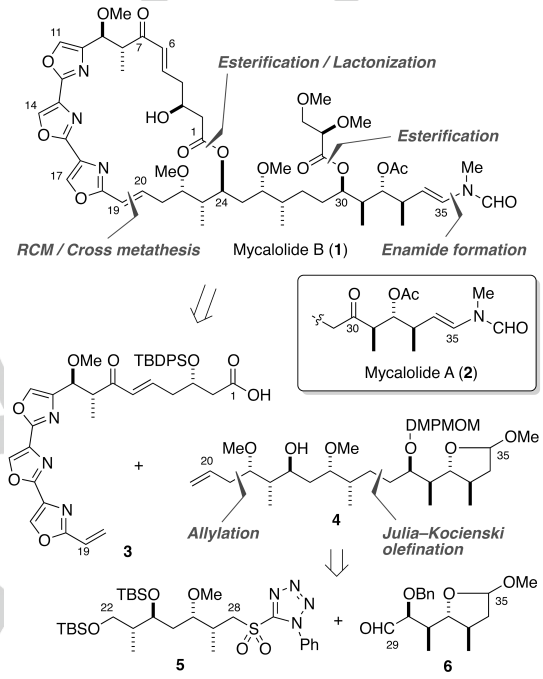
Total Synthesis of Mycalolides A and B via Olefin Metathesis **

Masaki Kita,* Hirotaka Oka, Akihiro Usui, Tomoya Ishitsuka, Yuzo Mogi, Hidekazu Watanabe, Masaki Tsunoda, and Hideo Kigoshi *

Abstract: *An asymmetric total synthesis of the tris-oxazole marine macrolides, mycalolides A and B is described. This synthesis involves the convergent assembly of highly functionalized C1–C19 tris-oxazole and C20–C35 side-chain segments through the use of olefin metathesis and esterification, as well as Julia–Kocienski olefination and enamide formation as key steps.*

Mycalolides are cytotoxic and antimycotic tris-oxazole macrolides, which was isolated from the marine sponge *Mycale* sp.[1] They inhibit actomyosin Mg^{2+}–ATPase [2] and show potent actin-depolymerizing activity by forming a 1:1 complex with monomeric molecule.[3] Mycalolide B (**1**) contains a 2,3-*O*-dimethyl-D-glyceryl ester moiety and 13 asymmetric centers as structural features, while a closely related mycalolide A (**2**) contains a ketone functionality at C30. Several tris-oxazole macrolides that are closely related to mycalolides have been isolated, such as ulapualides,[4] halichondramides,[5] jaspisamides,[6] and kabiramides;[7] all of these exhibit actin-depolymerizing activity and potent cytotoxicity, and some induce apoptosis in tumor cells.[8] Thus, these agents may be useful for the design and development of novel pharmacological tools for analyzing actin-mediated cell functions, such as muscle contraction, cell motility, and cytokinesis, as well as those of therapeutic agents.[9]

Mycalolides can be divided into two structurally characteristic parts: the C1–C24 tris-oxazole macrolactone and the C25–C35 side-chain functionalized by *N*-methyl enamide moiety. Studies on the structure–activity relationships [10] and photolabeling experiments [11] have established that the side-chain part of mycalolides is important for its ability to bind to and depolymerize actin. In addition, X-ray analyses of the actin–kabiramide C,[12] actin–jaspisamide A,[12] and actin–ulapualide A complexes [13] have revealed that their side-chain parts intercalate into the hydrophobic cleft between subdomains 1 and 3 of actin. Meanwhile, we recently synthesized the 19*E*- and 19*Z*-lactone analogs of mycalolides that lack the C25–C35 side-chain; these analogs exhibited moderate cytotoxicity against tumor cells (ca. 1/100 of **1**), but did not show actin-depolymerizing properties or antimycotic activity against pathogenic fungi.[14] Thus, both the side-chain and macrolactone moieties were suggested to be essential for the potent biological activities of the parent molecules.



Scheme 1. Strategies for the synthesis of mycalolides A and B.

Due to their extraordinary structures and biological activities, mycalolides and their congeners have received considerable attention in the synthetic community, and several approaches to the construction of conformationally-restricted tris-oxazole macrolactone structures have been described.[15] To date, total syntheses of mycalolide A (**2**) [16] and ulapualide A [17] have been accomplished, in which Yamaguchi lactonization, cyclization of the central oxazole ring, or intramolecular Horner–Wadsworth–Emmons olefination were used to construct macrocycles. However, no total synthesis of mycalolide B has been disclosed to date. We describe here the first total synthesis of (–)-mycalolide B (**1**) and the second synthesis of mycalolide A (**2**) through the use of olefin metathesis as a key step.

Based on the finding that olefin metathesis is a useful method for connecting the C19–C20 double bonds in mycalolide analogs,[10c,18] we designed a plan for the synthesis of **1** (Scheme 1). After disconnection of the C35 *N*-methyl enamide moiety and the C30 ester bond, the macrolactone structure of **1** could be divided into a C1–C19 tris-oxazole segment **3** and a C20–C35 side-chain segment **4**. We expected that the convergent assembly of **3** and **4** via esterification / ring-closing metathesis (RCM) would efficiently afford a key macrolactone.

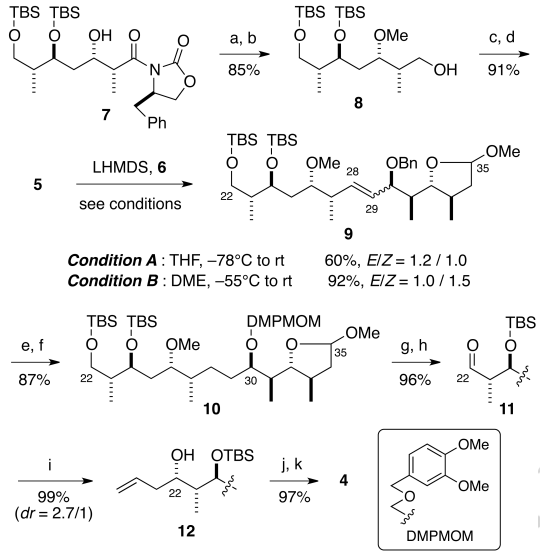
[*] Prof. Dr. M. Kita, H. Oka, A. Usui, T. Ishitsuka, Y. Mogi, H. Watanabe, M. Tsunoda, Prof. Dr. H. Kigoshi
Graduate School of Pure and Applied Sciences
University of Tsukuba
1-1-1 Tennodai, Tsukuba 305-8571 (Japan)
Fax: (+81) 29-853-4313
E-mail: mkita@chem.tsukuba.ac.jp; kigoshi@chem.tsukuba.ac.jp

[**] We thank Prof. Shigeki Matsunaga (The University of Tokyo) for providing natural mycalolide B. This work is supported in part by JSPS grants (25702047 to M.K. and 26242073 to H.K.) and by a Grant-in-Aid for Scientific Research on Innovative Areas from MEXT, Japan, "Chemical Biology of Natural Products." Support was also provided by the Naito Foundation. We thank Maiko Matsuki for preparation of **7**, and Toru Watanabe and Shun Watanabe for preparation of precursors of **3**.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie??.

Instead, cross metathesis of **3** and **4**, in which the carboxyl or hydroxyl groups are protected, and subsequent macrolactonization could also provide the same intermediate. While the side-chain segment **4** was previously synthesized,[10,18] in this study we planned to modify the synthetic route, which includes the Julia–Kocienski olefination [19] between phenyl tetrazole (PT)-sulfone **5** and aldehyde **6**.

Our synthesis started with the preparation of **5** (Scheme 2). Methylation of the known *syn*-aldol **7** [10b] with methyl trifluoromethanesulfonate (MeOTf) and removal of the chiral auxiliary with $LiBH_4$ yielded primary alcohol **8**. Conversion of **8** into the PT-sulfide with aryl disulfide/Bu_3P and subsequent oxidation with *m*-CPBA yielded PT-sulfone **5**.

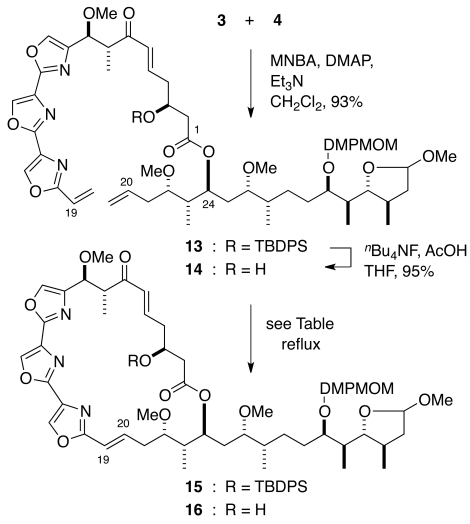


Scheme 2. Synthesis of the C20–C35 segment **4**. Reagents and conditions: a) MeOTf, 2,6-di-*tert*-butylpyridine, CH_2Cl_2; b) $LiBH_4$, EtOH, Et_2O–THF, –10 °C; c) 5,5'-dithiobis(1-phenyl-*1H*-tetrazole), tri-*n*-butylphosphine, THF; d) *m*CPBA, $NaHCO_3$, CH_2Cl_2; e) H_2, $Pd(OH)_2$/C (20 mol%), $NaHCO_3$, EtOH; f) 3,4-dimethoxybenzyloxymethyl chloride, *i*-Pr_2NEt, CH_2Cl_2; g) NH_4F, MeOH, 40 °C; h) Dess–Martin periodinane, pyridine, CH_2Cl_2; i) CH_2=$CHCH_2MgBr$, THF–Et_2O; j) MeI, NaH, THF; k) $^nBu_4NF$, THF, rt to 40 °C.

Next, Julia–Kocienski coupling was examined. Despite the sterically hindered, branched structures of both starting materials, treatment of **5** with LHMDS followed by the addition of aldehyde **6** [20] in THF at –78 °C afforded olefin **9** in 60% yield (condition A, *E*/*Z* = 1.2/1). After several attempts, the yield was improved to 92% (condition B, *E*/*Z* = 1/1.5) with the use of the same base in 1,2-dimethoxyethane (DME) at –55 °C to room temperature. While an excess amount of PT-sulfone **5** (2.5 eq.) was required to complete the reaction, this material was recovered quantitatively and reused.

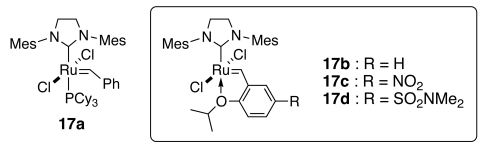
Catalytic hydrogenation of the C=C double bond and hydrogenolysis of the benzyl group from the *E*/*Z*-mixture of **9** proceeded concurrently with palladium (II) hydroxide on carbon. Subsequent protection of the C30 hydroxy group as a 3,4-dimethoxyphenylmethoxymethyl (DMPMOM) group afforded previously synthesized ether **10**.[10b] Selective deprotection of the TBS group in **10** with NH_4F and oxidation of the primary alcohol with Dess–Martin periodinane provided aldehyde **11**. Grignard reaction of **11** with allylmagnesium bromide resulted in a mixture of *S*- and *R*-alcohol **12** (*dr* = 2.7/1), which were separated by column chromatography.[21] Finally, methylation of the secondary alcohol in 22*S*-**12** and deprotection of the remaining TBS group with tetra-*n*-butylammonium fluoride (TBAF) gave the C20–C35 segment **4**.

With the side-chain segment **4** in hand, we initially considered the RCM approach to reduce unnecessary protection / deprotection steps (Scheme 3). Condensation of the C1–C19 segment **3** [18] with **4** by the Shiina procedure using 2-methyl-6-nitrobenzoic anhydride (MNBA) [22] afforded the RCM precursor **13**. We previously reported that treatment of **13** with 30 mol% of 2nd-generation Grubbs catalyst (**17a**) [23] in degassed refluxing toluene led to the decomposition of the starting material (entry 1).[18] However, in refluxing CH_2Cl_2, tris-oxazole lactone **15** was obtained as an *E*/*Z* mixture (40%, *E*/*Z* = 1.9:1, entry 2), while the reaction did not run to completion.



entry	s.m.	catalyst (30 mol%)	solvent (0.9 mM)	time (h)	yields (%)	
					product (19*E*/19*Z*)	s.m. recov.
1 [a]	**13**	**17a**	toluene	4	trace	– [b]
2	**13**	**17a**	CH_2Cl_2	3	40 (1.9:1.0)	31
3 [a]	**13**	**17b**	toluene	3	76 (1.0:1.2)	–
4	**13**	**17b**	CH_2Cl_2	37	37 (2.0:1.0)	40
5	**13**	**17b**	DCE	38	40 (1.0:1.0)	54
6	**13**	**17c**	CH_2Cl_2	24	69 (1.6:1.0)	–
7	**13**	**17d**	CH_2Cl_2	24	75 (1.7:1.0)	–
8	**14**	**17c**	CH_2Cl_2	24	63 (2.7:1.0)	–

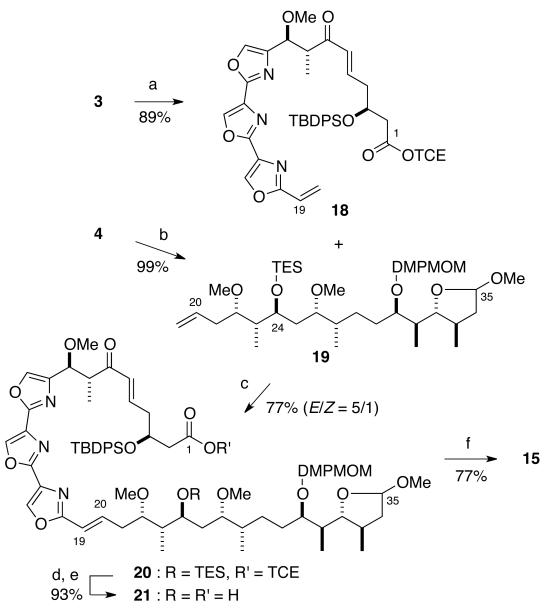
[a] See ref. 18.
[b] s. m. was decomposed and not recovered.



Scheme 3. Synthesis of macrolactones **15** and **16** via ring-closing metathesis.

Due to the instability of catalyst **17a** for the slow metathesis reaction of macrocycle precursors, we next examined 2nd-generation Hoveyda–Grubbs (*HG-II*) catalyst (**17b**).[24] We previously reported that treatment of **13** with 30 mol% **17b** in refluxing toluene afforded the RCM product **15** in higher yield but with undesired C19–C20 *Z*-isomer slightly preferred (76%, *E*/*Z* = 1/1.2, entry 3).[18] Meanwhile, in the model RCM reactions of C1–C24 macrolactone analogs, the solvent polarity was found to significantly affect the stereoselectivity; the

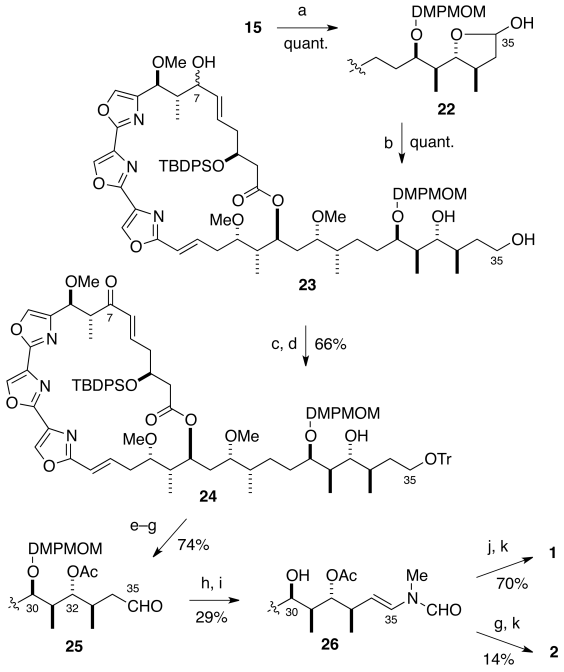
Z-isomer was preferred in *n*-hexane and toluene (*E*/*Z* = 1/1.9~2.5), while the *E*-isomer was preferred in CH_2Cl_2 (*E*/*Z* = 1.8/1).[14] In fact, for the RCM reaction of **13** with **17b** in refluxing CH_2Cl_2, the ratio was improved to 2.0:1, but the reaction did not run to completion, similar to the use of **17a** (entry 4). These results suggested that the C25–C35 segment in **13** minimally affected the stereoselectivity, but decreased the reactivity for RCM reactions, probably due to the steric hindrance in forming the ruthenocyclobutane intermediate. Under refluxing conditions in 1,2-dichloroethane (DCE), the stereoselectivity decreased to 1.0:1 (entry 5). To facilitate the initiation of the catalytic cycle at lower temperature, two highly reactive *HG-II* catalyst derivatives **17c** (Grela catalyst) [25] and **17d** (Zhan catalyst 1B) [26] were examined, in which nitro or *N*,*N*-dimethylsulfonamide groups are substituted on the 2-isopropoxybenzylidene ligand. Notably, the use of both electron-deficient catalysts similarly increased the yield of **15** to 69–75%, while stereoselectivity was still low (*E*/*Z* = 1.6–1.7/1, entries 6 and 7). We expected that such low stereoselectivity of RCM precursor **13** was due to the presence of structurally hindered C3 TBDPS group. For comparison, a C3 hydroxy analog **14** was prepared from **13** by the treatment with TBAF along with acetic acid (AcOH). With the use of catalyst **17c** in refluxing CH_2Cl_2, the stereoselectivity of C3 hydroxy macrolactone **16** was improved to 2.7:1, but the yield was lower than that of **15** (entry 8).



Scheme 4. Synthesis of **15** via macrolactonization. Reagents and conditions: a) 2,2,2-trichloroethanol, EDCI·HCl, DMAP, CH_2Cl_2; b) TESCl, ImH, DMF, 40 °C; c) **17b** (20 mol%), CH_2Cl_2, reflux; d) AcOH–THF–H_2O; e) Zn, 1 M NH_4OAc aq., THF; f) 2,4,6-trichlorobenzoyl chloride, *i*-Pr_2NEt, benzene, then dropwise addition into DMAP in benzene.

A cross metathesis / macrolactonization approach was examined next (Scheme 4). Condensation of carboxylic acid **3** with 2,2,2-trichloroethanol provided trichloroethyl (TCE) ester **18**. Triethylsilyl (TES) protection of the secondary alcohol in **4** gave silyl ether **19**. In contrast to the RCM reactions, treatment of **18** and **19** (1.2 equiv.) with 20 mol% of *HG-II* catalyst (**17b**) in refluxing CH_2Cl_2 (13 mM for **18**) preferentially yielded the coupling product **20** in an *E*-selective manner (*E*/*Z* = 5.0:1).[27] After the TES group in (*E*)-**20** was removed under mild acidic conditions, the resultant alcohol was treated with activated zinc in acetate buffer to afford seco acid **21**. Macrolactonization of **21** by the Yamaguchi procedure [28] readily proceeded to give the lactone **15**. Due to the higher stereoselectivity, the cross metathesis-macrolactonization approach was preferred to the RCM approach.

The stage was then set for functionalization of the last side-chain part (Scheme 5). Acidic hydrolysis of the C35 methyl acetal in **15** afforded hemiacetal **22**. Selective reductions of the five-membered hemiacetal in **22** using conventional hydride reagents were unsuccessful.[29] To our delight, however, Luche reduction of **22** at –20 °C exclusively led to 1,2-reduction of the C7 ketone followed by C35 hemiacetal reduction at 0 °C to afford triol **23** quantitatively (*dr* = 10:1 at C7). Next, trityl group protection of the primary alcohol, and chemoselective oxidation of the allylic alcohol with manganese dioxide gave ketone **24**. Subsequent acetylation of the remaining C32 secondary alcohol, removal of the trityl group with formic acid in ether, and oxidation of the primary alcohol with Dess–Martin periodinane gave aldehyde **25**. Dehydrating condensation with *N*-methylformamide under acidic conditions,[30] and deprotection of the DMPMOM group with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) afforded secondary alcohol **26**.



Scheme 5. Synthesis of mycalolides A and B. Reagents and conditions: a) 1 M HCl aq., 1,2-dimethoxyethane; b) $NaBH_4$, $CeCl_3·7H_2O$, MeOH, –20 to 0 °C; c) TrCl, pyridine; d) MnO_2, CH_2Cl_2; e) Ac_2O, DMAP, pyridine; f) HCOOH, Et_2O; g) Dess–Martin periodinane, pyridine, CH_2Cl_2; h) MeNHCHO, PPTS, hydroquinone, MS3A, benzene, reflux; i) DDQ, CH_2Cl_2, ^{t}BuOH, 1 M phosphate buffer (pH 6.0); j) 2,3-di-*O*-methyl-D-glyceric acid, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, benzene; k) ^{n}Bu_4NF, AcOH, THF.

Finally, condensation of **26** with 2,3-di-*O*-methyl-D-glyceric acid using the Yamaguchi procedure and removal of the C3 TBDPS group by TBAF along with AcOH furnished mycalolide B (**1**) in analytically pure form. The ^1H and ^{13}C NMR spectra of the synthetic mycalolide B are consistent with those of the natural product, along with its specific optical rotation {$[\alpha]_D^{25}$ –55 (*c* 0.55,

$CHCl_3$) for synthetic **1**; $[\alpha]_D$ –53 (*c* 1.3, $CHCl_3$) for natural **1** [1a]}. Synthetic **1** was also identical to an authentic sample on the basis of TLC and HPLC analysis. In addition, oxidation of the secondary alcohol in **26** with Dess–Martin periodinane gave authentic TBDPS-protected mycalolide A,[16] and removal of the TBDPS group afforded mycalolide A (**2**), whose ^{1}H NMR data coincided with the reported one.[1a,16]

In summary, we have developed a convergent approach for the synthesis of the tris-oxazole marine macrolides, and completed total synthesis of mycalolides A and B. The key elements in this synthesis include the use of RCM / cross metathesis and esterification as fragment coupling technology for complex building blocks that possess a variety of functional groups. Further studies on the synthesis and structure-activity relationships of mycalolides and related actin-targeting natural products, as well as on their mechanisms of action, are currently underway.

Keywords: marine natural product • total synthesis • olefin metathesis • macrolactonization

[1] a) N. Fusetani, K. Yasumuro, S. Matsunaga, K. Hashimoto, *Tetrahedron Lett.* **1989**, *30*, 2809–2812; b) S. Matsunaga, P. Liu, C. A. Celatka, J. S. Panek, N. Fusetani, *J. Am. Chem. Soc.* **1999**, *121*, 5605–5606; c) S. Wada, S. Matsunaga, S. Saito, N. Fusetani, S. Watabe, *J. Biochem.* **1998**, *123*, 946–952; d) P. Phuwapraisirisan, S. Matsunaga, R. W. M. van Soest, N. Fusetani, *J. Nat. Prod.* **2002**, *65*, 942–943; e) S. Tsukamoto, K. Koimaru, T. Ohta, *Mar. Drugs* **2005**, *3*, 29–35.

[2] a) S. Matsunaga, T. Sugawara, N. Fusetani, *J. Nat. Prod.* **1998**, *61*, 1164–1167; b) M. A. Rashid, K. R. Gustafson, J. H. Cardeilina II, M. R. Boyd, *J. Nat. Prod.* **1995**, *58*, 1120–1125.

[3] a) M. Hori, S. Saito, Y. Shin, H. Ozaki, N. Fusetani, H. Karaki, *FEBS Lett.* **1993**, *322*, 151–154; b) S. Saito, S. Watabe, H. Ozaki, N. Fusetani, H. Karaki, *J. Biol. Chem.* **1994**, *269*, 29710–29714.

[4] J. A. Roesener, P. J. Scheuer, *J. Am. Chem. Soc.* **1986**, *108*, 846–847.

[5] a) S. Matsunaga, N. Fusetani, K. Hashimoto, K. Koseki, M. Noma, H. Noguchi, U. Sankawa, *J. Org. Chem.* **1989**, *54*, 1360–1363; b) M. R. Kernan, T. F. Molinski, D. J. Faulkner, *J. Org. Chem.* **1988**, *53*, 5014–5020; c) S. –C. Chung, S. –H. Lee, K. H. Jang, W. Park, J. –E. Jeon, H. Oh, J. Shin, K. –B. Oh, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3198–3201.

[6] J. Kobayashi, O. Murata, H. Shigemori, *J. Nat. Prod.* **1993**, *56*, 787–791.

[7] a) S. Matsunaga, N. Fusetani, J. Hashimoto, *J. Am. Chem. Soc.* **1986**, *108*, 847–849; b) J. Tanaka, Y. Yan, J. Choi, J. Bai, V. A. Klenchin, I. Rayment, G. Marriott, *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 13851–13856.

[8] a) M. Kita, K. Yoneda, Y. Hirayama, K. Yamagishi, Y. Saito, Y. Sugiyama, Y. Miwa, O. Ohno, M. Morita, K. Suenaga, H. Kigoshi, *ChemBioChem* **2012**, *13*, 1754–1758; b) O. Ohno, M. Morita, K. Kitamura, T. Teruya, K. Yoneda, M. Kita, H. Kigoshi, K. Suenaga, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1467–1471; c) S. Y. Bae, G. D. Kim, J. Jeon, J. Shin, S. K. Lee, *Toxicology in Vitro* **2013**, *27*, 694–699.

[9] Reviews: a) K. Yamada, M. Ojika, H. Kigoshi, K. Suenaga, *Nat. Prod. Rep.* **2009**, *26*, 27–43; b) K. Yamada, M. Ojika, H. Kigoshi, K. Suenaga, *Proc. Jpn. Acad. Ser. B* **2010**, *86*, 176–189; c) M. Kita, H. Kigoshi, *Nat. Prod. Rep.* **2015**, *32*, 534–542.

[10] a) K. Suenaga, S. Miya, T. Kuroda, T. Handa, K. Kanematsu, A. Sakakura, H. Kigoshi, *Tetrahedron Lett.* **2004**, *45*, 5383–5386; b) K. Suenaga, T. Kimura, T. Kuroda, K. Matsui, S. Miya, S. Kuribayashi, A. Sakakura, H. Kigoshi, *Tetrahedron* **2006**, *62*, 8278–8290; c) T. Kimura, S. Kuribayashi, T. Sengoku, K. Matsui, S. Ueda, I. Hayakawa, K. Suenaga, H. Kigoshi, *Chem. Lett.* **2007**, *36*, 1490–1491; d) K. Kitamura, T. Teruya, T. Kuroda, H. Kigoshi, K. Suenaga, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1896–1898; e) K. Kobayashi, Y. Fujii, Y. Hirayama, S. Kobayashi, I. Hayakawa, H. Kigoshi, *Org. Lett.* **2012**, *14*, 1290–1293; f) I. Hayakawa, H. Kigoshi, *Heterocycles* **2015**, *91*, 1137–1155.

[11] a) T. Kuroda, K. Suenaga, A. Sakakura, T. Handa, K. Okamoto, H. Kigoshi, *Bioconjugate Chem.* **2006**, *17*, 524–529; b) M. Kita, Y. Hirayama, K. Yamagishi, K. Yoneda, R. Fujisawa, H. Kigoshi, *J. Am. Chem. Soc.* **2012**, *134*, 20314–20317.

[12] V. A. Klenchin, J. S. Allingham, R. King, J. Tanaka, G. Marriott, I. Rayment, I. *Nat. Struct. Biol.* **2003**, *10*, 1058–1063.

[13] J. S. Allingham, J. Tanaka, G. Marriott, I. Rayment, *Org. Lett.* **2004**, *6*, 597–599.

[14] M. Kita, H. Oka, A. Usui, T. Ishitsuka, Y. Mogi, H. Watanabe, H. Kigoshi, *Tetrahedron* **2012**, *68*, 8753–8760.

[15] Review: K. S. Yeung, I. Paterson, *Angew. Chem.* **2002**, *114*, 4826–4847; *Angew. Chem. Int. Ed.* **2002**, *41*, 4632–4653.

[16] a) P. Liu, J. S. Panek, *J. Am. Chem. Soc.* **2000**, *122*, 1235–1236; b) J. S. Panek, P. Liu, *J. Am. Chem. Soc.* **2000**, *122*, 11090–11097.

[17] a) S. K. Chattopadhyay, G. Pattenden, *Tetrahedron Lett.* **1998**, *39*, 6095–6098; b) S. K. Chattopadhyay, J. Kempson, A. McNeil, G. Pattenden, M. Reader, D. E. Rippon, D. Waite, *J. Chem. Soc. Perkin Trans. 1* **2000**, 2415–2428; c) S. K. Chattopadhyay, G. Pattenden, *J. Chem. Soc. Perkin Trans. 1* **2000**, 2429–2454; d) G. Pattenden, N. J. Ashweek, C. A. G. Baker–Glenn, G. M. Walker, J. G. K. Yee, *Angew. Chem.* **2007**, *119*, 4437–4441; *Angew. Chem. Int. Ed.* **2007**, *46*, 4359–4363; e) G. Pattenden, N. J. Ashweek, C. A. G. Baker–Glenn, J. Kempson, G, M. Walker, J. G. K. Yee, *Org. Biomol. Chem.* **2008**, *6*, 1478–1497.

[18] M. Kita, H. Watanabe, T. Ishitsuka, Y. Mogi, H. Kigoshi, *Tetrahedron Lett.* **2010**, *51*, 4882–4885.

[19] a) P. R. Blakemore, W. J. Cole, P. J. Kocienski, A. Morley, *Synlett*, **1998**, 26–28; b) P. R. Blakemore, *J. Chem. Soc. Perkin Trans. 1* **2002**, 2563–2585.

[20] H. Kigoshi, K. Suenaga, T. Mutou, T. Ishigaki, T. Atsumi, H. Ishiwata, A. Sakakura, T. Ogawa, M. Ojika, K. Yamada, *J. Org. Chem.* **1996**, *61*, 5326–5351.

[21] 22*R*-**12** was converted to the 22*S* isomer in 64% yield (2 steps). See the Supporting Information for details.

[22] a) I. Shiina, M. Kubota, R. Ibuka, *Tetrahedron Lett.* **2002**, *43*, 7535–7539; b) I. Shiina, M. Kubota, H. Oshiumi, M. Hashizume, *J. Org. Chem.* **2004**, *69*, 1822–1825.

[23] a) M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953–956; b) A. K. Chatterjee, T. –L. Choi, D. P. Sanders, R. H. Grubbs, *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.

[24] a) J. S. Kingsbury, J. P. A. Harrity, P. J. Bonitatebus, A. H. Hoveyda, *J. Am. Chem. Soc.* **1999**, *121*, 791–799; b) S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.

[25] a) K. Grela, S. Harutyunyan, A. Michrowska, *Angew. Chem.* **2002**, *114*, 4210–4212; *Angew. Chem. Int. Ed.* **2002**, *41*, 4038–4040; b) A. Michrowska, R. Bujok, S. Harutyunyan, V. Sashuk, G. Dolgonos, K. Grela. *J. Am. Chem. Soc.* **2004**, *126*, 9318–9325.

[26] Z. –Y. Zhan, WO Patent 2007003135, 2007.

[27] A homodimer of **19** was also formed (*E*/*Z* ~4/1, 8%), which could also be subjected to cross metathesis with **18**, or converted to **20** by ethenolysis. See the Supporting Information for details.

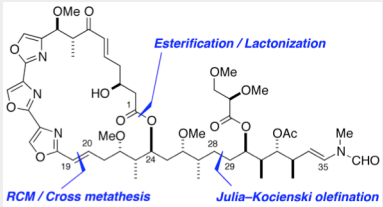
[28] J. Inanaga, K. Hirata, H. Saeki, T. Kabuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

[29] For example, sodium borohydride reduction of **22** at 0 °C preferred the 1,4-reduction of conjugated ketone (quant.), and sodium trimethoxyborohydride reduction at room temperature resulted in a mixture of unreacted conjugated ketone (45%) and α,β-saturated C7 alcohol (36%), while the hemiacetal was completely converted to 1,4-diol in both cases.

[30] To avoid the formation of several β-eliminated products including the demethoxy, deacetoxy, and de-DMPMOM ether groups, the reaction was stopped before the completion, and unreacted aldehyde **25** was recovered (33%).

COMMUNICATION

An asymmetric total synthesis of the tris-oxazole macrolides, mycalolides A and B, is described. This synthesis involves the convergent assembly of C1–C19 tris-oxazole and C20–C35 side-chain segments through the use of olefin metathesis and esterification as key steps.



Mycalolide B (**1**)

Masaki Kita, Hirotaka Oka, Akihiro Usui, Tomoya Ishitsuka, Yuzo Mogi, Hidekazu Watanabe, Masaki Tsunoda, Hideo Kigoshi**

Page No. – Page No.

Total Synthesis of Mycalolides A and B via Olefin Metathesis