Toward a New Palmerolide Assembly Strategy: Synthesis of C16–C24

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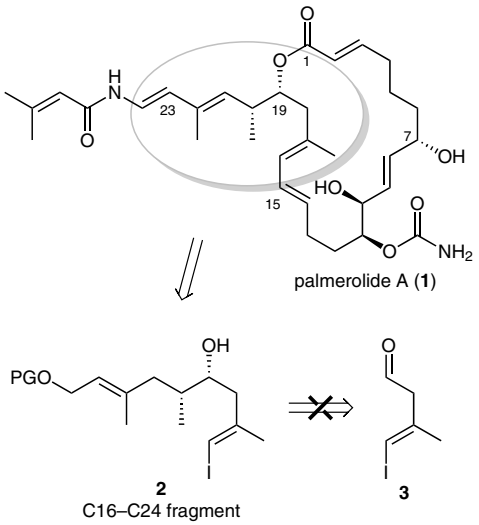
Received: 16.02.2012; Accepted after revision: 02.04.2012

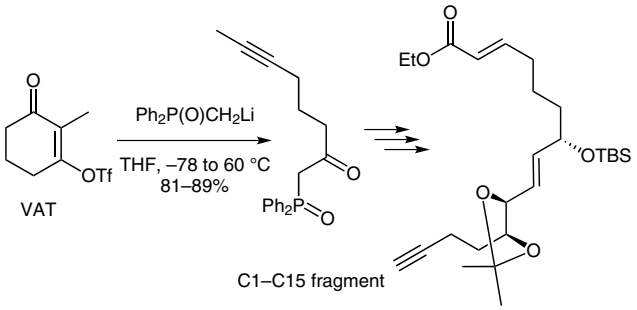
Abstract: Asymmetric synthesis of C16–C24 of palmerolide A is described, featuring convergent Negishi coupling, Singaram propargylation, and successful tactical maneuvering to address an unexpected allylic substitution reaction.

Key words: palmerolide, stereoselective synthesis, coupling, natural products, asymmetric catalysis

Palmerolide A (**1**, Scheme 1) has received considerable attention from the synthetic chemistry community,[2–4] owing to its trifecta of exciting biological activity, complex chemical structure, and limited natural supply.[5] The title compound[6] and several congeneric structures[7] were isolated from *Synoicum adareanum*, a tunicate species unique to the Antarctic marine environment. Palmerolide A is selectively cytotoxic to melanoma cells (e.g., UACC-62, LC_{50} 18 nM), and it is a potent inhibitor of vacuolar ATPase (IC_{50} 2 nM). While it may be tempting to connect these data points to suggest a mechanism of action, cytotoxicity data and inhibitory activity do not correlate well across the palmerolide family.[7] Thus, more research is needed to establish the therapeutic potential of the palmerolides as drug development leads for melanoma.[8,9]



Scheme 1 Palmerolide A (**1**), with emphasis on the C16–C24 region, and the targeted fragment **2**



Scheme 2 Previously reported synthesis of the C1–C15 subunit

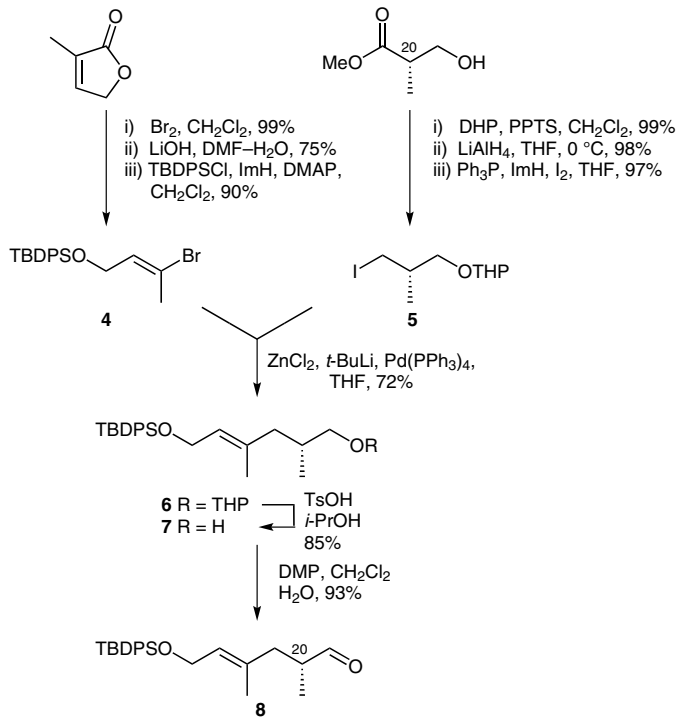
Our interest in the synthesis of palmerolide A grew out of ongoing methodology for the tandem addition–fragmentation of vinylogous acyl triflates (VAT).[10] Specifically, VAT fragmentation to produce alkyne-tethered β-keto phosphonates[10g] and phosphine oxides enables a concise approach to the C1–C15 subunit (Scheme 2).[4f] In the interest of making further contributions to the efficient chemical synthesis of the palmerolides, we report a convergent synthesis of the C16–C24 subunit. Our strategy is unique in that all previous syntheses involve side-chain fragments that either extend one carbon past or end one carbon shy of C24.[2–4] We also purposefully avoid the use of the potentially labile β,γ-unsaturated aldehyde **3** (Scheme 1), which figures prominently in all but one[3d] of the previous synthetic approaches to palmerolide A.

The first key step in the synthesis of the C16–C24 subunit is a Negishi coupling[11] between vinyl bromide **4**[12] and alkyl iodide **5**[13] (Scheme 3), which we prepared by analogy to reported procedures. Negishi coupling (→ **6**), THP hydrolysis (→ **7**), and oxidation of alcohol **7** provided aldehyde **8** in 57% overall yield.

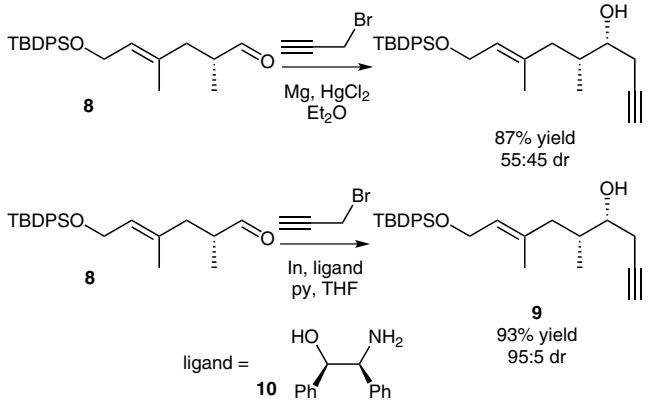
The next synthetic challenge was to set the C19–C20 *syn* stereochemistry. Based on the Felkin–Anh model, nucleophilic addition to chiral aldehyde **8** should favor the desired *syn* diastereomer.[14] However, steric differentiation between methyl and methylene is minimal, and substrate-controlled propargylation gave very poor diastereoselectivity (Scheme 4).

We thus focused our attention on reagent- or catalyst-controlled asymmetric propargylation of aldehydes. Singaram's propargylation[15] emerged as our preferred choice (Scheme 4) for its operational simplicity. Treatment of a THF solution of aldehyde **8** with propargyl bromide, indi-

SYNLETT 2012, 23, 1493–1496
Advanced online publication: 29.05.2012
DOI: 10.1055/s-0031-1290675; Art ID: ST-2012-S0145-L



Scheme 3 Convergent Negishi coupling for the preparation of aldehyde **8**

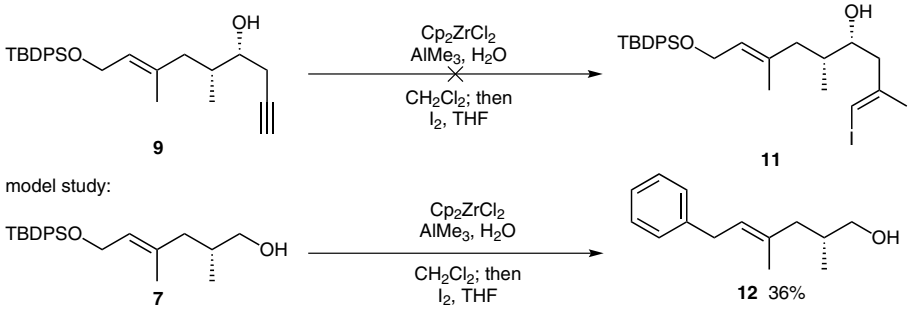


Scheme 4 Chiral aldehyde **8** showed minimal bias in the addition of propargyl Grignard (top), but catalyst control using Singaram's method efficiently provided alcohol **9** (bottom)

um metal, and pyridine in the presence of (commercially available) amino alcohol **10** provided homopropargyl alcohol **9** in 93% yield (95:5 dr). Chiral ligand **10** was recovered in 94% yield and reused with identical results.

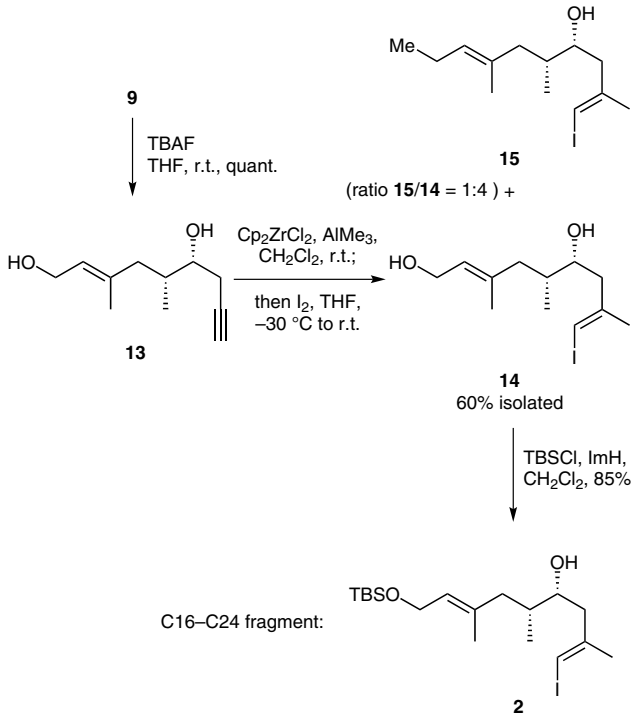
Negishi–Wipf[16] carbometalation–iodination (**9** → **11**) was supposed to conclude the synthesis of the C16–C24 subunit (Scheme 5), but unexpected complications arose. Standard conditions converted alkyne **9** into a complex mixture of products, one of which appeared to be the result of allylic substitution in which the TBDPS ether was replaced with a phenyl group. We repeated this experiment using alcohol **7**, which lacks the alkyne moiety, and proceeded to isolate allylbenzene **12** in 36% yield. Further details and observations fall outside the current focus, but the phenyl group presumably comes from the TBDPS ether. Others have noted that silyl ethers can be problematic in this reaction,[17] but we found no prior examples of this unusual allylic substitution.

After trying unsuccessfully to achieve the desired conversion by optimizing the experimental conditions, we changed the substrate (Scheme 6). We removed the



Scheme 5 Unexpected carbometalation difficulties (top), and an unusual substitution reaction under identical conditions (bottom)

TBDPS ether, subjected diol **13** to carbometalation (optimally without adding water[16a]), and thus obtained iodides **14** and **15** in a 4:1 ratio. The minor product (**15**, from OH → Me substitution, cf. Scheme 5) was easily separated from diol **14** using silica gel, and **14** was thus isolated in 60% yield. Selective protection of **14** gave TBS ether **2** in 85% yield,[18] completing the synthesis of our target C16–C24 subunit.



Scheme 6 Synthesis of target C16–C24 fragment

A C16–C24 fragment of palmerolide A has been prepared in seven steps (27% overall yield) from known compounds **4** and **5**, each of which was prepared in three steps. Highlights of this work include the convergent Negishi coupling and application of Singaram's indium-mediated propargylation reaction to set the C19–C20 *syn* stereochemistry. With efficient access to C1–C15 and C16–C24 fragments, what remains is fragment assembly and oxidative installation of the enamide moiety toward completion of the synthesis of palmerolide A. Efforts to this end are under way and will be reported in due course.

Acknowledgment

This research was supported by a grant from the National Science Foundation (NSF-CHE 0749918) and by the Florida State University Research Foundation. M.L. is a recipient of the CAPES-Fulbright Graduate Research Fellowship.

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Primary Data for this article are available online at http://www.thieme-connect.com/ejournals/toc/synlett and can be cited using the following DOI: 10.4125/pd0029th.

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(18) **Procedure and Data for C16–C24 Fragment 2**
To a solution of vinyl iodide **14** (20 mg, 0.062 mmol) in CH_2Cl_2 (3 mL) was added imidazole (8 mg, 0.12 mmol) and TBSCl (11 mg, 0.074 mmol) at r.t. The reaction mixture was stirred overnight and quenched with NH_4Cl. The solution was extracted with CH_2Cl_2 (3×) and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc–hexanes = 5:95) to yield vinyl iodide **2** as a colorless oil (23 mg, 85%). $[\alpha]_D^{25}$ 15.9 (*c* 5.32, CH_2Cl_2). IR (thin film): 3467 (br), 2954, 2928, 2856, 1462, 1379, 1252, 1050, 832, 773, 666 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.00 (d, *J* = 7.3 Hz, 1 H), 5.32–5.36 (m, 1 H), 4.19 (d, *J* = 6.2 Hz, 2 H), 3.62–3.68 (m, 1 H), 2.28–2.40 (m, 2 H), 2.12–2.20 (m, 1 H), 1.86 (d, *J* = 0.9 Hz, 3 H), 1.68–1.78 (m, 2 H), 1.60 (s, 3 H), 1.47 (d, *J* = 4.1 Hz, 2 H), 0.89 (s, 9 H), 0.84 (d, *J* = 6.8 Hz, 3 H), 0.06 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.3, 135.1, 126.6, 71.3, 60.1, 44.7, 43.5, 35.5, 25.9, 24.0, 18.4, 16.1, 13.3, –5.1. ESI-HRMS: *m/z* calcd for $C_{18}H_{35}O_2ISiNa$ $[M + Na^+]$: 461.1348; found: 461.1343.

