

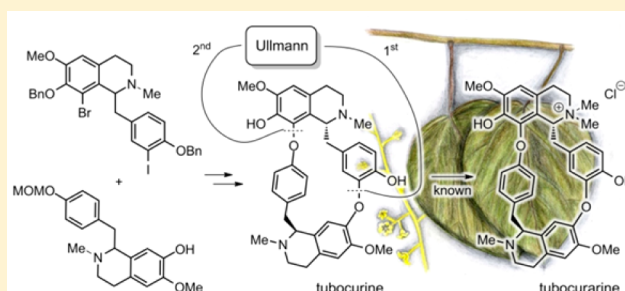
A Modular Access to (\pm)-Tubocurine and (\pm)-Curine - Formal Total Synthesis of Tubocurarine

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Supporting Information

ABSTRACT: Two consecutive Cu-catalyzed Ullmann-type C–O couplings permitted the first successful entry toward the curare alkaloids (\pm)-tubocurine and (\pm)-curine. Starting from vanillin, the synthetic sequence comprises 15 linear steps and includes a total of 24 transformations. In addition, the total synthesis of tubocurine represents a formal total synthesis of the famous arrow poison alkaloid tubocurarine.



INTRODUCTION

The curare alkaloids belong to the class of bisbenzylisoquinolines which constitute a family of almost 400 natural products found in diverse plant species (see Figure 1).^{1,2} They are

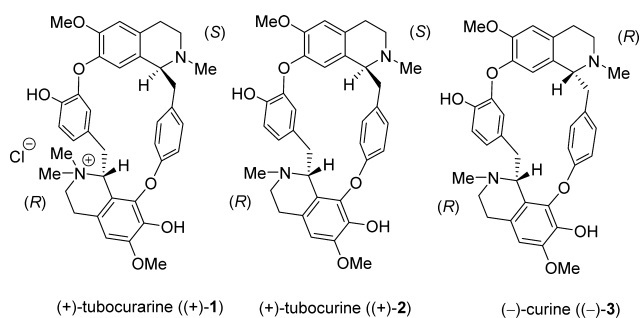


Figure 1. Structure of curare alkaloids.

characterized by at least one diaryl ether moiety linking two aromatic rings of each benzylisoquinoline unit. The most prominent representative of this compound class is (+)-tubocurarine ((+)-1) which is widely known as the active ingredient of the arrow poison curare.^{3,4} Curare was used for hunting animals for centuries by indigenous peoples in South America and also found application in modern medicine as a muscle relaxant in anesthesia since 1942. (+)-Tubocurarine ((+)-1) acts by inhibiting the nicotinic acetylcholine receptor (nAChR).⁵ While the bisbenzylisoquinoline alkaloids in general exhibit a wide variety of biological activities, only little is known about the biological activity of the other curare alkaloids. Nevertheless, this subgroup has been a target for total synthesis for decades, and first attempts were made by Kataoka,⁶ by Hellmann and Elser,⁷ as well as by Tolkachev and co-workers.⁸ In 1979, Naghaway and Soine reported the total synthesis of semisynthetic (+)-tubocurarine ((+)-1) by using natural

tubocurarine which was N-demethylated to (+)-tubocurine ((+)-2) by sodium thiophenolate and subsequently remethylated to result in (+)-tubocurarine ((+)-1) again.⁹

We aimed to develop a modular synthetic strategy toward the group of curare alkaloids to establish structure–activity relationships to these alkaloids. Herein, the first total synthesis of (\pm)-curine ((\pm)-3) and (\pm)-tubocurine ((\pm)-2) is presented, which also represents a formal total synthesis of tubocurarine (1).

RESULTS AND DISCUSSION

It was decided to perform two subsequent C–O-couplings of two 1-benzyltetrahydroisoquinoline subunits for the synthesis of the macrocyclic skeleton (see Scheme 1).

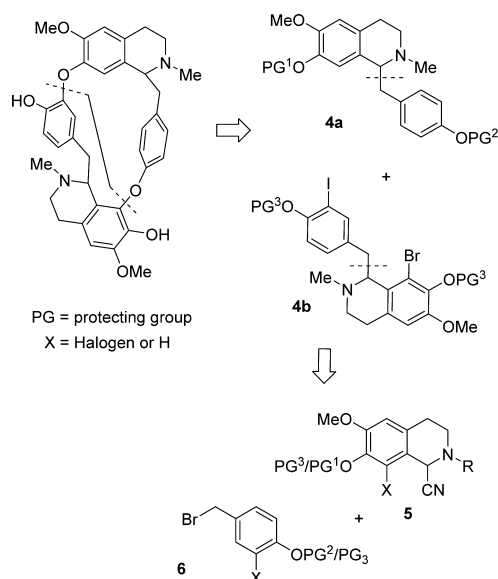
One benzylisoquinoline subunit should be equipped with two phenolic groups (diol 4a) and one should contain two halogen atoms (dihalide 4b). The dihalide subunit 4b should comprise one bromo substituent and one iodo substituent, which is installed at the less hindered and hence more reactive benzylic arene ring, and the bromo substituent should be installed at the less reactive tetrahydroisoquinoline core. For the diol subunit 4a, a benzylic protecting group and an orthogonally stable protecting group such as TIPS or MOM should be used. The 1-benzyl-1,2,3,4-tetrahydroisoquinolines should either be prepared by a self-developed umpolung/alkylation-reduction sequence^{10,11} starting from deprotonated α -aminonitrile 5 and the corresponding benzylic bromide 6 or by Bischler–Napieralski cyclization^{12–15} of suitable amide precursors.

The construction of the diol compound 4a should be accomplished by umpolung/alkylation reduction sequence from aminonitrile 5a and the corresponding benzylic bromide

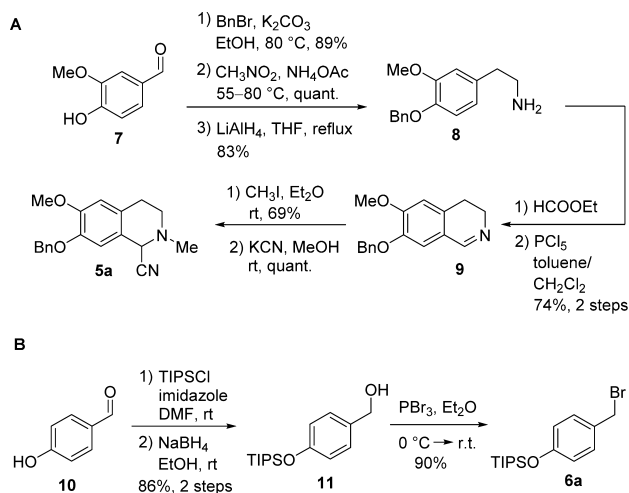
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Scheme 1. Retrosynthesis of Curare Alkaloids



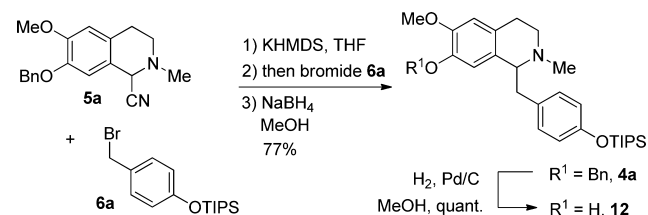
6a. The synthesis of the aminonitrile **5a** started with vanillin (**7**), which was O-benzylated and condensed with nitromethane to the corresponding β -nitrostyrene (Scheme 2A). Subsequent

Scheme 2. Synthesis of α -Aminonitrile **5a** (A) and Benzylic Bromide **6a** (B)

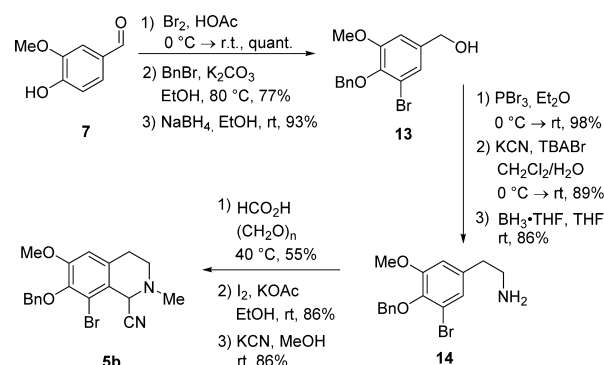
reduction with lithium aluminum hydride gave phenylethylamine **8** in 74% yield over three steps. N-Formylation of amine **8** with ethyl formate and subsequent Bischler–Napieralski cyclization gave 3,4-dihydroisoquinoline **9**, which was then N-methylated with iodomethane to furnish the N-methyliminium salt. Reaction with potassium cyanide furnished aminonitrile **5a** in a yield of 34% over seven linear steps. The benzylic bromide **6a** was synthesized starting from *p*-hydroxybenzaldehyde (**10**) by TIPS protection and reduction to the benzylic alcohol **11** and transformation to the benzylic bromide **6a** by phosphorus tribromide (Scheme 2B).

The syntheses of the aminonitrile **5a** and of the benzylic bromide **6a** are devoid of chromatographic purifications. The umpolung/alkylation-reduction sequence starting from aminonitrile **5a** was performed by deprotonation in THF with KHMDS at -78 °C, followed by addition of the benzylic

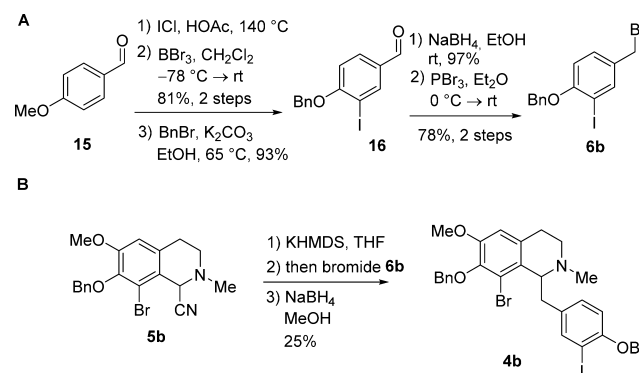
bromide **6a** at this temperature and subsequent reduction with sodium borohydride (Scheme 3). The TIPS protected 1-benzyltetrahydroisoquinoline **4a** was obtained in 77% yield, quantitative hydrolytic debenzoylation furnished building block **12**.

Scheme 3. Synthesis of 1-Benzyltetrahydroisoquinoline **4a** and Deprotection to **12**

For the preparation of the dihalide subunit **4b**, aminonitrile **5b** bearing a bromo substituent in the 8-position was synthesized starting from vanillin (**7**) over nine steps (Scheme 4).

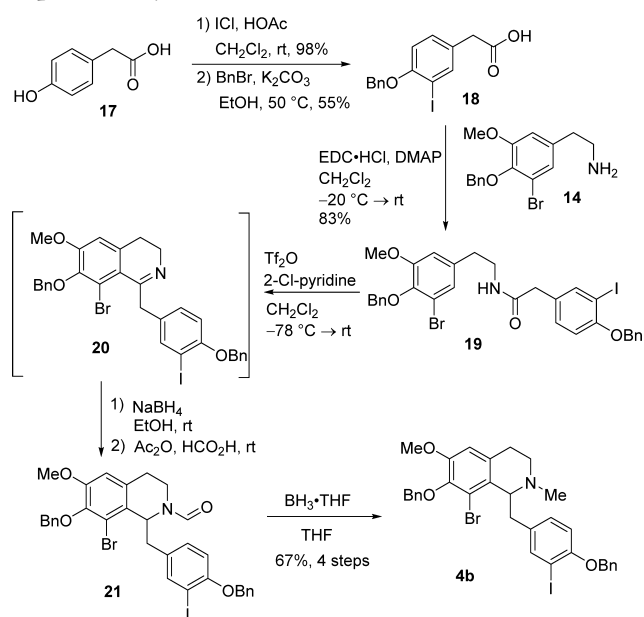
Scheme 4. Synthesis of α -Aminonitrile **5b**

The iodinated benzylic bromide **6b** was synthesized starting from *p*-anisaldehyde (**15**) (Scheme 5A). Unfortunately, the

Scheme 5. Synthesis of Benzylic Bromide **6b** (A) and 1-Benzyltetrahydroisoquinoline **4b** (B)

umpolung/alkylation-reduction sequence only gave low yields of the desired product **4b** in this case due to the steric hindrance imposed by the 8-bromo substituent (Scheme 5B).

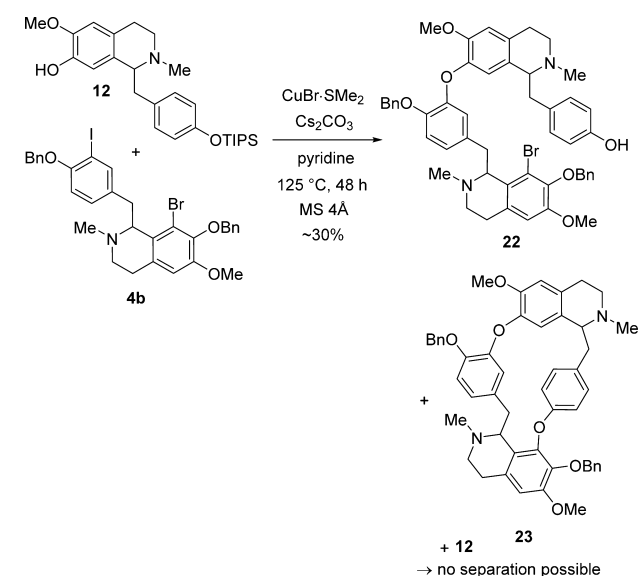
In order to improve the yields, a Bischler–Napieralski approach starting from the amide precursor **19** was attempted instead (Scheme 6).

Scheme 6. Synthesis of Dihalide **4b** through Bischler–Napieralski Cyclization

Synthesis of the amide precursor **19** was accomplished by coupling of the respective phenylacetic acid derivative **18** and phenylethylamine **14** with EDC hydrochloride and catalytic amounts of DMAP. Acid **18** was synthesized starting from *p*-hydroxyphenylacetic acid (**17**) by iodination with iodine monochloride and subsequent benzyl protection with benzyl bromide and was obtained in 43% yield over 2 steps (Scheme 6). Phenylethylamine **14** was obtained from vanillin (**7**) in 6 steps with over 45% yield (see Scheme 4). The cyclization of amide **19** was performed according to a synthetic procedure of Movassaghi and co-workers using triflic anhydride and 2-chloropyridine as the activating agents (Scheme 6). The crude cyclic imine **20** was subsequently reduced with sodium borohydride to the secondary amine, which was then *N*-formylated by formic acid/acetic acid anhydride to give formamide **21**. Reduction with borane tetrahydrofuran complex gave the desired *N*-methylated dihalide building block **4b** in 25% yield over 11 linear steps (Scheme 6).

Having both 1-benzylisoquinoline building blocks **12** and **4b** at hand, the reaction conditions for the first C–O coupling were explored.^{16–19} In preliminary studies with the electron-rich model system *p*-bromoanisole and *p*-methoxyphenol, we found out that ligands such as *N,N*-dimethylglycine as well as *n*-butylimidazole and copper bromide-dimethylsulfide complex showed a high catalytic activity in the Ullmann diaryl ether synthesis.²⁰

However, when the reaction conditions of the model system were applied to the more complex and sterically hindered system of **12** and **4b** (see Scheme 7), only low conversions were observed when using *N,N*-dimethylglycine, copper iodide, and potassium phosphate as the base. Even increasing the catalyst loading to equimolar amounts did not improve this situation. Furthermore, the application of reaction conditions already applied successfully by us in the total synthesis of the bisbenzylisoquinoline natural products O-methylauricine and tetramethylmagnolamine proved to be unsuccessful (*N,N*-dimethylglycine, Cs₂CO₃, DMF, microwave heating).²¹ Instead,

Scheme 7. C–O Coupling of **12** and **4b** to **22**

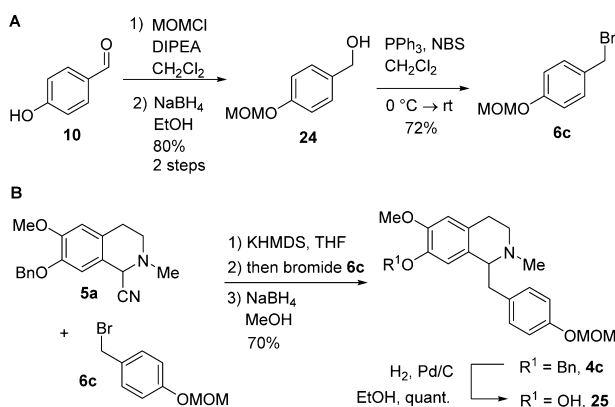
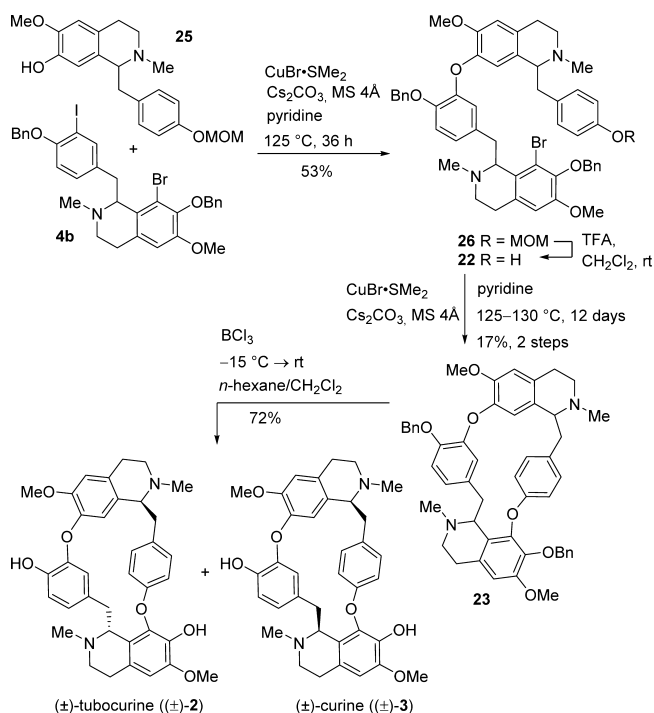
nearly quantitative deiodination of **4b** was observed as judged by HPLC/MS (Scheme 7).

A further efficient ligand/catalyst system, which had been identified in our previous model studies, was the copper bromide–dimethyl sulfide complex without any additional ligand.²⁰ The same catalyst proved to be successful in the synthesis of nelumboferin and isomeric head-to-tail linked bisbenzylisoquinolines reported by Yamada and co-workers.²² Furthermore, this catalyst was applied in the total synthesis of the vancomycin aglycone by Nicolaou and co-workers.²³

The use of copper bromide-dimethyl sulfide in combination with pyridine as the solvent and cesium carbonate as the base, which is based on a protocol by Yamada and co-workers, finally allowed conversion of **12** and **4b** to the seco-heterodimer **22** detected by HPLC/MS (Scheme 7). Interestingly, the TIPS protecting group of the formed seco-heterodimer is cleaved under these conditions to result in **22**, whereas the TIPS-protecting group of diol **12** remained untouched. Notably, due to cleavage of the TIPS-group of the seco-heterodimer **22**, the second C–O coupling furnishing the ring closed macrocyclic structure **23** was also detected by HPLC-MS (Scheme 7). The isolation of the seco-heterodimer **22** proved very difficult due to its amphoteric properties. The desired product was always isolated along with traces of unreacted starting material **12**.

For the next set of experiments, a MOM-protected diol unit **4c** was synthesized in order to achieve regioselectivity in the first Ullmann coupling under complete conversion of the diol **4c**. The MOM protecting group is not cleaved under basic conditions and orthogonally stable to the benzyl group. The deprotected MOM-benzyltetrahydroisoquinoline subunit **25** was obtained starting from aminonitrile **5a** (Scheme 8A) and the MOM-protected benzylic bromide **6c** (Scheme 8A) by the umpolung/alkylation reduction sequence and subsequent benzyl cleavage described above for the TIPS-protected diol **12** (see Scheme 8B).

Synthesis of the seco-heterodimer from **25** and **4b** was performed under the same set of reaction conditions as described in Scheme 7, and the seco-heterodimer **26** bearing the MOM group was obtained in a yield of 53% (Scheme 9). The Pd-catalyzed C–O coupling with Pd(OAc)₂ and *t*-BuXPhos²⁴ was also tested, but in terms of yield and byproduct

Scheme 8. Synthesis of Benzylic Bromide 6c (A) and 1-Benzyltetrahydroisoquinoline 25 (B)**Scheme 9. Synthesis of (±)-Tubocurine ((±)-2) and (±)-Curine ((±)-3)**

formation (deiodination), the palladium-catalyzed reactions were not competitive compared to the copper-mediated synthetic protocols.

Removal of the MOM-protecting group of **26** with trifluoroacetic acid furnished the seco-heterodimer **22**, which was obtained in high purity and could be used without further purification for the subsequent C–O coupling. The second C–O coupling of **22** was performed under the same reaction conditions as described for the synthesis of **26** at 130 °C, and the *O,O*-dibenzyl protected macrocyclic ring structure **23** was obtained in a yield of 17% over two steps as a mixture of diastereomers in a 1:1.8 ratio. The origin of this deviation from equimolarity is currently unclear. There may be a preferred ring closure in one of the diastereomeric seco-compounds **22** or an enrichment during chromatographic purification. The initial ratio could not be determined from the crude reaction mixture of **23** due to its complex composition. The lower yield of the second Ullmann reaction can be explained by competitive

debromination of **22** (Scheme 9), and the corresponding product could be identified by HPLC-MS (m/z 398.3 for $[M + 2H]^{2+}$) and ESI-HRMS (m/z calcd for $C_{50}H_{53}N_2O_6$ $[M + H]^+$: 777.3904, found: 777.3937). Removal of the benzyl ether protecting groups of **23** with BCl_3 furnished the natural product (±)-tubocurine ((±)-2) along with its naturally occurring diastereomer (±)-curine ((±)-3) in a yield of 72% in a diastereomeric ratio of 1:2 (Scheme 8). Reis and co-workers have shown that the ^{13}C NMR spectra of curine and tubocurine can be distinguished by the fact that C3' of curine is slightly deshielded compared to C3' of tubocurine. On the contrary, C8' of tubocurine has a high field shift compared to curine. In both diastereomers, the B-ring exhibits a half-chair conformation, and in curine, Ca' occupies a pseudoaxial position in this case. For tubocurine, Ca' takes a pseudoequatorial position. As a result, the $Ca'/C3'$ interaction is decreased, and the $Ca'/C8'$ interaction increases (anisotropy effect). These observations suggest that the obtained chemical shifts of the main diastereomer correspond to (±)-curine ((±)-2) and the chemical shifts of the minor diastereomer to (±)-tubocurine ((±)-3). The completed total synthesis of (±)-tubocurine ((±)-2) represents a formal total synthesis of tubocurarine (**1**).

In summary, the first racemic total synthesis of (±)-tubocurine ((±)-2) and (±)-curine ((±)-3) is accomplished starting from vanillin (**7**) by two subsequent Ullmann couplings of the two benzylisoquinoline subunits **25** and **4b**. The synthetic route involves 15 steps in the longest linear sequence and a total of 24 transformations. The combined overall yield of the diastereomeric mixture of **2** and **3** along the longest sequence amounts to 1.9%, the greatest losses result from the expectedly difficult C–O couplings in the final stages.

EXPERIMENTAL SECTION

All reactions involving air- or moisture-sensitive reagents or intermediates were performed under an inert atmosphere of argon in oven-dried glassware. If not mentioned otherwise, all reagents and solvents were obtained from commercial suppliers and used without further purification. Anhydrous THF and diethyl ether were distilled from sodium/benzophenone under argon. Anhydrous dichloromethane was distilled from calcium hydride. NMR spectra were recorded with a 300 MHz (300 MHz 1H and 75.5 MHz ^{13}C), 400 MHz (400 MHz 1H and 100.6 MHz ^{13}C), or 600 MHz spectrometer (600 MHz 1H and 151 MHz ^{13}C) with digital architecture equipped with 5 mm probes. The δ values were referenced to the residual solvent signal (for example $CHCl_3$, 7.26 ppm). IR spectra were recorded using a diamond ATR. ESI-HRMS spectra were recorded on a Q-TOF instrument with a dual source and a suitable external calibrant. Thin layer chromatography (TLC) was carried out on 0.25 mm silica gel plates with a fluorescence indicator. Flash chromatography was performed on 35–70 μm silica gel using the solvent systems indicated.

4-(Benzyloxy)-3-methoxybenzaldehyde. Synthesized according to a modified procedure of Dettlerbeck et al.²⁵ To vanillin (**7**) (30.0 g, 197 mmol, 1.0 equiv), dissolved in ethanol (400 mL), are added benzyl bromide (28.1 mL, 40.4 g, 236 mmol, 1.2 equiv) and potassium carbonate (40.9 g, 296 mmol, 1.5 equiv), and the reaction mixture is stirred for 12 h under reflux. After complete conversion (TLC), EtOH is removed by rotary evaporation, and the residue is taken up in water (400 mL). It is extracted with diethyl ether (3×150 mL), and the combined organic phases are dried over Na_2SO_4 . The solvent is removed in vacuo, and the product is obtained as yellow solid (42.4 g, 175 mmol, 89%). The product is sufficiently pure and can be used without further purification in the next step. R_f : 0.60 (cyclohexane/EtOAc = 2:1, Seebach reagent, UV). Mp: 61.0–62.0 °C (Et₂O). (Lit.: 60–62 °C).²⁶ 1H NMR (300 MHz, $CDCl_3$): δ [ppm] = 9.84 (s, 1H,

CHO), 7.29–7.46 (m, 7H, H-2, H-6, Ph), 6.99 (d, $J = 8.1$ Hz, 1H, H-5), 5.25 (s, 2H, CH₂-Ph), 3.95 (s, 3H, OCH₃).²⁶

1-(Benzyloxy)-2-methoxy-4-[(E)-2-nitroethenyl]benzene. Synthesized according to a modified procedure of Bergner et al.²⁷ 4-(benzyloxy)-3-methoxybenzaldehyde (40.0 g, 165 mmol, 1.0 equiv) is dissolved in nitromethane (330 mL), and ammonium acetate (12.7 g, 165 mmol, 1.0 equiv) is added. The reaction mixture is stirred for 2 h at 55 °C under TLC-control at specific time intervals. The temperature is increased to 80 °C until complete conversion is detected. The solvent is removed in vacuo, the residue is dissolved in dichloromethane (200 mL), and water (100 mL) is added. The organic phase is separated, and the aqueous phase is extracted with dichloromethane (3 × 200 mL). The combined organic phases are washed with water (150 mL) and dried over Na₂SO₄. After filtration, the solvent is removed in vacuo and furnishes the product (44.7 g, 157 mmol, 95%). The obtained yellow solid is sufficiently pure and can be used without further purification. R_f : 0.62 (cyclohexane/EtOAc = 2:1, Seebach reagent, vanillin/H₂SO₄ reagent, UV). Mp: 116.0–118.0 °C (dichloromethane). (Lit.: 119–121 °C (EtOH)).²⁸ ¹H NMR (300 MHz, CDCl₃): δ [ppm] = 7.95 (d, $J = 13.6$ Hz, 1H, =CH_α), 7.51 (d, $J = 13.6$ Hz, 1H, =CH_β), 7.30–7.45 (m, 5H, Ph), 7.10 (dd, $J = 8.4$ Hz, 2.1 Hz, 1H, H-6), 7.02 (d, $J = 2.1$ Hz, 1H, H-2), 6.92 (d, $J = 8.4$ Hz, 1H, H-5), 5.22 (s, 2H, CH₂-Ph), 3.93 (s, 3H, OCH₃).²⁸

2-[4-(Benzyloxy)-3-methoxyphenyl]ethylamine (8). Synthesized according to a modified procedure of Bermejo et al.²⁹ To a suspension of lithium aluminum hydride (7.97 g, 210 mmol, 4.0 equiv) in anhydrous THF (200 mL) at 0 °C, 1-(benzyloxy)-2-methoxy-4-[(E)-2-nitroethenyl]benzene (15.0 g, 52.6 mmol, 1.0 equiv) dissolved in THF (200 mL) is added dropwise. After complete addition, the reaction mixture is heated to reflux for 12 h. The mixture is then cooled to 0 °C, and sodium sulfate decahydrate is added cautiously in small portions until the exothermic reaction and the gas evolution ceases. It is warmed to room temperature, and the reaction mixture is filtered and the residue is washed with diethyl ether. The filtrate is evaporated to dryness, and the crude product is obtained as a yellow oil (11.4 g, 44.0 mmol, 83%). Compound 8 is sufficiently pure and can be used without further purification. R_f : 0.55 (dichloromethane/MeOH/NEt₃ = 2:2:1, ninhydrin reagent, UV). ¹H NMR (300 MHz, CDCl₃): δ [ppm] = 7.45–7.43 (m, 2H, H-2-Ph, H-6-Ph), 7.38–7.29 (m, 3H, H-3-Ph, H-4-Ph, H-5-Ph), 6.82 (d, $J = 8.1$ Hz, 1H, H-5), 6.74 (d, $J = 2.0$ Hz, 1H, H-2), 6.66 (dd, $J = 8.1$, 2.0 Hz, 1H, H-6), 5.12 (s, 2H, CH₂-Ph), 3.88 (s, 3H, OCH₃), 2.92 (t, $J = 6.8$ Hz, 2H, CH₂NH₂), 2.67 (t, $J = 6.8$ Hz, 2H, CH₂CH₂NH₂), 1.56 (s, br, 2H, NH₂).²⁸

N-[2-[4-(Benzyloxy)-3-methoxyphenyl]ethyl]formamide. Synthesized according to a procedure of Elliott et al.³⁰ Amine 8 (9.30 g, 36.1 mmol, 1.0 equiv) is dissolved in formic acid ethyl ester, and the reaction mixture is stirred for 12 h under reflux. After complete reaction, the solvent is removed in vacuo to furnish the product as a brownish oil (10.3 g, 36.1 mmol, quant.). The obtained product is sufficiently pure and can be used without further purification in the next step. R_f : 0.29 (EtOAc/cyclohexane = 100:1, Seebach reagent, UV). Major rotamer: ¹H NMR (300 MHz, CDCl₃): δ [ppm] = 8.08 (d, $J = 1.7$ Hz, 1H, CHO), 7.44–7.29 (m, 5H, Ph), 6.81 (d, $J = 8.1$ Hz, 1H, H-5), 6.73 (d, $J = 2.0$ Hz, 1H, H-2), 6.65 (d, $J = 8.1$, 2.0 Hz, 1H, H-6), 5.75 (s, br, 1H, NH), 5.12 (s, 2H, CH₂-Ph), 3.86 (s, 3H, OCH₃), 3.51 (pseudo-q, $J \approx 6.8$ Hz, 2H, CH₂CH₂Ar), 2.75 (t, $J = 6.8$ Hz, 2H, CH₂Ar). IR (ATR): $\nu = 3291$ (w), 3033 (w), 2935 (w), 2867 (w), 1663 (s), 1591 (w), 1511 (vs), 1453 (m), 1418 (m), 1383 (m), 1260 (vs), 1223 (vs), 1158 (m), 1139 (vs), 1024 (s), 913 (w), 736 (s), 696 (s) cm⁻¹. MS (ESI): m/z (%) = 286.1 (100) [M + H]⁺, 308.1 (67) [M + Na]⁺. The analytical data are in accordance with the literature.³¹

7-(Benzyloxy)-6-methoxy-3,4-dihydroisoquinoline (9). Synthesized according to a modified procedure of Rohloff et al.³² To a suspension of phosphorus pentachloride (3.45 g, 16.5 mmol, 1.1 equiv) in anhydrous toluene (10 mL) is added N-[2-[4-(benzyloxy)-3-methoxyphenyl]ethyl]formamide (4.32 g, 15.1 mmol, 1.0 equiv) dissolved in dichloromethane (10 mL) at room temperature. The reaction mixture is stirred for 15 h at room temperature, and water (100 mL) is added. The organic phase is separated, and the brown residue that forms during the reaction is taken up in methanol (20

mL). The aqueous phase and the methanol phase are combined and adjusted to pH 12 with solid potassium hydroxide at 0 °C. The mixture is extracted with dichloromethane (3 × 75 mL), and the combined organic phases are dried over Na₂SO₄. After filtration, the solvent is removed in vacuo and gives the crude product as a brown viscous oil (2.96 g, 11.0 mmol, 74%). The crude product 9 can be used without further purification. R_f : 0.50 (cyclohexane/EtOAc/NEt₃ = 6:4:1, Seebach reagent, ninhydrin reagent, UV). ¹H NMR (300 MHz, CDCl₃): δ [ppm] = 9.01 (s, 1H, H-1), 7.49 (s, 1H, H-8), 7.39–7.35 (m, 2H, H-2-Ph, H-6-Ph), 7.30–7.21 (m, 3H, H-3-Ph, H-4-Ph, H-5-Ph), 6.75 (s, 1H, H-5), 5.08 (s, 2H, CH₂-Ph), 3.88 (s, 3H, OCH₃), 3.85 (t, $J = 8.4$ Hz, 2H, H-3), 3.00 (t, $J = 8.4$ Hz, 2H, H-4). ¹³C NMR, HSQC, HMBC (100.6 MHz, CDCl₃): δ [ppm] = 164.0 (C=N), 157.6 (C-6), 147.7 (C-7), 135.8 (C-1-Ph), 133.1 (C-8a), 128.6 (C-3-Ph, C-5-Ph), 128.2 (C-4-Ph), 127.7 (C-2-Ph, C-6-Ph), 117.5 (C-8), 116.7 (C-5a), 111.2 (C-5), 71.2 (CH₂-Ph), 56.6 (OCH₃), 41.1 (C-3), 24.6 (C-4). MS (ESI): m/z (%) = 268.1 (100) [M + H]⁺. The analytical data are in accordance with the literature.²⁶

7-(Benzyloxy)-6-methoxy-2-methyl-3,4-dihydroisoquinolinium iodide. To a solution of imine 9 (2.49 g, 9.34 mmol, 1.0 equiv) in diethyl ether (20 mL) was added dropwise iodomethane (1.59 g, 11.2 mmol, 1.2 equiv) at room temperature. The reaction mixture is stirred at room temperature until complete conversion (15 h). The yellow precipitate is filtered and washed with diethyl ether. The product is obtained as a yellow solid (2.64 g, 6.45 mmol, 69%). R_f : 0.26 (dichloromethane/MeOH/NEt₃ = 1:1:0.5, Seebach reagent, UV). Mp: 177.0–178.0 °C (dichloromethane). (Lit.: 193–195 °C).³³ ¹H NMR, COSY (400 MHz, CDCl₃): δ [ppm] = 9.71 (s, 1H, H-1), 7.63 (s, 1H, H-8), 7.28–7.48 (m, 5H, Ph), 6.82 (s, 1H, H-5), 5.15 (s, 2H, CH₂-Ph), 3.94–3.98 (m, 5H, H-3, NCH₃), 3.87 (s, 3H, OCH₃), 3.27 (t, $J = 8.2$ Hz, 2H, H-4). ¹³C NMR, HSQC, HMBC (100.6 MHz, CDCl₃): δ [ppm] = 165.2 (C-1), 158.2 (C-7), 148.0 (C-6), 135.7 (C-1-Ph), 131.9 (C-4a), 128.8, 128.4, 128.0 (C-2-Ph, C-3-Ph, C-4-Ph, C-5-Ph, C-6-Ph), 117.6 (C-8), 116.9 (C-8a), 111.1 (C-5), 71.4 (CH₂-Ph), 56.9 (NCH₃), 50.2 (C-3), 47.9 (OCH₃), 25.7 (C-4). MS (ESI): m/z (%) = 282.2 (100) [M]⁺. The analytical data are in accordance with the literature.³³

7-(Benzyloxy)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (5a). 7-(Benzyloxy)-6-methoxy-2-methyl-3,4-dihydroisoquinolinium iodide (1.95 g, 4.76 mmol 1.0 equiv) is dissolved in MeOH (40 mL), and potassium cyanide (776 mg, 11.9 mmol, 2.5 equiv) is added portionwise at room temperature. The reaction mixture is stirred for 18 h at room temperature. Sat. NaHCO₃ solution is added (50 mL), and it is extracted with dichloromethane (3 × 75 mL). The combined organic phases are dried over Na₂SO₄, and the solvent is removed in vacuo. The product is obtained as brown oil (1.50 g, quant.) and crystallizes as a brown solid. The product 5a is sufficiently pure and can be used without further purification. R_f : 0.23 (dichloromethane/MeOH/NEt₃ = 10:1:0.5, Seebach reagent, UV). Mp: 125.0–126.0 °C (dichloromethane). ¹H NMR, COSY (400 MHz, CDCl₃): δ [ppm] = 7.28–7.44 (m, 5H, Ph), 6.69 (s, 1H, H-8), 6.64 (s, 1H, H-5), 5.06–5.16 (m, 2H, CH₂-Ph), 4.57 (s, 1H, H-1), 3.86 (s, 3H, OCH₃), 2.67–3.02 (m, 4H, H-3, H-4), 2.57 (s, 3H, NCH₃). ¹³C NMR, HSQC, HMBC (100.6 MHz, CDCl₃): δ [ppm] = 150.1 (C-6), 147.0 (C-7), 136.8 (C-1-Ph), 128.7 (C-3-Ph, C-5-Ph), 128.1 (C-4-Ph), 127.5 (C-2-Ph, C-6-Ph), 127.0 (C-4a), 121.2 (C-8a), 116.7 (CN), 112.5, 112.1 (C-8, C-5), 71.4 (CH₂-Ph), 55.6 (C-1), 55.1 (OCH₃), 48.5 (C-3), 43.8 (NCH₃), 28.2 (C-4). IR (ATR): $\nu = 3033$ (w), 2937 (w), 2805 (w), 1610 (m), 1517 (s), 1255 (vs), 1222 (vs), 1139 (s), 1127 (s), 734 (vs), 697 (vs) cm⁻¹. MS (ESI): m/z (%) = 282.1 (100) [M – CN]⁺. HRMS (ESI): m/z calcd for C₁₉H₂₁N₂O₂ [M + H]⁺: 309.1603, found: 309.1601.

3-Bromo-4-hydroxy-5-methoxybenzaldehyde. Vanillin (7) (25.0 g, 0.164 mol, 1.0 equiv) is dissolved in conc. acetic acid (300 mL), and bromine (9.90 mL, 29.9 g, 0.197 mol, 1.2 equiv) is added dropwise at 0 °C. The reaction mixture is warmed to room temperature within 3 h and is stirred at room temperature for 15 h. After completion of the reaction, water is added (500 mL), and the formed precipitate is filtered and washed with water. The off-white solid is dried in vacuo to furnish the title compound (37.9 g, 0.164

mol, quant.). R_f : 0.33 (cyclohexane/EtOAc = 2:1, Seebach reagent, UV). Mp: 162.0–163.0 °C (H₂O). (Lit.: 162–164 °C).³⁴ ¹H NMR (300 MHz, CDCl₃): δ [ppm] = 9.78 (s, 1H, CHO), 7.64 (d, J = 1.7 Hz, 1H, H-2), 7.36 (d, J = 1.7 Hz, 1H, H-6), 6.58 (s, 1H, OH), 3.98 (s, 3H, OCH₃). The analytical data are in accordance with the literature.³⁴

4-(Benzyloxy)-3-bromo-5-methoxybenzaldehyde. Synthesized according to the procedure described for the benzylation of vanillin. 3-Bromo-4-hydroxy-5-methoxybenzaldehyde (35.0 g, 151 mmol, 1.0 equiv) is reacted with benzyl bromide (21.5 mL, 31.0 g, 181 mmol, 1.2 equiv) and potassium carbonate (31.4 g, 227 mmol, 1.5 equiv) in ethanol (500 mL). The product (37.3 g, 116 mmol, 77%) crystallizes as a yellow solid. The product is sufficiently pure and can be used without further purification. R_f : 0.59 (cyclohexane/EtOAc = 2:1, Seebach reagent, UV). Mp: 43.5–45.0 °C (Et₂O). (Lit.: 44 °C (*n*-hexane)).³⁵ ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 9.84 (s, 1H, CHO), 7.66 (d, J = 1.7 Hz, 1H, H-2), 7.54–7.51 (m, 2H, H-2-Ph, H-6-Ph), 7.40–7.34 (m, 4H, H-3-Ph, H-4-Ph, H-5-Ph, H-6-Ph), 5.16 (s, 2H, CH₂-Ph), 3.94 (s, 3H, OCH₃). The analytical data are in accordance with the literature.³⁶

[4-(Benzyloxy)-3-bromo-5-methoxyphenyl]methanol (13). Sodium borohydride (10.2 g, 270 mmol, 1.5 equiv) is dissolved in ethanol (300 mL), and 4-(benzyloxy)-3-bromo-5-methoxybenzaldehyde (57.9 g, 180 mmol, 1.0 equiv) dissolved in ethanol (200 mL) is added dropwise at 0 °C. The reaction mixture is warmed to room temperature and stirred for 2 h. Water is added to the reaction mixture, and ethanol is removed by rotary evaporation. The residue is extracted with dichloromethane, and the combined organic phases are dried over Na₂SO₄. The solvent is removed in vacuo, and the product is obtained as yellow oil (54.1 g, 167 mmol, 93%). The product **13** is sufficiently pure and can be used without further purification. R_f : 0.33 (cyclohexane/EtOAc = 2:1, Seebach reagent, UV). ¹H NMR (300 MHz, CDCl₃): δ [ppm] = 7.54–7.56 (m, 2H, H-2-Ph, H-6-Ph), 7.31–7.41 (m, 3H, H-3-Ph, H-4-Ph, H-5-Ph), 7.12 (d, J = 1.9 Hz, 1H, H-2), 6.89 (d, J = 1.9 Hz, 1H, H-6), 5.01 (s, 2H, CH₂-Ph), 4.61 (s, 2H, CH₂OH), 3.87 (s, 3H, OCH₃), 1.80 (s, 1H, OH). The analytical data are in accordance with the literature.³⁷

2-(Benzyloxy)-1-bromo-5-(bromomethyl)-3-methoxybenzene. Synthesized according to a modified procedure of van Oeveren et al.³⁸ Alcohol **13** (30.0 g, 92.9 mmol, 1.0 equiv) is dissolved in anhydrous diethyl ether, and it is cooled to 0 °C. Phosphorus tribromide (8.65 mL, 25.0 g, 92.9 mmol, 1.0 equiv) dissolved in anhydrous diethyl ether (250 mL) is added dropwise at this temperature, and the mixture is stirred for 30 min. The reaction mixture is then warmed to room temperature, and water is added. It is extracted with diethyl ether, and the combined organic phases are dried over Na₂SO₄. The solvent is removed in vacuo, and the title compound is obtained as yellow oil (35.2 g, 91.2 mmol, 98%). The product is sufficiently pure and can be used without further purification. R_f : 0.70 (cyclohexane/EtOAc = 2:1, Seebach reagent, UV). ¹H NMR (300 MHz, CDCl₃): δ [ppm] = 7.53–7.57 (m, 2H, H-2-Ph, H-6-Ph), 7.29–7.43 (m, 3H, H-3-Ph, H-4-Ph, H-5-Ph), 7.19 (d, J = 2.0 Hz, 1H, H-6), 6.90 (d, J = 2.0 Hz, 1H, H-4), 5.03 (s, 2H, CH₂-Ph), 4.42 (s, 2H, CH₂Br), 3.88 (s, 3H, OCH₃). ¹³C NMR, HSQC, HMBC (75.5 MHz, CDCl₃): δ [ppm] = 154.0 (C-3), 145.5 (C-2), 137.0 (C-1-Ph), 134.9 (C-5), 128.6 (C-2-Ph, C-6-Ph), 128.4 (C-3-Ph, C-5-Ph), 128.2 (C-4-Ph), 125.4 (C-6), 118.0 (C-1), 112.5 (C-4), 74.9 (CH₂-Ph), 56.3 (OCH₃), 32.7 (CH₂Br). IR (ATR): ν = 3063 (w), 2938 (w), 1568 (m), 1483 (s), 1276 (vs), 1215 (s), 1145 (s), 1044 (vs), 969 (m), 696 (s) cm⁻¹. MS (FD): m/z (%) = 386.1 [M⁺]. HRMS data could not be obtained due to decomposition of the sample in aqueous acetonitrile.

[4-(Benzyloxy)-3-bromo-5-methoxyphenyl]acetonitrile. Synthesized according to a modified procedure of Javier et al.³⁹ 2-(Benzyloxy)-1-bromo-5-(bromomethyl)-3-methoxybenzene (14.3 g, 37.0 mmol, 1.0 equiv) is dissolved in dichloromethane/water (110 mL, 10:1), and the mixture is cooled to 0 °C. Potassium cyanide (3.60 g, 56.0 mmol, 1.5 equiv) and tetrabutylammonium bromide (3.01 g, 9.30 mmol, 0.3 equiv) are added at this temperature, and the reaction mixture is stirred for 1 h. It is warmed to room temperature and stirred for 12 h. To the reaction mixture is added sat. sodium hydrogen

carbonate solution, and it is extracted with toluene. The combined organic phases are dried over Na₂SO₄, and the solvent is removed in vacuo. The title compound is obtained as a colorless solid (10.9 g, 33.0 mmol, 89%) and can be used without further purification. Traces of the phase transfer catalyst can be removed extraction with diethyl ether/water or by flash column chromatography on silica gel (cyclohexane/ethyl acetate = 4:1). R_f : 0.24 (cyclohexane/EtOAc = 4:1, Seebach or ninhydrin reagent, UV). Mp: 76.5–77.5 °C (dichloromethane). ¹H NMR (300 MHz, CDCl₃): δ [ppm] = 7.51–7.56 (m, 2H, H-2-Ph, H-6-Ph), 7.30–7.42 (m, 3H, H-3-Ph, H-4-Ph, H-5-Ph), 7.10 (d, J = 2.1 Hz, 1H, H-2), 6.83 (d, J = 2.1 Hz, 1H, H-6), 5.03 (s, 2H, CH₂-Ph), 3.88 (s, 3H, OCH₃), 3.69 (s, 2H, CH₂CN). ¹³C NMR, HSQC, HMBC (75.5 MHz, CDCl₃): δ [ppm] = 154.2 (C-5), 145.2 (C-4), 136.8 (C-1-Ph), 128.5 (C-2-Ph, C-6-Ph), 128.4 (C-3-Ph, C-5-Ph), 128.2 (C-4-Ph), 126.8 (C-1), 124.2 (C-6), 118.6 (C-3), 117.4 (CN), 111.3 (C-2), 74.8 (CH₂-Ph), 56.2 (OCH₃), 23.1 (CH₂CN). IR (ATR): ν = 3089 (w), 3064 (w), 3032 (w), 3009 (w), 2941 (w), 2918 (w), 2879 (w), 2843 (w), 2252 (w), 1598 (m), 1571 (m), 1484 (m), 1463 (m), 1454 (m), 1416 (s), 1274 (s), 1231 (s), 1145 (s), 1045 (vs), 972 (s), 915 (w), 819 (w), 732 (m), 698 (m) cm⁻¹. MS (ESI): m/z (%) = 332.1 (27) [M + H]⁺, 354.1 (100) [M + Na]⁺. HRMS (ESI): m/z calcd for C₁₆H₁₄BrNO₂ [M + Na]⁺: 354.0106, found: 354.0106.

2-[4-(Benzyloxy)-3-bromo-5-methoxyphenyl]ethylamine (14). [4-(Benzyloxy)-3-bromo-5-methoxyphenyl]acetonitrile (10.9 g, 33.0 mmol, 1.0 equiv) is dissolved in anhydrous THF (100 mL), and borane tetrahydrofuran complex (1 M, 66 mL, 66.0 mmol, 2.0 equiv) is added at room temperature. The reaction mixture is stirred for 15 h at room temperature. Water is added, and the mixture is extracted with dichloromethane. The combined organic phases are dried over Na₂SO₄, and the solvent is removed in vacuo. The obtained yellow oil is purified by flash column chromatography on silica gel (chloroform/MeOH/NEt₃ = 5:1:1). The product **14** is furnished as a colorless viscous oil (9.00 g, 26.8 mmol, 81%). R_f : 0.47 (chloroform/MeOH/NEt₃ = 5:1:1, ninhydrin reagent, UV). ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 7.58–7.55 (m, 2H, H-2-Ph, H-6-Ph), 7.42–7.34 (m, 3H, H-3-Ph, H-4-Ph, H-5-Ph), 7.03 (d, J = 1.9 Hz, 1H, H-2), 6.75 (d, J = 1.9 Hz, 1H, H-6), 5.01 (s, 2H, CH₂-Ph), 4.15 (s, br, 2H, NH₂), 3.86 (s, 3H, OCH₃), 3.05 (t, J = 7.2 Hz, 2H, CH₂CH₂Ar), 2.81 (t, J = 7.2 Hz, 2H, CH₂CH₂Ar). ¹³C NMR, HSQC, HMBC (100.6 MHz, CDCl₃): δ [ppm] = 153.8 (C-5), 143.9 (C-4), 137.1 (C-1-Ph), 136.0 (C-1), 128.5 (C-2-Ph, C-6-Ph), 128.3 (C-3-Ph, C-5-Ph), 128.1 (C-4-Ph), 124.7 (C-2), 118.0 (C-3), 112.5 (C-6), 74.7 (CH₂-Ph), 56.2 (OCH₃), 42.4 (CH₂CH₂Ar), 37.3 (CH₂CH₂Ar). IR (ATR): ν = 3367 (w), 3089 (w), 3063 (w), 3031 (w), 3005 (w), 2937 (w), 2867 (w), 1661 (w), 1595 (m), 1565 (s), 1483 (s), 1462 (s), 1453 (s), 1412 (s), 1374 (m), 1300 (m), 1271 (s), 1225 (s), 1143 (s), 1044 (vs), 1002 (m), 975 (m), 914 (m), 842 (m), 817 (s), 696 (s) cm⁻¹. MS (ESI): m/z (%) = 338.0 (100) [M + H]⁺. HRMS (ESI): m/z calcd for C₁₆H₁₉BrNO₂ [M + H]⁺: 336.0599, found: 336.0602.

7-(Benzyloxy)-8-bromo-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline. Amine **14** (1.41 g, 4.19 mmol, 1.0 equiv) is dissolved in formic acid (90%, 250 mL), and paraformaldehyde (630 mg, 21.0 mmol, 5.0 equiv) is added. The reaction mixture is stirred for 42 h at 40 °C. Formic acid is removed in vacuo, and the residue is purified by flash column chromatography on silica gel (cyclohexane/EtOAc/NEt₃ = 6:4:1). The title compound is obtained as yellow oil (831 mg, 2.29 mmol, 55%). R_f : 0.34 (cyclohexane/EtOAc/NEt₃ = 6:4:1, Seebach reagent, UV). ¹H NMR, COSY (400 MHz, CDCl₃): δ [ppm] = 7.53–7.58 (m, 2H, H-2-Ph, H-6-Ph), 7.29–7.40 (m, 3H, H-3-Ph, H-4-Ph, H-5-Ph), 6.65 (s, 1H, H-5), 4.98 (s, 2H, CH₂-Ph), 3.83 (s, 3H, OCH₃), 3.50 (s, 2H, H-1), 2.89 (t, J = 5.7 Hz, 2H, H-3), 2.64 (t, J = 5.7 Hz, 2H, H-4), 2.50 (s, 3H, NCH₃). ¹³C NMR, HSQC, HMBC (100.6 MHz, CDCl₃): δ [ppm] = 151.8 (C-6), 143.3 (C-7), 137.3 (C-1-Ph), 131.4 (C-4a), 128.5 (C-2-Ph, C-6-Ph), 128.3 (C-3-Ph, C-5-Ph), 128.0 (C-4-Ph), 126.5 (C-8a), 118.3 (C-8), 111.7 (C-5), 74.6 (CH₂-Ph), 58.0 (C-1), 56.1 (OCH₃), 52.0 (C-3), 45.9 (NCH₃), 29.5 (C-4). IR (ATR): ν = 3064 (w), 2940 (w), 2807 (w), 1646 (w), 1598 (m), 1566 (m), 1483 (vs), 1464 (m), 1454 (m), 1324 (s), 1278 (m), 1215 (m), 1143 (s), 1028 (s), 698 (m) cm⁻¹. MS (ESI): m/z (%) =

362.1 (100) $[M + H]^+$. HRMS (ESI): m/z calcd for $C_{18}H_{21}BrNO_2$ $[M + H]^+$: 362.0756, found: 362.0750.

7-(Benzyloxy)-8-bromo-6-methoxy-2-methyl-3,4-dihydroisoquinolinium iodide. According to a modified procedure of Leonard and Leubner,⁴⁰ 7-(Benzyloxy)-8-bromo-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (1.30 g, 3.59 mmol, 1.0 equiv) is dissolved in EtOH (100 mL), and potassium acetate (1.90 g, 19.5 mmol, 4.3 equiv) is added at room temperature. Subsequently, iodine (3.81 g, 29.8 mmol, 6.5 equiv), dissolved in EtOH (50 mL), is added at room temperature, and the mixture is stirred for about 30 min at this temperature until TLC control shows complete conversion. To the reaction mixture is added water (150 mL), and it is extracted with dichloromethane (3 \times 100 mL). The combined organic phases are washed with sat. sodium thiosulfate solution (3 \times 75 mL) and dried over Na_2SO_4 . After filtration, the solvent is removed in vacuo, and the product **25** is obtained as yellow solid (1.50 g, 3.07 mmol, 86%). R_f : 0.65 (dichloromethane/MeOH = 5:1, Seebach reagent, UV). Mp: 144.0–155.0 °C under decomposition. 1H NMR, COSY (400 MHz, $CDCl_3$): δ [ppm] = 8.96 (s, 1H, H-1), 7.49–7.47 (m, 2H, H-2-Ph, H-6-Ph), 7.39–7.36 (m, 3H, H-3-Ph, H-4-Ph, H-5-Ph), 7.02 (s, 1H, H-5), 5.02 (s, 2H, CH_2 -Ph), 4.14 (t, J = 8.1 Hz, 2H, H-3), 4.02 (3H, OCH_3), 3.99 (s, 3H, NCH_3), 3.50 (t, J = 8.1 Hz, 2H, H-4). ^{13}C NMR, HSQC, HMBC, NOESY (100.6 MHz, $CDCl_3$): δ [ppm] = 163.6 (C-1), 161.8 (C-6), 145.4 (C-7), 137.6 (C-4a), 136.0 (C-1-Ph), 128.6 (C-2-Ph, C-6-Ph), 128.6 (C-4-Ph), 128.5 (C-3-Ph, C-5-Ph), 124.5 (C-8[#]), 117.0 (C-8a[#]), 111.5 (C-5), 75.2 (CH_2 -Ph), 57.4 (OCH_3), 50.3 (C-3), 49.6 (NCH_3), 26.6 (C-4). [#]signals may be interchanged. IR (ATR): ν = 3064 (w), 2940 (w), 2807 (w), 1658 (m), 1590 (m), 1544 (m), 1320 (m), 1295 (s), 1127 (m), 1022 (m), 909 (s), 727 (s) cm^{-1} . MS (ESI): m/z (%) = 362.0 (100) $[M]^+$. HRMS (ESI): m/z calcd for $C_{18}H_{19}BrNO_2$ $[M]^+$: 360.0599, found: 360.0597.

7-(Benzyloxy)-8-bromo-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (5b). Synthesized according to the procedure described for compound **5a**. 7-(Benzyloxy)-8-bromo-6-methoxy-2-methyl-3,4-dihydroisoquinolinium iodide (1.50 g, 3.07 mmol, 1.0 equiv) is reacted with potassium cyanide (1.00 g, 15.3 mmol, 5.0 equiv). The product is obtained as brown oil (1.02 g, 2.64 mmol, 86%) and is sufficiently pure for the next transformation. R_f : 0.62 (toluene/EtOAc/ NET_3 = 10/10/1, Seebach reagent, UV). 1H NMR, COSY (400 MHz, $CDCl_3$): δ [ppm] = 7.55–7.53 (m, 2H, H-2-Ph, H-6-Ph), 7.40–7.33 (m, 3H, H-3-Ph, H-4-Ph, H-5-Ph), 6.68 (s, 1H, H-5), 5.00 (s, 2H, CH_2 -Ph), 4.84 (s, 1H, H-1), 3.85 (s, 3H, OCH_3), 3.09–2.70 (m, 4H, H-3, H-4), 2.62 (s, 3H, NCH_3). ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ [ppm] = 153.6 (C-6), 144.0 (C-7), 137.0 (C-1-Ph), 132.1 (C-4a), 128.5 (C-2-Ph, C-6-Ph), 128.4 (C-3-Ph, C-5-Ph), 128.2 (C-4-Ph), 121.8 (C-8a[#]), 118.7 (C-8[#]), 115.2 (CN), 112.0 (C-5), 74.8 (CH_2 -Ph), 57.5 (C-1), 56.1 (OCH_3), 47.8 (C-3), 43.5 (NCH_3), 28.7 (C-4). [#]signals may be reversed. IR (ATR): ν = 3032 (w), 2839 (w), 1597 (m), 1566 (m), 1482 (s), 1464 (s), 1454 (s), 1371 (m), 1323 (m), 1278 (s), 1228 (s), 912 (s), 732 (s), 698 (s) cm^{-1} . MS (ESI): m/z (%) = 362.1 (100) $[M - CN]^+$. HRMS (ESI): m/z calcd for $C_{19}H_{20}BrN_2O_2$ $[M + H]^+$: 387.0708, found: 387.0699.

4-[[Tri(propan-2-yl)silyl]oxy]benzaldehyde. Synthesized according to a modified procedure of Ramaciotti et al.⁴¹ To a solution of 4-hydroxybenzaldehyde (**10**) (8.00 g, 65.5 mmol, 1.0 equiv) and imidazole (15.6 g, 223 mmol, 3.5 equiv) in DMF (25 mL) is added triisopropylsilyl chloride (12.6 g, 13.9 mL, 65.5 mmol, 1.0 equiv), and the reaction mixture is stirred for 2 h at room temperature. Water (20 mL) is added and the mixture is extracted with *n*-hexane (3 \times 20 mL). The combined organic layers are washed with brine and are dried over Na_2SO_4 . The solvent is removed in vacuo, and the product is obtained as yellow oil (16.8 g, 60.4 mmol, 92%). The product is sufficiently pure and can be used without purification in the next step. R_f : 0.78 (cyclohexane/EtOAc = 2:1, Seebach reagent, UV). 1H NMR (300 MHz, $CDCl_3$): δ [ppm] = 9.87 (s, 1H, CHO), 7.79–7.76 (AA'-part of an AA'XX'-system, 2H, H-2, H-6), 6.99–6.96 (XX'-part of an AA'XX'-system, 2H, H-3, H-5), 1.34–1.22 (m, 3H, CH), 1.12–1.05 (m, 18H, CH_3). The analytical data are in accordance with the literature.⁴²

(4-[[Tri(propan-2-yl)silyl]oxy]phenyl)methanol (11). Synthesized according to the procedure described for compound **13**. 4-[[Tri(propan-2-yl)silyl]oxy]benzaldehyde (16.8 g, 60.3 mmol, 1.0 equiv) is reacted with $NaBH_4$ (4.10 g, 108 mmol, 1.8 equiv) in EtOH (100 mL). The product is obtained as light yellow oil (15.8 g, 56.3 mmol, 93%). Compound **11** is sufficiently pure and can be used without purification in the next step. R_f : 0.52 (cyclohexane/EtOAc = 2:1, Seebach reagent, UV). 1H NMR (300 MHz, $CDCl_3$): δ [ppm] = 7.24–7.19 (AA'-part of an AA'XX'-system, 2H, H-3, H-5), 6.89–6.82 (XX'-part of an AA'XX'-system, 2H, H-2, H-6), 4.60 (s, 2H, CH_2OH), 1.31–1.19 (m, 3H, CH), 1.67 (s, br, 1H, OH), 1.11–1.05 (m, 18H, CH_3). The analytical data are in accordance with the literature.⁴²

[4-(Bromomethyl)phenoxy][tri(propan-2-yl)silane (6a). According to the procedure described for 2-(Benzyloxy)-1-bromo-5-(bromomethyl)-3-methoxybenzene. Alcohol **11** (4.50 g, 16.0 mmol, 1.0 equiv) is reacted with phosphorus tribromide (1.50 mL, 16.0 mmol, 1.0 equiv) in anhydrous diethyl ether (220 mL). The product is obtained as light yellow oil (4.97 g, 14.4 mmol, 90%). The product **6a** is sufficiently pure and can be used without purification in the next step. R_f : 0.86 (cyclohexane/EtOAc = 20:1, Seebach reagent, UV). 1H NMR (300 MHz, $CDCl_3$): δ [ppm] = 7.26–7.23 (AA'-part of an AA'XX'-system, 2H, H-3, H-5), 6.85–6.82 (XX'-part of an AA'XX'-system, 2H, H-2, H-6), 4.49 (s, 2H, CH_2Br), 1.31–1.19 (m, 3H, CH), 1.12–1.05 (m, 18H, CH_3). The analytical data are in accordance to the literature.⁴²

3-Iodo-4-methoxybenzaldehyde. Synthesized according to a modified procedure of Fujita et al.⁴³ *p*-Anisaldehyde (**15**) (10.0 g, 73.4 mmol, 1.0 equiv) is dissolved in acetic acid (50 mL), and iodine monochloride (13.9 g, 85.6 mmol, 1.2 equiv) is added. The reaction mixture is heated to 140 °C for 2–4 h. After complete conversion, the reaction mixture is cooled to room temperature, the pH of the reaction mixture is adjusted to pH 8 with 1 M NaOH solution, and it is extracted with chloroform (3 \times 75 mL). The combined organic phases are dried over Na_2SO_4 , and the solvent is removed in vacuo. The title compound is obtained as an off-white crystalline solid (15.0 g, 57.3 mmol, 78%). R_f : 0.56 (cyclohexane/EtOAc = 2:1, dinitrophenyl hydrazine reagent, UV). Mp: 103.0–107.0 °C (chloroform). 1H NMR (300 MHz, $CDCl_3$): δ [ppm] = 9.84 (s, 1H, CHO), 8.33 (d, J = 2.0 Hz, 1H, H-2), 7.88 (dd, J = 8.5, 2.0 Hz, 1H, H-6), 6.95 (d, J = 8.5 Hz, 1H, H-5), 4.00 (s, 3H, OCH_3). The analytical data are in accordance with the literature.⁴³

4-(Benzyloxy)-3-iodobenzaldehyde (16). Step 1: 3-Iodo-4-methoxybenzaldehyde (4.00 g, 15.3 mmol, 1.0 equiv) is dissolved in anhydrous dichloromethane (50 mL), and boron tribromide (4.29 mL, 45.3 mmol, 11.4 g, 3.0 equiv) is added dropwise at –78 °C. The reaction mixture is stirred for 12 h, and it is slowly warmed to room temperature within this time interval. To the reaction mixture is added water (50 mL), and it is extracted with dichloromethane (3 \times 50 mL). The combined organic phases are washed with brine (75 mL) and dried over Na_2SO_4 . After filtration, the solvent is removed in vacuo, and the obtained crude 4-hydroxy-3-iodobenzaldehyde (5.15 g) is directly used for the next step. Mp: 110.0–111.0 °C (dichloromethane). (Lit: 108–110 °C).⁴⁴ R_f : 0.37 (cyclohexane/EtOAc = 6:1, dinitrophenyl hydrazine reagent, UV). 1H NMR (300 MHz, $CDCl_3$): δ [ppm] = 9.80 (s, 1H, CHO), 8.22 (d, J = 2.0 Hz, 1H, H-2), 7.79 (dd, J = 8.4, 2.0 Hz, 1H, H-6), 7.10 (d, J = 8.4 Hz, 1H, H-5), 6.23 (s, br, 1H, OH). MS (ESI): m/z (%) = 248.9 (86) $[M + H]^+$. The analytical data are in accordance with the literature.⁴⁴

Step 2: Crude 4-hydroxy-3-iodobenzaldehyde (5.15 g, max. 15.3 mmol, 1.0 equiv) is dissolved in EtOH (30 mL), and potassium carbonate (4.30 g, 31.1 mmol, 2.0 equiv) and benzyl bromide (3.20 mL, 4.61 g, 26.9 mmol, 1.8 equiv) are added at room temperature. The reaction mixture is stirred for 5 h at 60 °C. After complete reaction, the reaction mixture is cooled to room temperature, water is added (50 mL), and it is extracted with diethyl ether (3 \times 100 mL). The combined organic phases are dried over Na_2SO_4 and filtered. The solvent is removed in vacuo, and the residue is purified by flash column chromatography on silica gel (cyclohexane/EtOAc = 10:1). The product **16** is obtained as an off-white crystalline solid (3.98 g, 11.8 mmol, 77% over 2 steps). R_f : 0.40 (cyclohexane/EtOAc = 5:1,

dinitrophenyl hydrazine reagent, UV). Mp: 65.4–68.6 °C (cyclohexane/EtOAc). ^1H NMR (300 MHz, CDCl_3): δ [ppm] = 9.81 (s, 1H, CHO), 8.33 (d, J = 2.0 Hz, 1H, H-2), 7.81 (dd, J = 8.5, 2.0 Hz, 1H, H-6), 7.51–7.48 (m, 2H, H-2-Ph, H-6-Ph), 7.44–7.35 (m, 3H, H-4-Ph, H-3-Ph, H-5-Ph), 6.95 (d, J = 8.5 Hz, 1H, H-5), 5.25 (s, 2H, CH_2 -Ph). ^{13}C NMR, HSQC, HMBC (75.5 MHz, CDCl_3): δ [ppm] = 189.5 (CHO), 161.9 (C-4), 141.3 (C-2), 135.6 (C-1-Ph), 132.0 (C-6), 131.6 (C-1), 128.9 (C-2-Ph, C-6-Ph), 128.4 (C-4-Ph), 127.1 (C-3-Ph, C-5-Ph), 112.1 (C-5), 87.2 (C-3), 71.3 (CH_2 -Ph). IR (ATR): ν = 3089 (w), 3063 (w), 3032 (w), 2929 (w), 2834 (w), 2810 (w), 2778 (w), 2727 (w), 1690 (vs), 1586 (vs), 1564 (s), 1485 (s), 1453 (s), 1369 (m), 1258 (vs), 1191 (vs), 1039 (m), 1013 (m), 890 (m), 812 (m), 736 (m), 696 (m) cm^{-1} . HRMS (ESI): m/z calcd for $\text{C}_{14}\text{H}_{11}\text{IO}_2\text{Na}$ [$\text{M} + \text{Na}$] $^+$: 360.9702, found: 360.9690.

[4-(Benzyloxy)-3-iodophenyl]methanol. Synthesized according to the procedure described for compound 13. Aldehyde 16 (1.98 g, 5.86 mmol, 1.0 equiv) is reacted with sodium borohydride (0.33 g, 8.79 mmol, 1.5 equiv) in EtOH (100 mL). The title compound is obtained as an off-white crystalline solid (1.94 g, 5.70 mmol, 97%). R_f : 0.15 (cyclohexane/EtOAc = 5:1, Seebach reagent, UV). Mp: 95.0–98.4 °C (Et_2O). ^1H NMR (400 MHz, CDCl_3): δ [ppm] = 7.81 (d, J = 2.1 Hz, 1H, H-2), 7.51–7.48 (m, 2H, H-2-Ph, H-6-Ph), 7.42–7.32 (m, 3H, H-3-Ph, H-4-Ph, H-5-Ph), 7.26 (dd, J = 8.3, 2.1 Hz, 1H, H-6), 6.83 (d, J = 8.3 Hz, 1H, H-5), 5.15 (s, 2H, CH_2 -Ph), 4.58 (s, 2H, CH_2OH), 1.78 (s, br, 1H, OH). ^{13}C NMR, HSQC, HMBC (100.6 MHz, CDCl_3): δ [ppm] = 156.8 (C-4), 138.5 (C-2), 136.5 (C-1-Ph), 135.5 (C-1), 128.7 (C-3-Ph, C-5-Ph), 128.5 (C-6), 128.0 (C-4-Ph), 127.1 (C-2-Ph, C-6-Ph), 112.7 (C-5), 87.0 (C-3), 71.1 (CH_2 -Ph), 64.2 (CH_2OH). IR (ATR): ν = 3332 (w, br), 3031 (w), 2925 (w), 1598 (m), 1488 (vs), 1453 (s), 1278 (s), 1252 (vs), 1044 (s), 1012 (s), 809 (s), 734 (s) cm^{-1} . MS (FD): m/z (%) = 340.2 [M^{+}]. MS (LIFDI-FD): m/z = 340.0 [M^{+}]. HRMS data could not be obtained due to poor ionization in ESI.

1-(Benzyloxy)-4-(bromomethyl)-2-iodobenzene (6b). Synthesized according to the procedure described for compound 6a. [4-(Benzyloxy)-3-iodophenyl]methanol (1.27 g, 3.73 mmol, 1.0 equiv) is reacted with phosphorus tribromide (1.00 g, 3.73 mmol, 1.0 equiv). The product is obtained as a yellow viscous oil (1.16 g, 2.87 mmol, 78%). The product 6b is sufficiently pure and can be used without further purification. R_f : 0.59 (cyclohexane/EtOAc = 5:1, Seebach reagent, UV). ^1H NMR (300 MHz, CDCl_3): δ [ppm] = 7.84 (d, J = 2.2 Hz, 1H, H-2), 7.50–7.47 (m, 2H, H-2-Ph, H-6-Ph), 7.43–7.34 (m, 3H, H-3-Ph, H-4-Ph, H-5-Ph), 7.30 (dd, J = 8.4, 2.2 Hz, 1H, H-6), 6.80 (d, J = 8.4 Hz, 1H, H-5), 5.16 (s, 2H, CH_2 -Ph), 4.42 (s, 2H, CH_2Br). ^{13}C NMR, HSQC, HMBC (75.5 MHz, CDCl_3): δ [ppm] = 157.4 (C-4), 140.3 (C-2), 136.3 (C-1-Ph), 132.3 (C-1), 130.4 (C-6), 128.8 (C-3-Ph, C-5-Ph), 128.1 (C-4-Ph), 127.1 (C-2-Ph, C-6-Ph), 112.1 (H-5), 86.9 (C-3), 71.1 (CH_2 -Ph), 32.4 (CH_2Br). IR (ATR): ν = 3061 (w), 2921 (w), 1571 (m), 1467 (vs), 1251 (s), 1182 (s), 1044 (m), 1030 (m), 783 (m), 754 (m) cm^{-1} . MS (LIFDI): m/z (%) = 401.9 [M^{+}]. HRMS data could not be obtained due to decomposition of the sample in aqueous acetonitrile.

7-(Benzyloxy)-6-methoxy-2-methyl-1-(4-[[tri(propan-2-yl)silyl]oxy]benzyl)-1,2,3,4-tetrahydroisoquinoline (4a). According to a modified synthetic procedure of Werner et al.¹⁰ α -Aminonitrile 5a (1.51 g, 4.88 mmol, 1.0 equiv) is reacted with KHMDS (1.25 g, 6.26 mmol, 1.3 equiv), benzylic bromide 6a (2.18 g, 6.35 mmol, 1.3 equiv), and sodium borohydride (1.00 g, 26.5 mmol, 5.4 equiv). The brown oily residue is purified by flash column chromatography on silica gel (cyclohexane/EtOAc/ NEt_3 = 6:2:1). The product 4a is obtained as light yellow oil (2.05 g, 3.76 mmol, 77%). R_f : 0.45 (cyclohexane/EtOAc/ NEt_3 = 6:2:1, Seebach reagent, UV). ^1H NMR, COSY (300 MHz, CDCl_3): δ [ppm] = 7.38–7.26 (m, 5H, Ph), 6.89–6.86 (AA' part of an AA'XX' system, 2H, H-2', H-6'), 6.78–6.75 (XX' part of an AA'XX' system, 2H, H-3', H-5'), 6.56 (s, 1H, H-5), 6.12 (s, 1H, H-8), 4.87–4.76 (m, 2H, CH_2 -Ph), 3.83 (s, 3H, OCH_3), 3.61 (dd, J = 7.5, 4.6 Hz, 1H, H-1), 3.16–3.02 (m, 2H, H-3_A, H- α), 2.79–2.55 (m, 4H, H-3_B, H- α _B, H-4), 2.51 (s, 3H, NCH_3), 1.29–1.19 (m, 3H, CH), 1.09–1.03 (m, 18H, CH_3). ^{13}C NMR, HSQC, HMBC (75.5 MHz, CDCl_3): δ [ppm] = 154.3 (C-4'), 147.8 (C-6), 145.5 (C-7), 137.3 (C-

1-Ph), 132.3 (C-1'), 130.7 (C-2', C-6'), 129.3 (C-8a), 128.4 (C-3-Ph, C-5-Ph), 127.6 (C-4-Ph), 127.3 (C-2-Ph, C-6-Ph), 126.6 (C-4a), 119.5 (C-3', C-5'), 113.7 (C-8), 111.6 (C-5), 70.8 (CH_2 -Ph), 65.0 (C-1), 55.9 (OCH_3), 47.2 (C-3), 42.7 (NCH_3), 40.4 (C- α), 25.9 (C-4), 18.0 (CH), 12.7 (CH_3). IR (ATR): ν = 3062 (w), 3031 (w), 2943 (m), 2866 (m), 1607 (m), 1508 (vs), (m), 1373 (m), 1258 (vs), 1224 (s), 1101 (m), 1014 (m), 912 (s), 883 (s), 734 (m), 695 (m) cm^{-1} . MS (ESI): m/z (%) = 546.1 (100) [$\text{M} + \text{H}$] $^+$. HRMS (ESI): m/z calcd for $\text{C}_{34}\text{H}_{48}\text{NO}_3\text{Si}$ [$\text{M} + \text{H}$] $^+$: 546.3403, found: 546.3398.

7-(Benzyloxy)-1-[4-(benzyloxy)-3-iodobenzyl]-8-bromo-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (4b). Method A: According to the procedure as described for compound 3a. α -Aminonitrile 5b (156 mg, 0.403 mmol, 1.0 equiv) is reacted with KHMDS (161 mg, 0.807 mmol, 2.0 equiv), benzylic bromide 6b (179 mg, 0.444 mmol, 1.1 equiv), and sodium borohydride (2.00 g, 52.8 mmol, 34.8 equiv). The brown residue is purified by flash column chromatography on silica gel (cyclohexane/EtOAc/ NEt_3 = 6:4:1). The product 4b is obtained as brown oil in a yield of 69.0 mg (0.101 mmol, 25%). R_f : 0.59 (cyclohexane/EtOAc/ NEt_3 = 6:4:1, Seebach reagent, UV).

Method B: Formamide 21 (4.77 g crude product, max. 6.61 mmol, 1.0 equiv) is dissolved in anhydrous THF (75 mL), and borane–THF complex (1M, 9.92 mL, 9.92 mmol, 1.5 equiv) is added at room temperature, and the reaction mixture is stirred for 12 h at this temperature. Water (50 mL) is added to the reaction mixture, and the mixture is extracted with EtOAc (4 \times 70 mL). The combined organic phases are dried over Na_2SO_4 , and the solvent is removed in vacuo. The residue is purified by flash column chromatography on silica gel (cyclohexane/EtOAc/ NEt_3 = 6:4:1). The product 4b is obtained as colorless oil (3.04 g, 4.44 mmol, 67% over 4 steps). R_f : 0.59 (cyclohexane/EtOAc/ NEt_3 = 6:4:1, Seebach reagent, UV). ^1H NMR, COSY (400 MHz, CDCl_3): δ [ppm] = 7.74 (d, J = 2.1 Hz, 1H, H-2'), 7.62–7.59 (m, 2H, H-2-Ph, H-6-Ph), 7.53–7.50 (m, 2H, H-2-Ph, H-6-Ph), 7.44–7.31 (m, 6H, 2 \times H-3-Ph, 2 \times H-4-Ph, 2 \times H-5-Ph), 7.24 (dd, J = 8.4, 2.1 Hz, 1H, H-6'), 6.79 (d, J = 8.4 Hz, 1H, H-5'), 6.64 (s, 1H, H-5), 5.14 (s, 2H, 4'- OCH_2 -Ph), 5.04 (s, 2H, 7'- OCH_2 -Ph), 3.97 (dd, J = 9.8, 3.0 Hz, 1H, H-1), 3.87 (s, 3H, OCH_3), 3.42–3.32 (m, 1H, H-3_A), 2.93–2.70 (m, 4H, H-3_B, H- α , H-4_A), 2.45–2.40 (m, 1H, H-4_B), 2.36 (s, 3H, NCH_3). ^{13}C NMR, HSQC, HMBC (100.6 MHz, CDCl_3): δ [ppm] = 155.6 (C-4'), 151.9 (C-6), 143.7 (C-7), 140.1 (C-2'), 137.4, 136.9 (2 \times C-1-Ph), 135.4 (C-1'), 132.0 (C-4a), 130.2 (C-6'), 129.5 (C-8a), 128.6 (C-3-Ph, C-5-Ph), 128.5 (C-2-Ph, C-6-Ph), 128.4 (C-3-Ph, C-5-Ph), 128.1, 127.9 (2 \times C-4-Ph), 127.1 (C-2-Ph, C-6-Ph), 120.2 (C-8), 112.4 (C-5'), 112.1 (C-5), 86.6 (C-3'), 74.7 (7'- OCH_2 -Ph), 71.0 (4'- OCH_2 -Ph), 64.2 (C-1), 56.2 (OCH_3), 44.3 (C-3), 42.6 (NCH_3), 38.4 (C- α), 23.4 (C-4). IR (ATR): ν = 3088 (w), 3063 (w), 3031 (w), 2938 (m), 2876 (w), 2772 (w), 2381 (m), 2327 (m), 2278 (m), 1595 (m), 1481 (s), 1463 (s), 1453 (s), 1376 (m), 1314 (s), 1256 (s), 1169 (m), 1103 (s), 1025 (m), 847 (m), 735 (s), 697 (s) cm^{-1} . HPLC-MS (ESI): m/z (%) = 686.0 (100) [$\text{M} + \text{H}$] $^+$. HRMS (ESI): m/z calcd for $\text{C}_{32}\text{H}_{32}\text{BrINO}_3$ [$\text{M} + \text{H}$] $^+$: 684.0610 found: 684.0602.

(4-Hydroxy-3-iodophenyl)acetic Acid. 2-(4-Hydroxyphenyl)-acetic acid (17) (5.00 g, 32.9 mmol, 1.0 equiv) is dissolved in dichloromethane (100 mL), and iodine monochloride (5.34 g, 32.9 mmol, 1.0 equiv) and acetic acid (0.10 mL, 1.64 mmol, 0.05 equiv) are added. The reaction mixture is stirred for 50 h at room temperature. After complete conversion, water (100 mL) is added, and the mixture is extracted with ethyl acetate (3 \times 100 mL). The combined organic phases are washed with sat. sodium thiosulfate solution and dried over Na_2SO_4 . After filtration, the solvent is removed in vacuo, and the residue is recrystallized from toluene. The product is obtained as an off-white solid (8.92 g, 32.1 mmol, 98%). R_f : 0.42 (cyclohexane/EtOAc = 1:1, Seebach reagent, UV). Mp: 98.5–100.5 °C (toluene). ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ [ppm] = 12.27 (s, br, 1H, COOH), 10.19 (s, 1H, OH), 7.55 (d, J = 2.1 Hz, 1H, H-2), 7.06 (dd, J = 8.3, 2.1 Hz, 1H, H-6), 6.81 (d, J = 8.3 Hz, 1H, H-5), 3.43 (s, 2H, CH_2). ^{13}C NMR, HSQC, HMBC (75.5 MHz, $\text{DMSO}-d_6$): δ [ppm] = 172.9 (COOH), 155.4 (C-4), 139.4 (C-2), 130.6 (C-6), 127.6 (C-1), 114.7 (C-5), 84.2 (C-3), 39.1 (CH_2). IR (ATR): ν = 2967 (w), 2940

(w), 2876 (w), 2840 (w), 1680 (vs), 1592 (vs), 1563 (w), 1490 (w), 1429 (w), 1319 (w), 1305 (w), 1267 (vs), 1185 (w), 1045 (m), 1013 (m), 940 (m), 823 (m), 765 (m), 629 (w) cm^{-1} . HRMS (ESI): m/z calcd for $\text{C}_8\text{H}_7\text{O}_3\text{INa}$ [$\text{M} + \text{Na}$] $^+$: 300.9338, found: 300.9333.

[4-(Benzyloxy)-3-iodophenyl]acetic Acid (18). (4-Hydroxy-3-iodophenyl)acetic acid (10.8 g, 38.8 mmol, 1.0 equiv) is dissolved in EtOH (200 mL), and potassium carbonate (16.1 g, 117 mmol, 3.0 equiv) is added. At room temperature, benzyl bromide (5.52 mL, 46.6 mmol, 1.2 equiv) is added dropwise. The reaction mixture is heated to 55 °C for 5 h. After complete conversion, ethanol is removed in vacuo, and to the residue water (80 mL) is added. The pH of the mixture is adjusted to pH \approx 2 with 1 M hydrochloric acid, and it is extracted with diethyl ether (3 \times 150 mL). The combined organic phases are washed with sat. ammonium chloride solution (100 mL) and dried over Na_2SO_4 . After filtration, the solvent is removed in vacuo, and the residue is purified by flash column chromatography (cyclohexane/EtOAc = 10:1). The product **18** is obtained as an off-white crystalline solid (7.80 g, 21.2 mmol, 55%). R_f : 0.34 (cyclohexane/EtOAc/HOAc = 2:1; Seebach reagent, UV). Mp: 103.4–107.6 °C (cyclohexane/EtOAc). ^1H NMR, COSY (300 MHz, CDCl_3): δ [ppm] = 7.73 (d, J = 2.2 Hz, 1H, H-2), 7.51–7.48 (m, 2H, H-2-Ph, H-6-Ph), 7.43–7.32 (m, 3H, H-3-Ph, H-4-Ph, H-5-Ph), 7.19 (dd, J = 8.4, 2.2 Hz, 1H, H-6), 6.81 (d, J = 8.4 Hz, 1H, H-5), 5.14 (s, 2H, CH_2 -Ph), 3.55 (s, 2H, CH_2). ^{13}C NMR, HSQC, HMBC (75.5 MHz, CDCl_3): δ [ppm] = 177.6 (COOH), 156.6 (C-4), 140.3 (C-2), 136.4 (C-1-Ph), 130.4 (C-6), 128.6 (C-3-Ph, C-5-Ph), 127.9 (C-4-Ph), 127.6 (C-1), 127.0 (C-2-Ph, C-6-Ph), 112.5 (C-5), 86.9 (C-3), 70.9 (CH_2 -Ph), 39.5 (CH_2). IR (ATR): ν = 3089 (br), 3063 (w), 3030 (w), 2912 (br, w), 2730 (w), 2661 (w), 2558 (w), 1705 (s), 1599 (w), 1487 (s), 1453 (m), 1404 (m), 1279 (m), 1253 (s), 1231 (s), 1156 (w), 1045 (s), 1022 (w), 932 (w), 794 (w), 735 (s), 635 (s) cm^{-1} . MS (ESI): m/z (%) = 390.9 (100) [$\text{M} + \text{Na}$] $^+$. HRMS (ESI): m/z calcd for $\text{C}_{15}\text{H}_{13}\text{IO}_3\text{Na}$ [$\text{M} + \text{Na}$] $^+$: 390.9807 found: 390.9810.

N-[2-[4-(Benzyloxy)-3-bromo-5-methoxyphenyl]ethyl]-2-[4-(benzyloxy)-3-iodophenyl]acetamide (19). Amine **14** (1.00 g, 2.97 mmol, 1.0 equiv), acid **18** (1.31 g, 3.56 mmol, 1.2 equiv), and DMAP (181 mg, 1.49 mmol, 0.5 equiv) are dissolved in anhydrous dichloromethane (50 mL), and the mixture is cooled to –20 °C. EDC hydrochloride (854 mg, 4.46 mmol, 1.5 equiv) is dissolved in anhydrous dichloromethane (10 mL) and the resulting solution is added dropwise at this temperature. The reaction mixture is stirred at this temperature and is warmed over 12 h to room temperature. Water is added, and the reaction mixture is extracted with dichloromethane. The combined organic phases are dried over Na_2SO_4 , and the solvent is removed in vacuo. The residue is purified by flash column chromatography on silica gel (dichloromethane/MeOH/ NEt_3 = 100:1:1). The product **19** is obtained as colorless solid (1.56 g, 2.27 mmol, 83%). R_f : 0.16 (dichloromethane/MeOH/ NEt_3 = 100:1:1; Seebach reagent, UV). Mp: 159.8–163.0 °C (dichloromethane/MeOH/ NEt_3). ^1H NMR, COSY (300 MHz, $\text{DMSO}-d_6$): δ [ppm] = 8.08 (t, J = 5.6 Hz, 1H, NH), 7.66 (d, J = 2.1 Hz, 1H, H-2'), 7.51–7.46 (m, 4H, 2 \times H-2-Ph, 2 \times H-6-Ph), 7.41–7.29 (m, 6H, 2 \times H-3-Ph, 2 \times H-4-Ph, 2 \times H-5-Ph), 7.15 (dd, J = 8.4, 2.1 Hz, 1H, H-6'), 6.98 (dd, J = 8.4 Hz, 1H, H-5'), 6.97 (d, J = 1.8 Hz, 1H, H-2), 6.90 (d, J = 1.8 Hz, 1H, H-6), 5.15 (s, 2H, 4'- OCH_2 -Ph), 4.91 (s, 2H, 4- OCH_2 -Ph), 3.80 (s, 3H, OCH_3), 3.32–3.25 (m, 4H, $\text{O}=\text{CCH}_2$, NCH_2CH_2), 2.67 (t, J = 7.0 Hz, 2H, NCH_2CH_2). ^{13}C NMR, HSQC, HMBC (75.5 MHz, $\text{DMSO}-d_6$): δ [ppm] = 170.1 (C=O), 155.4 (C-4'), 153.4 (C-5), 142.8 (C-4), 139.3 (C-2'), 137.4 (C-1), 137.1 (C-1-Ph), 136.8 (C-1-Ph), 131.0 (C-1'), 130.1 (C-6'), 128.5, 128.4, 128.3 (2 \times C-3-Ph, 2 \times C-5-Ph, C-2-Ph, C-6-Ph), 128.1, 127.8 (2 \times C-4-Ph), 127.2 (C-2-Ph, C-6-Ph), 124.1 (C-2), 116.7 (C-3), 113.1 (C-6), 112.8 (C-5') 86.6 (C-3'), 74.0 (4- OCH_2 -Ph), 70.1 (4'- OCH_2 -Ph), 56.1 (OCH_3), 40.8 ($\text{O}=\text{CCH}_2$), 40.0 (NCH_2CH_2). IR (ATR): ν = 3302 (s), 3089 (w), 3060 (w), 3034 (w), 2999 (w), 2960 (w), 2933 (w), 2874 (w), 1657 (s), 1566 (m), 1538 (s), 1486 (s), 1451 (s), 1433 (m), 1255 (s), 1226 (s), 1208 (s), 1189 (m), 698 (s), 661 (s) cm^{-1} . HRMS (ESI): m/z calcd for $\text{C}_{31}\text{H}_{29}\text{BrINO}_4\text{Na}$ [$\text{M} + \text{Na}$] $^+$: 708.0222, found: 708.0217.

7-(Benzyloxy)-1-[4-(benzyloxy)-3-iodobenzyl]-8-bromo-6-methoxy-1,2,3,4-tetrahydroisoquinoline. Step 1: According to a modified procedure of Movassaghi and Hill.¹⁴ Amide **19** (2.79 g, 4.07 mmol, 1.0 equiv) is dissolved in anhydrous dichloromethane (60 mL), and 2-chloropyridine (590 μL , 4.30 mmol, 1.1 equiv) dissolved in anhydrous dichloromethane (5.3 mL) is added. The reaction mixture is degassed with argon in an ultra sonicator and is cooled to –78 °C. At this temperature, Ti_2O (885 μL , 1.87 mmol, 0.5 equiv), dissolved in anhydrous dichloromethane (5 mL), is added dropwise. The reaction mixture is stirred for 5–45 min at –78 °C (conversion monitored by TLC, HPLC-MS) and is then cooled to room temperature and stirred for 5–10 min. 1 M NaOH (50 mL) is added, and the organic phase is separated. The solvent is removed in vacuo. The obtained intermediate **20** is sensitive to decomposition and is used in crude form for the next step. R_f : 0.24 (cyclohexane/EtOAc/ NEt_3 = 6:4:1; ninhydrin reagent, UV). HPLC-MS (ESI): m/z (%) = 668.1 (100) [$\text{M} + \text{H}$] $^+$.

Step 2: Imine **20** (max. 4.07 mmol, 1.0 equiv) is dissolved in EtOH (70 mL), and at room temperature, NaBH_4 (231 mg, 6.11 mmol, 1.5 equiv) is added portionwise. The reaction mixture is stirred for 12 h at this temperature. Water (200 mL) is added, and it is extracted with EtOAc (3 \times 100 mL). The combined organic phases are dried over Na_2SO_4 , and the solvent is removed in vacuo. The crude product (3.59 g) is used without purification for the next step. For NMR characterization, a sample of the title compound was purified by flash column chromatography on silica gel (cyclohexane/EtOAc/ NEt_3 = 6:2:1). R_f : 0.55 (cyclohexane/EtOAc/ NEt_3 = 6:4:1; ninhydrin reagent, UV). ^1H NMR, COSY (300 MHz, CDCl_3): δ [ppm] = 7.79 (d, J = 2.1 Hz, 1H, H-2'), 7.61–7.51 (m, 4H, 2 \times H-2-Ph, 2 \times H-6-Ph), 7.44–7.33 (m, 6H, 2 \times H-3-Ph, 2 \times H-4-Ph, 2 \times H-5-Ph), 7.28 (dd, J = 8.4, 2.1 Hz, 1H, H-6'), 6.84 (d, J = 8.4 Hz, 1H, H-5'), 6.67 (s, 1H, H-5), 5.16 (s, 2H, CH_2 -Ph), 5.06–4.99 (m, 2H, CH_2 -Ph), 4.24 (dd, J = 10.9, 2.7 Hz, 1H, H-1), 3.86 (s, 3H, OCH_3), 3.33–2.66 (m, 6H, H-3, H- α , H-4), 1.90 (s, br, 1H, NH). ^{13}C NMR, HSQC, HMBC (75.5 MHz, CDCl_3): δ [ppm] = 156.0 (C-4'), 152.0 (C-6), 143.6 (C-7), 140.0 (C-2'), 137.3, 136.7 (2 \times C-1-Ph), 134.7 (C-1'), 132.2 (C-4a'), 130.8 (C-8a'), 130.2 (C-6'), 128.7, 128.6, 128.4 (2 \times C-3-Ph, 2 \times C-5-Ph, C-2-Ph, C-6-Ph), 128.1, 127.9 (2 \times C-4-Ph), 127.1 (C-2-Ph, C-6-Ph), 119.1 (C-8), 112.9 (C-5'), 112.5 (C-5), 87.2 (C-3'), 74.8 (CH_2 -Ph), 71.0 (CH_2 -Ph), 57.1 (C-1), 56.2 (OCH_3), 36.9 (C-3), 36.7 (C- α), 29.2 (C-4). #signals may be interchanged. IR (ATR): ν = 3011 (w), 2938 (w), 1596 (m), 1480 (s), 1463 (m), 1454 (m), 1314 (m), 1254 (s), 1216 (s), 1103 (s), 1025 (m), 1004 (m), 747 (s) cm^{-1} . HPLC-MS (ESI): m/z = 670.1 [$\text{M} + \text{H}$] $^+$. HRMS (ESI): m/z calcd for: $\text{C}_{31}\text{H}_{30}\text{BrINO}_3$ [$\text{M} + \text{H}$] $^+$: 670.0454 found: 670.0467.

7-(Benzyloxy)-1-[4-(benzyloxy)-3-iodobenzyl]-8-bromo-6-methoxy-3,4-dihydroisoquinolin-2(1H)-carbaldehyde (21). Synthesized according to a modified procedure of Mewald et al.¹⁵ 7-(Benzyloxy)-1-[4-(benzyloxy)-3-iodobenzyl]-8-bromo-6-methoxy-1,2,3,4-tetrahydroisoquinoline (3.59 g, max. 4.07 mmol, 1.0 equiv) is dissolved in formic acid (50 mL), and acetic anhydride (107 mL) is added dropwise at 0 °C. The reaction mixture is stirred for 30 min at 0 °C and is warmed to room temperature. After complete conversion (TLC, HPLC-MS), solid K_2CO_3 is added portionwise at 0 °C until the reaction mixture is adjusted to pH \sim 8. The mixture is extracted with EtOAc (3 \times 100 mL), and the combined organic phases are dried over Na_2SO_4 . The solvent is removed in vacuo. The crude product **21** (3.33 g) is sufficiently pure and can be used without further purification for the next step. R_f : 0.24 (dichloromethane/MeOH = 100:1; ninhydrin reagent, UV). Major rotamer (rotamer ratio 3:1): ^1H NMR, COSY (300 MHz, CDCl_3): δ [ppm] = 7.71 (d, J = 2.1 Hz, 1H, H-2'), 7.66 (s, 1H, CHO), 7.59–7.56 (m, 2H, H-2-Ph, H-6-Ph), 7.52–7.48 (m, 2H, H-2-Ph, H-6-Ph), 7.44–7.31 (m, 6H, 2 \times H-3-Ph, 2 \times H-4-Ph, 2 \times H-5-Ph), 7.08 (dd, J = 8.4, 2.1 Hz, 1H, H-6'), 6.80 (d, J = 8.4 Hz, 1H, H-5'), 6.71 (s, 1H, H-5), 5.13–4.99 (m, 4H, 2 \times CH_2 -Ph), 4.75 (dd, J = 10.7, 2.5 Hz, 1H, H-1), 4.42 (ddd, J = 13.3, 6.8, 3.2 Hz, 1H, H-3 $_{\text{A}}$), 3.88 (s, 3H, OCH_3), 3.64–3.21 (m, 2H, H- α_{A} , H-3 $_{\text{B}}$), 3.01–2.47 (m, 3H, H- α_{B} , H-4). Minor rotamer: ^1H NMR, COSY (300 MHz, CDCl_3): δ [ppm] = 8.05 (s, 1H, CHO), 7.59–7.56 (m, 2H, H-2-Ph, H-6-Ph), 7.52–7.48 (m, 2H, H-2-Ph, H-6-Ph), 7.44–7.31 (m, 7H, H-2', 2 \times H-3-Ph, 2 \times H-4-Ph, 2 \times H-5-Ph), 7.14 (dd, J = 8.4, 2.1 Hz,

1H, H-6'), 6.76 (d, J = 8.4 Hz, 1H, H-5'), 6.62 (s, 1H, H-5), 5.80 (dd, J = 9.1, 3.8 Hz, 1H, H-1), 5.13–4.99 (m, 4H, $2 \times \text{CH}_2\text{-Ph}$), 3.86 (s, 3H, OCH_3), 3.64–3.21 (m, 3H, H- α_A , H-3), 3.01–2.47 (m, 3H, H- α_B , H-4). Major rotamer: ^{13}C NMR, HSQC, HMBC (75.5 MHz, CDCl_3) δ [ppm] = 161.5 (CHO), 156.4 (C-4'), 152.7 (C-6), 144.1 (C-7), 139.8 (C-2'), 137.0, 136.5 ($2 \times \text{C-1-Ph}$), 132.1 (C-1'), 131.3 (C-8a'), 130.3 (C-6'), 128.7 (C-3-Ph, C-5-Ph), 128.6 (C-2-Ph, C-6-Ph), 128.5 (C-3-Ph, C-5-Ph), 128.2, 127.9 ($2 \times \text{C-4-Ph}$), 127.7 (C4a'), 127.1 (C-2-Ph, C-6-Ph), 118.4 (C-8), 112.7 (C-5'), 112.2 (C-5), 87.2 (C-3'), 74.8 ($\text{CH}_2\text{-Ph}$), 71.0 ($\text{CH}_2\text{-Ph}$), 59.5 (C-1), 56.2 (OCH_3), 38.2 (C- α), 33.9 (C-3), 27.7 (C-4). #signals may be reversed. Minor rotamer: ^{13}C NMR, HSQC, HMBC (75.5 MHz, CDCl_3) δ [ppm] = 161.2 (CHO), 156.1 (C-4'), 152.5 (C-6), 144.3 (C-7), 140.2 (C-2'), 137.1, 136.6 ($2 \times \text{C-1-Ph}$), 132.0 (C-1'), 131.4 (C-8a'), 130.4 (C-6'), 128.6 (C-3-Ph, C-5-Ph), 128.5 (C-2-Ph, C-6-Ph), 128.4 (C-3-Ph, C-5-Ph), 128.2, 127.9 ($2 \times \text{C-4-Ph}$), 127.7 (C4a'), 127.0 (C-2-Ph, C-6-Ph), 119.0 (C-8), 112.5 (C-5'), 111.9 (C-5), 86.3 (C-3'), 74.8 ($\text{CH}_2\text{-Ph}$), 70.9 ($\text{CH}_2\text{-Ph}$), 52.3 (C-1), 40.0 (C-3), 37.3 (C- α), 29.3 (C-4). #signals may be reversed. IR (ATR): ν = 3089 (w), 3063 (w), 3031 (w), 3007 (w), 2935 (w), 2871 (w), 2782 (w), 1667 (vs), 1597 (m), 1484 (s), 1453 (m), 1401 (m), 1317 (m), 1236 (s), 1115 (m), 910 (m), 733 (s), 697 (s) cm^{-1} . HPLC-MS (ESI): m/z (%) = 698.1 (72) $[\text{M} + \text{H}]^+$. HRMS (ESI): m/z calcd for: $\text{C}_{32}\text{H}_{29}\text{BrINO}_4\text{Na}$ $[\text{M} + \text{Na}]^+$: 720.0222, found: 720.0220.

6-Methoxy-2-methyl-1-(4-[[tri(propan-2-yl)silyloxy]benzyl]-1,2,3,4-tetrahydroisoquinoline-7-ol (12). 1-Benzyltetrahydroisoquinoline **4a** (100 mg, 0.183 mmol, 1.0 equiv) is dissolved in MeOH (16 mL). Palladium on charcoal (10%, 21.8 mg, 11.0 mol %, 0.1 equiv) and acetic acid (0.5 mL) are added, and the reaction mixture is stirred for 15 h under an atmosphere of hydrogen (1 atm) at room temperature. After complete conversion (TLC), the reaction mixture is filtered over Celite, and the filtrate is evaporated to dryness. The residue is taken up in dichloromethane (30 mL) and washed with sat. sodium hydrogen carbonate solution (15 mL). The organic phase is dried over Na_2SO_4 , and the solvent is removed in vacuo. The product **12** is obtained as a yellow oil (87.7 mg, 0.18 mmol, quant.). R_f : 0.64 (cyclohexane/EtOAc/ NET_3 = 6:4:1, Seebach reagent, UV). ^1H NMR, COSY (400 MHz, CDCl_3): δ [ppm] = 6.96–6.93 (AA' part of an AA'XX' system, 2H, H-2', H-6'), 6.78–6.74 (XX' part of an AA'XX' system, 2H, H-3', H-5'), 6.51 (s, 1H, H-5), 6.33 (s, 1H, H-8), 5.46 (s, br, 1H, OH), 3.83 (s, 3H, OCH_3), 3.65 (t, J = 5.9 Hz, 1H, H-1), 3.15–3.12 (m, 1H, H-3 $_A$), 3.05–3.00 (m, 1H, H- α_A), 2.84–2.68 (m, 3H, H- α_B , H-3 $_B$, H-4 $_A$), 2.56–2.49 (m, 1H, H-4 $_B$), 2.45 (s, 3H, NCH_3), 1.29–1.21 (m, 3H, CH), 1.12–1.06 (m, 18H, CH_3). ^{13}C NMR, HSQC, HMBC (100.6 MHz, CDCl_3): δ [ppm] = 155.2 (C-4'), 145.1 (C-6), 143.4 (C-7), 132.4 (C-1'), 130.5 (C-2', C-6'), 130.3 (C-8a), 125.5 (C-4a), 119.5 (C-3', C-5'), 113.8 (C-8), 110.5 (C-5), 64.8 (C-1), 55.8 (OCH_3), 47.2 (C-3), 42.7 (NCH_3), 40.8 (C- α), 25.6 (C-4), 18.0 (CH), 12.7 (CH_3). IR (ATR): ν = 3186 (w), 2943 (w), 2866 (w), 1606 (w), 1509 (vs), 1463 (s), 1259 (vs), 1215 (m), 1015 (m), 912 (m), 882 (m) cm^{-1} . HR-MS (ESI): m/z calcd for $\text{C}_{27}\text{H}_{42}\text{NO}_3\text{Si}$ $[\text{M} + \text{H}]^+$: 456.2934, found: 456.2936.

4-([7-[2-(benzyloxy)-5-[[7-(benzyloxy)-8-bromo-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl]methyl]phenoxy]-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl]-methyl)phenol (22). Procedure A: Dihalide **4b** (177 mg, 0.259 mmol, 1.0 equiv) and diol **12** (142 mg, 0.311 mmol, 1.2 equiv) are dissolved in anhydrous pyridine (0.75 mL) in a round bottom tube. Molecular sieves 4 Å (150 mg), Cs_2CO_3 (211 mg, 0.648 mmol, 2.5 equiv), and $\text{CuBr}\cdot\text{SMe}_2$ (106 mg, 0.518 mmol, 2.0 equiv) are added under an atmosphere of argon, and the tube is sealed with a septum and PTFE tape. The reaction mixture is stirred for 15 min at room temperature and at 125 °C for 24 h. Stirring was continued for a further 12 h at 130 to 135 °C. The reaction mixture is filtered over Celite, and the filtrate is evaporated to dryness. The residue is purified by flash column chromatography on silica gel (chloroform/MeOH = 12:1). The product is obtained as a brown oil (67.0 mg, 0.0783 mmol, 30%) and contains traces of **23**, **12**, and deiodinated **4b**. HRMS (ESI): m/z calcd for $\text{C}_{50}\text{H}_{52}\text{BrN}_2\text{O}_6$ $[\text{M} + \text{H}]^+$: 855.3009, found: 855.3021. The analytical data are listed after procedure B.

Procedure B: Seco-heterodimer **26** (265 mg, 0.294 mmol, 1.0 equiv) is dissolved in dichloromethane (5 mL), and it is cooled to 0 °C. Trifluoroacetic acid (5 mL) is added dropwise at this temperature over a time interval of 5 h. The reaction mixture is stirred for 12 h at room temperature, and reaction control is performed by HPLC-MS. After complete conversion, sat. sodium hydrogen carbonate solution (20 mL) is added, and the mixture is extracted with dichloromethane (3×25 mL). The combined organic phases are dried over Na_2SO_4 , and the solvent is removed in vacuo. The crude product **22** (248 mg) is obtained as light yellow oil and is sufficiently pure and can be used without further purification for the next step. R_f : 0.23 (dichloromethane/MeOH = 10:1, Seebach reagent, UV). Diastereomeric mixture in a ratio of 1:1. Diastereomer A: ^1H NMR, COSY (600 MHz, CDCl_3): δ [ppm] = 7.57–7.55 (m, 2H, H-2-Ph, H-6-Ph), 7.43–7.23 (m, 7H, Ph, H-10), 7.12–7.06 (m, 2H, Ph), 6.96 (dd, J = 8.3, 2.1 Hz, 1H, H-14), 6.78 (d, J = 8.3 Hz, 1H, H-13), 6.70–6.68 (AA' part of an AA'XX' system, 2H, H-10', H-14'), 6.67 (s, 1H, H-5), 6.66 (s, 1H, H-5'), 6.34–6.31 (XX' part of an AA'XX' system, 2H, H-11', H-13'), 5.52 (s, 1H, H-8'), 5.02–4.80 (m, 4H, $\text{CH}_2\text{-Ph}$), 4.22 (dd, J = 10.8, 2.6 Hz, 1H, H-1), 3.88 (s, 3H, 6- OCH_3), 3.87 (s, 3H, 6'- OCH_3), 3.67–3.61 (m, 1H, H-3 $_A$), 3.47–3.41 (m, 1H, H-1'), 3.29–2.54 (m, 11H, H-3 $_B$, H-3', H-4, H-4', H- α , H- α'), 2.53 (s, 3H, 2'- NCH_3), 2.40 (s, 3H, 2- NCH_3). Diastereomer B: ^1H NMR, COSY (600 MHz, CDCl_3): δ [ppm] = 7.57–7.55 (m, 2H, H-2-Ph, H-6-Ph), 7.43–7.23 (m, 6H, H-Ph), 7.12–7.06 (m, 3H, H-Ph, H-14), 6.89 (d, J = 2.0 Hz, 1H, H-10), 6.84 (d, J = 8.4 Hz, 1H, H-13), 6.70–6.68 (AA' part of an AA'XX' system, 2H, H-10', H-14'), 6.67 (s, 1H, H-5), 6.62 (s, 1H, H-5'), 6.34–6.31 (XX' part of an AA'XX' system, 2H, H-11', H-13'), 5.67 (s, 1H, H-8'), 5.02–4.80 (m, 4H, $\text{CH}_2\text{-Ph}$), 4.31 (dd, J = 10.8, 2.0 Hz, 1H, H-1), 3.88 (s, 3H, 6- OCH_3), 3.81 (s, 3H, 6'- OCH_3), 3.56–3.50 (m, 2H, H-1', H-3 $_A$), 3.29–2.54 (m, 11H, H-3 $_B$, H-3', H-4, H-4', H- α , H- α'), 2.55 (s, 3H, 2'- NCH_3), 2.46 (s, 3H, 2- NCH_3). ^{13}C NMR, HSQC, HMBC (150.9 MHz, CDCl_3): δ [ppm] = 155.5, 155.1 (C-12, C-12'), 152.3 (C-6, C-6'), 149.4 (C-12), 149.0 (C-12'), 147.9 (C-6'), 147.5 (C-6'), 144.3 (C-7'), 144.1 (C-11'), 144.0 (C-7, C-7'), 143.4 (C-11), 143.3 (C-7'), 137.3 ($2 \times \text{C-1-Ph}$), 132.2 (C-9), 132.0 (C-9'), 130.8, 130.4 (C-10', C-14', C-10'', C-14''), 128.6 (2x, C-Ph), 128.5 (2x, C-Ph), 128.4 (C-Ph), 128.3, 128.2 (2x, C-Ph), 127.9, 127.6 (2x, C-Ph), 127.4, 127.3 (C-14), 127.1 (C-Ph), 126.9 (C-Ph), 123.8 (C-14'), 123.1 (C-10'), 122.8 (C-10), 120.4 (C-8, C-8'), 116.5 (C-8'), 116.4 (C-8'), 115.4, 115.1 (C-11', C-13', C-11'', C-13''), 114.4 (C-13'), 114.3 (C-13), 112.1 (2x), 112.0, 111.9 (C-5, C-5', C-5'', C-5''), 74.8 (7- $\text{OCH}_2\text{-Ph}$, 7'- $\text{OCH}_2\text{-Ph}$), 70.6, 70.5 (12- $\text{OCH}_2\text{-Ph}$, 12'- $\text{OCH}_2\text{-Ph}$), 65.7 (H-1'), 65.3 (H-1''), 64.2 (H-1), 62.1 (H-1'), 56.2 (2x, OCH_3), 56.1 (2x, OCH_3), 46.9 (C-3'), 46.6 (C-3'), 43.4 (C-3), 42.6 (C-3'), 42.4 (2'- NCH_3), 42.1 (2'- NCH_3), 41.7 (2'- NCH_3), 41.3 (2- NCH_3), 40.5 (C- α'), 40.3 (C- α''), 39.5 (C- α), 38.9 (C- α'), 25.6 (C-4'), 25.2 (C-4'), 22.1 (C-4), 21.8 (C-4). The resonances of C-4a, C-4a', C-8a, and C-8a' could not be identified. IR (ATR): ν = 3279 (w, br), 3065 (w), 3031 (w), 2951 (m), 2924 (m), 2855 (m), 1779 (w), 1742 (w), 1674 (m), 1614 (w), 1600 (w), 1515 (s), 1455 (s), 1385 (s), 1324 (w), 1270 (s), 1251 (m), 1196 (vs), 1147 (s), 1073 (w), 1027 (w, br), 838 (m), 800 (w), 722 (w), 699 (w) cm^{-1} . HPLC-MS (ESI): m/z (%) = 429.2 (100) $[\text{M} + 2\text{H}]^{2+}$. HRMS (ESI): m/z calcd for $\text{C}_{50}\text{H}_{52}\text{BrN}_2\text{O}_6$ $[\text{M} + \text{H}]^+$: 855.3009, found: 855.3022.

4-(Methoxymethoxy)benzaldehyde. Synthesized according to a procedure of Kagawa et al.⁴⁵ *p*-Hydroxybenzaldehyde (**10**) (10.0 g, 81.9 mmol, 1.0 equiv) is dissolved in dichloromethane (50 mL), and DIPEA (17.3 mL, 123 mmol, 1.5 equiv) as well as chloro(methoxy)methane (8.1 mL, 0.11 mmol, 1.3 equiv) are added. The reaction mixture is stirred at room temperature until TLC indicates complete conversion (12 h). To the reaction mixture is added water (50 mL), and it is extracted with dichloromethane (3×75 mL). The combined organic phases are dried over Na_2SO_4 and filtered, and the solvent is removed in vacuo. The obtained product is sufficiently pure and can be used without further purification. The title compound is obtained as light yellow oil (12.6 g, 75.9 mmol, 93%). R_f : 0.60 (cyclohexane/EtOAc = 2:1, Seebach reagent, UV). ^1H NMR (300 MHz, CDCl_3): δ [ppm] = 9.87 (s, 1H, CHO), 7.83–7.80 (AA' part of an AA'XX'

system, 2H, H-2, H-6), 7.14–7.11 (XX' part of an AA'XX' system, 2H, H-3, H-5), 5.23 (s, 2H, CH₂), 3.47 (s, 3H, OCH₃). The analytical data are in accordance with the literature.⁴⁶

[4-(Methoxymethoxy)phenyl]methanol (24). Synthesized according to the procedure described for compound 13. 4-(Methoxymethoxy)benzaldehyde (4.8 g, 29 mmol, 1.0 equiv) is reacted with sodium borohydride (1.6 g, 43 mmol, 1.5 equiv) in EtOH (100 mL). The product 24 is obtained as a colorless oil (4.3 g, 26 mmol, 86%). *R*_f: 0.48 (cyclohexane/EtOAc = 2:1, Seebach reagent, UV). ¹H NMR, COSY (300 MHz, CDCl₃): δ [ppm] = 7.27–7.24 (AA' part of an AA'XX' system, 2H, H-2, H-6), 7.02–6.99 (XX' part of an AA'XX' system, 2H, H-3, H-5), 5.15 (s, 2H, CH₂), 4.56 (s, 2H, CH₂OH), 3.46 (s, 3H, OCH₃), 2.35 (s, br, 1H, OH). ¹³C NMR, HSQC, HMBC (75.5 MHz, CDCl₃) δ [ppm] = 156.7 (C-4), 134.5 (C-1), 128.6 (C-2, C-6), 116.4 (C-3, C-5), 94.5 (CH₂), 64.8 (CH₂OH), 56.0 (OCH₃). The analytical data are in accordance with the literature.⁴⁷

1-(Bromomethyl)-4-(methoxymethoxy)benzene (6c). Synthesized according to a modified procedure of Yamaguchi et al.⁴⁸ Benzylic alcohol 24 (4.00 g, 23.8 mmol, 1.0 equiv) is dissolved in dichloromethane (100 mL), and *N*-bromosuccinimide (6.35 g, 35.7 mmol, 1.5 equiv) and triphenylphosphine (9.36 g, 35.7 mmol, 1.5 equiv) are added at 0 °C. The mixture is slowly warmed to room temperature, and the reaction mixture is stirred for 30 min at this temperature. To the reaction mixture is added brine (50 mL), and the organic phase is dried over Na₂SO₄. The solvent is removed in vacuo, and the residue is purified by flash column chromatography (cyclohexane/EtOAc = 10:1). The product 6c is obtained as a colorless oil (3.90 g, 16.9 mmol, 72%). It has to be noted that the product is unstable and should be freshly prepared for subsequent transformations. *R*_f: 0.68 (cyclohexane/EtOAc = 14:1, Seebach reagent, UV). ¹H NMR, COSY (300 MHz, CDCl₃): δ [ppm] = 7.34–7.31 (AA' part of an AA'XX' system, 2H, H-2, H-6), 7.02–6.99 (XX' part of an AA'XX' system, 2H, H-3, H-5), 5.18 (s, 2H, CH₂), 4.50 (s, 2H, CH₂Br), 3.48 (s, 3H, OCH₃). ¹³C NMR, HSQC, HMBC (75.5 MHz, CDCl₃) δ [ppm] = 157.4 (C-4), 131.3 (C-1), 130.5 (C-2, C-6), 116.6 (C-3, C-5), 94.4 (CH₂), 56.2 (OCH₃), 38.8 (CH₂Br). IR (ATR): ν = 2996 (w), 2899 (w), 1610 (m), 1510 (s), 1228 (s), 1199 (s), 1150 (vs), 1077 (s), 991 (vs), 921 (s), 832 (s) cm⁻¹. The analytical data are in accordance with the literature.⁴⁷

7-(Benzyloxy)-6-methoxy-1-[4-(methoxymethoxy)benzyl]-2-methyl-1,2,3,4-tetrahydroisoquinoline (4c). Synthesized according to the procedure described for compound 4a. α-Aminonitrile 5a (242 mg, 0.785 mmol, 1.0 equiv) is dissolved in anhydrous THF (2 mL), and the solution is cooled to –65 °C. KHMDS (313 mg, 15.7 mmol, 2.0 equiv), dissolved in anhydrous THF (1.5 mL), is added dropwise at this temperature, and the mixture is stirred for 5 min. Benzylic bromide 6c (200 mg, 0.864 mmol, 1.1 equiv) is added dropwise at –65 °C, and the reaction mixture is stirred for further 35 min at this temperature. NaBH₄ (0.5 g, 52.8 mmol, 5.0 equiv) and MeOH (1 mL) are added, and the reaction mixture is warmed to room temperature and stirred 3 h at this temperature. Sat. NaHCO₃ solution (20 mL) is added, and it is extracted with dichloromethane (3 × 75 mL). The combined organic phases are dried over Na₂SO₄, and the solvent is removed in vacuo. The residue is purified by flash column chromatography on silica gel (cyclohexane/EtOAc/NEt₃ = 6:4:1). The product 4c is obtained as yellow oil (240 mg, 0.554 mmol, 70%). *R*_f: 0.44 (cyclohexane/EtOAc/NEt₃ = 6:4:1, Seebach reagent, UV). ¹H NMR, COSY (400 MHz, CDCl₃): δ [ppm] = 7.33–7.25 (m, 5H, H-2-Ph, H-3-Ph, H-4-Ph, H-5-Ph, H-6-Ph), 6.98–6.91 (AA'XX' system, 4H, H-2', H-3', H-5', H-6'), 6.57 (s, 1H, H-5), 6.09 (s, 1H, H-8), 5.13 (s, 2H, CH₂), 4.89–4.75 (m, 2H, CH₂-Ph), 3.84 (s, 3H, OCH₃), 3.60 (dd, *J* = 7.4, 5.3 Hz, 1H, H-1), 3.43 (s, 3H, CH₂OCH₃), 3.19–3.03 (m, 2H, H-α_A, H-3_A), 2.86–2.57 (m, 4H, H-α_B, H-3_B, H-4), 2.50 (s, 3H, NCH₃). ¹³C NMR, HSQC, HMBC (100.6 MHz, CDCl₃): δ [ppm] = 155.7 (C-4'), 148.0 (C-6), 145.6 (C-7), 137.5 (C-1-Ph), 133.6 (C-1'), 130.9 (C-2', C-6'), 129.4 (C-8a), 128.5 (C-3-Ph, C-5-Ph), 127.8 (C-4-Ph), 127.4 (C-2-Ph, C-6-Ph), 126.7 (C-4a), 116.1 (C-3', C-5'), 113.9 (C-8), 111.8 (C-5), 94.7 (CH₂), 70.9 (CH₂-Ph), 64.9 (C-1), 56.0, 56.0 (2 × OCH₃), 47.1 (C-3), 42.8 (NCH₃), 40.3 (C-α), 25.8 (C-4). IR

(ATR): ν = 3062 (w), 3032 (w), 2997 (w), 2933 (w), 2849 (w), 2795 (w), 1606 (m), 1511 (s), 1453 (m), 1374 (m), 1257 (m), 1152 (m), 1078 (m), 1004 (m), 922 (m), 857 (m), 742 (m), 698 (m) cm⁻¹. HPLC-MS (ESI): *m/z* (%) = 434.2 (100) [M + H]⁺. HRMS (ESI): *m/z* calcd for C₂₇H₃₃NO₄ [M + H]⁺: 434.2331, found: 434.2337.

6-Methoxy-1-[4-(methoxymethoxy)benzyl]-2-methyl-1,2,3,4-tetrahydroisoquinoline-7-ol (25). Substrate 4c (99.0 mg, 0.228 mmol, 1.0 equiv) is dissolved in EtOH (10 mL), and palladium on charcoal (22 mg, 10%, 0.023 mmol, 0.1 equiv) is added under an atmosphere of argon. The reaction mixture is stirred for 12 h under an atmosphere of hydrogen (1 atm) at room temperature. The reaction mixture is filtered over Celite, and the filtrate is evaporated to dryness. The product 25 is obtained as yellow oil (78.4 mg, 0.23 mmol, quant.). It has to be noted that the product should be used directly in the next step or should be stored under inert atmosphere at –27 °C. *R*_f: 0.41 (cyclohexane/EtOAc/NEt₃ = 6:4:1, Seebach reagent, UV). ¹H NMR, COSY (400 MHz, CDCl₃): δ [ppm] = 7.04–7.02 (AA' part of an AA'XX' system, 2H, H-2', H-6'), 6.92–6.90 (XX' part of an AA'XX' system, 2H, H-3', H-5'), 6.53 (s, 1H, H-5), 6.37 (s, 1H, H-8), 5.14 (s, 2H, CH₂), 3.83 (s, 3H, OCH₃), 3.68 (t, *J* = 6.1 Hz, 1H, H-1), 3.47 (s, 3H, CH₂OCH₃), 3.21–3.08 (m, 2H, H-α_A, H-3_A), 2.86–2.72 (m, 3H, H-3_B, H-α_B, H-4_A), 2.59–2.53 (1H, H-4_B), 2.46 (s, 3H, NCH₃). ¹³C NMR, HSQC, HMBC (100.6 MHz, CDCl₃): δ [ppm] = 155.6 (C-4'), 145.4 (C-7), 143.6 (C-6), 133.3 (C-1'), 130.5 (C-2', C-6'), 129.9 (C-8a), 125.3 (C-4a), 116.1 (C-3', C-5'), 113.9 (C-8), 110.7 (C-5), 94.7 (CH₂), 64.7 (C-1), 56.0 (CH₂OCH₃), 55.9 (OCH₃), 46.9 (C-3), 42.5 (NCH₃), 40.8 (C-α), 25.1 (C-4). IR (ATR): ν = 3364 (vw), 3121 (w), 3063 (w), 2930 (w), 2849 (8w), 2790 (w), 1609 (m), 1510 (vs), 1464 (m), 1445 (m), 1372 (m), 1231 (s), 1199 (s), 1151 (s), 1077 (s), 999 (s), 920 (s), 833 (s), 731 (s) cm⁻¹. MS (ESI): *m/z* (%) = 344.2 (100) [M + H]⁺. HRMS (ESI): *m/z* calcd for C₂₀H₂₆NO₄ [M + H]⁺: 344.1862, found: 344.1871.

7-(Benzyloxy)-1-[4-(benzyloxy)-3-((6-methoxy-1-[4-(methoxymethoxy)benzyl]-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)oxy)benzyl]-8-bromo-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (26). Dihalide 4b (678 mg, 0.991 mmol, 1.5 equiv) and diol 25 (227 mg, 0.661 mmol, 1.0 equiv) are dissolved in anhydrous pyridine (1.5 mL) in a round bottom tube. Molecular sieves 4 Å (150 mg), cesium carbonate (579 mg, 1.78 mmol, 2.7 equiv), and CuBr·SMe₂ (146 mg, 0.727 mmol, 1.1 equiv) are added under argon atmosphere, and the reaction tube is closed with a septum and sealed with PTFE tape. The reaction mixture is stirred for 15 min at room temperature and is then stirred for 3 to 7 days at 125 °C (reaction control by HPLC-MS). The reaction mixture is filtered over Celite, and the filtrate is evaporated to dryness. The residue is purified by flash column chromatography (cyclohexane/ethyl acetate/NEt₃ or chloroform/MeOH = 12:1). The product 26 is obtained as light brown oil (315 mg, 0.350 mmol, 53%). *R*_f: 0.29 (cyclohexane/EtOAc/NEt₃ = 6:4:1, Seebach reagent, UV). Diastereomeric mixture in a ratio of 1:1. Diastereomer A: ¹H NMR, COSY (600 MHz, CDCl₃): δ [ppm] = 7.57–7.56 (m, 2H, Ar–H), 7.40–7.25 (m, 8H, Ar–H), 6.99–6.98 (m, 1H, H-10), 6.95–6.93 (m, overlapped with AA' part of an AA'XX' system, 3H, H-14, H-10', H-14'), 6.87 (dd, *J* = 8.2, 2.5 Hz, 1H, H-13), 6.81–6.78 (XX' part of an AA'XX' system, 2H, H-11', H-13'), 6.65 (s, 1H, H-5'), 6.61 (s, 1H, H-5), 6.45 (s, 1H, H-8'), 5.09–4.97 (m, 6H, CH₂OCH₃, 12'-OCH₂-Ph, 12-OCH₂-Ph), 3.92 (d, *J* = 9.7 Hz, 1H, H-1), 3.84 (s, 3H, OCH₃), 3.82 (s, 3H, OCH₃), 3.63 (t, *J* = 5.7 Hz, 1H, H-1'), 3.42 (s, 3H, CH₂OCH₃), 3.36–3.31 (m, 1H, H-3_A), 3.17–3.13 (m, 1H, H-3_A'), 2.96–2.70 (m, 8H, H-4_A, H-4_A', H-α', H-3_B, H-3_B'), 2.62–2.57 (m, 1H, H-4_B'), 2.45 (m, 4H, H-4_B, 2'-NCH₃), 2.29 (s, 3H, 2-NCH₃). Diastereomer B*: ¹H NMR, COSY (600 MHz, CDCl₃): δ [ppm] = 7.57–7.56 (m, 2H, Ar–H), 7.40–7.25 (m, 8H, Ar–H), 6.99–6.98 (m, 1H, H-10), 6.95–6.93 (m, overlapped with AA' part of an AA'XX' system, 3H, H-14, H-10', H-14'), 6.87 (dd, *J* = 8.2, 2.5 Hz, 1H, H-13), 6.81–6.78 (XX' part of an AA'XX' system, 2H, H-11', H-13'), 6.65 (s, 1H, H-5'), 6.61 (s, 1H, H-5), 6.45 (s, 1H, H-8'), 5.09–4.97 (m, 6H, CH₂OCH₃, 12'-OCH₂-Ph, 12-OCH₂-Ph), 3.92 (d, *J* = 9.7 Hz, 1H, H-1), 3.84 (s, 3H, OCH₃), 3.82 (s, 3H, OCH₃), 3.63 (t, *J* = 5.7 Hz, 1H, H-1'), 3.42 (s, 3H, CH₂OCH₃), 3.36–3.31 (m, 1H, H-3_A), 3.17–3.13 (m, 1H, H-3_A'), 2.96–2.70 (m,

8H, H-4_A, H-4_{A'}, H-α, H-α', H-3_B, H-3_{B'}), 2.62–2.57 (m, 1H, H-4_{B'}), 2.45 (m, 4H, H-4_B, 2'-NCH₃), 2.29 (s, 3H, 2-NCH₃). ¹³C NMR, HSQC, HMBC (150.9 MHz, CDCl₃): δ [ppm] = 155.4 (C-12'), 155.4 (C-12*), 151.8 (C-6, C-6*), 148.7, 148.6 (C-6', C-6'*), 147.8 (C-12, C-12*), 146.1, 146.0 (C-11, C-11*), 144.8, 144.7 (C-7', C-7'*), 143.6, 143.6 (C-7, C-7*), 137.6 (C-1-Ph, C-1-Ph*), 137.4 (C-1-Ph, C-1-Ph*), 134.4 (C-9, C-9*), 133.3, 133.2 (C-9', C-9'*), 131.9, 131.8 (C-8_A, C-8_{A'}), 130.4 (C-10', C-10'*), C-14', C-14'*), 130.0 (C-8_A, C-8_{A'}), 129.9 (C-4_A, C-4_{A'}), 129.3 (C-4_{A'}, C-4_{A'}), 128.5, 128.4, 128.3, 128.1, 127.6, 127.2 (2 × C-2-Ph, 2 × C-3-Ph, 2 × C-4-Ph, 2 × C-5-Ph, 2 × C-6-Ph, 2 × C-2-Ph*, 2 × C-3-Ph*, 2 × C-4-Ph*, 2 × C-5-Ph*, 2 × C-6-Ph*), 124.4, 124.3 (C-14, C-14*), 120.9, 120.8 (C-10, C-10*), 120.2 (C-8, C-8*), 117.6, 117.4 (C-8', C-8'*), 115.9 (C-11', C-11*), C-13', C-13*), 115.0 (C-13, C-13*), 112.4 (C-5', C-5'*), 112.0 (C-5, C-5*), 94.6 (CH₂, CH₂*), 74.7 (CH₂-Ph, CH₂-Ph*), 71.1, 71.0 (CH₂-Ph, CH₂-Ph*), 64.5, 64.4 (C-1, C-1*, C-1', C-1'*), 56.1 (4 × OCH₃), 56.0 (CH₂OCH₃, CH₂OCH₃*), 47.4 (C-3', C-3'*), 44.2, 44.1 (C-3, C-3*), 42.8 (2 × NCH₃), 42.6 (2 × NCH₃), 40.7 (2 × C-α', C-α'*), 39.0 (C-α, C-α*), 25.6 (C-4', C-4'*), 23.5, 23.4 (C-4, C-4*). IR (ATR): ν = 3088 (w), 3063 (w), 3032 (w), 2933 (m), 2849 (w), 2795 (w), 1610 (w), 1508 (vs), 1479 (m), 1463 (m), 1454 (m), 1444 (m), 1373 (m), 1315 (m), 1259 (s), 1226 (s), 1198 (s), 1151 (s), 1124 (s), 1103 (s), 1078 (s), 1005 (vs), 911 (s), 844 (w), 817 (w), 800 (w), 731 (vs), 697 (s) cm⁻¹. HPLC-MS (ESI): *m/z* (%) = 451.2 (100) [M + 2H]²⁺, 474.3 [M + 2Na]²⁺. HRMS (ESI): *m/z* calcd for C₅₂H₅₆BrN₂O₇ [M + H]⁺: 899.3271, found: 899.3265.

(±)-Tubocurine ((±)-2) and (±)-Curine ((±)-3). Step 1: Seco-heterodimer **22** (248 mg, 0.290 mmol, 1.0 equiv), molecular sieves 4 Å (150 mg), cesium carbonate (252 mg, 0.783 mmol, 2.7 equiv), and CuBr·SMe₂ (63.5 mg, 0.319 mmol, 1.1 equiv) are placed in a round bottom tube under argon atmosphere. The tube is closed with a septum, and anhydrous pyridine is added (0.75 mL). The reaction tube is sealed with PTFE tape, and the reaction mixture is stirred for 15 min at room temperature and is then stirred for 10 days at 125–130 °C. Reaction control is performed by HPLC-MS. After 10 days, additional CuBr·SMe₂ (115 mg, 0.58 mmol, 2.0 equiv) in anhydrous pyridine (0.5 mL) is added to the reaction mixture, and it is stirred for 2 days. The reaction mixture is filtered over Celite, and the filtrate is partitioned between dichloromethane (50 mL) and sat. sodium hydrogen carbonate solution (30 mL). It is extracted with dichloromethane (3 × 50 mL), and the combined organic phases are dried over Na₂SO₄. The solvent is removed in vacuo, and the residue is purified by flash column chromatography on silica gel (cyclohexane/EtOAc/NEt₃ = 6:4:1). The product **23** is obtained as light yellow oil (30.2 mg, 39.0 μmol, 17% over 2 steps). *R*_f: 0.29 (cyclohexane/EtOAc/NEt₃ = 6:4:1, Seebach reagent, UV). Diastereomeric mixture in a ratio of ~1:1.8. IR (ATR): ν = 3062 (w), 2933 (w), 2840 (w), 1606 (m), 1506 (vs), 1463 (m), 1454 (m), 1447 (m), 1266 (s), 1218 (s), 1122 (s), 1115 (s), 1024 (m), 911 (m), 733 (s) cm⁻¹. ESI-MS (ESI): *m/z* (%) = 388.5 (100) [M + H]⁺. HPLC-MS (ESI): *m/z* (%) = 388.4 (100) [M + 2H]²⁺. HRMS (ESI): *m/z* calcd for C₅₀H₅₁N₂O₆ [M + H]⁺: 775.3747, found: 775.3751.

Step 2: Compound **23** (11.3 mg, 14.6 μmol, 1.0 equiv) is dissolved in anhydrous dichloromethane (1 mL), and the solution is cooled to -19 °C. Boron trichloride (1 M in *n*-hexane, 73 μL, 72.9 μmol, 5.0 equiv) is added dropwise, and the mixture is stirred for 1 h at this temperature. Reaction control is performed by HPLC-MS. Additional boron trichloride (1 M in *n*-hexane, 75 μL, 4.2 equiv) is added dropwise at -19 °C. The reaction mixture is stirred for 1 h at this temperature, and after complete conversion (HPLC-MS), it is warmed to room temperature. Aqueous ammonia solution (15 mL, 27% in H₂O) is added to adjust the reaction mixture to pH ~ 8–9, and it is extracted with dichloromethane (3 × 25 mL). The combined organic phases are dried over Na₂SO₄, and the solvent is removed in vacuo. The residue is purified by flash column chromatography on silica gel (dichloromethane/MeOH = 10:1). Compounds **(±)-2** and **(±)-3** are obtained as a light yellow solid (6.2 mg, 10.4 μmol, 72%). *R*_f: 0.23 (chloroform/MeOH = 7:1, Seebach reagent, UV). Diastereomeric mixture in a ratio of 1:2. Major diastereomer: ¹H NMR, COSY (600 MHz, CDCl₃): δ [ppm] = 7.16–7.13 (m, 1H, H-14'), 6.94 (dd, *J* =

8.2, 2.0 Hz, 1H, H-14), 6.83 (d, *J* = 8.2 Hz, 1H, H-13), 6.70–6.67 (m, 4H, H-10, H-5', H-13', H-11'), 6.56 (s, 1H, H-5), 6.50–6.48 (m, 1H, H-10'), 5.95 (s, 1H, H-8'), 3.92 (s, 6H, OCH₃), 3.56–3.52 (m, 1H, H-1), 3.47 (d, *J* = 9.4 Hz, 1H, H-1'), 3.42–2.52 (m, 11H, H-3, H-3', H-4_A, H-4', H-α, H-α'), 2.55 (s, 3H, NCH₃), 2.45 (dd, *J* = 16.6, 4.3 Hz, 1H, H-4_B), 2.29 (s, 3H, NCH₃). Minor diastereomer*: ¹H NMR, COSY (600 MHz, CDCl₃): δ [ppm] = 7.16–7.13 (m, 1H, H-14'), 6.92 (dd, *J* = 8.4, 2.7 Hz, 1H, H-11'), 6.88–6.86 (m, 1H, H-14), 6.81 (d, *J* = 8.2 Hz, 1H, H-13), 6.77 (dd, *J* = 8.4, 2.8 Hz, 1H, H-13'), 6.64–6.62 (m, 2H, H-5', H-10'), 6.54 (s, 1H, H-5), 6.36 (d, *J* = 1.8 Hz, 1H, H-10), 5.93 (s, 1H, H-8'), 4.00 (d, *J* = 9.6 Hz, 1H, H-1'), 3.91 (s, 3H, OCH₃), 3.86 (s, 3H, OCH₃), 3.56–3.52 (m, 1H, H-1), 3.42–2.52 (m, 12H, H-3, H-3', H-4, H-4', H-α, H-α'), 2.52 (s, 3H, NCH₃), 2.27 (s, 3H, NCH₃). Major diastereomer: ¹³C NMR, HSQC, HMBC (150.9 MHz, CDCl₃): δ [ppm] = 155.5 (C-12'), 148.8 (C-6'), 146.6 (C-12, C-6), 144.3 (C-11), 143.5 (C-7'), 138.5 (C-8), 137.3 (C-7), 134.0 (C-9), 132.6 (C-9'), 132.5 (C-10'), 129.8 (C-14'), 127.0 (C-14), 124.5 (C-4_A), 121.2 (C-10), 120.2 (C-8'), 115.9 (C-11'), 115.4 (C-13), 113.3 (C-13'), 112.4 (C-5'), 108.2 (C-5), 65.8 (C-1'), 60.6 (C-1), 56.3, 56.2 (2 × OCH₃), 46.0 (C-3'), 44.1 (C-3), 42.5 (NCH₃), 41.9 (NCH₃), 40.1 (C-α), 39.8 (C-α'), 25.7 (C-4'), 22.1 (C-4). The resonances of C-4_{A'}, C-8_A, and C-8_{A'} could not be identified. Minor diastereomer*: ¹³C NMR, HSQC, HMBC (150.9 MHz, CDCl₃): δ [ppm] = 155.6 (C-12'), 148.6 (C-6'), 146.3 (C-6), 146.1 (C-12), 143.3 (C-11, C-7'), 137.5 (C-8), 136.9 (C-7), 133.0 (C-9), 132.8 (C-10'), 132.6 (C-9'), 130.2 (C-14'), 126.0 (C-14), 125.7 (C-4_A), 121.3 (C-10), 118.2 (C-8'), 115.5 (C-11'), 115.4 (C-13), 113.3 (C-13'), 112.0 (C-5'), 107.9 (C-5), 64.9 (C-1'), 59.5 (C-1), 56.3, 56.0 (2 × OCH₃), 47.1 (C-3'), 44.6 (C-3), 42.7 (2 × NCH₃), 40.5 (C-α), 39.3 (C-α'), 25.8 (C-4'), 23.1 (C-4). The resonances of C-4_{A'}, C-8_A and C-8_{A'} could not be identified. IR (ATR): ν = 3396 (w), 3002 (m), 2924 (m), 1611 (m), 1505 (vs), 1463 (m), 1447 (m), 1259 (s), 1215 (s), 1110 (s), 1058 (m), 1024 (m), 802 (m), 752 (vs) cm⁻¹. HPLC-MS (ESI): *m/z* (%) = 298.2 (100) [M + 2H]²⁺. HRMS (ESI): *m/z* calcd for C₃₆H₃₉N₂O₆ [M + H]⁺: 595.2808, found: 595.2814. The analytical data are in accordance with the literature.^{49,50}

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02647.

¹H and ¹³C NMR spectra of all synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

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