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Au(I)-Catalyzed Pictet–Spengler Reactions All around the Indole Ring

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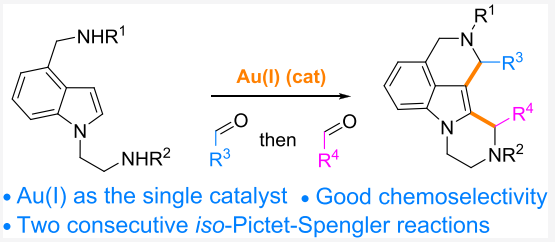
ABSTRACT: Au(I) complexes catalyze iso-Pictet–Spengler reactions. Ethylamine or methylamine chains were introduced at C2, C4, or the nitrogen atom of the indole ring, and the corresponding substrates were reacted in the presence of aldehydes and catalytic amounts of Au(I) complexes, leading to a variety 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 of 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*]isoquinolines **4**[7b,9] (Figure 1). These so-called iso-Pictet–Spengler reactions are far less studied than the venerable historical reaction, despite allowing access to interesting heterocycles.[10]

Our group has long been interested in the gold-catalyzed[11] functionalizations 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).

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.

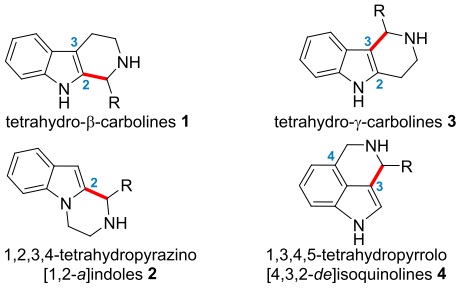
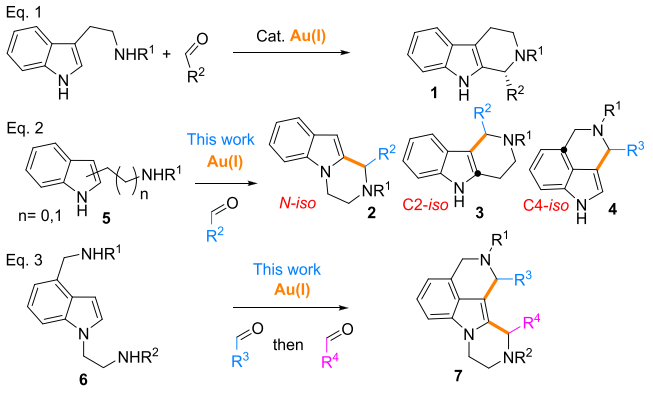


Figure 1. Tetrahydro-β-carbolines and congeners.

Scheme 1. Context of This Work



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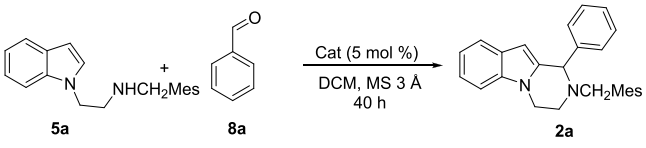
With a good knowledge of each of these different versions of the reaction, we could achieve a one-pot, selective process including successively a C4-iso- and an *N*-iso-Pictet−Spengler reaction for the synthesis of complex compounds **7** via the C3 then C2 ring-closures, with two different aldehydes (Scheme 1, eq 3). An initial version of this work was deposited elsewhere.[16]

RESULTS AND DISCUSSION

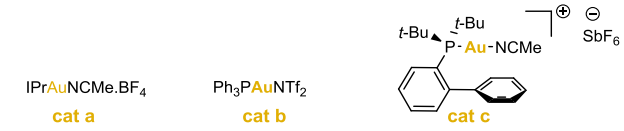
Our journey started with the study of the *N*-iso-Pictet−Spengler reactions from *N*-isotryptamine **5a** and benzaldehyde **8a**, reacted in toluene in the presence of molecular sieves over a 40 h period (Table 1, see also Table S1 in the Supporting Information). In the absence of catalyst, no background 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*-isotryptamines (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, reaching a 69% conversion, further optimized to 74% after a slight increase in the reaction temperature (entries 6 and 7). We have further checked that no background reaction occurs at this temperature in the absence of a catalyst (entry 8).

Table 1. Optimisation of the *N*-Iso-Pictet−Spengler Reaction



5a **8a** **2a**

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 toward 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 the 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 $Ph_3PAuNTf_2$ catalyst **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 the 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 **b**, compounds **3b** and **3c** bearing a 4-quinolinyl 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 the 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, though 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 the C4 atom of the indole ring and studied the reaction of tryptamine **5c** with *p*-bromobenzalehyde in the presence (plain curves) of the 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 a 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 a reasonable time, while conditions with solely Au(I)-catalyzed process can also be applied if required.

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).

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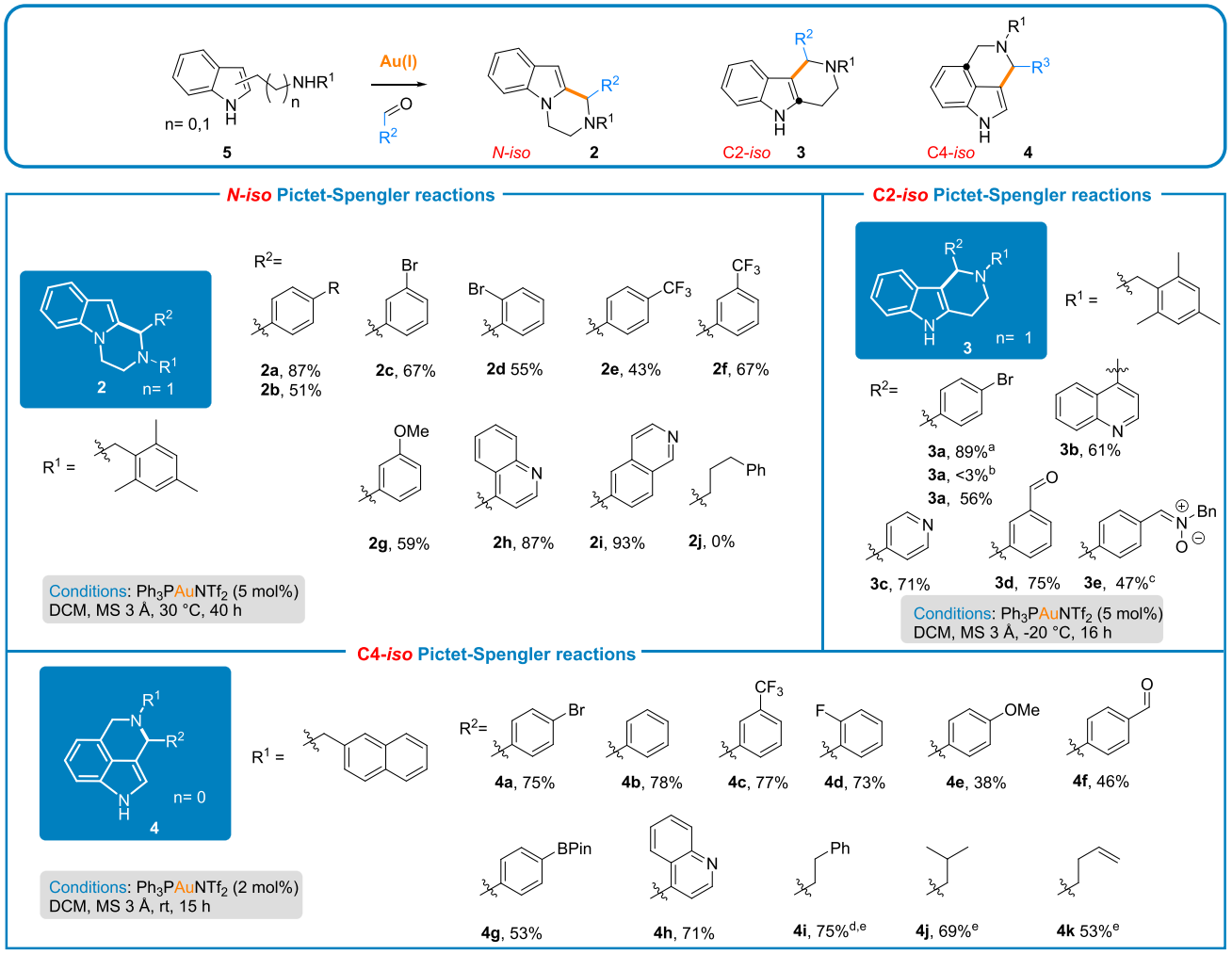
Scheme 2. Scope of the Different Versions of the Iso-Pictet–Spengler Reactions Studied



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

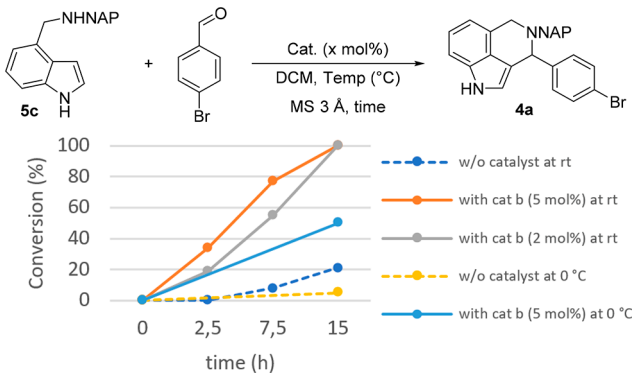


Figure 2. Reaction kinetic. Conversions were measured by ^{1}H NMR by measuring the ratio **5c**/**4a**.

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 functionalizations. Compound **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 a 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 an *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, the gold-catalyzed reaction of **5d** with benzaldehyde at 40 °C led to tetracyclic 2,3,8,9,10,11-hexahydro-1*H*-

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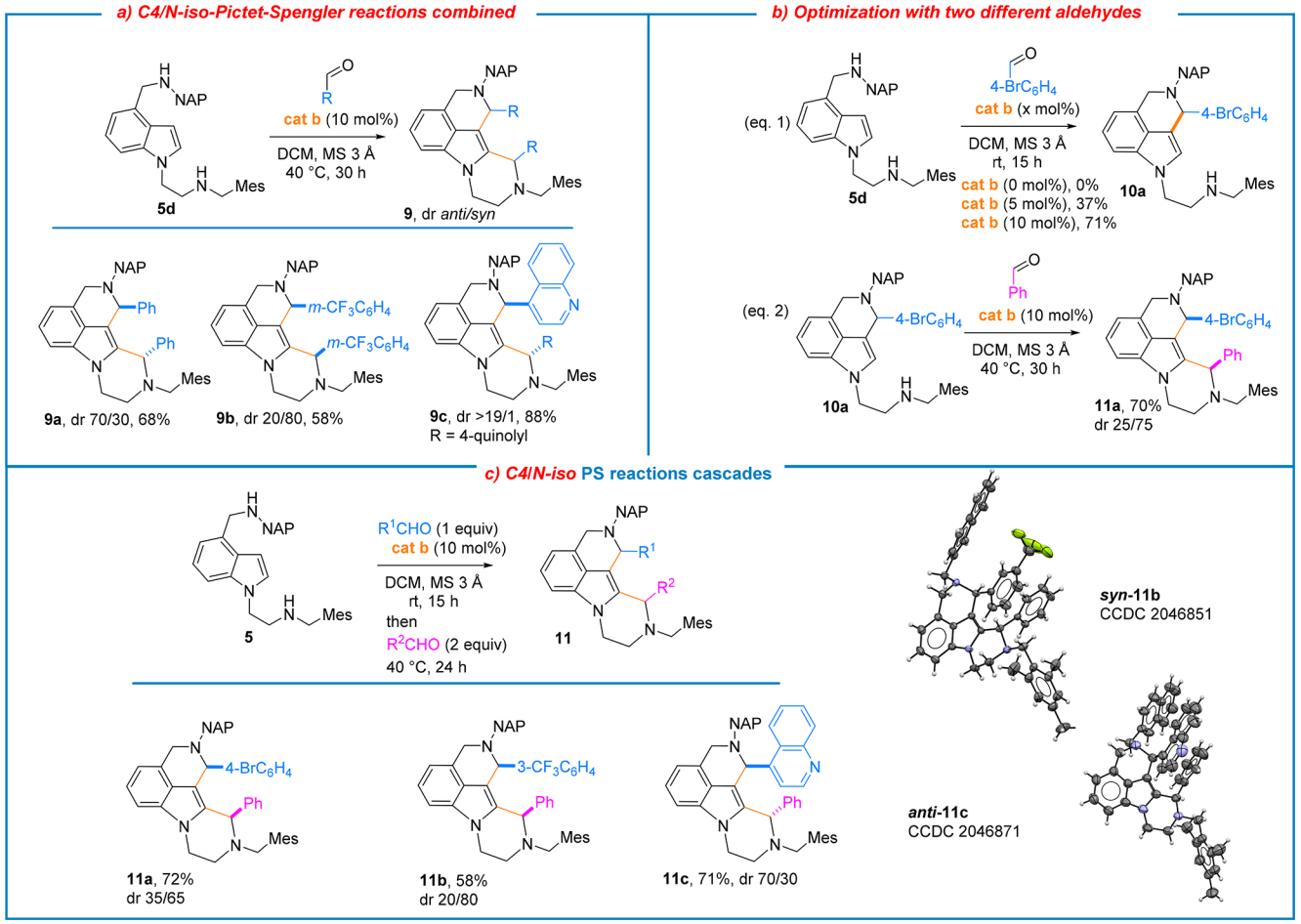
Scheme 3. Selective Bis-functionalization[a]



[a]The relative stereochemistry indicated is that of the major diastereomer.

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 3 a, 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 equiv 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 that (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

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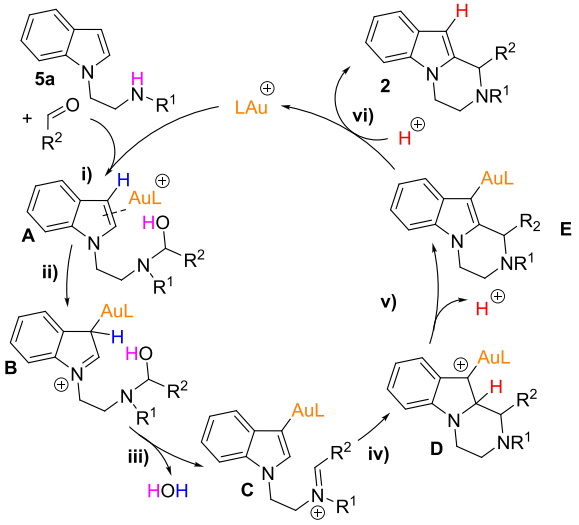
couples (phenyl, quinoline and their combination) lead mainly to the *anti*-isomer (**9a**, **9c**, **11c**).

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.

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

Scheme 4. Mechanistic Pathway in *N*-Iso-Pictet–Spengler Reactions



addition of the amine to the aldehyde leads to a 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 complex **D**. (v) The elimination of a proton via **E** and protodeauration then leads to 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–S3 in the Supporting Information).

CONCLUSION

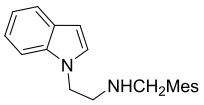
To conclude, we have developed Au(I)-catalyzed iso-Pictet–Spengler reactions by the introduction of the alkylamine chain around all of the different positions of the indole ring, allowing a trapping of the *in situ* generated iminium ion by either the C2 or C3 atom. This led to the isolation of numerous heterocyclic scaffolds. We have shown the high chemoselectivity enabled by Au(I)-catalyzed processes in these reactions, in particular by the 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. 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 follows: 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). Coupling constants (J) are given in hertz (Hz). Carbon multiplicities were determined by the DEPT135 experiment. Diagnostic correlations were obtained by two-dimensional COSY, HSQC, and NOESY experiments. Infrared spectra (IR) were recorded on a PerkinElmer 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 a 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 2 h under a vacuum at 200 °C before use. All reactions requiring heating were heated with an oil bath.

N*-Iso-Pictet–Spengler Reaction.** *Synthesis of 2-(1H-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) and 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 h. Then, the reaction medium was cooled to 0 °C before $NaBH_4$ (2 × 262 mg, 13.8 mmol, 1.80 equiv) was added; then the mixture was allowed to reach room temperature. After 1 h of 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, and then the combined organic phases were dried over $MgSO_4$ and evaporated under a 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 calcd 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*-isotryptamine **5a** (0.15 mmol), cat. **b**

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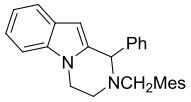
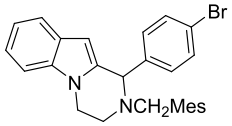
(5 mol %, 0.0075 mmol, 5.3 mg), and 3 Å molecular sieves (150 mg for 0.15 mmol of **5a**, powdered) in dichloromethane (1.5 mL of 0.15 mmol of **5a**) was stirred for 5 min at room temperature under an argon atmosphere. Subsequently, aldehyde (2.0 equiv, 0.30 mmol) was added, and the mixture was stirred for 40 h at 30 °C. For practical reasons, the excess of aldehyde was reduced at the end of the reaction by the mean of $NaBH_4$ to facilitate the purification. The reaction mixture was then cooled to 0 °C and methanol (1.5 mL of 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 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 **2**.

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



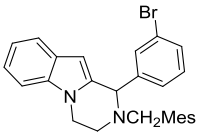
Compound **2a** was synthesized following general procedure 1 using tryptamine **5a** (44 mg, 0.15 mmol, 1.0 equiv), benzaldehyde (32 mg, 0.30 mmol, 2.0 equiv), and cat. **b** (5.3 mg, 0.0075 mmol) in DCM (1.5 mL). The desired product **2a** was obtained after column chromatography on silica gel (gradient 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}. ^1H 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). $^{13}C\{^1H\}$ 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 calcd 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-tetrahydropyrazino[1,2-a]indole ***2b***.



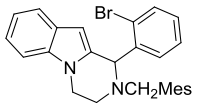
Compound **2b** was synthesized following general procedure 1 using tryptamine **5a** (44 mg, 0.15 mmol, 1.0 equiv), 4-bromobenzaldehyde (55 mg, 0.30 mmol, 2.0 equiv), and cat. **b** (5.3 mg, 0.0075 mmol) in DCM (1.5 mL). The desired product **2b** was obtained after column chromatography on silica gel (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, 1011 cm^{-1}. ^1H 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). $^{13}C\{^1H\}$ 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 calcd 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-tetrahydropyrazino[1,2-a]indole ***2c***.



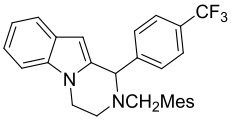
Compound **2c** was synthesized following general procedure 1 using tryptamine **5a** (44 mg, 0.15 mmol, 1.0 equiv), 3-bromobenzaldehyde (55 mg, 0.30 mmol, 2.0 equiv), and cat. **b** (5.3 mg, 0.0075 mmol) in DCM (1.5 mL). The desired product **2c** was obtained after column chromatography on silica gel (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}. ^1H 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). $^{13}C\{^1H\}$ 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 calcd 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-tetrahydropyrazino[1,2-a]indole ***2d***.



Compound **2d** was synthesized following general procedure 1 using tryptamine **5a** (44 mg, 0.15 mmol, 1.0 equiv), 2-bromobenzaldehyde (55 mg, 0.30 mmol, 2.0 equiv), and 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, 1024 cm ^{-11}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). $^{13}C\{^1H\}$ 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 calcd 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 general procedure 1 using tryptamine **5a** (44 mg, 0.15 mmol, 1.0 equiv), 4-trifluorobenzaldehyde (52 mg, 0.30 mmol, 2.0 equiv), and 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}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.52 (d, J =

https://doi.org/10.1021/acs.joc.1c00270
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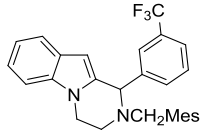
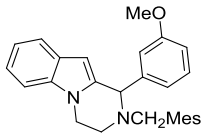
8.4 Hz, 2H), 7.46 (d, J = 7.9 Hz, 2H), 7.40 (d, J = 7.9 Hz, 1H), 7.21 (d, J = 8.1 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H), 7.01 (t, J = 7.5 Hz, 1H), 6.76 (s, 2H), 5.70 (s, 1H), 4.69 (s, 1H), 4.07 (dt, J = 11.6, 4.1 Hz, 1H), 3.92−3.85 (m, 1H), 3.57 (d, J = 12.4 Hz, 1H), 3.33 (d, J = 12.4 Hz, 1H), 3.11 (dt, 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). $^{13}C\{^1H\}$ 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 calcd 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***.



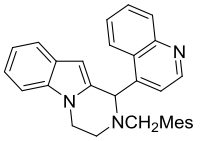
Compound **2f** was synthesized following general procedure 1 using tryptamine **5a** (44 mg, 0.15 mmol, 1.0 equiv), 3-trifluorobenzaldehyde (52 mg, 0.30 mmol, 2.0 equiv), and cat. **b** (5.3 mg, 0.0075 mmol) in DCM (1.5 mL). The desired product **2f** was obtained after column chromatography on silica 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}. ^1H 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). $^{13}C\{^1H\}$ 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 calcd 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***.



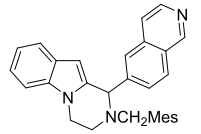
Compound **2g** was synthesized following general procedure 1 using tryptamine **5a** (44 mg, 0.15 mmol, 1.0 equiv), 3-methoxybenzaldehyde (41 mg, 0.30 mmol, 2.0 equiv), and cat. **b** (5.3 mg, 0.0075 mmol) in DCM (1.5 mL). The desired product **2g** was obtained after column chromatography on silica 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}. ^1H 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). $^{13}C\{^1H\}$ 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 calcd 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 general procedure 1 using tryptamine **5a** (44 mg, 0.15 mmol, 1.0 equiv), 4-quinolinaldehyde (47 mg, 0.30 mmol, 2.0 equiv), and 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}. ^1H 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). $^{13}C\{^1H\}$ 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 calcd for $C_{30}H_{30}N_3^+$, 432.2440 $[M + H]^+$; found, 432.2451.

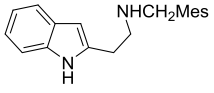
1-(Isoquinolin-6-yl)-2-(2,4,6-trimethylbenzyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole ***2i***.



H

Compound **2i** was synthesized following general procedure 1 using tryptamine **5a** (44 mg, 0.15 mmol, 1.0 equiv), 6-quinolinaldehyde (47 mg, 0.30 mmol, 2.0 equiv), and 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}. ^1H 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). $^{13}C\{^1H\}$ 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 calcd for $C_{30}H_{30}N_3^+$, 432.2440 $[M + H]^+$; found, 432.2427

C2-Iso-Pictet−Spengler Reaction. *Synthesis of 2-(1H-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

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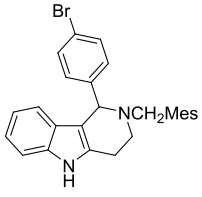
indole-2-carboxylic acid (16.1 g, 1.00 equiv, 100 mmol) in THF (75 mL) was added $LiAlH_4$ (7.9 g, 2.07 equiv, 207 mmol) at 0 °C in a 15 min period; the mixture was then allowed to warm to room temperature slowly and stirred at room temperature for about 3 h. The reaction was quenched with 2 M NaOH under 0 °C and extracted with EtOAc, dried over $MgSO_4$, and evaporated under a 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 a 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 to heat to 100 °C and following by TLC, and 30 min later, the reaction was completed and concentrated under a vacuum. The residue was then extracted with EtOAc, dried over $MgSO_4$, and evaporated under a 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 °C. After completion, 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; organic layers were combined and dried over $MgSO_4$, concentrated under a 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 h. Then $NaBH_4$ was added under 0 °C; 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 $MgSO_4$, evaporated under a vacuum, and extracted with EtOAc. The organic layers were combined and dried over $MgSO_4$, concentrated under a 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%). ^1H 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). $^{13}C\{^1H\}$ 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 calcd for $C_{20}H_{25}N_2^+$, 293.2012, $[M + H]^+$, found, 293.2009.

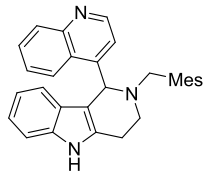
*General Procedure **2** for the Synthesis of Tetrahydro-1H-pyrido[4,3-b]indole **3**.* A mixture of 2-(1*H*-indol-2-yl)-*N*-(2,4,6-trimethylbenzyl)ethan-1-amine **5b** (1 equiv), cat. **b** (5 mol %), and 3 Å molecular sieves (150 mg for 0.15 mmol of **5b**, powdered) in dichloromethane (1.5 mL of 0.15 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-1H-pyrido[4,3-b]indole **3a**.*



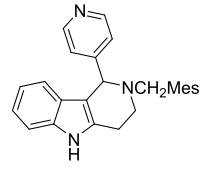
Compound **3a** was prepared according to general procedure 2 from **5b** (0.05 mmol, 1 equiv, 14.6 mg), 4-bromobenzaldehyde (0.1 mmol, 2 equiv, 18.5 mg), cat. **b** (5 mol %, 1.8 mg), 3 Å MS (50 mg), and anhydrous DCM under N_2, yielding product **3a** (12.7 mg, 0.028 mmol, 56%) as a pale yellow solid. ^1H 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). $^{13}C\{^1H\}$ 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 calcd 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-1H-pyrido[4,3-b]indole **3b**.*



Compound **3b** was prepared according to 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), 3 Å MS (50 mg), and anhydrous DCM under N_2, yielding product **3b** (13.1 mg, 0.03 mmol, 61%) as a pale yellow solid. ^1H 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). $^{13}C\{^1H\}$ 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 calcd 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-1H-pyrido[4,3-b]indole **3c**.*



Compound **3c** was prepared according to 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), 3 Å MS (50 mg), and anhydrous DCM under N_2, yielding product **3c** (13.4 mg, 0.04 mmol, 71%) as a pale yellow solid. ^1H 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). $^{13}C\{^1H\}$ 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 calcd for $C_{26}H_{28}N_3^+$, 382.2278 $[M + H]^+$, found, 382.2272.

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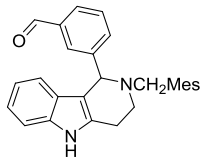
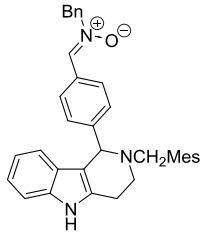
3-(2-(2,4,6-Trimethylbenzyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-1-yl)benzaldehyde ***3d***.



Compound **3d** was prepared according to 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 calcd for $C_{28}H_{29}N_2O^+$, 409.2274 [M + H]$^+$, found, 409.2273.

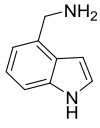
N-Benzyl-1-(4-(2-(2,4,6-trimethylbenzyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-1-yl)phenyl)methanimine oxide ***3e***.



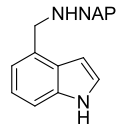
Compound **3e** was prepared according to general procedure 2 from **5c** (0.05 mmol, 1 equiv, 14.6 mg), (*Z*)-*N*-benzyl-1-(4-formylphenyl)-methanimine oxide (0.1 mmol, 2 equiv, 23.9 mg), cat. **b** (5 mol %, 1.8 mg), 3 Å MS (50 mg), and anhydrous DCM under N_2. The mixture was stirred at room temperature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

Note that the background reaction performed under the same conditions in the absence of a 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 calcd for $C_{35}H_{36}N_3O^+$, 514.2853 [M + H]$^+$, found, 514.2847.

C4-Iso-Pictet−Spengler Reaction. *Synthesis of Tryptamine* ***5c***.



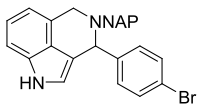
A mixture of 1*H*-indole-4-carbonitrile (10.0 g, 70.3 mmol, 1.0 equiv) in THF (100 mL) was added dropwise to a suspension of lithium aluminum hydride (5.70 g, 150 mmol, 2.1 equiv) in THF at 0 °C. The reaction was refluxed for 90 min and then allowed to cool to rt. Then, aqueous saturated solution of Rochelle's salt was added, and the mixture was stirred until full destruction of lithium salts. The reaction was filtered over silica, concentrated under a vacuum, and triturated in methanol. After filtration over Celite, the pure product **S6** was obtained by filtrate's concentration under a 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 h. 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 h of stirring, the volatiles were removed, and the crude was next diluted in ethyl acetate and water. After phase separation, the aqueous phase was extracted twice by ethyl acetate. The combined organic phases were dried over $MgSO_4$ and evaporated under a 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 calcd for $C_{20}H_19N_2$ [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 of 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 15 h. 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 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 %), and 3 Å MS (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 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 %), and 3 Å MS (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, 2*H*), 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),

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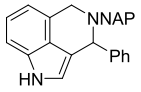
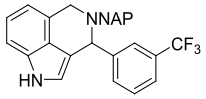
5.02 (s, 1H), 4.03 (d, J = 15.8 Hz, 1H), 3.85 (d, J = 13.5 Hz, 1H), 3.78 (d, J = 15.8 Hz, 1H), 3.69 (d, J = 13.5 Hz, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 141.8 (C_q), 137.3 (C_q), 133.5 (C_q), 133.5 (C_q), 132.9 (C_q), 131.4 (CH), 130.5 (CH), 128.7 (C_q), 128.1 (CH), 127.8 (CH), 127.7 (CH), 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 calcd for $C_{27}H_{22}{}^{79}BrN_2^+$, 453.0966 $[M + H]^+$; found, 453.0926, calcd 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***.



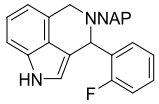
Compound **4b** was synthesized following general procedure 3 using tryptamine **5c** (50 mg, 0.17 mmol, 1.0 equiv), benzaldehyde (37 mg, 0.35 mmol, 2.0 equiv), cat. **b** (2.5 mg, 0.0034 mmol, 2 mol %), and 3 Å MS (82 mg) in DCM (2.4 mL). The desired product **4b** was obtained after column chromatography on silica gel (gradient from 0 to 15% heptane/EtOAc) as a white amorphous solid (50 mg, 0.13 mmol, 78%). ^1H 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). $^{13}C\{^1H\}$ 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 calcd 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***.



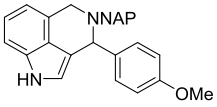
Compound **4c** was synthesized following general procedure 3 using tryptamine **5c** (50 mg, 0.17 mmol, 1.0 equiv), 3-(trifluoromethyl)-benzaldehyde (61 mg, 0.35 mmol, 2.0 equiv), cat. **b** (2.5 mg, 0.0034 mmol 2 mol %), and 3 Å MS (82 mg) in DCM (2.4 mL). The desired product **4c** was obtained after 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}. ^1H 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). $^{13}C\{^1H\}$ 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). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −62.3. HRMS (ESI): m/z calcd 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***.



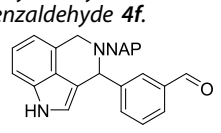
Compound **4d** was synthesized following general procedure 3 using tryptamine **5c** (50 mg, 0.17 mmol, 1.0 equiv), 2-fluorobenzaldehyde (43 mg, 0.35 mmol, 2.0 equiv), cat. **b** (6.5 mg, 0.0087 mmol, 5 mol %), and 3 Å MS (82 mg) in DCM (2.4 mL). The desired product **4d** was obtained after column 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}. ^1H 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). $^{13}C\{^1H\}$ 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 calcd 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 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 %), and 3 Å MS (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}. ^1H 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) $^{13}C\{^1H\}$ 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 calcd 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 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 %), and 3 Å MS (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}. ^1H 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). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 192.7 (CH), 144.2

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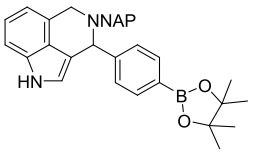
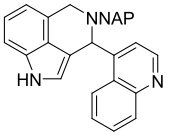
(Cq), 137.2 (Cq), 136.6 (Cq), 135.0 (CH), 133.7 (Cq), 133.5 (Cq), 133.0 (Cq), 130.4 (CH), 129.1 (CH), 128.5 (CH), 128.2 (CH), 127.8 (CH), 127.6 (CH), 127.3 (CH), 126.1 (CH), 125.7 (CH), 125.1 (Cq), 123.3 (CH), 119.7 (CH), 115.2 (CH), 112.7 (Cq), 109.2 (CH), 60.8 (CH), 58.9 (CH_2), 49.3 (CH_2). HRMS (ESI): *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***.



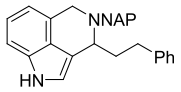
Compound **4g** was synthesized following general procedure 3 using tryptamine **5c** (50 mg, 0.17 mmol, 1.0 equiv), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (80 mg, 0.35 mmol, 2.0 equiv), cat. **b** (2.6 mg, 0.0034 mmol, 2 mol %), and 3 Å MS (82 mg) in DCM (2.5 mL). The desired product **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}. ^1H 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). $^{13}C\{^1H\}$ 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***.



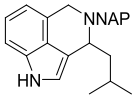
Compound **4h** was synthesized following general procedure 3 using tryptamine **5c** (50 mg, 0.17 mmol, 1.0 equiv), quinoline-4-carbaldehyde (55 mg, 0.35 mmol, 2.0 equiv), cat. **b** (2.6 mg, 0.0034 mmol, 2 mol %), and 3 Å MS (82 mg) in DCM (2.5 mL). The desired product **4h** was obtained after column 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, 757 cm^{-1}. ^1H 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), $^{13}C\{^1H\}$ 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* calcd for $C_{30}H_{24}N_3^+$, 426.1970 $[M + H]^+$; found, 426.1932.

4-(Naphthalen-2-ylmethyl)-3-phenethyl-1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline ***4i***.



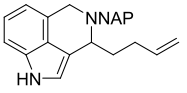
Compound **4i** was synthesized following general procedure 3 using tryptamine **5c** (50 mg, 0.17 mmol, 1.0 equiv), 3-phenylpropanal (47 mg, 0.35 mmol, 2.0 equiv), cat. **b** (6.5 mg, 0.0087 mmol, 5 mol %), and 3 Å MS (82 mg) in DCM (2.5 mL). The desired product **4i** was obtained after column chromatography 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}. ^1H 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). $^{13}C\{^1H\}$ 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* calcd for $C_{29}H_{27}N_2^+$, 403.2174 $[M + H]^+$; found, 403.2174.

3-Isobutyl-4-(naphthalen-2-ylmethyl)-1,3,4,5-tetrahydropyrrolo-[4,3,2-de]isoquinoline ***4j***.



Compound **4j** was synthesized following general procedure 3 using tryptamine **5c** (35 mg, 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 %), and 3 Å MS (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}. ^1H 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). $^{13}C\{^1H\}$ 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* calcd 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-tetrahydropyrrolo[4,3,2-de]isoquinoline ***4k***.



Compound **4k** was synthesized following general procedure 3 using tryptamine **5c** (50 mg, 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 %), and 3 Å MS (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}. ^1H 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,

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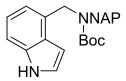
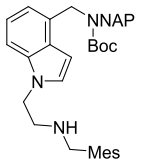
1H), 6.84 (d, J = 6.8 Hz, 1H), 5.87 (tdd, J = 6.7, 10.2, 17.1 Hz, 1H), 5.05 (dd, J = 2.1, 17.2 Hz, 1H), 4.95 (d, J = 9.9 Hz, 1H), 4.33 (d, J = 16.3 Hz, 1H), 4.04 (t, J = 7.6 Hz, 1H), 3.87 (d, J = 16.5 Hz, 1H), 3.77 (d, J = 13.5 Hz, 1H), 3.68 (d, J = 14.0 Hz, 1H), 2.38−2.24 (m, 2H), 2.07−1.98 (m, 1H), 1.78−1.69 (m, 1H). $^{13}C\{^1H\}$ 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 calcd for $C_{25}H_{25}N_2^+$, 353.2017 $[M + H]^+$; found, 353.2031.

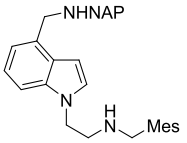
C4/*N*-Iso-Pictet−Spengler Reaction Cascades. *Synthesis of Tryptamine **5d**.*



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 $MgSO_4$ and concentrated under a 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 ^1H NMR and ^{13}C NMR. IR (neat): ν_{max} 3316, 2976, 2927, 1666, 1412, 1365, 1247, 1161, 1115, 752 cm^{-1}. ^1H 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). $^{13}C\{^1H\}$ 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 calcd for $C_{21}H_{19}N_2O_2^+$, 331.1447 $[M\text{-}t\text{Bu}\cdot + 2H]^+$; found, 331.1443, m/z calcd for $C_{27}H_{29}N_3NaO_2^+$, 450.2157 $[M + Na + CH_3CN]^+$; found, 450.2157.



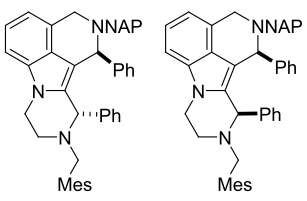
Acetonitrile (11.9 mL) was added to *tert*-butyl ((1*H*-indol-4-yl)methyl)(naphthalen-2-ylmethyl)carbamate (1.38 g, 3.57 mmol, 1.0 equiv), 2-chloroethan-1-amine hydrochloride (476 mg, 4.11 mmol, 1.15 equiv), sodium hydroxide (314 mg, 7.86 mmol, 2.2 equiv), and tetrabutylammonium hydrogensulfate (49 mg, 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 under a vacuum. This methodology routinely leads to 30−100% 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 $NaBH_4$ (148 mg, 3.93 mmol, 1.1 equiv) was added. Then the mixture was allowed to reach room temperature. After 1 h of 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, and then the combined organic phases were dried over $MgSO_4$ and evaporated under a 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, 15−70% over 2 steps). The product appears as rotamers by ^1H NMR and ^{13}C NMR. IR (neat): ν_{max} 2973, 2922, 2859, 1685, 1413, 1364, 1241, 1161, 1109, 748, 735 cm^{-1}. ^1H 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). $^{13}C\{^1H\}$ 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 calcd 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 a vacuum. The crude product was dissolved in EtOAc and 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 a vacuum to give the desired product **5d** (as an oil (650 mg, 1.41 mmol, 65%). ^1H 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). $^{13}C\{^1H\}$ 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 calcd 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 of 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 24 h. 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-1H-pyrazino[1′,2′:1,5]pyrrolo-[4,3,2-de]isoquinoline **9a**.*



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

Compound **9a** was synthesized following 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 %), and

https://doi.org/10.1021/acs.joc.1c00270
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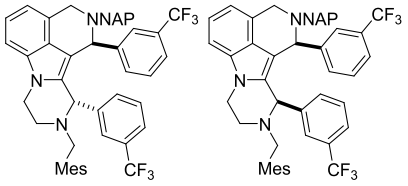
3 Å MS (104 mg) in DCM (3.1 mL) at 40 °C. Desired products **9a** were obtained after column chromatography on silica gel (gradient from 0 to 10% heptane/EtOAc) as white amorphous solids (95 mg, 0.15 mmol, 68%, dr 2:1 *anti*/*syn*). The following data is for compound *anti*-**9a**. IR (neat): ν_{max} 3055, 3027, 2960, 2921, 2852, 1450, 1262, 1076, 1028, 1016, 711; 697 cm^{-1}. ^1H 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). $^{13}C\{^1H\}$ 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 calcd for $C_{46}H_{44}N_3^+$, 638.3535 $[M + H]^+$; found, 638.3552. The following data is for compound *syn*-**9a**. IR (neat): ν_{max} 3056, 3027, 2921, 2853, 1451, 1291, 1265, 736, 696 cm^{-1}. ^1H 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). $^{13}C\{^1H\}$ 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 calcd for $C_{46}H_{44}N_3^+$, 638.3535 $[M + H]^+$; found, 638.3568.

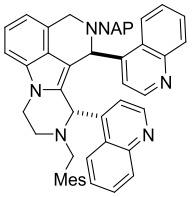
2-(Naphthalen-2-ylmethyl)-1,11-bis(3-(trifluoromethyl)phenyl)-10-(2,4,6-trimethylbenzyl)-2,3,8,9,10,11-hexahydro-1H-pyrazino-[1′,2′:1,5]pyrrolo[4,3,2-de]isoquinoline ***9b***.



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

Compound **9b** was synthesized following 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 %), and 3 Å MS (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%, dr 1:4 *anti*/*syn*). The following data is for compound *anti*-**9b**. IR (neat): ν_{max} 3334, 2970, 2924, 1327, 1163, 1120, 1094, 1072, 746, 702 cm^{-1}. ^1H 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). $^{13}C\{^1H\}$ 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). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −62.4, −62.8. HRMS (ESI): m/z calcd for $C_{48}H_{42}F_6N_3^+$ 774.3283 $[M + H]^+$; found, 774.3231. The following data is for compound *syn*-**9b**. IR (neat): ν_{max} 3340, 2973, 2924, 1327, 1163, 1119, 1092, 1071, 1047, 736, 700 cm^{-1}. ^1H 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). $^{13}C\{^1H\}$ 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). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −62.5, −62.9. HRMS (ESI): m/z calcd 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-dihydropyrrolo[4,3,2-de]isoquinolin-1(3H)-yl)-N-(2,4,6-trimethylbenzyl)ethan-1-amine ***9c***.



Compound **9c** was synthesized following 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 %), and 3 Å MS (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}. ^1H 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). $^{13}C\{^1H\}$ 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

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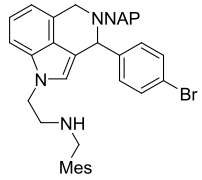
(CH), 116.2 (CH), 107.1 (CH), 104.7 (C_q), 59.0 (CH_2), 57.9 (CH), 53.0 (CH_2), 47.9 (CH_2), 45.4 (CH_2), 43.1 (CH_2), 21.0 (CH_3), 20.6 (CH_3). Note that one of the benzylic CH does not resonate well in the ^{13}C NMR spectrum; it is estimated around 67 ppm. HRMS (ESI): *m/z* calcd for $C_{52}H_{46}N_5^+$, 740.3753 [M + H]$^+$; found, 740.3784.

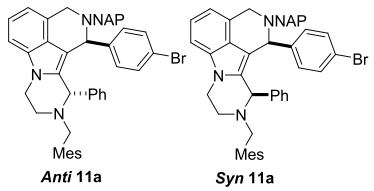
2-(3-(4-Bromophenyl)-4-(naphthalen-2-ylmethyl)-4,5-dihydropyrrolo[4,3,2-de]isoquinolin-1(3H)-yl)-N-(2,4,6-trimethylbenzyl)ethan-1-amine ***10a***.



A mixture of tryptamine **5d** (84 mg, 0.18 mmol, 1.0 equiv), cat. **b** (13.4 mg, 0.0182 mmol, 10 mol %), and 3 Å MS (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 was stirred at reflux for 24 h. 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}. ^1H 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). $^{13}C\{^1H\}$ 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* calcd for $C_{39}H_{39}{}^{79}BrN_3^+$, 628.2327 [M + H]$^+$; found, 628.2301. HRMS (ESI): *m/z* calcd for $C_{39}H_{39}{}^{81}BrN_3^+$, 630.2327 [M + H]$^+$; found, 630.2307.

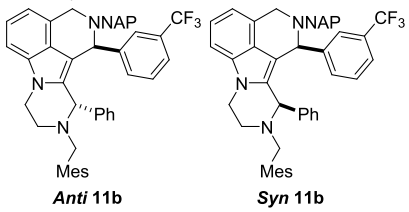
Scope of the C4/*N*-Iso-Pictet−Spengler Reaction Cascade with Two Different Aldehydes. *General Procedure 5*. A mixture of tryptamine **5d** (0.17 mmol), cat. **b** (10 mol %, 0.017 mmol), and 3 Å molecular sieves (82 mg for 0.17 mmol of **5d**, powdered) in dichloromethane (2.4 mL of 0.17 mmol of **5d**) 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 was stirred for 15 h. Then aldehyde **b** (2.0 equiv, 0.35 mmol) was added, and the mixture was stirred at reflux for 24 h. 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-1H-pyrazino-[1′,2′:1,5]pyrrolo[4,3,2-de]isoquinoline ***11a***.



In the 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 was 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%, dr 1:3 *anti/syn*). In the one-pot procedure, compound **11a** was synthesized following 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), and 3 Å MS (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%, dr 1:2 *anti/syn*). The following data is for compound *anti*-**11a**. IR (neat): ν_{max} 3054, 2922, 2852, 1484, 1451, 1289, 1263, 1010, 736, 698 cm^{-1}. ^1H 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). $^{13}C\{^1H\}$ 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* calcd for $C_{46}H_{43}{}^{79}BrN_3^+$ 716.2640 [M + H]$^+$; found, 716.2622, calcd for $C_{39}H_{39}{}^{81}BrN_3^+$ 718.2620 [M + H]$^+$; found, 718.2652. The following data is for compound *syn*-**11a**. IR (neat): ν_{max} 3054, 2958, 2924, 2871, 1485, 1451, 1364, 1290, 1010, 750, 698 cm^{-1}. ^1H 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). $^{13}C\{^1H\}$ 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* calcd for $C_{46}H_{43}{}^{79}BrN_3^+$, 716.2640 [M + H]$^+$; found, 716.2679, calcd 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-1H-pyrazino[1′,2′:1,5]pyrrolo[4,3,2-de]isoquinoline ***11b***.



Compound **11b** was synthesized following 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 %), 3 Å MS (104 mg), and 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%, dr 1:4 *anti/syn*). The following data is for compound *anti*-**11b**. IR (neat): ν_{max} 3057, 2926, 2852, 1451, 1329, 1163, 1124, 747, 704

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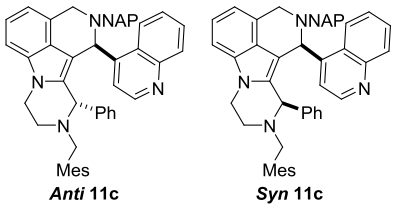
cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.88−7.84 (m, 1H), 7.78 (d, J = 8.0 Hz, 2H), 7.56 (s, 1H), 7.52−7.45 (m, 3H), 7.42 (d, J = 8.7 Hz, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.22 (s, 1H), 7.24−7.08 (m, 5H), 6.92 (t, J = 7.4 Hz, 2H), 6.81−6.77 (m, 3H), 6.72 (t, J = 7.3 Hz, 1H), 4.25 (s, 1H), 4.19 (td, J = 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, $^{1}J_{C-F}$ = 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, $^{3}J_{C-F}$ = 3.7 Hz, CH), 125.9 (CH), 125.5 (CH), 125.5 (C_q), 123.6 (q, C−F, $^{3}J_{C-F}$ = 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). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −62.3. HRMS (ESI): m/z calcd for $C_{47}H_{43}F_3N_3^+$, 706.3409 [M + H]$^+$; found, 706.3380. The following data is for compound *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, $^{1}J_{C-F}$ = 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, $^{3}J_{C-F}$ = 3.5 Hz, CH), 123.3 (q, C−F, $^{3}J_{C-F}$ = 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). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −62.3. HRMS (ESI): m/z calcd 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-1H-pyrazino-[1′,2′:1,5]pyrrolo[4,3,2-de]isoquinoline ***11c***.



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

Compound **11c** was synthesized following 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 %), 3 Å MS (62 mg), at 40 °C, and 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%, dr 2:1 *anti*/*syn*). The following data is for compound *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 calcd for $C_{49}H_{45}N_4^+$, 689.3644 [M + H]$^+$; found, 689.3622. The following data is for compound *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 calcd for $C_{49}H_{45}N_4^+$, 689.3644 [M + H]$^+$; found, 689.3593.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00270.

Details about optimization of the reactions, blank tests, NMR spectra, X-ray crystallography data, and mechanistic hypotheses (PDF)

Accession Codes

CCDC 2046851 and 2046871 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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

Notes

The authors declare no competing financial interest.

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