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Enantioselective Synthesis of the Proposed Structure of Cytotoxic Macrolides Iriomoteolide-1a and 1b

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Abstract

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 IC₅₀ value of 2 ng/mL. It also showed excellent cytotoxicity against Epstein-Barr virus (EBV)-infected human lymphocyte Raji cells (IC₅₀ = 3 ng/mL). The structure of iriomoteolide-1a (**1**; Figure 1) was elucidated based upon extensive 2D-NMR and mass spectroscopic studies. The relative and absolute configuration 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 G₂/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. 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

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

iriomoteolide-1a. So far, a number of synthetic studies of fragments have been reported⁷ 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 Julia-Kocienski olefination⁹ of aldehyde **2** and sulfone **3** followed by a Yamaguchi macrolactonization¹⁰ to form the 20-membered macrolide. The C¹-C¹⁵ subunit **2** can be obtained by another Julia-Kocienski olefination⁹ of sulfone **4** and aldehyde **5**. Sulfone **4** would be derived from a Sakurai reaction¹¹ of allyl silane **6** and aldehyde **7**. Both aldehyde **5** and sulfide **6** were synthesized by us previously.^{7a} The synthesis of C₁₆-C₂₃ 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 asymmetric crotylboration reaction on an aldehyde derived from **9**.¹² Asymmetric crotylboration of acetaldehyde will provide (2*S*, 3*S*)-3-methyl-4-pentene-2-ol (**9**).¹²

As outlined in Scheme 1, Sharpless asymmetric epoxidation¹³ of **10** provided optically active epoxide **11**. Epoxide ring scission utilizing LAH produced the corresponding diol, which was oxidized by a Parikh-Doering oxidation¹⁴ to furnish aldehyde **7** which was used for the next step without further purification. Sakurai reaction¹¹ between aldehyde **7**, and allyl silane **6** in the presence of TiCl₄ and triethylamine provided the corresponding alcohol in 83% yield (8:1 *dr*). A chelation-controlled addition¹⁵ with the α -hydroxyl group resulted in high diastereoselectivity, and the absolute configuration at C₁₃ was identified as *R* by observed NOESY as shown in the corresponding acetone **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 olefination⁹ 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 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*-methoxy-diisopinocampheylborane 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 ¹H-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 C¹⁶-C²³ fragment, sulfone **3**.

As shown in Scheme 3, Julia-Kocienski olefination⁹ between aldehyde **2** and sulfone **3** using KHMDS in 1,2-dimethoxyethane furnished the 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 MnO₂ followed by oxidation of the resulting aldehyde with sodium chlorite led to the corresponding *seco*-acid. Yamaguchi macrolactonization conditions¹⁰ 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 alcohol **22** with Dess-Martin periodinane¹⁷ 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 ¹H-NMR and ¹³C-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 structure 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 ¹H and ¹³C shifts at C₄ (3.98 ppm and 40.6 ppm for synthetic iriomoteolide-1a compared to 2.46 ppm and 47.9 ppm for the natural product) suggests an epimer at C₄ position. And the distinction of chemical shifts at C₂₄ (1.96 ppm and 20.8 ppm for synthetic **1** compared to 2.12 ppm and 23.8 ppm for natural **1**) also 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 delta ¹³C shifts is shown in the supporting information.

In summary, we have achieved the enantioselective synthesis 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 a convenient access to a variety of derivatives. Further investigations related to structural assignment as well as biological studies are in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Retrosynthetic analysis of iriomoteolide-1a.

Scheme 1.
Synthesis of C₁-C₁₅ subunit **2**

Scheme 2.
Synthesis of C₁₆-C₂₃ sulfone **3**

Scheme 3.
Synthesis of macrolactone **20**

Scheme 4.
 Synthesis of proposed structure of iriomoteolides