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Formal Synthesis of Palmerolide A, Featuring Alkynogenic Fragmentation and *syn*-Selective Vinylogous Aldol Chemistry

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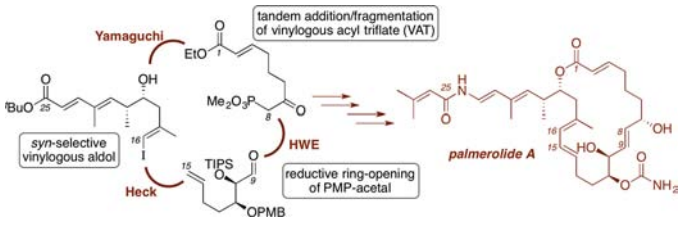
ABSTRACT



An enantioselective route to palmerolide A is described. The approach features original syntheses of three subunits, which are then assembled to produce a known late-stage intermediate and formally provide the highest overall yield of the natural product reported to date. Recent innovations in alkynogenic fragmentation and vinylogous aldol methodology figure prominently in the synthesis of the C1−C15 and C16−C25 subunits, respectively.

Macrolides from the palmerolide[1] family of Antarctic marine natural products are important targets for chemical synthesis. Preliminary cytotoxicity assays indicate that these compounds may be valuable for melanoma research,[2] and chemical synthesis is likely the best option for producing a reliable supply of palmerolide A and congeners.[3] Pioneering efforts from groups led by De Brabander[4] and Nicolaou/Chen[5] resulted in the total synthesis, structural reassignment, and several synthetic analogs[6] of palmerolide A. Hall and co-workers elegantly leveraged organoboron chemistry to achieve a third total synthesis,[7] and the Maier,[8] Kaliappan,[9] and Prasad[10] laboratories have each formally completed synthetic routes to palmerolide A. Several groups,[11] including

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(1) (a) Diyabalanage, T.; Amsler, C. D.; McClintock, J. B.; Baker, B. J. *J. Am. Chem. Soc.* **2006**, *128*, 5630–5631. (b) Lebar, M. D.; Baker, B. J. *Tetrahedron Lett.* **2007**, *48*, 8009–8010. (c) Riesenfeld, C. S.; Murray, A. E.; Baker, B. J. *J. Nat. Prod.* **2008**, *71*, 1812–1818. (d) Noguez, J. H.; Diyabalanage, T.; Miyata, Y.; Xie, X.-S.; Valeriote, F. A.; Amsler, C. D.; McClintock, J. B.; Baker, B. J. *Bioorg. Med. Chem.* **2011**, *19*, 6608–6614.

(2) The LC_{50} of palmerolide A against UACC-62 (melanoma) cells is 18 nM. Nanomolar activity was reported for other palmerolides and against other melanoma cell lines in the NCI's 60-cell line panel, whereas activity against nonmelanoma cell lines did not drop below micromolar levels. See ref 1.

(3) Geographical barriers and geopolitical restrictions make the natural source effectively inaccessible. The Antarctic Treaty (http://www.ats.aq) prohibits exploitation of Antarctic resources, which would include harvesting of the Antarctic tunicate *Synoicum adareanum* to secure large quantities of palmerolide A.

(4) Jiang, X.; Liu, B.; Lebreton, S.; De Brabander, J. K. *J. Am. Chem. Soc.* **2007**, *129*, 6386–6387.

(5) Nicolaou, K. C.; Guduru, R.; Sun, Y.-P.; Banerji, B.; Chen, D. Y.-K. *Angew. Chem., Int. Ed.* **2007**, *46*, 5896–5900.

(6) (a) Nicolaou, K. C.; Sun, Y.-P.; Guduru, R.; Banerji, B.; Chen, D. Y.-K. *J. Am. Chem. Soc.* **2008**, *130*, 3633–3644. (b) Nicolaou, K. C.; Leung, G. Y. C.; Dethe, D. H.; Guduru, R.; Sun, Y.-P.; Lim, C. S.; Chen, D. Y.-K. *J. Am. Chem. Soc.* **2008**, *130*, 10019–10023. (c) Ravu, V. R.; Leung, G. Y. C.; Lim, C. S.; Ng, S. Y.; Sum, R. J.; Chen, D. Y.-K. *Eur. J. Org. Chem.* **2011**, 463–468.

(7) Penner, M.; Rauniyar, V.; Kaspar, L. T.; Hall, D. G. *J. Am. Chem. Soc.* **2009**, *131*, 14216–14217.

(8) Jaegel, J.; Maier, M. E. *Synthesis* **2009**, 2881–2892.

(9) (a) Gowrisankar, P.; Pujari, S. A.; Kaliappan, K. P. *Chem.—Eur. J.* **2010**, *16*, 5858–5862. (b) Pujari, S. A.; Gowrisankar, P.; Kaliappan, K. P. *Chem.—Asian J.* **2011**, *6*, 3137–3151.

(10) (a) Prasad, K. R.; Pawar, A. B. *Org. Lett.* **2011**, *13*, 4252–4255. (b) Prasad, K. R.; Pawar, A. B. *Chem.—Eur. J.* **2012**, *18*, 15202–15206.

(11) (a) Kaliappan, K. P.; Gowrisankar, P. *Synlett* **2007**, 1537–1540. (b) Chandrasekhar, S.; Vijeender, K.; Chandrashekar, G.; Reddy, C. R. *Tetrahedron: Asymmetry* **2007**, *18*, 2473–2478. (c) Jaegel, J.; Schmauder, A.; Binanzer, M.; Maier, M. E. *Tetrahedron* **2007**, *63*, 13006–13017. (d) Cantagrel, G.; Meyer, C.; Cossy, J. *Synlett* **2007**, 2983–2986. (e) Lebar, M. D.; Baker, B. J. *Tetrahedron* **2010**, *66*, 1557–1562. (f) Jones, D. M.; Dudley, G. B. *Synlett* **2010**, 223–226. (g) Prasad, K. R.; Pawar, A. B. *Synlett* **2010**, 1093–1095. (h) Lisboa, M. P.; Jeong-Im, J. H.; Jones, D. M.; Dudley, G. B. *Synlett* **2012**, *23*, 1493–1496. (i) Wen, Z.-K.; Xu, Y.-H.; Loh, T.-P. *Chem.—Eur. J.* **2012**, *18*, 13284–13287.

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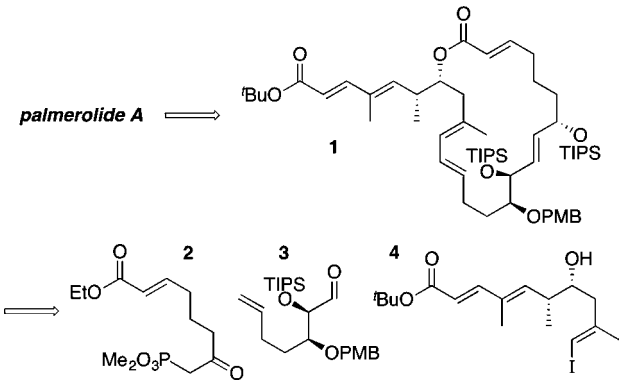
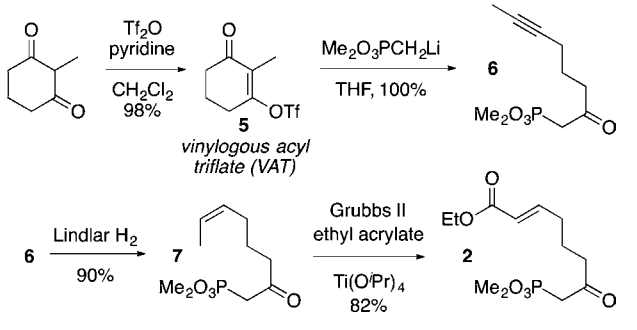
ours,[11f,h] have reported approaches to palmerolide A and, more recently, to palmerolide C.[12] Collectively, these studies provide insight into how one might generate significant quantities of synthetic palmerolides, but no current route reportedly produces palmerolide A in greater than 1% overall yield.

Scheme 1. Retrosynthetic Analysis: Identification of Three Key Subunits for Assembly to Palmerolide A



The consensus synthetic strategy for palmerolide A involves the convergent assembly of key subunits, but the questions of which subunits and how best to prepare and assemble them remain open. Here we disclose original, efficient, and stereoselective syntheses of key subunits **2**, **3**, and **4** (Scheme 1). We also describe how to assemble these subunits in good overall yield to provide macrolactone **1**, a late-stage intermediate in the Hall synthesis.[7] This work moves us significantly closer to the goal of developing a practical, scalable synthesis of palmerolide A; unresolved tactical challenges are presented and discussed throughout the manuscript.

Scheme 2. Synthesis of Phosphonate **2**[a]



[a] See Supporting Information for complete experimental details.

The synthesis of each of the three subunits is illustrated in Schemes 2–4, respectively. For phosphonate **2** (Scheme 2), we use nucleophile-triggered fragmentation of vinylogous acyl triflate **5**,[13] part of our ongoing alkynogenic fragmentation methodology,[14] to prepare alkynyl ketone **6**[15] on a multigram scale (98%, two steps).[16] Conversion of **6** into **2** is achieved by Lindlar semihydrogenation of the alkyne (**6** → **7**, 90%), followed by Grubbs cross-metathesis (**7** → **2**, 82%). The cross-metathesis event optimally requires adding titanium tetraisopropoxide, which likely prevents the Lewis basic β-keto phosphonate from binding to the ruthenium metal center and inhibiting metathesis.[17]

The synthesis of aldehyde **3** (Scheme 3) begins with Sharpless asymmetric dihydroxylation of known enoate **8**,[18] as we previously reported (75%, 99.6% ee).[11f] Here the alkyne serves as a masked alkene to avoid potential regioselectivity problems in the dihydroxylation. After the diol is in place, Lindlar semihydrogenation reveals the terminal alkene (98%), and the diol is converted to the *p*-methoxyphenyl (PMP) methylidene acetal (98%) to give rise to ester **9**. Treatment of **9** with excess DIBAL results in ester reduction and reductive acetal ring opening to give PMB-protected triol **10** (92%). The regioselective formation of **10** is consistent with internal coordination of an aluminum alkoxide (from ester reduction) to the proximal acetal oxygen to guide the reductive ring-opening event (cf. **9a**).[19] The primary alcohol of **10** is temporarily masked as a pivalate ester (93%), which is later removed using DIBAL after installing the secondary TIPS ether (92%, two steps). Dess–Martin oxidation (95%) then affords aldehyde **3**.

The third subunit, iodide **4** (Scheme 4), is available using Kalesse's new *syn*-selective variant[20] of the Kobayashi vinylogous aldol reaction.[21] Coupling of chiral *N*,*O*-ketene acetal **11**[20a] with iodo-aldehyde **12**[22] in the presence of titanium tetrachloride provides **13** (69%). Many different tactics have been reported for controlling the C19–C20 stereochemistry,[4–12] but this *syn*-selective vinylogous aldol

(12) Florence, G. J.; Wlochal, J. *Chem.—Eur. J.* **2012**, *18*, 14250–14254.

(13) Lisboa, M. P.; Hoang, T. T.; Dudley, G. B. *Org. Synth.* **2011**, *88*, 353–363.

(14) (a) Kamijo, S.; Dudley, G. B. *J. Am. Chem. Soc.* **2005**, *127*, 5028–5029. (b) Kamijo, S.; Dudley, G. B. *Org. Lett.* **2006**, *8*, 175–177. (c) Jones, D. M.; Kamijo, S.; Dudley, G. B. *Synlett* **2006**, 936–938. (d) Kamijo, S.; Dudley, G. B. *J. Am. Chem. Soc.* **2006**, *128*, 6499–6507. (e) Tummatorn, J.; Dudley, G. B. *J. Am. Chem. Soc.* **2008**, *130*, 5050–5051. (f) Tummatorn, J.; Dudley, G. B. *Org. Lett.* **2011**, *13*, 158–160. (h) Tummatorn, J.; Dudley, G. B. *Org. Lett.* **2011**, *13*, 1572–1575.

(15) Jones, D. M.; Lisboa, M. P.; Kamijo, S.; Dudley, G. B. *J. Org. Chem.* **2010**, *75*, 3260–3267.

(16) All yields refer to isolated quantities of material purified by column chromatography on silica gel or other methods and judged to be ≥95% pure by ^{1}H NMR spectroscopic analysis; see Supporting Information for details. For a commentary on the limitations of reporting yields by these and related techniques, see: Wernerova, M.; Hudlicky, T. *Synlett* **2010**, 2701–2707.

(17) (a) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130–9136. (b) Michaunt, A.; Boddaert, T.; Coquerel, Y.; Rodriguez, J. *Synthesis* **2007**, *18*, 2687–2871.

(18) Prepared in two steps (one pot) from 4-pentynol (85% yield); see: Vatèle, J.-M. *Tetrahedron Lett.* **2006**, *47*, 715–718.

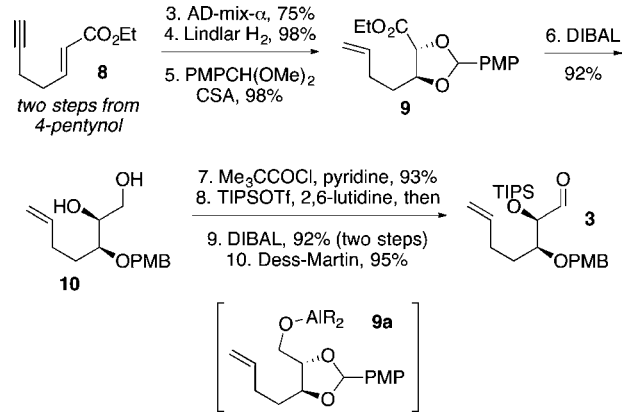
(19) For a related example, see: Heapy, A. M.; Wagner, T. W.; Brimble, M. M. *Synlett* **2007**, *15*, 2359–2362.

(20) (a) Symkenberg, G.; Kalesse, M. *Org. Lett.* **2012**, *14*, 1608–1611. (b) Mukaeda, Y.; Kato, T.; Hosokawa, S. *Org. Lett.* **2012**, *14*, 5298–5301.

(21) Shirokawa, S.-i.; Kamiyama, M.; Nakamura, T.; Okada, M.; Nakazaki, A.; Hosokawa, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 13604–13605.

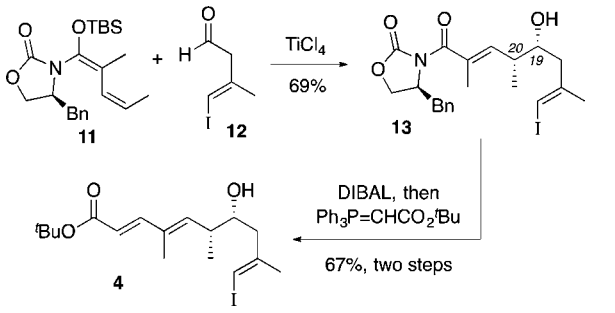
(22) Marshall, J. A.; Eidam, P. *Org. Lett.* **2004**, *6*, 445–448.

Scheme 3. Synthesis of Aldehyde **3**[a]



[a] See Supporting Information for complete experimental details. PMP = *p*-methoxyphenyl.

Scheme 4. Synthesis of Iodide **4**[a]



[a] See Supporting Information for complete experimental details.

reaction is perhaps ideal for the task at hand. *N*,*O*-Ketene acetal **11** is robust and easy to handle and delivers the desired C19−C20 *syn*-isomer with excellent diastereoselectivity,[23] so **11** is a valuable building block for construction of the palmerolide side chain. Iodo-aldehyde **12**, on the other hand, is unstable to storage, and it has a propensity to decompose even during the course of the reaction. We use excess **12** for the preparation of **13**, but alternative solutions could be useful here.[24] Homologation of **13** is achieved by DIBAL reduction of the imide and Wittig olefination of the resulting aldehyde to furnish subunit **4** (67%, two steps).

Our assembly of the three subunits is presented in Scheme 5. Horner−Wadsworth−Emmons (HWE) reaction of **2** and **3** was initially confounded by a tendency of phosphonate **2** to undergo base-mediated cyclization onto the tethered Michael acceptor (i.e., the unsaturated ester). Barium hydroxide[25] effectively suppresses the Michael-type *intra*molecular cyclization of **2** in favor of the desired *inter*molecular HWE olefination of aldehyde **3** to generate enone **14** in excellent yield (96%).

Borohydride reduction of **14** provides diastereomeric alcohols **15** and **16** (93%) in an approximately 1:1 ratio. These isomers are separable by chromatography on silica gel;[26] the undesired isomer (**16**) can be converted into **15** by Mitsunobu inversion with *p*-nitrobenzoic acid (74%) and selective cleavage of the *p*-nitrobenzoate ester (in the presence of the ethyl ester) with sodium azide in methanol (84%).[27] Attempts to produce **15** selectively using reagent control have not yet been successful, and we continue to seek practical solutions to this challenge.[28] Silylation and saponification of **15** give acid **17**, the C1−C15 section of palmerolide A.

Esterification of acid **17** with alcohol **4** using the Yamaguchi procedure (91%) is followed by Heck macrocyclization (59%) to provide **1**. The Maier lab[8] reported a similar Heck cyclization in the context of their formal synthesis of palmerolide A, and Hall and co-workers[7] converted macrolactone **1** into the natural product in six additional steps (8% yield).

In summary, innovative routes to three key subunits (**2**, **3**, and **4**) have been developed, and these subunits have been assembled to produce **1**, an advanced precursor of synthetic palmerolide A. We have prepared macrolactone **1** in 16% overall yield by a linear sequence of 16 steps from 4-pentynol, plus two auxiliary steps to invert alcohol **16** → **15**.

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. A third challenge relates to the instability of iodo-aldehyde **12**, which imposes practical constraints on the otherwise ideal Kalesse vinylogous aldol reaction (**11** → **13**).

The remaining challenges not withstanding, this work marks a significant step toward the goal of providing cost-effective access to synthetic palmerolide A. Virtues of this formal synthesis include the nucleophile-triggered

(23) Based on ^{1}H NMR analysis, we estimate the diastereoselectivity of the aldol reaction to be 97:3. The minor product is removed during chromatographic purification.

(24) In our hands, subunits **2** and **3** are significantly easier to prepare on a large scale than subunit **4**. This factor contributed to our strategic decision to introduce subunit **4** last during the assembly process.

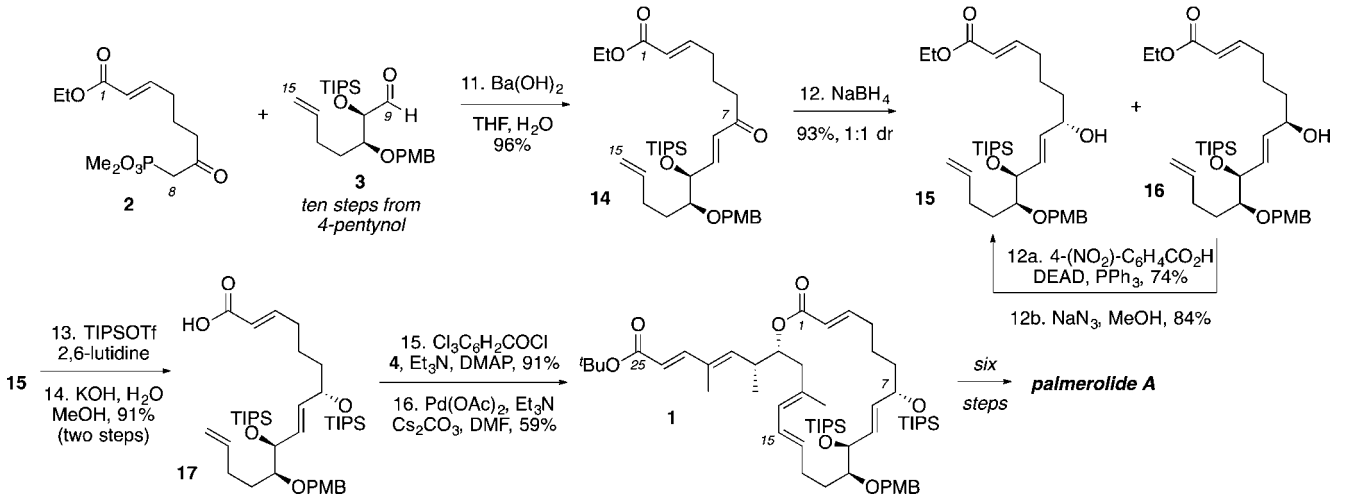
(25) (a) Alvarezibarra, C.; Arias, S.; Banon, G.; Fernandez, M. J.; Rodriguez, M.; Sinisterra, V. J. *J. Chem Soc., Chem. Commun.* **1987**, 1509–1511. (b) Paterson, I.; Yeung, K.-S.; Smaill, J. B. *Synlett* **1993**, 774–776. For recent examples of using $Ba(OH)_2$ for HWE reactions, see: (c) Crimmins, M. T.; Shamszad, M.; Mattson, A. E. *Org. Lett.* **2010**, *12*, 2614–2617. (d) Crimmins, M. T.; O'Bryan, E. A. *Org. Lett.* **2010**, *12*, 4416–4419. (e) Giannis, A.; Heretsch, P.; Sarli, V.; Stössel, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 7911–7914. (f) Winbush, S. M.; Mergott, D. J.; Roush, W. R. *J. Org. Chem.* **2008**, *73*, 1818–1829.

(26) Purification of the crude mixture on silica gel afforded pure **15** (38%), pure **16** (39%), and mixed fractions (15%) that were collected and repurified separately. See Supporting Information.

(27) Gómez-Vidal, J. A.; Forrester, M. T.; Silverman, R. B. *Org. Lett.* **2001**, *3*, 2477–2479.

(28) See ref 10 for related efforts using reagent control. We also explored the option of deferring this reduction until after the Heck cyclization to the macrolactone, but the cyclic ketone turns out to be a highly mismatched case; see also ref 4, pp S19−S20.

Scheme 5. Assembly of Subunits **2**, **3**, and **4** To Complete the Formal Synthesis of Palmerolide[a]



[a] See Supporting Information for complete details and experimental conditions.

alkynogenic fragmentation (**5**→**6**) en route to subunit **2**, the efficient barium hydroxide-mediated HWE coupling (**2** + **3** → **14**), a concise synthesis of subunit **4** by new vinylogous aldol chemistry, and facile annulation by the Yamaguchi/Heck sequence to deliver macrolactone **1**. Efforts to resolve the issues outlined above and to generate useful quantities of synthetic palmerolide A are in progress and will be fully disclosed in due course.

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Supporting Information Available. Experimental procedures, characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.