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Spiroketals

Model Studies towards Functionalized Bisbenzannulated [5,6]-Spiroketals

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Dedicated to Professor Horst Kunz on the occasion of his 75th birthday

Abstract: Following up on our previous model studies on the synthesis of simple bisbenzannulated [5,6]-spiroketals we here report the preparation of new examples of this entity with a variation in their substitution pattern. The regioselective introduction of functional groups in the C-3 or C-3′ positions (rubromycin numbering) may either take place prior to the spiroketalization by α-functionalizations of the ketone moiety of the precursor or in a subsequent step by the nucleophilic substitution of the benzylic hydroxy group of the previously described C-3-hydroxylated spiroketal. By applying these methods we could synthesize new methyl-substituted, hydroxylated, halogenated and amino-substituted bisbenzannulated [5,6]-spiroketals in good overall yields.

Introduction

In our previous study towards bisbenzannulated [5,6]-spiroketals we established a robust and modular entry to this unique class of molecules that represent the key structural feature of the rubromycin natural product family.[1] This highly convergent approach utilizes lithiated methoxyallene as a signature C_3-building block[2] and furnishes a set of differently substituted spiroketals, which all possess a benzylic hydroxy group at their C-3 position (rubromycin numbering; see Figure 1a). As the spiroketal scaffold has been recognized as crucial pharmacophore for the biological activity of the rubromycins (e.g. to inhibit human telomerase and HIV reverse transcriptase),[3] these small molecules are therefore attractive targets in their own right.[4] In this report, we would like to summarize some of our recent efforts towards the synthesis of simple bisbenzannulated [5,6]-spiroketals with a variation of the substitution pattern of their spiroketal core. As a viable model substrate we sought after the preparation of the simple ketone **1**, which may then be functionalized in its α-positions through regioselective enolate formation in order to introduce additional functional groups (Figure 1c).

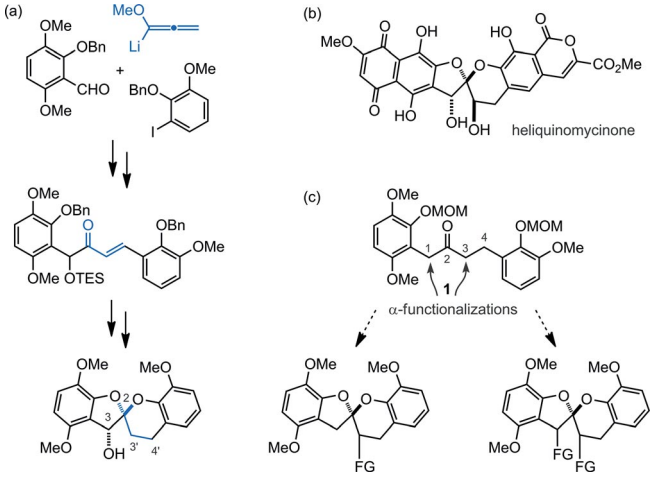

Figure 1. (a) Our previous methoxyallene-based approach towards simple bisbenzannulated [5,6]-spiroketals. (b) Heliquinomycinone, as an example of a rubromycin natural product. (c) Envisaged α-functionalizations of ketone **1** for the introduction of functional groups.

Results and Discussion

As illustrated in Scheme 1 the synthesis to the key intermediate ketone **1** commenced with the preparation of the known arenecarbaldehyde **3**. In modification of the original procedure,[5] the required Dakin oxidation of dimethoxybenzaldehyde **2** was achieved with 30 % aq. H_2O_2 in the presence of catalytic amounts of SeO_2 (Syper modification) instead of *m*-CPBA.[6] The replacement of the peracid by aq. H_2O_2 as stoichiometric oxidant greatly facilitated the preparation of the corresponding phenol, especially when the reaction was conducted on a larger scale (0.1 mol). Next, the alkylation of the phenol with MOMCl was followed by *ortho*-formylation to furnish **3**, which was then carried on to the benzylic bromide **4**. Its substitution with lithiated methoxyallene was followed by mild acidic hydrolysis of the primary allenyl adduct with dilute aq. H_2SO_4 to cleanly afford the enone **5**. This enone served as acceptor for the Cu^I-mediated conjugate addition of simple aryl Grignard reagents

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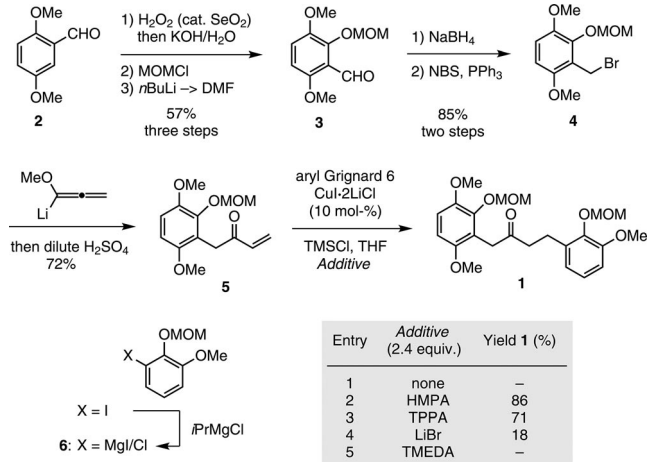
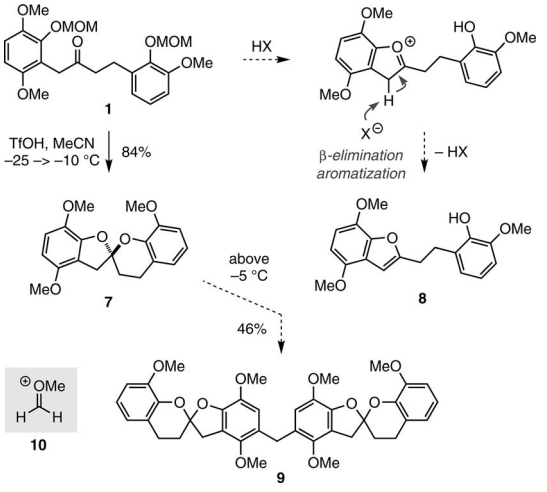
such as **6**,[7] which were conveniently prepared from their parent aryl iodides by a fast and clean magnesium/halogen exchange reaction according to a protocol of the Knochel group.[8] For the conjugate addition, best results were still obtained in the presence of 2.4 equiv. of HMPA and 2.0 equiv. of TMSCl in THF (–40 °C → room temp.) with a 1.2-fold excess of the aryl Grignard reagent **6**. Subsequent slightly acidic workup with saturated aq. NH_4Cl solution readily hydrolyzed the intermediate silyl enolether and reliably provided ketone **1** even on a multi-gram scale. Additionally, a brief survey of applicable substitutes for the carcinogenic HMPA revealed the analogous pyrrolidino derivative TPPA[9] to be almost equally efficient, whereas LiBr[10] gave the desired product only in minute amounts, and TMEDA[11] completely failed to promote the reaction.



Entry	*Additive* (2.4 equiv.)	Yield **1** (%)
1	none	–
2	HMPA	86
3	TPPA	71
4	LiBr	18
5	TMEDA	–

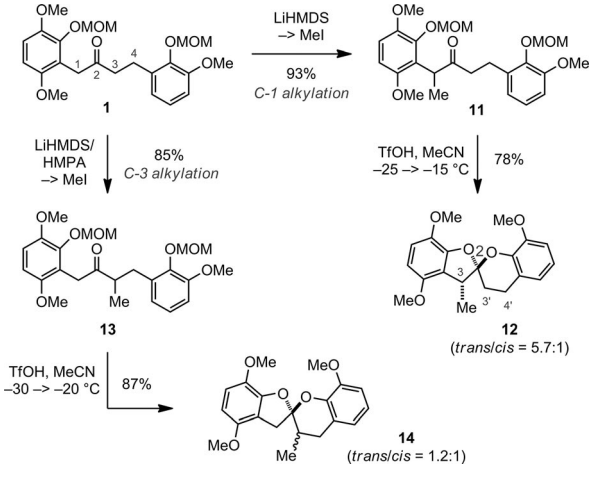
Scheme 1. Scalable route to ketone **1** and brief screening of various additives as replacement for HMPA.

First we evaluated conditions for the conversion of **1** into the simple and unfunctionalized [5,6]-spiroketal **7**, which represents the key structural feature of the natural product γ-rubromycin.[12] It has already been recognized that ketones such as **1** are highly susceptible to an irreversible β-elimination/aromatization process under strongly acidic or basic conditions.[13] Hence, a careful evaluation of the reaction conditions, including the screening of various Lewis and Brønsted acids as well as solvents, eventually identified catalytic amounts of triflic acid (10 mol-% TfOH) in MeCN as optimal to achieve a smooth conversion of **1** to spiroketal **7** with the formation of the undesired benzofuran derivative **8** being sufficiently suppressed.[14] Still, for optimal results the temperature profile (–25 to –10 °C) had to be accurately monitored as we observed the generation of a 1:1 mixture of diastereomeric diarylmethanes **9** at temperatures above –5 °C. Undoubtedly, its formation results from an initial Friedel–Crafts-type reaction of **7** with the electrophilic oxocarbenium ion **10** to form an intermediate *ortho*-quinone methide, which is immediately trapped by a second equivalent of **7**. The highly reactive species **10** is generated as by-product from the acid-induced fragmentation of the MOM groups and could in principle be scavenged by the addition of competing nucleophilic reagents such as 1,2,4-trimethoxybenzene (Scheme 2).[15]



Scheme 2. Synthesis of spiroketal **7** under mild acid conditions and formation of compound **9** as side product.

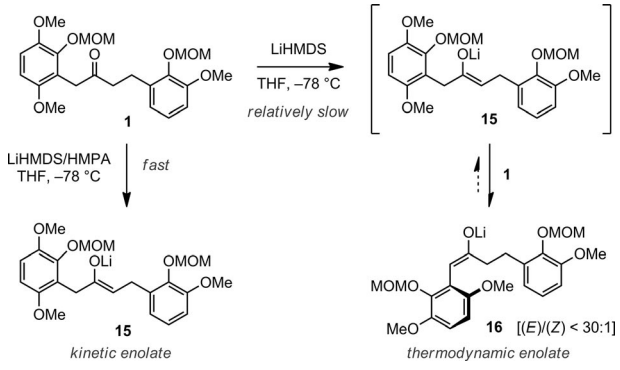
Next, we focused on the regioselective introduction of alkyl groups (e.g. methyl groups) at the C-3 and C-3′ positions of the spiroketal by α-alkylation of the parent ketone **1**. Sequential treatment of **1** with LiHMDS and MeI at low temperature (–78 °C) in THF cleanly furnished the C-1-methylated ketone **11**, which was further converted into spiroketal **12** with a preference for the *trans*-configured diastereoisomer as determined by ^1H NMR spectroscopy. A switch in regioselectivity for the α-alkylation of ketone **1** was efficiently achieved by the presence of HMPA, which led to the C-3-methylated ketone **13** along with ca. 10 % of its regioisomer **11**. Here, the acid-mediated spiroketalization gave the spiroketal **14** as a 1.2:1 mixture of inseparable isomers with essentially no stereoselection (Scheme 3).



Scheme 3. Regioselective access to the C-3- and C-3′-methyl-substituted bisbenzannulated [5,6]-spiroketals **12** and **14**.

As the base was employed in excess (2.0 equiv.) and as the order of addition of the reagents (base to the ketone or ketone to the base) did not noticeably affect the outcome of the regioselectivity, we assume that the deprotonation of **1** with LiHMDS to deliver the putative lithium enolate **15** had to occur relatively slow at –78 °C in THF. With ketone **1** still present in the reaction

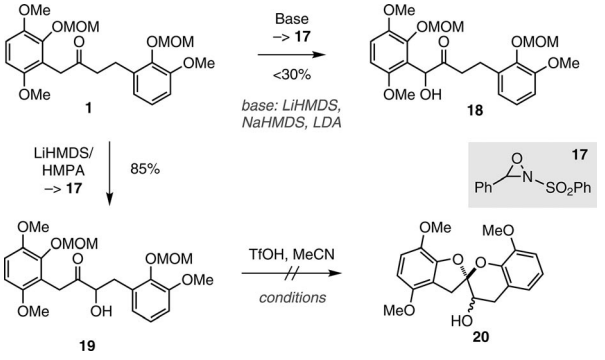
mixture, the thermodynamic enolate **16** [(*E*)/(*Z*) < 30:1] may be formed by equilibration within 30 min prior to its trapping with electrophiles. With the presence of HMPA in the reaction mixture, however, the deprotonation of **1** may be drastically accelerated, thus securing the kinetically controlled lithium enolate **15**. The enolate geometries as illustrated in Scheme 4 were determined by ^{1}H NMR spectroscopy of the respective silyl enolethers (see the Supporting Information).



Scheme 4. Additive-controlled regioselective formation of enolates **15** or **16** by starting from ketone **1**.

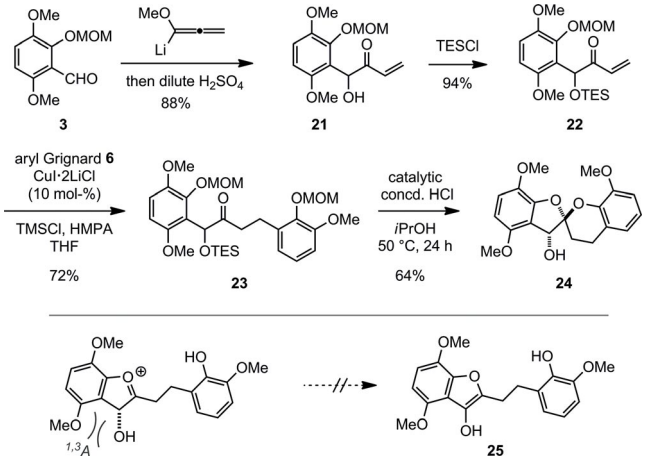
With a relatively good control over the regioselectivity for the α-functionalization of ketone **1** we considered the use of chiral electrophilic oxygen-transfer reagents to allow the reagent-controlled enantioselective introduction of hydroxy groups at the C-1 or C-3 positions.[16] Unfortunately, the sequential treatment of **1** with base and, e.g., camphorsulfonic acid derived oxaziridines completely failed to yield any C-1-oxidized ketone **18**. Some conversion could be achieved with the achiral and sterically less demanding Davis oxaziridine **17**,[17] but this required the warming up to room temperature and also resulted in a significant degree of unspecific decomposition of the substrate. The reluctance towards oxidation in the C-1 position with oxaziridines has also been recognized by the Kozlowski group during their studies towards purpuromycin.[18] A plausible explanation might be the effective shielding of the enolate faces by the two bulky *ortho* substituents (OMe and OMOM) at the adjacent aryl moiety. In contrast to this, the oxidation of the C-3 position of **1** went remarkably well to give **19**; however, this substrate then failed to undergo the spiroketalization to **20** under a variety of conditions and only resulted in a rapid decomposition. We speculate that a dehydration to an enone or its respective conjugated oxocarbenium ion may occur, which then is not capable to effectively engage in a spiroketalization anymore (Scheme 5).

With these results in mind we reverted to our initial strategy for the assembly of 3-hydroxylated spiroketals, which included the addition of lithiated methoxyallene to the arenecarbaldehyde **3** to give the α-hydroxy enone **21**.[1a] The temporary silylation of the benzylic hydroxy group with TESCl was necessary to allow the assembly of ketone **23** by Cu^I-mediated conjugate addition of aryl Grignard reagent **6**. The spiroketalization of **23** to **24** was routinely carried out in the presence of catalytic amounts of concentrated aq. hydrochloric acid (HCl) with *i*PrOH as solvent at elevated temperature (50 °C). The spiroketal was



Scheme 5. Attempts of α-hydroxylations of the C-1 and C-3 position via the enolates of ketone **1**.

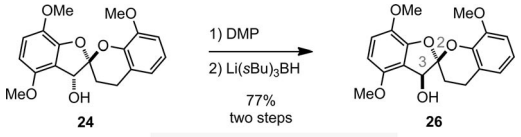
isolated as *trans*-configured diastereomer solely (*trans*/*cis* > 98:2), thus reflecting the thermodynamically equilibrated product ratio. In our previous model study we already found that for substrates with a benzylic hydroxy group slight heating was necessary – not only to achieve conversion, but also to accelerate the *cis*/*trans* equilibration.[1a] Importantly, under these conditions no β-elimination to the corresponding benzofuranone derivative **25** occurred, presumably due to an advantageous allylic strain ($^{1,3}A$) that is exerted by the adjacent methoxy group on the aryl moiety. This effectively prevents the intermediate oxocarbenium ion to undergo aromatization. In contrast to ketones such as **1** that are unsubstituted at C-1, the additional hydroxy group generally allows harsher reaction conditions to be employed for the crucial spiroketalization. Moreover, the use of MOM protecting groups and also reverting to a Cu^I-mediated strategy to assemble the two halves of the molecule, considerably shortened the route from arenecarbaldehyde **2** to the spiroketal **24** to a total of 9 steps in comparison to 14 steps in our previous study (Scheme 6).



Scheme 6. Improved route to the 3-hydroxy-substituted *trans*-configured spiroketal **24** via ketone **23**.

The benzylic hydroxy group of **24** can also serve as handle for diversification. First, the inversion of the 3-hydroxy configuration was examined, which was readily achieved by oxidation with Dess–Martin periodinane (DMP) to give the intermediate ketone. Its reduction with sterically demanding borohydride re-

agents (e.g. L-selectride) exclusively led to the *cis*-configured spiroketal **26**. Both diastereoisomers are readily distinguishable by comparison of diagnostic signals in their respective ^{1}H and ^{13}C NMR spectra, with significant differences in their chemical shifts of the 3-hydroxy hydrogen signals and those of the quaternary ketal carbon atom C-2. The downfield-shifted and broadened signal of the 3-hydroxy group of **26** is also indicative of a hydrogen-bonding interaction between this group and the dihydropyran ketal oxygen atom in solution. Further elucidation of the structure of **26** was provided by an X-ray crystal-structure analysis[19] that again highlights the almost planar structure of the dihydrobenzofuran moiety known for these entities (Scheme 7).[20] In the solid state two molecules of **26** are associated by two hydrogen bonds [O–O 3.013(2) Å; Figure 2].



$^{1}H/^{13}C$ NMR (δ in ppm)	3-OH	C-2
24	2.17 (d)	112.1
26	3.45 (br. s)	107.3

Scheme 7. Inversion of configuration at C-3 of compound **24** leading to *cis*-configured spiroketal **26**.

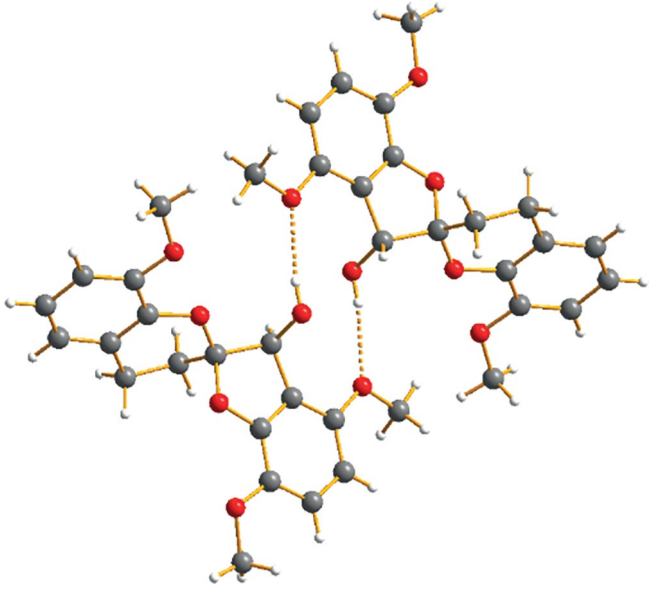
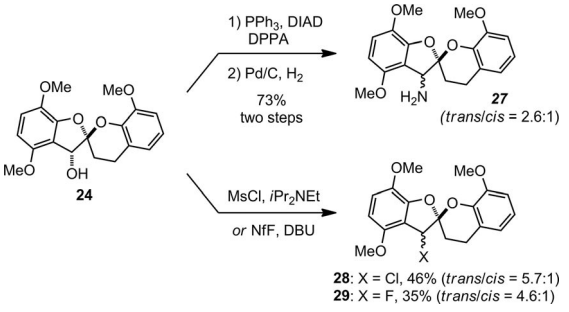


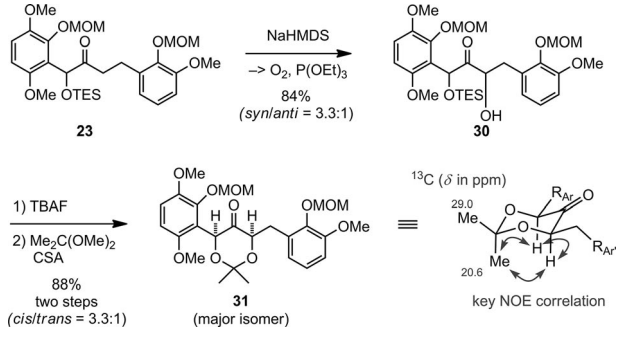
Figure 2. Molecular structure[21] of **26** displaying the hydrogen bonds. The second molecule is generated by the crystallographic inversion center.

Some examples for the diversification at the C-3 position are shown in Scheme 8. For instance, we converted **24** into its azide employing Mitsunobu conditions (Bose modification),[22] which was then reduced (Pd/C, H_2) to furnish a separable mixture of diastereomeric benzylic amines **27** (*trans*/*cis* = 2.6:1). The relative configurations were tentatively assigned according to the chemical shift of the quaternary ketal carbon atom C-2. The moderate preference for the *trans*-configured spiroketal suggests the intermediacy of a resonance-stabilized oxocarbenium ion at C-3 during the substitution process. Accordingly, deoxyhalogenations were readily achieved by treatment of alcohol **24** with methanesulfonyl chloride (MsCl) or nonaflyl fluoride (NfF)[23] to afford the corresponding chloro- and fluoro-substituted spiroketals **28** and **29**, respectively, in moderate yields and diastereoselectivities (Scheme 8).



Scheme 8. Conversion of **24** into the amino-, chloro- and fluoro-substituted spiroketals **27**–**29**.

Next, we investigated the introduction of the second hydroxy group in C-3 position that would provide an oxidation pattern as it was found in the spiroketal core of the natural product heliquinomycinone (Figure 1b). Therefore, directing a gentle stream of gaseous molecular oxygen (O_2) through a solution of the sodium enolate of protected ketone **23** in the presence of triethyl phosphite efficiently afforded the dihydroxylated ketone **30** as an inseparable 3.3:1 mixture of *syn*/*anti* diasteromers in 84 % yield (Scheme 9).[24]

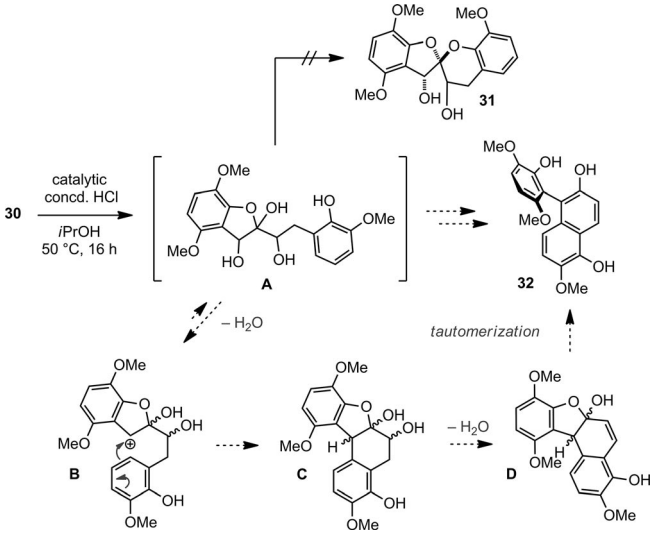


Scheme 9. Electrophilic hydroxylation of **23** leading to dihydroxylated ketone **30**, its conversion into acetonide **31**, and assignment of the relative configuration.

A subsequent formation of the corresponding acetonide **31** allowed the assignment of their relative configurations: the chemical shifts for the axial and equatorial acetonide methyl groups in the respective ^{13}C NMR spectra as well as key NOE correlations are in agreement with the assigned *syn* configuration for the major isomer.[25] The origin of the observed moderate diastereoselectivity is still unclear, but it may arise from a facial discrimination of the sodium (*Z*)-enolate by the adjacent bulky OTES group. It is still unclear why in this particular case the sterically more demanding Davis oxaziridine **17** cleanly led

to a 1:1 mixture of *syn*/*anti*-**30**, with no stereoselection at all (Scheme 9).

With α,α′-dihydroxy-substituted ketone **30** in hand we next looked into its ketalization to the spiroketal **31**. Unfortunately, treatment of **30** with acid did not lead to the desired spiroketal **31**, and the reaction was predominately characterized by unspecific decomposition. We could isolate a product in small amounts that we assigned as the atropisomeric naphthalene derivative **32**, which was found to be relatively labile and sensitive towards autoxidation in air. We speculate that the putative hemiketal **A** readily suffers an acid-mediated dehydration to produce the resonance-stabilized C-3 carbenium ion **B** followed by an intramolecular Friedel–Crafts alkylation to **C** and a second dehydration to **D** (or vice versa) to eventually form **32**. Strain release and tautomerization to the aromatic naphthalene portion may account as driving forces to favor this competing reaction pathway (Scheme 10).[26]



Scheme 10. Attempted spiroketalization of compound **30** and proposed reaction pathway to naphthalene derivative **32**.

Conclusions

This model study is a follow-up of our previous methoxyallene-based approach to simple bisbenzannulated [5,6]-spiroketals. An efficient Cu^{I}-mediated strategy for the assembly of the required basic spiroketalization precursors significantly improved the overall efficiency to these entities and allowed the rapid preparation of new spiroketals with different substitution patterns. In principle, the introduction of a more diverse set of substituents by α-functionalization of the key ketone **1** should be possible. However, some substitutents in the C-3 position of the spiroketalization precursors may not be well tolerated during the subsequent spiroketalization event, in particular if these substrates possess the propensity to undergo competing elimination reactions under acidic conditions. For that reason a simple spiroketal with two hydroxy groups (in C-3 and C-3′ positions) – as found in the core to the natural product heliquinomycinone – could not be accessed by this approach yet.

Experimental Section

General Information: See the Supporting Information.

Typical Experimental Procedures

1-[3,6-Dimethoxy-2-(methoxymethoxy)phenyl]but-3-en-2-one (5): To a cold (–78 °C) solution of methoxyallene (3.21 g, 45.8 mmol) in THF (50 mL) was added *n*BuLi (15.3 mL, 38.3 mmol, ca. 2.5 M in hexane). After 15 min at this temperature, benzylic bromide **4** (4.44 g, 15.3 mmol in 10 mL of THF) was added. The mixture was warmed up and stirred at room temperature for 2 h. Then dilute H_2SO_4 (5 % aq., 50 mL) and EtOAc were sequentially added. The layers were separated, and the aqueous phase was extracted three times with EtOAc. The combined organic layers were washed with satd. NaCl solution (aq.), dried with Na_2SO_4, filtered, and concentrated. Column chromatography (hexanes/EtOAc = 6:1) provided 2.92 g (72 %) of enone **5** as pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.50, 3.71, 3.79 (3 s, 3 H each, OMe), 3.98 (s, 2 H, 1-H), 5.07 (s, 2 H, OCH_2), 5.74 (dd, J = 1.5, 10.4 Hz, 1 H, 4-H), 6.29 (dd, J = 1.5, 17.5 Hz, 1 H, 4-H), 6.41 (dd, J = 10.4, 17.5 Hz, 1 H, 3-H), 6.58, 6.79 (2 d, J = 8.9 Hz, 1 H each, Ar) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 36.5 (t, C-1), 55.8, 56.1, 57.5 (3 q, OMe), 99.0 (t, OCH_2), 105.6, 111.1 (2 d, Ar), 118.5 (s, Ar), 127.7 (t, C-4), 135.5 (d, C-3), 145.3, 146.4, 152.1 (3 s, Ar), 197.8 (s, C-2) ppm. IR (ATR): $\tilde{\nu}$ = 3000–2835 (C–H), 1690 (C=O), 1615, 1595 (C=C), 1490, 1465, 1400 cm^{-1}. HRMS (ESI-TOF): calcd. for $[M + Na]^+$ 289.1052, found 289.1053. $C_{14}H_{18}O_5$ (266.3): C 63.15, H 6.81; found C 63.07, H 6.95.

1-[3,6-Dimethoxy-2-(methoxymethoxy)phenyl]-4-[3-methoxy-2-(methoxymethoxy)phenyl]butan-2-one (1): To a cold (–40 °C) and well-stirred solution of 1-iodo-3-methoxy-2-(methoxymethoxy)-benzene (2.04 g, 6.89 mmol) in THF (10 mL) was added *i*PrMgCl (ca. 1.7 M in THF, 3.75 mL, 6.35 mmol). This freshly prepared aryl Grignard reagent was then rapidly transferred by cannula into a mixture of enone **5** (1.41 g, 5.30 mmol), HMPA (2.20 mL, 12.7 mmol), CuI•2LiCl (0.10 M in THF, 2.50 mL) and TMSCl (1.34 mL, 10.6 mmol) in THF (30 mL) at –40 °C. The cooling bath was immediately removed and the mixture stirred at room temperature for 1 h. Then satd. NH_4Cl solution (aq.) and EtOAc were added. The layers were separated, and the aqueous phase was extracted three times with EtOAc. The combined organic layers were washed with satd. NaCl solution (aq.), dried with Na_2SO_4, filtered, and concentrated. Column chromatography (hexanes/EtOAc = 4:1 → 2:1) provided 1.98 g (86 %) of ketone **1** as pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.77 (m_c, 2 H, 3-H), 2.96 (m_c, 2 H, 4-H), 3.50, 3.56, 3.71, 3.78, 3.81 (5 s, 3 H each, OMe), 3.80 (s, 2 H, 1-H), 5.06, 5.07 (2 s, 2 H each, OCH_2), 6.56, 6.76 (2 d, J = 9.0 Hz, 1 H each, Ar), 6.75–6.78 (m, 2 H, Ar), 6.96 (t, J = 8.2 Hz, 1 H, Ar) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 24.5 (t, C-4), 38.8 (t, C-1), 42.3 (t, C-3), 55.6, 55.7, 56.1, 57.3, 57.5 (5 q, OMe), 98.8, 99.0 (2 t, OCH_2), 105.5, 110.2, 111.0 (3 d, Ar), 118.8 (s, Ar), 122.0, 124.1 (2 d, Ar), 135.6, 144.2, 145.3, 146.4, 152.0, 152.0 (6 s, Ar), 208.0 (s, C-2) ppm. IR (ATR): $\tilde{\nu}$ = 2995–2780 (C–H), 1710 (C=O), 1600, 1585, 1485, 1440 cm^{-1}. HRMS (ESI-TOF): calcd. for $[M + Na]^+$ 457.1838, found 457.1846. $C_{23}H_{30}O_8$ (434.5): calcd. C 63.58, H 6.96; found C 63.65, H 7.01.

4,7,8′-Trimethoxy-3*H*-spiro[benzofuran-2,2′-chroman] (7): To a cold (–25 °C) solution of ketone **1** (109 mg, 0.25 mmol) in MeCN (12.5 mL) was added TfOH (20 μL of a freshly prepared 1.3 M stock solution of TfOH in MeCN, 25 μM). The mixture was warmed up to –10 °C over 15 min. Then satd. Na_2CO_3 solution (aq. 1 mL), water, and EtOAc were sequentially added. The layers were separated, and the aqueous phase was extracted three times with EtOAc. The combined organic layers were washed with satd. NaCl solution (aq.), dried with Na_2SO_4, filtered, and concentrated. Column chromatog-

raphy (hexanes/EtOAc = 4:1) provided 69 mg (84 %) of spiroketal **7** as colorless solid. M.p. 118–122 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.17 (td, *J* = 5.8, 13.5 Hz, 1 H, 3′-H), 2.35 (ddd, *J* = 2.8, 5.8, 13.5 Hz, 1 H, 3′-H), 2.79 (ddd, *J* = 2.8, 5.6, 16.5 Hz, 1 H, 4′-H), 3.26, 3.57 (AB system, *J* = 16.8 Hz, 1 H each, 3-H), 3.29 (m_c, 1 H, 4′-H), 3.76, 3.78, 3.79 (3 s, 3 H each, OMe), 6.35 (d, *J* = 8.9 Hz, 1 H, 5-H), 6.69–6.76 (m, 3 H, 6-H, Ar), 6.84 (t, *J* = 7.9 Hz, 1 H, Ar) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.8 (t, C-4′), 30.6 (t, C-3′), 40.1 (t, C-3), 55.5, 55.9, 56.6 (3 q, OMe), 102.8, 109.9 (2 d, C-5, C-6), 110.2 (s, C-2), 112.6 (d, Ar), 114.0 (s, Ar), 120.5, 121.0 (2 d, Ar), 122.4, 138.9, 141.9, 147.3, 148.4, 150.4 (6 s, Ar) ppm. IR (ATR): $\tilde{\nu}$ = 3000–2835 (C–H), 1610, 1585, 1510, 1480, 1460, 1440 cm^{-1}. HRMS (ESI-TOF): calcd. for $[M + Na]^+$ 351.1208, found 351.1224. $C_{19}H_{20}O_5$ (328.4): calcd. C 69.50, H 6.14; found C 69.54, H 6.23.

4-[3,6-Dimethoxy-2-(methoxymethoxy)phenyl]-1-[3-methoxy-2-(methoxymethoxy)phenyl]pentan-3-one (11): To a cold (–78 °C) solution of ketone **1** (87 mg, 0.20 mmol) in THF (5 mL) was added dropwise LiHMDS (1.0 M in THF/ethylbenzene, 0.40 mL, 0.40 mmol). The mixture was stirred at this temperature for 30 min. Then methyl iodide (142 mg in 0.50 mL of THF, 1.00 mmol) was added. The mixture was warmed up and stirred at room temperature for 30 min. Then satd. NH_4Cl solution (aq.) and EtOAc were added. The layers were separated, and the aqueous phase was extracted three times with EtOAc. The combined organic layers were washed with satd. NaCl solution (aq.), dried with $MgSO_4$, filtered, and concentrated. Column chromatography (hexanes/EtOAc = 3:1) provided 83 mg (93 %) of **11** as pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.35 (d, *J* = 6.7 Hz, 3 H, Me), 2.55 (m_c, 2 H, 3-H), 2.90 (m_c, 2 H, 4-H), 3.52, 3.54, 3.66, 3.78, 3.78 (5 s, 3 H each, OMe), 4.02 (q, *J* = 6.7 Hz, 1 H, 1-H), 5.00, 5.02 (AB system, J_{AB} = 5.8 Hz, 1 H each, OCH_2), 5.08, 5.10 (AB system, J_{AB} = 6.0 Hz, 1 H each, OCH_2), 6.52, 6.74 (2 d, *J* = 9.2 Hz, 1 H each, Ar), 6.69–6.70 (m, 2 H, Ar), 6.91 (t, *J* = 8.0 Hz, 1 H, Ar) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.5 (q, Me), 24.8 (t, C-4), 40.3 (t, C-3), 43.8 (t, C-1), 55.4, 55.5, 56.0, 57.3, 57.4 (5 q, OMe), 98.7, 99.1 (2 t, OCH_2), 105.8, 110.0, 110.8, 121.9, 124.0 (5 d, Ar), 125.5, 135.9, 144.1, 144.7, 146.4, 151.4, 152.0 (7 s, Ar), 210.2 (s, C-2) ppm. IR (ATR): $\tilde{\nu}$ = 2935–2780 (C–H), 1710 (C=O), 1585, 1485, 1465, 1440 cm^{-1}. HRMS (ESI-TOF): calcd. for $[M + Na]^+$ 471.1995, found 471.2008. $C_{24}H_{32}O_8$ (448.5): calcd. C 64.27, H 7.19; found C 63.78, H 7.06.

4,7,8′-Trimethoxy-3-methyl-3*H*-spiro[benzofuran-2,2′-chroman] (12): To a cold (–25 °C) solution of **11** (225 mg, 0.50 mmol) in MeCN (10.0 mL) was added TfOH (25 µL of a freshly prepared 2.2 M stock solution of TfOH in MeCN, 50 µM). The mixture was warmed up to –15 °C over 15 min. Then satd. Na_2CO_3 solution (aq. 1 mL), water, and EtOAc were sequentially added. The layers were separated, and the aqueous phase was extracted three times with EtOAc. The combined organic layers were washed with satd. NaCl solution (aq.), dried with Na_2SO_4, filtered, and concentrated. Column chromatography (hexanes/EtOAc = 8:1) provided 25 mg of *cis*-**12**, 94 mg of *trans*-**12** and 15 mg as mixed fraction of both products as colorless solids in a combined yield of 78 %. *cis*-**12**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.51 (d, *J* = 7.2 Hz, 3 H, Me), 2.06 (m_c, 1 H, 3′-H), 2.28 (ddd, *J* = 2.9, 5.7, 13.5 Hz, 1 H, 3′-H), 2.77 (ddd, *J* = 2.9, 5.7, 16.2 Hz, 1 H, 4′-H), 3.26 (m_c, 1 H, 4′-H), 3.50 (q, *J* = 7.2 Hz, 1 H, 3-H), 3.76, 3.77, 3.80 (3 s, 3 H each, OMe), 6.36, 6.68 (2 d, *J* = 8.9 Hz, 1 H each, 5-H, 6-H), 6.71–6.75 (m, 2 H, Ar), 6.83 (t, *J* = 7.8 Hz, 1 H, Ar) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 12.4 (q, Me), 21.7 (t, C-4′), 30.3 (t, C-3′), 45.7 (d, C-3), 55.6, 56.4, 56.7 (3 q, OMe), 103.0 (d, C-5), 110.4 (s, C-2), 110.8 (d, Ar), 112.5 (d, C-6), 119.0 (s, Ar), 120.3, 121.1 (2 d, Ar), 122.7, 139.0, 142.4, 146.3, 148.6, 151.1 (6 s, Ar) ppm. *trans*-**12**: Melting range 125–135 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.32 (d, *J* = 7.3 Hz, 3 H, Me), 2.05 (td, *J* = 5.8, 13.4 Hz, 1 H, 3′-H), 2.32 (ddd, *J* = 2.4, 5.8, 13.4 Hz, 1 H, 3′-H), 2.83 (ddd, *J* = 2.4, 5.8, 16.5 Hz, 1 H, 4′-H), 3.30 (m_c, 1 H, 4′-H), 3.72, 3.73 (2 s, 3 H each, OMe), 3.76 (q, *J* = 7.3 Hz, 1 H, 3-H), 3.80 (s, 3 H, OMe), 6.36, 6.68 (2 d, *J* = 8.9 Hz, 1 H each, 5-H, 6-H), 6.70–6.75 (m, 2 H, Ar), 6.83 (t, *J* = 7.8 Hz, 1 H, Ar) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.0 (q, Me), 21.6 (t, C-4′), 25.9 (t, C-3′), 45.0 (d, C-3), 55.4, 56.0, 56.6 (3 q, OMe), 103.1 (d, C-5), 110.2 (d, Ar), 111.7 (s, C-2), 112.5 (d, C-6), 120.2 (s, Ar), 120.3, 121.0 (2 d, Ar), 122.8, 139.0, 142.1, 146.1, 148.4, 150.7 (6 s, Ar) ppm. *cis*/*trans*-**12**: IR (ATR): $\tilde{\nu}$ = 3000–2835 (C–H), 1735, 1605, 1585, 1510, 1485, 1460 cm^{-1}. HRMS (ESI-TOF): calcd. for $[M + Na]^+$ 365.1365, found 365.1375. $C_{20}H_{22}O_5$ (342.4): calcd. C 70.16, H 6.48; found C 70.14, H 6.51.

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