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# A synthetic entry to pladienolide B and FD-895

Alexander L. Mandel, Brian D. Jones, James J. La Clair and Michael D. Burkart*

*Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093, USA*

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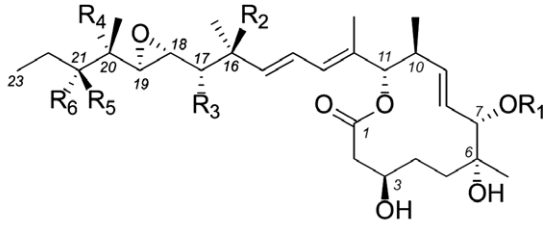
**Abstract**—Presented within are syntheses of the pladienolide B and FD-895 side-chains, as well as models of the essential ring-closing metathesis and Stille coupling that will be used to complete their total syntheses. Several analogs of the pladienolide B side-chain were also prepared in order to evaluate the scope of the methodology and to create a library of structures that could be used for stereochemical and SAR analyses.


The pladienolides (**1a**–**g**) are a set of highly bioactive macrocyclic polyketides isolated from an Okinawan strain of *Streptomyces platensis* (Fig. 1).[1] FD-895 (**1h**) was reported in 1994 from an isolate of *Streptomyces hygroscopicus*.[2]

This family of macrolides (**1a**–**h**) displays potent antiproliferative and tumor suppressive activity when assayed in both cell culture and xenograft models.[1a,c,2] Several members of the family, including pladienolide B (**1b**), inhibited tumor cell growth at low nanomolar concentrations. Subsequent cell cycle studies indicate that **1b** blocks cell growth in both the G1 and the G2/M phase, suggesting a unique mode of action. In addition, pladienolide B (**1b**) has been shown to deliver potent tumor regression and inhibition of mouse xenografts.

At the beginning of our studies, only the two-dimensional structures of **1a**–**h** were known. This combined with lack of access to the compounds themselves or their producer strains meant that we would have to determine the stereochemistry de novo.[4] Given recent advances in NMR techniques and the use of libraries to elucidate the three-dimensional configuration of natural products,[5] we felt that this study would provide an ideal platform to use chemical synthesis in concert with more traditional methods to determine the stereochemistry of these macrolides.[6] Moreover, the required general approaches to the stereochemistry of **1b** and **1h** are synthetic strategies that allow access to many analogs for future research on these promising lead compounds. In parallel, the methods developed in this research serve as a prelude to the total synthesis of the pladienolides and FD-895.[7]




| | | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | $R^6$ |
|---|---|---|---|---|---|---|---|
| pladienolide A | **1a** | H | H | H | H | OH | H |
| pladienolide B | **1b** | Ac | H | H | H | OH | H |
| pladienolide C | **1c** | Ac | H | H | H | =O | |
| pladienolide D | **1d** | Ac | OH | H | H | OH | H |
| pladienolide E | **1e** | Ac | H | H | OH | OH | H |
| pladienolide F | **1f** | H | OH | H | H | OH | H |
| pladienolide G | **1g** | H | H | H | OH | OH | H |
| FD-895 | **1h** | Ac | H | OH | H | $OCH_3$ | H |

**Figure 1.** Structures of the pladienolides (**1a**–**g**) and FD-895 (**1h**). The stereochemical assignments of pladienolide B (**1b**) and D (**1d**)[3] were recently determined by NMR and synthetic methods. Stereochemistries of other members of the family (**1a**, **1c**, **1e**–**g**) and FD-895 (**1h**) are expected to follow from **1b** and **1d**, but have yet to be confirmed.

Our general retrosynthetic analysis (Scheme 1) of the family began by visualizing a convergent union at the diene by a Stille coupling of side-chain **2** to core **3**. Stannane **2** was ideal because conditions for tin insertion do not cause side reactions with the C18–C19 epoxide.[8]

*Keywords*: Macrolides; Natural products; Antitumor agents; Metathesis; Analogs.
* Corresponding author. Tel.: +1 858 534 5673; fax: +1 858 822 2182; e-mail: mburkart@ucsd.edu

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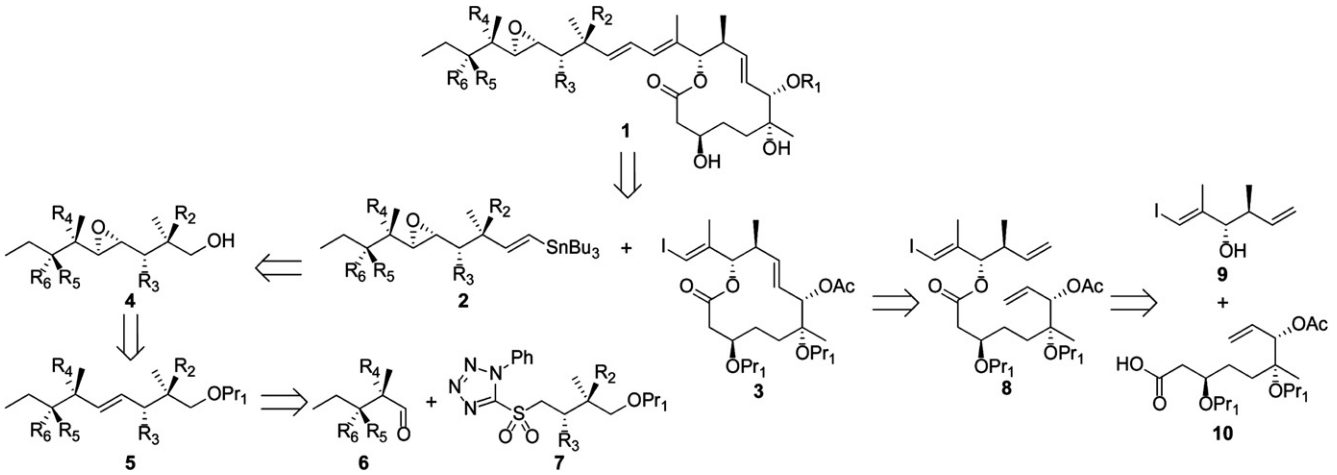


**Scheme 1.** Retrosynthetic analysis of the pladienolides (**1a**–**g**). A convergent strategy was developed to fuse the side-chain to macrolide core **3**. As depicted, the route developed from four fragments: aldehyde **6**, sulfone **7**, carbinol **9**, and carboxylic acid **10**.

Stannane **2** could then be derived from alcohol **4** that would result from epoxidation of olefin **5** using a suitable method.[9] Olefin **5** would follow naturally from a Julia–Kociensky reaction of aldehyde **6** and sulfone **7**.[10] Macrolide **3** would then be derived from a ring-closing metathesis of **8**. In turn, **8** could be prepared by coupling of alcohol **9** and carboxylic acid **10**. This two-step ester formation—RCM has precedent in our laboratory and elsewhere.[11] As this article was being prepared, Kotake indeed showed that these disconnections can be used to assemble pladienolide B (**1b**) and D (**1d**).[3]

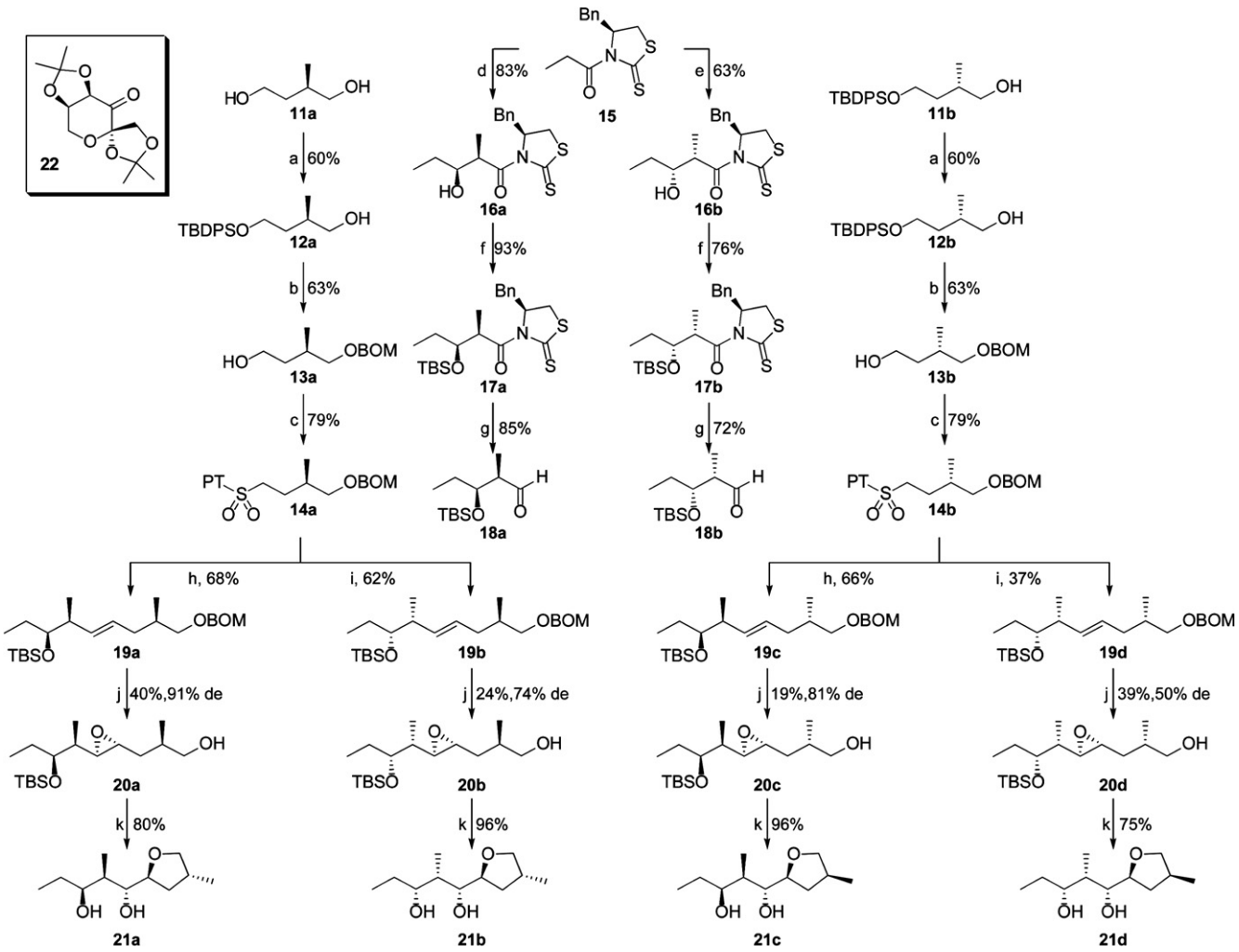
With a synthetic plan in hand, we turned to evaluate the complexity of the proposed synthetic endeavor. Without simplification, the total synthesis of all stereoisomers of **1b** would be a wasteful enterprise. By examining the $^1$H NMR data for pladienolide B (**1b**), the C18–C19 epoxide was assigned as a *trans*-epoxide based on presence of a 2.4 Hz coupling constant in $CDCl_3$[2]. We also assigned a *syn*-configuration at C20–C21 by the presence of a 4.1 Hz coupling constant for **1h** in $CDCl_3$ using *J*-value comparisons to literature examples.[12] Additionally, the C10–C11 diad had a 9.8 Hz coupling constant, which was indicative of *anti* stereochemistry at that position. Given these simplifications, we decided that we should prepare the four possible side-chain isomers of **1b**. The fragments were anticipated to be useful for comparison with degradation products of **1b**. They could also be used in the preparation of an NMR database.[13]

The synthesis of the pladienolide B side-chain began with the preparation of sulfone **14a** from commercially available R-2-methyl-1,4-butanediol (**11a**) (Scheme 2). Mono-protection of **11a** with TBDPSCl gave **12a** in 60% yield.[14] After purification, the material was protected with BOMCl and Hünig's base, and the crude material was treated with TBAF to afford alcohol **13a**. Mitsunobu displacement with 1H-phenyltetrazolethiol, followed by oxidation with ammonium molybdate and hydrogen peroxide, produced **14a** in 79% yield for the two steps.[15] Sulfone **14b** was prepared by repeating the procedure on the commercially available *S*-isomer **11b**.

Aldehydes **18a** and **18b** were accessed through the Crimmins chiral aldol protocol.[16] This methodology is uniquely suited to divergent approaches because reagent control directs the stereochemical outcome with a high diastereomeric excess. Starting from thiazolidinethione **15**, treatment with $TiCl_4$, (−)-sparteine, and *N*-methylpyrrolidinone afforded the Evans *syn*-aldol product **16a**, but by using $TiCl_4$ and Hünig's base without NMP the 'non-Evans' *syn*-aldol adduct **16b** was the product. Both substances were protected with TBSOTf to give **17a** and **17b**.[17] The chiral auxiliary was removed by treatment with DIBAL-H in toluene to offer aldehydes **18a** and **18b** in yields of 85% and 72%, respectively.[18]

A total of four Julia olefinations, **14a** + **18a**, **14a** + **18b**, **14b** + **18a**, and **14b** + **18b**, were conducted to produce olefins **19a**–**d** with yields ranging from 37% to 68% relative to the limiting aldehyde (Scheme 2). Conditions were refined as the process was repeated. While the addition of the aldehyde to the sulfone anion was conducted at low temperature, the reaction mixture required warming to room temperature immediately after addition was complete, otherwise aldehydes **18a**–**b** were returned and the sulfones **14a**–**b** decomposed. In addition, commercially available anhydrous glyme contained sufficient water (~10–50 ppm) to hinder the reaction, resulting in basic decomposition of aldehydes **18a**–**b**. This complication was in part responsible for the rather unpredictable yields of the couplings presented in Scheme 2.

At this stage, olefins **19a**–**d** could be epoxidized using the Shi protocol but subsequent conditions required to remove the BOM protecting group were incompatible with the epoxide. Acidic conditions were too harsh, and catalytic hydrogenation induced 5-*exo*-tet cyclization.[19] Interestingly, when a mixture of diastereomeric epoxides (i.e., **20a** and its 4*S*,5*S* diastereomer; prepared by oxidation with mCPBA) was hydrogenated, one diastereomer cyclized readily while the other remained mostly intact over 30 min of treatment with Pd on C under an $H_2$ atmosphere.




**Scheme 2.** Divergent synthesis of side-chain diastereomers. Reagents and conditions: (a) TBDPSCl, DBU, DMF, −50 °C; (b) i—BOMCl, DIPEA, $CH_2Cl_2$; ii—TBAF, wet THF; (c) i—1H-phenyltetrazolethiol, DIAD, $PPh_3$, $CH_2Cl_2$, 0 °C to rt; ii—$(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, $H_2O_2$, EtOH, 0 °C to rt; (d) $TiCl_4$, DIPEA, $CH_2Cl_2$, −78 °C; (e) $TiCl_4$, (−)-sparteine, NMP, $CH_2Cl_2$, −78 °C; (f) TBSOTf, DIPEA, $CH_2Cl_2$; (g) DIBAL-H, toluene, −78 °C; (h) KHMDS, DME, −78 °C, then add **18a** warm to rt; (i) KHMDS, DME, −78 °C, then add **18b** warm to rt; (j) i—Li wire, naphthalene, THF; ii—**22**, oxone, $K_2CO_3$, $Bu_4NHSO_4$, $CH_3CN$, $H_2O$, borax–EDTA buffer, 0 °C; (k) 35% $H_2SiF_6$, $CH_3CN$, rt, PT = 1H-phenyltetrazole.

The solution was to cleave the BOM ether prior to epoxidation. The stereoselectivities and yields of the epoxidations were unaffected by the presence of a free alcohol at the terminal position. Therefore, lithium naphthelenide was chosen for this deprotection since it would not reduce the olefin. Performing the reaction at room temperature resulted in yields of 54–82%.[20] The resulting alcohols were then epoxidized using the method of Shi.[9] While not air-sensitive, the Shi epoxidation demands precise conditions. When carried out at room temperature, yields were below 25% as most of the intermediate oxirane from **22** decomposed prior to epoxidation. At 0 °C, yields of product increased to between 40% and 55%. In the end, slow addition of oxone and pH control were shown to stabilize the oxirane and increase the output of epoxide.

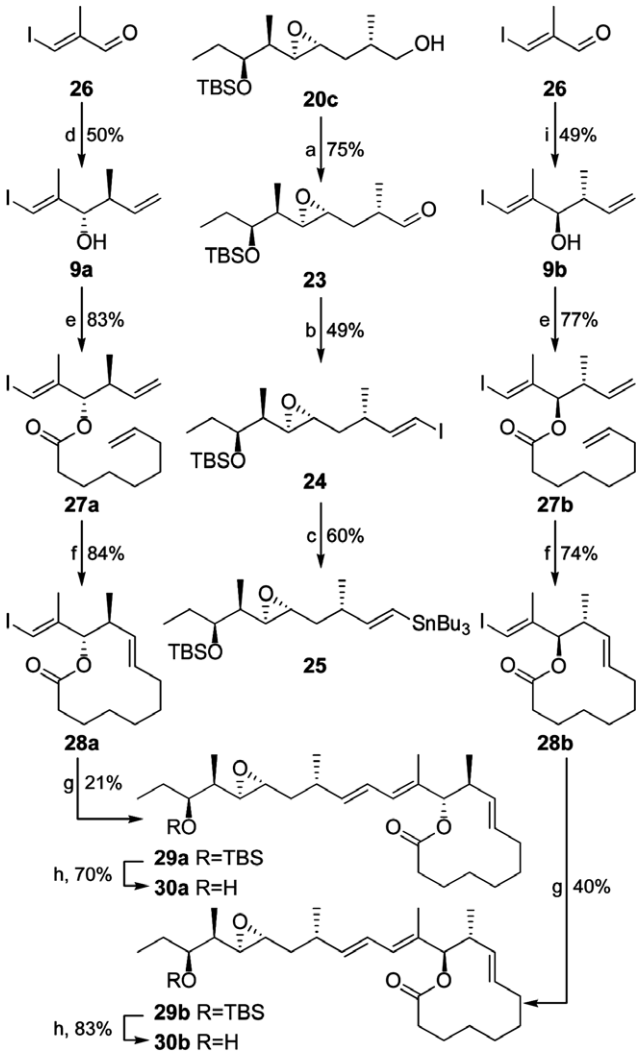
The Shi epoxidation was very sensitive to the stereochemistry already installed in the olefin. When installed *anti* to the adjacent C20 stereocenter as in **20a** and **20c**, the Shi epoxidation delivered a high diastereoselection as indicated by 91% and 81% de, respectively. However, the results were poor for **20b** and **20d**, which were recovered with 74% and 50% de, respectively. In addition, the yields of **20a–d** were modest at best, though the unreacted olefin could be recovered and re-reacted after purification.

Cleavage of the TBS ether without side-reactivity proved difficult. When treated with 1.25 equivalents of fluoride ion from 35% aqueous fluorosilicic acid[21] in acetonitrile, epoxides **20a–d** were deprotected and cyclized to the corresponding furans **21a–d** in seconds. TBAF worked over several days, but also resulted in the partial formation of cyclized furan. While this observation was not desired for synthetic progress, the introduction of the furan ring allowed each stereoisomer to be verified by NOE studies.[22] These furans would also be useful to compare with fragments obtained from an authentic sample of **1b**.

Unfortunately, direct correlation of $^1H$ or $^{13}C$ chemical shifts of **20a–d** also failed to produce a convincing argument to conclusively assign the stereochemistry of the pladienolide B (**1b**) side-chain. No trend existed between

protons and carbons from C15–C23 in **20a**–**d** when compared to **1a**–**h**.

Without a sample of **1b**, we turned to investigate the viability of our overall synthetic scheme (Scheme 1). Our studies began with a model using **20c**, which our NMR analysis determined was the most likely match to **1b** side-chain stereochemistry. Oxidation of **20c** with Dess–Martin periodinane buffered by solid $NaHCO_3$ afforded aldehyde **23** without cyclization to a tetrahydrofuran or lactol. Subsequent homologation using iodoform and chromium(II) chloride furnished vinyl iodide **24** with no detectable *Z*-isomer.[23] Iodide **24** was then converted to vinyl stannane **25** using a palladium catalyzed tin/halogen exchange.[24] Stannane **25** turned out to have the correct stereochemistry for the synthon to pladienolide B (**1b**) (Scheme 3).

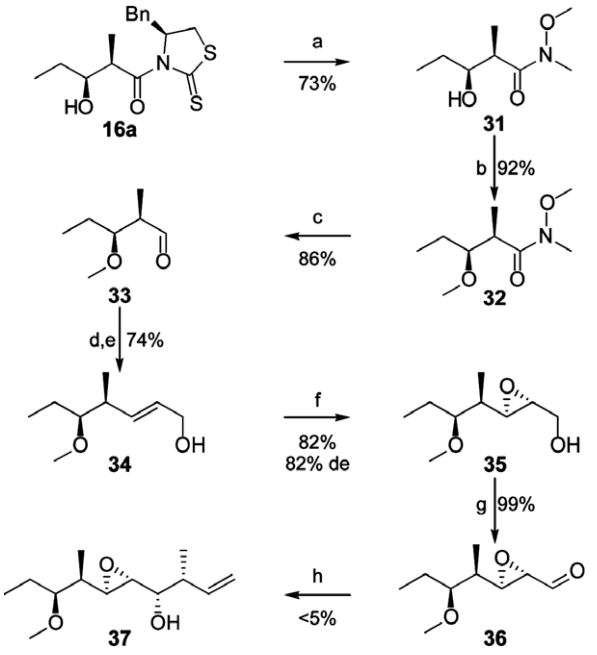



**Scheme 3.** Establishing the synthetic strategy through model studies. Reagents and conditions: (a) Dess–Martin periodinane, $NaHCO_3$, $CH_2Cl_2$, rt; (b) $CHI_3$, $CrCl_2$, THF, dioxane (1:6), rt; (c) $(Bu_3Sn)_2$, $Pd(PPh_3)_2Cl_2$, THF, 50 °C; (d) $^{d}Ipc_2BOMe$, KO$^{t}$Bu, $^{n}$BuLi, *trans*-2-butene, $BF_3{\cdot}Et_2O$, $Et_2O$, THF, −78 °C; (e) 8-octenoic acid, EDC, DMAP, DIPEA, THF, rt; (f) Grubbs second generation catalyst, $CH_2Cl_2$, reflux; (g) $Pd(MeCN)_2Cl_2$, DMF, rt; (h) HF·pyridine, rt; (i) $^{l}Ipc_2BOMe$, $^{t}$BuOK, $^{n}$BuLi, *trans*-2-butene, $BF_3{\cdot}Et_2O$, $Et_2O$, THF, −78 °C.

Next, model studies were conducted to demonstrate the application of the olefin metathesis—Stille relay. The approach began by crotylboration of aldehyde **26**[25] using the procedure of Brown.[26] Not knowing the absolute stereochemistry, we synthesized both *anti* stereoisomers **9a** and **9b** in modest yields. Subsequent esterification with 8-nonenoic acid afforded **27a** and **27b**. Ring-closing metathesis with the second generation Grubbs catalyst delivered lactone **28a** and **28b** in 84% and 74% yield, respectively. NMR confirmed that the olefin geometry was *E* and there was no detectable *Z*-isomer. This reactivity profile of RCM on 12-membered rings is nicely in accord with the synthesis of mycolactone carried out in our laboratory.[11] While not yet optimized, the Stille coupling between stannane **25** and **28a** does provide **29a** in 21% yield when run at 10 mg scale. Coupling **25** with **28b** afforded a better yield of **29b** at 40%. The reaction seems to stall, but additional catalyst does not move the reaction forward. It is interesting to note that these reactions contain an allylic acyl group, but no acetyl elimination occurs. In fact, it is possible to recover all of the iodide (**28a** or **28b**) from the reaction, although stannane **25** is lost. Subsequent TBS deprotection with HF·pyridine afforded pladienolide B analogs **30a** and **30b**. Comparing the NMR spectra of the analogs and authentic **1b** showed that neither are similar to pladienolide B (**1b**). This would have made the library approach a dubious method to determine the stereochemistry.

Because of the similarity of the pladienolides and FD-895, an effort has been launched to adapt the strategy for **1b** to synthesize **1h**, its cytotoxic cousin. As outlined in Scheme 4, all of the stereocenters in the FD-895 side-chain have been synthesized. The route begins by conversion of Crimmins aldol product **16a** to its corresponding Weinreb amide **31**.[16] Subsequent methylation to **32** followed by reduction afforded aldehyde **33** in 80% yield over the two steps. **33** was then homologated to allylic alcohol **34** in two steps by Horner–Wadsworth–Emmons olefination and subsequent reduction with DIBAL-H. After screening a variety of conditions, we found that the Sharpless epoxidation provided the most effective reaction, delivering **35** in 82% yield and 82% de. From there oxidation to **36** with IBX[27] proceeded in quantitative yield, and contrasted modest yields from the Parikh–Doering[28] and Dess–Martin[29] methods. Finally, crotylboration afforded **37**, albeit with low efficiency.

While not yet optimized, this route now provides the first access to the FD-895 side-chain. Efforts are now underway to complete the synthesis of the pladienolides (**1a**–**g**) and FD-895 (**1h**). We have illustrated through model studies the use of stannane **25** as it applies to the total synthesis of pladienolide B (**1b**). While not optimized, we have also shown how to construct the FD-895 side-chain, and it could be used in a similar manner to complete the synthesis of **1h**. Efforts have been underway to install the C3, C6, and C7 stereocenters in **10**. While Kotake has already demonstrated a route to **10**, their use of the Sharpless dihydroxylation to install the C6–C7 diad failed to provide good diastereoselection.[3]




**Scheme 4.** Synthesis of the FD-895 side-chain. (a) MeNHOM·HCl, imidazole, $CH_2Cl_2$, rt; (b) NaH, MeI, DMF, THF, 0 °C; (c) DIBAL-H, $CH_2Cl_2$, −78 °C; (d) triethylphosphonoacetate, NaH, THF, 0 °C; (e) DIBAL-H, $CH_2Cl_2$; (f) (−)-DET, $Ti(O^iPr)_4$, $^t$BuOOH, $CH_2Cl_2$, −10 °C; (g) IBX, EtOAc, reflux; (h) $^d$Ipc$_2$BOMe, $^t$BuOK, $^n$BuLi, *cis*-2-butene, $BF_3{\cdot}Et_2O$, THF.

Comparable observations were also obtained in our preliminary efforts to **10**. We are currently pursuing a route to **10** using the chiral pool to circumvent this problem.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2007.06.094.

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