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Synthesis of Iriomoteolide-1a C13−C23 Fragment via Asymmetric Conjugate Addition and Julia−Kocienski Coupling Reaction

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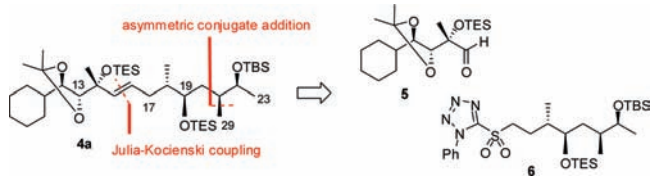
ABSTRACT



The key C13−C23 fragment toward the total synthesis of iriomoteolide-1a (1) has been constructed from an 1,2-acetonide containing aldehyde 5 via a Julia−Kocienski olefination with the C16−C23 segment 6. The key step involves stereoselective introduction of the C29 methyl group by a highly efficient CuI-Tol-BINAP-catalyzed asymmetric conjugate addition of methylmagnesium bromide to an α,β-unsaturated ester.

Recently, Tsuda and co-workers have reported isolation of a series of macrolides named iriomoteolides from marine dinoflagellates, *Amphidinium* sp., collected off the Iriomote Island of Japan.[1] Among them, iriomoteolide-1a (**1**) exhibited potent cytotoxicity against human B lymphocyte DG-75 cells with an IC_{50} of 2 ng/mL and Epstein−Barr virus (EBV)-infected human B lymphocyte Raji cells with an IC_{50} of 3 ng/mL.[1b] To date, this natural product has yet to surrender itself to any total synthesis. Nevertheless, Yang's group and Ghosh's group have reported synthesis of the C1−C12 fragment.[2] Moreover, Horne et al. lately has described the synthetic route of the cyclic hemiketal core of the molecule.[3] Its unique molecular structure and potent cytotoxicity have also attracted our interest in its synthesis. Herein, we report the synthesis of C13−C23 fragment of iriomoteolide-1a (**1**).

Our approach to the development of an efficient method for the construction of iriomoteolide-1a (**1**) is as shown in Scheme 1. The strategy involves stereoselective allylations of **3** (C1−C9 segment) and **4** (C13−C23 segment) by fragment **2** (C10−C12 segment), followed by a Yamaguchi macrolactonization between the C1-carbonyl and C19-hydroxyl group for construction of the macrolide ring. Fragment **4** in turn, can be obtained via Julia−Kocienski olefination between aldehyde **5** and sulfone **6**, with *E*-alkene geometry at C15−C16.

(1) The investigation of the *Amphidinium* strain HYA024 led to isolation of iriomoteolide-1a (**1**), -1b, and -1c. (a) Isolation and structural elucidation of iriomoteolide-1a (**1**): 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. (b) Isolation and structural elucidation of iriomoteolide-1b and -1c: Tsuda, M.; Oguchi, K.; Iwanmoto, R.; Okamoto, Y.; Fukushi, E.; Kawabata, J.; Ozawa, T.; Masuda, A. *J. Nat. Prod.* **2007**, *70*, 1661.

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(3) Xie, J.; Horne, D. A. *Tetrahedron Lett.* **2009**, *50*, 4485.

(4) The diastereoselectivity and enantioselectivity were determined by comparison with the NMR spectroscopic and HPLC analytical results of diastereomers obtained from this paper: Nots, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386.

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(6) Compound **11a** has also been used in an alternative synthesis of the C13−C23 fragment (results submitted for publication).

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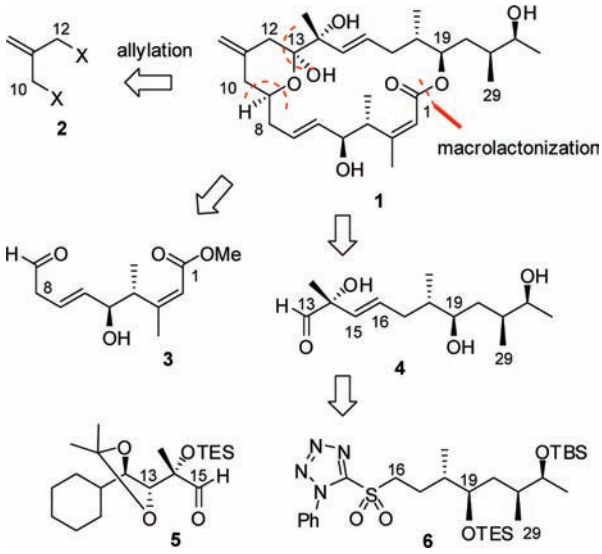
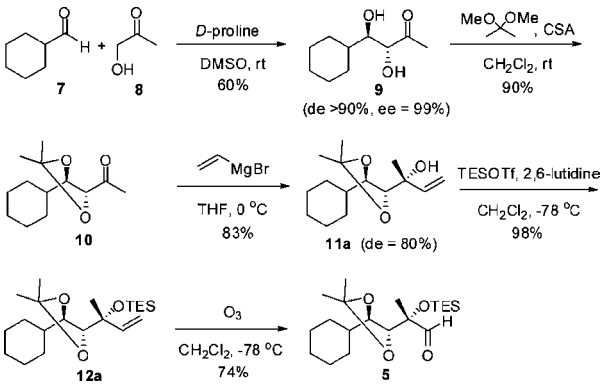
Scheme 1. Retrosynthetic Analysis of Iriomoteolide-1a (**1**)



Our synthesis of the aldehyde **5**, shown in Scheme 2, commences with cyclohexanecarbaldehyde **7** and hydroxyacetone **8**. The direct asymmetric aldol reaction catalyzed

Scheme 2. Synthesis of Aldehyde **5**



by D-proline provided *anti*-diol **9** in 60% yield, with a dr >20:1 and ee >99%.[4] Ensuing isoproylidene formation[5] was employed to protect the 1,2-diol. The Grignard derived from vinyl bromide was added smoothly to intermediate **10** leading ultimately to tertiary alcohol **11a**,[6] whose diastereomeric purity (80% de) was determined by ^{1}H NMR analysis. Subsequent silylation[7] followed by ozonolysis generated aldehyde **5**. The stereochemistries were further confirmed by X-ray structural analysis of PMB ether protected **11a** (Figure 1).

Our synthesis of sulfone **6** is depicted in Scheme 3. Silyl ether protection of (−)-methyl-L-lactate **13** followed by a one-pot DIBAL-H reduction−Wittig olefination[8] protocol afforded the *trans*-enoate **15** in 69% yield. By means of an asymmetric conjugate addition of Grignard reagents to α,β-

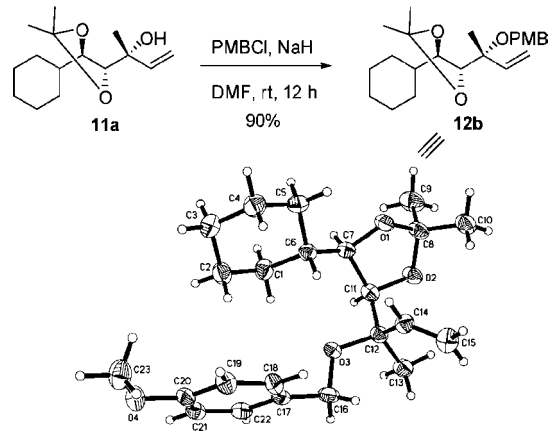


Figure 1. Stereochemical Determination of **11a**

unsaturated ester previously developed in our group, the C29 methyl moiety was stereoselectively introduced into the acyclic carbon chain **15** using (*R*)-Tol-BINAP, to give **16** in 94% de (Table 1).[9,10] Subsequently, DIBAL-H reduction followed by asymmetric Brown crotylation[11] of aldehyde **17** furnished **18** with two new stereogenic centers. Next, the secondary hydroxyl group in **18** was protected as the triethylsilyl ether. Following oxidation of the terminal olefin

Scheme 3. Synthesis of Sulfone **6**

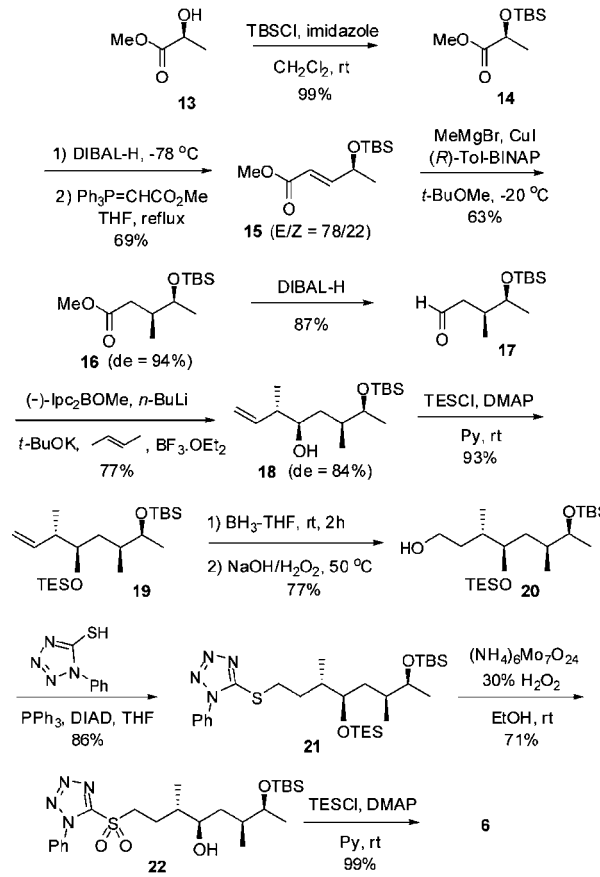
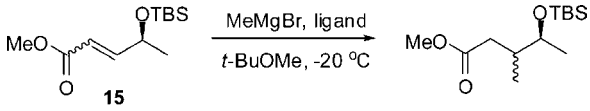


Table 1. 1,4-Michael Addition of MeMgBr to **15**[a]



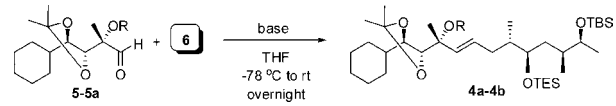
entry	ester	catalyst	yield (%)	*anti:syn*[b]
1	*trans*-**15**	10 mol % CuI	64	95:5
2	*trans*-**15**	2 mol % CuI + 3 mol % (*S*)-Tol-BINAP	60	>99:1
3	*trans*-**15**	2 mol % CuI + 3 mol % (*R*)-Tol-BINAP	63	3:97
4	*cis*-**15**	10 mol % CuI	0	

[a] All reactions were performed with **15** (0.5 mmol) and MeMgBr (2.5 mmol, 3 M in diethyl ether) in *t*-BuOMe (1 mL) at −20 °C. [b] Determined by crude ^{13}C NMR.

in **19** employing hydrogen peroxide as the oxidizing agent,[12] the resulting primary alcohol **20** was subjected to Mitsunobu protocol,[13] affording the desired aryl sulfide **21** in good yield. Finally, completion of the requisite sulfone **6** was achieved by oxidation using ammonium molybdate and hydrogen peroxide.[13]

With the aldehyde **5** and sulfone **6** in hand, we then carried out Julia−Kocienski olefination[14] (Table 2). The use of KHMDS (in toluene) provided **4a** (C13−C23 fragment) in only 29% isolated yield with low regioselectivity. Interestingly, when KHMDS (in THF) was used, the desired product was isolated as a single isomer, albeit in low yield (27%, Table 2, entry 2). In addition, replacement of the TES ether protecting group with a PMB ether proved detrimental, suggesting steric effect from the adjacent tertiary protected hydroxyl group in operation.

Table 2. Julia−Kocienski Olefination



entry	R	base (soln)	product (yield, %)	*E:Z*[a]
1	TES	KHMDS (in toluene)	**4a** (29)	60:40
2	TES	KHMDS (in THF)	**4a** (27)	>99:1
3	PMB	KHMDS (in toluene)	**4b** (trace)	

[a] The *E/Z* ratios were determined by ^{1}H NMR analysis of the crude product mixtures.

In summary, we have developed an asymmetric synthesis of the C13−C23 fragment of iriomoteolide-1a (**1**). Further work toward the total synthesis of iriomoteolide-1a (**1**) is in progress.

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Supporting Information Available: Additional experiment procedures, cif file of crystallographic data for compound **12b**, and NMR spectral data for reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Diastereoselectivity was determined by ^{13}C NMR by comparing an average of carbon signals with respective diastereomeric mixtures of the acyclic carbon chain. The stereochemistry was assigned on the basis of enantiomeric Tol-BINAP ligands.

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