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Au(I)-Catalyzed Pictet-Spengler Reactions all Around the Indole Ring

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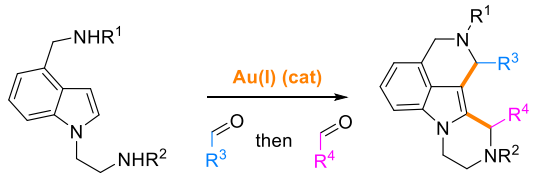


• Au(I) as the single catalyst • Good chemoselectivity
• Two consecutive *iso*-Pictet-Spengler reactions

ABSTRACT: Au(I) complexes catalyze iso-Pictet-Spengler reactions. Ethylamine or methylamine chains were introduced at C2, C4 or at the nitrogen atom of the indole ring, and the corresponding substrates were reacted in the presence of aldehydes and catalytic amounts of Au(I) complexes, leading to a variety of polycyclic scaffolds. Selectivity could be achieved in the course of a double iso-Pictet-Spengler reaction involving two successive aldehydes, leading to highly complex molecules.

INTRODUCTION

Indole alkaloids are an important class of heterocycles because of their prevalence natural and bioactive compounds.[1] Among these privileged scaffolds, tetrahydro-β-carbolines **1** are important molecules and their structural unit is embedded in numerous natural products, among which a huge number are bioactive.[2] The Pictet-Spengler reaction[3,4] combining tryptamines and aldehydes is unarguably the easiest and fastest way to prepare such scaffolds.[2b] Rich of more than a century of research, this reaction and its mechanism has been intensively studied[5] and applied to numerous total syntheses.[2b] Interestingly, because of the nucleophilicity of indole at C2 and C3,[6] numerous variants of the Pictet-Spengler reaction lead to structurally related compounds, such as 1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles **2**,[7] tetrahydro-γ-carbolines **3**,[8] and 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]isoquinoline **4** [7b, 9] (Figure 1). These so-called *iso*-Pictet-Spengler reactions are far less studied than the venerable historic reaction, despite allowing access to interesting heterocycles.[10]

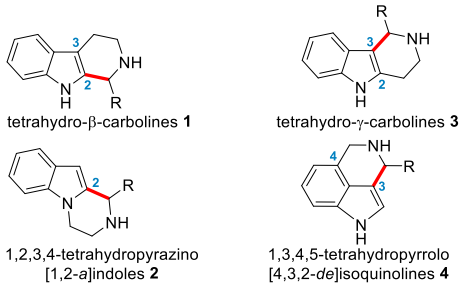
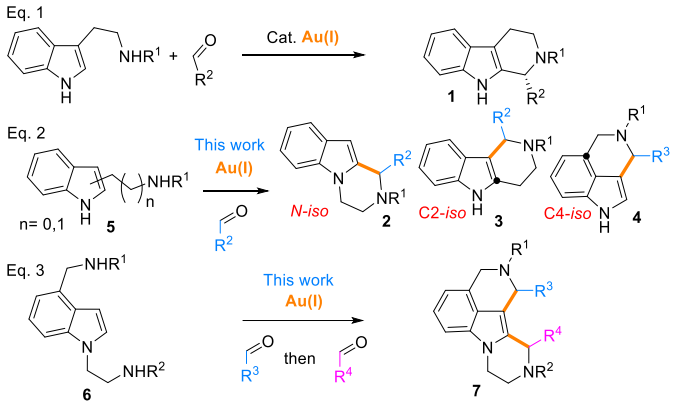


Figure 1. Tetrahydro-β-carbolines and congeners

Our group has long been interested in the gold-catalyzed[11] functionnalizations of indoles .[12,13] Recently, we discovered that Pictet-Spengler reactions could be catalyzed by Au(I) complexes[14,15] (Scheme 1, eq. 1). These reactions occur *via* a mechanism involving the auration of the indole ring that we established through both experimental and computational studies. We hypothesized that similar reactions catalyzed by Au(I) complexes should occur from the use of other regioisomeric alkylamines **5**. Herein, we show that it is possible to obtain regioisomeric compounds **2**, **3** and **4** from gold-catalyzed *iso*-Pictet-Spengler reactions (Scheme 1, eq. 2).



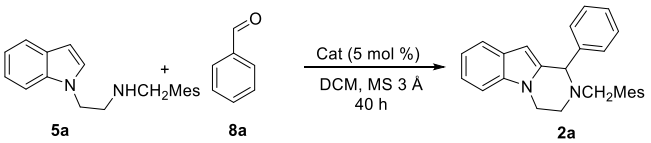
Scheme 1. Context of this work

For clarity purpose, we have defined the reactions as *N-iso*-, C2-*iso*- and C4-*iso*-Pictet-Spengler reactions, depending on the connecting atom of the indole ring to the alkylamine chain. With a good knowledge of each of these different versions of the reaction, we could achieve a one-pot, selective process including successively a C4-*iso* and a *N-iso*-Pictet-Spengler reaction for the synthesis of complex compounds **7** via the C3 then C2 ring-closures, with two different aldehydes (Scheme 1, eq. 3). An initial version of this work was deposited.[16]

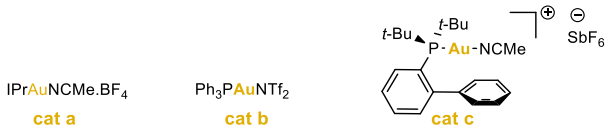
RESULTS AND DISCUSSION

Our journey started with the study of the *N-iso*-Pictet-Spengler reactions from *N-iso*-tryptamine **5a** and benzaldehyde **8a**, reacted in toluene in the presence of molecular sieves over a 40 h period (Table 1, see also Table S1 in the Supporting Information). In the absence of catalyst, no background reaction occurred (entry 1). Though counterintuitive, the reaction did not proceed either in the presence of an acidic catalyst, as previously reported[7d] for C3-unsubstituted *N-iso*-tryptamines (entry 2). We next screened a series of three Au(I) catalysts (entries 3-5), for which only the Gagosz catalyst[17] led to a moderate conversion (20%, entry 4). The solvent was replaced by DCM, allowing to reach a 69% conversion, further optimized to 74% after slight increase of the reaction temperature (entries 6-7). We have further checked that no background reaction occurs at this temperature in the absence of catalyst (entry 8).

Table 1. Optimisation of the *N-iso* Pictet-Spengler reaction



entry	Catalyst (mol%)	Solvent	T (°C)	Conv(%)[a]
1	-	PhMe/DCM	rt	0
2	$(PhO)_2POOH$	PhMe	rt	0
3	Cat a	PhMe	rt	0
4	Cat b	PhMe	rt	20
5	Cat c	PhMe	rt	Traces
6	Cat b	DCM	rt	69
7	Cat b	DCM	30	74
8	-	DCM	30	0



[a] Conversion were measured by ^{1}H NMR by measuring the ratio **5a**/**2a**.

We next engaged a number of aromatic aldehydes in the reaction (Scheme 2, *N-iso* Pictet-Spengler reaction). The reactions performed with benzaldehyde and *p*-bromobenzaldehyde led to **2a** and **2b** in 87% and 51% yields, respectively. A bromide group was tolerated at the *meta* and *para* positions, leading to compounds **2c** and **2d** in good yields. The reaction also proved compatible with aldehydes bearing electron-withdrawing CF_3 groups at the *para* and *meta* positions. When *m*-methoxybenzaldehyde **8g** was used, the corresponding product **2g** was obtained in 59% yield. 4- and 6-quinoline carbaldehydes then furnished compounds **2h** and **2i** in 87% and 93% yields, respectively. However, aliphatic aldehydes are not suitable substrates in this reaction, since 3-phenylpropanal did not lead to the expected compounds **2j**. An additional experiment performed in the presence of both benzaldehyde and 3-phenylpropanal (2 equiv. each) led only to the product **2a**, demonstrating the high chemoselectivity of this reaction towards arylaldehydes.

We switched to the gold-catalyzed C2-*iso*-Pictet-Spengler reaction, performed from isotryptamine **5b** and a range of aldehydes (Scheme 2, C2-*iso* Pictet-Spengler reaction). Of note, this reaction is characterized by a strong background reaction when performed in the absence of catalyst (89% conversion, see Table S2 in the supporting information). In view of potential future enantioselective applications, we sought for conditions ensuring a gold-catalyzed process. At 0 °C in the absence of catalyst, 23% conversion was obtained. However, this background reaction can be suppressed by decreasing the temperature to -20 °C. At this temperature, the tetrahydro-γ-carboline **3a** was obtained in 56% yield when the reaction was performed in the presence of complex **b** (5 mol%), testifying for a solely Au(I)-catalyzed process. Interestingly, the reaction showed a total selectivity between the nucleophilic C3 of the indole vs the potential reaction that could occur at the nitrogen atom. We screened a selection of functionalized arylaldehydes that could potentially result in reactivity issues if the reaction was acid-catalyzed and for each of these aldehydes, the absence of background reaction was checked at rt and -20 °C (see Figure S1 in the supporting information for details). In the presence of the gold(I) catalyst, compounds **3b** and **3c** bearing a 4-quinolynyl and 4-pyridyl chain, respectively, were obtained in good yields. Isophthalaldehyde led to

the product **3d** in 75% yield as a single product (no trace of doubly functionalized compound). Remarkably, despite a lower conversion and the need to react at rt, the reaction also tolerated an aldehyde bearing a nitrone function, known to be activated by Au(I) complexes,[18] leading to compound **3e** in 47% yield.[19] Comparatively, this kind of aldehyde would not be suitable in related acidic-catalyzed reactions, because of the activation of the highly electrophilic nitrone. All blank tests conducted with these aldehydes in the absence of catalyst show no conversion at -20 °C (and only little conversion at rt, see the supporting information for details).

We further moved toward the introduction of the alkylamine chain at C4 atom of the indole ring and studied the reaction of tryptamine **5c** with *p*-bromobenzalehyde in the presence (plain curves) of absence of catalyst (dashed curves) (Figure 2, see also Table S3 and Figure S2 in the Supporting Information). When the reaction was performed at 0 °C, the reaction performed in the absence of catalyst barely showed conversion (<5% conversion), while the same reaction in the presence of 5 mol% of **cat b** led to 50% conversion. At room temperature, we also observed a strong difference in the reaction kinetic, leading to 21% conversion in the absence of catalyst, while both 5 mol% and 2 mol% catalyst led to full conversions. The role of the gold catalyst is here again crucial to ensure full conversion over reasonable time, while conditions with solely Au(I)-catalyzed process can also be applied if required.

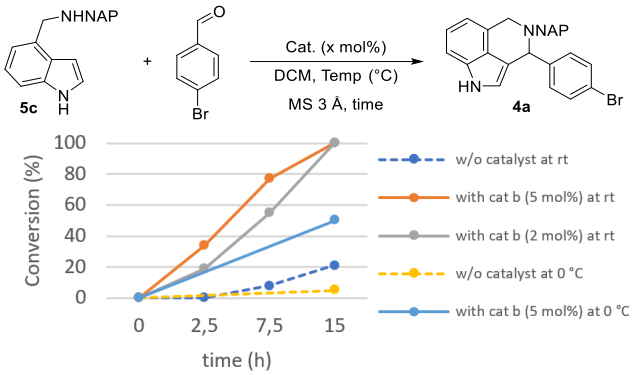


Figure 2. Reaction kinetic. Conversion were measured by ^{1}H NMR by measuring the ratio 5c/4a

Because of the attractively low 2 mol% catalyst loading, we selected the conditions at room temperature to study the scope of this reaction (Scheme 2, C4-*iso* Pictet-Spengler reaction). The reaction of **5c** with *p*-bromobenzaldehyde in DCM at room temperature in the presence of only 2 mol% of Gagosz catalyst led to the corresponding 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]isoquinoline **4a** in 75% isolated yield. Benzaldehyde and *m*-trifluoromethylbenzaldehyde also led to excellent yields in **4b,c**. A fluorine group at the *ortho* position was well tolerated, while a methoxy group at the *para* position led to a decrease of the reactivity (**4e**, 38% yield). The phthalaldehyde led to compound **4f** in 46% yield, this time accompanied by the dimeric product (ratio **4f**/dimer: 10/4). A boronate ester at the *para* position was tolerated, leading to **4g** in 53% yield, opening opportunities for subsequent cross-coupling functionnalizations. **4h**, bearing a quinolyl moiety was formed in 71% yield. Interestingly, aliphatic aldehydes were well converted to compounds **4i-k** in moderate to good yields, while the same reactions performed in the absence of catalyst resulted in no conversions (see Table S4 and Figure S3 in the supporting information for details). To date, this is the first time that we observed conversion in the course of any version of the four different Au(I)-catalyzed (*iso*)Pictet-Spengler reactions that we studied with aliphatic aldehydes.

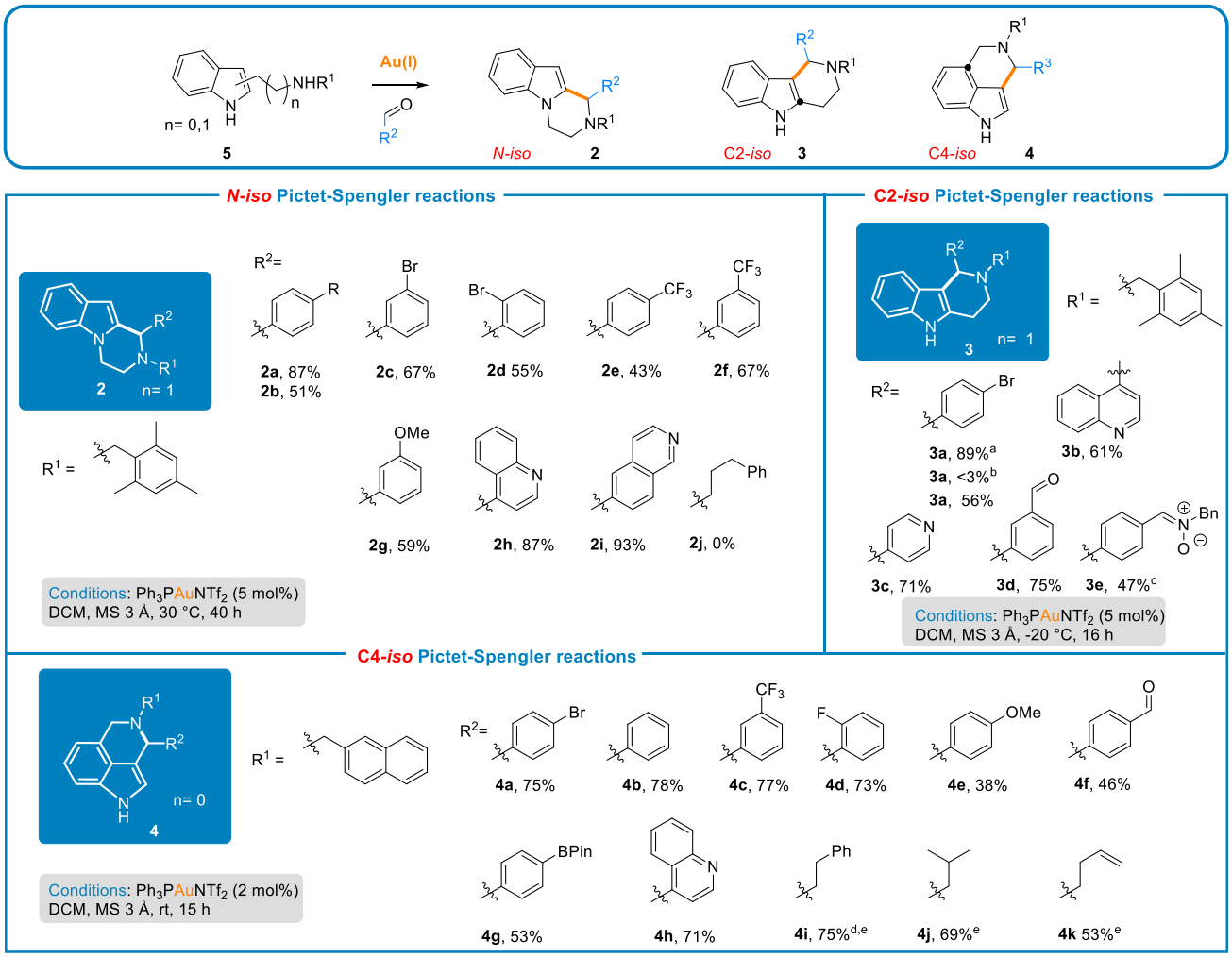
We next considered the possibility that an indole ring functionalized with two alkylamine chains at the *N*- and C4-position could undergo C2-C3 difunctionalization *via* a C4-*iso* and a *N-iso*-Pictet-Spengler cyclization cascade. For this purpose, we designed the diamine **5d**, keeping the same groups on the nitrogen atoms and slightly increased the temperature to 40 °C to ensure maximum conversion.
Indeed, gold-catalyzed reaction of **5d** with benzaldehyde at 40 °C led to tetracyclic 2,3,8,9,10,11-hexahydro-1*H*-pyrazino[1',2':1,5]pyrrolo[4,3,2-*de*]isoquinoline **9a** in 68% yield and a 70/30 diatereomeric ratio, in favor of the *anti* diastereoisomer (Scheme 3a, see also Table S5 in the Supporting Information for optimization).[20] To the best of our knowledge, this scaffold has never been reported. When the *meta*-trifluoromethylbenzaldehyde was used, compound **9b** was obtained in 58% yield, with the diasteromeric ratio in favor of the *syn* isomer. 4-Quinoline carboxaldehyde led to the amine **9c** in 88% yield and full *anti*-diastereoselectivity. We next reasoned that the C4-

iso Pictet-Spengler reaction, operating with lower catalyst loading and temperature, should occur faster than the *N-iso* reaction, requiring higher catalyst loading and temperature. Indeed, when **5d** was engaged in the reaction with 1 equivalent of *p*-bromobenzaldehyde, the C4-*iso* Pictet-Spengler product **10a** was selectively obtained at room temperature in 71% yield with 10 mol% **cat b** (Scheme 3b, eq. 1).

Control experiments revealed that: 1) no background reaction occurs in the absence of Au(I) catalyst on substrate **5d** and 2) it is necessary to increase the catalyst loading to ensure a good conversion in this step. Compound **10a** was then engaged in the *N-iso* Pictet-Spengler reaction with benzaldehyde that led to **11a** in 70% yield as a mixture of diastereomers (Scheme 3b, eq. 2, dr 25/75).
We then developed the one-pot formation of compounds **11** by sequential addition of two different aldehydes from **5d** in the presence of 10 mol% of the gold complex **b** as catalyst (Scheme 3c). After 15 h of reaction in the presence of *p*-bromobenzaldehyde (1 equiv) at room temperature, benzaldehyde was added to the reaction mixture and further 24 h reaction led to compound **11a** in 72% yield (dr 35/65) in favor of the *syn* isomer.

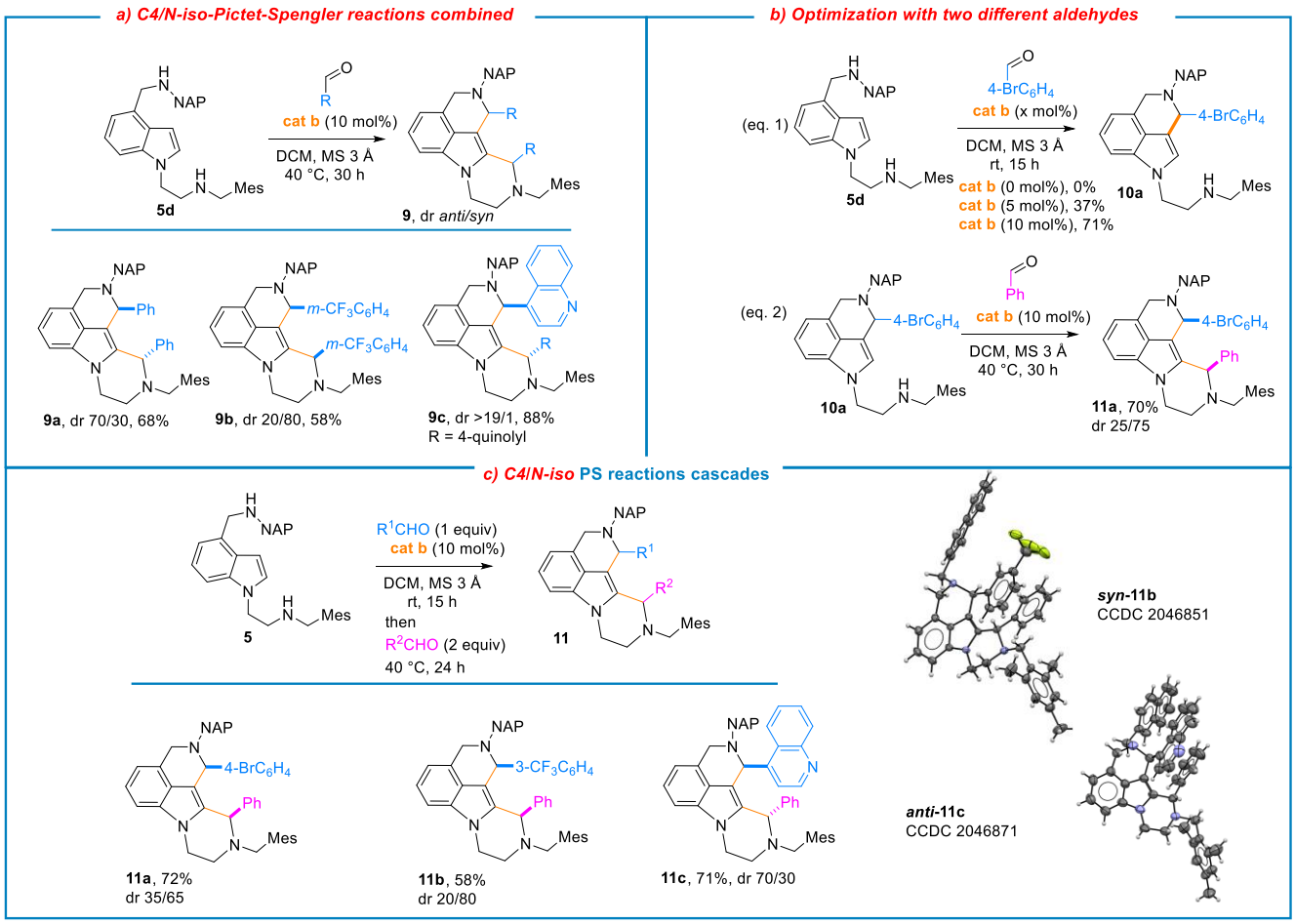
The same protocol was applied to another couple of aromatic aldehydes, leading to compound **11b** in good yields and good diastereoselectivity (dr 20/80). Gratifyingly, we obtained the X-ray structure of the *syn*-diastereomer of **11b** (CCDC 2046851). Beyond confirming its structure, it was helpful to further identify all other diastereomers of the series of compounds **9** and **11**. When 4-quinolinecarboxaldehyde was used in the first C4-*iso*-Pictet-Spengler step (requiring a higher 40 °C temperature), followed by benzaldehyde for the *N-iso* step, compound **11c** was obtained in 71% yield and diastereoselectivity in favor of the *anti*-isomer (CCDC 2046871). The diastereoselectivity of these reactions may be the result of electronic effects. Indeed, the X-ray structure of the *syn*-**11b** shows a pretty good superposition of the phenyl and the trifluoromethylphenyl ring with a distance between the two aryl planes of ca. 3.30 Å. As reviewed by Iverson, interactions between electron-poor/electron rich aryls may be referred to the favored "aromatic donor- acceptor interactions" or polar/π model.[21] This would explain the general trend to lead to the *syn*-diastereomer with electron-poor aryl (**9b**, **11a**, **11b**) while destabilizing interactions operating with electron-rich aryl rings couples (phenyl, quinoline and their combination) lead mainly to the *anti*-isomer (**9a**, **9c**, **11c**).

Gratifyingly, no need for an addition batch of catalyst was required for the application of this protocol. The formation of these compounds, as the result of two successive *iso*-Pictet-Spengler reactions with different aldehydes, opens avenues for the synthesis of highly functionalized and complex compounds. This strategy potentially offers unique opportunities for the exploration of chemical space in biological studies.



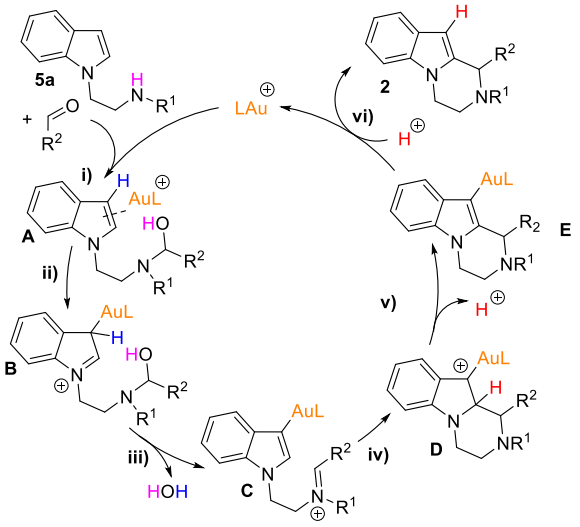
[a] Performed at room temperature in the absence of catalyst. [b] Performed at -20 °C in the absence of catalyst. [c] Performed at rt. [d] Performed with 5 mol% of $Ph_3PAuNTf_2$. [e] Conversion is 0% in the absence of catalyst.

Scheme 2. Scope of the different versions of the *iso*-Pictet-Spengler reactions studied



Scheme 3. Selective bis-functionnalization (the relative stereochemistry indicated is that of the major diastereomer)

The mechanistic hypothesis for these reactions relies on our previous gold-catalyzed "classical" Pictet-Spengler reactions[14a] and is illustrated below with the *N-iso*-version of the reaction (Scheme 4), with the following steps. (*i*) The spontaneous addition of the amine to the aldehyde leads to an hemiaminal (this step being potentially catalyzed by the Au(I) complex). (*ii*) The coordination of the indole ring leads to the η^2 and η^1-gold complexes **A** and **B**. (*iii*) The conversion of the latter to an iminium *via* an intramolecular abstraction of a proton and release of water generates **C**.[22] (*iv*) the nucleophilic addition to the iminium via C2 forms complex0 **D**. (*v*) The elimination of a proton *via* **E** and protodeauration then leads to the product **2** and the regeneration of the cationic Au(I) complex. Similar mechanisms can be involved for the C2- and C4-*iso*-Pictet-Spengler reactions (see Schemes S1, S2 and S3 in the supporting Information).



Scheme 4. Mechanistic pathway in *N-iso*-Pictet-Spengler reactions

CONCLUSION

To conclude, we have developed Au(I)-catalyzed *iso*-Pictet-Spengler reactions by introduction of the alkylamine chain around all the different positions of the

indole ring allowing a trapping of the *in situ* generated iminium ion by either the C2 or C3 atom. This led to the isolation of numerous heterocyclic scaffolds. We have showed the high chemoselectivity enabled by Au(I) catalyzed processes in these reactions, in particular by design of the *in situ* sequential cascade of C4- and *N-iso*-Pictet-Spengler reactions leading to highly complex polycyclic indolic arrangements. We are currently studying the enantioselective gold-catalyzed version of these reactions.

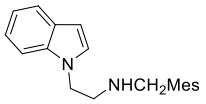
EXPERIMENTAL SECTION

Reactions were performed using oven-dried glassware under an argon atmosphere. All separations were carried out under flash-chromatographic conditions on silica gel (prepacked column, 230–400 mesh) at medium pressure (20 psi) with the use of a CombiFlash Companion. Reactions were monitored by thin-layer chromatography on Merck silica gel plates (60 F254 aluminum sheets), which were rendered visible by ultraviolet and spraying with vanillin (15%) + sulfuric acid (2.5%) in EtOH followed by heating. Reagent-grade chemicals were obtained from diverse commercial suppliers (Sigma-Aldrich, Acros Organics, Fluorochem, TCI and Alfa-Aesar) and were used as received. **^{1}H NMR** (500 or 300 MHz) and **^{13}C NMR** (125 or 75 MHz) spectra were recorded on Brücker Avance spectrometers at 298 K unless otherwise stated. Chemical shifts are given in ppm (δ) and are referenced to the internal solvent signal or to TMS used as an internal standard. Multiplicities are declared as follow: *s* (singlet), *brs* (broad singlet), *d* (doublet), *t* (triplet), *q* (quadruplet), *dd* (doublet of doublet), *ddd* (doublet of doublet of doublet), *dt* (doublet of triplet), *m* (multiplet), AB = AB quartet, AB*X* = ABX system. Coupling constants *J* are given in Hz. Carbon multiplicities were determined by DEPT135 experiment. Diagnostic correlations were obtained by two-dimensional COSY, HSQC and NOESY experiments. **Infrared spectra** (IR) were recorded on a Perkin-Elmer FT-IR system using diamond window Dura SamplIR II and the data are reported in reciprocal centimeters (cm-1). **High-resolution mass spectra (HRMS)** were recorded using a Micromass LCT Premier XE instrument (Waters) and were determined by electrospray ionization (ESI, TOF analyzer).

All reactions were accordingly performed using purified aldehydes. Aldehydes were purified by washing a solution of the aldehyde in Et_2O by NaOH (2 M in H_2O), followed by drying on $MgSO_4$ and filtration of the resulting solution on a short pad of silica gel, followed by concentration under vacuum. In addition, tryptamines were dissolved in EtOAc and washed by NaOH (2 M in H_2O) on a regular basis, to avoid undesired catalysis from potential protonated amines. Finally, molecular sieves must be powdered and activated for two hours under vacuum at 200 °C before use. All reactions requiring heating were heated with an oil bath.

N-Iso Pictet-Spengler reaction

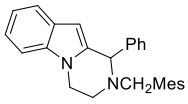
Synthesis of 2-(1*H*-indol-1-yl)-*N*-(2,4,6-trimethylbenzyl)ethan-1-amine **5a**



2-(1*H*-indol-1-yl)ethan-1-amine (prepared according to the procedure described by Verma in 84% yield) [7e] (1.5 g, 9.4 mmol, 1.00 equiv.), 2,4,6-trimethylbenzaldehyde (1,32 g, 8.9 mmol, 0.95 equiv.) were stirred in methanol (40 mL) under an argon atmosphere for 36 hours. Then, the reaction media was cooled to 0 °C before adding $NaBH_4$ (2 * 262 mg, 13.8 mmol, 1.80 equiv.), then the mixture was allowed to reach room temperature. After 1 hour stirring, the volatiles were removed and the crude mixture was next diluted in ethyl acetate and water. After the phases were separated, the aqueous phase was extracted twice by ethyl acetate then the combined organic phases were dried over $MgSO_4$ and evaporated under vacuum. The desired product **5a** was obtained after column chromatography on silica gel (gradient from 20 to 100 % Heptane:EtOAc) as a greenish oil (1.37 g, 4.7 mmol, 50 %). **IR (neat) ν_{max}** = 2915, 1612, 1511, 1462, 1313, 1113, 1012 cm^{-1}. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ = 7.67 (d, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.24 (td, *J* = 7.3, 0.7 Hz, 1H), 7.18-7.11 (m, 2H), 6.84 (s, 2H), 6.52 (d, *J* = 3.1 Hz, 1H), 4.29 (d, *J* = 6.3 Hz, 2H), 3.76 (s, 2H), 3.15 (t, *J* = 6.3 Hz, 1H), 2.29 (s, 6H), 2.27 (s, 3H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz)** δ = 137.1 (C_q), 136.8 (C_q), 136.2 (C_q), 133.2 (C_q), 129.2 (CH), 128.9 (C_q), 128.2 (CH), 121.7 (CH), 121.2 (CH), 119.5 (CH), 109.5 (CH), 101.5 (CH), 49.5 (CH_2), 47.7 (CH_2),46.8 (CH_2), 21.0 (CH_3), 19.7 (CH_3). **HRMS (ESI)**: *m/z*: calc for $C_{20}H_{25}N_2^+$ 293.2017 $[M+H]^+$, found 293.2007.

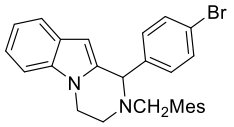
General procedure 1 for the synthesis of tetrahydropyrazino[1,2-*a*]indoles 2: A mixture of *N*-iso tryptamine **5a** (0.15 mmol), **Cat b** (5 mol %, 0.0075 mmol, 5.3 mg) and 3 Å molecular sieves (150 mg for 0.15 mmol of **5a**, powdered) in dichloromethane (1.5 mL for 0.15 mmol of **5a**) was stirred for 5 min at room temperature under an argon atmosphere. Subsequently, aldehyde (2.0 equiv., 0.30 mmol) was added and the mixture stirred for 40 h at 30 °C. For practical reasons, the excess of aldehyde was reduced at the end of the reaction by mean of $NaBH_4$ to facilitate the purification. The reaction mixture was then cooled to 0 °C and methanol (1.5 mL for 0.15 mmol of **5a**) alongside sodium borohydride (2.0 equiv.) was added to the reaction mixture. It was then allowed to reach room temperature and stirred for 1 hour. Then it was filtered under celite and silica was added. After evaporation of the volatiles, the silica mixture was purified by chromatography under silica gel to give the desired product **2**.

1-phenyl-2-(2,4,6-trimethylbenzyl)-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole **2a**



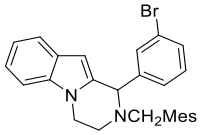
Compound **2a** was synthesized following the **General procedure 1** using tryptamine **5a** (44 mg, 0.15 mmol, 1.0 equiv.), benzaldehyde (32 mg, 0.30 mmol, 2.0 equiv.), **Cat b** (5.3 mg, 0.0075 mmol), in DCM (1.5 mL). The desired product **2a** was obtained after column chromatography on silica gel (gradient from 0 to 50 % Heptane:EtOAc) as a green amorphous solid (49 mg, 0.13 mmol, 87 %). **IR (neat) ν_{max}** = 2919, 1612, 1451, 1375, 1312, 1265, 1228, 1148, 1074 cm^{-1}. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ = 7.52 (d, *J* = 7.8 Hz, 1H), 7.50-7.46 (m, 2H), 7.42-7.36 (m, 3H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.20 (td, *J* = 7.0, 0.6 Hz, 1H), 7.12 (td, *J* = 7.0, 0.6 Hz, 1H), 6.88 (s, 2H), 5.82 (s, 1H), 4.69 (s, 1H), 4.16 (dt, *J* = 11.3, 3.6 Hz, 1H), 3.98 (dt, *J* = 10.4, 4.6 Hz, 1H), 3.71 (d, *J* = 12.5 Hz, 1H), 3.39 (d, *J* = 12.5 Hz, 1H), 3.21 (dt, *J* = 12.1, 4.1 Hz, 1H), 2.81 (td, *J* = 12.1, 4.0 Hz, 1H), 2.31 (s, 9H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz)** δ = 141.7 (C_q), 139.1 (C_q), 138.6 (C_q), 136.8 (C_q), 136.0 (C_q), 131.5 (C_q), 129.9 (CH), 129.3 (CH), 128.4 (C_q), 128.2 (CH), 128.1 (CH), 120.9 (CH), 120.4 (CH), 120.0 (CH), 108.9 (CH), 100.2 (C_q), 99.7 (CH), 67.6 (CH), 52.4 (CH_2), 47.0 (CH_2), 42.0 (CH_2), 21.1 (CH_3), 20.7 (CH_3). **HRMS (ESI)**: *m/z*: calc for $C_{27}H_{29}N_2^+$ 381.2331 $[M+H]^+$, found 381.2335

1-(4-bromophenyl)-2-(2,4,6-trimethylbenzyl)-1,2,3,4-tetrahydro-pyrazino[1,2-*a*]indole **2b**



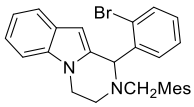
Compound **2b** was synthesized following the **General procedure 1** using tryptamine **5a** (44 mg, 0.15 mmol, 1.0 equiv.), 4-bromobenzaldehyde (55 mg, 0.30 mmol, 2.0 equiv.), **Cat b** (5.3 mg, 0.0075 mmol), in DCM (1.5 mL). The desired product **2b** was obtained after column chromatography on silica gel (gradient from 0 to 50 % Heptane:EtOAc) as a green amorphous solid (35 mg, 0.076 mmol, 51 %). **IR (neat) ν_{max}** = 2970, 1737, 1451, 1366, 1217, 1011cm^{-1}. **^{1}H NMR (CDCl$_3$, 500 MHz)** δ = 7.42-7.36 (m, 3H), 7.23 (d, *J* = 7.6 Hz, 1H), 7.18 (d, *J* = 8.1 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 7.00 (t, *J* = 7.4 Hz, 1H), 6.75 (s, 2H), 5.69 (s, 1H), 4.55 (s, 1H), 4.07-4.01 (m, 1H), 3.90-3.81 (m, 1H), 3.57 (d, *J* = 12.5 Hz, 1H), 3.28 (d, *J* = 12.5 Hz, 1H), 3.08 (d, *J* = 12.0 Hz, 1H), 2.81 (t, *J* = 9 Hz, 1H), 2.18 (s, 3H), 2.17 (s, 6H) . **^{13}C{^{1}H} NMR (CDCl$_3$, 75 MHz)** δ = 140.9 (C_q), 138.5 (C_q), 138.2 (C_q), 137.0 (C_q), 136.0 (C_q), 131.5 (CH), 131.4 (CH), 131.2 (Cq), 129.3 (CH), 128.3 (C_q), 122.0 (Cq), 121.2 (CH), 120.5 (CH), 120.1 (CH), 110.7 (C_q), 108.9 (C_q), 99.9 (CH), 66.6 (CH), 52.4 (CH_2), 46.8 (CH_2), 41.8 (CH_2), 21.1 (CH_3), 20.7 (CH_3). **HRMS (ESI)**: *m/z*: calc for $C_7H_{28}N_2Br^+$ 459.1436 $[M+H]^+$, found 459.1421

1-(3-bromophenyl)-2-(2,4,6-trimethylbenzyl)-1,2,3,4-tetrahydro-pyrazino[1,2-*a*]indole **2c**



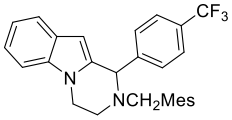
Compound **2c** was synthesized following the **General procedure 1** using tryptamine **5a** (44 mg, 0.15 mmol, 1.0 equiv.), 3-bromobenzaldehyde (55 mg, 0.30 mmol, 2.0 equiv.), **Cat b** (5.3 mg, 0.0075 mmol), in DCM (1.5 mL). The desired product **2c** was obtained after column chromatography on silica gel (gradient from 0 to 50 % Heptane:EtOAc) as a green amorphous solid (46 mg, 0.10 mmol, 67 %). **IR (neat) ν_{max}** = 2922, 2853, 1739, 1571, 1452, 1375, 1319, 1217, 1149, 1070 cm^{-1}. **^{1}H NMR (CDCl$_3$, 500 MHz)** δ = 7.61 (s, 1H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.37 (d, *J* = 7.7 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 1H), 7.22 (t, *J* = 7.9 Hz, 1H), 7.18 (t, *J* = 7.9 Hz, 1H), 7.10 (t, *J* = 7.9 Hz, 1H), 6.85 (s, 2H), 5.82 (s, 1H), 4.64 (s, 1H), 4.15-4.10 (m, 1H), 3.94 (td, *J* = 10.6, 4.4 Hz, 1H), 3.66 (d, *J* = 12.5 Hz, 1H), 3.39 (d, *J* = 12.5 Hz, 1H), 3.18 (dt, *J* = 11.9, 3.8 Hz, 1H), 2.79 (td, *J* = 11.0, 4.0 Hz, 1H), 2.27 (s, 9H). **^{13}C{^{1}H} NMR (CDCl$_3$, 75 MHz)** δ = 144.2 (C_q), 138.6 (C_q), 138.0 (C_q), 137.0 (C_q), 136.0 (C_q), 132.7 (CH), 131.2 (CH), 131.1 (C_q), 129.8 (CH), 129.4 (CH), 128.3 (CH), 128.3 (C_q), 122.4 (C_q), 121.2 (CH), 120.5 (CH), 120.1 (CH), 109.0 (CH), 100.2 (C_q), 99.9 (CH), 66.7 (CH), 52.5 (CH_2), 46.8 (CH_2), 41.8 (CH_2), 21.1 (CH_3), 20.6 (CH_3). **HRMS (ESI)**: *m/z*: calc for $C_{27}H_{28}N_2Br^+$ 459.1436 $[M+H]^+$, found 459.1428

1-(2-bromophenyl)-2-(2,4,6-trimethylbenzyl)-1,2,3,4-tetrahydro-pyrazino[1,2-*a*]indole **2d**



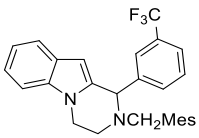
Compound **2d** was synthesized following the **General procedure 1** using tryptamine **5a** (44 mg, 0.15 mmol, 1.0 equiv.), 2-bromobenzaldehyde (55 mg, 0.30 mmol, 2.0 equiv.), **Cat b** (5.3 mg, 0.0075 mmol), in DCM (1.5 mL). The desired product **2d** was obtained after column chromatography on silica gel (gradient from 0 to 50 % Heptane:EtOAc) as a green amorphous solid (37 mg, 0.083 mmol, 55 %). **IR (neat) ν_{max}** = 2922, 2853, 1739, 1451, 1375, 1323, 1218, 1117, 1024cm^{-1}**^{1}H NMR (CDCl$_3$, 500 MHz)** δ = 7.54 (d, *J* = 7.9 Hz, 1H), 7.45 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.37 (d, *J* = 7.9 Hz, 1H), 7.21-7.14 (m, 2H), 7.10 (td, *J* = 5.0, 1.5 Hz, 1H), 7.06 (t, *J* = 5.0 Hz, 1H), 6.97 (t, *J* = 4.9 Hz, 1H), 6.74 (s, 2H), 5.68 (s, 1H), 5.25 (s, 1H), 4.04 (dt, *J* = 11.2, 2.7 Hz, 1H), 3.87 (dt, *J* = 11.2, 4.2 Hz, 1H), 3.53 (d, *J* = 12.5 Hz, 1H), 3.42 (d, *J* = 12.5 Hz, 1H), 3.07 (dq, *J* = 11.7, 2.0 Hz, 1H), 2.74 (td, *J* = 11.6, 3.6 Hz, 1H), 2.18 (s, 3H), 2.16 (6H). **^{13}C{^{1}H} NMR (CDCl$_3$, 75 MHz)** δ = 141.1 (C_q), 138.7 (C_q), 138.4 (C_q), 136.9 (C_q), 135.7 (C_q), 132.7 (CH), 132.6 (CH), 131.2 (C_q), 129.5 (CH), 129.3 (CH), 128.4 (C_q), 127.6 (CH), 125.4 (C_q), 121.0 (CH), 120.4 (CH), 120.0 (CH), 108.8 (CH), 100.2 (C_q), 99.0 (CH), 66.3 (CH), 52.3 (CH_2), 47.5 (CH_2), 42.5 (CH_2), 21.1 (CH_3), 20.8 (CH_3). **HRMS (ESI)**: *m/z*: calc for $C_{27}H_{28}N_2Br^+$ 459.1436 $[M+H]^+$, found 459.1430

1-(4-(trifluoromethyl)phenyl)-2-(2,4,6-trimethylbenzyl)-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole **2e**



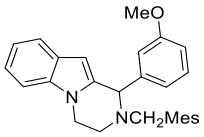
Compound **2e** was synthesized following the **General procedure 1** using tryptamine **5a** (44 mg, 0.15 mmol, 1.0 equiv.), 4-trifluorobenzaldehyde (52 mg, 0.30 mmol, 2.0 equiv.), **Cat b** (5.3 mg, 0.0075 mmol), in DCM (1.5 mL). The desired product **2e** was obtained after column chromatography on silica gel (gradient from 0 to 50 % Heptane:EtOAc) as a green amorphous solid (29 mg, 0.065 mmol, 43 %). **IR (neat) ν_{max}** = 2924, 1739, 1452, 1366, 1322, 1217, 1164, 1126, 1067, 1018 cm^{-1}. **^{1}H NMR (CDCl$_3$, 500 MHz)** δ = 7.52 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 7.9 Hz, 2H), 7.40 (d, *J* = 7.9 Hz, 1H), 7.21 (d, *J* = 8.1 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.76 (s, 2H), 5.70 (s, 1H), 4.69 (s, 1H), 4.07 (dt, *J* = 11.6, 4.1 Hz, 1H), 3.92-3.85 (m, 1H), 3.57 (d, *J* = 12.4 Hz, 1H), 3.33 (d, *J* = 12.4 Hz, 1H), 3.11 (dt, *J* = 12.2, 4.2 Hz, 1H), 2.74 (td, *J* = 10.8, 3.8 Hz, 1H), 2.18 (s, 3H), 2.17(s, 6H). **^{13}C{^{1}H} NMR (CDCl$_3$, 75 MHz)** δ = 146.0 (C_q), 138.5 (C_q), 137.6 (C_q), 137.1 (C_q), 136.1 (C_q), 131.1 (C_q), 130.0 (CH), 129.4 (CH), 128.3 (C_q), 127.9 (q, C-F, $^1J_{C-F}$ = 267.1 Hz, CF_3), 125.3 (q, C-F, $^3J_{C-F}$ = 3.3 Hz, CH), 121.3 (CH), 120.5 (CH), 120.2 (CH), 109.0 (CH), 100.2 (C_q), 100.0 (CH), 66.4 (CH), 52.4 (CH_2), 46.7 (CH_2), 41.6 (CH_2), 21.1 (CH_3), 20.7 (CH_3). **^{19}F NMR (CDCl$_3$, 282 MHz)** δ = -62.4. **HRMS (ESI)**: *m/z*: calc for $C_{28}H_{28}N_2F_3^+$ 449.2205 $[M+H]^+$, found 449.2195

1-(3-(trifluoromethyl)phenyl)-2-(2,4,6-trimethylbenzyl)-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole **2f**



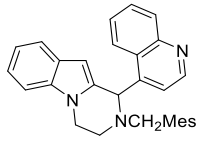
Compound **2f** was synthesized following the **General procedure 1** using tryptamine **5a** (44 mg, 0.15 mmol, 1.0 equiv.), 3-trifluorobenzaldehyde (52 mg, 0.30 mmol, 2.0 equiv.), **Cat b** (5.3 mg, 0.0075 mmol), in DCM (1.5 mL). The desired product **2f** was obtained after column chromatography on silica gel (gradient from 0 to 50 % Heptane:EtOAc) as a green amorphous solid (46 mg, 0.10 mmol, 67 %). **IR (neat) ν_{max}** = 2921, 1739, 1451, 1320, 1163, 1127, 1072 cm^{-1}. **^{1}H NMR (CDCl$_3$, 500 MHz)** δ = 7.76 (s, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.20 (t, *J* = 7.3 Hz, 1H), 7.11 (t, *J* = 7.4 Hz, 1H), 6.86 (s, 2H), 5.78 (s, 1H), 4.73 (s, 1H), 4.16 (dt, *J* = 10.6, 3.7 Hz, 1H), 3.97 (td, *J* = 10.7, 4.3 Hz, 1H), 3.63 (d, *J* = 12.5 Hz, 1H), 3.40 (d, *J* = 12.5 Hz, 1H), 3.20 (dt, *J* = 12.3, 4.1 Hz, 1H), 2.82 (td, *J* = 11, 3.8 Hz, 1H), 2.28 (s, 3H), 2.27 (s, 6H). **^{13}C{^{1}H} NMR (CDCl$_3$, 75 MHz)** δ = 143.0 (C_q), 138.5 (C_q), 137.9 (C_q), 137.1 (C_q), 136.1 (C_q), 133.1 (CH), 131.0 (C_q), 129.4 (CH), 128.7 (CH), 128.3 (C_q), 128.0 (q, C-F, $^1J_{C-F}$ = 274.4 Hz, CF_3), 126.5 (q, C-F, $^3J_{C-F}$ = 3.5 Hz, CH), 125.0 (q, C-F, $^3J_{C-F}$ = 3.5 Hz, CH), 121.3 (CH), 120.5 (CH), 120.2 (CH), 109.0 (CH), 100.2 (C_q), 100.0 (CH), 66.9 (CH), 52.5 (CH_2), 47.0 (CH_2), 41.8 (CH_2), 21.1 (CH_3), 20.6 (CH_3). **HRMS (ESI)**: *m/z*: calc for $C_{28}H_{28}N_2F_3^+$ 449.2205 $[M+H]^+$, found 449.2217.

1-(3-methoxyphenyl)-2-(2,4,6-trimethylbenzyl)-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole **2g**



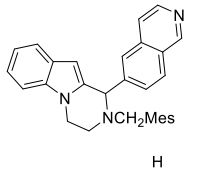
Compound **2g** was synthesized following the **General procedure 1** using tryptamine **5a** (44 mg, 0.15 mmol, 1.0 equiv.), 3-methoxybenzaldehyde (41 mg, 0.30 mmol, 2.0 equiv.), **Cat b** (5.3 mg, 0.0075 mmol), in DCM (1.5 mL). The desired product **2g** was obtained after column chromatography on silica gel (gradient from 0 to 50 % Heptane:EtOAc) as a green amorphous solid (36 mg, 0.088 mmol, 59 %). **IR (neat) ν_{max}** = 2952, 1739, 1599, 1486, 1452, 1375, 1321, 1265, 1148, 1044 cm^{-1}. **^{1}H NMR (CDCl$_3$, 500 MHz)** δ = 7.49 (d, *J* = 7.8 Hz, 1H), 7.30-7.25 (m, 2H), 7.17 (td, *J* = 7.6, 0.9 Hz, 1H), 7.08 (td, *J* = 7.5, 0.8 Hz, 1H), 7.05 (d, *J* = 7.5 Hz, 1H), 7.03-7.01 (m, 1H), 6.89 (ddd, *J* = 8.2, 2.6, 0.5 Hz, 1H), 6.84 (s, 2H), 5.83 (s, 1H), 4.64 (s, 1H), 4.13 (dt, *J* = 11.4, 3.8 Hz, 1H), 3.94 (ddd, *J* = 4.5, 10.2, 11.2 Hz, 1H), 3.78 (s, 3H), 3.71 (d, *J* = 12.5 Hz, 1H), 3.36 (d, *J* = 12.5 Hz, 1H), 3.18 (dt, *J* = 12.1, 4.0 Hz, 1H), 2.78 (m, 1H), 2.30 (s, 6H), 2.28 (s, 3H). **^{13}C{^{1}H} NMR (CDCl$_3$, 75 MHz)** δ = 159.7 (C_q), 143.2 (C_q), 138.8 (C_q), 138.6 (C_q), 136.8 (C_q), 136.0 (C_q), 131.5 (Cq), 129.3 (CH), 129.1 (CH), 128.4 (C_q), 122.3 (CH), 120.9 (CH), 120.4 (CH), 119.9 (CH), 114.9 (CH), 114,0 (CH), 108.9 (CH), 100.2 (C_q), 99.7 (CH), 67.5 (CH), 55.4 (CH_2), 47.0 (CH_2), 42.0 (CH_2), 21.1 (CH_3), 20.7 (CH_3). **^{19}F NMR (CDCl$_3$, 282 MHz)** δ = -62.6 **HRMS (ESI)**: *m/z*: calc for $C_{28}H_{31}N_2O^+$ 411.2436 $[M+H]^+$, found 411.2436

1-(quinolin-4-yl)-2-(2,4,6-trimethylbenzyl)-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole **2h**



Compound **2h** was synthesized following the **General procedure 1** using tryptamine **5a** (44 mg, 0.15 mmol, 1.0 equiv.), 4-quinolinaldehyde (47 mg, 0.30 mmol, 2.0 equiv.), **Cat b** (5.3 mg, 0.0075 mmol), in DCM (1.5 mL). The desired product **2h** was obtained after column chromatography on silica gel (gradient from 0 to 100 % Heptane:EtOAc) as a green amorphous solid (56 mg, 0.13 mmol, 87 %). **IR (neat) ν_{max}** = 2920, 1739, 1591, 1452, 1357, 1218, 1010 cm^{-1}. **^{1}H NMR (CDCl$_3$, 500 MHz)** δ = 8.76 (d, *J* = 4.5 Hz, 1hH), 8.05 (d, *J* = 8.3 Hz, 1H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.57 (td, *J* = 7.6, 0.9 Hz, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 7.9 Hz, 1H), 7.23 (d, *J* = 7.5 Hz, 1H), 7.22 (d, *J* = 5.2 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.79 (s, 2H), 5.81 (s, 1H), 5.34 (s, 1H), 4.18 (dt, *J* = 11.5, 5.2 Hz, 1H), 4.05 (tt, *J* = 7.8, 4.0 Hz, 1H), 3.66 (d, *J* = 12.7 Hz, 1H), 3.44 (d, *J* = 12.7 Hz, 1H), 3.26 (dt, *J* = 12.7, 5.0 Hz, 1H), 2.89-2.82 (m, 1H), 2.22 (s, 3H), 2.11 (s, 6H). **^{13}C{^{1}H} NMR (CDCl$_3$, 75 MHz)** δ = 150.0 (CH), 149.1 (C_q), 147.2 (C_q), 138.7 (C_q), 137.3 (C_q), 136.2 (C_q), 136.0 (Cq), 130.7 (C_q), 130.1 (CH), 129.4 (CH), 129.3 (CH), 128.3 (C_q), 127.2 (C_q), 126.2 (CH), 125.5 (CH), 122.7 (CH), 121.3 (CH), 120.6 (CH), 120.3 (CH), 109.0 (CH), 101.2 (C_q), 100.0 (CH), 62.7 (CH), 52.5 (CH_2), 46.7 (CH_2), 40.7 (CH_2), 21.1 (CH_3), 20.7 (CH_3). **HRMS (ESI)**: *m/z*: calc for $C_{30}H_{30}N_3^+$ 432.2440 $[M+H]^+$, found 432.2451.

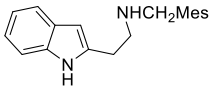
1-(isoquinolin-6-yl)-2-(2,4,6-trimethylbenzyl)-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole **2i**



Compound **2i** was synthesized following the **General procedure 1** using tryptamine **5a** (44 mg, 0.15 mmol, 1.0 equiv.), 6-quinolinaldehyde (47 mg, 0.30 mmol, 2.0 equiv.), **Cat b** (5.3 mg, 0.0075 mmol), in DCM (1.5 mL). The desired product **2i** was obtained after column chromatography on silica gel (gradient from 0 to 100 % Heptane:EtOAc) as a green amorphous solid (60 mg, 0.14 mmol, 93 %). **IR (neat) ν_{max}** = 2919, 1738, 1450, 1357, 1312, 1265, 1116, 1010 cm^{-1}. **^{1}H NMR (CDCl$_3$, 500 MHz)** δ = 8.93 (dd, *J* = 4.1, 1.5 Hz, 1H), 8.14 (d, *J* = 7.8 Hz, 1H), 8.09 (d, *J* = 8.8 Hz, 1H), 7.86 (d, *J* = 1.3 Hz, 1H), 7.80 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.41 (dd, *J* = 8.3, 4.3 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.19 (t, *J* = 7.3 Hz, 1H), 7.10 (t, *J* = 7.3 Hz, 1H), 6.84 (s, 2H), 5.80 (s, 1H), 4.87 (s, 1H), 4.17 (dt, *J* = 11.5, 3.9 Hz, 1H), 3.99 (td, *J* = 11.7, 4.5 Hz, 1H), 3.71 (d, *J* = 12.6 Hz, 1H), 3.45 (d, *J* = 12.6 Hz, 1H), 3.22 (dt, *J* = 12.1, 4.1 Hz, 1H), 2.85 (td, *J* = 11.0, 4.0 Hz, 1H), 2.28 (s, 6H), 2.27 (s, 3H). **^{13}C{^{1}H} NMR (CDCl$_3$, 75 MHz)** δ = 150.6 (CH), 148.5 (C_q), 140.1 (C_q), 138.5 (C_q), 138.0 (C_q), 136.9 (C_q), 136.1 (CH), 131.2 (CH), 131.1 (C_q), 129.6 (CH), 129.3 (CH), 128.3 (CH), 127.9 (C_q), 121.4 (CH), 121.1 (CH), 120.5 (CH), 120.0 (CH), 108.9 (CH), 100.1 (C_q), 100.0 (CH), 66.9 (CH), 52.5 (CH_2), 46.8 (CH_2), 41.8 (CH_2), 21.1 (CH_3), 20.7 (CH_3).**HRMS (ESI)**: *m/z*: calc for $C_{30}H_{30}N_3^+$ 432.2440 $[M+H]^+$, found 432.2427

C2-Iso Pictet-Spengler reaction

Synthesis of 2-(1*H*-indol-2-yl)-*N*-(2,4,6-trimethylbenzyl)ethan-1-amine **5b**



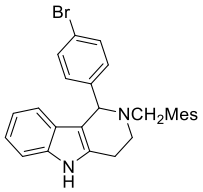
The synthesis of 2-(1*H*-indol-2-yl)ethan-1-amine was performed following procedures from the literature.[8d, 23] To a solution of Indole-2-carboxylic acid (16.1 g, 1.00 equiv., 100 mmol) in THF (75 mL) was added $LiAlH_4$ (7.9 g, 2.07 equiv., 207 mmol) at 0 ºC in a 15 min period, the mixture was then allowed to warm to room temperature slowly and stirring at room temperature for about 3 h. The reaction was quenched with 2M NaOH under 0 ºC and extracted with EtOAc, dried over $MgSO_4$ and evaporated under vacuum. The crude product was then purified by column chromatography to afford the corresponding (1*H*-indol-2-yl)methanol in 84 % yield (12.4 g, 84 mmol). To a solution of (1*H*-indol-2-yl)methanol (12.4 g, 1 equiv., 84 mmol) in MeCN (360 mL) was added MnO_2 (73 g, 10 equiv., 840 mmol) at room temperature and the mixture was stirred for 16 h, then the mixture was filtrated with celite and concentrated under vacuum. The crude product was used directly without purification. To the solution of crude 1*H*-indole-2-carbaldehyde (11.0 g, 1.00 equiv., 76.1 mmol) in $MeNO_2$ (70 mL) was added $AcONH_4$ (2.3 g, 0.39 mmol, 29 .7 mmol) at room temperature, the mixture was allowed heated to 100 ºC and following by TLC, 30 min later, the reaction was completed and concentrated under vacuum, the residue was then extracted with EtOAc and dried over $MgSO_4$ and evaporated under vacuum, leading to 2-(2-nitrovinyl)-1*H*-indole. It was then dissolved in THF (50 mL) and a suspension of $LiAlH_4$ (5.5 g, 1 equiv., 29 mmol) in THF (50 mL) was added dropwise at 0 ºC, after completed, the resulting mixture was stirred at room temperature for 3.5 h. The reaction solution was then quenched with NH_4Cl and extracted with EtOAc, combine the organic layer and dry over $MgSO_4$, concentrated under vacuum and purified by column chromatography to afford the corresponding 2-(1*H*-indol-2-yl)ethan-1-amine (2.4 g, 15 mmol, 52 %).[24]

A mixture of 2-(1*H*-indol-2-yl)ethan-1-amine (481 mg, 1.00 equiv., 3.00 mmol) and mesitaldehyde (467 mg, 1.05 equiv., 3.15 mmol) in MeOH (5 mL) under N_2 was stirred at room temperature for 16 hours, then $NaBH_4$ was added under 0 ºC, the mixture was allowed warm to room temperature and stirred at room temperature for another 1 h and water was added. After the phases were separated, the aqueous phase was extracted twice by ethyl acetate then the combined organic phases were dried over $MgSO_4$ and evaporated under vacuum. and extraction with EtOAc, combine the organic layer and dry over $MgSO_4$, concentrated under vacuum and purified by column chromatography to afford the corresponding 2-(1*H*-indol-2-yl)-*N*-(2,4,6-trimethylbenzyl)ethan-1-

amine **5b** (265 mg, 0.91 mmol, 30 %). **^{1}H NMR ($CDCl_3$, 500 MHz)** δ = 9.71 (bs, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 7.9 Hz, 1H), 7.09 (t, *J* = 7.0 Hz, 1H), 7.04 (t, *J* = 7.3 Hz, 1H), 6.89 (s, 1H), 6.20 (s, 1H), 3.81 (s, 2H), 3.08 (t, *J* = 5.8 Hz, 2H), 2.93 (t, *J* = 5.8 Hz, 2H), 2.39 (s, 6H), 2.28 (s, 3H), 1.42 (m, 1H). **^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz)** δ = 139.6 (C_q), 137.1 (C_q), 137.1 (C_q), 136.0 (C_q), 133.4 (C_q), 129.4 (CH), 128.6 (C_q), 121.0 (CH), 119.9 (CH), 119.5 (CH), 110.7 (CH), 99.3 (CH), 49.8 (CH_2), 47.9 (CH_2), 28.1 (CH_2), 21.1 (CH_3), 19.7 (CH_3). **HRMS (ESI)**: *m/z*: calc for $C_{20}H_{25}N_2^+$ 293.2012, $[M+H]^+$, found, 293.2009.

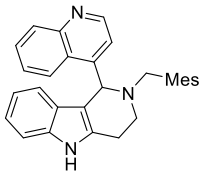
General procedure 2 for the synthesis of tetrahydro-1*H*-pyrido[4,3-*b*]indole 3: A mixture of 2-(1*H*-indol-2-yl)-*N*-(2,4,6-trimethylbenzyl)ethan-1-amine **5b** (1 equiv), **Cat b** (5 mol %) and 3 Å molecular sieves (150 mg for 0.15 mmol of **5b**, powdered) in dichloromethane (1.5 mL for 0.15 mmol of **5a**) was stirred for 5 min at room temperature under an argon atmosphere. Subsequently, aldehyde (2.0 equiv) was added and the mixture stirred at -20 °C for 16 h. Then it was filtered under celite and silica was added. After evaporation of the volatiles, the silica mixture was purified by chromatography under silica gel to give the desired product **3**.

1-(4-bromophenyl)-2-(2,4,6-trimethylbenzyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole **3a**



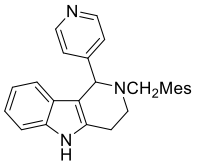
Compound **3a** was prepared according to the **general procedure 2** from **5b** (0.05 mmol, 1 equiv., 14.6 mg), 4-bromobenzaldehyde (0.1 mmol, 2 equiv., 18.5 mg), **Cat b** (5 mol %, 1.8 mg), 3 Å·MS (50 mg) and anhydrous DCM under N_2, yielding product **3a** (12.7 mg, 0.028 mmol, 56 %) as a pale yellow solid. **^{1}H NMR ($CDCl_3$, 300 MHz)** δ = 7.84 (bs, 1H), 7.37 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 7.9 Hz, 1H), 7.17 (d, *J* = 8.5 Hz, 2H), 7.11-7.05 (m, 1H), 6.93-6.88 (m, 1H), 6.83-6.79 (m, 3H), 4.64 (s, 1H), 3.77 (d, *J* = 12.4 Hz, 1H), 3.48 (d, *J* = 12.4 Hz, 1H), 3.09-2.99 (m, 1H), 2.84-2.69 (m, 3H), 2.27 (s, 3H), 2.19 (s, 6H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz)** δ = 142.6 (C_q), 138.6 (C_q), 136.6 (C_q), 136.1 (C_q), 133.5 (C_q), 132.5 (C_q), 131.4 (CH), 131.1 (CH), 129.2 (CH), 126.9 (C_q), 121.4 (CH), 121.0 (C_q), 119.7 (CH), 118.7 (CH), 111.0 (C_q), 110.7 (CH), 62.6 (CH), 51.2 (CH_2), 45.8 (CH_2), 22.7 (CH_2), 21.1 (CH_3), 20.4 (CH_3). **HRMS (ESI)**: *m/z*: calc for $C_{27}H_{28}BrN_2^+$ 459.1430 $[M+H]^+$, found, 459.1437.

1-(quinolin-4-yl)-2-(2,4,6-trimethylbenzyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole **3b**



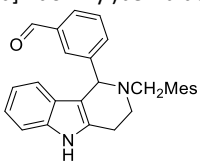
Compound **3b** was prepared according to the **general procedure 2** from **5b** (0.05 mmol, 1 equiv., 14.6 mg), quinoline-4-carbaldehyde (0.1 mmol, 2 equiv., 15.7 mg), **Cat b** (5 mol %, 1.8 mg), 3Å·MS (50 mg) and anhydrous DCM under N_2, yielding product **3b** (13.1 mg, 0.03 mmol, 61 %) as a pale yellow solid. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ = 8.68 (s, 1H), 8.09 (d, *J* = 8.2 Hz, 1H), 8.04 (s, 1H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.55 (bs, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.03 (bs, 1H), 6.91 (s, 2H), 6.86 (t, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 5.51 (s, 1H), 3.99 (d, *J* = 12.4 Hz, 1H), 3.63 (d, *J* = 12.5 Hz, 1H), 3.19-3.09 (m, 2H), 2.99-2.90 (m, 1H), 2.83-2.74 (m, 1H), 2.34 (s, 3H), 2.14 (s, 6H). **^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz)** δ = 150.0 (CH), 148.8 (C_q), 148.3 (C_q), 139.1 (C_q), 137.1 (C_q), 136.1 (C_q), 133.6 (C_q), 131.9 (C_q), 131.2 (C_q), 130.4 (CH), 129.8 (CH), 129.3 (CH), 128.9 (CH), 128.0 (C_q), 125.8 (CH), 125.1 (C_q), 122.4 (CH), 121.7 (CH), 119.8 (CH), 118.4 (CH), 110.8 (CH), 50.9 (CH_2), 46.8 (CH), 45.9 (CH_2), 21.2 (CH_2), 20.5 (CH_3), 20.2 (CH_3). **HRMS (ESI)**: *m/z*: calc for $C_{30}H_{30}N_3^+$ 432.2434 $[M+H]^+$, found, 432.2436.

1-(pyridin-4-yl)-2-(2,4,6-trimethylbenzyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole **3c**



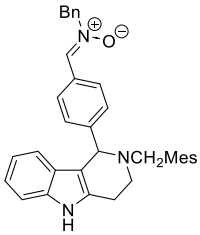
Compound **3c** was prepared according to the **general procedure 2** from **5c** (0.05 mmol, 1 equiv., 14.6 mg), isonicotinaldehyde (0.1 mmol, 2 equiv., 10.7 mg), **Cat b** (5 mol %, 1.8 mg), 3Å·MS (50 mg) and anhydrous DCM under N_2, yielding product **3c** (13.4 mg, 0.04 mmol, 71 %) as a pale yellow solid. **^{1}H NMR ($CDCl_3$, 300 MHz)** δ = 8.47 (d, *J* = 3.2 Hz, 2H), 8.15 (s, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.23 (d, *J* = 5.5 Hz, 2H), 7.15-7.07 (m, 1H), 6.98-6.87 (m, 2H), 6.85 (s, 2H), 4.73 (s, 1H), 3.82 (d, *J* = 12.4 Hz, 1H), 3.56 (d, *J* = 12.5 Hz, 1H), 3.07-2.83 (m, 3H), 2.77-2.66 (m, 1H), 2.28 (s, 3H), 2.20 (s, 6H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz)** δ = 153.7 (C_q), 148.9 (CH), 138.5 (C_q), 136.8 (C_q), 136.0 (C_q), 133.6 (C_q), 132.1 (C_q), 129.3 (CH), 126.9 (C_q), 124.8 (CH), 121.6 (CH), 119.9 (CH), 118.3 (CH), 110.9 (CH), 109.2 (C_q), 60.6 (CH), 51.0 (CH_2), 45.5 (CH_2), 21.7 (CH_2), 21.1 (CH_3), 20.2 (CH_3). **HRMS (ESI)**: *m/z*: calc for $C_{26}H_{28}N_3^+$ 382.2278 $[M+H]^+$, found, 382.2272.

3-(2-(2,4,6-trimethylbenzyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-1-yl)benzaldehyde **3d**



Compound **3d** was prepared according to the **general procedure 2** from **5c** (0.05 mmol, 1 equiv., 14.6 mg), isophthalaldehyde (0.1 mmol, 2 equiv., 10.7 mg), **Cat b** (5 mol %, 1.8 mg), 3 Å·MS (50 mg) and anhydrous DCM under N_2, yielding product **3d** (15.4 mg, 0.04 mmol, 75 %) as a pale yellow solid. **^{1}H NMR ($CDCl_3$, 300 MHz)** δ = 9.95 (s, 1H), 7.90 (bs, 1H), 7.84 (t, *J* = 1.5 Hz, 1H), 7.77 (dt, J_1 = 7.5 Hz, J_2 = 1.3 Hz, 1H), 7.58 (dt, J_1 = 7.7 Hz, J_2 = 1.3 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.30 (dt, J_1 = 8.1 Hz, J_2 = 0.8 Hz, 1H), 7.11-7.04 (m, 1H), 6.90-6.85 (m, 1H), 6.83 (s, 2H), 6.77 (d, *J*= 7.9 Hz, 1H), 4.77 (s, 1H), 3.76 (d, *J* = 12.4 Hz, 1H), 3.53 (d, *J* = 12.4 Hz, 1H), 3.12-3.00 (m, 1H), 2.85-2.73 (m, 3H), 2.27 (s, 3H), 2.18 (s, 6H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz)** δ = 192.9 (CH), 144.9 (C_q), 138.6 (C_q), 136.6 (C_q), 136.3 (C_q), 136.2 (C_q), 136.0 (CH), 133.6 (C_q), 132.4 (C_q), 131.3 (CH), 129.2 (CH), 128.8 (CH), 128.6 (CH), 126.7 (C_q), 121.4 (CH), 119.7 (CH), 118.5 (CH), 110.8 (CH), 63.0 (CH), 51.3 (CH_2), 45.9 (CH_2), 22.9 (CH_2), 21.1 (CH_3), 20.4 (CH_3). **HRMS (ESI)**: *m/z*: calc for $C_{28}H_{29}N_2O^+$ 409.2274 $[M+H]^+$, found, 409.2273.

N-benzyl-1-(4-(2-(2,4,6-trimethylbenzyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-*b*]indol-1-yl)phenyl)methanimine oxide **3e**



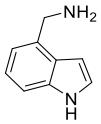
Compound **3e** was prepared according to the **general procedure 2** from **5c** (0.05 mmol, 1 equiv., 14.6 mg), (*Z*)-*N*-benzyl-1-(4-formylphenyl)methanimine oxide (0.1 mmol, 2 equiv., 23.9 mg), **Cat b** (5 mol %, 1.8 mg), 3 Å·MS (50 mg) and anhydrous DCM under N_2, stirred at room temperature for 60 hours, yielding product **3e** (65% conversion, 12.1 mg, 0.02 mmol, 47 %) as a white solid.

Note: the background reaction performed under the same conditions in the absence of catalyst is 26% after 60 h. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ = 8.11 (d, *J* = 7.9 Hz, 2H), 7.88 (s, 1H), 7.47 (d, *J* = 6.6 Hz, 2H), 7.42-7.33 (m, 6H), 7.25 (d, *J* = 7.9 Hz, 1H), 7.03 (t, *J* = 7.6 Hz, 1H), 6.82 (t, *J* = 7.5 Hz, 1H), 6.80 (s, 2H), 6.73 (d, *J* = 7.6 Hz, 1H), 5.04 (s, 2H), 4.67 (s, 1H), 3.73 (d, *J* = 12.4 Hz, 1H), 3.47 (d, *J* = 12.5 Hz, 1H), 3.06-2.98 (m, 1H), 2.81-2.67 (m, 3H), 2.25 (s, 3H), 2.17 (s, 6H). **^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz)** δ = 146.4 (C_q), 138.6 (C_q), 136.5 (C_q), 136.1 (C_q), 134.7 (CH), 133.5 (C_q), 133.4 (C_q), 132.5 (C_q), 129.9

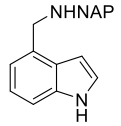
(CH), 129.5 (CH), 129.5 (C_q) 129.2 (CH), 129.2 (CH), 129.1 (CH), 128.5 (CH), 126.7 (C_q), 121.2 (CH), 119.6 (CH), 118.7 (CH), 111.3 (C_q), 110.6 (CH), 71.3 (CH_2), 63.9 (CH), 51.5 (CH_2), 46.0 (CH_2), 23.2 (CH_2), 21.1 (CH_3), 20.5 (CH_3). **HRMS (ESI)**: *m/z*: calc for $C_{35}H_{36}N_3O^+$ 514.2853 $[M+H]^+$, found, 514.2847.

C4-Iso Pictet-Spengler reaction

Synthesis of tryptamine 5c.



A mixture of 1*H*-indole-4-carbonitrile (10.0 g, 70.3 mmol, 1.0 equiv.) in THF (100 mL) was added dropwise to a suspension of lithium aluminum hydride (5.70 g, 150 mmol, 2.1 equiv.) in THF at 0 °C. The reaction was refluxed for 90 minutes then allowed to cool to rt. Then, aqueous saturated solution of Rochelle's salt was added and stirred until full destruction of lithium salts. The reaction was filtered over silica, concentrated under *vacuum* and triturated in methanol. After filtration over celite, the pure product **S6** was obtained by filtrate's concentration under *vacuum* as a light brown solid (9.10 g, 62.2 mmol, 88 %). The data correspond to those found in the literature.[25]

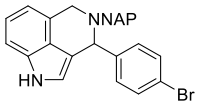


(1*H*-indol-4-yl)methanamine (2.00 mg, 13.6 mmol, 1.00 equiv.), and 2-naphthaldehyde (2.02 mg, 13.0 mmol, 0.95 equiv.) were stirred in methanol (68 mL) for 4 hours. Then, the reaction media was cooled to 0 °C before the addition of $NaBH_4$ (565 mg, 15.0 mmol, 1.1 equiv. in one portion). The mixture was allowed to warm up to room temperature. After 1 hour stirring, the volatiles were removed and the crude was next diluted in ethyl acetate and water. After phases separation, the aqueous phase was extracted twice by ethyl acetate. The combined organic phases were dried over $MgSO_4$ and evaporated under *vacuum*. The desired product **5c** was obtained after column chromatography on silica gel (gradient from 0 to 15 % DCM:MeOH) as a brown oil (3.30 g, 11.4 mmol, 84 %). **IR (neat) ν_{max}** = 3411, 3184, 3052, 2922, 2849, 1437, 1345, 818, 753 cm^{-1}. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ = 8.27 (bs, 1H), 7.87-7.76 (m, 4H), 7.53 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.50-7.42 (m, 2H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.23-7.20 (m, 1H), 7.19 (d, *J* = 7.3 Hz, 1H), 7.14 (d, *J* = 7.0 Hz, 1H), 6.23 (t, *J* = 2.1 Hz, 1H), 4.16 (s, 2H), 4.04 (s, 2H), 2.08 (bs, 2H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz)** δ = 137.8 (C_q), 136.1 (C_q), 133.6 (C_q), 132.7 (C_q), 131.9 (C_q), 128.2 (CH), 127.8 (CH), 127.7 (CH), 127.1 (C_q), 126.8 (CH), 126.7 (CH), 126.1 (CH), 125.6 (CH), 124.3 (CH), 122.0 (CH), 119.3 (CH), 110.3 (CH), 100.5 (CH), 53.4 (CH_2), 51.1 (CH_2). **HRMS (ESI)** *m/z*: calc for $C_{20}H_{18}N_2$ $[M+H]^+$ 287.1548, found 287.1542.

Scope of the 4-Iso Pictet-Spengler reaction

General procedure 3 for the synthesis of tetrahydropyrrolo[4,3,2-*de*]isoquinolines 4: A mixture of tryptamine **5c** (0.17 mmol), **Cat b** (2 mol %, 0.0034 mmol, 2.5 mg) and 3 Å molecular sieves (82 mg for 0.17 mmol of **5c**, powdered) in dichloromethane (2.4 mL for 0.17 mmol of **5c**) was stirred for 5 min at room temperature under an argon atmosphere. Subsequently, aldehyde (2.0 equiv., 0.35 mmol) was added and the mixture stirred for 15h. The mixture was filtered under celite and silica was added. After evaporation of the volatiles, the silica mixture was purified by chromatography under silica gel to give the desired product **4**.

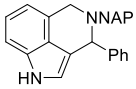
3-(4-bromophenyl)-4-(naphthalen-2-ylmethyl)-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]isoquinoline **4a**



Compound **4a** was synthesized following the **General procedure 3** using tryptamine **5c** (50 mg, 0.17 mmol, 1.0 equiv.), 4-bromobenzaldehyde (65 mg, 0.35 mmol, 2.0 equiv.), **Cat b** (2.5 mg, 0.0034 mmol, 2 mol%), M.S. 3Å (82 mg), in DCM (2.4 mL). The desired product **4a** was obtained after column chromatography on silica gel (gradient from 0 to 15 % Heptane:EtOAc) as a white amorphous solid (58 mg, 0.13 mmol, 75 %).

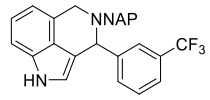
1 mmol scale procedure: Compound **4a** was synthesized following the **General procedure 3** using tryptamine **5c** (300 mg, 1.05 mmol, 1.0 equiv.), 4-bromobenzaldehyde (387 mg, 2.10 mmol, 2.0 equiv.), **Cat b** (15.5 mg, 0.021 mmol, 2 mol%), M.S. 3Å (503 mg), in DCM (15.0 mL). The desired product was obtained after column chromatography on silica gel (gradient from 0 to 15 % Heptane:EtOAc) as a white amorphous solid (289 mg, 0.64 mmol, 61 %). **IR (neat) ν_{max}** = 3406, 3052, 2959, 2926, 2838, 1484, 1264, 1070, 1010, 817, 752, 735 cm^{-1}. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ = 8.00 (bs, 1H), 7.85-7.77 (m, 3H), 7,72 (s, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.50-7.44 (m, *2H*), 7.43-7.40 (m, 2H), 7.24 (t, *J* = 8.0 Hz, 1H), 7.25-7.21 (m, 2H), 7.18 (t, *J* = 7.0 Hz, 1H), 6.81 (d, *J* = 4.9 Hz, 1H), 6.75 (s, 1H), 5.02 (s, 1H), 4.03 (d, *J* = 15.8 Hz, 1H), 3.85 (d, *J* = 13.5 Hz, 1H), 3.78 (d, *J* = 15.8 Hz, 1H), 3.69 (d, *J* = 13.5 Hz, 1H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz)** δ = 141.8 (C_q), 137.3 (C_q), 133.5 (C_q), 133.5 (C_q), 132.9 (C_q), 131.4 (CH), 130.5 (CH), 128.7 (C_q), 128.1 (CH), 127.8 (CH), 127.7 (CH), 127.4 (CH), 127.3 (CH), 126.0 (CH), 125.7 (CH), 125.2 (C_q), 123.2 (CH), 121.1 (C_q), 119.3 (CH), 115.1 (CH), 113.3 (C_q), 109.0 (CH), 60.9 (CH), 58.9 (CH_2), 49.4 (CH_2) **HRMS (ESI)**: *m/z*: calc for $C_{27}H_{22}{}^{79}BrN_2^+$ 453.0966 $[M+H]^+$, found 453.0926, calc for $C_{27}H_{22}{}^{81}BrN_2^+$ 455.0946 $[M+H]^+$, found 455.0925.

4-(naphthalen-2-ylmethyl)-3-phenyl-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]isoquinoline **4b**



Compound **4b** was synthesized following the **General procedure 3** using tryptamine **5c** (50 mg, 0.17 mmol, 1.0 equiv.), benzaldehyde (37 mg, 0.35 mmol, 2.0 equiv.), **Cat b** (2.5 mg, 0.0034 mmol, 2 mol%), M.S. 3Å (82 mg), in DCM (2.4 mL). The desired product **4b** was obtained after column chromatography on silica gel (gradient from 0 to 15 % Heptane:EtOAc) as a white amorphous solid (50 mg, 0.13 mmol, 78 %). **^{1}H NMR (DMSO-d_6, 500 MHz)** δ = 10.82 (s, 1H), 7.91-7.83 (m, 3H), 7.75 (s, 1H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.50-7.44 (m, 2H), 7.33-7.28 (m, 4H), 7.27-7.19 (m, 2H), 7.03 (t, *J* = 7.4 Hz, 1H), 6.92 (s, 1H), 6.68 (d, = *J* = 6.7 Hz, 1H), 5.07 (s, 1H), 3.85 (d, *J* = 5.6 Hz, 1H), 3.78-3.65 (m, 3H). **^{13}C{^{1}H} NMR (DMSO-d_6, 75 MHz)** δ = 142.5 (C_q), 137.4 (C_q), 133.2 (C_q), 132.9 (C_q), 132.3 (C_q), 128.2 (CH), 128.1 (CH), 127.8 (C_q), 127.7 (CH), 127.6 (CH), 127.5 (CH), 126.9 (CH), 126.8 (CH), 126.7 (CH), 126.0 (CH), 125.5 (CH), 124.9 (C_q), 121.9 (CH), 119.8 (CH), 113.6 (CH), 112.2 (C_q), 109.1 (CH), 61.0 (CH), 58.0 (CH_2), 48.5 (CH_2) **HRMS (ESI)**: *m/z*: calc for $C_{27}H_{23}N_2^+$ 375.1861 $[M+H]^+$, found 375.1841.

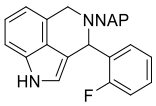
4-(naphthalen-2-ylmethyl)-3-(3-(trifluoromethyl)phenyl)-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]isoquinoline **4c**



Compound **4c** was synthesized following the **General procedure 3** using tryptamine **5c** (50 mg, 0.17 mmol, 1.0 equiv.), 3-(trifluoromethyl)benzaldehyde (61 mg, 0.35 mmol, 2.0 equiv.), **Cat b** (2.5 mg, 0.0034 mmol 2 mol%), M.S. 3Å (82 mg), in DCM (2.4 mL). The desired product **4c** was obtained after column chromatography on silica gel (gradient from 0 to 15 % Heptane:EtOAc) as a white amorphous solid (58

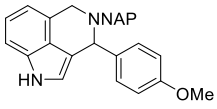
mg, 0.13 mmol, 77 %). **IR (neat) ν_{max}** = 3419, 3057, 2927, 1329, 1164, 1123, 1072, 753 cm^{-1}. **^{1}H NMR (CDCl$_3$, 500 MHz)** δ = 8.07 (brs, 1H), 7.86-7.80 (m, 2H), 7.80-7.76 (m, 1H), 7.73 (s, 1H), 7.69 (s, 1H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.48-7.42 (m, 1H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.29-7.24 (m, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 6.84-6.79 (m, 2H), 5.10 (s, 1H), 4.05 (d, *J* = 15.9 Hz, 1H), 3.86 (d, *J* = 13.5 Hz, 1H), 3.81 (d, *J* = 15.9 Hz, 1H), 3.71 (d, *J* = 13.6 Hz, 1H). **^{13}C{^{1}H} NMR (CDCl$_3$, 75 MHz)** δ = 144.0 (C$_q$), 137.2 (C$_q$), 133.6 (C$_q$), 133.5 (C$_q$), 133.0 (C$_q$), 132.1 (CH), 130.6 (q, C-F, $^2J_{C-F}$ = 32 Hz, C$_q$), 128.7 (CH), 128.6 (C$_q$), 128.2 (CH), 127.9 (CH), 127.8 (CH), 127.5 (CH), 127.3 (CH), 126.1 (CH), 125.7 (CH), 125.5 (q, C-F, $^3J_{C-F}$ = 4 Hz, CH), 125.1 (C$_q$), 124.4 (q, C-F, $^1J_{C-F}$ = 272 Hz, Cq), 124.1 (q, J_{C-F} = 4 Hz, CH), 123.3 (CH), 119.6 (CH), 115.2 (CH), 112.9 (C$_q$), 61.0 (CH), 58.9 (CH$_2$), 49.5 (CH$_2$). **^{19F} NMR (CDCl$_3$, 282 MHz)** δ = -62.3. **HRMS (ESI)**: *m/z*: calc for $C_{28}H_{22}F_3N_2^+$ 443.1735 [M+H]$^+$, found 443.1703.

3-(2-fluorophenyl)-4-(naphthalen-2-ylmethyl)-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]isoquinoline **4d**



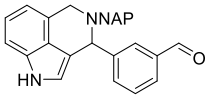
Compound **4d** was synthesized following the **General procedure 3** using tryptamine **5c** (50 mg, 0.17 mmol, 1.0 equiv.), 2-fluorobenzaldehyde (43 mg, 0.35 mmol, 2.0 equiv.), **Cat b** (6.5 mg, 0.0087 mmol, 5 mol%), M.S. 3Å (82 mg), in DCM (2.4 mL). The desired product **4d** was obtained after column chromatography on silica gel (gradient from 0 to 15 % Heptane:EtOAc) as a white amorphous solid (50 mg, 0.13 mmol, 73 %). **IR (neat) ν_{max}** = 3407, 3055, 2926, 2851, 1486, 1452, 1228, 755, 737 cm^{-1}. **^{1}H NMR (CDCl$_3$, 500 MHz)** δ = 8.00 (bs, 1H), 7.87-7.79 (m, 3H), 7,77 (s, 1H), 7.59 (d, *J* = 8.3, 1H), 7.51-7.44 (m, 2H), 7.30-7.23 (m, 2H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.15 (t, *J* = 9.2 Hz, 1H), 7.09 (t, *J* = 7.2 Hz, 1H), 7.00 (t, *J* = 7.4 Hz, 1H), 6.84 (d, *J* = 6.7 Hz, 1H), 6.74 (s, 1H), 5.60 (s, 1H), 4.08 (d, *J* = 15.8 Hz, 1H), 3.91 (d, *J* = 13.3 Hz, 1H), 3.87-3.79 (m, 2H). **^{13}C{^{1}H} NMR (CDCl$_3$, 75 MHz)** δ = 161.1 (d, C-F, $^1J_{C-F}$ = 247 Hz, Cq), 137.2 (C$_q$), 133.5 (C$_q$), 133.4 (C$_q$), 132.9 (C$_q$), 130.4 (d, C-F, $^3J_{C-F}$ = 3.8 Hz, CH), 129.7 (d, C-F, $^2J_{C-F}$ = 15.1 Hz, C$_q$), 128.9 (d, C-F, $^3J_{C-F}$ = 8.8 Hz, CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.6 (CH), 127.5 (CH), 125.9 (CH), 125.7 (C$_q$), 125.6 (CH), 123.9 (d, C-F, $^4J_{C-F}$ = 2.7 Hz, CH), 123.2 (CH), 118.8 (CH), 115.5 (d, C-F, $^2J_{C-F}$ = 22.5 Hz, CH), 115.0 (CH), 113.5 (C$_q$), 109.0 (CH), 59.0 (CH$_2$), 55.1 (CH), 49.1 (CH$_2$). **^{19}F NMR (CDCl$_3$, 282 MHz)** δ = -118.0. **HRMS (ESI)**: *m/z*: calc for $C_{27}H_{22}FN_2^+$ 393.1767 [M+H]$^+$, found 393.1756.

3-(4-methoxyphenyl)-4-(naphthalen-2-ylmethyl)-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]isoquinoline **4e**



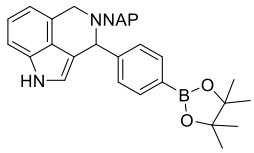
Compound **4e** was synthesized following the **General procedure 3** using tryptamine **5c** (54 mg, 0.19 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (51 mg, 0.38 mmol, 2.0 equiv.), **Cat b** (6.9 mg, 0.0094 mmol, 5 mol%), M.S. 3 Å (91 mg), in DCM (2.7 mL). The desired product **4e** was obtained after column chromatography on silica gel (gradient from 0 to 15 % Heptane:EtOAc) as a white amorphous solid (29 mg, 0.07 mmol, 38 %). **IR (neat) ν_{max}** = 3402, 3055, 2930, 2836, 1607, 1508, 1451, 1248, 1172, 1031, 819, 753 cm^{-1}. **^{1}H NMR (CDCl$_3$, 500 MHz)** δ = 8.01 (s, 1H), 7.86-7.78 (m, 3H), 7.75 (s, 1H), 7.60 (d, *J* = 8.3 Hz, 1H), 7.49-7.43 (m, 2H), 7.30-7.23 (m, 3H), 7.18 (t, *J* = 7.3 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 7.0 Hz, 1H), 6.77 (s, 1H), 5.05 (s, 1H), 4.08 (d, *J* = 15.7 Hz, 1H), 3.89 (d, *J* = 13.6 Hz, 1H), 3.83-3.77 (m, 1H), 3.80 (s, 3H), 3.70 (d, *J* = 14.0 Hz, 1H) **^{13}C{^{1}H} NMR (CDCl$_3$, 75 MHz)** δ = 206.3 (C$_q$), 158.9 (C$_q$), 137.7 (C$_q$), 134.8 (C$_q$), 133.6 (C$_q$), 133.5 (C$_q$), 132.9 (C$_q$), 129.9 (CH), 129.1 (C$_q$), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.5 (CH), 127.4 (CH), 126.0 (CH), 125.6 (CH), 125.5 (C$_q$), 123.1 (CH), 119.2 (CH), 115.0 (CH), 113.7 (CH), 108.9 (CH), 61.2 (CH), 58.7 (CH$_2$), 55.4 (CH$_3$), 49.6 (CH$_2$) **HRMS (ESI)**: *m/z*: calc for $C_{28}H_{25}N_2O^+$ 405.1967 [M+H]$^+$, found 405.1947.

3-(4-(naphthalen-2-ylmethyl)-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]isoquinolin-3-yl)benzaldehyde **4f**



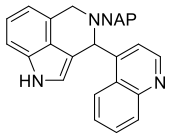
Compound **4f** was synthesized following the **General procedure 3** using tryptamine **5c** (76 mg, 0.27 mmol, 1.0 equiv.), isophthalaldehyde (71 mg, 0.53 mmol, 2.0 equiv.), **Cat b** (3.9 mg, 0.0053 mmol, 2 mol%), M.S. 3Å (130 mg), in DCM (3.8 mL). The desired product **4f** was obtained after column chromatography on silica gel (gradient from 0 to 15 % Heptane:EtOAc) as a white amorphous solid (50 mg, 0.12 mmol, 46 %). **IR (neat) ν_{max}** = 3406, 3054, 2925, 3838, 1693, 1600, 1584, 1445, 1342, 1146, 819, 754, 736 cm^{-1}. **^{1}H NMR (CDCl$_3$, 300 MHz)** δ = 9.97 (s, 1H), 8.12 (bs, 1H), 7.89-7.82 (m, 3H), 7.81-7.76 (m, 2H), 7.73 (s, 1H), 7.69 (d, *J* = 7.5 Hz, 1H), 7.61 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.50-7.42 (m, 3H), 7.29 (d, *J* = 7.7 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 6.83-6.81 (m, 2H), 5.16 (s, H), 4.05 (d, *J* = 15.7 Hz, 1H), 3.87 (d, *J* = 13.4 Hz, 1H), 3.82 (d, *J* = 16.0 Hz, 1H), 3.75 (d, *J* = 13.3 Hz, 1H). **^{13}C{^{1}H} NMR (CDCl$_3$, 75 MHz)** δ = 192.7 (CH), 144.2 (Cq), 137.2 (Cq), 136.6 (Cq), 135.0 (CH), 133.7 (Cq), 133.5 (Cq), 133.0 (Cq), 130.4 (CH), 129.1 (CH), 128.5 (CH), 128.2 (CH), 127.8 (CH), 127.6 (CH), 127.3 (CH), 126.1 (CH), 125.7 (CH), 125.1 (Cq), 123.3 (CH), 119.7 (CH), 115.2 (CH), 112.7 (Cq), 109.2 (CH), 60.8 (CH), 58.9 (CH$_2$), 49.3 (CH$_2$). **HRMS (ESI)**: *m/z*: calcd for $C_{28}H_{23}N_2O^+$ 403.1810 [M+H]$^+$, found 403.1797.

4-(naphthalen-2-ylmethyl)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]isoquinoline **4g**



Compound **4g** was synthesized following the **General procedure 3** using tryptamine **5c** (50 mg, 0.17 mmol, 1.0 equiv.), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (80 mg, 0.35 mmol, 2.0 equiv.), **Cat b** (2.6 mg, 0.0034 mmol, 2 mol%), M.S. 3 Å (82 mg), in DCM (2.5 mL). The desired product **4g** was obtained after column chromatography on silica gel (gradient from 0 to 15 % Heptane:EtOAc) as a white amorphous solid (46 mg, 0.09 mmol, 53 %). **IR (neat) ν_{max}** = 3362, 3053, 2977, 2932, 1604, 1449, 1397, 1359, 1322, 1143, 1087, 858, 750 cm^{-1}. **^{1}H NMR (CDCl$_3$, 300 MHz)** δ = 7.99 (brs, 1H), 7.86-7.73 (m, 6H), 7.57 (dd, *J* = 1.5; 8.4 Hz, 1H), 7.48-7.39 (m, 4H), 7.24 (d, *J* = 9.3 Hz, 1H), 7.16 (dd, *J* = 6.8; 8.3 Hz, 1H), 6.78 (d, *J* = 6.9 Hz, 1H), 6.70 (d, *J* = 1.2 Hz, 1H), 5.06 (s, 1H), 4.08 (d, *J* = 15.6 Hz, 1H), 3.92 (d, *J* = 13.4 Hz, 1H), 3.79 (d, *J* = 15.6 Hz, 1H), 3.66 (d, *J* = 13.4 Hz, 1H), 1.34 (s, 12H). **^{13}C{^{1}H} NMR (CDCl$_3$, 75 MHz)** δ = 146.1 (C$_q$), 137,6 (C$_q$), 134.9 (CH), 133.5 (C$_q$), 132.9 (C$_q$), 129.5 (C$_q$), 129.1 (C$_q$), 128.3 (2 CH), 128.0 (CH), 127.8 (CH), 127.8 (CH), 127.5 (CH), 127.4 (CH), 126.0 (C$_q$), 126.0 (CH), 125.6 (CH), 125.4 (C$_q$), 123.1 (CH), 119.2 (CH), 114.9 (CH), 114.8 (C$_q$), 108.9 (CH), 83.9 (C$_q$), 62.4 (CH), 59.0 (CH$_2$), 50.1 (CH$_2$), 25.0 (CH$_3$). **^{11}B NMR (CDCl$_3$, 160 MHz)** δ = 22.45. **HRMS (ESI)**: *m/z*: calcd for $C_{33}H_{34}BN_2O_2^+$ 501.2713 [M+H]$^+$, found 501.2689.

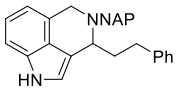
4-(naphthalen-2-ylmethyl)-3-(quinolin-4-yl)-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]isoquinoline **4h**



Compound **4h** was synthesized following the **General procedure 3** using tryptamine **5c** (50 mg, 0.17 mmol, 1.0 equiv.), quinoline-4-carbaldehyde (55 mg, 0.35 mmol, 2.0 equiv.), **Cat b** (2.6 mg, 0.0034 mmol, 2 mol%), M.S. 3

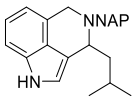
Å (82 mg), in DCM (2.5 mL). The desired product **4h** was obtained after column chromatography on silica gel (gradient from 0 to 15 % Heptane:EtOAc) as a white amorphous solid (53 mg, 0.12 mmol, 71 %). **IR (neat) ν_{max}** = 3054, 2839, 1590, 1508, 1445, 1345, 818, 757cm^{-1}. **^{1}H NMR (CDCl$_3$, 500 MHz)** δ = 8.76 (d, *J* = 4.4 Hz, 1H), 8.52 (brs, 1H), 8.30 (d, *J* = 8.5 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 7.88-7.78 (m, 3H), 7.75-7.70 (m, 2H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.51-7.44 (m, 3H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.11 (d, *J* = 4.3 Hz, 1H), 6.84 (d, *J* = 7.0 Hz, 1H),6.75 (s, 1H), 5.79 (s, 1H), 4.05 (d, *J* = 16.0 Hz, 1H), 4.02 (d, *J* = 14.2 Hz, 1H), 3.80 (d, *J* = 15..9 Hz, 1H), 3.73 (d, *J* = 14.2 Hz, 1H), **^{13}C{^{1}H} NMR (CDCl$_3$, 75 MHz)** δ = 150.1 (CH), 148.9 (C$_q$), 148.5 (C$_q$), 136.8 (C$_q$), 133.6 (C$_q$), 133.4 (C$_q$), 133.0 (C$_q$), 129.9 (CH), 129.2 (CH), 128.2 (C$_q$), 128.1 (CH), 127.9 (CH), 127.8 (CH), 127.8 (CH), 127.7 (CH), 127.3 (C$_q$), 126.3 (CH), 126.1 (CH), 125.8 (CH), 125.4 (CH), 125.4 (C$_q$), 123.4 (CH), 121.4 (CH), 119.6 (CH), 115.3 (CH), 112.0 (C$_q$), 109.3 (CH), 59.4 (CH$_2$), 59.2 (CH), 49.5 (CH$_2$). **HRMS (ESI)**: *m/z*: calc for $C_{30}H_{24}N_3^+$ 426.1970 [M+H]$^+$, found 426.1932.

4-(naphthalen-2-ylmethyl)-3-phenethyl-1,3,4,5-tetrahydro-pyrrolo[4,3,2-*de*]isoquinoline **4i**



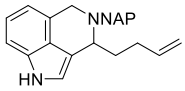
Compound **4i** was synthesized following the **General procedure 3** using tryptamine **5c** (50mg, 0.17 mmol, 1.0 equiv.), 3-phenylpropanal (47 mg, 0.35 mmol, 2.0 equiv.), **Cat b** (6.5 mg, 0.0087 mmol, 5 mol%), M.S. 3Å (82 mg), in DCM (2.5 mL). The desired product **4i** was obtained after column chromatography on silica gel (gradient from 0 to 15 % Heptane:EtOAc) as an oil (29 mg, 0.12 mmol, 75 %). **IR (neat) ν_{max}** = 3057, 2928, 2852, 1602, 1495, 1452, 820, 751, 699 cm^{-1}. **^{1}H NMR (CDCl$_3$, 300 MHz)** δ = 7.98 (brs, 1H), 7.92-7.80 (m, 3H), 7.72 (s, 1H), 7.62 (dd, *J* = 1.9, 8.5 Hz, 1H), 7.56-7.45 (m, 2H), 7-35-7.27 (m, 2H), 7.25-7.15 (m, 5H), 6.95 (d, *J* = 2.1 Hz, 1H), 6.88 (d, *J* = 7.0 Hz, 1H), 4.39 (d, *J* = 16.4 Hz, 1H), 4.10 (t, *J* = 7.5 Hz, 1H), 3.94 (d, *J* = 16.6 Hz, 1H), 3.82 (d, *J* = 13.6 Hz, 1H), 3.71 (d, *J* = 13.6 Hz, 1H), 3.01-2.82 (m, 2H), 2.39-2.17 (m, 1H), 2.07-1.90 (m, 1H). **^{13}C{^{1}H} NMR (CDCl$_3$, 75 MHz)** δ = 142.5 (C$_q$), 133.7 (C$_q$), 133.4 (C$_q$), 132.8 (C$_q$), 128.5 (CH), 128.4 (C$_q$), 128.4 (C$_q$), 128.3 (CH), 127.8 (CH), 127.8 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 125.8 (CH), 125.6 (CH), 125.4 (CH), 123.0 (CH), 118.3 (C$_q$), 118.2 (CH), 115.2 (CH), 114.1 (C$_q$), 108.8 (CH), 58.1 (CH$_2$), 56.8 (CH), 47.6 (CH$_2$), 36.7 (CH$_2$), 32.5 (CH$_2$). **HRMS (ESI)**: *m/z*: calc for $C_{29}H_{27}N_2^+$ 403.2174 [M+H]$^+$, found 403.2174.

3-isobutyl-4-(naphthalen-2-ylmethyl)-1,3,4,5-tetrahydro-pyrrolo[4,3,2-*de*]isoquinoline **4j**



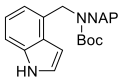
Compound **4j** was synthesized following the **General procedure 3** using tryptamine **5c** (35mg, 0.12 mmol, 1.0 equiv.), 3-methylbutanal (21 mg, 0.24 mmol, 2.0 equiv.), **Cat b** (1.8 mg, 0.0024 mmol, 2 mol%), M.S. 3 Å (58 mg), in DCM (1.8 mL). The desired product **4j** was obtained after column chromatography on silica gel (gradient from 0 to 15 % Heptane:EtOAc) as an oil (30 mg, 0.08 mmol, 69 %). **IR (neat) ν_{max}** = 3414, 3054, 2952, 2928, 2866, 1444, 821, 751 cm^{-1}. **^{1}H NMR (CDCl$_3$, 500 MHz)** δ = 7.93 (brs, 1H), 7.86-7.77 (m, 3H), 7.67 (s, 1H), 7.56 (d, *J* = 7.2 Hz, 1H), 7.48-7.43 (m, 2H), 7.26 (d, *J* = 8.1 Hz, 1H), 7.20 (dd, *J* = 1.0, 8.0 Hz, 1H), 6.89 (d, *J* = 1.4 Hz, 1H), 6.84 (d, *J* = 6.9 Hz, 1H), 4.31 (d, *J* = 16.4 Hz, 1H), 4.14 (t, *J* = 7.5 Hz, 1H), 3.86 (d, *J* = 16.4 Hz, 1H), 3.77 (d, *J* = 13.4 Hz, 1H), 3.66 (d, *J* = 13.5 Hz, 1H), 1.98 (sept, *J* = 6.8 Hz, 1H), 1.85-1.76 (m, 1H), 1.56-1.48 (m, 1H), 0.98 (d, *J* = 6.7 Hz, 1H), 0.91 (d, *J* = 6.6 Hz, 1H). **^{13}C{^{1}H} NMR (CDCl$_3$, 75 MHz)** δ = 138.0 (C$_q$), 133.8 (C$_q$), 133.5 (C$_q$), 132.9 (C$_q$), 128.4 (C$_q$), 127.8 (CH), 127.8 (CH), 127.6 (CH), 127.4 (CH), 125.9 (CH), 125.5 (CH), 124.9 (C$_q$), 123.1 (CH), 118.1 (CH), 115.2 (CH), 114.6 (C$_q$), 108.8 (CH), 58.3 (CH$_2$), 55.4 (CH), 47.5 (CH$_2$), 44.3 (CH$_2$), 24.5 (CH), 23.0 (CH$_3$), 22.9 (CH$_3$). **HRMS (ESI)**: *m/z*: calc for $C_{25}H_{27}N_2^+$ 355.2174 [M+H]$^+$, found 355.2143.

3-(but-3-en-1-yl)-4-(naphthalen-2-ylmethyl)-1,3,4,5-tetrahydro-pyrrolo[4,3,2-*de*]isoquinoline **4k**

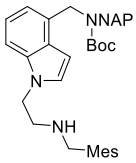


Compound **4k** was synthesized following the **General procedure 3** using tryptamine **5c** (50mg, 0.17 mmol, 1.0 equiv.), hex-5-enal (29 mg, 0.35 mmol, 2.0 equiv.), **Cat b** (2.6 mg, 0.0035 mmol, 2 mol%), M.S. 3 Å (82 mg), in DCM (2.5 mL). The desired product **4k** was obtained after column chromatography on silica gel (gradient from 0 to 15 % Heptane:EtOAc) as an oil (32 mg, 0.09 mmol, 53 %). **IR (neat) ν_{max}** = 3411, 3054, 2974, 2929, 2848, 1443, 1343, 1092, 909, 816, 750, 738 cm^{-1}. **^{1}H NMR (CDCl$_3$, 500 MHz)** δ = 7.94 (brs, 1H), 7.87-7.77 (m, 3H), 7.67 (s, 1H), 7.57 (d, *J* = 8.2 Hz, 1H), 7.50-7.43 (m, 2H), 7.26 (d, *J* = 8.1 Hz, 1H), 7.20 (dd, *J* = 0.9; 7.0 Hz, 1H), 6.90 (d, *J* = 1.2 Hz, 1H), 6.84 (d, *J* = 6.8 Hz, 1H), 5.87 (tdd, *J* = 6.7, 10.2, 17.1 Hz, 1H), 5.05 (dd, *J* = 2.1, 17.2 Hz, 1H), 4.95 (d, *J* = 9.9 Hz, 1H), 4.33 (d, *J* = 16.3 Hz, 1H), 4.04 (t, *J* = 7.6 Hz, 1H), 3.87 (d, *J* = 16.5 Hz, 1H), 3.77 (d, *J* = 13.5 Hz, 1H), 3.68 (d, *J* = 14.0 Hz, 1H), 2.38-2.24 (m, 2H), 2.07-1.98 (m, 1H), 1.78-1.69 (m, 1H). **^{13}C{^{1}H} NMR (CDCl$_3$, 75 MHz)** δ = 138.9 (CH), 137.8 (C$_q$), 133.8 (C$_q$), 133.5 (C$_q$), 132.9 (C$_q$), 128.3 (C$_q$), 127.9 (CH), 127.9 (CH), 127.8 (CH), 127.6 (CH), 127.4 (CH), 125.9 (CH), 125.5 (CH), 124.8 (C$_q$), 123.1 (CH), 118.4 (CH), 115.3 (CH), 114.7 (CH$_2$), 114.2 (C$_q$), 108.9 (CH), 58.4 (CH$_2$), 57.0 (CH), 47.6 (CH$_2$), 34.2 (CH$_2$), 30.5 (CH$_2$). **HRMS (ESI)**: *m/z*: calc for $C_{25}H_{25}N_2^+$ 353.2017 [M+H]$^+$, found 353.2031.

C4/*N*-Iso Pictet-Spengler reaction cascades
Synthesis of tryptamine 5d.

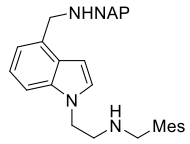


Et_3N (3.6 mL, 25.9 mmol, 5.0 equiv.) was added to a mixture of tryptamine **5c** (1.50 g, 5.18 mmol, 1.0 equiv.) and Boc_2O (1.70 g, 7.78 mmol, 1.5 equiv.) in dichloromethane (52 mL). After 4 h, TLC showed full completion. H_2O was added to the mixture, the layers were separated and the aqueous layer was extracted three times with DCM. The organic layer was dried over MgSO4, concentrated under *vacuum* and the crude product was purified by chromatography under silica gel to give the desired product *tert*-butyl ((1*H*-indol-4-yl)methyl)(naphthalen-2-ylmethyl)carbamate. (gradient from 0 to 20 % Heptane:EtOAc) as an oil (1.38 g, 3.57 mmol, 69 %). The product appears as rotamers by ^{1}H NMR and ^{13}C NMR. **IR (neat) ν_{max}** = 3316, 2976, 2927, 1666, 1412, 1365, 1247, 1161, 1115, 752 cm^{-1}. **^{1}H NMR (CDCl$_3$, 500 MHz)** δ = 8.30 (brs, 1H), 7.88-7.74 (m, 3H), 7.61 (s, 1H), 7.52-7.33 (m, 4H), 7.21 (t, *J* = 2.8 Hz, 1H), 7.18 (t, *J* = 7.7 Hz, 1H), 6.98 (d, *J* = 7.2 Hz, 1H), 6.72-6.50 (m, 1H), 4.86-4.67 (m, 2H), 4.63-4.43 (m, 2H), 1.55 (s, 9H). **^{13}C{^{1}H} NMR (CDCl$_3$, 75 MHz)** δ = 136.2 (C$_q$), 135.9 (C$_q$), 133.5 (C$_q$), 132.9 (C$_q$), 129.7 (C$_q$), 128.4 (CH), 127.9 (CH), 127.8 (CH), 126.8 (C$_q$), 126.4 and 126.2 (CH), 126.2 (CH), 126.1 and 125.8 (CH), 125.8 (CH), 124.2 (CH), 122.0 (CH), 120.1 and 118.8 (CH) 119.9 (C$_q$), 110.7 and 110.4 (CH), 101.6 and 100.9 (CH), 80.2 (C$_q$), 49.0 and 49.0 (CH$_2$), 47.6 (CH$_2$), 28.7 (CH$_3$). **HRMS (ESI)**: *m/z*: calc for $C_{21}H_{19}N_2O_2^+$ 331.1447 [M-tBu·+2H]$^+$, found 331.1443, *m/z*: calcd for $C_{27}H_{29}N_3Na\ O_2^+$ 450.2157 [M+Na+CH$_3$CN]$^+$, found 450.2157.



Acetonitrile (11.9 mL) was added on *tert*-butyl ((1*H*-indol-4-yl)methyl)(naphthalen-2-ylmethyl)carbamate (1.38 g, 3.57 mmol, 1.0 equiv.), 2-chloroethan-1-amine hydrochloride (476 mg, 4.11mmol, 1.15 equiv.), sodium hydroxide (314 mg, 7.86 mmol, 2.2 equiv.) and tetrabutylammo-

nium hydrogensulfate (49 mg, 0.14 mmol, 0.04 equiv.). The mixture was stirred at reflux for 24 h, then allowed to cool to rt, filtered over celite (wash with DCM), dried over K_2CO_3 and concentrated udder *vacuum*. This methodology routinely leads to 30 to 100 % conversions. The crude product was dissolved in MeOH (18 mL), and 2,4,6-trimethylbenzaldehyde (502 mg, 3.39 mmol, 0.95 equiv.) was added to the reaction mixture. After 16 h the reaction media was cooled to 0 °C before adding $NaBH_4$ (148 mg, 3.93 mmol, 1.1 equiv.), then the mixture was allowed to reach room temperature. After 1 hour stirring, the volatiles were removed and the crude was next diluted in ethyl acetate and water. After the phases were separated, the aqueous phase was extracted twice by ethyl acetate then the combined organic phases were dried over $MgSO_4$ and evaporated under vacuum. The crude mixture was then purified over column chromatography on silica gel to give the desired product *tert*-butyl (naphthalen-2-ylmethyl)((1-(2-((2,4,6-trimethylbenzyl)amino)ethyl)-1*H*-indol-4-yl)methyl)carbamate. (gradient from 20 to 50 % Heptane:EtOAc) as an oil (1.41 g, 2.51 mmol, 15 to 70 % over 2 steps). The product appears as rotamers by ^{1}H NMR and ^{13}C NMR. **IR (neat) ν_{max}** = 2973, 2922, 2859, 1685, 1413, 1364, 1241, 1161, 1109, 748, 735 cm^{-1}. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ = 7.90-7.74 (m, 3H), 7.61 (s, 1H), 7.54-7.30 (m, 4H), 7.19 (t, *J* = 7.8 Hz, 1H), 7.14 (d, *J* = 3 Hz, 1H), 6.98 (d, *J* = 7.2 Hz, 1H), 6.82 (s, 2H), 6.65-6.40 (m, 1H), 4.91-4.66 (m, 2H), 4.65-4.43 (m, 2H), 4.27 (t, *J* = 6.2 Hz, 2H), 3.74 (s, 2H), 3.13 (t, *J* = 6.2 Hz, 1H), 2.27 (s, 6H), 2.24 (s, 3H), 1.56 (s, 9H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz)** δ = 137.0 (C_q), 136.7 (C_q), 136.4 (C_q), 135.9 (C_q), 133.5 (C_q), 133.3 (c_q), 132.8 (C_q), 129.9 (C_q), 129.1 (2 CH), 128.3 (CH), 128.1 (CH), 127.8 (CH), 127.8 (CH), 126.8 (C_q), 126.5 and 126.2 (CH), 126.2 (CH), 126.0 and 125.8 (CH), 125.7 (CH), 121.5 (CH), 199.9 (C_q), 119.7 and 118.4 (CH), 109.0 and 108.8 (CH), 100.3 and 99.6 (CH), 80.1 (C_q), 49.5 (CH_2), 49.0 (CH_2), 47.6 (CH_2), 47.6 (CH_2), 46.9 (CH_2), 28.7 (3 CH_3), 21.0 (CH_3), 19.6 (CH_3). **HRMS (ESI)**: *m/z*: calc for $C_{37}H_{44}N_3O_2^+$ 562.3433 $[M+H]^+$, found 562.3376.

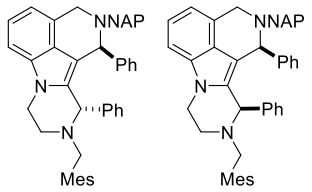


HCl (4 M in dioxane, 5.4 mL, 21.5 mmol, 10 equiv.) was added on **S8** (1.21 g, 2.15 mmol, 1.0 equiv.). The reaction mixture was then stirred for 20 h. The product precipitate was filtered, washed with 1,4-dioxane, and dried under *vacuum*. The crude product was dissolved in EtOAc then washed with a 1 M aqueous NaOH solution. After the phases were separated, the aqueous phase was extracted twice by EtOAc then the combined organic phases were dried over $MgSO_4$ and evaporated under vacuum. to give the desired product **5d**. (as an oil (650 mg, 1.41 mmol, 65 %). **^{1}H NMR ($CDCl_3$, 500 MHz)** δ = 7.85-7.79 (m, 4H), 7.52 (d, *J* = 9.0 Hz, 1H), 7.49-7.42 (m, 2H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.19 (t, *J* = 7.4 Hz, 2H), 7.16-7.10 (m, 2H), 6.79 (s, 1H), 6.54 (d, *J* = 3.2 Hz, 1H), 4.26 (t, *J* = 6.2 Hz, 2H), 4.14 (s, 2H), 4.03 (s, 2H), 3.72 (s, 2H), 3.12 (t, *J* = 6.4 Hz, 2H), 2.25 (s, 6H), 2.23 (s, 3H), 1.84-1.34 (bs, 2H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz)** δ = 138.1 (C_q), 137.0 (C_q), 136.6 (C_q), 136.3 (C_q), 133.6 (C_q), 133.3 (C_q), 132.8 (C_q), 132.5 (C_q), 129.1 (2 CH), 128.1 (CH), 128.0 (CH), 127.9 (C_q), 127.8 (CH), 127.8 (CH), 126.9 (CH), 126.7 (CH), 126.0 (CH), 125.6 (CH), 121.7 (CH), 119.0 (CH), 108.6 (CH), 99.5 (CH), 53.5 (CH_2), 51.2 (CH_2), 49.5 (CH_2), 47.6 (CH_2), 46.9 (CH_2), 21.0 (CH_3), 19.6 (CH_3). **HRMS (ESI)**: *m/z*: calc for $C_{32}H_{36}N_3^+$ 462.2909 $[M+H]^+$, found 462.2893.

Scope of the C4/*N*-Iso Pictet-Spengler reaction cascade with the same aldehyde

General procedure 4: A mixture of tryptamine **5d** (0.17 mmol), **Cat b** (10 mol %, 0.017 mmol,) and 3 Å molecular sieves (82 mg for 0.17 mmol of **5d**, powdered) in dichloromethane (2.4 mL for 0.17 mmol of **5d**) was stirred for 5 min at room temperature under an argon atmosphere. Subsequently, aldehyde (3.0 equiv., 0.17 mmol) was added and the mixture stirred at reflux for 24h. The mixture was filtered under celite and silica was added. After evaporation of the volatiles, the silica mixture was purified by chromatography under silica gel to give the desired product **9**.

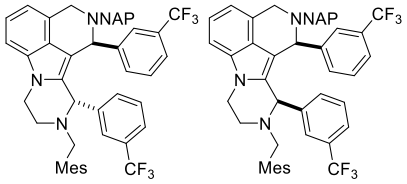
2-(naphthalen-2-ylmethyl)-1,11-diphenyl-10-(2,4,6-trimethylbenzyl)-2,3,8,9,10,11-hexahydro-1*H*-pyrazino[1',2':1,5]pyrrolo[4,3,2-*de*]isoquinoline **9a**



***Anti* 9a** ***Syn* 9a**

Compound **9a** was synthesized following the **General procedure 4** using tryptamine **5d** (100 mg, 0.22 mmol, 1.0 equiv.), benzaldehyde (69 mg, 0.65 mmol, 3.0 equiv.), **Cat b** (16.0 mg, 0.0217 mmol, 10 mol%), M.S. 3Å (104 mg), in DCM (3.1mL) at 40°C. Desired products **9a** were obtained after column chromatography on silica gel (gradient from 0 to 10 % Heptane:EtOAc) as white amorphous solids (95 mg, 0.15 mmol, 68 %, d.r 2:1 *anti*/*syn*). ***Anti* 9a : IR (neat) ν_{max}** = 3055, 3027, 2960, 2921, 2852, 1450, 1262, 1076, 1028, 1016, 711; 697 cm^{-1}. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ = 7.86-7.82 (m, 1H), 7.80-7.74 (m, 2H), 7.57 (s, 1H), 7.51-7.41 (m, 3H), 7.25-7.21 (m, 3H), 7.21-7.11 (m, 4H), 7.01-6.91 (m, 4H), 6.82-6.75 (m, 4H), 4.30 (s, 1H), 4.18 (td, *J* = 3.0, 11.5 Hz, 1H), 4.06 (dt, *J* = 4.0, 10.8 Hz, 1H), 3.85 (d, *J* = 16.0 Hz, 1H), 3.70 (s, 1H), 3.61 (d, *J* = 16.0 Hz, 1H), 3.56 (d, *J* = 14.0 Hz, 1H), 3.52 (d, *J* = 12.7 Hz, 1H), 3.47 (d, *J* = 13.9 Hz, 1H), 3.21 (d, *J* = 12.6 Hz, 1H), 3.12 (td, *J* = 3.2, 11.8 Hz, 1H), 2.74 (dt, *J* = 43.5, 11.3 Hz, 1H), 2.25 (s, 3H), 2.19 (s, 6H). **^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz)** δ = 140.9 (C_q), 138.8 (C_q), 137.5 (C_q), 136.8 (C_q), 135.6 (C_q), 132.6 (C_q), 132.0 (C_q), 131.9 (C_q), 131.8 (C_q), 130.4 (C_q), 129.1 (C_q), 128.8 (CH), 128.1 (CH), 127.5 (C_q), 127.0 (CH), 126.9 (CH), 126.8 (CH), 126.7 (CH), 126.4 (CH), 126.2 (CH), 125.8 (CH), 124.8 (CH), 124.4 (CH), 120.8 (CH), 114.2 (CH), 106.5 (C_q), 105.6 (CH), 67.3 (CH), 59.1 (CH), 57.8 (CH_2), 51.2 (CH_2), 46.4 (CH_2), 46.1 (CH_2), 42.0 (CH_2), 20.0 (CH_3), 19.6 (CH_3). **HRMS (ESI)**: *m/z*: calc for $C_{46}H_{44}N_3^+$ 638.3535 $[M+H]^+$, found 638.3552. ***Syn* 9a : IR (neat) ν_{max}** = 3056, 3027, 2921, 2853, 1451, 1291, 1265, 736, 696 cm^{-1}. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ = 7.91-7.81 (m, 3H), 7.68 (s, 1H), 7.59-7.47 (m, 3H), 7.23-7.15 (m, 2H), 6.98 (t, *J* = 7.2 Hz, 1H), 6.94-6.88 (m, 2H), 6.85-6.74 (m, 5H), 6.62 (t, *J* = 7.4 Hz, 1H), 6.54 (d, *J* = 7.4 Hz, 1H), 4.56 (s, 1H), 4.51 (s, 1H), 4.19 (td, *J* = 4.2, 11.2 Hz, 1H), 4.08 (ddd, *J* = 4.5, 9.5, 11.3 Hz, 1H), 3.88 (d, *J* = 16.3 Hz, 1H), 3.83-3.73 (m, 1H), 3.71-3.61 (m, 1H), 3.50 (d, *J* = 130 Hz, 1H), 3.49 (d, *J* = 12.4 Hz, 1H), 3.27 (d, *J* = 12.2 Hz, 1H), 3.16 (td, *J* = 4.3, 12.0 Hz, 1H), 2.77 (ddd, *J* = 3.5, 9.4, 12.1 Hz, 1H), 2.25 (s, 3H), 2.20 (s, 6H). **^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz)** δ = 140.1 (C_q), 139.3 (C_q), 138.5 (C_q), 136.7 (C_q), 133.6 (C_q), 133.4 (C_q), 133.0 (C_q), 131.5 (C_q), 131.5 (C_q), 130.1 (C_q), 129.5 (CH), 129.1 (CH), 128.8 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.6 (CH), 127.5 (C_q), 127.4 (CH), 127.2 (CH), 126.3 (CH), 126.0 (CH), 125.7 (C_q), 125.7 (CH), 121.9 (CH), 115.4 (CH), 106.8 (C_q), 106.7 (CH), 66.7 (CH), 60.1 (CH_2), 59.1 (CH), 52.0 (CH_2), 47.8 (CH_2), 46.5 (CH_2), 42.4 (CH_2), 21.0 (CH_3), 20.5 (CH_3). **HRMS (ESI)**: *m/z*: calc for $C_{46}H_{44}N_3^+$ 638.3535 $[M+H]^+$, found 638.3568.

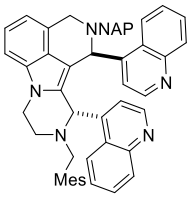
2-(naphthalen-2-ylmethyl)-1,11-bis(3-(trifluoromethyl)phenyl)-10-(2,4,6-trimethylbenzyl)-2,3,8,9,10,11-hexahydro-1*H*-pyrazino[1',2':1,5]pyrrolo[4,3,2-*de*]isoquinoline **9b**



***Anti* 9b** ***Syn* 9b**

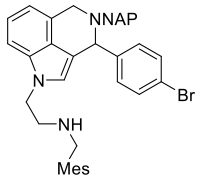
Compound **9b** was synthesized following the **General procedure 4** using tryptamine **5d** (100 mg, 0.22 mmol, 1.0 equiv.), 3-(trifluoromethyl)benzaldehyde (113.15 mg, 0.65 mmol, 3.0 equiv.), **Cat b** (16.0 mg, 0.0217 mmol, 10 mol%), M.S. 3Å (104 mg), in DCM (3.1 mL) at 40°C. Desired products **9b** were obtained after column chromatography on silica gel (gradient from 0 to 10 % Heptane:EtOAc) as white amorphous solids (98 mg, 0.12 mmol, 58 %, d.r 1:4 *anti*/*syn*). ***Anti* 9b : IR (neat) ν_{max}** = 3334, 2970, 2924, 1327, 1163, 1120, 1094, 1072, 746, 702 cm^{-1}. **^{1}H NMR (CDCl$_3$, 500 MHz)** δ = 7.87-7.84 (m, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.55-7.46 (m, 4H), 7.43-7.33 (m, 4H), 7.25 (s, 1H), 7.22-7.17 (m, 2H), 7.09 (d, *J* = 7.6 Hz, 1H), 6.99-6.93 (m, 2H), 6.83-6.78 (m, 2H), 4.33 (s, 1H), 4.21 (td, *J* = 2.8, 11.3 Hz, 1H), 4.08 (dt, *J* = 4.1, 11.2 Hz, 1H), 3.81 (d, *J* = 16.5 Hz, 1H), 3.66 (d, *J* = 8.2 Hz, 1H), 3.63 (s, 1H), 3.53 (d, *J* = 13.9 Hz, 1H), 3.48 (d, *J* = 14.0 Hz, 1H), 3.42 (d, *J* = 12.2 Hz, 1H), 3.23 (d, *J* = 12.3 Hz, 1H), 3.13 (td, *J* = 4.2, 11.8 Hz, 1H), 2.76 (dt, *J* = 3.8, 11.5 Hz, 1H), 2.24 (s, 3H), 2.16 (s, 6H). **^{13}C{^{1}H} NMR (CDCl$_3$, 75 MHz)** δ = 142.6 (C$_q$), 141.0 (C$_q$), 138.4 (C$_q$), 137.0 (C$_q$), 137.0 (C$_q$), 133 5 (C$_q$), 133.1 (C$_q$), 133.0 (C$_q$), 132.2 (CH), 132.2 (CH), 131.8 (C$_q$), 130.8 (C$_q$), 130.7 (C$_q$), 130.3 (C$_q$), 129.3 (CH), 128.8 (CH), 128.6 (CH), 128.3 (C$_q$), 128.3 (q, C-F, $^1J_{C-F}$ = 252.5 Hz, Cq), 128.1 (CH), 128.0 (q, C-F, $^1J_{C-F}$ = 248.3 Hz, Cq), 127.9 (CH), 127.7 (CH), 127.1 (CH), 127.0 (CH), 126.5 (d, $^3J_{C-F}$ = 3.3 Hz, CH), 126.0 (CH), 125.7 (d, C-F, $^3J_{C-F}$ = 3.9 Hz, CH), 125.6 (CH), 125.4 (C$_q$), 125.0 (d, C-F, $^3J_{C-F}$ = 3.3 Hz, CH), 123.9 (d, C-F, $^3J_{C-F}$ = 3.2 Hz, CH), 122.3 (CH), 115.5 (CH), 106.9 (CH), 106.8 (C$_q$), 67.8 (CH), 59.3 (CH), 58.7 (CH$_2$), 52.4 (CH$_2$), 47.6 (CH$_2$), 47.1 (CH$_2$), 42.9 (CH$_2$), 21.0 (CH$_3$), 20.5 (CH$_3$). **^{19F} NMR (CDCl$_3$, 282 MHz)** δ = -62.4, -62.8. **HRMS (ESI)**: *m/z*: calc for $C_{48}H_{42}F_6N_3^+$ 774.3283 [M+H]$^+$, found 774.3231. ***Syn* 9b : IR (neat) ν_{max}** = 3340, 2973, 2924, 1327, 1163, 1119, 1092, 1071, 1047, 736, 700cm^{-1}. **^{1}H NMR (CDCl$_3$, 500 MHz)** δ =7.93-7.83 (m, 3H), 7.69 (s, 1H), 7.58-7.50 (m, 3H), 7.28-7.19 (m, 3H), 7.14 (s, 3H), 7.08 (d, *J* = 7.7 Hz, 1H), 7.05-6.98 (m, 2H), 6.87-6.82 (m, H), 6.79 (t, *J* = 7.7 Hz, 1H), 6.69 (d, *J* = 7.7 Hz, 1H), 4.65 (s, 1H), 4.60 (s, 1H), 4.23 (td, *J* = 4.3, 11.2 Hz, 1H), 4.15 (dt, *J* = 3.2, 10.0 Hz, 1H), 3.80 (d, *J* = 16.1 Hz, 1H), 3.76 (d, *J* = 13.0 Hz, 1H), 3.67 (d, *J* = 14.1 Hz, 1H), 3.53 (d, *J* = 13.2 Hz, 1H), 3.43 (d, *J* = 12.5 Hz, 1H), 3.32 (d, *J* = 12.4 Hz, 1H), 3.17 (td, *J* = 4.0, 12.1 Hz, 1H), 2.82 (ddd, *J* = 3.7; 10.2; 12.6 Hz, 1H), 2.28 (s, 3H), 2.20 (s, 6H). **^{13}C{^{1}H} NMR (CDCl$_3$, 75 MHz)** δ = 141.3 (C$_q$), 141.0 (C$_q$), 138.4 (C$_q$), 137.0 (C$_q$), 136.9 (C$_q$), 133 6 (C$_q$), 133.3 (C$_q$), 133.1 (C$_q$), 132.7 (CH), 131.6 (CH), 130.8 (C$_q$), 130.5 (C$_q$), 129.8 (C$_q$), 129.4 (C$_q$), 129.3 (2CH), 128.4 (C$_q$), 128.3 (q, C-F, $^1J_{C-F}$ = 260.0 Hz, Cq), 128.3 (CH), 128.2 (CH), 127.9 (2 CH), 127.8 (CH), 127.8 (CH), 127.5 (CH), 127.4 (q, C-F, $^1J_{C-F}$ = 276.5 Hz, Cq), 126.6 (CH), 126.1 (q, C-F, $^3J_{C-F}$ = 3.3 Hz, CH), 125.8 (CH), 125.6 (C$_q$), 125.2 (q, C-F, $^3J_{C-F}$ = 3.8 Hz, CH), 124.5 (q, C-F, $^3J_{C-F}$ = 3.3 Hz, CH), 123.6 (q, C-F, $^3J_{C-F}$ = 3.3 Hz, CH), 122.4 (CH), 115.7 (CH), 107.0 (CH), 106.4 (C$_q$), 66.6 (CH), 59.6 (CH), 59.1 (CH$_2$), 52.3 (CH$_2$), 47.7 (CH$_2$), 46.6 (CH$_2$), 42.5 (CH$_2$), 21.0 (CH$_3$), 20.5 (CH$_3$). **^{19F} NMR (CDCl$_3$, 282 MHz)** δ = -62.5, -62.9. **HRMS (ESI)**: *m/z*: calc for $C_{48}H_{42}F_6N_3^+$ 774.3283 [M+H]$^+$, found 774.3218.

2-(4-(naphthalen-2-ylmethyl)-3-(quinolin-4-yl)-4,5-dihydro-pyrrolo[4,3,2-*de*]isoquinolin-1(3H)-yl)-*N*-(2,4,6-trimethylben-zyl)ethan-1-amine **9c**



Compound **9c** was synthesized following the **General procedure 4** using tryptamine **5d** (75 mg, 0.16 mmol, 1.0 equiv.), quinoline-4-carbaldehyde (77 mg, 0.49 mmol, 3.0 equiv.), **Cat b** (12.0 mg, 0.0162 mmol, 10 mol%), M.S. 3Å (78 mg), in DCM (2.3 mL) at 40°C. The desired product **9c** was obtained after column chromatography on silica gel (gradient from 40 to 60 % Heptane:EtOAc) as a single diastereoisomer (84 mg, 0.14 mmol, 88 %). **IR (neat) ν_{max}** = 3055, 2926, 1688, 1508, 1455, 1365, 1247, 1164, 756 cm^{-1}. **^{1}H NMR (CDCl$_3$, 500 MHz)** δ = 8.70 (s, 1H), 8.49 (bs, 1H), 8.13 (d, *J* = 8.6 Hz, 1H), 8.08 (bs, 1H), 7.84-7.79 (m, 1H), 7.74-7.64 (m, 3H), 7.56-7.42 (m, 3H), 7.40-7.21 (m, 6H), 7.21-6.97 (m, 3H), 6.80 (s, 2H), 6.77 (d, *J* = 7.3 Hz, 1H), 6.63 (d, *J* = 4.4 Hz, 1H), 4.94 (s, 1H), 4.46-4.32 (m, 2H), 3.98 (s, 1H), 3.64-3.49 (m, 2H), 3.42 (d, *J* = 16.7 Hz, 1H), 3.38-3.31 (2H), 3.31-3.20 (m, 1H), 3.02-2.73 (m, 2H), 2.27 (s, 3H), 2.11 (s, 6H). **^{13}C{^{1}H} NMR (CDCl$_3$, 75 MHz)** δ = 149.8 (CH), 149.7 (CH), 148.8 (C$_q$), 148.6 (C$_q$), 147.2 (C$_q$), 144.9 (C$_q$), 138.4 (C$_q$), 137.1 (C$_q$), 136.9 (C$_q$), 133.3 (C$_q$), 133.1 (C$_q$), 132.8 (C$_q$), 131.1 (C$_q$), 130.2 (C$_q$), 130.1 (CH), 129.7 (CH), 129.4 (CH), 129.2 (CH), 129.1 (CH), 128.8 (C$_q$), 127.9 (CH), 127,8 (CH), 127.7 (CH), 127.5 (C$_q$), 127.3 (CH), 127.1 (CH), 127.0 (C$_q$), 126.8 (C$_q$), 126.6 (CH), 125.9 (CH), 125.9 (CH), 125.6 (CH), 124.4 (CH), 123.0 (CH), 122.6 (CH), 120.9 (CH), 116.2 (CH), 107.1 (CH), 104.7 (C$_q$), 59.0 (CH$_2$), 57.9 (CH), 53.0 (CH$_2$), 47.9 (CH$_2$), 45.4 (CH$_2$), 43.1 (CH$_2$), 21.0 (CH$_3$), 20.6 (CH$_3$). Note that one of the benzylic CH does not resonate well in the 13C NMR spectrum, it is estimated around 67 ppm. **HRMS (ESI)**: *m/z*: calc for $C_{52}H_{46}N_5^+$ 740.3753 [M+H]$^+$, found 740.3784.

2-(3-(4-bromophenyl)-4-(naphthalen-2-ylmethyl)-4,5-dihydro-pyrrolo[4,3,2-*de*]isoquinolin-1(3*H*)-yl)-N-(2,4,6-trimethylben-zyl)ethan-1-amine **10a**

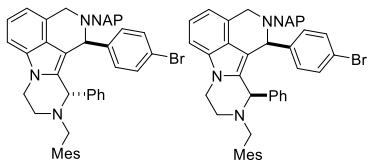


A mixture of tryptamine **5d** (84 mg, 0.18 mmol, 1.0 equiv.), **Cat b** (13.4 mg, 0.0182 mmol, 10 mol%) and M.S. 3Å (87 mg), in DCM (2.6 mL) was stirred for 5 min at room temperature under an argon atmosphere. Subsequently, 4-bromobenzaldehyde (34 mg, 0.18 mmol, 1.0 equiv.), was added and the mixture stirred at reflux for 24h. The mixture was filtered under celite and silica was added. After evaporation of the volatiles, the silica residue was purified by chromatography under silica gel gradient from 0 to 50 % Heptane:EtOAc) to give product **10a** as an oil (81 mg, 0.13 mmol, 71 %). **IR (neat) ν_{max}** = 3315, 3051, 2922, 2852, 1459, 1263, 1010, 734 cm^{-1}. **^{1}H NMR (CDCl$_3$, 300 MHz)** δ = 7.89-7.76 (m, 3H), 7.71 (s, 1H), 7.58 (d, *J* = 9.0 Hz, 1H), 7.52-7.45 (m, 2H), 7,44-7.37 (m, 2H), 7.26-7.14 (m, 4H), 6.83 (s, 2H), 6.79 (d, *J* = 6.6 Hz, 1H), 6.71 (s, 1H), 4.98 (s, 1H), 4.27 (t, *J* = 6.1 Hz, 2H), 4.05 (d, *J* = 15.8 Hz, 1H), 3.86 (d, *J* = 13.4 Hz, 1H), 3.79 (d, *J* = 16.2 Hz, 1H), 3.74 (s, 2H), 3.69 (d, *J* = 13.6 Hz, 1H), 3.16 (t, *J*= 5.8 Hz, 1H), 2.30-2.20 (m, 9H). **^{13}C{^{1}H} NMR (CDCl$_3$, 75 MHz)** δ =142.0 (C$_q$), 137.4 (C$_q$), 136.9 (C$_q$), 136.7 (C$_q$), 134.1 (C$_q$), 133.5 (C$_q$), 133.4 (C$_q$), 133.0 (C$_q$), 131.2 (CH), 130.5 (CH), 129.2 (CH), 129.0 (C$_q$), 128.1 (CH), 127.8 (CH), 127.8 (CH), 127.4 (CH), 127.4 (CH), 126.0 (CH), 125.7 (C$_q$), 125.7 (CH), 123.3 (CH), 122.8 (CH), 121.0 (C$_q$), 114.7 (CH), 112.5 (C$_q$), 107.6 (CH), 61.0 (CH$_2$), 58.9 (CH), 49.9 (CH$_2$), 49.6 (CH$_2$), 47.7 (CH$_2$), 47.1 (CH$_2$), 21.0 (CH$_3$), 19.6 (CH$_3$) **HRMS (ESI)**: *m/z*: calc for $C_{39}H_{39}{}^{79}BrN_3^+$ 628.2327 [M+H]$^+$, found 628.2301, calc for $C_{39}H_{39}{}^{81}BrN_3^+$ 630.2327 [M+H]$^+$, found 630.2307.

Scope of the C4/*N*-Iso Pictet-Spengler reaction cascade with two different aldehydes

General procedure 5: A mixture of tryptamine **5d** (0.17 mmol), **Cat b** (10 mol %, 0.017 mmol,) and 3 Å molecular sieves (82 mg for 0.17 mmol of **5d**, powdered) in dichloromethane (2.4 mL for 0.17 mmol of **5d**) was stirred for 5 min at room temperature under an argon atmosphere. Subsequently, aldehyde **a** (1.0 equiv., 0.17 mmol) was added and the mixture stirred for 15 h. Then aldehyde **b** (2.0 equiv., 0.35 mmol) was added and the mixture stirred at reflux for 24h. The mixture was filtered under celite and silica was added. After evaporation of the volatiles, the silica mixture was purified by chromatography under silica gel to give the desired product **11**.

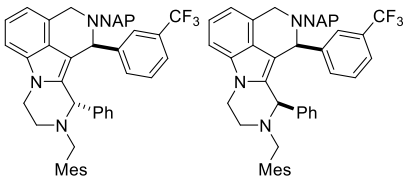
1-(4-bromophenyl)-2-(naphthalen-2-ylmethyl)-11-phenyl-10-(2,4,6-trimethylbenzyl)-2,3,8,9,10,11-hexahydro-1*H*-pyrazino[1',2':1,5]pyrrolo[4,3,2-*de*]isoquinoline **11a**



***Anti* 11a** ***Syn* 11a**

Sequential procedure: A mixture of tryptamine **10a** (65 mg, 0.14 mmol, 1.0 equiv.), **Cat b** (10.4 mg, 0.014 mmol, 10 mol %) and 3 Å molecular sieves (68 mg) in dichloromethane (2.0 mL) was stirred for 5 min at room temperature under an argon atmosphere. Subsequently, benzaldehyde (30 mg, 0.28 mmol, 2.0 equiv.) was added and the mixture stirred at 40°C for 24 h. The mixture was filtered under celite and silica was added. The desired products **11a** were obtained after column chromatography on silica gel (gradient from 0 to 10 % Heptane:EtOAc) as an oil (70 mg, 0.10 mmol, 70 %, d.r 1:3 *anti*/*syn*). **One-pot procedure:** Compound **11a** was synthesized following the **General procedure 5** using tryptamine **5d** (31 mg, 0.07 mmol, 1.0 equiv.), 4-bromobenzaldehyde (12 mg, 0.07 mmol, 1.0 equiv.), **Cat b** (5.0 mg, 0.0067 mmol, 10 mol%), then benzaldehyde (14 mg, 0.13 mmol, 2.0 equiv.), M.S. 3Å (32 mg), in DCM (1.0 mL). The desired products **11a** were obtained after column chromatography on silica gel (gradient from 0 to 10 % Heptane:EtOAc) as an oil (29 mg, 0.05 mmol, 72 %, d.r 1:2 *anti*/*syn*). ***Anti* 11a: IR (neat) ν_{max}** = 3054, 2922, 2852, 1484, 1451, 1289, 1263, 1010, 736, 698 cm^{-1}. **^{1}H NMR (CDCl$_3$, 500 MHz)** δ = 7.86-7.82 (m, 1H), 7.79-7.74 (m, 2H), 7.53 (s, 1H), 7.50-7.44 (m, 2H), 7.41 (d, *J* = 8.6 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 2H), 7.21-7.12 (m, 4H), 6.96 (t, *J* = 7.5 Hz, 2H), 6.83-6.78 (m, 5H), 6.76 (d, *J*= 6.7 Hz, 1H), 4.27 (s, 1H), 4.18 (td, *J* = 3.0, 11.1 Hz, 1H), 4.06 (dt, *J* = 4.2, 11.2 Hz, 1H), 3.78 (d, *J* = 16.2 Hz, 1H), 3.59 (d, *J* = 15.9 Hz, 1H), 3.59 (s, 1H), 3.55-3.50 (m, 2H), 3.44 (d, *J* = 13.8 Hz, 1H), 3.20 (d, *J* = 12.5 Hz, 1H), 3.12 (td, *J* = 2.9, 11.6 Hz, 1H), 2.73 (dt, *J* = 3.6, 11.3 Hz, 1H), 2.25 (s, 3H), 2.19 (s, 6H). **^{13}C{^{1}H} NMR (CDCl$_3$, 125 MHz)** δ = 141.2 (C_q), 139.7 (C_q), 138.5 (C_q), 137.5 (C_q), 136.7 (C_q), 133.6 (C_q), 133.0 (C_q), 133.0 (C_q), 131.3 (C_q), 131.0 (2 CH), 130.9 (CH), 129.8 (CH), 129.3 (C_q), 129.2 (CH), 128.2 (C_q), 128.0 (CH), 127.9 (CH), 127.7 (CH), 127.2 (CH), 127.2 (CH), 127.1 (C_q), 125.9 (CH), 125.5 (CH), 121.9 (CH), 120.7 (C_q), 115.3 (CH), 106.8 (C_q), 106.7 (CH), 68.4 (CH), 59.5 (CH), 58.8 (CH_2), 52.3 (CH_2), 47.3 (CH_2), 43.1 (2 CH_2), 21.0 (CH_3), 20.6 (CH_3). **HRMS (ESI)**: *m/z*: calc. for $C_{46}H_{43}{}^{79}BrN_3{}^+$ 716.2640 $[M+H]^+$, found 716.2622, calc. for $C_{39}H_{39}{}^{81}BrN_3{}^+$ 718.2620 $[M+H]^+$, found 718.2652. ***Syn* 11a: IR (neat) ν_{max}** = 3054, 2958, 2924, 2871, 1485, 1451, 1364, 1290, 1010, 750, 698 cm^{-1}. **^{1}H NMR (CDCl$_3$, 500 MHz)** δ = 7.88-7.82 (m, 3H), 7.66 (s, 1H), 7.53-7.46 (m, 3H), 7.22-7.14 (m, 2H), 7.00 (d, *J* = 8.3 Hz, 2H), 6.86-6.77 (m, 6H), 6.68 (t, *J* = 7.5, 2H), 6.40 (d, *J* = 8.5 Hz, 2H), 4.55 (s, 1H), 4.46 (s, 1H), 4.21-4.15 (m, 1H), 4.08 (dt, *J* = 4.2, 10.4 Hz, 1H), 3.81 (d, *J* = 16.3 Hz, 1H), 3.73 (d, *J* = 13.0 Hz, 1H), 3.65 (d, *J* = 16.1 Hz, 1H), 3.48 (d, *J* = 13.0 Hz, 1H), 3.48 (d, *J* = 12.6 Hz, 1H), 3.27 (d, *J* = 12.4 Hz, 2H), 3.20-3.11 (m, 1H), 2.76 (ddd, *J* = 3.5, 9.4, 12.0 Hz, 1H), 2.25 (s, 3H), 2.19 (s, 6H). **^{13}C{^{1}H} NMR (CDCl$_3$, 125 MHz)** δ = 139.5 (C_q), 139.5 (C_q), 138.5 (C_q), 137.3 (C_q) 136.7 (C_q), 133.6 (C_q), 133.4 (C_q), 133.0 (C_q), 131.7 (C_q), 131.4 (C_q), 130.5 (CH), 130.3 (CH), 129.6 (CH), 129.1 (CH), 128.4 (C_q), 128.1 (CH), 127.8 (CH), 127.8 (CH), 127.7 (CH), 127.7 (CH), 127.6 (CH), 126.1 (CH), 125.7 (CH), 125.7 (C_q), 122.0 (C_q), 122.0 (CH), 120.2 (C_q), 115.4 (CH), 106.8 (CH), 108,7 (C_q), 66.9 (CH), 59.5 (CH_2), 59.1 (CH), 52.1 (CH_2), 47.8 (CH_2), 46.5 (CH_2), 42.6 (CH_2), 21.0 (CH_3), 20.5 (CH_3). **HRMS (ESI)**: *m/z*: calc. for $C_{46}H_{43}{}^{79}BrN_3{}^+$ 716.2640 $[M+H]^+$, found 716.2679, calc. for $C_{39}H_{39}{}^{81}BrN_3{}^+$ 718.2620 $[M+H]^+$, found 718.2668.

2-(naphthalen-2-ylmethyl)-11-phenyl-1-(3-(trifluoromethyl)phenyl)-10-(2,4,6-trimethylbenzyl)-2,3,8,9,10,11-hexahydro-1*H*-pyrazino[1',2':1,5]pyrrolo[4,3,2-*de*]isoquinoline **11b**

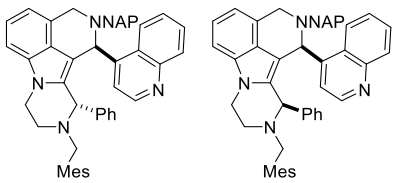


***Anti* 11b** ***Syn* 11b**

Compound **11b** was synthesized following the **General procedure 5** using tryptamine **5d** (100 mg, 0.22 mmol, 1.0 equiv.), 3-(trifluoromethyl)benzaldehyde (38 mg, 0.22 mmol, 1.0 equiv.), **Cat b** (16.0 mg, 0.0217 mmol, 10 mol%), M.S. 3Å (104 mg), then benzaldehyde (46 mg, 0.43 mmol, 2.0 equiv.), in DCM (3.0 mL). The desired products **11b** were obtained after column chromatography on silica gel (gradient from 0 to 10 % Heptane:EtOAc) as an oil (98 mg, 0.12 mmol, 58 %, d.r 1:4 *anti*/*syn*). ***Anti* 11b: IR (neat) ν_{max}** = 3057, 2926, 2852, 1451, 1329, 1163, 1124, 747, 704 cm^{-1}. **^{1}H NMR (CDCl$_3$, 500 MHz)** δ =7.88-7.84 (m, 1H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.56 (s, 1H), 7.52-7.45 (m, 3H), 7.42 (d, *J* = 8.7 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.22 (s, 1H), 7.24-7.08 (m, 5H), 6.92 (t, *J* = 7.4 Hz, 2H), 6.81-6.77 (m, 3H), 6.72 (t, *J* = 7.3 Hz, 1H), 4.25 (s, 1H), 4.19 (td, *J* = 2.8, 11.1 Hz, 1H), 4.05 (dt, *J* = 4.3, 11.5 Hz, 1H), 3.82 (d, *J* = 16.1 Hz, 1H), 3.68-3.61 (m, 2H), 3.56-3.46 (m, 3H), 3.19 (d, *J* = 12.5 Hz, 1H), 3.15-3.10 (m, 1H), 2.73 (dt, *J* = 3.5, 11.5 Hz, 1H), 2.25 (s, 3H), 2.19 (s, 6H). **^{13}C{^{1}H} NMR (CDCl$_3$, 125 MHz)** δ = 143.1 (C_q), 139.5 (C_q), 138.5 (C_q), 137.3 (C_q), 136.7 (C_q), 133.6 (C_q), 133.1 (C_q), 133.0 (C_q), 133.0 (C_q), 132.2 (C_q), 131.3 (C_q), 130.2 (CH), 129.8 (CH), 129.2 (q, C-F, $^1J_{C-F}$ = 251.9 Hz, Cq), 129.2 (CH), 128.3 (CH), 128.2 (C_q), 128.1 (CH), 128.1 (CH), 127.9 (CH), 127.9 (CH), 127.7 (CH), 127.2 (CH), 127.2 (CH), 126.1 (q, C-F, $^3J_{C-F}$ = 3.7 Hz, CH), 125.9 (CH), 125.5 (CH), 125.5 (C_q), 123.6 (q, C-F, $^3J_{C-F}$ = 3.7 Hz, CH), 122.0 (CH), 115.4 (CH), 106.8 (CH), 106.8 (C_q), 68.6 (CH), 59.4 (CH), 58.8 (CH_2), 52.3 (CH_2), 47.3 (CH_2), 47.3 (CH_2), 43.1 (CH_2), 21.0 (CH_3), 20.6 (CH_3). **^{19F} NMR (CDCl$_3$, 282 MHz)** δ = -62.3. **HRMS (ESI)**: *m/z*: calc for $C_{47}H_{43}F_3N_3{}^+$ 706.3409 $[M+H]^+$, found 706.3380. ***Syn* 11b: IR (neat) ν_{max}** = 3055, 2924, 2851, 1451, 1329, 1162, 1122, 1073, 748, 699 cm^{-1}. **^{1}H NMR (CDCl$_3$, 500 MHz)** δ = 7.90-7.81 (m, 3H), 7.66 (s, 1H), 7.54-7.47 (m, 3H), 7.25-7.14 (m, 3H), 7.00 (t, *J* = 8.6 Hz, 1H), 6.85 (d, *J* = 7.9 Hz, 2H), 6.82-6.78 (m, 3H), 6.76 (s, 1H), 6.74-6.69 (m, 2H), 6.61 (t, *J* = 7.6 Hz, 2H), 4.55 (s, 1H), 4.54 (s, 1H), 4.23-4.16 (m, 1H), 4.10 (dt, *J* = 3.6, 10.5 Hz, 1H), 3.77 (d, *J* = 16.5 Hz, 1H), 3.72 (d, *J* = 12.4 Hz, 1H), 3.63 (d, *J* = 16.4 Hz, 1H)., 3.52-3.43 (m, 2H), 3.24 (d, *J* = 12.5 Hz, 1H), 3.18-3.11 (m, 1H), 2.76 (ddd, *J* = 3.9, 10.1, 11.9 Hz, 1H), 2.25 (s, 3H), 2.18 (s, 6H). **^{13}C{^{1}H} NMR (CDCl$_3$, 125 MHz)** δ = 141.3 (C_q), 139.5 (C_q), 138.5 (C_q), 137.2 (C_q), 136.7 (C_q), 133.6 (C_q), 133.2 (C_q), 133.0 (C_q), 132.0 (C_q), 131.8 (C_q), 131.3 (C_q), 129.5 (CH), 129.2 (CH), 128.3 (C_q), 128.1 (q, C-F, $^1J_{C-F}$ = 275.8 Hz, C_q), 128.1 (CH), 127.8 (CH), 127.8 (3 CH), 127.6 (CH), 127.6 (CH), 127.5 (CH), 126.1 (CH), 125.7 (CH), 125.7

(CH), 125.5 (q, C-F, $^3J_{C-F}$ = 3.5 Hz, CH), 123.3 (q, C-F, $^3J_{C-F}$ = 3.8 Hz, CH), 122.0 (CH), 115.5 (CH), 106.9 (CH), 106.0 (C_q), 67.5 (CH), 59.6 (CH), 59.1 (CH_2), 52.2 (CH_2), 47.5 (CH_2), 46.8 (CH_2), 42.7 (CH_2), 21.0 (CH_3), 20.6 (CH_3). **^{19F} NMR ($CDCl_3$, 282 MHz)** δ = -62.3. **HRMS (ESI)**: *m/z*: calc for $C_{47}H_{43}F_3N_3^+$ 706.3409 $[M+H]^+$, found 706.3414.

2-(naphthalen-2-ylmethyl)-11-phenyl-1-(quinolin-4-yl)-10-(2,4,6-trimethylbenzyl)-2,3,8,9,10,11-hexahydro-1*H*-pyrazino[1',2':1,5]pyrrolo[4,3,2-*de*]isoquinoline **11c**



***Anti* 11c** ***Syn* 11c**

Compound **11c** was synthesized following the **General procedure 5** using tryptamine **5d** (60 mg, 0.13 mmol, 1.0 equiv.), quinoline-4-carbaldehyde (20 mg, 0.13 mmol, 1.0 equiv.), **Cat b** (9.6 mg, 0.0130 mmol, 10 mol%), M.S. 3Å (62 mg), at 40°C then benzaldehyde (28 mg, 0.26 mmol, 2.0 equiv.), in DCM (1.9 mL). The desired products **11c** were obtained after column chromatography on silica gel (gradient from 0 to 35 % Heptane:EtOAc) as an oil (64 mg, 0.09 mmol, 71 %, d.r 2:1 *anti*/*syn*). ***Anti* 11c: IR (neat) ν_{max}** = 3056, 2924, 2850, 1688, 1591, 1508, 1450, 1326, 1274, 758 cm^{-1}. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ = 8.70 (d, *J* = 4.5 Hz, 1H), 8.17 (d, *J* = 8.6 Hz, 1H), 7.85-7.81 (m, 1H), 7.77-7.70 (m, 3H), 7.65 (d, *J* = 9.3 Hz, 1H), 7.55 (s, 1H), 7.49-7.44 (m, 2H), 7.44-7.37 (m, 2H), 7.27 (d, *J* = 8.5 Hz, 1H), 7.22-7.13 (m, 4H), 7.04 (t, *J* = 7.4 Hz, 2H), 6.82 (s, 1H), 6.74 (d, *J* = 6.9 Hz, 1H), 6.62 (d, *J* = 4.4 Hz, 1H), 4.33 (s, 1H), 4.30-4.23 (m, 2H), 4.15 (dt, *J* = 4.2, 11.0 Hz, 1H), 3.62 (d, *J* = 18.3 Hz, 1H), 3.60 (s, 2H), 3.56 (d, *J* = 12.5 Hz, 1H), 3.47 (d, *J* = 16.5 Hz, 1H), 3.23-3.16 (m, 2H), 2.81 (dt, *J* = 3.1, 11.3 Hz, 1H), 2.27 (s, 3H), 2.24 (s, 6H). **^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz)** δ = 148.8 (CH), 147.7 (C_q), 147.1 (C_q), 138.9 (C_q), 137.5 (C_q), 136.3 (C_q), 135.7 (C_q), 132.6 (C_q), 132.4 (C_q), 132.0 (C_q), 131.9 (C_q), 130.1 (C_q), 128.8 (CH), 128.6 (CH), 128.2 (CH), 128.1 (CH), 127.5 (CH), 127.3 (CH), 126.9 (CH), 126.9 (CH), 126.7 (CH), 126.5 (CH), 126.3 (C_q), 125.0 (CH), 125.0 (CH), 124.7 (CH), 124.6 (CH), 121.2 (CH), 120.3 (CH), 114.9 (CH), 106.0 (CH), 103.7 (C_q), 81.7 (C_q), 67.8 (CH), 58.4 (CH_2), 56.9 (CH), 51.4 (CH_2), 46.5 (CH_2), 44.6 (CH_2), 42.3 (CH_2), 20.0 (CH_3), 19.6 (CH_3). **HRMS (ESI)**: *m/z*: calc for $C_{49}H_{45}N_4^+$ 689.3644 $[M+H]^+$, found 689.3622. ***Syn* 11c: IR (neat) ν_{max}** = 3058, 2924, 2851, 1694, 1612, 1508, 1451, 1345, 1275, 758 cm^{-1}. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ = 8.38 (d, *J* = 4.2 Hz, 1H), 8.00-7.86 (m, 4H), 7.74 (s, 1H), 7.57-7.50 (m, 4H), 7.33-7.26 (m, 2H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 6.94-6.87 (m, 2H), 6.83 (d, *J* = 6.7 Hz, 1H), 6.81 (s, 2H), 6.36 (bs, 1H), 6.22 (t, *J* = 7.8 Hz, 2H), 6.08 (t, *J* = 7.3 Hz, 1H), 5.31 (s, 1H), 4.65 (s, 1H), 4.28-4.22 (m, 1H), 4.15 (dt, *J* = 4.0, 10.9 Hz, 1H), 3.88 (d, *J* = 16.2 Hz, 1H), 3.78 (d, *J* = 12.7 Hz, 1H), 3.71 (d, *J* = 12.3 Hz, 1H), 3.63 (d, *J* = 16.5 Hz, 1H), 3.45 (d, *J* = 12.4 Hz, 1H), 3.25 (d, *J* = 12.1 Hz, 1H), 3.18 (td, *J* = 3.2, 11.5 Hz, 1H), 2.83 (dt, *J* = 3.8, 11.3 Hz, 1H), 2.25 (s, 3H), 2.20 (6H). **^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz)** δ = 150.6 (C_q), 149.1 (CH), 148.4 (C_q), 146.3 (C_q), 139.3 (C_q), 138.5 (C_q), 136.9 (C_q), 136.8 (C_q), 133.5 (C_q), 133.1 (C_q), 133.0 (C_q), 131.1 (C_q), 130.4 (C_q), 129.5 (CH), 129.2 (CH), 129.2 (CH), 128.7 (CH), 128.4 (CH), 128.1 (CH), 127.9 (CH), 127.9 (CH), 127.5 (CH), 127.0 (CH), 127.0 (C_q), 126.3 (CH), 126.0 (CH), 125.9 (C_q), 125.7 (CH), 124.5 (CH), 122.3 (CH), 121.4 (CH), 116.1 (CH), 107.0 (CH), 104.0 (C_q), 68.9 (CH), 59.5 (CH_2), 54.7 (CH), 52.6 (CH_2), 47.8 (CH_2), 47.4 (CH_2), 43.3 (CH_2), 21.0 (CH_3), 20.7 (CH_3). **HRMS (ESI)**: *m/z*: calc for $C_{49}H_{45}N_4^+$ 689.3644 $[M+H]^+$, found 689.3593.

ASSOCIATED CONTENT

Supporting Information

Details about optimization of the reactions, blank tests, NMR spectra, X-Ray Crystallography Data, Mechanistic Hypotheses. The Supporting Information is available free of charge on the ACS Publications website.

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Author Contributions

All authors have given approval to the final version of the manuscript.

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REFERENCES

1. See, for example: (a) Rahman, A.; Basha, A., *Indole Alkaloids*. Harwood accademic publishers: Reading, Berks, 1999. (b) Kawasaki, T.; Higuchi, K., Simple indole alkaloids and those with a nonrearranged monoterpenoid unit. *Nat. Prod. Rep.* **2005**, *22*, 761-793. (c) Gul, W.; Hamann, M. T., Indole alkaloid marine natural products: An established source of cancer drug leads with considerable promise for the control of parasitic, neurological and other diseases. *Life Sciences* **2005**, *78*, 442-453. (d) O'Connor, S. E.; Maresh, J. J., Chemistry and biology of monoterpene indole alkaloid biosynthesis. *Nat. Prod. Rep.* **2006**, *23*, 532-547.

2. For reviews, see: (a) Maity, P.; Adhikari, D.; Jana, A. K., An overview on synthetic entries to tetrahydro-β-carbolines. *Tetrahedron* **2019**, *75*, 965-1028. (b) Glinsky-Olivier, N.; Guinchard, X., Enantioselective Catalytic Methods for the Elaboration of Chiral Tetrahydro-β-carbolines and Related Scaffolds *Synthesis* **2017**, *49*, 2605-2620. (c) Cao, R.; Peng, W.; Wang, Z.; Xu, A., Beta-Carboline alkaloids: biochemical and pharmacological functions. *Curr. Med. Chem.* **2007**, *14*, 479-500.

3. (a) Pictet, A.; Spengler, T., On the formation of isochinolin-derivatives through the development of methylial on phenyl-aether, phenyl-alanin and tyrosin. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030-2036. (b) Tatsui, G., Über die Synthese von Carbolinderivaten. *Yakugaku Zasshi* **1928**, *48*, 453-459.

4. For reviews, see: (a) Calcaterra, A.; Mangiardi, L.; Delle Monache, G.; Quaglio, D.; Balducci, S.; Berardozzi, S.; Iazzetti, A.; Franzini, R.; Botta, B.; Ghirga, F., The Pictet-Spengler Reaction Updates Its Habits. *Molecules* **2020**, *25*. (b) Gholamzadeh, P., Chapter Three - The Pictet–Spengler Reaction: A Powerful Strategy for the Synthesis of Heterocycles. In *Advances in Heterocyclic Chemistry*, Scriven, E. F. V.; Ramsden, C. A., Eds. Academic Press: 2019; Vol. 127, pp 153-226. (c) Rao, R. N.; Maiti, B.; Chanda, K., Application of Pictet–Spengler Reaction to Indole-Based Alkaloids Containing Tetrahydro-β-carboline Scaffold in Combinatorial Chemistry. *ACS Comb. Sci.* **2017**, *19*, 199-228. (d) Ingallina, C.; D'Acquarica, I.; Delle Monache, G.; Ghirga, F.; Quaglio, D.; Ghirga, P.; Berardozzi, S.; Markovic, V.; Botta, B., The Pictet-Spengler Reaction Still on Stage. *Curr. Pharm. Des.* **2016**, *22*, 1808-1850. (e) Dalpozzo, R., The Chiral Pool in the Pictet–Spengler Reaction for the Synthesis of β-Carbolines. *Molecules* **2016**, *21*, 699. (f) Bijoy, K.; Piyush, K. A.; Sudhir, K. S.; Devesh, S.; Anil, K. M.; Mohammad, S.; Sahaj, G., Pictet-Spengler Reaction Revisited: Engineering of Tetherd Biheterocycles into Annulated Polyheterocycles. *Curr. Org. Synth.* **2012**, *9*, 357-376. (g) Stockigt, J.; Antonchick, A. P.; Wu, F. R.; Waldmann, H., The Pictet-Spengler Reaction in Nature and in Organic Chemistry. *Angew. Chem. Int. Ed.* **2011**, *50*, 8538-8564. (h) Lorenz, M.; Van Linn, M. L.; Cook, J. M., The Asymmetric Pictet-Spengler Reaction. *Curr. Org. Synth.* **2010**, *7*, 189-223. (i) Cox, E. D.; Cook, J. M., The Pictet-Spengler condensation - a new direction for an old reaction. *Chem. Rev.* **1995**, *95*, 1797-1842.

5. (a) Zheng, C.; You, S.-L., Exploring the Chemistry of Spiroindolenines by Mechanistically-Driven Reaction Development: Asymmetric Pictet–Spengler-type Reactions and Beyond. *Acc. Chem. Res.* **2020**, *53*, 974-987. (b) Zheng, C.; Xia, Z.-L.; You, S.-L., Unified Mechanistic Understandings of Pictet-Spengler Reactions. *Chem* **2018**, *4*, 1952-1966. (c) Unsworth, W. P., Understanding the Role of Spiroindolenines in Pictet-Spengler Reactions. *Chem* **2018**, *4*, 1767-1770. (d) Kowalski, P.; Mokrosz, J. L., Structure and spectral properties of beta-carbolines .9. New arguments against direct rearrangement of the spiroindolenine intermediate into beta-carboline system in the Pictet-Spengler cyclization. An MNDO approach. *Bull. Chem. Soc. Belg.* **1997**, *106*, 147-149. (e) Kowalski, P.; Bojarski, A. J.; Mokrosz, J. L., Structure and spectral properties of β-carbolines. 8. Mechanism of the Pictet-Spengler cyclization: An MNDO approach. *Tetrahedron* **1995**, *51*, 2737-2742. (f) Bailey, P. D., Direct proof of the involvement of a spiro intermediate in the Pictet-Spengler reaction. *J. Chem. Res.*

1987, 202-203. (g) Bailey, P. D., On the stereochemistry of the Pictet-Spengler reaction. *Tetrahedron Lett.* **1987**, *28*, 5181-5184. (h) Soerens, D.; Sandrin, J.; Ungemach, F.; Mokry, P.; Wu, G. S.; Yamanaka, E.; Hutchins, L.; Dipierro, M.; Cook, J. M., Study of the Pictet-Spengler reaction in aprotic media - Synthesis of the beta-galactosidase inhibitor, Pyridinindolol. *J. Org. Chem.* **1979**, *44*, 535-545. (i) Gobé, V.; Gandon, V.; Guinchard, X., Reactions Involving Tryptamines and δ-Allenyl Aldehydes: Competition between Pictet-Spengler Reaction and Cyclization to 1-Aminotetralins. *Adv. Synth. Catal.* **2018**, *360*, 1280-1288.

6. Lakhdar, S.; Westermaier, M.; Terrier, F.; Goumont, R.; Boubaker, T.; Ofial, A. R.; Mayr, H., Nucleophilic Reactivities of Indoles. *J. Org. Chem.* **2006**, *71*, 9088-9095.

7. (a) Wu, F.; Zhu, H.; Sun, L.; Rajendran, C.; Wang, M.; Ren, X.; Panjikar, S.; Cherkasov, A.; Zou, H.; Stöckigt, J., Scaffold Tailoring by a Newly Detected Pictet–Spenglerase Activity of Strictosidine Synthase: From the Common Tryptoline Skeleton to the Rare Piperazino-indole Framework. *J. Am. Chem. Soc.* **2012**, *134*, 1498-1500. (b) Schönherr, H.; Leighton, J. L., Direct and Highly Enantioselective Iso-Pictet–Spengler Reactions with α-Ketoamides: Access to Underexplored Indole Core Structures. *Org. Lett.* **2012**, *14*, 2610-2613. (c) Tiwari, R. K.; Verma, A. K.; Chhillar, A. K.; Singh, D.; Singh, J.; Kasi Sankar, V.; Yadav, V.; Sharma, G. L.; Chandra, R., Synthesis and antifungal activity of substituted-10-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indoles. *Bioorg. Med. Chem.* **2006**, *14*, 2747-2752. (d) Tiwari, R. K.; Singh, J.; Singh, D.; Verma, A. K.; Chandra, R., Highly efficient one-pot synthesis of 1-substituted-1,2,3,4-tetrahydropyrazino[1,2-a]indoles. *Tetrahedron* **2005**, *61*, 9513-9518. (e) Katritzky, A. R.; Verma, A. K.; He, H.-Y.; Chandra, R., Novel Synthesis of 1,2,3,4-Tetrahydropyrazino[1,2-a]indoles. *J. Org. Chem.* **2003**, *68*, 4938-4940. (f) Huo, H.-r.; Tang, X.-Y.; Gong, Y.-f., Metal-Free Synthesis of Pyrrolo[1,2-a]quinoxalines Mediated by TEMPO Oxoammonium Salts. *Synthesis* **2018**, *50*, 2727-2740. (g) Xu, H.; Fan, L.-l., Synthesis and antifungal activities of novel 5,6-dihydro-indolo[1,2-a]quinoxaline derivatives. *Eur. J. Med. Chem.* **2011**, *46*, 1919-1925. (h) Preetam, A.; Nath, M., An eco-friendly Pictet–Spengler approach to pyrrolo- and indolo[1,2-a]quinoxalines using p-dodecylbenzenesulfonic acid as an efficient Brønsted acid catalyst. *RCS Adv.* **2015**, *5*, 21843-21853.

8. (a) Voznesenskaia, N. G.; Shmatova, O. I.; Nenajdenko, V. G., Pictet–Spengler Synthesis of Perfluoroalkylated Tetrahydro-γ-carbolines and Tetrahydropyrrolopyrazines. *Synthesis* **2020**, *52*, 263-272. (b) Zhai, F.; Jordan, R. F., Complexation of an indole-based α-aminoimine ligand to Pd(II). *Inorg. Chim. Acta* **2018**, *482*, 491-496. (c) Urmode, T. D.; Dawange, M. A.; Shinde, V. S.; Kusurkar, R. S., Synthesis of spiroindolone scaffolds by Pictet-Spengler spirocyclisation using β-cyclodextrin-SO3H as a recyclable catalyst. *Tetrahedron* **2017**, *73*, 4348-4354. (d) Riesco-Domínguez, A.; van der Zwaluw, N.; Blanco-Ania, D.; Rutjes, F. P. J. T., An Enantio- and Diastereoselective Mannich/Pictet–Spengler Sequence To Form Spiro[piperidine-pyridoindoles] and Application to Library Synthesis. *Eur. J. Org. Chem.* **2017**, *2017*, 662-670. (e) Huang, L.; Dai, L.-X.; You, S.-L., Enantioselective Synthesis of Indole-Annulated Medium-Sized Rings. *J. Am. Chem. Soc.* **2016**, *138*, 5793-5796. (f) Li, X.; Chen, D.; Gu, H.; Lin, X., Enantioselective synthesis of benzazepinoindoles bearing trifluoromethylated quaternary stereocenters catalyzed by chiral spirocyclic phosphoric acids. *Chem. Commun.* **2014**, *50*, 7538-7541. (g) Lee, Y.; Klausen, R. S.; Jacobsen, E. N., Thiourea-Catalyzed Enantioselective Iso-Pictet–Spengler Reactions. *Org. Lett.* **2011**, *13*, 5564-5567. (h) Grigg, R.; Sridharan, V.; Sykes, D. A., Sonogashira/N-acyliminium ion aromatic π-cyclisation processes: access to tetra- and pentacyclic lactams. *Tetrahedron* **2008**, *64*, 8952-8962.

9. Patil, N. T.; Shinde, V. S.; Sridhar, B., Relay Catalytic Branching Cascade: A Technique to Access Diverse Molecular Scaffolds. *Angew. Chem. Int. Ed.* **2013**, *52*, 2251-2255.

10. For other C4-iso Pictet-Spengler reactions, see: (a) Abe, T.; Yamada, K., Concise Syntheses of Hyrtioreticulins C and D via a C-4 Pictet–Spengler Reaction: Revised Signs of Specific Rotations. *J. Nat. Prod.* **2017**, *80*, 241-245. (b) Abe, T.; Haruyama, T.; Yamada, K., C4 Pictet–Spengler Reactions for the Synthesis of Core Structures in Hyrtiazepine Alkaloids. *Synthesis* **2017**, *49*, 4141-4150.

11. (a) Cera, G.; Bandini, M., Enantioselective Gold(I) Catalysis with Chiral Monodentate Ligands. *Isr. J. Chem.* **2013**, *53*, 848-855. (b) Obradors, C.; Echavarren, A. M., Gold-Catalyzed Rearrangements and Beyond. *Acc. Chem. Res.* **2014**, *47*, 902-912. (c) Zi, W.; Toste, D. F., Recent advances in enantioselective gold catalysis. *Chem. Soc. Rev.* **2016**, *45*, 4567-4589. (d) Ranieri, B.; Escofet, I.; Echavarren, A. M., Anatomy of gold catalysts: facts and myths. *Org. Biomol. Chem.* **2015**, *13*, 7103-7118. (e) Dorel, R.; Echavarren, A. M., Gold(I)-Catalyzed Activation of Alkynes for the Construction of Molecular Complexity. *Chem. Rev.* **2015**, *115*, 9028-9072. (f) Mascareñas, J. L.; Varela, I.; López, F., Allenes and Derivatives in Gold(I)- and Platinum(II)-Catalyzed Formal Cycloadditions. *Acc. Chem. Res.* **2019**, *52*, 465-479.

12. (a) Pirovano, V., Gold-Catalyzed Functionalization Reactions of Indole. *Eur. J. Org. Chem.* **2018**, *2018*, 1925-1945. (b) Milcendeau, P.; Sabat, N.; Ferry, A.; Guinchard, X., Gold-catalyzed enantioselective functionalization of indoles. *Org. Biomol. Chem.* **2020**, *18*, 6006-6017.

13. (a) Zhang, Z.; Smal, V.; Retailleau, P.; Voituriez, A.; Frison, G.; Marinetti, A.; Guinchard, X., Tethered Counterion-Directed Catalysis: Merging the Chiral Ion-Pairing and Bifunctional Ligand Strategies in Enantioselective Gold(I) Catalysis. *J. Am. Chem. Soc.* **2020**, *142*, 3797-3805. (b) Sabat, N.; Soualmia, F.; Retailleau, P.; Benjdia, A.; Berteau, O.; Guinchard, X., Gold-Catalyzed Spirocyclization Reactions of *N*-Propargyl Tryptamines and Tryptophans in Aqueous Media. *Org. Lett.* **2020**, *22*, 4344-4349. (c) Magné, V.; Sanogo, Y.; Demmer, C. S.; Retailleau, P.; Marinetti, A.; Guinchard, X.; Voituriez, A., Chiral Phosphathiahelicenes: Improved Synthetic Approach and Uses in Enantioselective Gold(I)-Catalyzed [2+2] Cycloadditions of *N*-Homoallenyl Tryptamines. *ACS Catal.* **2020**, *10*, 8141-8148.

14. (a) Glinsky-Olivier, N.; Yang, S.; Retailleau, P.; Gandon, V.; Guinchard, X., Enantioselective Gold-Catalyzed Pictet–Spengler Reaction. *Org. Lett.* **2019**, *21*, 9446-9451. (b) Gobé, V.; Retailleau, P.; Guinchard, X., Self-Relay Gold(I)-Catalyzed Pictet-Spengler/Cyclization Cascade Reaction for the Rapid Elaboration of Pentacyclic Indole Derivatives. *Chem. Eur. J.* **2015**, *21*, 17587–17590.

15. For previous gold-catalyzed Picte-Spengler reactions, see: (a) Youn, S. W., Development of the Pictet−Spengler Reaction Catalyzed by $AuCl_3$/AgOTf. *J. Org. Chem.* **2006**, *71*, 2521-2523. (b) Subba Reddy, B. V.; Swain, M.; Reddy, S. M.; Yadav, J. S.; Sridhar, B., Gold-Catalyzed Domino Cycloisomerization/Pictet–Spengler Reaction of 2-(4-Aminobut-1-yn-1-yl)anilines with Aldehydes: Synthesis of Tetrahydropyrido[4,3-*b*]indole Scaffolds. *J. Org. Chem.* **2012**, *77*, 11355-11361.

16. Milcendeau, P.; Zhang, Z.; Glinsky-Olivier, N.; Van Elslande, E.; Guinchard, X., Au(I)-Catalyzed Pictet-Spengler Reactions: a Journey Around the Indole Ring. *ChemRxiv* **2020**, doi 10.26434/chemrxiv.13296446.v1.

17. Mézailles, N.; Ricard, L.; Gagosz, F., Phosphine Gold(I) Bis-(trifluoromethanesulfonyl)imidate Complexes as New Highly Efficient and Air-Stable Catalysts for the Cycloisomerization of Enynes. *Org. Lett.* **2005**, *7*, 4133-4136.

18. (a) Jónsson, H. F.; Fiksdahl, A., Studies on gold–nitrone systems. *Dalton Trans.* **2019**, *48*, 142-149. (b) Jónsson, H. F.; Evjen, S.; Fiksdahl, A., Gold(I)-Catalyzed [2 + 2 + 2] Cyclotrimerization of 1,3-Diarylpropargyl Acetals. *Org. Lett.* **2017**, *19*, 2202. (c) Evjen, S.; Fiksdahl, A., Gold(I)-catalysed [3+3] cycloaddition of propargyl acetals and nitrones. *Tetrahedron* **2016**, *72*, 3270-3276.

19. The conversion rate was 65%. The same reaction without catalyst led to a lower 25% conversion over 60 h.

20. Both *syn* and *anti* diastereomers of the series have a typical footprint in ^{1}H NMR spectra. NOESY experiments and Xray obtained in other compounds of the series allowed the determination of the relative configurations of all the products by analogy.

21. (a) Martinez, C. R.; Iverson, B. L., Rethinking the term "pi-stacking". *Chem. Sci.* **2012**, *3*, 2191-2201. (b) Cozzi, F.; Ponzini, F.; Annunziata, R.; Cinquini, M.; Siegel, J. S., Polar Interactions between Stacked π Systems in Fluorinated 1,8-Diarylnaphthalenes: Importance of Quadrupole Moments in Molecular Recognition. *Angew. Chem. Int. Ed.* **1995**, *34*, 1019-1020. (c) Hunter, C. A.; Sanders, J. K. M., The nature of .pi.-.pi. interactions. *J. Am. Chem. Soc.* **1990**, *112*, 5525-5534. (d) Wheeler, S. E.; Houk, K. N., Substituent Effects in the Benzene Dimer are Due to Direct Interactions of the Substituents with the Unsubstituted Benzene. *J. Am. Chem. Soc.* **2008**, *130*, 10854-10855.

22. Previous papers have hypothesized the potential involvement of Au(I) complexes and/or acidic protons in the formation of iminium from hemiaminal in related Au(I)-catalyzed reactions. However, our own results (see ref 14a) ruled out the possibility that protons were involved in that type of elementary step because reactions were enantioselective. For these reports, see ref 9 and: a) J. Qiao, X. Jia, P. Li, X. Liu, J. Zhao, Y. Zhou, J. Wang, H. Liu, F. Zhao, *Adv. Synth. Catal.* **2019**, *361*, 1419; b) N. T. Patil, A. K. Mutyala, P. G. Lakshmi, B. Gajula, B. Sridhar, G. R. Pottireddygari, T. P. Rao, *J. Org. Chem.* **2010**, *75*, 5963; c) T. Yang, L. Campbell, D. J. Dixon, *J. Am. Chem. Soc.* **2007**, *129*, 12070.

23. Schlegel, M.; Coburger, P.; Schneider, C., A Novel $Sc(OTf)_3$-Catalyzed (2+2+1)-Cycloannulation/Aza-Friedel–Crafts Alkylation Sequence toward Multicyclic 2-Pyrrolines. *Chem. Eur. J.* **2018**, *24*, 14207-14212.

24. Enders, D.; Wang, C.; Yang, X.; Raabe, G., One-Pot Organocatalytic Asymmetric Synthesis of 1*H*-Pyrrolo[1,2a]indol-3(2*H*)-ones via a Michael-Hemiaminalization-Oxidation Sequence. *Synlett* **2011**, *2011*, 469-472.

25. Robaa, D.; Enzensperger, C.; Abul Azm, S. E. D.; El Khawass, E. S.; El Sayed, O.; Lehmann, J., Dopamine Receptor Ligands. Part 18: Modification of the Structural Skeleton of Indolobenzazecine-Type Dopamine Receptor Antagonists. *J. Med. Chem.* **2010**, *53*, 2646-2650.