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Total Synthesis of the Antimalarial Ascidian Natural Product Albopunctatone

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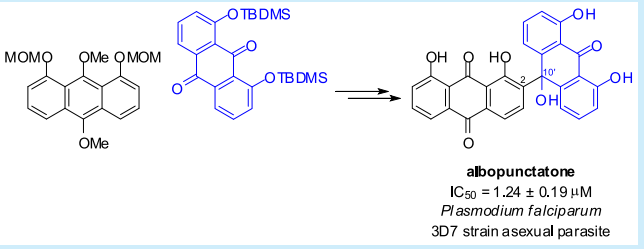
Supporting Information

ABSTRACT: The first approaches to the 10′-anthronyl-2-anthraquinone skeleton have been devised, allowing two syntheses of the marine natural product albopunctatone. Both routes involve regioselective addition of a nucleophilic masked anthraquinone to a protected chrysazin derivative; the best affords albopunctatone in five steps and 35% overall yield. Albopunctatone exhibits potent inhibitory activity against *Plasmodium falciparum* and negligible toxicity to a range of other microbial pathogens and mammalian cells.



Albopunctatone (**1**, Figure 1) is an anthronyl-anthraquinone (AAQ) isolated, in 2012 by Carroll's group, from the Great Barrier Reef ascidian *Didemnum albopunctatum*.[1] It is the first, and currently the only, C2−C10′ linked[2] AAQ to be isolated from a marine source; the 14 other reported natural products sharing this scaffold come from plants,[3−10] many of which are used in traditional medicine.[4,6,7,11,12] Indeed, the first described AAQ **2** (Figure 1) is a constituent of *Aloe maculata* (previously called *Aloe saponaria*), which is used in Southern Africa for the treatment of various ailments. In 2005, AAQ natural products were shown to inhibit the growth of *Plasmodium falciparum*,[12] and since this first report, several congeners have been found to display antimalarial activity.[9,10] Notable among these are the chrysophanol dimer **2** and chryslandicin (**3**), which exhibit potent activity against the chloroquine-resistant Dd2 strain of *P. falciparum*, with IC_{50} values of 0.4 μM and 0.2 μM, respectively,[13] while being relatively nontoxic to mammalian host cells. Albopunctatone (**1**) was reported to have comparatively moderate antimalarial activity (Dd2 IC_{50} 5.3 μM; chloroquine-sensitive 3D7 IC_{50} 4.4 μM), but a selective mode of action given a lack of activity against a range of normal and cancerous human cell lines, and the protist parasite *Trypanosoma brucei brucei* at concentrations up to 40 μM.[1]

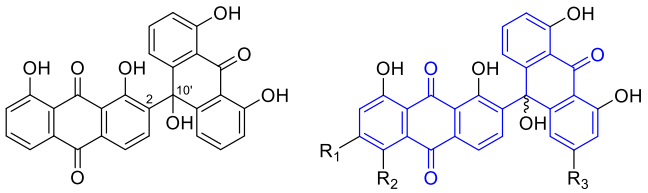
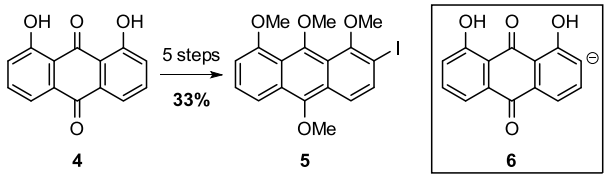


Figure 1. Structure of antimalarial AAQ natural products albopunctatone (**1**), chrysophanol dimer **2**, and chryslandicin (**3**). Compounds **2** and **3** have optical activity, but the absolute configuration is unknown.[3,4]

The AAQs are dimers or heterodimers of 1,8-dihydroxyanthraquinones. Albopunctatone (**1**) is the only example with a symmetrical monomeric unit, chrysazin (**4**, Scheme 1), and thus the only achiral AAQ. All chiral AAQs but one have been reported to have optical activity, and the configuration of the 10′ stereocenter has been determined in some cases,[8,9] suggesting that biosynthetic construction of the C2−C10′ bond is enzyme-catalyzed. Given that the AAQ scaffold (Figure 1, highlighted blue) had not been synthesized before, we

Scheme 1. Potential Nucleophilic Synthon, and Starting Materials, for the Synthesis of Albopunctatone



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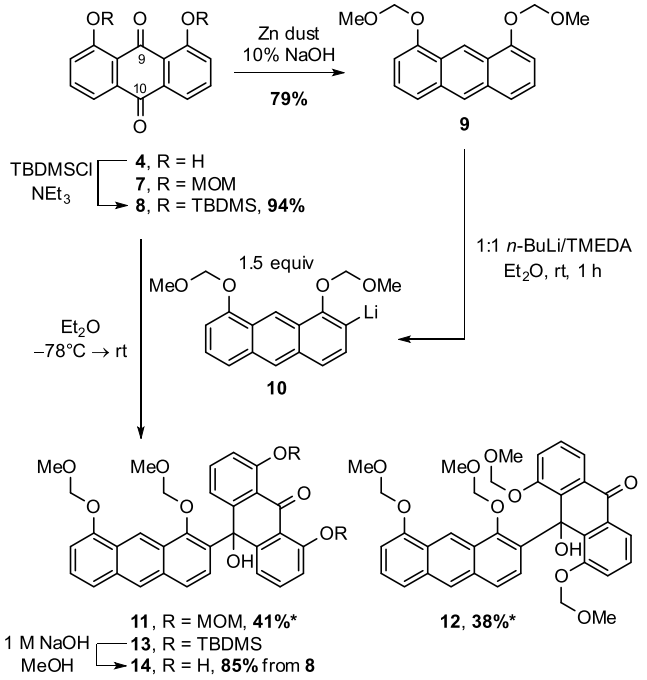
pursued the synthesis of albopunctatone as an entry point into this interesting class of antimalarials.

Our synthetic strategy mimics the likely biosynthesis of albopunctatone (**1**): dimerization of chrysazin (**4**) (Scheme 1). We envisaged regioselective addition of a nucleophilic 1,8-dihydroxyanthraquinone synthon equivalent to **6**, to a suitably protected chrysazin derivative. Initially it was proposed that the required nucleophile may be generated by lithium−iodine exchange of **5** (Scheme 1), which is easily prepared based upon previous experience.[14] However, the poor step economy in the synthesis of **5** led us to consider alternatives.

A nucleophilic anthraquinone synthon, generated by *ortho*-lithiation of 1,5-bis(methoxymethoxy)anthracene, was used by the Tius group in their synthesis of the *C*-glycosylanthraquinone antibiotic vineomycinone B_2 methyl ester.[15] Similar results were obtained with 1,8-bis(methoxymethoxy)-anthracene (**9**). This approach was appealing, as the two-step preparation of anthracene **9** from chrysazin (**4**) would also provide the necessary electrophilic partner **7** (Scheme 2).

Scheme 2. Construction of the Albopunctatone Carbon Skeleton from Anthryllithium 10



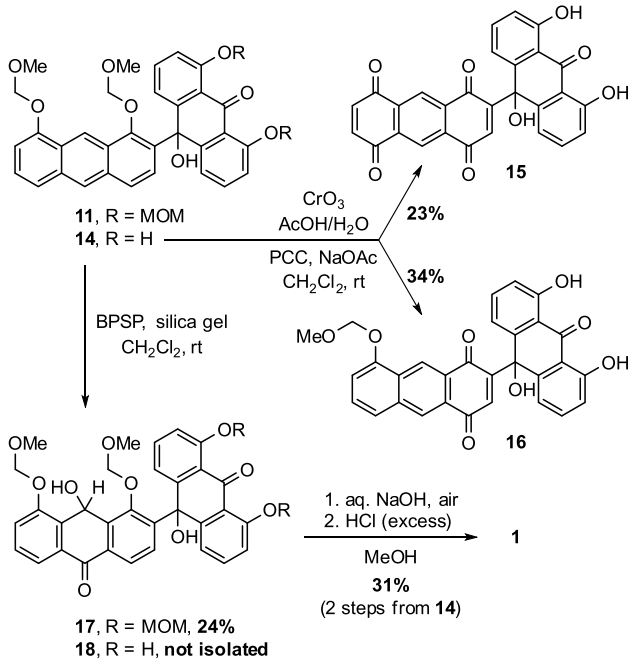
*^{1}H NMR yields. The isolated yields were 40% (**11**) and 19% (**12**).

The di-MOM acetal of chrysazin (**7**) was therefore prepared from chrysazin (**4**)[15] and reduced to anthracene **9** with zinc dust in refluxing aqueous hydroxide.[16] Directed *ortho*-lithiation of **9** under the reported conditions[15] gave good conversion to the lithioanthracene **10**, though D_2O-quenching experiments showed that the conversion could be improved slightly by simply halving the reaction time to 1 h (see Table S2). Subsequent addition of **10** to the anthraquinone **7** at 0 °C unexpectedly produced the two regioisomeric carbinols **11** and **12** in approximately equal amounts, despite the steric hindrance at C9. The regioselectivity was not improved at −78 °C (see Table S3). Yang and co-workers reported similar reactivity of a 1,8-dimethoxyanthraquinone with benzylmagnesium bromide as an obstacle during their total synthesis of clostrubin.[17] In the case of anthraquinone **7**, we suspect that the steric bulk of the MOM groups is countered by their ability to direct addition of lithioanthracene **10** to C9. This issue was addressed by the use of the noncoordinating *tert*-butyldimethylsilyl (TBDMS) protecting group in **8**.[18] Treatment of **8** with anthryllithium **10** afforded only one regioisomer, adduct **13**. The silyl ethers of **13** were unstable during workup and purification and, hence, were deliberately hydrolyzed,[19] delivering anthronylanthracene **14** in good yield.

Having constructed the carbon skeleton of albopunctatone (**1**), all that remained was to oxidize the anthracene moiety of **14**, restoring the anthraquinone 9,10-carbonyl groups. A similar oxidation was achieved by Tius and co-workers[15] with bispyridine silver permanganate (BPSP),[20,21] which has since been employed successfully to oxidize a variety of anthracenes to 9,10-anthraquinones.[22−24] It is implied in the literature that these oxidations are best conducted under anhydrous conditions; however, after taking care to ensure the oxidant, solvent, and silica gel were water-free, attempts to oxidize **14** only returned starting material.

Consequently, some alternative oxidants were trialled, with varied results. Periodate with catalytic permanganate[25] also failed to oxidize anthracene **14**. Chromic acid[26,27] proved too acidic, cleaving the methoxymethyl acetals and oxidizing the resulting phenolic moieties to give the 1,4,5,8-anthracenetetrone **15** (Scheme 3). Pyridinium chlorochromate over sodium

Scheme 3. Oxidation of Anthrylanthrones



acetate[28,29] left one MOM group intact, oxidizing only the internal ring to afford the 1,4-anthraquinone **16**. The low yields of these oxidation products **15** and **16** can, in part, be accounted for by the formation of significant quantities of the side product chrysazin (**4**).

Following these failures, BPSP was revisited as an oxidant, with further experiments on the tetra-MOM derivative **11** suggesting that the oxidation requires trace water. Using unactivated silica gel, and otherwise the same conditions as in previous unsuccessful experiments, the anthracene **11** was oxidized to hydroxyanthrone **17** with the desired anthronylanthraquinone a minor product (see p S17 in the Supporting

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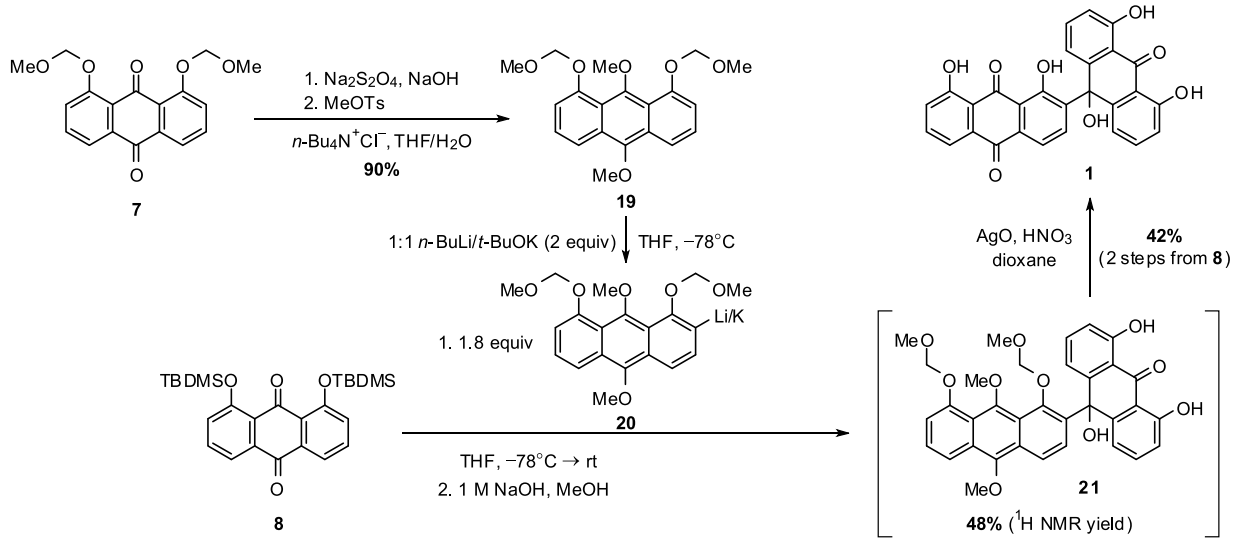
Scheme 4. A Second, More Efficient Route to Albopunctatone (1)



Information). When the di-MOM derivative **14** was subjected to these slightly modified conditions, the oxidation similarly stalled at the hydroxyanthrone **18**. We were discouraged from attempting to force the oxidation to completion by the observation that increasing amounts of the side-product chrysazin (**4**) were again formed as the reaction progressed.

Instead, any remaining BPSP was filtered off, and crude hydroxyanthrone **18** was treated with base to facilitate aerial oxidation to the anthraquinone.[30,31] In situ treatment with excess acid cleaved the MOM acetals and furnished albopunctatone (**1**) in 19% yield across the six synthetic steps from chrysazin (**4**) (Schemes 2 and 3).

The obstacles encountered in what was anticipated to be a routine oxidation of anthracene **14** encouraged a modified approach to **1** based around dimethoxyanthracene **19**, prepared via reductive methylation of anthraquinone **7** (Scheme 4). Directed *ortho*-metalation of **19** would provide a nucleophilic anthraquinone synthon amenable to subsequent oxidation to an anthraquinone; however, 9,10-dimethoxyanthracenes are susceptible to nucleophilic attack across their central ring,[32−34] making them incompatible with the standard organolithium bases (*n*-, *sec*-, and *t*-BuLi). Non-nucleophilic bases were therefore employed in initial attempts to metalate dimethoxyanthracene **19**, though neither lithium diisopropylamide nor lithium tetramethylpiperidide proved effective (see Table S4).

Matsumoto and co-workers avoided nucleophilic attack through use of the Lochmann−Schlosser superbase (1:1 mixture of *n*-BuLi and *t*-BuOK), which smoothly metallates dimethoxyanthracenes without competing C9/C10 addition.[33,34] Previous metalations of dimethoxyanthracenes generally used two equivalents of the Lochmann−Schlosser base.[33,34] The excess *n*-BuLi was expected to react competitively with electrophile **8**, hence, the metalation of dimethoxyanthracene **19** was attempted with a smaller excess of 1.2 equiv of *n*-BuLi−*t*-BuOK. In these experiments D_2O quenching indicated incomplete or very sluggish metalation, with 55% deuterium incorporation being the best result (see Table S4). Increasing the ratio of *t*-BuOK to *n*-BuLi increases the reactivity of the superbase in some deprotonations,[35] but in this case a 1:3 ratio of *n*-BuLi to *t*-BuOK completely suppressed metalation of **19**. Relenting, two equivalents of *n*-BuLi−*t*-BuOK were used to cleanly generate the metalloanthracene **20**. Treatment of **20** with the anthraquinone **8** afforded the adduct **21** in moderate yield. As predicted, side products resulting from the use of excess *n*-BuLi were observed. Isolation of the anthronylanthracene **21** proved difficult, so freshly prepared crude **21** was directly subjected to oxidative demethylation. The acidic conditions for the oxidation also effected global deprotection, simplifying the crude to essentially a mixture of chrysazin (**4**) and albopunctatone (**1**), from which **1** was easily isolated. This second route improved significantly on the original approach (Schemes 2 and 3), and afforded **1** in five synthetic steps and 35% overall yield from chrysazin (**4**).

The ^{1}H and ^{13}C NMR data for synthetic albopunctatone are in full agreement with those reported for the natural product,[1] and confirmed by a single crystal X-ray structure (Figure 2).

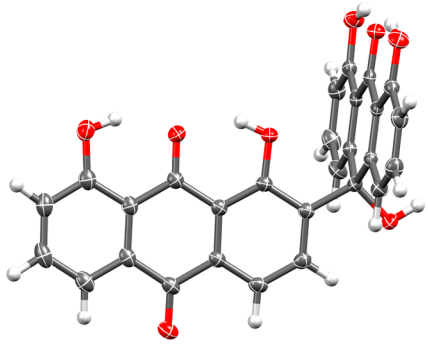


Figure 2. Representation[36] of the crystal structure of albopunctatone (**1**). Ellipsoids are shown at 50% probability amplitudes with hydrogen atoms assigned arbitrary radii. A disordered EtOAc molecule was omitted for clarity. CCDC Number 1918756.

With ample quantities on hand, the biological activity of albopunctatone was assessed against a small panel of microbial pathogens, specifically, *Mycobacterium tuberculosis*, *Leishmania donovani*, *Trypanosoma cruzi*, and *T. brucei. brucei.* No significant activity was observed against any of the microbes, nor the mammalian host cells (THP-1 for *L. donovani*, 3T3 cells for *T. cruzi*), or a control mammalian cell line (HEK-293). However, synthetic albopunctatone was found to have similar

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potency against *P. falciparum* 3D7 strain asexual parasite (IC_{50} = 1.24 ± 0.19 μM, Figure S1) to that previously reported for the ascidian-derived material.[1]

Given the common ancestry of plants and *Plasmodium* species,[37] and the demonstrated herbicidal activity of some antimalarials,[38] the effect of albopunctatone on *Arabidopsis thaliana* was also assessed; however, no herbicidal activity was observed up to 100 μM (Figure S2). This result could reflect a biological target only expressed in the parasite, and thus likely outside the apicoplast, or simply poor uptake in the plant. Thus, the intriguing biological target of albopunctatone remains unknown. Given the potent and highly selective antimalarial activity of the AAQs, further studies to elucidate this target are warranted. The syntheses presented herein provide the means to obtain the necessary materials to interrogate the mode of action of the AAQs.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01838.

Full synthetic experimental details and characterization data; crystallographic data for albopunctatone (**1**); ^{1}H and ^{13}C NMR spectra; antiplasmodial results; herbicidal assays (PDF)

Accession Codes

CCDC 1918756 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/, or by emailing deposit@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.
Biological assays against *L. donovani* amastigotes,[39] *T. cruzi* amastigotes,[40] *T. b. brucei*,[39,41] *P. falciparum* 3D7 asexual parasites,[39,42] *M. tuberculosis*,[43] and HEK-293 cells[39] were conducted as described previously.

■ ACKNOWLEDGMENTS

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(2) Previously isolated AAQs sharing the same backbone (Figure 1, highlighted blue) as albopunctatone have been numbered inconsistently. In some cases AAQs are numbered such that the anthraquinone and anthrone units are C7−C10′ linked,[4,5,9] and in others they are considered to be C10−C7′ linked.[3,6−8] The system employed by Hou et al. to number scutianthraquinones A−D[10] was applied to albopunctatone.

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