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Synthesis of oxidative dihydroxy metabolites of benzo[*c*]phenanthridines

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ABSTRACT

The synthesis of dihydroxybenzo[*c*]phenanthridines is described. 6-Bromo-2,3-dihydroxybenzaldehyde was reacted with naphtho[2,3-*d*][1,3]dioxol-5-amine via reductive amination to give the corresponding diol **19**, which was subsequently protected with ethoxymethyl chloride (EOMCl). Radical cyclization provided the EOM-protected dihydroxybenzo[*c*]phenanthridine **21**, the key intermediate for the synthesis of dihydroxybenzo[*c*]phenanthridines **1** and **2**. The use of the EOM-protecting group proved to be more favorable compared with a benzyl group. The high insolubility of chloride salts **1a** and **2a**, even in water, was overcome by the substitution of its chloride counter-anion with trifluoroacetate. Dihydroxy derivatives **1** and **2** are proposed as oxidative metabolites in the biosynthesis of the benzo[*c*]phenanthridine alkaloids.

1. Introduction

The family of benzo[*c*]phenanthridine alkaloids contains congeners with a wide range of biological activity (Fig. 1).[1] For example, sanguinarine exhibits multiple effects, such as antimicrobial[2] and antifungal.[1b] This active compound has been utilized in dental hygiene products[3] or as a feed additive.[4] Another derivative, nitidine, is a known inhibitor of topoisomerases I/II[5] and was also identified as the major antimalarial component isolated from extracts of *Toddalia asiatica*,[6] while chelerythrine, a regioisomer of nitidine, is a potent protein kinase C inhibitor.[7] The *O*-demethylated analog of chelerythrine, NK109,[8] was shown to have significant growth-inhibitory activity against some drug-resistant tumor cell lines. Likewise, synthetic analog NK314,[9] in which ring C was fused to a pyrrolidine cycle, exhibited anti-tumor activity as well.

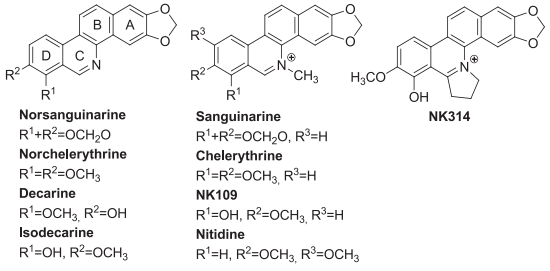

Fig. 1. Some benzo[*c*]phenanthridine alkaloids.

The main natural sources of benzo[*c*]phenanthridine alkaloids are Fumariaceae, Papaveraceae, and Rutaceae plants.[10a] Many syntheses or approaches leading to the benzo[*c*]phenanthridine tetracyclic core have been reported, but there is still demand for more practical syntheses of these compounds. Synthetic strategies are usually based on B- or C-ring closure utilizing various methodologies, such as free radical-mediated, aryne-mediated, Bischler–Napieralski, or transition metal-catalyzed reactions.[10,11] These syntheses are not simple with regard to the number of synthetic steps and frequently have low scope in terms of functional variety and tolerance.

Some research in the field of benzo[*c*]phenanthridine alkaloids has been dedicated to the metabolism of these derivatives.[12] As a result of these studies, the formation of dihydroxy oxidative metabolites was proposed (Fig. 2).

Recently, the metabolism of sanguinarine was proposed by Deroussent and co-workers.[12b] The dihydroxybenzo[*c*]phenanthridine **2** was observed as the dominant oxidative metabolite during incubation of sanguinarine with rat liver microsomes and recombinant human cytochrome P450 (CYP). This metabolite is formed via ring-cleavage and subsequent O-demethylation (Fig. 3).

Nevertheless, the evidence for these metabolites was often based only on interpretation of LC/MS[12b] analyses, which could be

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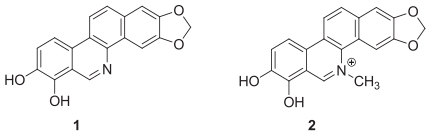


Fig. 2. Proposed oxidative metabolites.

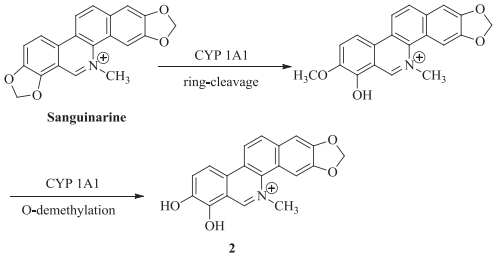


Fig. 3. Proposed metabolic pathway of the dihydroxybenzo[*c*]phenanthridine metabolite **2**.

potentially misleading. In such cases the comparison of analytical data of the sample with the synthetic standard may be very useful. Previously, we reported the synthesis of isodecarine as one of the anticipated metabolites.[11d]

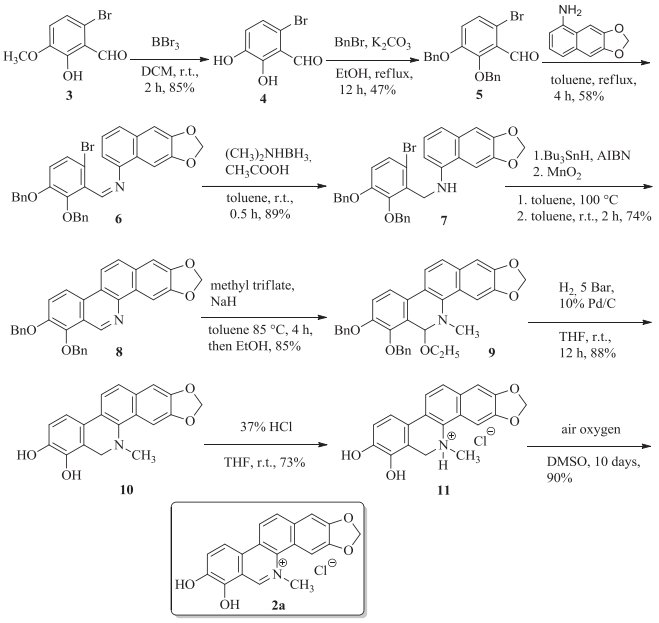
In this work we described the synthesis of the sanguinarine dihydroxy metabolite **2** and its *N*-demethylated analog **1**. This synthesis is applicable for preparation of a sufficient amount of these compounds to serve as analytical standards, which can be used for determination or identification of benzo[*c*]phenanthridine oxidative metabolites in natural sources. Furthermore, the dihydroxy derivatives **1** and **2** can be subjected to evaluate their biological activity, which has never been described. According to our best knowledge, the compound **2** has been described in several papers only as a product isolated from natural sources[12b,13] and characterized only by chromatography methods and mass spectrometry. Derivative **1** has never been described.

The synthesis of the desired dihydroxy compounds is based on our experience with the synthesis of isodecarine where the radical cyclization leading to ring C closure was used to accomplish the construction of the benzo[*c*]phenanthridine heterocyclic system.[11d] Since the selective O-demethylation in the presence of methylenedioxy moiety can be troublesome, the demethylation was carried out early in the synthesis. Furthermore, attention focused on the introduction of a benzyl or ethoxymethyl (EOM) protecting group in order to obtain the desired dihydroxy derivatives **1** and **2** in the final step. Another important aim of this work was to explore the scope of benzyl and EOM-protecting groups in the synthesis of particular benzo[*c*]phenanthridine intermediates.

2. Results and discussion

Commercially available 6-bromo-2-hydroxy-3-methoxybenzaldehyde **3** was chosen as a precursor for introduction of the ring D substituted with two hydroxy groups (Scheme 1). A modified demethylation procedure was carried out with boron tribromide to give dihydroxybenzaldehyde **4**.[14]

At first, benzyl bromide was used to protect both hydroxy groups under similar conditions reported by Rastetter.[15] The resulting benzyl-protected benzaldehyde **5** was condensed with naphtho[2,3-*d*][1,3]dioxol-5-amine[11j,k,16] to obtain aldimine **6**. In the first attempt, the reduction of **6** to amine **7** with sodium borohydride in DMF failed, even upon heating at 140 °C for 4 h. The conversion was insufficient and, moreover, formation of other unknown impurities was observed. Although aldimine reduction



Scheme 1. Using benzyl as the protecting group.

proceeded smoothly if the adjacent hydroxy group was unprotected,[11d] the benzyl protecting group at this position was not favorable for reduction with sodium borohydride. Alternative methodology[11i] utilizing dimethylaminoborane with acetic acid provided amine **7** in high yield and purity.

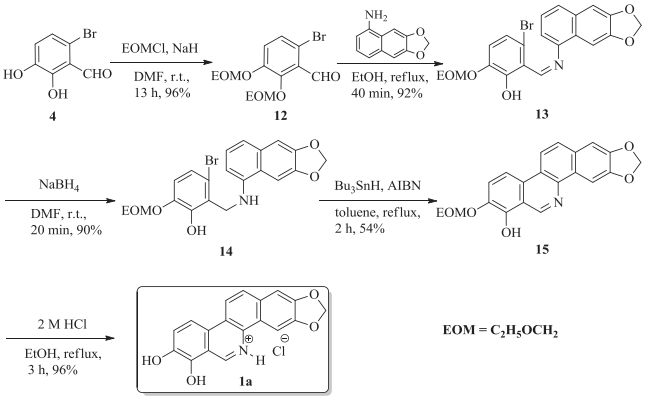
A radical cyclization[18] was applied to finish synthesis of the benzo[*c*]phenanthridine heterocyclic core.[11i,20] Using an excess of both tri-*n*-butyltin hydride and AIBN, which were added in two batches, increased the yield to 74% (purity above 90%) of the crude benzyl-protected benzo[*c*]phenanthridine **8**. Methylation of the phenanthridine nitrogen with methyl triflate[11c,d] in the presence of sodium hydride in toluene generated the corresponding quaternary salt in situ, which was not isolated, and directly transformed into the pseudobase **9** by treatment with ethanol. To obtain dihydroxybenzo[*c*]phenanthridine **2a** directly from the pseudobase **9**, an acid cleavage of the benzyl group with a strong acid was attempted on the basis of described cleavage procedures for similar derivatives.[11i] Treating pseudobase **9** with hydrochloric acid at 100 °C for 1 h gave only a complicated mixture. Debenzylation under catalytic hydrogenation at increased pressure gave dihydroxy derivative **10** as was reported under similar conditions by Nakanishi and coworkers.[8b]

The dihydroxybenzo[*c*]phenanthridine **10** is soluble in common solvents. The initially colorless solution turns a deep purple color indicating oxidation by air oxygen, which was confirmed by an LC/MS analysis showing formation of a product with molecular weight 320. If a tetrahydrofuran solution of the derivative **10** was acidified with hydrochloric acid, a yellow-orange hydrochloride salt **11** was precipitated. Surprisingly, the precipitate was almost insoluble in common solvents including water. The elemental analysis supports formation of hydrochloride salt **11**. In comparison with the precursor **10** its ^{1}H NMR spectrum was different and LC/MS analysis revealed identical retention time and molecular mass as expected.

When a DMSO solution of hydrochloride salt **11** was left in an NMR tube for 10 days, a yellow precipitate arose. Its ^{1}H NMR spectrum and LC/MS analysis confirmed structure assigned to quaternary salt **2a**. Evidently, spontaneous oxidation by air oxygen occurred again. Afterward, identical spectral data were observed at quaternary salts prepared via alternative synthetic routes.

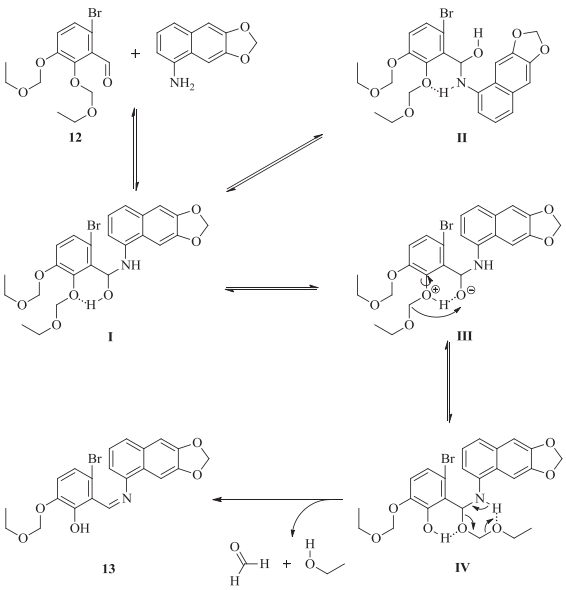
Despite the fact that it was possible to reach the quaternary salt **2a** via the route described in the Scheme 1, the synthesis was not practical. It was desirable to find a more suitable protecting group. An adequately acid labile protecting group able to be cleaved during transformation of a pseudobase to a quaternary salt under mild conditions could simplify the synthesis of the target dihydroxybenzo[*c*]phenanthridines **1a**,**b** and **2a**,**b**. The ethoxymethyl (EOM)[17] group was chosen due to it being commercially more affordable than the analogous MOM protecting group.[19]

Alkylation of the dihydroxybenzaldehyde **4** with ethoxymethyl chloride (EOMCl) provided the EOM-protected benzaldehyde **12** in an almost quantitative yield (Scheme 2). Unfortunately, subsequent condensation of naphtho[2,3-*d*][1,3]dioxol-5-amine with the benzaldehyde **12** proceeded with simultaneous cleavage of one EOM group to give the EOM-monoprotected aldimine **13** (portrayed in the *Z* isomeric form for better clarity with regard to the final benzo[*c*]phenanthridine heterocyclic system). If condensation was performed even in anhydrous toluene, still only the aldimine **13** was observed.



Scheme 2. Protection of hydroxy groups with the EOM group before the condensation step.

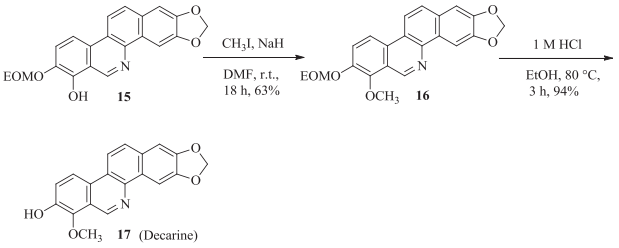
The cleavage of the *ortho*-positioned EOM-protecting group with respect to the aldehyde functionality might be promoted by intramolecular hydrogen bonds (Scheme 3). In the first step, the aminol **I** could be stabilized by an intramolecular hydrogen bond, as well as its conformer **II**. The aminol tautomer **III** induces the EOM group migration to form a presumed intermediate **IV** containing two intramolecular hydrogen bonds, which stabilize the intermediate and simultaneously promote the final irreversible elimination of ethanol and formaldehyde to afford the aldimine **13**.



Scheme 3. Proposed cleavage mechanism of the adjacent EOM-protecting group.

Despite the undesirable cleavage of the protecting group occurred it was still possible to continue the synthesis leading to non-methylated dihydroxybenzo[*c*]phenanthridines **1** (Scheme 2). Previous experiences with isodecarine synthesis showed that the adjacent non-substituted hydroxy group enabled a simple aldimine reduction under mild conditions and direct formation of an aromatized intermediate after radical cyclization without the need for additional treatment with an oxidation agent.[11d] An alternative hypothesis explaining spontaneous oxidation during the radical cyclization step (intramolecular hydride transfer in an organotin intermediate resulting in tributyltin hydride elimination) was also offered.[11d] Indeed, the mild reduction of aldimine **13** with sodium borohydride at room temperature led to the mono-protected amine **14** in high yield, and subsequent cyclization afforded directly the mono-protected benzo[*c*]phenanthridine **15** without use of manganese dioxide. A moderate yield in the cyclization step was partially caused by a competitive radical debromination of the starting amine **14**. A final cleavage of the remaining EOM group with diluted hydrochloric acid provided dihydroxybenzo[*c*]phenanthridine **1a** as a hydrochloride salt, which was almost insoluble in most common organic solvents and also in water. Its very low solubility in DMSO allowed only the reliable measurement of the ^{1}H NMR spectrum. Formation of the hydrochloride salt **1a** was also further supported by an elemental analysis.

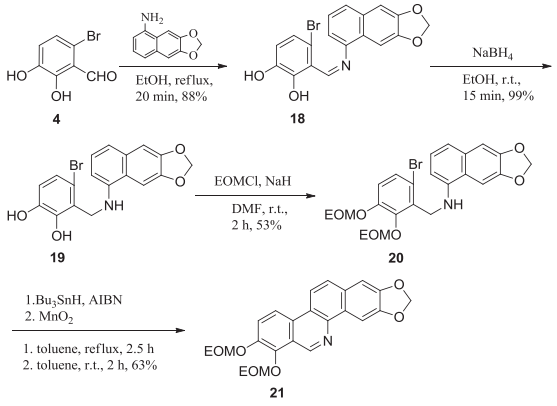
To prove the position of the free alcohol in benzo[*c*]phenanthridine **15** a two-step sequence leading to decarine was designed (Scheme 4). In the first step, methylation of the phenolic hydroxy group with methyl iodide gave benzo[*c*]phenanthridine **16**. Competitive alkylation of the phenanthridine nitrogen was not observed. The remaining EOM group was removed using dilute aqueous hydrochloric acid to provide decarine **17**. The melting point and ^{1}H NMR spectrum of the synthesized decarine were in accordance with reported experimental data.[11f,j]



Scheme 4. Position determination of the remaining EOM group.

Since one EOM group underwent cleavage during the condensation step (Scheme 2) the reduction of the aldimine functionality proceeded under milder conditions, contrary to the case when the adjacent hydroxy group remained protected. To avoid undesirable cleavage of the protecting group and make the reduction milder the synthetic strategy was changed. Thus both hydroxy groups were protected after the aldimine reduction was done (Scheme 5).

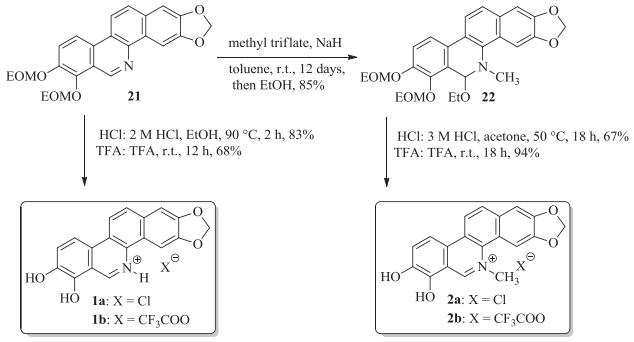
Condensation of the dihydroxybenzaldehyde **4** with naphtho[2,3-*d*][1,3]dioxol-5-amine provided the aldimine **18**, which was reduced to the amine **19**. Both synthetic steps took place smoothly with short reaction times and high yields. The reduction of the aldimine functionality was possible to carry out under very mild reaction conditions with sodium borohydride, in contrast to a similar reaction with benzyl-diprotected aldimine **6** (Scheme 1). Alkylation of the dihydroxy derivative **19** with ethoxymethyl chloride in the presence of sodium hydride afforded the EOM-



Scheme 5. Synthesis of the key EOM-protected intermediate **21** utilizing later introduction of the EOM-protecting group.

protected amine **20** in moderate yield (Scheme 5). Its subsequent radical cyclization gave the key EOM-protected benzo[*c*]phenanthridine **21**. As expected, both EOM-protected hydroxy groups necessitated additional oxidation with manganese dioxide of the in situ generated intermediate after radical cyclization. An attempt to cyclize non-protected amine **19** to provide directly benzo[*c*]phenanthridine core **1** led to a complicated mixture.

The EOM-protecting groups of the benzo[*c*]phenanthridine **21** were cleaved with hydrochloric acid to give the desired hydrochloride salt **1a** (Scheme 6). LC/MS analysis indicated that only one EOM group was easily cleaved under mild conditions, while the second EOM-protecting group required higher temperature to be removed. The different stability of both EOM-protecting groups is possible to explain by a conjugation of the pyridine ring with the *ortho*-positioned EOM-protected oxygen (Fig. 4).



Scheme 6. Synthesis endgame of dihydroxy derivatives **1** and **2**.

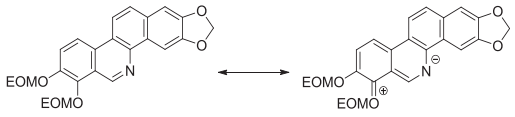
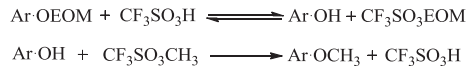


Fig. 4. Conjugation of the *ortho*-positioned EOM-protected oxygen with the pyridine ring.

The isolated dihydroxyhydrochloride salt **1a** was identical to the derivative **1a** synthesized via the route described above (Scheme 2). Due to poor solubility of the hydrochloride salt **1a** we focused on preparation of a trifluoroacetate salt in which we expected higher solubility. An alternative acid cleavage with neat TFA provided trifluoroacetate salt **1b** (Scheme 6) at room temperature. Indeed, substitution of the chloride for trifluoroacetate anion increased solubility of the trifluoroacetate salt **1b** in DMSO. Consequently, it was possible to measure its ^{13}C NMR spectrum where the trifluoroacetate anion was detected. Elemental analysis also supported formation of derivative **1b** as a trifluoroacetate salt.

To synthesize the desired quaternary salts **2a** and **2b** it was necessary to perform a transformation of the benzo[*c*]phenanthridine **21** into the pseudobase **22**. After treatment of the benzo[*c*]phenanthridine **21** with methyl triflate, isolation of the in situ generated quaternary salt was not possible, despite the alkylation being performed under strictly anhydrous conditions and fresh methyl triflate having been used. Formation of other methylated derivatives was observed. The pseudobase **22** was only obtained if the N-methylation was carried out in the presence of sodium hydride with subsequent ethanol addition. These facts indicated that TFA traces might be a trigger of a competitive reaction (Scheme 7) leading to methylated quaternary salts. The N-methylation step proceeded faster at 65 °C, however, the reaction sometimes failed at this elevated temperature. Room temperature was preferred for reproducibility of the reaction, even though a longer reaction time (12 days) was required.



Scheme 7. Assumed competitive methylation.

Preliminary attempts to convert the pseudobase **22** under mild conditions to the quaternary salt **2** brought remarkable results. Diluted acetic acid (20%) regioselectively cleaved one EOM group at room temperature over 72 h. The product was not isolated, only detected via LC/MS analysis. A different stability of both protecting groups was already encountered during the condensation step (Scheme 2) or deprotection of the benzo[*c*]phenanthridine **21**. As expected, both EOM-protecting groups were completely removed with hydrochloric acid at higher temperature to yield the desired quaternary salt **2a** as a deep yellow-orange precipitate with very poor solubility in water and common organic solvents (acetonitrile, acetone, THF, DMF, DMSO, ethanol, pyridine). To improve the solubility of the quaternary salt **2**, the pseudobase **22** was treated with neat TFA to give the quaternary trifluoroacetate salt **2b**. The NMR spectra and elemental analysis supported the anticipated structure of quaternary salts **2a** and **2b**.

3. Conclusions

In summary, dihydroxybenzo[*c*]phenanthridine derivatives **1**and **2** were prepared via several modified synthetic routes. The choice of protecting group was an important factor in the synthesis of both sets of derivatives. While application of the benzyl group was not favorable, the EOM-protecting group enabled the synthesis of the desired dihydroxy derivatives in reasonable yields. A different stability of EOM groups to acid cleavage was observed that might potentially be used for regioselective alkylation of the dihydroxybenzo[*c*]phenanthridine derivatives. A problem with the insolubility of dihydroxy chloride derivatives **1a** and **2a** was overcome by the treatment of the pseudobase **22** with TFA to afford, analogous, more soluble trifluoroacetate salts **1b** and **2b**. To conclude, the reported synthesis has the potential to be utilized for preparation of both dihydroxy synthetic derivatives **1** and **2**. Moreover, independent syntheses of these derivatives will enable the clarification of the metabolism of these alkaloids and the study of their biological activity.

4. Experimental section

4.1. General

All starting materials are commercially available. Commercial reagents were used without purification. Melting points were

determined on a Boetius stage and are uncorrected. The infrared (IR) spectra were measured via KBr disc method. Flash column chromatography was performed on silica gel (pore size 60 Å, 40–63 μm particle size). The LC/MS analyses were carried out on UHPLC–MS system consisting of UHPLC chromatograph with photodiode array detector and triple quadrupole mass spectrometer, using C18 column at 30 °C and flow rate of 800 μL/min. Mobile phase was (A) 0.01 M ammonium acetate in water, and (B) acetonitrile, linearly programmed from 10% to 80% B over 2.5 min, kept for 1.5 min. The column was re-equilibrated with 10% of solution B for 1 min. The APCI source operated at discharge current of 5 μA, vaporizer temperature of 400 °C, and capillary temperature of 200 °C. The HRMS analyses were carried out on HRMS-Exactive (Orbitrap) MS, Thermo, USA. The ^{1}H and ^{13}C NMR spectra were measured in DMSO-d_6 or $CDCl_3$ at 20 °C; chemical shifts δ are reported in parts per million.

*4.1.1. 6-Bromo-2,3-dihydroxybenzaldehyde (**4**).*[14a] 6-Bromo-2-hydr oxy-3-methoxybenzaldehyde (**3**) (4.78 g, 20.7 mmol) was dissolved in DCM (40 mL) and added dropwise under stirring during 30 min to an ice-cooled solution of BBr_3 (8.00 mL, 83.0 mmol) in DCM (60 mL). The reaction mixture was stirred for 2 h at room temperature and then water (100 mL) was added dropwise under ice-cooling and rigorous stirring. DCM was distilled off under reduced pressure. The resulting yellow precipitate was filtered off and washed with water. The crude product was crystallized from a mixture of water and methanol (3:2, v/v) to obtain yellow crystals (3.82 g, 85% yield). Mp 143–145 °C. R_f (toluene/acetonitrile, 10:1) 0.5. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.99 (d, J=8.4 Hz, 1H), 7.07 (d, J=8.4 Hz, 1H), 9.92 (br s, 1H), 10.19 (s, 1H), 11.50 (br s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 113.2, 118.0, 122.3, 123.8, 146.1, 152.0, 196.7. IR (cm^{-1}): 3390, 3085, 1638, 1441, 1382, 1275, 1195, 1013, 892, 717, 568. MS (APCI): m/z=214.8 and 216.8 [M−H]$^-$. Anal. Calcd for $C_7H_5BrO_3$ (217.0): C, 38.74; H, 2.32. Found C, 38.59; H, 2.51.

*4.1.2. 2,3-Bis(benzyloxy)-6-bromobenzaldehyde (**5**).* To a solution of the dihydroxybenzaldehyde **4** (1.09 g, 5.00 mmol) in anhydrous ethanol (7.5 mL) were added benzyl bromide (2.16 g, 12.6 mmol) and potassium carbonate (0.870 g, 6.30 mmol) under stirring at the room temperature under an argon atmosphere. The reaction mixture was refluxed for 12 h under continuous stirring. The ethanol was then evaporated under reduced pressure. Ethyl acetate (40 mL) and water (20 mL) were added to the resulting oily residue. The organic layer was separated and the water phase was additionally extracted with ethyl acetate (2×40 mL). The collected organic layers were washed with water (20 mL) and brine (20 mL), and dried over $MgSO_4$. Finally, ethyl acetate was evaporated under reduced pressure. The crude product was crystallized from ethanol (96%) to give (0.940 g, 47% yield) crystalline compound. Mp 69–71 °C. R_f (toluene/acetonitrile, 10:1) 0.9. ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.10 (s, 2H), 5.25 (s, 2H), 7.27–7.56 (m, 12H), 10.14 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 70.5, 75.6, 110.7, 119.7, 127.9, 128.1, 128.27, 128.3, 128.5, 128.7, 128.8, 129.5, 136.19, 136.24, 150.4, 151.6, 190.3. IR (cm^{-1}): 3063, 3029, 1703, 1567, 1456, 1367, 1301, 1253, 1231, 1061, 960, 697. MS (APCI): m/z=396.9 and 398.9 [M+H]$^+$. Anal. Calcd for $C_{21}H_{17}BrO_3$ (397.26): C, 63.49; H, 4.31. Found C, 63.57; H, 4.22.

*4.1.3. N-[2,3-Bis(benzyloxy)-6-bromo-benzylidene]naphtho-[2,3-d][1,3]dioxol-5-amine (**6**).* A solution of the benzaldehyde **5** (1.40 g, 3.52 mmol) and naphtho[2,3-*d*][1,3]dioxol-5-ylamine (0.660 g, 3.52 mmol) in toluene (30 mL) was heated to reflux for 4 h. After that, toluene was removed and the resulting dark yellow oily product crystallized from a mixture of toluene and ethanol. After standing at 2 °C for 18 h, the crystalline yellow compound (1.15 g, 58%), was filtered off, washed with ethanol, and dried. Mp 114–116 °C. R_f (toluene) 0.5. ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.12 (s, 2H), 5.27 (s, 2H), 6.12 (s, 2H), 6.84 (d, J=7.1 Hz, 1H), 7.19–7.48 (m, 11H), 7.48–7.57 (m, 4H), 7.64 (d, J=8.2 Hz, 1H), 8.64 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 70.9, 76.0, 100.3, 101.8, 104.1, 112.3, 112.4, 117.7, 125.2, 125.6, 125.9, 128.4, 128.7, 128.8, 128.9, 129.0, 129.1, 129.5, 130.8, 131.3, 137.0, 137.4, 147.9, 148.2, 148.3, 148.8, 152.1, 158.0. IR (cm^{-1}): 3032, 2899, 1628, 1462,l 1361, 1250, 1040. MS (APCI): m/z=566.0 and 568.0 [M+H]$^+$. Anal. Calcd for $C_{32}H_{24}BrNO_4$ (566.4): C, 67.85; H, 4.27; N, 2.47. Found: C, 67.95; H, 4.34; N, 2.36.

*4.1.4. N-[2,3-Bis(benzyloxy)-6-bromo-benzyl]naphtho[2,3-d][1,3]dioxol-5-amine (**7**).* To a solution of the amine **6** (280.0 mg, 0.490 mmol) and dimethylaminoborane complex (26.0 mg, 0.440 mmol) in toluene (4 mL) was added acetic acid (0.330 mL, 5.50 mmol), dropwise, under stirring. After 20 min of stirring at a room temperature, the reaction was quenched with 1 M HCl (2.3 mL) and continuously stirred for an additional 30 min. Subsequently, a solution of 5 M NaOH was added to the reaction mixture to make it strongly alkaline. The free base of the prepared amine was extracted with toluene (2×4 mL). Combined organic extracts were washed with water, brine, and dried over $MgSO_4$. Toluene was removed under reduced pressure and resulting oily product was triturated with ethanol (5 mL) to give a pale yellow compound (250.0 mg, 89% yield) of sufficient purity for a next step. A sample for analysis was prepared by recrystallization from an ethanol/chloroform mixture. Mp 165–167 °C. R_f (toluene) 0.6. ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.36 (d, J=3.7 Hz, 2H), 5.04 (s, 2H), 5.21 (s, 2H), 5.73 (t, J=3.7 Hz, 1H), 6.05 (s, 2H), 6.56 (d, J=7.5 Hz, 1H), 7.00 (d, J=8.1 Hz, 1H), 7.07–7.30 (m, 8H), 7.33–7.46 (m, 4H), 7.51 (d, J=7.0 Hz, 2H), 7.65 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 43.7, 70.7, 75.7, 99.5, 101.4, 103.7, 104.5, 115.5, 116.3, 119.6, 125.6, 125.9, 128.3, 128.4, 128.6, 128.7, 128.8, 129.0, 129.4, 131.5, 132.8, 137.3, 137.6, 144.0, 146.8, 147.3, 148.4, 151.7. IR (cm^{-1}): 3034, 1460, 1275, 1240, 1040. MS (APCI): m/z=568.0 and 570.0 [M+H]$^+$. Anal. Calcd for $C_{32}H_{26}BrNO_4$ (568.5): C, 67.61; H, 4.61; N, 2.46. Found: C, 67.66; H, 4.73; N, 2.41.

*4.1.5. 1,2-Bis(benzyloxy)-[1,3]dioxolo[4′,5′:4,5]benzo[1,2-c]-phenanthridine (**8**).* To a solution of the amine **7** (740.0 mg, 1.30 mmol) and Bu_3SnH (757.0 mg, 2.60 mmol) in toluene (30 mL) was added AIBN (320.0 mg, 1.95 mmol) at 70 °C. The formed solution was heated to reflux for 3 h. After that, the solution was cooled to 70 °C and an additional portion of Bu_3SnH (757.0 mg, 2.60 mmol) and AIBN (320.0 mg, 1.95 mmol) were added. Then a reaction mixture was refluxed for additional 4 h. The solution was cooled to room temperature, MnO_2 (1.0 g) was added, and resulting mixture was vigorously stirred for 2 h. The termination of oxidation depends on a quality of MnO_2.[21] Oxidation process was monitored with TLC using toluene as a mobile phase. The desired product exhibits yellow-green florescence at 366 nm. After oxidation was complete, the reaction mixture was filtered through Celite, and filtrate concentrated in vacuo. The resulting residue was extracted with cyclohexane (25 mL) to remove most of impurities. The undissolved solid was filtered off, washed with cyclohexane (3×3 mL), and dried to give a pale-yellow product (470.0 mg, 74% yield) in purity above 90% (HPLC analysis). A sample for analysis was prepared by recrystallization from a chloroform/cyclohexane mixture. Mp 192–195 °C. R_f (toluene) 0.4. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.36 (s, 4H), 6.15 (s, 2H), 7.27–7.32 (m, 2H), 7.33–7.49 (m, 6H), 7.54 (m, 3H), 7.67 (d, J=9.0 Hz, 1H), 7.85 (d, J=9.0 Hz, 1H), 8.35 (d, J=9.0 Hz, 2H), 8.71 (s, 1H), 9.79 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 72.3, 76.2, 77.3, 101.4, 102.3, 104.5, 118.3, 118.4, 120.0, 120.9, 121.5, 122.4, 127.1, 127.7, 128.3, 128.4, 128.6, 128.7, 128.8, 129.9, 136.8, 137.1, 144.9, 146.8, 148.4, 148.6, 148.7. IR (cm^{-1}): 3029, 2909, 1540, 1465, 1268, 1241,

1040. MS (APCI): m/z=486.3 $[M+H]^+$. Anal. Calcd for $C_{32}H_{23}NO_4$ (485.5): C, 79.16; H, 4.77; N, 2.88. Found: C, 79.32; H, 4.71; N, 2.67.

*4.1.6. 13-Ethoxy-1,2-bis(benzyloxy)-12-methyl-12,13-dihydro-[1,3]dioxolo[4′,5′:4,5]benzo[1,2-c]phenanthridine (**9**).* To a solution of the phenanthridine **8** (170.0 mg, 0.350 mmol) in anhydrous toluene (3 mL) was added NaH (42.0 mg; 1.75 mmol) followed by methyl triflate (230.0 mg; 1.40 mmol). The resulting suspension was stirred in a tightly sealed vial at 85 °C for 4 h. After cooling, ethanol (1 mL) was carefully added dropwise under cooling to the formed yellow suspension of the quaternary salt. The resulting colorless solution was evaporated to dryness after 15 min of stirring. The solid was suspended in water (3 mL), filtered off, washed with water, and dried to give a beige colored powder (162.0 mg, 85% yield) of about 90% purity, suitable for a next step. A sample for analysis was prepared by recrystallization from a chloroform/ethanol mixture. Mp 145–148 °C. R_f (toluene/MeOH, 200:1) 0.3. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10 (t, J=7.0 Hz, 3H), 2.65 (s, 3H), 3.57–3.69 (m, 1H), 3.87–4.02 (m, 1H), 5.06–5.32 (m, 4H), 5.69 (s, 1H), 6.07 (s, 2H), 7.15 (t, J=4.0 Hz, 2H), 7.30–7.57 (m, 11H), 7.58–7.70 (m, 2H), 7.80 (d, J=8.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.3, 40.7, 61.7, 71.2, 75.9, 84.8, 100.8, 101.1, 104.7, 114.9, 119.1, 120.3, 122.7, 123.4, 125.5, 126.4, 126.8, 127.1, 127.6, 128.1, 128.2, 128.5, 128.7, 131.1, 137.1, 138.0, 138.8, 146.1, 147.4, 148.0, 151.4. IR (cm^{-1}): 3031, 2868, 1496, 1467, 1240. MS (APCI): m/z=500.3 $[M+H-EtOH]^+$. Anal. Calcd for $C_{35}H_{31}NO_5$ (545.6): C, 77.04; H, 5.73; N, 2.57. Found: C, 77.12; H, 5.86; N, 2.51.

*4.1.7. 12,13-Dihydro-[1,3]dioxolo[4′,5′:4,5]benzo[1,2-c]-phenanthridine-1,2-diol (**10**).* The pseudobase **9** (65.5 mg, 0.120 mmol) in THF (10 mL) was hydrogenated with hydrogen (5 bar) under catalysis with 10%-Pd/C (20.0 mg). After 12 h of stirring, the catalyst was removed by filtration and the solution was evaporated to dryness. The residue was triturated with chloroform (5 mL) and the precipitated solid was filtered off to give white solid (33.9 mg, 88% yield). Mp 138–143 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.47 (s, 3H), 4.13 (s, 2H), 6.12 (s, 2H), 6.80 (d, J=8.2 Hz, 1H), 7.19 (d, J=8.2 Hz, 1H), 7.28 (s, 1H), 7.42–7.58 (m, 2H), 7.70 (d, J=8.6 Hz, 1H), 8.53 (s, 1H), 9.43 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 41.7, 48.8, 100.2, 101.6, 104.7, 114.5, 119.7, 120.6, 124.1, 124.3, 125.2, 125.4, 126.3, 130.6, 142.1, 142.6, 145.8, 147.5, 148.3. IR (cm^{-1}): 3361, 2956, 1499, 1474, 1286, 1250, 1039, 859. MS (APCI): m/z=322.1 $[M+H]^+$; 320.0 $[M-H]^-$. Anal. Calcd for $C_{19}H_{15}NO_4$ (321.3): C, 71.02; H, 4.71; N, 4.36. Found: C, 70.88; H, 4.62; N, 4.31.

*4.1.8. 12,13-Dihydro-[1,3]dioxolo[4′,5′:4,5]benzo[1,2-c]-phenanthridine-1,2-diol hydrochloride (**11**).* To a solution of the diol **10** (15.0 mg, 0.047 mmol) in THF (3 mL) was added an aqueous solution of 37%-HCl (0.5 mL). Under continuous stirring a hydrochloride salt started to precipitate slowly from the colorless solution. After 90 min the precipitated solid was filtered off, washed with water, and dried to give a yellow compound (12.2 mg, 73% yield). Mp 205–211 °C dec. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.76 (s, 3H), 4.10 (br s, 1H) 4.47 (s, 2H), 6.20 (s, 2H), 6.94 (d, J=8.2 Hz, 1H), 7.35 (d, J=8.4 Hz, 1H), 7.43 (s, 1H), 7.74–7.88 (m, 2H), 7.96 (s, 1H), 9.83 (br s). ^{13}C NMR (75 MHz, DMSO-d_6): the spectrum was not recorded due to low solubility. MS (APCI): m/z=322.1 $[M+H]^+$; 320.0 $[M-H]^-$. Anal. Calcd for $C_{19}H_{16}ClNO_4$ (357.8): C, 63.78; H, 4.51; N, 3.91. Found: C, 63.46; H, 4.65; N, 3.58.

*4.1.9. 6-Bromo-2,3-bis(ethoxymethoxy)benzaldehyde (**12**).* A solution of the dihydroxybenzaldehyde **4** (0.630 g, 2.90 mmol) in DMF (5 mL) was added dropwise under cooling (3–5 °C) and stirring to a suspension of sodium hydride (0.200 g, 8.30 mmol) in DMF (5 mL) under argon. Then to the continuously cooled and stirred orange suspension was added (chloromethoxy)ethane (0.750 g, 7.90 mmol). The reaction mixture was stirred for 13 h at room temperature. After that diethyl ether (20 mL) and water (30 mL) was added and the diethyl ether phase was separated. The water phase was additionally extracted with diethyl ether (2×20 mL). The collected organic phases were washed with brine (20 mL) and dried over $MgSO_4$. After evaporation of diethyl ether a yellow oil (0.930 g, 96% yield) was obtained. R_f (toluene/acetonitrile, 10:1) 0.6. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.10 (t, J=7.1 Hz, 3H), 1.13 (t, J=7.0 Hz, 3H), 3.68 (q, J=7.0 Hz, 2H), 3.71 (q, J=7.0 Hz, 2H), 5.18 (s, 2H), 5.31 (s, 2H), 7.35 (d, J=9.0 Hz, 1H), 7.47 (d, J=8.8 Hz, 1H), 10.24 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.8, 14.9, 64.2, 65.2, 93.4, 97.9, 111.8, 121.6, 129.4, 129.7, 149.2, 149.7, 190.4. IR (cm^{-1}): 2976, 2900, 1704, 1572, 1462, 1381, 1256, 1115, 945. HRMS (HESI): MH^+, found 333.0326 and 335.0305. $C_{13}H_{18}BrO_5$ requires 333.0332 and 335.0312.

*4.1.10. 3-Bromo-6-(ethoxymethoxy)-2-((naphtho[2,3-d][1,3]dioxol-5-ylimino)methyl)phenol (**13**).* A mixture of hot solutions of naphtho[2,3-*d*][1,3]dioxol-5-ylamine (493.0 mg, 2.63 mmol) in ethanol (22 mL) and benzaldehyde **12** (876.0 mg, 2.63 mmol) in ethanol (22 mL) was heated to reflux for 40 min. The desired compound started to precipitate. After cooling to 0 °C for 2 h, the precipitated solid was filtered off and washed with ethanol (10 mL) to give an orange crystalline compound (1.08 g, 92% yield) of sufficient purity for a subsequent synthesis. The sample for analysis was prepared by recrystallization from an ethanol/toluene mixture. Mp 143–146 °C. R_f (toluene) 0.4. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (t, J=7.0 Hz, 3H), 3.85 (q, J=7.0 Hz, 2H), 5.37 (s, 2H), 5.95–6.26 (m, 2H), 7.05–7.13 (m, 1H), 7.14–7.24 (m, 3H), 7.39 (t, J=7.8 Hz, 1H), 7.58 (s, 1H), 7.65 (d, J=8.1 Hz, 1H), 9.20 (s, 1H), 15.21 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.2, 64.7, 94.3, 99.6, 101.4, 104.0, 113.4, 117.5, 117.9, 120.6, 122.5, 124.6, 125.4, 126.8, 131.5, 144.0, 146.2, 148.4, 148.7, 155.0, 163.3. IR (cm^{-1}): 2968, 1592, 1471, 1244, 1108, 954. MS (APCI): m/z=444.1 and 446.1 $[M+H]^+$. Anal. Calcd for $C_{21}H_{18}BrNO_5$ (444.3): C, 56.77; H, 4.08; N, 3.15. Found: C, 56.39; H, 4.05; N, 2.96.

*4.1.11. 3-Bromo-6-(ethoxymethoxy)-2-((naphtho[2,3-d][1,3]dioxol-5-ylamino)methyl)phenol (**14**).* To a stirred solution of the aldimine **13** (1.00 g, 2.25 mmol) in DMF (15 mL) was added $NaBH_4$ (85.0 mg, 2.25 mmol). After 20 min, the colorless solution was poured into a mixture of acetic acid (0.25 mL) in water (20 mL). The resulting white emulsion was extracted with diethyl ether (3×15 mL). The collected diethyl ether phases were washed with water (3×10 mL), brine (15 mL), and dried over $MgSO_4$. After evaporation of diethyl ether a semi-solid compound (906.0 mg, 90% yield) of about 90% purity was afforded. The sample for analysis was purified by a flash column chromatography on silica gel and eluted with chloroform. R_f ($CHCl_3$/MeOH, 200:1) 0.5. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, J=7.0 Hz, 3H), 3.76 (q, J=7.1 Hz, 2H), 4.69 (s, 2H), 5.24 (s, 2H), 6.03 (s, 2H), 6.90 (d, J=7.1 Hz, 1H), 6.96–7.02 (m, 1H), 7.05–7.12 (m, 2H), 7.15–7.31 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.2, 45.2, 64.9, 94.7, 97.5, 101.1, 104.8, 107.0, 116.3, 117.3, 119.0, 120.9, 123.8, 124.2, 125.0, 131.4, 142.3, 144.6, 147.1, 147.4, 147.5. IR (cm^{-1}): 2971, 2888, 1535, 1467, 1244, 1036. HRMS (HESI): MH^+, found 446.0593 and 448.0570. $C_{21}H_{21}BrNO_5$ requires 446.0598 and 448.0577.

*4.1.12. 2-(Ethoxymethoxy)-[1,3]dioxolo[4′,5′:4,5]benzo[1,2-c]phenanthridin-1-ol (**15**).* To a solution of the phenol **14** (500.0 mg, 1.12 mmol) and Bu_3SnH (652.0 mg, 2.24 mmol) in toluene (30 mL), AIBN (276.0 mg, 1.68 mmol) was added at 70 °C. The reaction mixture was heated to reflux for 2 h under argon. After that toluene was evaporated on a rotovap and the residue was purified by a flash column chromatography on silica gel ($CHCl_3$/methanol, 160:1, v/v). The collected purified compound was triturated with ethanol (2 mL) to precipitate a pure compound (219.0 mg, 54% yield). The sample for analysis was prepared by recrystallization from an ethanol/toluene mixture. Mp 165–168 °C. R_f ($CHCl_3$/MeOH, 160:1) 0.3. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.17 (t, J=7.1 Hz, 3H), 3.79 (q,

J=7.1 Hz, 2H), 5.37 (s, 2H), 6.21 (s, 2H), 7.50 (s, 1H), 7.76 (d, *J*=9.0 Hz, 1H), 7.96 (d, *J*=8.9 Hz, 1H), 8.24 (d, *J*=9.0 Hz, 1H), 8.51 (d, *J*=9.0 Hz, 1H), 8.55 (s, 1H), 9.69 (s, 1H), 10.04 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.9, 63.8, 94.2, 101.0, 101.4, 104.3, 113.1, 117.6, 118.8, 119.6, 122.3, 126.8, 128.2, 129.4, 139.2, 141.4, 143.8, 146.4, 147.9, 148.0. IR (cm^{-1}): 2977, 2900, 1584, 1461, 1360, 1249, 1031. MS (APCI): *m*/*z*=364.2 [M+H]$^+$. Anal. Calcd for $C_{21}H_{17}NO_5$ (363.4): C, 69.41; H, 4.72; N, 3.85. Found: C, 69.47; H, 4.62; N, 3.62.

*4.1.13. 2-(Ethoxymethoxy)-1-methoxy-[1,3]dioxolo-[4′,5′:4,5]benzo [1,2-c]phenanthridine (**16**).* To a suspension of NaH (95%, 4.40 mg, 0.183 mmol) in anhydrous DMF (3 mL) was added the benzo[*c*] phenanthridine **15** (44.3 mg, 0.122 mmol) and, subsequently, methyl iodide (52.0 mg, 0.366 mmol). After 18 h of stirring, ethanol (0.5 mL) was added into a reaction mixture and allowed to react for 5 min. Organic solvents were evaporated and the desired compound precipitated from an oily residue by treating with water (3 mL). The solid was filtered off, washed with water, dried, and recrystallized from an ethanol/water mixture to give a pale yellow compound (29.0 mg, 63% yield). Mp 179–183 °C. R_f ($CHCl_3$) 0.4. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.17 (t, *J*=7.1 Hz, 3H), 3.79 (q, *J*=7.0 Hz, 2H), 4.08 (s, 3H), 5.46 (s, 2H), 6.22 (s, 2H), 7.52 (s, 1H), 7.86 (d, *J*=9.2 Hz, 1H), 7.99 (d, *J*=9.0 Hz, 1H), 8.53–8.57 (m, 2H), 8.58 (d, *J*=3.0 Hz, 1H), 9.63 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.9, 61.7, 64.1, 93.7, 100.9, 101.5, 104.4, 118.7, 119.5, 121.2, 122.6, 127.1, 128.1, 128.2, 129.5, 139.2, 145.3, 146.0, 146.8, 148.0, 148.1. IR (cm^{-1}): 2980, 2901, 1531, 1462, 1261, 1041. MS (APCI): *m*/*z*=378.2 [M+H]$^+$. Anal. Calcd for $C_{22}H_{19}NO_5$ (377.4): C, 70.02; H, 5.07; N, 3.71. Found: C, 70.14; H, 5.06; N, 3.64.

*4.1.14. 1-Methoxy-[1,3]dioxolo[4′,5′:4,5]benzo[1,2-c]phenanthridin-2-ol (**17**, Decarine).* The benzo[*c*]phenanthridine **16** (14.4 mg, 0.038 mmol) in a mixture of ethanol (1 mL) and 1 M HCl (0.4 mL) was heated in a sealed vial with stirring at 80 °C for 3 h. The solid was precipitated after adding water (1 mL) and filtered off, washed with water, and dried to give a yellow-orange powder (11.5 mg, 94% yield). Mp 243–245 °C.[11f] R_f ($CHCl_3$/MeOH, 160:1) 0.3. ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.10 (s, 3H), 6.24 (s, 2H), 7.51 (s, 1H), 7.58 (d, *J*=8.9 Hz, 1H), 8.01 (d, *J*=9.0 Hz, 1H), 8.48 (d, *J*=9.0 Hz, 1H), 8.51 (d, *J*=9.0 Hz, 1H), 8.66 (s, 1H), 9.53 (s, 1H), 10.10 (br s, 1H). IR (cm^{-1}): 3097, 2910, 2710, 1568, 1479, 1319, 1267, 1040. MS (APCI): *m*/*z*=320.2 [M+H]$^+$.

*4.1.15. 4-Bromo-3-((naphtho[2,3-d][1,3]dioxol-5-ylimino)methyl) benzene-1,2-diol (**18**).* A mixture of hot solutions of the aldehyde **4** (2.00 g, 9.22 mmol) in ethanol (35 mL) and naphtho[2,3-*d*][1,3] dioxol-5-ylamine (1.72 g, 9.20 mmol) in ethanol (100 mL) was heated to reflux for 20 min. After 2 h cooling at 0 °C, the precipitated compound was filtered off and washed with cold ethanol (20 mL) to give an orange crystalline compound (3.14 g, 88% yield) with sufficient purity for a subsequent synthesis. The sample for analysis was prepared by recrystallization from acetonitrile. Mp 228–232 °C. R_f ($CHCl_3$/MeOH, 80:1) 0.7. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.18 (s, 2H), 6.91 (d, *J*=8.5 Hz, 1H), 7.06 (d, *J*=8.5 Hz, 1H), 7.30–7.50 (m, 4H), 7.75 (d, *J*=7.9 Hz, 1H), 9.09 (s, 1H), 9.57 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 98.7, 102.2, 104.6, 114.0, 114.3, 117.0, 120.3, 123.2, 125.0, 125.3, 127.2, 131.6, 143.7, 146.8, 148.5, 148.9, 153.2, 163.8. IR (cm^{-1}): 3440, 2904, 1620, 1475, 1252, 1042. MS (APCI): *m*/*z*=386.2 and 388.2 [M+H]$^+$. Anal. Calcd for $C_{18}H_{12}BrNO_4$ (386.2): C, 55.98; H, 3.13; N, 3.63. Found: C, 56.06; H, 3.14; N, 3.53.

*4.1.16. 4-Bromo-3-((naphtho[2,3-d][1,3]dioxol-5-ylamino)methyl) benzene-1,2-diol (**19**).* To a stirred suspension of the aldimine **18** (1.20 g, 3.10 mmol) in ethanol (25 mL) was added $NaBH_4$ (117.0 mg, 3.10 mmol) under argon. After 15 min, the colorless solution was added to a cold mixture of acetic acid (0.15 mL) in water (150 mL). The resulting emulsion was diluted with brine (15 mL). After 15 min of stirring, the precipitated solid was filtered off, washed thoroughly with water, and dried in vacuo at 50 °C for 2 h to give a white powder (1.19 g, 99% yield) of a sufficient purity for a subsequent synthesis. The sample for analysis was prepared by recrystallization from a toluene/ethanol mixture. Mp 130–132 °C. R_f ($CHCl_3$/MeOH, 40:1) 0.6. ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.41 (s, 2H), 6.07 (s, 2H), 6.64 (d, *J*=7.4 Hz, 1H), 6.69 (d, *J*=8.6 Hz, 1H), 6.89 (d, *J*=8.2 Hz, 1H), 7.01 (d, *J*=8.2 Hz, 1H), 7.11 (t, *J*=8.0 Hz, 1H), 7.15 (s, 1H), 7.60 (s, 1H), 9.11 (br s, 1H), 9.65 (br s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 43.6, 99.2, 101.3, 104.2, 104.5, 114.2, 116.0, 116.5, 119.7, 122.9, 124.9, 125.5, 131.4, 143.7, 145.3, 146.3, 146.8, 147.2. IR (cm^{-1}): 3400, 2904, 1617, 1530, 1466, 1247, 1040. MS (APCI): *m*/*z*=388.2 and 390.2 [M+H]$^+$. Anal. Calcd for $C_{18}H_{14}BrNO_4$ (388.2): C, 55.69; H, 3.63; N, 3.61. Found: C, 55.80; H, 3.51; N, 3.69.

*4.1.17. N-(6-Bromo-2,3-bis(ethoxymethoxy)benzyl)naphtho-[2,3-d] [1,3]dioxol-5-amine (**20**).* A solution of the diol **19** (388.2 mg, 1.00 mmol) in anhydrous DMF was added dropwise to a stirred, cold (5 °C) suspension of sodium hydride (60.8 mg, 2.50 mmol) in anhydrous DMF (2 mL) under argon. After 10 min (chloromethoxy) ethane (189.0 mg, 2.00 mmol) was added to a reaction mixture under continuous stirring and cooling. The resulting reaction mixture was stirred for 10 min at 5 °C and then at room temperature for 2 h. The reaction was quenched with water (18 mL) and resulting mixture was extracted with diethyl ether (2×20 mL). The combined organic layers were washed with water (2×20 mL), brine (20 mL) and dried over $MgSO_4$. After evaporation of diethyl ether under reduced pressure the crude oily product was obtained and subsequently purified by the flash chromatography (deactivated silica gel with TEA, eluted with toluene/acetonitrile 100:2, v/v) to give the bis(ethoxymethoxy) derivative **20** as a yellow oil (265.3 mg, 53% yield). R_f (toluene/acetonitrile, 30:1) 0.5. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.00 (t, *J*=7.1 Hz, 3H), 1.15 (t, *J*=7.1 Hz, 3H), 3.63–3.74 (m, 4H), 4.41 (d, *J*=4.6 Hz, 2H), 5.16 (s, 2H), 5.27 (s, 2H), 5.65 (t, *J*=4.6 Hz, 1H), 6.06 (s, 2H), 6.60 (d, *J*=7.5 Hz, 1H), 7.00 (d, *J*=7.9 Hz, 1H), 7.08–7.17 (m, 3H), 7.37 (d, *J*=8.8 Hz, 1H), 7.65 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.8, 14.9, 43.1, 64.0, 64.8, 93.3, 97.5, 98.8, 100.8, 102.9, 103.9, 115.8, 116.8, 119.0, 124.9, 127.9, 128.6, 130.9, 132.2, 143.4, 146.2, 146.5, 146.7, 149.2. IR (cm^{-1}): 2980, 2888, 1702, 1535, 1467, 1245, 1113, 1038, 946, 842. HRMS (HESI): MH$^+$, found 504.1007 and 506.0989. $C_{24}H_{27}BrNO_6$ requires 504.1016 and 506.0996.

*4.1.18. 1,2-Bis(ethoxymethoxy)-[1,3]dioxolo[4′,5′:4,5]benzo[1,2-c] phenanthridine (**21**).* To a solution of the amine **20** (759.0 mg, 1.50 mmol) and Bu_3SnH (870.0 mg, 3.00 mmol) in toluene (30 mL), was added AIBN (377.0 mg, 2.3 mmol) at 70 °C. The formed solution was heated to reflux for 2 h. Due to a low conversion of the amine **20**, an additional portion of Bu_3SnH (248.0 mg, 0.850 mmol) and AIBN (69.0 mg, 0.410 mmol) were added at 70 °C. Heating to reflux was prolonged for an additional 30 min. The solution was cooled to room temperature. MnO_2 (1.15 g) was added and the resulting mixture was vigorously stirred for 2 h. After oxidation was complete (monitored via TLC), the reaction mixture was filtered through Celite and the filtrate concentrated in vacuo. The residue was extracted with cyclohexane (10 mL) at room temperature to remove most of impurities. The remaining insoluble solid was recrystallized from a cyclohexane/toluene mixture to give a light gray microcrystalline compound (399.0 mg, 63% yield). Mp 135–138 °C. R_f ($CHCl_3$/MeOH, 80:1) 0.3. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (td, *J*=7.0, 1.2 Hz, 6H), 3.85 (q, *J*=7.1 Hz, 2H), 3.99 (q, *J*=7.1 Hz, 2H), 5.39 (s, 2H), 5.49 (s, 2H), 6.12 (s, 2H), 7.28 (s, 1H), 7.71–7.91 (m, 2H), 8.32 (d, *J*=9.0 Hz, 2H), 8.71 (s, 1H), 9.80 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.8, 15.9, 65.4, 66.7, 95.1, 98.7, 102.0, 102.9, 105.0, 118.9, 119.1, 120.5, 122.7, 123.1, 127.7, 129.7, 129.8, 130.5, 140.8,

143.6, 147.3, 147.4, 149.0, 149.1. IR (cm^{-1}): 2983, 2904, 1529, 1460, 1258, 1102, 1050. MS (APCI): m/z=422.2 $[M+H]^+$. Anal. Calcd for $C_{24}H_{23}NO_6$ (421.4): C, 68.40; H, 5.50; N, 3.32. Found: C, 68.24; H, 5.55; N, 3.26.

*4.1.19. 13-Ethoxy-1,2-bis(ethoxymethoxy)-12-methyl-12,13-dihydro-[1,3]dioxolo[4′,5′:4,5]-benzo[1,2-c]phenanthridine (**22**).* To a stirred solution of the benzo[*c*]phenanthridine **21** (101.0 mg, 0.240 mmol) in anhydrous toluene (6 mL) was added sodium hydride (85.0 mg, 3.54 mmol) and then methyl triflate (191.0 mg, 1.17 mmol) with exclusion of air moisture. After 12 days of stirring, ethanol (1 mL) was carefully added dropwise to the formed yellow suspension of a quaternary salt under cooling. After 15 min of stirring, the resulting colorless solution was evaporated to dryness. The solid was suspended in water (5 mL), filtered off, washed with water, and dried to give a nearly white powder (98.0 mg, 85% yield) of sufficient purity for a next step. Mp 117–122 °C. R_f ($CHCl_3$/MeOH, 40:1) 0.4. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.09 (t, J=7.0 Hz, 3H), 1.28 (t, J=7.0 Hz, 3H), 1.34 (t, J=7.0 Hz, 3H), 2.77 (s, 3H), 3.58–4.14 (m, 6H), 5.18–5.41 (m, 4H), 5.74 (s, 1H), 6.08 (s, 2H), 7.15 (s, 1H), 7.30 (d, J=8.4 Hz, 1H), 7.49 (d, J=8.4 Hz, 1H), 7.63 (d, J=8.6 Hz, 1H), 7.69 (s, 1H), 7.80 (d, J=8.4 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 15.8, 15.9, 16.0, 41.2, 62.3, 65.1, 66.2, 77.9, 85.3, 94.6, 98.8, 101.3, 101.7, 105.3, 117.5, 120.0, 120.9, 124.0, 126.7, 126.9, 127.3, 131.8, 139.4, 144.8, 148.0, 148.6, 150.2. IR (cm^{-1}): 2975, 2899, 1494, 1465, 1241, 1114, 937. MS (APCI): m/z=436.3 $[M+H-EtOH]^+$. Anal. Calcd for $C_{27}H_{31}NO_7$ (481.5): C, 67.34; H, 6.49; N, 2.91. Found: C, 67.39; H, 6.71; N, 2.86.

*4.1.20. 1,2-Dihydroxy-[1,3]dioxolo[4′,5′:4,5]benzo[1,2-c]phenanthridin-12-ium chloride (**1a**).* (a) *From* **15**: A mixture of the benzo[*c*]phenanthridine **15** (50.0 mg, 0.138 mmol) in ethanol (5 mL) and 2 M HCl (1.5 mL) was heated to reflux for 3 h. The formed precipitate was filtered off, washed with water, and dried in vacuo at 60 °C to give an orange powder (40.2 mg, 86% yield). Mp over 300 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.24 (s, 2H), 7.56 (s, 1H), 7.63 (d, J=8.8 Hz, 1H), 8.02 (d, J=9.0 Hz, 1H), 8.24 (d, J=9.0 Hz, 1H), 8.49–8.60 (m, 2H), 9.64 (s, 1H), 10.11 (br s, 2H). IR (cm^{-1}): 3169, 2838, 1623, 1479, 1298, 1034. MS (APCI): m/z=306.2 $[M+H]^+$; 304.2 $[M-H]^-$. Anal. Calcd for $C_{18}H_{12}ClNO_4$ (341.8): C, 63.26; H, 3.54; N, 4.10. Found: C, 63.03; H, 3.77; N, 3.97.

(b) *From* **21**: A solution of the benzo[*c*]phenanthridine **21** (7.0 mg, 0.017 mmol) in ethanol (1.5 mL) and 2 M HCl (0.5 mL) was heated in a sealed vial at 90 °C for 2 h. The precipitate was filtered off, washed with water, and dried in vacuo at 60 °C to give an orange powder (4.2 mg, 74% yield) with the identical spectral properties as the compound prepared above.

*4.1.21. 1,2-Dihydroxy-[1,3]dioxolo[4′,5′:4,5]benzo[1,2-c]phenanthridin-12-ium trifluoroacetate (**1b**).* The benzo[*c*]phenanthridine **21** (40.0 mg, 0.095 mmol) was dissolved under stirring in TFA (2.0 mL) at room temperature. After 5 min, an orange solid, predominantly consisting of the monodeprotected compound, started to precipitate from a solution. Quantitative deprotection of both EOM groups was reached after 12 h under continuous stirring. Most of the TFA was removed in vacuo and the remaining part by co-distillation with methanol. The solid residue was suspended in water (2 mL), filtered off, washed with a small amount of water, and dried in vacuo at 60 °C to give an orange powder (27.0 mg, 68% yield). Mp 212–215 °C (dec). ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.23 (s, 2H), 6.74 (br s, 1H), 7.50 (s, 1H), 7.61 (d, J=8.6 Hz, 1H), 7.96 (d, J=9.0 Hz, 1H), 8.19 (d, J=8.6 Hz, 1H), 8.39–8.55 (m, 2H), 9.61 (s, 1H), 10.08 (br s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 100.9, 102.2, 105.2, 114.0, 117.9, 119.2, 121.3, 124.1, 126.8, 127.1, 128.0, 129.9, 136.1, 142.3, 143.3, 146.1, 148.6, 148.9, 158.9 (q, J=36.2 Hz, CF_3COO), CF_3 was not detected due to low concentration. IR (cm^{-1}): 3213, 2930, 1678, 1610, 1480, 1350, 1197, 1038. MS (APCI): m/z=306.2 $[M+H]^+$, 304.2 $[M-H]^-$. Anal. Calcd for $C_{20}H_{12}F_3NO_6$ (419.3): C, 57.29; H, 2.88; N, 3.34. Found: C, 57.39; H, 3.01; N, 3.25.

*4.1.22. 1,2-Dihydroxy-12-methyl-[1,3]dioxolo[4′,5′:4,5]-benzo[1,2-c]phenanthridin-12-ium chloride (**2a**).* A solution of the pseudobase **22** (25.0 mg, 0.052 mmol) in a mixture of acetone (1.5 mL) and 3 M HCl (0.5 mL) was heated under stirring at 50 °C for 18 h. The formed precipitate was filtered off, washed with water, and dried in vacuo at 60 °C to give a poorly soluble orange powder (12.5 mg, 68% yield). Mp over 300 °C dec. ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.90 (s, 3H), 6.33 (s, 2H), 7.74 (s, 1H), 7.90 (d, J=9.0 Hz, 1H), 8.18–8.28 (m, 2H), 8.34 (d, J=9.0 Hz, 1H), 8.67 (d, J=9.0 Hz, 1H), 9.99 (s, 1H), 11.04 (br s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): due to low solubility it was not possible to obtain the corresponding spectrum. IR (cm^{-1}): 3041, 1549, 1489, 1324, 1256, 1040, 931. MS (APCI): m/z=320.1 $[M]^+$. Anal. Calcd for $C_{19}H_{14}ClNO_4$ (355.8): C, 64.14; H, 3.97; N, 3.94. Found: C, 64.31; H, 4.06; N, 3.85.

*4.1.23. 1,2-Dihydroxy-12-methyl-[1,3]dioxolo[4′,5′:4,5]-benzo[1,2-c]phenanthridin-12-ium trifluoroacetate (**2b**).* The pseudobase **22** (24.0 mg; 0.05 mmol) was dissolved in TFA (1.1 mL) and allowed to stand with stirring for 18 h. After that, the excess of TFA was removed in vacuo, the residue suspended in DCM (1.5 mL), filtered off, washed with DCM, and dried in vacuo at 60 °C to give an orange powder (20.3 mg, 94% yield). Mp 215–225 °C dec (217.5–220 °C).[13b] ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.90 (s, 3H), 6.32 (s, 2H), 7.71 (s, 1H), 7.89 (d, J=8.8 Hz, 1H), 8.16–8.29 (m, 2H), 8.36 (d, J=8.8 Hz, 1H), 8.66 (d, J=8.8 Hz, 1H), 10.00 (s, 1H), 11.22 (br s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 52.2, 103.2, 104.7, 106.3, 114.5, 116.3, 119.2, 120.8, 125.9, 127.2, 128.8. 131.1, 131.5, 132.4, 144.6, 145.0, 149.0, 149.1, 151.1, 158.7 (q, J=36.6 Hz, CF_3COO), CF_3 was not detected due to low concentration. IR (cm^{-1}): 3415, 2907, 1688, 1549, 1487, 1324, 1039, 1197. MS (APCI): m/z=320.1 $[M]^+$. Anal. Calcd for $C_{21}H_{14}F_3NO_6$ (433.3): C, 58.21; H, 3.26; N, 3.23. Found: C, 57.96; H, 3.36; N, 3.40.

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Supplementary data

Spectroscopic data (^{1}H and ^{13}C NMR) of synthesized compounds **1a**–**22** are available in the Supplementary data. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.03.105.

References and notes

1. (a) Dvorak, Z.; Kuban, V.; Klejdus, B.; Hlavac, J.; Vicar, J.; Ulrichova, J.; Simanek, V. *Heterocycles* **2006**, *68*, 2403–2422; (b) Zdarilova, A.; Malikova, J.; Dvorak, Z.; Ulrichova, J.; Simanek, V. *Chem. Listy* **2006**, *100*, 30–41; (c) Simanek, V.; Vespalec, R.; Sedo, A.; Ulrichova, J.; Vicar, J. *NATO Sci. Ser., II* **2003**, *129*, 245–254; (d) Vavreckova, C.; Ulrichova, J. *Chem. Listy* **1994**, *88*, 238–248; (e) Ishikawa, T. *Med. Res. Rev.* **2001**, *21*, 61–72; (f) Simanek, V. In *The Alkaloids*; Brossi, A., Ed.; Academic: New York, NY, 1985; Vol. 26, pp 185–240; (g) Suffness, M.; Cordell, G. A. In *The Alkaloids*; Brossi, A., Ed.; Academic: New York, NY, 1985; Vol. 25, pp 178–189.
2. (a) Liu, H.; Wang, J.; Zhao, J.; Lu, S.; Wang, J.; Jiang, W.; Ma, Z.; Zhou, L. *Nat. Prod. Commun.* **2009**, *4*, 1557–1560; (b) Vrba, J.; Kosina, P.; Ulrichova, J.; Modriansky, M. *Toxicol. Lett.* **2004**, *151*, 375–387.
3. (a) Dzink, J. L.; Socransky, S. S. *Antimicrob. Agents Chemother.* **1985**, *27*, 663–665; (b) Walterova, D.; Ulrichova, J.; Valka, I.; Vicar, J.; Vavreckova, C.; Taborska, E.; Harkrader, R. J.; Meyer, D. L.; Cerna, H.; Simanek, V. *Acta Univ. Palacki. Olomuc., Fac. Med.* **1995**, *139*, 7–16.
4. (a) Vrublova, E.; Vostalova, J.; Vecera, R.; Klejdus, B.; Stejskal, D.; Kosina, P.; Zdarilova, A.; Svobodova, A.; Lichnovsky, V.; Anzenbacher, P.; Dvorak, Z.; Vicar, J.; Simanek, V.; Ulrichova, J. *Food Chem. Toxicol.* **2008**, *46*, 2546–2553; (b) Juskiewicz, J.; Gruzauskas, R.; Zdunczyk, Z.; Semaskaite, A.; Jankowski, J.; Totilas, Z.;

Jarule, V.; Sasyte, V.; Zdunczyk, P.; Raceviciute-Stupeliene, A.; Svirmickas, G. *J. Anim. Physiol. Anim. Nutr.* **2011**, *95*, 171–178.
5. Wang, L. K.; Johnson, R. K.; Hecht, S. M. *Chem. Res. Toxicol.* **1993**, *6*, 813–818.
6. Gakunju, D. M. N.; Mberu, E. K.; Dossaji, S. F.; Gray, A. I.; Waigh, R. D.; Waterman, P. G.; Watkins, W. M. *Antimicrob. Agents Chemother.* **1995**, *39*, 2606–2609.
7. Chmura, S. J.; Dolan, M. E.; Cha, A.; Mauceri, H. J.; Kufe, D. W.; Weichselbaum, R. R. *Clin. Cancer Res.* **2000**, *6*, 737–742.
8. (a) Kanzawa, F.; Nishio, K.; Ishida, T.; Fukuda, M.; Kurokawa, H.; Fukumoto, H.; Nomoto, Y.; Fukuoka, K.; Bojanowski, K.; Saijo, N. *Br. J. Cancer* **1997**, *76*, 571–581; (b) Nakanishi, T.; Masuda, A.; Suwa, M.; Akiyama, Y.; Hoshino-Abe, N.; Suzuki, M. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2321–2323.
9. (a) Hisatomi, T.; Sueoka-Aragane, N.; Sato, A.; Tomimasu, R.; Ide, M.; Kurimasa, A.; Okamoto, K.; Kimura, S.; Sueoka, E. *Blood* **2011**, *117*, 3575–3584; (b) Toyoda, E.; Kagaya, S.; Cowell, I. G.; Kurosawa, A.; Kamoshita, K.; Nishikawa, K.; Iiizumi, S.; Koyama, H.; Austin, C. A.; Adachi, N. *J. Biol. Chem.* **2008**, *283*, 23711–23720.
10. For some reviews, see: (a) Dostál, J.; Potáček, M. *Collect. Czech. Chem. Commun.* **1990**, *55*, 2840–2873; (b) Ishikawa, T.; Ishii, T. *Heterocycles* **1999**, *50*, 627–639; (c) Harayama, T. *Heterocycles* **2005**, *65*, 697–713; (d) Mackay, S. P.; Meth-Cohn, O.; Waigh, R. D. *Adv. Heterocycl. Chem.* **1996**, *67*, 345–389.
11. For some examples, see: (a) Lv, P.; Huang, K.; Xie, L.; Xu, X. *Org. Biomol. Chem.* **2011**, *9*, 3133–3135; (b) Blanchot, M.; Candito, D. A.; Larnaud, F.; Lautens, M. *Org. Lett.* **2011**, *13*, 1486–1489; (c) Ishihara, Y.; Azuma, S.; Choshi, T.; Kohno, K.; Ono, K.; Tsutsumi, H.; Ishizu, T.; Hibino, S. *Tetrahedron* **2011**, *67*, 1320–1333; (d) Styskala, J.; Cankar, P.; Soural, M.; Hlavac, J.; Hradil, P.; Vicar, J.; Simanek, V. *Heterocycles* **2007**, *73*, 769–775; (e) Le, T. N.; Cho, W. *Chem. Pharm. Bull.* **2006**, *54*, 476–480; (f) Harayama, T.; Sato, T.; Nakano, Y.; Abe, H.; Takeuchi, Y. *Heterocycles* **2003**, *59*, 293–301; (g) Moreno, I.; Tellitu, I.; Etayo, J.; SanMartín, R.; Dominguez, E. *Tetrahedron* **2001**, *57*, 5403–5411; (h) Nakanishi, T.; Suzuki, M. *Org. Lett.* **1999**, *1*, 985–988; (i) Nakanishi, T.; Suzuki, M.; Mashiba, A.; Ishikawa, K.; Yokotsuka, T. *J. Org. Chem.* **1998**, *63*, 4235–4239; (j) Kessar, S. V.; Gupta, Y. P.; Balakrishnan, P.; Sawal, K. K.; Mohammad, T.; Dutt, M. *J. Org. Chem.* **1988**, *53*, 1708–1713; (k) Smidrkal, J. *Collect. Czech. Chem. Commun.* **1984**, *49*, 1412–1420.
12. For some examples, see: (a) Kosina, P.; Vacek, J.; Papousková, B.; Stiborova, M.; Styskala, J.; Cankar, P.; Vrublova, E.; Vostalova, J.; Simanek, V.; Ulrichova, J. *J. Chromatogr., B* **2011**, *879*, 1077–1085; (b) Deroussent, A.; Ré, M.; Hoellinger, H.; Cresteil, T. *J. Pharm. Biomed. Anal.* **2010**, *52*, 391–397; (c) Dvorak, Z.; Simanek, V. *Curr. Drug Metab.* **2007**, *8*, 173–176; (d) Tandon, S.; Das, M.; Khanna, S. K. *Drug Metab. Dispos.* **1993**, *21*, 194–197.
13. (a) Tolkachev, O. N.; Savina, A. A.; Sheichenko, V. I.; Proskudina, V. V. *Pharm. Chem. J.* **1999**, *33*, 323–325; (b) Lasskaya, O. E.; Tolkachev, O. N. *Khim. Prir. Soedin.* **1978**, 764–767.
14. (a) Smidrkal, J. *Collect. Czech. Chem. Commun.* **1982**, *47*, 2140–2144; (b) Dalacker, F.; Schleuter, H. J.; Schneider, P. Z. *Naturforsch. B: Anorg. Chem., Org. Chem.* **1986**, *41B*, 1273–1280.
15. Rastetter, W. H.; Ericson, T. J.; Venuti, M. C. *J. Org. Chem.* **1981**, *46*, 3579–3590.
16. Harayama, T.; Shibaike, K. *Heterocycles* **1998**, *49*, 191–196.
17. (a) Azzena, U.; Dettori, G.; Pirredu, R.; Pisano, L. *Tetrahedron* **2004**, *60*, 1617–1623; (b) Schaper, U. A. *Synthesis* **1981**, 794–796.
18. (a) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073–3100; (b) Bowman, W. R.; Bridge, C. F.; Brookes, P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1–14; (c) Zard, S. Z. *Synlett* **1996**, 1148–1154.
19. Reggelin, M.; Doerr, S. *Synlett* **2004**, 1117.
20. (a) Ramani, P.; Fontana, G. *Tetrahedron Lett.* **2008**, *49*, 5262–5264; (b) Rosa, A. M.; Prabhakar, S.; Lobo, A. M. *Tetrahedron Lett.* **1990**, *31*, 1881–1884.
21. (a) Cahiez, G.; Alami, M. In *Handbook of Reagents for Organic Synthesis, Oxidizing and Reducing Agents*; Burke, S. D., Danheiser, R. L., Eds.; John Wiley and Sons: Chichester, UK, 1999; pp 231–236; (b) Fatiadi, A. J. *Synthesis* **1976**, 65–104; (c) Fatiadi, A. J. *Synthesis* **1976**, 133–167; (d) Hudlicky, M. *Oxidations in Organic Chemistry*; American Chemical Society: Washington, 1990; (e) Attenburrow, J.; Cameron, A. F. B.; Chapman, J. H.; Evans, R. M.; Hems, B. A.; Jansen, A. B. A.; Walker, T. *J. Chem. Soc.* **1952**, 1094–1111; (f) Mancera, O.; Rosenkranz, G.; Sondheimer, F. *J. Chem. Soc.* **1953**, 2189–2191; (g) Henbest, H. B.; Jones, E. R. H.; Owen, T. C. *J. Chem. Soc.* **1957**, 4909–4912; (h) Gritter, R. J.; Wallace, T. J. *J. Org. Chem.* **1959**, *24*, 1051–1056; (i) Pratt, E. F.; Van de Castle, J. F. *J. Org. Chem.* **1961**, *26*, 2973–2975; (j) Harfenist, M.; Bavley, A.; Lazier, W. A. *J. Org. Chem.* **1954**, *19*, 1608–1616; (k) Henbest, H. B.; Thomas, A. *J. Chem. Soc.* **1957**, 3032–3039; (l) Cohen, N.; Banner, B. L.; Blount, J. F.; Tsai, M.; Saucy, G. *J. Org. Chem.* **1973**, *38*, 3229–3239.