ORGANIC LETTERS

2011
Vol. 13, No. 15
3940–3943

Synthesis of a Pladienolide B Analogue with the Fully Functionalized Core Structure

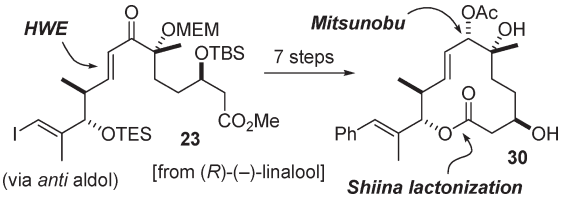
Sarah Müller,[†] Timo Mayer,[†] Florenz Sasse,[‡] and Martin E. Maier*,[†]

Institut für Organische Chemie, Universität Tübingen, Auf der Morgenstelle 18, 72076 Tübingen, Germany, and Abteilung Chemische Biologie Helmholtz-Zentrum für Infektionsforschung, Inhoffenstrasse 7, 38124 Braunschweig, Germany

martin.e.maier@uni-tuebingen.de

Received May 31, 2011

ABSTRACT



Starting from (*R*)-(−)-linalool (6), terminus differentiation and chain extension via aldol type reactions led to ketophosphonate 16 (C1−C8 building block). In a Horner−Wadsworth−Emmons reaction, 16 reacted with aldehyde 22, which contained the vicinal *anti*-Me−OH pattern and a vinyl iodide function, to provide the C1−C13 part of pladienolide B. After Shiina macrolactonization, reduction of the enone 26 gave the core structure 27. A Stille cross-coupling of vinyl iodide 27 with tributylphenylstannane eventually furnished analogue 30.

A living cell can be considered as a very complex factory. While there might be many menial tasks, most of the cellular processes are highly complex. Disfunctions in key processes cause diseases, like cancer. In deciphering biological processes, natural products are still an important tool and the discovery of natural products often identifies new biological targets to treat diseases. Illustrative examples in this regard are the pladienolides and FR901464 (Figure 1). Appropriately labeled and modified derivatives of pladienolide B[1−3] (**1**) and FR901464[4,5] (**4**) showed that the strong antitumor activities of these natural products are connected with interference of the splicing process.[6−8] Protein production in eukaryotic cells requires removal of introns from the initial transcript, the pre-mRNA, by the spliceosome before the mature mRNA is released to the cytosol. The splicing process involves well organized binding and release of several small nuclear ribonucleoproteins (snRNPs), like U1, U2, U4/U6−U5

[†] Institut für Organische Chemie, Universität Tübingen.
[‡] Abteilung Chemische Biologie Helmholtz-Zentrum für Infektionsforschung.

(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.; Kawamura, 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) Isolation and structure: (a) Nakajima, H.; Sato, B.; Fujita, 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) For recent total syntheses and synthetic studies, see: (a) Thompson, C. F.; Jamison, T. F.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 9974–9983. (b) Motoyoshi, H.; Horigome, M.; Ishigami, K.; Yoshida, T.; Horinouchi, S.; Yoshida, M.; Watanabe, H.; Kitahara, T. *Biosci. Biotechnol. Biochem.* **2004**, *68*, 2178–2182. (c) Motoyoshi, H.; Horigome, M.; Watanabe, H.; Kitahara, T. *Tetrahedron* **2006**, *62*, 1378–1389. (d) Albert, B. J.; Sivaramakrishnan, A.; Naka, T.; Czaicki, N. L.; Koide, K. *J. Am. Chem. Soc.* **2007**, *129*, 2648–2659. (e) Osman, S.; Albert, B. J.; Wang, Y.; Li, M.; Czaicki, N. L.; Koide, K. *Chem.—Eur. J.* **2011**, *17*, 895–904.

(6) Pladienolide study: Kotake, 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.

(7) FR901464 (spliceostatin A) 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.

(8) For a summary, see: Rymond, B. *Nat. Chem. Biol.* **2007**, *3*, 533–535.

(9) (a) van Alphen, R. J.; Wiemer, E. A. C.; Burger, H.; Eskens, F. A. L. M. *Br. J. Cancer* **2009**, *100*, 228–232. (b) House, A. E.; Lynch, K. W. *J. Biol. Chem.* **2008**, *283*, 1217–1221.

10.1021/ol201464m
Published on Web 06/27/2011

to the pre-mRNA. As ribozymes they are responsible for the transesterification reactions that cut out the introns.[9] During the early stages of the splicing process the U2 snRNP binds with two protein subunits SF3a and SF3b to the RNA. Affinity-based studies showed that pladienolide B and spliceostatin A (**5**), a stable derivative of FR901464, bind to a subunit of SF3b, the protein SAP130.[6−8] The disturbed splicing process is probably detected by check points causing cell cycle arrest.

Therefore, these natural products represent interesting lead structures for synthesis programs. A derivative of pladienolide B, E7107 (**3**), was even advanced to clinical trials, although the outcome of this study has not yet been published. The group of Webb prepared several derivatives of FR901464 that contributed to the structure−activity relationship.[10] They argue that **1** and **4** are similar in that the epoxy group and the *O*-acetyl groups have the same distance in both molecules.

Pladienolide B (**1**) was isolated by scientists from Eisai Co., Ltd. from *Streptomyces platensis* Mer-11107.[1,2] Among several related macrolides, pladienolide B and D were the most active ones with IC_{50} values in the low nanomolar range in the cell proliferation assay with the human colon cancer cell line WiDr (**1**, 0.86 nM; **2**, 5.9 nM).[11] They were discovered in a screen that revealed compounds which inhibit the reaction of tumor cells to hypoxia (oxygen deficiency). The structural features of pladienolide B include a 12-membered macrolactone ring containing a vicinal diol with one of the alcohols being allylic and the other one tertiary. Challenging features in the side chain are the conjugated *E*,*E*-diene and the epoxide function. So far one total synthesis by Kotake et al.,[11] a synthesis of the macrolactone part lacking the complete side chain,[12] and the synthesis of the side chain were reported.[13] The Burkart group could also demonstrate the attachment of the side chain to a model lactone by Stille coupling.[13]

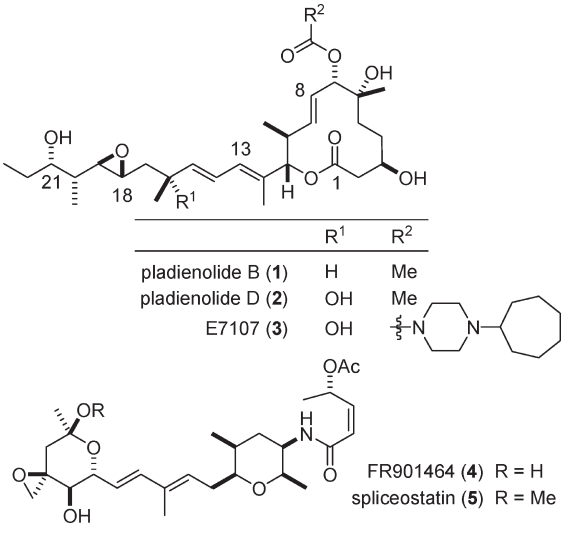


Figure 1. Structures of spliceosome inhibitors of the pladienolide and FR901464 type.

According to our synthetic plan (Figure 2) the side chain would be attached by a cross-coupling reaction at the C13−C14 bond, with a vinyl iodide substituent emerging from the macrolactone. The allylic alcohol at C7 was envisioned to come from an enone precursor ***A*** which offered the possibility of creating the C8−C9 double bond by a Horner−Wadsworth−Emmons (HWE) reaction. This could even be used for macrolactone formation. Alternatively, Yamaguchi and Mitsunobu lactonization were considered. This led to the two building blocks ***C*** and ***D***. The tertiary alcohol function in ***D*** could derive from the natural product (*R*)-(−)-linalool. In this paper we illustrate the synthesis of the pladienolide B core featuring a vinyl iodide side chain that presents itself for cross-coupling reactions.

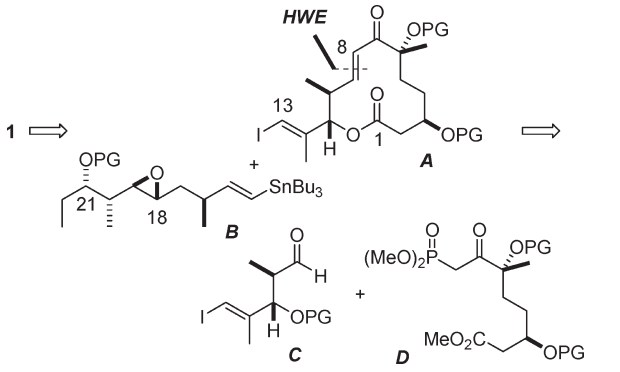


Figure 2. Retrosynthetic plan for pladienolide B (**1**).

First, (*R*)-(−)-linalool (**6**) was converted to the corresponding MEM ether (MEMCl, iPr_2NEt, room temperature) in almost quantitative yield. Next, the higher substituted double bond was oxidized to the corresponding diol **8** using osmium-catalyzed dihydroxylation. Oxidative cleavage of the diol **8** ($NaIO_4$, THF/H_2O) furnished aldehyde **9**.[14] This aldehyde (0.6 equiv) was entered into a Nagao acetate aldol reaction[15] with thiazolidinethione **10** in the presence of $Sn(OTf)_2$ (1.34 equiv) and *N*-ethylpiperidine (1.46 equiv) in CH_2Cl_2 at −78 °C to provide aldol

(10) (a) Lagisetti, C.; Pourpak, A.; Jiang, Q.; Cui, X.; Goronga, T.; Morris, S. W.; Webb, T. R. *J. Med. Chem.* **2008**, *51*, 6220–6224. (b) Lagisetti, C.; Pourpak, A.; Goronga, T.; Jiang, Q.; Cui, X.; Hyle, J.; Lahti, J. M.; Morris, S. W.; Webb, T. R. *J. Med. Chem.* **2009**, *52*, 6979–6990.

(11) 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. Corrigendum: *Angew. Chem., Int. Ed.* **2007,** *46*, 8734.

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

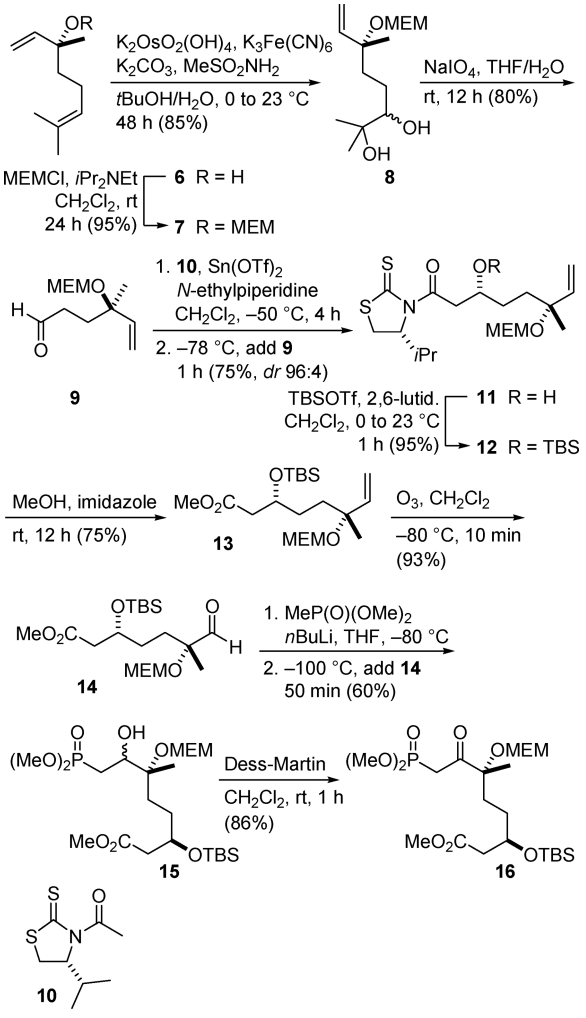
(13) Mandel, A. L.; Jones, B. D.; La Clair, J. J.; Burkart, M. D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5159–5164.

(14) For related sequences starting from linalool, see: (a) Li, G.; Yang, X.; Zhai, H. *J. Org. Chem.* **2008**, *74*, 1356–1359. (b) Sabitha, G.; Prasad, M. N.; Bhikshapathi, M.; Yadav, J. S. *Synthesis* **2010**, 807–810. (c) Canterbury, D. P.; Micalizio, G. C. *Org. Lett.* **2011**, *13*, 2384–2387.

(15) (a) Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391–2393. (b) Nagao, Y.; Dai, W. M.; Ochiai, M.; Shiro, M. *J. Org. Chem.* **1989**, *54*, 5211–5217. (c) Delaunay, D.; Toupet, L.; Corre, M. L. *J. Org. Chem.* **1995**, *60*, 6604–6607.

product **11** in 75% yield.[16] Silylation of the alcohol (TBSOTf, 2,6-lutidine) was followed by transesterification to methyl ester **13**. At this stage the terminal double bond was cleaved by ozonolysis yielding aldehyde **14** in good yield. To prepare ketophosphonate **16**, aldehyde **14** was reacted with lithiated dimethyl methyl phosphonate at −100 °C. Oxidation of the obtained alcohol **15** with the Dess−Martin reagent delivered ketophosphonate **16** (Scheme 1).

Scheme 1. Synthesis of Ketophosphonate **16** from (*R*)-(−)-Linalool



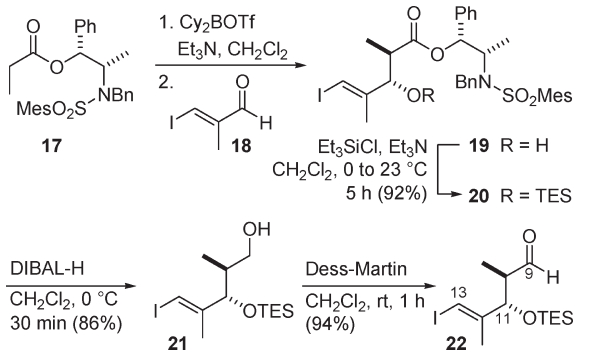
The other fragment aldehyde **22** was prepared essentially according to the literature.[17] A Masamune−Abiko aldol reaction[18] between aldehyde **18** and chiral ester **17** followed by silylation of the aldol product provided ester **20** in good overall yield (Scheme 2). Reduction of ester **20** with DIBAL-H (2.5 equiv) in CH_2Cl_2 furnished primary alcohol **21**. Its oxidation delivered the C9−C13 fragment, aldehyde **22**.

(16) Performing the aldol reaction at a later stage with the enone present caused problems during cleavage of the auxiliary.

(17) Menche, D.; Hassfeld, J.; Li, J.; Mayer, K.; Rudolph, S. *J. Org. Chem.* **2009**, *74*, 7220–7229.

(18) Abiko, A. *Acc. Chem. Res.* **2004**, *37*, 387–395.

Scheme 2. Synthesis of Aldehyde **22** by an *anti* Aldol Reaction



The crucial HWE reaction between phosphonate **16** and aldehyde **22** turned out to be rather challenging. Most of the known literature methods were inefficient and seemingly led to destruction of the sensitive aldehyde **22**. Eventually, performing the reaction with dried BaO in Et_2O, which contained a trace of water, produced enone **23** in a very efficient way.[19] Toward the *seco* acid **25**, methyl ester **24** was saponified with trimethyltin hydroxide in dichloroethane,[20] since basic hydrolysis was detrimental in this case. Subsequently, selective cleavage of the triethylsilyl ether using DDQ[21] in a CH_3CN/H_2O mixture delivered *seco* acid **25**. Macrolactonization was initially tried under Yamaguchi conditions. However, in this case, the yield never exceeded 50%. In contrast, lactonization with the Shiina anhydride in the presence of DMAP induced lactone formation in almost quantitative yield.[22,23] We next faced the problem of diastereoselective enone reduction. This was performed using Luche conditions ($NaBH_4$, $CeCl_3 \cdot 7H_2O$) in MeOH but led to the C7 epimer **27**. The stereochemistry at C7 was inferred from the corresponding Mosher ester.[24] Thus, in benzene-d_6 as a solvent the expected shift differences were observed for the Mosher esters prepared from **27**. For example, the 6-CH_3 group in the (*S*)-**27** Mosher derivative is shifted to higher field due to the influence of the phenyl group. By way of contrast, 9-H experienced a high field shift in the (*R*)-**27** Mosher derivative. To show that the vinyl iodide is suitable for chain extension, we performed a Stille cross-coupling with

(19) (a) Ibarra, C. A.; Arias, S.; Fernández, M. J.; Sinisterra, J. V. *J. Chem. Soc., Perkin Trans. 2* **1989**, 503–508. (b) Paterson, I.; Yeung, K.-S.; Smaill, J. B. *Synlett* **1993**, 774–776. (c) Radosevich, A. T.; Chan, V. S.; Shih, H.-W.; Toste, F. D. *Angew. Chem., Int. Ed.* **2008**, *47*, 3755–3758.

(20) (a) Mascaretti, O. A.; Furlán, R. L. E. *Aldrichimica Acta* **1997**, *30*, 55–68. (b) Nicolaou, K. C.; Estrada, A. A.; Zak, M.; Lee, S. H.; Safina, B. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 1378–1382.

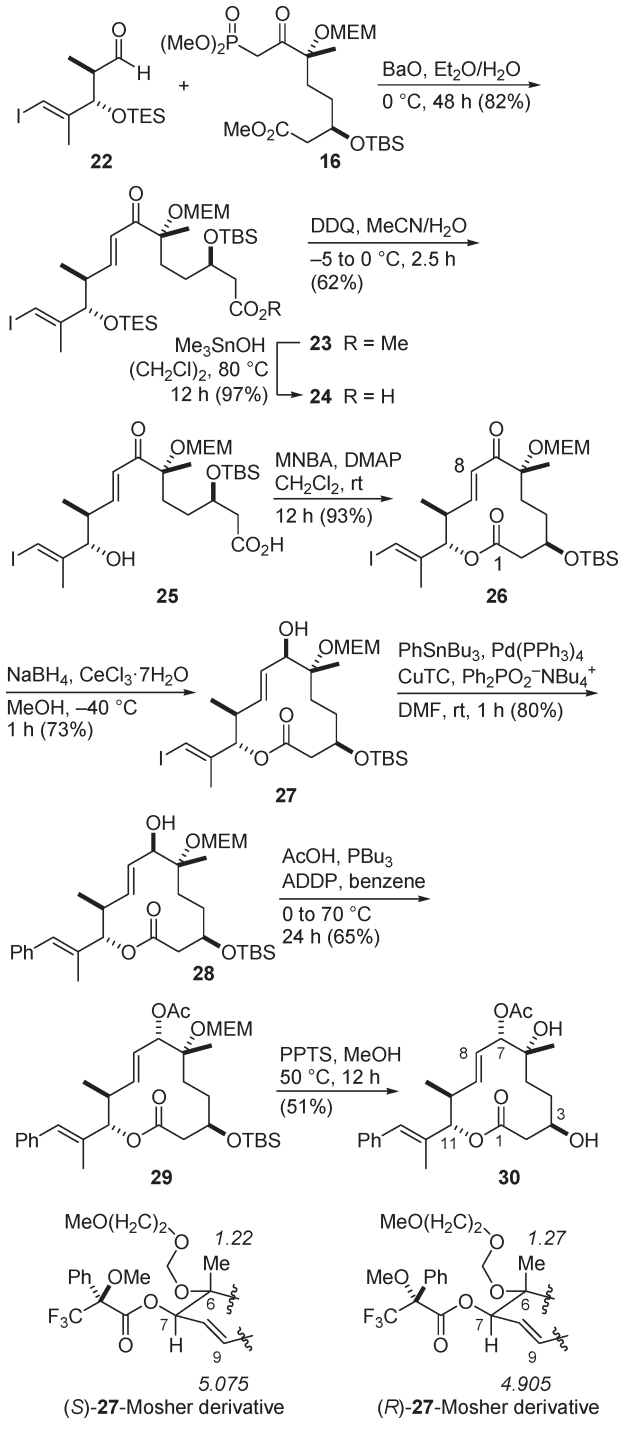
(21) (a) Oku, A.; Kinugasa, M.; Kamada, T. *Chem. Lett.* **1993**, *22*, 165–168. (b) Imuta, S.; Tanimoto, H.; Momose, M. K.; Chida, N. *Tetrahedron* **2006**, *62*, 6926–6944.

(22) (a) Shiina, I.; Kubota, M.; Oshiumi, H.; Hashizume, M. *J. Org. Chem.* **2004**, *69*, 1822–1830. (b) Shiina, I. *Tetrahedron* **2004**, *60*, 1587–1599. (c) Shiina, I.; Hashizume, M.; Yamai, Y.-s.; Oshiumi, H.; Shimazaki, T.; Takasuna, Y.-j.; Ibuka, R. *Chem.—Eur. J.* **2005**, *11*, 6601–6608.

(23) For a review, see: Shiina, I. *Chem. Rev.* **2007**, *107*, 239–273.

(24) Kusumi, T.; Ooi, T.; Ohkubo, Y.; Yabuuchi, T. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 965–980.

Scheme 3. Formation of Enone **23** by a Horner–Wadsworth–Emmons Reaction Followed by Macrolactonization of the Derived *seco* Acid to Lactone **26**[a]



[a] CuTC = copper(I)-thiophene-2-carboxylate; MNBA = 2-methyl-6-nitrobenzoic anhydride; ADDP = azodicarboxylic acid dipiperidide.

tributylphenylstannane in the presence of $Pd(PPh_3)_4$, CuTC, and $Ph_2PO_2^-NBu_4^+$ in DMF.[25] This way styrene **28** could be obtained in 80% yield. The acetate group was then introduced by a modified Mitsunobu reaction[26,27] in 65% yield. Finally, both protecting groups were removed from lactone **29** with PPTS in MeOH resulting in pladienolide analogue **30** in 51% yield after preparative TLC (Scheme 3).

In a cell proliferation assay[28,29] against L929 mouse fibroblasts, pladienolide analogue **30** was inactive up to 4 μg mL^{-1}. This underscores the role of the epoxide-containing side chain for binding and supports the hypothesis of Webb.[10]

In summary, we demonstrated a novel strategy to the core structure of pladienolide B. Starting from the monoterpene (*R*)-(−)-linalool (**6**), ketophosphonate **16** was prepared. After oxidative cleavage of the higher substituted double bond on **6**, an acetate aldol reaction set the stereocenter at C3. The aldehyde function, derived from the other double bond, allowed for extension to the ketophosphonate **16**. An HWE reaction of **16** with aldehyde **22** produced enone **23**. The corresponding *seco* acid **25** could be cyclized in very high yield to the macrolactone **26** using the Shiina reagent. The C7 stereocenter was established by Luche reduction followed by Mitsunobu reaction to introduce the acetate group. In a Stille reaction with phenylstannane, we were able to show that the vinyl iodide allows for the introduction of substituents to the side chain.

Acknowledgment. Financial support by the Deutsche Forschungsgemeinschaft (Grant MA 1012/24-1) and the Fonds der Chemischen Industrie is gratefully acknowledged. This work was carried out within the framework of COST action CM0804–Chemical Biology with Natural Products. We thank Bettina Hinkelmann (HZI Braunschweig) and Tatjana Hirsch (HZI Braunschweig) for excellent technical assistance with the cytotoxicity assay.

Supporting Information Available. Experimental procedures and characterization for all new compounds reported and copies of NMR spectra for important intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

(25) (a) Srogl, J.; Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1997**, *119*, 12376–12377. (b) Fürstner, A.; Funel, J.-A.; Tremblay, M.; Bouchez, L. C.; Nevado, C.; Waser, M.; Ackerstaff, J.; Stimson, C. C. *Chem. Commun.* **2008**, 2873–2875.

(26) Tsunoda, T.; Yamamiya, Y.; Itô, S. *Tetrahedron Lett.* **1993**, *34*, 1639–1642.

(27) For reviews, see: (a) Hughes, D. L. *Org. React.* **1992**, *42*, 335–656. (b) Dembinski, R. *Eur. J. Org. Chem.* **2004**, 2763–2772. (c) Swamy, K. C. K.; Kumar, N. N. B.; Balaraman, E.; Kumar, K. V. P. P. *Chem. Rev.* **2009**, *109*, 2551–2651.

(28) Staton, C. A.; Stribbling, S. M.; Tazzyman, S.; Hughes, R.; Brown, N. J.; Lewis, C. E. *Int. J. Exp. Pathol.* **2004**, *85*, 233–248 and references therein.

(29) Vintonyak, V. V.; Calà, M.; Lay, F.; Kunze, B.; Sasse, F.; Maier, M. E. *Chem.—Eur. J.* **2008**, *14*, 3709–372.