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A Novel Synthetic Route for 1,2'-Binaphthalene Derivatives, Analogues of Isodiospyrin

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ABSTRACT

A new synthetic route for 1,2'-binaphthalenes was developed. 4,5,8'-Trimethoxy-2,3'-dimethyl-[1,2']-binaphthalenyl-1'-ol (20) was synthesized by aryl-aryl coupling of the prefixed aryloxymethyl-aryl intermediate followed by reductive cleavage of the ethereal bridge. Compound 20 was further oxidized with Fremy's salt to give 4,5,8'-trimethoxy-2,3'-dimethyl-[1,2']-binaphthalenyl-1',4'-dione (21). Preliminary studies showed that compound 21 was active against *Leishmania mexicana* (LV78) promastigotes, but was inactive against the cell growth of a variety of human tumor cell lines.

Key words: 1,2'-Binaphthalenes; 1,2'-Bisnaphthoquinones; Synthesis; Antileishmanial activity; L. mexicana; Promastigote.

INTRODUCTION

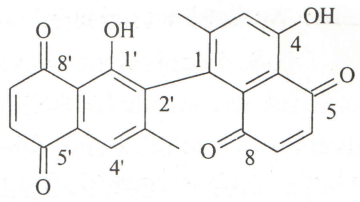
Nature provides a vast number of biaryl products with great structural diversity. Among biaryl products, various binaphthalenes, binaphthoquinones, and naphthyl-isoquinolines, which frequently bear an axially chiral conformation, have been isolated from microorganisms and higher plants that exhibit potent biological activities.[1,2] For example, (-)-isodiospyrin (**1**) bearing an unsymmetrical 1,2'-binaphthoquinoid chromophore was isolated from the roots of *Diospyros* and *Euclea* species.[3-5] Diospyrin (**2**), a 1,1'-binaphthoquinoid derivative, was obtained from *Diospyros montana* Roxb.[6,7] 2,2'-Binaphthalene derivative, gossypol (**3**), was isolated from *Gossypium* species[8] and has been studied as a male antifertility agent in China. The two representative naphthyl-isoquinoline alkaloids, ancistrocladine (**4**) and dioncophylline A (**5**), were found in lianas of the genera *Ancistrocladus*[9] and *Triphyophyllum peltatum*,[10,11] respectively. The latter has been found to have fungicidal,[12] insect growth retarding and antifeedant activity,[13] and, in particular, activity against malaria parasites.[14]

The naturally occurring quinonoid compounds

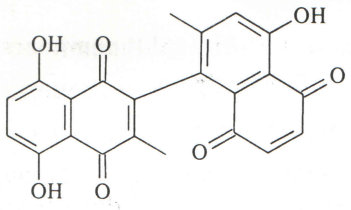
Dedicated to The 10th Anniversary of Professor Sheng-Teh Lu's Death

have attracted our attention, since these agents often act a vital links in one-electron transformation and thus produce pronounced cytotoxicity and other biological activities.[2] Of these derivatives, (-)-isodiospyrin (**1**) and its monomer, 7-methyljuglon (**7**) were revealed to have potent antitumor activity against human KB epidermic carcinoma, A-549 lung carcinoma, HCT-8 and Co-115 colon carcinoma cells *in vitro*.[15,16] Isodiospyrin is also a dual DNA topoisomerase I and II α inhibitor.[17] The inhibition of the catalytic activity of human topoisomerase I by isodiospyrin is 10-fold more potent as compared to camptothecin,[17] a potent antineoplastic natural product and topoisomerase I inhibitor.[18] The isomer, diospyrin (**2**), was also cytotoxic to several human tumor cell lines in culture.[19] Ray *et al.* reported that diospyrin significantly inhibited the growth of *Leishmania donovani* promastigotes.[20] This agent also inhibited the catalytic activity of DNA topoisomerase I of the parasite and induced DNA topoisomerase I-mediated cleavage *in vitro*, suggesting that the binaphthoquinonoid derivatives exert their inhibitory effect by binding to the enzyme and stabilizing the Topo I-DNA cleavable complex. However, diospyrin did not inhibit topoisomerase II of *L. donovani* and required much higher concentrations to inhibit calf thymus topoisomerase I. Based on the biological properties of isodiospyrin and diospyrin, they can be exploited for rational drug design to develop new anticancer agents or drugs against human leishmaniasis.

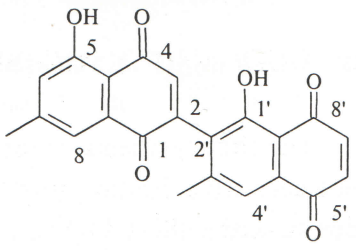
Leishmania species are kinetoplastide protozoa obligatory intracellular parasites that are responsible for a wide spectrum of diseases, ranging from local, self-healing skin ulcers (cutaneous, leishmaniasis) to visceral leishmaniasis (VL), in which infection is located in the spleen and liver.[21] VL is invariably fatal if not treated. These diseases



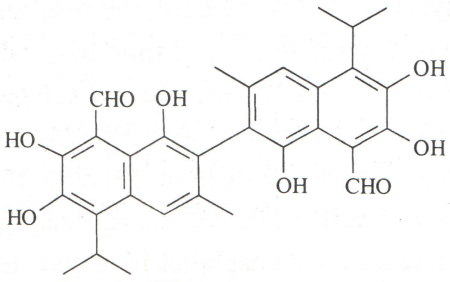
1 Isodiospyrin



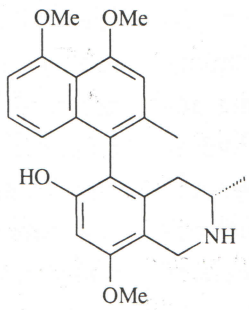
2 8'-Hydroxyisodiospyrin



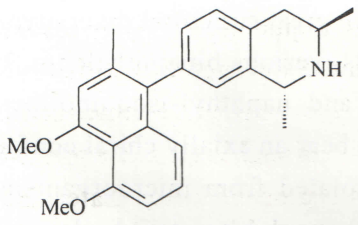
3 Diospyrin



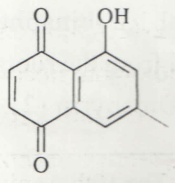
4 Gossypol



5 Ancistrocladine



6 Dioncophylline



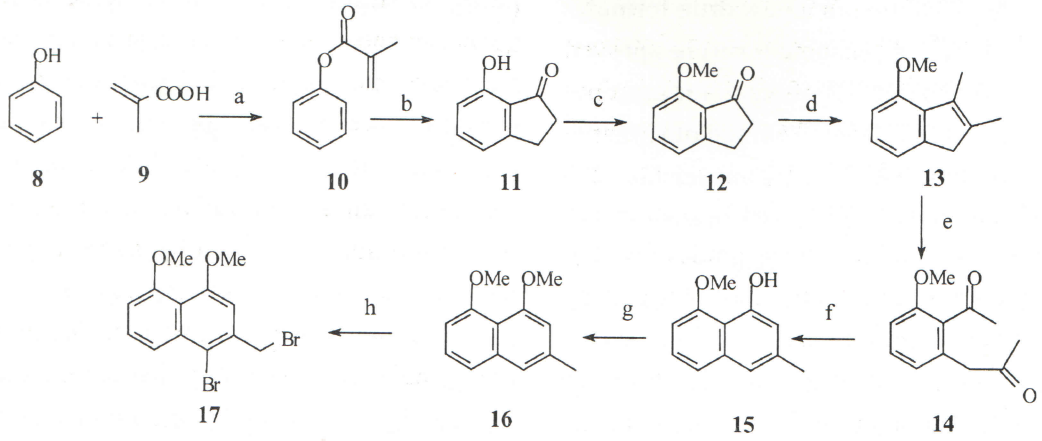
7 7-Methyljuglone

have ~1.5 - 2 million new cases and 350 million people are at risk.[22] Although a new drug formulation of amphotericin B (liposome form) has proved to be effective, it remains out of reach for most patients because of its high cost.[23] On the other hand, miltefosine, currently used for its antileishmanial properties (clinical trial in phase III in India), was the first highly efficient oral treatment against VL.[24] Unfortunately, current therapies are inadequate since the resistance to miltefosine has already been observed due to interaction with P-gp.[25] Research on new antileishmanial drugs is still necessary for the treatment of this disease. During the course of developing a synthetic route for 1,2'-binaphthoquinoid derivatives, we found that the product 4,5,8'-trimethoxy-2,3'-dimethyl-[1,2']-binaphthalenyl-1',4'-dione (**21**) exhibited potent antileishmanial effects. In this paper, we described a novel synthetic route for [1,2']-binaphthalenyl-1',4'-dione (**21**).

RESULTS AND DISCUSSION

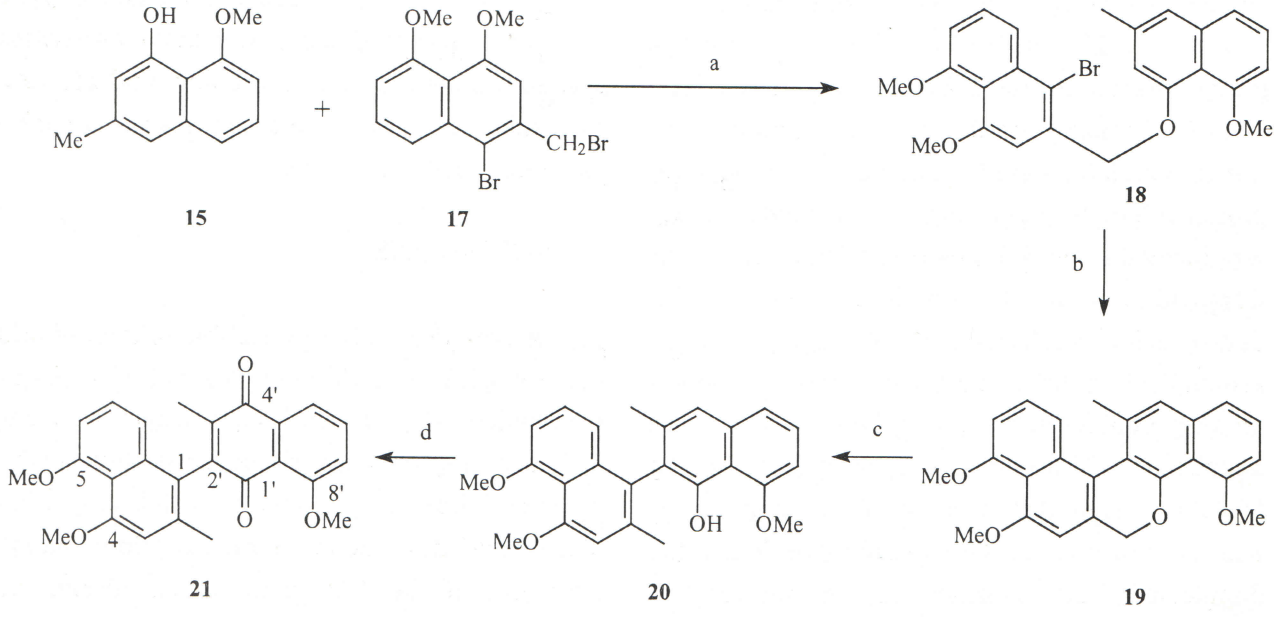
The first synthesis of the 1,2'-binaphthoquinone derivative, isodiospyrin (**1**) and related compounds, was achieved by Laatsch.[26] Racemic isodiospyrin was obtained in low yield (8%) together with 5,5'-dihydroxy-7,7'-dimethyl-6,6'-binaphthyl-1,4:1',4'-diquinone (13%) by oxidative coupling of 3-methyl-5,8-dimethoxy-3-methyl-1-naphthol. Apparently, the oxidative dimerization of 1-naphthol occurs through a C1-C2' and C2-C2' coupling and lacks regioselectivity. Later, Baker and coworkers prepared isodiospyrin (**1**) and 8'-hydroxyisospyrin (**2**) in 6 steps from the C1-C2' aryl-aryl coupling of a 2-(1,4,5,8-tetramethoxynaphthalene-2-yl)-dihydrooxazole derivative with an excess of the Grignard reagent derived from 2-bromo-3-methyl-1,4,5,8-tetramethoxynaphthalene *via* an asymmetric synthesis of the atropisomers.[27] To develop a new synthetic approach for 1,2'-binaphthoquinoids, we modified the synthetic method reported by Bringmann *et al.*[28-30] The known 1-hydroxy-8-methoxy-3-methylnaphthalene (**15**)[30] and 4-bromo-3-bromomethyl-1,8-dimethoxynaphthalene (**17**)[31] were used as the key intermediates for preparing our target compound (Schemes 1 and 2). Compound **15** was prepared from phenol in 6 steps by following the procedure previously described (Scheme 1).[30] It should be noted that compound **15** is extremely unstable and decomposed in one month even when it was stored in the refrigerator. Treatment of **15** with Me_2SO_4/NaOH/dichloromethane in the presence of phase-transfer catalysis of benzyl tri-*n*-butylammonium chloride afforded 1,8-dimethoxy-3-methylnaphthalene (**16**) in almost quantitative yield. Although, the conversion of **16** to the dibromonaphthalene **17** was described in a communication paper,[30] a detailed procedure for preparing **17** was not available. The yield of dibromo **17** varied (30 - 60%) depending on the reaction conditions. When compound **16** was treated with *N*-bromosuccinimide (NBS, 4 equivalents was required) and 2,2'-azobisisobutyronitrile (AIBN) in a large amount of solvent (dry cyclohexane), dibromo **17** was obtained in yields of 55 - 60% by irradiation. Occasionally, the reaction was not completed and the monobromo products (bromination occurred either on the aromatic ring or methyl group) were detected from the reaction mixture by NMR spectral analysis. If this is the case, the reaction mixture must be filtered to remove solid by-products and the monobromo intermediates isolated from the filtrate were retreated with NBS/AIBN and irradiation to give the desired dibromo **17**. Compound **17** was purified by column chromatography and then reacted with naphthol **15** to give the prefixed naphthalenyloxymethyl-naphthalene **18** in good yield in a mixture of dichloromethane and 1N NaOH in the presence of phase transfer catalyst

Scheme 1



Reagents and conditions: a: DCC/Et_3N/THF, reflux, 3 h then r.t., 24 h, 60 %; b: $AlCl_3$/NaCl, 220-230 °C, 37-40 %; c: Me_2SO_4/NaOH, CH_2Cl_2/H_2O, benzyltri-*n*-butylammonium chloride, r.t., 3 h, 100 %; d: MeMgI/Et_2O, 0 °C then r.t. 1.5 h, 84 e: $KMnO_4/NaIO_4$, r.t., 6 days, 77 %; f: 0.2N KOH/MeOH, r.t., 25 min, then HCl, 70 %; g: Me_2SO_4/NaOH, CH_2Cl_2/H_2O, benzyltri-*n*-butylammonium chloride, r.t., 3 h, 80 %; h: NBS/AIBN, IR irradiation, reflux, 4 h, 60 %.

Scheme 2



Reagents and conditions: a: 1N NaOH/CH_2Cl_2/$PhCH_2N(n\text{-}C_4H_9)_3Cl_2$, r.t., 6 h, 77%; b: $Pd(PPh_3)Cl_2$/NaOAc/DMA, 130 °C, 3 h, 70%; c: $Li(C_6H_5)_2$/THF, -100 °C, 1.5 h, 60%; d: Fremy's salt/K_2HPO_4/TBAB/CH_2Cl_2/H_2O, r.t., 18 h, 97%.

$[PhCH_2N^+(n\text{-}C_4H_7)_3]Cl^-$. The ether **18** was then converted into the pentacyclic **19** in 70% yield *via* intramolecular C-C-coupling by treatment with bis-(triphenylphosphine) palladium dichloride/NaOAc

in *N*,*N*-dimethylacetamide at 130 °C for 2 h. Recleavable ring opening of **19** to the desired 1,2'-dinaphthalene **20** in 60% yield was achieved by treatment with lithium-biphenyl adduct[30] in dry THF at -100 °C for 2 h. Compound **20** was further oxidized to 1,2'-binaphoqunoid **21** in high yield by Fremy's salt in a two-phase system (H_2O/CH_2Cl_2) under the catalysis of tetrabutylammonium bromide (TBAB).

All new compounds were characterized by spectroscopic and analytical methods. The methylene protons of compound **18** appeared at δ 5.43 as a singlet, while the same methylene protons of the racemic pentacyclic derivative **19** had different chemical shifts and appeared at δ 4.87 and 5.27 (each 1H, d, J = 12.6 Hz). The protons of the methyl function in compounds **18** and **19** appeared at δ 2.46 and 2.31, respectively. In comparison to the chemical shifts of the methyl group of **15**, **16**, and **20** by NOESY experiment, the methyl at δ 1.97 was assigned to C3-Me of the 1-methoxynaphthalene fragment in **20**, since irradiation of the methyl group enhanced the intensity of the singlet at δ 7.33 (C4'-H). Similarly, irradiation of the methyl function at δ 2.18 increased the signal of the aromatic proton at δ 6.89, suggesting that the methyl group was located at the C3' position of the 1-naphthol fragment in **20**. In addition, the irradiation of the doublet at δ 7.44 affected the triplet signal at δ 7.35, also indicating that this set should have a complementary doublet in the higher field. So, when the doublet at δ 6.77 was irradiated, enhancement of the triplet at 7.35 confirmed its closeness to the previous set of protons of the naphthol half. When the doublet at δ 6.80 was irradiated, the triplet at 7.18 was affected. The deshielded proton with a signal at δ 6.89 belongs to the same set of protons as confirmed by irradiation of the methyl signal at δ 1.97 when the NOE on the C4'-H singlet and a cross peak at δ 6.89 were observed.

Although diospyrin has previously been reported to be active against *L. donovani* promastigotes,[33] Yardley *et al.*[34] found that the natural product was inactive against *L. donovani* amastigotes in macrophages. The dimethyl ether derivative of diospyrin, however, was more active than the parent compound, inducing 33.4% inhibition at 10 μM. The hydroquinoid derivatives had improved activity (73.8% inhibition at 3 μM) against intracellular amastigotes despite showing toxicity to macrophages at the same concentration. The preliminary biological studies revealed that compound **21** displayed significant inhibition against *Leishmania mexicana* (LV 78) promastigotes *in vitro*. Further evaluation of the antileishmanial effects of this compound is required to compare with other antileishmanial agents active against *L. mexicana* amastigotes in macrophages. The detailed antileishmanial activities of a series of binaphthoquinoids and anthraquinones will be published later.

As described previously, both isodiospyrin and diospyrin exhibited potent antitumor activities. The antitumor evaluation of compound **21**, however, showed it was inactive against a variety of human tumor cells in culture.

CONCLUSIONS

A new derivative of 1,2'-binaphthoquinoid, namely 4,5,8'-trimethoxy-2,3'-dimethyl-[1,2']-binaphthalenyl-1',4'-dione (**21**), was synthesized by C-C-coupling of the prefixed binaphthyl methyl ether **18** followed by oxidation with Fremy's salt. The method described in our paper allows smooth synthesis of the 1,2'-binaphthalene derivative. However, an asymmetric synthesis of the atropisomers of 1,2'-binaphthalenes cannot be achieved.

As described previously, isodiospyrin was more cytotoxic than diospyrin to several human tumor cells *in vitro*. For inhibition of topoisomerase I, isodiospyrin was also more potent than diospyrin. It

clearly suggests that the position of the quinone moiety in the molecule of both agents may be important for their cytotoxicity. Recently, Oliveira-Brett *et al.*[35] studied the reaction of the antitumor β-lapachone, which bears a 1,2-naphthoquinone, in the presence of L-cysteine and 2-mercaptoethanol. They suggested that the antitumor mechanism of β-lapachone could be explained *via* interaction with Topo I. It was clearly demonstrated that thiol-containing enzymes, such as topoisomerases, might attack the quinone moiety *via* Michael addition. The four carbonyl functions in isodiospyrin are located at the C5, 8, 5', and 8' positions of the 1,2'-binaphthlene chromophore, while the carbonyl groups in diospyrin are located at the C1, 4, 5', and 8' positions. On the basis of these observations, isodiospyrin can more readily undergo nucleophilic attack of thiol-containing enzymes than diospyrin since there is less steric hindrance for the Michael addition. Additionally, early studies on the electrochemical characteristics of diospyrin also suggested that the antitumor and antileishmanial properties of this natural product may result from a facile electron-transfer mechanism *via* redox cycling.[36] Consequently, it can explain why compound **21**, which bears only one naphthoquinone chromophore, has no antitumor activity. Nevertheless, the current study revealed that compound **21** was shown to have potent antileishmanial activity. The results suggest that 1,2'-binaphthoquinoids having two naphthoquinone chromophores located at the position similar to isodiospyrin may be necessary for their antitumor and antiparasitic activity.

EXPERIMENTAL

THF and ether were freshly distilled from sodium/benzophenone. Dimethylacetamide was distilled over CaH_2, and *c*-hexane was dried over the molecular sieves 3Å. Other materials were used as received from commercial suppliers. Melting points were determined on a Fargo melting point apparatus and are uncorrected. Column chromatography was carried out over silica gel G60 (70-230 mesh, ASTM, Merck). Analytical and preparative thin layer chromatography was performed on precoated silica gel G60 F 254 (Merck) plates with short wave length UV light for visualization. Elemental analyses were done on a Heraeus CHN-O Rapid instrument. ^{1}H NMR spectra were recorded on a Brucker AMX-400 and AMX-500 spectrometers with Me_4Si as internal standard. ^{1}H NMR assignments for new compounds **19** - **21** were conducted by 2D COSY experiments in standard pulse sequences in phase-sensitive mode. NOE experiments were made by means NOE difference technique, with an irradiation time of 2 s and a relaxation delay of 4 s.

The known compounds **10** - **17** were prepared by following the procedures developed by Bringmann *et al.*[28-30] However, the detailed procedure for the synthesis of dibromonaphthalene **17** is described in the Experimental Section.

4-Bromo-3-bromomethyl-1,8-dimethoxy-naphthalene (17)[30]

Compound **16** (2.0 g, 9.8 mmol), AIBN (1.6 g, 9.74 mmol) and NBS (3.6 g, 20.2 mmol) were mixed in dry *c*-hexane and the reaction mixture was refluxed and irradiated (IR lamp, 250 W) with stirring under an Ar atmosphere for 2 h. Additional amounts of NBS (1.78 g, 10 mmol) was then added and the reaction mixture was gently refluxed for further 2 h. After cooling, the mixture was filtered and the filter cake was washed with $CHCl_3$. The combined filtrate and washings were evaporated *in vacuo* to dryness. The product **17** was purified by column chromatography (hexane/CH_2Cl_2, 1:1 v/v); 2.2 g (59.6%); mp 147-148 °C (Lit.[30] 144 °C); ^{1}H NMR ($CDCl_3$): δ 3.98 (6H, *s*, 2 × OCH_3), 4.80 (2H,

s, $ArCH_2$), 6.87 (1H, *s*, ArH), 6.95 (1H, *m*, ArH), 7.50 (1H, *t*, *J* = 7.7 Hz, ArH), 7.96 (1H, *d*, *J* = 8.4 Hz, ArH).

1-Bromo-4,5-dimethoxy-2-(8-methoxy-3-methylnaphthalen-1-yloxymethyl)-naphthalene (18)

A solution of **17** (955 mg, 2.64 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a mixture of **15** (496 mg, 2.65 mmol), benzyltri-*n*-butylammonium chloride (400 mg, 1.28 mmol), 1N aq. NaOH (80 mL) and CH_2Cl_2 (80 mL) and the reaction mixture was vigorously stirred for 6 h. The organic layer was separated, washed with water, dried over Na_2SO_4, filtered and concentrated *in vacuo* to dryness. The residue was crystallized from EtOH/EtOAc (1:1, v/v) to afford **18**, 950 mg, (77.2%); mp 181-182 °C; ^{1}H NMR ($CDCl_3$): δ 2.46 (3H, *s*, $ArCH_3$), 3.94 (3H, *s*, OCH_3), 3.97 (6H, *s*, 2 × OCH_3), 5.43 (2H, *s*, $ArCH_2$), 6.82 (1H, *m*, ArH), 6.88 (1H, *s*, ArH), 6.93 (1H, *d*, *J* = 7.8 Hz, ArH), 7.25 (2H, *d*, *J* = 5.8 Hz, ArH), 7.32-7.37 (2H, *m*, 2 × ArH), 7.50 (1H, *t*, *J* = 7.9 Hz, ArH), 7.59 (1H, *s*, ArH), 7.98 (1H, *d*, *J* = 8.6 Hz, ArH). Anal. Calcd for $C_{25}H_{23}O_4Br$: C, 64.25; H, 4.96. Found: C, 64.58; H, 5.15.

4,8,9-Trimethoxy-13-methyl-6*H*-5-oxabenzo-[c]chrysene (19)

A mixture of **18** (520 mg, 1.1 mmol), NaOAc (140 mg, 1.7 mmol), and $Pd(PPh_3)Cl_2$ (80 mg, 0.11 mmol) was placed in a three necked flask fitted with a condenser. Freshly distilled dimethylacetamide (75 mL) was transferred to the reaction mixture and bubbled with dry nitrogen for 2.5 h. The reaction mixture was heated to 130 °C for 3 h with stirring and then was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with water, dried over Na_2SO_4 and evaporated *in vacuo* to dryness. The product **18** was purified by liquid column chromatography (EtOAc/hexane, 1:9 v/v), 301 mg (70%); mp 208- 210 °C; ^{1}H NMR ($CDCl_3$): δ 2.31 (3H, *s*, $ArCH_3$), 3.99, 4.00, 4.04 (each 3H, *s*, 3 × OCH_3), 4.87 and 5.27 (2H, each *d*, *J* = 12.6 Hz, $ArCH_2$), 6.80 (1H, *dd*, *J* = 1.6, 6.8 Hz, ArH), 6.82 (1H, *s*, ArH), 6.85 (1H, *d*, *J* = 7.4 Hz, ArH), 7.26 (2H, *m*, 2 × ArH), 7.34 (1H, *d*, *J* = 6.9 Hz, ArH), 7.36 (1H, *s*, ArH), 7.40 (1H, *s*, ArH). Anal. Calcd for $C_{25}H_{22}O_4$: C, 77.70; H, 5.74. Found: C, 77.51; H, 5.83.

4,5,8'-Trimethoxy-2,3'-dimethyl-[1,2']binaphthalenyl-1'-ol (20)

Lithium (15.0 mg, 2.16 mmol) was dissolved in a mixture of biphenyl (140 mg, 90 mmol) and dry THF (2 mL) under an Ar atmosphere. The resulting blue-green lithium-biphenyl adduct solution was then added to a solution of **19** (53 mg, 0.137 mmol) in dry THF (2 mL) at -100 °C for 1.5 h with vigorously stirring. The reaction was quenched with 5% aq. AcOH and extracted with ether (5 × 10 mL). The ether extracts were combined, washed with water, dried over Na_2SO_4 and evaporated *in vacuo* to dryness. The product was purified by preparative thin layer chromatography (PLC, EtOAc/hexane, 3:7 v/v); 32 mg (60%); mp 221-223 °C; ^{1}H NMR ($CDCl_3$): δ 1.97 and 2.18 (each 3H, *s*, 2 × CH_3), 4.00, 4.01, 4.05 (each 3H, *s*, 3 × OCH_3), 6.77 (1H, *d*, *J* = 7.6 Hz, ArH), 6.80 (1H, *d*, *J* = 7.7 Hz, ArH), 6.89 (1H, *s*, ArH), 6.91 (1H, *d*, *J* = 8.6 Hz, ArH), 7.18 (1H, *t*, *J* =7.6 Hz, ArH), 7.33 (1H, *s*, ArH), 7.35 (1H, *t*, *J* =8.6 Hz, ArH), 7.44 (1H, *d*, *J* = 7.3 Hz, ArH), 9.45 (1H, *s*, OH, exchangeable). Anal. Calcd for $C_{25}H_{24}O_4$: C, 77.30; H, 6.23. Found: C, 76.95; H, 6.12.

4,5,8'-Trimethoxy-2,3'-dimethyl-[1,2']-binaphthalenyl-1',4'-dione (21)

Potassium nitrosodisulfonate (Fremy's salt, 130 mg, wet, freshly prepared according to the

method of Zimmer *et al.*[37]) was added to a solution of **20** (15.1 mg, 0.0388 mmol), dipotassium hydrogen phosphate (70 mg) and tetrabutylammonium bromide (129 mg, 0.4 mmol) in a mixture of CH_2Cl_2 (1 mL) and water (2 mL). The reaction mixture was stirred at room temperature for 18 h. The reaction was monitored by TLC analysis (SiO_2, EtOAc/Hexanes, 1:2 v/v). After all starting material was consumed, the organic layer was separated, washed with brine (3 × 0.5 mL), dried (Na_2SO_4) and evaporated *in vacuo* to dryness. The product **21** was purified by PLC (EtOAc/Hexanes, 2:3 v/v); 15.1 mg (96.8%); mp. 196-197 °C (decomp.); ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm: 1.82 (3H, *s*, C3-CH_3), 2.22 (3H, *s*, C3'-CH_3), 3.93, 3.97, 4.01 (each 3H, *s*, OCH_3), 6.99 (1H, *d*, *J* = 5.7 Hz, C7'-H), 6.79 (1H, *d*, *J* = 8.0 Hz, C7-H), 6.78 (1H, *s*, C2-H), 7.30 (1H, *d*, *J* = 6.8 Hz, C5-H), 7.23 (1H, *t*, *J* = 6.6 Hz, C6-H), 7.71 (1H, *t*, *J* = 6.5 Hz, C6'-H), 7.87 (1H, *d*, *J* = 6.3 Hz, C5'-H). Anal. Calcd for $C_{25}H_{22}O_5$: C, 74.61; H, 5.51. Found: C, 74.51; H, 5.72.

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REFERENCES

1. Thomson, R. H. Naturally Occurring Quinones, II, Academic Press, London-New York.
2. O'Brien, P. J. Molecular Mechanisms of Quinone Cytotoxicity. *Chem.-Biol. Interactions* **1991**, *80*, 1-41.
3. Sidhu, G. S.; Prasad, K. K. (-) Isodiospyrin - a Novel Binaphthoquinone Showing Atropisomerism and Other Extractives from *Diospyros Chloroxylon*. *Tetrahedron Lett.* **1967**, *8*, 2905-2910.
4. Fallas, A. L.; Thomson, R. H. *Ebenaceae* Extractives. Part III. Binaphthoquinones from *Diospyros* Species. *J. Chem. Soc. (C)* **1968**, 2279-2282.
5. Yoshihira, K.; Tezuka, M.; Natori, S. Naphthoquinone Derivatives from *Diospyros* Sp. Bisisodiospyrin, a Tetrameric Naphthoquinone. *Tetrahedron Lett.* **1970**, *11*, 7-10.
6. Kapil, R. S.; Dhar, M. M. Chemical Constituents of *Diospyros Montana*. I. Isolation of Diospyrin, a New Binaphthyl Derivative. *J. Sci. & Ind. Res.* **1961**, *20B*, 498-500.
7. Yan, X.-Z.; Kuo, Y.-H.; Lee, T.-J.; Shih, T.-S.; Chen, C.-H.; McPhail, D. R.; McPhail, A. T.; Lee, K. H. Cytotoxic Components of *Diospyros morrisiana*. *Phytochemistry* **1989**, *28*, 1541-1543.
8. Dechary, J. M.; Pradel, P. Occurrence of (+)-Gossypol in *Gossypium* Species. *J. Am. Oil. Chem. Soc.* **1971**, *48*, 563-564.
9. Govindachari, T. R.; Parthasarthy, P. C. Alkaloids of *Ancistrocladaceae*. *Heterocycles* **1977**, *7*, 661-684.
10. Bringmann, G.; Rübenacker, M.; Jansen, J. R.; Schetzow, D.; Ake Assi, L. On the Structure of the Dioncophyllaceae Alkaloids Dioncophylline a ("Triphyophylline") and "O-Methyl-Triphyophylline". *Tetrahedron Lett.* **1990**, *31*, 639-642.
11. Bringmann, G.; Jansen, J. R.; Reuscher, H.; Rübenacker, M.; Peters, K.; von Schnering, H. G. First Total Synthesis of (-)-Dioncophylline A ("Triphyophylline") and of Selected Stereoisomers: Complete (revised) Stereostructure. *Tetrahedron Lett.* **1990**, *31*, 643-646.

12. Bringmann, G.; Ake Assi, L.; Rubenacker, M.; Ammermann, E.; Lorenz, G. *German Patent D. O. S. DE* 4117080 A1, November 26, 1992; *European Patent EP* 0515856 A1, December 02, 1992.
13. Bringmann, G.; Gramatzki, S.; Grimm, C.; Proksch, P. Feeding Detergency and Growth Retarding Activity of the Naphthylisoquinoline Alkaloid Dioncophylline A against *Spodoptera Littoralis*. *Phytochemistry* **1992**, *31*, 3821-3825.
14. Francois, G.; Bringmann, G.; Phillipson, J. D.; Ake Assi, L.; Dochez, C.; Rübenacker, M.; Schneider, C.; Wery, M.; Warhurst, D. C.; Kirby, G. C. Activity of Extracts and Naphthylisoquinoline Alkaloids from *Triphyophyllum Peltatum*, *Ancistrocladus Abbreviatus* and *A. Bartery* against *Plasmodium Falciparum In Vitro*. *Phytochemistry* **1994**, *35*, 1461-1464.
15. Chen, H.-J.; Lee, K.-H.; Hwang, J. DNA Topoisomerase I as Target for Anticancer Drug Design. 1997 PSCT Medicinal Chemistry Symposium, Kaohsiung, Taiwan, p 23.
16. Gafner, F.; Chapuis, J.-C.; Msonthi, J. D.; Hostetmann, K. Cytotoxic Naphthoquinones, Molluscicidal Saponins and Flavonoids from *Diospyros zombensis*. *Phytochemistry* **1987**, *26*, 2501-2503.
17. Ting, C.-Y. The Mechanistic Study of Isodiospyrin Inhibition on Human DNA Topoisomerase I and IIα. 2003, Ph. D. thesis.
18. Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPail. A. T.; Sim, G. A. Plant Antitumor Agents. I. The Isolation and Structure of Camptothecin, a Novel Alkaloidal Leukemia and Tumor Inhibitor from Camptotheca Acuminata. *J. Am. Chem. Soc.* **1966**, *88*, 3888-3890.
19. Pal, S.; Banerjee, A.; Hazra, B. Pharmacological Studies on the Effect of the Treatment of Swiss A Mice with Diospyrin, a Tumor-inhibitory Plant Product, and its Synthetic Derivatives. *Phytoter. Res.* **1996**, *10*, 393- 397.
20. Ray, S.; Hazra, B.; Mittra, B.; Das, A.; Majumder, H. K. Diospyrin, A Bisnaphthoquinone: A Novel Inhibitor of Type I DNA Topoisomerase of *Leishmania donovani*. *Mol. Pharmacol.* **1998**, *54*, 994-999.
21. Pearson, R. D.; Sousa, A. Q. Clinical spectrum of leishmaniasis. *Clin Infect. Dis.* **1996**, *22*, 1-13.
22. Desjeux, P. Leishmania and HIV in gridlock. Publication nos. WHO/CTD/LEISH/98.9, UNAIDS/98.23. Geneva, World Health Organization, 1998.
23. Sundar, S. Drug Resistance in Indian Visceral Leishmaniasis. *Tropical Medicine and International Health* **2001**, *11*, 849-854.
24. Thankaur, C. P.; Kanyok, T. P.; Pandey, A. K.; Sinha, G. P.; Messik, C.; Olliaro, P. Treatment of Visceral Leishmaniasis with Injectable Paromomycin (Aminosidine). An Open-label Randomized Phase-II Clinical Study. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **2000**, *94*, 432-433.
25. Rybczynska, M.; Gudmundesson, O. Progress in Understanding the Structure-Activity Relationships of P-glycoprotein. *Adv. Drug Delivery Rev.* **2002**, 315-460.
26. Laatsch, H. Isodiospyrin und Elliptinon - Syntheses 6,6-Dimerer Bijuglone durch Phenoloxidation. *Liebigs Ann. Chem.* **1984**, 319-339.
27. (a) Baker, R. W.; Liu, S., Sargent, M. V.; Skelton, B. W., White, A. H. Absolute Stereochemistry of 1,2'-Linked Bi(naphthoquinone)s. *Chem. Commun.*, **1997**, 451-452. (b) Baker, R. W.; Liu, S., Sargent, M. V. Synthesis and Absolute Configuration of Axially Chiral Binaphthoquinones. *Aust. J. Chem.* **1998**, *51*, 255-266.

28. Bringmann, G.; Jansen, J. R. Acetogenine Isochinolin-Alkaloide, 7. Einfache Synthesen Nützlisher Diketo-Bausteine für Biomimetishe Isochinolin- und Naphthalin-Synthesen. *Liebigs Ann. Chem.* **1985**, 2116-2125.
29. Bringmann, G. Acetogenine Isochinolin-Alkaloide, 8. Biomimetische Synthesen beider Molekülhälfen der *Ancistrocladus*- und der *Triphyophyllum*–Alkaloide aus gemeninsamen Vorstufen. *Liebigs Ann. Chem.* **1985**, 2126-2134.
30. Bringmann, G. A Short Biomimetic Synthesis of the Isoquinoline and the Naphthalene Moieties of Ancistrocladus Alkaloids from Common β-Polycarbonyl Precursors. *Tetrahedron Lett.* **1982**, *23*, 2009-2012.
31. (a) Bringmann, G.; Jansen, J. R. A First and General Route to Naphthylisoquinoline Alkaloids: the Total Synthesis of O-Methyl-tetradehydro-triphyophylline. *Tetrahedron Lett.* **1984**, *25*, 2537-2540. (b) Bringmann, G.; Jansen, J. R. Chiral Economy with Respect to Rotational Isomerism: Rational Synthesis of Hamatine and (Optionally) Ancistrocladine from Joint Helical Precursors. *Heterocycles* **1989**, *28*, 137-142.
32. Eisch, J. J. Chemistry of Alkali Metal-unsaturated Hydrocarbon Adducts. III. Cleavage Reactions by Lithium-Biphenyl Solutions in Tetrahydrofuran. *J. Org. Chem.* **1963**, *28*, 707-710.
33. Hazra, B.; Ghosh, R.; Banerjee, A.; Roy, D. K. Inhibitory Activity of Diospyrin towards *L. donovani* Promastigotes *In Vitro*. *IRCS Med. Sci.* **1986**, *14*, 593-594.
34. Yardley, V.; Snowdon, D.; Croft, S.; Hazra, B. *In Vitro* Activity of Diospyrin and Derivatives against *Leishmania donovani*, *Tripanosoma cruzi* and *Tripanosoma brucei brucei*. *Phytoter. Res.* **1996**, *10*, 559-562.
35. Oliveira-Brett, A. M.; Goulart, M. O. F.; Abreu, F. C. Reduction of Lapachones and Their Reaction with L-Cysteine and Mercaptoethanol on Glassy Carbon Electrodes. *Bioelectrochemistry* **2002**, *56*, 53-55.
36. Kovacic, P.; Ames, J. R.; Grogan, J. W.; Hazra, B.; Ryan, D. Anticancer Quinines and Quinolines: Mode of Action via Electron Transfer and Oxidative Stress. In. *The Chemistry and Interfacial Behavior of Biological Molecules*. Ed. By Dryhurst and Niki, K. **1988**, pp 295-307. Plenum Press, New York.
37. Zimmer, H.; Lankin, D. C.; Horgan, S. W. Oxidation with Potassium Nitrosodisulfonate (Fremy's Radical). The Teuber Reaction. *Chem. Rev.* **1971**, *71*, 229-246.