Total Synthesis of Mycalolides A and B through Olefin Metathesis

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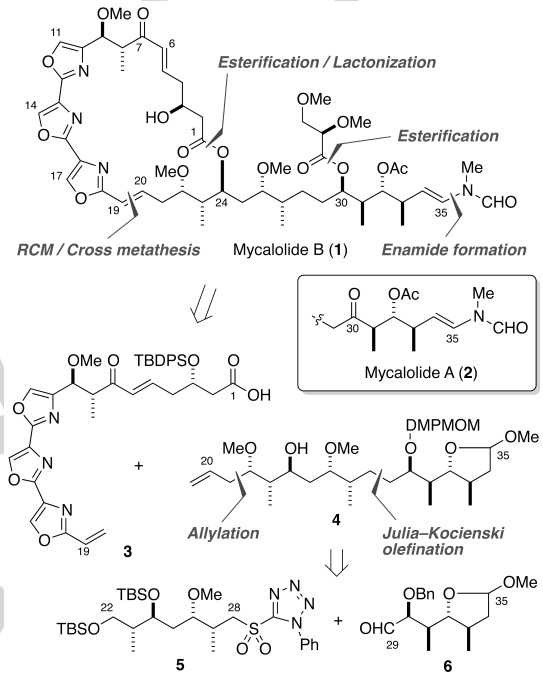
Masaki Kita,* Hirotaka Oka, Akihiro Usui, Tomoya Ishitsuka, Yuzo Mogi, Hidekazu Watanabe, Masaki Tsunoda, and Hideo Kigoshi *

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.

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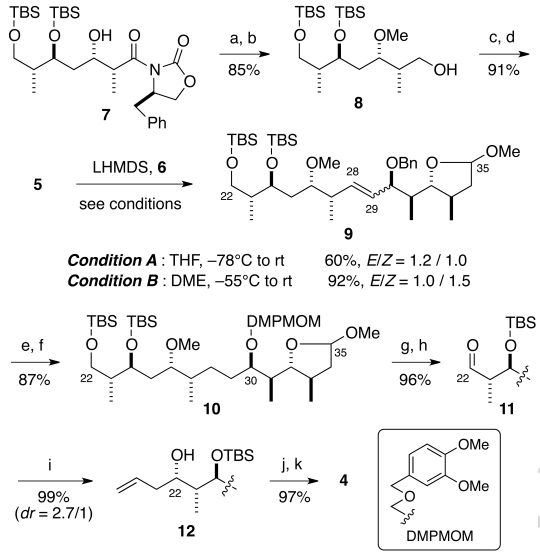
Instead, cross metathesis of **3** and **4**, in which the carboxyl or hydroxyl groups are protected, and subsequent macrolactonization could also provide the same intermediate. While the side-chain segment **4** was previously synthesized,[10,18] in this study we planned to modify the synthetic route, 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**.

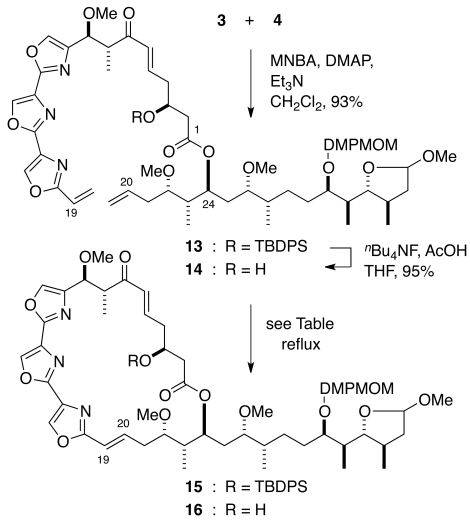


Scheme 2. Synthesis of the C20–C35 segment **4**. Reagents and conditions: a) MeOTf, 2,6-di-*tert*-butylpyridine, CH_2Cl_2; b) $LiBH_4$, EtOH, Et_2O–THF, –10 °C; c) 5,5'-dithiobis(1-phenyl-*1H*-tetrazole), tri-*n*-butylphosphine, THF; d) *m*CPBA, $NaHCO_3$, CH_2Cl_2; e) H_2, $Pd(OH)_2$/C (20 mol%), $NaHCO_3$, 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.

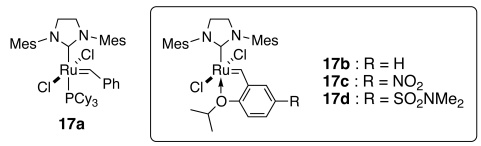
Catalytic hydrogenation of the C=C double bond and hydrogenolysis of the benzyl group from the *E*/*Z*-mixture of **9** proceeded concurrently with palladium (II) hydroxide on carbon. Subsequent protection of the C30 hydroxy group as a 3,4-dimethoxyphenylmethoxymethyl (DMPMOM) group afforded previously 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)	–

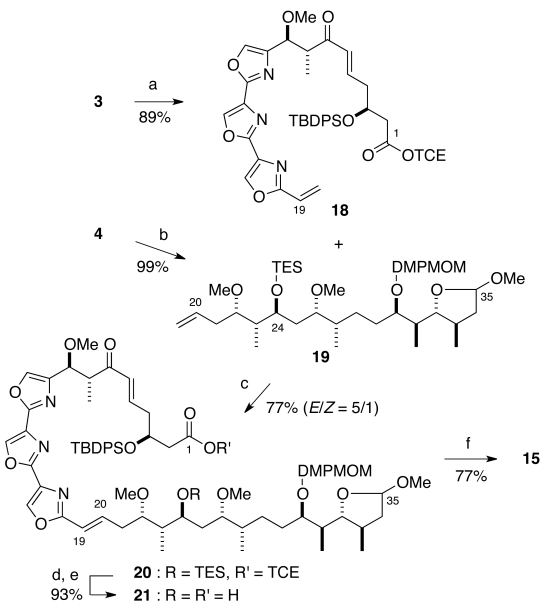
[a] See ref. 18.
[b] s. m. was decomposed and not recovered.



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

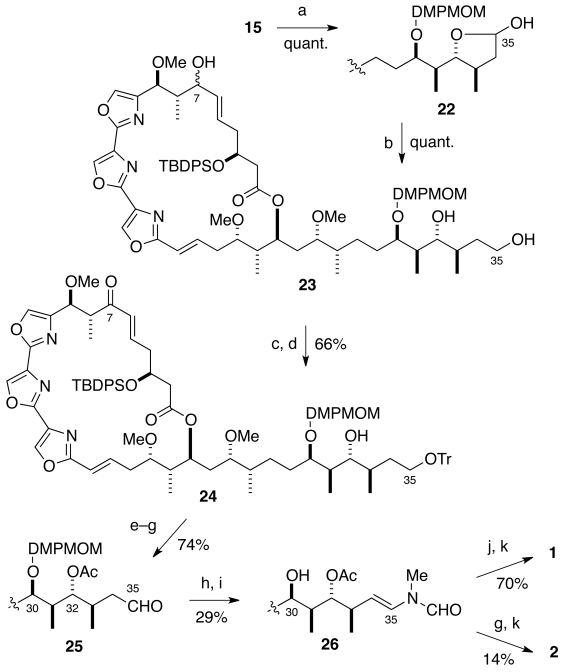
Z-isomer was preferred in *n*-hexane and toluene (*E*/*Z* = 1/1.9~2.5), while the *E*-isomer was preferred in CH_2Cl_2 (*E*/*Z* = 1.8/1).[14] In fact, for the RCM reaction of **13** with **17b** in refluxing CH_2Cl_2, the ratio was improved to 2.0:1, but the reaction did not run to completion, similar 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

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

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[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.

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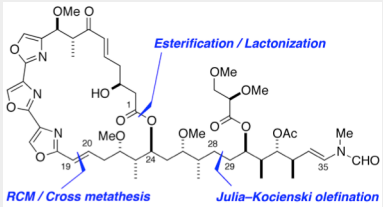
[29] For example, sodium borohydride reduction of **22** at 0 °C preferred the 1,4-reduction of conjugated ketone (quant.), and sodium trimethoxyborohydride reduction at room temperature resulted in a mixture of unreacted conjugated ketone (45%) and α,β-saturated C7 alcohol (36%), while the hemiacetal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

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Total Synthesis of Mycalolides A and B via Olefin Metathesis