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Formal total synthesis of Palmerolide A

Bighnanshu K. Jena, Debendra K. Mohapatra *

Natural Products Chemistry Division, CSIR-Indian Institute of Chemical Technology, Hyderabad 500 007, India

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ABSTRACT

A stereoselective formal total synthesis of the 20-membered marine macrolide Palmerolide A, a highly potent antitumor agent, is described. The key steps involved in this synthesis are reductive elimination, Sharpless asymmetric dihydroxylation, protecting group dependent ring-closing metathesis reaction, Sharpless asymmetric epoxidation, Takai olefination and macrolactonization via Heck coupling reaction.

1. Introduction

A significant number of macrocyclic natural products from marine flora and fauna have been extensively used in past and present for the treatment of many diseases and serve as compounds of interest both in their natural form and as templates for synthetic modification for the development of several novel therapeutic agents many of which are already been marketed as drugs.[1] A natural product enters into the drug discovery process through its potency, selectivity, and pharmacokinetic traits required for portraying it as a clinically useful drug agent. During the search for new potent drug molecules, Baker and co-workers[2] in 2006 reported the isolation and structural determination of Palmerolide A, the most prominent member of Palmerolide group, which is mainly due to its cytotoxicity, from the Antarctic marine tunicate *Synoicum adareanum*. Palmerolide A is a complex natural product comprising of a side chain containing an enamide, a 1,3-diene system, a carbamate moiety, five stereogenic centers, seven unsaturations with *E*-configuration and 20-membered macrolide ring. This natural product demonstrated extraordinary cytotoxic activity against the melanoma cell lines UACC-62 (LC_{50}=18 nM)[3] by inhibiting the proliferation of vacuolar ATPase with an IC_{50} of 2 nM. The remarkable 10^3 in vitro selectivity index for the melanoma cell lines prompted further biological evaluation of the compound. These findings coupled with the scarce natural abundance of Palmerolide A generated considerable interest in its chemical synthesis.[4] Several synthetic endeavours towards Palmerolide A led to the first total synthesis and revision of stereochemistry by De Brabander's group.[4a] Afterwards two more total syntheses by Nicolaou,[4b–d] and Hall,[4e] five formal syntheses[5] and several approaches,[6] including ours[6i] towards Palmerolide A have been reported in the literature (see Fig. 1).

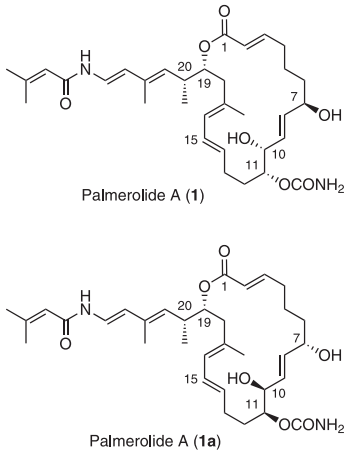

Fig. 1. Structures of originally proposed (**1**) and revised Palmerolide A (**1a**).

Considering all these synthetic reports, a distinct retrosynthesis of macrolactone core **2** including intramolecular Heck coupling,[7] intermolecular Yamaguchi reaction,[8] protecting group dependent ring-closing metathesis reaction for the building of fragment **3**,

* Corresponding author. Tel./fax: +91 40 27193128; e-mail address: mohapatra@iict.res.in (D.K. Mohapatra).

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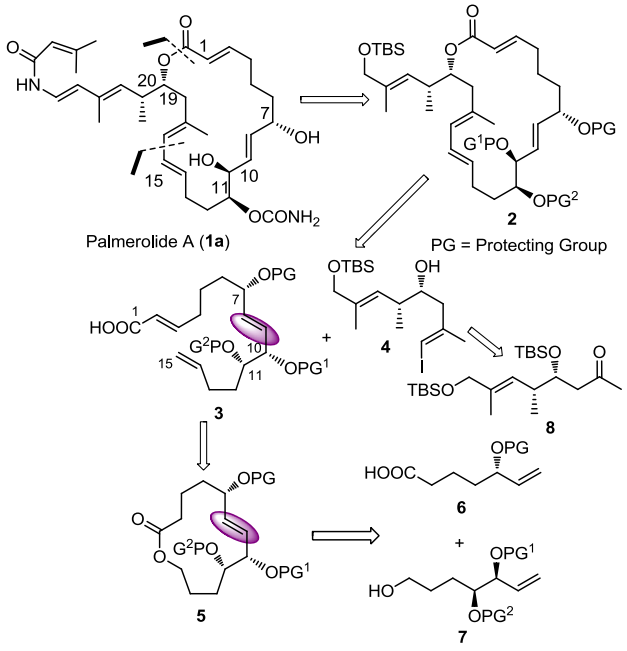
regioselective reductive opening of epoxide by Me_3Al[9] and Takai olefination[10] of methyl ketone to form vinyl iodide for the construction of C16–C23 fragment was envisioned. Different established methodologies for the construction of intermediates were taken up to ensure an easy access to synthesize the required stereoisomers and other variants of Palmerolide A. As part of our ongoing research program on the synthesis of biologically active natural and unnatural products using protecting group dependent ring-closing metathesis approach,[11] the synthesis of macrolactone core **2** was targeted, which is a late-stage intermediate of Palmerolide A leading to a formal total synthesis of the target molecule.

According to the retrosynthetic analysis of Palmerolide A (**1a**) as shown in Scheme 1, macrolactone core **2** could be constructed through esterification of **3** and **4**, followed by intramolecular Heck coupling.[7] Fragment **3** could be obtained from the 13-membered macrolactone **5**, which in turn could be prepared from **6** and **7** via coupling, followed by ring-closing metathesis reaction of the resulting diene compound.[12]

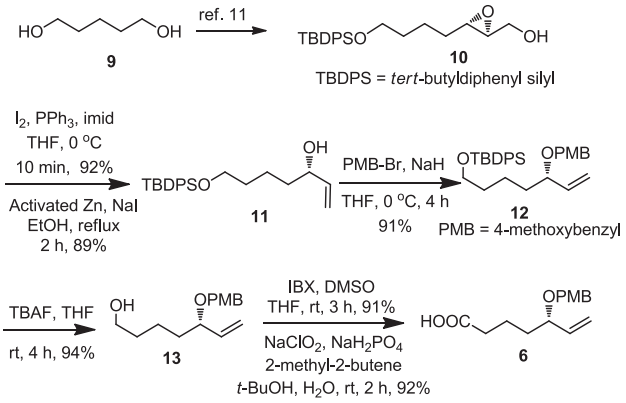


Scheme 1. Retrosynthetic analysis of Palmerolide A.

2. Results and discussion

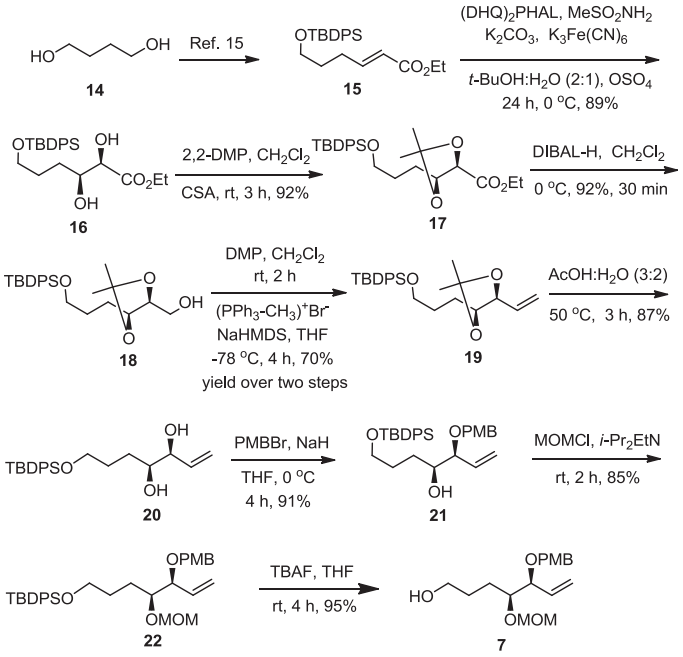
The synthesis of acid fragment **6** commenced with 1,5-pentane diol **9**, which was converted to epoxy alcohol **10**[13] in 90% yield and with 97% ee through its corresponding allylic alcohol by treating with (+)-diethyl tartrate in presence of $Ti(O^iPr)_4$ and *t*- BuOOH under Katsuki-Sharpless[14] conditions. Conversion of alcohol **10** to the corresponding iodo derivative, subsequent reductive elimination using Zn/EtOH[15] afforded secondary allylic alcohol **11** in 82% yield over two steps (Scheme 2). The resulting alcohol was masked as its PMB-ether with PMB-Br in presence of NaH. Desilylation of **12** by treatment with TBAF generated primary alcohol **13** in 94% yield. The primary alcohol **13** was oxidized to corresponding aldehyde using IBX[16] followed by subsequent oxidation under Pinnick conditions using $NaClO_2$ furnishing acid fragment **6** in 84% yield over two steps.[17]

The synthesis of alcohol fragment **7** started with commercially available 1,4-butane diol following a literature protocol,[18] to obtain α,β-unsaturated ester **15**. The olefin was treated with osmium tetroxide and AD-mix-α under Sharpless asymmetric dihydr



Scheme 2. Synthesis of the acid fragment **6**.

oxylation conditions[19] to give diol **16** (89% yield with 98% ee). Protection of the diol moiety as its acetonide **17** was achieved by treating diol **16** with 2,2-dimethoxypropane in presence of catalytic amount of CSA in 92% yield. The ester group was then transformed to the corresponding terminal alkene by a three step sequence involving reduction of **17** using DIBAL-H in CH_2Cl_2 at −78 °C to afford primary alcohol **18**, which on oxidation with Dess-Martin periodinane in CH_2Cl_2 and subsequent one carbon homologation with $PPh_3{=}CH_2$ furnished alkene **19** in 70% yield over three steps (Scheme 3). Removal of isopropylidene group was effected with AcOH-H_2O leading to diol **20** in 87% yield.[20]



Scheme 3. Synthesis of the alcohol fragment **7**.

Selective PMB protection for the allylic hydroxyl group present in **20** with *p*-methoxybenzyl bromide (PMB-Br) in presence of NaH furnished **21** in 91% yield with 5–7% bis-PMB protected product.[21] The remaining free alcohol **21** was masked as its MOM-ether **22** with methoxymethyl chloride (MOMCl) and *N*,*N*-diisopropylethylamine (DIPEA) in CH_2Cl_2. Having synthesized **6** and **7**, the coupling of both the fragments was initially attempted under Yamaguchi conditions[8], which afforded the ester **23a** in low yield with the mixed anhydride as the byproduct. Similarly, coupling in the presence of dicyclohexyl carbodiimide (DCC)[22a–c] and 4-