ORGANIC LETTERS

2010
Vol. 12, No. 14
3120−3123

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

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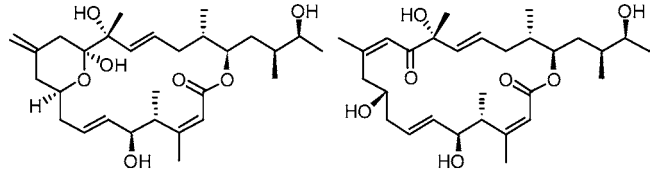
Received May 13, 2010

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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10.1021/ol101105v © 2010 American Chemical Society
Published on Web 06/18/2010

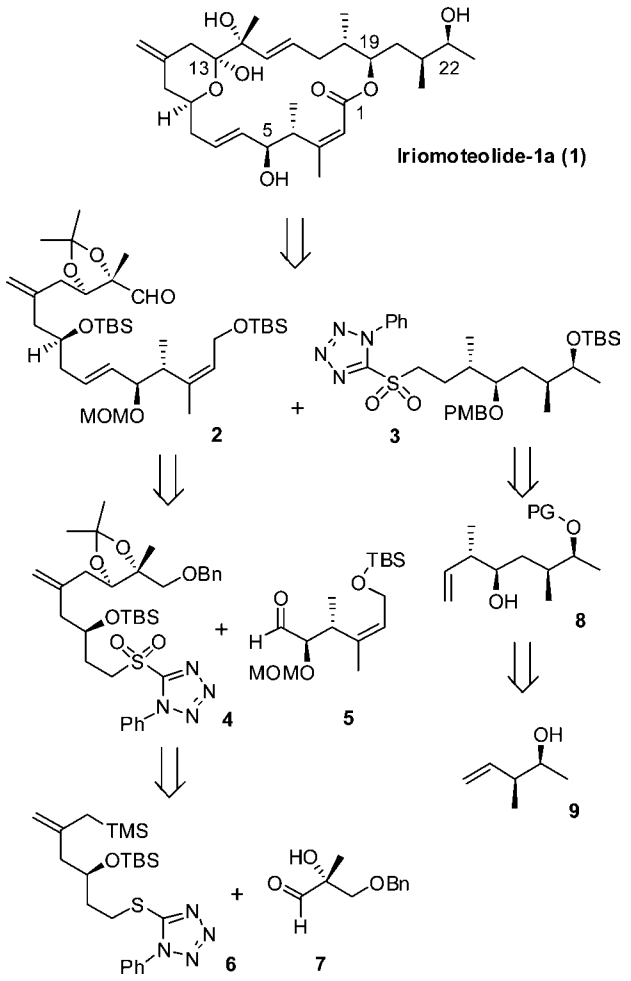
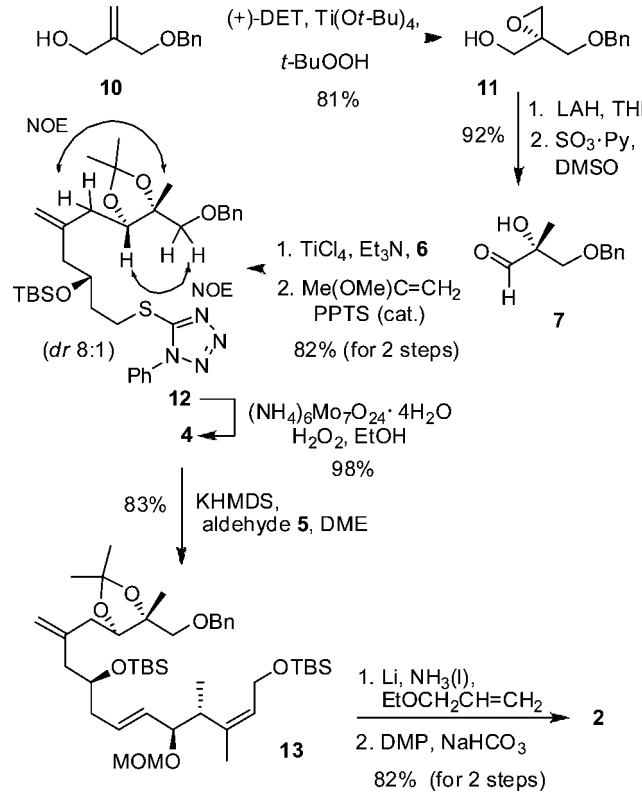


Figure 1. Retrosynthetic analysis of iriomoteolide-1a.

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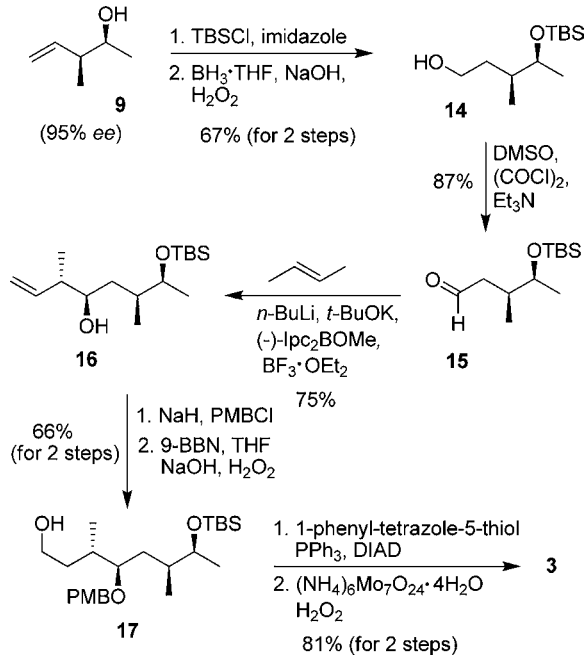
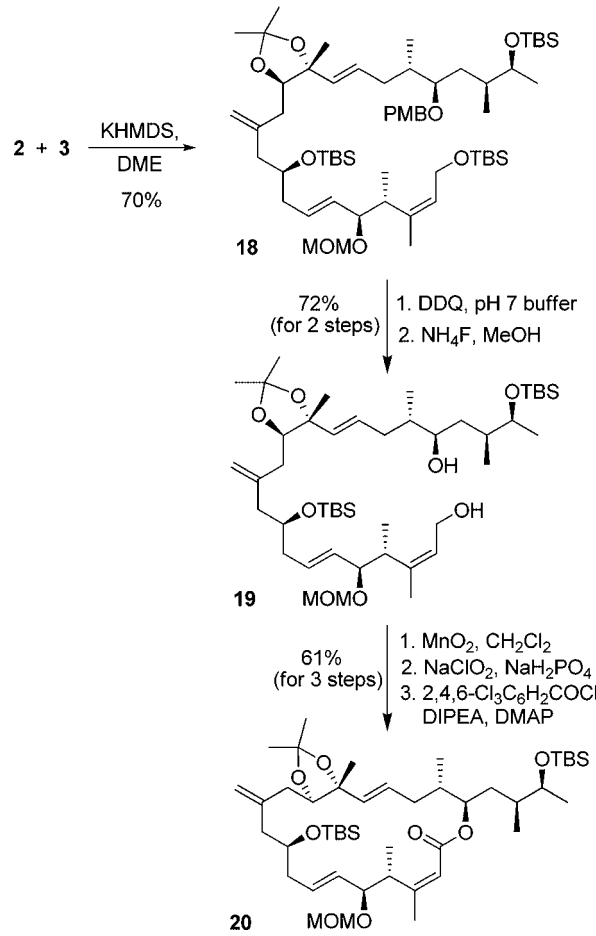
Scheme 2. Synthesis of $C_{16}-C_{23}$ Sulfone **3**



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 ^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 $C_{16}-C_{23}$ 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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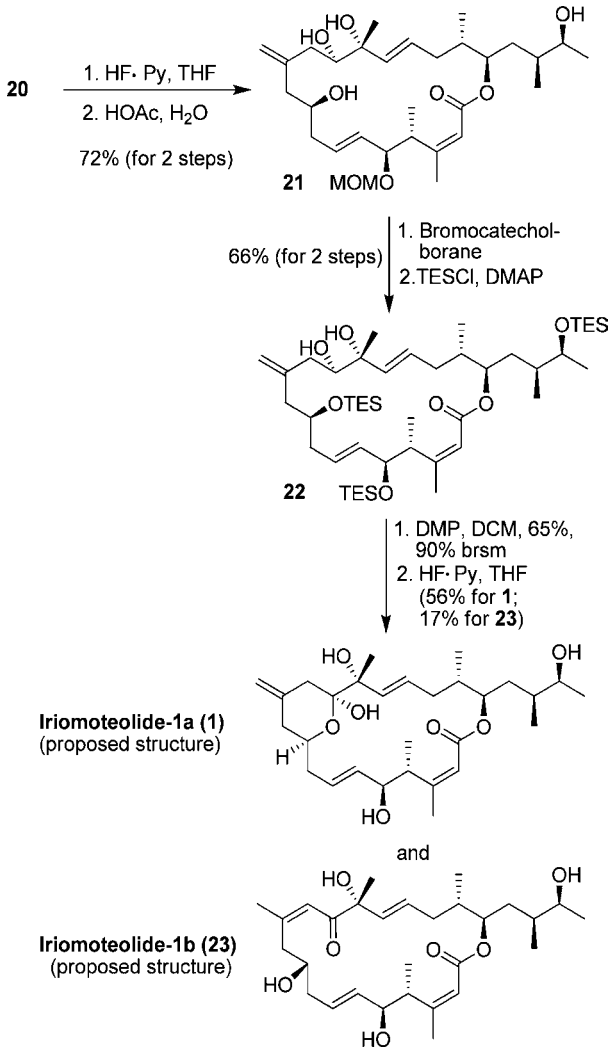
Scheme 4. Synthesis of the Proposed Structure of Iriomoteolides



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.

Acknowledgment. This research is supported in part by the National Institutes of Health. We thank Mr. David D. Anderson (Purdue University) for his assistance with NOESY studies.

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.

OL101105V

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