Tetrahedron Letters 50 (2009) 1416–1418

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Stereoselective synthesis of the C_1–C_{12} segment of iriomoteolide-1a: a very potent macrolide antitumor agent

Arun K. Ghosh *, Hao Yuan

Departments of Chemistry and Medicinal Chemistry, Purdue University, West Lafayette, IN 47907, USA

ARTICLE INFO

Article history:
Received 5 November 2008
Revised 24 December 2008
Accepted 9 January 2009
Available online 14 January 2009

ABSTRACT

A stereoselective synthesis of the C_1–C_{12} segment of the potent cytotoxic macrolide, iriomoteolide 1a, has been accomplished. The key steps involve an enzymatic kinetic resolution of a β-hydroxy amide, a Pd-catalyzed cross-coupling to construct a substituted allylsilane, a highly and stereoselective conjugate addition of lithium dimethylcopper to an α,β-acetylenic ester and an elaboration of the C_6–C_7 trans-olefin geometry by a Julia-Kocienski olefination.

Macrocyclic marine natural products are a rich source of potent and structurally novel anticancer agents with clinical potential.[1] Over the years, Kobayashi and co-workers have reported isolation of a variety of structurally diverse macrolides known as amphidinolides from marine dinoflagellates, *Amphidinium* Sp.[2] Recently, Tsuda and co-workers isolated iriomoteolide-1a (**1**), a 20-membered macrolide from *Amphidinium* Sp. from benthic sea sand collected off Iriomote island in Japan.[3] Iriomoteolide-1a displayed remarkably potent cytotoxicity against human B lymphocyte DG-75 cells with an IC_{50} value of 2 ng/mL. Furthermore, it has shown cytotoxicity against Epstein-Barr virus—infected human B lymphocyte Raji cells with IC_{50} value of 3 ng/mL. Despite its potent activity, the biological mechanism of action of iriomoteolide-1a is currently unknown. The gross structure of **1** was established by extensive mass spectroscopy and NMR studies.[3] The unique structural features of iriomoteolide-1a coupled with its potent antitumor activity attracted our interest in its synthesis and structure-activity studies. Herein, we report synthesis of the C_1–C_{12} segment of iriomoteolide 1a in which the key steps involve lipase-catalyzed kinetic resolution of a β-hydroxy amide, a highly stereoselective conjugate addition, and a Julia-Kocienski olefination to install the C_6–C_7 trans-olefin geometry. Thus far, only Yang and co-workers have reported the synthesis of C_1–C_{12} fragment of iriomoteolide 1a, and the total synthesis of iriomoteolide has not yet been achieved.[4]

As shown in Figure 1, our synthetic strategy of iriomoteolide 1a is convergent, and involves the assembly of fragments **2** (C_1–C_{12} segment) and **3** (C_{13}–C_{23} segment) by a Sakurai reaction[5] and subsequent macrolactonization between the C_{19}-hydroxyl group and the C_1-carboxylic acid. Segment **2** was can be synthesized by a Julia-Kocienski olefination reaction[6] between sulfone **4** and aldehyde **5**. This reaction is expected to establish the C_6–C_7 trans-olefin geometry.

The synthesis of sulfone **4** was carried out as shown in Scheme 1. Deprotonation of *N*-methoxy-*N*-methylacetamide by lithium diisopropylamide followed by reaction of the resulting enolate with acrolein at −78 °C gave racemic alcohol **6** in 91% yield. The racemic alcohol **6** was then exposed to an enzymatic acylation reaction using lipase PS-30 in pentane in the presence of excess vinyl acetate at 25 °C for 30 h to provide enantio-enriched acetate derivative **7** in 49% yield and alcohol (*R*)-(+)-**6** in 45% yield.[7] The alcohol was

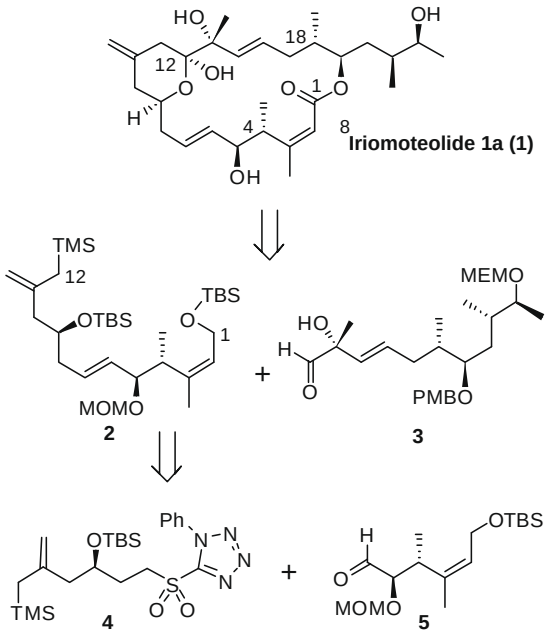
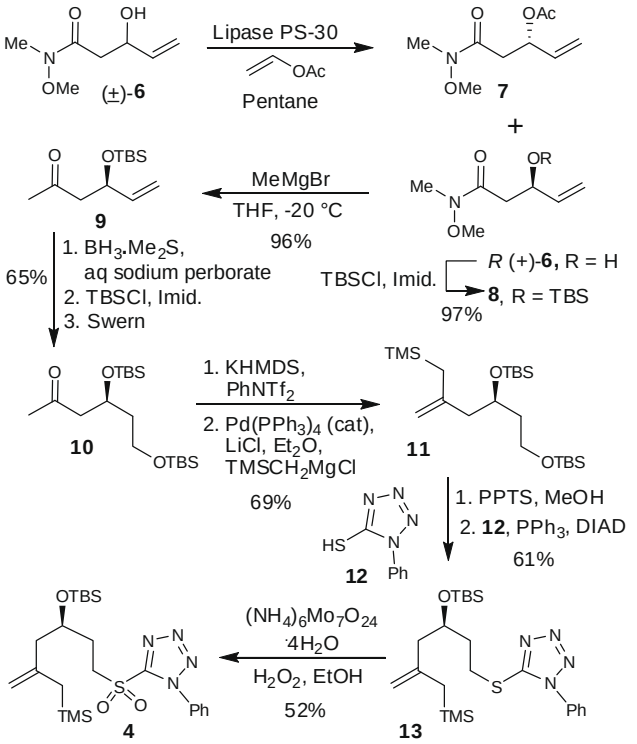


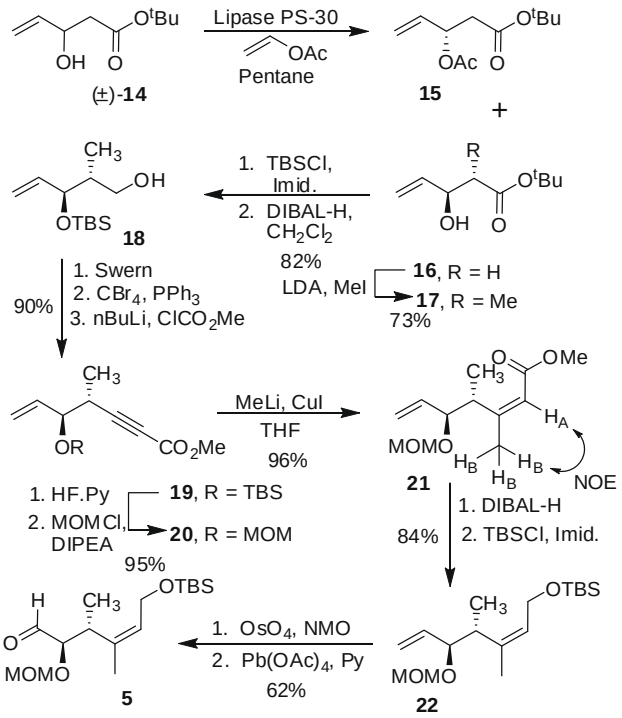
Figure 1. Retrosynthetic analysis of iriomoteolide 1a.

* Corresponding author. Tel.: +1 765 494 5323; fax: +1 765 496 1612.
E-mail address: akghosh@purdue.edu (A.K. Ghosh).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.01.043



Scheme 1. Synthesis of sulfone **4**.



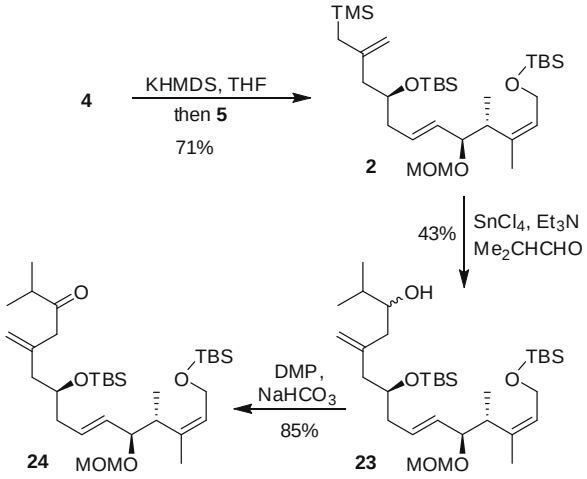
Scheme 2. Synthesis of aldehyde **5**.

converted to its corresponding Mosher's ester, and an optical purity of 97% ee was determined by ^{19}F NMR analysis.[8] Protection of alcohol R(+)-**6** with *tert*-butyldimethylsilyl chloride and imidazole provided silyl ether **8**. Reaction of **8** with methylmagnesium bromide furnished methyl ketone **9** in 96% yield. Treatment of **9** with borane dimethylsulfide complex resulted in hydroboration of the olefin as well as in the reduction of the ketone providing a diol. The resulting diol was selectively protected to give the bis-silyl ether. Swern oxidation of the resulting alcohol furnished methyl ketone **10**. Treatment of methyl ketone **10** with KHMDS and phenyl triflimide in THF from −100 °C to −78 °C gave the corresponding vinyl triflate. Cross-coupling[9] of the triflate and trimethylsilylmethylmagnesium chloride in the presence of a catalytic amount of $Pd(PPh_3)_4$ (7 mol %) afforded the allyl silane **11** in 69% yield in two steps. Treatment of silyl ether **11** with pyridinium *p*-toluenesulfonate in methanol at 23 °C for 4 h resulted in the deprotection of the primary silyl ether to provide the corresponding alcohol. A Mitsunobu reaction of the alcohol with 1-phenyl-1*H*-tetrazole-5-thiol furnished the sulfide **13**. It was oxidized by hydrogen peroxide in the presence of ammonium molybdate to furnish sulfone **4**, as one of the Julia-Kocienski olefination precursors.

The synthesis of aldehyde is outlined in Scheme 2. Enolization of *tert*-butylacetate using lithium diisopropylamide followed by reaction of the resulting enolate with acrolein at −78 °C gave racemic alcohol **14** in 90% yield.[10] The racemic alcohol **14** was then exposed to lipase PS-30 in pentane in the presence of excess vinyl acetate at 30 °C for 19 h to provide acetate derivative **15** and enantio-enriched alcohol **16** in 47% and 44% yields, respectively.[11] The alcohol was converted to the corresponding Mosher ester, and ^{19}F NMR analysis revealed optical purity to be 98% ee.[8] Treatment of alcohol **16** with lithium diisopropylamide followed by reaction of the resulting dianion with methyl iodide as described by Seebach and co-workers afforded the anti-alcohol **17** as a single isomer by ^{1}H-NMR analysis.[12] Protection of alcohol as TBS-ether followed by DIBAL-H reduction afforded alcohol **18**. Swern oxidation of **18** followed by subjection of the resulting aldehyde to Corey-Fuchs' homologation[13] aldehyde **5**. Using carbon tetrabromide and triphenyl-phosphine in dichloromethane at 0 °C to 23 °C for 30 min afforded the corresponding dibromo olefin in 90% yield for two steps. Treatment of the dibromide with butyl lithium followed by reaction of the derived alkynyl anion with methyl chloroformate furnished the alkynyl ester **19** in near quantitative yield. Removal of the TBS-ether by exposure to HF·pyridine followed by protection of the alcohol as a MOM-ether with MOMCl and diisopropylethylamine afforded **20** in 95% yield. Alkynyl ester **20** was treated with freshly prepared Me_2CuLi[14] to provide the *Z*-olefin **21** as a single product in 96% isolated yield. The observed NOESY among the protons is consistent with the assigned *Z*-olefin geometry in ester **21**. DIBAL-H reduction followed by protection with *tert*-butyldimethylsilyl chloride furnished the silyl ether **22**. Selective oxidative cleavage of the terminal olefin provided the other Julia-Kocienski olefination precursor, aldehyde **5**.

With the aldehyde and sulfone in hand, we then carried out Julia-Kocienski olefination as shown in Scheme 3. Thus, treatment of sulfone **4** with KHMDS in THF followed by addition of aldehyde **5** provided **2** (C_1–C_{12} segment) in 71% isolated yield.[15] To test the feasibility of the Sakurai reaction, we have investigated reaction of allyl silane **2** with isobutylaldehyde as a model. As shown, the reaction of **2** with 1.5 equiv of isobutylaldehyde in the presence of 1.5 equiv of $SnCl_4$ and 0.5 equiv of Et_3N at −78 °C for 10 min in CH_2Cl_2 afforded alcohol **23** as a mixture (1:1.5) of diastereoisomers in 43% yield. Dess–Martin Periodinane oxidization of the alcohol mixture furnished ketone **24** in 85% yield.[15]

In summary, a highly stereocontrolled synthesis of the C_1–C_{12} fragment of iriomoteolide 1a has been achieved. Lipase-catalyzed kinetic resolution of β-hydroxy amide provided the key starting material for the synthesis. Other important steps involve a Pd-catalyzed cross-coupling reaction, a highly stereoselective conjugate addition of methylcuprate to an α,β-acetylenic ester, and elaboration of the C_6–C_7 trans-olefin geometry by a Julia-Kocienski olefin-



Scheme 3. Synthesis of ketone **24**.

ation reaction. Sakurai reaction of **2** with isobutylaldehyde followed by oxidation of the resulting alcohol provided ketone **24** in modest yield. Further work toward the total synthesis of iriomoteolide-1a is in progress.

Acknowledgment

This research is supported in part by the National Institutes of Health.

References and notes

1. Harris, C. R.; Danishefsky, S. J. *J. Org. Chem.* **1999**, *64*, 8434.
2. Kobayashi, J.; Kubota, T. *J. Nat. Prod.* **2007**, *70*, 451.
3. 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.
4. Fang, L.; Xue, H.; Yang, J. *Org. Lett.* **2008**, *10*, 4645.
5. Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, 1295.
6. Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26.
7. Enzymatic resolution of β-hydroxy amide, particularly with Weinreb amide, has not been reported. For enzymatic resolution of β-hydroxy ester, see: Vrielynck, S.; Vandewalle, M.; García, A. M.; Mascareñas, J. L.; Mouriño, A. *Tetrahderon Lett.* **1995**, *36*, 9023.
8. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
9. Enev, V. S.; Kachlig, H.; Mulzer, J. *J. Am. Chem. Soc.* **2001**, *123*, 10764.
10. Ghosh, A. K.; Kulkarni, S. *Org. Lett.* **2008**, *10*, 3907.
11. Pollini, G. P.; Risi, C. D.; Lumento, F.; Marchetti, P.; Zanirato, V. *Synlett* **2005**, 164.
12. (a) Seebach, D.; Aebi, J.; Wasmuth, D. *Organic Synthesis*; John Wiley and Sons: New York, 1990. Collect. Vol. III. pp 153–159; (b) Hermann, J. L.; Schlessinger, R. A. *Tetrahedron Lett.* **1973**, *14*, 2429.
13. Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769.
14. Corey, E. J.; Katzenel, J. *J. Am. Chem. Soc.* **1969**, *91*, 1851.
15. All new compounds gave satisfactory spectroscopic and analytical results. Compound **2**: ^{1}H NMR ($CDCl_3$): δ 5.66 (dt, J = 15.5, 7.0 Hz, 1H), 5.38 (t, J = 5 Hz, 1H), 5.25 (dd, J = 15.5, 9.0 Hz, 1H), 4.65 (d, J = 7.0 Hz, 1H), 4.60 (d, J = 2.5 Hz, 1H), 4.57 (d, J = 2.5 Hz, 1H), 4.37 (d, J = 7.0 Hz, 1H), 4.31 (dd, J = 7.2, 13.0 Hz 1H), 4.23–4.16 (m, 1H), 3.85–3.79 (m, 1H), 3.31 (s, 3H), 2.67–2.64 (m, 1H), 2.31–2.20 (m, 2H), 1.68 (br s, 3H), 0.92 (d, J = 6.9 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.06–0.01 (m, 21H). Compound **24**: ^{1}H NMR ($CDCl_3$): δ 5.67 (dt, J = 15, 7.0 Hz, 1H), 5.42 (t, J = 4.5 Hz, 1H), 5.28 (dd, J = 15, 8.0 Hz, 1H), 5.00 (s, 1H), 4.94 (s, 1H), 4.67 (d, J = 7.0 Hz, 1H), 4.41 (d, J = 7.0 Hz, 1H), 4.33 (dd, J = 13.0, 5 Hz, 1H), 4.20 (dd, J = 13.0 Hz, 1H), 3.87 (t, J = 5.0 Hz, 1H), 3.83 (t, J = 9.0 Hz, 1H), 3.34 (s, 3H), 3.24 (AB, J_{AB} = 16.0 Hz, ΔV_{AB} = 32.5 Hz, 2H), 2.75–2.71 (m, 1H), 2.72–2.67 (m, 1H), 2.33–2.26 (m, 2H), 2.25–2.20 (m, 2H), 1.72 (br s, 3H), 1.13 (s, 3H), 1.12 (s, 3H), 0.92 (d, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.06–0.01 (m, 12H); MS (EI), m/z = 619 $(M+Na)^+$.