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Synthesis of the Originally Proposed Structure of Palmerolide C

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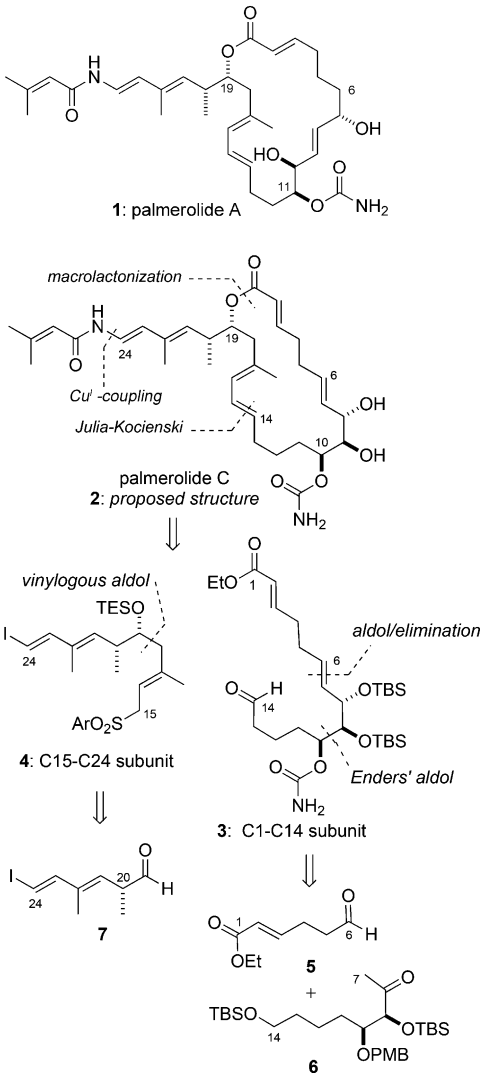
In 2006, Baker and co-workers reported the isolation of palmerolide A,[1] the first member of a unique family of polyketide-derived macrolides from the Antarctic tunicate *Synoicum adareanum* collected in the shallow waters surrounding Anvers Island on the Antarctic Peninsula.[2,3] Significant synthetic attention was drawn to palmerolide A (**1**, Scheme 1) given its remarkable selectivity towards human melanoma cancer cell lines (UACC-62 and Mi14 $IC_{50}=24$ and 76 nM, respectively), culminating in three total syntheses and numerous synthetic studies to date.[4,5] Alongside palmerolide A, eight further palmerolides were co-isolated from *S. adraneum*.[2] Within this family of macrolides, palmerolide C (**2**) is a constitutional isomer of **1** that displays similar activity towards the UACC-62 human melanoma cell line ($IC_{50}=110$ nM).[2a,6] Structurally, palmerolide C shares many features with **1**, supporting a common biogenesis,[1c] including the elaborate side chain appended at C20, containing an *E,E*-dienamide (C21–C24), whereas the 20-membered macrolide core retains the *E,E*-diene at C14–C17. However, palmerolide C differs markedly within the C6–C11 region, with an *E* alkene at C6 and a contiguous stereotriad spanning C8–C10. The absolute configuration of the stereotriad was proposed as 8*S*, 9*S*, 10*S* on the basis of C8-Mosher ester analysis and *J*-based configurational analysis, as shown in **2**.[6] To date no total synthesis of palmerolide C has been reported and herein we report our efforts towards this goal, culminating in the synthesis of the initially proposed structure **2** and a reassignment of the structure of palmerolide C based on our re-evaluation of available spectroscopic data.[6,7]

As outlined in Scheme 1, our strategy towards **2** was reliant on late-stage enamide installation and macrolactonization with the assembly of the carbon skeleton arising from the Julia–Kocienski olefination[8] at C14–C15 between the fully elaborated coupling partners aldehyde **3** (C1–C14) and sulfone **4** (C15–C24), which we viewed advantageous in terms of minimizing the number of post-coupling operations. In turn, the synthesis of the two key coupling partners was envisaged to arise from the application of suitable aldol-based coupling strategies. The C1–C14 aldehyde **3** would be reliant on an aldol/elimination/reduction sequence using C1–C6 aldehyde **5** and C7–C14 methyl ketone **6**. In turn the C15–C24 subunit **4** would rely on an ambitious vinylogous Mukaiyama aldol reaction reliant on Felkin–Anh induction from the α-chiral iododiene aldehyde **7** to control the introduction of the C19 stereocenter.[9]



Scheme 1. Synthetic strategy for originally proposed structure of palmerolide C. Ar = 1-phenyltetrazole, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl.

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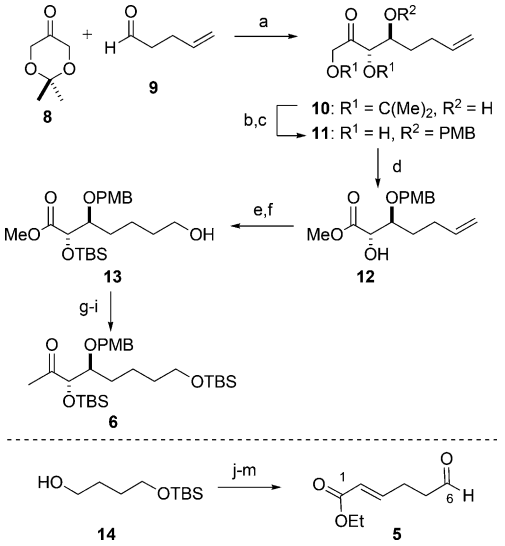
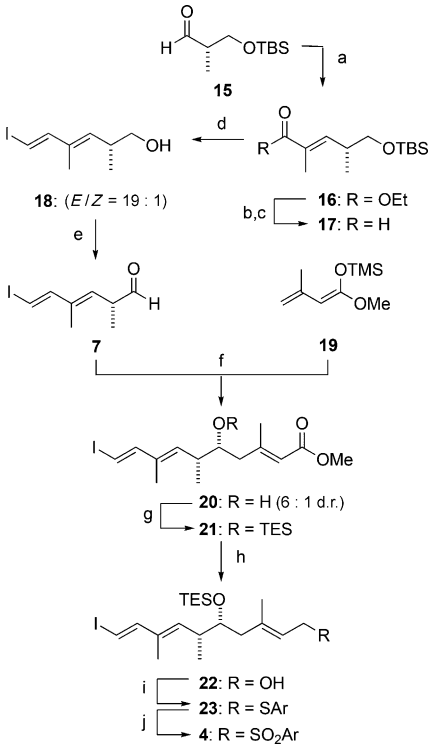


Scheme 2. Synthesis of C1–C14 subunit **3**: a) 30 mol% (*S*)-proline, $CHCl_3$, RT, 5 days, 44% (96% *ee*); b) PMBTCA, $La(OTf)_3$, $PhCH_3$, 0°C to RT, 6 h (77%); c) *p*-TsOH·H_2O, MeOH, RT, 2 h (92%); d) i) H_5IO_6, THF/H_2O, 0°C to RT, 12 h; ii) MeI, K_2CO_3, DMF, 0°C, 2 h (64%); e) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78°C, 2 h (98%); f) i) thexylBH_2, THF, 0°C, 1 h; ii) H_2O_2 (30% aq), NaOH (10 wt% aq), 0°C, 20 min (96%); g) TBSCl, ImH, CH_2Cl_2, RT, 10 h (92%); h) (MeO)NHMe·HCl, *i*PrMgCl, THF, −40°C, 4 h (97%); i) MeMgBr, THF, 0°C, 1 h (96%); j) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, 1 h; Et_3N, −78°C to RT, 1 h (80%); k) $(EtO)_2P(O)CH_2CO_2Et$, LiCl, *i*PrNEt$_2$, MeCN, RT, 18 h (77%); l) CSA (10 mol%), CH_2Cl_2/MeOH (4:1), 0°C, 1.5 h (98%); m) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, 1 h; Et_3N, −78°C to RT, 1 h (87%). PMBTCA = *para*-methoxybenzyl trichloroacetimidate, OTf = trifluoromethanesulfonate, *p*-TsOH·H_2O = *para*-tolunenesulfonic acid monohydrate, TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate, thexyl = 2,3-dimethyl-2-butyl, TBSCl = *tert*-butyldimethylsilyl chloride, ImH = imidazole, CSA = (±)-camphorsulfonic acid.



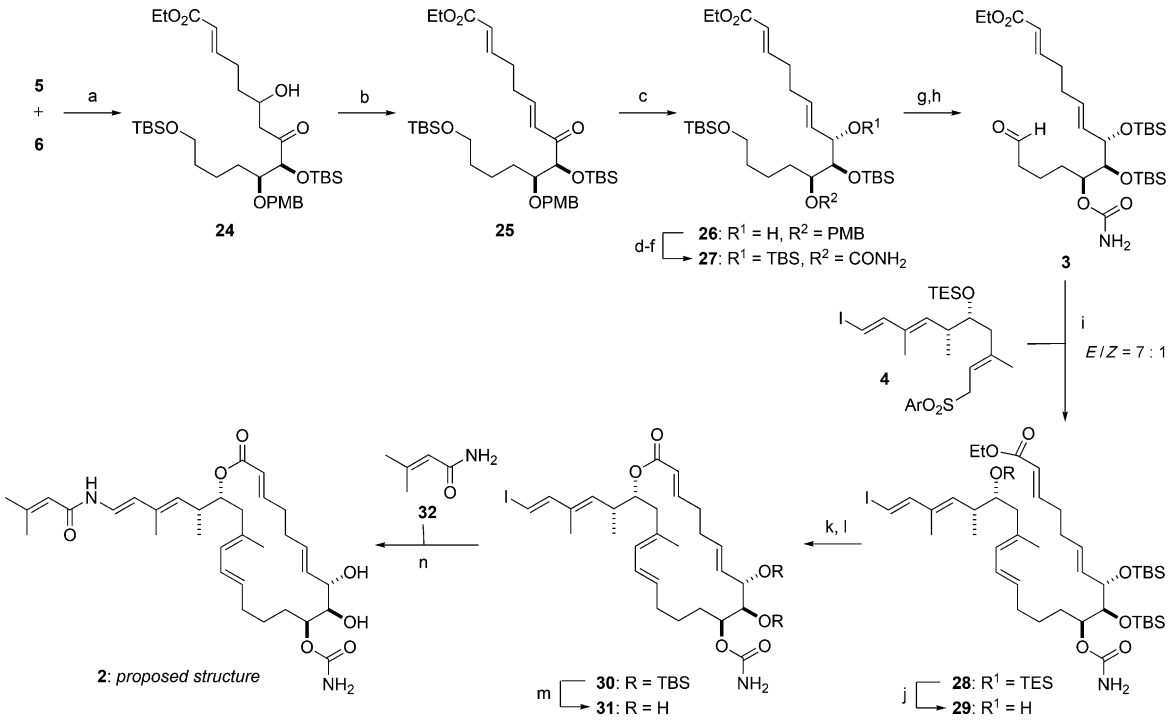
Scheme 3. Synthesis of C15–C24 subunit **4**: a) $(EtO)_2P(O)CH(CH_3)CO_2Et$, $Ba(OH)_2$, wet THF, 0°C, 10 h (76%, *E*/*Z* = 7:1); b) DIBAL, CH_2Cl_2, −78°C, 4 h (81%); c) DMP, $NaHCO_3$, CH_2Cl_2, 0°C, 1 h (90%); d) i) $CrCl_2$, CHI_3, THF, 1,4-dioxane, RT, 2 h; ii) TBAF, THF, 0°C to RT, 1 h (90%, *E*/*Z* = 19:1); e) DMP, $NaHCO_3$, CH_2Cl_2, 0°C, 1 h (90%); f) $BF_3{\cdot}Et_2O$, CaH_2, CH_2Cl_2, −95°C, 2 h (70%, 6:1 d.r.); g) TESOTf, 2,6-lutidine, CH_2Cl_2, −78°C, 2 h (96%); h) DIBAL, CH_2Cl_2, −78°C, 2 h (81%); i) 1H-mercaptophenyltetrazole, DIAD, PPh_3, THF, 0°C to RT, 1 h (80%); j) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, H_2O_2, HMPA, MeOH, 0°C to RT, 12 h (95%). Ar = 1-phenyltetrazole, DIBAL = diisobutylaluminium hydride, TBAF = tetrabutylammonium fluoride, DMP = Dess–Martin periodinane, TESOTf = triethylsilyl trifluoromethanesulfonate, DIAD = diisopropyl azodicarboxylate, HMPA = hexamethylphosphoramide.

As shown in Scheme 2, the synthesis of the C1–C14 subunit **3** began with Enders' proline-catalyzed organocatalytic cross aldol reaction of dioxanone **8** and aldehyde **9** to introduce the *anti*-configured C8 and C9 stereocenters.[10] Reaction of **8** and **9** with 30 mol% (*S*)-proline in chloroform over five days provided *anti*-aldol adduct **10** in 44% yield with 96% enantiomeric excess (*ee*). PMB ether formation and acetonide deprotection provided ketodiol **11** in 71% yield over two steps. Regioselective oxidative cleavage of **11** with periodic acid and methylation of the intermediate carboxylic acid gave α-hydroxyester **12** (64%).[11] Protection of the α-hydroxyl as its TBS ether (98%) was followed by hydroboration with thexylborane to provide **13** (96%). TBS protection, conversion of the resulting ester to the Weinreb amide and subsequent addition of MeMgBr provided efficient access to the C7–C14 methyl ketone **6**, (86% from **13**) in readiness for the aldol/elimination sequence to introduce the C6–C7 alkene. The required C1–C6 aldehyde **5**[12] was readily prepared from mono-TBS-protected 1,4-butanediol **14** in 53% yield over four steps.

As outlined in Scheme 3, preparation of the C15–C24 subunit began with the homologation of the readily available α-chiral aldehyde **15**[13] to install the C21 *E*-trisubstituted alkene. Reaction of **15** and triethyl 2-phosphonopropionate under the conditions described by Paterson and co-workers ($Ba(OH)_2$ in wet THF) provided the *E*-trisubstituted enoate **16** (76%, *E*/*Z* = 7:1).[14,15] DIBAL reduction and subsequent reoxidation of the intermediate alcohol with Dess–Martin periodinane gave aldehyde **17** in preparation for the installation of the sensitive C24-vinyl iodide. Initially, Takai olefination[16] of **17** proved troublesome due to the propensity of the intermediate to both isomerize and decompose upon isolation. Gratifyingly, this issue was resolved by submitting the crude reaction products directly to TBAF to give alcohol **18** in excellent yield and selectivity (90% over two steps, *E*/*Z* = 19:1). Dess–Martin periodinane oxidation of **18** provided aldehyde **7** in preparation for the vinylogous Mukaiyama aldol reaction to introduce the C19-stereocenter.[9] Treatment of **7** and silyl ketene acetal **19** with $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at −95°C provided the desired γ-adduct **21** preferentially with good levels of Felkin–Anh induction (70%, d.r. = 6:1).[17] Chromatographic separation provided **21** as a single

pure diastereomer, which was readily protected as its TES ether **22** (TESOTf/2,6-lutidine, 96%). The resulting ester was reduced with DIBAL to give alcohol **23**. Treatment of **23** with 1*H*-mercaptophenyltetrazole under Mitsunobu conditions (80%) gave sulfide **24**. The use of HMPA as a co-solvent with MeOH in the oxidation of **24** with H_2O_2 and ammonium molybdate proved critical in providing access to sulfone **4** in 95% yield,[18] in preparation for the C14–C15 Julia–Kocienski olefination.

With the key subunits in hand, attention turned to their assembly beginning with the aldol/elimination coupling of **5** and **6** to install the C6–C7 alkene (Scheme 4). Thus, enolization of **6** with *c*-Hex_2BCl/Et_3N and addition of aldehyde **5** followed by mild oxidative work-up provided aldol adduct **24** in 90% yield, as an inconsequential 1.6:1 mixture of diastereomers.[19,20] Treatment of **24** with Martin sulfurane promoted elimination to provide the *E*-enone **25** exclusively in 95% yield.[21] Reduction of enone **25** under Luche conditions ($NaBH_4$, $CeCl_3$, −78°C) proceeded with high levels of substrate control over the C7 stereocenter to give alcohol **26** in 94% yield.[22,23] Formation of the TBS ether at C7 (87%) was then followed by oxidative cleavage of the C10-PMB ether with DDQ (88%) and carbamate formation (72%) to provide **27**. The fully elaborated C1–C14 aldehyde **3** was completed in two further steps involving selective primary TBS ether deprotection at C14 with CSA in CH_2Cl_2/MeOH (93%) and Dess–Martin oxidation (80%). Having established access to **3**, our attention turned to the final C14–C15 coupling to introduce the *E,E*-diene motif and the completion of the putative structure of palmerolide C. In practice, treatment of sulfone **4** with NaHMDS in THF at −78°C followed by the addition of aldehyde **3** proceeded smoothly to give the *E,E*-diene **28** in 78% yield ($E/Z = 6:1$) completing the C1–C24 carbon skeleton.[8] Selective deprotection of the C19-TES ether with HF·pyridine/pyridine (88%) provided **29**. At this stage the minor *Z,E*-diene from the coupling reaction was separated by chromatography. Subsequent cleavage of the C1-ethyl ester with KOTMS provided the intermediate *seco*-acid, which smoothly underwent macrolactonization under Yamaguchi conditions to provide the 20-membered macrolide **30** in 71% yield over two steps.[24] Removal of the remaining TBS ethers at C8 and C9 was then effected by treatment of **30** with TBAF in THF to give the advanced precursor **31** (85%). Following extensive optimization of the protocol developed by Nicolaou and Chen for palmerolide A,[4b–e] the installation of the terminal enamide by the Buchwald Cu-catalyzed coupling[25] of **31** and amide **32** with CuI (2 equiv), K_2CO_3 (5 equiv), and *N,N′*-dimethylethylene-



Scheme 4. Completion of the originally proposed structure of palmerolide C: a) i) Compound **6**, *c*Hex_2BCl, Et_3N, Et_2O, −78°C, 0.5 h; ii) compound **5**, −78°C, 2 h; iii) H_2O_2 (30% aq), pH 7 buffer, MeOH, 0°C, 0.5 h (90%); b) $[C_6H_5C(CF_3)_2O]_2S(C_6H_5)_2$, CH_2Cl_2, −10°C, 1 h (95%); c) $CeCl_3{\cdot}7H_2O$, $NaBH_4$, MeOH, −78°C, 1 h (94%); d) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78°C, 2 h (87%); e) DDQ, CH_2Cl_2, pH 7 buffer, 0°C, 1 h (88%); f) $Cl_3CC(O)NCO$, CH_2Cl_2, 0°C to RT 1 h; then Al_2O_3, CH_2Cl_2, RT, 16 h (72%); g) CSA, CH_2Cl_2/MeOH (6:1), 0°C, 1 h (93%); h) DMP, $NaHCO_3$, CH_2Cl_2, 0°C, 1 h (80%); i) NaHMDS, THF, −78°C, 1 h (78%, $E/Z = 7:1$); j) HF·pyr, pyr, THF, 0°C, 1 h (88%); k) KOTMS, THF, 0°C, 10 h; l) i) 2,4,6-trichlorobenzoyl chloride, Et_3N, PhMe, RT, 1 h; ii) DMAP, RT, 15 h (71% from **29**); m) TBAF, THF, 0°C to RT, 2 h (85%); n) CuI, K_2CO_3, *N,N′*-dimethylethylenediamine, DMF, RT, 1 h (53%). *c*Hex = cyclohexyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, NaHMDS = sodium bis(trimethylsilyl)-amide, Ar = 1-phenyltetrazole, HF·pyr = hydrogen fluoride pyridine complex, pyr = pyridine, KOTMS = potassium trimethylsilanolate, DMAP = 4-*N,N*-dimethylaminopyridine, DMF = *N,N*-dimethylformamide.

diamine (3 equiv) in degassed DMF provided **2** in 53% isolated yield completing the synthesis of the proposed structure of palmerolide C (**2**).

At this point, comparison of the ^{1}H NMR spectroscopic data of our synthetic material **2** with that reported for palmerolide C in both [D_6]DMSO and [D_3]MeCN did not match.[26] There were distinct differences between the H8, H9, and H10 resonances suggesting that at least one of the three stereocenters within the C8–C10 stereotriad had been incorrectly assigned. Based on the available spectroscopic data, we undertook a re-evaluation of the original *J*-based configurational analysis.[6,27] The initial assignment for palmerolide C proposed a *syn* relationship between H8–H9 and an *anti* relationship between H9–H10 as shown in Figure 1

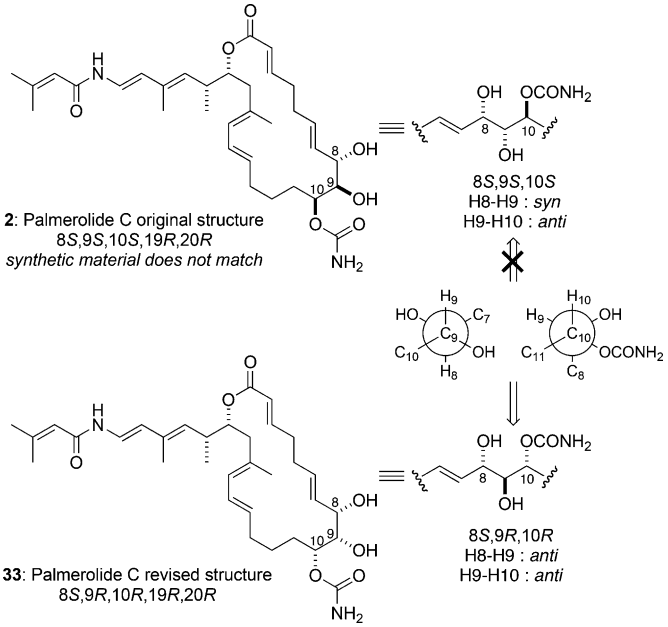


Figure 1. Reassignment of palmerolide C based on re-evaluation of *J*-based configurational analysis data (Newman projections reproduced from ref. [6]).

with the 8*S*,9*S*,10*S* configuration (Figure 1). However, the Newman projections presented suggested *anti* relationships between both H8–H9 and H9–H10. Based on this analysis we propose the reassignment of the stereotriad as 8*S*,9*R*,10*R* and the revised structure of palmerolide C to be as depicted in structure **33**.

In summary, we have completed a highly stereocontrolled synthesis of **2**, the originally proposed structure of palmerolide C. The synthesis proceeds in 23 steps in the longest linear sequence. The use of a fully functionalized C1–C14 subunit **3** and incorporating the *E,E*-iododiene in **4** enables an efficient five-step endgame following the final key C14–C15 bond construction. Further studies are currently underway to secure the unambiguous structural identity of palmerolide C.

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Keywords: macrolide · melanoma · natural products · structure elucidation · total synthesis

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