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Catalytic Asymmetric Synthesis of Palmerolide A via Organoboron Methodology

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Numerous natural products and their synthetic derivatives are used as pharmaceutical drugs.[1] Ongoing efforts to identify new substances with extraordinary properties have recently uncovered palmerolide A (**1**), a complex polyunsaturated macrolide isolated by Baker and coworkers from a marine invertebrate (*Synoicum adareanum*) found in the Antarctic Ocean.[2] Palmerolide A embeds five stereogenic centers and seven unsaturations, including a dienamide. It demonstrates a very potent and unusually selective antitumor activity when assayed with melanoma cell lines, and its potency is ascribed to a low-nanomolar inhibition of vacuolar ATPase.[2] The need for treatment of metastatic melanoma is dire, as few cancers are as aggressive and current chemotherapies are rarely effective.[3] Because the ecosystem from which palmerolide A originates is remote and fragile, the development of efficient synthetic routes could ensure its supply or lead to improved analogues. Groups led by De Brabander[4] and Nicolaou and Chen[5] revised the stereochemistry of palmerolide A and achieved total syntheses of its correct structure. Approaches to various fragments were also reported.[6] Taking those reports into account, we envisioned a distinct retrosynthesis of **1** that would exploit catalytic asymmetric organoboron methodologies developed in our group for C−C bond formation and control of the four secondary carbinols.

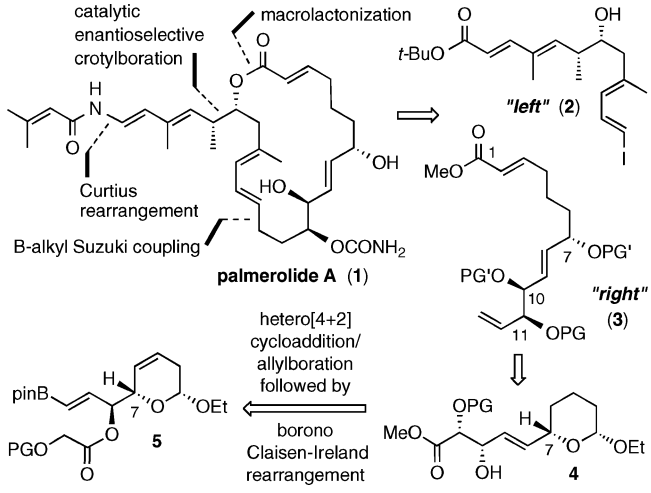
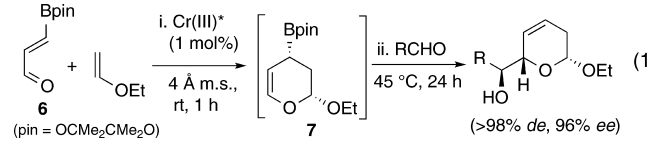


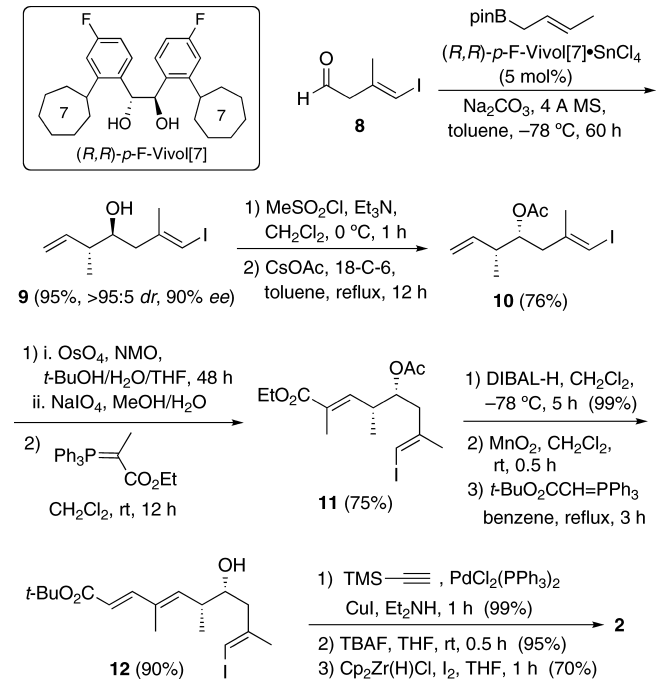
Figure 1. Structure of (−)-palmerolide A (**1**) and proposed retrosynthesis.

The projected retrosynthesis of Figure 1 foresaw a macrolactonization preceded by a convergent assembly of two fragments, **2** and **3**, via an sp^2−sp^3 B−alkyl Suzuki coupling. The left fragment **2** contains a syn propionate unit that could be accessed using our chiral Brønsted acid-catalyzed enantioselective crotylboration methodology.[7] It was thought that the right, 13-carbon fragment **3** could be derived from pyran **4**, which would originate from an unprecedented Claisen−Ireland [3,3] rearrangement on an alkenylboronate substrate, **5**.[8] This strategy would exploit the boronate substituent as a masked alcohol and provide the requisite differentiation of the C11 secondary alcohol over those of C10 and C7. Precursor **5** would come from our enantioselective hetero[4 + 2] cycloaddition/allylboration reaction[9] catalyzed by Jacobsen's chiral chromium complex (eq 1),[10] with 3-boronoacrolein pinacolate (**6**) serving the dual functions of heterodiene and substrate for allylboration with intermediate cycloadduct **7**:



The construction of fragment **2** required as a precursor the sensitive β,γ-unsaturated aldehyde **8** (Scheme 1).[4,5] Enantioselective *E*-crotylboration[7] of freshly distilled **8** catalyzed by *p*-F-Vivol[7]•$SnCl_4$ produced the anti propionate **9** in a remarkable yield of 95% with 90% ee.[11] Inversion of configuration with concomitant protection of the secondary alcohol gave **10**. This step was followed by oxidative cleavage of the terminal alkene and Wittig olefination; the resulting unsaturated ester **11** was further extended to give dienoate **12**. In turn, the alkenyl iodide unit of **12** was extended into iodobutadiene **2** in a high-yielding three-step sequence based on a Sonogashira coupling and alkyne hydrozirconation.

Scheme 1

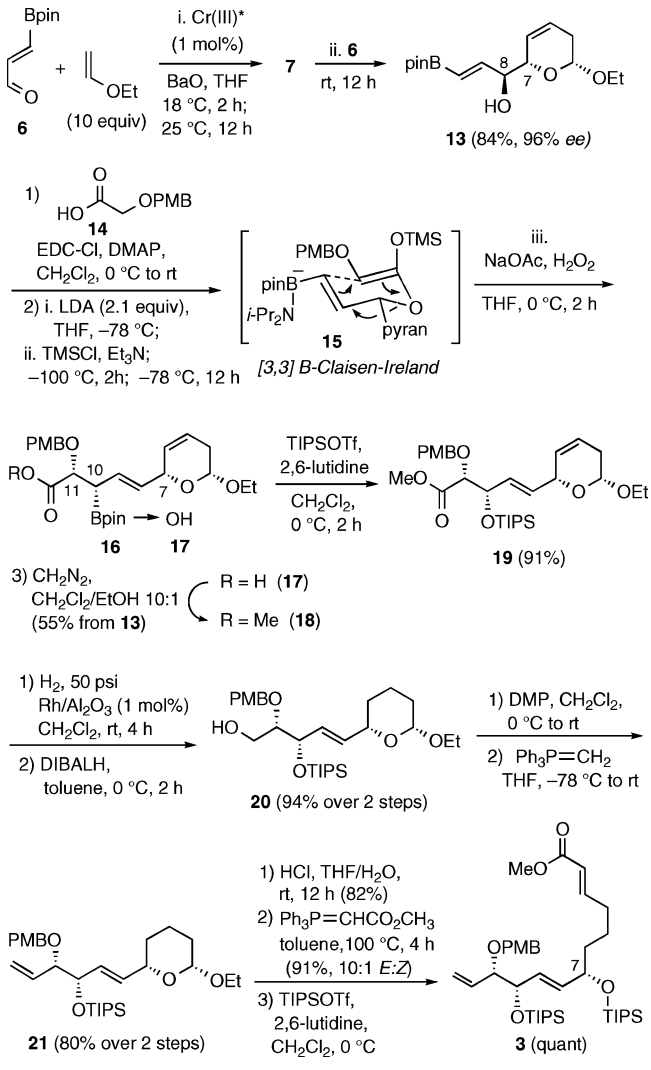


The synthesis of fragment **3** began with the preparation of pyranyl alkenylboronate **13** via a catalytic enantioselective hetero[4 + 2] cycloaddition/allylboration involving 2 mol of **6** and ethyl vinyl ether (Scheme 2).[9] Acylation of the alcohol with **14** afforded the requisite precursor for the key Claisen−Ireland rearrangement.[8] Subsequent formation of enolsilane **15** required 2 equiv of base (the first equivalent most likely being trapped by the Lewis acidic boronate), and warming the mixture triggered the desired rearrangement to give **16**. As depicted

10.1021/ja906429c CCC: $40.75

in the chairlike transition structure (**15**), the diastereoselectivity was controlled by the configuration of C8. Without delay, the alkylboronate group of crude product **16** was oxidized with retention of stereochemistry to give **17**, and the carboxylic acid was esterified by treatment with diazomethane to produce **18** as a single stereoisomer with a good overall yield of 55% over five stages.[12] From **18**, an efficient sequence led to terminal alkene **21**. Finally, hydrolysis of the acetal and a Wittig olefination of the resulting hydroxyaldehyde gave fragment **3** after silylation of the C7 hydroxyl.

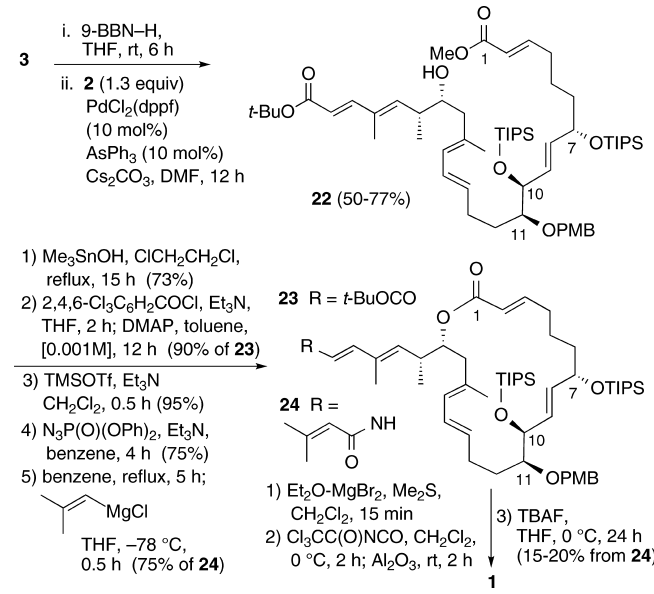
Scheme 2



The key B−alkyl Suzuki coupling of fragments **2** and **3** was successful, giving **22** in 50−77% unoptimized yield (Scheme 3). Selective hydrolysis of the methyl ester set the stage for the Yamaguchi macrolactonization, which occurred uneventfully to produce **23** in 90% yield. Transformation of the dienoate of **23** into dienamide **24** through a Curtius rearrangement followed the approach of De Brabander and co-workers.[4] The synthesis of **1** was then completed via nucleophilic cleavage of the PMB ether, carbamate formation, and simultaneous deprotection of the C7 and C10 hydroxyls. Although these final operations were not yet optimized, a sufficient amount of purified sample was obtained to confirm the authenticity of synthetic **1**.[13]

This total synthesis of (−)-palmerolide A was accomplished from **6** in a longest sequence of 21 steps (0.8% overall yield) without resorting to stoichiometric chiral auxiliaries or the chiral pool. The right half was constructed with a new variant of the Claisen−Ireland rearrangement exploiting an alkenylboronate as a masked hydroxyl, which provided the requisite differentiation of two secondary carbinols.

Scheme 3



The left half featured the first application of a Vivol·$SnCl_4$-catalyzed enantioselective crotylboration in the context of a complex target. This distinct strategy centered on organoboron methodology could pave the way to the design of simplified analogues of palmerolide.

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Supporting Information Available: Full experimental details and reproductions of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The reported[7c] *p*-F-Vivol[8]·$SnCl_4$ catalyst gave 95% yield and 84% ee.
(12) The relative stereochemistry of **18** was determined by X-ray crystallographic analysis of the C10 *p*-nitrobenzoate (CCDC 742294).
(13) See details and comparison of spectral data in the Supporting Information.

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