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PII: S0040-4039(13)00664-3
DOI: http://dx.doi.org/10.1016/j.tetlet.2013.04.069
Reference: TETL 42837

To appear in: *Tetrahedron Letters*

Received Date: 16 February 2013
Revised Date: 15 April 2013
Accepted Date: 17 April 2013

Please cite this article as: Jena, B., Mohapatra, D.K., Synthesis of the C1-C15 fragment of palmerolide A via protecting group dependent RCM reaction, *Tetrahedron Letters* (2013), doi: http://dx.doi.org/10.1016/j.tetlet.2013.04.069

Graphical Abstract

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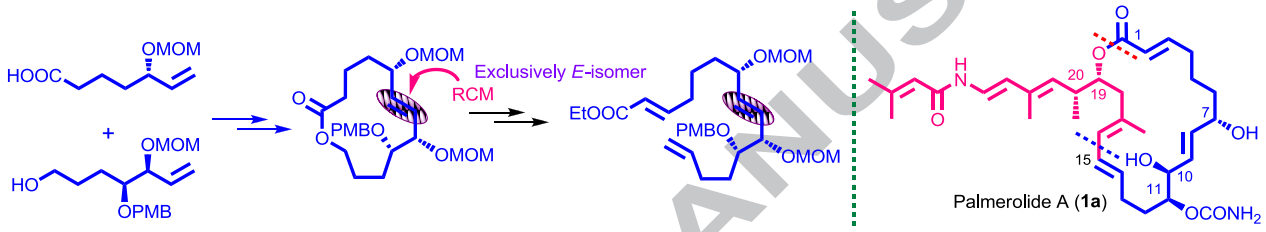

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TETRAHEDRON LETTERS

Synthesis of the C1-C15 fragment of palmerolide A via protecting group dependent RCM reaction

Bighnansu Jena, and Debendra K. Mohapatra*

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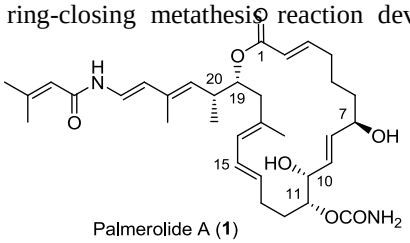
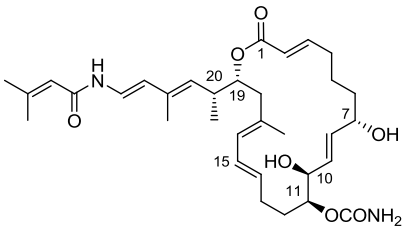
Abstract— The steric effect of protecting groups on the outcome of the ring-closing metathesis reaction has been studied for the construction of key 13-membered macrolactone. The protocol has been successfully utilized for the synthesis of C1-C15 fragment of palmerolide A in a highly convergent and concise manner.

Natural products synthesis has stimulated incredible advance in the development, testing, and demonstration of methods and strategies for the complex arrangements of functionality and stereochemistry in the target molecule. To date numerous complex natural products and their simpler synthetic derivatives are used as pharmaceutical agents.[1] Ongoing efforts to identify new natural products with extraordinary properties, Baker and co-workers isolated palmerolide A (Figure 1), a complex polyunsaturated macrolide with an impressive molecular architecture and biological profile, from the circumpolar marine tunicate *Synoicum* adareanum, which is commonly found in the shallow waters around Anvers Island on the Antarctic peninsula. This marine natural product found to exhibit excellent antitumor activity against a number of cell lines in the 60 cell panel of the National Cancer Institute (NCI).[2] Specifically, it exhibits potent cytotoxicity against the melanoma cell lines UACC-62 (LC_{50} = 18 nM). Palmerolide A appears to act on melanoma cells through inhibition of vacuolar ATPase with an IC_{50} of 2 nM.[3] The remarkable 10^3 *in vitro* selectivity index for the melanoma cells over other most sensitive cell lines tested prompted further biological evaluation of the compound. The impressive biological properties of palmerolide A, along with its extremely limited supply and for further structure-activity studies, prompted us to undertake its chemical synthesis. Several groups have reported on the synthesis of palmerolide A.[4] An elegant study by De Brabander's group disclosed the first total synthesis of **1** and revised the stereochemistry of the natural product.[4a] Subsequently Nicolaou[4b-d], and Hall[4e] also reported the total synthesis of palmerolide A. Formal total syntheses[5] and approaches to various fragments[6] were also reported. Notable approach for construction of the 1,4-alkenol C7-C11 fragment include an intramolecular Wittig reaction followed by reduction and a Claisen-Ireland rearrangement of an alkenyl boronate.[4e] Considering all these synthetic reports, we envisioned a distinct retrosynthesis of fragment **3** (Scheme 1) that would take advantage of protecting group dependent ring-closing metathesis reaction developed in our group.



Palmerolide A (**1**)



Palmerolide A (**1a**)

Figure 1. Structures of originally proposed (**1**) and revised (**1a**) palmerolide A

Key words: Natural products, palmerolide A, cytotoxic, Sharpless dihydroxylation, Heck coupling, ring-closing metathesis reaction.
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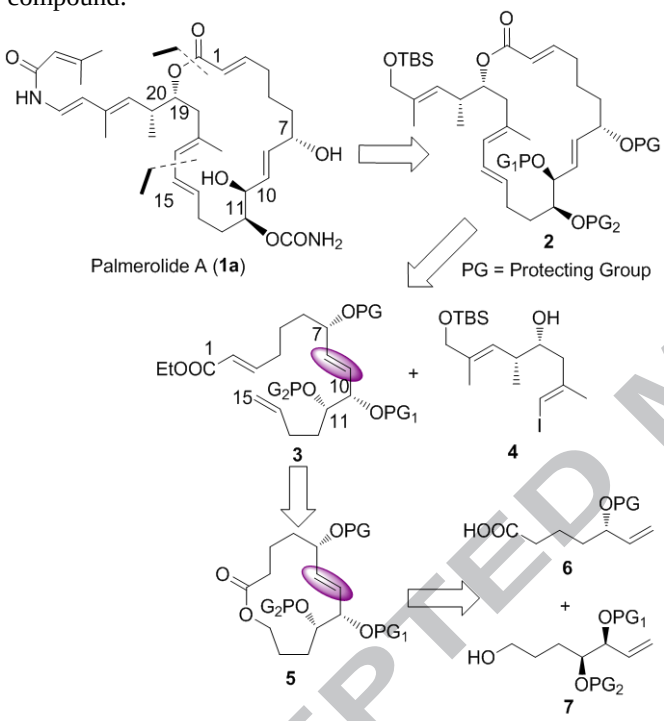
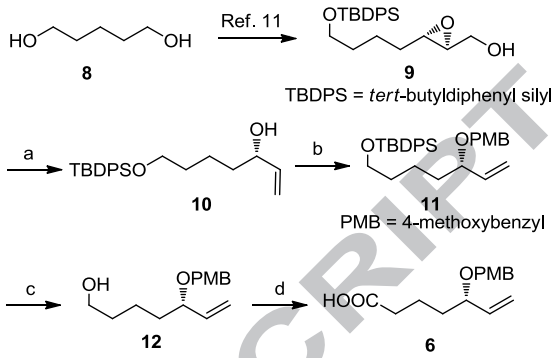
As part of our ongoing research program on the synthesis of biologically active natural and unnatural products using protecting group dependent ring-closing metathesis approach,[7] we became interested in the synthesis of C1-C15 fragment of palmerolide A.

According to our retrosynthetic analysis of palmerolide A (**1a**) shown in Scheme 1, macrolactone core **2** could be constructed through esterification of **3** and **4**, followed by intramolecular Heck coupling.[8] 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.[9]



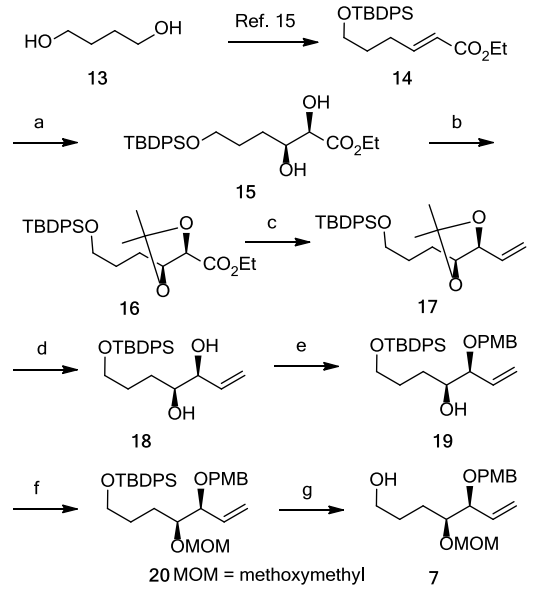
Scheme 1: Retrosynthetic analysis of palmerolide A

The synthesis of acid fragment **6** began with 1,5-pentane diol **8**, which was converted to epoxy alcohol **9**[10] in 90% yield and with 97% ee through its corresponding allylic alcohol by treating with (+)-diethyl tartrate in presence of Ti(O^{i}Pr) and *t*BuOOH under Katsuki-Sharpless[11] conditions. The primary alcohol group of **9** was transformed into its corresponding iodo derivative with I_2 in presence of Ph_3P and imidazole. The reductive opening of the epoxide ring of the iodo compound with Zn in refluxing ethanol[12] afforded secondary allylic alcohol **10** in 82% yield over two steps (Scheme 2), which was protected as its *p*-methoxybenzyl ether with PMBBr in presence of NaH. Silylether deprotection of **11** with 1M solution of tetrabutylammonium fluoride (TBAF) in THF provided **12** in 94% yield. The primary alcohol **12** was then oxidized with 2-iodoxybenzoic acid (IBX)[13] to furnish the corresponding aldehyde. Further oxidation[14] of the intermediate aldehyde with $NaClO_2$ in the presence of NaH_2PO_4 and 2-methyl-2-butene as a scavenger, under Pinnick conditions,[14] gave caboxylic acid **6** in 87% yield over two steps.



Scheme 2. Reagents and conditions: (a) (i) I_2, PPh_3, imidazole, THF, 0 °C, 10 min, 92%; (ii) Activated Zn, NaI, EtOH, reflux, 2 h, 89%; (b) PMB-Br, NaH, THF, 0 °C, 4 h, 91%; (c) TBAF, THF, rt, 4 h, 94%; (d) (i) IBX, DMSO, THF, rt, 3 h, 91%; (ii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O, rt, 2 h, 92%.

The synthesis of alcohol fragment **7** commenced with commercially available 1,4-butane diol. Following a literature protocol,[15] α,β-unsaturated ester **14** was obtained. Sharpless asymmetric dihydroxylation[16] with AD-mix-α (89% yield with 98% ee) followed by protection of resulting 1,2-diol with 2,2-dimethoxypropane in presence

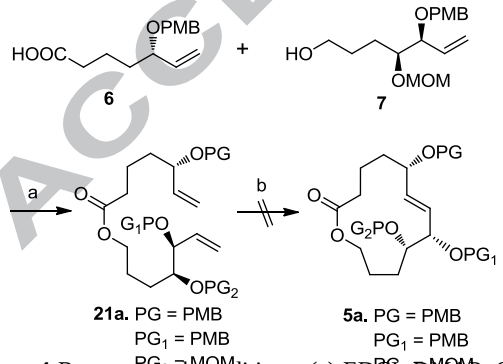


Scheme 3. Reagents and conditions: (a) AD-mix-α, $MeSO_2NH_2$, K_2CO_3, $K_3Fe(CN)_6$, *t*-BuOH:H_2O (2:1), OSO_4, 24 h, 0 °C, 89%; (b) 2,2-DMP, CH_2Cl_2, CSA, rt, 3 h, 92%; (c) (i) DIBAL-H, CH_2Cl_2, 0 °C, 30 min; (ii) DMP, CH_2Cl_2, rt, 2 h; (iii) $(PPh_3\text{-}CH_3)^+Br^-$, NaHMDS, THF, −78 °C to 0 °C, 4 h, 70% yield over three steps; (d) AcOH:H_2O (3:2), 50 °C, 3 h, 87%; (e) PMBBr, NaH, THF, 0 °C, 4 h, 91%; (f) MOMCl, *i*-Pr_2EtN, rt, 2 h, 85%; (g) TBAF, THF, rt, 4 h, 95%.

of catalytic amount of camphorsulfonic acid (CSA) gave the acetonide **16** in 92% yield. Reduction of the ester group of **16** with diisobutylaluminium hydride (DIBAL-H) in

CH_2Cl_2 at −78 °C led to the corresponding primary alcohol, which on oxidation with Dess-Martin periodinane in CH_2Cl_2 and subsequent one carbon homologation with $PPh_3{=}CH_2$ gave alkene **17** in 70% yield over three steps (Scheme 3). The isopropylidene group was removed upon treatment with AcOH-H_2O at room temperature to afford diol **18** in 87% yield.[17] The allylic hydroxyl group in **18** was selectively masked as its PMB ether with *p*-methoxybenzyl bromide (PMBBr) in presence of NaH in 91% yield with 5-7% bis-PMB protected product.[18] The homoallylic alcohol **19** was protected as its MOM ether **20** with methoxymethyl chloride (MOMCl) and *N*,*N*-diisopropylethylamine (DIPEA) in CH_2Cl_2. Subsequent silylether deprotection, using 1M solution of TBAF in THF at room temperature, afforded the desired alcohol fragment **7** in 95% yield.

Having synthesized **6** and **7**, we proceeded further with their coupling and the ring closing metathesis reaction. The coupling of acid **6** and alcohol **7** was initially attempted under Yamaguchi conditions[19] which afforded the ester in low yield with the mixed anhydride as the byproduct. Similarly, coupling in the presence of dicyclohexyl carbodiimide (DCC)[20] and 4-dimethylaminopyridine (DMAP) gave an inseparable mixture of insoluble dicyclohexyl urea along with the product. Notably, when the coupling reaction carried out in presence of EDCI[21] and DMAP in CH_2Cl_2, the desired diene ester **21** was obtained in 86% yield, which set the stage for crucial ring-closing metathesis reaction (Scheme 4). Unfortunately, refluxing the diene ester with Grubbs' 2nd generation catalyst in CH_2Cl_2 under high dilution conditions failed to furnish the desired product leading to complete recovery of the starting material. We envisaged that steric congestion due to bulky PMB-protecting group around the reacting centers might act as a temporary constraint, preventing the participation of Grubbs' catalyst to disallow the macrolactone formation.



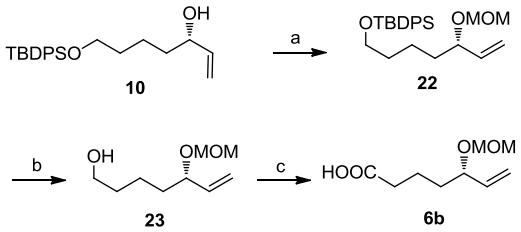
Scheme 4 Reagents and conditions: (a) EDCI, DMAP, CH_2Cl_2, 0 °C to rt, 10 h, 86%; (b) Grubbs' 2nd generation catalyst, CH_2Cl_2, reflux, no reaction.

At this juncture, we thought of investigating the above reaction with a set of ring-closing metathesis precursors by only changing the protecting group of allylic alcohol. During the process, precursors bearing dibenzyl (diBn) (**21b**), di-*tert*-butyldimethylsilyl (diTBS) (**21c**) failed to produce the desired macrolactone with complete recovery of the starting material. To our surprise, tri-MOM diene ester (**21d**) was converted to the corresponding lactone in 70% yield with 20% starting material recovery in 12 h (entry **5d**). By increasing the duration of heating from 12 h to 36 h, the starting material was completely consumed and the 13-membered lactone obtained in 78% yield (entry **5e**) (Table 1). Subsequently, when diol diene ester **21f** was treated with Grubbs' 2nd generation catalyst under high dilution conditions, required 13-membered macrolactone (entry **5f**) was formed in 82% yield with complete *E*-selectivity (J = 15.9 Hz) and there was no detectable amount of *Z*-configured macrolactone. We imagined that it could be due to forbearance of Grubbs' catalyst with activated nucleophile in the form of free allylic alcohol group.

Table 1 Protecting group dependent RCM for 13-membered lactone

Sl. No.	PG	PG_1	PG_2	Duration (in hour)	RCM (Yield %)	Starting Material Recovery (%)
5a	PMB	PMB	MOM	24	0	100
5b	Bn	Bn	MOM	24	0	100
5c	TBS	TBS	MOM	24	0	100
5d	MOM	MOM	MOM	12	70	20
5e	MOM	MOM	MOM	36	78	0
5f	H	H	MOM	12	82	

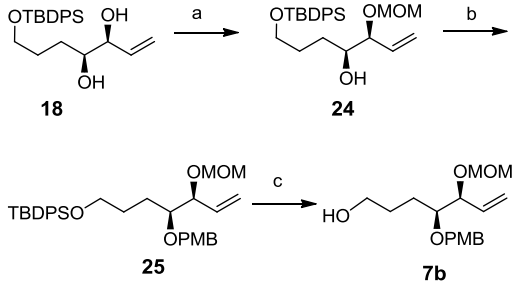
Keeping in mind for the future formal total synthesis of palmerolide A, protecting groups in the fragments **6** and **7** were manipulated few steps before esterification, which was achieved based on our previous approach. Compound **10** was treated with MOMCl in presence of DIPEA in CH_2Cl_2 to give the MOM-ether **22** in 91% yield (Scheme 5). By employment the same reaction sequence of Scheme 2 involving TBAF-induced silyl deprotection, oxidation with IBX and further oxidation under Pinnick conditions, the MOM-ether **23** was then converted to the desired carboxylic acid **6b** in 89% yield over two steps.



Scheme 5 Reagents and conditions*:* (a) MOMCl, *i*-Pr_2Et N, 2 h, rt, 91%; (b) TBAF, THF, rt, 4 h, 93%; (c) (i) IBX, DMSO, THF, rt, 3 h; (ii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O, rt, 2 h, 81% (over two steps).

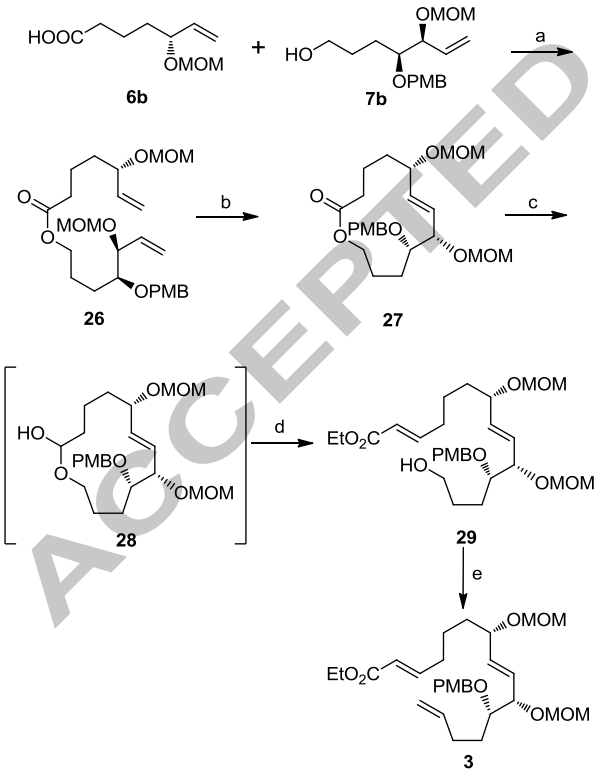
The allylic hydroxyl group in **18** was selectively masked as its MOM ether **24** with MOMCl and DIPEA in CH_2Cl_2 at 0 °C. The hydroxyl group of **24** was then protected as its

PMB ether **25** with PMBBr in presence of NaH in 91% yield. Removal of silyl group was achieved with 1M solution of TBAF in THF at room temperature in 94% yield to complete the synthesis of alcohol fragment (Scheme 6).



Scheme 6 Reagents and conditions : (a) MOMCl, *i*-Pr_2EtN, 2 h, 0 ^oC, 85% (b) PMB-Br, NaH, THF, 0 ^oC, 6 h, 91%; (c) TBAF, THF, rt, 3 h, 94%.

The required di-MOM protected diene ester **26** was synthesized following the earlier strategy described in Scheme 4, which sets the stage for crucial RCM reaction. The 13-membered macrolactone formation proceeded smoothly with Grubbs 2nd generation catalyst under refluxing conditions to afford **27** in 75% yield with exclusive formation of *E*-isomer. Although the next step



Scheme 7 Reagents and Conditions: (a) EDCI, DMAP, CH_2Cl_2, 0 ^oC to rt.,10 h, 84%; (b) Grubbs' 2nd generation catalyst, CH_2Cl_2, reflux, 32 h, 75%; (c) DIBAL-H, CH_2Cl_2, −78 ^oC, 15 min; (d) $Ph_3P{=}CHCO_2Et$, benzene, reflux, 2 h, 77% over two steps; (e) (i) DMP, CH_2Cl_2, $NaHCO_3$, 0 ^oC to rt, 2 h; (ii) $(PPh_3\text{-}CH_3)^+Br^-$, *n*BuLi, THF, −78 ^oC to 0 ^oC, 3 h, 78% over two steps.

was not so much apparent as reported for the most cases of 5- and 6-membered lactones, gratifyingly, the 13-membered macrolactone **27** was transformed into the corresponding lactol **28** with DIBAL-H in CH_2Cl_2 at −78 ^oC. Subsequent two carbon homologation afforded α,β-unsaturated ester **29** as the only product in 77% yield over two steps (Scheme 7). Finally, oxidation of the primary alcohol group with Dess-Martin periodinane followed by one carbon homologation with $PPh_3{=}CH_2$ in THF yielded the required C1-C15 fragment **3** of palmerolide A.

In summary, we have studied the steric effect of protecting groups on the outcome of the ring-closing metathesis reaction for the construction of 13-membered macrolactone. The two fragments bearing alcohol and carboxylic acid functionality, respectively, were synthesized from commercially available cheaper starting materials in a concise manner following well-established chemistry. Coupling of the two fragments followed by ring-closing metathesis reaction led to the synthesis of C1-C15 fragment of palmerolide A. Application of the above protocol towards the formal total synthesis of palmerolide A and its derivatives with various ring size is underway and will be reported in due course.

Acknowledgments

BJ thanks the Council of Scientific and Industrial Research (CSIR), New Delhi, India, for the financial assistance in the form of fellowship. DKM thanks the Council of Scientific and Industrial Research (CSIR), New Delhi, India, for a research grant (INSA Young Scientist Award Scheme).

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