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Published on Web 04/26/2007

Total Synthesis and Structure Revision of the Marine Metabolite Palmerolide A

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A unique natural product termed palmerolide A was recently isolated from the antarctic marine tunicate *Synoicum adareanum* by Baker and co-workers.[1] The structure and absolute stereochemistry of palmerolide A, expressed by formula **1** (Scheme 1), was solved by NMR studies and reveals a 20-membered macrolide decorated with a polyunsaturated *N*-acyl dienamine side chain distinct from the *N*-acyl enamine found in salicylihalamide and related natural products.[2] Palmerolide is a differential cytotoxin with an activity profile that correlates to V-ATPase inhibitors.[1] Subsequent in vitro studies confirmed that palmerolide A is indeed a potent inhibitor of bovine brain V-ATPase ($IC_{50} \approx 2$ nM).[1,3] Palmerolide was isolated from an organism found in one of the most inaccessible areas of the world, which in conjunction with commercial exploitation prohibited by the Antarctic Treaty will severely limit access to this compound from natural sources.[4] Therefore, total synthesis remains as the only option to ensure investigation of palmerolide's promising antitumor properties. Herein, we present our synthetic efforts that led to the conclusion that (−)-palmerolide A is in fact a diastereomer of the proposed structure **1**, that is, structure *ent*-**24** (Scheme 4).

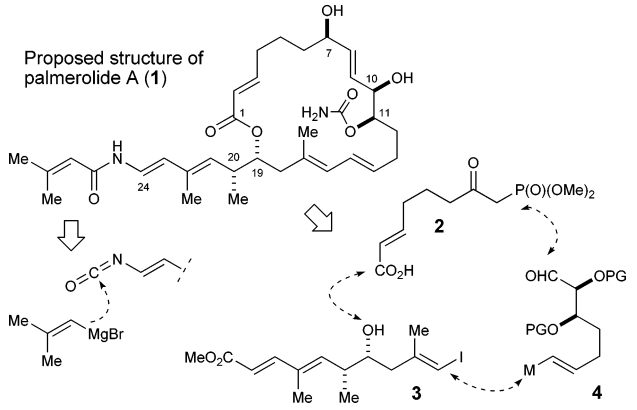
We envisioned constructing palmerolide from fragments **2**−**4** via cross-coupling (**3** + **4**), followed by esterification with enoic acid **2**, a fragment with a keto-phosphonate positioned to induce macrocyclization via Horner−Wadsworth−Emmons olefination (Scheme 1). A Curtius rearrangement followed by isocyanate-trapping with 2-Me-propenylmagnesium bromide will install the sensitive *N*-acyl dienamine functionality at the final stages.[5]

The synthesis of fragment **3** began by a vinylogous Mukaiyama aldol addition of vinylketene silyl *N*,*O*-acetal **5**[6] to aldehyde **6**[7] according to Kobayashi et al.[6] to furnish alcohol **7** in excellent yield and diastereoselectivity (Scheme 2).[8] A Mitsunobu inversion provided the desired syn isomer **8**. Simultaneous reductive cleavage of the auxiliary and the benzoate provided an aldehyde that was homologated with PPh_3CHCO_2Me. Cross-coupling partner **3** was thus obtained in 49% overall yield from **5**.

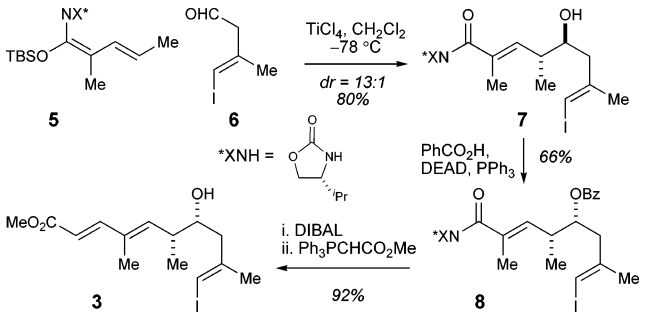
The synthetic equivalent of fragment **4**, alkenylboronate **13**, was derived from D-arabitol. Benzylidene acetal formation and oxidative α-diol cleavage yielded aldehyde **9** (Scheme 3).[9] Silylation, Wittig homologation, and hydrogenation gave diol **11**. Bis-silylether formation and ester reduction then provided aldehyde **12**, a material that was condensed with pinacol dichloromethylboronate ($CrCl_2$, LiI) to yield vinylboronate **13**.[10]

After substantial experimentation, we found that Suzuki coupling of vinyl iodide **3** and vinylboronate **13** was best performed with catalytic $Pd(PPh_3)_4$ and thallium carbonate as the base (Scheme 4).[11] The coupled diene **14** thus obtained was esterified with fragment **2**.[12,13] Stirring the corresponding ester **15** in acidic MeOH

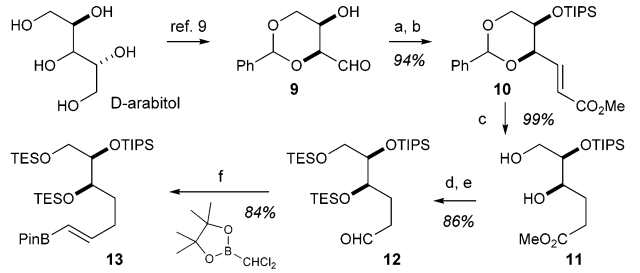
Scheme 1



Scheme 2



Scheme 3 [a]

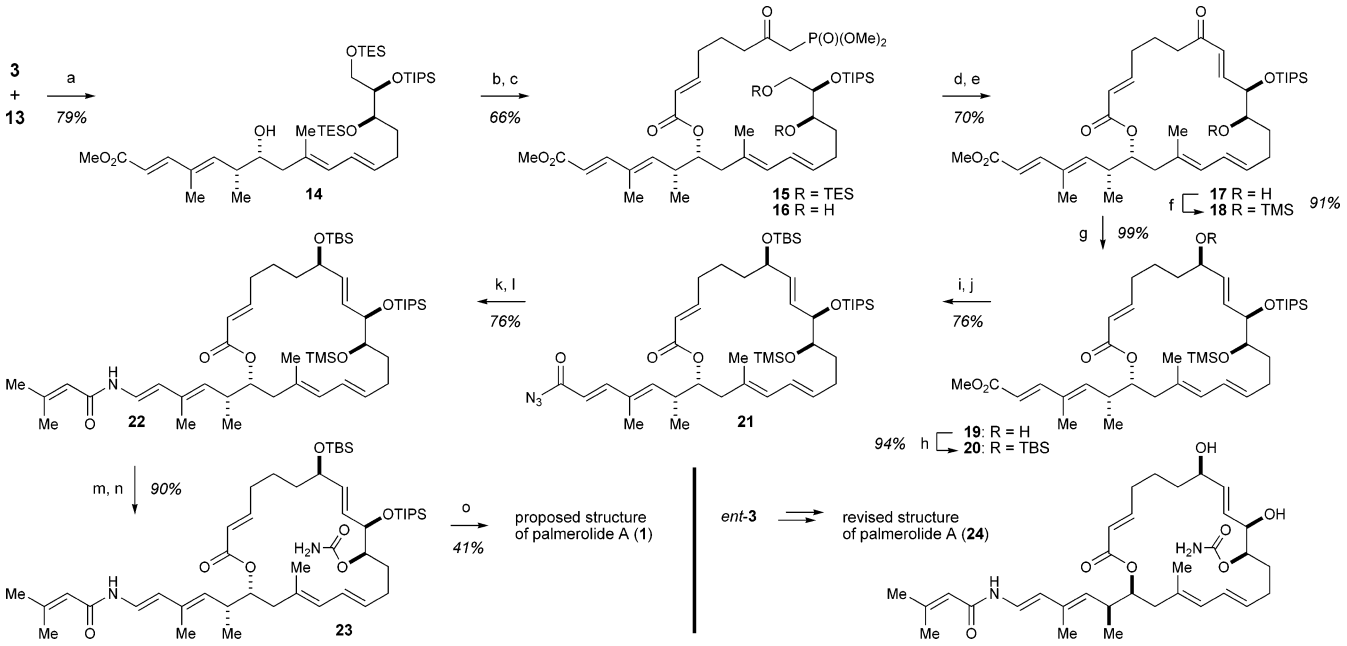


[a] Conditions: (a) Ph_3PCHCO_2Me, PhMe, reflux (99%); (b) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (c) Pd/C, H_2, EtOAc, room temp (95%, two steps); (d) TESCl, imidazole, DMF, room temp (93%); (e) DIBAL, CH_2Cl_2, −78 °C (93%); (f) $CrCl_2$, LiI, THF, room temp (84%).

then provided diol **16**. Selective oxidation[14] of the primary alcohol followed by Horner−Wadsworth−Emmons mediated macrocyclization yielded macrolactone **17** (70%).[15] Silylation (→ **18**), CBS-reduction (→ **19**, dr = 4:1),[16] and protection furnished TBS-ether **20**. Ester hydrolysis ($(Bu_3Sn)_2O$, 81%)[17] set the stage for a Curtius rearrangement via azide **21**. Addition of 2-Me-propenylmagnesium

10.1021/ja0715142 CCC: $37.00

Scheme 4 [a]



[a] Conditions: (a) cat. $Pd(Ph_3)_4$, Tl_2CO_3, THF/H_2O, room temp (79%); (b) **2**, 2,4,6-Cl_3BzCl, NEt_3, DMAP, PhMe, room temp (69%); (c) PPTS, MeOH, 0 °C (95%); (d) $PhI(OAc)_2$, TEMPO, CH_2Cl_2/H_2O, room temp; (e) K_2CO_3, 18-crown-6, PhMe, 60 °C (70%, two steps); (f) TMSCl, Et_3N, cat. DMAP, CH_2Cl_2, room temp (91%); (g) (*S*)-CBS, BH_3, THF, −40 °C (99%); (h) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C (94%); (i) $(Bu_3Sn)_2O$, PhMe, 80 °C (81%); (j) $(PhO)_2P(O)N_3$, NEt_3, benzene, room temp (92%); (k) benzene, reflux; (l) 2-Me-1-propenylmagnesium bromide, −78 °C (76%, two steps); (m) HF·py, py, THF, room temp (95%); (n) $Cl_3CC(O)NCO$, CH_2Cl_2, 0 °C; Al_2O_3, room temp (95%); (o) TBAF, THF, 0 °C (41%).

bromide to the isocyanate generated from heating acyl azide **21** yielded **22** (76%).

Selective trimethylsilyl ether deprotection enabled introduction of the carbamate at C11 (**23**, 95%),[18] an operation that was followed by fluoride-mediated deprotection to afford target structure **1**. Unfortunately, the NMR data obtained for **1** was incongruent with those reported for the natural isolate, indicating that the relative stereochemical assignment needed to be revisited.[1]

Confidence in the stereochemical assignment of synthetic **1** was founded on (1) Mosher ester analysis of C7-alcohol **19**,[19] (2) C10, C11 stereochemistry from *D*-arabitol, and (3) X-ray analysis of fragment **7** (C19,20 stereochemistry).[8] The natural absolute configuration at C7 and C10 was ascertained by Mosher ester analysis.[1] The relative C10−C11 and C19−C20 stereochemistry of natural palmerolide A also seemed founded on solid footing, including *J*-based H−H and C−H coupling constant analysis, and NOE-difference spectroscopy.[1] In contrast, we found the interpretation of the ROESY data parlaying stereochemistry from C11 to C19 less convincing[1] and decided to funnel our synthetic efforts toward diastereomer **24**. Its synthesis followed the chemistry outlined in Scheme 4 but starting with the enantiomer of vinyl iodide **3**, *ent*-**3**.[19]

Gratifyingly, the NMR spectra, TLC, and analytical HPLC behavior of synthetic **24** and natural palmerolide A are indistinguishable.[19] To our surprise however, the synthetic and natural isolate were not completely indistinguishable by virtue of the mirror image CD-spectra obtained for **24** and natural palmerolide A. The inescapable conclusion is that the structure of (−)-palmerolide A has to be revised to structure *ent*-**24**.[20] Current efforts are underway to produce the bioactive enantiomer of palmerolide and congeners.

Acknowledgment. This work was supported by the NIH (Grant CA90349), the Robert A. Welch Foundation, and Merck Research Laboratories. We thank Dr. R. Akella for crystallographic analysis and Prof. B. Baker for a sample of natural palmerolide and helpful discussions regarding palmerolide stereochemistry.

Supporting Information Available: Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) See Supporting Information for details.
(20) Prof. Baker informed us that their reported[1] absolute stereochemical assignment is in doubt because of erroneous Cahn−Ingold−Prelog prioritization of their Mosher ester derivatives.

JA0715142