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Synthesis of C1-C15 of palmerolide A: tactical advances that can lead to better design strategies for polyketide synthesis

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ABSTRACT

A streamlined synthesis of a C1-C15 fragment of palmerolide A is described. Key tactical advances (vis-à-vis previous reports from the Dudley laboratory) include diastereoselective reduction (>20:1 dr) of a C7 ketone using DIP chloride and a modified protecting group strategy that enables both improved step count and end-game efficiency. Asymmetric reduction of linear alkyl vinyl ketone derivatives is a largely unsolved problem in organic synthesis. DIP chloride has been uniquely effective for asymmetric reduction of the alkyl vinyl ketone derivatives in the present study.

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1. Introduction

Palmerolide A (**1**) is a macrolide natural product isolated from a protected species of Antarctic tunicate, *Synicum adareanum*.¹ It is selectively cytotoxic to melanoma cells, perhaps by virtue of its ability to inhibit V-ATPase.² Previous work on the synthesis of palmerolide A was reviewed in 2013;³ a strategic paradigm of fragment assembly was identified as common to the previous syntheses of and synthetic approaches to palmerolide A. More recent work⁴ also fits within this established paradigm.

Among the unresolved tactical challenges associated with the synthesis of palmerolide A are the stereocontrolled reduction of C7 ketones and key late-stage protecting group manipulations.³ In our formal synthesis of palmerolide A, we settled for non-selective reduction of a C7 ketone with NaBH₄, followed by chromatographic separation of the resulting diastereomers and Mitsunobu inversion of the undesired stereoisomer.⁵ As we stated in summary of our formal synthesis, “*Diastereoselective C7 ketone reduction is perhaps the most overt challenge that remains to be addressed, and refinement of the protecting group strategy is also in order: late-stage cleavage of the PMB and TIPS ethers are reportedly inefficient (16% combined). Improvements in these two areas would impact the quantitative metrics (e.g., step-count and overall yield) associated with the efficiency of this route.*”⁵ Here we report solutions to both of these challenges in the context of an optimized synthesis of a known⁶ C1-C15 fragment of palmerolide A from which the natural product can formally be produced.

Scheme 1. Summary of previously reported C1-C15 fragment synthesis, from ref. 5. C7 Ketone reduction was nonselective, and the chosen protecting groups (R¹ and R²) cannot be cleaved efficiently in the latter stages of the synthesis.

Our previous synthesis⁵ of a C1-C15 fragment is summarized in Scheme 1. Aldehyde **4** (10 steps from 4-pentynol) and β-keto phosphonate **3** (4 steps, leveraging alkynogenic fragmentation methodology from our laboratories⁷) were merged using Ba(OH)₂ in a Horner–Wadsworth–Emmons (HWE) olefination reaction. Enone **5a** was then processed into a suitable C1-C15 fragment.

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Scheme 2. Streamlined synthesis of enone **5b**.

A streamlined synthesis of enone **5b** is presented in Scheme 2. The two-step process of oxidation of 4-pentynol and olefination to generate enoate **6** was telescoped into a one-pot procedure, followed by Sharpless asymmetric dihydroxylation and Lindlar alkyne semi-hydrogenation to produce ester diol **8**. Diol **8** can be protected regioselectively by treatment with TBS triflate and 2,6-lutidine,⁸ followed by MOM chloride. The TBS and MOM protecting groups are easier to cleave than the PMB and TIPS groups we previously employed (cf. **5a**, Scheme 1). The MOM group additionally facilitates partial reduction of ester **10** to aldehyde **11** (Scheme 2), which we attribute to a stabilizing chelate interaction in the tetrahedral intermediate. In the event, crude aldehyde **11** was isolated but not purified before HWE coupling⁹ with β -keto phosphonate **3** to provide enone **5b**.

Table 1. Screening of conditions for the diastereoselective reduction of enones **5** (**5a** and **5b**).

5a ($R^1=\text{TIPS}$, $R^2=\text{PMB}$)
5b ($R^1=\text{MOM}$, $R^2=\text{TBS}$)

12a ($R^1=\text{TIPS}$, $R^2=\text{PMB}$)
12b ($R^1=\text{MOM}$, $R^2=\text{TBS}$)

Entry	Reducing agent	Conditions	12	Yield ^a	dr ^b
1 ^c	NaBH ₄	MeOH, rt	12a	95%	1:1
2	(<i>R</i>)-CBS	THF, −40 °C	12a	90%	1:1
3	NaBH ₄	MeOH, rt	12b	95%	1:1
4	(−)-BINAL (3 equiv)	THF −90→−78 °C	12b	70%	3:1
5	(+)-DIP-Cl (2 equiv)	THF −78 °C→rt	12b	70%	1:10
6	(−)-DIP-Cl (2 equiv)	THF −78 °C→rt	12b	70%	10:1
7	(−)-DIP-Cl (6 equiv)	THF −78→−40 °C	12b	80%	>20:1

^aIsolated yield. ^bDiastereomeric ratio (dr) determined by Mosher ester analysis; see Supplementary materials. ^cSee ref 5.

Efforts to achieve a stereoselective C7 ketone reduction are highlighted in Table 1. We previously observed effectively no selectivity in the reductions of enone **5a** with either NaBH₄ or (*R*)-CBS (entries 1 and 2). Reduction of enone **5b** with NaBH₄ was similarly non-selective (entry 3), whereas (-)-BINAL¹⁰ gave modest diastereoselectivity (entry 4). Best results were obtained using diisopinocampheyl chloroborane (DIP-Cl)¹¹. Reduction of enone **5b** with (+)-DIP-Cl produced the undesired diastereomer (not shown) of **12b** as the major product (entry 5), whereas reduction with (-)-DIP-Cl produced predominantly the desired diastereomer (**12b**, entry 6). The yield and diastereoselectivity were improved by lowering the temperature and increasing the stoichiometry of (-)-DIP-Cl, optimally producing **12b** in 80% yield and >20:1 dr as determined by Mosher analysis.^{12,13}

Finally, newly formed C7 alcohol **12b** was protected as its MOM ether (**2b**, Eq 1), which is a known precursor to synthetic palmerolide A.⁶ This 8-step synthesis of **2b** saves ≥ 5 linear steps compared to the previous syntheses of **2a**⁵ and **2b**,⁶ respectively. More importantly, it addresses two significant tactical weaknesses of our previous formal synthesis of palmerolide A:⁵ non-stereoselective C7 ketone reduction and inefficient protecting group manipulations. Efforts to complete a more efficient and scalable synthesis of palmerolide A and analogues are in progress and will be reported in due course.

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 13. See Supplementary material for details.
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