Model Studies for the Synthesis of Heliquinomycin: Preparation of New Spiroketals

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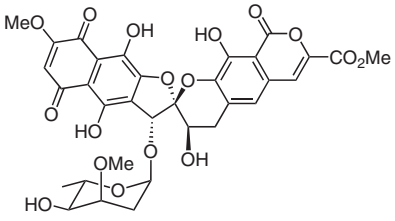
Abstract: New model compounds were investigated within our efforts to synthesize the natural product heliquinomycin. We could provide good evidence that electronic effects prevent the spiroketal formation of compounds such as **5** incorporating an isocoumarin moiety. As a consequence, precursors **16** and **26** were prepared, which do not exert the strong electron-withdrawing effect of the methoxycarbonyl group present in **5**. Dihydroisocumarin derivative **10** and phthalide **25** were coupled by Heck reactions with enone **4** to provide the required precursors **16** and **26**. After reductive debenzylation the resulting intermediates were treated with anhydrous hydrochloric acid in alcohols to give spiroketals **18**–**20** and **28**, **29** in reasonable yields. The spiroketalizations occur under thermodynamic control affording products with the hydroxyl group in a *trans*-relationship with respect to the pyran oxygen atom. Attempts to oxidatively convert dihydroisocumarin **19** into an isocoumarin derivative failed. In one attempt a ring contraction to new spiroketal **24** was observed.

Key words: acetals, spiro compounds, Heck reaction, natural products, heliquinomycin

Heliquinomycin (**1**), first isolated by Chino et al.[1] from *Streptomyces sp.* MJ 929-SF2, belongs to a family of natural metabolites called rubromycins, which exhibit antibiotic, cytostatic, and antimicrobial activity. The basic structure of the rubromycin family[2] consists of a highly functionalized naphthoquinone moiety, which is linked to an isocoumarin unit through a 5,6-spiroketal system (Figure 1). Heliquinomycin (**1**) is a selective inhibitor of human DNA-helicase[3]and unique from other members of the rubromycin family by the fact that the 3′-hydroxy functionality is further linked to the rare carbohydrate L-cymarose. In spite of these intriguing structural and biological activities of this molecule, apart from several model studies carried out by various research groups,[4] only a single total synthesis of the aglycon of racemic heliquinomycin has been reported in the literature.[5] In addition to this, the first total synthesis of γ-rubromycin, was recently completed by Kita and co-workers employing Pummerer-type rearrangement reactions as key steps.[6]

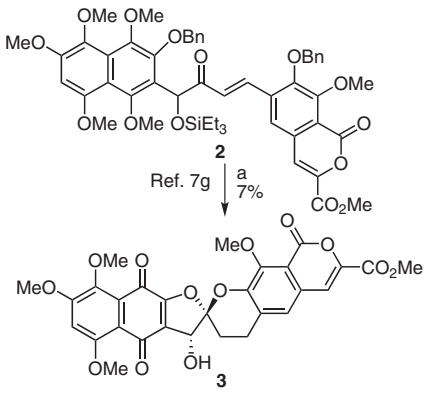
Our group has been actively involved for the past few years in synthesizing various building blocks such as a highly functionalized naphthaldehyde unit[7a] that may serve as precursor to the 'western hemisphere' of the natural product, derivatized 6-iodoisocoumarin unit **5**[7b,c] for



heliquinomycin (**1**)

Figure 1 A prominent member of the rubromycin family: heliquinomycin (**1**)

the 'eastern side', and the carbohydrate L-cymarose[7d] for the 'southern part' of 5,6-spiroketal linkage. First model studies were also carried out, initially to verify that the spiroketalization of phenolic hydroxyl groups is a viable strategy to obtain bis-benzannulated spiroketals.[7e–f] With these preliminary studies and syntheses of various building blocks in hand, we wish to describe in the present report the serious difficulties encountered during model studies with isocoumarin building block **5**, the identification of various factors inhibiting spiroketalization, the successful thermodynamically controlled spiroketalization with the newly synthesized dihydroisocoumarin moiety, and our endeavors to reinstall the double bond from the dihydroisocoumarin unit at the last stage of the synthesis. Finally, an alternative strategy employing a functionalized phthalide intermediate is described. This moiety should enable the construction of the isocoumarin ring in the later stage of the synthesis.



Dimethylated 3'-hydroxy-β-rubromycin

Scheme 1 Spiroketalization of the advanced intermediate **2**. *Reagents and conditions*: a) *i*: Pd/C, H_2, MeOH, r.t., 2 d, *ii*: concd HCl (cat.), *i*-PrOH, 40 °C, 2 d.

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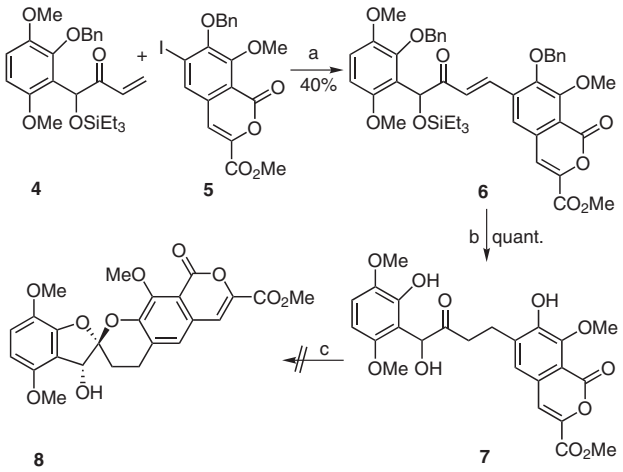
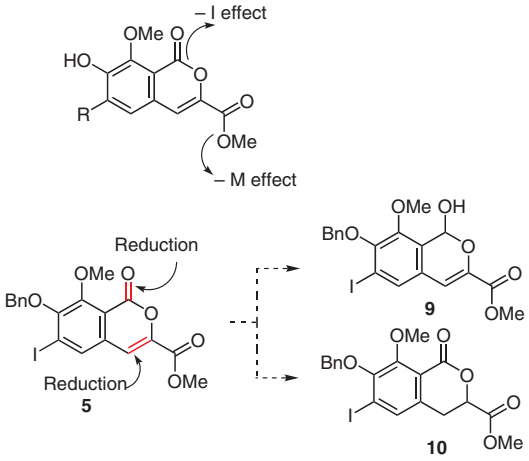
In our earlier communication,[7f] we had described the successful spiroketalization of a bisphenolic ketone derived from the pentamethoxy-substituted naphthaldehyde and simple iodinated benzene derivatives, which confirmed our strategy towards the planned total synthesis of heliquinomycin (**1**). After completion of these model studies, the advanced precursor **2** with the newly synthesized 6-iodoisocoumarin in the eastern part was investigated.[7g] Unfortunately, the expected spiroketal **3** was isolated only in a very low yield of 7% (Scheme 1).

Certainly, the spiroketalization of **2** is not smooth and inhibited by unknown effects at this stage. Therefore, to ascertain and overcome the factors inhibiting the spiroketalization, once again we resumed our model studies with α-siloxyenone **4** derived from 2,6-(dimethoxy)benzaldehyde[7f] as shown in Scheme 2. However, all our attempts to transform bisphenolic ketone **7** into spiroketal **8** under various reaction conditions using Brønsted or Lewis acids resulted either in the recovery or complete decomposition of **7** affording unidentifiable mixtures.



Scheme 2 Attempted spiroketalization with compound **7** containing an isocoumarin fragment. *Reagents and conditions*: a) $Pd(OAc)_2$ (10 mol%), $NaHCO_3$, *n*-Bu_4NCl, 3 Å MS, DMF, 60 °C, 17 h; b) Pd/C (10 mol%), H_2 (1 atm), MeOH, r.t., 3 d; c) Brønsted or Lewis acids (*p*-TsOH·H_2O, $MgSO_4$, Amberlyst-15, aq HCl, etc.).

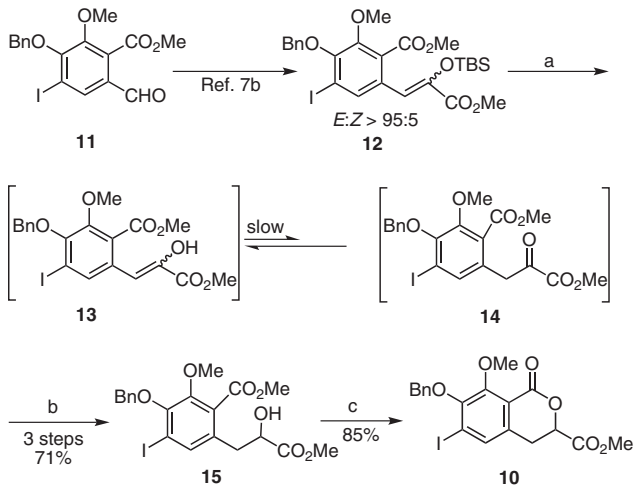
Meanwhile Kozlowski et al.[4f] reported a failed attempt to spiroketalize an advanced precursor with an isocoumarin fragment in their endeavor towards the synthesis of purpuromycin. They concluded from their model studies that the presence of electron-withdrawing groups in the isocoumarin unit dramatically diminishes the nucleophilicity of the phenolic hydroxyl group engaged in the spiroketalization. Our results are in complete agreement with Kozlowski's observation. The negative mesomeric and inductive effects exerted by the functional groups present in the isocoumarin ring dramatically decelerate the ring closure (Scheme 3). Hence we wanted to increase the nucleophilicity of the phenolic hydroxyl group by selectively breaking the conjugation of an ester or lactone carbonyl group using reducing agents. Disappointingly, all our attempts to selectively prepare compounds such as **9** or **10** in high yields from **5** were not successful.



Scheme 3 Electronic factors diminishing the nucleophilicity of the phenolic hydroxyl group in the isocoumarin unit.

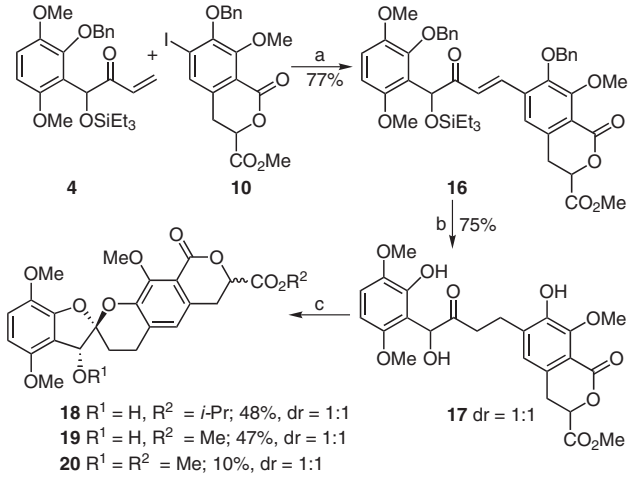
At this point, we developed an alternative strategy to reduce the double bond in the isocoumarin ring of **5** at an earlier stage of our 6-iodoisocoumarin synthesis as shown in Scheme 4. We assumed that the Wittig–Horner adduct **12** derived from highly functionalized carbaldehyde **11**, available from vanillin according to our earlier reported procedure,[7b] can be desilylated under mild conditions to provide enol **13**, which on tautomerization should afford α-keto ester **14**. This intermediate should be reduced selectively to the α-hydroxy ester **15** that can undergo lactonization to **10** by acid- or base-catalyzed reaction. Gratifyingly, the HW-adduct **12** was successfully desilylated within a few minutes to give the enol **13** by using a mixture of TBAF/AcOH in 1:1 ratio at –78 °C. All our attempts to isolate the desilylated adduct in its keto or enol form resulted in the fast intramolecular cyclization to 6-iodoisocoumarin **5**. Therefore, we reduced the keto group of α-keto ester **14** in situ directly after its generation by using sodium borohydride. This protocol afforded the α-hydroxy ester **15** in an overall yield of 71%. The intramolecular lactonization required fine tuning of the reaction conditions and after several trials we could successfully transform α-hydroxy ester **15** using *p*-toluenesulfonic acid as catalyst to provide 6-iododihydroisocoumarin **10** in good yield (Scheme 4).

Spiroketal precursor **17** was prepared according to our earlier standard conditions. Thus, TES-protected enone **4** was coupled with newly synthesized 6-iododihydroisocoumarin **10** under palladium catalysis[8] to afford **16** in good yield. A slight modification of the palladium-catalyzed hydrogenation of **16** at 8 atmospheres decreased the reaction time drastically from 3 days to 5 hours (compare Scheme 2) without compromising the yield of bisphenolic ketone **17** (Scheme 5). Due to the stereogenic center in the isocoumarin part, the product was obtained as a 1:1 mixture of two diastereomers. In one of our initial experiments, the precursor **17**, on treatment with anhydrous



Scheme 4 Synthesis of 6-iododihydroisocoumarin **10**. *Reagents and conditions*: a) TBAF/AcOH (1:1), THF, –78 °C, 5 min; b) $NaBH_4$ (1.1 equiv), THF, –78 to –30 °C, 5 h; c) *p*-TsOH·H_2O (1.0 equiv), toluene, 70 °C, 2 h.

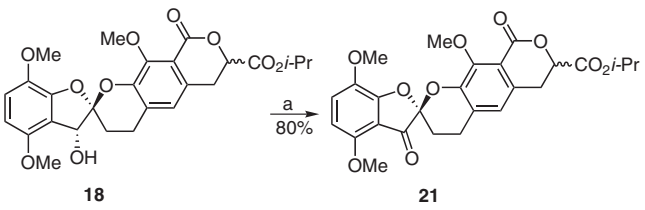
hydrochloric acid, generated in situ from a mixture of acetyl chloride and isopropyl alcohol, underwent spontaneous spiroketalization to afford the spiroketal **18** as a mixture of diastereomers in 48% yield.



Scheme 5 Synthesis and spiroketalization of precursor **17** with a dihydroisocoumarin fragment. *Reagents and conditions*: a) $Pd(OAc)_2$ (10 mol%), $NaHCO_3$, *n*-Bu_4NCl, DMF, 60 °C, 16 h; b) H_2 (8 atm), Pd/C (10 mol%), MeOH, r.t., 5 h; c) AcCl (10 equiv), *i*-PrOH or MeOH, $HC(OMe)_3$ (2 equiv), 60 °C, 16–48 h.

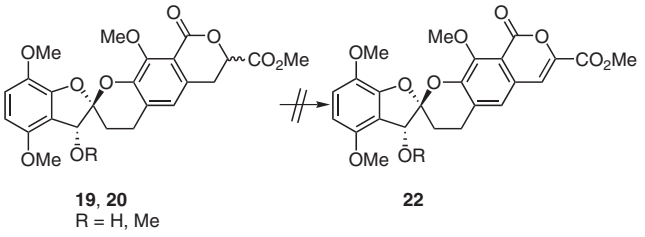
As found in our earlier studies, the thermodynamically more stable *trans*-5,6-spiroketal linkage was formed. Under these reaction conditions, we also observed transesterification in the lactone ring of **18** to provide the isopropyl ester (Scheme 5). Therefore, our subsequent spiroketalization of **17** was carried out using methanol as solvent and we were pleased to obtain the expected spiroketal **19** as a mixture of diastereomers in 47% yield along with another product **20** in which the benzylic hydroxyl group at C-3′ of the spirolinkage was solvolytically displaced by MeOH (also see ref.[7f]). The spiroketals **18**, **19**, and **20** were completely characterized by spectroscopic techniques and the diastereomeric ratio was found to be approximately 1:1. The diastereomeric mixture of **19** should not pose serious threat to our synthetic endeavor since the stereogenic center in the lactone ring will vanish when the required double bond in the dihydroisocoumarin moiety is reinstalled. With precursor **17** we performed the first successful spiroketalization of a heliquinomycin model compound including an isocoumarin derivative on the eastern side.

The next task in completing the model studies was the regeneration of the double bond in the dihydroisocoumarin moiety of spiroketals **18** and **19**. In one of our preliminary experiments, treatment of spiroketal **18** with DDQ in refluxing chlorobenzene resulted in the oxidation of 3′-hydroxyl group to afford the spiroketone **21** instead of the expected dehydrogenation of the lactone ring (Scheme 6).



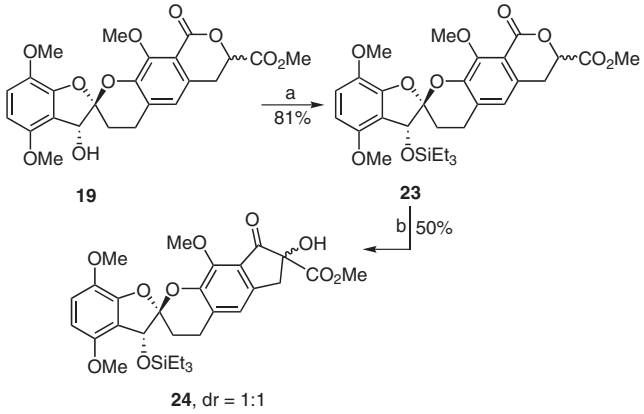
Scheme 6 Oxidation of **18** leading to compound **21**. *Reagents and conditions*: a) DDQ (6.0 equiv), PhCl, 140 °C, 16 h.

Other test reactions to regenerate the double bond in spiroketal **19** using *N*-bromosuccinimide bromination followed by elimination resulted in an unidentifiable mixture of products from which we could not detect the desired product **22**. Our oxidation experiments of spiroketals **19** or **20** with mild oxidizing agents such as DDQ, MnO_2, and IBX also resulted either in the recovery of starting material or in the complete decomposition of spiroketals **19** or **20** leading to unidentifiable products (Scheme 7).



Scheme 7 Attempted experiments to regenerate the double bond in **19**, **20** under various conditions. *Reagents and conditions*: a) R = H, *i*: NBS, AIBN, CCl_4, reflux, 3 h, *ii*: Et_3N, reflux, 3 h; b) R = H, DDQ, toluene, 100 °C, 24 h; c) R = Me, MnO_2, THF, reflux, 22 h; d) R = Me, IBX, PhF, 85 °C, 48 h.

Our final experiment to regenerate the double bond was performed with triethylsilyl-protected spiroketal **23** by deprotonation with lithium hexamethyldisilazane and (attempted) selenylation. Unexpectedly, a ring contraction afforded the α-hydroxycyclopentanone spiroketal **24** as a 1:1 mixture of diastereomers. Apparently, the intermediate ester enolate attacks the neighboring lactone carbonyl

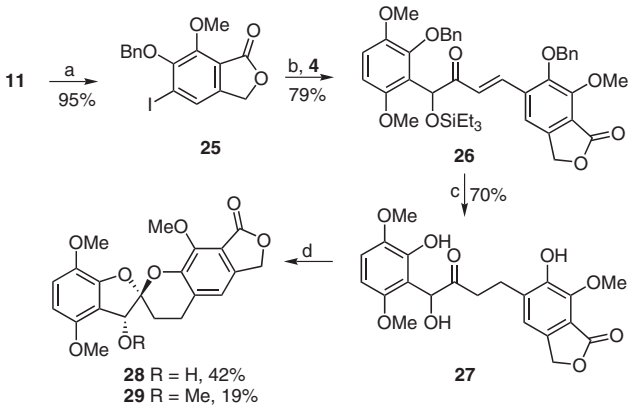


Scheme 8 Unexpected ring contraction of lactone **23** to hydroxy cyclopentanone **24**. *Reagents and conditions*: a) Et_3SiCl, *i*-Pr_2NEt, DMF, r.t., 15 h; b) *i*: LiHMDS (1.2 equiv), THF, –78 °C, 20 min; *ii*: PhSeCl (1.5 equiv), THF, –78 to 0 °C, 4 h.

group leading to cyclopentanone derivative **24** (Scheme 8).

The model studies with the dihydroisocoumarin system showed that the thermodynamically controlled spiroketalization is feasible by fine tuning of electronic and nucleophilic factors present in the isocoumarin ring system. Nevertheless, complications arose during purification (formation of diastereomers) and in particular during attempted regeneration of the double bond in spiroketals **18**, **19**, and **20**. These problems urged us to conceive an alternative synthetic strategy. Based on our earlier experiences, the proposed new approach should enable the construction of a 5,6-spiroketal moiety without an additional stereogenic center and also provide a possible route to regenerate the isocoumarin system in a later stage of the synthesis. In our new approach via phthalide intermediate **25** we hoped to fulfill the necessary requirements (Scheme 9).

Similar to the synthesis of isocoumarin and dihydroisocoumarin building blocks, we began our sequence towards the phthalide moiety with highly functionalized benzaldehyde intermediate **11**. Reduction of this aldehyde with $NaBH_4$ in ethanol afforded directly 5-iodophthalide **25**. α-Triethylsiloxy enone **4** was coupled with **25** by palladium-catalyzed Heck reaction under Jeffery's ligand-free conditions at 60 °C to provide the adduct **26** in 79% yield. Hydrogenation of this compound to saturate the double bond and to cleave all the protecting groups resulted in the formation of the desired spiroketalization precursor bis(phenolic) hydroxyketone **27** in 70% yield. Spiroketalization of this compound was performed following similar reaction conditions as described for the model studies with the dihydroisocoumarin fragment. Thus, mixing acetyl chloride with anhydrous methanol in situ generates anhydrous hydrochloric acid, which catalyzes the spiroketalization of precursor **27** to give 5,6-spiroketals **28** and **29** in 42 and 19% yield, respectively.



Scheme 9 Synthesis of phthalide spiroketals **28** and **29**. *Reagents and conditions*: a) $NaBH_4$, EtOH, r.t., 1 h; b) $Pd(OAc)_2$ (10 mol%), $NaHCO_3$, *n*-Bu_4NCl, DMF, 60 °C, 12 h; c) H_2 (8 atm), Pd/C (10 mol%), MeOH, r.t., 5 h; d) AcCl (10 equiv), MeOH, $HC(OMe)_3$, 0 °C to r.t., 25 h.

TLC analysis of the reaction mixture showed distinct spots for both spiroketals **28** and **29** without any trace of diastereomers. Compared to the synthesis of dihydroisocoumarin spiroketal **19** purification was simple in this case and can be easily performed by column chromatography without the need of HPLC. Also, NMR spectroscopy confirmed that only one diastereomer was formed, which is predicted to be the thermodynamically more stable *trans*-5,6-spiroketal **28** according to our earlier preliminary studies (Scheme 9). Starting from spiroketals such as **28**, the future task will be the construction of the isocoumarin system from the five-membered lactone ring.

In summary, we have confirmed that the ketalization to construct the 5,6-spiroketal moiety was the crucial step towards the total synthesis of heliquinomycin (**1**). Our initial model studies with isocoumarin fragment **5** on the eastern hemisphere showed that the spiroketalization is either inefficient or does not take place due to the strongly decreased nucleophilicity of the phenolic hydroxyl group. Breaking the conjugation by synthesizing dihydroisocoumarin **10** enabled the spiroketalization successfully, but the generation of an additional chiral center and the failure to regenerate the double bond from the spiroketal **19** led to abandon this dihydroisocoumarin approach. Another promising strategy via a highly functionalized phthalide intermediate **25**, without the above mentioned complications, afforded 5,6-spiroketals **28** and **29** with exclusive *trans* diastereoselectivity. The conversion of the five-membered lactone ring into the six-membered isocoumarin ring of **22** is currently in progress and construction of the corresponding spiroketals with highly functionalized pentamethoxynaphthaldehyde will be reported in due course.

Reactions involving moisture-sensitive reactants were performed in flame-dried glassware under argon, reagents being added via a syringe. Purchased chemicals were used without further purification. CH_2Cl_2, cyclohexane, PhCl, and MeCN were distilled from CaH_2 and toluene over Na. THF was distilled from sodium benzophenone ketyl. Anhyd DMF was purchased from Aldrich and stored over 4 Å molecular sieves. Products were purified by flash chromatography on silica gel (230–400 mesh, Merck). Preparative HPLC was

carried out on a nucleosil 50–5 column (diameter 32 mm, length 250 mm) and detection was carried out with a Knauer visible UV-detector (λ = 254 nm) and a Knauer refractometer. NMR spectra were recorded on Bruker (AC 250, AM 270, AC 500) and JEOL (Eclipse 500) instruments. Chemical shifts are reported relative to $CHCl_3$ (^1H: δ = 7.24, ^{13}C: δ = 77.0), DMSO (^1H: δ = 2.49, ^{13}C: δ = 39.7) and $SiMe_4$ (^1H: δ = 0.00). The numbering of carbon atoms for NMR assignments for the structures **6**, **7**, **15**, **10**, **16**–**21**, **23**–**29** is depicted in Figure 2.

IR spectra were recorded on a Nicolet spectrometer (FTIR 5 SXC) and MS spectra (EI, FAB) on Finnigan instruments (MAT 711, MAT CH7A and CH5DF). CHN-analyses were performed on a PerkinElmer elemental analyzer. Reported melting points (determined with a Büchi MP 510 apparatus) are uncorrected.

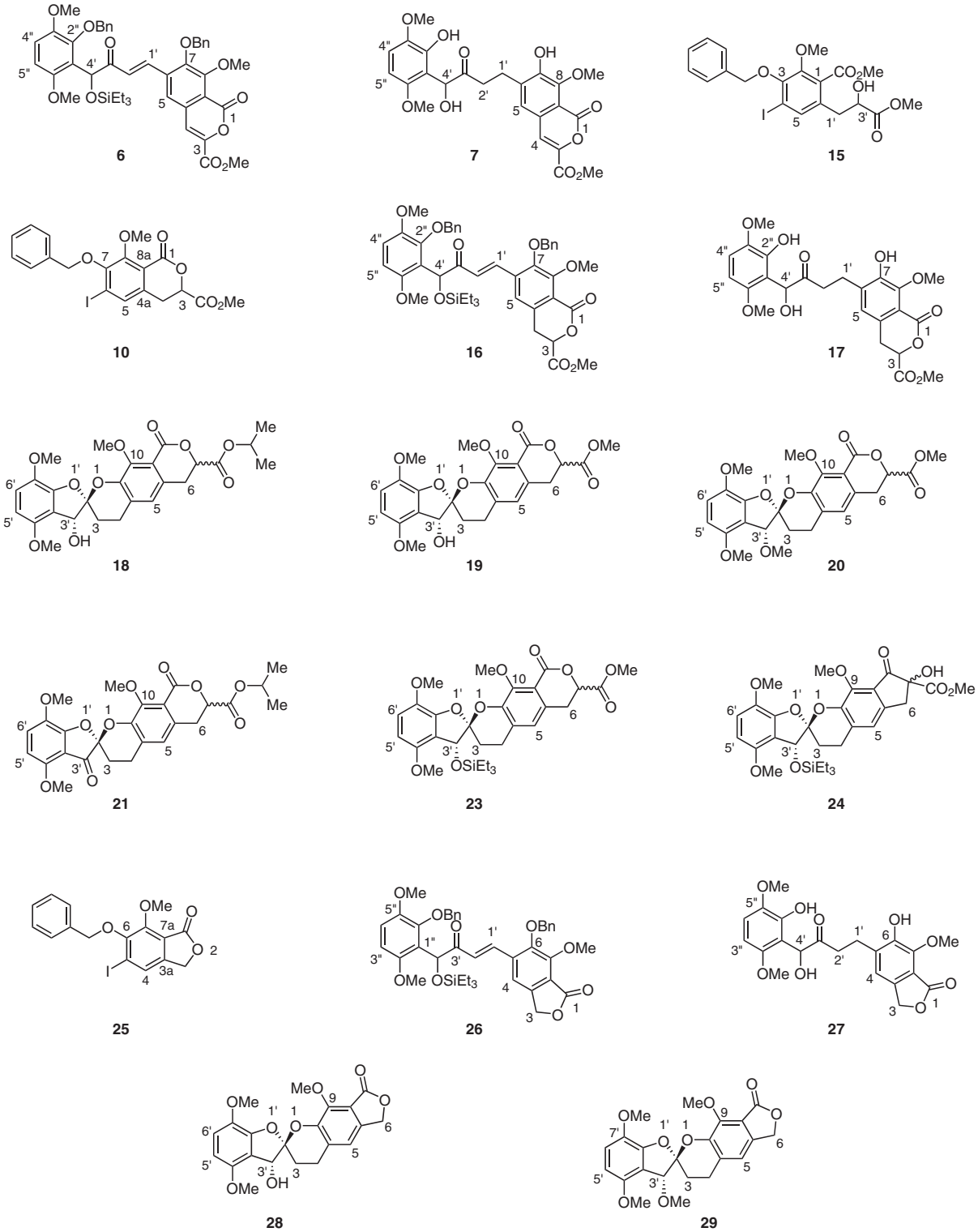


Figure 2 Numbering of carbon atoms for NMR assignments in structures **6**, **7**, **15**, **10**, **16**–**21**, **23**–**29**

Methyl 7-Benzyloxy-6-[4-(2-benzyloxy-3,6-dimethoxyphenyl)-3-oxo-4-(triethylsiloxy)but-1-enyl]-8-methoxy-1-oxo-1*H*-isochromene-3-carboxylate (6)

To a solution of α-triethylsiloxyenone **4** (0.285 g, 0.644 mmol) and 6-iodoisocoumarin **5** (0.315 g, 0.676 mmol) in anhyd DMF (6 mL) were added $Pd(OAc)_2$ (0.014 g, 0.064 mmol), *n*-Bu_4NCl (0.178 g, 0.644 mmol), MS 3Å (0.10 g), and $NaHCO_3$ (0.14 g, 1.60 mmol). The mixture was stirred at 60 °C under argon for 17 h. After cooling the mixture to r.t., it was diluted with EtOAc (50 mL) and washed with H_2O (2 × 25 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were washed with brine (25 mL), and dried ($MgSO_4$). The solvent was filtered, evaporated under reduced pressure, and the crude residue was purified through silica gel column chromatography using hexane–EtOAc (3:1) as eluent to afford the adduct **6**; yield: 0.20 g (40%); yellow foamy liquid; R_f = 0.20 (4:1 hexane–EtOAc).

IR (film): 3030 (=C–H), 2955–2835 (C–H), 2835 (OCH_3), 1745 (C=O), 1690 (C=O), 1590 (C=C), 1490 cm^{-1} (C–C).

^1H NMR (500 MHz, $CDCl_3$): δ = 0.61, 0.87 (q, t, ^3J = 7.8 Hz, 6 H, 9 H, $SiEt_3$), 3.76, 3.79, 3.96, 3.98 (4 s, 3 H each, OMe), 5.01, 5.05 (AB system, $^2J_{A,B}$ = 10.7 Hz, 2 H, OCH_2Ph), 5.06, 5.11 (AB system, $^2J_{A,B}$ = 10.7 Hz, 2 H, OCH_2Ph), 5.67 (s, 1 H, 4′-H), 6.61, 6.87 (2 d, ^3J = 9.1 Hz, 1 H each, 5″-H, 4″-H), 7.07 (s, 1 H, 4-H), 7.15, 7.22 (2 t, ^3J = 7.4 Hz, 1 H, 2 H, Ph), 7.29, 7.33 (2 t, ^3J = 7.3 Hz, 1 H, 2 H, Ph), 7.39–7.45 (m, 6 H, Ph, 5-H, 2′-H), 7.80 (d, ^3J = 16.2 Hz, 1 H, 1′-H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 4.8, 6.8 (t, q, $SiEt_3$), 52.9, 56.1, 56.5, 62.1 (4 q, OMe), 71.7 (d, C-4′), 75.2, 76.4 (2 t, OCH_2Ph), 106.5 (d, C-5″), 112.2 (d, C-5), 113.5 (d, C-4″), 117.1 (s, Ar), 121.2 (d, C-4), 125.4, 127.2 (2 s, Ph), 127.6, 128.0, 128.2, 128.55, 128.6, 128.9 (6 d, Ph), 131.9, 133.4 (2 d, C-2′, C-1′), 136.2, 137.9, 138.1, 142.6, 147.3, 147.4, 151.9, 152.9, 156.0 (9 s, Ph, Ar), 156.9 (s, C-1), 160.8 (s, *C*O_2Me), 200.6 (s, C-3′).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{44}H_{48}O_{11}Si$ + Na^+: 803.2858; found: 803.2898.

Methyl 7-Hydroxy-6-[4-hydroxy-4-(2-hydroxy-3,6-dimethoxyphenyl)-3-oxobutyl]-8-methoxy-1-oxo-1*H*-isochromene-3-carboxylate (7)

Pd/C (0.010 g, 0.009 mmol) was suspended in MeOH (5 mL) and H_2 was bubbled via a needle through the suspension for 30 min. A solution of the adduct **6** (0.070 g, 0.090 mmol) in MeOH (5 mL) was added to the suspension and stirred under H_2 atmosphere (1 atm) for 3 d. The mixture was filtered through a pad of Celite and washed with anhyd MeOH (6 × 5 mL). The filtrate was concentrated under reduced pressure and the crude product **7** was utilized for the attempted spiroketalization without further purification; yield: 0.044 g (quant); yellow foamy liquid; R_f = 0.10 (1:1 hexane–EtOAc).

^1H NMR (250 MHz, $CDCl_3$): δ = 2.71–2.74, 2.94–3.01 (2 m, 2 H each, CH_2), 3.68, 3.78, 3.91, 3.93 (4 s, 3 H each, OMe), 5.28 (s, 1 H, OH), 5.54 (br s, 1 H, 4′-H), 6.28, 6.71 (2 d, ^3J = 8.5 Hz, 1 H each, 5″-H, 4″-H), 7.04, 7.28 (2 s, 1 H each, 4-H, 5-H).

Methyl 3-(Benzyloxy)-4-iodo-2-methoxy-6-(3-methoxy-2-hydroxy-3-oxopropyl)benzoate (15)

Under argon, the adduct **12**[7c] (4.00 g, 6.53 mmol) was dissolved in THF (100 mL) and cooled to –78 °C. A freshly prepared 1:1 mixture of TBAF (1 M in THF, 6.53 mL, 6.53 mmol) and glacial AcOH (0.37 mL, 6.53 mmol) was added and the mixture was stirred for 5 min at the same temperature. Then $NaBH_4$ (0.25 g, 6.53 mmol) was added and stirring was continued for 5 h at –78 to –30 °C. The mixture was quenched by the addition of sat. aq NH_4Cl (20 mL) at –30 °C and extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with H_2O (25 mL), brine (10 mL), and dried ($MgSO_4$). After filtration, the organic solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography using hexane–EtOAc (4:1 to 3:2) as eluent; yield: 2.32 g (71%); pale yellow viscous liquid; R_f = 0.35 (3:2 hexane–EtOAc).

IR (KBr): 3485 (O–H), 3030 (=C–H), 3000–2950 (C–H), 2870 (OCH_3), 1735 (C=O), 1605–1555 (C=C), 1010 cm^{-1} (C–O).

^1H NMR (500 MHz, $CDCl_3$): δ = 2.80 (dd, ^2J = 14.2 Hz, ^3J = 8.4 Hz, 1 H, 1′-H), 3.07 (dd, ^2J = 14.2 Hz, ^3J = 4.1 Hz, 1 H, 1′-H), 3.20 (d, ^3J = 6.2 Hz, 1 H, OH), 3.78, 3.88, 3.93 (3 s, 3 H each, OMe), 4.37 (ddd, ^3J = 8.4 Hz, ^3J = 6.2 Hz, ^3J = 4.1 Hz, 1 H, 2′-H), 4.97 (s, 2 H, OCH_2Ph), 7.34, 7.39 (2 t, ^3J = 7.2 Hz, 1 H, 2 H, Ph), 7.49 (s, 1 H, 5-H), 7.55 (d, ^3J = 7.2 Hz, 2 H, Ph).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 37.4 (t, C-1′), 52.8, 52.9, 62.1 (3 q, OMe), 71.3 (d, C-2′), 75.2 (t, OCH_2Ph), 95.6 (s, C-4), 128.6, 128.7, 128.9 (3 d, Ph), 130.6 (s, C-6), 132.7 (s, C-1), 136.3 (d, C-5), 136.6 (s, Ph), 150.5 (s, C-2), 151.0 (s, C-3), 167.8 (s, *C*O_2Me), 174.4 (s, C-3′).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{20}H_{21}IO_7$ + Na^+: 523.0229; found: 523.0206.

Anal. Calcd for $C_{20}H_{21}IO_7$ (500.0): C, 48.02; H, 4.23. Found: C, 48.11; H, 4.13.

Methyl 7-Benzyloxy-6-iodo-8-methoxy-1-oxo-isochromene-3-carboxylate (10)

A solution of **15** (0.385 g, 0.77 mmol) in toluene (20 mL) was stirred with *p*-TsOH·H_2O (0.146 g, 0.77 mmol) at 70 °C under argon for 2 h and the reaction was monitored by TLC. The mixture was cooled to r.t., washed with 5% aq $NaHCO_3$ (20 mL) and brine (20 mL). The aqueous layer was extracted with EtOAc (2 × 25 mL) and the combined organic extracts were dried ($MgSO_4$). After filtration, the organic solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography using hexane–EtOAc (7:3) as eluent; yield: 0.306 g (85%); colorless solid; mp 131–133 °C; R_f = 0.44 (3:2 hexane–EtOAc).

IR (KBr): 2995 (=C–H), 2950–2930 (C–H), 2865–2850 (OCH_3), 1770 (C=O), 1725 (C=O), 1675–1555 (C=C), 990–970 cm^{-1} (C–O).

^1H NMR (500 MHz, $CDCl_3$): δ = 3.17, 3.32 (2 dd, ^2J = 16.4 Hz, ^3J = 5.3 Hz, 2 H, 4-H), 3.72, 3.95 (2 s, 3 H each, OMe), 5.01, 5.07 (AB system, $^2J_{A,B}$ = 10.3 Hz, 2 H, OCH_2Ph), 5.06 (t, ^3J = 5.3 Hz, 1 H, 3-H), 7.34, 7.39 (2 t, ^3J = 7.1 Hz, 1 H, 2 H, Ph), 7.45 (s, 1 H, 5-H), 7.54 (d, ^3J = 7.1 Hz, 2 H, Ph).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 30.5 (t, C-4), 53.2, 62.3 (2 q, OMe), 74.5 (d, C-3), 75.5 (t, OCH_2Ph), 101.1, 119.8 (2 s, C-6, C-8a), 128.66, 128.7, 129.0 (3 d, Ph), 132.8 (d, C-5), 134.2, 136.5, 152.9, 155.3, 160.0, 169.3 (6 s, C-4a, Ph, C-7, C-8, C-1, *C*O_2Me).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{19}H_{17}IO_6$ + H^+: 469.0148; found: 469.0151.

Anal. Calcd for $C_{19}H_{17}IO_6$ (468.0): C, 48.74; H, 3.66. Found: C, 48.64; H, 3.71.

Methyl (*E*)-7-(Benzyloxy)-6-[4-(2-(benzyloxy)-3,6-dimethoxyphenyl)-3-oxo-4-(triethylsiloxy)but-1-enyl]-8-methoxy-1-oxo-isochromene-3-carboxylate (16)

To a solution of triethylsiloxyenone **4** (0.289 g, 0.655 mmol) and 6-iododihydroisocoumarin **10** (0.279 g, 0.595 mmol) in DMF (5 mL) were added $Pd(OAc)_2$ (0.013 g, 0.0595 mmol), *n*-Bu_4NCl (0.165 g, 0.595 mmol) and $NaHCO_3$ (0.125 g, 1.49 mmol). The mixture was stirred at 60 °C under argon for 16 h, then cooled to r.t., diluted with EtOAc (25 mL). The organic phase was washed with H_2O (2 × 15 mL), brine (15 mL), and dried ($MgSO_4$). After filtration, the solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography using hexane–EtOAc (3:2) as

eluent to afford **16** as a 1:1 mixture of diastereomers; yield: 0.358 g (77%); pale yellow foamy liquid; R_f = 0.35 (3:2 hexane–EtOAc).

IR (film): 3030 (=C–H), 3000–2875 (C–H), 2835 (OCH_3), 1760 (C=O), 1740 (C=O), 1555 (C=C), 1005 cm^{-1} (C–O).

^1H NMR (500 MHz, $CDCl_3$): δ = 0.57, 0.84 (q, t, ^3J = 7.8 Hz, 6 H, 9 H, $SiEt_3$), 3.08–3.16, 3.24–3.29 (2 m, 1 H each, 4-H), 3.72, 3.74, 3.74, 3.75, 3.76, 3.78, 3.94, 3.94 (8 s, 1.5 H each, OMe), 4.88–4.95, 4.98–5.02, 5.05–5.08 (3 m, 5 H, 2 × OCH_2Ph, 3-H), 5.64 (s, 1 H, 4′-H), 6.59, 6.60 (2 d, ^3J = 9.0 Hz, 0.5 H each, 5″-H), 6.81, 6.85 (2 br d, ^3J = 16.3 Hz, 0.5 H each, 2′-H), 6.86 (d, ^3J = 9.0 Hz, 1 H, 4″-H), 7.14–7.22, 7.26–7.34, 7.39–7.43 (3 m, 3 H, 4 H, 4 H, Ph, 5-H, Ph), 7.77, 7.79 (2 d, ^3J = 16.3 Hz, 0.5 H each, 1′-H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 4.9, 6.9 (t, q, $SiEt_3$), 31.0 (t, C-4), 53.1, 56.2, 56.6, 62.1 (4 q, OMe), 71.8, 74.7 (2 d, C-4′, C-3), 75.5, 76.2 (2 t, OCH_2Ph), 106.6, 113.4 (2 d, C-5″, C-4″), 119.6 (s, C-8a), 120.5 (d, C-2′), 125.5 (s, C-1″), 126.2 (d, C-5), 128.2, 128.3, 128.4, 128.5, 128.7, 128.9 (6 d, Ph), 132.5 (s, C-4a), 134.0 (d, C-1′), 136.0, 136.6, 138.0, 147.5, 151.5, 152.0, 156.2, 160.1, 169.4, 200.6 (10 s, C-6, Ph, C-6″, C-7, C-2″, C-8, C-1, CO_2Me, C-3′); the two diastereomers show only one set of ^{13}C signals.

MS (EI, 80 eV, 150 °C): *m*/*z* (%) = 782 (<1, $[M]^+$), 419 (29), 387 (100), 267 (23), 91 (14, $[C_7H_7]^+$).

Anal. Calcd for $C_{44}H_{50}O_{11}Si$ (782.3): C, 67.50; H, 6.44. Found: C, 67.09; H, 6.25.

Methyl 7-Hydroxy-6-[4-hydroxy-4-(2-hydroxy-3,6-dimethoxyphenyl)-3-oxobutyl]-8-methoxy-1-oxo-3,4-dihydro-1*H*-isochromene-3-carboxylate (17)

A solution of the Heck adduct **16** (0.150 g, 0.192 mmol) in MeOH (10 mL) was added to Pd/C (0.020 g, 0.019 mmol) in a Büchi high pressure reaction bottle. The mixture was stirred under H_2 (8 atm) for 5 h. The Pd/C was filtered through a pad of Celite and washed with anhyd MeOH (6 × 5 mL). The filtrate was concentrated and the crude product was purified by silica gel column chromatography using MeOH–CH_2Cl_2 (1:19) as eluent to afford **17** as a 1:1 mixture of diastereomers; yield: 0.070 g (75%); pale yellow-white foam; R_f = 0.50 (1:19 MeOH–CH_2Cl_2).

IR (film): 3430 (O–H), 3000–2840 (C–H), 1755, 1725 (C=O), 1610, 1600, 1490 (C=C) 1460, 1440, 1430 (C=C), 1250, 1070, 1030 cm^{-1} (C–O).

^1H NMR (500 MHz, $CDCl_3$): δ = 2.61–2.71, 2.82–2.93 (2 m, 2 H each, CH_2), 3.07, 3.11 (2 dd, $^2J \approx$ 16.5 Hz, $^3J \approx$ 3.7 Hz, 0.5 H each, 4-H), 3.26, 3.29 (2 dd, $^2J \approx$ 16.5 Hz, $^3J \approx$ 3.7 Hz, 0.5 each, 4-H), 3.67, 3.68, 3.69, 3.70, 3.80, 3.81, 3.90, 3.90 (8 s, 1.5 H each, OMe), 4.06–4.11, 5.03–5.06 (2 m, 1 H each, 4′-OH, 3-H), 5.49, 5.51 (2 d, ^2J = 4.2 Hz, 0.5 H each, 4′-H), 6.15, 6.26 (br s, 2 H, ArO*H*), 6.30, 6.32, 6.73, 6.74 (4 d, ^3J = 9.0 Hz, 0.5 H each, 5″-H, 4″-H), 6.66, 6.69 (2 s, 0.5 H each, 5-H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 25.0, 35.5, 36.3 (3 t, C-2′, C-4, C-1′), 52.9, 55.9, 56.6, 62.3 (4 q, OMe), 71.7, 74.8 (2 d, C-4′, C-3), 101.6, 110.9 (2 d, C-5″, C-4″), 115.0 (s, Ar), 123.9 (d, C-5), 124.1, 128.1, 133.8, 141.4, 144.9, 147.1, 148.0, 152.2 (8 s, Ar, Ph), 160.3, 169.6 (2 s, C-1, CO_2Me), 208.8 (s, C-3′); the two diastereomers show only one set of ^{13}C signals.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{24}H_{26}O_{11}$ + Na^+: 513.1372; found: 513.1369.

Spiroketals 18, 19, and 20; General Procedure

AcCl (10 equiv) was added dropwise to a solution of **17** (1 equiv) and $HC(OMe)_3$ (2 equiv) in *i*-PrOH or MeOH (25 mL) at r.t. The resulting solution was further stirred at 60 °C under argon for the time indicated in the individual experiment. Sat. aq $NaHCO_3$ (10 mL) was added to the cooled reaction mixture and extracted with EtOAc (4 × 50 mL). The combined EtOAc layers were washed with H_2O (5 × 20 mL), brine (25 mL), and the organic phase was dried ($MgSO_4$). The solvent was filtered, concentrated under reduced pressure to afford the residue, which was purified by silica gel column chromatography using MeOH–CH_2Cl_2 (1:99) as eluent to afford spiroketals **18**, **19**, and **20** as a 1:1 mixture of diastereomers. A final purification was performed by HPLC.

Spiroketal 18

According to the general procedure, AcCl (0.11 mL, 1.53 mmol) was added dropwise to a solution of **17** (0.075 g, 0.153 mmol) and $HC(OMe)_3$ (0.033 mL, 0.306 mmol) in *i*-PrOH (25 mL) at r.t., and stirred at 60 °C for 16 h and worked up as mentioned above to afford **18**; yield: 0.036 g (48%, after column chromatography, purity ca. 90%, 1:1 mixture of diastereomers); pale yellow foamy liquid; final HPLC purification: t_R = 5.46 min (1:2.3 *i*-PrOH–hexane).

IR (film): 3490 (O–H), 2975–2835 (C–H), 1730, 1720 (C=O), 1610, 1510, 1375 (C–H), 1265 cm^{-1} (C–O).

^1H NMR (500 MHz, $CDCl_3$): δ = 1.17–1.21, 2.17–2.25, 2.44–2.49 (3 m, 6 H, 1 H, 1 H, Me, 3-H), 2.86 (s, 0.5 H, 3′-OH), 2.87–2.92 (m, 1 H, 4-H), 2.94 (s, 0.5 H, 3′-OH), 3.11, 3.14 (2 dd, $^2J \approx$ 16.0 Hz, $^3J \approx$ 5.7 Hz, 0.5 H each, 6-H), 3.17–3.21 (m, 1 H, 4-H), 3.24, 3.27 (2 dd, $^2J \approx$ 16.0 Hz, $^3J \approx$ 5.7 Hz, 0.5 H each, 6-H), 3.68, 3.73, 3.85 (3 s, 3 H each, OMe), 4.94–5.04 (m, 2 H, 7-H, C*H*Me_2), 5.34, 5.35 (2 s, 0.5 H each, 3′-H), 6.41, 6.42, 6.80, 6.81 (4 d, ^3J = 8.9 Hz, 0.5 H each, 5′-H, 6′-H), 6.73, 6.74 (2 s, 0.5 H each, 5-H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.55, 21.58 (2 q, Me), 21.7 (t, C-4), 21.88, 21.92 (2 q, Me), 23.9, 24.0 (2 t, C-3), 30.79, 30.84 (2 t, C-6), 55.8, 56.9, 61.5 (3 q, OMe), 69.93, 69.96 (2 d, *C*HMe_2), 74.80, 74.86 (2 d, C-7), 76.3 (d, C-3′), 103.7 (d, C-5′), 111.6, 111.7 (2 s, Ar), 115.48, 115.52 (2 d, C-6′), 116.5 (s, C-2), 117.2, 117.3 (2 s, Ar), 122.6 (d, C-5), 129.3, 129.4, 130.0, 130.1, 139.25, 139.27, 145.8, 148.1, 150.66, 150.70, 151.27, 151.31 (12 s, Ar), 160.3, 168.6, 168.8 (3 s, C-9, CO_2i-Pr).

HRMS (ESI): *m*/*z* calcd for $C_{26}H_{29}O_{10}$ + H^+: 501.1761; found: 501.1742.

Spiroketals 19 and 20

According to the general procedure, AcCl (0.29 mL, 4.08 mmol) was added dropwise to a solution of **17** (0.20 g, 0.408 mmol) and $HC(OMe)_3$ (0.089 mL, 0.816 mmol) in MeOH (25 mL) at r.t. The resulting solution was stirred at 60 °C for 48 h and worked up as mentioned above to afford a mixture of **19** and **20**.

Spiroketal 19

Yield: 0.090 g (47%, 1:1 diastereomers); colorless solid; mp 219–220 °C; t_R = 4.70 min (1:3 *i*-PrOH–hexane).

IR (KBr): 3510 (O–H), 2990–2835 (C–H), 1730 (C=O), 1510, 1365 (C–H), 1265 cm^{-1} (C–O).

^1H NMR (500 MHz, $CDCl_3$): δ = 2.18–2.22 (m, 1 H, 3-H), 2.24 (d, ^3J = 4.6 Hz, 1 H, 3′-OH), 2.47 (ddd, ^2J = 14.1 Hz, ^3J = 6.2 Hz, ^3J = 2.5 Hz, 1 H, 3-H), 2.90 (ddd, ^2J = 17.2 Hz, ^3J = 6.2 Hz, ^3J = 2.5 Hz, 1 H, 4-H), 3.16 (dd, ^2J = 16.3 Hz, ^3J = 5.5 Hz, 1 H, 6-H), 3.19–3.23 (m, 1 H, 4-H), 3.27 (dd, ^2J = 16.3 Hz, ^3J = 5.5 Hz, 1 H, 6-H), 3.69, 3.71, 3.74, 3.85 (4 s, 3 H each, OMe), 5.03 (t, ^3J = 5.5 Hz, 1 H, 7-H), 5.35 (d, ^3J = 4.6 Hz, 1 H, 3′-H), 6.41 (d, ^3J = 8.9 Hz, 1 H, 5′-H), 6.74 (s, 1 H, 5-H), 6.81 (d, ^3J = 8.9 Hz, 1 H, 6′-H); only one set of ^1H signals was observed.

^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.9, 23.9, 30.6 (3 t, C-4, C-3, C-6), 52.9, 55.8, 56.9, 61.5 (4 q, OMe), 74.7, 76.3 (2 d, C-7, C-3′), 103.7 (d, C-5′), 111.6 (s, Ar), 115.5 (d, C-6′), 116.5, 116.9 (2 s, C-2, Ar), 122.6 (d, C-5), 129.3, 130.2, 139.3, 145.9, 148.1, 150.8, 151.3 (7 s, Ar), 160.1, 169.7 (2 s, C-9, CO_2Me); only one set of ^{13}C signals was observed.

MS (EI, 80 eV, 190 °C): *m*/*z* (%) = 472 (82, $[M]^+$), 454 (50, $[M - H_2O]^+$), 266 (47), 207 (100).

Anal. Calcd for $C_{24}H_{24}O_{10}$ (472.1): C, 61.01; H, 5.12. Found: C, 61.26; H, 5.26.

Spiroketal 20

Yield: 0.020 g (10%, 1:1 diastereomers); colorless solid; melting range 175–190 °C; final HPLC purification: t_R = 2.68 min (1:3 *i*-PrOH–hexane).

IR (KBr): 2955–2850 (C–H), 1750, 1730 (C=O), 1605, 1510, 1365 (C–H), 1265 cm^{-1} (C–O).

^1H NMR (500 MHz, $CDCl_3$): δ = 2.15–2.21, 2.47–2.50, 2.85–2.89 (3 m, 1 H each, 3-H, 4-H), 3.13–3.29 (m, 3 H, 4-H, 6-H), 3.52, 3.53, 3.64, 3.65, 3.70, 3.72, 3.73, 3.74, 3.84, 3.85 (10 s, 1.5 H each, OMe), 4.94 (s, 1 H, 3′-H), 4.99 (dd, ^3J = 6.6 Hz, ^3J = 5.0 Hz, 0.5 H, 7-H), 5.02 (t, ^3J = 5.0 Hz, 0.5 H, 7-H), 6.42 (d, ^3J = 9.1 Hz, 1 H, 5′-H), 6.73 (s, 1 H, 5-H), 6.80, 6.81 (2 d, ^3J = 9.1 Hz, 0.5 H each, 6′-H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.9, 22.0 (2 t, C-4), 24.0, 24.1 (2 t, C-3), 30.5, 30.6 (2 t, C-6), 52.8, 52.9, 55.7, 55.8, 56.9, 57.0, 58.5, 58.6, 61.3, 61.4 (10 q, OMe), 74.6, 74.7 (2 d, C-7), 83.4, 83.9 (2 d, C-3′), 103.7 (d, C-5′), 111.1, 111.2 (2 s, Ar), 115.2 (s, C-2), 115.4, 115.6 (2 d, C-6′), 116.8, 116.9 (2 s, Ar), 122.5, 122.6 (2 d, C-5), 129.3, 129.4, 130.31, 130.34, 139.3, 139.4, 145.8*, 148.5, 148.6, 150.7, 150.8, 151.8* (12 s, Ar), 160.0 (s, C-9), 169.4, 169.7 (2 s, CO_2Me); * signals with higher intensities.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{25}H_{26}O_{10}$ + Na^+: 509.1424; found: 509.1465.

Oxidized Spiroketal 21

To a solution of **18** (5 mg, 0.009 mmol, mixture of diastereomers) in anhyd chlorobenzene (2 mL) was added DDQ (13 mg, 0.06 mmol) and the mixture was heated to reflux at 140 °C for 16 h under argon (TLC monitoring). Then the mixture was cooled to r.t., quenched with sat. aq $NaHCO_3$ (2 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with H_2O (25 mL), brine (20 mL), and dried ($MgSO_4$). After filtration and evaporation of solvent under reduced pressure, the residue was chromatographed with silica gel using MeOH–CH_2Cl_2 (1:50) as eluent to afford **21**; yield: 4 mg (ca. 80%, 1:1 diastereomers); pale yellow liquid; R_f = 0.40 (1:19 MeOH–CH_2Cl_2).

^1H NMR (500 MHz, $CDCl_3$): δ = 1.12–1.21 (m, 6 H, Me), 2.06–2.12, 2.23–2.32, 2.91–2.95 (3 m, 1 H each, 3-H, 4-H), 3.13–3.31 (m, 3 H, 6-H, 4-H), 3.84, 3.85, 3.85, 3.86, 3.93, 3.94 (6 s, 1.5 H each, OMe), 4.97–5.03 (m, 2 H, 7-H, C*H*Me_2), 6.43, 6.44 (2 d, ^3J = 8.8 Hz, 0.5 H each, 5′-H), 6.74, 6.75 (2 s, 0.5 H each, 5-H), 7.14, 7.15 (2 d, ^3J = 8.8 Hz, 0.5 H each, 6′-H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.59, 21.61 (2 q, Me), 21.70 (t, C-4), 21.71, 21.9 (2 q, Me), 25.2, 25.3 (2 t, C-3), 30.79, 30.84 (2 t, C-6), 56.3, 56.4, 57.02, 57.06, 61.74, 61.75 (6 q, OMe), 70.01, 70.04 (2 d, *C*HMe_2), 74.75, 74.79 (2 d, C-7), 102.0, 102.1 (2 d, C-5′), 103.5, 109.25, 109.26 (3 s, Ar), 117.6, 117.8 (2 d, C-6′), 122.3, 123.4 (2 d, C-5), 123.1, 123.2, 128.85, 128.9, 129.9, 130.0, 139.67, 139.69, 145.76, 145.81, 150.6, 150.7, 152.50, 152.51, 160.0, 160.1 (16 s, Ar), 160.18, 160.23 (2 s, C-9), 168.62, 168.63 (2 s, CO_2i-Pr), 192.47, 192.49 (2 s, C-3′).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{26}H_{26}O_{10}$ + Na^+: 521.1424; found: 521.1443.

Triethylsilyl Ether Protected Spiroketal 23

i-Pr_2NEt (0.22 mL, 0.127 mmol) was added to a stirred solution of **19** (0.020 g, 0.042 mmol, mixture of 1:1 diastereomers) in DMF (1 mL) under argon, followed by dropwise addition of Et_3SiCl (0.16 mL, 0.093 mmol) at r.t. The mixture was stirred for 15 h and quenched with sat. aq $NaHCO_3$ (2 mL) and extracted with EtOAc (5 × 10 mL). The combined organic layers were washed with H_2O (2 × 10 mL), brine (10 mL), and dried ($MgSO_4$). The solvent was filtered, evaporated under reduced pressure, and the residue was chromatographed on silica gel using MeOH–CH_2Cl_2 (1:50) as eluent to afford the spiroketal **23**; yield: 0.020 g (81%, two diastereomers in a ratio of 85:15); colorless solid; mp 172–173 °C; R_f = 0.50 (1:19 MeOH–CH_2Cl_2).

IR (KBr): 2955–2835 (C–H), 1750, 1740 (C=O), 1605, 1510, 1365 (C–H), 1265 cm^{-1} (C–O).

^1H NMR (500 MHz, $CDCl_3$): δ (major diastereomer) = 0.65–0.71 (m, 6 H, $SiEt_3$), 0.93 (t, ^3J = 7.7 Hz, 9 H, $SiEt_3$), 2.00–2.08 (m, 1 H, 3-H), 2.49 (ddd, ^2J = 13.9 Hz, ^3J = 6.0 Hz, ^3J = 2.5 Hz, 1 H, 3-H), 2.86 (ddd, ^2J = 17.2 Hz, ^3J = 6.0 Hz, ^3J = 2.5 Hz, 1 H, 4-H), 3.15 (dd, ^2J = 16.2 Hz, ^3J = 6.3 Hz, 1 H, 6-H), 3.18–3.21 (m, 1 H, 4-H), 3.25 (dd, ^2J = 16.2 Hz, ^3J = 5.0 Hz, 1 H, 6-H), 3.64, 3.73, 3.75, 3.80 (4 s, 3 H each, OMe), 5.00 (dd, ^3J = 6.3 Hz, ^3J = 5.0 Hz, 1 H, 7-H), 5.33 (s, 1 H, 3′-H), 6.37 (d, ^3J = 8.8 Hz, 1 H, 5′-H), 6.74 (s, 1 H, 5-H), 6.78 (d, ^3J = 8.8 Hz, 1 H, 6′-H).

^{13}C NMR (126 MHz, $CDCl_3$): δ (major diastereomer) = 4.9, 6.9 (t, q, $SiEt_3$), 22.1, 22.4, 30.7 (3 t, C-4, C-3, C-6), 52.9, 54.9, 56.9, 61.5 (4 q, OMe), 74.7, 77.3 (2 d, C-7, C-3′), 103.1 (d, C-5′), 111.8 (s, Ar), 114.8 (d, C-6′), 116.9, 117.1 (2 s, C-2, Ar), 122.6 (d, C-5), 129.3, 130.4, 139.2, 146.0, 148.1, 150.8, 151.2 (7 s, Ar), 160.1, 169.5 (2 s, C-9, CO_2Me).

^1H NMR (500 MHz, $CDCl_3$): δ (minor diastereomer) = 5.31 (s, 1 H, 3′-H), 6.36, 6.76 (2 d, ^3J = 8.8 Hz, 1 H each, 5′-H, 6′-H).

MS (EI, 80 eV, 160 °C): *m*/*z* (%) = 586 (47, $[M]^+$), 557 (15, $[M - C_2H_5]^+$), 454 (100, $[M - Et_3SiOH]^+$), 321 (87), 207 (100).

Anal. Calcd for $C_{30}H_{38}O_{10}Si$ (586.2): C, 61.41; H, 6.53. Found: C, 61.23; H, 6.27.

Ring Contracted Spiroketal 24

LiHMDS (0.1 M in THF, 0.41 mL, 0.041 mmol) was added dropwise to a solution of spiroketal **23** (0.020 g, 0.034 mmol) in THF (5 mL) at –78 °C under argon and stirred for 20 min resulting in the formation of a yellow solution. A THF (3 mL) solution of PhSeCl (9 mg, 0.0512 mmol) was added to the mixture at –78 °C and stirred for further 4 h while the temperature was slowly warmed to 0 °C. The mixture was quenched with sat. aq NH_4Cl (1.0 mL) and extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with H_2O (20 mL), brine (10 mL), and dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure, the residue was purified by silica gel column chromatography using MeOH–CH_2Cl_2 (1:99) as eluent.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{30}H_{39}O_{10}Si$ + H^+: 587.2313; found: 587.2337.

The 1:1 mixture of diastereomers of **24** was separated by HPLC.

Diastereomer a of 24

Yield: 5 mg (25%); colorless liquid; t_R = 3.76 min (1:19 *i*-PrOH–hexane).

IR (film): 3465 (O–H), 2950–2830 (C–H), 1745, 1715 (C=O), 1610, 1510, 1265 cm^{-1} (C–O).

^1H NMR (500 MHz, $CDCl_3$): δ = 0.64–0.74 (m, 6 H, $SiEt_3$), 0.94 (t, ^3J = 8.0 Hz, 9 H, $SiEt_3$), 2.06–2.13 (m, 1 H, 3-H), 2.51 (ddd, ^2J = 13.7 Hz, ^3J = 6.2 Hz, ^3J = 2.5 Hz, 1 H, 3-H), 2.95 (ddd, ^2J = 17.4 Hz, ^3J = 6.2 Hz, ^3J = 2.5 Hz, 1 H, 4-H), 3.08 (d, ^2J = 17.1 Hz, 1 H, 6-H), 3.31 (ddd, ^2J = 17.4 Hz, ^3J = 12.4 Hz, ^3J = 6.2 Hz, 1 H, 4-H), 3.58 (d, ^2J = 17.1 Hz, 1 H, 6-H), 3.69, 3.71, 3.72, 3.81 (4 s, 3 H each, OMe), 3.87 (s, 1 H, OH), 5.31 (s, 1 H, 3'-H), 6.37, 6.78 (2 d, ^3J = 8.8 Hz, 1 H each, 5′-H, 6′-H), 6.93 (s, 1 H, 5-H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 4.9, 6.9 (t, q, $SiEt_3$), 22.9, 24.3, 37.9 (3 t, C-4, C-3, C-6), 53.4, 54.9, 57.0, 61.6 (4 q, OMe), 76.6 (d, C-3′), 81.4 (s, C-7), 103.1 (d, C-5′), 111.9 (s, Ar), 115.2 (d, C-6′), 117.3 (s, C-2), 120.7 (d, C-5), 124.2, 134.3, 139.3, 144.35, 144.36, 147.7, 148.1, 151.2 (8 s, Ar), 171.9, 197.8 (2 s, CO_2Me, C-8).

Diastereomer b of 24

Yield: 5 mg (25%); colorless liquid; t_R = 4.15 min (1:19 *i*-PrOH–hexane).

IR (film): 3460 (O–H), 2950–2835 (C–H), 1745, 1715 (C=O), 1610, 1510, 1265 cm^{-1} (C–O).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.66–0.71 (m, 6 H, $SiEt_3$), 0.94 (t, ^3J = 8.0 Hz, 9 H, $SiEt_3$), 2.06–2.12 (m, 1 H, 3-H), 2.49 (ddd, ^2J = 14.0 Hz, ^3J = 6.0 Hz, ^3J = 2.5 Hz, 1 H, 3-H), 2.93 (ddd, ^2J = 17.3 Hz, ^3J = 6.0 Hz, ^3J = 2.5 Hz, 1 H, 4-H), 3.09 (d, ^2J = 17.1 Hz, 1 H, 6-H), 3.31 (ddd, ^2J = 17.3 Hz, ^3J = 12.4 Hz, ^3J = 6.0 Hz, 1 H, 4-H), 3.56 (d, ^2J = 17.1 Hz, 1 H, 6-H), 3.73, 3.75, 3.76, 3.81 (4 s, 3 H each, OMe), 3.89 (s, 1 H, OH), 5.34 (s, 1 H, 3′-H), 6.37, 6.78 (2 d, ^3J = 8.8 Hz, 1 H each, 5′-H, 6′-H), 6.91 (s, 1 H, 5-H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 5.0, 6.9 (t, q, $SiEt_3$), 22.9, 24.5, 38.0 (3 t, C-4, C-3, C-6), 53.5, 54.9, 56.8, 61.7 (4 q, OMe), 76.9 (d, C-3′), 81.3 (s, C-7), 103.0 (d, C-5′), 112.1 (s, Ar), 114.7 (d, C-6′), 117.1 (s, C-2), 120.7 (d, C-5), 124.2, 134.2, 139.2, 144.23, 144.28, 147.5, 148.1, 151.2 (8 s, Ar), 172.1, 197.9 (2 s, CO_2Me, C-8).

6-Benzyloxy-5-iodo-7-methoxy-2-benzofuran-1(3*H*)-one (25)

$NaBH_4$ (0.043 g, 1.14 mmol) was added to a solution of aldehyde **11**[7c] (0.43 g, 1.00 mmol) in anhyd EtOH (20 mL) at r.t. and the mixture was stirred for 1 h. A colorless precipitate appeared in the mixture as the reduction progressed. The excess of EtOH was evaporated under reduced pressure keeping the bath temperature at 30–40 °C. The colorless residue obtained was dissolved in CH_2Cl_2 (25 mL), and quenched with sat. aq NH_4Cl (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic layers were washed with H_2O (25 mL), brine (25 mL), and dried ($MgSO_4$). After filtration and evaporation of the solvent, the crude product **25** was purified by silica gel column chromatography using hexane–EtOAc (3:2) as eluent; yield: 0.376 g (95%); colorless crystals; mp 106–108 °C; R_f = 0.30 (4:1 hexane–EtOAc).

IR (KBr): 3085–2845 (=C–H, C–H), 1750 cm^{-1} (C=O).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.11 (s, 3 H, OMe), 5.05, 5.16 (2 s, 2 H each, OCH_2Ph, 3-H), 7.35 (t, ^3J = 6.9 Hz, 1 H, Ph), 7.39 (t, $^3J \approx$ 7.0 Hz, 2 H, Ph), 7.55 (d, ^3J = 6.9 Hz, 2 H, Ph), 7.60 (s, 1 H, 4-H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 62.9 (q, OMe), 67.9, 75.7 (2 t, OCH_2Ph, C-3), 102.5, 119.3 (2 s, Ar), 126.9 (d, C-4), 128.6*, 128.8 (2 d, Ph), 136.3, 144.5, 151.6, 151.7 (4 s, Ph, Ar), 167.8 (s, C-1); * signal with higher intensity.

MS (EI, 80 eV, 100 °C): *m*/*z* (%) = 395 (23, $[M]^+$), 91 (100, $[C_7H_7]^+$).

Anal. Calcd for $C_{16}H_{13}IO_4$ (395.9): C, 48.51; H, 3.31. Found: C, 49.30; H, 3.43.

5-{(1*E*)-4-[2-(Benzyloxy)-3,6-dimethoxyphenyl]-4-(triethylsiloxy)-3-oxo-but-1-enyl}-7-methoxy-6-(benzyloxy)-2-benzofuran-1(3*H*)one (26)

Analogous to the procedure for the preparation of **16**, a mixture of triethylsiloxyenone **4** (1.53 g, 3.47 mmol), 5-iodophthalide **25** (1.25 g, 3.16 mmol), $Pd(OAc)_2$ (0.071 g, 0.316 mmol), *n*-Bu_4NCl (0.876 g, 3.16 mmol), and $NaHCO_3$ (0.662 g, 7.87 mmol) in DMF (16 mL) was used for the Heck reaction; yield: 1.77 g (79%); pale yellow viscous liquid; R_f = 0.63 (2:3 hexane–EtOAc).

IR (film): 3085–2835 (=C–H, C–H), 1760 cm^{-1} (C=O).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.59, 0.86 (q, t, ^3J = 8.0 Hz, 6 H, 9 H, $SiEt_3$), 3.75, 3.79, 4.10 (3 s, 3 H each, OMe), 4.96 (AB system, $^2J_{A,B}$ = 10.8 Hz, 2 H, OCH_2Ph), 5.07 (AB system, $^2J_{A,B}$ = 10.8 Hz, 2 H, OCH_2Ph), 5.15 (s, 2 H, 3-H), 5.67 (s, 1 H, 4′-H), 6.61 (d, ^3J = 9.1 Hz, 1 H, 3″-H), 6.86–6.88 (m, 2 H, 4″-H, 4-H), 7.19 (t, ^3J = 7.2 Hz, 1 H, Ph), 7.23 (t, ^3J = 7.4 Hz, 2 H, Ph), 7.29 (t, ^3J = 7.2 Hz, 1 H, Ph), 7.32–7.37 (m, 3 H, Ph), 7.41–7.45 (m, 4 H, 2′-H, Ph), 7.85 (d, ^3J = 16.2 Hz, 1 H, 1′-H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 4.8, 6.8 (t, q, $SiEt_3$), 56.1, 56.5, 62.7 (3 q, OMe), 68.8 (t, C-3), 71.7 (d, C-4′), 75.3, 76.5 (2 t, OCH_2Ph), 106.5 (d, C-3″), 113.4 (d, C-4″), 114.3 (d, C-4), 118.6, 125.5 (2 s, Ph), 126.3, 127.5, 128.15, 128.21, 128.5, 128.6, 128.8 (7 d, Ph, C-2′), 134.5 (d, C-1′), 136.4, 137.5, 138.0 142.5, 147.35, 147.40, 150.6, 151.9, 152.8 (9 s, Ar), 168.3 (s, C-1), 200.7 (s, C-3′).

MS (EI, 80 eV, 240 °C): *m*/*z* (%) = 710 (7, $[M]^+$), 387 (86), 267 (65), 91 (100, $[C_7H_7]^+$).

Anal. Calcd for $C_{41}H_{46}O_9Si$ (710.3): C, 69.27; H, 6.52. Found: C, 68.86; H, 6.42.

6-Hydroxy-5-[4-hydroxy-4-(2-hydroxy-3,6-dimethoxyphenyl)-3-oxobutyl]-7-methoxyisobenzofuran-1(3*H*)one (27)

Analogous to the procedure for the synthesis of **17**, a solution of **26** (1.30 g, 1.83 mmol) was added to a suspension of Pd/C (0.194 g, 0.183 mmol) in MeOH (20 mL) and subjected to high pressure (8 atm) hydrogenation; yield: 0.535 g (70%); pale yellow liquid; R_f = 0.48 (3:7 hexane–EtOAc).

IR (film): 3405 (O–H), 3000–2840 (C–H), 1745, 1720 (C=O), 1615, 1600, 1490 (C=C), 1470, 1435, 1400 (C=C), 1250, 1055, 1025 cm^{-1} (C–O).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.71 (m, 2 H, 2′-H), 2.97 (t, ^3J = 7.1 Hz, 2 H, 1′-H), 3.69, 3.80 (2 s, 3 H each, OMe), 4.10 (br s, 1 H, OH), 4.16 (s, 3 H, OMe), 5.12, 5.54 (2 s, 2 H, 1 H, 3-H, 4′-H), 6.08, 6.15 (2 br s, 1 H each, OH), 6.30, 6.72 (2 d, ^3J = 8.8 Hz, 1 H each, 3″-H, 4″-H), 6.82 (s, 1 H, 4-H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 25.3, 36.5 (2 t, C-2′, C-1′), 56.0, 56.5, 63.1 (3 q, OMe), 69.2 (t, C-3), 71.7 (d, C-4′), 101.5, 111.0 (2 d, C-3″, C-4″), 112.8, 114.4 (2 s, Ar), 117.6 (d, C-4), 135.4, 138.8, 141.4, 144.4, 145.1, 146.5, 152.1 (7 s, Ar), 168.9 (s, C-1), 208.6 (s, C-3′).

MS (EI, 80 eV, 160 °C): *m*/*z* (%) = 418 (16, $[M]^+$), 183 (86), 154 (79), 139 (100), 111 (45), 55 (27).

Anal. Calcd for $C_{21}H_{22}O_9$ (418.1): C, 60.28; H, 5.30. Found: C, 59.98; H, 5.54.

Spiroketals 28 and 29

To a solution of ketone **27** (0.520 g, 1.24 mmol) in MeOH (35 mL) were added dropwise $HC(OMe)_3$ (0.27 mL, 2.48 mmol) and AcCl (0.88 mL, 12.4 mmol) at 0 °C over a period of 5 min. The reaction mixture was then stirred at r.t. for 25 h. The excess of MeOH was evaporated under reduced pressure and the residue was dissolved in EtOAc (50 mL) and quenched with sat. aq $NaHCO_3$ (10 mL). The organic phase was washed with H_2O (2 × 20 mL), brine (20 mL), and dried ($MgSO_4$). The solvent was filtered and concentrated to afford the crude products **28** and **29**, which were purified by silica gel column chromatography using hexane–EtOAc (1:1 to 1:4) as eluent.

Spiroketal 28

Yield: 0.208 g (42%); colorless solid; mp 227–228 °C; R_f = 0.54 (1:4 hexane–EtOAc).

IR (KBr): 3525 (O–H), 3090, 3000 (=CH), 2975–2840 (C–H), 1765 (C=O), 1510, 1450 (C=C), 1375, 1365 (C–H), 1270 cm^{-1} (C–O).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.11 (ddd, ^2J = 14.0 Hz, ^3J = 10.8 Hz, ^3J = 8.0 Hz, 1 H, 4-H), 2.35 (dt, ^2J = 14.0 Hz, ^3J = 5.2 Hz, 1 H, 4-H), 3.05 (m_c, 2 H, 3-H), 3.65, 3.67, 3.80 (3 s, 3 H each, OMe), 5.00 (s, 1 H, 3′-H), 5.21, 5.25 (AB system, $^2J_{A,B}$ = 16 Hz, 2 H, 6-H), 5.94 (s, 1 H, OH), 6.54, 6.92 (2 d, ^3J = 8.8 Hz, 1 H each, 5′-H, 6′-H), 7.16 (s, 1 H, 5-H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 22.6, 24.3 (2 t, C-3, C-4), 56.2, 56.8, 62.1 (3 q, OMe), 69.2 (t, C-6), 75.5 (d, C-3′), 104.8 (d, C-5′), 112.1 (s, Ar), 115.3 (d, C-6′), 116.1, 117.6 (2 s, C-2, Ar), 118.2 (d, C-5), 132.6, 139.4, 140.95, 145.2, 147.1, 148.0, 151.7 (7 s, Ar), 168.7 (s, C-8).

MS (EI, 80 eV, 180 °C): *m*/*z* (%) = 400 (49, $[M]^+$), 382 (41, $[M - H_2O]^+$), 207 (100), 181 (26).

Anal. Calcd for $C_{21}H_{20}O_8$ (400.1): C, 63.00; H, 5.03. Found: C, 62.64; H, 5.39.

Spiroketal 29

Yield: 0.097 g (19%); pale yellow solid; mp 166–168 °C; R_f = 0.68 (1:4 hexane–EtOAc).

IR (KBr): 2935–2835 (C–H), 1755 (C=O), 1510, 1450 (C=C), 1365 (C–H), 1265 cm^{-1} (C–O).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.22 (ddd, ^2J = 13.6 Hz, ^3J = 12.4 Hz, ^3J = 6.2 Hz, 1 H, 4-H), 2.50 (ddd, ^2J = 13.6 Hz, ^3J = 6.2 Hz, ^3J = 3.0 Hz, 1 H, 4-H), 2.96 (ddd, ^2J = 17.3 Hz, ^3J = 6.2 Hz, ^3J = 3.0 Hz, 1 H, 3-H), 3.29 (ddd, ^2J = 17.3 Hz, ^3J = 12.4 Hz, ^3J = 6.2 Hz, 1 H, 3-H), 3.53, 3.73, 3.78, 3.85 (4 s, 3 H each, OMe), 4.95 (s, 1 H, 3′-H), 5.12, 5.15 (AB system, $^2J_{A,B}$ = 15.6 Hz, 2 H, 6-H), 6.43, 6.81 (2 d, ^3J = 8.8 Hz, 1 H each, 5′-H, 6′-H), 6.89 (s, 1 H, 5-H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 22.6, 24.0 (2 t, C-3, C-4), 55.7, 56.9, 58.5, 61.9 (4 q, OMe), 68.3 (t, C-6), 83.8 (d, C-3′), 103.7 (d, C-5′), 111.3 (s, Ar), 115.1 (s, C-2), 115.4 (d, C-6′), 115.9 (s, Ar), 116.4 (d, C-5), 132.1, 139.3, 139.5, 144.9, 147.6, 148.5, 151.7 (7 s, Ar), 168.7 (s, C-8).

MS (EI, 80 eV, 130 °C): *m*/*z* (%) = 414 (74, $[M]^+$), 382 (100, $[M - MeOH]^+$), 221 (85).

Anal. Calcd for $C_{22}H_{22}O_8$ (414.1): C, 63.76; H, 5.35. Found: C, 63.48; H, 5.55.

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