Total Synthesis

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Total Synthesis of Mycalolides A and B through Olefin Metathesis

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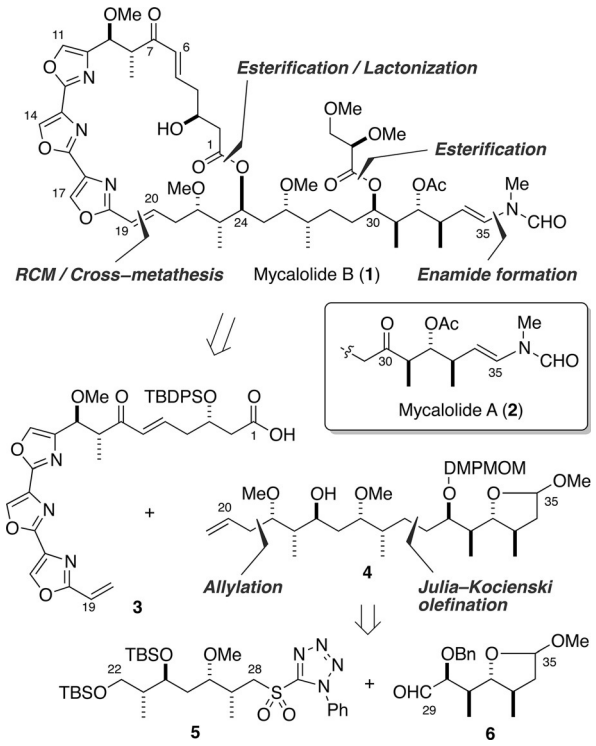
Abstract: *An asymmetric total synthesis of the trisoxazole marine macrolides mycalolides A and B is described. This synthesis involves the convergent assembly of highly functionalized C1–C19 trisoxazole and C20–C35 side-chain segments through the use of olefin metathesis and esterification as well as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

Mycalolides, isolated from the marine sponge *Mycale* sp., are cytotoxic and antimycotic trisoxazole macrolides.[1] Mycalolides inhibit the enzyme actomyosin Mg^{2+}-ATPase[2] and show potent actin-depolymerizing activity by forming a 1:1 complex with the 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 the C30 position (Scheme 1). Several trisoxazole 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 trisoxazole macrolactone and the C25–C35 side chain functionalized by an *N*-methyl enamide moiety. Studies on the structure–activity relationships[10] and photolabeling experiments[11] have established that the side-chain component of mycalolides is important for its ability to bind to and depolymerize actin. Additionally, X-ray analyses of the actin–kabiramide C,[12] actin–jaspisamide A,[12] and actin–ulapualide A complexes[13] have revealed that the aliphatic side chains of the macrolides intercalate into the hydrophobic cleft between subdomains 1 and 3 of actin. More recently, we synthesized the 19*E*- and 19*Z*-lactone analogues of mycalolides that lack the C25–C35 side chain.[14] These analogues exhibited moderate cytotoxicity against tumor cells (circa 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. Bn = benzyl; TBDPS = *tert*-butyldiphenylsilyl; TBS = *tert*-butyldimethylsilyl; DMPMOM = 3,4-dimethoxyphenylmethoxymethyl; RCM = ring-closing metathesis.

As a result of 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 trisoxazole 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 reported to date. We describe herein the first total synthesis of (−)-mycalolide B (**1**) and the second total synthesis of mycalolide A (**2**) using 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

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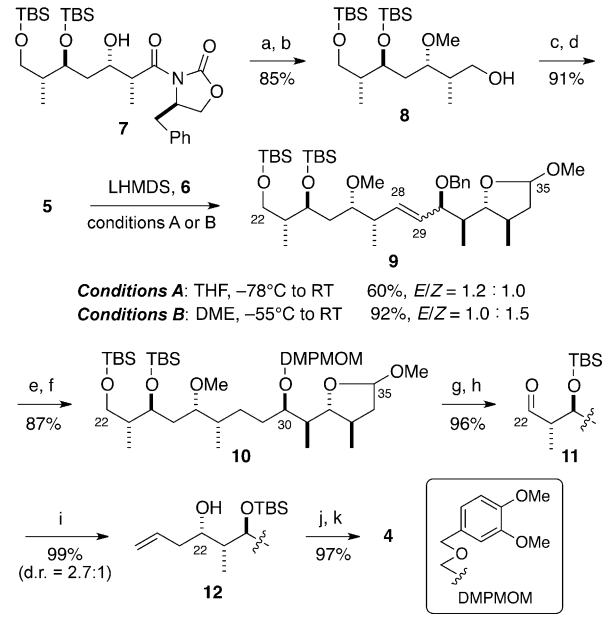
mycalolide analogues,[10c,18] we designed a plan for the synthesis of **1** (Scheme 1). After disconnection of the C35 *N*-methyl enamide moiety and the C30 ester bond, the macrolactone structure of **1** could be divided into a C1–C19 trisoxazole segment **3** and a C20–C35 side-chain segment **4**. We expected that the convergent assembly of **3** and **4** through esterification/ring-closing metathesis (RCM) would efficiently afford a key macrolactone. Instead, cross-metathesis of **3** and **4**, in which the carboxy or hydroxy groups are protected, and subsequent macrolactonization could also provide the same intermediate. Although the side-chain segment **4** was previously synthesized,[10,18] in this study we planned to modify the synthetic route to include a Julia–Kocienski olefination[19] between PT–sulfone **5** (PT = phenyl tetrazole) and aldehyde **6**.

Our synthesis started with the preparation of **5** (Scheme 2). Methylation of the known *syn*-aldol **7**[10b] with



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 (320:1 v/v), −10 °C; c) 5,5′-dithiobis(1-phenyl-1*H*-tetrazole), tri-*n*-butylphosphine, THF; d) *m*CPBA, $NaHCO_3$, CH_2Cl_2; e) $Pd(OH)_2$/C (20 mol%), H_2, $NaHCO_3$, EtOH; f) 3,4-dimethoxybenzyloxymethyl chloride, iPr_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 (3.4:1 v/v); j) MeI, NaH, THF; k) nBu_4NF, THF, RT to 40 °C.

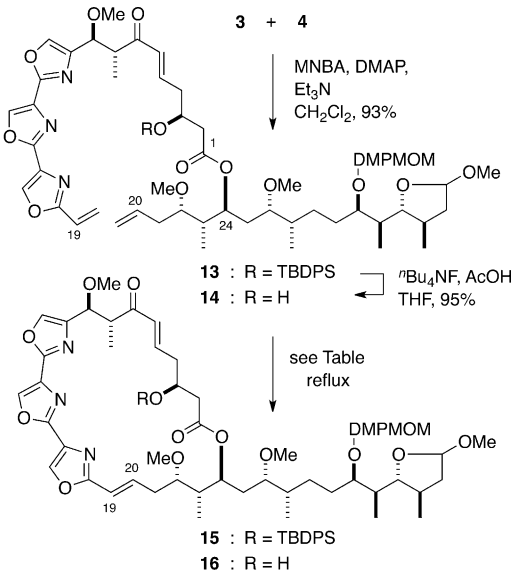
methyl trifluoromethanesulfonate (MeOTf) and removal of the chiral auxiliary with $LiBH_4$ yielded primary alcohol **8**. Conversion of **8** into the PT–sulfide with aryl disulfide/$^nBu_3P$ and subsequent oxidation with *meta*-chloroperbenzoic acid (*m*-CPBA) yielded PT–sulfone **5**.

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

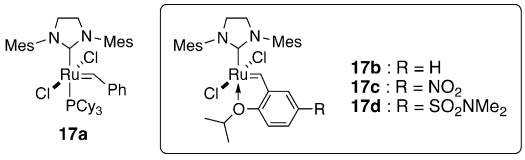
Catalytic hydrogenation of the C=C double bond and hydrogenolysis of the benzyl group from the *E*/*Z* mixture of **9** proceeded concurrently with palladium(II) hydroxide on carbon. Subsequent protection of the C30 hydroxy group as a 3,4-dimethoxyphenylmethoxymethyl (DMPMOM) group afforded the previously 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**. The Grignard reaction of **11** with allylmagnesium bromide resulted in the formation of **12** as a mixture of *S* and *R* alcohols (d.r. = 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). Using the procedure of Shiina et al., condensation of the C1–C19 segment **3**[18] with **4** using 2-methyl-6-nitrobenzoic anhydride (MNBA)[22] afforded the RCM precursor **13**. We previously reported that treatment of **13** with 30 mol% of second-generation Grubbs catalyst (**17a**)[23] in degassed toluene heated to reflux led to the decomposition of the starting material (Scheme 3, entry 1).[18] However, in CH_2Cl_2 heated at reflux, trisoxazole lactone **15** was obtained as an *E*/*Z* mixture (entry 2; 40% yield, $E/Z = 1.9{:}1$), although the reaction did not go to completion.

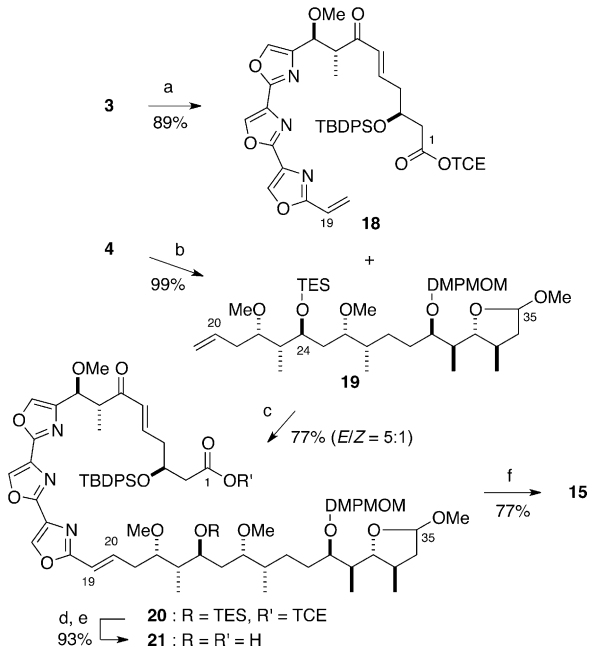
As a result of the instability of catalyst **17a** for the slow metathesis reaction of macrocycle precursors, we next examined the second-generation Hoveyda–Grubbs (HG-II) catalyst (**17b**).[24] We previously reported that treatment of **13** with **17b** (30 mol%) in toluene heated at reflux afforded the RCM product **15** in higher yield but with the undesired C19–C20 *Z* isomer slightly preferred (entry 3; 76% yield, $E/Z = 1{:}1.2$).[18] However, in the model RCM reactions of C1–C24 macrolactone analogues, the solvent polarity was found to significantly affect the stereoselectivity. Notably, the *Z* isomer was preferred in *n*-hexane and toluene ($E/Z = 1{:}1.9$–$1{:}2.5$), whereas 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 CH_2Cl_2 heated at reflux, the *E*/Z ratio was improved to 2.0:1 (entry 4), but the reaction did not go to completion, similar to the use of **17a** (entry 2). These results suggested that the C25–C35 segment in **13** minimally affected the stereoselectivity but decreased the reactivity for RCM reactions, probably because of the steric hindrance in forming the ruthenocyclobutane intermediate. In 1,2-dichloroethane (DCE) heated at reflux, the stereoselectivity decreased to 1.0:1.0 (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 employed, in which nitro or *N*,*N*-dimethylsulfonamide groups are substi-



entry	s.m.	catalyst [30 mol%]	solvent [0.9 mM]	time [h]	yields [%] product (19*E*/19*Z*)	yields [%] 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)	–



Scheme 3. Synthesis of macrolactones **15** and **16** through ring-closing metathesis. DMAP = 4-dimethylaminopyridine. s.m. recov. = starting material recovered. [a] See Ref. [18]. [b] Starting material decomposed and was not recovered.

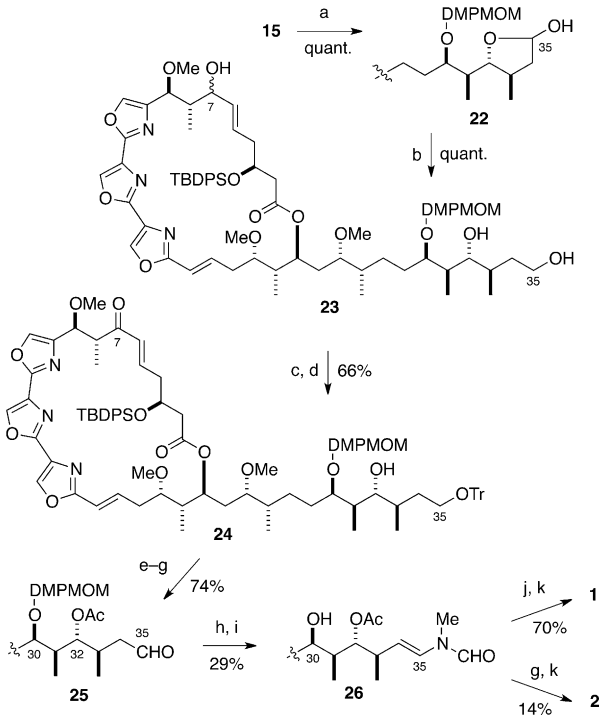


Scheme 4. Synthesis of **15** through macrolactonization. Reagents and conditions: a) 2,2,2-trichloroethanol, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI·HCl), DMAP, CH_2Cl_2; b) TESCl, Imidazole (ImH), DMF, 40 °C; c) **17b** (20 mol%), CH_2Cl_2, reflux; d) AcOH, THF, H_2O; e) Zn, 1 M NH_4OAc (aq), THF; f) 2,4,6-trichlorobenzoyl chloride, iPr_2NEt, benzene, then dropwise addition into DMAP in benzene.

tuted 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 (entries 6 and 7; $E/Z = 1.6{:}1$ and 1.7:1, respectively). We expected that such low stereoselectivity of the RCM precursor **13** was due to the presence of the structurally hindered C3 TBDPS group. For comparison, a C3 hydroxy analogue **14** was prepared from **13** by the treatment with TBAF along with acetic acid (AcOH). With the use of catalyst **17c** in CH_2Cl_2 heated at reflux, the stereoselectivity of the C3 hydroxy macrolactone **16** was improved to 2.7:1, but the yield was lower than that of **15** (entry 8).

A cross-metathesis/macrolactonization approach was next examined (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 the HG-II catalyst (**17b**) in CH_2Cl_2 heated at reflux (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** using the procedure of Yamaguchi et al.[28] readily proceeded to give the lactone **15**. As a result of the higher stereoselectivity, the cross-metathesis/macrolactonization approach was preferred to the RCM approach.

We next set out to functionalize the last side-chain section (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 (d.r. = 10:1 at C7). Next, trityl group (Tr) 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) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, 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, pyridinium *para*-toluenesulfonate (PPTS), hydroquinone, MS3A (3 Å molecular sieves), benzene, reflux; i) DDQ, CH_2Cl_2, *t*BuOH, phosphate buffer (1 M, pH 6.0); j) 2,3-di-*O*-methyl-D-glyceric acid, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, benzene; k) nBu$_4$NF, AcOH, THF.

Finally, condensation of **26** with 2,3-di-*O*-methyl-D-glyceric acid using the procedure of Yamaguchi et al.[28] and removal of the C3 TBDPS group by TBAF along with AcOH furnished mycalolide B (**1**) in analytically pure form. The ^{1}H and ^{13}C NMR spectra of the synthetic mycalolide B are consistent with those of the natural product, as is 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 the natural product **1**[1a]). Synthetic **1** was also found to be identical to an authentic sample on the basis of TLC and HPLC analysis. Additionally, 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**). The ^{1}H NMR spectrum of this compound corresponded to that of the reported compound.[1a,16]

In summary, we have developed a convergent approach for the synthesis of the trisoxazole marine macrolides and have completed the total syntheses of mycalolides A and B. The key components of this synthesis include the use of RCM/cross-metathesis and esterification as a fragment-coupling method 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.

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Keywords: esterification · macrolactonization · natural products · olefin metathesis · total synthesis

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[27] A homodimer of **19** was also formed ($E/Z \approx 4{:}1$; 8% yield), which could also be subjected to cross-metathesis with **18**, or converted into **20** by ethenolysis. See the Supporting Information for details.

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

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