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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 sp³-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 sp² hybridized carbons and few stereocenters, representing the adoption of robust sp²-sp² 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 sp³ hybridized carbon atoms are known to have favorable drug-like properties and higher possibility of reaching the clinic.[3] In comparison of aliphatic and aromatic heterocycles, the former have a better pharmacokinetic profile.[4] The synthesis of libraries containing molecules with several stereocenters and a high percentage of sp³ carbons from readily accessible building blocks is challenging, and our group have engaged in efforts to develop novel and reliable methods for their synthesis.[5]

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 sp³ 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 sp³ carbons and stereocenters (Scheme 1, A). 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](image)

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 NaIO₄ 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 reaction followed by oxidative cleavage and aldehyde reduction generating 3a-3f.

2. TBTU, DIPEA, amine, 15 min
3. THF or MeCN, reflux, overnight

1. CH₂Cl₂, 0 °C to rt., 1h
2. TBU, DIPEA, amine, 15 min
3. THF or MeCN, reflux, overnight

The benzyl group was removed either by 1-chloroethyl chloroformate or hydrogenation with Pd(OH)₂/C, and the

2. NaH,THF , reflux, 1h, 2h
3. NaH,THF , reflux, 2h, 3h
4. TFA, CH₂Cl₂, r.t., 3 h
5. CH₂Cl₂, 0 °C, 10 min
6. NaN₃, DMF, 90 °C, 16 h
7. 1, 2. NaH,THF , reflux, 2h, 3h
8. NaO, Cs₂CO₃, DMF, 90 °C, 16 h

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 Pd(OH)₂/C, and the
resulting product used directly in the next step. The pyrrolidine amine reacted with isocyanates, sulfonyl chlorides, acyl chlorides and aldehydes/NaBH(OAc)₃ to provide a small library of compounds with different functionalities (Scheme 5). To demonstrate the orthogonality of the two nitrogen protecting groups, 8e was N-debenzylated and the respective amine functionalized with 3-chlorophenyl isocyanate and 4-toluenesulfonyl chloride to give 11d and 12e (Scheme 5), respectively.

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/NaBH(OAc)₃, respectively (Scheme 6).

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
molecular weight between 325 and 525, an Fsp3 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 Fsp3 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. (3R,3aR,4R,5S,6R,7aR)-2-benzyl-N-cyclohexyl-1,2,3,6,7a-hexahydro-3a,6-epoxyisoindole-3-carboxamide (1a). N-Allylbenzyl amine (3.70 g, 25.1 mmol) and glyoxylic acid monohydrate (3.47 g, 37.7 mmol) were dissolved in CH2Cl2 (25 mL, 1 M) and the mixture was cooled to 0 °C. The mixture was added 2-furanylorbornic 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 CHCl3 (50 mL) and H2O (75 mL) was added and the layers separated. The aqueous phase was extracted with CH2Cl2 (2 × 50 mL) and the combined organic layers were dried over Na2SO4 and stripped down to 50 mL. To the solution was added DIPEA (6.55 mL, 73.7 mmol) and TBTU (8.67 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 (2.0 mL, 30.1 mmol) and the mixture stirred 10 min at rt. Then, sat. aq. NaHCO3 (50 mL) was added and the layers separated. The aqueous phase was extracted with CH2Cl2 (2 × 50 mL) and the combined organic layers were dried over Na2SO4 and concentrated in vacuo. The residue was filtered through a silica plug (EIOAc:heptane 4:1, Rf = 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 (EIOAc:heptane 1:1, Rf = 0.2) to give the title compound as a white solid (5.96 g, 67%). 1H NMR (400 MHz, CDCl3) δ 7.57 (d, J = 8.3 Hz, 1H), 7.32 – 7.14 (m, 5H), 6.22 (d, 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). 13C NMR (101 MHz, CDCl3) δ 169.5, 138.4, 135.7, 134.7, 129.0 (2C), 128.7 (2C), 127.8, 96.1, 80.1, 69.4, 59.8, 58.5, 47.5, 42.3, 33.7, 33.1, 29.7, 27.5, 24.9, 24.8. HRMS (ESI) m/z: [M+H+] Calcd for C22H31N2O4 389.2440; Found 389.2448.

Representative procedure for the dihydroxylation. (±) (3R,3aR,4R,5S,6R,7aR)-2-benzyl-N-cyclohexyl-4,5-dihydroxyoctahydro-3a,6-epoxyisoindole-3-carboxamide (2a). Compound 1a (5.26 g, 14.9 mmol) was dissolved in acetone (50 mL, 0.3 M) and added N-methylmorpholin-N-oxide (2.27 g, 19.4 mmol). 0.9% K2OsO4.2H2O (50 mg, 0.14 mmol) in H2O (5 mL) was added and stirred overnight at rt. Then H2O (50 mL) was added and the mixture was filtered. The filter cake was washed with H2O and heptane and then dried in vacuo to give the title compound as a white solid (5.06 g, 88%). 1H NMR (400 MHz, CDCl3) 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). 13C NMR (101 MHz, CDCl3) δ 171.4, 138.0, 128.93(2C), 128.84 (2C), 127.8, 97.3, 64.4, 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 [M+H+] Calcd for C22H31N2O4 387.2278; Found 387.2304.

Representative procedure for the oxidative cleavage and aldehyde reduction. (±) (2R,3aR,5R,6R,6aR)-5-benzyl-N-cyclohexyl-2-bis(hydroxymethyl)hexahydro-2H-furo[2,3-c]pyrrole-6-carboxamide (3a). Compound 2a (3.59 g, 9.29 mmol) was dispersed in MeOH:H2O (9:1, 30 mL), added NaBH4 (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 CH3Cl (50 mL) and sat. aq. NaHCO3 (50 mL) and the phases were separated. The aqueous phase was extracted with CH3Cl (2 × 50 mL) and the combined organic layers were dried over Na2SO4 and concentrated in vacuo. The residue was purified by flash column chromatography (EIOAc:MeOH 19:1, Rf = 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); 13C NMR (101 MHz, DMSO) δ 168.2, 138.0, 128.7 (2C), 128.2 (2C), 127.0, 94.8, 73.9, 73.6, 63.5, 62.6, 57.3, 57.1, 47.2, 43.7, 33.0, 32.3, 32.18, 25.1, 24.7, 24.6. HRMS (ESI) m/z [M+H+] Calcd for C22H33N2O4 387.2224; Found 387.2448.

(4a) Compound 3a (2.17 g, 5.62 mmol) was dissolved in CH2Cl2 (25 mL), added Et3N (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 CH2Cl2 (25 mL) was added and the layers were separated. The aqueous phase was extracted with CH2Cl2 (2 × 50 mL) and the combined organic layers were dried over Na2SO4 and concentrated in vacuo. To the residue was added heptane and the mixture was filtered to provide the title compound

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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 – 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), 1.26 – 1.11 (m, 3H).

**Compound [R]**

13C NMR (101 MHz, CDCl3) δ 171.3, 163.6 (d, JCF = 21.3 Hz), 102.4 (d, JCF = 10.8 Hz, 1H), 107.9 (d, JCF = 10.4 Hz, 1H), 91.1 (d, JCF = 10.4 Hz, 1H), 87.8 (d, JCF = 10.4 Hz, 1H), 82.3 (d, JCF = 9.7 Hz, 1H), 78.2, 71, 69.8, 67.7, 57.7, 55.1, 50.5, 49.6, 46.1, 42.3, 30.4, 30.2, 25.3, 25.0, 25.4. HRMS (ESI) m/z [M+H+] Calcd for C26H32FN2O4 437.2391; Found 437.2409.

Representative procedure for substitution with phenols. (±) 2-(3-fluorophenoxy)methyl)octahydro-6H-furo[2,3-c]pyrrolo[3,4-b]pyrrole-6-one (7c).

**Compound [R]**

13C NMR (101 MHz, CDCl3) δ 171.3, 163.6 (d, JCF = 21.3 Hz), 102.4 (d, JCF = 10.8 Hz, 1H), 107.9 (d, JCF = 10.4 Hz, 1H), 87.8 (d, JCF = 10.4 Hz, 1H), 82.3 (d, JCF = 9.7 Hz, 1H), 78.2, 71, 69.8, 67.7, 57.7, 55.1, 50.5, 49.6, 46.1, 42.3, 30.4, 30.2, 25.3, 25.0, 25.4. HRMS (ESI) m/z [M+H+] Calcd for C26H32FN2O4 437.2391; Found 437.2391.

Representative procedure for the substitution with phthalimide. (±) 2-(3-fluorophenoxy)methyl)octahydro-6H-furo[2,3-c]pyrrolo[3,4-b]pyrrole-6-one (7c).

13C NMR (101 MHz, CDCl3) δ 171.3, 163.6 (d, JCF = 21.3 Hz), 102.4 (d, JCF = 10.8 Hz, 1H), 107.9 (d, JCF = 10.4 Hz, 1H), 87.8 (d, JCF = 10.4 Hz, 1H), 82.3 (d, JCF = 9.7 Hz, 1H), 78.2, 71, 69.8, 67.7, 57.7, 55.1, 50.5, 49.6, 46.1, 42.3, 30.4, 30.2, 25.3, 25.0, 25.4. HRMS (ESI) m/z [M+H+] Calcd for C26H32FN2O4 437.2391; Found 437.2391.

Representative procedure for the substitution with phthalimide. (±) 2-(3-fluorophenoxy)methyl)octahydro-6H-furo[2,3-c]pyrrolo[3,4-b]pyrrole-6-one (7c).

13C NMR (101 MHz, CDCl3) δ 171.3, 163.6 (d, JCF = 21.3 Hz), 102.4 (d, JCF = 10.8 Hz, 1H), 107.9 (d, JCF = 10.4 Hz, 1H), 87.8 (d, JCF = 10.4 Hz, 1H), 82.3 (d, JCF = 9.7 Hz, 1H), 78.2, 71, 69.8, 67.7, 57.7, 55.1, 50.5, 49.6, 46.1, 42.3, 30.4, 30.2, 25.3, 25.0, 25.4. HRMS (ESI) m/z [M+H+] Calcd for C26H32FN2O4 437.2391; Found 437.2391.

Representative procedure for the substitution with phthalimide. (±) 2-(3-fluorophenoxy)methyl)octahydro-6H-furo[2,3-c]pyrrolo[3,4-b]pyrrole-6-one (7c).

13C NMR (101 MHz, CDCl3) δ 171.3, 163.6 (d, JCF = 21.3 Hz), 102.4 (d, JCF = 10.8 Hz, 1H), 107.9 (d, JCF = 10.4 Hz, 1H), 87.8 (d, JCF = 10.4 Hz, 1H), 82.3 (d, JCF = 9.7 Hz, 1H), 78.2, 71, 69.8, 67.7, 57.7, 55.1, 50.5, 49.6, 46.1, 42.3, 30.4, 30.2, 25.3, 25.0, 25.4. HRMS (ESI) m/z [M+H+] Calcd for C26H32FN2O4 437.2391; Found 437.2391.
was added and the layers were separated. The aqueous phase was extracted with CH₂Cl₂ (2 x 10 mL) and the combined organic layers were dried over Na₂SO₄ 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 for 1h at rt. The compound was then purified directly by preparative HPLC to give the title compound as a white amorphous solid (7 mg, 26%).

HRMS (ESI) m/z [M+H⁺] Calcd for C₂₉H₃₆N₃O₄ 490.2700; Found 490.2669.

Representative procedure for acylation using acyl chlorides. (±) (2R,3aR,5aR,8aS)-7-cyclohexyl-5-(5-methylthiophen-2-ylmethyl)-2-(phenoxymethyl)octahydro-6H-furo[2,3-c]pyrrolo[3,4-b]pyrrole-6-one (13a). Amine salt 10b (20 mg, 0.06 mmol) was taken up in DMF (1 mL), DIPEA (21 μL, 0.122 mmol) and o-tolyl isocyanate (10 μL, 0.061 mmol) and the mixture was stirred for 16 h at rt. The compound was then purified directly by preparative HPLC to give the title compound as a yellow oil (91 mg, 53%). 1H NMR (400 MHz, CDCl₃) δ 9.10 (s, 1H), 7.70 (d, J = 8.0 Hz, 1H), 6.98 (t, J = 7.4 Hz, 1H), 6.94 – 6.89 (m, 2H), 6.74 (d, J = 3.1 Hz, 1H), 6.65 (dd, J = 3.1, 1.0 Hz, 1H), 4.61 – 4.48 (m, 1H), 4.31 (d, J = 14.2 Hz, 1H), 4.14 (d, J = 14.2 Hz, 1H), 4.00 (d, J = 10.1, 3.5 Hz, 1H) 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 (d, J = 9.3, 4.1 Hz, 1H), 2.70 – 2.61 (m, 1H), 2.44 (s, 3H), 2.10 – 1.98 (m, 1H), 1.95 (d, 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); 13C NMR (101 MHz, CDCl₃) δ 170.7, 158.9, 140.5, 139.2, 129.6 (2C), 125.7, 124.6, 121.2, 114.7 (2C), 129.7, 87.8, 77.4, 71.1, 70.2, 57.5, 51.8, 50.3, 50.4, 49.3, 35.4, 30.2, 26.5, 25.5, 15.6. HRMS (ESI) m/z [M+H⁺] Calcd for C₂₇H₂₇N₃O₄ 467.2357; Found 467.2360.

Representative procedure for reductive alkylation using aldehydes. (±) (2R,3aR,5aR,8aS)-7-cyclohexyl-5-(5-methylthiophen-2-ylmethyl)-2-(phenoxymethyl)octahydro-6H-furo[2,3-c]pyrrolo[3,4-b]pyrrole-6-one (14a). Amine salt 10a (16 mg, 0.046 mmol) was taken up in DMF (1 mL) and DIPEA (9 μL, 0.069 mmol), 5-methylthiophen-2-carboxylic acid (9 mg, 0.069 mmol) and NaBH(OAc)₃ (15 mg, 0.069 mmol) 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, CDCl₃) 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), 4.14 (d, J = 14.2 Hz, 1H), 4.04 (d, 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 (d, J = 9.3, 4.1 Hz, 1H), 2.70 – 2.61 (m, 1H), 2.44 (s, 3H), 2.10 – 1.98 (m, 1H), 1.95 (d, 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); 13C NMR (101 MHz, CDCl₃) δ 170.7, 158.9, 140.5, 139.2, 129.6 (2C), 125.7, 124.6, 121.2, 114.7 (2C), 129.7, 87.8, 77.4, 71.1, 70.2, 57.5, 51.8, 50.3, 50.4, 49.3, 35.4, 30.2, 26.5, 25.5, 15.6. HRMS (ESI) m/z [M+H⁺] Calcd for C₂₇H₂₇N₃O₄ 467.2357; Found 467.2360.

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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