ORGANIC LETTERS

2013
Vol. 15, No. 19
5102–5105

Total Synthesis of (+)-Gregatin B and E

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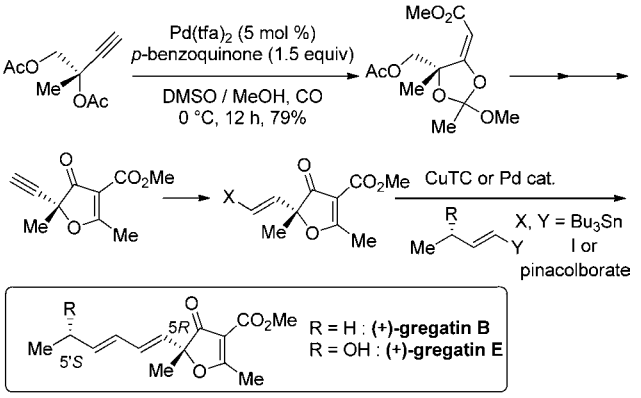
Received August 27, 2013

ABSTRACT



The first total synthesis of (+)-gregatin E and a new total synthesis of (+)-gregatin B are described. Key features of our synthetic approach involve a palladium-catalyzed cyclization−methoxycarbonylation of optically active propargylic acetate and a Suzuki−Miyaura coupling or CuTC-mediated coupling reaction. The absolute configuration of (+)-gregatin E (5*R*,5′*S*) is proposed.

Gregatins, aspertetronins, and penicilliols are natural products isolated from *Cephalosporium gregatum*, *Aspergillus rugulosus*, and *Penicillium daleae*, respectively, which possess 4-oxo-3-furancarboxylate skeletons.[1] Initially, the core structures of these compounds were believed to be furan-2(5*H*)-ones **1** (Figure 1). However, the originally proposed structure has been revised twice. Most recently, Burghart−Stoll and Brückner reported the total synthesis and structural revision of gregatins A−D and aspertetronins A and B, together with a plausible structural revision of gregatin E[1b,2] based on ^{1}H NMR spectroscopic comparison to related compounds.[3] The absolute and relative configurations of gregatin E have not yet been determined.

Previously, we reported the Pd^{II}-catalyzed cyclization−methoxycarbonylation of propargylic acetates[4a] and its application to the construction of the 2,5,5-trialkyl-4,5-dihydro-4-oxo-3-furancarboxylate skeleton **3**.[4b] For the construction of the diene moiety of the side chain, this precedent[3a] utilized dehydration of the corresponding homoallylic alcohols. This method may not be suitable for the synthesis of (+)-gregatin E (**3a**) bearing an additional hydroxy group in the side chain. In this paper, we would like to report the first total synthesis of (+)-gregatin E (**3a**) and a new total synthesis of (+)-gregatin B based on

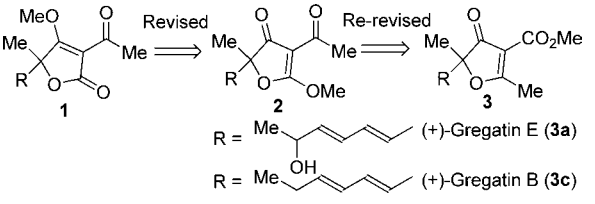


Figure 1. Original **1**, revised **2**, and rerevised structure of gregatins **3**.

(1) (a) Ballantine, J. A.; Ferrito, V.; Hassall, C. H.; Jones, V. I. P. *J. Chem. Soc.* **1969**, 56–61. (b) Kobayashi, K.; Ui, T. *Tetrahedron Lett.* **1975**, 4119–4122. (c) 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*, 1881–1816.

(2) Zhan, Z.-J.; Jin, J.-P.; Ying, Y.-M.; Shan, W.-G. *Helv. Chim. Acta* **2011**, *94*, 1454–1458.

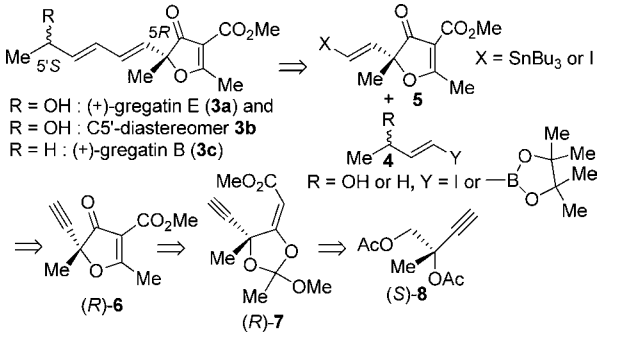
(3) (a) Burghart-Stoll, H.; Brückner, R. *Eur. J. Org. Chem.* **2012**, *2012*, 3978–4017. (b) Burghart-Stoll, H.; Brückner, R. *Org. Lett.* **2011**, *13*, 2730–2733.

(4) (a) Kato, K.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett.* **2002**, *43*, 6587–6590. (b) Kato, K.; Nouchi, H.; Ishikura, K.; Takaishi, S.; Motodate, S.; Tanaka, H.; Okudaira, K.; Mochida, T.; Nishigaki, R.; Shigenobu, K.; Akita, H. *Tetrahedron* **2006**, *62*, 2545–2554.

10.1021/ol402472q
Published on Web 09/25/2013

our carbonylation chemistry and Pd- or Cu-mediated coupling reactions.[5]

Scheme 1. Retrosynthetic Analysis of (+)-Gregatins B and E

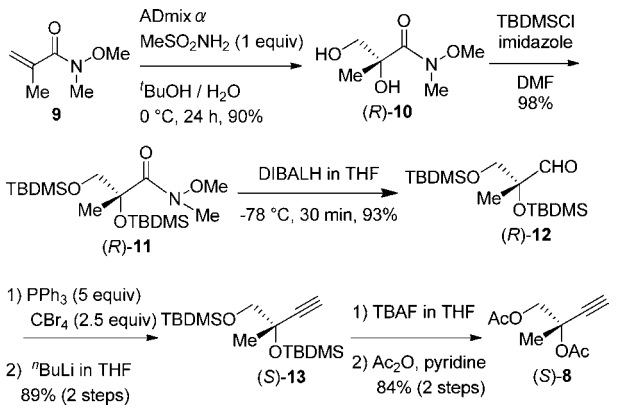


Retrosynthetically, gregatins B and E (**3a** and **3c**) can be obtained by the coupling reaction of a vinyl iodide with a vinyl stannane or borate, which may be derived from 2-butyne and (*R*)-**6** (Scheme 1). The 4-oxo-3-furancarboxylate skeleton of (*R*)-**6** can be constructed by Knoevenagel–Claisen type condensation of the corresponding γ-acetoxy-β-ketoester, which can be obtained by hydrolysis of the orthoester (*R*)-**7**.[4] The synthesis of (*R*)-**7** can be achieved by Pd^{II}-catalyzed cyclization–methoxycarbonylation of optically active propargyl acetate (*S*)-**8**.

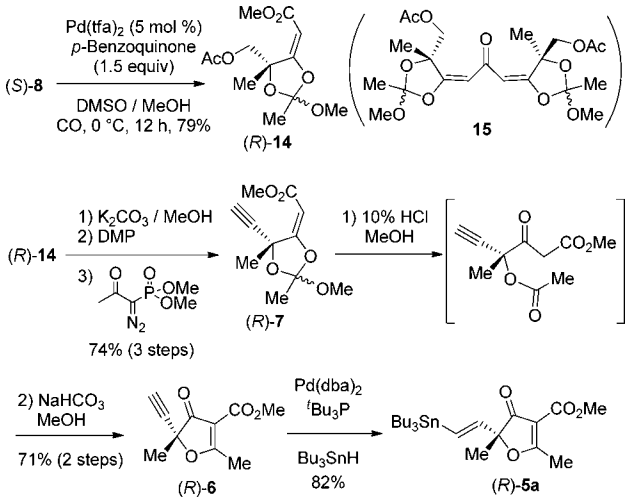
Since the configuration of gregatin E (**3a**) was unknown (C5 and C5′), we assumed the same absolute configuration at C5 as established for gregatins A–D.[3] Thus, the total synthesis started with the preparation of the optically active propargyl acetate (*S*)-**8** in seven steps according to the reported procedure (Scheme 2).[6] Asymmetric dihydroxylation of the Weinreb amide **9** derived from methacrylic acid gave diol (*R*)-**10** in 90% yield with 92% ee. Silylation of (*R*)-**10** followed by reduction with DIBAL afforded the aldehyde (*R*)-**12** in 91% yield (two steps). Corey–Fuchs homologation and subsequent desilylation gave the corresponding diol, which was converted to propargyl acetate (*S*)-**8** in 75% yield (four steps).

The synthesis of the vinyl stannane (*R*)-**5a** is detailed in Scheme 3. The oxidative cyclization–carbonylation of propargyl acetate (*S*)-**8** mediated by Pd^{II} in DMSO/MeOH afforded cyclic orthoester (*R*)-**14** in 79% yield as the sole product. When the reaction was performed in MeOH, dimeric ketone **15** was obtained in 10% yield together with (*R*)-**14** (59%).[7] Although we do not have a clear explanation for the solvent effects at this stage, we

Scheme 2. Preparation of Diacetate (*S*)-**8**



Scheme 3. Synthesis of Vinyl Stannane **5** (right half)



tentatively assumed that DMSO acted as a ligand[8] to prevent the dimerization. The acetoxymethyl group in (*R*)-**14** was transformed into the desired terminal alkyne via a three-step sequence: hydrolysis of (*R*)-**14**, followed by oxidation to afford the corresponding aldehyde, which was treated with Ohira–Bestmann reagent[9] to afford terminal alkyne (*R*)-**7** in 74% yield (three steps). According to our previously reported procedure,[4b] the 4-oxo-3-furancarboxylate skeleton was constructed via a two-step sequence: acid treatment of the orthoester (*R*)-**7** followed by Knoevenagel–Claisen type condensation to give the 4-oxo-3-furancarboxylate **6** in 71% yield (two steps). Regioselective palladium-catalyzed hydrostannylation of **6** afforded vinyl stannane (*R*)-**5a** in 82% yield.[10]

Since the absolute configuration of the secondary alcohol in the side chain (C5′) was unknown, both enantiomers

(5) (a) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748–2749. (b) Wang, M.; Lin, Z. *Organometallics* **2010**, *29*, 3077–3084. (c) Burghart-Stoll, H.; Kapferer, T.; Brückner, R. *Org. Lett.* **2011**, *13*, 1016–1019.

(6) (a) Knight, D. W.; Qing, X. *Tetrahedron Lett.* **2009**, *50*, 3534–3537. (b) Avenoza, A.; Cativiela, C.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahedron: Asymmetry* **2001**, *12*, 1383–1388.

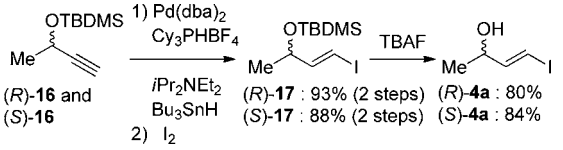
(7) (a) Cyclization–carbonylation–cyclization coupling reactions of propargyl acetates; Yasuhara, S.; Sasa, M.; Kusakabe, T.; Takayama, H.; Kimura, M.; Mochida, T.; Kato, K. *Angew. Chem., Int. Ed.* 2011, *50*, 3912–3915. (b) The use of $(CH_3CN)_2PdCl_2$ resulted in decreased yields of (*R*)-**14** (67%).

(8) Diao, T.; White, P.; Guzei, I.; Stahl, S. S. *Inorg. Chem.* **2012**, 11898–11909.

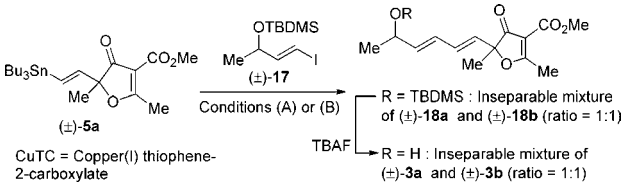
(9) (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561–564. (b) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521–522.

(10) Darwish, A.; Lang, A.; Kim, T.; Chong, J. M. *Org. Lett.* **2008**, *10*, 861–864.

Scheme 4. Synthesis of Iodoalkene **4** (left half)



Scheme 5. Preliminary Experiments for the Coupling Reaction[a]



[a] Conditions: (A) $(Ph_3P)_4Pd$, CuI, THF, reflux, 7 h, 41%; (B) CuTC (1.5 equiv), NMP, 0−10 °C, 5 h, 82%.

of the vinyl iodide [(*R*)-**4a** and (*S*)-**4a**] were prepared independently (Scheme 4). Hydrostannylation[11] of known silyl ether **16**[12] followed by treatment with iodine, and subsequent desilylation, afforded (*R*)-**4a** and (*S*)-**4a** in good yields.

With vinyl stannane (*R*)-**5a** and vinyl iodides (*R*)-**4a** and (*S*)-**4a** in hand, the stage was now set for the coupling reaction. In preliminary experiments (Scheme 5), the Stille coupling reaction[13] of (±)-**5a** with vinyl iodide (±)-**17** was investigated [$(Ph_3P)_4Pd$, CuI, refluxed for 7 h in THF]. An inseparable mixture of (±)-**18a** and (±)-**18b** (1:1) was obtained in 41% yield along with a mixture of unidentified compounds. The yield was improved (82%) using the CuTC-mediated coupling reaction.[5] Unfortunately, fluoride-mediated desilylation (TBAF, HF−pyridine, and HF−Et_3N) of the mixture of (±)-**18a** and (±)-**18b** failed. A mixture of (±)-**3a** and (±)-**3b** was obtained in 25% yield, due to the instability of the products under the current reaction conditions.

Thus, we turned our attention to the reaction of unprotected vinyl iodides (*R*)-**4** and (*S*)-**4** (Scheme 6). Although the Stille coupling reaction of (±)-**5a** with vinyl iodide (±)-**4a** failed,[14] the CuTC-mediated coupling reaction gave good results. (+)-Gregatin E (**3a**) and its diastereomer (+)-**3b** were obtained from (*S*)-**4a** and (*R*)-**4a** in 77% and 84% yields, respectively. The ^1H NMR data of these diastereomers matched those provided in the literature.[1b] Although the ^1H- and ^{13}C NMR spectra of (+)-**3a** were extremely similar to those of (+)-**3b**,[15] the absolute configuration of natural (+)-gregatin E was proposed to be (5*R*, 5′*S*) based on the melting point.

Scheme 6. Total Synthesis of (+)-Gregatin E (**3a**) and Its Diastereomer **3b**

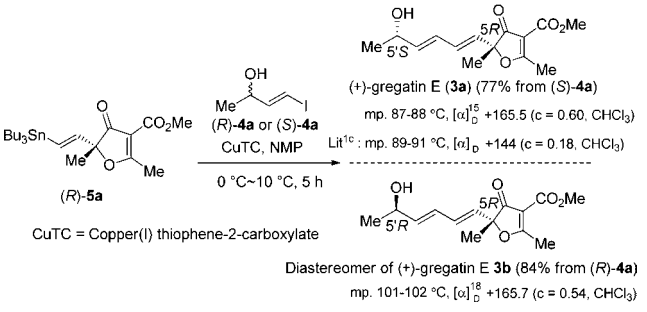
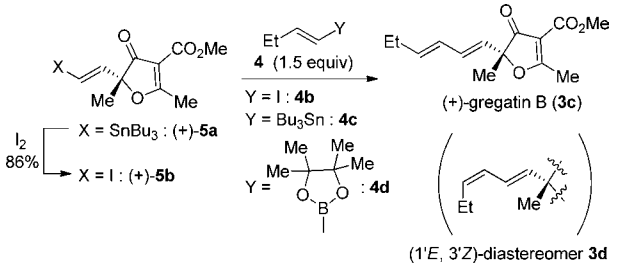


Table 1. Total Synthesis of (+)-Gregatin B (**3c**)[a]



entry	5	4	conditions	yield (%)	3c/3d
1	(±)-**5a**	**4b**	(A)	46	1/1.2
2	(±)-**5a**	**4b**	(B)	84	7.7/1
3	(±)-**5b**	**4c**	(A)	60	>99/1
4	(+)-**5b**	**4d**	(C)	80	>99/1

[a] Conditions: (A) $PdCl_2(CH_3CN)_2$ (10 mol %), CuI (20 mol %), DMF, rt, 6.5 h; (B) CuTC (1.7 equiv), NMP, 0 °C, 2.5 h; (C) $Pd(Ph_3P)_4$ (10 mol %), TBAF (1.5 equiv), THF, 10 °C, 13 h.

Next, similar coupling reactions were investigated for the synthesis of (+)-gregatin B (**3c**) (Table 1). Stille coupling reaction of (±)-**5a** with vinyl iodide **4b**[16] gave a mixture of (±)-**3c** and (±)-**3d** in 46% yield (ratio = 1:1.2) (entry 1).[5c,17] The yield was improved by using the CuTC-mediated coupling reaction, but (±)-**3d** was still produced as a minor product (entry 2). As mentioned above [Scheme 5, condition (A)], isomerization of the olefinic configuration was not observed when using sterically bulky vinyl iodide (±)-**17**. Therefore, we next investigated the Stille coupling reaction of **4c**[18] with sterically bulky vinyl iodide (±)-**5b** prepared from (±)-**5a** (entry 3). (±)-**3c** was obtained in 60% yield without isomerization. Using the Suzuki−Miyaura coupling reaction, the yield of (+)-**3c** was improved (80%) without erosion of the double

(11) Darwish, A.; Chong, J. M. *Tetrahedron* **2012**, *68*, 654–658.
(12) Robinson, J. E.; Brimble, M. A. *Org. Biomol. Chem.* **2007**, *5*, 2572–2582.
(13) Stille, J. K. *Angew. Chem., Int. Ed.* **1986**, *25*, 508–519.
(14) Complex mixture was obtained.
(15) See the Supporting Information.
(16) Alexakis, A.; Duffault, J. M. *Tetrahedron Lett.* **1988**, *29*, 6243–6246.
(17) The similar isomerization during the Stille or Suzuki coupling reaction has been reported. Reaction of (*Z*)-alkenyl halides: (a) Lu, G.-P.; Voigtritter, K. R.; Cai, C.; Lipshutz, B. H. *Chem. Commun.* **2012**, *48*, 8661–8663. (b) Lu, G.-P.; Voigtritter, K. R.; Cai, C.; Lipshutz, B. H. *J. Org. Chem.* **2012**, *77*, 3700–3703. For the reaction of (*E*)-alkenyl halides, see ref 5c.
(18) Jackson, S. K.; Banfield, S. C.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 1215–1218.

bond stereochemistry (entry 4). Spectroscopic data of both (+)-**3c** and (±)-**3d** were in full agreement with those reported by Brückner and Burghart-Stoll.

In conclusion, the first total synthesis of (+)-gregatin E (**3a**) and a new total synthesis of (+)-gregatin B (**3c**) have been achieved. The furanone skeleton was effectively constructed based on Pd^{II}-catalyzed cyclization–methoxycarbonylation of optically active propargyl acetate (*S*)-**8**. The (*E*,*E*)-diene moiety was successfully prepared by a Pd^{II}- or CuTC-mediated coupling reaction with retention of the olefinic configuration. This methodology is applicable for the synthesis of penicilliols A and B bearing a hydroxy group in the (*E*,*E*)-diene side chain.

The detailed reaction mechanism for the isomerization during the coupling reaction is now under investigation in our laboratory.

Acknowledgment. This work was supported by a JSPS KAKENHI grant (no. 24790026).

Supporting Information Available. Experimental procedures, spectroscopic data, copy of NMR spectra. This material is available free of charge via Internet at http://pubs.acs.org.

The authors declare no competing financial interest.