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Improved Synthesis of Natural Isomeric Naphthoxanthenones

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ABSTRACT: 5-methoxy-1*H*-naphtho[2,1,8-*mna*]xanthen-1-one (**1**) and 5-methoxy-3*H*-naphtho[2,1,8-*mna*]xanthen-3-one (musafluorone **2**), a pair of positional isomers isolated from *Wachendorfia thyrsiflora* and *Musa acuminata*, were synthesized in six steps in an overall yield of 53 % and 59 % starting from the corresponding methoxyphenalenones and employing an acid mediated cyclocondensation strategy. Preliminary assays demonstrated the intercalation ability of compounds **1** and **2** into DNA.

Keywords: Naphthoxanthenones, phenylphenalenones, cyclocondensation

Introduction

In 2002 Opitz and coworkers reported on the occurrence of 5-methoxy-1*H*-naphtho[2,1,8-*mna*]xanthen-1-one (**1**) and 5-methoxy-3*H*-naphtho[2,1,8-*mna*]xanthen-3-one (**2**) in plants of *Wachendorfia thyrsiflora* and *Musa acuminata* respectively[1]. Apart from their chemotaxonomic interest, these isomers encompass some structural features of biological and chemical relevance. For instance, their intrinsic push-pull (donor-π-acceptor) chromophore (**Fig. 1**) represents a desirable feature in chemical gap engineering [2]. Moreover, their "bay" region (C-10 through C-11, Fig. 1) in conjunction with their phenalenone core stimulates questions concerning their biological potential in photochemotherapy [3-5].

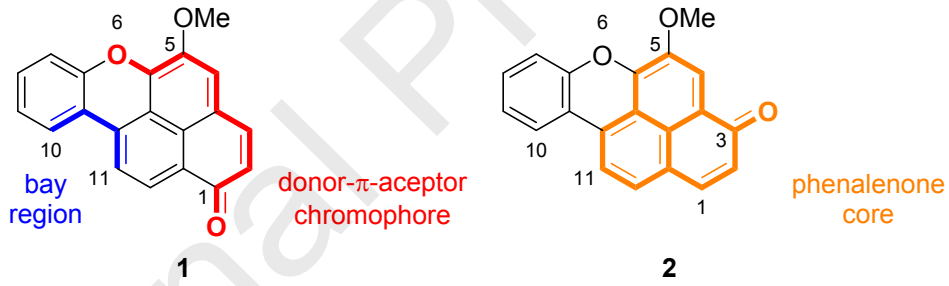


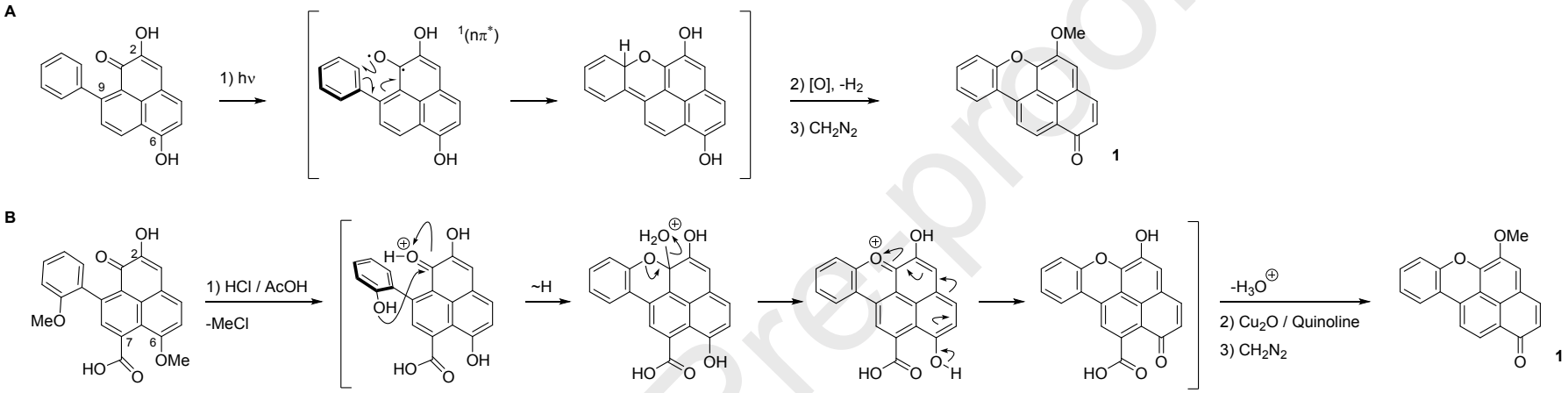
Figure 1. Some salient features of compounds **1** and **2**.

Unfortunately, because of their minute occurrence in phenylphenalenone-producing plants [1,6], these naphthoxanthenones seem to be accessible only by total synthesis.

Historically, the dominant strategy for the generation of the heterocyclic ring of naphthoxanthenones has been the cyclisation of a properly substituted phenylphenalenone (**Scheme 1**). Such a cyclization can be performed in two different ways, namely, photocyclization and cyclocondensation [7-9]. In the former case, the carbonyl group of the

excited molecule interacts with the peri-located phenyl ring [10]. In contrast, the cyclocondensation process employs an ortho-phenolic group in the peri-located phenyl ring to engage the carbonyl group of the phenalenone core (**Scheme 1**) [9]. Although comparative studies are scarce, it seems that the cyclocondensation strategy offers advantages in terms of yield and scalability at least for the synthesis of naphthoxanthenium salts [11].

Compound **1** has been prepared previously employing both strategies (**Scheme 1**). The first one, a semisynthetic preparation via photocyclization of lachnanthocarphone (2,6-dihydroxy-9-phenylphenalen-1-one), was reported without yield (**Scheme 1** part **A**) [7]. The second one employed a sequence of demethylation, decarboxylative-cyclocondensation and methylation using 2-hydroxy-6-methoxy-9-(2-methoxyphenyl)-1-oxo-1*H*-phenalene-7-carboxylic acid as substrate (**Scheme 1** part **B**) but again, no yield was reported for the entire sequence [9]. For the synthesis of compound **2**, a photocyclization strategy was employed culminating in a 3% overall yield after nine steps [12]. Here we wish to report our synthetic efforts aimed at the improvement of the synthesis of compounds **1** and **2**.



Scheme 1. Synthetic strategies reported in the preparation of 5-methoxy-1*H*-naphtho[2,1,8-*mna*]xanthen-1-one (**1**). A) Photocyclization [7]. B) Cyclocondensation [9].

Our synthetic strategy, illustrated with compound **1**, adopted the cyclocondensation for the generation of the heterocyclic ring of the target molecules with concomitant generation of the carbonyl group (**Fig. 2**). The precursor for this step could be generated by the well-known conjugated addition of Grignard reagents to position C-9 of a suitable substituted phenalenone [13-14] which in turn can be prepared via annulation or cyclization of a naphthalene substrate (**Fig. 2**) [12, 15-16].

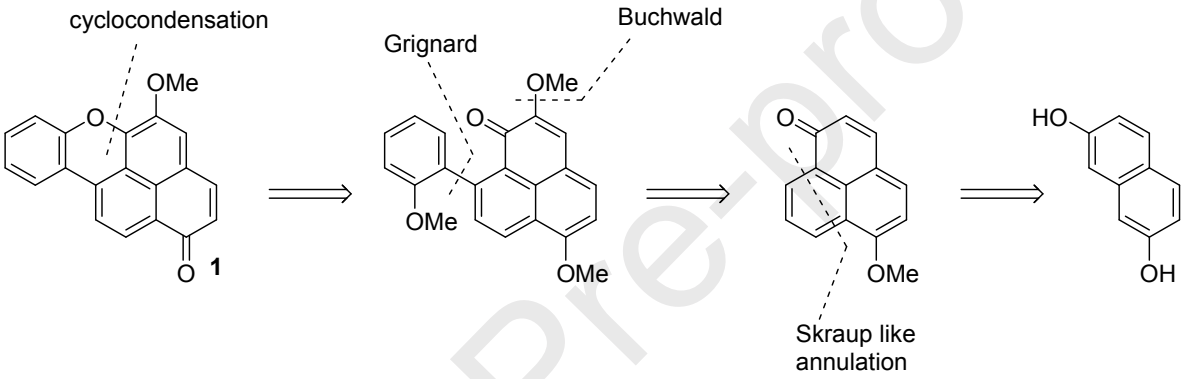


Figure 2: Synthetic strategy adopted for the generation of compound **1**.

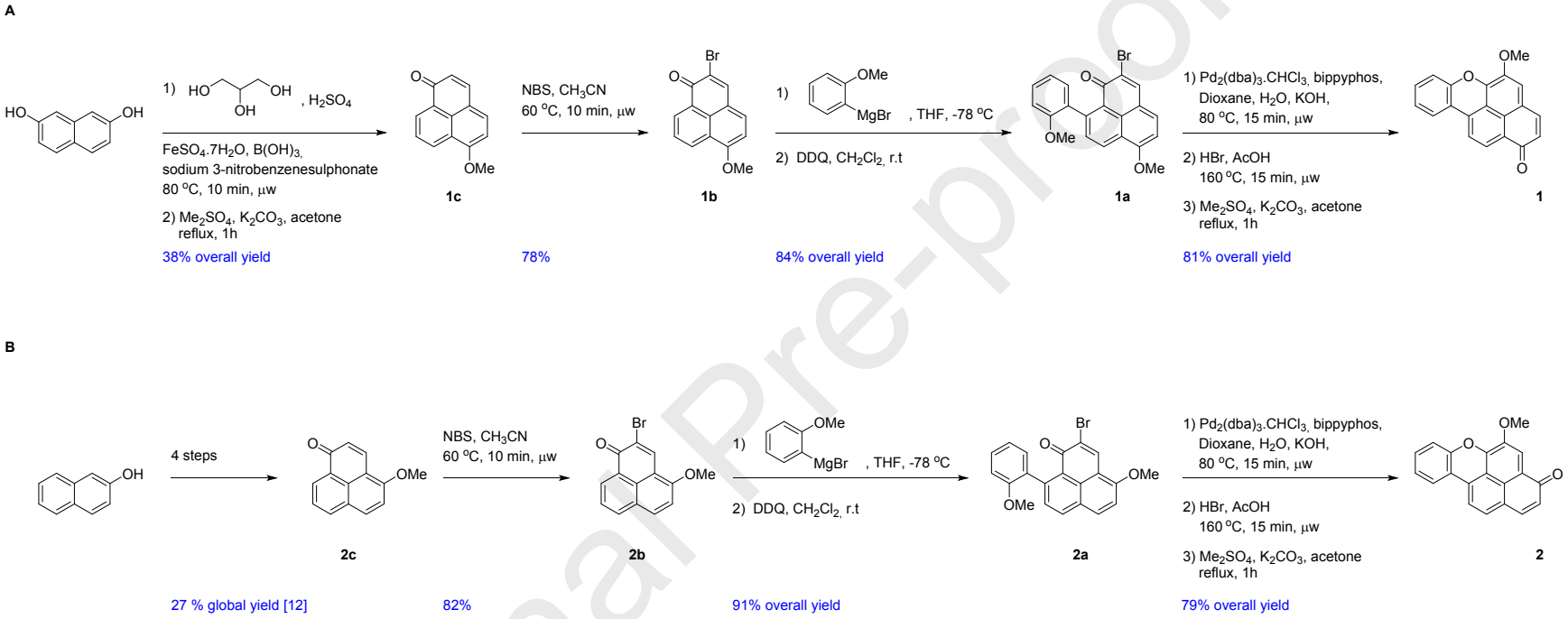
Results and discussion

Initial efforts towards **1** commenced from 6-methoxyphenalenone (**1c**) which was generated via microwave assisted Skraup-like annulation between 2,7-dihydroxynaphthalene and glycerol [15-16] (**Scheme 2** part **A**). Treatment of the crude product with dimethylsulphate afforded the desired starting material in 38% yield. This protocol, although far from optimum, represents a significant improvement over previous methods [16]. Bromination of **1c** by means of NBS afforded 2-bromo-6-methoxyphenalenone (**1b**) in 78%. Treatment of compound **1b** with 2-methoxyphenylmagnesium bromide followed by DDQ

dehydrogenation afforded the desired 2-bromo-6-methoxy-9-(2-methoxyphenyl)phenalenone (**1a**) in 84% yield (**Scheme 2**). Although somewhat risky due to the possibility of halogen-metal exchange, this order of events proved experimentally more convenient in terms of yield and ease of purification than the conjugated addition-bromination sequence. Aromatic substitution of (**1a**) was achieved by adapting the Stradiotto modification to the Buchwald hydroxylation [17-18]. Thus, microwave irradiation of (**1a**) with KOH under $Pd_2(dba)_3$/bippyphos catalysis afforded the phenolic analog of (**1a**). The sensitivity of the hydroxylated compound prompted the execution of the next steps without extensive purification. Hence, demethylation by means of HBr/AcOH caused the desired cyclocondensation and the reaction crude was immediately methylated to afford 5-methoxy-1*H*-naphtho[2,1,8-*mna*]xanthen-1-one (**1**) in a gratifyingly 81% from (**1a**) (**Scheme 2** part **A**).

The use of the Buchwald reaction in this sequence bypassed the long standing problem of methoxyperinaphthenone hydroxylation for which only partial solutions via Jacobsen epoxidation were previously reported [12, 16, 19].

Extrapolation of these methods towards compound **2** commenced with 4-methoxyphenalenone (**2c**) which was obtained in four steps from 2-naphthol according to our previous report [12]. Treatment of **2c** with NBS afforded the corresponding 2-bromo-4-methoxyphenalenone (**2b**) in 82% yield. Grignard addition proceeded smoothly to provide the corresponding 2-bromo-4-methoxy-9-(2-methoxyphenyl)-1*H*-phenalen-1-one (**2a**) in 91% yield after DDQ treatment. Buchwald hydroxylation, demethylation (cyclocondensation) and methylation sequence afforded compound **2** in 79% yield (**Scheme 2** part **B**).



Scheme 2: Synthesis of compounds **1** (part **A**) and **2** (part **B**) starting from the corresponding methoxyphenalenones **1c** and **2c**.

With compounds **1** and **2** at hand, we proceeded to test their DNA intercalation ability by adding an ethanolic solution of **1** or **2** instead of ethidium bromide in the well of a typical DNA electrophoresis. Figure S1 (supporting information) shows the electrophoretic mobility of compounds **1** and **2** in conjunction with DNA ladder samples but not by themselves. This result argues in favor of the DNA intercalation ability of the title compounds. Moreover, if such intercalation occurs in the cell, a hampering effect on DNA replication must be expected which should result in smaller genomic-DNA degradation products. This behavior was demonstrated by means of a comet-assay on HaCaT human keratinocytes which displayed significant genomic-DNA damage with a 22 ± 2 and 33 ± 5 percentage of DNA in "tail" for compounds **1** and **2** respectively at concentrations of 50 μg/mL (**Fig. S2-S3**, supporting information). These comet-values are contrasted against ethidium bromide (a well-known DNA intercalator) for which a value of 19 ± 9 was found in the same assay at the same concentration (supplementary information).

Conclusions

In conclusion, a synthesis of 5-methoxy-1*H*-naphtho[2,1,8-*mna*]xanthen-1-one (**1**) and 5-methoxy-3*H*-naphtho[2,1,8-*mna*]xanthen-3-one (**2**) was achieved in five steps starting from the corresponding methoxyphenalenone in a 53% and 59% global yield respectively using a cyclocondensation as the key step. The employment of the Buchwald hydroxylation for the substitution of a bromomethoxyphenalenone significantly improved the yields by avoiding the difficult epoxidation of methoxyphenalenones. The synthesis is suitable for the

preparation of the title compounds in the 1 mmol scale. Initial explorations demonstrated the DNA-intercalation properties of compounds **1** and **2**.

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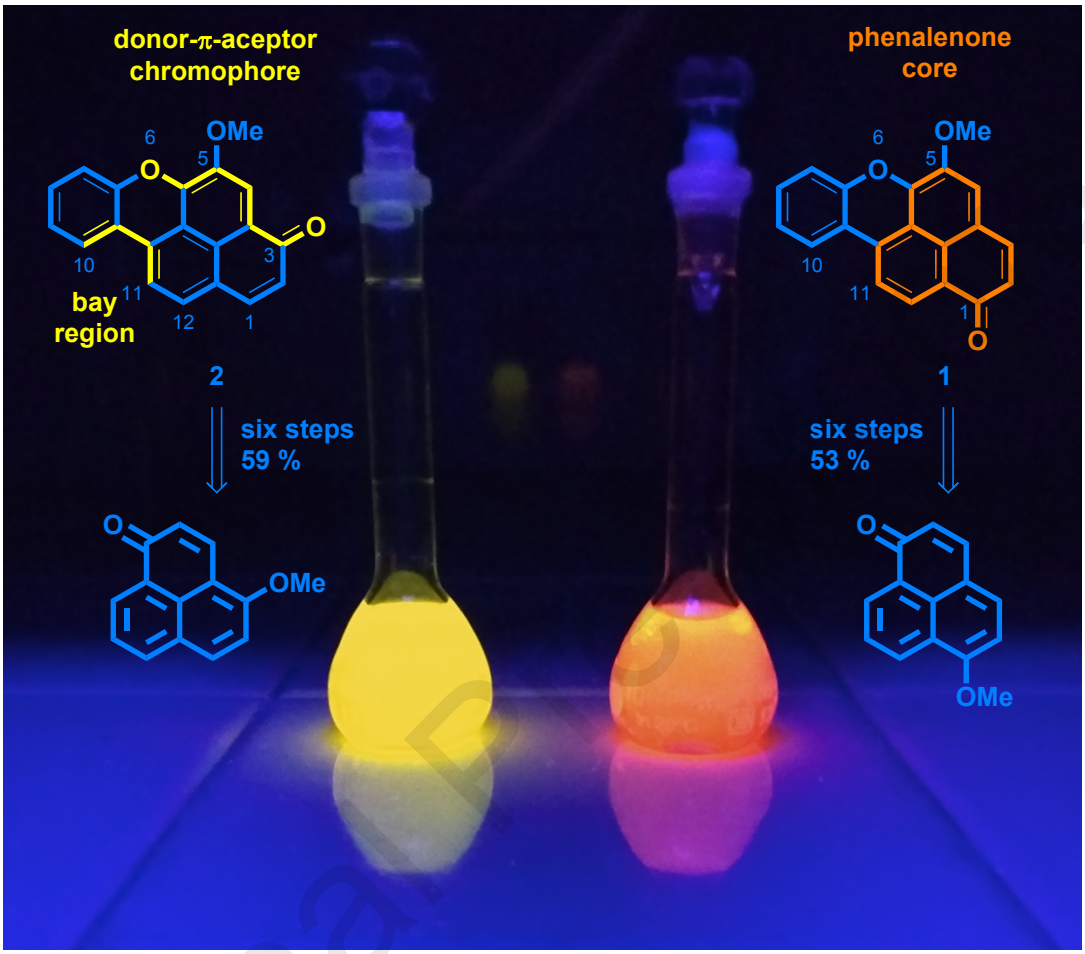
Graphycal Abstract



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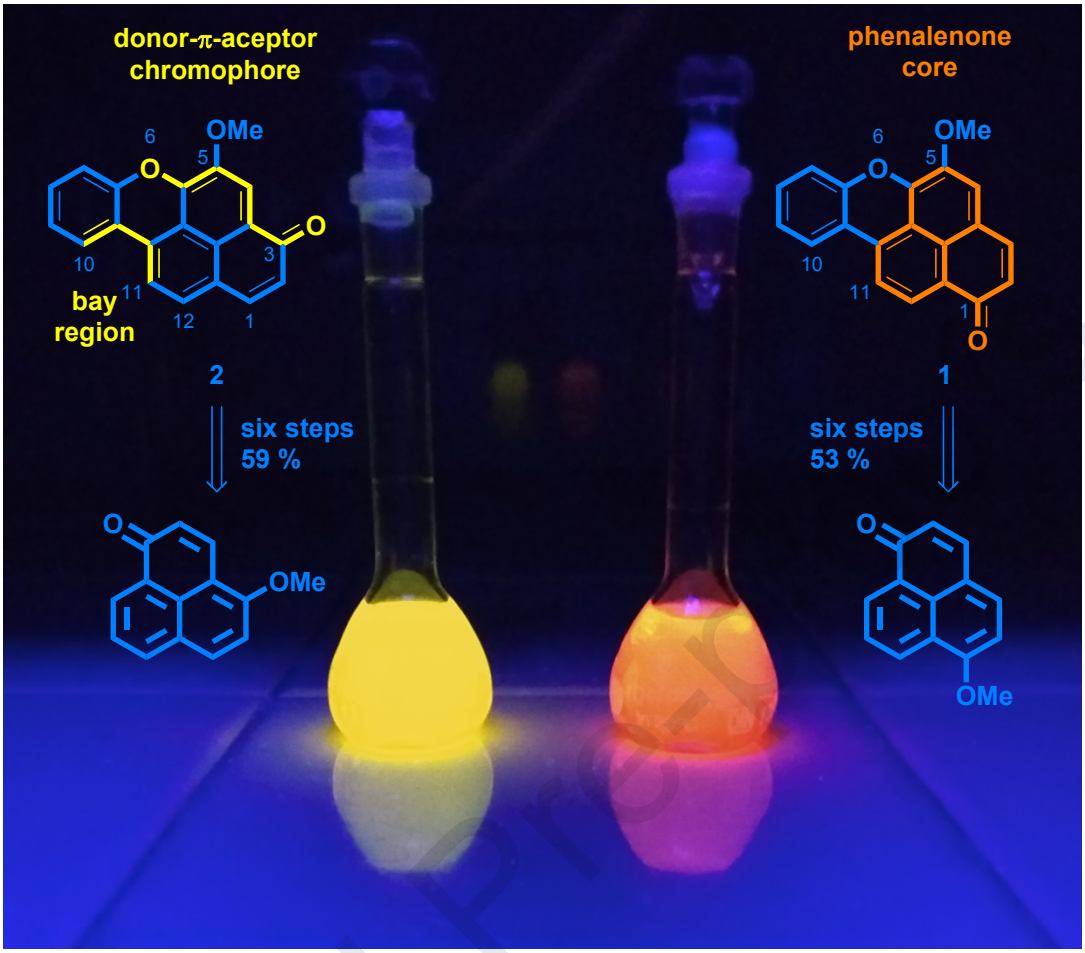

Highlights:

- A pair of natural isomeric naphthoxanthenones were prepared with efficiency and in the mmol scale
- Cyclocondensation and Buchwald hydroxylation were implemented as key steps
- The compounds show DNA-intercalation ability

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: