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Total Synthesis of cyclo-Mumbaistatin Analogues through Anionic Homo-Fries Rearrangement

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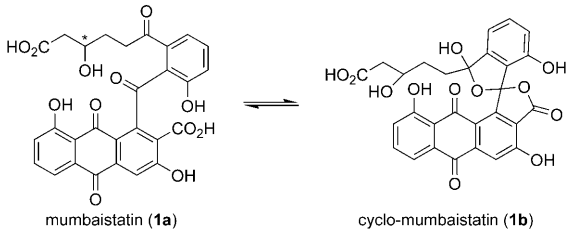
Abstract: The structurally unique polyketide mumbaistatin is the strongest naturally occurring inhibitor of glucose-6-phosphate translocase-1 (G6P-T1), which is a promising target for drugs against type-2 diabetes mellitus and angiogenic processes associated with brain tumor development. Despite its high relevance, mumbaistatin has so far withstood all attempts towards its total synthesis. In the present study an efficient total synthesis of a deoxy-mumbaistatin analogue containing the complete carbon skeleton and a spirolactone motif closely resembling the natural product in its cyclized form was elaborated. Key steps of the synthesis are a Diels–Alder cycloaddition for the construction of the fully functionalized anthraquinone moiety and an anionic homo-Fries rearrangement to build up the tetra-*ortho*-substituted benzophenone core motif, from which a spiroketal lactone forms in a spontaneous process. The elaborated strategy opens an entry to a variety of new analogs of mumbaistatin and cyclo-mumbaistatin and may be exploited for the total synthesis of the natural product itself in the future.

Keywords: natural products · phosphatase inhibitor · polyketides · spirolactones · total synthesis

Introduction

In 1997, Ramakrishna and co-workers discovered a novel natural product by cultivation of the microorganism *Streptomyces sp*. DSM 11641, isolated from a soil sample from the Hiranyakeshi river bed near Amboli, in Maharashtra, India.[1] According to the north Indian metropolis Mumbai (formerly Bombay) the compound was named mumbaistatin (**1**, Scheme 1). The unique structure of this polyketide was elucidated two years later by extensive 2D NMR studies and by single crystal X-ray analysis of a trimethylated dehydration product.[2] Based on these studies, mumbaistatin is supposed to exist in an equilibrium between the "open" diketo (**1a**) and a "closed" spiroketal lactone form (**1b**, referred to as cyclo-mumbaistatin). The absolute configuration of the only stereocenter in the alkyl side chain of **1** could not be determined. However, the stereocenter is supposed to be *S*-configured based on the comparison with the known naphthoquinone antibiotic juglomycin D[3] and its quasi-dimerization product juglorubin,[4] which were both isolated as fermentation products from the same *Streptomyces* strain and assumed to be formed in a related biosynthetic pathway.



Scheme 1. Equilibrium between the "open" diketo form (**1a**) and the "closed" spirocyclic form (**1b**) of mumbaistatin.

Biological studies unveiled mumbaistatin to be the strongest naturally occurring inhibitor of glucose-6-phoshate translocase 1 (G6P-T1) known to date ($IC_{50}=5$ nM).[2] G6P-T1 is part of the glucose-6-phosphatase (G6Pase) enzyme complex, which catalyzes the breakdown of glucose-6-phosphate (G6P) into glucose and phosphate. This process represents the terminal step in both pathways of the hepatic glucose production, gluconeogenesis and glucogenolysis. The activity of G6Pase is several folds higher in diabetic animals and probably in diabetic humans, which results in an increased hepatic glucose production and an elevated blood sugar level. Hence, the regulation of this enzyme is a highly interesting target for pharmacological intervention in the treatment of the non-insulin dependent type II diabetes mellitus (NIDDM).[5] Moreover, recent studies revealed G6P translocase to play a crucial role in the proliferation of brain tumors.[6] Since glioma growth often cannot be suspended by conventional methods, for example, surgical resection or radiation, the selective regulation of G6P activity offers a

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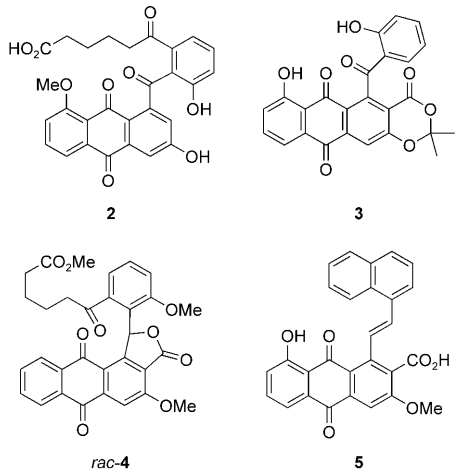
promising therapeutic approach. In this sense, the elaboration of a synthetic access to mumbaistatin (**1**) and derivatives thereof would constitute an important contribution towards the development of new and improved antidiabetic drugs as well as in the fight against cancer.

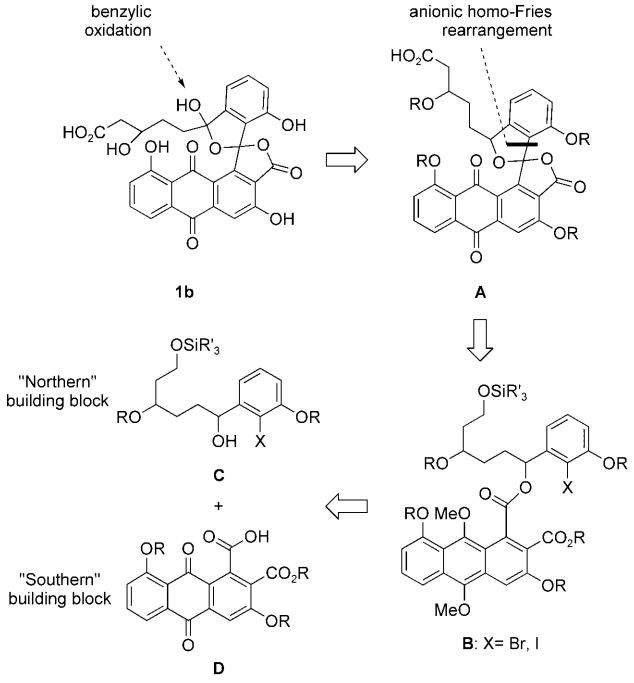
The outstanding biological properties of mumbaistatin have stimulated extensive efforts towards the total synthesis of this natural product and its structural analogues. First studies in the groups of Schmalz[7] and Krohn[8] led to the preparation of the tri-*ortho*-substituted benzophenones **2** and **3** (Scheme 2) following different strategies. While the anthraquinone **2** was synthesized through nucleophilic addition of an aryllithium species to a 1-formyl anthracene derivative and subsequent oxidation of the resulting benzhydrol,[7] the benzophenone scaffold of **3** was constructed in a base-catalyzed aldol-type cyclization, followed by bromine-mediated photooxidation of the resulting diarylmethane intermediate.[8] In a second-generation approach, we later succeeded in the synthesis of lactone *rac*-**4**, which for the first time displayed the complete carbon skeleton of mumbaistatin.[9] Key steps of the elaborated sequence were a Pd-catalyzed Stille cross-coupling to generate a tetra-*ortho*-substituted diarylmethane intermediate and a titanium-mediated alkynylation of an aldehyde to introduce the upper (alkyl) side chain. Some semi-synthetic mumbaistatin analogues were also prepared by Khosla and co-workers starting from a fermentation-derived anthraquinone precursor.[10] In the course of subsequent structure activity relationships studies, the simplified derivative AD4-015 (**5**) was identified as a fairly potent G6P-T1 inhibitor ($IC_{50} = 2.5\ \mu M$).



Scheme 2. Mumbaistatin analogues synthesized in previous studies.

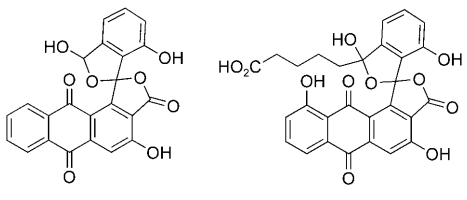
Despite all efforts, none of the synthetic strategies developed so far allowed to construct the tetra-*ortho*-substituted benzophenone core of mumbaistatin (or the spiroketal lactone system, respectively) with the proper functionalization pattern. We herein disclose the results of a study, which (following a new strategy) has led to the development of an efficient total synthetic access to close structural analogs of cyclo-mumbaistatin (**1b**).

General synthetic concept: Our new synthetic strategy (Scheme 3) is based on the consideration that the intrinsic propensity of the natural product to undergo spiro-lactonization might be exploited in a beneficial manner. Thus, we envisioned a spiro compound of type **A** to be a suitable pre-target structure from which the natural product would arise upon benzylic oxidation (e.g., via radical bromination) and global deprotection. Conceiving the pivotal spiroketal-lactone scaffold of **A** as a masked tetra-*ortho*-substituted benzophenone subunit, its construction by means of an anionic homo-Fries rearrangement of a diester of type **B** seemed feasible.[11] The required dimethoxyanthracene **B** in turn could be derived from a "Southern" anthraquinone carboxylic acid **D**, and a "Northern" building block **C** through simple esterification.



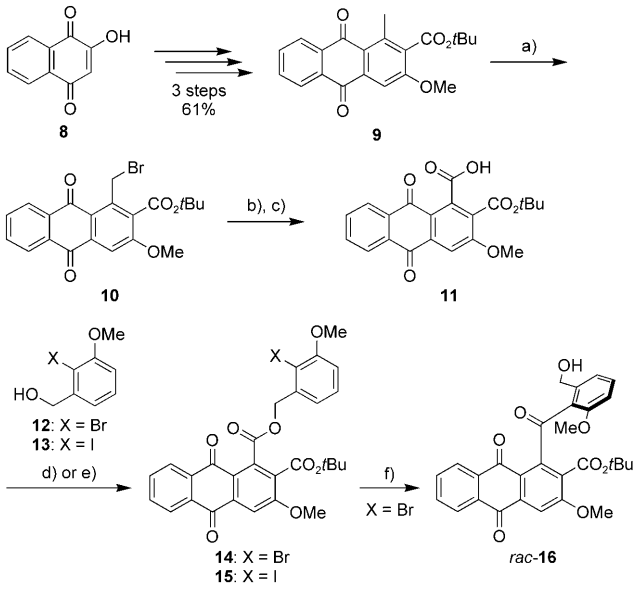
Scheme 3. Retrosynthetic analysis of cyclo-mumbaistatin (**1b**).

To examine the general feasibility of the synthetic concept, our first studies (presented in this work) focused on the most challenging task, that is, the construction of the spirolactone core motif, as represented by the model system *rac*-**6** (see below). Subsequently, we intended to probe the developed protocols also in the synthesis of deoxy-cyclo-



mumbaistatin (*rac*-**7**). Noteworthy, these two model compounds by themselves constitute potentially active agents and would be of value to gain insights into structure–activity relationships (SAR) of mumbaistatin-related compounds.

Evaluation of the strategy in the model series: According to our synthetic plan, a first goal was the preparation of the anthraquinone **11** as a simplified "Southern" building block of type **D** lacking one oxy-substituent (Scheme 4). As an appropriate precursor of **11** we considered the anthraquinone **9** which we had previously synthesized from naphthoquinone **8** exploiting a Diels–Alder cycloaddition to assemble the carbon skeleton.[9,12]



Scheme 4. Preparation of the diesters **14** and **15** and initial studies on the anionic homo-*Fries* rearrangement. a) NBS (1.95 equiv), BP (20 mol%), CCl_4, reflux, *hν* (vis), 24 h, 93%; b) NMO, RT, 16 h, 66%; c) $NaClO_2$, NaH_2PO_4, 2-methylbut-2-ene, THF/H_2O, 0°C to RT, 21 h, 83%; d) **12**, DIAD, PPh_3, THF, 0°C, then RT, 6 h, 64% of **14**; e) **13**, DIAD, PPh_3, THF, 0°C, then RT, 2 h, 88% of **15**; f) **14**, *t*BuLi (2.0 equiv), THF, −100 to −78°C, 45 min, 25%.

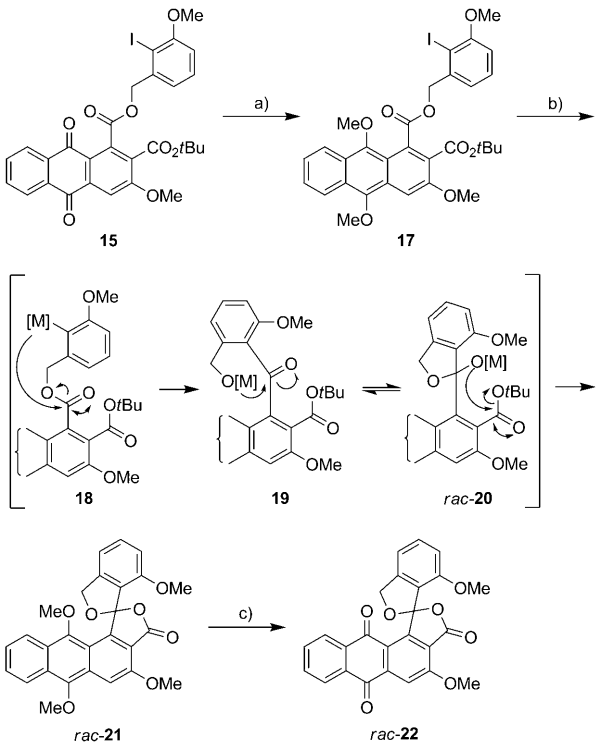
Initial attempts to directly convert the anthraquinone **9** into the monoester **11** failed. No conversion could be detected on treatment of **9** with various common reagents for benzylic oxidation, such as $KMnO_4$/pyridine,[13] $(Bu_4N)MnO_4$/pyridine,[14] $Na_2Cr_2O_7{\cdot}2H_2O$,[15] CrO_3/H_5IO_6,[16] *N*-hydroxyphthalimide/$Co(OAc)_2/O_2$,[17] $RuCl_3{\cdot}H_2O$/NaOCl/Bu_4NBr,[18] $NaIO_4$/LiBr/H_2SO_4,[19] $FeCl_3{\cdot}6H_2O$/*t*BuOOH.[20] We therefore had to perform the oxidation of the methyl substituent stepwise. After light-induced radical bromination of **9** using NBS in the presence of dibenzoyl peroxide (BP),[9,10] the resulting benzylic bromide **10** was converted into the corresponding aldehyde by reaction with *N*-methylmorpholine-*N*-oxide (NMO) in DMSO.[21] Other oxidation reagents such as $NaHCO_3$/DMSO,[22] IBX,[23] $NaIO_4$/DMF[24] or trimethylamine-*N*-oxide[25] turned out to be less effective. Finally, Pinnick oxidation[26] of the air- and light-sensitive aldehyde intermediate furnished the carboxylic acid **11**. This way, the anthraquinone building block **11** was obtained in six steps from naphthoquinone **8** with a satisfying overall yield of 31%.

As model "Northern" building blocks the haloarenes **12**[27] and **13**[28] were both prepared from 3-methoxy-benzylic alcohol through *ortho*-lithiation/halogenation. The reaction of the alcohols **12** and **13** with the acid **11** under Mitsunobu conditions then afforded the esters **14** and **15**, respectively, in good yield.[29]

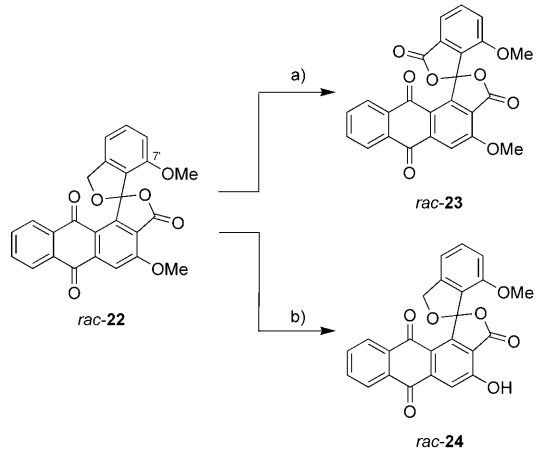
At this point, we asked ourselves whether **14** or **15** could possibly be used as substrates for the planned anionic homo-Fries rearrangement (in order to save additional protection–deprotection operations). The question was whether the halogen–metal exchange could be performed in the presence of the unprotected anthraquinone substructure.[30,31] For that reason, bromide **14** was treated with *t*BuLi (2 equiv) at −100°C in the expectation that the resulting aryllithium species would undergo the envisioned rearrangement. Much to our delight, the benzophenone *rac*-**16** could indeed be isolated (as a mixture of two atropisomers) after protic workup. However, this encouraging initial result was impaired by a poor yield (25%) and low reproducibility. Attempts to optimize the reaction by varying the amount of *t*BuLi or to substitute it by *n*BuLi or mesityllithium (THF, −78°C)[34] were not successful. Hoping that a more rapid iodine/lithium exchange[32] could possibly suppress side reactions, the aryl iodide **15** was subjected to the same conditions as before (2.0 equiv of *t*BuLi, THF, −100°C). However, only a complex mixture was formed. Attempts to generate an aryl–magnesium (instead of an aryl–lithium) intermediate by reacting **15** either with magnesium or with neopentylmagnesium bromide[34] also failed. In the latter case, only nucleophilic addition of the Grignard reagent to an anthraquinone carbonyl group was observed.

We therefore returned to our original plan (Scheme 3) and protected the reactive anthraquinone moiety as a 9,10-dimethoxyanthracene derivative. The reductive methylation of **15** with $Na_2S_2O_4$/KOH/MeI (in THF/water) was achieved under phase-transfer catalysis to furnish the rearrangement precursor **17** in good yield (Scheme 5).[35]

To induce the key rearrangement of **17** through halogen–metal exchange several reagents were tested (*t*BuLi, *n*BuLi, MeLi, PhLi and *i*PrMgCl). Among those, Knochel's "Turbo Grignard" solution gave the best results.[36] Thus, when the anthracene **17** was treated slowly with a commercial solution of *i*PrMgCl·LiCl in THF at −15°C followed by heating the mixture to 50°C the spirolactone *rac*-**21** was isolated in 63% yield after workup with aqueous NH_4Cl. We suppose that the deprotonated hemiacetal *rac*-**20** (resulting as an intermediate from the homo-Fries rearrangement of **18**) undergoes spontaneous lactonization to give *rac*-**21** as indicated in Scheme 5. It should be emphasized that heating the dark reaction mixture (50°C, 2 h) proved to be essential to initiate the rearrangement. When the reaction mixture was stirred at ambient temperature for one day, only proto-dehalogenated starting material was recovered after aqueous workup.



Scheme 5. Synthesis of the spirolactone *rac*-**22** through anionic homo-Fries rearrangement of the anthracene **17** and subsequent oxidation. a) $Na_2S_2O_4$, KOH, MeI, Bu_4NBr, THF/H_2O, 0 °C to RT, over night, 78 %; b) *i*PrMgCl·LiCl 1:1 (1.05 equiv), THF, −15 to RT, then 50 °C, 2 h, 63 %; c) AgO, HNO_3, 1,4-dioxane, RT, 20 min, 86 %.



Scheme 6. Benzylic oxidation and mono-demethylation of *rac*-**22**. a) i) NBS, BP (10 mol %), benzene, *hν* (vis), RT, 16 h, ii) KOH/H_2O, RT, 12 h, iii) HCl/H_2O, 35 %; b) BBr_3 (10 equiv), CH_2Cl_2, −78 °C, 1.5 h, 81 %.

This indicates that the iodine–magnesium exchange proceeds smoothly at lower temperatures, but the reaction of the arylmagnesium intermediate **18** (i.e., the key rearrangement) takes place only at elevated temperature. After treatment of the trimethoxyanthracene *rac*-**21** with silver(II) oxide in dioxane/4 N HNO_3[37] the anthraquinone derivative *rac*-**22** was obtained in high yield. This compound represents the first synthetic mumbaistatin analog possessing the spirolactone substructure of the natural product.

For the completion of the synthesis of pseudo acid *rac*-**6** we next intended to introduce the benzylic hydroxyl group by means of a radical bromination-substitution sequence.[38] Hence, spiro compound *rac*-**22** was reacted with NBS (2.2 equiv) and benzyol peroxide (10 mol %) under irradiation with visible light (Scheme 6). After hydrolysis of the crude product with aqueous KOH the "spiro-anhydride" *rac*-**23** was isolated in moderate yield, probably emerging from a dibrominated intermediate. Since the introduction of the hydroxy group (preparation of *rac*-**6**) could also not be achieved with 1 equiv of NBS or with cerium ammonium nitrate (CAN) as an oxidant, we decided to focus our efforts on the synthesis of the deoxy-cyclo-mumbaistatin derivative *rac*-**7**. In this context, we used anthraquinone *rac*-**22** as a model system to probe the deprotection of the phenol functions. During these investigations a remarkable resistance of the "Northern" methoxy group towards common reagents for aryl-methyl ether cleavage became apparent. For example, treatment of *rac*-**22** with BBr_3 at −78 °C[39] furnished the mono-demethylated product *rac*-**24** (Scheme 6). The one methoxy group remained unaffected by BBr_3 even after 1 d at ambient temperature. Also, treatment of *rac*-**22** with BF_3·Me_2S[40] only afforded *rac*-**24**, while a significant degree of decomposition was observed with other protocols (AlI_3/Bu_4NI in refluxing benzene;[41] LiSEt in DMF under microwave heating[42]). The inertness of the methoxy group at C-7′ towards demethylation becomes plausible by regarding the X-ray structure of *rac*-**22** (Figure 1).[56] The anthra[2,1-*c*]furan-3,6,11-trione "paddle" seems to effectively shield the methoxy oxygen towards coordination of a Lewis acid, thus preventing the required activation of the O-aryl fragment as a leaving group.

Using *rac*-**22** as a model, we have demonstrated the general possibility to achieve benzylic oxidation. Also, we learned that an easier removable phenol protecting group (such as MOM) will be required to allow a late deprotection of the

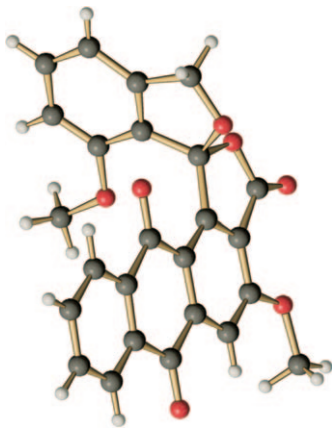


Figure 1. Structure of spirolactone *rac*-**22** in the crystalline state (C black, H white, O red).[56]

"Northern" molecule part. With this knowledge, we next turned towards the application of the developed strategy in the preparation of more complex compounds related to the deoxy-cyclo-mumbaistatin derivative *rac*-**7**.

Synthesis of a deoxy-cyclo-mumbaistatin analogue: As a fully functionalized "Southern" building block we selected the anthraquinone **34**, exhibiting a second methoxy group at C-8. For its synthesis we intended to follow the established Diels–Alder cycloaddition pathway shown in Scheme 7. For this purpose, a short access to chlorojuglone **30** was elaborated. In the first step the aerobic oxidation of 1,5-dihydroxynaphthalene (**28**) using substoichiometric amounts of freshly recrystallized copper(I) chloride to furnish juglone (**29**) was achieved in yields according to those reported in the literature.[43] Dichlorination of **29** and subsequent thermal elimination of HCl afforded chlorojuglone **30**[44] and its regioisomer as a mixture, the separation of which could not be accomplished by column chromatography. Fortunately, the desired naphthoquinone **30** could be obtained in pure form by recrystallization of the crude material from chloroform at room temperature. X-ray analysis[56] of suitable crystals (Figure 2) confirmed the constitution of **30** as the regioisomer needed in the subsequent cycloaddition. The required electron-rich diene **27**[9] was obtained as a moisture-sensitive mixture of *E*- and *Z*-isomers after C-acetylation of *tert*-butyl acetoacetate (**25**) with AcCl in the presence of $MgCl_2$ and pyridine followed by treatment of the resulting di-β-keto ester **26** with *N*,*O*-bis(trimethylsilyl)acetamide (BSA).[12c–e,i] The key cycloaddition between the dienophile **30** and **27** was accomplished by heating in toluene to 110 °C for 40 h. The crude cycloaddition product was stirred with wet THF followed by treatment of the (chromatographed) mixture with K_2CO_3 in methanol to complete aromatization and *O*-desilylation. This way, the pure anthraquinone **31** was isolated in good yield. Its constitution was assigned by 2D NMR spectroscopy and additionally confirmed by X-ray crystallography of a sample recrystallized from chloroform (Figure 2).[56]

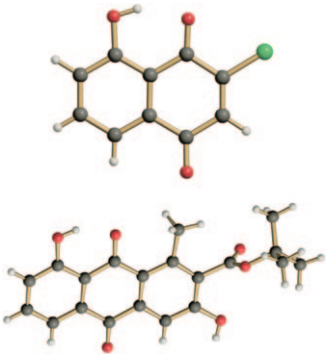
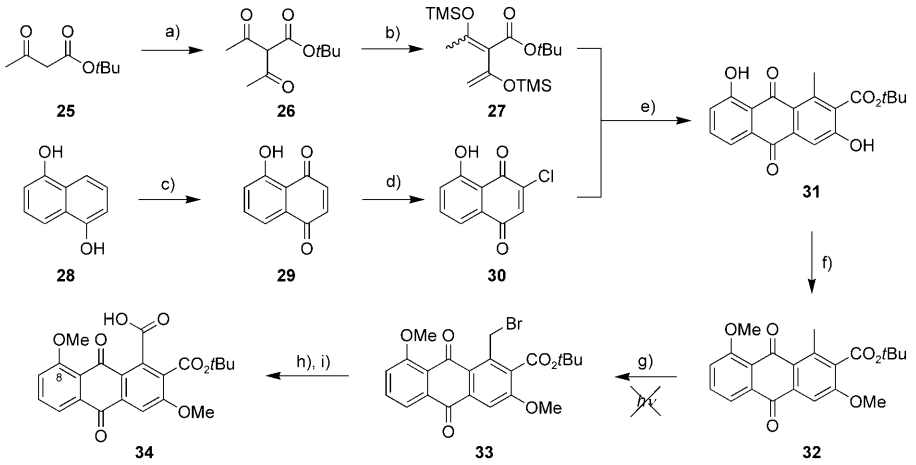


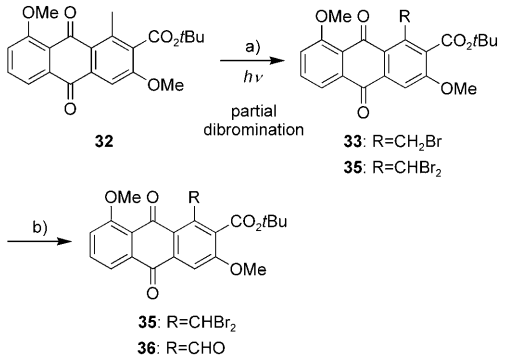
Figure 2. Structure of chlorojuglone **30** (top) and the anthraquinone carboxylic acid ester **31** (bottom) in the crystalline state (C black, H white, O red, Cl green).[56]



Scheme 7. Synthesis of the anthraquinone dicarboxylic acid monoester **34** through a Diels–Alder cycloaddition. a) AcCl, pyridine, $MgCl_2$, CH_2Cl_2, 0 °C to RT, 2 h, 98 %; b) BSA, 0 °C to RT, 2.5 d, 84 %; c) CuCl, air, CH_3CN, RT, 9 h, 52 %; d) Cl_2, AcOH, 30 min, RT; then EtOH, reflux, 30 min, 56 %; e) toluene, 110 °C, 40 h; then THF/H_2O, RT, SiO_2; then K_2CO_3, MeOH, 58 %; f) K_2CO_3, MeI, acetone, reflux, 20 h, 97 %; g) NBS (2.2 equiv), BP (20 mol %), CCl_4, reflux, 48 h, 72 %; h) NMO, DMSO, RT, 20 h, 61 %; i) $NaClO_2$, NaH_2PO_4, 2-methylbut-2-ene, THF/H_2O, 0 °C to RT, 17 h, 74 %.

After protection of both hydroxyl groups present in **31** (MeI, K_2CO_3) the resulting di-*O*-methylated compound **32** was subjected to benzylic bromination. The mono-bromide **33** was finally converted into the acid **34** under the proven conditions (compare Scheme 4) by treatment with NMO and subsequent oxidation of the aldehyde intermediate with sodium chlorite (Scheme 7).

Noteworthy is the fact that the conversion of **32** into the mono-bromide **33** required special optimization. Initially, we conducted the radical bromination of **32** under the same conditions as used before for the preparation of the anthraquinone **10** (1.95 equiv of NBS, 20 mol % of benzoylperoxide, reflux, irradiation with light), however, an inseparable 1:1.3 mixture of the mono- and the dibrominated compounds **33** and **35** was obtained (Scheme 8). While the dibromide **35** could be separated from the aldehyde **36** after the subsequent step (reaction with NMO), all our efforts to transform **35** into **36** (e.g., by hydrolysis in the presence of $AgNO_3$[45] or by reaction with DMSO[46]) failed. This forced us to optimize the conditions for the bromination of **32**. Reduction of the amounts of NBS to one equivalent or even less still resulted in the formation of a mixture of **33** and **35**, alongside with starting material. Finally, we found that the pure mono-brominated compound **33** is exclusively formed in good yield when the radical bromination is performed in



Scheme 8. Photo-induced benzylic dibromination of anthraquinone **32**. a) NBS (1.95 equiv), BP (20 mol%), CCl_4, reflux, *hν* (vis), 24 h; b) NMO, DMSO, RT, 20 h, 30% of **35** and 34% of **36** (yields over 2 steps).

the dark (CCl_4, reflux), even if an excess of NBS is used (Scheme 7).

To rationalize the different behavior of substrates **9** and **32** under the light-induced bromination conditions we had to consider the different reactivity of the primarily formed mono-bromides. It is known that 1-alkyl-9,10-anthraquinones can undergo a photo-induced H atom transfer according to a Norrish type II process (Scheme 9).[47,48] The formed species of type **37a** (diradical) or **37b** (photoenol) may then react with NBS (or bromine) to give a dibromide of type **35**. An explanation why only the dimethoxyanthraquinone **33** (but not the monomethoxy analogue **10**) further reacts under the photochemical bromination conditions can be gained by comparison of the UV/Vis absorption spectra of the two substrates (Figure 3). Obviously, the second methoxy group present in **33** gives rise to an additional band of absorption between 360 and 430 nm. Thus, in contrast to **10** compound **33** can absorb visible light and is prone to a subsequent Norrish type II-initiated bromination according to Scheme 9.

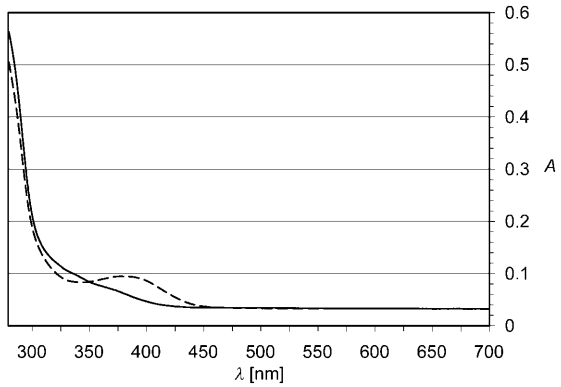
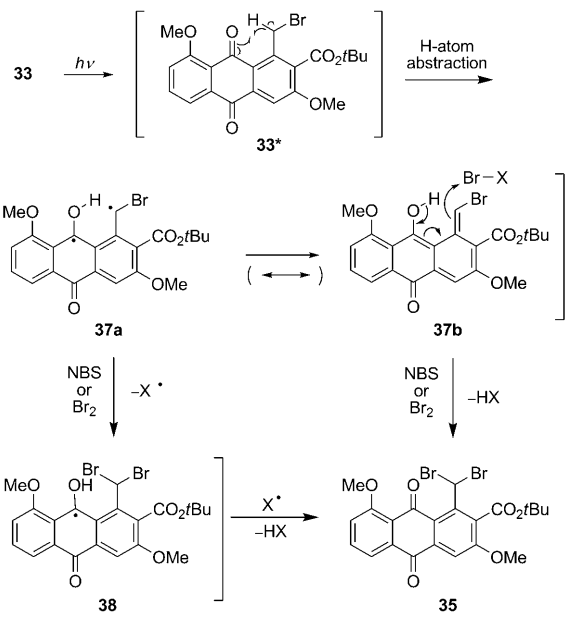
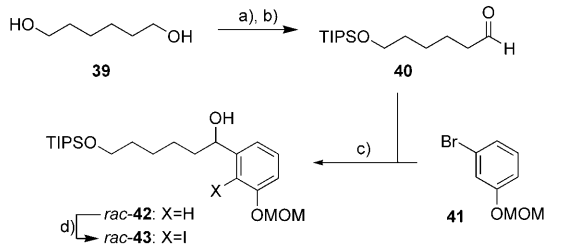


Figure 3. UV/Vis spectra of the monobrominated anthraquinones **10** (——) and **33** (-----), both recorded at 25°C using DMSO as solvent.

Having succeeded in the optimization of the bromination and the preparation of the anthraquinone carboxylic acid **34** on a gram scale (Scheme 7), the remaining task was to conclude the synthesis of a deoxy-cyclo-mumbaistatin derivative. As a promising "Northern" building block we chose the benzylic alcohol *rac*-**43** (Scheme 10) containing an easier removable methoxymethyl (MOM) protecting group for the phenolic OH to facilitate the final deprotection.



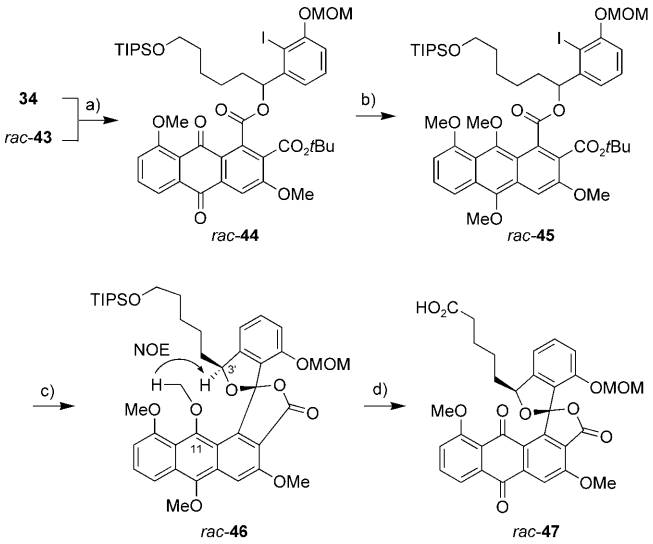
Scheme 9. Formation of dibromide **35** in the presence of light.



Scheme 10. Synthesis of the "Northern" deoxy building block *rac*-**43**. a) NaH, TIPSCl, THF, 0°C to RT, 30 min, 53%; b) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, −78°C to RT, 90 min, 81%; c) **41** + *n*BuLi, THF, −78°C, 15 min, $CeCl_3$, −78°C, 45 min, then addn. of **40**, −78°C to RT, 12 h, 83%; d) *n*BuLi, toluene, −50°C to RT, 4 h, then I_2, −50°C to RT, 12 h, 79%.

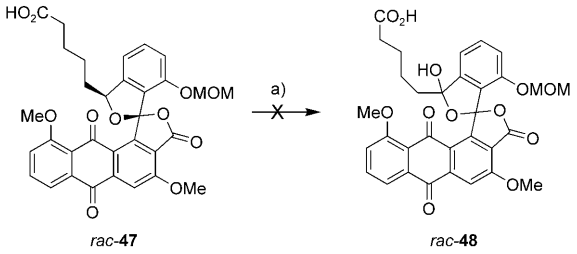
The carbon skeleton of *rac*-**43** was assembled by addition of an arylmetal nucleophile derived from bromide **41** to aldeyde **40**. The latter was prepared by mono-TIPS protection of 1,6-hexandiol (**39**)[49,50] followed by Swern oxidation.[51] Metalation of **41** was performed with *n*BuLi and the lithiated intermediate was slowly added to a solution of $CeCl_3$ in THF.[52,53] The resulting solution of the less-basic organocerium reagent was then reacted with the aldehyde **40** to afford the benzylic alcohol *rac*-**42** in good yield. *ortho*-Lithiation of *rac*-**42** with *n*BuLi followed by addition of an ethereal solution of iodine finally furnished the iodide building block *rac*-**43**.

As shown in Scheme 11, the coupling of the "Northern" and the "Southern" fragments **34** and *rac*-**43** was then achieved satisfactorily again under Mitsunobu conditions. After conversion of the anthraquinone *rac*-**44** into the rearrangement precursor *rac*-**45**[54] by reductive methylation the anionic homo-Fries rearrangement was probed applying the elaborated reaction conditions. In fact, when iodide *rac*-**45** was reacted with a slight excess of *i*PrMgCl·LiCl 1:1 the expected spirolactone *rac*-**46** was formed in even higher yield (76%) as compared to the simpler analogue *rac*-**15**. The transformation proceeded with a pronounced diastereoselectivity (d.r. 8:1 to 13:1). The relative configuration of the major diastereomer (*rac*-**46**) was assigned by NOESY NMR spectroscopy (NOE between the protons of the OMe group at C-11 and H-3′). Global oxidation of *rac*-**46** with Jones reagent[55] at 0°C directly afforded the cyclo-mumbaiststain derivative *rac*-**47** in 59% yield under liberation of the anthraquinone substructure and installation of the carboxyl group at the end of the side chain.



Scheme 11. Coupling of the "Northern" and the "Southern" building block and final steps to complete the cyclo-mumbaistatin derivative *rac*-**47**. a) PPh_3, DIAD, THF, 0°C, then RT, 2.5 h, 73%; b) $Na_2S_2O_4$, KOH, MeI, Bu_4NBr, THF/H_2O, 0°C to RT, 15 h, 53%; c) *i*PrMgCl·LiCl 1:1, THF, −15°C to 1.5 h, then 50°C, 2 h, 76%, d.r. 13:1; d) Jones reagent, acetone, 0°C, 30 min, 59%.

While compound *rac*-**47** already displayed a close structural relationship to the natural product (**1b**) itself, its planned conversion into deoxy-cyclo-mumbaistatin *rac*-**7** (see above) proved to be difficult and, so far, all our attempts to introduce a benzylic hydroxyl group into the spirolactone *rac*-**47** failed. For instance, when *rac*-**47** was subjected to the conditions of a radical bromination and subsequent basic hydrolysis (compare Scheme 6) the expected pseudo acid *rac*-**48** could not be detected in the resulting complex mixture of products (Scheme 12).



Scheme 12. Attempted hydroxylation of *rac*-**47**. a) NBS (2.7 equiv), BP (10 mol%), benzene, *hv*, RT, 30 h, then KOH, THF/H_2O, 1 h.

Conclusion

We have developed a new and efficient strategy for the total synthesis of compounds containing the complete carbon skeleton and the functional core motif (spiroketal-lactone) of the naturally occurring G6P-T1 inhibitor mumbaistatin in its cyclic form (**1b**). The study disclosed here has culminated in the preparation of the deoxydealkyl derivative *rac*-**24** and the more elaborated cyclo-mumbaistatin analogue *rac*-**47**. Key elements of the strategy include: i) The generation of the anthraquinone part by Diels–Alder cycloaddition, ii) the pre-attachment of a "Northern" building block to the "Southern" anthraquinone fragment through Mitsunobu esterification, and iii) the construction of the tetra-*ortho*-substituted benzophenone substructure by means of an anionic homo-Fries rearrangement which leads directly to the spiroketal-lactone moiety in a domino-type process. We are confident that the strategy developed and the experience collected in the course of this study form a promising basis for the synthesis of mumbaistatin and further relevant analogs in the future.

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