ORGANIC LETTERS

2008
Vol. 10, No. 20
4645−4648

Synthesis of the C1−C12 Fragment of Iriomoteolide 1a by Sequential Catalytic Asymmetric Vinylogous Aldol Reactions

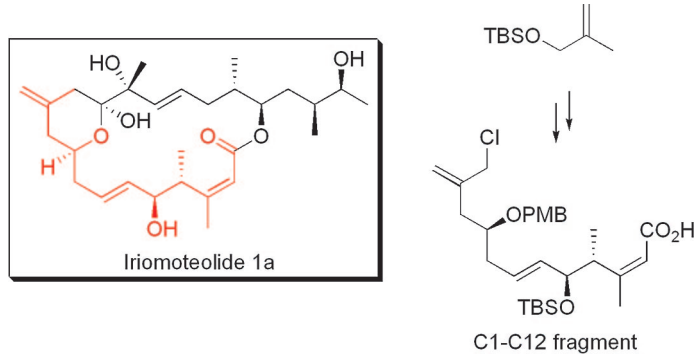
Lijing Fang, Haoran Xue, and Jiong Yang*

Department of Chemistry, Texas A&M University, College Station, Texas 77842-3092

yang@mail.chem.tamu.edu

Received August 19, 2008

ABSTRACT



An efficient synthesis of the C1−C12 fragment of iriomoteolide 1a has been accomplished via sequential application of two catalytic, asymmetric, vinylogous aldol reactions: a catalytic vinylogous aldol reaction was used to enantioselectively introduce the C5−C8 segment, and a second catalytic vinylogous aldol reaction was used to install the remaining two stereocenters and a stereodefined alkene in the form of an α,β-unsaturated δ-lactone in one step.

Marine dinoflagellates of the genus *Amphidinium* produce a variety of structurally unique cyclic and acyclic polyketide natural products.[1] One class are macrolides, collectively designated as amphidinolides. They are characterized by highly oxygenated macrolactones of various ring sizes and side chains of different lengths and substitutions. The potent cytotoxicity and the unique molecular structure of amphidinolides attracted the attention of synthetic chemists and the syntheses of several of these macrolides have been reported.[2] Continued research of *Amphidinium* species in the laboratory of Tsuda led to the isolation of three related macrolides that were previously unknown.[3] These 20-membered macrolides were named iriomoteolides, presumably because the macrolide-producing strain (HYA024) was collected off the Iriomote Island of Japan. Iriomoteolide 1a was shown to be potently cytotoxic to human B lymphocyte DG-75 cells (IC_{50} 2 ng/mL) and Epstein−Barr virus infected human B lymphocyte Raji cells (IC_{50} 3 ng/mL).[3b] We recently initiated a research program aimed at synthesizing and functionally characterizing natural prod-

(1) (a) Kobayashi, J.; Kubota, T. *J. Nat. Prod.* **2007**, *70*, 451. (b) Kobayashi, J.; Tsuda, M. *Nat. Prod. Rep.* **2004**, *21*, 77.

(2) For some examples since 2006, see: (a) Lu, L.; Zhang, W.; Carter, R. *J. Am. Chem. Soc.* **2008**, *130*, 7253. (b) Fürstner, A.; Bouchez, L. C.; Funel, J.-A.; Liepins, V.; Poree, F.-H.; Gilmour, R.; Beaufils, F.; Laurich, D.; Tamiya, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 9265. (c) Fürstner, A.; Larionov, O.; Fluegge, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 5545. (d) Jin, J.; Chen, Y.; Li, Y.; Wu, J.; Dai, W.-M. *Org. Lett.* **2007**, *9*, 2585. (e) Va, P.; Roush, W. R. *Tetrahedron* **2007**, *63*, 5768. (f) Kim, C. H.; An, H. J.; Shin, W. K.; Yu, W.; Woo, S. K.; Jung, S. K.; Lee, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 8019. (g) Va, P.; Roush, W. R. *J. Am. Chem. Soc.* **2006**, *128*, 15960. (h) Fürstner, A.; Kattnig, E.; Lepage, O. *J. Am. Chem. Soc.* **2006**, *128*, 9194. (i) Deng, L.-S.; Huang, X.-P.; Zhao, G. *J. Org. Chem.* **2006**, *71*, 4625. (j) Ghosh, A. K.; Gong, G. *J. Org. Chem.* **2006**, *71*, 1085.

(3) (a) Tsuda, M.; Oguchi, K.; Iwamoto, R.; Okamoto, Y.; Fukushi, E.; Kawabata, J.; Ozawa, T.; Masuda, A. *J. Nat. Prod.* **2007**, *70*, 1661. (b) 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.

10.1021/ol801940r CCC: $40.75
Published on Web 09/24/2008

ucts that may be biologically useful. Iriomoteolide 1a (**1**) is one of the molecules of interest because of its unique molecular structure, potent cytotoxicity, and unknown mode of action.[4]

We planned to develop a convergent and flexible route that would allow efficient preparation of iriomoteolide 1a and its analogues for biological studies. As shown in Figure 1, synthesis of the six-membered cyclic hemiketal

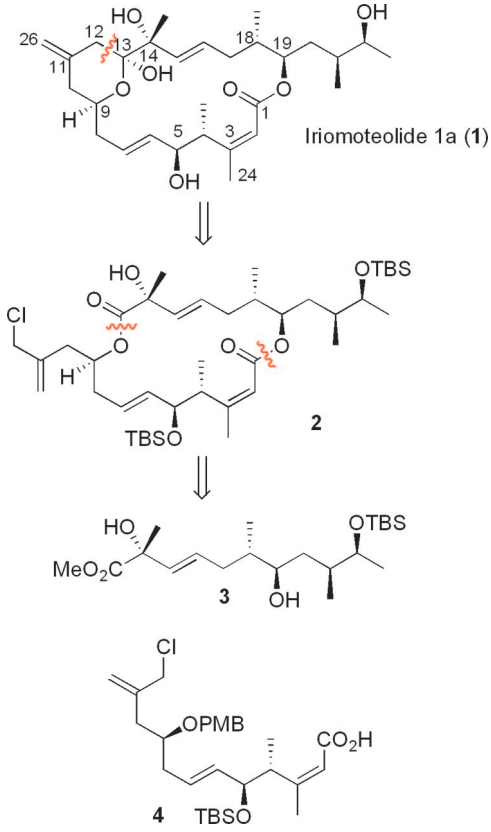
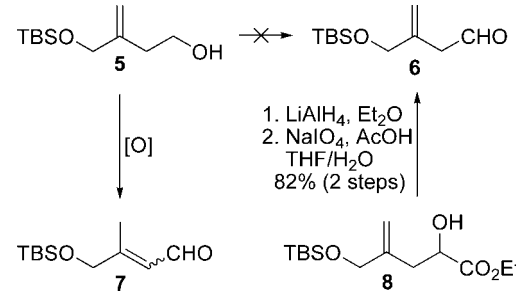


Figure 1. Retrosynthetic analysis.

would employ a late-stage intramolecular nucleophilic cyclization of an allylmetal species derived from allyl chloride **2**.[5] The macrocycle of **2** in turn can be prepared by sequential inter- and intramolecular esterifications of two subunits (**3** and **4**) of comparable complexity. We report herein the successful synthesis of **4** using a strategy based on sequential application of catalytic asymmetric vinylogous aldol reactions.

The synthesis started from preparation of aldehyde **6** (Scheme 1). Aldehydes with β,γ-unsaturation are susceptible

Scheme 1. Synthesis of **6**



to double bond migration to give rise to the thermodynamically more stable α,β-unsaturated aldehydes. Indeed, oxidation of **5**[6] under a variety of conditions (Jone's, PDC, Swern, IBX, etc.) generated α,β-unsaturated aldehyde **7** as the only product. While the combination of CrO_3 and pyridine[7] turned out to be marginally useful and gave rise to a mixture of **6** and **7** (~3:1, 70% overall), we decided to search for an alternative route because of the low efficiencies involved in both the preparation of **5** and the oxidation step. We resorted to oxidative cleavage of the vicinal diol derived from **8**[6] by $LiAlH_4$ reduction to synthesize **6**. Oxidative cleavage of the diol with $NaIO_4$ again gave rise to a mixture of **6** and **7** (~1:2) under standard conditions.[8] Fortunately, we discovered during reaction optimization that the double bond migration can be suppressed by addition of 0.4 equiv of acetic acid, and the β,γ-unsaturated aldehyde **6** was isolated as the only product under these conditions. Aldehyde **6** can be stored at −20 °C for at least four months without significant rearrangement or decomposition.

With aldehyde **6** in hand, we sought to use a catalytic, enantioselective, vinylogous aldol reaction to efficiently install the C5−C8 fragment.[9] We were pleased to find that the coupling of **6** and the ethyl crotonate-derived silyl dienolate **9** was effected under the Lewis base catalyzed, Lewis acid mediated conditions developed by Denmark with *S,S*-bisphosphoramide **I** as a chiral ligand (Scheme 2).[10] The coupled product **10** was generated in 72% yield with >95% enantiomeric excess. The absolute configuration of the newly generated C9 stereocenter was assigned as *S* by analogy to that reported for this catalytic system.[10] The secondary hydroxyl group in **10** was protected as the *p*-methoxybenzyl ether, and the resulting ester **11** was converted to aldehyde **12** by DIBAL-H reduction and PCC oxidation.

(4) Amphidinolide H, a member of this class of natural products, has been shown to target Actin: (a) Saito, S.-Y.; Feng, J.; Kira, A.; Kobayashi, J.; Ohizumi, Y. *Biochem. Biophys. Res. Commun.* **2004**, *320*, 961. (b) Usui, T.; Kazami, S.; Dohmae, N.; Mashimo, Y.; Kondo, H.; Tsuda, M.; Terasaki, A. G.; Ohashi, K.; Kobayashi, J.; Osada, H. *Chem. Biol.* **2004**, *11*, 1269. However, its molecular structure is very different from that of iriomoteolide 1a.

(5) For examples: (a) Heumann, L. V.; Keck, G. E. *Org. Lett.* **2007**, *9*, 1951. (b) Smith, A. B., III; Razler, T. M.; Meis, R. M.; Pettit, G. R. *Org. Lett.* **2006**, *8*, 797.

(6) (a) Mikami, K.; Ohmura, H.; Yamanaka, M. *J. Org. Chem.* **2002**, *68*, 1081. (b) Mikami, K.; Shimizu, M.; Nakai, T. *J. Org. Chem.* **1991**, *56*, 2952.

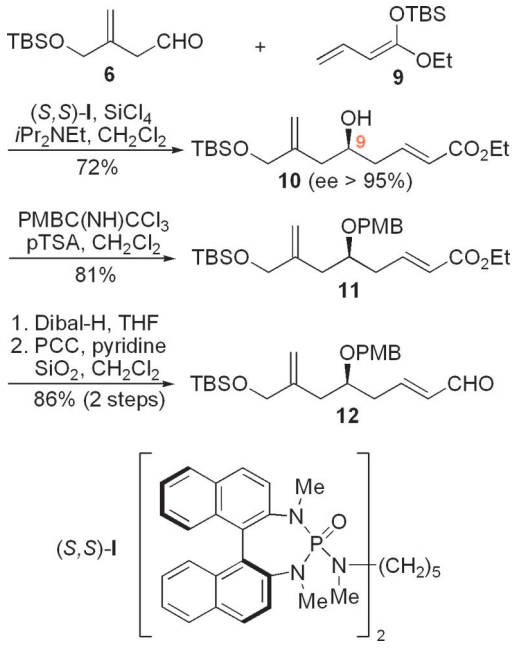
(7) Sanchez, C. C.; Keck, G. E. *Org. Lett.* **2005**, *7*, 3053.

(8) Wee, A. G.; Slobodian, J. *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley and Sons: New York, NY, 1995; Vol. 7, pp 4613−4616.

(9) (a) Denmark, S. E.; Heemstra, J. R., Jr.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4682. (b) Casiraghi, G.; Zanardi, F. *Chem. Rev.* **2000**, *100*, 1929.

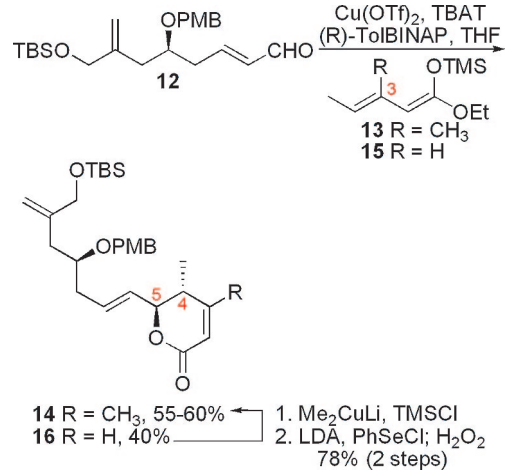
(10) (a) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560. (b) Denmark, S. E.; Beutner, G. L.; Wynn, T.; Eastgate, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 3774. (c) Denmark, S. E.; Beutner, G. L. *J. Am. Chem. Soc.* **2003**, *125*, 7800.

Scheme 2. Synthesis of **12**



With efficient access to **12** secured, we turned our attention to the assembly of the remaining part of **4**. We envisioned α,β-unsaturated δ-lactone **14** as a convenient intermediate since it houses all the necessary structural elements in the form of a multisubstituted lactone. A variety of methods have been reported for the stereoselective synthesis of α,β-unsaturated δ-lactones.[11] However, they all require the use of a stoichiometric amount of chiral auxiliaries and/or multiple steps. We were attracted to reports by Campagne that catalytic vinylogous aldol coupling of γ-substituted silyl dienolates with aldehydes led to enantioselective formation of *trans*-disubstituted α,β-unsaturated δ-lactones in the presence of Carreira's catalyst.[12,13] The possibility of applying this transformation to introduce the remaining part of **4** in one step was too tantalizing to ignore. However, we were not without concern since ethyl silyl dienolate **13**,[14] which was required for the synthesis of **14**, was C3 substituted, and the influence of this methyl substitution over the coupling reaction was unknown. Our experiments showed that vinylogous aldol coupling between **12** and **13** did occur, and a mixture of **14** and its 4*S*,5*S* diastereomer (~1.3:1) was generated in a yield of 55−60% (Scheme 3). Unfortunately, the diastereoselectivity of this coupling could not be improved despite extensive experimentation. A solution was eventually found that involved vinylogous aldol coupling between aldehyde **12** and ethyl

Scheme 3. Second Vinylogous Aldol Reaction

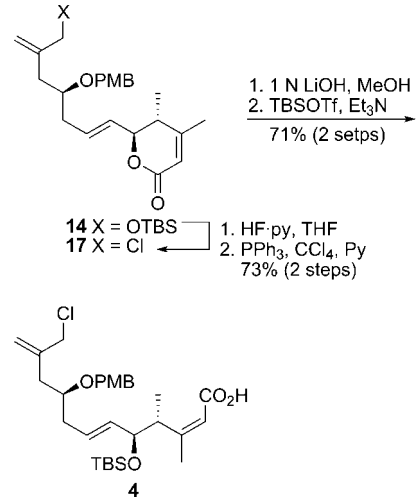


silyl dienolate **15**.[12] The α,β-unsaturated δ-lactone **16** was isolated as a ~5:1 mixture with its 4*S*,5*S* diastereomer. It was converted to **14** by 1,4-addition with Me_2CuLi and PhSeCl mediated dehydrogenation to introduce the C3 methyl group. Consistent with previous reports, formation of diastereomeric mixtures of linear coupling products is the reaction pathway that is responsible for most of the side products in both of these vinylogous aldol reactions.[12]

The TBS protection of **14** was removed by HF•py, and the resulting allylic alcohol was converted to chloride **17** by standard conditions (Scheme 4). Finally, basic hydrolysis of **17** and selective silylation of the C5 hydroxyl group by TBSOTf allowed preparation of **4** in 71% yield.

In summary, an efficient approach for the synthesis of the C1−C12 fragment of iriomoteolide 1a has been developed. All stereocenters of this fragment were constructed by catalytic asymmetric reactions involving reagent control. A catalytic vinylogous aldol reaction was used to introduce the C5−C8

Scheme 4. Synthesis of **4**



(11) (a) Boucard, V.; Broustal, G.; Campagne, J. M. *Eur. J. Org. Chem.* **2007**, 225. (b) Marco, J. A.; Carda, M.; Murga, J.; Falomir, E. *Tetrahedron* **2007**, *63*, 2929.

(12) (a) Bazán-Tejeda, E.; Bluet, G.; Broustal, G.; Campagne, J.-M. *Chem. Eur. J.* **2006**, *12*, 8358. (b) Bluet, G.; Bázan-Tejeda, B.; Campagne, J.-M. *Org. Lett.* **2001**, *3*, 3807.

(13) (a) Pagenkopf, B. L.; Krüger, J. K.; Stojanovic, A.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 3124. (b) Krüger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837.

(14) Cameron, D. W.; Looney, M. G.; Pattermann, J. A. *Tetrahedron Lett.* **1995**, *36*, 7555.

fragment enantioselectively. A second catalytic vinylogous aldol reaction was used to install the remaining two stereocenters and a stereodefined alkene in the form of an α,β-unsaturated δ-lactone in one step. The synthesis of building block **3** and its coupling with **4** to synthesize iriomoteolide 1a is in progress and will be reported in due course.

Acknowledgment. Financial support was provided by the Texas A&M University and The Welch Foundation. We thank Dr. Shane Tichy, Laboratory for Biological Mass Spectrometry (TAMU), for mass spectral analyses. We thank Professor Daniel Romo of Texas A&M University 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.

OL801940R