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Total Synthesis of the Spliceosome Modulator Pladienolide B via Asymmetric Alcohol-Mediated *syn*- and *anti*-Diastereoselective Carbonyl Crotylation

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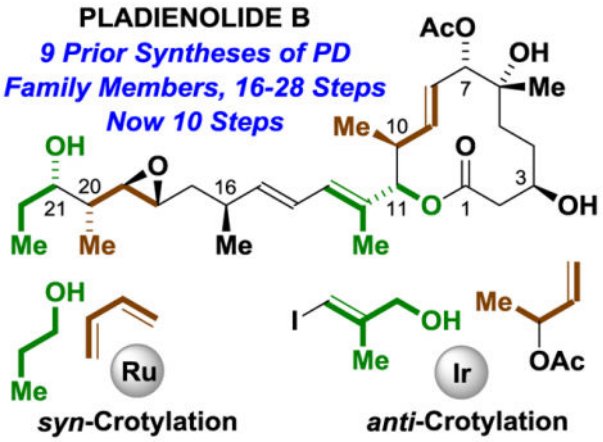
Graphical Abstract



Total Synthesis Fueled by Alcohol. The potent spliceosome modulator pladienolide B, which bears 10 stereogenic centers, is prepared in 10 steps (LLS). Asymmetric alcohol-mediated carbonyl crotylations catalyzed by ruthenium and iridium that occur with *syn*- and *anti*-diastereoselectivity, respectively, were used to form the C20-C21 and C10-C11 C-C bonds.

Keywords

Enantioselective; Hydrogen Transfer; Iridium; Ruthenium; Cancer

The pladienolides are a family of 12-membered macrolides isolated in 2004 by researchers at Eisai from the culture broth of Mer-11107, an engineered strain of *Streptomyces platensis* (Figure 1).[1] Earlier in 1994, a related polyketide, FD-895, was isolated from the Okinawan soil bacteria *Streptomyces hygroscopicus A-9561*.[2] The pladienolides were identified in a cell-based reporter assay for hypoxia-induced gene expression controlled by human VEGF promoter[1a] and were shown to inhibit proliferation of multiple drug resistant human cancer cells at low nanomolar IC_{50} values.[3] In 2007, researchers at Eisai determined that the

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pladienolides bind splicing factor 3b (SF3b),[4,5] inducing cell cycle arrest at both G1 and G2/M phase. In 2018, researchers at the Max Planck Institute for Biophysical Chemistry and H3 Biomedicine, Inc., obtained a crystal structure of SF3b bound by pladienolide B, providing precise insight into its mode of action.[6] Eisai launched two phase I clinical trials of pladienolide analogue E7107,[7] which were discontinued due to side-effects involving vision loss. Interest in anti-cancer drugs that target the spliceosome persisted, and in 2017 the pladienolide derivative H3B-8800 developed by Eisai and H3 Biomedicine, Inc. was granted orphan drug status by the FDA for treatment of myelogenous and chronic myelomonocytic leukemia.[8]

Although pladienolide and its derivatives show great promise *vis-á-vis* cancer treatment, concise routes to compounds of this class remain elusive. To date, four total syntheses of pladienolide B (and its C7 epimer) and have been reported,[9] along with the total synthesis of FD-895 (and its C17 epimer).[10] These routes range in length between 16–22 steps (LLS) (Figure 1). The manufacturing routes to the clinical candidate E7107 involves a 6 step (LLS) semi-synthesis from Pladienolide D[11a] and, according the patent literature, H3B-8800 is prepared in 8 steps (LLS) from synthetic pladienolide D prepared using Kotake's route,[9a] giving a total of 28 steps (LLS).[11b] Finally, the syntheses of pladienolide and FD-895 substructures also have been disclosed.[12] As documented in the review literature,[13] catalytic methods for the direct enantioselective conversion of lower alcohols to higher alcohols developed in our laboratory have the potential to streamline type 1 polyketide total synthesis by circumventing discrete alcohol-to-carbonyl redox reactions and operations associated with the installation and removal of chiral auxiliaries and protecting groups.[14] To enable more concise entry to the pladienolides and related clinical candidates, the total synthesis of pladienolide B, the most potent member of this class, was undertaken. Here, using asymmetric alcohol-mediated carbonyl crotylations catalyzed by ruthenium[15] and iridium[16] that occur with *syn*- and *anti*-diastereoselectivity, we report the total synthesis of pladienolide B in 10 steps (LLS).

Our retrosynthesis of pladienolide B maximizes convergency for optimal step-economy (Scheme 1). Specifically, it was anticipated pladienolide B could be formed via Suzuki cross-coupling of Fragments **A** and **B**, as similar Stille cross-couplings were used to in the total syntheses of pladienolide B reported by Chandrasekhar[9c] and Maier,[9d] and Burkart's synthesis of FD-895.[10a] Also, a related Suzuki coupling was used in the total synthesis of 6-deoxypladienolide D reported by Keaney.[9e] Fragment **A** was envisioned to arise from Fragments **C** and **D** via Yamaguchi esterification[17] followed by Grubbs' ring-closing metathesis, as practiced in all prior total syntheses of the pladienolides and FD-895 with the exception of Maier's synthesis.[9d] Fragment **C** is accessible via dienolate-mediated epoxide ring opening. A related ring-opening of an epoxide lacking the C6 methyl group was used by Ghosh in the total syntheses of pladienolide B.[9b] Fragment **D** is accessible via asymmetric iridium-catalyzed *anti*-crotylation of alcohol **10** using α-methyl allyl acetate **11** as the crotyl donor.[16] Fragment **B** could be obtained from Fragments **E** and **F** through a sequence involving Grubbs' cross-metathesis, Shi epoxidation[19] and Cu-catalyzed alkyne hydroboration. Fragment **E** is accessible via asymmetric ruthenium-catalyzed *syn*-crotylation of *n*-propanol using butadiene as the crotyl donor.[15] Finally, fragment **F** can be

prepared via asymmetric iridium-catalyzed reductive allylation of the acetylenic aldehyde **12** mediated by 2-propanol using allyl acetate as pronucleophile,[18] followed by propargyl substitution with inversion using the Normant reagent.[20] Thus, a total of three C-C bonds are formed via asymmetric alcohol-mediated carbonyl allylation (C16-C17) and crotylation (C20-C21 and C10-C11), the latter with both *syn*- and *anti*-diastereoselectivity.

The synthesis of Fragment **A** begins with the kinetic resolution of the doubly allylic alcohol **1**, which is prepared from methacrolein and the vinyl Grignard reagent,[21] using the Sharpless asymmetric epoxidation (Scheme 2).[22] Exclusive epoxidation of the more substituted alkene was observed, providing glycidol **2** in highly enantiomerically enriched form. The unprotected epoxide was exposed to the dienolate derived from *tert*-butyl acetoacetate followed by acetic anhydride to form the product of epoxide ring opening **3** in 86% yield.[23] Compound exists as a dynamic mixture of hydroxy ketone **3** and, predominantly, the 5-membered lactol. If the free hydroxyl is present at C7 (rather than the acetate), a six-membered lactol is formed that does not participate in the subsequent ketone reduction (not shown). Ruthenium-catalyzed transfer hydrogenation of **3** mediated by formic acid enables access to the β-hydroxy ester **4** as a 4:1 mixture of diastereomers.[24] Acidic cleavage of the *tert*-butyl ester gave the carboxylic acid, which was isolated as a single stereoisomer. Treatment of the hydroxy acid with *tert*-butyldimethylsilyl chloride results in silylation of both the C1 carboxylic acid and C3 hydroxyl groups. Addition of methanolic K_2CO_3 to the reaction mixture results in concomitant cleavage of the silyl ester and the C7 acetate[25] to furnish the C6-C7 diol, Fragment **C**. Under Yamaguchi conditions, Fragment **C** and Fragment **D** undergo esterification to form compound **5** despite the presence of the unprotected C7 hydroxyl.[17,26] The formation of Fragment **D** is accomplished via asymmetric iridium-catalyzed alcohol-mediated carbonyl *anti*-crotylation[16] of the allylic alcohol **10**, which is prepared via zirconium-catalyzed carboalumination of progaryl alcohol (Scheme 3).[27] Finally, ring-closing metathesis of **5** followed by acetylation of the C7 hydroxyl with acidic workup provides Fragment **A**. It is worth noting that although allyl acetates are well-established participants in diverse metathetic processes, attempted metathesis of the C7 allyl acetates **6** and **7** resulted in low conversion accompanied by formation of the unanticipated C-C bond cleavage side-products, methyl ketones **8** and **9**.[28]

With Fragment **A** in hand, the preparation of Fragment **B**, and therefrom, the total synthesis of pladienolide **B** could be achieved (Scheme 4). The formation of Fragment **B** begins with conversion of propargyl alcohol **13** to Fragment **F** via acylation with methyl chloroformate followed by methyl-substitution of the mixed carbonate using the Normant reagent.[20] Propargyl alcohol **13** is prepared via asymmetric iridium-catalyzed reductive coupling of acetylenic aldehyde **12** and allyl acetate mediated by 2-propanol (Scheme 3).[18] Although a slight erosion in enantiomeric enrichment was observed in each step of the conversion of propargyl alcohol **13** to Fragment **F**, the latter could be formed in 91% enantiomeric excess. Cross-metathesis of Fragments **E** and **F** catalyzed by the second-generation Grubbs catalyst was followed by concomitant fluoride-mediated removal of the silyl protecting groups to provide compound **15**, which was isolated as a single stereoisomer. In the cross-metathesis, an excess of Fragment **E** was required to suppress homo-coupling of Fragment **F**. Excess Fragment **E** could be recovered in 46% yield and recycled. The 1,5-acetylenic olefin **14**

readily underwent highly chemo- and diastereoselective Shi epoxidation[19] and alkyne hydroboration[29] to deliver Fragment **B**. Finally, Suzuki cross-coupling under conditions reported by Keaney[9e] provided pladienolide B in a total of 10 steps (LLS), the shortest route to any pladienolide family member reported to date.[30]

In conclusion, by maximizing convergency and exploiting diverse metal-mediated methods for C-C coupling, a concise total synthesis of the spliceosome modulator pladienolide B was achieved. Among the 10 stereogenic centers found in pladienolide B, half are formed using catalytic asymmetric alcohol-mediated carbonyl additions. Specifically, enantioselective alcohol-mediated carbonyl crotylations catalyzed by ruthenium and iridium that occur with *syn*- and *anti*-diastereoselectivity, respectively, were used to forge the C20-C21 and C10-C11 C-C bonds. Additionally, an enantioselective asymmetric iridium-catalyzed reductive coupling of acetylenic aldehyde **12** with allyl acetate mediated by 2-propanol was used to form forge the C16-C17 bond. It is our hope that the present synthetic route will broader access to pladienolide and related clinical candidates for cancer chemotherapy that target the spliceosome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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[30]. While our manuscript was under review, Rhoades et al. reported total syntheses of pladienolide B and H3B-8800 using our method for enantioselective iridium-catalyzed anti-crotylation (DOI: 10.1021/jacs.1c01135). As their aldehyde starting material is not commercially available and requires a 2 step synthesis, their routes to pladienolide B and H3B-8800 are each 10 steps (10 LLS; 25 TS and 10 LLS; 21 TS, respectively), making their longest linear sequence to pladienolide B equivalent in length to own.

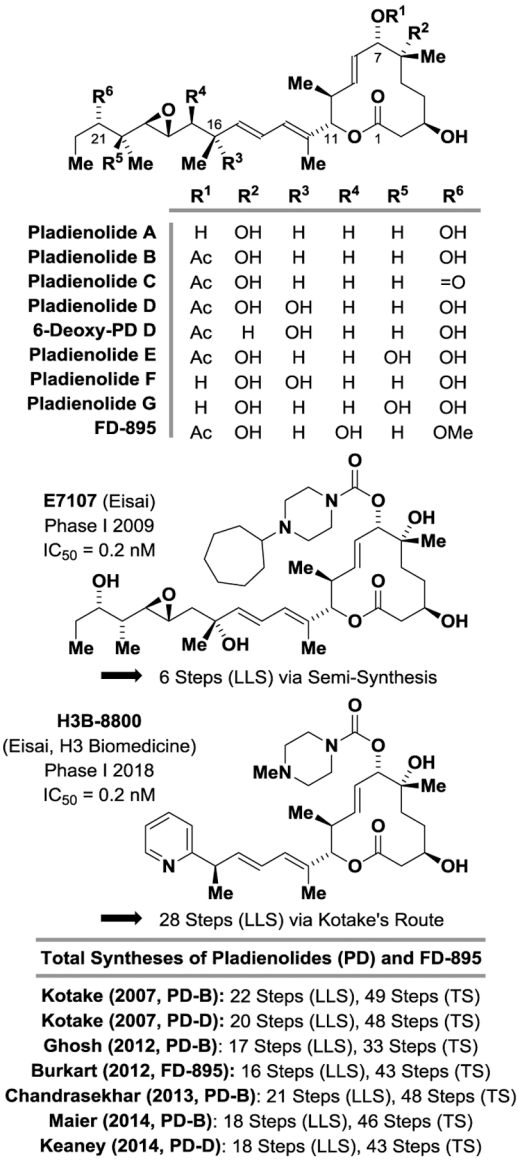
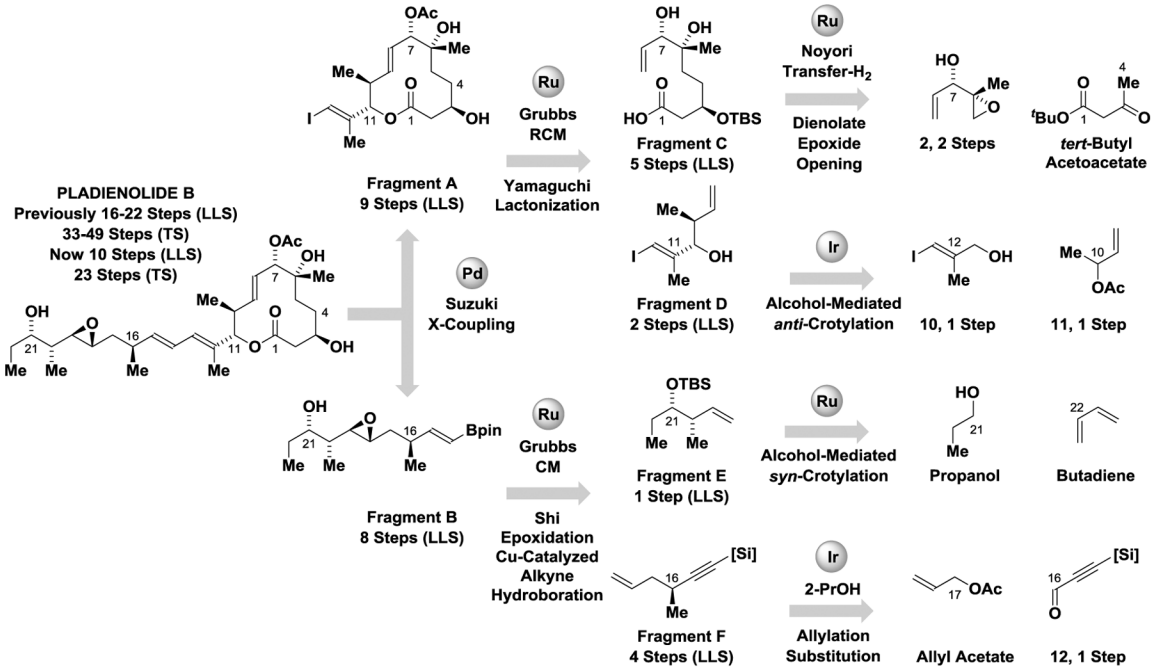


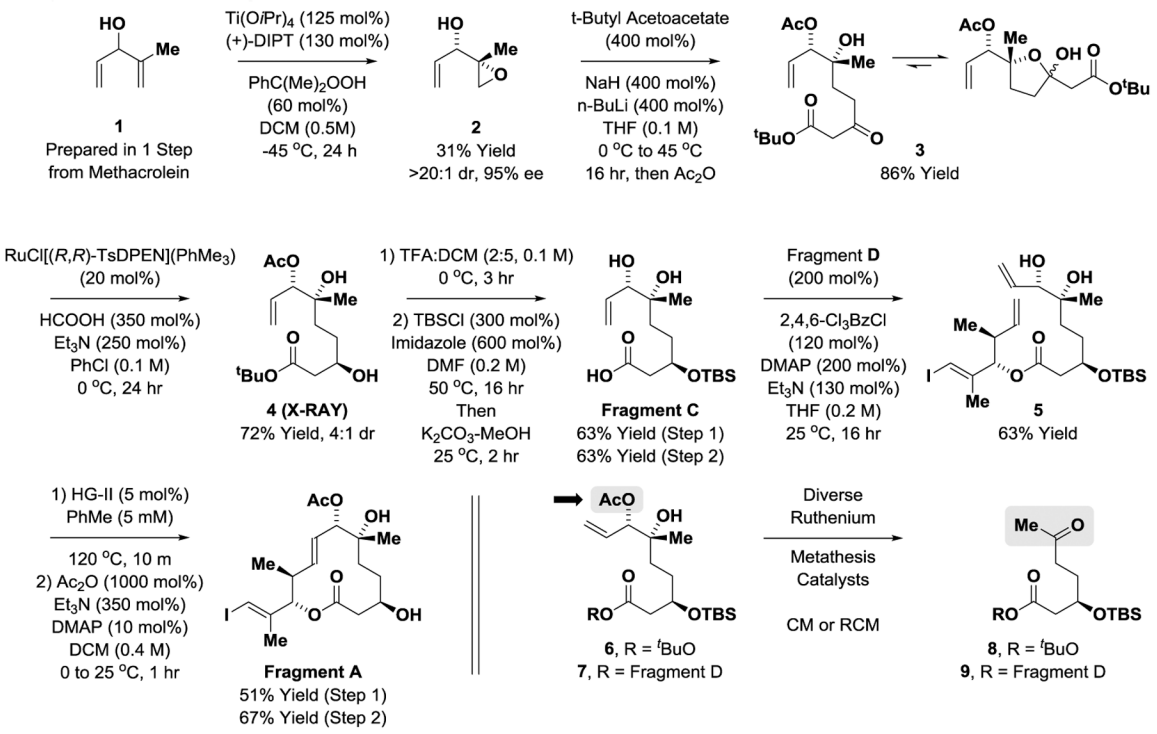
Figure 1.

Pladienolides A-G, FD-895 and related clinical candidates E7107 and H3B-8800. LLS = Longest Linear Sequence. TS = Total Steps.



Scheme 1.

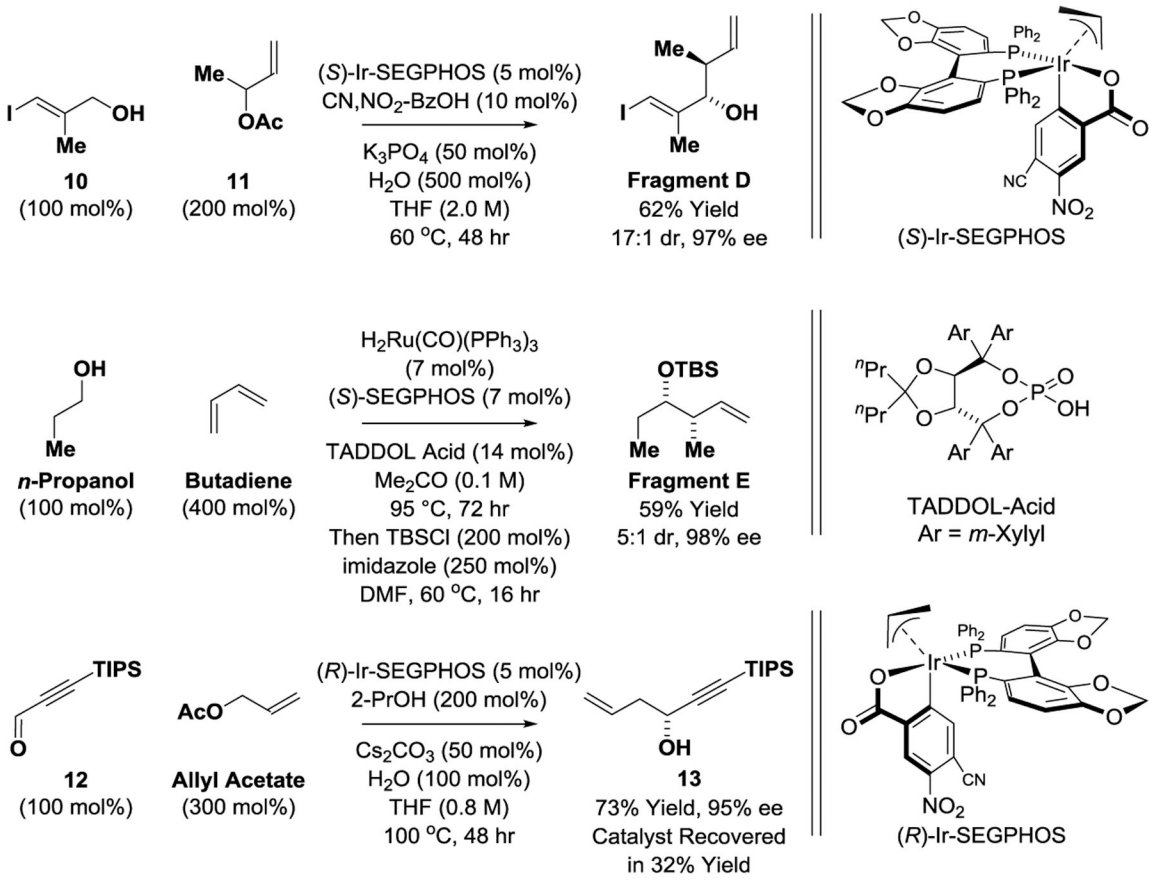
Retrosynthetic analysis of pladienolide b: maximizing convergency for step-economy.



Scheme 2.

Synthesis of Fragment A.[a]

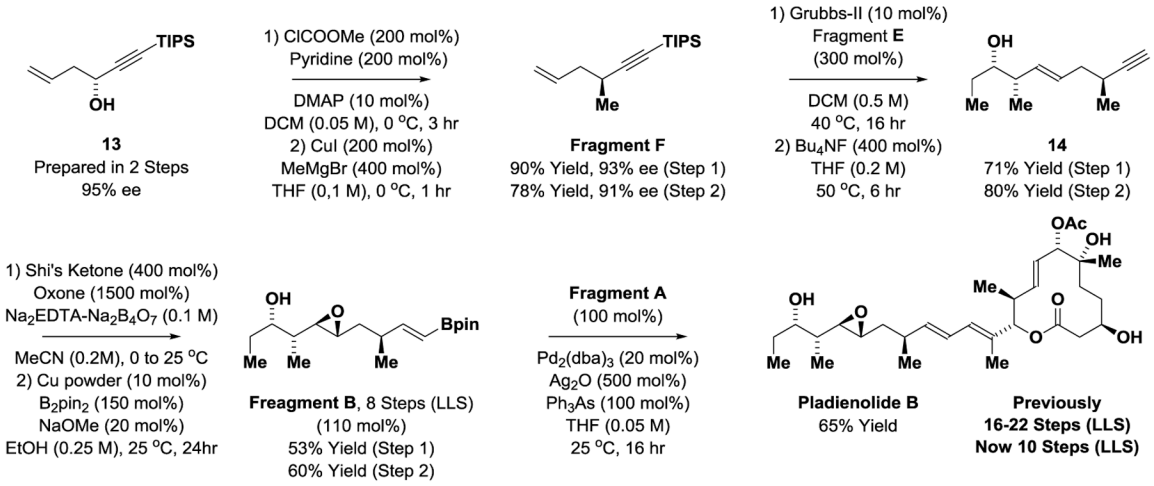
[a]Yields are of material isolated by silica gel chromatography. Enantioselectivities were determined by chiral stationary phase HPLC analysis. See Supporting Information for further experimental details.



Scheme 3.

Catalytic enantioselective *anti*- and *syn*-crotylations of allylic alcohol **10** and propanol to form Fragments **D** and **E**, respectively, and the catalytic enantioselective allylation of acetylenic aldehyde **12** mediated by 2-propanol to form propargyl alcohol **13**.

[a]Yields are of material isolated by silica gel chromatography. Enantioselectivities were determined by chiral stationary phase HPLC analysis. See Supporting Information for further experimental details.



Scheme 4.

Synthesis of Fragment B and total synthesis of pladienolide B.[a]

[a]Yields are of material isolated by silica gel chromatography. Enantioselectivities were determined by chiral stationary phase HPLC analysis. See Supporting Information for further experimental details.