



Stereoselective synthesis of the C₁–C₁₂ 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

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ABSTRACT

A stereoselective synthesis of the C₁–C₁₂ 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 C₆–C₇ trans-olefin geometry by a Julia-Kocienski olefination.

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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 IC₅₀ value of 2 ng/mL. Furthermore, it has shown cytotoxicity against Epstein-Barr virus-infected human B lymphocyte Raji cells with IC₅₀ 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 C₁–C₁₂ 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 C₆–C₇ trans-olefin geometry. Thus far, only Yang and co-workers have reported the synthesis of C₁–C₁₂ 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** (C₁–C₁₂ segment) and **3** (C₁₃–C₂₃ segment) by a Sakurai reaction⁵ and subsequent macrolactonization between the C₁₉-hydroxyl group and the C₁-carboxylic acid. Segment **2** was can be synthesized by a Julia-Kocienski olefination⁶ between sulfone **4** and aldehyde **5**. This reaction is expected to establish the C₆–C₇ 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

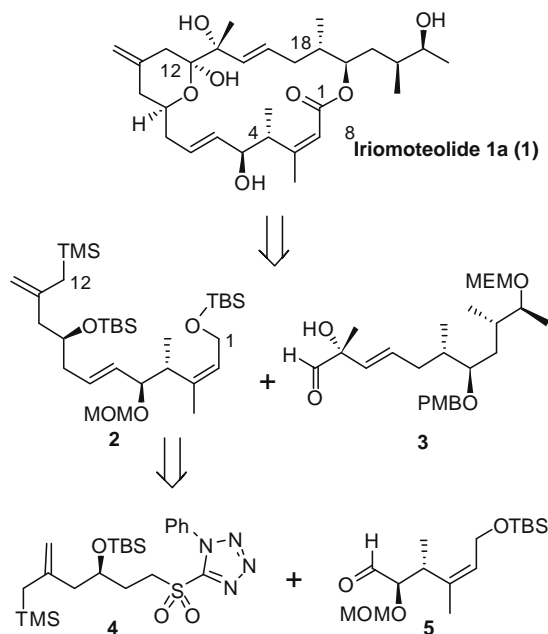
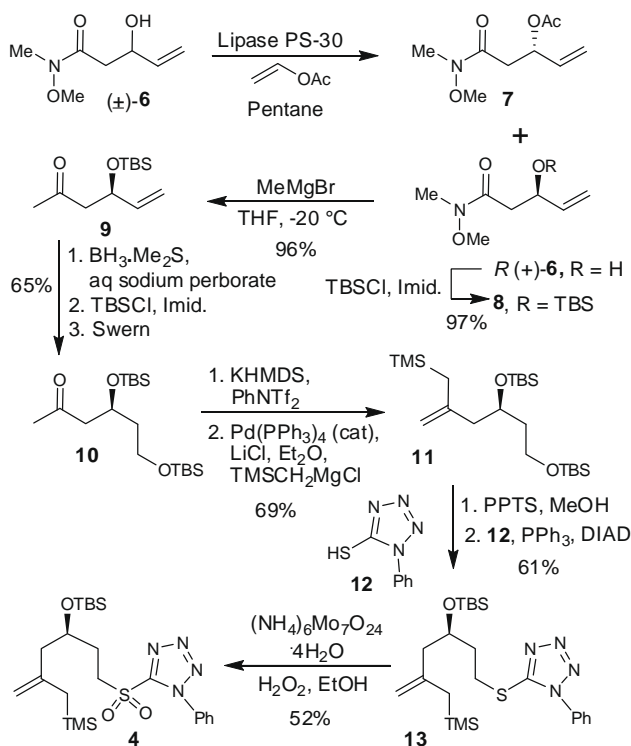


Figure 1. Retrosynthetic analysis of iriomoteolide 1a.

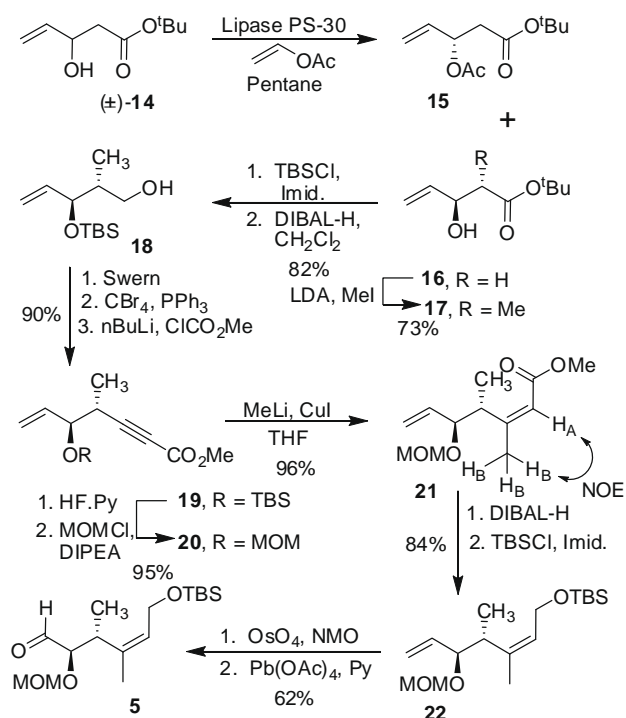
* Corresponding author. Tel.: +1 765 494 5323; fax: +1 765 496 1612.
E-mail address: akghosh@purdue.edu (A.K. Ghosh).



Scheme 1. Synthesis of sulfone 4.

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 $-100\text{ }^{\circ}\text{C}$ to $-78\text{ }^{\circ}\text{C}$ gave the corresponding vinyl triflate. Cross-coupling⁹ of the triflate and trimethylsilylmethylmagnesium chloride in the presence of a catalytic amount of $\text{Pd}(\text{PPh}_3)_4$ (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 $23\text{ }^{\circ}\text{C}$ 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 $-78\text{ }^{\circ}\text{C}$ 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 $30\text{ }^{\circ}\text{C}$ 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 ^1H -NMR analysis.¹² Protection of alcohol as TBS-ether followed by DIBAL-H reduction afforded alcohol 18. Swern oxidation of 18 followed by subject-

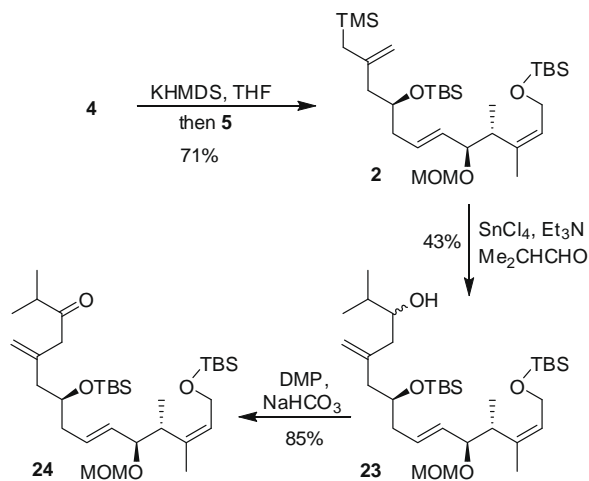


Scheme 2. Synthesis of aldehyde 5.

tion of the resulting aldehyde to Corey-Fuchs' homologation¹³ aldehyde 5. Using carbon tetrabromide and triphenylphosphine in dichloromethane at $0\text{ }^{\circ}\text{C}$ to $23\text{ }^{\circ}\text{C}$ 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 ($\text{C}_1\text{--}\text{C}_{12}$ segment) in 71% isolated yield.¹⁵ To test the feasibility of the Sakurai reaction, we have investigated reaction of allyl silane 2 with isobutyraldehyde as a model. As shown, the reaction of 2 with 1.5 equiv of isobutyraldehyde in the presence of 1.5 equiv of SnCl_4 and 0.5 equiv of Et_3N at $-78\text{ }^{\circ}\text{C}$ for 10 min in CH_2Cl_2 afforded alcohol 23 as a mixture (1:1.5) of diastereoisomers in 43% yield. Dess–Martin Periodinane oxidation of the alcohol mixture furnished ketone 24 in 85% yield.¹⁵

In summary, a highly stereocontrolled synthesis of the $\text{C}_1\text{--}\text{C}_{12}$ 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 $\text{C}_6\text{--}\text{C}_7$ 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 iriomo-teolide-1a is in progress.

Acknowledgment

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- All new compounds gave satisfactory spectroscopic and analytical results. Compound **2**: $^1\text{H NMR}$ (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**: $^1\text{H NMR}$ (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, $J_{\text{AB}} = 16.0$ Hz, $\Delta V_{\text{AB}} = 32.5$ 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), $m/z = 619$ ($\text{M}+\text{Na}$) $^+$.