Synthetic Studies on Mycalolide B: Synthesis of the C7–C35 Fragment

Tomoyuki Kimura, Satomi Kuribayashi, Tetsuya Sengoku, Keita Matsui, Shoko Ueda,
Ichiro Hayakawa, Kiyotake Suenaga, and Hideo Kigoshi*
Graduate School of Pure and Applied Sciences, University of Tsukuba, Tennoudai 1-1-1, Tsukuba 305-8571

(Received October 3, 2007; CL-071097; E-mail: kigoshi@chem.tsukuba.ac.jp)

Mycalolide B, a cytotoxic macrolide isolated from a marine sponge of the genus *Mycale*, has an actin depolymerizing activity. This paper reports the synthesis of C7–C35 fragment of mycalolides via cross olefin metathesis reaction between trisoxazole fragment and side-chain fragment.

Mycalolide B (**1**) (Figure 1) is a cytotoxic and antifungal macrolide isolated from a sponge of the genus *Mycale* by Fusetani and his co-workers.[1] Mycalolide B (**1**) inhibits actomyosin Mg^{2+}–ATPase and also depolymerizes actin in the same manner as aplyronine A (**2**).[2,3] Panek and Liu reported the total synthesis of mycalolide A, a congener of mycalolide B.[4] Our investigation on the structure–activity relationship of **2**,[5] the X-ray crystal structure analysis,[6] and photo affinity labeling experiments[7] displays the great importance of the side-chain moiety in the actin depolymerizing activity. In connection with these studies, we were interested in the unique biological activity and structure of mycalolides and started synthetic studies on this molecule. We have reported the synthesis and actin-depolymerizing activity of side-chain analog of **1**.[8] This paper describes synthesis of the C7–C35 fragment **3**, which is an important intermediate for synthesis of mycalolides.

Retrosynthetic analysis of mycalolide B (**1**) is shown in Scheme 1. Through cleavage of the macrolide linkage and the C5–C6 olefinic bond, mycalolide B is divided into fragments **3**, **4**, and methylphosphonate. Fragment **3** will be obtained by olefin cross metathesis between two fragments **5** and **6**. Fragment **5** is synthesized from compound **7**, an intermediate for the synthesis of a side-chain analog of mycalolides.[8] Fragment **6** is synthesized from a serine derivative **8**.

The synthesis of fragment **5** was started with compound **7**[8] (Scheme 2). Selective removal of the primary TBS group of **7** gave a primary alcohol, which was oxidized to aldehyde **9**. The Grignard reaction gave the secondary alcohols **10a** and **10b**. The stereochemistry of the major isomer **10a** was determined by modified Mosher's ester analysis.[9] Alcohol **10a** was converted into the fragment **5**.

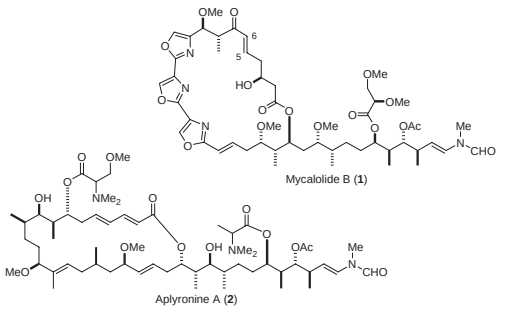
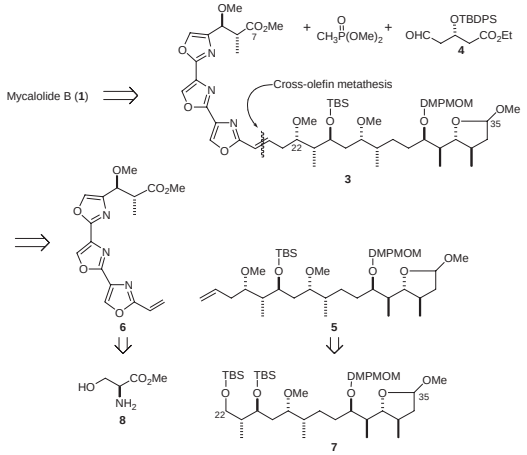


Figure 1. Mycalolide B and aplyronine A.

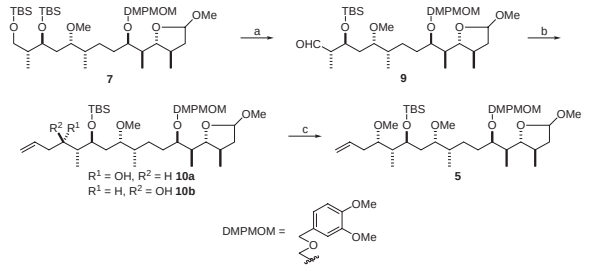
The trisoxazole fragment **6** was synthesized from aldehyde **11**[10] (Scheme 3). The crotylboration between a Roush's boronate[11] and **11** afforded the homoallylic alcohol **12** (91%), the secondary hydroxy group of which was methylated to give the methyl ether **13**. Oxidative cleavage of the olefin moiety in **13** followed by reduction with $NaBH_4$ gave a primary alcohol (59% in 3 steps), which was protected to afford pivalate **14** (85%). Hydrolysis of acetonide and Boc groups in **14** gave the amino alcohol **15**.

Condensation between serine derivative **8** and acrylic acid gave amide **16**. Cyclodehydration, oxidation, and hydrolysis gave oxazole **17**. Condensation between **15** and **17** gave amide **18**. However, cyclodehydration and oxidation reactions gave a complex mixture, maybe, because of instability of the olefin moiety in **18** under the reaction conditions.[12]

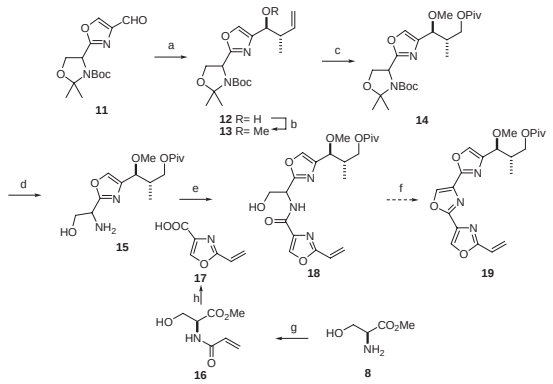
So, we decided to introduce the olefin moiety in later stage of the synthesis (Scheme 4). Condensation between **15** and 4-oxazolcarboxylic acid gave amide **20**. Cyclodehydration of **20** by using DAST and subsequent oxidation with nickel peroxide[13] afforded trisoxazole **21**. Chlorination and the Stille cross-cou-



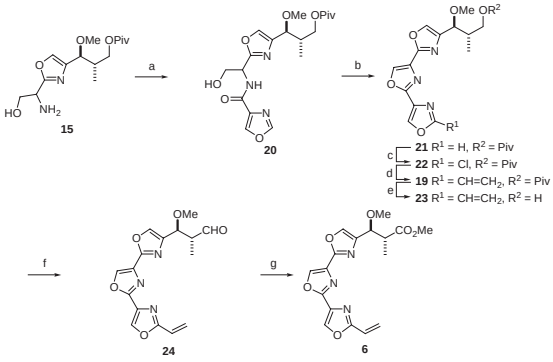
Scheme 1. Retrosynthetic analysis.



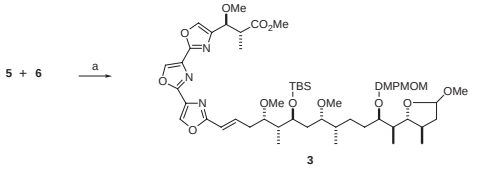
Scheme 2. (a) i) NH_4F, MeOH (84%), ii) Dess–Martin periodinane, CH_2Cl_2 (96%), (b) allylmagnesium bromide, THF, 64% (**12a**), 23% (**12b**), (c) MeI, NaH, THF (98%).



Scheme 3. (a) (*R*,*R*)-Roush's boronate, toluene, MS4A (91%), (b) MeI, NaH, THF, (c) i) OsO_4, NMO, THF, H_2O then $NaIO_4$, ii) $NaBH_4$, EtOH (59% in 3 steps), iii) PivCl, Py (85%), (d) HCl, AcOEt (84%), (e) EDC, HOBt, CH_2Cl_2 (74%), (f) i) DAST, CH_2Cl_2, ii) DBU, $BrCCl_3$, CH_2Cl_2, (g) acrylic acid, DCC, CH_2Cl_2 (78%), (h) i) DAST, CH_2Cl_2, ii) DBU, $BrCCl_3$, CH_2Cl_2 (30% in 2 steps), iii) LiOH, THF, H_2O (78%).



Scheme 4. (a) 4-Oxazolcarboxylic acid, EDC, HOBt, CH_2Cl_2 (84%), (b) i) DAST, CH_2Cl_2 (82%), ii) NiO_2, benzene (51%), (c) LHMDS, C_2Cl_6, THF (77%), (d) vinyltributyltin, $PdCl_2(PPh_3)_2$, CH_2Cl_2 (82%), (e) DIBAL, CH_2Cl_2 (57%), (f) Dess–Martin periodinane, CH_2Cl_2, (g) i) $NaClO_2$, $NaH_2PO_4 \cdot 2H_2O$, 2-methyl-2-butene, *t*-BuOH/CH_2Cl_2 = 2/1, ii) $TMSCHN_2$, MeOH/CH_2Cl_2 = 2/1 (53% in 3 steps).



Scheme 5. (a) 2nd Hoveyda–Grubbs catalyst (0.5 mol %), CH_2Cl_2 (54%).

pling reaction[14] gave olefin **19**. Removal of the pivaloyl group and oxidation gave aldehyde **24**. Finally, oxidation and treatment with $TMSCHN_2$ gave fragment **6**.

The cross olefin metathesis reaction with fragments **5** (1 equiv.) and **6** (2 equiv.) gave fragment **3**[15] in 54% yield along with Z-isomer (15%) (Scheme 5).

In summary, we synthesized the C7–C35 fragment **3**, an important intermediate for synthesis of mycalolides. Further synthetic studies of mycalolide B are now in progress.

This study was supported in part by the 21st COE program and Grants-in-Aid for Scientific Research on Priority Areas (No. 16073204) and for Young Scientists (B) (No. 18710180) from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and by the Asahi Glass Foundation.

References and Notes

1 a) N. Fusetani, K. Yasumuro, S. Matsunaga, K. Hashimoto, *Tetrahedron Lett.* **1989**, *30*, 2809. b) S. Matsunaga, P. Liu, C. A. Celatka, J. S. Panek, N. Fusetani, *J. Am. Chem. Soc.* **1999**, *121*, 5605.

2 M. Ojika, H. Kigoshi, Y. Yoshida, T. Ishigaki, M. Nisiwaki, I. Tsukada, M. Arakawa, H. Ekimoto, K. Yamada, *Tetrahedron* **2007**, *63*, 3138.

3 S. Saito, S. Watabe, H. Ozaki, N. Fusetani, H. Karaki, *J. Biol. Chem.* **1994**, *269*, 29710.

4 a) P. Liu, J. S. Panek, *J. Am. Chem. Soc.* **2000**, *122*, 1235. b) J. S. Panek, P. Liu, *J. Am. Chem. Soc.* **2000**, *122*, 11090.

5 a) K. Suenaga, N. Kamei, Y. Okugawa, M. Takagi, A. Akao, H. Kigoshi, K. Yamada, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 269. b) H. Kigoshi, K. Suenaga, M. Takagi, A. Akao, K. Kanematsu, N. Kamei, Y. Okugawa, K. Yamada, *Tetrahedron* **2002**, *58*, 1075.

6 K. Hirata, S. Muraoka, K. Suenaga, T. Kuroda, K. Kato, H. Tanaka, M. Yamamoto, M. Takata, K. Yamada, H. Kigoshi, *J. Mol. Biol.* **2006**, *356*, 945.

7 T. Kuroda, K. Suenaga, A. Sakakura, T. Handa, K. Okamoto, H. Kigoshi, *Bioconjugate Chem.* **2006**, *17*, 524.

8 a) K. Suenaga, S. Miya, T. Kuroda, T. Handa, K. Kanematsu, A. Sakakura, H. Kigoshi, *Tetrahedron Lett.* **2004**, *45*, 5383. b) K. Suenaga, T. Kimura, T. Kuroda, K. Matsui, S. Miya, S. Kuribayashi, A. Sakakura, H. Kigoshi, *Tetrahedron* **2006**, *62*, 8278.

9 a) J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512. b) S. Yamaguchi, F. Yasuhara, K. Kabuto, *Tetrahedron*, **1976**, *32*, 1363. c) I. Ohtani, T. Kusumi, Y. Kashman, H. Kakisawa, *J. Am. Chem. Soc.* **1991**, *113*, 4092.

10 N. Endoh, K. Tsuboi, R. Kim, Y. Yonezawa, C. Shin, *Heterocycles* **2003**, *60*, 1567.

11 W. R. Roush, K. Ando, D. B. Powers, A. D. Palkowitz, R. L. Halterman, *J. Am. Chem. Soc.* **1990**, *112*, 6339.

12 Compounds **17** and **18** were easily polymerized at room temperature.

13 D. L. Evans, D. K. Minster, U. Jordis, S. M. Hecht, A. L. Mazzu, Jr., A. I. Meyers, *J. Org. Chem.* **1979**, *44*, 497.

14 a) J. M. Atkins, E. Vedejs, *Org. Lett.* **2005**, *7*, 3351. b) G. L. Young, S. A. Smith, R. J. K. Taylor, *Tetrahedron Lett.* **2004**, *45*, 3797.

15 $[\alpha]_D^{26}$ −28.5 (*c* 0.09, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.27 (s, 1H), 7.70 (s, 1H), 6.93–6.81 (m, 4H), 6.44 (d, J = 16.2 Hz, 1H), 4.89 (d, J = 4.8 Hz, 1H), 4.84 (d, J = 6.0 Hz, 1H), 4.82 (d, J = 6.0 Hz, 1H), 4.59 (s, 2H), 4.39 (d, J = 9.4 Hz, 1H), 4.06 (m, 1H), 3.94 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.74 (s, 3H), 3.57 (dd, J = 6.6, 9.8 Hz, 1H), 3.35 (s, 3H), 3.33 (s, 3H), 3.29 (s, 3H), 3.28 (s, 3H), 3.17 (m, 1H), 3.10 (m, 1H), 3.01 (m, 1H), 2.58 (m, 1H), 2.45 (m, 1H), 2.23 (m, 1H), 2.09 (dd, J = 7.6, 13.1 Hz, 1H), 1.78 (m, 2H), 1.69–1.47 (m, 4H), 1.47–1.13 (m, 4H), 1.10 (d, J = 6.6 Hz, 3H), 1.03 (d, J = 7.1 Hz, 3H), 0.94 (d, J = 6.7 Hz, 3H), 0.89 (d, J = 7.0 Hz, 3H), 0.86 (d, J = 6.9 Hz, 3H), 0.84 (s, 9H), 0.00 (s, 3H), −0.06 (s, 3H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 162.1, 156.4, 155.5, 149.2, 148.8, 140.0, 138.8, 138.8, 138.6, 137.2, 131.7, 131.0, 130.7, 120.7, 118.1, 111.6, 111.1, 104.8, 94.6, 87.4, 82.7, 82.3, 78.6, 78.1, 69.9, 69.6, 57.8, 57.3, 57.3, 56.1, 56.0, 54.6, 52.0, 44.7, 43.6, 43.3, 42.6, 36.0, 34.8, 34.0, 32.9, 30.8, 27.1, 26.0, 26.0, 26.0, 20.3, 18.2, 15.9, 14.0, 9.4, 9.0, −3.9, −4.5, HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{55}H_{85}NaN_3O_{15}Si$ 1078.5648; found 1078.5635.

Published on the web (Advance View) November 17, 2007; doi:10.1246/cl.2007.1490