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Highly Selective Three-Step Synthesis of Rhein in Chloroaluminate Molten Salt: Preclusion of the Hayashi Rearrangement

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An expeditious, three-step synthesis of rhein (**2**) was optimized starting from bis(*N*,*N*-diethyl)-5-methoxybenzene-1,3-dicarboxamide. The key final step, involving deprotection/cyclization of *ortho*-benzoylbenzoic acid **9** in acidic chloroaluminate molten salts, yielded the desired natural product with high selectivity and good overall yield by precluding the competitive Hayashi rearrangement.

Introduction

Diacerhein (**1**) is known to be useful in the treatment of diseases related to abnormal degeneration of the connective tissue and, more particularly, in the treatment of inflammatory states of the joints such as rheumatoid arthritis, osteoarthritis, and osteoporosis (Figure 1). This molecule is also used in the treatment of acute respiratory syndrome of adult and pulmonary emphysema.[1] Rhein (**2**), the active metabolite, is reported to have beneficial activity in the treatment of nephropatic diabetes,[2] which is another disease where overproduction of interleukin-1 is involved.[3–5] Of particular interest, the naturally occurring rhein (**2**), which can be directly extracted from *Cassia tora* (leguminosae), also exhibits promising antifungal properties.[6]

The wide spectrum of biological activities exhibited by rhein and diacerhein make the availability of the molecule of paramount importance for the elucidation of their mechanism of action and for clinical trials. To date, diacerhein (**1**) has been mainly produced through semisynthetic methods on an industrial scale by oxidation and acetylation of naturally occurring aloin (**4**), which is obtained from the Chinese herb *Rheum officinale* (rhubarb).[7–11] However, this route requires tedious extractions and the product may be contaminated by the mutagenic byproduct aloe-emodin

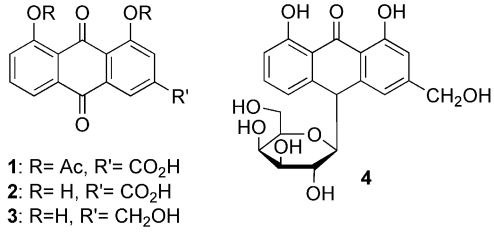

Figure 1. Structure of diacerhein (**1**), rhein (**2**), aloe-emodin (**3**), and aloin (**4**).

(**3**), precluding its use as a pharmaceutical drug. To overcome these problems, many synthetic approaches have been developed, some of which involve Diels–Alder reactions,[12] tandem processes[13–15] (Stobbe condensation or Michael addition followed by cyclization), or organometallic routes[16] (condensation of lithium salts with benzynes). Our group recently reported a new synthesis of **2** by the Fries rearrangement.[17] However, these routes are often multistep or difficult to adapt to large-scale synthesis. Quite recently, a new contribution from this laboratory has been published that describes a shorter, five-step route to rhein (**2**).[18] In this communication, we disclose a more expedient total synthesis of rhein (**2**) that requires only three steps. The key step is based on a regioselective directed *ortho*-metalation (DOM) reaction, followed by the addition of the organometallic reagent onto an acyl chloride, affording advanced benzophenone intermediate **8** directly (Scheme 1). Acidic hydrolysis of the amide bonds of **8**, followed by a one-pot demethylation/cyclization step, afforded target **2** in 66% overall yield. After optimization of the last cyclization step, it was found that conducting the reaction in inorganic liquid or molten salt prevented the undesired Hayashi rearrangement, which was responsible for the concomitant

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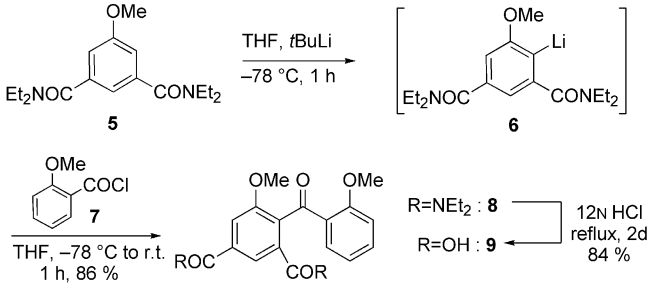
formation of rhein isomer **11** (Scheme 2). This kinetic effect enabled the preparation of rhein (**2**) in high yield, with excellent overall selectivity.

Results and Discussion

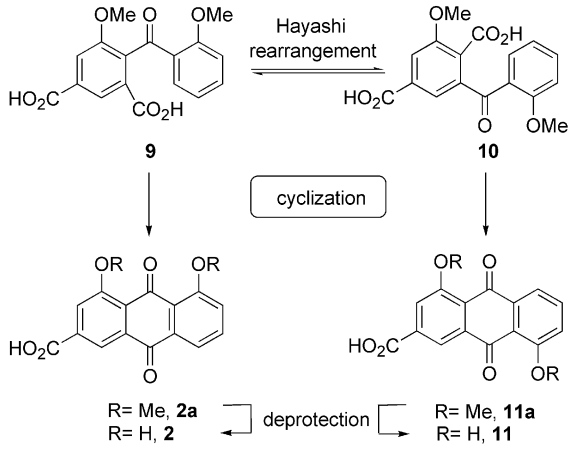
The short synthesis started with the selective DOM of bis(*N*,*N*-diethyl)-5-methoxybenzene-1,3-dicarboxamide (**5**), followed by addition to commercially available *ortho*-anisoylchloride (**7**), leading to benzophenone **8** in 86% yield (Scheme 1).



Scheme 1. Preparation of *ortho*-benzoylbenzoic acid **9**.

The remarkable regioselectivity of the DOM reaction was assessed quite recently in our laboratory in the course of the synthesis of rhein.[18] The condensation of lithiated intermediate species **6** with electrophilic acyl chloride **7** was effected without the need for a transmetalation step with other metals such as copper, aluminum, palladium, or zinc, as is usually required. This crucial transmetalation step is often performed to prevent the addition of the lithiated carbanion on the electrophilic aryl ketone that is generated in situ.[19–21] In our case, neither the transmetalation step nor the use of electrophiles such as the Weinreb amide were needed for the preparation of key compound **8**, which was simply obtained by adding the lithiated species to the acyl chloride at –78 °C (reverse addition). In the second step, the amide groups of **8** were hydrolyzed in concentrated hydrochloric acid to afford *ortho*-benzoylbenzoic acid **9**. Many attempts to cyclize keto-carboxylic acid **9** into anthraquinone **2a** (Scheme 2), under known conditions by using either catalytic or stoichiometric amounts of boron trifluoride, aluminum trichloride, polyphosphoric acid (PPA), sulfuric acid, boric acid, trifluoromethanesulfonic acid, or methanesulfonic acid, were unsuccessful, even at high temperatures. These conditions often led to no reaction (Nafion-H resin), unidentified side products, or degradation of starting material **9** (see the Supporting Information for details).

The use of commercially available, room-temperature ionic liquids such as 1-hexyl-3-methylimidazolium tetrafluoroborate or 1,2-dimethyl-3-propylimidazolium bis(trifluoromethylsulfonyl)imide as a substitute solvent and catalyst failed to yield **2a**; however, when the reaction was conducted in a molten salt composed of $AlCl_3$ and NaCl ($xAlCl_3 = 0.41$) at higher temperature (160 °C), the one-pot demethylation/cyclization of **9** to rhein (**2**) was achieved.

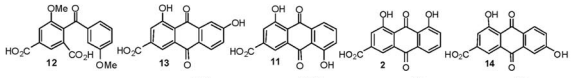
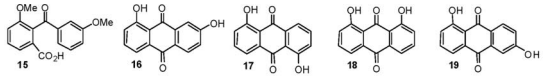
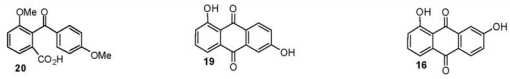
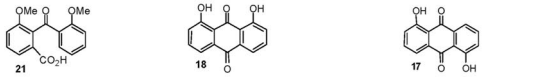
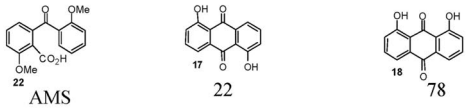
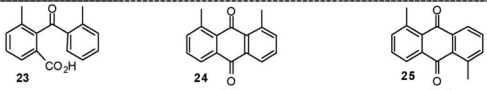
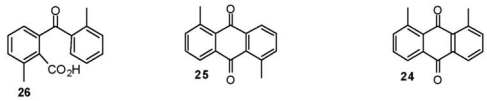
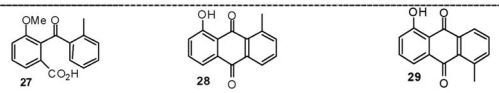
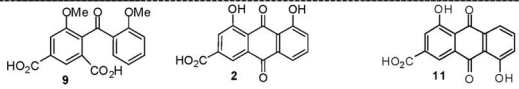


Scheme 2. Hayashi rearrangement and cyclization of **9** and **10**.

Unfortunately, the product was contaminated with its isomer **11** in a 1:1 ratio, resulting from the Hayashi rearrangement of **9** to isomer **10** (Scheme 2; Table 1, Entry 9).[17,22] The use of lower temperatures (<100 °C) under the same conditions was ineffective and resulted in only limited conversion of **9** (<7%), even after prolonged reaction times. The equilibrium existing between the two *ortho*-benzoylbenzoic acid isomers, which interconvert through the Hayashi rearrangement, can be controlled and, in some instances, avoided.[22,23] This feature gave us the opportunity to optimize the experimental conditions to preclude the formation of **10** from **9**. Molten salts have been known for some time and are sometimes preferred to lower-melting ionic liquids and molecular solvents[24] because of their unique physical and chemical properties and, more importantly, their ability to increase the reactivities and selectivities of a range of transformations.[25] In the case of the chloroaluminate inorganic melt for the binary system $AlCl_3$/NaCl, depending on the molar ratio x of $AlCl_3$, three types of melts can be distinguished: acidic if $x > 0.5$ due to the increasing concentration of $[Al_2Cl_7]^-$ and $[Al_3Cl_{10}]^-$ Lewis acids, neutral if $x = 0.5$, and basic if $x < 0.5$, accounting for the presence of an excess amount of $[Cl]^-$ Lewis base.[24,26,27] Owing to their intrinsic properties, binary molten salts might also influence the selectivity of the cyclization of **9**. As a consequence, we investigated this transformation in more detail for closely related substrates with the goal of applying the best conditions to substrate **9**. Accordingly, compounds **12**, **15**, **20**–**23**, **26**, and **27** were prepared by known procedures (Supporting Information) and subjected to both basic molten salts (BMS; $xAlCl_3 = 0.41$) and acidic molten salts (AMS; $xAlCl_3 = 0.67$) of $AlCl_3$/NaCl; the results are summarized in Table 1.

Initially, it appeared that compounds **12**, **15**, and **20** did not equilibrate through the Hayashi rearrangement regardless of the acidic or basic nature of the molten salt, as cyclized products **2**, **14**, **16**, **18**, and **19** arising from initial equilibration of the starting materials were not formed (Table 1, Entries 1–3). For these substrates, two possible positions (*ortho* and *para*, or two *meta*) on the benzoyl moiety bearing the electron-donating methoxy group are available

Table 1. Demethylation/Friedel–Crafts acylation of *ortho*-benzoylbenzoic acids in molten salts.

Entry	Reagents/ AMS or BMS[a]	Direct cyclisation products[b,c]		Hayashi rearranged and cyclized products	
1					
	AMS	16	84	0	0
	BMS	31	69	0	0
2					
	AMS	18	82	0	0
	BMS	80	20	0	0
3					
	AMS	100		0	
	BMS	100		0	
4					
	AMS	80		20	
	BMS	86		14	
5					
	AMS	22		78	
	BMS	16		84	
6					
	AMS	15		85	
	BMS	24		76	
7					
	AMS	88		12	
	BMS	88		12	
8					
	AMS	47		53	
	BMS	67		33	
9					
	AMS	95		5	
	BMS	50		50	

[a] AMS: acidic $AlCl_3$/NaCl molten salt, $x(AlCl_3)$ = 0.67; BMS: basic $AlCl_3$/NaCl molten salt, $x(AlCl_3)$ = 0.41. [b] Cyclized anthraquinone product ratio was determined by analysis of the ^1H NMR spectrum of the crude reaction mixture, after structure assignment by 1D and 2D NMR spectroscopic analysis of the purified products.[28] [c] The conversion of the starting material was always quantitative, and the overall yield of isolated anthraquinones was in the range 78–92% (see Experimental Section).

for direct acylation. It is assumed that the rate of the Hayashi rearrangement followed by intramolecular acylation is likely lower than the rate of the direct Friedel–Crafts reaction for **12**, **15**, and **20**. Experimentally, it was found that for **12** and **15**, the cyclization in acidic molten salt was *ortho*-selective and afforded **11** and **17** as the major products, respectively (Table 1, Entries 1 and 2). However, when the reaction was carried out in BMS, the selectivity was completely reversed to that observed for **15**, and *para*-cyclization product **16** predominated (**16/17**, 4:1). This dramatic inversion of selectivity was not observed for substrate **12**, for which the composition of the molten salt had a lower influence, although the selectivity in favor of **11** was decreased (*ortho*/*para* cyclization products ratio **11/13** ≈ 2:1) in BMS.[28] Subjecting **21** to the cyclization conditions, regardless of the composition of the melt, led to approximately the same 4:1 ratio of direct acylation product **18** with respect to the rearranged Hayashi/cyclized and deprotected compound **17** (Table 1, Entry 4). In contrast, *ortho*-benzoylbenzoic acid **22** afforded the same anthraquinone isomers **17** and **18** in the same ratio (≈1:4) as that obtained for **21**, which accounts for about 80% of the Hayashi rearrangement, regardless of the acidic or the basic nature of the molten salt (Table 1, Entry 5).

This result can be explained by considering the equilibrium that exists between isomers **21** and **22**, which can interconvert through the Hayashi rearrangement. Interestingly, when regioisomers **23** and **26** were treated under the same molten salt conditions, products **24** and **25**[22b] were always formed in an approximate 1:4 ratio (Table 1, Entries 6 and 7), regardless of the acidic–basic nature of the melt and the structure of the starting *ortho*-benzoylbenzoic acids due to prior equilibration through the Hayashi rearrangement. In contrast to the results obtained previously for isomers **21** and **22**, the selectivity for **23** and **26** was reversed; this behavior is ascribed to the differing nature of the substituents (MeO vs. Me) on the starting materials.

Moreover, the product distribution found using substrates **23** and **26** under molten salt conditions is in agreement with results reported by Cristol et al., who observed the propensity of **23** to rapidly equilibrate with **26** in sulfuric acid.[22b]

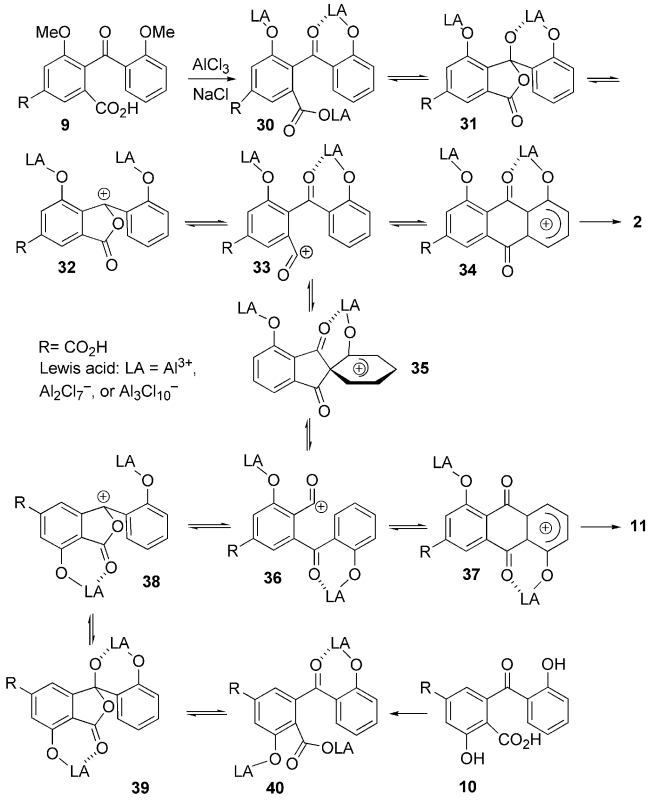
We were finally interested in testing the reactivity of substrate **27** bearing both methoxy and methyl groups on the *ortho*-benzoylbenzoic acid. It appeared that the presence of both substituents renders the Hayashi rearrangement less favorable for substrate **27** than for **23**. Whereas **27** equilibrates to a **28/29** ratio of either 2:1 or ≈1:1(Table 1, Entry 8) in BMS or AMS, respectively, **23** rearranges to a larger extent to produce **24** and **25** in an approximate 1:3 (BMS) or 1:4 ratio (AMS).

From the results obtained with these probe substrates, it is difficult to draw any general rule that would predict the structure of the cyclized product on the basis of the nature of the chloroaluminate salt and the substitution pattern of the *ortho*-benzoylbenzoic acids. It turned out that our initial attempts at the cyclization of substrate **9** gave a 1:1 mixture of desired rhein (**2**) and unwanted isomer **11** in basic inor-

ganic liquid (Table 1, Entry 9).[29] However, when the reactivity of **9** was tested in acidic melt we were gratified to observe that the direct cyclization afforded desired product **2** with a high **2/11** selectivity of 95:5.[29] Only 5% of **11** was formed due to prior Hayashi rearrangement of **9**. This result probably stems from a dramatic increase in the rate of direct cyclization of **9**, thus avoiding the Hayashi equilibration.

The remarkable selectivity exhibited in acidic chloroaluminate inorganic liquid is ascribed to the intrinsic chemical properties of the molten salt, which contains charged functional groups such as cations, free anions, and polymeric units or structons.[30] The overall acidic molten salt effect on the selectivity of the reaction is not yet completely understood. Nevertheless, explanations can be drawn by taking into account the existing noncoordinating strong Lewis acidic $Al_2Cl_7^-$ and $Al_3Cl_{10}^-$ entities present in the AMS.[24,26,27] These species govern the interactions between the different positively charged fleeting organic intermediates encountered during the reversible Hayashi equilibrium rearrangement and, therefore, their relative stability.[31–33] Inspired by the representation of Cristol,[22b] a rational mechanism can be drawn (Scheme 3) that involves spirocyclic cation **35** as a common key intermediate during the Hayashi rearrangement. A rationalization of the selectivity observed for **9** might be explained by a comparison of the relative stabilities of fleeting intermediates **32** and **38** and/or **33** and **36**. Acylium cation **32** is most likely stabilized by the electron-donating mesomeric effect of the two methoxy groups present in the *ortho*-positions of the aromatic groups, which makes this intermediate more stable than **38** in acidic chloroaluminate salt due to the additional stabilization provided by the noncoordinating strong Lewis acid species $Al_2Cl_7^-$ and $Al_3Cl_{10}^-$.

It can then be assumed that, under acidic conditions, the formation of species **33** has a lower activation energy and cyclizes faster than it equilibrates to less-stable **36**, leading predominantly to the formation of **2**. It is reasonable to postulate that the enhancement in the rate of the reaction accounts for the control of the regioselectivity of the reaction, which is most likely due to the general effect of ionic liquids.[34]



Scheme 3. Plausible mechanism for the demethylation/cyclization and Hayashi rearrangement of **9**.

Conclusions

In summary, this study reports a new, short synthesis of rhein in three steps with a global overall yield of 66%, in acidic chloroaluminate molten salt. The high selectivity observed might be due to the acidic nature of the melt, which dramatically increases the rate of the key cyclization step and prevents the Hayashi rearrangement. This work represents a new example of a selective transformation in molten salt, which is considered to be a green solvent.

Experimental Section

General: The synthesis of the starting *ortho*-benzoylbenzoic acids **9**, **12**, **15**, **20**, **21**, and **27** is described in the Supporting Information. Substrates **22**, **23**, and **26** were prepared as described by Cristol et al.[22b] $AlCl_3$ and NaCl were purchased from Aldrich and used without further purification. The chemical isolated yields were obtained from reactions performed on 0.1-mmol scale of the starting *ortho*-benzoylbenzoic acids.

General Procedure for Friedel–Crafts Acylation in Molten Salt

In Acidic Molten Salt (AMS; xAlCl$_3$ = 0.67): Under an argon atmosphere, a round-bottom flask was charged with $AlCl_3$ (2.80 g, 21 mmol, 2.0 equiv.) and NaCl (0.61 g, 10.4 mmol, 1.0 equiv.), and the mixture was heated to 150–155 °C. When the medium became liquid, *ortho*-benzoylbenzoic acid (0.1 mmol) was added. The reaction mixture was stirred for 14 h at 155–160 °C until complete conversion of the starting material. The reaction mixture was cooled to room temperature, then slowly decomposed by adding distilled water (15 mL), and extracted with ethyl acetate (2 × 10 mL). The combined organic phase was dried with Na_2SO_4, filtered, concentrated to afford the crude reaction mixture. Purification by column chromatography on silica gel (ethyl acetate/cyclohexane) afforded pure anthraquinone isomers as solids.

In Basic Molten Salt (BMS; xAlCl$_3$ = 0.41): The BMS was prepared by using a mixture of $AlCl_3$ (2.80 g, 21 mmol, 1.0 equiv.) and NaCl (1.76 g, 3.0 mmol, 1.43 equiv.), and the reaction was performed as described above for the AMS.

Preparation of Rhein (2) in AMS: The general procedure was used starting from **9** (29 mg, 0.1 mmol) to give **2** and **11** (**2/11**, 95:5),

which was isolated as an orange solid (92%, 28.5 mg). The recorded spectroscopic data for **2** were in accordance with reported analytical data.[29]

1,5-Dihydroxyanthraquinone-3-carboxylic Acid (11): Yield (**13/11**, ≈1:4; in AMS): 23.4 mg (83%). R_f = 0.50 (ethyl acetate/methanol/water, 100:13:10). M.p. 278–281 °C. IR (KBr): $\tilde{\nu}$ = 3199, 2996, 1715, 1686, 1636, 1610, 1578, 1411, 1374, 1280, 1250, 971, 774 cm^{-1}. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 7.40 (d, J = 8.6 Hz, 1 H, ArH), 7.76 (d, J = 1.7 Hz, 1 H, ArH), 7.78 (m, 1 H, ArH), 7.83 (t, J = 7.9 Hz, 1 H, ArH), 8.12 (d, J = 1.7 Hz, 1 H, ArH), 12.43 (s, 1 H, ArOH), 12.46 (s, 1 H, ArOH) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 115.6, 118.2, 118.5, 119.2, 124.4, 125.0, 132.7, 133.1, 137.5, 138.0, 161.3, 161.7, 165.2, 186.5, 186.8 ppm. MS (IC, NH$_3$): m/z = 283 [M – H]$^+$.

1,7-Dihydroxyanthraquinone-3-carboxylic Acid (13): Yield (**13/11**, ≈1:2; in BMS): 25.1 mg (89%). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.20 (dd, J = 8.7, 2.5 Hz, 1 H, ArH), 7.42 (d, J = 2.5 Hz, 1 H, ArH), 7.62 (s, 1 H, ArH), 7.98 (d, J = 8.4 Hz, 1 H, ArH), 8.00 (s, 1 H, ArH), 12.16 (s, 1 H, ArOH), 13.6 (s, 1 H, ArOH) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 112.1, 119.9, 122.2, 123.2, 125.0, 130.0, 132.4, 133.7, 134.8, 137.9, 161.1, 163.3, 165.4, 179.8, 187.8 ppm. MS (IC, NH$_3$): m/z = 283 [M – H]$^+$.

1,7-Dihydroxyanthraquinone (16): Yield (**16/17**, 4:1; in BMS): 21.5 mg (90%). R_f = 0.38 (ethyl acetate/cyclohexane, 3:7). M.p. 270 °C. IR (KBr): $\tilde{\nu}$ = 3085, 2923, 1729, 1667, 1631, 1459, 1465, 1364, 1300, 1328, 1046, 967, 784 cm^{-1}. ^{1}H NMR (600 MHz; CDCl$_3$/[D$_4$]MeOD, 2:1): δ = 7.17 (dd, J = 8.4, 2.5 Hz, 1 H, ArH), 7.23 (dd, J = 8.1, 1.3 Hz, 1 H, ArH), 7.61 (t, J = 2.5 Hz, 1 H, ArH), 7.66 (dd, J = 8.1, 7.5 Hz, 1 H, ArH), 7.75 (dd, J = 7.5, 1.3 Hz, 1 H, ArH), 8.12 (t, J = 8.4 Hz, 1 H, ArH), 12.56 (s, 2 H, ArOH) ppm. ^{13}C NMR (50 MHz, CDCl$_3$/[D$_4$]MeOD, 2:1): δ = 112.1, 116.1, 118.9, 122.1, 123.5, 125.2, 130.0, 133.4, 134.9, 137.2, 161.4, 163.2, 180.5, 188.3 ppm. MS (IC, NH$_3$): m/z = 239 [M – H]$^+$.

1,6-Dihydroxyanthraquinone (19): Yield (in AMS): 20.4 mg (85%). R_f = 0.38 (ethyl acetate/cyclohexane, 3:7). M.p. 273–275 °C. IR (KBr): $\tilde{\nu}$ = 3091, 2976, 1724, 1667, 1650, 1594, 1380, 1332, 1255, 1187, 1037, 773 cm^{-1}. ^{1}H NMR (300 MHz; CDCl$_3$/[D$_4$]MeOD, 2:1): δ = 7.18 (dd, J = 8.6, 2.6 Hz, 1 H, ArH), 7.26 (d, J = 8.3 Hz, 1 H, ArH), 7.55 (t, J = 2.6 Hz, 1 H, ArH), 7.60 (t, J = 8.3, J = 7.5 Hz, 1 H, ArH), 7.76 (d, J = 7.5 Hz, 1 H, ArH), 8.18 (t, J = 8.6 Hz, 1 H, ArH), 12.82 (s, 2 H, ArOH) ppm. ^{13}C NMR (50 MHz; CDCl$_3$/[D$_4$]MeOD, 2:1): δ = 113.0, 119.2, 121.4, 124.2, 124.5, 129.7, 133.6, 135.7, 135.9, 161.9, 163.6, 183.0, 187.7 ppm. MS (IC, NH$_3$): m/z = 241 [M + H]$^+$.

1-Methyl-8-hydroxyanthraquinone (28): Yield (**28/29**, ≈47:53; in AMS): 16.8 mg (78%). R_f = 0.85 (ethyl acetate/cyclohexane, 1:1). IR (KBr): $\tilde{\nu}$ = 3079, 2989, 2932, 1720, 1689, 1646, 1622, 1463, 1299, 917, 760, 739 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.88 (s, 3 H, ArMe), 7.29 (m, 1 H, ArH), 7.58–7.69 (m, 3 H, ArH), 7.80 (d, J = 7.5 Hz, 1 H, ArH), 8.24 (d, J = 7.2 Hz, 1 H, ArH), 12.87 (s, 1 H, ArOH) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 24.0, 117.1, 119.0, 124.6, 126.4, 132.0, 133.0, 133.9, 135.2, 136.2, 138.6, 142.6, 162.5, 183.1, 191.3 ppm. MS (IC, NH$_3$): m/z = 238 [M]$^+$.

1-Methyl-8-hydroxyanthraquinone (29): Yield (**29/28**, ≈57:43; in AMS): 16.9 mg (78%). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.66 (s, 3 H, Me), 7.29 (m, 1 H, ArH), 7.58–7.69 (m, 4 H, ArH), 8.06 (d, J = 7.5 Hz, 1 H, ArH), 8.24 (d, J = 7.2 Hz, 1 H, ArH), 12.55 (s, 1 H, ArOH) ppm. MS (IC, NH$_3$): m/z = 238 [M]$^+$.

Supporting Information (see footnote on the first page of this article): Details and experimental procedures for the preparation of original benzophenone derivatives by DOM; analytical data for all new amides and carboxylic compounds.

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