DOI: 10.1002/ejoc.200600353

Preparation of Highly Alkoxy-Substituted Naphthaldehyde Derivatives – A Regioselective Approach to Building Blocks for the Synthesis of Rubromycins

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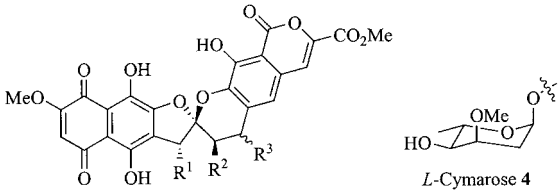
Keywords: Naphthaldehydes / Arynes / Cycloaddition / Oxidation / Boronic acids

An efficient synthesis of highly substituted naphthaldehyde derivatives **8** was required for the planned synthesis of compounds of the rubromycin family. Three different routes towards this goal were attempted. Route I started with 1,5-dihydroxynaphthalene (**10**), and the pentaalkoxy-substituted naphthaldehyde **17** was obtained in a straightforward sequence in moderate overall yield. Route II employed an aryne cycloaddition to generate the functionalized naphthalene skeleton. This sequence smoothly provided the bromonaphthalene derivative **19**, which served as a very suitable precursor of aldehyde **24**, boronic acid **25**, and finally the unsymmetrically substituted hexaalkoxynaphthalene derivative **18**. Unfortunately, though, the regioselective formylation of **18** to provide the desired aldehyde **8a** was not possible, this key compound being obtained only in low yield. Whereas an attempted Claisen rearrangement of *O*-allylated derivative **30** furnished the wrong regioisomer **33**, the *ortho*-Fries rearrangement of the easily available carbamate **34** smoothly afforded the expected amide **35**, which turned out to be essentially inert and could not be converted into the corresponding naphthaldeyde **8b**. We therefore developed Route III, involving an alternative aryne cycloaddition and a subsequent regioselective ring-opening of the tricyclic adduct **41**. This sequence enabled us to efficiently prepare acetal **44**, which was transformed into the desired highly substituted and regioselectively protected naphthaldehyde derivative **8b**. The synthesis of this key compound could be achieved in a 12-step sequence in an overall yield of 9%. Our planned rubromycin synthesis was successfully verified by the conversion of **8b** into the protected α-hydroxy enone **7b** by addition of lithiated methoxyallene followed by hydrolysis and subsequent silylation of intermediate **7a**.

Introduction

Members of the known class of rubromycins such as γ-rubromycin (**1**),[1] purpuromycin (**2**)[2] and heliquinomycin (**3**)[3] are structurally related pigments displaying a broad range of biological activity (Figure 1). While γ-rubromycin (**1**) is known to be a potent inhibitor of DNA-polymerase, a reverse transcriptase of HI virus type 1,[4] purpuromycin (**2**) displays activity against bacteria and fungi[2] and is a potential topical agent for vaginal infections.[5] Heliquinomycin (**3**), in contrast, proved to be a selective inhibitor of DNA-helicase.[3] The basic structure of the rubromycins combines a naphthoquinone moiety with a 5,6-spiroketal fused with an isocoumarin derivative. Despite the interesting biological properties and intriguing molecular architectures of these natural products, only the synthesis of racemic heliquinomycinone (the aglycon of **3**) has been reported so far.[6] Some model studies have also been undertaken.[7,8]

Here we wish to present our studies dealing with the regioselective construction of highly alkoxy-substituted naphthaldehydes for employment as key building blocks in a general approach towards rubromycins. Our retrosynthetic analysis envisaged the spiroketal **5** (Scheme 1) serving as a suitable precursor for their synthesis. Compound **5** was expected to be accessible through Pd-catalysed C–C coupling of an iodinated isocoumarin derivative **6**[9] with a naphthyl-substituted α-hydroxy enone derivative **7** and subsequent ketal formation. The synthesis of the required enone **7** was in turn expected to be achievable by addition of lithiated allene derivative **9** (which can bear a chiral auxiliary R*)[10] to the functionalized naphthaldehyde **8**, followed by acidic hydrolysis of the alkoxyallene moiety.[11]



γ-Rubromycin **1**: $R^1 = R^2 = R^3 = H$
Purpuromycin **2**: $R^1 = R^2 = H$, $R^3 = OH$
Heliquinomycin **3**: R^1 = *O*-Cymarose, $R^2 = OH$, $R^3 = H$

Figure 1. Compounds of the rubromycin family.

For the development of a suitable synthesis for the construction of hexasubstituted naphthaldehyde **8** we pursued three different strategies. Most obviously, a simple functionalized naphthalene skeleton such as **10** and subsequent in-

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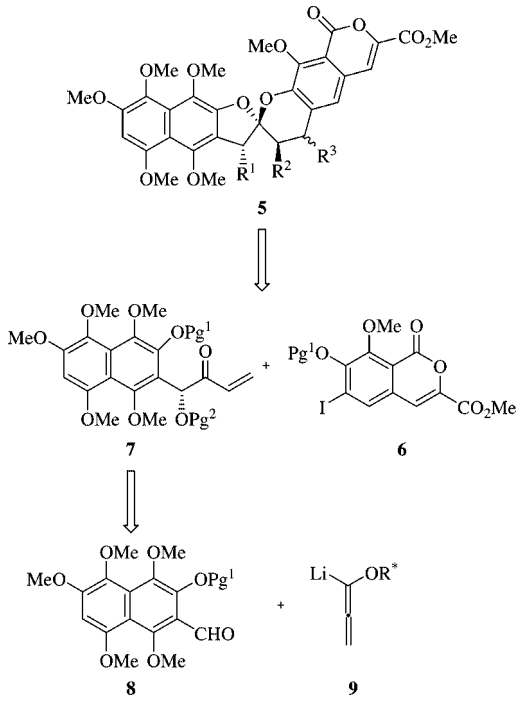
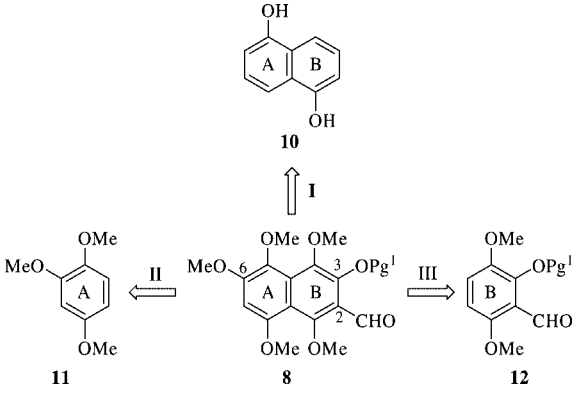


Scheme 1. Retrosynthetic analysis of rubromycins (Pg = protecting group).

stallation of the required functionalities was worth examining first (Route I, Scheme 2). Alternatively, one could also start from the functionalized benzene derivatives **11** or **12**, which already match ring A or ring B of naphthalene derivative **8** (Routes II and III, Scheme 2). It was anticipated that the naphthalene skeleton might be establishable at a later stage by aryne cycloadditions employing furan as an easily accessible second C_4 building block. These approaches should allow easier control of regioselectivity.

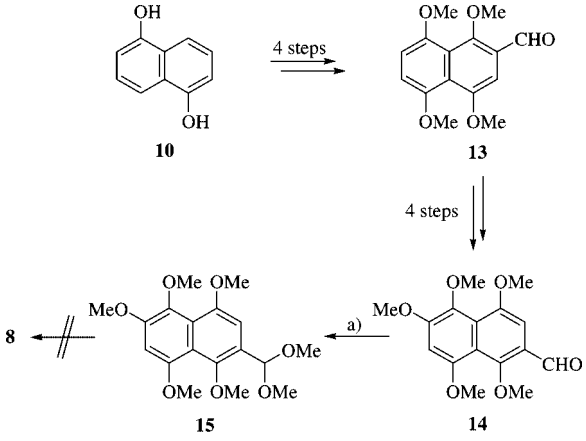


Scheme 2. Retrosynthetic analysis of naphthaldehyde **8** (Routes I, II, III).

Results and Discussion

Route I: "Naphthalene Approach"

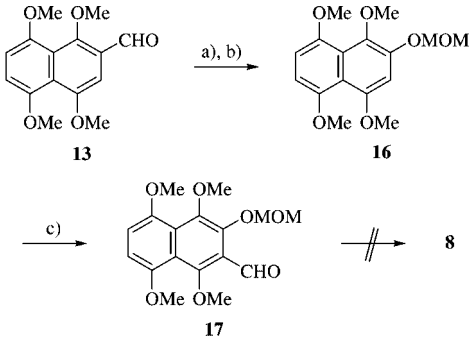
For our intended synthesis of naphthaldehyde **8** we had to consider that differentiation at C-3 and C-6 is crucial for the further construction of rubromycins. Furthermore, the regioselective introduction of the formyl group at the C-2 position was crucial. We initially attempted to synthesize **8** starting from commercially available 1,5-dihydroxynaphthalene (**10**). The known naphthaldehyde **13** could be synthesized according to literature procedures in four steps,[12] whilst installation of the required methoxy group in the 6-position was achieved in another four known steps and finally afforded naphthaldehyde **14**,[13] which was subsequently protected as the acetal to yield compound **15**. Unfortunately, though, we were not able to introduce the required 3-hydroxy group regioselectively (Scheme 3).



a) $CH(OMe)_3$, *p*TsOH, MeOH, r.t., 16 h, 97%.

Scheme 3. Synthesis of aldehyde **14** and acetal **15** by Route I.

Through the use of the symmetric naphthalene derivative **10**, however, we were able to prepare naphthaldehyde **17**, lacking the 6-methoxy group, as depicted in Scheme 4. Baeyer–Villiger oxidation of **13** and subsequent MOM protection of the resulting naphthol gave **16**, albeit in low overall yield. Ensuing *ortho*-formylation resulted in the formation of naphthaldehyde **17** in 34% yield, though the level of conversion was only moderate and 47% of the starting material **16** was recovered. Again, regioselective introduc-



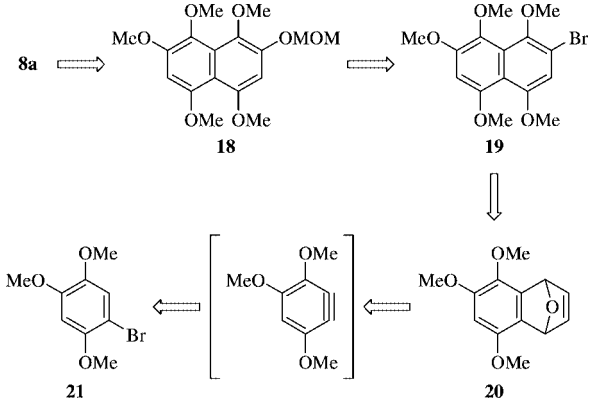
a) (i) MCPBA, $NaHCO_3$, CH_2Cl_2, r.t., 12 h, (ii) NH_3/MeOH, r.t., 10 min; b) NaH, MOMCl, DMF, r.t., 2 h, 21%; c) (i) *n*BuLi, TMEDA, THF, 0 °C, 2 h, (ii) DMF, –78 °C→r.t., 34%.

Scheme 4. Synthesis of the MOM-protected aldehyde **17** by Route I.

tion of the required methoxy group in the 6-position was not possible.

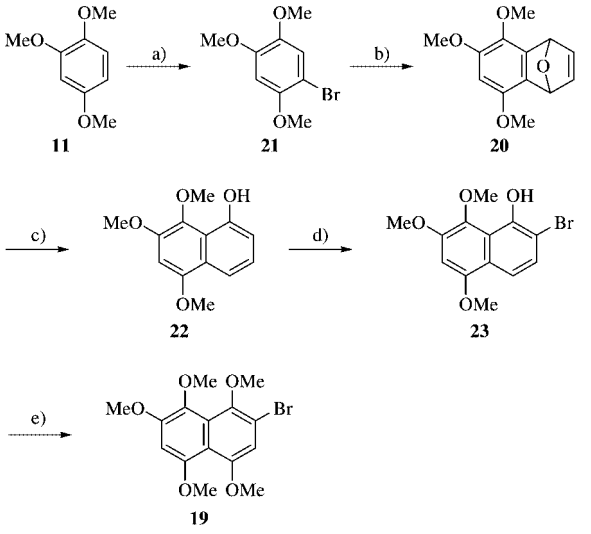
Route II: "Construction of Ring B by Aryne Cycloaddition"

Since the regioselective synthesis of **8** by employment of simple symmetric starting materials such as **10** (Route I, Scheme 2) had proved not to be possible, we changed our approach, the intent being to use easily accessible substituted benzene derivatives and to construct the naphthalene core of **8** at a later stage of the synthesis (Route II, Scheme 2). With results published by Clive et al.[14] in mind, we decided to start from 1,2,4-trimethoxybenzene derivative **21**, which already matches the substitution pattern of ring A of our target structure **8**. Application of an aryne cycloaddition as key step and subsequent regioselective ring cleavage of the resulting Diels–Alder adduct **20** was expected to result in the formation of the basic naphthalene skeleton (Scheme 5), and further transformations were then expected to afford the bromo-substituted naphthalene **19**, which was expected to be convertible into the MOM-protected naphthalene **18**. Finally, introduction of the required formyl function in a regioselective manner by taking advantage of the *ortho*-directing properties of the MOM group in **18** was expected to result in the formation of naphthaldehyde **8a** (Pg^1 = MOM).



Scheme 5. Retrosynthetic analysis of precursor **18** required for synthesis of **8a** (Route II).

The implementation of this concept is shown in Scheme 6. As reported previously,[14] 1,2,4-trimethoxybenzene (**11**) was brominated and subjected to base-induced elimination followed by cycloaddition in the presence of furan as dienophile, which resulted in the smooth formation of tricyclic compound **20** in excellent yield. Regioselective ring-opening[15] with catalytic amounts of perchloric acid provided the naphthalene core **22** in quantitative yield,[14] and subsequent *ortho*-bromination with pyridinium perbromide (PHBP) resulted in the formation of **23**. With this crucial compound in hand, we focused on the oxidation of ring B of the naphthalene derivative to afford the corresponding quinone. Application of Jones reagent as described by Clive et al., however, gave the quinone only in very low yield, with oxidation of the trimethoxy-substituted ring A also occurring. Superior results were achieved by employing ceric ammonium nitrate (CAN) as oxidant. It turned out that yields were higher when the crude quinone derivative was directly reduced and *O*-methylated without further purification, this procedure affording the pentamethoxy-substituted 2-bromonaphthalene **19** in 46% overall yield.

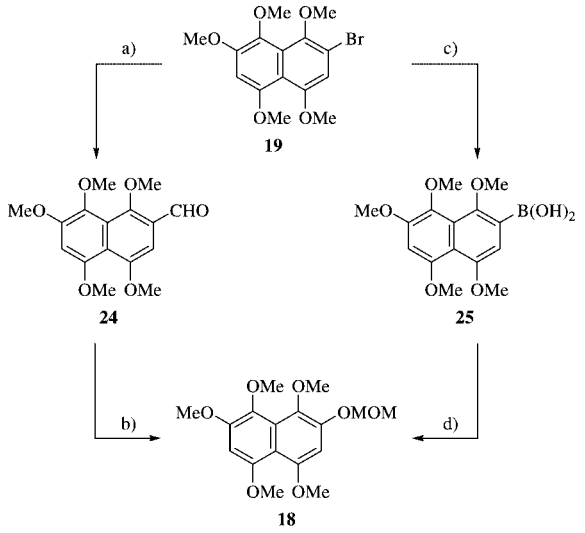


a) Br_2, $CHCl_3$, 0 °C, 4 h, quant.; b) LDA, furan, –78 °C→r.t., 22 h, quant.; c) $HClO_4$ (cat.), THF, r.t., 3 d, quant.; d) PHBP, THF, r.t., 5 h, 60%, e) (i) CAN (20% in H_2O), CH_3CN, r.t., 45 min (ii) $Na_2S_2O_4$, TBABr (cat.), CH_2Cl_2/H_2O (2:1), r.t., 3 h, (iii) Me_2SO_4, NaOH, TBABr (cat.), CH_2Cl_2, r.t., 18 h, 46%.

Scheme 6. Synthesis of hexasubstituted naphthalene derivative **19** by Route II.

In order to obtain the desired MOM-protected naphthol **18** (Scheme 7), we converted **19** into the corresponding naphthaldehyde **24** by halogen/metal exchange and subsequent addition of dimethylformamide as electrophile. Although aldehyde **24** was accessible in excellent yield, the planned Baeyer–Villiger oxidation turned out to be problematic, either with no reaction occurring at all or with complex product mixtures being formed. Finally, with *meta*-chloroperbenzoic acid in the presence of sodium hydrogencarbonate, followed by protection of the intermediate naphthol with chloromethyl methyl ether, we succeeded in the preparation of **18**, albeit in very poor overall yield. Instead of using naphthaldehyde **24** as precursor, we therefore decided to prepare the corresponding boronic acid **25**, which was smoothly accessible in excellent yield from **18** by halogen/metal exchange and addition of trimethyl borate. Treatment of **25** with hydrogen peroxide and sodium hydroxide followed by immediate protection of the resulting highly unstable naphthol derivative furnished **18** in good overall yield.

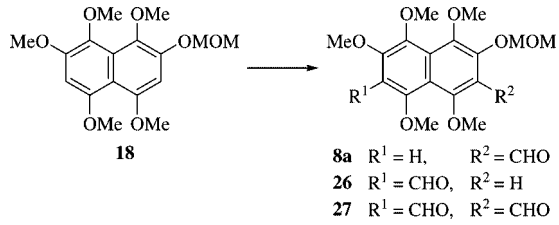
We expected that the *ortho*-directing properties of the MOM group in the (almost symmetrical) naphthalene intermediate **18** should allow regioselective metallation, and that subsequent quenching with dimethylformamide as electrophile should then provide the desired naphthaldehyde **8a**. However, although we applied various conditions, no satis-



a) *t*BuLi, DMF, THF, –95 °C, 10 min, –95 °C → r.t., 30 min, 91%; b) (i) MCPBA, $NaHCO_3$, CH_2Cl_2, r.t., 17 h, (ii) MeOH/NH_3, r.t., 15 min, (iii) NaH, MOMCl, r.t., 22 h, 31%; c) *t*BuLi, $B(OMe)_3$, THF, –95 °C, 10 min, –95 °C → r.t., 30 min, 92%; d) (i) H_2O_2, NaOH, MeOH, r.t., 10 min, (ii) DIPEA, MOMCl, CH_2Cl_2, r.t., 23 h, 68%.

Scheme 7. Synthesis of MOM-protected naphthalene derivative **18**.

factory results could be obtained. Initial trials employing *n*-butyllithium in the presence of TMEDA and subsequent quenching with DMF at low temperatures (–78 °C) resulted in poor conversion and formation of **8a** in only 11% yield (Scheme 8 and Table 1, Entry 1). Moreover, the undesired regioisomer **26** was also formed in almost equal quantities (9% yield), which indicates that the *ortho*-directing properties of the MOM group are too weak in relation to those of the 6-methoxy group. Conversion was slightly improved by raising the temperature of the metallation to 0 °C, followed by addition of DMF at –45 °C, but no regioselectivity could be observed, **8a** and **26** being obtained virtually as a 1:1 mixture. Unexpectedly, formation of the diformylated naphthalene derivative **27** was observed as side product (Table 1, Entry 2). A change of the solvent from tetrahydrofuran to diethyl ether and performance of the reaction at –20 °C improved neither the regioselectivity nor the yields, whilst formation of **27** was again observed (Table 1, Entry 3). Despite numerous experiments we were unable to find appropriate conditions for the intended regioselective *ortho*-formylation of compound **18**. In a further attempt to solve this problem we also prepared the naphthalene derivative bearing a 6-isopropoxy group to sterically block the formation of the undesired isomer during the formylation,[16] but the conversion for this derivative was even lower (<10%). A possible explanation for the low reactivity in the metallation and *ortho*-formylation may lie in the formation of stable aggregates between the alkyllithium compounds and the methoxy groups of the naphthalene derivatives.



Scheme 8. Synthesis of formylnaphthalene derivative **8a**.

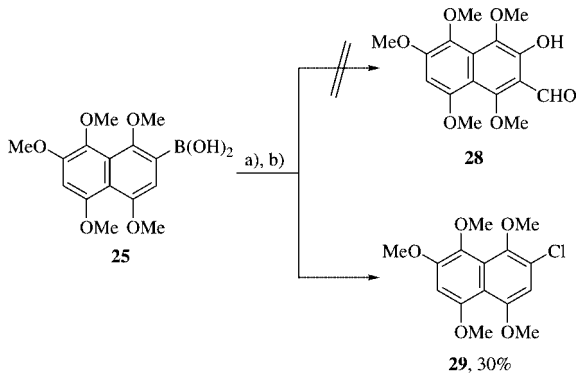
As a consequence of these disappointing results we had to modify our approach. Instead of introducing the required formyl function through an *ortho*-metallation, this was now planned to be directly accomplished by a Vilsmeier–Haack-type reaction. For this purpose, boronic acid **25** was readily converted into the corresponding naphthol and was subsequently treated with a mixture of phosphoryl chloride and dimethylformamide. Surprisingly, though, this resulted in the formation of chloronaphthalene derivative **29** rather than **28** (Scheme 9). Although it is known that phosphoryl chloride can be used to introduce chlorine into aromatic compounds, this usually requires electron-deficient systems to stabilize the carbanionic species formed in situ.[17] We have no straightforward mechanistic explanation for the transformation **25** → **29**. When boronic acid **25** was first treated with phosphoryl chloride and subsequently oxidized the desired aldehyde **28** was isolated in low yield, but it contained many impurities.

Another variation envisaged as possibly leading to the required naphthaldehyde **8** involved the synthesis of the allyl ether **30**, followed by a Claisen rearrangement to provide **32** (Scheme 10). The plan was to subsequently convert the propenyl substituent at C-3 of **32** into a formyl group by double-bond isomerization and oxidative degradation. Gratifyingly, the required allyl ether **30** was easily prepared by oxidation of **25** and subsequent treatment with allyl bromide in 49% overall yield. The Claisen rearrangement of **30** indeed smoothly occurred in dimethylformamide at reflux, but much to our surprise the single product isolated in 80% yield was the C-1-allylated enone **33** rather than the ex-

Table 1. *ortho*-Metallation and subsequent formylation of **18** according to Scheme 8.

Entry	Conditions	Yield [%]			
		8a	**26**	**27**	**18**
1[a]	1. *n*BuLi (2.0 equiv.), TMEDA (2.0 equiv.), THF, –40 °C, 1 h 2. DMF, –78 °C → room temp., 15 h	11	9	–	24
2[b]	1. *n*BuLi (1.2 equiv.), TMEDA (1.2 equiv.), THF, 0 °C, 1.5 h 2. DMF, –45 °C → room temp., 19 h	23	26	<4	48
3[b]	1. *n*BuLi (1.2 equiv.), TMEDA (1.2 equiv.), Et_2O, –20 °C, 1.5 h 2. DMF, –20 °C → room temp., 3 h	17	20	9	33

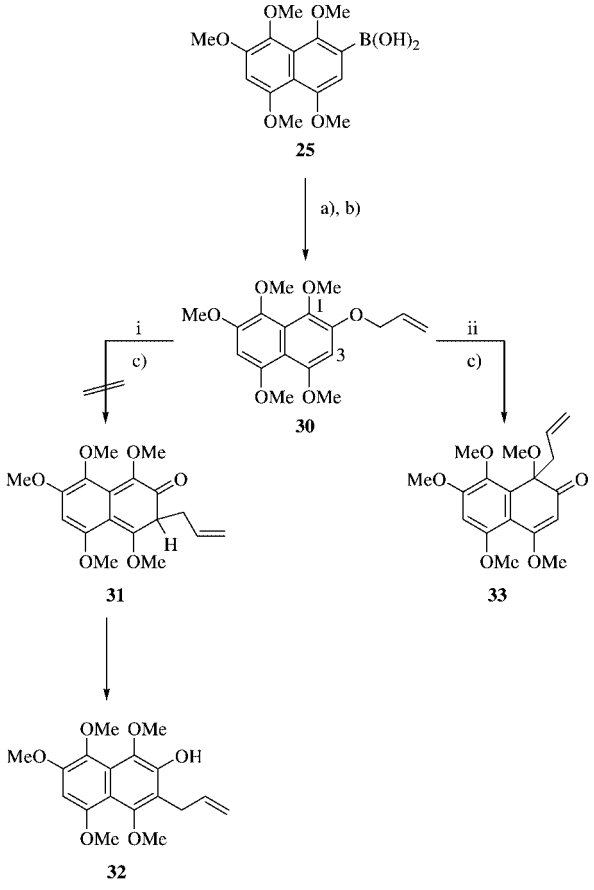
[a] Yields determined after HPLC purification. [b] Yields estimated by ^1H NMR spectroscopy.



a) H_2O_2, NaOH, MeOH, r.t., 10 min, b) $POCl_3$, DMF, $CHCl_3$, reflux, 4 h.

Scheme 9. Attempt to prepare formylated naphthalene derivative **28**.

pected **32**. In retrospect this outcome can be rationalized by presumed intermediates of the two possible pathways (Pathways i and ii, Scheme 10). While Pathway i involves intermediate **31**, which has suffered considerable "loss of aromaticity", Pathway ii directly yields **33**, in which the aromatic π-system of ring A is still intact. This may be the

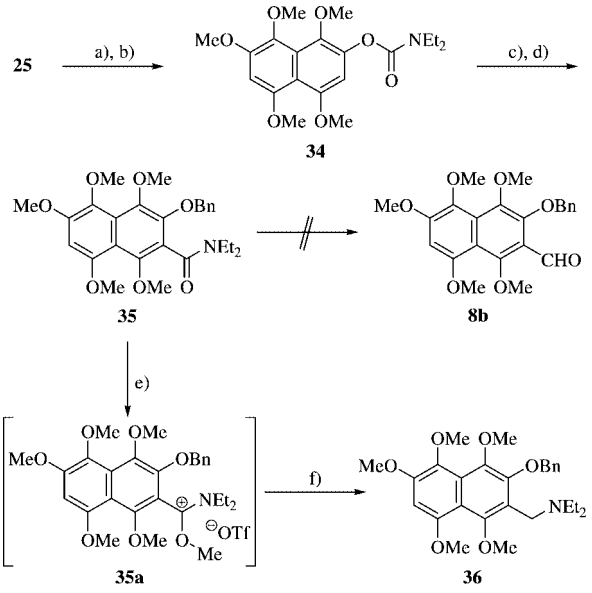


a) H_2O_2, NaOH, MeOH, r.t., 10 min; b) K_2CO_3, allyl bromide, DMF, r.t., 15 h, 49%; c) DMF, reflux, 7 h, 80%.

Scheme 10. Synthesis and Claisen rearrangement of *O*-allylated naphthalene derivative **30**.

major reason for the preference for Pathway ii in the allyl migration.[18]

Our "last hope" approach to aldehyde **8**, again employing the naphthylboronic acid **25** as a crucial intermediate, was intended to take advantage of an *ortho*-Fries rearrangement of carbamate **34**.[19] This compound was smoothly prepared in good yield, again by oxidation of **25**, followed by protection with carbamoyl chloride (Scheme 11). *ortho*-Metallation resulted in rapid rearrangement of the amide, and the primarily formed naphthol was protected with benzyl bromide to give a 59% yield of diethylamide **35**. The very severe steric hindrance of the two alkoxy substituents *ortho* to the diethylamide function causes highly restricted rotation and therefore compound **35** exists as a 1:1 mixture of non-biaryl atropisomers. High-temperature NMR studies were conducted, but no coalescence temperature was reached below 178 °C.

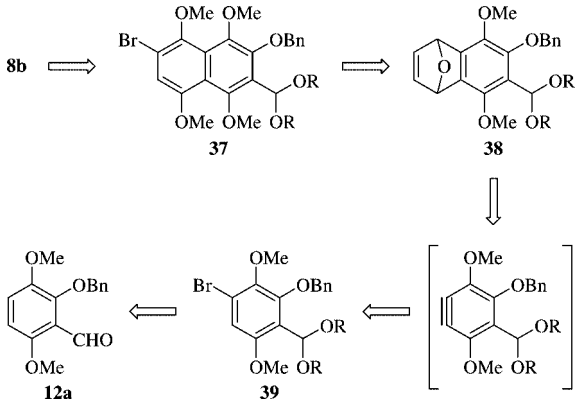


a) H_2O_2, NaOH, MeOH, r.t., 10 min; b) NaHMDS, Et_2NCOCl, DMF, r.t., 21 h, 59%; c) *t*BuLi, THF, –78 °C→r.t., 19 h; d) K_2CO_3, BnBr, DMF, 60 °C, 18 h, 73%; e) MeOTf, CH_2Cl_2, r.t., 21 h, reflux, 3 h; (f) $NaBH_4$, THF, r.t., 16 h, 61%.

Scheme 11. Synthesis of naphthyl-substituted amide **35** by *ortho*-Fries rearrangement of compound **34** and its attempted conversions into aldehyde **8b**.

We now expected that **8b** (R = Bn) would be accessible by reduction of the amide function of **35**; however, this turned out to be extremely stable to the many reagents applied. Initially we tried to reduce the amide directly to the aldehyde by use of DIBAL, DIBAL/*n*BuLi and the Schwartz reagent, but only starting material **35** was recovered in all cases. Even highly active hydride sources such as lithium aluminium hydride or superhydride did not result in any reaction. This extremely low reactivity of the amide function of **35** towards hydride attack is probably due to the extreme steric hindrance mentioned above. The very strongly electron-donating properties of the naphthyl substituents, bearing no fewer than six alkoxy groups, should not be operative in the assumed perpendicular arrangement of the carbonyl group and the naphthalene ring.

In order to enhance the reactivity of **35** towards nucleophiles we alkylated its carbonyl group, by employing Meerwein's salt or methyl triflate. Salt formation could be confirmed by a shift to lower field in the ^{1}H NMR spectrum, but no reagent out of DIBAl, sodium cyanoborohydride, L-selectride, lithium aluminium hydride or superhydride gave any reduction. Instead, mixtures of the salt and the amide were obtained; possibly the hydride attack occurs at the methyl group of the salt instead at the sterically strongly hindered carbon atom, resulting in a nucleophilic substitution reaction and the recovery of starting material **35**. Surprisingly, though, in the case of sodium borohydride as hydride source we observed transformation of the salt **35a** into amine **36** in good yield. We have no straightforward explanation for this result.[20]

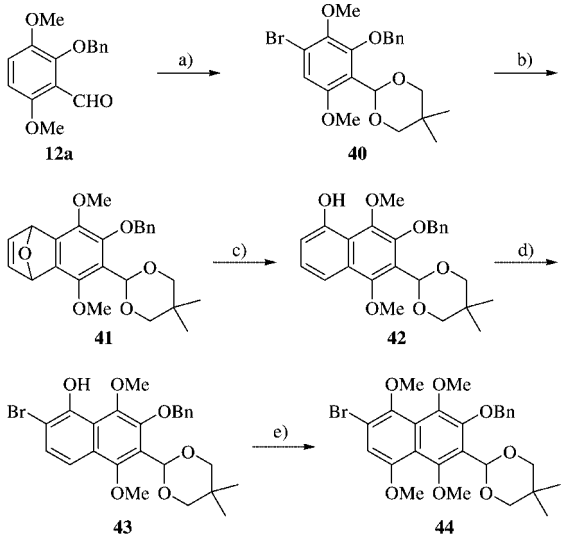


Scheme 12. Retrosynthetic analysis of precursor **37** required for synthesis of aldehyde **8b** (Route III).

Route III: "Construction of Ring A by Aryne Cycloaddition"

The frustrating results obtained in the different variations of Route II prompted us to change the concept once again. Instead of using 1,2,4-trimethoxybenzene (**11**) (Route II, Scheme 2), we chose as starting material the substituted benzaldehyde **12a**, which constitutes the core of ring B of naphthaldehyde **8b** (Route III). This approach possesses the advantage that **12a** can be prepared by literature procedures in a few steps[7b,7c,21] and that it already matches the required substitution pattern for ring B. Of particular importance is the fact that **12a** already bears the required formyl function, which should considerably facilitate the regioselective construction of **8b**. Finally, this approach would allow us to take advantage of the well-elaborated results obtained during our attempts to prepare the naphthalene core in Route II. Starting from **12a**, we therefore envisaged essentially the same strategy as described earlier (Scheme 12): protection of the aldehyde and introduction of a bromide were expected to afford **39** and, analogously to the results described above, treatment of bromobenzene derivative **39** with strong base in the presence of furan was expected to result in the formation of tricycle **38**. It was then hoped that regioselective ring-opening, *ortho*-bromination and a subsequent oxidation/reduction sequence to afford brominated naphthalene derivative **37** would finally allow its conversion into **8b** by an Ullmann-type coupling.

The implementation of this strategy is shown in Scheme 13. Bromination of **12a** under buffered conditions, followed by protection of the formyl group as a dioxane, afforded the aryne precursor **40** in excellent yield. Bromobenzene **40** was readily converted by treatment with LDA into the corresponding aryne, which was efficiently trapped with an excess of furan, quantitatively furnishing tricyclic compound **41**. The subsequent regioselective ring-opening required fine-tuned reaction conditions,[22] and naphthol derivative **42** was obtained in 83% yield and in a 95:5 ratio of regioisomers. Subsequent *ortho*-bromination with pyridinium perbromide yielded **43**, at which stage only one regioisomer could be detected in the proton NMR spectrum. Utilization of the oxidation/reduction sequence designed in Route II, followed by immediate methylation of the resulting naphthol, afforded the naphthalene derivative **44** in 36% yield over three steps.

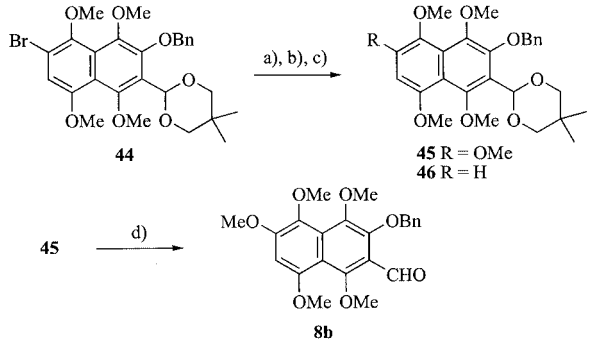


a) (i) Br_2, NaOAc, HOAc, r.t., 2 h, (ii) $HOCH_2C(CH_3)_2CH_2OH$, $HC(OMe)_3$, nBu_4NBr_3, CH_2Cl_2, r.t., 3 h, 85%; b) LDA, Furan, −78 °C → r.t., 23 h, quant.; c) $HOCH_2C(CH_3)_2CH_2OH$, $HC(OMe)_3$, pTsOH·H_2O, CH_2Cl_2, reflux, 19 h, 83%; d) PHBP, THF, r.t., 3 h, 92%, e) (i) CAN (20% in H_2O), CH_3CN, r.t., 1 h (ii) $Na_2S_2O_4$, TBABr (cat.), CH_2Cl_2/H_2O (2:1), r.t., 3 h, (iii) Me_2SO_4, NaOH, TBABr (cat.), CH_2Cl_2, r.t., 15 h, 36%.

Scheme 13. Synthesis of bromonaphthalene derivative **44** by Route III.

According to our plan, we now attempted to replace the bromo substituent in **44** with a methoxy group in an Ullmann-type reaction. However, treatment of **44** with an excess of sodium methoxide in the presence of copper(I) iodide and collidine at reflux in dimethylformamide did not result in any substitution of the bromide.[23] After several unsuccessful attempts we therefore decided to follow the well-established "detour" and first prepared the corresponding boronic acid (Scheme 14). Halogen/metal exchange in **44** and subsequent quenching with trimethyl bo-

rate, oxidation and methylation of the resulting naphthol rather efficiently afforded the desired pentamethoxy-substituted naphthalene derivative **45** in 46% overall yield. As a side product, the debrominated naphthalene derivative **46** was isolated in 19% yield, which is probably due to incomplete reaction of the intermediate lithium species with trimethyl borate.



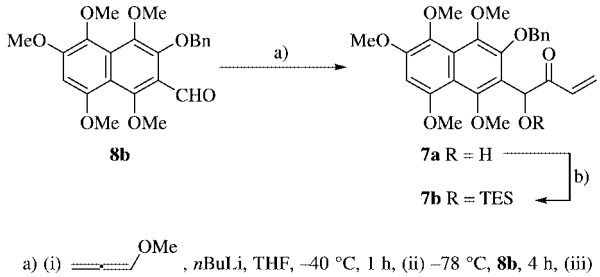
a) *n*BuLi, $B(OMe)_3$, THF, –100 °C→r.t., 30 min; (b) H_2O_2, NaOH, MeOH, r.t., 10 min; c) Me_2SO_4, NaOH, TBABr, r.t., 20 h, 46% **45**, 19% **46**; d) HOAc (80%), r.t., 4 h, 81%.

Scheme 14. Synthesis of hexaalkoxy-substituted naphthaldehyde **8b** according to Route III.

With **45** in hand, our intended synthesis was almost complete, and acetal cleavage by treatment with aqueous acetic acid provided target compound **8b** in 81% yield. In summary, the desired naphthaldehyde **8b** had been synthesized in a 12-step sequence and, considering its complexity, the overall yield of 9% (with respect to aldehyde **12a**) is very satisfactory. Substituted benzaldehyde **12a** was prepared by literature procedures in four consecutive steps and in a 62% yield starting from the commercially available 2,5-dimethoxybenzaldehyde.[7b,7c,21] Altogether, target compound **8b** was prepared in 16 steps and in an overall yield of 6%.

Conversion of the Naphthaldehyde into an α-Hydroxy Enone

Having succeeded in developing a good synthesis of naphthaldehyde **8b**, we subsequently conducted preliminary experiments intended to validate our strategy for the planned total synthesis of compounds of the rubromycin family. As set out in our strategy depicted in Scheme 1, we combined naphthaldehyde **8b** with lithiated methoxyallene and subsequently hydrolysed the resulting allene adduct, which resulted in the formation of the expected α-hydroxy enone **7a** (Scheme 15) in quantitative yield. Adjacent protection of the benzylic hydroxy function as a silyl ether was also successful and the corresponding enone **7b** was obtained in good yield.



a) (i) OMe, *n*BuLi, THF, –40 °C, 1 h, (ii) –78 °C, **8b**, 4 h, (iii) H_2SO_4 (5%), –78 °C→0 °C, 1 h; b) DIPEA, TESCl, DMF, r.t., 6 h, 64%.

Scheme 15. Synthesis of α-hydroxy enone **7a** from key aldehyde **8b** and lithiated methoxyallene and its conversion into **7b**.

Conclusions

In this report we describe our efforts to develop a regioselective synthesis of naphthaldehydes such as **8a** and **8b**, required as central building blocks in a general approach to rubromycins. Three different strategies are presented, each starting from a simple symmetric naphthalene derivative such as **10** or from suitably substituted benzene derivatives. Eventually, the synthesis was accomplished in a concise and efficient manner by applying a cycloaddition of an aryne intermediate and a subsequent regioselective ring-opening as key steps. Starting from a known substituted benzaldehyde derivative, the desired naphthaldehyde **8b** was obtained in a 12-step sequence and in an overall yield of 9%. Furthermore, the naphthaldehyde could be transformed into the corresponding triethylsilyl-protected α-hydroxy enone **7b** by treatment with lithiated methoxyallene, acidic hydrolysis and subsequent protection. This successful conversion demonstrates the suitability of the naphthaldehyde building block **8b** for our future construction of rubromycins, and the preparation of rubromycin model compounds based on this approach employing lithiated alkoxyallenes and aldehydes such as **8** will be reported in due course.[24]

Although many dead ends in the pathway to naphthaldehydes **8** are described in this report, the reactions and side reactions of these highly substituted naphthalene derivatives should be of interest. For the generation of the hydroxy groups of naphthol derivatives we generally employed boronic acids such as **25** as crucial intermediates (e.g., transformation of **25** into **18**, **30** or **34**). These boronic acids could also be very useful for palladium-catalysed reactions, to afford a variety of highly functionalized and substituted naphthalene derivatives of high diversity. The Claisen rearrangement of *O*-allylated naphthalene derivatives such as **30**, which in our hands furnished the interesting naphthalene-2-one derivative **33**, should also be of interest.

Experimental Section

General Methods: Reactions were generally performed under argon in flame-dried flasks, and solvents and reagents were added by syringe. Solvents were dried by standard procedures. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone under argon. Products were purified by flash chromatography on silica gel (230–400 mesh, Merck). Unless otherwise stated, yields refer to analytically pure samples. 2-Benzyloxy-3,6-dimethoxybenzaldehyde,[7b,7c,21] 2-bromo-5,7,8-trimethoxynaphthalen-1-ol,[14] chloromethoxymethane[25] and 1-methoxypropa-1,2-diene[26] were synthesized according to literature procedures. 2,5-Dimethoxybenzalde-

hyde (97%), 1,2,4-trimethoxybenzene (99%) and pyridinium perbromide (95%) were purchased from Acros and used as obtained, whilst trimethyl borate (99.999%) was purchased from Sigma–Aldrich. Other reagents were purchased and were used as received without purification unless otherwise stated. ^{1}H [$CHCl_3$ (δ = 7.26 ppm) or TMS (δ = 0.00 ppm) as internal standard] and ^{13}C NMR spectra [$CDCl_3$ (δ = 77.2 ppm) as internal standard] were recorded with Bruker AM 270 (270 MHz), AMX 500 (500 MHz) and Joel Eclipse 500 (500 MHz) instruments in $CDCl_3$ solutions. Integrals are in accordance with assignments; coupling constants are given in Hz. IR spectra were measured with an FT-IRD spectrometer (Nicolet 5 SXC). MS and HRMS analyses were performed with Finnigan MAT 711 (EI = 80 eV, 8 kV), MAT CH7A (EI = 80 eV, 3 kV) and CH5DF (FAB = 3 kV) instruments. Elemental analyses were carried out with "CHN-Analyzer 2400" (Perkin–Elmer), "Vario EL" or "Vario EL III" (Elementar) instruments. Melting points were measured with a Reichert "Thermovar" apparatus or a Büchi "Büchi 510" apparatus and are uncorrected.

General Procedure 1. Oxidation of Naphthylboronic Acids: Hydrogen peroxide (30%, 5 equiv.) and aqueous sodium hydroxide (2.5 M, 5 equiv.) were added to a solution of the naphthylboronic acid (1 equiv.) in methanol (20 mL) and the resulting mixture was stirred at room temp. for 10 min. Satd. aq. NH_4Cl solution (20 mL) was added and the mixture was extracted with dichloromethane or ethyl acetate (3 × 20 mL). The combined organic layers were dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Since the crude naphthols rapidly decompose, they were used directly in the next step without further purification.

2-Dimethoxymethyl-1,4,5,6,8-pentamethoxynaphthalene (15): Trimethyl orthoformate (0.13 mL, 1.2 mmol) and *p*-toluenesulfonic acid (4 mg, 3 mol-%), were added at room temp. to a solution of compound **14** (221 mg, 0.72 mmol) in methanol/chloroform (3:1, 4 mL). After stirring for 16 h, the mixture was treated with potassium carbonate (spatula tip) and filtered, and the solvent was removed under reduced pressure. The residue was dissolved in chloroform (10 mL), washed once with water, dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to afford **15** (247 mg, 97%) as a greenish, viscous oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 3.44 (s, 6 H, OCH_3), 3.78, 3.81, 3.97 (3 × s, 3 H each, OCH_3), 3.98 (s, 6 H, OCH_3), 5.75 [s, 1 H, C*H*(OCH_3)$_2$], 6.75, 6.99 (2 × s, 1 H each, 2 Ar) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 54.3,* 56.6,* 57.3, 61.6, 63.0 (5 × q, OCH_3), 98.3, 100.0, 104.8 [3 × d, *C*H(OCH_3)$_2$, Ar], 116.9, 124.1, 125.4, 138.4, 148.2, 150.3, 152.1, 152.9 (8 × s, Ar) ppm; *signal with higher intensity. IR (film): $\tilde{\nu}$ = 2970–2840 (CH), 1600, 1460 (C=C, Ar) cm^{-1}. MS (EI = 80 eV, 65 °C): *m*/*z* (%) = 352 (100) [M]$^+$, 322 (97) [M – CH_2O]$^+$, 291 (62), 275 (24), 261 (38), 232 (39), 218 (45), 75 (36). HRMS (EI = 80 eV, 60 °C): calcd. for $C_{18}H_{24}O_7$ 352.15219; found 352.15422.

1,4,5,8-Tetramethoxy-2-(methoxymethoxy)naphthalene (16): MCPBA (12.1 g, 70–75%, ca. 49 mmol) was added in small portions at 0 °C to a solution of **13** (5.00 g, 18.1 mmol) in dichloromethane (200 mL) and the suspension was stirred at room temp. overnight. The mixture was washed with 10% aq. $Na_2S_2O_3$ solution (2 × 40 mL), the layers were separated, and the combined aqueous phases were extracted with dichloromethane (1 × 30 mL). The combined organic layers were dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The residue was dissolved in a satd. solution of ammonia in methanol (200 mL) and stirred at room temp. for 10 min. After removal of the solvent under reduced pressure, the corresponding crude naphthol (1.78 g) was obtained and was immediately used without further purification. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 3.81, 3.88, 3.91, 3.92 (4 × s, 3 H each, OCH_3), 6.64–6.79 (m, 3 H, Ar) ppm. The naphthol was dissolved in DMF (5 mL), added at room temp. to a suspension of sodium hydride (324 mg, 60% in paraffin oil, 8.09 mmol) in DMF (25 mL) and stirred for 30 min. Methoxymethyl chloride (0.56 mL, 7.41 mmol) was added, and the solution was stirred for 1 h and quenched by addition of water followed by extraction with pentane (3 × 20 mL). The combined organic layers were dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Chromatography on silica gel (hexane/ethyl acetate, 1:1) afforded **16** (1.19 g, 21%) as a yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 3.57, 3.83, 3.88, 3.91, 3.92 (5 × s, 3 H each, OCH_3), 5.29 (s, 2 H, O*C*H_2OCH_3), 6.67, 6.78 (2 × d, *J* = 8.3 Hz, 1 H each, Ar), 6.84 (s, 1 H, Ar) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 56.3, 57.1, 57.3, 57.4, 61.8 (5 × q, OCH_3), 96.4 (t, O*C*H_2OCH_3), 101.5, 106.1, 108.4 (3 × d, Ar), 116.5, 123.8, 139.0, 147.7, 150.1, 151.4, 153.6 (7 × s, Ar) ppm. IR (film): $\tilde{\nu}$ = 3075 (=CH), 2990–2830 (C–H), 1600, 1520, 1470 (C=C, Ar) cm^{-1}. MS (EI = 80 eV, 150–200 °C): *m*/*z* (%) = 308 (100) [M]$^+$, 280 (13), 250 (12), 259 (93), 45 (43). HRMS (EI = 80 eV, 150–200 °C): calcd. for $C_{16}H_{20}O_6$ 308.12599; found 308.12422.

1,4,5,8-Tetramethoxy-3-(methoxymethoxy)naphthalene-2-carbaldehyde (17): *n*-Butyllithium (2.71 mL, 2.5 M in hexanes, 6.78 mmol) was added at 0 °C to a solution of compound **16** (930 mg, 3.02 mmol) and TMEDA (1.0 mL, 6.64 mmol) in THF (30 mL). The mixture was stirred for 1 h and cooled to –78 °C, and DMF (0.94 mL, 12.1 mmol) was added. After stirring for another 2 h, the mixture was allowed to warm to room temp., quenched with satd. aq. NH_4Cl solution (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Chromatography on silica gel (hexane/ethyl acetate, 1:1) afforded **17** (343 mg, 34%) as a yellow oil, together with **16** (441 mg, 47%). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 3.58, 3.83, 3.87, 3.91, 3.93 (5 × s, 3 H each, OCH_3), 5.20 (s, 2 H, O*C*H_2OCH_3), 6.77, 6.90 (2 × d, *J* = 8.8 Hz, 1 H each, Ar), 10.55 (s, 1 H, CHO) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 56.7, 57.0, 57.6, 61.7, 64.7 (5 × q, OCH_3), 100.3 (t, O*C*H_2OCH_3), 106.6, 110.3 (2 × d, Ar), 122.2, 125.5, 145.2, 146.2, 149.9, 151.3, 157.8 (7 × s, Ar), 190.1 (d, CHO) ppm; the signal for one quaternary carbon atom could not be assigned. IR (film): $\tilde{\nu}$ = 3070 (=CH), 2990–2830 (C–H), 1690 (C=O), 1610, 1570 (C=C, Ar) cm^{-1}. MS (EI = 80 eV, 30–40 °C): *m*/*z* (%) = 336 (8) M]$^+$, 307 (76) [M – CHO]$^+$, 290 (17), 276 (27), 264 (15), 263 (79), 235 (100), 145 (15). HRMS (EI = 80 eV, 30–40 °C): calcd. for $C_{17}H_{20}O_7$ 336.12091; found 336.12244.

2-Bromo-1,4,5,7,8-pentamethoxynaphthalene (19): An aqueous solution of ceric ammonium nitrate (26.3 g in 150 mL H_2O, 47.9 mmol) was added at room temp. to a vigorously stirred solution of compound **23** (5.00 g, 16.0 mmol) in acetonitrile (240 mL). After 45 min, the mixture was extracted with chloroform (3 × 50 mL) and the combined organic layers were washed once with brine, dried with $MgSO_4$ and filtered, the solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane (200 mL) and water (100 mL). Tetra-*n*-butylammonium bromide (0.10 g, 0.32 mmol) and sodium dithionite (8.34 g, 47.9 mmol) were added and the mixture was stirred at room temp. for 3 h. The layers were separated, the aqueous phase was extracted with dichloromethane (3 × 50 mL), the combined organic layers were washed once with brine, dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (200 mL), and tetra-*n*-butylammonium bromide (0.10 g, 0.32 mmol) and dimethyl sulfate (22.8 mL, 0.24 mol) were added. The mixture was cooled to 0 °C, aqueous sodium hydroxide (96 mL, 2.5 M, 0.24 mol) was added dropwise,

and the mixture was stirred at room temp. for 18 h. Brine was added, the layers were separated, and the aqueous phase was extracted with dichloromethane (3×100 mL). The combined organic layers were washed with 10% aqueous ammonia solution (3×130 mL), dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The black residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 3:1), furnishing **19** as a light brown solid (2.64 g, 46%, m.p. 99–100 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.82, 3.85, 3.91, 3.93, 3.99 (5×s, 3 H each, OCH_3), 6.73, 6.81 (2×s, 1 H each, Ar) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 56.7, 57.0, 57.7, 61.9, 62.1 (5×q, OCH_3), 98.1, 108.5 (2×d, Ar), 114.4, 116.2, 126.7, 136.5, 145.5, 151.1, 154.0, 154.8 (8×s, Ar) ppm. IR (KBr): $\tilde{\nu}$ = 3000 (=CH), 2965–2930 (C–H), 2840 (OCH_3), 1600–1580 (C=C, Ar) cm^{-1}. $C_{15}H_{17}BrO_5$ (357.2): calcd. C 50.44, H 4.80; found C 50.31, H 4.67.

1,4,5,7,8-Pentamethoxynaphthalene-2-carbaldehyde (24): *tert*-Butyllithium (1.15 mL, 1.5 M in hexanes, 1.72 mmol) was added at –95 °C to a solution of compound **19** (513 mg, 1.44 mmol) in THF (11 mL), immediately followed by addition of DMF (0.45 mL, 5.85 mmol). After stirring for 10 min, the mixture was allowed to warm to room temp. over 30 min and was then quenched with satd. aq. NH_4Cl solution (10 mL). The aqueous phase was extracted with ethyl acetate (2×10 mL) and the combined organic layers were washed once with brine, dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Chromatography on silica gel (hexane/ethyl acetate, 4:1) afforded **24** (402 mg, 91%) as a yellow solid (m.p. 118–120 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.85, 3.95, 3.96, 3.97, 4.02 (5×s, 3 H each, OCH_3), 6.89 (s, 1 H, 6-H), 7.00 (s, 1 H, 3-H), 10.58 (s, 1 H, CHO) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 56.6, 56.8, 58.1, 62.2, 65.7 (5×q, OCH_3), 98.5, 101.3 (2×d, Ar), 117.9, 126.1, 126.7, 138.4, 151.3, 154.2, 154.9, 156.1 (8×s, Ar), 190.6 (d, CHO) ppm. IR (KBr): $\tilde{\nu}$ = 3000 (=CH), 2960–2930 (C–H), 2860–2840 (OCH_3), 1675 (C=O), 1595 (C=C, Ar) cm^{-1}. $C_{16}H_{18}O_6$ (306.3): calcd. C 62.74, H 5.92; found C 62.50, H 5.92.

(1,4,5,7,8-Pentamethoxynaphthalen-2-yl)boronic Acid (25): *tert*-Butyllithium (0.45 mL, 1.5 M in hexanes, 0.68 mmol) was added to a solution of compound **19** (208 mg, 0.58 mmol) in THF (4.5 mL) at –95 °C, immediately followed by addition of trimethyl borate (0.26 mL, 2.33 mmol). After stirring for 10 min, the mixture was allowed to warm to room temp. over 30 min and then quenched with satd. aq. NH_4Cl solution (10 mL). The aqueous phase was extracted with ethyl acetate (2×10 mL) and the combined organic layers were washed once with brine, dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Chromatography on silica gel (hexane/ethyl acetate, 1:1) afforded **25** (172 mg, 92%) as a light brown solid (m.p. 48–51 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.78, 3.83, 3.95, 3.96, 4.00 (5×s, 3 H each, OCH_3), 6.80, 7.07 (2×s, 1 H each, Ar), 7.17 [s, 2 H, $B(OH)_2$] ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 56.70, 56.76, 56.78, 62.2, 64.0 (5×q, OCH_3), 99.1, 108.2 (2×d, Ar), 117.1, 124.8, 136.6, 150.4, 153.5, 154.6, 156.0 (7×s, Ar) ppm; the signal for one quaternary carbon atom could not be assigned. IR (KBr): $\tilde{\nu}$ = 3380 (OH), 3020–3000 (=CH), 2990–2930 (C–H), 2835 (OCH_3), 1600 (C=C, Ar), 1455–1350 (C–H) cm^{-1}. $C_{15}H_{19}BO_7$ (322.1): calcd. C 55.93, H 5.95; found C 55.54, H 5.73.

1,2,4,5,8-Pentamethoxy-7-(methoxymethoxy)naphthalene (18). Method 1: MCPBA (324 mg, 1.31 mmol) and sodium hydrogencarbonate (110 mg, 1.31 mmol) were added at 0 °C to a solution of naphthaldehyde **24** (161 mg, 0.53 mmol) in dichloromethane (10 mL). The mixture was stirred at room temp. for 17 h and quenched by addition of satd. aq. $NaHCO_3$ solution (10 mL) and satd. aq. $Na_2S_2O_3$ solution (10 mL). The layers were separated, the organic layer was dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The residue was then dissolved in a satd. solution of ammonia in methanol (20 mL) and stirred at room temp. for 15 min. The solvent was removed under reduced pressure, the crude naphthol was dissolved in DMF (10 mL) and cooled to 0 °C, and sodium hydride (53 mg, 60% in paraffin oil, 1.33 mmol) was added. The suspension was stirred at room temp. for 1 h and MOMCl (0.1 mL, 1.32 mmol) was added. After stirring for 22 h, the mixture was quenched with water (10 mL) and extracted with diethyl ether (3×20 mL). The combined organic layers were washed with brine (2×20 mL), dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Chromatography on silica gel (hexane/ethyl acetate, 1:1) afforded **18** (56 mg, 31%) as a yellow oil, which slowly crystallized upon storage. **Method 2:** Treatment of naphthylboronic acid **25** (680 mg, 2.11 mmol) as described in General Procedure 1 afforded the corresponding crude naphthol as a yellow oil, which was immediately dissolved in dichloromethane (15 mL) and cooled to 0 °C. DIPEA (1.1 mL, 6.43 mmol) and MOMCl (0.32 mL, 4.21 mmol) were added and the mixture was stirred at room temp. for 23 h. After quenching with water (15 mL), the aqueous phase was extracted with dichloromethane (3×20 mL). The combined organic layers were dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Chromatography on silica gel (hexane/ethyl acetate, 1:1) afforded **18** (482 mg, 68%) as a yellow solid (m.p. 75–76 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.58, 3.82, 3.83, 3.91, 3.92, 3.98 (6×s, 3 H each, OCH_3), 5.30 (s, 2 H, OCH_2-OCH_3), 6.60, 6.72 (2×s, 1 H each, Ar) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 56.5, 56.8, 57.1, 57.6, 62.0, 62.1 (6×q, OCH_3), 96.2 (t, OCH_2OCH_3), 96.4, 98.2 (2×d, Ar), 111.5, 127.0, 136.7, 137.3, 148.4, 150.6, 154.4, 154.6 (8×s, Ar) ppm. IR (KBr): $\tilde{\nu}$ = 3000 (=CH), 2960–2905 (C–H), 2835 (OCH_3), 1605–1590 (C=C, Ar), 1485–1440 (C–H) cm^{-1}. $C_{17}H_{22}O_7$ (338.4): calcd. C 60.35, H 6.55; found C 60.36, H 6.62.

Representative Example for the Halogen/Metal Exchange of 18 and Subsequent DMF Quench: *n*-Butyllithium (0.19 mL, 2.5 M in hexanes, 0.48 mmol) was added at 0 °C to a stirred solution of **18** (136 mg, 0.40 mmol) and TMEDA (70 μL, 0.47 mmol) in THF (6 mL). After 1.5 h, the solution was cooled to –45 °C, DMF (0.12 mL, 1.56 mmol) was added, and the mixture was allowed to warm to room temp. overnight. After 19 h, the reaction was quenched by addition of satd. aq. NH_4Cl solution (10 mL), the layers were separated, and the aqueous phase was extracted with dichloromethane (3×15 mL). The combined organic layers were dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to afford a mixture (146 mg) of **8a** (23%), **26** (26%), **27** (< 4%) and starting material **18** (48%) as a yellow oil. The yields were determined by ^{1}H NMR (the analytic data were obtained from a different experiment after HPLC purification of the mixture).

1,4,5,6,8-Pentamethoxy-3-(methoxymethoxy)naphthalene-2-carbaldehyde (8a): Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.62, 3.82, 3.85, 3.89, 4.01, 4.02 (6×s, 3 H each, OCH_3), 5.23 (s, 2 H, OCH_2OCH_3), 6.68 (s, 1 H, Ar), 10.53 (s, 1 H, CHO) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 56.7, 57.0, 57.9, 62.0, 62.1, 65.0 (6×q, OCH_3), 96.3 (d, Ar), 100.4 (t, OCH_2OCH_3), 113.9, 120.5, 129.9, 136.8, 143.8, 146.9, 153.3, 155.3, 159.5 (9×s, Ar), 189.8 (d, CHO) ppm. IR (film): $\tilde{\nu}$ = 3110–3000 (=CH), 2990–2930 (C–H), 2845 (OCH_3), 1740–1645 (C=O), 1600, 1565 (C=C, Ar), 1455–1420 (C–H) cm^{-1}. $C_{18}H_{22}O_8$ (366.4): calcd. C 59.01, H 6.05; found C 59.55, H 5.66.

1,3,4,5,8-Pentamethoxy-6-(methoxymethoxy)naphthalene-2-carbaldehyde (26): Yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 3.59, 3.85, 3.880, 3.884, 3.97, 3.99 (6×s, 3 H each, OCH_3), 5.35 (s, 2 H, OCH_2OCH_3), 6.88 (s, 1 H, Ar), 10.52 (s, 1 H, CHO) ppm.

1,3,4,5,8-Pentamethoxy-6-(methoxymethoxy)naphthalene-2,7-dicarbaldehyde (27): Yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 3.62, 3.89, 3.93, 4.03 (4×s, 3 H, 6 H, 6 H, 3 H, OCH_3), 5.28 (s, 2 H, OCH_2OCH_3), 10.54, 10.57 (2×s, 1 H each, CHO) ppm.

2-Chloro-1,4,5,7,8-pentamethoxynaphthalene (29): Naphthylboronic acid **25** (103 mg, 0.32 mmol) afforded the corresponding crude naphthol as described in General Procedure 1, and this was immediately dissolved in chloroform (7 mL) and added to a solution of phosphoryl chloride (0.15 mL, 1.63 mmol) and DMF (0.12 mL, 1.56 mmol) in chloroform (1 mL). The mixture was heated to reflux for 4 h, cooled to 0 °C and quenched with water (10 mL). The aqueous phase was extracted with dichloromethane (4×10 mL), the combined organic layers were dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Chromatography on silica gel (hexane/ethyl acetate, 2:1) afforded **29** (30 mg, 30%) as a brown solid (m.p. 79–82 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.81, 3.84, 3.89, 3.91, 3.97 (5×s, 3 H each, OCH_3), 6.64, 6.70 (2×s, 1 H each, Ar) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 56.6, 56.8, 57.5, 61.8, 62.1 (5×q, OCH_3), 97.7, 105.7 (2×d, Ar), 113.8, 126.1, 126.7, 136.4, 144.2, 151.1, 153.9, 154.7 (8×s, Ar) ppm. IR (KBr): $\tilde{\nu}$ = 3000 (=CH), 2960–2920 (C–H), 2835 (OCH_3), 1600–1590 (C=C, Ar), 1470–1320 (C–H) cm^{-1}. $C_{15}H_{17}ClO_5$ (312.7): calcd. C 57.61, H 5.48; found C 57.28, H 5.29.

2-Allyloxy-1,4,5,7,8-pentamethoxynaphthalene (30): Naphthylboronic acid **25** (296 mg, 0.92 mmol) afforded the corresponding crude naphthol as described in General Procedure 1, and this was immediately dissolved in DMF (10 mL). Potassium carbonate (254 mg, 1.84 mmol) and, after 30 min at room temp., allyl bromide (0.14 mL, 1.61 mmol) were added. After additional 15 h, the mixture was diluted with water (20 mL), the layers were separated, and the aqueous phase was extracted with ethyl acetate (4×20 mL). The combined organic layers were washed with water (2×20 mL), dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Chromatography on silica gel (hexane/ethyl acetate, 1:1) afforded **30** (151 mg, 49%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.80, 3.81, 3.85, 3.88, 3.93 (5×s, 3 H each, OCH_3), 4.68 (td, J = 1.5, 5.3 Hz, 2 H, 1′-H), 5.25 (qd, J = 1.5, 10.5 Hz, 1 H, 3′-H), 5.43 (qd, J = 1.5, 17.2 Hz, 1 H, 3′-H), 6.09 (tdd, J = 5.3, 10.5, 17.2 Hz, 1 H, 2′-H), 6.51, 6.54 (2×s, 1 H each, Ar) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 54.3, 57.0, 57.2, 61.7, 61.8 (5×q, OCH_3), 70.5 (t, C-1′), 95.6, 97.0 (2×d, Ar), 110.7 (s, Ar), 117.4 (t, C-3′), 127.0 (s, Ar), 133.8 (d, C-2′), 136.3, 136.8, 149.4, 150.4, 154.2, 154.4 (6×s, Ar) ppm. IR (film): $\tilde{\nu}$ = 3080 (=CH), 2990–2930 (C–H), 2840 (OCH_3), 1645–1600 (C=C, Ar) cm^{-1}. MS (EI = 80 eV, 70 °C): m/z (%) = 335 (12), 334 (57) $[M]^+$, 319 (9) $[M-CH_3]^+$, 278 (22) $[M-C_3H_4O]^+$, 266 (16), 265 (100), 235 (20), 41 (27), 28 (15). HRMS (EI = 80 eV, 90 °C): calcd. for $C_{18}H_{22}O_6$ 334.14163; found 334.14222. $C_{18}H_{22}O_6$ (334.4): calcd. C 64.66, H 6.63; found C 64.56, H 6.63.

1-Allyl-1,4,5,7,8-pentamethoxy-1*H*-naphthalen-2-one (33): Compound **30** (51 mg, 0.15 mmol) was dissolved in DMF (10 mL) and heated to reflux for 7 h. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (3×20 mL), the combined organic layers were dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Chromatography on silica gel (hexane/ethyl acetate, 1:1) afforded **33** (41 mg, 80%) as an orange solid (m.p. 127–128.5 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.76–2.82 (m, 1 H, 1′-H), 3.01 (s, 3 H, OCH_3), 3.35–3.41 (m, 1 H, 1′-H), 3.86, 3.878, 3.885, 3.96 (4×s, 3 H each, OCH_3), 4.78 (d, J = 10.2 Hz, 1 H, 3′-H), 4.89 (d, J = 17.0 Hz, 1 H, 3′-H), 5.23–5.33 (m, 1 H, 2′-H), 5.66 (s, 1 H, 3-H), 6.61 (s, 1 H, Ar) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 44.0 (t, C-1′), 53.1, 55.8, 56.4, 57.6, 61.0 (5×q, OCH_3), 82.7 (s, C-1), 99.5 (d, Ar), 100.9 (d, C-3), 111.3 (s, Ar), 118.4 (t, C-3′), 131.6 (d, C-2′), 135.8, 143.2, 155.6, 156.3, 171.5 (5×s, Ar, C-4), 197.9 (s, CO) ppm. IR (KBr): $\tilde{\nu}$ = 3080–3000 (=CH), 2980–2940 (C–H), 2845, 2825 (OCH_3), 1640 (C=O), 1605–1555 (C=C, Ar), 1485–1440 (C–H) cm^{-1}. MS (EI = 80 eV, 120 °C): m/z (%) = 334 (32) $[M]^+$, 319 (4) $[M-CH_3]^+$, 293 (8) $[M-C_3H_5]^+$, 266 (16), 265 (100), 235 (11), 41 (8) $[C_3H_5]^+$. HRMS (EI = 80 eV, 120 °C): calcd. for $C_{18}H_{22}O_6$ 334.14163; found 334.14261.

1,4,5,7,8-Pentamethoxynaphthalen-2-yl Diethylcarbamate (34): Naphthylboronic acid **25** (320 mg, 0.99 mmol) afforded the corresponding crude naphthol as described in General Procedure 1, and this was immediately dissolved in DMF (7 mL), treated with sodium bis(trimethylsilyl)amide (1.5 mL, 2 M in THF, 3.00 mmol) and stirred at 0 °C for 10 min. The mixture was stirred at room temp. for 1 h and *N*,*N*-diethylcarbamoyl chloride (0.25 mL, 1.97 mmol) was added dropwise. After 20 h, the mixture was diluted with water (15 mL) and extracted with dichloromethane (3×20 mL). The combined organic layers were dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Chromatography on silica gel (hexane/ethyl acetate, 1:1) afforded **34** (229 mg, 59%) as a tawny solid (m.p. 118–121 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20, 1.30 [2×t, J = 6.9 Hz, 3 H each, $N(CH_2CH_3)_2$], 3.40, 3.51 [2×q, J = 6.9 Hz, 2 H each, $N(CH_2CH_3)_2$], 3.78, 3.79, 3.88, 3.89, 3.95 (5×s, 3 H each, OCH_3), 6.53, 6.65 (2×s, 1 H each, Ar) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 13.4, 14.2, 41.9, 42.2 [2×q, 2×t, $N(CH_2CH_3)_2$], 56.5, 56.7, 57.7, 62.0, 62.4 (5×q, OCH_3), 97.4, 101.6 (2×d, Ar), 113.1, 126.6, 136.9, 139.7, 142.6, 150.5, 153.7, 154.1, 154.6 (9×s, Ar, CO) ppm. IR (KBr): $\tilde{\nu}$ = 3080 (=CH), 2975–2875 (C–H), 2840 (OCH_3), 1720 (C=O), 1600 (C=C, Ar), 1470–1340 (C–H) cm^{-1}. $C_{20}H_{27}NO_7$ (393.4): calcd. C 61.06, H 6.92, N 3.56; found C 60.93, H 6.94, N 3.49.

***N*,*N*-Diethyl 3-Benzyloxy-1,4,5,6,8-pentamethoxynaphthalene-2-carboxamide (35):** *tert*-Butyllithium (0.70 mL, 1.5 M in hexanes, 1.05 mmol) was added at –78 °C to a stirred solution of compound **34** (353 mg, 0.90 mmol) in THF (7 mL) and the mixture was allowed to warm to room temp. overnight. After 19 h, it was quenched by addition of brine (10 mL) and extracted with dichloromethane (5×20 mL). The combined organic layers were dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to afford the crude naphthol, which rapidly decomposed and was therefore immediately used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.04, 1.27 [2×t, J = 7.2 Hz, 3 H each, $N(CH_2CH_3)_2$], 3.14, 3.27, 3.35 [AB parts of two ABX_3 systems, J_{AX} = J_{BX} = 7.2 Hz, J_{AB} = 14.3 Hz, 1 H each, $N(CH_2CH_3)_2$], 3.76, 3.827, 3.830, 3.96, 3.98 (5×s, 3 H each, OCH_3), 3.80–3.93 [m, 1 H, $N(CH_2CH_3)_2$], 6.42 (br s, 1 H, OH), 6.56 (s, 1 H, Ar) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 12.9, 14.0, 39.0, 43.2 [2×q, 2×t, $N(CH_2CH_3)_2$], 56.69, 56.75, 62.1, 62.7, 63.7 (5×q, OCH_3), 94.5 (d, Ar), 112.0, 118.3, 125.6, 135.1, 135.7, 144.2, 149.9, 150.7, 154.2 (9×s, Ar), 165.6 (s, CO) ppm. The crude naphthol was dissolved in DMF (10 mL) and stirred with potassium carbonate (248 mg, 1.79 mmol) at room temp. for 1 h. Benzyl bromide (0.32 mL, 2.69 mmol) was added, and the mixture was heated to 60 °C for 18 h and then quenched by addition of water (20 mL) and extracted with dichloromethane (4×20 mL). The combined organic layers were dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Chromatography on silica gel (hexane/ethyl acetate, 2:1), followed by removal of remaining DMF under reduced pressure ($6.1 \cdot 10^{-2}$ mbar, 50 °C) af-

forded **35** (319 mg, 73%) as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.00, 1.21 [2×t, J = 7.1 Hz, 3 H each, $N(CH_2CH_3)_2$], 3.11, 3.16, 3.48, 3.66 [AB parts of two ABX_3 systems, $J_{AX} = J_{BX}$ = 7.1 Hz, J_{AB} = 14.3 Hz, 1 H each, $N(CH_2CH_3)_2$], 3.85, 3.87, 3.98, 4.00 (4×s, 3 H, 6 H, 3 H, 3 H, OCH_3), 5.17, 5.30 (AB system, J_{AB} = 10.7 Hz, 1 H each, OCH_2Ph), 6.67 (s, 1 H, Ar), 7.29–7.38, 7.51–7.52 (2 m, 3 H, 2 H, Ph) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 13.0, 14.0, 39.1, 43.5 [2×q, 2×t, $N(CH_2CH_3)_2$], 56.89, 56.93, 62.1, 62.3, 63.8 (5×q, OCH_3), 76.0 (t, OCH_2Ph), 96.2 (d, Ar), 114.7, 124.5, 126.9 (3×s, Ar), 127.8, 128.27, 128.32 (3×d, Ph), 136.8, 138.1, 144.1, 146.8, 149.1, 150.5, 153.8 (7×s, Ar, Ph), 165.9 (s, CO) ppm. IR (film): $\tilde{\nu}$ = 3080 (=CH), 2990–2930 (C–H), 2840 (OCH_3), 1645–1600 (C=C, Ar) cm^{-1}. MS (EI = 80 eV, 70 °C): m/z (%) = 483 (23) $[M]^+$, 365 (22), 364 (100), 293 (54), 277 (10), 100 (11) $[C_5H_{10}NO]^+$, 91 (44) $[C_7H_7]^+$, 72 (11) $[C_4H_{10}N]^+$. HRMS (EI = 80 eV, 130 °C): calcd. for $C_{27}H_{33}NO_7$ 483.22571; found 483.22638.

[(3-Benzyloxy-1,4,5,6,8-pentamethoxynaphthalen-2-yl)methyl]diethylamine (36): Methyl triflate (0.15 mL, 1 M in CH_2Cl_2, 0.15 mmol) was added at 0 °C to a stirred solution of **35** (37 mg, 0.08 mmol) in dichloromethane (3 mL). After 15 min, stirring was continued at room temp. for 21 h. A second portion of methyl triflate (0.15 mL, 1 M in CH_2Cl_2, 0.15 mmol) was added and the mixture was heated at reflux for 3 h. The solvent was removed under reduced pressure and the residue dissolved in THF (2 mL). Sodium borohydride (12 mg, 0.32 mmol) was added at room temp., and the mixture was stirred for additional 16 h, acidified to pH = 2 by addition of 1 M hydrochloric acid and diluted with water. The layers were separated and the aqueous phase was extracted with dichloromethane (3×15 mL). The combined organic layers were dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Chromatography on silica gel (hexane/ethyl acetate, 2:1) afforded **36** (23 mg, 61%) as a yellow solid (m.p. 150–152.5 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.12 [t, J = 6.9 Hz, 6 H, $N(CH_2CH_3)_2$], 2.67, 2.91 [AB parts of two ABX_3 systems, $J_{AX} = J_{BX}$ = 6.9 Hz, J_{AB} = 13.5 Hz, 2 H each, $N(CH_2CH_3)_2$], 3.68, 3.88, 3.89, 3.98, 4.01 (5×s, 3 H each, OCH_3), 4.14 (s, 2 H, 1′-H), 5.18 (br s, 2 H, OCH_2Ph), 6.69 (s, 1 H, Ar), 7.31–7.40, 7.47–7.49 (2 m, 3 H, 2 H, Ph) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 10.3, 51.8 [q, t, $N(CH_2CH_3)_2$], 53.2 (t, C-1′), 56.9, 57.2, 61.9, 62.2, 62.7 (5×q, OCH_3), 75.6 (t, OCH_2Ph), 96.8 (d, Ar), 114.2, 117.0, 127.6 (3×s, Ar), 128.4, 128.6, 128.9 (3×d, Ph), 136.8, 137.1, 143.7, 150.2, 151.0, 153.6, 154.3 (7×s, Ph, Ar) ppm. IR (KBr): $\tilde{\nu}$ = 3090–3030 (=CH), 2990–2930 (C–H), 2840 (OCH_3), 1605–1575 (C=C, Ar), 1455–1420 (C–H) cm^{-1}. MS (EI = 80 eV, 120 °C): m/z (%) = 469 (36) $[M]^+$, 396 (100), 381 (53), 307 (96), 306 (33), 291 (34), 278 (38), 277 (47), 263 (26), 249 (37), 91 (47) $[C_7H_7]^+$, 86 (26). HRMS (EI = 80 eV, 120 °C): calcd. for $C_{27}H_{35}NO_6$ 469.24643; found 469.24533.

2-(2-Benzyloxy-5-bromo-3,6-dimethoxyphenyl)-5,5-dimethyl-1,3-dioxane (40): Sodium acetate (12.1 g, 0.150 mol) was added to a solution of compound **12a** (20.1 g, 0.074 mol) in glacial acetic acid (400 mL). Bromine (4.2 mL, 0.82 mol) was added dropwise over 20 min, and the mixture was stirred at room temp. for an additional 2 h, diluted with water (200 mL) and extracted with dichloromethane (3×100 mL). The combined organic layers were washed twice with water and twice with satd. aq. $NaHCO_3$ solution, dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to afford the corresponding bromination product (23.3 g) as a red oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.81, 3.87 (2×s, 3 H each, OCH_3), 5.11 (s, 2 H, OCH_2Ph), 7.30 (s, 1 H, Ar), 7.33–7.37, 7.38–7.40 (2 m, 3 H, 2 H, Ph), 10.21 (s, 1 H, CHO) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 56.7, 62.6 (2×q, OCH_3), 76.3 (t, OCH_2Ph), 112.5 (s, Ar), 121.4 (d, Ar), 125.6 (s, Ar), 128.6, 128.8 (2×d, Ph), 136.3, 149.8, 150.1, 150.8 (4×s, Ph, Ar), 188.9 (d, CHO) ppm. The crude bromination product was dissolved in dichloromethane (200 mL), 2,2-dimethylpropane-1,3-diol (26.3 g, 0.250 mol), trimethyl orthoformate (11.6 mL, 0.11 mol) and tetra-*n*-butylammonium tribromide (1.60 g, 3.32 mmol) were added, and the mixture was stirred at room temp. for 3 h. Satd. aq. Na_2CO_3 solution (150 mL) was added, the layers were separated, and the aqueous phase was extracted with dichloromethane (2×70 mL). The combined organic layers were dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Chromatography on silica gel (hexane/ethyl acetate, 5:1) afforded **40** (27.5 g, 85%) as a yellow solid (m.p. 92–92.5 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.72, 1.28 (2×s, 3 H each, CH_3), 3.47, 3.70 (2×d, J = 10.9 Hz, 2 H each, OCH_2), 3.81, 3.87 (2×s, 3 H each, OCH_3), 4.98 (s, 2 H, OCH_2Ph), 5.77 (s, 1 H, 2′-H), 7.10 (s, 1 H, Ar), 7.30–7.33, 7.35–7.38, 7.45–7.47 (3 m, 1 H, 2 H, 2 H, Ph) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.9, 23.2 (2×q, CH_3), 30.5 (s, C-5′), 56.5, 62.3 (2×q, OCH_3), 76.2 (t, OCH_2Ph), 78.2 (t, OCH_2), 98.1 (d, C-2′), 112.4 (s, Ar), 117.5 (d, Ar), 127.6 (s, Ar), 128.0, 128.4, 128.5 (3×d, Ph), 137.5, 146.7, 149.8, 150.0 (4×s, Ph, Ar) ppm. IR (KBr): $\tilde{\nu}$ = 3070–3000 (=CH), 2970–2865 (C–H), 2840 (OCH_3), 1495–1440 (C=C, Ar, Ph) cm^{-1}. $C_{21}H_{25}BrO_5$ (437.3): calcd. C 57.67, H 5.76; found C 57.63, H 5.63.

4-Benzyloxy-5-(5,5-dimethyl-1,3-dioxan-2-yl)-3,6-dimethoxy-11-oxatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5,9-tetraene (41): *n*-Butyllithium (40 mL, 2.5 M in hexanes, 0.10 mol) was added at –25 °C to a solution of diisopropylamine (15 mL, 0.11 mol) in THF (100 mL). The mixture was stirred for 30 min, cooled to –78 °C and added through Teflon tubing to a cooled (–78 °C) solution of compound **40** (27.5 g, 62.9 mmol) and furan (135 mL, 1.86 mol) in THF (300 mL) over 1 h. The solution was allowed to warm to room temp. overnight. After 23 h, water (200 mL) was slowly added and the mixture was extracted with diethyl ether (3×100 mL). The combined organic layers were dried with $MgSO_4$ and filtered, and the solvents were removed under reduced pressure to afford **41** (26.9 g, quant.) as a light brown solid, which was used without further purification. In a second experiment a small amount of **41** was purified by chromatography on silica gel (hexane/ethyl acetate, 2:1) to provide **41** as a colourless solid (m.p. 119–120 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.72, 1.29 (2×s, 3 H each, CH_3), 3.44, 3.68 (2×m$_c$, 2 H each, OCH_2), 3.86, 3.89 (2×s, 3 H each, OCH_3), 4.95 (s, 2 H, OCH_2Ph), 5.70 (s, 1 H, 2′-H), 5.96, 5.99 (2×dd, J = 0.9, 1.7 Hz, 1 H each, 1-H, 8-H), 6.99, 7.02 (2×dd, J = 1.7, 5.6 Hz, 1 H each, 9-H, 10-H), 7.31–7.34, 7.36–7.40, 7.43–7.46 (3 m, 1 H, 2 H, 2 H, Ph) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.9, 23.1 (2×q, CH_3), 30.5 (s, C-5′), 61.3, 62.2 (2×q, OCH_3), 76.7 (t, OCH_2Ph), 78.2, 78.3 (2×t, OCH_2), 80.7, 81.1 (2×d, C-1, C-8), 98.3 (d, C-2′), 122.2 (s, Ar), 128.0, 128.4, 128.5 (3×d, Ph), 134.4, 137.6, 140.7 (3×s, Ar, Ph), 142.0, 142.9 (2×d, C-9, C-10), 143.5, 148.2, 148.8 (3×s, Ar) ppm. IR (KBr): $\tilde{\nu}$ = 3085–3035 (=CH), 2995–2870 (C–H), 2830 (OCH_3), 1615, 1595 (C=C, Ar, Ph), 1470, 1460 (C–H) cm^{-1}. $C_{25}H_{28}O_6$ (424.5): calcd. C 70.74, H 6.65; found C 70.45, H 6.41.

7-Benzyloxy-6-(5,5-dimethyl-1,3-dioxan-2-yl)-5,8-dimethoxynaphthalen-1-ol (42): 2,2-Dimethylpropane-1,3-diol (5.97 g, 57.3 mmol), trimethyl orthoformate (6.30 mL, 57.6 mmol) and *p*-toluenesulfonic acid (2.20 g, 11.6 mmol) were added to a solution of compound **41** (4.87 g, 11.5 mmol) in dichloromethane (60 mL). The mixture was heated to reflux for 19 h, diluted with diethyl ether (100 mL) and washed once with water and once with brine. The combined aqueous phases were extracted with diethyl ether (2×50 mL), the combined organic layers were dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Chromatography on silica gel (hexane/ethyl acetate, 5:1 → 2:1) af-

forded **42** (4.03 g, 83%) as a yellow oil (mixture of regioisomers in a ratio of 95:5). In addition, 767 mg (16%) of **41** was re-isolated. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.76, 1.30 (2×s, 3 H each, CH_3), 3.58, 3.77 (2×d, J = 11.1 Hz, 2 H each, OCH_2), 3.99, 4.08 (2×s, 3 H each, OCH_3), 5.12 (s, 2 H, OCH_2Ph), 5.94 (s, 1 H, 2′-H), 6.90 (m_c, 1 H, Ar), 7.31–7.36, 7.39–7.42 (2 m, 2 H each, Ph), 7.51, 7.60 (2 m_c, 2 H, 1 H, Ar, Ph), 9.61 (s, 1 H, OH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 22.0, 23.4 (2×q, CH_3), 30.6 (s, C-5′), 62.5, 63.8 (2×q, OCH_3), 77.0 (t, OCH_2Ph), 78.6 (t, OCH_2), 98.6 (d, C-2′), 111.5, 114.2 (2×d, Ar), 118.8, 124.0 (2×s, Ar), 126.7 (d, Ar), 128.1* (s, Ar, Ph), 128.4, 128.5 (2×d, Ph), 137.6, 144.7, 145.8, 152.6, 153.9 (5×s, Ar, Ph) ppm; *signal with higher intensity. IR (film): $\tilde{\nu}$ = 3345 (OH), 3090–3030 (=CH), 2985–2870 (C–H), 2845 (OCH_3), 1605, 1505 (C=C, Ar, Ph), 1455–1440 (C–H) cm^{-1}. MS (EI = 80 eV, 130 °C): m/z (%) = 424 (18) $[M]^+$, 333 (30) $[M - C_7H_7]^+$, 305 (100), 219 (54), 115 (35) $[C_6H_{11}O_2]^+$, 91 (81) $[C_7H_7]^+$, 41 (54). HRMS (EI = 80 eV, 130 °C): calcd. for $C_{25}H_{28}O_6$ 424.18860; found 424.18794. Characteristic ^{1}H NMR (500 MHz, $CDCl_3$) signals of the regioisomer of **42** [6-benzyloxy-7-(5,5-dimethyl-1,3-dioxan-2-yl)-5,8-dimethoxynaphthalen-1-ol]: δ = 3.98, 4.06 (2×s, 3 H each, OCH_3), 5.18 (s, 2 H, OCH_2Ph), 5.90 (s, 1 H, 2′-H), 6.87, 7.61 (2×m_c, each 1 H, Ar), 9.50 (s, 1 H, OH) ppm.

7-Benzyloxy-2-bromo-6-(5,5-dimethyl-1,3-dioxan-2-yl)-5,8-dimethoxynaphthalen-1-ol (43): Pyridinium perbromide (639 mg, 2.00 mmol) was added to a solution of compound **42** (530 mg, 1.25 mmol) in THF (15 mL). The mixture was stirred at room temp. for 3 h, diluted with diethyl ether and washed twice with satd. aq. $Na_2S_2O_3$ solution (2×20 mL) and once with brine (20 mL). The aqueous phase was extracted once with diethyl ether (30 mL), the combined organic layers were dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Chromatography on silica gel (hexane/ethyl acetate, 5:1) afforded **43** (576 mg, 92%) as a brown oil, which slowly crystallized upon storage (m.p. 133–136 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.77, 1.30 (2×s, 3 H each, CH_3), 3.56, 3.77 (2×d, J = 10.9 Hz, 2 H each, OCH_2), 3.97, 4.09 (2×s, 3 H each, OCH_3), 5.12 (s, 2 H, OCH_2Ph), 5.91 (s, 1 H, 2′-H), 7.34–7.37, 7.39–7.42, 7.48–7.50 (3 m, 1 H, 2 H, 4 H, Ph, Ar), 10.33 (s, 1 H, OH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 22.0, 23.4 (2×q, CH_3), 30.6 (s, C-5′), 62.7, 64.0 (2×q, OCH_3), 77.1 (t, OCH_2Ph), 78.6 (t, OCH_2), 98.4 (d, C-2′), 105.9 (s, Ar), 115.3 (d, Ar), 119.2, 124.5, 127.0 (3×s, Ar), 128.3, 128.5, 128.6, 130.4 (4×d, Ph, Ar), 137.3, 144.0, 146.7, 150.1, 152.7 (5×s, Ph, Ar) ppm. IR (KBr): $\tilde{\nu}$ = 3295 (OH), 3110–3030 (=CH), 2985–2870 (C–H), 2845 (OCH_3), 1605 (C=C, Ar, Ph), 1490–1420 (C–H) cm^{-1}. $C_{25}H_{27}BrO_6$ (503.4): calcd. C 59.65, H 5.41; found C 59.11, H 5.21.

2-(3-Benzyloxy-6-bromo-1,4,5,8-tetramethoxynaphthalen-2-yl)-5,5-dimethyl-1,3-dioxane (44): An aqueous solution of ceric ammonium nitrate (967 mg in 5 mL H_2O, 1.76 mmol) was added at room temp. to a stirred solution of compound **43** (296 mg, 0.59 mmol) in acetonitrile (20 mL). After 1 h, the mixture was diluted with water and extracted with chloroform (3×30 mL), the combined organic layers were washed once with brine, dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (20 mL) and water (10 mL), tetra-*n*-butylammonium bromide (4 mg, 0.01 mmol) and sodium dithionite (307 mg, 1.76 mmol) were added, and the mixture was stirred at room temp. for 3 h. Dichloromethane and brine were added, the layers were separated, the aqueous phase was extracted with dichloromethane (3×30 mL), and the combined organic layers were washed once with brine, dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (20 mL), and tetra-*n*-butylammonium bromide (4 mg, 0.01 mmol) and dimethyl sulfate (0.84 mL, 8.86 mmol) were added. After the mixture had been cooled to 0 °C, aqueous sodium hydroxide solution (3.5 mL, 2.5 M, 8.75 mmol) was added dropwise and the mixture was stirred at room temp. for 15 h. Brine was added, the layers were separated, and the aqueous phase was extracted with dichloromethane (3×30 mL). The combined organic layers were washed with 10% aqueous ammonia solution (3×30 mL), dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Column chromatography on silica gel (hexane/ethyl acetate, 5:1), followed by removal of remaining dimethyl sulfate under reduced pressure ($5.8 \cdot 10^{-2}$ mbar, 100 °C), afforded **44** (117 mg, 36%) as a yellow foam (m.p. 55–57 °C). According to the ^{1}H NMR spectrum, this sample contained small amounts of the corresponding aldehyde (purity of **44** > 94%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.75, 1.25 (2×s, 3 H each, CH_3), 3.58, 3.76 (2×d, J = 10.9 Hz, 2 H each, OCH_2), 3.82, 3.83, 3.87, 3.94 (4×s, 3 H each, OCH_3), 5.22 (s, 2 H, OCH_2Ph), 6.00 (s, 1 H, 2′-H), 6.90 (s, 1 H, Ar), 7.30–7.34, 7.37–7.40, 7.55–7.57 (3 m, 1 H, 2 H, 2 H, Ph) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 22.0, 23.4 (2×q, CH_3), 30.6 (s, C-5′), 56.6, 61.9, 62.3, 64.1 (4×q, OCH_3), 76.6 (t, OCH_2Ph), 78.5 (t, OCH_2), 98.7 (d, C-2′), 109.5 (d, Ar), 116.2, 119.1, 125.2, 126.9 (4×s, Ar), 127.8, 128.3* (2×d, Ph), 138.2, 144.4, 145.7, 150.1, 152.9, 153.4 (6×s, Ph, Ar) ppm; *signal with very high intensity. IR (KBr): $\tilde{\nu}$ = 3090–3030 (=CH), 2990–2900 (C–H), 2840 (OCH_3), 1590–1575 (C=C, Ar, Ph), 1455–1425 (C–H) cm^{-1}. $C_{27}H_{31}BrO_7$ (547.4): calcd. C 59.24, H 5.71; found C 59.21, H 5.72.

2-(3-Benzyloxy-1,4,5,6,8-pentamethoxynaphthalen-2-yl)-5,5-dimethyl-1,3-dioxane (45): *n*-Butyllithium (0.55 mL, 2.5 M in hexanes, 1.38 mmol) was added at –100 °C to a solution of compound **44** (630 mg, 1.15 mmol) in THF (15 mL), immediately followed by addition of trimethyl borate (0.51 mL, 4.57 mmol). After stirring for 10 min, the mixture was allowed to warm to room temp. over 30 min and quenched with satd. aq. NH_4Cl solution (10 mL). The aqueous phase was extracted with ethyl acetate (2×10 mL), the combined organic layers were washed once with brine, dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The crude boronic acid was then treated with hydrogen peroxide (0.58 mL, 30%, 5.75 mmol) and aqueous sodium hydroxide solution (2.30 mL, 2.5 M, 5.75 mmol) as described in General Procedure 1 to afford the corresponding naphthol, which was used immediately without further purification. It was dissolved in dichloromethane (15 mL), tetra-*n*-butylammonium bromide (8 mg, 0.02 mmol) and dimethyl sulfate (0.55 mL, 5.80 mmol) were added, and the mixture was cooled to 0 °C. Aqueous sodium hydroxide solution (2.30 mL, 2.5 M, 5.75 mmol) was added, and the mixture was stirred at room temp. for 20 h, diluted with brine and extracted with dichloromethane (4×30 mL). The combined organic layers were washed with 10% aqueous ammonia solution (3×30 mL), dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Column chromatography on silica gel (hexane/ethyl acetate, 3:1) afforded **45** (261 mg, 46%) as an auburn oil, together with **46** (104 mg, 19%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.74, 1.24 (2×s, 3 H each, CH_3), 3.58, 3.76 (2×d, J = 10.9 Hz, 2 H each, OCH_2), 3.82, 3.83, 3.88, 3.96, 3.99 (5×s, 3 H each, OCH_3), 5.22 (s, 2 H, OCH_2Ph), 6.00 (s, 1 H, 2′-H), 6.64 (s, 1 H, Ar), 7.29–7.33, 7.37–7.40, 7.57–7.59 (3 m, 1 H, 2 H, 2 H, Ph) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.9, 23.4 (2×q, 2×CH_3), 30.5 (s, C-5′), 56.7,* 61.9, 62.1, 63.9 (4×q, OCH_3), 76.5 (t, OCH_2Ph), 78.4* (t, OCH_2), 96.0 (d, Ar), 98.8 (d, C-2′), 114.5, 122.2, 127.2 (3×s, Ar), 127.6, 128.19, 128.25 (3×d, Ph), 128.4, 138.5, 144.2, 149.5, 150.5, 152.6, 153.9 (7×s, Ar, Ph) ppm; *signal with higher intensity. IR (film): $\tilde{\nu}$ = 3090–3030 (=CH), 2990–2900 (C–H), 2840 (OCH_3), 1605–1575 (C=C, Ar, Ph), 1455–1425 (C–H)

cm^{-1}. MS (EI = 80 eV, 40 °C): *m/z* (%) = 498 (32) $[M]^+$, 380 (21), 379 (100), 293 (24), 263 (12), 115 (5) $[C_6H_{11}O_2]^+$, 91 (17) $[C_7H_7]^+$. HRMS (EI = 80 eV, 40 °C): calcd. for $C_{28}H_{34}O_8$ 498.22537; found 498.22477.

2-(3-Benzyloxy-1,4,5,8-tetramethoxynaphthalen-2-yl)-5,5-dimethyl-1,3-dioxane (46): ^1H NMR (270 MHz, $CDCl_3$): δ = 0.75, 1.24 (2 × s, 3 H each, CH_3), 3.59, 3.77 (2 × d, J = 11.6 Hz, 2 H each, OCH_2), 3.83, 3.88, 3.92, 3.94 (4 × s, 3 H each, OCH_3), 5.20 (s, 2 H, OCH_2Ph), 6.03 (s, 1 H, 2′-H), 6.73, 6.81 (2 × d, J = 8.5 Hz, 1 H each, Ar), 7.31–7.42, 7.57 (m, m_c, 3 H, 2 H, Ph) ppm.

3-Benzyloxy-1,4,5,6,8-pentamethoxynaphthalene-2-carbaldehyde (8b): Compound **45** (104 mg, 0.21 mmol) was dissolved in acetic acid (5 mL, 80%) and stirred at room temp. for 4 h. The mixture was diluted with water and extracted with diethyl ether (3 × 10 mL), the combined organic layers were dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to afford crude **8b** (86 mg). After chromatography on silica gel (hexane/ethyl acetate, 3:1), pure **8b** (70 mg, 81%) was obtained as a yellow solid (m.p. 115–118 °C). ^1H NMR (500 MHz, $CDCl_3$): δ = 3.86, 3.88, 3.90, 4.01, 4.02 (5 × s, 3 H each, OCH_3), 5.17 (s, 2 H, OCH_2Ph), 6.68 (s, 1 H, Ar), 7.31–7.34, 7.37–7.40, 7.57–7.58 (3 m, 1 H, 2 H, 2 H, Ph), 10.48 (s, 1 H, CHO) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 56.7, 57.0, 62.1,* 64.8 (4 × q, OCH_3), 76.1 (t, OCH_2Ph), 96.2 (d, Ar), 113.9, 120.7 (2 × s, Ar), 128.2, 128.5, 128.9 (3 × d, Ph), 129.9, 136.7, 137.4, 144.4, 148.7, 153.1, 155.3, 158.9 (8 × s, Ph, Ar), 189.7 (d, CHO) ppm; *signal with higher intensity. IR (KBr): $\tilde{\nu}$ = 3110–3030 (=CH), 2990–2880 (C–H), 2840 (OCH_3), 1685 (C=O), 1600, 1565 (C=C, Ar, Ph), 1495–1420 (C–H) cm^{-1}. $C_{23}H_{24}O_7$ (412.4): calcd. C 66.98, H 5.87; found C 66.98, H 5.95.

1-(3-Benzyloxy-1,4,5,6,8-pentamethoxynaphthalen-2-yl)-1-hydroxybut-3-en-2-one (7a): *n*-Butyllithium (0.17 mL, 2.5 M in hexanes, 0.43 mmol) was added at –40 °C to a solution of methoxyallene (60 μL, 0.72 mmol) in THF (4 mL) and the solution was stirred for 1 h. The reaction mixture was then cooled to –78 °C, a solution of naphthaldehyde **8b** (90 mg, 0.22 mmol) in THF (3 mL) was added, and stirring was continued for an additional 4 h. The reaction mixture was quenched by addition of aq. sulfuric acid (10 mL, 5%) and allowed to warm to 0 °C over 1 h. Satd. aq. $NaHCO_3$ solution (10 mL) was added and the mixture was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed once with satd. aq. $NaHCO_3$ solution (20 mL), dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to afford **7a** (117 mg, quant.) as a yellow oil. Compound **7a** was used in the next step without further purification. The analytic data were obtained from a second experiment; chromatography on silica gel (hexane/ethyl acetate, 2:1) afforded **7a** as a yellow solid (m.p. 105–107 °C). ^1H NMR (500 MHz, $CDCl_3$): δ = 3.79, 3.861, 3.863, 3.97, 4.00 (5 × s, 3 H each, OCH_3), 4.36 (d, J = 4.0 Hz, 1 H, OH), 5.16, 5.30 (AB system, J_{AB} = 10.7 Hz, 2 H, OCH_2Ph), 5.58 (dd, J = 2.3, 9.8 Hz, 1 H, 4-H), 5.71 (d, J = 4.0 Hz, 1 H, 1-H), 6.23 (dd, J = 2.3, 17.5 Hz, 1 H, 4-H), 6.29 (dd, J = 9.8, 17.5 Hz, 1 H, 3-H), 6.68 (s, 1 H, Ar), 7.31–7.34, 7.37–7.40, 7.51–7.53 (3 m, 1 H, 2 H, 2 H, Ph) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 56.8, 56.9, 61.97, 61.98, 63.8 (5 × q, OCH_3), 71.2 (d, C-1), 75.8 (t, OCH_2Ph), 96.3 (d, Ar), 114.4, 123.3, 127.3 (3 × s, Ar), 128.1, 128.46, 128.54 (3 × d, Ph), 129.0 (t, C-4), 131.5 (d, C-3), 136.7, 137.5, 144.0, 148.7, 150.8, 152.1, 153.6 (7 × s, Ph, Ar), 198.2 (s, CO) ppm. IR (KBr): $\tilde{\nu}$ = 3450 (OH), 3110–3030 (=CH), 2995–2860 (C–H), 2840 (OCH_3), 1705 (C=O), 1620–1575 (C=C, Ar, Ph), 1500–1405 (C–H) cm^{-1}. $C_{26}H_{28}O_8$ (468.5): calcd. C 66.66, H 6.02; found C 66.23, H 5.75.

1-(3-Benzyloxy-1,4,5,6,8-pentamethoxynaphthalen-2-yl)-1-triethylsilyloxybut-3-en-2-one (7b): Triethylsilyl chloride (50 μL, 0.47 mmol) was added to a solution of crude compound **7a** (117 mg, max. 0.22 mmol) and diisopropylethylamine (0.11 mL, 0.64 mmol) in DMF (3 mL). The mixture was stirred at room temp. for 6 h, quenched with satd. aq. Na_2CO_3 solution (10 mL) and extracted with diethyl ether (3 × 15 mL). The combined organic layers were dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Chromatography on silica gel (hexane/ethyl acetate, 4:1) afforded **7b** (82 mg, 64%) as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.59, 0.82 [q, t, J = 8.0 Hz, 6 H, 9 H, $OSi(CH_2CH_3)_3$], 3.81, 3.853, 3.855, 3.94, 3.99 (5 × s, 3 H each, OCH_3), 5.13, 5.35 (AB system, J_{AB} = 10.8 Hz, 2 H, OCH_2Ph), 5.51 (dd, J = 2.1, 10.5 Hz, 1 H, 4-H), 5.59 (s, 1 H, 1-H), 6.25 (dd, J = 2.1, 17.4 Hz, 1 H, 4-H), 6.66 (s, 1 H, Ar), 6.88 (dd, J = 10.5, 17.4 Hz, 1 H, 3-H), 7.29–7.33, 7.35–7.38, 7.48–7.51 (3 m, 1 H, 2 H, 2 H, Ph) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 4.8, 6.8 [q, t, $OSi(CH_2CH_3)_3$], 56.8, 57.2, 61.9, 62.0, 63.9 (5 × q, OCH_3), 72.6 (d, C-1), 75.8 (t, OCH_2Ph), 96.6 (d, Ar), 114.7, 126.6, 127.08 (3 × s, Ar), 127.1 (t, C-4), 127.9, 128.37, 128.41 (3 × d, Ph), 131.6 (d, C-3), 136.8, 138.0, 143.7, 148.9, 150.4, 151.9, 153.7 (7 × s, Ph, Ar), 200.4 (s, CO) ppm. IR (film): $\tilde{\nu}$ = 3110–3030 (=CH), 2990–2875 (C–H), 2840 (OCH_3), 1715, 1695 (C=O), 1605–1580 (C=C, Ar, Ph), 1500–1400 (C–H) cm^{-1}. MS (EI = 80 eV, 100 °C): *m/z* (%) = 584 (13), 583 (44), 582 (97) $[M]^+$, 529 (11), 528 (28), 527 (100), 466 (12), 465 (49), 464 (10), 407 (32), 86 (35), 84 (56), 75 (11), 73 (20), 57 (15), 51 (20), 49 (63), 44 (12), 42 (10). HRMS (EI = 80 eV, 100 °C): calcd. for $C_{32}H_{42}O_8Si$ 582.26489; found 582.26555.

Acknowledgments

The authors thank the Fonds der Chemischen Industrie (Kekulé fellowship for S. S.) and the Schering AG for generous support of this research. We also thank Dr. R. Zimmer for his assistance during the preparation of this manuscript.

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Received: April 24, 2006
Published Online: August 2, 2006

