Organic LETTERS

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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

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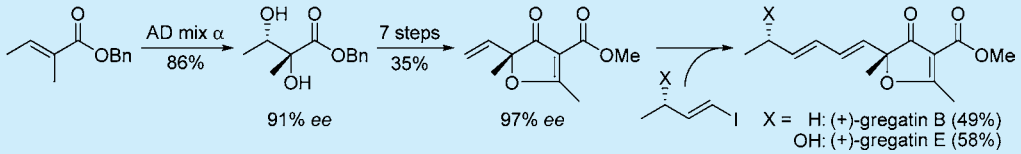
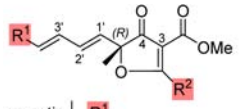
Supporting Information



ABSTRACT: We synthesized the dextrorotatory enantiomers of gregatin B (1.3 g scale) and E, establishing their diene side chains in the last step by Heck coupling with variable iodoolefins. Their counterpart was synthesized in 30% overall yield and with high enantiopurity (97% *ee*) from benzyl tiglate, beginning with an asymmetric dihydroxylation. The stereostructure of gregatin E followed from HPLC comparisons between the four synthetic stereoisomers of this compound and natural gregatin E, which we isolated from *Cadophora gregata*.

The gregatins (Figure 1) are secondary metabolites from the fungus *Cadophora gregata*.[1,2] They are phytotoxins and



gregatin	R^1	R^2
A	Me–CH_2–	(*E*)-CH=CH–Me
B		–Me
C		(*S*)-CH_2–CH(OH)–Me
D		(*R*)-CH_2–CH(OH)–Me
E	(*S*)- or (*R*)-Me–CH(OH)–	–Me

Figure 1. The Gregatins A–E have been known for decades.[1] Their original structures were revised twice.[3,5]

display antimicrobial activity.[1] The structures initially attributed to gregatin A and B[1] (and to their congeners C–E[1]) were synthesized by Clemo and Pattenden in 1982.[3] They turned out to be distinct from the natural products.[3,4] The gregatin formulas advocated thereupon[3] yielded to a synthesis from our group in 2011, which targeted gregatin B.[5] Yet *our* material differed from the natural product, too. The rerevised scaffold of the gregatins, which we put forward thereupon, was read from a side product, which our misled approach to gregatin B had afforded in trace amounts. This insight allowed reaching the gregatins A–D by synthesis purposefully[5b] and assigning their 3D-structures concomitantly.[5b]

Accessing the hexadiene side chain of the mentioned gregatins from *trans*-$H_3C-CH_2-CH_2-CH=CH-CH=O$ and the lithium enolate of Seebach's pivaldehyde acetal of L-lactic acid[6] gave a 93:7 mixture of the respective *E,E*- and *Z,E*-isomers.[5b] This ratio increased to 98:2 when we processed *trans*-$H_3C-CH_2-CH=CH-CH_2-CH=O$ likewise.[5b] Analogous routes to synthetic gregatin E would have constructed *its* side chain from *trans*-$H_3C-C(O_{protected})H-CH_2-CH=CH-CH=O$ or, considering the promise of higher *E,E*-selectivity, preferably from *trans*-$H_3C-C(O_{protected})H-CH=CH-CH-CH=O$. Making the latter building block would entail a non-negligible number of steps, which would have to deal with an aggravating factor: At the outset of the present study, the side-chain configuration of gregatin E was unknown. Circumventing these constraints we now synthesized gregatin B, gregatin E,[7] and *epi*-gregatin E[7] by a different strategy. Its objectives were (1) to establish the diene moiety without a *Z*-configuration and (2) to introduce the side-chain stereocenter as late as possible.

We addressed the mentioned objectives concomitantly as revealed by our retrosynthetic analysis (Scheme 1). We traced back the (*R,E,E*)- or (*S,E,E*)-configured 5-hydroxyhexa-1,3-diene side chain of gregatin E—or whatever hexa-1,3-diene a different gregatin would require—to an *E,E*-selective[8] Heck coupling as its origin. It would engage an appropriately substituted (*E*)-1-iodobut-1-ene and the vinyl substituent of an appropriately substituted furanone (shown in the upper right-hand corner of the scheme). The vinyl group should arise from the β-elimination of a secondary mesylate. The latter was present in every precursor except in the starting olefin and in the product of its asymmetric dihydroxylation. This is because these mesylates represent a protected alcohol of sorts. The furanone core should be established by a Knoevenagel-type condensation[9] (right-hand part of Scheme 1). It would start from a β-ketoester, which looked like it originated from a Claisen condensation. In fact this compound would be made by condensing an activated α-acyloxy-

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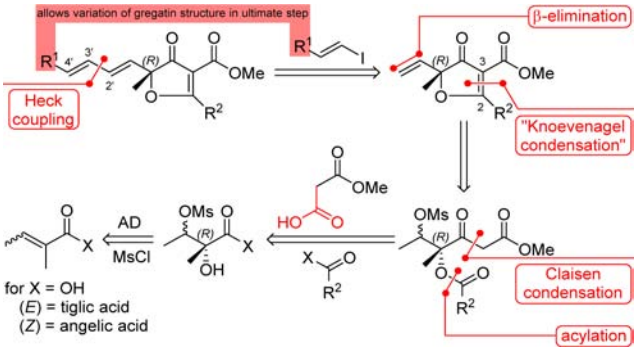
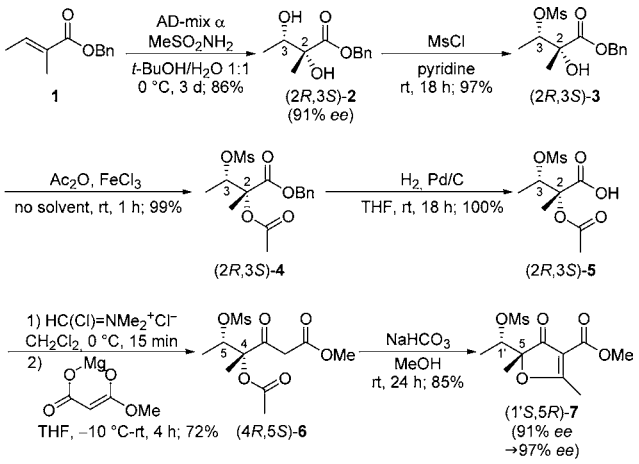
Scheme 1. Our Second Generation Retrosynthetic Analysis of the Gregatins



β-mesyloxy carboxylic acid with the "dianion" of monomethyl malonate (bottom of Scheme 1).

Our synthesis began with a $(DHQ)_2PHAL$-mediated Sharpless dihydroxylation of benzyl tiglate (**1**; Scheme 2). It established the diol (2*R*,3*S*)-**2** with 91% *ee*.[10] The secondary hydroxy group was mesylated selectively.[11] The acetylation of the resulting tertiary alcohol (2*R*,3*S*)-**3** was performed in pure Ac_2O [→ (2*R*,3*S*)-**4**]. AgOTf as a catalyst[12] did not work reproducibly whereas $FeCl_3$ did (other than in a related derivatization,[5b] we omitted a cosolvent). In contrast, attempted acetylations using AcCl in CH_2Cl_2 with catalytic DMAP effected no acetylation at all. The benzyl ester moiety in triester (2*R*,3*S*)-**4** was cleaved hydrogenolytically in THF[13] [→ (2*R*,3*S*)-**5**].

Scheme 2. Part I of Our Second Generation Route to Gregatins: Obtaining the [(Mesyloxy)ethyl]furanone (1′*S*,5*R*)-7

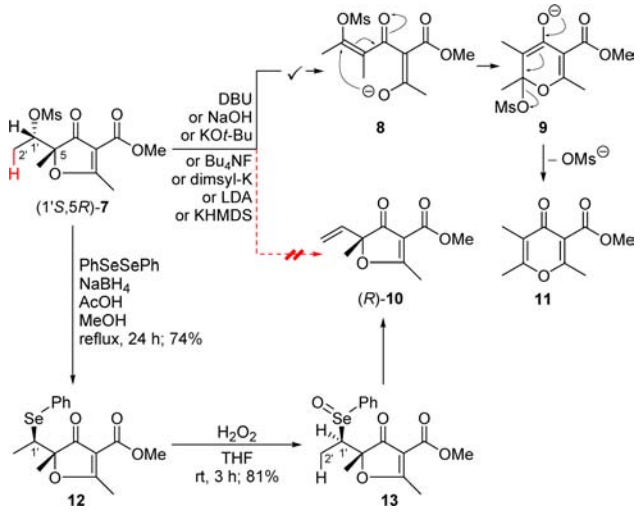


The C_2-elongation of the carboxylic acid (2*R*,3*S*)-**5** to the β-ketoester (4*R*,5*S*)-**6** was difficult to realize (Scheme 2). This was mostly because the mesylate had to be left intact.[14] This limited "allowed" conditions for activating the carboxylic acid (2*R*,3*S*)-**5** chemoselectively and for engaging the resulting intermediate in a chemoselective Claisen(-type) condensation. The last-mentioned need suggested using stabilized rather than simple enolates.[15] Experimenting accordingly we found that many activating agents [$(COCl)_2$,[16] $(COCl)_2$ + cat. DMF,[17] CDI[18]] and nucleophile/base pairs (potassium monomethyl malonate/NEt_3 + $MgCl_2$,[19] Meldrum's acid/pyridine[20]) failed to extend the acid (2*R*,3*S*)-**5** to the β-ketoester (4*R*,5*S*)-**6** or would achieve that transformation irreproducibly. At long last a suspension of Vilsmeyer reagent[21] proved fastest and cleanest at activating the mesylated carboxylic acid (2*R*,3*S*)-**5**. Employing it had the additional benefit that the reaction progress could be monitored by watching the solid disappear. The resulting carboxylic chloride acylated the "dianion" of monomethyl malonate generated from monomethyl malonate and 2 equiv of *i*PrMgCl in THF.[22] It, too, was a suspended solid. It dissolved gradually after the carboxylic chloride was added, to proceed toward the β-ketoester (4*R*,5*S*)-**6** (72% yield).

The subsequent Knoevenagel-type condensation[9] delivered the furanone (1′*S*,5*R*)-**7** under mildly basic conditions ($NaHCO_3$ in MeOH) in 85% yield (Scheme 2). Again, the mesylate had not been affected. Initially, the enantiopurity of (1′*S*,5*R*)-**7** was 91% *ee*. This value equaled the *ee* which had resulted from the Sharpless dihydroxylation **1** → (2*R*,3*S*)-**2**. To our delight the *ee* of (1′*S*,5*R*)-**7** became 97% after precipitating crystals of *rac*-(1′*S*,5*R*)-**7** (no rotatory power!) from the supernatant oil. This improvement followed from an analysis of the follow-up product (*R*)-**10** of such an "optically enriched specimen" of (1′*S*,5*R*)-**7** by chiral HPLC.[23]

The upper part of Scheme 3 summarizes our efforts at effecting the β-elimination of 1′-OMs and 2′-H from the secondary mesylate (1′*S*,5*R*)-**7** to reach the vinyl-substituted furanone (*R*)-**10**. We failed no matter which base/solvent combination we used:[24] Either the unchanged mesylate (1′*S*,5*R*)-**7** was reisolated (up to quantitative yield) or a ring expansion to the pyranone **11**[25] occurred (up to 84% yield).[26] The conversion of the mesylate (1′*S*,5*R*)-**7** into the vinyl-substituted furanone (*R*)-**10** was accomplished via the small detour depicted in the lower part of Scheme 3. We substitued the mesyloxy group with buffered[27] phenyl selenide[28] (→ 74% **12**). With H_2O_2 in amine-free THF we oxidized to the corresponding selenoxide(s). A β-elimination,[29] still in the absence of amines, was complete within 3 h at rt. It furnished the vinyl-substituted furanone (*R*)-**10** in 81% yield.

Scheme 3. Part II of our Second Generation Route to Gregatins: Forming the Vinyl-Furanone (*R*)-10 without an Interfering Ring Enlargement



The vinyl-substituted furanone (*R*)-**10** was a Heck coupling step short of reaching our target gregatins shown in Scheme 4. In each case the nucleophilic component was the vinylfuranone (*R*)-**10**. The electrophilic components were the (*E*)-1-iodobut-1-ene **14**[30] or the (*E*)-3-hydroxy-1-iodobut-1-enes[31] (*S*)-**16**

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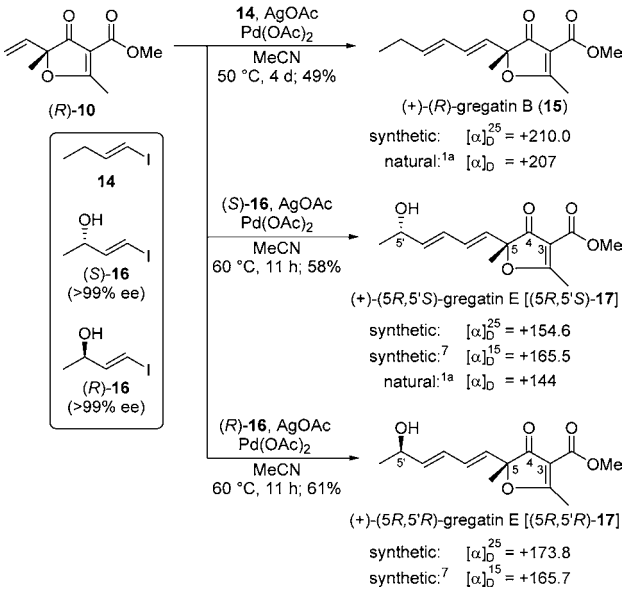
Scheme 4. Part III of our Second Generation Route to Gregatins: Converting the Vinyl-Furanone (*R*)-10 into Gregatin B and the Dextrorotatory Diastereomers of Gregatin E



(>99% *ee*) and (*R*)-**16** (>99% *ee*). The Heck coupling between vinylfuranone (*R*)-**10** (2.00 g) and 2.0 equiv of (*E*)-1-iodobut-1-ene **14** furnished (+)-(*R*)-gregatin B (**15**, 1.26 g) in 49% yield (97% *ee*). Its side-chain configurations were exclusively *E*. The Heck couplings between the vinylfuranone (*R*)-**10** and the (*S*)- and (*R*)-enantiomer of (*E*)-3-hydroxy-1-iodobut-1-ene (**16**) were conducted similarly but on a smaller (70 mg) scale. They delivered the diastereomers (+)-(5*R*,5′*S*)-**17** and (+)-(5*R*,5′*R*)-**17** of gregatin E in 58% and 61% yield, respectively. Again, the side-chain configurations were exclusively *E*.

Whether our Heck coupling product (+)-(5*R*,5′*S*)-**17** or its diastereomer (+)-(5*R*,5′*R*)-**17** equals natural gregatin E was not revealed unequivocally by their specific rotations because they are too alike: $[\alpha]_D^{25}$ = +154.6 (*c* = 0.78, $CHCl_3$), $[\alpha]_D^{25}$ = +173.8 (*c* = 0.78, $CHCl_3$), and $[\alpha]_D$ = +144 (*c* = 0.18, $CHCl_3$),[1a] respectively. Indeed, independent syntheses by another group, which paralleled our own study, used a completely different strategy, requiring 16 linear steps,[7] which provided the same diastereomers (+)-(5*R*,5′*S*)-**17** {$[\alpha]_D^{15}$ = +165.5 (*c* = 0.60, $CHCl_3$)} and (+)-(5*R*,5′*R*)-**17** {$[\alpha]_D^{15}$ = +165.7 (*c* = 0.54, $CHCl_3$)}.[7] Their specific rotations had been even less indicative than our values. As a consequence the other workers compared the melting points of their compounds [(+)-(5*R*,5′*S*)-**17**: 87−88 °C;[7] (+)-(5*R*,5′*R*)-**17**: 101−102 °C[7]] with that of the natural product (mp 89−91 °C[1a]). Their inference was that (+)-(5*R*,5′*S*)-**17** equals gregatin E.[32] We felt that this conclusion was not safe beyond reasonable doubt.

We therefore tailored an unquestionable configurational proof by the following measures: (1) We obtained the two stereoisomers of structure **17**, which are missing in Scheme 4.[33] (2) The resulting set of all conceivable gregatin E candidates was differentiated by chiral HPLC.[34,35] (3) We cultivated *Cadophora gregata*,[36,37] extracted the culture broth, and isolated natural gregatin E. (4) The latter compound and the four gregatin E candidates were compared by chiral HPLC.[35] The result was that natural gregatin E is (5*R*,5′*S*)-**17**. This is identical with what the earlier workers had suggested.[7]

Comprising 9 linear steps and affording a 15% overall yield or more, our "second generation gregatin syntheses" disclosed in Schemes 2−4 demonstrate the viability of the novel approach outlined in Scheme 1. Future work will reveal whether the same strategy suits synthesizing, and clarifying configurationally, the following natural products as well: (+)-penicilliol A,[38] (+)-penicilliol B,[38] (−)-graminin A,[39] (+)-cyclogregatin,[40] and (+)-huaspenone A.[41]

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, copies of NMR spectra for all new compounds. HPLC diagrams for the assignment of the stereostructure of natural gregatin E. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(1) (a) (First) Isolation of these compounds: Kobayashi, K.; Ui, T. *Tetrahedron Lett.* **1975**, *16*, 4119−4122. (b) Naming of these compounds: Kobayashi, K.; Ui, T. *Physiol. Plant Pathol.* **1977**, *11*, 55−60.

(2) *Cadophora gregata* was originally named *Cephalosporinum gregatum* [Allington, W. B.; Chamberlain, D. W. *Phytopathology* **1948**, *38*, 793−802; cited according to http://www.indexfungorum.org/Names/NamesRecord.asp?RecordID=284846 (15.07.14)]. It was first renamed to *Phialophora gregata* [Gams, W. *Chephalosporinum-artige Schimmelpilze*, **1971**, ISBN: 3437301179, p 199; cited according to http://www.indexfungorum.org/Names/NamesRecord.asp?RecordID=319845 (15.07.14)] and finally re-renamed to *Cadophora gregata* (Harrington, T. C.; McNew, D. L. *Mycotaxon* **2003**, *87*, 141−151).

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(8) Heck couplings of vinyl compounds with 1-iodoalk-1-enes giving acceptor-free (*E,E*)-1,3-dienes stereoselectively: (a) Jeffery, T. *J. Chem.*

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(10) For dihydroxylating benzyl tiglate (**1**) in the presence of AD-mix α and $MeSO_2NH_2$, >98% *ee* was reported: Shao, H.; Rueter, J. K.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 5240−5244.

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(12) Das, R.; Chakraborty, D. *Synthesis* **2011**, 1621−1625.

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(14) The mesyloxy group in the carboxylic acid (2*R*,3*S*)-**5** looks sensitive to a β-elimination or might participate in a Grob fragmentation.

(15) A SciFinder search of 1- or 2-step C_2 elongations of carboxylic *acids* giving β-ketoesters by acylating malonic acid-based nucleophiles gave 1159 hits for carboxylic acids with 2 H atoms at C-α, 543 hits for exactly 1 H atom at C-α, and 131 hits without H atoms at C-α (17. 7. 2014).

(16) For example, used by: Xu, L.; Jin, J.; Lal, M.; Daublain, P.; Newcomb, M. *Org. Lett.* **2007**, *9*, 1837−1840.

(17) For example, used by: Padwa, A.; Snyder, J. P.; Curtis, E. A.; Sheehan, S. M.; Worsencroft, K. J.; Kappe, C. O. *J. Am. Chem. Soc.* **2000**, *122*, 8155−8167.

(18) For example, used by: Shimada, N.; Oohara, T.; Krishnamurthi, J.; Nambu, H.; Hashimoto, S. *Org. Lett.* **2011**, *13*, 6284−6287.

(19) For example, used by: Mai, A.; Massa, S.; Rotili, D.; Simeoni, S.; Ragno, R.; Botta, G.; Nebbioso, A.; Miceli, M.; Altucci, L.; Brosch, G. *J. Med. Chem.* **2006**, *49*, 6046−6056.

(20) For example, used by: Hannah, D.; Knight, R. L.; Lock, C. J.; Ortmans, I.; Owen, D. A.; Pegurier, C.; Raphy, G.; Watson, R. J. WO 2008/031556.

(21) For instance: Audoly, L. P. WO 2005/102389.

(22) The initial inspiration was from ref 18.

(23) Chiralpak AD-H column; *n*-heptane/iPrOH (97:3), 1.0 mL/min; $\lambda_{detector}$ = 220 nm. The enantiomers of **10** eluted in the order (*S*)-**10** (t_R = 27 min) and (*R*)-**10** (t_R = 29 min).

(24) Representative examples: Supporting Information.

(25) Compound **11** might be the first nonannulated and unbridged ester of a 2,5,6-trialkylpyran-4-one-3-carboxylic acid. (a) Cyclohexane-annulated esters thereof: Takeuchi, N.; Nakagawa, H.; Kamisato, M.; Tobinaga, S. *Chem. Pharm. Bull.* **1980**, *28*, 2460−2467. (b) Lactones thereof: Chantegrel, B.; Nadi, A. I.; Gelin, S. *Synthesis* **1982**, 1107−1109. (c) Bridged dimers thereof: Siddiq, M.; Khan, A. W. *J. Park. Chem. Soc.* **1992**, *14*, 215−218.

(26) This undesired course may start with a β-elimination, which splits the 1′-H and the 2-O bond. It would deliver the intermediate **8**. Being both an enolate and an enone, **8** might undergo an intramolecular oxa-Michael addition. If the resulting enolate **9** expels a mesylate anion, the pyranone **11** would be accomplished.

(27) When forming the selenide **12** the medium must be neutral such that the base-promoted rearrangement to the pyranone **11** cannot interfere.

(28) Initial conditions: Hamon, D. P. G.; Tuck, K. L. *Tetrahedron* **2000**, *56*, 4829−4835. EtOH was substituted by MeOH to prevent transesterification.

(29) Initial conditions: Ley, S. V.; Tackett, M. N.; Maddess, M. L.; Anderson, J. C.; Brennan, P. E.; Cappi, M. W.; Heer, J. P.; Helgen, C.; Kori, M.; Kouklovsky, C.; Marsden, S. P.; Norman, J.; Osborn, D. P.; Palomero, M. Á.; Pavey, J. B. J.; Pinel, C.; Robinson, L. A.; Schnaubelt, J.; Scott, J. S.; Spilling, C. D.; Watanabe, H.; Wesson, K. E.; Willis, M. C. *Chem.—Eur. J.* **2009**, *15*, 2874−2914.

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(31) The iodobutenols (*S*)- and (*R*)-**15** were derived in 2 steps from (*S*)- and (*R*)-but-3-yne-2-ol, respectively, by hydrostannylation (Lee, T.; Kim, S. *Tetrahedron: Asymmetry* **2003**, *14*, 1951−1954) and Sn/I exchange (Yu, L.; Cui, J.; Padakanti, P. K.; Engel, L.; Bagchi, D. P.; Kotzbauer, P. T.; Tu, Z. *Bioorg. Med. Chem.* **2012**, *20*, 4625−4634).

(32) Our mp: 94 °C for (+)-(5*R*,5′*S*)-**17**, 103 °C for (+)-(5*R*,5′*S*)-**17**.

(33) (a) A Heck coupling analogous to b and c of Scheme 4 between *rac*-**10** and iodobutene *rac*-**16** gave a 25:25:25:25 mixture of (5*R*,5′*S*)-**17**, (5*S*,5′*S*)-**17**, (5*R*,5′*R*)-**17**, and (5*S*,5′*R*)-**17**. (b) The Heck coupling b of Scheme 4 starting from vinylfuranone (*R*)-**10** with 97% *ee* and iodobutene (*S*)-**16** with 99% *ee* should give a 98.0:1.5:0.5:0.0 mixture of (5*R*,5′*S*)-**17**, (5*S*,5′*S*)-**17**, (5*R*,5′*R*)-**17**, and (5*S*,5′*R*)-**17** (found: 98.7:0.6:0.7:0.0). (c) The Heck coupling c of Scheme 4 starting from vinylfuranone (*R*)-**10** with 97% *ee* and iodobutene (*R*)-**16** with 99% *ee* should give a 0.5:0.0:98.0:1.5 mixture of (5*R*,5′*S*)-**17**, (5*S*,5′*S*)-**17**, (5*R*,5′*R*)-**17**, and (5*S*,5′*R*)-**17** (found: 1.0:0.0:98.6:0.4). (d) Comparing the **17**-isomers from (b) vs (a) allowed identifying (5*R*,5′*S*)-**17** (most abundant isomer) and (5*S*,5′*R*)-**17** (missing isomer). (e) Comparing the **17**-isomers from (c) vs (a) allowed identifying (5*R*,5′*R*)-**17** (most abundant isomer) and (5*S*,5′*S*)-**17** (missing isomer).

(34) Chiralpak OD-3 column; *n*-heptane/iPrOH (98:2), 1.0 mL/min; $\lambda_{detector}$ = 250 nm. The gregatin E candidates eluted in the order (5*R*,5′*R*)-**17** (t_R = 44 min), (5*R*,5′*S*)-**17** (t_R = 48 min), (5*S*,5′*R*)-**17** (t_R = 69 min), and (5*S*,5′*S*)-**17** (t_R = 139 min).

(35) HPLC diagrams: Supporting Information.

(36) We obtained *Cadophora gregata* (*Phialophora gregata f. sp. adzukicola* T96-1,[2] MAFF No. 241056) from the NIAS Genebank Project of the National Institute of Agrobiological Sciences, Japan. This particular strain was isolated and characterized by Kondo et al.: (a) Kondo, N.; Fujita, S.; Murata, K.; Ogoshi, A. *Plant Dis.* **1998**, *82*, 928−930. (b) Kondo, N.; Shimada, H.; Fujita, S. *J. Gen. Plant Pathol.* **2009**, *75*, 181−187.

(37) Details of the cultivation of *C. gregata*, workup, and chromatography: Supporting Information.

(38) (a) Isolation and structure attribution: Kimura, T.; Takeuchi, T.; Kumamoto-Yonezawa, Y.; Ohashi, E.; Ohmori, H.; Masutani, C.; Hanaoka, F.; Sugawara, F.; Yoshida, H.; Mizushina, Y. *Bioorg. Med. Chem.* **2009**, *17*, 1811−1816. (b) Proposed structure revision: Reference 5b.

(39) (a) Isolation and structure attribution: Kobayashi, K.; Ui, T. *J. Chem. Soc., Chem. Commun.* **1977**, 774a−774a. (b) Proposed structure revision: Reference 5b.

(40) (a) Isolation and structure attribution: Anke, H.; Casser, I.; Schrage, M.; Steglich, W. *J. Antibiot.* **1988**, *17*, 1681−1684. (b) Proposed structure revision: Reference 5b.

(41) (a) Isolation and structure attribution: Zhan, Z.-J.; Jin, J.-P.; Ying, Y.-M.; Shan, W.-G. *Helv. Chim. Acta* **2011**, *94*, 1454−1458. (b) Proposed structure revision: Reference 5b.