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LETTERS

Synthetic studies of mycalolide B, an actin-depolymerizing marine macrolide: construction of the tris-oxazole macrolactone using ring-closing metathesis

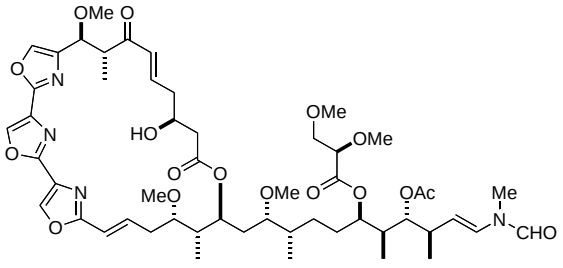
Masaki Kita, Hidekazu Watanabe, Tomoya Ishitsuka, Yuzo Mogi, and Hideo Kigoshi*

Department of Chemistry, Graduate School of Pure and Applied Sciences, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8571, Japan.

Abstract—Tris-oxazole macrolactone **2**, a key intermediate of mycalolide B (**1**), which has 13 stereogenic centers, was synthesized through the use of ring-closing metathesis (RCM). The *E*/*Z* ratio of the RCM product **2** was reversed by the use of CH_2Cl_2 and toluene, whereas a cross metathesis reaction yielded the C1–C35 long-chain compound **19** in a highly *E*-selective manner. Thus, the loss of flexibility in aliphatic carbon chains and the steric hinderance of β- and γ-substituents of the C20 olefin in the precursor **11** may affect the stereoselectivity in RCM reactions.

Mycalolide B (**1**) is a cytotoxic and antifungal macrolide isolated from the marine sponge *Mycale* sp. It bears a unique tris-oxazole structure and 13 stereogenic centers (Fig. 1).[1] This compound also inhibits actomyosin Mg^{2+}–ATPase and shows potent actin-depolymerizing activity by sequestering G-actin and forming a 1:1 complex.[2] Mycalolides can be divided into two characteristic parts: the C1–C24 macrolactone and the C25–C35 side-chain moieties. Studies of the structure-activity relationship [3] and photo-affinity labeling experiments [4] have established that the side-chain part of **1** is critically important for its ability to bind to and depolymerize actin. Several tris-oxazole macrolides closely related to mycalolides have been isolated, such as ulapualides,[5] halichondramides,[6] jaspisamides,[7] and kabiramides;[8] all of which exhibit potent actin-depolymerizing properties. These agents may be useful for the development of novel pharmacological tools for analyzing actin-mediated cell functions, such as muscle contraction, cell motility, and cytokinesis. Furthermore, it is noteworthy that aplyronine A, which has an actin-binding side-chain moiety similar to mycalolides, exhibits potent antitumor activity *in vivo* against P388 leukemia and several cancers.[9,10] Thus, mycalolides and related actin-targeting natural products have great potential as preclinical candidates for use in cancer chemotherapy.

Due to their extraordinary structures and important biological activities, several synthetic studies on tris-oxazole-containing macrolides have been reported.[11] Recently, total syntheses of mycalolide A [12] and ulapualide A [13] have been accomplished, in which Yamaguchi lactonization, cyclization of the central oxazole ring, or intramolecular Horner–Wadsworth–Emmons olefination were used to construct macrocycles. Subsequent studies have shown that olefin metathesis is a useful method for connecting the C19–C20 double bonds in mycalolide analogs.[14] Here we describe the synthesis of tris-oxazole macrolactone **2**, a key synthetic intermediate of mycalolides, through the use of ring-closing metathesis (RCM). We expected that the convergent assembly of three fragments via Ni/Cr-mediated Nozaki–Hiyama–Kishi coupling [15] at C6–C7, esterification, and RCM at the C19–C20 olefin could efficiently afford **2**.



Mycalolide B (**1**)

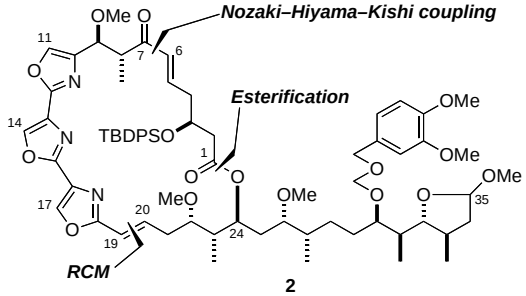


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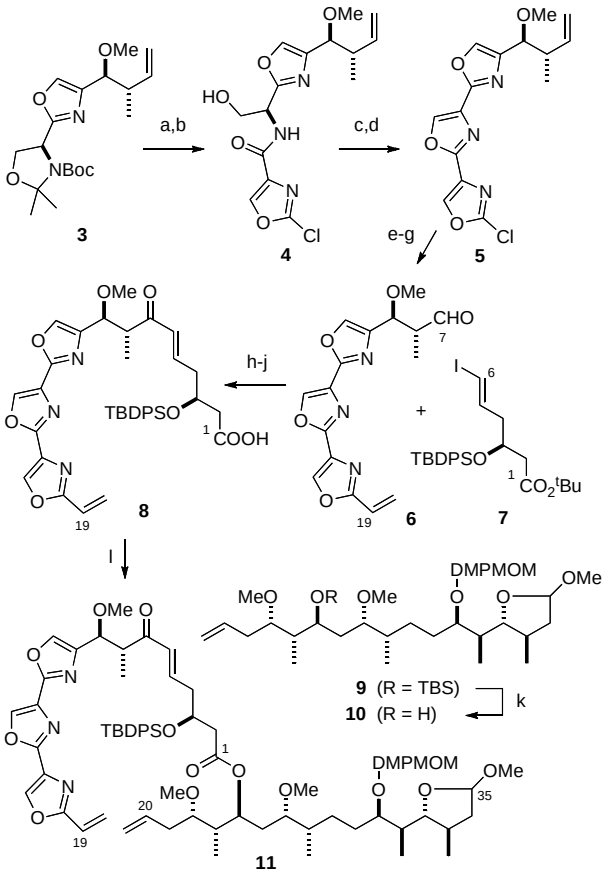
Figure 1.

The synthesis started with removal of the Boc and acetonide groups of the previously reported oxazole (–)-**3** [14] under acidic conditions, and subsequent condensation with 2-chloroxazole-4-carboxylic acid [16] afforded amide **4** (77%, 2 steps) (Scheme 1). Due to the considerable instability of the 2-vinyloxazole moieties under basic and dehydration conditions, we planned to introduce the vinyl group to the oxazole ring after construction of the tris-oxazole structure. Dehydrating cyclization of **4** by diethylaminosulfur trifluoride (DAST) [17] gave an oxazoline intermediate (85%), which was oxidized with a combination of bromotrichloromethane and 1,8-diazabicycloundec-7-ene (DBU) [18] at room temperature to give tris-oxazole **5** (98% based on recovered starting material).[19] We found that acetonitrile is a better solvent than the conventional CH_2Cl_2 in this reaction. Catalytic dihydroxylation of **5** with OsO_4–NMO and Migita–Stille coupling with tri-*n*-butylvinyltin furnished a vinyloxazole intermediate, and this was transformed into aldehyde **6** via oxidative cleavage of the 1,2-diol with $NaIO_4$ (73%, 3 steps).

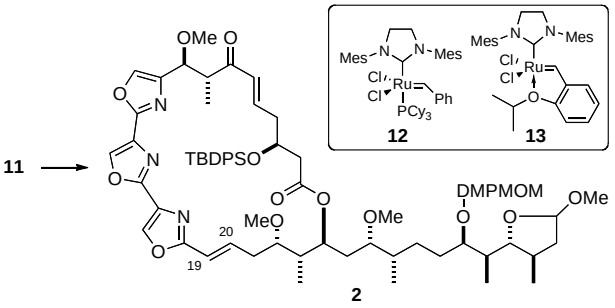


Scheme 1. Synthesis of the RCM precursor **11**. Reagents and conditions: (a) 3 M HCl, EtOAc, rt; (b) 2-chlorooxazole-4-carboxylic acid, EDCI·HCl, HOBt, Et_3N, CH_2Cl_2, 0 °C to rt, 77% in 2 steps; (c) DAST, CH_2Cl_2, –78 to 0 °C, 85%; (d) DBU, $BrCCl_3$, MeCN, rt, 54% (98% brsm); (e) OsO_4, NMO, THF–^{t}BuOH–H_2O, rt; (f) tri-*n*-butylvinyltin, $PdCl_2(PPh_3)_2$, 1,4-dioxane, reflux; (g) $NaIO_4$, EtOH–H_2O, rt, 73% in 3 steps; (h) **7**, $CrCl_2$–$NiCl_2$, THF–DMF, rt; (i) DMP, pyridine, CH_2Cl_2, rt, 71% in 2 steps; (j) TFA, CH_2Cl_2, 0 °C, 90%; (k) TBAF, THF, 40 °C, 97%; (l) **10**, MNBA, Et_3N, DMAP, CH_2Cl_2, rt, 55%.

Fragment coupling between **6** and vinyl iodide **7** [12] by a Ni/Cr-mediated coupling reaction was followed by oxidation of the C7 allylic alcohol with Dess–Martin periodinane (DMP) [20] to afford a ketone (71%, 2 steps), the *tert*-butyl group of which was removed to give carboxylic acid **8** (90%). Removal of the *tert*-butyldimethylsilyl (TBS) group in **9** [14,3b,21] by tetra-*n*-butylammonium fluoride (TBAF) gave C20–C35 fragment **10** (97%), which was condensed with **8** by the Shiina procedure [22] to afford the RCM precursor **11** in 55% yield.

With the key intermediate **11** in hand, RCM reactions were examined (Table 1). First, treatment of **11** with 30 mol% of 2nd-generation Grubbs catalyst (**12**) [23] in degassed refluxing toluene led to decomposition of the starting material and gave a complex mixture (entry 1). We assumed that the low reactivity of **11** toward RCM reactions would be due to the electron-deficient C19 olefin. To overcome this problem, more thermally-stable and highly-active catalyst was considered. Treatment of **11** with 30 mol% of 2nd-generation Hoveyda–Grubbs catalyst (**13**) [24] in refluxing CH_2Cl_2 (0.8 mM) yielded tris-oxazole lactone **2** as a separable 2:1 mixture of stereoisomers in 30% yield (entry 2).[25–27] With the use of toluene as a solvent (0.9 mM), the yield of **2** was improved to 76%, but the *E*/*Z*-product ratio was changed to 1:1.2 (entry 3).

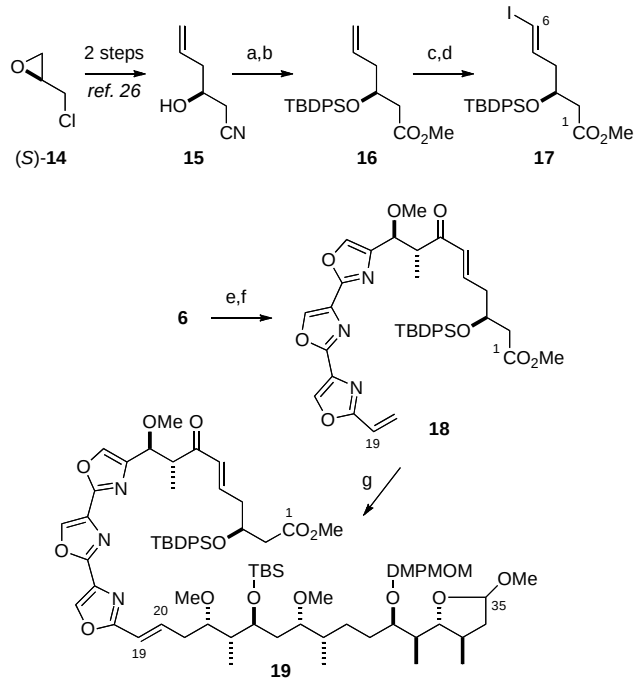
Table 1. Ring-closing metathesis of **11**.



Entry	Catalyst (30 mol%)	Reaction conditions	Yields (%)	
			Product	19*Z*-isomer
1	**12**	toluene, reflux, 4 h	trace [a]	trace
2	**13**	CH_2Cl_2, reflux, 24 h	20 [b]	10
3	**13**	toluene, reflux, 3 h	34	42

[a] S.m. was decomposed and not recovered.
[b] S.m. was recovered (50%).

For comparison, we also used a cross-metathesis reaction (Scheme 2). Acidic treatment of cyanide **15** in aqueous MeOH, which was prepared from (*S*)-epichlorohydrin (**14**),[28] and protection of the hydroxyl group gave **16** (60% in 2 steps). Ozonolysis of the terminal olefin (80%) and Takai olefination [29] gave vinyl iodide **17** (66%, *E*/*Z* = 11/1). Nozaki–Hiyama–Kishi coupling between compounds **6** and **17** gave an allylic alcohol (87%), which was oxidized with DMP to afford the C1–C19 ketone **18** in 84% yield. In contrast to the RCM reactions, treatment of the C1–C19 segment **18** (1.2 equiv.) and the C20–C35 segment **9** with 50 mol% of catalyst **13** in refluxing CH_2Cl_2 (7 mM for **9**) for 25 h yielded the C1–C35 long-chain compound **19** in a highly *E*-selective manner (66%, *E*/*Z* = 5:1).[25,30–32]



Scheme 2. Cross metathesis reaction. Reagents and conditions: (a) conc. H_2SO_4, MeOH–H_2O, reflux; (b) TBDPSCl, imidazole, DMF, rt, 60% in 2 steps; (c) O_3, CH_2Cl_2, –78°C, then Me_2S, –78 °C to rt, 80%; (d) $CrCl_2$, CHI_3, 1,4-dioxane–THF, rt, 65%; (e) **17**, $CrCl_2$–$NiCl_2$, THF–DMF, rt, 87%; (f) DMP, pyridine, CH_2Cl_2, rt, 84%; (g) **9**, **13** (50 mol%), CH_2Cl_2, reflux, 55 % with 11% of 19*Z*–isomer.

Our work demonstrated that the RCM reaction of **11** proceeded with low stereoselectivity, unlike the cross-metathesis reaction of **18**. The *E*/*Z* ratios did not significantly change during the course of the metathesis reactions, and thus the formation of C=C bonds in **2** and **19** would take place under kinetic control. In the ruthenocyclobutane intermediate for the desired 19*E*-isomer of **2**, the oxazole rings and C21–C35 alkyl chain are located in an *anti*-orientation. Due to the rigidness of the tris-oxazole and α,β-unsaturated ketone moieties, the *anti*-ruthenocyclobutane intermediate would be more strained than the *syn*-intermediate, which may affect the stereoselectivity in RCM reactions.

In conclusion, we achieved the synthesis of tris-oxazole macrolactone **2** through the use of RCM reactions as a key step, which includes all of the 13 stereogenic centers and the whole carbon framework of mycalolide B (**1**). Also, this key intermediate possesses a common framework for mycalolides and related actin-depolymerizing tris-oxazole macrolides. Studies on the total synthesis of mycalolide B (**1**) as well as on the stereoselectivity of RCM reactions, and especially solvent effects, are currently underway.

Acknowledgements

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19 NiO_2 oxidation of oxazoline intermediate also afforded **8**, but low yield (~30%) and significant loss of starting material recovery, probably due to the strong coordination of bis- or tris-oxazole nitrogen atoms to nickel atom.

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21 Although configuration of the C35 acetal carbon in **9** has not been determined, **9** is a single stereoisomer. See ref. 3b.

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25 The stereochemistry of the C19 olefins in **2** and **19** was established based on $^3J_{H19,H20}$ values (15.8 and 15.9 Hz). In contrast, the $^3J_{H19,H20}$ values of 19*Z*-**2** and 19*Z*-**19** were 11.4 and 11.3 Hz, respectively.

26 Spectral data for **2**: R_f 0.12 (hexane/EtOAc = 1/1); $[\alpha]_D^{24}$ –26.2 (*c* 0.030, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (s, 1H, H-14), 8.06 (s 1H, H-17), 7.71–7.67 (m, 4H, –Si(^{t}Bu)*Ph*$_2$), 7.66 (s, 1H, H-11), 7.42–7.34 (m, 6H, –Si(^{t}Bu)*Ph*$_2$), 7.15–7.06 (m, 2H, H-5, H-20), 6.90–6.80 (m, 3H, –C$_6$*H*$_3$(OMe)$_2$), 6.32 (d, *J* = 15.8 Hz, 1H, H-19), 5.90 (d, *J* = 16.2 Hz, 1H, H-6), 5.12 (m, 1H, H-24), 4.86 (d, *J* = 4.7 Hz, 1H, H-35), 4.81–4.79 (AB quart, *J* = 11.2 Hz, 2H, –OC*H*$_2$O–), 4.56 (s, 2H, –OC*H*$_2$Ar), 4.43 (m, 1H, H-22), 4.37 (d, *J* = 9.5 Hz, 1H, H-9), 4.28 (m, 1H, H-3), 4.19 (m, 1H, H-26), 4.02 (m, 1H, H-30), 3.87 (s, 3H, –O*Me*), 3.86 (s, 3H, –O*Me*), 3.54 (m, 1H, H-32), 3.26 (s, 3H, –O*Me*), 3.24 (s, 3H, –O*Me*), 3.22 (s, 3H, –O*Me*), 3.10 (s, 3H, –O*Me*), 2.98 (m, 1H), 2.74–2.70 (m, 2H), 2.45–2.28 (m, 2H), 1.80 (m, 4H), 1.66–1.40 (m, 10H), 1.08 (d, *J* = 6.6 Hz, 3H), 1.03 (s, 9H, –Si(*^{t}Bu*)Ph$_2$), 0.88–0.77 (m, 12H); IR ($CHCl_3$) 2930, 1733, 1654, 1516, 1458, 1381, 1262, 1106, 1027, 755, 704 cm^{-1}; HRMS (ESI) *m/z* 1282.6232 (calcd for $C_{70}H_{93}N_3NaO_{18}Si$ $[M+Na]^+$, Δ +1.0 mmu).

27 The dimer of **11** was not formed.

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30 Spectral data for **19**: R_f 0.10 (hexane/EtOAc = 1/1); $[\alpha]_D^{25}$ –15.5 (*c* 0.415, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.33 (s, 1H, H-14), 8.28 (s, 1H, H-17), 7.69 (s, 1H, H-11), 7.69–7.64 (m, 4H, –Si(^{t}Bu)*Ph*$_2$), 7.42–7.36 (m, 6H, –Si(^{t}Bu)*Ph*$_2$), 6.93–6.75 (m, 5H, H-5, H-20, –C$_6$*H*$_3$(OMe)$_2$), 6.44 (d, *J* = 15.9 Hz, 1H, H-19), 6.11 (d, *J* = 15.7 Hz, 1H, H-6), 4.89 (d, *J* = 4.9 Hz, 1H, H-35), 4.83 (s, 2H, –OC*H*$_2$O–), 4.59 (s, 2H, –OC*H*$_2$Ar), 4.39 (d, *J* = 10.0 Hz, 1H, H-9), 4.32 (m, 1H, H-3), 4.07 (m, 1H, H-30), 3.92 (m, 1H, H-24), 3.89 (s, 3H, –O*Me*), 3.87 (s, 3H, –O*Me*), 3.58 (dd, *J* = 6.8, 9.5 Hz, 1H, H-22), 3.56 (s, 3H, –O*Me*), 3.44 (m, 1H, H-32), 3.36 (s, 3H, –O*Me*), 3.33 (s, 3H, –O*Me*), 3.29 (s, 3H, –O*Me*), 3.20 (m, 1H, H-26), 3.17 (s, 3H, –O*Me*), 3.03 (m, 1H), 2.60 (m, 1H), 2.53–2.39 (m, 5H), 2.30–2.05 (m, 3H), 1.87–1.73 (m, 2H), 1.69–1.12 (m, 7H), 1.11 (d, *J* = 6.5 Hz, 3H), 1.04 (s, 9H, –Si(*^{t}Bu*)Ph$_2$), 0.95 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 7.6 Hz, 3H), 0.87–0.82 (m, 6H), 0.84 (s, 9H, –Si(*^{t}Bu*)Me$_2$), 0.00 (s, 3H, –Si(^{t}Bu)*Me*$_2$), –0.06 (s, 3H, –Si(^{t}Bu)*Me*$_2$); ^{13}C NMR (150 MHz, $CDCl_3$) δ201.8, 171.4, 161.9, 156.1, 155.5, 148.9, 148.5, 142.7, 139.8, 138.6 (2C), 138.5, 137.2, 135.9 (2C), 135.8 (2C), 133.4 (2C), 132.9, 131.5, 130.7, 130.5, 129.9, 129.8, 127.7 (2C), 127.6 (2C), 120.5, 118.0, 111.3, 110.8, 104.6, 94.4, 87.1, 82.5, 82.1, 78.4, 77.5, 69.6, 69.4, 69.2, 57.6, 57.2, 56.9, 55.9, 55.8, 54.5, 51.5, 46.9, 43.4, 43.1, 42.5, 41.5, 40.2, 35.9, 34.6, 33.7, 32.6, 30.6, 26.9, 26.9, 26.9, 26.8, 25.8, 25.8, 25.8, 20.1, 19.2, 18.0, 15.8, 14.1, 9.2, 8.8, –4.1, –4.7; IR ($CHCl_3$) 1733, 1664, 1517, 1464, 1380, 1260, 1096, 1029, 919, 823 cm^{-1}; HRMS (ESI) *m/z* 725.8638 (calcd for $(C_{77}H_{111}N_3Na_2O_{17}Si_2)/2$ $[M+2Na]^{2+}$, Δ +1.4 mmu).

31 The C20–C35 dimer was afforded in 15% yield, and the dimer of **18** was not formed.

32 Model reactions for the cross-metathesis of 2-vinyloxazole derivatives using catalyst **13** in toluene at 40 °C also preferentially yielded *E*-isomer, but the selectivity was lower than in the case of CH_2Cl_2 (*E*/*Z* = 2.0~1.5:1). Thus, the difference of solvent (CH_2Cl_2 and toluene) rather than reaction temperature may affect the stereoselectivity in the RCM reactions of **11**.

Keywords: Actin-depolymerizing compound; Ring-closing metathesis; Tris-oxazole macrolide; Synthesis of marine natural products.

* Corresponding author. Tel./fax: +81 29 853 4313.
E-mail address: kigoshi@chem.tsukuba.ac.jp (H. Kigoshi).