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A Shimizu Non-Aldol Approach to the Formal Total Synthesis of Palmerolide A

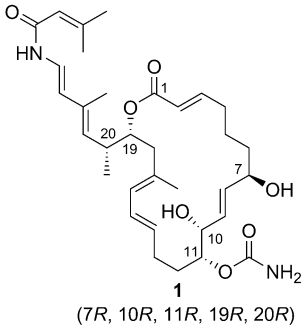
Sandip A. Pujari, Parthasarathy Gowrisankar, and Krishna P. Kaliappan*[a]

Abstract: A formal total synthesis of palmerolide A has been accomplished by assembling three fragments by means of successive Julia–Kocienski olefination, Yamaguchi esterification, and ring-closing metathesis (RCM). Our initial efforts to combine the first two fragments through a Julia–Kocienski reaction between a secondary sulfone and a ketone were not successful; nevertheless, it was feasible between a primary sulfone and aldehyde. Yamaguchi esterification with the third fragment then set the stage for a RCM reaction. Initial failure of the RCM with a PMB-ether adjacent to the olefins and the difficulty in cleaving the PMB-ether prompted us to change the choice of protecting groups, which then paved the way to the macrocyclic core of palmerolide A.

Keywords: Julia–Kocienski reaction · macrolides · melanoma · ring-closing metathesis · Yamaguchi esterification

Introduction

The chemical and biological diversity found in nature has always inspired and fascinated synthetic chemists and at the same time provided opportunities for the isolation, structural elucidation, and synthesis of various complex natural products. In the past, most of these biologically potent molecules were mainly isolated from plants or microorganisms such as bacteria and fungi.[1] In recent times, there has been a steady growth in the isolation of lead compounds from marine sources because of advances in technology used for their isolation and characterization, and developments in synthetic chemistry.[2] The ocean is a rich source of marine natural products, many of which have been found to be potent therapeutic agents against many deadly diseases, such as cancer and acquired immuno-deficiency syndrome (AIDS).[3] Among the various sources of marine natural products, the chemical diversity available in the Antarctic Ocean has not been explored for several decades owing to the extreme climate and difficulties associated with product isolation. Furthermore, as natural products isolated from this area are only available in limited quantities, it was essential to make these natural products as well as their analogues for further biological studies and hence they are attractive target molecules for total synthesis. Recently, during the course of their investigation of the bioactivity among the Antarctic ecosystem, Baker and co-workers isolated a macrocyclic polyketide palmerolide A (**1**) from Antarctic tunicate *Synoicum adareanum*.[4] Palmerolide A (Scheme 1) exhibits potent and selective cytotoxicity against melanoma, a deadly form of skin cancer. It is interesting to note that palmerolide A has been isolated from a place where there is no sunlight, and yet it has the potential to fight a disease that comes from exposure to the sun. Among all skin cancers, melanoma is known to spread aggressively and requires chemotherapy for its treatment. Unfortunately, current chemotherapeutic agents used for the treatment of melanoma are less selective. However, preliminary biological studies on



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(7*R*, 10*R*, 11*R*, 19*R*, 20*R*)

Scheme 1. Proposed structure of palmerolide A.

[a] S. A. Pujari, Dr. P. Gowrisankar, Prof. Dr. K. P. Kaliappan
Department of Chemistry
Indian Institute of Technology, Bombay
Powai, Mumbai-400076 (India)
Fax: (+22) 2576-7152
E-mail: kpk@chem.iitb.ac.in

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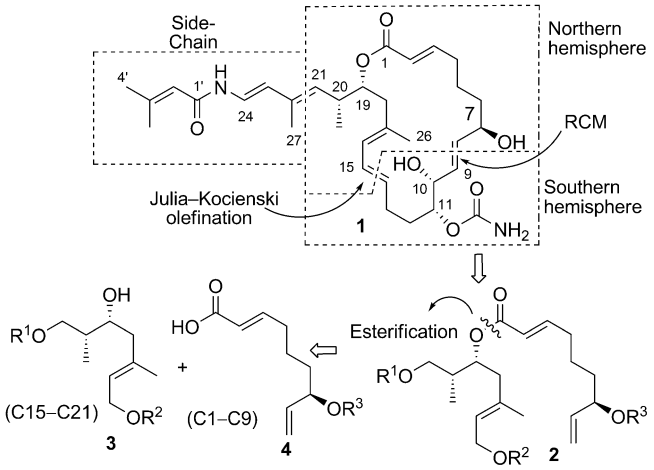
palmerolide A are very promising in terms of selectively targeting the melanoma cells. Palmerolide A exhibits cytotoxic activity against melanoma cell line UACC-62 with a LC_{50} value of 18 nM. Further biological studies revealed that it shows modest activity against colon cancer cell line HCC-2998 as well as renal cancer cell line RXF 393 (LC_{50} = 6.5 μM), whereas all other cell lines tested by the NCI-60 cell line panel (National Cancer Institute) remains inactive. The in vitro selectivity index of this molecule falls in the range of ca. 10^3 for the melanoma cells over the most-sensitive cell lines that were tested. Palmerolide A also appears to act on melanoma cells through the inhibition of vacuolar-ATPase with an IC_{50} of 2 nM.

The structure of palmerolide A **1** has been assigned based on high-field NMR spectroscopic and Mosher's ester stereochemical studies.[4] The relative and absolute configurations of 7*R* and 10*R* were determined based on the Mosher's ester derivative of the two free secondary alcohols at the C7 and C10 positions, whilst the stereochemistry at C11, C19, and C20 were assigned by using through-space coupling NMR analysis, such as rotating frame nuclear Overhauser effect spectroscopy (ROESY) and nuclear Overhauser effect spectroscopy (NOESY) experiments with respect to C10 interactions through space. Intriguing structural features of palmerolide A include an enamide side-chain, a carbamate moiety, five chiral centers, and a 1,3-diene system in the core of the 20-membered macrocyclic lactone.

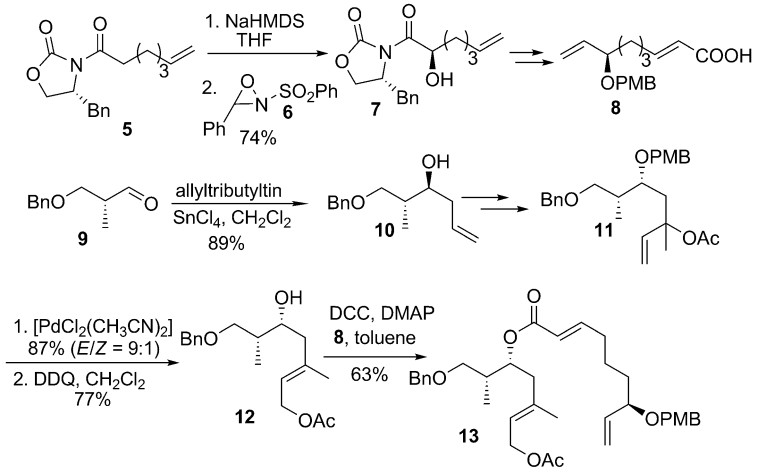
Although palmerolide A has shown impressive and promising biological properties against melanoma cancer cells, only a few milligrams of the material could be derived from each sea squirt. Furthermore, the Antarctic treaty,[5] which prohibits the commercial exploitation of marine sources, hinders the isolation of this promising drug-like natural product from this source. The promising antitumor properties of palmerolide A, coupled with its extremely limited supply, have attracted much attention from the synthetic community. As a result three total syntheses,[6–8] a couple of formal syntheses,[9] and six partial syntheses[10a–f] have already been reported in the literature.

In view of its novel molecular architecture coupled with biological properties, we became interested in the synthesis of palmerolide A. We initiated a program for the total synthesis of palmerolide A as soon as the isolation of this interesting natural product was reported and so our initial synthetic strategy has been mainly focused on the proposed structure (**1**; Scheme 2). A closer look at the molecule suggested that palmerolide A could be divided into three portions, namely a northern hemisphere (C1–C9 and C15–C21 connected *via* C19 oxygen atom), a southern hemisphere (C10–C14), and a side-chain (C22–C24 and C1′–C4′ connected through a nitrogen atom). From a synthetic point of view, we opted to construct the southern hemisphere at a late stage as it could be easily synthesized by a Sharpless asymmetric dihydroxylation route. We also felt that the northern hemisphere looked more challenging because of the presence of adjacent chiral centers, a substituted double bond with *E* geometry, and therefore a convenient route for this fragment will facilitate our plan to achieve the total synthesis of palmerolide A.



Scheme 2. Retrosynthesis of proposed structure **1**.

Thus, the northern hemisphere of palmerolide A **1** was targeted as an initial phase of our inquiry by means of coupling of acid (**8**) and alcohol (**12**) fragments (Scheme 3). The acid fragment (**8**) was obtained by asymmetric α-alkylation of oxazolidinone **5** with Davis reagent **6** followed by cross-metathesis with methyl acrylate as key steps. Alcohol **12** has been successfully synthesized through a chelation-controlled

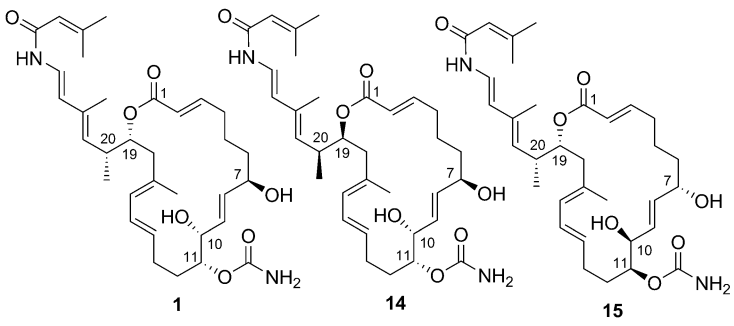


Scheme 3. Synthesis of the northern hemisphere of proposed structure **1**. NaHMDS = sodium bis(trimethylsilyl)amide, THF = tetrahydrofuran, Bn = benzyl, PMB = *para*-methoxybenzyl, Ac = acetyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMAP = 4-dimethylaminopyridine.

CHEMISTRY
AN ASIAN JOURNAL

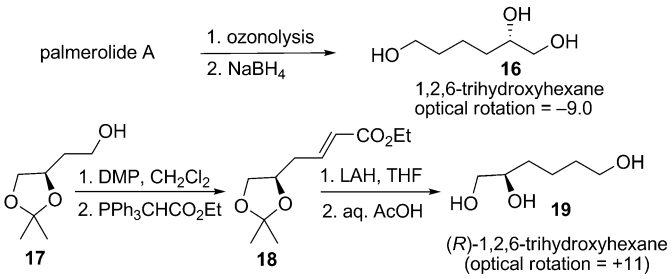
addition of allyl stannane to aldehyde **9** and palladium-catalyzed allylic rearrangement of allyl acetate **11** as the key steps. A DCC-mediated esterification of acid **8** and alcohol **12** furnished the northern hemisphere (**13**) of palmerolide A.[10a]

Subsequently, during the course of our work on the total synthesis of palmerolide A, De Brabander's group reported[6] the first total synthesis of the originally assigned structure of palmerolide A (**1**). However, the spectral data of the synthetic isomer did not match with that of the natural product, thereby suggesting that its structure needed to be revised. Although the absolute configuration at the C7 and C10 positions were assigned based on Mosher's ester analysis, the stereochemical assignment at the C19 and C20 positions was less convincing. Taking this into account, assuming that these two stereocenters might have the opposite configuration, De Brabander's group synthesized 19-*epi*-20-*epi* diastereomer **14** of the originally proposed structure **1** (Scheme 4). Interestingly, this time, the spectral data and its HPLC behavior matched with that of the natural isolate; however, the CD (circular dichroism) spectra obtained was found to be the mirror image of the naturally occurring isomer. This provided the indirect evidence for the absolute configuration of chiral centers present in palmerolide A and they proposed that the structure of palmerolide A should be revised as **15** (*ent*-19-*epi*-20-*epi*-**1**).



Scheme 4. Structures of palmerolide A.

Meanwhile, in order to verify the assignment of absolute configuration, Baker's group carried out a controlled reductive ozonolysis of the natural isolate to obtain the triol (**16**) as one of the fragments (Scheme 5).[10g] Although, the magnitude of its optical rotation closely matched to that of same triol obtained through chemical synthesis, the sign of rotation was found to be opposite. These studies also suggested that the natural product has the *S* configuration at the C7 position rather than the originally proposed *R* configuration. After revisiting the absolute stereochemical assignment, Baker's group realized that Cahn–Ingold–Prelog prioritization of their Mosher ester derivatives to assign the stereochemistry at the C7 and C10 positions was incorrect. Because the configuration at the C11 position was derived from the C10 stereocenter, it was also revised. Thus, the stereochemistry of the natural product at the C7, C10, and C11 positions should be (*S*,*S*,*S*), and not (*R*,*R*,*R*).



Scheme 5. Synthesis employed by Baker and co-workers and comparison of triol **19**. DMP = 2,2-dimethoxypropane, LAH = lithium aluminum hydride.

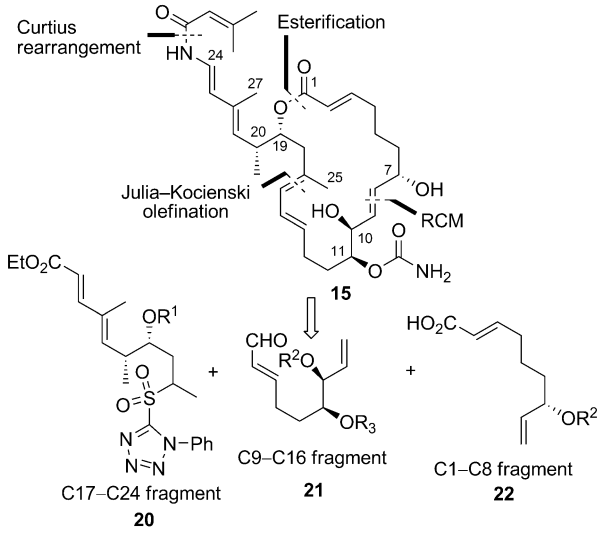
This assignment was further confirmed by the total synthesis of **15** from Nicolaou's[7a,b] group. These findings have been taken into account to revise the originally proposed structure **1** as **15** (Scheme 4). Furthermore, Nicolaou's group carried out systematic biological studies on several analogues of palmerolie A,[7c] which revealed that the carbamate and enamide moieties are essential for its biological properties, whereas the C7 hydroxy group is not necessary. Moreover, the steric environment around the C1–C8 domain of palmerolide A could not be tolerated at the active site of the enzyme.[7d]

After the disclosure of the revised structure of palmerolide A, we modified our strategy and accomplished the formal synthesis of palmerolide A using palladium-catalyzed hydrogenolysis, Julia–Kocienski olefination, Yamaguchi esterification, and ring-closing metathesis (RCM) as the key steps.[9b] Herein, we present a full account which highlights our cumulative efforts that eventually led to the synthesis of an advanced intermediate present in Nicolaou's synthesis of palmerolide A.

Results and Discussion

First-Generation Strategy

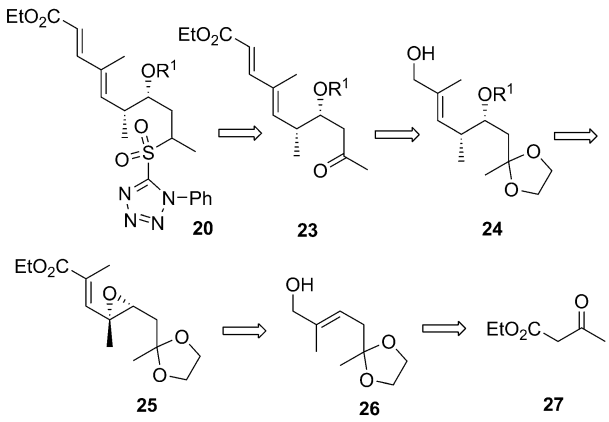
Encouraged from our earlier experience and success in synthesizing natural and unnatural products using a metathetic approach,[11] we planned to exploit a RCM[12] as a key step for the synthesis of palmerolide A. Accordingly, our retrosynthetic analysis featured the strategic disconnection of the target molecule into three different fragments: **20** (C17–C24), **21** (C9–C16), and **22** (C1–C8). A Julia–Kocienski reaction[13] between fragments **20** and **21** could be envisioned to construct the C9–C24 framework (Scheme 6). We also anticipated that the Yamaguchi esterification[14] of the C9–C24 fragment with acid **22** would then set the stage for the key RCM[12a,b] to assemble the macrocyclic core of palmerolide A. The acid sensitive *N*-acyl dienamine functionality could be introduced at a late stage of the synthesis by using a Curtius rearrangement.[15]



Scheme 6. Retrosynthesis of **15**.

As a part of our new synthesis of this molecule, we also deliberated utilizing the non-aldol approach developed by Shimizu and co-workers[16] to construct the C7–C24 fragment (**20**), as against the classical aldol reaction. This methodology, a palladium-catalyzed hydrogenolysis of alkenyloxirane, although a powerful tool to construct *syn* or *anti* tetrahedral centers, has been rarely explored in the synthesis of natural products.

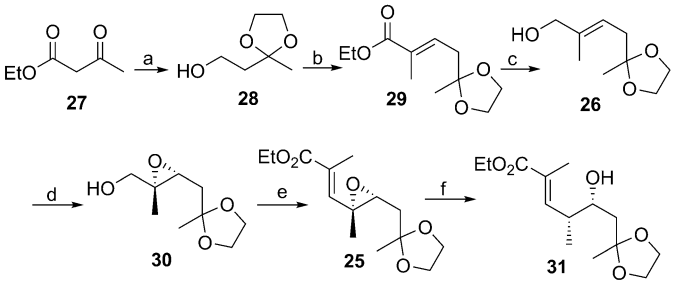
We envisioned that the sulfone (**20**), a first building block required for the Julia–Kocienski olefination, could arise from the ketodiene ester **23**, which could then be converted into an acid azide at the C24 position, which is required for the Curtius rearrangement (Scheme 7). The ester (**23**) could be obtained from allylic alcohol **24**, which, in turn, could be synthesized from alkenyloxirane **25** using the key reaction mentioned above. Sharpless asymmetric epoxidation[17] of allylic alcohol **26** followed by oxidation and Wittig olefination could afford chiral alkenyloxirane **25**. In turn, alcohol **26** could be synthesized starting from inexpensive ethylacetoacetate **27** in a few steps.



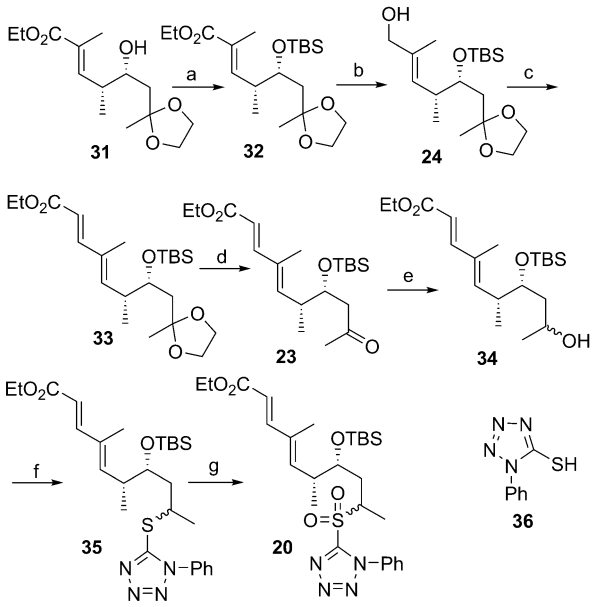
Scheme 7. Retrosynthesis of fragment **20**.

Thus, our synthesis of the C17–C24 fragment **20** began with the oxidation of known alcohol **28**[18] to the corresponding aldehyde, which upon Wittig reaction gave ester **29** as the sole product (Scheme 8). Subsequent reduction of ester **29** with LAH furnished alcohol **26** which was then subjected to Katsuki–Sharpless asymmetric epoxidation[19] to produce epoxide **30** in good yield (90% *ee* based on ^{19}F NMR analysis of its Mosher's ester derivative). The latter compound was then oxidized to the corresponding aldehyde with IBX and subsequent Wittig reaction of the resultant aldehyde afforded ester **25** (85% yield over two steps). With sufficient quantities of ester **25** in hand, we next examined the application of stereoselective palladium-mediated hydrogenolysis.[20] Gratifyingly, exposure of **25** to $[Pd_2(dba)_3CHCl_3]$ and Bu_3P in the presence of Et_3N and HCOOH at ambient temperature furnished compound **31** in excellent yield.

Protection of alcohol **31** as its TBS ether **32** (Scheme 9) followed by reduction of ester with LAH afforded the alcohol (**24**). The aldehyde obtained upon oxidation of **24** with MnO_2, was homologated with Ph_3PCHCO_2Et to furnish ester **33** in 78% yield over two steps (trace amounts of readily separable *Z*-isomer were also formed). The geometry of the major *E* isomer of **33** was confirmed by ^{1}H NMR spectroscopy from its coupling constant ($J = 15.6$ Hz). However, removal of the ketal was found to be more difficult than initially anticipated owing to concomitant elimination even under mild acid treatment. After examining several conditions, we found that the neutral conditions developed by Lipshutz et al.[21] resolved this issue to afford ketone **23** in good yield. Thus, ketone **23** was reduced with $NaBH_4$ to furnish a mixture of alcohols **34** that were then converted into sulfide **35** under Mitsunobu conditions. Subsequent oxidation with ammonium molybdate delivered the sulfone **20**, a key intermediate and one of the fragments required for the Julia–Kocienski reaction.



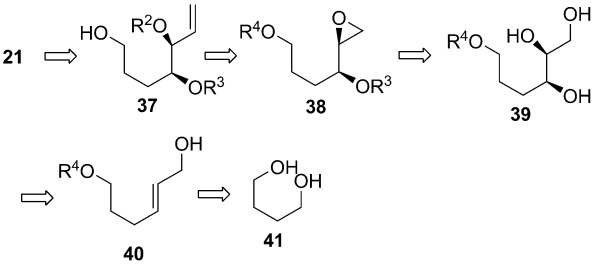
Scheme 8. Synthesis of intermediate **31** a) i: Ethylene glycol, *cat.* PTSA, toluene, reflux, 4 h, 83%; ii: LAH, Et_2O, 1 h, RT, 92%; b) i: IBX, EtOAc, reflux, 6 h; ii: $Ph_3PC(CH_3)CO_2Et$, toluene, RT, 3 h, 85% over 2 steps; c) LAH, Et_2O, 1 h, RT, 96%; d) D-(−)-DIPT, $Ti(iPrO)_4$, CH_2Cl_2, 4 Å M.S., cat. CaH_2, TBHP, −25 °C, 4 h, 90%; e) i: IBX, EtOAc, reflux, 6 h; ii: $Ph_3PC(CH_3)CO_2Et$, toluene, RT, 3 h, 89% over 2 steps; f) $[Pd_2(dba)_3CHCl_3]$, HCO_2H, nBu_3P, Et_3N, 1,4-dioxane, RT, 16 h, 94%. PTSA = 4-toluene sulphonic acid, DIPT = diisopropyl tartarate, M.S. = molecular seives, TBHP = *tert*-butyl hydroperoxide, IBX = 2-iodoxy benzoic acid, dba = dibenzylideneacetone.



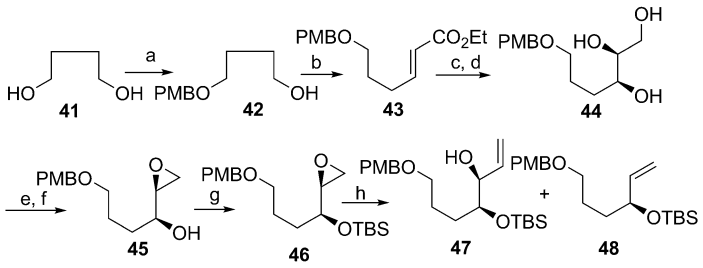
Scheme 9. Synthesis of intermediate **20**. a) TBSOTf, CH_2Cl_2, Et_3N, 0 °C, 1 h, 82 %; b) LAH, Et_2O, 2 h, RT, 82 %; c) i: MnO_2, CH_2Cl_2, RT, 3 h; ii: Ph_3PCHCO_2Et, toluene, reflux, 18 h, 80 % over 2 steps; d) $[PdCl_2(CH_3CN)_2]$, acetone, RT, 2 h, 78 %; e) $NaBH_4$, EtOH, 0 °C to RT, 3 h, 93 %; f) DIAD, PPh_3, THF, **36**, 0 °C to RT, 6 h, 60 %; (g) $(NH_4)_6Mo_7O_{24}$, EtOH, H_2O_2, RT, 12 h, 90 %. TBSOTf = *tert*-butyldimethylsilyl trifluromethane sulphonate, DIAD = diisopropyl azodicarboxylate.

The C9–C16 fragment **21**, the second building block required for Julia–Kocienski coupling could arise from the homologation of alcohol **37** which, in turn, could be accessed through opening of the epoxide (**38**) with trimethylsulfonium ylide.[22] Epoxide **38** could be traced back to triol **39** by a selective tosylation of the primary alcohol followed by treatment with base. It was clear that triol **39** could be easily obtained through a Sharpless asymmetric dihydroxylation[23] of allylic alcohol **40**, which could be easily realized by manipulation of the commercially available 1,4-butanediol **41** (Scheme 10).

Thus, the synthesis of the C9–C16 subunit began with the selective monoprotection of 1,4-butane diol as its PMB ether (**42**;[24] Scheme 11). The Swern oxidation of alcohol **42** led to an aldehyde that was immediately homologated using Wittig olefination to afford the α,β-unsaturated ester **43** in good yield. Ester **43** was then reduced with DIBAL-H to



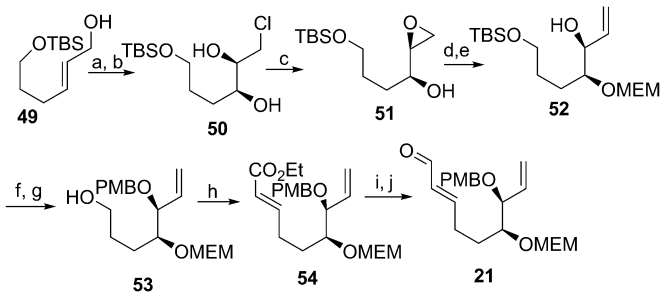
Scheme 10. Retrosynthesis of fragment **21**.



Scheme 11. Synthesis of intermediate **47**. a) KOH, DMSO, PMBCl, 0 °C, 2 h, 76 %; b) i: oxalylchloride, DMSO, CH_2Cl_2, −78 °C, 30 min, Et_3N, RT; ii: Ph_3PCHCO_2Et, toluene, RT, 5 h, 80 % over 2 steps; c) DIBAL-H, CH_2Cl_2, −78 °C, 1 h, 92 %; d) AD-mix-α, $CH_3SO_2NH_2$, $NaHCO_3$, *t*BuOH/H_2O, 0 °C, 24 h, 56 %; e) TsCl, Py, DMAP, 0 °C, 5 h; f) K_2CO_3, MeOH, 0 °C, 2 h, 71 % over 2 steps; g) TBSCl, CH_2Cl_2, imidazole, RT, 16 h, 68 %; h) $(CH_3)_3SI$, *n*BuLi, Et_2O, −15 °C to RT, 85 %. DMSO = dimethyl sulfoxide, PMBCl = 4-methoxybenzyl chloride, DIBAL-H = diisobutylaluminium hydride, TsCl = 4-toluenesulfonyl chloride, Py = pyridine, DMAP = 4-*N*,*N*-dimethylaminopyridine.

the corresponding allylic alcohol, which upon Sharpless asymmetric dihydroxylation with AD-mix-α, afforded the triol **44** in moderate yield. The selective tosylation of primary alcohol **44** using TsCl/Py at 0 °C followed by treatment with K_2CO_3/MeOH afforded the epoxy-alcohol **45**, and the secondary alcohol was subsequently protected as its TBS ether **46**. However, opening of the epoxide **46** with trimethylsulfonium ylide using tetrahydrofuran as a solvent did not proceed as anticipated, to afford the alcohol **47**. When tetrahydrofuran was replaced by diethyl ether, complete consumption of the starting material was observed;[25] however, product **47** has always been accompanied by an unexpected compound (**48**) in the ratio of 2:1 which underscored the change of protecting groups and so the scheme was modified accordingly.

As indicated by the modified strategy, known allylic alcohol **49**[26] was halogenated to deliver an allylic chloride (Scheme 12), which was then subjected to Sharpless asym-



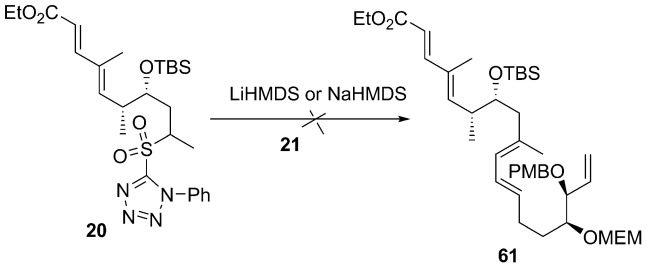
Scheme 12. Synthesis of fragment **21**. a) PPh_3, CCl_4, $NaHCO_3$, reflux, 6 h, 82 %; b) AD-mix-α, $CH_3SO_2NH_2$, $NaHCO_3$, *t*BuOH/H_2O, 0 °C, 24 h, 92 %; c) K_2CO_3, MeOH, RT, 3 h, 82 %; d) MEMCl, *i*Pr_2NEt, CH_2Cl_2, 16 h, 83 %; e) $(CH_3)_3SI$, *n*BuLi, THF, −15 °C to RT, 90 %; f) NaH, DMF, PMBBr, RT, 1 h, 87 %; g) TBAF, THF, RT, 2 h, 88 %; h) i: DMP, CH_2Cl_2, RT, 3 h; ii: Ph_3PCHCO_2Et, CH_2Cl_2, RT, 5 h, 77 % over 2 steps; i) DIBAL-H, CH_2Cl_2, −78 °C, 1 h, 88 %; j) MnO_2, CH_2Cl_2, RT, 92 %. MEMCl = methoxyethoxymethyl chloride, TBAF = tetra *n*-butylammonium fluoride, DMP = Dess–Martin periodinane.

metric dihydroxylation with AD-mix-α in buffer solution[27] to give the *syn* diol (**50**) in excellent yield. The treatment of halohydrin **50** with anhydrous K_2CO_3 in methanol led to the formation of the epoxide (**51**; 88% *ee* was observed based on ^{19}F NMR analysis of the Mosher's ester derivative). Epoxy-alcohol **41** was then protected as its MEM-ether, which upon treatment with trimethylsulfonium ylide gave allylic alcohol **52**. It is interesting to note that this reaction proceeded smoothly in tetrahydrofuran, unlike **46**. After protecting the free hydroxy group as its PMB ether, the TBS group was removed by TBAF to afford compound **53** in good yield. Oxidation of alcohol **53** with the Dess–Martin reagent, followed by Wittig reaction of the resultant aldehyde furnished ester **54** as a single isomer. The complete reduction of ester **54** with DIBAL-H followed by allylic oxidation with MnO_2 provided aldehyde **21**, the other key fragment required for Julia–Kocienski reaction.

The synthesis of third fragment **22** began with the Swern oxidation of the known alcohol **56**[26] to corresponding aldehyde, which upon treatment with vinyl Grignard gave the racemic allylic alcohol **57** (Scheme 13). Katsuki–Sharpless kinetic resolution[28] using D-(−)-diisopropyltartrate furnished enantiomerically enriched alcohol **57** in 42% yield (95% *ee* based on analysis of the Mosher's ester derivative). The alcohol **57** was then protected as its PMB ether **58** and subsequent cleavage of the silyl ether provided the alcohol **59**. Wittig reaction of the aldehyde derived from alcohol **59**, afforded ester **60** in good yield. Saponification of ester **60** using LiOH gave the required acid (**22**).

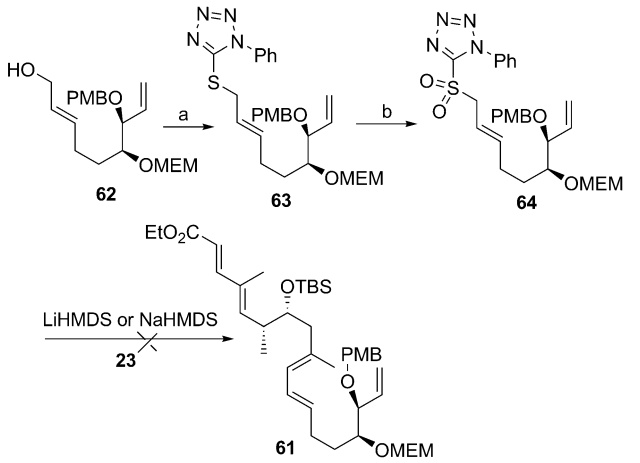
Attempted Julia–Kocienski Reaction

Having synthesized the three fragments required for the synthesis of palmerolide A, the next decisive task was to couple these fragments sequentially. Though the Julia–Kocienski coupling between a secondary sulfone and an aldehyde has been utilized in the synthesis of several natural products,[29] all our attempts to successfully accomplish this key reaction between **20** and **21** were unsuccessful (Scheme 14). Presumably, the failure of the reaction can be attributed to the bulky nature of the secondary sulfone (**20**) which might not be a good nucleophile.



Scheme 14. Attempted Julia–Kocienski reaction.

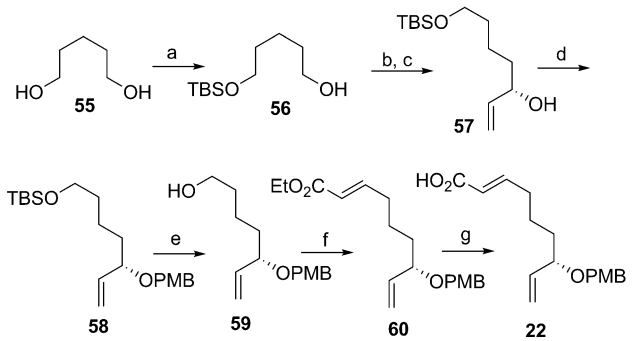
Alternatively, the desired product (**61**) could also be obtained from a Julia–Kocienski reaction between primary sulfone **64** and ketone **23**.[30] Accordingly, the alcohol **62** derived from DIBAL-H reduction of ester **54** was treated with thiol **36** under Mitsunobu conditions, and subsequent oxidation of the resulting thio-ether afforded sulfone **64**. However, sulfone **64** also failed to undergo a Julia–Kocienski reaction with ketone **23** (Scheme 15).



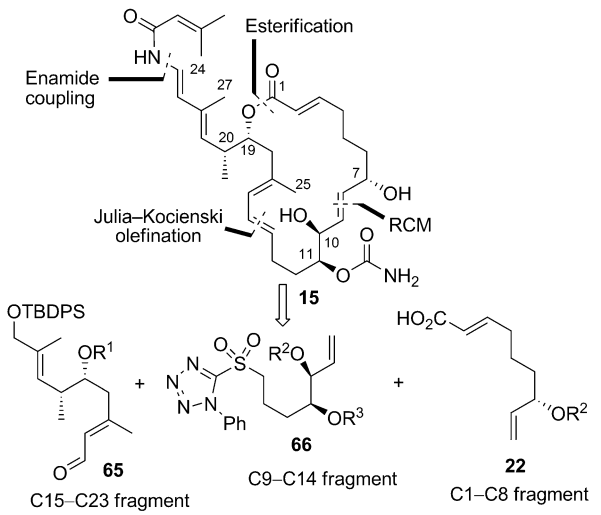
Scheme 15. Attempted Julia–Kocienski reaction. a) DIAD, PPh_3, THF, **36**, 0°C, 2 h, 86%; b) $(NH_4)_6Mo_7O_{24}$, EtOH, H_2O_2, RT, 12 h, 55%.

Second-Generation Strategy

These disappointing results underlined the need for a revised synthetic strategy at this stage. As an alternative, a more-feasible strategy for the completion of the synthesis was pursued, wherein the C15−C23 fragment (**65**) was changed so that it will now act as an electrophile and the C9−C14 fragment (**66**) was altered to incorporate a primary sulfone group and no change was made to the C1−C8 subunit **22** (Scheme 16).

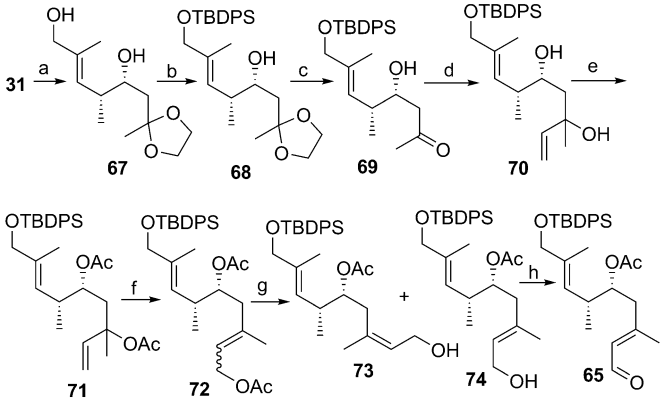


Scheme 13. Synthesis of intermediate **22**. a) NaH, THF, TBSCl, RT, 3 h, 66%; b) i: oxalylchloride, DMSO, CH_2Cl_2, −78°C, 30 min, Et_3N, RT; ii: $CH_2CHMgBr$, THF, 0°C to RT, 5 h, 60% over 2 steps; c) D-(−)-DIPT, $Ti(iPrO)_4$, CH_2Cl_2, 4 Å M.S., cat. CaH_2, TBHP, −22°C, 4 d, 42%; d) NaH, DMF, PMBBr, RT, 1 h, 82%; e) TBAF, THF, RT, 2 h, 96%; f) i: oxalylchloride, DMSO, CH_2Cl_2, −78°C, 30 min, Et_3N, RT; ii: Ph_3PCHCO_2Et, CH_2Cl_2, RT, 5 h, 91% over 2 steps; g) LiOH, THF/MeOH/H_2O (1:1:2), 4 h, RT, 90%.



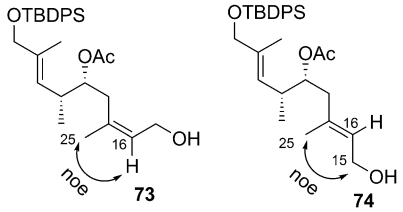
Scheme 16. Revised retrosynthesis of **15**.

With these considerations in mind, construction of the C15−C23 subunit commenced with the reduction of hydroxy ester **31** with DIBAL-H to afford diol **67** (Scheme 17). The primary alcohol was then selectively protected as its TBDPS ether and subsequent removal of the ketal under neutral conditions gave the ketone (**69**) in good yield. Addition of the vinyl Grignard to this ketone, followed by acetylation of the resulting diol, afforded the diacetate **71**. A palladium(II)-catalyzed isomerization of allylic acetate[31] gave an inseparable diastereomeric mixture of **72**. The selective cleavage of terminal acetate was achieved using ammonia/methanol, and at this stage it became possible to separate the two diastereomers (**73** and **74**) by column chromatography on silica gel ($E/Z = 7.5:1$). The required *E* isomer (**74**) was then subjected to MnO_2 oxidation to give aldehyde **65**, which was used immediately for the Julia–Kocienski olefination.



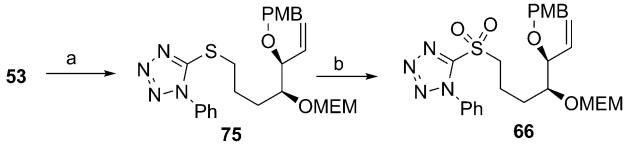
Scheme 17. Synthesis of fragment **60**. a) DIBAL-H, CH_2Cl_2, −78 °C, 1 h, 74 %; b) TBDPSCl, CH_2Cl_2, imidazole, RT, 2 h, 85 %; c) $[PdCl_2(CH_3CN)_2]$, acetone, RT, 2 h, 89 %; d) $CH_2CHMgBr$, THF, 0 °C to RT, 5 h, 73 %; e) Ac_2O, Py, DMAP, 50 °C, 16 h, 78 %; f) $[PdCl_2(CH_3CN)_2]$, THF, RT, 6 h, 88 %; g) sat. NH_3-MeOH, RT, 16 h, 70 %; h) MnO_2, CH_2Cl_2, RT, 2 h, 92 %. TBDPSCl = *tert*-butyldiphenylsilyl chloride.

In the case of *E* isomer **74**, a strong NOE cross-peak was observed between the C15 methylene group and C25 methyl group, but the same information was absent for **73**. Furthermore, a NOE cross-peak was observed for the protons of the C25 methyl group and the C16 olefinic hydrogen atom in the *Z* isomer (**73**), but it was not observed in the case of *E* isomer (**74**, Scheme 18).



Scheme 18. NOE correlation.

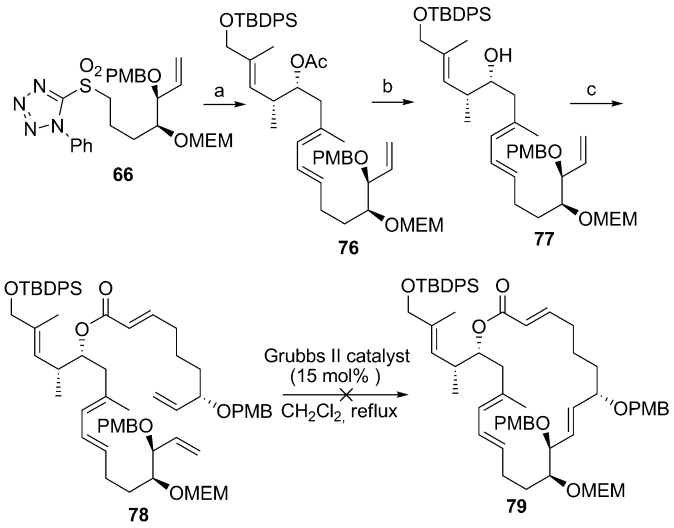
With ready access to the C15−C23 subunit **65**, we then took up the task of synthesizing the C9−C14 subunit. Accordingly, exposure of alcohol **53** to thiol **36** under Mitsunobu conditions afforded thio-ether **75**, which upon further oxidation furnished the sulfone **66** in 91 % yield (Scheme 19).



Scheme 19. Synthesis of fragment **66**. a) DIAD, PPh_3, THF, **36**, 0 °C, 2 h, 89 %; b) $(NH_4)_6Mo_7O_{24}$, EtOH, H_2O_2, RT, 12 h, 91 %.

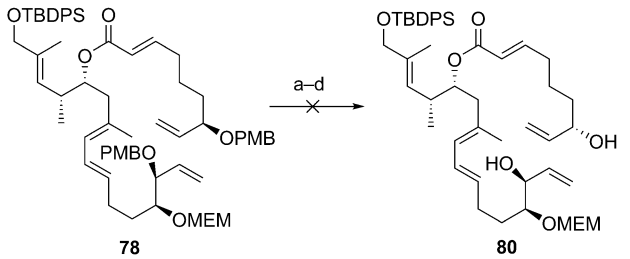
Now with the revised subunits in hand, we then examined the feasibility of a Julia–Kocienski olefination of the C15−C23 and C9−C14 fragments. Accordingly, sulfone **66** was treated with aldehyde **65** using an excess of LiHMDS (3 equiv) under "Barbier-type" reaction conditions.[32] To our delight, the reaction proceeded smoothly to provide the diene **76** in 60 % yield with good selectivity ($E/Z = 92:8$ by ^1H NMR spectroscopy; $J = 14.9$ Hz for the *E* isomer). After successfully coupling the above two fragments, the acetate group in **76** was reductively removed with DIBAL-H to give free alcohol **77**, which on esterification with acid **22** following a Yamaguchi procedure, afforded the RCM precursor **78** in 67 % yield (Scheme 20).

Having the RCM precursor **78** in hand, the supposed last hurdle in the synthesis, ring closure, was then attempted. Anticipating that the PMB group adjacent to the olefin would enhance the RCM reaction to afford the *trans* product,[33] the diene **78** was subjected to RCM with Grubbs' second generation catalyst. Unfortunately, under a variety of conditions the reaction did not proceed to give the required product (**79**) and, more often than not, only starting material was recovered. We reasoned that perhaps the steric



Scheme 20. Attempted RCM reaction. a) LiHMDS, THF, **65**, −78 °C, 1 h, 60 %; b) DIBAL-H, CH_2Cl_2, −78 °C, 2 h, 78 %; c) 2,4,6-trichlorobenzoyl chloride, Et_3N, **22**, DMAP, toluene, RT, 2 h, 67 %. LiHMDS = lithium bis(trimethylsilyl)amide.

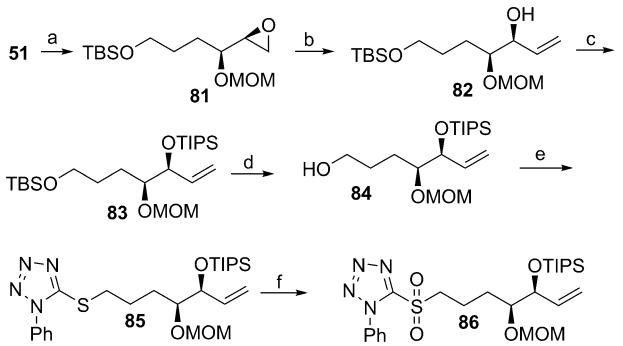
crowding near olefins could not be tolerated to achieve the ring-closure. At this stage it had become clear that the free hydroxy group is required to trigger the RCM (also considering Nicolaou's synthesis[7a,b]). However, attempts to generate the free hydroxy groups by cleaving the PMB ether failed to deliver the desired product **80** (Scheme 21). It appears that the presence of a highly substituted 1,3-diene might have caused the decomposition of **78**, as a similar problem has been encountered in the literature during deprotection of a PMB ether in the presence of a conjugated diene.[9a,34]



Scheme 21. Attempted cleavage of PMB-ether. a) DDQ, pH 7 buffer, CH_2Cl_2, 0 °C to RT, 16 h; b) DDQ, CH_2Cl_2, H_2O, 0 °C to RT, 16 h; c) DDQ, pH 7 buffer, *t*BuOH, CH_2Cl_2, H_2O, 0 °C to RT, 16 h; d) CAN, CH_3CN, H_2O, 0 °C to RT, 2 h. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, CAN = ceric ammonium nitrate.

The failure of the RCM reaction with the PMB ether, and subsequent difficulty in the cleavage of the PMB group, forced us to replace the PMB group with a TIPS protecting group. The TIPS group could be removed easily without affecting other functionalities present in the molecule. Accordingly we have revised fragments **66** and **22**, whilst keeping fragment **65** intact.

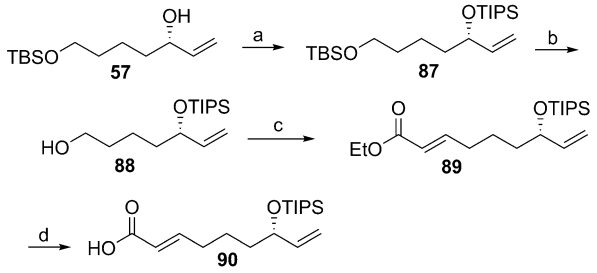
Now, the synthesis of the revised sulfone fragment **86** commenced with the opening of epoxide **81**, derived from alcohol **51**, with trimethylsulfonium ylide to afford the allylic alcohol **82** in 81 % yield (Scheme 22). Alcohol **82** was then protected as its TIPS ether and subsequent cleavage of the TBS ether gave the alcohol **84**. Mitsunobu reaction of alcohol **84** with *N*-phenyltetrazolethiol afforded the sulfide (**85**), which upon further oxidation afforded the sulfone (**86**).



Scheme 22. Synthesis of fragment **86**. a) MOMCl, *i*Pr_2NEt, CH_2Cl_2, 16 h, 83 %; b) $(CH_3)_3SI$, *n*BuLi, THF, −18 °C to RT, 1 h, 81 %; c) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to RT, 1 h, 87 %; d) AcOH/THF/H_2O (3:1:1), RT, 6 h, 86 %; e) **36**, PPh_3, DIAD, THF, −20 °C, 1 h, 92 %; f) $(NH_4)_6Mo_7O_{24}$, H_2O_2, EtOH, 0 °C to RT, 12 h, 94 %. MOMCl = methoxymethyl chloride, TIPSOTf = triisopropylsilyl triflurometh ane sulfonate.

The synthesis of acid fragment **90** embarked with the protection of allylic alcohol **57** as its TIPS ether and subsequent cleavage of TBS ether generated the alcohol **88**.[35] After the oxidation of alcohol **88**, the resultant aldehyde was subjected to the Wittig reaction to produce the conjugated ester **89**. Saponification of ester **89** using LiOH gave acid **90** in 66 % yield (Scheme 23).

Having secured all the coupling partners in sufficient quantities, the key Julia–Kocienski olefination between compound **86** and aldehyde **65** was attempted and, without any further surprises, this reaction proceeded smoothly to afford



Scheme 23. Synthesis of fragment **90**. a) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to RT, 1 h, 87 %; b) AcOH/THF/H_2O (3:1:1), RT, 6 h, 76 % c) i: IBX, EtOAc, reflux, 5 h; ii: $EtO_2CCH_2(O)P(OEt)_2$, *i*Pr_2NEt, LiCl, THF, RT, 12 h, 80 % (2 steps); d) LiOH, H_2O/THF/CH_3OH (2:1:1), 0 °C to RT, 8 h, 66 %.

CHEMISTRY
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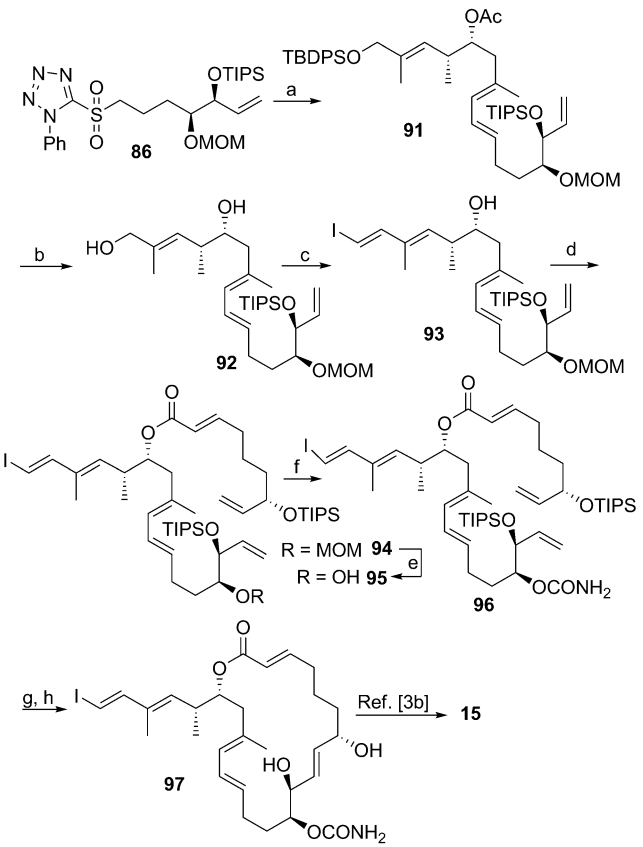

Scheme 24. Synthesis of macrocycle **97**. a) LiHMDS, **65**, THF, −78 °C, 45 min. 80 %; b) NaOH, CH_3OH, reflux, 10 h, 70 %; c) i: MnO_2, CH_2Cl_2, RT, 6 h; ii: $CrCl_2$, CHI_3, THF, 0 °C, 1 h, 72 % (2 steps); d) 2,4,6-trichlorobenzoylchloride, Et_3N, benzene, RT, 1 h, then DMAP, **90**, RT, 1 h. 68 %; e) AcCl, EtOH, THF, 60 °C, 10 min. 62 %; f) $Cl_3CCONCO$, CH_2Cl_2, 0 °C, 1 h, then basic Al_2O_3, 0 °C to RT, 1 h, 78 %; g) TBAF, THF, 0 °C, 4 h, 66 %; h) Grubbs II catalyst (5 mol %), CH_2Cl_2, RT, 1 h, 70 %.

the required *E* olefin (**91**) in 80 % yield (Scheme 24). Then, a one-pot cleavage of TBDPS ether and the acetyl group was successfully accomplished using alkaline methanolic solution heated to reflux without affecting the TIPS ether.[36] The introduction of a vinyl iodide, required for the Buchwald coupling, was then accomplished in a couple of steps through selective oxidation of the allylic alcohol and Takai olefination.[37] Yamaguchi esterification of **93** with acid **90** proceeded smoothly to afford ester **94** in 63 % yield. At this point, selective-cleavage of the MOM-ether and introduction of the carbamate group were investigated.

After screening several conditions, we observed that exposure of the MOM-ether (**94**) to the AcCl in mixture of ethanol and tetrahydrofuran at elevated temperature found to be an effective method to afford the alcohol (**95**) in good yield.[38] Treatment of this alcohol with trichloroacetylisocyanate followed by hydrolysis with basic alumina afforded carbamate **96**. Both of the TIPS groups were then easily cleaved using TBAF to afford the corresponding diol which smoothly underwent RCM in the presence of Grubbs′ second generation catalyst to afford the macrocycle (**97**). This intermediate has been already converted into palmerolide A using Buchwald coupling by Nicolaou's group[7b] and hence we have successfully accomplished the formal total synthesis of palmerolide A.

Summary

In summary, we have developed an efficient strategy for the formal total synthesis of palmerolide A. The key features of our synthesis include the installation of *syn* stereocenters in the C15−C23 fragment by employing a Sharpless epoxidation prior to palladium-catalyzed hydrogenolysis, whilst the other three stereocenters at C10, C11 and C7 present in the molecule were introduced by Sharpless asymmetric dihydroxylation and Sharpless kinetic resolution, respectively. Initial efforts to construct the 14*E*−16*E* diene using a Julia–Kocienski reaction either with secondary sulfone **20** or with the ketone **23** were not successful but the same could be obtained with primary sulfone **66** and an aldehyde **65**. Yamaguchi esterification was employed to afford the RCM precursor. The RCM reaction was found to be ineffective with a PMB-ether adjacent to olefins, but proceeded smoothly with the free diol, affording the macrocycle (**97**).

Experimental Section

Unless otherwise noted, all starting materials and reagents were obtained from commercial suppliers and used after further purification. Tetrahydrofuran was distilled from sodium benzophenone ketyl and toluene from sodium. Dichloromethane, hexanes, and pyridine were freshly distilled from calcium hydride. All solvents used for the routine isolation of products and chromatography were reagent grade and glass distilled. Air- and moisture-sensitive reactions were performed under an argon/ultra-high-purity nitrogen atmosphere. Flash chromatography was performed on silica gel (100–200 mesh, Aceme) with indicated solvents. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica plates (60F-254) using UV light as the visualizing agent and 7 % ethanolic phosphomolybdic acid and heat as the developing agents. ^1H and ^{13}C NMR spectra were recorded either on a Varian AS 400, a Varian ASM 300, or a Bruker 700 MHz instrument. (For the spectral data of compounds **25**, **26**, **29**–**31**, **50**, **51**, **57**, **67**–**69**, **73**, **74**, and **81**–**97**; see the Supporting Information of Ref. [9b].

*Compound **32***

To a solution of alcohol **31** (500 mg, 1.84 mmol) in anhydrous CH_2Cl_2 (10 mL) was added triethylamine (770 μL, 5.51 mmol), and the solution was allowed to stir for 5 min. TBSOTf (850 μL, 3.6 mmol) was added dropwise over 5 min and reaction mixture was stirred for 1 h at 0 °C. The reaction was quenched by adding a saturated solution of $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash chromatography (20–30 % ethyl acetate/hexanes) to give the silyl ether **32** (610 mg, 86 %) as a viscous liquid. $R_f = 0.68$ (30 % ethyl acetate/hexanes); $[\alpha]_D^{25} = +6.03$ ($c = 0.65$, $CHCl_3$); IR (neat): $\tilde{\nu} =$ 1712, 1378, 1253, 1147, 1074, 1029, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.78$ (dq, $J = 10.1$, 1.2 Hz, 1H), 4.25–4.10 (m, 2H), 3.98–3.84 (m, 4H), 3.81 (dt, $J = 8.5$, 2.7 Hz, 1H), 2.82–2.78 (m, 1H), 2.08 (dd, $J =$ 14.9, 8.8 Hz, 1H), 1.84 (d, $J = 1.5$ Hz, 3H), 1.76 (dd, $J = 14.6$, 3.1 Hz, 1H), 1.32 (s, 3H), 1.28 (t, $J = 7.3$ Hz, 3H), 0.98 (d, $J = 6.7$ Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.03 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 168.4, 146.6, 125.9, 108.9, 70.8, 64.5, 64.1, 60.3, 43.6, 37.8, 25.8, 24.5, 18.0,

14.2, 12.4, 12.1, −4.4, −4.9 ppm; HRMS (ESI-TOF): calcd. for $C_{20}H_{38}O_5SiNa$ *m/z* 409.2386, found *m/z* 409.2371.

Compound ***24***

To a stirred solution of ester **32** (570 mg, 1.47 mmol) in diethyl ether (15 mL) at 0 °C was added LAH (112 mg, 2.95 mmol) in portions over a period of 20 min. The resultant mixture was warmed to RT and stirred for 1 h. The reaction was quenched by the careful addition of mixture of $NaSO_4$·10·H_20/Celite (4 g, 1:1) at 0 °C and the resulting suspension was allowed to stir at RT for 3 h. The mixture was passed through a pad of Celite and the filtrate was concentrated under reduced pressure. The residue was then purified by flash chromatography (30–40 % ethyl acetate/hexanes) to afford **24** (420 mg, 82 %) as colorless oil. R_f = 0.42 (30 % ethyl acetate/hexanes); $[\alpha]_D^{25}$ = −5.07 (*c* = 0.68, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3272 (b), 1472, 1378, 1254, 1132, 1029, 947, 836, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.40 (dd, *J* = 9.5, 1.2 Hz, 1H), 3.98–3.88 (m, 6H), 3.76 (dt, *J* = 7.9, 3.4 Hz, 1H), 2.68–2.63 (m, 1H), 2.03 (dd, *J* = 14.7, 7.9 Hz, 1H), 1.68 (d, *J* = 1.2 Hz, 3H), 1.16 (dd, *J* = 14.7, 3.4 Hz, 1H), 1.33 (s, 3H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.01 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.2, 131.3, 109.1, 71.9, 69.2, 64.5, 64.1, 43.7, 37.0, 25.9, 24.6, 18.1, 13.8, 13.6, −4.38, −4.63 ppm; HRMS (ESI-TOF): calcd. for $C_{18}H_{36}O_4SiNa$ *m/z* 367.2281, found *m/z* 367.2287.

Compound ***33***

To a solution of alcohol **24** (380 mg, 1.1 mmol) in anhydrous CH_2Cl_2 (8 mL) was added MnO_2 (960 mg, 11 mmol) under a nitrogen atmosphere. The suspension was stirred at the RT for 2 h. The mixture was filtered through a pad of Celite and filtrate was concentrated in vacuo to afford the aldehyde (320 mg) which was used in the next step without further purification.

A mixture of the above aldehyde (320 mg, 0.94 mmol) and carboethoxymethylenetriphenyl phosphorane (490 mg, 1.4 mmol) in anhydrous toluene (8 mL) was refluxed for 16 h. After evaporation of the solvent in vacuo, the resultant residue was purified by flash chromatography (10–15 % ethyl acetate/hexanes) to afford **33** (310 mg, 80 %) as a colorless oil. R_f = 0.42 (10 % ethyl acetate/hexanes); $[\alpha]_D^{25}$ = +8.7 (*c* = 0.58, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 1722, 1657, 1463, 1378, 1257, 1178, 1034, 836, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.29 (dd, *J* = 15.6, 0.61 Hz, 1H), 5.89 (d, *J* = 9.5 Hz, 1H), 5.79 (d, *J* = 15.6 Hz, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 3.99–3.79 (m, 5H), 2.87–2.82 (m, 1H), 2.05 (dd, *J* = 14.7, 7.9 Hz, 1H), 1.79 (d, *J* = 1.2 Hz, 3H), 1.33 (s, 3H), 1.30 (t, *J* = 7.3 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.02 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.5, 149.8, 146.7, 131.2, 115.7, 108.9, 71.4, 64.5, 64.1, 60.0, 43.5, 38.0, 25.8, 24.5, 18.0, 14.3, 13.0, 12.3, −4.4, −4.7 ppm; HRMS (ESI-TOF): calcd. for $C_{22}H_{40}O_5SiNa$ *m/z* 435.6253, found *m/z* 435.6248.

Compound ***23***

To a solution of ketal **33** (180 mg, 0.44 mmol) in 4.0 mL of acetone was added a solution of $[PdCl_2(CH_3CN)_2]$ (1.2 mg, 0.004 mmol, 1 mol %) in acetone (0.5 mL) at 0 °C. The mixture was allowed to stir at RT for 2 h. After removing solvents, the residue was purified by flash chromatography on silica gel (5–10 % ethyl acetate/hexanes) to afford the ketone **23** (120 mg, 78 %) as a viscous oil. R_f = 0.40 (8 % ethyl acetate/hexanes); $[\alpha]_D^{25}$ = +24.53 (*c* = 0.60, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 1718, 1625, 1472, 1367, 1257, 1175, 1097, 1029, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 15.6 Hz, 1H), 5.81 (d, *J* = 15.6 Hz, 1H), 5.72 (d, *J* = 10.1 Hz, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 4.11 (dd, *J* = 11.3, 5.8 Hz, 1H), 2.67–2.59 (m, 1H), 2.56 (t, *J* = 6.4 Hz, 1H), 2.19–2.09 (m, 1H), 2.12 (s, 3H), 1.79 (d, *J* = 1.2 Hz, 3H), 1.29 (t, *J* = 7.0 Hz, 3H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.85 (s, 9H), 0.09 (s, 3H), 0.04 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.9, 167.3, 149.2, 143.9, 132.5, 116.3, 71.7, 60.0, 48.9, 39.3, 31.3, 25.7, 17.9, 15.4, 14.2, 12.4, −4.6, −4.7 ppm; HRMS (ESI-TOF): calcd. for $C_{20}H_{37}O_4SiNa$ *m/z* 369.2461, found *m/z* 369.2445.

Compound ***34***

To a stirred solution of ketone **23** (310 mg, 0.842 mmol) in ethanol (5.0 mL) was added sodium borohydride (64 mg, 1.68 mmol) in one portion at 0 °C and stirring was continued for 3 h at the same temperature and then at RT for 30 min. The reaction was quenched by adding 1 mL of water, and the solvent was removed in vacuo. The product was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (20–40 % ethyl acetate/hexanes) to afford (1:3, based on ^1H NMR) diastereomeric mixture of alcohol **34** (290 mg, 93 %) as a viscous liquid. R_f = 0.41 (20 % ethyl acetate/hexanes); $[\alpha]_D^{25}$ = +12.83 (*c* = 0.75, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3367 (b), 1723, 1650, 1462, 1374, 1257, 1216, 1032, 761 cm^{-1}; ^1H NMR of major isomer (400 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 15.6 Hz, 1H), 5.87 (d, *J* = 9.8 Hz, 1H), 5.81 (dd, *J* = 15.6, 4.6 Hz, 1H), 4.22 (q, *J* = 7.3 Hz, 2H), 3.94–3.84 (m, 1H), 3.79–3.76 (m, 1H), 2.86–2.78 (m, 1H), 2.37–2.34 (m, 1H), 1.79 (d, *J* = 1.2 Hz, 3H), 1.66–1.59 (m, 1H), 1.31 (t, *J* = 7.0 Hz, 3H), 1.19 (d, *J* = 6.1 Hz, 3H), 1.03 (d, *J* = 6.7 Hz, 3H), 0.88 (s, 9H), 0.095 (s, 3H), 0.094 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.45, 167.41, 149.4, 149.3, 143.8, 143.6, 132.5, 132.3, 116.3, 116.0, 109.9, 76.6, 75.3, 74.9, 66.1, 64.6, 60.17, 60.13, 42.3, 42.2, 38.8, 38.4, 25.8, 25.7, 24.1, 23.9, 17.9, 17.2, 15.7, 14.2, 12.47, 12.42, −4.24, −4.27, −4.48, −4.58 ppm; HRMS (ESI-TOF): calcd. for $C_{20}H_{38}O_4SiNa$ *m/z* 393.2437, found *m/z* 393.2428.

Compound ***35***

To a stirred solution of triphenylphosphine (330 mg, 1.25 mmol), 1-phenyl-1*H*-tetrazole-5-thiol (210 mg, 1.17 mmol) and alcohol **34** (290 mg, 0.78 mmol) in anhydrous THF (6 mL) at 0 °C was added DIAD (230 μL, 1.17 mmol). The solution was stirred at the same temperature for 1 h and then at RT for 12 h. The solvent was evaporated to one fourth of its volume under vacuum and the resultant residue was purified by flash column chromatography (5–15 % ethyl acetate/hexanes) to afford **35** (250 mg, 60 %) as viscous oil. R_f = 0.38 (15 % ethyl acetate/hexanes); $[\alpha]_D^{25}$ = +19.16 (*c* = 0.53, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 1715, 1626, 1500, 1388, 1258, 1175, 1028, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.60–7.52 (m, 5H), 7.28 (d, *J* = 15.9, 13.7 Hz, 1H), 5.84–5.76 (m, 2H), 4.24–4.18 (m, 2H), 4.13–4.01 (m, 1H), 3.82–3.72 (m,1H), 2.74–2.68 (m, 1H), 1.97–1.80 (m, 2H), 1.78 (d, *J* = 1.2 Hz, 3H), 1.30 (t, *J* = 7.0 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.86 (s, 9H), 0.038 (s, 3H), 0.015 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.3, 167.2, 153.4, 149.25, 149.22, 144.1, 143.7, 133.7, 132.4, 132.2, 129.9, 129.64, 129.62, 123.9, 123.8, 116.2, 73.4, 73.0, 60.0, 41.6, 41.4, 41.3, 41.2, 38.6, 37.8, 25.7, 22.7, 22.4, 17.9, 15.4, 14.7, 14.2, 12.4, 12.3, −4.21, −4.25, −4.43, −4.49 ppm; HRMS (ESI-TOF): calcd. for $C_{27}H_{43}O_3N_4SSiNa$ *m/z* 531.2825, found *m/z* 531.2831.

Compound ***20***

To a solution of **35** (210 mg, 0.39 mmol) in 1.3 mL of ethanol at 0 °C was added ammonium heptamolybdate tetrahydrate (49 mg, 0.039 mmol) and H_2O_2 (230 μL, 30 % w/v aq. solution). The reaction mixture was stirred at RT for 16 h, quenched with 10 % aq. solution of Na_2SO_3 (8 mL), the ethanol was distilled off and the aqueous layer was extracted with dichloromethane (3 × 10). The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (10–20 % ethyl acetate/hexanes) to afford the sulfone **20** (200 mg, 90 %) as a pale yellow oil. R_f = 0.42 (20 % ethyl acetate/hexanes); $[\alpha]_D^{25}$ = +16.44 (*c* = 0.68, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 1713, 1625, 1498, 1462, 1339, 1260, 1097, 1028, 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.57 (m, 5H), 7.27 (d, *J* = 15.6, 1H), 5.82 (d, *J* = 15.8 Hz, 1H), 5.73 (d, *J* = 9.5 Hz, 1H), 4.22 (q, *J* = 7.0 Hz, 2H), 3.97–3.93 (m, 1H), 2.76–2.65 (m, 1H), 2.41–2.31 (m, 1H), 1.80 (d, *J* = 6.7 Hz, 3H), 1.76–1.61 (m, 1H), 1.52 (d, *J* = 7.0 Hz, 3H), 1.30 (t, *J* = 7.3 Hz, 3H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 0.09 (s, 3H), 0.07 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.3, 167.2, 152.57, 152.54, 149.0, 148.9, 142.9, 142.2, 133.1, 133.09, 133.07, 131.4, 131.3, 129.6, 129.56, 129.52, 125.3, 129.2, 123.9, 116.7, 116.5, 73.5, 72.5, 60.2, 58.7, 58.5, 39.2, 38.5, 33.6, 32.6, 25.7, 18.0, 17.9, 16.0, 15.3, 15.1, 14.2, 14.1, 13.8, 12.54, 12.52, −4.06, −4.25, −4.27, −4.3 ppm; HRMS (ESI-TOF): calcd. for $C_{27}H_{43}O_5N_4SSiNa$ *m/z* 585.2543, found *m/z* 585.2568.

Compound ***44***

A solution of DIBAL-H (1 M in toluene, 60 mL, 60 mmol) was added at −78 °C to a solution of ester **43** (6.0 g, 21.58 mmol) in CH_2Cl_2 (150 mL)

and stirred for 1 h. The reaction mixture was treated with a saturated solution of sodium potassium tartrate (25 mL) and the mixture was stirred until the solution became clear. The organic layer was separated from the reaction mixture and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by column chromatography (30–40% ethyl acetate/hexanes) afforded the alcohol (4.72 g, 92%) as a viscous oil.[24a] R_f=0.40 (30% ethyl acetate/hexanes); IR (neat): $\tilde{\nu}$=3423, 1687, 1612, 1513, 1463, 1302, 1248, 1174, 1093, 1034, 970 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ=7.26 (d, J=8.8 Hz, 2H), 6.88 (d, J=8.6 Hz, 2H), 5.71–5.59 (m, 2H), 4.43 (s, 2H), 4.07 (d, J=4.6 Hz, 2H), 3.80 (s, 3H), 3.45 (t, J=6.4 Hz, 2H), 2.16–2.10 (m, 2H), 1.76 (s, 1H), 1.72–1.65 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=159.0, 132.3, 130.5, 129.3, 129.2, 113.6, 72.4, 69.2, 63.5, 55.2, 29.0, 28.7 ppm.

To a stirred solution of AD-mix α (7.0 g) in 23 mL of *t*BuOH/H_2O (1:1), methanesulfonamide (485 mg, 5.08 mmol), and $K_2OsO_2(OH)_4$ were added and the mixture was stirred for 15 min. The reaction mixture was cooled to 0°C and a solution of above alcohol (750 mg, 3.18 mmol) in 1 mL of *t*BuOH/H_2O (1:1) was added and stirred for overnight at 0°C. The mixture was quenched with a saturated solution of Na_2SO_3 and stirred for 1 h. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product was purified by flash chromatography (60–80% ethyl acetate/hexanes) to afford triol **44** (500 mg, 58%) as a viscous liquid. R_f=0.19 (80% ethyl acetate/hexanes); $[\alpha]_D^{25}$=−4.44 (c=0.50, $CHCl_3$); IR (neat): $\tilde{\nu}$=3392 (b), 2618, 1731(b), 1464, 1248, 1175, 1090, 1032, 820 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ=7.25 (d, J=8.6 Hz, 2H), 6.88 (d, J=8.6 Hz, 2H), 4.46 (s, 2H), 3.81 (s, 3H), 3.75–3.62 (m, 6H), 1.79–1.61 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=159.3, 129.8, 129.4, 113.8, 73.8, 72.8, 72.3, 70.1, 64.7, 55.2, 31.2, 26.1 ppm; HRMS (ESI-TOF): calcd. for $C_{14}H_{22}O_5Na$ m/z 293.1365 found m/z 293.1378.

*Compound **45***

p-TsCl (1.06 g, 5.56 mmol) was added to a mixture of triol **44** (1.0 g, 3.7 mmol) and DMAP (catalytic amount) in pyridine (8 mL) at 0°C over 1 h, and the mixture was stirred at same temperature for overnight. After quenching with H_2O and extracting with ethyl acetate (5×20 mL), the organic layer was washed with $CuSO_4$ solution, dried over Na_2SO_4, and concentrated. The crude tosylate product was immediately used in the next step. R_f=0.63 (70% ethyl acetate/hexanes); $[\alpha]_D^{25}$=+1.43 (c=0.63, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ=7.79 (d, J=8.2 Hz, 2H), 7.34 (d, J=8.5 Hz, 2H), 7.24 (d, J=8.6 Hz, 2H), 6.88 (d, J=8.6 Hz, 2H), 4.44 (s, 2H), 4.09 (dd, J=10.4, 4.9 Hz, 1H), 4.03 (dd, J=10.4, 6.4 Hz, 1H), 3.81 (s, 3H), 3.77–3.43 (m, 4H), 2.45 (s, 3H), 1.75–1.58 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=159.3, 145.0, 132.6, 129.9, 129.6, 129.4, 127.9, 113.8, 72.8, 71.8, 71.2, 70.3, 70.0, 55.2, 31.4, 26.2, 21.6 ppm.

Anhydrous K_2CO_3 (325 mg, 2.4 mmol) was added to a solution of the above tosylate (1 g, 4 mmol) in methanol (6 mL) at 0°C and the mixture was stirred at RT for 45 min. The reaction mixture was filtered through a pad of Celite and washed thoroughly with ethyl acetate. The filtrate was concentrated and the residue was purified by silica gel chromatography (50–60% ethyl acetate/hexanes) to give epoxy alcohol **45** (420 mg, 71% for two steps) as viscous oil. R_f=0.44 (50% ethyl acetate/hexanes); $[\alpha]_D^{25}$=−3.35 (c=0.65, $CHCl_3$); IR (neat): $\tilde{\nu}$=3412, 1611, 1513, 1358, 1248, 1175, 1097, 1034, 971, 816 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ=7.26 (d, J=8.5 Hz, 2H), 6.88 (d, J=8.5 Hz, 2H), 4.45 (s, 2H), 3.81 (s, 3H), 3.49 (t, J=5.8 Hz, 2H), 3.49–3.47 (m, 1H), 2.98 (ddd, J=4.9, 4.0, 2.7 Hz, 1H), 2.79 (dd, J=4.9, 4.0 Hz, 1H), 2.71 (dd, J=4.9, 2.7 Hz, 1H), 1.80–1.66 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=159.1, 130.1, 129.3, 113.7, 72.6, 71.3, 69.8, 55.27, 55.23, 44.8, 31.5, 25.8 ppm; HRMS (ESI-TOF): calcd. for $C_{14}H_{20}O_4Na$ m/z 275.1259, found m/z 275.1254.

*Compound **46***

To a stirred solution of epoxy alcohol **45** (500 mg, 1.98 mmol) and imidazole (405 mg, 5.95 mmol) in CH_2Cl_2 (30 mL) was added TBSCl (655 mg, 4.36 mmol) at 0°C, and the reaction mixture was stirred at RT for 12 h. The reaction mixture was quenched with water and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. Flash column chromatography (20–30% ethyl acetate/hexanes) of the crude product gave compound **46** (480 mg, 68%) as a colorless oil. R_f=0.48 (20% ethyl acetate/hexanes); $[\alpha]_D^{25}$=−3.82 (c=0.65, $CHCl_3$); IR (neat): $\tilde{\nu}$=2950, 2930, 2856, 1613, 1514, 1464, 1249, 1099, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ=7.25 (d, J=8.2 Hz, 2H), 6.88 (d, J=8.5 Hz, 2H), 4.42 (s, 2H), 3.80 (s, 3H), 3.46–3.42 (m, 2H), 3.28–3.23 (m, 1H), 2.91 (ddd, J=6.7, 4.3, 2.7 Hz, 1H), 2.77 (dd, J=4.9, 4.0 Hz, 1H), 2.54 (dd, J=4.9, 2.7 Hz, 1H), 1.76–1.56 (m, 4H), 0.89 (s, 9H), 0.11 (s, 3H), 0.05 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=159.1, 130.5, 129.2, 113.7, 74.4, 72.5, 69.8, 55.9, 55.2, 44.8, 31.3, 25.8, 25.6, 18.1, −4.4, −5.0 ppm; HRMS (ESI-TOF): calcd. for $C_{20}H_{34}O_4SiNa$ m/z 389.2124, found m/z 389.2109.

*Compound **47***

To a suspension of trimethylsulfonium iodide (800 mg, 3.9 mmol) in diethyl ether (6.5 mL) at −18°C was added *n*BuLi (1.6 M in hexanes, 2.3 mL, 3.51 mmol) and the reaction was warmed to −13°C for 20 min. A solution of epoxy alcohol **46** (180 mg, 0.50 mmol) in diethyl ether (2.5 mL) was added via syringe at −18°C and the reaction was warmed to −10°C. The white slurry was stirred for 2 h at this temperature and quenched by the addition of MeOH (1 mL) at RT. The mixture was filtered through Celite and washed with ethyl acetate. The filtrate was concentrated and purified by flash chromatography (5–20% ethyl acetate/hexanes) to afford **47** (110 mg) and **48** (50 mg) as a clear liquid.

Data for **47**: R_f=0.37 (10% ethyl acetate/hexanes); $[\alpha]_D^{25}$=−1.56 (c=0.64, $CHCl_3$); IR (neat): $\tilde{\nu}$=3400, 1613, 1513, 1463, 1249, 1099, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ=7.25 (d, J=8.2 Hz, 2H), 6.87 (d, J=8.5 Hz, 2H), 5.83 (ddd, J=16.2, 10.4, 5.5 Hz, 1H), 5.31 (dt, J=17.1, 1.8 Hz, 1H), 5.18 (dt, J=10.4, 1.5 Hz, 1H), 4.43 (s, 2H), 3.99–3.98 (m, 1H), 3.81 (s, 3H), 3.63–3.59 (m, 1H), 3.42–3.93 (m, 2H), 2.33 (d, J=6.1 Hz, 1H), 1.70–1.50 (m, 4H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=159.0, 138.4, 130.5, 129.2, 116.0, 113.7, 75.0, 74.2, 72.4, 70.0, 55.2, 30.2, 25.8, 25.2, 18.0, −4.2, −4.5 ppm; HRMS (ESI-TOF): calcd. for $C_{21}H_{36}O_4SiNa$ m/z 403.2281, found m/z 403.2273.

Data for **48**: R_f=0.67 (10% ethyl acetate/hexanes); $[\alpha]_D^{25}$=+2.89 (c=0.63, $CHCl_3$); IR (neat): $\tilde{\nu}$=3446, 1611, 1513, 1463, 1250, 1097, 1036, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ=7.26 (d, J=8.5 Hz, 2H), 6.86 (d, J=8.5 Hz, 2H), 5.78 (ddd, J=17.1, 10.4, 6.1 Hz, 1H), 5.13 (dt, J=17.1, 1.2 Hz, 1H), 5.02 (dt, J=10.4, 1.2 Hz, 1H), 4.43 (s, 2H), 4.10 (q, J=6.1 Hz, 1H), 3.81 (s, 3H), 3.44 (t, J=6.1 Hz, 2H), 1.71–1.52 (m, 4H), 0.89 (s, 9H), 0.04 (s, 3H), 0.02 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=159.0, 141.6, 130.7, 129.2, 113.7, 113.6, 73.6, 72.4, 70.0, 55.2, 34.5, 25.8, 25.4, 18.2, −4.4, −4.8 ppm; HRMS (ESI): calcd. for $C_{20}H_{34}O_3SiNa$ m/z 373.2175, found m/z 373.2159.

*Compound **52***

To a solution of above epoxide **51** (2.8 g, 11.43 mmol) in anhydrous CH_2Cl_2 was added diisopropylethylamine (7.1 mL, 41.2 mmol) and MEM-Cl (2.3 mL, 20.5 mmol) successively at 0°C under nitrogen atmosphere. After being stirred for 16 h at RT, the reaction mixture was diluted with ethyl acetate and washed with water. Two layers were separated and the organic layer was washed with brine and dried over Na_2SO_4. The solvent was evaporated and the crude compound was purified by column chromatography (10–20% ethyl acetate/hexanes) to afford MEM-ether (3.1 g, 83%) as a colorless liquid. R_f=0.43 (20% ethyl acetate/hexanes); $[\alpha]_D^{25}$=−21.01(c=0.78, $CHCl_3$); IR (neat): $\tilde{\nu}$=1472, 1256, 1102, 1040, 836, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=4.94 (d, J=6.7 Hz, 1H), 4.77 (d, J=7.0 Hz, 1H), 3.78–3.68 (m, 2H), 3.64–3.60 (m, 2H), 3.56 (t, J=4.6 Hz, 2H), 3.38 (s, 3H), 3.36–3.31 (m, 1H), 2.98 (ddd, J=7.0, 4.2, 2.7 Hz, 1H), 2.77 (dd, J=4.8, 4.3 Hz, 1H), 1.67–1.56 (m, 4H), 0.88 (s, 9H), 0.04 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=94.4, 71.6, 67.0, 62.7, 58.8, 54.5, 43.8, 28.5, 25.8, 18.2, −5.4 ppm; HRMS (ESI-TOF): calcd. for $C_{16}H_{34}O_5SiNa$ m/z 357.2073, found m/z 357.2079.

To a suspension of trimethylsulfonium iodide (6.20 g, 30.54 mmol) in THF (58 mL) at −18°C was added *n*BuLi (1.6 M in hexanes, 18.4 mL,

29.5 mmol) and the reaction mixture was stirred at the same temperature for 5 min, then warmed to between −10 and −12 °C for 30 min. A solution of the above epoxide (1.7 g, 5.09 mmol) in THF (15 mL) was added via cannula at −18 °C and the reaction was allowed to warm slowly to RT over a period of 1 h. The white slurry was quenched by the addition of MeOH (1 mL), and stirred for 10 min at RT. The mixture was filtered through a pad of Celite and the filtrate was concentrated to dryness. The residue was purified by flash column chromatography (15–25% ethyl acetate/hexanes) to provide **52** (1.6 g, 90%) as a clear liquid. R_f=0.29 (20% ethyl acetate/hexanes); $[\alpha]_D^{25}$=+12.4 (c=1.70, $CHCl_3$); IR (neat): $\tilde{\nu}$=3435, 3051, 2771, 1472, 1256, 1103, 1041, 926, 836, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=5.84 (ddd, J=17.1, 10.7, 6.4 Hz, 1H), 5.36 (ddd, J=17.1, 3.1, 1.5 Hz, 1H), 5.21 (ddd, J=10.4, 3.1, 1.5 Hz, 1H), 4.81 (ABq, J=7.3 Hz, 2H), 4.03 (t, J=6.4 Hz, 1H), 3.82 (ddd, J=9.2, 4.8, 4.0 Hz, 1H), 3.72 (dt, J=9.2, 4.3 Hz, 1H), 3.60 (t, J=5.8 Hz, 2H), 3.56 (t, J=4.5 Hz, 2H), 3.48–3.45 (m, 1H), 3.39 (s, 3H), 1.69–1.45 (m, 4H), 0.89 (s, 9H), 0.04 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=137.3, 116.8, 96.1, 83.3, 74.8, 71.6, 67.7, 62.9, 58.9, 28.3, 27.6, 25.9, 18.3, −5.4 ppm; HRMS (ESI-TOF): calcd. for $C_{17}H_{36}O_5SiNa$ m/z 371.2230, found m/z 371.2230.

*Compound **53***

To a stirred suspension of NaH (350 mg, 8.75 mmol) in DMF (2 mL) at 0 °C was added a solution of alcohol **52** (1.5 g, 4.31 mmol) in DMF (8 mL). After stirring for 30 min. at RT, *para*-methoxybenzyl bromide (0.95 mL, 6.46 mmol) was added in one portion at 0 °C. The reaction mixture was stirred for 2 h at RT and diluted with ethyl acetate (20 mL) followed by addition of saturated NH_4Cl solution (20 mL) and stirred for 12 h in order to decompose excess *para*-methoxybenzyl bromide. The organic phase was separated and the aqueous layer was further extracted with ethyl acetate (3×20 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated. The crude product was purified by column chromatography using 10–20% of ethyl acetate/hexanes as eluent to afford the corresponding PMB-ether (1.75 g, 87%) as a colorless oil. R_f=0.74 (20% ethyl acetate/hexanes); $[\alpha]_D^{25}$=−1.67 (c=0.80, $CHCl_3$); IR (neat): $\tilde{\nu}$=1614, 1514, 1471, 1462, 1250, 1099, 1039, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.23 (d, J=8.6 Hz, 2H), 6.86 (d, J=8.6 Hz, 2H), 5.79 (ddd, J=17.1, 10.4, 7.6 Hz, 1H), 5.32–5.26 (m, 2H), 4.84 (d, J=7.0 Hz, 1H), 4.77 (d, J=7.0 Hz, 1H), 4.55 (d, J=11.3 Hz, 1H), 4.30 (d, J=11.4 Hz, 1H), 3.80 (s, 3H), 3.71 (q, J=4.6 Hz, 2H), 3.57 (t, J=5.8 Hz, 2H), 3.50 (t, J=4.8 Hz, 2H), 3.37 (s, 3H), 1.69–1.42 (m, 6H), 0.88 (s, 9H), 0.03 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=159.0, 135.5, 130.6, 129.2, 118.5, 113.6, 95.8, 81.8, 79.5, 71.7, 70.1, 67.1, 63.1, 58.9, 55.2, 28.7, 27.1, 25.9, 18.2, −5.4 ppm; HRMS (ESI-TOF): calcd. for $C_{25}H_{44}O_6SiNa$ m/z 491.2805, found m/z 491.2828.

To a stirred solution of above TBS-ether (1.68 g, 3.4 mmol) in THF (10 mL) at 0 °C was added TBAF (5.8 mL, 5.8 mmol, 1 M in THF) and then allowed to stir at RT for 2 h. The reaction mixture was concentrated and purified by silica gel column chromatography (50–70% ethyl acetate/hexanes) to afford the alcohol **53** (0.97 g, 88%) as colorless oil. R_f=0.14 (50% ethyl acetate/hexanes); $[\alpha]_D^{25}$=−13.98 (c=0.73, $CHCl_3$); IR (neat): $\tilde{\nu}$=3417, 2931, 2712, 1613, 1248, 1036, 931 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.23 (d, J=8.8 Hz, 2H), 6.86 (d, J=8.6 Hz, 2H), 5.79 (ddd, J=17.1, 10.7, 7.6 Hz, 1H), 5.34–5.28 (m, 2H), 4.87 (d, J=7.0 Hz, 1H), 4.77 (d, J=7.0 Hz, 1H), 4.56 (d, J=11.3 Hz, 1H), 4.29 (d, J=11.6 Hz, 1H), 3.84–3.49 (m, 1H), 3.38 (s, 3H), 1.7–1.47 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=158.9, 135.1, 130.4, 129.2, 118.7, 113.6, 95.9, 81.7, 79.5, 71.7, 70.1, 67.2, 62.6, 58.9, 55.1, 28.4, 27.1 ppm; HRMS (ESI-TOF): calcd. for $C_{19}H_{30}O_6Na$ m/z 377.1940, found m/z 377.1923.

*Compound **54***

To a stirred solution of alcohol **53** (55 mg, 0.15 mmol) in CH_2Cl_2 (3 mL) at 0 °C was added DMP (130 mg, 0.31 mmol) in a single portion. The reaction mixture was stirred for 3 h at RT. It was then quenched with saturated $NaHCO_3$ (2 mL, containing 0.5 g of $Na_2S_2O_3$) and the crude aldehyde was isolated by extraction with CH_2Cl_2 (2×10 mL). The organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was used for further reaction without any purification.

A mixture of the above aldehyde (65 mg) and carboethoxymethylenetriphenyl phosphorane (110 mg, 0.31 mmol) in anhydrous toluene (4 mL) was stirred at RT for 5 h under nitrogen atmosphere. After evaporation of the solvent in vacuo, the resultant residue was purified by flash chromatography (20–30% ethyl acetate/hexanes) to afford **54** (50 mg, 77% for 2 steps). R_f=0.51 (30% ethyl acetate/hexanes); $[\alpha]_D^{25}$=−6.4 (c=0.78, $CHCl_3$); IR (neat): $\tilde{\nu}$=2930, 1718, 1655, 1613, 1514, 1249, 1037, 932, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.23 (d, J=8.5 Hz, 2H), 6.93 (dt, J=15.8, 6.7 Hz, 1H), 6.87 (d, J=8.8 Hz, 2H), 5.84–5.75 (m, 2H), 5.35–5.28 (m, 2H), 4.83 (d, J=7.0 Hz, 1H), 4.76 (d, J=7.0 Hz, 1H), 4.56 (d, J=11.6 Hz, 1H), 4.28 (d, J=11.6 Hz, 1H), 4.18 (q, J=7.3 Hz, 2H), 3.85–3.76 (m, 1H), 3.80 (s, 3H), 3.75–3.60 (m, 3H), 3.51 (t, J=4.9 Hz, 2H), 3.37 (s, 3H), 2.31–2.22 (m, 1H), 2.18–2.10 (m, 1H), 1.79–1.71 (m, 1H), 1.61–1.53 (m, 1H), 1.28 ppm (t, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.5, 159.1, 148.6, 135.0, 130.3, 129.3, 121.4, 118.8, 113.6, 95.9, 81.2, 79.0, 71.6, 70.0, 67.3, 60.0, 58.9, 55.1, 29.0, 28.0, 14.1 ppm; HRMS (ESI-TOF): calcd. for $C_{23}H_{34}O_7Na$ m/z 445.2202, found m/z 445.2219.

*Compound **21***

To a stirred solution of ester **54** (340 mg, 0.81 mmol) in dry CH_2Cl_2 (8 mL) was added a solution of DIBAL-H (2.0 mL, 2.0 mmol, 1 M solution in toluene) at −78 °C. After being stirred at same temperature for 1 h, the reaction mixture was quenched with saturated solution of potassium-sodium-tartrate (5 mL), and stirred for 3 h at RT and extracted with CH_2Cl_2 (3×50 mL). The organic layer was washed with brine, dried over Na_2SO_4, concentrated, and the crude product was purified by flash column chromotography (50–70% ethyl acetate/hexanes) to afford the alcohol **62** (270 mg, 88%) as colorless oil. R_f=0.18 (50% ethyl acetate/hexanes); $[\alpha]_D^{25}$=−7.34 (c=0.88, $CHCl_3$); IR (neat): $\tilde{\nu}$=3445, 2930, 1612, 1514, 1248, 1036, 931 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.24 (d, J=8.5 Hz, 2H), 6.87 (d, J=8.8 Hz, 2H), 5.80 (ddd, J=17.4, 10.7, 7.6 Hz, 1H), 5.69–5.57 (m, 2H), 5.34–5.27 (m, 2H), 4.83 (d, J=7.0 Hz, 1H), 4.76 (d, J=7.0 Hz, 1H), 4.55 (d, J=11.6 Hz, 1H), 4.29 (d, J=11.6 Hz, 1H), 4.06 (s, 2H), 3.83–3.81 (m, 1H), 3.80 (s, 3H), 3.77–3.60 (m, 3H), 3.51 (t, J=4.5 Hz, 2H), 3.37 (s, 3H), 2.15–1.99 (m, 2H), 1.74–1.61 (m, 1H), 1.56–1.47 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=159.0, 135.2, 132.4, 130.4, 129.3, 118.6, 95.8, 81.3, 78.9, 71.6, 70.0, 67.2, 63.5, 58.9, 55.1, 30.1, 28.0 ppm; HRMS (ESI-TOF): calcd. for $C_{21}H_{32}O_6Na$ m/z 403.2097, found m/z 403.2104.

To a stirred suspension of MnO_2 (160 mg, 1.85 mmol) in dry CH_2Cl_2 (4 mL), a solution of alcohol **62** (70 mg, 0.185 mmol) in CH_2Cl_2 (2 mL) was added dropwise and stirred for 2 h at RT. The mixture was filtered through a pad of Celite and filtrate was concentrated in vacuo to afford a crude aldehyde **21** (150 mg, 92%) which was used in the next step without further purification. R_f=0.51 (50% ethyl acetate/hexanes).

*Compound **58***

To a stirred suspension of NaH (470 mg, 11.7 mmol, 60% in mineral oil) in DMF (1 mL) at 0 °C was added dropwise a solution of alcohol **57** (1.3 g, 5.32 mmol). After stirring for 20 min at 0 °C, a freshly prepared *para*-methoxybenzyl bromide (1.5 mL, 10.7 mmol) was added in one portion at the same temperature. The reaction mixture was stirred for 1 h at RT and diluted with ethyl acetate (20 mL) followed by addition of a saturated NH_4Cl solution (15 mL). The organic phase was separated and the aqueous layer was further extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated. The crude product was purified by flash column chromatography (5–10% ethyl acetate/hexanes) to afford the compound **58** (1.6 g, 82%) as colorless oil. R_f=0.75 (10% ethyl acetate/hexanes); $[\alpha]_D^{25}$=−24.4 (c=0.80, $CHCl_3$); IR (neat): $\tilde{\nu}$=2932, 2857, 1614, 1514, 1249, 1100, 1039, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.25 (d, J=8.3 Hz, 2H), 6.86 (d, J=8.4 Hz, 2H), 5.72 (ddd, J=17.1, 10.4, 7.6 Hz, 1H), 5.23–5.17 (m, 2H), 4.52 (d, J=11.3 Hz, 1H), 4.28 (d, J=11.6 Hz, 1H), 3.80 (s, 3H), 3.69 (q, J=6.7 Hz, 1H), 3.58 (t, J=6.4 Hz, 2H), 1.65–1.60 (m, 1H), 1.52–1.33 (m, 5H), 0.89 (s, 9H), 0.03 ppm (s, 6H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 139.1, 130.8, 129.2, 116.9, 113.6, 80.2, 69.6, 63.0, 55.1, 35.2, 32.6, 25.9, 21.6, 18.3, −5.3 ppm; HRMS (ESI-TOF): calcd. for $C_{21}H_{36}O_3SiNa$ *m/z* 387.2331, found *m/z* 387.2354.

Compound ***59***

To a solution of silyl ether **58** (1.50 g, 4.12 mmol) in THF (20 mL) was added TBAF (8.5 mL, 8.5 mmol, 1 M in THF) at 0 °C. After being stirred at RT for 2 h, the reaction mixture was concentrated and purified by flash chromatography (40–50 % ethyl acetate/hexanes) to afford alcohol **59** (1.04 g, 96 %) as a colorless oil. R_f = 0.28 (30 % ethyl acetate/hexanes); $[\alpha]_D^{25}$ = −35.17 (*c* = 0.78, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3401 (b), 2937, 2861, 1612, 1513, 1248, 1173, 1034, 927 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.73 (ddd, *J* = 17.1, 10.4, 7.9 Hz, 1H), 5.24–5.18 (m, 2H), 4.52 (d, *J* = 11.6 Hz, 1H), 4.27 (d, *J* = 11.3 Hz, 1H), 3.74–3.68 (m, 1H), 3.62 (t, *J* = 6.4 Hz, 2H), 1.69–1.37 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 138.9, 130.6, 129.3, 117.0, 113.6, 80.0, 69.6, 62.6, 55.2, 35.0, 32.4, 21.4 ppm; HRMS (ESI-TOF): calcd. for $C_{15}H_{22}O_3Na$ *m/z* 273.1467, found *m/z* 273.1463.

Compound ***60***

Anhydrous DMSO (630 μL, 8.85 mmol) was added dropwise to a cold (−78 °C) solution of oxalylchloride (630 μL, 7.2 mmol) in dry CH_2Cl_2 (14 mL) and stirred for 15 min. A solution of the alcohol **59** (1.0 g, 4.0 mmol) in dry CH_2Cl_2 (7 mL) was added dropwise and stirred at −78 °C for 30 min. Et_3N (2.8 mL, 20 mmol) was added to the reaction mixture and stirred at −78 °C for 5 min and then it was allowed to warm to 0 °C over 20 min. The reaction mixture was quenched with water and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to afford a crude aldehyde (1.0 g) as pale yellow oil.

To a stirred solution of the above aldehyde (1.0 g, 3.95 mmol) in CH_2Cl_2 (15 mL) was added carboethoxymethylenetriphenyl phosphorane (2.1 g, 6.0 mmol) at RT. The mixture was stirred for 5 h and then concentrated in vacuo. The residue was purified by column chromatography (15–30 % ethyl acetate/hexanes) to provide the ester **60** (1.05 g, 91 % for 2 steps) as colorless oil. R_f = 0.33 (20 % ethyl acetate/hexanes); $[\alpha]_D^{25}$ = −29.21 (*c* = 0.50, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 2924, 2852, 1720, 1653, 1514, 1464, 1248, 1173, 1038 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.6 Hz, 2H), 6.93 (dt, *J* = 15.6, 7.0 Hz, 1H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.79 (dt, *J* = 15.6, 1.5 Hz, 1H), 5.71 (ddd, *J* = 17.4, 10.4, 7.9 Hz, 1H), 5.25–5.18 (m, 2H), 4.52 (d, *J* = 11.3 Hz, 1H), 4.26 (d, *J* = 11.6 Hz, 1H), 3.80 (s, 3H), 3.72–3.67 (m, 1H), 2.17 (q, *J* = 6.7 Hz, 2H), 1.63–1.47 (m, 4H), 1.28 ppm (t, *J* = 4.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166, 158.9, 148.3, 138.8, 130.6, 129.2, 121.3, 117.0, 113.6, 79.6, 69.6, 59.9, 55.1, 34.8, 31.8, 23.7, 14.1 ppm; HRMS (ESI-TOF): calcd. for $C_{19}H_{26}O_4Na$ *m/z* 341.1729, found *m/z* 341.1722.

Compound ***22***

A solution of compound **60** (300 mg, 0.94 mmol) in THF/MeOH/H_2O (1:1:2, 6 mL) was treated with LiOH (120 mg, 2.86 mmol) at RT. The reaction mixture was stirred at the same temperature for 4 h, and solvents were removed in vacuo. The aqueous phase was washed with diethyl ether and the aqueous layer was acidified with 10 % aq. citric acid, and extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resultant acid was purified by silica gel column chromatography (20–40 % ethyl acetate/hexanes) to afford the acid **22** (250 mg, 90 %) as a colorless viscous oil. R_f = 0.25 (20 % ethyl acetate/hexanes); $[\alpha]_D^{25}$ = −31.9 (*c* = 0.55, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 1697, 1652, 1613, 1513, 1248, 1036, 821 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.5 Hz, 2H), 7.05 (dt, *J* = 15.6, 6.7 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.79 (dt, *J* = 15.6, 1.5 Hz, 1H), 5.72 (ddd, *J* = 17.1, 10.4, 7.9 Hz, 1H), 5.25–5.5.18 (m, 2H), 4.53 (d, *J* = 11.6 Hz, 1H), 4.26 (d, *J* = 1.6 Hz, 1H), 3.80 (s, 3H), 3.79–3.67 (m, 1H), 2.22–2.17 (m, 2H), 1.66–1.47 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 159.1, 151.9, 138.8, 130.6, 129.4, 120.7, 117.3, 113.7, 79.6, 69.6, 55.2, 34.8, 32.0, 23.7 ppm; HRMS (ESI-TOF): calcd. for $C_{17}H_{22}O_4Na$ *m/z* 313.1416, found *m/z* 313.1415.

Compound ***63***

To a stirred solution of triphenylphosphine (105 mg, 0.39 mmol), 1-phenyl-1*H*-tetrazole-5-thiol (57 mg, 0.31 mmol) and alcohol **62** (100 mg, 0.26 mmol) in anhydrous THF (5 mL) was added DIAD (80 μL, 0.39 mmol) at 0 °C. The solution was stirred at the same temperature for 2 h. The solvent was evaporated to one fourth of its volume under vacuum and the resultant residue was treated with saturated solution of $NaHCO_3$ (5 mL) and diluted with ethyl acetate (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by flash column chromatography (5–15 % ethyl acetate/hexanes) to give **63** (120 mg, 86 %). R_f = 0.25 (20 % ethyl acetate/hexanes); $[\alpha]_D^{25}$ = −0.70 (*c* = 0.63, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 1613, 1514, 1500, 1386, 1247, 1174, 1111, 1036, 762 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73–7.50 (m, 5H), 7.22 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.78 (ddd, *J* = 17.8, 10.8, 7.5 Hz, 1H), 5.64–5.55 (m, 1H), 5.34–5.24 (m, 2H), 4.81 (d, *J* = 7.0 Hz, 1H), 4.74 (d, *J* = 7.0 Hz, 1H), 4.55 (d, *J* = 11.3 Hz, 1H), 4.28 (d, *J* = 11.6 Hz, 1H), 3.98 (d, *J* = 7.3 Hz, 2H), 3.84–3.80 (m, 1H), 3.79 (s, 3H), 3.78–3.65 (m, 2H), 3.64–3.52 (m, 1H), 3.49 (t, *J* = 4.6 Hz, 2H), 3.36 (s, 3H), 2.15–1.95 (m, 2H), 1.76–1.25 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 153.8, 136.5, 135.1, 133.6, 130.4, 129.9, 129.6, 129.2, 124.2, 123.8, 123.7, 123.1, 118.6, 113.6, 95.8, 81.2, 79.0, 71.6, 70.0, 67.2, 58.9, 55.1, 35.4, 29.8, 28.1, 21.8 ppm; HRMS (ESI-TOF): calcd. for $C_{26}H_{36}O_5N_4SNa$ *m/z* 563.2304, found *m/z* 563.2289.

Compound ***64***

To a solution of **63** (120 mg, 0.22 mmol) in 750 μL of ethanol at 0 °C was added ammonium heptamolybdate tetrahydrate (28 mg, 0.022 mmol) and H_2O_2 (130 μL, 30 % w/v aq. solution). The reaction mixture was stirred at RT for 12 h and quenched with 10 % aq. solution of Na_2SO_3 (5 mL). Ethanol was distilled off and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (20–30 % ethyl acetate/hexanes) to give sulfone **64** (70 mg, 55 %) as a pale yellow oil. R_f = 0.20 (20 % ethyl acetate/hexanes); $[\alpha]_D^{25}$ = −1.03 (*c* = 1.28, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 2928, 1966, 1514, 1498, 1346, 1248, 1153, 1036, 930, 822 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73–7.55 (m, 5H), 7.22 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.93 (dt, *J* = 15.6, 6.7 Hz, 1H), 5.77 (ddd, *J* = 17.6, 10.7, 7.6 Hz, 1H), 5.50–5.43 (m, 1H), 5.33–5.25 (m, 2H), 4.79 (d, *J* = 7.0 Hz, 1H), 4.73 (d, *J* = 7.0 Hz, 1H), 4.54 (d, *J* = 11.6 Hz, 1H), 4.35 (d, *J* = 7.0 Hz, 2H), 4.28 (d, *J* = 11.3 Hz, 1H), 3.81–3.78 (m, 1H), 3.79 (s, 3H), 3.58–3.51 (m, 1H), 3.49 (t, *J* = 4.9 Hz, 2H), 2.19–2.01 (m, 2H), 1.68–1.45 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 153.0, 144.4, 135.0, 132.9, 131.3, 130.3, 129.5, 129.3, 125.1, 118.7, 113.6, 113.1, 95.9, 81.1, 78.9, 71.6, 70.0, 67.3, 59.6, 58.8, 55.1, 29.4, 28.6 ppm; HRMS (ESI-TOF): calcd. for $C_{28}H_{36}O_7N_4SNa$ *m/z* 595.2202, found *m/z* 595.2193.

Compound ***75***

To a solution of **53** (500 mg, 1.42 mmol), triphenylphosphine (560 mg, 2.12 mmol) and 1- phenyl-1*H*-tetrazole-5-thiol **36** (300 mg, 1.70 mmol) in dry THF (20 mL) at 0 °C was added DIAD (420 μL, 2.12 mmol) dropwise. The reaction mixture was stirred at the same temperature for 2 h, then quenched with saturated $NaHCO_3$ solution and extracted with ethyl acetate (3 × 10). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by chromatography on silica gel (20–30 % ethyl acetate/hexanes) gave **75** (650 mg, 89 %) as a colorless viscous oil. R_f = 0.40 (20 % ethyl acetate/hexanes); $[\alpha]_D^{25}$ = −4.75 (*c* = 0.85, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 2927, 1613, 1514, 1500, 1387, 1247, 1037, 931, 762 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.51 (m, 5H), 7.22 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.79 (ddd, *J* = 18.0, 10.7, 7.6 Hz, 1H), 5.33–5.27 (m, 2H), 4.83 (d, *J* = 7.0 Hz, 1H), 4.75 (d, *J* = 7.3 Hz, 1H), 4.55 (d, *J* = 11.6 Hz, 1H), 4.27 (d, *J* = 11.6 Hz, 1H), 3.83–3.51 (m, 4H), 3.78 (s, 3H), 3.49 (t, *J* = 4.6 Hz, 2H), 3.42–3.17 (m, 2H), 3.35 (s, 3H), 1.93–1.54 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1, 154.2, 135.0, 133.7, 130.3, 129.9, 129.6, 129.3, 123.7, 118.8, 113.6, 95.8, 81.2, 78.9, 71.6, 70.1, 67.3, 58.8, 55.1,

33.2, 29.6, 25.1 ppm; HRMS (ESI-TOF): calcd. for $C_{26}H_{35}O_5N_4SNa$ *m/z* 515.2328, found *m/z* 515.2328.

Compound ***66***

To a solution of **75** (530 mg, 1.03 mmol) in EtOH (3.5 mL) were added ammonium heptamolybdate tetrahydrate (128 mg, 0.103 mmol) and 30% H_2O_2 (600 μL) at 0 °C and the mixture was stirred for 12 h at RT. The reaction mixture was diluted with 10% aqueous $Na_2S_2O_3$, ethanol was concentrated under reduced pressure and the aqueous layer was extracted with ethyl acetate (3×15 mL). The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to give a crude residue, which was purified by flash chromatography (20% ethyl acetate/hexanes) to deliver the sulfone **66** (520 mg, 91%) as colorless viscous oil. R_f=0.40 (20% ethyl acetate/hexanes); $[\alpha]_D^{25}=-7.34$ (c=0.88, $CHCl_3$); IR (neat): $\tilde{\nu}$= 2931, 2890, 1613, 1514, 1498, 1463, 1342, 1248, 1153, 1036, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.73–7.65 (m, 2H), 7.63–7.55 (m, 3H), 7.22 (d, J=8.5 Hz, 2H), 6.86 (d, J=8.6 Hz, 2H), 5.77 (ddd, J=17.7, 10.7, 7.3 Hz, 1H), 5.36–5.29 (m, 2H), 4.85 (d, J=7.0 Hz, 1H), 4.75 (d, J= 7.3 Hz, 1H), 4.55 (d, J=11.3 Hz, 1H), 4.28 (d, J=11.6 Hz, 1H), 3.84 (dd, J=6.7, 0.6 Hz, 1H), 3.79 (s, 3H), 3.77–3.61 (m, 5H), 3.48 (t, J=4.6 Hz, 2H), 3.35 (s, 3H), 2.08–1.92 (m, 2H), 1.82–1.74 (m, 1H), 1.66–1.58 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=158.9, 153.2, 134.5, 132.8, 131.2, 130.0, 129.4, 129.1, 124.8, 120.9, 119.0, 113.5, 95.8, 81.0, 78.4, 71.4, 70.0, 67.3, 58.7, 55.6, 54.9, 28.9, 18.2 ppm; HRMS (ESI-TOF): calcd. for $C_{26}H_{35}O_7N_4SNa$ *m/z* 569.2046, found *m/z* 569.2023.

Compound ***76***

A solution of sulfone **66** (490 mg, 0.89 mmol) and aldehyde **65** (400 mg, 0.81 mmol) in anhydrous THF (4 mL) was cooled to −78 °C. To this, a solution of freshly prepared LiHMDS (0.5 M in THF, 5.2 mL, 2.6 mmol) was added. After being stirred for 1 h at −78 °C, the reaction was quenched with water and extracted with ethyl acetate (4×15 mL). The combined organic extract was dried over Na_2SO_4 and purified by silica gel column chromatography (20–40% ethyl acetate/hexanes) to afford the diene **76** (360 mg, 60%) as a colorless viscous material. R_f=0.48 (20% ethyl acetate/hexanes); $[\alpha]_D^{25}=+1.43$ (c=0.63, $CHCl_3$); IR (neat): $\tilde{\nu}$=2930, 2857, 1736, 1613, 1514, 1372, 1246, 1112, 1039, 824, 705 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ=7.71–7.66 (m, 4H), 7.44–7.35 (m, 6H), 7.24 (d, J=8.5 Hz, 2H), 6.86 (d, J=8.5 Hz, 2H), 6.16 (dd, J=14.9, 10.9 Hz, 1H), 5.85–5.73 (m, 2H), 5.50 (dt, J=14.3, 6.7 Hz, 1H), 5.35–5.27 (m, 2H), 4.93–4.88 (m, 1H), 4.84 (d, J=7.0 Hz, 1H), 4.78 (d, J=7.0 Hz, 1H), 4.55 (d, J= 11.6 Hz, 1H), 4.29 (d, J=11.6 Hz, 1H), 4.05 (s, 2H), 3.84–3.61 (m, 5H), 3.51 (t, J=4.9 Hz, 2H), 3.37 (s, 3H), 2.67–2.61 (m, 1H), 2.28 (dd, J= 13.7, 2.8 Hz, 1H), 2.18–1.94 (m, 3H), 1.98 (s, 3H), 1.74–1.49 (m, 2H), 1.72 (s, 3H), 1.59 (s, 3H), 1.06 (s, 9H), 0.96 ppm (d, J=6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.5, 159.0, 135.4, 135.3, 134.9, 133.8, 133.7, 132.3, 132.2, 130.5, 129.6, 129.3, 127.6, 126.9, 125.6, 118.6, 113.6, 95.9, 81.4, 79.2, 75.7, 71.7, 70.1, 68.5, 67.2, 58.9, 55.2, 42.6, 35.8, 30.5, 28.7, 26.7, 20.9, 16.7, 16.6, 16.5, 13.8 ppm; HRMS (ESI-TOF): calcd. for $C_{49}H_{68}O_8SiNa$ *m/z* 835.4581 found *m/z* 835.4594.

Compound ***77***

To a solution of acetate **76** (320 mg, 0.40 mmol) in CH_2Cl_2 (10 mL) was added DIBAL-H (1.18 mL, 1.18 mmol, 1 M in toluene) at −78 °C. The solution was stirred at the same temperature for 2 h. The reaction mixture was treated with a saturated solution of sodium potassium tartarate (5 mL) and the mixture was stirred until the solution became clear. The organic layer was separated from the reaction mixture and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic extracts were washed with water, brine, and dried over Na_2SO_4. Concentration of the solution followed by column purification on silica gel (20–30% ethyl acetate/hexanes) afforded the alcohol **77** (220 mg, 78%) as a viscous oil. R_f=0.40 (20% ethyl acetate/hexanes); $[\alpha]_D^{25}=+4.10$ (c=0.60, $CHCl_3$); IR (neat): $\tilde{\nu}$=3469 (b), 2930, 2857, 1612, 1514, 1462, 1249, 1112, 1037, 824, 704 cm^{-1};^1H NMR (400 MHz, $CDCl_3$): δ=7.69–7.66 (m, 4H), 7.44–7.35 (m, 6H), 7.24 (d, J=8.5 Hz, 2H), 6.86 (d, J=8.5 Hz, 2H), 6.22 (dd, J=14.9, 10.9 Hz, 1H), 5.86–5.76 (m, 2H), 5.57 (dt, J=14.9, 6.7 Hz, 1H), 5.35–5.27 (m, 3H), 4.84 (d, J=7.0 Hz, 1H), 4.78 (d, J=7.0 Hz, 1H), 4.56 (d, J=11.3 Hz, 1H), 4.29 (d, J=11.6 Hz, 1H), 4.07 (s, 2H), 3.83–3.75 (m, 1H), 3.79 (s, 3H), 3.72 (q, J=4.6 Hz, 2H), 3.68–3.61 (m, 1H), 3.55–3.38 (m, 1H), 3.51 (t, J=4.9 Hz, 2H), 3.37 (s, 3H), 2.50–2.44 (m, 1H), 2.32 (d, J=13.4 Hz, 1H), 2.22–2.04 (m, 2H), 1.94 (dd, J=13.8, 10.4 Hz, 1H), 1.76–1.49 (m, 2H), 1.73 (s, 3H), 1.62 (s, 3H), 1.06 (s, 9H), 1.04 ppm (d, J=6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=159.0, 135.5, 135.3, 134.6, 133.9, 133.8, 133.1, 132.8, 130.5, 129.5, 129.3, 127.8, 127.6, 126.7, 126.5, 118.7, 113.6, 95.9, 81.4, 79.2, 73.0, 71.7, 70.0, 68.8, 67.2, 58.9, 55.1, 45.5, 38.2, 30.5, 28.8, 26.8, 19.3, 16.7, 16.5, 13.9 ppm; HRMS (ESI-TOF): calcd. for $C_{47}H_{66}O_7SiNa$ *m/z* 793.4476, found *m/z* 793.4460.

Compound ***78***

A mixture of compound **22** (110 mg, 0.38 mmol), 2,4,6-trichlorobenzoyl chloride (60 μL, 0.38 mmol) and Et_3N (100 μL, 0.68 mmol) in toluene (1.5 mL) was stirred at rt for 2 h to give a solution of mixed anhydride. This solution (600 μL) was then added to a solution of compound **77** (110 mg, 0.14 mmol) and DMAP (36 mg, 0.30 mmol) in toluene (2 mL) under argon atmosphere at RT and stirred for 2 h. The reaction mixture was quenched with water and the mixture was extracted with ethyl acetate (3×10 mL). The combined organic layers were dried and concentrated to afford a residue that was purified by column chromatography (15–25% ethyl acetate/hexanes) to afford the ester **78** (105 mg, 67%) as a viscous oil. R_f=0.46, (20% ethyl acetate/hexanes); $[\alpha]_D^{25}=-5.54$ (c=0.48, $CHCl_3$); IR (neat): $\tilde{\nu}$=3071, 2930, 2857, 1716, 1514, 1249, 1038, 823 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.70–7.65 (m, 4H), 7.44–7.35 (m, 6H), 7.27–7.22 (m, 4H), 6.89–6.82 (m, 5H), 6.15 (dd, J=14.9, 10.7 Hz, 1H), 5.84–5.66 (m, 4H), 5.50–5.43 (m, 4H), 5.36–5.17 (m, 5H), 4.98–4.93 (m, 1H), 4.83 (d, J=7.0 Hz, 1H), 4.77 (d, J=7.0 Hz, 1H), 4.55 (d, J= 11.6 Hz, 1H), 4.51 (d, J=11.6 Hz, 1H), 4.27 (d, J=12.2 Hz, 1H), 4.25 (d, J=11.9 Hz, 1H), 4.04 (s, 2H), 3.84–3.75(m, 1H), 3.79 (s, 3H), 3.79 (s, 3H), 3.74–3.54 (m, 4H), 3.49 (t, J=4.3 Hz, 2H), 3.36 (s, 3H), 2.69–2.64 (m, 1H), 2.32 (dd, J=14.4, 4.0 Hz, 1H), 2.26–1.98 (m, 5H), 1.83–1.42 (m, 6H), 1.72 (s, 3H), 1.57 (s, 3H), 1.05 (s, 9H), 0.96 ppm (d, J=6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=116.2, 159.0, 148.6, 138.9, 135.4, 135.3, 134.7, 133.8, 133.7, 132.3, 132.1, 130.7, 130.5, 129.5, 129.3, 129.2, 127.6, 126.8, 125.7, 121.5, 118.6, 117.1, 113.7, 113.6, 95.9, 81.4, 79.7, 79.2, 77.3, 77.1, 75.7, 71.6, 70.0, 69.6, 68.6, 67.2, 58.9, 55.2, 55.1, 42.3, 35.7, 34.9, 31.9, 30.6, 28.8, 26.8, 23.8, 19.2, 16.7, 16.6, 13.8 ppm; HRMS (ESI-TOF): calcd. $C_{64}H_{86}O_{10}SiNa$ for *m/z* 1065.5888, found *m/z* 1065.5919.

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[1] D. J. Newman, G. M. Cragg, K. M. Snader, *Nat. Prod. Rep.* **2000**, *17*, 215–234.
[2] R. Singh, M. Sharma, P. Joshi, D. S. Rawat, *Anticancer Agents Med. Chem.* **2008**, *8*, 603–617.
[3] a) M. Donia, M. T. Hamann, *Lancet Infect. Dis.* **2003**, *3*, 338–348; b) R. K. Jha, X. Zi-rong, *Mar. Drugs* **2004**, *2*, 123–146.
[4] T. Diyabalanage, C. D. Amsler, K. B. Iken, J. B. McClintock, B. J. Baker, *J. Am. Chem. Soc.* **2006**, *128*, 5630–5631.
[5] For more information on the Antarctic Treaty, see: http://www.ats.aq/e/ep.htm.
[6] X. Jiang, B. Liu, S. Lebreton, J. K. De Brabander, *J. Am. Chem. Soc.* **2007**, *129*, 6386–6387.
[7] a) K. C. Nicolaou, R. Guduru, Y.-P. Sun, B. Banerji, D. Y.-K. Chen, *Angew. Chem.* **2007**, *119*, 6000–6004; *Angew. Chem. Int. Ed.* **2007**, *46*, 5896–5900; b) K. C. Nicolaou, R. Guduru, Y.-P. Sun, B. Banerji, D. Y.-K. Chen, *J. Am. Chem. Soc.* **2008**, *130*, 3633–3644; c) K. C. Nicolaou, G. Y. C. Leung, D. H. Dethe, R. Guduru, Y.-P. Sun, C. S. Lim, D. Y.-K. Chen, *J. Am. Chem. Soc.* **2008**, *130*, 10019–10023;

d) V. R. Ravu, G. Y. C. Leung, C. S. Lim, S. Y. Ng, R. J. Sum, D. Y.-K. Chen, *Eur. J. Org. Chem.* **2011**, 463–468.

[8] M. Penner, V. Rauniyar, L. T. Kaspar, D. G. Hall, *J. Am. Chem. Soc.* **2009**, *131*, 14216–14217.

[9] For the formal synthesis, see: a) J. Jägel, M. Maier, *Synthesis* **2009**, 2881–2892; b) P. Gowrisankar, S. A. Pujari, K. P. Kaliappan, *Chem. Eur. J.* **2010**, *16*, 5858–5862.

[10] For the partial synthesis, see: a) K. P. Kaliappan, P. Gowrisankar, *Synlett* **2007**, 1537–1540; b) G. Cantagrel, C. Meyer, J. Cossy, *Synlett* **2007**, 2983–2986; c) S. Chandrasekhar, K. Vijeender, G. Chandrashekar, Ch. Raji Reddy, *Tetrahedron: Asymmetry* **2007**, *18*, 2473–2478; d) J. Jägel, A. Schmauder, M. Binanzer, M. Maier, *Tetrahedron* **2007**, *63*, 13006–13017; e) D. M. Jones, G. B. Dudley, *Synlett* **2010**, 223–226; f) K. R. Prasad, A. B. Pawar, *Synlett* **2010**, 1093–1095; For degradative study see: g) M. D. Lebar, B. J. Baker, *Tetrahedron Lett.* **2007**, *48*, 8009–8010.

[11] a) K. P. Kaliappan, N. Kumar, *Tetrahedron Lett.* **2003**, *44*, 379–381; b) K. P. Kaliappan, R. S. Nandurdikar, *Chem. Commun.* **2004**, 2506–2507; c) K. P. Kaliappan, N. Kumar, *Tetrahedron* **2005**, *61*, 7461–7469; d) K. P. Kaliappan, R. S. Nandurdikar, *Org. Biomol. Chem.* **2005**, *3*, 3613–3614; e) K. P. Kaliappan, V. Ravikumar, *Org. Biomol. Chem.* **2005**, *3*, 848–851; f) K. P. Kaliappan, R. S. Nandurdikar, M. M. Shaikh, *Tetrahedron* **2006**, *62*, 5064–5073; g) K. P. Kaliappan, V. Ravikumar, S. A. Pujari, *Tetrahedron Lett.* **2006**, *47*, 981–984; h) K. P. Kaliappan, V. Ravikumar, *J. Org. Chem.* **2007**, *72*, 6116–6126; i) K. P. Kaliappan, V. Ravikumar, *Synlett* **2007**, 0977–0980; j) K. P. Kaliappan, A. V. Subrahmanyam, *Org. Lett.* **2007**, *9*, 1121–1124; k) K. P. Kaliappan, D. Si, *Synlett* **2009**, 2441–2444; l) K. P. Kaliappan, P. Das, *J. Org. Chem.* **2009**, *74*, 6266–6274; m) A. V. Subrahmanyam, K. Palanichamy, K. P. Kaliappan, *Chem. Eur. J.* **2010**, *16*, 8545–8556.

[12] For selected recent reviews on metathesis, see: a) M. Schuster, S. Blechert, *Angew. Chem.* **1997**, *109*, 2124–2144; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2036–2056; b) R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, *54*, 4413–4450; c) S. K. Armstrong, *J. Chem. Soc. Perkin Trans. 1* **1998**, 371–388; d) A. J. Phillips, A. D. Abell, *Aldrichimica Acta* **1999**, *32*, 75–85; e) D. L. Wright, *Curr. Org. Chem.* **1999**, *3*, 211–240; f) M. L. Randall, M. L. Snapper, *Strem Chem.* **1998**, *17*, 1–9; g) L. Yet, *Chem. Rev.* **2000**, *100*, 2963–3007; h) M. E. Maier, *Angew. Chem.* **2000**, *112*, 2153–2157; *Angew. Chem. Int. Ed.* **2000**, *39*, 2073–2077; i) R. Roy, S. Das, *Chem. Commun.* **2000**, 519–529; j) A. Fürstner, *Angew. Chem.* **2000**, *112*, 3140–3172; *Angew. Chem. Int. Ed.* **2000**, *39*, 3012–3043; k) S. Kotha, N. Sreenivasachary, *Indian J. Chem.* **2001**, *40(B)*, 763–780; l) T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18–29; m) *Handbook of Metathesis*, *Vol. 1–3* (Ed.: R. H. Grubbs), Wiley-VCH, Weinheim, **2003**; n) J. Prunet, *Angew. Chem.* **2003**, *115*, 2932–2936; *Angew. Chem. Int. Ed.* **2003**, *42*, 2826–2830; o) R. H. Grubbs, *Tetrahedron* **2004**, *60*, 7117–7140; p) A. H. Hoveyda, D. G. Gillingham, J. J. V. Veldhuizen, O. Kataoka, S. B. Garber, J. S. Kingsbury, J. P. Harrity, *Org. Biomol. Chem.* **2004**, *2*, 8–23; q) B. Schmidt, *Eur. J. Org. Chem.* **2004**, 1865–1880; r) A. Giessert, S. T. Diver, *Chem. Rev.* **2004**, *104*, 1317–1382; s) D. J. Wallace, *Angew. Chem.* **2005**, *117*, 1946–1949; *Angew. Chem. Int. Ed.* **2005**, *44*, 1912–1915; t) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4564–4601; *Angew. Chem. Int. Ed.* **2005**, *44*, 4490–4527; u) A. Gradillas, J. Pèrez-Castells, *Angew. Chem.* **2006**, *118*, 6232–6247; *Angew. Chem. Int. Ed.* **2006**, *45*, 6086–6101.

[13] a) P. J. Kocienski, B. Lythgoe, S. Ruston, *J. Chem. Soc. Perkin Trans. 1* **1978**, 829–834; b) P. J. Kocienski, B. Lythgoe, D. A. Roberts, *J. Chem. Soc. Perkin Trans. 1* **1978**, 834–837; c) P. J. Kocienski, B. Lythgoe, S. Ruston, *J. Chem. Soc. Perkin Trans. 1* **1979**, 1290–1293; d) P. J. Kocienski, B. Lythgoe, I. Waterhouse, *J. Chem. Soc. Perkin Trans. 1* **1980**, 1045–1050; e) P. R. Blakemore, W. J. Cole, P. J. Kocienski, A. Morley, *Synlett* **1998**, 26–28; f) P. R. Blakemore, *J. Chem. Soc. Perkin Trans. 1* **2002**, 2563–2585.

[14] J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

[15] Y. Wu, X. Liao, R. Wang, ; X.-S. Xie, J. K. De Brabander, *J. Am. Chem. Soc.* **2002**, *124*, 3245–3253; X.-S. Xie, J. K. De Brabander, *J. Am. Chem. Soc.* **2002**, *124*, 3245–3253.

[16] M. Oshima, H. Yamazaki, I. Shimizu, M. Nisar, J. Tsuji, *J. Am. Chem. Soc.* **1989**, *111*, 6280–6287.

[17] a) T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976; b) Z.-M. Wang, W.-S. Zhou, G.-Q. Lin, *Tetrahedron Lett.* **1985**, *26*, 6221–6224.

[18] J. Tan, M. A. Ciufolini, *Org. Lett.* **2006**, *8*, 4771–4774.

[19] J. Lu, J. Ma, X. Xie, B. Chen, X. She, X. Pan, *Tetrahedron: Asymmetry* **2006**, *17*, 1066–1073.

[20] a) I. Shimizu, K. Hayashi, N. Ide, M. Oshima, *Tetrahedron* **1991**, *47*, 2991–2998; b) K. Nagasawa, I. Shimizu, T. Nakata, *Tetrahedron Lett.* **1996**, *37*, 6881–6884.

[21] B. H. Lipshutz, D. Pallart, J. Monforte, H. Kotsuki, *Tetrahedron Lett.* **1985**, *26*, 705–708.

[22] L. Alcaraz, J. J. Harnett, C. J. Mioskowski, P. Martel, T. Le Gall, D.-S. Shin, J. R. Falck, *Tetrahedron Lett.* **1994**, *35*, 5449–5452.

[23] a) K. P. M. Vanhessche, Z.-M. Wang, K. B. Sharpless, *Tetrahedron Lett.* **1994**, *35*, 3469–3472; For a recent review, see: b) H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483–2547.

[24] a) P. Kumar, M. S. Bodas, *J. Org. Chem.* **2005**, *70*, 360–363; b) P. Kumar, V. S. Naidu, *J. Org. Chem.* **2005**, *70*, 4207–4210; c) K. Hirai, H. Ooi, T. Esumi, Y. Iwabuchi, S. Hatakeyama, *Org. Lett.* **2003**, *5*, 857–859.

[25] J. W. Bode, E. M. Carreira, *J. Org. Chem.* **2001**, *66*, 6410–6424.

[26] S. Mann, S. Carillon, O. Breyne, A. Marquet, *Chem. Eur. J.* **2002**, *8*, 439–450.

[27] T. Yoshimitsu, J. J. Song, G. Q. Wang, S. Masamune, *J. Org. Chem.* **1997**, *62*, 8978–8979.

[28] Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, K. B. Sharpless, *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.

[29] a) P. R. Blakemore, P. J. Kocienski, S. Marzcak, J. Wicha, *Synthesis* **1999**, 1209–1215; b) J. S. Yadav, G. Rajaiah, *Synlett* **2004**, 1743–1746; c) G. Pattenden, D. A. Stoker, N. M. Thomson, *Org. Biomol. Chem.* **2007**, *5*, 1776–1788.

[30] a) H. Hilperta, B. Wirz, *Tetrahedron* **2001**, *57*, 681–694; b) Q. Zhang, Y. Wu, *Tetrahedron* **2007**, *63*, 10189–10201.

[31] L. E. Overman, F. M. Knoll, *Tetrahedron Lett.* **1979**, *20*, 321–324.

[32] D. Schweitzer, J. J. Kane, D. Strand, P. McHenry, M. Tenniswood, P. Helquist, *Org. Lett.* **2007**, *9*, 4619–4622.

[33] D. K. Mohapatra, D. K. Ramesh, M. A. Giardello, M. S. Chorghade, M. K. Gurjar, R. H. Grubbs, *Tetrahedron Lett.* **2007**, *48*, 2621–2625.

[34] a) S. Li, X. Xiao, X. Yan, X. Liu, R. Xu, D. Bai, *Tetrahedron* **2005**, *61*, 11291–11298; b) T. Onoda, R. Shirai, S. Iwasaki, *Tetrahedron Lett.* **1997**, *38*, 1443–1446; c) B. M. Trost, J. Y. L. Chung, *J. Am. Chem. Soc.* **1985**, *107*, 4586–4588; d) J. T. Feutrill, M. J. Lilly, M. A. Rizzacasa, *Org. Lett.* **2000**, *2*, 3365–3367.

[35] W.-R. Li, S.-Y. Han, M. M. Joullié, *Tetrahedron* **1993**, *49*, 785–802.

[36] a) S. Hatakeyama, H. Irie, T. Shintani, Y. Noguchi, H. Yamada, M. Nishizawa, *Tetrahedron* **1994**, *50*, 13369–13376; b) D. R. Williams, K. G. Meyer, *J. Am. Chem. Soc.* **2001**, *123*, 765–766.

[37] K. Takai, K. Nitta, K. Utimoto, *J. Am. Chem. Soc.* **1986**, *108*, 7408–7410.

[38] S. S. Harried, C. P. Lee, G. Yang, T. I. H. Lee, D. C. Myles, *J. Org. Chem.* **2003**, *68*, 6646–6660.

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