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

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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


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 sp²-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 sp³-rich cores through diversity-oriented synthesis.[3] However, routine syntheses of such sp³-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 sp³-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 sp³-rich library based on a 3-component Petasis/Diels–Alder strategy.[7] This sequence in combination with two ring opening/closing metathesis (ROM/RCM) cascade reactions enabled us to access different, diverse and sp³-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 R³ 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 R¹ 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...
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.

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 to provide aryl ether. 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, sulfonylation, or acylation to provide 9-14 in high yields 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 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 alylated 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 2: Petasis 3-component reaction accessing key intermediates 5-7.

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, 16 h. (d) 5% Pd/C, HCOONa, MeOH, reflux, 1.5 h. (e) CyCHO, NaBH4, CN, HOAc, MeOH, 20 °C, 18 h. (f) thiophene-2-carboxylic acid, DIPEA, DMF, 0 °C, 1 h. (g) cyclopentyl isocyanate, DMF, 20 °C, 18 h. (h) nicotinaldehyde, NaBH4, CN, MeOH, 20 °C, 18 h. (i) n-HexNCO, DMF, 20 °C, 18 h. (j) 2-fluorobenzaldehyde, NaBH4, CN, MeOH, 20 °C, 18 h. (k) 5-hydroxy-2-methylpyridine, PPh3, DEAD, THF, 0–20 °C, 18 h. (l) valeraldehyde, NaBH4, CN, MeOH, 20 °C, 18 h. (m) i-PrNCO, DMF, 20 °C, 18 h. (n) i-PrNHC(O), 86%.
followed by reductive alkylation. Then, benzyl deprotection and derivatisation was achieved by removal of the Boc-group with TFA in the same reaction sequence (Scheme 6). First, 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 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 protection 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.

Conclusions

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 aluminium 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 µm, 2.1 x 50 mm; column temp: 65 °C; flow: 0.6 mL/min), as well as a SQD ESI MS detector. Eluents A1 (0.1% HCOOH in H2O), A2 (0.1% NH4COOH), B1 (0.1% HCOOH in MeCN) and B2 (0.1% NH4COOH 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 an ACQUITY UPLC system.

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 Geliduran® 60 silica gel (40-63 µm 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. *synthesised from 21, †synthesised from 23, ‡synthesised from 28, §synthesised from 41.
All purified compounds have been routinely characterized by 1H NMR, 13C 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 13C NMR), and analyzed via the NMR software MestReNova (version 6.2.1-7569). 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 CDCl₃, and the signals were adjusted relative to this position (δ 7.26 ppm for 1H NMR and δ 77.2 ppm for 13C NMR). For spectra recorded in DMSO-d₆, the signals were adjusted relative to the DMSO signal (δ 2.5 ppm for 1H NMR and δ 39.5 ppm for 13C NMR). For spectra recorded in CD₂OD, signal were adjusted relative to this position (δ 3.31 ppm for 1H NMR and δ 49.00 ppm for 13C 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**

Benzyamine 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 HCOONH₄ (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.

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

Benzyamine or olefin (2.05 mmol) was dissolved in EtOH:H₂O (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. NaHCO₃ (25 mL) and CH₂Cl₂ (25 mL). The two phases were separated and the aqueous phase extracted with CH₂Cl₂ (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 CH₂Cl₂ (7 mL). Aldehyde (1.74 mmol, 1.25 equiv.) was added followed by NaBH(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. NaHCO₃ (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 MeOH:H₂O (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 H₂O (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 CH₂Cl₂ (3 x 60 mL) and the combined organic layers were dried over Na₂SO₄ 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 CH₂Cl₂ (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 (0.96 mmol, 2 equiv.) was added and the mixture was stirred for another 30 min. The mixture
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\textsubscript{2}Cl\textsubscript{2} (8 mL), added Et\textsubscript{3}N (312 \mu L, 2.24 mmol, 1.5 equiv.) and cooled to 0 °C. The mixture was added sulfon 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-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\textsubscript{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\textsubscript{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 removed and the mixture was stirred 1 h at 20 °C. The crude was dissolved in CH\textsubscript{2}Cl\textsubscript{2} (36 mL, 0.4 M), added Et\textsubscript{3}N (6 mL, 4.5 M) and 3 Å molecular sieves were added, and the mixture was stirred 1 h at 20 °C. The crude was dissolved in CH\textsubscript{2}Cl\textsubscript{2} (30 mL) and the mixture was stirred 1 h at 20 °C. Then sat. aq. NaHCO\textsubscript{3} (100 mL) was added and the layers were separated. The aqueous phase was extracted with CH\textsubscript{2}Cl\textsubscript{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.

**Sulfonylation of amines**

2-Hydroxypent-4-enoic acid 5 (*S2*). To a solution of allyl bromide (11.3 mL, 131 mmol) in THF:H\textsubscript{2}O (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 aqeous phase was extracted with CH\textsubscript{2}Cl\textsubscript{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 %). *\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 5.79 (ddt, J = 17.1, 10.2, 6.9 Hz, 1H), 5.22 – 5.12 (m, 1H), 2.46 (dtt, J = 14.9, 6.9, 1.3 Hz, 1H), 1.58 (d, J = 0.8 Hz, 3H). *\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ 177.6, 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-one (S3)**. 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\textsubscript{4} (40 g) was added and the mixture was stirred 1 h at 20 °C. Then sat. aq. NaHCO\textsubscript{3} (200 mL) was added and the layers were separated. The aqueous phase was extracted with CH\textsubscript{2}Cl\textsubscript{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 any purification.

**Library A-C Scaffold and Library Production**

Tert-butyl ((3S,3aR,6R,7aR)-2-benzyl-3-(hydroxymethyl)2,3,7,7a-tetrahydro-3a,6-epoxyisoxindol-6(1H)-
allylbenzylamine (6.5, 2.9 Hz, 1H), 1.41 (s, 9H), 1.40 – 1.22 (m, 2H). 13C NMR (101 MHz, CDCl3) δ 3.17 (t, J = 9.6 Hz, 1H), 2.99 (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 = 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), 138.4 (minor rotamer), 138.4 (major rotamer), 136.9 (major rotamer), 136.6 (minor rotamer), 136.4 (major rotamer), 136.1 (minor rotamer), 135.7 (minor rotamer), 133.8 (major rotamer), 133.1 (minor rotamer), 131.5 (major rotamer), 131.0 (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 (minor rotamer), 49.8 (major rotamer), 45.2, 36.0 (major rotamer), 35.9 (minor rotamer), 32.6 (major rotamer), 32.5 (minor rotamer, 3C), 28.6 (3C). HRMS (ESI) calcd for C15H21N3O2 [M+H+] 401.2435, found 401.2468.

Tert-butyl (((3S*,3aR*,6R*,7aR*)-2-benzyl-3-((2-methoxyphenoxy)methyl)-2,3,7,7a-tetrahydro-3a,6-epoxysindol-6(1H)-ylyl)methyl)(methyl)carbamate (6). To a solution of 5-allyl-2,2-dimethyl-1,3-dioxolan-4-ol (54) (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-(5-((tert-butoxycarbonyl)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 (30 mL) was then added and the layers were separated. The aqueous phase was extracted with CH2Cl2 (2 x 50 mL) and the combined organic layers were dried over sodium sulfate, 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 = 1:4) to give the desired compound as a yellow oil (11.5 g, 44% over 5 steps, 13C NMR (101 MHz, CDCl3) δ 172.3, 156.2, 138.0, 137.3, 135.3, 134.0, 133.6, 131.0, 130.8, 128.9, 127.8, 126.5, 122.4, 121.0, 115.1 (major rotamer), 115.0 (minor rotamer), 112.64 (major rotamer), 112.61 (minor rotamer), 112.59 (minor rotamer), 109.6, 108.9, 106.3, 105.1, 96.2, 92.4, 47.4, 45.3, 32.2, 28.5 (major rotamer, 3C). HRMS (ESI) calcd for C20H20N3O5 [M+H+] 455.2540, found 455.2575.

1-((3S*,3aR*,6R*,7aR*)-2-benzyl-3-(2-Methoxyphenoxymethyl)hexahydropyrano[3,2-b]pyridine-2,3-dione (5). General Method F was applied to tert-butyl (((3S*,3aR*,6R*,7aR*)-2-benzyl-3-(2-methoxyphenoxy)methyl)-2,3,7,7a-tetrahydro-3a,6-epoxysindol-6(1H)-ylyl)methyl)(methyl)carbamate (6) to give the title compound as a yellow oil (0.68 g, 31%). 1H NMR (400 MHz, CDCl3) δ 7.37 – 7.25 (m, 5H), 6.76 (dd, J = 10.3, 6.9, 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, 128.6, 132.6 (2C), 127.4 (2C), 117.6, 97.8, 91.6 (major rotamer), 91.1 (minor rotamer), 79.8 (major rotamer), 79.6 (minor rotamer), 69.7, 69.3, 58.7, 58.5, 50.6 (minor rotamer), 49.6 (major rotamer), 45.7, 37.0, 35.9, 32.5, 28.6 (3C). HRMS (ESI) calcd for C15H21N3O2 [M+H+] 441.2748, found 441.2770.
methoxyphenoxymethyl)-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-6(1H)-yl)methyl)methylcarbamate (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, Rf = 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), 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 (d, 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, 139.6, 139.5, 132.0, 128.3 (2C), 29.7, 70.3, 67.0, 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-(((3S*,3aR*,6S*,7aR*)-3-((2-Methoxyphenoxy)methyl)-2-(Cyclohexylmethyl)-3-((2-methoxyphenoxymethyl)methyl)hexahydro-3a,6-epoxyisoindol-6(1H)-yl)methyl)-N-methylacetamide (9). General Method H was applied to 1-(((3S*,3aR*,6S*,7aR*)-3-((2-Methoxyphenoxy)methyl)hexahydro-3a,6-epoxyisoindol-6(1H)-yl)-methyl)methylacetamide (8) (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 B was then applied to the crude (38 mg, 0.09 mmol) and cyclopentyl isocyanate (15 µL, 0.135 mmol). The reaction mixture was purified 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 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), 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 (d, 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, 139.6, 139.5, 132.0, 128.3 (2C), 29.7, 70.3, 67.0, 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-(((3S*,3aR*,6S*,7aR*)-3-((2-Methoxyphenoxy)methyl)-2-(Cyclohexylmethyl)-3-((2-methoxyphenoxymethyl)methyl)hexahydro-3a,6-epoxyisoindol-6(1H)-yl)methyl)-N-methylacetamide (10). General Method H was applied to 1-(((3S*,3aR*,6S*,7aR*)-3-((2-Methoxyphenoxy)methyl)hexahydro-3a,6-epoxyisoindol-6(1H)-yl)-methyl)methylacetamide (8) (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 B was then applied to the crude (38 mg, 0.09 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 (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), 3.88 – 3.63 (m, 5H), 3.37 (q, J = 8.9 Hz, 1H), 3.27 – 3.11 (m, 1H), 3.07 (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, 112.1, 113.5, 93.4 (major rotamer), 93.3 (major rotamer), 88.3 (major 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 (major rotamer), 46.8 (major rotamer), 42.1 (major rotamer), 41.6 (major rotamer), 37.9 (major rotamer), 35.5 (major rotamer), 32.3 (minor rotamer), 31.9 (major rotamer), 28.6, 21.9 (minor rotamer) 21.8 (major rotamer). HRMS (ESI) calcd for C₂₅H₂₅N₂O₃ [M+H⁺] 471.1948, found 471.1948.
...steps).  $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.12 – 4.01 (m, 1H), 3.98 (dd, $J = 9.7, 5.3, 3.6$ 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). 

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 171.24 (major 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 (major rotamer), 113.6 (major rotamer), 113.4 (minor rotamer), 112.0, 94.3 (minor rotamer), 94.1 (major rotamer), 88.3 (major rotamer), 60.7 (minor rotamer), 58.8 (minor rotamer). 

$^2$J (rotamer), 32.7 (major rotamer), 32.4 (minor rotamer), 29.9, 28.5 (rotamer), 28.6 (major rotamer), 23.71 (minor rotamer), 23.69, 21.83 (minor rotamer), 21.79 (major rotamer). HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{35}\text{N}_2\text{O}_5$: $M^+\text{H}^+$ 472.2806, found 472.2809.

$N$-$((3S*,3aR*,6S*,7aR*)-2-(2-Methoxyphenoxy)methyl)-2-(pyridin-3-ylmethyl)hexahydro-3a,6-epoxyisoindol-6(1H-ylyl)methyl-N-methylmethanesulfonamide (13). General Method K was applied to $1$-$((3S*,3aR*,6S*,7aR*)-2-benzyl-3-(2-methoxyphenoxy)methylhexahydro-3a,6-epoxyisoindol-6(1H-ylyl))methyl$-N-methylenemanthate ($S$) (105 mg, 0.258 mmol) and methanesulfonyl chloride (24 $\mu$L, 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 $\mu$L, 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). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.54 (d, $J = 2.0$ Hz, 1H), 8.47 (dd, $J = 4.8, 1.6$ Hz, 1H), 7.65 (d, $J = 7.8, 2.0$ 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 (d, $J = 9.6, 5.5$ 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, 5H), 2.90 – 2.74 (m, 1H), 2.68 (t, $J = 7.0$ Hz, 1H), 1.98 – 1.80 (m, 2H), 1.74 – 1.56 (m, 1H), $^1$C NMR (101 MHz, CDCl$_3$) $\delta$ 150.3, 149.9, 148.5, 148.4, 148.3 (rotamer), 56.0 (minor rotamer), 55.9 (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 (major rotamer), 32.0 (minor rotamer), 28.7 (major rotamer), 28.6 (minor rotamer), 23.8 (major rotamer), 23.71 (minor rotamer), 23.69, 21.83 (minor rotamer). HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{35}\text{N}_2\text{O}_5$: $M^+\text{H}^+$ 472.2806, found 472.2809.

$N$-$((3S*,3aR*,6S*,7aR*)-2-(2-Fluorobenzyl)-3-(((6-methoxyphenoxy)methyl)hexahydro-3a,6-epoxyisoindol-6(1H-ylyl))methyl)methyl)$-N$-methylmethanesulfonamide ($S$) (105 mg, 0.258 mmol) and then the crude (165 mg, 0.53 mmol) and 2-fluorobenzaldehyde (83 $\mu$L, 0.79 mmol) were subjected to General Method D. The benzylic containing was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH with 5 % of NH$_2$OH (25 % aq) 98:2, $R_f = 0.25$) to give the title compound as a colorless oil (196 mg, 88 %). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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 (br. s, $J = 13.4$ Hz, 1H) HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{35}\text{N}_2\text{O}_5$: $M^+\text{H}^+$ 472.2806, found 472.2809.
0.90 (t, J = 7.0 Hz, 3H). 13C NMR (101 MHz, CDCl3) 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, 122.1, 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 C18H17FN2O2 [M+H]+ 482.1377, found 482.1376.

1-(((3S*,3aR*,6S*,7aR*)-2-(Fluorobenzyl))-3-((6-methylenepyridin-3-yl)oxy)methyl)hexahydro-3a,6-epoxyisoindol-6(1H)-yl)methyl)-1-methylurea (17). General Method F was applied to (17) (20 mg, 0.05 mmol) and isopropyl isocyanate (5.7 µL, 0.06 mmol) and thiophene-2-carbonyl chloride (8 µL, 0.077 mmol) to give the desired compound as an amorphous white solid (19.8 mg, 86% over three steps). 1H NMR (400 MHz, CDCl3) 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 (11H), 4.11 – 3.78 (m, 1H), 3.75 – 3.30 (m, 2H), 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, 1H), 1.86 – 1.43 (m, 7H, 0.95 (t, J = 7.5 Hz, 3H). 13C NMR (101 MHz, CDCl3) δ 161.5, 157.7, 149.5, 141.1, 137.4, 134.7, 130.1, 123.8, 122.6, 119.2, 117.0, 93.5, 90.8, 77.4, 70.5, 63.9, 58.1, 46.8, 46.4, 38.8, 38.6, 38.3, 32.7, 27.0, 18.5, 8.9 HRMS (ESI) calcd for C28H32ClIN3O3 [M+H]+ 503.1848, found 503.1845.

Tert-butyl (((2R*,3aR*,5aS*,6S*,9aS*)-2-ethyl-5-benzyl-6-hydroxy-2-vinyl-2,3a,4,5,6,7-octahydrofuro[3,2-c]indol-2-yl)methyl)carbamate (18). A stirred solution of tert-butyl (((2R*,3aR*,5aS*,6S*,9aS*)-2-ethyl-5-benzyl-6-hydroxy-2-vinyl-2,3a,4,5,6,7-octahydrofuro[3,2-c]indol-2-yl)methyl)carbamate (18) (120 mg, 0.21 mmol) was applied to column chromatography on silica gel (4:1 CHCl3/MeOH). The crude mixture was dissolved in MeOH (50 mL). A solution of HCl in MeOH (20 µL) was added. The mixture was stirred for 3 h at room temperature and the mixture was concentrated under reduced pressure and used directly in the next step without further purification.

(3-C-Cloro)-1-(((2S*,3aR*,5aS*,6S*,9aR*)-2-ethyl-6-hydroxy-5-(pyridin-3-yl)methyl)decahydrofuro[3,2-c]indol-6-yl)methyl)carbamate (19). General Method G was applied to (19) (20 mg, 61% over three steps). 1H NMR (400 MHz, CDCl3) δ 8.52 (s, 1H), 7.52 – 7.28 (m, 1H), 7.28 – 6.98 (m, 4H), 5.43 (broad s, 1H), 4.04 (dd, J = 16.1 Hz, 5.7 Hz, 1H), 4.04 (dd, J = 13.3 Hz, 1.4 Hz, 1H), 3.49 (d, J = 16.1 Hz, 1H), 3.44 (d, J = 17.0 Hz, 1H), 2.89 (t, J = 4.9 Hz, 1H), 2.02 – 1.82 (m, 1H), 1.74 (dd, J = 12.0, 8.8, 4.1 Hz, 1H), 1.67 – 1.46 (m, 4H), 1.15 (d, J = 6.2 Hz, 3H), 1.13 (d, J = 6.1 Hz, 3H). 13C NMR (101 MHz, CDCl3) δ 183.5 (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 = 13.6 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 C28H32ClIN3O3 [M+H]+ 527.1848, found 527.1849.

Tert-butyl (((2S*,3aR*,5aS*,6S*,9aR*)-2-ethyl-6-hydroxy-2-vinyl-2,3a,4,5,6,7-octahydrofuro[3,2-c]indol-2-yl)methyl)carbamate (18). A stirred solution of tert-butyl (((2S*,3aR*,5aS*,6S*,9aR*)-2-ethyl-6-hydroxy-2-vinyl-2,3a,4,5,6,7-octahydrofuro[3,2-c]indol-2-yl)methyl)carbamate (18) (120 mg, 0.21 mmol) was applied to column chromatography on silica gel (4:1 CHCl3/MeOH). The crude mixture was dissolved in MeOH (50 mL). A solution of HCl in MeOH (20 µL) was added. The mixture was stirred for 3 h at room temperature and the mixture was concentrated under reduced pressure and used directly in the next step without further purification.
1-[(tert-butyl)-6-methyl (2R*,3aR*,6R*,6aR*)-5-benzyl-6-$\alpha$-vinyl-3,4,5,6,6a-hexahydro-2'H-spiro[furo[2,3-c]pyrrole-2,3'-pyridine]-1'-6(6'H)-dicarboxylate (21). Methyl (3R*,3aR*,6R*,7aR*)-6-[(allyl[(tert-butoxycarbonyl)amino)methyl]-2-benzyl-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisooindole-3-carboxylate (7) (5.0 g, 11 mmol) was dissolved in CH$_2$Cl$_2$ (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$_2$Cl$_2$ (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 for 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$_2$Cl$_2$ (50 mL) and the layers were separated. The aqueous phase was extracted with CH$_2$Cl$_2$ (2 x 50 mL) and the combined organic layers were dried over Na$_2$SO$_4$ 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, 7H), 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 = 16.6 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); 13C NMR (101 MHz, CDCl$_3$) δ 170.9, 162.2, 137.8, 137.5, 128.2, 127.4, 127.0, 126.1, 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 (two rotamers). HRMS (ESI) calcd for C$_{28}$H$_{40}$N$_3$O$_4$ [M+H$^+$] 482.3013, found 482.3044.

Tert-butyl (2R*,3aR*,6R*,6aR*)-5-benzyl-6-$\alpha$-vinyl-3,4,5,6,6a-hexahydro-2'H-spiro[furo[2,3-c]pyrrole-2,3'-pyridine]-1'-6(6'H)-dicarboxylate (22). General Method I was applied to (2R*,3aR*,6R*,6aR*)-5-benzyl-6-$\alpha$-vinyl-3,4,5,6,6a-hexahydro-2'H-spiro[furo[2,3-c]pyrrole-2,3'-pyridine]-1'-6(6'H)-dicarboxylate (21) (1.73 g, 3.68 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 = 16.5, 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, 2H), 2.11 – 1.97 (m, 1H), 1.88 (dd, J = 13.5, 8.4 Hz, 1H), 1.76 – 1.54 (m, 4H), 1.47 (s, 9H); 13C NMR (101 MHz, CDCl$_3$) δ 169.5, 164.8, 159.3, 139.1, 132.9, 120.8 (4C), 127.2 (2C), 125.1, 114.6, 96.8, 82.5, 80.1, 72.3, 60.5, 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 C$_{29}$H$_{41}$NO$_3$ [M+H$^+$] 494.3013, found 494.3015.

Tert-butyl (2R*,3aR*,6R*,6aR*)-5-benzyl-6-(isopropylcarbomoyl)-6-$\alpha$-vinyl-3,4,5,6,6a-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 (2R*,3aR*,6R*,6aR*)-5-benzyl-6-$\alpha$-vinyl-3,4,5,6,6a-hexahydro-2'H-spiro[furo[2,3-c]pyrrole-2,3'-pyridine]-1'-6(6'H)-dicarboxylate (21) (2.166 g, 6.96 mmol). General Method J was applied to the crude carboxylic acid (1.53 g, 3.47 mmol) and i-Pr$_2$NH (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 (1.51 g, 91%). 1H NMR (400 MHz, CDCl$_3$) δ 7.39 – 7.16 (m, 5H), 6.88 – 6.49 (m, 4H), 6.03 – 5.87 (m, 1H), 5.84 – 5.66 (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); 13C 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, 123.6, 123.4, 123.3, 86.3, 85.0, 79.8, 55.9, 57.9, 51.3, 47.1, 44.2, 40.6, 37.5, 28.6 (2C), 22.9 (major rotoram, 2C). HRMS (ESI) calcd for C$_{30}$H$_{39}$N$_2$O$_4$ [M+H$^+$] 482.2988, found 482.2985.
Flash column chromatography (EtOAc:MeOH 9:2, 164 µL, 1.74 mmol). The crude mixture was purified directly using flash column chromatography (EtOAc:MeOH 9:2, Rf = 0.2) to give the title compound as a yellow solid (697 mg, 95%).

**General Method B**

Following this reaction, **General Method H** was applied to yield the title compound as a yellow solid (697 mg, 95%).

**General Method B** was applied to **General Method B** was applied to 26. **General Method A** was applied to **General Method B** was applied to give the title compound as a white foam (25 mg, 93%).

**1H NMR (400 MHz, CDCl3) δ 7.64 – 7.35 (m, 5H), 7.37 – 7.20 (m, 4H), 7.18 – 7.10 (m, 1H), 5.30 (s, 1H), 5.29 (s, 1H), 4.42 – 4.21 (m, 1H), 3.87 (dd, d = 10.7, 2.9 Hz, 1H), 2.97 (s, 1H), 2.59 – 2.27 (m, 6H), 1.97 – 1.86 (m, 1H), 1.77 – 1.70 (m, 1H), 2.26 (s, 1H). HRMS (ESI) calcd for C23H36N3O3S [M+H+] 486.2754. **General Method B** was applied to **General Method B** was applied to 27. **General Method B** was applied to **General Method B** was applied to give the title compound as a white solid (245 mg, 95%). The amine was used directly without further purification.

**General Method B** was applied to **General Method B** was applied to give the title compound as a white solid (245 mg, 95%). The amine was used directly without further purification.

**General Method B** was applied to **General Method B** was applied to give the title compound as a white solid (245 mg, 95%). The amine was used directly without further purification.

**General Method B** was applied to **General Method B** was applied to give the title compound as a white solid (245 mg, 95%). The amine was used directly without further purification.

**General Method B** was applied to **General Method B** was applied to give the title compound as a white solid (245 mg, 95%). The amine was used directly without further purification.

**General Method B** was applied to **General Method B** was applied to give the title compound as a white solid (245 mg, 95%). The amine was used directly without further purification.

**General Method B** was applied to **General Method B** was applied to give the title compound as a white solid (245 mg, 95%). The amine was used directly without further purification.
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);

13C NMR (101 MHz, CDCl3) δ 169.6, 163.3, 157.9, 149.3, 138.9, 136.9, 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) calcld for C25H37N4O3S [M+H+] = 441.2880, found 441.2889.

Tert-butyl (2S*,3aR*,6R*,6aR*)-6a-Ethyl-5-(isopropylcarbamoyl)-6-(pyrrolidine-1-carbonyl)hexahydrospiro[furo[2,3-c]pyrrole-2,3'-piperidine]-1'-carboxylate (35): General Method G was applied to tert-butyl (2S*,3aR*,6R*,6aR*)-6a-ethyl-6-(isopropylcarbamoyl)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 amine (567 mg, 1.39 mmol) and isopropyl isocyanate (145 µL, 1.47 mmol). The crude mixture was purified directly using flash column chromatography (EtOAc:MeOH 9:1, Rf = 0.2) to give the title compound as a white solid (685 mg, 95%).

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); 13C NMR (101 MHz, CDCl3) δ 170.8, 156.6, 143.7, 136.9, 127.3, 97.7, 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) calcld for C26H42N3O4S [M+H+] = 492.2867, found 492.2874.

Tert-butyl (2S*,3aR*,6R*,6aR*)-6a-Ethyl-6-(pyrrolidin-2-ylmethyl)-5-(pyridin-2-ylmethyl)-6-(pyrrolidine-1-carbonyl)hexahydrospiro[furo[2,3-c]pyrrole-2,3'-piperidine]-1'-carboxylate (36): 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 (35) (87 mg, 0.18 mmol). General Method E was applied to the resulting amine (23 mg, 0.045 mmol) and benzaldehyde (8.8 µL, 0.086 mmol). Mixing was purified directly by preparative HPLC to give a white solid (14 mg, 63%).

1H NMR (400 MHz, CDCl3) 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, 1H), 1.77 – 1.49 (m, 2H), 1.13 (t, J = 6.4 Hz, 3H), 0.87 (t, J = 7.3 Hz, 3H), 0.86 (t, J = 7.3 Hz, 3H);

13C NMR (101 MHz, CDCl3) δ 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, 46.5, 46.9, 42.6, 39.6, 26.9, 26.3, 24.3, 23.6, 23.2 (2C), 21.6, 8.9. HRMS (ESI) calcld for C26H37N4O3S [M+H+] = 483.3330, found 483.3384.

Tert-butyl (2S*,3aR*,6R*,6aR*)-6a-Ethyl-6-(isopropylcarbamoyl)-5-benzyl-6-(pyrrolidine-1-carbonyl)-3,3a,4,5,6,6a-hexahydro-2'H-spiro[furo[2,3-c]pyrrole-2,3'-piperidine]-1'-carboxylate (37) (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). Mixing was purified directly by preparative HPLC to give a white solid (13 mg, 57%).

1H NMR (400 MHz, CDCl3) 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 (s, J = 13.3 Hz, 1H), 2.41 (s, 3H), 2.15 – 1.96 (m, 1H), 1.54 – 1.38 (m, 6H), 1.22 (d, J = 6.4 Hz, 3H), 1.15 (d, J = 6.6 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H), 0.86 (t, J = 7.3 Hz, 3H), 0.86 (t, J = 7.3 Hz, 3H);

13C NMR (101 MHz, CDCl3) δ 170.8, 156.6, 143.7, 136.9.
123.9 (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) calcld for C_{30}H_{43}N_{4}O_{5}S [M+H]^{+} 547.2949, found 547.2947.

\[(2S*,3aR*,6R*,6aR*)-6a-Ethyl-5-(methylsulfonyl)hexahydrospiro[furo[2,3-c]pyrrole-2,3'-piperidine]-5(3H)-carboxamide (38). General Method F was applied to tert-butyli \[(2S*,3aR*,6R*,6aR*)-6a-ethyl-5-(isopropylcarbamoyl)hexahydrospiro[furo[2,3-c]pyrrole]-5-carboxylic acid (18 mg, 0.017 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 (13 mg, 69%). \[1^H NMR (400 MHz, CDCl3) \delta 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, 9.78 Hz, 1H), 4.45 (d, J = 12.9 Hz, 1H), 4.11 – 4.00 (m, 2H), 3.96 – 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), 0.75 – 0.39 (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, 7H, 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, CDCl3) \delta 170.5, 169.7, 136.3, 129.8, 128.7, 128.6, 126.2, 124.4, 122.7, 114.0, 96.8, 85.2, 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) calcld for C_{27}H_{38}N_{4}O_{4}S [M+H]^{+} 498.3072, found 498.3071.

\[(2S*,3aR*,6R*,6aR*)-6a-Ethyl-N-isocyanatohexahydrospiro[furo[2,3-c]pyrrole-2,3'-piperidine]-5(3H)-dicarboxamide (39). General Method G was applied to \[(2S*,3aR*,6R*,6aR*)-6a-ethyl-N-isopropylhexahydrospiro[furo[2,3-c]pyrrole-2,3'-piperidine]-6-carboxamide (30) (20 mg, 0.050 mmol) and hexyl isocyanate (8.8 µL, 0.060 mmol) to give after preparative HPLC the title compound as a white foam (18 mg, 69%). \[1^H NMR (400 MHz, CDCl3) \delta 7.46 – 7.13 (m, 3H), 7.38 – 7.23 (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 (d, J = 13.0, 3.0 Hz, 1H), 2.01 – 1.56 (m, 6H), 1.56 – 1.37 (m, 3H), 1.31 – 1.20 (m, 4H), 1.13 (d, J = 6.6 Hz, 3H, 0.75 (t, J = 7.4 Hz, 3H), 0.72 (s, 3H), 0.64 (s, 3H), 0.40 (s, 3H), 0.39 (s, 3H); \[^{13}C NMR (101 MHz, CDCl3) \delta 170.6, 169.7, 157.7, 136.3, 129.7, 128.7 (2C), 126.6 (2C), 97.5, 84.3, 81.7, 70.0, 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) calcld for C_{27}H_{40}N_{4}O_{4}S [M+H]^{+} 527.3592, found 527.3612.

\[(2S*,3aR*,6R*,6aR*)-1'-Benzyloxymethyl-5-(cyclohexylmethyl)-6a-ethyl-N-isopropylhexahydrospiro[furo[2,3-c]pyrrole-2,3'-piperidine]-6-carboxamide (40). General Method E was applied to \[(2S*,3aR*,6R*,6aR*)-1'-benzyl-6a-ethyl-N-isopropylhexahydrospiro[furo[2,3-c]pyrrole-2,3'-piperidine]-6-carboxamide (S10) (17 mg, 0.043 mmol) and cyclohexane carboxaldehyde (7.7 µL, 0.064 mmol) gave after preparative HPLC the title compound as a white foam (15 mg, 72%). \[1^H NMR (400 MHz, CDCl3) \delta 7.47 – 7.31 (m, 5H), 6.76 (s, 0.5H), 6.49 (d, J = 7.8 Hz, 1H), 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, 1H), 2.08 – 1.95 (m, 1H, 1.85 – 1.60 (m, 10H), 1.55 – 1.42 (m, 2H), 1.34 – 1.05 (m, 1H), 0.99 – 0.58 (m, 5H) (two rotamers). \[^{13}C NMR (101 MHz, CDCl3) \delta 170.5, 168.7, 163.3, 129.8, 128.7, 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) calcld for C_{38}H_{56}N_{8}O_{8}S [M+H]^{+} 699.3534, found 699.3594.
preparative HPLC the title compound as a white foam (17 mg, 68%). ^1H NMR (400 MHz, CDCl$_3$) $\delta$ 7.78 (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), 3.5 (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), 3.2 (d, $J = 12.3$ Hz, 1H), 3.10 – 2.98 (m, 1H), 2.93 (s, 3H), 2.8 (ddd, $J = 10.0, 1.3, 0.9$ Hz, 1H), 2.52 – 2.45 (m, 1H), 1.95 (s, 3H), 1.5 (d, $J = 13.5, 2.0$ Hz, 1H), 1.44 (ddd, $J = 13.9, 10.5, 6.9, 3.7$ 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, CDCl$_3$) $\delta$ 169.6, 138.6, 128.2, 126.0, 123.1, 96.6, 83.6, 79.1, 60.9, 55.2, 53.2, 45.7, 45.5, 40.8, 39.9, 37.9, 37.0, 28.5, 23.0, 22.94, 22.91, 8.3. HRMS (ESI) calcd for C$_2$H$_3$N$_2$O$_2$S$^+ [M+H]$^+$ 470.2142, found 470.2181.

(2S*,3aR*,6R*,6aR*)-6a-Ethyl-5-(1H-indole-5-carbonyl)N-isopropyl-1'-{(methylsulfonyl)hexahydropyrrole-2,3,5-piperidine}-6-carboxamide (44). Following General Method J using (2S*,3aR*,6R*,6aR*)-6a-ethyl-N-isopropyl-1'-{(methylsulfonyl)hexahydropyrrole-2,3,5-piperidine}-6-carboxamide (S11v) (24 mg, 0.064 mmol), indole-5-carboxylic acid (14 mmg, 0.064 mmol) gave after preparative HPLC the title compound as a white foam (15 mg, 74%). ^1H NMR (400 MHz, CDCl$_3$) $\delta$ 9.07 (s, 1H), 7.90 (s, 1H), 7.46 – 7.16 (m, 3H), 6.56 (dd, $J = 2.9$, 1.1 Hz, 2H), 4.87 (s, 1H), 4.31 – 4.01 (m, 2H), 3.53 (dd, $J = 11.4$, 2.6 Hz, 1H), 1.31 (m, $J = 4.8$, 9.0 Hz, 4H), 2.93 – 2.87 (m, 1H), 2.83 (s, 3H), 1.99 – 1.92 (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, CDCl$_3$) $\delta$ 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 C$_{24}$H$_{34}$N$_2$O$_4$S$^+ [M+H]$^+$ 517.2479, found 517.2476.

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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.

* Petasis/Diels-Alder

Library synthesis*
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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