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Asymmetric Synthesis of the C(7)−C(23) Fragment of Iriomoteolide-1a

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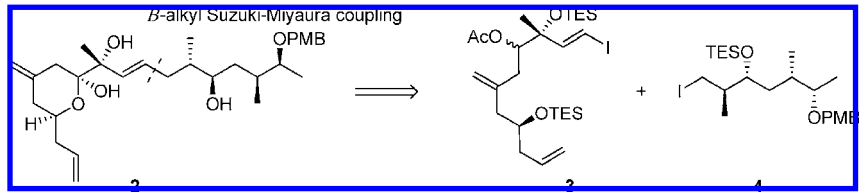
ABSTRACT



An efficient synthesis of the C(7)−C(23) fragment 2 of iriomoteolide-1a (1) has been accomplished via a *B*-alkyl Suzuki−Miyaura cross-coupling reaction followed by deprotection and cyclization to form the cyclic hemiketal core.

Iriomoteolide-1a (**1**) is a potent cytotoxic 20-membered ring macrolide isolated from the *Amphidinium* sp. strain HYA024. The structure of **1** was elucidated by Tsuda's group in 2007.[1] IC_{50} values for **1** against human B lymphocyte DG-75 cells and Epstein−Barr virus infected human B lymphocytes (Raji cells) are an impressive 2 and 3 ng/mL, repectively. Structurally, iriomoteolide-1a contains several unique structural features. Among them is the cyclic hemiketal core that bears an exocyclic methylene unit. Appended to this core is the C(14)−C(23) fragment that is composed of a chiral tertiary allylic alcohol side chain. This side chain is further asymmetrically juxtaposed with two different sets of methyl and alcohol groups. Herein, we describe an efficient asymmetric approach to construct the entire C(7)−C(23) fragment of iriomoteolide-1a, which includes the cyclic hemiketal core.

Thus far, the total synthesis of irimoteolide-1a has not been reported, but several laboratories have completed the synthesis of various fragments. Yang's group[2a] and Ghosh's group[2b] have reported the synthesis of fragment C(1)−C(12) of iriomoteolide-1a. Recently, our group[2c] described the synthesis of the hemiketal core of iriomoteolide-1a. Finally,

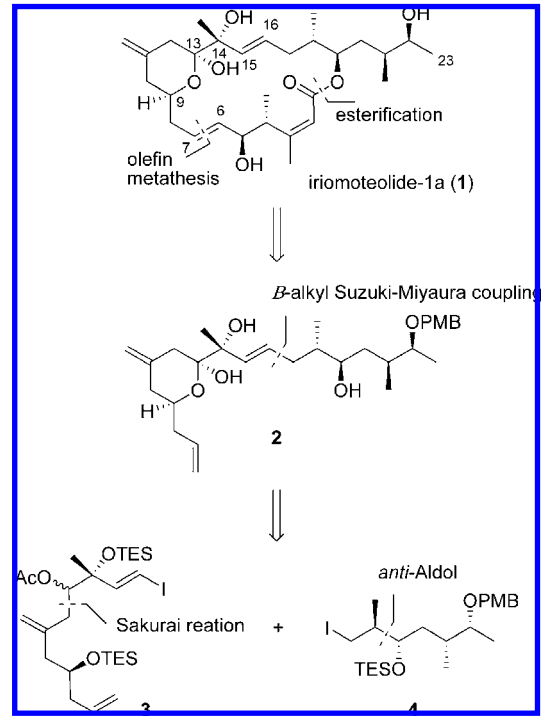


Figure 1. Retrosythetic analysis of iriomoteolide-1a.

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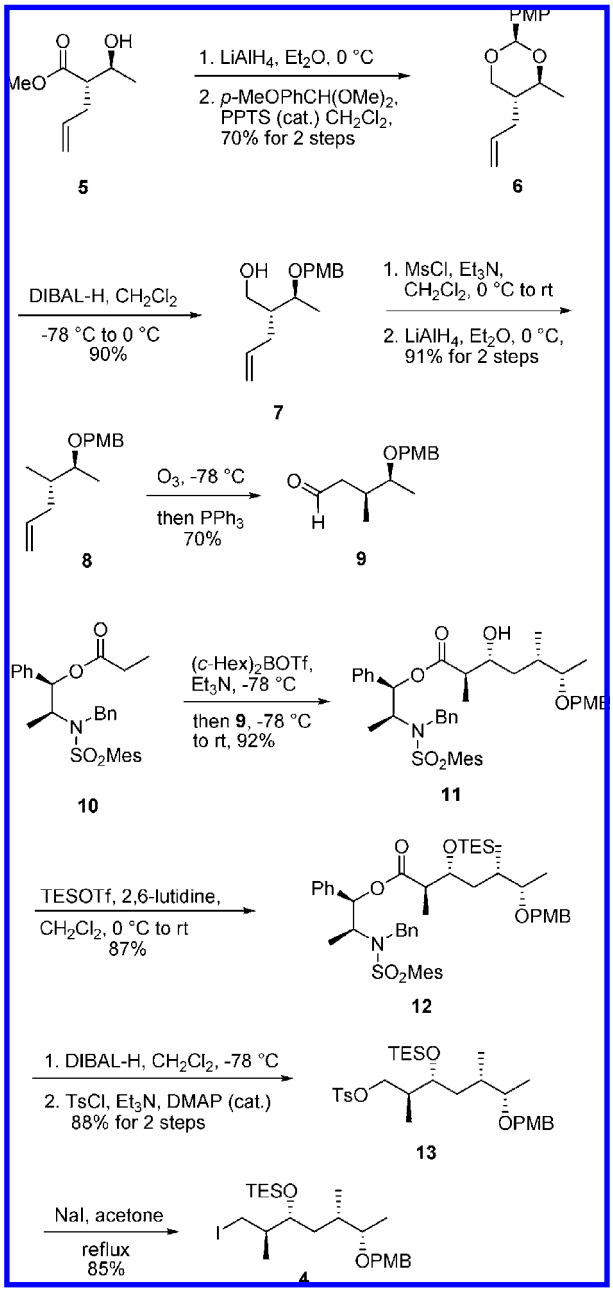
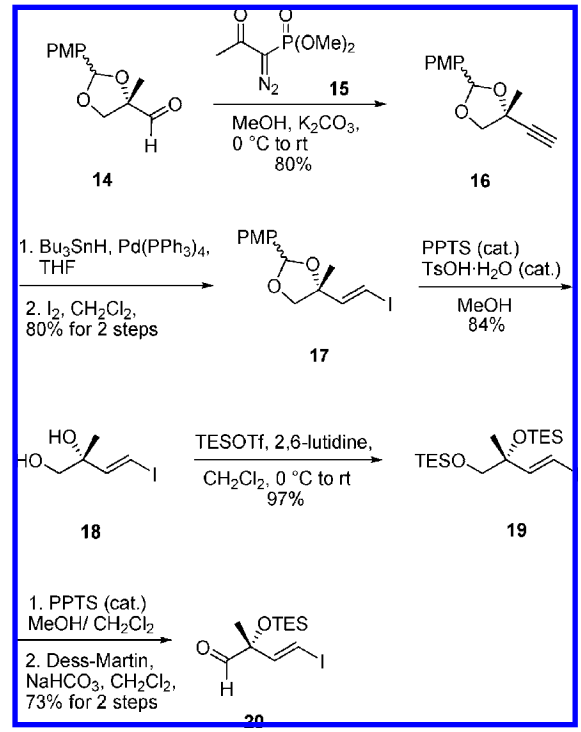
Scheme 1. Synthesis of **4**



Scheme 2. Synthesis of **20**



Loh's group[2d] recently reported the synthesis of the C(13)−C(23) fragment.

The retrosynthetic strategy for iriomoteolide-1a is shown in Figure 1. The final assembly of **1** consists of combining fragment C(1)−C(6) to the relatively large C(7)−C(23) fragment **2**. The C(7)−C(23) fragment can be further dissected into smaller subunits **3** and **4**, which can be joined by a *B*-alkyl Suzuki−Miyaura cross-coupling reaction.[3] Vinyl and alkyl iodides **3** and **4** are approached using Sakurai and *anti*-aldol reactions, respectively.

Starting from (3*S*)-methyl hydroxybutyrate, allylation provided **5** in good yield with high dr.[4] Reduction of **5** with $LiAlH_4$ followed by treatment with 4-methoxybenzaldehyde dimethyl acetal afforded acetal **6**. Selective reduction with DIBAL-H generated primary alcohol **7**, which was converted to **8** via mesylation and reduction. Ozonolysis of the terminal alkene provided aldehyde **9**. In the presence of **10** and $(c\text{-Hex})_2BOTf$ the *anti*-aldol product, **11**, was obtained in excellent yield and good dr.[5] The newly formed secondary alcohol was protected as its TES ether. DIBAL-H reduction of **12** yielded the corrseponding primary alcohol, but because of difficulties in separation of the desired product from the chiral auxiliary, the crude mixture was treated with excess TsCl. This afforded tosylate **13** in pure form and excellent yield as well as recovery of the chiral auxiliary after purification by chromatography. Displacement of tosylate **13** with iodide under Finkelstein conditions afforded the Suzuki−Miyaura coupling partner, **4**.

Our attention next turned to the preparation of Suzuki−Miyaura coupling partner **3**, which began with aldehyde **14**.[2c] Homologation of **14** with Bestmann−Ohira reagent **15**[6] produced alkyne **16**. Hydrohalogenation[7] of **16** by sequential treatment with tributyltin hydride in the presence of Pd-

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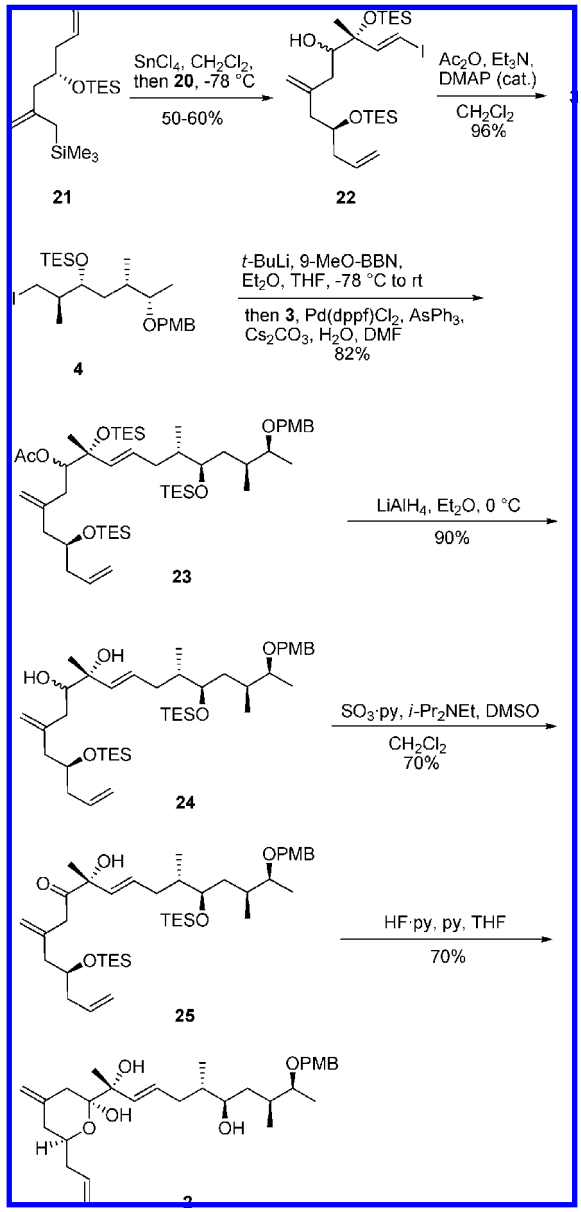
Scheme 3. Synthesis of **2**



$(PPh_3)_4$ followed by iodination afforded *E*-vinyl iodide **17**. Conversion of acetal **17** into bisTES ether **19** allowed for selective deprotection of the primary TES group and subsequent oxidation[8] to yield aldehyde **20**. This versatile intermediate respresents a key structural component to which the remainder of the fragment can be linked in a bidirectional manner.

Sakurai reaction[9] between aldehyde **20** and allylsilane **21**[2c] was initially attempted with $BF_3{\cdot}OEt_2$. Although these conditions were successfully adopted in our previous model system, only a trace amount of desired product **22** was observed. Fortunately, when $SnCl_4$ was used, product **22** was obtained in decent yield and 4:1 dr. The configuration of the newly formed chiral center was not determined at this time; however, a chelation-controlled addition product is anticipated. Note that the chirality at this center is lost in subsequent steps via oxidation to the ketone functionality. To prevent migration of the TES group in **22** during the Suzuki−Miyaura coupling, the alcohol moiety was protected as the corresponding acetate to furnish **3** in high overall efficiency.

With the two Suzuki−Miyaura coupling fragments in hand, vinyl iodide **3** and alkyl iodide **4** underwent smooth coupling[10] in excellent yield to afford the linear C(7)−C(23) fragment **23** of iriomoteolide-1a. Upon $LiAlH_4$ cleavage of the acetate functionality of **23**, concomitant deprotection of the vicinal tertiary TES group was observed, producing diol **24** in excellent yield. The secondary TES group was untouched during this process. Interestingly, this sequence may have general implications for the selective removal of TES groups over others that are not vicinal to acetates. Oxidation of diol **23** produced β,γ-unsaturated ketone **25**. Following conditions previously developed by our lab for cyclization to the hemiketal unit,[2c] treatment of **25** with HF·pyridine produced **2**. Under these conditions, double bond migration of the β,γ-unsaturated ketone to an α,β-unsaturated system was not observed.

In summary, an asymmetric synthesis of the C(7)−C(23) fragment of iriomoteolide-1a has been achieved in a relatively efficient manner using a *B*-alkyl Suzuki−Miyaura cross-coupling approach. This is the most advanced intermediate en route to the natural product to date. Pivotal to the synthesis is aldehyde **20**, which bears the requisite tertiary chiral center and vinyl iodide group and serves as a versatile intermediate to which the remaining structural components can be assembled in a bidirectional manner. The viability of a late stage hemiketal formation has also been demonstrated. With the construction of fragment **2**, efforts toward the completion of the natural product are currently ongoing.

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

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