Journal of Saudi Chemical Society (2016) xxx, xxx–xxx

King Saud University

Journal of Saudi Chemical Society

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Stereo selective synthesis of C3–C12 fragment of iriomoteolide-1a

Gangavaram V.M. Sharma [a], **Karnekanti Rajender** [a,b,*]

[a] *Organic and Biomolecular Chemistry Division, CSIR-Indian Institute of Chemical Technology, Hyderabad 500 007, India*
[b] *Govt. Polytechnic, Warangal, Telangana State 506007, India*

Received 6 October 2015; accepted 31 January 2016

KEYWORDS

Iriomoteolide-1a;
Mannich reaction;
Sharpless epoxidation;
Keck allylation;
Cross-metathesis

Abstract A convergent and flexible synthetic route for the synthesis of C3–C12 fragment of iriomoteolide-1a is described. The key steps are: Mannich reaction, Keck asymmetric allylation, Sharpless asymmetric epoxidation and cross-metathesis protocol.

1. Introduction

Members of *Amphidinium* sps. are among the most abundant and diverse sand-dwelling benthic dinoflagellates worldwide [1–4], and have been proven to be important sources of structurally unique polyketides [5–7]. Iriomoteolides [8,9] were isolated from the strain HYA024 Tsuda *et. al.* by the continued research of *Amphidinium* species. Iromoteolide-1a **1** is a 20 membered macrolide class of natural product, with nine asymmetric carbons, a pyran ring, a quaternary carbon, two *trans* double bonds, one tri substituted *cis* double bond and an *exo*-methylene on pyran ring. The structural features coupled with biological activities of **1** attracted several synthetic strategies [10–20] was shown to be potently cytotoxic to human B lymphocyte DG-75 cells (IC_{50} 2 ng/mL) and Epstein-Barr virus infected human B lymphocyte Raji cells (IC_{50} 3 ng/mL) [6].

2. Results and discussion

Herein, we disclose a concise and executable synthesis for C3–C12 fragment **2** of the proposed structure of iriomoteolide 1a **1**.

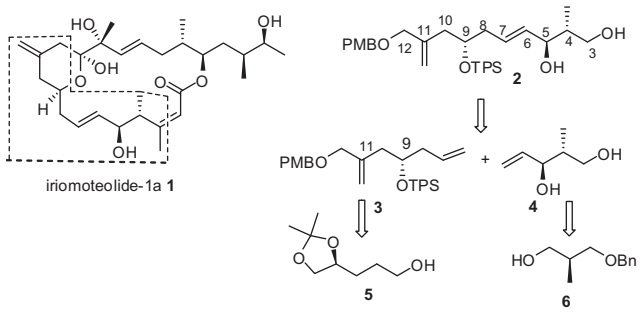
The retrosynthesis of **2** is depicted in Scheme 1. The fragment **2** could be realized from **3** and **4** by cross-metathesis reaction. In turn **3** could be prepared from **5**, while fragment **4** could be planned from alcohol **6**. Thus, the C-9 stereo center is realized from D-mannitol, while the C-5 hydroxy along with olefin is created by Sharpless epoxidation and fragmentation reaction.

Thus, for the synthesis of olefin **3**, the known alcohol **5** [21] was subjected to oxidation with IBX in EtOAc at reflux for 1 h to give aldehyde **5a**, which was subjected to Mannich reaction [22] on treatment with CH_2Br_2 and Et_2NH in CH_2Cl_2 at room temperature for 3 h to afford aldehyde **7** in 56% yield (Scheme 2). Reduction of enal **7** with $NaBH_4$ in MeOH at 0 °C to room temperature for 1 h gave alcohol **8** (83%), which

* Corresponding author at: Organic and Biomolecular Chemistry Division, CSIR-Indian Institute of Chemical Technology, Hyderabad 500 007, India.
E-mail address: rajenderpoly@gmail.com (K. Rajender).
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jscs.2016.01.008



Scheme 1 Retrosynthetic strategy of iriomoteolide-1a **1**.

on reaction with PMBBr and NaH in THF at 0 °C to room temperature for 3 h afforded **9** (78%). Acetonide deprotection in **9** with $CuCl_2{\cdot}2H_2O$ [23] in CH_3CN at 0 °C to room temperature for 1 h gave diol **10** in 78% yield. Regioselective protection of primary alcohol in **10** with benzoyl chloride, Et_3N and n-Bu_2SnO [24] in CH_2Cl_2 at 0 °C to room temperature for 1 h furnished **11** (85%), which on further reaction with p-TsCl, Et_3N and DMAP (cat.) in CH_2Cl_2 at room temperature for 5 h afforded tosylate **11a**. Treatment of **11a** with K_2CO_3 in methanol at 0 °C to room temperature for 1 h furnished the epoxide **12** in 84% yield. Reaction of epoxide **12** with vinylmagnesium bromide in the presence of CuI [25,26] in THF at −20 °C for 30 min gave homoallylic alcohol **13** (90%), which on silylation with TPSCl and imidazole and DMAP (cat.) in CH_2Cl_2 afforded ether **3** in 86% yield.

Alternatively, fragment **3** was synthesized from 1,4-butanediol derived aldehyde **14** [27] in a short route with better yields. Accordingly, aldehyde **14** on catalytic asymmetric Keck [28,29] allylation with (*R,R*)-BINOL, allytri-*n*-butyltin and Ti(O^iPr)$_4$ furnished **15** in 81% yield (Scheme 3). Silylation of **15** with TPSCl and imidazole in CH_2Cl_2 afforded ether **16** (95%), which on oxidative deprotection of PMB ether with DDQ in aq. CH_2Cl_2 at 0 °C to room temperature for 1 h gave alcohol **17** in 90% yield. Swern oxidation of **17** followed by treatment of **17a** with CH_2Br_2 and Et_2NH in CH_2Cl_2 afforded **18** in 55% yield. Reduction of **18** with $NaBH_4$ gave alcohol **19** (83%), which on protection with PMBBr and NaH afforded **3** in 90% yield.

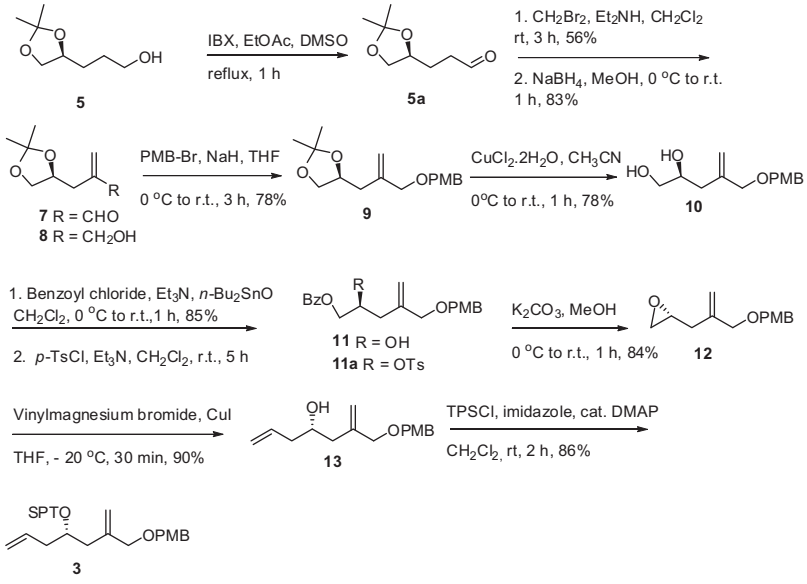
For the synthesis of fragment **4**, the known alcohol **6** [30] on oxidation under Swern conditions and subsequent Wittig reaction with **6a** in benzene at reflux for 1 h afforded ester **20** in 89% yield (Scheme 4). Reduction of **20** with DIBAL-H in CH_2Cl_2 at 0 °C to room temperature for 1 h gave the allylic alcohol **21** in 86% yield. Sharpless asymmetric epoxidation of **21** with (−)-DIPT, Ti(O^iPr)$_4$ and cumenehydroperoxide in CH_2Cl_2 at −20 °C for 5 h furnished epoxide **22** in 81% yield. Epoxy alcohol **22** on reaction with iodine, Ph_3P and imidazole in THF at 0 °C to room temperature for 30 min afforded the corresponding iodide **22a**, which on treatment with NaI and Zn dust [31] in MeOH at reflux for 4 h furnished olefin **23** in 78% yield. Silylation of **23** with TBSCl and imidazole in CH_2Cl_2 at 0 °C to room temperature for 1 h gave ether **24** (84%). Reaction of **24** with lithium naphthalenide (LN) [32] in THF at −20 °C for 30 min gave alcohol **25** in (86%).

Cross metathesis reaction of olefins **25** and **3** with Grubbs-II catalyst [33–36] in toluene at reflux for 6 h met with failure to give **26** (Scheme 5).

Attributing such a failure to get **26** to the bulky TBS group present in **25**, **3** was subjected to desilylation with TBAF in THF at 0 °C to room temperature for 4 h to give the diol **27** in 78% yield (Scheme 5). Reaction of **3** with **27** using 10 mol % of Grubbs-II catalyst in toluene at reflux afforded **2** (48%), which constitutes the C3–C12 fragment.

3. Conclusions

In summary, an efficient approach for the synthesis of the C3–C12 fragment of iriomoteolide-1a has been developed. Mannich reaction was used to install the *exo*-double bond, homoallylic hydroxy stereocenter was achieved from chiron approach as well as from asymmetric approach and the allylic



Scheme 2 Synthesis of compound **3**.