ORGANIC LETTERS

2011
Vol. 13, No. 10
2730–2733

A Serendipitous Synthesis of (+)-Gregatin B, Second Structure Revisions of the Aspertetronins, Gregatins, and Graminin A, Structure Revision of the Penicilliols

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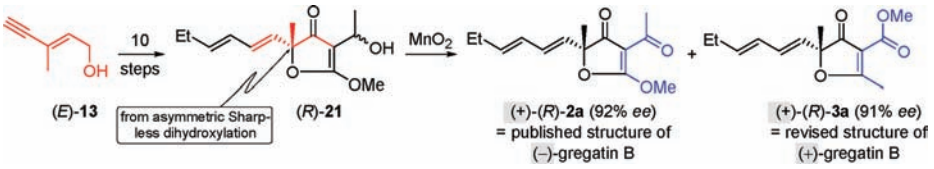
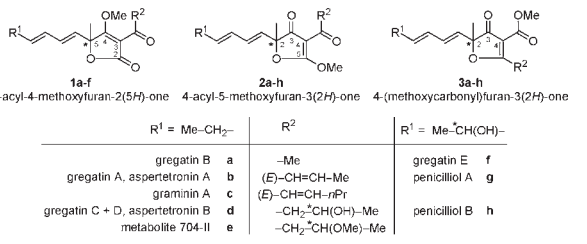
Received March 30, 2011

ABSTRACT



A $(DHQN)_2AQN$-promoted asymmetric dihydroxylation (92% *ee*) of the allyl chloride derived from enynol (*E*)-13 and an 8-step sequence provided access to the hydroxyethylated furanone (*R*)-21. Oxidation with MnO_2 furnished 50% furanone (+)-(*R*)-2a and 2.7% isomeric furanone (+)-(*R*)-3a. (*R*)-2a possesses the accepted constitution of (+)-gregatin B but its spectra are different. Surprisingly, (+)-(*R*)-3a equals the natural product. Analogous structure reassignments are due for the gregatins A and C–E, the aspertetronins A–B, graminin A, and the penicilliols A and B.

(+)-Aspertetronin A and (−)-aspertetronin B are natural products from *Aspergillus rugulosus*.[1] Degradation and correlation studies led to the conclusion that they are the furan-2(5*H*)-ones **1b** and **d**, respectively (Figure 1).[1] The optical antipodes of aspertetronin A and B are natural products as well, isolated from *Cephalosporium gregatum*[2] and called[3] (−)-gregatin A[4,5] and (+)-gregatin D,[4] respectively. (+)-Gregatin B,[4] (+)-gregatin C, and (+)-gregatin E were first isolated from the same source,[2] named analogously,[3] and believed to be the furan-2(5*H*)-ones **1a**, **d**, and **f**, respectively. "Metabolite (+)-704-II"[6] possesses the connectivity **1e** of a methyl ether of gregatin D. (−)-Graminin A from *Cephalosporium gramineum*[7] was assigned the analogous structure **1c**. *Rac*-**1a**[8–10] and *rac*-**1b**[8] were synthesized early on. The distinctness of their spectral properties from those of the natural products sparked the suggestion that the latter are the



R^1 = Me–CH_2–		R^2	R^1 = Me-*CH(OH)–	
gregatin B	a	–Me	gregatin E	f
gregatin A, aspertetronin A	b	(*E*)–CH=CH–Me	penicilliol A	g
graminin A	c	(*E*)–CH=CH–*n*Pr		
gregatin C + D, aspertetronin B	d	$–CH_2$-*CH(OH)–Me	penicilliol B	h
metabolite 704-II	e	$–CH_2$-*CH(OMe)–Me		

Figure 1. Original (**1a**–**f**,[1,2,4,6,7] **2g**,[12] **h**[12]), revised (**2a**–**f**,[8,11] **3g**,[a] **h**[a]), and re-revised[a] (**3a**–**f**) structures of gregatins A [(−)-**b**[2,4,5]], B [(+)-**a**[2,4]], C [(+)-**d**[2]], D [(+)-**d**[2,4]], and E [(+)-**f**[2]], aspertetronins A [(+)-**b**[1]] and B [(−)-**d**[1]], graminin A [(−)-**c**[7]], metabolite 704-II [(+)-**e**[6]], and penicilliols A [(+)-**g**[12]] and B [(+)-**h**[12]]. [a] This work.

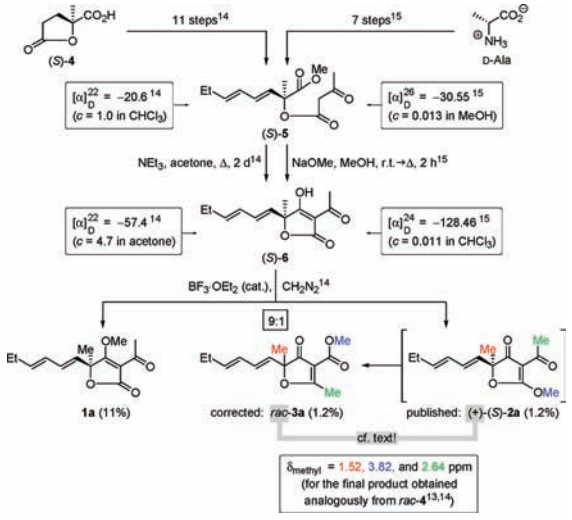
(1) Ballantine, J. A.; Ferrito, V.; Hassall, C. H.; Jones, V. I. P. *J. Chem. Soc.* **1969**, 56–61.
(2) Kobayashi, K; Ui, T. *Tetrahedron Lett.* **1975**, 4119–4122.
(3) Kobayashi, K.; Ui, T. *Physiol. Plant Pathol.* **1977**, *11*, 55–60.
(4) Second isolation of this compound (from *Aspergillus panamensis*): Anke, H.; Schwab, H.; Achenbach, H. *J. Antibiot.* **1980**, *33*, 931–939.
(5) Third isolation (from *Phialophora gregata*): Taylor, S. L.; Peterson, R. E.; Gray, L. E. *Appl. Environ. Microbiol.* **1985**, *50*, 1328–1329.
(6) First isolation of this compound (from *Aspergillus panamensis*): ref 4.
(7) Kobayashi, K.; Ui, T. *J. Chem. Soc., Chem. Comm.* **1977**, 774–774.
(8) (a) Clemo, N. G.; Pattenden, G. *Tetrahedron Lett.* **1982**, *23*, 585–588. (b) Clemo, N. G.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2407–2411.

10.1021/ol2008318
Published on Web 04/28/2011

furan-3(2*H*)-ones **2a** and **b**.[8,11] The presence of the same substructure was suggested for family members **c**–**f**, too.[8] (+)-Penicilliol A (**2g**) and (+)-penicilliol B (**2h**), which were isolated from *Penicillium daleae* very recently, were assumed right away to represent furan-3(2*H*)-ones.[12]

Takaiwa and Yamashita reported the first syntheses of racemic[13,14] and (+)-gregatin B[14] from lactone carboxylic acids *rac*- or (*S*)-**4**, respectively (Scheme 1). Treatment of the derived acyltetronic acids *rac*- or (*S*)-**6** with diazomethane and BF_3 etherate gave 11% *rac*- or (*S*)-**1a** and 1.2% of the elusive gregatin B. The latter was optically inactive using *rac*-6 and dextrorotatory using (*S*)-**6**. These observations, matching ^{1}H NMR and IR data, and their

Scheme 1. Purported Synthesis[14] of the (*S*)-Enantiomer of the Revised[8] Structure **2a** of (+)-Gregatin B from (*S*)-**4** but in Actual Fact Racemic Syntheses[13,14] of the Re-revised Structure **3a**[a]

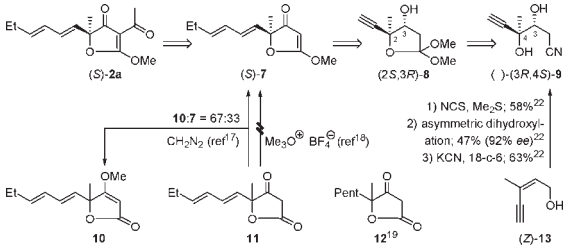


[a] Formal total synthesis of gregatin B from D-alanine[15].

synthetic design led to the belief that natural gregatin B is (*S*)-**2a**. This view was corroborated by a formal total synthesis of gregatin B from D-alanine, which merged into the Takaiwa/Yamashita route[13,14] at intermediate (*S*)-**6**.[15] However, as we will show, (+)-gregatin B possesses structure (*R*)-**3a** rather than (*S*)-**2a**.

While the compounds compiled in Figure 1 exhibit some pharmacological promise,[16] they have been studied so little let alone varied structurally that developing a generalizable synthetic access appeared worthwhile. Our route emerged from a retrosynthetic analysis exemplified for the purported[14] structure (*S*)-**2a** of natural gregatin B in Scheme 2. We planned to obtain (*S*)-**2a** from furanone (*S*)-**7** by a lithiation/acetylation sequence. Furanone (*S*)-**7** was known not to be a viable *O*-methylation product of the "underlying" ketolactone **11**[17,18] even if the required transformation worked well with ketolactone **12**.[19] We considered (*S*)-**7** as a C,C-coupling product between a but-1-enyl reagent and a hydrometalation or -halogenation product of the C≡C-containing ortholactone (2*S*,3*R*)-**8**. Most orthoesters stem from alcoholyses of imidoester hydrochlorides.[20] Hence, (2*S*,3*R*)-**8** was to be made by a Pinner cyclization[21] of the known[22] dihydroxynitrile (3*R*,4*S*)-**9** and a subsequent methanolysis.

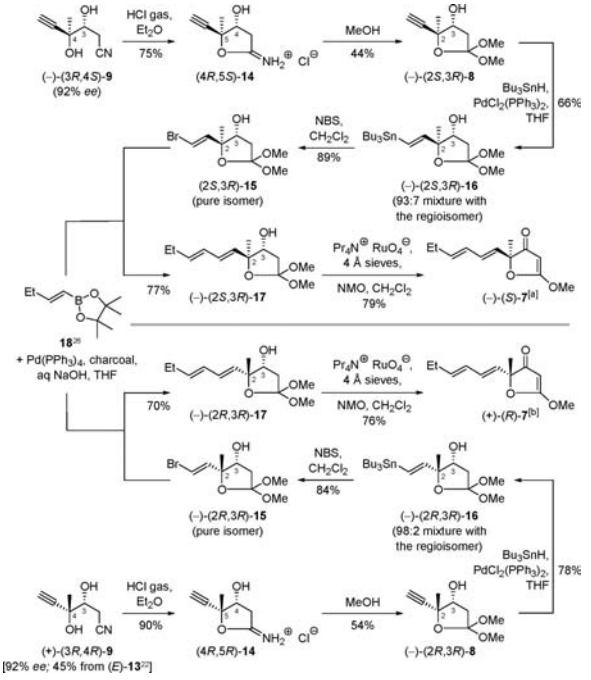
Scheme 2. Retrosynthetic Analysis of the Revised[8]—and Seemingly Confirmed[14,15]—Structure (*S*)-**2a** of (+)-Gregatin B



The imidolactone hydrochloride (4*R*,5*S*)-**14** was obtained as a crystalline compound from dihydroxynitrile (3*R*,4*S*)-**9** and HCl gas (Scheme 3, upper half). Methanolysis provided the ortholactone (2*S*,3*R*)-**8** and hydrostannylation of the C≡C bond[23] a 93:7 mixture of stannane (2*S*,3*R*)-**16** and its regioisomer. Treatment with NBS[24] led to the corresponding bromoolefin (2*S*,3*R*)-**15**. Coupling[25]

(9) Takeda, K.; Kubo, H.; Koizumi, T.; Yoshii, E. *Tetrahedron Lett*. **1982**, *23*, 3175–3178.
(10) Miyata, O.; Schmidt, R. R. *Tetrahedron Lett*. **1982**, *23*, 1793–1796.
(11) The revisions **1a**→**2a** and **1a**→**2a** were driven by the mismatch between data of **1** vs. the natural products but based on little *positive* evidence because the reference compounds cited in Clemo, N. G.; Pattenden, G. *Tetrahedron Lett*. **1982**, *23*, 589–592 and ref 8b contain fewer C=O groups than **1** or **2**.
(12) 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.
(13) Takaiwa, A.; Yamashita, K. *Agric. Biol. Chem*. **1982**, *46*, 1721–1722.
(14) Takaiwa, A.; Yamashita, K. *Agric. Biol. Chem*. **1984**, *48*, 2061–2065.
(15) Matsuo, K.; Kanayama, M.; Xu, J. Y.; Takeuchi, R.; Nishiwaki, K.; Asaka, Y. *Heterocycles* **2005**, *65*, 1609–1614.
(16) Gregatin B and E act antimicrobially,[2] gregatin A-D and metabolite 704-II antibacterially,[4] (+)-penicilliol A and B inhibit DNA polymerase.[12]
(17) Methylation of *rac*-**11** with diazomethane furnished 18% *rac*-**7** as the minor constituent of a separable mixture with **10** (37% yield): Effenberger, F.; Syed, J. *Tetrahedron Asymmetry* **1998**, *9*, 817–825.
(18) Attempted methylation of (*R*)-**11** with Meerweiń's salt led to decomposition: Kapferer, T. *Dissertation*; Universität Freiburg, 2006; pp 132-133.
(19) Kapferer, T.; Brückner, R.; Herzig, A.; König, W. A. *Chem.—Eur. J*. **2005**, *11*, 2154–2162.
(20) Lebel, H.; Grenon, M. In *Science of Synthesis – Houben-Weyl Methods of Organic Chemistry*, Vol. 22; Charette, A., Ed.; Thieme: Stuttgart, NY, 2005; pp 669–748.
(21) Review: (a) DeWolfe, R. H. *Synthesis* **1974**, 153–172. Cyclization of parent compound: (b) Topchiev, K. S.; Kirmalova, M. L. *Dokl. Akad. Nauk SSSR* 1948, *63*, 281–284 (*Chem. Abstr*. **1949**, *43*, 2579). Recent examples: (c) Fleming, F. F.; Wei, G.; Steward, O. W. *J. Org. Chem*. **2008**, *73*, 3674–3679 and ref 39 therein.
(22) Burghart-Stoll, H.; Kapferer, T.; Brückner, R. *Org. Lett*. **2011**, *13*, 1016–1019.
(23) ProcedureBetzer, J.-F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem*. **1997**, *62*, 7768–7780.
(24) Procedures: (a) Wipf, P.; Coish, P. D. G. *J. Org. Chem*. **1999**, *64*, 5053–5061. (b) Malecka, R. E., J.; Gallagher, W. P. *Org. Lett*. **2001**, *3*, 4173–4176.

Scheme 3. Synthesis of the Precursor (−)-(*S*)-**7** of the Hitherto Accepted Structure **2a** of (+)-Gregatin B (top half); synthesis of Antipode (+)-(*R*)-**7** via Diastereomeric Intermediates (bottom half)[28,29]

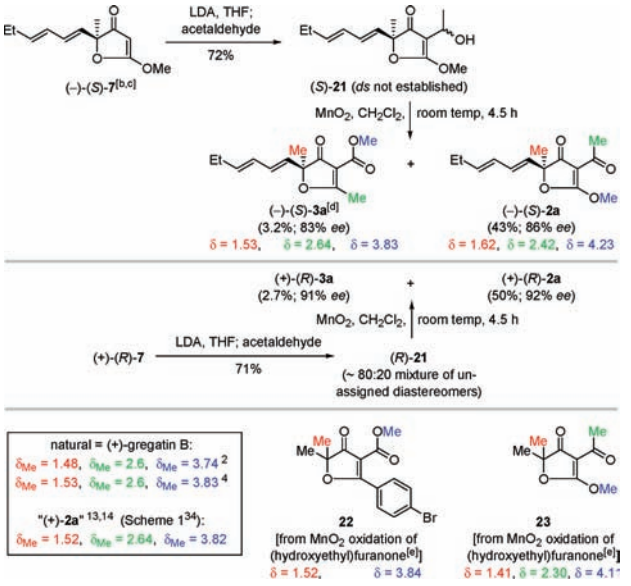


[a] $[\alpha]_D^{20} = +53.8$ ($c = 1.03$ in $CHCl_3$). [b] $[\alpha]_D^{20} = -49.1$ ($c = 1.04$ in $CHCl_3$).

with boronate **18**[26] completed the hexadienyl side-chain, delivering (2*S*,3*R*)-**17**. Oxidation with $Pr_4N^{\oplus}$ $RuO_4^{\ominus}$/NMO[27] was accompanied by the loss of methanol and afforded the desired furanone (*S*)-**7**. In anticipation of the need of an HPLC determination of the enantiopurity of our gregatin-to-be, we prepared the enantiomeric furanone (*R*)-**7**, too (Scheme 3, lower half): by subjecting dihydroxynitrile (3*R*,4*R*)-**9**[22]—a diastereomer of the previous starting material (3*R*,4*S*)-**9**—to the same sequence of steps, which had led to (*S*)-**7**.

Scheme 4 supplements the 4-acetylation of furanones (*S*)- and (*R*)-**7**. This transformation worked poorly in one step (LDA or RLi; AcX) but satisfyingly if realized in two steps: (1) successive treatment with LDA and acetaldehyde;[30] (2) oxidation by ca. 40 equiv of "active MnO_2".[31,32] Starting

Scheme 4. Elaboration of Furanones (*S*)- and (*R*)-**7**[35a]



[a] Attribution of structure (*R*)-**3a** to (+)-gregatin B based on total synthesis, methyl-singlet ^{1}H-NMR [a] shift values, and X-ray crystallography. [a] The solvent was $CDCl_3$ except for the quote from refs 13 and 14 in which case the solvent was CCl_4. [b] $[\alpha]_D^{20} = -47.6$ ($c = 1.1$ in $CHCl_3$). [c] Since progress required an efficient access this sample of (*S*)-**7** was not prepared as specified in Scheme 3 [top half; 1.9% overall yield from (*Z*)-**13**] but by converting (*E*)-**13** into (−)-(3*S*,4*S*)-**9**[22] (85% *ee*) and proceeding analogously as shown in Scheme 3 (bottom half) for the transformation of (+)-(3*R*,4*R*)-**9** into (*R*)-**7** (details: Supporting Information; 5.1% overall yield). [d] $[\alpha]_D^{20} = -184$ ($c = 0.09$ in $CHCl_3$). [e] Complete synthesis: Supporting Information.

from (*S*)-**7**, we obtained (*S*)-**2a**, which was levorotatory (31% over the 2 steps; 86% *ee*[33]). It differed in this respect and ^{1}H NMR spectroscopically from Takaiwás and Yamashitás synthetic "(+)-(*S*)-**2a**" (Scheme 1) and from (+)-gregatin B. Surprisingly, (*S*)-**21** and MnO_2 also gave a little (−)-(*S*)-**3a** (83% *ee*[33]). The latter showed the same ^{1}H NMR spectrum as (+)-gregatin B and (!) the mentioned "(+)-(*S*)-**2a**".[34] The structures of compounds **2a** and **3a** followed from ^{1}H NMR similarities between **2a** and compound **23** and between **3a** and compound **22** (Table 1). The structures of the reference compounds emerged from X-ray analyses (Scheme 4, bottom).[35]

(25) Procedure: Hanisch, I.; Brückner, R. *Synlett* **2000**, 374–378. The addition of charcoal was suggested by Prof. P. Vogel (EPF Lausanne).

(26) Compound **18** was prepared by a cp_2ZrHCl-mediated pinacolboration of but-1-yne following a procedure by Wang, Y. D.; Kimball, G.; Prashad, A. S.; Wang, Y. *Tetrahedron Lett.* **2005**, *46*, 8777–8780.

(27) Procedure:Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639–666.

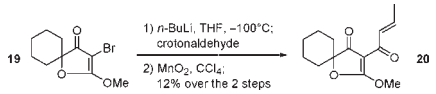
(28) In conjuncture with other findings (ref 29) these syntheses of (*S*)- and (*R*)-**7** proved that the asymmetric dihydroxylations en route to (3*R*,4*S*)- *and* (3*R*,4*R*)-**9**[22] proceed in accordance with "Sharpless/Norrby orientations" of the C=C bonds in the transition state.

(29) Burghart-Stoll, H.; Böhnke, O.; Brückner, R. *Org. Lett.* **2011**, *13*, 1020–1023.

(30) The conditions for this step were gleaned from analogous functionalizations of a 4-methoxyfuran-2(5*H*)-one; these are described in ref 8b.

(31) Review: Fatiadi, A. J. *Synthesis* **1976**, 65–104.

(32) This transformation exemplifies a 2-step sequence, for which we know a single precedent (**19**→**20**); the initiation step differed, though:[9]

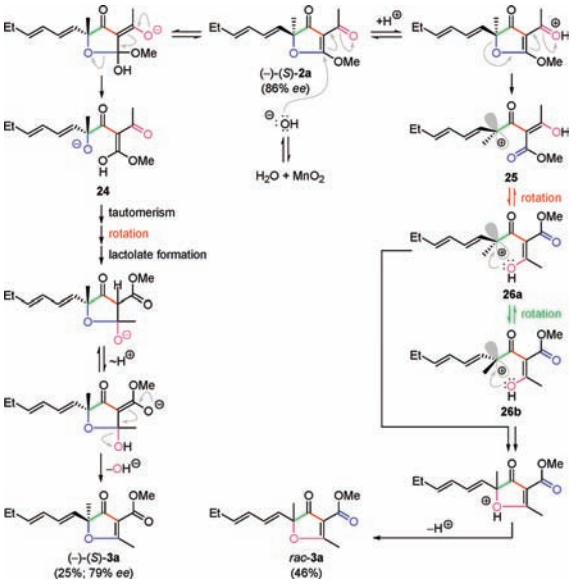


(33) The enantiopurity of this compound was determined by HPLC (for details see Supporting Information).

(34) "(+)-(*S*)-**2a**" from Scheme 1 is **3a** by the ^{1}H NMR comparisons in Scheme 4 yet our preparations of (−)-(*S*)- and (+)-(*R*)-**3a** show that the descriptors "(+)" and "(*S*)" do not match for any enantiomer of **3a**. The easiest way of reconciliating the findings of refs 13 and 14 with ours assumes that their **3a** was (1) racemic [cf. our acid-catalyzed isomerization (−)-(*S*)-**2a**→*rac*-**3a**; Scheme 5] and (2) dextrorotatory because of an unnoticed impurity.

(35) CCDC 813695 and 813696 contain the crystallographic data for this paper. These data can be obtained free of charge from *The Cambridge Crystallographic Data Centre* via the link www.ccdc.cam.ac.uk/data_request/cif.

Scheme 5. Isomerizations of (−)-(*S*)-**2a** Giving (−)-(*S*)-**3a** (left side) or *rac*-**3a** (right side) and Rationalizations for Their Course



Successive treatments with LDA and acetaldehyde and oxidation with MnO_2 turned furanone (*R*)-**7** into (+)-(*R*)-**2a** (36%; 92% *ee*[33]) and (+)-(*R*)-**3a** (2%; 91% *ee*[33]). (+)-(*R*)-**3a** was a solid (mp = 78 °C; ref 2, 80−81 °C; ref 4, oil) and identical with natural gregatin B {$[\alpha]_D^{20}$ = +211 (*c* = 0.08 in $CHCl_3$); ref 2, $[\alpha]_D$ = +207 (*c* = 0.84 in $CHCl_3$); ref 4, $[\alpha]_D$ = +205 (*c* = 0.1 in $CHCl_3$)}.

Further experimentation (Scheme 5) revealed that (−)-(*S*)-**2a** (86% *ee*[33]) became a progenitor of (−)-(*S*)-**3a** when exposed to MnO_2 (150 equiv, CH_2Cl_2, room temp, 2 d) and a progenitor of *rac*-**3a** when treated with *p*TsOH·H_2O (CH_2Cl_2, room temp, 1 h). The former conditions resemble those of our serendipitous routes to (−)-(*S*)- and (+)-(*R*)-**3a** (Scheme 4). The latter conditions are commemorative of the $BF_3 \cdot Et_2O$ environment, in which Takaiwa and Yamashita[13,14] allegedly obtained "(+)-(*S*)-**2a**" but in fact probably *rac*-**3a**[34] (Scheme 1). Our deliberate isomerizations (−)-(*S*)-**2a**→**3a** were allowed to reach completion as judged by TLC. In the MnO_2 case we isolated 25% (−)-(*S*)-**3a** (79% *ee*[33]) and in the *p*TsOH.H_2O case 46% nearly racemic **3a** [2% *ee*[33] favoring the (*S*)-enantiomer]. Accordingly, MnO_2-mediation retains the C_{quat}−O bond while Brønsted acid catalysis breaks it − as the mechanisms imply, which are suggested in Scheme 5: $HO^{\ominus}$ formed from H_2O, which is omnipresent in MnO_2[31] opens (−)-(*S*)-**2a** to give **24** by a nucleophilic vinylic substitution via addition and elimination. Tautomerism, hemiacetal-anion ("lactolate") formation, and loss of $HO^{\ominus}$ establish ring (−)-(*S*)-**3a**. The protonation-induced isomerization of (−)-(*S*)-**2a** seems to follow an S_N1 course. It starts with the heterolysis of the C_{quat}−O bond. The resulting pentadienyl cation **25** is destabilized by a tetraoxygenated substituent (perhaps less if twisted as drawn). Conformational changes **26a** ⇌ **26b** and ion capture would give ring *rac*-**3a**.

Table 1. ^{1}H-NMR Juxtaposition of Type-**2** and Type-**3** Furanones (Structure-Differentiating Motifs and Shifts on Grey Background)

type-**2** furanone	field strength / MHz	solvent	$\delta_{methyl\ singlets}$ / ppm 2-Me	4-C(=O)Me	5-OMe
iso-**22**[a]	300	$CDCl_3$	1.56	absent	4.21
23	500	$CDCl_3$	1.41	2.30	4.11
(*R*)-**2a**	300	$CDCl_3$	1.62	2.42	4.23
type-3 furanone			2-Me	5-Me	4-CO_2Me
22	300	$CDCl_3$	1.52	absent	3.84
iso-**23**[b]	300	$CDCl_3$	1.42	2.61	3.84
synthetic (*R*)-**3a**	400	$CDCl_3$	1.52	2.64	3.83
"(+)-**2a**[14]" ≡ *rac*-**3a**	100	$CDCl_3$	1.52	2.64	3.82
natural **3a** (gregatin B) ref.[2]	90	CCl_4	1.48	2.6	3.74
natural **3a** (gregatin B) ref.[4]	90	$CDCl_3$	1.53	2.6	3.83
3b (gregatin A[4])	250	$CDCl_3$	1.53	absent	3.83
3b (aspertetronin A[1])	60	CCl_4	1.48	absent	3.74
3c (graminin A[7])	90	CCl_4	1.48	absent	3.74
3d (gregatin C[2])	90	CCl_4	1.50	absent	3.74
3d (gregatin D) ref.[7]	90	CCl_4	1.50	absent	3.74
3d (gregatin D) ref.[4]	250	$CDCl_3$	1.53	absent	3.83
3d (aspertetronin B[1])	60	CCl_4	1.50	absent	3.75
3e (metabolite 704-II[4])	90	$CDCl_3$	1.53	absent	3.83
3f (gregatin E[2])	90	CCl_4	1.50	2.60	3.74
3g (penicilliol A[12])	400	$CDCl_3$	1.57	absent	3.84
3h (penicilliol B[12])	400	$CDCl_3$	1.56	absent	3.84

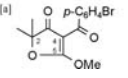
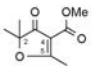
[a]  (cf. Supporting Information). [b]  (cf. Supporting Information)

Table 1 lists the ^{1}H NMR shifts of the methyl singlets of various furan-3(*2H*)-ones from the current study, refs 13 and 14, and the natural products shown in Figure 1. The δ-values of the highlighted protons cluster in specific ranges. This suggests that the gregatins A and C−E, the aspertetronins A and B, graminin A, and the penicilliols A and B are rather type-**3** furanones than, as has been believed hitherto, type-**2** furanones. The kind of structure revision, which this implies is identical to how the real structure (*R*)-**3a** of (+)-gregatin relates to the connectivity in (*S*)-**2a**.

The emergence of (*R*)-**3a** from the current study (Scheme 3, bottom, + Scheme 4, center) represents the first total synthesis of (+)-gregatin. It relies on an asymmetric dihydroxylation and a Pinner cyclization/methanolysis route to an ortholactone. It ends with a low-yielding but novel furanone rearrangement. Targeted syntheses of gregatin B and its congeners are now conceivable.

Acknowledgment. Dedicated to Prof. Horst Prinzbach on the occasion of his 80th birthday. We are grateful to Dr. Manfred Keller (Institut für Organische Chemie und Biochemie, Universität Freiburg) for NMR support and to Dr. Jens Geier (ibid.) for the X-ray analyses.

Supporting Information Available. Procedures, characterizations, copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.