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Total Synthesis of 6-Deoxypladienolide D and Assessment of Splicing Inhibitory Activity in a Mutant SF3B1 Cancer Cell Line

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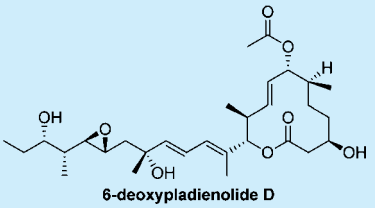
Supporting Information

ABSTRACT: A total synthesis of the natural product 6-deoxypladienolide D (**1**) has been achieved. Two noteworthy attributes of the synthesis are (1) a late-stage allylic oxidation which proceeds with full chemo-, regio-, and diastereoselectivity and (2) the development of a scalable and cost-effective synthetic route to support drug discovery efforts. 6-Deoxypladienolide D (**1**) demonstrates potent growth inhibition in a mutant SF3B1 cancer cell line, high binding affinity to the SF3b complex, and inhibition of pre-mRNA splicing.



The pladienolides, a family of macrocyclic polyketide natural products produced by the *Streptomyces* strain, have demonstrated potent growth inhibition in a variety of cancer cell lines.[1,2] In 2007, it was discovered that pladienolide B binds to SF3b (a subunit of the spliceosome) and inhibits the conversion of pre-mRNA to mRNA.[3] The impressive biological activity and unique mechanism of action of the pladienolides have prompted several total syntheses and analogue efforts.[4]

SF3B1 is a component of the U2 snRNP complex of the spliceosome and is involved in the recognition of splice sites during early spliceosomal assembly.[5] Beginning in 2011, recurrent heterozygous mutations in SF3B1 have been identified in chronic lymphocytic leukemia, myelodysplastic syndrome, chronic myelomonocytic leukemia, uveal melanoma, breast, and pancreatic cancers.[6] We[7] and others[8] have recently disclosed that mutations in SF3B1 have neomorphic activity through the production of aberrantly spliced transcripts. In addition, we have shown that E7107,[9] a semisynthetic derivative of pladienolide D and potent splicing inhibitor, demonstrates apoptosis in mutant SF3B1 cancer cells and tumor regression in mutant SF3B1 xenograft models.[7] These promising results indicate that small molecules which are capable of modulating and/or inhibiting splicing in mutant SF3B1 cancers could have significant therapeutic potential.

Advances in biosynthetic genetic engineering through postpolyketide modification have been utilized to generate new natural products in recent years.[10] The biosynthesis of one of these natural products, 6-deoxypladienolide D (**1**), along with the synthesis of several analogues, has been disclosed previously.[11] These analogues were accessed by direct modification of the natural product, and this semisynthetic approach was limited by the scarce supply of 6-deoxypladienolide D and the lack of synthetic accessibility to most regions of the molecule. For these reasons, coupled with the burgeoning interest to identify chemical matter able to modulate splicing in newly discovered mutant SF3B1 cancers, a total synthesis of 6-deoxypladienolide D using versatile and modular fragments was initiated.

From a retrosynthetic perspective, Suzuki coupling[12] was envisioned to append vinyl pinacol boronate **2** (accessible from olefin **3**[4a]) and macrocyclic vinyl iodide **4** using a disconnection strategy similar to that employed by Maier et al.[4d] and Burkart et al.[4c] in their pladienolide B syntheses (Figure 1). Given the importance of developing a cost-effective synthetic route and factoring the 6-deoxy variant into consideration, (−)-citronellal was viewed as an ideal starting material for the C1−C8 portion of the macrocycle due to its exceptionally low cost and annual production on metric ton scale.[13] While a citronellal-based route was attractive from the standpoint of locking the C6-stereochemistry, our strategy for stereoselective installation of the C7-alcohol was uncertain at the outset. It was envisioned that a substrate-controlled oxidation from the convex face of the macrocycle could conceivably be achieved at a late stage in the synthesis. In turn, the macrocycle core could be assembled through esterification and ring closing metathesis (RCM).[4c,j,14] The homoallylic alcohol **5** could be prepared from diethyl methylmalonate (**6**) via asymmetric crotylation, and carboxylic acid **7** could arise from (−)-citronellal (**8**).

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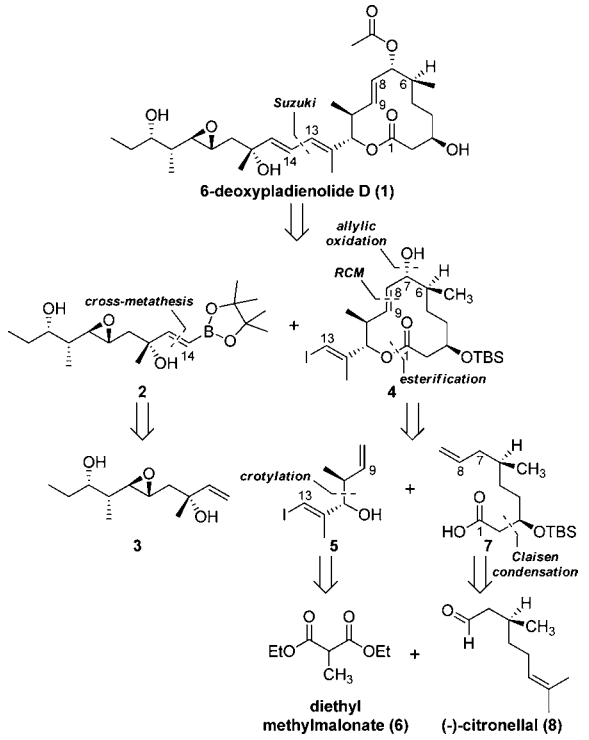


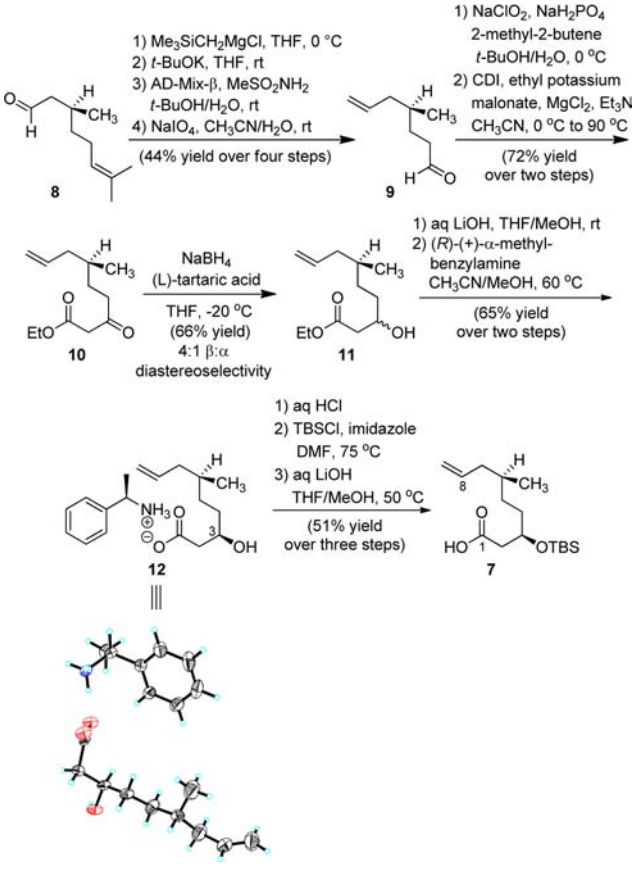
Figure 1. Retrosynthetic analysis of 6-deoxypladienolide D (**1**).

The synthesis of the C1−C8 fragment is described in Scheme 1. (−)-Citronellal (**8**), available from various suppliers for ∼$20/kg, was methylenated using Peterson olefination conditions in 67% yield.[15] Chemoselective dihydroxylation of the monosubstituted olefin followed by oxidative cleavage provided aldehyde **9**. Pinnick oxidation[16] gave rise to the carboxylic acid, which was then activated with 1,1′-carbonyldiimidazole (CDI) in order to undergo a Claisen condensation and decarboxylation to afford ester **10**. Reagent-controlled reduction of the ketone using $NaBH_4$/L-tartaric acid afforded alcohol **11** as a 4:1 ratio of diastereomers favoring the desired β-epimer.[4j] At this stage of the synthesis, a crystalline intermediate was sought to improve diastereopurity. However, due to the lipophilic nature of the intermediates in this sequence, crystallization attempts were unsuccessful. Ultimately, a chiral resolution of the corresponding carboxylic acid in the presence of (*R*)-(+)-α-methylbenzylamine provided crystalline amine salt **12** with >96% diastereopurity. An X-ray crystal structure of **12** was obtained and confirmed the desired C3 stereochemistry. A three-step sequence (acidification, silylation, and regeneration of the free carboxylic acid) afforded carboxylic acid **7**.

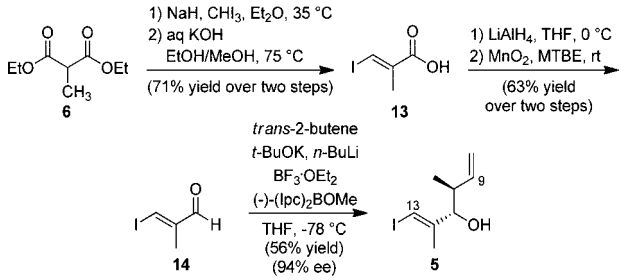
Chiral C9−C13 homoallylic alcohol **5** was prepared as described in Scheme 2. Diethyl methylmalonate (**6**) was alkylated with iodoform, and a base-mediated hydrolysis/decarboxylation/elimination gave carboxylic acid **13** as a single isomer. Carboxylic acid reduction and oxidation of the resulting alcohol provided aldehyde **14**. Installation of the desired crotyl fragment could be accomplished either through an Abiko−Masamune aldol reaction[17] (which required subsequent manipulations) or a direct crotylation (Leighton et al.[18] or Brown et al.[19]). The Brown crotylation was selected for scale-up due to bulk reagent availability, cost, and step count considerations, and it afforded the C9−C13 homoallylic alcohol **5** in 56% yield and 94% ee.

With the C1−C8 and C9−C13 fragments in hand, attention turned to macrocyclization (Scheme 3). EDC-mediated coupling of homoallylic alcohol **5** and carboxylic acid **7** proceeded smoothly. Ring-closing metathesis (RCM) using Hoveyda−Grubbs second-generation catalyst in toluene at 50 °C in the presence of 1,4-benzoquinone[20] provided macrocycle **15**.

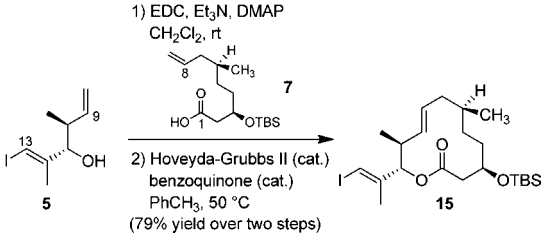
Scheme 1. Synthesis of the C1−C8 Fragment 7



Scheme 2. Synthesis of C9−C13 Fragment 5



Scheme 3. Formation of Macrocycle 15



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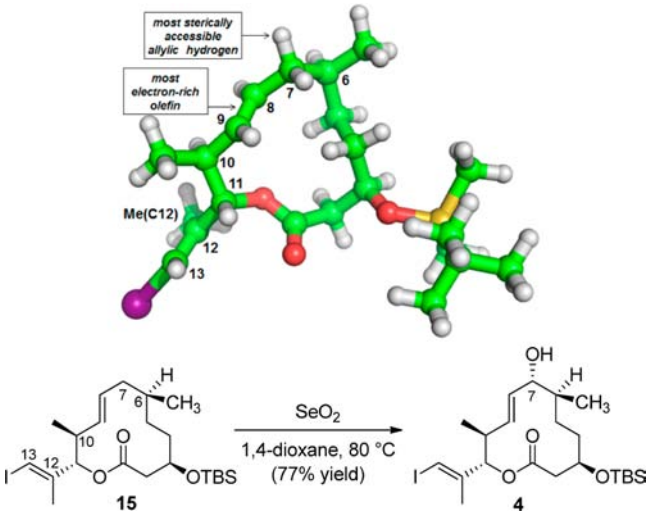
The stage was set for exploring the pivitol C7-alcohol installation. Computational modeling indicated that the conformational rigidity of macrocycle **15**, along with the steric bulk exerted by the adjacent C6-methyl and neighboring C10-methyl substituents, might be able to afford regio- and facial control (Scheme 4). Chemoselectivity was also a consideration

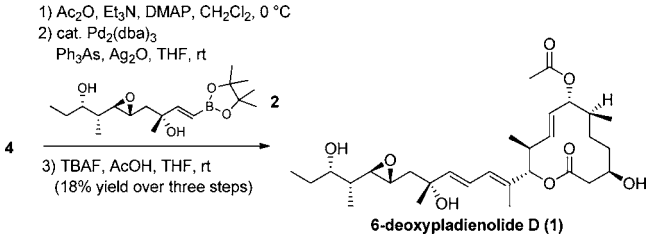
Scheme 4. Computational Modeling and Allylic Oxidation of 15



for this allylic oxidation due to the presence of the C12−C13 olefin, but modeling also suggested that the C13-iodine substituent might serve to diminish its reactivity.[21] Gratifyingly, exposure of **15** to selenium dioxide provided the desired alcohol **4** in 77% yield with complete chemoselectivity, regioselectivity, and diastereoselectivity.[22−24]

Alcohol **4** was acetylated with acetic anhydride in 87% yield (Scheme 5). Vinyl pinacol boronate **2** was accessed in a single

Scheme 5. Synthesis of 6-Deoxypladienolide D (1)



step from known olefin **3**[4a] (see the Supporting Information). Room-temperature Suzuki conditions were employed to append the sensitive epoxide-containing fragment **2** to the macrocycle, and TBAF desilylation afforded the natural product 6-deoxypladienolide D (**1**). ^{1}H NMR and LCMS data matched the values previously reported for the biosynthesized natural product, and additional spectroscopic analysis (^{13}C NMR, COSY, and HRMS) further corroborated its structure.[11]

6-Deoxypladienolide D (**1**) was tested in a cell viability assay with Panc 05.04 cells, a mutant SF3B1$^{Q699H/K700E}$ pancreatic cancer cell line, and it demonstrated single-digit nanomolar growth inhibitory activity and significant cellular lethality (E_{max}) (Table 1).[7] The on-mechanism activity of **1** was assessed with a suite of additional biochemical and cellular splicing assays. 6-Deoxypladienolide D (**1**) exhibited potent binding affinity to the

Table 1. Biological Data of 1 in Mutant SF3B1 Assays

Panc 05.04 SF3B1$^{Q699H/K700E}$	GI_{50} (nM)	8.1 ± 3.2
cell viability assay	E_{max} (%)	−69.5 ± 11.2
binding assay SF3B1^{K700E}	IC_{50} (nM)	4.0 ± 1.3
in vitro splicing assay SF3B1^{K700E}	IC_{50} (nM)	910 ± 30
cell PD assay SF3B1^{K700E} COASY^{MUT} mRNA	IC_{50} (nM)	3.8 ± 2.4

SF3b complex (SF3B1^{K700E}) and the ability to inhibit conversion of pre-mRNA to mRNA in a functional assay. Furthermore, it was shown that **1** inhibited the production of an aberrantly spliced transcript (COASY^{MUT}) which had been previously observed in Panc 05.04 cells.[7]

In summary, the first total synthesis of 6-deoxypladienolide D (**1**) has been accomplished. This convergent synthetic route has been designed to use inexpensive commercially available starting materials and reagents to facilitate scalability and support analog efforts. This total synthesis exhibits a late-stage, substrate-controlled allylic oxidation which installs the requisite C7 alcohol. In addition, biochemical and cellular assays demonstrate that 6-deoxypladienolide D (**1**) is a potent splicing inhibitor which causes cellular lethality in a mutant SF3B1 cancer cell line.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, spectral data, computational modeling, X-ray crystallographic analysis, and biological assay protocols have been provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(21) Atomic charges for the C8−C9 olefin (average = −0.1776) and C12−C13 olefin (average = −0.1171) from Mulliken population analysis indicate that the C12−C13 olefin is more electron-deficient due to its less negative value.

(22) The only side product was the C7-ketone (∼10% yield), and it was readily removed by column chromatography.

(23) Alternatively, this allylic oxidation can be performed using *catalytic* selenium dioxide (0.2 equiv) with 2-iodoxybenzoic acid (IBX) (1.5 equiv) as stoichiometric oxidant in 1,4-dioxane at 80 °C in 41% yield (66% BORSM).

(24) Allylic oxidation was also attempted on noniodine-containing substrates in which the C14 methine was present. However, on these substrates, a significant amount of undesired oxidation at the C12-vinyl methyl substituent was observed. This observation further highlights the essential steric and/or electronic contribution of the iodine atom in this reaction.