Total Synthesis and Biological Evaluation of (−)Apicularen A and Analogues Thereof

K. C. Nicolaou,*[a, b] David W. Kim,[b] Rachid Baati,[a] Aurora O'Brate,[c] and Paraskevi Giannakakou[c]

Abstract: Apicularen A (**1**) and related benzolactone acylenamines belong to a growing class of novel natural products possessing highly cytotoxic properties. The challenging structure of **1** includes a 10-membered macrolactone ring, a tetrahydropyran system, an *o,m*-substituted phenol and a doubly unsaturated acyl group attached on the side chain enamine functionality. The total synthesis of apicularen A described herein involves a strategy equivalent to its proposed biosynthesis and entails a reiterative two-step procedure featuring allylation and ozonolytic cleavage to grow the molecule's chain by one acetate unit at a time. The developed synthetic technology was applied to the construction of a series of apicularen A analogues whose biological evaluation established a set of structure–activity relationships in this new area of potential importance in cancer chemotherapy.

Keywords: acylenamines · antitumor agents · apicularen · macrolactonization · total synthesis

Introduction

As part of a search for new cytotoxic agents to be used as potential anticancer drugs, the Höfle–Jansen group isolated, in 1998, apicularen A[1] (**1**; see Figure 1), a potent substance with a novel molecular architecture and an impressive biological profile. Isolated from a variety of strains of the myxobacterial genus *Chondromyces* (i.e. *C. apiculatus, C. lanuginosus, C. pediculatus, and C. robustus*), this naturally occurring substance exhibits extremely high potency against a range of human cancer cells, including ovarian, prostate, lung, kidney, leukemia, cervix, and histocytic cell lines. IC_{50} values against these cells range from 0.1 to 3.0 ng mL^{-1} and, most importantly, activity has been found against the multidrug-resistant KB-V1 cell line. It was recently reported that apicularen A exerts its antitumor properties through inhibition of angiogenesis.[2]

Apicularen is grouped in the so-named benzolactone enamide family of compounds (some members of which are shown in Figure 1) whose mechanism of action remained a mystery until a team at the National Cancer Institute (NCI) tested them against their 60-cell antitumor screen.[3,4] These investigators made the connection between the salicylihalamides,[5a] oximidines,[5b] and lobatamides[5c–e] with bafilomycin and concanamycin,[6] natural products whose mode of action was known to involve inhibition of vacuolar-type (H^+)-ATPases (V-ATPases).[7] Apicularen A was also found to be implicated in such inhibition, thereby, clarifying somewhat its mechanism of action. In view of the impressive selectivity[8] exhibited against various V-ATPases, these compounds hold considerable promise for the treatment of a number of diseases, including diabetes, Alzheimer's disease, cardiovascular disorders, osteoporosis, and cancer.[9]

From the architectural point of view, apicularen A (**1**) comprises of a 10-membered macrolide ring that includes a salicylic acid residue and a bridging oxygen atom forming a tetrahydropyran residue. In addition, the macrocycle carries a multiunsaturated chain consisting of an acylenamine moiety and a *Z,Z*-diene system. Complicating apicularen's total synthesis are, in addition to these sensitive structural elements, four stereogenic centers, all residing on the macrocyclic system. Due to the structural novelty represented by apicularen A and its potent biological activity, a total synthesis of this natural product and an avenue to analogue construction was deemed important. Laboratories have re-

[a] Prof. K. C. Nicolaou, Dr. R. Baati
Department of Chemistry and The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
Fax: (+1) 858-784-2469
E-mail: kcn@scripps.edu

[b] Prof. K. C. Nicolaou, D. W. Kim
Department of Chemistry and Biochemistry
University of California San Diego
9500 Gilman Drive, La Jolla, CA 92093 (USA)

[c] A. O'Brate, Dr. P. Giannakakou
Winship Cancer Institute, Emory University School of Medicine
Atlanta, GA 30322 (USA)

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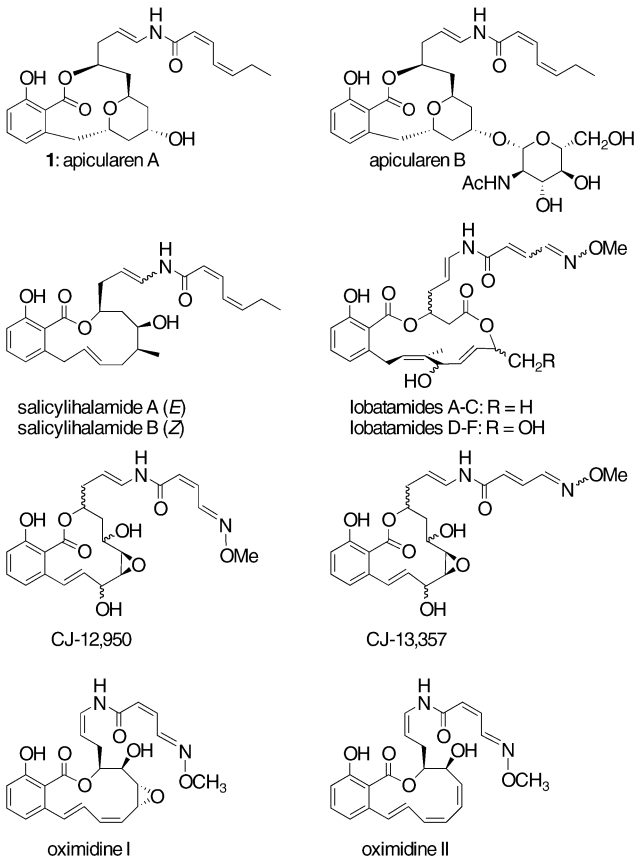


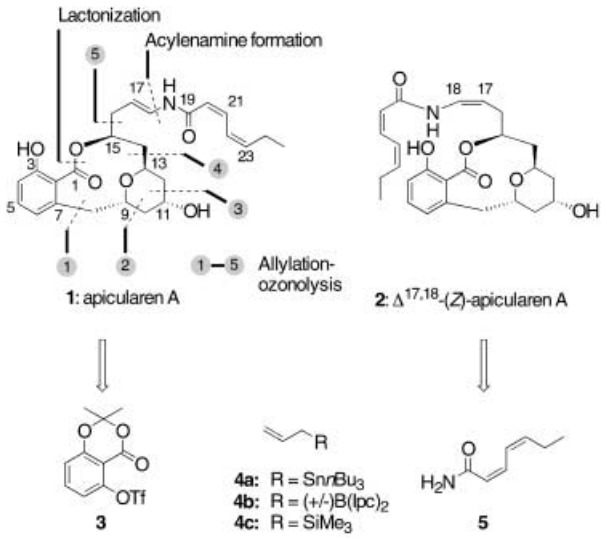
Figure 1. Apicularen A (**1**) and related benzolactone acylenamine natural products.

ported synthetic studies[10] in this area, including a total synthesis[11a] by DeBrabander and co-workers and a formal synthesis[11c,d] by R. J. K. Taylor and co-workers. In a preliminary communication, [11b] we reported the total synthesis of apicularen A and its $\Delta^{17,18}$ *Z* analogue. Herein, we describe the details of this strategy and its application to the construction of a number of analogues which were designed for chemical biology studies that revealed further structure–activity relationships within this family of compounds.

Results and Discussion

The structure of apicularen A (**1**) is intriguing from the biosynthetic standpoint in that it was determined[1b] to arise from eleven acetate units which account for all its carbon atoms except for C-17 (which comes from glycine), C-25 (which derives from methionine), and C-18 whose origin remains unknown. Our intention was to devise both a "biomimetic" strategy toward apicularen A and to apply it to the synthesis of various side-chain analogues.

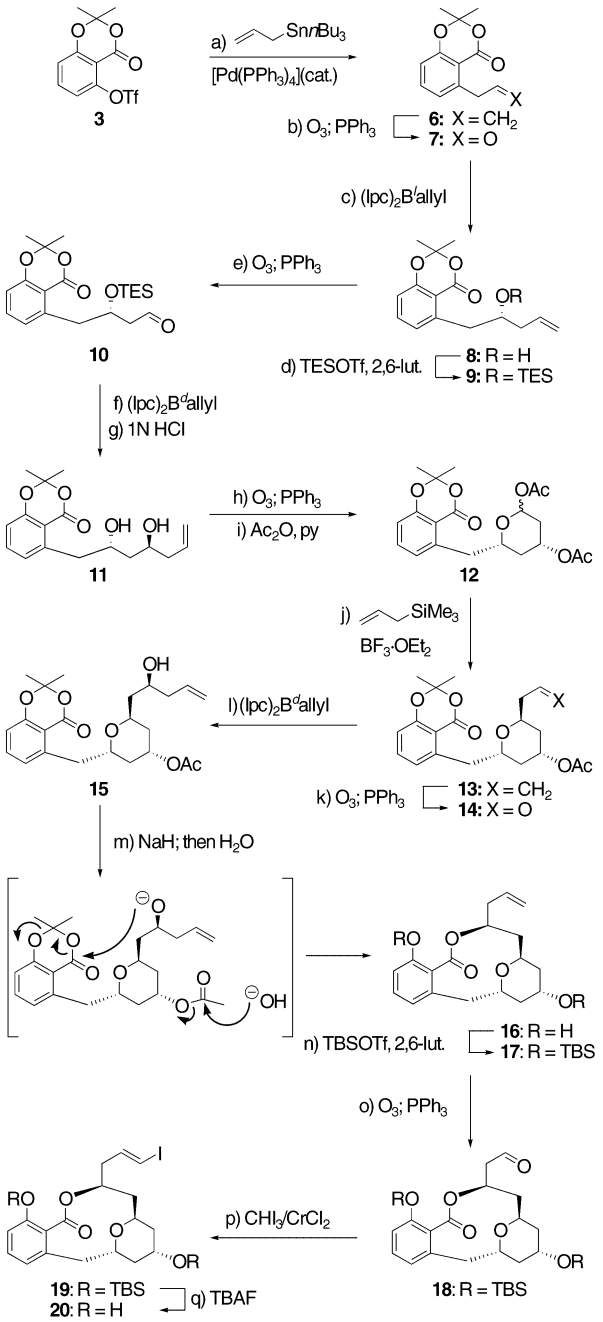
Retrosynthetic analysis: Scheme 1 depicts a retrosynthetic analysis of apicularen A (**1**) that is based on the premise that an allylation–ozonolysis sequence serves as a provider of the acetate unit (to be reiterated five times). Further disconnections of **1** at the macrolactone and acylenamine sites revealed three key building blocks, **3**, **4a–c**, and **5**.[12–14] If



Scheme 1. Molecular structure and retrosynthetic analysis of apicularen A (**1**) and its $\Delta^{17,18}$ *Z* isomer (**2**). Ipc = isopinocampheyl; Tf = trifluoromethanesulfonate.

successful, such a strategy could be considered "biomimetic" to the extent that the allylation–ozonolysis protocol introduces a two-carbon unit equivalent to the acetate moiety to the growing chain. Closing the macrolide ring before or after completing the acylenamine side chain was then expected to furnish, upon deprotection, the natural product. The strategy derived from this analysis was ideal for application to the construction of side-chain analogues since this moiety was to be introduced in the final phase of the synthesis.

Total synthesis of apicularen A: The designed synthetic strategy towards apicularen A (**1**) required macrolactone **20** as an advanced intermediate, a substance whose construction is shown in Scheme 2. Commencing from commercially available 2,6-dihydroxybenzoic acid, the acetonide triflate **3** was synthesized according to a literature procedure[12a] and then allowed to react in a Stille[15] fashion with allylstannane **4a** in the presence of catalytic [$Pd(PPh_3)_4$] and LiCl in refluxing THF to afford terminal olefin **6** in 99% yield. Ozonolytic cleavage (O_3; PPh_3) at the olefinic bond in **6** gave aldehyde **7**, whose reaction with Brown's allylborane at −100 °C (Ipc_2B^lallyl, prepared from (+)-Ipc_2BOMe)[13] allowed asymmetric allylation to furnish **8** in 70% yield and 95% *ee* (as determined by Mosher ester formation).[16] Protection of the newly generated alcohol in **8** with TESOTf and 2,6-lutidine led to silyl ether **9** (83% yield) which was then subjected to ozonolysis cleavage as described above to give aldehyde **10**. Reiteration of the allylation step on this new aldehyde using Ipc_2B^dallyl (prepared from (−)-Ipc_2BOMe)[13] at −100 °C led to the desired 1,3-diol and its diastereoisomer in a 4:1 ratio. To facilitate chromatographic separation of the product from the interfering Ipc alcohol, the TES group was removed by exposing the crude product mixture to (aq) HCl and then subjecting the resulting mixture to flash column chromatography leading to pure **11** (62% over two steps from **10**) plus its diastereoisomer (not shown, 16%). Ozonolytic cleavage of **11** (O_3; PPh_3) was ac-

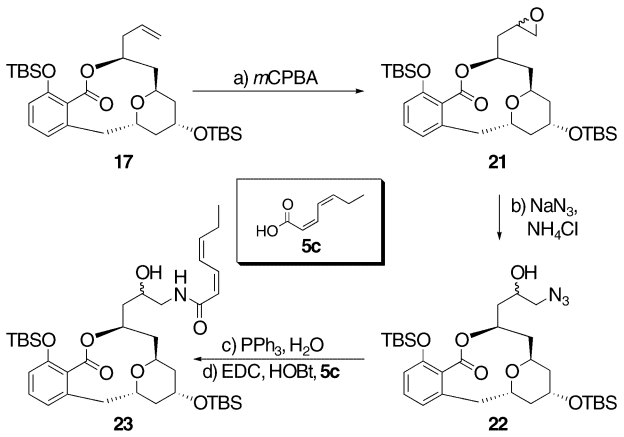


Scheme 2. Construction of advanced intermediate **20**. a) allyl-tri-*n*-butyltin (1.2 equiv), LiCl (3.0 equiv), $[Pd(PPh_3)_4]$ (2.0 mol%), THF, reflux, 12 h, 99%; b) O_3, CH_2Cl_2, −78°C, 1 h; Me_2S (20 equiv), 25°C; then PPh_3 (4.0 equiv), 1 h, 92%; c) $(Ipc)_2B^l$allyl (2.0 equiv), Et_2O, −100°C, 2 h, 70%; d) TESOTf (2.0 equiv), 2,6-lut. (4.0 equiv), CH_2Cl_2, 25°C, 3 h, 83%; e) O_3, CH_2Cl_2, −78°C, 1 h; Me_2S (20 equiv), 25°C; then PPh_3 (4.0 equiv), 1 h, 95%; f) $(Ipc)_2B^d$allyl (2.0 equiv), Et_2O, −100°C, 2 h; g) 1N HCl, 4 h, 62% over two steps; h) O_3, CH_2Cl_2, −78°C, 1 h; Me_2S (20 equiv), 25°C; then PPh_3 (4.0 equiv), 1 h; i) Ac_2O, py, 1 h, 83 % over two steps; j) allyltrimethylsilane (5.0 equiv), $BF_3{\cdot}OEt_2$ (1.1 equiv), CH_3CN, 0°C, 1 h, 97%; k) O_3, CH_2Cl_2, −78°C, 1 h; Me_2S (20 equiv), 25°C; then PPh_3 (4.0 equiv), 4 h, 98%; l) $(Ipc)_2B^d$allyl (2.0 equiv), Et_2O, −100°C, 2 h, 74%; m) NaH (7.0 equiv), THF, 25°C, 1 h; then H_2O (5.0 equiv), 25°C, 4 h, 75%; TBSOTf (4.0 equiv), 2,6-lut. (8.0 equiv), CH_2Cl_2, 25°C, 4 h, 99%; o) O_3, CH_2Cl_2, −78°C, 1 h; Me_2S (20 equiv), 25°C; then PPh_3 (4.0 equiv), 1 h, 95%; p) CHI_3 (4.0 equiv), $CrCl_2$ (12 equiv), THF, 25°C, 12 h, 80%; q) TBAF (5.0 equiv), THF, 25°C, 8 h, 80%. 2,6-lut.=2,6-lutidine, py=pyridine, TES=triethylsilyl, TMS=trimethylsilyl, TBS=*tert*-butyldimethylsilyl, TBAF=tetra-*n*-butylammonium fluoride.

companied by lactol formation and the resulting compound was engaged as its acetate derivative (**12**, ca. 1:1.2 mixture of anomers) with Ac_2O-py (83% overall yield from **11**). Stereoselective formation (>95%) of the tetrahydropyran ring was then accomplished by reaction of **12** with allyltrimethylsilane (**4a**) in the presence of $BF_3{\cdot}OEt_2$ in acetonitrile. Reiteration of the ozonolysis–allylation protocol with Ipc_2B^dallyl as described above then led sequentially to **14** (98% yield) and **15** (74% yield, 85:15 diastereomeric ratio).

The next step, aiming at formation of the macrocycle, parallels the NaH procedure utilized by DeBrabander and Bhattacharjee[17] in their synthesis of apicularen A. However, in this instance the use of excess NaH (7.0 equiv) in THF at ambient temperature, followed by addition of 5.0 equivalents of water (after the macrocycle was formed) resulted in complete deprotection, furnishing the dihydroxylactone **16** in 75% yield. The structure of this compound (**16**) was unambiguously assigned by X-ray crystallography analysis (see ORTEP drawing, Figure 2). Having constructed the key element of the macrocyclic ring, and diverting from previous syntheses, we protected the two hydroxy groups of **16** as TBS ethers (TBSOTf, 2,6-lut., 99% yield) to afford **17**,[18] whose ozonolytic (O_3; PPh_3) cleavage led to aldehyde **18** (95% yield). Takai iodo-olefination ($CrCl_2$–CHI_3)[19] of **18** then furnished *trans*-iodo-olefin **19** together with its *cis* isomer in a 4:1 isomeric ratio (80% combined yield). Finally, desilylation (TBAF) at both oxygen atoms gave the targeted intermediate **20** in 80% yield.

The next projected step in the synthesis was the coupling of the appropriate doubly unsaturated amide **5** to the synthesized vinyl iodide **20** by employing copper(I) thiophene carboxylate (CuTC)[20] and Rb_2CO_3. Primary amide **5** (Scheme 1) was secured by a literature procedure[14a] but unfortunately initial attempts to attach it to **20** failed.[11d] While the reasons for this fruitless attempt are still not clear, we immediately adopted a second plan which entailed going through the sequence outlined in Scheme 3. Thus,



Scheme 3. Synthesis of late stage intermediate **23**. a) *m*CPBA (4.5 equiv), $NaHCO_3$ (4.5 equiv), CH_2Cl_2, 25°C, 24 h, 87%; b) NaN_3 (10.0 equiv), NH_4Cl (5.0 equiv), MeOH/H_2O= (1:1 v(v), reflux, 20 h, 72%; c) PPh_3 (1.6 equiv), H_2O, (2.0 equiv), THF, 40°C, 20 h; d) EDC (1.5 equiv), HOBt (1.7 equiv), acid **5c** (1.5 equiv), DIEPA (2.2 equiv), CH_2Cl_2, 25°C, 3 h, 65% over two steps. *m*CPBA=3-chloroperoxybenzoic acid, EDC=1-[3-dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, HOBt=1-hydroxybenzotriazole hydrate, DIEA=*N*,*N*=diisopropylethylamine.

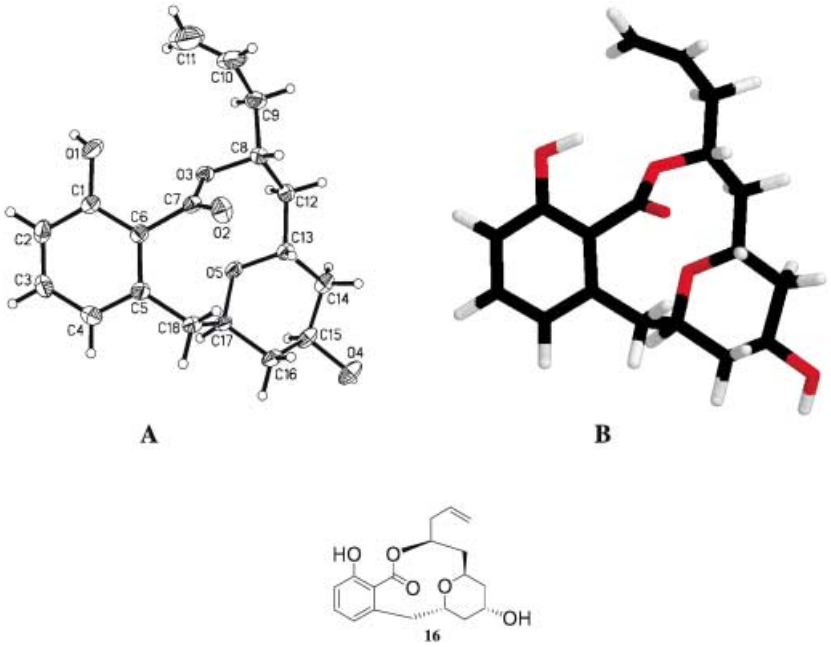
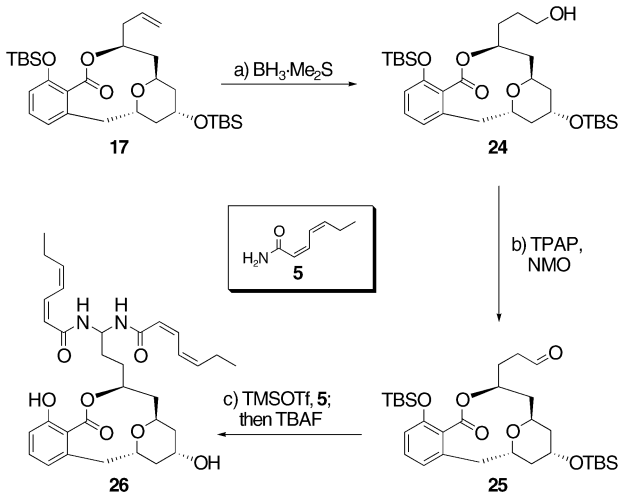


Figure 2. ORTEP drawing (**A**) obtained from X-ray crystallographic analysis and MM2 calculated minimum energy conformation (**B**) of compound **16**.

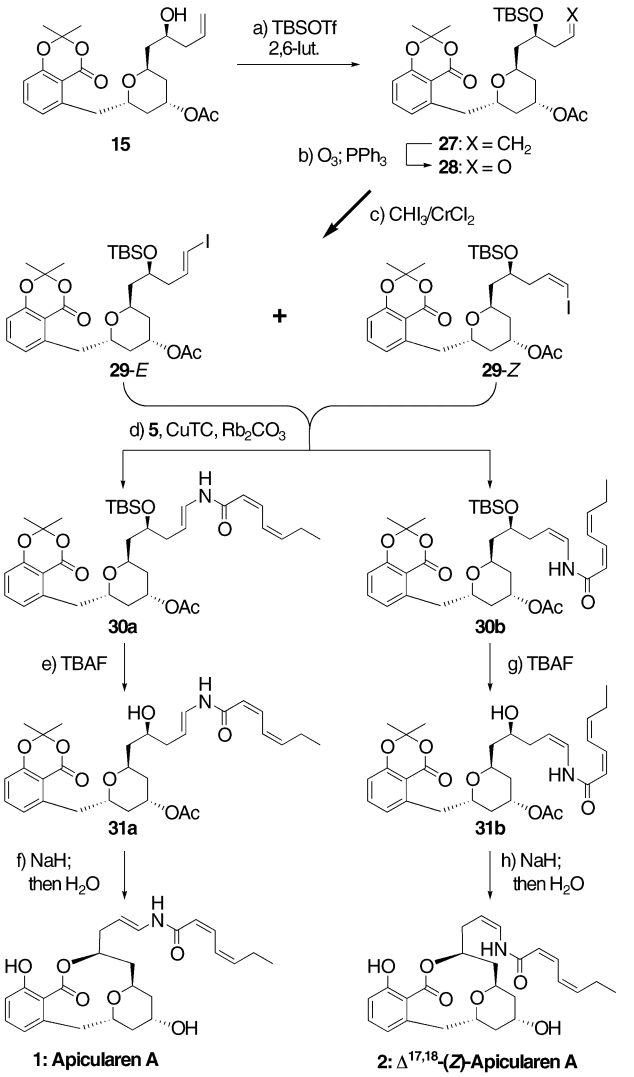
olefin **17** (Scheme 2) was epoxidized with *m*CPBA to afford terminal epoxide **21** which was obtained as a diastereomeric mixture (87% yield, ca. 1:1, inconsequential). Regioselective opening of the epoxide moiety in **21** with NaN_3 yielded hydroxy azide **22** as a mixture of two diastereoisomers in 72% yield. Reduction of this azide mixture according to the Staudinger conditions[21] (PPh_3; H_2O) furnished the corresponding hydroxy amine mixture which was coupled with carboxylic acid **5c** under the influence of EDC and HOBt to afford hydroxy amide **23** (65% overall yield, mixture of two diastereoisomers). Expecting to effect elimination of H_2O from **23** to furnish the desired acylenamine functionality, we then proceeded to subject this intermediate to appropriate dehydrating conditions, but, unfortunately again, we faced a resilient substrate, leading either to starting material or decomposition under a variety of conditions.

In pursuing another elimination-based strategy, we sought to take advantage of a similar step utilized in the synthesis of salicylihalamide by Labrecque et al.[14a] as shown in Scheme 4. Thus, intermediate **17** (Scheme 2) was now hydroborated with $BH_3{\cdot}Me_2S$ under sonication conditions[22] and the resulting borane oxidatively ($NaHCO_3$–H_2O_2) converted to primary alcohol **24** (71% yield). Oxidation of **24** under TPAP–NMO conditions[23] led to aldehyde **25** in 99% yield and exposure of the latter compound to two equivalents of amide **5** in the presence of TMSOTf followed by TBAF addition furnished bisamide **26**. All attempts to eliminate one of the amide groups from **26**, however, including identical conditions (NaH, $PhCF_3$, Δ) to those previously employed[24] for such a reaction failed, once again.

Faced with these barricades and in view of the extensive literature precedent for enamide formation by the CuTC-mediated route,[25] we decided to revisit this possibility, this time employing an open-chain vinyl iodide, a substrate which, it was reasoned, might enjoy better reactivity by virtue of its higher flexibility. This hypothesis led us to adopt substrate **15** as a starting point and a new sequence for the final drive towards apicularen A (**1**). Proceeding as summarized in Scheme 5, this new strategy paid handsome dividends, delivering not only **1** but also its $\Delta^{17,18}$ *Z* stereoisomer (**2**). Thus, protection of the free hydroxy group in **15** with a TBS group (TBSOTf-2,6-lut., 94% yield) followed by the usual ozonolytic cleavage (O_3; PPh_3, 89% yield) gave aldehyde **28** via intermediate **27**. Takai extension ($CrCl_2$-CHI_3) of the latter compound then produced vinyl iodide **29** in 91% yield (containing ca. 10% *cis*-isomer), setting the stage for the crucial installation of the acylenamine chain. Pleasantly, exposure of a mixture of (*E*)-**29** and its *Z* stereoisomer (*Z*)-**29** to CuTC and Rb_2CO_3 in the presence of excess amide **5** in DMA at 90°C, furnished smoothly the desired enamide[26] products **30a** and **30b** (41 and 4% yields, respectively). After chromatographic separation, each silyl ether derivative (**30a** and **30b**) was separately treated with TBAF in THF at ambient temperature leading to hydroxy compounds **31a** and **31b** in 80 and 60% yields, respectively. Exposure to excess NaH of **31a** and **31b** in THF at ambient temperature, followed by addition of water led



Scheme 4. Synthesis of apicularen A bisamide derivative **26**. a) $BH_3{\cdot}Me_2S$ (5.0 equiv), THF, 25°C, ultrasound, 30 min; then $NaHCO_3$, H_2O_2, 1 h, 71°C; b) TPAP (5 mol%), NMO (2.0 equiv), 4 Å MS, CH_2Cl_2, 25°C, 2 h, 99%; c) TMSOTf (0.5 equiv), **5** (2.0 equiv), 1,2-dichloroethane, 25°C, 12 h; then TBAF (5.0 equiv), 25°C, 1 h, 75%.



Scheme 5. Total synthesis of apicularen A (**1**) and its $\Delta^{17,18}$ *Z* isomer (**2**). a) TBSOTf (2.0 equiv), 2,6-lut. (4.0 equiv), CH_2Cl_2, 25 °C, 4 h, 94 %; b) O_3, CH_2Cl_2, −78 °C, 1 h; DMS (20 equiv), 25 °C, then PPh_3 (4.0 equiv), 1 h, 89 %; c) CHI_3 (4.0 equiv), $CrCl_2$ (12 equiv), THF, 25 °C, 12 h, 91 %; d) CuTC (1.0 equiv), Rb_2CO_3 (3.0 equiv), amide **5** (3.0 equiv), DMA, 90 °C, 12 h, **30a** 41 %, **30b** 4 %; e) TBAF (5.0 equiv), THF, 25 °C, 4 h, 80 %; f) NaH (7.0 equiv), THF, 25 °C, 1 h; then H_2O (5.0 equiv), 25 °C, 4 h, 50 %; g) TBAF (5.0 equiv), THF, 25 °C, 4 h, 60 %; h) NaH (7.0 equiv), THF, 25 °C, 1 h; then H_2O (5.0 equiv), 25 °C, 4 h, 34 %.

to both macrolactonization and global deprotection, furnishing **1** and **2** (50 and 34 % overall yield, respectively). Synthetic **1** exhibited identical chromatographic and spectroscopic data to those exhibited by a natural sample[27] and to those reported in the literature.[1]

Design, synthesis, and biological activity of apicularen A analogues: The assumption that the acylenamine side chain plays a crucial role in the manifestation of apicularen's biological activity strengthen by the observation that compound **16** (Scheme 2) which lacks such a moiety, was devoid of significant cytotoxicity[11a] led us to design analogues with the intact side chain, varying only at the acyl group.[28] Thus, analogues **2**, **26**, **31a**, **32**–**44** (Table 1) were designed and synthesized from the advanced intermediate **29** and the corresponding primary amides according to Scheme 5 (in comparable yields to those for apicularen A). The C-11 acetate derivatives (i.e. **31a**, **32**, **35**, **39**, **43**, and **44**) were found as byproducts in the final step and/or were deliberately synthesized by omission of H_2O at the final step. These analogues were designed to test the effect of esterification at C-11, substitutions at the acyl moiety site, and whether the macrolide ring was necessary or not. Biological evaluation of these analogues against the 1A9 human ovarian carcinoma cell line were carried out and the data are reported in Table 1 as IC_{50} values (next to the compound structure). These results indicate that acetylation at the hydroxy group leads to some loss of activity (except in the case of **35** and **34** although experimental error has not been ruled out) which may be in line with the loss of activity in apicularen B where this alcohol is glycosylated. In addition, apicularen analogue **32** possessing the natural side chain still retained extremely high activity with only a fourfold loss (IC_{50} = 3.2 nM). Interestingly, the $\Delta^{17,18}$ (*Z*) apicularen A isomer (**2**), although less potent by more than a factor of 100, maintains considerable cytotoxicity (IC_{50} = 70.7 nM)[29] as compared to the natural substance (IC_{50} = 0.86 nM). The bisamide analogue **26** does not exhibit any cytotoxicity at concentrations up to 1500 nM underscoring the importance of the enamide double bond, while acyl group substituents proved quite interesting as modulators of biological activity. Thus, analogues with short aromatic chains (e.g. **33**, **36**, and **37**) proved inactive or relatively weak whereas those with comparable side chain as that of apicularen A exhibited significant activity (e.g. **34**, **35**, and **38**–**41**) with compound **41** being the most potent of all synthesized analogues (IC_{50} = 1.73 nM). Interestingly, the significant cytotoxicity associated with the open-chain analogues **31a**, **43**, and **44**, with analogue **31a** being the most active (IC_{50} = 35 nM) which are consistent with the findings by Porco, Jr. and co-workers[25a] of non-macrolactone lobatamide analogues. This finding points the way for a new generation of potential mimics of apicularen A lacking the macrolide ring and which may prove easier to access than the natural substance.

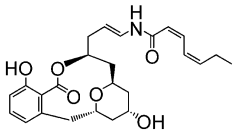
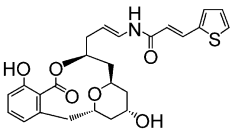
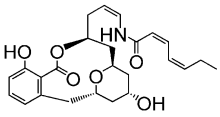
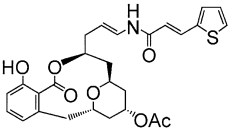
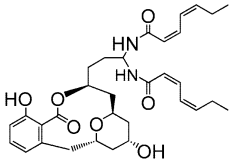
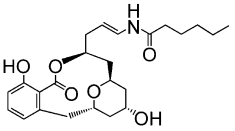
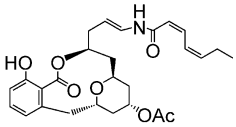
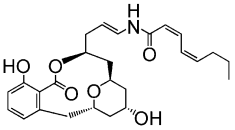
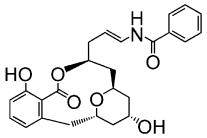
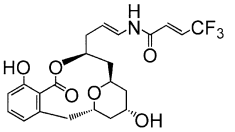
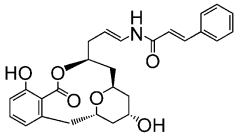
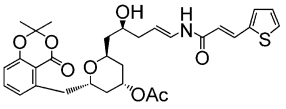
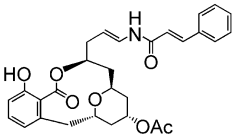
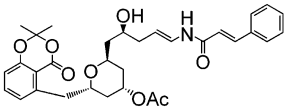
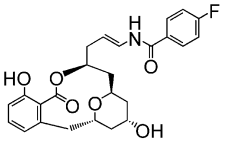
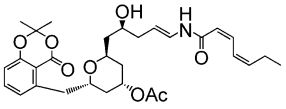
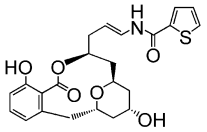
Conclusion

A concise total synthesis of apicularen A (**1**) and its $\Delta^{17,18}$ (*Z*) isomer (**2**) has been devised and executed in 16 linear steps. This strategy was adopted for the construction of a series of analogues of the natural substance, biological evaluation of which established a set of interesting structure activity relationships (SAR). These SAR studies confirmed the importance of the acylenamine side chain for antitumor activity and point to some possible new directions for future studies in this field.

Experimental Section

General procedures: All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise

Table 1. Cytotoxicity (IC_{50} values) of apicularen A (**1**) and analogues (**2**, **26**, **31a**, **32**–**44**) against the 1A9 human ovarian carcinoma cell line.

Compound no.	Strucuture	IC_{50} value	Compound no.	Strucuture	IC_{50} value
apicularen A (**1**)		(0.78 ± 0.4) nM	**38**		(41.3 ± 5.8) nM
$\Delta^{17,18}$ *Z*-apicularen A (**2**)		(70.7 ± 10.4) nM	**39**		(102.3 ± 20.7) nM
26		> 1500 nM	**40**		(23.9 ± 6.6) nM
32		3.2 nM	**41**		(1.73 ± 0.6) nM
33		> 1500 nM	**42**		> 1500 nM
34		50 nM	**43**		357 nM
35		(30.3 ± 4.6) nM	**44**		387 nM
36		> 1500 nM	**31a**		35 nM
37		(805.5 ± 145) nM			

The antiproliferative effects of these compounds against the 1A9 human ovarian carcinoma cells were assessed in a 72 h growth inhibition assay using the SRB (sulforhodamine-B) assay.[30] IC_{50} is defined as the concentration that leads to 50% growth inhibition. IC_{50} values for each compound are given in nm and represent the mean of 3–6 independent experiments ± standard error of the mean (SEM). IC_{50} values without an SEM value reflect a single growth inhibition experiment.

noted. Dry tetrahydrofuran (THF), toluene, diethyl ether (ether), and methylene chloride (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an ethanolic solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker DRX-600, DRX-500, AMX-500 or AMX-400 instruments and calibrated by using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, quin = quintuplet, sext = sextet, sep = septet, b = broad. IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrometer. Electrospray ionization mass spectrometry (ESIMS) experiments were performed on an API 100 Perkin Elmer SCIEX single quadrupole mass spectrometer at 4000V

emitter voltage. High-resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions with NBA as the matrix or using MALDI. Melting points (m.p.) are uncorrected and were recorded on a Thomas-Hoover Unimelt capillary melting point apparatus. DCE = 1,2 dichloroethane. DMA = *N,N*-dimethylacetamide. KHMDS = potassium bis(trimethylsilyl)amide. BORSM = based on recovered starting material. CuTC was prepared according to a published procedure.[20] CuTC was found to be slightly unstable in solvent, therefore, degassing DMA was deemed necessary. Phosphate buffer used had a 0.01 M sodium phophate concentration.

Diene carboxylic acid 5c: To a solution of ester **5b** (see reference [14]) (237.1 mg, 1.69 mmol) in MeOH (20 mL) at room temperature was added in one portion $Ba(OH)_2 \cdot H_2O$ (4.2 g, 13.3 mmol). The reaction mixture was stirred for 20 h and then added to 1 N (aq) HCl (50 mL). More acid solution was added until the solid formed had completely dissolved giving a clear solution. The resulting mixture was extracted with ether (3 × 15 mL) and the combined organic layer was washed with brine (50 mL), dried with $MgSO_4$, filtered and concentrated in vacuo. The product was purified by flash column chromatography (silica) to yield carboxylic acid **5c** as a colorless oil (191 mg, 90%). **5c**: $R_f = 0.82$ (silica gel, hexanes:EtOAc, 1:2); IR (film): $\tilde{\nu}_{max} = 2966, 1690, 1625, 1590, 1455, 1290, 1243, 1220, 932, 855, 832, 626\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.21$ (dd, $J = 11.5, 11.4$ Hz, 1H), 7.03 (dd, $J = 11.6, 11.5$ Hz, 1H), 5.94 (m, 1H), 5.67 (d, $J = 11.6$ Hz, 1H), 2.31–2.25 (m, 2H), 1.03 ppm (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 171.1, 144.0, 140.6, 123.8, 116.7, 20.8, 13.9$ ppm; MS (ESI) for $C_7H_{10}O_2$ $[M+K^+]$ calcd 165, found 165; MS (GC/MS) for $C_7H_{10}O_2$ $[H^+]$ calcd 126, found 126.

Terminal olefin 6: To a solution of $[Pd(PPh_3)_4]$ (720 mg, 0.62 mmol), LiCl (4 g, 0.094 mol), in degassed, dry THF (100 mL) at room temperature was added a solution of acetonide triflate **3** (10 g, 0.031 mol), and allyltributyltin (10 mL, 0.032 mol) in degassed dry THF (200 mL). The reaction mixture was heated to reflux and stirred at that temperature for 48 h. The reaction mixture was cooled to room temperature and diluted with ether (200 mL). The resulting solution was then washed with water (200 mL), 10% (aq) NH_4OH (200 mL), and brine (200 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The product was purified by flash column chromatography (silica) to yield terminal olefin **6** as a colorless oil (6.62 g, 99%). **6**: $R_f = 0.56$ (silica gel, EtOAc:hexanes, 1:4); IR (film): $\tilde{\nu}_{max} = 3002, 1731, 1696, 1631, 1602, 1584, 1472, 1449, 1384, 1314, 1296, 1267, 1208, 1079, 1038, 920, 808, 773, 691\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.41$ (dd, $J = 8.2, 7.6$ Hz, 1H), 6.94 (d, $J = 7.6$ Hz, 1H) 6.82 (d, $J = 8.2$ Hz, 1H), 6.01 (ddt, $J = 16.7, 10.3, 6.7$ Hz, 1H), 5.05–4.99 (m, 2H), 3.87 (d, $J = 6.7$ Hz, 2H), 1.68 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 160.3, 157.1, 145.2, 136.7, 135.3, 124.9, 116.0, 115.6, 112.0, 105.1, 38.2, 25.6$ ppm; MS (ESI) for $C_{13}H_{14}O_3$ $[M+Na^+]$ calcd 241, found 241.

Aldehyde 7: A solution of terminal olefin **6** (230 mg, 1.05 mmol) in dichloromethane (10 mL) was cooled to −78 °C. A flow of ozone was passed through the solution until it turned blue. The excess ozone was then purged with oxygen until the solution became clear again. The reaction mixture was quenched with dimethyl sulfide (1.55 mL, 21.1 mmol) at −78 °C and then allowed to warm to ambient temperature. Triphenylphosphine (276 mg, 1.05 mmol) was added and the resulting mixture was stirred at room temperature for an additional 5 h period, before concentrating under vacuo. The aldehyde was purified by flash column chromatography (silica) to yield aldehyde **7** as a sticky yellow solid (217 mg, 94%). **7**: $R_f = 0.17$ (silica gel, EtOAc:hexanes, 1:4); IR (film): $\tilde{\nu}_{max} = 2995, 2833, 1731, 1700, 1607, 1582, 1482, 1326, 1295, 1202, 1052, 934, 691\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 9.80$ (s, 1H), 7.47 (t, $J = 7.9$ Hz, 1H), 6.92 (d, $J = 8.3$ Hz, 1H), 6.87 (d, $J = 7.5$ Hz, 1H), 4.18 (s, 2H), 1.71 ppm (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 198.2, 160.9, 157.2, 137.0, 135.6, 126.4, 117.0, 112.6, 105.8, 49.1, 25.6$ ppm; HRMS (MALDI-FTMS) for $C_{12}H_{12}O_4$ $[M+H^+]$ calcd 221.0808, found 221.0805.

Homoallylic alcohol 8: $Ipc_2B^{\prime}$allyl (60 mL of 1 M solution in pentane) was added to a flask containing ether (30 mL) and the mixture was cooled to −100 °C (methanol–liquid nitrogen). A precooled (−100 °C) solution of aldehyde **7** (8.67 g, 39.37 mmol) in dichloromethane (100 mL) was then transferred dropwise using a cannula into the $Ipc_2B^{\prime}$allyl solution and the resulting mixture was stirred at −100 °C for 2 h. The reaction mixture was warmed to 0 °C and then quenched with ethanol (50 mL). Hydrogen peroxide (30%, 100 mL) was added, followed by phosphate buffer (pH 7, 100 mL). The reaction mixture was warmed to room temperature and stirred for 18 h. The solution was then diluted with water (100 mL) and extracted with ether (3 × 200 mL). The combined organic solution was washed with brine (200 mL), dried with $MgSO_4$, filtered and concentrated in vacuo. The product was purified by flash column chromatography (silica) to yield homoallylic alcohol **8** as a pale colorless oil (7.2 g, 70%). **8**: $R_f = 0.13$ (silica gel, EtOAc:hexanes, 1:4); $[\alpha]_D = -40.6$ ($c = 0.79$, acetone); IR (film): $\tilde{\nu}_{max} = 3431, 2920, 1731, 1600, 1582, 1314, 1270, 1208, 1046, 921, 697\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.42$ (t, $J = 7.9$ Hz, 1H), 6.96 (d, $J = 7.4$ Hz, 1H), 6.84 (d, $J = 8.3$ Hz, 1H), 5.89 (dddd, $J = 17.3, 10.2, 7.1, 7.1$ Hz, 1H), 5.13 (m, 2H), 3.90 (m, 1H), 3.31 (m, 1H), 3.15 (m, 1H), 2.38 (m, 1H), 2.35 (m, 2H), 1.69 (s, 3H), 1.67 ppm (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 161.6, 157.1, 144.1, 135.3, 134.8, 126.5, 117.9, 116.0, 112.8, 105.3, 72.1, 42.2, 41.1, 25.8, 25.4$ ppm; HRMS (MALDI-FTMS) for $C_{15}H_{18}O_4$ $[M+Na^+]$ calcd 285.1097, found 285.1097.

TES-protected derivative 9: To a solution of alcohol **8** (3.11 g, 0.012 mol) in dichloromethane (250 mL) at 0 °C was sequentially added 2,6-lutidine (7 mL) followed by dropwise addition of TESOTf (8 mL). The reaction mixture was stirred at 0 °C for 2 h, quenched with methanol (50 mL), and then allowed to warm to room temperature. After stirring for an additional 30 min, the solution was concentrated in vacuo and the crude product was purified by flash column chromatography (silica) to yield TES-protected derivative **9** as a colorless oil (2.7 g, 83%). **9**: $R_f = 0.68$ (silica gel, EtOAc:hexanes, 1:6); $[\alpha]_D = -64.6$ ($c = 1.67$, acetone); IR (film): $\tilde{\nu}_{max} = 2954, 2877, 1739, 1607, 1580, 1476, 1378, 1296, 1208, 1044, 913, 726\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.34$ (dd, $J = 8.1, 6.8$ Hz, 1H), 6.94 (d, $J = 6.8$ Hz, 1H), 6.81 (d, $J = 8.1$ Hz, 1H), 5.97–5.88 (m, 1H), 5.06–5.03 (m, 2H), 4.07–4.02 (m, 1H), 3.48–3.44 (dd, $J = 12.6, 4.1$ Hz, 1H), 2.88–2.84 (dd, $J = 12.6, 8.3$ Hz, 1H), 2.32–2.22 (m, 2H), 1.69 (s, 3H), 1.66 (s, 3H), 0.80 (t, $J = 7.9$ Hz, 9H), 0.45–0.31 ppm (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 160.4, 157.0, 144.7, 135.0, 134.7, 127.8, 116.9, 115.7, 112.1, 105.0, 71.9, 42.7, 42.2, 25.7, 25.5, 6.8, 4.8$ ppm; HRMS (MALDI-FTMS) for $C_{21}H_{32}O_4Si$ $[M+Na^+]$ calcd 399.1962, found 399.1967.

Aldehyde 10: A solution of olefin **9** (3.29 g, 8.74 mmol) in dichloromethane (200 mL) was cooled to −78 °C. A flow of ozone was passed through the solution until it turned blue. The excess ozone was then purged with oxygen until the solution became clear again. The reaction mixture was quenched with dimethyl sulfide (13 mL, 0.177 mol) and then allowed to warm to room temperature. Triphenylphosphine (2.3 g, 8.77 mol) was added and the resulting mixture was stirred at that temperature for an additional 5 h period. Concentration in vacuo followed by flash column chromatography (silica) gave aldehyde **10** as a sticky yellow solid (3.13 g, 95%). **10**: $R_f = 0.39$ (silica gel, EtOAc:hexanes, 1:6); $[\alpha]_D = +33.1$ ($c = 0.8$, acetone); IR (film): $\tilde{\nu}_{max} = 2958, 2883, 1731, 1607, 1582, 1476, 1389, 1301, 1270, 1208, 1058, 1002, 740\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 9.81$ (dd, $J = 2.6, 2.2$ Hz, 1H), 7.39 (dd, $J = 7.92, 7.44$ Hz, 1H), 6.92 (d, $J = 7.44$ Hz, 1H), 6.85 (d, $J = 7.92$ Hz, 1H), 4.56–4.52 (m, 1H), 3.32 (dd, $J = 12.5, 5.5$ Hz, 1H), 3.24 (dd, $J = 12.5, 7.2$ Hz, 1H), 2.54 (ddd, $J = 15.3, 5.9, 2.6$ Hz, 1H), 2.48 (ddd, $J = 15.3, 5.1, 2.2$ Hz, 1H), 1.69 (s, 3H), 1.68 (s, 3H), 0.84 (t, $J = 7.9$ Hz, 9H), 0.47 ppm (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 202.2, 160.4, 157.2, 142.9, 135.1, 127.5, 116.3, 112.2, 105.3, 68.4, 51.1, 42.9, 25.7, 25.6, 6.7, 4.7$ ppm; HRMS (MALDI-FTMS) for $C_{20}H_{30}O_5Si$ $[M+Na^+]$ calcd 401.1755, found 401.1793.

Dihydroxy olefin 11: A solution of Ipc_2B^{d}allyl (14 mL of 1 M solution in pentane) in ether (40 mL) was cooled to -100 °C (methanol–liquid nitrogen). A solution of aldehyde **10** (3.38 g, 8.93 mmol) in ether (60 mL) and was also cooled to −100 °C and then added dropwise to the Ipc_2B^{d}allyl solution using a cannula. The resulting mixture was stirred at −100 °C for 2 h before quenching at 0 °C with ethanol (10 mL). Hydrogen peroxide (30%, 20 mL) was added at 0 °C followed by phosphate buffer (pH 7, 20 mL). The reaction mixture was warmed to ambient temperature and stirred for 18 h. The resulting reaction mixture was then diluted with water (20 mL) and extracted with ether (3 × 100 mL). The combined organic layer was washed with brine (40 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude alcohol so obtained was dissolved in THF (125 mL) and the solution cooled to 0 °C before 0.5 N (aq) HCl (5 mL) was added dropwise. After stirring for 1 h, the solution was warmed to room temperature and then diluted with water and extracted with ether (3 × 100 mL). The combined organic layer was washed with brine (100 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The

product containing **11** and its diastereoisomer (ca. 4:1 ratio) was purified by flash column chromatography (silica) to yield pure dihydroxy olefin **11** as a colorless oil (1.7 g, 62%). **11**: R_f=0.24 (silica gel, EtOAc:hexanes, 1:1); $[\alpha]_D$=−17.1 (c=1.08, acetone); IR (film): $\tilde{\nu}_{max}$=3404, 2939, 1728, 1606, 1584, 1478, 1445, 1390, 1318, 1268, 1207, 1058, 919, 781, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.42 (dd, J=8.1, 7.7 Hz, 1H), 6.96 (d, J=7.7 Hz, 1H), 6.84 (d, J=8.1 Hz, 1H), 5.84–5.76 (m, 1H), 5.11–5.07 (m, 2H), 4.16–4.12 (m, 1H), 4.03–3.98 (m, 1H), 3.27 (dd, J=13.1, 4.2 Hz, 1H), 3.20 (dd, J=13.1, 8.1 Hz, 1H), 3.02 (bs, 1H), 2.62 (bs, 1H), 2.30–2.20 (m, 2H), 1.74–1.71 (m, 2H), 1.68 (s, 3H), 1.67 ppm (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=161.6, 157.2, 143.9, 135.4, 134.8, 126.5, 117.9, 116.0, 112.7, 105.4, 70.5, 68.3, 42.5, 42.0, 41.9, 25.7, 25.5 ppm; HRMS (MALDI-FTMS) for $C_{17}H_{22}O_5$ [M+Na$^+$] calcd 329.1359, found 329.1367.

Diacetate 12: A solution of diol **11** (700 mg, 2.28 mmol) in dichloromethane (100 mL) was cooled to −78°C. A flow of ozone was passed through the solution until it turned blue. The excess ozone was then purged with oxygen until the solution became clear again. The reaction mixture was quenched with dimethylsulfide (3.35 mL, 46.62 mmol) at −78°C and then allowed to warm to room temperature. Triphenylphosphine (598 mg, 2.28 mmol) was added and the reaction mixture was stirred at room temperature for an additional 5 h period, before concentrating under vacuo. To a cold (0°C) solution of this crude lactol in pyridine (80 mL) was added 4-DMAP (28 mg, 0.228 mmol) followed by acetic anhydride (9.54 mL, 101.1 mmol) and with stirring. The mixture was then allowed to warm to room temperature and stirred for 14 h before it was diluted with 1N (aq) HCl (50 mL) and extracted with ether (3×50 mL). The combined solution was washed with 1 N (aq) HCl (2×40 mL), brine (50 mL), dried with $MgSO_4$, filtered and concentrated in vacuo. The product was purified by flash column chromatography (silica) yielding diacetate **12** as a sticky white foam, (747.4 mg, 83% from **11**). **12** (mixture of anomer, ca. 1:1.2): R_f=0.26 (silica gel, EtOAc:hexanes, 1:3); IR (film): $\tilde{\nu}_{max}$=2929, 1739, 1605, 1585, 1478, 1447, 1370, 1314, 1299, 1268, 1227, 1171, 1038, 925, 777 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.39 (m, 1H), 7.00 (d, J=7.9 Hz, minor), 6.94 (d, J=7.4 Hz, major, 1H), 6.83 (d, J=7.9 Hz, 1H), 6.21 (s, major, 1H), 5.58 (d, J=10.1 Hz, minor), 5.16–5.11 (m, major, 1H), 4.94–4.89 (m, minor), 4.18–4.16 (m, major, 1H), 3.82–3.77 (m, minor), 3.55–3.36 (m, 2H), 3.26–3.20 (m, 1H), 2.20–2.02 (m, 2H), 2.04–1.98 (m, 6H), 1.69 (s, 3H), 1.67 (s, 3H), 1.51–1.40 ppm (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=170.2, 170.1, 169.3, 168.8, 160.6, 160.5, 157.0, 142.5, 142.0, 135.1, 135.0, 126.5, 126.3, 116.1, 112.5, 112.3, 105.2 (two peaks), 73.0, 70.3, 68.2, 66.3, 39.7, 39.3, 36.4, 36.0, 35.8, 34.4, 25.7 (two peaks), 25.5, 25.4, 21.2, 21.1 (two peaks), 21.0 ppm; (two isomers); HRMS (MALDI-FTMS) for $C_{20}H_{24}O_8$ [M+Na$^+$] calcd 415.1316, found 415.1355.

Terminal olefin 13: To a solution of diacetate **12** (787.2 mg, 2.00 mmol) in acetonitrile (50 mL) at 0°C was added allyltrimethylsilane (1.6 mL). Boron trifluoride diethyl etherate (0.29 mL) was added dropwise, and the reaction mixture was stirred at 0°C for 1 h before quenching with saturated (aq) $NaHCO_3$ (30 mL). The mixture was then extracted with ether (3×50 mL), washed with brine (100 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The product was purified by flash column chromatography (silica) to yield terminal olefin **13** as a colorless oil (730.0 mg, 97%). **13**: R_f=0.54 (silica gel, EtOAc:hexanes, 1:3); $[\alpha]_D$=−55.4 (c=0.72, acetone); IR (film): $\tilde{\nu}_{max}$=2929, 1734, 1607, 1585, 1479, 1446, 1380, 1312, 1241, 1041, 925, 781 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.38 (dd, J=8.1, 7.7 Hz, 1H), 6.96 (d, J=7.7 Hz, 1H), 6.82 (d, J=8.1 Hz, 1H), 5.60–5.52 (m, 1H), 5.09–5.04 (m, 1H), 4.95 (dd, J=17.1, 1.1 Hz, 1H), 4.89 (dd, J=9.8, 1.1 Hz, 1H), 4.06–4.01 (m, 1H), 3.98–3.93 (m, 1H), 3.36 (dd, J=13.2, 4.2 Hz, 1H), 3.27 (dd, J=13.2, 8.5 Hz, 1H), 2.38–2.32 (m, 1H), 2.16–2.11 (m, 1H), 2.05–2.00 (m, 1H), 2.03 (s, 3H), 1.81–1.77 (m, 1H), 1.72–1.66 (m, 1H), 1.68 (s, 3H), 1.67 (s, 3H), 1.53–1.47 ppm (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=170.4, 160.5, 157.0, 143.8, 134.9, 134.6, 126.6, 116.9, 115.7, 112.3, 105.1, 70.8, 69.6, 67.4, 39.6, 36.7, 36.4, 33.7, 25.7, 25.6, 21.4 ppm; HRMS (MALDI-FTMS) for $C_{21}H_{26}O_6$ [M+H$^+$] calcd 375.1802, found 375.1816.

Aldehyde acetate 14: A solution of terminal olefin **13** (983 mg, 2.61 mmol) in dichloromethane (150 mL) was cooled to −78°C. A flow of ozone was passed through the solution until it turned blue. The excess ozone was then purged with oxygen until the solution became clear again. The reaction mixture was quenched with dimethyl sulfide (3.8 mL, 51.7 mmol) and then allowed to warm to room temperature. Triphenylphosphine (685 mg, 2.61 mmol) was added and the resulting mixture was stirred at that temperature for an additional 5 h period. Concentrating in vacuo followed by flash column chromatography (silica) yielded aldehyde acetate **14** as a colorless syrup (966.4 mg, 98%). **14**: R_f=0.43 (silica gel, EtOAc:hexanes, 1:1); $[\alpha]_D$=−66.5 (c=3.02, acetone); IR (film): $\tilde{\nu}_{max}$=2942, 1731, 1606, 1585, 1480, 1449, 1381, 1313, 1240, 1042, 922, 781 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=9.52 (dd, J=2.2, 1.8 Hz, 1H), 7.38 (dd, J=8.4, 7.7 Hz, 1H), 6.92 (d, J=7.7 Hz, 1H), 6.83 (d, J=8.4 Hz, 1H), 5.07–5.02 (m, 1H), 4.65–4.60 (m, 1H), 4.01–3.96 (m, 1H), 3.41–3.25 (m, 2H), 2.71 (ddd, J=16.2, 9.1, 2.9 Hz, 1H), 2.41 (ddd, J=16.2, 5.0, 1.5 Hz, 1H), 2.08–2.02 (m, 1H), 2.05 (s, 3H), 1.83–1.73 (m, 2H), 1.69 (s, 3H), 1.68 (s, 3H), 1.62–1.56 ppm (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=200.4, 170.3, 160.6, 157.1, 143.5, 135.0, 126.5, 116.0, 112.1, 105.2, 70.5, 67.0, 65.7, 46.5, 39.2, 35.6, 34.3, 25.7, 25.6, 21.3 ppm; HRMS (MALDI-FTMS) for $C_{20}H_{24}O_7$ [M+Na$^+$] calcd 399.1414, found 399.1419.

Homoallylic alcohol 15: Ipc_2B^dallyl (1.2 mL of a 1M solution in pentane) was added to a flask containing ether (10 mL) and the reaction mixture was cooled to −100°C (methanol–liquid nitrogen). A precooled (−100°C) solution of **14** (219 mg, 0.582 mmol) in ether (15 mL) was then added dropwise using a cannula into the Ipc_2B^dallyl solution and the resulting mixture was stirred at −100°C for 2 h. The reaction mixture was warmed to 0°C and then quenched with ethanol (5 mL). Hydrogen peroxide (30%, 10 mL) was added, followed by phosphate buffer (pH 7, 10 mL). The reaction mixture was warmed to room temperature and stirred for 18 h. The solution was then diluted with water (10 mL) and extracted with ether (3×30 mL). The combined solution was washed with brine (40 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The product was purified by flash column chromatography (silica) to yield homoallylic alcohol **15** as a colorless oil (156.0 mg, 64% of the major isomer) and a small amount of its epimer, epi-**15** (24.2 mg, 10%). **15**: R_f=0.4 (silica gel, EtOAc:hexanes, 1:2); $[\alpha]_D$=−103.7 (c=1.34, acetone); IR (film): $\tilde{\nu}_{max}$=3512, 2930, 1731, 1605, 1584, 1478, 1448, 1316, 1240, 1042, 921, 780 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.41 (dd, J=8.4, 7.4 Hz, 1H), 6.93 (d, J=7.4 Hz, 1H), 6.85 (d, J=8.4 Hz, 1H), 5.71–5.63 (m, 1H), 5.08–5.03 (m, 1H), 5.00–4.97 (m, 2H), 4.26–4.22 (m, 1H), 4.10–4.05 (m, 1H), 3.65–3.62 (m, 2H), 3.11–3.07 (dd, J=13.2, 9.2 Hz, 1H), 2.70 (bs, 1H), 2.18–1.99 (m, 3H), 2.05 (s, 3H), 1.79–1.68 (m, 3H), 1.77 (s, 3H), 1.70 (s, 3H), 1.59–1.56 (m, 1H), 1.38–1.34 ppm (ddd, J=14.7, 2.6, 2.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=170.3, 160.7, 157.4, 143.2, 135.1, 134.6, 126.4, 117.3, 116.4, 112.1, 105.4, 71.8, 71.5, 70.2, 67.0, 41.6, 39.7, 37.8, 36.0, 35.5, 26.3, 25.0, 21.3 ppm; HRMS (MALDI-FTMS) for $C_{23}H_{30}O_7$ [M+Na$^+$] calcd 441.1884, found 441.1887.

Cyclized aldehyde 18: A solution of **17** (137.2 mg, 0.251 mmol) in dichloromethane (20 mL) was cooled to −78°C. A flow of ozone was passed through the solution until it turned blue. The excess ozone was then purged with oxygen until the solution became clear again. The reaction mixture was quenched with dimethylsulfide (0.4 mL, 5.45 mol) at −78°C and then allowed to warm to room temperature. Triphenylphosphine (100 mg, 0.381 mol) was added and the resulting mixture was stirred at room temperature for an additional 5 h period, before concentrating under vacuo. Aldehyde **18** was purified by flash column chromatography (silica) to yield cyclized aldehyde **18** as a sticky yellow solid (97.9 mg, 71%). **18**: R_f=0.17 (silica gel, hexanes:EtOAc, 5:1); $[\alpha]_D$=+31.8 (c=0.44, acetone); IR (film): $\tilde{\nu}_{max}$=3410, 2952, 2929, 2858, 1730, 1695, 1577, 1465, 1383, 1360, 1283, 1254, 1107, 1083, 1066, 837, 778 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ=9.83 (s, 1H), 7.14 (dd, J=8.3, 7.9 Hz, 1H), 6.76 (d, J=7.9 Hz, 1H), 6.70 (d, J=8.3 Hz, 1H), 6.11–6.09 (m, 1H), 4.40–4.38 (m, 1H), 4.08–4.04 (m, 1H), 3.97–3.93 (m, 1H), 3.58 (dd, J=14.5, 11.0 Hz, 1H), 2.87–2.71 (m, 2H), 2.37 (d, J=14.9 Hz, 1H), 1.94–1.90 (m, 1H), 1.87–1.81 (m, 1H), 1.72–1.69 (m, 1H), 1.64–1.58 (m, 2H), 1.53–1.50 (m, 1H), 0.95 (s, 9H), 0.92 (s, 9H), 0.23 (s, 3H), 0.19 (s, 3H), 0.07 ppm (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=199.5, 169.4, 151.7, 139.9, 129.8, 127.7, 122.9, 116.8, 74.4, 68.5, 65.3, 64.7, 48.5, 39.8, 39.5, 38.7, 37.7, 25.8, 25.7, 18.2, 18.0, −4.0, −4.4, −4.8, −4.9 ppm; HRMS (MALDI-FTMS) for $C_{29}H_{48}O_6Si_2$ [M+Na$^+$] calcd 571.2881, found 571.2882.

Bis-TBS-protected vinyl iodide 19: To a solution of $CrCl_2$ (263 mg, 2.140 mmol) in dry THF (10 mL) was added at room temperature a mixture of aldehyde **18** (97.9 mg, 0.1784 mmol), and iodoform (284 mg, 0.7213 mmol), in dry THF (20 mL). Almost immediately the reaction mixture turned reddish-brown and after 3 h of stirring at room temperature, it

was poured onto brine (30 mL) and extracted with ether (3×10 mL). The combined organic layer was then washed with brine (50 mL), dried with $MgSO_4$, filtered and concentrated in vacuo. The product was purified by flash column chromatography (silica) to yield bis-TBS-protected vinyl aldehyde **19** as a yellow oil (95.4 mg, 80% of *trans:cis* (4:1) inseparable mixture of isomers). **19** (ca. 4:1 mixture of *trans:cis* isomers): R_f=0.51 (silica gel, hexanes:EtOAc, 5:1); IR (film): $\tilde{\nu}_{max}$=3434, 2952, 2917, 2858, 1730, 1718, 1577, 1465, 1389, 1360, 1289, 1260, 1113, 1083, 1060, 948, 831, 778, 737, 672 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ=7.13 (dd, J=8.1, 7.7 Hz, 1H), 6.75 (d, J=7.7 Hz, 1H), 6.70 (d, J=8.1 Hz, 1H), 6.59–6.53 (m, 1H), 6.39–6.34 (m, minor), 6.18 (d, J=14.3 Hz, 1H), 5.74–5.70 (m, minor), 5.66–5.60 (m, 1H), 4.34–4.30 (m, 1H), 4.09–4.05 (m, 1H), 3.97–3.93 (m, 1H), 3.55 (dd, J=14.5, 11.0 Hz, 1H), 2.52–2.35 (m, 3H), 1.94–1.89 (m, 1H), 1.81–1.75 (m, 1H), 1.66–1.48 (m, 4H), 0.98 (s, 9H), 0.92 (s, 9H), 0.26 (s, 3H), 0.22 (s, 3H), 0.07 ppm (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=169.7, 151.6, 140.9, 139.7, 136.6, 129.6, 127.9, 122.9, 116.7, 78.0, 74.3, 71.9, 65.4, 41.3, 39.6, 38.8 (two peaks), 37.8, 25.8, 25.7, 18.2, 18.0, −4.0, −4.4, −4.8 ppm (two peaks); (two isomers); HRMS (MALDI-FTMS) for $C_{30}H_{49}IO_5Si_2$ [M + Na^+] calcd 695.2055, found 695.2023.

Dihydroxy vinyl iodide 20: To a solution of bis-TBS-protected vinyl iodide **19** (ca. 4:1 *trans:cis* mixture of isomers, 35.7 mg, 0.053 mmol) in THF (10 mL) was added at room temperature TBAF (1.0 M THF solution, 0.5 mL, 0.50 mmol). The reaction mixture was stirred for 5 h at room temperature and then quenched with saturated (aq) NH_4Cl (10 mL) and extracted with ether (3×10 mL). The combined organic layer was washed with brine (20 mL), dried with $MgSO_4$, filtered and concentrated in vacuo. The product was purified by flash column chromatography (silica) to yield dihydroxy vinyl iodide **20** as a yellow oil (23.1 mg, 98% ca. 4:1 ratio of *trans:cis* isomers). **20** (ca. 4:1 mixture of *trans:cis* isomers): R_f=0.17 (silica gel, hexanes:EtOAc, 1:1); IR (film): $\tilde{\nu}_{max}$=3366, 2955, 2920, 1713, 1690, 1643, 1608, 1578, 1461, 1361, 1290, 1261, 1114, 1073, 1055, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.20 (dd, J=8.5, 7.3 Hz, 1H), 6.83 (d, J=8.5 Hz, 1H), 6.76 (d, J=7.3 Hz, 1H), 6.61–6.54 (m, 1H), 6.26 (d, J=14.7 Hz, 1H), 5.99 (bs, 1H), 5.65–5.58 (m, minor), 5.57–5.50 (m, 1H), 4.34–4.28 (m, 1H), 4.09–4.03 (m, 1H), 3.92–3.84 (m, 1H), 3.52 (dd, J=14.2, 11.0 Hz, 1H), 2.48–2.42 (m, 3H), 2.00 (ddd, J=12.9, 4.6, 4.6 Hz, 1H), 1.91–1.79 (m, 2H), 1.69–1.54 ppm (m, 4H); ^{13}C NMR (150 MHz, [D_6]acetone): δ=169.2, 164.0, 154.3, 142.9, 140.1, 140.3, 125.2, 122.2, 114.3, 78.1, 73.6, 67.9, 64.8, 41.5, 40.3, 39.8, 39.6, 38.9 ppm; (two isomers); HRMS (MALDI-FTMS) for $C_{18}H_{21}IO_5$ [M+Na^+] calcd 467.0326, found 467.0319.

Epoxide 21: To a solution of olefin **17** (21.3 mg, 0.039 mmol) in dichloromethane (5 mL) was added *m*CPBA (98 mg, 0.312 mmol) and $NaHCO_3$ (28.8 mg, 0.343 mmol). The reaction mixture was heated at reflux for 24 h and then cooled to room temperature. To the solution was added saturated (aq) $NaHCO_3$ (10 mL) and the resulting mixture was extracted with ether (3×10 mL). The combined organic layer was washed with brine (10 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The epoxide was purified by flash column chromatography (silica) to yield epoxide **21** as a mixture of diastereomeric epoxides (ca. 1:1) as a yellow oil (20.5 mg, 94%). **21** (ca. 1:1 ratio): R_f=0.34 (silica gel, hexanes:EtOAc, 5:1); IR (film): $\tilde{\nu}_{max}$=2952, 2852, 1716, 1579, 1460, 1361, 1286, 1249, 1105, 1068, 837, 775 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ=7.10 (dd, J=8.3, 7.4 Hz, 1H), 6.73 (d, J=7.4 Hz, 1H), 6.67 (d, J=8.3 Hz, 1H), 1.51–1.71 (m, 1H), 4.36–4.31 (m, 1H), 4.05–3.93 (m, 2H), 3.56–3.51 (m, 1H), 3.09–3.05 (m, 1H), 2.78–2.77 (m, 1H), 2.52–2.48 (m, 1H), 2.35 (d, J=14.5 Hz, 1H), 2.08–1.78 (m, 4H), 1.70–1.47 (m, 4H), 0.93 (s, 9H), 0.89 (s, 9H), 0.18 (s, 6H), 0.04 ppm (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=169.6 (two peaks), 151.7, 139.7 (two peaks), 129.6, 128.1, 128.0, 123.0, 122.9, 117.0, 116.8, 74.2 (two peaks), 71.9, 71.2, 65.4, 65.2, 49.1, 48.8, 47.0, 46.8, 39.7, 39.6 (two peaks), 39.2, 38.9, 38.3, 37.9, 37.6, 25.8, 25.7 (two peaks), −4.0, −4.1, −4.4, −4.8 ppm (two peaks); (two isomers); HRMS (MALDI-FTMS) for $C_{30}H_{50}O_6Si_2$ [M+Na^+] calcd 585.3038, found 585.3037.

Hydroxy azide 22: To a solution of epoxide **21** (ca. 1:1 mixture of isomers, 40 mg, 0.071 mmol) in methanol/water (8:1 v/v, 10 mL) was added sodium azide (46.2 mg, 0.711 mmol) and ammonium chloride (19 mg, 0.355 mmol). The reaction mixture was refluxed for 20 h and then cooled to room temperature. The resulting solution was diluted with water (20 mL) and extracted with ether (3×10 mL). The combined organic layer was then washed with brine (20 mL), dried with $MgSO_4$, filtered, and evaporated in vacuo. The product was purified by flash column chromatography (silica) to yield a mixture of diastereoisomers (ca. 1:1) of a light yellow oil (38.2 mg, 89%). **22** (diastereoisomer B): R_f=0.45 (diastereoisomer B) (silica gel, hexanes:EtOAc, 3:1); $[\alpha]_D$=+29.1 (c=0.44, acetone); IR (film): $\tilde{\nu}_{max}$=3438, 2952, 2857, 2098, 1717, 1575, 1456, 1284, 1249, 1106, 1065, 840, 774, 668 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ=7.12 (dd, J=7.4, 7.9 Hz, 1H), 6.74 (d, J=7.4 Hz, 1H), 6.70 (d, J=7.9 Hz, 1H) 5.72–5.67, (m, 1H), 4.33–4.30 (m, 1H), 4.06–4.02 (m, 1H), 3.97–3.92 (m, 2H), 3.52 (dd, J=11.2, 14.3 Hz, 1H), 3.36–3.30 (m, 2H), 2.43 (d, J=3.5 Hz, 1H), 2.35 (d, J=14.9 Hz, 1H), 1.93–1.82 (m, 3H), 1.78–1.74 (m, 1H), 1.61–1.57 (m, 2H), 1.49–1.46 (m, 1H), 1.41 (s, 1H), 0.95 (s, 9H), 0.89 (s, 9H), 0.21 (s, 3H), 0.17 (s, 3H), 0.04 ppm (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=169.6, 151.6, 139.6, 129.7, 128.1, 123.2, 117.5, 74.2, 72.2, 68.4, 65.3, 64.9, 56.7, 39.6 (two peaks), 39.2, 38.8, 37.8, 25.9, 25.8, 18.5, 18.0, −4.0, −4.3, −4.8 ppm (two peaks); HRMS (MALDI-FTMS) for $C_{30}H_{51}N_3O_6Si_2$ [M + Na^+] calcd 628.3208, found 628.3206.

Hydroxy amide 23: To a solution of azide **22** (115.6 mg, 0.1902 mmol) in THF (20 mL) was added H_2O (2 drops) and triphenylphosphine (80 mg, 0.305 mmol). The reaction mixture was then heated to 40 °C, and stirred for 18 h. The resulting solution was then cooled to room temperature, concentrated in vacuo, and dried under high vacuum. To the crude amine so obtained was added dichloromethane (20 mL), diene carboxylic acid **5c** (29.2 mg, 0.2317 mmol), DIEA (0.06 mL, 0.3451 mmol), EDC (44.4 mg, 0.2316 mmol), and HOBt (35.4 mg, 0.2620 mmol). The reaction mixture was stirred at room temperature for 3 h and then concentrated in vacuo. The product was purified by column chromatography (silica) to yield hydroxyl amide **23** as a yellow oil (ca. 1:1 mixture of diastereoisomers, 85.1 mg, 65% from **22**). **23** (ca. 1:1 mixture of diastereoisomers): R_f=0.23 (silica gel, hexanes:EtOAc, 2:1); IR (film): $\tilde{\nu}_{max}$=3349, 2953, 2918, 1860, 1735, 1715, 1645, 1464, 1278, 1255, 1086, 1063, 836, 778 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ=7.24–7.20 (m, 1H), 7.13–7.09 (m, 1H), 6.77–6.69 (m, 3H), 5.96 (t, J=5.5 Hz, 1H), 5.82–5.77 (m, 1H), 5.73–5.65 (m, 1H), 5.57 (d, J=11.4 Hz, 1H), 4.33–4.26 (m, 1H), 4.04–3.93 (m, 3H), 3.56–3.50 (m, 2H), 3.36 (dd, J=15.1, 9.4 Hz, 1H), 3.25–3.21 (m, 1H), 2.37 (d, J=14.7 Hz, 1H), 2.26–2.21 (m, 2H), 2.04–1.98 (m, 1H), 1.90–1.70 (m, 3H), 1.64–1.45 (m, 4H), 1.00 (t, J=7.7 Hz, 3H), 0.93 (s, 9H), 0.88 (s, 9H), 0.39 (s, 6H), 0.34 ppm (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=170.1, 169.5, 167.4, 166.9, 152.0, 151.9, 141.6, 141.4, 139.6, 139.3, 135.6, 135.4, 129.6, 129.6, 128.3, 127.5, 123.8, 123.8, 123.4, 123.2, 120.0, 119.9, 117.6, 117.3, 74.1, 73.3, 72.7, 72.3, 68.8, 67.3, 66.5, 65.6, 65.3, 65.0, 45.5, 44.7, 39.8, 39.7 (two peaks), 39.5, 39.4, 39.1, 38.8, 38.3, 37.9, 26.0, 25.8 (two peaks), 20.7, 18.6, 18.5, 18.0 (two peaks), 14.0, −3.9 (two peaks), −4.2, −4.3, −4.8 (three peaks), −4.9 ppm; (two isomers); HRMS (MALDI-FTMS) for $C_{37}H_{61}NO_7Si_2$ [M + Na^+] calcd 710.3879, found 710.3873.

Primary alcohol 24: To a solution of olefin **17** (192 mg, 0.351 mmol) in THF (20 mL) was added $BH_3{\cdot}Me_2S$ (0.333 mL, 3.51 mmol) and the reaction mixture was subjected to sonication for 1.5 h at room temperature. Phosphate buffer (pH 7, 1 mL) was then added to the reaction mixture and the resulting solution was diluted with ether (20 mL). Hydrogen peroxide (30%, 1.0 mL) was added dropwise and the reaction mixture was extracted with ether (3×20 mL). The combined organic layer was washed with brine (20 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The product was purified by flash column chromatography (silica) to yield primary alcohol **24** as a light yellow oil (141 mg, 71%). **24**: R_f=0.70 (silica gel, hexanes:EtOAc, 1:1); $[\alpha]_D$=+31.0 (c=0.21, acetone); IR (film): $\tilde{\nu}_{max}$=3435, 2953, 2923, 2853, 1714, 1694, 1669, 1649, 1633, 1463, 1393, 1362, 1287, 1252, 1106, 1066 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=7.12 (dd, J=8.1, 7.4 Hz, 1H), 6.74 (d, J=7.4 Hz, 1H), 6.70 (d, J=8.1 Hz, 1H), 5.62–5.59 (m, 1H), 4.35–4.31 (m, 1H), 4.08–4.05 (m, 1H), 4.00–3.96 (m, 1H), 3.71–3.65 (m, 2H), 3.53 (dd, J=14.7, 10.6 Hz, 1H), 2.38 (dd, J=14.7, 1.3 Hz, 1H), 1.94–1.83 (m, 2H), 1.79–1.67 (m, 3H), 1.66–1.49 (m, 6H), 0.97 (s, 9H), 0.91 (s, 9H), 0.22 (s, 3H), 0.21 (s, 3H), 0.07 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.8, 151.7, 139.5, 129.4, 128.3, 123.0, 117.0, 73.9, 73.7, 65.5 (two peaks), 62.6, 39.6, 39.0, 38.2, 31.1, 29.7, 28.4, 25.8, 25.7, 18.3, 18.0, −4.1, −4.2, −4.8 (two peaks); HRMS (MALDI-FTMS) for $C_{30}H_{52}O_6Si_2$ [M + Na^+] calcd 587.3194, found 587.3205.

Aldehyde 25: To a solution of alcohol **24** (10 mg, 0.018 mmol) in dichloromethane (5 mL) was added at 0 °C, NMO (3.11 mg, 0.027 mmol) and 4 Å molecular sieves (9 mg) followed by TPAP (1 mg, 0.0028 mmol),

in one portion. The reaction mixture was stirred for 1 h at 0 °C and then filtered through a short pad of silica and the pad was washed with a solution of hexanes:EtOAc (1:1). The resulting solution was concentrated in vacuo and the product was purified by flash column chromatography (silica) to yield aldehyde **25** as a yellow oil (9.8 mg, 99 %). **25**: R_f = 0.53 (silica gel, hexanes:EtOAc, 7:3); $[\alpha]_D$ = +28.6 (c = 0.29, acetone); IR (film): $\tilde{\nu}_{max}$ = 3413, 2955, 2919, 2851, 1725, 1572, 1461, 1390, 1361, 1284, 1249, 1108, 1067, 838, 779 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.78 (s, 1H), 7.10 (dd, J = 8.1, 7.4 Hz, 1H), 6.72 (d, J = 7.3 Hz, 1H), 6.68 (d, J = 8.1 Hz, 1H), 5.59–5.54 (m, 1H), 4.32–4.27 (m, 1H), 4.05–4.01 (m, 1H), 3.96–3.92 (m, 1H), 3.50 (dd, J = 14.7, 11.0 Hz, 1H), 2.71–2.57 (m, 2H), 2.35 (dd, J = 14.7, 1.1 Hz, 1H), 1.99–1.79 (m, 4H), 1.63–1.46 (m, 4H), 0.94 (s, 9H), 0.88 (s, 9H), 0.20 (s, 3H), 0.19 (s, 3H), 0.04 ppm (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 201.2, 169.7, 151.7, 139.6, 129.6, 128.0, 123.1, 117.0, 74.1, 72.9, 65.4, 65.3, 39.9, 39.5, 39.1, 39.0, 38.1, 26.7, 25.8, 25.7, 18.4, 18.0, −4.0, −4.1, −4.8 (two peaks); HRMS (MALDI-FTMS) for $C_{30}H_{50}O_6Si_2$ [M + Na$^+$] calcd 585.3038, found 585.3022.

Bisamide 26: To a solution of aldehyde **25** (47 mg, 0.0834 mmol) and amide **5** (20.9 mg, 0.1672 mmol) in 1,2-dichloroethane (4 mL) was added dropwise at room temperature TMSOTf (7.55 μL, 0.0417 mmol) and the resulting mixture was stirred for 24 h. Phosphate buffer (pH 7, 5.0 mL) was added and the resulting reaction mixture was extracted with dichloromethane (3 × 5 mL). The combined organic layer was washed with brine (10 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude bis-TBS-protected amide was dissolved in THF (10 mL) and TBAF (1.0 M THF solution, 0.3 mL, 0.30 mmol) was added dropwise to the resulting solution. The reaction mixture was stirred for 1 h at room temperature and then quenched with saturated (aq) NH_4Cl (10 mL) and extracted with ether (3 × 5 mL). The combined organic layer was then washed with brine (10 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The product was purified by column chromatography (silica) to yield bisamide **26** as a white solid (35.4 mg, 75 %). **26**: R_f = 0.28 (silica gel, EtOAc); $[\alpha]_D$ = −9.4 (c = 3.5, acetone); IR (film): $\tilde{\nu}_{max}$ = 3277, 2962, 2931, 2872, 1707, 1651, 1625, 1584, 1460, 1290, 1255, 1208, 1119 cm^{-1}; ^{1}H NMR (600 MHz, [D$_6$]acetone) δ 8.60 (bs, 1H), 7.62–7.4 (m, 4H), 7.10 (dd, J = 8.3, 7.9 Hz, 1H), 6.79–6.74 (m, 3H), 6.69 (d, J = 7.9 Hz, 1H), 5.77–5.72 (m, 4H), 5.69–5.62 (m, 1H), 5.46–4.41 (m, 1H), 4.24–4.21 (m, 1H), 3.99–3.75 (m, 3H), 3.32 (dd, J = 15.5, 9.7 Hz, 1H), 2.43 (d, J = 15.5 Hz, 1H), 2.26–2.21 (m, 4H), 2.03–1.90 (m, 3H), 1.84–1.78 (m, 1H), 1.66–1.43 (m, 6H), 0.97 ppm (t, J = 7.6 Hz, 6H); ^{13}C NMR (125 MHz, [D$_6$]acetone): δ = 169.5, 166.2, 166.1, 154.2, 140.8 (two peaks), 140.0, 135.8, 135.7, 130.2, 125.6, 125.3 (two peaks), 122.3, 121.7, 121.6, 114.5, 74.0, 73.4, 68.4, 64.8, 57.2, 54.5, 40.4, 39.8, 39.3, 31.7, 31.3, 21.0 (two peaks), 14.3 ppm (two peaks); HRMS (MALDI-FTMS) for $C_{32}H_{42}N_2O_7$ [M + Na$^+$] calcd 589.2890, found 589.2903.

Terminal olefin 27: To a solution of aldehyde **15** (153.7 mg, 0.367 mmol) in dichloromethane (20 mL) at 0 °C was added sequentially 2,6-lutidine (171 μL, 1.468 mmol) followed by dropwise addition of TESOTf (169 μL, 0.7359 mmol). The reaction mixture was stirred at 0 °C for 2 h, quenched with methanol (10 mL) and allowed to warm to room temperature. After stirring for an additional 30 min, the solution was concentrated in vacuo and purified by flash column chromatography (silica) to yield terminal olefin **27** as a colorless oil (183.6 mg, 94 %). **27**: R_f = 0.42 (silica gel, EtOAc:hexanes, 1:4); $[\alpha]_D$ = −45.5 (c = 3.52, acetone); IR (film): $\tilde{\nu}_{max}$ = 2955, 2931, 2861, 1731, 1608, 1584, 1478, 1449, 1378, 1314, 1296, 1243, 1079, 1043, 914, 838, 808, 773 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.37 (dd, J = 7.9, 7.4 Hz, 1H), 6.97 (d, J = 7.4 Hz, 1H), 6.81 (d, J = 7.9 Hz, 1H), 5.70–5.63 (m, 1H), 5.05–5.00 (m, 1H), 4.96–4.91 (m, 2H), 4.18–4.14 (m, 1H), 3.91–3.87 (m, 1H), 3.49–3.45 (m, 1H), 3.43 (dd, J = 13.4, 3.3 Hz, 1H), 3.12 (dd, J = 13.1, 8.8 Hz, 1H), 2.09–2.06 (m, 3H), 2.02 (s, 3H), 1.75–1.66 (m, 3H), 1.68 (s, 3H), 1.64 (s, 3H), 1.51–1.40 (m, 2H), 0.81 (s, 9H), −0.09 (s, 3H), −0.09 ppm (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.3, 160.4, 157.0, 143.8, 135.0, 134.8, 126.8, 116.8, 115.8, 112.3, 105.0, 69.7, 68.5, 67.6, 67.5, 40.9, 39.7, 38.8, 36.5, 34.4, 26.1, 25.8, 25.1, 21.4, 17.9, −4.6, −4.8; HRMS (MALDI-FTMS) for $C_{29}H_{44}O_7Si$ [M + Na$^+$] calcd 555.2748, found 555.2741.

Aldehyde 28: A solution of olefin **27** (183.6 mg, 0.345 mmol) in dichloromethane (20 mL) was cooled to −78 °C. A flow of ozone was passed through the solution until it turned blue. The excess ozone was then purged with oxygen until the solution became clear again. The reaction mixture was quenched with dimethylsulfide (0.5 mL, 20.0 mmol) at −78 °C and then allowed to warm to room temperature. Triphenylphosphine (90.5 mg, 0.345 mmol) was added and the reaction mixture was stirred at room temperature for an additional 5 h period, before concentrating in vacuo. The aldehyde was purified by flash column chromatography (silica) to yield aldehyde **28** as a colorless syrup (163.4 mg, 89 %). **28**: R_f = 0.18 (silica gel, EtOAc:hexanes, 1:4); $[\alpha]_D$ = −48.4 (c = 3.03, acetone); IR (film): $\tilde{\nu}_{max}$ = 2955, 2931, 2861, 1731, 1713, 1608, 1584, 1478, 1449, 1378, 1314, 1296, 1243, 1208, 1079, 1044, 926, 838, 808, 779, 732, 703 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.48 (bs, 1H), 7.37 (dd, J = 7.9, 7.5 Hz, 1H), 6.96 (d, J = 7.5 Hz 1H), 6.83 (d, J = 7.9 Hz, 1H), 5.05–5.00 (m, 1H), 4.19–4.17 (m, 1H), 3.99–3.87 (m, 2H), 3.40 (dd, J = 12.9, 3.3 Hz, 1H), 3.10 (dd, J = 12.9, 8.5 Hz, 1H), 2.39–2.30 (m, 2H), 2.09–2.06 (m, 1H), 2.02 (s, 3H), 1.99–1.94 (m, 1H), 1.72–1.65 (m, 2H), 1.69 (s, 3H), 1.64 (s, 3H), 1.50–1.45 (m, 1H), 1.42–1.38 (m, 1H), 0.78 (s, 9H), −0.06 (s, 3H), −0.10 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 202.3, 170.3, 160.4, 157.1, 143.6, 134.8, 127.0, 116.0, 112.3, 105.2, 69.6, 67.4, 67.2, 65.1, 49.6, 39.9, 39.0, 36.4, 34.9, 26.3, 25.6, 25.0, 21.3, 17.8, −4.6, −5.0 ppm; HRMS (MALDI-FTMS) for $C_{28}H_{42}O_8Si$ [M + Na$^+$] calcd 557.2541, found 557.2545.

Vinyl iodide 29: To a solution of $CrCl_2$ (450 mg, 3.6615 mmol) in dry THF (10 mL) at room temperature was added a solution of aldehyde **28** (163.4 mg, 0.3056 mmol), and iodoform (486 mg, 1.234 mmol), in dry THF (15 mL). Almost immediately the reaction turned reddish-brown and after 3 h of stirring at room temperature, the reaction was poured onto brine (20 mL) and extracted with ether (3 × 10 mL). The combined organic layer was then washed with brine (20 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The product was purified by flash column chromatography (silica) to yield vinyl iodide **29** as a yellow oil (183.2 mg, 91 % ca. 9:1 *trans*:*cis* mixture). **29**: R_f = 0.25 (silica gel, EtOAc:hexanes, 1:4); IR (film): $\tilde{\nu}_{max}$ = 2955, 2951, 2861, 1737, 1608, 1584, 1478, 1449, 1378, 1314, 1296, 1243, 1073, 1044, 967, 920, 838, 803, 773 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.38 (dd, J = 8.3, 7.9 Hz, 1H), 6.96 (d, J = 7.9 Hz, 1H), 6.85 (d, J = 8.3 Hz, 1H), 6.34–6.29 (m, 1H), 5.87 (d, J = 12.7 Hz, 1H), 5.17–5.12 (m, minor), 5.06–5.01 (m, major, 1H), 4.26–4.24 (m, minor), 4.14–4.12 (m, major, 1H), 3.94–3.87 (m, 1H), 3.56–3.53 (m, minor), 3.46–3.38 (m, major, 2H), 3.17–3.08 (m, 1H), 2.09–1.96 (m, 3H), 2.03 (s, major, 3H), 2.02 (s, minor), 1.87–1.75 (m, 1H), 1.70 (s, 3H), 1.64 (s, 3H), 1.70–1.64 (m, 2H), 1.51–1.45 (m, 1H), 1.42–1.32 (m, 1H), 0.83 (s, minor), 0.81 (s, major, 9H), −0.06 (s, minor), −0.10 ppm (s, major, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.4, 170.3, 160.4 (two peaks), 157.2, 157.0, 143.8, 143.7, 143.5, 143.4, 135.0, 134.8, 126.8, 126.6, 115.9 (two peaks), 112.3, 112.2, 105.1 (two peaks), 76.5, 76.4, 70.9, 69.6, 68.1, 67.9, 67.5, 67.4, 66.0, 42.9, 42.4, 42.1, 39.8, 38.9, 37.1, 36.5, 36.0, 34.8, 34.7, 26.3, 25.8 (two peaks), 25.7, 25.4, 25.0, 21.4, 17.9 (two peaks), −4.7, −4.8; (two isomers); HRMS (MALDI-FTMS) for $C_{29}H_{43}IO_7Si$ [M + Na$^+$] calcd 681.1715, found 681.1711.

***trans*-Enamide 30a**: To an oven-dried flask was added CuTC (3.5 mg, 0.018 mmol), Rb_2CO_3 (13.0 mg, 0.056 mmol), and amide **5** (5.0 mg, 0.039 mmol) and dry dimethylacetamide (5 mL) and the mixture was degassed under high vacuum until bubbling had ceased. To a separate oven-dried flask was added vinyl iodide **29** (11.9 mg, 0.018 mmol) and dry dimethylacetamide (5 mL) and the solution was degassed under high vacuum until bubbling ceased. The solution of vinyl iodide **29** was transferred to the CuTC-Rb_2CO_3-amide **5** mixture and the reaction mixture was placed under high vacuum once again. The suspension was purged with argon and then heated to 90 °C and stirred for 15 h at that temperature. The resulting dark reddish-brown solution was cooled to room temperature and poured onto phosphate buffer (pH 7, 5 mL) and extracted with ether (3 × 5 mL). The combined organic layer was then washed with brine (10 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude mixture so obtained was purified by column chromatography (silica) to yield in order of elution starting vinyl iodide **29** (6.8 mg), *cis*-enamide **30b** (0.5 mg, 4 %), and *trans*-enamide **30a** (4.9 mg, 41 %). **30a**: R_f = 0.5 (silica gel, EtOAc:hexanes, 1:2); $[\alpha]_D$ = -7.04 (c = 2.8, acetone); IR (film): $\tilde{\nu}_{max}$ = 3450, 3319, 2955, 2931, 2861, 1731, 1713, 1642, 1584, 1455, 1373, 1242, 1208, 1088, 1044, 838, 779 cm^{-1}; ^{1}H NMR (600 MHz, [D$_6$]acetone): δ = 9.05 (bd, J = 10.8 Hz, 1H), 7.55–7.50 (m, 2H), 7.08 (d, J = 7.44 Hz, 1H), 6.89 (d, J = 7.92 Hz, 1H), 6.84 (dd, J = 11.9, 11.4 Hz, 1H), 6.77 (dd, J = 14.5, 10.6 Hz, 1H), 5.80–5.76 (m, 1H), 5.73 (d, J = 11.4 Hz, 1H), 5.25 (dt, J = 14.5, 7.4 Hz, 1H), 5.04–4.97 (m, 1H), 4.21–4.17 (m, 1H), 3.94–3.89 (m, 1H), 3.50–3.46 (m, 1H), 3.41 (dd, J = 12.7, 3.5 Hz, 1H), 3.15 (dd,

J = 12.9, 8.6 Hz, 1H), 2.29–2.24 (m, 2H), 2.16–2.04 (m, 2H), 2.06–2.04 (m, 1H), 2.00 (s, 3H), 1.84–1.79 (m 1H), 1.76–1.74 (m, 1H), 1.70–1.67 (m, 1H), 1.69 (s, 3H), 1.65 (s, 3H), 1.47–1.41 (m, 2H), 1.00 (t, J = 7.44 Hz, 3H), 0.83 (s, 9H), −0.6 ppm (s, 6H); ^{13}C NMR (150 MHz, [D$_6$]acetone): δ = 170.4, 163.5, 160.7, 157.8, 144.6, 141.3, 136.6, 135.8, 127.9, 125.8, 125.4, 120.9, 116.6, 113.4, 108.8, 105.8, 70.4, 70.0, 68.5, 68.0, 40.5, 39.5 (two peaks), 37.5, 35.4, 26.3, 26.2, 25.0, 21.2, 21.0, 18.5, 14.3, −4.4, −4.5; HRMS (MALDI-FTMS) for $C_{36}H_{53}NO_8Si$ [M + Na$^+$] calcd 678.3432, found 678.3439.

***cis*-Enamide 30b**: R_f = 0.81 (silica gel, EtOAc:hexanes, 1:1); $[\alpha]_D$ = −81.8 (c = 0.11, acetone); IR (film): $\tilde{\nu}_{max}$ = 3412, 2953, 2926, 2860, 1734, 1649, 1504, 1478, 1452, 1386, 1320, 1293, 1241, 1202, 1077, 1044, 834, 808, 775 cm^{-1}; ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 8.69 (bd, J = 10.7 Hz, 1H), 7.52–7.46 (m, 2H), 7.10 (dd, J = 7.7, 1.1 Hz, 1H), 6.92 (dd, J = 8.1, 1.1 Hz, 1H), 6.84 (dt, J = 11.8, 1.1 Hz, 1H), 6.80–6.76 (m, 1H), 5.84–5.75 (m, 2H), 5.04–4.98 (m, 1H), 4.69–4.64 (m, 1H), 4.28–4.24 (m, 1H), 3.99–3.91 (m, 1H), 3.65–3.61 (m, 1H), 3.43–3.38 (m, 1H), 3.27–3.23 (m, 1H), 2.30–2.15 (m, 4H), 2.06–1.90 (m, 4H), 1.89–1.83 (m, 1H), 1.78–1.73 (m, 1H), 1.70–1.64 (m, 7H), 1.52–1.41 (m, 2H), 0.99 (t, J = 7.7 Hz, 3H), 0.86 (s, 9H), −0.01 (s, 3H), −0.02 ppm (s, 3H); ^{13}C NMR (150 MHz, [D$_6$]acetone): δ = 170.3, 163.9, 160.9, 157.9, 144.5, 141.5, 136.8, 135.8, 127.9, 125.4, 123.4, 120.9, 116.7, 113.5, 107.8, 105.9, 70.7, 69.9, 68.1, 67.9, 40.2, 39.6, 36.9, 35.6, 33.6, 26.2, 26.1, 25.2, 21.2, 21.0, 18.5, 14.3, −4.4, −4.5 ppm; HRMS (MALDI-FTMS) for $C_{36}H_{53}NO_8Si$ [M + Na$^+$] calcd 678.3432, found 678.3422.

Hydroxy *trans*-enamide 31a: To a solution of TBS-protected *trans*-enamide **30a** (39.2 mg, 0.0598 mmol) in THF (10 mL) at room temperature was added TBAF (1.0 M THF solution, 0.3 mL, 0.30 mmol). The reaction mixture was stirred for 17 h at ambient temperature and then quenched with saturated (aq) NH_4Cl (10 mL) and extracted with ether (3 × 10 mL). The combined organic layer was then washed with brine (10 mL), dried with $MgSO_4$, filtered and concentrated in vacuo. The product was purified by flash column chromatography (silica) to yield hydroxyl *trans*-enamide **31a** as a light yellow oil (25.8 mg, 80%). **31a**: R_f = 0.40 (silica gel, EtOAc:hexanes, 2:8); $[\alpha]_D$ = −80.4 (c = 0.28, acetone); IR (film): $\tilde{\nu}_{max}$ = 3416, 2965, 1723, 1640, 1580, 1521, 1485, 1379, 1242, 1212, 1046 cm^{-1}; ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 8.98 (d, J = 10.3 Hz, 1H), 7.55–7.49 (m, 2H), 7.05 (dd, J = 7.7, 1.1 Hz, 1H), 6.91 (dd, J = 8.1, 1.1 Hz, 1H), 6.84 (ddd, J = 11.8, 11.8, 1.1 Hz, 1H), 6.77 (ddt, J = 14.7, 10.7, 1.5 Hz, 1H), 5.82–5.75 (m, 1H), 5.72 (d, J = 11.4 Hz, 1H), 5.16 (dt, J = 14.3, 7.4 Hz, 1H), 5.08–5.00 (m, 1H), 4.30–4.22 (m, 1H), 4.04–3.96 (m, 1H), 3.54 (dd, J = 13.2, 3.7 Hz, 1H), 3.52–3.45 (m, 1H), 3.16 (d, J = 3.3 Hz, 1H), 3.13 (dd, J = 12.8, 8.4 Hz, 1H), 2.31–2.23 (m, 2H), 2.10–1.98 (m, 3H), 2.00 (s, 3H), 1.84–1.72 (m, 2H), 1.71–1.67 (m, 7H), 1.55–1.41 (m, 2H) 0.99 ppm (t, J = 3.9 Hz, 3H); ^{13}C NMR (125 MHz, [D$_6$]acetone): δ = 170.4, 163.5, 160.8, 158.0, 144.4, 141.3, 136.6, 135.9, 127.7, 125.5, 125.4, 120.9, 116.7, 113.3, 109.2, 106.0, 70.9, 70.8, 70.6, 67.8, 40.5, 39.0, 38.5, 37.3, 35.4, 26.0, 25.4, 21.2, 21.0, 14.3 ppm; HRMS (MALDI-FTMS) for $C_{30}H_{39}NO_8$ [M + Na$^+$] calcd 564.2568, found 564.2580.

Hydroxy *cis*-enamide 31b: To a solution of TBS-protected *cis*-enamide **30b** (40.4 mg, 0.0616 mmol) in THF (10 mL) at room temperature was added TBAF (1.0 M THF solution, 0.31 mL, 0.310 mmol) in THF. The reaction mixture was stirred for 17 h at ambient temperature and then quenched with saturated (aq) NH_4Cl (10 mL) and extracted with ether (3 × 10 mL). The combined organic layer was washed with brine (10 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The product was purified by flash column chromatography (silica) to yield hydroxyl *cis*-enamide **31b** as a yellow oil (19.9 mg, 60%). **31b**: R_f = 0.61 (silica gel, EtOAc:hexanes, 2:1); $[\alpha]_D$ = −40.8 (c = 0.6, acetone); IR (film): $\tilde{\nu}_{max}$ = 3456, 3350, 2962, 2927, 2856, 1729, 1682, 1647, 1606, 1582, 1505, 1482, 1447, 1376, 1318, 1288, 1265, 1241, 1212, 1077, 1047, 965, 923, 812 cm^{-1}; ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 8.86 (bd, J = 10.7 Hz, 1H), 7.52–7.46 (m, 2H), 7.05 (d, J = 7.7 Hz, 1H), 6.92 (d, J = 8.1 Hz, 1H), 6.84 (dt, J = 11.8, 1.2 Hz, 1H), 6.78–6.73 (m, 1H), 5.82–5.75 (m, 2H), 5.04–4.99 (m, 1H), 4.72–4.66 (m, 1H), 4.29–4.25 (m, 1H), 4.04–3.99 (m, 1H), 3.64–3.58 (m, 1H), 3.52–3.47 (m, 2H), 3.19 (dd, J = 13.2, 8.4 Hz, 1H), 2.30–2.23 (m, 2H), 2.18–2.07 (m, 3H), 1.99 (s, 3H), 1.83–1.77 (m, 2H), 1.69–1.67 (m, 7H), 1.53–1.48 (m, 1H), 1.46–1.43 (m, 1H), 0.99 ppm (t, J = 7.7 Hz, 3H); ^{13}C NMR (150 MHz, [D$_6$]acetone): δ = 170.4, 163.9, 160.9, 158.0, 144.3, 141.5, 136.8, 135.9, 127.7, 125.4, 123.7, 121.0, 116.8, 113.3, 107.8, 106.0, 70.9, 70.8, 70.6, 67.8, 40.4, 39.0, 37.1, 35.5, 34.1, 25.9, 25.5, 21.2, 21.0, 14.3 ppm; HRMS (MALDI-FTMS) for $C_{30}H_{39}NO_8$ [M + Na$^+$] calcd 564.2568, found 564.2555.

Apicularen A (1): To a solution of *trans*-enamide **31a** (25 mg, 0.0462 mmol) in THF (5 mL) at room temperature was added NaH (60%, 12.9 mg, 0.323 mmol) and the reaction mixture was stirred for 2 h at which time the macrocyclization was complete (monitored by TLC). Water (5.0 equiv) was then added and the reaction mixture was stirred for 24 h. Saturated (aq) NH_4Cl (5 mL) was then added and the reaction mixture was extracted with ether (3 × 10 mL), dried with $MgSO_4$, filtered and concentrated in vacuo. Flash column chromatography (silica) gave apicularen A (**1**) as a white solid (10.1 mg, 50%). **1**: R_f = 0.27 (silica gel, EtOAc:hexanes 9:1); $[\alpha]_D$ = −21.0 (c = 0.2, acetonitrile); HRMS (MALDI-FTMS) calcd for $C_{25}H_{31}NO_6$ [M + Na$^+$] 464.2043, found 464.2052. The ^{1}H and ^{13}C NMR data for the synthetic material were identical to those reported for the natural product.[1b]

***cis*-Apicularen A (2)**: To a solution of *cis*-enamide **31b** (19.9 mg, 0.0367 mmol) in THF (5 mL) at room temperature was added NaH (60%, 29 mg, 0.725 mmol) and the reaction mixture was stirred for 2 h at which time the macrocyclization was complete (monitored by TLC). Water (5.0 equiv) was then added and the reaction mixture was stirred for 24 h. Saturated (aq) NH_4Cl (5 mL) was then added and the reaction mixture was extracted with ether (3 × 10 mL), dried with $MgSO_4$, filtered and concentrated in vacuo. Flash column chromatography (silica) gave apicularen analogue (**2**) as a white solid (5.5 mg, 34%). **2**: R_f = 0.32 (silica gel, EtOAc:hexanes 4:1); $[\alpha]_D$ = +10.0 (c = 0.2, acetone); IR (film): $\tilde{\nu}_{max}$ = 3354, 2955, 2919, 2849, 1719, 1702, 1684, 1655, 1661, 1237, 1619, 1578, 1508, 1461, 1420, 1372, 1290, 1208, 1102, 1078, 1055, 1020 cm^{-1}; ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 8.80 (bd, J = 10.7 Hz, 1H), 8.45 (s, 1H), 7.49 (ddd, J = 11.4, 11.4, 1.1 Hz, 1H), 7.10 (dd, J = 8.4, 7.4 Hz, 1H), 6.86–6.80 (m, 2H), 6.77 (d, J = 8.4 Hz, 1H), 6.69 (d, J = 7.4 Hz, 1H), 5.83 (d, J = 12.5 Hz, 1H), 5.82–5.76 (m, 1H), 5.47 (m, 1H), 4.81 (dt, J = 9.2, 7.5 Hz, 1H), 4.28–4.24 (m, 1H), 4.00–3.96 (m, 1H), 3.89–3.85 (m, 1H), 3.77 (d, J = 4.0 Hz, 1H), 3.35 (dd, J = 14.7, 10.3 Hz, 1H), 2.44–2.37 (m, 3H), 2.29–2.23 (m, 2H), 1.94–1.90 (m, 1H), 1.86–1.79 (m, 1H), 1.68–1.63 (m, 1H), 1.60–1.56 (m, 1H), 1.53–1.46 (m, 2H), 0.99 ppm (t, J = 7.5 Hz, 3H); ^{13}C NMR (150 MHz, [D$_6$]acetone): δ = 169.3, 164.0, 154.2, 141.6, 140.2, 137.0, 130.2, 125.8, 125.4, 123.9, 122.2, 120.8, 114.3, 106.5, 73.8, 73.7, 67.7, 64.8, 40.1, 39.9, 39.5, 39.1, 32.1, 21.0, 14.3 ppm; HRMS (MALDI-FTMS) calcd for $C_{25}H_{31}NO_6$ [M + Na$^+$] 464.2043, found 464.2039.

11-OAc Apicularen A (32): To a solution of **31a** (10.4 mg, 0.0192 mmol) in THF (5 mL) was added NaH (60%, 15.4 mg, 0.385 mmol) at room temperature. The reaction mixture was stirred for 2 h, then quenched with saturated (aq) NH_4Cl (5 mL) and extracted with ether (3 × 10 mL). The combined organic layer was then washed with brine (5 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The product was purified by flash column chromatography (silica) to yield 11-OAc apicularen A **32** as a yellow oil (6.5 mg, 70%). **32**: R_f = 0.58 (silica gel, EtOAc:hexanes 2:1); $[\alpha]_D$ = −10.0 (c = 0.06, acetone); IR (film): $\tilde{\nu}_{max}$ = 3350, 2962, 2927, 2856, 1729, 1711, 1694, 1681, 1653, 1535, 1517, 1500, 1464, 1365, 1288, 1247, 1118, 1077, 1047, 953, 806, 771 cm^{-1}; ^{1}H NMR (600 MHz, [D$_6$]acetone): δ = 9.08 (bd, J = 10.1 Hz, 1H), 8.42 (s, 1H), 7.50 (m, 1H), 7.11 (dd, J = 7.9, 7.9 Hz, 1H), 6.91–6.82 (m, 2H), 6.78 (d, J = 7.9 Hz, 1H), 6.71 (d, J = 7.9 Hz, 1H), 5.81–5.72 (m, 2H), 5.45–5.43 (m, 1H), 5.27–5.21 (m, 1H), 5.01–4.97 (m, 1H), 4.24 (m, 1H), 3.94–3.91 (m, 1H), 3.34 (dd, J = 14.3, 10.3 Hz, 1H), 2.44 (m, 1H), 2.35–2.33 (m, 2H), 2.29–2.24 (m, 2H), 2.05–2.01 (m, 1H), 2.00 (s, 3H), 1.84–1.78 (m, 1H), 1.76–1.72 (m, 1H), 1.65–1.59 (m, 3H), 0.99 ppm (t, J = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, [D$_6$]acetone): δ = 170.3, 169.6, 163.6, 154.2, 141.5, 139.9, 136.8, 130.4, 126.3, 125.5, 125.4, 122.2, 120.8, 114.5, 107.9, 74.1, 73.7, 68.6, 67.2, 39.3, 39.1, 36.3, 36.2, 35.1, 21.2, 21.0, 14.3 ppm; HRMS (MALDI-FTMS) calcd for $C_{27}H_{33}NO_7$ [M + Na$^+$] 506.2149, found 506.2151.

Apicularen analogue 33: **(see *cis*-apicularen A (2) for macrocyclization and simultaneous acetate deprotection procedure):** 31% yield; light yellow oil: R_f = 0.29 (silica gel, EtOAc:hexanes, 4:1); $[\alpha]_D$ = +3.3 (c = 0.09, acetone); IR (film): $\tilde{\nu}_{max}$ = 3417, 2954, 2906, 2859, 1711, 1682, 1652, 1634, 1575, 1539, 1462, 1290, 1260, 1094, 1076, 1053, 952, 797, 774 cm^{-1}; ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 9.52 (bd, J = 10.1 Hz, 1H), 8.38 (s, 1H), 7.96–7.94 (m, 2H), 7.55–7.45 (m, 3H), 7.10 (dd, J = 8.1, 7.7 Hz, 1H), 7.04 (dd, J = 14.5, 10.1 Hz, 1H), 6.74 (d, J = 8.1 Hz, 1H), 6.69 (d, J = 7.7 Hz, 1H), 5.49–5.41 (m, 2H), 4.29–4.25 (m, 1H), 4.00–3.85 (m, 2H), 3.78 (d, J = 4.1 Hz, 1H), 3.35 (dd, J = 14.7, 9.9 Hz, 1H), 2.45–2.37 (m, 3H),

1.96–1.82 (m, 2H), 1.70–1.46 ppm (m, 4H); ^{13}C NMR (125 MHz, [D$_6$]acetone): δ = 169.3, 164.4, 154.2, 140.2, 134.9, 132.3, 130.2, 129.2, 128.2, 126.7, 125.4, 122.2, 114.4, 108.9, 74.0, 73.7, 67.9, 64.8, 40.2, 39.9, 39.5, 38.9, 36.4 ppm; HRMS (MALDI-FTMS) for $C_{25}H_{27}NO_6$ [M + Na$^+$] calcd 460.1730, found 460.1726.

Compound 33a: (see *trans*-enamide 30a for a representative procedure for CuTC-induced acylenamine formation): 37% yield; colorless oil: R_f = 0.39 (silica gel, hexanes:EtOAc, 2:1); $[\alpha]_D$ = −64.3 (c = 0.23, acetone); IR (film): $\tilde{\nu}_{max}$ = 2955, 2919, 2861, 1731, 1713, 1666, 1643, 1608, 1584, 1537, 1519, 1484, 1455, 1384, 1360, 1320, 1296, 1255, 1079, 1061, 1044, 961, 932, 832, 808, 773, 709 cm^{-1}; ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 9.45 (bd, J = 10.3 Hz, 1H), 7.93–7.91 (m, 2H), 7.56–7.45 (m, 4H), 7.09 (dd, J = 7.9, 1.1 Hz, 1H), 6.96–6.91 (m, 1H), 6.90 (dd, J = 8.1, 1.1 Hz, 1H), 5.41 (dt, J = 14.7, 6.6 Hz, 1H), 5.01 (m, 1H), 4.25–3.91 (m, 2H), 3.58–3.37 (m, 2H), 3.19 (dd, J = 12.9, 8.1 Hz, 1H), 2.23–2.02 (m, 3H), 1.99 (s, 3H), 1.88–1.75 (m, 2H), 1.71–1.63 (m, 7H), 1.53–1.39 (m, 2H), 0.85 (s, 9H), −0.03 (s, 3H), −0.04 ppm (s, 3H); ^{13}C NMR (125 MHz, [D$_6$]acetone): δ = 170.4, 164.4, 160.8, 157.8, 144.6, 135.9, 135.1, 132.3, 129.2, 128.2, 127.9, 126.2, 116.6, 113.4, 109.7, 105.9, 70.4, 70.1, 68.5, 68.0, 40.5, 39.4, 37.6, 37.5, 35.5, 26.3, 26.2, 25.0, 21.2, 18.5, −4.4, −4.5; HRMS (MALDI-FTMS) for $C_{36}H_{49}NO_8Si$ [M + Na$^+$] calcd 674.3119, found 674.3112.

Compound 33b: (see hydroxyl enamide 31a and 31b for a representative procedure for TBAF-induced deprotections): 73% yield; yellow oil: R_f = 0.38 (silica gel, hexanes:EtOAc, 1:2); $[\alpha]_D$ = −80.8 (c = 0.25, acetone); IR (film): $\tilde{\nu}_{max}$ = 3452, 3345, 2941, 1729, 1646, 1604, 1580, 1479, 1373, 1295, 1248, 1200, 1052, 957 cm^{-1}; ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 9.39 (d, J = 10.3 Hz, 1H), 7.97–7.91 (m, 2H), 7.55–7.42 (m, 4H), 7.06 (d, J = 7.7 Hz, 1H), 6.96–6.85 (m, 2H), 5.40 (dt, J = 14.3, 7.7 Hz, 1H), 5.08–4.96 (m, 1H), 4.33–4.22 (m, 1H), 4.07–3.99 (m, 1H), 3.56–3.52 (m, 2H), 3.21 (d, J = 3.3 Hz, 1H), 3.15 (dd, J = 12.9, 8.5 Hz, 1H), 2.17–2.04 (m, 3H), 1.99 (s, 3H), 1.85–1.72 (m, 2H), 1.71 (s, 3H), 1.70–1.68 (m, 1H), 1.66 (s, 3H), 1.59–1.51 (m, 1H), 1.48–1.40 ppm (m, 1H); ^{13}C NMR (150 MHz, [D$_6$]acetone): δ = 170.4, 164.3, 161.1, 158.0, 144.4, 135.9, 135.1, 132.3, 129.2, 128.2, 127.7, 125.9, 116.8, 113.3, 110.3, 106.4, 70.9, 70.8, 70.7, 67.9, 40.6, 39.0, 38.5, 37.3, 35.5, 26.0, 25.4, 21.2 ppm; HRMS (MALDI-FTMS) for $C_{30}H_{35}NO_8$ [M + Na$^+$] calcd 560.2255, found 560.2264.

Apicularen analogue 34: 46% yield; yellow solid: R_f = 0.30 (silica gel, hexanes:EtOAc, 1:9); $[\alpha]_D$ = −13.8 (c = 0.42, acetone); IR (film): $\tilde{\nu}_{max}$ = 3401, 2943, 2919, 2849, 1731, 1713, 1678, 1661, 1614, 1537, 1519, 1455, 1349, 1290, 1261, 1237, 1220, 1120, 1091, 1055, 803, 761 cm^{-1}; ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 9.25 (d, J = 10.6 Hz, 1H), 8.46 (s, 1H), 7.68 (d, J = 15.4 Hz, 1H), 7.66–7.63 (m, 2H), 7.52–7.44 (m, 3H), 7.18 (t, J = 8.1 Hz, 1H), 7.03 (bdd, J = 14.3, 10.2 Hz, 1H), 6.85 (d, J = 8.1 Hz, 1H), 6.77 (d, J = 7.3 Hz, 1H), 6.75 (d, J = 15.4 Hz, 1H), 5.57–5.48 (m, 1H), 5.39 (dt, J = 14.3, 7.3 Hz, 1H), 4.37–4.30 (m, 1H), 4.12–4.03 (m, 1H), 4.00–3.91 (m, 1H), 3.85 (d, J = 4.1 Hz, 1H), 3.42 (dd, J = 13.9, 10.1 Hz, 1H), 2.51 (d, J = 13.9 Hz, 1H), 2.46 (m, 2H), 2.05–1.97 (m, 1H), 1.95–1.88 (m, 1H), 1.80–1.72 (m, 1H), 1.70–1.65 (m, 1H), 1.62–1.52 ppm (m, 2H); ^{13}C NMR (125 MHz, [D$_6$]acetone): δ = 169.3, 163.0, 154.3, 141.4, 140.2, 136.0, 130.5, 130.2, 129.7, 128.5, 126.4, 125.5, 122.2, 121.9, 114.4, 108.5, 74.2, 73.7, 68.0, 64.9, 40.3, 39.9, 39.6, 38.9, 36.3 ppm; HRMS (MALDI-FTMS) for $C_{27}H_{29}NO_6$ [M + Na$^+$] calcd 486.1887, found 486.1906.

Compound 34a: 41% yield; colorless oil: R_f = 0.40 (silica gel, hexanes: EtOAc, 2:3); $[\alpha]_D$ = −97.5 (c = 0.16, acetone); IR (film): $\tilde{\nu}_{max}$ = 2953, 2930, 2859, 1729, 1652, 1610, 1527, 1444, 1343, 1289, 1242, 1058, 969, 916, 827, 779 cm^{-1}; ^{1}H NMR (600 MHz, [D$_6$]acetone): δ = 9.16 (d, J = 10.6 Hz, 1H), 7.65–7.50 (m, 4H), 7.45–7.32 (m, 3H), 7.09 (d, J = 7.7 Hz, 1H), 6.91 (d, J = 8.3 Hz, 1H), 6.86 (dd, J = 14.5, 10.5 Hz, 1H), 6.67 (d, J = 15.8 Hz, 1H), 5.23 (dt, J = 14.5, 7.0 Hz, 1H), 5.05–4.95 (m, 1H), 4.25–4.17 (m, 1H), 3.97–3.88 (m, 1H), 3.54–3.46 (m, 1H), 3.41 (dd, J = 12.7, 3.5 Hz, 1H), 3.17 (dd, J = 13.2, 8.8 Hz, 1H), 2.19–2.04 (m, 3H), 1.99 (s, 3H), 1.86–1.81 (m, 1H), 1.78–1.74 (m, 1H), 1.69–1.65 (m, 7H), 1.49–1.40 (m, 2H), 0.85 (s, 9H), −0.05 ppm (s, 6H); ^{13}C NMR (150 MHz, [D$_6$]acetone): δ = 170.4, 162.9, 160.8, 157.8, 144.6, 141.4, 136.1, 135.9, 130.4, 129.7, 128.5, 127.9, 125.9, 121.9, 116.6, 113.4, 109.6, 105.8, 70.4, 70.0, 68.5, 68.0, 40.5, 39.5, 37.5, 37.4, 35.4, 26.4, 26.2, 25.0, 21.2, 18.5, −4.4, −4.5 ppm; HRMS (MALDI-FTMS) for $C_{38}H_{51}NO_8Si$ [M + Na$^+$] calcd 700.3276, found 700.3295.

Apicularen analogue 35: 85% yield; yellow oil: R_f = 0.75 (silica gel, hexanes:EtOAc, 15:85), $[\alpha]_D$ = −12.4 (c = 0.33, acetone); IR (film): $\tilde{\nu}_{max}$ = 3405, 2953, 2923, 2843, 1729, 1713, 1694, 1659, 1643, 1613, 1583, 1538, 1518, 1463, 1433, 1362, 1347, 1292, 1247, 1122, 1076, 1051, 1031, 981 cm^{-1}; ^{1}H NMR (600 MHz, [D$_6$]acetone): δ = 9.18 (d, J = 10.1 Hz, 1H), 8.43 (s, 1H), 7.61–757 (m, 3H), 7.41–7.36 (m, 3H), 7.11 (dd, J = 7.9, 7.4 Hz, 1H), 6.96 (dd, J = 14.3, 10.1 Hz, 1H), 6.78 (d, J = 7.9 Hz, 1H), 6.72 (d, J = 7.4 Hz, 1H), 6.67 (d, J = 15.8 Hz, 1H), 5.47–5.45 (m, 1H), 5.31 (dt, J = 14.3, 7.2 Hz, 1H), 5.01–4.97 (m, 1H), 4.27–4.22 (m, 1H), 3.96–3.92 (m, 1H), 3.34 (dd, J = 14.5, 10.6 Hz, 1H), 2.46–2.36 (m, 3H), 2.03–1.96 (m, 1H), 1.99 (s, 3H), 1.86–1.73 (m, 2H), 1.66–1.60 ppm (m, 3H); ^{13}C NMR (150 MHz, [D$_6$]acetone): δ = 170.3, 169.6, 163.0, 154.2, 141.4, 139.9, 136.0, 130.5, 130.4, 129.7, 128.5, 126.5, 125.5, 122.2, 121.9, 114.5, 108.3, 74.1, 73.7, 68.6, 67.3, 39.3, 39.1, 36.3, 36.2, 35.1, 21.2 ppm; HRMS (MALDI-FTMS) for $C_{29}H_{31}NO_7$ [M + Na$^+$] calcd 528.1993, found 528.1995.

Apicularen analogue 36: 57% yield; colorless oil: R_f = 0.25 (silica gel, EtOAc:hexanes, 4:1); $[\alpha]_D$ = +2.5 (c = 0.2, acetone); IR (film): $\tilde{\nu}_{max}$ = 3378, 2943, 2919, 2849, 1731, 1708, 1684, 1655, 1637, 1602, 1584, 1543, 1496, 1460, 1437, 1420, 1378, 1361, 1284, 1261, 1232, 1161, 1120, 1073, 955, 855, 803 cm^{-1}; ^{1}H NMR (600 MHz, [D$_6$]acetone): δ = 9.54 (bd, J = 10.1 Hz, 1H), 8.38 (s, 1H), 8.03–8.01 (m, 2H), 7.24–7.21 (m, 2H), 7.10 (dd, J = 8.3, 7.4 Hz, 1H), 7.02 (dd, J = 14.5, 10.1 Hz, 1H), 6.76 (d, J = 8.3 Hz, 1H), 6.69 (d, J = 7.4 Hz, 1H), 5.48–5.41 (m, 2H), 4.29–4.24 (m, 1H), 3.99–3.85 (m, 2H), 3.78 (d, J = 3.9 Hz, 1H), 3.35 (dd, J = 14.7, 10.3 Hz, 1H), 2.44–2.37 (m, 3H), 1.96–1.84 (m, 2H), 1.70–1.46 ppm (m, 4H); ^{13}C NMR (150 MHz, [D$_6$]acetone): δ = 169.3, 164.0, 163.4, 154.2, 140.2, 133.3, 130.9, 130.8, 130.2, 130.0, 126.7, 122.2, 116.1, 116.0, 114.4, 109.1, 74.0, 73.7, 67.9, 64.9, 40.2, 39.9, 39.5, 38.9, 36.3 ppm; HRMS (MALDI-FTMS) for $C_{25}H_{26}FNO_6$ [M + Na$^+$] calcd 478.1636, found 478.1628.

Compound 36a: 47% yield; yellow oil: R_f = 0.45 (silica gel, hexanes: EtOAc, 2:1); $[\alpha]_D$ = −52.1 (c = 0.33, acetone); IR (film) $\tilde{\nu}_{max}$ 2949, 2928, 2856, 1735, 1683, 1653, 1637, 1606, 1581, 1498, 1473, 1380, 1360, 1319, 1293, 1242, 1077, 1056, 1048, 959, 836, 810, 774 cm^{-1}; ^{1}H NMR (600 MHz, [D$_6$]acetone): δ = 9.50 (bd, J = 10.1 Hz, 1H), 8.00–7.98 (m, 2H), 7.54 (dd, J = 7.9, 7.5 Hz, 1H), 7.25–7.22 (m, 2H), 7.09 (d, J = 7.9 Hz, 1H), 6.94–6.89 (m, 2H), 5.39 (dt, J = 14.5, 8.2 Hz, 1H), 5.01 (m, 1H), 4.25–4.21 (m, 1H), 3.95–3.91 (m, 1H), 3.57–3.53 (m, 1H), 3.40–3.37 (m, 1H), 3.19 (dd, J = 13.2, 8.3 Hz, 1H), 2.22–2.01 (m, 3H), 1.99 (s, 3H), 1.87–1.75 (m, 2H), 1.71–1.63 (m, 7H), 1.52–1.39 (m, 2H), 0.85 (s, 9H), −0.03 (s, 3H), −0.04 ppm (s, 3H); ^{13}C NMR (150 MHz, [D$_6$]acetone): δ = 170.4, 166.3, 164.7, 163.4, 160.8, 157.8, 144.5, 135.9, 131.5, 130.9, 130.8, 127.9, 126.1, 116.6, 116.1, 116.0, 113.4, 109.9, 105.9, 70.4, 70.1, 68.5, 68.0, 40.5, 39.4, 37.5, 37.4, 35.5, 26.3, 26.2, 25.0, 21.2, 18.5, −4.4, −4.5 ppm; HRMS (MALDI-FTMS) for $C_{36}H_{48}FNO_8Si$ [M + Na$^+$] calcd 692.3025, found 692.3020.

Compound 36b: 42% yield; light yellow oil: R_f = 0.16 (silica gel, hexanes: EtOAc, 1:1); $[\alpha]_D$ = −39.4 (c = 0.16, acetone); IR (film): $\tilde{\nu}_{max}$ = 3436, 2955, 2919, 1731, 1713, 1661, 1642, 1602, 1578, 1531, 1502, 1478, 1455, 1378, 1320, 1296, 1267, 1237, 1208, 1161, 1049, 967, 926, 850 cm^{-1}; ^{1}H NMR (600 MHz, [D$_6$]acetone): δ = 9.39 (bd, J = 10.1 Hz, 1H), 8.01–7.99 (m, 2H), 7.51 (dd, J = 7.9, 7.9 Hz, 1H), 7.24–7.21 (m, 2H), 7.05 (d, J = 7.9 Hz, 1H), 6.91–6.87 (m, 2H), 5.39 (dt, J = 14.5, 7.3 Hz, 1H), 5.02 (m, 1H), 4.29–4.26 (m, 1H), 4.01–3.99 (m, 1H), 3.54–3.52 (m, 2H), 3.20 (d, J = 3.1 Hz, 1H), 3.14 (dd, J = 12.9, 8.5, Hz, 1H), 2.14–2.03 (m, 3H), 1.99 (s, 3H), 1.81–1.74 (m, 2H), 1.70–1.64 (m, 7H), 1.55–1.41 ppm (m, 2H); ^{13}C NMR (150 MHz, [D$_6$]acetone): δ = 170.4, 166.3, 164.7, 163.3, 160.9, 158.0, 144.4, 135.9, 131.5, 130.8 (two peaks), 127.7, 125.8, 116.8, 116.1, 116.0, 113.3, 110.4, 106.1, 71.0, 70.8, 70.6, 67.9, 40.6, 39.0, 38.5, 37.3, 35.5, 26.0, 25.4, 21.2 ppm; HRMS (MALDI-FTMS) for $C_{30}H_{34}FNO_8$ [M + Na$^+$] calcd 578.2161, found 578.2168.

Apicularen analogue 37: 41% yield; yellow oil: R_f = 0.13 (silica gel, EtOAc:hexanes, 4:1); $[\alpha]_D$ = +2.5 (c = 0.24, acetone); IR (film): $\tilde{\nu}_{max}$ = 3362, 2927, 2856, 1723, 1694, 1635, 1617, 1582, 1535, 1506, 1465, 1418, 1359, 1288, 1265, 1177, 1118, 1077, 1053, 953 cm^{-1}; ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 9.51 (bd, J = 10.3 Hz, 1H), 8.40 (s, 1H), 7.79 (dd, J = 3.7, 1.1 Hz, 1H), 7.72 (dd, J = 5.1, 1.1 Hz, 1H), 7.13 (dd, J = 5.1, 3.7, 1H), 7.10 (dd, J = 8.4, 7.3 Hz, 1H), 6.95 (dd, J = 14.3, 10.3 Hz, 1H), 6.77 (d, J = 8.4 Hz, 1H), 6.69 (d, J = 7.3 Hz, 1H), 5.48–5.44 (m, 1H), 5.37 (dt, J = 14.3, 7.4 Hz, 1H), 4.27–4.25 (m, 1H), 4.00–3.85 (m, 2H), 3.78 (d, J = 4.1 Hz, 1H), 3.35 (dd, J = 14.9, 9.7 Hz, 1H), 2.44–2.35 (m, 3H), 1.96–1.81 (m, 2H), 1.70–1.65 (m, 1H), 1.60–1.46 ppm (m, 3H); ^{13}C NMR (150 MHz, [D$_6$]acetone): δ = 169.3, 159.3, 154.2, 140.5, 140.2, 131.9, 130.2, 128.9, 128.6, 126.1, 125.5, 122.2, 114.4, 108.8, 74.0, 73.8, 67.8, 64.8, 40.2, 39.9,

39.5, 38.9, 36.3 ppm; HRMS (MALDI-FTMS) for $C_{23}H_{25}NO_6S$ [M + Na^+] calcd 466.1295, found 466.1282.

Compound 37a: 43% yield; light yellow oil: R_f=0.39 (silica gel, hexanes: EtOAc, 2:1); $[\alpha]_D$=−54.4 (c=0.16, acetone); IR (film): $\tilde{\nu}_{max}$=3476, 3346, 2954, 2918, 2859, 1729, 1652, 1634, 1605, 1575, 1533, 1474, 1379, 1355, 1320, 1296, 1248, 1076, 1041, 958, 928, 833, 774, 726 cm^{-1}; ^1H NMR (600 MHz, [D$_6$]acetone): δ=9.44 (bd, J=10.1 Hz, 1H), 7.76–7.71 (m, 2H), 7.54 (dd, J=8.3, 7.4 Hz, 1H), 7.14–7.13 (m, 1H), 7.09 (d, J=7.4 Hz, 1H), 6.90 (d, J=8.3 Hz, 1H), 6.86 (dd, J=14.5, 10.1 Hz, 1H), 5.34 (dt, J=14.5, 6.7 Hz, 1H), 5.03–4.98 (m, 1H), 4.24–4.20 (m, 1H), 3.94–3.91 (m, 1H), 3.57–3.53 (m, 1H), 3.41–3.37 (m, 1H), 3.19 (dd, J=12.7, 8.3 Hz, 1H), 2.21–2.01 (m, 3H), 1.99 (s, 3H), 1.86–1.75 (m, 2H), 1.70–1.64 (m, 7H), 1.51–1.41 (m, 2H), 0.85 (s, 9H), −0.03 (s, 3H), −0.04 (s, 3H); ^{13}C NMR (150 MHz, [D$_6$]acetone): δ=170.4, 160.8, 159.2, 157.8, 144.5, 140.5, 135.8, 131.8, 128.8, 128.6, 127.9, 125.7, 116.6, 113.4, 109.6, 105.8, 70.4, 70.0, 68.5, 68.0, 40.5, 39.3, 37.5, 37.4, 35.5, 26.3, 26.2, 25.0, 21.2, 18.5, −4.4, −4.6; HRMS (MALDI-FTMS) for $C_{34}H_{47}NO_8SSi$ [M + Na^+] calcd 680.2684, found 680.2681.

Compound 37b: 74% yield; yellow oil: R_f=0.13 (silica gel, 1:1 hexanes: EtOAc); $[\alpha]_D$=−50.6 (c=0.17, acetone); IR (film): $\tilde{\nu}_{max}$=3409, 2927, 2845, 1729, 1711, 1682, 1635, 1606, 1582, 1535, 1506, 1470, 1447, 1418, 1376, 1359, 1318, 1294, 1271, 1241, 1206, 1047 cm^{-1}; ^1H NMR (600 MHz, [D$_6$]acetone): δ=9.36 (bd, J=10.1 Hz, 1H), 7.78–7.71 (m, 2H), 7.51 (dd, J=7.9, 7.4 Hz, 1H), 7.14 (dd, J=5.0, 3.7 Hz, 1H), 7.05 (d, J=7.4 Hz, 1H), 6.90 (d, J=7.9 Hz, 1H), 6.83 (dd, J=14.5, 10.1 Hz, 1H), 5.33 (dt, J=14.5, 7.4 Hz, 1H), 5.05–5.00 (m, 1H), 4.28–4.25 (m, 1H), 4.02–3.98 (m, 1H), 3.54–3.52 (m, 2H), 3.20 (d, J=3.5 Hz, 1H), 3.14 (dd, J=12.9, 8.5 Hz, 1H), 2.14–2.03 (m, 3H), 1.99 (s, 3H), 1.81–1.73 (m, 2H), 1.70–1.66 (m, 7H), 1.52 (ddd, J=14.5, 4.6, 4.6 Hz, 1H), 1.44 ppm (ddd, J=12.8, 9.6, 9.5 Hz, 1H); ^{13}C NMR (150 MHz, [D$_6$]acetone): δ=170.4, 160.9, 159.2, 158.0, 144.4, 140.5, 135.9, 131.9, 128.8, 128.6, 127.7, 125.3, 116.8, 113.3, 110.2, 106.1, 70.9, 70.8, 70.5, 67.9, 40.6, 39.0, 38.4, 37.3, 35.4, 26.0, 25.4, 21.2 ppm; HRMS (MALDI-FTMS) for $C_{28}H_{33}NO_8S$ [M + Na^+] calcd 566.1819, found 566.1809.

Apicularen analogue 38: 57% yield; colorless oil: R_f=0.25 (silica gel, hexanes:EtOAc, 5:95); $[\alpha]_D$=−21.8 (c=0.11, acetone); IR (film): $\tilde{\nu}_{max}$= 3307, 3248, 2919, 2848, 1701, 1648, 1607, 1590, 1542, 1460, 1290, 1219, 1114, 1078 cm^{-1}; ^1H NMR (500 MHz, [D$_6$]acetone): δ=9.14 (d, J=10.3 Hz, 1H), 8.38 (s, 1H), 7.73 (d, J=15.4 Hz, 1H), 7.53 (d, J=4.7 Hz, 1H), 7.36 (d, J=3.7 Hz, 1H), 7.15–7.07 (m, 2H), 6.94 (dd, J=13.6, 10.7 Hz, 1H), 6.77 (d, J=8.1 Hz, 1H), 6.69 (d, J=7.7 Hz, 1H), 6.43 (d, J=15.4 Hz, 1H), 5.47–5.40 (m, 1H), 5.32 (dt, J=14.3, 7.3 Hz, 1H), 4.32–4.20 (m, 1H), 4.03–3.94 (m, 1H), 3.92–3.84 (m, 1H), 3.75 (d, J=4.0 Hz, 1H), 3.34 (dd, J=14.7, 10.3 Hz, 1H), 2.44 (d, J=14.7 Hz, 1H), 2.36 (t, J=6.8 Hz, 2H), 1.97–1.81 (m, 2H), 1.73–1.65 (m, 1H), 1.61–1.44 ppm (m, 3H); ^{13}C NMR (150 MHz, [D$_6$]acetone): δ=169.1, 162.7, 154.2, 140.9, 140.1, 134.1, 131.4, 130.4, 128.8, 128.4, 126.3, 125.3, 122.1, 120.6, 114.3, 108.3, 74.2, 73.5, 67.9, 64.8, 40.2, 39.8, 39.5, 38.7, 36.2 ppm; HRMS (MALDI-FTMS) for $C_{25}H_{27}NO_6S$ [M + Na^+] calcd 492.1451, found 492.1429.

Compound 38a: 41% yield; colorless oil: R_f=0.20 (silica gel, hexanes: EtOAc, 7:3); $[\alpha]_D$=−113.2 (c=0.23, acetone); IR (film): $\tilde{\nu}_{max}$=3270, 2954, 2919, 1860, 1725, 1707, 1660, 1613, 1584, 1537, 1454, 1366, 1237, 1084, 967, 831, 773 cm^{-1}; ^1H NMR (500 MHz, [D$_6$]acetone): δ=9.11 (d, J=10.3 Hz, 1H), 7.75 (d, J=15.4 Hz, 1H), 7.57–7.50 (m, 2H), 7.38–7.34 (m, 1H), 7.13–7.05 (m, 2H), 6.91 (dd, J=8.5, 1.1 Hz, 1H), 6.82 (bdd, J= 14.3, 10.7 Hz, 1H), 6.41 (d, J=15.4 Hz, 1H), 5.21 (dt, J=14.3, 7.0 Hz, 1H), 5.06–4.98 (m, 1H), 4.25–4.17 (m, 1H), 3.96–3.88 (m, 1H), 3.54–3.46 (m, 1H), 3.42 (dd, J=12.9, 3.7 Hz, 1H), 3.16 (dd, J=12.8, 8.4 Hz, 1H), 2.19–2.03 (m, 3H), 2.00 (s, 3H), 1.87–1.82 (m, 1H), 1.79–1.75 (m, 1H), 1.71–1.66 (m, 7H), 1.50–1.35 (m, 2H), 0.85 (s, 9H), −0.08 ppm (s, 6H); ^{13}C NMR (125 MHz, [D$_6$]acetone): δ=170.3, 162.5, 160.6, 157.7, 144.5, 140.9, 135.7, 134.0, 131.3, 128.9, 128.4, 127.8, 125.8, 120.6, 116.5, 113.3, 109.2, 105.7, 70.3, 70.0, 68.3, 67.9, 40.4, 39.5, 37.3 (two peaks), 35.3, 26.3, 26.1, 24.9, 21.1, 18.5, −4.5, −4.6 ppm; HRMS (MALDI-FTMS) for $C_{36}H_{49}NO_8SSi$ [M + Na^+] calcd 706.2840, found 706.2831.

Apicularen analogue 39: 20% yield; colorless oil: R_f=0.70 (silica gel, hexane:EtOAc, 5:95); $[\alpha]_D$=−23.6 (c=0.11, acetone); IR (film): $\tilde{\nu}_{max}$= 3318, 3107, 2954, 2895, 1707, 1642, 1607, 1584, 1460, 1413, 1290, 1243, 1119, 1072, 967 cm^{-1}; ^1H NMR (600 MHz, [D$_6$]acetone): δ=9.16 (d, J= 10.1 Hz, 1H), 8.46 (s, 1H), 7.73 (d, J=15.3 Hz, 1H), 7.53 (d, J=4.8 Hz, 1H), 7.36 (d, J=3.1 Hz, 1H), 7.15–7.08 (m, 2H), 6.94 (dd, J=14.5, 10.6 Hz, 1H), 6.79 (d, J=7.9 Hz, 1H), 6.71 (d, J=7.5 Hz, 1H), 6.42 (d, J= 15.3 Hz, 1H), 5.51–5.43 (m, 1H), 5.31 (dt, J=14.5, 7.4 Hz, 1H), 5.04–4.96 (m, 1H), 4.30–4.22 (m, 1H), 3.98–3.90 (m, 1H), 3.35 (dd, J=14.5, 10.6 Hz, 1H), 2.45 (d, J=14.5 Hz, 1H), 2.41–2.34 (m, 2H), 2.06–1.94 (m, 2H), 2.00 (s, 3H), 1.87–1.74 (m, 2H), 1.66–1.61 ppm (m, 2H); ^{13}C NMR (150 MHz, [D$_6$]acetone): δ=170.2, 169.7, 162.6, 154.1, 140.7, 139.8, 134.1, 131.4, 130.3, 128.9, 128.4, 126.4, 125.4, 122.1, 120.6, 114.4, 108.2, 74.0, 73.6, 68.5, 67.2, 39.2, 38.9, 36.2, 36.1, 35.0, 21.1 ppm; HRMS (MALDI-FTMS) for $C_{27}H_{29}NO_7S$ [M + Na^+] calcd 534.1557, found 534.1567.

Apicularen analogue 40: 59% yield; light yellow oil: R_f=0.13 (4:1 EtOAc:hexanes); $[\alpha]_D$=+2.2 (c=0.09, acetone); IR (film): $\tilde{\nu}_{max}$=3366, 2954, 2919, 2849, 1731, 1713, 1696, 1660, 1643, 1613, 1584, 1555, 1537, 1519, 1455, 1373, 1360, 1284, 1261, 1108, 1261, 1108, 1091, 1078, 961, 797 cm^{-1}; ^1H NMR (600 MHz, [D$_6$]acetone): δ=8.85 (bd, J=10.6 Hz, 1H), 8.37 (s, 1H), 7.09 (d, J=7.9, 7.4 Hz, 1H), 6.80 (dd, J=14.5, 10.6 Hz, 1H), 6.76 (d, J=7.9 Hz, 1H), 6.69 (d, J=7.4 Hz, 1H), 5.42–5.37 (m, 1H), 5.17 (dt, J=14.5, 7.2 Hz, 1H), 4.26–4.21 (m, 1H), 4.00–3.78 (m, 3H), 3.33 (dd, J=14.5, 10.1 Hz, 1H), 2.44–2.30 (m, 3H), 2.18 (t, J=7.4 Hz, 2H), 1.95–1.79 (m, 2H), 1.69–1.45 (m, 6H), 1.33–1.24 (m, 4H), 0.87 ppm (t, J=7.0 Hz, 3H); ^{13}C NMR (150 MHz, [D$_6$]acetone): δ=170.4, 169.3, 154.2, 140.2, 130.2, 126.4, 125.5, 122.2, 114.4, 106.8, 74.3, 73.7, 67.9, 64.9, 40.2, 39.9, 39.5, 38.9, 36.4, 36.2, 32.1, 25.8, 23.0, 14.2 ppm; HRMS (MALDI-FTMS) for $C_{24}H_{33}NO_6$ [M + Na^+] calcd 454.2200, found 454.2207.

Compound 40a: 50% yield; light yellow oil: R_f=0.38 (silica gel, hexanes: EtOAc, 2:1); $[\alpha]_D$=−60.0 (c=0.11, acetone); IR (film): $\tilde{\nu}_{max}$=2955, 2931, 2861, 1731, 1713, 1661, 1643, 1608, 1584, 1537, 1519, 1472, 1455, 1378, 1314, 1298, 1249, 1079, 1044, 961, 838, 808, 779 cm^{-1}; ^1H NMR (500 MHz, [D$_6$]acetone): δ=8.81 (bd, J=10.3 Hz, 1H), 7.53 (dd, J=8.1, 7.7 Hz, 1H), 7.07 (dd, J=7.5, 1.1 Hz, 1H), 6.89 (dd, J=8.1, 1.1 Hz, 1H), 6.69 (dd, J=14.5, 10.3 Hz, 1H), 5.08 (dt, J=14.5, 6.8 Hz, 1H), 5.03–4.98 (m, 1H), 4.20–3.82 (m, 2H), 3.49–3.38 (m, 2H), 3.15 (dd, J=12.8, 8.4 Hz, 1H), 2.17 (t, J=7.3 Hz, 2H), 2.14–2.02 (m, 3H), 1.99 (s, 3H), 1.84–1.73 (m, 2H), 1.69–1.65 (m, 7H), 1.59 (quin, J=7.3 Hz, 2H), 1.47–1.39 (m, 2H), 1.31–1.26 (m, 4H), 0.89–0.86 (m, 3H), 0.83 (s, 9H), −0.06 ppm (s, 6H); ^{13}C NMR (125 MHz, [D$_6$]acetone): δ=170.4, 170.3, 160.7, 157.8, 144.6, 135.8, 127.9, 125.9, 116.6, 113.4, 107.7, 105.8, 70.4, 70.1, 68.4, 68.0, 40.4, 39.6, 37.4, 37.3, 36.5, 35.4, 32.1, 26.4, 26.2, 25.9, 25.0, 23.1, 21.2, 18.5, 14.2, −4.4, −4.5; HRMS (MALDI-FTMS) for $C_{35}H_{55}NO_8Si$ [M + Na^+] calcd 668.3589, found 668.3572.

Compound 40b: 47% yield; light yellow oil: R_f=0.19 (silica gel, hexanes: EtOAc, 1:1); $[\alpha]_D$=−45.9 (c=0.17, acetone); IR (film): $\tilde{\nu}_{max}$=3354, 2955, 2929, 2861, 1731, 1713, 1661, 1643, 1608, 1584, 1537, 1519, 1478, 1449, 1378, 1308, 1296, 1261, 1243, 1044, 961, 926, 814 cm^{-1}; ^1H NMR (600 MHz, [D$_6$]acetone): δ=8.73 (bd, J=10.1 Hz, 1H), 7.50 (dd, J=7.9, 7.4 Hz, 1H), 7.04 (d, J=7.4 Hz, 1H), 6.90 (d, J=7.9 Hz, 1H), 6.67 (dd, J= 14.3, 10.1 Hz, 1H), 5.08 (dt, J=14.3, 7.2 Hz, 1H), 5.04–4.99 (m, 1H), 4.27–3.97 (m, 2H), 3.53 (dd, J=12.7, 3.5 Hz, 1H), 3.49–3.42 (m, 1H), 3.13–3.10 (m, 2H), 2.16 (t, J=7.4 Hz, 2H), 2.05–2.01 (m, 3H), 1.99 (s, 3H), 1.80–1.71 (m, 2H), 1.69–1.67 (m, 7H), 1.58 (quin, J=7.4 Hz, 2H), 1.50–1.41 (m, 2H), 1.33–1.24 (m, 4H), 0.87 ppm (t, J=6.8 Hz, 3H); ^{13}C NMR (150 MHz, [D$_6$]acetone): δ=170.4, 170.3, 160.9, 158.0, 144.4, 135.9, 127.7, 125.6, 116.8, 113.3, 108.8, 106.0, 71.0, 70.8, 70.6, 67.8, 40.5, 39.0, 38.4, 37.3, 36.4, 35.4, 32.1, 26.1, 25.8, 25.4, 23.0, 21.2, 14.2 ppm; HRMS (MALDI-FTMS) for $C_{29}H_{41}NO_8$ [M + Na^+] calcd 554.2724, found 554.2732.

Apicularen analogue 41: 47% yield; white solid: R_f=0.14 (silica gel, EtOAc:hexanes, 4:1); $[\alpha]_D$=−3.2 (c=0.19, acetone); IR (film): $\tilde{\nu}_{max}$= 3366, 2955, 2919, 2861, 1725, 1713, 1696, 1643, 1590, 1537, 1514, 1461, 1367, 1284, 1261, 1208, 1120, 1079, 1026, 803 cm^{-1}; ^1H NMR (600 MHz, [D$_6$]acetone): δ=9.08 (bd, J=10.1 Hz, 1H), 8.37 (bs, 1H), 7.58–7.54 (m, 1H), 7.09 (dd, J=8.3, 7.4 Hz, 1H), 6.90–6.83 (m, 2H), 6.76 (d, J=8.3 Hz, 1H), 6.68 (d, J=7.4 Hz, 1H), 5.82–5.78 (m, 1H), 5.73 (d, J=11.4 Hz, 1H), 5.43–5.40 (m, 1H), 5.24 (dt, J=14.5, 7.4 Hz, 1H), 4.27–4.23 (m, 1H), 4.01–3.95 (m, 1H), 3.88–3.84 (m, 1H), 3.76 (bd, J=4.0 Hz, 1H), 3.33 (dd, J=14.7, 9.8 Hz, 1H), 2.42 (d, J=14.9 Hz, 1H), 2.34–2.22 (m, 4H), 1.93–1.79 (m, 2H), 1.69–1.65 (m, 1H), 1.58–1.39 (m, 5H), 0.90 ppm (t, J=7.4 Hz, 3H); ^{13}C NMR (150 MHz, [D$_6$]acetone): δ=169.3, 163.6, 154.3, 140.2, 139.8, 136.9, 130.2, 126.3, 126.2, 125.5, 122.3, 120.8, 114.4, 108.0, 74.2, 73.7, 68.0, 64.9, 40.3, 39.9 (two peaks), 38.9, 36.4, 29.7, 23.3,

13.9 ppm; HRMS (MALDI-FTMS) for $C_{26}H_{33}NO_6$ [M + Na^+] calcd 478.2200, found 478.2200.

Compound 41a: 50% yield; colorless oil: R_f=0.26 (silica gel, hexanes: EtOAc, 2:1); $[\alpha]_D$=−72.3 (c=0.39, acetone); IR (film): $\tilde{\nu}_{max}$=3457, 3316, 2952, 2917, 2858, 1736, 1653, 1606, 1583, 1518, 1477, 1454, 1371, 1295, 1242, 1078, 1054, 954, 931, 837, 778 cm^{-1}; ^1H NMR (500 MHz, [D_6]acetone): δ=9.05 (bd, J=10.3 Hz, 1H), 7.60–7.52 (m, 2H), 7.08 (d, J=7.7 Hz, 1H), 6.89 (d, J=8.1 Hz, 1H), 6.85 (dd, J=11.6, 11.4 Hz, 1H), 6.77 (dd, J=14.3, 10.3 Hz, 1H), 5.82–5.77 (m, 1H), 5.73 (d, J=11.4 Hz, 1H), 5.15 (dt, J=14.3, 7.3 Hz, 1H), 5.04–4.98 (m, 1H), 4.21–4.17 (m, 1H), 3.93–3.88 (m, 1H), 3.51–3.46 (m, 1H), 3.43–3.40 (m, 1H), 3.15 (dd, J=12.8, 8.4 Hz, 1H), 2.28–2.21 (m, 2H), 2.16–2.03 (m, 3H), 1.99 (s, 3H), 1.84–1.74 (m, 2H), 1.69–1.65 (m, 7H), 1.49–1.39 (m, 4H), 0.91 (t, J=7.3 Hz, 3H), 0.83 (s, 9H), −0.06 ppm (s, 6H); ^{13}C NMR (125 MHz, [D_6]acetone): δ=170.4, 163.5, 160.7, 157.8, 144.6, 139.7, 136.8, 135.8, 127.9, 126.2, 125.8, 120.9, 116.6, 113.4, 108.8, 105.8, 70.4, 70.0, 68.5, 68.0, 40.5, 39.5 (two peaks), 37.5, 35.4, 29.7, 26.3, 26.2, 25.0, 23.3, 21.2, 18.5, 13.9, −4.4, −4.5 ppm; HRMS (MALDI-FTMS) for $C_{37}H_{55}NO_8Si$ [M + Na^+] calcd 692.3589, found 692.3569.

Compound 41b: 39% yield; yellow oil: R_f=0.39 (silica gel, EtOAc:hexanes, 2:1); $[\alpha]_D$=−58.0 (c=0.15, acetone); IR (film): $\tilde{\nu}_{max}$=3413, 2955, 2919, 2861, 1731, 1643, 1608, 1519, 1478, 1449, 1373, 1296, 1243, 1208, 1044, 961, 926, 814, 779 cm^{-1}; ^1H NMR (500 MHz, [D_6]acetone): δ=8.98 (bd, J=10.3 Hz, 1H), 7.56 (dd, J=11.6, 11.5 Hz, 1H), 7.50 (dd, J=8.3, 7.5 Hz, 1H), 7.04 (dd, J=7.5, 1.0 Hz, 1H), 6.90 (dd, J=8.3, 1.0 Hz, 1H), 6.84 (ddd, J=11.7, 11.6, 1.1 Hz, 1H), 6.75 (dd, J=14.5, 10.3 Hz, 1H), 5.81–5.76 (m, 1H), 5.72 (d, J=11.7, 1H), 5.16 (dt, J=14.5, 7.4 Hz, 1H), 5.05–4.99 (m, 1H), 4.27–4.23 (m, 1H), 4.02–3.96 (m, 1H), 3.54 (dd, J=13.0, 3.5 Hz, 1H), 3.51–3.46 (m, 1H), 3.16 (d, J=3.7 Hz, 1H), 3.12 (dd, J=13.0, 8.6 Hz, 1H), 2.26–2.21 (m, 2H), 2.17–2.03 (m, 3H), 1.99 (s, 3H), 1.81–1.71 (m, 2H), 1.70–1.66 (m, 7H), 1.52–1.38 (m, 4H), 0.90 ppm (t, J=7.4 Hz, 3H); ^{13}C NMR (125 MHz, [D_6]acetone): δ=170.4, 163.5, 160.9, 158.0, 144.4, 139.7, 136.8, 135.9, 127.7, 126.2, 125.5, 120.9, 116.8, 113.3, 109.2, 106.0, 70.9, 70.8, 70.6, 67.8, 40.5, 39.0, 38.5, 37.3, 35.4, 29.7, 26.1, 25.4, 23.3, 21.2, 13.9 ppm; HRMS (MALDI-FTMS) for $C_{31}H_{41}NO_8$ [M + Na^+] calcd 578.2724, found 578.2708.

Apicularen analogue 42: 24% yield; colorless oil: ^1H NMR (500 MHz, [D_6]acetone): δ=9.52 (bd, J=8.1 Hz, 1H), 8.42 (bs, 1H), 7.09 (J=8.5, 7.7 Hz, 1H), 6.90–6.79 (m, 3H), 6.76 (d, J=8.5 Hz, 1H), 6.69 (d, J=7.7 Hz, 1H), 5.45–5.39 (m, 2H), 4.28–4.19 (m, 1H), 4.01–3.84 (m, 2H), 3.76 (d, J=4.4 Hz, 1H), 3.32 (dd, J=14.0, 9.6 Hz, 1H), 2.44–2.33 (m, 3H), 1.93–1.80 (m, 2H), 1.69–1.46 ppm (m, 4H); HRMS (MALDI-FTMS) for $C_{22}H_{24}F_3NO_6$ [M + Na^+] calcd 478.1448, found 478.1450.

Compound 42a: 36% yield; colorless oil: R_f=0.28 (silica gel, hexanes: EtOAc, 2:1); $[\alpha]_D$=−55.0 (c=0.22, acetone); IR (film): $\tilde{\nu}_{max}$=3281, 2929, 2858, 1736, 1695, 1653, 1577, 1542, 1477, 1448, 1342, 1307, 1248, 1136, 1078, 1054, 966, 837, 778 cm^{-1}; ^1H NMR (600 MHz, [D_6]acetone): δ=9.45 (bd, J=9.6 Hz, 1H), 7.53 (dd, J=8.3, 7.4 Hz, 1H), 7.08 (d, J=7.4 Hz, 1H), 6.90 (d, J=8.3 Hz, 1H), 6.85–6.74 (m, 3H), 5.32 (dt, J=14.0, 7.3 Hz, 1H), 5.00 (m, 1H), 4.20 (m, 1H), 3.92 (m, 1H), 3.52 (m, 1H), 3.40 (dd, J=12.8, 3.7 Hz, 1H), 3.17, (dd, J=12.8, 8.3 Hz, 1H), 2.19–2.10 (m, 2H), 2.05–2.02 (m, 1H), 1.99 (s, 3H), 1.88–1.83 (m, 1H), 1.76–1.74 (m, 1H), 1.69–1.65 (m, 7H), 1.48–1.41 (m, 2H), 0.84 (s, 9H), −0.05 (s, 3H), −0.06 ppm (s, 3H); ^{13}C NMR (150 MHz, [D_6]acetone): δ=170.3, 160.8, 159.7, 157.8, 144.6, 135.8, 132.8 (q, J=6.1), 127.9, 127.8 (q, J=34.6), 125.1, 121.7, 116.6, 113.4, 112.1, 105.9, 70.4, 69.9, 68.4, 68.0, 40.5, 39.5, 37.4, 37.2, 35.5, 26.4, 26.2, 25.0, 21.2, 18.5, −4.4, −4.5 ppm; HRMS (MALDI-FTMS) for $C_{33}H_{46}F_3NO_8Si$ [M + Na^+] calcd 692.2837, found 692.2812.

Compound 42b: 44% yield; colorless oil: R_f=0.36 (silica gel, EtOAc: hexanes, 2:1); $[\alpha]_D$=−70.0 (c=0.14, acetone); IR (film): $\tilde{\nu}_{max}$=3401, 2931, 1731, 1713, 1696, 1661, 1649, 1608, 1584, 1537, 1478, 1455, 1378, 1349, 1308, 1267, 1138, 1055, 967, 808, 785 cm^{-1}; ^1H NMR (600 MHz, [D_6]acetone): δ=9.41 (bd, J=9.6 Hz, 1H), 7.50 (dd, J=8.3, 7.4 Hz, 1H), 7.04 (d, J=7.4 Hz, 1H), 6.90 (d, J=8.3 Hz, 1H), 6.84–6.73 (m, 3H), 5.34 (dt, J=14.5, 7.4 Hz, 1H), 5.01 (m, 1H), 4.28–4.24 (m, 1H), 4.02–3.97 (m, 1H), 3.54–3.49 (m, 2H), 3.22 (d, J=3.5 Hz, 1H), 3.13 (dd, J=12.9, 8.6 Hz, 1H), 2.13–2.03 (m, 3H), 1.99 (s, 3H), 1.80–1.73 (m, 2H), 1.69–1.67 (m, 7H), 1.52–1.41 ppm (m, 2H); ^{13}C NMR (150 MHz, [D_6]acetone): δ=170.4, 160.9, 159.7, 158.0, 144.4, 135.9, 132.8 (q, J=6.1), 127.8 (q, J=34.2), 127.7, 124.8, 121.7, 116.8, 113.3, 112.4, 106.0, 70.9, 70.6, 70.5, 67.8, 40.6, 39.1, 38.2, 37.3, 35.4, 26.0, 25.4, 21.2 ppm; HRMS (MALDI-FTMS) for $C_{27}H_{32}F_3NO_8$ [M + Na^+] calcd 578.1972, found 578.1957.

Compound 43: 65% yield; yellow oil: R_f=0.30 (silica gel, hexanes: EtOAc, 3:7), $[\alpha]_D$=−64.6 (c=0.15, acetone); IR (film): $\tilde{\nu}_{max}$=3471, 3283, 2931, 2860, 1731, 1707, 1648, 1607, 1584, 1531, 1478, 1443, 1290, 1237, 1043, 961 cm^{-1}; ^1H NMR (500 MHz, [D_6]acetone): δ=9.11 (d, J=10.3 Hz, 1H), 7.74 (d, J=15.4 Hz, 1H), 7.55–7.48 (m, 2H), 7.35 (d, J=3.3 Hz, 1H), 7.10 (dd, J=4.8, 3.3 Hz, 1H), 7.05 (dd, J=7.7, 1.1 Hz, 1H), 6.90 (dd, J=8.5, 1.1 Hz, 1H), 6.81 (bdd, J=14.3, 10.7 Hz, 1H), 6.42 (d, J=15.4 Hz, 1H), 5.24 (dt, J=14.3, 7.4 Hz, 1H), 5.07–4.99 (m, 1H), 4.32–4.24 (m, 1H), 4.04–3.96 (m, 1H), 3.54 (dd, J=13.2, 3.7 Hz, 1H), 3.52–3.47 (m, 1H), 3.22 (d, J=3.3 Hz, 1H), 3.14 (dd, J=12.9, 8.8 Hz, 1H), 2.12–2.03 (m, 3H), 2.00 (s, 3H), 1.85–1.75 (m, 2H), 1.71–1.68 (m, 7H),1.54–1.42 ppm (m, 2H); ^{13}C NMR (125 MHz, [D_6]acetone): δ=170.3, 162.6, 160.8, 157.9, 144.3, 140.9, 135.8, 134.0, 131.3, 128.9, 128.4, 127.6, 125.6, 120.6, 116.7, 113.2, 109.6, 105.9, 70.8, 70.6, 70.4, 67.7, 40.4, 39.0, 38.3, 37.2, 35.3, 26.9, 25.3, 21.1 ppm; HRMS (MALDI-FTMS) for $C_{30}H_{35}NO_8S$ [M + Na^+] calcd 592.1975, found 592.1969.

Compound 44: 61% yield; yellow oil: R_f=0.40 (silica gel, hexanes: EtOAc, 2:3); $[\alpha]_D$=−66.2 (c=0.13, acetone); IR (film): $\tilde{\nu}_{max}$=3416, 1730, 1651, 1604, 1580, 1533, 1479, 1450, 1228, 1049 cm^{-1}; ^1H NMR (500 MHz, [D_6]acetone): δ=9.10 (d, J=10.5 Hz, 1H), 7.63–7.56 (m, 3H), 7.51 (dd, J=8.1, 7.7 Hz, 1H), 7.44–7.36 (m, 3H), 7.05 (dd, J=7.7, 1.1 Hz, 1H), 6.91 (dd, J=8.5, 1.1 Hz, 1H), 6.83 (dd, J=14.3, 10.3 Hz, 1H), 6.67 (d, J=15.4 Hz, 1H), 5.24 (dt, J=14.3, 7.3 Hz, 1H), 5.10–4.97 (m, 1H), 4.27 (sext, J=5.2 Hz, 1H), 4.04–3.96 (m, 1H), 3.54 (dd, J=12.8, 3.7 Hz, 1H), 3.52–3.49 (m, 1H), 3.21 (d, J=3.3 Hz, 1H), 3.13 (dd, J=12.8, 8.8 Hz, 1H), 2.11–2.03 (m, 3H), 2.01 (s, 3H), 1.84–1.74 (m, 2H), 1.75–1.73 (m, 7H), 1.55–1.49 (m, 1H), 1.48–1.40 ppm (m, 1H); ^{13}C NMR (125 MHz, [D_6]acetone): δ=170.4, 162.9, 160.9, 158.0, 144.4, 141.4, 136.1, 135.9, 130.4, 129.7, 128.5, 127.7, 125.7, 122.0, 116.8, 113.3, 109.7, 106.1, 70.9, 70.7, 70.6, 67.9, 40.5, 39.1, 38.5, 37.3, 35.4, 26.1, 25.4, 21.2 ppm; HRMS (MALDI-FTMS) for $C_{32}H_{37}NO_8$ [M + Na^+] calcd 586.2411, found 586.2399.

Methyl ester 45a: To a solution of *cis*-2-hexene-1-ol (2 g, 20.0 mmol) in dichloromethane (40 mL) was added at 0°C, 4 Å MS (10 g), and NMO (3.5 g, 30.0 mmol). TPAP (351 mg, 1.00 mmol) was then added in one portion. The reaction mixture was stirred at 0°C for an additional 1 h to complete the formation of aldehyde. A separate flask was charged with bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl) phosphonate (4.22 mL, 20.0 mmol), THF (250 mL), [18]crown-6 (26.4 g, 100.0 mmol), and cooled to −78°C. After the mixture was stirred at −78°C for 10 min, KHMDS (0.5 M toluene solution, 40 mL, 20 mmol) was added dropwise to this second reaction mixture to form the phosphonate anion (0.5 h). The crude aldehyde solution was then added to the phosphonate solution and stirred for 20 min before quenching with saturated (aq) NH_4Cl (100 mL). The reaction mixture was allowed to warm to room temperature then extracted with ether (3×40 mL). The combined organic layer was then washed with brine (50 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The product was purified by flash column chromatography (silica) to yield methyl ester **45a** as a clear liquid (2.28 g, 74%). **45a**: R_f=0.58 (silica gel, hexanes:EtOAc, 9:1); IR (film): $\tilde{\nu}_{max}$=2955, 2872, 1719, 1631, 1590, 1443, 1367, 1226, 1173, 997, 826, 785 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.25 (dd, J=11.4, 11.4 Hz, 1H), 6.92 (ddd, J=11.7, 11.4, 1.1 Hz, 1H), 5.93–5.86 (m, 1H), 5.65 (d, J=11.7 Hz, 1H), 3.70 (s, 3H), 2.25–2.19 (m, 2H), 1.43 (sext, J=7.3 Hz, 2H), 0.90 ppm (t, J=7.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=167.0, 141.6, 139.2, 124.5, 116.8, 51.1, 29.5, 22.5, 13.7 ppm; MS (GC/MS) for $C_9H_{14}O_2$ [H^+] calcd 154, found 154.

Carboxylic acid 45b: To a solution of ester **45a** (816.7 mg, 5.296 mmol) in MeOH (50 mL) was added in one portion $Ba(OH)_2{\cdot}H_2O$ (11.0 g, 58.1 mmol) at room temperature. The reaction mixture was stirred for 20 h, and then quenched with a solution of 1 N (aq) HCl (100 mL). More of the (aq) HCl solution was added until the solid formed had completely dissolved giving a clear solution. The reaction mixture was extracted with ether (3×50 mL) and the combined organic layer was washed with brine (50 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The product was purified by flash column chromatography to yield a colorless oil (595 mg, 80%). **45b**: R_f=0.80 (silica gel, hexanes:EtOAc, 1:2); IR (film): $\tilde{\nu}_{max}$=2966, 2578, 1696, 1625, 1590, 1455, 1290, 1243, 1214, 938,

879, 832, 785, 673, 820 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.25$ (dd, $J = 11.6$, 11.4 Hz, 1H), 7.03 (dd, $J = 11.7$, 11.6 Hz, 1H), 5.95 (m, 1H), 5.67 (d, $J = 11.4$ Hz, 1H), 2.27–2.21 (m, 2H), 1.44 (sext, $J = 7.3$ Hz, 2H), 0.91 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 171.9$, 142.7, 141.3, 124.6, 116.4, 29.5, 22.5, 13.7 ppm; MS (GC/MS) for $C_8H_{12}O_2$ $[H^+]$ calcd 140, found 140.

Amide 45c: To a solution of carboxylic acid **45b** (333.1 mg, 2.376 mmol) in THF (40 mL) at 0°C was added triethylamine (0.36 mL, 2.583 mmol). Ethyl chloroformate (0.25 mL, 2.615 mmol) was added and the reaction mixture was stirred at 0°C for 30 min. The reaction mixture was then allowed to warm to room temperature and liquid ammonia (ammonia gas condensed using dry ice and acetone) was added and stirred for an additional 20 min. The reaction mixture was then stirred and allowed to warm to ambient temperature then concentrated in vacuo. The product was purified by column chromatography to yield a white solid (221.2 mg, 67%). **45c**: $R_f = 0.34$ (silica gel, hexanes:EtOAc, 1:2); IR (film): $\tilde{\nu}_{max} =$ 3389, 3190, 2955, 2872, 1649, 1608, 1455, 1378, 1320, 1267, 1226, 1002, 961, 908, 861, 826, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.25$–7.20 (m, 1H), 6.79 (ddd, $J = 11.6$, 11.4, 1.1 Hz, 1H), 5.85–5.80 (m, 1H), 5.72 (bs, 1H), 5.63 (d, $J = 11.4$ Hz, 1H), 5.52 (bs, 1H), 2.22–2.18 (m, 2H), 1.42 (sext, $J = 7.3$ Hz, 2H), 0.90 ppm (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 168.6$, 140.3, 136.4, 124.4, 119.2, 29.4, 22.5, 13.7 ppm; HRMS (MALDI-FTMS) for $C_8H_{13}NO$ $[M + H^+]$ calcd 140.1070, found 140.1070.

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