# An Efficient Synthesis of the Potent Dopamine $D_1$ Agonist Dinapsoline by Construction and Selective Reduction of 2'-Azadimethoxybenzanthrone

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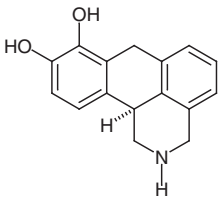
**Abstract:** 8,9-Dihydroxy-2,3,7,11b-tetrahydro-1*H*-naphth[1,2,3-*de*]isoquinoline (dinapsoline, **1**) is a potent dopamine $D_1$ receptor agonist with potential antiparkinsonian activity. A new synthesis was developed with the fully aromatic compound **2** as the key intermediate. The synthesis herein described is suitable for a larger scale preparation of dinapsoline compared to the previously known methods. Furthermore, the unproductive protection/deprotection step of the nitrogen is circumvented by maintaining a high oxidation state of the isoquinoline moiety throughout the synthesis. The construction of the framework was accomplished by Friedel–Crafts acylation and a Suzuki cross-coupling reaction between the commercially available 4-bromoisoquinoline and aryl boronic acid **5**, the latter demanding the transformation of the lithiation-directing amide back to a carboxylic acid functionality. The selective reduction was carried out stepwise with sodium borohydride and sodium cyanoborohydride. The new synthesis is high yielding and reduces the number of transformations in the previously reported methods.

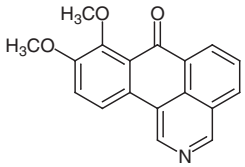
**Key words:** regioselective reduction, boron, Suzuki cross-coupling, electrophilic aromatic substitution, acylation, hydrogenation, amide hydrolysis, cyclization

We have previously reported the synthesis and pharmacological evaluation of 8,9-dihydroxy-2,3,7,11b-tetrahydro-1*H*-naphth[1,2,3-*de*]isoquinoline (dinapsoline, **1**),[1,2] a potent full dopamine $D_1$ agonist containing a rigid β-phenyldopamine pharmacophore. Meanwhile, very promising, though so far unpublished data from pharmacological studies with this substance made it desirable to develop a more straightforward procedure for a large scale preparation of dinapsoline (**1**).

The original synthesis was rather long and, due to the central ring-closure step that proved to be unsuitable for scaleup, only small quantities could be obtained. We report herein an alternative formal synthesis of dinapsoline (**1**) using a different strategy for the construction of the carbon framework, employing the aromatic intermediate **2**. The unproductive protection/deprotection sequence of the original synthesis[1] and its improved modification[2] is thereby circumvented, and the convenience of the well-established chemistry of the benzanthrones[3] is utilized.




**1**



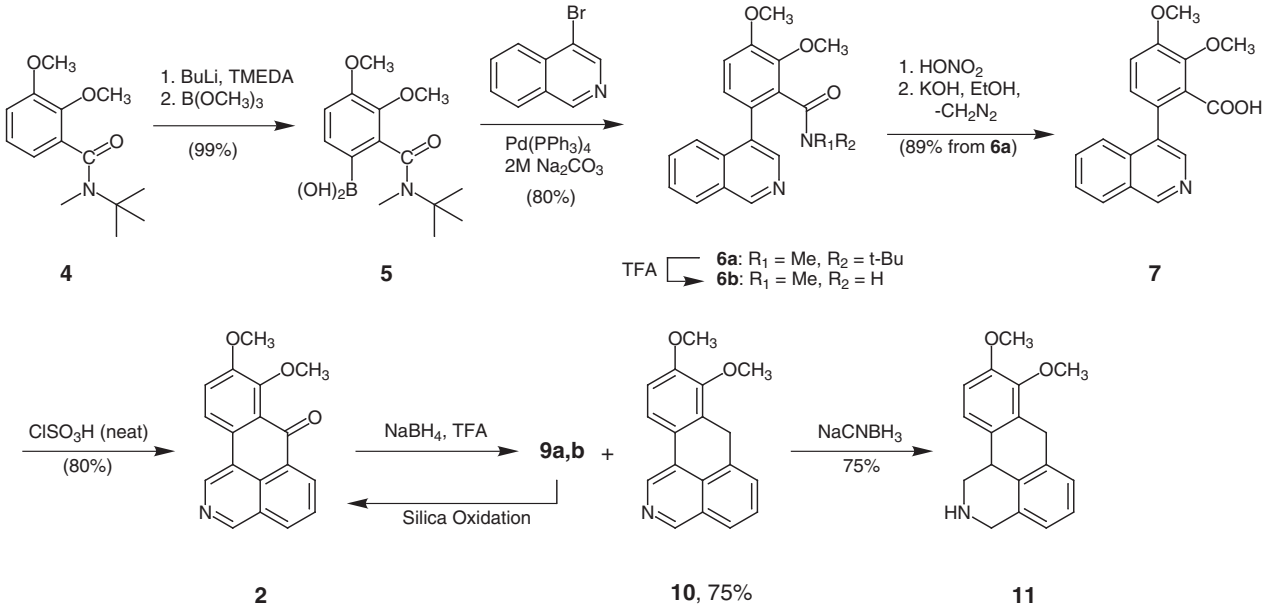

**2**

The skeleton of dinapsoline (**1**) resembles that of the benzanthrones. Our newly envisioned approach relied on the construction of the carbon framework in a highly oxidized state with subsequent selective reduction to the desired functionalities. The aromatic compound **2**, a 2'-azabenzanthrone, was therefore chosen as the primary synthetic goal. Although only one example for a compound with a ring system like **2** is reported in the literature,[4] the chemistry of benzanthrones and related compounds was well established in the 1930s, when these compounds were industrially used as precursors for dyes.[3] That knowledge, combined with modern Pd(0)-mediated methods for the construction of biaryls, was utilized to develop an elegant synthesis of the tetracyclic molecule.

Conversion of 2,3-dimethoxybenzoic acid to its *N*-methyl-*tert*-butylamide **4** protected the carbonyl function as well as allowing functionalization in the ortho position by the directing properties of this amide in lithiation reactions. Metalation and lithium–boron exchange[5] provided the boronic acid **5** in excellent yields (Scheme). Pd-catalyzed Suzuki cross-coupling with commercially available 4-bromoisoquinoline afforded **6a**.[2,6,7] This biaryl has considerable steric bulk, as evidenced by its $^1$H NMR spectra, in which two distinct atropisomers are evident.

Earlier attempts to hydrolyze the analogous diethylamide (**6**, $R_1 = R_2 =$ Et) prepared by essentially the same method, were not successful. Indeed, the recalcitrant nature of *N,N*-dialkylbenzamides is well recognized, and especially 2,6-disubstituted secondary benzamides are essentially inert to hydrolysis.[8–10] We therefore employed the methodology of Reitz,[9] using the *N*-methyl-*tert*-butylamide as a directing group, which can be cleaved stepwise under relatively mild conditions. Deprotection of amide **6a** was achieved in high overall yield by first cleaving off the *t*-butyl with trifluoroacetic acid, giving methylamide **6b**, followed by nitrosation and hydrolysis of the *N*-nitrosamide to give the free carboxylic acid **7**. This acid is best isolated and stored as its hydrochloride or trifluoroacetate, due to the hygroscopic character of the amphoteric compound.

Formation of **7** was always accompanied by small amounts of its ethyl ester. This byproduct, however, could easily be hydrolyzed to the acid. Although this deprotec-



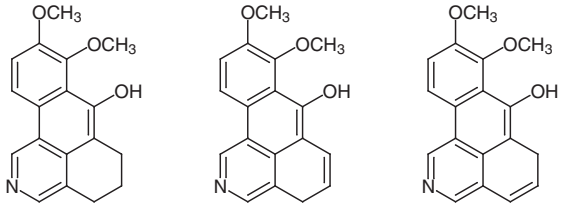

**Scheme**

tion protocol is high yielding and suitable for a large scale, it involves the generation of diazomethane in the final step, which demands the use of special glassware and precautions. In attempts to circumvent this problem, we also prepared an oxazoline protected analogue of boronic acid **5** from 2,3-dimethoxybenzoic acid (**3**) by brominating with dibromodimethylhydantoin (DBDMH),[11] formation of the oxazoline by fusing with the appropriate amino alcohol,[12] halogen-metal exchange, and quenching with trimethyl borate. This compound however, in our hands failed to give satisfactory results in the cross-coupling reaction with 4-bromoisoquinoline, probably due to the even greater steric bulk of the projected biaryl, compared to **6a**.

In another approach to prepare carboxylic acid **7**, we attempted to switch the reactivities of the two partners in the cross-coupling reaction. There are two literature reports of 4-boronated isoquinolines that had been employed in a Suzuki reaction. Nevertheless, our attempts to couple either diethyl(4-isoquinolyl)borane[13] or (4-isoquinolyl)boronic acid[14] with methyl 2-bromo-5,6-dimethoxybenzoate[15] under the reported conditions failed.

The intramolecular Friedel–Crafts acylation as a ring-closing step is well established in the chemistry of anthraquinones and benzanthrones,[3] and we found the reaction conditions for a similar carbocyclic framework[16] readily applicable to heterocyclic acid **7**. Although the reaction conditions are rather harsh, ketone **2** could nevertheless be obtained in high yields and purity. Trials to utilize oleum as the cyclization reagent or the use of an organic solvent gave inferior results.

The conversion of **2** to **1** demanded the selective reduction of both the biarylketone and the heterocyclic ring of the isoquinoline. In our initial trials to reduce **2**, we hoped to accomplish the transformation of both moieties in one step by means of catalytic hydrogenation. Under a variety of conditions however, ring B was usually the target of attack and partially saturated. For example, hydrogenation with $PtO_2$ in acetic acid yielded the azaphenanthrene **8**, while Pd/C in ethanol led to a mixture of the isomers **9a,b**.



**8** **9a** **9b**

Although it is usually possible to control the regioselectivity of the hydrogenation of isoquinolines,[17] no catalytic reduction of the heterocyclic ring could be achieved by this means. We therefore examined selective methods for biarylketone reduction. The action of triethylsilane in TFA[18] on **2** afforded one isomer of **9** (the regiochemistry of the double bond was not elucidated), while sodium borohydride/$AlCl_3$ reduction in THF[19] afforded no isolable products. Finally, the method of Gribble,[20] using $NaBH_4$ in TFA yielded the desired benzanthrene **10**, but this method also formed small amounts of **9**. Fortuitously, during chromatographic workup **9** was found to reoxidize back to the starting material **2**, which could be recycled. The effective yield of **10** was therefore 75% (Scheme).

Dinapsoline dimethyl ether (**11**) was obtained by further reduction of **10** with sodium cyanoborohydride. This

compound was identical to the product prepared by the original method. Demethylation of **11** with $BBr_3$ gave dinapsoline (**1**) as described previously.[1]

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. $^1$H NMR spectra were recorded on a Bruker ARX 300 MHz spectrometer. Chemical shifts are reported in δ values (ppm) relative to an internal standard of TMS in $CDCl_3$. High resolution CI and EI mass spectra were obtained within 0.0015 amu. The ionization gas for CIMS and High Resolution CIMS was isobutane. Microanalyses were obtained from the Purdue Microanalytical Laboratory. Solvents and reagents were used as purchased unless noted otherwise.

**2,3-Dimethoxy-*N*-*tert*-butyl-*N*-methylbenzamide (4)**

A solution of 2,3-dimethoxybenzoic acid (**3**; 24.75 g, 136 mmol) in $CH_2Cl_2$ (500 mL) was cooled by means of an external ice-bath and oxalyl chloride (30 mL) was added dropwise over 10 min, followed by DMF (2.0 mL). The mixture was stirred for 70 min at 0 °C and then 2 h at r.t. The solution was then evaporated to dryness (40 °C bath temperature) and dried in vacuo to give 27.5 g (quant.) of a solid. A part of this crude acid chloride (8.32 g, 41.5 mmol) was dissolved in anhyd THF (15 mL) and added to a cooled (0 °C) solution of methyl-*tert*-butylamine (5.0 mL, 40.9 mmol) and $Et_3N$ (5.82 mL, 41.8 mmol) in anhyd THF (100 mL). The mixture was stirred overnight, filtered, the precipitate washed with THF and the filtrate evaporated to yield 10.13 g of crude product. This solid was recrystallized from $Et_2O$/hexanes to give pure amide **4**, yield: 9.48 g (91%); mp 101.5 °C.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 7.01 (t, 1 H, *J* = 7.8 Hz, Ar-H), 6.83 (dd, 1 H, *J* = 7.7, 1.0 Hz, Ar-H), 6.75 (dd, 1 H, *J* = 7.8, 1.0 Hz, Ar-H), 3.81 (s, 3 H, $OCH_3$), 3.80 (s, 3 H, $OCH_3$), 2.73 (s, 3 H, $NCH_3$), 1.48 (s, 9 H, *t*-$C_4H_9$).

MS (CI): *m*/*z* (%) = 252 ($M^+$ + 1, 100), 196 (28).

Anal. calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N 5.57. Found: C, 67.11; H, 8.36; N 5.45.

**3,4-Dimethoxy-2-(*tert*-butylmethylcarbamoyl)phenylboronic Acid (5)**

Compound **4** (20.88 g, 83.19 mmol) in anhyd THF (100 mL) was added to a solution of TMEDA (13.8 mL, 91.5 mmol), 1.3 M BuLi in cyclohexane (70 mL, 91.5 mmol) and anhyd THF (450 mL) at −78 °C. The resulting creamy suspension was maintained at −78 °C for 45 min, and trimethyl borate (28.4 mL, 250 mmol) was added at once. This mixture was stirred for 6 h while gradually warming to r.t. The solution was acidified with 1 N HCl and brine was added. The phases were separated, the aqueous layer washed with $Et_2O$, and the combined organic phases washed with aq sat $Na_2CO_3$ solution and brine. After drying ($Na_2SO_4$) and evaporation 24.8 g (99%) of product was obtained as a white powder with a melting range of 153−160 °C. This crude material was used directly in the next step.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, 1 H, *J* = 8.3 Hz, Ar-H), 6.91 (d, 1 H, *J* = 8.3 Hz, Ar-H), 6.24 [br s, 2 H, $B(OH)_2$], 3.87 (s, 3 H, $OCH_3$), 3.81 (s, 3 H, $OCH_3$), 2.76 (s, 3 H, $NCH_3$), 1.55 (s, 9 H, *t*-$C_4H_9$).

MS (CI): *m*/*z* (%) = 296 ($M^+$ + 1, 100), 278 (23), 252 (28), 222 (20), 196 (11).

HRMS: *m*/*z* Calcd for $C_{14}H_{22}BNO_5$ 295.9686. Found: 295.9678.

**4-[3,4-Dimethoxy-2-(*tert*-butylmethylcarbamoyl)phenyl]isoquinoline (6a)**

The crude boronic acid **5** (24.8 g, 82.37 mmol) from the previous step, 4-bromoisoquinoline (16.48 g, 79.23 mmol), $(Ph_3P)_4Pd$ (2.50 g), toluene (250 mL), EtOH (120 mL), and 2 M $Na_2CO_3$ solution (100 mL, 200 mmol) were heated at reflux under Ar for 6 h. After cooling, the mixture was separated, the organic phase washed once with brine, and the combined aqueous phases were extracted with toluene. The combined organic phases were washed with $H_2O$ and filtered through a pad of Celite. After evaporation 33.8 g of crude product was obtained that was recrystallized from $Et_2O$/$CH_2Cl_2$/hexanes to give 17.70 g of product in the first crop and an additional 6.21 g upon evaporation of the mother liquors and a second crystallization. The combined yield was 23.91 g (80%); mp 136 °C. An analytical sample was recrystallized from $Et_2O$; mp 138 °C.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 9.20 (br s, 1 H, Ar-H), 8.61 and 8.27 (2 s, 1 H, Ar-H), 7.96 and 7.93 (m and d, 1 H, *J* = 7.2 Hz, Ar-H), 7.75−7.55 (m, 3 H, Ar-H), 7.02 (m, 2 H, Ar-H), 3.93 (s, 3 H, $OCH_3$), 3.91 and 3.90 (2 s, 3 H, $OCH_3$), 2.75 and 2.37 (2 s, 3 H, $NCH_3$), 1.00 and 0.98 (2 s, 9 H, *t*-$C_4H_9$).

MS (CI): *m*/*z* (%) = 379 ($M^+$ + 1, 100%).

Anal. calcd for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.92; N 7.40. Found: C, 73.07; H, 6.86; N 7.48.

**4-[3,4-Dimethoxy-2-(methylcarbamoyl)phenyl]isoquinoline (6b)**

TFA (100 mL) was slowly added to the amide **6a** (23.88 g, 63.23 mmol). After the solid had dissolved, the mixture was heated at reflux for 2.5 h, until no starting material remained according to TLC. After cooling, the solution was evaporated to yield the TFA salt of **6b** as an amber gum. This material was used in the next step without further purification. An analytical sample was recrystallized from MeOH/$CHCl_3$/$Et_2O$ to give white crystals; mp 196 °C.

$^1$H NMR (300 MHz, $CDCl_3$, TFA salt): δ = 9.60 (s, 1 H, Ar-H), 8.50 (s, 1 H, Ar-H), 8.40 (d, 1 H, *J* = 8.0 Hz, Ar-H), 8.08 (dt, 1 H, *J* = 7.9, 1.1 Hz, Ar-H), 7.96 (m, 2 H, Ar-H), 7.39 (br s, 1 H, NH), 7.19 (d, 1 H, *J* = 8.5 Hz, Ar-H), 7.11 (d, 1 H, *J* = 8.5 Hz, Ar-H), 3.99 (s, 3 H, $OCH_3$), 3.96 (s, 3 H, $OCH_3$), 2.71 (d, 3 H, *J* = 4.9 Hz, $NCH_3$).

MS (CI): *m*/*z* = 323 ($M^+$ + 1, 100).

Anal. calcd for $C_{21}H_{19}F_3N_2O_5$: C, 57.80; H, 4.39; N 6.42. Found: C, 57.62; H, 4.31; N 6.44.

**4-(2-Carboxy-3,4-dimethoxyphenyl)isoquinoline (7)**

The crude TFA salt of **6b** obtained above was dissolved in a mixture of AcOH (70 mL) and $Ac_2O$ (400 mL). The solution was cooled to 0 °C and stirred with a mechanical stirrer while $NaNO_2$ (100.0 g) was added in portions over 3 h. The mixture was stirred overnight while cooling was maintained with an ice bath. After filtration, the solids were washed with $Ac_2O$ and $Et_2O$, and the combined organic phases were evaporated, with the bath temperature not exceeding 45 °C. The residue was dissolved in $CH_2Cl_2$ (400 mL) and washed with 2 N NaOH until the washings remained basic. The combined aqueous layers were washed with $CH_2Cl_2$, and the organic solution was dried ($MgSO_4$). After evaporation and drying in vacuo 22.5 g of the *N*-nitrosamide was obtained as an orange solid. This material was dissolved in a mixture of $Et_2O$ (200 mL) and EtOH (20 mL) and added dropwise to a solution of KOH (15.0 g) in 80% EtOH (150 mL), maintained at ~90 °C in a DIAZALD™ apparatus with glacial AcOH in the receiving flask. After that a mixture of $Et_2O$ (50 mL) and EtOH (50 mL) was added dropwise to the reaction mixture to ensure that all of the generated diazomethane had been removed by azeotropic distillation. $H_2O$ (50 mL) was added and the mixture was heated to reflux for 1 h. After evaporation of EtOH, $H_2O$ (200 mL) was added and the mixture was extracted with $CH_2Cl_2$. Evaporation of the solvent yielded 1.40 g (6%) of the ethyl ester of acid **7**. The remaining aqueous layer was made slightly acidic by addition of 2 N HCl and extracted thoroughly with $CHCl_3$. Evaporation of the solvent yielded 20.8 g of material that was

dissolved in 2 N HCl (250 mL) and extracted with $CHCl_3$. The $CHCl_3$ phase was reextracted with 2 N HCl and the combined aqueous phases were evaporated to dryness. Residual $H_2O$ was removed by azeotropic distillation with toluene on the rotary evaporator. The remaining solid was dissolved in absolute EtOH and precipitated with $Et_2O$ to afford 18.55 g (85%) of the HCl salt of acid **7** as a slightly amber powder. The ethyl ester of acid **7** obtained above could be converted to the free acid by standard procedures, giving a combined yield of 89% starting from *N*-methyl-*tert*-butylamide **6a**. For analytical purposes, the TFA-salt of acid **7** was prepared; mp 165 °C.

$^1$H NMR (300 MHz, $CDCl_3$, TFA salt): δ = 9.64 (d, 1 H, *J* = 2.1 Hz, Ar-H), 8.47 (s, 1 H, Ar-H), 8.39 (d, 1 H, *J* = 8.2 Hz, Ar-H), 7.97 (t, 1 H, *J* = 7.3 Hz, Ar-H), 7.87 (t, 1 H, *J* = 7.3 Hz, Ar-H), 7.72 (d, 1 H, *J* = 8.2 Hz, Ar-H), 7.33 (d, 1 H, *J* = 8.5 Hz, Ar-H), 7.19 (d, 1 H, *J* = 8.5 Hz, Ar-H), 3.94 (s, 3 H, $OCH_3$), 3.85 (s, 3 H, $OCH_3$).

MS (CI): *m*/*z* (%) = 310 ($M^+$ + 1, 100), 292 (38).

Anal. calcd for $C_{20}H_{20}F_3NO_5$: C, 56.74; H, 3.81; N 3.31. Found: C, 56.52; H, 3.90; N 3.21.

### 8,9-Dimethoxy-7-oxo-7*H*-naphth[1,2,3-*de*]isoquinoline (5,6-Dimethoxy-*bz*-2-azabenzanthrone, 2)

Chlorosulfonic acid (18.0 mL) was slowly added to the HCl salt of **7** (4.00 g, 11.58 mmol) at 0 °C. This mixture was stirred at r.t. for 44 h, then cooled back to 0 °C and carefully hydrolyzed by the dropwise addition of $H_2O$. The mixture was made basic with 25% NaOH and extracted thoroughly with $CHCl_3$. Drying ($MgSO_4$) and evaporation of the solvent yielded 2.69 g (80%) **2** as dark orange crystals in high purity, melting at 208 °C. A sample was recrystallized from DMF and dried over $P_2O_5$, yielding **2** as tiny yellow needles; mp 222–223 °C.

$^1$H NMR (300 MHz, DMSO): δ = 9.60 (s, 1 H, Ar-H), 9.46 (s, 1 H, Ar-H), 8.66 (dd, 1 H, *J* = 7.5, 1.1 Hz, Ar-H), 8.56 (dd, 1 H, *J* = 7.8, 1.1 Hz, Ar-H), 8.48 (d, 1 H, *J* = 9.0 Hz, Ar-H), 8.00 (t, 1 H, *J* = 7.8 Hz, Ar-H), 7.57 (d, 1 H, *J* = 8.9 Hz, Ar-H), 3.94 (s, 3 H, $OCH_3$), 3.88 (s, 3 H, $OCH_3$).

MS (CI): *m*/*z* = 292 ($M^+$ + 1, 100%).

Anal. calcd for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50; N 4.81. Found: C, 74.10; H, 4.33; N 4.78.

### 8,9-Dimethoxy-7-hydroxy-5,6-dihydro-4*H*-naphth[1,2,3-*de*]isoquinoline (8)

Ketone **2** (1.00 g, 3.44 mmol) was dissolved in AcOH (40 mL) and shaken for 9 h with $PtO_2$ (10 mg) in a Parr apparatus at 60 psi hydrogen pressure. The solution was evaporated to dryness and filtered through a short column of silica with $CHCl_3$/MeOH/$NH_4OH$ (100:4:1) as the solvent. After drying ($MgSO_4$) and evaporation of the solvent the remaining solids were recrystallized from $CH_2Cl_2$ / $Et_2O$ yielding 0.63 g (62%) of **8** as deep red crystals; mp 133 °C.

$^1$H NMR (300 MHz, DMSO): δ = 9.70 (s, 1 H, Ar-H), 8.74 (d, 1 H, *J* = 8.9 Hz, Ar-H), 8.30 (s, 1 H, Ar-H), 7.58 (d, 1 H, *J* = 9.0 Hz, Ar-H), 4.04 (s, 3 H, $OCH_3$), 4.00 (s, 3 H, $OCH_3$), 3.33 (m, 4 H), 2.95 (m, 2 H).

MS (CI): *m*/*z* (%) = 296 ($M^+$ + 1, 85), 278 (100).

Anal. calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N 4.74. Found: C, 73.05; H, 5.63; N 4.71.

### 8,9-Dimethoxy-7-hydroxy-*H*-naphth[1,2,3-*de*]isoquinoline (9)

Ketone **2** (0.50 g, 1.72 mmol) was dissolved in TFA (5.5 mL). Triethylsilane (1.89 mL, 11.86 mmol) was added at once, and the mixture was stirred at r.t. for 15 h. After addition of a few drops of $H_2O$, the solution was evaporated to dryness and filtered through a short column of silica gel with $CHCl_3$/MeOH/$NH_4OH$ (100:4:1) as the solvent. This procedure gave 0.38 g (75%) of **9** as bright orange crystals. On heating in a melting point apparatus the crystals started to darken at 162 °C, and finally decomposed at 204 °C. On heating in an open container in an oven at 140 °C overnight the compound quantitatively reoxidized back to ketone **2**.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 10.41 (br s, 1 H, OH), 9.49 (s, 1 H, Ar-H), 8.35 (dd, 1 H, *J* = 9.0, 2.7 Hz, Ar-H), 8.06 (s, 1 H, Ar-H), 7.53 (dd, 1 H, *J* = 9.3, 2.8 Hz, Ar-H), 6.56 (dd, 1 H, *J* = 9.8, 2.0 Hz, Ar-H), 6.29 (m, 1 H, Ar-H), 4.07 (s, 3 H, $OCH_3$), 4.00 (s, 3 H, $OCH_3$), 3.46 (br s, 2 H).

MS (CI): *m*/*z* (%) = 294 ($M^+$ + 1, 100), 278 (61).

HRMS: *m*/*z* Calcd for $C_{18}H_{15}NO_3$: 294.1130. Found: 294.1131.

### 8,9-Dimethoxy-7*H*-naphth[1,2,3-*de*]isoquinoline (10)

Ketone **2** (4.50 g, 15.46 mmol) in TFA (90 mL) was cooled to 0 °C. $NaBH_4$ pellets (3.01 g, 82.0 mmol) were added one by one in a constant stream of argon. The mixture was stirred at 0 °C for 30 min and then 4.5 h at r.t., when TLC indicated the complete conversion of starting material. The solution was hydrolyzed by the addition of $H_2O$ (40 mL) and most of the liquid was evaporated. It was then cooled to 0 °C and basified by addition of 25% NaOH. This mixture was extracted with $CHCl_3$ and evaporated to yield 3.54 g of crude product, which was purified by flash chromatography ($CHCl_3$/$Et_2O$/$NH_4OH$, silica gel) to give 2.64 g (62%) of the product; mp 183 °C. Some starting material (0.81 g, 18%) was also recovered.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 9.04 (s, 1 H, Ar-H), 8.95 (s, 1 H, Ar-H), 7.84 (d, 1 H, *J* = 8.8 Hz, Ar-H), 7.78 (dd, 1 H, *J* = 7.9, 1.4 Hz, Ar-H), 7.62 (dd, 1 H, *J* = 7.2, 1.6 Hz, Ar-H), 7.56 (t, 1 H, *J* = 7.5 Hz, Ar-H), 6.95 (d, 1 H, *J* = 8.8 Hz, Ar-H), 5.53 (br s, 2 H, $CH_2$), 3.94 (s, 3 H, $OCH_3$), 3.93 (s, 3 H, $OCH_3$).

MS (CI): *m*/*z* = 278 ($M^+$ + 1, 100%).

Anal. calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N 5.05. Found: C, 77.58; H, 5.33; N 4.96.

### 8,9-Dimethoxy-2,3,7,11b-tetrahydro-1*H*-naphth[1,2,3-*de*]isoquinoline (11)

The benzanthrene **10** (3.05 g, 11.01 mmol) was suspended in anhyd MeOH (100 mL) and dissolved upon addition of 3 M HCl in MeOH (15 mL). To this solution powdered $NaBH_3CN$ (4.15 g, 66.06 mmol) was added in portions under argon. A few drops of methanolic bromocresol green solution were added which turned the color of the reaction to brown-blue. The reaction mixture was acidified (the color of the reaction turned yellow) and maintained acidic by adding 3 M methanolic HCl solution through a dropping funnel. When the yellow color persisted, and further addition of HCl did not result in gas evolution, the solution was evaporated to dryness. The residue was partitioned between $Na_2CO_3$ solution and $CH_2Cl_2$, the phases were separated and the aqueous layer was extracted with $CH_2Cl_2$. The organic phase was acidified with a solution of 48% HBr (2.50 g) in EtOH (30 mL) and evaporated to dryness. The crude salt was recrystallized once from EtOH/toluene and a second time from EtOH/EtOAc to yield 2.99 g (75%) of **11** HBr-salt as very fluffy yellowish needles; mp 247 °C. This material showed identical spectroscopic properties to the material obtained by the original method.[1]

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