JOC Article

Atropo-Enantioselective Total Synthesis of Knipholone and Related Antiplasmodial Phenylanthraquinones†

Gerhard Bringmann,*,‡ Dirk Menche,‡ Jürgen Kraus,‡ Jörg Mühlbacher,‡ Karl Peters,§
Eva-Maria Peters,§ Reto Brun,|| Merhatibeb Bezabih,⊥ and Berhanu M. Abegaz⊥

Institut für Organische Chemie, Universität Würzburg, Am Hubland, D-97074 Würzburg, Germany,
Max-Planck-Institut für Festkörperforschung, Heisenbergstrasse 1, D-70506 Stuttgart, Germany,
Schweizerisches Tropeninstitut, Socinstrasse 57, CH-4002 Basel, Switzerland, and Department of
Chemistry, University of Botswana, Private Bag 0022, Gaborone, Botswana

bringman@chemie.uni-wuerzburg.de

Received March 18, 2002

The "lactone concept" has been efficiently employed for the first atropo-enantioselective synthesis of knipholone and related natural phenylanthraquinones. Besides the regio- and stereoselective construction of the biaryl axis, another important step was the "synthetically late" introduction of the *C*-acetyl group, either by a Friedel−Crafts type acetylation or by an *ortho*-selective Fries rearrangement first tested on simplified model systems and subsequently applied to the highly atroposelective preparation of the natural products and of simplified analogs thereof for biotesting. The synthetic availability of these natural biaryls, their precursors, and their unnatural analogs permitted a broader investigation of the antiplasmodial activities of these interesting biaryls.

Introduction

About 2 million people per year worldwide, mostly in developing countries, die of malaria,[1] making the search for new remedies against this most important tropical infectious disease an urgent task.[2] As a result of not only the rapid spreading of malaria but also the increasing resistance to the still widely used chloroquine, new antimalarials are urgently needed.[3] Recently, natural phenylanthraquinones such as **1a**−**d** have been shown to possess good to high antiplasmodial activity in vitro against *Plasmodium falciparum*,[4] the carrier of the most lethal malaria tropica, making them a new potential lead structure against this tropical disease.

The occurrence of knipholone [(*M*)-**1a**], first isolated from *Kniphofia foliosa*,[5] has long been considered to be confined to this Asphodelaceae species and has even been regarded as a taxonomic marker for the plant.[6] Recently, however, **1a** has been found in *Bulbine* and *Bulbinella* species (likewise Aphodelaceae) too,[7] and a number of closely related compounds, differing only in the *O*-methylation pattern of the acetylphloroglucinol unit and/or in the oxidation state of the tricyclic portion (anthraquinone vs anthrone), such as **1b**,[8] **1c**,[9] and **1d**[10] have been described.[11] All of these constitutionally unsymmetric natural biaryls[12] are optically active ($[\alpha]^{20}_{D} > 0$) and thus configurationally stable, but only for **1a** and **1b** has the axial configuration recently been elucidated using Boltzman-weighted quantum chemical CD calculations.[13] In this article, we describe the elaboration of a synthetic strategy for the atropo-enantiodivergent construction of such phenylanthraquinones leading to the first total synthesis of these axially chiral natural products and simplified analogs and report on their antiplasmodial

---

* To whom correspondence should be addressed. Phone: +49 931 888 5323. Fax: +49 931 888 4755.

† Dedicated to Professor Ekkehard Winterfeldt on the occasion of his 70th birthday. Part 100 of the series "Novel Concepts in Directed Biaryl Synthesis". For part 99, see: Tasler, S.; Bringmann, G. *Chem. Rec.* **2002**, *2*, 114−127.

‡ Universität Würzburg.

§ Max-Planck-Institut, Stuttgart.

|| Schweizerisches Tropeninstitut.

⊥ University of Botswana.

(1) (a) Backmund, M. *Fortschr. Med.* **1999**, *117*, 20. (b) Backmund, M.; von Zielonka, M.; Hartmann, W. J.; Hesse, J.; Eichenlaub, D. *Fortschr. Med.* **1999**, *117*, 24.

(2) WHO. *Malaria Weekly*; **1996**, June 3, 11.

(3) For a selection of promising new antimalarials, see: (a) Jomaa, H.; Wiesner, J.; Sanderbrand, S.; Altincicek, B.; Weidemeyer, C.; Hintz, M.; Türbachova, I.; Eberl, M.; Zeidler, J.; Lichtenthaler, H. K.; Soldati, D.; Beck, E. *Science* **1999**, *285*, 1573. (b) Bringmann, G.; Feineis, D. *Act. Chim. Thérapeut.* **2000**, *26*, 151. (c) Ying, L.; Zhu, Y.-M.; Jiang, H.-J.; Pan, J.-P.; Wu, G.-S.; Wu, J.-M. *J. Med. Chem.* **2000**, *43*, 1635.

(4) Bringmann, G.; Menche, D.; Bezabih, M.; Abegaz, B. M.; Kaminsky, R. *Planta Med.* **1999**, *65*, 757.

(5) Dagne, E.; Steglich, W. *Phytochemistry* **1984**, *23*, 1729.

(6) van Wyk, B.-E.; Yenesew, A.; Dagne, E. *Biochem. Syst. Ecol.* **1995**, *23*, 277 and references therein.

(7) (a) van Staden, F.; Drewes, E. S. *Phytochemistry.* **1994**, *35*, 685. (b) Bringmann, G.; Menche, D.; Brun, R.; Msuta, T.; Abegaz; B. M. *Eur. J. Org. Chem.* **2002**, 1107.

(8) Dagne, E.; Yenesew, A. *Phytochemistry* **1993**, *34*, 1440.

(9) Bezabih, M.; Motlhagodi, S.; Abegaz, B. M. *Phytochemistry* **1997**, *46*, 1063.

(10) Bezabih, M.; Abegaz, B. M. *Phytochemistry* **1998**, *48*, 1071.

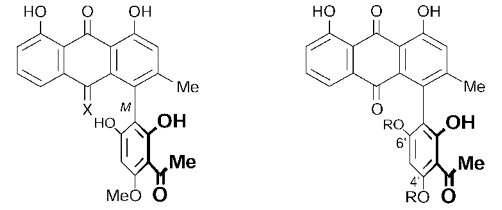
(11) Some of these plants have considerable importance in traditional medicine: (a) Watt, J. M.; Breyer-Brandwijk, M. G. *The Medicinal and Poisonous Plants of Southern and Eastern Africa*, 2nd ed.; Livingstone: Edinburgh, 1962; pp 568−574, 695, 707. (b) Gelfand, M.; Mavi, S.; Drummond, R. B.; Ndemera, B. *The Traditional Medical Practitioner in Zimbabwe*; Mambo Press: Gweru, 1993; p 89.

(12) For a first comprehensive review on naturally occurring biaryls, see: Bringmann, G.; Günther, C.; Ochse, M.; Schupp, O., Tasler, S. *Progress in the Chemistry of Organic Natural Products*; Herz, W., Falk, H., Kirby, G. W., Moore, R. E., Tamm, C., Eds.; Springer-Verlag: Wien, New York, 2001; Vol. 82, pp 1−249.

(13) Bringmann, G.; Kraus, J.; Menche, D.; Messer, K. *Tetrahedron* **1999**, *55*, 7563.

10.1021/jo020189s CCC: $22.00

activities. Part of this work has previously been reported in preliminary form.[4,14]



	X		R
(*M*)-**1a** Knipholone	O	(*P*)-**1c** 6'-*O*-Methylknipholone	Me
(*M*)-**1b** Knipholone Anthrone	H_2	(*M*)-**1d** 4'-*O*-Demethylknipholone	H

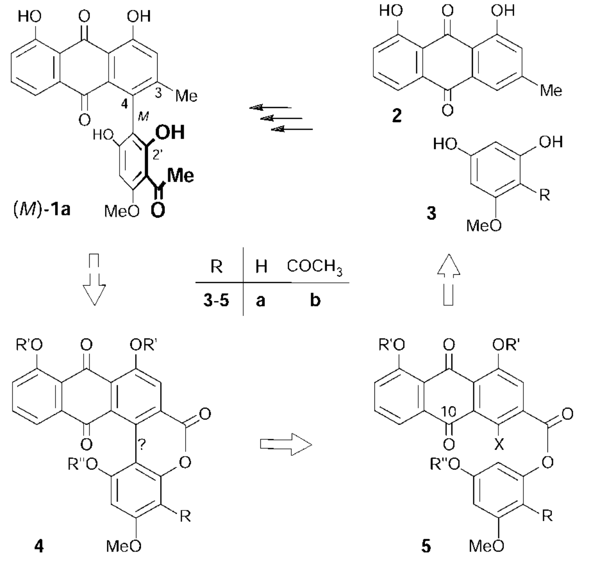
(configuration established in this paper)

Results and Discussion

A characteristic structural feature of knipholone (**1a**) is the rotationally hindered and thus stereogenic biaryl axis. The substitution pattern of **1a** and related anthraquinones, in particular the presence of a C_1 substituent (the methyl group at C-3) and an oxygen function (e.g., the OH group at C-2′) next to the axis, suggested to build up **1a** according to the "lactone method", a strategy for the regioselective and atropo-enantiodivergent construction of even highly hindered biaryls, which has already been used for the synthesis of numerous bioactive natural biaryls and useful biaryl reagents.[15,16] The corresponding retrosynthetic concept is shown in Scheme 1. A key intermediate of our approach would thus be a biaryl lactone of type **4**, either already equipped with the ultimate *C*-acetyl group as in **4b** or being still without it as in **4a**. These bridged biaryls were planned to be obtained by intramolecular coupling of the corresponding esters **5** (e.g., with $X = Br$), which in turn should best be accessible from chrysophanol (**2**) and a suitably functionalized phloroglucinol part, **3a** or **3b**. Before embarking on a total synthesis, a number of issues had to be addressed beforehand, among them the question of when to introduce the acetyl group and the general problem of whether lactone structures of type **4** would be accessible in the usual way from **5**, despite the additional steric hindrance and electronic impact exerted by the carbonyl function at C-10,[17] and whether the lactone would (hopefully) be configurationally unstable, to permit the atroposelective ring cleavage to occur economically, with *dynamic* kinetic resolution.

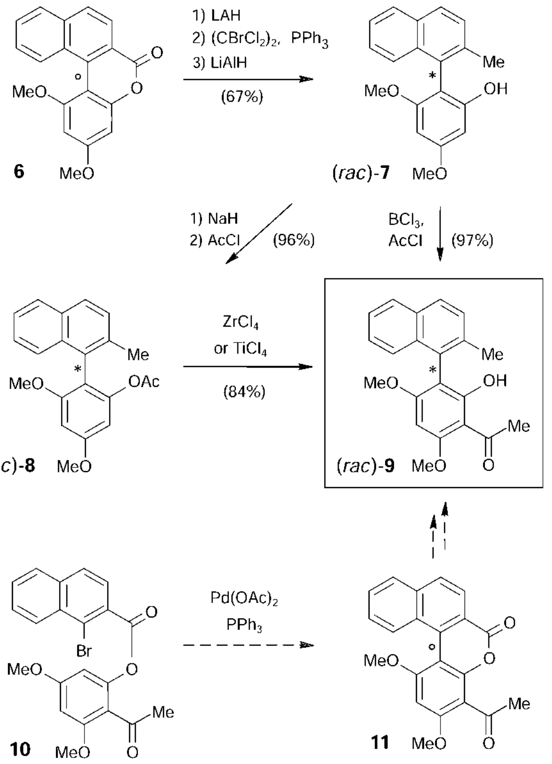
Using a very simplified synthetic model (Scheme 2), we first investigated at what stage an efficient introduction of the *C*-acetyl group might best be achieved, for which we considered two main strategies. The first approach, an early introduction of the acetyl group, implied an ester such as **10** as a key intermediate, while the second one, to first build up the biaryl bond and then to incorporate the acetyl group at a later stage, just required the "standard" lactone **6** as a building block.

SCHEME 1



? configurational stability initially unknown R', R'': protective groups

SCHEME 2



○ : configurationally unstable * : configurationally stable, but racemic

To test the first approach, ester **10**, as prepared from 2-hydroxy-4,6-dimethoxyacetophenone[18] and 1-bromo-2-naphthoic acid[19] (not shown, see Experimental Section), was submitted to the conditions of a Heck-type intramo-

---

(14) Bringmann, G.; Menche, D. *Angew. Chem., Int. Ed.* **2001**, *40*, 1687.

(15) Bringmann, G.; Breuning, M.; Tasler, S. *Synthesis* **1999**, 525.

(16) Bringmann, G.; Menche, D. *Acc. Chem. Res.* **2001**, *34*, 615.

(17) For an easier comparison of the compounds presented herein, the numbering of the "free" anthraquinone chrysophanol (**2**) was applied to the quinoid moiety of the respective phenylanthraquinones **5**, **17**, **30**, and **35**. In the Experimental Section, the correct numbering according to the IUPAC nomenclature has been used.

(18) Cunningham, B. D. M.; Lowe, P. R.; Threadgill, M. D. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1275.

(19) Cornejo, J. J.; Ghodsi, S.; Johnson, R. D.; Woodling, R.; Rickborn, B. *J. Org. Chem.* **1983**, *48*, 3869.

lecular coupling reaction that had previously been efficiently used in numerous syntheses of a broad variety of most different biaryl lactones.[15,16] A number of other catalysts, additives, and reaction conditions were also tried, but none of them produced the desired lactone **11**. Attempts to first protect the ketone function of **10** before the coupling reaction, either as an acetal or as a thioacetal, likewise failed. With 1,2-ethanediol there was no reaction, whereas with 1,2-ethanedithiol cleavage of the ester occurred, making it feasible to try the second strategy, introducing the acetyl group at a later stage starting from lactone **6**.[20] As previously shown,[21] this bridged biaryl is configurationally unstable and can be cleaved highly atropo-enantioselectively by a number of chiral nucleophiles, leading to the corresponding open biaryls, which are configurationally stable. For a first proof of concept concerning the introduction of the *C*-acetyl group, however, no optically active material was required, so that it sufficed to cleave the ring with the achiral and thus cheap reducing agent LAH to give, after stepwise deoxygenation of the side chain, the racemic biaryl **7**. Using this substrate, the introduction of the *C*-acetyl group succeeded both directly, by Friedel–Crafts acetylation,[22] and in a two-step procedure, by an *ortho*-selective Fries reaction[23] on ester **8**, and provided the *C*-acetyl compound **9** in good yields, without any cleavage of the methyl ether.

We then proceeded to test the applicability of our lactone methodology to phenylanthraquinone-type structures such as **4a** at the level of the still simplified and easily accessible but closer model compound **17** (Scheme 3). Both, the bromo- and the iodoacid **16a** and **16b** were prepared by the corresponding Sandmeyer reaction from **13**, which was in turn accessible from 2-methylanthraquinone (**12**).[24] Cyclization of the resulting bromoester **14** under typical Heck conditions, with the reagent combination $Pd(OAc)_2/PPh_3/NaOAc$, proceeded smoothly and in good yield, to give the desired key intermediate **17**, which was obtained as the only detectable product, so that a further optimization of the reaction by using the corresponding iodoester was not required. An X-ray analysis of **17**, besides confirming the constitution, revealed the expectedly highly distorted helicene-like structure, as a consequence of the steric constraints exerted by the *ortho* substituents next to the newly generated biaryl bond. In particular the carbonyl oxygen at C-10[17] is largely twisted out of the previously planar anthraquinone system.

Initial attempts using achiral nucleophiles such as LAH to test the reactivity of **17** soon revealed that the lactone functionality can be selectively reduced without attacking the quinoid system. For an atroposelective cleavage of the bridge, chiral *H*-nucleophiles, such as the oxazaborolidine–borane system, seemed particularly promising. The CBS reaction,[25] originally developed for the enantioselective reduction of ketones, has proven to be an efficient tool for the stereoselective cleavage of biaryl lactones[15,16,26] and of related nonbiarylic hetero-

SCHEME 3

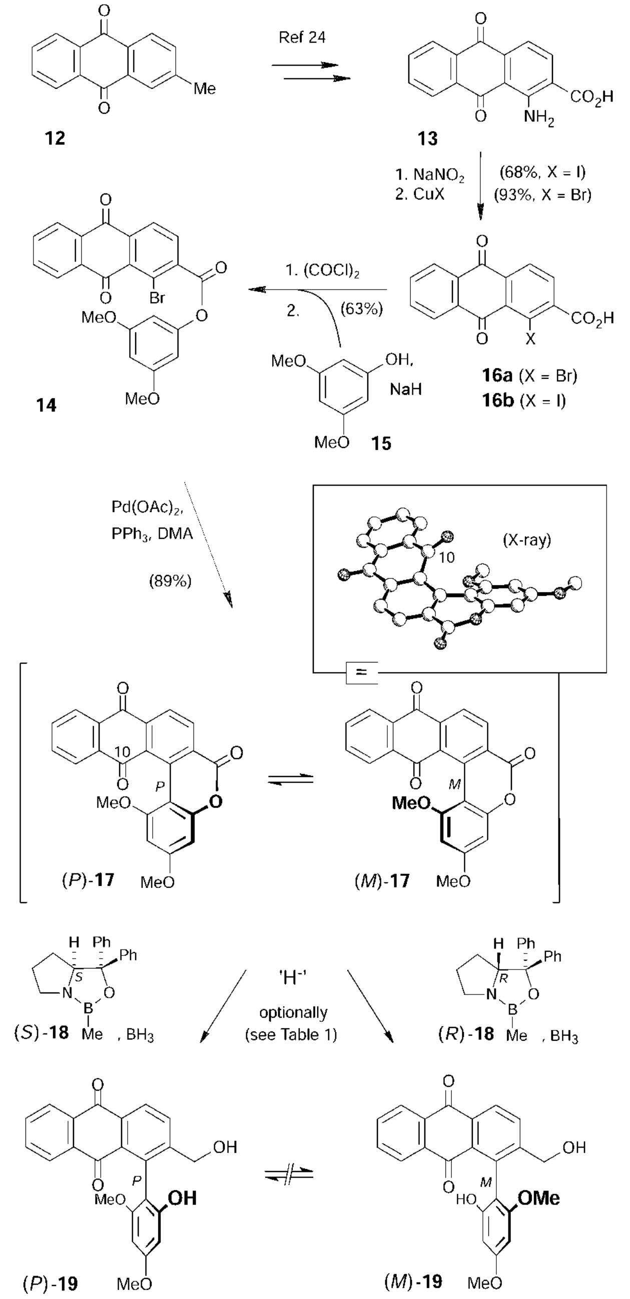


TABLE 1. Results of the Reductive Ring Cleavage Reaction of 17

H	(*P*):(*M*)	
(*R*)-**15**·BH_3, 25 °C	25:75	analytical scale
(*S*)-**15**·BH_3, 0 °C	85:15	67% yield
LAH	50:50	71% yield

---

[20] Bringmann, G.; Hartung, T.; Göbel, L.; Schupp, O.; Ewers, C. L. J.; Schöner, B.; Zagst, R.; Peters, K.; von Schnering, H. G.; Burschka, C. *Liebigs Ann. Chem.* **1992**, 225.

[21] Bringmann, G.; Heubes, M.; Breuning, M.; Göbel, L.; Ochse, M.; Schöner, B.; Schupp, O. *J. Org. Chem.* **2000**, *65*, 722.

[22] For a similar Friedel–Crafts acylation, see ref 18.

[23] For related Fries rearrangements, see: (a) Harowven, D. C.; Dainty, R. F. *Tetrahedron Lett.* **1996**, *37*, 7659. (b) Lin, G.-Q.; Zhong, M. *Tetrahedron Lett.* **1997**, *38*, 1087.

[24] For the synthesis of **13** a three-step procedure according to the following references was used: (a) Locher, A.; Fierz, H. E. *Helv. Chim. Acta* **1927**, *10*, 642. (b) BASF, *Fortschr. Teerfarbenfabr. Verw. Industriezweige* **1909**, *10*, 601. (c) Morley, J. O. *Synthesis* **1976**, 528.

[25] Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.

[26] Bringmann, G.; Pabst, T.; Henschel, P.; Kraus, J.; Peters, K.; Peters, E.-M.; Rycroft, D. S.; Connolly, J. D. *J. Am. Chem. Soc.* **2000**, *122*, 9127.

cycles with stereogenic centers.[26] As in all those cases before, reduction proceeded smoothly, permitting access atropodivergently both to the (*P*)- or, optionally, to the corresponding (*M*)-alcohol **19**, depending on the oxazaborolidine enantiomer used, (*S*)-**18** or (*R*)-**18**. The enantiomeric ratios and yields obtained indicate that this cleavage reaction proceeds according to the principle of a dynamic kinetic resolution (e.g., er 85:15, 67% yield), showing that, despite the molecular distortion, lactone **17** is configurationally unstable and thus allows the efficient conversion of the entire (racemic!) lactone material into essentially one (or, optionally, the other) enantiomeric ring cleavage product, which constitutes one of the advantages of the lactone approach.

The absolute configurations of the atropo-enantiomeric ring cleavage products **19** became evident from the analogous products of the authentic, correctly substituted lactones subsequently prepared (see below), leading to the genuine natural products. For an additional confirmation already at this stage of the synthesis and at the level of a biaryl derivative with an entirely different, nonquinoid chromophore, **19** was converted into the correspondingly configured phenylanthracene leuco-diacetate **20** (Figure 1), whose absolute configuration was established by quantum chemical circular dichroism (CD) calculations, a valuable stereoanalytical tool as already demonstrated in numerous previous cases.[27,28] The CD spectrum calculated for (*M*)-**20** showed a good agreement with the experimental one for the enantiomer of **19** that had been obtained when using (*S*)-**18** as the *H*-nucleophile for the ring cleavage of **17**, whereas the spectrum calculated for (*P*)-**20** was nearly opposite to the experimental one, especially in the diagnostically significant[27] short-wavelength part (Figure 1).

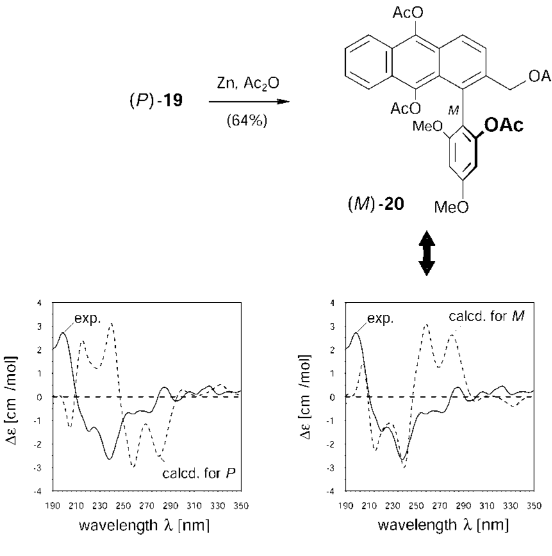
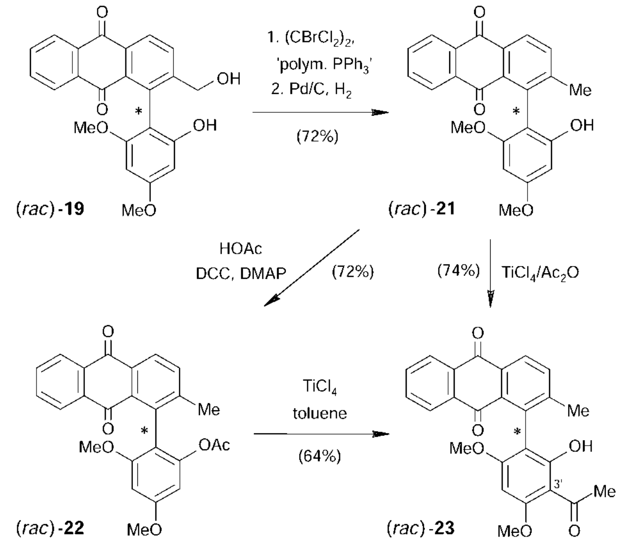


FIGURE 1. Elucidation of the absolute configuration of (*P*)-**19** by comparison of the experimental CD spectrum of its leucoacetate **20** (—) with the CD data calculated for the two atropo-enantiomeric forms of **20** (- - -).

SCHEME 4



* : configurationally stable, but racemic

For the preparation of the knipholone model analog **23** (at this level again racemic; see Scheme 4), neither the reduction of the side chain nor the introduction of the *C*-acetyl group succeeded by using the protocols established above (see Scheme 2). Thus, attempted side-chain deoxygenation of **19** by hydroxy/bromine exchange with subsequent LAH reduction predominantly reduced the quinoid system, and the previous conditions for the *C*-acetylation of **7** (see Scheme 2) did not give any reaction for **21**. The reduction of the side chain of **19** finally succeeded by hydrogenolysis of the intermediate bromide with Pd/C as the catalyst; an additional improvement in the hydroxy/halogen exchange was achieved by the use of polymer-bound triphenylphosphine, which can readily be discarded by simple filtration, further increasing the yield up to 72%. For the introduction of the C_2 unit at C-3′ of the target molecule, the stronger acetylating reagent combination $TiCl_4/Ac_2O$ had to be applied or, for the corresponding Fries rearrangement, higher reaction temperatures, to give the (still deoxygenated) model knipholone **23**.

For the synthesis of the authentic, genuine natural phenylanthraquinones, a 1,8-dioxygenated anthraquinone building block was required. A broad variety of synthetic pathways to natural and unnatural hydroxyanthraquinones are known,[29,30] of which, because of the cheap commercial availability of the starting materials and the convergence of the synthesis, the cycloaddition of naphthoquinones such as juglone (**24**) and dienes such as **25**[30] (see Scheme 5) was chosen for the straightforward

---

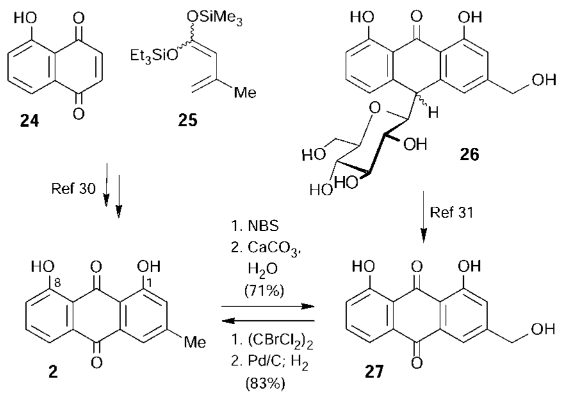
[27] Bringmann, G.; Busemann, S. In *Natural Product Analysis*; Schreier, P., Herderich, M., Humpf, H.-U., Schwab, W., Eds.; Vieweg: Braunschweig 1998; pp 195−212.

[28] Bringmann, G.; Mühlbacher, J.; Repges, C.; Fleischhauer, J. *J. Comput. Chem.* **2001**, *22*, 1273.

[29] (a) Eder, R.; Widmer, C. *Helv. Chim. Acta* **1923**, *6*, 419. (b) Mühlemann, H. *Pharm. Acta Helv.* **1948**, *23*, 257. (c) Birch, A. J.; Powell, V. H. *Tetrahedron Lett.* **1970**, *40*, 3467. (d) Banville, J.; Brassard, P. *J. Chem. Soc., Perkin Trans. 1* **1976**, 613. (e) Krohn, K. *Tetrahedron Lett.* **1980**, *21*, 3557. (f) Savard, J.; Brassard, P. *Tetrahedron* **1984**, *40*, 3455. (g) Jung, M.; Lowe, J. A., III.; Lyster, M. A.; Node, M.; Pfluger, R. W.; Brown, R. W. *Tetrahedron* **1984**, *40*, 4751. (h) Watanabe, M.; Fukuda, T.; Miyashita, T.; Furukawa, S. *Fac. Pharm. Sci.* **1985**, *105*, 11. (i) Cameron, D. W.; Feutrill, G. I.; Gamble, G. B.; Stavrakis, J. *Tetrahedron Lett.* **1986**, *27*, 4999. (j) Khanapure, S. P.; Reddy, R. T.; Biehl, E. R. *J. Org. Chem.* **1987**, *52*, 5685. (k) Krohn, K.; Khanbabaee, K. *Liebigs Ann. Chem.* **1993**, 905.

[30] Khan, A. T.; Blessing, B.; Schmidt, R. R. *Synthesis* **1994**, 255.

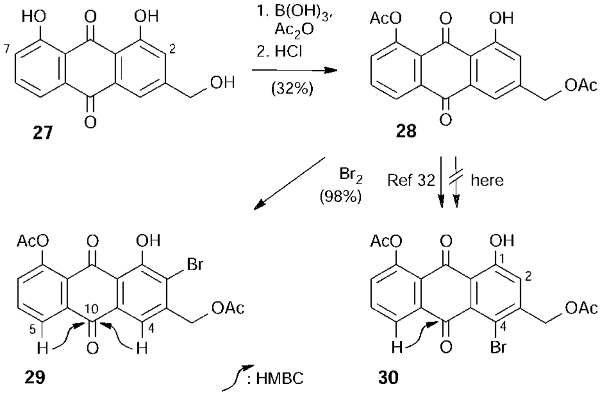
SCHEME 5



construction of chrysophanol (**2**). For the already side-chain oxygenated building block aloe-emodin (**27**), which is likewise a natural product, a direct, *partial* synthesis from the likewise commercially available (though quite expensive) natural *C*-glycoside aloin (**26**)[31] was preferred. As shown in this paper, chrysophanol and aloe-emodin can easily be interconverted, by benzylic halogenation of **2** with subsequent hydrolysis and by the above-mentioned two-step hydrogenolysis procedure for the side-chain deoxygenation of **27**, giving the presented synthesis a high flexibility.

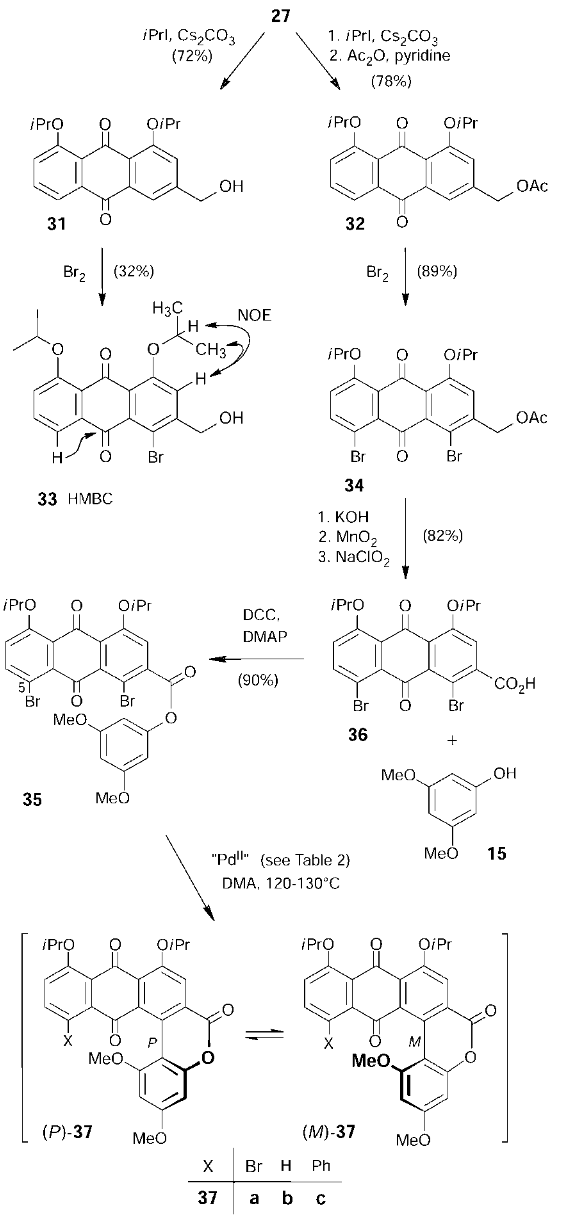
Likewise simple seemed the halogenation at the required coupling position, since a three-step procedure for the introduction of bromine into the 4-position of aloe-emodin (**27**) had already been reported in the literature,[32] by bromination of the diacetate **28** (see Scheme 6).[33] The product now obtained by the published protocol, however, although displaying the same physical data as those reported in the literature (and also the same yield), turned out not to be the postulated 4-bromo derivative **30**[17] but the respective 2-isomer, **29**, as was unambiguously shown by NMR, in particular by HMBC interactions of both, H-4 and H-5, to C-10 (see Scheme 6). The likewise attempted direct bromination of free, unprotected aloe-emodin (**27**) itself preferentially took place in the undesired 2- and 7-positions. This inherent reactivity could not be overcome even by a variety of different brominating reagents and solvent systems or by applying most different reaction conditions.

SCHEME 6



The desired functionalization of **27** was finally attained after sterically shielding the "Northern" part of the molecule by converting the phenolic OH groups into isopropyl ethers as in **31** and subsequent treatment with Br_2 to produce **33**, whose correct bromination site was unambiguously deduced from NMR experiments (see Scheme 7) and X-ray data.[34] As a result of the formation of further regioisomeric or over-reacted bromination products and the sensitivity of the side chain toward oxidation, however, the obtained yields were only moderate (32%) and could not be improved by using other

SCHEME 7



X	Br	H	Ph
37	**a**	**b**	**c**

---

(31) Rychener, M.; Steiger, W. *Pharm. Acta Helv.* **1989**, *64*, 8.

(32) Alexander, J.; Bhatia, A. V.; Mitscher, L. A.; Omoto, S.; Suzuki, T. *J. Org. Chem.* **1980**, *45*, 20.

(33) In the literature, a direct bromination of chrysophanol (**2**) has also been described, yet leading to a variety of products: (a) Chumbalov, T. K.; Muzychkina, R. A.; Zhusupova, G. E.; Nazarova, V. D.; Chanysheva, I. S. *S. Rab. Khim., Kaz. Univ.* **1973**, *3*, 57; *Chem. Abstr.* **1974**, *81*, 135801. (b) Chumbalov, T. K.; Chanysheva, I. S.; Zhusupova, G. E.; Muzychkina, R. A.; Sheinchenko, V. I. *Zh. Fiz. Khim.* **1979**, *53*, 186; *Chem. Abstr.* **1979**, *90*, 185882.

(34) Peters, K.; Peters, E.-M.; Menche, D.; Bringmann, G. Unpublished results.

TABLE 2. Results of the Intramolecular Coupling Reactions of 35

catalyst	base	time [h]	**37a** [%]	**37b** [%]	**37c** [%]
$PdCl_2(PPh_3)_2$ (0.5 equiv)	NaOAc	10		5.4	46
$PdCl_2(PPh_3)_2$ (0.5 equiv)	NaOAc	2	17	6	12
$Pd(OAc)_2$ (0.2 equiv), PPh_3	NaOAc	6	36	12	
$Pd(OAc)_2$ (0.4 equiv), PPh_3	NaOAc	5	32	6	
$Pd(OAc)_2$ (0.6 equiv), PPh_3	NaOAc	4.5	59	7	
$Pd(OAc)_2$ (0.8 equiv), PPh_3	NaOAc	2	22	8	
$Pd(OAc)_2$/P(*o*-tolyl)$_3$ (0.6 equiv)	NaOAc	2	14		
$Pd(OAc)_2$ (0.6 equiv), PPh_3	NaOPiv	1−2	68	5	

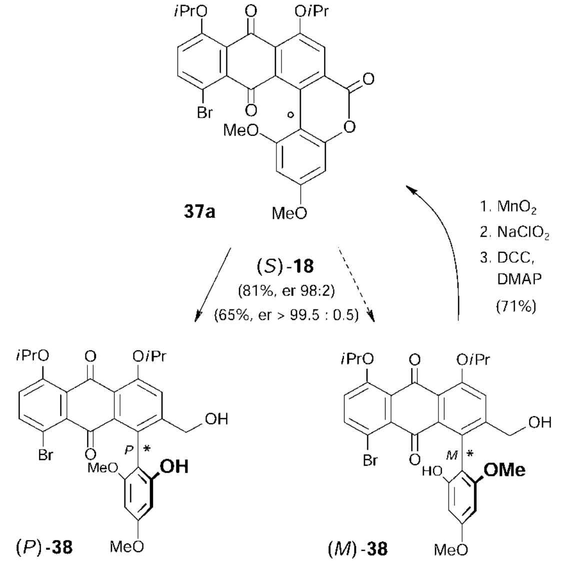
procedures. Different from the model compounds described above, a regioselective nitration (in this case for 1-*O*,8-*O*-dimethylchrysophanol and 1-*O*,8-*O*-dimethylaloe-emodin) failed because of formation of chromatographically very similar regioisomeric products or decomposition, as did attempts to introduce the bromine by a DOM (directed *ortho* metalation) strategy either on **31** or on the corresponding aldehyde or acid (not shown).

All of these problems were overcome by protecting the oxidation-sensitive side chain by *O*-acetylation and then using bromine in excess, thus directly giving the dibromo derivative **34** in a reliably high yield. By saponification and stepwise oxidation (MnO_2, $NaClO_2$) to the respective acid **36**, followed by esterification with the dimethoxyphenol **15** using Steglich's procedure,[35] which proved to be superior to the alternative to proceed via the corresponding acid chloride as above for **16a**, the dibromo ester **35** became available on a multigram scale (Scheme 7).

Despite the additional bromine substituent at C-5,[17] the intramolecular coupling of **35** proceeded smoothly to give the desired, still monobrominated lactone **37a** (Scheme 7, Table 2), proving the applicability of the lactone methodology even to substrates with two electronically similar aryl-bromine bonds. For this cyclization, the use of Pd(II)acetate was most efficient, while entirely unexpectedly $PdCl_2(PPh_3)_2$ produced significant quantities (up to 46%) of the additionally phenylated derivative **37c**. Short reaction times and the use of sodium pivalate as a sterically more demanding base,[36] as compared to sodium acetate, further improved the yields, whereas in contrast to previous cases[37] the use of the Herrmann−Beller catalyst[38] was less effective.

The stereochemical key step of the synthesis, the atroposelective reductive ring cleavage of **37a**, was thoroughly optimized with respect to nucleophiles, solvents, and reaction temperatures. As for the model lactone **17** (see Scheme 3), the best results were obtained using Corey's oxazaborolidine−borane system, providing the phenylanthraquinone (*P*)-**38** in very good optical (er 98:2) and chemical (81%) yields (Scheme 8). Its enantiomeric purity was further enhanced by a simple crystallization step. The possibility to reoxidize (MnO_2, $NaClO_2$) and subsequently recycle (DCC, DMAP) the undesired enantiomer (practically spoken, the mother liquor material), literally by recyclization back to the lactone **37a**, as exemplarily shown for (*M*)-**38** in Scheme 8, permitted transformation of an even larger portion of the starting material into the desired product enantiomer, here into (*P*)-**38**.

SCHEME 8



A remaining synthetic problem was the reductive elimination of the additional bromine substituent at C-5. One of the methods for such aromatic hydrodehalogenation reactions in the field of anthraquinones, the use of $Na_2S_2O_4$,[39] led to the cleavage[40] of the biaryl bond as shown for (*P*)-**38** to give **31** and **15** (Scheme 9), while formic acid in combination with Pd/C[41] preferentially reduced the quinoid system, e.g., converting **37a** to **41**. The desired transformation could finally be effected by Pd-catalyzed hydrogenolysis in the presence of a mild buffer (NaOAc) to avoid an acid-induced cleavage of the *O*-isopropyl groups by the HBr formed. The conditions were optimized such that via (*M*)-**39** simultaneously the desired methyl group at C-2 was obtained to give (*P*)-**40** in a one-pot reaction. Thus, the additional bromine at C-5 ultimately had not required any additional steps for its introduction or for its reductive elimination but had significantly increased the efficacy of the synthesis. Stronger bases, such as NEt_3, gave the undesired cyclic ether **42**. From the diastereotopic character of the benzylic portions in the bridge (partially overlayed by the $OCH(CH_3)_2$ multiplet (see Scheme 9), this bridged biaryl was shown to be chiral on the NMR time scale but (as expected from the similarity to the corresponding lactone **37a**) should be configurationally unstable from DNMR investigations.[21]

Initial attempts to achieve the last synthetic key step, the introduction of the still required C_2 unit, by acetylating (*P*)-**40** directly or by a Fries rearrangement of its 2′-*O*-acetate ester (not shown) as above for (*rac*)-**7** (see

---

(35) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.

(36) Hosoya, T.; Takashiro, E.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1994**, *116*, 1004.

(37) (a) Bringmann, G.; Hinrichs, J.; Kraus, J.; Wuzik, A.; Schulz, T. *J. Org. Chem.* **2000**, *65*, 2508. (b) Bringmann, G.; Ochse, M.; Götz, R. *J. Org. Chem.* **2000**, *65*, 2069.

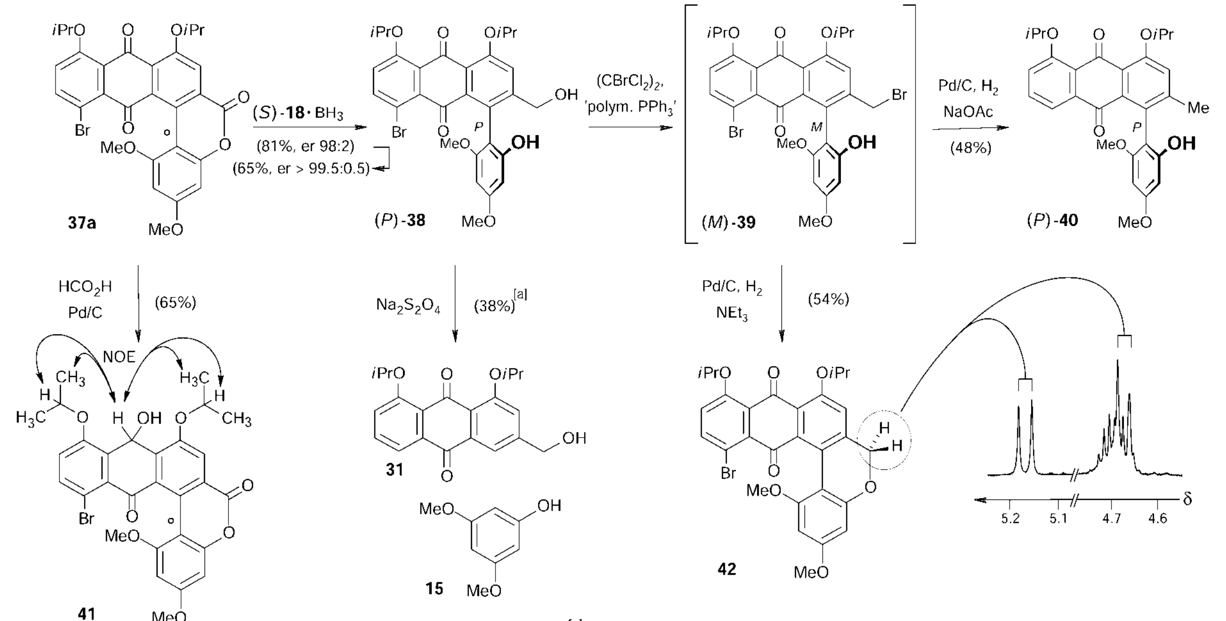
(38) Herrmann, W. A.; Brossmer, C.; Öfele, K.; Reisinger, C.-P.; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *25*, 1844.

(39) (a) Yosioka, I.; Yamauchi, H.; Morimoto, K.; Kitagawa, I. *Tetrahedron Lett.* **1968**, *9*, 1149. (b) Banville, J.; Grandmaison, J.-L.; Lang, G.; Brassard, P. *Can. J. Chem.* **1974**, *52*, 80.

(40) For related biaryl cleavage reactions, see refs 5 and 8.

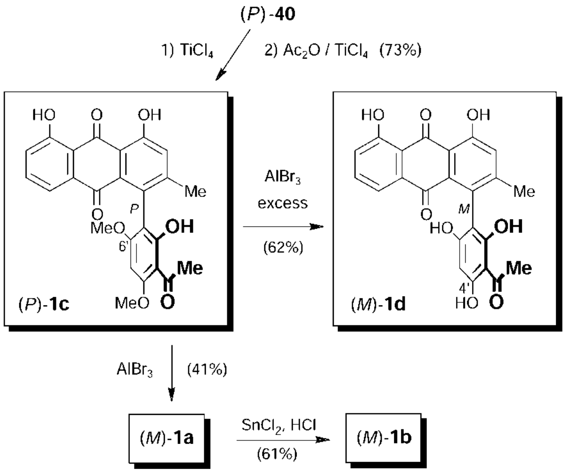
(41) (a) Cortese, N. A.; Heck, R. F. *J. Org. Chem.* **1977**, *42*, 3491. (b) Pandey, P. N.; Purkayastha, M. L. *Synthesis* **1982**, 876.

SCHEME 9



[a]: Reaction was performed with the corresponding atropo-enantiomer

SCHEME 10



Scheme 2), only led to a cleavage of the *O*-isopropyl ethers. After a complete directed *O*-deprotection in the anthraquinone part, however, acetylation proceeded smoothly and in high yields, this time necessitating a 2-fold excess in both the lewis acid ($TiCl_4$) and the acetylating agent (Ac_2O) (Scheme 10), to give 6′-*O*-methylknipholone (**1c**), the first natural phenylanthraquinone synthetically attained. Selective mono-*O*-demethylation of **1c** at C-6′[42] using $AlBr_3$ gave the target molecule knipholone (**1a**), whose reduction using a standard procedure for anthraquinones[43] provided its anthrone **1b**. The fully *O*-demethylated derivative **1d** was obtained when using $AlBr_3$ in excess. All of the phenylanthraquinones **1a**−**d** are natural products and were found to be completely identical to authentic samples from *Bulbine capitata* and *Kniphofia foliosa*[8−10] in all their chromatographic, physical, spectral, and chiroptical data. Thus, **1c** and **1d** must be stereochemically identical[44] both with knipholone and its anthrone, i.e., all of them with the $COCH_3$ portion "above" the anthraquinone plane, and must have the stereostructures shown in Scheme 10 now established by the synthetic work presented here.

The absolute configurations of knipholone (**1a**) and its anthrone (**1b**) in turn had previously been established by Boltzmann-weighted quantum chemical CD calculations[13] and were now confirmed to be *M* by molecular dynamics based quantum chemical CD calculations.

The MD simulations were performed using the MM3 force field,[45] arbitrarily starting with the (*M*)-enantiomers of the compounds. The simulations were calculated for a total time period of 500 ps, recording the structure every 0.5 ps for further calculations.

For the 1000 structures thus collected for each compound, single CD spectra were calculated and then, differently from the previous[13] Boltzmann-weighting, averaged arithmetically to give theoretical overall spectra. To take into account systematic shifts of the calculated CD spectra, a "UV correction" was carried out for each calculated spectrum as introduced earlier.[27] The good agreements between the calculated overall CD spectra for the (*M*)-compounds with the experimental ones (Figure 2) permitted an unambiguous attribution of the absolute configuration of both **1a** and **1b** as *M*.

The synthetic availability of the compounds presented herein permitted the evaluation of their antimalarial potential in vitro against *Plasmodium falciparum*. The authentic natural products **1a**−**d**, but also some of their synthetic biarylic precursors, e.g., **38** and **40**, and to a smaller degree the dideoxy analogs **19**, **21**, and **23**,

---

[42] For a related regioselective cleavage of xanthoxylline (2-acetyl-3,5-dimethoxyphenol), but under more drastic conditions, see: Jain, A. C.; Gupta, S. M.; Bambah, P. *Indian J. Chem., Sect. B* **1985**, *24*, 393.

[43] For related reductions of anthraquinones, see: Auterhoff, H.; Scherff, F. C. *Arch. Pharm. (Weinheim, Ger.)* **1960**, *293*, 918.

[44] Note that the opposite descriptor of **1c** as compared to those of **1a**, **1b**, and **1d** is only due to the CIP formalism.

[45] Cui, W.; Li, F.; Allinger, N. L. *J. Am. Chem. Soc.* **1993**, *115*, 2943.

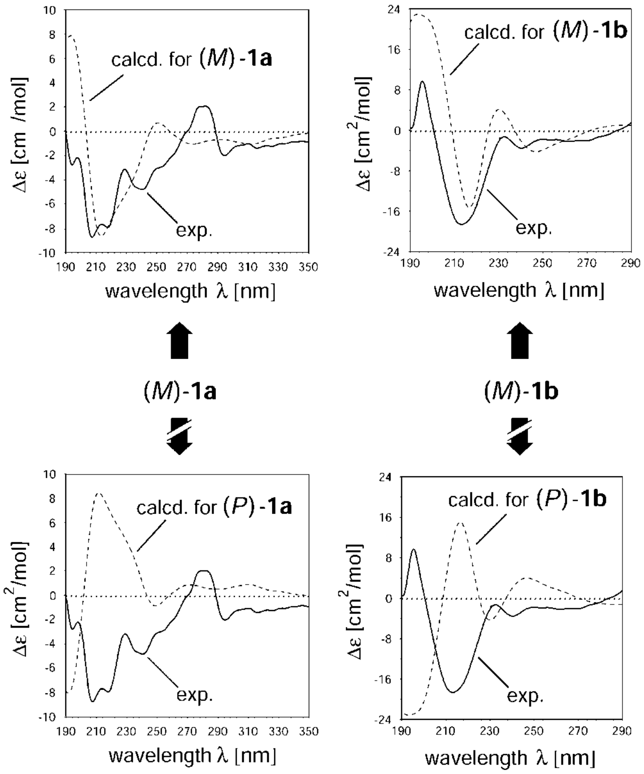


FIGURE 2. Confirmation of the absolute configuration of **1a** and **1b** (- - -), by comparison of the CD spectra calculated for both (*M*)- and (*P*)-**1a**, as well as (*M*)- and (*P*)-**1b**, with the experimental data (—).

TABLE 3. Activities of Selected Phenylanthraquinones and Compounds Derived Thereof against *P. falciparum* (strain K1), *T. cruzi*, *T. brucei rhodesiense*, and *L. donovani* and Cytotoxicities against Rat Skeletal Myoblast Cells (L6)

	IC_{50} [μg/mL]				IC_{50}/MIC [μg/mL]
compd	*P. falciparum*	*T. cruzi*	*T. b. rhodes*	*L. donova*	cytotoxicity (L6)
std	0.141[a]	0.398[b]	0.0024[c]	48.2[d]	2.8 (IC_{50})[e] >90 (MIC)
1a	0.672	7.61	9.31	>30	33 (MIC)
1b	0.149	1.5	13.12	ne[f]	3.7 (MIC)
1c	1.06	nd[g]	nd[g]	nd[g]	nd[g]
1d	0.512	13.65	5.7	>10	30 (MIC)
2	>5.00	nd[g]	nd[g]	>30	>90 (MIC)
3b	>5.00	86.0	24.2	>30	na[h]
(*rac*)-**9**	>5.00	nd[g]	32.25	>30	90 (MIC)
13	>5.00	44.1	2.86	>10	88.0 (IC_{50})
15	>5.00	nd[g]	nd[g]	>30	>90 (MIC)
(*M*)-**20**	>5.00	38.6	3.34	>30	>90 (IC_{50})
(*rac*)-**19**	1.05	13.13	15.05	>30	90
(*rac*)-**21**	0.677	13.26	2.91	22.7[i]	67.4 (MIC)
(*rac*)-**23**	1.17	>90	4.6	>30	>90 (MIC)
26	>5.00	>90	11.36	>30	>90 (MIC)
27	>5.00	4.84	10.68	>3.3	10 (IC_{50})
32	>5.00	85.8	2.765	>30	>90 (IC_{50})
37a	>5.00	2.27	4.185	>30	58.2 (IC_{50})
(*M*)-**38**	0.714	16.8	2.875	>10	18.9 (IC_{50})
(*P*)-**38**	0.326	7.58	5.505	>10	10.3 (IC_{50})
41	>5.00	82.82	29.48	>30	31.4 (MIC)
(*P*)-**40**	0.739	8.52	6.31	>10	16.9 (MIC)

[a] Chloroquine. [b] Benznidazole. [c] Melarsoprol. [d] Pentostam. [e] Mefloquine. [f] Not evaluated due to cytotoxicity. [g] Not determined. [h] Not applicable, activity did not substantiate cytotoxicity. [i] Macrophages infected with axenic amastigotes.

showed moderate to good activities with IC_{50} values from 1.17 μg/mL for (*rac*)-**21** to 0.326 μg/mL for (*P*)-**38**. The best results were obtained for the anthrone **1b** (IC_{50} 0.149 μg/mL), being in the range of the standard chloroquine (IC_{50} 0.141 μg/mL), while its quinoid synthetic precursor (*P*)-**38** was less active (IC_{50} 0.326 μg/mL). As revealed by comparing **21** and **40** with the corresponding acetyl derivatives **23** and **1d**, the *C*-acetyl group in the lower part of the molecule does not seem to be important to achieve good activities. The presence of an intact, full phenylanthraquinone molecular framework, however, appears to be essential. Not only the lactone-type structures **41** and **37a** but also all of the phenyl-devoid anthraquinones (e.g., **2**, **13**, **26**, **27**, and **32**) and the acetylphloroglucinol building blocks (e.g., **3b**), as well as the simplified phenylnaphthalenes (e.g., **9**), are completely inactive. Likewise inactive is the biarylic but nonquinoid phenylanthracene (*M*)-**20**. None of the phenylanthraquinones showed any cytotoxicity on mammalian cells, revealing this antiplasmodial activity to be quite specific.

With respect to these activities, further investigations of other antiprotozoal properties, viz., against *Trypanosoma cruzi* (the pathogen of Chagas disease), *T. brucei rhodesiense* (causing the African sleeping sickness), and *Leishmania donovani* (responsible for leishmaniasis), seemed promising. Knipholone (**1a**), its natural derivatives, and some of its synthetic biphenylic precursors such as **37**, **38**, and **40**, as well as their dideoxy analogs **19** and **21**, displayed moderate to good activities against *T. cruzi*, with the anthrone **1b** being the most potent compound (IC_{50} 1.5 μg/mL). It is interesting to note that in this case likewise the mere anthraquinone building block **27**, which had no effect against *P. falciparum* (see above), was now shown to be active against this pathogen also. Only very low activities of the compounds studied were observed against *T. b. rhodesiense*, with mostly no activity against *L. donovani*, showing again the above-reported antiplasmodial activities to be quite pathogen specific.

Conclusions

Based on the lactone concept, the first successful synthetic approach toward natural knipholone-type phenylanthraquinones is described. After the elaboration of solutions to the main synthetic problems using simplified model compounds, key steps of the synthesis were the regioselective 2-fold halogenation of the respective anthraquinone building block, the intramolecular biaryl coupling of the respective trioxyphenyl dibromoanthraquinone carboxylate ester, the atropo-enantiodivergent ring cleavage of the configurationally unstable biaryl lactone using chiral *H*-nucleophiles with dynamic kinetic resolution, and the introduction of the *C*-acetyl group.

By this strategy, knipholone (**1a**), knipholone anthrone (**1b**), 6′-*O*-methylknipholone (**1c**), and 4′-*O*-demethylknipholone (**1d**) were obtained. This first total synthesis of natural phenylanthraquinones simultaneously permitted a stereochemical correlation among the compounds.

On the basis of the now attained synthetic availability of these natural products, their precursors, and structural analogs, the antiplasmodial activities of such knipholone-type phenylanthraquinones were broadly tested and were shown to result from a combination of the anthraquinone portion and the acetylphloroglucinol unit being fixed together via the biaryl bond. The highest antiplasmodial activity has so far been obtained for the natural phenylanthrone **1b**.

Experimental Section

General Methods. HPLC−UV: HPLC with syringe loading sample injector, UV detector, and integrator. Column: Chiralcel OD-H, 4.6 mm × 250 mm, 0.5 mL/min, hexane/*i*-PrOH = 70:30 for **19** [t_R = 30 min for (*M*)-**19**, t_R = 35 min for (*P*)-**19**] and 65:35 for **38** [t_R = 29 min for (*P*)-**38**, t_R = 46 min for (*M*)-**38**]. For preparative HPLC an LC 25 mm module with two Nova-Pak C-18 column segments (25 mm × 100 mm) and a pump with a flow of 4.0 mL min^{-1} and UV detection at 254 nm was used (solvent $MeOH/H_2O$ = 75:25, acidified with 0.1% TFA). Source of compounds: **2**,[30] **6**,[20] **13**,[24] **16b**,[48] **27**,[31] **28**,[32] 2-acetyl-3,5-dimethoxyphenol,[18] and 1-bromo-2-naphthoic acid[19] were prepared according to literature procedures. All palladium-catalyzed coupling reactions were performed in carefully baked flasks (heating by a heatgun for 5 min under vacuum). For further general procedures (i.e., $[\alpha]_D$, mp, NMR, IR, MS) see ref 7b.

(*rac*)-1-(2′,4′-Dimethoxy-6′-hydroxyphenyl)-2-methylnaphthalene [(*rac*)-7]. A solution of **6** (800 mg, 2.61 mmol) in 25 mL of dry THF was treated with 198 mg (5.22 mmol) of LAH at 0 °C and stirred for 30 min at 0 °C and for 30 min at room temperature. The reaction mixture was cautiously hydrolyzed with 1 M HCl. The aqueous phase was thoroughly extracted with Et_2O. The combined organic phases were dried ($MgSO_4$) and the solvent evaporated. Filtration through a short silica gel column (CH_2Cl_2) and subsequent recrystallization from CH_2Cl_2/petroleum ether afforded colorless crystals of (*rac*)-2-hydroxymethyl-(2′,4′-dimethoxy-6′-hydroxyphenyl)-naphthalene (674 mg, 2.17 mmol, 83%): mp 165−166 °C (lit.[46] 165−166 °C).

A solution of this phenol (301 mg, 971 μmol) in 25 mL of CH_2Cl_2 was treated at 0 °C under nitrogen with PPh_3 (382 mg, 1.46 mmol) and stirred at 0 °C for 30 min. $(CBrCl_2)_2$ (475 mg, 1.46 mmol) was added and the reaction mixture was allowed to warm to room temperature within 3 h and stirred for further 5 h at this temperature. After evaporation of the solvent the residue was passed through a short silica gel column (petroleum ether/Et_2O = 3:1) to afford a white solid (320 mg) which was dissolved in 10 mL of dry Et_2O, subsequently treated with LAH (61.2 mg, 1.61 mmol), and stirred at room temperature for 3 h. After cautious hydrolysis of the reaction mixture with H_2O and 2 M HCl, the aqueous phase was thoroughly extracted with CH_2Cl_2. Drying of the combined organic phases ($MgSO_4$) and evaporation of the solvent under reduced pressure afforded (*rac*)-**7** (230 mg, 781 μmol, 81%) as a slightly yellow solid, which was obtained as colorless crystals from CH_2Cl_2/petroleum ether: mp 153 °C; IR (KBr) ν 3400, 3020, 2930, 2900, 2820, 1605, 1560, 1135, 1090 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.26 (s, 3H), 3.62 (s, 3H), 3.88 (s, 3H), 6.25 (d, J = 2.9 Hz, 1H), 6.31 (d, J = 2.9 Hz, 1H), 7.32−7.49 (m, 4H), 7.82−7.87 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 20.2, 55.4, 55.7, 91.7, 92.7, 106.3, 125.2, 126.5, 127.3, 128.1, 128.5, 128.8, 132.4, 133.3, 137.2, 154.5, 158.7, 161.3; MS (EI) *m*/*z* 294 (100) $[M^{+\bullet}]$, 279 (18), 263 (10). Anal. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.17. Found: C, 77.17; H, 6.03.

(*rac*)-1-(2′-Acetoxy-4′,6′-dimethoxyphenyl)-2-methylnaphthalene [(*rac*)-8]. A suspension of NaH (net weight: 4.48 mg, 187 μmol, from ca. 7.5 mg in mineral oil) in 0.5 mL of dry THF was treated dropwise at 0 °C with a solution of (*rac*)-**7** (50 mg, 170 μmol) in 0.5 mL of dry THF. After 2 h a solution of AcCl (15 μL, 16.6 mg, 210 μmol) in 1 mL of CH_2Cl_2 was added within 20 min at 0 °C. The mixture was stirred for 3 h. Evaporation of the solvent and filtration of the residue through a silica gel column (petroleum ether/Et_2O = 3:1) afforded (*rac*)-**8** (54.9 mg, 163 μmol, 96%) as a yellow powder, which was crystallized from CH_2Cl_2/petroleum ether: mp 111 °C; IR (KBr) ν 3020, 2980, 2940, 2920, 1745, 1600, 1560, 1200, 1185, 1145, 1080; ^1H NMR (250 MHz, $CDCl_3$) δ 1.55 (s, 3H), 2.22 (s, 3H), 3.89 (s, 3H), 3.66 (s, 3H), 6.44 (d, J = 2.3 Hz, 1H), 6.55 (d, J = 2.3 Hz, 1H), 7.31−7.41 (m, 4H), 7.73−7.81 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 20.2, 20.2, 55.5, 55.9, 96.8, 99.6, 114.0, 124.6, 125.6, 125.7, 127.5, 127.7, 128.4, 129.1, 131.8, 132.9, 135.6, 150.3, 156.0, 160.5, 168.8; MS (EI) *m*/*z* 336 (26) $[M^{+\bullet}]$, 294 (100), 279 (13). Anal. Calcd for $C_{21}H_{20}O_4$: C, 74.98; H, 5.99. Found: C, 75,68; H, 5,72.

(*rac*)-1-(5′-Acetyl-2′,4′-dimethoxy-6′-hydroxyphenyl)-2-methylnaphthalene [(*rac*)-9]. (A) By Friedel−Crafts Acylation of (*rac*)-7. BCl_3 (102 μL, 1 M solution in hexane) was treated dropwise with a solution of (*rac*)-**7** (30.0 mg, 102 μmol) in 1 mL of CH_2Cl_2 at −10 °C. After 5 min AcCl (120 μL of a 1 M solution in CH_2Cl_2) was added and the mixture was heated under reflux for 3 h and then allowed to cool to room temperature. After cautious hydrolysis with 1 M HCl, the aqueous phase was thoroughly extracted with CH_2Cl_2 and the combined organic phases were dried ($MgSO_4$). Evaporation of the solvent, column chromatography, and recrystallization from CH_2Cl_2/petroleum ether afforded (*rac*)-**7** (33.3 mg, 99.0 μmol, 97%) as fine colorless needles. **(B) By Fries Rearrangement of (*rac*)-8 Using $ZrCl_4$.** A suspension of $ZrCl_4$ (28.0 mg, 120 μmol) in 1 mL of dry CH_2Cl_2 was treated dropwise with (*rac*)-**8** (10.0 mg, 29.7 μmol) in 500 μL of CH_2Cl_2. The reaction mixture was stirred vigorously at room temperature for 15 h. Evaporation of the solvent and flash chromatography afforded (*rac*)-**8** (7.11 mg, 21.1 μmol, 71%) as a colorless powder, identical to the material obtained above. **(C) By Fries Rearrangement of (*rac*)-8 Using $TiCl_4$.** A 50-μL portion of a 1 M solution of $TiCl_4$ in benzene was treated dropwise with (*rac*)-**8** (7.00 mg, 20.8 μmol) in 200 μL of dry benzene and refluxed for 1 h. Evaporation of the solvent, column chromatography, and crystallization from CH_2Cl_2/petroleum ether afforded (*rac*)-**8** (5.88 mg, 17.5 μmol, 84%) as colorless needles, identical to the material obtained above: mp 202 °C; IR (KBr) ν 3400, 3020, 2980, 2945, 2920, 1600, 1580, 1550, 1265, 1205, 1120, 1105; ^1H NMR (250 MHz, $CDCl_3$) δ 2.25 (s, 3H), 2.70 (s, 3H), 3.73 (s, 3H), 4.03 (s, 3H), 6.15 (s, 1H), 7.28−7.46 (m, 4H), 7.77−7.84 (m, 2H), 13.87 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 20.3, 55.5, 55.7, 86.1, 106.1, 108.0, 124.5, 125.2, 125.7, 127.5, 128.1, 128.5, 129.4, 132.1, 132.9, 135.1, 163.3, 163.5, 163.7, 203.4; MS (EI) *m*/*z* 336 (60) $[M^{+\bullet}]$, 321 (100). Anal. Calcd for $C_{21}H_{20}O_4$: C, 74.98; H, 5.99. Found: C, 75.63; H, 6.13.

2′-Acetyl-3′,5′-dimethoxyphenyl 1-Bromo-2-naphthoate (10). A solution of 2-acetyl-3,5-dimethoxyphenol[18] (645 mg, 3.29 mmol) in 8 mL of THF was added within 20 min to a suspension of NaH (86.9 mg, 3.62 mmol) in 4 mL of dry THF at 0 °C and stirred at 0 °C for 1 h. A solution of 1-bromo-2-naphthoyl chloride[20] (887 mg, 3.29 mmol) in 12 mL of CH_2Cl_2 was added dropwise within 25 min and the mixture was stirred for 3 h at room temperature. The residue as obtained after evaporation of the solvent was dissolved in 20 mL of CH_2Cl_2 and washed twice with 5 mL of H_2O. The organic phase was separated and dried ($MgSO_4$). Evaporation of the solvent and recrystallization from CH_2Cl_2/petroleum ether yielded **8** (1.23 g, 2.87 mmol, 87%) as colorless crystals: mp 146 °C; IR (KBr) ν 3050, 3000, 2960, 2920, 2830, 1740, 1660, 1595, 1555, 1245, 1220, 1140, 1110, 1065; ^1H NMR (250 MHz, $CDCl_3$) δ 2.54 (s, 3H), 3.87 (s, 3H), 3.89 (s, 3H), 6.46 (d, J = 2.2 Hz, 1H), 6.43 (d, J = 2.2 Hz, 1H), 7.58−7.71 (m, 2H), 7.84−7.99 (m, 3H), 8.45−8.50 (m, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 32.0, 55.7, 55.9, 96.8, 100.1, 117.0, 123.3, 126.2, 128.1, 128.1, 128.3, 128.3,

---

(46) Bringmann, G.; Hartung, T.; Göbel, L.; Schupp, O.; Peters, K.; von Schnering, H. G. *Liebigs Ann. Chem.* **1992**, 769.

(47) Whitmore, F. C.; Carnahan, F. L. *J. Am. Chem. Soc.* **1929**, *51*, 856.

(48) Scholl, R. *Monatsh. Chem.* **1913**, *34*, 1011.

128.6, 130.2, 132.2, 135.5, 149.7, 159.5, 162.4, 165.3, 199.3; MS (EI) *m/z* 430/428 (3/2) [M$^{+\bullet}$], 349 (16), 235/233 (82/82), 126 (100). Anal. Calcd for $C_{19}H_{18}O_3$: C, 58.76; H, 3.99. Found: C, 59.05; H, 3.79.

1-Bromoanthraquinone-2-carboxylic Acid (16a). $CuSO_4\cdot 5H_2O$ (41.6 g, 165 mmol) and NaBr (25.7 g, 250 mmol) were dissolved with gentle heating in 150 mL of H_2O and treated dropwise with a solution of $Na_2SO_3\cdot 7H_2O$ (7.00 g, 17 mmol) in 50 mL of H_2O. The white precipitate of CuBr was filtered, washed twice with 50 mL of H_2O, and dissolved in 65 mL of HBr (48%).

A solution of **13 (**4.00 g, 15.0 mmol) in 60 mL of concentrated H_2SO_4 was diluted with H_2O until the acid began to precipitate. The acid was then redissolved by adding concentrated H_2SO_4. $NaNO_2$ (1.24 g, 18 mmol) was added at 0 °C and the mixture was stirred for 10 min and subsequently added dropwise at 0 °C to the above prepared solution of CuBr. The mixture was allowed to warm to room temperature, stirred 1 h at 60 °C, and afterward cooled to 0 °C. The precipitated solid was filtered and washed twice with 10 mL of H_2O to afford **16a** (4.56 g, 13.8 mmol, 93%) as a brown solid, which was crystallized from EtOH: mp 262−263 °C (lit.[47] 267−268 °C); IR (KBr) ν 3040, 1690, 1660, 1560; ^1H NMR (250 MHz, DMSO-d_6) δ 7.91−7.94 (m, 2H), 7.93 (d, J = 7.9 Hz, 1H), 8.14−8.20 (m, 2H), 8.28 (d, J = 7.9 Hz, 1H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 117.4, 126.2, 126.9, 127.0, 131.1, 131.9, 131.9, 134.1, 134.2, 134.8, 136.1, 144.6, 168.1, 181.1, 181.4; MS (EI) *m/z* 332/330 (58/57) [M$^{+\bullet}$], 304/302 (14/13), 287/285 (18/18) [M − CO_2H]$^+$, 150 (100).

1-Iodoanthraquinone-2-carboxylic Acid (16b). H_2O was added to a solution of **13** (100 mg, 374 μmol) in 1.5 mL of concentrated H_2SO_4 until the acid began to precipitate. The acid was then redissolved by addition of concentrated H_2SO_4, subsequently treated with $NaNO_2$ (31.0 mg, 449 μmol), and stirred at room temperature for 10 min. This solution was cooled to 0 °C and a solution of KI (200 mg, 1.2 mmol) in 2 mL of H_2O was added. The reaction mixture was allowed to warm to room temperature and stirred at 60 °C for 1 h. After cooling to 0 °C precipitated **16b** was filtered and recrystallized from EtOH to afford **16b** (96.0 mg, 254 μmol, 68%) as a yellow powder: mp 266−268 °C (lit.[48] 266−267 °C); IR (KBr) ν 3040, 2990, 1720, 1560, 1550; ^1H NMR (250 MHz, DMSO-d_6) δ 7.43 (d, J = 7.8 Hz, 1H) 7.84−7.95 (m, 2H), 8.11−8.19 (m, 2H), 8.13 (d, J = 7.9 Hz, 1H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 92.6, 126.0, 127.0, 127.3, 129.9, 132.1, 132.5, 132.6, 133.9, 134.0, 134.5, 171.2, 181.2, 182.2; MS (EI) *m/z* 378 (45) [M$^{+\bullet}$], 333 (3), 305 (4), 43 (100).

3′,5′-Dimethoxyphenyl 1-Bromoanthraquinone-2-carboxylate (14). A suspension of NaH (35.0 mg, 1.45 mmol) in 1 mL of THF was treated dropwise with a solution of **15** (186 mg, 1.21 mmol) in 2 mL of THF at 0 °C and stirred for 1 h at room temperature. A mixture of **16a** (400 mg, 1.20 mmol) was treated under nitrogen with 1.5 mL (2.22 g, 17.5 mmol) of $(COCl)_2$ in 8 mL of dry CH_2Cl_2 and 5 drops of dry DMF and refluxed for 1 h. The solvent and unreacted $(COCl)_2$ were evaporated. The residue was suspended in 10 mL of dry CH_2Cl_2 and added dropwise to the above prepared solution of the phenolate of **15**. The resulting mixture was stirred at room temperature for 3 h after which 2 mL of H_2O and 2 mL of 1 M HCl were cautiously added. The mixture was thoroughly extracted with CH_2Cl_2. Drying of the combined organic phases ($MgSO_4$), filtration through a silica gel column (petroleum ether/EtOAc = 8:2), and recrystallization from CH_2Cl_2/petroleum ether afforded **14** (378 mg, 810 μmol, 67%) as a yellow powder: mp 164−165 °C; IR (KBr) ν 3030, 2980, 2930, 2810, 1725, 1650, 1600, 1575, 1145, 1130 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3,79 (s, 6H), 6.37 (t, J = 2.2 Hz, 1H), 6.46 (d, J = 2.2 Hz, 2H), 7.76−7.82 (m, 2H), 7.89 (d, J = 8.0 Hz, 1H), 8.20−8.28 (m, 2H), 8.40 (d, J = 8.0 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 55.6, 98.7, 99.9, 119.9, 126.4, 126.9, 127.3, 127.8, 132.1, 132.7, 133.4, 134.2, 134.5, 134.9, 137.0, 142.5, 151.8, 161.3, 165.1, 181.4, 181.6; MS (EI) *m/z* 468/466 (2/2) [M$^{+\bullet}$], 387 (90), 315/313 (75/75), 150 (100). Anal. Calcd for $C_{23}H_{15}BrO_6$: C, 59.12; H, 3.24. Found: C, 59.22; H, 3.25.

1,3-Dimethoxy-6*H*-anthra[2,1-*c*]benzopyran-6,9,14-trione (17). A mixture of ester **14** (200 mg, 428 μmol), PPh_3 (22.5 mg, 85.6 μmol), $Pd(OAc)_2$ (9.7 mg, 42.8 μmol), and NaOAc (70.2 mg, 82.0 μmol) was heated at 60 °C for 1 h at 10^{-2} mbar. Freshly distilled DMA (4 mL) was added and the reaction mixture was stirred at 120 °C for 1 h. Evaporation of the solvent, column chromatography on silica gel (petroleum ether/EtOAc = 2:1), and recrystallization from CH_2Cl_2/petroleum ether afforded **17** (147 mg, 381 mmol, 89%) as a red powder: mp 279−280 °C; IR (KBr) ν 2930, 2900, 2830, 1730, 1660, 1600, 1580, 1250, 1145, 1100 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3,71 (s, 3H), 3.90 (s, 3H), 6.36 (d, J = 2.4 Hz, 1H), 6.55 (d, J = 2.4 Hz, 1H), 7.81−7.87 (m, 2H), 8.13−8.17 (m, 1H), 8.28−8.32 (m, 1H), 8.31 (d, J = 8.1 Hz, 1H), 8.54 (d, J = 8.1 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 55.3, 55.8, 93.6, 96.1, 102.5, 124.7, 125.5, 126.5, 127.2, 132.7, 132.9, 133.6, 134.6, 134.7, 135.6, 137.3, 153.7, 157.2, 160.3, 162.9, 182.3, 185.4; MS (EI) *m/z* 386 (10) [M$^{+\bullet}$], 355 (100), 340 (14). Anal. Calcd for $C_{23}H_{14}O_6$: C, 71.51; H, 3.65. Found: C, 71.27; H, 3.52.

(*rac*)-2-Hydroxymethyl-1-(2′,4′-dimethoxy-6′-hydroxyphenyl)-anthraquinone [(*rac*)-19]. A solution of 70.0 mg (181 μmol) of lactone **17** in 10 mL of dry THF was treated dropwise at 0 °C with 400 μmol of LAH (1.0 M solution in THF). After 3 h of stirring at this temperature, H_2O (10 mL) and aqueous HCl (1 M, 10 mL) were cautiously added and the suspension was thoroughly extracted with EtOAc (20 mL). Evaporation of the dried ($MgSO_4$) solvent and flash chromatography (silica gel, CH_2Cl_2/EtOAc = 7:3) afforded (*rac*)-**19** (50.2 mg, 128 μmol, 71%), which was crystallized from CH_2Cl_2/petroleum ether: mp 201 °C; IR (KBr) ν 3450, 2900, 1650, 1560, 1480, 1340, 1250, 1140, 1080 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$/DMSO-d_6) δ 3.44 (s, 3H), 3.69 (s, 3H), 4.24 (d, J = 15.0 Hz, 1H), 4.34 (d, J = 15.0 Hz, 1H), 6.01 (d, J = 2.1 Hz, 1H), 6.12 (d, J = 2.5 Hz, 1H), 7.54−7.59 (m, 2H,), 7.92−7.97 (m, 2H,), 8.07−8.10 (m, 1H), 8.24 (d, J = 7.9 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$/DMSO-d_6) δ 54.8, 55.2, 61.9, 90.3, 94.0, 107.1, 126.0, 126.7, 126.7, 131.3, 131.6, 132.5, 132.9, 133.1, 133.5, 133.7, 134.5, 149.7, 154.6, 157.2, 160.2, 183.1, 183.4; MS (EI) *m/z* 390 (36) [M$^{+\bullet}$], 359 (4) [M − CH_3O]$^+$, 341 (100). Anal. Calcd for $C_{23}H_{18}O_6$: C, 70.76; H, 4.65. Found: C, 70.20; H, 4.52.

Atroposelective Ring Cleavage of 17 (Analytical Scale). The solvent was removed in vacuo from a commercial solution of (*R*)-**18** (1.0 M in toluene, 39 μL, 39 μmol) and the residue was dissolved in dry THF (500 μL). This solution was treated under argon with a solution of the BH_3−THF complex (1.0 M in THF, 52 μL) and stirred for 30 min at room temperature. After dropwise addition of a suspension of the lactone **17** (5.00 mg, 12.9 μmol) in dry THF (500 μL), the solution was stirred for 21 h at this temperature, then H_2O (1 mL) and 2 M HCl (1 mL) were added, and the aqueous phase was extracted with EtOAc. The organic phase was purified by TLC (petroleum ether/EtOAc = 4:2) and the enantiomeric ratio of the product alcohols (*P*)- and (*M*)-**19** was determined by analytical HPLC to be 25:75.

Atroposelective Ring Cleavage of 17 (Preparative Scale). As described above, a solution of (*S*)-**18** (715 μmol) and the BH_3−THF complex (1.0 M in THF, 950 mL) in 1 mL of dry THF was prepared and stirred for for 30 min at room temperature. A solution of **17** (92.0 mg, 238 μmol) in dry THF (1 mL) was added dropwise at 0 °C, the solution was stirred for 2 h at this temperature, then H_2O (1 mL) and 2 M HCl (1 mL) were added, and the aqueous phase was thoroughly extracted with EtOAc. The combined organic phases were dried ($MgSO_4$) and the solvents were removed in vacuo. After flash chromatography of the residue on silica gel (CH_2Cl_2/EtOAc = 2:1), (*P*)-**19** (62.2 mg, 159 μmol, 67%) was obtained as a red powder (er 85:15): mp 193−202 °C; $[\alpha]^{22}_D$ = +26.1 (*c* 0.01, MeOH); the spectroscopic data were identical to those of (*rac*)-**19**.

***(M)*-9,10-Diacetoxy-2-acetoxymethyl-1-(2′-acetoxy-4′,6′-dimethoxyphenyl)-anthracene [*(M)*-20].** A solution of (*P*)-**19** (47.0 mg, 120 μmol, er 85:15) in 1.5 mL of Ac_2O and 2 mL of pyridine was stirred at 50 °C for 10 min and then treated with zinc dust (150 mg, 2.29 mmol). After further stirring for 15 min at this temperature, the zinc was removed by filtration, the mixture was poured onto ice (5 g), and 2 M HCl (5 mL) was added. Thorough extraction with EtOAc, drying of the combined organic extracts ($MgSO_4$), evaporation of the solvent, and subsequent flash chromatography (CH_2Cl_2/EtOAc = 10:1) yielded (*M*)-**20** (43.0 mg, 76.7 μmol, 64%) as a colorless solid, fluorescent at 366 nm: mp 185−190 °C; IR (KBr) ν 2958, 2927, 2856, 1766, 1735, 1619, 1365, 1263, 1197, 1090, 800; $[\alpha]^{22}_{D}$ = +30.9 (*c* 0.01, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (s, 3H), 1.84 (s, 3H), 2.07 (s, 3H), 2.65 (s, 3H), 3.67 (s, 3H), 3.89 (s, 3H), 4.82−5.00 (m, 2H), 6.52−6.54 (m, 2H), 7.44−7.52 (m, 2H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.7 (m, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 8.02 (d, *J* = 9.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 19.9, 20.8, 21.0, 55.7, 55.9, 64.1, 96.5, 114.3, 121.5, 122.00, 122.3, 124.6, 125.1, 126.6, 140.6, 168.4, 169.4, 170.7; MS (EI) *m/z* 560 (15) $[M^{+\bullet}]$, 518 (90), 476 (65), 374 (100). Anal. Calcd for $C_{31}H_{28}O_{10}$: C, 66.43; H, 5.00. Found: C, 66.23; H, 5.12.

(*rac*)-1-(2′,4′-Dimethoxy-6′-hydroxyphenyl)-2-methylanthraquinone [(*rac*)-21]. A solution of (*rac*)-**21** (15.0 mg, 38.4 μmol) in 600 μL of dry CH_2Cl_2 was treated at room temperature with polymer-bound PPh_3 (52.0 mg, 153.7 μmol) and stirred at this temperature for 15 min. Then 24.0 mg (73.7 μmol) of $(CBrCl_2)_2$ was added and the suspension was stirred for 10 min at room temperature. The mixture was filtered through a pad of Celite, which was subsequently thoroughly washed with CH_2Cl_2. The solvent of the combined organic phases was evaporated and the residue was dissolved in 4 mL of dry MeOH, after which Pd/C (10%, 5.00 mg) and 6.20 mg (75.6 μmol) NaOAc were added and the mixture was hydrogenated for 2 h at 2 bar. Filtration, evaporation of the solvent, and flash chromatography on silica gel (CH_2Cl_2/EtOAc = 7:3) afforded (*rac*)-**21** as a yellow oil (7.62 mg, 20.4 μmol, 53%), which was crystallized from CH_2Cl_2/petroleum ether: mp 180 °C; IR (KBr) ν 3400, 2960, 1650, 1575, 1310, 1280, 1140, 810 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.17 (s, 3H), 3.62 (s, 3H), 3.87 (s, 3H), 6.25 (d, *J* = 2.1 Hz, 1H,), 6.28 (d, *J* = 2.3 Hz, 1H), 7.70−7.73 (m, 3H), 8.10−8.15 (m, 1H), 8.22−8.26 (m, 1H), 8.32 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 20.6, 55.3, 55.7, 92.0, 93.6, 108.5, 126.6, 126.6, 127.4, 127.8, 132.8, 132.9, 133.2, 133.6, 134.0, 134.7, 135.5, 148.0, 153.1, 157.4, 160.9, 183.4, 183.8; MS (EI) *m/z* 374 (100) $[M^{+\bullet}]$, 343 (47) $[M - CH_3O]^+$, 315 (27). Anal. Calcd for $C_{23}H_{18}O_5$: C, 73.79; H, 4.85. Found: C, 74.07; H, 4.90.

(*rac*)-1-(2′-Acetoxy-4′,6′-dimethoxyphenyl)-2-methylanthraquinone [(*rac*)-22]. A solution of (*rac*)-**21** (18.1 mg, 48.4 μmol), 10.0 μL (9.52 mg, 159 μmol) of HOAc, and a catalytic quantity of DMAP in 500 μL of dry CH_2Cl_2 was treated at 0 °C with 32.8 mg (159 μmol) DCC. The mixture was stirred for 5 min at 0 °C and 1 h at room temperature. After filtration the solution was washed twice with aqueous HCl (0.5 M, 1 mL) and twice with a saturated solution of $NaHCO_3$ (1 mL) and subsequently dried ($MgSO_4$). Evaporation of the solvent and flash chromatography (silica gel, CH_2Cl_2/MeOH = 100:0.2) yielded (*rac*)-**22** (15.0 mg, 36.0 μmol, 75%) as a yellow solid: mp 218−220 °C; IR (KBr) ν 2910, 1740, 1650, 1570, 1310, 1280, 1190, 1140, 1115 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.73 (s, 3H), 2.16 (s, 3H), 3.71 (s, 3H), 3.88 (s, 3H), 6.40 (s, 1H), 6.54 (s, 1H), 7.65−7.74 (m, 3H), 8.12−8.17 (m, 1H), 8.24−8.27 (m, 1H), 8.30 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.2, 21.9, 55.5, 56.2, 90.9, 92.2, 93.3, 127.1, 127.2, 127.4, 127.4, 131.2, 133.3, 133.5, 133.5, 133.9, 134.0, 134.9, 145.3, 154.1, 156.8, 160.5, 171.7, 183.0, 183.4; MS (EI) *m/z* 417 (42) $[M^{+\bullet}]$, 375 (100), 344 (35). Anal. Calcd for $C_{25}H_{20}O_6$: C, 72.11; H, 4.84. Found: C, 72.10; H, 4.72.

(*rac*)-1-(5′-Acetyl-2′,4′-dimethoxy-6′-hydroxyphenyl)-2-methylanthraquinone [(*rac*)-23]. (A) By Friedel−Crafts Acylation of (*rac*)-21. A solution of (*rac*)-**21** (5.00 mg, 13.4 μmol) in 1 mL of dry CH_2Cl_2 was treated with 6 μL (10.3 mg, 54.4 μmol) of $TiCl_4$ at −10 °C and 2 μL (2.18 mg, 21.2 μmol) of Ac_2O and was stirred at this temperature for 30 min. After addition of H_2O (1 mL) and aqueous HCl (2 M, 1 mL) the aqueous phase was extracted thoroughly with EtOAc (5 mL). The combined organic phases were dried ($MgSO_4$) and the solvent was evaporated. Flash chromatography (CH_2Cl_2/EtOAc = 100:1) afforded (*rac*)-**23** (4.23 mg, 10.2 μmol, 76%) as a yellow powder. **(B) By Fries Rearrangement of (*rac*)-22.** A solution of (*rac*)-**22** (6.00 mg, 14.4 μmol) in 2 mL of dry toluene was treated under argon with 5 μL (8.65 mg, 45.6 μmol) of $TiCl_4$ and refluxed for 2 h. After hydrolysis with 2 mL of H_2O and 2 mL of aqueous HCl (2 M), the mixture was thoroughly extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$), the solvent was evaporated, and the crude product was purified by flash chromatography (CH_2Cl_2/EtOAc = 100:1) to afford (*rac*)-**23** (3.84 mg, 9.21 μmol, 64%), identical to the material obtained above. Mp 188 °C; IR (KBr) ν 3448, 2927, 2852, 1673, 1619, 1277, 1125, 716 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18 (s, 3H), 2.69 (s, 3H), 3.76 (s, 3H), 4.02 (s, 3H), 6.15 (s, 1H), 7.66−7.73 (m, 3H), 8.08−8.11 (m, 1H), 8.24−8.26 (m, 1H), 8.31 (d, *J* = 7.8 Hz, 1H), 13.89 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.6, 33.3, 55.4, 55.7, 86.3, 106.3, 109.6, 126.5, 127.3, 127.3, 132.1, 133.0, 133.0, 133.3, 133.8, 134.5, 134.8, 135.1, 146.8, 162.2, 162.3, 163.1, 183.6, 183.9, 203.6; MS (EI) *m/z* 416 (83) $[M^{+\bullet}]$, 401 (100), 385 (27). Anal. Calcd for $C_{25}H_{20}O_6$: C, 72.11; H, 4.84. Found: C, 72.14; H, 4.56.

3-Hydroxymethyl-1,8-dihydroxyanthraquinone (Aloe-emodin, 27) from 2. A solution of **2** (1.00 g, 3.94 mmol) in 30 mL of dry CCl_4 was treated under argon with NBS (771 mg, 4.33 mmol) and $(PhCO_2)_2$ (104 mg, 433 μmol) and refluxed for 6 h, after which the reaction mixture was allowed to cool to room temperature. The crude bromomethyl derivative as obtained after filtration and evaporation of the solvent was dissolved in 20 mL of dioxane. $CaCO_3$ (1.50 g, 15 μmol) and H_2O (20 mL) were added and the resulting mixture was stirred at 120 °C for 7 h. Evaporation of the solvent and subsequent flash chromatography on silica gel (CH_2Cl_2/EtOAc = 100:1) afforded **27** (756 mg, 2.80 mmol, 71%), which crystallized from EtOH: mp 223−224 °C (lit.[31] 213−214 °C).

1,8-Dihydroxy-3-methylanthraquinone (Chrysophanol, 2) from 27. A solution of **27** (1.00 g, 3.70 mmol) in 50 mL of dry CH_2Cl_2 was treated at room temperature with polymer-bound PPh_3 (1.89 g, 5.55 mmol) and stirred at this temperature for 15 min. $(CBrCl_2)_2$ (1.81 g, 5.55 mmol) was added and the suspension was stirred for 30 min at room temperature. The mixture was filtered through a pad of Celite and the Celite was washed thoroughly with CH_2Cl_2. The solvent of the combined organic phases was evaporated and the residue was suspended in 20 mL of dry MeOH. Pd/C (10%, 500 mg) was added and the mixture was hydrogenated for 1 h at 4 bar. Filtration and recrystallization from EtOH yielded **2** as a yellow solid (780 mg, 3.07 mmol, 83%): mp 196−197 °C (lit.[30] 194−195 °C).

8-Acetoxy-3-acetoxymethyl-2-bromo-1-hydroxyanthraquinone (29) (i.e., original protocol for the postulated synthesis of **30** from **28**[32]). A solution of **28** (100 mg, 282 μmol) in 3 mL of dry $CHCl_3$ and 1 mL of glacial HOAc was treated with acetamide (190 mg, 3.17 mmol) and 190 μL (592 mg, 3.70 mmol) of Br_2 in 1 mL of glacial HOAc. The mixture was refluxed for 9 h. After cooling to room temperature the organic phase was washed twice with 2 mL of H_2O and dried (Na_2SO_4). Evaporation of the solvent afforded **29** (120 mg, 276 μmol, 98%) (lit.[32] for **30**, 97%) as a yellow powder, which was crystallized from toluene: mp 205−206 °C (lit.[32] for **30**, 207−209 °C); IR (KBr) ν 3400, 3060, 2940, 2920, 1750, 1725, 1660, 1620, 1575, 1240, 1180; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.24 (s, 3H), 2.47 (s, 3H), 5.28 (s, 2H), 7.45 (dd, *J* = 8.2 Hz, *J* = 1.2 Hz, 1H), 7.84 (s, 1H), 7.85 (dd, *J* = 7.9 Hz, *J* = 7.9 Hz, 1H), 8.28 (dd, *J* = 7.9 Hz, *J* = 1.2 Hz, 1H), 13.34 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 20.8, 21.2, 65.3, 116.0, 117.9, 119.2, 124.3, 126.1, 130.5, 131.0, 135.1, 136.0, 145.0, 150.7, 159.1, 169.5, 170.3, 181.1, 187.5; MS (EI) *m/z* 434/432 (0.3/0.5) $[M^{+\bullet}]$, 353 (6), 348/346 (8/10), 311 (8), 269 (20), 43 (100). Anal. Calcd for $C_{19}H_{13}BrO_7$: C, 52.67; H, 3.02. Found: C, 52.57; H, 3.14.

3-Hydroxymethyl-1,8-diisopropoxyanthraquinone (31). A suspension of **27** (1.00 g, 3.70 mmol) in 10 mL of acetone was treated with Cs_2CO_3 (7.30 g, 22.2 mmol) and *i*-PrI (10 mL, 5.88 g, 35.0 mmol) and refluxed for 12 h. Evaporation of the solvent and column chromatography on silica gel (petroleum ether/EtOAc = 7:3) afforded 3-isopropoxymethyl-1,8-diisopropoxyanthraquinone (103 mg, 259 μmol, 7%) as a yellow oil and **31** (1.08 g, 3.03 mmol, 82%), which was obtained from CH_2Cl_2/petroleum ether as a yellow powder.

3-Isopropoxymethyl-1,8-diisopropoxyanthraquinone. IR (CCl_4) ν 3400, 2940, 2900, 2840, 1710, 1655, 1580, 1570, 1270, 1100 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.22 (d, J = 6.1 Hz, 6H), 1.42 (d, J = 6.0 Hz, 6H), 1.43 (d, J = 6.1 Hz, 6H), 3.68 (sept, J = 6.1 Hz, 1H), 4.52−4.68 (m, 2H), 4.56 (s, 2H), 7.27 (dd, J = 8.4 Hz, J = 0.8 Hz, 1H), 7.31−7.32 (m, 1H), 7.54 (dd, J = 7.8 Hz, J = 7.6 Hz, 1H), 7.73 (d, J = 1.5 Hz, 1H), 7.79 (dd, J = 7.6 Hz, J = 1.2 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 22.1, 68.2, 69.2, 73.1, 73.2, 118.6, 119.7, 120.5, 123.2, 128.6, 130.9, 133.2, 134.9, 135.1, 145.5, 157.9, 158.2, 182.8, 184.2; MS (EI) *m/z* 353 (12) $[M - C_3H_7]^+$, 311 (2), 149 (100). Anal. Calcd for $C_{24}H_{28}O_5$: C, 72.71; H, 7.12. Found: C, 72.41; H, 7.30.

3-Hydroxymethyl-1,8-diisopropoxyanthraquinone (31). Mp 118−119 °C; IR (KBr) ν 3400, 2940, 2900, 2840, 1710, 1655, 1580, 1570, 1270, 1100; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.43 (d, J = 6.1 Hz, 6H), 1.45 (d, J = 6.0 Hz, 6H), 4.62 (sept, J = 6.1 Hz, 1H), 4.63 (sept, J = 6.0 Hz, 1H), 4.77 (s, 2H), 7.29 (dd, J = 8.5 Hz, J = 1.0 Hz, 1H), 7.33 (d, J = 0.9 Hz, 1H), 7.56 (dd, J = 8.2 Hz, J = 7.8 Hz, 1H), 7.69 (m, 1H, 4-H), 7.79 (dd, J = 7.6 Hz, J = 1.2 Hz, 1H, 5-H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.7, 63.6, 72.5, 72.8, 116.5, 118.9, 119.4, 122.2, 123.6, 125.2, 133.1, 134.2, 134.5, 147.9, 157.5, 157.8, 182.0, 183.5; MS (EI) *m/z* 311 (55) $[M - C_3H_7]^+$, 270 (73), 241 (100). Anal. Calcd for $C_{21}H_{22}O_5$: C, 71.17; H, 5.97. Found: C, 71.08; H, 6.09.

1-Bromo-2-hydroxymethyl-4,5-diisopropoxyanthraquinone (33). A solution of **32** (54.0 mg, 152 μmol), 13.0 mg (158 μmol) NaOAc, and one crystal of I_2 in 6 mL of $CHCl_3$ was treated dropwise with 160 μL (160 μmol) of a solution of Br_2 in CCl_4 (1 M) and heated under reflux for 3 h. Evaporation of the solvent and column chromatography on silica gel (petroleum ether/EtOAc = 6:4) afforded **33** (21.1 mg, 48.6 μmol, 32%), which was crystallized from CH_2Cl_2/petroleum ether: mp 152−153 °C; IR (CCl_4) ν 3040, 2940, 2910, 1710, 1115, 1065 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.42 (d, J = 6.1 Hz, 6H), 1.44 (d, J = 6.0 Hz, 6H), 4.64 (sept, J = 6.1 Hz, 1H), 4.66 (sept, J = 6.1 Hz, 1H), 4.72 (s, 2H), 7.21 (dd, J = 8.4 Hz, J = 1.2 Hz, 1H), 7.51 (s, 1H), 7.54 (dd, J = 8.1 Hz, J = 7.7, 1H), 7.63 (dd, J = 7.7 Hz, J = 1.3, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 22.0, 65.0, 73.3, 73.6, 119.1, 120.6, 121.6, 125.7, 127.3, 128.8, 130.9, 133.4, 136.7, 156.7, 156.8, 181.9, 184.4; MS (EI) *m/z* 391/389 (100/97) $[M - C_3H_7]^+$, 350/348 (68/81) 269 (70). HRMS calcd for $C_{21}H_{21}BrO_5$ 442.2354, found: 442.2355.

3-Acetoxymethyl-1,8-diisopropoxyanthraquinone (32). A mixture of **27** (14.8 g, 54.8 mmol), Cs_2CO_3 (258 g, 785 mmol), and *i*-PrI (200 mL, 340 g, 2.00 mol) in 200 mL of acetone was refluxed for 48 h. The crude product, as obtained after filtration and evaporation of the solvent, was dissolved in 150 mL of Ac_2O and treated with 5 mL of pyridine. The mixture was stirred for 5 h at 70 °C and subsequently poured onto 500 g of crushed ice for hydrolysis of the Ac_2O. The suspension was then stirred at 50 °C for 30 min. After cooling to room temperature crystallization was completed at 0 °C. Filtration and subsequent recrystallization from EtOH afforded **32** (17.0 g, 42.8 mmol, 78%) as a yellow powder: mp 155 °C; IR (KBr) ν 2940, 2900, 1715, 1655, 1585, 1570, 1420, 1270, 1220, 1030 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.45 (d, J = 6.1 Hz, 6H), 1.45 (d, J = 6.0 Hz, 6H), 2.16 (s, 3H), 4.58−4.68 (m, 2H), 5.16 (s, 2H), 7.25 (m, 1H, 2-H), 7.30 (dd, J = 8.2 Hz, J = 1.2 Hz, 1H), 7.57 (dd, J = 8.2 Hz, J = 8.4 Hz, 1H), 7.79−7.83 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 20.9, 22.0, 65.3, 73.2, 73.4, 118.2, 119.4, 121.4, 122.8, 125.6, 125.9, 133.3, 135.0, 135.2, 141.7, 157.9, 158.2, 170.6, 181.7, 184.0; MS (EI) *m/z* 396 (0.3) $[M^{+\bullet}]$, 353 (76), 270 (100). Anal. Calcd for $C_{23}H_{24}O_6$: C, 69.68; H, 6.10. Found: C, 69.18; H, 6.36.

2-Acetoxymethyl-1,8-dibromo-4,5-diisopropoxyanthraquinone (34). A mixture of **32** (10.7 g, 27.1 mmol) and NaOAc (11.1 g, 136 mmol) in 75 mL of $CHCl_3$ and 75 mL of CCl_4 was treated with Br_2 (11.2 mL, 34.7 g, 217 mmol) and refluxed for 3 h. After cooling to room temperature the reaction mixture was washed twice with a saturated aqueous $NaHSO_3$ solution (50 mL) and twice with H_2O (50 mL). The organic phase was dried ($MgSO_4$) and the solvent was evaporated. Recrystallization of the residue from EtOH afforded **34** (11.7 g, 21.1 mmol, 89%) as a yellow powder: mp 148 °C; IR (KBr) ν 2950, 1750, 1720, 1600, 1250, 1200, 1020 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.40 (d, J = 6.1 Hz, 6H), 1.41 (d, J = 6.1 Hz, 6H), 2.18 (s, 3H), 4.51−4.63 (m, 2H), 5.26 (s, 2H), 7.03 (d, J = 9.3 Hz, 1H), 7.24 (s, 1H), 7.71 (d, J = 9.0 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.0, 22.0, 65.9, 73.8, 74.0, 110.6, 111.1, 121.2, 121.9, 127.3, 127.9, 135.6, 136.2, 139.1, 142.4, 155.8, 156.0, 170.4, 180.6, 184.7; MS (EI) *m/z* 556/554/552 (1/2/1) $[M^{+\bullet}]$, 513/511/509 (23/44/20), 349/347 (79/89), 43 (100). Anal. Calcd for $C_{23}H_{22}Br_2O_6$: C, 49.84; H, 4.00. Found: C, 49.71; H, 4.00.

1,8-Dibromo-4,5-diisopropoxyanthraquinone-2-carboxylic Acid (36). A mixture of **34** (10.0 g, 18.1 mmol) and 10 mL of aqueous NaOH (5%) in 400 mL of MeOH was stirred at 70 °C for 2 h. After evaporation of the solvent the residue was dissolved in 100 mL of EtOAc and washed twice with 70 mL of H_2O. Drying ($MgSO_4$) of the organic phase and evaporation of the solvent yielded 1,8-dibromo-4,5-diisopropoxy-2-hydroxymethylanthraquinone (8.43 g, 16.7 mmol, 91%) as a red oil, which was crystallized from CH_2Cl_2/petroleum ether: mp 114−116 °C; IR (KBr) ν 3400, 2940, 1650, 1550, 1250, 1180, 1090, 1020 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.38 (d, J = 6.0 Hz, 6H), 1.39 (d, J = 6.1 Hz, 6H), 4.81 (s, 2H), 4.50−4.67 (m, 2H), 7.02 (d, J = 9.0 Hz, 1H), 7.44 (s, 1H), 7.69 (d, J = 9.0 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.0, 63.8, 72.5, 72.7, 108.4, 109.5, 118.5, 120.9, 125.3, 126.9, 134.5, 134.5, 137.9, 146.4, 154.9, 155.0, 179.9, 183.7; MS (EI) *m/z* 514/512/510 (2/4/3) $[M^{+\bullet}]$, 471/469/467 (41/76/42), 430/428/426 (50/100/62). Anal. Calcd for $C_{21}H_{20}Br_2O_5$: C, 49.25; H, 3.94. Found: C, 49.11; H, 3.68.

A solution of 1,8-dibromo-4,5-diisopropoxy-2-hydroxymethylanthraquinone (8.00 g, 15.6 mmol) in 200 mL of CH_2Cl_2 was treated with activated MnO_2 (6.81 g, 78.1 mmol) and stirred at room temperature for 1 h, after which more activated MnO_2 (2.72 g, 31.2 mmol) was added. Filtration of the mixture over a Celite pad and evaporation of the solvent afforded 7.40 g (14.5 mmol, 93%) 1,8-dibromo-3-formyl-4,5-diisopropoxyanthraquinone, which was crystallized from EtOH: mp 169−171 °C; IR (KBr) ν 2950, 2940, 2850, 1675, 1555, 1270, 1190, 960, 920 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.39 (d, J = 6.1 Hz, 6H), 1.41 (d, J = 6.1 Hz, 6H), 4.66 (sept, J = 6.1 Hz, 1H), 4.69 (sept, J = 6.1 Hz, 1H), 7.04 (d, J = 8.2 Hz, 1H), 7.64 (s, 1H), 7.72 (d, J = 9.1 Hz, 1H), 10.54 (s, 1H, CHO); ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.8, 21.9, 73.4, 73.7, 110.4, 114.1, 119.3, 121.7, 127.5, 131.1, 135.4, 136.7, 137.5, 139.3, 155.7, 156.0, 180.2, 183.7, 191.4; MS (EI) *m/z* 512/510/508 (1/2/1) $[M^{+\bullet}]$, 469/467/465 (17/33/18), 428/426/424 (53/100/45). Anal. Calcd for $C_{21}H_{20}Br_2O_5$: C, 49.44; H, 3.56. Found: C, 49.21; H, 3.57.

A solution of the above prepared 1,8-dibromo-3-formyl-4,5-diisopropoxyanthraquinone in 300 mL of dioxane was treated with a solution of NaOAc (4.42 g, 53.9 mmol) in 100 mL of H_2O and 100 mL of HOAc, a solution of amidosulfuric acid (2.62 g, 27.0 mmol) in 200 mL of H_2O, and with a solution of $NaClO_2$ (80% technical grade, 2.44 g, 27.0 mmol) in 200 mL of H_2O and stirred at room temperature for 90 min. The solution was concentrated in vacuo to 200 mL and extracted twice with 50 mL of CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), the solvent was evaporated, and the residue was crystallized from EtOH to afford **36** (7.09 g, 13.5 mmol, 97%) as a yellow powder: mp 191−192 °C; IR (KBr) ν

2950, 2900, 1690, 1675, 1435, 1320, 1190, 920 cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$) δ 1.38 (d, J = 6.2 Hz, 6H), 1.39 (d, J = 6.1 Hz, 6H), 4.50−4.64 (m, 2H), 7.02 (d, J = 9.2 Hz, 1H), 7.38 (s, 1H), 7.70 (d, J = 8.6 Hz, 1H); ^{13}C NMR (63 MHz, CDCl$_3$) δ 21.9, 73.7, 73.7, 107.9, 110.4, 120.8, 121.7, 127.6, 128.6, 135.6, 136.7, 139.1, 141.0, 155.4, 155.9, 168.1, 180.3, 184.3; MS (EI) m/z 527/525/523 (3/4/2) [M$^{+\bullet}$], 485/483/481 (17/30/15), 444/442/440 (56/100/51). Anal. Calcd for $C_{21}H_{18}Br_2O_6$: C, 47.94; H, 3.45. Found: C, 47.68; H, 3.42.

3′,5′-Dimethoxyphenyl 1,8-Dibromo-4,5-diisopropoxyanthraquinone-2-carboxylate (35). A solution of **36** (6.00 g, 11.4 mmol), **15** (2.11 g, 13.7 mmol), and DMAP (100 mg, 819 μmol) in 5 mL of dry CH_2Cl_2 and 1 mL of dry DMF was treated at 0 °C under argon with 2.82 g (13.7 mmol) DCC. The mixture was stirred for 5 min at 0 °C and 30 min at room temperature. After filtration the solution was washed twice with aqueous HCl (0.5 M, 1 mL) and twice with a saturated solution of $NaHCO_3$ (1 mL). The organic phase was dried ($MgSO_4$), the solvent evaporated and the residue crystallized from EtOH to yield **35** (6.67 g, 10.3 mmol, 90%) as a yellow powder: mp 155−156 °C; IR (KBr) ν 2960, 2905, 1730, 1675, 1600, 1480, 1370, 1145 cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$) δ 1.41 (d, J = 5.9 Hz, 6H), 1.43 (d, J = 5.9 Hz, 6H), 3.75 (s, 3H), 4.52−4.71 (m, 2H), 6.40 (t, J = 2.3 Hz, 1H), 6.46 (d, J = 2.1 Hz, 2H), 7.04 (d, J = 9.1 Hz, 1H), 7.43 (s, 1H), 7.73 (d, J = 8.9 Hz, 1H); ^{13}C NMR (63 MHz, CDCl$_3$) δ 21.9, 55.6, 73.6, 74.0, 98.7, 99.9, 108.1, 110.5, 120.9, 121.7, 127.5, 129.2, 135.5, 136.7, 139.3, 139.9, 151.9, 155.6, 156.0, 161.3, 164.6, 180.9, 183.9; MS (EI) m/z 649/647/645 (0.2/0.5/0.2) [M$^+$ − CH$_3$]$^+$, 621/619/617 (1/2/1), 583/581 (100/93). Anal. Calcd for $C_{21}H_{20}Br_2O_5$: C, 52.59; H, 3.96. Found: C, 52.06; H, 3.97.

General Procedure for the Intramolecular Coupling of 35 (Table 2). A flame-dried flask was charged with **35** (1.0 equiv), the specified catalyst [$PdCl_2(PPh_3)_2$ or $Pd(OAc)_2/PPh_3$ (ratio 1/2)], and the specified base (2 equiv) and dried in vacuo (10^{-2} mbar) for 1−2 h at 60 °C. Dry DMA was added to yield a suspension approximately 0.05 M of **35**. The mixture was degassed three times and heated under argon for the specified time at 120−130 °C before it was allowed to cool to room temperature. The mixture was diluted with EtOAc, washed sequentially with 2 M HCl and saturated aqueous NaCl solution, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography on silica gel (CH_2Cl_2/EtOAc = 100:2) gave the lactones **37c**, **37a**, and **37b** in this order of elution with the specified yields.

13-Phenyl-1,3-dimethoxy-8,10-diisopropoxy-6*H*-anthra[2,1-*c*]benzopyran-6,9,14-trione (37c): mp 174−182 °C; IR (KBr) ν 3050, 3030, 2950, 2905, 1715, 1665, 1605, 1430, 1300, 1095, 815 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.48 (d, J = 6.1 Hz, 12H), 3.20 (s, 3H), 3.78 (s, 3H), 4.64−4.81 (m, 2H), 5.94 (d, J = 2.3 Hz, 1H), 6.42 (d, J = 2.3 Hz, 1H), 7.26−7.36 (m, 3H), 7.29 (d, J = 8.7 Hz, 1H), 7.48 (d, J = 8.6 Hz, 1H), 7.57−7.59 (m, 2H), 7.93 (s, 1H,); ^{13}C NMR (101 MHz, CDCl$_3$) δ 22.1, 21.9, 55.6, 57.4, 73.1, 73.2, 93.5, 96.7, 102.9, 116.8, 124.1, 125.4, 126.8, 127.4, 128.1, 129.3, 131.2, 132.2, 134.9, 137.8, 138.5, 139.6, 152.2, 155.5, 156.3, 156.4, 160.6, 161.4, 182.0, 184.5; MS (EI) m/z 578 (25) [M$^{+\bullet}$], 547 (35), 505 (61), 463 (100). Anal. Calcd for $C_{35}H_{30}O_8\cdot 1/2CH_2Cl_2$ (content of CH_2Cl_2 confirmed by ^{1}H NMR on material freshly dissolved in CDCl$_3$): C, 68.65; H, 5.03. Found: C, 68.40; H, 5.25.

13-Bromo-1,3-dimethoxy-8,10-diisopropoxy-6*H*-anthra[2,1-*c*]benzopyran-6,9,14-trione (37a): mp 138 °C; IR (KBr) ν 2950, 1710, 1660, 1190, 1100 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 1.40−1.56 (m, 12H), 3.67 (s, 3H), 3.87 (s, 3H), 4.64 (sept, J = 6.1 Hz, 1H), 4.77 (sept, J = 6.1 Hz, 1H), 6.35 (d, J = 2.3 Hz), 6.53 (d, J = 2.3 Hz, 1H), 7.12 (d, J = 9.2 Hz, 1H), 7.80 (d, J = 8.9 Hz, 1H), 7.94 (s, 1H); ^{13}C NMR (63 MHz, CDCl$_3$) δ 19.2, 21.9, 22.4, 55.8, 57.7, 73.1, 73.3, 93.8, 96,4, 102.5, 110.2, 116.7, 121.3, 123.6, 125.6, 128.0, 128.7, 133.0, 137.9, 139.2, 152.4, 155.6, 155.9, 156.9, 160.4, 161.8, 180.1, 184.4; MS (EI) m/z 582/580 (5/5) [M$^{+\bullet}$], 509/507 (9/6), 467/465 (15/11), 183 (100). Anal. Calcd for $C_{29}H_{25}BrO_8$: C, 59.91; H, 4.33. Found: C, 59.66; H, 4.25.

1,3-Dimethoxy-8,10-diisopropoxy-6*H*-anthra[2,1-*c*]benzopyran-6,9,14-trione (37b): mp 175 °C; IR (KBr) ν 2950, 2910, 1708, 1660, 1602, 1576, 1214, 1100,732 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.43−1.55 (m, 12H), 3.66 (s, 3H), 3.87 (s, 3H), 4.67 (sept, J = 6.0 Hz, 1H), 4.78 (sept, J = 6.0 Hz, 1H), 6.33 (d, J = 2.5 Hz, 1H), 6.52 (d, J = 2.5 Hz, 1H), 7.28 (dd, J = 7.8 Hz, J = 2.0 Hz), 7.57−7.64 (m, 2H), 7.99 (s, 1H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 21.8, 22.0, 22.0, 22.1, 55.5, 55.7, 72.9, 73.1, 93.7, 96.0, 102.4, 117.7, 118.0, 120.8, 124.0, 125.3, 125.5, 129.3, 133.6, 136.6, 136.7, 152.7, 156.2, 156.3, 157.6, 160.4, 161.7, 180.6, 186.7; MS (EI) m/z 502 (22) [M$^{+\bullet}$], 471 (8), 429 (60), 387 (100). Anal. Calcd for $C_{29}H_{26}O_8$: C, 69.31; H, 5.21. Found: C, 69.48; H, 5.18.

(*P*)-8-Bromo-4,5-diisopropoxy-1-(2′,4′-dimethoxy-6′-hydroxyphenyl)-2-hydroxymethylanthraquinone [(*P*)-38]. As described for **17**, a solution of (*S*)-**18** (360 μmol) and the BH$_3$−THF complex (1.0 M in THF, 480 μL) in 1 mL of dry THF was prepared and stirred for 30 min at room temperature. After dropwise addition of a solution of the lactone **37a** (69.8 mg, 120 μmol) in dry THF (1 mL) at 0 °C, the mixture was stirred for 1 h at this temperature, then H_2O (1 mL) and 2 M HCl (1 mL) were added, and the aqueous phase was thoroughly extracted with EtOAc. The combined organic phases were dried ($MgSO_4$) and the solvents were removed in vacuo. After flash chromatography of the residue on silica gel (CH_2Cl_2/EtOAc = 7:3), (*P*)-**38** (56.9 mg, 97.2 mmol, 81%) was obtained as a yellow solid (er 98:2). Crystallization from CH_2Cl_2/Et_2O/hexane yielded yellow crystals (45.6 mg, 77.9 mmol, 65%; er > 99.5:0.5): mp 122−124 °C; $[\alpha]^{20}_{D}$ = −28 (c 0.01, MeOH); IR (KBr) ν 3120, 2950, 1660, 1570, 1190, 1090 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.37−1.44 (m, 12H), 3.59 (s, 3H), 3.76 (s, 3H), 4.33 (d, J = 13.7 Hz, 1H), 4.42 (d, J = 13.7 Hz, 1H), 4.55 (sept, J = 5.8 Hz, 1H), 4.67 (sept, J = 5.8 Hz, 1H), 6.12 (d, J = 1.8 Hz, 1 H), 6.20 (d, J = 1.8 Hz, 1H), 6.97 (d, J = 8.8 Hz, 1H), 7.43 (s, 1H), 7.60 (d, J = 8.8 Hz, 1 H); ^{13}C NMR (63 MHz, CDCl$_3$) δ 21.9, 22.0, 55.1, 55.6, 62.8, 72.7, 73.5, 91.3, 94.1, 105.7, 109.8, 118.9, 121.3, 122.4, 124.6, 128.0, 135.6, 137.4, 138.4, 148.0, 154.9, 155.8, 155.8, 157.2, 160.7, 182.4, 186.3; MS (EI) m/z 586/584 (54/54) [M$^{+\bullet}$], 543/541 (44/39), 495/493 (20/19), 453/451 (100/100). Anal. Calcd for $C_{29}H_{29}BrO_8$: C, 59.50; H, 4.99. Found: C, 59.59; H, 4.74.

Oxidation and Recyclization of 38 Back to Lactone 37a. A solution of **38** (10.0 mg, 17.1 μmol, as obtained from the mother liquor) in 10 mL of CH_2Cl_2 was treated with MnO_2 (50.0 mg, 581 μmol) and stirred at room temperature for 2 h. After filtration through a Celite pad the solvent was evaporated in vacuo and the residue was dissolved in 1 mL of dioxane. A solution of NaOAc (13.0 mg, 158 μmol) in 0.5 mL of HOAc and 0.5 mL of H_2O, 6.2 mg (63.8 μmol) amidosulfuric acid, and 6.0 mg (66.4 μmol) $NaClO_2$ (80% technical grade) were added and the resulting mixture was stirred at room temperature for 30 min. The solvent was evaporated, and the residue was dissolved in 5 mL of CH_2Cl_2 and washed twice with 5 mL of H_2O. After evaporation of the dried ($MgSO_4$) solvent the residue was dissolved in 2 mL of CH_2Cl_2 and treated under argon at 0 °C with 6.0 mg (29.1 μmol) DCC and a catalytic quantity of DMAP, and the mixture was stirred for 1 h at room temperature. Evaporation of the solvent and purification by flash chromatography (silica gel, CH_2Cl_2/EtOAc = 100:2) yielded **37a** (7.1 mg, 12.2 μmol, 71%) as a red solid, identical to the material obtained above.

13-Bromo-1,3-dimethoxy-8,10-diisopropoxy-9-hydroxy-6*H*-anthra[2,1-*c*]benzopyran-6,14-dione (41). A mixture of **37a** (20.0 mg, 34.4 μmol) and Pd/C (10%, 3.67 mg) in 0.8 mL of NEt_3 and 0.1 mL of DMF was treated under argon with 1.45 μL of formic acid, stirred at 50 °C for 135 min, and allowed to cool to room temperature. After addition of 1 mL of 1 M HCl, the mixture was thoroughly extracted with EtOAc. Drying of the combined organic phases ($MgSO_4$), evaporation of the solvent, and flash chromatography (silica gel, CH_2Cl_2/EtOAc

= 100:2) afforded **41a** (13.0 mg, 22.3 μmol, 65%), which crystallized from CH_2Cl_2/petroleum ether as yellow needles: mp 174 °C; IR (KBr) ν 3463, 3097, 2979, 2932, 1731, 1686, 1619, 1450, 1272, 1112, 947, 815; ^1H NMR (250 MHz, $CDCl_3$) δ 1.43−1.57 (m, 12H), 3.70 (s, 3H), 3.86 (s, 3H), 4.70 (sept, *J* = 6.0 Hz, 1H), 4.87 (sept, *J* = 6.0 Hz, 1H), 6.33 (d, *J* = 2.4 Hz, 1H), 6.41 (s, 1H), 6.52 (d, *J* = 2.3 Hz, 1H), 7.02 (d, *J* = 9.4 Hz, 1H), 7.71 (d, *J* = 9.9 Hz, 1H), 7.86 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 22.3, 22.5, 22.7, 56.1, 57.9, 58.7, 72.1, 72.3, 94.0, 96.4, 103.3, 111.3, 113.6, 118.2, 123.3, 125.3, 132.6, 133.8, 136.1, 136.2, 152.9, 154.4, 155.7, 156.6, 161.7, 161.9, 185.4; MS (EI) *m/z* 584/582 (46/60) [$M^{+\bullet}$], 553/551 (55/55), 536/534 (47/46), 493/491 (76/72), 451/449 (100/88). Anal. Calcd for $C_{29}H_{27}BrO_8$: C, 59.70; H, 4.66. Found: C, 59.63; H, 4.38.

Reductive Cleavage of (*M*)-38. To a solution of (*M*)-**38** (20.0 mg, 34.2 μmol) in 2 mL of 5% NaOH was added $Na_2S_2O_4$ (180 mg, 1.03 mmol) and the mixture was stirred at 50 °C for 1 h. The solution was acidified and thoroughly extracted with EtOAc. Evaporation of the dried extract and purification by flash chromatography on silica gel (CH_2Cl_2/MeOH = 100:0 → 100:2) afforded **15** (2.8 mg, 18.1 μmol, 53%) and **31** (4.6 mg, 13.0 μmol, 38%). Compounds **15** and **31** were found to be identical to an authentic sample (Fluka) and synthetic material (see above) by TLC and ^1H NMR.

13-Bromo-1,3-dimethoxy-8,10-diisopropoxy-6*H*-anthra[2,1-*c*]benzopyran-9,14-dione (42). A solution of (*P*)-**38** (20.0 mg, 34.2 μmol) in 1 mL of dry CH_2Cl_2 was treated at room temperature with polymer-bound PPh_3 (46.3 mg, 136 μmol) and stirred at this temperature for 15 min. $(CBrCl_2)_2$ (21.4 mg, 65.6 μmol) was added and the suspension stirred for 10 min at room temperature. The mixture was filtered through a pad of Celite, which was washed thoroughly with CH_2Cl_2. The solvent of the combined organic phases was evaporated and the residue was dissolved in 4 mL of dry MeOH. Pd/C (10%, 5.00 mg) and 20 μL of NEt_3 were added and the mixture was hydrogenated for 15 min at 3.5 bar. Filtration, evaporation of the solvent, and flash chromatography on silica gel (CH_2Cl_2/EtOAc = 7:3) afforded **42** as a yellow oil (10.5 mg, 18.5 μmol, 54%), which was crystallized from CH_2Cl_2/petroleum ether: mp 123 °C; IR (KBr) ν 2940, 2900, 1660, 1590, 1430, 1260, 1190, 1140, 1090, 1040; ^1H NMR (600 MHz, CD_3SOCD_3) δ 1.28 (d, *J* = 6.1 Hz, 3H), 1.31 (d, *J* = 6.0 Hz, 3H), 1.34 (d, *J* = 6.0 Hz, 3H), 1.39 (d, *J* = 6.1 Hz, 3H), 3.58 (s, 3H), 3.80 (s, 3H), 4.65−4.71 (m, 2H), 4.66 (d, *J* = 13.4 Hz, 1H), 4.99 (d, *J* = 14.1 Hz, 1H), 6.26 (d, *J* = 2.3 Hz, 1H), 6.34 (d, *J* = 2.3 Hz, 1H), 7.37 (s, 1H), 7.38 (d, *J* = 9.2 Hz, 1H), 7.89 (d, *J* = 9.0 Hz, 1H); coalescence of the diastereotopic benzylic protons at 4.66 and 4.99 ppm was nearly reached at 140 °C; ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.9, 22.1, 22.2, 55.5, 57.0, 69.5, 73.6, 73.8, 94.2, 94.8, 106.6, 110.5, 115.8, 119.4, 121.9, 124.5, 129.5, 133.4, 135.9, 138.7, 141.7, 155.6, 156.1, 156.6, 158.1, 161.2, 181.2, 184.9; MS (EI) *m/z* 568/566 (53/53) [$M^{+\bullet}$], 526/524 (13/13), 495/493 (77/75), 453/451 (100/97). HRMS calcd for $C_{29}H_{27}BrO_7$ 566.0940, found: 566.0933.

(*P*)-4,5-Diisopropoxy-1-(2′,4′-dimethoxy-6′-hydroxyphenyl)-2-methylanthraquinone [(*P*)-40]. Crude (*M*)-**39**, prepared as described above for **42** from (*P*)-**38** (80.0 mg, 137 μmol), polymer-bound PPh_3 (185 mg, 544 μmol), and $(CBrCl_2)_2$ (85.6 mg, 262 μmol), was dissolved in 10 mL of dry MeOH. Pd/C (10%, 20.0 mg) and 26.8 mg (151 μmol) NaOAc were added and the mixture was hydrogenated for 2 h at 3.5 bar. Filtration, evaporation of the solvent, and flash chromatography on silica gel (CH_2Cl_2/EtOAc = 7:3) afforded (*P*)-**40** (32.2 mg, 65.6 μmol, 48%) as a yellow oil: $[\alpha]^{22}_D$ = +88 (*c* 0.01, MeOH); IR (KBr) ν 3380, 2940, 2903, 1650, 1580, 1305, 1220, 905 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.40−1.49 (m, 12H), 2.08 (s, 3H), 3.60 (s, 3H), 3.84 (s, 3H), 5.52−4.70 (m, 2H), 6.18 (d, *J* = 2.3 Hz, 1H), 6.27 (d, *J* = 2.1 Hz, 1H), 6.97 (s, 1H), 7.06 (d, *J* = 9.1 Hz, 1H), 7.73 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.9, 22.0, 22.1, 55.5, 56.3, 73.2, 92.4, 93.2, 119.4, 120.1, 122.9, 123.5, 123.7, 126.0, 127.5, 133.1, 134.8, 135.1, 144.3, 153.9, 156.8, 157.8, 158.0, 160.7, 181.2; MS (EI) *m/z* 490 (54) [$M^{+\bullet}$], 447 (100), 405 (27). Anal. Calcd for $C_{29}H_{27}BrO_7$: C, 71.01; H, 6.16. Found: C, 70.62; H, 5.95.

(*P*)-6′-*O*-Methylknipholone [(*P*)-1c]. A solution of (*P*)-**40** (25.0 mg, 50.9 μmol) in 1 mL of CH_2Cl_2 was cooled to −20 °C, treated with $TiCl_4$ (35 μL, 60.1 mg, 334 μmol), and then allowed to warm to room temperature over a period of 2 h. 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 flash chromatography (silica gel, CH_2Cl_2/EtOAc = 10:2) yielded (*P*)-4,5-dihydroxy-1-(2′,4′-dimethoxy-6′-hydroxyphenyl)-2-methylanthraquinone (18.4 mg, 45.3 μmol, 89%) as a red amorphous solid: $[\alpha]^{23}_D$ = −31 (*c* 0.021, MeOH); IR (KBr) ν 3443, 2927, 2852, 1629, 1583, 1459, 1098, 800 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.09 (s, 3H), 3.62 (s, 3H), 3.85 (s, 3H), 6.22 (d, *J* = 2.3 Hz, 1H), 6.25 (d, *J* = 2.3 Hz, 1H), 7.21 (dd, *J* = 8.1 Hz, *J* = 1.5 Hz, 1H), 7.23 (s, 1H), 7.58 (dd, *J* = 7.8, *J* = 7.8, 1H), 7.62 (dd, *J* = 7.5 Hz, *J* = 1.5 Hz, 1H), 11.99 (s, 1H), 12.58 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.0, 55.3, 55.7, 91.9, 93.7, 108.0, 115.1, 115.6, 120.0, 123.6, 125.4, 127.3, 132.4, 152.5, 153.5, 157.5, 160.8, 161.8, 162.8, 182.6, 192.9; MS (EI) *m/z* 406 (7.3) [$M^{+\bullet}$], 375 (5) [$M^+ - OCH_3$], 56 (100). Anal. Calcd for $C_{23}H_{18}O_7$: C, 67.98; H, 4.46. Found: C, 67.72; H, 4.17.

A solution of (*P*)-4,5-dihydroxy-1-(2′,4′-dimethoxy-6′-hydroxyphenyl)-2-methylanthraquinone (20.0 mg, 49.2 μmol) in 1 mL of dry CH_2Cl_2 was treated at −20 °C with 11 μL (18.7 mg, 99.3 μmol) of $TiCl_4$ and 9 μL (10.1 mg, 98.4 μmol) of Ac_2O, stirred at this temperature for 10 min, and allowed to warm to room temperature over 110 min. After addition of H_2O (1 mL) and aqueous HCl (2 M, 1 mL) the aqueous phase was extracted thoroughly with EtOAc (5 mL). The combined organic phases were dried ($MgSO_4$) and the solvent was evaporated. Flash chromatography (silica gel, CH_2Cl_2/EtOAc = 10:2) afforded (*P*)-**1c** (18.0 mg, 40.3 μmol, 82%) as red solid: mp 262−263 °C (lit.[9] 255−260 °C); $[\alpha]^{22}_D$ = +121 (*c* 0.01, $CHCl_3$) (lit.[9] +130, *c* 0.2, $CHCl_3$); IR (KBr) ν 2925, 2847, 1616, 1593, 1461, 1278, 1211, 1128, 796 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.11 (s, 3H), 2.67 (s, 3H), 3.77 (s, 3H), 4.00 (s, 3H), 6.13 (s, 1H), 7.21 (dd, *J* = 8.1 Hz, *J* = 1.7 Hz, 1H), 7.24 (d, *J* = 0.8 Hz, 1H), 7.56 (dd, *J* = 7.8 Hz, *J* = 7.6 Hz, 1H), 7.60 (dd, *J* = 7.6 Hz, *J* = 1.7 Hz, 1H), 12.07 (s, 1H), 12.59 (s, 1H), 13.88 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.0, 33.3, 55.4, 55.7, 86.3, 106.3, 109.0, 115.0, 115.7, 119.7, 123.5, 125.2, 128.4, 131.4, 134.7, 136.8, 151.5, 161.8, 162.4, 162.5, 162.6, 163.1, 182.5, 193.0, 199.2; MS (EI) *m/z* 448 (99) [$M^{+\bullet}$], 433 (100).

(*M*)-4′-*O*-Demethylknipholone [(*M*)-1d]. A solution of **1c** (5.00 mg, 11.2 μmol) in 1 mL of chlorobenzene was treated under argon with $AlBr_3$ (30.0 mg, 112 μmol) and stirred at 80 °C for 1.5 h. After cooling to room temperature 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 extracts, evaporation of the solvent, and purification by preparative HPLC afforded (*M*)-**1d** (2.92 mg, 6.94 μmol, 62%) as a red solid: mp 216−217 °C (lit.[10] 210−212 °C); $[\alpha]^{23}_D$ = +113 (*c* 0.01, MeOH) (lit.[10] +104, *c* 0.02, MeOH); IR (KBr) ν 3431, 2928, 2840, 1676, 1622, 1282, 1200, 1135 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 2.14 (s, 3H), 2.66 (s, 3H), 6.05 (s, 1H), 7.24 (dd, *J* = 8.3 Hz, *J* = 1.3 Hz, 1H), 7.26 (s, 1H), 7.54 (dd, *J* = 7.6 Hz, *J* = 1.0 Hz, 1H), 7.65 (dd, *J* = 8.3 Hz, *J* = 7.6 Hz, 1H), 8.85 (s, 1H), 11.97 (s, 1H), 12.51 (s, 1H), 14.19 (s, 1H); ^{13}C NMR (101 MHz, CD_3OD) δ 21.4, 33.4, 95.9, 103.5, 107.6, 116.8, 120.2, 120.5, 124.6, 125.7, 130.1, 133.2, 136.0, 138.5, 153.3, 160.8, 162.5, 162.7, 163.1, 163.3, 183.6, 194.0, 204.4; MS (EI) *m/z* 420 (56) [$M^{+\bullet}$], 405 (26), 44 (100).

(*M*)-Knipholone [(*M*)-1a]. To a solution of (*P*)-**1c** (10.0 mg, 22.3 μmol) in 1 mL of chlorobenzene was added $AlBr_3$ (36.0 mg, 134 μmol) in four equal portions over a period of 2 h in a way that after each addition at room temperature, the reaction mixture was heated to 80 °C for 15 min, after which it was cooled again down to room temperature in order to add the next portion of $AlBr_3$ and then the mixture was again stirred at 80 °C. After cooling to room temperature, 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 extracts, evaporation of the solvent, and purification by preparative HPLC afforded (*M*)-**1a** (3.84 mg, 9.14 μmol, 41%) as a red solid, which was crystallized from CH_2Cl_2/petroleum ether: mp 219−220 °C (lit.[5] 225 °C); $[\alpha]^{22}_{D} = +78$ (*c* 0.01, MeOH) (lit.[5] +80, *c* 0.01, MeOH); IR (KBr) ν 3442, 2928, 1682, 1397, 1200, 1135 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 2.14 (s, 3H), 2.66 (s, 3H), 6.05 (s, 1H), 7.24 (dd, $J = 8.3$ Hz, $J = 1.3$ Hz, 1H), 7.26 (s, 1H), 7.54 (dd, $J = 7.6$ Hz, $J = 1.0$ Hz, 1H), 7.65 (dd, $J = 8.3$ Hz, $J = 7.6$ Hz, 1H), 8.85 (s, 1H), 11.97 (s, 1H), 12.51 (s, 1H), 14.19 (s, 1H); ^{13}C NMR (101 MHz, CD_3OD) δ 21.4, 33.4, 95.9, 103.5, 107.6, 116.8, 120.2, 120.5, 124.6, 125.7, 130.1, 133.2, 136.0, 138.5, 153.3, 160.8, 162.5, 162.7, 163.1, 163.3, 183.6, 194.0, 204.4; MS (EI) *m/z* 434 (100) $[M^{+\bullet}]$, 419 (79), 401 (14).

(*M*)-Knipholone Anthrone [(*M*)-1b]. To a solution of (*M*)-**1a** (2.12 mg, 4.88 μmol) in 2 mL of glacial HOAc was added 2 mL of 40% $SnCl_2$ solution in concentrated HCl. The resulting solution was refluxed for 2 h, cooled, and poured into 20 mL of brine and the whole was thoroughly extracted with EtOAc. Evaporation of the combined dried extracts and chromatography on silica gel (CH_2Cl_2/MeOH = 100:0.5) afforded (*M*)-**1b** (1.32 mg, 3.14 μmol, 64%) as a red solid, which was crystallized from acetone/petroleum ether: mp 236−237 °C (lit.[8] 240−242 °C); $[\alpha]^{23}_{D} = +183$ (*c* 0.001, acetone) (lit.[8] +200, *c* 0.001, Me_2O); IR (KBr) ν 3200, 1605, 1450, 1410, 1360, 1265, 1110 cm^{-1}; ^1H NMR (600 MHz, CD_3SOCD_3) δ 2.03 (s, 3H), 2.61 (s, 3H), 3.92 (s, 3H), 3.94 (s, 1H), 3.97 (s, 1H), 6.26 (s, 1H), 6.87 (dd, $J = 8.2$ Hz, $J = 0.7$ Hz, 1H), 6.90 (s, 1H), 6.92 (dd, $J = 7.7$ Hz, $J = 1.0$ Hz, 1H), 7.52 (dd, $^3J = 8.0$ Hz, $^3J = 7.8$ Hz, 1H), 10.6 (s, 1H), 12.2 (s, 1H), 12.3 (s, 1H), 14.2 (s, 1H); ^{13}C NMR (151 MHz, CD_3SOCD_3) δ 20.5, 30.9, 32.6, 55.7, 91.1, 95.9, 103.5, 104.8, 114.8, 115.0, 115.9, 119.3, 124.0, 136.4, 141.2, 142.4, 148.8, 161.4, 161.7, 162.3, 162.7, 163.7, 193.4, 202.6; MS (EI) *m/z* 420 (100) $[M^{+\bullet}]$, 405 (15), 378 (7), 239 (93).

Biological Experiments. *Plasmodium falciparum.* Antiplasmodial activity was determined using the K1 strain (resistant to chloroquine and pyrimethamine). A modification of the $[^3H]$-hypoxanthine incorporation assay[49] was used.[50] 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. From the sigmoidal inhibition curve the IC_{50} value was calculated. The assays were run in duplicate and repeated at least once.

Trypanosoma cruzi. Rat skeletal myoblasts (L-6 cells) were seeded in 96-well microtiter plates at 2000 cells/well/100 μL in RPMI 1640 medium with 10% FBS and 2 mM L-glutamine. After 24 h 5000 trypomastigotes of *T. cruzi* (Tulahuen strain C2C4 containing the galactosidase (Lac Z) gene) were added. The plates were incubated at 37 °C in 5% CO_2 for 2 d before the medium was removed and replaced by a serial 3-fold drug dilution. After another incubation period of 4 d, the substrate CPRG/Nonidet was added to the wells. The color reaction that developed during the following 2−4 h was read photometrically at 540 nm. IC_{50} values were calculated from the sigmoidal inhibition curve. Cytotoxicity was assessed in the same assay using noninfected L-6 cells and the same serial drug dilution. The MIC was determined microscopically after 4 d.

Trypanosoma b. rhodesiense. Minimum Essential Medium (50 μL) supplemented according to Baltz et al.[51] with 2-mercaptoethanol and 15% heat-inactivated horse serum was added to each well of a 96-well microtiter plate. Serial drug dilutions were added to the wells. Then 50 μL of trypanosome suspension (*T. b. rhodesiense* STIB 900) were added to each well and the plate incubated at 37 °C under a 5% CO_2 atmosphere for 72 h. Alamar Blue (10 μL) was added to each well and incubation was continued for a further 2−4 h. The plate was then read at an excitation wavelength of 530 nm and an emission wavelength of 590 nm.[52] Fluorescence development was expressed as percentage of the control, and IC_{50} values were determined.

Leishmania donovani. Mouse peritoneal macrophages were seeded in RPMI 1640 medium with 10% heat-inactivated FBS into 16-chamber slides. After 24 h *L. donovani* amastigotes (strain MHOM-ET-67/L82) were added at a ratio of 3:1 (amastigotes to macrophages). The medium containing free amastigotes was replaced by fresh medium 4 h later. The next day the medium was replaced by fresh medium containing different drug concentrations. The slides were incubated at 37 °C under a 5% CO_2 atmosphere for 96 h. Then the medium was removed, and the slides were fixed mith MeOH and stained with Giemsa. The ratio of infected to noninfected macrophages was determined microscopically, expressed as percentage of the control, and the IC_{50} value was calculated by linear regression.

Computational Methods. The conformational analysis of (*P*)-**19** was performed using the semiempirical AM1[53] method as implemented in the program package Vamp 6.5[54] starting from geometries preoptimized by the Tripos[55] force field.

The molecular dynamics simulations of **1a** and **1b** were performed using the MM3[45] force field as implemented in the molecular modeling package Sybyl 6.7,[55] with a time step of 2 fs. Bond lengths were constrained using the SHAKE algorithm.[56] The molecule was weakly coupled to a virtual thermal bath at $T = 300$ K,[57] with a temperature relaxation time $\tau = 0.2$ ps.

The wave functions for the calculation of the rotational strengths for the electric transitions from the ground state to excited states were obtained by CNDO/S-CI calculations[58,59] with a CI expansion including 576 singly occupied configurations and the ground state determinant. These calculations were carried out by the use of the BDZDO/MCDSPD[59] program package. For a better visualization, the rotational strengths were transformed into $\Delta\epsilon$ values and superimposed with a Gaussian band shape function.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft (SFB 347 and Graduiertenkolleg “Elektronendichte”), the Fonds der Chemischen Industrie, the DAAD (fellowship to D.M.), and the UNDP/World Bank/WHO Special Programme. Particular thank is due to Elke Gobright and Christian Scheurer for carrying out the in vitro assays and to

---

(49) Desjardins, R. E.; Canfield, C. J.; Haynes, D.; Chulay, J. *Antimicrob. Agents Chemother.* **1979**, *16*, 710.

(50) Ridley, R. G.; Hofheinz, W.; Matile, H.; Jacquet, C.; Dorn, A.; Masciadri, R.; Jolidon, S.; Richter, W. F.; Guenzi, A.; Girometta, M. A.; Urwyler, H.; Huber, W.; Thaitong, S.; Peters, W. *Antimicrob. Agents Chemother.* **1996**, *40*, 1846.

(51) Baltz, T.; Baltz, D.; Giroud, C.; Crockett, J. *EMBO J.* **1985**, *4*, 1273.

(52) Räz, B.; Iten, M.; Grether-Bühler, Y.; Kaminsky, R.; Brun, R. *Acta Trop.* **1997**, *68*, 139.

(53) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

(54) Rauhut, G.; Chandrasekhar, J.; Alex, A.; Beck, B.; Sauer, W.; Clark, T. *VAMP 6.5*; Oxford Molecular Ltd., The Medewar Centre, Oxford Science Park, Sandford-on-Thames, Oxford, OX4 4GA, England.

(55) *SYBYL*; Tripos Associates, 1699 St. Hanley Road, Suite 303, St. Louis, MO 63144.

(56) van Gunsteren, W. F.; Berendsen, H. J. C. *Mol. Phys.* **1977**, *34*, 1311.

(57) Berendsen, H. J. C.; Postma, J. P. M.; van Gunsteren, W. F.; DiNola, A.; Haak, J. R. *J. Chem. Phys.* **1984**, *81*, 3684.

(58) Del Bene, J.; Jaffé, H. H. *J. Chem. Phys.* **1968**, *48*, 1807.

(59) Downing, J. W., Program Packet BDZDO/MCDSPD, Department of Chemistry and Biochemistry, University of Colorado, Boulder, USA.; modified by Fleischhauer, J.; Schleker, W.; Kramer; B.; ported to Linux by Gulden, K.-P.

Valeska Barthel for technical support. B.M.A. is grateful to the University of Botswana for a useful grant, and M.B. thanks Deutscher Akademischer Austauschdienst–Natural Products Research Network for Eastern and Central Africa (DAAD-NAPRECA) for a fellowship.

Supporting Information Available: Copies of the ^{1}H and ^{13}C NMR spectra for **33** and **42** and X-ray crystallographic data for **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO020189S