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

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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 a substituted allylsilane, a highly regio- and stereoselective conjugate addition of lithium dimethylcopper to an *α*, *β*-acetylenic esters 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 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 cytoxicity 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 coworkers 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 planned to 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

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with acrolein at −78 °C gave racemic alcohol **6** in 91% yield. The racemic alcohol **6** was then exposed to 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 converted to its corresponding Mosher's ester and 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 the hydroboration of the olefin as well as 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**, one of the Julia-Kocienski olefination precursors.

The synthesis of aldehyde **5** and its subsequent conversion to C_1-C_{12} segment (**2**) 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 enantioenriched 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 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 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 are 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 diastereoisomer 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 regioselective and stereoselective conjugate addition of methylcuprate to an *α*, *β*-acetylenic esters and elaboration of the C_6-C_7 trans-olefin geometry by a Julia-Kocienski olefination 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.

Acknowledgments

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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 (brs, 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, 5Hz, 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} = 16.0Hz, ΔV_{AB} = 32.5Hz, 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 (brs, 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 $(M^+Na)^+$.

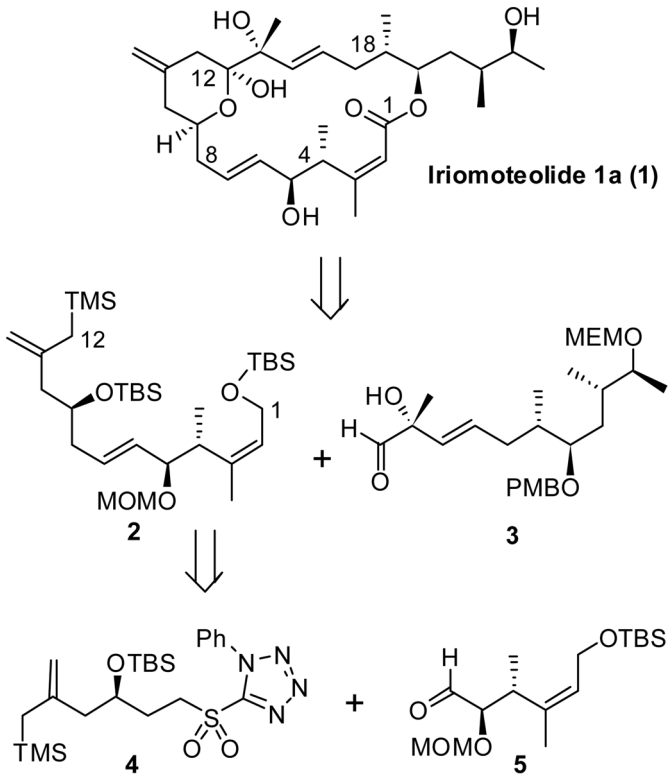
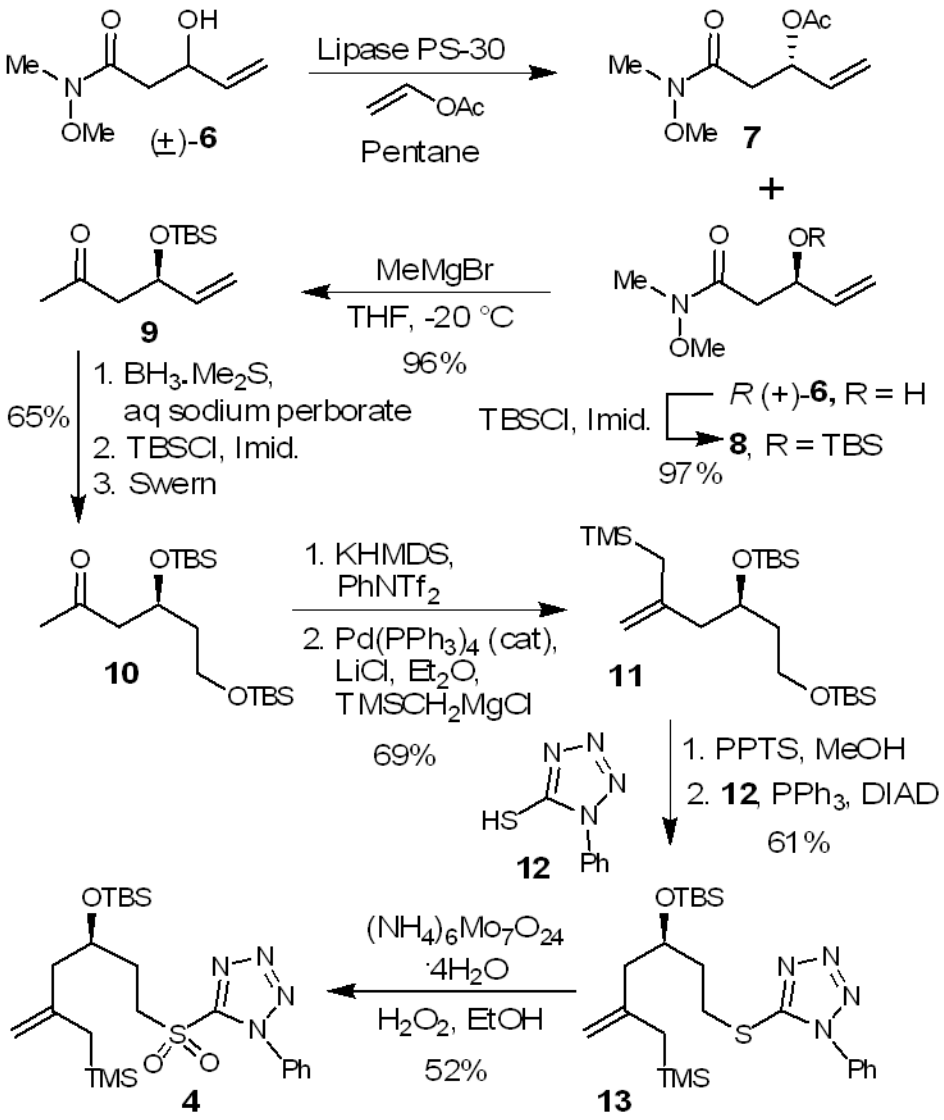
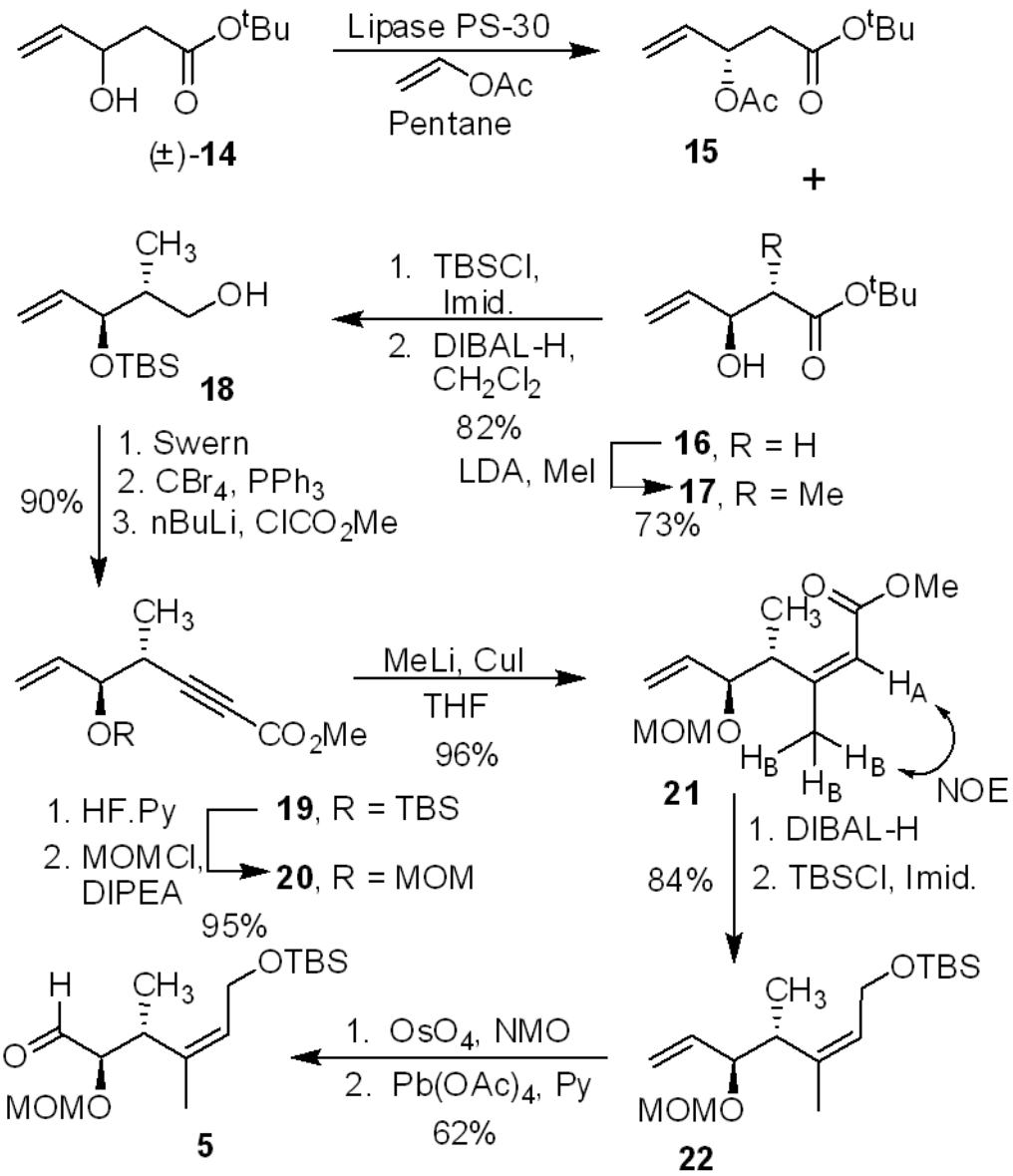


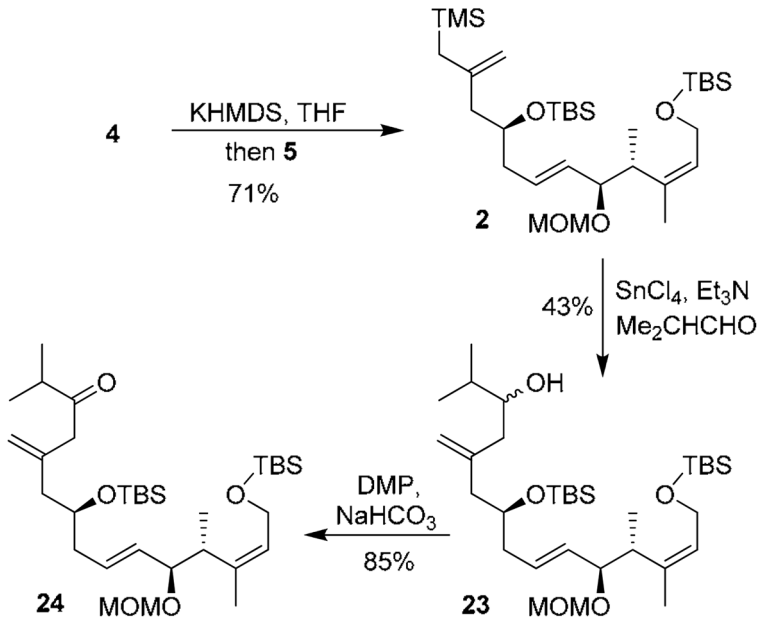
Figure 1.
Retrosynthetic analysis of iriomoteolide 1a



Scheme 1.
Synthesis of sulfone **4**



Scheme 2.
Synthesis of aldehyde **5**



Scheme 3.
Synthesis of ketone **24**