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Stereoselective Synthesis of the C1−C11 and C12−C34 Fragments of Mycalolide A

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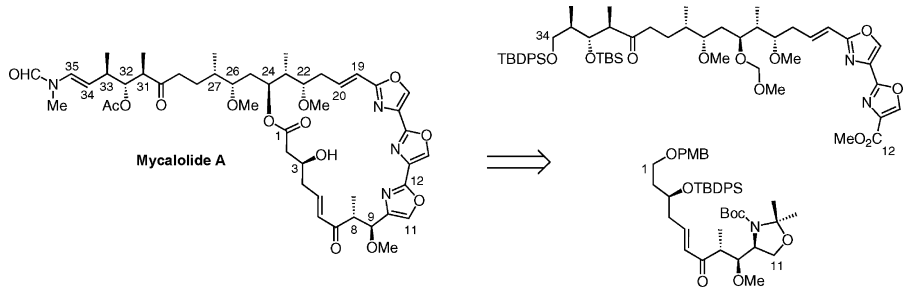
ABSTRACT



A convergent synthesis of the C1−C11 and C12−C34 fragments of mycalolide A is described. Synthetic highlights include a highly *E*-selective cross-metathesis between a vinyl-functionalized bis-oxazole unit and a polypropionate side chain to introduce the C19−C20 double bond and an enzymatic desymmetrization of a *meso*-diol in addition to five stereoselective allylations/crotylations to control the 11 stereogenic centers present in the natural product.

In 1989, Fusetani et al. reported the isolation of mycalolide A (Scheme 1), a secondary metabolite produced by a sponge of the genus *Mycale* sp. collected in the Gokasho Bay of the Kii Peninsula in Japan.[1] This secondary metabolite exhibited antifungal activity against a variety of pathogenic fungi as well as a strong activity against B-16 melanoma cells with IC_{50} values ranging from 0.5 to 1.0 ng/mL (Scheme 1). In addition, it was shown to selectively inhibit the actomyosin Mg^{2+}-ATPase suggesting that it acts as an actin-depolymerization agent.[2]

From a structural perspective, mycalolide A constitutes one of the first known members of a vast family of marine macrolides containing a unique tris-oxazole unit which includes the ulapualides,[3] the jaspisamides,[4] the halishigamides,[5] the kabiramides,[6] and the halichondramides.[7] Its structure, which was elucidated through a combination of chemical degradation, extensive ^{1}H and ^{13}C NMR analysis, and structural correlation experiments,[8] consists of a 25-membered macrolide attached to a highly functionalized aliphatic polyketide side chain bearing eight of the 11 stereogenic centers present in the natural product.

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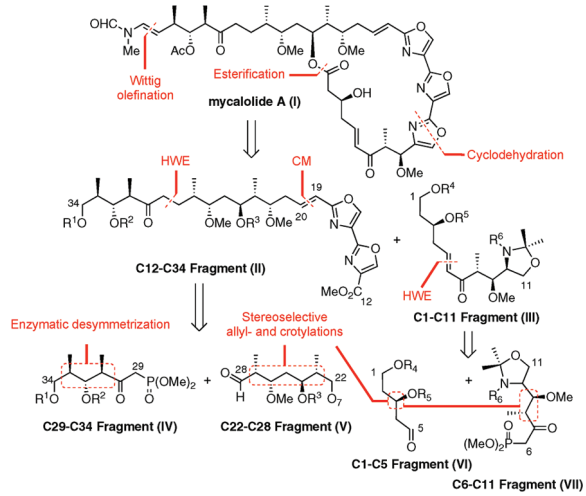
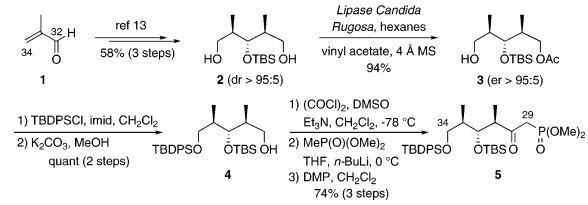
Scheme 1. Retrosynthesis of mycalolide A.



Scheme 2. Synthesis of the C29−C34 β-Ketophosphonate **5**



The promising biological properties displayed by mycalolide A in conjunction with its challenging structure and the fact that only one total synthesis has been reported so far[9,10] prompted us to initiate studies toward its total synthesis. We describe here the results of our endeavor.

Our strategy for the synthesis of mycalolide A relied on four key disconnections: an unusual cross-metathesis (CM) between a vinyl-functionalized bis-oxazole unit and the C20−C34 polypropionate fragment bearing a terminal olefin, an esterification to link the C12−C34 fragment **II** and the C1−C11 fragment **III**, a Robinson−Gabriel-type cyclodehydration to form the third oxazole ring and concomitantly generate the macrolide, and a Wittig olefination using an *N*-methylformamide phosphonium salt to install the enamide moiety and complete the synthesis of the natural product (Scheme 1).

Our first instinct when trying to devise a straightforward strategy to access mycalolide A was to apply a CM between a vinyl-functionalized mono-, bis-, or tris-oxazole unit and a terminal olefin. Interestingly, however, despite the plethora of examples which have been reported in the literature in the field of CM within the last couple of decades,[11] there has only been a few examples involving vinyl-functionalized azoles.[10s,12] In this context, and with the scope to validate this strategy, we embarked on the synthesis of the two CM coupling partners.

The preparation of the C20−C34 fragment of mycalolide A relied on a Horner−Wadsworth−Emmons (HWE) reaction between a C29−C34 β-ketophosphonate of type **IV** and a C22−C28 aldehyde of type **V**. The synthesis of the former began by the preparation of *meso*-diol **2** which was obtained in three steps and 58% overall yield starting from methacrolein (**1**) and following a reported procedure (Scheme 2).[13] The resulting *meso*-diene was then subjected to a diastereoselective double hydroboration (9-BBN, THF, −85 °C) which, upon oxidation, delivered the *meso*-diol **2** in 70% yield (dr >95:5). Desymmetrization of the latter through a lipase-mediated acetylation (*Candida rugosa*, vinyl acetate, hexane, 4 Å MS, 36 h)[14] afforded the corresponding monoacetate **3** in 97% yield as a single stereoisomer (er >95:5).[15] Protection of the remaining primary alcohol as a *tert*-butyldiphenylsilyl ether (TBDPSCl, imidazole, CH_2Cl_2) and saponification of the acetate group (K_2CO_3, MeOH) led to alcohol **4** which was eventually oxidized under Swern conditions to provide the corresponding aldehyde. The aldehyde was then treated with a THF solution of $LiCH_2P(O)(OMe)_2$ (prepared in situ from methyl dimethyl phosphonate, *n*-BuLi, THF, 0 °C)[16] to afford the β-hydroxyphosphonate intermediate. The latter was ultimately oxidized to the corresponding β-ketophos-

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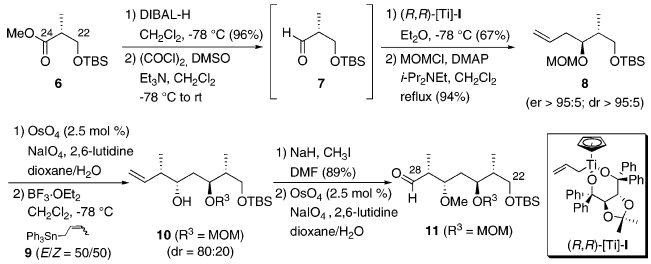
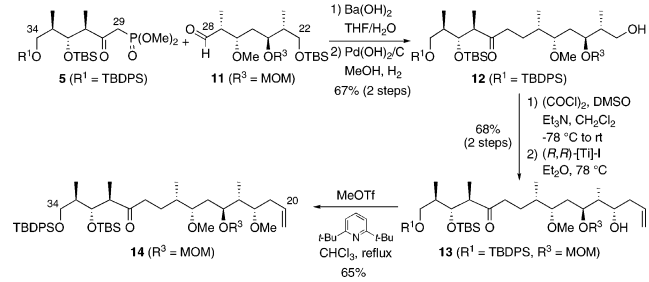
(15) The enantiomeric excess of **13** was measured by ^{1}H NMR of the corresponding mandelic ester, while the assignment of the absolute configuration was made by comparison with the $[\alpha]_D$ reported in the literature for the known compound ($[\alpha]^{20}_D$ −8.2, *c* 2.36, $CHCl_3$);^{exp} ($[\alpha]^{20}_D$ −8.6, *c* 2.37, $CHCl_3$)^{lit}.

Scheme 3. Synthesis of the C22−C28 Aldehyde **11**



Scheme 4. Synthesis of the CM Coupling Partner **14**



phonate **5** thus completing the synthesis of the C29−C34 subunit in nine steps and 40.3% overall yield starting from methacrolein **1** (Scheme 2).

The construction of the C22−C28 aldehyde subunit commenced from commercially available (*R*)-Roche ester and proceeded through an initial three-step sequence which included the protection of the primary alcohol as a TBS ether **6**, the reduction of the ester moiety, and the oxidation of the resulting alcohol to the corresponding aldehyde (Scheme 3). The latter was then subjected to a diastereoselective allylation using the (*R*,*R*)-[Ti]-**I** complex (THF, −78 °C)[17] to afford the corresponding homoallylic alcohol (64.3% yield from **6**, dr >95:5, er >95:5)[18,19] which was subsequently protected as a methoxymethyl ether (MOMCl, DMAP, *i*-PrNEt$_2$, CH_2Cl_2, reflux, 94% yield). Olefin **8** was then engaged in an OsO_4-catalyzed oxidative cleavage (OsO_4, $NaIO_4$, 2,6-lutidine, dioxane/H_2O),[20] and the resulting aldehyde was treated with (*E*/*Z*)-triphenyl crotylstannane **9**[21] under Keck's conditions[22] (BF_3•OEt_2, CH_2Cl_2, −78 °C) to effect a substrate-controlled diastereoselective crotylstannylation (83%, dr 80:20).[19,23,24] The resulting alcohol **10** was then converted to a methoxy ether (CH_3I, NaH, DMF, 89% yield) and the terminal olefin subjected to an OsO_4-catalyzed oxidative cleavage, thus completing the synthesis of the C22−C28 aldehyde subunit **11** in nine steps and 45.7% overall yield starting from the (*R*)-Roche ester.

With the two fragments **5** and **11** in hand, the stage was set for the key HWE olefination which would afford the C22−C34 polypropionate fragment of mycalolide A (Scheme 4). Hence, *β*-ketophosphonate **5** was treated with $Ba(OH)_2$•$8H_2O$[25] in wet THF (THF/H_2O = 40:1) followed by aldehyde **11** to provide the coupled product as a single (*E*)-isomer in 80% yield (Scheme 4). Reduction of the enone to the corresponding ketone using $Pd(OH)_2$/C in MeOH under a hydrogen atmosphere occurred with concomitant cleavage of the C22 primary TBS ether[26] thus affording alcohol **12** in 85% yield. Swern oxidation to the corresponding aldehyde and treatment with the (*R*,*R*)-[Ti]-**I** complex (Et_2O, −78 °C) installed the (22*S*) stereogenic center and provided homoallylic alcohol **13** as a single stereoisomer in 68% yield over two steps (dr >95:5).[27] As an attempt to methylate the C22 hydroxyl group using NaH/MeI had caused epimerization at C31, milder conditions were applied. To our delight, exposure of **13** to MeOTf and 2,6-di-*tert*-butylpyridine in refluxing $CHCl_3$ produced the desired methylated product **14** as a single stereoisomer in 65% yield (93% based on recovered starting material). The preparation of the C20−C34 polyketide fragment of mycalolide A was thus achieved in 14 steps and 13.2% overall yield starting from methacrolein **1**.

With the C20−C34 fragment secured, we next turned our attention toward the synthesis of the vinyl-functionalized bisoxazole subunit which would be engaged in the key CM (Scheme 5). Hence, treatment of acrylamide **15** and ethyl bromopyruvate **16** with $NaHCO_3$ (THF, 55 °C) followed by TFAA (THF, 0 °C) and saponification of the resulting ester using LiOH•H_2O in a THF/H_2O mixture afforded carboxylic acid **17** in 72% yield over three steps. The latter was then coupled with (±)-serine methyl ester hydrochloride using standard conditions (EDC, HOBt, NMM, CH_2Cl_2)[28] to afford *β*-hydroxy amide **18** (72% yield) which in turn was engaged

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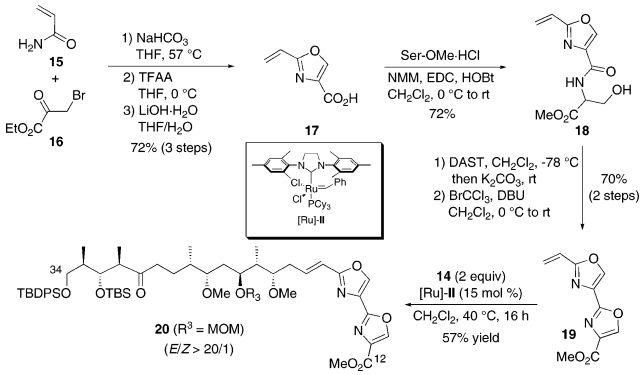
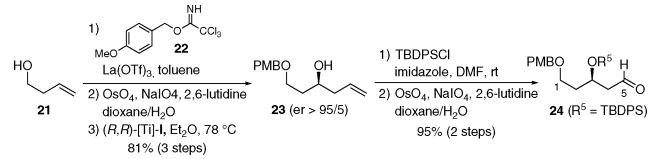
(27) The absolute configuration of the C22 stereogenic center was determined as (22*S*) by ^{1}H NMR analysis of the corresponding (*R*)- and (*S*)-mandelic esters.

Scheme 5. Synthesis of the C12−C34 Fragment **20**



Scheme 6. Synthesis of the C1−C5 Fragment **24**

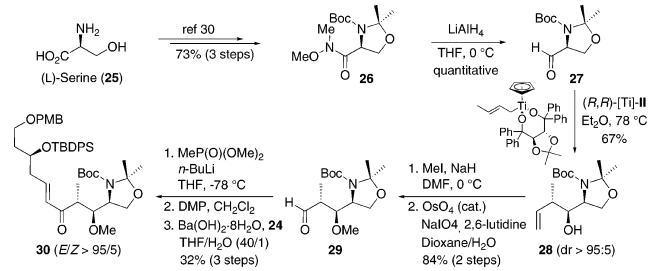


in a sequential DAST-mediated cyclodehydration (CH_2Cl_2, −78 °C)/dehydrobromination ($BrCCl_3$, DBU, CH_2Cl_2, 0 °C) that led to the desired bisoxazole **19** in 70% yield over two steps. The C20−C34 polyketide fragment **14** and bisoxazole **19** were then coupled using Grubbs second-generation catalyst, [Ru]-**II** (CH_2Cl_2, 40 °C, 16 h), to afford the C12−C34 fragment of mycalolide A **20** in a moderate 57% yield and an excellent *E*-stereoselectivity (*E*/*Z* > 20:1).

The synthesis of the C1−C11 fragment of mycalolide A relied on a HWE between a C1−C5 aldehyde of type **VI** and a C6−C11 β-ketophosphonate of type **VII**. The former was prepared starting from 3-buten-1-ol (**21**) (Scheme 6). Hence, **21** was first converted into the corresponding *para*-methoxybenzyl ether using trichloroacetimidate **22** in the presence of a catalytic amount of $La(OTf)_3$ (toluene, rt, 95% yield). An OsO_4-catalyzed oxidative cleavage then afforded the corresponding aldehyde[19] which was subsequently treated with the (*R*,*R*)-[Ti]-**II** complex to provide homoallylic alcohol **23** in 85% yield over two steps (er >95:5).[29] The latter was then protected as a TBS ether, and the terminal olefin was finally oxidatively cleaved to unveil the desired aldehyde **24** in 95% yield over two steps.

The synthesis of the C6−C11 β-ketophosphonate, on the other hand, began with the preparation of the Weinreb amid **26** starting from L-serine **25** according to a reported procedure[30] (73% over three steps) (Scheme 7). Weinreb amide **26** was then reduced to the corresponding aldehyde **27** using $LiAlH_4$ (THF, 0 °C, quantitative) and immediately engaged in a diastereoselective crotyltitanation using the (*R*,*R*)-[Ti]-**II** complex (Et_2O, −78 °C) to afford the corresponding homoallylic alcohol **28** in decent yield and excellent selectivity (67% yield, dr >95:5). Methyl ether formation (MeI, NaH, DMF, 0 °C) followed by OsO_4-catalyzed oxidative cleavage of the terminal olefin then furnished aldehyde **29** in 84% yield over two steps. Immediate treatment with $LiCH_2P(O)(OMe)_2$ ($MeP(O)(OMe)_2$, *n*-BuLi, THF, 0 °C) followed by a Dess−Martin periodinane (DMP)-mediated oxidation of the resulting β-hydroxyphosphonate then supplied the desired β-ketophosphonate in 46% yield. A $Ba(OH)_2$-mediated HWE olefination between the C1−C5 aldehyde and the C6−C11 β-ketophosphonate finally afforded the desired C1−C11 fragment of mycalolide A, compound **30**, in 69% yield (*E*/*Z* > 95:5). This sequence was thus carried out in 10 steps and 13.1% overall yield starting from (L)-serine **25**.

Scheme 7. Synthesis of the C1−C11 Fragment **30**



In conclusion, we have completed the synthesis of the C1−C11 and C12−C34 fragments of mycalolide A. The synthesis includes a highly *E*-selective cross-metathesis between a vinyl-functionalized bis-oxazole unit and a polypropionate side chain to introduce the C19−C20 double bond, an enzymatic desymmetrization of a *meso*-diol to control the three stereogenic centers at C31, C32, and C33, and five stereoselective allylations/crotylations to control the stereogenic centers at C3, C8, C9, C22, C24, C26, and C27. Future efforts will be dedicated in coupling the two fragments together, performing the Robinson−Gabriel-type cyclodehydration to form the macrolide and introducing the enamide moiety through a Wittig olefination to complete the synthesis. These efforts will be reported in due course.

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Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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