Total synthesis of the proposed structure of iriomoteolide-1a†

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Received 28th March 2010, Accepted 21st April 2010
First published as an Advance Article on the web 18th May 2010
DOI: 10.1039/c0cc00628a

The total synthesis of the proposed structure of iriomoteolide-1a has been accomplished *via* a Yamaguchi esterification and ring closing metathesis sequence between the C(7)–C(23) and newly synthesized *Z*-alkenoic acid C(1)–C(6) fragments. The spectral data of the synthetic 1, however, is at odds with data reported for the natural product, thus bringing into question the original structural assignment.

In 2007, Tsuda's group isolated a potent cytotoxic 20-membered ring macrolide iriomoteolide-1a[1] (**1**) from the *Amphidinium* sp. strain HYA024. The structure elucidation was mainly based on 2D-NMR spectroscopy and mass spectral analysis. Because iriomoteolide-1a possesses extremely potent biological activity against human B lymphocyte DG-75 cells and Epstein-Barr virus-infected human B lymphocytes (Raji cells), the total synthesis of this cytotoxic 20-membered ring macrolide is being pursued by a number of different groups. Thus far, the total synthesis of iriomoteolide-1a has not been reported, but several laboratories have completed the synthesis of various advanced fragments.[2,3]

Herein, we report the total synthesis of the proposed structure of iriomoteolide-1a, which we and others[4] independently found at odds with the original structural assignment of the natural product.

The retrosynthetic strategy for iriomoteolide-1a is shown in Fig. 1. The final assembly of **1** by this route consists of coupling the previously synthesized hemiketal fragment **2**[3b] with acid fragment C(1)–C(6) **3** *via* an esterification and ring closing metathesis.[5] Fragment **3** can be prepared from known diol **4**[6] which harbors the two requisite chiral centers.

The preparation of acid fragment **3** starts from known diol **4** (Scheme 1). Treatment of diol **4** with 4-methoxybenzaldehyde dimethyl acetal followed by selective reduction with DIBAL-H afforded primary alcohol **5**, which was oxidized to aldehyde **6** with Dess–Martin periodinane.[7] Conversion of **6** to propionate **7** was achieved *via* two steps. Addition of propionate **7** with methyllithium in the presence of copper(I) iodide[8] generated *Z*-alkenoic ester **8**. Ester saponification using 1 M LiOH in MeOH–THF gave acid fragment **3** in high yield upon acid work-up.

With secondary alcohol **2** and acid **3** in hand, esterification was accomplished under Yamaguchi conditions[9] (Scheme 2). Treatment of **3** with 2,4,6-trichlorobenzoyl chloride and Et_3N, followed by addition of DMAP and alcohol **2** generated desired product **9** in 50–60% yield, with some decomposed material due to instability of the exocyclic methylene-bearing ketal unit.[10] Deprotection of the PMB group afforded precursor **10**, which is primed for ring closing metathesis.

To improve the yield of the above esterification step and avoid a difficult chromatographic separation from side-products, an alternative strategy for preparing the penultimate intermediate **10** was pursued. This approach involved performing the esterification prior to the hemiketal ring formation.

Starting with the previously synthesized fragment **11**,[3b] PMB exchange of the TES protecting group was successfully achieved in three steps to afford vinyl iodide **14**.[11] Suzuki–Miyaura coupling[12] between **14** and **15**[3b] produced C(7)–C(23) fragment **16** in good yield. Selective deprotection of the TES protecting group afforded alcohol **17** for Yamaguchi esterification. As anticipated, the yield of esterification between **17** and acid **3** jumped to 93%, avoiding decomposition of the sensitive hemiketal functionality experienced in the conversion of **2** to **9**. Removal of the two Si protecting groups with TBAF produced **19** (Scheme 3).

All that remained in the completion of the total synthesis of **1** (Scheme 4) was two key synthetic manoeuvres: hemiketal ring formation and ring closure. Diol **19** was oxidized to β,γ-unsaturated ketone **20** with SO_3·Py. Global deprotection along with concomitant hemiketal cyclization was observed upon treatment of **20** with DDQ, to afford intermediate **10** in 67% yield. The C(13) stereochemistry of ketal **10** was

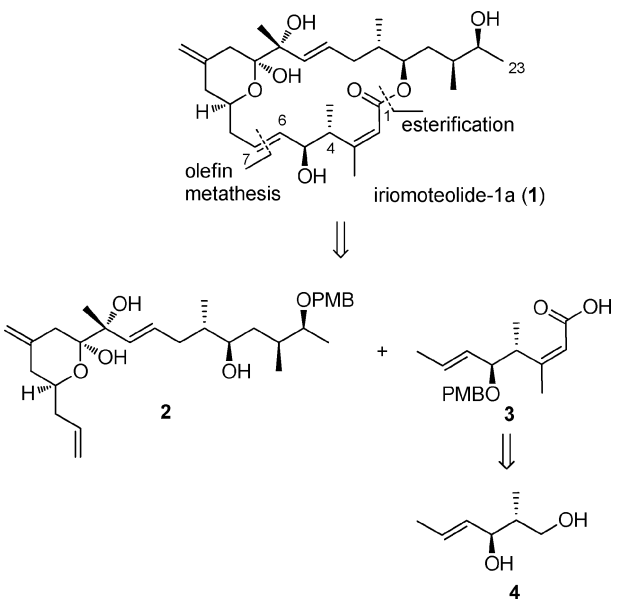

Fig. 1 Retrosynthetic analysis of iriomoteolide-1a.

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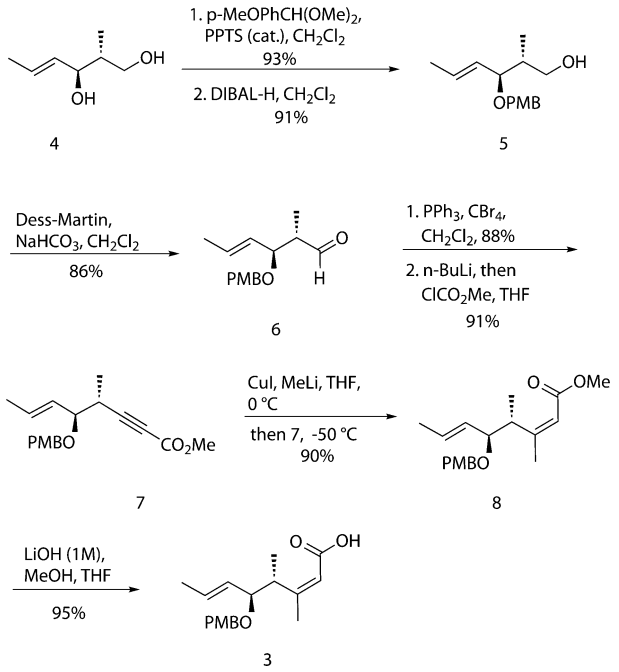
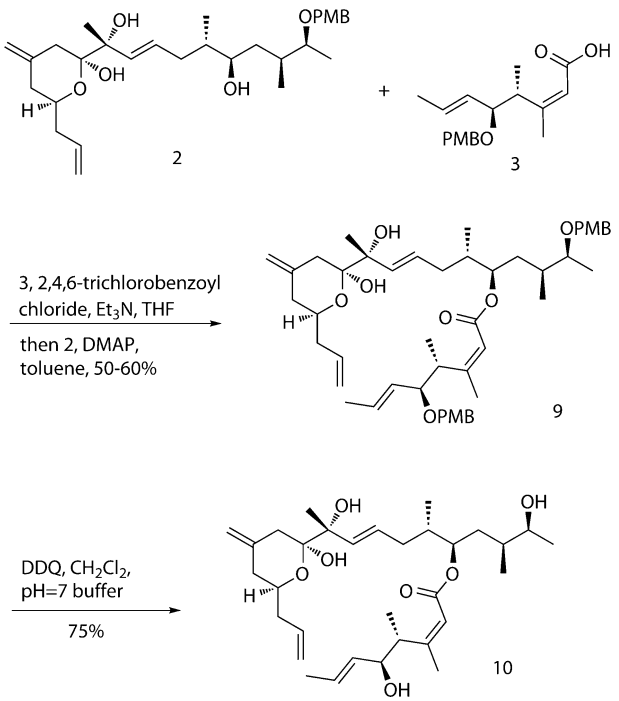
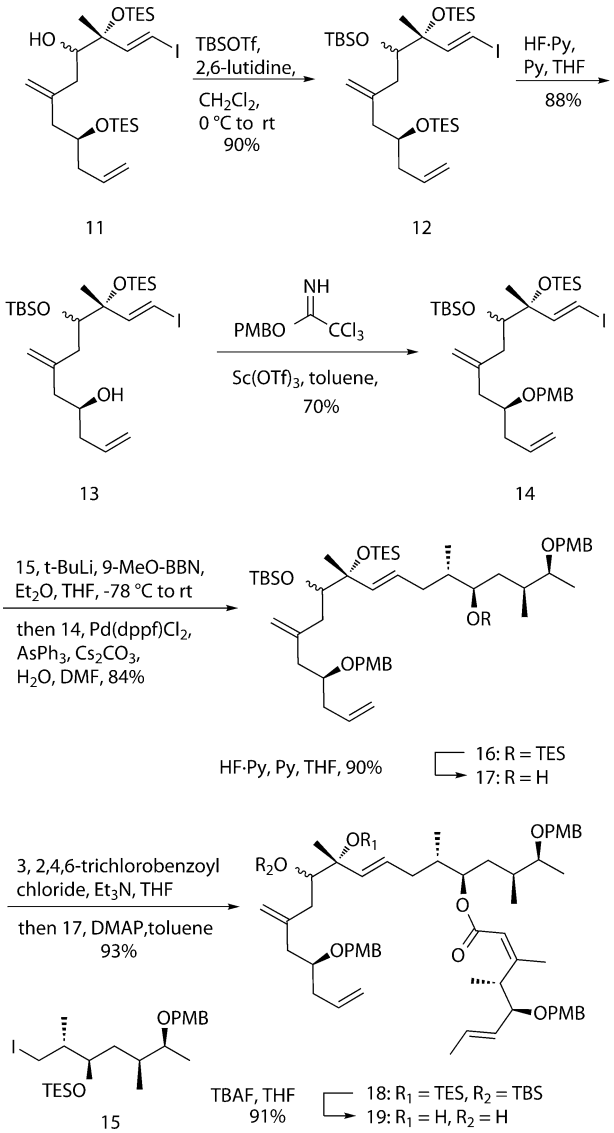
† Electronic supplementary information (ESI) available: Experimental procedures and characterization data for all new compounds. See DOI: 10.1039/c0cc00628a



Scheme 1 Synthesis of acid fragment **3**.



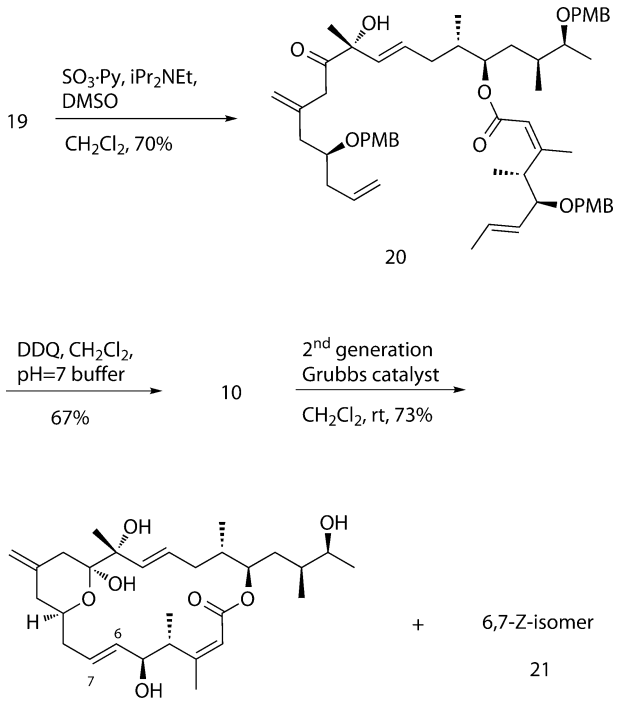
Scheme 2 Synthesis of **10**.



Scheme 3 Synthesis of **19**.

confirmed through an observed ROSEY interaction between H(9) and C(13)–OH. After the successful preparation of **10** by two different strategies, treatment with 2nd generation Grubbs' catalyst[13] gave *E*- and *Z*-products iriomoteolide-1a (**1**) and **21** in 2.5 : 1 ratio, respectively. ^{1}H and ^{13}C NMR spectral data of synthetic iriomoteolide-1a (**1**) did not agree with that reported for the natural material.[1,14] While minor inconsistencies are noted throughout the spectra, the main discrepancies reside with the proton and carbon chemicals shifts at C(4). The H(4) hydrogen resonates at 3.95 ppm and the carbon-13 shift occurs at 41.0 ppm for synthetic iriomoteolide-1a (**1**) compared to 2.46 ppm and 47.9 ppm for the natural compound **1**, respectively. Attempts to prepare crystalline derivatives of **1** have not been successful; however, the significant difference in NMR spectral data brings into question the original structural assignment of the natural product. Based on the chemical shift of H(4) in the natural product, it is likely that the C(2)–C(3) double bond configuration of natural product is *E* instead of *Z*. Finally, anticancer activity for synthetic **1** was examined in two different cell lines (Raji and A431) and no significant cytotoxicity was observed at 10 μM concentration.

In summary, the first total synthesis of the proposed structure of iriomoteolide-1a has been accomplished by applying a late stage Yamaguchi esterification and ring closing metathesis reaction. The key advanced ring closing metathesis precursor, **10**, was prepared by two different routes, the latter of which proved more efficient. At this stage, we do not have



Scheme 4 Completion of the total synthesis of **1**.

an alternative structure for iriomoteolide-1a. Efforts along these lines are currently in-progress.

Support from Chugai Pharmaceutical Co. and the Caltech/City of Hope Medical Research Fund is gratefully acknowledged. Y. M. is supported by an Irell and Manella Graduate School Merit Fellowship. The authors thank Professor Jiong Yang for kindly sharing his results on iriomoteolide-1a and Brian Stoltz for helpful discussions.

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14 A complete listing of ^{1}H and ^{13}C NMR spectral data for natural and synthetic iriomoteolide-1a is provided in the ESI †.

