Bulbine-Knipholone, a New, Axially Chiral Phenylanthraquinone from *Bulbine abyssinica* (Asphodelaceae): Isolation, Structural Elucidation, Synthesis, and Antiplasmodial Activity[‡]

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A new natural phenylanthraquinone, bulbine-knipholone (**6**), has been isolated from the African plant species *Bulbine abyssinica* (Asphodelaceae). Its structure was determined by spectroscopic and degradative methods. With the aid of the "lactone concept", an atropo-enantioselective total synthesis has been elaborated, confirming the full absolute structure. Bulbine-knipholone exhibits antiplasmodial activity.

Introduction

Bulbine abyssinica A. Rich, an erect plant widespread in Eastern and Southern Africa, grows from a vertical rhizome with fleshy roots.[1] A milk decoction of the roots is applied to cure body rash and sexually transmitted diseases, while related *Bulbine* species are used for the treatment of various ailments such as bacterial and fungal infections, eczema, venereal diseases, and rheumatism.[2] Previous chemical investigations on the genus *Bulbine* have resulted in the isolation of antioxidant isofuranonaphthoquinones such as **1** (see Figure 1),[3] DNA-intercalating[4] and antileukemic[5] anthraquinones such as chrysophanol (**2**) and aloe-emodin (**3**),[6] and axially chiral phenylanthraquinones with good antiplasmodial activities,[7] among them knipholone (**4**)[8,9] and isoknipholone (**5**).[10] These promising bioactivities and the importance of *Bulbine* plants in traditional medicine make the search for, and synthetic availability of, further metabolites rewarding goals. In this paper we report on the isolation, structural elucidation, and stereoselective synthesis of bulbine-knipholone (**6**), a new, optically active phenylanthraquinone with antiplasmodial activities, from the roots of *Bulbine abyssinica*.

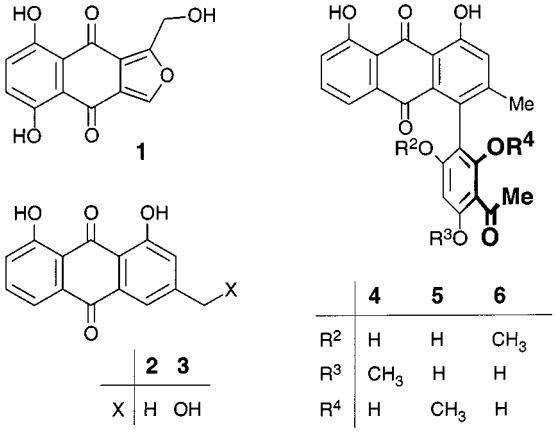

Figure 1. Bioactive natural products from African *Bulbine* species

Results and Discussion

B. abyssinica was collected from the Medicinal Plant Garden of the University of Botswana, Gaborone, Botswana, in February 2001. Fractionation of the CH_2Cl_2/MeOH (1:1) extract of the roots by CC on silica gel and finally by preparative HPLC on RP-18 gave 2.3 mg of an amorphous red solid. The UV/Vis spectrum indicated the compound to be an anthraquinone derivative, and HRMS analysis established the same molecular formula as for knipholone (**4**) ($C_{24}H_{18}O_8$). ^{1}H NMR spectra of **6** similarly closely resembled those of **4**, showing signals indicative of a moiety related to chrysophanol (**2**): two chelated hydroxy

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groups (δ = 11.97 and 12.50, Figure 2), an ABC pattern for the protons in the 5-, 6-, and 7-positions, a one-proton singlet at δ = 7.30 for 2-H, and a three-proton singlet for a methyl group (δ = 2.12). The remaining ^{1}H NMR signals similarly suggested the presence of an acetylphloroglucinol methyl ether unit with singlets for 5′-H (δ = 6.41), for the COMe group (δ = 2.68), and for the OMe group (δ = 3.68). In comparison with the resonance of the *O*-methyl group of **4** (δ = 3.90), this last signal was strongly shifted to high field, indicating the influence of a ring current effect due to the proximity of an aryl residue (here the anthraquinone moiety). Irradiation of these OMe protons showed signal enhancement of 5′-H. Consequently, compound **6** must have the constitution shown in Figure 2; it is thus an isomer of knipholone (**4**), with the *O*-methyl group not at C-4′ but at C-6′, and likewise an isomer of isoknipholone (**5**). Its structure was further confirmed by HMBC (Heteronuclear Multiple Bond Correlation) and HMQC (Heteronuclear Multiple Quantum Correlation) interactions. For this new phenylanthraquinone we suggest the name bulbine-knipholone.

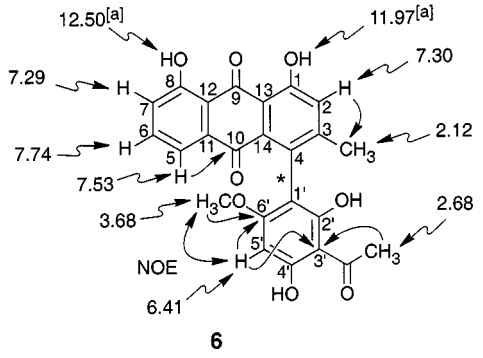
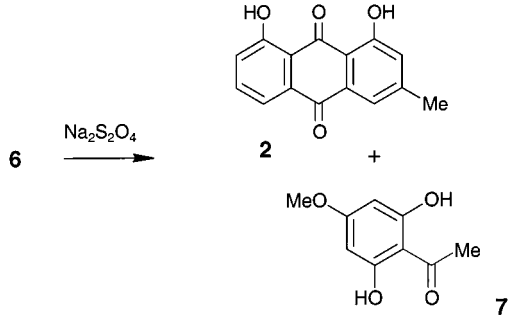


Figure 2. Selected ^{1}H NMR shifts (δ values in ppm), together with HMBC (single arrows) and NOE interactions (double arrows) of bulbine-knipholone (**6**); [a] may be interchanged

Further proof of its constitution was obtained by reductive cleavage of the biaryl system with $Na_2S_2O_4$[11] (see Scheme 1), which afforded the expected aromatic aryl fragments − chrysophanol (**2**) and 2,6-dihydroxy-4-methoxyacetophenone (**7**, alias 2-acetylphloroglucinol 5-*O*-methyl ether or 3′-*O*-demethylxanthoxylline), also a natural product[12] − both fully identical in all respects with independently synthesized authentic material (see below) and with literature data.[13,14]

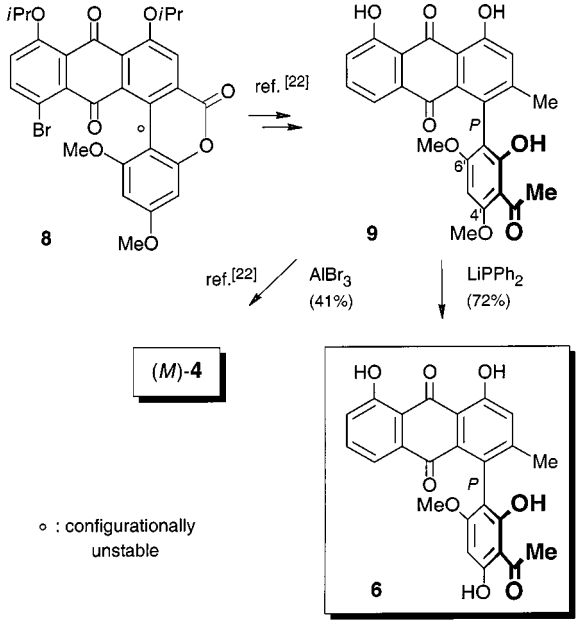
Besides bulbine-knipholone (**6**), the known phenylanthraquinones knipholone (**4**),[8] knipholone anthrone,[15] 6′-*O*-methylknipholone,[10] and 4′-*O*-demethylknipholone[16] were also detected in the crude extract of the roots of *Bulbine abyssinica*, by means of HPLC comparison with the previously synthesized authentic compounds as reference materials.[17]

Because of hindered rotation around the central biaryl bond, bulbine-knipholone is configurationally stable and optically active − a property also observed for all the other known natural 4-phenylanthraquinones.[8,9,15,18] The absolute configuration of knipholone (**4**) itself has recently been elucidated by quantum chemical CD calculations.[19] The similarity of the CD spectrum of the new phenylanthraquinone **6** with that of knipholone (**4**)[19] was itself indicative of stereochemical identity of the two compounds, thus suggesting that **6** was *P*-configured.[20]



Scheme 1. Reductive cleavage of bulbine-knipholone (**6**) to give the known natural products chrysophanol (**2**) and 2,6-dihydroxy-4-methoxyacetophenone (**7**)

This opened the possibility of rationally elaborating a directed synthesis of **6** from the same synthetic precursors as had previously been used for **4**,[21] hence obtaining further rigorous evidence of the absolute stereostructure of **6**. A key intermediate in the first − and as yet only − total synthesis of **4**[21] by the "lactone method"[22] had been the configurationally unstable biaryl lactone **8** (see Scheme 2), easily prepared by intramolecular coupling, which was opened atropo-enantioselectively, ultimately giving 6′-*O*-methylknipholone (**9**), also a natural product.

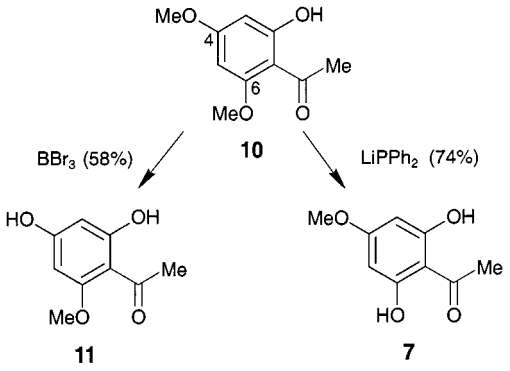


Scheme 2. Stereochemical identity of **4** and **6** as deduced from their joint synthesis from **9**

Regioselective ether cleavage of the 6′-*O*-Me group of **9** with $AlBr_3$ had previously[21] given knipholone (**4**). In the

present case, however, a reagent that would selectively remove the *O*-methyl group at C-4′ (i.e., next to the *C*-acetyl group) was required. This was found in the less common reagent $LiPPh_2$,[23] which, when tested on the anthraquinone-free compound xanthoxylline (2-hydroxy-4,6-dimethoxyacetophenone, **10**) as a model substrate (see Table 1), proved to be the reagent of choice, affording highly site-selective cleavage of the acetyl-adjacent methyl ether.[24]

Table 1. Regiodivergent *O*-demethylation of xanthoxylline (**10**)



Reagent[a]	Solvent	*T* [°C]	Product yield (%)[a]	
			11	**7**
BBr_3	CH_2Cl_2	25	58	24
$AlCl_3$	C_6H_5Cl[b]	120−150	55	22
$LiPPh_2$	THF	25	n.d.[c]	74 ←
NaSEt	DMF	80−140	−	−[d]

[a] Isolated yield after flash chromatography. [b] For a similar cleavage reaction, see ref.[25] [c] n.d.: not detected. [d] No reaction.

In contrast to the anthracene-free model compound **10**, which required 2.2 equiv. of the phosphorus reagent (see Table 1), not less than 6 equiv. was needed for the conversion of **9** into **6** (Scheme 2), apparently because of the two additional acidic OH groups on the anthraquinone part of **9**. The product thus obtained in high yield proved to be chromatographically and spectroscopically fully identical with the new natural product from *B. abyssinica* described in this paper. Moreover, as expected, the chiroptical properties matched perfectly. Bulbine-knipholone is therefore indeed *P*-configured and has the stereostructure shown in Scheme 2. It is noteworthy that not only **4**, **6**, and **9**, but all of the natural phenylanthraquinones so far investigated configurationally, have the same stereochemical array at the axis, with the $COCH_3$ portion above the anthraquinone plane.[17] This supports our previous biosynthetic assumption[21] of a "directed", truly enzyme-controlled biaryl coupling of knipholone-type phenylanthraquinones in the plants.

The synthesis of bulbine-knipholone (**6**) based on the "lactone approach" furnished sufficient material for assessment of its bioactivities. In view of the recently discovered promising antimalarial potential[7] of some related phenylanthraquinones, compound **6** was tested against the erythrocytic stages of strains of *Plasmodium falciparum* (K1 strain) showing activity (IC_{50} = 751 ng mL^{-1}) in the range of knipholone (IC_{50} = 627 ng mL^{-1}), but still not quite as potent as the as yet most active phenylanthraquinone knipholone anthrone (IC_{50} = 149 ng mL^{-1}) and the standard chloroquine (IC_{50} = 141 ng mL^{-1}). Bulbine-knipholone did not exhibit any cytotoxic effects on mammalian cells below 90 μg mL^{-1} (highest concentration tested).

Conclusion

In summary, a new axially chiral phenylanthraquinone, bulbine-knipholone from *B. abyssinica*, has been discovered. Its constitution, as established i.a. by NMR investigations, was further corroborated chemically, by reductive cleavage of the stereogenic biaryl axis. CD investigation determined the absolute configuration at the axis, and this was further confirmed by its atropo-enantioselective total synthesis, including a highly regioselective *O*-demethylation reaction, first developed on a simplified model system. Bulbine-knipholone showed antiplasmodial activity in vitro. This once again emphasizes the antimalarial potential of knipholone-type phenylanthraquinones and makes the search for further natural or synthetically modified derivatives with even better activities a potentially rewarding goal.

Experimental Section

General Remarks: ^1H NMR (400 MHz) and ^{13}C NMR (101 MHz) spectra were measured with Bruker AMX 400 and Bruker DMX 600 machines with CD_3COCD_3 (δ = 2.05 and δ = 21.8) and CD_3OD (δ = 3.30 and δ = 49.0) as the solvent and internal ^1H and ^{13}C standards. Proton-detected, heteronuclear correlations were measured by HMQC (Heteronuclear Multiple Quantum Correlation, optimized for $^1J_{HC}$ = 145 Hz) and HMBC (optimized for $^nJ_{HC}$ = 7.0 Hz). For further general procedures see ref.[26]

Plant Material: The plants were collected by one of us (D. M.) in the Medicinal Plant Garden of the University of Botswana, Gaborone (Botswana), and were identified by Mr. G. Pole (Royal Botanical Garden, Kew, UK). Samples are deposited in the Herbarium of Botswana (codes BA 204 and BA 206) and in the Herbarium Bringmann (code 59), Institute of Organic Chemistry, University of Würzburg.

Bulbine-Knipholone (6). − By Isolation from *B. abyssinica*: Dried roots of *B. abyssinica* (20 g) were powdered and then extracted with a mixture of CH_2Cl_2 and MeOH (1:1) at room temp. for 24 h, to yield 1.2 g of a brownish crude extract, which was chromatographed on silica gel with CH_2Cl_2/EtOAc as the eluent (100:0 up to 100:20). Further purification by HPLC, with a Guard Pak C-18 column (3.9 × 20 mm) and a Nova Pak C-18 column (4 μm, 3.9 × 150 mm) from Waters (Eschborn, Germany), an LC-10 ATVP pumping unit (Shimadzu Corporation, Japan) with a flow of 0.5 mL min^{-1}, and an SPD-M10 AV Shimadzu diode array detector (solvent: MeOH/H_2O, 70:30, acidified with 0.1% trifluoroacetic acid), gave **6** (2.3 mg) as an amorphous red solid; m.p. 284−288 °C. $[\alpha]_D^{20}$ = +174 (*c* = 0.0087, MeOH). UV (EtOH): λ_{max}

(lg ε) = 206 (1.27), 225 (1.58), 254 (0.96), 287 (0.94), 431 (0.36) nm. CD: $\Delta\varepsilon_{280} = +2.25$, $\Delta\varepsilon_{235} = -2.59$, $\Delta\varepsilon_{220} = -4.16$ (EtOH). IR (KBr): $\tilde{\nu}$ = 3435, 2924, 2852, 1682, 1629, 1205, 720 cm^{-1}. ^1H NMR (400 MHz, CD_3COCD_3): δ = 2.12 (s, 3 H, $ArCH_3$), 2.68 (s, 3 H, $ArCOCH_3$), 3.68 (s, 3 H, $ArOCH_3$), 6.41 (s, 1 H, 5′-H), 7.29 (dd, *J* = 7.6, 1.0 Hz, 1 H, 7-H), 7.30 (s, 1 H, 2-H), 7.53 (dd, *J* = 7.6, 1.0 Hz, 1 H, 5-H), 7.74 (dd, *J* = 7.6, 7.6 Hz, 1 H, 6-H), 12.0 (s, 1 H), 12.0−12.3 (s, 2 H), 12.5 (s, 1 H). ^{13}C NMR (101 MHz, CD_3COCD_3): δ = 21.0 ($ArCH_3$), 33.1 ($CO\mathit{C}H_3$), 56.1 (OCH_3), 92.1 (C-5′), 106.1 (C-3′), 108.2 (C-1′), 115.7 (C-13), 116.5 (C-12), 120.1 (C-5), 124.0 (C-7), 125.2 (C-2), 129.4 (C-4), 132.9 (C-14), 135.7 (C-11), 138.1 (C-6), 153.0 (C-3), 161.5 (C-8), 162.4 (C-1), 163.0, 163.6, 163.7 (C-2′/C-4′/C-6′), 182.7 (C-10), 194.1 (C-9), 204.3 ($Ar\mathit{C}OCH_3$). The ^{13}C assignments were achieved by HMQC and HMBC experiments. MS (EI, 70 eV): *m*/*z* (%) = 434 $[M]^+$ (100), 419 $[M - CH_3]^+$ (46), 403 $[M - OCH_3]^+$ (31), 392 $[M - COCH_2]^+$ (27), 361 $[392 - OCH_3]^+$ (16). HRMS: 434.1000 ($C_{24}H_{18}O_8$: calcd. 434.1001). The known natural products knipholone (**4**), knipholone anthrone, 6′-*O*-methylknipholone, and 4′-*O*-demethylknipholone were identified in the crude extract by HPLC coelution analysis, with the previously synthesized compounds as reference materials.[17]

Reductive Cleavage of 6: $Na_2S_2O_4$ (3 mg, 17 μmol) was added to a solution of **6** (2.0 mg, 4.6 μmol) in 5% NaOH (1 mL), and the reaction mixture was stirred for 1 h at 70 °C. The solution was acidified and thoroughly extracted with EtOAc. Evaporation of the solvent from the dried ($MgSO_4$) organic phases and purification by flash chromatography on silica gel (CH_2Cl_2) afforded the anthraquinone **2** (0.7 mg, 2.8 μmol, 61%) and 2,6-dihydroxy-4-methoxyacetophenone (**7**, 0.5 mg, 2.7 μmol, 60%). These cleavage products were identical to authentic chrysophanol (Fluka) and to synthetic **7**, as obtained by cleavage from xanthoxylline (**10**, see below), by TLC and ^1H NMR.

4,6-Dihydroxy-2-methoxyacetophenone (11): BBr_3 (4.00 mL, 4.00 mmol, 1 M in CH_2Cl_2) was added under argon to a cooled (0 °C) solution of **10**[27] (400 mg, 2.04 mmol) in dry CH_2Cl_2 (30 mL). After this had stirred for 3 h at room temp.,[28] MeOH was added, the solvent was evaporated in vacuo, and the residue was purified by flash chromatography on silica gel with CH_2Cl_2/MeOH as the eluent (100:0 up to 100:3). Crystallization from EtOH yielded **11** (215 mg, 1.18 mmol, 58%); m.p. 204 °C (ref.[25] 204−205 °C). The spectroscopic data were identical to those reported in ref.[18]

2,6-Dihydroxy-4-methoxyacetophenone (7): A solution of $HPPh_2$ (0.5 mL, 538 mg, 2.89 mmol) in dry THF (3 mL) in a flame-dried flask was treated dropwise, at 0 °C under argon, with a cold solution of *n*-butyllithium in hexane (2.5 M, 1.27 mL, 3.18 mmol). Stirring was continued, and the red solution was allowed to warm to room temp. over a period of 20 min. A solution of **10**[27] (100 mg, 649 μmol) in dry THF (5 mL) was treated at 0 °C under argon with an $LiPPh_2$ solution (2.4 mL, 1.43 mmol $LiPPh_2$), prepared according to the procedure given above, and stirred at 50 °C for 1 h. H_2O (3 mL) and 2 M aqueous HCl (3 mL) were added, and the mixture was thoroughly extracted with EtOAc. Drying ($MgSO_4$) of the combined organic phases, evaporation of the solvent, purification by flash chromatography on silica gel with CH_2Cl_2/MeOH (100:0 up to 100:3) as the eluent, and crystallization from EtOH/H_2O afforded **7** (87.4 mg, 480 μmol, 74%); m.p. 139−140 °C (ref.[13] 142−143 °C). The spectroscopic data were identical to those reported in ref.[13]

Bulbine-Knipholone (6). − By Regioselective *O*-Demethylation of (*P*)-9: Compound (*P*)-**9** (27.5 mg, 61.4 μmol), as obtained by total synthesis,[17,21] was dissolved in dry THF (2 mL), treated at 0 °C with an $LiPPh_2$ solution (0.6 mL, 364 μmol) as prepared above, and stirred at 70 °C for 3 h. After the mixture had cooled, H_2O (1 mL) and 2 M HCl (1 mL) were added, and the mixture was thoroughly extracted with EtOAc. Drying ($MgSO_4$) of the combined organic phases, evaporation of the solvent, and purification by HPLC with a preparative LC 25 mm module with two Nova-Pak C-18 column segments (25 × 100 mm each) from Waters (Eschborn, Germany) and a 510 pump (Waters, Eschborn, Germany), a flow of 4.0 mL min^{-1}, and UV detection at 254 nm (solvent: MeOH/H_2O, 75:25, acidified with 0.1% trifluoroacetic acid), afforded (*P*)-**6** (19.2 mg, 44.2 μmol, 72%) as an amorphous red solid, fully identical in all respects to the material obtained above.

***Plasmodium falciparum* and Cytotoxicity Assay:** Antiplasmodial activity was determined with the K1 strain (resistant to chloroquine and pyrimethamine) of *P. falciparum*. A modification of the [^3H]-hypoxanthine incorporation assay[29] was used.[30] Briefly, infected human red blood cells were exposed to serial drug dilutions in microtiter plates for 48 h at 37 °C in a gas mixture with reduced oxygen and elevated CO_2. [^3H]-Hypoxanthine was added to each well, and after further incubation for 24 h, the wells were harvested on glass fiber filters and counted in a liquid scintillation counter. The IC_{50} value was calculated from the sigmoidal inhibition curve. The assays were run in duplicate and repeated at least once. Cytotoxicity was tested against rat skeletal muscle myoblast (L-6) cells.[31]

Acknowledgments

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