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Synthesis of the Macrocyclic Core of Iriomoteolide 3a

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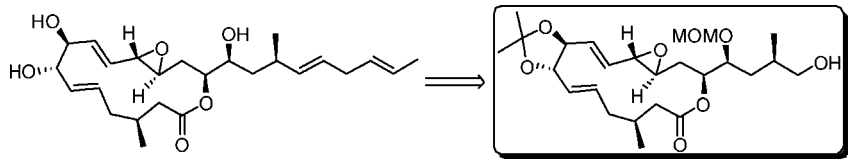
ABSTRACT



Iriomoteolide-3a

The asymmetric synthesis of the fully functionalized macrocyclic core of iriomoteolide 3a, a cytotoxic 15-membered macrolide, is disclosed. The key steps involve Sharpless asymmetric dihydroxylation, Sharpless asymmetric epoxidation, olefin cross-metathesis, Yamaguchi esterification, and a ring-closing metathesis reaction for macrocyclization.

Recently, Tusda and co-workers have reported the isolation of a cytotoxic macrolide iriomoteolide 3a (**1**, Figure 1) from a marine dinoflagellate *Amphidinium* sp. (strain HYA024), collected off the Iriomote Island of Japan.[1] Prior to isolation of this macrolide they have also found iriomoteolides 1a−c (20-membered macrolides) from the same strain.[2] However, iriomoteolide 3a is a 15-membered macrolide having an allylic epoxide, three hydroxyl groups, two methyl branches and with a new carbon skeleton compared to the known 15-membered macrolides.[3] Iriomoteolide 3a (**1**) and its 7,8-*O*-isopropylidene derivative (**2**) displayed a potent cytotoxicity against human B lymphocyte DG-75 cells (IC_{50} = 0.08 and 0.02 μg/mL, respectively) and Raji cells (IC_{50} = 0.05 and 0.02 μg/mL, respectively). The distinctive structural features and biological activities together with our interest on macrolides[4] have driven us to the synthesis of iriomoteolide 3a. Recently, various synthetic approaches toward the synthesis of iriomoteolide 1a have been reported.[5] The first total synthesis of iriomoteolide 3a has appeared while this paper was under review.[6] Herein, we report an asymmetric approach to the fully functionalized macrocyclic core of iriomoteolide 3a.

From a retrosynthetic perspective, we planned that the side chain installation onto macrocyclic core **3** would be the late stage reaction. The 15-membered macrolide **3** in turn can be achieved from two fragments, **4** and **5**, via esterification followed by a ring-closing metathesis reaction. The synthesis of fragment **4** was envisioned from a subunit **6**, using stereoselective methylation and Sharpless asymmetric epoxidation as the key steps. Further analysis of **5** revealed two subunits **7** and **8**, which could be coupled by olefin cross-

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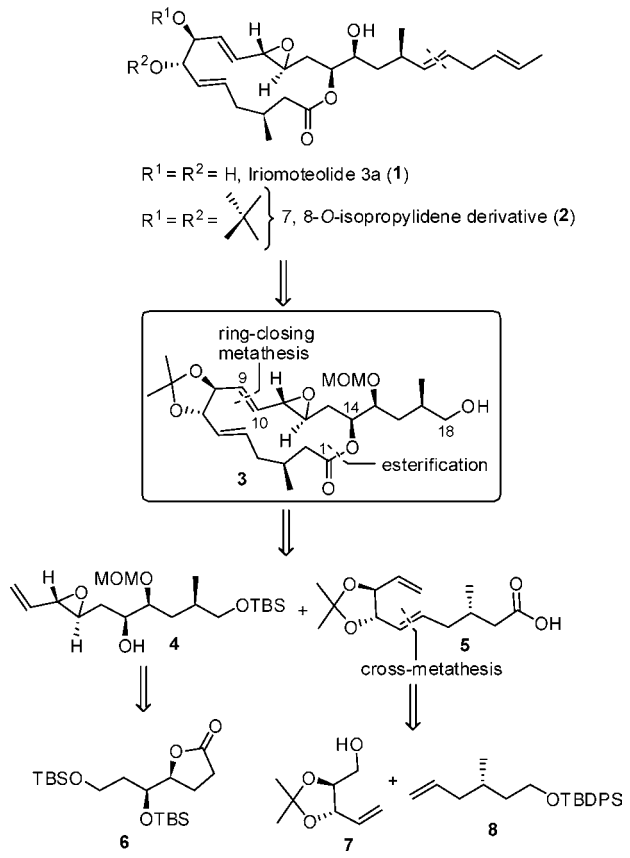
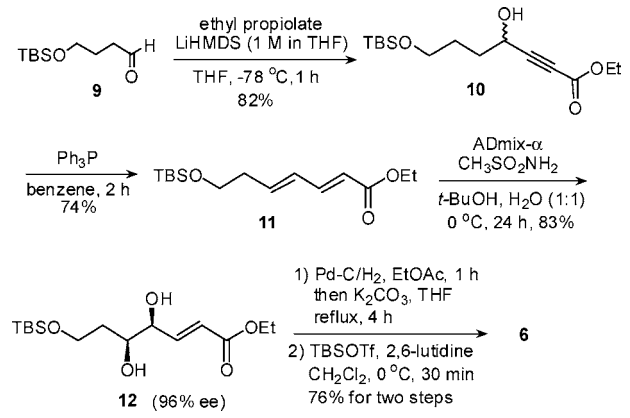


Figure 1. Structures of iriomoteolide 3a (**1**) and acetonide (**2**) and their retrosynthetic analysis.

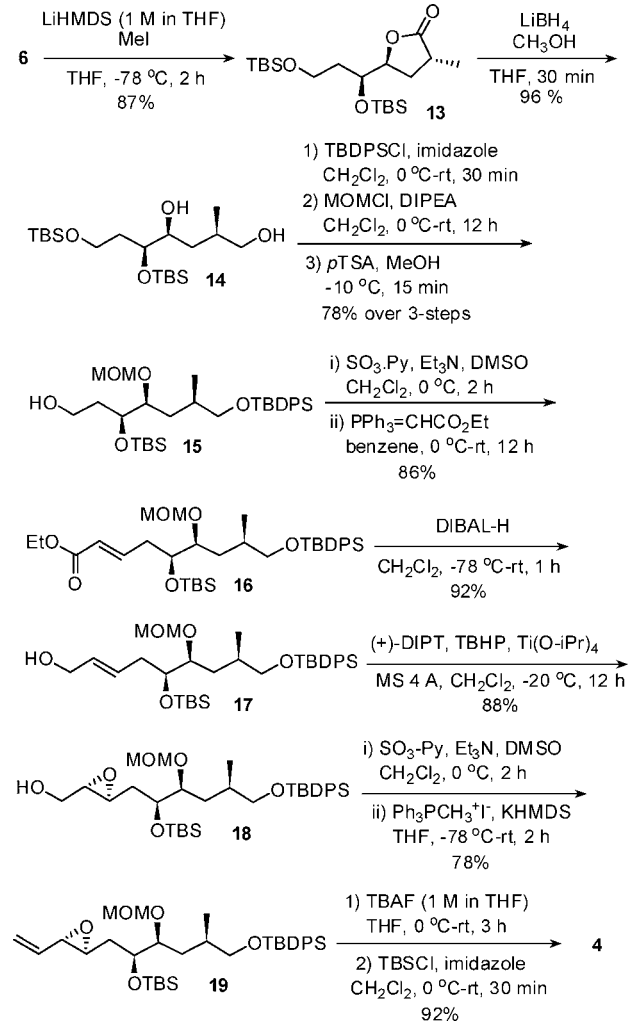
metathesis (Figure 1). The protective group in subunit **7** was chosen as ketal for vicinal 7,8-diol, which is based on the precedence that the isopropylidene derivative **2** showed activity comparable with that of the natural product.

Scheme 1. Synthesis of Fragment **6**



The synthesis of fragment **6** is outlined in Scheme 1. This was commenced from the known aldehyde **9**, derived from commercially available 1,4-butane diol using a two step sequence.[7] The addition of lithiated ethyl propiolate to aldehyde **9** provided the propargylic alcohol **10** (82%),[8] which underwent Ph_3P-mediated "allene"-type rearrangement to give (*E*,*E*)-diene **11** in 74% yield.[9] A stereo- and regioselective dihydroxylation of **11** was achieved via Sharpless asymmetric dihydroxylation, using ADmix-α to obtain diol **12** in 80% yield with 96% enantioselectivity.[10] Hydrogenation of **12** (Pd−C in EtOAc) followed by K_2CO_3-mediated cyclization[8b] and subsequent protection of the free secondary hydroxyl group as *tert*-butyldimethyl silyl (TBS) ether provided the fully protected lactone **6** in 76% yield for the two steps.

Scheme 2. Synthesis of Fragment **4**



The subunit **6** was transformed to the desired key fragment **4** as shown in Scheme 2. Initially, the introduction of the

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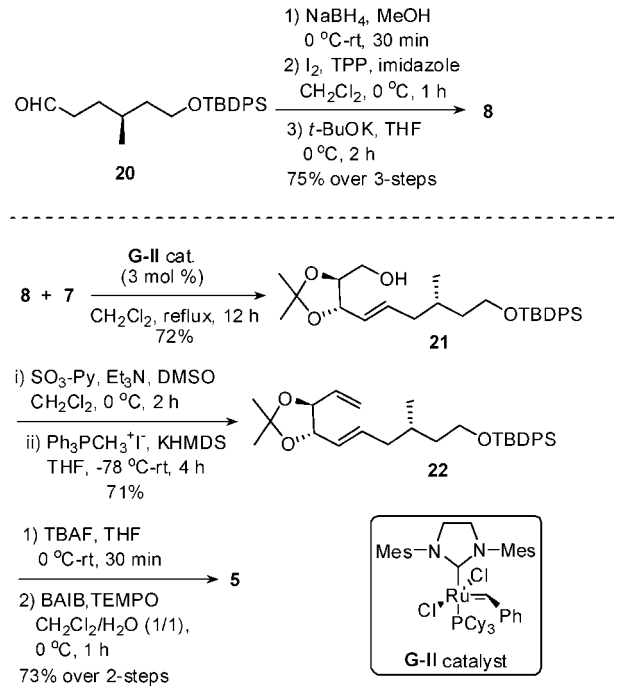
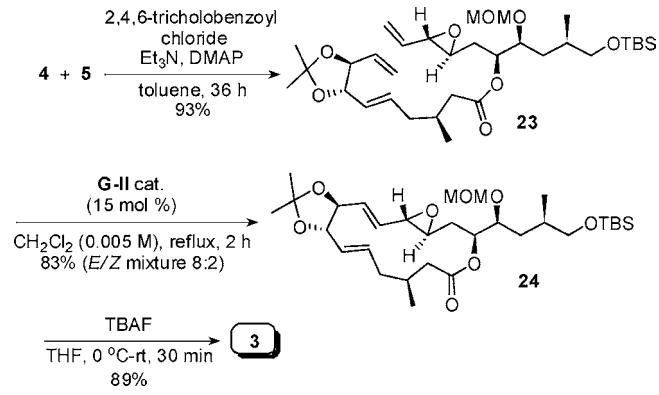
C-17 methyl stereocenter was accomplished through a stereoselective methylation of **6** with use of LiHMDS/MeI at −78 °C to afford exclusively **13** in 87% yield,[11] which was confirmed by NOE studies. The reduction of lactone **13** with $LiBH_4$ provided the diol **14** in 96% yield. A three-step protection−deprotection sequence involving selective protection of the primary hydroxyl group in **14** as *tert*-butyldiphenyl silyl (TBDPS) ether (imidazole, TBDPSCl), secondary hydroxyl as methoxy methyl (MOM) ether (DIPEA, MOMCl), and selective deprotection of primary TBS ether (*p*TSA, MeOH) produced the alcohol **15** in 78% yield over three steps. The free alcohol was then oxidized by using Parikh−Doering oxidation (SO_3•Py, DMSO)[12] to the corresponding aldehyde followed by a Wittig two-carbon homologation (Ph_3P=CHCOOEt) and gave α,β-unsaturated ester **16** (86%) as the (*E*)-isomer (>98%). The ester **16** was reduced with DIBAL-H at −78 °C to allylic alcohol **17** in 92% yield. The requisite chiral epoxide was introduced at this stage via a Sharpless asymmetric epoxidation reaction,[13] using (+)-diisopropylethyl tartrate to yield epoxide **18** in 88% with good stereoselectivity. The conversion of epoxy alcohol **18** to allylic epoxide **19** was accomplished via SO_3•Py mediated oxidation followed by one-carbon Wittig methylenation (78% yield over two steps). To make the epoxide **19** ready for the esterification reaction with fragment **5**, we needed to deprotect the TBS ether to obtain a free hydroxyl group. Consequently, we have chosen a two-step protecting group manipulation involving deprotection of both the silyl groups in **19** (TBAF) followed by selective protection of the resulting primary hydroxyl group as a TBS ether to produce fragment **4** in 92% yield.

The synthesis of fragment **5** started with the known aldehyde **20** (Scheme 3), derived from commercially available (*S*)-citronellol.[14] Sodium borohydride reduction of aldehyde **20** followed by the iodination of the resulting alcohol (I_2/Ph_3P) and subsequent elimination under *t*-BuOK conditions afforded the subunit **8** in 75% yield over three steps. At this point, compound **8** was coupled with the known fragment **7** (obtained from (+)-diethyl tartrate)[15] under olefin cross-metathesis conditions, using second generation Grubbs catalyst[16] to obtain the desired alkene **21** in 72% yield as the (*E*)-isomer (observed by ^{1}H NMR). Parikh−Doering oxidation of **21** followed by Wittig methylenation of the resulting aldehyde afforded the alkene **22** (71%). The conversion of alkene **22** to the desired fragment **5** was successfully accomplished by the deprotection of the TBDPS group with TBAF in THF followed by BAIB/TEMPO-mediated oxidation[17] of the resulting alcohol to carboxylic acid in 73% yield over two steps.

Scheme 3. Synthesis of Fragment **5**



Scheme 4. Construction of Macrocycle **3**



Having both the desired fragments **4** and **5** in hand, we turned to fasten these together to obtain the 15-membered macrocycle **3** (Scheme 4). Thus, the esterification of alcohol **4** with carboxylic acid **5** was carried out under Yamaguchi conditions[18] to produce compound **23** in 93% yield. This

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set the stage for the macrocyclization by ring-closing metathesis. Reaction of **23** with second-generation Grubbs catalyst in refluxing dichloromethane provided the separable mixture of *E*/*Z*-isomers (8:2) in 71% yield.[19] Finally, the major required (*E*)-isomer **24** was subjected to desilylation under TBAF conditions to give the macrocyclic core **3** in 89% yield. The structure of macrolactone **3** was fully characterized by ^{1}H NMR, ^{13}C NMR, and mass spectral data.

In conclusion, a convergent synthesis of the 15-membered macrocyclic core of iriomoteolide 3a has been demonstrated. Both Sharpless reactions (epoxidation and dihydroxylation) and a cross-metathesis reaction were efficiently used for the preparation of key intermediates. The salient features of the approach include an efficient and scalable synthesis of two fragments, **4** and **5**, in a stereoselective manner and the use of ring-closing metathesis for macrocyclization. We believe that this approach sets the stage for total synthesis as well as entry to a diversity of analogues through the installation of various side chains. Studies in this direction are underway.

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Supporting Information Available: Spectroscopic and analytical data and expeimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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