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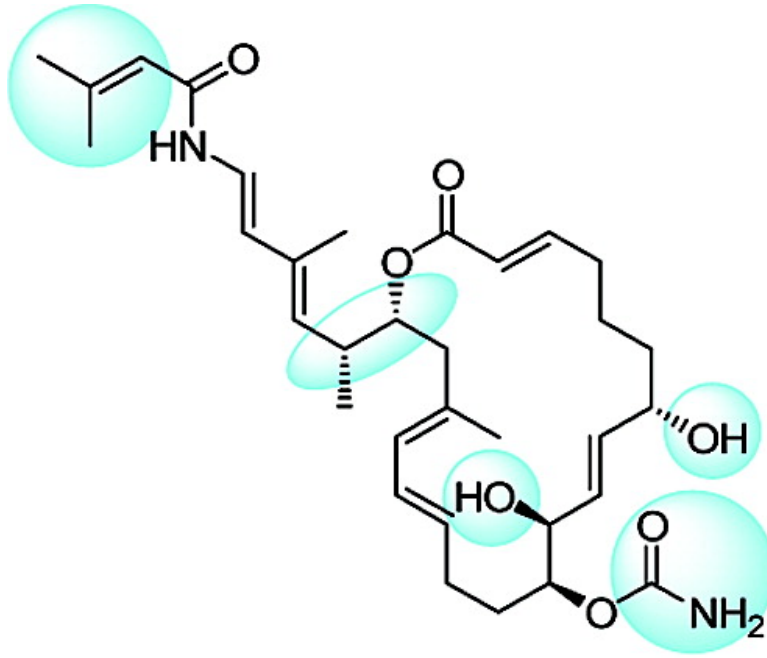

Palmerolide A SARs

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Chemical Synthesis and Biological Evaluation of Palmerolide A Analogues

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Abstract: Molecular design and chemical synthesis of several palmerolide A analogues allowed the first structure activity relationships (SARs) of this newly discovered marine antitumor agent. From several analogues synthesized and tested (*ent*-**1**, **5**−**14**, **21**−**26**, **50**, **51**), compounds **25** (with a phenyl substituent on the side chain) and **51** (lacking the C-7 hydroxyl group) were the most interesting, exhibiting approximately a 10-fold increase in potency and equipotency, respectively, to the natural product. These findings point the way to more focused structure activity relationship studies.

Introduction

Intelligence gathering on molecules from nature has amassed an invaluable body of knowledge and established itself as a leading and fertile avenue for drug discovery and development, as amply demonstrated over the past century.[1] The recently reported antitumor properties [selective cytotoxicity against melanoma cancer cells UACC-62 (LC50 = 18 nM)] of palmerolide A (**1**, Figure 1), a substance isolated from the circumpolar tunicate *Synoicum adareanum* collected from the waters around Anvers Island on the Antarctic Peninsula,[2] promise a new chapter in cancer research, provided chemical synthesis can deliver sufficient quantities of the compound and its congeners for further biological investigations. Indeed, synthetic studies directed toward palmerolide A culminated in total syntheses of both *ent*-palmerolide A (*ent*-**1**, Figure 2)[3,4] and naturally occurring palmerolide A,[4] as well as several diastereoisomers and analogues [**5**−**13** (Figure 2), **14** (Table 1)][4] of the natural product. Most importantly, these studies resulted in the revision of the structure of palmerolide A to that represented by structure **1**. In this article we report the application of our developed synthetic technologies to the construction of several new palmerolide A analogues [**21**−**26** (Table 1) and **50**, **51** (Scheme 2)] and the biological evaluation of all synthesized palmerolides against an array of tumor cells.

Results and Discussion

Recognizing the structural and biological similarity between palmerolide A (**1**) and other enamide containing ATPase inhibitors,[5] a series of enamide analogues (**21**−**26**) were prepared as illustrated in Table 1. Thus, under our carefully optimized conditions, the application of the Buchwald copper-catalyzed coupling (CuI, K_2CO_3 and *N*,*N*′-dimethylethylenediamine)[6] allowed the coupling of macrocyclic iodide **14**[4] and

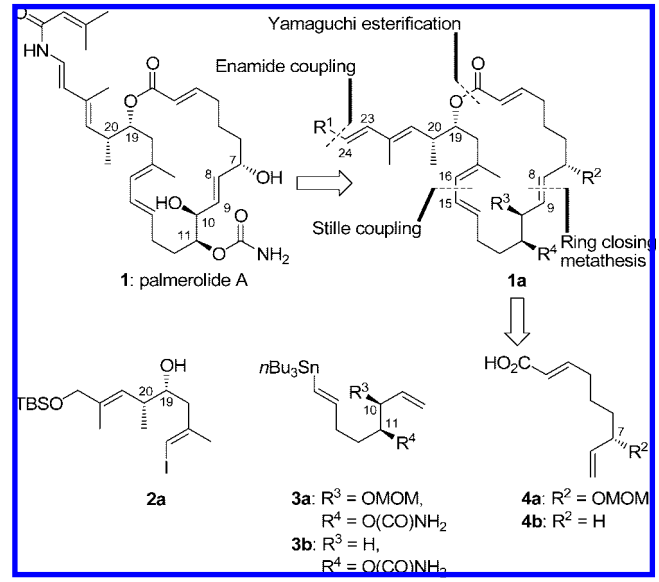

Figure 1. Structure of palmerolide A (**1**) and retrosynthetic analysis of the palmerolide structure (**1a**) leading to building blocks **2a**, **3a**, **3b**, **4a**, and **4b**. TBS = *tert*-butyldimethylsilyl; MOM = methoxymethyl.

† Additional affiliations at The Scripps Research Institute and University of California, San Diego.

(1) Nicolaou, K. C.; Montagnon, T. *Molecules That Changed The World*; Wiley-VCH: Weinheim, 2008; p 366.
(2) Diyabalanage, T.; Amsler, C. D.; McClintock, J. B.; Baker, B. J. *J. Am. Chem. Soc.* **2006**, *128*, 5630–5631.
(3) Jiang, X.; Liu, B.; Lebreton, S.; De Brabander, J. K. *J. Am. Chem. Soc.* **2007**, *129*, 6386–6387.
(4) (a) Nicolaou, K. C.; Guduru, R.; Sun, Y.-P.; Banerji, B.; Chen, D. Y.-K. *Angew. Chem., Int. Ed.* **2007**, *46*, 5896–5900. (b) Nicolaou, K. C.; Sun, Y.-P.; Guduru, R.; Banerji, B.; Chen, D. Y.-K. *J. Am. Chem. Soc.* **2008**, *130*, 3633–3644.
(5) Xie, X.-S.; Padron, D.; Liao, X.; Wang, J.; Roth, M. G.; De Brabander, J. K. *J. Biol. Chem.* **2004**, *279*, 19755–19763.
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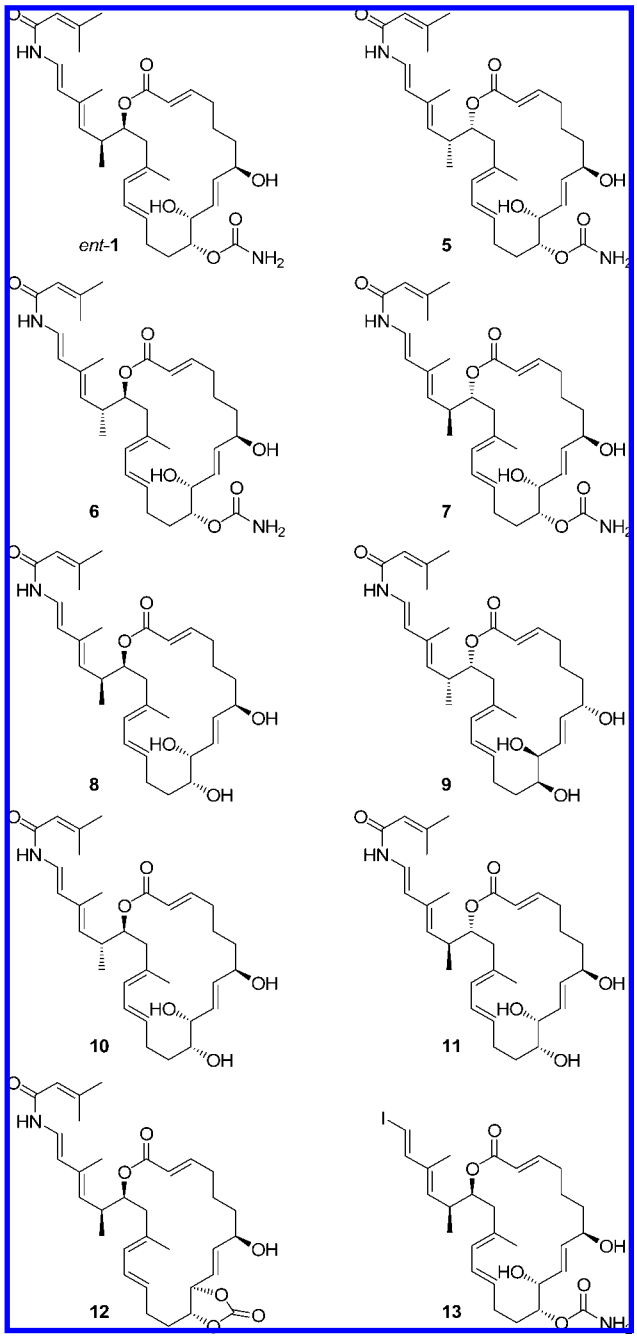


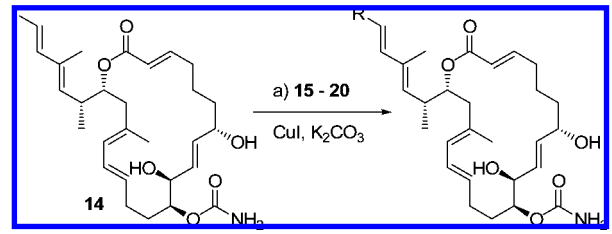
Figure 2. Synthesized palmerolide A diastereoisomers and analogues (*ent*-**1**, **5**−**13**).[4]

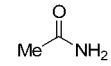
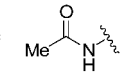
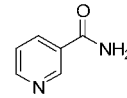
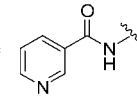
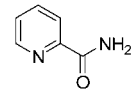
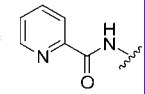
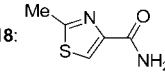
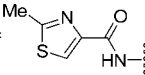
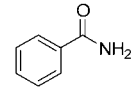
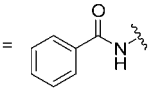
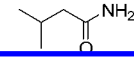
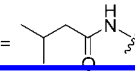
primary amides **15**−**20**[7] to afford palmerolide A analogues **21**−**26** in moderate to good yields (31−54%), as summarized in Table 1.

In addition to the side-chain enamide analogues, a number of macrolide analogues of palmerolide A were designed and pursued by chemical synthesis as shown in Schemes 1 and 2. In these designs we sought single deletions of the hydroxyl groups situated on the 20-membered macrocycle (i.e., **50** and **51**, Scheme 2) as well as the deletion of both hydroxyl groups (i.e., **52**, Scheme 2). For the synthesis of these analogues, and according to our general strategy (Figure 1), fragments vinyl

(7) The primary amides were prepared from the corresponding carboxylic acids [DCC, *N*-hydroxysuccinimide, NH_4OH].

Table 1. Preparation of Palmerolide A Analogues **21**−**26** through Copper-Mediated Coupling Reactions[a]



Entry	Amide	Yield (%)	Product
1	**15**: 	47	**21**: R = 
2	**16**: 	40	**22**: R = 
3	**17**: 	54	**23**: R = 
4	**18**: 	31	**24**: R = 
5	**19**: 	44	**25**: R = 
6	**20**: 	41	**26**: R = 

[a] Reagents and conditions: **15**−**20** (2.0 equiv), CuI (1.5 equiv), K_2CO_3 (5.0 equiv), *N*,*N*′-dimethylethylenediamine (3.0 equiv), DMF, 23 °C, 1 h. DMF = *N*,*N*′-dimethylformamide.

stannane **3b** and carboxylic acid **4b** were required. Their constructions are shown in Scheme 1. Thus, asymmetric Keck allylation[8] of aldehyde **27**[4] under the standard conditions [(*R*)-BINOL, Ti(O*i*-Pr)$_4$; then *n*-Bu_3Sn(allyl)], followed by removal of the TMS group (K_2CO_3, MeOH) from the resulting product, furnished allylic alcohol **28** in 97% overall yield and >90% ee (by Mosher ester analysis).[9] Installation of the carbamate group [$Cl_3C(CO)NCO$, K_2CO_3, 98% yield],[10] followed by manipulation of the acetylenic moiety [(*i*) $AgNO_3$, NBS; (*ii*) Pd(dba)$_2$ cat., *n*-Bu_3SnH],[11] then led to the desired vinyl stannane **3b** (72% overall yield). The carboxylic acid fragment **4b** was prepared from 6-heptene-1-ol (**30**) by a three-step sequence involving oxidation (NMO, TPAP cat., 80% yield),[12] Wittig olefination ($Ph_3P{=}CHCO_2Me$, 72% yield), and saponification (aq. KOH, 90% yield) as shown in Scheme 1.

With all building blocks (**2a**,[4] **3a**,[4] **3b**, **4a**,[4] **4b**) in hand the next task became their union and further elaboration as summarized in Scheme 2. In accordance with our previously established procedures,[4] hydroxy vinyl iodide **2a** was coupled

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(9) For asymmetric Brown allylation of 4-pentynal to give *ent*-**28**, see: (a) White, J. D.; Kim, T.-S.; Nambu, M. *J. Am. Chem. Soc.* **1995**, *117*, 5612–5613.

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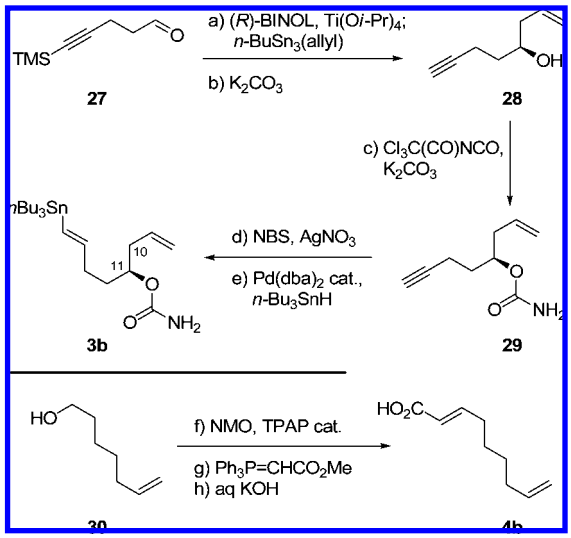
Scheme 1. Synthesis of Vinyl Stannane **3b** and Carboxylic Acid **4b**[a]



[a] Reagents and conditions: (a) (*R*)-BINOL (0.4 equiv), Ti(O*i*-Pr)$_4$ (0.8 equiv), 4 Å molecular sieves, CH_2Cl_2, reflux, 1 h; then **27**, *n*-Bu_3Sn(allyl) (1.1 equiv), CH_2Cl_2, −78 → −20 °C, 24 h; (b) K_2CO_3 (3.0 equiv), MeOH, 23 °C, 7 h, 97% (> 90% ee), two steps; (c) trichloroacetyl isocyanate (2.0 equiv), CH_2Cl_2, 23 °C, 1 h; then K_2CO_3 (3.0 equiv), MeOH, 23 °C, 1 h, 98%; (d) NBS (1.2 equiv), $AgNO_3$ (0.1 equiv), acetone, 23 °C, 1 h, 90%; (e) $Pd(dba)_2$ (0.05 equiv), PPh_3, (0.2 equiv), *n*-Bu_3SnH (2.2 equiv), THF, 30 min, 23 °C, 80% (> 95:5 *E*/*Z* stereoselectivity); (f) NMO (4.5 equiv), TPAP (0.03 equiv), CH_2Cl_2, 23 °C, 1 h, 80%; (g) $Ph_3P{=}CHCO_2Me$ (1.2 equiv), CH_2Cl_2, 23 °C, 8 h, 72%; h) KOH (5.0 equiv), dioxane/H_2O (4:1), 23 °C, 24 h, 90%. TMS = trimethylsilyl; DIP = diisopinocampheyl; NBS = *N*-bromosuccinimide; dba = dibenzylideneacetone; TPAP = tetra-*n*-propylammonium perruthenate; NMO = *N*-methylmorpholine-*N*-oxide.

with carboxylic acids **4a** and **4b** under Yamaguchi conditions[13] (2,4,6-trichlorobenzoyl chloride, Et_3N, 4-DMAP) to afford esters **31** (90% yield) and **32** (90% yield), respectively. Attachment of the vinyl stannane **3b** to ester vinyl iodides **31** and **32**, and vinyl stannane **3a** to **32** through Stille coupling[14] reactions [$Pd(dba)_2$ cat., $AsPh_3$, LiCl] led to hexaenes **33** (56% yield) and **43** (63% yield), and **38** (65% yield), respectively. These products were then converted to the required ring closing metathesis[15] substrates **37** (four steps, 43% overall yield), **42** (four steps, 30% overall yield), and **46** (three steps, 51% overall yield) by standard procedures involving TBAF-induced desilylation (**34**, **39**, **44**), DMP oxidation (**35**, **40**, **45**), Takai olefination[16] ($CrCl_2$, CHI_3; **36**, **41**, **46**), and MOM removal (TMSCl, MeOH; **37**, **42**). Interestingly, while **37** and **42** underwent smooth ring closing metathesis with Grubbs II catalyst [CH_2Cl_2, 0.005 M, 25 °C] to afford the desired macrocycles **47** (78% yield) and **48** (81% yield), respectively, substrate **46** (lacking both allylic hydroxyl groups) failed to afford any macrocyclic product (i.e., **49**) under the same or more forcing conditions, leading instead to decomposition and/or polymerization. These observations suggest further mechanistic investigations in order to clarify the reasons behind the requirement for at least one allylic hydroxyl group for ring closure in these systems. Finally, installation of the enamide moiety onto the growing molecules (**47** and **48**) through the

(13) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.
(14) Yin, L.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133–173.
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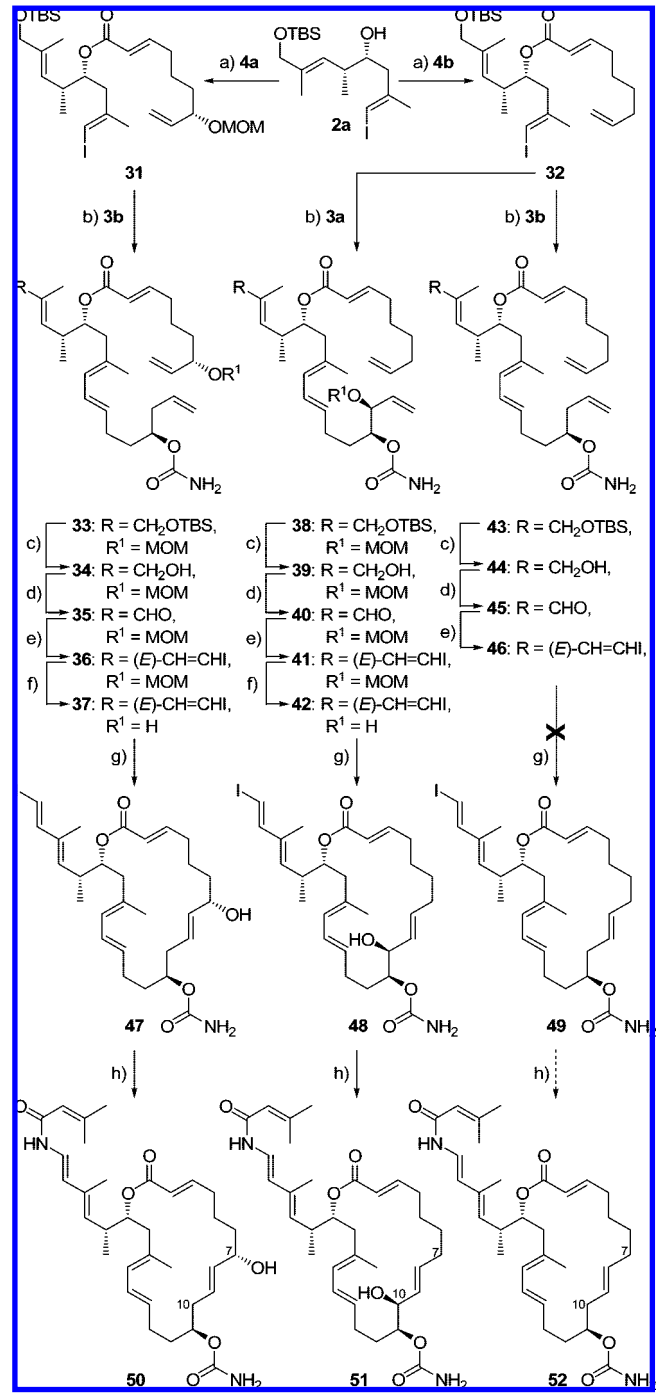
Scheme 2. Synthesis of Palmerolide A Analogues **50** and **51**[a]



[a] Reagents and conditions: (a) 2,4,6-trichlorobenzoyl chloride (1.1 equiv), Et_3N (2.0 equiv), **4a** or **4b** (1.2 equiv), 4-DMAP (1.0 equiv), toluene, 23 °C, 12 h, **31**: 90%; **32**: 90%; (b) **3a** or **3b** (1.2 equiv), $Pd(dba)_2$ (0.25 equiv), $AsPh_3$ (3.0 equiv), LiCl (3.0 equiv), NMP, 23 °C, 12 h, **33**: 56%; **38**: 65%; **43**: 63%; (c) TBAF (1.0 M in THF, 1.2 equiv), THF, 23 °C, 1 h, **34**: 80%; **39**: 80%; **44**: 80%; (d) Dess−Martin periodinane (1.1 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 23 °C, 20 min, **35**: 78%; **40**: 75%; **45**: 80%; (e) $CrCl_2$ (10.0 equiv) CHI_3 (3.0 equiv), THF/dioxane (1:6), 23 °C, 2 h, **36**: 80% (>95:5 *E*/*Z*); **41**: 81% (>95:5 *E*/*Z*); **46**: 80% (>95:5 *E*/*Z*); (f) TMSCl (5.0 equiv), MeOH, 40 °C, 1 h, **37**: 87%; **42**: 62%; (g) Grubbs II cat. (0.05 equiv), CH_2Cl_2, 23 °C, 1 h, **47**: 78%, **48**: 81%; (h) 3-methyl-2-butenamide (2.0 equiv), CuI (1.5 equiv), K_2CO_3 (6.0 equiv), *N*,*N*′-dimethylethylenediamine (3.0 equiv), DMF, 23 °C, 1 h, **50**: 45%, **51**: 40%. 4-DMAP = 4-dimethylamminopyridine; TBAF = tetra-*n*-butylammonium fluoride; NMP = *N*-methylpyrrolidone.

Table 2. Cytotoxicity of Natural and Synthetic Palmerolides against Selected Cancer Cell Lines (GI_{50} Values in μM)[a]

entry	cell line/ compound	UACC-62[c]	MCF-7[c]	SF268[c]	NCI-H460[c]	IA9[d]	PTX22[d]	A8[d]
1	doxorubicin	0.294 ± 0.141	0.056 ± 0.005	0.129 ± 0.048	0.008 ± 0.001	0.033 ± 0.007	0.201 ± 0.049	0.051 ± 0.017
2	Taxol	0.022 ± 0.016	0.006 ± 0.001	0.026 ± 0.011	0.007 ± 0.001	0.006 ± 0.001	0.079 ± 0.001	0.021 ± 0.015
3	natural **1**[b]	0.057 ± 0.007	0.040 ± 0.007	0.030 ± 0.012	0.010 ± 0.001	0.038 ± 0.003	0.066 ± 0.007	0.018 ± 0.003
4	synthetic **1**	0.062 ± 0.001	0.065 ± 0.011	0.048 ± 0.006	0.017 ± 0.004	0.059 ± 0.001	0.073 ± 0.005	0.049 ± 0.004
5	*ent*-**1**	8.077 ± 0.194	6.260 ± 0.174	9.475 ± 0.593	6.589 ± 0.054	>10	>10	8.844 ± 1.301
6	**5**	>10	>10	>10	>10	>10	>10	>10
7	**6**	5.398 ± 0.362	5.415 ± 0.247	6.830 ± 0.077	6.108 ± 0.134	>10	7.052 ± 0.474	8.634 ± 1.860
8	**7**	8.129 ± 1.187	5.567 ± 0.255	7.961 ± 0.584	7.028 ± 0.192	7.131 ± 1.143	5.865 ± 0.590	6.145 ± 0.922
9	**8**	8.768 ± 0.698	7.299 ± 0.430	9.638 ± 0.362	8.664 ± 0.494	>10	>10	8.477
10	**9**	0.322 ± 0.088	0.200 ± 0.026	0.281 ± 0.118	0.075 ± 0.003	0.288 ± 0.017	0.627 ± 0.016	0.083 ± 0.006
11	**10**	>10	>10	>10	>10	>10	>10	>10
12	**11**	>10	8.257 ± 0.047	>10	>10	>10	>10	>10
13	**12**	>10	>10	>10	>10	>10	>10	>10
14	**13**	>10	8.786 ± 0.152	>10	>10	>10	>10	>10
15	**14**	>10	7.025 ± 0.362	>10	6.837 ± 0.223	>10	>10	8.851
16	**21**	>10	>10	>10	7.291 ± 0.137	7.774 ± 1.094	>10	6.700 ± 0.411
17	**22**	0.641 ± 0.000	0.755 ± 0.004	0.592 ± 0.007	0.430 ± 0.047	0.618 ± 0.051	0.741 ± 0.003	0.460 ± 0.042
18	**23**	0.735 ± 0.084	0.796 ± 0.166	0.491 ± 0.132	0.078 ± 0.001	0.378 ± 0.141	0.889 ± 0.029	0.072 ± 0.004
19	**24**	8.822 ± 0.083	7.397 ± 0.262	>10	3.796 ± 0.306	7.944 ± 0.430	>10	3.514 ± 1.379
20	**25**	0.009 ± 0.001	0.007 ± 0.000	0.007 ± 0.001	0.007 ± 0.000	0.009 ± 0.001	0.039 ± 0.002	0.006 ± 0.000
21	**26**	0.067 ± 0.000	0.071 ± 0.008	0.054 ± 0.000	0.061 ± 0.000	0.067 ± 0.002	0.081 ± 0.006	0.057 ± 0.001
22	**50**	6.979 ± 0.531	7.585 ± 0.252	8.764 ± 0.315	6.396 ± 0.106	7.135 ± 0.667	8.062 ± 0.037	6.691 ± 0.439
23	**51**	0.063 ± 0.001	0.074 ± 0.000	0.060 ± 0.004	0.055 ± 0.002	0.072 ± 0.001	0.076 ± 0.000	0.061 ± 0.013

[a] Antiproliferative effects of tested compounds against human tumor cell lines and drug-resistant cell lines in a 48 h growth inhibition assay using the sulforhodamine B staining methods. Human cancer cell lines: breast (MCF-7), lung (NCI-H460), CNS (SF268), melanoma (UACC62), ovarian (IA9), and its drug-resistant mutants PTX22 (Taxol-resistant) and A8 (epothilone-resistant). Growth inhibition of 50% (GI_{50}) is calculated as the drug concentration which caused a 50% reduction in the net protein increase in control cells during drug incubation. GI_{50} values for each compound are given in μM and represent the mean of 2−5 independent experiments ± standard error of the mean. [b] A natural sample of **1** was kindly provided by Professor B. J. Baker, University of South Florida, Tampa. [c] These cell lines were provided by the National Cancer Institute (NCI), Division of Cancer Treatment and Diagnosis (DCTD). [d] These cell lines were provided by Professor Paraskevi Giannakakou, Weill Medical College of Cornell University.

developed copper-catalyzed protocol allowed access to palmerolide A analogues **50** (45% yield) and **51** (40% yield), respectively, while analogue **52** remained elusive through this particular strategy.

The synthesized compounds were tested against a panel of cancer cells, including breast (MCF-7), melanoma (UACC-62), CNS (SF268), lung (NCI-H460), ovarian (1A9), Taxol-resistant ovarian (PTX22),[17] and epothilone-resistant ovarian (A8)[18] cells using doxorubicin, Taxol, and natural palmerolide A (**1**) as standards; the results are summarized in Table 2. Both natural and synthetic palmerolide A (**1**) exhibited the same potent activity against all cell lines tested, whereas *ent*-**1** was at least 100-fold less active than **1**. Simultaneously inverting the stereochemistry at C-7/C-10/C-11 (compound **5**), C-7/C-10/C-11/C-19 (compound **6**), and C-7/C-10/C-11/C-20 (compound **7**) resulted in significant loss of activity. However, removing the carbamate group from the C-11 oxygen of palmerolide A (**1**) (compound **9**) resulted in a *ca*. 5-fold decrease of activity across most of the cell lines, whereas the same change in *ent*-**1** (compound **8**) did not have much effect on its potency. Removing the carbamate group from diastereoisomers **6** and **7** (compounds **10** and **11**) did not have a significant effect on the potency of these analogues. The carbonate derivative (compound **12**) of decarbamated *ent*-**1** was also devoid of significant activity and so were the vinyl iodide precursors of *ent*-**1** and **1** (compounds **13** and **14**). These findings point to the importance of the enamide functionality for the biological activities of palmerolide A.

Some interesting trends were observed upon changing the enamide appendage. Thus, substituting the isopropene moiety of palmerolide A with a methyl group (compound **21**) resulted in more than a 100-fold loss of activity, whereas polar groups such as those embedded in pyridine enamide analogues **22** and **23** and thiazole analogue **24** retained some activity. A rather dramatic reversal of this trend, however, occurred when the enamide side chain was restored to a nonpolar aromatic system as in compound **25** which exhibited almost a 10-fold increase in potency from that of palmerolide A (**1**) against several of the cells tested. Interestingly, when the isopropene substituent on the enamide moiety of palmerolide A was changed to its saturated counterpart (compound **26**), its potency remained more or less intact. Finally, it was intriguing to observe that while analogue **50** (lacking the C-10 hydroxyl group) has lost significant activity across the entire panel of cell lines tested, analogue **51** (missing the C-7 hydroxyl group) exhibited equipotent activity to palmerolide A. Considering the easier access through chemical synthesis to such deoxygenated analogues, than the natural substance, this finding is valuable and path pointing for future explorations within the field.

Conclusion

The described chemistry rendered several palmerolide A analogues for biological evaluation, allowing the first structure activity relationships (SARs) of this newly discovered and promising antitumor agent to be elucidated. These early conclusions point the way for further, more focused studies aiming at the design and synthesis of even more potent and selective palmerolide A analogues as biological tools and potential drug candidates.

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Supporting Information Available: Experimental procedures and compound characterization (PDF, CIF). This material is available free of charge via Internet at http://pubs.acs.org.

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