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A versatile approach to 1-oxo-, 1-oxo-3,4-dihydro- and 1,3,4-trioxo isoquinoline alkaloids and first total synthesis of the dimeric 1-oxoisoquinoline alkaloids berbanine and berbidine

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ABSTRACT

We have worked out a very short approach to 1-oxoisoquinoline alkaloids starting from readily available 2-bromobenzamides utilizing a 2-ethoxyvinylboronate as a C_2 building block for introduction of the C-3,C-4 unit of the isoquinoline core. TFA-mediated cyclization of crude *ortho*-ethoxyvinyl benzamides gave 1-oxoisoquinolines in one single operation. Further modifications of these compounds opened an access to the other chemotypes. In total, 14 alkaloids from four chemotypes (five 1-oxoisoquinolines, six 1-oxo-3,4-dihydroisoquinolines, one 1,3,4-trioxoisoquinoline, and two dimeric isoquinoline alkaloids) were obtained in this investigation. With this approach we improved the total syntheses of the monomeric oxoisoquinolines, and worked out the first total syntheses of the dimeric alkaloids berbanine and berbidine.

1. Introduction

1-Oxoisoquinoline alkaloids are a small class of natural products from plants from different families (Berberidaceae, Ranunculaceae, Menispermaceae, Papaveraceae), and most of these small molecules are found together with larger isoquinoline-type alkaloids such as benzylisoquinolines, bisbenzylisoquinolines, protoberberines and others [1], whereby very high similarities in the substitution patterns of co-occurring alkaloids from the different classes (typically methoxy and/or hydroxy or methylenedioxy groups at the benzenoid ring) were observed. This raised the hypothesis that the small 1-oxoisoquinolines arise from their larger congeners by catabolic processes in the plant cells [2]. *In vitro* degradation of bisbenzylisoquinoline alkaloids by photooxidation [3,4] or chemical and enzymatic methods [5] has been shown to provide products that are identical with some of the isolated 1-oxoisoquinoline alkaloids. However, experimental verification of this hypothesis on a cellular basis is still missing.

The most frequently identified subclasses of this chemotype are 1-oxoisoquinolines like alkaloids **1b-f** and their naturally occurring 3,4-dihydro analogues (e.g., **2a-f**), and even a 1,3,4-trioxoisoquinoline (**3**) has been isolated from *Menispermum dauricum* [6] (Fig. 1).

Further, two "dimeric" 1-oxoisoquinoline alkaloids, characterized by a diaryl ether connection have been identified from different *Berberis* species. Berbidine (**4**) [2], is characterized by the combination of a 1-oxo-3,4-dihydroisoquinoline moiety with a 1,2,3,4-tetrahydroisoquinoline unit, whereas berbanine (**5**) [7] contains one fully aromatic isoquinoline unit. Most likely, also these alkaloids arise from intracellular oxidative degradation of bisbenzylisoquinoline alkaloids. As mentioned above, this hypothesis is supported by the fact that bisbenzylisoquinolines bearing identical substitution patterns were identified in the same plants [2,8]. Further other products of formal oxidative cleavage of bisbenzylisoquinoline alkaloids, albeit resulting from less extensive degradation are known from nature, e.g., sindamine (**6**) [9] having the same substitution pattern as berbidine (**4**) and the macrocyclic bisbenzylisoquinoline alkaloid berbamine (**7**) [3] (Fig. 2).

Despite the reason for oxidative degradation of complex alkaloids to the smaller 1-oxoisoquinolines (**1**–**6**) is obscure, these compounds most likely are more than simply waste products of plant cells. Some of these oxidized products show noteworthy biological activities like vasorelaxant [10], cytotoxic [11] and hepatoprotective [12]. Further, diverse biological activities have been

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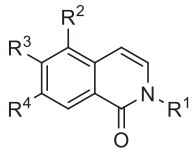
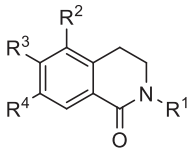
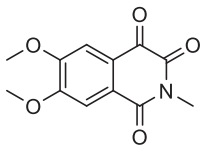


1a-f



2a-f

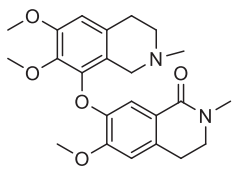


3

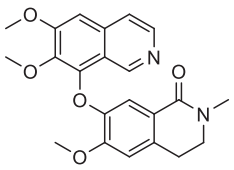
1a R^1 = H, R^2 = H, R^3, R^4 = OMe
1b R^1 = Me, R^2 = H, R^3 ,R^4 = OMe
1c R^1 = H, R^2 = H, R^3 = OMe, R^4 = OH
1d R^1 = Me, R^2 = H, R^3 = OMe, R^4 = OH
1e R^1 = Me, R^2, R^3, R^4 = OMe
1f R^1 = H, R^2 = H, R^3-R^4 = OCH_2O

2a R^1 = H, R^2 = H, R^3, R^4 = OMe
2b R^1 = Me, R^2 = H, R^3, R^4 = OMe
2c R^1 = H, R^2 = H, R^3 = OMe, R^4 = OH
2d R^1 = Me, R^2 = H, R^3 = OMe, R^4 = OH
2e R^1 = Me, R^2, R^3, R^4 = OMe
2f R^1 = H, R^2 = H, R^3-R^4 = OCH_2O

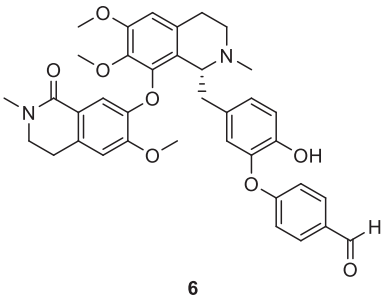
Fig. 1. Three types of isoquinoline alkaloids: 1-oxoisoquinolines (**1a-f**), 1-oxo-3,4-dihydro analogues **2a-f**, and even a 1,3,4-trioxoisoquinoline **(3).**



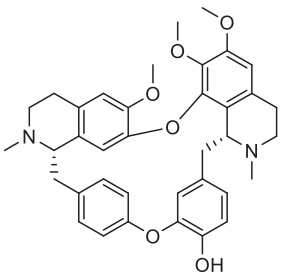
4
berbidine



5
berbanine



6
sindamine



7
berbamine

Fig. 2. "Dimeric" 1-oxoisoquinoline alkaloids berbidine **(4)** and berbanine **(5)**, the natural bisbenzylisoquinoline derivative sindamine **(6)**, and putative natural precursor berbamine **(7).**

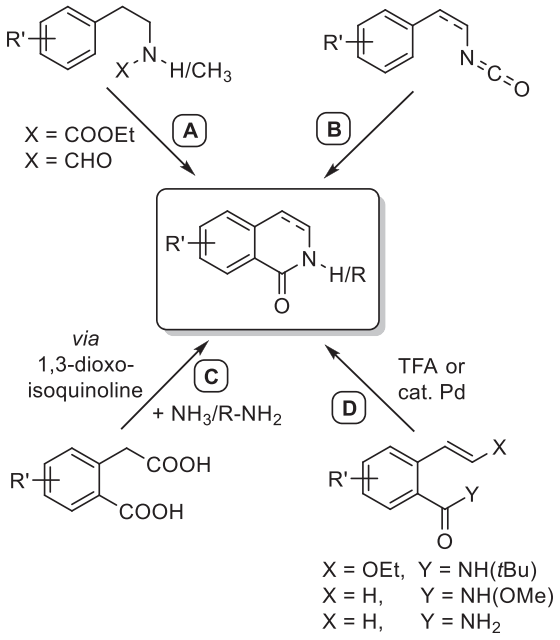


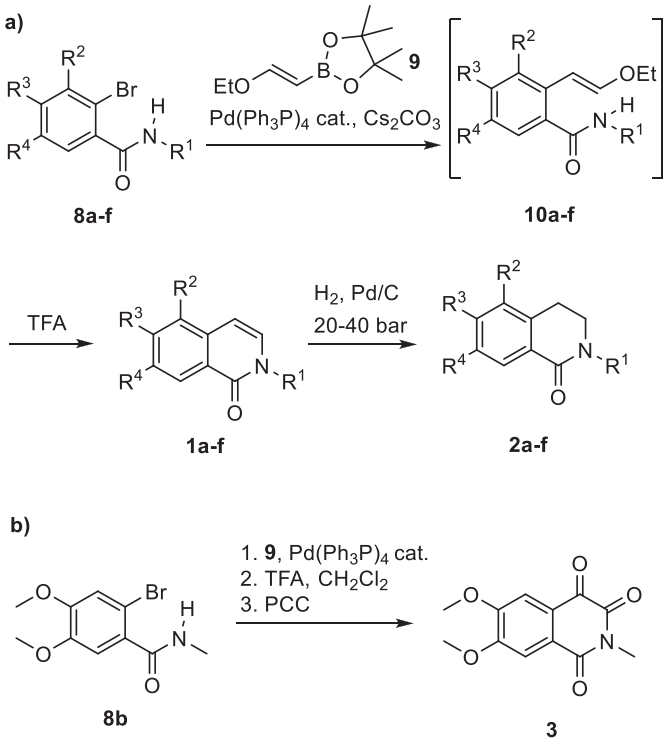
Fig. 3. Published routes to 1-oxoisoquinoline alkaloids (see text).

published for synthetic 1-oxoisoquinolines, as summarized in Refs. [13,14]. But in many reported investigations, only a limited number of compounds has been tested on the same target, most likely due to limited availability of diverse substance libraries of 1-oxoisoquinolines.

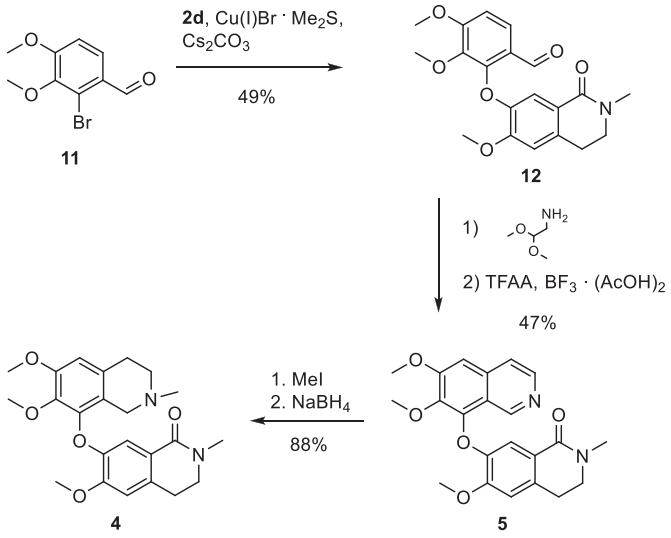
Hence, effective and flexible synthetic approaches for the diverse subtypes of 1-oxoisoquinoline alkaloids are still strongly demanded.

Previous approaches to the 1-oxoisoquinoline alkaloids of type **1**–**3** involved Bischler-Napieralski-type cyclization of phenylethylamine derivatives like ethyl carbamates or isocyanates (Fig. 3, routes A and B) with acidic reagents (polyphosphoric acid [15], $POCl_3$ [16,17], triflic anhydride/DMAP [18]) and cyclization of *N*-formyl derivatives and subsequent *N*-methylation/oxidation of the resulting 3,4-dihydroisoquinolines [8,19]. However, regioisomeric products can be formed in these cyclizations. Alternatively, poorly accessible ring-substituted homophthalic acids can be condensed with amines to give 1,3-dioxoisoquinolines and further be converted into 1-oxoisoquinolines by controlled reduction (Fig. 3, route C) [14]. An alternative approach starting from homophthalic acids includes Vilsmeier formylation and decarboxylation steps [20]. Fully aromatic isoquinolines provide the corresponding 1-oxoisoquinolines *via* *N*-methylation and oxidation with $K_3Fe(CN)_6$ [8]. Finally, a few publications report on the cyclization of benzoic esters (or amides) bearing an acetaldehyde equivalent in *ortho* position to give 1-oxoisoquinolines (Fig. 3, route D). The required acetaldehyde equivalents were constructed either by oxidative cleavage of a dimethylallyl residue [13], *via* TMS-acetylene residues introduced by Sonogashira coupling [21] or *via* introduction of a 2-ethoxyvinyl residue into an *ortho*-brominated *N*-*tert*-butylbenzamide using *trans*-2-ethoxyvinylboronic acid pinacol ester (**9**, see Scheme 1) under Suzuki conditions [22]. Upon heating the obtained Suzuki product with TFA under microwave irradiation, cyclization and cleavage of the *N*-*tert*-butyl residue takes place giving *N*-unsubstituted 1-oxoisoquinolines. Related procedures giving 1-oxo-3,4-dihydroisoquinolines through *ortho*-ethenyl intermediates (obtained by Heck olefination with gaseous ethylene [23] or Rh-catalyzed direct vinylation using toxic ethenyl tributylstannane [24]) require an additional Pd-catalyzed step for ring closure.

Based on Toure's approach [22] we present here an advanced protocol for the synthesis of 1-oxo- and 1-oxo-3,4-dihydroisoquinoline alkaloids using *trans*-2-ethoxyvinylboronic



Scheme 1. a) Synthesis of 1-oxoisoquinolines **1a-f** and subsequent catalytic hydrogenation to give 3,4-dihydro-1-oxoisoquinoline alkaloids **2a-f** (for definition of the residues R^1-R^4, see Fig. 1). b) Synthesis of 1,3,4-trioxoisoquinoline alkaloid **3.**



Scheme 2. Synthesis of alkaloids berbanine **(5)** and berbidine (**4).**

acid pinacol ester (**9**) as a versatile C_2 building block for the introduction of the C-3,C-4 unit of the target compounds. This building block has meanwhile found considerable attention in the synthesis of condensed heteroaromatic ring systems, e.g. indoles [25], pyrido [3,4-*d*]pyrimidines [26] and naphthyridines [27], and has considerable advantages over the alternative stannane-based building block [28,29]. In contrast to the protocol of Toure et al. [22], which provides in the first instance *N*-unsubstituted 1-oxoisoquinolines after acid catalyzed cyclization, we intended to provide an easy introduction of *N*-alkyl residues at an early stage of the synthesis, since most of the 1-oxoisoquinoline alkaloids of interest bear an *N*-methyl group. Subsequent *N*-methylation using iodomethane of the unsubstituted 1-oxoisoquinolines following Toure's protocol is not an option for 1-oxoisoquinolines bearing a free phenol such as our targeted compounds **1c** and **1d**. This should be accomplished by starting from appropriate primary or secondary benzamide building blocks. Further, we intended to explore whether ring closure and reduction of the C-3,C-4 double bond can be accomplished in one single operation. Comparable alkylations of nitrogen-containing functional groups (amides, carbamates, ureas, sulfinamides) using free or masked aldehydes (acetals, enol ethers) under reductive conditions (typically organosilane-TFA combinations) had been published before [30–33]. Very recently, our group reported on convenient *N*-arylethylations of aromatic amines and *N*-heterocycles with (2-methoxyvinyl)arenes using triethylsilane and TFA [34,35]. A further extension of our approach was aimed at the synthesis of 1,3,4-trioxoisoquinolines (see alkaloid **3** [6]) from intermediates of type **1** or **2**, including a final oxidation step with chromium reagents [36,37].

Next, with the 1-oxo-3,4-dihydroisoquinoline alkaloid thalifoline (**2d**) in hand we aimed to synthesize the "dimeric" alkaloids berbanine (**5**) and berbidine (**4**). The diaryl ether bridge should be built up by an Ullmann-type C–O coupling of **2d** with the suitably substituted benzaldehyde **11** (Scheme 2). To access the isoquinoline moiety in berbanine (**5**) a Pomeranz-Fritsch reaction should be conducted with the intermediate **12**. Subsequent *N*-methylation of berbanine (**5**) and reduction of the resulting isoquinolinium should provide berbidine (**4**).

2. Results and discussion

The required *ortho*-brominated primary and *N*-methylbenzamides, except commercially available **8f**, were obtained in yields mostly higher than 90% under standard conditions [38] from commercially available ring-substituted bromobenzoic acids *via* activation with thionyl chloride, followed by amidation with either aqueous ammonia to give primary amides **8a/8c** or methylamine to give the corresponding *N*-methyl benzamides **8b/8d/8e**. Construction of the fused pyridone ring was accomplished in a convenient two-step procedure. First, Suzuki-type cross-coupling with 2-ethoxyvinylboronate **9** under Pd catalysis [28] gave clean conversion (TLC control) into the expected ethoxyvinyl derivatives **10a-f**. The crude reaction mixture was then treated with excess TFA to achieve cyclization to 1-oxoisoquinoline **1a** (most likely not a natural product) and the alkaloids **1b** [1], *N*-demethyldoryphornine (**1c**)[6], doryphornine (**1d**), thalactamine (**1e**), and the unnamed alkaloid **1f** [1] in overall yields ranging from 68 to 92%. Noteworthy, this protocol is compatible with unprotected phenolic groups (see **1c** and **1d**). To the best of our knowledge, this represents the hitherto shortest synthetic approach to *N*-substituted 1-oxoisoquinoline alkaloids.

Next we intended to extend this methodology to the synthesis of the corresponding 3,4-dihydro analogues **2a-f** by subsequent reduction of the C-3,C-4 double bonds of the 1-oxoisoquinolines **1a-f**, preferably in a single operation along with the cyclization step. For this purpose, reduction with triethylsilane-TFA appeared most promising and straightforward, since TFA was already used as an acid for the preceding cyclization reaction. We investigated the feasibility of this approach with **1b**, but unfortunately, this reduction could neither be achieved by treating crude intermediate enol ether **10b** with a TFA-triethylsilane mixture under various conditions, nor could pure 1-oxoisoquinoline **1b** be converted into its 3,4-dihydro derivative under triethylsilane-TFA treatment at ambient or elevated temperatures. Consequently, an alternative reduction protocol had to be applied in order to obtain the 1-oxo-

3,4-dihydroisoquinoline alkaloids. We investigated a number of reduction protocols that had been applied successfully for related substrates (triethylsilane-Pd on carbon [39], sodium borohydride-Pd on carbon [40], sodium borohydride [41], zinc-acetic acid [42], aluminium chloride-cyclohexane [43]), but did not achieve reduction with any of them. Finally, as a low-pressure catalytic hydrogenation under palladium catalysis had been applied by Jangir et al. [14] for the synthesis of the 1-oxo-3,4-dihydroisoquinoline alkaloid oyxhydrastinine, we submitted the 1-oxoisoquinolines to catalytic hydrogenation. However, attempts at low hydrogen pressure gave only very poor conversions, but in accordance with a single example published by Ajao and Bird [44] at 20–40 bar clean reduction of the double bond was obtained giving the 3,4-dihydro-1-oxoisoquinoline alkaloids corydaldine **2a** [45], *N*-methylcorydaldine **2b** [46], northalifoline **2c** [47], thalifoline **2d** [48], *N*-methylthalidaldine **2e** [46] and noroxyhydrastine **2f** [48] in high yields (Scheme 1a). By using Pd/C as catalyst for the hydrogenation we found a less cost-intensive method compared to Toure's protocol, in which PtO_2 is used.

By an extension of this approach, a new approach to 1,3,4-trioxoisoquinoline alkaloid **3** was found. As shown for related 1-oxoisoquinolines before [36,37], chromate oxidation allowed direct conversion of **8b** into the corresponding trione **3**. The alkaloid was obtained in 20% yield in one single operation (cross-coupling/cyclization/oxidation) by simply adding pyridinium chlorochromate to the solution of crude **1b** in dichloromethane/TFA (Scheme 1b). Due to its exceptional shortness, this approach compares favorably with previously published total syntheses of alkaloid **3**, either by oxidation of different intermediates [49–51] or by diverse cyclization reactions [52,53].

Finally, we utilized 1-oxodihydroisoquinoline thalifoline (**2d**) as building block for the first total syntheses of the "dimeric" 1-oxoisoquinoline alkaloids berbidine (**4**) and berbanine (**5**). Formally, an Ullmann-type coupling of phenolic compound **2d** with 8-bromo-6,7-dimethoxyisoquinoline would lead to the desired alkaloid **5**. However, this approach was not promising, as Knabe and coworkers [54] reported on unsuccessful attempts for achieving Ullmann couplings of this compound with a 7-hydroxyisoquinoline in their attempts to synthesize alkaloid phaeantharine. So we decided to perform an Ullman coupling with 2-bromo-3,4-dimethoxybenzaldehyde (**11**), and to construct the fully aromatic isoquinoline unit of alkaloid berbanine (**5**) subsequently in a Pomeranz-Fritsch reaction. Fortunately, Ullmann-type coupling of phenolic compound **2d** with 2-bromo-3,4-dimethoxybenzaldehyde (**11**), readily available from 2-bromo-3-hydroxy-4-methoxybenzaldehyde *via* *O*-methylation [55], gave the diaryl ether **12** in 49% yield. For this conversion we applied a coupling protocol that was recently optimized by us for related Ullmann couplings in the course of the total syntheses of the bisbenzylisoquinoline alkaloids tetrandrine/isotetrandrine [56], utilizing copper(I) bromide-dimethyl sulfide complex as catalyst and cesium carbonate as base [57]. Alkaloid berbanine (**5**) was obtained from intermediate **12** in a Pomeranz-Fritsch reaction using aminoacetaldehyde dimethyl acetal and boron trifluoride/acetic acid complex as Lewis acid according to a procedure of Patel [58] in 47% yield. To our surprise, the NMR data of synthetic berbanine (**5**) were not in accordance with the data published by Host'álková et al. [7] for the natural product isolated from *Berberis vulgaris*. The most distinctive deviation in the ^{1}H NMR is the signal of 1-H of the isoquinoline moiety. In our spectrum it appears as a singlet at 9.16 ppm whereas Host'álková et al. report a doublet at 9.23 (J = 5.9 Hz). Finally we found that Host'álková et al. most likely reported the NMR data of protonated berbanine (**5**). We converted synthetic berbanine into its hydrochloride salt, and the NMR data of this salt and those reported for isolated berbanine were almost identical (for details, see Supporting Information).

Conversion of berbanine (**5**) into its *N*-methylated 1,2,3,4-tetrahydro analogue berbidine (**4**) was achieved in two steps according to a method of Chan et al. [59]. *N*-Methylation of the fully aromatic isoquinoline moiety in **5** with iodomethane gave an isoquinolinium salt, which was reduced with sodium borohydride to give alkaloid **4** in 88% yield over both steps (Scheme 2). Berbidine (**4**) has previously been obtained only by photooxidative degradation of the bisbenzylisoquinoline alkaloids isotetrandrine [4] and phlebicine [60].

3. Conclusion

In summary, we have worked out a very short approach to 1-oxoisoquinoline alkaloids utilizing a 2-ethoxyvinylboronate **9** as a C_2 building block for introduction of the C-3,C-4 unit of the isoquinoline core. In total, 14 alkaloids from four chemotypes were obtained in this investigation. This approach has a number of advantages: a) it uses easily accessible *ortho*-bromobenzamides as precursors, b) the method allows the synthesis of both *N*-unsubstituted and *N*-methylated products, and thus is more flexible than Toure's protocol [22] which starts from *N*-*tert*-butylbenzamides, and leads to *N*-unsubstituted products in the first instance, c) *N*-methylated products are obtained without the need for using hazardous methylation agents, d) in contrast to other approaches (e.g., Ref. [18]), there is no need for protecting phenolic groups, e) the formed alkaloids are not contaminated with isomeric by-products, f) the obtained 1-oxoisoquinolines can easily be converted into 1-oxo-3,4-dihydroisoquinoline alkaloids by catalytic hydrogenation and into 1,3,4-trioxoisoquinolines by dichromate oxidation.

Further, the first total syntheses of the "dimeric" 1-oxoisoquinoline alkaloids berbidine (**4**) and berbanine (**5**) were accomplished using alkaloid thalifoline (**2d**) as a building block. The overall yield along the longest sequence amounts 18% for berbanine (**5**) and 16% for berbidine (**4**).

4. Experimental section

4.1. General reagent and analytical information

All solvents were p.a. grade and/or purified following standard procedures. Chemical reagents were purchased from Sigma Aldrich (Schnelldorf, Germany), ABCR (Karlsruhe, Germany), Fluorochem (Derbyshire, United Kingdom), Acros (Geel, Belgium), Thermo Fisher Scientific GmbH (Dreieich, Germany) or Fluka Chemie AG (Buchs, Switzerland). Melting points were determined by open capillary method on a SMP10 device (Stuart Equipment, Staffordshire, United Kingdom). The values are reported in °C and are uncorrected. NMR spectra were recorded on an Avance III HD 400 MHz Bruker BioSpin spectrometer (Bruker, Billerica, USA). NMR spectra were recorded in deuterated solvents and chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS (δ = 0.00)) or relative to residual solvent peaks ($CDCl_3$ (δ = 7.26/77.16), DMSO-d_6 (δ = 2.50/39.52), methanol-d_4 (δ = 4.87/49.00)). J values are given in hertz (Hz). The spin multiplicity is expressed as: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or combinations thereof. Signal assignments were carried out based on ^{1}H, ^{13}C, HMBC, HSQC and COSY spectra. HRMS were performed by electrospray ionization (ESI) on a Thermo Finnigan LTQ instrument (Thermo Fisher Scientific, Waltham, USA) and by electron impact ionization (EI) on a JMS GCmate II instrument (Jeol, Beabody, USA). All reactions were monitored by thin-layer chromatography (TLC) using polyester

sheets POLYGRAM SIL G/UV 254, coated with 0.2 mm silica gel (Macherey-Nagel, Düren, Germany). Mass spectrometry was performed by atmospheric pressure solids analysis probe (ASAP) *via* atmospheric-pressure chemical ionization (APCI) on an expression^{L} CMS device (Advion, Ithaca, USA). Purification by flash column chromatography (FCC) was performed using silicagel 60 (0.040–0.063 mm, 230–400 mesh ASTM) (Fa. Merck, Darmstadt, Germany).

4.2. General procedures

4.2.1. General procedure A: syntheses of the 2-bromobenzamides (8a-e)

To the respective 2-bromobenzoic acid (2-bromo-4,5-dimethoxybenzoic acid, 2-bromo-5-hydroxy-4-methoxybenzoic acid or 2-bromo-3,4,5-trimethoxybenzoic acid) (1 eq) was added thionyl chloride (1 M in CH_2Cl_2, 2 mL per mmol carboxylic acid) and the reaction mixture was stirred at 76 °C for 7 h. After cooling to room temperature, the volatiles were removed *in vacuo* and the amine (44 eq of conc. aqueous NH_3 solution or methyl amine, respectively) was added at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and allowed to warm up to room temperature while stirring overnight. The mixture was acidified with conc. HCl and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4 and the solvents were removed *in vacuo*.

4.2.2. General procedure B: One pot Suzuki cross-coupling and ring closure leading to 1a-f

The respective 2-bromobenzamide **8a-f** (1 eq, typically 1–2 mmol), tetrakis(triphenylphosphine)palladium(0) (0.05 eq) and *trans*-2-ethoxyvinylboronic acid pinacol ester (1.5 eq) were dissolved in degassed 1,4-dioxane (6 mL/mmol amide) (3 × vacuum/3 × nitrogen) under nitrogen atmosphere and stirred at room temperature for 10 min. A solution of cesium carbonate (3 eq) in degassed water (2 mL/mmol amide) (3 × vacuum/3 × nitrogen) under nitrogen atmosphere was added and the reaction mixture was stirred at 75 °C for 19 h. After cooling to room temperature, TFA (2 mL) was added at 0 °C and the reaction mixture was stirred for 3 h at room temperature. Then, satd. aqueous NH_4Cl solution (15 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography, using the appropriate eluent.

4.2.3. General procedure C: catalytic hydrogenation of the 1-oxoisoquinolines to give 2a-f

The 1-oxoisoquinoline **1a-f** (1 eq) was dissolved in ethanol (15 mL/mmol) and a catalytic amount of 10% palladium on activated charcoal (10–40 mol %) and glacial acetic acid (2.5 mL/mmol) were added. The reaction mixture was hydrogenated at 20–40 bar and 35 °C for 3–12 d. After complete conversion, the mixture was filtered over celite, the celite washed with methanol and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography, using the appropriate eluent.

4.3. Compounds

4.3.1. 2-Bromo-4,5-dimethoxybenzamide (8a)

Synthesized following general procedure A, using 2-bromo-4,5-dimethoxybenzoic acid (0.522 g, 2.00 mmol), thionyl chloride (1 M in CH_2Cl_2, 4 mL, 4 mmol, 2 eq) and with conc. aqueous NH_3 solution (25%, 10 mL, 44 eq), yielding **8a** (0.496 g, 1.91 mmol, 96%) as a light brown solid. mp: 182 °C (ref. [61]: 178 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (s, 1H, 6-H), 7.01 (s, 1H, 3-H), 6.50 (s, 1H, NH_2), 6.13 (s, 1H, NH_2), 3.90 (s, 3H, 5-OCH_3), 3.90 (s, 3H, 4-OCH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.5 (*C*=O), 151.4 (C-4), 148.6 (C-5), 127.6 (C-1), 116.1 (C-3), 113.6 (C-6), 110.4 (C-2), 56.5 (5-OCH_3), 56.3 (4-OCH_3). HR-ESI-MS: *m/z* = calcd. for $C_9H_{11}BrNO_3$ $[M+H]^+$: 259.99168, 261.98964, found: 259.99173, 261.98973.

4.3.2. 2-Bromo-4,5-dimethoxy-N-methylbenzamide (8b)

Synthesized following general procedure A, using 2-bromo-4,5-dimethoxybenzoic acid (1.04 g, 4.00 mmol), thionyl chloride (1 M in CH_2Cl_2, 8 mL, 8 mmol, 2 eq) and methylamine (30% in water, 21 mL, 44 eq), yielding **8b** (0.988 g, 3.60 mmol, 90%) as a white solid. mp: 145 °C (ref. [62]: 119–121 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (s, 1H, 6-H), 6.98 (s, 1H, 3-H), 6.28 (s, 1H, N*H*), 3.89 (s, 3H, 9-OCH_3), 3.88 (s, 3H, 4-OCH_3), 3.01 (d, *J* = 4.9 Hz, 3H, NCH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.6 (*C*=O), 150.9 (C-4), 148.6 (C-5), 129.2 (C-1), 115.9 (C-3), 113.1 (C-6), 109.8 (C-2), 56.4 (5-OCH_3), 56.3 (4–OCH_3), 26.9 (NCH_3). HR-ESI-MS: *m/z* = calcd. for $C_{10}H_{13}BrNO_3$ $[M+H]^+$: 274.00733, 276.00529, found: 274.00759, 276.00559.

4.3.3. 2-Bromo-5-hydroxy-4-methoxy-benzamide (8c)

Synthesized following general procedure A, using 2-bromo-5-hydroxy-4-methoxybenzoic acid (0.494 g, 2.00 mmol), thionyl chloride (1 M in CH_2Cl_2, 4 mL, 4 mmol, 2 eq) and with conc. aqueous NH_3 solution (25%, 10 mL, 44 eq), yielding **8c** (0.382 g, 1.55 mmol, 78%) as a white solid. mp: 218 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.49 (s, 1H, O*H*), 7.63 (s, 1H, NH_2), 7.35 (s, 1H, NH_2), 7.09 (s, 1H, 3-H), 6.84 (s, 1H, 6-H), 3.79 (s, 3H, 4-OCH_3). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 169.0 (*C*=O), 149.1 (C-4), 145.8 (C-5), 131.4 (C-1), 116.4 (C-3), 115.8 (C-6), 107.4 (C-2), 56.3 (4-OCH_3). HR-ESI-MS: *m/z* = calcd. for $C_8H_9BrNO_3$ $[M+H]^+$: 245.97658, 247.97453, found: 245.97609, 247.97407.

4.3.4. 2-Bromo-5-hydroxy-4-methoxy-N-methylbenzamide (8d)

Synthesized following general procedure A, using 2-bromo-5-hydroxy-4-methoxybenzoic acid (0.988 g, 4.00 mmol), thionyl chloride (1 M, 8 mL, 8 mmol, 2 eq) and methylamine (30% in water, 20 mL, 44 eq), yielding **8d** (0.997 g, 3.88 mmol, 97%) as a white solid. mp: 196 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.50 (s, 1H, O*H*), 8.10 (q, *J* = 4.3 Hz, 1H, NH_2), 7.09 (s, 1H, 6-H), 6.79 (s, 1H, 3-H), 3.79 (s, 3H, 4-OCH_3), 2.70 (d, *J* = 4.6 Hz, 3H, NCH_3). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 167.4 (*C*=O), 148.9 (C-4), 145.7 (C-5), 131.2 (C-1), 116.1 (C-6), 115.6 (C-3), 107.3 (C-2), 56.0 (4-OCH_3), 26.0 (C-5). HR-ESI-MS: *m/z* = calcd. for $C_9H_{11}BrNO_3$ $[M+H]^+$: 259.99223, 261.99018, found: 259.99183, 261.98991.

4.3.5. 2-Bromo-3,4,5-trimethoxy-N-methylbenzamide (8e)

Synthesized following general procedure A, using 2-bromo-3,4,5-trimethoxybenzoic acid (**9**) (0.150 g, 0.515 mmol), thionyl chloride (1 M in CH_2Cl_2, 1 mL, 1 mmol, 2 eq) and methylamine (30% in water, 2.7 mL, 44 eq), yielding **8e** (0.111 g, 0.365 mmol, 71%) as a white solid. mp: 115 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.97 (s, 1H, 6-H), 3.89 (s, 3H, 5-OCH_3), 3.88 (s, 3H, 3-OCH_3), 3.86 (s, 3H, 4-OCH_3), 3.01 (d, *J* = 4.9 Hz, 3H, NCH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.0 (*C*=O), 153.1 (C-5), 151.1 (C-3), 144.7 (C-4), 108.9 (C-6), 106.4 (C-2), 61.3 (5-OCH_3), 61.2 (3-OCH_3), 56.4 (4-OCH_3), 26.9 (NCH_3). HR-ESI-MS: *m/z* = calcd. for $C_{11}H_{15}BrNO_4$ $[M+H]^+$: 304.01790, 306.01585, found: 304.01797, 306.01611.

4.3.6. 6,7-Dimethoxyisoquinolin-1(2H)-one (1a)

Synthesized following general procedure B, using 2-bromo-4,5-dimethoxybenzamide (**8a**) (0.322 g, 1.24 mmol), tetrakis(-triphenylphosphine)palladium(0) (0.068 g, 0.059 mmol, 0.047 eq) and *trans*-2-ethoxyvinylboronic acid pinacol ester (0.37 mL, 1.8 mmol, 1.4 eq) in 10 mL 1,4-dioxane, adding cesium carbonate

(1.15 g, 3.52 mmol, 2.85 eq) in 2.5 mL water and TFA (2 mL). Work up and purification by flash column chromatography (50:1 CH_2Cl_2/MeOH) yielded **1a** (0.221 g, 1.08 mmol, 87%) as a light brown solid. mp: 239 °C (ref. [63]: 227–230 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.52 (s, 1H, N*H*), 7.77 (s, 1H, 8-H), 7.12 (d, J = 7.0 Hz, 1H, 3-H), 6.92 (s, 1H, 5-H), 6.51 (d, J = 7.1 Hz, 1H, 4-H), 4.02 (s, 3H, 7-OCH_3), 4.00 (s, 3H, 6-OCH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.6 (C-1), 154.0 (C-6), 149.5 (C-7), 134.0 (C-4a), 126.4 (C-3), 119.9 (C-8a), 107.1 (C-8), 106.7 (C-4), 106.3 (C-5), 56.4 (7-OCH_3), 56.3 (6-OCH_3). HR-EI-MS: m/z = calcd. for $C_{11}H_{11}NO_3$ $[M]^{\cdot+}$: 205.0733, found: 205.0724.

4.3.7. 6,7-Dimethoxy-2-methylisoquinolin-1(2H)-one (1b)

Synthesized following general procedure B, using 2-bromo-4,5-dimethoxy-*N*-methylbenzamide (**8b**) (0.453 g, 1.65 mmol), tetrakis(triphenylphosphine)palladium(0) (0.096 mg, 0.083 mmol, 0.050 eq) and *trans*-2-ethoxyvinylboronic acid pinacol ester (0.53 mL, 2.5 mmol, 1.5 eq) in 15 mL 1,4-dioxane, adding cesium carbonate (1.62 g, 4.96 mmol, 3.00 eq) in 3 mL water and TFA (2 mL). Work up and purification by flash column chromatography (50:1 CH_2Cl_2/MeOH) yielded **1b** (0.306 mg, 1.40 mmol, 85%) as a light orange solid. mp: 109 °C (ref. [64]: 112 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (s, 1H, 8-H), 7.00 (d, J = 7.3 Hz, 1H, 3-H), 6.85 (s, 1H, 5-H), 6.40 (d, J = 7.2 Hz, 1H, 4-H), 4.00 (s, 3H, 7-OCH_3), 3.97 (s, 3H, 6-OCH_3), 3.60 (s, 3H, NCH_3). ^{13}C NMR (101 MHz, $CDCl_3$): 162.1 (C-1), 153.4 (C-6), 149.4 (C-7), 132.7 (C-3), 131.2 (C-4a), 120.3 (C-8a), 107.7 (C-8), 106.1 (C-5), 105.6 (C-4), 56.3 (7-OCH_3), 56.2 (6-OCH_3), 37.3 (NCH_3). HR-EI-MS: m/z = calcd. for $C_{12}H_{13}NO_3$ $[M]^{\cdot+}$: 219.0890, found: 219.0888.

4.3.8. 7-Hydroxy-6-methoxyisoquinolin-1(2H)-one (N-demethyldoryphornine) (1c)

Synthesized following general procedure B, using 2-bromo-4-methoxy-5-hydroxy-benzamide (**8c**) (0.322 mg, 1.31 mmol), tetrakis(triphenylphosphine)palladium(0) (0.072 g, 0.062 mmol, 0.047 eq) and *trans*-2-ethoxyvinylboronic acid pinacol ester (0.40 mL, 1.9 mmol, 1.4 eq) in 10 mL 1,4-dioxane, adding cesium carbonate (1.21 g, 3.72 mmol, 2.84 eq) in 2.8 mL water and TFA (2 mL). Work up and purification by flash column chromatography (40:1 CH_2Cl_2/MeOH) yielded **1c** (0.175 g, 0.915 mmol, 70%) as a light brown solid. mp: 282 °C (ref. [65]: 257–259 °C). ^{1}H NMR (400 MHz, methanol-d_4): δ = 7.63 (s, 1H, 8-H), 7.12 (s, 1H, 5-H), 7.04 (d, J = 7.1 Hz, 1H, 3-H), 6.63 (d, J = 7.1 Hz, 1H, 4-H), 4.00 (s, 3H, 6-OCH_3). ^{13}C NMR (101 MHz, methanol-d_4): δ = 164.4 (C-1), 154.7 (C-6), 148.3 (C-7), 134.9 (C-4a), 126.5 (C-3), 121.2 (C-8a) 111.5 (C-8), 108.1 (C-5), 107.6 (C-4), 56.5 (6-OCH_3). HR-EI-MS: m/z = calcd. for $C_{10}H_9NO_3$ $[M]^{\cdot+}$: 191.0577, found: 191.0579.

4.3.9. 7-Hydroxy-6-methoxy-2-methylisoquinolin-1(2H)-one (doryphornine) (1d)

Synthesized following general procedure B, using 2-bromo-4-methoxy-5-hydroxy-*N*-methylbenzamide (**8d**) (0.476 g, 1.83 mmol), tetrakis(triphenylphosphine)palladium(0) (0.110 g, 0.092 mmol, 0.050 eq) and *trans*-2-ethoxyvinylboronic acid pinacol ester (0.58 mL, 2.8 mmol, 1.5 eq) in 10 mL 1,4-dioxane, adding cesium carbonate (1.87 g, 5.73 mmol, 3.00 eq) in 4 mL water and TFA (2 mL). Work up and purification by flash column chromatography (30:1 CH_2Cl_2/MeOH) yielded **1d** (0.344 g, 1.68 mmol, 92%) as a light brown solid. mp: 217 °C (ref. [1]: 215–217 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (s, 1H, 8-H), 6.96 (d, J = 7.3 Hz, 1H, 3-H), 6.85 (s, 1H, 5-H), 6.69 (s, 1H, O*H*), 6.40 (d, J = 7.2 Hz, 1H, 4-H), 3.99 (s, 3H, 6-OCH_3), 3.60 (s, 3H, NCH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.1 (C-1), 151.6 (C-6), 146.2 (C-7), 132.2 (C-3), 130.8 (C-4a), 120.9 (C-8a), 111.8 (C-8), 105.9 (C-5), 105.7 (C-4), 56.2 (C-10), 37.2 (C-9). HR-EI-MS: m/z = calcd. for $C_{11}H_{11}NO_3$ $[M]^{\cdot+}$: 205.0733, found: 205.0727.

4.3.10. 5,6,7-Trimethoxy-2-methylisoquinolin-1(2H)-one (thalactamine) (1e)

Synthesized following general procedure B, using 2-bromo-3,4,5-trimethoxy-*N*-methylbenzamide (**8e**) (0.465 g, 1.53 mmol), tetrakis(triphenylphosphine)palladium(0) (0.088 g, 0.076 mmol, 0.050 eq) and *trans*-2-ethoxyvinylboronic acid pinacol ester (0.49 mL, 2.3 mmol, 1.5 eq) in 15 mL 1,4-dioxane, adding cesium carbonate (1.49 g, 4.59 mmol, 3.00 eq) in 3 mL water and TFA (2 mL). Work up and purification by flash column chromatography (100:1 CH_2Cl_2/MeOH) yielded **1e** (0.261 g, 1.05 mmol, 69%) as a light brown solid. mp: 120 °C (ref. [1]: 111–112 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (s, 1H, 8-H), 6.98 (d, J = 7.4 Hz, 1H, 3-H), 6.70 (d, J = 7.8 Hz, 1H, 4-H), 3.98 (s, 3H, 5-OCH_3), 3.97 (s, 3H, 7-OCH_3), 3.96 (s, 3H, 6-OCH_3), 3.60 (s, 3H, NCH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.0 (C-1), 153.3 (C-7), 147.5 (C-5), 145.7 (C-6), 130.7 (C-3), 127.1 (C-8a), 122.4 (C-4a), 104.1 (C-8), 100.5 (C-4), 61.7 (5-OCH_3), 61.2 (6-OCH_3), 56.3 (7-OCH_3), 37.3 (NCH_3). HR-ESI-MS: m/z = calcd. for $C_{13}H_{16}NO_4$ $[M+H]^+$: 250.10738, found: 250.10755.

4.3.11. [1,3]Dioxolo[4,5-g]isoquinolin-5(6H)-one (1f)

Synthesized following general procedure B, using 6-bromobenzo[*d*][1,3]dioxole-5-carboxamide (**8f**) (0.400 g, 1.64 mmol), tetrakis(triphenylphosphine)palladium(0) (0.095 g, 0.082 mmol, 0.050 eq) and *trans*-2-ethoxyvinylboronic acid pinacol ester (0.52 mL, 2.5 mmol, 1.5 eq) in 15 mL 1,4-dioxane, adding cesium carbonate (1.60 g, 4.92 mmol, 3.00 eq) in 3 mL water and TFA (2 mL). Work up and washing the crude product with CH_2Cl_2 yielded **1f** (0.210 g, 1.11 mmol, 68%) as a light brown solid. mp: 266 °C (ref. [1]: 268–270 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.14 (s, 1H, N*H*), 7.49 (s, 1H, 8-H), 7.13 (s, 1H, 5-H), 7.07–7.03 (m, 1H, 3-H), 6.44 (d, J = 7.1 Hz, 1H, 4-H), 6.14 (s, 2H, OCH_2O). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 161.1 (C-1), 151.4 (C-6), 147.1 (C-7), 135.1 (C-4a), 127.5 (C-3), 121.3 (C-8a), 104.7 (C-5), 104.0 (C-4, C-8), 101.8 (OCH_2O). HR-EI-MS: m/z = calcd. for $C_{10}H_7NO_3$ $[M]^{\cdot+}$: 189.0420, found: 189.0420.

4.3.12. 6,7-Dimethoxy-3,4-dihydroisoquinolin-1(2H)-one (corydaldine) (2a)

Synthesized following general procedure C, hydrogenating 6,7-dimethoxyisoquinolin-1(2*H*)-one (**1a**) (0.230 g, 1.12 mmol) at 30 bar for 3 d, using palladium on activated charcoal (35 mol %, 0.42 g) in 15 mL EtOH and 5.6 mL AcOH. Purification by flash column chromatography (40:1 CH_2Cl_2/MeOH) yielded **2a** (0.210 mg, 1.01 mmol, 90%) as a white solid. mp: 159 °C (ref. [66]: 174–177 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (s, 1H, 8-H), 6.67 (s, 1H, 5-H), 6.21 (s, 1H, N*H*), 3.92 (s, 6H, 6-OCH_3, 7-OCH_3), 3.55 (td, J = 6.7, 2.8 Hz, 2H, 3-H), 2.93 (t, J = 6.7 Hz, 2H, 4-H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.6 (C-1), 152.3 (C-6), 148.2 (C-7), 132.8 (C-4a), 121.5 (C-8a), 110.3 (C-8), 109.7 (C-5), 56.3 (7-OCH_3), 56.2 (6-OCH_3), 40.7 (C-3), 28.2 (C-4). HR-EI-MS: m/z = calcd. for $C_{11}H_{13}NO_3$ $[M]^{\cdot+}$: 207.0890, found: 207.0889.

4.3.13. 6,7-Dimethoxy-2-methyl-3,4-dihydroisoquinolin-1(2H)-one (N-methylcorydaldine) (2b)

Synthesized following general procedure C, hydrogenating 6,7-dimethoxy-2-methylisoquinolin-1(2*H*)-one (**1b**) (0.214 g, 0.976 mmol) at 40 bar for 5 d, using palladium on activated charcoal (10 mol %, 0.10 g) in 15 mL EtOH and 5.6 mL AcOH. Purification by flash column chromatography (50:1 CH_2Cl_2/MeOH) yielded **2b** (0.138 g, 0.624 mmol, 64%) as a white solid. mp: 125 °C (ref. [67]: 123–124 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (s, 1H, 8-H), 6.62 (s, 1H, 5-H), 3.92 (s, 3H, 7-OCH_3), 3.91 (s, 3H, 6-OCH_3), 3.54 (t, J = 6.8 Hz, 2H, 3-H), 3.13 (s, 3H, NCH_3), 2.93 (t, J = 6.8 Hz, 2H, 4-H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.0 (C-1), 151.8 (C-6), 148.1 (C-7), 131.7 (C-4a), 122.1 (C-8a), 110.6 (C-8), 109.4 (C-5), 56.2 (7-OCH_3),

56.1 (6-OCH$_3$), 48.5 (C-3), 35.3 (NCH$_3$), 27.7 (C-4). HR-EI-MS: *m/z* = calcd. for $C_{12}H_{15}NO_3$ [M]$^{\cdot+}$: 221.1046, found: 221.1044.

4.3.14. 7-Hydroxy-6-methoxy-3,4-dihydroisoquinolin-1(2H)-one (northalifoline) (2c)

Synthesized following general procedure C, hydrogenating 7-hydroxy-6-methoxyisoquinolin-1(*2H*)-one (**1c**) (0.100 g, 0.523 mmol) at 30 bar for 3 d, using palladium on activated charcoal (20 mol %, 0.11 g) in 7.5 mL EtOH and 1.3 mL AcOH. Purification by flash column chromatography (40:1 CH_2Cl_2/MeOH) yielded **2c** (0.074 g, 0.38 mmol, 73%) as a white solid. mp: 235 °C (ref. [47]: 222–224 °C). ^{1}H NMR (400 MHz, methanol-d_4): δ = 7.36 (s, 1H, 8-H), 6.84 (s, 1H, 5-H), 3.92 (s, 3H, 6-OC*H*$_3$), 3.57–3.38 (m, 2H, 3-H), 2.90 (t, *J* = 6.7 Hz, 2H, 4-H). ^{13}C NMR: (101 MHz, methanol-d_4): δ = 196.8 (C-1), 181.0 (C-6), 174.7 (C-7), 161.8 (C-4a), 150.5 (C-8a), 143.1 (C-8), 139.2 (C-5), 84.6 (6-OCH$_3$), 69.3 (C-3), 56.8 (C-4). HR-ESI-MS: *m/z* = calcd. for $C_{10}H_{12}NO_3$ [M+H]$^+$: 194.08117, found: 194.08122.

4.3.15. 7-Hydroxy-6-methoxy-2-methyl-3,4-dihydroisoquinolin-1(2H)-one (thalifoline) (2d)

Synthesized following general procedure C, hydrogenating 7-hydroxy-6-methoxy-2-methylisoquinolin-1(*2H*)-one (**1d**) (0.254 g, 1.24 mmol) at 20 bar for 3 d, and using palladium on activated charcoal (10 mol %, 0.13 g) in 15 mL EtOH and 3 mL AcOH. Purification by flash column chromatography (30:1 CH_2Cl_2/MeOH) yielded **2d** (0.221 mg, 1.07 mmol, 86%) as a white solid. mp: 219 °C (ref. [13]: 210–211 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (s, 1H, 8-H), 6.60 (s, 1H, 5-H), 6.20 (s, 1H, O*H*), 3.91 (s, 3H, 6-OC*H*$_3$), 3.52 (t, *J* = 6.7 Hz, 2H, 3-H), 3.12 (s, 3H, NC*H*$_3$), 2.91 (t, *J* = 6.7 Hz, 2H, 4-H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.0 (C-1), 149.7 (C-6), 144.8 (C-7), 130.9 (C-4a), 122.7 (C-8a), 114.6 (C-8), 109.0 (C-5), 56.1 (6-OCH$_3$), 48.6 (C-3), 35.3 (NCH$_3$), 27.7 (C-4). HR-EI-MS: *m/z* = calcd. for $C_{11}H_{13}NO_3$ [M]$^{\cdot+}$: 207.0890, found: 207.0895.

4.3.16. 5,6,7-Trimethoxy-2-methyl-3,4-dihydroisoquinolin-1(2H)-one (N-methylthalidaldine) (2e)

Synthesized following general procedure C, hydrogenating 5,6,7-trimethoxy-2-methylisoquinolin-1(*2H*)-one (**1e**) (0.100 mg, 0.401 mmol) at 40 bar for 12 d, using palladium on activated charcoal (40 mol %, 0.16 g) in 9 mL EtOH and 3.3 mL AcOH. Purification by flash column chromatography (50:1 CH_2Cl_2/MeOH) yielded **2e** (0.042 g, 0.17 mmol, 42%) as a white solid. mp: 110 °C (ref. [68]: 104–106 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (s, 1H, 8-H), 3.91 (s, 3H, 7-OC*H*$_3$), 3.89 (s, 3H, 6-OC*H*$_3$), 3.85 (s, 3H, 5-OC*H*$_3$), 3.52 (t, *J* = 6.8 Hz, 2H, 3-H), 3.13 (s, 3H,NC*H*$_3$), 2.93 (t, *J* = 6.8 Hz, 2H, 4-H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.7 (C-1), 152.4 (C-7), 149.5 (C-5), 145.2 (C-6), 124.9 (C-8a), 124.8 (C-4a), 107.1 (C-8), 61.1 (6-OCH$_3$), 61.0 (5-OCH$_3$), 56.3 7-OCH$_3$), 48.3 (C-3), 35.4 (NCH$_3$), 21.4 (C-4). HR-EI-MS: *m/z* = calcd. for $C_{13}H_{17}NO_4$ [M]$^{\cdot+}$:251.1152, found: 251.1152.

4.3.17. 7,8-Dihydro-[1,3]dioxolo[4,5-g]isoquinolin-5(6H)-one (noroxyhydrastine) (2f)

Synthesized following general procedure C, hydrogenating [1,3] dioxolo[4,5-g]isoquinolin-5(*6H*)-one (**1f**) (0.100 g, 0.529 mmol) at 20 bar for 3 d, using palladium on activated charcoal (20 mol %, 0.11 g) in 7 mL EtOH and 1.3 mL AcOH. Purification by flash column chromatography (40:1 CH_2Cl_2/MeOH) yielded **2f** (0.023 g, 0.12 mmol, 23%) as a white solid. mp: 189 °C (ref. [66]: 185–187 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (s, 1H, 8-H), 6.65 (s, 1H, 5-H), 6.21 (s, 1H, N*H*), 5.99 (s, 2H, OC*H*$_2$O), 3.52 (td, *J* = 6.7, 2.8 Hz, 2H, 3-H), 2.90 (t, *J* = 6.7 Hz, 2H, 4-H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.2 (C-1), 150.9 (C-6), 147.0 (C-7), 134.7 (C-4a), 123.0 (C-8a), 108.1 (C-8), 107.4 (C-5), 101.6 (OCH$_2$O), 40.4 (C-3), 28.6 (C-4). HR-EI-MS: *m/z* = calcd. for $C_{10}H_9NO_3$ [M]$^{\cdot+}$: 191.0577, found: 191.0575.

4.3.18. 6,7-Dimethoxy-2-methylisoquinoline-1,3,4(2H)-trione (3)

2-Bromo-4,5-dimethoxy-*N*-methylbenzamide **8b** (0.296 g, 1.08 mmol), tetrakis(triphenylphosphine)palladium(0) (0.062 mg, 0.054 mmol, 0.050 eq) and *trans*-2-ethoxyvinylboronic acid pinacol ester (**9**, 0.34 mL, 1.6 mmol, 1.5 eq) were dissolved in degassed 1,4-dioxane (10 mL) under nitrogen atmosphere and stirred at room temperature for 10 min. A solution of cesium carbonate (1.06 g, 3.24 mmol, 3.00 eq) in degassed water (2 mL) was added under nitrogen atmosphere and the reaction mixture was stirred at 75 °C for 19 h. After cooling to room temperature, satd. aqueous NH_4Cl solution (15 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and the solvent was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (4 mL) and TFA (2 mL) was added at 0 °C. The reaction mixture was allowed to warm up to room temperature and stirred for 3 h. Then pyridinium chlorochromate (1.16 g, 5.40 mmol, 5.00 eq) was added and the mixture was stirred at room temperature for 19 h. Water (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with satd. aqueous $NaHCO_3$ solution (20 mL), brine (20 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography (50:1 CH_2Cl_2/MeOH), yielding **3** (0.054 g, 0.22 mmol, 20%) as a greenish yellow solid. mp: 276 °C (ref. [49]: 273 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (s, 1H, 8-H), 7.58 (s, 1H, 5-H), 4.08 (s, 3H,7-OC*H*$_3$), 4.03 (s, 3H, 6-OC*H*$_3$), 3.46 (s, 3H, NC*H*$_3$). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.5 (C-4), 162.5 (C-1), 157.9 (C-3), 155.8 (C-7), 154.1 (C-6), 125.4 (C-8a), 125.0 (C-4a), 110.7 (C-8), 108.5 (C-5), 57.0 (7-OCH$_3$), 56.9 (6-OCH$_3$), 27.6 (NCH$_3$). HR-EI-MS: *m/z* = calcd. for $C_{12}H_{11}NO_5$ [M]$^{\cdot+}$: 249.0632, found: 249.0629.

4.3.19. 3,4-Dimethoxy-2-((6-methoxy-2-methyl-3,4-dihydroisoquinolin-1(2H)-one-7-yl)oxy)benzaldehyde (12)

A mixture of **2d** (0.368 g, 1.77 mmol), 2-bromo-3,4-dimethoxybenzaldehyde (**11**, 0.435 g, 1.77 mmol, 1.00 eq), copper(I) bromide-dimethyl sulfide complex (0.365 g, 1.77 mmol, 1.00 eq) and cesium carbonate (1.735 g, 5.32 mmol, 3.00 eq) was suspended in dry and degassed pyridine (7.5 mL) under nitrogen atmosphere in a pressure tube. The reaction mixture was heated in the tightly closed tube at 110 °C for 48 h. After cooling to room temperature, the mixture was filtered over silica and the silica washed with EtOAc. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography (40:60 EtOAc/H_2Cl_2), yielding the desired product (**12**) (0.323 g, 0.87 mmol, 49%) as a light yellow solid. mp: 129 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.10 (d, *J* = 0.9 Hz, 1H, C*H*O), 7.70 (d, *J* = 8.9 Hz, 1H, 6′-H), 7.31 (s, 1H, 8-H), 6.87 (d, *J* = 8.8 Hz, 1H, 5′-H), 6.74 (s, 1H, 5-H), 3.98 (s, 3H, 6-OC*H*$_3$), 3.94 (s, 3H, 4′-OC*H*$_3$), 3.69 (s, 3H, 3′-OC*H*$_3$), 3.51 (t, *J* = 6.7 Hz, 2H, 3-H), 3.06 (s, 3H, NC*H*$_3$), 2.95 (t, *J* = 6.7 Hz, 2H, 4-H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 188.2 (*C*HO), 164.2 (C-1), 159.4 (C-4′), 151.7 (C-6), 151.6 (C-2′), 147.6 (C-7), 141.4 (C-3′), 133.7 (C-4a), 124.4 (C-6′), 123.4 (C-1′), 122.2 (C-8a), 115.0 (C-8), 110.3 (C-5), 109.0 (C-5′), 60.9 (3′-OCH$_3$), 56.3, 56.2 (4-'OCH$_3$, 6-OCH$_3$), 48.2 (C-3), 35.0 (NCH$_3$), 27.7 (C-4). HR-ESI-MS: *m/z* = calcd. for $C_{23}H_{29}N_2O_5$ [M+H]$^+$: 372.14416, found: 372.14389.

4.3.20. Berbanine (5)

Diarylether **12** (0.150 g, 0.404 mmol) and aminoacetaldehyde dimethyl acetal (48.4 μL, 0.444 mmol, 1.10 eq) were dissolved in anhydrous toluene (5.0 mL) and a small amount of molecular sieves 4 Å was added. The mixture was heated at 100 °C for 4 h under nitrogen atmosphere. After cooling to room temperature, the mixture was filtered to remove the molecular sieves and the solvent was evaporated *in vacuo*. The oily residue was suspended in

trifluoroacetic anhydride (TFAA, 5.0 mL) at 0 °C and added dropwise to a mixture of boron trifluoride acetic acid complex (112 μL, 0.808 mmol, 2.00 eq) in 2.0 mL TFAA at 0 °C. The reaction mixture was allowed to warm up to ambient temperature and stirred for 18 h. The mixture was poured into ice-water, basified with 25% aqueous NH_3 (pH 12–14) and extracted with $CHCl_3$ (3 × 50 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography (5% MeOH and 2% NEt_3 in EtOAc) to give the title compound as a white solid (75.2 mg, 0.191 mmol, 47%). mp: 126 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.16 (s, 1H, 1′-H), 8.40 (d, J = 5.7 Hz, 1H, 3′-H), 7.50 (d, J = 5.7 Hz, 1H, 4′-H), 7.20 (s, 1H, 8-H), 6.99 (s, 1H, 5′-H), 6.78 (s, 1H, 5-H), 4.04 (s, 3H, 6-OCH_3), 4.01 (s, 3H, 6′-OCH_3), 3.85 (s, 3H, 7′-OCH_3), 3.49 (t, J = 6.9 Hz, 2H, 3-H), 3.01 (s, 3H, NCH_3), 2.95 (t, J = 6.7 Hz, 2H, 4-H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.3 (C-1), 156.9 (C-6′), 151.8 (C-6), 147.5 (C-7), 146.7 (C-1′), 143.4 (C-3′), 143.0 (C-8′), 142.1 (C-7′), 134.0 (C-4a′), 133.7 (C-4a), 122.3 (C-8a), 119.6 (C-8a′), 119.3 (C-4′), 114.9 (C-8), 110.4 (C-5), 102.7 (C-5′), 61.3 (7′-OCH_3), 56.5 (6-OCH_3), 56.2 (6′-OCH_3), 48.3 (C-3), 35.1 (NCH_3), 27.8 (C-4). HR-ESI-MS: m/z = calcd. for $C_{23}H_{29}N_2O_5$ $[M+H]^+$: 395.16015, found: 395.15963.

4.3.21. Berbidine (4)

Berbanine (**5**, 0.040 g, 0.101 mmol) was dissolved in acetone (1.0 mL) and iodomethane (63 μL, 1.01 mmol, 10 eq) was added. The mixture was stirred at 45 °C for 3.5 h. After cooling to room temperature, the volatiles were removed *in vacuo*. The obtained methiodide was dissolved in 1.5 mL of a mixture of 4% water in MeOH (vol %), the mixture cooled to 0 °C and sodium borohydride (19.2 mg, 0.507 mmol, 5 eq) was added portion wise. The reaction was stirred for 1 h, while it was allowed to warm to room temperature. The solvent was removed *in vacuo*, the residue treated with water (20 mL) and brought to pH 12–14 with 2M NaOH solution, and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification of the crude product by flash column chromatography (5% MeOH and 2% NEt_3 in EtOAc → 7.5% MeOH and 2% NEt_3 in EtOAc) yielded berbidine (**4**) (36.5 mg, 0.089 mmol, 88%) as a white solid. mp: 113 °C (ref. [3]: 128–130 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (s, 1H, 8-H), 6.71 (s, 1H, 5-H), 6.53 (s, 1H, 5′-H), 3.98 (s, 3H, 6-OCH_3), 3.82 (s, 3H, 6′-OCH_3), 3.64 (s, 3H, 7′-OCH_3), 3.50 (t, J = 6.7 Hz, 2H, 3-H), 3.45 (s, 2H, 1′-H), 3.05 (s, 3H, 2-NCH_3), 2.93 (t, J = 6.7 Hz, 2H, 4-H), 2.87 (t, J = 6.0 Hz, 2H, 4′-H), 2.66 (t, J = 6.0 Hz, 2H, 3′-H), 2.38 (s, 3H, 2′-NCH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.5 (C-1), 152.1 (C-6′), 151.7 (C-6), 146.9 (C-7), 144.8 (C-8′), 139.8 (C-7′), 132.8 (C-4a), 129.9 (C-4a′), 122.3 (C-8a), 121.2 (C-8a′), 114.1 (C-8), 110.3 (C-5), 109.4 (C-5′), 61.0 (7′-OCH_3), 56.4 (6-OCH_3), 56.1 (6′-OCH_3), 52.4 (C-3′), 52.3 (C-1′), 48.4 (C-3), 45.9 (2′-NCH_3, 35.1 (2-NCH_3), 29.1 (C-4′), 27.8 (C-4). The NMR data are mainly in agreement with literature values [2,4,60]. HR-ESI-MS: m/z = calcd. for $C_{23}H_{29}N_2O_5$ $[M+H]^+$: 413.20710, found: 413.20637.

4.3.22. Berbanine ·HCl

Berbanine (**5**, 23.0 mg, 0.0583 mmol) was dissolved in 2 mL 1,4-dioxane and treated with an excess of HCl (4.0 M in 1,4-dioxane). The resulting precipitate was vacuum filtered over a Buchner funnel and washed with diethyl ether. The desired product was obtained as a yellow solid (23.3 mg, 0.0542 mmol, 93%). mp: 186–188 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.22 (d, J = 5.3 Hz, 1H, 1′-H), 8.32 (br s, 1H, 3′-H), 7.96 (d, J = 6.2 Hz, 1H, 4′-H), 7.20 (s, 1H, 5′-H), 7.19 (s, 1H, 8-H), 6.81 (s, 1H, 5-H), 4.13 (s, 3H, 6′-OCH_3), 4.01 (s, 3H, 6-OCH_3), 3.93 (s, 3H, 7′-OCH_3), 3.54 (t, J = 6.7 Hz, 2H, 3-H), 3.04 (s, 3H, NCH_3), 2.98 (t, J = 6.8 Hz, 2H, 4-H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 164.0 (C-1), 162.1 (C-6′), 151.7 (C-6), 146.3 (C-7), 145.0 (C-7′), 143.5 (C-8′), 139.4 (C-1′), 137.1 (C-4a′), 135.1 (C-4a), 131.1 (C-3′), 122.7 (C-4′), 122.3 (C-8a), 119.5 (C-8a′), 114.8 (C-8), 110.9 (C-5), 103.0 (C-5′), 61.5 (7′-OCH_3), 57.2 (6′-OCH_3), 56.5 (6-OCH_3), 48.2 (C-3), 35.2 (NCH_3), 27.8 (C-4).

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at https://doi.org/10.1016/j.tet.2020.131150. These data include MOL files and InChiKeys of the most important compounds described in this article.

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