Natural Products

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Total Synthesis of the Originally Proposed and Revised Structures of Palmerolide A**

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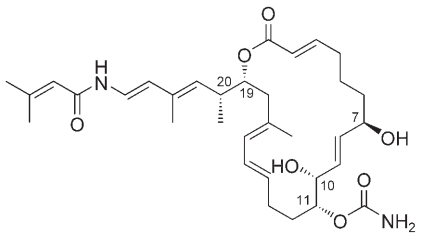
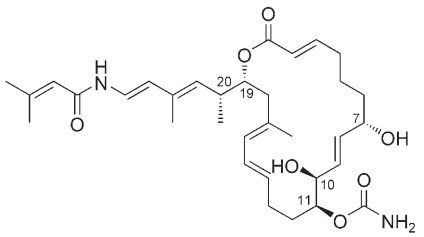
Palmerolide A (Figure 1) is a recently reported polyketide secondary metabolite with an impressive molecular architecture and biological profile.[1] This marine natural product was isolated from the circumpolar tunicate *Synoicum adareanum*, which is commonly found in the shallow waters around Anvers Island on the Antarctic Peninsula, and exhibits unusual selectivity against a number of cell lines in the 60 cell panel of the National Cancer Institute (NCI). Specifically, palmerolide A was found to exhibit potent activity against the melanoma cell line UACC-62 ($LC_{50} = 18$ nM), only modest cytotoxicity against the colon cancer cell line HCC-2998 ($LC_{50} = 6.5$ μM) and the renal cancer cell line RXF 393 ($LC_{50} = 6.5$ μM), and virtually no effect ($LC_{50} > 10$ μM) against other cell lines, thus demonstrating a selectivity index of 10^3 among the cell lines tested. Interestingly, palmerolide A displayed an activity profile in the NCI 60 cell line panel that correlated with that of vacuolar ATPase inhibitors.[2] Palmerolide A was shown to inhibit V-ATPase with an IC_{50} value of 2 nM and to be active in the NCI's hollow fiber assay. The intriguing biological properties of palmerolide A, along with its relative scarcity, prompted us to undertake its chemical synthesis.

Inspection of the proposed structure of palmerolide A (**1a**) reveals a 20-membered macrolide, an enamide-containing side chain, 7 olefinic bonds (3 of which are trisubstituted), and a carbamate moiety. Based on detailed NMR spectroscopic analysis, the relative and absolute configuration of this natural product was put forward as that shown in structure **1a** (Figure 1), although the structural assignments at C19 and C20 were not error proof. Specifically, while the NOE interactions and coupling constants exhibited by palmerolide A may exclude the two *anti* C19/C20 diastereomers, both *syn* structures could be possible. Furthermore, while Mosher ester studies suggested the absolute stereochemistry at the C7, C10, and C11 positions, the low optical rotation of the natural product[1] did not bode well for its diagnostic value as a means to confirm its absolute stereochemistry. Most recently, these suspicions were confirmed by an elegant study by De Brabander and co-workers (which culminated in the total synthesis of the unnatural enantiomer of palmerolide A),[3] with the structural revision of not only the relative stereochemistry between the C7–C11 and C19–C20 domains, but also of the absolute configuration of the molecule. Herein, we report our own efforts in this area that culminated in total syntheses of, among several isomers, the originally proposed structure **1a** and the revised structure **1b** (Figure 1) of palmerolide A by a modular and flexible strategy that allows access to variants of the palmerolide A molecule as depicted retrosynthetically in Scheme 1.

It was envisioned that a Stille coupling reaction, a Yamaguchi esterification, a ring-closing metathesis, and an enamide coupling reaction would serve to assemble and



1a: originally proposed structure (7*R*,10*R*,11*R*,19*R*,20*R*)



1b: revised structure (7*S*,10*S*,11*S*,19*R*,20*R*)

Figure 1. Originally proposed (**1a**) and revised (**1b**) structures of palmerolide A.

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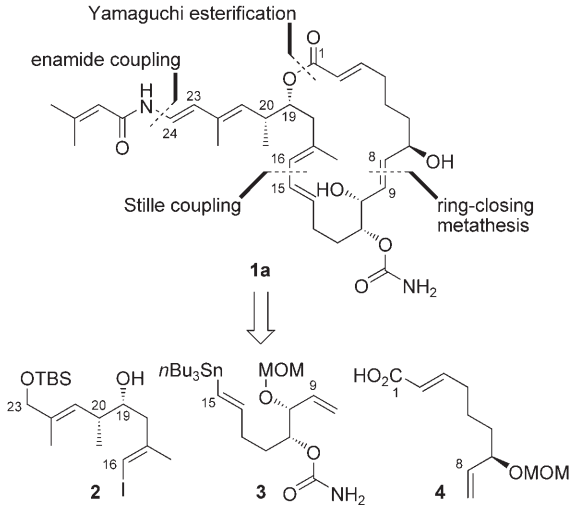
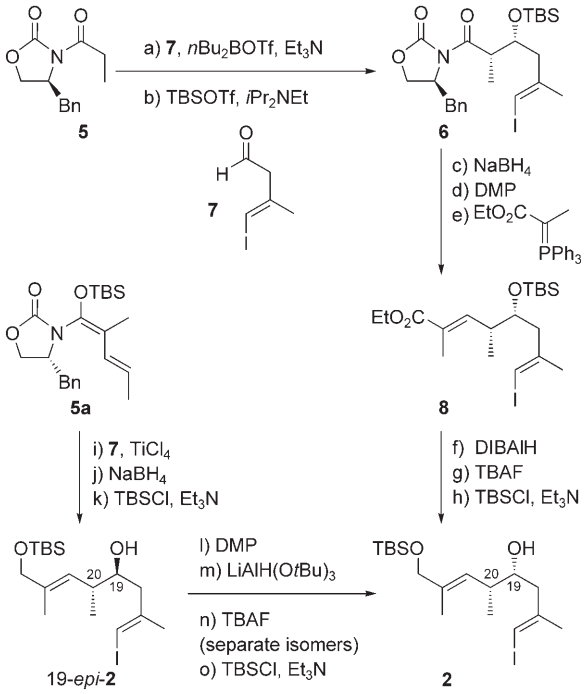
Supporting information for this article (including selected data for compounds **23**, **25**, **1a**, **25b**, and **1b**) is available on the WWW under http://www.angewandte.org or from the author.



Scheme 1. Retrosynthetic analysis of the originally proposed palmerolide A structure (**1a**). MOM = methoxymethyl, TBS = *tert*-butyldimethylsilyl.

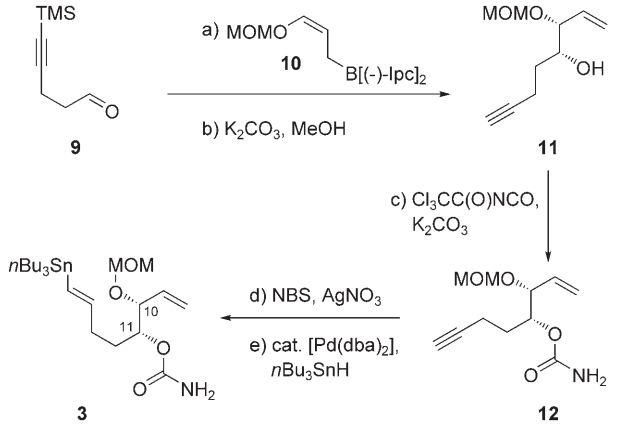


Scheme 2. Construction of C16–C23 vinyl iodide fragments **2** and 19-*epi*-**2**. Reagents and conditions: a) **7** (2.5 equiv), nBu$_2$BOTf (1.0 M in CH_2Cl_2, 1.2 equiv), Et_3N (1.0 equiv), CH_2Cl_2, −78 °C, 12 h, 46% (>95% *de*); b) TBSOTf (1.2 equiv), iPr$_2$NEt (1.5 equiv), CH_2Cl_2, 0 °C, 30 min, 86%; 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 (2.5 equiv), CH_2Cl_2, 23 °C, 12 h, 56% for the 2 steps; f) DIBAlH (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), DMAP (0.2 equiv), CH_2Cl_2, 0→23 °C, 2 h, 92%; i) **7** (2.0 equiv), $TiCl_4$ (1.0 equiv), CH_2Cl_2, −78 °C, 19 h, 83% (>95% *de*); j) $NaBH_4$ (4.0 equiv), THF/H_2O (20:1), 23 °C, 12 h, 84%; k) TBSCl (1.2 equiv), Et_3N (1.5 equiv), DMAP (0.2 equiv), CH_2Cl_2, 0→23 °C, 2 h, 92%; l) DMP (1.2 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 23 °C, 20 min, 90%; m) LiAlH(O*t*Bu)$_3$ (1.0 M in THF, 3.0 equiv), LiI (5.0 equiv), Et_2O, −78 °C, 1 h, 92% (ca. 3:1 mixture of *syn*/*anti* diastereomers); n) TBAF (1.0 M in THF, 1.2 equiv), THF, 23 °C, 1 h, 85%; o) TBSCl (1.2 equiv), Et_3N (1.5 equiv), DMAP (0.2 equiv), CH_2Cl_2, 0→23 °C, 2 h, 92%. Bn = benzyl, DIBAlH = diisobutylaluminum hydride, DMAP = 4-dimethylaminopyridine, DMP = Dess–Martin periodinane, TBAF = tetra-*n*-butylammonium fluoride, Tf = trifluoromethanesulfonyl.

elaborate the three key building blocks **2**–**4** shown in Scheme 1 into the final structure **1a**. The adopted routes to these intermediates were designed with maximum flexibility to deliver all possible stereoisomers and other variants of the palmerolide molecule for structural and biological studies.

Scheme 2 summarizes the construction of the vinyl iodide fragment **2** that began with imide **5** (prepared in 92% yield by reaction of (*S*)-(−)-4-benzyl-2-oxazolidinone with propionic acid chloride in the presence of *n*BuLi). Thus, treatment of **5** with nBu$_2$BOTf/Et_3N[4] followed by reaction of the resulting boron enolate with vinyl iodide aldehyde **7** (prepared in 2 steps and 81% overall yield from 3-butyn-1-ol by standard methods),[5] and silylation (TBSOTf/iPr$_2$NEt) of the so-obtained hydroxy intermediate furnished the TBS ether **6** in 40% overall yield and greater than 95% *de*. Reductive removal of the oxazolidinone chiral auxiliary ($NaBH_4$, 66% yield), followed by oxidation (DMP) and Wittig homologation (PPh_3 = C(Me)CO_2Et, 56% yield for the 2 steps) led to the ethyl ester **8**, whose conversion into the targeted iodide **2** was readily accomplished in 3 steps: 1) DIBAlH, 80% yield, 2) TBAF, 85% yield, and 3) TBSCl/Et_3N/DMAP, 92% yield. Alternatively, starting from dienolate **5a** (prepared by coupling (*R*)-(+)-4-benzyl-2-oxazolidinone with (*E*)-2-methyl-2-pentenoic acid in the presence of PivCl/Et_3N/LiCl in 91% yield, followed by dienolate formation under the influence of sodium hexamethyldisilazane, and trapping with TBSCl in 94% yield), vinylogous Mukaiyama aldol reaction with the vinyl iodide aldehyde **7** under the conditions described by Kobayashi and co-workers[6] ($TiCl_4$, 83% yield, >95% *de*) furnished the expected hydroxy compound.[7] The chiral auxiliary was then reductively removed ($NaBH_4$, 84% yield) to afford, after selective silylation (TBSCl/Et_3N/DMAP, 92% yield), the intermediate 19-*epi*-**2**. The latter compound was then converted into **2** by oxidation/reduction (DMP, 90% yield; LiAlH(O*t*Bu)$_3$/LiI, 92% yield ca. 3:1 *syn*/*anti* mixture) followed by desilylation/chromatographic separation (TBAF, 85% yield, silica gel) and selective silylation (TBSCl/Et_3N/DMAP, 92% yield). The isomeric vinyl iodides *ent*-**2** and 20-*epi*-**2** were similarly prepared from *ent*-**5** and *ent*-**5a**.

Scheme 3 depicts the construction of the stannane fragment **3**. Reaction of aldehyde **9** (prepared in 2 steps from 4-pentyn-1-ol by standard methods)[8] with [(*Z*)-γ-(methoxymethoxy)allyl]-(−)-diisopinocampheylborane (**10**, freshly prepared from methoxymethyl allyl ether, *s*BuLi, (−)-Ipc$_2$BOMe and BF_3·Et_2O)[9] in THF at −78 °C afforded, upon desilylation (K_2CO_3/MeOH), the hydroxy acetylene **11** in good overall yield (74% for the 2 steps) and excellent stereoselectivity (>95% *de* (NMR) and >90% *ee* (Mosher ester)). Finally, installation of the carbamate group ($Cl_3CC(O)NCO/K_2CO_3$/MeOH, quant.),[10] followed by manipulation of the acetylenic moiety 1) $AgNO_3$/NBS;

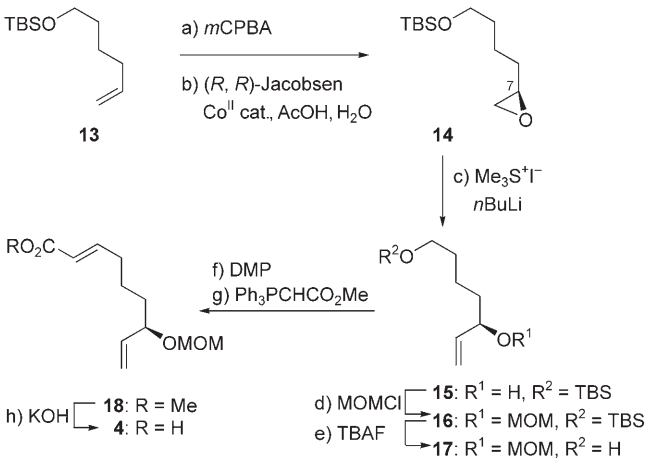


Scheme 3. Synthesis of C9–C15 vinyl stannane fragment **3**. Reagents and conditions: a) **10** (1.0 equiv), THF, −78→23 °C, 12 h; b) K_2CO_3 (5.0 equiv), MeOH, 23 °C, 5 h, 74% for the 2 steps from **10**; c) trichloroacetyl isocyanate (3.0 equiv), CH_2Cl_2, 23 °C, 1 h; then K_2CO_3 (3.0 equiv), MeOH, 23 °C, 1 h, quant.; d) NBS (1.1 equiv), $AgNO_3$ (0.05 equiv), acetone, 23 °C, 30 min, 81%; e) $[Pd(dba)_2]$ (0.2 equiv), PPh_3 (0.8 equiv), nBu_3SnH (2.2 equiv), THF, 23 °C, 30 min, 77% (>95:5 *E*/*Z* stereoselectivity). Ipc = isopinocampheyl; NBS = *N*-bromosuccinimide; dba = dibenzylideneacetone.

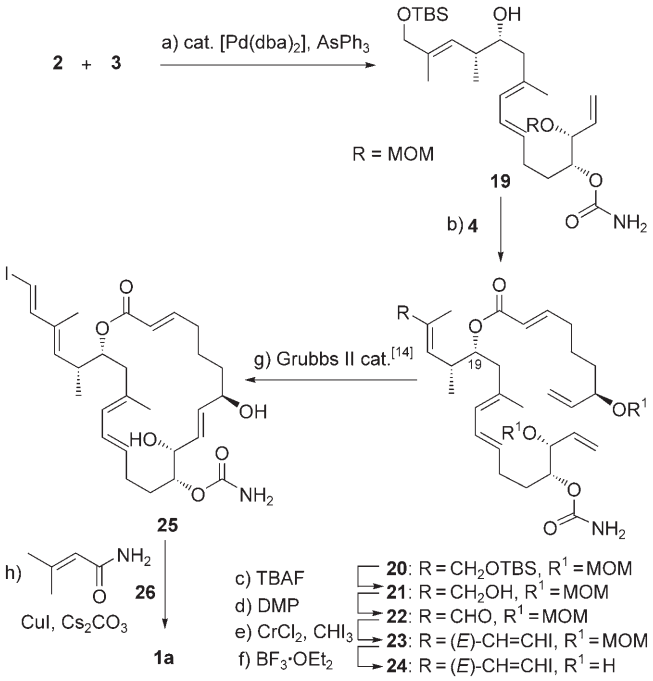
2) cat. $[Pd(dba)_2]$/nBu_3SnH, 62% overall yield)[11] gave the desired vinyl stannane **3**. A similar sequence from **9** employing (+)-Ipc_2BOMe led sequentially to *ent*-**11** and *ent*-**3**.

The third required fragment **4** was prepared through a Jacobsen resolution[12] as outlined in Scheme 4. Thus, *m*CPBA-mediated epoxidation of the TBS-protected 5-hexene-1-ol (**13**), followed by exposure to (*R*,*R*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminecobalt(II) catalyst (5 mol%), AcOH (0.01 equiv) and H_2O (0.5 equiv) in CH_2Cl_2, led smoothly to enantiomerically enriched (>99% *ee*, Mosher ester analysis) epoxide **14** in 47% yield (maximum 50%).[12b] Epoxide opening with the sulfur ylide derived from $Me_3S^+I^-$ and *n*BuLi[13] led to allylic alcohol **15** (90% yield), whose conversion into carboxylic acid **4** involved MOM protection (**16**, 85% yield), desilylation (**17**, 95% yield), oxidation (DMP, 95% yield), Wittig reaction with $Ph_3P{=}CHCO_2Me$ (**18**, 90% yield), and saponification (aq KOH, 85% yield). Employing the same starting material **13**, the identical sequence, and the corresponding (*S*,*S*)-Jacobsen Co^{II} catalyst allowed the construction of *ent*-**4** via *ent*-**14**.

With all three key building blocks **2**–**4** in hand, we then turned our attention to their assembly and elaboration to our original target **1a**. In considering the sequence of reactions to construct the macrocycle, we opted for the one shown in Scheme 5 in which the ring-closing metathesis[14] was reserved as the last step, while the Stille coupling[15] reaction was chosen to begin the process, thus leaving the Yamaguchi esterification[16] as the middle reaction. Thus, reaction of the vinyl iodide **2** with stannane **3** in the presence of catalytic



Scheme 4. Construction of C1–C8 carboxylic acid fragment **4**. Reagents and conditions: a) *m*CPBA (1.3 equiv), CH_2Cl_2, 0→23 °C, 3 h, 90%; b) (*R*,*R*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminecobalt(II) (5 mol%), AcOH (0.01 equiv), H_2O (0.5 equiv), CH_2Cl_2, 0→23 °C, 24 h, 47% (>99% *ee*); c) $Me_3S^+I^-$ (4.0 equiv), *n*BuLi (1.6 M in hexanes, 5.8 equiv), THF, −30→23 °C, 5 h, 90%; d) MOMCl (4.0 equiv), iPr_2NEt (2.0 equiv), CH_2Cl_2, 0→23 °C, 6 h, 85%; e) TBAF (1.0 M in THF, 1.2 equiv), THF, 23 °C, 2 h, 95%; f) DMP (1.5 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 23 °C, 2 h, 95%; g) $Ph_3P{=}CHCO_2Me$ (1.2 equiv), CH_2Cl_2, 23 °C, 16 h, 90%; h) KOH (5.0 equiv), dioxane/H_2O (4:1), 23 °C, 24 h, 85%. *m*CPBA = *meta*-chloroperoxybenzoic acid.



Scheme 5. Coupling of fragments **2**, **3**, and **4**, and completion of the total synthesis of the originally proposed structure **1a**. Reagents and conditions: a) $[Pd(dba)_2]$ (0.25 equiv), $AsPh_3$ (3.0 equiv), LiCl (3.0 equiv), NMP, 23 °C, 12 h, 67%; b) 2,4,6-trichlorobenzoyl chloride (1.1 equiv), Et_3N (1.5 equiv), **4** (1.1 equiv), DMAP (1.1 equiv), toluene, 23 °C, 12 h, 61%; c) TBAF (1.0 M in THF, 1.5 equiv), THF, 23 °C, 2 h; d) DMP (1.2 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 23 °C, 30 min, 79% for the 2 steps; e) $CrCl_2$ (10.0 equiv), CHI_3 (6.0 equiv), THF/dioxane (1:6), 23 °C, 2 h, 80% (>95:5 *E*/*Z*); f) $BF_3{\cdot}Et_2O$ (6.0 equiv), Me_2S, 23 °C, 30 min, 46% (+10% of mono-MOM intermediates; g) Grubbs II cat. (0.2 equiv), CH_2Cl_2, 23 °C, 1 h, 76%; h) **26** (2.0 equiv), CuI (1.0 equiv), Cs_2CO_3 (1.0 equiv), *N*,*N*′-dimethylethylenediamine (2.0 equiv), DMF, 23 °C, 7 h, 44% based on 36% recovered starting material (+10% of decarbamated **1a**). NMP = *N*-methylpyrrolidone; DMF = *N*,*N*′-dimethylformamide.

$[Pd(dba)_2]$, $AsPh_3$, and LiCl provided tetraene **19** in 67% yield. Incorporation of carboxylic acid **4** into the growing molecule was then facilitated by 2,4,6-trichlorobenzoyl chloride in the presence of Et_3N and DMAP, to furnish ester **20** (61% yield). Conversion of **20** into vinyl iodide **23** was achieved in three steps: 1) TBAF-induced desilylation to **21**, 2) oxidation with DMP to **22** (79% for the two steps), and 3) olefination with $CrCl_2/CHI_3$[17] to give **23** in 80% yield. Removal of the two MOM groups from **23** ($BF_3{\cdot}Et_2O/Me_2S$)[18] led to the desired precursor **24** (46% yield with 10% of recovered mono-MOM intermediates, which were recycled), thus setting the stage for the much-anticipated ring-closing metathesis. Gratifyingly, exposure of bisallylic compound **24** to Grubbs II catalyst in CH_2Cl_2 solution at ambient temperature led to the smooth and exclusive formation of the macrocycle **25** (76% yield) with *trans* geometry at the newly formed double bond as confirmed by NMR spectroscopy ($^{H-H}J_{8,9}$=15.5 Hz). Finally, installation of the enamide moiety to afford structure **1a** was achieved through application of the Buchwald copper-catalyzed protocol (**26**, CuI/Cs_2CO_3/*N*,*N*′-dimethylethylenediamine)[19] in 44% yield based on 36% recovered starting material and 10% decarbamated **1a**.

Although similar, the ^{1}H NMR spectroscopic data of synthetic **1a** did not match those reported[1] for the natural palmerolide A, with notable differences for H7 and H10. At this stage we became convinced that the true structure of palmerolide A must be 19-*epi*-20-*epi*-**1a** (*ent*-**1b**) which became our next target. After reaching *ent*-**1b** (from *ent*-**2**, **3**, and **4**, and following the developed synthetic technology), whose ^{1}H NMR data corresponded to those reported for the natural substance, we learned[3] of the revised structure of palmerolide A (**1b**), which immediately became our next priority to synthesize. The total synthesis of **1b** was accomplished from fragments **2**, *ent*-**3**, and *ent*-**4** following the same strategy as that described for the synthesis of **1a** (and *ent*-**1b**) as delineated in Scheme 5. The final stages and advanced intermediates of the total synthesis of **1b** are shown in Scheme 6. Synthetic **1b** exhibited identical physical properties (^{1}H and ^{13}C NMR spectra, and MS) to those reported[1] for natural palmerolide A. In particular, the identical circular dichroism (CD) spectrum and sign of optical rotation of synthetic **1b** to those reported for natural palmerolide A unambiguously validated its absolute configuration and, thus, of the natural product.[3] The CD spectra of both synthetic palmerolide A enantiomers **1b** and *ent*-**1b** shown in Figure 2, corresponded with those published for the natural product and its enantiomer.[3]

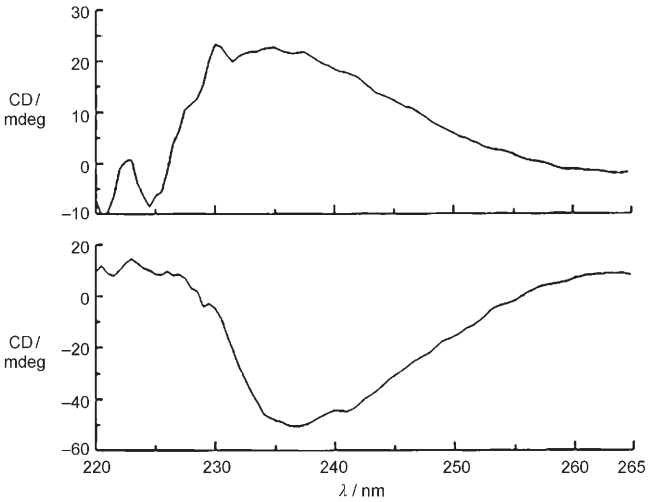


Figure 2. CD spectra of *ent*-**1b** (top, $CHCl_3$, 25 °C, 0.0013 M) and of **1b** (bottom, $CHCl_3$, 25 °C, 0.0025 M).

The described chemistry once again demonstrates the power of the olefin metathesis reaction in complex molecule construction,[14b,c] and delivered the originally proposed[1] structure **1a**, the revised structure **1b**,[3] and its enantiomer *ent*-**1b** of palmerolide A.[20] Furthermore, the flexibility of the strategy to deliver either configuration at each stereocenter allows construction of all stereoisomers of this valuable substance for biological studies.

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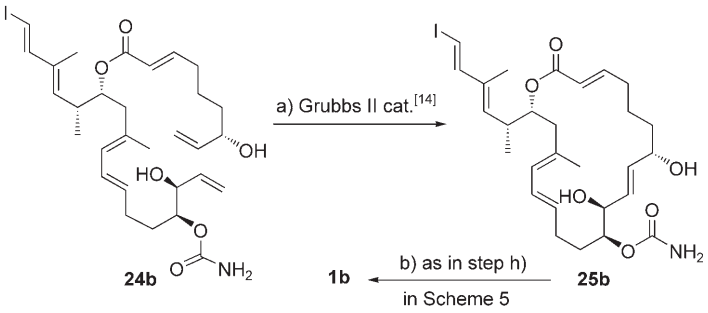

Scheme 6. Final stages of the total synthesis of the revised structure **1b**. Reagents and conditions: a) Grubbs II cat. (0.2 equiv), CH_2Cl_2, 23 °C, 1 h, 72%; b) **26** (2.0 equiv), CuI (1.0 equiv), Cs_2CO_3 (1.0 equiv), *N*,*N*′-dimethylethylenediamine (2.0 equiv), DMF, 23 °C, 7 h, 50% based on 38% recovered starting material (+10% of decarbamated **1b**).

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[20] The isomers of palmerolide A, 19-*epi*-**1a** and 20-*epi*-**1a**, were also synthesized by employing the appropriate building blocks. Full details will be reported in due course.

