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Rubromycins

Towards γ-Rubromycin: Model Studies, Development of a C_3 Building Block, and Synthesis of 4′-Silyl-γ-rubromycin

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Abstract: The human telomerase inhibitor γ-rubromycin belongs to a class of natural products, which features a rare [5,6]-bisbenzannulated spiroketal core as its central structural motif. Also termed "aromatic spiroketals", these scaffolds pose great challenges to total synthesis. The ideal approach through an acid-mediated spiroketalization event is demanding, since this transformation is susceptible to even slight electronic alterations on the polyaromatic ring system. Herein, we report our strategy towards this class of natural products, that led to the identification of an electronically well-balanced spiroketalization precursor and eventually culminated in the preparation of an unnatural 4′-silyl-substituted γ-rubromycin derivative in racemic form. In the course of this study, we additionally introduced a new type of γ-silylated allylic phosphonate reagents that served as valuable C_3 building blocks to forge the spiroketalization precursor in a convergent manner.

Introduction

The rubromycins comprise a unique family of highly oxygenated natural products that are of polyketide origin, first described by Brockmann et al. with the isolation and characterization of the parent compound γ-rubromycin (**1**).[1] Since then, the isolation of several congeners has been reported, including for instance heliquinomycin (**2**),[2] purpuromycin (**3**),[3] griseorhodin A (**4**),[4] and most recently hyaluromycin (**5**).[5] Structurally, all these natural products share a unique bisbenzannulated [5,6]-spiroketal core, which conjoints a naphtharazin portion with an isocoumarin moiety and significantly varies in the degree and pattern of oxygenation (Figure 1).

The biological evaluation of the rubromycins has revealed a wide range of potential therapeutic attributes, including cytotoxic, antimicrobial, and antibacterial activities and also inhibitory effects towards human telomerase and HIV reverse transcriptase.[6,7] In light of this promising biological profile and due to their attractive molecular architecture, several complementary approaches towards their synthesis have been reported in recent years.[8] An initial accomplishment in the total synthesis of these natural products was published by Danishefsky et al. in 2001, who first disclosed the assembly of racemic heliquinomycinone, the aglycon of heliquinoymcin (**2**).[9] Later, the laboratories of Kita (2007)[10] and Pettus (2011)[11] succeeded in the synthesis of (±)-γ-rubromycin (**1**), and formal total syntheses of this natural product were reported by the groups of Brimble (2009)[12] and Li (2012).[13]

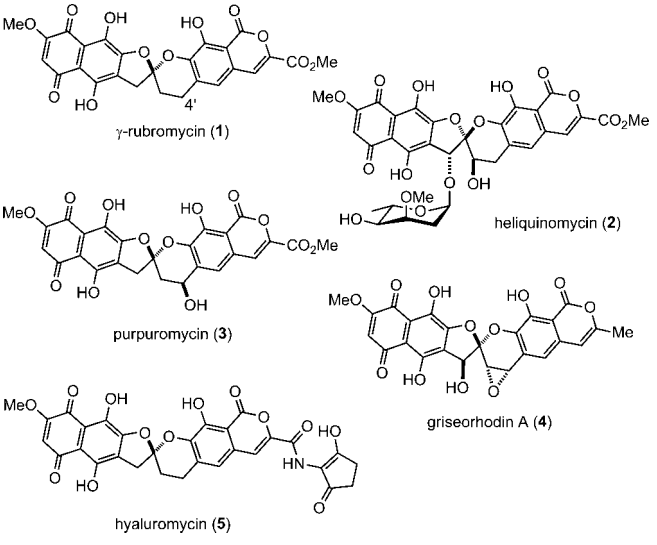

Figure 1. Selected members of the rubromycin natural product family.

Over the last few years, our group has constantly contributed to this research area, mainly focusing on the assembly of model substrates and of important molecule fragments.[14] In a continued effort to achieve the total synthesis of members of this class of biologically active natural products, here we detail our discoveries during our approach to bisbenzannulated [5,6]-spiroketals. Based on these results an efficient and scalable route to the natural product (±)-γ-rubromycin (**1**) was previously communicated.[15]

Results and Discussion

General Considerations

In the context of rubromycin synthesis, a straightforward way to construct the pivotal spiroketal core would include acid-

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mediated ketal formation from dihydroxy ketone precursors such as **6** (see Figure 2). Yet, neither of the previously known two successful total syntheses of (±)-γ-rubromycin relied on this kind of strategy, but rather devised elegant routes to circumvent this approach. Initially unexpectedly, compounds like **6** preferably undergo an irreversible β-elimination/aromatization sequence (via **7**) to the naphthofuran **8** instead of forming the desired spiroketal **9**. This tendency is even more pronounced for substrates, which possess a fully elaborated isocoumarin domain, a behavior that could experimentally be substantiated by the group of Kozlowski[16] and by our group.[14c] Apparently, intrinsic electronic properties are responsible for this observation as the phenolic oxygen atom of the isocoumarin portion suffers from a markedly reduced nucleophilicity as a result of its conjugation to the remote methoxycarbonyl moiety. The spiroketalization outcome of "aromatic precursors" is particularly sensitive towards alterations to the substitution pattern of the aromatic portions. In extreme cases, as for instance for compound **6**, the spiroketalization event may even be completely shut down.

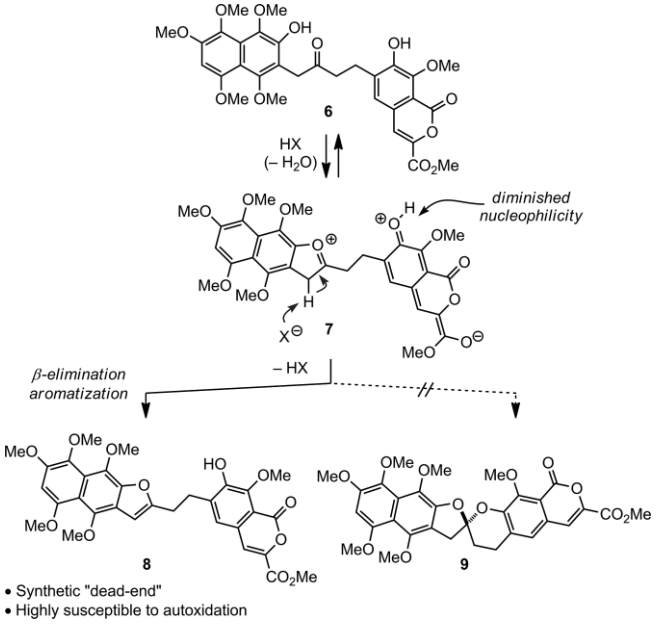


Figure 2. Spiroketalization versus β-elimination/aromatization pathway.

Aware of these synthetic challenges, we envisaged a late-stage elaboration of the isocoumarin fragment *after* the crucial acid-mediated spiroketalization as a viable solution, a strategy that has also already been implemented by Brimble and Li in their respective formal total syntheses of (±)-γ-rubromycin. After reexamining our approach, we considered the replacement of the isocoumarin fragment by a synthetic equivalent that would possess attenuated electron-withdrawing properties, but that would already incorporate all functional groups required for the late-stage construction of the isocoumarin domain. In addition, we intended to selectively oxidize the electron-rich naphthalene portion to the corresponding γ-naphthoquinone prior to the spiroketalization in order to mitigate the propensity of this fragment to undergo unspecific oxidative decomposition during this event. Hence, in line with our previous strategy, we pursued a convergent approach to the electronically well-balanced key intermediate **10** and therefore dissected this target into two main halves, the naphthalene fragment **11** and the functionalized aryl iodide **13**, which would eventually be linked through lithiated methoxyallene **12**[17] as a central C_3 building block (Figure 3).

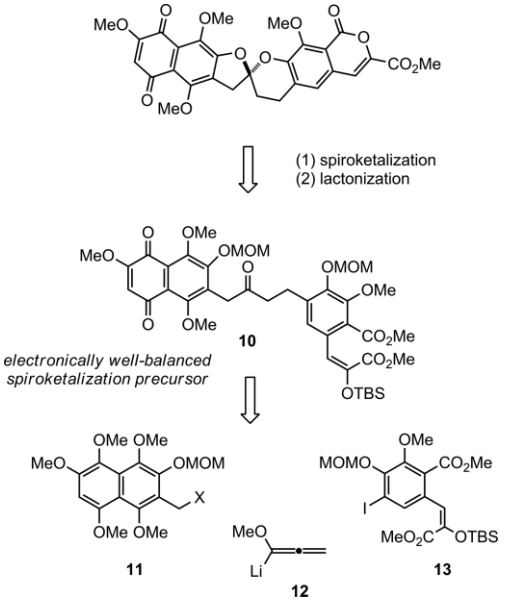
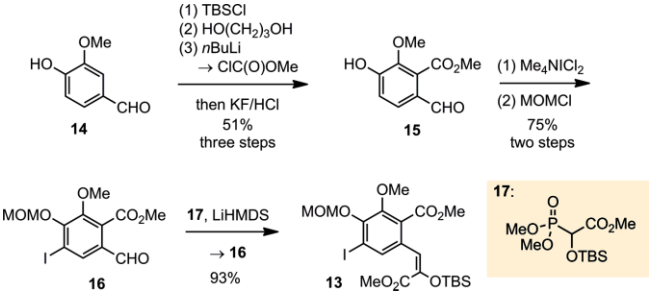


Figure 3. Retrosynthesis based on the use of lithiated methoxyallene **12** as C_3 building block (X = suitable nucleofuge).

Evaluation of the Spiroketalization/Lactonization Sequence

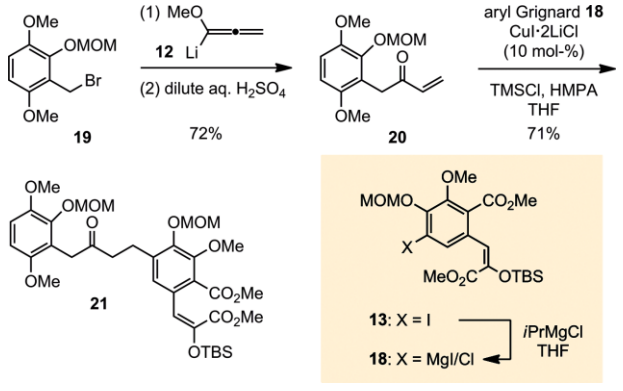
In order to demonstrate the feasibility of the planned strategy, we first prepared the functionalized aryl iodide **13**, which was readily accessed from vanillin (**14**) by a short route that was previously described by our group.[18] Here, the introduction of the methoxycarbonyl group at C-3 of vanillin required three steps (by the site-selective metallation of the intermediate acetal, not shown) to yield **15** after hydrolysis in moderate yield (Scheme 1). Next, *ortho*-iodination and *O*-alkylation with MOMCl led to compound **16**, which in turn was subjected to Horner–Wadsworth–Emmons (HWE) olefination employing



Scheme 1. Synthesis of functionalized aryl iodide **13** starting from vanillin (**14**).

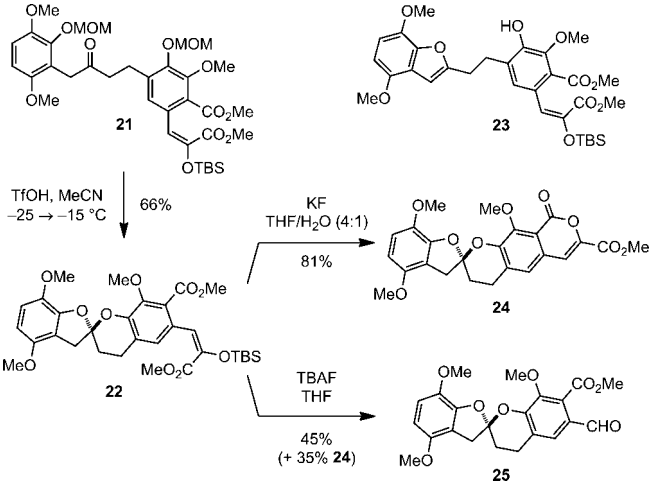
dimethyl phosphonate **17**[19] to afford the desired building block **13** on a multigram scale.

With sufficient quantities of aryl iodide **13** in hand, we next focused on the assembly of a model substrate suitable for the evaluation of the planned spiroketalization/lactonization sequence. As outlined in Scheme 2, a halogen/metal exchange with *i*PrMgCl according to Knochel's procedure[20] conveniently generated the aryl Grignard reagent **18**, that was then added to the methoxyallene-derived enone **20**[14d] mediated by cuprous iodide in the presence of the co-solvent HMPA and TMSCl.[21] An ensuing hydrolysis of the intermediate trimethylsilyl enol ether (not shown) with dilute sulfuric acid in THF afforded the pure 1,4-addition product **21** on a gram scale in good yield. It is worth noting that despite its high degree of functionalization the magnesium reagent **18** displayed a remarkable stability (no noticeable decomposition up to 0 °C in THF) presumably due to the beneficial complexation of the metal atom by the MOM group in the *ortho* position.



Scheme 2. Assembly of the functionalized model substrate **21** from enone **20** and Grignard reagent **18**.

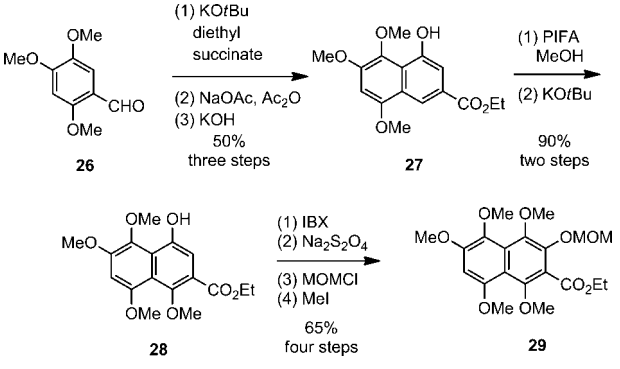
The functionalized model substrate **21** was then subjected to the crucial acid-mediated [5,6]-spiroketalization. In our previous studies we had already identified that catalytic amounts of triflic acid (TfOH) in MeCN at low temperatures could be used to induce the spiroketalization (Scheme 3), while the prevalent benzofuran formation (**21** → **23**) was sufficiently suppressed at the same time.[14d,22] In this event, the cleavage of the MOM ethers occurred chemoselectively, while the potentially acid-labile TBS enol ether remained untouched, a prerequisite for the success of this transformation. Subsequently, the advanced spiroketal **22** was treated with potassium fluoride (KF) in a mixture of THF/H_2O (4:1) to trigger the lactonization to the simplified and masked γ-rubromycin congener **24**. Rather unexpectedly, the use of TBAF (1 M in THF) partially led to the formation of aryl aldehyde **25**, presumably resulting from the conjugate addition of water to the intermediate α-hydroxy enone during aqueous workup, followed by a retro-aldol-type fragmentation (not shown). Still, with the efficient preparation of compound **24**, we established a robust route that we planned to utilize in the synthesis of γ-rubromycin during the next stage of our investigation.



Scheme 3. Triflic-acid-mediated spiroketalization of **21** to **22** and subsequent lactonization to the simplified and masked γ-rubromycin congener **24**.

Towards the Naphthalene Portion of γ-Rubromycin

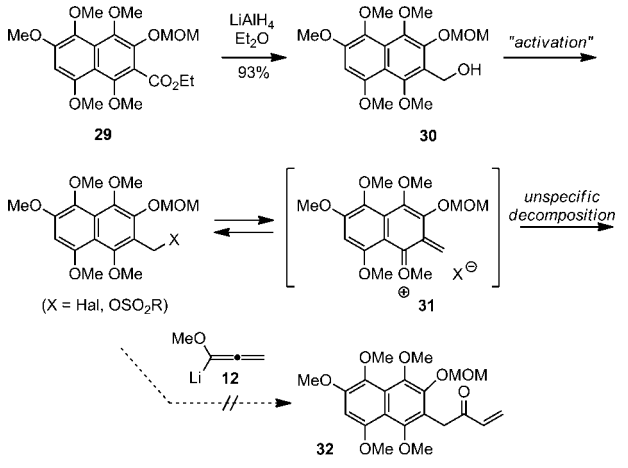
In order to apply this promising strategy to the synthesis of γ-rubromycin, we first needed to access the highly oxygenated naphthalene fragment of this molecule in the form of the ethoxycarbonyl-substituted naphthalene derivative **29** (Scheme 4). For that purpose, we adopted a route previously disclosed by the group of Kozlowski, starting from trimethoxybenzaldehyde **26**.[23] This short sequence, which can be used to yield multigram quantities of **29**, includes a Stobbe condensation with ethyl succinate followed by an intramolecular Friedel–Crafts-type acylation to build up the naphthalene scaffold (**26** → **27**). Next, regioselective introduction of a methoxy group by oxidative dearomatization with bis(trifluoroacetoxy)-iodobenzene (PIFA) in methanol and subsequent base-induced tautomerization led to the naphthol derivative **28**. The oxidation of this compound with 2-iodoxybenzoic acid (IBX) then afforded an *ortho*-quinone (not shown), which was reduced to its respective catechol with $Na_2S_2O_4$ and further *O*-alkylated sequentially with MOMCl and MeI to yield **29**.



Scheme 4. Nine-step synthesis of ethoxycarbonyl-substituted naphthalene derivative **29**. PIFA = bis(trifluoroacetoxy)iodobenzene; IBX = 2-iodoxybenzoic acid.

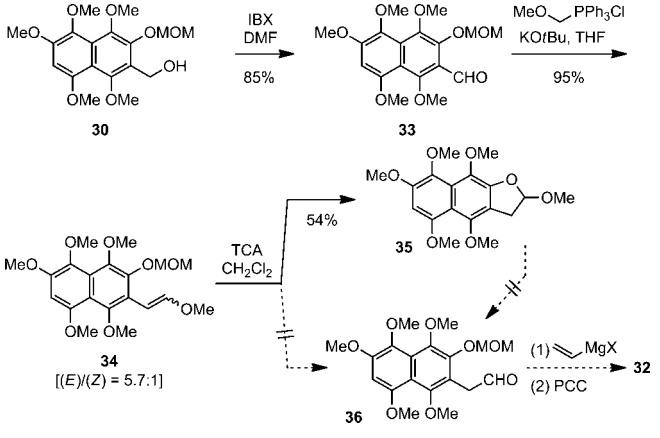
As shown in Scheme 5, substrate **29** was readily reduced by $LiAlH_4$ to hydroxymethyl-substituted naphthalene derivative **30**. However, despite extensive experimentation, the primary alco-

hol **30** could not be converted into a compound with a suitable leaving group, which would be compatible with the intended substitution reaction with lithiated methoxyallene (**12**). Unfortunately, all attempts to convert **30** into the corresponding primary halides or different sulfonic acid esters, for instance, led to its immediate decomposition. It is plausible to assume a facile heterolysis of the formed product as a result of the extraordinarily electron-rich nature of the hexaalkoxy-substituted naphthalene ring leading to a quinone-methide-like species (**30** → **31**).



Scheme 5. Reduction of ester **29** to alcohol **30** and failed attempted conversions into activated derivatives resulting in inaccessibility of enone **32** through the methoxyallene approach.

The inaccessibility of enone **32** through a methoxyallene-based route prompted us to explore various stepwise methods towards this substrate. A promising approach, amongst others, included the Wittig homologation of naphthaldehyde **33**, readily obtained by oxidation of **30** with IBX (Scheme 6). Its reaction with the ylide derived from (methoxymethyl)triphenylphosphonium chloride[24] afforded the expected naphthyl-substituted enol ether **34** [(*E*)/(*Z*) = 5.7:1]. The intended synthesis of aldehyde **36** by hydrolysis of the enol ether moiety of **34** (with trichloroacetic acid, for instance) led to the undesired formation

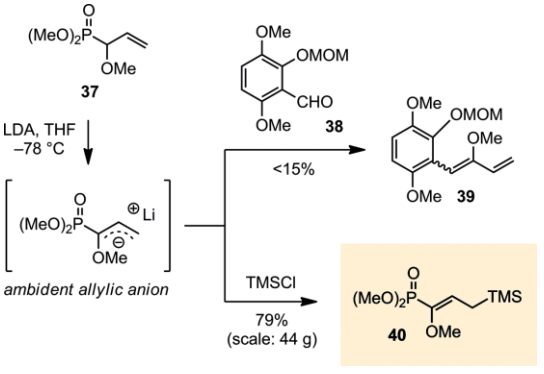


Scheme 6. Attempted route towards stepwise elaboration of **32** through Wittig homologation of **33**. IBX = 2-iodoxybenzoic acid; TCA = trichloroacetic acid.

of methyl hemiketal **35**, generated through interception of the intermediate oxocarbenium ion by the adjacent MOM group. Unfortunately, **35** was highly susceptible to oxidation and not suitable for conversion into aldehyde **36** in order to perform the planned addition of the vinyl Grignard reagent followed by oxidation to yield **32**.

Introduction of Allylic Phosphonates as C_3 Building Blocks

In light of the encouraging reactivity of aldehyde **33** in olefinations and with the demand for a simple reagent – ideally a C_3 building block – to access the required enone, we directed our attention to the known α-methoxy-substituted allylic phosphonate **37** (Scheme 7).[25] If this reagent could successfully be employed in an HWE-type olefination with aldehyde **33**, the resultant 2-methoxybutadiene derivative (not shown) should give access to the desired enone **32** after hydrolysis of its enol ether moiety.

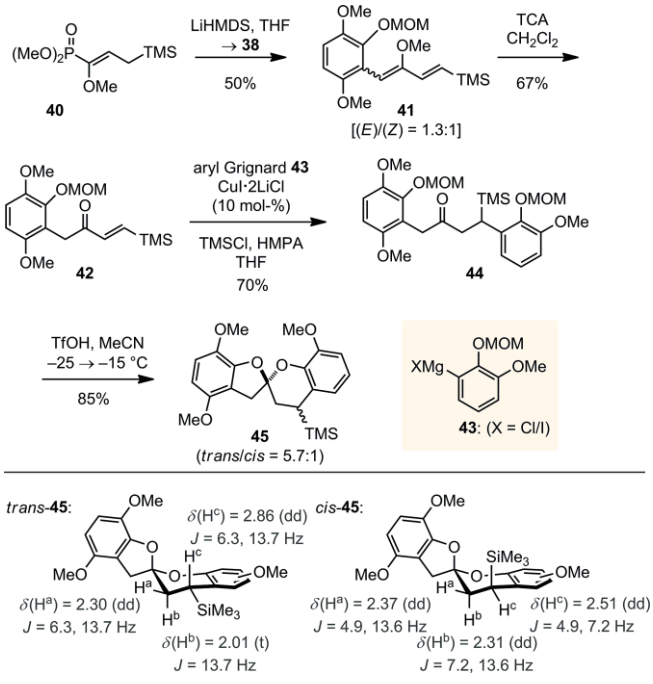


Scheme 7. Reaction of lithiated **37** with aryl aldehyde **38** and preparation of γ-trimethylsilyl-substituted allylic phosphonate **40**.

The α-methoxy-substituted allylic phosphonate **37** is readily metallated with LDA to generate an acceptor-stabilized ambident allylic anion, which in turn is preferentially quenched with electrophiles at its γ-position (Scheme 7). The regioselectivity of this reaction, however, may also depend on the nature of the electrophile employed, taking steric and electronic factors into account.[26] Not entirely unexpectedly, the trapping of lithiated **37** with the sterically congested aryl aldehyde **38**[27] yielded less than 15 % of the desired 2-methoxybutadiene derivative **39**. An anticipated in situ transmetallation with $TiCl(OiPr)_3$ or $TiCl_2(OiPr)_2$ in order to control the regioselectivity (as reported for similar phosphine oxides with simple aryl aldehydes)[28] just led to complete disintegration of the sensitive aldehyde **38**. We therefore envisaged a temporary, but robust, blockage of the γ-site by, for instance, silylation with TMSCl, leading to a new type of α-methoxy-γ-silyl-substituted allylic phosphonate reagent **40**.[29]

The applicability of the new reagent **40** in the context of our strategy to γ-rubromycin was again first demonstrated with the preparation of simple model spiroketals (Scheme 8). Thus, deprotonation of phosphonate **40** with LiHMDS and subsequent trapping with aryl aldehyde **38** afforded the expected 2-methoxybutadiene **41** (50 % yield, not optimized). Hydrolysis under mild acidic conditions furnished β-trimethylsilyl-substi-

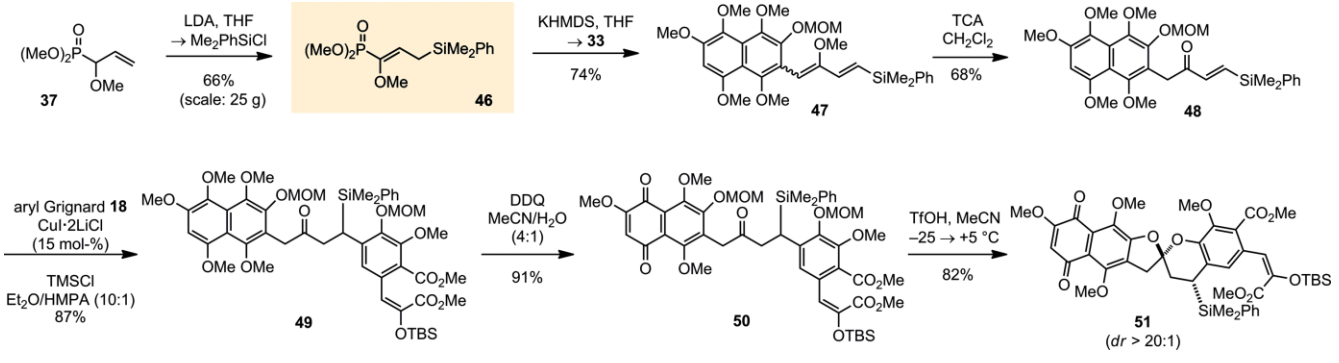
tuted enone **42** (Scheme 8), which served as suitable acceptor for the cuprous iodide mediated conjugate addition of aryl Grignard reagent **43** to give ketone **44**. In spite of the additional steric demand exerted by the bulky silyl group at the β-carbon atom, the merging of both halves of the molecule proceeded remarkably well. Triflic acid induced the spiroketalization, furnishing the desired product **45** with a good degree of diastereoselection (*dr* = 5.7:1) in favor of the *trans* isomer. Comparison of diagnostic ^{1}H NMR signals and their coupling constants allowed the stereochemical assignment of the diastereomers.



Scheme 8. Application of γ-trimethylsilyl-substituted allylic phosphonate **40** in the preparation of simple model [5,6]-spiroketal **45** via silylated enone **42** and characteristic ^{1}H NMR signals of the two diastereomers.

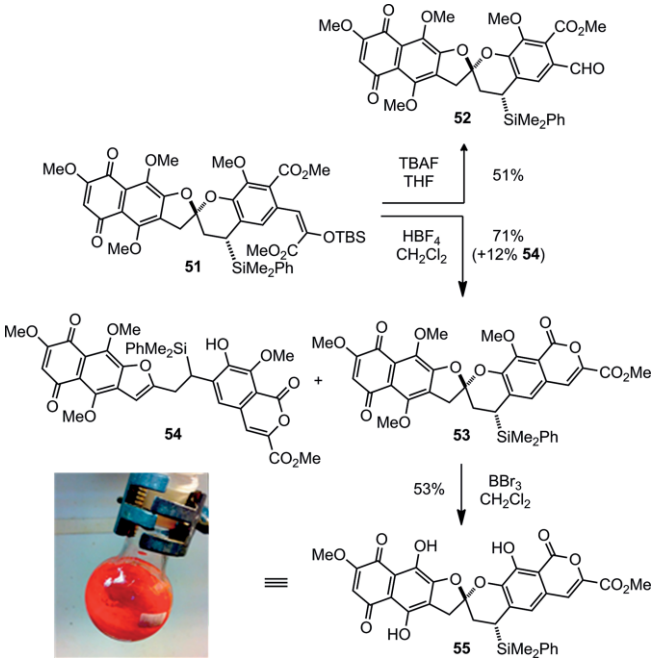
With the use of phosphonate **40** we established a complementary approach towards functionalized [5,6]-spiroketals starting from aryl aldehydes instead of benzylic alcohols. Consequently, our studies focused on the elaboration of phosphonate reagents that would finally provide a potential handle for further functionalizations at the pyran backbone of the spiroketal moiety. The installation of an aryl-substituted silyl group should enable a late-stage Tamao–Fleming-type oxidation,[30] either to introduce an oxygen atom at C-4′ [as is found in the natural product purpuromycin (**3**); see Figure 1] or to ensure a formal protodesilylation in a subsequent defunctionalization step leading to γ-rubromycin (**1**). Thus, we started the synthetic sequence by employing the dimethyl(phenyl)silyl-substituted allylic phosphonate **46** that was readily obtained on a decagram scale (Scheme 9). Metallation of **46** with KHMDS followed by addition to aldehyde **33** afforded 2-methoxybuta-1,3-diene **47** in 74 % yield, which was hydrolyzed to enone **48** in good yield. We were pleased to find that the conjugate addition of the previously utilized highly functionalized aryl Grignard reagent **18** to enone **48** proceeded smoothly to give after acidic hydrolysis **49** in 87 % yield. In the next step, the oxidation of the naphthalene portion with DDQ occurred regioselectively to afford the respective γ-naphthoquinone derivative **50**. This substrate represents the initially anticipated electronically well-balanced key intermediate (see Figure 3), albeit with an additional silyl group attached. As expected, treatment of **50** with TfOH in MeCN (–25 °C to 5 °C) cleanly afforded spiroketal **51** essentially as a single diastereomer with no detectable formation of the corresponding naphthofuran derivative. The α-siloxypropenoate side chain of precursor **50** is probably twisted out of plane for steric reasons and as a consequence the nucleophilicity of the phenolic hydroxy group is sufficiently high to allow smooth spirocyclization to **51**.

The final steps that are needed to complete the synthesis of γ-rubromycin would include lactonization to generate the isocoumarin unit and a proto-desilylation reaction, expected to be feasible through a two-step oxidation/deoxygenation sequence. We therefore treated compound **51** with an excess of fluoroboric acid–diethyl ether in dichloromethane, leading to the formation of spiroketal **53** in 71 % yield along with minor amounts of naphthofuran derivative **54**. Under these conditions, the lactonization proceeded smoothly without the aforementioned fragmentation of the silyl enol ether moiety (compare the reaction **51** → **52** in the presence of TBAF); however, the anticipated fluorodearylation reaction at the silicon atom (as the initial step of an intended Tamao–Fleming oxidation) did not occur. Surprisingly, the dimethyl(phenyl)silyl moiety remained untouched, even under prolonged reaction times and at elevated temperatures (50 °C, sealed tube). More excessive heating gradually led to the irreversible formation of **54**. Never-



Scheme 9. Synthesis of the advanced "aromatic spiroketal" **51** via ketone **50** employing allylic phosphonate **46** as key C_3 building block.

theless, we could convert **53** into racemic 4′-silyl-γ-rubromycin **55** in moderate yield by treatment with boron tribromide (Scheme 10). This product represents the first synthetic example of a derivative of this natural product class bearing a silyl group attached to the [5,6]-spiroketal backbone. Despite this remarkable achievement it seems unlikely to obtain γ-rubromycin (**1**) itself from the intermediates described here, since the pivotal silyl group could not be removed under sufficiently mild conditions. Yet, based on the strategy developed in this account, we could successfully accomplish the total synthesis of (±)-γ-rubromycin (**1**) when we incorporated the more electron-rich dimethyl(*para*-methoxyphenyl)silyl group into the allylic phosphonate reagent, as already reported in our previous communication.[15]



Scheme 10. Formation of the isocoumarin-spiroketal **53** and subsequent *O*-demethylation to 4′-silyl-γ-rubromycin **55** (reaction flask containing 36 mg of nicely colored final product **55**).

Conclusions

In this account we disclose the development of a convergent synthetic strategy that would eventually pave the way to the natural product (±)-γ-rubromycin. Crucial to the success was the adoption of a late-stage isocoumarin formation that occurred after the pivotal spiroketalization step employing an electronically well-balanced key intermediate. For the construction of this substrate, however, our first-choice approach via lithiated methoxyallene – that worked remarkably well for the preparation of various simplified model compounds – had to be abandoned due to the intrinsic lability of the intermediate naphthylmethyl alcohol **30**. The required adjustments to our synthetic route finally led to the development of new γ-silylated allylic phosphonate reagents (**40** and **46**), which perfectly complement methoxyallene as C_3 building blocks. Their first application finally resulted in the preparation of 4′-silyl-γ-rubromycin **55**, but we also expect these reagents to be valuable for other synthetic endeavors.

Experimental Section

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

Methyl 6-{(*E*)-2-[(*tert*-Butyldimethylsilyl)oxy]-3-methoxy-3-oxoprop-1-en-1-yl}-4-{4-[3,6-dimethoxy-2-(methoxymethoxy)phenyl]-3-oxobutyl}-2-methoxy-3-(methoxymethoxy)benzoate (21): To a cold (–40 °C) and well-stirred solution of aryl iodide **13** (1.36 g, 2.40 mmol) in THF (12 mL) was added *i*PrMgCl (ca. 1.7 M in THF, 1.42 mL, 2.41 mmol). This freshly prepared aryl Grignard reagent was rapidly transferred through a cannula to a mixture of enone **20**[14d] (0.59 g, 2.20 mmol), HMPA (2.20 mL, 5.31 mmol), CuI·2LiCl (0.10 M in THF, 2.20 mL), and TMSCl (0.56 mL, 4.43 mmol) in THF (30 mL) at –40 °C. The cooling bath was immediately removed, and the mixture was stirred at r.t. for 1 h. Then satd. NH_4Cl solution (aq.) and EtOAc were added. The layers were separated and the aq. phase was extracted with EtOAc (3 ×). The combined organic layers were washed with satd. NaCl solution (aq.), dried with Na_2SO_4, filtered, and concentrated. Column chromatography (silica gel; hexanes/EtOAc, 4:1 → 2:1) provided ketone **21** (1.10 g, 71 %) as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.19, 0.95 (2 s, 6 H, 9 H, $OSiMe_2tBu$), 2.68–2.72 (m, 2 H, 3-H), 2.87–2.90 (m, 2 H, 4-H), 3.49, 3.52, 3.53, 3.71, 3.77 (5 s, 3 H each, OMe), 3.79 (s, 2 H, 1-H), 3.81, 3.84 (2 s, 3 H each, OMe), 5.06, 5.07 (2 s, 2 H each, OCH_2), 6.32 (d, J = 0.7 Hz, 1 H, 1′-H), 6.56, 6.76 (2 d, J = 9.1 Hz, 1 H each, Ar), 6.75 (s, 1 H, Ar) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = –5.0, 18.2, 25.5 (q, s, q, $OSiMe_2tBu$), 24.2 (t, C-4), 38.8 (t, C-1), 42.0 (t, C-3), 51.6, 52.2, 55.7, 56.0, 57.47, 57.49, 61.3 (7 q, OMe), 99.0, 99.1 (2 t, OCH_2), 105.5, 111.0 (2 d, Ar), 117.0 (d, C-1′), 118.7 (s, Ar), 126.1 (d, Ar), 126.5, 128.8, 137.3, 142.7, 145.3, 146.3, 147.4, 149.5, 151.9 (9 s, Ar, C-2′), 164.8, 167.4 (2 s, C=O), 207.5 (s, C-2) ppm. IR (ATR): $\tilde{\nu}$ = 3000–2835 (C–H), 1725 (C=O), 1635 (C=C), 1595, 1560, 1490 cm^{-1}. HRMS (ESI-TOF): calcd. for $[M + Na]^+$ 729.2918; found 729.2950. $C_{35}H_{50}O_{13}Si$ (706.8): calcd. C 59.47, H 7.13; found C 59.41, H 7.14.

Methyl 6′-{(*E*)-2-[(*tert*-Butyldimethylsilyl)oxy]-3-methoxy-3-oxoprop-1-en-1-yl}-4,7,8′-trimethoxy-3*H*-spiro[benzofuran-2,2′-chroman]-7′-carboxylate (22): To a cold (–25 °C) solution of ketone **21** (151 mg, 0.21 mmol) in MeCN (11 mL) was added TfOH (20 μL of a freshly prepared 1.0 M stock solution of TfOH in MeCN, 20 μM). The mixture was warmed up to –15 °C during 30 min. Then satd. Na_2CO_3 solution (aq., 1 mL), water, and EtOAc were sequentially added. The layers were separated, and the aq. phase was extracted with EtOAc (3 ×). The combined organic layers were washed with satd. NaCl solution (aq.), dried with Na_2SO_4, filtered, and concentrated. Column chromatography (silica gel; hexanes/EtOAc, 4:1) provided spiroketal **22** (85 mg, 66 %) as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.20, 0.97 (2 s, 6 H, 9 H, $OSiMe_2tBu$), 2.20 (m_c, 1 H, 3′-H), 2.36 (ddd, J = 2.6, 5.8, 13.3 Hz, 1 H, 3′-H), 2.79 (ddd, J = 2.4, 5.8, 16.7 Hz, 1 H, 4′-H), 3.24, 3.50 (AB system, J_{AB} = 16.7 Hz, 1 H each, 3-H), 3.26 (m_c, 1 H, 4′-H), 3.63, 3.69, 3.76, 3.81, 3.82 (5 s, 3 H each, OMe), 6.35 (s, 1 H, 1″-H), 6.37, 6.71 (2 d, J = 8.9 Hz, 1 H each, 5-H, 6-H), 6.76 (s, 1 H, 5′-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = –4.90, –4.89, 18.2, 25.5 (2 q, s, q, $OSiMe_2tBu$), 21.9 (t, C-4′), 30.1 (t, C-3′), 40.0 (t, C-3), 51.7, 52.1, 55.6, 56.8, 61.5 (5 q, OMe), 103.1 (d, C-5), 110.1 (s, C-2), 113.0 (d, C-6), 113.9 (s, Ar), 117.4 (d, C-1″), 124.2 (s, Ar), 124.7 (d, C-5′), 125.2, 126.3, 138.9, 142.4, 144.5, 145.5, 147.2, 150.4 (8 s, Ar, C-2″), 165.0, 167.6 (2 s, C=O) ppm. IR (ATR): $\tilde{\nu}$ = 3000–2855 (C–H), 1730 (C=O), 1630, 1610 (C=C), 1570, 1510 cm^{-1}. HRMS (ESI-TOF): calcd. for $[M + Na]^+$ 623.2288; found 623.2278. $C_{31}H_{40}O_{10}Si$ (600.7): calcd. C 61.98, H 6.71; found C 61.95, H 6.89.

Methyl 4,7,10′-Trimethoxy-9′-oxo-4′,9′-dihydro-3*H*,3′*H*-spiro[benzofuran-2,2′-pyrano[4,3-*g*]chromene]-7′-carboxylate (24): To a cold (0 °C) solution of spiroketal **22** (80 mg, 0.13 mmol)

in THF (2.5 mL) and water (0.6 mL) was added KF (30 mg, 0.53 mmol). The mixture was stirred at this temperature for 90 min. Then water and EtOAc were sequentially added. The layers were separated, and the aq. phase was extracted with EtOAc (3 ×). The combined organic layers were washed with satd. NaCl solution (aq.), dried with Na_2SO_4, filtered, and concentrated. Column chromatography (silica gel; hexanes/EtOAc, 1:1) provided spiroketal **24** (49 mg, 81 %) as a colorless solid. M.p. 207–209 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.26 (m_c, 1 H, 3′-H), 2.43 (ddd, J = 2.0, 6.2, 13.6 Hz, 1 H, 3′-H), 2.95 (ddd, J = 2.0, 5.6, 16.9 Hz, 1 H, 4′-H), 3.30, 3.58 (AB system, J_{AB} = 16.9 Hz, 1 H each, 3-H), 3.42 (m_c, 1 H, 4′-H), 3.73, 3.79, 3.81, 3.92 (4 s, 3 H each, OMe), 6.40, 6.72 (2 d, J = 8.9 Hz, 1 H each, 5-H, 6-H), 7.01 (s, 1 H, 5′-H), 7.30 (s, 1 H, 6′-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 22.4 (t, C-4′), 29.5 (t, C-3′), 39.9 (t, C-3), 52.7, 55.6, 56.7, 61.5 (4 q, OMe), 103.4 (d, C-5), 110.1 (s, C-2), 112.2 (d, C-6′), 112.8 (d, C-6), 113.6, 115.0 (2 s, Ar), 123.1 (d, C-5′), 128.9, 131.6, 138.9 (3 s, Ar), 141.6 (s, C-7′), 146.8, 148.1, 150.4, 150.6 (4 s, Ar), 157.0, 161.0 (2 s, C=O) ppm. IR (ATR): $\tilde{\nu}$ = 3015–2840 (C–H), 1740 (C=O), 1645, 1610 (C=C), 1555, 1510 cm^{-1}. HRMS (ESI-TOF): calcd. for [M + Na]$^+$ 477.1162; found 477.1160. $C_{24}H_{22}O_9$ (454.4): calcd. C 63.43, H 4.88; found C 63.32, H 4.76.

1-[3,6-Dimethoxy-2-(methoxymethoxy)phenyl]-4-[3-methoxy-2-(methoxymethoxy)phenyl]-4-(trimethylsilyl)butan-2-one (44): To a cold (–40 °C) and well-stirred solution of 1-iodo-3-methoxy-2-(methoxymethoxy)benzene (75 mg, 0.25 mmol) in THF (3 mL) was added *i*PrMgCl (ca. 1.7 M in THF, 0.15 mL, 0.25 mmol). This freshly prepared aryl Grignard reagent was rapidly added by syringe to a mixture of enone **42** (60 mg, 0.18 mmol), HMPA (75 µL, 0.43 mmol), CuI•2LiCl (0.10 M in THF, 0.20 mL), and TMSCl (45 µL, 0.35 mmol) in THF (5 mL) at –40 °C. The cooling bath was immediately removed, and the mixture was stirred at r.t. for 15 min. Then satd. NH_4Cl solution (aq.) and EtOAc were added. The layers were separated, and the aq. phase was extracted with EtOAc (3 ×). The combined organic layers were washed with satd. NaCl solution (aq.) and concentrated. The residual oil was dissolved in THF (5 mL), and H_2SO_4 (5 % aq., 0.5 mL) was added at r.t. After completion of the hydrolysis of the silyl enol ether (ca. 15 min, according to TLC), water and EtOAc were added. The layers were separated, and the aq. phase was extracted with EtOAc (2 ×). The combined organic layers were washed with satd. NaCl solution (aq.), dried with Na_2SO_4, filtered, and concentrated. Column chromatography (silica gel; hexanes/EtOAc, 4:1) provided ketone **44** (63 mg, 70 %) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = –0.07 (s, 9 H, TMS), 2.79 (dd, J = 5.1, 17.5 Hz, 1 H, 3-H), 3.00 (dd, J = 10.0, 17.5 Hz, 1 H, 3-H), 3.33 (dd, J = 5.1, 10.0 Hz, 1 H, 4-H), 3.41, 3.63, 3.64 (3 s, 3 H each, OMe), 3.74 (s, 2 H, 1-H), 3.77, 3.80 (2 s, 3 H each, OMe), 4.97, 4.98 (AB system, J_{AB} = 5.6 Hz, 1 H each, OCH_2), 5.09, 5.11 (AB system, J_{AB} = 5.0 Hz, 1 H each, OCH_2), 6.53, 6.76 (2 d, J = 8.9 Hz, 1 H each, Ar), 6.57 (dd, J ≈ 1.4, 8.0 Hz, 1 H, Ar), 6.65 (dd, J ≈ 1.4, 8.2 Hz, 1 H, Ar), 6.94 (t, J ≈ 8.0 Hz, 1 H, Ar) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = –2.9 (q, TMS), 22.8 (d, C-4), 39.0 (t, C-1), 42.1 (t, C-3), 55.5, 55.6, 56.2, 57.3, 57.4 (5 q, OMe), 98.4, 98.9 (2 t, OCH_2), 105.5, 108.3, 111.1 (3 d, Ar), 118.91, 118.92 (s, d, Ar), 123.4 (d, Ar), 138.1, 142.6, 145.3, 146.4, 152.0, 152.6 (6 s, Ar), 207.3 (s, C-2) ppm. IR (ATR): $\tilde{\nu}$ = 2995–2835 (C–H), 1715 (C=O), 1595, 1580, 1490, 1475, 1440 cm^{-1}. HRMS (ESI-TOF): calcd. for [M + Na]$^+$ 529.2234; found 529.2249. $C_{26}H_{38}O_8Si$ (506.7): calcd. C 61.63, H 7.56; found C 61.48, H 7.57.

Trimethyl(4,7,8′-trimethoxy-3*H*-spiro[benzofuran-2,2′-chroman]-4′-yl)silane (45): To a cold (–25 °C) solution of ketone **44** (49 mg, 0.10 mmol) in MeCN (4 mL) was added TfOH (7 µL of a freshly prepared 1.3 M stock solution of TfOH in MeCN, 10 µM). The mixture was warmed up to –15 °C during 20 min. Then satd. Na_2CO_3 solution (aq., 1 mL), water, and EtOAc were sequentially added. The layers were separated, and the aq. phase was extracted with EtOAc (3 ×). The combined organic layers were washed with satd. NaCl solution (aq.), dried with Na_2SO_4, filtered, and concentrated. Column chromatography (silica gel; hexanes/EtOAc, 4:1) provided spiroketal **45** (34 mg, 85 %) as a mixture of diastereomers (*trans*/*cis* = 5.7:1) as a colorless oil. For analytical purposes, the diastereomers were separated by HPLC (Merck LiChrosorb Diol-5µ; 32 × 125 mm, 5 % *i*PrOH/hexanes, flow 28 mL min^{-1}, 13 bar). HRMS (ESI-TOF): calcd. for [M + Na]$^+$ 401.1784; found 401.1793.

Isomer *trans*-45: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.12 (s, 9 H, TMS), 2.01 (t, J = 13.7 Hz, 1 H, 3′-H), 2.30 (dd, J = 6.3, 13.7 Hz, 1 H, 3′-H), 2.86 (dd, J = 6.3, 13.7 Hz, 1 H, 4′-H), 3.26, 3.59 (AB system, J_{AB} = 16.7 Hz, 1 H each, 3-H), 3.72, 3.76, 3.80 (3 s, 3 H each, OMe), 6.34, 6.68 (2 d, J = 8.9 Hz, 1 H each, 5-H, 6-H), 6.66–6.67 (m, 1 H, Ar), 6.80–6.83 (m, 2 H, Ar) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = –1.7 (q, TMS), 20.1 (d, C-4′), 33.5 (t, C-3′), 40.3 (t, C-3), 55.6, 55.9, 56.7 (3 q, OMe), 102.7, 108.9 (2 d, Ar), 109.0 (s, C-2), 112.7 (d, Ar), 114.2 (s, Ar), 120.4, 120.5 (2 d, Ar), 125.4, 138.9, 141.7, 147.4, 148.9, 150.5 (6 s, Ar) ppm.

Isomer *cis*-45: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.10 (s, 9 H, TMS), 2.31 (dd, J = 7.2, 13.6 Hz, 1 H, 3′-H), 2.37 (dd, J = 4.9, 13.6 Hz, 1 H, 3′-H), 2.51 (dd, J = 4.9, 7.2 Hz, 1 H, 4′-H), 3.19, 3.41 (AB system, J_{AB} = 16.9 Hz, 1 H each, 3-H), 3.74, 3.77, 3.78 (3 s, 3 H each, OMe), 6.34, 6.70* (2 d, J = 8.7 Hz, 1 H each, 5-H, 6-H), 6.64–6.66 (m, 1 H, Ar), 6.70* (m, 1 H, Ar), 6.82 (t, J = 7.9 Hz, 1 H, Ar) ppm; * signals are overlapping. ^{13}C NMR (126 MHz, $CDCl_3$): δ = –1.4 (q, TMS), 23.9 (d, C-4′), 33.1 (t, C-3′), 39.8 (t, C-3), 55.6, 55.9, 56.8 (3 q, OMe), 102.8, 108.5 (2 d, Ar), 110.5 (s, C-2), 112.7 (d, Ar), 114.0 (s, Ar), 119.9, 120.5 (2 d, Ar), 125.7, 139.2, 141.1, 147.6, 148.9, 150.4 (6 s, Ar) ppm.

Dimethyl [(*E*)-1-Methoxy-3-(trimethylsilyl)prop-1-en-1-yl]phosphonate (46): To a cooled (–78 °C) and well-stirred solution of diisopropylamine (*i*Pr$_2$NH, 14.8 mL, 105 mmol) in THF (100 mL) was added *n*BuLi (2.5 M in hexanes, 42.0 mL, 105 mmol). After the mixture had been kept at this temperature for 15 min, phosphonate **37** (17.2 g, 95 mmol) was added dropwise, resulting in a bright orange-colored solution. After 15 min, chlorodimethyl(phenyl)silane (18.8 g, 110 mmol) was added. Then, the mixture was warmed up and stirred at r.t. for 1 h. Next, satd. NH_4Cl solution (aq.), water, and Et_2O were added. The layers were separated and the aq. phase was extracted with Et_2O (2 ×). The combined organic layers were washed with satd. NaCl solution (aq.), dried with Na_2SO_4, filtered, and concentrated. The resulting residue (oil) was subjected to high-vacuum distillation. One fraction (boiling range: 70–140 °C at 55 mTorr) was isolated that contained phosphonate **46** (25.0 g, 84 %) as a colorless liquid (n_D^{19} = 1.513). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.33 (s, 6 H, $SiMe_2Ph$), 1.94 (dd, $^4J_{P,H}$ = 2.3, J = 8.9 Hz, 2 H, 3-H), 3.53 (d, $^4J_{P,H}$ = 0.9 Hz, 3 H, 1-OMe), 3.67 (d, $^3J_{P,H}$ = 11.2 Hz, 6 H, POMe), 6.10 (dd, J = 8.9, $^3J_{P,H}$ = 18.6 Hz, 1 H, 2-H), 7.33–7.35, 7.49–7.51 (2 m, 3 H, 2 H, $SiMe_2Ph$) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = –3.2 (q, $SiMe_2Ph$), 16.8 (dt, $^3J_{P,C}$ = 12.5 Hz, C-3), 52.3 (dq, $^2J_{P,C}$ = 5.2 Hz, POMe), 59.4 (dq, $^3J_{C,P}$ = 2.1 Hz, 1-OMe), 127.8, 129.2 (2 d, Ph), 131.2 (dd, $^2J_{P,C}$ = 34.8 Hz, C-2), 133.4 (d, Ph), 137.6 (s, Ph), 143.0 (d, $^1J_{P,C}$ = 215.8 Hz, C-1) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 16.5 ppm. IR (ATR): $\tilde{\nu}$ = 3070–2850 (C–H), 1625 (C=C), 1460, 1430, 1315, 1250 (P=O) cm^{-1}. HRMS (ESI-TOF): calcd. for [M + Na]$^+$ 337.1001; found 337.0986. $C_{14}H_{23}O_4PSi$ (314.4): calcd. C 53.48, H 7.37; found C 53.49, H 7.37.

{(*E*/*Z*)-3-Methoxy-4-[1,4,5,6,8-pentamethoxy-3-(methoxymethoxy)naphthalen-2-yl]buta-1,3-dien-1-yl}dimethyl(phenyl)silane (47): To a cooled (–40 °C) solution of phosphonate **46** (0.79 g, 2.50 mmol) in THF (20 mL) was added KHMDS (0.70 M in toluene, 3.60 mL, 2.50 mmol). The mixture was stirred at this

temperature for 15 min, then cooled to –78 °C, and aldehyde **33** (0.73 g, 2.00 mmol, dissolved in 5 mL of THF) was added dropwise. After 15 min, the cooling bath was removed, and the mixture was stirred at r.t. for 1 h. Then satd. NH_4Cl solution (aq.) and EtOAc were added. The layers were separated, and the aq. phase was extracted with EtOAc (2 ×). The combined organic layers were washed with satd. NaCl solution (aq.), dried with Na_2SO_4, filtered, and concentrated. Column chromatography (silica gel; hexanes/EtOAc, 3:1) provided butadiene **47** [mixture of (*E*)/(*Z*) isomers, 0.82 g, 74 %] as a pale yellow oil. IR (ATR): $\tilde{\nu}$ = 3065–2840 (C–H), 1605 (C=C), 1565, 1455, 1430 cm^{-1}. HRMS (ESI-TOF): calcd. for $[M + Na]^+$ 577.2234; found 577.2224. $C_{30}H_{38}O_8Si$ (554.7): calcd. C 64.69, H 6.90; found C 64.99, H 6.89.

Isomer (*E*)-47: ^1H NMR (400 MHz, $CDCl_3$): δ = 0.41 (s, 6 H, $SiMe_2Ph$), 3.52, 3.53, 3.72, 3.84, 3.87, 3.96, 3.99 (7 s, 3 H each, OMe), 5.18 (s, 2 H, OCH_2), 5.91 (s, 1 H, 4-H), 6.43, 6.53 (2 d, *J* = 18.6 Hz, 1 H each, 1-H, 2-H), 6.66 (s, 1 H, Ar), 7.35–7.40 (m, 3 H, Ph), 7.45–7.60 (m, 2 H, Ph) ppm.

Isomer (*Z*)-47: ^1H NMR (400 MHz, $CDCl_3$): δ = 0.28 (s, 6 H, $SiMe_2Ph$), 3.49, 3.65, 3.83, 3.85, 3.96, 4.00 (6* s, 3 H each, OMe), 5.07 (s, 2 H, OCH_2), 5.79 (s, 1 H, 4-H), 6.46, 6.54 (2 d, *J* = 18.8 Hz, 1 H each, 1-H, 2-H), 6.67 (s, 1 H, Ar), 7.35–7.40 (m, 3 H, Ph), 7.45–7.60 (m, 2 H, Ph) ppm; * one signal for OMe could not be assigned properly.

(*E*)-4-[Dimethyl(phenyl)silyl]-1-[1,4,5,6,8-pentamethoxy-3-(methoxymethoxy)naphthalen-2-yl]but-3-en-2-one (48): To a cooled (0 °C) solution of butadiene **47** (0.68 g, 1.23 mmol) in CH_2Cl_2 (15 mL) was added trichloroacetic acid (TCA, 200 mg, 1.23 mmol). The mixture was stirred at r.t. for 3 h. Then, satd. Na_2CO_3 solution (aq.), water, and CH_2Cl_2 were added. The layers were separated, and the aq. phase was extracted with CH_2Cl_2 (2 ×). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. Column chromatography (silica gel; hexanes/EtOAc, 3:1) provided enone **48** (0.46 g, 68 %) as a pale yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.42 (s, 6 H, $SiMe_2Ph$), 3.47, 3.67, 3.78, 3.81, 3.95, 3.99 (6 s, 3 H each, OMe), 4.16 (s, 2 H, 1-H), 5.20 (s, 2 H, OCH_2), 6.653 (s, 1 H, Ar), 6.656, 7.29 (2 d, *J* = 19.1 Hz, 1 H each, 3-H, 4-H), 7.31–7.39 (m, 3 H, Ph), 7.46–7.49 (m, 2 H, Ph) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = –3.2 (q, $SiMe_2Ph$), 36.5 (t, C-1), 56.8*, 57.6, 61.6, 61.8, 62.3 (5 q, OMe), 96.2 (d, Ar), 99.8 (t, OCH_2), 114.4, 119.8, 125.8 (3 s, Ar), 127.9, 129.4, 133.8 (3 d, Ph), 136.5 (s, Ph), 136.6, 142.5 (2 s, Ar), 142.9 (d, C-3), 144.3 (d, C-4), 147.8, 149.8, 151.2, 152.9 (4 s, Ar), 197.8 (s, C-2) ppm; * signal of higher intensity. IR (ATR): $\tilde{\nu}$ = 3070–2840 (C–H), 1685 (C=O), 1600 (C=C), 1455, 1440, 1425 cm^{-1}. HRMS (ESI-TOF): calcd. for $[M + Na]^+$ 563.2077; found 563.2069. $C_{29}H_{36}O_8Si$ (540.7): calcd. C 64.42, H 6.71; found C 64.45, H 6.79.

Methyl 6-{(*E*)-2-[(*tert*-Butyldimethylsilyl)oxy]-3-methoxy-3-oxoprop-1-en-1-yl}-4-{1-[dimethyl(phenyl)silyl]-3-oxo-4-[1,4,5,6,8-pentamethoxy-3-(methoxymethoxy)naphthalen-2-yl]butyl}-2-methoxy-3-(methoxymethoxy)benzoate (49): To a cooled (–40 °C) and well-stirred solution of aryl iodide **13** (585 mg, 1.03 mmol) in Et_2O (18.0 mL) and THF (4.5 mL) was slowly added *i*PrMgBr (3.00 M in 2-Me-THF, 0.36 mL, 1.03 mmol). To redissolve partially precipitated material, the mixture was quickly warmed to –20 °C and then recooled to –40 °C. Then, a mixture of enone **48** (280 mg, 0.52 mmol dissolved in 5.5 mL of Et_2O), HMPA (0.52 mL, 2.97 mmol), CuI•2LiCl (0.10 M in THF, 0.77 mL), and TMSCl (0.27 mL, 3.20 mmol) was rapidly added to the Grignard reagent. The cooling bath was immediately removed, and the mixture was stirred at r.t. for 30 min. Then satd. NH_4Cl solution (aq.) and EtOAc were added. The layers were separated, and the aq. phase was extracted with EtOAc (2 ×). The combined organic layers were washed with satd. NaCl solution (aq.) and concentrated. The residual oil was dissolved in THF (10 mL), and H_2SO_4 (5 % aq., 2 mL) was added at 0 °C. After completion of the hydrolysis of the silyl enol ether (ca. 20 min, according to TLC), water and EtOAc were added. The layers were separated, and the aq. phase was extracted with EtOAc (2 ×). The combined organic layers were washed with satd. NaCl solution (aq.), dried with Na_2SO_4, filtered, and concentrated. Column chromatography (silica gel; hexanes/EtOAc, 4:1 → 3:1) provided ketone **49** (443 mg, 87 %) as a pale yellow, highly viscous oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.19, 0.20, 0.21 (3 s, 6 H, 3 H, 3 H, $SiMe_2Ph$, $OSiMe_2tBu$), 0.96 (s, 9 H, $OSiMe_2tBu$), 2.77 (dd, *J* = 3.9, 17.7 Hz, 1 H, 3-H), 2.99 (dd, *J* = 10.7, 17.7 Hz, 1 H, 3-H), 3.33, 3.45 (2 s, 3 H each, OMe), 3.53 (dd, *J* = 3.9, 10.7 Hz, 1 H, 4-H), 3.55, 3.60, 3.73, 3.76, 3.77 (5 s, 3 H each, OMe), 3.79 (s, 2 H, 1-H), 3.81, 3.90, 3.95 (3 s, 3 H each, OMe), 5.09 (s, 4 H, OCH_2), 6.37 (s, 1 H, 1′-H), 6.56 (s, 1 H, Ar), 6.61 (s, 1 H, Ar), 7.22–7.32 (m, 3 H, Ph), 7.36–7.41 (m, 2 H, Ph) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = –5.7, –5.02, –4.99, –4.3 (4 q, $OSiMe_2tBu$, $SiMe_2Ph$), 18.1, 25.4 (s, q, $OSiMe_2tBu$), 22.9* (d, C-4), 39.4 (t, C-1), 41.9 (t, C-3), 51.6, 52.0, 56.66, 56.70, 57.3, 57.6, 61.3, 61.4, 61.7, 61.8 (10 q, OMe), 96.1 (d, Ar), 98.7, 99.5 (2 t, OCH_2), 114.3 (s, Ar), 118.2 (d, C-1′), 119.7 (s, Ar), 122.7 (d, Ar), 124.7, 125.7 (2 s, Ar), 127.5 (d, Ph), 128.9 (s, Ar), 129.1, 133.9 (2 d, Ph), 136.5 (s, Ar), 136.6 (s, Ph), 139.7, 142.3 (2 s, Ar), 142.4 (s, C-2′), 145.8, 147.5, 149.7, 150.2, 151.0, 152.8 (6 s, Ar), 164.4, 167.5 (2 s, C=O), 207.9 (s, C-2) ppm. IR (ATR): $\tilde{\nu}$ = 2975–2855 (C–H), 1730 (C=O), 1635, 1605 (C=C), 1560 cm^{-1}. HRMS (ESI-TOF): calcd. for $[M + Na]^+$ 1003.3944; found 1003.3982. $C_{50}H_{68}O_{16}Si_2$ (981.2): calcd. C 61.20, H 6.99; found C 61.43, H 6.55.

Methyl 6-{(*E*)-2-[(*tert*-Butyldimethylsilyl)oxy]-3-methoxy-3-oxoprop-1-en-1-yl}-4-{1-[dimethyl(phenyl)silyl]-3-oxo-4-[1,4,6-trimethoxy-3-(methoxymethoxy)-5,8-dioxo-5,8-dihydronaphthalen-2-yl]butyl}-2-methoxy-3-(methoxymethoxy)benzoate (50): To a cooled (0 °C) solution of ketone **49** (440 mg, 0.45 mmol) in MeCN (10.0 mL) and H_2O (2.5 mL) was added DDQ (135 mg, 0.59 mmol) in one portion. After the mixture had been kept at this temperature for 20 min, water and EtOAc were added. The layers were separated, and the aq. phase was extracted with EtOAc (3 ×). The combined organic layers were washed with satd. NaCl solution (aq.), dried with Na_2SO_4, filtered, and concentrated. The residue was filtered through a plug of Al_2O_3 with EtOAc as eluent and concentrated to provide ketone **50** (388 mg, 91 %) as a yellow/orange resin. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.195, 0.198, 0.22, 0.25 (4 s, 3 H each, $SiMe_2Ph$, $OSiMe_2tBu$), 0.97 (s, 9 H, $OSiMe_2tBu$), 2.75 (dd, *J* = 4.0, 17.7 Hz, 1 H, 3-H), 3.03 (dd, *J* = 10.8, 17.7 Hz, 1 H, 3-H), 3.28, 3.47 (2 s, 3 H each, OMe), 3.53 (dd, *J* = 4.0, 10.8 Hz, 1 H, 4-H), 3.587, 3.593, 3.76 (3 s, 3 H each, OMe), 3.78* (2 s, 3 H, 2 H, OMe, 1-H), 3.81, 3.82 (2 s, 3 H each, OMe), 5.04, 5.05 (AB system, J_{AB} = 5.6 Hz, 2 H, OCH_2), 5.06, 5.07 (AB system, J_{AB} = 5.0 Hz, 2 H, OCH_2), 5.95 (s, 1 H, 6″-H), 6.35 (d, *J* = 0.7 Hz, 1 H, 1′-H), 6.62 (s, 1 H, Ar), 7.30–7.36 (m, 3 H, Ph), 7.42–7.46 (m, 2 H, Ph) ppm; * signals are overlapping. ^{13}C NMR (126 MHz, $CDCl_3$): δ = –5.8, –4.99, –4.95, –4.2 (4 q, $OSiMe_2tBu$, $SiMe_2Ph$), 18.2, 25.4 (s, q, $OSiMe_2tBu$), 23.1* (d, C-4), 39.1 (t, C-1), 42.6 (t, C-3), 51.6, 52.1, 56.2, 57.55, 57.57, 61.28, 61.31, 61.9 (8 q, OMe), 98.8, 99.6 (2 t, OCH_2), 110.1 (d, C-6″), 117.9 (d, C-1′), 120.2 (s, Ar), 122.8 (d, Ar), 124.5, 125.0, 126.8 (3 s, Ar), 127.7, 129.3 (2 d, Ph), 132.9 (s, Ar), 134.0 (d, Ph), 136.5 (s, Ph), 139.1 (s, Ar), 142.6 (s, C-2′), 146.1, 149.7, 150.2, 155.0, 155.7, 159.1 (6 s, Ar), 164.4, 167.4 (2 s, C=O), 178.9, 183.3 (2 s, C-8″, C-5″), 206.0 (s, C-2) ppm; * broad signal. IR (ATR): $\tilde{\nu}$ = 3000–2855 (C–H), 1730 (C=O), 1680, 1645, 1630 (C=C), 1590, 1555, 1460, 1435 cm^{-1}. HRMS (ESI-TOF): calcd. for $[M + Na]^+$ 973.3474; found 973.3497. $C_{48}H_{62}O_{16}Si_2$ (951.2): calcd. C 60.61, H 6.57; found C 60.70, H 6.66.

Methyl 6-{(*E*)-2-[(*tert*-Butyldimethylsilyl)oxy]-3-methoxy-3-oxoprop-1-en-1-yl}-4-[dimethyl(phenyl)silyl]-4′,7′,8,9′-tetramethoxy-5′,8′-dioxo-5′,8′-dihydro-3′*H*-spiro[chroman-2,2′-naphtho-

[2,3-*b*]furan]-7-carboxylate (51): To a cooled (–25 °C) solution of ketone **50** (385 mg, 0.41 mmol) in MeCN (22.5 mL) was added TfOH (12 mg, 80 µmol). The mixture was warmed up to +5 °C over 2 h. Then satd. Na_2CO_3 solution (aq.), water and EtOAc were added. The layers were separated, and the aq. phase was extracted with EtOAc (3 ×). The combined organic layers were washed with satd. NaCl solution (aq.), dried with Na_2SO_4, filtered, and concentrated. Column chromatography (silica gel; CH_2Cl_2/Et_2O, 10:1) provided spiroketal **51** (*dr* > 20:1, 280 mg, 82 %) as a yellow solid. M.p. 79–83 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.17, 0.96 (2 s, 6 H, 9 H, $OSiMe_2tBu$), 0.34, 0.43 (2 s, 3 H each, $SiMe_2Ph$), 2.15 (t, $J \approx 13.7$ Hz, 1 H, 3′-H), 2.26 (dd, $J \approx 7.2$, 14.0 Hz, 1 H, 3′-H), 3.02 (dd, $J \approx 7.2$, 12.3 Hz, 1 H, 4′-H), 3.32, 3.59 (AB system, J_{AB} = 17.4 Hz, 1 H each, 3-H), 3.54, 3.60, 3.69, 3.79, 3.80, 3.87 (6 s, 3 H each, OMe), 5.93 (s, 1 H, 6-H), 6.33 (s, 1 H, 1′′-H), 6.72 (s, 1 H, 5′-H), 7.32–7.40 (m, 3 H, Ph), 7.47–7.51 (m, 2 H, Ph) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = –5.0, 18.2, 25.5 (q, s, q, $OSiMe_2tBu$), –4.2, –3.7 (2 q, $SiMe_2Ph$), 20.3 (d, C-4′), 32.9 (t, C-3′), 39.7 (t, C-3), 51.5, 52.1, 56.2, 60.7, 61.0, 61.6 (6 q, OMe), 109.6 (s, C-2), 109.8 (d, C-6), 117.9 (d, C-1′′), 119.2 (s, Ar), 124.2 (d, C-5′), 125.2, 125.3, 126.4, 127.2, 127.3 (5 s, Ar), 128.1, 129.6, 133.6 (3 d, Ph), 136.8 (s, Ph), 141.8 (s, Ar), 142.5 (s, C-2′′), 143.5, 146.2, 152.9, 155.1 (4 s, Ar), 159.2 (s, C-7), 164.4, 167.3 (2 s, C=O), 179.2 (s, C-8), 183.7 (s, C-5) ppm. IR (ATR): $\tilde{\nu}$ = 2950–2855 (C–H), 1730 (C=O), 1680, 1645, 1635 (C=C), 1590 cm^{-1}. HRMS (ESI-TOF): calcd. for $[M + Na]^+$ 867.2844; found 867.2884. $C_{44}H_{52}O_{13}Si_2$ (845.0): calcd. C 63.54, H 6.20; found C 63.05, H 6.30.

Methyl 4-(Dimethyl(phenyl)silyl)-6-formyl-4′,7′,8,9′-tetramethoxy-5′,8′-dioxo-5′,8′-dihydro-3′*H*-spiro[chroman-2,2′-naphtho-[2,3-*b*]furan]-7-carboxylate (52): To a cooled (–78 °C) solution of spiroketal **51** (25 mg, 30 µmol) in THF (3.0 mL) was added TBAF (50 µL, 50 µmol, 1.0 M in THF). The mixture was stirred at this temperature for 15 min. The cooling bath was removed, and satd. NaCl solution (aq.) and EtOAc were added. After the mixture was warmed to r.t., the layers were separated, and the aq. phase was extracted with EtOAc (2 ×). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. Column chromatography (silica gel; CH_2Cl_2/Et_2O, 10:1) provided spiroketal **52** (10 mg, 51 %) as a yellow solid. Melting range: 105–115 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.41, 0.43 (2 s, 3 H each, $SiMe_2Ph$), 2.21 (dd, J = 12.7, 14.1 Hz, 1 H, 3-H), 2.40 (dd, J = 7.2, 14.1 Hz, 1 H, 3-H), 3.12 (ddd, J = 0.7, 7.2, 12.7 Hz, 1 H, 4-H), 3.42, 3.66 (AB system, J_{AB} = 17.5 Hz, 1 H each, 3′-H), 3.60, 3.68, 3.82, 3.90, 3.92 (5 s, 3 H each, OMe), 5.95 (s, 1 H, 6′-H), 7.25 (d, J = 1.0 Hz, 1 H, 5-H), 7.40–7.46 (m, 3 H, Ph), 7.53–7.56 (m, 2 H, Ph), 9.55 (s, 1 H, CHO) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = –4.7, –3.7 (2 q, $SiMe_2Ph$), 20.3 (d, C-4), 32.5 (t, C-3), 39.7 (t, C-3′), 52.8, 56.3, 60.9, 61.2, 61.9 (5 q, OMe), 109.5 (s, C-2), 109.8 (d, C-6′), 119.6, 125.7 (2 s, Ar), 126.3 (s, C-6), 126.9, 127.0, 127.5 (3 s, Ar), 127.9 (d, C-5), 128.4, 130.0, 133.9 (3 d, Ph), 136.4 (s, Ph), 141.8, 146.7, 149.7, 153.0, 154.9 (5 s, Ar), 159.3 (s, C-7′), 166.7 (s, C=O), 179.1 (s, C-8′), 183.6 (s, C-5′), 189.2 (d, CHO) ppm. IR (ATR): $\tilde{\nu}$ = 3410 (OH, hydrate), 3020–2850 (C–H), 1730 (C=O), 1465 cm^{-1}. HRMS (ESI-TOF): calcd. for $[M + Na]^+$ 681.1768; found 681.1804. $C_{35}H_{34}O_{11}Si$ (658.7): calcd. C 63.82, H 5.20; found C 63.40, H 5.15.

Methyl 4′-[Dimethyl(phenyl)silyl]-4,7,9,10′-tetramethoxy-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 (53): To a solution of **51** (145 mg, 0.17 mmol) in dry CH_2Cl_2 (8.6 mL) in a 50 mL pressure tube was added HBF_4•Et_2O (0.23 mL, 1.70 mmol). The mixture was heated to 50 °C for 30 min. Then, satd. Na_2CO_3 solution (aq.), water, and CH_2Cl_2 were added. The layers were separated, and the aq. phase was extracted with CH_2Cl_2 (2 ×). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. Column chromatography (silica gel; CH_2Cl_2/Et_2O, 5:1) provided a yellow solid (99 mg), which contained spiroketal **53** (71 %) and naphthofuran derivative **54** (12 %, tentatively assigned), as judged by ^{1}H NMR spectroscopy. Melting range: 110–130 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.41 (s, 6 H, $SiMe_2Ph$), 2.27 (dd, $J \approx 11.9$, 14.3 Hz, 1 H, 3′-H), 2.43 (dd, $J \approx 7.9$, 14.3 Hz, 1 H, 3′-H), 3.19 (dd, $J \approx 7.5$, 10.9 Hz, 1 H, 4′-H), 3.41, 3.71 (AB system, J_{AB} = 17.6 Hz, 1 H each, 3-H), 3.60, 3.70, 3.82, 3.91, 3.92 (5 s, 3 H each, OMe), 5.95 (s, 1 H, 6-H), 6.91 (d, J = 1.1 Hz, 1 H, 5′-H), 7.08 (s, 6′-H), 7.40–7.47 (m, 3 H, Ph), 7.49–7.53 (m, 2 H, Ph) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = –4.7, –3.7 (2 q, $SiMe_2Ph$), 21.7 (d, C-4′), 32.7 (t, C-3′), 39.7 (t, C-3), 52.8, 56.3, 60.8, 61.2, 61.7 (5 q, OMe), 109.5 (s, C-2), 109.9 (d, C-6), 112.2 (d, C-6′), 114.0, 119.6 (2 s, Ar), 122.3 (d, C-5′), 125.6, 127.1 (2 s, Ar), 128.4 (d, Ph), 129.4 (s, Ar), 130.1, 133.8 (2 d, Ph), 135.3 (s, Ar), 136.0 (s, Ph), 141.7, 141.9 (2 s, Ar, C-7′), 147.1, 151.1, 153.0, 155.0 (4 s, Ar), 156.8 (s, C-9′), 159.2 (s, C-7), 160.9 (s, C=O), 179.2 (s, C-8), 183.6 (s, C-5) ppm. IR (ATR): $\tilde{\nu}$ = 3050–2850 (C–H), 1740 (C=O), 1680, 1645, 1625 (C=C), 1590 cm^{-1}. HRMS (ESI-TOF): calcd. for $[M + Na]^+$ 721.1717; found 721.1741. $C_{37}H_{34}O_{12}Si$ (698.7): calcd. C 63.60, H 4.90; found C 63.47, H 4.96.

Methyl 4′-[Dimethyl(phenyl)silyl]-4,9,10′-trihydroxy-7-methoxy-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 (55): To a cooled (–78 °C) solution of spiroketal **53** (72 mg, 0.10 mmol) in CH_2Cl_2 (10 mL) was added BBr_3 (1.0 M in CH_2Cl_2, 0.62 mL, 0.62 mmol). The mixture was warmed up to –30 °C over 90 min, and water was added. The layers were separated, and the aq. phase was extracted with CH_2Cl_2 (3 ×). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. Column chromatography (silica gel; CH_2Cl_2/Et_2O, 3:1) provided spiroketal **55** (36 mg, 53 %) as a red solid. Melting range: 260–265 °C. ^{1}H NMR (700 MHz, $CDCl_3$): δ = 0.41 (s, 6 H, $SiMe_2Ph$), 2.22 (t, $J \approx 14.3$ Hz, 1 H, 3′-H), 2.40 (dd, $J \approx 7.1$, 14.0 Hz, 1 H, 3′-H), 3.26 (dd, $J \approx 7.1$, 12.5 Hz, 1 H, 4′-H), 3.36, 3.72 (AB system, J_{AB} = 18.2 Hz, 1 H each, 3-H), 3.90, 3.93 (2 s, 3 H each, OMe), 6.15 (s, 1 H, 6-H), 6.74 (s, 1 H, 5′-H), 7.16 (s, 1 H, 6′-H), 7.38–7.47 (m, 3 H, Ph), 7.52–7.57 (m, 2 H, Ph), 10.92, 12.24, 13.01 (3 s, each 1 H, OH) ppm. ^{13}C NMR (176 MHz, $CDCl_3$): δ = –4.5, –3.3 (2 q, $SiMe_2Ph$), 21.2 (d, C-4′), 33.0 (t, C-3′), 39.4 (t, C-3), 52.9 (q, 7-OMe), 56.7 (q, OMe), 105.6 (s, C-9a′), 106.3 (s, C-4a), 110.0 (d, C-6), 110.3 (s, C-2), 112.9 (d, C-6′), 113.8 (s, Ar), 117.7 (d, C-5′), 123.0, 127.0 (2 s, Ar), 128.4, 130.0, 133.8 (3 d, Ph), 135.2 (s, Ar), 136.4 (s, Ph), 141.0 (s, Ar), 141.1 (s, C-7′), 150.2 (s, Ar), 150.9 (s, C-10′), 153.6 (s, C-4), 159.0 (s, C-9′), 159.9 (s, C-7), 160.5 (s, C=O), 164.8 (s, Ar), 178.8 (s, C-8), 183.5 (s, C-5) ppm. IR (ATR): $\tilde{\nu}$ = 3050–2850 (C–H), 1735 (C=O), 1685, 1610, 1430 cm^{-1}. HRMS (ESI-TOF): calcd. for $[M + Na]^+$ 679.1248; found 679.1266. $C_{34}H_{28}O_{12}Si$ (656.7): calcd. C 62.19, H 4.30; found C 62.19, H 4.30.

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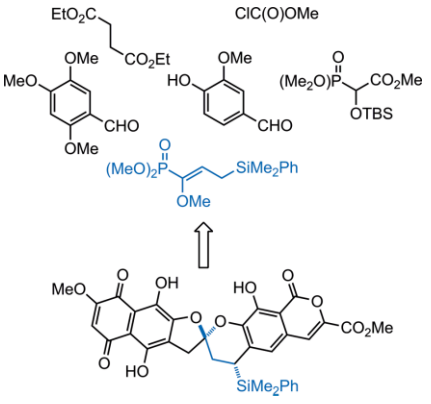

Condense and merge! A concise strategy for the highly convergent assembly for rubromycin-type "aromatic" spiroketals with the help of allylic phosphonates as central C_3 building blocks is presented.

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