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Enantioselective Syntheses of the Proposed Structures of Cytotoxic Macrolides Iriomoteolide-1a and -1b

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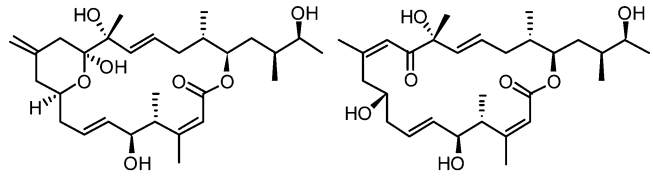
ABSTRACT



Iriomoteolide-1a (1) (proposed structure)

Iriomoteolide-1b (23) (proposed structure)

Enantioselective total syntheses of the proposed structures of macrolide cytotoxic agents iriomoteolide-1a and -1b have been accomplished. The synthesis was carried out in a convergent and stereoselective manner. However, the present work suggests that the reported structures have been assigned incorrectly. The synthesis features Julia−Kocienski olefination, Sharpless asymmetric epoxidation, Brown asymmetric crotylboration, a Sakurai reaction, an aldol reaction, and enzymatic resolution as the key steps.

Marine dinoflagellates are a rich source of diverse macrolide natural products known as amphidinolides.[1] In 2007, Tsuda and co-workers isolated iriomoteolide-1a (**1**), a 20-membered macrolide from a benthic dinoflagellate *Amphidinium* sp. (strain HYA024) collected off Iriomote Island in Japan.[2] It exhibited potent cytotoxicity against human B lymphocyte DG-75 cells with an IC_{50} value of 2 ng/mL. It also showed excellent cytotoxicity against Epstein−Barr virus (EBV)-infected human lymphocyte Raji cells (IC_{50} = 3 ng/mL). The structure of iriomoteolide-1a (**1**, Figure 1) was elucidated on the basis of extensive 2D-NMR and mass spectroscopic studies. The relative and absolute configurations were assigned using NMR through conformational analyses and derivatization of **1** with Mosher's reagent.[2]

As part of our continuing interests in the chemistry and biology of macrolide antitumor agents, we recently reported the synthesis and biological evaluation of marine natural products laulimalide and peloruside A and B.[3,4] We have established that both laulimalide and pelorusides A and B are novel microtubule-stabilizing agents that have shown synergistic effects with Taxol.[5] Furthermore, they arrest the cell cycle at the G_2/M phase, but they do not bind to the taxoid site of β-tubulin.[6] Interestingly, iriomoteolide-1a (**1**) possesses common structural features inherent to both laulimalide and pelorusides. Thus far, the biological mechanism of action of iriomoteolide-1a has not been elucidated.

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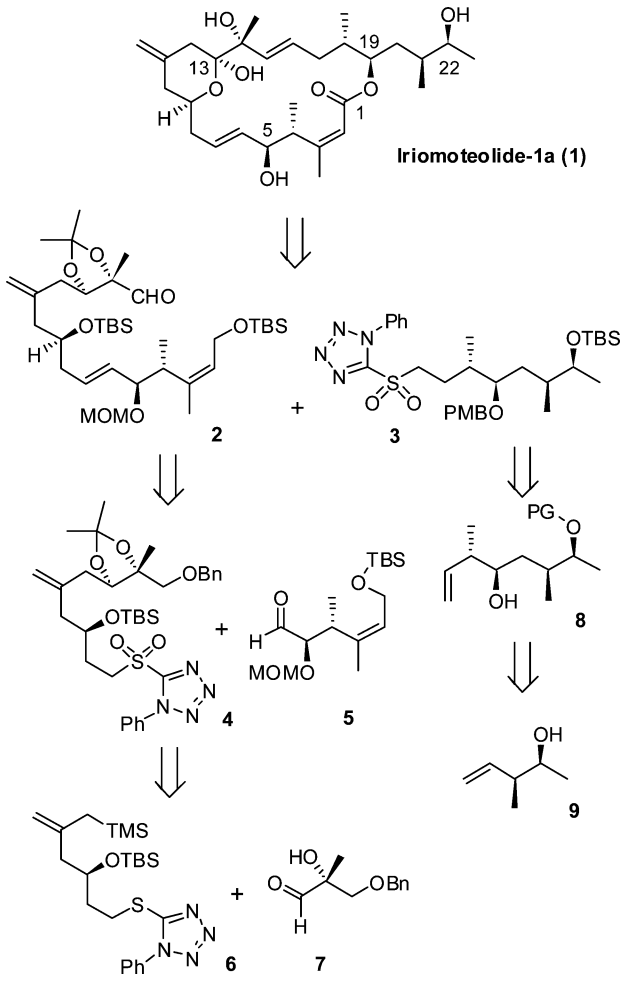
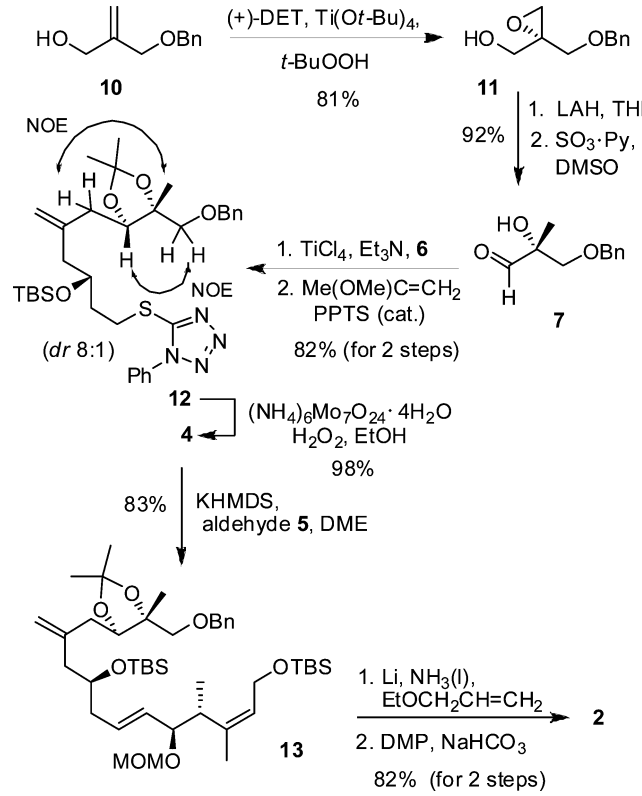


Figure 1. Retrosynthetic analysis of iriomoteolide-1a.

The unique structural features, potent cytotoxic properties and lack of detailed biological studies related to mechanism of action, attracted our interest in the synthesis and biological studies of iriomoteolide-1a. So far, a number of synthetic studies of fragments have been reported,[7] and a total synthesis of the proposed structure has been disclosed recently.[8] Herein, we report our preliminary investigation leading to a convergent and highly stereoselective synthesis of the proposed structure of iriomoteolide-1a. The present work suggested an incorrect assignment of the reported structure of iriomoteolide-1a.

At the outset, we planned to develop a highly convergent and asymmetric synthesis route to provide access to a variety of designed structural variants for biological studies. As shown in Figure 1, our convergent strategy relies upon a

Scheme 1. Synthesis of C_1-C_{15} Subunit **2**



Julia−Kocienski olefination[9] of aldehyde **2** and sulfone **3** followed by a Yamaguchi macrolactonization[10] to form the 20-membered macrolide. The C_1-C_{15} subunit **2** can be obtained by another Julia−Kocienski olefination[9] of sulfone **4** and aldehyde **5**. Sulfone **4** would be derived from a Sakurai reaction[11] of allyl silane **6** and aldehyde **7**. Both aldehyde **5** and sulfide **6** were synthesized by us previously.[7a] The synthesis of $C_{16}-C_{23}$ fragment **3** can be carried out by hydroboration of olefin **8** followed by conversion of the resulting alcohol to sulfone **3**. Alcohol **8** would be obtained by an asymmetric crotylboration reaction on an aldehyde derived from **9**.[12] Asymmetric crotylboration of acetaldehyde will provide (2*S*,3*S*)-3-methyl-4-penten-2-ol (**9**).[12]

As outlined in Scheme 1, Sharpless asymmetric epoxidation[13] of **10** provided optically active epoxide **11**. Epoxide ring scission utilizing LAH produced the corresponding diol, which was oxidized by a Parikh−Doering oxidation[14] to furnish aldehyde **7** which was used for the next step without

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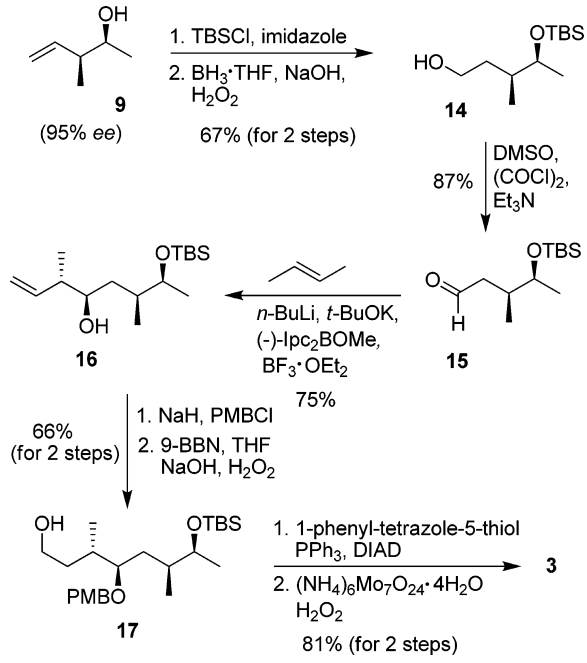
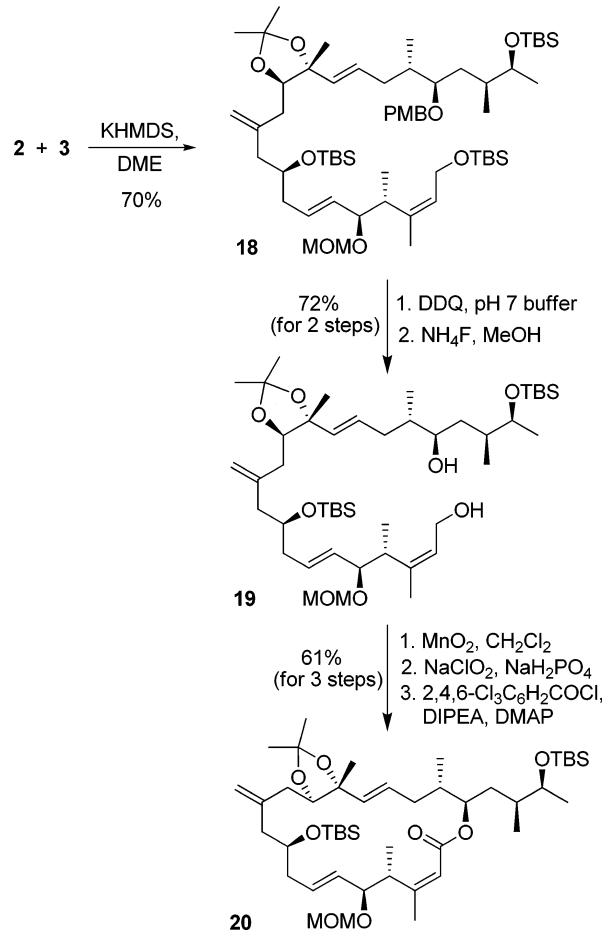
Scheme 2. Synthesis of $C_{16}-C_{23}$ Sulfone **3**



Scheme 3. Synthesis of Macrolactone **20**



further purification. Sakurai reaction[11] between aldehyde **7** and allyl silane **6** in the presence of $TiCl_4$ and triethylamine provided the corresponding alcohol in 83% yield (8:1 dr). A chelation-controlled addition[15] with the α-hydroxyl group resulted in high diastereoselectivity, and the absolute configuration at C_{13} was identified as *R* by observed NOESY as shown in the corresponding acetonide **12**. However, this center will be removed in a late stage via oxidation to the corresponding ketone. Protection of the resulting diol with 2-methoxypropene in the presence of a catalytic amount of PPTS afforded **12**. It was oxidized by ammonium molybdate and hydrogen peroxide to afford sulfone **4**.

The synthesis of aldehyde **5** was carried out as described previously.[7a] A Julia−Kocienski olefination[9] between aldehyde **5** and sulfone **4** utilizing KHMDS furnished the *E*-olefin **13** as a single isomer in 83% yield. Removal of the benzyl group with lithium and liquid ammonia in the presence of allyl ethyl ether followed by Dess−Martin oxidation[17] produced the C1−C15 fragment, aldehyde **2**.

The synthesis of sulfone **3** is shown in Scheme 2. Brown's crotylboration reaction using *cis*-2-butene, (+)-*B*-methoxydiisopinocampheylborane, and acetaldehyde gave *syn*-alcohol **9**.[12] Protection of the alcohol with *tert*-butyldimethylsilyl chloride and imidazole followed by hydroboration of the olefin afforded alcohol **14**. Swern oxidation furnished the aldehyde **15**. A second Brown crotylboration utilizing (−)-*B*-methoxydiisopinocampheylborane and *trans*-2-butene led to *anti*-alcohol **16** as a mixture (10:1) of diastereomers (by ^{1}H NMR analysis). Protection of alcohol **16** with 4-methoxybenzyl chloride followed by hydroboration with 9-BBN afforded the alcohol **17**. A Mitsunobu reaction between alcohol **17** and 1-phenyl-1*H*-tetrazole-5-thiol followed by oxidation of the corresponding sulfide with ammonium molybdate and hydrogen peroxide led to $C_{16}-C_{23}$ fragment, sulfone **3**.

As shown in Scheme 3, a Julia−Kocienski olefination[9] between aldehyde **2** and sulfone **3** using KHMDS in 1,2-dimethoxyethane furnished olefin **18**. Treatment of **18** with DDQ in DCM and pH 7 buffer followed by ammonium fluoride in methanol produced diol **19**. Selective oxidation of the allyl alcohol with MnO_2 followed by oxidation of the resulting aldehyde with sodium chlorite led to the corresponding *seco*-acid. Yamaguchi macrolactonization conditions[10] produced the macrolactone **20**.

The completion of the synthesis of the proposed structure of iriomoteolide-1a is shown in Scheme 4. Removal of silyl ether and acetonide protecting groups was carried out by sequential treatment with HF•Py and aqueous acetic acid to provide **21**. Removal of the MOM-protecting group was effected by exposure to bromocatechol borane.[16] The free alcohols were selectively protected with triethylsilyl chloride in the presence of DMAP to afford diol **22**. Oxidation of

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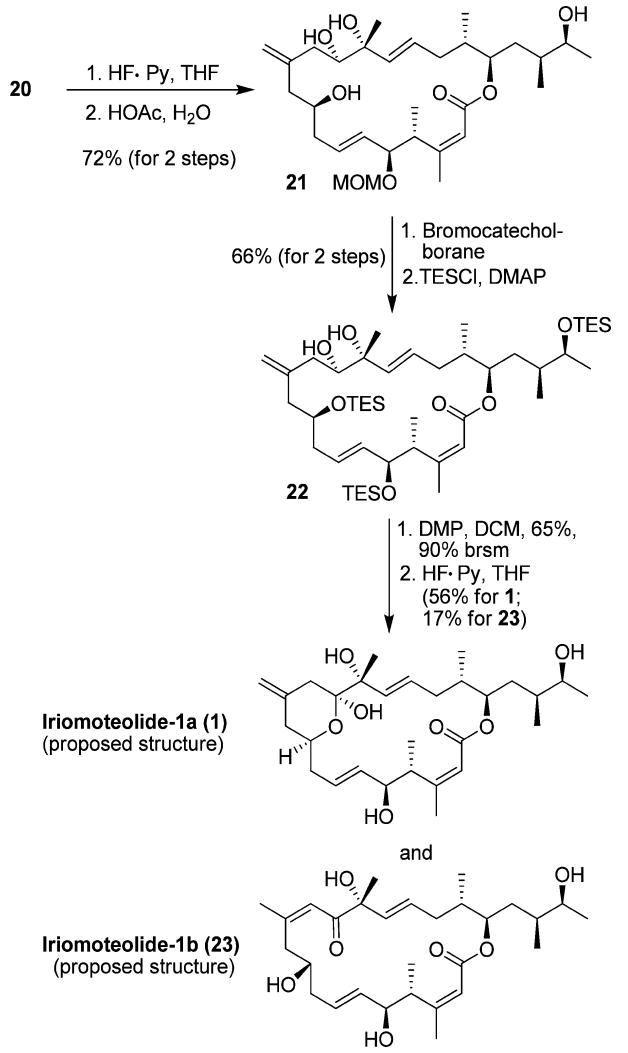
Scheme 4. Synthesis of the Proposed Structure of Iriomoteolides



alcohol **22** with Dess−Martin periodinane[17] followed by removal of the silyl ethers with HF·Py complex[7d] resulted in a mixture (3:1) of the proposed structure of iriomoteolide-1a (**1**) and iriomoteolide-1b (**23**).[18] Both products were separated by silica gel chromatography. The ^{1}H NMR and ^{13}C NMR spectral data of synthetic iriomoteolide-1a (**1**) or synthetic iriomoteolide-1b (**23**), however, did not match with the data reported for natural iriomoteolide-1a and -1b. Our syntheses of both iriomoteolide-1a (structure **1**) and iriomoteolide-1b (structure **23**) now suggested that the structures of both natural iriomoteolide-1a and iriomoteolide-1b have been assigned incorrectly. While there are many minor differences between the two spectra, the major discrepancy of ^{1}H and ^{13}C shifts is at C_4 (3.98 ppm and 40.6 ppm for synthetic iriomoteolide-1a compared to 2.46 ppm and 47.9 ppm for the natural product) which suggests an epimer at the C_4 position. Also a distinction of chemical shifts at C_{24} (1.96 and 20.8 ppm for synthetic **1** compared to 2.12 and 23.8 ppm for natural **1**) reveals that the enoate double bond configuration might be *E* instead of *Z*. The detailed comparison of NMR data including 2D-NMR of iriomoteolide-1a and histogram charts of δ ^{13}C shifts are shown in the Supporting Information.

In summary, we have achieved the enantioselective syntheses of the proposed structures of iriomoteolide-1a and iriomoteolide-1b. The synthesis featured a very effective Sakurai reaction and Julia−Kocienski olefinations. Other key reactions included Sharpless asymmetric epoxidation and Brown asymmetric crotylboration reactions. The synthesis will also provide convenient access to a variety of derivatives. Further investigations related to structural assignments as well as biological studies are in progress.

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Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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