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Enantioselective Synthesis of a Diastereomer of Iriomoteolide-1a. What Is the Correct Structure of the Natural Product?

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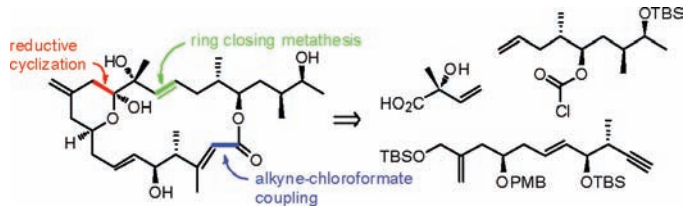
ABSTRACT



An enantioselective approach to a diastereomer of iriomoteolide-1a is described. Highlighted is a SmI_2-mediated intramolecular reductive cyclization approach to complex cyclic hemiketals. An acetylide−chloroformate coupling strategy is also featured. Our results show that the structures of iriomoteolide-1a−1c require careful reassessment.

Amphidinolides are a group of macrolides isolated from marine dinoflagellates *Amphidinium* sp.[1] In addition to exhibiting unique molecular structures, many of these natural products show potent cytotoxicity against human cancer cell lines. Total syntheses of a number of amphidinolides have been reported,[2] leading to reassignment of the relative and/or absolute configuration of several members of the group.[3] Iriomoteolide-1a−1c are recent additions to this interesting group of natural products.[4] Isolated from a benthic HYA024 strain of *Amphidinium* sp., iriomoteolide-1a was characterized as a unique 20-membered macrolide by 1D and 2D NMR analysis, while iriomoteolide-1b and -1c were described as isomeric and homologous to iriomoteolide-1a (Figure 1). Iriomoteolide-1a was reported to be cytotoxic toward human B lymphocyte DG-75 cells (IC_{50} 2 ng/mL) and Epstein−Barr virus infected B lymphocyte Raji cells (IC_{50} 3 ng/mL). This exceptional cytotoxicity rivals that of many well-known natural anticancer agents in clinical use. The unique molecular structure and potent cytotoxicity of iriomoteolide-1a attracted the attention of synthetic chemists and a number of synthetic studies have been reported.[5,6] Recently, Horne and co-workers completed the first synthesis of the originally proposed structure of iriomoteolide-1a and reported the inconsistency of its spectra with those of the natural product.[7] This prompted us to report our synthetic studies toward iriomoteolide-1a.

(1) For some recent reviews: (a) Kobayashi, J. *J. Antibiot.* **2008**, *61*, 271–284. (b) Kobayashi, J.; Kubota, T. *J. Nat. Prod.* **2007**, *70*, 451–460. (c) Kobayashi, J.; Tsuda, M. *Nat. Prod. Rep.* **2004**, *21*, 77–93.

(2) For a list of these total syntheses, see the Supporting Information of Bates, R. H.; Shotwell, J. B.; Roush, W. R. *Org. Lett.* **2008**, *10*, 4343–4346. See also the references cited in refs 5b and 6.

(3) For some examples, see: (a) Lu, L.; Zhang, W.; Carter, R. G. *J. Am. Chem. Soc.* **2008**, *130*, 7253–7255. (b) Ghosh, A. K.; Gong, G. *J. Am. Chem. Soc.* **2004**, *126*, 3704–3705. (c) Trost, B. M.; Harrington, P. E. *J. Am. Chem. Soc.* **2004**, *126*, 5028–5029. (d) Williams, D. R.; Meyer, K. G. *J. Am. Chem. Soc.* **2001**, *123*, 765–766. (e) Williams, D. R.; Myers, D. R.; Mi, L. *Org. Lett.* **2000**, *2*, 945–948.

(4) (a) Tsuda, M.; Oguchi, K.; Iwamoto, R.; Okamoto, Y.; Kobayashi, J.; Fukushi, E.; Kawabata, J.; Ozawa, T.; Masuda, A.; Kitaya, Y.; Omasa, K. *J. Org. Chem.* **2007**, *72*, 4469–4474. (b) Tsuda, M.; Oguchi, K.; Iwamoto, R.; Okamoto, Y.; Fukushi, E.; Kawabata, J.; Ozawa, T.; Masuda, A. *J. Nat. Prod.* **2007**, *70*, 1661–1663.

(5) Part of this work has been presented at the 239th ACS National Meeting: (a) Yang, J.; Fang, L.; Yang, F. Abstracts of Papers. *239th ACS National Meeting*; Mar 21−25, 2010, San Francisco, CA; American Chemical Society: Washington, DC, 2010; ORGN-123. (b) Fang, L.; Xue, H.; Yang, J. *Org. Lett.* **2008**, *10*, 4645–4648.

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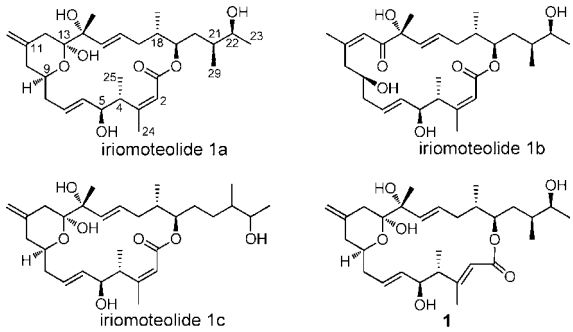


Figure 1. Original iriomoteolide-1a−1c and compound **1**.

From the outset, we aimed to develop a flexible synthetic route that would enable subsequent structure−activity relationship (SAR) and mode-of-action studies of this potent cytotoxin. To maximize synthetic convergency, our synthetic plan relied on a late-stage intramolecular reductive cyclization of iodoester **2** to introduce the six-membered hemiketal (Figure 2). We previously reported the synthesis of the C1−C12 fragment of the originally proposed iriomoteolide-1a by sequential catalytic asymmetric vinylogous aldol reactions.[5] However, during our studies, it became clear that the C2−C3 double bond of the natural product should be revised to 2*E* instead of the originally proposed 2*Z* configuration.[8] Thus, we adjusted our synthetic plan to target the diastereomeric 2*E* isomer **1** rather than the originally proposed iriomoteolide-1a. In the revised synthetic plan, macrocycle **2** would be prepared by ring-closing metathesis across the C15−C16 double bond of diene **3**, which in turn would be assembled from building blocks **4**−**6**. Importantly, it was expected that coupling of terminal alkyne **4** and chloroformate **5** followed by conjugate addition of the Gilman reagent would allow stereoselective formation of the trisubstituted C1-alkenoic ester moiety. The C13-ester of **3** would be prepared by the Mitsunobu reaction of carboxylic acid **6** and the C9-alcohol derived from **4**.

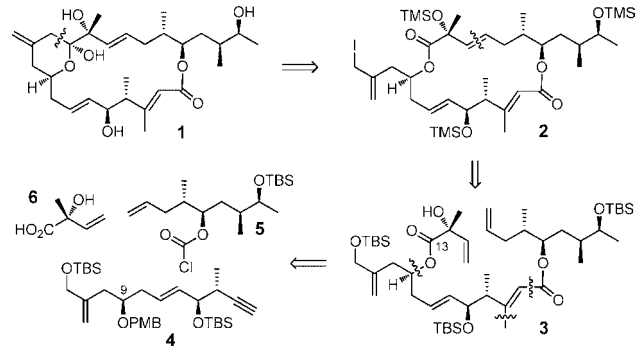
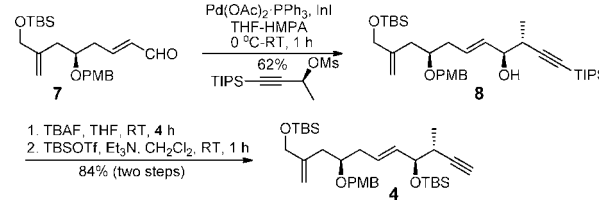


Figure 2. Synthetic plan.

Our synthesis commenced with aldehyde **7**, prepared from *β*-methallyl alcohol in eight steps as we had previously described (Scheme 1).[5] In the presence of $Pd(OAc)_2$•PPh_3, the *anti*-homopropargylic alcohol **8** was prepared from aldehyde **7** by addition of the triisopropylsilylallenylindium reagent generated in situ from (*S*)-4-triisopropylsilyl-3-butyn-2-yl mesylate.[9] Global desilylation of alkyne **8** with TBAF followed by reprotection of the diol allowed efficient synthesis of building block **4**.

Scheme 1. Synthesis of Building Block **4**



Preparation of chloroformate **5** started from the known alcohol **9** (Scheme 2).[10] Silylation of **9** followed by hydroboration and Swern oxidation gave aldehyde **10**.[11] Brown asymmetric crotylation of **10** and protection of the resulting secondary hydroxy group as the PMB ether led to alkene **11**,[10] which was subjected to a three-step homologation sequence (hydroboration, Swern oxidation, and Wittig olefination) to give homologated alkene **12**. The PMB ether **12** was oxidatively hydrolyzed with DDQ, and building block **5** was synthesized by reaction of the secondary alcohol with triphosgene.[12]

With both of the key building blocks in hand, our attention was turned to their coupling and conversion to the trisubstituted 2*E*-alkenoic ester **14**. For this purpose, deprotonation

(6) (a) Ghosh, A. K.; Yuan, H. *Tetrahedron Lett.* **2009**, *50*, 1416–1418. (b) Xie, J.; Horne, D. A. *Tetrahedron Lett.* **2009**, *50*, 4485–4487. (c) Chin, Y.-J.; Wang, S.-Y.; Loh, T.-P. *Org. Lett.* **2009**, *11*, 3674–3676. (d) Ye, Z.; Deng, L.; Qian, S.; Zhao, G. *Synlett* **2009**, 2469–2472. (e) Xie, J.; Ma, Y.; Horne, D. A. *Org. Lett.* **2009**, *11*, 5082–5084. (f) Wang, S.-Y.; Chin, Y.-J.; Loh, T.-P. *Synthesis* **2009**, 3557–3564. (g) Paterson, I.; Rubenbauer, P. *Synlett.* **2010**, 571–574. (h) Li, S.; Chen, Z.; Xu, Z.; Ye, T. *Chem. Commun.* **2010**, *46*, Advance Article, DOI: 10.1039/c0cc00915f.

(7) (a) Xie, J.; Ma, Y.; Horne, D. A. *Chem. Commun.* **2010**, *46*, Advance Article, DOI: 10.1039/c0cc00628a. (b) Xie, J.; Ma, Y.; Horne, D. A. Abstracts of Papers. *239th ACS National Meeting*; March 21−25, 2010, San Francisco, CA; American Chemical Society: Washington, DC, 2010; ORGN-131.

(8) In ref 4a, the C2−C3 double bond was assigned as *Z* based on the chemical shift (δ_H 2.12, δ_C 23.8) of Me-24 and the ROESY correlation for H2 (δ_H 6.02)/Me-24 (δ_H 2.10) in C_6D_6. However, the reported ^{1}H NMR chemical shift of Me-24 is actually consistent with an *E*- rather than *Z*-alkenoic ester (see ref 13), and we suspect that the aforementioned weak ROESY correlation is actually due to H2/Me-24 COSY correlation. It is known that COSY correlations are also present in ROESY spectra. These correlations are superfluous and should be ignored. (For a reference, see: Macura, S.; Huang, Y.; Suter, D.; Ernst, R. R. *J. Magn. Reson.* **1981**, *43*, 259–281). In addition, we observed a strong ROESY correlation for H-2/Me-25 in both $CDCl_3$ and C_6D_6 from the spectra provided in the Supporting Information of ref 4a. This also strongly supports a 2*E*-alkenonic ester rather than the originally assigned 2*Z*-isomer.

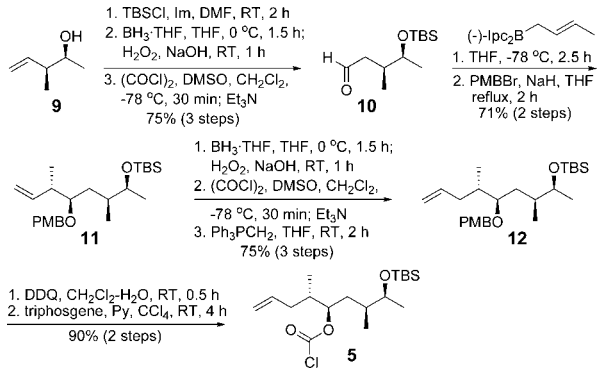
(9) (a) Marshall, J. A. *J. Org. Chem.* **2007**, *72*, 8153–8166. (b) Marshall, J. A.; Eidam, P.; Eidam, H. S. *J. Org. Chem.* **2006**, *71*, 4840–4844.

(10) (a) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293–294. (b) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919–5923.

(11) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185.

(12) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885–888.

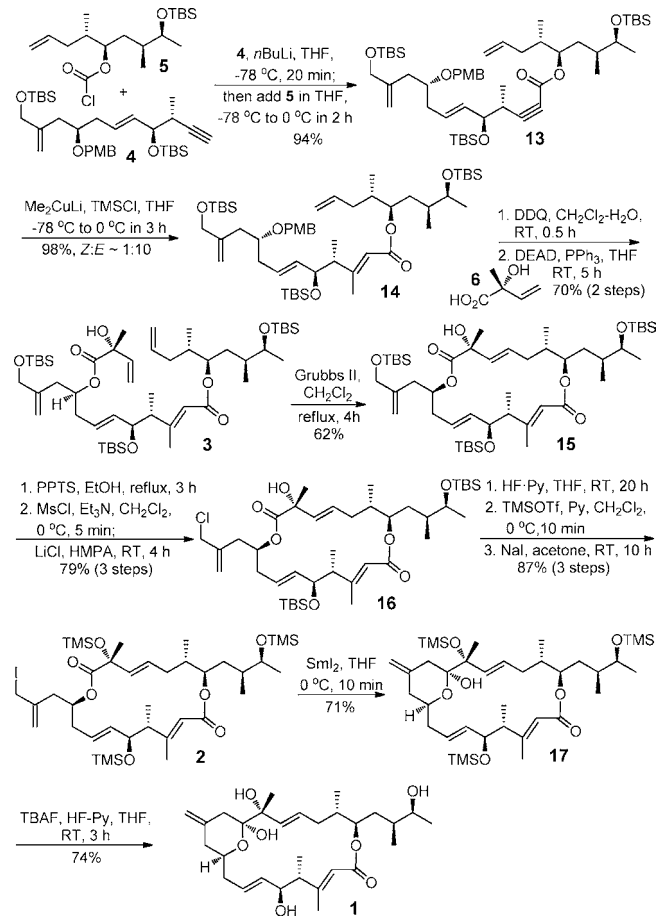
Scheme 2. Synthesis of Building Block **5**



of acetylene **4** with *n*-BuLi followed by reaction with chloroformate **5** generated the desired alkynoic ester **13** in 94% yield (Scheme 3). This alkynoic ester could be conveniently converted to either of the two isomeric trisubstituted alkenoic esters by conjugate addition of Me_2CuLi. A *Z*-configuration of the C2−C3 double bond could be secured when the conjugate addition was carried out at −20 °C and quenched at low temperature (not shown). The 2*E*-trisubstituted alkenoic ester **14** was selectively generated (*Z*:*E* ∼ 1:10) when the reaction was carried out in the presence of TMSCl and the silyl ketene acetal intermediate hydrolyzed by standard aqueous workup. The assignment of the C2−C3 double-bond geometry was straightforward based on the characteristic chemical shift of Me-24 in the 300 MHz ^{1}H NMR spectrum in $CDCl_3$. A δ_H (Me-24) of 2.13 ppm for **14** is consistent with an *E*-trisubstituted alkenoic ester, while a δ_H (Me-24) of 1.83 ppm for the other isomer (not shown) is consistent with a *Z*-alkenoic ester.[13] Mechanistic considerations of the carbocupration reaction, which has been well studied,[14] are also consistent with these assignments. Importantly, the reported δ_H (Me-24) of 2.12 ppm for the natural product is consistent with that observed for the (2*E*)-alkenoic ester **14**.

With the C1-trisubstituted alkenoic ester functionality secured, the C13 ester was introduced by oxidative hydrolysis of the C9 PMB ether of **14** with DDQ followed by the Mitsunobu reaction with α-hydroxy acid **6**.[15,16] The strategic decision of carrying out macrocyclization of **3** by ring-closing metathesis was quite demanding.[17] It required selective activation of two of the five double bonds of the cyclization

Scheme 3. Synthesis of **1**



precursor. Moreover, stereochemical control of the resulting C15−C16 double bond was also necessary. Thus, we were gratified to observe that ring-closing metathesis of **3** indeed provided the macrocyclic bis-lactone **15** in 62% yield with the second-generation Grubb's catalyst, with the desired *E*-isomer being formed exclusively. To prepare for the intramolecular reductive cyclization, compound **15** was converted to allyl iodide **2** by standard functional group manipulations. Employing the intramolecular reductive cyclization conditions recently reported by Keck,[18] formation of the six-membered hemiketal of **17** was successfully implemented as originally planned by treating the iodoester **2** with SmI_2.[19] It is noteworthy that the desired reductive cyclization occurred selectively in the presence of a myriad of other functional groups. Finally, the hemiketal **1**, which existed as an equilibrating mixture with the ketol form (∼ 5:1), was obtained by global desilylation of **17** with TBAF-HF-py.[20] The ^{1}H and ^{13}C NMR spectra of **1** were in full agreement with the structure assigned. However, they did

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(14) Nilsson, K.; Andersson, K.; Ullenius, C.; Gerold, A.; Krause, N. *Chem.—Eur. J.* **1998**, *4*, 2051, and references cited therein.

(15) For two reviews of the Mitsunobu reaction, see: (a) Mitsunobu, O. *Synthesis* **1981**, 1–28. (b) Kumara Swamy, K. C.; Bhuvan Kumar, N. N.; Balaraman, E.; Pavan Kumar, K. V. P. *Chem. Rev.* **2009**, *109*, 2551–2651.

(16) Zhang, D.; Bleasdale, C.; Golding, B. T.; Watson, W. P. *Chem. Commun.* **2000**, 1141–1142.

(17) For some reviews, see: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012–3043. (c) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592–4633. (d) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238. (e) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490–4527.

(18) Heumann, L. V.; Keck, G. E. *Org. Lett.* **2007**, *9*, 1951–1954.

(19) Preliminary studies using model substrates showed that the tertiary C14 hydroxy group had to be protected. Fang, L. Yang, J. Unpublished results.

(20) (a) Gaffney, B. L.; Jones, R. A. *Tetrahedron Lett.* **1982**, *23*, 2257–2260. (b) Coleman, R. S.; Li, J.; Navarro, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 1736–1739.

not agree with those reported for iriomoteolide-1a. Even though we were unable to obtain a single crystal of **1** or an advanced intermediate for X-ray crystallographic analysis, the stereochemistry of the chiral centers of **1** was independently verified by the modified Mosher's ester method,[21] comparison with known compounds, or comparison with samples prepared by other methods (see the Supporting Information).

Comparison of the 500 MHz ^{1}H and 125 MHz ^{13}C NMR spectra of **1** with those reported for iriomoteolide-1a suggests that we have prepared a diastereomer of iriomoteolide-1a, and it appears that the natural product is epimeric to **1** at one or more stereocenters.[22] Tsuda and co-workers assigned the plannar structure of iriomoteolide-1a by standard 2D NMR techniques, while the relative and absolute configurations of its chiral centers were assigned by *J*-based configuration analysis and the modified Mosher's ester method, respectively.[21,23] The *J*-based configuration analysis has been extremely useful for conformational and stereochemical studies of organic compounds and has been widely used to elucidate the relative stereochemical relationships of chiral centers of complex organic compounds. However, we were puzzled by the configuration analysis of the C4−C5 and C21−C22 stereocenters in the original report.[4a] Specifically, Tsuda and co-workers reported the values of the $^{13}C-^{1}H$ coupling constants $^{3}J_{C5/H25}$, $^{3}J_{C21/H23}$, and $^{3}J_{C22/H29}$ as part of their *J*-based configuration analysis. However, H23, H25, and H29 each belongs to a conformationally unbiased methyl group, and thus, these coupling constants, to the best of our knowledge, provide no stereochemical information. While their original intention of measuring those coupling constants is not clear to us, it appears that the reported *J*-configuration analysis is questionable and the original assignment of the relative stereochemical configurations at C4−C5 and C21−C22 is not reliable. Since the rest of the chiral centers of iriomoteolide 1a were to a large part assigned by correlation with C4−C5 and C21−C22, their assignments are also questionable.

We synthesized additional diastereomers **18** and **19** following similar routes (Figure 3). However, their spectra are also different from those of the natural product.

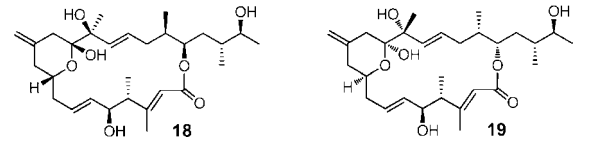

Figure 3. Diastereomers **18** and **19**.

Even though the stereochemical structure of iriomoteolide-1a still awaits elucidation, we have developed a concise and flexible synthetic route for this purpose. It proceeds in 22 steps for the longest linear sequence to arrive at **1**, a likely diastereomer of iriomoteolide-1a. Importantly, our synthetic route, which relies on reagent control to introduce most of the chiral centers, is flexible enough to allow systematic variations of the stereocenters that are required to elucidate the stereochemical structure of the natural product. Highlighted is an unprecedented strategic application of SmI_2-mediated intramolecular reductive cyclization to synthesize complex cyclic hemiketals.[24] The synthesis also features an acetylide−chloroformate coupling strategy which, to the best of our knowledge, has rarely been applied in such a complex setting. Our results show that the structure of iriomoteolide-1a requires careful reassessment. Since the structures of iriomoteolide-1b and -1c were assigned by analogy to that of iriomoteolide-1a,[4b] our results also bring into question their structures. Our current efforts are focused on applying this synthetic route to prepare select diastereomers of **1** to identify the stereochemical structure of the natural product.

Acknowledgment. Financial support was provided by Texas A&M University and The Welch Foundation (A-1700). We thank Prof. David Horne of Beckman Research Institute at City of Hope for sharing his results. We thank Prof. Daniel Romo of Texas A&M University, Prof. Dirk Menche of Ruprecht-Karls-Universität Heidelberg, and Prof. Tadeusz Molinski of University of California, San Diego, for helpful discussions.

Supporting Information Available: Experimental details and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) For two recent reviews for structural misassignment of natural products, see: (a) Nicolaou, K. C.; Snyder, S. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1012−1044. (b) Maier, M. E. *Nat. Prod. Rep.* **2009**, *26*, 1105–1124.

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(24) Williams and co-workers recently described a similar intramolecular Nozaki−Hiyama reductive cyclization of formate esters: Williams, D. R.; Walsh, M. J.; Miller, N. A. *J. Am. Chem. Soc.* **2009**, *131*, 9038–9045.