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Petasis/Diels-Alder/Cyclization Cascade Reactions for the Generation of Scaffolds with Multiple Stereogenic Centers and Orthogonal Handles for Library Production

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Abstract: A new effective strategy for the synthesis of sp^3 -rich small molecules for library production is presented. The key steps to generate complexity involve Petasis 3-component reaction followed by an intramolecular Diels-Alder and cyclization to generate a densely enriched tricyclic or tetracyclic scaffolds with 3–4 stereocenters with 3 handles for decoration. The strategy was used for the production of 143 molecules for the European Lead Factory.

Introduction

The impact of small organic molecules on quality-of-life in modern society cannot be understated. In fact, most marketed drugs are small organic molecules, which in 2017 comprised 34 out of 46 new FDA approved drugs.^[1] Current libraries for high-throughput screening (HTS) are highly populated with flat aromatic scaffolds, containing a high percentage of sp^2 hybridized carbons and few stereocenters, representing the adoption of robust sp^2 - sp^2 cross-coupling reactions by the drug discovery community.^[2] Therefore, there is a need for novel 3-dimensionally complex structures, which occupy a different area of chemical space. Molecules containing a high percentage of sp^3 hybridized carbon atoms are known to have favorable drug-like properties and higher possibility of reaching the clinic.^[2b] In comparison of aliphatic and aromatic heterocycles, the former have a better pharmacokinetic profile.^[3] The synthesis of libraries containing molecules with several stereocenters and a high percentage of sp^3 carbons from readily accessible building blocks is challenging, and our group have engaged in efforts to develop novel and reliable methods for their synthesis.^[4] Some of the libraries have been included in the public compound collection (PCC) of the European Lead Factory (ELF), a private-public European partnership involving pharmaceutical companies, small and medium enterprises

(SMEs), and universities that aim the discovery of new and innovative leads for drug discovery.^[5] The PCC intends to explore an underrepresented area of chemical space by the production of three-dimensionally complex scaffolds, and so far, PCC scaffolds have a higher percentage of sp^3 hybridized carbons when compared to other commercial and corporate screening compound collections.^[6]

Herein, we present a short, efficient and versatile synthetic strategy for library production of complex tricyclic and tetracyclic scaffolds (Scheme 1). The strategy relies on the use of the Petasis 3-component reaction^[7] followed by an amide coupling and an intramolecular Diels-Alder reaction to create a core rich in sp^3 carbons and stereocenters (Scheme 1, A).^[8] Oxidative cleavage followed by aldehyde reduction generates a diol (Scheme 1, B), which can be cyclized intramolecularly to generate a pyrrolidinone ring (Scheme 1, C). The free hydroxyl can then be used either for further diversification (Scheme 1, D) or cyclized again to give a spiro azetidine ring (Scheme 1, E).

Scheme 1. A Petasis/Diels-Alder/cyclization strategy for library synthesis

Results and Discussion

The synthetic route started with a Petasis 3-component reaction^[7] between a furanyl boronic acid, allylbenzylamine and glyoxylic acid to give an amino acid intermediate. This was coupled with various amines and subjected to refluxing THF or acetonitrile to produce compounds **1a–1f** in good yields (47–67%, over three steps). The alkene was dihydroxylated using catalytic osmium and NMO as re-oxidant to generate the *syn*-diols

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2a, **2c** and **2d** in good to excellent yields (73–92%). The diol was oxidatively cleaved using NaIO_4 followed by reduction of the formed dialdehyde, to afford the diol in good yields for cyclohexyl and butyl (**3a** and **3c**), and a moderate yield for the cyclopropyl analogue (**3d**). The oxidation, oxidative cleavage and reduction could also be achieved in a 3-step fashion, which was performed for alkenes **1b**, **1e** and **1f**, which gave the diols **3b**, **3e** and **3f** in moderate to good yields (44–70% over three steps).

Scheme 2. Petasis/Acylation/Diels-Alder followed by oxidative cleavage and aldehyde reduction generating **3a–3f**.

After establishing an efficient protocol for the synthesis of the diols, we set out to investigate the ring closure-substitution sequence. Initially, reductive cyclization of the dialdehyde intermediate was attempted but only led to complex reaction mixtures without formation of the desired compounds. Thus, it was decided to start from the diol instead. The first attempt was to investigate Mitsunobu-chemistry as the cyclization strategy, which generally only gave trace amounts of product and many side products. Ultimately, we investigated turning the two alcohols into leaving groups. While conversion to a dichloride gave several by-products, it was found out that dimesylation was a good starting point for cyclization processes. The dimesylate **4a** (Scheme 3) was obtained in quantitative yield from the diol, and by subsequent treatment with NaH , the cyclized compound **5a** could be isolated in excellent yields (94%, over two steps), having a mesylate-group ready for functionalization. In case of compound **3f**, mesylation of the diol followed by deprotection of the amine and treatment with NaH , led to the synthesis of the desired product in 35 % yield. We then explored the scope of mesylate substitution by allowing compound **5a** to react with

different *O* and *N* nucleophiles (Scheme 3). The mesylate could be substituted with pyrrolidine (**6a**), phenol (**7a**) and phthalimide (**8a**) in 53% to 71% yields (Scheme 3).

Scheme 3. Cyclization of **3a** and **3f**

For library production of the tricyclic scaffold, we decided to focus on the phenol and phthalimide, the latter providing further access to two orthogonal vectors by either functionalization of the pyrrolidine nitrogen obtained from benzyl deprotection, or the primary nitrogen resulting from phthalimide deprotection. To investigate the best conditions for library production, a subset of compounds with different substituents (Scheme 4, **7b–7e**, **8b** and **8c**) were synthesized in moderate to good yields (28–82%). Cyclopropyl derivative (**7d**) did not give good yields in the early steps, and as a result it was not carried forward for library production.

Scheme 4. Cyclization and functionalization of **3b–3e**

The benzyl group was removed either by 1-chloroethyl chloroformate or hydrogenation with $\text{Pd}(\text{OH})_2/\text{C}$, and the

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resulting product used directly in the next step. The pyrrolidine amine reacted with isocyanates, sulfonyl chlorides, acyl chlorides and aldehydes/ $\text{NaBH}(\text{OAc})_3$ to provide a small library of compounds with different functionalities (Scheme 5). To demonstrate the orthogonality

of the two nitrogen protecting groups, **8c** was *N*-debenzylated and the respective amine functionalized with 3-chlorophenyl isocyanate and 4-toluenesulfonyl chloride to give **11d** and **12e** (Scheme 5), respectively.

Scheme 5. Production of the first library

The second library was generated from the removal of the phthalimide with hydrazine to give a primary amine, which was used directly in library production. It was decorated with ureas, sulfonamides, amides and two methyl groups by

reaction with isocyanates, sulfonyl chlorides, acyl chlorides and formaldehyde/ $\text{NaBH}(\text{OAc})_3$, respectively (Scheme 6).

Scheme 6. Production of the second library

The optimized conditions were used to synthesize a library for HTS. Considering the low molecular weight of the core

scaffold (180 for the tricyclic scaffold) and low clog P, it allowed the synthesis of a library of 143 compounds with a

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molecular weight between 325 and 525, an F_{sp}^3 between 0.28 and 0.67, and clog P below 5. The properties of the 143 compounds are shown in Figure 1.

Figure 1. Physicochemical properties of the library compounds

Conclusions

In conclusion, a robust method for the synthesis of highly complex tricyclic and tetracyclic scaffolds with high F_{sp}^3 and several stereocenters using cheap and readily available starting materials was developed. A library of 143 compounds was produced and will be used for HTS in the ELF.

Experimental Section

Representative procedure for the Petasis 3-component reaction, amide coupling and Diels-Alder sequence. (3*R*,3*aR*,6*R*,7*aR*)-2-benzyl-*N*-cyclohexyl-1,2,3,6,7,7*a*-hexahydro-3*a*,6-epoxyisoindole-3-carboxamide (1*a*). *N*-Allylbenzyl amine (3.70 g, 25.1 mmol) and glyoxylic acid monohydrate (3.47 g, 37.7 mmol) were dissolved in CH_2Cl_2 (25 mL, 1 M) and the mixture was cooled to 0 °C. To the mixture was added 2-furanylboronic acid (4.22 g, 37.7 mmol) portion wise and the mixture was stirred 10 min at 0 °C and 50 min at rt. Then CH_2Cl_2 (50 mL) and H_2O (75 mL) was added and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic layers were dried over Na_2SO_4 and stripped down to 50 mL. To the solution was added DIPEA (6.55 mL, 37.7 mmol) and TBTU (8.87 g, 27.6 mmol), and the mixture was stirred for 5 min and cooled to 0 °C. To the solution was slowly added cyclohexyl amine (2.9 mL, 30.1 mmol) and the mixture stirred 10 min at rt. Then, sat. aq. NaHCO_3 (50 mL) was added and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was filtered through a silica plug (EtOAc:heptane 4:1, R_f = 0.2). The residue was taken up in THF (50 mL, 0.5 M) and stirred overnight at reflux where after it was concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc:heptane 1:1, R_f =

0.2) to give the title compound as a white solid (5.96 g, 67%). ^1H NMR (400 MHz, CDCl_3) δ 7.57 (d, J = 8.3 Hz, 1H), 7.32 – 7.14 (m, 5H), 6.22 (dd, J = 5.9, 1.5 Hz, 1H), 6.17 (d, J = 5.9 Hz, 1H), 4.95 (dd, J = 4.3, 1.4 Hz, 1H), 3.81 (d, J = 12.7 Hz, 1H), 3.78 – 3.68 (m, 1H), 3.53 (d, J = 12.7 Hz, 1H), 3.44 (s, 1H), 3.16 (dd, J = 8.3, 7.0 Hz, 1H), 2.21 (dd, J = 10.3, 8.9 Hz, 1H), 1.89 – 1.73 (m, 3H), 1.69 – 1.50 (m, 4H), 1.39 – 1.02 (m, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ 169.5, 138.4, 135.7, 134.7, 129.0 (2C), 128.7 (2C), 127.6, 98.2, 80.1, 69.4, 59.8, 58.3, 47.5, 42.3, 33.7, 33.1, 29.7, 25.7, 24.9, 24.8. HRMS (ESI) m/z : $[\text{M}+\text{H}^+]$ Calcd for $\text{C}_{22}\text{H}_{29}\text{N}_2\text{O}_2$ 353.2224; Found 353.2223.

Representative procedure for the dihydroxylation. (±) (3*R*,3*aR*,4*R*,5*S*,6*R*,7*aR*)-2-benzyl-*N*-cyclohexyl-4,5-dihydroxyoctahydro-3*a*,6-epoxyisoindole-3-carboxamide (2*a*). Compound 1*a* (5.26 g, 14.9 mmol) was dissolved in acetone (50 mL, 0.3 M) and added *N*-methyl-morpholin-*N*-oxide (2.27 g, 19.4 mmol). 0.9% $\text{K}_2\text{OsO}_4 \cdot 2\text{H}_2\text{O}$ (50 mg, 0.14 mmol) in H_2O (5 mL) was added and stirred overnight at rt. Then H_2O (50 mL) was added and the mixture was filtered. The filter cake was washed with H_2O and heptane and then dried *in vacuo* to give the title compound as a white solid (5.06 g, 88%). ^1H NMR (400 MHz, CDCl_3) δ 8.08 (d, J = 7.1 Hz, 1H), 7.32 – 7.10 (m, 5H), 6.56 (s, 1H), 4.35 (d, J = 4.4 Hz, 1H), 3.91 (d, J = 5.6 Hz, 1H), 3.83 – 3.71 (m, 4H), 3.65 (d, J = 11.8 Hz, 2H), 3.18 (t, J = 8.1 Hz, 1H), 2.31 (t, J = 9.2 Hz, 1H), 2.00 (d, J = 7.4 Hz, 1H), 1.90 – 1.37 (m, 7H), 1.36 – 1.22 (m, 2H), 1.20 – 0.98 (m, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 171.4, 138.0, 128.93 (2C), 128.84 (2C), 127.8, 97.3, 84.4, 75.3, 71.3, 68.6, 60.8, 59.7, 48.2, 42.1, 33.0, 32.5, 31.0, 25.5, 24.72, 24.69. HRMS (ESI) m/z $[\text{M}+\text{H}^+]$ Calcd for $\text{C}_{22}\text{H}_{31}\text{N}_2\text{O}_4$ 387.2278; Found 387.2304.

Representative procedure for the oxidative cleavage and aldehyde reduction. (±) (2*R*,3*aR*,6*R*,6*aR*)-5-benzyl-*N*-cyclohexyl-2,6a-bis(hydroxymethyl)hexahydro-2*H*-furo[2,3-*c*]pyrrole-6-carboxamide (3*a*). Compound 2*a* (3.59 g, 9.29 mmol) was dispersed in MeOH: H_2O (9:1, 30 mL), added NaIO_4 (2.98 g, 13.9 mmol) and the mixture was stirred at rt. After 1 h, water (50 mL) and CH_2Cl_2 (50 mL) were added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic layers were concentrated *in vacuo*. The residue was dissolved in MeOH (30 mL), cooled to 0 °C and then added NaBH_4 (850 mg, 20.4 mmol) portion wise. After stirring for 30 min at 0 °C the mixture was concentrated *in vacuo*. The residue was taken in CH_2Cl_2 (50 mL) and sat. aq. NaHCO_3 (50 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 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:MeOH 19:1, R_f = 0.2) to give the title compound as a white solid (3.36 g, 93%). ^1H NMR (400 MHz, DMSO) δ 7.57 (d, J = 8.4 Hz, 1H), 7.38 – 7.22 (m, 5H), 4.64 (dd, J = 6.2, 4.9 Hz, 1H), 4.39 (dd, J = 7.4, 4.8 Hz, 1H), 4.07 (td, J = 8.8, 4.1 Hz, 1H), 3.71 (d, J = 12.9 Hz, 1H), 3.66 – 3.58 (m, 1H), 3.55 (dt, J = 11.3, 4.1 Hz, 1H), 3.47 – 3.34 (m, 3H), 3.24 (d, J = 12.9 Hz, 1H), 3.06 (t, J = 8.6 Hz, 1H), 3.00 (s, 1H), 2.61 (q, J = 8.2 Hz, 1H), 2.07 (t, J = 8.8 Hz, 1H), 1.78 – 1.61 (m, 5H), 1.60 – 1.45 (m, 2H), 1.32 – 1.18 (m, 4H), 1.21 – 1.03 (m, 1H); ^{13}C NMR (101 MHz, DMSO) δ 168.2, 138.0, 128.7 (2C), 128.2 (2C), 127.0, 94.6, 79.3, 76.4, 63.5, 62.6, 57.3, 57.1, 47.2, 43.7, 33.0, 32.23, 32.18, 25.1, 24.7, 24.6. HRMS (ESI) m/z $[\text{M}+\text{H}^+]$ Calcd for $\text{C}_{22}\text{H}_{33}\text{N}_2\text{O}_4$ 389.2440; Found 389.2448.

(±) ((2*R*,3*aR*,6*R*,6*aR*)-5-benzyl-6-(cyclohexylcarbamoyl)hexahydro-6*aH*-furo[2,3-*c*]pyrrole-2,6a-diyl)bis(methylene) dimethanesulfonate (4*a*). Compound 3*a* (2.17 g, 5.62 mmol) was dissolved in CH_2Cl_2 (28 mL), added Et_3N (2.36 mL, 18.9 mmol) and cooled to 0 °C. Then MsCl (1.37 mL, 11.2 mmol) was added slowly. After 10 min, water (50 mL) and CH_2Cl_2 (25 mL) was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. To the residue was added heptane and the mixture was filtered to provide the title compound

as a white solid (3.02 g, 99%). ¹H NMR (400 MHz, CDCl₃) δ 7.40 – 7.22 (m, 5H), 6.93 (s, 1H), 4.46 (s, 1H), 4.37 – 4.24 (m, 3H), 4.21 (d, *J* = 10.5 Hz, 1H), 3.93 (d, *J* = 12.9 Hz, 1H), 3.87 – 3.75 (m, 1H), 3.41 – 3.10 (m, 3H), 3.08 (s, 3H), 3.03 (s, 3H), 2.84 (dd, *J* = 15.5, 8.5 Hz, 1H), 2.22 (s, 1H), 2.00 – 1.83 (m, 3H), 1.81 – 1.67 (m, 3H), 1.66 – 1.56 (m, 1H), 1.46 – 1.30 (m, 2H), 1.28 – 1.11 (m, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 167.5, 136.9, 128.9 (2C), 128.8 (2C), 128.0, 93.1, 77.1, 70.9, 70.2, 58.7, 56.9, 48.1, 46.1, 44.7, 37.7, 37.5, 33.1, 32.2, 25.5, 24.9, 24.9, 8.7. HRMS (ESI) *m/z* [M+H]⁺ Calcd for C₂₄H₃₇N₂O₈S₂ 545.1986; Found 545.1998.

(±) ((2*R*,3*AR*,5*A**R*,8*A**S*)-5-benzyl-7-cyclohexyl-6-oxooctahydro-2*H*-furo[2,3-*c*]pyrrolo[3,4-*b*]pyrrol-2-yl)methyl methanesulfonate (5a).** Compound **3a** (568 mg, 1.46 mmol) was dissolved in dry THF (5 mL), added Et₃N (630 μL, 4.39 mmol) and cooled to 0 °C. Then MsCl (250 μL, 3.22 mmol) was added. After stirring for 15 min, 55% NaH in mineral oil (255 mg, 8.77 mmol) was added and the mixture was stirred 2 h at 60 °C. The mixture was then cooled to rt and added H₂O (50 mL) and sat. aq. NaHCO₃ (10 mL), followed by CH₂Cl₂ (50 mL). The layers were separated and the aqueous phase was extracted with CH₂Cl₂ (2 x 25 mL) and the combined organic layers were concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc:heptane 3:2, *R_f* = 0.2) to give the title compound as a white solid (618 mg, 94%). ¹H NMR (400 MHz, CDCl₃) δ 7.35 (d, *J* = 7.1 Hz, 2H), 7.33 – 7.27 (m, 2H), 7.23 (t, *J* = 7.1 Hz, 1H), 4.51 – 4.38 (m, 1H), 4.34 (dd, *J* = 11.1, 2.9 Hz, 1H), 4.17 (dd, *J* = 11.1, 5.7 Hz, 1H), 4.10 (d, *J* = 6.2 Hz, 1H), 4.03 – 3.94 (m, 1H), 3.51 – 3.41 (m, 3H), 3.05 (s, 3H), 2.84 (dd, *J* = 9.2, 6.8 Hz, 1H), 2.67 – 2.59 (m, 1H), 2.55 (dd, *J* = 9.3, 4.2 Hz, 1H), 2.04 – 1.91 (m, 1H), 1.88 – 1.76 (m, 3H), 1.78 – 1.59 (m, 3H), 1.44 – 1.22 (m, 5H), 1.15 – 1.02 (m, 1H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 169.7, 138.8, 128.5 (2C), 128.2 (2C), 126.8, 92.3, 77.0, 71.0, 71.0, 57.7, 55.3, 51.2, 49.7, 47.6, 36.7, 33.0, 29.5, 29.4, 25.1, 25.0, 24.9. HRMS (ESI) *m/z* [M+H]⁺ Calcd for C₂₃H₃₃N₂O₅S 449.2105; found 449.2157.

(±) (2*R*,3*AR*,5*A**R*,8*A**S*)-5-benzyl-7-cyclohexyl-2-(pyrrolidin-1-ylmethyl)octahydro-6*H*-furo[2,3-*c*]pyrrolo[3,4-*b*]pyrrol-6-one (6a).** Compound **4a** (345 mg, 0.633 mmol) was dissolved in dry THF (4 mL), cooled to 0 °C and added 55% NaH (83 mg, 1.90 mmol) and the mixture was stirred 10 min. Then the reaction mixture was stirred at reflux for 30 min, whereupon NaI (190 mg, 1.27 mmol) and pyrrolidine (0.211 mL, 1.27 mmol) was added and the mixture was stirred at reflux for another 6 h. The reaction was then cooled to 0 °C and water (40 mL) was added followed by CH₂Cl₂ (50 mL). The layers were separated and the aqueous phase was extracted with CH₂Cl₂ (2 x 50 mL) and the combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography (MeOH:CH₂Cl₂ 1:9, *R_f* = 0.2) to give the title compound as an amorphous yellow solid (189 mg, 71%). ¹H NMR (400 MHz, CDCl₃) δ 7.34 (d, *J* = 7.1 Hz, 2H), 7.31 – 7.24 (m, 2H), 7.20 (t, *J* = 7.1 Hz, 1H), 4.48 – 4.30 (m, 1H), 4.16 (d, *J* = 13.3 Hz, 1H), 4.03 – 3.91 (m, 2H), 3.52 – 3.41 (m, 2H), 3.35 (s, 1H), 2.90 – 2.78 (m, 6H), 2.72 (dd, *J* = 12.9, 7.8 Hz, 1H), 2.57 – 2.51 (m, 1H), 2.46 (dd, *J* = 9.3, 5.1 Hz, 1H), 1.96 – 1.84 (m, 3H), 1.83 – 1.62 (m, 8H), 1.43 – 1.22 (m, 4H), 1.16 – 0.97 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 170.9, 139.1, 128.9 (2C), 128.3 (2C), 126.9, 92.6, 77.4, 71.8, 59.7, 58.2, 56.0, 54.6 (2C), 51.9, 50.2, 48.6, 37.0, 30.3, 30.2, 25.51, 25.49, 25.4, 23.4 (2C). HRMS (ESI) *m/z* [M+H]⁺ Calcd for C₂₆H₃₈N₃O₂ 424.2959; Found 424.2974.

(±) (3*AR*,5*A**R*,8*A**S*)-5'-benzyl-7'-cyclohexyl-1-methylhexahydrospiro[azetidine-3,2'-furo[2,3-*c*]pyrrolo[3,4-*b*]pyrrol]-6'(3'*H*)-one (9a).** Compound **3f** (100 mg/0.19 mmol) was dissolved in CH₂Cl₂ (2 mL, 0.1 M), added Et₃N (79 μL, 0.56 mmol) and cooled to 0 °C. Then MsCl (33.4 μL, 0.56 mmol) was added slowly. After 10 min, water (50 mL) and CH₂Cl₂ (25 mL) were 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 Na₂SO₄ and concentrated *in vacuo*. The crude was dissolved in 30% of TFA in DCM (2 mL) and stirred at room

temperature for 2 h. A sat aq NaHCO₃ was added slowly until neutralization of the acid and the aqueous phase extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude was solubilized in dry THF (10 mL) and 55 % NaH (25 mg/0.56 mmol) was added slowly. The mixture was stirred at reflux for 2 hours. Then, it was cooled to room temperature and NaI (56 mg, 0.38 mmol) and dry DMF (2 mL) were added and stirred for 4 hours. 50 mL of water were added to the reaction and extracted with ethyl acetate (3 x 50 mL). The combined organic phases were washed with brine (2 x 50 mL), dried over Na₂SO₄, filtered and concentrated. The crude was purified by silica gel flash chromatography (MeOH (5% NH₄OH (30% aq)):CH₂Cl₂, 96:4, *R_f* = 0.3) to give the title compound as a light yellow oil (26 mg/35 %). ¹H NMR (400 MHz, CDCl₃) δ 7.37 – 7.32 (m, 2H), 7.32 – 7.26 (m, 2H), 7.25 – 7.17 (m, 1H), 4.15 (d, *J* = 13.2 Hz, 1H), 4.03 (d, *J* = 13.2 Hz, 1H), 4.01 – 3.93 (m, 1H), 3.52–3.49 (m, 1H), 3.46 – 3.39 (m, 3H), 3.35 (d, *J* = 10.1 Hz, 1H), 3.15–3.10 (m, 2H), 2.75 (dd, *J* = 9.7, 7.1 Hz, 1H), 2.61 – 2.51 (m, 2H), 2.36 (s, 3H), 2.28 (dd, *J* = 12.9, 9.4 Hz, 1H), 2.13 (dd, *J* = 12.9, 3.3 Hz, 1H), 1.84 – 1.61 (m, 5H), 1.45 – 1.21 (m, 4H), 1.09–1.04 (m, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 170.5, 139.1, 129.1 (2C), 128.2 (2C), 127.0, 92.2, 80.1, 70.9, 69.8, 67.7, 57.7, 55.1, 51.6, 50.2, 49.6, 46.1, 42.3, 30.4, 30.2, 25.53, 25.50, 25.47. HRMS (ESI) *m/z* [M+H]⁺ Calcd for C₂₄H₃₄N₃O₂ 396.2646; Found 393.2656.

Representative procedure for substitution with phenols. (±) ((2*R*,3*AR*,5*A**R*,8*A**S*)-5-benzyl-7-butyl-2-(3-fluorophenoxy)methyl)octahydro-6*H*-furo[2,3-*c*]pyrrolo[3,4-*b*]pyrrol-6-one (7c).** Compound **3c** (353 mg, 0.97 mmol) was dissolved in THF (10 mL), added Et₃N (0.407 mL, 2.92 mmol) and cooled to 0 °C. Then MsCl (0.196 mL, 2.4 mmol) was added slowly. After 10 min, water (10 mL) and CH₂Cl₂ (10 mL) were added and the layers separated. The aqueous phase was extracted with CH₂Cl₂ (2 x 10 mL) and the combined organic layers were dried using Na₂SO₄ and concentrated *in vacuo*. The crude was dissolved in dry THF (5 mL), cooled to 0 °C and added 55% NaH (255 mg, 5.85 mmol) and stirred 10 min. Then, the reaction mixture was stirred at 60 °C for 1 h. The reaction was cooled to room temperature and quenched with water (5 mL) and extracted with DCM (3 x 5 mL). The combined organic layers were dried using Na₂SO₄ and concentrated *in vacuo*. The residue was taken up in DMF (5 mL) and Cs₂CO₃ (952 mg, 2.92 mmol) and 3-fluorophenol (0.26 mL, 2.92 mmol) were added and heated at 90 °C for 1 h. The reaction was cooled to room temperature and water (20 mL) and EtOAc (20 mL) were added and the layers separated. The aqueous phase was extracted with EtOAc (2 x 20 mL) and the combined organic layers were washed with NaOH 1M (2 x 20 mL), brine (2 x 20 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by semi-automated flash chromatography (Puriflash @ 25g, EtOAc in heptane (5 to 45%); EtOAc:heptane 1:1, *R_f* = 0.45) to give the compound as a viscous oil that solidifies upon standing (179 mg, 42%). ¹H NMR (400 MHz, CDCl₃) δ 7.45 (d, *J* = 7.2 Hz, 2H), 7.38 (t, *J* = 7.2 Hz, 2H), 7.34 – 7.24 (m, 2H), 6.80 – 6.68 (m, 3H), 4.65 – 4.52 (m, 1H), 4.28 (d, *J* = 13.4 Hz, 1H), 4.12 – 4.07 (m, 2H), 4.03 (dd, *J* = 10.0, 5.6 Hz, 1H), 3.64 (d, *J* = 10.4 Hz, 1H), 3.57 (d, *J* = 10.4 Hz, 1H), 3.53 (s, 1H), 3.45 – 3.29 (m, 2H), 2.98 (dd, *J* = 9.3, 7.0 Hz, 1H), 2.84 – 2.68 (m, 1H), 2.59 (dd, *J* = 9.4, 5.1 Hz, 1H), 2.07 (dt, *J* = 12.5, 9.1 Hz, 1H), 1.96 (ddd, *J* = 12.5, 6.0, 2.2 Hz, 1H), 1.66 – 1.51 (m, 2H), 1.49 – 1.35 (m, 2H), 1.01 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 171.3, 163.6 (d, *J*_{CF} = 245.3 Hz), 160.1 (d, *J*_{CF} = 10.8 Hz), 138.9, 130.3 (d, *J*_{CF} = 10.0 Hz), 128.9 (2C), 128.2 (2C), 126.9, 110.4 (d, *J*_{CF} = 2.8 Hz), 107.9 (d, *J*_{CF} = 21.3 Hz), 102.4 (d, *J*_{CF} = 24.9 Hz), 92.7, 78.2, 71.4, 70.2, 58.1, 56.0, 55.9, 49.0, 41.8, 34.5, 29.1, 20.0, 13.9. HRMS (ESI) *m/z* [M+H]⁺ Calcd for C₂₆H₃₂FN₂O₄ 437.2391; Found 437.2409.

Representative procedure for the substitution with phthalimide. (±) (((2*R*,3*AR*,5*A**R*,8*A**S*)-5-benzyl-7-butyl-6-oxooctahydro-2*H*-furo[2,3-*c*]pyrrolo[3,4-*b*]pyrrol-2-yl)methyl)isoindoline-1,3-dione (8b).** Compound **3c** (306 mg, 0.84 mmol) was dissolved in THF (8 mL), added Et₃N (0.351 mL, 2.5 mmol) and cooled to 0 °C. Then MsCl (0.164 mL, 2.12 mmol) was added slowly. After 10 min, water (10 mL) and CH₂Cl₂ (10 mL)

was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2×10 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude was dissolved in dry THF (8 mL), cooled to 0°C , added 55% NaH (220 mg, 5 mmol) and stirred 10 min. Then, the reaction mixture was stirred at 60°C for 1 h. The reaction was cooled to room temperature and quenched with water (10 mL) and extracted with DCM (3×10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was taken up in DMF (5 mL) and potassium phthalimide (233 mg, 1.26 mmol) was added and heated at 90°C for 16 h. The reaction was cooled to room temperature and water (10 mL) and CH_2Cl_2 were added and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (2×10 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, $R_f = 0.1$) to give the title compound as a white solid (192 mg, 48%). ^1H NMR (400 MHz, CDCl_3) δ 7.86 (dd, $J = 5.5, 3.0$ Hz, 2H), 7.73 (dd, $J = 5.5, 3.0$ Hz, 2H), 7.36 – 7.29 (m, 2H), 7.29 – 7.25 (m, 2H), 7.24 – 7.17 (m, 1H), 4.48 (tt, $J = 12.1, 6.0$ Hz, 1H), 4.16 (d, $J = 13.4$ Hz, 1H), 3.94 (d, $J = 13.4$ Hz, 1H), 3.84 (dd, $J = 13.9, 7.4$ Hz, 1H), 3.73 (dd, $J = 13.9, 4.7$ Hz, 1H), 3.54 (d, $J = 10.5$ Hz, 1H), 3.48 (d, $J = 10.5$ Hz, 1H), 3.33 (s, 1H), 3.28 (td, $J = 7.1, 1.5$ Hz, 2H), 2.84 (dd, $J = 9.3, 6.9$ Hz, 1H), 2.63 (dq, $J = 7.0, 4.7$ Hz, 1H), 2.45 (dd, $J = 9.4, 5.0$ Hz, 1H), 1.96 – 1.81 (m, 2H), 1.56 – 1.44 (m, 2H), 1.37 – 1.26 (m, 2H), 0.93 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 171.4, 168.4 (2C), 139.1, 134.2 (2C), 132.1 (2C), 128.9 (2C), 128.3 (2C), 127.0, 123.5 (2C), 92.4, 77.3, 71.4, 57.8, 56.3, 56.0, 49.1, 42.0, 41.9, 36.0, 29.2, 20.1, 13.9. HRMS (ESI) m/z [M+H] $^+$ Calcd for $\text{C}_{28}\text{H}_{32}\text{N}_3\text{O}_4$ 474.2387; Found 474.2368.

Representative procedures for the *N*-benzyl deprotection. ($\pm$) (2*R*,3*aR*,5*aR*,8*aS*)-7-(phenoxymethyl)octahydro-6*H*-furo[2,3-*c*]pyrrolo[3,4-*b*]pyrrol-6-one (10*a*). **Deprotection with 1-chloroethyl chloroformate.** Compound **7a** (160 mg, 0.36 mmol) was taken in dry dichloromethane (10 mL), placed under nitrogen at 0°C and 1-chloroethyl chloroformate was added dropwise (58 μL , 0.54 mmol). The reaction was heated at reflux until no starting material was present. The solvent was evaporated under reduced pressure and the crude taken up in methanol where it was stirred for 30 min under reflux. The solvent was evaporated and the solid obtained was triturated with diethyl ether. The solid was washed twice with diethyl ether to give the compound as a white solid (141 mg/quant). The crude was used directly in the next step without further purification. ($\pm$) (2*R*,3*aR*,5*aR*,8*aS*)-7-(2-methoxyethyl)-2-(phenoxymethyl)octahydro-6*H*-furo[2,3-*c*]pyrrolo[3,4-*b*]pyrrol-6-one (10*b*). **Deprotection by hydrogenation.** Compound **7b** (75 mg, 0.178 mmol) was dissolved in MeOH (5 mL) and 20 % Pd(OH) $_2$ /C (24 mg) and HCOONH_4 (112 mg, 1.78 mmol) was added and the mixture was stirred for 24 h at reflux. The mixture was then filtered over a pad of celite and washed with ethyl acetate and CH_2Cl_2 . The solvent was evaporated to give the title compound as a yellow oil (59 mg/quant). The crude was used directly in the next step without further purification.

Representative procedure for the urea formation using isocyanates. ($\pm$) (2*R*,3*aR*,5*aR*,8*aS*)-7-cyclohexyl-6-oxo-2-(phenoxymethyl)-*N*-(*o*-tolyl)octahydro-5*H*-furo[2,3-*c*]pyrrolo[3,4-*b*]pyrrole-5-carboxamide (11*a*). Amine salt **10a** (20 mg, 0.051 mmol) was taken in DMF (1 mL), DIPEA (21 μL , 0.122 mmol) and *o*-tolyl isocyanate (10 μL , 0.061 mmol) was added and the mixture was stirred 1 h at rt. The compound was then purified directly by preparative HPLC to give the title compound as a white powder (13 mg, 53%). ^1H NMR (400 MHz, CDCl_3) δ 9.10 (s, 1H), 7.70 (d, $J = 8.0$ Hz, 1H), 7.31 (dd, $J = 8.6, 7.4$ Hz, 2H), 7.20 – 7.12 (m, 2H), 7.03 – 6.89 (m, 4H), 4.75 – 4.62 (m, 1H), 4.50 (s, 1H), 4.15 (dd, $J = 10.3, 3.0$ Hz, 1H), 4.05 – 3.99 (m, 1H), 3.97 (dd, $J = 10.3, 4.5$ Hz, 1H), 3.81 (dd, $J = 11.2, 8.5$ Hz, 1H), 3.61 (dd, $J = 11.2, 8.9$ Hz, 1H), 3.50 (d, $J = 10.6$ Hz, 1H), 3.43 (d, $J = 10.6$ Hz, 1H), 2.83 (q, $J = 7.5$ Hz, 1H), 2.35 (s, 3H), 2.23 (ddd, $J = 13.1, 9.2, 7.0$ Hz, 1H), 2.12 (ddd, $J = 13.1, 6.3, 1.3$ Hz, 1H), 1.90 – 1.63 (m, 5H), 1.49 – 1.27 (m, 4H), 1.20 – 1.02 (m, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 171.0, 162.2, 158.7, 156.5, 137.7, 130.4, 129.7, 128.8,

126.4, 123.4, 122.3, 121.4, 114.6, 93.3, 78.6, 69.6, 68.0, 51.9, 51.6, 51.0, 47.7, 31.0, 30.3, 30.0, 25.42, 25.35, 25.28, 18.6. HRMS (ESI) m/z [M+H] $^+$ Calcd for $\text{C}_{29}\text{H}_{36}\text{N}_3\text{O}_4$ 490.2700; Found 490.2669.

Representative procedure for acylation using acyl chlorides. ($\pm$) (2*R*,3*aR*,5*aR*,8*aS*)-7-(2-methoxyethyl)-2-(phenoxymethyl)-5-(thiophene-2-carbonyl)octahydro-6*H*-furo[2,3-*c*]pyrrolo[3,4-*b*]pyrrol-6-one (13*a*). Amine salt **10b** (20 mg, 0.06 mmol) was taken up in DMF (1 mL), DIPEA (16 μL , 0.09 mmol) was added followed by 2-thiophenecarbonyl chloride (9.6 μL , 0.09 mmol) and the mixture was stirred 1 h at rt. The compound was then purified directly by preparative HPLC to give the title compound as a white amorphous solid (7 mg, 26%). ^1H NMR (400 MHz, CDCl_3) δ 8.13 (broad s, 1H), 7.52 (dd, $J = 5.0, 1.0$ Hz, 1H), 7.37 – 7.31 (m, 2H), 7.08 (dd, $J = 5.0, 3.8$ Hz, 1H), 7.00 (tt, $J = 7.5, 1.0$ Hz, 1H), 6.97 – 6.90 (m, 2H), 4.99 (s, 1H), 4.49 (tq, $J = 8.0, 4.7, 4.0$ Hz, 1H), 4.36 (d, $J = 13.0$ Hz, 1H), 4.06 (dd, $J = 10.1, 3.2$ Hz, 1H), 3.95 (dd, $J = 10.1, 4.8$ Hz, 1H), 3.78 (d, $J = 10.5$ Hz, 1H), 3.74 – 3.48 (m, 6H), 3.38 (s, 3H), 2.96 (tq, $J = 8.8, 4.0$ Hz, 1H), 2.29 (dt, $J = 12.9, 8.3$ Hz, 1H), 2.12 (broad s, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 169.4, 163.8, 158.5, 137.9, 130.9, 130.0, 129.5 (2C), 127.3, 121.2, 114.5 (2C), 93.7, 79.1, 70.4, 69.8, 68.8, 58.8, 55.4, 51.2, 47.5, 42.8, 34.9. HRMS (ESI) m/z [M+H] $^+$ Calcd for $\text{C}_{23}\text{H}_{27}\text{N}_2\text{O}_5\text{S}$ 443.1635; Found 443.1652.

Representative procedure for reductive alkylation using aldehydes. ($\pm$) (2*R*,3*aR*,5*aR*,8*aS*)-7-cyclohexyl-5-(5-methylthiophen-2-yl)methyl)-2-(phenoxymethyl)octahydro-6*H*-furo[2,3-*c*]pyrrolo[3,4-*b*]pyrrol-6-one (14*a*). Amine salt **10a** (18 mg, 0.046 mmol) was taken up in DMF (1 mL) and DIPEA (9 μL , 0.069 mmol), 5-methylthiophene-2-carbaldehyde (9 mg, 0.069 mmol), and $\text{NaBH}(\text{OAc})_3$ (15 mg, 0.069 mmol) was added and the mixture was stirred for 16 h at rt. The compound was then purified directly by preparative HPLC to give a white powder (12 mg, 54%). ^1H NMR (400 MHz, CDCl_3) δ 7.29 (dd, $J = 8.7, 7.4$ Hz, 2H), 6.96 (t, $J = 7.4$ Hz, 1H), 6.94 – 6.89 (m, 2H), 6.74 (d, $J = 3.1$ Hz, 1H), 6.56 (dd, $J = 3.1, 1.0$ Hz, 1H), 4.61 – 4.48 (m, 1H), 4.31 (d, $J = 14.2$ Hz, 1H), 4.20 (d, $J = 14.2$ Hz, 1H), 4.04 (dd, $J = 10.1, 3.5$ Hz, 1H), 4.00 – 3.94 (m, 2H), 3.57 (s, 1H), 3.52 (d, $J = 10.3$ Hz, 1H), 3.48 (d, $J = 10.3$ Hz, 1H), 2.95 – 2.80 (m, 1H), 2.71 (dd, $J = 9.3, 4.1$ Hz, 1H), 2.70 – 2.61 (m, 1H), 2.44 (s, 3H), 2.10 – 1.99 (m, 1H), 1.95 (ddd, $J = 12.4, 6.2, 2.7$ Hz, 1H), 1.85 – 1.61 (m, 5H), 1.47 – 1.21 (m, 4H), 1.14 – 1.00 (m, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 170.7, 158.9, 140.5, 139.2, 129.6 (2C), 125.7, 124.6, 121.2, 114.7 (2C), 92.7, 78.7, 77.4, 71.1, 70.2, 57.5, 51.8, 50.3, 50.1, 49.4, 35.0, 30.4, 30.2, 25.6, 25.5, 15.6. HRMS (ESI) m/z [M+H] $^+$ calcd for $\text{C}_{27}\text{H}_{35}\text{N}_2\text{O}_3\text{S}$ 467.2363; Found 467.2380.

Representative procedure for phthalimide deprotection. ($\pm$) (2*R*,3*aR*,5*aR*,8*aS*)-2-(aminomethyl)-5-benzyl-7-butyloctahydro-6*H*-furo[2,3-*c*]pyrrolo[3,4-*b*]pyrrol-6-one (15*a*). Compound **8a** (126 mg, 0.27 mmol) was taken up in EtOH (4 mL) and hydrazine monohydrate (39 μL , 0.80 mmol) was added and the mixture was stirred 2 h at reflux. The mixture was then cooled to rt and the mixture was filtered. The filter cake was washed with CH_2Cl_2 and the filtrate was concentrated *in vacuo*. The residue was resolved in CH_2Cl_2 and the mixture was filtered again and then concentrated *in vacuo* to give the title compound as colorless oil (91 mg, quant.), that was used directly in the next step without further purification.

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FULL PAPER

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FULL PAPER

Synthesis of tricyclic and tetracyclic scaffolds with 3-4 stereocenters, high Fsp³, low MW and 3 handles for decoration is described. The key steps to generate complexity highlight Petasis 3-component reaction followed by an intramolecular Diels-Alder and cyclization cascade. The strategy was used for the production of 143 molecules for the European Lead Factory public compound collection.

*Petasis/Diels-Alder

Library synthesis*

Thomas Flagstad, Carlos M. G. Azevedo, Geanna Min, Anthony Willaume, Rémy Morgentin, Thomas E. Nielsen, * Mads H. Clausen *

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**Petasis/Diels-Alder/Cyclization
Cascade Reactions for the
Generation of Scaffolds with Multiple
Stereogenic Centers and Orthogonal
Handles for Library Production**