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A Formal Total Synthesis of Palmerolide A

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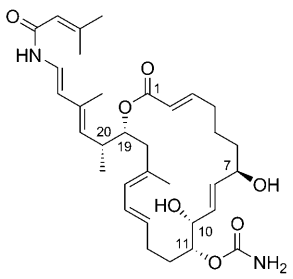
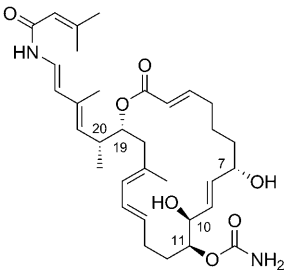
The marine environment continues to be a rich source for novel secondary metabolites with complex molecular architectures that show exceptional biological activity. In particular, the Antarctic Ocean provides a unique chemical diversity, since this ecosystem was isolated and not explored for more than 20 million years.[1] However, the Antarctic treaty[2] prohibiting commercial exploitation of marine sources hinders the progress of promising drug-like natural products isolated from this area. Nevertheless, it provides an opportunity for synthetic chemists to play a significant role to convert this promise into reality by synthesizing these natural products in sufficient quantities. One such natural product, a polyketide macrolide palmerolide A, was recently isolated by Baker's group from the circumpolar tunicate *Synoicum adareanum*.[3a] It exhibits cytotoxic activity against melanoma cell line UACC-62 with the LC_{50} of 18 nM and modest activity against colon cancer cell line HCC-2998. This marine natural product appears to act on melanoma cells through inhibition of vacuolar ATPase with an IC_{50} of 2 nM. The structure of palmerolide A was assigned as **1** based on a high-field NMR spectroscopy and Mosher's ester stereochemical studies.[3a]

The promising antitumor properties of palmerolide A coupled with its extremely limited supply have attracted much attention from the synthetic community. From a synthetic point of view, palmerolide A is a challenging 20-membered macrolide with an enamide side chain, a labile carbamate moiety, five chiral centers, and a 1,3-diene system in the core of an α,β-unsaturated macrocyclic lactone. De Brabander and co-workers reported the first total synthesis of originally assigned structure **1** and also deduced the correct relative stereochemistry and synthesized *ent*-palmerolide A.[4] Nicolaou and co-workers independently reported



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



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

the synthesis of the revised structure of palmerolide A (**1a**), its enantiomer, and the originally proposed structure by using ring-closing metathesis (RCM) as the key reaction.[5] Recently Hall and co-workers explored the organoboron methodology to synthesize palmerolide A.[6] Apart from these total syntheses, one formal synthesis,[7e] and a few partial synthetic approaches have been reported,[7] including one from our group.[7a] Nicolaou and co-workers also disclosed the synthesis and evaluation of a library of palmerolide analogues.[8]

As a part of our ongoing research program on the synthesis of biologically active natural and unnatural products using a metathetic approach,[9] we became interested in the total synthesis of palmerolide A and herein we disclose the synthesis of macrocycle **2**, which is the key intermediate in the total synthesis of palmerolide A reported by Nicolaou and co-workers.

The key steps in our convergent strategy for palmerolide A, as illustrated in Scheme 1, involve the formation of a *syn* aldol by Shimizu reaction,[10] assembly of subunits **3** and **4** by Julia–Kocienski reaction,[11] Yamaguchi esterification,[12] and finally cyclization by RCM.[13]

The synthesis of C15–C23 fragment **3** began with the oxidation of known alcohol **6**[14] by 1-hydroxy-1,2-benziodoxol-3(1*H*)-one-1-oxide (IBX) to the corresponding aldehyde, which upon Wittig reaction furnished the ester **7** (Scheme 2). Reduction of this ester with LAH provided the

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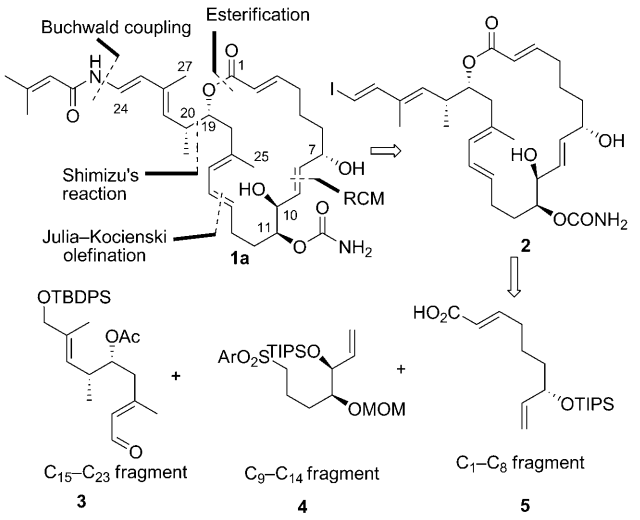
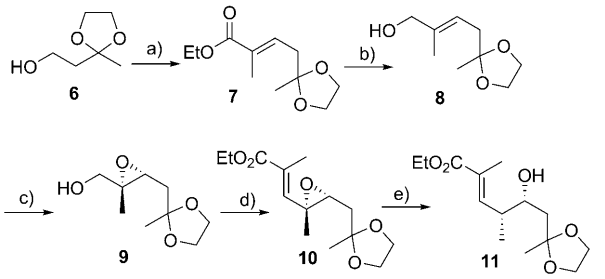
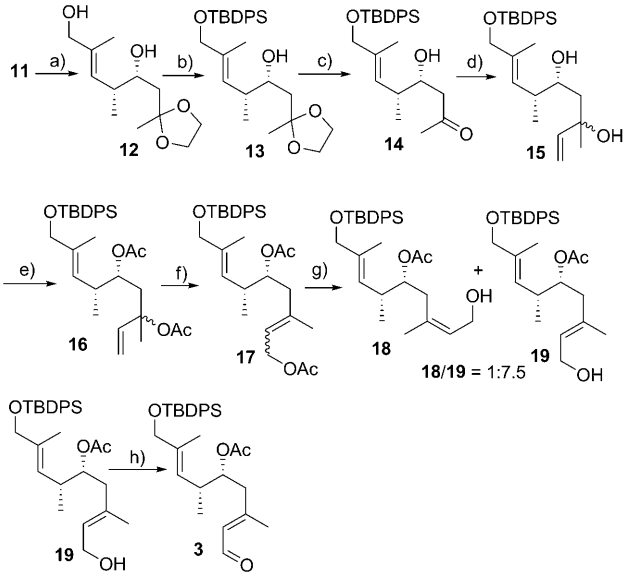


Scheme 1. Retrosynthesis of palmerolide A (**1a**). TIPS = triisopropylsilyl, TBDPS = *tert*-butyldiphenylsilyl, MOM = methoxymethyl.



Scheme 2. Synthesis of intermediate **11**. a) i) IBX, ethyl acetate, reflux, 6 h; ii) $PPh_3C(CH_3)CO_2Et$, toluene, RT, 3 h, 85% (2 steps); b) lithium aluminum hydride (LAH), diethyl ether, 0 °C to RT, 2 h, 96%; c) D-(−)-diisopropyl tartrate (DIPT), $Ti(iPrO)_4$, CH_2Cl_2, 4 Å molecular sieves, CaH_2, *t*BuOOH, −25 °C, 4 h, 90%; d) i) IBX, ethyl acetate, reflux, 6 h; ii) $PPh_3C(CH_3)CO_2Et$, toluene, RT, 3 h, 89% (2 steps); e) $[Pd_2(dba)_3]\cdot CHCl_3$ (dba = dibenzylideneacetone), HCO_2H, nBu_3P, Et_3N, 1,4-dioxane, RT, 16 h, 94%.



Scheme 3. Synthesis of fragment **3**. a) Diisobutylaluminum hydride (DIBAL-H), CH_2Cl_2, −78 °C, 1 h, 74%; b) TBDPSCl, CH_2Cl_2, imidazole, RT, 2 h, 85%; c) $PdCl_2\cdot 2CH_3CN$, acetone, 0 °C, 30 min, 89%; d) $CH_2CHMgBr$, THF, 0 °C to RT, 5 h, 73%; e) Ac_2O, py, 4-dimethylaminopyridine (DMAP), 50 °C, 16 h, 78%; f) $PdCl_2\cdot 2CH_3CN$, THF, RT, 6 h, 88%; g) NH_3/MeOH, RT, 16 h, 70% **19**, 9% **18**; h) MnO_2, CH_2Cl_2, RT, 2 h, 92%.

alcohol **8**, which was then subjected to Katsuki–Sharpless asymmetric epoxidation[15] to produce epoxide **9** (90% enantiomeric excess (*ee*) based on ^{19}F NMR spectroscopy analysis of its Mosher ester derivative) in 90% yield.

Oxidation of **9** followed by one more Wittig reaction smoothly afforded the ester **10**. At this stage, a stereoselective Pd-catalyzed hydrogenolysis[10] was carried out to give the *syn*-alkoxy ester **11** in 94% yield. Earlier synthetic approaches reported for this molecule involve the construction of *syn* C19–C20 chiral centers by using classical asymmetric aldol approaches. This non-aldol approach, developed by Shimizu and co-workers,[10] is a high-yielding reaction and has been rarely explored in the synthesis of natural products.

The hydroxy ester **11** was easily reduced with DIBAL-H to diol **12** (Scheme 3), and the primary alcohol was then selectively protected as TBDPS ether **13**. Attempts to cleave the ketal **13** under mild acidic conditions led to the formation of elimination product significantly. After some experimentation, this difficulty was circumvented by transketalization using $PdCl_2\cdot 2CH_3CN$ and acetone to furnish the ketone **14** in good yield.[16] Addition of vinyl Grignard reagent to the ketone **14** followed by acetylation of the resultant diol afforded the diacetate **16**. A palladium(II)-catalyzed rearrangement of allylic acetate[17] gave an inseparable diastereomeric mixture of **17**. Selective cleavage of terminal acetate, achieved by treating with saturated solution of NH_3-MeOH, made it possible to separate the diastereomers **18** and **19** by column chromatography ($E/Z = 7.5:1$), which were identified by 2D-NOE NMR spectroscopy experiments. The required *E* isomer **19** was then subjected to oxidation with MnO_2 to give the fragment **3** required for Julia–Kocienski reaction.

With good quantities of **3** in hand, our next task was to synthesize the other fragment **4** required for Julia-Kocienski reaction, which commenced with the halogenation of known allyl alcohol **20**[18] to allyl chloride **21** by using an Appel reaction (Scheme 4).[19] Sharpless dihydroxylation of allyl chloride **21** gave a chlorohydrin, which upon treatment with K_2CO_3 provided the epoxy alcohol **22** (88% *ee* based on ^{19}F NMR spectroscopy analysis of the Mosher's ester derivative). The secondary alcohol was then protected as its MOM-ether **23** before treating with dimethylsulfonium ylide to obtain the allylic alcohol **24** in 81% yield.[20] Protection of the free alcohol as the TIPS ether and selective cleavage of the primary *tert*-butyldimethylsilyl (TBS) group yielded

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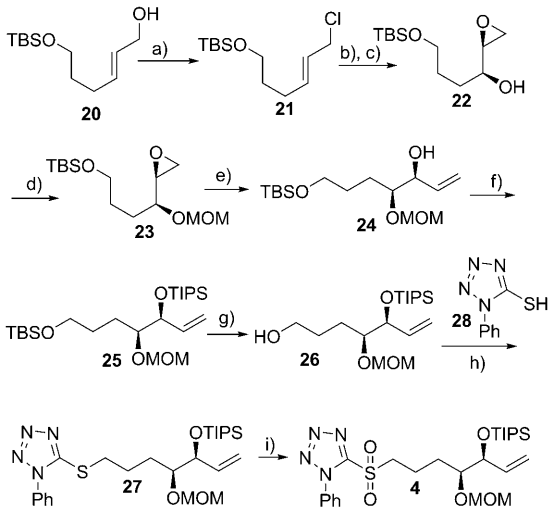
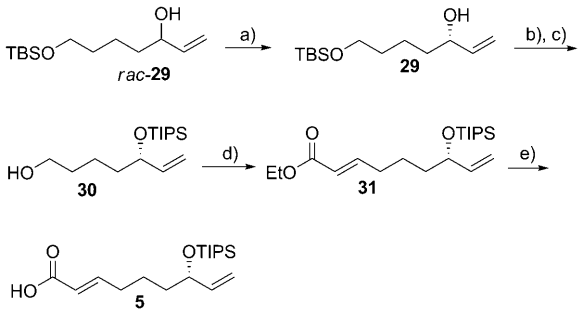


Scheme 4. Synthesis of fragment **4**. a) PPh_3, CCl_4, $NaHCO_3$, reflux, 6 h, 82%; b) AD-mix-α, $CH_3SO_2NH_2$, $NaHCO_3$, *t*BuOH/H_2O, 0°C, 24 h, 92%; c) K_2CO_3, MeOH, RT, 3 h, 82%; d) MOMCl, *i*Pr_2NEt, CH_2Cl_2, 2 h, 92%; e) $(CH_3)_3SI$, *n*BuLi, THF, −18°C to RT, 1 h, 81%; f) triisopropylsilyl trifluoromethanesulfonate (TIPSOTf), 2,6-lutidine, CH_2Cl_2, 0°C to RT, 1 h, 87%; g) AcOH/THF/H_2O (3:1:1), RT, 6 h, 86%; h) **28**, PPh_3, diisopropyl azodicarboxylate (DIAD), THF, −20°C, 1 h, 92%; i) $(NH_4)_6Mo_7O_{24}$, H_2O_2, EtOH, 0°C to RT, 12 h, 94%.

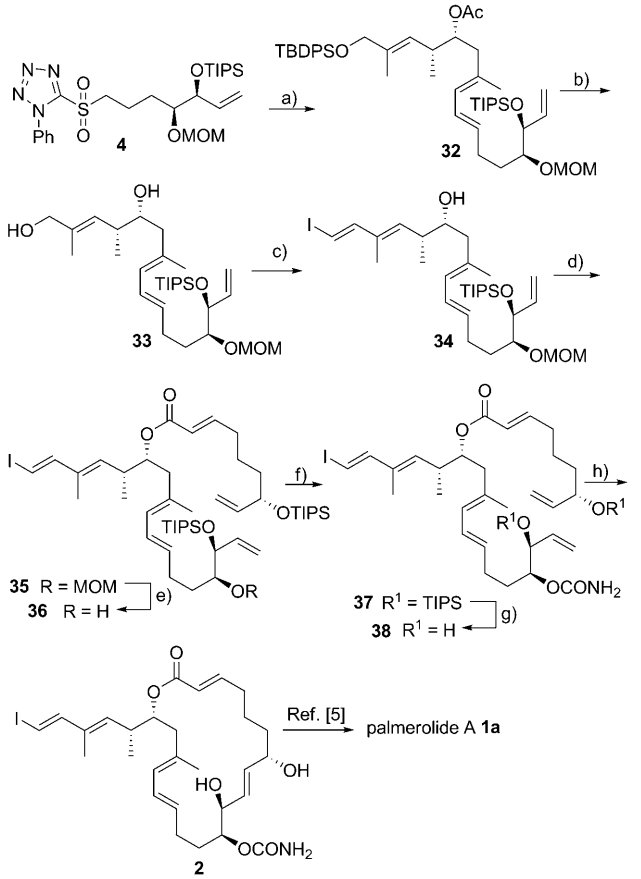
the alcohol **26** in good yield. The synthesis of key sulfone fragment **4** was accomplished by a Mitsunobu reaction on **26** with *N*-phenyl-tetrazolethiol **28** followed by oxidation.

Synthesis of the remaining fragment **5** began with the Sharpless kinetic resolution[21] of known alcohol *rac*-**29**,[22] affording the enantiomerically enriched allylic alcohol **29** (95% *ee* based on Mosher's ester derivative) in good yield. Protection of the alcohol as its TIPS ether followed by selective cleavage of primary TBS ether delivered the primary alcohol **30**.[23] IBX oxidation followed by Horner–Wadsorth–Emmons reaction of the resulting aldehyde afforded the conjugated ester **31**, which upon saponification with LiOH furnished the acid **5** (Scheme 5).



Scheme 5. Synthesis of fragment **5**. a) D-(−)-DIPT, Ti(*i*PrO)$_4$, CH_2Cl_2, 4 Å molecular sieves, CaH_2, *t*BuOOH, −22°C, 6 d, 42%; b) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0°C to RT, 1 h, 87%; c) AcOH/THF/H_2O (3:1:1), RT, 6 h, 76% d) i) IBX, EtOAc, reflux, 5 h.; ii) $EtO_2CCH_2P(O)(OEt)_2$, diisopropylethylamine (DIPEA), LiCl, THF, RT, 12 h, 80% (2 steps, *E*/*Z* >95:5); e) LiOH, H_2O/THF/CH_3OH (2:1:1), 0°C to RT, 8 h, 68%.

Having synthesized all the three fragments, we then focused our attention on coupling these fragments to accomplish the synthesis of palmerolide A. As anticipated, the key Julia–Kocienski olefination between sulfone **4** and aldehyde **3** proceeded smoothly to afford the required *E* olefin **32** in 80% yield (Scheme 6). A one-pot cleavage of TBDPS ether



Scheme 6. Synthesis of macrocycle **2**. a) LiHMDS (HMDS = hexamethyldisilazane), **3**, THF, −78°C, 45 min. 80% (>95:5 *E*/*Z*); b) NaOH, CH_3OH, reflux, 10 h, 78%; c) i) MnO_2, CH_2Cl_2, RT, 6 h; ii) $CrCl_2$, CHI_3, THF, 0°C, 1 h, 72% (>95:5 *E*/*Z*) (2 steps); d) **5**, 2,4,6-trichlorobenzoyl chloride, Et_3N, benzene, RT, 1 h, then DMAP, **34**, RT, 1 h, 68%; e) AcCl, EtOH, THF, 60°C, 10 min. 70%; f) $Cl_3CCONCO$, CH_2Cl_2, 0°C, 1 h, then basic Al_2O_3, 0°C to RT, 1 h, 80%; g) tetrabutylammonium fluoride (TBAF), THF, 0°C, 4 h, 66%; h) Grubbs second generation catalyst (5 mol%) CH_2Cl_2, RT, 1 h, 70%.

and acetate was successfully achieved by an alkaline solution in methanol at elevated temperature led to the diol **33**.[24] The allylic alcohol was then selectively oxidized with MnO_2 to an aldehyde, which upon Takai olefination[25] paved the way to the vinyl iodide **34**. Yamaguchi esterification with acid **5** provided the ester **35**, which was then subjected to MOM ether cleavage. After screening various conditions, the MOM group was successfully cleaved by a mixture of acetyl chloride, EtOH, and THF at elevated temperature to furnish the desired alcohol **36** in good yield.[26] Treatment of this alcohol with trichloroacetylisocyanate fol-

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lowed by basic alumina afforded the carbamate **37**. Both TIPS groups were cleaved by using TBAF (5 equiv) at 0 °C to afford the desired diol **38**, an advanced intermediate in Nicolaou's synthesis of palmerolide A. The key RCM reaction of **38** with the Grubbs catalyst (G-II) also proceeded smoothly to provide the macrocyclic core **2** of palmerolide A, as reported by Nicolaou and co-workers.[5] The spectral data of **2** matches with that reported,[5,7e] and thus a formal synthesis of palmerolide A has been successfully accomplished.

In summary, we have successfully completed a concise formal synthesis of palmerolide A by synthesizing the macrocycle **2**, an advanced intermediate in Nicolaou's synthesis of palmerolide A, in 0.87 % overall yield for a longest linear sequence of 24 steps, starting from alcohol **6**. The key features of our synthesis involve the installation of *syn* stereocenters at C_{19}–C_{20} by exploring Sharpless epoxidation prior to Pd-catalyzed hydrogenolysis, while the other three stereocenters at C_{10}, C_{11}, and C_7 were introduced by Sharpless asymmetric dihydroxylation and Sharpless kinetic resolution. The 14*E*–16*E* diene was installed through a Pd-catalyzed allylic rearrangement coupled with Julia–Kocienski reaction. Towards the end, Yamaguchi esterification and RCM were employed to construct the 20-membered macrocycle.

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Keywords: antitumor agents · Julia–Kocienski reaction · metathesis · natural products · structure elucidation

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