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Studies towards the total synthesis of mumbaistatin: synthesis of highly substituted benzophenone and anthraquinone building blocks

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Abstract—Model compounds and building blocks for a planned total synthesis of the highly potent glucose-6-phosphate (G6P) translocase inhibitor mumbaistatin (**1**) and structural analogs were elaborated: compound **1** represents a lead structure in the development of potential new antidiabetic drugs. With the model substrate **20** it was demonstrated that highly functionalized, tetra-*ortho*-substituted benzophenones can be prepared by nucleophilic addition of an aryllithium-building block to a benzaldehyde followed by oxidation. For compound **37**, a potential precursor of the anthraquinone part of mumbaistatin, various approaches via aryne/phthalide annulations were developed and evaluated. The required functionalized arenes were prepared exploiting, among others, regioselective bromination and *ortho*-lithiation reactions. Coupling reactions of the anthracene–carbaldehyde **44** derived from **37** with various metalated arenes proved to be unexpectedly difficult and failed so far.

1. Introduction

Mumbaistatin (**1**), an aromatic anthraquinone polyketide isolated from a culture of streptomyces DSM 11641, is the strongest naturally occurring inhibitor of glucose-6-phosphate translocase (G6P-T1) known today.[1] G6P-T1 is a part of the glucose-6-phosphatase (G6Pase) enzyme complex,[2] which catalyzes the release of glucose from glucose-6-phosphate (G6P) in both pathways of endogenous hepatic glucose production, gluconeogenesis and glucogenolysis. Inhibitors of G6Pase[3] are therefore of high interest for the regulation of blood glucose and thus for the treatment of the non-insulin-dependent type II diabetes mellitus (NIDDM).[4] Because the control of hyperglycemia in NIDDM cannot satisfactorily be achieved by pharmacological interventions with common antidiabetic drugs, the development of new improved therapeutic approaches represents an important goal. Taking **1** as a lead structure, the elaboration of synthetic approaches to this and related compounds (mumbaistatin analogs) would pave the way for further biological studies (incl. SAR) and the discovery of new compounds as potential antidiabetic drugs.

2. General strategy

Our strategy for the synthesis of mumbaistatin and analogs thereof is based on the retrosynthetic analysis shown in Scheme 1. Because the diketoacid functionality tends to irreversibly form spiroketals with the secondary alcohol under acidic conditions,[1b] it seemed advisable to set up the sensitive functionalities in a late stage of the synthesis. Therefore, we envisioned to employ a pre-target molecule of type **3** in which all the carbonyl groups are masked as protected or free alcohols and could be set free in the final stage of the synthesis through an oxidation/deprotection cascade. The connection of the two aromatic parts to the benzhydrol **3** could possibly be achieved by nucleophilic addition of a lithiated arene intermediate of type **4** to an anthracene carbaldehyde **5**. Such arylanion-benzaldehyde couplings have been successfully used before in the synthesis of various sterically hindered tetra-*ortho*-substituted benzophenones including the prominent PKC inhibitor balanol.[5] To set up the heavily functionalized anthraquinone structure, we intended to employ an aryne-phthalide annulation, which we had utilized previously in the synthesis of the decarboxy-mumbaistatin analog **2** (Fig. 1) following a related strategy.[6]

3. Synthesis of a tetra-*ortho*-substituted benzophenone

For the planned synthesis of mumbaistatin, we selected a bis-*ortho*-substituted aldehyde building block bearing a

Keywords: mumbaistatin; benzophenones; anthraquinones; arynes; total synthesis; G6Pase; diabetes.

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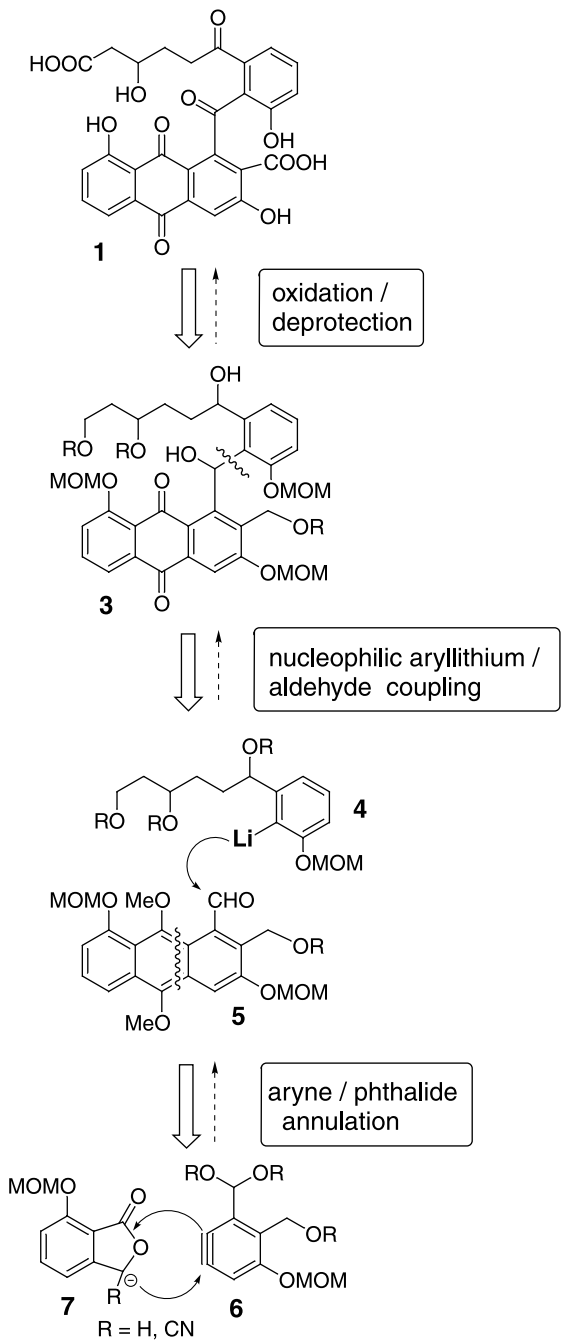


Scheme 1. Retrosynthetic analysis for mumbaistatin (**1**).

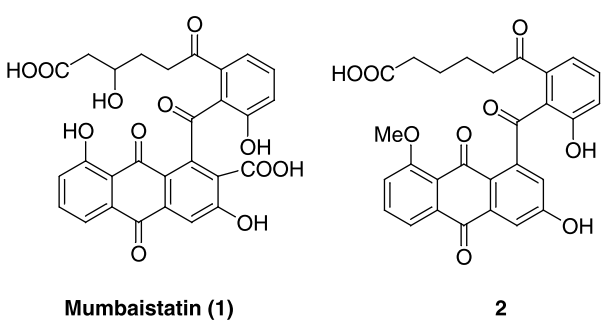
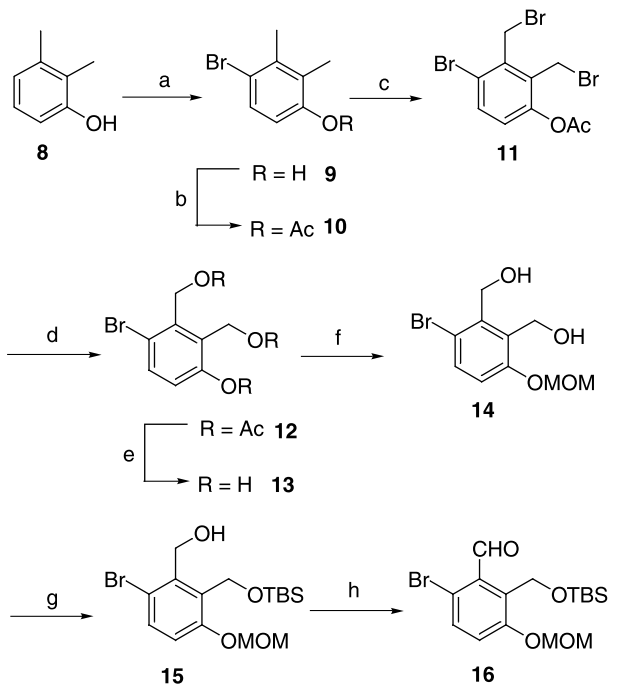


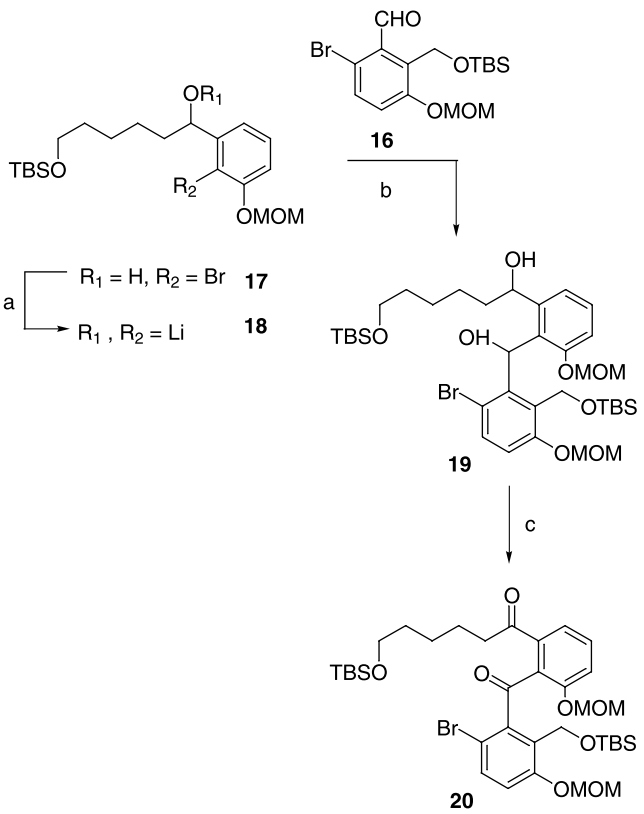
Figure 1. Structure of mumbaistatin (**1**) and the simplified analog **2** previously synthesized.[6]



Scheme 2. Synthesis of the benzaldehyde **16**. (a) NBS, CH_3CN, 2 h, rt, 84%; (b) Ac_2O, pyridine, 2 h, rt, 90%; (c) NBS, CCl_4, $h\nu$, 3.5 h, reflux, 95%; (d) AcOH, NaOAc, 20 h, reflux, 88%; (e) 1N LiOH, dioxane, 1 h, rt, 95%; (f) NaH, MOMCl, DMF, 1 h, rt, 31% (52% rec. s.m.); (g) NEt_3, TBSCl, CH_2Cl_2, −15°C to rt, 1.5 h, 51%; (h) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, −78°C to rt, 90%.

protected hydroxymethyl substituent as a precursor of the benzoic acid functionality. To evaluate whether such an electrophile could be successfully coupled with a nucleophile of type **4**, we applied the aldehyde **16** as a model substrate, which was synthesized in eight steps starting from 2,3-dimethylphenol **8** as follows (Scheme 2): bromination of **8** with NBS in acetonitrile[7] and acetylation was followed by benzylic photo-bromination using NBS in carbon tetrachloride.[8] The tribromide **11** was converted into triol **13** in a two-step procedure by acetolysis using NaOAc/Ac_2O and subsequent saponification with LiOH in dioxane. This efficient five-steps sequence afforded the triol **13** in total yield of 60%. Selective protection of the phenol as a MOM–ether was achieved in only moderate yield of 31% (52% based on recovered starting material) using NaH/MOMCl. The following silylation showed a 4.1:1 regioselectivity towards the desired isomer, giving TBS–ether **15** in 51% yield. Final oxidation of the remaining benzylic alcohol under Swern-conditions produced benzaldehyde **16** in 90% yield (Scheme 3).

To test the coupling reaction, we used the *o*-bromobenzylic alcohol derivative **17**[6] as a model substrate. Treatment of **17** with 2 equiv. of *n*-BuLi generated the corresponding lithiodianion **18**, which was reacted with aldehyde **16**. The crude product, i.e. an inseparable mixture of the diastereomeric benzhydrols **19** and debrominated **17**, was directly oxidized using IBX in DMSO.[9] The tetra-*ortho*-substituted benzophenone **20** was isolated in 38% yield (two steps). Thus, with this model system it was clearly demonstrated that sterically hindered benzophenones related to mumbaistatin can be prepared (albeit in a moderate yield) using the arylanion/benzaldehyde approach.



Scheme 3. Synthesis of the model benzophenone **20**. (a) **17**, 2 equiv. *n*-BuLi, THF, −78°C; (b) **16**, −78°C to rt; (c) IBX, DMSO, 6 h, rt, 38% (two steps).

4. Synthesis of an anthraquinone building block

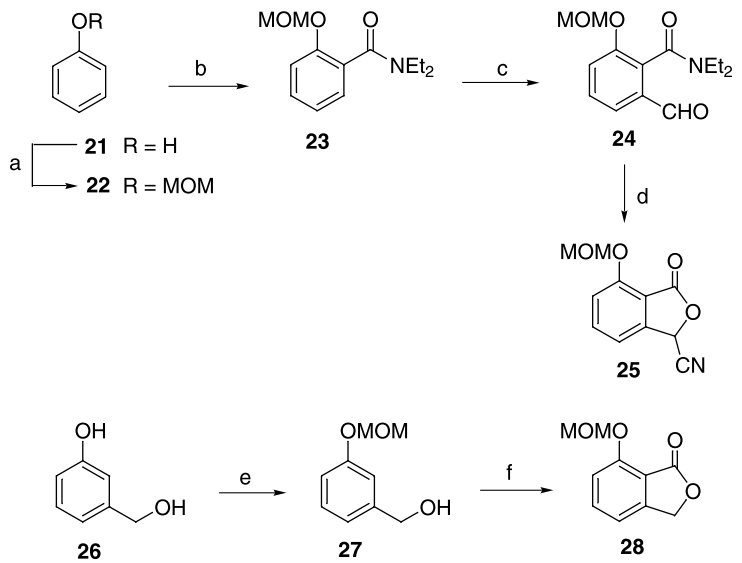
While **20** represents a useful intermediate for the synthesis of some mumbaistatin analogues, a fully elaborated anthraquinone building block would be needed for the total synthesis of the natural product itself following the convergent approach developed earlier.[6]

Therefore, we wanted to investigate the possibility to couple the 'northern' nucleophile with an anthraquinone building block of type **5** (Scheme 1). For the construction of the corresponding structurally complex anthraquinone moiety, a convergent annulation strategy seemed to be attractive,[10] in which the central ring is constructed from two arene building blocks. As in our earlier study, we intended to use the aryne-phthalide annulation reaction developed by Sammes[11] and Biehl.[12] We therefore had to prepare phthalides (as precursors of **7**) and a fully functionalized bromide-building block as a precursor of an aryne of type **6** with the aldehyde function masked as an acetal.

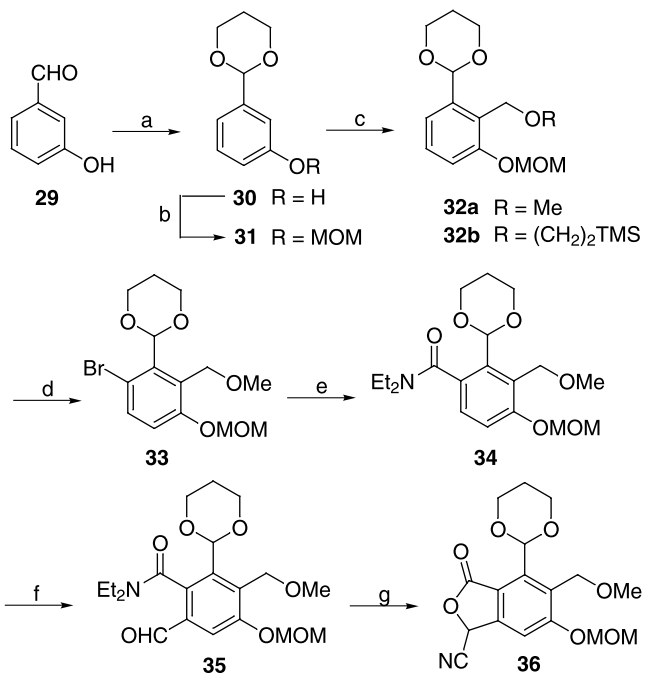
4.1. Preparation of phthalides

For the aryne-phthalide-annulation, either unsubstituted isobenzofuranones or phthalides bearing a cyano-substituent in the benzylic position can be applied (vide infra). The MOM-protected phthalides (**25** and **28**) were synthesized applying *ortho*-lithiation[13] strategies (Scheme 4). For the synthesis of the cyanophthalide **25** we used an iterative double metallation/alkylation approach: lithiation of MOM-phenol **22** followed by addition of *N*,*N*-diethylcarbamoylchloride gave **23**, which was then subjected to a second directed *ortho*-metallation by treatment with *s*-BuLi under Beak/Snieckus[14] conditions. Subsequent addition of DMF and aqueous workup gave the corresponding benzaldehyde **24**, which was directly converted into the cyanophthalide **25** with TMSCN following the procedure of Yoshii.[15]

This four-step sequence produced **25** in an overall yield of 63%. The non-cyano substituted phthalide **28** was synthesized in two steps from the commercial diol **26** by chemoselective MOM-protection of the more acidic phenol functionality, lithiation of the resulting intermediate **27** (under modified literature conditions) and quenching of the resulting dianion with dry ice. After acidic workup, the isobenzofuranone **28** was obtained in 54% overall yield (Scheme 4).



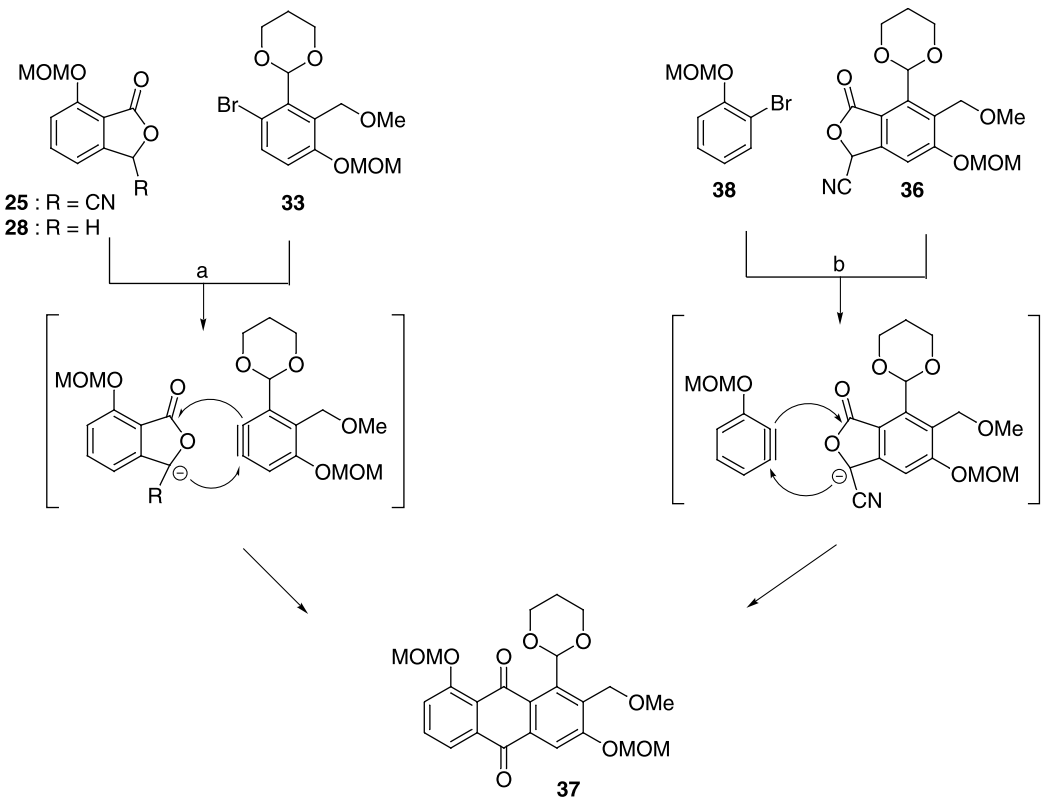
Scheme 4. Synthesis of the phthalides **25** and **28**. (a) NaH, MOMCl, DMF, rt, 94%; (b) *n*-BuLi, TMEDA, then $ClCONEt_2$, THF, −78°C to rt, 91%; (c) *s*-BuLi, TMEDA, then DMF, THF, −78°C to rt, 78%; (d) TMSCN, cat. KCN/18-C-6, CH_2Cl_2, 0°C to rt, then AcOH, rt, 74% (94% rec. s.m.); (e) NaH, MOMCl, THF, 0°C to rt, 84%; (f) *n*-BuLi, benzene, rt, then dry ice, THF, −78°C to rt, then AcOH, rt, 64%.



Scheme 5. Synthesis of the aromatic building blocks **33** and **36** as aryne- or arynophile precursors. (a) $HO(CH_2)_3OH$, cat. *p*TsOH, benzene/THF 6:1, 24 h reflux, 90%; (b) NaH, MOMCl, DMF, 1 h, 0°C to rt, 99%; (c) *n*-BuLi, benzene, rt, then MOMCl (for **32a**) or SEMCl (for **32b**), THF, −20°C to rt, 74% (**32a**) or 68% (**32b**); (d) 3 equiv. NBS, AcOH, NaOAc, 10 h, rt, 81%; (e) *t*-BuLi, THF, −100°C, then $ClCONEt_2$, −100°C to rt, 75%; (f) *s*-BuLi, TMEDA, THF, −20°C, then DMF, 45%; (g) TMSCN, cat. KCN/18-C-6, CH_2Cl_2, 0°C to rt, then AcOH, rt, 71%.

4.2. Synthesis of the aromatic building blocks 33 and 36

We next turned to the preparation of the coupling partner for the envisioned anthraquinone annulation. Because the sequence for the synthesis of bromide **16** was rather long (Scheme 2), we developed a new approach towards such compounds: as shown in Scheme 5, bromide **33** was prepared in a short sequence by alkylation of the protected 3-hydroxy-benzaldehyde **31** with a suitable C_1-electrophile followed by regioselective bromination. Starting from **29**, a highly practical two-step procedure was developed for the synthesis of the protected derivative **31**. Treatment of **29** with 1,3-propandiol in the presence of *p*TsOH in a refluxing benzene/THF mixture (6+1) under azeotropical removal of water gave the corresponding crystalline 1,3-dioxane derivative **30** in significantly higher yield (90%) as compared to the literature procedures. After MOM-protection of the phenol functionality, regioselective *ortho*-lithiation of **31**[16] with *n*-BuLi was best performed in benzene as a solvent. Reaction of the lithiated intermediate with MOMCl gave the methoxymethyl-substituted product **32a**. Alternatively, alkylation with SEMCl afforded the (2-TMS-ethyl)-protected benzylic alcohol **32b** also in good yield. The subsequent (regioselective) bromination proved to be much more difficult than expected: reaction of **32a** with bromine or NBS in various chlorinated or polar aprotic solvent systems (tetrachloromethane, chloroform, dichloromethane, DMF, acetonitrile, 1,4-dioxane and mixtures of these solvents) gave only low yields of **33** due to incomplete conversion, inseparability of starting material and product, and, most seriously, cleavage of the acid-labile 1,3-dioxane protective group. After considerable experimentation it was



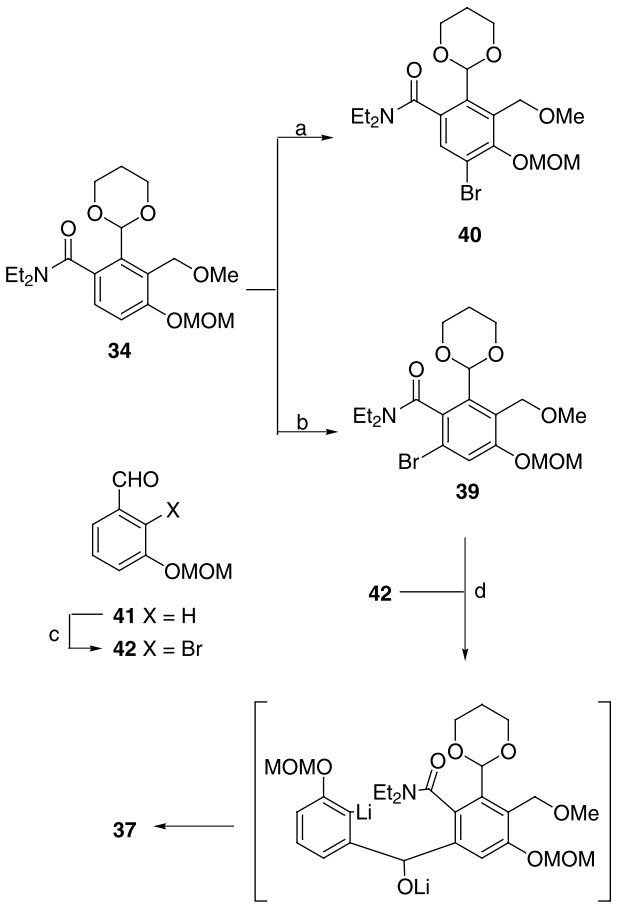
Scheme 6. Synthesis of anthraquinone **37** using aryne/phthalide annulation reactions. (a) **25**, 4 equiv. LiTMP, THF, −78°C, then 2 equiv. **33**, −43°C to rt, 27% or **28**, 4 equiv. LiTMP, THF, −78°C, then 2 equiv. **33**, −43°C to rt, then air, 32%; (b) **36**, 6 equiv. LiTMP, THF, −78°C, then 5 equiv. **38**, −43°C to rt, 43%.

found that this challenging bromination could be achieved with an excess of NBS in a saturated solution of sodium acetate in glacial acetic acid. Under these (unusual) conditions[17] the brominated product **33** was obtained in 81% yield after chromatographic purification as a pure regioisomer (Scheme 5).

We also investigated the possibility of switching the retrosynthetic disconnection for the anthraquinone core. For this purpose, the bromide **33** was converted into the phthalide **36** (Scheme 5), which could then be employed as an 'arynophil' in the reaction with an aryne derived from MOM-protected 2-bromophenol (**38**). Starting from **33**, bromine–lithium exchange followed by addition of diethylcarbamoylchloride gave benzamide **34** in 75% yield together with 21% of the debrominated starting material (**32a**). The rather moderate yield of this transformation (compared to the reaction **22**→**23**) may reflect the high sterical hindrance within the bis-*ortho*-substituted 2-phenyl-1,3-dioxane system. This hindrance also leads to a reduced conformational mobility of the 1,3-dioxane substituent, which is indicated in the ^{1}H NMR spectrum of **34** by the splitting of the two methylene hydrogens of the CH_2OMe group, which disappears upon warming. Moreover, the benzamide **34** proved to be rather reluctant towards further deprotonation (D*o*M). Even with 3–4 equiv. of a base (*s*-BuLi/TMEDA) at −20°C (higher temperatures led to decomposition) the aldehyde **35** was obtained only in 45% yield after trapping the anion with DMF. Other electrophiles such as TMSCl or $BrF_2C–CF_2Br$ (vide infra) gave similar yields for the respective products. All attempts to improve the yield of **35** by varying the base and other reaction parameters (temperature, solvent, additives) were not successful, and even the LICKOR 'superbase' (KO*t*Bu/*n*-BuLi)[18] was not able to deprotonate the benzamide **34**. It seems that **34** strongly prefers a conformation, which disfavors the *ortho*-lithiation (shielding of the aromatic *ortho*-proton by the *N*,*N*-diethylamide substituent). Following the established protocol, **35** was converted into the cyanophthalide **36** in good yield.

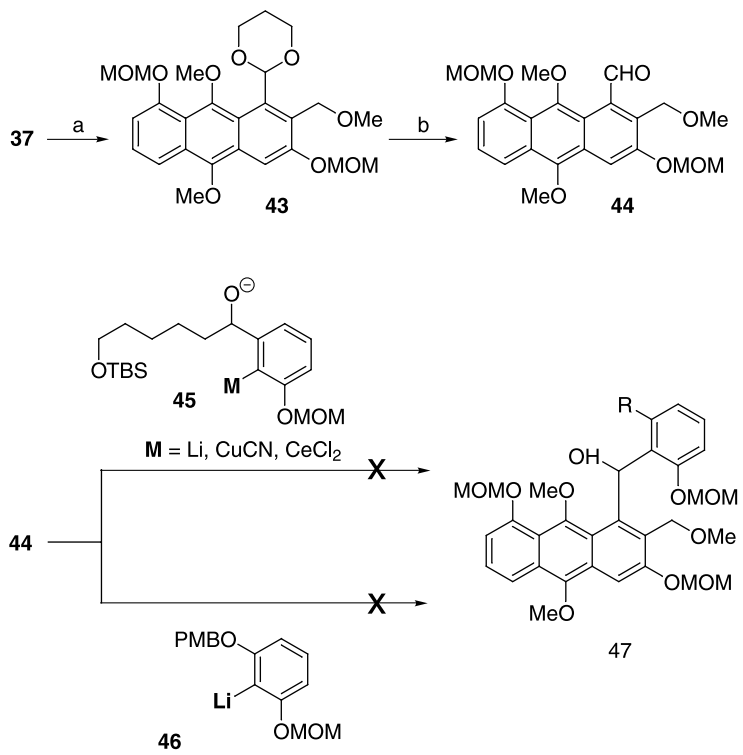
4.3. Assembly of the anthraquinone building block 37

Having succeeded in preparing the building block **33** and the phthalides **25**, **28** and **36**, we next investigated the synthesis of the anthraquinone **37** (Scheme 6). For the planned anthraquinone (see Scheme 1) formation, which is based on the early work of Hauser, Kraus, Kelly and others about annulation reactions using phthalide anions or cycloadditions involving isobenzofuranes,[19] two alternative protocols involving arynes are known in the literature: while Sammes[11] employs deprotonated phthalides (such as **28**) in the reaction with the aryne, Biehl[12] introduced stabilized anions derived from cyanophthalides (such as **25** and **36**) for the same purpose. For the first approach towards **37**, we employed the phthalides **25** and **28** (Scheme 6). The 'cycloaddition' reactions were performed under the conditions optimized earlier[6] by pre-formation of the respective phthalide anion at −78°C (4 equiv. of LiTMP as base) followed by addition of bromide **33** and allowing the mixture to warm up to room temperature. Under these conditions, **33** forms an aryne[20] by 1,2-elimination of HBr, while the phthalides are deprotonated in benzylic position.



Scheme 7. Synthesis of anthraquinone **37** using an anionic cyclisation. (a) *t*-BuLi, TMEDA, THF, −78°C, then $C_2Br_2F_4$, 71%; (b) *s*-BuLi, TMEDA, THF, −30°C, then $C_2Br_2F_4$, 41%; (c) 1.1 equiv. *n*-BuLi, 1.2 equiv. $MeNHCH_2CH_2NMe_2$, benzene, 0°C to rt, 30 min, **41**, 0°C to rt, 30 min, 3 equiv. PhLi, rt, 10 h, 4 equiv. $C_2B_2F_4$, THF, 83%; (d) **39**, *n*-BuLi, THF, −78°C, then **42**, −30°C, 2 h, then 2 equiv. *t*-BuLi, −78°C to rt, then water, air, 2 h, max. 14%.

When **28** was employed, a stream of air was bubbled through the crude reaction mixture in order to oxidize the primary product to the anthraquinone. To our disappointment, all the reactions proceeded rather sluggishly affording the desired product (**37**) in only low yield. With 2 equiv. of the aryne-precursor **33**, moderate yields could be achieved. The unsubstituted, easier accessible phthalide **28** gave slightly better yields (32%) than the cyanophthalide **25** (27%). The annulation proved to be highly regioselective, giving the 'head to head' product **37** as the only detected product. The observed regioselectivity, which was secured by NOE and long range NMR measurements, corresponds to an attack of the phthalide anion at the less electron-rich position of the aryne as indicated in Scheme 6. In the second aryne-phthalide route, the cyanophthalide **36** was (as its anion) reacted with a large excess (5 equiv.) of the intermediate aryne derived from 2-bromo-MOM-phenol **38**. Even the key reaction to form the anthraquinone **37** did now proceed with an appreciable yield of 43%, the efficiency of the overall sequence for the preparation of cyanophthalide **36** was not competitive, due to the low reactivity of benzamide **34** with respect to deprotonation and the resulting low yield of **35** (Scheme 5). Thus, this route did not provide any advantage compared to the first approach towards **37** (coupling of **28** and **33**).



Scheme 8. Synthesis of the anthracene carbaldehyde **44** from anthraquinone **37** and unsuccessful coupling experiments of **44** with various organometallic nucleophiles. (a) $Na_2S_2O_4$, KOH, cat. Bu_4NBr, $(Me)_2SO_4$, THF/H_2O, 18 h, rt, 63%; (b) 10% H_2SO_4 absorbed on silica, CH_2Cl_2, 3 days, rt, 72%.

As a third convergent approach towards the anthraquinone building block **37** we also considered to probe the Snieckus 'anionic Friedel–Crafts equivalent' strategy.[21,22] In this tandem-sequence, a lithiated benzamide is first fused to a second aromatic system, which, after lithiation, undergoes an anionic (Parham-) cyclisation. This methodology has been successfully used in the synthesis of various aromatic and heteroaromatic ring systems.[21,22] Applied to the preparation of anthraquinones, a lithiated benzamide must first be reacted with a 2-bromobenzaldehyde. In the second step, bromine–lithium exchange initiates an intramolecular nucleophilic attack to the amide functionality. Final air-oxidation gives the anthraquinones. Metallation of benzamide **34** under the conditions mentioned above and reaction with $BrF_2C–CF_2Br$ gave bromide **39** in a moderate yield of 41% (Scheme 7). Attempts to improve the yield by using *t*-BuLi/TMEDA at −78°C gave a surprising result: in this case the regioisomeric bromide **40**, arising from *ortho*-lithiation directed by the MOM instead of the benzamide group, was cleanly formed in 71% as the sole regioisomer. This unique regioselectivity, which is in contrast to the normal hierarchy of DMG's,[23] may be attributed again to the sterical crowding within the system: at low temperature the usually stronger directing benzamide cannot easily adopt the conformation required for the directed metallation process, and the more flexible MOM group takes over the directing business. The constitutional assignment of both bromides (**39** and **40**) is based on ^1H and ^{13}C NMR spectroscopy including NOE and long range coupling measurements. The second aromatic building block for the planned tandem-lithiation reaction, the 2-bromobenzaldehyde derivative **42**, was prepared from the MOM-protected 3-hydroxybenzaldehyde **41** in a one-step procedure using the in situ protection/*ortho*-lithiation methodology developed by Comins.[24] Employing **39**, the tandem key transformation was carried out by bromine–lithium exchange (using BuLi) followed by addition of aldehyde **42**, addition of further BuLi and final aerial oxidation. To our disappointment, only low yields of anthraquinone **29** were obtained in numerous attempts, 14% being the best result (Scheme 7). In all experiments, the debrominated starting material (**34**) was isolated as the main product in 70–80% yield. This indicated that the metallation of **39** must have taken place, but the further reaction of the sterically hindered aryllithium species with the aldehyde **42** did obviously not proceed to a significant extend. Variation of the metallation conditions (*n*-BuLi, *t*-BuLi, cosolvents, etc.) and the reaction temperature (up to room temperature) gave no improvement. In conclusion, the aryne-phthalide reaction between **28** and **33** (Scheme 6) until now seems to be the method of choice for the preparation of anthraquinone **37**, although the overall yield starting from 3-hydroxybenzaldehyde is only around 10%.

5. Attempts to prepare the anthracenophenones 47/48

To prepare an anthracene carbaldehyde of type **5** for the crucial coupling reaction, the quinone moiety of **37** had to be protected by reductive methylation and the aldehyde had to be set free selectively (Scheme 8). The method of Kraus[25] ($Na_2S_2O_4/KOH/Me_2SO_4$ in THF/H_2O in the presence of a phase-transfer catalyst) afforded the 9,10-dimethoxyanthracene **43**. The final hydrolysis of the 1,3-dioxane protective group was selectively achieved using 10% H_2SO_4 adsorbed on silica[26] without effecting the MOM groups. The aldehyde **44** proved to be unstable towards light and air, longer standing times in solution led to rapid degradation.

For the anticipated construction of the anthracenophenone system, various organometallic arene nucleophiles related to the upper part of mumbaistatin were tested as coupling partners for the aldehyde **44**. First, we used nucleophiles derived from bromide **17**, which were generated by bromine–lithium exchange and (appropriate) trans-metallation. The reactions were performed under the optimized conditions we developed for the preparation of the benzophenone **20** (Scheme 3). The soft arylcopper- and the almost non-basic arylcerium nucleophile showed no reaction, leaving the aldehyde unchanged. When the aldehyde was treated with the lithium compound **18**, part of the material reacted (judged from the TLC of the crude reaction mixture), but due to fast decomposition during workup and chromatography, we were unable to isolate the new compound. Finally we moved to the resorcinol lithium nucleophile **46** (synthesized with high yield in four steps from resorcinol monobenzoate by MOM-protection, saponification of the benzoate, alkylation with PMB-Cl and final *ortho*-lithation using *n*-BuLi in hexane). Reaction of **46** with **44** proceeded under formation of a coupling product, but again minutes after chromatography the product fractions changed color, and only decomposed material was isolated. It seems that the coupling products derived from aldehyde **44** are even more unstable than the starting material itself.

6. Conclusion

Following a convergent strategy towards the potent G6Pase inhibitor mumbaistatin (**1**), we have elaborated synthetic schemes allowing the preparation of various aromatic and anthraquinone building blocks. While the key-assembly of the northern and 'southern' molecule parts to form a tetra-*ortho*-substituted bezophenone was successfully probed in the model series (preparation of compound **20**), a related transformation employing the sensitive anthracene aldehyde **44** failed so far. Nevertheless, we are optimistic that the developed strategies and building blocks will prove their value for the synthesis of the natural product and structural analogs thereof in the future. For example, by changing the order of the steps during the connection of the building blocks, a benzhydrol of type **19** could be protected and used in an aryne/phthalide-annulation with isobenzofuranones **25** or **28** to produce the anticipated pre-target molecule of type **3**. This is subject of current investigations in these laboratories.

7. Experimental

7.1. General information

Melting points (MP) were determined in open capillary tubes measured on a Büchi Melting Point B-545 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 250, 300 or 500 MHz instruments and are referenced to the non-deuterated impurities of the used solvents ($CDCl_3$, CD_3OD, d_6-DMSO) as internal standard. The spectra are reported in ppm using the following abbreviations to express the multiplicities: s=singlet; d=doublet; t=triplet; q=quartet; m=multiplet; b=broad. ^{13}C chemical shifts were determined using ^{1}H-decouplet spectra, the number of protons bound directly was determined employing the DEPT sequence (q=CH_3; t=CH_2; d=CH; s=quaternary carbon). Some assignments are based on two-dimensional spectra additionally recorded. IR-spectra were recorded on a Perkin–Elmer Paragon 1000 FT-IR spectrometer using the ATR-technique. Gas-chromatography (GC) and low-resolution mass spectra (EI, 70 eV) were recorded on an Agilent HP 6890 GC–MS system using an Optima 1 MS column with H_2 as carrier-gas (flow 10 psi). Temperature programs are presented as following: starting temperature$_{\text{length of stay (min)}}$→(°C/min)→end temperature$_{\text{length of stay (min)}}$. Given are the retention times and the purities calculated from the uncorrected FID-integrations. High-resolution mass spectra (HRMS) were recorded on a Finnigan MAT 900S (ESI). Analytical thin-layer chromatography (TLC) was performed on silica coated alumina plates. Flash chromatography was performed on Merck silica gel 60 (230–400 mesh). Reagents were supplied by Aldrich, Merck, Fluka, Acros and Chemetall and 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 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 with organometallic reagents were carried out under a positive atmosphere of dry argon in oven-dried glassware by using Schlenk techniques. Solvents and solutions were added with syringes through rubber septa. organometallic reagents (*n*-, *sec*-, *t*-BuLi, PhLi) were titrated with menthol in THF in the presence of 1,10-phenanthroline prior to use.

7.1.1. 4-Bromo-2,3-dimethylphenol (9). To a solution of 10.995 g (90 mmol) of 2,3-dimethylphenol (**8**) in 300 ml of dry acetonitrile was added 15.218 g (85.5 mmol) of NBS. The solution was stirred for 1.5 h. Then for 2–3 times portions of 800 mg (4.5 mmol) of NBS were added followed by stirring for another 30 min and TLC-control, until the starting material was completely consumed. The solvent was evaporated, and 50 ml of carbon tetrachloride were added. The succinimide precipitate was removed by filtration. After evaporation of the solvent, the product started to crystallize out of the mixture. Recrystallization gave 15.201 g (75.6 mmol, 84%) of compound **9** as colorless needles. Mp 84–85°C. TLC (cyclohexane/ethyl acetate 6:1) R_f=0.35. IR (ATR): $\tilde{\nu}$ (cm^{-1})=3270 (br, m), 1772 (m), 1700 (s), 1573 (m), 1455 (m), 1427 (m), 1272 (s), 1175 (s), 1067 (s), 998 (m). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=2.20 (s, 3H, H at C7 or C8), 2.35 (s, 3H, H at C7 or C8), 6.52 (d, 1H, ^{3}J=8.5 Hz, H at C6), 7.21 (d, 1H, ^{3}J=8.5 Hz, H at C5). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=19.9, 29.5 (each q, C7, C8), 113.9 (d, C6), 116.3, 124.6 (each s, C1, C4), 129.8 (d, C5), 137.4 (s, C3), 152.7 (s, C1). GC–MS (Optima 1 MS, 10 psi, $50°_2$→(10°/min)→$300°_{10}$): t_{Ret}=14.74 min, GC-purity 98%. MS (EI, 70 eV): 202/204 (79, $[M]^+$), 185/187 (8, $[M-OH]^+$), 171/173 (4, [M−OH, −CH3]$^+$), 121/123 (100), 107 (95), 91 (72), 77 (67), 63 (23), 39 (29). HR-MS (EI): calcd 199.9837 for C_8H_9BrO, found 199.984.

7.1.2. 4-Bromo-2,3-dimethylphenyl-1-acetate (10). A solution of 14.074 g (70 mmol) of phenol **9** in 60 ml of pyridine was treated with 29.8 ml (315 mmol) of acetic acid anhydride. The resulting solution was stirred for 2 h at rt. The pyridine and the Ac_2O were removed under reduced pressure. The residue was purified by flash chromatography (500 g of silica, cyclohexane/ethyl acetate 4:1) to give 15.315 g (63 mmol, 90%) of **10** as a white crystalline solid. Mp: 50–51°C. TLC (cyclohexane/ethyl acetate 4:1) R_f=0.45. IR (ATR): $\tilde{\nu}$ (cm^{-1})=2359 (w), 1759 (s), 1456 (m), 1364 (s), 1215 8 (s), 1204 (s), 1171 (s), 1065 (m), 1009 (w), 878 (w). ^1H NMR (300 MHz, $CDCl_3$): δ=2.15 (s, 3H, CH_3 of C1–OAc), 2.28 (s, 3H, H at C7 or C8), 2.36 (s, 3H, H at C7 or C8), 6.74 (d, 1H, ^3J=8.5 Hz, H at C6), 7.39 (d, 1H, ^3J=8.5 Hz, H at C5). ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.83 (q, *C*H_3 of C1–OAc), 20.01, 20.77 (each q, C7, C8), 120.72 (d, C6), 122.39 (s, C2), 130.25 (d, C5), 130.67 (s, C4), 137.86 (s, C3), 148.26 (s, C1), 169.19 (s, C(O)OMe of C1–OAc). GC–MS (Optima 1 MS, 10 psi, 50°$_2$→(10°/min)→300°$_5$): t_{Ret}=15.45 min, purity 99%. MS (EI, 70 eV): 242/244 (12, $[M]^+$), 202/202 (100, $[M-COCH_3]^+$), 185/187 (4, $[M-Ac-OH]^+$), 164 (8), 121 (85), 107 (50), 91 (54), 77 (33), 63 (19), 43 (48). HR-MS (EI): calcd 199.9837 for C_8H_9BrO $[M-CH_2C{=}O]$, found 199.984.

7.1.3. 4-Bromo-2,3-bis(bromomethyl)phenyl-1-acetate (11). A solution of 14.586 g (60 mmol) of compound **10** dissolved in 350 ml of dry carbon tetrachloride was refluxed for 3.5 h under irradiation of a 150 W photolight. After the succinimide was filtered off, the solvent was evaporated. The residue was recrystallized from cyclohexane/ethyl acetate to give 22.850 g (57 mmol, 97%) of tribromide **11** as colorless needles. Mp: 80–81°C. TLC (cyclohexane/ethyl acetate 2:1) R_f=0.3. IR (ATR): $\tilde{\nu}$ (cm^{-1})=1746 (s), 1580 (m), 1455 (s), 1436 (s), 1286 (s), 1204 (s), 1178 (s), 1156 (s), 1119 (s), 1098 (m), 1019 (m). ^1H NMR (300 MHz, $CDCl_3$): δ=2.37 (s, 3H, CH_3 of C1–OAc), 4.58, 4.76 (each s, 2H, H on C7, C8), 7.01 (d, 1H, ^3J=8.5 Hz, H on C6), 7.57 (d, 1H, ^3J=8.5 Hz, H on C5). ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.0 (q, *C*H_3 of C1–OAc), 24.0, 29.3 (each t, C7, C8), 117.5 (d, C6), 124.7, 125.6 (each s, C2, C4), 134.0 (d, C5), 137.1 (s, C3), 153.7 (s, C1), 168.9 (s, *C*(O)OMe of C1–OAc). GC–MS (Optima 1 MS, 10 psi, 50°$_2$→(25°/min)→300°$_{10}$): t_{Ret}=11.1 min, purity 99%. MS (EI, 70 eV): 402 (4, $[M]^+$), 358 (35, $[M-Ac]^+$), 321 (8, $[M-Br]^+$), 279 (69, $[M-Br-Ac]^+$), 200 (46, $[M-2Br-Ac]^+$), 171 (13), 145 (6), 122 (26), 107 (21), 91 (47), 77 (9), 63 (27), 43 (100). HR-MS (EI): calcd 399.8132 for $C_{10}H_9Br_3O_2$, found 399.813.

7.1.4. Acetic acid 2,3-diacetoxy-6-bromophenylester (12). 22.850 g (57 mmol) of tribromide **11** were dissolved in 300 ml of glacial acetic acid. After addition of 18.705 g (228 mmol) of sodium acetate the reaction mixture was refluxed for 20 h. Afterwards the acetic acid was evaporated. The residue was dissolved in ethyl acetate. The organic phase was filtered, washed with 1N HCl, water and brine and dried over $MgSO_4$. The solvent was evaporated, and the residue, which solidified overnight, was recrystallized from hexane/ethyl acetate to give 18.016 g (50.2 mmol, 88%) of triacetate **12** as colorless crystalline solid. Mp: 75–76°C. TLC (cyclohexane/ethyl acetate 1:1) R_f=0.25. IR (ATR): $\tilde{\nu}$ (cm^{-1})=2356 (w), 1737 (s), 1455 (m), 1375 (m), 1289 (m), 1229 (s), 1195 (s), 1174 (s), 1062 (w), 1025 (s). ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)=1.99, 2.06 (each s, 3H, CH_3 of OAc), 2.09 (s, 3H, CH_3 of OAc), 5.21 (d, 2H, J=9.5 Hz, H at C7 or C8), 5.35 (d, 2H, J=11.5 Hz, H at C7 or C8), 6.94 (dd, 1H, J=36 Hz, ^3J=8.5 Hz, H at C4), 7.56 (dd, 1H, J=40 Hz, ^3J=8.5 Hz, H at C5). GC–MS (Optima 1 MS, 10 psi, 50°$_2$→(25°/min)→300°$_5$): t_{Ret}=11.1 min, purity 99%. MS (EI, 70 eV): 316/318 (3, $[M-CH_2C{=}O]^+$), 279 (15, $[M-Br]^+$), 256/258 (9, $[M-Ac, -OAc]^+$), 237 (14, $[M-Br, -Ac]^+$), 214/216 (13, $[M-2Ac, -OAc]^+$), 187 (5), 177 (39, $[M-Br, -OAc]^+$), 135 (21), 122 (6), 107 (16), 91 (8), 77 (8), 43 (100). HR-MS (EI): calcd 317.9927 for $C_{12}H_{13}O_5Br$ $[M-CH_2C{=}O]$, found 317.992.

7.1.5. 4-Bromo-2,3-bis(hydroxymethyl)phenol (13). A solution of 17.959 g (50 mmol) of compound **12** in 250 ml of 1,4-dioxane was treated with 250 ml of a 1 M aqueous solution of LiOH. The mixture was stirred for 1 h at rt. The dioxane was removed under reduced pressure. The aqueous solution was cooled to 0°C and acidified with 2N HCl. The reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the product solidified upon standing overnight. After recrystallization from hexane/ethyl acetate and intensive drying in high vacuum, 11.210 g (47.5 mmol, 95%) of triol **13** was achieved as yellow solid. Mp: 179–180°C. TLC (cyclohexane/ethyl acetate 1:1) R_f=0.1. IR (ATR): $\tilde{\nu}$ (cm^{-1})=3271 (br, s), 2902 (m), 1579 (s), 1441 (s), 1347 (m), 1285 (s), 1172 (s), 1126 (m), 1045 (m), 995 (s). ^1H NMR (300 MHz, $CDCl_3$): δ=4.84 (s, 2H, H at C7), 4.85 (s, 2H, H at C8), 6.71 (d, 1H, H at C6), 7.34 (d, 1H, H at C5). ^{13}C NMR (75 MHz, $CDCl_3$): δ=57.2 (t, C7), 62.3 (t, C8), 118.0 (d, C6), 115.5 (s, C4), 129.7 (s, C2), 133.8 (d, C5), 140.6 (s, C3), 157.1 (s, C1). MS (EI, 70 eV)): 234/232 (18/20, $[M]^+$), 216/214 (33/30, $[M-H_2O]^+$), 199 (4), 185/187 (17/19), 168 (7), 157 (10), 135 $[M-Br-H_2O]^+$), 107 (100), 89 (17), 79 (62), 77 (65), 63 (23). HR-MS (EI): calcd 233.9715 for $C_8H_9BrO_3$, found 233.971.

7.1.6. 4-Bromo-2,3-bis(hydroxymethyl)methoxy-methoxybenzene (14). 880 mg of a 60% dispersion of sodium hydride in oil were placed in a flask under argon. After washing with dry hexane, the NaH was suspended in 40 ml of dry DMF. The cooled (0°C) suspension was slowly treated with a solution of 4.720 g (20 mmol) of phenol **13** in 30 ml of dry DMF. After the emission of hydrogen had ceased, the mixture was stirred for 30 min at rt. The cooled (0°C) reaction mixture was treated with 1.65 ml (22 mmol) of MOMCl [CAUTION: Due to the carcinogenity of MOMCl all operations involving this reagent should be performed in a well working fume hood!]. Stirring was continued for 1 h at rt, before 100 ml of an ice cooled NH_4Cl solution was added. The mixture was extracted with MTBE. The combined organic layers were washed with 1N NaOH solution, water and brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by flash-chromatography (200 g of silica, cyclohexane/ethyl acetate 1:1) to give 1.718 g (6.2 mmol, 31%) of MOM–ether **14** as a white oil which solidified upon standing. Up to 40% of the starting material **13** could be recovered by acidifying the NaOH washing layers and extraction with MTBE. Mp: 69–70°C. TLC (cyclohexane/ethyl acetate 1:1) R_f=0.15. IR

(ATR): $\tilde{\nu}$ (cm^{-1})=3338 (br, m), 2932 (m), 2896 (m), 1574 (m), 1453 (s), 1254 (s), 1203 (s), 1178 (s), 1151 (s), 1132 (s), 1088 (s), 1050 (s), 989 (s), 919 (s). ^{1}H NMR (300 MHz, CD_3OD): δ (ppm)=3.46 (s, 3H, CH_3 of C1–OMOM), 4.85, 4.89 (each s, 2H, C7, C8), 5.22 (s, 2H, CH_2 of C3–OMOM), 7.06 (d, 1H, ^3J=9 Hz, H at C6), 7.49 (d, 1H, ^3J=9 Hz, H at C5). MS (EI, 70 eV): 276 (15, $[M]^+$), 244/246 (36/34, $[M-H-OCH_3]^+$), 226/228 (45/50, $[M-H-OCH_3-H_2O]^+$), 216 (70), 214 (85), 187 (25), 135 (68), 108 (35), 107 (100), 77 (82). HR-MS (EI): calcd 275.9997 for $C_{10}H_{13}BrO_4$, found 275.998.

7.1.7. 6-Bromo-2-*tert*butyldimethylsilanyloxymethyl-3-methoxymethoxybenzylic alcohol (15). A solution of 1.998 g (7.2 mmol) of compound **14** in 25 ml of dry dichloromethane was cooled to −15°C and treated with 2.0 ml of triethylamine. A solution of 1.296 g (8.6 mmol) of TBSCl was slowly added, and the resulting mixture was stirred for 1 h at −15°C. The temperature was raised to rt, and 1 ml of methanol was added. After stirring was continued for 1 h, 100 ml of water was added. After phase separation, the aqueous solution was extracted with MTBE. 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 (150 g of silica, cyclohexane/ethyl acetate 6:1) to give 1.410 g (3.6 mmol, 51%) of silylether **15** and 0.335 g (0.86 mmol, 12%) of the regioisomer. TLC (cyclohexane/ethyl acetate 6:1) R_f=0.45. ^{1}H NMR (300 MHz, CD_3OD): δ (ppm)=0.12 (s, 6H, CH_3 of Si(Me)$_2$), 0.90 (s, 9H, CH_3 of Si–C(Me)$_3$), 3.46 (s, 3H, CH_3 of C3–OMOM), 4.88 (s, 2H, H at C7), 4.97 (s, 2H, H at C8), 5.21 (s, 2H, CH_2 of C3–OMOM), 7.05 (d, 1H, ^3J=9 Hz, H at C4), 7.49 (d, 1H, ^3J=9 Hz, H at C5). ^{13}C NMR (75 MHz, CD_3OD): δ (ppm)=−5.2 (q, 2CH_3 of Si(Me)$_2$), 19.2 (s, C of Si–C(Me)$_3$), 26.4 (q, 3CH_3 of Si–C(Me)$_3$), 56.6 (q, CH_3 of C3–OMOM), 57.6 (t, C8), 62.0 (t, C7), 96.2 (t, CH_2 of C3–OMOM), 117.3 (d, C4), 118.7 (s, C6), 132.1 (s, C2), 134.2 (d, C5), 141.5 (s, C1), 156.2 (s, C3). MS (EI, 70 eV): 335/335 (38/44, $[M-t\text{Bu}]^+$), 303 (45), 275 (50), 273 (85), 243 (8), 227 (32), 197 (23), 177 (7), 171 (12), 139 (5), 89 (30), 75 (100). HR-MS (EI): calcd 333.0157 for $C_{12}H_{18}BrO_4Si$ ($[M-t\text{Bu}]^+$), found 333.015.

7.1.8. 6-Bromo-3-methoxymethoxy-2-*tert*butyldimethylsiloxymethylbenzaldehyde (16). A solution of 1.130 g (2.9 mmol) of benzylic alcohol **15** in 40 ml of dry dichloromethane was cooled to −78°C and 0.45 ml (6.4 mmol) of dry DMSO was added. After 5 min 0.27 ml (3.2 mmol) of oxalylchloride was added, and the solution turned milky white. After being stirred for 1.5 h at −78°C, 2.0 ml (14.5 mmol) of triethylamine was added, and stirring was continued for 30 min while the temperature was allowed to rise to rt. After addition of 50 ml of sat. NH_4Cl solution the phases where separated, and the aqueous layer was extracted with MTBE. The combined organic layers where 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 6:1) to give 1.016 g (2.6 mmol, 90%) of aldehyde **16** as a pale yellow oil. TLC (cyclohexane/ethyl acetate 6:1) R_f=0.2. IR (ATR): $\tilde{\nu}$ (cm^{-1})=2948 (s), 2924 (s), 2850 (m), 1704 (s), 1571 (m), 1450 (s), 1386 (m), 1359 (m), 1305 (w), 1248 (s), 1201 (s), 1180 (s), 1154 (s), 1064 (s), 985 (s), 921 (s), 837 (s). ^{1}H NMR (300 MHz, d_6-Benzol): δ=0.097 (s, 6H, CH_3 of Si(Me)$_2$), 0.93 (s, 9H, CH_3 of SiC(CH$_3$)$_3$), 3.06 (s, 3H, CH_3 of C3–OMOM), 4.65 (s, 2H, C8), 5.00 (s, 2H, CH_2 of C3–OMOM), 6.70 (d, 1H, ^3J=9 Hz, H at C4), 7.06 (d, 1H, ^3J=9 Hz, H at C5), 10.38 (s, 1H, H at C7). ^{13}C NMR (75 MHz, d_6-Benzol): δ=−5.33 (q, CH_3 of Si(CH$_3$)$_2$), 18.55 (s, Si–C), 25.95 (q, CH_3 of SiC(CH$_3$)$_3$), 40.59 (t, C8), 55.76 (q, CH_3 of C3–OMOM), 94.86 (t, CH_2 of C3–OMOM), 115.38 (s, C2), 119.08 (d, C4), 132.37 (s, C6), 133.37 (d, C5), 136.49 (s, C1), 154.67 (s, C3), 192.74 (d, C7).-GC (HP 1, 25 psi, 100°$_5$→(10°/min)→300°$_5$): t_{Ret}=14.7 min, purity 98%. MS (ESI): 389.3/391.3 ($[M]^+$), 411.3/413.3 ($[M+Na]^+$). HR-MS (ESI): calcd 332.9981 for $C_{16}H_{25}BrSiO_4$, found 332.998.

7.1.9. 1-(2-{[6-Bromo-2-(*tert*butyldimethylsilanyloxymethyl)-3-methoxymethoxyphenyl]-hydroxy-methyl}-3-methoxymethoxy-phenyl)-6-(*tert*-butyldimethyl-silanyloxy)-hexan-1-ol (19). 920 mg (2.06 mmol) of bromide **17**[6] was dissolved in 10 ml of dry THF under argon. The solution was cooled to −78°C, and 2.65 ml of *n*-BuLi (1.6 M solution in hexane) was added. After 10 min a solution of 535 mg of benzaldehyde **16** in 10 ml of dry THF was added slowly via syringe. The mixture was stirred overnight, while the temperature slowly raised to rt. After addition of 20 ml of sat. NH4Cl-solution the THF was distilled of the mixture, and the aqueous residue was extracted with ethyl acetate. The organic layer was washed with brine and dried over $MgSO_4$. The solution was filtered through a pad of silica, and the solvent was evaporated. The resulting crude product containing **19** was directly used in the following oxidation reaction.

7.1.10. 1-(2-{[6-Bromo-2-(*tert*butyldimethyl-silanyloxymethyl)-3-methoxymethoxy-phenyl]-hydroxy-methyl}-3-methoxymethoxy-phenyl)-6-(*tert*-butyl-dimethyl-silanyloxy)-hexan-1-ol (20). The crude product of the coupling reaction was dissolved in 15 ml of dry DMSO. 1.40 g (5 mmol) of IBX were added in one portion, and the mixture was stirred for 6 h. After addition of 2 ml of water the mixture was filtered through a bed of Na_2SO_4/celite and rinsed with 30 ml of MTBE. The solution was washed with 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 9:1) to give 385 mg (0.51 mmol, 38% over two steps) of the benzophenone **20** as a brown oil. TLC (cyclohexane/ethyl acetate 9:1) R_f=0.15. IR (ATR): $\tilde{\nu}$ (cm^{-1})=2924 (s), 2894 (s), 2851 (s), 1698 (s), 1651 (s), 1573 (s), 1462 (s), 1449 (s), 1402 (m), 1273 (s), 1250 (s), 1201 (m), 1183 (m), 1153 (s), 1131 (s), 1079 (s), 985 (s), 922 (s). ^{1}H NMR (300 MHz, d_6-Benzol): δ (ppm)=−0.15, −0.04 (each s, 3H, CH_3 of C20–OSi(Me)$_2$), 0.04 (s, 6H, CH_3 of C1–OSi(Me)$_2$), 0.79 (s, 9H, CH_3 of C20–OSi–*t*Bu), 0.96 (s, 9H, CH_3 of C1–OSi–*t*Bu), 1.48–1.57 (m, 6H, H at C2, C3, C4), 1.90–2.00 (m, 2H, H at C5), 2.99 (s, 3H, CH_3 of C11–OMOM), 3.07 (s, 3H, CH_3 of C16–OMOM), 3.53 (t, 2H, ^3J=6 Hz, H at C1), 4.50, 4.62 (each d, 1H, ^3J=7 Hz, H at C20), 4.68, 4.72 (each d, 1H, J=7 Hz, CH_2 of C11–OMOM), 4.84 (s, 2H, CH_2 of C16–OMOM), 6.69 (dd, 1H ^3J=7 Hz, ^4J=1.2 Hz, H at C10), 6.75 (d, 1H, ^3J=9 Hz, H at C17), 6.95 (dd, 1H, ^3J=8.5 Hz, ^4J=1.2 Hz, H at C8), 7.03 (dd, 1H,

^3J=8.5, 7 Hz, H at C9), 7.19 (d, 1H, ^3J=9 Hz, H at C18). ^{13}C NMR (75 MHz, d_6-Benzol): δ (ppm)=−5.8, −5.6 (each q, $(CH_3)_2$Si of C20−OTBS), −5.1 (q, $(CH_3)_2$Si of C1−OTBS), 18.5 (s, $(Me)_3CSi$ of C20−OTBS), 18.7 (s, $(Me)_3CSi$ of C1−OTBS), 24.4 (t, C3), 25.8 (t, C4), 26.15, 26.2 (each q, 3C, $(CH_3)_3CSi$ of C1−OTBS, C20−OTBS), 33.2 (t, C2), 43.2 (t, C5), 55.7 (q, CH_3 of C11−OMOM), 56.0 (q, CH_3 of C16−OMOM); 57.6 (t, C20), 63.2 (t, C1), 94.8 (t, 2C: CH_2 of C1−OMOM, C20−OMOM), 111.1 (d, C17), 115.8 (d, C10), 119.8 (d, C8), 125.7 (s, C15), 128.8 (d, C9), 132.2, 134.4, 145.2 (s, C14), 147.7 (s, C7), 154.7 (s, C16), 158.2 (s, C11), 193.5 (s, C6), 205.3 (s, C13). MS (ESI): 777/775 (55/45, $[M+Na]^+$), 707 (16), 663 (100), 633 (20), 529 (12), 339 (64). HR-MS (ESI): calcd 775.2673 for $C_{36}H_{57}BrO_8Si_2$+Na, found 775.266.

7.1.11. MOM-phenol (22). 4.40 g of a 60% sodium hydride oil dispersion (110 mmol NaH), 9.411 g (100 mmol) of phenol (**21**) and 8.2 ml (110 mmol) of MOMCl in 350 ml of dry THF were reacted under the same conditions as described above (prepn of **14**) to give 12.988 g (94 mmol, 94%) of MOM-phenol (**22**) as colorless liquid which did not need further purification. TLC (cyclohexane/ethyl acetate 1:1) R_f=0.7. IR (ATR): $\tilde{\nu}$=2894 (w), 2359 (w), 1597 (w), 1274 (s), 1259 (s), 1006 (w), 920 (w), 763 (s). ^{1}H NMR (250 MHz, $CDCl_3$): δ=3.48 (s, 3H, CH_3 of C1−OMOM), 5.16 (s, 2H, CH_2 of C_1−OMOM), 6.97−7.07 (m, 3H, H at C2, C4, C6), 7.25−7.33 (m, 2H, ^3J=8 Hz, H at C3, C5). ^{13}C NMR (63 MHz, $CDCl_3$): δ=55.9 (q, CH_3 of C1−OMOM), 94.4 (t, CH_2 of C1−OMOM), 116.2 (d, C2/C4), 121.8 (d, C4), 129.4 (d, C3/C5), 157.2 (s, C1). GC−MS (Optima 1 MS, 10 psi, 50°$_2$→(25°/min)→300$_{5°}$): t_{Ret}=4.95 min, 99% pure; MS(EI): 138 (36, $[M]^+$), 108 (18, $[M+H-OCH_3]^+$), 93 (3), 77 (23, $[M-OCH_2OCH_3]^+$), 65 (16), 49 (16), 45 (100), 39 (14). HR-MS (EI): calcd 138.068 for $C_8H_{10}O_2$, found 138.068.

7.1.12. 2-Methoxymethoxy-*N*,*N*-diethylbenzamide (23). 8.874 g (64.2 mmol) of MOM−phenol 22 were dissolved in 250 ml of anhydrous THF. At 0°C 12.5 ml (83.5 mmol) of TMEDA followed by 52.2 ml of *n*-Buli (1.6 M in hexane, 83.5 mmol) were added slowly via syringe. The solution was stirred for 2.5 h at 0°C. After being cooled to −78°C, a solution of 12.2 ml (96.3 mmol) of freshly distilled *N*,*N*-diethylcarbamoylchloride in 40 ml of THF were added slowly to the reaction mixture. The yellow solution was stirred overnight while the reaction was allowed to slowly come to rt. The reaction was quenched by addition of 100 ml of a saturated NH_4Cl solution. The mixture was extracted with ethyl acetate (3×300 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 (400 g of silica, cyclohexane/ethyl acetate 3:2) to give 13.858 g (58.4 mmol, 91%) of the benzamide **23** as a yellow oil. TLC (cyclohexane/ethyl acetate 3:2) R_f=0.2. IR (ATR): $\tilde{\nu}$=2969 (m), 2932 (m), 1628 (s), 1599 (s), 1489 (m), 1472 (s), 1456 (s), 1427 (s), 1378 (m), 1362 (m), 1311 (m), 1291 (m), 1273 (m), 1232 (s), 1200 (m), 1152 (s), 1120 (m), 1075 (s), 1041 (m), 988 (s), 941 (m). ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.01 (t, 3H, ^3J=7 Hz, H at C10 or C11), 1.22 (t, 3H, ^3J=7 Hz, H at C10 or C11), 3.14 (q, 2H, ^3J=7 Hz, H at C8, C9), 3.44 (s, 3H, CH_3 of C2−OMOM), 3.61 (br d, 1H, J=6.5 Hz, H at C8 or C9), 5.14 (br d, 2H, J=3 Hz, CH_2 of C2−OMOM), 6.99 (dt, 1H, ^3J=7.5 Hz, ^4J=1 Hz, H at C3), 7.08−7.19 (m, 2H, H at C4, C5), 7.27 (dt, 1H, ^3J=8 Hz, ^4J=12 Hz, H at C6). ^{13}C NMR (63 MHz, $CDCl_3$): δ=12.8, 14.0 (each q, C10, C11), 38.7, 42.7 (each t, C8, C9), 56.1 (q, CH_3 of C2−OMOM), 94.8 (t, CH_2 of C2−OMOM), 114.9 (d, C3), 122.0, 127.4 (each d, C4, C5), 127.9 (s, C1), 129.8 (d, C6), 152.8 (s, C2), 168.5 (s, C7). GC−MS (Optima 1 MS, 10 psi, 50°$_2$→(10°/min)→300°$_5$): t_{Ret}=8.5 min, 99% pure; MS(EI): 237 (35, $[M]^+$), 222 (19, $[M-CH_3]^+$), 206 (17, $[M-OCH_3]^+$),192 (19, $[M-CH_2OCH_3]^+$), 176 (22, $[M-OCH_2OCH_3]^+$), 165 (58, $[M-NEt_2]^+$), 149 (14), 135 (40), 121 (46), 107 (10), 92 (28), 72 (65), 45 (100). HR-MS (EI): calcd 237.1365 for $C_{13}H_{19}NO_3$, found 237.137.

7.1.13. 2-Formyl-6-methoxymethoxy-*N*,*N*-diethyl-benzamide (24). 83.5 ml of *s*BuLi (1.3 M in hexane, 108.8 mmol) were dissolved in 200 ml of dry THF. At −78°C 16.3 ml (108.8 mmol) of TMEDA were added, followed by a solution of 18.430 g (77.7 mmol) of benzamide **23** in 50 ml of THF 15 min later. The reaction mixture was stirred for 1 h at −78°C and for 2 h at −30°C. The red suspension was cooled to −78°C, and 12.0 ml (155 mmol) of anhydrous DMF were added dropwise. The mixture was stirred overnight while slowly warming up to rt. After the reaction was quenched by addition of 50 ml of saturated NH_4Cl solution, the THF was distilled off under reduced pressure. The aqueous residue was extracted with dichloromethane (3×100 ml). The combined organic layers were washed with brine and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure and purification of the residue by flash chromatography (400 g of silica, cyclohexane/ethyl acetate 1:3) afforded 16.075 g (60.6 mmol, 78%) of 2-formyl-6-methoxymethoxy-*N*,*N*-diethyl-benzamide **24** as an orange oil. TLC(cyclohexane/ethyl acetate 1:3) R_f=0.2. IR (ATR): $\tilde{\nu}$=3355 (br, s), 1697 (m), 1633 (s), 1557 (m), 1538 (m), 1505 (m), 1456 (m), 1252 (m), 1152 (m), 1019 (m), 921 (m). ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.01 (t, 3H, ^3J=7 Hz, H at C10 or C11), 1.28 (t, 3H, ^3J=7 Hz, H at C10 or C11), 3.10 (q, 2H, ^3J=7 Hz, 2H at C8 or C9), 3.46 (s, 3H, CH_3 of C6−OMOM), 3.61 (q, 2H, ^3J=7 Hz, H at C8 or C9), 5.18 (s, 2H, CH_2 of C6−OMOM), 7.37−7.46 (m, 2H, H at C4 and C3 or C5), 7.56 (dd, 1H, ^3J=6.5 Hz, ^4J=2.5 Hz, H at C3 or C5), 9.97 (s, 1H, H at C12). ^{13}C NMR (63 MHz, $CDCl_3$): δ=12.6, 13.8 (each q, C10, C11), 38.9,42.7 (each t, C8, C9), 56.4 (q, CH_3 of C6−OMOM), 95.0 (t, CH_2 C6−OMOM), 120.5, 122.8 (each d, C3, C5), 129.9 (d, C4), 133.7 (s, C2), 153.4 (s, C6), 165.6 (s, C7), 190.4 (s, C12). GC−MS (Optima 1 MS, 10 psi, 50°$_2$→(25°/min)→300°$_5$): t_{Ret}=9.5 min, 98% pure; MS(EI): 265 (7, $[M]^+$), 251 (3), 236 (29, $[M-C_2H_5]^+$), 220 (2), 204 (4), 193 (13, $[M-NEt_2]^+$), 179 (7), 163 (6), 149 (23), 134 (6), 121 (10), 86 (11), 72 (51), 45 (100). HR-MS (EI): calcd 265.1314 for $C_{14}H_{19}NO_4$, found 265.131.

7.1.14. 3-Cyano-7-methoxymethoxy-1(3*H*)isobenzo-furanone (25). 13.265 g (50 mmol) of 2-formyl-6-methoxy-methoxy-*N*,*N*-diethylbenzamide **24** was dissolved in 250 ml of dry CH_2Cl_2. At 0°C 650 mg (10 mmol) of KCN and 2.043 g (10 mmol) of 18-crown-6 were added followed by 9.4 ml of TMSCN 10 min later. The reaction mixture was stirred for 30 min at 0°C and for additional 3 h at rt. The solvent was evaporated under reduced pressure. The flask

was closed with a rubber septum, and 40 ml of glacial acetic acid were added. [CAUTION: This reaction should be performed in a well working, closed fume hood due to the danger of exposure of HCN] The solution was stirred overnight at rt. After addition of 100 ml of 1N NaOH solution the 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 by flash chromatography (400 g of silica, cyclohexane/ethyl acetate 3:1) to give 8.070 g (36.8 mmol, 74%; 93% based on recovered starting material) of cyanophthalide **25** as an orange oil, which slowly crystallized at 4°C.-MP: 67–68°C-TLC (cyclohexane/ethyl acetate 2:1) R_f=0.35. IR (ATR): $\tilde{\nu}$=2936 (m), 1772 (s), 1602 (s), 1483 (s), 1453 (m), 1279 (s), 1265 (s), 1234 (s), 1196 (s), 1152 (s), 1092 (s), 1075 (m), 1060 (m), 994 (s), 955 (s), 921 (s). ^{1}H NMR (250 MHz, $CDCl_3$): δ=3.47 (s, 3H, CH_3 of C7–OMOM), 5.34 (s, 2H, CH_2 of C7–OMOM), 6.03 (s, 1H, H at C3), 7.24 (d, 1H, ^3J=7.5 Hz, H at C6), 7.29 (d, 1H, ^3J=8.5 Hz, H at C4), 7.69 (dd, 1H, ^3J=8.5, 7.5 Hz, H at C5). ^{13}C NMR (63 MHz, $CDCl_3$): δ=56.6 (q, CH_3 of C7–OMOM), 64.7 (d, C3), 94.7 (t, CH_2 of C7–OMOM), 112.2 (s), 114.0 (s), 115.2, 116.6 (each d, C4, C6), 137.5 (d, C5), 143.8 (s), 156.5 (s, C7), 165.2 (s, C1). GC–MS (Optima 1 MS, 10 psi, 50°$_2$→(25°/min)→300$_{5°}$): t_{Ret}=9.2 min, 98% pure; MS(EI): 219 (3, $[M]^+$), 188 (12), 159 (13), 130 15), 119 (5), 114 (3), 45 (100).- HRMS (EI): calcd 219.0531 for $C_{11}H_9NO_4$, found 219.052.

7.1.15. 3-Methoxymethoxybenzylic alcohol (27). 4.40 g of a 60% sodium hydride oil dispersion (55 mmol NaH), 6.207 g (50 mmol) of 3-hydroxybenzylic alcohol **26** and 8.2 ml (55 mmol) of MOMCl in 170 ml of dry THF were reacted under the same conditions as described for **14** to give 7.056 g (42 mmol, 84%) of 3-methoxymethoxy-benzylic alcohol **27** as a colorless liquid after purification with flash chromatography (250 g of silica, cyclohexane/ethyl acetate 2.1). TLC (cyclohexane/ethyl acetate 2:1) R_f=0.25. IR (ATR): $\tilde{\nu}$=3389 (br, m), 2930 (m), 2898 (m), 2824 (m), 1585 (s), 1486 (s), 1451 (s), 1403 (m), 1362 (m), 1314 (m), 1250 (s), 1206 (s), 1149 (s), 1077 (s), 1006 (s), 921 (s). ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.91 (br s, 1H, OH), 3.39 (s, 3H, CH_3 of C3–OMOM), 4.64 (s, 2H, H at C7), 5.16 (s, 2H, CH_2 of C3–OMOM), 6.92–7.03 (m, 3H), 7.22–7.28 (m, 1H). ^{13}C NMR (63 MHz, $CDCl_3$): δ=56.0 (q, CH_3 of C3–OMOM), 65.1 (t, C7), 94.3 (t, CH_2 of C3–OMOM), 114.6, 115.4 (each d, C2, C4), 120.3 (d, C6), 129.6 (d, C5), 142.6 (s, C1), 157.4 (s, C3). GC–MS (Optima 1 MS, 10 psi, 50°$_2$→(25°/min)→300°$_5$): t_{Ret}=7.2 min, 97% pure; MS(EI): 168 (30, $[M]^+$), 153 (2), 138 (12), 123 (2), 107 (7), 92 (8), 77 (16), 45 (100). HR-MS (EI): calcd 168.0786 for $C_9H_{12}O_3$, found 168.078.

7.1.16. 7-Methoxymethoxy-(3*H*)isobenzofuran-1-one (28). 3.304 g (20 mmol) of 3-methoxymethoxybenzylic alcohol **27** was dissolved in 200 ml of dry benzene. 32 ml of *n*-BuLi (1.6 M solution in hexane) was added via syringe, and the solution was stirred for 3 h at rt. The solution turned orange. An argon-flushed flask was charged with a handful of dry ice in 200 ml of dry THF. The aryllithium solution was added slowly via transfer cannula. The yellow suspension was stirred overnight during which the temperature was allowed to raise to rt. The solvent was evaporated under reduced pressure. The residue was dissolved in 100 ml of glacial acetic acid and stirred for 3 h at rt. The acetic acid was distilled off under reduced pressure. The residue was dissolved in 200 ml of MTBE and washed with saturated K_2CO_3 solution, water and brine. After drying over $MgSO_4$, the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (200 g of silica, cyclohexane/ethyl acetate 3:1) to give 2.486 g (12.8 mmol, 64%, 85% based on recovered starting material) of **28** as a yellow solid. An analytical sample was recrystallized from hexane/chloroform to give colorless crystals. Mp: 78°C. TLC (cyclohexane/ethyl acetate 3:1) R_f=0.12. IR (ATR): $\tilde{\nu}$=3502 (br, m), 2932 (m), 1757 (s), 1611 (s), 1600 (s), 1483 (s), 1454 (m), 1315 (m), 1268 (m), 1250 (s), 1202 (s), 1151 (s), 1051 (m), 1019 (s), 922 (s). ^{1}H NMR (250 MHz, $CDCl_3$): δ=3.42 (s, 3H, CH_3 of C7–OMOM), 5.15 (s, 2H, H at C3), 5.28 (s, 2H, CH_2 of C7–OMOM), 7.00 (dd, 1H, ^3J=7.5 Hz, ^4J=0.5 Hz, H at C4 or C6), 7.09 (dd, 1H, ^3J=8.5 Hz, ^4J=0.5 Hz, H at C4 or C6), 7.50 (dd, 1H, ^3J=8.5, 7.5 Hz, H at C5). ^{13}C NMR (63 MHz, $CDCl_3$): δ=56.3 (q, CH_3 of C7–OMOM), 68.5 (t, C3), 94.5 (t, CH_2 of C7–OMOM), 114.3, 114.7 (each d, C4, C6), 135.8 (d, C5), 148.9 (s, C3a), 156.0 (s, C7), 168.7 (s, C1); the signal for C7a was not detectable. GC–MS (Optima 1 MS, 10 psi, 50°$_2$→(25°/min)→300°): t_{Ret}=8.5 min, 96%, MS: 193 (13, $[M-1]^+$), 179 (9, $[M-CH_3]^+$), 163 (40, $[M-OCH_3]^+$), 149 (6), 134 (45), 119 (10), 105 (25), 91 (8), 45 (100). HR-MS (EI): calcd 194.0579 for $C_{10}H_{10}O_4$, found 194.058.

7.1.17. 2′-(3-Hydroxyphenyl)-[1′,3′]-dioxane (30). In a flask equipped with reflux condenser and dean-stark device 12.212 g (100 mmol) of 3-hydroxybenzaldehyde (**29**) was dissolved in 250 ml of benzene and 50 ml of THF. 22 ml (300 mmol) of 1,3-propandiol and 570 mg (3 mol%) of *p*-toluenesulfonic acid was added and the reaction mixture was refluxed for 24 h. After being transferred into a separatory funnel, 100 ml of water was added. After phase separation, the aqueous phase was extracted with ethyl acetate (3×100 ml). The combined organic layers were washed with brine and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave a yellow oil which crystallized overnight at 4°C. The material was purified by recrystallization from hexane/ethyl acetate. The mother liquor was concentrated in vacuo and the residue was purified by flash chromatography. All in all 16.150 g (90 mmol, 90%) of 2′-(3-hydroxyphenyl)-[1′,3′]-dioxane **30** were obtained as white crystalline solid. Mp: 108°C. TLC (cyclohexane/ethyl acetate 4:1) R_f=0.13. IR (ATR): $\tilde{\nu}$=3348 (br, m), 2965 (m), 2856 (m), 2359 (w), 1603 (m), 1592 (m), 1456 (m), 1427 (w), 1393 (m), 1377 (m), 1337 (m), 1307 (m), 1281 (m), 1236 (m), 1172 (m), 1156 (m), 1145 (s), 1099 (s), 998 (m), 928 (m), 916 (m). ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.43 (ttd, 1H, J=13.5, 13 Hz, H_{eq} at C5′), 2.11–2.31 (m, 1H, H_{ax} at C5′), 3,95, 4.00 (each d, 1H, H_{ax} at C4′, C6′), 4.22–4.29 (m, 2H, each 1H_{eq} at C4′, C6′), 5.28 (s, 1H, OH), 5.45 (s, 1H, H at C2′), 6.74 (ddd, 1H, ^3J=8 Hz, ^4J=2.5, 1 Hz, H at C4), 6.93 (ψt, 1H, H at C2), 7.00 (d, 1H, ^3J=8 Hz, H at C6), 7.19 (t, 1H, ^3J=8 Hz, H at C5). ^{13}C NMR (63 MHz, $CDCl_3$): δ=25.7 (t, C4′), 67.4 (t, 2C, C4′, C6′), 101.4 (d, C2′), 113.0 (d, C4), 115.9 (d, C2), 118.4 (d, C6), 129.6 (d, C5), 140.0 (s, C1), 155.6 (s, C3).

GC–MS (Optima 1 MS, 10 psi, $50°_2\rightarrow(25°/min)\rightarrow300°_5$): t_{Ret}=9.5 min, 97% pure; MS(EI): 180 (43, $[M]^+$), 179 (85, $[M-H]^+$), 163 (23), 138 (7), 122 (50), 121 (100), 107 (6), 87 (35), 65 (26), 39 (22).

7.1.18. 2′-(3-Methoxymethoxyphenyl)-[1′,3′]-dioxane (31). 7.00 g of a 60% sodium hydride oil dispersion (175 mmol NaH), 26.300 g (1460 mmol) of 2′-(3-hydroxyphenyl)-[1′,3′]-dioxane **30** and 13.3 ml (175 mmol) of MOMCl in 400 ml of anhydrous DMF were reacted under the same conditions as described for **14** to give 32.499 g (145 mmol, 99%) of MOM protected dioxane **31** as a yellow oil. TLC (cyclohexane/ethyl acetate 3:1) R_f=0.3. IR (ATR): $\tilde{\nu}$=2956 (s), 2849 (s), 1676 (m), 1588 (s), 1488 (s), 1453 (s), 1376 (s), 1315 (m), 1275 (s), 1236 (s), 1208 (m), 1151 (s), 1100 (s), 989 (s), 921 (s). ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.41 (br d, 1H, J=13.5 Hz, H_{eq} at C5′), 2.10–2.29 (m, 1H, H_{ax} at C5′), 3.95, 3.99 (each m, 1H, H_{ax} at C4′, C6′), 4.20–4.27 (m, 2H, each 1H_{eq} at C4′, C6′), 3.45 (s, 3H, CH_3 of C3–OMOM), 5.16 (s, 2H, CH_2 of C3–OMOM), 5.45 (s, 1H, H at C2′), 6.97 (ddd, 1H, ^3J=8 Hz, ^4J=2.5, 1 Hz), 7.07–7.16 (m, 2H), 7.22–7.30 (m, 1H). ^{13}C NMR (63 MHz, $CDCl_3$): δ=25.7 (t, C4′), 55.9 (q, CH_3 of C3–OMOM), 67.3 (t, 2C: C4′, C6′), 94.3 (t, CH_2 C3–OMOM), 101.3 (d, C2′), 113.5, 115.9, 119.5 (each d, C2, C4, C6), 129.3 (d, C5), 140.2 (s, C1), 157.2 (s, C3). GC–MS (Optima 1 MS, 10 psi, $50°_2\rightarrow(25°/min)\rightarrow300°_5$): t_{Ret}=9.9 min, 98%. MS(EI): 224 (29, $[M]^+$), 223 (28), 193 (7, $[M-OCH_3]^+$), 179 (8, $[M-CH_2OCH_3]^+$), 163 (10, $[M-OCH_2OCH_3]^+$), 136 (18, $[M-CH_3-$dioxane$]^+$), 121 (7), 103 (6), 87 (20), 65 (10), 45 (100).

7.1.19. 2′-[2-Methoxymethyl-3-(methoxymethoxy)-phenyl]-[1′,3′]-dioxane (32a). 11.210 g (50 mmol) of dioxane **31** was dissolved in 200 ml of anhydrous benzene. Under cooling (ice bath) 46.9 ml of *n*-BuLi (75 mmol, 1.6 M in hexane) was added slowly via syringe. After the solution was stirred for 4 h at rt turning brown, 50 ml of dry THF was added, and the solution was cooled with an −43°C cooling bath. When the solution started to freeze, a solution of 6.50 ml (85 mmol) of MOMCl (which was stored 30 min over K_2CO_3 prior to use) in 20 ml of dry THF was added. The resulting yellow mixture was stirred overnight while the temperature was allowed to rise to rt. After quenching with 100 ml of saturated NH4Cl solution, the phases were separated, and the aqueous layer was extracted with ethyl acetate (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 by flash chromatography (500 g of silica, cyclohexane/ethyl acetate 7:2) to give 9.926 g (37 mmol, 74%) of **32a** as a yellow oil. TLC (cyclohexane/ethyl acetate 4:1) R_f=0.13. IR (ATR): $\tilde{\nu}$=2355 (w), 1692 (w), 1588 (m), 1462 (m), 1375 (m), 1247 (m), 1148 (s), 1111 (m), 1086 (s), 1055 (s), 982 (s), 949 (m), 921 (m), 860 (w). ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.42 (septd, 1H, J=13.5, 1.5 Hz, H_{eq} at C5′), 2.13–2.32 (m, 1H, H_{ax} at C5′), 3.36 (s, 3H, CH_3 of C7–OMe), 3.45 (s, 3H, CH_3 of C3–OMOM), 3.99 (dt, J=13.5, 2 Hz, 2H, each 1H_{ax} at C4′, C6′), 4.21–4.28 (m, 2H, each 1H_{eq} at C4′, C6′), 4.65 (s, 2H, H at C7), 5.17 (s, 2H, CH_2 of C3–OMOM), 5.80 (s, 1H, H at C2′), 7.08 (dd, 1H, ^3J=8 Hz, ^4J=1.5 Hz, H at C4), 7.26 (t, 1H, ^3J=8 Hz, H at C5), 7.35 (dd, 1H, ^3J=8 Hz, ^4J=1.5 Hz, H at C6). ^{13}C NMR (63 MHz, $CDCl_3$): δ=25.8 (t, C5′), 56.0, 57.2 (each q, CH_3 of C7–OMe, C3–OMOM), 64.4 (t, C7), 67.5 (t, 2C, C4′, C6′), 94.8 (t, CH_2 of C3–OMOM), 99.4 (d, C2′), 115.1 (d, C4), 119.8 (d, C6), 124.4 (s, C2), 129.3 (d, C5), 139.5 (s, C1), 155.7 (s, C3). GC–MS (Optima 1 MS, 10 psi, $50°_2\rightarrow(10°/min)\rightarrow300°_5$): t_{Ret}=19.8 min, 96% pure, MS(EI): 268 (18, $[M]^+$), 236 (18, $[M-H-OCH_3]^+$), 221 (13, $[M-H-OCH_3-CH_3]^+$), 206 (2), 191 (10), 176 (13), 165 (13), 150 (6), 135 (10), 120 (19), 105 (10), 45 (100). HR-MS (EI): calcd 268.131 for $C_{14}H_{20}O_5$, found 268.131.

7.1.20. 2′-[6-Bromo-3-methoxymethoxy-2-methoxymethyl-phenyl]-[1′,3′]-dioxane (33). 9.927 g (37 mmol) of **32a** was dissolved in a solution of 18.3 g (225 mmol) sodium acetate in 300 ml of glacial acetic acid. The solution was cooled to 5°C, and 19.760 g of NBS was added in portions. The solution turned clear orange after 1 h and was stirred at rt overnight. After addition of 100 ml of dichloromethane the mixture was cooled in an ice bath, and 300 ml of 2 M NaOH was added. Then solid NaOH and later K_2CO_3 were added in portions, until the aqueous phase was almost neutralized. The phases were separated, and the aqueous layer was extracted with dichloromethane (4×200 ml). The combined organic layers were washed with saturated K_2CO_3 solution, saturated $Na_2S_2O_3$ solution and brine and dried over $MgSO_4$. After evaporation of the solvent the residue was purified by flash chromatography (400 g of silica, cyclohexane/ethyl acetate 3:1) to give 10.413 g (30 mmol, 81%) of bromide **33** as an orange oil. TLC (cyclohexane/ethyl acetate 3:1) R_f=0.15. IR (ATR): $\tilde{\nu}$=2959 (m), 2921 (m), 2847 (m), 1575 (m), 1457 (s), 1393 (m), 1374 (m), 1258 (s), 1234 (m), 1151 (s), 1115 (s), 1088 (s), 1059 (s), 989 (s), 950 (s), 900 (m). ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.44 (br d, 1H, J=13.5 Hz, H_{eq} at C5′), 2.19–2.34 (m, 1H, H_{ax} at C5′), 3.41 (s, 3H, CH_3 of C7–OMe), 3.44 (s, 3H, CH_3 of C3–OMOM), 3.97 (dt, 2H, J=12.5, 2.5 Hz, each 1H_{ax} at C4′, C6′), 4.24–4.30 (m, 2H, each 1H_{eq} at C4′, C6′), 4.87 (s, 2H, H at C7), 5.17 (s, 2H, CH_2 of C3–OMOM), 6.14 (s, 1H, H at C2′), 6.97 (d, 1H, ^3J=9 Hz, H at C4), 7.43 (d, 1H, ^3J=9 Hz, H at C5). ^{13}C NMR (63 MHz, $CDCl_3$): δ=25.8 (t, C5′), 56.0 (q, CH_3 of C3–OMOM), 58.4 (q, CH_3 of C7–OMe), 65.4 (t, C7), 67.9 (t, 2C, C4′, C6′), 94.7 (t, CH_2 of C3–OMOM), 103.6 (d, C2′), 115.5 (s, C6), 117.3 (d, C4), 129.3 (s, C2), 133.4 (d, C5), 136.4 (s, C1), 156.6 (s, C3). GC–MS (Optima 1 MS, 10 psi, $50°_2\rightarrow(25°/min)\rightarrow300°_5$): t_{Ret}=11.7 min, 95% pure; MS (EI): 346/348 (18.5/18, $[M]^+$), 316 (10), 301 (16), 286 (4), 271 (4), 256 (7), 243 (12), 228 (5), 213 (18), 170 (9), 133 (9), 105 (16), 87 (17), 75 (19), 45 (100). HR-MS (EI): calcd 346.042 for $C_{14}H_{19}O_5Br$, found 346.042.

7.1.21. 2-[1′,3′]Dioxane-2′-yl-*N*,*N*-diethyl-4-methoxymethoxy-3-methoxymethyl-benzamide (34). In a 500 ml argon-flushed three-necked flask 10.063 g (mmol) of arylbromide **33** was dissolved in 200 ml of dry THF. At −95°C 35.0 ml *t*-BuLi (1.7 M in pentane, 59.5 mmol) was added via syringe. The solution turned dark brown. After 5 min a solution of 12.9 ml (101.5 mmol) of freshly distilled *N*,*N*-diethylcarbamoylchloride in 40 ml of dry THF was added. After 60 min at −95°C the solution was allowed to rise to rt over 3 h. After stirring for 1 h at rt, the reaction was quenched by addition of 10 ml of ethanol. The solvent was evaporated under reduced pressure. The residue was

purified by flash chromatography (300 g of silica, ethyl acetate/ethanol 20:1) to give 7.987 g (21.8 mmol, 75%) of benzamide **34** as a red viscous oil, which became a brown glassy solid after a few days at 4°C. 1.637 g (6.1 mmol, 21%) of the debrominated starting material 20 could also be isolated, which could be reused. Mp: 76.5°C. TLC (ethyl acetate/ethanol 20:1): R_f=0.2. IR (ATR): $\tilde{\nu}$=2965 (m), 2929 (m), 1626 (s), 1596 (m), 1455 (m), 1427 (m), 1377 (m), 1287 (m), 1253 (m), 1210 (m), 1150 (s), 1115 (s), 1089 (s), 1059 (s), 988 (s), 926 (m). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.95 (t, 3H, J=7 Hz, H at C10), 1.24 (t, 3H, J=7 Hz, H at C11), 1.38 (br d, 1H, J=13.5 Hz, H_{eq} at C5′), 2.19 (m, 1H, H_{ax} at C5′), 3.02 (sex, 1H, J=7 Hz, H at C9), 3.20 (sex, 1H, J=7 Hz, H at C9), 3.21 (sex, 1H, J=7 Hz, H at C8), 3.40 (s, 3H, CH_3 of C12–OMe), 3.45 (s, 3H, CH_3 of C4–OMOM), 3.83 (m, 1H, H_{ax} at C6′), 3.86 (br d, 1H, J=7 Hz, H at C8), 3.87 (m, 1H, H_{ax} at C4′), 4.18 (t, 1H, J=11 Hz, H_{eq} at C4′), 4.22 (t, 1H, J=11 Hz, H_{eq} at C6′), 4.71/4.82 (each d, 1H, J=10 Hz, H at C12), 5.19 (s, 2H, CH_2 of C4–OMOM), 5.68 (s, 1H, H at C2′), 7.07 (s, 1H, H at C6), 7.09 (s, 1H, H at C5). ^{13}C NMR (75 MHz, $CDCl_3$): δ=12.4 (q, C10), 13.5 (q, C11), 25.7 (t, C5′), 38.5 (t, C8), 42.8 (t, C9), 56.0 (q, CH_3 of C4–OMOM), 58.4 (q, CH_3 of C12–OMe), 65.2 (t, C12), 67.4 (t, C4′), 67.6 (t, C6′), 94.6 (t, CH_2 of C4–OMOM), 100.6 (d, C2′), 115.3 (d, C5), 126.4 (s, C3), 127.4 (d, C6), 130.6 (s, C1), 134.9 (s, C2), 156.6 (s, C4), 170.4 (s, C7). GC–MS (Optima 1 MS, 10 psi, 50°$_2$→(25°/min)→300°$_5$): t_{Ret}=13.0 min, 98% pure; MS(EI): 367 (2, $[M]^+$), 352 (8), 336 (7), 320 (9), 295 (33), 266 (20), 237 (18), 219 (21), 204 (13), 177 813), 161 (16), 133 (15), 105 (15), 45 (100). HR-MS (EI): calcd 367.1995 for $C_{19}H_{29}NO_6$, found 367.199.

7.1.22. 2-[1′,3′]Dioxan-2′-yl-*N*,*N*-diethyl-6-formyl-4-methoxymethoxy-3-methoxymethyl-benzamide (35). 9.6 ml of *s*-BuLi (1.3 M in cyclohexane) was dissolved in 40 ml of dry THF. At −78°C, 1.5 ml (12.5 mmol) of TMEDA was added, followed by a solution of 1.836 g (5 mmol) of benzamide **34** in 20 ml of dry THF 15 min later. The solution turned dark brown. After 1 h at −78°C and 3 h at −30°C, the mixture was recooled to −78°C, and a solution of 1.2 ml (15 mmol) of anhydrous DMF in 10 ml of THF was added. The yellow solution was stirred overnight while the temperature was allowed to rise to rt. After addition of 20 ml of saturated NH_4Cl solution the THF was distilled off under reduced pressure. The aqueous residue was extracted with ethyl acetate (3×30 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, ethyl acetate/ethanol 30:1) to give 1.005 g (2.25 mmol, 45%) of **35** as a red oil. TLC (ethyl acetate/ethanol 30:1) R_f=0.25. IR (ATR): $\tilde{\nu}$=2966 (s), 2928 (s), 1692 (s), 1626 (s), 1591 (s), 1432 (s), 1380 (s), 1314 (s), 1289 (s), 1234 (s), 1151 (s), 1126 (s), 1096 (s), 1061 (s), 998 (s), 951 (s). ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.93 (t, 3H, J=7 Hz, H at C11), 1.22 (t, 3H, J=7 Hz), 1.42 (br d, 2H, J=13.5 Hz, H_{eq} at C5′), 2.12–2.29 (m, 1H, H_{ax} at C5′), 2.92–3.23 (m, 3H, H at C8, C9), 3.42, 3.45 (each s, 3H, CH_3 of C12–OMe, C4–OMOM), 3.77–3.94 (m, 3H, H at C8, each 1H_{ax} at C4′, C6′); 4.22 (m, 2H, each 1H_{eq} at C4′, C6′); 4.75 (d, 1H, J=10 Hz, H at C12), 4.91 (d, 1H, J=10 Hz, H at C12), 5.26 (s, 2H, CH_2 of C4–OMOM), 5.69 (s, 1H, H at C2′), 7.64 (s, 1H, H at C5), 9.92 (s, 1H, H at C13). ^{13}C NMR (63 MHz, $CDCl_3$): δ=12.4 (q, C10), 13.4 (q, C9), 25.6 (t, C5′), 38.8 (t, C8), 43.0 (t, C9), 56.3 (q, CH_3 of C4–OMOM), 58.7 (q, CH_3 of C12–OMe), 65.2 (t, C12), 67.5, 67.6 (each t, C4′, C6′), 94.5 (t, CH_2 of C4–OMOM), 100.3 (d, C2′), 113.9 (d, C5), 133.0, 133.0, 133.1, 135.8 (each s, C1, C2, C3, C5), 157.0 (s, C4), 167,1 (s, C7), 190.1 (s, C13). GC–MS (Optima 1 MS, 10 psi, 50°$_2$→(25°/min)→300°$_5$): t_{Ret}=13.8 min, 98% pure; MS(EI): 395 (5, $[M]^+$), 380 (3), 366 (30), 348 (9), 323 (30),3 22 (29), 306 (3), 292 (5), 262 810), 247 (40), 232 (20), 218 (8), 189 (25), 161 (15), 133 (15), 45 (100). HRMS (EI): calcd 395.1944 for $C_{16}H_{29}NO_7$, found 395.194.

7.1.23. 4-[1′,3′]Dioxan-2′-yl-6-methoxymethoxy-5-methoxymethyl-3-oxo-1,3-dihydroisobenzo-furan-1-carbonitrile (36). 160 mg (0.4 mmol) of benzaldehyde **35** was dissolved in 5 ml of dry CH_2Cl_2. At 0°C 4 mg (0.05 mmol) of KCN and 10 mg (0.05 mmol) of 18-crown-6 was added, followed by 0.2 ml of TMSCN 10 min later. The reaction mixture was stirred for 30 min at 0°C and for additional 3 h at rt. The solvent was evaporated under reduced pressure. The flask was closed with a rubber septum, and 3 ml of glacial acetic acid were added. The solution was stirred overnight at rt. After addition of 1N NaOH solution the mixture 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 under reduced pressure, the residue was purified by flash chromatography (30 g of silica, ethyl acetate/ethanol 70:1) to give 89 mg (0.25 mmol, 64%; 92% based on recovered starting material) of cyanophthalide **35** as an orange oil. TLC (ethyl acetate/ethanol 70:1) R_f=0.45. IR (ATR): $\tilde{\nu}$= 3319 (br, m), 2924 (m), 1772 (s), 1600 (s), 1456 (m), 1416 (m), 1307 (s), 1251 (m), 1235 (m), 1151 (s), 1081 (s), 1063 (s), 991 (s), 955 (s), 925 (s). ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.48 (br d, 1H, J=13.5 Hz, H_{eq} at C5′), 2.29 (m, 1H, H_{ax} at C5′), 3.42, 3.45 (each s, 3H, CH_3 of C9–OMe, C6–OMOM), 3.98–4.09 (m, 2H, each 1H_{ax} at C4′, C6′), 4.21–4.27 (m, 2H, each 1H_{eq} at C4′, C6′), 4.87/4.98 (each d, 1H, J=10 Hz, H at C9), 5.28/5.36 (each d, 1H, J=7 Hz, CH_3 of C6–OMOM), 5.94 (s, 1H, H at C2′), 6.80 (s, 1H, H at C1), 7.29 (s, 1H, H at C7). ^{13}C NMR (63 MHz, $CDCl_3$): δ=25.8 (t, C5′), 56.5, 58.7 (each q, CH_3 of C9–OMe, C6–OMOM), 64.4 (d, C1), 65.5 (t, C9), 67.8 (t, 2C: C4′, C6′), 94.4 (t, CH_2 of C6–OMOM), 95.8 (d, C2′), 107.9 (d, C7), 113.7, 113.8 (each s, C5, C8), 131.3, 139.0, 144.0 (each s, C1a, C3a, C4), 163.1 (s, C6), 166.5 (s, C3). GC–MS (Optima 1 MS, 10 psi, 150°$_2$→(10°/min)→300°$_5$): t_{Ret}=12.9 min, 95% pure; MS(EI): 349 (19, $[M]^+$), 317 (2), 302 (5), 261 (2), 246 (8), 231 (4), 215 (8), 186 (5), 147 (2), 103 (6), 75 (13), 45 (100). HR-MS(EI): calcd 349.1161 for $C_{17}H_{19}NO_7$, found 349.116.

7.1.24. 1-[1′,3′]Dioxan-2′-yl-3,8-bismethoxymethoxy-2-methoxymethylanthraquinone (37). *Method A*. 3.4 ml (20 mmol) of freshly distilled 2,2,6,6-tetramethylpiperidin was dissolved in 10 ml of dry THF. At −78°C 12.5 ml of *n*-BuLi (1.6 M in hexane, 20 mmol) was added. The mixture was stirred for 30 min before 0.971 g (5 mmol) of phthalide **28** in 10 ml of THF was added slowly via syringe. After 30 min at −78°C the solution had turned intensive red. After allowing the mixture to warm to −43°C (by changing the cooling bath), a solution of 3.471 g (10 mmol) of bromide

33 in 15 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 20 ml of saturated NH_4Cl solution the THF was distilled off the mixture under reduced pressure. The aqueous residue was extracted with dichloromethane (4x30 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 (50 g of silica, cyclohexane/ethyl acetate 1:3) to give 733 mg (1.6 mmol, 32%) of anthraquinone **37** as a yellow oil.

Method B. 3.4 ml (20 mmol) of freshly distilled 2,2,6,6-tetramethylpiperidin was dissolved in 10 ml of dry THF. At −78°C 12.5 ml of *n*-BuLi (1.6 M in hexane, 20 mmol) was added. The mixture was stirred for 30 min before 1.095 g (5 mmol) of cyanophthalide **25** in 10 ml of THF was added slowly via syringe. After 30 min at −78°C the solution had turned intensive red, and the mixture was allowed to warm to −43°C. A solution of 3.478 g (10 mmol) of bromide **33** in 15 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 618 mg (1.35 mmol, 27%) of anthraquinone **37** as a yellow oil.

Method C. 70 mg (0.2 mmol) of cyanophthalide **36**, 217 mg (1 mmol) of 2-methoxymethoxyphenylbromide **38** and 1.5 mmol of LiTMP in 6 ml of dry THF were reacted under the same conditions as described in Method B. Isolation and purification by flash chromatography gave 37 mg (0.08 mmol, 43%) of anthraquinone **37** as a yellow oil. TLC (cyclohexane/ethyl acetate 1:3) R_f=0.2. IR (ATR): $\tilde{\nu}$=2922 (s), 2823 (m), 1768 (m), 1730 (s), 1667 (s), 1579 (s), 1464 (s), 1407 (s), 1248 (s), 1151 (s), 752 (s). ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.48 (br d, 1H, J=12.5 Hz, H_{eq} on C5′), 2.34 (m, 1H, H_{ax} on C5′), 3.45 (s, 3H, CH_3 of C11−OMe), 3.46 (s, 3H, CH_3 of C3−OMOM), 3.54 (s, 3H, CH_3 of C8−OMOM), 4.09 (br dt, 2H, J=12.5, 2.5 Hz, each 1H_{ax} on C4′, C6′), 4.28 (m, 2H, each 1H_{eq} on C4′, C6′), 5.06 (s, 2H, H on C11), 5.33 (s, 2H, CH_2 of C8−OMOM), 5.37 (s, 2H, CH_2 of C3−OMOM), 6.56 (s, 1H, H on C2′), 7.48 (dd, 1H, ^3J=8.5 Hz, ^4J=1 Hz, H on C7), 7.57 (dd, 1H, ^3J=8.5 Hz, ^4J=7.5 Hz, H on C6), 7.84 (dd, 1H, ^3J=7.5 Hz, ^4J=1 Hz, H on C5), 7.88 (s, 1H, H on C4). ^{13}C NMR (125 MHz, $CDCl_3$): δ=25.9 (t, C5′), 56.3 (q, *C*H$_3$ of C3−OMOM), 56.5 (q, *C*H$_3$ of C8−OMOM), 58.7 (q, *C*H$_3$ of C11−OMe), 66.1 (t, C11), 67.8 (t, 2C, C4′, C6′), 94.0 (t, *C*H$_2$ of C3−OMOM), 95.6 (t, *C*H$_2$ of C8−OMOM), 99.3 (d, C2′), 111.9 (d, C4), 120.6 (d, C5), 123.0 (d, C7), 125.8 (s, C8a), 129.5 (s, C9a), 133.6 (d, C6), 134.4 (s, C4a), 134.6 (s, C5a), 134.9 (s, C2), 139.6 (s, C1), 156.4 (s, C8), 160.1 8s, C3), 182.9 (s, C10), 184.9 (s, C9). HR-MS(EI): calcd 458.1577 for $C_{24}H_{26}O_9$, found 458.157.

7.1.25. 6-Bromo-2-[1′,3′]dioxan-2′-yl-*N*,*N*-diethyl-4-methoxymethoxy-3-methoxymethyl-benzamide (39). 9.6 ml of *s*-BuLi (1.3 M in cyclohexane) was placed in 40 ml of dry THF under argon. At −78°C, 1.5 ml (12.5 mmol) of TMEDA was added, followed by 1.836 g (5 mmol) of benzamide **34** in 20 ml of dry THF 15 min later. The solution turned dark brown. After 1 h at −78°C and 3 h at −30°C, the mixture was recooled to −78°C, and 1.8 ml (15 mmol) of tetrafluorodibromoethane in 10 ml of THF was added. The yellow solution was stirred overnight while the temperature was allowed to rise to rt. After addition of 20 ml of saturated NH_4Cl solution the THF was distilled off under reduced pressure. The aqueous residue was extracted with ethyl acetate (3×30 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, ethyl acetate/ethanol 30:1) to give 0.915 g (2.05 mmol, 41%) of bromide **39** as a red oil. TLC (ethyl acetate/ethanol 30:1) R_f=0.25. IR (ATR): $\tilde{\nu}$=2966 (s), 2928 (s), 1632 (s), 1583 (s), 1430 (s), 1379 (s), 1284 (s), 1234 (s), 1207 (s), 1150 (s), 1121 (s), 1090 (s), 1060 (s), 989 (s), 946 (s), 927 (s). ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.04 (t, 3H, J=7 Hz, H at C11), 1.26 (t, 3H, J=7 Hz, H at C10), 1.38 (br d, 1H, J=13.5 Hz, H_{eq} at C5′), 2.12–2.27 (m, 1H, H_{ax} at C5′), 3.00–3.24 (m, 2H, each 1H at C8, C9), 3.38 (s, 3H, CH_3 of C12−OMe), 3.43 (s, 3H, CH_3 of C4−OMOM), 3.46–3.65 (m, 2H, each 1H at C8, C9), 3.73–3.90 (m, 2H, each 1H_{ax} at C4′, C6′), 4.14–4.26 (m, 2H, each 1H_{eq} at C4′, C6′), 4.67 (d, 1H, J=10 Hz, H at C12), 4.85 (d, 1H, J=10 Hz, H at C12), 5.17 (s, 2H, CH_2 of C4−OMOM), 5.55 (s, 1H, H at C2′), 7.31 (s, 1H, H at C5). ^{13}C NMR (63 MHz, $CDCl_3$): δ=12.3 (q, C10), 13.2 (q, C11), 25.6 (t, C5′), 38.5 (t, C8), 42.9 (t, C9), 56.1 (q, *C*H$_3$ of C4−OMOM), 58.4 (q, *C*H$_2$ of C12−OMe), 65.2 (t, C12), 67.5, 67.6 (each t, C4′, C6′), 94.6 (t, *C*H$_2$ of C4−OMOM), 101.0 (d, C2′), 119.6 (d, C6), 119.9 (s, C5), 126.4, 131.2, 136.4 (each s, C1, C2, C3), 157.1 8s, C4), 167.4 (s, C7). GC−MS (Optima 1 MS, 10 psi, 150°$_2$→(10°/min)→300°$_5$): t_{Ret}=11.9 min, purity 97%; MS(EI): 447, 445 (1, $[M]^+$), 432, 430 (1), 415 (5), 400 (7), 373 (15), 344 (8), 315 (10), 299 (18), 284 (8), 257 (6), 45 (100). HR-MS(EI): calcd 445.1100 for $C_{19}H_{28}NO_6Br$, found 445.110.

7.1.26. 5-Bromo-2-[1′,3′]dioxan-2′-yl-*N*,*N*-diethyl-4-methoxymethoxy-3-methoxymethyl-benzamide (40). To a solution of 1.836 g (5 mmol) of benzamide **39** in 60 ml of dry THF at −78°C was added 1.5 ml (10 mmol) of TMEDA followed by 5.9 ml of *t*-BuLi (1.7 M in pentane) 5 min later. The solution turned dark red. After stirring for 1 h at −78°C and 2 h at −30°C the solution was cooled to −78°C, and 1.8 ml (15 mmol) of tetrafluorodibromoethane in 10 ml of THF was added. The yellow solution was stirred overnight while the temperature was allowed to slowly rise to rt. Workup and purification as described for **39** gave 1.584 g (3.55 mmol, 71%) of bromide **40** as a red gum. TLC (ethyl acetate/ethanol 30:1) R_f=0.25. IR (ATR): $\tilde{\nu}$=2965 (s), 2928 (s), 1631 (s), 1580 (m), 1556 (m), 1455 (s), 1426 (s), 1378 (s), 1346 (m), 1290 (s), 1235 (s), 1203 (s), 1154 (s), 1114 (s), 1090 (s), 1025 (m), 1004 (s), 943 (s). ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.98 (t, 3H, J=7 Hz, H at C11), 1.23 (t, 3H, J=7 Hz, H at C10), 1.37 (br d, 1H, J=12.5 Hz, H_{eq} at C5′), 2.16 (m, 1H, H_{ax} at C5′), 3.03 (m, 1H, H at C9), 3.17 (m, 1H, H at C9), 3.22 (m, 1H, H at C8), 3.41 (s, 3H, CH_3 of C12−OMe), 3.65 (s, 3H, CH_3 of C4−OMOM), 3.82 (m, 1H, H at C8), 3.83 (m, 2H, each 1H_{ax} at C4′, C6′), 4.19 (br dt, 2H, J=12, 4.5 Hz, each 1H_{ax} at C4′, C6′), 4.70/4.74 (each d,

1H, J=10 Hz, H at C12), 5.09/5.11 (each d, 1H, J=5 Hz, CH_2 of C4−OMOM), 5.64 (s, 1H, H at C2′), 7.35 (s, 1H H at C6). ^{13}C NMR (63 MHz, $CDCl_3$): δ=12.4 (q, C10), 13.5 (q, C11), 25.6 (t, C5′), 38.6 (t, C8), 42.8 (t, C9), 58.0 (q, CH_2 of C4−OMOM), 58.4 (q, CH_2 of C12−OMe), 66.0 (t, C12), 67.4, 67.5 (each t, C4′, C6′), 100.0 (d, C3′), 100.7 (t, CH_2 of C4−OMOM), 118.4 (s, C5), 131.2 (d, C6), 132.9 (s, C1), 134.5 (s, C3), 134.6 (s, C2), 154.1 (s, C4), 168.6 (s, C7). GC−MS (Optima 1 MS, 10 psi, 50°$_2$→(25°/min)→300°$_5$): t_{Ret}=13.9 min, 94% pure; MS(EI): 447, 445 (1, $[M]^+$), 432, 430 (10), 415 (8), 400 (7), 373 (15), 344 (8), 328 (22), 312 (28), 297 (18), 284 (8), 257 (6), 241 (12), 213 (10), 45 (100). HR-MS(EI): calcd 445.1100 for $C_{19}H_{28}NO_6Br$, found 445.110.

7.1.27. 2-Bromo-3-methoxymethoxybenzaldehyde (42). To a solution of 3.4 ml (26 mmol) of *N*,*N*,*N*′-trimethylethylendiamine and 40 ml of anhydrous benzene was added 15 ml of *n*-BuLi (1.6 M in hexane, 24 mmol) slowly at 0°C. The solution was stirred for 30 min at rt. At 0°C 3.324 g (20 mmol) of 3-methoxymethoxybenzaldehyde **41** in 20 ml of benzene was added and the resulting solution was stirred for 30 min at rt. 35 ml PhLi (1.8 M in cyclohexane/ether, 60 mmol) was added and the reaction mixture was stirred for 24 h at rt. 40 ml of dry THF was added to the resulting brown suspension. The mixture was cooled to −43°C, and 9.6 ml (80 mmol) of tetrafluorodibromoethane was added dropwise. The cooling bath was removed and the solution was stirred for 2 h during which the temperature was allowed to rise to rt. After additional 2 h at rt the reaction was quenched by addition of 50 ml of saturated NH_4Cl solution. The solvent was distilled off the mixture under reduced pressure. The aqueous residue was extracted with dichloromethane (3×100 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 (250 g of silica, cyclohexane/ethyl acetate 5:1) to give 4.080 g (16.6 mmol, 83%) of bromide **42** as an orange oil. TLC (cyclohexane/ethyl acetate 5:1) R_f=0.2. IR (ATR): $\tilde{\nu}$=2897 (w), 1689 (s), 1566 (s), 1459 (m), 1434 (m), 1379 (m), 1257 (s), 1235 (s), 1203 (m), 1150 (s), 1083 (s), 1006 (s), 920 (s). ^{1}H NMR (250 MHz, $CDCl_3$): δ=3.51 (s, 3H, CH_3 of C3−OMO), 5.27 (s, 2H, CH_2 of C3−OMOM), 7.31−7.36 (m, 2H), 7.55 (dd, 1H, ^3J=7 Hz, ^4J=2.5 Hz), 10.40 (s, 1H, H at C7). ^{13}C NMR (63 MHz, $CDCl_3$): δ=56.5 (q, CH_3 of C3−OMOM), 95.2 (t, CH_2 of C3−OMOM), 118.0 (s, C2), 121.1, 122.8, 128.3 (each d, C4, C5, C6), 134.8 (s, C1), 154.2 (s, C3), 192.1 (d, C7). GC−MS (Optima 1 MS, 10 psi, 150°$_2$→(10°/min)→300°$_5$): t_{Ret}=4.8 min, 96% pure; MS(EI): 246, 244 (9, $[M]^+$), 213 (3), 143 (4), 92 (4), 75 (6), 63 (9), 45 (100). HRMS (EI): calcd 243.9735 for $C_9H_9BrO_3$, found 243.975.

7.1.28. 1-[1′,3′]Dioxan-2′-yl-3,8-bismethoxymethoxy-2-methoxymethylanthraquinone (37). *Method D*. In a 25 ml argon-flushed schlenk flask 300 mg (0.67 mmol) of bromobenzamide **39** was dissolved in 5 ml of dry THF. At −78°C 0.42 ml of *n*-BuLi (1.6 M, 0.67 mmol) was added, and the mixture was stirred for 15 min. Then 328 mg (1.34 mmol) of bromobenz-aldehyde **42** in 5 ml of THF was added, and the solution was stirred for 1 h at −78°C and for 2 h at −30°C. The solution was recooled to −78°C, and 0.84 ml of *n*-BuLi (1.34 mmol) was added. After 2 h the cooling bath was removed and the solution was stirred overnight at rt. Then the flask was opened and the brown mixture was stirred for 2 h while a slight steam of air was passed through it. Isolation and purification as described in method A gave 43 mg (0.09 mmol, 14%) of anthraquinone **37** as a yellow oil.

7.1.29. 2′-(9,10-Dimethoxy-3,8-bismethoxymethoxy-2-methoxymethylanthracen-1-yl)-[1′,3′]-dioxane (43). 916 mg (2 mmol) of the anthraquinone **37** and 80 mg of tetrabutylammoniumbromide were dissolved in 8 ml of THF and 4 ml of water. 1.567 g (9 mmol) of sodium dithionite and 5 min later 1.650 g (30 mmol) of KOH was added. After additional 5 min 2.85 ml (30 mmol) of dimethylsulfate 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 10 ml of saturated NH_4Cl solution and extracted with ethyl acetate (5×20 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 (50 g silica, cyclohexane/ethyl acetate 1:1) to give 615 mg (1.26 mmol, 63%) of the methoxyanthracene **43** as yellow foam. TLC (cyclohexane/ethyl acetate 1:1): R_f=0.2. IR (ATR): $\tilde{\nu}$=2927 (s), 2839 (s), 2243 (m), 1730 (m), 1609 (s), 1556 (s), 1523 (s), 1448 (s), 1394 (s), 1352 (s), 1313 (s), 1223 (s), 1145 (s), 1124 (s), 854 (s). ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.48 (br d, 1H, J=13.5 Hz, H_{ax} on C5′), 2.28−2.46 (m, 1H, H_{eq} on C5′), 3.52 (s, 3H, CH_3), 3.54 (s, 3H, CH_3), 3.63 (s, 3H, CH_3), 3.79 (s, 3H, CH_3), 3.97 (s, 3H, CH_3), 4.00−4.13 (m, 2H, each $1H_{eq}$ on C4′, C6′), 4.28−4.35 (m, 2H, each $1H_{ax}$ on C4′, C6′), 5.20 (s, 2H, H on C11), 5.40 (s, 3H, CH_3 of C2−OMOM), 5.40 (s, 3H, CH_3 of C8−OMOM), 7.02 (dd, 1H, ^3J=7.5 Hz, ^4J=1 Hz, H on C7), 7.23 (s, 1H, H on C2′), 7.32 (dt, 1H, ^3J=8.5, 7.5 Hz, H on C6), 7.71 (s, 1H, H on C4), 7.88 (dd, 1H ^3J=8.5 Hz, ^4J=1 Hz, H on C5). ^{13}C NMR (63 MHz, $CDCl_3$): δ=26.0 (t, C5′), 56.1 (q), 56.5 (q,), 58.5 (q), 62.1 (q), 63.6 (q), 67.3 (t, C11), 67.9 (t, 2C, C4′, C6′), 94.3, 96.1 (each t, CH_2 of C3−OMOM, C8−OMOM), 101.3, 103.4 (each d, C4, C7), 109.5 (d), 116.1 (d), 118.3 (s), 121.0 (s), 125.4 (d), 126.4 (s), 127.4 (s), 132.0 (s), 135.3 (s), 146.3 (s, C3/8), 150.5 (s, C3/8), 153.6, 154.3 (each s, C9, C10). GC−MS (Optima 1 MS, 10 psi, 150°$_2$→(10°/min)→300°$_5$): t_{Ret}=17.9 min, 94% pure; MS(EI): 488 (65, $[M]^+$), 473 (11), 457 (10), 413 (24), 384 (16), 339 (50), 279 (46), 251 (16), 223 (8), 181 (6), 152 (10), 75 (12). HR-MS (EI): 488.2046 calcd for $C_{26}H_{32}O_9$, found 488.205.

7.1.30. 9,10-Dimethoxy-3,8-methoxymethoxy-2-methoxymethylanthracene-1-carbaldehyde (44). 2.54 g of silica was suspended in 11 ml of dichloro-methane. 250 mg 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 absorbed on the silica. 254 mg (0.52 mmol) of anthracenyl-[1.3]dioxane in 4 ml of dichloromethane was added dropwise. The yellow suspension soon turned 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 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 1 M NaOH solution, water and brine and dried over $MgSO_4$. After evaporation of the solvent the residue was purified by flash chromatography (25 g silica, cyclohexane/ethyl acetate 3:2) to give 161 mg of **44** (0.375 mmol, 72%) as a brown solidified oil. TLC (cyclohexane/ethyl acetate 3:2): R_f=0.2. IR (ATR): $\tilde{\nu}$=3371 (br, m), 2930 (m), 2896 (m), 2824 (m), 1692 (s), 1608 (s), 1561 (m), 1526 (s), 1449 (s), 1431 (s), 1397 (m), 1355 (s), 1225 (s), 1206 (s), 1150 (s), 1038 (s), 1013 (s), 973 (s), 920 (s). ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.40 (s, 3H, CH_3), 3.52 (s, 3H, CH_3), 3.59 (s, 3H, CH_3), 3.69 (s, 3H, CH_3), 4.00 (s, 3H, CH_3), 4.71 (s, 2H, CH_2), 5.27 (s), 5.37 (s, 2H, CH_2 of OMOM), 5.39 (s, 2H, CH_2 of OMOM), 7.06 (d, 1H, J=7.5 Hz, H on C7), 7.35 (dd, 1H, ^3J=8.5, 7.5 Hz, H on C6), 7.70 (s, 1H, H on C4), 7.90 (d, 1H, ^3J=8.5 Hz, H on C5), 10.68 (s, 1H, H on C11). ^{13}C NMR (75 MHz, $CDCl_3$): δ=56.3, 56.6 (each q, CH$_3$ of C3–OMOM, C8–OMOM), 58.6 (q, CH$_3$ of C12–OMe), 62.4, 63.0 (each q, CH$_3$ of C9–OMe, C10–OMe), 65.2 (t, C12), 94.6, 96.1 (each t, CH$_2$ of C3–OMOM, C8–OMOM), 103.0, 109.4 (each d, C4, C7), 116.2 (d, C5), 117.1 (s), 120.5 (s), 125.4 (s), 126.0 (d, C6), 127.5 (s), 128.1 (s), 138.5 (s, C1), 146.9, 148.7 (each s, C9, C10), 153.0, 153.3 (each s, C3, C8), 193.9 (d, C11). GC–MS (Optima 1 MS, 10 psi, 200°$_2$→(10°/min)→300°$_5$): t_{Ret}=8.0 min, 95% pure; MS(EI): 430 (17, [M]$^+$), 401 (2), 386 (7), 354 (10), 339 (24), 310 (11), 295 (26), 279 (16), 251 (14), 223 (7), 208 (5), 181 (5), 152 (11), 115 (5), 75 (34), 45 (100). HRMS (EI): calcd 430.1628 for $C_{23}H_{26}O_8$, found 430.163.

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