Total Synthesis of (−)-Mycalolide A

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In 1989 Fusetani and co-workers reported the isolation and planar structure of (−)-mycalolide A (**1**), a new secondary metabolite produced by a sponge of the genus *mycale* sp.[1] This macrolide belongs to a unique class of tris-oxazole containing natural products including ulapulides,[2] halichondramides,[3] and kabiramides,[4] which display a range of potent biological activities. Foremost among these is mycalolide A, which exhibits potent antifungal activity against a wide array of pathogenic fungi and cytotoxicity toward B-16 melanoma cells with IC_{50} values of 0.5−1.0 ng/mL.[1] Mycalolide A also specifically inhibits the actomyosin Mg^{2+}-ATPase,[5] and serves as a novel actin depolymerizing agent which may find eventual applications in the pharmacological area for probing actin-mediated cell functions.[6] Recently we have established the relative and absolute stereochemistry of the mycalolides through a combination of chemical degradation, extensive ^1H and ^{13}C NMR analysis, and structural correlation experiments.[7] The unique structural features of these tris-oxazole containing macrolides have provided the motivation for the development of synthetic strategies toward these natural products.[8] In this communication, we report the first total synthesis of (−)-mycalolide A (**1**), which also confirms the relative and absolute stereochemical assignment of this natural product.[9]

In planning our synthesis of mycalolide A, convergency was of course an essential component. Our second consideration was to extend the utility of chiral silane reagents in the area of acyclic stereocontrol, and to integrate the use of asymmetric catalysis with stoichiometric processes in assembling complex molecules. Retrosynthetic analysis of **1** led to fragments **2** and **3** through cleavage of the macrolide linkage and the C19−C20 olefin bond (Figure 1). In the synthetic direction, union of **2** and **3** via a Schlosser−Wittig reaction[10] would be followed by macrocyclization. Further disconnection of **2** at the C6−C7 σ bond produced

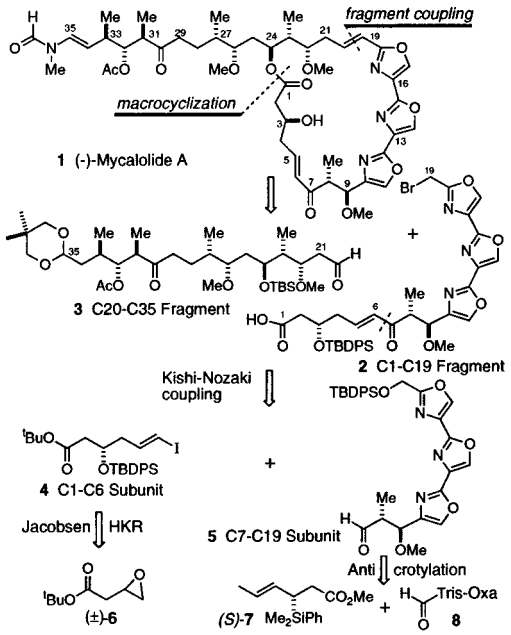

Figure 1. Retrosynthetic analysis of mycalolide A (**1**).

subunits **4** and **5**, which served as our initial targets. It was envisioned that the stereogenic center of **4** could be accessed by a hydrolytic kinetic resolution (HKR) of terminal epoxide **6**,[11] and the anti stereochemical relationship at the C8 and C9 in **5** would be established utilizing our chiral silane methodology.[12]

Synthesis of subunit **4** (Scheme 1), was initiated by HKR of the racemic epoxide **6**.[13] Thus, (±)-**6** was subjected to the resolution conditions as described by Jacobsen and co-workers,[11] providing (*R*)-**6** of 99% ee in 94% yield.[14] Nucleophilic epoxide ring opening using higher order cuprate **9**,[15] followed by stannane−iodine exchange and protection of the hydroxyl as its TBDPS ether, furnished **4** in four steps (64% overall).

Construction of subunit **5** and introduction of the C8−C9 stereocenters (Scheme 2) required an anti selective crotylation with the tris-oxazole aldehyde **8**.[8f] In the presence of the bidentate Lewis acid $TiCl_4$, the condensation between (*S*)-**7** and **8** provided homoallylic alcohol **12** in 65% yield with high diastereoselectivity (anti/syn > 30:1). This condensation proceeded presumably through a synclinal transition state, where $TiCl_4$ simultaneously coordinates to the aldehyde carbonyl and the oxazole nitrogen to form a five-membered chelate, forcing a turnover of the transition state-controlled π-facial discrimination to deliver high anti selectivity.[16] Methylation of alcohol **12** (Ag_2O/MeI), dihydroxylation of olefin **13** (OsO_4/TMANO), and cleavage of the resulting diol ($Pb(OAc)_4$) completed the preparation of **5**.

The assembly of **2** was accomplished by a Kishi−Nozaki coupling[17] between **4** and **5** (Scheme 3). Treatment of **4** and **5** with $NiCl_2$−$CrCl_2$ in THF/DMF at RT afforded allylic alcohol **14** in 80% yield, as a 1:1 mixture of the stereoisomers. This material was subjected to Dess−Martin[18] oxidation to provide enone **15** quantitatively. Selective deprotection of the primary

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(13) Racemic **6** was prepared by epoxidation of *tert*-butyl vinyl acetate with *m*-CPBA, which was in turn prepared according to the procedure in: Ozeki, T.; Kusaka, M. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 1995−1998.

(14) The kinetic resolution yield is expressed as a percentage of the theoretical maximum yield of 50%; the ee was determined by HPLC analysis of the phenylthio derivatives of **6** with a Chiracel OD column.

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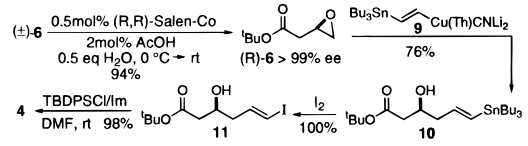
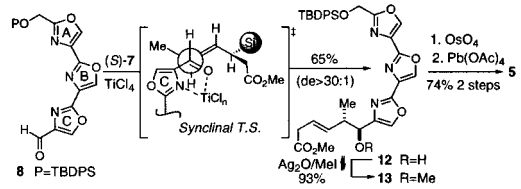
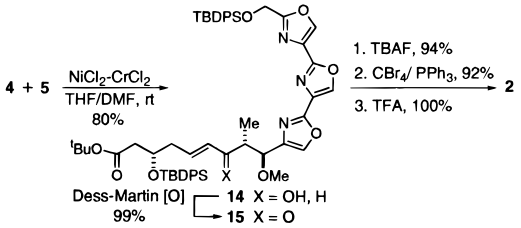
Scheme 1



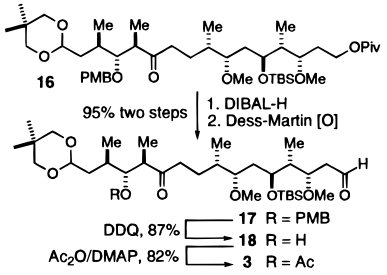
Scheme 2



Scheme 3



Scheme 4

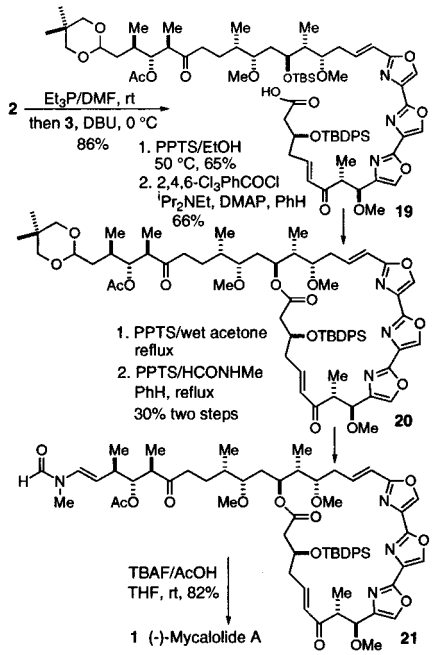


TBDPS ether with $^{n}Bu_4NF$ followed by conversion of the resulting alcohol to the benzylic bromide (CBr_4/PPh_3) and hydrolysis of the *tert*-butyl ester with TFA, completed the synthesis of fragment **2**.

At this stage, **3** was prepared for coupling, which necessitated a four-step sequence (Scheme 4) beginning with intermediate **16**.[7] Removal of the pivalate group (DIBAL-H) also effected the reduction of the ketone to yield a 3:2 mixture of the epimeric alcohols, which without separation, was subjected to a Dess−Martin oxidation[18] to provide keto aldehyde **17** in 95% yield (two steps). Completion of fragment **3** was achieved by deprotection of the PMB group using DDQ and installation of an acetyl group at C-32 hydroxyl, which is required in the natural product.

With sufficient quantities of fragments **2** and **3** available, execution of the Schlosser−Wittig[10] coupling would construct the C19−C20 trans olefin and set the stage for macrocyclization (Scheme 5). The task of achieving a union between these

Scheme 5



fragments using a phosphorus-based olefination was not at first regarded as a difficult one, given the precedence set by Armstrong[19] and Evans,[20] who successfully constructed an (*E*)-olefinated mono-oxazole in their calyculin syntheses. We had also established precedence in model studies of the construction of the tris-oxazole (*E*)-olefin by a similar protocol.[8g] However, the olefination between **2** and **3** proved to be challenging. Conventional bases such as LDA, KHMDS, and KO^{t}Bu with different solvent systems failed to deliver a useful yield of the desired product. Further experiments with hindered amine bases were carried out to circumvent this problem. Gratifyingly, when aldehyde **3** and the in situ generated Wittig salt derived from **2** were treated with DBU at 0 °C, the desired product **19** was formed as a single olefin isomer in 86% yield. After removal of the TBS group (PPTS/EtOH, 65%), the resulting seco acid was subjected to Yamaguchi conditions,[21] providing macrocycle **20** in 66% yield.

Completion of the synthesis of mycalolide A would now require the installation of the terminal *N*-methyl formamide and removal of the TBDPS hydroxyl protecting group at C3. The former was accomplished by hydrolysis of the acetal (PPTS/wet acetone, reflux), followed by vinyl formamide formation (PPTS/HCONHMe),[8a] while the deprotection step proceeded smoothly with TBAF/AcOH.[22] The synthetic **1** and natural **1** are identical in all aspects including ^{1}H NMR, ^{13}C NMR, IR, $[\alpha]_D$, and TLC Rf values in three different solvent systems.

The first total synthesis of (−)-mycalolide A has been achieved employing a highly convergent and stereocontrolled strategy. The synthesis serves to confirm the relative and absolute stereochemistry,[7] as well as illustrate the application of two complementary chemical processes in the field of asymmetric synthesis, HKR, and chiral silane based methodology for the synthesis of complex molecules.

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Supporting Information Available: Experimental procedures, physical and spectral data for all new compounds; photocopies of ^{1}H NMR and ^{13}C NMR spectra of synthetic **1**, comparison of ^{1}H NMR spectra between synthetic **1** and natural **1** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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