ORGANIC LETTERS

2005
Vol. 7, No. 6
1085−1087

Synthesis of the Proposed Structure of Feigrisolide C

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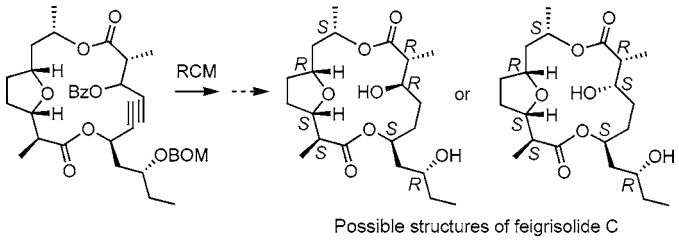
Received January 4, 2005

ABSTRACT



Possible structures of feigrisolide C were synthesized via ring-closing olefin metathesis reaction of a diester derivative prepared from 8-*epi*-nonactic acid, but physical characteristics of the synthetic samples did not match with those of the natural sample of feigrisolide C.

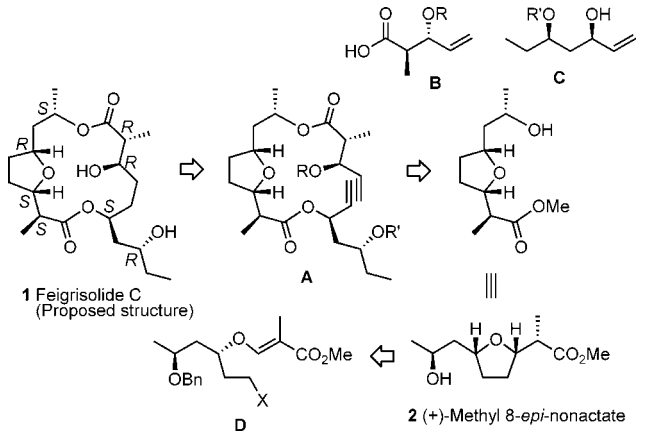
Feigrisolide C (**1**) is a 15-membered macrodiolide isolated from the culture broth of *Streptomyces griseus* (strain GT 051022).[1] It is a medium inhibitor of 3α-hydroxysteroid dehydrogenase and exhibits 50% inhibition of Coxsackie virus B3 at 25 μg/mL. It was also claimed to be a metabolite of *Streptomyces* sp. 6167 of marine origin.[2]

Ring-closing olefin metathesis reaction of the diene intermediate **A** was envisaged as a key step in the synthesis of feigrisolide C (**1**). The diester **A** was to be prepared from (+)-methyl 8-*epi*-nonactate (**2**), the unsaturated carboxylic acid **B**, and the allylic alcohol **C** (Scheme 1). Radical cyclization reaction of a β-alkoxymethacrylate intermediate **D**[3] would supply the key intermediate **2**.

Methyl (*S*)-(+)-3-hydroxybutyrate (**3**) was reacted with the lithium enolate of *tert*-butyl acetate to yield the β-keto ester product, which was converted into the benzylidene acetal ester **4** via stereoselective syn reduction and acetalization.[4] The mixed hydride reduction of **4** proceeded regioselectively to produce 5-benzyloxyhexane-1,3-diol, and tosylation of the primary hydroxyl group provided the secondary alcohol **5**. The reaction of **5** with excess methyl 3,3-dimethoxy-2-methylpropionate (**6**) under acidic conditions led to the formation of the β-alkoxymethacrylate moiety, and the intermediate **7** was obtained after iodide substitution. Low-temperature radical cyclization reaction of **7** in the presence of tributylstannane and triethylborane led to the stereoselective formation (14:1) of the *threo* product[5] in good yield (92%), which was transformed into **2** after benzyl deprotection via hydrogenolysis (Scheme 2).

The (*Z*)-boron enolate of the chiral imide **8** reacted with acrolein to produce the *syn*-aldol imide **9**.[6] Mitsunobu

Scheme 1. Retrosynthetic Analysis

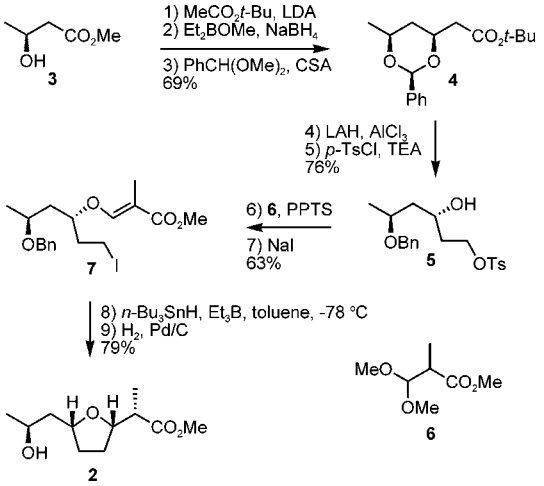


(1) Tang, Y.-Q.; Sattler, I.; Thiericke, R.; Grabley, S. *J. Antibiot.* **2000**, *53*, 934−943.

(2) Sobolevskaya, M. P.; Fotso, S.; Havash, U.; Denisenko, V. A.; Helmke, E.; Prokofeva, N. G.; Kuznetsova, T. A.; Laatsch, H.; Elyakov, G. B. *Chem. Nat. Comp.* **2004**, *40*, 282−285.

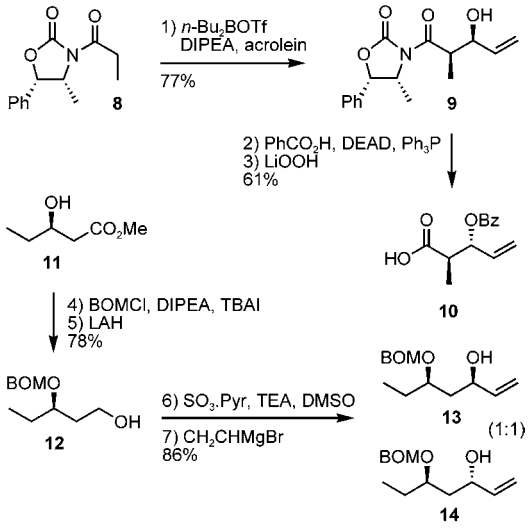
10.1021/ol0500160 CCC: $30.25
Published on Web 02/17/2005

Scheme 2. Synthesis of (+)-Methyl 8-*epi*-Nonactate (**2**)



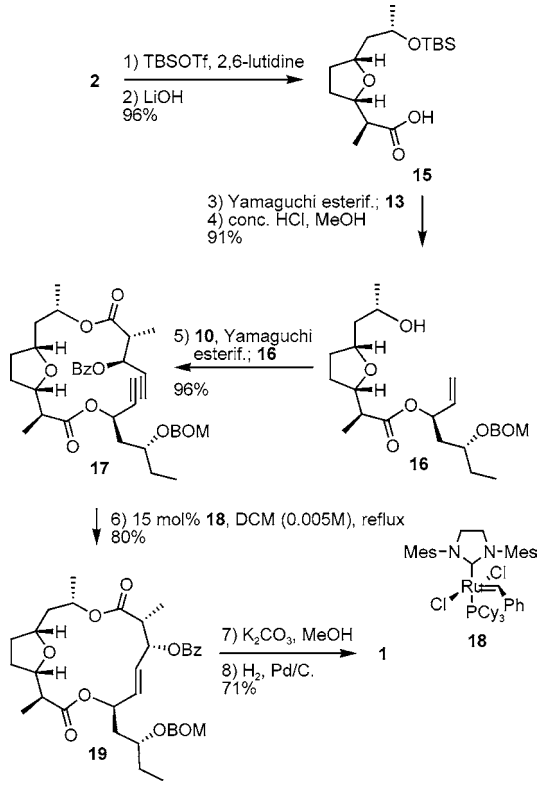
reaction of **9** with benzoic acid and subsequent basic hydrolysis[7] led to the *anti*-aldol benzoate acid **10**. For preparation of the allylic alcohol fragment, methyl (*R*)-3-hydroxypentanoate (**11**)[8] was converted into the BOM-protected diol **12**, which was further transformed into a 1:1 mixture of the allylic alcohols **13** and **14** via oxidation and reaction with vinyl Grignard reagent[9] (Scheme 3).

Scheme 3. Preparation of B and C Fragments



The TBS-protected 8-*epi*-nonactic acid **15** was prepared from the methyl ester **2** via a two-step sequence. Yamaguchi esterification reaction[10] of the carboxylic acid **15** and the allylic alcohol **13** proceeded efficiently, and TBS deprotection of the product ester led to the hydroxy ester **16**. A second Yamaguchi reaction of the acid **10** and the alcohol **16** provided the pivotal diester intermediate **17**. The crucial ring-closing metathesis reaction of **17** proceeded in the presence of the Grubbs catalyst **18**[11] to give the unsaturated macrodiolide **19** in 80% yield (Scheme 4).

Scheme 4. Synthesis of the Macrodiolide **1**



The first-generation Grubbs catalyst did not work in this case, and the benzoate protection for the allylic alcohol moiety in **17** was important, as neither the corresponding TBS-ether nor the free alcohol produced the proper macrodiolides.[12] It is also to be noted that the trans isomer **19**

(3) For selected examples of radical cyclizations of β-alkoxyacrylates and related compounds, see: (a) Lee, E.; Jeong, E. J.; Kang, E. J.; Sung, L. T.; Hong, S. K. *J. Am. Chem. Soc.* **2001**, *123*, 10131−10132. (b) Lee, E.; Choi, S. J.; Kim, H.; Han, H. O.; Kim, Y. K.; Min, S. J.; Son, S. H.; Lim, S. M.; Jang, W. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 176−178. (c) Lee, E.; Song, H. Y.; Kang, J. W.; Kim, D.-S.; Jung, C.-K.; Joo, J. M. *J. Am. Chem. Soc.* **2002**, *124*, 384−385. (d) Jeong, E. J.; Kang, E. J.; Sung, L. T.; Hong, S. K.; Lee, E. *J. Am. Chem. Soc.* **2002**, *124*, 14655−14662. (e) Song, H. Y.; Joo, J. M.; Kang, J. W.; Kim, D.-S.; Jung, C.-K.; Kwak, H. S.; Park, J. H.; Lee, E.; Hong, C. Y.; Jeong, S.; Jeon, K.; Park, J. H. *J. Org. Chem.* **2003**, *68*, 8080−8087. (f) Keum, G.; Kang, S. B.; Kim, Y.; Lee, E. *Org. Lett.* **2004**, *6*, 1895−1897.

(4) This is an improved version of the previous synthesis. See: Lee, E.; Sung, L. T.; Hong, S. K. *Bull. Kor. Chem. Soc.* **2002**, *23*, 1189−1190.

(5) Lee, E.; Choi, S. J. *Org. Lett.* **1999**, *1*, 1127−1128.

(6) For an example of acrolein aldol reactions, see: Sunazuka, T.; Hirose, T.; Shirahata, T.; Harigaya, Y.; Hayashi, M.; Komiyama, K.; Omura, S. *J. Am. Chem. Soc.* **2000**, *122*, 2122−2123.

(7) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141−6144.

(8) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856−5858.

(9) Structure determination of **13** and **14** was carried out by NMR analysis of the (*O*)-acetyl (*S*)-mandelates: for example, the methyl triplet signal of the derivative from **13** was found at δ 0.74 and the corresponding signal of the derivative from **14** was found at δ 0.93.

(10) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993.

(11) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

(12) For similar results, see: Paquette, L. A.; Efremov, I. *J. Am. Chem. Soc.* **2001**, *123*, 4492−4501.

was the sole product. Benzoate deprotection of **19** and subsequent hydrogenation then led to the macrodiolide **1**.

The spectroscopic data of **1** did not match with those of feigrisolide C, and it was clear that the macrodiolide **1** did not represent the true structure of feigrisolide C. Careful examination of the original paper revealed that the authors had originally intended to propose the 3′-epimer **20** as the structure of feigrisolide C[13] (Figure 1).

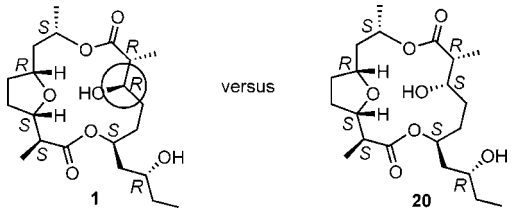


Figure 1. Possible structures of feigrisolide C.

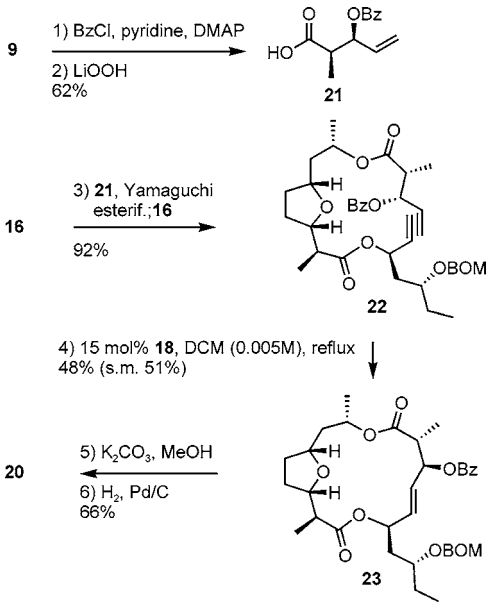
For synthesis of **20**, the *syn*-aldol benzoate acid **21** was prepared from **9** in two steps. Esterification reaction of **21** and **16** was carried out uneventfully to provide the diester **22**. Ring-closing metathesis reaction of **22** was less efficient than in the case of **17**, but eventually, the reaction provided a moderate yield of the macrodiolide **23**.[14] Usual basic deprotection and subsequent hydrogenation led to the epimeric structure **20** (Scheme 5).

Unfortunately, comparison of the spectroscopic data of **20** with those of the natural product revealed that the structure **20** did not represent the true structure of feigrisolide C. Identification of the real structure of feigrisolide C requires further investigation, but the present studies present more examples of the ring-closing metathesis reaction in the preparation of relatively strained macrodiolide systems.

(13) This was confirmed by private communication with Dr. I. Sattler. We also thank Dr. Sattler for spectroscopic data and a sample of feigrisolide C.

(14) In this case, a small amount of the cis isomer was also produced.

Scheme 5. Synthesis of the 3′-Epimer **20**



Acknowledgment. Authors thank Center for Marine Natural Products and Drug Discovery (Seoul National University and the Ministry of Maritime Affairs and Fisheries, Republic of Korea) for a MarineBio 21 grant (2004) and Center for Bioactive Molecular Hybrids (Yonsei University and KOSEF) for a research grant (2004). Brain Korea 21 graduate fellowship grants to W. H. Kim, L. T. Sung, and S. M. Lim are gratefully acknowledged.

Supporting Information Available: Experimental procedures, ^{1}H NMR and ^{13}C NMR spectra of **1**, **20**, and feigrisolide C, and ^{13}C NMR spectra of the intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0500160