Azaanthracenones

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Total Syntheses of Cytotoxic, Naturally Occurring Kalasinamide, Geovanine, and Marcanine A**

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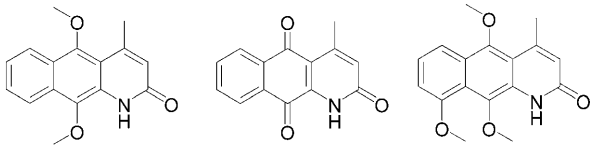
Azaanthracenones are a pharmacologically interesting class of natural compounds. The first representative of an azaanthraceneone isolated from natural sources was geovanine (**3**; Scheme 1). It was isolated from wood from the trunk of

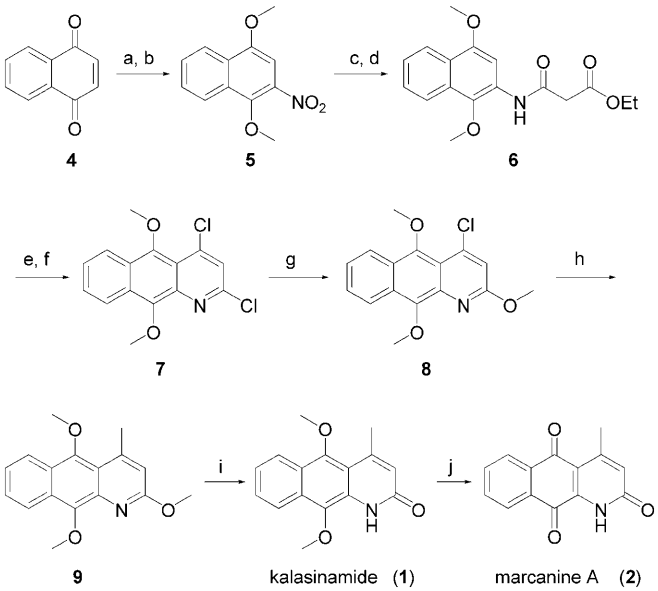


Scheme 1. Structures of naturally occurring azaanthracenones.

Annona ambotay in 1987 by de Oliveira et al.[1a] Several years later, Dos Santos et al.[1b] reported the isolation from *Annona dioica* collected in Brazil, but no total synthesis has been published so far. Kalasinamide (**1**) was discovered by Tuchinda et al.[2] in 2000 in *Polyalthia suberosa* collected in Thailand. Very recently Gandy and Piggott published the first total synthesis of kalasinamide (**1**).[3] Marcanine A (**2**) was isolated by Soonthornchareonnon et al.[4] in 1999 from *Goniothalamus marcani* in Thailand. Perez et al. reported its synthesis several years before the isolation.[5]

Azaanthracenones show several biological activities. Soonthornchareonnon et al.[4a] reported on the cytotoxicity of marcanine A and its derivitives, which displayed IC_{50} values between 80 nM and 2.1 μM against several human tumor cell lines. Ichino et al.[4c] found marcanine A to have in vitro antimalarial activity against the drug-resistant K1 strain of *Plasmodium falciparum*. Ruomy et al.[4d] reported the isolation of another azaanthracenone and found activity against *Plasmodium falciparum*.

We report here on the first total synthesis of geovanine (**3**) along with new syntheses of marcanine A (**2**) and kalasinamide (**1**). Three key steps were crucial to the new synthetic approach to kalasinamide and marcanine A (Scheme 2). The



Scheme 2. Reagents and conditions: a) Pd/C, H_2, THF; Me_2SO_4, reflux; b) HNO_3, DCM; c) Ni, H_2, 75% over three steps; d) malonic acid diethyl ester, 140°C, 3 h, 85%; e) 5% NaOH, 60°C, 3 h, 93%; f) $POCl_3$, reflux, 2 h, 85%; g) MeONa, MeOH, RT, 3 d, 98%; h) MeMgCl, THF, $MnCl_2$, 0°C, 2 h, 80%; i) TMSCl, NaI, MeCN, RT 4 h, 95%; j) CAN, MeCN/H_2O, RT, 4 h, 71%. DCM = dichloromethane, CAN = ceric ammonium nitrate.

first is the nitration of dimethoxynaphthalene. This reaction has been reported several times; however, yields were poor in almost all cases.[6] Oxidative demethylation usually leads to significant amounts of naphthoquinone as the side product.[7] The best yields are obtained by the addition of nitric acid to a solution of the starting compound in dichloromethane in the presence of silica gel. A similar method was reported first by Tapia et al.[8] However, substantial alterations were necessary for its application to a larger scale reaction. After optimization the nitration step leading to **5** was achieved in over 90% yield.

The second key step is the cyclization of a malonic acid amide in the presence of phosphorus oxychloride.[9] After optimization this conversion proceeded smoothly providing **7** in 85% yield. Differentiation between the two chloride residues at the pyridine ring of **7** was possible by treatment with sodium methoxide in methanol/THF at room temperature over 24 h. Dimethoxylation was not observed, even at increased temperatures and reaction times. These results clearly differ from the analogous reaction of 2,4-dichloro-5,8-dimethoxyquinoline (**10**): under similar reaction conditions, the monomethoxylated products **11** and **12** were obtained in a 1:1 ratio (Scheme 3).[10]

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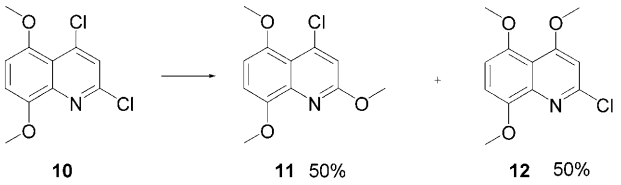
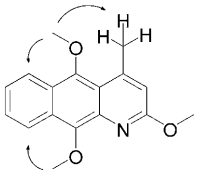


Scheme 3. Reagents and conditions: MeONa, MeOH, RT, 3 d.

The third key step is the replacement of the remaining chloride with a methyl group. Manganese(II) chloride catalyzed alkylation[11] in THF with the corresponding Grignard reagent furnished the desired product in excellent yield.

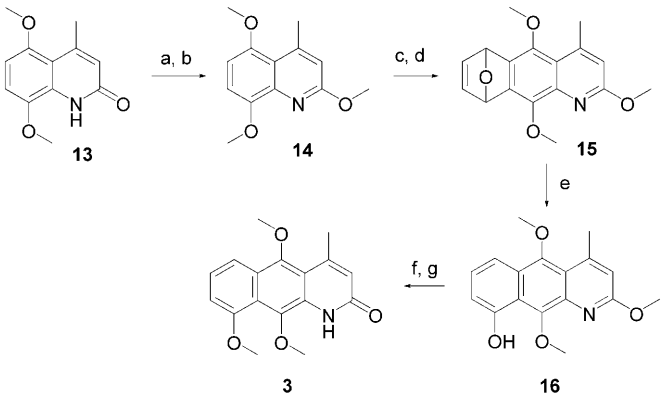


Scheme 4. NOE interactions observed for intermediate **9**.

To prove the selectivity of the sequence of methoxylation and methylation, NOE experiments were conducted with **9**. The interactions shown in Scheme 4 were found.

The $MnCl_2$-catalyzed alkylation can be used to introduce a large variety of residues. Investigations will be made in order to determine the scope of this method. Demethoxylation of **9** was achieved by treatment with TMSCl and NaI in acetonitrile[12] at room temperature and provided **1** in good yield. Demethylation of the hydroquinone dimethyl ether was conducted in the presence of ceric ammoniun nitrate (CAN),[13] yielding mercanine A (**2**) as a yellow powder.

Geovanine (**3**) was prepared in only nine steps from 2,5-dimethoxyaniline (Scheme 5). Intermediate **13** was prepared in 65% yield over two steps by modification of a procedure described by Brody et al.[14] Deoxychlorination with phosphorus oxychloride[15] and subsequent dehalomethoxylation[16] yielded **14** in 90% yield. Bromination with 1.05 equiv NBS[17] proved to be superior to all other methods tested for the next step (Scheme 5). Bromination with Br_2 in chloroform,[18] for example, led to extensive demethylation at C2 of the pyridine moiety as a result of the presence of free hydrobromic acid. The selectivity of the bromination with NBS was about 88%. As both regioisomers could be used in the following reaction this did not affect overall yields.



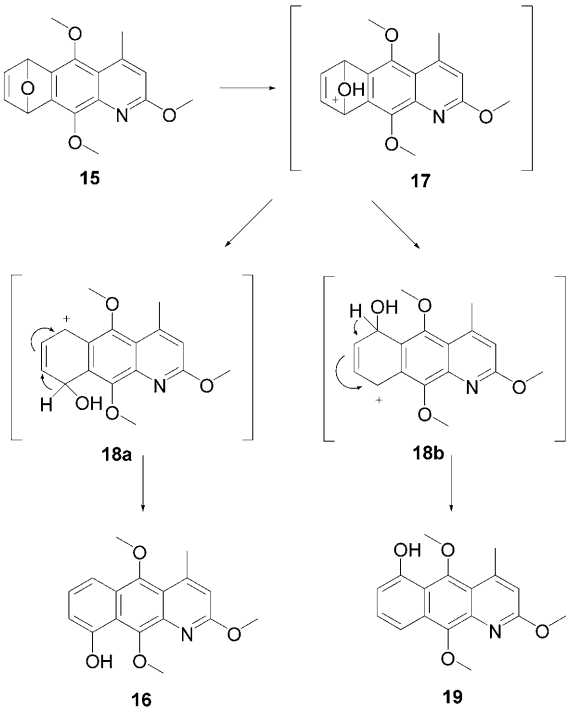
Scheme 5. Reagents and conditions: a) $POCl_3$, reflux, 3 h; b) MeOK, MeOH, reflux, 5 h, 89% over 2 steps; c) NBS, DCM, RT 2 h, 90%; d) LDA, THF, furan, −78 °C, 3 h, quant.; e) *p*-toluenesulfonic acid, THF, reflux, 20 h, 56%; f) MeI, NaH, DMF/THF, 96%; g) TMSCl, NaI, MeCN, RT 4 h, 85%. NBS = *N*-bromosuccinimide, LDA = lithium diisopropylamide.

Attachment of ring C was achieved by treating the bromide with lithium diisopropylamide (LDA) at −78 °C in the presence of furan.[19] Similar methods have been applied to aromatic compounds, but to our knowledge this is the first report on its application to heteroaromatic compounds. Acidic cleavage of the oxygen bridge mediated by *para*-toluenesulfonic acid[20] provided free phenol **16**. When dichloromethane was used as the solvent, as described in the literature, the reaction time exceeded several months; it was therefore replaced by THF. Only very small amounts (less than 2%) of the other phenolic isomer were obtained. Treatment of **15** with $HClO_4$[20b] did not lead to any detectable amount of product. Refluxing in hydrochloric acid or acetic acid was not an option owing to the lability of the 2-methoxy moiety.

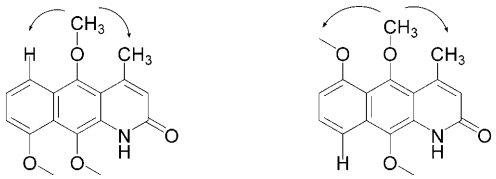
The two transition-state structures **18a** and **18b** can be invoked in the cleavage of the oxygen bridge (Scheme 6). However, **18a** is formed predominantly as a result of the electron-donating effect of both substituents on the pyridine moiety. Consequently the desired product **16** is formed with high selectivity.[21] Traces of the undesired isomer could be easily removed by recrystallization.

Methylation of phenol **16** could not be achieved with MeI and K_2CO_3 but proceeded smoothly in the presence of sodium hydride.[22] TMS-I mediated demethoxylation[12] at the pyridine residue provided geovanine (**3**) in good yield (Scheme 5).

At this stage NOE experiments were conducted in order to prove the selectivity of the ring opening (Scheme 7).



Scheme 6. Possible transition states and products of the acid-catalyzed ring opening of **15**.



3 20

Scheme 7. Anticipated NOE interactions for isomers **3** and **20.**

Whereas in isomer **3** one methoxy residue should show long-range couplings with both the adjacent aromatic H and the aromatic methyl group, in **20** each of the two central methoxy groups would display only one of these couplings. The long-range couplings we obtained proved that the structures of isomer **3** and our product are identical (for details see the Supporting Information).

Geovanine has been isolated twice. De Oliveira et al. reported only ^{1}H NMR data and could not determine which of the isomers had been isolated. Several years later, Dos Santos et al. isolated a mixture of the two isomers and published ^{1}H and ^{13}C NMR data. The two isomers were distinguished by HBBD, DEPT, COSY and NOE experiments. Our results show that these first assignments were not entirely accurate (see the Supporting Information). At least two of the reported carbon signals seem to belong to the wrong isomer.

Compound **2** showed good results in cytotoxicity tests against two human cancer cell lines. The IC_{50} values obtained with the synthetic marcanine A were comparable to those reported for the isolated natural product (HeLa S3: 0.75 ± 0.03 μM; Hep G2: 1.54 ± 0.78 μM).

In conclusion, we have implemented the first total synthesis of geovanine (**3**). Thereby we were able to prove the position of the 8-methoxy group and assign all of the signals in the ^{13}C NMR spectrum. Moreover, we conducted new total syntheses of the natural compounds marcanine A (**2**) and kalasinamide (**1**). For this purpose we developed two basically new synthetic approaches to this class of natural compounds. Both routes offer excellent perspectives for the synthesis of numerous new azaanthracenones. In the light of the increasing need for new cytostatica we believe that these results may contribute to substantial progress in this field.

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