EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

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To be cited as: Eur. J. Org. Chem. 10.1002/ejoc.201601225

Link to VoR: http://dx.doi.org/10.1002/ejoc.201601225

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Lessons Learned During Spiroketalization Experiments – Progress and Setbacks in the Preparation of Oxygenated Rubromycins and Synthesis of 3´-Desoxyheliquinomycinone

Michael Wilsdorf*,[a] Sebastian Sörgel,[a] Hans-Ulrich Reissig*[a]

Abstract: In this account we disclose our results on the synthesis of 3-hydroxy-substituted rubromycin derivatives. We re-evaluate our methoxyallene-based first generation approach to this class of natural products, that so far suffered from a notoriously inefficient late-stage spiroketalization step. While resuming again to model studies we recognized that the success of this acid-mediated key transformation is highly solvent-dependent. Methanol turned out to be the solvent of choice. With one substrate an unepected intramolecular Friedel-Crafts type alkylation provided an interesting hexacyclic side-product. Based on these observations and with several adjustments to the synthetic route, but still maintaining the original retrosynthetic strategy, we here present a second generation approach that eventually allowed the preparation of several rubromycin derivatives (in up to >100 mg scale) for the first time.

Introduction

To date about twenty different members of natural products of the rubromycin class are described (Figure 1).[1] This relatively small group of compounds is characterized by a unique [5,6]-bisbenzannulated spiroketal core, which is flanked by a polyaromatic framework of remarkably high oxygen content (C:O-ratio up to 58:42). The central spiroketal motif is further decorated with a diversifying pattern of oxygenation in various stereochemical arrays. Despite this differentiation, these compounds may be divided into two main subclasses: (a) those having a methylene moiety at the C-3 position (rubromycin numbering, e.g. β-rubromycin **1**) and (b) those bearing a hydroxy group at this site. The latter group may best be represented by heliquinomycin (**2**)[2] that possesses an α-glycosidic linkage at C-3 to the rare desoxysugar cymarose, or the DK-compounds such as DK-7814-C (**3**), whose absolute configuration at C-3 is still not determined.[1e]

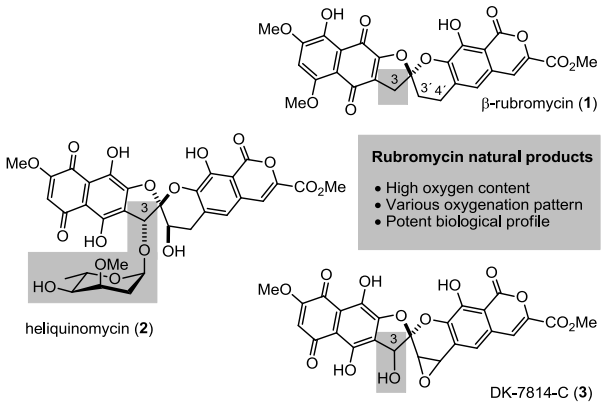

Figure 1. Representative examples from the rubromycin family.

In light of their intriguing molecular architecture, various research groups have directed considerable efforts towards their synthesis over the recent years.[3] Despite of notable success in this field of research, efficient synthetic approaches to rubromycins with a hydroxyl group at the C-3 position still remain scarce and challenging. Only few successful examples are known, namely the assembly of racemic heliquinomycinone (the aglycon of **2**) by the Danishefsky group,[4] the preparation of spiroketals related to purpuromycin by Kozlowksi[5] and a di-*O*-methyl-substituted 3-hydroxy β-rubromycin derivative (**7**) by our group briefly mentioned in our review.[1a] Due to the potential biological profile of these natural products a flexible and efficient synthetic entry is highly desirable that would ideally enable the rapid assembly of various congeners, but also would allow a high throughput of material for further biological evaluation. In this account we re-evaluate the pivotal spiroketalization step, discuss the factors which potentially influence this delicate transformation and briefly lay out a second generation synthesis which allows the generation of larger quantities of C-3 oxygenated rubromycin derivatives (>100 mg) for the first time.

Results and Discussion

First Route

As part of our efforts towards the total synthesis of heliquinomycin (**2**) we established a convergent synthetic route that also capitalizes lithiathed methoxyallene as a valuable C_3 building block (Scheme 1).[6] The Heck reaction of enone **4** with a highly substituted naphthyl group[7] with iodoisocoumarin derivative **5**[8] proceeded uneventfully furnishing precursor **6** in

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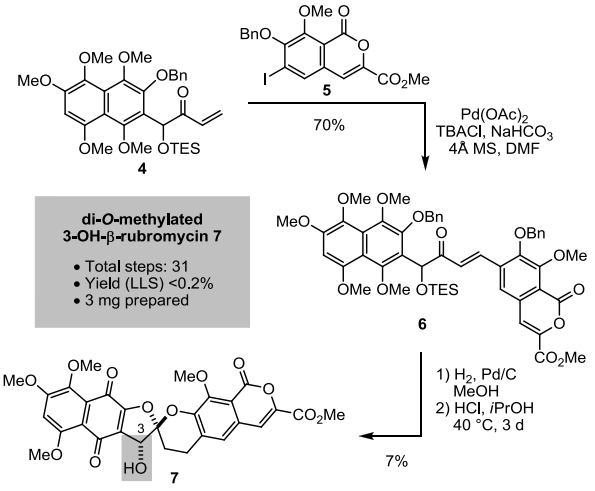
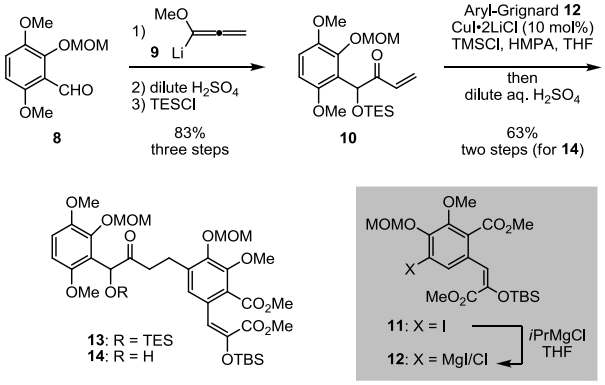
70% yield. However, a disappointingly low overall yield (7%) was observed after the anticipated hydrogenation and deprotection of **6** followed by the acid-mediated spiroketalization to compound **7**. In contrast to our previous studies with simple model substrates,[6] this particular transformation was mainly accompanied by decomposition of the valuable spiroketalization precursor (not shown) what eventually required tedious HPLC purification to isolate **7** as reddish powder in only minute amounts (3 mg).[9] Interestingly, during this transformation an autoxidation of the electron-rich naphthalene portion to its corresponding β-naphthoquinone also took place. No identifiable by-products could be isolated from the reaction mixture. The preparation of compound **7** required in total 31 steps and proceeded with less than 0.2% overall yield (longest linear sequence = LLS). Needless to say that a more efficient strategy was required.



Scheme 1. First route: Heck reaction of enone **4** with **5** to precursor **6** and its conversion into di-*O*-methylated 3-OH-β-rubromycin **7**.

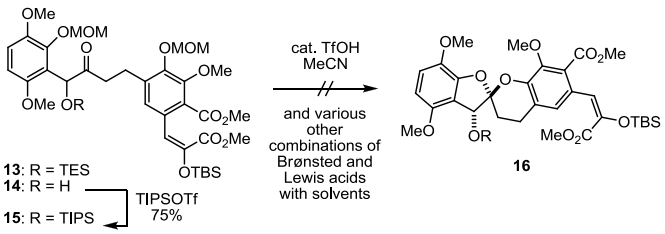
Model Studies

In order to reinvestigate the pivotal spiroketalization step we first reverted to the preparation of advanced model substrate **14** with an "open form" isocoumarin moiety (Scheme 2). This substrate was assembled in a convergent manner on gram scale through the cuprous(I)-mediated conjugate addition of the known aryl-Grignard reagent **12**[3f,10] to the methoxyallene-derived enone **10**.[11] A subsequent hydrolysis of the intermediate silyl enol ether (not shown) was required and was achieved by treatment of the crude 1,4-addition product with dilute aqueous H_2SO_4 in THF to yield **13**. Notably, a prolonged treatment with acid eventually led to the cleavage of the labile TES-ether to give ketone **14** in essentially the same overall yield.



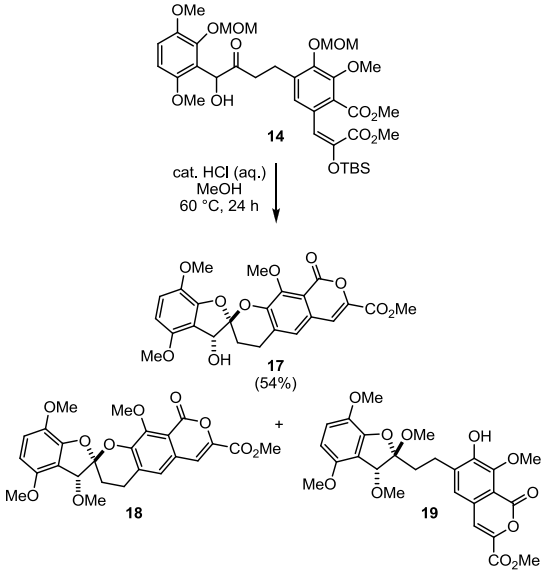
Scheme 2. Assembly of advanced model substrate **14** with the "open form" isocoumarin moiety.

As previously detailed in our total synthesis of the natural product (±)-γ-rubromycin and in our studies on C-3 unsubstituted rubromycin derivatives,[3f] the usage of the "open form" isocoumarin portion provided a satisfactory solution to the otherwise kinetically strongly retarded spiroketalization reaction, as it was observed for substrates with a fully elaborated isocoumarin portion (unfavorable -M and -I effects were proposed to prevent the ketalization).[12] We also found that the combination of catalytic amounts of triflic acid (TfOH) in acetonitrile (MeCN) initiated the chemoselective hydrolysis of the MOM-ethers and smoothly promoted the pivotal spiroketalization at ambient conditions, while keeping all other acid-sensitive functionalities intact. Importantly, the formation of the isocoumarin moiety occurred *after* the spiroketalization in a separate step and was triggered by the hydrolysis of the acid-labile TBS-enol ether. With these results in mind, we hoped to achieve the spiroketalization of ketone **14** under the same conditions, however predominately observed the gradual decomposition of this substrate, presumably *via* autoxidation of the electron-rich arene portion after cleavage of the MOM-ethers. A brief survey of Brønsted and Lewis acids in combination with various aprotic solvents (including for instance *p*TSA in toluene[5] or $NaHSO_4$ on SiO_2 in CH_2Cl_2[3b]) were not productive and either resulted in unspecific decomposition of the starting material or in no conversion at all. The decoration of the 3-hydroxyl group with a more robust triisopropylsilyl (TIPS) group (**15**) was also not beneficial for the outcome of this transformation (Scheme 3).



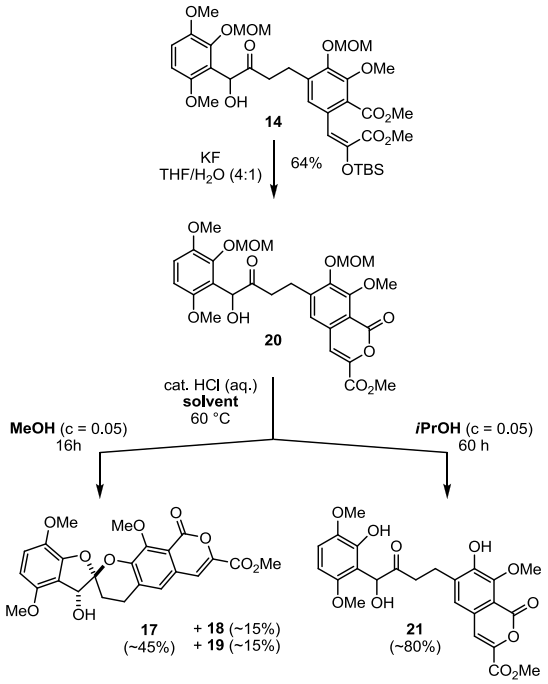
Scheme 3. Unsuccessful attempts of the spiroketalization of "open form" 3-OR-substituted model compounds **13**-**15**.

During our search for suitable reaction conditions, a positive result was obtained by treatment of **14** with aq. hydrochloric acid (HCl) in methanol (MeOH) at elevated temperatures (60 °C). In this specific case, we were able to isolate the spiroketal **17** as the major product in 54% yield, along with an inseparable mixture of 3-methoxy-substituted spiroketal **18** and monocyclization product **19** in a combined yield of 14% (Scheme 4). It merits to note, that all three products already incorporated a fully elaborated isocoumarin moiety, and that a separate step to form this heterocycle unit was not necessary.



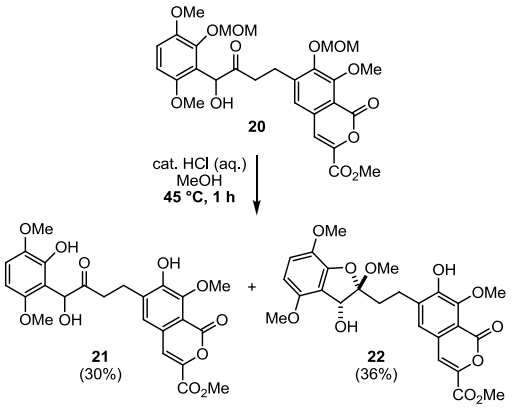
Scheme 4. First positive result for the conversion of model compound **14** to spiroketal **17**.

The monitoring of the conversion of **14** into **17** with thin layer chromatography (TLC) indicated a fast hydrolysis of all acid-labile functional groups of compound **14**, that also included the lactonization to the isocoumarin portion *prior* to the formation of any spiroketalization product. We noted that at least three reaction intermediates were formed and that eventually heating (60 °C) was required to converge them into the spiroketals **17** and **18**. Due to the isolation of ketal **19** we also speculated that methanol may compete as nucleophile with the spiroketalization event by trapping the transient oxocarbenium ion (not shown) on the way to **17**. However, in contrast to our previous hypothesis, the spiroketalization of substrates that possess an isocoumarin moiety may indeed be feasible. To confirm this assumption we prepared the substrate **20** by treating ketone **14** with potassium fluoride (KF).[11] This material was then subjected to catalytic amounts of aq. HCl in MeOH and again gave the desired spiroketal **17** as the major product (Scheme 5). Remarkably, the subtle change from MeOH to *i*PrOH – the previous solvent of choice for the spirokelalization reactions of simple model substrates[7] – led to the complete suppression of any formation of spiroketal **17** and only gave deprotected acyclic ketone **21** even under extended reaction times.



Scheme 5. Spiroketalization of **20** in methanol and in *iso*-propanol.

We also subjected substrate **20** to catalytic amounts of aq. HCl in methanol at 45 °C and aborted the reaction after 1 h, conditions that furnished ketone **21** and monocyclization product **22** in almost equimolar amounts (Scheme 6). With this experimental set-up, we recognized that ketal **22** is a crucial intermediate for the successful spiroketalization. The formation of the spiroketal **17** was yet only productive in MeOH and since in *i*PrOH as bulk solvent none of a respective monocyclization product was observed – presumably due to unfavorable steric effects. We therefore propose the intermediacy of **22** and the proper choice of solvent to be essential for the success of this transformation.

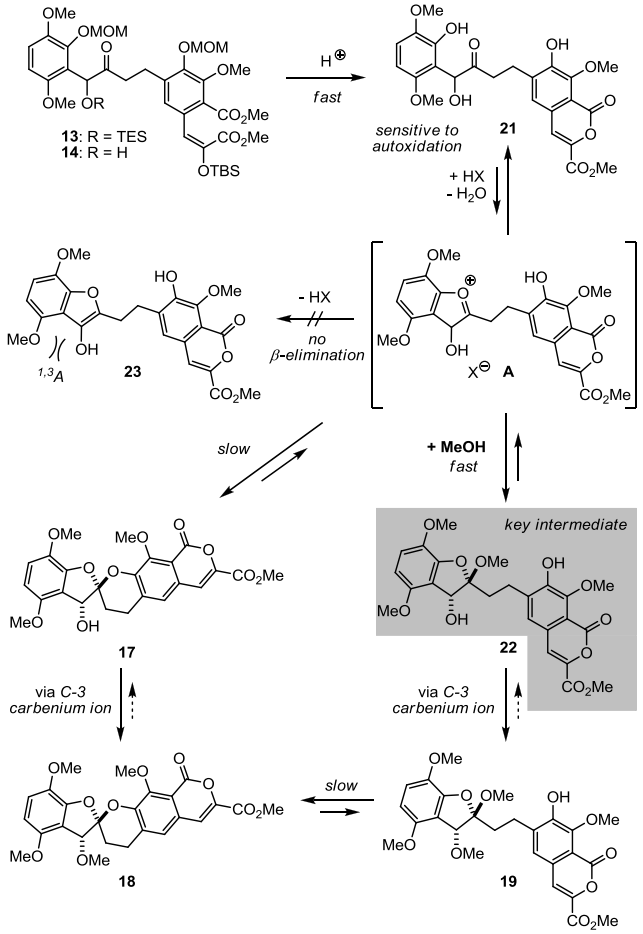


Scheme 6. Identification of monocyclization product **22** as key intermediate in the spiroketalizaton event.

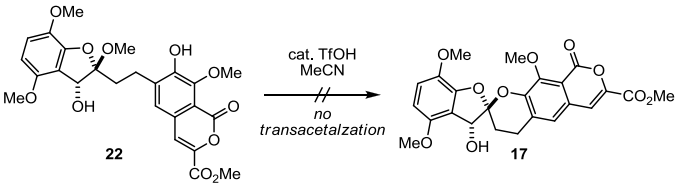
Based on these observations, we propose the following reaction pathway towards the 3-hydroxy-substituted spiroketal **17**, starting from spiroketalization precursors **13**, **14** or **20** (Scheme 7). When these substrates are subjected to catalytic amounts of aq. HCl in methanol, MOM-deprotection quickly generates ketone **21**. This particular substrate is susceptible to oxidative degradation and may also contribute to the gradual decomposition that is frequently observed for compounds of these types, especially during extended reaction times. Yet, in the presence of methanol the stable monocyclization product **22** is formed by fast nucleophilic trapping of oxocarbenium ion **A**, thus productively shifting the equilibrium away from **21**. Intermediate **22** therefore serves as a reservoir for the continuous generation of **A** and helps to increase the concentration of this reactive species. Elevated temperatures are required to achieve the spiroketalization to **17** or **18** that are both isolated as their thermodynamically favored *trans*-configured diastereomers exclusively.[11] Notably, no aromatizing β-elimination reaction to benzofuran derivative **23** occurs, presumably due to the allylic $^{1,3}A$-strain that is exerted by the adjacent methoxy group on the arene moiety of **A**. The formation of products **18** and **19** may result from solvolysis of the corresponding spiroketal or ketal at C-3 *via* their resonance-stabilized benzylic carbenium ions (not shown). A reverse ring-opening reaction, e. g. **18**→**19** cannot be excluded and could also contribute to the formation of ketal **19** to a minor extend.

The crucial role of methanol to act as trapping nucleophile for the transient oxocarbenium ion was further substantiated by the attempt to perform the transacetalization of methyl ketal **22** to **17** with TfOH in acetonitrile at ambient temperature (Scheme 8). No spiroketal was formed under these conditions, but the starting material decomposed instead, presumably *via* the intermediancy of labile ketone **21**. This experiment again highlights the complementary conditions that are required for substrates that are unsubstituted at C-3 and for those with a hydroxyl group at this position.[3f,11]

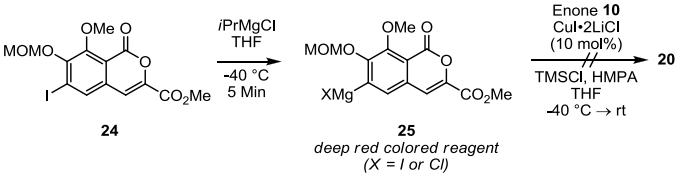
As demonstrated with the assembly of spiroketal **17** from ketone **20**, it is not essential for the spiroketalization precursor to bear an "open-form" isocoumarin portion. We therefore briefly examined an alternative approach towards ketone **20** by subjecting iodo isocoumarin derivative **24** to the halogen/metal exchange reaction with *i*PrMgCl (Scheme 9).[13] Upon addition of *i*PrMgCl to to **24** at -40 °C, the Grignard reagent **25** is apparently formed instantly, as indicated by the deep-red coloration of the reaction mixture, yet it remained unreactive towards methoxyallene-derived enones in the presence of copper(I) salts.[14] We suspect the Grignard reagent **25** to be too electron-deficient, therefore hampering a putative transmetalation to the required Normant cuprate. Additionally, this magnesium organyl displays just a moderate stability in comparison to aryl Grignard-reagent **12**, as we could isolate the dehalogenated isocoumarin derivative in only 30% after aqueous work-up (not shown).[15] Consequently, we did not spend more efforts into optimizing this approach, since Grignard-reagent **12** had already offered an excellent solution of this problem.



Scheme 7. Proposed reaction pathway to the spiroketals **17** and **18** with ketal **22** as crucial reservoir intermediate.



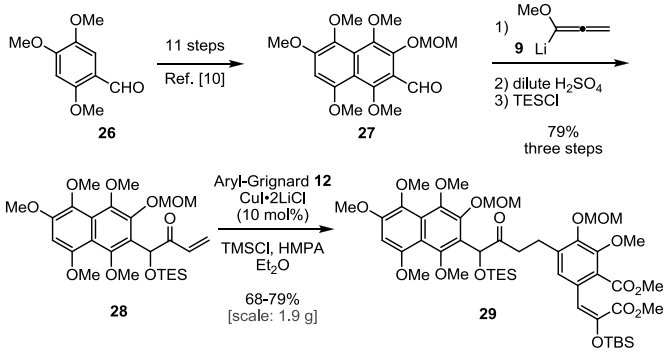
Scheme 8. Unsuccessful attempt to generate spiroketal **17** from ketal **22** with trifilic acid in acetonitrile.



Scheme 9. Failed alternative approach towards ketone **20** *via* Grignard-reagent **25**.

Synthesis of a 3´-Desoxyheliquinomycinone Derivative

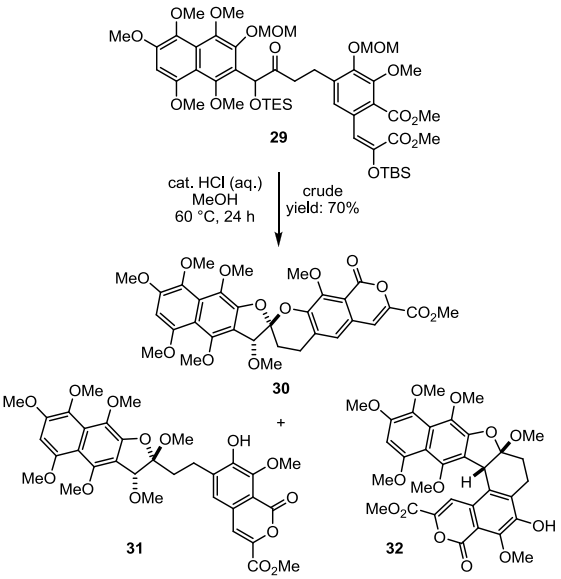
With the results of the model study and the mechanistic knowledge in mind, we next reverted to our initial goal: the assembly of 3-hydroxyl-substituted rubromycins. According to our previously described approach towards γ-rubromycin, the synthetic work started with the preparation of naphthalene carbaldehyde **27** that is available in 11 steps, starting from 2,4,5-trimethoxybenzaldehyde (**26**).[10,16] With sufficient quantities of **27** in hand, the next steps towards enone **28** were straightforward (Scheme 10), involving the addition of lithiated methoxyallene (**9**) to **27**, followed by hydrolysis of the intermediate allenyl adduct with dilute aqueous sulfuric acid and subsequent silylation of the secondary alcohol with chlorotriethylsilane (TESCl). As anticipated, enone **28** served as suitable electrophile for the conjugate addition of aryl Grignard-reagent **12**, providing the advanced spiroketalization precursor **29** on gram scale in 68-79% yield on multiple runs.



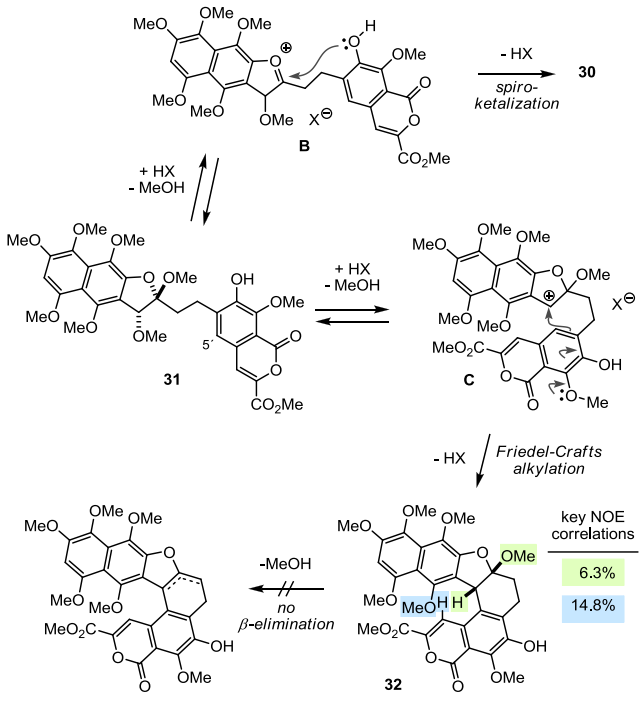
Scheme 10. Conversion of naphthalene carbaldehyde **27** to the advanced spiroketalization precursor **29**.

Next, ketone **29** was subjected to catalytic amounts of aq. HCl in MeOH and heated to 60 °C for 24 h to yield a mixture of spiroketal **30**, the tentatively assigned monocyclization product **31** and the unexpected hexacyclic product **32** (Scheme 11). The three compounds are formed in nearly equal amounts as judged by the ^{1}H NMR spectrum of the crude product mixture. Due to their similar polarities, a separation and purification by HPLC was required to order to obtain pure samples **30** and **32** for final analytical characterization, whereas **31** decomposed upon an attempt of its isolation.

From the product distribution we assume, that upon treatment of ketone **29** with HCl in MeOH methyl ketal **31** is quickly generated and that by elimination of methanol in different positions this compound can either form oxocarbenium ion **B** or the highly stabilized carbenium ion **C** (Scheme 12). Albeit proceeding at low rates, the interception of **B** with the phenolic hydroxy group of the isocoumarin moiety produces spiroketal **30**, whereas species **C** may undergo a competing Friedel-Crafts type alkylation by addition to the C-5´ of the isocoumarin fragment to generate the *cis*-fused methyl ketal **32**. It should be noted that this product does not undergo further elimination of methanol to its respective pentamethoxy naphthofuran or its isomer for instance. Apparently, an elimination would exert an enormous strain into these already highly rigidified structures, as it is exemplified by the remarkably large NOE correlation (14.5%) of 6´-H of the isocoumarin moiety and the 4-OMe group of the naphthalene fragment in **32**.

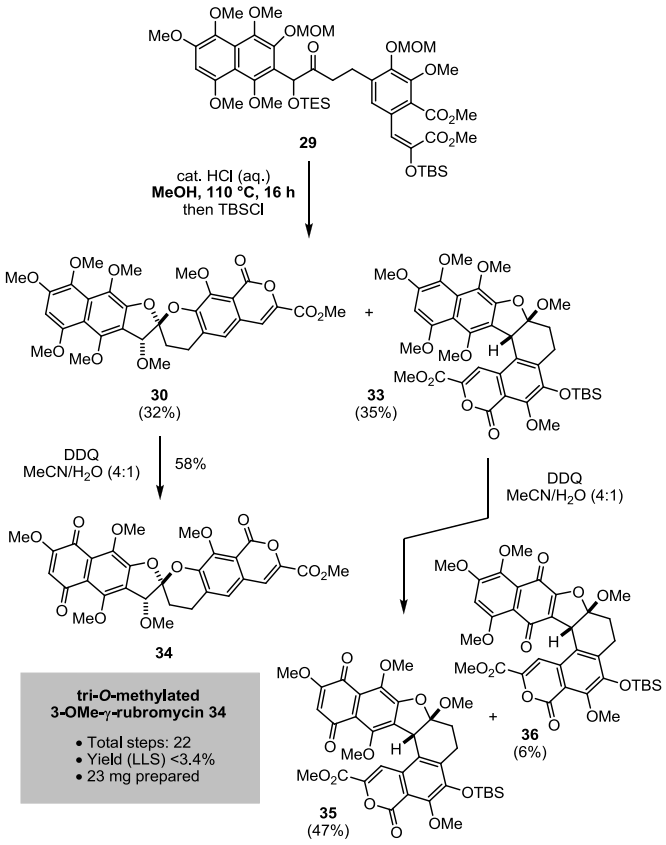


Scheme 11. Treatment of **29** with cat. HCl in MeOH leading to spiroketal **30** and compounds **31** and **32**.



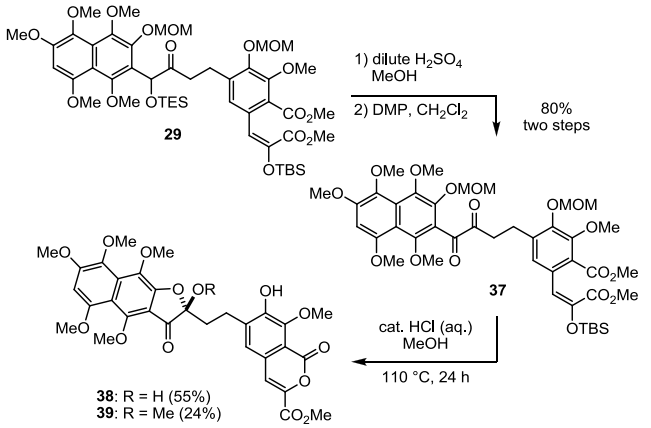
Scheme 12. Competing reaction pathways: spiroketalization *vs*. Friedel-Crafts type alkylation; key NOE correlations in methyl ketal **32**.

In order to ensure the complete conversion of intermediate **31** to either spiroketal **30** or to hexacyclic compound **32**, the reaction was also run at 110 °C in a sealed pressure tube under an atmosphere of argon for 16 h (Scheme 13). The work-up just included the filtration of the crude mixture through a small plug of silica gel followed by treatment of the crude product with TBSCl to affect the silylation of the free hydroxy group of **32**. This subtle difference of polarity of the two products was sufficient to allow the clean separation of silylated methyl hemiketal **33** from spiroketal **30** by column chromatography, thus affording both products in acceptable 35% and 32% yield respectively. Yet, regardless of reaction temperature and time, the ratio of the products remained essentially the same. The subsequent treatment of spiroketal **30** with dicyanodichloro benzoquinone (DDQ) afforded the di-*O*-methyl-substituted 3-methoxy-γ-rubromycin derivative **34** in 58% yield, whereas the oxidation of **33** gave a separable mixture of the γ- and the β-naphthoquinoide compounds **35** and **36** in a combined moderate yield of 53%.



Scheme 13. Conversion of ketone **29** into spiroketal **30** and *O*-silylated Friedel-Crafts alkylation product **33** and subsequent DDQ oxidations to γ-rubromycin derivative **34** and to β- and γ-naphthoquinones **35** and **36**.

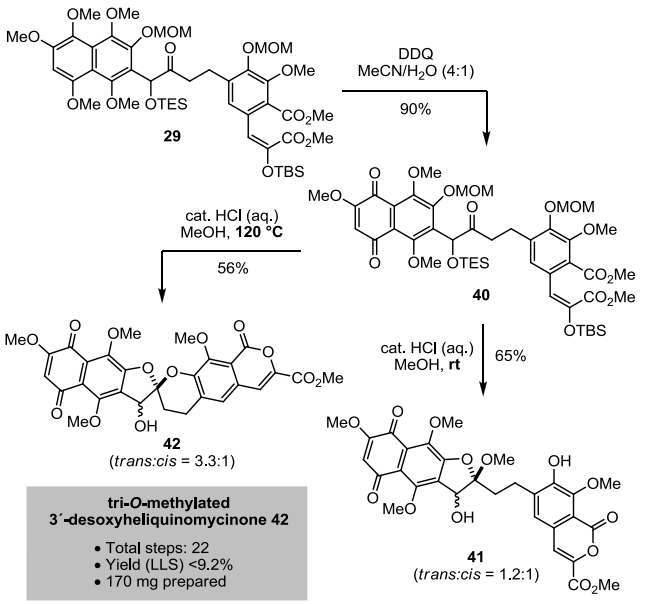
After these promising achievements towards the synthesis of 3-methoxy-substituted rubromycin derivatives, we next sought to "fine-tune" the pivotal spiroketalization precursor in order to mitigate the propensity for the formation of the carbenium ion at C-3 that causes the undesired Friedel-Crafts type alkylation (**29**→**32**). We therefore prepared the naphthyl-substituted 1,2-diketone **37** in good overall yield by treatment of **29** with dilute aqueous hydrochloric acid in MeOH to cleave the TES ether, followed by the oxidation of the secondary alcohol with Dess-Martin periodinane (DMP) (Scheme 14). Yet, despite of the literature precedence by the Kozlowski group[5] who described the spiroketalization of a similar diketone analogue, no spiroketal could be isolated upon heating of **37** in MeOH with catalytic amounts of HCl. Instead, most of the diketone was converted into a mixture of the hemiketal **38** and the methyl ketal **39** (ca. 2:1). The generation of a transient oxocarbenium ion from **38** or **39** may be strongly impeded by the electron-withdrawing keto group at C-3. An alternative excessive heating of **37** in toluene in the presence of *p*-toluenesulfonic acid (*p*TSA), as suggested by Kozlowksi´s protocol, just led only to the unspecific and complete decomposition of diketone **37**. Hence this approach *via* diketone **37**, that was supposed to allow the preparation of rubromycin analogs employing the additional carbonyl group, turned out to be a dead-end pathway.



Scheme 14. Synthesis of naphthyl-substituted 1,2-diketone **37** and attempted spiroketalization.

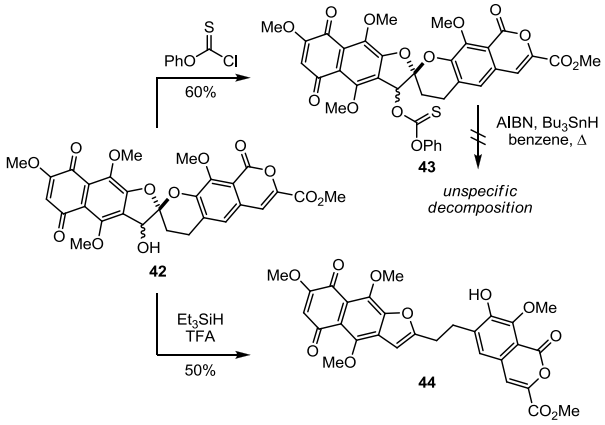
However, a viable solution of this synthetic challenge was already found by us during our total synthesis of (±)-γ-rubromycin. Balanced electronic properties of the pivotal precursor were achieved by the chemoselective oxidation of the pentamethoxy naphthalene portion prior to the spiroketalization.[3f,10] According to this strategy, treatment of ketone **29** with DDQ cleanly gav.e γ-naphthoquinone **40** (Scheme 15). As anticipated, stiring of **40** in MeOH in the presence of catalytic amounts of hydrochloric acid for 24 h at room temperature led to the formation of stable methyl ketal **41**, while heating up to 120 °C was necessary to achieve conversion of **41** to spiroketal **42**. Yet, with this protocol tri-*O*-methylated 3´-deoxyheliquinomycinone **42** was prepared as a mixture of diastereomers in a remarkable yield of 56%. From the fact that this product contains a hydroxyl group at C-3 rather than a methoxy group it is evident that the formation of a C-3

carbenium ion and subsequent solvolysis is strongly impeded due to the electron-withdrawing effect of the naphthoquinone unit. An essentially pure product could be obtained by the consecutive filtration of the crude reaction mixture through a plug of silica gel and basic alumina oxide. *Via* this route we have prepared up to 170 mg of **42** in a single run.



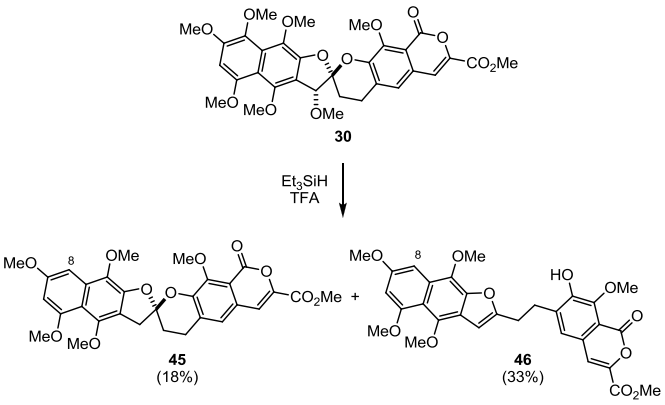
Scheme 15. Oxidation of **29** to naphthochinone **40** and spiroketalization to tri-*O*-methylated 3´-desoxyheliquinomycinone **42**.

After having successfully accomplished the synthesis the racemic 3-hydroxylated γ-rubromycin derivatives **34** and **42**, we next briefly investigated, whether these substrates may also serve as precursors for an approach to γ-rubromycin. In a first trial we looked into the radical deoxygenation of **42** *via* the thiocarbonate **43**, however this approach failed, as **43** suffered unspecific decomposition upon heating in the presence of azo(bisisobutyronitrile) (AIBN) and tributylstannane (Bu_3SnH) in benzene (Scheme 16).[17] Alternatively, under the conditions of a ionic reduction (Et_3SiH, TFA)[3d], the deoxygenation indeed occurred, but a subsequent opening of the spiroketal to naphthofurane **44** – a compound with structural similarity to α-rubromycin[18] – could not be avoided.

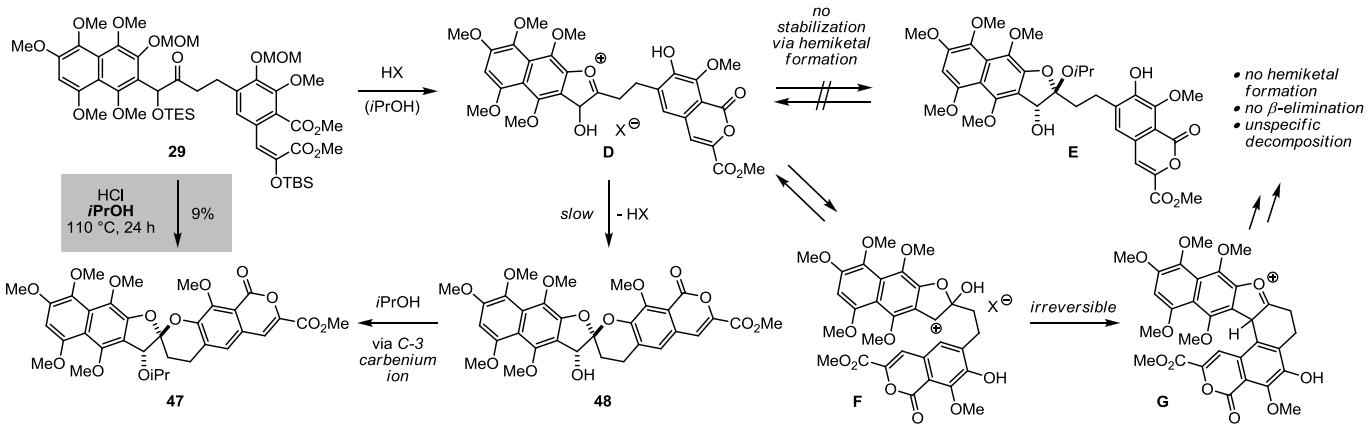


Scheme 16. Attempts to deoxygenate **42** at C-3 to access a γ-rubromycin precursor.

In a third attempt to achieve the deoxygenation at C-3, we subjected 3-methoxy-substituted spiroketal **30** to Et_3SiH in TFA, assuming that the "reduced naphthalene" portion may help to support the intermediate C-3 carbenium ion formation due to its electron-donating effect (Scheme 17). Yet, a mixture of spiroketal **45** and naphthofuran **46** (ratio ca. 1:2) was obtained in a combined yield of 51% (not optimized). The predominant formation of **46** was surprising, as the Li group reported the clean deoxygenation of a similar substrate to its respective spiroketal during their formal total synthesis of γ-rubromycin.[3d] Strikingly, the electron-rich naphthalene portion of these substrates additionally experienced a reduction at C-8, presumably *via* a protonation of the aromatic framework, followed by hydride addition and rearomatization through elimination of MeOH.[19] In light of this disappointingly low-yielding reaction sequence (**29**→**30**→**45**, 5.8% over two steps), we decided to disclaim this "deoxygenation approach" towards the natural product γ-rubromycin. As previously reported for this specific goal, we reverted to an alternative strategy for the assembly of C-3 deoxygenated spiroketals employing γ-silylated allylic phosphonate reagents as novel C_3 building block.[10]



Scheme 17. Attempt to deoxygenate **30** at C-3 to access a γ-rubromycin precursor and formation of 8-demethoxylated compounds **45** and **46**.



Scheme 18. Proposed decomposition pathway of substrate **29** *via* **D**→**F**→**G** due to missing stabilization by the solvent *i*PrOH.

In the context of our efforts of rubromycin/heliquinomycinone syntheses the acid-mediated spiroketalization of advanced substrates with a fully-elaborated isocoumarin domain proved to be more challenging than initially anticipated. The present study demonstrates that the success of this delicate transformation strongly depends on the proper choice of solvent methanol. As outlined in an illuminating experiment (Scheme 18), we subjected ketone **29** to catalytic amounts of hydrochloric in iso-propanol in order to imitate the conditions applied in our initial approach to compound **6** (Scheme 1). After 24 h at elevated temperature (110 °C) in a pressure tube we isolated the 3-isopropoxy-substituted spiroketal **47** only in poor 9% yield, whereas the major portion of the starting material decomposed to an undefined black tar. This result is in line with the previous experimental outcome of Scheme 1. As expected, the putative oxocarbenium ion **D** lacks trapping by the much slower interception with *i*PrOH (no *iso*-propyl ketal B was observed) and therefore it may predominately decompose *via* the irreversible Friedel-Crafts type sequence **D** → **F** → **G**. The incorporation of *i*PrOH in **47** most likely occurred after the spiroketalization (**D** → **48**). As the product of our initial experiment in Scheme 1, the di-*O*-methylated 3-hydroxy β-rubromycin derivative **7** did not incorporate *i*PrOH at its C-3 position, we conclude that a partial autoxidation of the highly electron-rich naphthalene portion to its β-quinone had occurred in the reaction vessel during the extended reaction time of three days, but prior to the spiroketalization. This partial oxidation may be the reason for **7** to be obtained at all, since the electron-deficient character of the naphthoquinone portion prevented the putative intermediate oxocarbenium ion to decompose *via* the Friedel-Crafts type pathway.

Conclusions

With the experiments described in this study we were able to significantly improve the synthesis of C-3 hydroxy-substituted rubromycin derivatives. We could gain insight into the factors that influence the pivotal acid-mediated spiroketalization step, and could further expand the scope of this strategy for the preparation of this natural products class. Most strikingly, the choice of solvent had a tremendous impact on the outcome of the key spiroketalization reaction that proceeds with C-3 oxygenated compounds much more reluctant than that of compounds bearing just a methylene moiety in this position.[3f,10]. A 1,2-diketone moiety as present in compound **37** turned out to be an unfavorable functional group for the spiroketal formation. In the context of C-3 hydroxyl-substituted rubromycin derivatives, the use of methanol as exclusive bulk solvent is the all-dominant factor for the success of this transformation. In combination with our preceding report,[10] we now offer two robust and complementary strategies for the construction of the central [5,6]-bisbenzannulated spiroketal core of rubromycins that either possess a hydroxy group at C-3 or are unsubstituted at this position. Moreover, we expect that these synthetic routes could further be streamlined that would allow the preparation of rubromycin derivatives in gram quantities.

Experimental Section

For general information, details of all experiments and copies of NMR spectra see Supporting Information.

(*E*)-Methyl 7-(Benzyloxy)-6-{4-[3-(benzyloxy)-1,4,5,6,8-pentamethoxynaphthalen-2-yl]-3-oxo-4-[(triethylsilyl)oxy]but-1-en-1-yl}-8-methoxy-1-oxo-1*H*-isochromene-3-carboxylate (6): Molecular sieves (117 mg, 4Å), $NaHCO_3$ (35 mg, 0.42 mmol) and TBACl (46 mg, 0.27 mmol) were suspended in DMF (4 mL) and stirred for 15 min at rt.

Iodoisocoumarin **5**[8] (78 mg, 0.17 mmol) and enone **4**[7] (96 mg, 0.16 mmol) were added (dissolved in 4 mL DMF) and the mixture was stirred for additional 15 min at rt. $Pd(OAc)_2$ (2 mg, 9 µmol) was added and the suspension was stirred at 60 °C for 24 h. Then water EtOAc were added. The layers were separated and the aq. phase was extracted with EtOAc (3 x). The combined organic layers were dried with $MgSO_4$, filtered and concentrated. Column chromatography (silica gel, hexanes/EtOAc = 1:1) provided 103 mg (70%) of enone **6** as yellow solid.

Melting range: 72–82 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.63, 0.85 (q, t, *J* = 7.9 Hz, 6 H, 9 H, $OSiEt_3$), 3.84, 3.850, 3.854, 3.94, 3.97, 3.99* (7 s, 3 H each, OMe), 5.03, 5.08 (AB-system, J_{AB} = 10.7 Hz, 1 H each, OCH_2), 5.19, 5.36 (AB-system, J_{AB} = 11.0 Hz, 1 H each, OCH_2), 5.67 (s, 1 H, 1-H), 6.68 (s, 1 H, Ar), 7.04 (bs, 1 H, 6-H), 7.13 (m_c, 1 H, Ar), 7.21–7.25, 7.28–7.34, 7.40–7.46 (3 m, 3 H, 3 H, 5 H, Ph, 3-H, 7-H), 7.84 (d, *J* = 16.4 Hz, 1 H, 4-H) ppm; * signal of double intensity. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 4.6, 6.7 (q, t, $OSiEt_3$), 52.9, 56.7, 57.1, 61.8, 61.9, 62.0, 63.8 (7 q, OMe), 72.6 (d, C-1), 75.1, 76.3 (2 t, OCH_2), 96.7 (d, Ar), 112.1 (d, C-7), 114.4, 117.0 (2 s, Ar), 121.0 (d, C-6), 126.6, 126.7 (2 s, Ar), 127.0, 127.4, 127.6, 128.2, 128.4, 128.5, 128.7 (7 d, C-3, Ph), 131.8 (s, Ar), 133.5 (d, C-4), 136.0, 136.7, 138.0, 142.5, 143.8, 148.4, 150.4, 151.7, 152.8, 153.6, 155.9, 156.7 (12 s, Ph, Ar), 156.7, 160.7 (2 s, C=O), 200.6* (s, C-2) ppm; * C-2 was assigned *via* HMBC. IR (KBr): υ = 3090–3030 (C=C), 2955–2875 (C-H), 1745–1690 (C=O), 1605–1545 (C=C, Ar), 1455–1415 (C-H) cm^{-1}. HRMS (EI): m/z calc. for $[M]^+$: 920.3439; found: 920.3453.

Methyl 3-Hydroxy-5,7,8,10'-tetramethoxy-4,9,9'-trioxo-4,4',9,9'-tetrahydro-3*H*,3'*H*-spiro[naphtho-[2,3-*b*]furan-2,2'-pyrano[4,3-*g*]chromene]-7'-carboxylate (7): Pd/C (7 mg, 8 µmol mmol, 10 wt%) in MeOH (4 mL) was saturated with hydrogen gas for 30 min. Then enone **6** (73 mg, 0.08 mmol in 4 mL MeOH) was added and the mixture was stirred for 48 h at rt under an atmosphere of hydrogen. The mixture was filtered through a short plug of silica gel (EtOAc as eluent) and the filtrate was concentrated. The residue was taken up in *i*PrOH (8 mL), HCl (37% aq., one drop ~ 50 µL) was added and the mixture was stirred at 40 °C for 84 h. Then sat. $NaHCO_3$ sol. (aq.) and EtOAc were added. The layers were separated and the aq. phase was extracted with EtOAc (3 x). The combined organic layers were dried with $MgSO_4$, filtered and concentrated to give 62 mg of a red residue. Filtration though a plug of silica gel (CH_2Cl_2 + 4% MeOH) gave 50 mg of a red solid which was further subjected to purification with HPLC (Nucleosil 50-5, CH_2Cl_2 + 2% MeOH) to give 3 mg (7%) of spiroketal 7 as red solid.

M. p. 214–217 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.31 (ddd, *J* = 5.9, 13.2, 14.4 Hz, 1 H, 3'-H), 2.64 (ddd, *J* = 2.2, 5.9, 14.4 Hz, 1 H, 3'-H), 3.10 (ddd, *J* = 2.2, 5.9, 17.3 Hz, 1-H, 4'-H), 3.25–3.32 (m, 2 H, 4'-H, OH), 3.72, 3.85, 3.89, 3.93, 3.94 (5 s, 3 H each, OMe), 5.41 (s, 1 H, 3-H), 6.58 (s, 1 H, 6-H), 7.17 (s, 1 H, 5'-H), 7.35 (s, 1 H, 6'-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.8 (t, C-4´), 23.5 (t, C-3´), 52.8, 56.4, 56.0, 61.4, 61.9 (5 q, OMe), 74.3 (d, C-3), 102.2 (d, C-6), 105.6 (s, Ar), 112.0 (d, C-6´), 113.9 (s, C-2), 115.0, 115.4 (2 s, Ar), 122.9 (d, C-5´), 125.0, 129.7, 132.1 (3 s, Ar), 142.0 (s, C-7´), 147.4, 148.7 (s, C-8), 150.5 (s, Ar), 156.2 (s, C-5), 156.7 (s, C-9´), 160.0 (s, C-7), 161.0 (s, C=O), 170.8 (s, C-4), 175.4 (s, Ar), 180.9 (s, C-9) ppm. UV (CH_2Cl_2): λ_{max} (ε) = 214 nm (26600), 279 (18700), 309 (13700), 337 (6500), 483 (320). HRMS (EI): m/z calc. for $[M]^+$: 580.1211; found: 580.1220.

(*E*)-Methyl 6-{2-[(*tert*-Butyldimethylsilyl)oxy]-3-methoxy-3-oxoprop-1-en-1-yl}-4-{4-[3,6-dimeth-oxy-2-(methoxymethoxy)phenyl]-3-oxo-4-[(triethylsilyl)oxy]butyl}-2-methoxy-3-(methoxymeth-oxy)benzoate (13) and **(*E*)-Methyl 6-{2-[(*tert*-Butyldimethylsilyl)oxy]-3-methoxy-3-oxoprop-1-en-1-yl}-4-{4-[3,6-dimethoxy-2-(methoxymethoxy)phenyl]-4-hydroxy-3-oxobutyl}-2-methoxy-3-(methoxymethoxy)benzoate (14)**: To a cold (-40 °C) and well-stirred solution of aryl iodide **11**[3f] (1.25 g, 2.20 mmol) in THF (10 mL) was added *i*PrMgCl (ca. 1.7 M in THF, 1.30 mL, 2.21 mmol). *Via* a transfer cannula this freshly prepared aryl-Grignard reagent was rapidly transferred to a mixture of enone **10**[5] (0.79 g, 2.00 mmol), HMPA (0.84 mL, 2.03 mmol), CuI·2LiCl (0.10 M in THF, 2.00 mL) and TMSCl (0.51 mL, 4.03 mmol) in THF (20 mL) at -40 °C. The cooling bath was immediately removed and the mixture was stirred at rt for 1 h. Then sat. NH_4Cl sol. (aq.) and EtOAc were added. The layers were separated and the aq. phase was extracted with EtOAc (3 x). The combined organic layers were washed with sat. NaCl sol. (aq.) and concentrated. The residual oil was dissolved in THF (10 mL), cooled to 0 °C and treated with 5% aq. H_2SO_4 (10 mL). After completion of the hydrolysis of the silylenolether (ca. 30 min, according to TLC), water and EtOAc were added. The layers were separated and the aq. phase was extracted with EtOAc (2 x). The combined organic layers were washed with sat. NaCl sol. (aq.), dried with Na_2SO_4, filtered and concentrated. Column chromatography (silica gel, hexanes/EtOAc = 4:1 → 2:1) provided 1.05 g (63%) of ketone **13** as pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.20, 0.96 (2 s, 6 H, 9 H, $OSiMe_2tBu$), 0.49–0.58, 0.83 (m, t, *J* = 8.0 Hz, 6 H, 9 H, $OSiEt_3$), 2.73–2.80 (m, 1 H, 3-H), 2.86–3.07 (m, 3 H, 3-H, 4-H), 3.53, 3.54, 3.56, 3.72, 3.78, 3.82, 3.84 (7 s, 3 H each, OMe), 5.07, 5.12 (AB-system, J_{AB} = 5.0 Hz, 1 H each, OCH_2), 5.09 (s, 2 H, OCH_2), 5.48 (s, 1 H, 1-H), 6.34 (s, 1 H, 1´-H), 6.57, 6.82 (2 d, *J* = 8.9 Hz, 1 H each, Ar), 6.80 (s, 1 H, Ar) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = -4.9, 18.2, 25.5 (q, s, q, $OSiMe_2tBu$), 4.6, 6.6 (q, t, $OSiEt_3$), 24.3 (t, C-4), 38.7 (t, C-3), 51.6, 52.2, 56.0, 56.4, 57.6, 57.8, 61.4 (7 q, OMe), 71.9 (d, C-1), 99.2, 99.6 (2 t, OCH_2), 106.6, 112.9 (2 d, Ar), 117.1 (d, C-1´), 125.0 (s, Ar), 126.2 (d, Ar), 126.5, 128.9, 137.8, 142.8, 144.9, 146.9, 147.5, 149.6, 152.0 (9 s, Ar, C-2´), 164.8, 167.5 (2 s, C=O), 210.5 (s, C-2) ppm. IR (ATR): υ = 3000–2840 (C-H), 1730 (C=O), 1635 (C=C), 1595, 1560, 1490 cm^{-1}. HRMS (ESI-TOF): m/z calc. for $[M + Na]^+$: 859.3732; found: 859.3720. Anal. calc. for $C_{41}H_{64}O_{14}Si_2$ (837.1): C 58.83, H 7.71; found: C 58.87, H 7.69.

Longer reaction times (control by TCL) for the hydrolysis of the silylenolether affected the hydrolysis of the TES-ether to give **14** in the same overall yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.18, 0.95 (2 s, 6 H, 9 H, $OSiMe_2tBu$), 2.47–2.68 (m, 2 H, 3-H), 2.84–3.00 (m, 2 H, 4-H), 3.50*, 3.54, 3.71, 3.79*, 3.83 (7 s, 3 H each, OMe), 4.16 (bs, 1 H, OH), 5.05, (s, 1 H, OCH_2), 5.08, 5.13 (AB-system, J_{AB} = 5.7 Hz, 1 H each, OCH_2), 5.49 (bd, 1 H, 1-H), 6.29 (s, 1 H, 1´-H), 6.59, 6.84 (2 d, *J* = 9.0 Hz, 1 H each, Ar), 6.71 (s, 1 H, Ar) ppm; * signal of double intensity. ^{13}C NMR (126 MHz, $CDCl_3$): δ = -4.9, 18.2, 25.5 (q, s, q, $OSiMe_2tBu$), 24.4 (t, C-4), 38.0 (t, C-3), 51.6, 52.2, 56.0, 56.2, 57.6, 57.8, 61.4 (7 q, OMe), 71.5 (d, C-1), 99.1, 99.4 (2 t, OCH_2), 106.5, 113.0 (2 d, Ar), 116.9 (d, C-1´), 122.0 (s, Ar), 126.1 (d, Ar), 126.7, 128.9, 136.9, 142.8, 145.5, 146.6, 147.4, 149.6, 151.8 (9 s, Ar, C-2´), 164.8, 167.3 (2 s, C=O), 208.5 (s, C-2) ppm. IR (ATR): υ = 3465 (OH), 2995–2840 (C-H), 1730 (C=O), 1630 (C=C), 1595, 1560, 1490 cm^{-1}. HRMS (ESI-TOF): m/z calc. for $[M + Na]^+$: 745.2868; found: 745.2909. Anal. calc. for $C_{35}H_{50}O_{14}Si$ (722.8): C 58.16, H 6.97; found: C 58.16, H 7.00.

Methyl 3-Hydroxy-4,7,10'-trimethoxy-9'-oxo-4',9'-dihydro-3*H*,3'*H*-spiro[benzofuran-2,2'-pyrano-[4,3-*g*]chromene]-7'-carboxylate (17) and **Methyl 3,4,7,10'-Tetramethoxy-9'-oxo-4',9'-dihydro-3*H*,3'*H*-spiro[benzofuran-2,2'-pyrano[4,3-*g*]chromene]-7'-carboxylate (18)** and **Methyl 7-Hydroxy-8-methoxy-1-oxo-6-[2-(-2,3,4,7-tetramethoxy-2,3-dihydrobenzofuran-2-yl)ethyl]-1*H*-isochromene-3-carboxylate (19)**: To a solution of ketone **14** (361 mg, 0.50 mmol) in MeOH (10 mL) in a pressure tube (volume: 20 mL, argon atmosphere) was added HCl (37% aq., 0.1 mL). The mixture was heated to 60 °C and stirred at this temperature for 24 h. After cooling to rt, the crude reaction mixture was

concentrated and purified by column chromatography (silica gel, hexanes/EtOAc = 2:1 → 1:1) to provide 126 mg (54%) of spiroketal **17** as colorless solid and 36 mg (ca. 14%) of a mixture of spiroketals **18** and **19**. For analytical purposes, the separation of **18** and **19** was achieved with HPLC (Nucleosil 50-5, 10% *i*PrOH/hexanes).

Data of compound **17**:

Melting range: 185–190 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.28 (m_c, bs, 2 H, 3´-H, OH), 2.53 (ddd, *J* = 2.7, 6.2, 14.3 Hz, 1 H, 3´-H), 3.04 (ddd, *J* = 2.7, 5.6, 17.2 Hz, 1 H, 4´-H), 3.33 (m_c, 1 H, 4´-H), 3.72, 3.74, 3.85, 3.92 (4 s, 3 H each, OMe), 5.40 (s, 1 H, 3-H), 6.43, 6.81 (2 d, *J* = 8.9 Hz, 1 H, 5-H, 6-H), 7.10 (s, 1 H, 5´-H), 7.31 (s, 1 H, 6´-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 22.0 (t, C-4´), 23.6 (t, C-3´), 52.7, 55.6, 56.7, 61.5 (4 q, OMe), 76.2 (d, C-3), 103.7 (d, C-5), 111.8 (s, C-2), 112.2 (d, C-6´), 115.0 (s, Ar), 115.3 (d, C-6), 116.2 (s, Ar), 123.2 (d, C-5´), 129.1, 132.4, 139.1 (3 s, Ar), 141.6 (s, C-7´), 147.8, 147.9, 150.5, 151.1 (4 s, Ar), 157.0, 161.0 (2 s, C=O) ppm. IR (ATR): υ = 3465 (OH), 3020–2850 (C-H), 1740 (C=O), 1645, 1610 (C=C), 1555, 1510 cm^{-1}. HRMS (ESI-TOF): m/z calc. for $[M + Na]^+$: 493.1111; found: 493.1086. Anal. calc. for $C_{24}H_{22}O_{10}$ (470.4): C 61.28, H 4.71; found: C 61.46, H 5.02.

Data of compound **18**:

M.p. >250 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.25 (m_c, 1 H, 3´-H), 2.56 (ddd, *J* = 2.8, 6.3, 14.2 Hz, 1 H, 3´-H), 3.02 (ddd, *J* = 2.8, 5.8, 17.2 Hz, 1 H, 4´-H), 3.33 (m_c, 1 H, 4´-H), 3.55, 3.68, 3.73, 3.86, 3.93 (5 s, 3 H each, OMe), 4.98 (s, 1 H, 3-H), 6.45, 6.82 (2 d, *J* = 8.9 Hz, 1 H each, 5-H, 6-H), 7.11 (s, 1 H, 5´-H), 7.31 (s, 1 H, 6´-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 22.1 (t, C-4´), 23.8 (t, C-3´), 52.7, 55.7, 56.9, 58.2, 61.4 (5 q, OMe), 83.7 (d, C-3), 103.8 (d, C-5), 111.3 (s, C-2), 112.2 (d, C-6´), 115.0 (s, Ar), 115.5 (d, C-6), 123.2 (d, C-5´), 129.1, 132.4, 139.3 (3 s, Ar), 141.7 (s, C-7´), 147.9, 148.4, 150.6, 151.7 (4 s, Ar), 157.0, 161.0 (2 s, C=O) ppm; one signal (s, Ar) at approx. 116 ppm could not be detected. IR (ATR): υ = 3005–2850 (C-H), 1740 (C=O), 1645, 1605 (C=C), 1560, 1510 cm^{-1}. HRMS (ESI-TOF): m/z calc. for $[M + Na]^+$: 507.1267; found: 507.1232. Anal. calc. for $C_{25}H_{24}O_{10}$ (484.5): C 61.98, H 4.99; found: C 61.95, H 5.10.

Data of compound **19**:

Melting range: 70–90 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.32, 2.52, 2.88, 2.99 (4 m_c, 1 H each, 3´-H, 4´-H), 3.38, 3.48, 3.82, 3.84, 3.93, 4.03 (6 s, 3 H each, OMe), 4.69 (s, 1 H, 3-H), 6.41, 6.82 (2 d, *J* = 8.9 Hz, 1 H each, 5-H, 6-H), 6.76 (bs, 1 H, OH), 7.21 (s, 1 H, 5´-H), 7.37 (s, 1 H, 6´-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 25.7 (t, C-4´), 28.7 (t, C-3´), 49.8, 52.7, 55.5, 56.8, 57.8, 62.7 (6 q, OMe), 82.6 (d, C-3), 103.2 (d, C-5), 112.8 (d, C-6´), 113.8 (s, Ar), 114.6 (s, C-2), 114.9 (d, C-6), 115.8 (s, Ar), 124.6 (d, C-5´), 128.5, 137.8, 139.6 (3 s, Ar), 141.2 (s, C-7´), 147.3, 148.7, 150.1, 151.7 (4 s, Ar), 157.4, 160.9 (2 s, C=O) ppm. IR (ATR): υ = 3400 (OH), 3000–2850 (C-H), 1735 (C=O), 1640, 1605 (C=C), 1510 cm^{-1}. HRMS (ESI-TOF): m/z calc. for $[M + Na]^+$: 539.1529; found: 539.1510. Anal. calc. for $C_{26}H_{28}O_{11}$ (516.5): C 60.46, H 5.46; found: C 60.75, H 5.62.

Methyl 6-{4-[3,6-Dimethoxy-2-(methoxymethoxy)phenyl]-4-hydroxy-3-oxobutyl}-8-methoxy-7-(methoxymethoxy)-1-oxo-1*H*-isochromene-3-carboxylate (20): To a cold (0 °C) solution of ketone **14** (0.45 g, 0.62 mmol) in THF (10 mL) and water (4 mL) was added KF (0.07 g, 1.20 mmol). The mixture was stirred for 10 min at this temperature. Then water and EtOAc were sequentially added. The layers were separated and the aq. phase was extracted with EtOAc (3 x). The combined organic layers were washed with sat. NaCl sol. (aq.), dried with Na_2SO_4, filtered and concentrated. Column chromatography (silica gel, hexanes/EtOAc = 1:1) provided 0.23 g (64%) of ketone **20** as colorless solid.

Melting range: 36–41 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.69 (dt, *J* = 2.9, 7.4 Hz, 2 H, 3-H), 3.05 (t, *J* = 7.4 Hz, 2 H, 4-H), 3.50, 3.51, 3.67, 3.77, 3.86, 3.90 (6 s, 3 H each, OMe), 4.12 (bs, 1 H, OH), 5.05, 5.09 (AB-system, J_{AB} = 5.6 Hz, 1 H each, OCH_2), 5.14, 5.16 (AB-system, J_{AB} = 5.8 Hz, 1 H each, OCH_2), 5.50 (s, 1 H, 1-H), 6.56, 6.83 (2 d, *J* = 9.0 Hz, 1 H each, Ar), 7.09 (s, 1 H, 6-H), 7.28 (s, 1 H, 7-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 24.8 (t, C-4), 36.9 (t, C-3), 52.7, 55.9, 56.1, 57.6, 57.8, 61.6 (6 q, OMe), 71.5 (d, C-1), 99.4, 99.7 (2 t, OCH_2), 106.5 (d, Ar), 112.0 (d, C-7), 112.8 (d, Ar), 115.2, 121.7 (2 s, Ar), 124.4 (d, C-6), 132.1 (s, Ar), 142.2 (s, C-8), 144.4, 145.2, 146.5, 151.2, 151.6, 154.2 (6 s, Ar), 156.9, 160.6 (2 s, C=O), 208.0 (s, C-2) ppm. IR (ATR): υ = 3460 (OH), 2995–2840 (C-H), 1740 (C=O), 1645 (C=C), 1595, 1550, 1490 cm^{-1}. HRMS (ESI-TOF): m/z calc. for $[M + Na]^+$: 599.1741; found: 599.1740. Anal. calc. for $C_{28}H_{32}O_{13}$ (576.5): C 58.33, H 5.59; found: C 58.49, H 5.77.

Methyl 7-Hydroxy-6-[4-hydroxy-4-(2-hydroxy-3,6-dimethoxyphenyl)-3-oxobutyl]-8-methoxy-1-oxo-1*H*-isochromene-3-carboxylate (21) and **Methyl 7-Hydroxy-6-[2-(-3-hydroxy-2,4,7-trimeth-oxy-2,3-dihydrobenzofuran-2-yl)ethyl]-8-methoxy-1-oxo-1*H*-isochromene-3-carboxylate (22)**: To a solution of ketone **20** (51 mg, 0.09 mmol) in MeOH (4 mL) was added HCl (37% aq., 50 µL). The mixture was heated to 45 °C and stirred at this temperature for 1 h. After cooling to rt, the crude reaction mixture was concentrated and purified by column chromatography (silica gel, hexanes/EtOAc = 2:1 → 1:1) to provide 16 mg (36%) of methyl ketal **22** and 13 mg (30%) of ketone **21**, both as colorless solids.

Data of compound **21**:

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.66–2.86, 2.96–3.10 (2 m, 4 H, 3-H, 4-H), 3.69, 3.81, 3.94, 3.97 (4 s, 3 H each, OMe), 5.56 (bs, 1 H, 1-H), 5.95 (s, 1 H, OH), 6.30, 6.73 (2 d, *J* = 8.9 Hz, 1 H each, Ar), 6.49 (s, 1 H, OH), 7.06 (s, 1 H, 6-H), 7.30 (s, 1 H, 7-H) ppm. This compound is literature-known.[12b]

Data of compound **22**:

Melting range: 96–105 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.27–2.33 (m, 2 H, 3´-H, OH), 2.53–2.59 (m, 1 H, 3´-H), 2.98 (m_c, 2 H, 4´-H), 3.43, 3.83, 3.84, 3.93, 4.01 (5 s, 3 H each, OMe), 5.14 (s, 1 H, 3-H), 6.38, 6.81 (2 d, *J* = 8.9 Hz, 1 H each, 5-H, 6-H), 6.84 (bs, 1 H, OH), 7.22 (s, 1 H, 5´-H), 7.36 (s, 1 H, 6´-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 25.9 (t, C-4´), 28.8 (t, C-3´), 50.0, 52.7, 55.6, 56.8, 62.7 (5 q, OMe), 75.2 (d, C-3), 103.2 (d, C-5), 112.8 (d, C-6´), 113.9 (s, Ar), 114.9 (s, C-2), 115.1 (d, C-6), 117.1 (s, Ar), 124.6 (d, C-5´), 128.6, 137.5, 139.4 (3 s, Ar), 141.3 (s, C-7´), 147.4, 148.2, 129.9, 151.1 (4 s, Ar), 157.4, 160.9 (2 s, C=O) ppm. IR (ATR): υ = 3380 (OH), 3000–2810 (C-H), 1730 (C=O), 1645, 1605 (C=C), 1560, 1510, 1480 cm^{-1}. HRMS (ESI-TOF): m/z calc. for $[M + Na]^+$: 525.1373; found: 525.1349. Anal. calc. for $C_{25}H_{26}O_{11}$ (502.5): C 59.76, H 5.22; found: C 59.90, H 5.45.

1-[1,4,5,6,8-Pentamethoxy-3-(methoxymethoxy)naphthalen-2-yl]-1-[(triethylsilyl)oxy]but-3-en-2-one (28): To a cold (-78 °C) solution of methoxyallene (1.75 g, 25.0 mmol) in THF (50 mL) was added *n*BuLi (7.9 mL, 18.8 mmol, ca. 2.4 M in hexane). After 15 min at this temperature, naphthalene carbaldehyde **27**[3f, 10] (2.30 g, 6.3 mmol in 10 mL THF) was added and the mixture was stirred at this temperature for 30 min. Then dilute H_2SO_4 sol. (aq. 5 %, 50 mL) and EtOAc were sequentially added. The layers were separated and the aq. phase was extracted with EtOAc (3 x). The combined organic layers were washed with sat. NaCl sol. (aq.), dried with Na_2SO_4, filtered and concentrated. Column chromatography (hexanes/EtOAc = 3:1) provided 2.49 g (94%) of the naphthalene carbaldehyde-derived enone as pale yellow, highly viscous oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.60, 3.77, 3.78, 3.79, 3.95, 3.98 (6 s, 3 H each, OMe), 4.43 (d, *J* = 5.1 Hz, 1 H, OH), 5.25, 5.28 (AB-system, J_{AB} = 5.4 Hz, 1 H each, OCH_2), 5.62 (dd, *J* = 1.6, 10.4 Hz, 1 H, 4-H), 5.74 (d, *J* = 5.1 Hz, 1 H, 1-H), 6.30 (dd, *J* = 1.6, 17.4 Hz, 1 H, 4-H), 6.40 (dd, *J* = 10.4, 17.4 Hz, 1 H, 3-H), 6.66 (s, 1 H, Ar) ppm. ^{13}C NMR (126 MHz,

$CDCl_3$): δ = 56.7, 56.8, 57.9, 61.7, 61.9, 63.7 (6 q, OMe), 71.1 (d, C-1), 96.3 (d, Ar), 100.3 (t, OCH_2), 114.4, 123.2, 127.0 (3 s, Ar), 128.8 (t, C-4), 131.6 (d, C-3), 136.5, 142.9, 147.3, 150.7, 152.0, 153.6 (6 s, Ar), 198.2 (s, C-2) ppm. IR (ATR): υ = 3450 (OH), 2995–2840 (C-H), 1700 (C=O), 1605 (C=C), 1455 cm^{-1}. HRMS (ESI-TOF): m/z calc. for $[M + Na]^+$: 445.1475; found: 445.1484. Anal. calc. for $C_{21}H_{26}O_9$ (422.4): C 59.71, H 6.20; found: C 59.73, H 6.25.

To a cold (0 °C) solution of naphthalene carbaldehye-derived enone (0.34 g, 0.80 mmol) in DMF (4 mL) were sequentially added *i*Pr_2NEt (0.42 mL, 2.40 mmol), chlorotriethylsilane (0.24 g, 1.60 mmol) and DMAP (10 mg, 0.08 mmol). The mixture was allowed to warm up to rt and was stirred for 2 h. Then sat. NH_4Cl sol. (aq.) and EtOAc were added. The layers were separated and the aq. phase was extracted with EtOAc (3 x). The combined organic layers were washed with sat. NaCl sol. (aq.), dried with Na_2SO_4, filtered and concentrated. Column chromatography (hexanes/EtOAc = 4:1) provided 358 mg (83%) of **28** as pale yellow oil, which solidified under high vacuum.

M.p. 62–66 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.65, 0.87 (q, t, *J* = 7.9 Hz, 6 H, 9 H, $OSiEt_3$), 3.59, 3.79, 3.80, 3.81, 3.92, 3.98 (6 s, 3 H each, OMe), 5.25, 5.31 (AB-system, J_{AB} = 5.3 Hz, 1 H each, OCH_2), 5.61 (dd, *J* = 2.1, 10.6 Hz, 1 H, 4-H), 5.68 (s, 1 H, 1-H), 6.34 (dd, *J* = 2.1, 17.4 Hz, 1 H, 4-H), 6.64 (s, 1 H, Ar), 6.98 (dd, *J* = 10.6, 17.4 Hz, 1 H, 3-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 4.7, 6.7 (q, t, $OSiEt_3$), 56.7, 57.1, 57.8, 61.5, 61.8, 63.7 (6 q, OMe), 72.3 (d, C-1), 96.5 (d, Ar), 100.1 (t, OCH_2), 114.6, 126.1, 126.8 (3 s, Ar), 127.1 (t, C-4), 131.7 (d, C-3), 136.5, 142.8, 146.9, 150.4, 151.9, 153.6 (6 s, Ar), 199.7 (s, C-2) ppm. IR (ATR): υ = 3000–2840 (C-H), 1735, 1715 (C=O), 1695, 1605 (C=C), 1500, 1455 cm^{-1}. HRMS (ESI-TOF): m/z calc. for $[M + Na]^+$: 559.2339; found: 559.2349. Anal. calc. for $C_{27}H_{40}O_9Si$ (536.7): C 60.42, H 7.51; found: C 60.40, H 7.60.

(*E*)-Methyl 6-{2-[(*tert*-Butyldimethylsilyl)oxy]-3-methoxy-3-oxoprop-1-en-1-yl}-2-methoxy-3-(methoxymethoxy)-4-{3-oxo-4-[1,4,5,6,8-pentamethoxy-3-(methoxymethoxy)naphthalen-2-yl]-4-[(triethylsilyl)-oxy]butyl}benzoate (29): To a cooled (-40 °C) and well-stirred solution of aryl iodide **11** (1.98 g, 3.50 mmol) in Et_2O (50.0 mL) and THF (12.5 mL) was slowly added *i*PrMgBr (ca. 3.0 M in 2-methyltetrahydrofuran, 1.16 mL, 3.50 mmol). For re-dissolving of partially precipitated material, the mixture was quickly warmed to -20 °C and then re-cooled to -40 °C. Then, a mixture of enone **28** (1.34 g, 2.50 mmol dissolved in 10.0 mL Et_2O), HMPA (2.50 mL, 14.4 mmol), CuI·2LiCl (0.20 M in THF, 1.88 mL) and TMSCl (1.09 g, 10.0 mmol) was rapidly added to the Grignard-reagent. The cooling bath was immediately removed and the mixture was stirred for 1 h at rt. Then sat. NH_4Cl sol. (aq.) and EtOAc were added. The layers were separated and the aq. phase was extracted with EtOAc (2 x). The combined organic layers were washed with sat. NaCl sol. (aq.) and concentrated. The residual oil was dissolved in THF (50 mL) and 5% aq. H_2SO_4 (10 mL) was added at 0 °C. After completion of the hydrolysis of the silylenolether (ca. 1 h according to TLC), water and EtOAc were added. The layers were separated and the aq. phase was extracted with EtOAc (2 x). The combined organic layers were washed with sat. NaCl sol. (aq.), dried with Na_2SO_4, filtered and concentrated. Column chromatography (silica gel, hexanes/EtOAc = 5:1) provided 1.93 g (79%) of ketone **29** as pale yellow, highly viscous oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.19, 0.95 (2 s, 6 H, 9 H, $OSiMe_2tBu$), 0.61, 0.84 (q, t, *J* = 7.9 Hz, 6 H, 9 H, $OSiEt_3$), 2.80 – 3.11 (m, 4 H, 3-H, 4-H), 3.50, 3.56, 3.57, 3.78, 3.79, 3.80, 3.81, 3.84, 3.92, 3.98 (10 s, 3 H each, OMe), 5.09 (s, 2 H, OCH_2), 5.20, 5.29 (AB-system, J_{AB} = 4.9 Hz, 1 H each, OCH_2), 5.53 (s, 1 H, 1-H), 6.34 (s, 1 H, 1´-H), 6.64 (s, 1 H, Ar), 6.82 (s, 1 H, Ar) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = -4.9, 18.2, 25.5 (q, s, q, $OSiMe_2tBu$), 4.7, 6.7 (q, t, $OSiEt_3$), 24.4 (t, C-4), 38.7 (t, C-3), 51.5, 52.2, 56.7, 57.1, 57.6, 57.7, 61.3, 61.5, 61.8, 63.7 (10 q, OMe), 72.7 (d, C-1), 96.6 (d, Ar), 99.1, 100.1 (2 t, OCH_2), 114.5 (s, Ar), 117.2 (d, C-1´), 126.2 (d, Ar), 126.4, 126.7, 128.9, 136.5, 137.9, 142.7, 147.5, 149.6, 150.4, 151.8, 153.5 (11 s, Ar, C-2´), 164.7, 167.5 (2 s, C=O), 210.5 (s, C-2) ppm; two signals (s, Ar) could not be detected. IR (ATR): υ = 3050–2850 (C-H), 1735 (C=O), 1605 (C=C), 1455 cm^{-1}. HRMS (ESI-TOF): m/z calc. for $[M + Na]^+$: 999.4206; found: 999.4181. Anal. calc. for $C_{48}H_{72}O_{17}Si_2$ (977.2): C 58.99, H 7.43; found: C 58.95, H 7.42.

Methyl 3,4,5,7,8,9,10'-Heptamethoxy-9'-oxo-4',9'-dihydro-3*H*,3'*H*-spiro[naphtho[2,3-*b*]furan-2,2'-pyrano[4,3-*g*]chromene]-7'-carboxylate (30) and **Methyl 6-Hydroxy-5,8a,10,11,12,14,15-hepta-methoxy-4-oxo-7,8,8a,15b-tetrahydro-4*H*-naphtho[2',3':2,3]benzofuro[4,5-*f*]isochromene-2-carboxylate (32)**: To a solution of ketone **29** (70 mg, 72 µmol) in MeOH (3.0 mL) in a pressure tube (volume: 20 mL, argon atmosphere) was added HCl (37% aq., 20 µL). The mixture was heated to 60 °C and stirred at this temperature for 24 h. After cooling to rt, the crude reaction mixture was concentrated and filtered through a short plug of silica gel (eluent: hexanes/EtOAc = 1:1). The filtrate was concentrated and a yellow solid (30 mg, ca. 75% yield based on the recovered mass) was obtained, which contained an inseparable mixture of spiroketal **30**, methyl ketal **31** and hexacyclic methyl ketal **32** as judged by ^{1}H NMR spectroscopy. For analytical purposes, the separation of the products was achieved with HPLC (Nucleosil 50-5, 30% *i*PrOH/hexanes), however, methyl ketal **31** decomposed under these specific conditions and could not be isolated in analytically pure form.

Data of compound **31**:

Melting range: 100–110 °C. ^{1}H NMR (700 MHz, $CDCl_3$): δ = 2.27 (m_c, 1 H, 3´-H), 2.67 (ddd, *J* = 2.1, 6.2, 13.8 Hz, 1 H, 3´-H), 3.07 (ddd, *J* = 2.1, 5.9, 17.1 Hz, 1 H, 4´-H), 3.33 (m_c, 1 H, 4´-H), 3.57, 3.58, 3.66, 3.76, 3.92, 3.94, 3.98, 4.01 (8 s, 3 H each, OMe), 5.07 (s, 1 H, 3-H), 6.62 (s, 1 H, 6-H), 7.14 (s, 1 H, 5´-H), 7.33 (s, 1 H, 6´-H) ppm. ^{13}C NMR (176 MHz, $CDCl_3$): δ = 22.0 (t, C-4´), 23.7 (t, C-3´), 52.7, 56.61*, 56.65, 58.2, 61.2, 61.9, 63.1 (7 q, OMe), 82.9 (d, C-3), 94.8 (d, C-6), 111.0 (s, C-2), 112.2 (d, C-6´), 113.5, 115.0, 118.2 (3 s, Ar), 123.2 (d, C-5´), 128.6, 129.1, 132.4, 133.5, 136.8 (5 s, Ar), 141.7 (s, C-7´), 147.6, 148.9, 150.4, 150.9, 151.7, 153.9 (6 s, Ar), 157.0 (s, C-9´), 161.0 (s, C=O) ppm; * signal of higher intensity. IR (ATR): υ = 3050–2850 (C-H), 1740 (C=O), 1645, 1605 (C=C), 1465 cm^{-1}. HRMS (ESI-TOF): m/z calc. for $[M + Na]^+$: 647.1741; found: 647.1695. Anal. calc. for $C_{32}H_{32}O_{13}$ (624.6): C 61.54, H 5.16; found: C 60.70, H 5.58.

Data of compound **32**:

M.p. 123–126 °C. ^{1}H NMR (700 MHz, $CDCl_3$): δ = 1.62 (td, *J* = 3.4, 13.6 Hz, 1 H, 8-H), 2.42 (m_c, 1 H, 7-H), 2.80 (td, *J* = 3.3, 13.6 Hz, 1 H, 8-H), 3.20 (bs, 3 H, 15-OMe), 3.28 (td, *J* = 3.3, 16.3 Hz, 1 H, 7-H), 3.59 (s, 3 H, 8a-OMe), 3.82, 3.85, 3.93, 3.95, 3.97, 3.98 (6 s, 3 H each, OMe), 5.22 (s, 1 H, 15b-H), 6.48 (s, 1 H, 13-H), 6.50 (s, 1 H, 6-OH), 8.05 (s, 1 H, 1-H) ppm. ^{13}C NMR (176 MHz, $CDCl_3$): δ = 20.2 (t, C-7), 33.2 (t, C-8), 47.2 (d, C-15b), 50.7 (q, C(8a)-OMe), 52.7, 56.4, 56.7, 61.8, 62.0 (5 q, OMe), 62.6 (q, C(15)-OMe), 62.8 (q, OMe), 94.3 (d, C-13), 110.8 (d, C-1), 112.6, 114.2 (2 s, Ar), 115.8 (s, C-8a), 119.2, 127.8, 128.1, 131.4, 131.6, 136.0, 136.6 (7 s, Ar) 140.2 (s, C-2), 146.1, 148.1, 150.2, 150.3, 150.4, 153.0 (6 s, Ar), 157.8 (s, C-4), 161.2 (s, C=O) ppm. IR (ATR): υ = 3385 (OH), 3020–2850 (C-H), 1730 (C=O), 1635, 1605 (C=C), 1465 cm^{-1}. HRMS (ESI-TOF): m/z calc. for $[M + Na]^+$: 647.1741; found: 647.1731. Anal. calc. for $C_{32}H_{32}O_{13}$ (624.6).

Methyl 6-[(*tert*-Butyldimethylsilyl)oxy]-5,8a,10,11,12,14,15-hepta-methoxy-4-oxo-7,8,8a,15b-tetra-hydro-4*H*-naphtho[2',3':2,3]benzo-furo[4,5-*f*]isochromene-2-carboxylate (33): To a solution of ketone **29** (240 mg, 0.25 mmol) in MeOH (10.0 mL) in a pressure tube (volume: 20 mL, argon atmosphere) was added HCl (37% aq., 50 µL). The mixture

was heated to 110 °C and stirred at this temperature for 16 h. After cooling to rt, the crude reaction mixture was concentrated and filtered through a short plug of silica gel (eluent: hexanes/EtOAc = 1:1). The filtrate was concentrated to a yellow solid, which was disolved in CH_2Cl_2 (5.0 mL) and sequentially treated with *i*Pr_2NEt (0.11 mL, 0.65 mmol), TBSCl (63 mg, 0.43 mmol) and DMAP (5 mg, 0.04 mmol). After 30 min at rt, water and CH_2Cl_2 were added. The layers were separated and the aq. phase was extracted with CH_2Cl_2 (2 x). The combined organic layers were dried with Na_2SO_4, filtered and concentrated. Column chromatography (hexanes/EtOAc = 1:1 → 1:1 (+5% acetone)) provided 63 mg (35%) of hexacyclic methyl ketal **33** and 49 mg (32%) of spiroketal **30**, both as beige solids.

Data of compound **33**:

Melting range: 95–100 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.03, 0.18, 0.94 (3 s, 3 H, 3 H, 9 H, $OSiMe_2$*t*Bu), 1.57 (td, *J* = 3.3, 13.4 Hz, 1 H, 8-H), 2.29 (m_c, 1 H, 7-H), 2.77 (td, *J* = 3.3, 13.4 Hz, 1 H, 8-H), 3.07 (bs, 3 H, 15-OMe), 3.29 (td, *J* = 3.3, 15.9 Hz, 1 H, 7-H), 3.57 (s, 3 H, 8a-OMe), 3.81, 3.82, 3.85, 3.92, 3.94* (6 s, 3 H each, OMe), 5.22 (s, 1 H, 15b-H), 6.49 (s, 1 H, 13-H), 8.00 (s, 1 H, 1-H) ppm; * signal of double intensity. ^{13}C NMR (126 MHz, $CDCl_3$): δ = -4.4, -4.3, 18.6, 25.8 (2 q, s, q, $OSiMe_2$*t*Bu), 21.3 (t, C-7), 33.8 (t, C-8), 47.1 (d, C-15b), 50.6 (q, C(8a)-OMe), 52.7, 56.3, 56.5, 61.5, 61.7, 61.9 (6 q, OMe), 62.4 (q, C(15)-OMe), 94.1 (d, C-13), 110.2 (d, C-1), 112.6, 115.4 (2 s, Ar), 115.8 (s, C-8a), 119.2, 127.7, 129.5, 130.7, 131.4, 136.4 (6 s, Ar), 140.7 (s, C-2), 141.7, 148.2, 150.16, 150.17, 150.3, 151.6, 153.0 (7 s, Ar), 157.6 (s, C-4), 161.2 (s, C=O) ppm. IR (ATR): υ = 3050–2850 (C-H), 1740 (C=O), 1630, 1600 (C=C), 1570 cm^{-1}. HRMS (ESI-TOF): *m*/*z* calc. for $[M + Na]^+$: 761.2605; found: 761.2621. Anal. calc. for $C_{38}H_{46}O_{13}Si$ (738.8): C 61.77, H 6.16; found: C 62.33, H 6.28.

Methyl 3,4,7,9,10'-Pentamethoxy-5,8,9'-trioxo-4',5,8,9'-tetrahydro-3*H*,3'*H*-spiro[naphtho[2,3-*b*]furan-2,2'-pyrano[4,3-*g*]chromene]-7'-carboxylate (34): To a cooled (0 °C) solution of spiroketal **30** (42 mg, 67 µmol) in MeCN (4 mL) and H_2O (1 mL) was added DDQ (23 mg, 0.1 mmol) in one portion. After 20 min at this temperature water and EtOAc were added. The layers were separated and the aq. phase was extracted with EtOAc (3 x). The combined organic layers were washed with sat. NaCl sol. (aq.), dried with Na_2SO_4, filtered and concentrated. The residue was first filtered through a plug of Al_2O_3 (EtOAc as eluent), concentrated again and was then purified by column chromatography (silica gel, hexanes/EtOAc = 1:1, then CH_2Cl_2/Et_2O = 4:1 → 2:1) to provide 23 mg (58%) of γ-naphtho-quinone **34** as yellow solid.

Melting range: 220–225 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.25 (m_c, 1 H, 3´-H), 2.62 (ddd, *J* = 2.1, 6.0, 14.0 Hz, 1 H, 3´-H), 3.08 (ddd, *J* = 2.1, 5.8, 17.1 Hz, 1 H, 4´-H), 3.33 (m_c, 1 H, 4´-H), 3.65, 3.68, 3.76, 3.83, 3.92, 3.99 (6 s, 3 H each, OMe), 5.04 (s, 1 H, 3-H), 5.99 (s, 1 H, 6-H), 7.15 (s, 1 H, 5´-H), 7.32 (s, 1 H, 6´-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.7 (t, C-4´), 23.5 (t, C-3´), 52.8, 56.3, 59.6, 61.0, 61.5, 62.6 (6 q, OMe), 83.4 (d, C-3), 110.1 (d, C-6), 111.9* (d, s, C-6´, C-2), 115.3, 119.8 (2 s, Ar), 123.2 (d, C-5´), 127.4, 127.8, 129.7, 131.8 (4 s, Ar), 142.0 (s, C-7´), 142.4, 147.1, 150.4, 154.7, 155.9 (5 s, Ar), 156.7 (s, C-9´), 159.3 (s, C-7), 160.8 (s, C=O), 179.1 (s, C-8), 183.3 (s, C-5) ppm; * signals are overlapping. IR (ATR): υ = 2960–2850 (C-H), 1740 (C=O), 1685, 1645, 1630 (C=C), 1580 cm^{-1}. HRMS (ESI-TOF): m/z calc. for $[M + Na]^+$: 617.1271; found: 617.1278. Anal. calc. for $C_{30}H_{26}O_{13}$ (594.5): C 60.61, H 4.41; found: C 60.62, H 4.42.

Methyl 6-[(*tert*-Butyldimethylsilyl)oxy]-5,8a,10,12,15-pentamethoxy-4,11,14-trioxo-7,8,8a,11,14,-15b-hexahydro-4*H*-naphtho[2',3':2,3]-benzofuro[4,5-*f*]isochromene-2-carboxylate (35) and **Methyl 6-[(*tert*-Butyldimethylsilyl)oxy]-5,8a,11,12,14-pentamethoxy-4,10,15-trioxo-7,8,8a,10,15,15b-hexahydro-4*H*-naphtho[2',3':2,3]benzofuro[4,5-*f*]iso-chromene-2-carboxylate (36)**: To a cooled (0 °C) solution of **33** (60 mg, 96 µmol) in MeCN (4 mL) and H_2O (1 mL) was added DDQ (34 mg, 0.15 mmol) in one portion. After 15 min at this temperature water and EtOAc were added. The layers were separated and the aq. phase was extracted with EtOAc (3 x). The combined organic layers were washed with sat. NaCl sol. (aq.), dried with Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography [silica gel, hexanes/EtOAc = 1:1 → hexanes/EtOAc = 1:1 (+5% acetone)) to provide 32 mg (47%) of γ-naphthoquinone **35** and 4 mg (6%) of β-naphthoquinone **36**, both as yellow solids.

Data of compound **35**:

Melting range: 130–135 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.08, 0.20, 0.96 (3 s, 3 H, 3 H, 9 H, $OSiMe_2$*t*Bu), 1.56 (td, *J* = 3.2, 13.6 Hz, 1 H, 8-H), 2.18 (m_c, 1 H, 7-H), 2.77 (dt, *J* = 3.4, 13.6 Hz, 1 H, 8-H), 3.25 (s, 3 H, 15-OMe), 3.34 (td, *J* = 3.4, 16.0 Hz, 1 H, 7-H), 3.57 (s, 3 H, 8a-OMe), 3.80 (s, 3 H, 12-OMe), 3.82, 3.95, 3.99 (3 s, 3 H each, OMe), 5.15 (s, 1 H, 15b-H), 5.89 (s, 1 H, 13-H), 7.90 (s, 1 H, 1-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = -4.4, -4.2, 18.6, 25.9 (2 q, s, q, $OSiMe_2$*t*Bu), 21.1 (t, C-7), 32.9 (t, C-8), 47.7 (d, C-15b), 51.1 (q, 8a-OMe), 52.9 (q, OMe), 56.3 (q, 12-OMe), 61.0, 61.6 (2 q, OMe), 62.0 (q, 15-OMe), 109.7 (d, C-1), 110.1 (d, C-13), 115.7 (s, Ar), 117.7 (s, C-8a), 118.2, 126.6, 128.0, 128.5, 129.6 (5 s, Ar), 141.00, 141.05, 141.1 (3 s, Ar, C-2, C-6), 148.2, 151.9, 154.7 (3 s, Ar), 157.1 (s, C-4), 157.3, 159.0 (2 s, Ar), 161.1 (s, C=O), 179.3 (s, C-11), 183.2 (s, C-14) ppm. IR (ATR): υ = 3020–2855 (C-H), 1740 (C=O), 1680, 1640, 1630 (C=C) cm^{-1}. HRMS (ESI-TOF): m/z calc. for $[M + Na]^+$: 731.2136; found: 731.2137.

Data of compound **36**:

Melting range: 172–177 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.15, 0.23, 0.99 (3 s, 3 H, 3 H, 9 H, $OSiMe_2$*t*Bu), 1.52 (td, *J* = 3.5, 13.5 Hz, 1 H, 8-H), 2.29 (m_c, 1 H, 7-H), 2.77 (td, *J* = 3.2, 13.5 Hz, 1 H, 8-H), 3.36 (td, *J* = 3.2, 16.2 Hz, 1 H, 7-H), 3.57 (s, 3 H, 8a-OMe), 3.82, 3.87, 3.88, 3.94, 3.96 (5 s, 3 H each, OMe), 5.00 (s, 1 H, 15b-H), 6.69 (s, 1 H, 13-H), 8.08 (s, 1 H, 1-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = -4.14, -4.12, 18.7, 26.0 (2 q, s, q, $OSiMe_2$*t*Bu), 21.2 (t, C-7), 31.9 (t, C-8), 48.1 (d, C-15b), 51.2 (q, 8a-OMe), 52.7, 56.2, 57.0, 61.3, 61.6 (5 q, OMe), 102.8 (d, C-13), 110.6 (d, C-1), 113.6, 116.0 (2 s, Ar), 117.7 (s, C-8a), 123.4, 126.0, 127.7, 130.0 (4 s, Ar), 140.4 (s, C-2), 140.8, 144.7, 147.9, 151.7 (4 s, Ar), 157.4, 157.7, 157.8 (3 s, Ar, C-4), 159.2 (s, Ar), 161.4 (s, C=O), 177.0 (s, C-10), 180.1 (s, C-15) ppm. IR (ATR): υ = 2955–2850 (C-H), 1740 (C=O), 1680, 1650 (C=C), 1555 cm^{-1}. HRMS (ESI-TOF): m/z calc. for $[M + Na]^+$: 731.2136; found: 731.2143.

(*E*)-Methyl 6-{2-[(*tert*-Butyldimethylsilyl)oxy]-3-methoxy-3-oxoprop-1-en-1-yl}-2-methoxy-3-(methoxymethoxy)-4-{3-oxo-4-[(triethylsilyl)-oxy]-4-[1,4,6-trimethoxy-3-(methoxymethoxy)-5,8-dioxo-5,8-dihydro-naphthalen-2-yl]butyl}benzoate (40): To a cooled (0 °C) solution of **29** (0.48 g, 0.49 mmol) in MeCN (8 mL) and H_2O (2 mL) was added DDQ (0.13 g, 0.59 mmol) in one portion. After 20 min at this temperature water and EtOAc were added. The layers were separated and the aq. phase was extracted with EtOAc (3 x). The combined organic layers were washed with sat. NaCl sol. (aq.), dried with Na_2SO_4, filtered and concentrated. The residue was first filtered through a plug of Al_2O_3 (EtOAc as eluent), concentrated again and was then purified by column chromatography (silica gel, hexanes/EtOAc = 2:1) to provide 0.42 g (90%) of ketone **40** as yellow, highly viscous oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.19, 0.95 (2 s, 6 H, 9 H, $OSiMe_2$*t*Bu), 0.60, 0.83 (q, t, *J* = 8.0 Hz, 6 H, 9 H, $OSiEt_3$), 2.84 – 2.99 (m, 3 H, 3-H, 4-H), 3.15–3.23 (m, 1 H, 3-H), 3.54, 3.55, 3.56, 3.82, 3.83, 3.84, 3.95, 3.86 (8 s, 3 H each, OMe), 5.10 (s, 2 H, OCH_2), 5.20, 5.28 (AB-system, J_{AB} = 5.2 Hz, 1 H each, OCH_2), 5.45 (s, 1 H, 1-H), 6.00 (s, 1 H, 6´´-H), 6.34 (s, 1 H, 1´-H), 6.83 (s, 1 H, Ar) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = -4.9,

18.2, 25.5 (q, s, q, $OSiMe_2tBu$), 4.5, 6.6 (q, t, $OSiEt_3$), 24.2 (t, C-4), 38.7 (t, C-3), 51.6, 52.2, 56.3, 57.6, 58.1, 61.3, 61.4, 63.4 (8 q, OMe), 72.0 (d, C-1), 99.2, 100.4 (2 t, OCH_2), 110.5 (d, C-6´´), 117.1 (d, C-1´), 120.9, 125.8 (2 s, Ar), 126.2 (d, Ar), 126.6, 128.9, 137.5, 138.8, 142.8, 147.6, 149.6, 150.1, 154.9, 155.8, 159.2 (11 s, Ar, C-2´), 164.7, 167.4 (2 s, C=O), 179.0, 182.8 (2 s, C-8´´, C-5´´), 210.0 (s, C-2) ppm. IR (ATR): υ = 3050–2850 (C-H), 1735 (C=O), 1685, 1650, 1630 (C=C), 1555 cm^{-1}. HRMS (ESI-TOF): m/z calc. for $[M + Na]^+$: 969.3736; found: 969.3733. Anal. calc. for $C_{46}H_{66}O_{17}Si_2$ (947.2): C 58.33, H 7.02; found: C 58.29, H 7.01.

Methyl 7-Hydroxy-6-(2-((2*R*,3*R*)-3-hydroxy-2,4,7,9-tetramethoxy-5,8-dioxo-2,3,5,8-tetrahydro-naphtho[2,3-*b*]furan-2-yl)ethyl)-8-methoxy-1-oxo-1*H*-isochromene-3-carboxylate (41) and **Methyl 3-Hydroxy-4,7,9,10'-tetramethoxy-5,8,9'-trioxo-4',5,8,9'-tetrahydro-3*H*,3'*H*-spiro-[naphtha[2,3-*b*]-furan-2,2'-pyrano[4,3-*g*]chromene]-7'-carboxylate (42):** To a solution of γ-naphthoquinone **40** (475 mg, 0.50 mmol) in MeOH (12 mL) in a pressure tube (volume: 20 mL, argon atmosphere) was added HCl (37% aq., 75 µL). The mixture was heated to 120 °C and stirred at this temperature for 24 h. After cooling to rt, the crude reaction mixture was concentrated and filtered through a short plug of silica gel (eluent: EtOAc + 10% acetone). The filtrate was concentrated again and filtered through a short plug of Al_2O_3 (CH_2Cl_2 + 10% MeOH as eluent). The filtrate was concentrated and diluted with CH_2Cl_2 (2 mL). Addition of Et_2O and hexane induced the precipitation of a yellow solid (185 mg), which contained a mixture of *cis*/*trans*-**42** (56%) and methyl ketal **41** (8%) as judged by ^1H NMR spectroscopy. For analytical purposes, the separation of the diastereomeres of **42** and methyl ketal **41** was achieved with HPLC (Nucleosil 50-5, 2% MeOH/CH_2Cl_2).

Data of compound *cis*-**42**:

Melting range: 154–164 °C. ^1H NMR (700 MHz, $CDCl_3$): δ = 2.31 (m_c, 1 H, 3´-H), 2.42 (ddd, *J* = 2.8, 5.6, 13.8 Hz, 1 H, 3´-H), 3.06 (ddd, *J* = 2.8, 5.4, 17.2 Hz, 1 H, 4´-H), 3.35 (m_c, 1 H, 4´-H), 3.83, 3.84, 3.87, 3.95, 4.06 (5 s, 3 H each, OMe), 5.42 (s, 1 H, 3-H), 5.99 (s, 1 H, 6-H), 7.18 (s, 1 H, 5´-H), 7.34 (s, 1 H, 6´-H) ppm; signal for OH not detected. ^{13}C NMR (176 MHz, $CDCl_3$): δ = 21.9 (t, C-4´), 27.8 (t, C-3´), 52.9, 56.3, 61.3, 62.0, 62.5 (5 q, OMe), 76.0 (d, C-3), 108.2 (s, C-2), 110.2 (d, C-6), 111.8 (d, C-6´), 115.6, 120.2 (2 s, Ar), 123.2 (d, C-5´), 127.3, 127.6, 130.1, 131.5, 141.9 (5 s, Ar), 142.2 (s, C-7´), 146.8, 150.5, 154.5, 155.0 (4 s, Ar), 156.7 (s, C-9´), 159.2 (s, C-7), 160.8 (s, C=O), 179.2 (s, C-8), 183.3 (s, C-5) ppm. IR (ATR): υ = 3450 (OH), 2950–2855 (C-H), 1740 (C=O), 1680, 1640 (C=C), 1580, 1470, 1455 cm^{-1}. HRMS (ESI-TOF): m/z calc. for $[M + Na]^+$: 603.1115; found: 603.1090.

Data of compound *trans*-**42**:

Melting range: 157–172 °C. ^1H NMR (700 MHz, $CDCl_3$): δ = 2.34 (m_c, 1 H, 3´-H), 2.65 (ddd, *J* = 2.6, 5.9, 14.1 Hz, 1 H, 3´-H), 3.12 (ddd, *J* = 2.6, 5.9, 17.4 Hz, 1 H, 4´-H), 3.34 (m_c, 1 H, 4´-H), 3.73, 3.74, 3.83, 3.93, 4.07 (5 s, 3 H each, OMe), 5.49 (s, 1 H, 3-H), 5.90 (s, 1 H, 6-H), 7.16 (s, 1 H, 5´-H), 7.32 (s, 1 H, 6´-H) ppm; signal for OH not detected. ^{13}C NMR (176 MHz, $CDCl_3$): δ = 21.8 (t, C-4´), 23.5 (t, C-3´), 52.8, 56.4, 61.1, 61.6, 61.8 (5 q, OMe), 76.0 (d, C-3), 110.2 (d, C-6), 112.0 (d, C-6´), 112.6 (s, C-2), 115.3, 118.8 (2 s, Ar), 123.3 (d, C-5´), 127.2, 127.3, 129.7, 132.0, 141.7 (5 s, Ar), 142.0 (s, C-7´), 147.3, 150.4, 154.4, 156.1 (4 s, Ar), 156.9 (s, C-9´), 159.2 (s, C-7), 160.9 (s, C=O), 179.0 (s, C-8), 183.4 (s, C-5) ppm. IR (ATR): υ = 3400 (OH), 2950–2850 (C-H), 1740 (C=O), 1685, 1645 (C=C), 1585, 1470, 1455 cm^{-1}. HRMS (ESI-TOF): m/z calc. for $[M + Na]^+$: 603.1115; found: 603.1056.

Data of compound **41**:

Melting range: 136–146 °C. ^1H NMR (700 MHz, $CDCl_3$): δ = 2.36–2.40 (m, 1 H, 3´-H), 2.59–2.63 (m, 1 H, 3´-H), 2.97–3.01 (m, 2 H, 4´-H), 3.48 (s, 3 H, 2-OMe), 3.83, 3.94, 3.96, 4.03, 4.04 (5 s, 3 H each, OMe), 5.20 (s, 1 H, 3-H), 5.92 (s, 1 H, 6-H), 6.77 (bs, 1 H, OH), 7.25 (s, 1 H, 5´-H), 7.38 (s, 1 H, 6´-H) ppm; signal for OH not detected. ^{13}C NMR (176 MHz, $CDCl_3$): δ = 25.7 (t, C-4´), 28.4 (t, C-3´), 50.3 (2-OMe), 52.8, 56.3, 61.1, 62.0, 62.9 (5 q, OMe), 74.9 (d, C-3), 110.2 (d, C-6), 112.7 (d, C-6´), 114.0 (s, Ar), 116.4 (s, C-2), 118.7 (s, Ar), 124.6 (d, C-5´), 127.1, 128.8, 129.0, 137.0, 141.5 (5 s, Ar), 142.3 (s, C-7´), 147.4, 149.7, 154.3, 156.6 (4 s, Ar), 157.3 (s, C-9´), 159.2 (s, C-7), 160.8 (s, C=O), 179.3 (s, C-8), 183.5 (s, C-5) ppm. IR (ATR): υ = 3390 (OH), 2950–2855 (C-H), 1735 (C=O), 1680, 1640 (C=C), 1580, 1455 cm^{-1}. HRMS (ESI-TOF): m/z calc. for $[M + Na]^+$: 635.1377; found: 635.1310.

Methyl 4,5,7,9,10'-Pentamethoxy-9'-oxo-4',9'-dihydro-3*H*,3'*H*-spiro-[naphtho[2,3-*b*]furan-2,2'-pyrano[4,3-*g*]chromene]-7'-carboxylate (45) and **Methyl 7-Hydroxy-8-methoxy-1-oxo-6-[2-(4,5,7,9-tetrameth-oxynaphtho[2,3-*b*]furan-2-yl)ethyl]-1*H*-isochromene-3-carboxylate (46)**: To a 1:1 mixture of **30** and **32** (60 mg, corresponds to ca. 30 mg (ca. 48 µmol) of spiroketal **30**) in TFA (2.5 mL) was added Et_3SiH (80 µL, 0.50 mmol). The reaction mixture was heated to 50 °C for 10 min. Then sat. $NaHCO_3$ sol (aq.) and EtOAc were added. The layers were separated and the aq. phase was extracted with EtOAc (2 x). The combined organic layers were dried with Na_2SO_4, filtered and concentrated. Column chromatography (silica gel, hexanes/EtOAc = 2:1) provided 11 mg of γ-naphthofuran **46** (33% based on **30**) as beige solid. A second fraction (24 mg) contained **32** and spiroketal **45**. Purification with HPLC recovered **32** and gave 5 mg of spiroketal **45** (18% based on **30**) as beige solid.

Data of compound **45**:

Melting range: 105–115 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.35 (m_c, 1 H, 3´-H), 2.51 (ddd, *J* = 2.1, 6.0, 13.7 Hz, 1 H, 3´-H), 3.03 (ddd, *J* = 2.1, 6.2, 17.4 Hz, 1 H, 4´-H), 3.46 (m, 1 H, 4´-H), 3.47, 3.75 (AB-system, J_{AB} = 16.8 Hz, 1 H each, 3-H), 3.71, 3.80, 3.87, 3.90, 3.93, 3.97 (6 s, 3 H each, OMe), 6.44 (d, *J* = 2.4 Hz, 1 H, 6-H), 6.99 (d, *J* = 2.4 Hz, 1 H, 8-H), 7.13 (s, 1 H, 5´-H), 7.33 (s, 1 H, 6´-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 22.8 (t, C-4´), 29.7 (t, C-3´), 39.2 (t, C-3), 52.8, 55.3, 56.0, 60.2, 61.4, 61.7 (6 q, OMe), 92.7 (d, C-8), 97.4 (d, C-6), 110.0 (s, C-2), 112.2 (d, C-6´), 112.5, 115.1, 115.7, 116.8 (4 s, Ar), 123.0 (d, C-5´), 129.0, 131.5, 132.6 (3 s, Ar), 141.7 (s, C-7´), 145.5, 148.0, 148.3, 150.6 (4 s, Ar), 157.0 (s, C-9´), 157.4, 158.3 (2 s, C-5, C-7), 161.0 (s, C=O) ppm. IR (ATR): υ = 2955–2850 (C-H), 1740 (C=O), 1645, 1620 (C=C), 1515 cm^{-1}. HRMS (ESI-TOF): m/z calc. for $[M + Na]^+$: 587.1529; found: 587.1525.

Data of compound **46**:

M.p. 121–125 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.16–3.28 (m, 4 H, 3´-H, 4´-H), 3.89, 3.92, 3.95, 3.98, 4.03, 4.18 (6 s, 3 H each, OMe), 6.46 (d, *J* = 2.3 Hz, 1 H, 6-H), 6.58 (s, 1 H, 3-H), 6.65 (bs, 1 H, OH), 7.13 (d, *J* = 2.3 Hz, 1 H, 8-H), 7.15 (s, 1 H, 5´-H), 7.30 (s, 1 H, 6´-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 27.7 (t, C-4´), 28.9 (t, C-3´), 52.8, 55.3, 56.0, 60.7, 62.7, 62.9 (6 q, OMe), 91.9 (d, C-8), 97.5 (d, C-6), 100.4 (d, C-3), 112.7 (d, C-6´), 113.3, 113.9, 121.8 (3 s, Ar), 124.7 (d, C-5´), 127.8, 128.5, 133.6, 136.4 (4 s, Ar), 141.3 (s, C-7´), 143.7, 144.1, 147.2, 149.9 (4 s, Ar), 157.0 (s, C-9´), 157.3, 157.5, 157.6 (3 s, C-2, C-5, C-7), 160.7 (s, C=O) ppm. IR (ATR): υ = 3350 (OH), 3020–2850 (C-H), 1730, 1715 (C=O), 1640, 1615 (C=C) cm^{-1}. HRMS (ESI-TOF): m/z calc. for $[M + Na]^+$: 587.1529; found: 587.1520.

Acknowledgements

Support of this work by Bayer HealthCare AG is most gratefully acknowledged. The help of C. Groneberg with HPLC separations, of the NMR spectroscopy service team of Dr. A.

Schäfer and of the mass spectrometry team of Dr. A. Springer are also most gratefully acknowledged.

Keywords: 3-Hydroxyrubromycins • Spiro Compounds • Solvent Effects • Natural Products • Friedel-Crafts Alkylation

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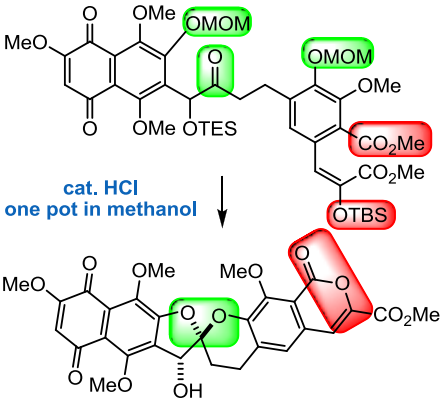
FULL PAPER

Methanol pops in, pops out. The inconspicuous action of methanol changes the game for the delicate, acid-mediated spiroketalization of the synthesis of C-3 hydroxy-substituted rubromycin spiroketals.



Rubromycins

Michael Wilsdorf, Sebastian Sörgel, Hans-Ulrich Reissig

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Lessons Learned During Spiroketalization Experiments – Progress and Setbacks in the Synthesis of Oxygenated Rubromycins and Synthesis of 3´-Desoxyheliquinomycinone