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Enantioselective Formal Synthesis of Palmerolide A

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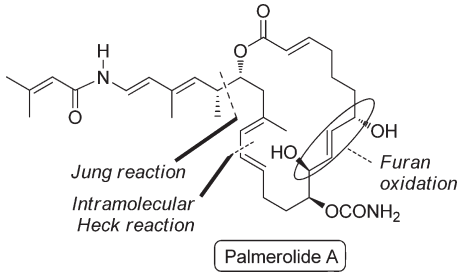
ABSTRACT



Enantioselective formal synthesis of macrolactone palmerolide A, a polyketide marine natural product, is described. Key strategies in the synthesis include the oxidative furan ring-opening of a chiral furyl carbinol for the installation of the 1,4-dienol core and a Jung nonaldol−aldol reaction for the dienamide core.

A large number of natural products isolated from various sources continue to play a pivotal role in drug discovery. In a quest of natural products with potent activity, Baker and co-workers isolated palmerolide A **1**, a 20-membered macrolactone from the marine tunicate *Synoicum adareanum* found in the Antarctic region.[1] Palmerolide A **1** possesses seven unsaturations that include a conjugated dienamide, conjugated diene, α,β-unsaturated ester, 1, 4-alkenol with an adjacent carbamate, and five chiral centers. Palmerolide A is found to exhibit excellent antitumor activity against melanoma cancer cells, which is attributed to its potent inhibitory activity against vacuolar ATPase. Owing to the useful biological profile of **1** and the treaty that prohibits commercial exploitation of Antarctic resources, the development of a synthetic strategy that allows the synthesis of palmerolide A and an array of its analogues is warranted. De Brabander's group disclosed the first total synthesis of **1** and revised the stereochemistry of the natural product.[2a] Two more total syntheses from the groups of Nicolaou[2b−d] and Hall[2e] were reported recently, while two formal syntheses[3] and approaches to various fragments of **1** have also appeared.[4] Key disconnections in the reported syntheses include assembly of the macrolactone core of **1** employing an intramolecular Wittig−Horner olefination, ring-closing metathesis (RCM), intramolecular Heck reaction, and Yamaguchi lactonization by the De Brabander, Nicolaou, Maier, and Hall groups, respectively. Notable approaches for construction of the 1,4-alkenol C7−C11 fragment include an intramolecular Wittig reaction followed by reduction and a Claisen−Ireland rearrangement of an alkenylboronate, while approaches for the synthesis of the C16−C23 fragment include, in general, either an aldol reaction or crotylboration. Herein, we report the synthesis of **1**, different from the previous reported syntheses for the installation of the

(1) (a) Diyabalanage, T.; Amsler, C. D.; McClintock, J. B.; Baker, B. J. *J. Am. Chem. Soc.* **2006**, *128*, 5630. (b) Lebar, M. D.; Baker, B. J. *Tetrahedron Lett.* **2007**, *48*, 8009.

(2) (a) Jiang, X.; Liu, B.; Lebreton, S.; De Brabander, J. K. J. *Am. Chem. Soc.* **2007**, *129*, 6386. (b) Nicolaou, K. C.; Guduru, R.; Sun, Y. P.; Banerji, B.; Chen, D. Y. K. *Angew. Chem., Int. Ed.* **2007**, *46*, 5896. (c) Nicolaou, K. C.; Sun, Y. P.; Guduru, R.; Chen, D. Y. K. *J. Am. Chem. Soc.* **2008**, *130*, 3633. (d) Nicolaou, K. C.; Leung, Y. C. G.; Dethe, D. H.; Guduru, R.; Sun, Y. P.; Lim, C. S.; Chen, D. Y. K. *J. Am. Chem. Soc.* **2008**, *130*, 10019. (e) Penner, M.; Rauniyar, V.; Kaspar, L. T.; Hall, D. G. *J. Am. Chem. Soc.* **2009**, *131*, 14216.

(3) (a) Jägel, J.; Maier, M. E. *Synthesis* **2009**, 2881. (b) Gowrisankar, P.; Pujari, S. A.; Kaliappan, K. P. *Chem.—Eur. J.* **2010**, *16*, 5858.

(4) (a) Jones, D. M.; Dudley, G. B. *Synlett* **2010**, 223. (b) Lebar, M. D.; Baker, B. J. *Tetrahedron* **2010**, *66*, 1557. (c) Prasad, K. R.; Pawar, A. B. *Synlett* **2010**, 1093. (d) Kaliappan, K. P.; Gowrisankar, P. *Synlett* **2007**, 1537. (e) Cantagrel, G.; Meyer, C.; Cossy, J. *Synlett* **2007**, 2983. (f) Chandrasekhar, S.; Vijeender, K.; Chandrasekhar, G.; Reddy, C. R. *Tetrahedron: Asymmetry* **2007**, *18*, 2473. (g) Jägel, J.; Schmauder, A.; Binanzer, M.; Maier, M. E. *Tetrahedron* **2007**, *63*, 13006.

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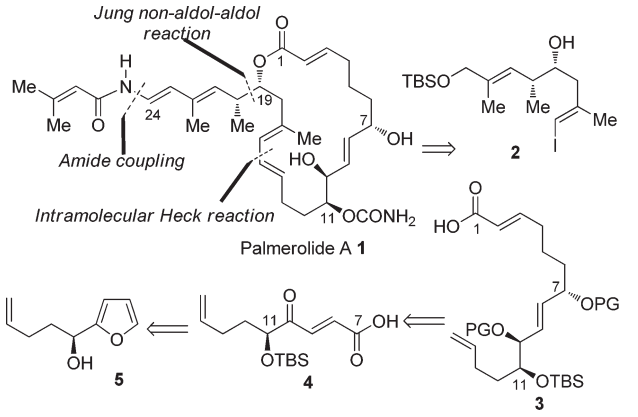
chiral components, relying on the Jung rearrangement and oxidative furan ring-opening of a chiral furyl carbinol.

The sketch of our approach for the synthesis of **1** is depicted in Scheme 1. It is envisaged to construct the macrolactone via an intramolecular Heck coupling of the two fragments **2** and **3.** Synthesis of the C16−C23 fragment **2** is anticipated through the nonaldol−aldol reaction developed by Jung et al.,[5] while the C1−C15 fragment **3** is envisioned by elaboration of the γ-ketoalkenoic acid **4** derived from the furyl carbinol **5**.

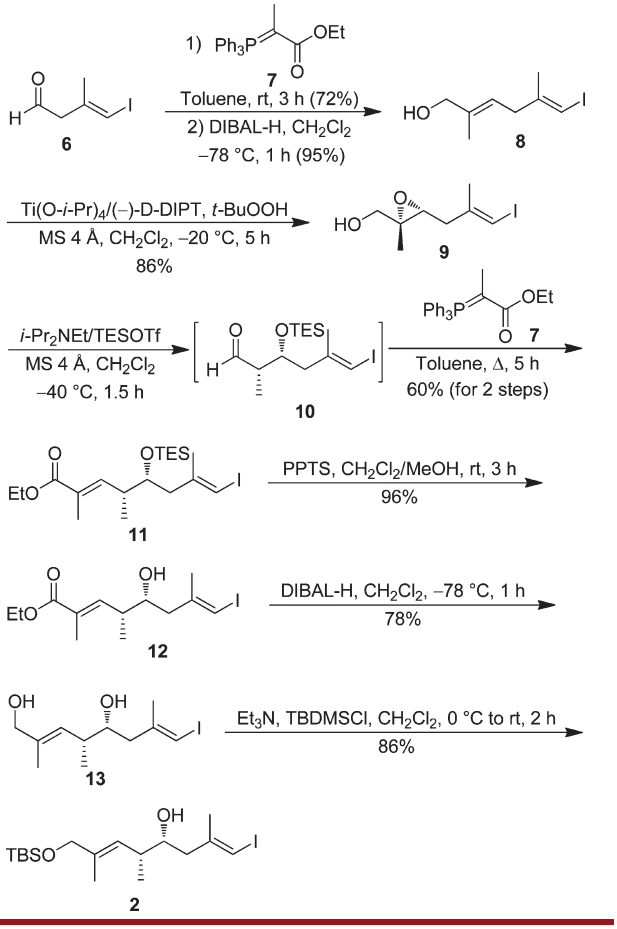
Scheme 1. Palmerolide A and Retrosynthesis



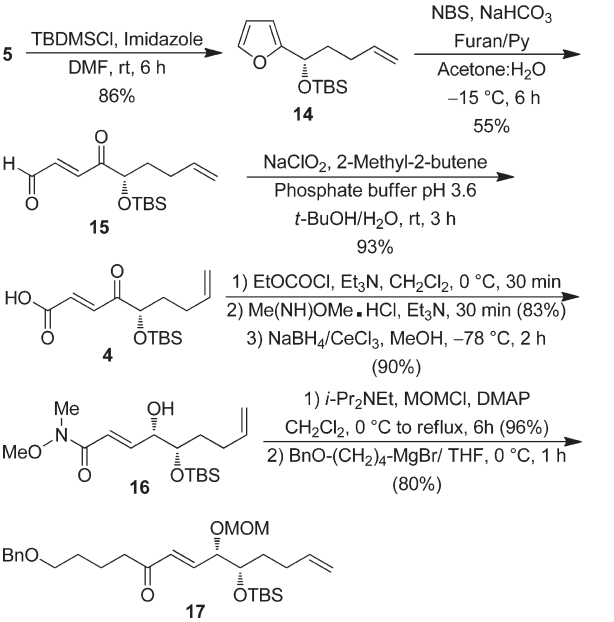
Accordingly, the synthetic sequence commenced with the synthesis of allylic alcohol **8** from the known aldehyde **6**[6] involving a sequence of Wittig olefination with the ylide $Ph_3P{=}C(Me)CO_2Et$ **7** and reduction of the resultant ester. Epoxidation of the allylic alcohol **8** under Sharpless conditions afforded the epoxide **9** (86% yield).[7] Reaction of **9** under Jung reaction conditions with TESOTf and $^{i}Pr_2NEt$ resulted in the aldehyde **10**, which without further purification was treated with the Wittig ylide **7** to afford the α,β-unsaturated ester **11** in 60% yield for two steps. Deprotection of the silyl ether in **11** gave the hydroxy ester **12** in 96% yield. Reduction of **12** with DIBAL-H afforded the diol **13**, which on selective protection of the primary hydroxy group as the TBS ether furnished the required C16−C23 fragment **2** in 86% yield (Scheme 2).

For the synthesis of the C1−C15 fragment, transformation of the furyl carbinol **5** to the alkenoic acid **4** was

Scheme 2. Synthesis of the C16−C23 Fragment of Palmerolide A



Scheme 3. Synthesis of the γ-Ketoalkenoic Acid



chosen as the pivotal step. Thus, **5**[8] was transformed to the silylether **14**, which on reaction with NBS in presence of

(5) (a) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1993**, *115*, 12208. (b) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1997**, *119*, 12150.

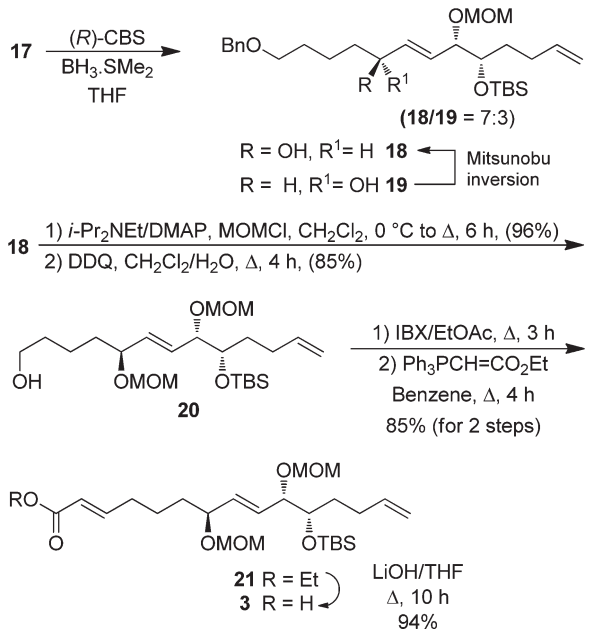
(6) (a) Marshall, J. A.; Eidam, P. *Org. Lett.* **2004**, *6*, 445. (b) Amans, D.; Bellosta, V.; Cossy, J. *Org. Lett.* **2007**, *9*, 1453.

(7) Enatiopurity of the epoxide **9** was not determined at this stage. However, a convincing and indirect proof for the high enantiopurity of **9** is evident from its convesrion to enantiopure **2** (Scheme 2), which exhibited optical rotration and spectral data identical to that reported by Nicolaou et al. (ref 2c).

(8) Fürstner, A.; Nagano, T. *J. Am. Chem. Soc.* **2007**, *129*, 1906.

(9) For similar oxidation of furans with NBS, see: (a) Kobayashi, Y.; Nakano, M.; Kumar, G. B.; Kishihara, K. *J. Org. Chem.* **1998**, *63*, 7505. (b) Schreiber., S.; Berger, E. M.; Burke, M. D. *J. Am. Chem. Soc.* **2004**, *126*, 14095.

Scheme 4. Synthesis of the C1−C15 Fragment of Palmerolide A

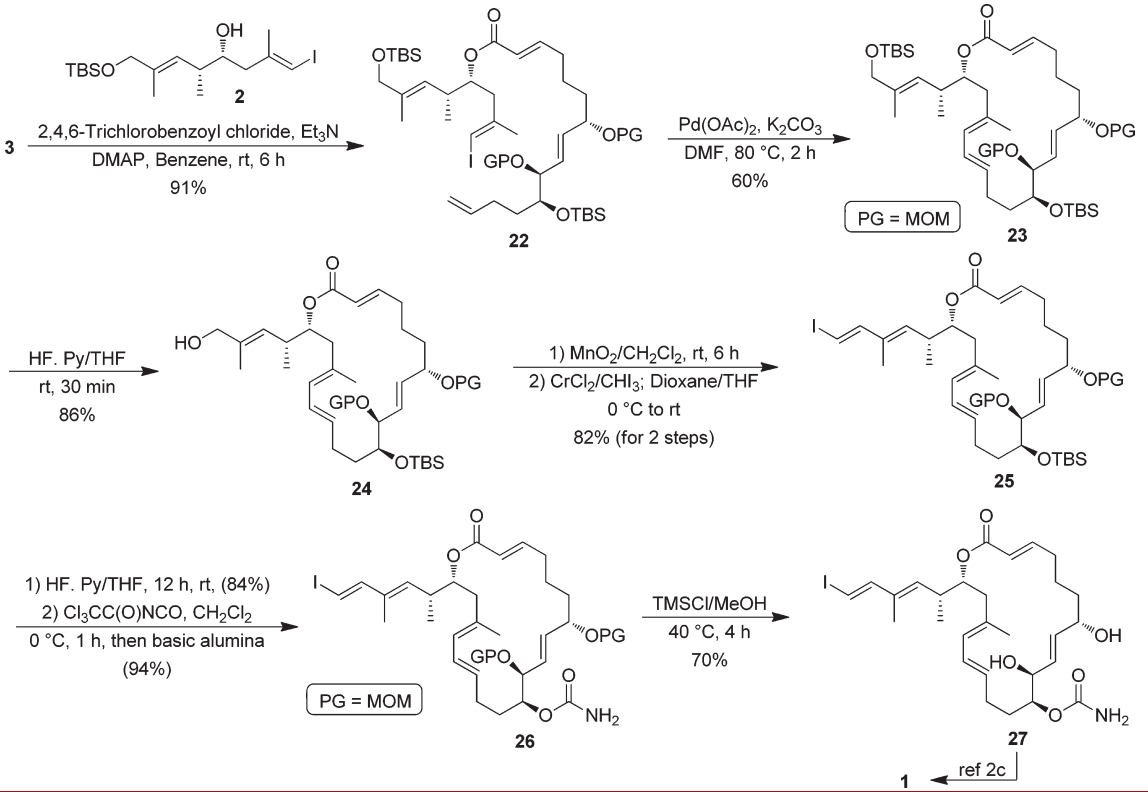


water and pyridine furnished the unsaturated aldehyde **15** in 55% yield.[9] Oxidation of the aldehyde with $NaClO_2$ afforded the required acid **4** in 93% yield. Conversion of the acid to the Weinreb amide utilizing the mixed anhydride method and subsequent reduction of the ketone with $NaBH_4$ in presence of $CeCl_3$ afforded the alcohol **16** in good yield and in excellent stereoselectivity.[10] Alcohol **16** was transformed to the corresponding MOM ether which on reaction with 4-benzyloxybutylmagnesium bromide yielded the ketone **17** in 80% yield (Scheme 3).

Reduction of **17** with an (*R*)-CBS reagent[11] furnished a separable mixture of alcohols in 90% yield (**18/19** = 7:3). Minor isomer **19** was converted to the required isomer **18** involving Mitsunobu inversion in 64% yield, making it a convenient process for the synthesis of **18**. Protection of the secondary alcohol in **18** as the MOM ether (96% yield) and subsequent debenzylation using DDQ produced **20** in 85% yield. Oxidation of **20** with IBX to the aldehyde and further Wittig olefination of the resultant aldehyde furnished the α,β-unsaturated ester **21** in 95% yield. Saponification of **21** with LiOH produced acid **3**, the C1−C15 fragment of palmerolide A (Scheme 4).

After successfully procuring the alcohol and acid fragements **2** and **3**, esterification was effected under Yamaguchi conditions[12] to yield the ester **22** in 91% yield. Intramolecular Heck coupling was performed on **22** to afford the macrolactone **23** in 60% yield.[13] Selective deprotection of the primary silyl ether in **23** furnished the alcohol **24** (86% yield), which was converted to the vinyl iodide **25** involving oxidation to the aldehyde followed by Takai olefination.[14] Deprotection of the TBS ether in **25** and introduction of the carbamate yielded **26** in excellent yield. The MOM ethers were unmasked by treating **26** with

Scheme 5. Formal Total Synthesis of Palmerolide A



TMSCl in MeOH to furnish **27** in 70% yield the spectral data of which is in complete agreement with that reported in literature.[2c] Since conversion of **27** to palmerolide A **1** by CuI-mediated coupling with dimethylacrylamide has been reported in literature, the present sequence constitutes a formal total synthesis of palmerolide A **1** (Scheme 5).

In conclusion, a formal total synthesis of palmerolide A is accomplished from readily available furyl carbinol. The main feature of the synthesis includes the construction of the C1−C15 fragment by elaboration of the keto acid derived from oxidation of 2-furylcarbinol. Expedient synthesis of the C16−C23 fragment showcased the usefulness of a Jung nonaldol−aldol reaction.

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

(10) Formation of the other diastereomer was not observed within detectable limits in the ^{1}H NMR.

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(13) Formation of only the *E,E* diene is observed within detectable limits by NMR. For recent approaches involving intramolecular Heck reaction in macrolactone synthesis, see: (a) Li, P.; Li, J.; Arikan, F.; Ahlbrecht, W.; Dieckmann, M.; Menche, D. *J. Am. Chem. Soc.* **2009**, *131*, 11678. (b) Menche, D.; Hassfeld, J.; Li, J.; Rudolph, S. *J. Am. Chem. Soc.* **2007**, *129*, 6100. (c) Menche, D.; Hassfeld, J.; Li, J.; Mayer, K.; Rudolph, S. *J. Org. Chem.* **2009**, *74*, 7220. (d) Li, P.; Li, J.; Arikan, F.; Ahlbrecht, W.; Dieckmann, M.; Menche, D. *J. Org. Chem.* **2010**, *75*, 2429.

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