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An Efficient Route to Emodic Amine and Analogous *O*-Methyl Protected Derivatives Starting from Emodin

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Summary. Emodic amine could be synthesized in a five-step approach in excellent overall yield by following a modified *Curtius* rearrangement strategy, starting from the naturally occurring emodin. This unique emodin derived 6-amino substituted polyhydroxylated anthraquinone may serve as a promising synthon for a new class of amino functionalized photodynamically active hypericin derivatives. In addition, the partially *O*-methyl protected 6-amino- and 6-carboxy-anthraquinones could be synthesized in high yields *via* selective *O*-methyl ether cleavage from the corresponding tri-*O*-methyl derivatives.

Keywords. Anthraquinones; *Curtius* rearrangement; Emodic amine; Selective *O*-methyl ether cleavage; Microwave assisted synthesis.

Introduction

The polyhydroxylated anthraquinone emodin (**1**, 1,3,8-trihydroxy-6-methyl-9,10-anthraquinone) is a wide-spread natural product occurring in fungi, lichens, and a variety of plants (*e.g.* rhubarb, aloe) which exhibits tumor cell-growth inhibition [1], antibiotic [2], anti-viral [3], and cytostatic [4] activity. There is a continued interest in the syntheses of new anthraquinone derivatives, either as promising biologically active compounds or as valuable synthons for the preparation of photodynamically active hypericin derivatives, which is one of the main interests in our research group [5]. Polyhydroxylated anthraquinones bearing amino groups appear to be found rather seldom in nature. Thus, to the best of our knowledge 5-aminophyscion (**2**, 5-amino-1,8-dihydroxy-3-methoxy-6-methyl-9,10-anthraquinone [6]) isolated by *Steglich et al.* [7] from the fungal species *Dermocybe canaria* constitutes the only natural representative of an amino substituted emodin derivative (see Fig. 1). Further examples for amino substituted anthraquinones are the powerful

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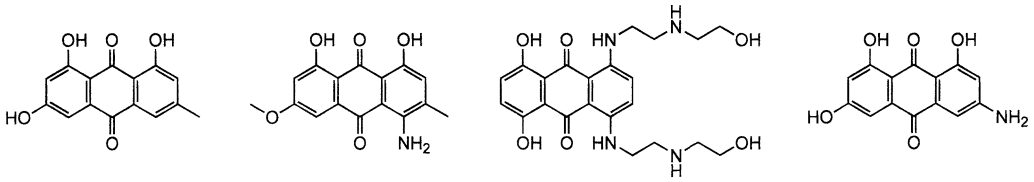


Fig. 1. Structures of emodin (**1**), 5-aminophyscion (**2**), mitoxantrone (**3**), and emodic amine (**4**)

cytostatic drug mitoxantrone (**3**) as well as a series of highly cytotoxic and cytostatic 4-amino analogues of **1** recently synthesized by *Teich et al.* [8]. In addition, there exists a wide range of highly functionalized mainly 1,4- or 1,8-bisamino substituted synthetic dyes [9].

The transformation of the methyl group in position 6 of emodin (**1**) into the amino functionality of 1,3,8-trihydroxy-6-amino-9,10-anthraquinone (**4**, emodic amine), gaining access to a new class of amino anthraquinones, was targeted (see Fig. 1). The novel emodic amine (**4**) might act as a valuable synthon for the preparation of a promising new class of amino substituted photodynamically active hypericin derivatives. Furthermore, the syntheses of the corresponding *O*-methyl protected analogues of **4** represent a second target of this work.

Results and Discussion

To the best of our knowledge, up to now no efforts have been undertaken to convert the methyl group of emodin (**1**) into the amino functionality. In principle, there are several classical synthesis strategies conceivable allowing access to amino derivatives, like the *Curtius* [10], *Hofmann* [11], *Lossen* [12], and *Schmidt* [13] rearrangements. Due to the fact that all of these strategies require the corresponding carboxylic acid as starting material, our first target was the transformation of the methyl group of **1** to the carboxylic group. Emodin (**1**), isolated from natural source (*Cortex frangulae*) [14], was protected as the 1,3,8-trimethoxy-6-methyl-9,10-anthraquinone (**5**) by microwave (MW) assisted [15] or conventional [16] synthesis both in 98% yield. The oxidation of **5** to 1,3,8-trimethoxy-6-carboxy-9,10-anthraquinone (**6**, tri-*O*-methyl emodic acid) was performed by using tetrabutylammonium permanganate (*TBAP*) [17] in pyridine at 80°C for 2 h in 88% yield. It should be stressed, that the initiation of this reaction may vary depending on the scale as well as the moisture content of the oxidizing reagent and therefore the progress of the reaction has to be controlled by TLC to avoid overoxidation. In contrast to *Di Napoli*'s multistep synthesis [18] of **6**, which is based on a total synthesis anthraquinone ring closure strategy, we were able to obtain **6** in an efficient two step synthesis starting from **1** with an overall yield of 86% (see Fig. 2).

The conversion of tri-*O*-methyl emodic acid (**6**) to 1,3,8-trimethoxy-6-amino-9,10-anthraquinone (**8**, tri-*O*-methyl emodic amine), *via* the carbamic ester **7** was performed by a modified one-step *Curtius* rearrangement [19]. For this purpose diphenylphosphoryl azide (*DPPA*), which was first reported by *Shioiri et al.* [20], constitutes a convenient reagent for the conversion of carboxylic acids to the

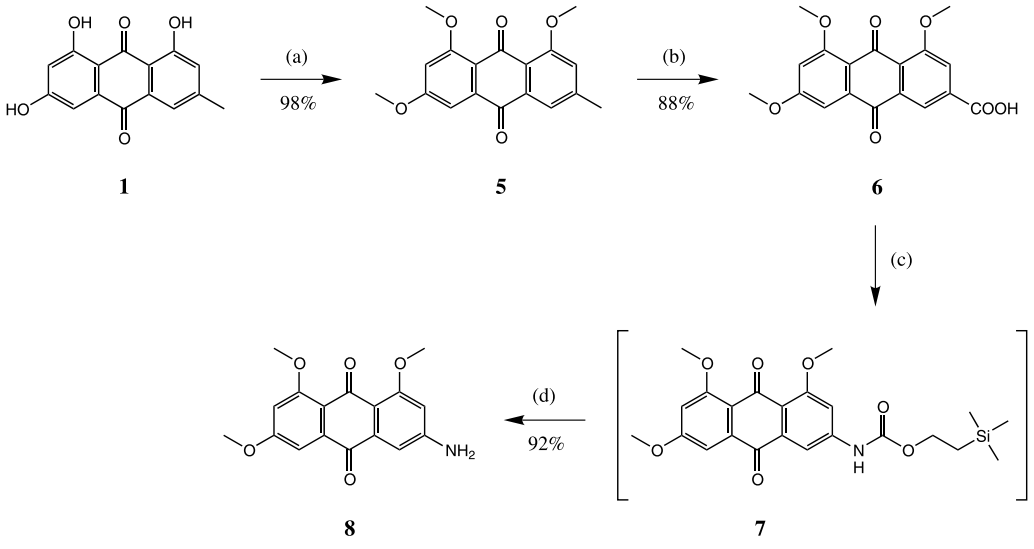


Fig. 2. Synthesis of tri-*O*-methyl emodic amine (**8**) from emodin (**1**): (a) *cf.* Ref. [15]: Me_2SO_4/K_2CO_3/tetrabutylammonium bromide, MW (600 W), 75°C, 20 min; (b) *TBAP*/pyridine, 80°C, 2 h; (c) dry dioxane/*TEA*/*DPPA*/*TMSE*, 80°C, 15 h; (d) *Me*OH/KOH (1 *M*)/H_2O, reflux, 12 h

corresponding carbamates followed by the *in situ* treatment with 2-(trimethylsilyl) ethanol (*TMSE*) to the intermediate carbamic esters. In analogy to this route, **6** was treated with triethylamine (*TEA*) and *DPPA* in dry dioxane at 80°C for 2.5 h. After addition of *TMSE* and heating at 80°C for further 12 h the generated carbamate was converted *in situ* to the intermediate carbamic ester 1,3,8-trimethoxy-6-[(trimethylsilylethoxycarbonyl)amino]-9,10-anthraquinone (**7**) in quantitative yield. Finally, **7** was hydrolyzed with KOH/*Me*OH/H_2O under reflux for 12 h to obtain the tri-*O*-methyl protected amine **8** in 92% yield based on **6** after column chromatography. It is noteworthy, that the main impurity constitutes an unpolar yellow colored fraction consisting of unhydrolyzed **7**, which could be recycled. Interestingly enough, full conversion of **7** to **8** could not be achieved at any time and it should be noted, that this behavior seems to be a characteristic of this reaction. Accordingly, tri-*O*-methyl emodic amine (**8**) could be obtained from emodin (**1**) in a four-step synthesis with an overall yield of 79% (see Fig. 2). It might be also noted, that the application of the *Hofmann* rearrangement was put aside due to the rather low yield of 49% obtained in the synthesis of 1,3,8-trimethoxy-6-carbamoyl-9,10-anthraquinone (**9**) starting from **6**. The possible syntheses of **8** *via* a *Lossen* or *Schmidt* strategy, which seems also feasible was not performed because of the known disadvantages, like low yield protocols and unpleasant reagents [12, 13]. Thus, the *Curtius* rearrangement turned out to be the most efficient method for the preparation of **8**.

Selective O-Methyl Ether Cleavage

To reach our main target, which constitutes the synthesis of emodic amine (**4**), full *O*-methyl deprotection of **8** has to be performed. In analogy to *Steglich et al.* [21]

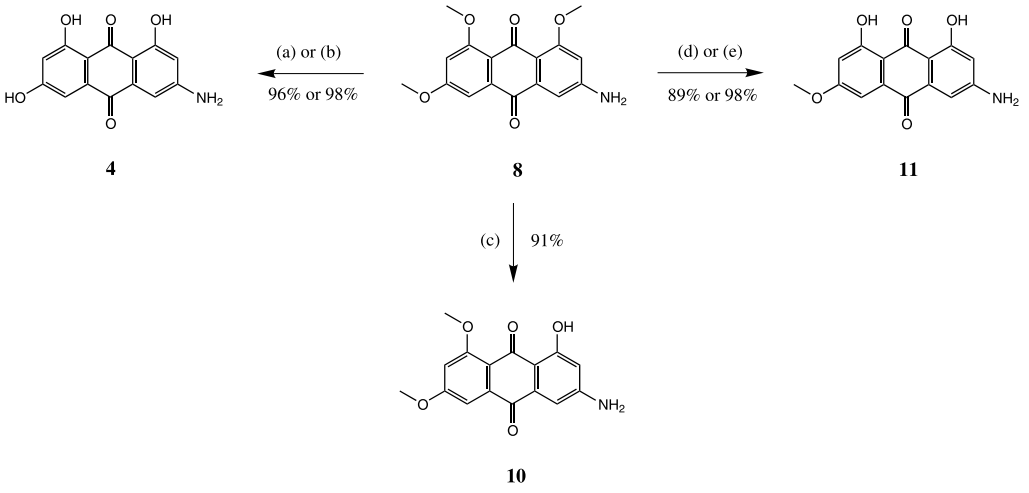
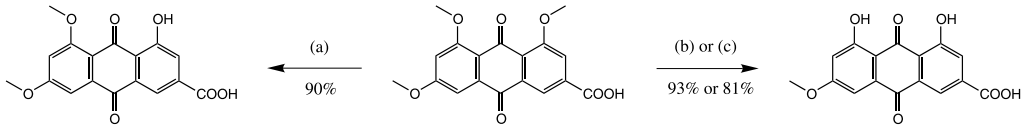


Fig. 3. Selective deprotection of tri-*O*-methyl emodic amine (**8**) to emodic amine (**4**), di-*O*-methyl emodic amine (**10**), and mono-*O*-methyl emodic amine (**11**): (a) pyridinium chloride, 150°C, 6 h; (b) pyridinium chloride, MW (600 W), reflux, 2 min; (c) BBr_3/CH_2Cl_2, −7°C to 1°C, 1 h; (d) HBr/*Ac*OH, reflux, 1 h; (e) HBr, reflux, 30 min

and previous results of our group [22], the total deprotection of 1,3,8-trimethoxy anthraquinones by means of BBr_3 seemed to be suitable for this purpose. In this specific case, the treatment of **8** with an excess of BBr_3 starting from 0°C to room temperature within 2 h, followed by 2 h reflux afforded **4** in yields <26%, with 1,3-dimethoxy-8-hydroxy-6-amino-9,10-anthraquinone (**10**, di-*O*-methyl emodic amine) as the main product. Neither modifications concerning the molar excess of reagent nor the temperature as well as reaction time could improve this result. Furthermore, *Brockmann*'s deprotection [23] of methyl ethers using KI/H_3PO_4 under rather harsh conditions caused only destruction of **8**. Finally, application of *Hassall*'s deprotection [24] using a pyridinium chloride melt at 150°C for 6 h turned out to be the method of choice for the complete *O*-methyl ether cleavage of **8** to **4** in 96% yield (see Fig. 3).

In addition, an improved variation of *Hassall*'s method [24] could be achieved by using pyridinium chloride in combination with microwave assisted synthesis. Thus, a mixture of **8** and pyridinium chloride was molten in the microwave unit (600 W) within 1 min and kept at gentle reflux (225°C) for further 1 min to obtain **4** in 98% yield. All in all, the promising synthon and interesting amino analogue of emodin (**1**), the target compound **4**, could be obtained from **1** in an efficient five-step synthesis with an excellent overall yield of 78%.

Beside the synthesis of tri-*O*-methyl emodic amine (**8**) and its full deprotection to **4** mentioned above, we also investigated the selective mono- and dideprotection of **8** to the corresponding di-*O*-methyl emodic amine (**10**) as well as 1,8-dihydroxy-3-methoxy-6-amino-9,10-anthraquinone (**11**, mono-*O*-methyl emodic amine), shown in Fig. 3. In analogy to our recently published improved procedure [22] for the selective mono-ether cleavage of 1,3,8-trimethoxyanthraquinones, **8** was converted to **10** by means of BBr_3/CH_2Cl_2 (−7°C to 1°C, 1 h) in 91% yield. Finally, the mono-*O*-



12 **6** **13**

Fig. 4. Selective deprotection of tri-*O*-methyl emodic acid (**6**) to di-*O*-methyl emodic acid (**12**) and mono-*O*-methyl emodic acid (**13**): (a) BBr_3/CH_2Cl_2, −7°C to 1°C, 1 h; (b) HBr/*Ac*OH, reflux, 1.5 h; (c) HBr, reflux, 1 h

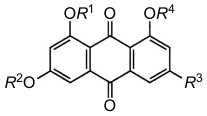
methyl protected amine **11** was prepared in high yield *via* selective methyl ether cleavage of **8** using either the system HBr/*Ac*OH under reflux for 1 h (89%) or HBr under reflux for 30 min (98%). Both partially *O*-methyl protected emodic amines **10** and **11** could be synthesized in five steps with excellent overall yields (>72%) starting from **1**.

For the realization of the abovementioned efficient route to emodic amine (**4**) and its *O*-methyl protected derivatives **8**, **10**, and **11**, tri-*O*-methyl emodic acid (**6**) served as a key intermediate. In addition, **6** also turned out to act as a valuable starting material for the first synthesis of 1,3-dimethoxy-8-hydroxy-6-carboxy-9,10-anthraquinone (**12**, di-*O*-methyl emodic acid) by using BBr_3/CH_2Cl_2 (−7°C to 1°C, 1 h) in 90% yield (see Fig. 4). The synthesis of 1,8-dihydroxy-3-methoxy-6-carboxy-9,10-anthraquinone (**13**, mono-*O*-methyl emodic acid) has already been reported by *Bloomer et al.* [25]. However, these authors followed an inconvenient multistep cycloaddition approach. Starting from **6**, we were now able to efficiently synthesize **13** *via* a selective *O*-methyl ether cleavage, using either the system HBr/*Ac*OH under reflux for 1 h (93%) or HBr under reflux in 1 h (81%) in excellent yields. Accordingly, we also developed a high yield protocol for the three step syntheses of the partially *O*-methyl protected emodic acid derivatives **12** and **13**, starting from the natural compound emodin (**1**) in overall yields of >78%.

Conclusion

An efficient route to emodin derived 6-amino anthraquinones was achieved. This was realized following a *Curtius* rearrangement strategy in excellent overall yields starting from the natural product emodin (**1**). The main target emodic amine (**4**) might act as a promising precursor for an interesting new class of amino functionalized hypericin derivatives. In addition, the polyhydroxylated amino anthraquinone **4** and its analogous *O*-methyl protected derivatives **8**, **10**, and **11** might possess bioactive relevance. Compounds **4** and **7**–**12** (see Table 1) could be synthesized for the first time and were fully characterized on the basis of their IR, UV/Vis, mass, ^1H and ^{13}C NMR spectra, particularly by 2D NMR measurements including HSQC, HMBC, and N*O*ESY experiments. In contrast to inconvenient multistep cycloaddition approaches described in literature, compounds **6** and **13** could also be efficiently synthesized in excellent yields starting from **1**.

Table 1. Overview concerning novel emodin derived anthraquinone derivatives



Entry	R^1	R^2	R^3	R^4	Yield %	t/T	mp/°C	R_f
4	H	H	NH_2	H	96[a], 98[b]	6 h/150°C[a], MW/600 W/2 min[b]	>250[e]	0.42[g]
6	CH_3	CH_3	COOH	CH_3	88	2 h/80°C	242–244	0.36[h]
7	CH_3	CH_3	$NHCOO(CH_2)_2$–$Si(CH_3)_3$	CH_3	–[c]	15 h/80°C	>180[e]	0.85[i]
8	CH_3	CH_3	NH_2	CH_3	92[d]	12 h/80°C	253–255	0.52[g]
9	CH_3	CH_3	$CONH_2$	CH_3	49	5 h/5°C to reflux	>315[e]	0.43[j]
10	CH_3	CH_3	NH_2	H	91	1 h/−7 to 1°C	257–258	0.73[g]
11	H	CH_3	NH_2	H	89[a], 98[b]	1 h/reflux[a], 0.5 h/reflux[b]	266–268	0.79[g]
12	CH_3	CH_3	COOH	H	90	1 h/−7 to 1°C	>278[e]	0.10[g]
13	H	CH_3	COOH	H	93[a], 81[b]	1.5 h/reflux[a], 1 h/reflux[b]	>298[e, f]	0.08[g]

[a] Method A (see experimental part); [b] method B (see experimental part); [c] intermediate; [d] based on **6**; [e] decomposition; [f] Ref. [25] 312°C (sealed tube); [g] $CHCl_3$:*Me*OH = 10:1; [h] $CHCl_3$:*Et*OH = 1:2; [i] $CHCl_3$:*Et*OH = 10:1; [j] $CHCl_3$:*Ac*O*Et* = 10:1

Experimental

All solvents were of *p.a.* quality and dried by conventional means if necessary. Reagents were supplied by commercial sources and were used without further purification. Melting points were measured on a *Kofler* melting point microscope (Reichert, Vienna). ^{1}H NMR spectra were recorded on a Bruker Avance DRX 500 MHz spectrometer using a TXI cryoprobe with *z*-gradient coil. All NMR experiments were performed with *DMSO*-d_6 as the solvent at 30°C. ^{13}C NMR spectra and 2D NMR experiments were performed using standard pulse sequences as provided by the manufacturer. Typical 90° hard pulse durations were 8.2 μs (^{1}H) and 16.6 μs (^{13}C), 90° pulses in decoupling experiments were set to 67 μs. HSQC and HMBC experiments were optimized for coupling constants of 145 Hz for single quantum correlations and 10 Hz for multi-bond correlations. N*O*ESY mixing time was set to 400 ms. IR, UV/Vis, and mass spectra were recorded using the Bruker Tensor 27, Varian Cary 100 Bio UV/Vis, Hewlett Packard 5989 quadrupole, and Fisons MD 800 instruments. Microwave assisted synthesis was performed on an MLS-ETHOS 1600 microwave unit with Terminal 320 from MLS-Milestone. 1,3,8-Trihydroxy-6-methyl-9,10-anthraquinone (**1**, emodin) was isolated from *Cortex frangulae* according to Ref. [14]. 1,3,8-Trimethoxy-6-methyl-9,10-anthraquinone (**5**, tri-*O*-methyl emodin) was prepared by means of microwave assisted synthesis according to Ref. [15]. Column chromatography was carried out on silica gel 0.060–0.200 mm (pore diameter 6 nm). All novel compounds were judged to be pure (>97%) by means of their ^{1}H NMR spectra and chromatography.

1,3,8-Trihydroxy-6-amino-9,10-anthraquinone (**4**, $C_{14}H_9NO_5$)

Method A: A mixture of 6.0 mg (0.0192 mmol) **8** and 500 mg (4.33 mmol) pyridinium chloride was molten at 150°C under Ar and kept at this temperature for 6 h. After cooling the solid was taken up

with distilled H_2O and extracted with *Ac*O*Et*. The organic layer was washed twice with distilled H_2O, dried over Na_2SO_4, filtered, evaporated to dryness, and chromatographed ($CHCl_3$:*Me*OH = 10:1) to afford 5.0 mg (0.0184 mmol, 96%) **4** as a red solid.

Method B (microwave assisted synthesis): A mixture of 6.0 mg (0.0192 mmol) **8** and 1.0 g (8.65 mmol) pyridinium chloride was irradiated in the microwave unit for 2 min at 600 W under Ar. The mixture was molten within the first minute followed by gentle reflux ($t \sim 225°C$) for the second minute. After cooling the work-up was performed according to method A to afford 5.1 mg (0.0188 mmol, 98%) **4** as a red solid. Mp >250°C (decomp.); TLC: $R_f = 0.27$ ($CHCl_3$:*Ac*O*Et* = 1:1), $R_f = 0.42$ ($CHCl_3$:*Me*OH = 10:1); ^{1}H NMR (500 MHz): $\delta = 12.46$ (s, 1-OH), 12.29 (s, 8-OH), 11.08 (s_{br}, 3-OH), 7.07 (s, ar-H4), 7.01 (s, ar-H5), 6.94 (s_{br}, 6-NH_2), 6.55 (s, ar-H2), 6.23 (s, ar-H7) ppm; ^{13}C NMR (125 MHz): $\delta = 186.8$ (C9), 182.0 (C10), 164.4 (C8), 164.2 (C3), 163.8 (C1), 156.7 (C6), 134.9 (C4a), 134.5 (C10a), 108.8 (C9a), 108.2 (C5), 108.1 (C2 and C4), 104.9 (C8a), 102.4 (C7) ppm; ESI-MS (*Me*OH + 1% NH_3; $c \sim 1\ mg \cdot cm^{-3}$, negative ion mode): $m/z = 270$ ($[M-H]^-$); IR (KBr): $\bar{\nu} = 3469$, 3371, 3237, 2924, 2853, 1727, 1622, 1468, 1402, 1324, 1291, 1267, 1214, 1157, 1113, 1026, 1004, 913, 849, 773, 665 cm^{-1}; UV-Vis ($CHCl_3$, $c = 5.53 \cdot 10^{-5}\ mol \cdot dm^{-3}$): $\lambda_{max}(\varepsilon) = 258$ (9660), 303 (13770), 478 (2600) nm ($dm^3 \cdot mol^{-1} \cdot cm^{-1}$); UV-Vis (*Me*OH, $c = 5.53 \cdot 10^{-5}\ mol \cdot dm^{-3}$): $\lambda_{max}(\varepsilon) = 204$ (12310), 224 (12770), 258 (12180), 307 (14510), 385 (1680), 491 (3160) nm ($dm^3 \cdot mol^{-1} \cdot cm^{-1}$).

1,3,8-Trimethoxy-6-carboxy-9,10-anthraquinone (**6**)

A solution of 1.548 g (4.80 mmol) tetrabutylammonium bromide in 3 cm^3 distilled H_2O was added dropwise to a stirred solution of 0.759 g (4.80 mmol) finely ground $KMnO_4$ in 9 cm^3 distilled H_2O. The resulting purple highly viscous mixture was stirred for 1 h at room temperature and the produced tetrabutylammonium permanganate (*TBAP*) was filtered, washed twice with distilled H_2O, and quickly treated with freshly dried diethyl ether. Within 1 h a solution of 1.497 g (4.14 mmol) *TBAP* in 22 cm^3 pyridine was added to a solution of 251.0 mg (0.810 mmol) **5** in 7 cm^3 pyridine at 80°C under Ar. The reaction was controlled by TLC, and after 125 min the mixture was cooled and 2.5 g (13.15 mmol) of ground $Na_2S_2O_5$ were added. After stirring for 15 min on an ice bath, the mixture was evaporated to dryness and the residue was taken up in 20 cm^3 distilled H_2O. The brown suspension was acidified to $pH = 1$ by adding concentrated HCl and the precipitate was centrifuged, washed three times with distilled H_2O, dried under vacuum over P_2O_5, and chromatographed ($CHCl_3$:*Et*OH = 3:1) to afford 115.1 mg (0.336 mmol, 42%) **6**. A further crop of 127.0 mg (0.371 mmol, 46%) **6** could be isolated by extraction of the second and third yellow colored aqueous washing solutions with *Ac*O*Et* to yield a total amount of 242.1 mg (0.707 mmol, 88%) **6** as a yellow solid. Mp 242–244°C; TLC: $R_f = 0.36$ ($CHCl_3$:*Et*OH = 1:2), $R_f = 0.0$ ($CHCl_3$:*Ac*O*Et* = 1:2); ^{1}H NMR (500 MHz): $\delta = 13.60$ (s_{br}, 6-COOH), 8.19 (s, ar-H5), 7.91 (s, ar-H7), 7.22 (d, $J = 2.1$ Hz, ar-H4), 7.02 (d, $J = 2.1$ Hz, ar-H2), 3.98 (s, 8-OCH_3), 3.96 (s, 3-OCH_3), 3.92 (s, 1-OCH_3) ppm; ^{13}C NMR (125 MHz): $\delta = 182.5$ (C10), 179.5 (C9), 165.7 (6-COOH), 163.1 (C3), 161.2 (C1), 158.9 (C8), 135.6 (C6), 135.1 (C10a or C4a), 134.2 (C4a or C10a), 126.1 (C8a), 118.6 (C5), 118.5 (C7), 117.6 (C9a), 105.1 (C2), 102.5 (C4), 56.41 (8-OCH_3), 56.36 (1-OCH_3), 55.88 (3-OCH_3) ppm; NCI-MS (solid probe, CH_4): $m/z = 342$ ($[M]^-$); IR (KBr): $\bar{\nu} = 3486$, 3091, 2922, 2850, 1723, 1655, 1598, 1562, 1460, 1413, 1331, 1235, 1071, 1012, 948, 873, 750 cm^{-1}; UV-Vis (*DMSO*, $c = 1.24 \cdot 10^{-5}\ mol \cdot dm^{-3}$): $\lambda_{max}(\varepsilon) = 276$ (85890), 405 (3950) nm ($dm^3 \cdot mol^{-1} \cdot cm^{-1}$); UV-Vis ($CHCl_3$): $\lambda_{max}(A) = 274$ (100), 330 (33), 402 (27) nm (rel. int.).

1,3,8-Trimethoxy-6-[(trimethylsilylethoxycarbonyl)amino]-9,10-anthraquinone
(**7**, $C_{23}H_{27}NO_7Si$)

To a solution of 48.0 mg (0.140 mmol) **6** dissolved in 1.5 cm^3 dry 1,4-dioxane at 80°C under Ar, 25.6 mg (0.25 mmol) triethylamine were added and stirred for 15 min. After addition of 64.0 mg (0.230 mmol) diphenylphosphoryl azide the reaction mixture was stirred for further 2.5 h followed by the addition of 54.0 mg (0.460 mmol) 2-(trimethylsilyl)ethanol. The resulting mixture was kept at 80°C for 12 h, cooled, and evaporated to dryness to obtain the intermediate carbamic ester **7** in quantitative yield as a yellow solid. At that point it should be mentioned, that the isolation of **7** was

performed once for full analytical and spectroscopic characterization. From the synthesis point of view, **7** hydrolyses to **8** even during the work-up (*e.g.* evaporation of the solvent at elevated temperature) and therefore **7** acts only as an intermediate in the conversion of **6** to **8**. Mp >180°C (decomp.); TLC: $R_f = 0.85$ ($CHCl_3$:*Et*OH = 10:1), $R_f = 0.43$ ($CHCl_3$:*AcOEt* = 1:1); ^{1}H NMR (500 MHz): $\delta = 7.97$ (s, ar-H7), 7.42 (s, ar-H5), 7.33 (s, ar-H4), 6.96 (s, 6-NHCO-), 6.79 (s, ar-H2), 4.32 (t, $J = 8.3$ Hz, $-OCH_2-$), 4.03 (s, 8-OCH_3), 3.98 (s, 1-OCH_3), 3.96 (s, 3-OCH_3), 1.09 (t, $J = 8.3$ Hz, $-CH_2Si-$), 0.10 (s, $-Si(CH_3)_3$) ppm; ^{13}C NMR (125 MHz): $\delta = 184.1$ (C10), 181.0 (C9), 163.9 (C3), 162.1 (C1), 161.7 (C8), 153.4 (–NHCO–), 143.3 (C6), 136.5 (C4a), 135.6 (C10a), 119.2 (C8a), 118.7 (C9a), 107.9 (C5), 107.3 (C7), 105.8 (C2), 102.3 (C4), 64.50 ($-O-CH_2-$), 57.75 (1-OCH_3 or 8-OCH_3), 56.72 (8-OCH_3 or 1-OCH_3), 56.07 (3-OCH_3), 17.93 ($-CH_2-Si-$), −1.27 ($-Si(CH_3)_3$) ppm; NCI-MS (solid probe, CH_4): $m/z = 457$ ($[M]^-$); IR (KBr): $\bar{\nu} = 3337$, 3086, 2926, 2854, 1728, 1663, 1586, 1531, 1457, 1336, 1255, 1221, 1141, 1061, 1010, 983, 956, 925, 892, 857, 759 cm^{-1}; UV-Vis ($CHCl_3$, $c = 1.01 \cdot 10^{-5}$ mol · dm^{-3}): $\lambda_{max}(\varepsilon) = 287$ (17440), 416 (2190) nm ($dm^3 \cdot mol^{-1} \cdot cm^{-1}$).

1,3,8-Trimethoxy-6-amino-9,10-anthraquinone (**8**, $C_{17}H_{15}NO_5$)

The intermediate carbamic ester **7** was dissolved in 100 cm^3 1 *M* KOH in methanol containing 100 mm^3 distilled H_2O and refluxed under Ar for 12 h. The conversion was controlled by TLC. After cooling the mixture was neutralized with 2 *M* HCl on an ice bath under stirring followed by evaporation of the solvent. The residue was dissolved in $CHCl_3$ and washed twice with distilled H_2O. The organic layer was dried (Na_2SO_4), filtered, evaporated, and chromatographed ($CHCl_3$:*Me*OH = 10:1) to afford 40.4 mg (0.129 mmol, 92% based on **6**) **8** as a red solid. Mp 253–255°C; TLC: $R_f = 0.64$ ($CHCl_3$:*Et*OH = 5:1), $R_f = 0.52$ ($CHCl_3$:*Me*OH = 10:1), $R_f = 0.08$ ($CHCl_3$:*AcOEt* = 1:1); ^{1}H NMR (500 MHz): $\delta = 7.14$ (d, $J = 2.5$ Hz, ar-H4), 6.93 (d, $J = 2.5$ Hz, ar-H2), 6.89 (d, $J = 2.2$ Hz, ar-H5), 6.53 (d, $J = 2.2$ Hz, ar-H7), 6.33 (s_{br}, 6-NH_2), 3.91 (s, 3-OCH_3), 3.86 (s, 1-OCH_3), 3.78 (s, 8-OCH_3) ppm; ^{13}C NMR (125 MHz): $\delta = 184.0$ (C10), 178.5 (C9), 162.6 (C3), 161.4 (C8), 160.9 (C1), 153.8 (C6), 135.5 (C4a or C10a), 135.3 (C10a or C4a), 118.0 (C9a), 112.4 (C8a), 105.2 (C2), 103.4 (C5), 101.9 (C4), 101.5 (C7), 56.25 (1-OCH_3), 55.71 (3-OCH_3), 55.57 (8-OCH_3) ppm; ESI-MS (*Me*OH:*DMSO* = 5:1 + 2% CF_3COOH, $c \sim 1$ mg · cm^{-3}, positive ion mode): $m/z = 314$ ($[M + H]^+$); NCI-MS (solid probe, CH_4): $m/z = 313$ ($[M]^-$); IR (KBr): $\bar{\nu} = 3476$, 3352, 3228, 2924, 2852, 1637, 1604, 1558, 1440, 1353, 1320, 1268, 1149, 1022, 976, 945, 881, 834, 662 cm^{-1}; UV-Vis (*DMSO*, $c = 1.51 \cdot 10^{-5}$ mol · dm^{-3}): $\lambda_{max}(\varepsilon) = 266$ (7660), 304 (10700) nm ($dm^3 \cdot mol^{-1} \cdot cm^{-1}$); UV-Vis ($CHCl_3$, $c = 1.21 \cdot 10^{-5}$ mol · dm^{-3}): $\lambda_{max}(\varepsilon) = 294$ (18060), 439 (1400) nm ($dm^3 \cdot mol^{-1} \cdot cm^{-1}$).

1,3,8-Trimethoxy-6-carbamoyl-9,10-anthraquinone (**9**, $C_{18}H_{15}NO_6$)

To a stirred suspension of 60.9 mg (0.178 mmol) **6** in 40 cm^3 dry benzene at 5–10°C under Ar, a solution of 200 mm^3 (2.32 mmol) oxalyl chloride in 10 cm^3 benzene was added within 30 min. After warming up to room temperature within 30 min the mixture was refluxed for 3 h, followed by cooling and evaporation of the solvent. The yellow acid chloride was dissolved in 50 cm^3 benzene and cooled to 5–10°C. A solution of 215 mm^3 (3.33 mmol) NH_3 (32% aq) in 3 cm^3 distilled H_2O was added slowly under stirring within 15 min. After further 15 min of stirring and warming up to room temperature, the mixture was stirred for another 30 min. The yellow precipitate was filtered, washed three times with distilled H_2O, and dried under vacuum over P_2O_5 to afford 29.6 mg (0.087 mmol, 49%) **9**. Mp >315°C (decomp.); TLC: $R_f = 0.83$ ($CHCl_3$:*Me*OH = 5:2), $R_f = 0.43$ ($CHCl_3$:*Et*OH = 10:1); ^{1}H NMR (500 MHz): $\delta = 8.35$ (s_{br}, 6-$CONH_\alpha$), 8.17 (d, $J = 1.2$ Hz, ar-H5), 7.90 (d, $J = 1.2$ Hz, ar-H7), 7.68 (s_{br}, 6-$CONH_\beta$), 7.21 (d, $J = 2.4$ Hz, ar-H4), 7.01 (d, $J = 2.4$ Hz, ar-H2), 3.96 (s, 8-OCH_3), 3.95 (s, 3-OCH_3), 3.91 (s, 1-OCH_3) ppm; ^{13}C NMR (125 MHz): $\delta = 182.8$ (C10), 179.7 (C9), 166.1 (6-$CONH_2$), 163.6 (C3), 161.1 (C1), 158.8 (C8), 138.7 (C6), 135.6 (C4a or C10a), 134.0 (C10a or C4a), 125.0 (C8a), 117.6 (C9a), 117.4 (C7), 117.2 (C5), 105.0 (C2), 102.4 (C4), 56.49 (1-OCH_3 or 8-OCH_3), 56.39 (8-OCH_3 or 1-OCH_3), 55.93 (3-OCH_3) ppm; ESI-MS (*Me*OH:*DMSO* = 3:1 + 2% CF_3COOH, $c \sim 1$ mg · cm^{-3}, positive ion mode): $m/z = 342$ ($[M + H]^+$); IR (KBr): $\bar{\nu} = 3389$, 3149, 3025, 2955, 2925, 2854, 1736, 1667, 1627, 1597, 1564, 1493, 1466, 1453, 1410, 1359, 1326, 1301,

1242, 1199, 1163, 1126, 1074, 1013, 948, 868, 836, 753, 698 cm^{-1}; UV-Vis (*DMSO*, $c = 2.23 \cdot 10^{-5}$ $mol \cdot dm^{-3}$): $\lambda_{max}(\varepsilon) = 274$ (14710), 401 (4080) nm ($dm^3 \cdot mol^{-1} \cdot cm^{-1}$); UV-Vis ($CHCl_3$, $c = 6.89 \cdot 10^{-5}$ $mol \cdot dm^{-3}$): $\lambda_{max}(\varepsilon) = 277$ (4230), 406 (1220) nm ($dm^3 \cdot mol^{-1} \cdot cm^{-1}$).

1,3-Dimethoxy-8-hydroxy-6-amino-9,10-anthraquinone (**10**, $C_{16}H_{13}NO_5$)
A stirred solution of 6.9 mg (0.0220 mmol) **8** in 1.5 cm^3 CH_2Cl_2 was flushed with Ar and cooled to −7°C. To this solution 8.7 mm^3 (0.0903 mmol) BBr_3 were added through a septum by means of a syringe and the mixture was stirred for 1 h ($T_{end} = 1$°C). The reaction mixture was poured into ice/H_2O and extracted with $CHCl_3$. The organic layer was dried (Na_2SO_4), filtered, and evaporated to dryness to yield 6.0 mg (0.0200 mmol, 91%) **10** as a red solid. Mp 257–258°C; TLC: $R_f = 0.45$ ($CHCl_3$:*AcOEt* = 1:1), $R_f = 0.73$ ($CHCl_3$:*Me*OH = 10:1); ^{1}H NMR (500 MHz): $\delta = 13.58$ (s, 8-OH), 7.26 (d, $J = 1.9$ Hz, ar-H4), 6.97 (d, $J = 1.9$ Hz, ar-H2), 6.92 (d, $J = 1.7$ Hz, ar-H5), 6.61 (s_{br}, 6-NH_2), 6.24 (d, $J = 1.7$ Hz, ar-H7), 3.95 (s, 3-OCH_3), 3.92 (s, 1-OCH_3) ppm; ^{13}C NMR (125 MHz): $\delta = 184.3$ (C9), 182.7 (C10), 164.6 (C8), 164.0 (C3), 162.5 (C1), 155.4 (C6), 136.5 (C4a), 133.4 (C10a), 114.4 (C9a), 106.6 (C8a), 106.0 (C5), 104.7 (C2), 104.2 (C4), 103.3 (C7), 56.44 (1-OCH_3), 55.92 (3-OCH_3) ppm; ESI-MS (*Me*OH:*DMSO* = 6:1 + 1% HCOOH, $c \sim 1$ $mg \cdot cm^{-3}$, positive ion mode): $m/z = 300$ ($[M + H]^+$); IR (KBr): $\bar{\nu} = 3458$, 3357, 3237, 2923, 2852, 1730, 1671, 1618, 1595, 1557, 1495, 1452, 1424, 1405, 1348, 1325, 1298, 1266, 1244, 1220, 1190, 1149, 1061, 1032, 1009, 948, 888, 842, 812, 753 cm^{-1}; UV-Vis ($CHCl_3$, $c = 1.20 \cdot 10^{-5}$ $mol \cdot dm^{-3}$): $\lambda_{max}(\varepsilon) = 255$ (15050), 300 (20830), 465 (2260) nm ($dm^3 \cdot mol^{-1} \cdot cm^{-1}$); UV-Vis (*Me*OH, $c = 1.20 \cdot 10^{-5}$ $mol \cdot dm^{-3}$): $\lambda_{max}(\varepsilon) = 221$ (21380), 241 (13880), 256 (14210), 305 (16820), 491 (1700) nm ($dm^3 \cdot mol^{-1} \cdot cm^{-1}$).

1,8-Dihydroxy-3-methoxy-6-amino-9,10-anthraquinone (**11**, $C_{15}H_{11}NO_5$)
Method A: To a refluxing solution of 6.9 mg (0.0220 mmol) **8** in 3 cm^3 of glacial acetic acid under Ar, 350 mm^3 HBr (47% aq) were added and heated for 60 min. The mixture was cooled, poured into ice/H_2O, and neutralized with saturated $NaHCO_3$ solution. After extraction with $CHCl_3$ the organic layer was dried (Na_2SO_4), filtered, evaporated to dryness, and chromatographed ($CHCl_3$:*Me*OH = 10:1) to yield 5.6 mg (0.0196 mmol, 89%) **11** as a red solid.

Method B: A solution of 12.0 mg (0.0383 mmol) **8** in 4 cm^3 HBr (47% aq) was refluxed for 30 min under Ar to yield 10.7 mg (0.0375 mmol, 98%) of **11** after work-up according to method A. Mp 266–268°C; TLC: $R_f = 0.65$ ($CHCl_3$:*AcOEt* = 1:1), $R_f = 0.79$ ($CHCl_3$:*Me*OH = 10:1); ^{1}H NMR (500 MHz): $\delta = 12.56$ (s, 8-OH), 12.25 (s, 1-OH), 7.16 (d, $J = 2.2$ Hz, ar-H4), 7.04 (d, $J = 2.0$ Hz, ar-H5), 7.01 (s_{br}, 6-NH_2), 6.82 (d, $J = 2.2$ Hz, ar-H2), 6.25 (d, $J = 2.0$ Hz, ar-H7), 3.91 (s, 3-OCH_3) ppm; ^{13}C NMR (125 MHz): $\delta = 186.7$ (C9), 181.7 (C10), 164.9 (C3), 164.5 (C8), 163.7 (C1), 156.9 (C6), 134.6 (C4a), 134.5 (C10a), 109.7 (C9a), 108.4 (C5), 106.9 (C4), 106.7 (C2), 105.0 (C8a), 102.3 (C7), 56.09 (3-OCH_3) ppm; ESI-MS (*Me*OH:*DMSO* = 6:1 + 1% HCOOH, $c \sim 1$ $mg \cdot cm^{-3}$, positive ion mode): $m/z = 286$ ($[M + H]^+$); IR (KBr): $\bar{\nu} = 3486$, 3440, 3381, 3362, 3246, 2954, 2924, 2852, 1731, 1631, 1609, 1598, 1572, 1481, 1462, 1442, 1421, 1386, 1326, 1313, 1299, 1271, 1242, 1217, 1190, 1167, 1156, 1113, 1039, 837, 760, 720 cm^{-1}; UV-Vis ($CHCl_3$, $c = 1.20 \cdot 10^{-5}$ $mol \cdot dm^{-3}$): $\lambda_{max}(\varepsilon) = 256$ (15140), 303 (21030), 475 (3780) nm ($dm^3 \cdot mol^{-1} \cdot cm^{-1}$); UV-Vis (*Me*OH, $c = 1.20 \cdot 10^{-5}$ $mol \cdot dm^{-3}$): $\lambda_{max}(\varepsilon) = 223$ (23050), 240 (14470), 257 (15100), 308 (18160), 493 (3050) nm ($dm^3 \cdot mol^{-1} \cdot cm^{-1}$).

1,3-Dimethoxy-8-hydroxy-6-carboxy-9,10-anthraquinone (**12**, $C_{17}H_{12}O_7$)
A stirred solution of 6.4 mg (0.0187 mmol) **6** in 1.5 cm^3 CH_2Cl_2 was flushed with Ar and cooled to −7°C. To this solution 7.3 mm^3 (0.0757 mmol) BBr_3 were added through a septum by means of a syringe and the mixture was stirred for 1 h ($T_{end} = 1$°C). The reaction mixture was poured into ice/H_2O and extracted with *AcOEt*. The organic layer was dried (Na_2SO_4), filtered, and evaporated to dryness to yield 5.5 mg (0.0167 mmol, 90%) **12** as a yellow solid. Mp >278°C (decomp.); TLC: $R_f = 0.47$ ($CHCl_3$:*Me*OH = 3:2), $R_f = 0.10$ ($CHCl_3$:*Me*OH = 10:1); ^{1}H NMR (500 MHz): $\delta = 13.62$ (s_{br}, 6-COOH), 13.07 (s, 8-OH), 8.08 (s, ar-H5), 7.71 (s, ar-H7), 7.33 (s, ar-H4), 7.06 (s, ar-H2), 4.00 (s,

3-OCH_3), 3.99 (s, 1-OCH_3) ppm; ^{13}C NMR (125 MHz): $\delta = 186.2$ (C9), 181.5 (C10), 165.5 (6-COOH), 165.4 (C3), 163.3 (C1), 161.3 (C8), 136.7 (C4a or C10a), 136.6 (C10a or C4a), 132.7 (C6), 124.1 (C7), 119.1 (C8a), 118.0 (C5), 114.0 (C9a), 104.9 (C4), 104.5 (C2), 56.69 (1-OCH_3), 56.24 (3-OCH_3) ppm; ESI-MS (*Me*OH:*DMSO* = 6:1 + 1% NH_3, $c \sim 1\,mg \cdot cm^{-3}$, negative ion mode): $m/z = 327$ ($[M - H]^-$); IR (KBr): $\bar{\nu} = 3131$, 2925, 2854, 1730, 1670, 1631, 1593, 1545, 1479, 1464, 1438, 1396, 1370, 1338, 1282, 1248, 1208, 1187, 1170, 1109, 1051, 1030, 986, 881, 771 cm^{-1}; UV-Vis ($CHCl_3$, $c = 9.29 \cdot 10^{-5}\,mol \cdot dm^{-3}$): $\lambda_{max}(\varepsilon) = 241$ (10050), 278 (9160), 425 (4070) nm ($dm^3 \cdot mol^{-1} \cdot cm^{-1}$); UV-Vis (*Me*OH, $c = 5.57 \cdot 10^{-5}\,mol \cdot dm^{-3}$): $\lambda_{max}(\varepsilon) = 205$ (16100), 228 (17410), 274 (10300), 423 (4200) nm ($dm^3 \cdot mol^{-1} \cdot cm^{-1}$).

1,8-Dihydroxy-3-methoxy-6-carboxy-9,10-anthraquinone (**13**)
Method A: To a refluxing solution of 6.2 mg (0.0181 mmol) **6** in 3 cm^3 of glacial acetic acid under Ar, 500 mm^3 HBr (47% aq) were added and heated for 90 min. The mixture was cooled, poured into ice/H_2O, and neutralized with saturated $NaHCO_3$ solution. After extraction with $CHCl_3$ the organic layer was evaporated to dryness to yield 5.3 mg (0.0169 mmol, 93%) **13** as a yellow solid.

Method B: A solution of 5.0 mg (0.0146 mmol) **6** in 1.75 cm^3 HBr (47% aq) was refluxed for 60 min under Ar to yield 3.7 mg (0.0118 mmol, 81%) **13** after work-up according to method A. Mp >298°C (decomp.) (Ref. [25] 312°C (sealed tube)); TLC: $R_f = 0.44$ ($CHCl_3$:*Me*OH = 3:2), $R_f = 0.08$ ($CHCl_3$:*Me*OH = 10:1); ^1H NMR (500 MHz): $\delta = 13.72$ (s_{br}, 6-COOH), 12.10 (s, 1-OH), 12.02 (s, 8-OH), 8.12 (s, ar-H5), 7.75 (s, ar-H7), 7.23 (s, ar-H4), 6.91 (s, ar-H2), 3.95 (s, 3-OCH_3) ppm; ^{13}C NMR (125 MHz): $\delta = 189.6$ (C9), 180.7 (C10), 166.4 (C3), 165.4 (6-COOH), 164.6 (C1), 161.1 (C8), 137.7 (C6 or C10a), 134.8 (C4a), 133.6 (C10a or C6), 124.2 (C7), 118.8 (C5), 118.5 (C8a), 110.2 (C9a), 107.9 (C4), 106.7 (C2), 56.45 (3-OCH_3) ppm; ESI-MS (*Me*OH:*DMSO* = 6:1 + 1% NH_3, $c \sim 1\,mg \cdot cm^{-3}$, negative ion mode): $m/z = 313$ ($[M–H]^-$); IR (KBr): $\bar{\nu} = 3067$, 2956, 2925, 2854, 1698, 1626, 1611, 1571, 1481, 1434, 1397, 1313, 1276, 1250, 1211, 1165, 1094, 1029, 1016, 980, 918, 906, 789, 772, 667 cm^{-1}; UV-Vis ($CHCl_3$, $c = 8.00 \cdot 10^{-5}\,mol \cdot dm^{-3}$): $\lambda_{max}(\varepsilon) = 250$ (7830), 275 (7260), 441 (4600) nm ($dm^3 \cdot mol^{-1} \cdot cm^{-1}$); UV-Vis (*Me*OH, $c = 7.73 \cdot 10^{-5}\,mol \cdot dm^{-3}$): $\lambda_{max}(\varepsilon) = 206$ (10670), 228 (12450), 250 (7170), 272 (7320), 436 (4210) nm ($dm^3 \cdot mol^{-1} \cdot cm^{-1}$).

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