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Studies toward the Total Synthesis of Mumbaistatin, a Highly Potent Glucose-6-phosphate Translocase Inhibitor. Synthesis of a Mumbaistatin Analogue

Florian Kaiser,[†] Lothar Schwink,[‡] Janna Velder,[†] and Hans-Günther Schmalz*,[†]

Institut für Organische Chemie, Universität zu Köln, Greinstrasse 4, D-50939 Köln, Germany, and Aventis Pharma Deutschland GmbH, Industriepark Hoechst, G838, D-65926 Frankfurt am Main, Germany

schmalz@uni-koeln.de

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A strategy for the total synthesis of the highly potent glucose-6-phosphate translocase inhibitor mumbaistatin (**1**) and structural analogues was elaborated. Such compounds represent a lead structure in the development of potential new drugs for the treatment of diabetes. To evaluate the general strategy, the close mumbaistatin analogue **10** was synthesized in a convergent manner. The anthraquinone building block **20** was efficiently prepared via aryne/phthalide annulation. After conversion of **20** into the corresponding 9,10-dimethoxyanthracene-1-carbaldehyde derivative (**13**), coupling with a lithiated arene (**12**) and subsequent multiple oxidation under Jones conditions yielded the mumbaistatin analogue **10**. The preparation of the functionalized arene intermediates was achieved exploiting highly regioselective bromination and *ortho*-lithiation reactions.

Introduction

With more than 200 million people afflicted worldwide, *diabetes mellitus* is the most common of the endocrine diseases. Most of the patients (almost 90%) are suffering from type 2 diabetes, the non-insulin-dependent diabetes mellitus (NIDDM).[1] While the type 1 diabetes and some of the type 2 patients need insulin, NIDDM is commonly treated with diet and with oral hypoglycemic agents. As recent studies[2] suggest, controlling hyperglycemia in NIDDM is often not possible, not even by intensive pharmacological intervention with insulin or common antidiabetic agents (such as sulfonylureas). Therefore, the search for new improved therapeutic approaches represents an extremely important goal.

To reduce fasting blood glucose in NIDDM, hepatic glucose production is an attractive target for therapeutic intervention.[3] The two metabolic ways by which the liver produces glucose are gluconeogenesis and glycogenolysis. The final step of both of these pathways, the cleavage of glucose-6-phosphate (G6P) to liberate glucose, is catalyzed by the same enzyme, i.e., glucose-6-phosphatase (G6Pase).[4] One part of this multicomponent enzyme system is the transport protein glucose-6-phosphate translocase (G6P-T1), which mediates the entry of G6P through the membrane into the endoplasmic reticulum. Accordingly, inhibitors of G6P-T1 are of outstanding interest as potential drugs for the treatment of diabetes type 2 by regulating hepatic glucose production.

In recent years, several natural products have been identified as selective inhibitors of G6P-T1.[5] These include the weak but selective compound chlorogenic acid[6] (which served as a lead structure for the development of some highly potent G6P-T1 inhibitors)[7] and the kodaistatins[8] A and C, which exhibit IC_{50} values in the 100 nM range (Figure 1). However, the most powerful natural inhibitor of G6P-T1 known to date ($IC_{50} = 5$ nM) is mumbaistatin (**1**), a compound which was isolated in 1997 by Ramakrishna et al. (Aventis Pharma) from cultures of *Streptomyces* sp. DSM 11641.[9] The structure of this acid-labile diketoacid was disclosed in 2001.[10] The

[†] Universität zu Köln.
[‡] Aventis Pharma Deutschland GmbH.

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(9) Ramakrishna, N. V. S.; Swamy, K. H. S.; Kumar, E. K. S. V.; Kushwaha, M. M. S.; Kota, S.; Raman, M.; Tare, S. D.; Deshmukh, S. K.; Schummer, D.; Kurz, M.; Kogler, H. Patents PTC/EP99/04127 and WO 99-67408 A1.

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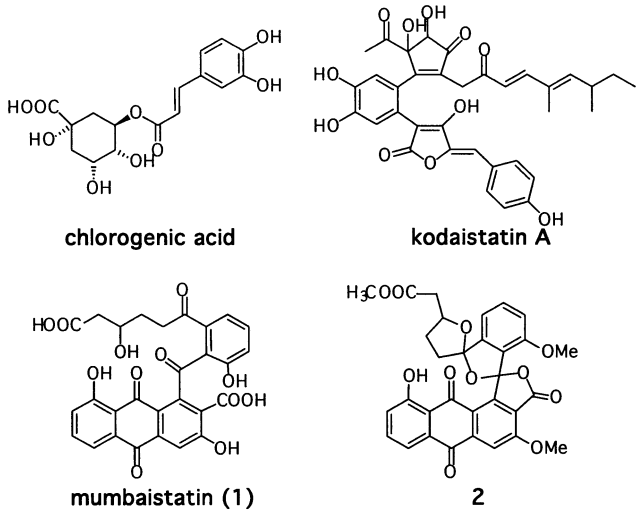
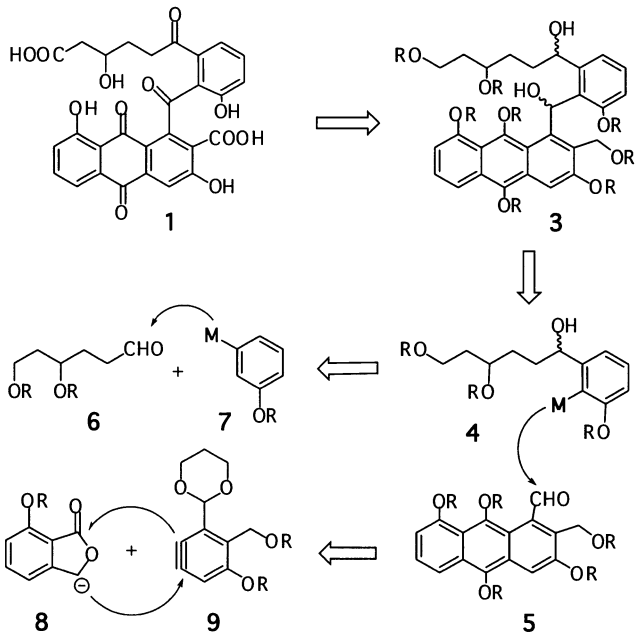


FIGURE 1. Natural G6P-T1 inhibitors chlorogenic acid, kodaistatin A, mumbaistatin (**1**), and the methylated dispiroketal **2** derived from **1**.

structure elucidation is based on extensive 2D-NMR spectroscopy and on a single-crystal X-ray structure analysis of the dispiroketal **2**, a triply methylated dehydration product obtained (among other compounds) from **1** by treatment with diazomethane in methanol. The absolute configuration of the side chain stereocenter in **1** is uncertain. It was only tentatively assigned as *S* by comparison with the configuration of juglomycin D,[11] a known naphthoquinone antibiotic which was also isolated from the same fermentation.

Mumbaistatin (**1**) shows a completely new and exciting structure. The molecule comprises an anthraquinone moiety similarly substituted as some known anthraquinones, for example, aloesapponarin 1[12] and K1115A.[13] The other subunit is a novel aromatic diketocarboxylic acid. Mumbaistatin can be regarded as a tetra-*ortho*-substituted benzophenone, which is a common biosynthetic intermediate of xanthones, spirocoumarins, and other aromatic polyketides.[14] It has been suggested that *o*-carboxybenzophenones are biosynthetically formed by oxidative cleavage of anthraquinones.[15] Thus, one might suggest that mumbaistatin derives from an (up to now unknown[16]) angucylic bisanthraquinone precursor formed from a single polyketide chain. Alternatively, it cannot be excluded that mumbaistatin may be formed by condensation of two C_{14}-polyketide moieties related to juglomycin C, an abundant metabolite of *Streptomyces* cultures.[11]

SCHEME 1. General Retrosynthetic Scheme for a Synthesis of Mumbaistatin (1)



Besides the general challenge to synthesize an important and demanding new target molecule, a total synthetic approach toward mumbaistatin would also serve several specific goals: First, it would provide an additional proof of its structure including the absolute configuration. Second, a flexible synthetic approach to this new lead structure would pave the way for the synthesis of simplified analogues, which could then be screened to study structure−activity relationships (SARs) and to identify new compounds as potential antidiabetic drugs.

In this work, we disclose the results of a synthetic study which so far has culminated in the total synthesis of a closely related analogue of mumbaistatin.

General Strategic Considerations

The main challenges in the synthesis of mumbaistatin are (1) the preparation of the highly substituted anthraquinone moiety, (2) the connection of the two aromatic parts to establish the tetra-*ortho*-substituted benzophenone substructure, and (3) the setup of the acid- and base-sensitive diketoacid structure without triggering an intramolecular aldol reaction or dispiroketal formation. Thus, a synthetic tactic should be applied in which the sensitive functionalities are released at a very late stage of the synthesis. Therefore, we envision employing a compound of type **3** as the pretarget molecule (Scheme 1), in which all the carbonyl groups are masked as protected or free alcohols and could be set free in the final steps of the synthesis through an oxidation/deprotection cascade. For the connection of the two aromatic parts we intend to react a metalated intermedi-

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(12) (a) Yagi, A.; Makino, K.; Nishioka, I. *Chem. Pharm. Bull.* **1974**, *22*, 1159−1166. (b) Mammo, W.; Dagne, E.; Steglich, W. *Phytochemistry* **1992**, *31*, 3577−3582. (c) Roberge, G.; Brassard, P. *Synthesis* **1979**, 148−150. (d) Cameron, D. W.; Deutscher, D. J.; Feutrill, G. I.; Griffith, P. G. *Aust. J. Chem.* **1981**, *34*, 2401−2421.

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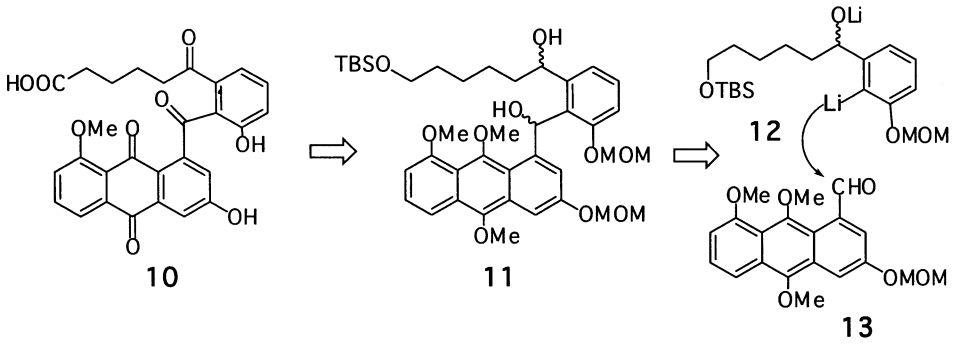
(15) For an example of the oxidative generation of tetra-*ortho*-substituted benzophenones from anthraquinones by mimicking this biosynthetic pathway, see: Franck, B.; Berger-Lohr, B. *Angew. Chem.* **1975**, *87*, 845−846.

(16) For an example of an angucyclic "triple-anthraquinone" natural product derived from juglomycin, see: Costa, M. A. C.; Silva, A. M. S.; Alves, A. C.; Seabra, R. S. *Nat. Prod. Lett.* **1999**, *13*, 269−276.

SCHEME 2. A Strategy for the Synthesis of the Mumbaistatin Analogue 10



ate of type **4** with an anthracenecarbaldehyde of type **5** to form a benzhydrol. This strategy seems particularly promising because related arylanion−benzaldehyde approaches have been successfully used before in the synthesis of sterically highly hindered benzophenones,[17] including the prominent natural product balanol.[18]

While the building block **4** could be prepared from a side chain aldehyde (**6**) and a metalated arene (**7**) in a straightforward manner, the construction of the anthraquinone unit is less obvious. After analyzing several alternatives, we aim to use a convergent approach[19] in which the central ring is constructed. For instance, nucleophilic addition of a phthalide anion to an (in situ generated) aryne represents an attractive possibility (Scheme 1).[20]

A Plan for the Synthesis of a Mumbaistatin Analogue

To probe the general feasibility of the chosen strategy (Scheme 1), we decided in the study reported here to first focus on the simplified mumbaistatin analogue **10**, which could also be of value for SAR studies. As shown in Scheme 2, the retrosynthetic analysis for this compound leads back to the tri-*ortho*-substituted benzhydrol derivative **11**, which in turn should result from the attack of an aryllithium species (**12**) on the anthracene-1-carbaldehyde **13** as a masked anthraquinone. The lithiated intermediate **12** could be generated by either *ortho*-lithiation or bromine−lithium exchange from a corresponding arene or bromoarene precursor. As a protecting group for the two phenolic OH groups of **10**, the MOM group was considered to be particularly suitable because the deprotection should be possible under mild Lewis acidic conditions.

Preparation of an Anthraquinone Building Block

As a precursor of the fully protected aldehyde building block **13** (Scheme 2), we intended to prepare anthraquinone **20** (Scheme 3) according to the concept shown in Scheme 1. Because aryl bromides are easily accessible precursors for arynes, we considered **17**, in which both the phenol and the benzaldehyde are protected as an acetal, as a suitable intermediate for the formal cycloaddition step leading to **20**. Halogenation of 3-hydroxybenzaldehyde **14** afforded the known bromide **15**,[21] which was converted into the doubly protected derivative **17** in almost quantitative yield (Scheme 3).

For the anticipated anthraquinone formation, which is based on the early work of Hauser, Kraus, Kelly, and others about annulation reactions using phthalide anions[24a] or cycloadditions involving isobenzofurans,[24b] two alternative protocols involving arynes are known in the literature: While Sammes[22] employed deprotonated phthalides (such as **18)** in the reaction with the aryne, Biehl[23] introduced stabilized anions derived from cyanophthalides (such as **19**) for the same purpose.

Thus, for the preparation of **20** the two phthalides **18**[25] and **19**[26] were employed, which were synthesized according to literature procedures[25d,26b] involving *ortho*-lithi-

(17) (a) Townsend, C. A.; Graybill, T. L.; Casillas, E. G.; Pal, K. *J. Am. Chem. Soc.* **1912**, *34*, 7729−7746. (b) Katoh, T.; Ohmuri, O. *Tetrahedron Lett.* **2000**, *41*, 465−469. (c) Katoh, T.; Ohmuri, O.; Iwasaki, K.; Inoue, M. *Tetrahedron* **2002**, *58*, 1289−1299. (d) Iikubo, K.; Ishikawa, Y.; Ando, N.; Umezawa, K.; Nishiyama, S. *Tetrahedron Lett.* **2002**, *43*, 291−293.

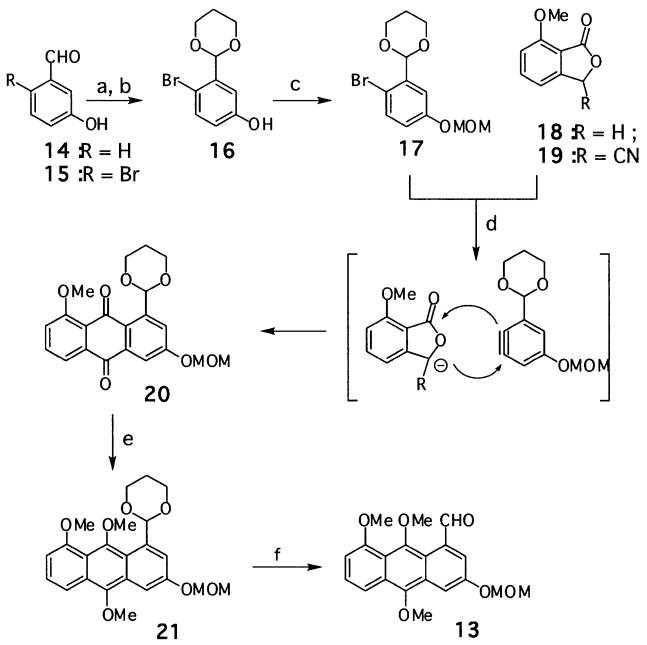
(18) Several tactics for the assembly of the benzophenone part of balanol have been developed. (a) Reaction of aryllithium compounds with benzaldehydes followed by oxidation: Hollinshead, S. P.; Nichols, J. B.; Wilson, J. W. *J. Org. Chem.* **1994**, *59*, 6703−6709. (b) Anionic homo-Fries rearrangement: Lampe, J. W.; Hughes, P. F.; Biggers, C. K.; Smith, S. H.; Hu, H. *J. Org. Chem.* **1996**, *61*, 4572−4581. Nicolaou, K. C.; Bunnage, M. E.; Koide, K. *Chem.—Eur. J.* **1995**, *1*, 454−466. (c) Reaction of a phenyl Grignard reagent with a benzoyl chloride: Adams, C. P.; Fairway, S. M.; Hardy, C. J.; Hibbs, D. E.; Hursthouse, M. B.; Morley, A. D.; Sharp, B. W.; Vicker, N.; Warner, I. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2355−2362. (d) Cleavage of $FeCp^+$-complexed xanthones: Andersson, C.-M.; Storm, J. P. *J. Org. Chem.* **2000**, *65*, 5264−5274. (e) Intramolecular Heck reaction with subsequent olefin cleavage: Skrydstrup, T.; Denieul, M.-P.; Laursen, B.; Hazell, R. *J. Org. Chem.* **2000**, *65*, 6052−6060. Laursen, B.; Denieul, M.-P.; Skrydstrup, T. *Tetrahedron* **2002**, *58*, 2231−2238. However, many other approaches failed due to the strong sterical hindrance of the tetra-*ortho*-substituted benzophenone system, and examples can be found in the literature cited above.

(19) For reviews about the synthesis of anthraquinones/anthracyclines, see: (a) Krohn, K. *Angew. Chem.* **1986**, *98*, 788−805; *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 790−807. (b) Krohn, K. *Tetrahedron* **1990**, *46*, 291−318. For reviews about the synthesis of angucyclines, see: (c) Krohn, K. *Eur. J. Org. Chem.* **2002**, 1351−1362. (d) Krohn, K.; Rohr, J. *Top. Curr. Chem.* **1997**, *188*, 127−196. For general reviews about quinones, see: (e) Owton, M. W. *J. Chem. Soc., Perkin Trans.* **1999**, 2409−2420. (f) Thomson, R. H. *Naturally Occuring Quinones: Recent Advances*, 4th ed.; Blackie Academic & Professional: London, 1997. (g) Thomson, R. H. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1992; Vol. 9, pp 311−531. (h) Gallagher, P. T. *Contemp. Org. Synth.* **1996**, *3*, 433−446.

(20) For general reviews, see: (a) Hoffman, R. W. *Dehydrobenzene and cycloalkynes*; Academic Press: New York, 1967. (b) Kessar, S. V. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, pp 483−515. For reviews dealing with the use of arynes in total synthesis, see: (c) Biehl, E. R.; Khanapure, S. P. *Acc. Chem. Res.* **1989**, *22*, 275−281. (d) Castedo, L.; Guitian, E. *Stud. Nat. Prod. Chem.* **1989**, *3*, 417−454.

(21) (a) Danckwortt, P. *Ber. Dtsch. Chem. Ges.* **1910**, *42*, 4163−71. For a recent reexamination of the regioselectivity of the bromination of 3-hydroxybenzaldehyde, see: (b) Léo, P.-M.; Morin, C.; Philouze, C. *Org. Lett.* **2002**, *4*, 2711−2714.

SCHEME 3[a]



[a] Reagents and conditions: (a) Br_2, $CHCl_3/CH_3CN$ (10:1), 3 h, rt, 78%; (b) $HO(CH_2)_3OH$, catalytic *p*TsOH, benzene/THF, 24 h, reflux, 99%; (c) NaH, (MOM)Cl, DMF, 98%; (d) **18**, 4 equiv of LiTMP, THF, −78 °C, then 2 equiv of **17**, −43 °C to rt, then air, 45%, or **19**, 4 equiv of LiTMP, THF, −78 °C, then 2 equiv of **17**, −43 °C to rt, 35%; (e) $Na_2S_2O_4$, KOH, Bu_4NBr, Me_2SO_4, THF/H_2O, 65%; (f) 10% aqueous H_2SO_4 adsorbed onto silica, CH_2Cl_2, 3 d, rt, 81%.

ation reactions.[27] The "cycloaddition" reactions were performed by preformation of the respective phthalide anion at −78 °C (4 equiv of base) followed by addition of **17** and allowing the mixture to warm to room temperature. When **18** was employed, a stream of air was bubbled through the crude reaction mixture to oxidize the primary product to the anthraquinone. To our disappointment, all the reactions proceeded rather sluggishly, affording the desired product **20** only in low yield. Various bases and conditions were tested. With LiTMP, the anthraquinone **20** was formed, whereas other nonnucleophilic bases were not suitable (LiHMDS) or gave even lower yields (LDA; LIDACOR = LDA/KO*t*Bu). To obtain acceptable results, 2 equiv of the aryne precursor **17** was necessary. Fortunately, the more accessible phthalide **18** gave slightly better yields (45%) than the cyanophthalide **19** (35%). The annulation proved to be highly regioselective, giving the "head to head" product **20** as the only detected product.[28] The observed regioselectivity corresponds to an attack of the phthalide anion at the less electron-rich position of the aryne as indicated in Scheme 2. The structure of the anthraquinone **20** was unequivocally proven by means of a crystal structure analysis.[29]

To complete the synthesis of the building block **13**, the quinone moiety had to be protected by reductive methylation[30] and the aldehyde had to be set free selectively. After having tried several common procedures for the reductive methylation without success, the method of Kraus[31] ($Na_2S_2O_4$/KOH/Me_2SO_4 in THF/H_2O in the presence of a phase-transfer catalyst) afforded the 9,10-dimethoxyanthracene derivative **21** in a yield of 65%. The final hydrolysis of the 1,3-dioxane moiety was selectively achieved using 10% H_2SO_4 adsorbed onto silica[32] to give rise to the aldehyde **13** in high yield (81%). It should be mentioned that the proper choice of reaction parameters proved to be absolutely crucial in this reaction. For instance, with 15% H_2SO_4 adsorbed onto silica both acetal functionalities were affected, and other acidic reagents such as PPTS or acetic acid also led to a partial deprotection of the MOM group as well.

Synthesis of the "Northern" Building Block

With the anthracenecarbaldehyde **13** in our hands, our next task was the preparation of a suitable precursor for the aryllithium species **12**, i.e., **24**, **25**, or **26** (Scheme 4). Assembly of this molecule was achieved by reacting the side chain aldehyde **22** with an appropriate arylmetal reagent derived from aryl bromide **23**. Aldehyde **22**[33] was prepared according to literature procedures by mono-TBS protection of 1,6-hexanediol[34] followed by oxidation under *Swern* conditions.[35] Metalation of **23** was initially per-

(22) (a) Sammes, P. G.; Dodsworth, D. J. *J. Chem. Soc., Chem. Commun.* **1979**, 33−34. (b) Dodsworth, D. J.; Calcagno, M.-P.; Ehrmann, E. U.; Devadas, B.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2120−2124. For examples of this reaction in the total synthesis of natural products, see: (c) Townsend, C. A.; Davis, S. G.; Christensen, S. B.; Link, J. C.; Lewis, C. P. *J. Am. Chem. Soc.* **1981**, *103*, 6885−6888. (d) Townsend, C. A.; Christensen, B. S.; Davis, S. G. *J. Chem. Soc., Perkin Trans. 1* **1988**, 839−861. (e) Townsend, C. A.; Isomura, Y.; Davis, S. G.; Hodge J. A. *Tetrahedron* **1989**, *45*, 2263−2276. (f) Graybill, T. L.; Pal, K.; McGuire, S. M.; Brobst, S. W.; Townsend, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 8306−8308. (g) See ref 15a.

(23) (a) Khanapure, S. P.; Reddy, R. T.; Biehl, E. R. *J. Org. Chem.* **1987**, *52*, 5685−5690. (b) Khanapure, S. P.; Biehl, E. R. *Synthesis* **1991**, 33−36. (c) Biehl, E. R.; Deshmukh, A. R.; Dutt, M. *Synthesis* **1993**, 885−888.

(24) (a) For a review dealing with annulation reactions using stabilized phthalide anions, see: Mitchell, A. S.; Russell, R. A. *Tetrahedron* **1995**, *51*, 5207−5236. For reviews dealing with cycloadditions of isobenzofuranes, see: (b) Narasimhan, N. S.; Mali, R. S. *Top. Curr. Chem.* **1997**, *138*, 63−147. (c) Rodrigo, R. *Tetrahedron* **1988**, *44*, 2093. (d) Friedrichsen, W. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: London, 1999; Vol. 73, p 1.

(25) (a) Li, T.; Wu, Y. *J. Am. Chem. Soc.* **1981**, *103*, 7007. (b) Kraus, G. A.; Cho, H.; Crowley, S.; Roth, B.; Prugh, S. *J. Org. Chem.* **1983**, *48*, 3439−3444. (c) Freskos, J. N.; Morrow, G. W.; Swenton, J. S. *J. Org. Chem.* **1985**, *50*, 805−810. (d) Okazaki, K.; Nomura, K.; Yoshii, E. *Synth. Commun.* **1987**, *17*, 1021−1028.

(26) (a) Blair, J.; Brown, J. J.; Newbold, G. T. *J. Chem. Soc.* **1955**, 708−712. (b) Dodsworth, D. J.; Calcagno, M.-P.; Ehrmann, E. U.; Devadas, B.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2120−2124.

(27) (a) Gschwind, H. W.; Rodriguez, H. R. *Org. React. (N.Y.)* **1979**, *26*, 1−360. (b) Snieckus, V. *Bull. Soc. Chim. Fr.* **1988**, 67−78. (c) Narasimhan, N. S.; Mali, R. S. *Top. Curr. Chem.* **1987**, *138*, 63. (d) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879−933.

(28) High (almost perfect) regioselectivities in such aryne/phthalide reactions were also described by Sammes and Biehl. However, in our case the formation of **20** did not proceed very cleanly, giving a lot of side products. Although we tried to separate and analyze all the fractions detectable by TLC, it cannot be excluded that traces of the regioisomer of **20** were formed. A major side product, occurring in varying yields (10−20%), was tentatively assigned as a symmetric dimer of the bromide **17** (on the basis of NMR analysis).

(29) For an ORTEP diagram and details of the X-ray crystal structure analysis of **20**, see the Supporting Information.

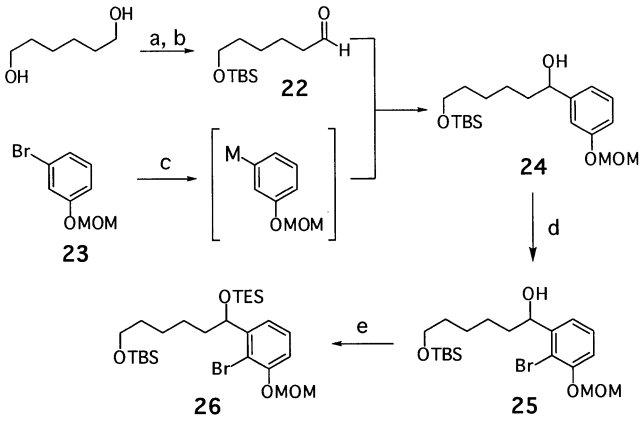
(30) An alternative for the protection of anthraquinones against nucleophilic attack is the reduction to the corresponding anthracenes. This possibility was not investigated because of the known sensitivity and poor solubility of certain anthracenes. For an example, see: Tius, M. A.; Gomez-Galeno, J.; Gu, X., Zaidi, J. H. *J. Am. Chem. Soc.* **1991**, *113*, 3, 5775−5783.

(31) Kraus, G. A.; Man, T. O. *Synth. Commun.* **1986**, *16*, 1037−1042.

(32) Huet, F.; Lechevallier, A.; Pellet, M.; Conia, J. M. *Synthesis* **1978**, 63−65.

(33) Otera, J.; Nozaki, H. *Tetrahedron Lett.* **1986**, *27*, 5743−5746.

SCHEME 4[a]



[a] Reagents and conditions: (a) NaH, DMF, 1,6-hexanediol, (TBS)Cl, 0 °C to rt, 65%; (b) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, −78 °C to rt, 95%; (c) **23** (prepared from 3-bromophenol, NaH, (MOM)Cl, DMF, 0 °C to rt, 99%), *n*BuLi, THF, −78 °C, then $CeCl_3$, THF, −78 °C, 1 h, then **22**, −78 °C to rt, 86%; (d) *n*BuLi, toluene, rt, then $C_2Br_2F_4$, −43 °C to rt, 83%; (e) imidazole, catalytic DMAP, (TES)Cl, CH_2Cl_2, rt, 91%.

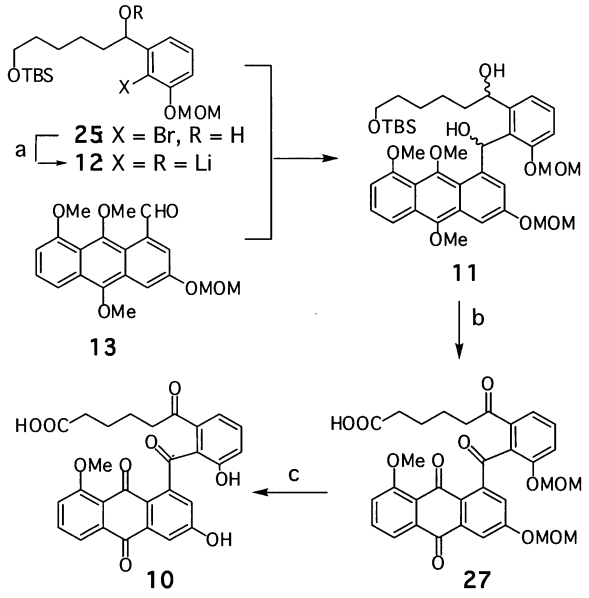
formed with *n*BuLi; however, reaction of the resulting aryllithium species with **22** gave **24** in only 49% yield. In this reaction, the desired nucleophilic attack is in competition with enolate formation. The less basic Grignard reagent afforded **24** in an increased yield of 66%. Transmetalation of the aryllithium intermediate to an almost nonbasic organocerium reagent[36] **(**by treatment with anhydrous $CeCl_3$) and subsequent reaction with **22** gave **24**[37] in a high yield of 86%.

Ortho-lithiation[38] of **24** with *n*BuLi in toluene and subsequent quenching of the resulting dianion with tetrafluorodibromoethane afforded the bromide **25** in 83% yield besides small amounts (<5%) of a regioisomeric bromide, which could be easily separated by chromatography. Part of the material (**25**) was converted into the TES-protected derivative **26** by treatment with Et_3SiCl in the presence of imidazole and DMAP.

Completion of the Synthesis

Having successfully synthesized both the anthracenecarbaldehyde **13** and the northern arene part (**25** or **26**, respectively), the coupling of these building blocks was the next task of the planned synthesis (Scheme 2). After

SCHEME 5[a]



[a] Reagents and conditions: (a) 2 equiv of *n*BuLi, THF, −78 °C, then addition of **13**, −78 °C to rt, 52%; (b) 12 equiv of Jones reagent, acetone, rt, 55%; (c), (TMS)I, CH_2Cl_2/CH_3CN (1:1), powdered molecular sieves 4 Å, −30 to 0 °C, 72%.

conversion of **25** to the lithium derivative **12** by bromine−lithium exchange, the subsequent reaction with the aldehyde **13** proceeded smoothly to give the benzhydrol **11** in 52% yield as a mixture of (racemic) diastereomers in a ratio of 55:45 according to HPLC (Scheme 5).[39] The diastereomers could not be separated through thin-layer or flash chomatography.

Because the TES-protected aryl bromide **26** gave comparable results in the coupling step, we used the unprotected diol **11**, directly obtained from **25**, for the final steps of the synthesis. Treatment of **11** with an excess of Jones reagent[40] led to multiple oxidation of the molecule, affording **27** in 55% yield. In this remarkable reaction, the anthraquinone, the two ketone functionalities, and the carboxylic acid function at the end of the side chain acid are established, the latter under cleavage of the primary silyl ether. The diketoacid **27** proved to be highly acid-sensitive; already traces of HCl effected a partial hydrolysis of one of the MOM ethers. Complete deprotection of both MOM groups was achieved employing (TMS)Br[41] at 0 °C or (TMS)I at −30 °C to yield the envisioned mumbaistatin analogue **10** as a yellow powder.

Conclusion

We have described a first synthetic study toward the natural G6Pase inhibitor mumbaistatin and related structures. The chosen strategy is highly convergent; it

(34) McDougal, P.; Rico, J.; Oh, Y.-I.; Condon, B. *J. Org. Chem.* **1986**, *51*, 3388−3390.

(35) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651−1660.

(36) (a) Imamoto, T.; Sugiura, Y.; Takiyama, M. *Tetrahedron Lett.* **1984**, *25*, 4233−4236. (b) Imamoto, T.; Kusumoto, T.; Tawayarama, Y.; Sugiura, Y.; Mita, T. *J. Org. Chem.* **1984**, *49*, 3904−3911. (c) For a recent review, see: Liu, H.-J.; Shia, K.-S.; Shang, X.; Zhu, B.-Y. *Tetrahedron* **1999**, *55*, 3803−3830. (d) For an example of the addition of an arylcerium compound to an alkylaldehyde, see: Seto, M.; Morihira, K.; Horiguchi, Y.; Kuwajima, I. *J. Org. Chem.* **1994**, *59*, 3165−3174.

(37) We also prepared **24** by reaction of a metalated C_5 side chain with 3-methoxymethoxybenzaldehye, but the yield of this coupling reaction was only moderate. For further details, see the Supporting Information.

(38) For *ortho*-lithiations of MOM-protected phenols, see: (a) Ronald, R. C. *Tetrahedron Lett.* **1975**, *34*, 3973−3974. (b) Christensen, H. *Synth. Commun.* **1975**, *5*, 65. (c) Townsend, C. A.; Bloom, L. M. *Tetrahedron Lett.* **1981**, *40*, 3923−3924. (d) Ronald, R. C.; Winkle, M. R. *J. Org. Chem.* **1982**, *47*, 2101−2108. (e) Ronald, R. C.; Winkle, M. R. *Tetrahedron* **1983**, *39*, 2031−2042.

(39) As some orientating experiments have shown, the dianion **12** also reacts with certain bis-*ortho*-substituted benzaldehydes to give, after oxidation, tetra-*ortho*-substituted benzophenones. This indicates the general potential of the strategy also for a future total synthesis of mumbaistatin itself.

(40) Bowden, K.; Heilbron, I. M.; Jones, E. R. H. *J. Chem. Soc.* **1946**, 39−45.

(41) Hanessian, S.; Delorme, D.; Dufresne, Y. *Tetrahedron Lett.* **1984**, *25*, 2515−2518.

involves the coupling of the "northern" part as an aryllithium reagent with a 9,10-dimethoxyanthracenecarbaldehyde representing the ("southern") anthraquinone part. As an important additional feature of the strategy, the potentially sensitive functionalization pattern of the target molecules (anthraquinone−diketoacid structure) is established in a very late stage of the synthesis by means of a multioxidation reaction.

The feasibility of the concept was demonstrated by the successful synthesis of a closely related mumbaistatin analogue (**10**) in a total of only 15 steps (longest linear sequence, 9 steps) starting from commercially available 3-hydroxybenzaldehyde and 3-bromophenol. The construction of the anthraquinone ring system was achieved using an aryne/phthalide annulation as a key reaction.

The short and rather flexible approach should also allow for the synthesis of a broad range of other mumbaistatin-related structures for SAR studies. Current investigations in this laboratory are focusing on the exploitation of the developed synthetic strategies and building blocks both for the total synthesis of mumbaistatin itself and for the synthesis of new analogues.

Experimental Section

Melting points (mp's) were determined in open capillary tubes and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a 250, 300, or 500 MHz instrument and are referenced to the nondeuterated impurities of the used solvents ($CDCl_3$, CD_3OD, d_6-DMSO) as internal standard. The spectra are reported in parts per million using the following abbreviations to express the multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad. ^{13}C chemical shifts were determined using ^{1}H-decoupled spectra. The number of protons bound directly was determined employing the DEPT sequence (q = CH_3; t = CH_2; d = CH; s = quarternary carbon). IR spectra were recorded using the ATR technique. Gas chromatography (GC) and low-resolution mass spectra (EI, 70 eV) were recorded on a GC−MS system using H_2 as carrier gas (flow 10 psi). Given are the purities calculated from the uncorrected FID integrations. High-resolution mass spectrometry (HRMS) was performed in EI or ESI mode. Analytical thin-layer chromatography (TLC) was performed on silica-coated alumina plates containing fluorescent indicator, visualized by UV light or by staining with a cerium reagent (prepared by dissolving 2 g of phosphomolybdic acid and 1 g of cerium(IV) sulfate in a mixture of 10 mL of concd H_2SO_4 and 90 mL of water) followed by heating. Flash chromatography was performed on silica gel 60 (230−400 mesh). A silica gel:crude product ratio of 25−100:1 by weight and flow rates of 10−20 mL/s were normally employed for flash chromatography. Commercial reagents were used without further purification unless otherwise noted. THF and toluene were freshly distilled from sodium benzophenone ketyl, and dichloromethane was distilled from CaH_2. Other reaction solvents (acetonitrile, benzene, hexane, DMF, DMSO) were purchased in HPLC-pure quality and stored under argon over molecular sieves. Bulk solvents for chromatography and extraction were distilled prior to use. All reactions involving organometallic reagents were carried out under a positive atmosphere of dry argon in oven-dried glassware using Schlenk techniques. Solvents and solutions were added with syringes through rubber septa. Organolithium reagents (*n*-, *s*-, and *t*BuLi, PheLi) were titrated against menthol in THF in the presence of 1,10-phenanthroline prior to use.

4-Bromo-3-[1′,3′]dioxan-2′-ylphenol (16). In a 500 mL three-necked flask equipped with a reflux condenser 10.049 g (50 mmol) of 2-bromo-5-hydroxybenzaldehyde (**15**) was dissolved in 200 mL of benzene and 40 mL of THF. After addition of 18.2 mL (250 mmol) of 1,3-propanediol and 285 mg of *p*TsOH (3 mol %) the mixture was refluxed for 24 h. After the mixture was transferred into a separatory funnel, 100 mL of water was added. Phase separation was followed by extraction of the aqueous phase with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solution was filtered through a short pad of silica and diluted with ethyl acetate. Removal of the solvent under reduced pressure gave 12.850 g (49.5 mmol, 99%) of **16** as a yellow solid. An analytical sample was recrystallized from hexane/ethyl acetate. Mp: 78−79 °C. TLC (cyclohexane/ethyl acetate, 4:1): R_f = 0.25. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.44 (dtt, 1 H, J = 13.5 Hz), 2.12−2.28 (m, 1 H), 2.98 (br s, 1 H), 4.01 (dt, 2 H, J = 12.5 Hz), 4.22−4.28 (ψdd, 2 H), 5.70 (s, 1 H), 6.61 (dd, 1 H, ^3J = 8.5 Hz, ^4J = 3.0 Hz), 7.15 (d, 1 H, ^4J = 3.0 Hz), 7.30 (d, 1 H, ^3J = 8.5 Hz). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 25.6 (t), 67.6 (t, 2 C), 100.8 (d), 111.9 (s), 115.2 (d), 118.0 (d), 133.4 (d), 137.7 (s), 155.6 (s). GC purity: 98%. MS (EI): *m*/*z* 258/260 (30/31, $[M]^+$), 243 (12), 201 (50), 179 (28), 143 (8), 122 (37), 107 (48), 87 (100). HRMS (EI): *m*/*z* calcd for $C_{10}H_{11}BrO_3$ 257.9891, found 257.988.

2′-(2-Bromo-5-methoxymethoxyphenyl)[1′,3′]dioxane (17). A 250 mL argon-flushed three-necked flask was charged with 2.096 g of sodium hydride (60% oil dispersion; 1.258 g, 52.4 mmol, of sodium hydride). The sodium hydride was washed twice with 30 mL of hexane to remove the oil. After addition of 80 mL of anhydrous DMF, the suspension was cooled to 0 °C. A 12.336 g (47.6 mmol) sample of the dioxane **16** in 20 mL of anhydrous DMF was added slowly, and the reaction mixture was stirred at rt for an additional 30 min. To the cooled solution (0 °C) was slowly added 4.0 mL of (MOM)Cl (*caution: due to the carcinogenity of (MOM)Cl all operations involving this reagent should be performed in a well-working fume hood!*) via syringe. The yellow solution was stirred for 60 min at rt before the reaction was quenched by addition of 100 mL of saturated NH_4Cl solution. The solution was extracted with MTBE (3 × 250 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solution was filtered through a short pad of silica and diluted with ethyl acetate. The solvent was evaporated under reduced pressure to give 14.280 g (47.1 mmol, 99%) of the MOM ether **17** as a yellow solid, which did not need further purification. An analytical sample was recrystallized from hexane/ethyl acetate. Mp: 68 °C. TLC (cyclohexane/ethyl acetate, 5:1): R_f = 0.25. IR (ATR): $\tilde{\nu}$ = 2951, 2851, 1593, 1557, 1473, 1387, 1267, 1227, 1206, 1170, 1146, 1098, 1078, 1039, 1002, 987, 956 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.40 (d, 1 H, J = 13.5 Hz), 2.17−2.24 (m, 1 H), 3.41 (s, 3 H), 4.03−3.92 (m, 2 H), 4.19−4.26 (m, 2 H), 5.12 (s, 2 H), 5.66 (s, 1 H), 6.86 (dd, 1 H, ^4J = 3.0 Hz, ^3J = 9.0 Hz), 7.34 (d, 1 H, ^4J = 3.0 Hz), 7.38 (d, 1 H, ^3J = 9.0 H). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 25.5 (t), 56.0 (q), 67.4 (t, 2 C), 94.3 (t,), 100.6 (d), 113.8 (s), 115.6 (d), 118.3 (d), 133.2 (d), 138.3 (s), 156.6 (s). GC purity: 97%. MS (EI): *m*/*z* 304 (3, $[M]^+$), 302 (3, $[M]^+$), 281 (6), 223 (3, $[M - Br]^+$), 207 (18, $[M - Br - CH_3 - H]^+$), 191 (5), 122 (20), 108 (70), 107 (90). HRMS (EI): *m*/*z* calcd for $C_{12}H_{15}BrO_4$ 302.016, found 302.016.

1-[1′,3′]Dioxan-2′-yl-8-methoxy-3-(methoxymethoxy)-anthraquinone (20). Method A. In a 250 mL argon-flushed three-necked flask 12.6 mL (74 mmol) of freshly distilled 2,2,6,6-tetramethylpiperidine was dissolved in 40 mL of dry THF. At −78 °C 46.3 mL of *n*BuLi (1.6 M in hexane) was added. The mixture was stirred for 30 min before 3.022 g (18.5 mmol) of phthalide **18** in 40 mL of THF was added slowly via syringe. After 30 min at −78 °C the solution had turned an intense red. After the mixture was allowed to warm to −43 °C (by changing the cooling bath), a solution of 11.212 g (37 mmol) of bromide **17** in 50 mL of THF was added via syringe. After 2 h the cooling bath was removed, and the solution was stirred overnight. Then the flask was opened, and the brown mixture was stirred for 2 h while a slight steam of air was passed through it. After addition of 50 mL of saturated NH_4Cl

solution the THF was distilled off the mixture under reduced pressure. The aqueous residue was extracted with dichloromethane (4 × 100 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (200 g of silica; cyclohexane/ethyl acetate, 1:2) to give 2.895 g (7.5 mmol, 45%) of anthraquinone **20** as a yellow solid. Crystallization from hexane/ethyl acetate gave yellow crystals.

Method B. In a 250 mL argon-flushed three-necked flask 6.8 mL (40 mmol) of freshly distilled 2,2,6,6-tetramethylpiperidin was dissolved in 20 mL of dry THF. At −78 °C 25 mL of *n*BuLi (1.6 M in hexane) was added. The mixture was stirred for 30 min before 1.892 g (10 mmol) of cyanophthalide **19** in 20 mL of THF was added slowly via syringe. After 30 min at −78 °C the solution had turned an intense red. After the mixture was allowed to warm to −43 °C (by changing the cooling bath), a solution of 6.061 g (20 mmol) of bromide **17** in 30 mL of THF was added via syringe. After 2 h the cooling bath was removed, and the solution was stirred overnight. The reaction was quenched by addition of 50 mL of saturated NH_4Cl solution. Isolation and purification of the product following the procedure described in method A gave 1.344 g (3.5 mmol, 35%) of anthraquinone **20** as a yellow solid. Mp: 112 °C. TLC (cyclohexane/ethyl acetate, 1:2): R_f = 0.15. IR (ATR): $\tilde{\nu}$ = 2957, 2848, 1729, 1668, 1595, 1467, 1413, 1377, 1354, 1258, 1148, 1103, 1076, 1032, 983, 923, 889 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.44 (br d, 1 H, J = 13.4 Hz), 2.11−2.31 (m, 1 H), 3.44 (s, 3 H), 3.98 (s, 3 H), 4.09 (m, 2 H), 4.20 (m, 2 H), 5.28 (s, 2 H), 6.65 (s, 1 H), 7.27 (dd, 1 H, ^3J = 7.5 Hz, J = 1 Hz), 7.59 (t, 1 H, ^3J = 8 Hz), 7.84 (m, 3 H). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 25.8 (t), 56.4 (q), 56.6 (q), 67.5 (t), 67.6 (t), 93.9 (t), 97.6 (d), 113.3 (d), 118.2 (d), 119.8 (d), 121.2 (d), 123.2 (s), 126.5 (s), 134.1 (d), 134.7 (s), 135.5 (s), 159.7 (s), 160.2 (s), 183.3 (s), 183.6 (s). GC purity: 97%. MS (EI): *m*/*z* 384 (12, $[M]^+$), 356 (3), 340 (4), 325 (36), 312 (12), 295 (29), 281 (11), 253 (6), 197 (4), 45 (100). HRMS (EI): *m*/*z* calcd for $C_{21}H_{20}O_7$ 384.121, found 384.121.

2′-(8,9,10-Trimethoxy-3-(methoxymethoxy)anthracen-1-yl)[1′,3′]dioxane (21). In a 25 mL Schlenk flask 1.152 g (3 mmol) of the anthraquinone **20** and 120 mg of tetrabutylammonium bromide were dissolved in 10 mL of THF and 4 mL of water. A 1.567 g (9 mmol) sample of sodium dithionite and 5 min later 1.930 g (35 mmol) of potassium hydroxide were added. After an additional 5 min 2.85 mL (30 mmol) of dimethyl sulfate was added dropwise. The mixture was stirred for 18 h at rt, until the starting material was completely consumed (TLC control). The mixture was poured into a separatory funnel charged with 20 mL of saturated NH_4Cl solution and extracted with ethyl acetate (5 × 25 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure the residue was purified by flash chromatography (60 g of silica; cyclohexane/ethyl acetate, 2:1) to give 808 mg (1.96 mmol, 65%) of the methoxyanthracene **21** as a yellow foam. TLC (cyclohexane/ethyl acetate, 2:1): R_f = 0.25. IR (ATR): $\tilde{\nu}$ = 2951, 2840, 1728, 1621, 1537, 1451, 1431, 1397, 1383, 1355, 1328, 1260, 1231, 1141, 1102, 1078, 1030, 986 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.49 (d, 1 H, J = 13.5 Hz), 2.31 (m, 1 H), 3.50 (s, 3 H), 3.85 (s, 3 H), 3.98 (s, 3 H), 4.06 (s, 3 H), 4.15 (br d, 2 H, J = 11.5 Hz), 4.29 (ψdd, 2 H), 5.33 (s, 2 H), 6.74 (dd, 1 H, J_o = 7.5 Hz, J = 1 Hz), 6.94 (s, 1 H), 7.35 (dd, 1 H, J = 8.5 Hz, J = 7.5 Hz), 7.70 (d, 1 H, J = 2.5 Hz), 7.81 (dd, 1 H, J = 8.5 Hz, J = 1 Hz), 7.83 (d, 1 H, J = 2.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.0 (t), 56.14 (q, 2 C), 62.1 (q), 63.7 (q), 67.7 (t, 2 C), 94.2 (t), 99.8 (d), 103.2 (d), 103.4 (d), 114.7 (d), 117.3 (s), 120.2 (s), 120.6 (d), 125.5 (d), 127.3 (s), 127.5 (s), 137.5 (s), 146.8 (s), 150.7 (s), 154.4 (s), 156.4 (s). GC purity: 96%. MS (EI): *m*/*z* 414 (84, $[M]^+$), 399 (24, $[M - CH_3]^+$), 383 (5, $[M - OCH_3]^+$), 369 (20, $[M - CH_2OCH_3]^+$), 355 (3, $[M - OCH_2OCH_3]^+$), 341 (37), 327 (34), 311 (49), 297 (20), 281 (17), 267 (23), 253 (16). HRMS (EI): *m*/*z* calcd for $C_{23}H_{26}O_7$ 414.168, found 414.168.

8,9,10-Trimethoxy-3-(methoxymethoxy)anthracene-1-carbaldehyde (13). In a 100 mL flask 5.0 g of silica was suspended in 14 mL of dichloromethane. A 500 mg sample of a 10% aqueous H_2SO_4 solution was added dropwise under stirring, and the mixture was stirred for 30 min until the aqueous phase was fully adsorbed onto the silica. A 497 mg (1.2 mmol) sample of anthracenyl[1,3]dioxane **21** in 6 mL of dichloromethane was added dropwise. The yellow suspension soon became red. The flask was closed, and the mixture was stirred for 72 h at rt. After addition of some potassium carbonate the mixture was stirred for a further 30 min before it was filtered through a sintered funnel. The silica was washed with ethyl acetate and methanol. The solution was collected, and the solvent was removed under reduced pressure. The residue was dissolved in 50 mL of dichloromethane. The solution was washed with a 1 M NaOH solution, water, and brine and dried over $MgSO_4$. After evaporation of the solvent the residue was purified by flash chromatography (50 g of silica; cyclohexane/ethyl acetate, 2:1) to give 344 mg (0.96 mmol, 81%) of **13** as an orange oil, which slowly crystallized to give a yellow solid. Mp: 94 °C. TLC (cyclohexane/ethyl acetate, 2:1): R_f = 0.35. IR (ATR): $\tilde{\nu}$ = 3290, 1681, 1612, 1558, 1533, 1455, 1397, 1358, 1231, 1152, 1066, 1018 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 3.52 (s, 3 H), 3.76 (s, 3 H), 4.03 (s, 3 H), 4.07 (s, 3 H), 5.35 (s, 2 H), 6.79 (d, 1 H, J_o = 8.5 Hz), 7.38 (ψt, 1 H), 7.44 (d, 1 H, J_m = 2.5 Hz), 7.80−7.85 (m, 2 H), 10.92 (s, 1 H). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 56.1 (q), 56.3 (q), 62.5 (q), 63.2 (q,), 94.5 (t), 103.9 (d), 106.4 (d), 114.8 (d), 117.5 (s), 120.3 (s), 121.4 (d), 126.2 (d), 126.6 (s), 128.2 (s), 138.4 (s), 147.4 (s), 149.7 (s), 154.2 (s), 156.3 (s), 194.4 (d). GC purity: 99%. MS (EI): *m*/*z* 356 (81, $[M]^+$), 341 (50, $[M - CH_3]^+$), 327 (5), 326 (5), 311 (50, $[M - CH_2OCH_3]^+$), 296 (10), 281 (11), 266 (9), 253 (9). HRMS (EI): *m*/*z* calcd for $C_{20}H_{20}O_6$ 356.1259, found 356.126.

6-(*tert*-Butyldimethylsilanoxyl)-1′-(3′-methoxymethoxyphenyl)hexan-1-ol (24). A 250 mL argon-flushed three-necked flask was charged with 9.900 g of anhydrous cerium(III) chloride in 50 mL of dry THF. The mixture was stirred for 4 h at rt and occasionally sonicated in an ultrasound cleaning bath (30 min) until the mixture became a fine white suspension. The flask was then cooled to −78 °C. In a separate 100 mL argon-flushed three-necked flask, 8.140 g of 3-methoxymethoxyphenyl bromide **23** was dissolved in 30 mL of dry THF. After the solution was cooled to −78 °C, 23.5 mL of *n*BuLi (1.6 M in hexane) was added via syringe, and the resulting brown solution was stirred for 15 min. Then the solution was transferred to the flask containing the cerium chloride suspension by means of a transfer needle. The reaction mixture was stirred for 1 h at −78 °C, upon which the solution turned an intense yellow. A 5.754 g (25 mmol) sample of 6-*tert*-butyldimethylsiloxyhexanal **22** was added, and the mixture was stirred overnight while it was allowed to slowly come to rt. After the reaction was quenched with 50 mL of $NaHCO_3$, the mixture was transferred to a separatory funnel. After phase separation the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with water and brine and dried over $MgSO_4$. After filtration and removal of the solvent under reduced pressure, the crude product was purified by flash chromatography (300 g of silica; cyclohexane/ethyl acetate, 6:1) to give 7.833 g (21.4 mmol, 86%) of **24** as a colorless oil. TLC (cyclohexane/ethyl acetate, 6:1): R_f = 0.18. IR (ATR): $\tilde{\nu}$ = 3430, 2928, 2854, 1584, 1485, 1470, 1461, 1402, 1315, 1248, 1149, 1079, 1017, 993, 923, 833 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.01 (s, 6 H), 0.86 (s, 9 H), 1.33−1.51 (m, 6 H), 1.69−1.75 (m, 2 H), 3.46 (s, 3 H), 3.56 (t, 2 H, ^3J = 6.5 Hz), 4.61 (br s), 5.15 (s, 2 H), 6.90−7.02 (m, 3 H), 7.24 (t, 1 H, J = 8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.3 (s, 2 C), 18.3 (s), 25.6 (t), 25.7 (t), 25.9 (q, 3 C), 32.7 (t), 39.0 (t), 56.0 (q), 63.1 (t), 74.4 (d), 94.4 (t), 113.8 (d), 115.1 (d), 119.4 (d), 129.4 (d), 146.7 (s), 157.4 (s). GC purity: 98%. MS:

m/*z* 311 (1, [M − *t*Bu]$^+$), 309 (7), 294 (3), 279 (13, [M − *t*Bu − 2Me]$^+$), 263 (96), 250 (33), 231 (40), 207 (65), 187 (95), 182 (31), 168 (29), 165 (15). HRMS (EI): *m*/*z* calcd for $C_{16}H_{27}SiO_4$ (M − *t*Bu$^+$) 311.1678, found 311.168.

1-(2′-Bromo-3′-methoxymethoxyphenyl)-6-(*tert*-butyldimethylsilanyloxy)hexan-1-ol (25). In an argon-flushed 500 mL three-necked flask 7.320 g (19.9 mmol) of benzylic alcohol **24** was dissolved in 200 mL of dry toluene. After the solution was cooled to −43 °C, 43.5 mL of *n*BuLi (1.6 M in hexane, 69.6 mmol) was added slowly via syringe. After 30 min the cooling bath was removed, and the reaction mixture was stirred for 4 h at rt. The orange solution was cooled to −43 °C, and 40 mL of dry THF was added. After 10 min 8.4 mL (69.6 mmol) of tetrafluordibromoethane was added dropwise. The reaction mixture was allowed to slowly warm to rt while being stirred overnight. After the reaction was quenched with 100 mL of saturated NH_4Cl solution, the THF was distilled off under reduced pressure. The reaction mixture was extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was purified through flash chromatography (300 g of silica; cyclohexane/ethyl acetate, 7:1) to give 7.391 (16.5 mmol, 83%) of **25** as a pale yellow oil. TLC (cyclohexane/ethyl acetate, 7:1): R_f = 0.2. IR (ATR): $\tilde{\nu}$ = 3419, 2927, 2854, 1462, 1437, 1255, 1203, 1153, 1086, 1019, 923, 833, 774 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.01 (s, 6 H), 0.86 (s, 9 H), 1.34−1.70 (m, 8 H), 2.15 (d, 1 H, ^3J = 3.5 Hz), 3.49 (s, 3 H), 3.57 (t, 2 H, ^3J = 6.5 Hz), 5.09 (quin, 1 H, J = 4 Hz), 5.22 (s, 2 H), 7.02 (dd, 1 H, ^4J = 2.5 Hz, ^3J = 7.5 Hz), 7.17−7.23 (m, 2 H). ^{13}C NMR (63 MHz, $CDCl_3$): δ = −5.3 (q, 2 C), 18.3 (s), 25.6 (t), 25.9 (q, 3 C), 26.9 (t), 32.7 (t), 37.5 (t), 56.4 (q), 63.2 (t), 72.9 (d), 95.1 (t), 112.7 (s), 114.6 (d), 120.3 (d), 128.1 (d), 145.8 (s), 153.4 (s). GC purity: 97%. MS (EI): *m*/*z* 389 (>1, [M − *t*Bu]$^+$), 373 (1, [M − *t*Bu − O]$^+$), 359 (7), 343/341 (6), 329/327 (5), 311/309 (19), 283/285 (7), 267 (19), 248 (13), 231/229 (19), 201 (8). HRMS (EI): *m*/*z* calcd for $C_{16}H_{26}BrSiO_4$ (M − *t*Bu)$^+$ 389.0783, found 389.078.

2′-Bromo-1′-[6-(*tert*-butyldimethylsilanyloxy)-1-triethylsilanyloxyhexyl]-3′- methoxymethoxybenzene (26). An argon-flushed 100 mL Schlenk flask was charged with 895 mg (2 mmol) of benzylic alcohol **25** in 15 mL of dry dichloromethane. After addition of 680 mg (10 mmol) of imidazole and 2 mg of DMAP the solution was cooled to 5 °C. Over 15 min a solution of 0.5 mL (3 mmol) of (TES)Cl in 5 mL of anhydrous dichloromethane was added drop by drop, and the resulting solution was stirred for 8 h at rt. After the reaction was quenched with 10 mL of saturated NH_4Cl solution, the phases were separated. The aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by flash chromatography (60 g of silica; cyclohexane/ethyl acetate, 30:1) to yield 1.045 g (1.86 mmol, 93%) of **26** as a pale yellow oil. TLC (cyclohexane/ethyl acetate, 30:1): R_f = 0.2. IR (ATR): $\tilde{\nu}$ = 2928, 2872, 2853, 1591, 1569, 1461, 1435, 1410, 1385, 1358, 1305, 1255, 1203, 1153, 1097, 999, 938, 923, 832 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.02 (s, 6 H), 0.53 (t, 6 H, ^3J = 7.5 Hz), 0.87 (s, 9 H), 0.83−0.94 (m, 9 H), 1.30−1.62 (m, 8 H), 3.51 (s, 3 H), 3.57 (t, 2 H, ^3J = 6.5 Hz), 5.07 (dd, 1 H, ^4J = 4 Hz, ^3J = 7.5 Hz), 5.21, 5.23 (each d, AB system, 1 H, ^2J = 6.5 Hz), 6.99 (dd, 1 H, ^3J = 5.5 Hz, ^4J = 4 Hz), 7.16−7.23 (m, 2 H). ^{13}C NMR (63 MHz, $CDCl_3$): δ = −5.3 (q, 2 C), 4.7 (t, 2 C), 6.7 (q, 3 C), 18.4 (s), 25.5 (t), 25.7 (t), 26.0 (q, 3 C), 32.8 (t), 39.2 (t), 56.4 (q), 63.2 (t), 73.3 (d), 95.4 (t), 111.9 (s), 114.1 (d), 121.3 (d), 127.7 (d), 146.9 (s), 153.1 (s). GC purity: 98%. MS (EI): *m*/*z* 503 (1, [M − *t*Bu]$^+$), 473 (5, [M − Et$_3$]$^+$), 451 (5), 429 (5), 379 (5), 361/359 (35), 341 (7), 329 (22), 327 (24), 311/309 (65), 287 (23), 285 (28), 267 (38), 265 (40), 248 (55). HRMS (EI): *m*/*z* calcd for $C_{22}H_{40}Si_2O_4Br$ (M − *t*Bu)$^+$ 503.1648, found 503.165.

6-(*tert*-Butyldimethylsilanoxy)-1-{2-[hydroxy-(8,9,10-trimethoxy-3-methoxymethoxyanthracen-1-yl)methyl]-3-methoxymethoxyphenyl}hexan-1-ol (11). In an argon-flushed Schlenk tube 371 mg (0.83 mmol) of bromide **25** was dissolved in 5 mL of dry THF. At −78 °C, 1.05 mL of *n*BuLi (1.6 M in hexane, 1.65 mmol) was added and the resulting yellow solution was stirred for 30 min. Then 267 mg (0.75 mmol) of aldehyde **13** in 5 mL of THF was added slowly, and the mixture was stirred overnight while the temperature was allowed to slowly rise to rt. After addition of 5 mL of saturated NH_4Cl solution the THF was distilled off the mixture. The aqueous residue was extracted with dichloromethane (4 × 10 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. After evaporation of the solvent the residue was purified by flash chromatography (50 g of silica; cyclohexane/ethyl acetate, 3:1) to give 284 mg (0.4 mmol, 52%) of benzhydrol **11** as a brown oil. A 135 mg (0.367 mmol, 44%) yield of debrominated starting material and 60 mg (0.17 mmol, 22%) of aldehyde **13** could also be collected. The product was obtained as a 1.38:1 mixture of diastereomers (determined by HPLC); the following presents the analytical data for the mixture. TLC (cyclohexane/ethyl acetate, 2:1): R_f = 0.2. IR (ATR): $\tilde{\nu}$ = 3322, 2929, 2852, 1622, 1537, 1461, 1429, 1398, 1354, 1291, 1245, 1222, 1203, 1151, 1132, 1081, 1066, 1005, 833 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 54 °C): δ = 0.00/0.06 (s, 6 H), 0.81/0.86 (s, 9 H), 1.10−1.55 (m, 4 H), 1.25−1.61 (m, 2 H), 1.67−1.92 (m, 2 H), 3.28/3.30 (s, 3 H), 3.40/3.44 (s, 3 H), 3.46/3.52 (t, 2 H, J = 6.5 Hz), 3.99/4.03 (s, 3 H), 4.03/4.04 (s, 3 H), 4.03/4.03 (s, 3 H), 4.91/5.10 (t, 1 H, J = 7.5 Hz), 5.03/5.10 (br d, 2 H), 5.09/5.22 (d, 2 H), 6.79/6.80 (d, 1 H, J = 7 Hz), 6.84/6.84 (d, 1 H, J = 2.5 Hz), 7.03/7.06 (m, 1 H), 7.33/7.37 (m, 1 H), 7.32/7.39 (s, 1 H), 7.35/7.40 (m, 1 H), 7.32/7.41 (m, 1 H), 7.65/7.67 (d, 1 H, J = 2.5 Hz), 7.84/7.85 (dd, 1 H, J = 8.5 Hz, J = 1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, 54 °C): δ = −5.28/−5.35 (q, 2 C), 18.28/18.31 (s), 25.94/25.98 (s, 3 C), 25.98/26.0 (t), 26.31/26.37 (t), 32.87/32.91 (t), 35.08 (br)/38.86 (t), 55.97/56.05 (q), 56.05/56.07 (q), 56.31/56.35 (q), 62.20/62.25 (q), 63.25/63.31 (t), 64.45/64.67 (q), 68.58/69.17 (d), 69.95/71.83 (d), 94.38/94.44 (t), 95.10/95.15 (t), 102.27/104.28 (d), 104.60/104.65 (d), 113.19/113.61 (d), 114.91/114.91 (d), 117.84/118.05 (s), 120.29/121.61 (d), 120.74/121.02 (s), 121.12/121.82 (d), 125.82/125.82 (d), 127.81/128.08 (s), 128.18/128.26 (s), 128.18/129.85 (s), 128.76/129.00 (d), 141.62 (br)/142.17 (s), 145.97 (br)/148.54 (s), 147.89/147.92 (s), 149.29/149.74 (s), 153.67/153.92 (s), 154.42/154.85 (s), 156.59/156.71 (s). HPLC purity: 95%. MS (EI, 70 eV): *m*/*z* 724 (3, [M]$^+$), 705 (30), 682 (22), 661 (8), 615 (5), 570 (2), 513 (5), 477 (5). HRMS (EI): *m*/*z* calcd for $C_{40}H_{56}SiO_{10}$ 724.3643, found 724.364.

6-[3-Methoxymethoxy-2-(8-methoxy-3-methoxymethoxy-9,10-anthraquinone-1-carbonyl)phenyl]-6-oxohexanoic Acid (27). A 200 mg (0.276 mmol) sample of diol **11** was dissolved in 2 mL of acetone. At 0 °C 1.4 mL of Jones reagent (5 mmol) was added dropwise. The brown mixture was stirred for 3 h at rt. The mixture was diluted with 20 mL of ethyl acetate, and 2-propanol was added dropwise. After filtration through a pad of florisil and addition of 10 mL of water, the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by flash chromatography (60 g of silica; cyclohexane/ethyl acetate, 1:2, + 1% acetic acid) to give 89 mg (0.152 mmol, 55%) of acid **27** as a yellow oil. TLC (cyclohexane/ethyl acetate/acetic acid, 33:66:1): R_f = 0.2. The NMR spectra showed that the product was a mixture of the bis-MOM-protected diketoacid **27** and the corresponding partially deprotected mono-MOM-protected diketoacid. HRMS (ESI): *m*/*z* calcd for $C_{32}H_{30}O_{11}Na$ 613.1686, found 613.169.

6-[3-Hydroxy-2-(3-hydroxy-8-methoxy-9,10-anthraquinone-1-carbonyl)phenyl]-6-oxohexanoic Acid (10). In an argon-flushed 10 mL Schlenk flask 65 mg of **27** was dissolved in 2 mL of dichloromethane and 2 mL of acetonitrile. After addition of 20 mg of powdered 4 Å molecular sieves, the

mixture was cooled to −30 °C. A 0.12 mL sample of (TMS)I was added dropwise. The solution turned dark green. After the mixture was stirred for 3 h at −30 °C, the temperature was allowed to rise to 0 °C. After 30 min the reaction was quenched by addition of 3 mL of $NaHCO_3$ solution. The mixture was transferred to a separatory funnel and diluted with 20 mL each of ethyl acetate and water. The aqueous phase was acidified with 0.5 M HCl. After separation of the phases the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine and dried with $MgSO_4$. After evaporation of the solvent the residue was purified by flash chromatography (20 g of silica; cyclohexane/ethyl acetate/acetic acid, 25:75:1) to give 40 mg (0.08 mmol, 72%) of **10** as a yellow powder. TLC (cyclohexane/ethyl acetate/acetic acid, 25:75:1): $R_f = 0.17$. IR (ATR): $\tilde{\nu} = 3335, 1644, 1583, 1463, 1350, 1256, 1169, 1135, 1069, 1022, 937\ cm^{-1}$. ^1H NMR (250 MHz, CD_2Cl_2): $\delta = 1.64$ (m, 4 H), 2.24 (br t, 2 H, $J = 7$ Hz), 2.31 (s, 1 H), 2.82 (br t, 2 H, $J = 7$ Hz), 3.86 (s, 3 H), 6.77 (dd, 1 H; $J = 7.5$ Hz, $J = 1$ Hz), 6.88 (dd, 1 H, $J = 8$ Hz, $J = 1$ Hz), 6.93 (d, 1 H, $J = 2.5$ Hz), 7.09−7.23 (m, 1 H), 7.43−7.47 (m, 1 H), 7.54 (d, 1 H, $J = 2.5$ Hz), 7.72 (t, 1 H, $J = 7.5$ Hz), 7.84 (dd, 1 H, $J = 8$ Hz, $J = 1$ Hz). ^{13}C NMR (63 MHz, CD_2Cl_2): $\delta = 25.1$ (t), 26.1 (t), 36.1 (t), 43.7 (t), 56.9 (q), 113.3 (d), 118.5 (d), 119.7 (d), 119.9 (d), 120.0 (d), 120.6 (d), 121.9 (s), 126.3 (s). 127.4 (s), 135.7 (d), 136.3 (s), 136.3 (d), 136.6 (s), 147 4 (s), 148.2 (s), 160.9 (s), 161.7 (s), 163.7 (s), 179.1 (s), 182.9 (s), 184.2 (s), 197.9 (s), 209.6 (s). MS (EI, 20 eV): *m*/*z* 502 (25, $[M]^+$), 484 (10, $[M - CH_3 - 3H]^+$), 438 (12), 415 (20), 401 (100, $[M\ (CH_2)_4COOH]^+$), 341 (7), 325 (6), 281 (21), 253 (15), 136 (25), 121 (62), 93 (15), 73 (11), 57 (18), 55 (26). HRMS (EI): *m*/*z* calcd for $C_{28}H_{22}O_9$ 502.1263, found 502.126.

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Supporting Information Available: Further characteristic data for all compounds (GC−MS conditions and retention times, NMR peak assignments, full list of IR and MS data), experimental procedures and data of compounds **15**, **18**, **19**, **22**, and **23**, a representation of the crystal structure of compound **20** and X-ray crystallographic data, description of an alternative synthesis of compound **24** (including all additional experimental data), and figures showing the ^1H and ^{13}C NMR spectra of compound **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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