doi.org/10.1002/cbdv.202300181

RESEARCH ARTICLE

CHEMISTRY & BIODIVERSITY

Syntheses and Antibacterial Evaluation of New *Penicillium* Metabolites Gregatins G and Thiocarboxylics C

Franziska Gillsch,[a] Fredrick Mbui,[b, c] Ursula Bilitewski,[b] and Rainer Schobert*[a]

[a] Organic Chemistry Laboratory, University Bayreuth, Universitätsstrasse 30, 95440 Bayreuth, Germany, e-mail: Rainer.Schobert@uni-bayreuth.de

[b] Department of Compound Profiling and Screening, Helmholtz Center for Infection Research GmbH, Inhoffenstrasse 7, 38124 Braunschweig, Germany

[c] Department of Biochemistry and Biotechnology, Technical University of Kenya, P.O. Box 52428 – 00200 Nairob Kenya

Two pairs of side-chain epimeric 3-methoxycarbonyl-dihydrofuran-4-ones with structures purported for thiocarboxylics $C_{1/2}$ and gregatins $G_{1/2}$, isolated from *Penicillium* sp. Sb62, were synthesised for the first time in five steps and 17–25% yield. Key steps were a Suzuki cross-coupling, a Yamaguchi esterification, and a base-induced Knoevenagel-type condensation. The optimum protecting group for the 10-OH group in the dienyl side-chain, orthogonal to necessary protecting groups on O-10 of the furanone, was found to be *t*-butyldiphenylsilyl (TBDPS). The specific rotations of our synthetic products deviated markedly from those reported for the natural isolates. In contrast to the isolates, the synthetic products were not active against *Escherichia coli* and *Staphylococcus aureus* bacteria.

Keywords: 3-furanone, bioactivity, gregatin, penicillium, thiocarboxylic.

Introduction

The 3-methoxycarbonyl-dihydrofuran-4-one motif is rare in natural products with gregatins A–E,[1–4] aspertetronins A and B,[5,6] graminins A and B[7] and huspenones A and B[6] having been studied in more detail. In 2020 seven known and ten novel (**1**–**6**) methyl 4-oxo-dihydrofuran-3-carboxylates, including four pairs of epimers, were isolated by *Ruan et al.*[8] from the fungus *Penicillium* sp. Sb62. They comprise gregatin F (**5**) and G (**6**), and the thiophenyl substituted thiocarboxylics A–D (**1**–**4**) (*Figure 1*).

Eight of the new natural products **3**–**6** feature a 10-hydroxylated side-chain giving rise to four pairs of epimers since C-5 is *R*-configured throughout. The side-chains carry either one (**4** and **5**) or two alkenes (**1**–**3** and **6**). All new compounds **1**–**6** showed

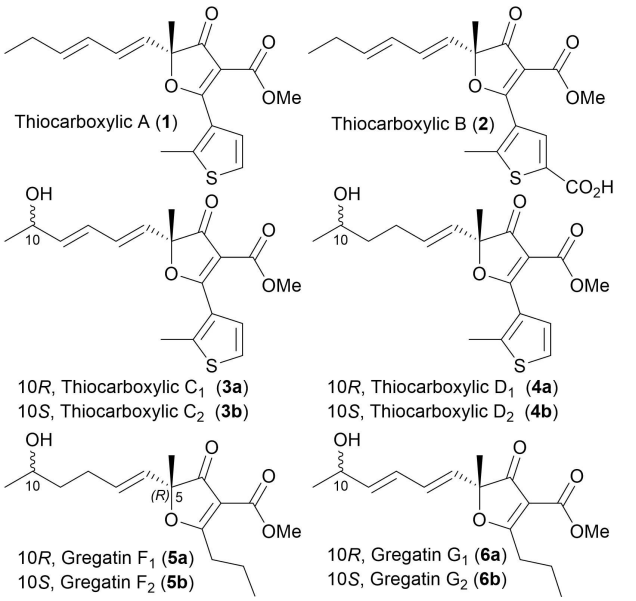
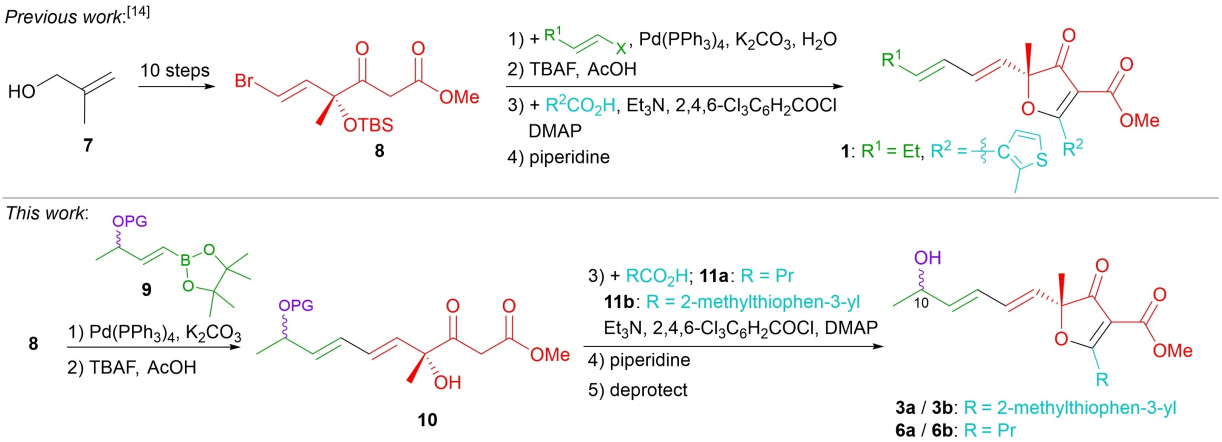


Figure 1. Structures of the thiocarboxylics A–D (**1**–**4**) and gregatins F (**5**) and G (**6**).

Supporting information for this article is available on the WWW under https://doi.org/10.1002/cbdv.202300181



Scheme 1. *Previous work*: synthesis of methyl 4-oxo-dihydrofuran-3-carboxylates such as thiocarboxylic A (**1**) with flexibility as to the 2-aryl and 5-alkadienyl residues.[14] *This work*: extension to analogs thiocarboxylic C (**3**) and gregatin G (**6**), carrying additional stereogenic alcohols, using suitable protecting groups.

antimicrobial activity against *Escherichia coli*, *Staphylococcus aureus*, and *Candida albicans* with MIC values ranging from 0.9 to 7.0 μg/mL.

Brückner et al.[9–11] and *Kato et al.*[12,13] published five different syntheses of related dihydrofuranones, e.g., of gregatins A,[10] B,[9–12] C,[10] D,[10] E,[11,12] aspertetronin A[10] and graminin A.[13] Previously, our group reported a new approach to the natural product class of 3-methoxycarbonyl-dihydrofuran-4-ones which allows a more flexible introduction of both residues at C-2 and C-5 of the furanones at a late stage, rendering the majority of the natural products of this class easily accessible (*Scheme 1*, *previous work*).[14] R^1 of the alkenyl side-chain was introduced via a Suzuki cross-coupling of vinyl bromide **8**, synthesized in 10 steps from 2-methylallyl alcohol **7**, and R^2 via a Yamaguchi esterification of the deprotected coupling product alcohol and a subsequent ring-closing Knoevenagel-type condensation. In this way, we synthesised thiocarboxylic A (**1**) for the first time and three derivatives of it with variance in R^1 and R^2.[14]

Herein we report an extension of this synthetic route, accommodating OH-groups in the side-chain at C-10 by identifying protecting groups that are compatible with the OTBS group in precursor **8**. The resulting product epimers gregatin G_1 (**6a**) and G_2 (**6b**), and thiocarboxylic C_1 (**3a**) and C_2 (**3b**) were also evaluated for their antibiotic activities in comparison to the natural isolates.

Results and Discussion

We intended to synthesise thiocarboxylic C (**3**) and gregatin G (**6**) by first reacting vinyl bromide **8**[14] with boronate **9**, carrying an aptly protected hydroxy group at a stereogenic center, in a Suzuki cross-coupling (*Scheme 1*, *this work*). After cleavage of the TBS group, tertiary alcohol **10** should be converted to the corresponding β-ketoacyl esters by a Yamaguchi esterification with carboxylic acids **11**, introducing R. The five-membered ring was to be closed by a base-induced Knoevenagel-type condensation to afford the respective *O*-protected dihydrofuranones. Deprotection of the secondary alcohol would eventually furnish thiocarboxylics C_1 (**3a**) and C_2 (**3b**), or gregatins G_1 (**6a**) and G_2 (**6b**).

Due to the TBS group in vinyl bromide **8** and the functionalities of the natural products, the choice of protecting groups for boronates **9** is limited. *Kato et al.* described that the fluoride-mediated desilylation of a TBS group at the same position in racemic gregatin E only led to a maximum yield of 25% because of the instability of the product under these conditions.[12] Since we were not sure whether the natural products would be more stable under basic or acidic deprotection conditions, we tried two different orthogonal protecting group strategies, employing TBDPS and 2-methoxyethoxymethyl (MEM) as protecting groups for the secondary alcohol. We started with the *R*-configured boronates **9a**[1] and **9b**[1] to get gregatin G_1

[1]The synthesis of the boronates **9a**–**c** can be found in detail in the *Supporting Information*.

(**6a**) and thiocarboxylic C_1 (**3a**) before synthesising their epimers **3b** and **6b**.

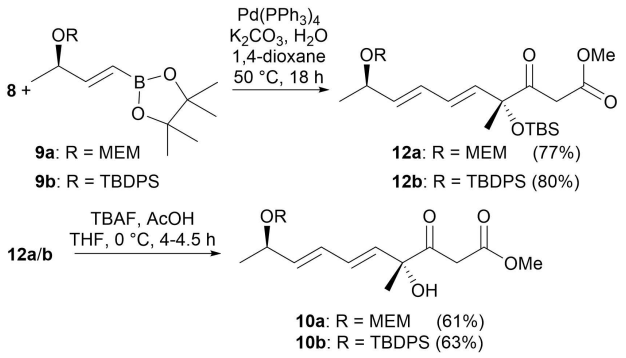
The Suzuki cross-couplings of vinyl bromide **8** and the boronates **9a** or **9b** were run under the conditions already elaborated in our earlier work, using 8 mol% $Pd(PPh_3)_4$ in the presence of K_2CO_3 (*Scheme 2*).[14] (*E,E*)-Dienes **12a** and **12b** were obtained with good yields and void of (*Z*)-isomers. Cleavage of the TBS group of **12a** or **12b** with tetra-*n*-butylammonium fluoride (TBAF) and AcOH afforded β-keto-γ-hydroxyesters **10a** or **10b** in moderate yields, irrespective of the second protecting group.

Contrary to our original plan we tried to convert alcohol **10a** in one step into furanone **14a** with butyryl chloride and Et_3N according to the procedure of *Burghart-Stoll* and *Brückner*[10] (*Scheme 3*, *left*). The problem was that ester **13a**, which formed in situ, did not react completely to furanone **14a** and that the two compounds could not be separated fully by column chromatography due to virtually equal polarity, as to TLC. After three purification cycles by column chromatography, we obtained only 39% of pure dihydrofuranone **14a** and 17% of diester **13a**. Next, we prepared furanone **14b** in two steps. Yamaguchi esterification[14] of alcohol **10b** with butyric acid (**11a**) gave pure ester **13b** which was submitted to a Knoevenagel-type cyclisation with $NaHCO_3$ (*Scheme 3*, *right*).[10,15] The 53% yield of **14b** over these two steps was slightly better than that of the single-step approach. In addition, compounds **13b** and **14b** could be easily purified by a single column chromatography.

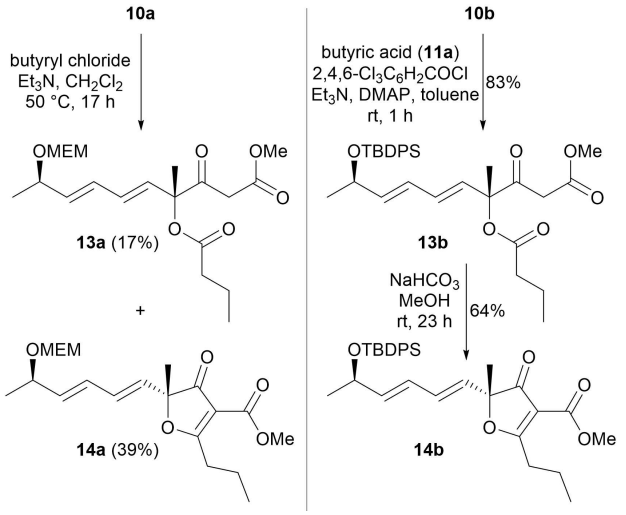
Based on these results, we decided to stick to the original plan to synthesise the differently protected precursors for thiocarboxylic C_1 **16a** and **16b** in two steps (*Scheme 4*).

Starting from alcohols **10a**, or **10b** we obtained **16a** and **16b** with yields of 70% and 77% for the esterification with 2-methylthiophene-3-carboxylic acid (**11b**), and 56% and 66% for the ring-closure. The results of the final cleavage of the MEM and TBDPS groups, respectively, are shown in *Table 1*. Gregatin G_1 (**6a**) was obtained by deprotection of **14a** under (Lewis)[16] acidic[17,18] conditions, yet only in yields of 11–32% because of the instability of **6a** under these conditions (entries 1–3). For example, using $ZnBr_2$,[16] the dihydrofuranone ring of **14a** partly opened to give back the acyclic diester **13a** (entry 1).

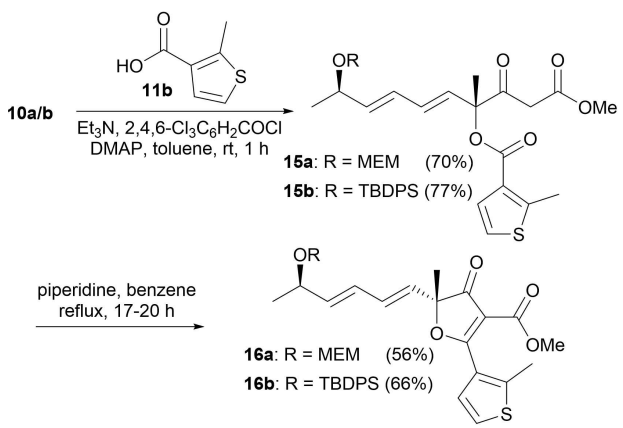
Deprotection of **16a** under the same conditions failed to give thiocarboxylic C_1 (**3a**) because the electron-rich heteroarene destabilises the furanone even more (entry 4). With trifluoroacetic acid (TFA),[19]



Scheme 2. Synthesis of tertiary alcohols **10** with MEM (**10a**) or TBDPS (**10b**) protected secondary alcohols.

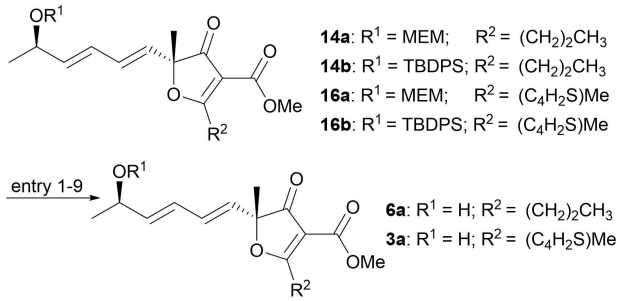


Scheme 3. *Left*: One-step synthesis of MEM-protected furanone **14a** starting from alcohol **10a**; *right*: synthesis of TBDPS-protected furanone **14b** in two condensation steps starting from alcohol **10b**.



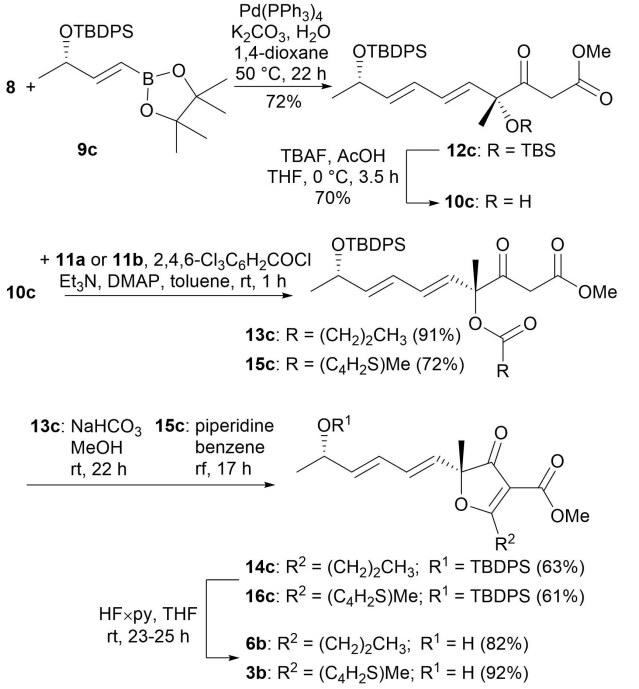
Scheme 4. Two-step synthesis of furanones **16a** and **16b**, carrying a thiophene moiety, starting from alcohols **10a** or **10b**.

Table 1. Cleavage of the MEM and TBDPS groups of compounds **14** and **16** to afford gregatin G_1 (**6a**) and thiocarboxylic C_1 (**3a**); conditions and yields.



entry	educt	conditions	product	yield [%]
1[16]	**14a**	(A)	**6a**	23
2[17]	**14a**	(B)	**6a**	11
3[18]	**14a**	(C)	**6a**	32
4[16]	**16a**	(A)	**3a**	–
5[19]	**16a**	(D)	**3a**	–
6[18]	**16a**	(C)	**3a**	22
7[20]	**14b**	(E)	**6a**	64
8[20]	**16b**	(E)	**3a**	–
9[21]	**16b**	(F)	**3a**	96

Conditions: (A) $ZnBr_2$, CH_2Cl_2, r.t., 22; (B) PPTS, *t*BuOH, refl., 24; (C) conc. HCl, MeOH, r.t., 24; (D) TFA, CH_2Cl_2, r.t., 1; (E) TBAF, THF, 45 °C, 7; (F) HF·py, THF, r.t., 23.



Scheme 5. Synthesis of thiocarboxylic C_2 (**3b**) and gregatin G_2 (**6b**) in five steps starting from vinyl bromide **8**.

16a was even completely decomposed (entry 5), while when treated with conc. HCl[18] gave product **3a** with 22% yield (entry 6). Desilylation of TBDPS ether **14b** with TBAF[20] at 45 °C afforded gregatin G_1 (**6a**) with a yield of 64% (entry 7), which was acceptable, given the low yields of the attempts to cleave off the MEM group. Though we had already suspected that the desilylation of **16b** with TBAF might proceed less well than that of **14b** due to the thiophene moiety, the complete decomposition occurring under these conditions came as a surprise (entry 8). However, thiocarboxylic C_1 (**3a**) was obtained with an excellent yield of 96% upon treating silyl ether **16b** with 80 equivalents of HF-pyridine (entry 9).[21] Related to starting vinyl bromide **8**, thiocarboxylic C_1 (**3a**) was obtained with an overall yield of 25% when using a TBDPS protecting group, and with a mere 4% yield when using a MEM group. Gregatin G_1 (**6a**) was synthesised with a total yield of 6% (MEM) and 17% (TBDPS).

Since for both natural products the yields of all steps, and especially those of the final deprotection, were better when using TBDPS as the protecting group of the secondary alcohol, we decided to prepare gregatin G_2 (**6b**) and thiocarboxylic C_2 (**3b**) also with this protecting group strategy (*Scheme 5*). Hence, we performed the Suzuki cross-coupling of vinyl bromide **8** with the TBDPS protected, *S*-configured boronate **9c**[1] and obtained the coupling product **12c** with 72% yield. The latter was desilylated with TBAF and AcOH to give alcohol **10c**, which was esterified with butyric acid (**11a**) or 2-methylthiophene-3-carboxylic acid (**11b**) to give the esters **13c** or **15c** with 91% and 72% yield, respectively. The Knoevenagel-type reaction of **13c** was induced by $NaHCO_3$ and that of **15c** by piperidine, and afforded the dihydrofuranones **14c** and **16c** with yields slightly above 60%. The final cleavage of the TBDPS group using HF-pyridine gave thiocarboxylic C_2 (**3b**) and gregatin G_2 (**6b**) in good yields. Related to **8**, the overall yields amounted to 24% (**6b**) and 20% (**3b**).

The NMR data of our synthetic thiocarboxylic C_1 (**3a**), C_2 (**3b**), gregatin G_1 (**6a**) and G_2 (**6b**) agreed well with those reported in the literature[8] for the isolates (*cf. Supporting Information*). Not so the specific rotations. While synthetic thiocarboxylic C_1 (**3a**) showed an $[\alpha]_D^{25} = -99$ ($c = 0.25$, $CHCl_3$) and synthetic compound **3b** an $[\alpha]_D^{27} = -108$ ($c = 1.0$, $CHCl_3$), a value of $[\alpha]_D^{20} = -44$ ($c = 0.1$, $CHCl_3$)[8] was reported for isolate **3a** and $[\alpha]_D^{20} = -40$ ($c = 0.1$, $CHCl_3$)[8] for isolate **3b**. The values for gregatin G_1 (**6a**) and G_2 (**6b**) also differed from those of the isolate. The values of the isolates with $[\alpha]_D^{20} = +177$ ($c = 0.1$, $CHCl_3$)[8] for **6a** and $[\alpha]_D^{20} =$

+171 ($c=0.1$, $CHCl_3$)[8] for **6b** are higher than the values of our synthetic compounds with $[\alpha]_D^{25}=+96$ ($c=0.50$, $CHCl_3$) for **6a** and $[\alpha]_D^{25}=+104$ ($c=1.00$, $CHCl_3$) for **6b**. These deviations might be due to impurities of the isolated compounds as visible in their ^{1}H-NMR spectra.[8]

As *Ruan et al.* had reported antimicrobial activity of their isolated thiocarboxylic $C_{1/2}$ (**3a**,**b**) with MIC of 10.5 and 21 μM and of gregatin $G_{1/2}$ (**6a**,**b**) with MIC of 8.7 μM against *E. coli* and *S. aureus*,[8] we also tested our synthetic products **3a**, **3b**, **6a** and **6b** for their activities against these bacteria (*cf. Supporting Information*). However, they were all virtually inactive with IC_{50} values beyond the highest tested concentration of 100 μM. They proved also not cytotoxic in concentrations up to 100 μM against cell lines A549 (human lung carcinoma), L929 (mouse fibroblasts) and Huh7 (human hepatocellular carcinoma). A plausible assumption for the activities of the natural isolates observed by Ruan *et al.* would be the presence of other, unidentified active metabolites.

Conclusions

Based on our recently established synthetic approach to natural products with 3-methoxycarbonyl-dihydrofuran-4-one structures,[14] we now synthesised two pairs of epimers of more complex furanones, bearing an additional stereogenic center in the 5-alkadienyl side-chain. Compounds supposed to have these structures were isolated by *Ruan et al.* in 2020.[8] We tested two different orthogonal protecting group strategies, and identified TBDPS as the protecting group of choice for the secondary alcohol of the side-chain. Starting from a TBS-protected vinyl bromide with β-ketoester functionality, we built up gregatin G_1 and G_2 as well as thiocarboxylic C_1 and C_2 by a sequence of Suzuki cross-coupling, Yamaguchi esterification, base-induced Knoevenagel-type condensation, and two desilylation steps. The total yields over these five steps ranged from 17% to 25%. As was the case with thiocarboxylic A,[14] our synthetic gregatins $G_{1/2}$ and thiocarboxylics $C_{1/2}$ exhibited specific rotations and antibiotic activities strikingly at variance with those reported of the natural isolates. In contrast to the isolates, our synthetic products showed no antibiotic activity against *Escherichia coli* and *Staphylococcus aureus*. Given the matching NMR spectra, an erroneous structure assignment of the natural isolates appears rather unlikely, whereas the entrainment of trace amounts of other active *Penicillium* metabolites remains conceivable.

Experimental Section

General Information

Melting points were determined with a Büchi M-565 melting point apparatus and are uncorrected. Optical rotations were measured at 589 nm (Na–D line) on a PerkinElmer 241 Polarimeter using solutions in $CHCl_3$. IR spectra were recorded with a FT-IR spectrophotometer equipped with an ATR unit. ^{1}H-NMR and ^{13}C-NMR spectra were obtained using a Bruker Avance III HD 500 spectrometer. Chemical shifts of NMR signals are given using the residual solvent peak as an internal standard, i.e., 7.26 ppm (proton) and 77.16 ppm (carbon) for $CDCl_3$. High resolution mass spectra were obtained with a UPLC/Orbitrap MS system in ESI mode. Analytical HPLC measurements were carried out on a Shimadzu Nexera XR with autosampler SIL-20 A using a Knauer Eurospher II C-18 column (150×4 mm), pore size 100 Å, particle size 3 μm. Detection was executed by a diode array detector SPD–M20 A.

Chemicals. All reagents were purchased from commercial sources and were used without further purification. All anhydrous solvents were used as supplied, except tetrahydrofuran (THF), toluene and 1,4-dioxane which were freshly distilled over sodium/benzophenone, and benzene, MeOH and CH_2Cl_2 which were dried over molecular sieves (3 Å). Moisture or air sensitive reactions were routinely carried out in oven-dried glassware under an argon atmosphere using standard Schlenk technique.

Chromatography. Analytical thin layer chromatography (TLC) was carried out using Merck silica gel $60GF_{254}$ pre-coated aluminum-backed plates. The compounds were visualized with UV light (254 nm) and/or ceric ammonium molybdate (CAM). Column chromatography was performed at medium pressure using dry packed Macherey-Nagel silica gel 60, pore size 40–63 μm with the eluent specified.

General Procedures

*Suzuki Cross-Coupling of Vinyl Bromide **8** with Boronates **9a–c**[1] Into (E,E)-Dienes **12a–c***

The Suzuki coupling was carried out under an argon atmosphere using standard Schlenk technique for

oxygen exclusion. To a stirred solution of vinyl bromide **8** (1.00 equiv.) in dry 1,4-dioxane was added $Pd(PPh_3)_4$ (8 mol%) and the reaction mixture was stirred for 5 min at ambient temperature. Boronic ester **9a**, **9b** or **9c** (1.40–1.50 equiv.) in 1,4-dioxane and K_2CO_3 (2.00 equiv.) in H_2O were added. The reaction mixture was heated to 50 °C and stirred for 18–22 at this temperature. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2 and the phases were separated. The organic phase was washed with sat. aqueous NH_4Cl, H_2O and brine and was dried over Na_2SO_4. The volatiles were evaporated under reduced pressure. Purification of the residue by column chromatography (**12a**: 5% to 10% AcOEt in *n*-pentane; **12b** and **12c**: 2% AcOEt in *n*-pentane) afforded coupling product **12**.

Desilylation of the Coupling Products **12a–c** *Into Alcohols* **10a–c**

Silyl ether **12** (1.00 equiv.) was dissolved in dry THF and AcOH (2.0 equiv.) and TBAF (1M in THF, 2.00 equiv.) were added to the solution at 0 °C. After 3.5–4.5 at 0 °C sat. aqueous NH_4Cl and sat. aqueous $NaHCO_3$ were added and the layers were separated. The aqueous layer was extracted three times with CH_2Cl_2, the combined organic phases were dried over Na_2SO_4 and the solvent was evaporated. The residue was purified by column chromatography (**10a**: 50% AcOEt in *n*-pentane; **10b** and **10c**: 20% AcOEt in *n*-pentane) to yield γ-hydroxy-β-ketoester **10**.

Yamaguchi Esterification of γ-hydroxy-β-ketoesters **10a–c** *Into β-ketoacyl Esters* **13b–c** *and* **15a–c**

A stirred solution of alcohol **10** (1.15 equiv.) and 2-methylthiophene-3-carboxylic acid (**11b**, 1.00 equiv.) or butyric acid (**11a**, 1.00 equiv.) in dry toluene was treated with Et_3N (3.00 equiv.), 2,4,6-trichlorobenzoyl chloride (1.58 equiv.) and DMAP (1.50 equiv.). The reaction mixture was stirred at room temperature for 1 before being quenched with sat. aqueous $NaHCO_3$. After phase separation the aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and volatiles were evaporated under reduced pressure. Purification of the residue by column chromatography (**13b**, **13c**, **15b** and **15c**: 10% AcOEt in *n*-pentane; **15a**: 20% AcOEt in *n*-pentane) afforded esters **13b–c** or **15**.

Knoevenagel-Type Condensation of **15a–c** *Into 3-furanones* **16a–c**

Ester **15** (1.00 equiv.) was dissolved in dry benzene and piperidine (5.00 equiv.) was added to the solution at room temperature. The reaction mixture was heated at reflux for 17–20 before it was allowed to cool to room temperature. The volatiles were removed in vacuo and the remainder was purified by column chromatography (**16a**: 20% AcOEt in *n*-pentane, **16b**: 10% AcOEt in *n*-pentane; **16c**: 10% to 20% AcOEt in *n*-pentane) to obtain product **16**.

Knoevenagel-Type Condensation of **13b–c** *Into 3-furanone* **14b–c**

Compound **13b** or **13c** (1.00 equiv.) was dissolved in dry MeOH and $NaHCO_3$ (2.50 equiv.) was added to the solution at room temperature. The reaction mixture was stirred for 22–23 at this temperature before being quenched with H_2O. After phase separation the aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and volatiles were evaporated under reduced pressure. Purification of the residue by column chromatography (10% AcOEt in *n*-pentane) afforded product **14b–c**.

Conversion of Alcohol **10a** *Into Ester* **13a** *and 3-furanone* **14a**

A stirred solution of alcohol **10a** (1.00 equiv.) in dry CH_2Cl_2 was treated with butyryl chloride (3.00 equiv.) and Et_3N (6.00 equiv.). The reaction mixture was heated at reflux for 17 before being quenched with H_2O. The phases were separated and the aqueous phase was extracted three times with Et_2O. The combined organic phases were dried over Na_2SO_4 and volatiles were evaporated under reduced pressure. Purification of the residue by three column chromatography runs (20% AcOEt in *n*-pentane) afforded product **14a** together with ester **13a**.

Synthesis of Gregatin G_1 (**6a**)

[2]Silyl ether **14b** (1.00 equiv.) was dissolved in dry THF and TBAF (1M in THF, 4.00 equiv.) was added to the solution at 0 °C. After 6.5 h at 0 °C sat. aqueous NH_4Cl was added and the layers were separated. The

[2]Only the TBDPS deprotection is mentioned. The MEM deprotection can be found in the *Supporting Information*.

aqueous layer was extracted three times with CH_2Cl_2, the combined organic phases were dried over Na_2SO_4 and the solvent was evaporated. The residue was purified by column chromatography (30% to 40% AcOEt in *n*-pentane) to yield gregatin G_1 (**6a**).

*Desilylation of the TBDPS-Group to Obtain Thiocarboxylic $C_{1,2}$ (**3a**,[2]**b**) and Gregatin G_2 (**6b**)*

Silyl ether **14c**, **16b** or **16c** (1.00 equiv.) was dissolved in dry THF and 70% HF-pyridine (80.0 equiv.) was added to the solution at 0 °C. After 23–25 at room temperature sat. aqueous K_2CO_3 and H_2O were added and the layers were separated. The aqueous layer was extracted three times with Et_2O, the combined organic phases were washed with sat aqueous $CuSO_4$ and were dried over Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography (**3a** and **6b**: 30% to 50% AcOEt in *n*-pentane; **3b**: 30% to 40% AcOEt in *n*-pentane) to yield the natural products **3a**, **3b** or **6b**.

Acknowledgements

We thank M. Drösemeyer (COPS,I) for her excellent assistance with antimicrobial and cytotoxicity assays. Open Access funding enabled and organized by Projekt DEAL.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contribution Statement

The manuscript was written through substantial contributions of all authors (FG, chemical synthesis and analytics; FM and UB, biotests and data evaluation; RS, supervision, manuscript drafting). All authors have given approval to the final version of the manuscript.

References

[1] K. Kobayashi, T. Ui, 'Isolation of Phytotoxic Substances Produced by *Cephalosporium gregatum* Allington & Chamberlain', *Tetrahedron Lett.* **1975**, *16*, 4119–4122.
[2] K. Kobayashi, T. Ui, 'Wilt-inducing Antibiotic Compounds Produced by *Cephalosporium gregatum*', *Physiol. Plant Pathol.* **1977**, *11*, 55–60.
[3] H. Anke, H. Schwab, H. Achenbach, 'Tetronic Acid Derivatives from *Aspergillus panamensis*', *J. Antibiot.* **1980**, *33*, 931–939.
[4] S. L. Taylor, R. E. Peterson, L. E. Gray, 'Isolation of Gregatin A from *Phialophora gregata* by Preparative High-Pressure Liquid Chromatography', *Appl. Environ. Microbiol.* **1985**, *50*, 1328–1329.
[5] J. A. Ballantine, V. Ferrito, C. H. Hassall, V. I. P. Jones, 'Aspertetronin A and B, two novel tetronic acid derivatives produced by a blocked mutant of *Aspergillus rugulosus*', *J. Chem. Soc. C.* **1969**, 56–61.
[6] Z.-J. Zhan, J.-P. Jin, Y.-M. Ying, W.-G. Shan, 'Furanone Derivatives from *Aspergillus* sp. XW-12, an Endophytic Fungus in *Huperzia serrata*', *Helv. Chim. Acta* **2011**, *94*, 1454–1458.
[7] K. Kobayashi, T. Ui, 'Graminin A, a New Toxic Metabolite from *Cephalosporium gramineum* nisikado & ikata', *J. Chem. Soc. Chem. Commun.* **1977**, 774.
[8] J.-L. Chang, H.-Z. Xu, J. Zhou, M. Zhou, X. Zhang, Y. Guo, H.-L. Ruan, 'Antimicrobial Furancarboxylic Acids from *Penicillium* sp.', *J. Nat. Prod.* **2020**, *83*, 3606–3613.
[9] H. Burghart-Stoll, R. Brückner, 'A Serendipitous Synthesis of (+)-Gregatin B, Second Structure Revisions of the Aspertetronins, Gregatins, and Graminin A, Structure Revision of the Penicilliols', *Org. Lett.* **2011**, *13*, 2730–2733.
[10] H. Burghart-Stoll, R. Brückner, 'Total Syntheses of the Gregatins A–D and Aspertetronin A: Structure Revisions of These Compounds and of Aspertetronin B, Together with Plausible Structure Revisions of Gregatin E, Cyclogregatin, Graminin A, the Penicilliols A and B, and the Huaspenones A and B', *Eur. J. Org. Chem.* **2012**, 3978–4017.
[11] F. Weber, R. Brückner, 'Total Syntheses of the Dihydrofuranonecarboxylate Natural Products Gregatin B and E: Gram-Scale Synthesis of (+)-Gregatin B and Unambiguous Assignment of the Stereostructure of (+)-Gregatin E', *Org. Lett.* **2014**, *16*, 6428–6431.
[12] T. Kusakabe, Y. Kawai, K. Kato, 'Total Synthesis of (+)-Gregatin B and E', *Org. Lett.* **2013**, *15*, 5102–5105.
[13] Y. Ito, T. Kusakabe, Y. D. Dhage, K. Takahashi, K. Sakata, H. Sasai, K. Kato, 'Total Synthesis of (−)-Graminin A Based on Asymmetric Cyclization Carbonylation of Propargyl Acetate', *J. Org. Chem.* **2019**, *84*, 16268–16277.
[14] F. Gillsch, F. Mbui, U. Bilitewski, R. Schobert, 'Synthesis and Bioactivity of Thiocarboxylic A and Derivatives', *J. Nat. Prod.* **2022**, *85*, 2828–2835.
[15] K. Kato, H. Nouchi, K. Ishikura, S. Takaishi, S. Motodate, H. Tanaka, K. Okudaira, T. Mochida, R. Nishigaki, K. Shigenobu, H. Akita, 'A Facile Access to Spiro Furanone Skeleton Based on Pd(II)-Mediated Cyclization-Carbonylation of Propargylic Esters', *Tetrahedron* **2006**, *62*, 2545–2554.
[16] L. Koser, V. M. Lechner, T. Bach, 'Biomimetic Total Synthesis of Enterocin', *Angew. Chem. Int. Ed.* **2021**, *60*, 20269–20273.

[17] U. Nookaraju, A. Harbindu, A. D. Bhise, B. M. Sharma, P. Kumar, 'First Total Synthesis of Seimatopolide B', *RSC Adv.* **2012**, *2*, 11231–11234.
[18] P. V. Ramachandran, J. S. Chandra, M. V. R. Reddy, 'Stereoselective Syntheses of (+)-Goniodiol, (−)-8-Epigoniodiol, and (+)-9-Deoxygoniopypyrone via Alkoxyallylboration and Ring-Closing Metathesis', *J. Org. Chem.* **2002**, *67*, 7547–7550.
[19] T. Kawaguchi, N. Funamori, Y. Matsuya, H. Nemoto, 'Total Synthesis of Macrosphelides A, B, and E: First Application of Ring-Closing Metathesis of Macropsphelide Synthesis', *J. Org. Chem.* **2004**, *69*, 505–509.
[20] Y. Zhu, K. Burgess, 'Asymmetric Hydrogenation Approaches to Valuable, Acyclic 1,3-Hydroxymethyl Chirons', *J. Am. Chem. Soc.* **2008**, *130*, 8894–8895.
[21] D. Das, J. Halder, R. Bhuniya, S. Nanda, 'Stereoselective Synthesis of Enantiopure Oxetanes, a Carbohydrate Mimic, an ε-Lactone, and Cyclitols from Biocatalytically Derived β-Hydroxy Esters as Chiral Precursors', *Eur. J. Org. Chem.* **2014**, 5229–5246.

Received February 7, 2023
Accepted March 8, 2023

