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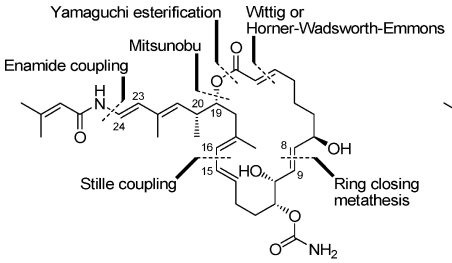
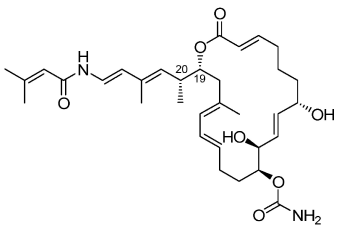
J. Am. Chem. Soc., **2008**, 130 (11), 3633-3644 • DOI: 10.1021/ja710485n



1: palmerolide A
(originally proposed structure)



ent-(19-*epi*-20-*epi*-**1**): palmerolide A
(revised structure)

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Total Synthesis of the Originally Proposed and Revised Structures of Palmerolide A and Isomers Thereof

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Abstract: Palmerolide A is a recently disclosed marine natural product possessing striking biological properties, including potent and selective activity against the melanoma cancer cell line UACC-62. The total syntheses of five palmerolide A stereoisomers, including the originally proposed (**1**) and the revised [*ent*-(19-*epi*-20-*epi*-**1**)] structures, have been accomplished. The highly convergent and flexible strategy developed for these syntheses involved the construction of key building blocks **2**, 19-*epi*-**2**, 20-*epi*-**2**, *ent*-**2**, **3**, *ent*-**3**, **4**, and *ent*-**4**, and their assembly and elaboration to the target compounds. For the union of the building blocks, the Stille coupling reaction, Yamaguchi esterification, Horner−Wadsworth−Emmons olefination, and ring-closing metathesis reaction were employed, the latter being crucial for the stereoselective formation of the macrocycle of the palmerolide structure. The Horner−Wadsworth−Emmons olefination and the Yamaguchi lactonization were also investigated and found successful as a means to construct the palmerolide macrocycle. The syntheses were completed by attachment of the enamide moiety through a copper-catalyzed coupling process.

Introduction

Treacherous habitats often harbor creatures that produce secondary metabolites possessing extraordinary molecular architectures and distinct biological properties that contribute to the organisms' survival and continuing existence. Palmerolide A (**1**, originally proposed structure, Figure 1) is such a compound. Isolated from circumpolar tunicate *Synoicum adareanum* collected from around Anvers Island on the Antarctic Peninsula, palmerolide A was reported by the Baker group in 2006.[1] This naturally occurring substance was found to exhibit potent cytotoxicities against the melanoma cancer cell line UACC-62 (LC_{50} of 18 nM). Strikingly, palmerolide A demonstrated only modest activity against colon cancer cell line HCC-2998 ($LC_{50} = 6.5\ \mu M$) and renal cancer cell line RXF 393 ($LC_{50} = 6.5\ \mu M$) and virtually no activity against all other cell lines tested within the 60 cell line panel of the National Cancer Institute (NCI). This remarkable 10^3 in vitro selectivity index for the melanoma cells over the most sensitive cell lines tested prompted further evaluation of the compound, which revealed its activity in the NCI's hollow fiber assay and its potent inhibitory action against vacuolar ATPase ($IC_{50} = 2$ nM). This biological profile correlates well with other enamide-containing V-ATPase inhibitors.[2]

The intriguing structural motifs and biological properties of palmerolide A prompted synthetic studies that culminated first in its structural revision through the total synthesis of its enantiomer (De Brabander et al.)[3a] and then in its total synthesis (Nicolaou et al.).[4] In this article, we describe in detail our work in the area that resulted in the total syntheses of the originally proposed structure of palmerolide A (**1**), the revised structure *ent*-(19-*epi*-20-*epi*-**1**), and the palmerolide A isomers 19-*epi*-**1**, 20-*epi*-**1**, and 19-*epi*-20-*epi*-**1** (Figure 1).

Results and Discussion

Retrosynthetic Analysis. In view of our intended structural and biological investigations and to assess the feasibility of a variety of options for closing the palmerolide A macrocycle, we opted for a modular and flexible approach as we pondered its retrosynthetic analysis. The originally proposed palmerolide A structure (**1**) is characterized by a 20-membered macrolide system containing four *E*-olefinic bonds, two of which were conjugated to each other. The macrocycle of the molecule is adorned with four stereogenic centers carrying two hydroxyl groups, a carbamate moiety, and a side chain, itself featuring an additional stereogenic center and a conjugated enamide. Shown in Scheme 1 is our general retrosynthetic analysis encompassing the various disconnections we applied to the molecule, which led to the three key building blocks required for its construction, fragments **2** ($C_{16}-C_{23}$), **3** (C_9-C_{15}), and **4** (C_1-C_8). Relying on a Stille coupling reaction, an enamide coupling

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10.1021/ja710485n CCC: $40.75

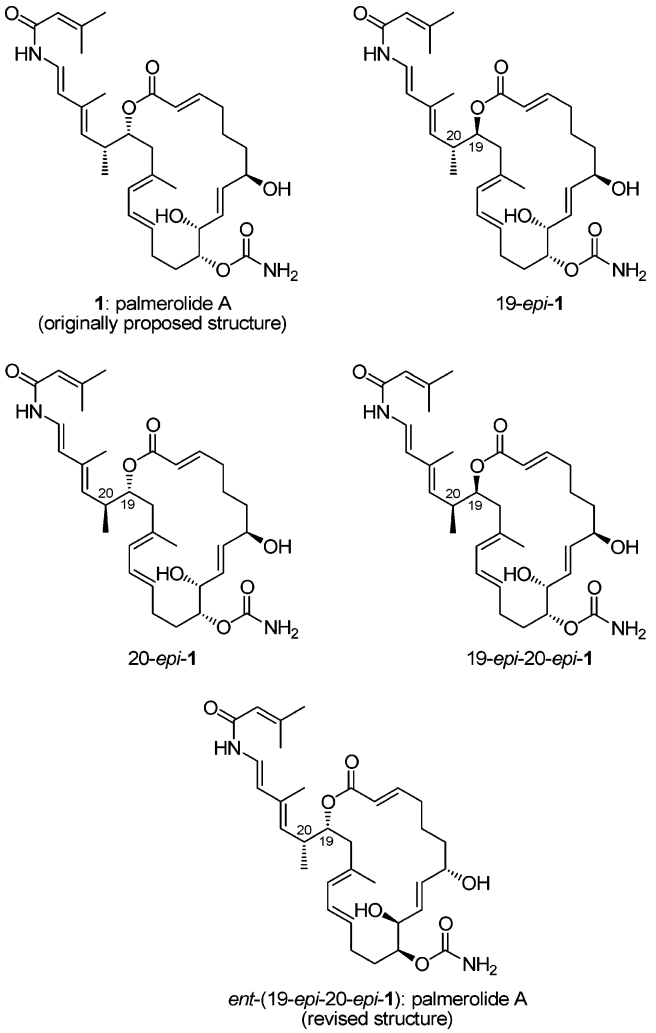
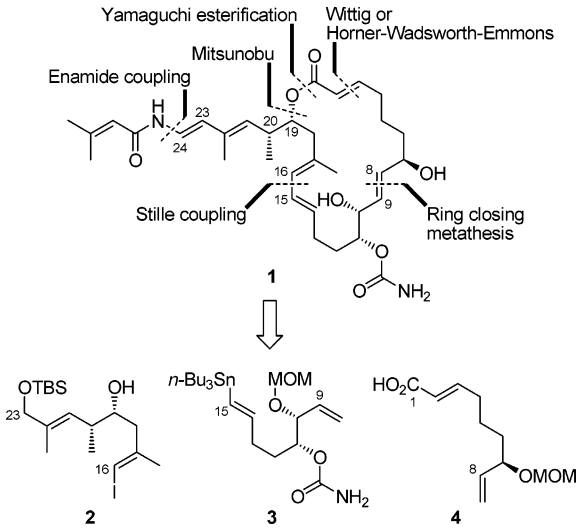


Figure 1. Structures of palmerolide A isomers synthesized in this work.

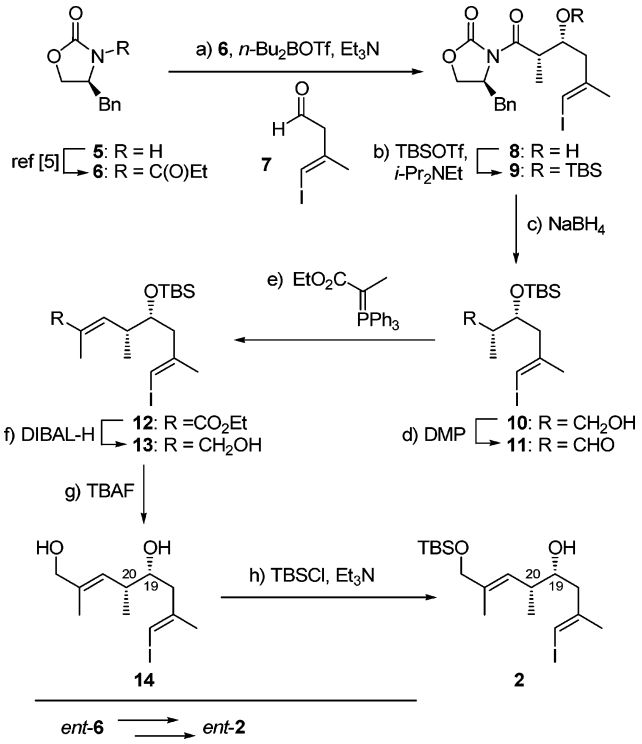
Scheme 1. General Retrosynthetic Analysis of Originally Proposed Structure for Palmerolide A (**1**) and Building Blocks **2**, **3**, and **4**[a]



[a] MOM = methoxymethyl; TBS = *tert*-butyldimethylsilyl.

reaction, a Yamaguchi esterification, a Wittig or Horner−Wadsworth−Emmons olefination, and an olefin metathesis, this analysis offered the opportunity to devise one or more highly convergent strategies toward the target molecule and related

Scheme 2. Construction of $C_{16}-C_{23}$ Vinyl Iodide Fragments **2** and *ent*-**2**[a]



[a] Reagents and conditions: (a) **7** (2.5 equiv), *n*-Bu_2BOTf (1.0 M in CH_2Cl_2, 1.2 equiv), Et_3N (1.0 equiv), CH_2Cl_2, −78 °C, 12 h, 46% (>95% de); (b) TBSOTf (1.2 equiv), *i*-Pr_2NEt (1.5 equiv), CH_2Cl_2, 0 °C, 30 min, 84%; (c) $NaBH_4$ (5.0 equiv), THF/H_2O (5:1), 0 → 23 °C, 3 h, 66%; (d) DMP (1.2 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 23 °C, 30 min; (e) PPh_3=C(Me)CO_2Et (3.0 equiv), CH_2Cl_2, 23 °C, 12 h, 56% for the two steps; (f) DIBAL-H (1.0 M in toluene, 2.5 equiv), CH_2Cl_2, −78 °C, 30 min, 80%; (g) TBAF (1.0 M in THF, 1.5 equiv), THF, reflux, 2 h, 85%; (h) TBSCl (1.2 equiv), Et_3N (1.5 equiv), 4-DMAP (0.2 equiv), CH_2Cl_2, 0 → 23 °C, 2 h, 92%. Bn = benzyl, THF = tetrahydrofuran, OTf = trifluoromethanesulfonate, DMP = Dess−Martin periodinane, DIBAL-H = diisobutylaluminum hydride, TBAF = tetra-*n*-butylammonium fluoride, 4-DMAP = 4-dimethylaminopyridine.

structures. Furthermore, the macrocycle could, in principle, be forged by one of four different reactions as outlined in Scheme 1. It was our intention to explore as many of these possibilities as possible once we had secured the required building blocks (**2**−**4**), whose constructions were also devised with optimum flexibility in mind with regards to stereochemical control.

Construction of Building Blocks. Having defined the required building blocks, their constructions began in earnest. Two syntheses of vinyl iodide **2** were developed. The first route (Scheme 2) began with the boron-mediated *syn*-aldol reaction between ethyl ketone **6**, derived from (*S*)-(+)-4-benzyl-2-oxazolidinone (**5**) (*n*-BuLi, EtCOCl, 92% yield),[5] and vinyl iodide aldehyde **7** (prepared in two steps from 3-butyn-1-ol, 81% yield)[6] under the standard conditions (*n*-Bu_2BOTf-Et_3N)[5] to afford *β*-hydroxy ketone **8** in 46% yield [>95% de, by ^1H NMR (600 MHz) analysis] as shown in Scheme 2. The rather modest yield in this reaction was attributed to the sensitivity of aldehyde **7** under the reaction conditions, and whereas a much improved yield was obtained under $TiCl_4$/(−)-sparteine-mediated

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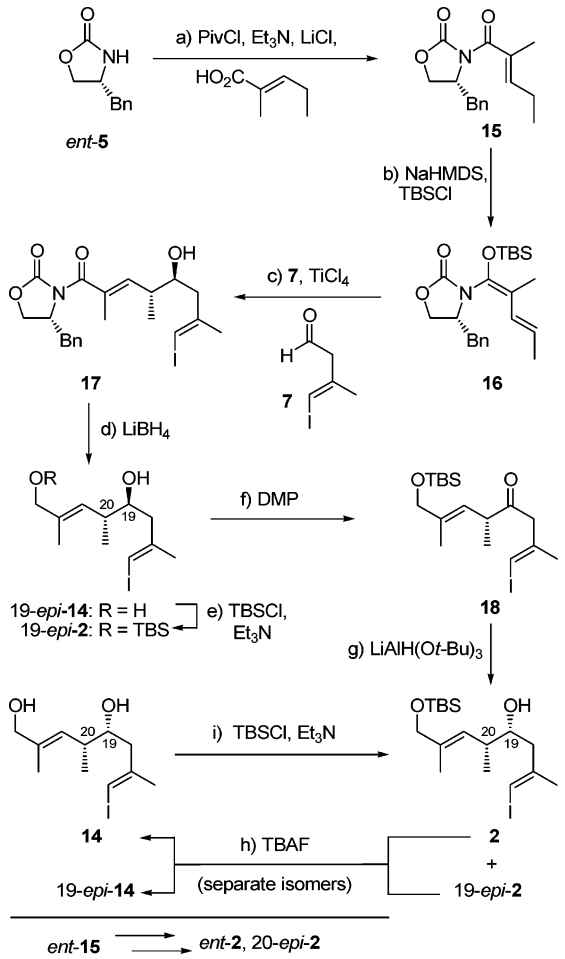
conditions,[7] a diastereo-random mixture (ca. 1:1) was observed under the reaction conditions. Protection of β-hydroxy ketone **8** as its TBS ether (TBSOTf, *i*-Pr_2NEt, **9**, 84% yield), followed by reductive removal of the oxazolidinone chiral auxiliary ($NaBH_4$, 66% yield) and oxidation of the resulting primary alcohol (**10**) with DMP (for abbreviations of reagents and protecting groups, see legends in schemes)[8] afforded aldehyde **11**. Extension of this aldehyde through Wittig reaction [PPh_3=C(Me)CO_2Et, 56% yield for the two steps from **10**] followed by DIBAL-H reduction of the resulting enoate (**12**) furnished allylic alcohol **13** (80% yield), whose desilylation (TBAF, 85% yield)/resilylation (TBSCl, Et_3N, 92% yield) led to the targeted vinyl iodide **2**.

Alternatively, application of a vinylogous aldol reaction on aldehyde **7** offered a more direct and expedient entry into the $C_{16}-C_{23}$ backbone of vinyl iodide **2** and its isomers, as shown in Scheme 3. Thus, the reaction of imide **15** [prepared by unifying (*R*)-(+)-4-benzyl-2-oxazolidinone (*ent*-**5**) and *E*-2-methyl-2-pentenoic acid in the presence of PivCl, Et_3N, and LiCl, 91% yield] with NaHMDS followed by interception of the transient enolate with TBSCl afforded dienol silyl ether **16** in 95% yield and as a single geometrical isomer. The vinylogous aldol reaction of **16** with aldehyde **7** under the conditions described by Kobayashi[9] ($TiCl_4$) yielded hydroxy vinyl iodide **17** in 83% yield and in a 18:1 diastereomeric ratio (by ^1H NMR spectroscopic analysis, 600 MHz). Reductive cleavage of the oxazolidinone moiety from **17** ($LiBH_4$, 93% yield) afforded diol 19-*epi*-**14**, whose monosilylation (TBSCl, Et_3N, 94%) yielded vinyl iodide 19-*epi*-**2**. An oxidation (DMP, 93% yield) / reduction [LiAlH(O*t*-Bu)$_3$, 91% yield] sequence also allowed entry into vinyl iodide **2** through the intermediacy of ketone **18**. The reduction step of this sequence proceeded in high yield but furnished a mixture (ca. 3:1) of **2** and 19-*epi*-**2**, the two isomers yielding to chromatographic separation after desilylation with TBAF (87% yield). The individual diols (**14** and 19-*epi*-**14**) were then silylated at the primary position (TBSCl, Et_3N, 92% yield) to afford pure vinyl iodides **2** and 19-*epi*-**2**. A similar oxidation/reduction sequence could also be performed on alcohol **17** to obtain a C_{19} mixture of stereoisomers albeit with no selectivity (ca. 1:1 ratio). Starting with *ent*-**6** and *ent*-**15** and following a similar sequence as that shown in Schemes 2 and 3, the preparations of *ent*-**2** and 20-*epi*-**2** were also accomplished, thus completing the set of all four stereoisomers of vinyl iodide **2**.

The vinyl stannane **3** and its enantiomer, *ent*-**3**, were prepared from TMS acetylene aldehyde **19** as summarized in Scheme 4. The chosen route relied on Brown's hydroxy-crotylation technology.[10] Thus, treatment of aldehyde **19** (prepared from 4-pentyn-1-ol in two steps, 90% yield)[11] with in situ-generated [(*Z*)-γ-(methoxymethoxy)allyl]-(−)-diisopinocampheylborane, [(−)-**20**], (from methoxymethyl allyl ether, *s*-BuLi, (−)-Ipc_2-BOMe and $BF_3{\cdot}OEt_2$) in THF at −78 to 23 °C afforded, upon desilylation (K_2CO_3, MeOH), hydroxy acetylene **21** in good

Scheme 3. Alternative Synthesis of $C_{16}-C_{23}$ Vinyl Iodide Fragments **2** and *ent*-**2**, and Construction of Anti Isomers 19-*epi*-**2** and 20-*epi*-**2**.[a]



[a] Reagents and conditions: (a) *E*-2-methyl-2-pentenoic acid (1.0 equiv), Et_3N (2.5 equiv), PivCl (1.0 equiv), CH_2Cl_2, −78 → 23 °C, 1 h; then *ent*-**5**, LiCl (1.5 equiv), CH_2Cl_2, 23 °C, 12 h, 91%; (b) NaHMDS (1.5 equiv), TBSCl (2.0 equiv), THF, −78 °C, 1.5 h, 95%; (c) **7** (2.0 equiv), $TiCl_4$ (1.0 equiv), CH_2Cl_2, −78 °C, 19 h, 83% (18:1 dr); (d) $LiBH_4$ (1.5 equiv), Et_2O/MeOH (20:1), 0 °C, 4 h, 93%; (e) TBSCl (1.2 equiv), Et_3N (1.5 equiv), 4-DMAP (0.2 equiv), CH_2Cl_2, 0 → 23 °C, 2 h, 94%; (f) DMP (1.2 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 23 °C, 20 min, 93%; (g) LiAlH(O*t*-Bu)$_3$ (1.0 M in THF, 3.0 equiv), LiI (5.0 equiv), Et_2O, −78 °C, 1 h, 91% (ca. 3:1 mixture of *syn*/*anti* diastereomers); (h) TBAF (1.0 M in THF, 1.2 equiv), THF, 23 °C, 1 h, **14**: (65%), 19-*epi*-**14**: (22%); (i) TBSCl (1.2 equiv), Et_3N (1.5 equiv), 4-DMAP (0.2 equiv), CH_2Cl_2, 0 → 23 °C, 2 h, 92%. Piv = trimethylacetyl, NaHMDS = sodium hexamethyldisilazide.

overall yield (78% for the two steps) and excellent diastereoselectivity [>95% de, ^1H NMR spectroscopic analysis (600 MHz); >90% ee, ^1H NMR (600 MHz) analysis of the corresponding *R* and *S* Mosher esters].[12] Attachment of the carbamate group [$Cl_3CC(O)NCO$, K_2CO_3, MeOH, 100% yield][13] onto alcohol **21** followed by treatment with NBS and $AgNO_3$ furnished bromide **23** (90% yield) through acetylenic **22**. Finally, exposure of **23** to *n*-Bu_3SnH in the presence of catalytic amounts of $Pd(dba)_2$ led to the targeted fragment **3** in 77% yield. We chose to adopt this two-step procedure[14] to introduce the vinyl stannane moiety into acetylene **22** (and later alkyne intermediates) as our initial attempts to directly hydrostannate acetylene

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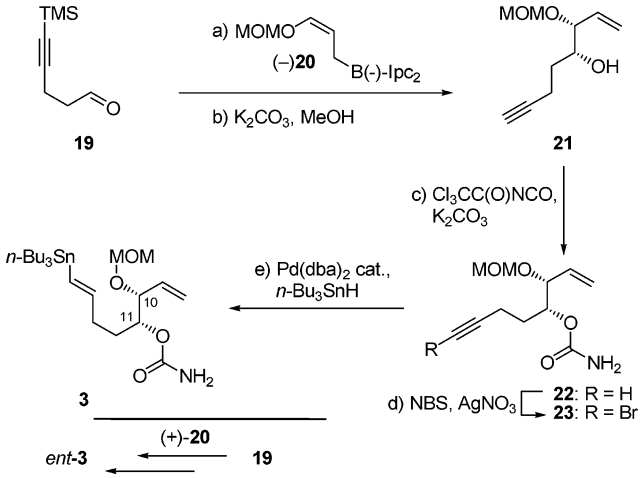
Scheme 4. Construction of C_9-C_{15} Vinyl Stannane Fragments **3** and *ent*-**3**[a]

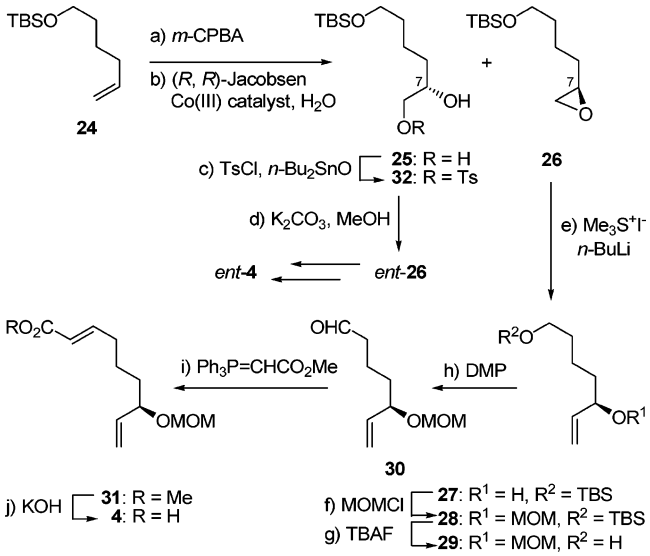


[a] Reagents and conditions: (a) Methoxymethyl allyl ether (1.3 equiv), *s*-BuLi (1.0 equiv), THF, −78 °C, 30 min; then (−)-Ipc_2BOMe (1.0 M in THF, 1.0 equiv), −78 °C, 1 h; then $BF_3{\cdot}Et_2O$ (1.25 equiv), **19** (1.0 equiv), −78 → 23 °C, 15 h; (b) K_2CO_3 (3.0 equiv), MeOH, 23 °C, 7 h, 78% for the two steps from **19**; (c) trichloroacetyl isocyanate (3.0 equiv), CH_2Cl_2, 23 °C, 1 h; then K_2CO_3 (3.0 equiv), MeOH, 23 °C, 1 h, 100%; (d) NBS (1.1 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, 23 °C, 1 h, 77%. Ipc = isopinocampheyl, NBS = *N*-bromosuccinimide, DBA = dibenzylideneacetone.

22 [$Pd(PPh_3)_2Cl_2$, *n*-Bu_3SnH] led to a mixture of regioisomeric stannanes. In a similar fashion, *ent*-**3** was prepared starting with **19** and employing (+)-Ipc_2BOMe as shown in Scheme 4.

Fragments **4** and *ent*-**4** were prepared from the TBS-protected 5-hexene-1-ol (**24**) through the application of a Jacobsen hydrolytic kinetic resolution[15a] as shown in Scheme 5. Thus, *m*-CPBA-mediated epoxidation of **24** (90% yield), followed by exposure of the resulting racemic epoxide to 5 mol % of (*R*,*R*)-*N*,*N*′-bis(3,5-di-*t*-butylsalicylidene)-1,2-cyclohexanediaminato-(2-)]cobalt(II) (Jacobsen catalyst), acetic acid (0.01 equiv), and H_2O (0.55 equiv) in CH_2Cl_2 led to the smooth formation of enantiomerically enriched diol **25** [43% yield, >90% ee by measurement of its optical rotation and that of later intermediates *ent*-**26** and *ent*-**27**, and Mosher ester ^1H NMR (600 MHz) analysis of *ent*-**27**, vide infra] and epoxide **26** [47% yield, >90% ee by Mosher ester ^1H NMR (600 MHz) analysis of **27**, vide infra].[15b] The diol was converted to the primary tosylate (TsCl, *n*-Bu_2SnO, **32**, 78% yield),[16] and thence to epoxide *ent*-**26** (K_2CO_3, MeOH, 82% yield). Epoxide **26** was reacted with the sulfur ylide derived from $Me_3S^+I^-$ (*n*-BuLi)[17] to afford hydroxy olefin **27** (90% yield), which was protected as a MOM ether (MOMCl, *i*-Pr_2NEt, 85% yield) and desilylated (TBAF, 95% yield), leading to primary alcohol **29** via intermediate **28**. Finally, DMP oxidation of **29** furnished aldehyde **30** (95% yield), whose Wittig reaction with $PPh_3{=}CHCO_2Me$ (90% yield) led, upon saponification (KOH, 85% yield) to carboxylic acid fragment **4**. Following a similar sequence, epoxide *ent*-**26** was converted to *ent*-**4** (Scheme 5).

Scheme 5. Construction of C_1-C_8 Carboxylic Acid Fragments **4** and *ent*-**4**[a]



[a] Reagents and conditions: (a) *m*-CPBA (1.3 equiv), $NaHCO_3$ (2.0 equiv), CH_2Cl_2, 0 → 23 °C, 2 h, 90%; (b) (*R*,*R*)-*N*,*N*′-bis(3,5-di-*t*-butylsalicylidene)-1,2-cyclohexanediaminato(2-)]cobalt (II) (5 mol %), AcOH (0.01 equiv), H_2O (0.55 equiv), CH_2Cl_2, 0 → 23 °C, 24 h, **25**: (43%, >90% ee), **26**: (47%, >90% ee); (c) *p*-TsCl (1.0 equiv), *n*-Bu_2SnO (0.2 equiv), Et_3N (1.0 equiv), CH_2Cl_2, 23 °C, 2 h, 78%; (d) K_2CO_3 (1.5 equiv), $MeOH/CH_2Cl_2$ (10:1), 0 → 23 °C, 2 h, 82%; (e) $Me_3S^+I^-$ (4.0 equiv), *n*-BuLi (1.6 M in THF, 5.8 equiv), THF, −30 → 23 °C, 5 h, 90%; (f) MOMCl (4.0 equiv), *i*-Pr_2NEt (2.0 equiv), CH_2Cl_2, 0 → 23 °C, 6 h, 85%; (g) TBAF (1.0 M in THF, 1.2 equiv), THF, 23 °C, 2 h, 95%; (h) DMP (1.5 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 23 °C, 2 h, 95%; (i) $Ph_3P{=}CHCO_2Me$ (1.0 equiv), CH_2Cl_2, 23 °C, 16 h, 90%; (j) KOH (5.0 equiv), dioxane/H_2O (4:1), 23 °C, 24 h, 85%. *m*-CPBA = *meta*-chloroperoxybenzoic acid; *p*-TsCl = *para*-toluenesulfonyl chloride.

Assembly of Building Blocks and Completion of the Total Synthesis of the Originally Proposed Structure of Palmerolide A. With all of the required building blocks in hand, we then proceeded to assemble them toward the targeted structure that was originally proposed for palmerolide A (**1**). From all of the possible strategies, we first opted to pursue the one involving the olefin metathesis[18] reaction to construct the macrocycle of the molecule. To that end, and as is shown in Scheme 6, vinyl iodide **2** and vinyl stannane **3** were coupled under Stille conditions[19] [$Pd(dba)_2$ catalyst, $AsPh_3$, LiCl] to afford tetraene **33** in 67% yield. Presented with its free hydroxyl group at C_{19}, the latter compound was esterified with carboxylic acid **4** under Yamaguchi conditions[20] (2,4,6-trichlorobenzoyl chloride, Et_3N, 4-DMAP) furnishing **34** in 61% yield. The same intermediate **34** could be reached from intermediates **2**−**4** by reversing the order of their coupling (i.e., **2** + **4**; then **3**), a sequence that proceeded through intermediate **35**, which gave a higher overall yield (59% for the two steps). From hexaene ester **34**, and on the basis of what we learned in scouting the road ahead, we decided at this juncture to follow the sequence depicted in Scheme 6 toward our final destination. Thus, desilylation of **34** (TBAF, 78% yield) followed by DMP oxidation of the resulting alcohol (**36**, 84% yield) led to aldehyde **37**, whose Takai iodo-

(15) (a) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307−1315. (b) Preparation of *ent*-**26** using an identical procedure has been previously reported: Myers, A.; Lanman, B. A. *J. Am. Chem. Soc.* **2002**, *124*, 12969−12971.
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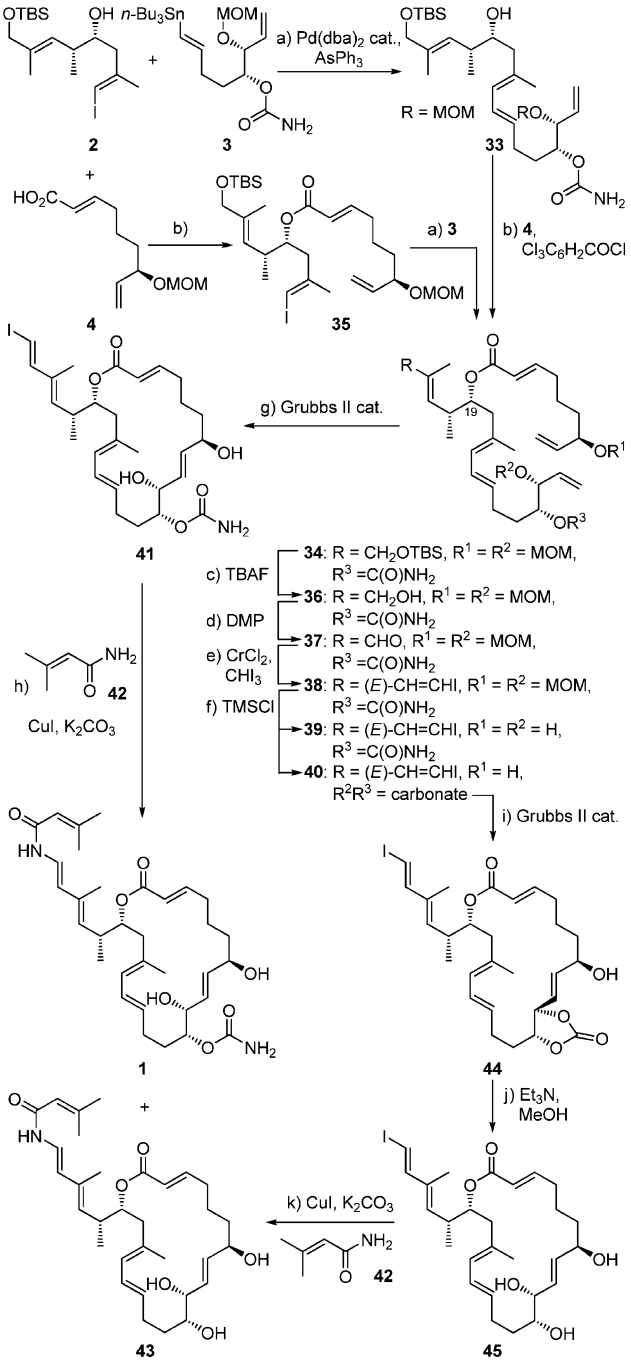
(17) Alcaraz, L.; Harnett, J. J.; Mioskowski, C.; Martel, J. P.; Le Gall, T.; Shin, D.-S.; Falck, J. R. *Tetrahedron Lett.* **1994**, *35*, 5449−5452.
(18) (a) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117−7140. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490−4527. (c) Gradillas, A.; Perez-Castells, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6086−6101.
(19) Yin, L.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133−173.
(20) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993.

Scheme 6. Coupling of Fragments **2**, **3**, and **4**, and Completion of the Total Synthesis of the Originally Proposed Structure of Palmerolide A (**1**) and Its Decarbamated Version **43**[a]



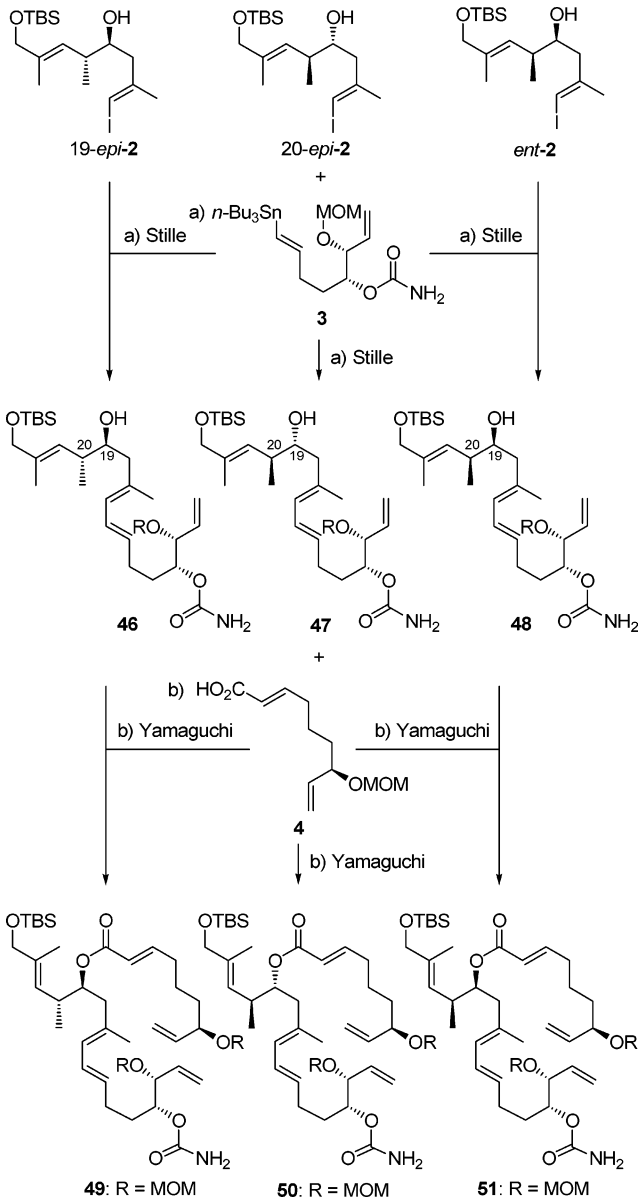
[a] Reagents and conditions: (a) $Pd(dba)_2$ (0.15 equiv), $AsPh_3$ (3.0 equiv), LiCl (3.0 equiv), NMP, 23 °C, 12 h, **33**: (67%, via **2**+**3**), **34**: (67%, via **3**+**35**); (b) 2,4,6-trichlorobenzoyl chloride (1.1 equiv), Et_3N (1.5 equiv), **4** (1.1 equiv), 4-DMAP (1.1 equiv), 23 °C, 12 h, **34**: (61%, via **4**+**33**), **35**: (88%, via **2**+**4**); (c) TBAF (1.0 M in THF, 1.5 equiv), THF, 23 °C, 2 h, 78%; (d) DMP (1.2 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 23 °C, 30 min, 84%; (e) $CrCl_2$ (10.0 equiv), CHI_3 (3.0 equiv), THF/dioxane (1:6), 23 °C, 2 h, 80% (>95:5 *E*/*Z*); (f) TMSCl (10 equiv), MeOH, 40 °C, 1 h, **39**: (67%), **40**: (10%); (g) Grubbs II catalyst (0.05 equiv), CH_2Cl_2 (c = 0.005 M), 23 °C, 1 h, 81% (>95:5 *E*/*Z*); (h) **42** (2.0 equiv), CuI (1.5 equiv), K_2CO_3 (6.0 equiv), *N*,*N*′-dimethylethylenediamine (3.0 equiv), DMF, 23 °C, 1 h, **1**: (31%), **43**: (<5%), **41**: (10%); (i) Grubbs II catalyst (0.2 equiv), CH_2Cl_2 (c = 0.005 M), 23 °C, 4 h, 72% (>95:5 *E*/*Z*); (j) Et_3N/MeOH/H_2O (1:5:1), 40 °C, 4 h, 57%; (k) **42** (2.0 equiv), CuI (1.5 equiv), K_2CO_3 (5.0 equiv), *N*,*N*′-dimethylethylenediamine (2.0 equiv), DMF, 23 °C, 1 h, 45%. NMP = *N*-methylpyrrolidone; DMF = *N*,*N*′-dimethylformamide, TMS = trimethylsilyl.

olefination[21] ($CrCl_2$, CHI_3, 80% yield) gave iododiene **38**. The obligatory removal of both MOM protecting groups prior to the ring-closing metathesis (the ring-closing metathesis did not proceed as we expected with the MOM groups on) proved challenging but eventually was achieved satisfactorily under the influence of TMSCl[22] to afford diol **39** (67% yield), together with small amounts of the cyclic carbonate byproduct **40** (10%). With precursor **39** in hand, we were pleased to find that its exposure to Grubbs II catalyst[18a] in CH_2Cl_2 (c = 0.005 M) at ambient temperature led to the formation of the much anticipated macrocycle **41** as a single geometrical isomer and in 81% yield. The *E* geometry of the newly generated double bond was proven by ^{1}H NMR spectroscopy ($J_{8,9}$ = 15.5 Hz). Both the requirement of the free hydroxyl group on the ring-closing metathesis substrate and the stereoselectivity of the ring closure are interesting. We have no clear explanation for these observations except for a speculation regarding coordination phenomena. The final hurdle before arrival at the targeted structure was overcome when dienyl iodide **41** was successfully coupled to amide **42** under the conditions developed by Buchwald et al.[23] (CuI, Cs_2CO_3, and *N*,*N*′-dimethylethylenediamine), furnishing the originally proposed structure of palmerolide A (**1**) in 24% yield, together with decarbamated **43** (10% yield) and recovered starting material (**41**, 36%). Decarbamated **43** could be significantly reduced by exchanging Cs_2CO_3 with rigorously dried (by heating under vacuum) K_2CO_3, thereby furnishing **1** with an improved yield of 31% and trace amounts of **43** (<5%). Decarbamated **43** was also accessed via the ring-closing olefin metathesis of cyclic carbamate **40** (Grubbs II catalyst, 72% yield), followed by hydrolysis of the resulting cyclic carbamate **44** ($Et_3N-MeOH-H_2O$, 57% yield) and enamide coupling (**42**, CuI, K_2CO_3, *N*,*N*′-dimethylethylenediamine, 45% yield). Whereas **43** may serve as an interesting analog for biological evaluation, the palmerolide A structure synthesized did not exhibit the same spectroscopic data as those reported in the isolation article.[1] At this juncture we became convinced that the originally proposed structure for palmerolide A (**1**) was incorrect.

Total Syntheses of Alternative Palmerolide A Structures 19-*epi*-20-*epi*-1, 19-*epi*-1, and 20-*epi*-1. Faced with the nonidentity of synthetic **1** with the natural substance, we revisited the original publication disclosing the structure of palmerolide A in search of alternative structures that may fit the reported spectroscopic data.[1] Whereas in that study, Mosher ester analysis suggested the absolute configuration at C_7, C_{10}, and C_{11}, the stereochemical assignments of C_{19} and C_{20} were deduced indirectly on the basis of NOE correlations for the protons situated on the chain spanning C_{11} to C_{21}. Our analysis of the Baker spectroscopic data based on manual molecular modeling suggested that 19-*epi*-20-*epi*-**1** [possessing the 19(*S*),20(*S*) configuration, Figure 1] also fulfilled the observed NOEs and coupling constant (^{1}H $J_{19,20}$) observed for the natural product. In addition to this structure, we also decided to target 19-*epi*-**1** [19(*S*),20(*R*), Figure 1] and 20-*epi*-**1** [19(*R*),20(*S*), Figure 1], if nothing else, for their value in structure activity relationship studies that we intended to carry out.

(21) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408−7410.
(22) Beumer, R.; Bayon, P.; Bugada, P.; Ducki, S.; Mongelli, N.; Sirtori, F. R.; Telser, J.; Gennari, C. *Tetrahedron* **2003**, *59*, 8803−8820.
(23) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667−3669.

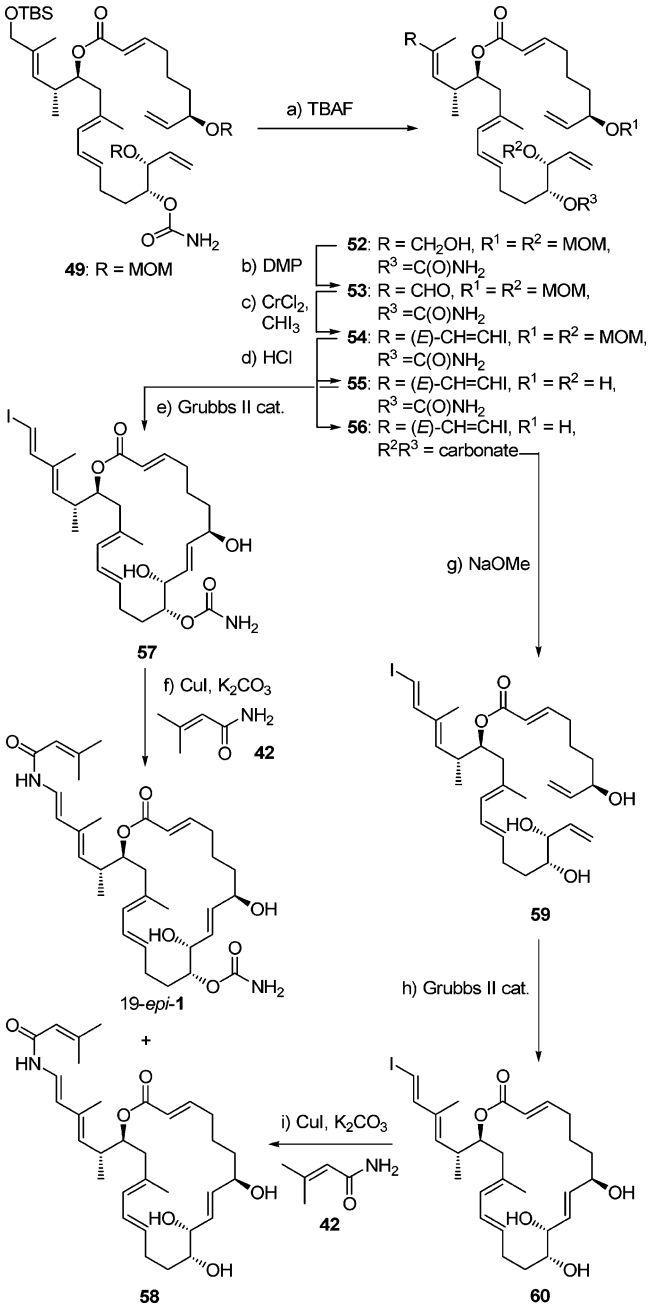
Scheme 7. Coupling of Building Blocks 19-*epi*-**2**, 20-*epi*-**2**, and *ent*-**2** with Fragments **3** and **4** to Generate Intermediates **49**, **50** and **51**[a]



[a] Reagents and conditions: (a) $Pd(dba)_2$ (0.3 equiv), **3** (1.3 equiv), $AsPh_3$ (2.0 equiv), LiCl (3.0 equiv), NMP, 23 °C, 12 h, **46**: (61%), **47**: (63%), **48**: (50%); (b) 2,4,6-trichlorobenzoyl chloride (1.5 equiv), Et_3N (5.0 equiv), **4** (1.5 equiv), 4-DMAP (1.0 equiv) 23 °C, 12 h, **49**: (63%), **50**: (74%), **51**: (50%).

The syntheses of 19-*epi*-**1**, 20-*epi*-**1**, and 19-*epi*-20-*epi*-**1** followed the same general sequence already developed for the originally proposed structure of palmerolide A (**1**). Scheme 7 outlines the assembly of the appropriate building blocks, 19-*epi*-**2**, 20-*epi*-**2**, *ent*-**2**, and **3**, to afford tetraenes **46** (61% yield), **47** (63% yield), and **48** (50% yield) through Stille coupling reactions [$Pd(dba)_2$ catalyst, $AsPh_3$, LiCl], which were converted to hexaene esters **49** (63% yield), **50** (74% yield), and **51** (50% yield), respectively, through Yamaguchi reactions (2,4,6-trichlorobenzoyl chloride, Et_3N, 4-DMAP) in readiness for further elaboration at the C_{23} terminus to the desired vinyl iodides. As outlined in Schemes 8−10 and starting from **49** (Scheme 8), **50** (Scheme 9), and **51** (Scheme 10), TBAF desilylation, DMP oxidation, and Takai olefination faithfully delivered the targeted

Scheme 8. Elaboration of Intermediate **49** Leading to Palmerolide A Isomer 19-*epi*-**1** and Its Decarbamated Version **58**[a]

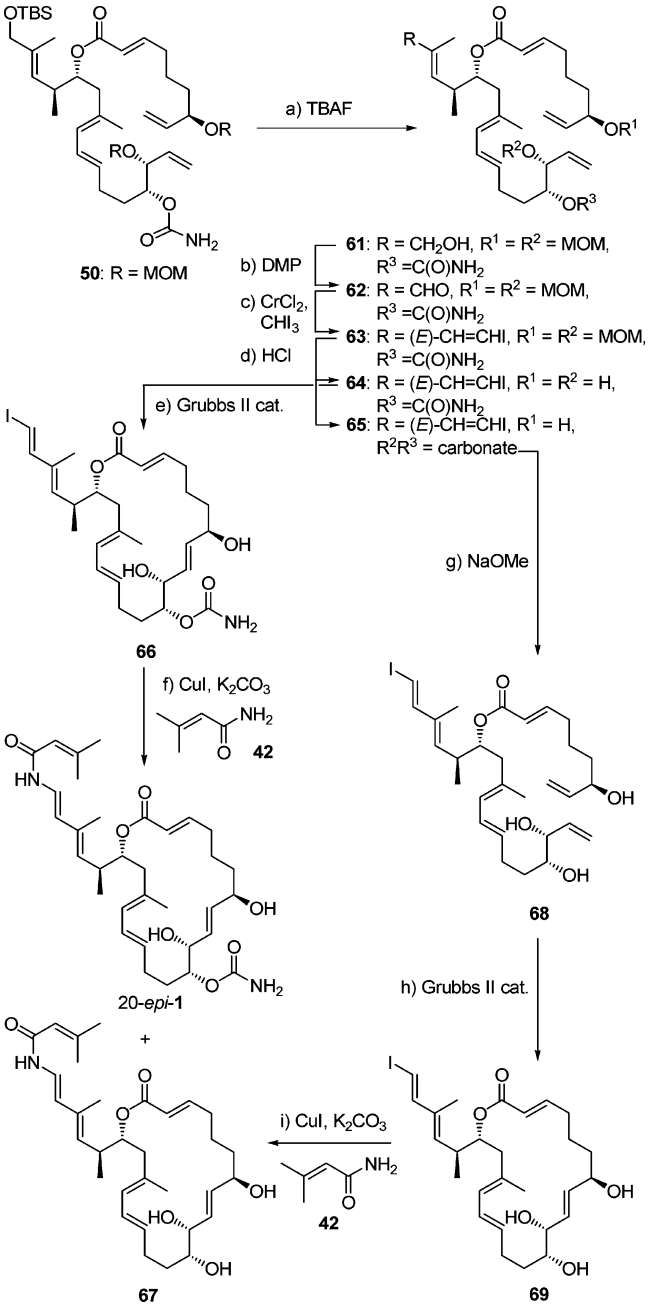


[a] Reagents and conditions: (a) TBAF (2.0 equiv), THF, 23 °C, 2 h, 87%; (b) DMP (1.5 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 23 °C, 30 min, 80%; (c) $CrCl_2$ (10.0 equiv), CHI_3 (3.0 equiv), THF/dioxane (1:6), 23 °C, 2 h, 81% (>95:5 *E*/*Z*); (d) 3 N HCl/EtOH (1:5), 80 °C, 50 min, **55**: (67%), mono-deprotected products: (15%), **56**: (10%); (e) Grubbs II catalyst (0.2 equiv), CH_2Cl_2 (c = 0.002 M), 23 °C, 2 h, 62% (>95:5 *E*/*Z*); (f) **42** (2.0 equiv), CuI (1.0 equiv), K_2CO_3 (5.0 equiv), *N*,*N*′-dimethylethylenediamine (3.0 equiv), DMF, 23 °C, 1 h, 19-*epi*-**1**: (37%), **58**: (10%); (g) NaOMe (15 equiv), MeOH, 23 °C, 2 h, 56%; (h) Grubbs II catalyst (0.2 equiv), CH_2Cl_2 (c = 0.002 M), 23 °C, 2 h, 65% (>95:5 *E*/*Z*); (i) **42** (2.0 equiv), CuI (1.5 equiv), K_2CO_3 (6.0 equiv), *N*,*N*′-dimethylethylenediamine (3.0 equiv), DMF, 23 °C, 1 h, 45%.

vinyl iodides **54**, **63**, and **72** in 56, 56, and 50% yields, respectively, over the three steps. Upon removal of the methoxy methyl ethers guarding the two allylic hydroxyls (**55** and **64** by ethanolic HCl,[24] and **73** by TMSCl), ring-closing metathesis

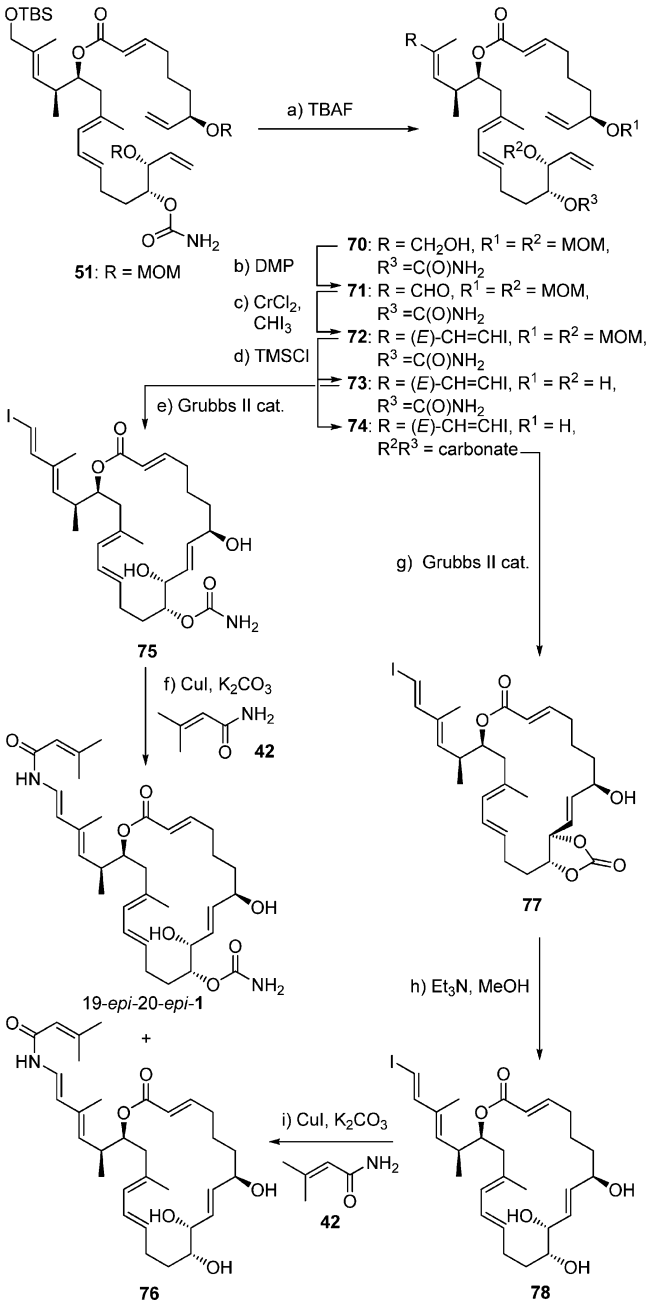
(24) Auerbach, J.; Weinreb, S. M. *Chem. Commun.* **1974**, *8*, 298−299.

Scheme 9. Elaboration of Intermediate **50** Leading to Palmerolide A Isomer 20-*epi*-**1** and Its Decarbamated Version **67**[a]



[a] Reagents and conditions: (a) TBAF (2.0 equiv), THF, 23 °C, 2 h, 85%; (b) DMP (1.5 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 23 °C, 30 min, 81%; (c) $CrCl_2$ (10.0 equiv), CHI_3 (3.0 equiv), THF/dioxane (1:6), 23 °C, 2 h, 81% (>95:5 *E*/*Z*); (d) 3 N HCl/EtOH (1:5), 80 °C, 50 min, **64**: (62%), mono-deprotected products: (18%), **65**: (13%); (e) Grubbs II catalyst (0.2 equiv), CH_2Cl_2 (c = 0.002 M), 23 °C, 2 h, 66% (>95:5 *E*/*Z*); (f) **42** (2.0 equiv), CuI (1.0 equiv), K_2CO_3 (5.0 equiv), *N*,*N*′-dimethylethylenediamine (3.0 equiv), DMF, 23 °C, 1 h, 20-*epi*-**1**: (40%), **67**: (11%); (g) NaOMe (15 equiv), MeOH, 23 °C, 2 h, 55%; (h) Grubbs II catalyst (0.05 equiv), CH_2Cl_2 (c = 0.002 M), 23 °C, 2 h, 63% (>95:5 *E*/*Z*); (i) **42** (2.0 equiv), CuI (1.5 equiv), K_2CO_3 (6.0 equiv), *N*,*N*′-dimethylethylenediamine (3.0 equiv), DMF, 23 °C, 1 h, 42%.

Scheme 10. Elaboration of Intermediate **51** Leading to Palmerolide A Isomer 19-*epi*-20-*epi*-**1** and Its Decarbamated Version **76**[a]



[a] Reagents and conditions: (a) TBAF (1.0 M in THF, 1.5 equiv), THF, 23 °C, 2 h 77%; (b) DMP (1.2 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 23 °C, 30 min, 85%; (c) $CrCl_2$ (10.0 equiv), CHI_3 (3.0 equiv), THF/dioxane (1:6), 23 °C, 2 h, 77% (>95:5 *E*/*Z*); (d) TMSCl (10 equiv), MeOH, 40 °C, 1 h, **73**: (74%), **74**: (12%); (e) Grubbs II catalyst (0.05 equiv), CH_2Cl_2 (c = 0.005 M), 23 °C, 1 h, 80% (>95:5 *E*/*Z*); (f) **42** (2.0 equiv), CuI (1.5 equiv), K_2CO_3 (6.0 equiv), *N*,*N*′-dimethylethylenediamine (3.0 equiv), DMF, 23 °C, 1 h, 19-*epi*-20-*epi*-**1**: (55%), **76**: (<5%), **75**: (7%); (g) Grubbs II catalyst (0.2 equiv), CH_2Cl_2 (c = 0.005 M), 23 °C, 4 h, 76% (>95:5 *E*/*Z*); (h) Et_3N/MeOH/H_2O (1:5:1), 40 °C, 6 h, 62%; i) **42** (2.0 equiv), CuI (1.5 equiv), K_2CO_3 (5.0 equiv), *N*,*N*′-dimethylethylenediamine (3.0 equiv), DMF, 23 °C, 1 h, 54%.

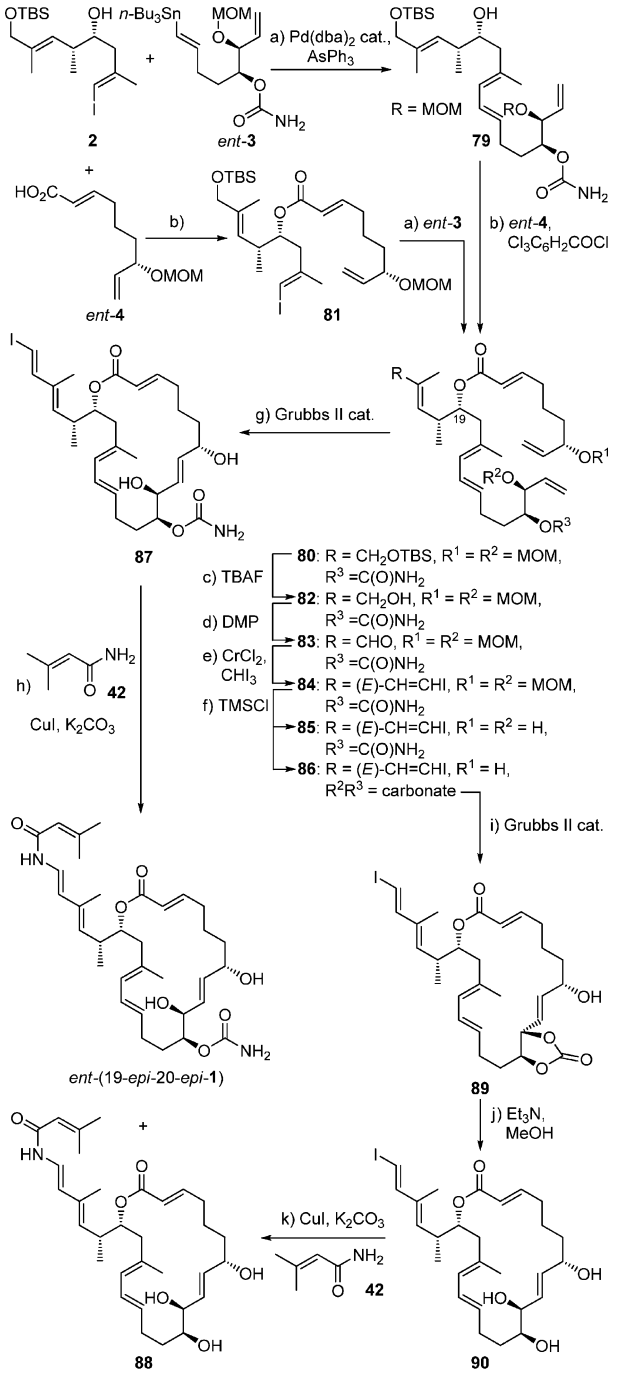
facilitated by the Grubbs II catalyst smoothly afforded macrocycles **57** (Scheme 8), **66** (Scheme 9), and **75** (Scheme 10) (42, 41, and 59% yields for the two steps, respectively), setting the stage for the final installation of the enamide moiety. The later objective was accomplished through copper-mediated coupling with primary amide **42** under the Buchwald conditions as described earlier (CuI, K_2CO_3, *N*,*N*′-dimethylethylenediamine), furnishing 19-*epi*-**1** (37% yield, Scheme 8), 20-*epi*-**1** (40% yield, Scheme 9), and 19-*epi*-20-*epi*-**1** (55% yield, Scheme 10), accompanied by their corresponding decarbamated products (**58**, 10% yield, Scheme 8; **67**, 11% yield, Scheme 9; **76**, <5% yield,

Scheme 10). Decarbamated **58**, **67**, and **76** were also accessed via the hydrolysis of cyclic carbamates **56**, **65** (NaOMe, **59**: 56% and **68**:55% yield) and **77** ($Et_3N-MeOH-H_2O$, **78**:62% yield), respectively, and ring-closing metathesis (Grubbs II catalyst, **58**:65%, **66**:63%, and **77**:76% yields) and enamide coupling (CuI, K_2CO_3, *N*,*N*′-dimethylethylenediamine; **58**:45%, **67**:42%, and **76**:54%). We were pleased to find that, whereas the ^1H NMR spectroscopic data of 19-*epi*-**1** and 20-*epi*-**1** did not match those reported for the natural product, those of 19-*epi*-20-*epi*-**1** did. It was at this juncture that we learned of the work of De Brabander and co-workers[3a] in which so elegantly they synthesized 19-*epi*-20-*epi*-**1**, and proposed, based on circular dichroism (CD) measurements, its enantiomer [*ent*-(19-*epi*-20-*epi*-**1**)] as the true structure of the natural product.[25] The latter compound [*ent*-(19-*epi*-20-*epi*-**1**)], therefore, became our next and ultimate target for synthesis.

Total Synthesis of *ent*-(-19-*epi*-20-*epi*-1), the Revised Structure of Palmerolide A. Having developed all of the chemistry needed for the total synthesis of the revised structure of palmerolide A, *ent*-(19-*epi*-20-*epi*-**1**) was soon reached starting from fragments **2**, *ent*-**3**, and *ent*-**4**, and proceeding as outlined in Scheme 11. Thus, Stille coupling of vinyl iodide **2** with vinyl stannane *ent*-**3** under the standard conditions of Pd-$(dba)_2$ catalyst, $AsPh_3$, and LiCl, followed by Yamaguchi-type esterification with *ent*-**4**, furnished hexaene ester **80** via hydroxy tetraene **79** in 32% overall yield for the two steps. Reversing the coupling sequence (**2** + *ent*-**4**, then *ent*-**3**) also led to hexaene **80**, with a much improved yield of 55% for the two steps. Elaboration of **80** to cyclization precursor **85** through the established, four-step sequence (34% overall yield) allowed us to reach, through ring-closing metathesis under the Grubbs II catalyst conditions, macrocycle **87** in 81% yield. The completion of the synthesis of *ent*-(19-*epi*-20-*epi*-**1**) required installment of the enamide tail, a task that was accomplished as before (**42**, CuI, K_2CO_3, *N*,*N*′-dimethylethylenediamine, 46% yield plus <5% of decarbamated **88** and 5−10% recovered starting material **87**). Similar to the chemistry described for the conversion of **74** to **76** as shown in Scheme 10, cyclic carbonate **86** faithfully delivered decarbamated **88** after a three-step sequence [(i) Grubbs II catalyst, 75% yield; (ii) $Et_3N-MeOH-H_2O$, 65% yield; and (iii) CuI, K_2CO_3, *N*,*N*′-dimethylethylenediamine, 51% yield]. Much to our delight, and as expected, synthetic *ent*-(19-*epi*-20-*epi*-**1**) displayed identical physical properties (^1H and ^{13}C NMR spectra, Mass spec) to those reported for natural palmerolide A[1] and exhibited by our synthetic 19-*epi*-20-*epi*-**1**. Most importantly, the matching CD curve (Figure 2) and optical rotation (α_D) of the synthetic material with those of the natural product unambiguously confirmed its structure.[26]

Having secured palmerolide A [*ent*-(19-*epi*-20-*epi*-**1**)] as described above, we then decided to attempt the daring maneuver of employing the olefin metathesis reaction as the last step to construct the molecule. Such an approach required

Scheme 11. Coupling of Fragments **2**, *ent*-**3**, and *ent*-**4**, and Completion of the Total Synthesis of the Revised Palmerolide A Structure, *ent*-(19-*epi*-20-*epi*-**1**) and Its Decarbamated Version **88**[a]



[a] Reagents and conditions: (a) $Pd(dba)_2$ (0.15 equiv), $AsPh_3$ (3.0 equiv), LiCl (3.0 equiv), NMP, 23 °C, 12 h, **79**: (56%, via **2**+*ent*-**3**), **80**: (66%, *ent*-**3**+**81**); (b) 2,4,6-trichlorobenzoyl chloride (1.1 equiv), Et_3N (1.5 equiv), *ent*-**4** (1.1 equiv), 4-DMAP (1.1 equiv), 23 °C, 12 h, **80**: (58%, via *ent*-**4**+**79**), **81**: (84%, via **2**+*ent*-**4**); (c) TBAF (1.0 M in THF, 1.5 equiv), THF, 23 °C, 2 h, 76%; (d) DMP (1.2 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 23 °C, 30 min, 84%; (e) $CrCl_2$ (10.0 equiv), CHI_3 (3.0 equiv), THF/dioxane (1:6), 23 °C, 2 h, 79% (>95:5 *E*/*Z*); (f) TMSCl (10 equiv), MeOH, 40 °C, 1 h, **85**: (67%), **86**: (10%); (g) Grubbs II catalyst (0.05 equiv), CH_2Cl_2 (*c* = 0.005 M), 23 °C, 1 h, 81% (>95:5 *E*/*Z*); (h) **42** (2.0 equiv), CuI (1.5 equiv), K_2CO_3 (6.0 equiv), *N*,*N*′-dimethylethylenediamine (3.0 equiv), DMF, 23 °C, 1 h, *ent*-(19-*epi*-20-*epi*-**1**): (46%), **88**: (<5%), **87**: (5−10%); (i) Grubbs II catalyst (0.2 equiv), CH_2Cl_2 (*c* = 0.005 M), 23 °C, 4 h, 75% (>95:5 *E*/*Z*); (j) $Et_3N/MeOH/H_2O$ (1:5:1), 40 °C, 6 h, 65%; (k) **42** (2.0 equiv), CuI (1.5 equiv), K_2CO_3 (5.0 equiv), *N*,*N*′-dimethylethylenediamine (3.0 equiv), DMF, 23 °C, 1 h, 51%.

(25) The absolute stereochemistry of C_7 was also subsequently determined by degradation of natural palmerolide A and comparison of the optical rotation of a fragment with a synthetic sample, see, Lebar, M. D.; Baker, B. J. *Tetrahedron Lett.* **2007**, *48*, 8009−8010.

(26) Synthetic palmerolide A [*ent*-(19-*epi*-20-*epi*-**1**)]: $[\alpha]_D^{25} = -95$ (MeOH, *c* = 0.12); natural palmerolide A: $[\alpha]_D^{25} = -99$ (MeOH, *c* = 0.24). This value is significantly higher than that reported in the original isolation paper: $[\alpha]_D^{24} = -1.6$ (MeOH, *c* = 0.5); see ref 1. We thank Professor Bill J. Baker (University of South Florida, Tampa) for kindly providing us with a sample of authentic palmerolide A.

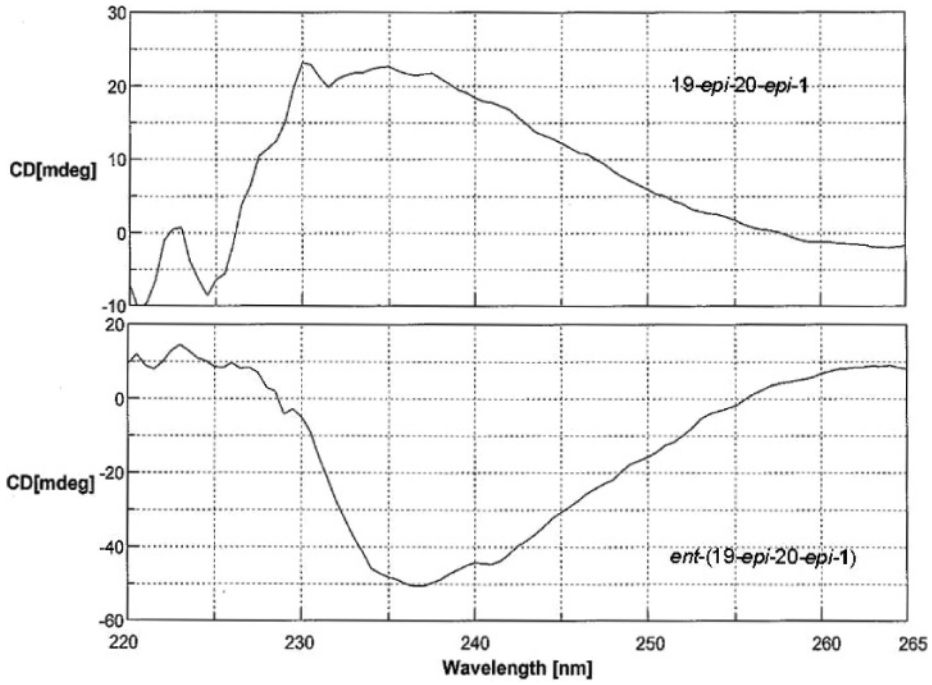
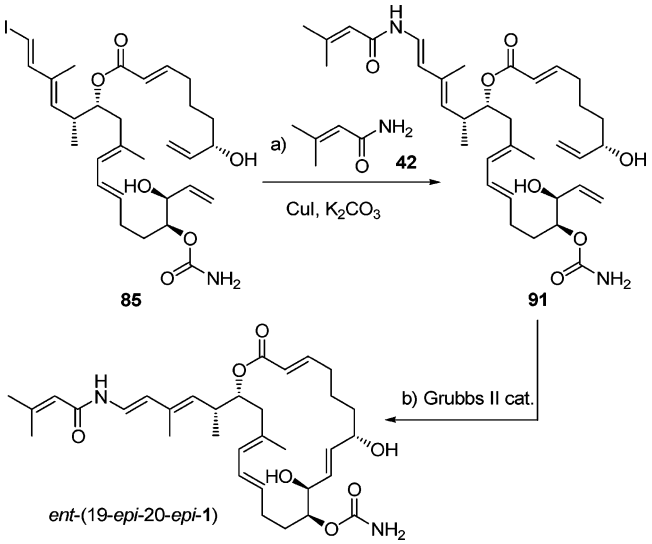


Figure 2. CD spectra of 19-*epi*-20-*epi*-**1** (top, $CHCl_3$, 25 °C, 0.0013 M) and of *ent*-(19-*epi*-20-*epi*-**1**) (bottom, $CHCl_3$, 25 °C, 0.0025 M).

Scheme 12. Total Synthesis of Palmerolide A [*ent*-(19-*epi*-20-*epi*-**1**)] through Olefin Metathesis as the Final Step[a]



[a] Reagents and conditions: (a) **42** (2.0 equiv), CuI (1.5 equiv), K_2CO_3 (6.0 equiv), *N*,*N*′-dimethylethylenediamine (3.0 equiv), DMF, 23 °C, 1 h, 46%; (b) Grubbs II catalyst (0.2 equiv), CH_2Cl_2 (c = 0.005 M), 23 °C, 2 h, 73% (>95:5 *E*/*Z*).

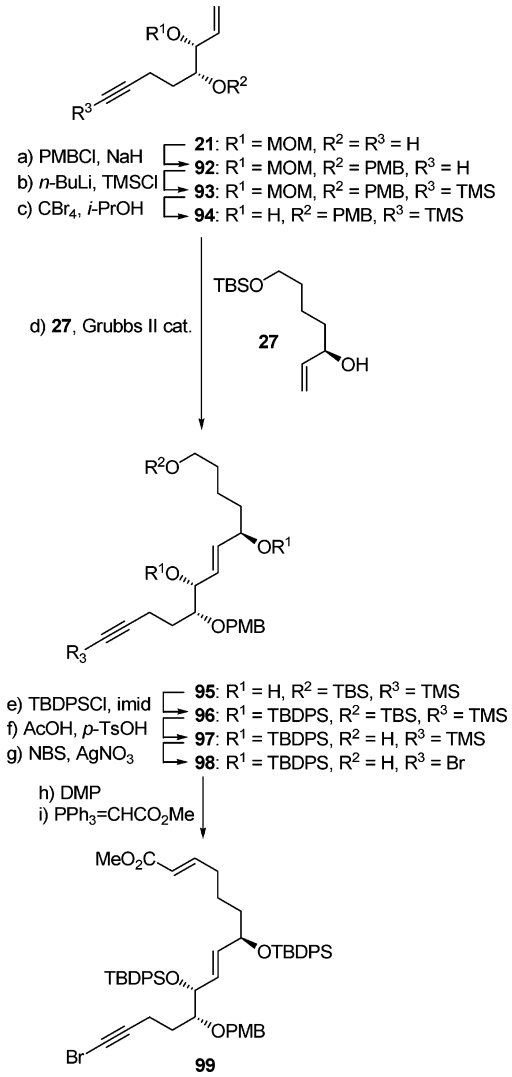
octaolefin **91** (Scheme 12) as a precursor, a compound that was obtained from vinyl iodide **85** through coupling with enamide **42** in the presence of CuI, K_2CO_3, and *N*,*N*′-dimethylethylenediamine (46% yield). Pleasantly, when subjected to the metathesis conditions (Grubbs II catalyst, CH_2Cl_2, 23 °C), octaolefin **91** underwent smooth ring closure to produce palmerolide A [*ent*-(19-*epi*-20-*epi*-**1**)] in 73% yield. Considering the presence of so much carbon unsaturation and several functional groups in substrate **91**, this application of the olefin metathesis reaction is impressive indeed and demonstrates the extreme power of this process for complex molecule construction.[18b,c]

Alternative Macrocyclization Strategies. Whereas the ring-closing metathesis reaction proved to be both pleasing and practical in its delivery of the palmerolide A structure, it was of interest to us, at least for comparison purposes, to explore other modes of cyclization to construct the macrocycle of the molecule. As depicted in Scheme 1, and already discussed above, the alternative methods for macrocycle formation included the intramolecular versions of the HWE olefination, the Stille coupling, the Yamaguchi esterification, and the Mitsunobu reaction. All four strategies required pre-installation of the C_8/C_9 *trans*-olefinic linkage followed by further manipulation to the appropriate macrocyclization precursors. The two initially needed intermediates, alcohol **98** and methyl ester **99**, were synthesized as summarized in Scheme 13. Thus, the previously synthesized (Scheme 4) hydroxy acetylene **21** was sequentially converted to PMB ether **92** (NaH, PMBCl, 91% yield), TMS acetylene **93** (*n*-BuLi, TMSCl, 92% yield), and hydroxy derivative **94** (CBr_4, *i*-PrOH, 69% yield).[27]The latter deprotection to liberate the allylic hydroxyl group was deemed important for the success of the intended cross-metathesis in light of our experience with the metathesis-based ring closure (vide supra) where a free OH group was required. Indeed, cross metathesis between allylic alcohols **94** and **27** (2.0 equiv, prepared as per Scheme 5) in the presence of Grubbs II catalyst yielded the desired *trans*-olefin **95** in 41% yield (unoptimized), together with the cross metathesis dimer of **27**, which could be employed instead of **27** for the cross metathesis reaction with **94**, thus minimizing the losses from this side-reaction. The conversion of **95** to **98** and **99** required further functional group manipulations as follows: (i) TBDPSCl, imid (**96**, 84% yield); (ii) AcOH, *p*-TsOH (**97**, 77% yield); (iii) NBS, $AgNO_3$, (**98**, 78% yield);[28] and (iv) DMP oxidation, followed by olefination with $Ph_3P{=}CHCO_2Me$ (**99**, 76% yield for the two steps).

Construction of macrocycle **105** through intramolecular HWE olefination was the first mode of macrocyclization attempted; the results are shown in Scheme 14. The required ester

(27) Lee, A. S. Y.; Hu, Y. J.; Chu, S. F. *Tetrahedron* **2001**, *57*, 2121−2126.
(28) Nishikawa, T.; Shibuya, S.; Hosokawa, S.; Isobe, M. *Synlett* **1994**, *7*, 485−486.

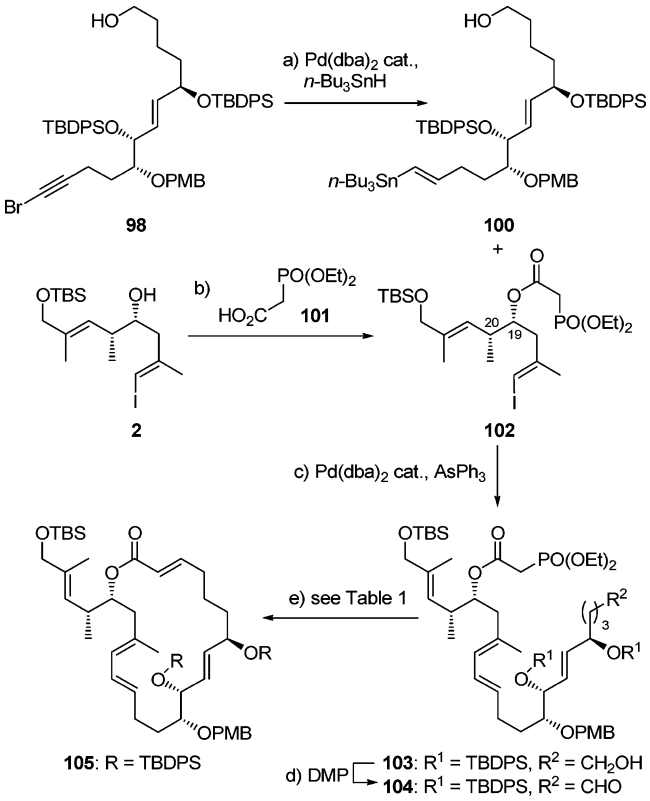
Scheme 13. Construction of Enynes **98** and **99**[a]



[a] Reagents and conditions: (a) NaH (1.3 equiv), PMBCl (1.2 equiv), DMF, 23 °C, 5 h, 91%; (b) *n*-BuLi (1.3 equiv), TMSCl (1.2 equiv), THF, −70 °C, 2 h, 92%; (c) CBr_4 (0.2 equiv), *i*-PrOH, 82 °C, 2 h, 69%; (d) **27** (2.0 equiv), Grubbs II catalyst (0.1 equiv), CH_2Cl_2, 23 °C, 12 h, 41% (>95:5 *E*/*Z*); (e) TBDPSCl (2.5 equiv), imidazole (8.0 equiv), DMF, 23 °C, 8 h, 84%; (f) *p*-TsOH (catalyst), HOAc/H_2O (7:1), 23 °C, 3 h, 77%; (g) $AgNO_3$ (1.0 equiv), NBS (1.1 equiv), acetone, 23 °C, 12 h, 78%; (h) DMP (1.5 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 23 °C, 20 min, 86%; (i) $Ph_3P{=}CHCO_2Me$ (1.2 equiv), CH_2Cl_2, 23 °C, 12 h, 88%. PMB = *para*-methoxybenzyl, TBDPS = *tert*-butyldiphenylsilyl, *p*-TsOH = *para*-toluenesulfonic acid.

phosphonate aldehyde precursor **104** was secured through Stille coupling [$Pd(dba)_2$, $AsPh_3$, LiCl, 74% yield] of vinyl stannane **100** [obtained by the $Pd(dba)_2$-catalyzed addition of *n*-Bu_3SnH to bromo acetylene **98**, 89% yield] with vinyl iodide **102** (prepared by the DCC esterification of hydroxy vinyl iodide **2** with carboxylic acid **101**, 85% yield) followed by DMP oxidation of the resulting hydroxy ester **103** (85% yield). Table 1 shows the four different conditions tried for the cyclization of phosphonate aldehyde **104**, all of which proved to be successful in producing the desired *E* α,β-unsaturated macrolide **105** in yields ranging from 50 to 73%.[3a] The Masamune−Roush protocol[29] (*i*-Pr_2NEt, LiCl) gave the best result in this instance,

Scheme 14. Construction of Macrocycle **105** through Intramolecular Horner−Wadsworth−Emmons Olefination[a]



[a] Reagents and conditions: (a) PPh_3 (0.2 equiv), $Pd(dba)_2$ (0.1 equiv), *n*-Bu_3SnH (2.0 equiv), THF, 23 °C, 1 h, 89%; (b) **101** (2.0 equiv), DCC (2.0 equiv), 4-DMAP (0.5 equiv), CH_2Cl_2, 23 °C, 12 h, 85%; (c) **96** (1.0 equiv), $Pd(dba)_2$ (0.3 equiv), $AsPh_3$ (2.0 equiv), LiCl (3.0 equiv), NMP, 23 °C, 12 h, 74%; (d) DMP (1.5 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 23 °C, 20 min, 85%. DCC = *N*,*N*′-dicyclohexylcarbodiimide.

Table 1. Construction of Macrocycle **105** via Intramolecular Horner−Wadsworth−Emmons Olefination[a]

entry	base	solvent	temperature (°C)	time (h)	yield (%)[b]
1	K_2CO_3 (12.0 equiv)/ 18−Crown−6	toluene	25	12	66
2	*i*−Pr_2NEt (10.0 equiv)/ LiCl[c]	acetonitrile[d]	25	12	73
3	NaH (2.7 equiv) with 4 Å MS	THF	25	6	62
4	NaHMDS (2.0 equiv)	THF	−78 → 0	2	50

[a] All reactions were carried out on 0.015 mmol scale, c = 0.001 M, under an argon atmosphere. [b] Isolated yield. [c] LiCl was dried over a heatgun under vacuum for 20 min before use. [d] Anhydrous acetonitrile was used as received without further distillation.

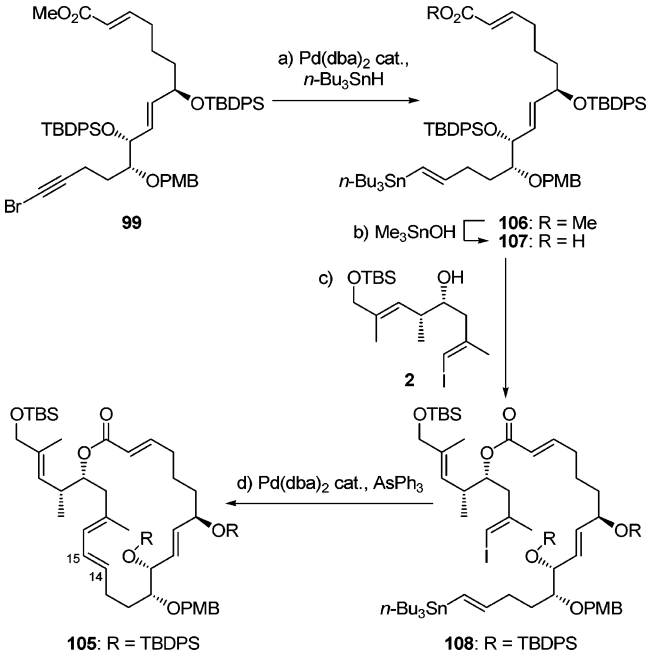
making this procedure comparable with the RCM method discussed above.

Scheme 15 depicts the construction of macrocycle **105** from vinyl iodide vinyl stannane precursor **108** through the intramolecular Stille coupling reaction. Precursor **108** was prepared from bromo acetylene **99** by a three-step sequence involving: (i) reaction with *n*-Bu_3SnH in the presence of $Pd(dba)_2$ catalyst (to afford stannane **106**); (ii) saponification with Me_3SnOH[30] (to afford carboxylic acid **107**); and (iii) esterification with hydroxy vinyl iodide **2** under the influence of 2,4,6-trochlo-

(29) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183−2186.

(30) Nicolaou, K. C.; Estrada, A. A.; Zak, M.; Lee, S. H.; Safina, B. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 1378−1382.

Scheme 15. Construction of Macrocycle **105** through Intramolecular Stille Coupling[a]



[a] Reagents and conditions: (a) PPh_3 (0.2 equiv), $Pd(dba)_2$ (0.1 equiv), *n*-Bu_3SnH (2.1 equiv), THF, 23 °C, 1 h, 68%; (b) Me_3SnOH (10.0 equiv), 1,2-dichloroethane, 90 °C, 12 h, 70%; (c) 2,4,6-trichlorobenzoyl chloride (1.5 equiv), Et_3N (5.0 equiv), toluene, 23 °C, 1 h; then **2** (1.2 equiv), 4-DMAP (1.0 equiv), toluene, 23 °C, 3 h, 78%; (d) $Pd(dba)_2$ (0.4 equiv), $AsPh_3$ (2.0 equiv), LiCl (3.0 equiv), NMP (c = 0.001 M), 23 °C, 12 h, 45% (plus 22% yield at an unidentified isomer, not separable by chromatography).

Table 2. Construction of Macrocycle **105** via Mitsunobu Cyclization[a]

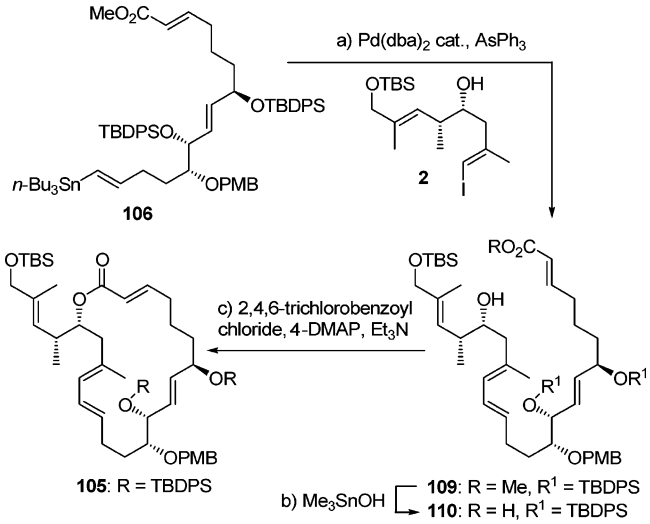
entry	azodicarboxylate	solvent	yield (%)[b]
1	DIAD (10.0 equiv)	THF	NR[c]
2	DIAD (10.0 equiv)	benzene	NR[c]
3	DEAD (10.0 equiv)	THF	**113**[d] (40)
4	DEAD (10.0 equiv)	toluene	**105** (31), **114**[d] (34)

[a] All of the reactions were carried out with Ph_3P (10.0 equiv) in dilute solution (0.001 M) under an argon atmosphere at 23 °C for 1.5 h. [b] Isolated yield. [c] No reaction. [d] Structure was suggestive by ^1H NMR and LCMS.[32] DIAD = diisopropyl azodicarboxylate; DEAD = diethyl azodicarboxylate.

robenzoyl chloride, Et_3N, and 4-DMAP (37% overall yield). The Stille coupling-based macrocyclization of **108** proceeded in the presence of $Pd(dba)_2$ catalyst and $AsPh_3$ and LiCl to afford the desired product **105** in modest yield (67%, crude). However, the product was accompanied by an unidentified geometric isomer, which could not be chromatographically removed, making this strategy unattractive for further exploitation.

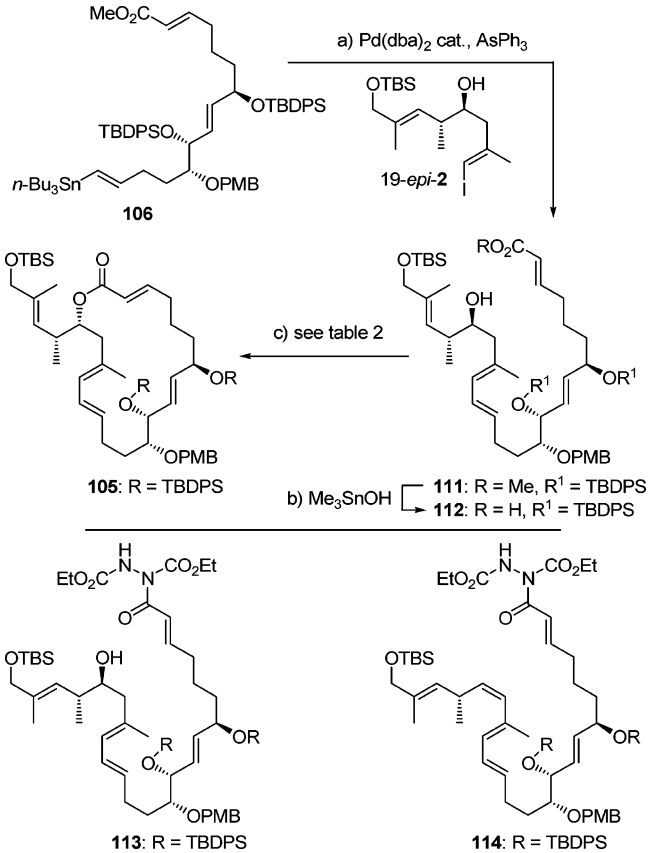
In contrast to the above Stille coupling-based cyclization, the Yamaguchi protocol proved to be highly efficient in forming the palmerolide A macrocycle **105** as shown in Scheme 16. Thus, seco hydroxy acid **110** was prepared by standard chemistry involving Stille coupling of vinyl stannane **106** with vinyl iodide **2** [$Pd(dba)_2$ catalyst, $AsPh_3$, LiCl] to afford pentaene methyl ester **109** (73% yield), which was then saponified in the presence of Me_3SnOH in 86% yield. Reaction of hydroxy acid **110** with 2,4,6-trichlorobenzoyl chloride in the presence of Et_3N and 4-DMAP furnished macrolide **105** in 81% yield, proving this method of ring closure to be competitive with the RCM method described above.

Scheme 16. Construction of Macrocycle **105** through Yamaguchi Macrolactonization[a]



[a] Reagents and conditions: (a) **2** (1.0 equiv), $Pd(dba)_2$ (0.3 equiv), $AsPh_3$ (2.0 equiv), LiCl (3.0 equiv), NMP, 23 °C, 12 h, 73%; (b) Me_3SnOH (10.0 equiv), 1,2-dichloroethane, 90 °C, 12 h, 86%; (c) 2,4,6-trichlorobenzoyl chloride (15 equiv), Et_3N (20 equiv), THF, 23 °C, 2 h; then 4-DMAP (40 equiv), toluene (c = 0.001 M), 23 °C, 12 h, 81%.

Scheme 17. Construction of Macrocycle **105** through Mitsunobu Cyclization[a]



[a] Reagents and conditions: (a) 19-*epi*-**2** (1.0 equiv), $Pd(dba)_2$ (0.3 equiv), $AsPh_3$ (2.0 equiv), LiCl (3.0 equiv), NMP, 23 °C, 12 h, 71%; (b) Me_3SnOH (10.0 equiv), 1,2-dichloroethane, 90 °C, 12 h, 80%.

The final macrocyclization study, that involved the intramolecular Mitsunobu[31] reaction and required vinyl iodide 19-*epi*-**2**

(31) Hughes, D. L. *Org. React.* **1992**, *42*, 335−656.

to deliver macrocycle **105** (as a consequence of the expected inversion of configuration at C_{19}), is shown in Scheme 17. Thus, Stille coupling of **106** with 19-*epi*-**2** as before afforded pentaene **111** (71% yield), whose hydrolysis with Me_3SnOH furnished the desired seco hydroxy acid **112** (80% yield). Of the various Mitsunobu conditions examined (shown in Table 2), the DEAD-Ph_3P reagent combination in toluene proved to be the best in delivering macrocycle **105** (31% yield). Byproducts in these reactions included the hydroxy DEAD-conjugate **113** and the eliminated DEAD-conjugate **114** as indicated in Table 2 and Scheme 17.[32]

Conclusion

A highly convergent, modular and stereochemically flexible synthetic strategy allowed access to several palmerolide A isomers, including the originally proposed (**1**) and revised [*ent*-(19-*epi*-20-*epi*-**1**)] structures of the natural product and stereoisomers 19-*epi*-**1**, 20-*epi*-**1**, and 19-*epi*-20-*epi*-**1**. From the five different modes of ring closure examined, the most efficient processes for the construction of the palmerolide A macrocycle were found to be the olefin ring-closing metathesis[18] and the Yamaguchi macrolactonization.[33] The late-stage conversion of polyolefin **91** to *ent*-(19-*epi*-20-*epi*-**1**) illustrated, once again, the power of ring-closing metathesis in the construction of complex molecular scaffolds.[18b,c] In addition to providing several palmerolide A stereoisomers, the described synthetic technologies are capable of delivering designed analogs of the natural product for chemical biology studies. Such studies are currently underway in these laboratories.

Acknowledgment. Professor K.C. Nicolaou is also at the Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037 (USA), and Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093 (USA). We thank Ms. Doris Tan (ICES) for high-resolution mass spectrometric (HRMS) assistance. We also thank Professor Bill J. Baker (University of South Florida, Tampa) for kindly providing a sample of authentic palmerolide A. Financial support for this work was provided by A*STAR, Singapore.

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

JA710485N

(32) For an earlier report of a similar DEAD conjugate, see, Lafontaine, J. A.; Provencal, D. P.; Gardelli, C.; Leahy, J. W. *J. Org. Chem.* **2003**, *68*, 4215−4234.

(33) Parenty, A.; Moreau, X.; Campagne, J.-M. *Chem. Rev.* **2006**, *106*, 911−939.