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Enantioselective Synthesis of the C1–C6 and C7–C23 Fragments of the Proposed Structure of Iriomoteolide 1a

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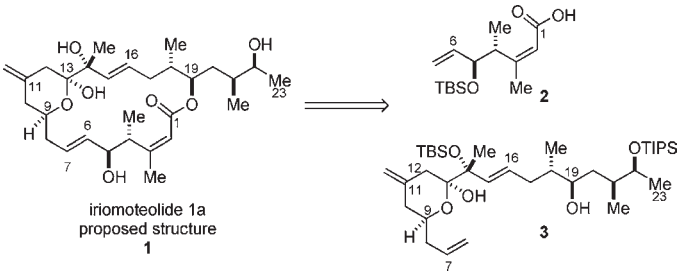
ABSTRACT



Synthesis of the C1–C6 and C7–C23 fragments of the proposed structure of iriomoteolide 1a has been accomplished. Key steps include a cross metathesis to form the C15–C16 *E* olefin and a chelation controlled Grignard addition to form the tertiary alcohol at C14. Notably, 7 of the 9 stereocenters of the proposed structure have been set using various aldol reactions employing metallo enolates of thiazolidinethiones.

In 2007, Tsuda and co-workers isolated a novel macrolide from the dinoflagellate *sp. Amphdinium* strain HYA024, identified as iriomoteolide 1a (**1**).[1] The natural product exhibits potent cytotoxicity against the human B lymphocyte DG-75 cells (IC_{50} = 0.002 mg/mL), which is 20 times more potent than doxorubicin (IC_{50} = 0.04 mg/mL), a common chemotherapy agent.[1] Additionally, iriomoteolide 1a also displays activity against Epstein–Barr virus (EBV) infected human B-lymphocyte Raji cells (IC_{50} = 0.003 mg/mL).[1] Because of the attractive biological profile and the unique structural attributes of iriomoteolide 1a, several laboratories have undertaken the total synthesis of **1**. The groups of Loh,[2] Paterson,[3] Zhao,[4] Li,[5] and Dai[6] have reported creative approaches to complex fragments of **1**, while Horne,[7] Ghosh,[8] and Yang[9] have completed the total synthesis of macrolactone **1**. During the course of their synthetic studies, Horne,[7] Ghosh,[8] and Yang[9] independently ascertained that the proposed structure of iriomoteolide 1a had been misassigned (Figure 1).

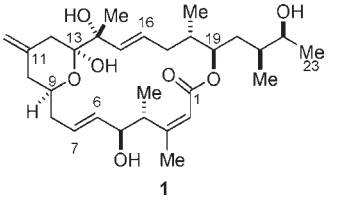


Figure 1. Iriomoteolide 1a proposed structure.

Our interest in the total synthesis of iriomoteolide 1a stems from the inherent ability of the thiazolidinethione chiral auxiliary to access all possible polyketide subunits using simple variations of aldol reaction conditions. Once a

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convergent route to the proposed structure is developed, appropriate diastereomers can be rapidly prepared in a highly convergent fashion in an effort to elucidate the actual structure of the natural product. The retrosynthetic analysis is shown in Figure 2. It was envisioned that iriomoteolide 1a would arise via a late stage Yamaguchi esterification[10] between acid **2** and secondary alcohol **3** followed by a ring closing metathesis to construct the C6–C7 alkene and install the macrocyclic ring of **1**. A cross metathesis of enone **4** with PMB ether **5** would form the C15–C16 *E* olefin, while a nonselective aldol between a C12–C23 methyl ketone and aldehyde **6** would assemble the C11–C12 bond.

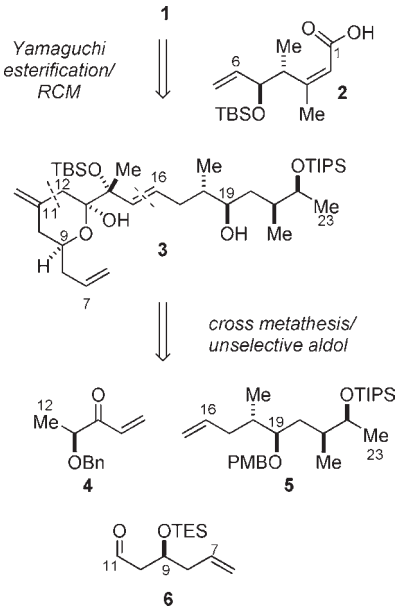


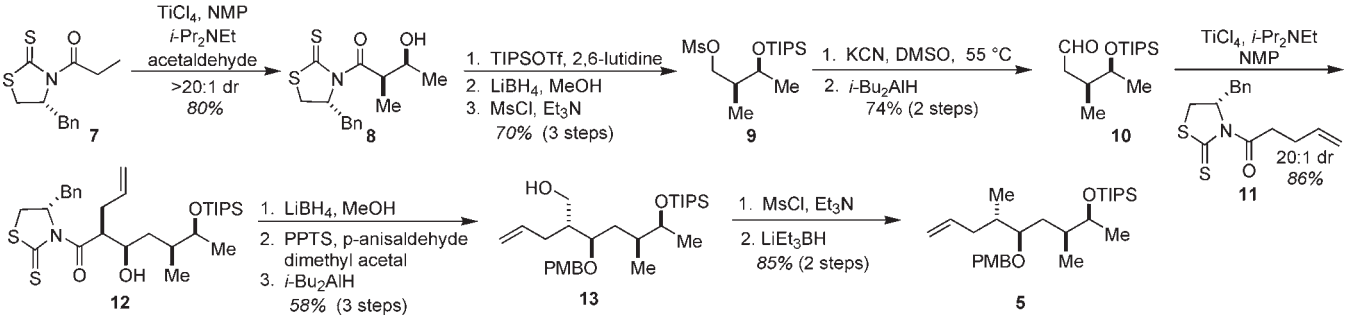
Figure 2. Retrosynthetic analysis of iriomoteolide 1a.

Preparation of the C16–C23 PMB ether **5** commenced with an Evans *syn* aldol with thioimide **7** and acetaldehyde to provide the secondary alcohol **8** in 80% yield and 20:1 dr (Scheme 1).[11] Protection of the secondary alcohol as the TIPS ether and cleavage of the chiral auxiliary delivered a primary alcohol, which underwent a one-carbon homologation by first transforming the primary alcohol into mesylate **9** followed by stirring with KCN. Isolation of the nitrile proved difficult, so the crude mixture was reduced directly with *i*-Bu_2AlH, to provide aldehyde **10**. Aldehyde **10** was then subjected to a second Evans *syn* aldol with thioimide **11**, generating secondary alcohol **12** in 86% yield and >20:1 dr.[12] Reductive cleavage of the chiral auxiliary with $LiBH_4$ provided a diol, which cleanly underwent an acetal formation–reduction sequence to regioselectively mask the secondary alcohol as PMB ether **13**. Exposure of the resultant primary alcohol to mesyl chloride followed by $LiEt_3BH$ reduction generated PMB ether **5** in 12 steps and 18% overall yield.

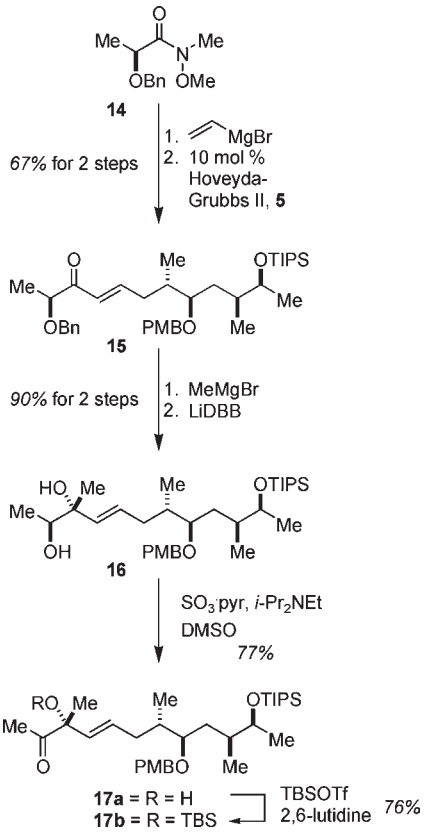
The C12–C15 fragment was synthesized beginning with commercially available (*S*)-ethyl lactate, which was transformed in two steps via a known procedure to the benzyl protected Weinreb amide **14** (Scheme 2).[13] Exposure of Weinreb amide **14** to excess vinyl Grignard reagent provided **4** (Figure 2), which was utilized in a cross metathesis with PMB ether **5** to deliver exclusive formation of the *E* isomer **15** in 67% yield over two steps. A chelation-controlled addition of methyl magnesium bromide to ketone **15** provided the tertiary alcohol **16** as the only detectable diastereomer after reductive cleavage of the benzyl ether with lithium 4,4-di-*t*ert-butylbiphenylide (LDBB).[14] Oxidation of the secondary alcohol to the ketone under Parikh–Doering conditions[15] produced the ketone **17a**. Protection of the tertiary alcohol as its TBS ether provided the C12–C23 fragment **17b**. The stereochemistry of the tertiary alcohol at C14 was deduced by forming the five-membered acetonide **18** from diol **16** (Scheme 3). The C14 stereochemistry was assigned as (*R*) based on observed NOESY correlation between the C13 hydrogen and C14 methyl group as well as the C15 hydrogen and C13 methyl group.

With ketone fragment **17a** in hand, attention turned to the preparation of aldehyde **6**. Beginning with an acetate aldol utilizing mesityl substituted thiazolidinethione **19**[16] and 3-butenal,[17] secondary alcohol **20** was generated in 70% yield and >20:1 dr (Scheme 4). Protection of the resulting secondary alcohol as the TES ether and reductive cleavage of the chiral auxiliary furnished aldehyde **6**. A nonselective aldol between ketone **17a** and aldehyde **6**

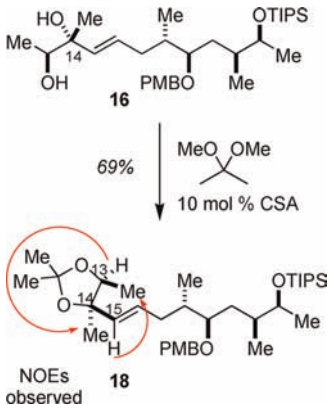
Scheme 1. Preparation of the C_{16}–C_{23} Fragment of Iriomoteolide 1a



Scheme 2. Synthesis of the $C_{12}-C_{23}$ Fragment **17**



Scheme 3. Stereochemical Proof for the Absolute Stereochemistry of the C_{14} Tertiary Alcohol



delivered the secondary alcohol as an inconsequential ca. 1:1 mixture of diastereomers at C11.

Cleavage of the TES ether and spontaneous ketalization to form a mixed methyl ketal was accomplished under mild conditions utilizing catalytic triphenyl phosphonium hydrobromide salt to deliver an unstable mixed methyl ketal.[18] The resultant alcohol was used directly in the subsequent Ley oxidation[19] to afford ketone **21**. The C11 exocyclic methylene proved challenging to install: attempts to install the C11 exocyclic olefin under standard methylenation conditions (Wittig, Tebbe,[20] Tour,[21] Takai–Nozaki[22]) in the presence of the free tertiary alcohol at C14 (**21**) resulted in either elimination or no reaction, likely due to the presence of the free alcohol at C14. Attempts to protect the free alcohol of **21** directly with TESOTf, TMSOTf, or TMSCl resulted in formation of the C11 mixed silyl ketal, wherein the silyl triflate or silyl chloride behaved as Lewis acids due to the crowded steric environment, rather than silylating agents as in similar systems.[23] Fortunately, the C14 tertiary alcohol of **17a** could be protected as the TBS ether prior to the aldol addition to form **17b**. Aldol reaction of ketone **17b** and aldehyde **6** followed by treatment as before generated mixed ketal **22**. The exocyclic methylene was then successfully installed in 77% yield employing the Tebbe reagent.[20] Cleavage of the PMB ether was accomplished with DDQ, which also cleaved the mixed methyl ketal to deliver hemiketal **3**.

Synthesis of the C1–C6 fragment **2** began with a known Evans *anti* aldol with thioimide **23** and cinnamaldehyde[24] followed by a Hoveyda–Grubbs catalyzed ethylene cross metathesis to install terminal olefin **24** (Scheme 5). Protection of the secondary alcohol as the TBS ether and cleavage of the chiral auxiliary afforded aldehyde **25**, which was subjected to a Corey–Fuchs homologation[25] to deliver ynoate **26**. Methyl cuprate addition was used to form enoate **27**, and the olefin geometry was confirmed by observed NOESY correlations between the C2 hydrogen and C3 methyl group. Cleavage of the methyl ester to the acid was accomplished with LiOH and MeOH to provide

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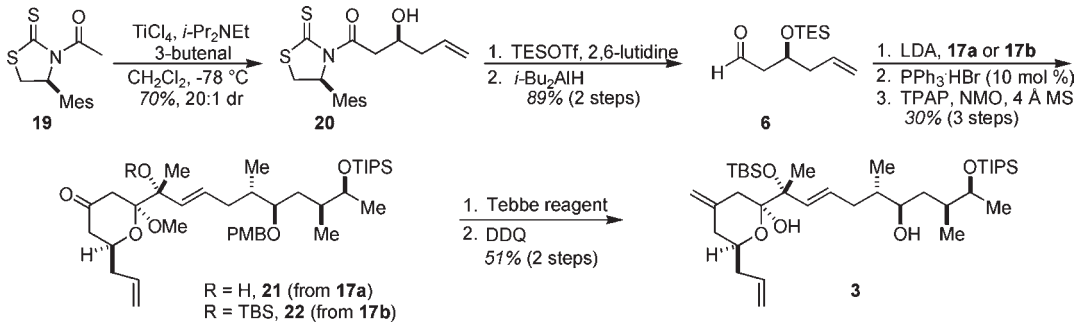
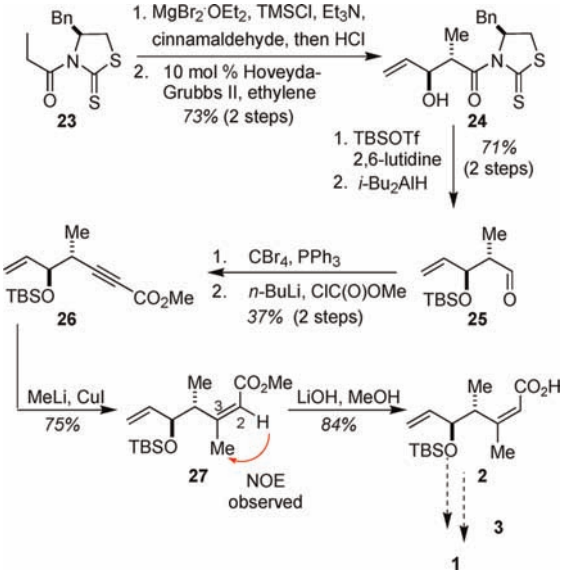
Scheme 4. Preparation of the C_7–C_{23} Fragment **3**



Scheme 5. Preparation of the C_1–C_6 Fragment **2** and Proposed Completion of **1**



acid **2** in 63% yield over two steps. Completion of the synthesis of **1** would require esterification of acid **2** with alcohol **3** and deprotection of the silyl ethers followed by RCM to generate the proposed structure of iriomoteolide 1a, in a similar strategy to that employed by Horne.[7]

In summary, a concise and convergent approach to the proposed structure of iriomoteolide 1a has been developed. Key steps include a cross metathesis to form the C15–C16 bond and an acetate aldol to form the C21–C22 bond. The thiazolidinethione chiral auxiliary was exploited to create seven of the nine stereocenters of iriomoteolide 1a through various aldol additions. Importantly, simple changes in the reagents utilized in these aldol additions can facilitate access to other possible stereoisomers. Since the proposed structure of the natural product has been incorrectly assigned, our current efforts are directed toward utilizing our approach to prepare diastereomers of the reported structure in an effort to elucidate the correct structure of the natural product.

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

The authors declare no competing financial interest.