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# Enantioselective Synthesis of Pladienolide B and Truncated Analogues as New Anticancer Agents

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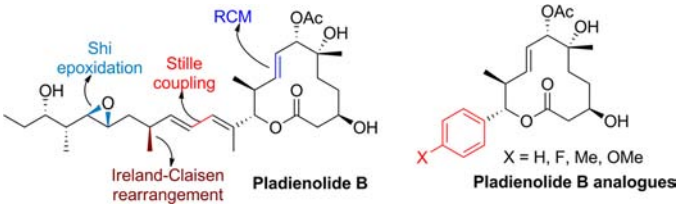
## ABSTRACT




**An enantioselective synthesis of natural anticancer macrolide pladienolide B is described. The synthetic highlights include Sharpless asymmetric epoxidation, ring closing metathesis (RCM), Ireland–Claisen rearrangement, Shi epoxidation, and Pd-catalyzed Stille coupling as key steps. The synthetic route also allowed the synthesis of the truncated analogues (41a–d) of pladienolide B.**

Unicellular microbes have been the treasure houses of many bioactivities. These natural compounds play a major role in identifying novel biological targets as well as leads in pharmaceuticals. Around a decade ago, Sakai et al.[1,2] identified a fermentation broth of *Streptomyces platensis* Mer-11107 which was inhibiting hypoxia induced VEGF expression. A careful bioassay guided fractionation and further purification led them to isolate seven macrolides, which were named pladienolides. These molecules were capable of inhibiting the proliferation of cancer cell lines with nanomolar activities.[3] Another unique feature of these compounds is inhibition of splicing of pre-mRNA and generating an antitumor effect; prior to this discovery, the only other natural product which showed this property was FR901464.[4–6] Within four years after the isolation of pladienolides, one analogue of pladienolide B (**1**), E7107 (**3**),[7] has entered clinical trials (Figure 1).

Pladienolide B comprises a 12-membered macrolactone having four embedded stereocenters including a vicinal diol. Also, the C11 of the macrocycle has a dodecyl side chain with epoxide functionality, two unsaturations with *E*-geometry, two asymmetric methyl groups, and a secondary hydroxy group. The pladienolides based on the structure can be considered as a natural hybrid of deoxymethynolide[8] (12-membered macrolactone) and herboxidiene[9] (the side chain of the natural product). Thus, our own interest in developing natural product hybrids with anticancer activities attracted us toward this "natural hybrid".

The very exciting "fast track" entry into clinical trials coupled with the complexity in the macrolactone and side chains attracted several synthetic groups across the globe toward this natural product. To date, the groups

(1) (a) Sakai, T.; Sameshima, T.; Matsufuji, M.; Kawamura, N.; Dobashi, K.; Mizui, Y. *J. Antibiot.* **2004**, *57*, 173–179. (b) Sakai, T.; Asai, N.; Okuda, A.; Kuwamura, N.; Mizui, Y. *J. Antibiot.* **2004**, *57*, 180–187.

(2) Stereochemistry: Asai, N.; Kotake, Y.; Niijima, J.; Fukuda, Y.; Uehara, T.; Sakai, T. *J. Antibiot.* **2007**, *60*, 364–369.

(3) Biological activity: Mizui, Y.; Sakai, T.; Iwata, M.; Uenaka, T.; Okamoto, K.; Shimizu, H.; Yamori, T.; Yoshimatsu, K.; Asada, M. *J. Antibiot.* **2004**, *57*, 188–196.

(4) FR901464: (a) Nakajima, H.; Sato, B.; Fujuta, T.; Takase, S.; Terano, H.; Okuhara, M. *J. Antibiot.* **1996**, *49*, 1196–1203. (b) Nakajima, H.; Hori, Y.; Terano, H.; Okuhara, M.; Manda, T.; Matsumoto, S.; Shimomura, K. *J. Antibiot.* **1996**, *49*, 1204–1211. (c) Nakajima, H.; Takase, S.; Terano, H.; Tanaka, H. *J. Antibiot.* **1997**, *50*, 96–99.

(5) Pladienolide B study: Katake, B. Y.; Sagane, K.; Owa, T.; Mimori-Kiyosue, Y.; Shimizu, H.; Uesugi, M.; Ishihama, Y.; Iwata, M.; Mizui, Y. *Nat. Chem. Biol.* **2007**, *3*, 570–575.

(6) FR901464 study: Kaida, D.; Motoyoshi, H.; Tashiro, E.; Nojima, T.; Hagiwara, M.; Ishigami, K.; Watanabe, H.; Kitahara, T.; Yoshida, T.; Nakajima, H.; Tani, T.; Horinouchi, S.; Yoshida, M. *Nat. Chem. Biol.* **2007**, *3*, 576–583.

(7) (a) Bonnal, S.; Vigevani, L.; Valcarcel, J. *Nat. Rev. Drug Discovery* **2012**, *11*, 847–859. (b) Folco, E. G.; Coli, K. E.; Reed, R. *Genes Dev.* **2011**, *25*, 440–444.

(8) Lambalot, R. H.; Cane, D. E. *J. Antibiot.* **1992**, *45*, 1981–1982.

(9) Isaac, B. G.; Ayer, S. W.; Elliott, R. C.; Stonard, R. J. *J. Org. Chem.* **1992**, *57*, 7220–7226.

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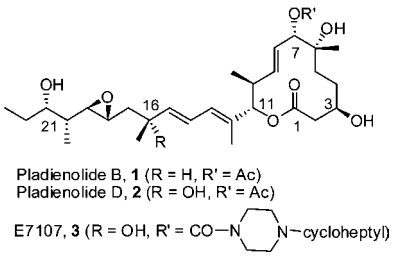
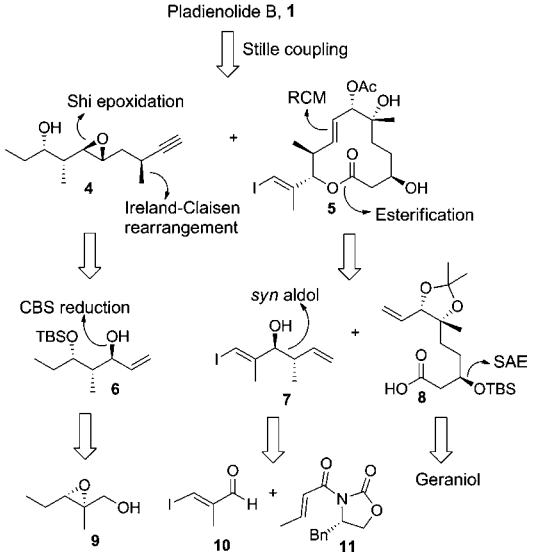



**Figure 1.** Pladienolide B, D, and E7107.

of Kotake[10a] and Ghosh[10b] have reported the total synthesis of potent macrolide pladienolide B. Burkart et al.[10c] reported their synthetic efforts toward the construction of side chains, whereas the group of Jensen[11] published the macrocyclic core of the (−)-pladienolide B. Maier[12a] and Webb[12b] have accomplished progress in the synthesis of pladienolide B based analogues.

**Scheme 1.** Retrosynthetic Analysis of Pladienolide B, **1**




As depicted in Scheme 1, the typical dissection of pladienolide B would provide two synthons, the side chain **4** (C14−C23 unit) and the macrolactone **5** (C1−C13 unit). We anticipated that a Stille type coupling would allow us to stitch these fragments with ease. The macrolactone **5** in turn could be built from hydroxy vinyl iodide **7** and carboxylic acid **8**. The hydroxy vinyl iodide **7** could be constructed by coupling vinyl iodo aldehyde **10** and Evan's amide **11**, whereas the acid **8** could be built from geraniol. The other epoxy alkyne **4** was planned from the epoxy alcohol **9** through the intermediate **6**. This retrosynthetic planning was designed keeping in mind that the analogue synthesis becomes easier. Thus, most of the key steps were planned in such a way that a simple change of a reagent would allow us to synthesize the other chiral variants as well as the side chain and other key functionalities.

The synthetic endeavor began from commercially available geraniol which was subjected to Sharpless asymmetric epoxidation[13] followed by benzyl protection of alcohol with NaH and BnBr providing the epoxy benzyl ether **12** in 79% yield (two steps). Perchloric acid mediated hydrolysis[14] of the epoxy functionality to the diol and ketalization of vicinal diol to **13** in 78% yield (two steps) were very smoothly executed. The ozonolysis of the trisubstituted olefinic functionality in **13** generated the aldehyde which allowed homologation of α,β-unsaturated ester **14** using (carbethoxymethylene)triphenylphosphorane in benzene. The DIBAL-H reduction of **14** gave allylic alcohol which set the stage for yet another Sharpless asymmetric epoxidation to provide chiral epoxy alcohol **15** (64% yield, two steps). The reductive opening of epoxide **15** to 1,3-diol **16** was achieved with Red-Al[15] in THF at −40 °C in 84% yield (1,2-diol was removed by treating the crude reaction mixture with $NaIO_4$ in THF/$H_2O$). The disilylation of 1,3-diol **16** and subsequent debenzylation with Raney-Ni[16] produced primary alcohol **17** (87%, two steps). This primary alcohol **17** was oxidized with Dess−Martin periodinane and subsequent Wittig methylenation affording **18** in 78% yield (for two steps). The selective cleavage of primary silyl ether in **18** using HF·py followed by one-step oxidation of the corresponding alcohol with BAIB/TEMPO furnished acid **8** in a straightforward manner (Scheme 2).

As shown in Scheme 3, the hydroxy vinyl iodide **7** was prepared starting from aldehyde **10**[17] which upon *syn* aldol[18] condensation with Evan's amide **11** provided the adduct **19** with good diastereoselectivity (25:1). This, upon silylation with TBSOTf, followed by auxiliary removal with $LiBH_4$ furnished the primary alcohol **20** (68%, two steps). The deoxygenation[19] of the primary hydroxyl group

(10) (a) Kanada, R. M.; Itoh, D.; Nagai, M.; Niijima, J.; Asai, N.; Mizui, Y.; Abe, S.; Kotake, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 4350–4355. (b) Ghosh, A. K.; Anderson, D. D. *Org. Lett.* **2012**, *14*, 4730–4733. (c) Mandal, A. L.; Jones, B. D.; La Clair, J. J.; Burkart, M. D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5159–5164.

(11) Skaaderup, P. R.; Jensen, T. *Org. Lett.* **2008**, *10*, 2821–2824.

(12) (a) Müller, S.; Mayer, T.; Sasse, F.; Maier, M. E. *Org. Lett.* **2011**, *13*, 3940–3943. (b) Gundluru, M. K.; Pourpak, A.; Cui, X.; Morris, S. W.; Webb, T. R. *MedChemComm* **2011**, *2*, 904–908.

(13) (a) Molawi, K.; Delpont, N.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 3517–3519. (b) Mohapatra, D. K.; Pramanik, C.; Chorghade, M. S.; Gurjar, M. K. *Eur. J. Org. Chem.* **2007**, 5059–5063. (c) Hashimoto, M.; Harigaya, H.; Yanagiya, M.; Shirahama, H. *J. Org. Chem.* **1991**, *56*, 2299–2311.

(14) Gonzalez, I. C.; Forsyth, C. J. *J. Am. Chem. Soc.* **2000**, *122*, 9099–9108.

(15) Steven, M. V. *Tetrahedron Lett.* **1982**, *23*, 4541–4544.

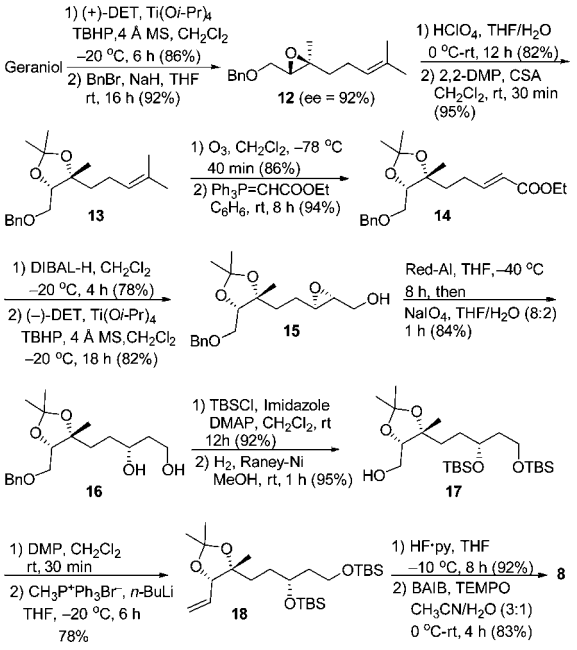
(16) (a) Peterson, I.; Maltas, P.; Dalby, S. M.; Lim, J. H.; Anderson, E. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 2749–2753. (b) Tanimoto, T.; Gerritz, S. W.; Sawabe, A.; Noda, T.; Filla, S. A.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 673–675.

(17) (a) Xiao, Y.; Liu, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 9722–9725. (b) Menche, D.; Mayer, K.; Kerstin, J.; Li, J.; Rudolph, S. *J. Org. Chem.* **2009**, *74*, 7220–7229. (c) White, J. D.; Blakemore, P. R.; Green, N. J.; Hauser, E. B.; Holoboski, M. A.; Keown, L. E.; Nylund Kolz, C. S.; Phillips, B. W. *J. Org. Chem.* **2002**, *67*, 7750–7760.

(18) (a) Fleming, K. N.; Taylor, R. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 1728–1730. (b) Smith, A. B.; Adams, C. M.; Barbosa, S. A. L.; Degan, A. P. *J. Am. Chem. Soc.* **2003**, *125*, 350–351.

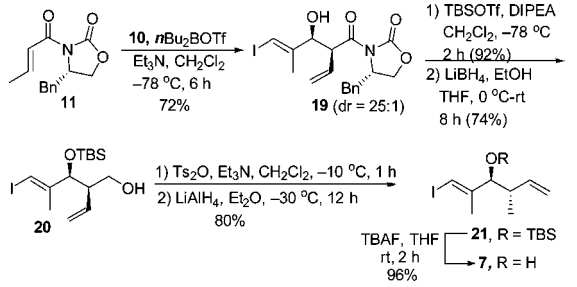
(19) Roush, W. R.; Bannister, T. D.; Wendt, M. D.; Jablonowski, J. A.; Scheidt, K. A. *J. Org. Chem.* **2002**, *67*, 4275–4283.

**Scheme 2.** Synthesis of Acid Fragment **8**



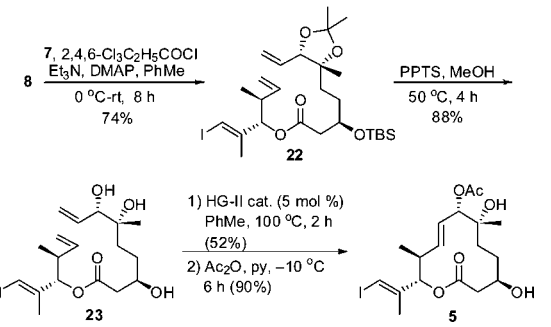

was accomplished in two steps *via* tosylation followed by reduction with $LiAlH_4$ to attain the compound **21** in 80% yield (two steps). Finally, desilylation of **21** using TBAF in THF gave the desired synthon **7** in 96% yield.

**Scheme 3.** Synthesis of Vinyl Iodide, **7**




The construction of the macrolactone core **5** with the vinyl iodide appendage **7** for further extension is achieved as shown in Scheme 4. Thus, the esterification of **8** with alcohol **7** was realized under Yamaguchi conditions[20] to furnish the highly diverse and fully functionalized ester **22**. Attempts to perform the ring-closing olefin metathesis (RCM) with both first and second generation Grubb's catalysts on diolefinic acetonide **22** were futile. To our moderate satisfaction however, RCM with Hoveyda–Grubb's second generation catalyst (HG-II, 5 mol %) worked in the absence of the isopropylidine group in **22**. Under an acid medium, **22** was hydrolyzed to corresponding triol **23** in 88% yield. Thus, the triol **23** under the influence of the HG-II catalyst in the presence of 1,4-benzoquinone provided the macrolactone and regioselective acetylation of the allylic hydroxy group with $Ac_2O$ in pyridine at −10 °C and very efficiently furnished acetate **5** in 47% yield (two steps).

**Scheme 4.** Synthesis of Macrolactone **5**




The side chain **4** was synthesized starting from known epoxy alcohol **9**[21] in 14 steps as delineated in Scheme 5. The regioselective opening of epoxide[22] **9** *via* intramolecular hydride transfer gave the silyloxy aldehyde **24** (78%) with dr = 50:1 ($^1$H NMR analysis). The enone **25** was obtained from **24** in two steps. The vinylmagnesium bromide addition onto aldehyde **24** followed by oxidation with $MnO_2$ was very high yielding. The enone **25** underwent enantioselective reduction[23] with (*S*)-CBS reagent and $BH_3 \cdot SMe_2$ to allylic alcohol **6** (82%, dr = 95:5). Propionylation of alcohol **6** furnished ester **26** (95%), and Ireland–Claisen rearrangement[24] on **26** with LDA and TBSCl in the presence of HMPA gave **27** very successfully to install the additional asymmetric carbon (C16). Thus-obtained **27** was reduced with $LiAlH_4$ to primary alcohol **28** (75%). The Corey protocol[25] was employed to synthesize the alkyne **30** via dibromide **29** in 82% yield (two steps). Desilylation of **30** with TBAF afforded the homoallylic alcohol **31** which was subjected to Shi epoxidation conditions[26] to produce epoxy alkyne **4**.

(20) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

(21) (a) Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 464–465. (b) Shimizu, I.; Hayashi, K.; Osima, M. *Tetrahedron Lett.* **1990**, *31*, 4757–4758. (c) Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 3099–3104. (d) Yadav, J. S.; Pratap, T. V.; Rajender, V. *J. Org. Chem.* **2007**, *72*, 5882–5885.

(22) (a) Jung, M. E.; Lee, W. S.; Sun, D. *Org. Lett.* **1999**, *1*, 307–309. (b) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1997**, *119*, 12150–12158. (c) Yadav, J. S.; Rao, R. N.; Kumar, B. P.; Somaiah, R.; Ravinder, K.; Reddy, B. V. S.; Khazim Al Ghamdi, A. *Synthesis* **2011**, 3168–3172.

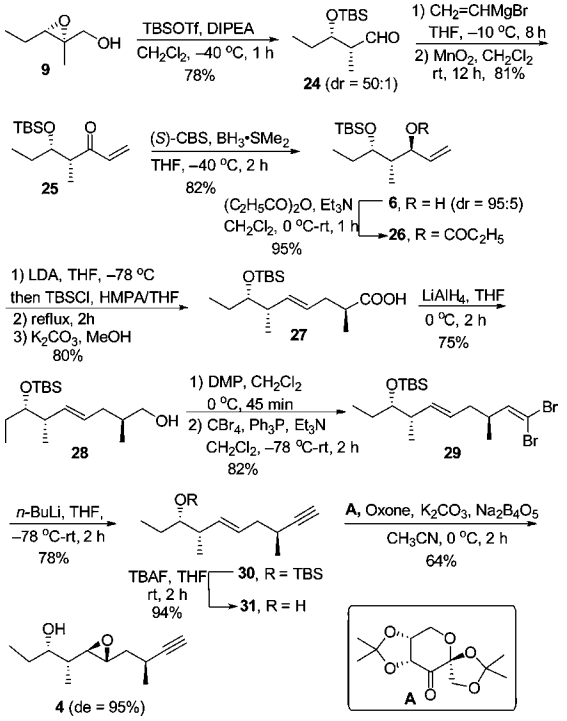
(23) (a) Gille, A.; Hiersemann, M. *Org. Lett.* **2010**, *12*, 5258–5261. (b) Haustedt, L. O.; Panicker, S. B.; Kleinert, M.; Hartung, I. V.; Eggert, U.; Niess, B.; Hoffmann, H. M. R. *Tetrahedron* **2003**, *59*, 6967–6978.

(24) (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868–2877. (b) Noyori, R.; Kurimoto, I. *J. Org. Chem.* **1986**, *51*, 4322–4323.

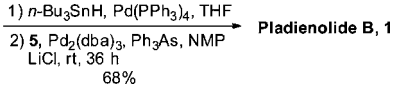
(25) (a) Tietze, L. F.; Gericke, K. M.; Singidi, R. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 6990–6993. (b) Shin, Y.; Fournier, J.-H.; Fukui, Y.; Brueckner, A. M.; Curran, D. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 4634–4637. (c) Aoyagi, S.; Wang, T.-C.; Kibayashi, C. *J. Am. Chem. Soc.* **1993**, *115*, 11393–11409. (d) Baker, R.; Boyes, R. H. O.; Broom, D. M. P.; O'Mahony, M. J.; Swain, C. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1613–622.

(26) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224–11235.

**Scheme 5.** Synthesis of Side Chain **4**



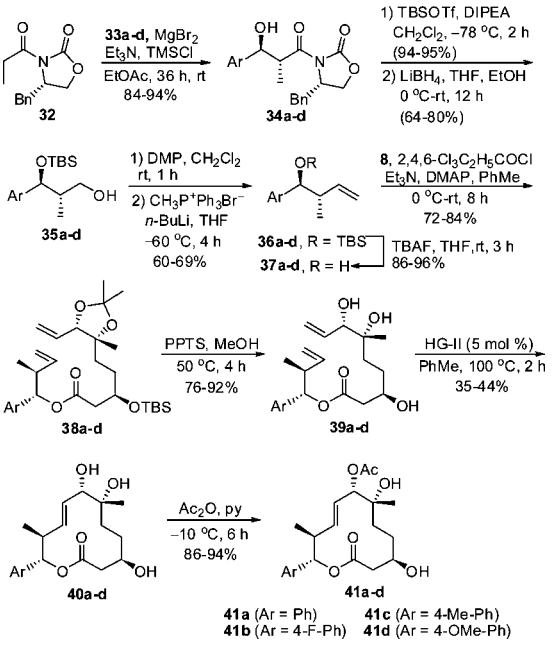

**Scheme 6.** Synthesis of Pladienolide B, **1**




The final coupling of the vinyl iodide **5** and alkyne **4** was accomplished under Stille conditions[27] to obtain the desired pladienolide B, **1**, in 68% yield as shown in Scheme 6. The spectral data of our synthetic pladienolide B {$[\alpha]_D^{28}$ = +7.18 (*c* 0.68, MeOH)} is in good accordance with reported data for the natural pladienolide B {Lit.[1,10a,10b] $[\alpha]_D^{27}$ = +7.9 (*c* 1.1, MeOH)}.

To further demonstrate the synthetic flexibility of this strategy, the key synthon **8** was made in substantial quantities and appended with various aryl side chains as shown in Scheme 7. This allowed us to quickly install aryl groups to generate four truncated analogues of pladienolide B.

**Scheme 7.** Synthesis of Pladienolide B Analogues




$MgBr_2$-catalyzed *anti* aldol condensation[28] of the Evan's amide **32** with aldehydes (**33a**–**d**) generated *anti*-aldol adducts **34a**–**d**. The silylation was realized with TBSOTf followed by reductive cleavage of the chiral auxiliary which was achieved with $LiBH_4$ to synthesize alcohols **35a**–**d**. The one-carbon homologation via oxidation and Wittig reaction furnished olefins **36a**–**d**, which were subsequently deprotected by the addition of TBAF yielding **37a**–**d**. Under Yamaguchi esterification conditions acid **8** reacted with alcohols **37a**–**d** and provided the substrates for RCM, **38a**–**d**. Removal of all protecting groups was realized by treating with PPTS in MeOH to give the triols **39a**–**d**. The RCM reaction was uneventfully yielded **40a**–**d**, and regioselective acetylation of triol realized truncated analogues **41a**–**d**. These analogues were synthesized only to prove the flexibility with which our synthesis was planned and many analogues could be made on demand.[29]

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**Supporting Information Available.** Full experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(27) (a) Kajikawa, T.; Aoki, K.; Singh, R. S.; Iwashita, T.; Kusumoto, T.; Frank, H. A.; Hashimoto, H.; Katsumura, S. *Org. Biomol. Chem.* **2009**, *7*, 3723–3733. (b) Villa, R.; Mandel, A. L.; Jones, B. D.; La Clair, J. J.; Burkart, M. D. *Org. Lett.* **2012**, *14*, 5396–5399.

(28) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392–393.

(29) The growth inhibitory activity of the synthetic pladienolide B, **1**, showed comparable data with the natural ones as reported. Also, the truncated analogues have shown almost equal activity indicating that the side chain is not very essential. However, more SAR studies are essential to conclude this fact (see Supporting Information).