (m, 3H), 1.67 (q, J = 7.2 Hz, 2H), 1.57 (t, J = 11.8 Hz, 1H), 1.49 – 1.38 (m, 1H), 1.13 (d, J = 6.5 Hz, 3H), 1.08 (d, J = 6.5 Hz, 3H), 0.94 (t, J = 7.3 Hz, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 171.3, 168.3, 136.6, 129.6, 128.6 (2C), 126.5 (2C), 95.2, 82.1, 70.5, 52.9, 50.5, 47.9, 43.6, 41.5, 40.0, 37.5, 29.8, 25.0, 23.1, 22.8, 22.5, 8.3, 5.4, 5.3. HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{38}\text{N}_3\text{O}_5\text{S}$ [$\text{M}+\text{H}^+$] 504.2527, found 504.2539.

($2S^*,3aR^*,6R^*,6aR^*$)-6a-Ethyl-1'-pentyl-5-(thiophene-2-carbonyl)hexahydrospiro[furo[2,3-c]pyrrole-2,3'-piperidine]-6-carboxamide (**30**). **General Method I** was applied to methyl ($2S^*,3aR^*,6R^*,6aR^*$)-6a-ethyl-1'-pentyl-5-(thiophene-2-carbonyl)hexahydrospiro[furo[2,3-c]pyrrole-2,3'-piperidine]-6-carboxylate (**24**) (158 mg, 0.352 mmol). The carboxylic acid (20 mg, 0.046 mmol) and NH_4Cl (7.4 mg, 0.14 mmol) were used following **General Method J**. The mixture was purified using preparative HPLC to provide the title compound as a white solid (12 mg, 59%). ^1H NMR (400 MHz, CDCl_3) δ 7.52 (d, J = 3.4 Hz, 1H), 7.49 (d, J = 4.9 Hz, 1H), 7.12 – 7.03 (m, 1H), 6.97 (s, 1H), 5.78 (s, 1H), 4.98 (s, 1H), 4.42 – 4.21 (m, 1H), 3.87 (dd, J = 10.7, 2.9 Hz, 1H), 2.97 (s, 1H), 2.59 – 2.27 (m, 6H), 2.17 – 1.99 (m, 2H), 1.99 – 1.76 (m, 2H), 1.73 – 1.49 (m, 4H), 1.40 – 1.07 (m, 6H), 1.01 (t, J = 7.3 Hz, 3H), 0.82 (t, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 171.7, 162.40, 138.1, 130.7, 130.6, 127.5, 93.7, 82.5, 70.6, 63.0, 58.6, 55.44, 53.3, 46.5, 41.8, 37.4, 29.7, 27.0, 25.5, 22.6, 22.5, 14.2, 9.0. HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{36}\text{N}_3\text{O}_3\text{S}$ [$\text{M}+\text{H}^+$] 434.2472, found 434.2485.

($2S^*,3aR^*,6R^*,6aR^*$)-6a-Ethyl-*N,N*-dimethyl-1'-pentyl-5-(thiophene-2-carbonyl)hexahydrospiro[furo[2,3-c]pyrrole-2,3'-piperidine]-6-carboxamide (**31**). **General Method I** was applied to methyl ($2S^*,3aR^*,6R^*,6aR^*$)-6a-ethyl-1'-pentyl-5-(thiophene-2-carbonyl)hexahydrospiro[furo[2,3-c]pyrrole-2,3'-piperidine]-6-carboxylate (**24**) (158 mg, 0.352 mmol). The carboxylic acid (20 mg, 0.046 mmol) and dimethylamine hydrochloride (11 mg, 0.14 mmol) were used following **General Method J**. The mixture was purified using preparative HPLC to provide the title compound as a white solid (12 mg, 56%). ^1H NMR (400 MHz, CDCl_3) δ 7.50 (dd, J = 3.7, 0.7 Hz, 1H), 7.43 (d, J = 5.0 Hz, 1H), 7.02 (dd, J = 4.9, 3.9 Hz, 1H), 5.30 (s, 1H), 4.34 (dd, J = 10.4, 9.1 Hz, 1H), 3.90 (dd,

$J = 10.7, 3.2$ Hz, 1H), 3.26 (s, 3H), 2.99 (dd, $J = 9.9, 6.9$ Hz, 1H), 2.90 (s, 3H), 2.87 – 2.82 (m, 1H), 2.77 – 2.61 (m, 1H), 2.53 – 2.40 (m, 2H), 2.37 – 2.22 (m, 2H), 1.98 (dd, $J = 13.6, 8.0$ Hz, 1H), 1.85 – 1.74 (m, 1H), 1.69 – 1.50 (m, 6H), 1.33 – 1.24 (m, 2H), 1.16 – 1.02 (m, 4H), 0.90 (t, $J = 7.4$ Hz, 3H), 0.75 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 170.3, 162.0, 138.2, 130.8, 130.6, 127.6, 94.9, 82.2, 67.3, 61.3, 57.9, 55.7, 53.0, 47.4, 41.8, 38.1, 37.5, 35.9, 29.4, 27.5, 24.8, 22.3, 21.9, 14.1, 8.9. HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{40}\text{N}_3\text{O}_3\text{S}$ [$\text{M}+\text{H}^+$] 462.2785, found 462.2837.

($2\text{S}^*, 3\text{aR}^*, 6\text{R}^*, 6\text{aR}^*$)-6a-Ethyl-N-(2-methoxyethyl)-1'-pentyl-5-(thiophene-2-carbonyl)hexahydrospiro[furo[2,3-c]pyrrole-2,3'-piperidine]-6-carboxamide (**32**). **General Method I** was applied to methyl ($2\text{S}^*, 3\text{aR}^*, 6\text{R}^*, 6\text{aR}^*$)-6a-ethyl-1'-pentyl-5-(thiophene-2-carbonyl)hexahydrospiro[furo[2,3-c]pyrrole-2,3'-piperidine]-6-carboxylate (**24**) (158 mg, 0.352 mmol). The carboxylic acid (20 mg, 0.046 mmol) and 2-methoxyethylamine (8 μL , 0.092) was used following **General Method J**. The mixture was purified using preparative HPLC to provide the title compound as a white solid (9 mg, 41%). ^1H NMR (400 MHz, CDCl_3) δ 8.49 (s, 1H), 7.54 (d, $J = 3.3$ Hz, 1H), 7.49 (d, $J = 4.8$ Hz, 1H), 7.12 – 7.01 (m, 1H), 4.91 (s, 1H), 4.32 (t, $J = 9.6$ Hz, 1H), 4.15 – 3.83 (m, 1H), 3.59 – 3.33 (m, 4H), 3.30 (s, 3H), 2.98 (s, 1H), 2.83 – 2.35 (m, 6H), 2.25 – 1.78 (m, 4H), 1.77 – 1.30 (m, 6H), 1.28 – 1.09 (m, 4H), 1.00 (t, $J = 7.2$ Hz, 3H), 0.83 (t, $J = 6.8$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 169.6, 168.2, 138.2, 130.7, 130.5, 127.5, 94.3, 82.0, 71.1, 71.0, 61.7, 58.8, 58.1, 55.5, 52.9, 46.7, 42.0, 39.3, 37.2, 29.5, 27.1, 24.8, 22.4, 21.9, 14.2, 8.9. HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{42}\text{N}_3\text{O}_4\text{S}$ [$\text{M}+\text{H}^+$] 492.2891, found 492.2944.

($2\text{S}^*, 3\text{aR}^*, 6\text{R}^*, 6\text{aR}^*$)-N-Cyclopentyl-6a-ethyl-5-(pyridin-2-ylmethyl)-6-(pyrrolidine-1-carbonyl)hexahydrospiro[furo[2,3-c]pyrrole-2,3'-piperidine]-1'-carboxamide (**33**). **General Method F** was applied to *tert*-butyl ($2\text{S}^*, 3\text{aR}^*, 6\text{R}^*, 6\text{aR}^*$)-6a-ethyl-5-(pyridin-2-ylmethyl)-6-(pyrrolidine-1-carbonyl)hexahydrospiro[furo[2,3-c]pyrrole-2,3'-piperidine]-1'-carboxylate (**26**) (85 mg, 0.17 mmol). Following this reaction, **General Method G** was applied to TFA amine salt (37 mg, 0.059 mmol) and cyclopentyl isocyanate (8 μL , 0.071 mmol) to provide the desired product as a white solid (19 mg, 61%) from purification using the preparative HPLC. ^1H NMR (400 MHz, CDCl_3) δ 8.56 (dd, $J = 5.3, 1.7$ Hz, 1H), 7.64 (td, $J = 7.7, 1.7$ Hz, 1H), 7.21 (d, $J = 3.9$ Hz, 1H), 7.20 (d, $J = 3.8$ Hz, 1H), 6.39 (br. s, 1H), 4.26 – 4.07 (m, 2H), 4.05 – 3.89 (m, 2H), 3.83 – 3.72 (m, 3H), 3.58 – 3.47 (m, 1H), 3.48 – 3.38 (m, 1H), 3.38 – 3.30 (m, 1H), 3.18 (d, $J = 12.9$ Hz, 1H), 3.12 – 3.00 (m, 1H), 2.97 – 2.85 (m, 2H), 2.70 (dd, $J = 9.8, 8.0$ Hz, 1H), 2.00 – 1.88 (m, 3H), 1.87 – 1.75 (m, 5H), 1.76 – 1.67 (m, 1H), 1.66 – 1.57 (m, 3H), 1.55 – 1.38 (m, 6H), 1.37 – 1.25 (m, 2H), 0.86 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 169.6, 163.3, 157.9, 149.3, 136.9, 123.4, 122.8, 97.9, 83.8, 73.2, 61.3, 56.3, 53.1, 52.9, 47.0, 46.0, 45.6, 43.2, 38.5, 33.4, 33.2, 28.4, 26.3, 24.2, 23.9, 23.8, 23.7 (2C), 8.7. HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{44}\text{N}_5\text{O}_3$ [$\text{M}+\text{H}^+$] 510.3439, found 510.3493.

1-($2\text{S}^*, 3\text{aR}^*, 6\text{R}^*, 6\text{aR}^*$)-6a-Ethyl-5-(pyridin-2-ylmethyl)-6-(pyrrolidine-1-carbonyl)hexahydrospiro[furo[2,3-c]pyrrole-2,3'-piperidine]-1'-yl)ethan-1-one (**34**). **General Method F** was applied to *tert*-butyl ($2\text{S}^*, 3\text{aR}^*, 6\text{R}^*, 6\text{aR}^*$)-6a-ethyl-5-(pyridin-2-ylmethyl)-6-(pyrrolidine-1-carbonyl)hexahydrospiro[furo[2,3-c]pyrrole-2,3'-piperidine]-1'-carboxylate (**26**) (85 mg, 0.17 mmol). Following this reaction, **General Method J** was applied to TFA amine salt (24 mg, 0.060 mmol) and acetic acid (4.5 μL , 0.078 mmol) to give after preparative HPLC the title compound as a white foam (14 mg, 54%). ^1H NMR (400 MHz, CD_3OD) δ 8.51 – 8.44 (m, 1H), 7.89 – 7.81 (m, 1H), 7.75 – 7.66 (m, 1H), 7.36 – 7.32 (m, 1H), 4.13 – 3.99 (m, 2H), 3.80 – 3.69 (m, 1H), 3.64 – 3.34 (m, 7H), 3.33 –

3.26 (m, 3H), 2.85 (dd, $J = 9.6, 7.8$ Hz, 1H), 2.78 – 2.65 (m, 1H), 2.12 (s, 2.4H, major rotamer), 1.99 – 1.68 (m, 8.6H), 1.70 – 1.55 (m, 2H), 1.55 – 1.45 (m, 1H), 0.98 – 0.81 (m, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 171.5, 170.0, 159.0, 149.3, 138.9, 126.0, 125.4, 98.2, 85.6, 77.1, 61.4, 59.6, 51.9, 47.5, 47.1, 47.0, 40.9, 38.6, 30.3, 27.1, 27.0, 25.0, 24.6, 21.3, 8.4 (major rotamers). HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{37}\text{N}_4\text{O}_3$ [$\text{M}+\text{H}^+$] 441.2860, found 441.2895.

Tert-butyl ($2\text{S}^*, 3\text{aR}^*, 6\text{R}^*, 6\text{aR}^*$)-6a-Ethyl-5-(isopropylcarbamoyl)-6-(pyrrolidine-1-carbonyl)hexahydrospiro[furo[2,3-c]pyrrole-2,3'-piperidine]-1'-carboxylate (**35**). **General Method B** was applied to *tert*-butyl ($2\text{S}^*, 3\text{aR}^*, 6\text{R}^*, 6\text{aR}^*$)-5-benzyl-6-(pyrrolidine-1-carbonyl)-6a-vinyl-3,4a,4,5,6,6a-hexahydro-2'H-spiro[furo[2,3-c]pyrrole-2,3'-pyridine]-1'(6'H)-carboxylate (**22**) (1.32g, 2.68 mmol). Following this reaction, **General Method G** was applied to amine (567 mg, 1.39 mmol) and isopropyl isocyanate (145 μL , 1.47 mmol). The crude mixture was purified directly using flash column chromatography ($\text{EtOAc}:\text{MeOH}$ 9:1, $R_f = 0.2$) to give the title compound as a white solid (685 mg, >95%). ^1H NMR (400 MHz, CDCl_3) δ 4.93 (s, 1H), 4.75 (s, 1H), 4.18 – 3.72 (m, 5H), 3.72 – 3.45 (m, 3H), 3.41 – 3.26 (m, 1H), 3.11 – 2.43 (m, 3H), 2.13 – 1.52 (m, 12H), 1.44 (s, 9H), 1.20 – 1.03 (m, 6H), 0.90 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 170.7, 156.6, 154.5, 96.5, 82.6, 79.5, 68.4, 53.8, 51.8, 47.2, 46.5, 45.7, 44.3, 42.5, 40.7, 38.9, 28.9, 28.5, 28.1, 26.3 (3C), 24.5, 24.4, 23.5, 8.9. HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{45}\text{N}_4\text{O}_5$ [$\text{M}+\text{H}^+$] 493.3384, found 493.3409.

($2\text{S}^*, 3\text{aR}^*, 6\text{R}^*, 6\text{aR}^*$)-1'-Benzyl-6a-ethyl-N-isopropyl-6-(pyrrolidine-1-carbonyl)tetrahydrospiro[furo[2,3-c]pyrrole-2,3'-piperidine]-5(3H)-carboxamide (**36**). **General Method F** was applied to *tert*-butyl ($2\text{S}^*, 3\text{aR}^*, 6\text{R}^*, 6\text{aR}^*$)-6a-ethyl-5-(isopropylcarbamoyl)-6-(pyrrolidine-1-carbonyl)hexahydrospiro[furo[2,3-c]pyrrole-2,3'-piperidine]-1'-carboxylate (**35**) (87 mg, 0.18 mmol). **General Method E** was applied to resulting amine (23 mg, 0.045 mmol) and benzaldehyde (8.8 μL , 0.086 mmol). Mixture was purified by preparative HPLC to give a white solid (14 mg, 63%). ^1H NMR (400 MHz, CDCl_3) δ 7.41 – 7.37 (m, 3H), 7.35 – 7.30 (m, 2H), 4.87 (s, 1H), 4.06 – 3.83 (m, 5H), 3.65 – 3.44 (m, 2H), 3.44 – 3.30 (m, 1H), 3.27 (d, $J = 8.7$ Hz, 1H), 2.95 – 2.74 (m, 3H), 2.45 – 2.19 (m, 2H), 2.07 – 1.76 (m, 6H), 1.77 – 1.49 (m, 6H), 1.13 (t, $J = 6.4$ Hz, 6H), 0.89 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 170.1, 156.7, 131.0, 129.3 (2C), 129.1 (2C), 97.5, 81.9, 68.0, 61.3, 60.1, 53.8, 51.0, 47.3, 46.6, 45.8, 42.6, 42.4, 36.9, 28.0, 26.3, 24.3, 23.6, 23.2 (2C), 21.6, 8.9. HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{43}\text{N}_4\text{O}_3$ [$\text{M}+\text{H}^+$] 483.3330, found 483.3384.

($2\text{S}^*, 3\text{aR}^*, 6\text{R}^*, 6\text{aR}^*$)-6a-Ethyl-N-isopropyl-6-(pyrrolidine-1-carbonyl)-1'-tosyltetrahydrospiro[furo[2,3-c]pyrrole-2,3'-piperidine]-5(3H)-carboxamide (**37**). **General Method F** was applied to *tert*-butyl ($2\text{S}^*, 3\text{aR}^*, 6\text{R}^*, 6\text{aR}^*$)-6a-ethyl-5-(isopropylcarbamoyl)-6-(pyrrolidine-1-carbonyl)hexahydrospiro[furo[2,3-c]pyrrole-2,3'-piperidine]-1'-carboxylate (**35**) (87 mg, 0.18 mmol). **General Method K** was applied to the resulting amine (20 mg, 0.040 mmol) and 4-toluenesulfonyl chloride (12 mg, 0.062 mmol). Mixture was purified directly by preparative HPLC to give a white solid (13 mg, 57%). ^1H NMR (400 MHz, CDCl_3) δ 7.56 (d, $J = 8.2$ Hz, 2H), 7.29 (d, $J = 8.2$ Hz, 2H), 4.71 (s, 1H), 4.51 (d, $J = 7.6$ Hz, 1H), 4.11 (t, $J = 9.4$ Hz, 1H), 4.07 – 3.89 (m, 2H), 3.73 (d, $J = 11.5$ Hz, 1H), 3.63 (d, $J = 11.0$ Hz, 1H), 3.59 – 3.42 (m, 3H), 3.43 – 3.29 (m, 1H), 3.03 – 2.85 (m, 1H), 2.52 (d, $J = 13.3$ Hz, 1H), 2.41 (s, 3H), 2.15 – 1.96 (m, 3H), 1.94 – 1.53 (m, 9H), 1.54 – 1.38 (m, 1H), 1.22 (d, $J = 6.4$ Hz, 3H), 1.15 (d, $J = 6.6$ Hz, 3H), 0.89 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 170.8, 156.6, 143.7, 133.6,

129.9 (2C), 127.4 (2C), 96.6, 82.7, 68.8, 54.6, 54.5, 47.2, 46.7, 46.0, 45.7, 42.7, 40.9, 38.0, 28.2, 26.3, 24.4, 23.6 (2C), 23.4, 21.6, 8.9. HRMS (ESI) calcd for $C_{28}H_{43}N_4O_5S$ $[M+H]^+$ 547.2949, found 547.2947.

(2*S**,3*aR**,6*R**,6*aR**)-6*a*-Ethyl-1'-isonicotinoyl-*N*-isopropyl-6-(pyrrolidine-1-carbonyl)tetrahydrospiro[furo[2,3-*c*]pyrrole-2,3'-piperidine]-5(3*H*)-carboxamide (**38**). **General Method F** was applied to *tert*-butyl (2*S**,3*aR**,6*R**,6*aR**)-6*a*-ethyl-5-(isopropylcarbamoyl)-6-(pyrrolidine-1-carbonyl)hexahydrospiro[furo[2,3-*c*]pyrrole-2,3'-piperidine]-1'-carboxylate (**35**) (87 mg, 0.18 mmol). **General Method I** was then applied to resulting amine (22 mg, 0.043 mmol) and isonicotinic acid (7 mg, 0.056 mmol). The crude mixture was purified using preparative HPLC to give the title compound as a white solid (15 mg, 69%). 1H NMR (400 MHz, $CDCl_3$) δ 8.69 (dd, J = 4.5, 1.5 Hz, 2H), 7.31 (d, J = 5.1 Hz, 1H), 7.24 (dd, J = 4.5, 1.5 Hz, 2H), 4.83 (s, 1H), 4.68 (d, J = 7.8 Hz, 1H), 4.45 (d, J = 12.9 Hz, 1H), 4.11 – 4.00 (m, 2H), 3.98 – 3.83 (m, 1H), 3.71 (dd, J = 9.4, 3.1 Hz, 1H), 3.57 – 3.48 (m, 2H), 3.45 (d, J = 13.5 Hz, 1H), 3.40 – 3.32 (m, 1H), 3.07 – 2.93 (m, 2H), 2.81 (d, J = 13.1 Hz, 1H), 2.12 (d, J = 13.1 Hz, 1H), 2.05 – 1.77 (m, 7H), 1.74 – 1.58 (m, 2H), 1.44 – 1.34 (m, 1H), 1.12 (d, J = 3.6 Hz, 3H), 1.11 (d, J = 3.8 Hz, 3H), 0.93 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 163.0, 156.5, 150.4 (2C), 144.0, 121.0 (2C), 96.8, 82.5, 68.3, 53.5, 50.8, 47.6, 47.2, 46.8, 45.8, 42.6, 40.7, 39.0, 28.2, 26.3, 24.9, 24.4, 23.6, 23.4, 8.9. HRMS (ESI) calcd for $C_{27}H_{40}N_5O_4$ $[M+H]^+$ 498.3075, found 498.3072.

(2*S**,3*aR**,6*R**,6*aR**)-1'-Benzoyl-6*a*-ethyl-*N*5-hexyl-*N*6-isopropyltetrahydrospiro[furo[2,3-*c*]pyrrole-2,3'-piperidine]-5,6(3*H*)-dicarboxamide (**39**). **General Method G** was applied to (2*S**,3*aR**,6*R**,6*aR**)-1'-benzoyl-6*a*-ethyl-*N*-isopropylhexahydrospiro[furo[2,3-*c*]pyrrole-2,3'-piperidine]-6-carboxamide (**S10**) (20 mg, 0.050 mmol) and hexyl isocyanate (8.8 μ L, 0.060 mmol) to give after preparative HPLC the title compound as a white foam (18 mg, 69%). 1H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.38 (m, 3H), 7.38 – 7.32 (m, 2H), 6.49 (d, J = 7.4 Hz, 1H), 4.82 (t, J = 5.1 Hz, 1H), 4.38 (s, 1H), 4.09 – 3.94 (m, 2H), 3.89 – 3.72 (m, 1H), 3.52 – 3.38 (m, 1H), 3.38 – 3.06 (m, 4H), 2.97 – 2.74 (m, 1H), 2.10 (dd, J = 13.0, 3.0 Hz, 1H), 2.01 – 1.56 (m, 6H), 1.56 – 1.37 (m, 3H), 1.31 – 1.20 (m, 6H), 1.13 (d, J = 6.6 Hz, 3H), 1.10 (d, J = 6.5 Hz, 3H), 0.96 (t, J = 7.4 Hz, 3H), 0.90 – 0.80 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 169.9, 157.5, 136.3, 129.7, 128.7 (2C), 126.6 (2C), 95.7, 82.3, 70.0, 51.7, 47.9, 45.4, 41.4, 41.2, 41.0, 40.4, 38.8, 31.7 (2C), 30.3, 27.2, 26.6, 24.4, 22.7, 22.5, 14.2, 8.8. HRMS (ESI) calcd for $C_{30}H_{47}N_4O_4$ $[M+H]^+$ 527.3592, found 527.3612.

(2*S**,3*aR**,6*R**,6*aR**)-1'-Benzoyl-5-(cyclohexylmethyl)-6*a*-ethyl-*N*-isopropylhexahydrospiro[furo[2,3-*c*]pyrrole-2,3'-piperidine]-6-carboxamide (**40**). **General Method E** was applied to (2*S**,3*aR**,6*R**,6*aR**)-1'-benzoyl-6*a*-ethyl-*N*-isopropylhexahydrospiro[furo[2,3-*c*]pyrrole-2,3'-piperidine]-6-carboxamide (**S10**) (17 mg, 0.043 mmol) and cyclohexane carbaldehyde (7.7 μ L, 0.064 mmol) gave after preparative HPLC the title compound as a white foam (15 mg, 72%). 1H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.31 (m, 5H), 6.76 (s, 0.5H), 6.49 (d, J = 7.8 Hz, 0.5H), 4.34 (d, J = 12.4 Hz, 1H), 4.18 – 3.98 (m, 1H), 3.80 (d, J = 13.0 Hz, 0.5H), 3.53 – 3.42 (m, 1H), 3.41 – 3.20 (m, 1.5H), 3.20 – 2.86 (m, 2H), 2.74 – 2.56 (m, 1H), 2.45 – 2.22 (m, 1.5H), 2.08 – 1.95 (m, 1.5H), 1.88 – 1.60 (m, 10H), 1.55 – 1.42 (m, 2H), 1.34 – 1.05 (m, 11H), 0.99 – 0.58 (m, 5H) (two rotamers). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 169.7, 136.3, 129.8, 128.7, 128.6, 127.8, 126.8, 96.2, 84.7, 81.4, 62.5, 58.3, 57.3, 51.9, 47.8, 46.1, 42.3, 40.6, 38.5, 38.2, 36.1, 32.0, 31.6, 31.2, 28.5, 26.8, 26.2,

22.9, 8.2 (major rotamers). HRMS (ESI) calcd for $C_{30}H_{46}N_3O_3$ $[M+H]^+$ 496.3534, found 496.3594.

(2*R**,3*aR**,6*R**,6*aR**)-5-Benzyl-*N*-isopropyl-1'-(methylsulfonyl)-6*a*-vinyl-1',3,3*a*,4,5,6,6*a*,6'-octahydro-2'*H*-spiro[furo[2,3-*c*]pyrrole-2,3'-pyridine]-6-carboxamide (**41**). **General Method F** was applied to *tert*-butyl (2*R**,3*aR**,6*R**,6*aR**)-5-benzyl-6-(isopropylcarbamoyl)-6*a*-vinyl-3,3*a*,4,5,6,6*a*-hexahydro-2'*H*-spiro[furo[2,3-*c*]pyrrole-2,3'-pyridine]-1'(6*H*)-carboxylate (**23**) (1.439 g, 2.99 mmol). **General Method K** was applied to amine (570 mg, 1.49 mmol) and methanesulfonyl chloride (210 μ L, 1.79 mmol) purified using flash column chromatography (EtOAc:heptane 3:2, R_f = 0.1) to give the title compound as a white solid (485 mg, 71%). 1H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 2H), 7.28 (d, J = 7.1 Hz, 3H), 6.57 (d, J = 8.2 Hz, 1H), 5.96 (dd, J = 17.3, 10.7 Hz, 1H), 5.79 (dt, J = 10.2, 2.0 Hz, 1H), 5.69 (dt, J = 10.2, 3.1 Hz, 1H), 5.26 (dd, J = 17.3, 1.3 Hz, 1H), 5.10 (dd, J = 10.7, 1.3 Hz, 1H), 4.15 – 3.98 (m, 1H), 3.89 (d, J = 13.0 Hz, 1H), 3.87 – 3.79 (m, 1H), 3.66 (dt, J = 17.4, 2.5 Hz, 1H), 3.55 (d, J = 12.5 Hz, 1H), 3.46 (d, J = 2.0 Hz, 1H), 3.43 (d, J = 2.7 Hz, 1H), 3.35 (s, 1H), 3.29 (t, J = 8.6 Hz, 1H), 2.92 (s, 3H), 2.88 – 2.79 (m, 1H), 2.50 (t, J = 9.0 Hz, 1H), 2.05 – 1.90 (m, 2H), 1.13 (d, J = 4.0 Hz, 3H), 1.11 (d, J = 3.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 138.6, 137.8, 133.4, 129.0, 128.7 (2C), 127.6 (2C), 123.1, 114.0, 96.6, 81.9, 78.7, 58.5, 58.0, 53.2, 46.9, 44.2, 40.7, 38.8, 36.8, 23.1, 22.9. HRMS (ESI) calcd for $C_{24}H_{34}N_3O_4S$ $[M+H]^+$ 460.2265, found 460.2298.

(2*S**,3*aR**,6*R**,6*aR**)-6*a*-Ethyl-*N*-isopropyl-1'-(methylsulfonyl)hexahydrospiro[furo[2,3-*c*]pyrrole-2,3'-piperidine]-6-carboxamide (**S11**). (2*R**,3*aR**,6*R**,6*aR**)-5-benzyl-*N*-isopropyl-1'-(methylsulfonyl)-6*a*-vinyl-1',3,3*a*,4,5,6,6*a*,6'-octahydro-2'*H*-spiro[furo[2,3-*c*]pyrrole-2,3'-pyridine]-6-carboxamide (**41**) (365 mg, 0.79 mmol) was hydrogenated following **General Method B** to give the title compound as a white solid (298 mg, 95%). The amine was used directly without further purification.

(2*S**,3*aR**,6*R**,6*aR**)-6*a*-Ethyl-*N*6-isopropyl-1'-(methylsulfonyl)-*N*5-(*o*-tolyl)tetrahydrospiro[furo[2,3-*c*]pyrrole-2,3'-piperidine]-5,6(3*H*)-dicarboxamide (**42**). **General Method G** was applied to (2*S**,3*aR**,6*R**,6*aR**)-6*a*-ethyl-*N*-isopropyl-1'-(methylsulfonyl)hexahydrospiro[furo[2,3-*c*]pyrrole-2,3'-piperidine]-6-carboxamide (**S11**) (20 mg, 0.054 mmol) and *o*-tolyl isocyanate (6.8 μ L, 0.064 mmol) and provide after preparative HPLC, the title compound as a white foam (19 mg, 72%). 1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 7.9 Hz, 1H), 7.13 (dd, J = 9.8, 3.3 Hz, 2H), 6.98 (td, J = 7.5, 1.1 Hz, 1H), 6.33 (s, 1H), 6.23 (d, J = 7.7 Hz, 1H), 4.42 (s, 1H), 4.10 (t, J = 9.5 Hz, 1H), 4.02 (dq, J = 13.2, 6.6 Hz, 1H), 3.63 (dd, J = 9.6, 3.3 Hz, 1H), 3.59 – 3.49 (m, 2H), 2.98 (t, J = 8.2 Hz, 1H), 2.87 – 2.76 (m, 2H), 2.73 (s, 3H), 2.38 (d, J = 13.6 Hz, 1H), 2.25 (s, 3H), 1.93 – 1.54 (m, 7H), 1.13 (d, J = 6.6 Hz, 3H), 1.11 (d, J = 6.6 Hz, 3H), 0.98 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 154.6, 137.0, 130.5, 129.3, 126.6, 124.0, 122.4, 95.9, 82.0, 70.6, 54.5, 53.3, 46.4, 45.6, 41.7, 40.5, 38.3, 36.3, 28.0, 23.6, 22.5, 22.5, 17.9, 9.0. HRMS (ESI) calcd for $C_{25}H_{39}N_4O_5S$ $[M+H]^+$ 507.2636, found 507.2645.

(2*S**,3*aR**,6*R**,6*aR**)-6*a*-Ethyl-*N*-isopropyl-1'-(methylsulfonyl)-5-(thiophen-3-ylmethyl)hexahydrospiro[furo[2,3-*c*]pyrrole-2,3'-piperidine]-6-carboxamide (**43**). **General Method E** was applied to (2*S**,3*aR**,6*R**,6*aR**)-6*a*-ethyl-*N*-isopropyl-1'-(methylsulfonyl)hexahydrospiro[furo[2,3-*c*]pyrrole-2,3'-piperidine]-6-carboxamide (**S11**) (20 mg, 0.053 mmol) and 3-thiophenecarboxaldehyde (7.5 μ L, 0.080 mmol) gave after

preparative HPLC the title compound as a white foam (17 mg, 68%). ¹H NMR (400 MHz, CDCl₃) δ 7.28 (dd, *J* = 4.9, 3.0 Hz, 1H), 7.13 (d, *J* = 2.6 Hz, 1H), 6.99 (dd, *J* = 4.9, 1.2 Hz, 1H), 6.54 (d, *J* = 8.1 Hz, 1H), 4.25–4.01 (m, 1H), 3.85 (d, *J* = 13.4 Hz, 1H), 3.53–3.42 (m, 2H), 3.43–3.35 (m, 1H), 3.35–3.28 (m, 1H), 3.31 (s, 1H), 3.20 (d, *J* = 12.3 Hz, 1H), 3.10–2.98 (m, 1H), 2.93 (s, 3H), 2.58 (td, *J* = 10.0, 1.9 Hz, 1H), 2.52–2.45 (m, 1H), 1.95 (dd, *J* = 13.5, 2.0 Hz, 1H), 1.84 (dddd, *J* = 13.9, 10.5, 6.9, 3.7 Hz, 1H), 1.80–1.62 (m, 4H), 1.62–1.43 (m, 2H), 1.17 (d, *J* = 6.3 Hz, 3H), 1.15 (d, *J* = 6.4 Hz, 3H), 0.89 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 169.6, 138.6, 128.2, 126.0, 123.1, 96.9, 83.6, 79.1, 59.1, 55.2, 53.2, 45.7, 45.5, 40.8, 39.9, 37.4, 37.0, 28.5, 23.0, 22.94, 22.91, 8.3. HRMS (ESI) calcd for C₂₂H₃₆N₃O₄S₂ [M+H]⁺ 470.2142, found 470.2181.

(2*S**,3*aR**,6*R**,6*aR**)-6*a*-Ethyl-5-(1*H*-indole-5-carbonyl)-*N*-isopropyl-1'-(methylsulfonyl)hexahydrospiro[furo[2,3-*c*]pyrrole-2,3'-piperidine]-6-carboxamide (**44**). Following General Method J using (2*S**,3*aR**,6*R**,6*aR**)-6*a*-ethyl-*N*-isopropyl-1'-(methylsulfonyl)hexahydrospiro[furo[2,3-*c*]pyrrole-2,3'-piperidine]-6-carboxamide (**S11v**) (24 mg, 0.064 mmol), indole-5-carboxylic acid (14 mg, 0.084 mmol) gave after preparative HPLC the title compound as a white foam (25 mg, 74%). ¹H NMR (400 MHz, CDCl₃) δ 9.07 (s, 1H), 7.90 (s, 1H), 7.46–7.16 (m, 3H), 6.56 (dd, *J* = 29.2, 11.9 Hz, 2H), 4.87 (s, 1H), 4.31–4.01 (m, 2H), 3.53 (dd, *J* = 11.4, 2.6 Hz, 1H), 3.18 (dt, *J* = 48.2, 9.0 Hz, 4H), 2.93–2.87 (m, 1H), 2.83 (s, 3H), 1.99–1.82 (m, 4H), 1.71–1.51 (m, 4H), 1.17–1.15 (m, 6H), 1.03 (t, *J* = 7.3 Hz, 3H) (major rotamer); ¹³C NMR (101 MHz, CDCl₃) δ 171.9, 168.7, 137.1, 127.3, 126.9, 125.7, 121.7, 120.9, 111.2, 103.1, 94.9, 81.2, 69.3, 55.7, 55.4, 46.2, 45.2, 41.6, 40.5, 37.8, 37.7, 26.9, 22.7, 22.6, 22.5, 8.9 (major rotamer). HRMS (ESI) calcd for C₂₆H₃₇N₄O₅S [M+H]⁺ 517.2479, found 517.2476.

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Keywords: Drug discovery; Heterocycles; Cycloaddition

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

Layout 1:

FULL PAPER

An efficient and rapid route to three structurally distinct scaffolds (A–C) from a single precursor which in turn is available through a one-pot Petasis 3-component-reaction–Diels-Alder cascade reaction. We demonstrate the versatility of the approach through the synthesis of 35 exemplary compounds from the three scaffolds, as well as by the production of 2188 final compounds, which have been included in the Joint European Compound Library of the European Lead Factory.

Library synthesis*

Thomas Flagstad, Carlos M. G. Azevedo, Nikolaj S. Troelsen, Geanna K. Min, Yohan Macé, Anthony Willaume, Rachel Guilleux, Mélanie Velay, Karine Bonnet, Remy Morgentin, Thomas E. Nielsen, * Mads H. Clausen*

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Generation of a Heteropolycyclic and Sp³-Rich Scaffold for Library Synthesis from a Highly Diastereoselective Petasis/Diels-Alder and ROM-RCM Reaction Sequence

* Petasis/Diels-Alder