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

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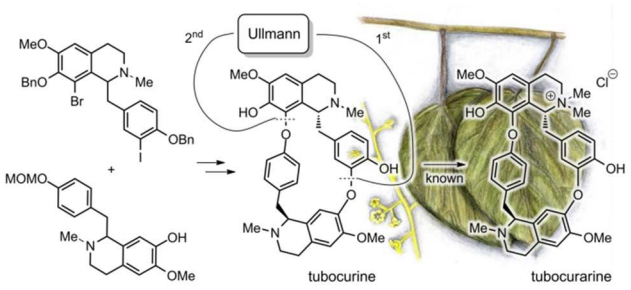


Abstract:

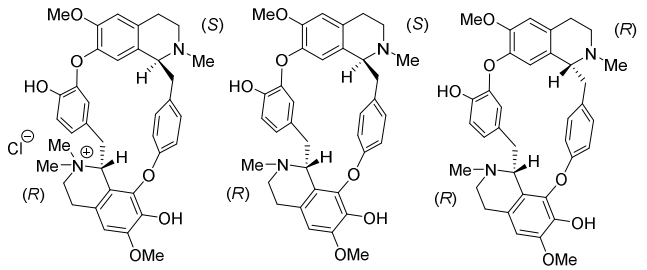
Two consecutive Cu-catalyzed Ullmann-type C–O couplings permitted the first successful entry towards the curare alkaloids (±)-tubocurine and (±)-curine. Starting from vanillin, the synthetic sequence comprises of 15 linear steps and includes a total of 24 transformations. In addition, the total synthesis 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

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).[5-6] 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 Hellmann and Elser[7] and 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 towards the group of curare alkaloids to establish structure-activity relationships to these alkaloids. Herein, the first total synthesis of (±)-curine ((±)-**3**) and (±)-tubocurine ((±)-**2**) is presented which also represents a formal total synthesis of tubocurarine (**1**).

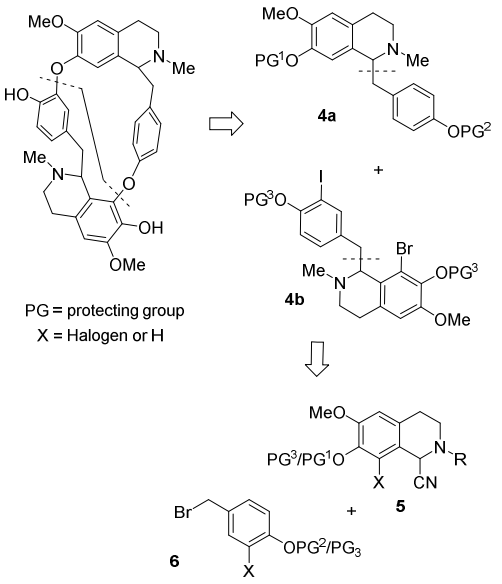


(+)-tubocurarine ((+)-**1**) (+)-tubocurine ((+)-**2**) (–)-curine ((–)-**3**)

Figure 1: Structure of curare alkaloids.

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).

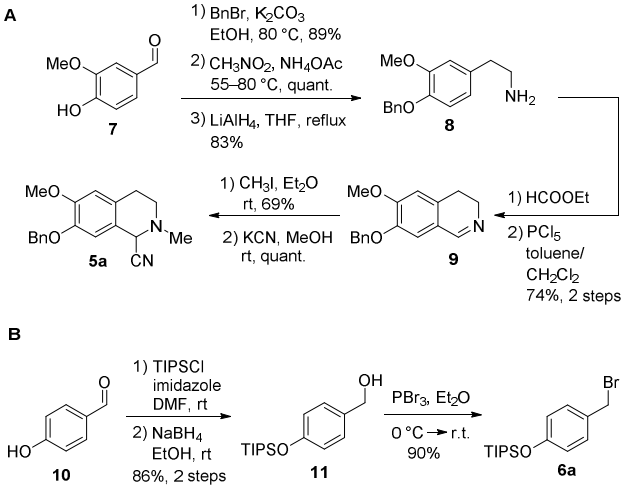


Scheme 1: Retrosynthesis of curare alkaloids.

One benzylisoquinoline subunit should be equipped with two phenolic groups (diol **4a**) and one dihalogenated benzylisoquinoline (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 tetrohydroisoquinoline 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 a deprotonated α-aminonitrile **5** and

the corresponding benzylic bromide **6** or by Bischler-Napieralski cyclization[12-15] of suitable amide precursors.

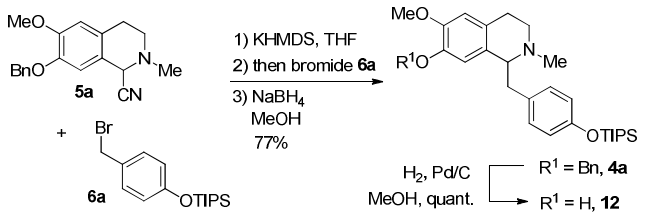
The construction of the diol compound **4a** should be accomplished by umpolung/alkylation reduction sequence from aminonitrile **5a** and the corresponding benzylic bromide **6a**. The synthesis of the aminonitrile **5a** started with vanillin (**7**), which was O-benzylated and condensed with nitromethane to the corresponding β-nitrostyrene (scheme 2, A). Subsequent reduction with lithium aluminum hydride gave phenylethylamine **8** in 74% yield over three steps. N-Formylation of amine **8** with ethyl formate to the formamide 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 then 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 phosphorous tribromide (scheme 2, B).



Scheme 2: Synthesis of α-aminonitrile 5a (A) and benzylic bromide 6a (B).

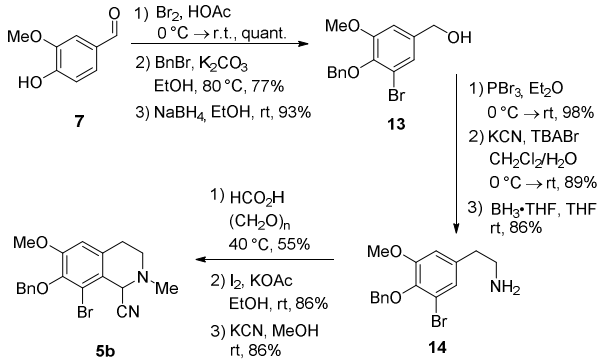
The syntheses of the aminonitrile **5a** and of the benzylic bromide **6a** are devoid of chromatographic purifications. The umpolung/alkylation-reduction sequence starting from

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 hydrogenolytic debenzylation furnished building block **12**.



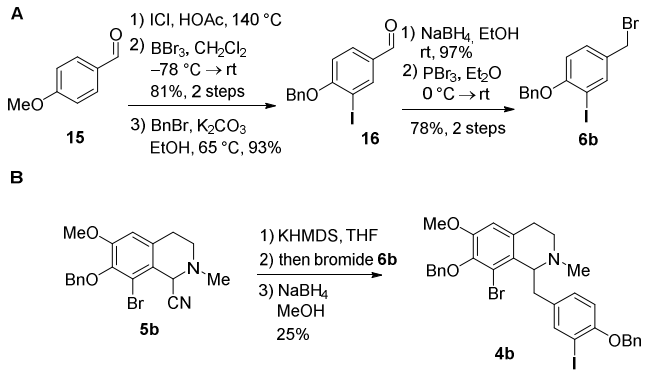
Scheme 3: Synthesis of 1-benzyltetrahydrosioquinoline 4a and deprotection to 12.

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



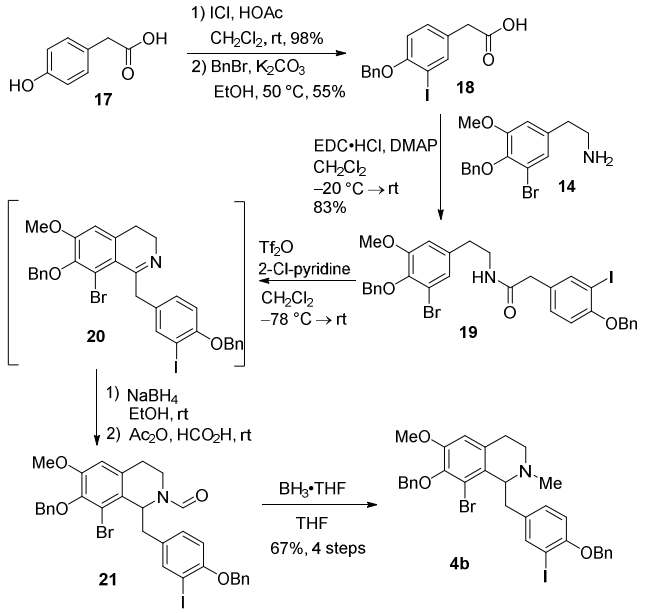
Scheme 4: Synthesis of α-aminonitrile 5b.

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



Scheme 5: Synthesis of benzylic bromide 6b (A) and 1-benzyltetrahydrosioquinoline 4b (B).

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



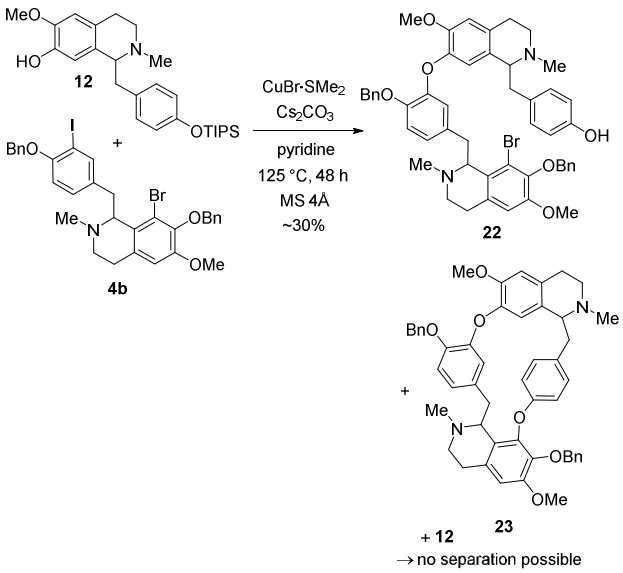
Scheme 6: Synthesis of dihalide 4b through Bischler-Napieralski cyclization.

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 over 45% yield (see scheme 4). The cyclization of amide **19** was performed by 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 and 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-methyldauricine and tetramethylmagnolamine proved to be unsuccessful (*N,N*-dimethylglycine, Cs_2CO_3, DMF, microwave heating).[21] Instead, nearly quantitative deiodination of **4b** was observed as judged by HPLC/MS (scheme 7).

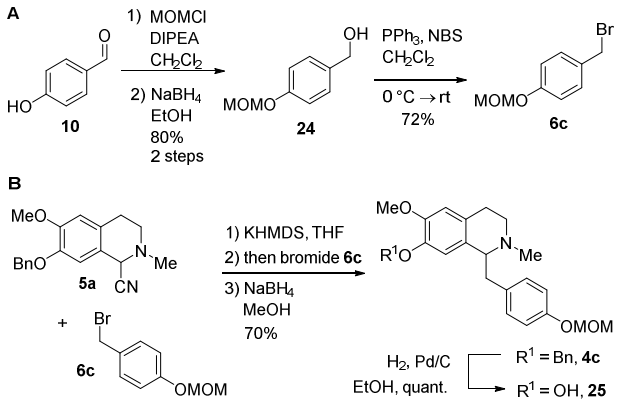


Scheme 7: C–O coupling with 12 and 4b to 22.

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 protocol proved to be successful in the synthesis of nelumboferin and isomeric head-to-tail linked bisbenzylisquinolines reported by Yamada and coworkers.[22] Furthermore, this catalyst was applied in the total synthesis of the vancomycin aglycone by Nicolaou and coworkers.[23]

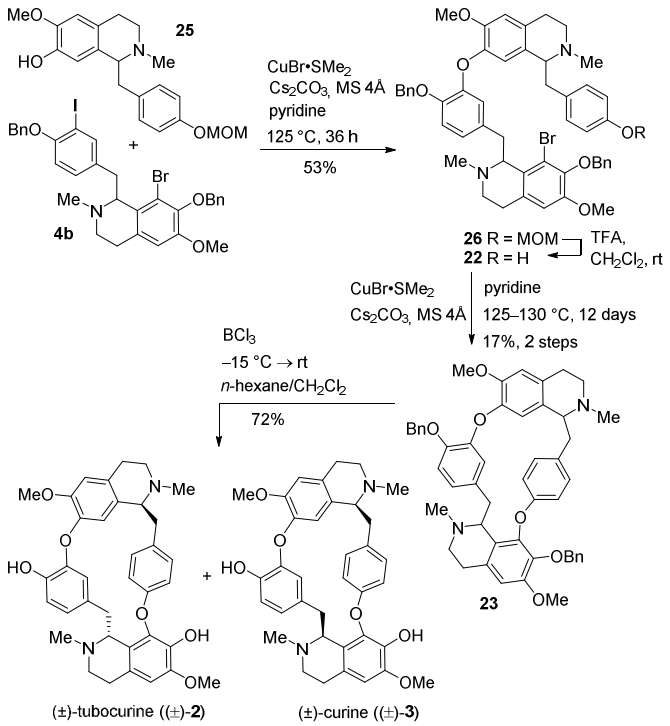
The use of copper bromide-dimethyl sulfide in combination with pyridine as the solvent and cesium carbonate as the base which is based on a protocol by Yamada and co-workers finally allowed conversion of **12** and **4b** to the seco-heterodimer **22** detected by HPLC/MS (scheme 7). Interestingly, the 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 macro cyclic 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 2A) 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).



Scheme 8: Synthesis of benzylic bromide 6c (A) and 1-benzyltetrahydrosioquinoline 25 (B).

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*-BuXPhos[24] was also tested, but in terms of yield and byproduct formation (deiodination), the palladium-catalyzed reactions were not competitive compared to the copper-mediated synthetic protocols.



Scheme 9: Synthesis of (±)-tubocurine ((±)-2) and (±)-curine ((±)-3).

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 as crude product for the subsequent C–O coupling. The second C–O coupling of **22** was performed under the same reactions 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), the corresponding product could be identified by HPLC-MS (*m/z* 398.3 for $[M+2H]^{2+}$) and ESI-HRMS (*m/z* calculated 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 natural 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, Cα' occupies a pseudo-axial position in this case. For tubocurine, Cα' takes a pseudo-equatorial position. As a result, the Cα'/C3' interaction is decreased and the Cα'/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 destilled from calcium hydride. NMR spectra were recorded with a 300 MHz (300 MHz ^{1}H and 75.5 MHz ^{13}C), 400 MHz (400 MHz ^{1}H and 100.6 MHz ^{13}C), or 600 MHz spectrometer (600 MHz ^{1}H 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 Detterbeck et al.[25] To vanillin (**7**) (30.0 g, 197 mmol, 1.0 eq.), dissolved in ethanol (400 mL), it is added benzyl bromide (28.1 mL, 40.4 g, 236 mmol, 1.2 eq.) and potassium carbonate (40.9 g, 296 mmol, 1.5 eq.) and the reaction mixture is stirred for 12 hours 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 x 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. $\mathbf{R}_f$: 0.60 (cyclohexan/EtOAc = 2:1, Seebach reagent, UV). **mp**: 61.0–62.0 °C (Et_2O). (Lit.: 60–62°C).[26] **^{1}H NMR** (300 MHz, $CDCl_3$): δ [ppm] = 9.84 (s, 1H, C*H*O), 7.29–7.46 (m, 7H, H-2, H-6, H-2-Ph, H-3-Ph, H-4-Ph, H-5-Ph, H-6-Ph), 6.99 (d, J = 8.1 Hz, 1H, H-5), 5.25 (s, 2H, CH_2-Ph), 3.95 (s, 3H, OCH_3).[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 eq.) is dissolved in nitromethane (330 mL) and ammonium acetate (12.7 g, 165 mmol, 1.0 eq.) is added. The reaction mixture is stirred for two hours 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 and 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 x 200 mL). The combined organic phases are washed with water (150 mL) and dried over Na_2SO_4. 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. $\mathbf{R_f}$: 0.62 (cyclohexan/EtOAc=2:1, Seebach reagent, vanillin/H_2SO_4 reagent, UV). **mp**: 116.0–118.0 °C (dichloromethane). (Lit.: 119–121°C (EtOH)).[28] **^{1}H NMR** (300 MHz, $CDCl_3$): 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, H-2-Ph, H-3-Ph, H-4-Ph, H-5-Ph, H-6-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, CH_2-Ph), 3.93 (s, 3H, OCH_3).[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 eq.) 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 eq.) dissolved in THF (200 mL) is added dropwise. After complete addition the reaction mixture is heated to reflux for 12 hours. The reaction is then cooled to 0 °C and sodium sulfate decahydrate is added cautiously in small portions until the exothermic reaction and the gas evolution deceases. It is warmed to room temperature and the

reaction mixture is filtered and it 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%). The product **8** is sufficiently pure and can be used without further purification. $\mathbf{R}_f$: 0.55 (dichloromethane/MeOH/NEt_3 = 2:2:1, ninhydrin reagent, UV). **^{1}H NMR** (300 MHz, $CDCl_3$): 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, C*H*$_2$-Ph), 3.88 (s, 3H, OC*H*$_3$), 2.92 (t, *J* = 6.8 Hz, 2H, C*H*$_2$$NH_2$), 2.67 (t, *J* = 6.8 Hz, 2H, C*H*$_2$$CH_2NH_2$), 1.56 (s, br, 2H, N*H*$_2$).[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 eq.) is dissolved in formic acid ethylester and the reaction mixture is stirred for 12 hours 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. $\mathbf{R}_f$: 0.29 (EtOAc/cyclohexane =100:1, Seebach reagent, UV). Major rotamer: **^{1}H NMR** (300 MHz, $CDCl_3$): δ [ppm] = 8.08 (d, *J* = 1.7 Hz, 1H, C*H*O), 7.44–7.29 (m, 5H, H-2-Ph, H-3-Ph, H-4-Ph, H-5-Ph, H-6-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, N*H*), 5.12 (s, 2H, C*H*$_2$-Ph), 3.86 (s, 3H, OC*H*$_3$), 3.51 (pseudo-q, *J* ≈ 6.8 Hz, 2H, C*H*$_2$$CH_2$Ar), 2.75 (t, *J* = 6.8 Hz, 2H, C*H*$_2$Ar). **IR (ATR):** ν = 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) $[M+Na]^+$. method C. 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 phosphorous pentachloride (3.45 g, 16.5 mmol, 1.1 eq.) in anhydrous toluene (10 mL) is added *N*-{2-[4-(benzyloxy)-3-methoxyphenyl]ethyl}formamide (4.32 g, 15.1 mmol, 1.0 eq.) dissolved in dichloromethane (10 mL) at room temperature. The reaction mixture is stirred for 15 hours 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 will be adjusted to pH 12 with solid potassium hydroxide at 0 °C. It is extracted with dichloromethane (3 x 75 mL) and the combined organic phases are dried over Na_2SO_4. 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. $\mathbf{R_f}$: 0.50 (cyclohexane/EtOAc/NEt_3 = 6:4:1, Seebach reagent, ninhydrin reagent, UV). **^{1}H NMR** (300 MHz, $CDCl_3$): 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, CH_2-Ph), 3.88 (s, 3H, OCH_3), 3.85 (t, *J* = 8.4 Hz, 2H, H-3), 3.00 (t, *J* = 8.4 Hz, 2H, H-4). **^{13}C NMR, HSQC, HMBC** (100.6 MHz, $CDCl_3$): 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 (*C*H_2-Ph), 56.6 (O*C*H_3), 41.1 (C-3), 24.6 (C-4). **MS (ESI):** *m/z (%)* = 268.1 (100) $[M+H]^+$. method A. 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 eq.) in diethyl ether (20 mL) it is added dropwise iodomethane (1.59 g, 11.2 mmol, 1.2 eq.) at room temperature. The reaction mixture is stirred at room temperature until complete conversion (15 hours). 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/NEt_3 = 1:1:0.5, Seebach reagent, UV). **mp**: 177.0–178.0 °C (dichloromethane). (Lit.: 193–195°C).[33] **^{1}H NMR, COSY** (400 MHz, $CDCl_3$): δ [ppm] = 9.71 (s, 1H, H-1), 7.63 (s, 1H, H-8), 7.28–7.48 (m, 5H, H-2-Ph, H-3-Ph, H-4-Ph, H-5-Ph, H-6-Ph), 6.82 (s, 1H, H-5), 5.15 (s, 2H, CH_2-Ph), 3.94–3.98 (m, 5H, H-3, NCH_3), 3.87 (s, 3H, OCH_3), 3.27 (t, *J* = 8.2 Hz, 2H, H-4). **^{13}C NMR, HSQC, HMBC** (100.6 MHz, $CDCl_3$): 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 (*C*H_2-Ph), 56.9 (N*C*H_3), 50.2 (C-3), 47.9 (O*C*H_3), 25.7 (C-4). **MS (ESI):** *m/z (%)* = 282.2 (100) $[M–I]^+$. method C. **HPLC-MS (ESI):** *m/z (%)* = 282.2 (100) $[M–I]^+$. method A, t_R= 0.3 min. 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 eq.) is dissolved in MeOH (40 mL) and potassium cyanide (776 mg, 11.9 mmol, 2.5 eq.) is added portionwise at room temperature. The reaction mixture is stirred for 18 hours at room temperature. Sat. $NaHCO_3$ solution is added (50 mL) and it is extracted with dichloromethane (3 x 75 mL). The combined organic phases are dried over Na_2SO_4 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/NEt_3 = 10:1:0.5, Seebach reagent, UV). **mp**: 125.0–126.0 °C (dichloromethane). **^{1}H NMR, COSY** (400 MHz, $CDCl_3$): δ [ppm] = 7.28–7.44 (m, 5H, H-2-Ph, H-3-Ph, H-4-Ph, H-5-Ph, H-6-Ph), 6.69 (s, 1H, H-8), 6.64 (s, 1H, H-5), 5.06–5.16 (m, 2H, CH_2-Ph), 4.57 (s, 1H, H-1), 3.86 (s, 3H, OCH_3), 2.67–3.02 (m, 4H, H-3, H-4), 2.57 (s, 3H, NCH_3). **^{13}C**

NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): 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 (*C*N), 112.5, 112.1 (C-8, C-5), 71.4 (*C*H_2-Ph), 55.6 (C-1), 55.1 (O*C*H_3), 48.5 (C-3), 43.8 (N*C*H_3), 28.2 (C-4). **IR (ATR):** ν = 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) $[M–CN]^+$. method A. **HR-MS (ESI):** *m/z (%)* = calculated for $C_{19}H_{21}N_2O_2$ $[M+H]^+$: 309.1603, found: 309.1601.

3-Bromo-4-hydroxy-5-methoxybenzaldehyde Vanillin (**7**) (25.0 g, 0.164 mol, 1.0 eq.) is dissolved in conc. acetic acid (300 mL) and bromine (9.90 mL, 29.9 g, 0.197 mol, 1.2 eq.) is added dropwise at 0 °C. The reaction mixture is warmed to room temperature within three hours and is stirred at room temperature for 15 hours. After completion of reaction water is added (500 mL) and the formed precipitate is filtered and washed with water. The off-white solid is dried in oil pump vacuum to furnish the title compound (37.9 g, 0.164 mol, quant.). $\mathbf{R}_f$: 0.33 (cyclohexane/EtOAc = 2:1, Seebach reagent, UV). **mp**: 162.0–163.0 °C (H_2O). (Lit.: 162–164 °C).[34] **^{1}H NMR** (300 MHz, $CDCl_3$): δ [ppm] = 9.78 (s, 1H, C*H*O), 7.64 (d, *J* = 1.7 Hz, 1H, H-2), 7.36 (d, *J* = 1.7 Hz, 1H, H-6), 6.58 (s, 1H, O*H*), 3.98 (s, 3H, OCH_3). 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 eq.) is reacted with benzyl bromide (21.5 mL, 31.0 g, 181 mmol, 1.2 eq.) and potassium carbonate (31.4 g, 227 mmol, 1.5 eq.) 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 (Et_2O). (Lit.: 44°C (*n*-hexane).[35] **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 9.84 (s, 1H, C*H*O), 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), 5.16 (s, 2H, CH_2-Ph), 3.94 (s, 3H, OCH_3). 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 eq.) is dissolved in ethanol (300 mL) and 4-(benzyloxy)-3-bromo-5-methoxybenzaldehyde (57.9 g, 180 mmol, 1.0 eq.) dissolved in ethanol (200 mL) is added dropwise at 0 °C. The reaction mixture is warmed to room temperature and stirred for 2 hours. It is added water 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 Na_2SO_4. 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). **^{1}H NMR** (300 MHz, $CDCl_3$): 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, CH_2-Ph), 4.61 (s, 2H, CH_2OH), 3.87 (s, 3H, OCH_3), 1.80 (s, 1H, O*H*). 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 eq.) is dissolved in anhydrous diethyl ether and it is cooled to 0 °C. Phosphorous tribromide (8.65 mL, 25.0 g, 92.9 mmol, 1.0 eq.) dissolved in anhydrous diethyl ether (250 mL) is added dropwise at this temperature and it is stirred for 30 minutes. 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 Na_2SO_4. 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. $\mathbf{R_f}$: 0.70 (cyclohexane/EtOAc = 2:1, Seebach reagent, UV). **^{1}H NMR** (300 MHz, $CDCl_3$): δ [ppm] = 7.53–7.57 (m, 2H, H-2-Ph, H-6-Ph), 7.297.43 (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, C*H*$_2$-Ph), 4.42 (s, 2H, C*H*$_2$Br), 3.88 (s, 3H, OC*H*$_3$). **^{13}C NMR, HSQC, HMBC** (75.5 MHz, $CDCl_3$): 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 (*C*H$_2$-Ph), 56.3 (O*C*H$_3$), 32.7 (*C*H$_2$Br). **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$^{+\bullet}$]. HRMS data could not be obtained due to decomposition of the sample in aqueous acetonitrile.

[4-(Benzyloxy)-3-bromo-5-methoxyphenyl]acetonitrile 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 eq.) is dissolved in dichloromethane/water (110 mL, 10:1) and it is cooled to 0 °C. Potassium cyanide (3.60 g, 56.0 mmol, 1.5 eq.) and tetrabutylammonium bromide (3.01 g, 9.30 mmol, 0.3 eq.) is added at this temperature and the reaction mixture is stirred for one hour. It is warmed to room temperature and stirred for 12 hours. To the reaction mixture it is added sat. sodium hydrogencarbonate solution and it is extracted with toluene. The combined organic phases are dried over Na_2SO_4 and the solvent is removed in vacuo. The title compound is obtained as 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). $\mathbf{R_f}$: 0.24 (cyclohexane/EtOAc =

4:1, Seebach or ninhydrin reagent, UV). **mp**: 76.5–77.5 °C (dichloromethane). **^{1}H NMR** (300 MHz, $CDCl_3$): 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, C*H*$_2$-Ph), 3.88 (s, 3H, OC*H*$_3$), 3.69 (s, 2H, C*H*$_2$CN). **^{13}C NMR, HSQC, HMBC** (75.5 MHz, $CDCl_3$): 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 (*C*N), 111.3 (C-2), 74.8 (*C*H$_2$-Ph), 56.2 (O*C*H$_3$), 23.1 (*C*H$_2$CN). **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) $[M+Na]^+$ method C. **HR-MS (ESI):** *m/z* = calculated for $C_{16}H_{14}BrNO_2$ $[M+Na]^+$: 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 eq.) is dissolved in anhydrous THF (100 mL) and borane tetrahydrofuran complex (1 M, 66 mL, 66.0 mmol, 2.0 eq.) is added at room temperature. The reaction mixture is stirred for 15 hours at room temperature. Water is added and it is extracted with dichloromethane. The combined organic phases are dried over Na_2SO_4 and the solvent is removed in vacuo. The obtained yellow oil is purified by flash column chromatography on silica gel (chloroform/MeOH/NEt_3 = 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/NEt_3 = 5:1:1, ninhydrin reagent, UV). **^{1}H NMR** (400 MHz, $CDCl_3$): 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, C*H*$_2$-Ph), 4.15 (s, br, 2H, N*H*$_2$), 3.86 (s, 3H, OC*H*$_3$), 3.05 (t, *J* = 7.2 Hz, 2H, C*H*$_2$CH$_2$Ar), 2.81 (t, *J* = 7.2 Hz, 2H, CH$_2$C*H*$_2$Ar). **^{13}C NMR, HSQC, HMBC** (100.6 MHz, $CDCl_3$): 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 (CH$_2$-Ph), 56.2 (OCH$_3$), 42.4 (CH$_2$CH$_2$Ar), 37.3 (CH$_2C$H$_2$Ar). **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]$^+$, method C. **HR-MS (ESI):** *m/z* = calculated for $C_{16}H_{19}BrNO_2$ [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 eq.) is dissolved in formic acid (90%-ig, 250 mL) and paraformaldehyde (630 mg, 21.0 mmol, 5.0 eq.) is added. The reaction mixture is stirred for 42 hours at 40 °C. Formic acid is removed in vacuo and the residue is purified by flash column chromatography on silica gel (cyclohexane/EtOAc/NEt$_3$ = 6:4:1). The title compound is obtained as yellow oil (831 mg, 2.29 mmol, 55%). $\mathbf{R}_f$: 0.34 (cyclohexane/EtOAc/NEt$_3$ = 6:4:1, Seebach reagent, UV). **^{1}H NMR, COSY** (400 MHz, $CDCl_3$): 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, CH_2-Ph), 3.83 (s, 3H, OCH_3), 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, NCH_3). **^{13}C NMR, HSQC, HMBC** (100.6 MHz, $CDCl_3$): 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 (CH$_2$-Ph), 58.0 (C-1), 56.1 (OCH_3), 52.0 (C-3), 45.9 (NCH$_3$), 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]$^+$, method C. **HR-MS (ESI):** *m/z* = calculated 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 eq.) is dissolved in EtOH (100 mL) and potassium acetate (1.90 g, 19.5 mmol, 4.3 eq.) is added at room temperature. Subsequently, iodine (3.81 g, 29.8 mmol, 6.5 eq.), dissolved in EtOH (50 mL), is added at room temperature and it is stirred for about 30 minutes at this temperature until TLC control shows complete conversion. To the reaction mixture it is added water (150 mL) and it is extracted with dichloromethane (3 x 100 mL). The combined organic phases are washed with sat. sodium thiosulfate solution (3 x 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%). $\mathbf{R}_f$: 0.65 (dichloromethane/MeOH = 5:1, Seebach reagent, UV). **mp:** 144.0–155.0 °C under decomposition. **^{1}H 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 (*C*H_2-Ph), 57.4 (O*C*H_3), 50.3 (C-3), 49.6 (N*C*H_3), 26.6 (C-4). $^{\#}$signals may be reversed. **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) $[M–I]^+$. method C. **HR-MS (ESI):** *m/z* = calculated for $C_{18}H_{19}BrNO_2$ $[M–I]^+$: 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 eq.) is reacted with potassium cyanide (1.00 g, 15.3 mmol, 5.0 eq.). The product is obtained as brown oil (1.02 g, 2.64 mmol, 86 %). The product **5b** is sufficiently pure and can be used without further purification. $\mathbf{R_f}$: 0.62 (toluene/EtOAc/NEt_3 = 10/10/1, Seebach reagent, UV). **^{1}H 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, C*H*$_2$-Ph), 4.84 (s, 1H, H-1), 3.85 (s, 3H, OC*H*$_3$), 3.09–2.70 (m, 4H, H-3, H-4), 2.62 (s, 3H, NC*H*$_3$). **^{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 (*C*N), 112.0 (C-5), 74.8 (*C*H$_2$-Ph), 57.5 (C-1), 56.1 (O*C*H$_3$), 47.8 (C-3), 43.5 (N*C*H$_3$), 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) $[M–CN]^+$. method C. **HR-MS (ESI):** *m/z* = calculated 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 eq.) and imidazole (15.6 g, 223 mmol, 3.5 eq.) in DMF (25 mL) is added triisopropylsilyl chloride (12.6 g, 13.9 mL, 65.5 mmol, 1.0 eq.) and the reaction mixture is stirred for 2 hours at room temperature. Water (20 mL) is added and is extracted with *n*-hexane (3 x 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. $\mathbf{R}_f$: 0.78 (cyclohexane/EtOAc = 2:1, Seebach reagent, UV). **^{1}H NMR** (300 MHz, $CDCl_3$): δ [ppm] = 9.87 (s, 1H, C*H*O), 7.79–7.76 (AA'-part of a AA'XX'-system, 2H, H-2, H-6), 6.99–6.96 (XX' part of a AA'XX' system, 2H, H-3, H-5), 1.34–1.22 (m, 3H, C*H*), 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 eq.) is reacted with $NaBH_4$ (4.10 g, 108 mmol, 1.8 eq.) in EtOH (100 mL). The product is obtained as light yellow oil (15.8 g, 56.3 mmol, 93%). The product **11** is sufficiently pure and can be used without purification in the next step. $\mathbf{R}_f$: 0.52 (cyclohexane/EtOAc = 2:1, Seebach reagent, UV). **^{1}H NMR** (300 MHz, $CDCl_3$): δ [ppm] = 7.24–7.19 (AA' part of a AA'XX' system, 2H, H-3, H-5), 6.89–6.82 (XX' part of a AA'XX' system, 2H, H-2, H-6), 4.60 (s, 2H, CH_2OH), 1.31–1.19 (m, 3H, C*H*), 1.67 (s, br, 1H, O*H*), 1.11–1.05 (m, 18 H, 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 eq.) is reacted with phosphorous tribromide (1.50 mL, 16.0 mmol, 1.0 eq.) 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. $\mathbf{R}_f$: 0.86 (cyclohexane/EtOAc = 20:1, Seebach reagent, UV). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ [ppm] = 7.26–7.23 (AA' part of a AA'XX' system, 2H, H-3, H-5), 6.85–6.82 (XX' part of a

AA'XX' system, 2H, H-2, H-6), 4.49 (s, 2H, CH_2Br), 1.31–1.19 (m, 3H, C*H*), 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 eq.) is dissolved in acetic acid (50 mL) and iodine monochloride (13.9 g, 85.6 mmol, 1.2 eq.) is added. The reaction mixture is heated to 140 °C for 2–4 hours. After complete conversion, the reaction mixture is cooled to room temperature and the pH of the reaction mixture is adjusted to pH 8 with 1 M NaOH solution and it is extracted with chloroform (3 x 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%). $\mathbf{R_f}$: 0.56 (cyclohexane/EtOAc = 2:1, dinitrophenyl hydrazine reagent, UV). **mp**: 103.0–107.0°C (chloroform). **^{1}H NMR** (300 MHz, $CDCl_3$): δ [ppm] = 9.84 (s, 1H, C*H*O), 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 eq.) is dissolved in anhydrous dichloromethane (50 mL) and boron tribromide (4.29 mL, 45.3 mmol, 11.4 g, 3.0 eq.) 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 it is added water (50 mL) and it is extracted with dichloromethane (3 x 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] $\mathbf{R_f}$: 0.37 (cyclohexane/EtOAc = 6:1, dinitrophenyl hydrazine reagent, UV). **^{1}H NMR** (300 MHz,

$CDCl_3$): δ [ppm] = 9.80 (s, 1H, C*H*O), 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, O*H*). **MS (ESI):** *m/z (%)* = 248.9 (86) $[M+H]^+$. method C. 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 eq.) is dissolved in EtOH (30 mL) and potassium carbonate (4.30 g, 31.1 mmol, 2.0 eq.) and benzyl bromide (3.20 mL, 4.61 g, 26.9 mmol, 1.8 eq.) are added at room temperature. The reaction mixture is stirred for 5 hours 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 x 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). $\mathbf{R}_f$: 0.40 (cyclohexane/EtOAc = 5:1, dinitrophenyl hydrazine reagent, UV). **mp**: 65.4–68.6 °C (cyclohexane/EtOAc). **^{1}H NMR** (300 MHz, $CDCl_3$): δ [ppm] = 9.81 (s, 1H, C*H*O), 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 (*C*HO), 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}. **HR-MS (ESI):** *m/z* = calculated for $C_{14}H_{11}IO_2Na$ $[M+Na]^+$: 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 eq.) is reacted with sodium borohydride (0.33 g, 8.79 mmol, 1.5 eq.) in EtOH (100 mL). The title compound is obtained as an off-white crystalline solid (1.94 g, 5.70 mmol, 97%). $\mathbf{R}_f$: 0.15 (cyclohexane/EtOAc = 5:1, Seebach reagent, UV). **mp**: 95.0–98.4 °C (Et_2O). **^{1}H 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, C*H*$_2$-Ph), 4.58 (s, 2H, C*H*$_2$OH), 1.78 (s, br, 1H, O*H*). **^{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 (*C*H$_2$-Ph), 64.2 (*C*H$_2$OH). **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 [$M^{+\bullet}$]. **MS (LIFDI-FD):** *m/z (%)* = 340.0 [$M^{+\bullet}$]. 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 eq.) is reacted with phosphorous tribromide (1.00 g, 3.73 mmol, 1.0 eq.). 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. $\mathbf{R}_f$: 0.59 (cyclohexane/EtOAc = 5:1, Seebach reagent, UV). **^{1}H 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, C*H*$_2$-Ph), 4.42 (s, 2H, C*H*$_2$Br). **^{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 (*C*H$_2$-Ph),

32.4 (*C*H_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-FD):** *m/z (%)* = 401.9 [$M^{+\bullet}$]. 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 eq.) is reacted with KHMDS (1.25 g, 6.26 mmol, 1.3 eq.), benzylic bromide **6a** (2.18 g, 6.35 mmol, 1.3 eq.) and sodium borohydride (1.00 g, 26.5 mmol, 5.4 eq.). 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%). $\mathbf{R}_f$: 0.45 (cyclohexane/EtOAc/NEt_3 = 6:2:1, Seebach reagent, UV). **^{1}H NMR, COSY** (300 MHz, $CDCl_3$): δ [ppm] = 7.38–7.26 (m, 5H, H-2-Ph, H-3-Ph, H-4-Ph, H-5-Ph, H-6-Ph), 6.89–6.86 (AA‘ part of a AA’XX‘ system, 2H, H-2‘, H-6‘), 6.78–6.75 (XX‘ part of a 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-$α_A$), 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, C*H*), 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 (*C*H_2-Ph), 65.0 (C-1), 55.9 (O*C*H_3), 47.2 (C-3), 42.7 (N*C*H_3), 40.4 (C-α), 25.9 (C-4), 18.0 (*C*H), 12.7(*C*H_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) $[M+H]^+$. Method A. **HR-MS (ESI):** *m/z* = calculated for $C_{34}H_{48}NO_3Si$ $[M+H]^+$: 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 eq.) is reacted with KHMDS (161 mg, 0.807 mmol, 2.0 eq.), benzylic bromide **6b** (179 mg, 0.444 mmol, 1.1 eq.) and sodium borohydride (2.00 g, 52.8 mmol, 34.8 eq.). 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%). $\mathbf{R}_f$: 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 eq.) is dissolved in anhydrous THF (75 mL) and borane–THF complex (9.92 mL, 9.92 mmol, 1.5 eq.) ia added at room temperature and the reaction mixture is stirred for 12 hours at this temperature. Water (50 mL) is added to the reaction mixture and it is extracted with EtOAc (4 x 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). $\mathbf{R}_f$: 0.59 (cyclohexane/EtOAc/NEt_3 = 6:4:1, Seebach reagent, UV). **^{1}H 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 × H-3-Ph, 2 × H-4-Ph, 2 × 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 × 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 × 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-O*C*H_2-Ph), 71.0 (4’-O*C*H_2-Ph), 64.2 (C-1), 56.2 (O*C*H_3), 44.3 (C-3), 42.6 (N*C*H_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) $[M+H]^+$, method B, t_R= 3.2min. **HR-MS (ESI):** *m/z* = calculated for: $C_{32}H_{32}BrINO_3$ $[M+H]^+$: 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 eq.) is dissolved in dichloromethane (100 mL) and iodine monochloride (5.34 g, 32.9 mmol, 1.0 eq.) and acetic acid (0.10 mL, 1.64 mmol, 0.05 eq.) is added. The reaction mixture is stirred for 50 hours at room temperature. After complete conversion it is added water (100 mL) and it is extracted with ethyl acetate (3 x 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%). $\mathbf{R_f}$: 0.42 (cyclohexane/EtOAc = 1:1, Seebach reagent, UV). **mp**: 98.5–100.5 °C (toluene). **^{1}H NMR** (300 MHz, DMSO-d_6): δ [ppm] = 12.27 (s, br, 1H, COO*H*), 10.19 (s, 1H, O*H*), 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, DMSO-d_6): δ [ppm] = 172.9 (*C*OOH), 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 (*C*H_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}. **HR-MS (ESI):** *m/z* = calculated for $C_8H_7O_3INa$ $[M+Na]^+$: 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 eq.) is dissolved in EtOH (200 mL) and potassium carbonate (16.1 g, 117 mmol, 3.0 eq.) is added. At room temperature benzyl bromide (5.52 mL, 46.6 mmol, 1.2 eq.) is added dropwise. The reaction mixture is heated to 55 °C for 5 hours. 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 ≈ 2 with 1 M hydrochloric acid and it is extracted with diethyl ether (3 x 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%). $\mathbf{R_f}$: 0.34 (cyclohexane/EtOAc/HOAc = 2:1, Seebach reagent, UV). **mp**: 103.4–107.6 °C (cyclohexane/EtOAc). **^{1}H 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, C*H*$_2$-Ph), 3.55 (s, 2H, C*H*$_2$). **^{13}C NMR, HSQC, HMBC** (75.5 MHz, $CDCl_3$): δ [ppm] = 177.6 (*C*OOH), 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 (*C*H_2-Ph), 39.5 (*C*H_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) $[M+Na]^+$. method C. **HR-MS (ESI):** *m/z* = calculated for $C_{15}H_{13}IO_3Na$ $[M+Na]^+$: 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 eq.), acid **18** (1.31 g, 3.56 mmol, 1.2 eq.) and DMAP (181 mg, 1.49 mmol, 0.5 eq.) is dissolved in anhydrous dichloromethane (50 mL) and it is cooled to –20 °C. EDC hydrochloride (854 mg, 4.46 mmol, 1.5 eq.) is dissolved in anhydrous dichloromethane (10 mL) and is added dropwise at this temperature. The reaction mixture is stirred at this temperature and is warmed over 12 hours to room temperature. It is added water 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%). $\mathbf{R_f}$: 0.16 (dichloromethane/MeOH/NEt_3 = 100:1:1, Seebach reagent, UV). **mp:** 159.8–163.0 °C (dichloromethane/MeOH/NEt_3). **^{1}H NMR, COSY** (300 MHz, DMSO-d_6): δ [ppm] = 8.08 (t, *J* = 5.6 Hz, 1H, N*H*), 7.66 (d, *J* = 2.1 Hz, 1H, H-2‘), 7.51–7.46 (m, 4H, 2 × H-2-Ph, 2 × H-6-Ph), 7.41–7.29 (m, 6H, 2 × H-3-Ph, 2 × H-4-Ph, 2 × 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, C=OCH_2, NCH_2CH_2), 2.67 (t, *J* = 7.0 Hz, 2H, NCH_2CH_2). **^{13}C NMR, HSQC, HMBC** (75.5 MHz, 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 × C-3-Ph, 2 × C-5-Ph, C-2-Ph, C-6-Ph), 128.1, 127.8 (2 × 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-O*C*H_2-Ph), 70.1 (4‘-O*C*H_2-Ph), 56.1 (O*C*H_3), 40.8 (C=O*C*H_2), 40.0 (NCH_2CH$_2$) 34.4 (NCH$_2$*C*H$_2$). **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}. **HR-MS (ESI):** *m/z* = calculated for $C_{31}H_{29}BrINO_4Na$ $[M+Na]^+$: 708.0222, found: 708.0217.

7-(Benzyloxy)-1-[4-(benzyloxy)-3-iodobenzyl]-8-bromo-6-methoxy-1,2,3,4-tetrahydroisoquinoline Step 1: Synthesized according to a modified procedure of Movassaghi and Hill.[14] Amide **19** (2.79 g, 4.07 mmol, 1.0 eq) is dissolved in anhydrous dichloromethane (60 mL) and 2-chloro pyridine (590 µL, 4.30 mmol, 1.1 eq.), 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 Tf_2O (885 µL, 1.87 mmol, 0.5 eq.), 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. It is added 1 M NaOH (50 mL) 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. $\mathbf{R}_f$: 0.24 (cyclohexane/EtOAc/NEt_3 = 6:4:1, ninhydrin reagent, UV). **HPLC-MS (ESI):** *m/z (%)* = 668. 1 (100) $[M+H]^+$, method B, t_R= 3.2 min. Step 2: Imine **20** (max. 4.07 mmol, 1.0 eq.) is dissolved in EtOH (70 mL) and at room temperature $NaBH_4$ (231 mg, 6.11 mmol, 1.5 eq.) is added portionwise. The reaction mixture is stirred for 12 hours at this temperature. It is added water (200 mL) and it is extracted with EtOAc (3 x 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). $\mathbf{R}_f$: 0.55 (cyclohexane/EtOAc/NEt_3 = 6:4:1, ninhydrin reagent, UV). **^{1}H 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 × H-2-Ph, 2 × H-6-Ph), 7.44–7.33 (m, 6H, 2 × H-3-Ph, 2 × H-4-Ph, 2

× 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, C*H*$_2$-Ph), 5.06–4.99 (m, 2H, C*H*$_2$-Ph), 4.24 (dd, *J* = 10.9, 2.7 Hz, 1H, H-1), 3.86 (s, 3H, OC*H*$_3$), 3.33–2.66 (m, 6H, H-3, H-α, H-4), 1.90 (s, br, 1H, N*H*). **^{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 × 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 × C-3-Ph, 2 × C-5-Ph, C-2-Ph, C-6-Ph), 128.1, 127.9 (2 × 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 (*C*H$_2$-Ph), 71.0 (*C*H$_2$-Ph), 57.1 (C-1), 56.2 (O*C*H$_3$), 36.9 (C-3), 36.7 (C-α), 29.2 (C-4). $^{\#}$signals may be reversed. **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 $[M+H]^+$. method B, t_R= 3.2 min. **HR-MS (ESI):** *m/z* = calculated for : $C_{31}H_{30}BrINO_3$ $[M+H]^+$: 670.0454 found: 670.0467.

7-(Benzyloxy)-1-[4-(benzyloxy)-3-iodbenzyl]-8-brom-6-methoxy-3,4-dihydroisoquinolin-2(1*H*)-carbaldehyde (21) 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 eq.) 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 minutes 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 ~ 8. It is extracted with EtOAc (3 x 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): **^{1}H NMR, COSY** (300 MHz, $CDCl_3$): δ [ppm] = 7.71 (d, *J* = 2.1 Hz, 1H, H-2‘), 7.66 (s, 1H, C*H*O), 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 × H-3-Ph, 2 × H-4-Ph, 2 × 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 × 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$_A$), 3.88 (s, 3H, OCH_3), 3.64–3.21 (m, 2H, H-α$_A$, H-3$_B$,), 3.01–2.47 (m, 3H, H-α$_B$, H-4). Minor rotamer: **^{1}H NMR, COSY** (300 MHz, $CDCl_3$): δ [ppm] = 8.05 (s, 1H, C*H*O), 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 × H-3-Ph, 2 × H-4-Ph, 2 × 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 × CH_2-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 (*C*HO), 156.4 (C-4‘),152.7 (C-6), 144.1 (C-7), 139.8 (C-2‘), 137.0, 136.5 (2 × 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 × 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 (*C*H_2-Ph), 71.0 (*C*H_2-Ph), 59.5 (C-1), 56.2 (O*C*H_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 (*C*HO), 156.1 (C-4‘), 152.5 (C-6), 144.3 (C-7), 140.2 (C-2‘), 137.1, 136.6 (2 × 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 × 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 (*C*H_2-Ph), 70.9 (*C*H_2-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) $[M+H]^+$. method B, t_R= 4.4 min. **HR-MS (ESI):** *m/z* = calculated for: $C_{32}H_{29}BrINO_4Na$ $[M+Na]^+$: 720.0222 , found: 720.0220.

6-Methoxy-2-methyl-1-(4-{[tri(propan-2-yl)silyl]oxy}benzyl)-1,2,3,4-tetrahydroisoquinoline-7-ol (12) 1-Benzyl tetrahydoisoquinoline **4a** (100 mg, 0.183 mmol, 1.0 eq.) is dissolved in MeOH (16 mL). Palladium on charcoal (10%, 21.8 mg, 11.0 mol%, 0.1 eq.) and acetic acid (0.5 mL) is added and the reaction mixture is stirred for 15 hours 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.). $\mathbf{R}_f$: 0.64 (cyclohexane/EtOAc/NEt_3 = 6:4:1, Seebach reagent, UV). **^{1}H NMR, COSY** (400 MHz, $CDCl_3$): δ [ppm] = 6.96–6.93 (AA' part of a AA'XX' system, 2H, H-2', H-6'), 6.78–6.74 (XX' part of a 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, O*H*), 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, C*H*), 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 (O*C*H_3), 47.2 (C-3), 42.7 (N*C*H_3), 40.8 (C-α), 25.6 (C-4), 18.0 (*C*H), 12.7 (*C*H_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* = calculated for $C_{27}H_{42}NO_3Si$ $[M+H]^+$: 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 eq.) and diol **12** (142 mg, 0.311 mmol, 1.2 eq.) are dissolved in anhydrous pyridine (0.75 mL) in a reaction tube. Molecular sieves 4 Å (150 mg), Cs_2CO_3 (211 mg, 0.648 mmol, 2.5 eq.) and $CuBr{\cdot}SMe_2$ (106 mg, 0.518 mmol, 2.0 eq.) are added under an atmosphere of argon and the reaction tube is sealed with a septum and PTFE tape. The reaction mixture is stirred for 15 minutes at room temperature and is then stirred at 125 °C for 24 hours. It is stirred for further 12 hours 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**. **HR-MS (ESI):** *m/z (%)* = calculated for $C_{50}H_{52}BrN_2O_6$ $[M+H]^+$: 855.3009, found: 855.3021. The analytical data are in accordance to procedure B. Procedure B: Seco-heterodimer **26** (265 mg, 0.294 mmol, 1.0 eq.) 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 hours. The reaction mixture is stirred for 12 hours at room temperature and recation control is perfomred by HPLC-MS. After complete conversion sat. sodium hydrogencarbonate solution (20 mL) is added and it is extracted with dichloromethane (3 x 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. $\mathbf{R_f}$**:** 0.23 (dichloromethane/MeOH = 10:1, Seebach reagent, UV). Diastereomeric mixture in a ratio of 1:1. Diastereomer A: **^{1}H 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, H-Ph, H-10), 7.12–7.06 (m, 2H, H-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 a 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 a AA’XX‘ system, 2H, H-11‘, H-13‘), 5.52 (s, 1H, H-8‘), 5.02–4.80 (m, 4H, CH_2-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: **^{1}H 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 a 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 a AA’XX‘ system, 2H, H-11‘, H-13‘), 5.67 (s, 1H, H-8‘), 5.02–4.80 (m, 4H, CH_2-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 × 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 (2 x), 112.0, 111.9 (C-5, C-5*, C-5‘, C-5‘*), 74.8 (7-O*C*H$_2$-Ph, 7*-O*C*H$_2$-Ph), 70.6, 70.5 (12-O*C*H$_2$-Ph, 12*-O*C*H$_2$-Ph), 65.7 (H-1‘), 65.3 (H-1‘*), 64.2 (H-1), 62.1 (H-1*), 56.2 (2x, O*C*H$_3$), 56.1 (2x, O*C*H$_3$), 46.9 (C-3‘*), 46.6 (C-3‘), 43.4 (C-3), 42.6 (C-3*), 42.4 (2‘*-N*C*H$_3$), 42.1 (2‘-N*C*H$_3$), 41.7 (2*-N*C*H$_3$), 41.3 (2-N*C*H$_3$), 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). C-4a, C-4a’, C-8a and C-8a’ could not be determined. **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) $[M+2H]^{2+}$. method B, t_R= 2.8 min. **HR-MS (ESI):** *m/z* = calculated for $C_{50}H_{52}BrN_2O_6$ $[M+H]^+$: 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 eq.) is dissolved in dichloromethane (50 mL) gelöst and DIPEA (17.3 mL, 123 mmol, 1.5 eq.) and Chloro(methoxy)methane (8.1 mL, 0.11 mmol, 1.3 eq.) is added. The reaction mixture is stirred at room temperature until TLC indicates complete conversion (12 hours). To the reaction mixture it is added water (50 mL) and it is extracted with dichloromethane (3 x 75 mL). The combined organic phases are dried over Na_2SO_4, it is 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%). $\mathbf{R}_f$: 0.60 (cyclohexane/EtOAc = 2:1, Seebach reagent, UV). **^{1}H NMR** (300 MHz, $CDCl_3$): δ [ppm] = 9.87 (s, 1H, C*H*O), 7.83–7.80 (AA' part of a AA'XX'-system, 2H, H-2, H-6), 7.14–7.11 (XX' part of a AA'XX' system, 2H, H-3, H-5), 5.23 (s, 2H, CH_2), 3.47 (s, 3H, OCH_3). 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 eq.) is reacted with sodium borohydride (1.6 g, 43 mmol, 1.5 eq.) in EtOH (100 mL). The product **24** is obtained as a colorless oil (4.3 g, 26 mmol, 86%). $\mathbf{R}_f$: 0.48 (cyclohexane/EtOAc = 2:1, Seebach reagent, UV). **^{1}H NMR, COSY** (300 MHz, $CDCl_3$): δ [ppm] = 7.27–7.24 (AA' part of a AA'XX' system, 2H, H-2, H-6), 7.02–6.99 (XX' part of a AA'XX'system, 2H, H-3, H-5), 5.15 (s, 2H, CH_2), 4.56 (s, 2H, CH_2OH), 3.46 (s, 3H, OCH_3), 2.35 (s, br, 1H, O*H*). **^{13}C NMR, HSQC, HMBC** (75.5 MHz,

$CDCl_3$) δ [ppm] = 156.7 (C-4), 134.5 (C-1), 128.6 (C-2, C-6), 116.4 (C-3, C-5), 94.5 (*C*H_2), 64.8 (*C*H_2OH), 56.0 (O*C*H_3). 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 eq) is dissolved in dichloromethane (100 mL) and N-bromosuccinimide (6.35 g, 35.7 mmol, 1.5 eq.) and triphenylphosphine (9.36 g, 35.7 mmol, 1.5 eq.) is added at 0°C. It is slowly warmed to room temperature and the reaction mixture is stirred for 30 minutes at this temperature. To the reaction mixture is added brine (50 mL) and the organic phase is dried over Na_2SO_4. 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. $\mathbf{R}_f$: 0.68 (cyclohexane/EtOAc = 14:1, Seebach reagent, UV). **^{1}H NMR, COSY** (300 MHz, $CDCl_3$): δ [ppm] = 7.34–7.31 (AA' part of a AA'XX' system, 2H, H-2, H-6), 7.02–6.99 (XX' part of a AA'XX' system, 2H, H-3, H-5), 5.18 (s, 2H, C*H*$_2$), 4.50 (s, 2H, C*H*$_2$Br), 3.48 (s, 3H, OC*H*$_3$). **^{13}C NMR, HSQC, HMBC** (75.5 MHz, $CDCl_3$) δ [ppm] = 157.4 (C-4), 131.3 (C-1), 130.5 (C-2, C-6), 116.6 (C-3, C-5), 94.4 (*C*H_2), 56.2 (O*C*H_3), 38.8 (*C*H_2Br). **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 eq.) is dissolved in anhydrous THF (2 mL) and it is cooled to –65 °C. KHMDS (313 mg, 15.7 mmol, 2.0 eq.), dissolved in anhydrous THF (1.5 mL)

is added dropwise at this temperature and it is stirred for 5 minutes. Benzylic bromide **6c** (200 mg, 0.864 mmol, 1.1 eq.) is added dropwise at –65 °C and the reaction mixture is stirred for further 35 minutes at this temperature. $NaBH_4$ (0.5 g, 52.8 mmol, 5.0 eq.) and MeOH (1 mL) is added and the reaction mixture is warmed to rrom temperature and is stirred 3 hours at this temperature. It is added sat. $NaHCO_3$ solution (20 mL) and it is extracted with dichloromethane (3 x 75 mL). The combine dorganic 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 **4c** is obtained as yellow oil (240 mg, 0.554 mmol, 70%). $\mathbf{R_f}$: 0.44 (cyclohexane/EtOAc/NEt_3 = 6:4:1, Seebach reagent, UV). **^{1}H NMR, COSY** (400 MHz, $CDCl_3$): 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, CH_2), 4.89–4.75 (m, 2H, CH_2-Ph), 3.84 (s, 3H, OCH_3), 3.60 (dd, J = 7.4, 5.3 Hz, 1H, H-1), 3.43 (s, 3H, CH_2OCH_3), 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, NCH_3). **^{13}C NMR, HSQC, HMBC** (100.6 MHz, $CDCl_3$): 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 (CH_2), 70.9 (CH_2-Ph), 64.9 (C-1), 56.0, 56.0 (2 x OCH_3), 47.1 (C-3), 42.8 (NCH_3), 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) $[M+H]^+$, method B, t_R= 2.5 min. **HR-MS (ESI):** *m/z* = calculated for $C_{27}H_{32}NO_4$ $[M+H]^+$: 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 eq.) is dissolved in EtOH (10 mL) and palladium on charcoal (22 mg, 10%, 0.023 mmol, 0.1 eq.) is added under an atmosphere of argon. The reaction mixture is stirred for 12 hours 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. $\mathbf{R}_f$: 0.41 (cyclohexane/EtOAc/NEt_3 = 6:4:1, Seebach reagent, UV). **^{1}H NMR, COSY** (400 MHz, $CDCl_3$): δ [ppm] = 7.04–7.02 (AA' part of a AA'XX' system, 2H, H-2', H-6'), 6.92–6.90 (XX' part of a AA'XX' system, 2H, H-3', H-5'), 6.53 (s, 1H, H-5), 6.37 (s, 1H, H-8), 5.14 (s, 2H, CH_2), 3.83 (s, 3H, OCH_3), 3.68 (t, J = 6.1 Hz, 1H, H-1), 3.47 (s, 3H, CH_2OCH_3), 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, NCH_3). **^{13}C NMR, HSQC, HMBC** (100.6 MHz, $CDCl_3$): 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 (CH_2), 64.7 (C-1), 56.0 (CH_2OCH_3), 55.9 (OCH_3), 46.9 (C-3), 42.5 (NCH_3), 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) $[M+H]^+$, method B, t_R = 1.4 min. **HR-MS (ESI):** *m/z* = calculated for $C_{20}H_{26}NO_4$ $[M+H]^+$: 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 eq.) and diol **25** (227 mg,

0.661 mmol, 1.0 eq.) are dissolved in anhydrous pyridine (1.5 mL) in a reaction tube. Molecular sieves 4 Å (150 mg), cesium carbonate (579 mg, 1.78 mmol, 2.7 eq.) and CuBr·SMe_2 (146 mg, 0.727 mmol, 1.1 eq.) is 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 minutes 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/NEt_3 oder chloroform/MeOH = 12:1). The product **26** is obtained as light brown oil (315 mg, 0.350 mmol, 53%). $\mathbf{R}_f$: 0.29 (cyclohexane/EtOAc/NEt_3 = 6:4:1, Seebach reagent, UV). Diastereomeric mixture in a ratio of 1:1. Diastereomer A: **^{1}H NMR, COSY** (600 MHz, $CDCl_3$): 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 a 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 a 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, CH_2OCH_3, 12'-OCH_2-Ph, 12-OCH_2-Ph), 3.92 (d, *J* = 9.7 Hz, 1H, H-1), 3.84 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.63 (t, *J* = 5.7 Hz, 1H, H-1'), 3.42 (s, 3H, CH_2OCH_3), 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'-NCH_3), 2.29 (s, 3H, 2-NCH_3). Diastereomer B*: **^{1}H NMR, COSY** (600 MHz, $CDCl_3$): 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 a 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 a 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, CH_2OCH_3, 12'-OCH_2-Ph, 12-OCH_2-Ph), 3.92 (d, *J* = 9.7 Hz, 1H, H-1), 3.84 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.63 (t, *J* = 5.7 Hz, 1H, H-1'), 3.42 (s, 3H, CH_2OCH_3), 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'-NCH_3), 2.29 (s, 3H, 2-NCH_3). **^{13}C NMR, HSQC, HMBC** (150.9 MHz, $CDCl_3$): 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-8a, C-8a*), 130.4 (C-10', C-10'*, C-14', C-14'*), 130.0 (C-8a', C-8a'*), 129.9 (C-4a, C-4a*), 129.3 (C-4a', C-4a'*), 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 (CH_2, CH_2*), 74.7 (CH_2-Ph,CH_2-Ph*), 71.1, 71.0 (CH_2-Ph,CH_2-Ph*), 64.5, 64.4 (C-1, C-1*, C-1', C-1'*), 56.1 (4 x OCH_3), 56.0 (CH_2OCH_3, CH_2OCH_3*), 47.4 (C-3', C-3'*), 44.2, 44.1 (C-3, C-3*), 42.8 (2 × NCH_3), 42.6 (2 × NCH_3), 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 $[M+2Na]^{2+}$, method B, t_R= 2.7 min. **HR-MS (ESI):** *m/z* = calculated for $C_{52}H_{56}BrN_2O_7$ $[M+H]^+$: 899.3271, found: 899.3265.

(±)-Tubocurine ((±)-2) and (±)-Curine ((±)-3) Step 1: Seco-heterodimer **22** (248 mg, 0.290 mmol, 1.0 eq.), molecular sieves 4 Å (150 mg), cesium carbonate (252 mg, 0.783 mmol, 2.7 eq.) and CuBr·SMe_2 (63.5 mg, 0.319 mmol, 1.1 eq.) are placed in a reaction 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 minutes 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 $CuBr{\cdot}SMe_2$ (115 mg, 0.58 mmol, 2.0 eq.) dissolved 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 hydrogencarbonate solution (30 mL). It is extracted with dichlormethane (3 x 50 mL) and the combined organic phases are dried over Na_2SO_4. The solvent is removed in vacuo and the residue is purified by flash column chromatography on silica gel (cyclohexane/EtOAc/NEt_3 = 6:4:1). The product **23** is obtained as light yellow oil (30.2 mg, 39.0 µmol, 17% over 2 steps). $\mathbf{R_f}$: 0.29 (cyclohexane/EtOAc/NEt_3 = 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) $[M+2H]^{2+}$, method B, t_R= 2.8 min. **HR-MS (ESI):** *m/z (%)* = calculated for $C_{50}H_{51}N_2O_6$ $[M+H]^+$: 775.3747, found: 775.3751. Step 2: Compound **23** (11.3 mg, 14.6 µmol, 1.0 eq.) is dissolved in anhydrous dichloromethane (1 mL) and it is cooled to –19 °C. Boron trichloride (1 M in *n*-hexane, 73 µL, 72.9 µmol, 5.0 eq.) is added dropwise and it is stirred for one hour at this temperature. Reaction control is performed by HPLC-MS. Additional boron trichloride (1 M in *n*-hexane, 75 µL, 4.2 eq.) is added dropwise at –19 °C. It is stirred for one hour at this temperature and after complete conversion (HPLC-MS) the reaction mixture is warmed to room temperature. It is added aqueous ammonia solution (15 mL, 27% in H_2O) to adjust the reaction mixture to pH ~ 8–9 and it is extracted with dichloromethane (3 x 25 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 (dichloromethane/MeOH = 10:1). The

products (±)-**2** and (±)-**3** are obtained as light yellow solid (6.2 mg, 10.4 µmol, 72%). $\mathbf{R}_f$: 0.23 (chloroform/MeOH = 7:1, Seebach reagent, UV). Diastereomeric mixture in a ratio of 1:2. Major diastereomer: **^{1}H NMR, COSY** (600 MHz, $CDCl_3$): 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, OCH_3), 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, NCH_3), 2.45 (dd, *J* = 16.6, 4.3 Hz, 1H, H-4$_B$), 2.29 (s, 3H, NCH_3). Minor diastereomer*: **^{1}H NMR, COSY** (600 MHz, $CDCl_3$): 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, OCH_3), 3.86 (s, 3H, OCH_3), 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, NCH_3), 2.27 (s, 3H, NCH_3). Major diastereomer: **^{13}C NMR, HSQC, HMBC** (150.9 MHz, $CDCl_3$): 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-4a), 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 × O*C*H_3), 46.0 (C-3‘), 44.1 (C-3), 42.5 (N*C*H_3), 41.9 (N*C*H_3), 40.1 (C-α), 39.8 (C-α‘), 25.7 (C-4‘), 22.1 (C-4). C-4a’, C-8a and C-8a’ could not be determined. Minor diastereomer*: **^{13}C NMR, HSQC, HMBC** (150.9 MHz, $CDCl_3$): 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-4a), 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 × O*C*H_3), 47.1 (C-3‘), 44.6 (C-3), 42.7 (2 × N*C*H_3), 40.5 (C-α), 39.3 (C-α‘), 25.8 (C-4‘), 23.1 (C-4). C-4a’, C-8a and C-8a’

could not be determined. **IR (ATR):** ν = 3396 (w), 3002 (m), 2924 8m), 1611 (m), 1505 (vs), 1463 (m), 1447 (m), 1259 (s), 1215 8s), 1110 (s), 1058 (m), 1024 (m), 802 (m), 752 (vs) cm^{-1}. **HPLC-MS (ESI):** *m/z (%)* = 298.2 (100) $[M+2H]^{2+}$, method B, t_R= 1.9 min. **HR-MS (ESI):** *m/z* = calculated for $C_{36}H_{39}N_2O_6$ $[M+H]^+$: 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

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^1H and ^{13}C NMR spectra of all synthesized compounds

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Notes

The authors declare no competing financial interest.

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