relation between interconnectivity in a network model and the experimental tortuosity factor).[9, 21, 38, 39]

Our data demonstrate that a significant enhancement in the performance of CEC over capillary HPLC lies in the different dimension of the perfusion mechanism. The intraparticle tortuosity factor τ_{intra} plays a key role in achieving that goal in both cases, and may also have a sensitive influence on pore migration for charged solutes. Further development in CEC particle technology should focus on the minimum pore size of the through-pore network which still allows a significant intraparticle EOF at decent buffer concentrations, while keeping the surface-to-volume ratio of the pore space attractive for the separation (gigapores, which are used in pressure-driven flows, are not required for electroosmotic perfusion). CEC is easily realized with nanoparticles using hierarchically structured media of micrometer dimension, which leaves molecular diffusion as the ultimate limitation to performance.[40, 41] Thus, the perfusive EOF field translates to an even higher separation efficiency than can currently be achieved in CEC, increased mass sensitivity in on-line coupling schemes (such as nano-ESI-MS), and the possibility of using pressurized CEC for higher analysis speed and flow stability, without significant increase in dispersion.

Received: October 30, 2000 [Z16012]

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First, Atropo-Enantioselective Total Synthesis of the Axially Chiral Phenylanthraquinone Natural Products Knipholone and 6′-*O*-Methylknipholone**

Gerhard Bringmann* and Dirk Menche

Dedicated to Professor Wolfgang Kiefer on the occasion of his 60th birthday

Among the more than one hundred anthraquinone natural products with biaryl axes,[1] phenylanthraquinones,[2–4] like knipholone (**1a**)[2] and 6′-*O*-methylknipholone (**1b**),[3] occupy a special position: Since they are constitutionally unsymmetric, they are most likely formed biosynthetically by a directed, enzymatic biaryl coupling and not merely by a "chemical" dimerization of the corresponding monoanthraquinones. A further hint at such an enzymatic origin of **1a** and **1b** is the fact that they are optically active and are thus axially chiral. First isolated by Dagne and Steglich in 1984,[2] knipholone (**1a**) and related phenylanthrachinones have been found in numerous African plant species of the genera *Bulbine*, *Bulbinella*, and *Kniphofia* (all Asphodelaceae),[4] which are widely used in folk medicine.[2, 5]

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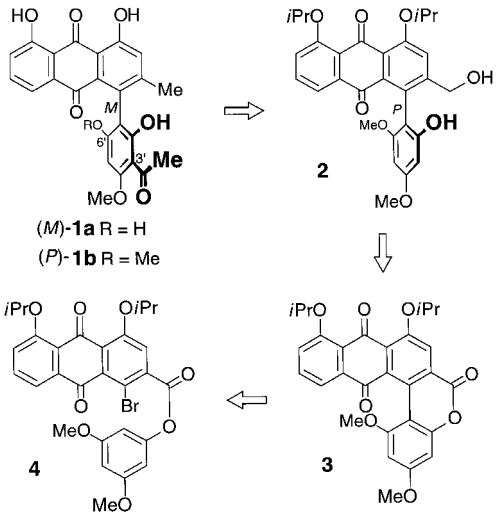
[**] Novel Concepts in Directed Biaryl Synthesis, Part 93. This work was supported by the Deutsche Forschungsgemeinschaft (grant: SFB 347) and by the Fonds der Chemischen Industrie. We thank Prof. B. M. Abegaz und Dr. M. Bezabih for an authentic sample of 6′-*O*-methylknipholone and for valuable discussions. We thank J. Kraus for helpful suggestions and V. Barthel for technical support. Part 92: G. Bringmann, J. Hinrichs, K. Peters, E.-M. Peters, *J. Org. Chem.* **2001**, *66*, 629 – 632.

Only recently the axial configuration of knipholone (**1a**) has been determined to be *M*, by quantum chemical CD calculations.[6] Due to its interesting structure (including the rotationally hindered biaryl axis) and its good antimalarial activity with only little cytotoxicity,[7] knipholone (**1a**) constitutes an attractive synthetic target, as do related phenylanthraquinone natural products. In this paper, we report on the atroposelective total synthesis of knipholone (**1a**) and the likewise naturally occurring 6′-*O*-methyl ether **1b** and, thus, on the first stereoselective approach to axially chiral anthraquinone natural products.[8]

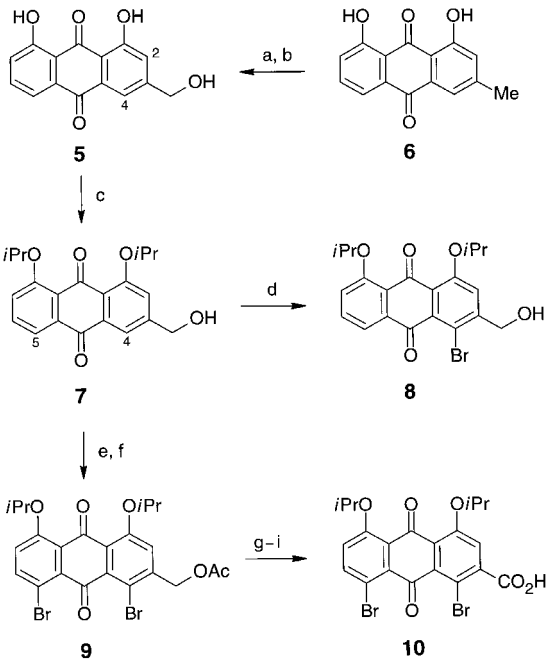
For the directed construction of the biaryl axis we chose the "lactone method" as developed in our group.[9] Envisaged key steps of the resulting synthetic strategy (Scheme 1) were the intramolecular biaryl coupling of the bromoester **4** to give the biaryl lactone **3**, the atropo-enantioselective cleavage of **3** to provide the "open" biaryl **2**, and the regioselective introduction of an acetyl group on C-3′.



Scheme 1. Retrosynthetic analysis of knipholone (**1a**) and its 6′-*O*-methyl ether **1b**.

The "upper" molecular halves of the target molecules **1a** and **1b** correspond to the natural product chrysophanol (**6**). For the synthesis of a suitably functionalized anthraquinone building block (Scheme 2), one can start directly from the likewise natural[10] aloe-emodin (**5**), whose side chain is already oxygenated. This can be conveniently obtained in large quantities from purchasable aloin[11] or, as we describe here, from chrysophanol (**6**), which is commercially available or can easily be prepared by total synthesis.[12]

Radical side-chain bromination of **6** with subsequent bromine/hydroxy group exchange gave aloe-emodin (**5**) in a smooth reaction; compound **5** can be now conveniently prepared on a multi-gram scale. A selective bromination of the diacetate of **5** in the 4-position, as required, has already been described in the literature.[13] However, this actually takes place exclusively at C-2 under the given conditions, so that a different synthetic strategy had to be pursued here. The desired activation of the 4-position was finally successful, as could be unambiguously shown by NMR spectroscopy (HMBC, NOE), after steric blocking of the "northern part"



Scheme 2. Synthesis of the anthraquinone building block **10**. a) NBS, $(PhCO_2)_2$, CCl_4, reflux, 6 h; b) $CaCO_3$, dioxane/H_2O, 120 °C, 7 h, 71 % (over two steps); c) *i*PrI, Cs_2CO_3, acetone, reflux, 4 d, 72 %; d) Br_2, NaOAc, $CHCl_3/CCl_4$, reflux, 2 h, 32 %; e) Ac_2O, pyridine, 50 °C, 3 h, 94 %; f) Br_2 (4 equiv), NaOAc, $CHCl_3/CCl_4$, 70 °C, 3 h, 89 %; g) KOH, MeOH, 70 °C, 2 h, 91 %; h) MnO_2, CH_2Cl_2, RT, 6 h, 93 %; i) $NaClO_2$, amidosulfuric acid, NaOAc, dioxane/H_2O/HOAc, RT, 97 %. NBS = *N*-bromosuccinimide.

of **5** by O-isopropylation and subsequent bromination of **7** to give **8** (Scheme 2).

Due to the necessary resolution of regioisomeric bromination products, the sensitivity of the side chain to oxidation under the bromination conditions, and the low yields that were obtained, it seemed, however, far more convenient to introduce *two* bromo-substituents, that is, at C-4 *and* C-5, straightaway after protection of the free hydroxy group of **7** by O-acetylation. The bromination then proceeded smoothly to give **9** in 89 % yield. The second bromine at C-5, which was functionally not required, did not interfere with any of the following reaction steps (see below). From **9**, the anthraquinone carboxylic acid **10** could easily be prepared by hydrolysis of the ester and stepwise oxidation (Scheme 2).

Thus, the building block **10** was available in a suitably activated and protected form and in sufficient quantities. For the "lower" half of the molecule, which in its free form is also a natural product (xanthoxylin),[14] the precursor was, however, not a trioxyacetophenone, but the acetyl-free phenolic compound **11** (Scheme 3). According to preliminary investigations it seemed more favorable not to have the acetyl group (as present in **1a** and **1b**) in the molecule from the beginning, but to introduce it only after the scheduled subsequent reduction steps.

The ester **12**, synthesized from **10** and **11**, was submitted to the conditions of a Pd-catalyzed intramolecular biaryl coupling.[9] The concern that the "lower" carbonyl group of the quinoid system (C-10) might prevent or, at least, hamper the ring closure to form the lactone **13** proved to be unfounded: In

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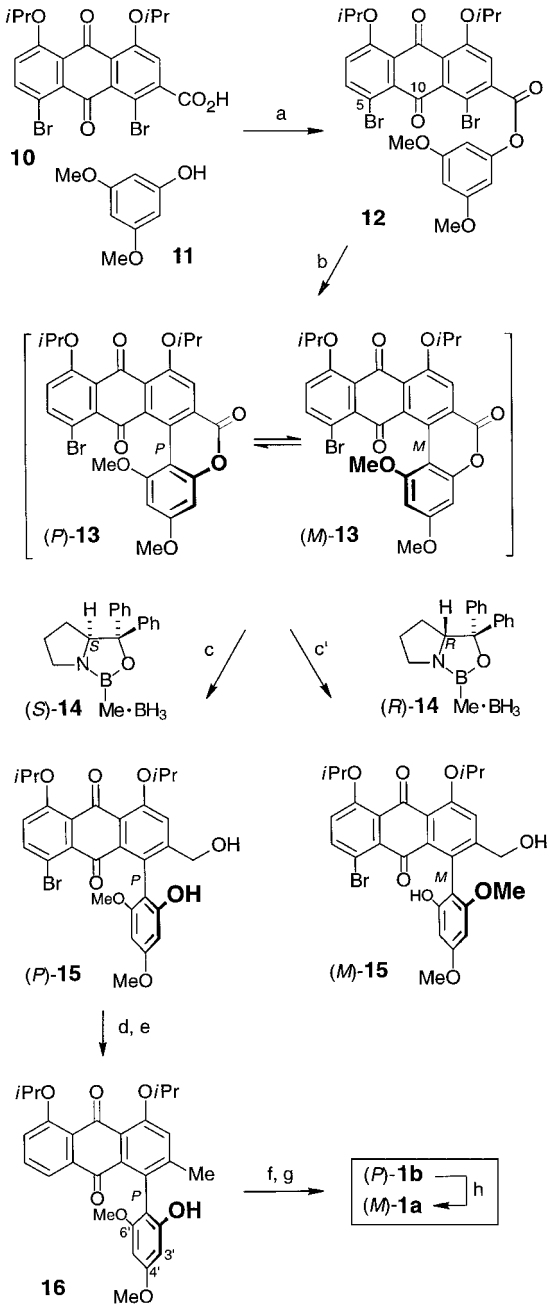

Scheme 3. Atropo-enantioselective coupling of the molecular halves of knipholone (**1a**). a) DCC, DMAP, CH_2Cl_2/DMF, 0 °C → RT, 1 h, 90 %; b) $Pd(OAc)_2$ (60 mol %), PPh_3 (1.2 equiv), NaOPiv (2 equiv), DMA, 130 °C, 4.5 h, 68 %; c) (*S*)-**14** (3 equiv), BH_3 (4 equiv), THF, 0 °C, 1 h, 81 %, 96 % *ee* (after crystallization from dichloromethane/diethyl ether/*n*-hexane > 99 % *ee*); c′) analogous procedure with (*R*)-**14**; d) $(CBrCl_2)_2$ (1.5 equiv), polymer-bound PPh_3 (3 equiv), CH_2Cl_2, RT, 10 min; e) Pd/C (10 mol %), H_2, MeOH, 48 % (over 2 steps); f) $TiCl_4$ (6 equiv), CH_2Cl_2, −20 °C → RT, 2 h, 89 %; g) Ac_2O, $TiCl_4$, −20 °C → RT, 1 h, 82 %; h) $AlBr_3$ (5 equiv), chlorobenzene, 80 °C, 2 h, 41 %. DCC = *N*,*N*′-dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, DMA = *N*,*N*-dimethylacetamide, NaOPiv = sodium pivalate.

the presence of $Pd(OAc)_2$, **12** was smoothly coupled intramolecularly to give **13**. The bromine atom at C-5, which was not required for the cyclization, remained unaffected.

Through the following conversions (see below) it became obvious that—despite the oxygen functionality at C-10—the bridged biaryl **13** was configurationally unstable; this fortunate circumstance permitted the subsequent ring-cleavage reactions to be performed highly efficiently, according to the principle of a dynamic kinetic resolution. The oxazaborolidine-assisted borane reduction, which has also been successfully used on previous occasions, proved to be the most effective method for this purpose.[9, 15] By means of this so-called CBS reaction,[16] the lactone in the rapidly interconverting mixture of the atropo-enantiomers (*P*)-**13** ⇄ (*M*)-**13** could be cleaved selectively; such that depending on the oxazaborolidine enantiomer used, (*S*)-**14** or (*R*)-**14**, either the desired atropisomer (*P*)-**15** or, optionally, the undesired "wrong" enantiomer (*M*)-**15** could be obtained in high atropisomeric excesses (up to 96 % *ee*) through an atropo-enantiodivergent reaction.[17] The optical purity of the product (for example, of the required *P* isomer) could be further enhanced (to > 99 % *ee*) by a simple crystallization step. The small quantities of the (almost) racemic mother liquor thus obtained (14 % *ee*) can—if desired—be recycled into the process, by oxidation (MnO_2, $NaClO_2$) and cyclization (DCC, DMAP) back to the configurationally unstable lactone (71 % chemical yield).

With the phenylanthraquinone framework now constructed enantioselectively, including the correct configuration at the biaryl axis, the benzylic oxygen function of **15** was reductively eliminated by hydroxy/bromine group exchange and hydrogenolytic removal of the bromine substituent. For this, the reaction conditions could be controlled in such a way that, within a one-pot reaction, the additional, no longer required bromine functionality at C-5 was simultaneously removed. After cleavage of the *O*-isopropyl protective groups with titanium tetrachloride, the likewise $TiCl_4$-mediated, strictly regioselective introduction of the acetyl group at C-3′ was achieved by the use of acetic anhydride. The 6-*O*-methylknipholone (**1b**) thus obtained proved to be chromatographically and spectroscopically identical with authentic **1b** from *Bulbine capitata*.[3] This first synthesis of a phenylanthraquinone natural product confirms, in all details, the structure as established by Abegaz and co-workers.[3]

For the synthesis of knipholone (**1a**) itself, it was still necessary to cleave the methoxy group at C-6′. While nucleophilic reagents (such as $LiPH_2$[18]) almost exclusively attacked the "wrong" ether functionality at C-4′, a selective O-demethylation of the 6′-oxygen functionality was achieved with $AlBr_3$. The (+)-knipholone (**1a**) thus obtained was identical in all respects to an authentic sample from *Bulbine frutescens*[6] and to the data[2] published for **1a** by Dagne and Steglich.

As demonstrated for the atropo-enantiodivergent cleavage of **13** to form (*P*)- or (*M*)-**15**, the strategy for the first synthesis of knipholone (**1a**) and 6′-*O*-methylknipholone (**1b**) presented here can, in principle, likewise be adopted for the synthesis of the other respective atropo-enantiomeric product (*ent*-**1a** or *ent*-**1b**). Analogously, the concept should be easily applicable to the synthesis of the other phenylanthraquinones and -anthrones described in the literature,[2–4] and, furthermore, to the preparation of unnatural analogues with possibly even better antimalarial activities. This work is presently under investigation.

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Experimental Section

Compound **13**: A mixture of **12** (1.00 g, 1.51 mmol), palladium(II) acetate (203 mg, 910 μmol), triphenylphosphane (475 mg, 1.81 mmol), and sodium pivalate (375 mg, 3.02 mmol) were dried in vacuo (10^{-2} mbar) for 1.5 h at 60 °C, and then dry *N*,*N*-dimethylacetamide (40 mL) was added. The orange-colored suspension was degassed three times and heated under argon for 4.5 h at 130 °C. After cooling to room temperature, the dark brown suspension was diluted with ethyl acetate, washed sequentially with 2N HCl and saturated aqueous NaCl solution, dried (Mg_2SO_4), and concentrated in vacuo. After flash chromatography on silica gel (dichloromethane/ethyl acetate 100:2), **13** (597 mg, 1.03 mmol, 68 %) was obtained as a red solid, which was crystallized from dichloromethane/petroleum ether. M.p. 138 °C; IR (KBr): $\tilde{\nu}$ = 2950, 1710, 1660, 1190, 1100 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.40 – 1.56 (m, 12H; $CH(CH_3)_2$), 3.67 (s, 3H; OCH_3), 3.87 (s, 3H; OCH_3), 4.64 (sept, J = 6.1 Hz, 1H; $CH(CH_3)_2$), 4.77 (sept, J = 6.1 Hz, 1H; $CH(CH_3)_2$), 6.35 (d, J = 2.3 Hz, 1H; H-3′ or H-5′), 6.53 (d, J = 2.3 Hz, 1H; H-3′ or H-5′), 7.12 (d, J = 9.2 Hz, 1H; H-7), 7.80 (d, J = 8.9 Hz, 1H; H-6), 7.94 (s, 1H; H-2); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 19.23 ($CH(CH_3)_2$), 21.88 ($CH(CH_3)_2$), 22.36 ($CH(CH_3)_2$), 55.75 (OCH_3), 57.69 (OCH_3), 73.11 ($CH(CH_3)_2$), 73.30 ($CH(CH_3)_2$), 93.79, 96,37, 102.53, 110.18, 116.67, 121.30, 123.62, 125.60, 128.02, 128.73, 133.02, 137.89, 139.21, 152.44, 155.61, 155.86, 156.85, 160.41, 161.75, 180.07 (C=O), 184.03 (C=O); MS (70 eV): *m*/*z* (%): 582/580 (5/5) [M^+], 509/507 (9/6) [$M^+ - C_4H_9O^+$], 467/465 (15/11) [$M^+ - C_8H_{19}^+$], 183 (100); elemental analysis (%): calcd for $C_{29}H_{25}O_8Br$ (581.42): C 59.91, H 4.33; found: C 59.66, H 4.25.

Compound (*P*)-**15**: The solvent was removed in vacuo from a solution of (*S*)-**14** (1.0 M in toluene, 360 μL, 360 μmol) and the residue was dissolved under argon in dry THF (1 mL). This solution was treated with a solution of the BH_3 – THF complex (1.0 M in THF, 480 mL) and stirred for 30 min at room temperature. After dropwise addition of a solution of the lactone **13** (69.8 mg, 120 μmol) in dry tetrahydrofuran (1 mL) at 0 °C the solution was stirred for 1 h at this temperature, then water (1 mL) and 2N HCl (1 mL) were added and the aqueous phase was thoroughly extracted with ethyl acetate. The combined organic phases were dried ($MgSO_4$) and the solvents were removed in vacuo. After flash chromatography of the residue on silica gel (dichloromethane/ethyl acetate 7:3), (*P*)-**15** (56.9 mg, 97.2 μmol, 81 %) was obtained as a yellow solid (96 % *ee*). Crystallization from dichloromethane/diethyl ether/*n*-hexane yielded yellow crystals (45.6 mg, 77.9 mmol, 65 %; > 99 % *ee*). M.p. 122 – 124 °C; $[\alpha]_D^{20} = -28$ (c = 0.01 in methanol); IR (KBr): $\tilde{\nu}$ = 3120 (br., OH), 2950, 1660, 1570, 1190, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.37 – 1.44 (m, 12H; $CH(CH_3)_2$), 3.59 (s, 3H; OCH_3), 3.76 (s, 3H; OCH_3), 4.33 (d, J = 13.7, 1H; CHHOH), 4.42 (d, J = 13.7, 1H; CHHOH), 4.55 (sept, J = 5.8 Hz, 1H; $CH(CH_3)_2$), 4.67 (sept, J = 5.8 Hz, 1H; $CH(CH_3)_2$), 6.12 (d, J = 1.8 Hz, 1H; H-3′ or H-5′), 6.20 (d, J = 1.8 Hz, 1H; H-3′ or H-5′), 6.97 (d, J = 8.8 Hz, 1H; H-7), 7.43 (s, 1H; H-2), 7.60 (d, J = 8.8 Hz, 1H; H-6); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 21.88 ($CH(CH_3)_2$), 21.98 ($CH(CH_3)_2$), 55.06 (OCH_3), 55.57 (OCH_3), 62.76 (CH_2OH), 72.73 ($CH(CH_3)_2$), 73.46 ($CH(CH_3)_2$), 91.32, 94.05, 105.66, 109.82, 118.94, 121.31, 122.43, 124.61, 128.01, 135.62, 137.44, 138.41, 147.96, 154.94, 155.78, 155.84, 157.21, 160.73, 182.40 (C=O), 186.23 (C=O); MS (70 eV): *m*/*z* (%): 586/584 (54/54) [M^+], 543/541 (44/39) [$M^+ - C_3H_6^+$], 495/493 (20/19) [$M^+ - CH_4O_2^+$], 453/451 (100/100) [$M^+ - C_7H_{17}O_2^+$]; elemental analysis (%): calcd for $C_{29}H_{25}O_8Br$ (585.45): C 59.50, H 4.99; found: C 59.59, H 4.74.

Received: November 23, 2000 [Z16167]

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[17] a) Enantiomeric ratios were determined by HPLC analysis on chiral phase: Daicel Chiralcel OD-H, 25 cm, 4.6 mm diameter, detection at 280 nm, flow: 0.5 mL min^{-1}, eluent: *n*-hexane/2-propanol 65:35, retention times: 29 min for (*P*)-**15** and 46 min for (*M*)-**15**; b) Attribution of the axial configuration of the alcohol **15** was done by CD spectroscopy and by correlation with the stereochemically known[6] final product **1a**.

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High-Temperature Synthesis of an Open-Framework Compound, $Na_2Cs_2Cu_3(P_2O_7)_2Cl_2$ (CU-4), by Molten-Salt Methods**

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Porous materials have stimulated much interest for their applications in catalysis, ion-exchange, separation, sensor, and molecular recognition.[1] Transition metal containing microporous (TMCM) solids have attracted particular attention because of their unique functions, such as redox catalysis,[2]

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[**] Financial support for this research (DMR-9612148, DMR-0077321 and EPS-9977797) and the single-crystal X-ray diffractometer (CHE-9207230) from the National Science Foundation is gratefully acknowledged.

  1433-7851/01/4009-1690 $ 17.50+.50/0