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Povarov reaction, scope and limitations: Preparation of diversely heterocyclic tetrahydro-1*H*-cyclopenta[*c*]quinolines

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Parallel synthesis of diverse heterocyclic-tetrahydro-1*H*-cyclopenta[*c*]quinolines in excellent yields and high endo diastereoselectivity has been described herein. These compounds are highly functionalized natural product-like tricyclic systems, which may be useful as biologically relevant targets. Fine tuning of the reaction conditions need to be performed depending on the nature and molecular structure of the heterocyclic aromatic carbaldehyde, as well as the choice of the Lewis acid catalyst. Synthesis of the heterocyclic aromatic aldehyde precursors of the Povarov Reaction is also described.

Keywords: Povarov reaction, multicomponent reaction, parallel synthesis, cycloaddition, imines, alkenes, diastereoselectivity, scandium, heterocycles, tetrahydroquinolines, aldehydes

The chemical generation of molecular diversity represents one of the most significant paradigm shifts in modern science with the goal to mimic natural products and, therefore, finding biologically interesting compounds.

The tetrahydroquinoline derivatives are an important class of natural products that exhibit biological activities in front of several targets[1]. Moreover, they are useful derivatives as pesticides, antioxidants, and corrosion inhibitors[2]. Therefore, a variety of approaches have been developed for their synthesis.[3] Among them, the aza-Diels–Alder reaction of electron-rich dienophiles with *N*-aryl aldimines to obtain the tetrahydroquinolines is one of the most powerful methods, and it has been reported to improve the reaction by using various metal catalysts and different acids[3].

In our previous publications we have described the preparation of substituted tetrahydro-1*H*-cyclopenta[*c*]quinolines and hexahydro-2*H*-pyrano[3,2-*c*]quinolines *via* the one-pot condensation of aldehydes, anilines and cyclopentadiene or dihydropyranes respectively, in presence of Lewis acids as catalyst[4]. The cycloaddition reaction resulted in the formation of *endo* or *exo* isomer depending on the nature of the Lewis acid and the aromatic substitution of the starting materials.

In our ongoing research project focused on catalytic diastereoselective MCRs, we were interested in examining the scope of the Lewis acid-catalyzed three-component Povarov reaction using highly diverse heterocyclic aldehydes as starting materials as few reports can be found in the literature (mainly pyridinecarbaldehydes)[5].

Herein, we describe the preparation of diversely substituted tetrahydro-1*H*-cyclopenta[*c*]quinolines *via* Povarov reaction using parallel synthesis, fine-tuning of the reaction conditions and proper choice of the catalytic Lewis acid depending on the nature of the heterocyclic aldehyde precursor. Preparation of these diverse heterocyclic aromatic carbaldehydes is also reported.

List of Abbreviations

CAN = acetonitrile; DCM = dichloromethane; IEDAA = Inverse electron-demand aza Diels-Alder; NBS = *N*-Bromosuccinimide; NMP = *N*-methylpyrrolidone; TMEDA = Tetramethyletylenediamine

Results and Discussion

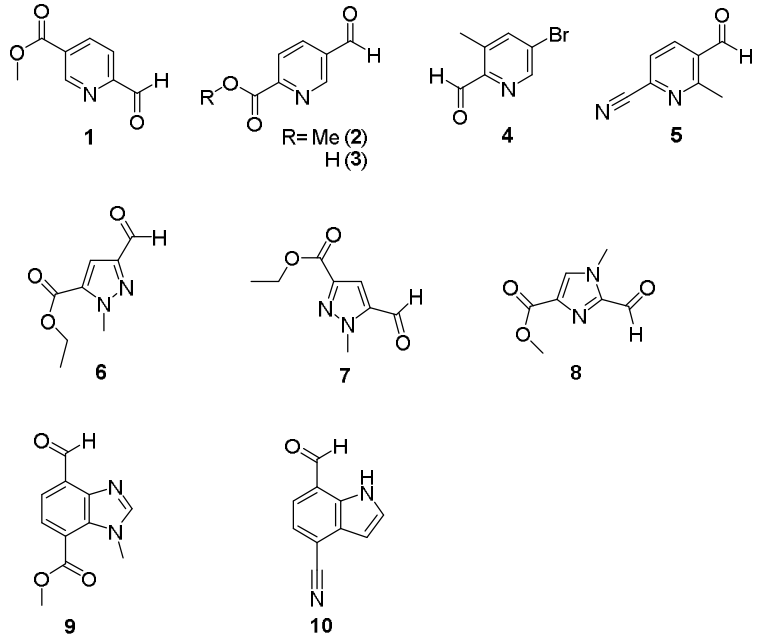
The main aim of this work was to increase the molecular diversity of the tetrahydro-1*H*-

cyclopenta[*c*]quinolones, which have complex natural product-like tricyclic architectures that could have interesting biological properties. Thus, the preparation of highly functionalised heterocyclic aldehydes as tetrahydroquinoline precursors was the starting point of this work.

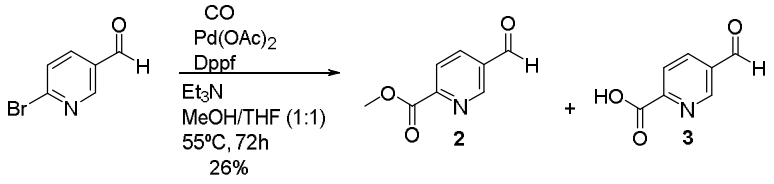
Ten highly substituted heterocyclic carbaldehydes were chosen based on more common and diverse nitrogen containing heterocycles such as pyridines, pyrazoles, imidazoles, benzimidazoles and indoles. (Scheme I)

Despite the fact that the aldehydes **1**-**6** and **10** were commercially available we were forced to prepare the aldehydes **2**-**6** and **10** due to their high prices or/and reduced availability, and, following reported methods in the bibliography but with slight synthetic improvements for the aldehydes **2** (Ref 6), **3** (Ref 7), **4** (Ref 8) and **6**-**7** (Ref 9). In addition, it is worth noting that the preparation of aldehydes **5**, **8**, **9** and **10** were not described before in the bibliography (Scheme II-VIII).

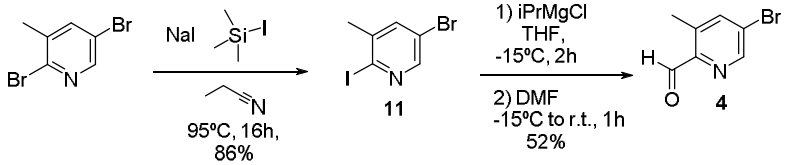
Early investigations were carried out to study the Povarov reaction using commercially available methyl 6-formylpyridine-3-carboxylate (**1**) and methyl 5-formylpyridine-2-carboxylate (**2**), *p*-toluidine and cyclopentadiene (which was freshly distilled from dicyclopentadiene before using it, and stored under −18ºC in order to avoid its dimerization). Application



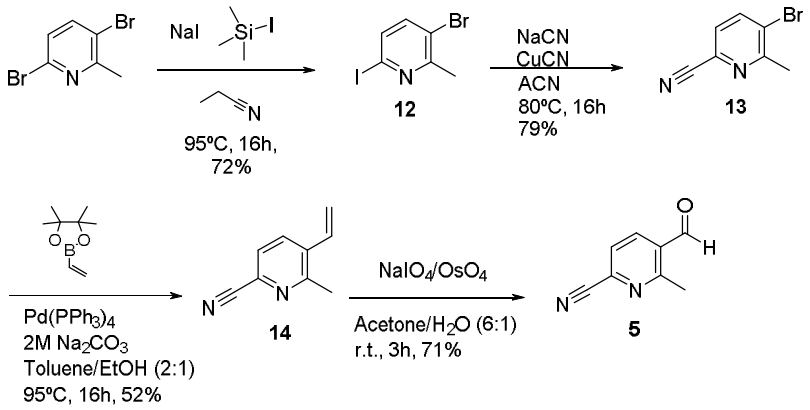
Scheme I — Heterocyclic carbaldehyde starting materials for the Povarov reaction (**1**-**10**)



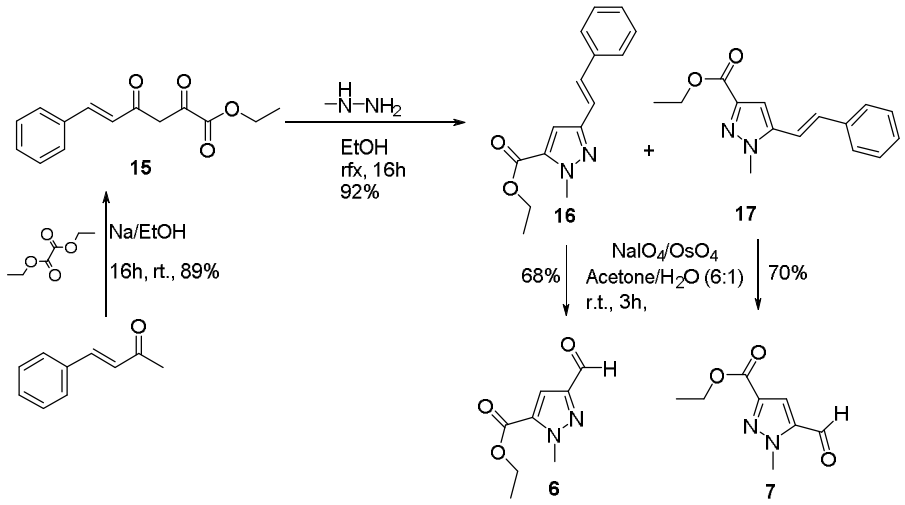
Scheme II — Preparation of methyl 5-formylpyridine-2-carboxylate **2** and 5-formylpyridine-2-carboxylic acid **3**



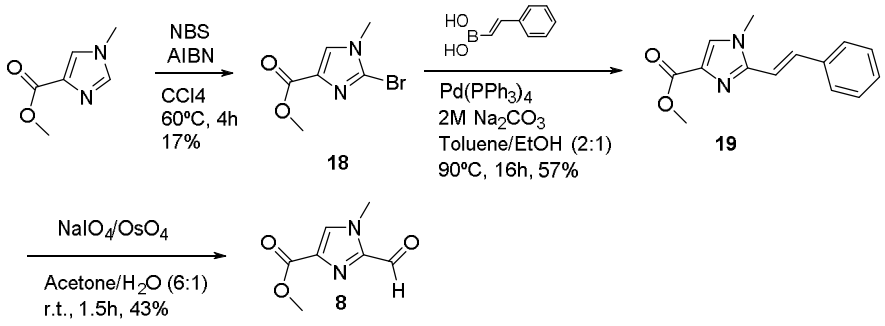
Scheme III — Preparation of 5-bromo-3-methylpyridine-2-carbaldehyde **4**



Scheme IV — Preparation of 5-formyl-6-methylpyridine-2-carbonitrile **5**



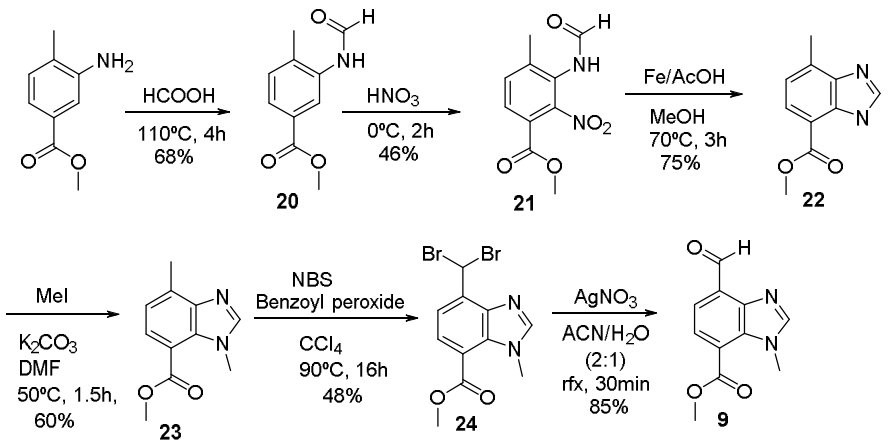
Scheme V — Preparation of ethyl 3-formyl-1-methyl-1*H*-pyrazole-5-carboxylate **6** and ethyl-5-formyl-1-methyl-1*H*-pyrazole-3-carboxylate **7**



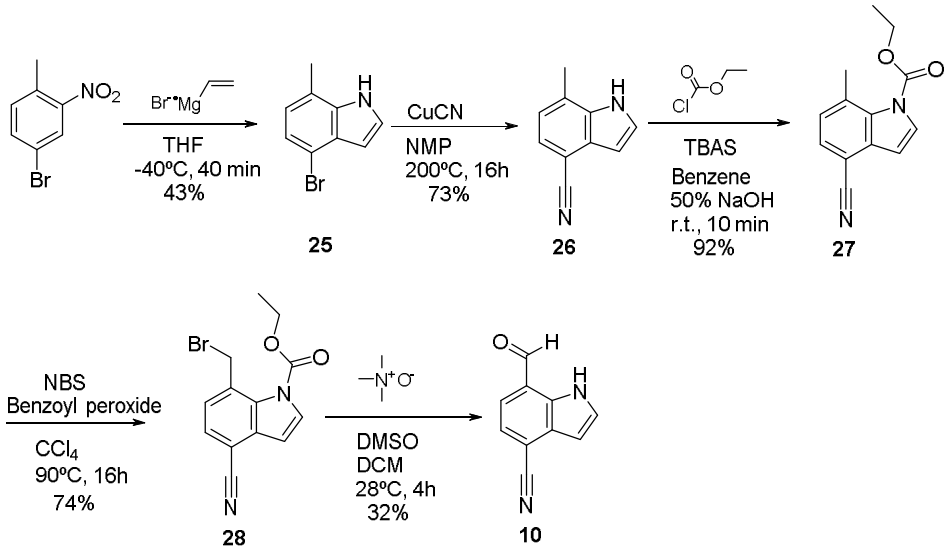
Scheme VI — Preparation of methyl 2-formyl-1-methyl-1*H*-imidazole-4-carboxylate **8**

of our previously reported optimized Povarov reaction conditions[4a] of $Sc(OTf)_3$ (10 mol%) in acetonitrile (ACN) at RT for 16 h led to the formation of methyl tetrahydroquinoline esters **29a** and **29b** in good yield (78% & 53% respectively) and both with high *endo* diastereoselectivity (>98%). However, attempts to apply these optimized reaction conditions to 5-formylpyridine-2-carboxylic acid (**3**) was unsuccessful and no conversion was achieved at all.

This may be due to the chelation of the Scandium (Sc) atom with the hetereoatoms present in the pyridine 2-carboxylic acid ring. Nevertheless, when aldehyde **3** was treated with *p*-toluidine and $BF_3{\cdot}OEt_2$ (2 equivalents) as Lewis acid at 25°C for 24 h in ACN



Scheme VII — Preparation of methyl 7-formyl-3-methyl-3*H*-benzo[*d*]imidazole-4-carboxylate **9**

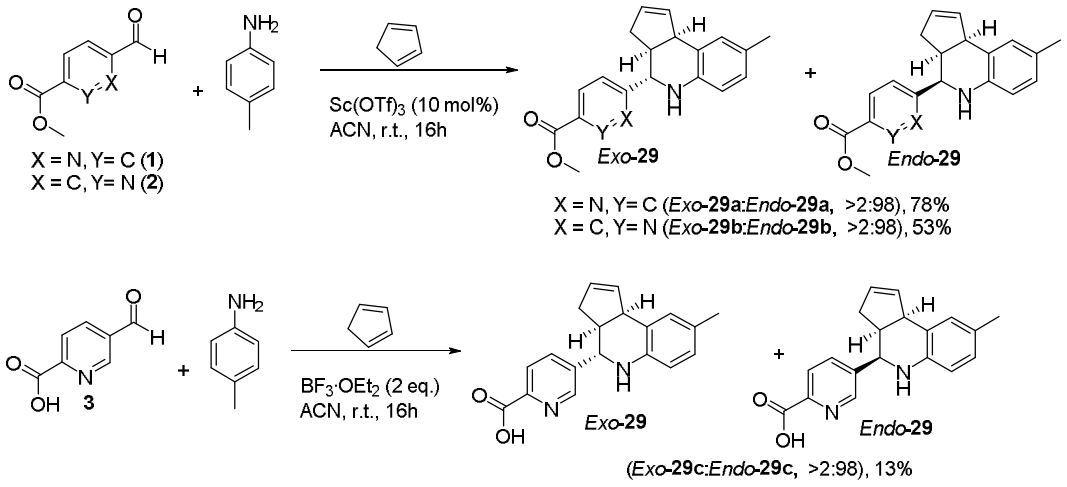


Scheme VIII — Preparation of 7-formyl-1*H*-indole-4-carbonitrile **10**

as a solvent, 41% conversion was achieved as evidenced by HPLC to obtain the desired tetrahydroquinoline **29c** in high *endo* diastereoselectivity (>98%). However, yield for the preparation of **29c** dropped to 13% after purification by reverse phase chromatography (Scheme IX).

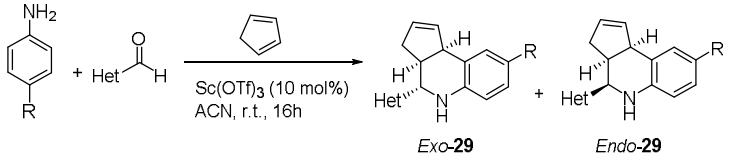
To this end, we decided to investigate the scope and limitations of the Povarov reaction depending on the nature of the heterocyclic aldehyde. Thus, the prepared heterocyclic aldehydes (**4**-**10**) were investigated with to our optimized conditions of $Sc(OTf)_3$ (10 mol%) in ACN at RT for 16 h (Table I).

The pyridinecarbaldehydes (**1**, **2**, **4**, **5**) gave good yields and excellent *endo* diastereoselectivity due to the π-deficient nature of the pyridine ring which favoured the reaction conversion (Table I, entries 1-4). Pyrazole carbaldehyde (**7**) also gave excellent yields and *endo* diastereoselectivity (Table I, entries 7, 8) and unexpectedly the pyrazole carbaldehyde (**6**) gave much lower yield keeping the high *endo* diastereoselectivity. This result may be due to the chelation of the pyrazole α-nitrogen atom by the side of the aldehyde group with the Sc atom in the imine intermediate state. (Table I, entries 5, 6). In addition, when the imidazole carbaldehyde analogues (**8** and **9**) were subjected to the Povarov reaction conditions using $Sc(OTf)_3$ (10 mol%), poor conversion (21%) was achieved for the imidazole carbaldehyde (**8**) and no conversion was observed for the benzimidazol carbaldehyde (**9**), even when the reaction mixture was heated at 50°C. Nevertheless, the reaction conversion substantially rose to 45% when the imidazol carbaldehyde (**8**) was treated with a high amount of



Scheme IX — Preparation of tetrahydro-1*H*-cyclopenta[*c*]quinolines

Table I — Formation of tetrahydroquinolines **29** from the $Sc(OTf)_3$-catalyzed three-component coupling reaction of anilines, heterocyclic aldehydes and cyclopentadiene[a]



Entry	Aniline (R)	Aldehyde (Het)	Product	Yield (%)[b]	dr[c] (*exo*/*endo*)
1	Me	**1**	**29a**	78	≥2:98
2	Me	**2**	**29b**	53	≥2:98
3	Cl	**4**	**29d**	84	≥2:98
4	Me	**5**	**29e**	93	≥2:98
5	Me	**6**	**29f**	46	≥2:98
6	OMe	**6**	**29g**	34	12:88
7	Me	**7**	**29h**	91	≥2:98
8	OMe	**7**	**29i**	91	≥2:98
9	Cl	**8**	**29j**	48[d]	≥2:98
10	OMe	**9**	**29k**	NR[e]	–
11	OMe	**10**	**29l**	35[f]	≥2:98

[a] Aniline (1eq.), Aldehyde (1eq.), cyclopentadiene (5eq.). [b] Overall yield is referred to the *endo* diastereoisomer. [c] Determined by the relative integrations of HPLC chromatogram peaks corresponding to the *exo*/*endo* isomers in the crude reaction mixture. [d] $Sc(OTf)_3$ (1 equivalent) was used to improve the reaction conversion. [e] No reaction was observed using 1 eq., $Sc(OTf)_3$ and even heating at 50°C. [f] $Sc(OTf)_3$ (0.5 equivalent) and heating at 50°C were used to achieve total reaction conversion.

$Sc(OTf)_3$ (1 equivalent) because the excess of Lewis acid may neutralise the basicity of the imidazole ring. (Table I, entry 9). However, no improvements in the reaction conversion was found when the benzimidazole carbaldehyde (**9**) was used in the above reaction conditions (Table I, entry 10). In addition, benzimidazolyl-tetrahydro-1*H*-cyclopenta[*c*] quinoline (**29k**) was eventually prepared using $BF_3{\cdot}OEt_2$ (2 equivalents) at 50°C for 16 h in DCM as a solvent leading to a mixture of (13:87) *exo/endo* diastereoisomers in moderate yield (49%). Furthermore, indolyl carbaldehyde (**10**) under $Sc(OTf)_3$ (10 mol%) reaction conditions gave low reaction conversion (13%) which was improved to 70% by increasing the amount of $Sc(OTf)_3$ (50 mol%) and the temperature (50ºC). The desired indolyl-tetrahydro-1*H*-cyclopenta[*c*]quinoline (**29l**) was obtained in moderate yield (35%) with high *endo* diastereoselectivity (>98%) after purification by flash chromatography (Table I, entry 11).

Experimental Section

HPLC-UV-MS was performed on a Waters Alliance HT 2795 HPLC with detection performed by Photodiode Array Detector 2996 and Micromass ZQ spectrometer operating in electrospray ionization mode. The XBridgeTM C18 (3.5 µm 4.6 × 50 mm) HPLC column was used, temperature: 25°C; rate 2.0 mL/min; eluent: A = HCOOH 10 mM, B = ACN:MeOH:HCOOH (1:1:0.05); gradient: 95 to 0% A in 5.5 min, 0% A 3 min, 0 to 95% A 0.5 min. ^{1}H NMR spectra were recorded on a Varian Mercury-400 Fourier Transform Spectrometer operating at 400 MHz. NMR spectra were obtained as $CDCl_3$ solutions (reported in δ, ppm), using chloroform as the reference standard (δ 7.26) or DMSO-d_6 (δ 2.50). The following abbreviations are used for peak multiplicities s (singlet), d (doublet), t (triplet), m (multiplet), br (broadened), dd (doublet of doublets), dt (doublet of triplets), and td (triplet of doublets). Coupling constants, are reported in Hertz (Hz).

Compounds were prepared using a parallel approach synthesis, as assessed using the aforementioned standard spectroscopic techniques, in ≥ 95% purity unless otherwise stated. Starting materials were either procured from commercial sources or prepared as described herein. Column chromatography was performed either by flash chromatography (40-65 µm silica gel) or using an automated purification system (SP1 Purification System from Biotage®), which was also used for the reverse C18 chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents unless otherwise stated. Microwave reactions were performed in a Discovery CEM® system.

Methyl 5-formylpyridine-2-carboxylate, 2 and 5-formylpyridine-2-carboxylic acid, 3

To a solution of 6-bromopyridine-3-carbaldehyde (2.69 mmol, 500 mg) dissolved in a mixture of MeOH (2.7 mL) and DMF (2.7 mL) was added Et_3N (5.38 mmol, 0.75 mL). To this solution palladium (II) acetate (0.07 mmol, 15 mg), and 1,1-bis(diphenylphosphino)ferrocene (0.14 mmol, 75 mg) were added. The mixture was bubbled with carbon monoxide gas. The resulting solution was heated at 55°C for 48 h. Total conversion was not achieved, and again Et_3N (2.69 mmol, 0.38 mL), palladium (II)acetate (0.03 mmol, 8 mg), and 1,1-bis (diphenylphosphino)ferrocene (0.07 mmol, 38 mg) were added. The mixture was bubbled with carbon monoxide gas. The resulting solution was heated at 55°C for 24 h. The crude product was poured into water and extracted with ethyl acetate. The aqueous layer was concentrated under reduced pressure to dryness. The crude was dissolved in ethyl acetate and the organic layer was washed with saturated Na_2CO_3, dried with anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 30 mg (Yield: 7%) of the compound methyl 5-formyl pyridine-2-carboxylate **2**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.11 (1H, s), 8.94 (1H, s), 8.19-8.17 (1H, m), 8.03-7.97 (1H, m), 2.66 (3H, s).

On the other hand, the aqueous layer was concentrated under reduced pressure to dryness and the crude material was directly purified by reverse C_{18} chromatography to give 84 mg (Yield: 19%) of the compound 5-formylpyridine-2-carboxylic acid **3**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.6 (1H, s), 10.19 (1H, s), 9.17 (1H, s), 8.42 (1H, d, J = 8 Hz), 8.21 (1H, d, J = 8 Hz).

5-Bromo-2-iodo-3-methylpyridine, 11

Sodium iodide (2 eq., 16 mmol, 2.40 g) and 2,5-dibromo-3-methylpyridine (7.97 mmol, 2 g) were combined in propionitrile (20 mL) and the resulting slurry was stirred under nitrogen for 5 min. Iodotrimethylsilane (0.2 eq., 1.6 mmol, 0.23 mL) was added and the reaction mixture was heated at 95°C with stirring under nitrogen for 16 h. The slurry was cooled to RT, diluted with a 1:1 mixture of ethyl acetate and water. The mixture was stirred for 15 min and the aqueous and organic phases were separated. The organic layer was washed sequentially with saturated aqueous sodium bicarbonate solution, sodium thiosulfate (5% aqueous solution) and brine. The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford the desired product which was purified by flash chromatography over silica gel using an elution of 13% ethyl acetate in hexane to give 2.03 g (Yield: 86%) of the title compound **11** as an oil. ESI-MS: *m/z* 298 $[M + H]^+$.

5-Bromo-3-methylpyridine-2-carbaldehyde, 4

A solution of 5-bromo-2-iodo-3-methylpyridine **11** (6.71 mmol, 2 g) in dry THF (42 mL) was degassed with argon. The solution was cooled to −15°C, *i*-PrMgCl (2M in THF, 26.84 mmol, 13.4 mL) was added and the reaction was stirred for 2 h at −15°C. Then, dry DMF (33.55 mmol, 2.6 mL) was added and the reaction was allowed to warm over 1 h. The reaction was quenched with aqueous 1M HCl and

extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. Purification of the crude material by flash chromatography over silica gel using an elution of 10% ethyl acetate in hexane afforded 673 mg (Yield: 52%) of the title compound **4**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.14 (1H, s), 8.71-8.70 (1H, m), 7.82-7.80 (1H, m), 2.66 (3H, s).

3-Bromo-6-iodo-2-methylpyridine, 12

Sodium iodide (2 eq., 16 mmol, 2.40 g) and 2,5-dibromo-6-methylpyridine (2.0 g, 8.0 mmol) were combined in propionitrile (20 mL) and the resulting slurry was stirred under nitrogen for 5 min. Iodotrimethylsilane (0.2 eq., 1.6 mmol, 0.23 mL) was added and the reaction mixture was heated at 95°C with stirring under nitrogen for 16 h. The slurry was cooled to RT, diluted with a 1:1 mixture of ethyl acetate and water. The mixture was stirred for 15 min and the aqueous and organic phases were then separated. The organic layer was washed sequentially with saturated aqueous sodium bicarbonate solution, sodium thiosulfate (5% aqueous solution) and brine. The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford the desired product which was purified by flash chromatography over silica gel using an elution of 4% ethyl acetate in hexane to give 1.72 g (Yield: 72%) of the title compound **12** as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (2H, s), 2.63 (3H, s); ESI-MS: *m/z* 298 $[M + H]^+$.

5-Bromo-6-methylpyridine-2-carbonitrile, 13

Under an inert atmosphere, 3-bromo-6-iodo-2-methylpyridine **12** (4.19 mmol, 1.25 g) in acetonitrile (15 mL) was combined with copper cyanide (0.5 eq., 2.0 mmol, 185 mg) and sodium cyanide (0.8 eq., 3.35 mmol, 165 mg). The reaction mixture was stirred for 30 min and heated at 80°C with stirring under nitrogen for 16 h. The slurry was cooled to RT, diluted with a 0.5M aqueous solution of ammonia and stirred for 15 min, filtered over Celite® and the filter cake was washed with ethyl acetate. Organic layer was then separated. The organic layer was washed sequentially with 0.5M aqueous solution of ammonia and brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford the desired product which was purified by flash chromatography over silica gel using an elution of 7% ethyl acetate in hexane to give 650 mg (Yield: 79%) of the title compound **13** as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (1H, d, *J* = 8.4 Hz), 7.40 (1H, d, *J* = 8.4 Hz), 2.17 (3H, s); ESI-MS: *m/z* 197 $[M + H]^+$.

6-Methyl-5-vinylpyridine-2-carbonitrile, 14

An argon degassed solution of 5-bromo-6-methylpyridine-2-carbonitrile **13** (3.3 mmol, 650 mg), 4,4,5,5,-tetramethyl-2-vinyl-1,3,2-dioxaborolane (3.3 mmol, 0.56 mL), tetrakis(triphenylphosphine)palladium (5 mol %, 0.16 mmol, 190 mg) and 2N aqueous sodium carbonate solution (3.4 eq., 11.22 mmol, 5.60 mL) in toluene/ethanol (2:1, 45 mL) was heated at 95°C with stirring for 16 h. The slurry was cooled to RT, diluted with ethyl acetate and water. Organic layer was then separated. The organic layer was washed with brine and dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford the desired product which was purified by flash chromatography over silica gel using an elution of 20% ethyl acetate in hexane to give 246 mg (Yield: 52%) of the title compound **14** as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (1H, d, *J* = 8.0 Hz), 7.52 (1H, d, *J* = 8.0 Hz), 6.89 (1H, dd, *J* = 17.6 & 10.8 Hz), 5.79 (1H, d, *J* = 17.2 Hz), 5.58 (1H, d, *J* = 10.8 Hz), 2.62 (3H, s); ESI-MS: *m/z* 145 $[M + H]^+$.

5-Formyl-6-methylpyridine-2-carbonitrile, 5

6-Methyl-5-vinylpyridine-2-carbonitrile **14** (1.7 mmol, 245 mg) was dissolved in acetone/water (6:1, 21 mL) and then OsO_4 (0.74 eq., 1.3 mmol, 330 mg) and $NaIO_4$ (3eq, 5.1 mmol, 1.09 g) were added. The resulting mixture was kept at RT for 3 h. The reaction mixture was filtered. The filtrate was diluted with ethyl acetate. The organic layer was then separated and washed by saturated aqueous sodium carbonate solution and brine, then dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford the desired product which was purified by flash chromatography over silica gel using an elution of 40% ethyl acetate in hexane to give 178 mg (Yield: 71%) of the title compound **5** as a solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.38 (1H, s), 8.23 (1H, d, *J* = 8.4 Hz), 7.73 (1H, d, *J* = 8.0 Hz), 2.94 (3H, s).

2-Methyl-5-styryl-2*H*-pyrazole-3-carboxylic acid ethyl ester, 16, and 1-methyl-5-styryl-1*H*-pyrazole-3-carboxylic acid ethyl ester, 17

Sodium pellets (1eq, 0.1 mol, 2.3 g) were slowly added in absolute ethyl alcohol (100 mL). After the reaction of sodium, the solvent was removed under reduced pressure and anhydrous ether (130 mL) was added. The reaction mixture was cooled to −5°C, and

a solution of 4-phenyl-3-buten-2-one (14.6 g, 0.1 mol) and diethyl oxalate (1.2 eq., 0.12 mol, 16 mL) in anhydrous ether (25 mL) was added over 30 min. After stirring for 16 h at RT, the yellow solid was filtered and washed with ether. The sample was dried for 1 h at RT and the solid was partitioned between dichloromethane (600 mL) and 1N sulfuric acid (200 mL). The organic layer was then separated and dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford 22.05 g (Yield: 89%) of (*E*)-ethyl 2,4-dioxo-6-phenylhex-5-enoate **15** as a yellowish solid, which was used in the next step without further purification. ESI-MS: *m/z* 247 $[M + H]^+$.

A solution of (*E*)-ethyl 2,4-dioxo-6-phenylhex-5-enoate **15** (0.01 mol, 2.5 g) and methylhydrazine (1.2 eq., 0.012 mol, 0.65 mL) in ethanol was heated at reflux for 16 h. The solvent was removed under vacuum and the residue was purified by flash chromatography over silica gel using hexane and ethyl acetate as eluents. At 20% of ethyl acetate in hexane elutes first the isomer 1-methyl-5-styryl-1*H*-pyrazole-3-carboxylic acid ethyl ester **17** affording 710 mg as a solid. Then, at 40% of ethyl acetate in hexane elutes 2-methyl-5-styryl-2*H*-pyrazole-3-carboxylic acid ethyl ester **16** with 1.64 g as a solid (overall reaction yield: 92%).

1-Methyl-5-styryl-1*H*-pyrazole-3-carboxylic acid ethyl ester, 17: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (2H, dd, *J* = 8.8 & 1.6 Hz), 7.35 (2H, t, *J* = 7.2 Hz), 7.28-7.24 (1H, m), 7.14 & 7.11 (1H, 2s), 7.07 & 7.03 (1H, 2s), 7.01 (1H, s), 4.36 (2H, q, *J* = 6.8 Hz), 4.18 (3H, s), 1.40 (3H, t, *J* = 6.8 Hz); ESI-MS: *m/z* 257 $[M + H]^+$.

2-Methyl-5-styryl-2*H*-pyrazole-3-carboxylic acid ethyl ester, 16: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51-7.48 (2H, m), 7.41-7.36 (2H, m), 7.34-7.28 (1H, m), 7.10 & 7.06 (1H, 2s), 7.02 (1H, s), 6.92 & 6.87 (1H, 2s), 4.41 (2H, q, *J* = 7.2 Hz), 4.00 (3H, s), 1.41 (3H, t, *J* = 7.2 Hz); ESI-MS: *m/z* 257 $[M + H]^+$.

3-Formyl-1-methyl-1*H*-pyrazole-5-carboxylic acid ethyl ester, 6

The following compound was prepared using the same methodology as in compound **5** using 2-methyl-5-styryl-2*H*-pyrazole-3-carboxylic acid ethyl ester **16** (2.73 mmol, 700 mg) for 1.5 h. Purification of the crude material using flash chromatography over silica gel using an elution of 26% ethyl acetate in hexane afforded 340 mg (Yield: 68%) of the title compound **6** as a solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.96 (1H, s), 7.33 (1H, s), 4.36 (2H, q, *J* = 6.8 Hz), 4.28 (3H, s), 1.39 (3H, t, *J* = 7.6 Hz).

5-Formyl-1-methyl-1*H*-pyrazole-3-carboxylic acid ethyl ester, 7

The following compound was prepared using the same methodology as in compound **5** using 1-methyl-5-styryl-1*H*-pyrazole-3-carboxylic acid ethyl ester **17** (1.0 mmol, 256 mg) for 2 h. Purification of the crude material using flash chromatography over silica gel using an elution of 25% ethyl acetate in hexane afforded 255 mg (Yield: 70%) of the title compound **7** as a solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.88 (1H, s), 7.41 (1H, s), 4.43 (2H, q, *J* = 6.8 Hz), 4.25 (3H, s), 1.41 (3H, t, *J* = 7.6 Hz).

Methyl 2-bromo-1-methyl-1*H*-imidazole-4-carboxylate, 18

To a solution of methyl 1-methyl-1*H*-imidazole-4-carboxylate (14.3 mmol, 2 g) in CCl_4 (40 mL), NBS (15.3 mmol, 2.72 g) and AIBN (0.715 mmol, 117 mg) were added. The reaction mixture was heated for4 h at 60°C and then cooled to RT. The solvent was evaporated. The reaction crude was purified by flash chromatography over silica gel using an elution of 8% methanol in ethyl acetate to afford 529 mg (Yield:17%) of the title compound **18**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (1H, s), 3.91 (3H, s), 3.67 (3H, s); ESI-MS: *m/z* 219 $[M + H]^+$.

Methyl 1-methyl-2-styryl-1*H*-imidazole-4-carboxylate, 19

A solution of methyl 2-bromo-1-methyl-1*H*-imidazole-4-carboxylate **18**, 2.41 mmol, 529 mg), 2-phenylvinylboronic acid (2.41 mmol, 357 mg), tetrakis(triphenylphosphine)palladium (5% w/w, 27 mg) and 2N aqueous sodium carbonate solution (8.21 mmol, 4 mL) in toluene/ethanol (2:1, 18 mL) was degassed by argon and heated at 90ºC for 16 h, then cooled to RT and concentrated. The reaction crude was purified by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents to give 337 mg (Yield: 57%) of methyl 1-methyl-2-styryl-1*H*-imidazole-4-carboxylate **19**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (1H, s), 7.75 (1H, brs), 7.55 (2H, d, *J* = 7.2 Hz), 7.50 (1H, brs), 7.41-7.30 (3H, m), 7.28-7.23 (1, m), 3.93 (3H, s), 3.86 (3H, s); ESI-MS: *m/z* 243 $[M + H]^+$.

Methyl 2-formyl-1-methyl-1*H*-imidazole-4-carboxylate, 8

Methyl 1-methyl-2-styryl-1*H*-imidazole-4-carboxylate (**19**)(1.4 mmol, 337 mg), was dissolved in acetone/water (6:1, 10.5 mL) OsO_4 (1.04 mmol, 264 mg) and $NaIO_4$ (4.2 mmol, 899 mg) were added. The resulting mixture was kept at RT for 1.5 h and then filtered. The solid was washed with ethyl acetate and the filtrate was concentrated under reduce pressure to afford the desired product which was purified by flash chromatography over silica gel using an elution of 100% ethyl acetate in hexanes to afford 102 mg (Yield: 43%) of the title compound **8** as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.31 (1H, s), 8.06 (1H, s), 3.87 (3H, s), 3.86 (3H, s); ESI-MS: *m/z* 169 $[M + H]^+$.

Methyl 3-formamido-4-methylbenzoate, 20

A solution of methyl 3-amino-4-methylbenzoate (30.27 mmol, 5 g) in formic acid (1.12 mmol, 42 mL) was heated at 110°C for 4 h. The reaction mixture was cooled to RT, diluted with ethyl acetate and water. Organic layer was then separated and washed with water (x3), dried over anhydrous sodium sulphate, filtered and concentrated under reduce pressure to afford 4 g (Yield: 68%) of the title product **20**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.72 (1H, s), 8.44 (1H, d, *J* = 2 Hz), 8.34 (1H, s), 7.64 (1H, dd, *J* = 8 & 1.6 Hz), 7.36 (1H, d, *J* = 7.6 Hz), 3.83 (3H, s), 2.31 (3H, s); ESI-MS: *m/z* 226 $[M + H]^+$.

Methyl 3-formamido-4-methyl-2-nitrobenzoate, 21

Fuming nitric acid (15 mL) was cooled at 0°C and methyl 3-formamido-4-methylbenzoate (**20**)(22.1 mmol, 4.27 g) was added in small portions over 45 min. The reaction mixture was stirred at 0°C for an additional 1 h, and then ice water (50 g) was added and stirred for 1.5 h at RT. The precipitated solid was filtered, washed with water and dried to afford 2.4 g (Yield: 46%) of the title compound **21** which was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.09 (1H, s), 8.25 (1H, s), 8.34 (1H, s), 7.88 (1H, d, *J* = 8 Hz), 7.68 (1H, d, *J* = 8 Hz), 3.83 (3H, s), 2.28 (3H, s).

Methyl 7-methyl-3*H*-benzo[*d*]imidazole-4-carboxylate, 22

To a solution of methyl 3-formamido-4-methyl-2-nitrobenzoate (**21**) (2.1 mmol, 500 mg) in methanol (5 mL) iron powder (10.5 mmol, 587 mg) and acetic acid (2.3 mL) were added. The reaction mixture was heated at 70°C for 3 h and then cooled at RT, filtered and the filter was washed with ethyl acetate. The solvent was evaporated. The crude product was dissolved in ethyl acetate and saturated aqueous sodium bicarbonate solution. The organic layer was separated, washed with water and brine, dried over magnesium sulphate and concentrated to afford 300 mg (Yield: 75%) of the title compound **22** which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.5 (1H, brs), 8.12 (1H, s), 7.85 (1H, d, *J* = 7.6 Hz), 7.14 (1H, d, *J* = 7.6 Hz), 3.99 (3H, s), 2.75 (3H, s); ESI-MS: *m/z* 191 $[M + H]^+$.

Methyl 3,7-dimethyl-3*H*-benzo[*d*]imidazole-4-carboxylate, 23

To a solution of methyl 7-methyl-3*H*-benzo[*d*]imidazole-4-carboxylate (**22**)(0.34 mmol, 64 mg) in DMF (2 mL) iodomethane (0.51 mmol, 0.032 mL) and potassium carbonate (1.7 mmol, 235 mg) were added. The reaction mixture was heated at 50°C for 1.5 h and then partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic layer was separated, washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate, filtered and concentrated to afford 42 mg (Yield: 60%) of the title compound **23** which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (1H, s), 7.79 (1H, d, *J* = 7.6 Hz), 7.08 (1H, d, *J* = 8 Hz), 4.05 (3H, s), 3.95 (3H, s), 2.71 (3H, s); ESI-MS: *m/z* 205 $[M + H]^+$.

Methyl 7-(dibromomethyl)-3-methyl-3*H*-benzo[*d*] imidazole-4-carboxylate, 24

To a solution of methyl 3,7-dimethyl-3*H*-benzo[*d*]imidazole-4-carboxylate (**23**)(1.2 mmol, 246mg) in CCl_4 (12 mL), NBS (3.6 mmol, 641 mg) and benzoyl peroxide (0.12 mmol, 29 mg) were added. The reaction mixture was heated for 16 h at 90°C and then cooled at RT. The solvent was evaporated and the reaction crude was purified by flash chromatography over silica gel using an elution of 63% DCM in hexanes to afford 210 mg (Yield: 48%) of the title compound **24**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (2H, m), 7.78 (1H, d, *J* = 8 Hz), 7.58 (1H, s), 4.06 (3H, s), 3.98 (3H, s); ESI-MS: *m/z* 363 $[M + H]^+$.

Methyl 7-formyl-3-methyl-3*H*-benzo[*d*]imidazole-4-carboxylate, 9

To a solution of methyl 7-(dibromomethyl)-3-methyl-3*H*-benzo[*d*]imidazole-4-carboxylate (**24**) (0.7 mmol, 255 mg) in acetonitrile (10 mL) and water

(5 mL) $AgNO_3$ (2.1 mmol, 359 mg) was added, the mixture was heated for 30 min under reflux. The reaction mixture was cooled down, the AgBr was filtered off and washed with ethyl acetate. The combined filtrate was washed with brine, dried over anhydrous magnesium sulfate and concentrated to dryness to afford 130 mg (Yield: 85%) of the title compound **9** which was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.82 (1H, s), 8.55 (1H, s), 7.82 (1H, d, *J* = 7.6 Hz), 7.75 (1H, d, *J* = 8 Hz), 3.98 (3H, s), 3.96 (3H, s); ESI-MS: *m/z* 219 $[M + H]^+$.

4-Bromo-7-methyl-1*H*-indole, 25

A solution of 4-bromo-1-methyl-2-nitrobenzene (11.57 mmol, 2.5 g) in THF (116 mL) under nitrogen atmosphere was cooled to −40°C and vinyl magnesium bromide (46.28 mmol, 46 mL) was added. The reaction mixture was stirred for 40 min and quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with ethyl acetate twice and the combined organic layers were dried with Na_2SO_4, filtered and concentrated. The crude product thus obtained was dissolved in THF (35 mL) and cooled to 0°C. 0.5 N HCl (4.4 mL) was added and the reaction mixture was stirred at 0°C for 1 h, then it was quenched with $NaHCO_3$ (44 mL). The aqueous layer was extracted with ethyl acetate twice and the combined organic extracts were dried with Na_2SO_4, filtered and concentrated. Purification of the crude material by flash chromatography over silica gel using an elution of 11% ethyl acetate in hexanes afforded 1.05 g (Yield: 43%) of the pure title compound **25**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (1H, brs), 7.28-7.26 (1H, m), 7.21 (1H, d, *J* = 7.2 Hz), 6.87 (1H, d, *J* = 6.8 Hz), 6.63-6.61 (1H, m), 2.47 (3H, s).

7-Methyl-1*H*-indole-4-carbonitrile, 26

4-Bromo-7-methyl-1*H*-indole(**25**) (4.76 mmol, 1 g) and copper (I) cyanide (6.19 mmol, 558 mg) were mixed in *N*-methyl-2-pyrrolidinone (14 mL). The mixture was heated at 200°C for 16 h. The reaction was diluted with DCM and filtered through a pad of Celite® and concentrated to dryness. Purification of the crude material by flash chromatography over silica gel using an elution of 21% ethyl acetate in hexane afforded 550 mg (Yield: 73%) of the pure title compound **26**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (1H, brs), 7.42 (1H, d, *J* = 7.2 Hz), 7.40-7.38 (1H, m), 7.05 (1H, d, *J* = 8 Hz), 6.79-6.78 (1H, m), 2.58 (3H, s).

Ethyl 4-cyano-7-methyl-1*H*-indole-1-carboxylate, 27

To a solution of 7-methyl-1*H*-indole-4-carbonitrile (**26**)(4.48 mmol, 700 mg) in benzene (8.5 mL), 50% NaOH solution (3.5 mL) and a catalytic amount of tetrabutylammonium hydrogen sulphate were added and stirred vigorously for 15 min. Ethyl chloroformate (8.96 mmol, 0.857 mL) was slowly added (15 min). The two-phase system was stirred at RT for 10 min and diluted with water (15 mL). The organic layer was separated, and the aqueous layer was extracted with benzene. The combined organic extracts were dried over anhydrous sodium sulfate and concentrated to dryness to afford 944 mg (Yield: 92%) of the title compound **27**which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (1H, d, *J* = 3.6 Hz), 7.49 (1H, d, *J* = 7.2 Hz), 7.17 (1H, d, *J* = 8 Hz), 6.82 (1H, d, *J* = 4 Hz), 4.48 (2H, q, *J* = 7.2 Hz), 2.72 (3H, s), 1.47 (3H, t, *J* = 7.2 Hz).

Ethyl 7-(bromomethyl)-4-cyano-1*H*-indole-1-carboxylate, 28

To a solution of 4-cyano-7-methyl-1*H*-indole-1-carboxylate(**27**) (5.26 mmol, 1.2 g) in CCl_4 (35 mL), NBS (15.78 mmol, 2.8 g) and benzoyl peroxide (0.526 mmol, 128 mg) were added. The reaction mixture was heated for 16 h at 90°C. The reaction was cooled down and the precipitate of succinimide and unreacted NBS was removed by filtration and washed with DCM. Solvent was evaporated.The crude product was purified by flash chromatography over silica gel using an elution of 6% ethyl acetate in hexane to afford 1.2 g (Yield: 74%) of the title compound **28**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (1H, d, *J* = 4 Hz), 7.56 (1H, d, *J* = 7.6 Hz), 7.37 (1H, d, *J* = 7.6 Hz), 6.88 (1H, d, *J* = 4 Hz), 5.19 (2H, s), 4.55 (2H, q, *J* = 7.2 Hz), 1.51 (3H, t, *J* = 7.2 Hz).

7-Formyl-1*H*-indole-4-carbonitrile, 10

To a solution of ethyl 7-(bromomethyl)-4-cyano-1*H*-indole-1-carboxylate (**28**) (1.18 mmol, 235 mg) in dichloromethane (8 mL) at 0ºC, trimethylamine oxide (4.72 mmol, 352 mg) in DMSO (2.7 mL) was added. The reaction was warmed at 28ºC for 4 h.To this reaction mixture water was added, and the organic layer was extracted with Et_2O, dried over Na_2SO_4 and concentrated under reduce pressure. The crude product was purified by flash chromatography over silica gel using an elution of 30% ethyl acetate in

hexane to give the desired product slightly impure which was triturated in hexane, filtered and washed with hexane to afford 214 mg (Yield: 32%) of the title compound **10**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.16 (1H, brs), 10.28 (1H, s), 7.91 (1H, d, *J* = 7.2 Hz), 7.78 (1H, d, *J* = 7.6 Hz), 7.70 (1H, d, *J* = 2.4 Hz), 6.74 (1H, d, *J* = 2.8 Hz).

Methyl 6-((3aS,4R,9bR)-3a,4,5,9b-tetrahydro-8-methyl-3*H*-cyclopenta[*c*]quinolin-4-yl)pyridine-3-carboxylate, *endo*-29a

General Procedure for Povarov Reaction: A catalytic amount of scandium trifluoromethane sulfonate (0.1 eq., 0.1 mmol, 49 mg) in anhydrous acetonitrile (5 mL) was added methyl-6-formylnicotinate (1 mmol, 165 mg), 4-methylaniline (1 mmol, 170 mg), and freshly distilled cyclopentadiene (5 eq, 5 mmol, 0.40 mL). The reaction mixture was stirred at RT for 16 h. HPLC analysis showed total conversion. Solvent was evaporated and purification of the crude material by flash chromatography over silica gel using hexane and ethyl acetate as eluents afforded 249 mg (Yield: 78%) of the title compound (*endo*-**29a**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.19 (1H, dd, *J* = 2.4 & 1.6 Hz), 8.31 (1H, dd, *J* = 8.0 & 2.0 Hz), 7.54 (1H, d, *J* = 8.0 Hz), 6.89 (1H, s), 6.73 (1H, dd, *J* = 8.0 & 2.0 Hz), 6.64 (1H, d, *J* = 8.0 Hz), 5.84-5.81 (1H, m), 5.62-5.61(1H, m), 4.75 (1H, d, *J* = 3.2 Hz), 4.13-4.16 (1H, m), 3.97 (3H, s), 3.33 (1H, dq, *J* = 8.8 & 3.2 Hz), 2.46-2.39 (1H, m), 2.25 (3H, s), 1.86-1.79 (1H, m); ESI-MS: *m/z* 321 $[M + H]^+$.

Methyl 5-((3aS, 4R, 9bR)-3a, 4, 5, 9b-tetrahydro-8-methyl-3*H*-cyclopenta[*c*]quinolin-4-yl)pyridine-2-carboxylate, *endo*-29b

The following compound was prepared using the same methodology as in compound **29a** using methyl 5-formylpyridine-2-carboxylate (**2**) (29 mg, 0.18 mmol) and *p*-toluidine (19 mg, 0.18 mmol). Solvent was evaporated and purification of the crude material by flash chromatography over silica gel using hexane and ethyl acetate as eluents afforded 30 mg (Yield: 53%) of the title compound(*endo*-**29b**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.77 (1H, s), 8.06-8.00 (2H, m), 6.83 (1H, s), 6.72 (1H, d, *J* = 8 Hz), 6.23 (1H, d, *J* = 8 Hz), 5.85 (1H, m), 5.61 (1H, s), 5.56 (1H, m), 4.63 (1H, d, *J* = 2.8 Hz), 4.01 (1H, d, *J* = 8.8 Hz), 3.95 (3H, s), 3.00-2.97 (1H, m), 2.42-2.36 (1H, m), 2.16 (3H, s), 1.66-1.60 (1H, m).

5-((3aS, 4R, 9bR)-3a, 4, 5, 9b-tetrahydro-8-methyl-3*H*-cyclopenta[*c*]quinolin-4-yl)pyridine-2-carboxylic acid, *endo*-29c

To a solution of 5-formylpyridine-2-carboxylic acid (**3**) (60 mg, 0.4 mmol) in anhydrous ACN (15 mL) was added *p*-toluidine (43 mg, 0.4 mmol), cyclopentadiene (163 mL, 2 mmol) and $BF_3{\cdot}Et_2O$ (101 mL, 0.8 mmol). The reaction mixture was stirred 16 h at RT. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and methanol (0.1% formic acid) as eluents gave 17 mg (Yield: 13%) of the title compound *endo*-**29c**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.77 (1H, s), 8.06-8.00 (2H, m), 6.83 (1H, s), 6.72 (1H, d, *J* = 8 Hz), 6.23 (1H, d, *J* = 8 Hz), 5.85 (1H, m), 5.61 (1H, s), 5.56 (1H, m), 4.63 (1H, d, *J* = 2.8 Hz), 4.01 (1H, d, *J* = 8.8 Hz), 3.00-2.97 (1H, m), 2.42-2.36 (1H, m), 2.16 (3H, s), 1.66-1.60 (1H, m); ESI-MS: *m/z* 307 $[M + H]^+$.

(3aS,4R,9bR)-4-(5-Bromo-3-methylpyridin-2-yl)-8-chloro-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinolone, *endo*-29d

The following compound was prepared using the same methodology as in compound **29a** using 5-bromo-3-methylpyridine-2-carbaldehyde (**4**) (1.17 mmol, 235 mg) and 4-chloroaniline (1.17 mmol, 150 mg). The reaction mixture was stirred at RT for 16 h. Solvent was evaporated and purification of the crude material by flash chromatography over silica gel using an elution of 9% ethyl acetate in hexanes afforded 370 mg (Yield: 84%) of the pure title compound *endo*-**29d**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (1H, d, *J* = 2.4 Hz), 7.67 (1H, d, *J* = 2.4 Hz), 7.06 (1H, d, *J* = 2.4 Hz), 6.98 (1H, dd, *J* = 8.8 & 2.4 Hz), 6.75 (1H, d, *J* = 8.4 Hz), 5.79-5.75 (1H, m), 5.66-5.63 (1H, m), 4.83 (1H, d, *J* = 3.2 Hz), 4.14-4.10 (1H, m), 3.26-3.18 (1H, m), 2.60-2.50 (1H, m), 2.41 (3H, s), 1.76-1.68 (1H, m); ESI-MS: *m/z* 375 $[M + H]^+$.

5-((3aS,4R,9bR)-3a,4,5,9b-tetrahydro-8-methyl-3*H*-cyclopenta[*c*]quinolin-4-yl)-6-methylpyridine-2-carbonitrile, *endo*-29e

The following compound was prepared using the same methodology as in compound **29a**using 5-formyl-6-methylpyridine-2-carbonitrile (**5**) (1 mmol) and 4-methylaniline (1 mmol). Purification of the crude material by flash chromatography over silica gel using hexane and ethyl acetate as eluents afforded 281 mg (Yield: 93%) of the title compound *endo*-**29e**.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.07 (1H, d, *J* = 8.0 Hz), 7.89 (1H, d, *J* = 8.0 Hz), 6.82 (1H, s), 6.69 (1H, dd, *J* = 8.0 & 1.6 Hz), 6.58 (1H, d, *J* = 7.6 Hz), 5.86-5.83 (1H, m), 5.54(1H, d, *J* = 4.8 Hz), 5.40 (1H, s), 4.67 (1H, d, *J* = 2.8 Hz), 4.03-4.00 (1H, m), 3.29 (3H, s), 3.00-2.95 (1H, m), 2.40-2.33 (1H, m), 2.13 (3H, s), 1.57-1.51 (1H, m); ESI-MS: *m/z* 302 $[M + H]^+$.

Ethyl 3-((3aS,4R,9bR)-3a,4,5,9b-tetrahydro-8-methyl-3*H*-cyclopenta[*c*]quinolin-4-yl)-1-methyl-1*H*-pyrazole-5-carboxylate, endo-29f

The following compound was prepared using the same methodology as in compound **29a** using 3-formyl-1-methyl-1*H*-pyrazole-5-carboxylic acid ethyl ester (**6**) (1 mmol) and 4-methylaniline (1 mmol). Purification of the crude material by flash chromatography over silica gel using hexane and ethyl acetate as eluents afforded 128 mg (yield 46%) of the title compound*endo*-**29f**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.87 (1H, s), 6.82 (1H, s), 6.80 (1H, dd, *J* = 8.0 & 2.0 Hz), 6.60 (1H, d, *J* = 8.4 Hz), 5.83-5.79 (1H, m), 5.67-5.65 (1H, m), 4.63 (1H, d, *J* = 3.2 Hz), 4.37 (2H, q, *J* = 7.6 Hz), 4.16 (3H, s), 4.07 (1H, d, *J* = 7.6 Hz), 3.20-3.12 (1H, m), 2.64-2.56 (1H, m), 2.23 (3H, s), 2.14-2.07 (1H, m), 1.39 (3H, t, *J* = 7.6 Hz); ESI-MS: *m/z* 338 $[M + H]^+$.

Ethyl 3-((3aS,4R,9bR)-3a,4,5,9b-tetrahydro-8-methoxy-3*H*-cyclopenta[*c*]quinolin-4-yl)-1-methyl-1*H*-pyrazole-5-carboxylate, *endo*-29g

The following compound was prepared using the same methodology as in compound **29a**using 3-formyl-1-methyl-1*H*-pyrazole-5-carboxylic acid ethyl ester (**6**) (1 mmol) and 4-methoxyaniline (1 mmol). Purification of the crude material (mixture 12:88 of exo/endo diastereomers) by flash chromatography over silica gel using hexane and ethyl acetate as eluents afforded 94 mg (Yield: 34%) of the title compound *endo*-**29g** ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.82 (1H, s), 6.64-6.58 (3H, m), 5.82-5.78 (1H, m), 5.68-5.65 (1H, m), 4.59 (1H, d, *J* = 3.6 Hz), 4.37 (2H, q, *J* = 7.6 Hz), 4.16 (3H, s), 4.07 (1H, d, *J* = 7.6 Hz), 3.75 (3H, s), 3.20-3.12 (1H, m), 2.62-2.54 (1H, m), 2.15-2.08 (1H, m), 1.37 (3H, t, *J* = 7.6 Hz); . ESI-MS: *m/z* 354 $[M + H]^+$.

Ethyl 5-((3aS,4R,9bR)-3a,4,5,9b-tetrahydro-8-methyl-3*H*-cyclopenta[*c*]quinolin-4-yl)-1-methyl-1*H*-pyrazole-3-carboxylate, *endo*-29h

The following compound was prepared using the same methodology as in compound **29a** using 5-formyl-1-methyl-1*H*-pyrazole-3-carboxylic acid ethyl ester (**7**) (1 mmol.) and 4-methylaniline (1mmol). Solvent was evaporated and purification of the crude material by flash chromatography over silica gel using hexane and ethyl acetate as eluents afforded 229 mg (Yield: 91%) of the title compound *endo*-**29h**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.88 (2H, m), 6.82 (1H, dd, *J* = 8.4 & 2 Hz), 6.54 (1H, d, *J* = 7.6 Hz), 5.82-5.80 (1H, m), 5.67-5.66 (1H, m), 4.65 (1H, d, *J* = 3.2 Hz), 4.45-4.34 (2H, m), 4.12-4.07 (1H, m), 3.96 (3H, s), 3.60 (1H, s), 3.05-2.98 (1H, m), 2.73-2.66 (1H, m), 2.24 (3H, s), 2.00-1.92 (1H, m), 1.40 (3H, t, *J* = 7.6 Hz); ESI-MS: *m/z* 338 $[M + H]^+$.

Ethyl 5-((3aS,4R,9bR)-3a,4,5,9b-tetrahydro-8-methoxy-3*H*-cyclopenta[*c*]quinolin-4-yl)-1-methyl-1*H*-pyrazole-3-carboxylate, *endo*-29i

The following compound was prepared using the same methodology as in compound **29a** using 5-formyl-1-methyl-1*H*-pyrazole-3-carboxylic acid ethyl ester (**7**) (1 mmol) and 4-methoxyaniline (1 mmol). Solvent was evaporated and purification of the crude material by flash chromatography over silica gel using hexane and ethyl acetate as eluents afforded 190 mg (Yield: 91%) of the title compound *endo*-**29i**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.88 (1H, s), 6.65-6.57 (3H, m), 5.82-5.78 (1H, m), 5.69-5.66 (1H, m), 4.62 (1H, d, *J* = 2.8 Hz), 4.45-4.36 (2H, m), 4.13-4.01 (1H, m), 3.96 (3H, s), 3.75 (3H, s), 3.52 (1H, s), 3.03-3.00 (1H, m), 2.73-2.66 (1H, m), 2.04-1.94 (1H, m), 1.40 (3H, t, *J* = 7.2 Hz); ESI-MS: *m/z* 354 $[M + H]^+$.

Methyl 2-((3aS,4R,9bR)-8-chloro-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinolin-4-yl)-1-methyl-1*H*-imidazole-4-carboxylate, *endo*-29j

The following compound was prepared using the same methodology as in compound **29a** using methyl 2-formyl-1-methyl-1*H*-imidazole-4-carboxylate (**8**) (0.48 mmol, 80 mg),4-chlorobenzenamine (0.48 mmol, 62 mg) and scandium trifluoromethane sulfonate (1 eq., 0.48 mmol, 237 mg). Solvent was evaporated and purification of the crude material by reverse $C_{18}$to afford 80 mg (Yield: 48%) of the title compound*endo*-**29j** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (1H, s), 7.45 (1H, s), 7.04 (1H, d, *J* = 2.4 Hz), 6.96 (1H, dd, *J* = 8.8 & 2.4 Hz), 6.60 (1H, d, *J* = 8.4 Hz), 5.89 (1H, brs), 5.72 (1H, brs), 5.62 (1H, d, *J* = 3.6 Hz), 4.10-4.08 (1H, m), 3.96 (3H, s), 3.89 (3H, s), 3.13-3.10 (1H, m), 2.68-2.61 (1H, m), 2.07-2.02 (1H, m); ESI-MS: *m/z* 344 $[M + H]^+$.

Methyl 7-((3aS,4R,9bR)-3a,4,5,9b-tetrahydro-8-methoxy-3*H*-cyclopenta[*c*]quinolin-4-yl)-3-methyl-3*H*-benzo[*d*]imidazole-4-carboxylate, *endo*-29k

Boron trifluoride diethyletherate (2 eq., 0.24 mmol, 30 uL) in anhydrous dichloromethane (2 mL) was added to 7-formyl-3-methyl-3*H*-benzo[*d*]imidazole-4-carboxylate **9** (0.12 mmol, 25 mg), *p*-anisidine (0.12 mmol, 0.15 mg), and cyclopentadiene (5 eq., 0.6 mmol, 0.064 mL). The reaction mixture was heated at 50°C for 24 h. Solvent was evaporated and purification of the crude material (mixture 13:87 of exo/endo diastereomers) by flash chromatography over silica gel using an elution of 100% ethyl acetate in hexane afforded 23 mg (Yield: 49%) of the title compound *endo*-**29k** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (1H, d, *J* = 7.6 Hz), 7.87 (1H, s), 7.50 (1H, d, *J* = 8 Hz), 6.74 (1H, s), 6.65-6.61 (2H, m), 5.82 (1H, brs), 5.62 (1H, brs), 5.40 (1H, d, *J* = 2.8 Hz), 4.22 (1H, brs), 4.05 (3H, s), 3.98 (3H, s), 3.76 (3H, s), 2.65-2.55 (1H, m), 1.73-1.69 (1H, m), 1.17-1.13 (1H, m); ESI-MS: *m/z* 390 $[M + H]^+$.

7-((3aS,4R,9bR)-3a,4,5,9b-Tetrahydro-8-methoxy-3*H*-cyclopenta[*c*]quinolin-4-yl)-1*H*-indole-4-carbonitrile, *endo*-29l

A catalytic amount of scandium trifluoromethane sulfonate (0.5 eq., 0.41 mmol, 202 mg) in anhydrous acetonitrile (10 mL) was added to a mixture of 7-formyl-1*H*-indole-4-carbonitrile(**10**)(0.82 mmol, 140 mg), *p*-anisidine (0.82 mmol, 101 mg)and freshly distilled cyclopentadiene (5 eq., 4.1 mmol, 0.33 mL). The reaction mixture was heated at 50°C for 16 h. Solvent was evaporated and purification of the crude material by flash chromatography over silica gel using an elution of 20% ethyl acetate in hexanes afforded 97 mg (Yield: 35%) of the pure title compound *endo*-**29l**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.79 (1H, brs), 7.48 (1H, d, *J* = 7.6 Hz), 7.41 (1H, m), 7.20 (1H, d, *J* = 7.6 Hz), 6.80 (1H, m), 6.71-6.68 (3H, m), 5.92-5.88 (1H, m), 5.68-5.64 (1H, m), 4.92 (1H, d, *J* = 3.6 Hz), 4.16-4.14 (1H, m), 3.90 (1H, brs), 3.79 (3H, s), 3.14-3.06 (1H, m), 2.68-2.60 (1H, m), 1.86-1.79 (1H, m); ESI-MS: *m/z* 342 $[M + H]^+$.

Conclusions

We have synthesized diverse heterocyclic-tetrahydro-1*H*-cyclopenta[*c*]quinolinesusing parallel synthesis in excellent yields and high *endo* diastereoselectivity. These products are highly functionalized natural product-like tricyclic systems, which may be useful as biologically relevant targets. Fine tuning of the reaction conditions need to be performed depending on the nature and molecular structure of the heterocyclic aromatic carbaldehyde, as well as the choice of the Lewis acid.

Further investigations are ongoing to establish the scope of the Povarov reaction using electron rich dienophiles such as 3,4-dihydro-2*H*-pyran from the heterocyclic aromatic carbaldehydes prepared in this report.

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