Synthesis and Biological Evaluation of Apicularen A Analogues

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Reactions between amide anions and propanal derivatives containing benzolactone components at their 3-positions produced hemiaminals, which were dehydrated via the corresponding acetates to provide the apicularen A analogues **21**, **29**, **34**, **38**, and **41**. Of these, **21** and **29** contain the intact enamide side chain of apicularen A but have modifications in the macrolactone core. On the other hand, compounds **34**, **38**, and **41** are characterized by the natural core structure but are modified in the enamide part. Biological studies showed that **21** and **29** are quite active but that the other three analogues show only minor activities. The 11-deoxy analogue **21** turned out to be the most active compound against a mdr cell line. It can be concluded that the macrolactone part of apicularen A will tolerate modifications to some degree, whereas the enamide part is rather sensitive towards structural modifications.

Natural products have proven indispensable for the discovery of novel targets relevant to the treatment of various diseases.[1] In addition, the rational selection of targets based on knowledge of biochemical and signal transduction pathways has become an interesting alternative.[2] In the case of antitumor compounds, the search for novel drug candidates generally starts with screening for cytotoxic activity of extracts obtained from natural sources. Compounds such as taxol or epothilone, for example, were discovered in this way. In recent years this classic approach has resulted in the discovery of several cytotoxic compounds that make up the family of the benzolactone enamides (Figure 1).[3] Prominent members of this family include apicularen A (**1**),[4] the salicylihalamides,[5] the oximidines,[6] and the lobatamides.[7] Even though these benzolactones have been isolated from various sources, their structures and modes of action share common features, as they each contain a macrocyclic salicylate ring with an enamide side chain.

Activity profiling of several benzolactone enamides revealed them to be potent inhibitors of mammalian vacuolar (H^+)-ATPases.[8] These protein pumps are located in various cellular membranes and move protons out of the cytoplasm (into lysosomes, for example). Thereby the pH is adjusted to around 5, which is optimal for hydrolytic enzymes. Further biochemical studies revealed that salicylihalamide binds to the V_o domain of the proton pump.[9] Salicylihalamide A ((*E*)-**2**), and probably also the other benzolactone

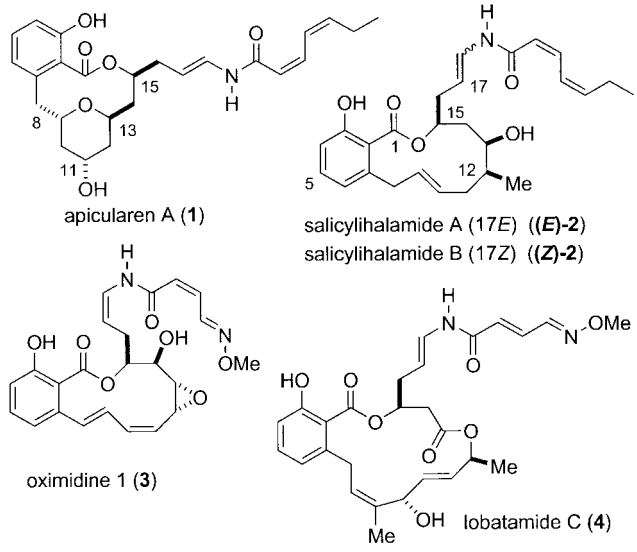

Figure 1. Structures of important benzolactone enamides.

enamides, are conditionally irreversible inhibitors of the ATPase, with the enamide having a central role in the inhibition process. It seems that the V-ATPase is covalently trapped by the iminium ion resulting from protonation of the enamide. Hydrolysis of this intermediate aminal derivative could then yield the three fragments **G**, **C**, and **F** (Figure 2).

Among the benzolactones, apicularen A (**1**) is unique in that it contains an ether bridge in the macrolactone ring. With regard to the pyran ring, the substituents extending to the macrolactone are in a *trans* orientation. The compound was isolated by the Höfle group from a myxobacteria strain and it shows very strong cytotoxic activity.[4] Feeding experiments showed apicularen A to be a polyke-

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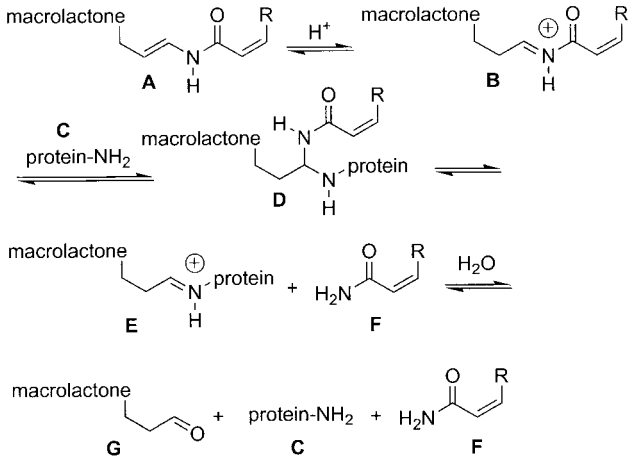


Figure 2. Possible role of the enamide part in the reversible inhibition of the V-ATPase protein.

tide assembled from eight acetates, and four total syntheses of apicularen A have so far been published.[10,11,12,13] Three of these syntheses proceed through a *trans* pyran (cf. **I**) containing the benzoic acid and the sector with the secondary alcohol as substituents. Subsequently, lactonization is achieved under basic conditions (Figure 3). The synthesis by our group first creates a 12-membered lactone ring (cf. **J**) followed by a transannular etherification reaction to afford the desired *trans* pyran ring with excellent selectivity (*trans*/*cis* = 25:1). That this reaction is indeed feasible was shown by us in an earlier model study.[14]

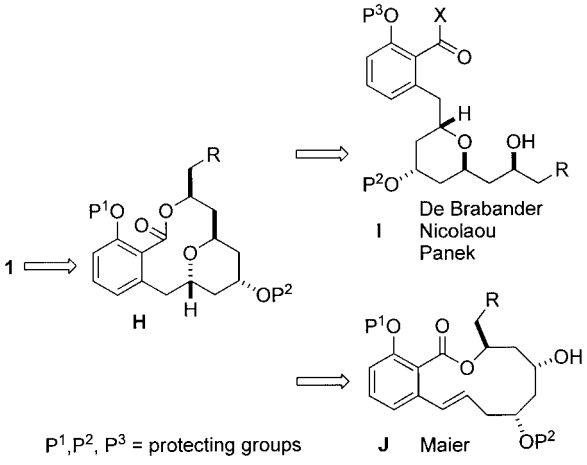


Figure 3. General strategies to reach the macrocyclic core of apicularen A.

In the total synthesis of apicularen A, three different strategies for the creation of the enamide part have been used. Thus, the enamide could be fashioned from an α,β-unsaturated carboxylic acid by Curtius rearrangement, followed by trapping of the intermediate vinyl isocyanate with an organometallic nucleophile.[10] This approach hinges upon the availability of a suitable nucleophile. Another method is based on a cross-coupling reaction between an amide and a vinyl iodide.[11,12] Our method generates the enamide from the *N*-acylated hemiaminal by dehydration.[15] The hemiaminal was in turn prepared by addition of the amide anion to the aldehyde. Finally, several groups have reported synthetic studies[16] or formal total syntheses of apicularen A. Rizzacasa's approach involves an acid-mediated transannular conjugate addition of a macrocyclic hydroxy enone,[17] whilst Rychnovsky's formal total synthesis employs an intramolecular Diels–Alder reaction on a functionalized *trans* pyran to create both the 10-membered macrocycle and the aromatic ring.[18,19]

With regard to structure/activity relationships, some analogues based on salicylihalamide A and apicularen A have been prepared; representative salicylihalamide analogues, together with activity data, are shown in Figure 4. A study by De Brabander et al. found that the enamide is important, but that modifications on the hexadienoyl fragment are tolerated up to a certain chain length.[20] Comparison of **6** and **7** shows that removal of the macrocyclic double bond has a detrimental effect; similar observations were made by Smith et al.[21] Thus, removal of the substituents and the endocyclic double bond attenuates the biological activity. The macrolactone ring seems to be important but not critical. A recent study by De Brabander introduced more dramatic changes in the aryl sector, the macrolactone part, and the acyl groups (Figure 4).[22] Thus, it seems that the salicylate is required for activity, an alkynoate in the side chain is more active than a comparable carbamate (cf. **8** and **9**), and the presence of the ether function in the macrolactone supports the notion that modifications in the aliphatic sector are tolerated.

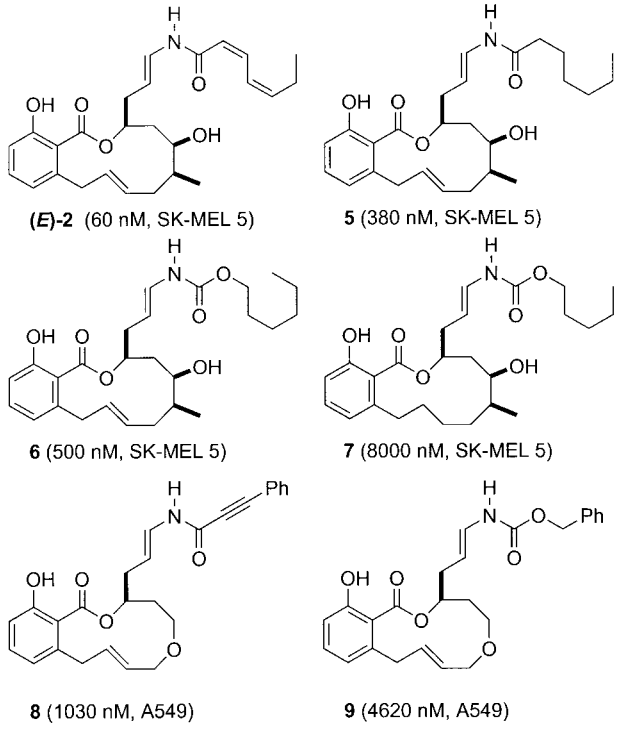


Figure 4. Cytostatic effects (IC_{50} values) of salicylihalamide and analogues. SK-MEL 5 is a melanoma cell line; A549 is a human non-small cell lung tumor cell line.

For apicularen A, fewer analogues have so far been published, although apicularen A is in general more potent than salicylihalamide if tested on the same cell line. Again, the acyl part of the enamide can be modified, but without the enamide there is no activity.[10] A study by Nicolaou et al. concurs closely with the observations mentioned above (Figure 5);[11b] variations in the acyl part of the enamide, for example, are tolerated provided that the acyl part is neither too short nor too long. Minor modifications in the macrolactone, such as acetylation of the 11-OH function, cause only a small loss of activity.

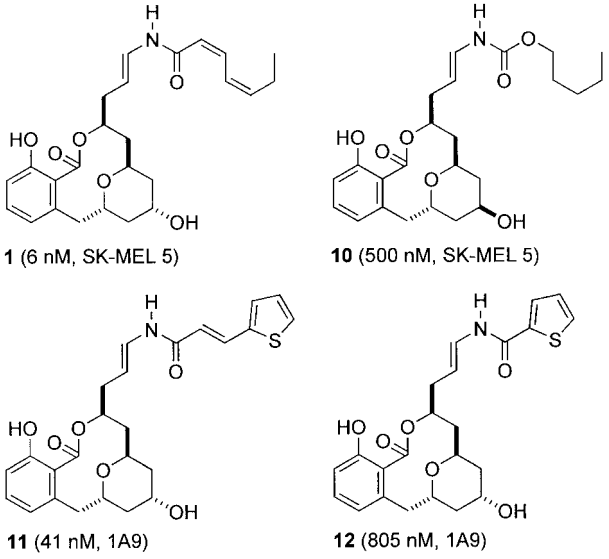
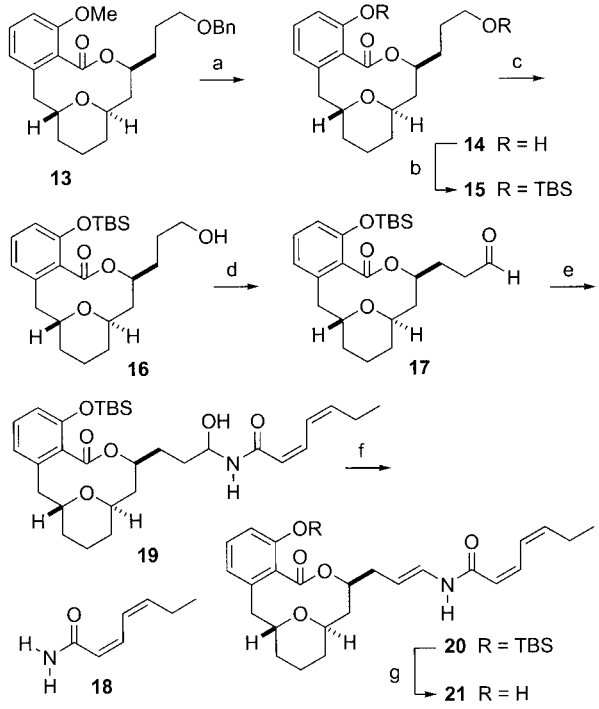


Figure 5. Cytostatic effects (IC_{50} values) of some apicularen A analogues. 1A9 is a human ovarian carcinoma cell line. The IC_{50} value of apicularen A in this cell line is 0.8 nM.

Since our total synthesis is rather distinct from other approaches, it offers the opportunity to prepare novel apicularen A analogues. In particular, analogues with a 12-membered macrolactone ring—that is, compounds lacking the transannular ether bridge—might be accessible. In addition, modifications in the acyl part of the enamide were considered. For the synthesis of various analogues the two macrolactone-substituted propanol derivatives **16** and **25**, emanating from our previous model study and the total synthesis project, were prepared, and these alcohols were then converted into enamides via the corresponding aldehydes by the established technology. In addition, the apicularen aldehyde **30** was extended to provide three different enamides.

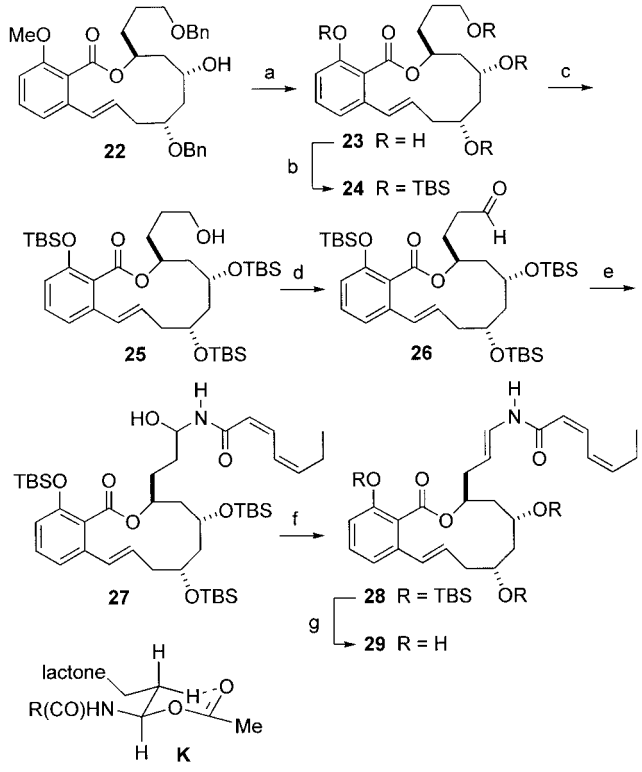
The synthesis of the analogue **21** (11-deoxy-api) is shown in Scheme 1. The macrolactone **13** was prepared as described previously.[14] Cleavage of the ether protecting groups with 9-iodo-9-borabicyclo[3.3.1]nonane provided the dihydroxylactone **14** in excellent yield.[23] Complete silylation gave the disilyl ether **15**, and subsequently the primary silyl ether was cleaved with catalytic amounts of scandium(III) triflate in wet acetonitrile.[24] Oxidation of the primary alcohol **16** with NMO in the presence of TPAP provided the aldehyde **17**, and the hemiaminal **19** was prepared by treatment of the aldehyde **17** with the anion of the heptadienamide[15] **18**. The hemiaminal was formed as a 1:1 mixture of diastereomers, and elimination of water to afford the desired enamides could be achieved by stirring the hemiaminals with acetic anhydride and pyridine, first at room temperature and then at reflux. The (*E*)-enamide **20** was the major isomer and was obtained pure by chromatography. The major isomer **20** was deprotected with TASF in DMF.[25] With TBAF in THF some isomerization of the (*Z*,*Z*)-heptadienamide to the corresponding (*E*,*Z*) isomer was observed.



Scheme 1. Synthesis of 11-deoxy-api (**21**) from the macrolactone **13**. a) 9-I-9-BBN (4 equiv.), CH_2Cl_2, 23 °C, 20 s, 92%; b) TBSCl (4 equiv.), imidazole (8 equiv.), DMAP (cat.), CH_2Cl_2, 23 °C, 16 h, 93%; c) $Sc(OTf)_3$ (0.5 mol%), H_2O (5 equiv.), CH_3CN, 23 °C, 1 h, 88%; d) NMO (1.5 equiv.), TPAP, (0.15 equiv.), CH_2Cl_2, 0 °C, 1 h, 95%; e) **18** (2.4 equiv.), DIBAL (2.1 equiv.), THF, 0 °C, 30 min, add **17**, 0 °C, 16 h, 92%; f) Ac_2O (15 equiv.), pyridine (30 equiv.), THF, 23 °C, 40 h, reflux, 48 h, 16% of (*Z*)-**20** and 53% of (*E*)-**20**; g) TASF (2.5 equiv.), DMF, 23 °C, 1 h, 92%. 9-I-9-BBN = 9-iodo-9-borabicyclo[3.3.1]nonane, DMAP = 4-(dimethylamino)pyridine, TPAP = tetra-*n*-propylammonium perruthenate, NMO = *N*-methylmorpholine *N*-oxide.

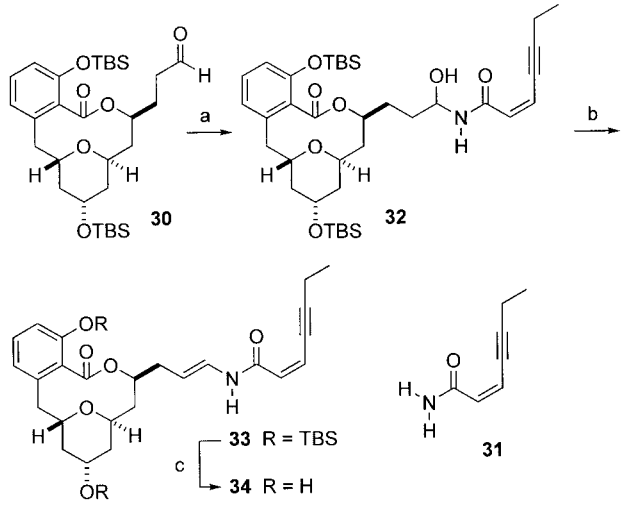
Analogue **29** (open-api) was obtained in a similar manner (Scheme 2). Alcohol **25** was prepared from the macrolactone **22**, an advanced intermediate in our total synthesis of apicularen A.[13] Complete ether cleavage of **22** by treatment with 9-I-9-BBN gave the very polar tetraol **23**. This compound was not isolated, but rather was directly silylated with an excess of *tert*-butyldimethylsilyl chloride in DMF. The yield for the two-step procedure was 68%. For the selective cleavage of the primary silyl ether, camphorsulfonic acid (CSA) in a mixture of dichloromethane/methanol proved to be suitable. The remainder of the sequence was more or less identical to that described above and involved oxidation to the aldehyde **26**, hemiaminal formation to pro-

vide **27**, dehydration, and deprotection to give the enamide **29**. In this and the other cases, the (*E*)-enamide was the major isomer. This is attributed to a pseudo-equatorial orientation of the macrolactone and amide substituents in the chair-like Chugaev elimination (cf. **K**). An alternative explanation for the observed (*E*) selectivity would be that the reaction proceeds via an intermediate acyliminium ion.



Scheme 2. Synthesis of open-api (**29**) from the 12-membered macrolactone **22**. a) 9-I-9-BBN (6 equiv.), CH_2Cl_2, 23 °C, 150 s; b) TBSCl (12 equiv.), imidazole (14 equiv.), DMAP (0.8 equiv.), DMF, 23 °C, 72 h, 68% from **22**; c) (±)-CSA (0.2 equiv.), CH_2Cl_2/MeOH (2:1), 0 °C, 3 h, 70%; d) NMO (1.5 equiv.), TPAP, (0.15 equiv.), CH_2Cl_2, 0 °C, 1 h, 98%; e) **18** (2.4 equiv.), DIBAL (2.1 equiv.), THF, 0 °C, 30 min, add **26**, 0 °C, 16 h, 57%; f) Ac_2O (15 equiv.), pyridine (30 equiv.), THF, 23 °C, 40 h, reflux, 48 h, 3% of (*Z*)-**28** and 38% of (*E*)-**28**; g) TASF (10 equiv.), DMF, 23 °C, 36 h, 64%.

In addition to the two analogues **21** and **29**, the apicularen aldehyde **30** was also converted into the enamide **34** by use of the enynamide[15] **31** (Scheme 3). In this case the yield for the enamide formation to **33** was moderate. Again, complete desilylation provided the analogue **34**.



Scheme 3. Synthesis of enyne-api (**34**) from the macrolactone aldehyde **30** and the enynamide **31**. a) **31** (2.4 equiv.), DIBAL (2.1 equiv.), THF, 0 °C, 30 min, add **30**, 0 °C, 16 h, 68%; b) Ac_2O (15 equiv.), pyridine (30 equiv.), THF, 23 °C, 40 h, reflux, 48 h, 9% of (*Z*)-**33** and 29% of (*E*)-**33**; c) TASF (5 equiv.), DMF, 23 °C, 21 h, 58%.

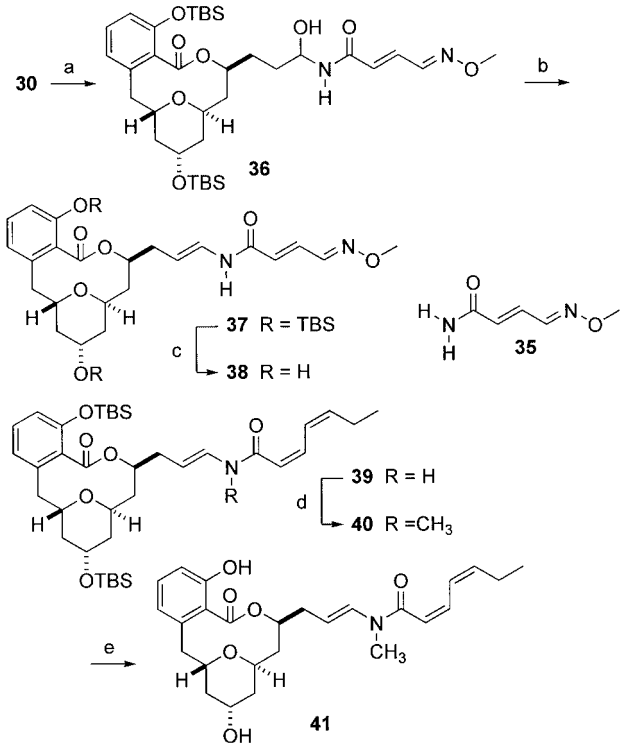
Since several of the benzolactone enamides, such as CJ-12,950, several lobatamides, YM-75518D, and oximidines contain an unsaturated amide that is terminated with an oxime ether, the amide[26] **35** was subjected to the hemiaminal formation with aldehyde **30**. In this case elimination of water from the hemiaminal **36** resulted in an almost 1:1 mixture of the (*Z*)- and (*E*)-enamides (Scheme 4). Here, the corresponding (*Z*)-amide (of compound **35**) was not available since it undergoes facile isomerization to the (*E*) isomer. Chromatographic separation of the enamide isomers and deprotection afforded oxime-api (**38**). Finally, the apicularen A precursor[13] **39** was methylated at the amide by treatment with NaH and methyl iodide in THF. NMR analysis showed this compound to be a mixture of rotamers. Deprotection of **40** with TASF furnished *N*-methyl apicularen A (**41**) as a mixture of rotamers.

Biological Studies

Apicularen A (**1**), salicylihalamide A ((***E*)-2**), and the analogues **21**, **29**, **34**, **38**, and **41** were then tested against various cell lines, and the corresponding IC_{50} values are listed in Table 1. In general it can be said that apicularen A (**1**) is

Table 1. Cytotoxicity values (IC_{50}, nM) of several benzolactone enamides.

Cell line	Origin	Species	api-A (**1**)	N-Me-api (**41**)	11-deoxy-api (**21**)	open-api (**29**)	oxime-api (**38**)	enyne-api (**34**)	sali A (**2-*E***)
L-929	connective tissue	mouse	6.8	770	19	200	1800	4550	57
Y1	connective tissue	rat	2.3	770	8.2	200	900	910	23
KB-3–1	cervix carcinoma	human	2.3	660	7.1	180	1130	1820	6.8
KB-V1	multiple drug-resistant cell line	human	15.9	1980	2.4	1360	9000	9100	9.1
KB-V1	mdr cell line + 11 μM verapamil	human	6.8	1100	3.5	910	4500	2730	6.8



Scheme 4. Synthesis of the apicularen analogues **38** and **41** containing the apicularen core structure but with different amide side chains. a) **35** (2.4 equiv.), DIBAL (2.1 equiv.), THF, 0 °C, 30 min, add **30**, 0 °C, 16 h, 82%; b) Ac_2O (15 equiv.), pyridine (30 equiv.), THF, 23 °C, 40 h, reflux, 48 h, 29% of (*Z*)-**37** and 37% of (*E*)-**37**; c) TASF (5 equiv.), DMF, 23 °C, 21 h, 75%; d) NaH (1.1 equiv.), THF, 0 °C, 1 h, add MeI (1.1 equiv.), 23 °C, 16 h, 80%; e) TASF (5 equiv.), DMF, 23 °C, 21 h, 75%.

the most active compound in the series, followed by 11-deoxy-api (**21**) and open-api (**29**). The other compounds [*N*-Me-api (**41**), oxime-api (**38**), and enyne-api (**34**)] are significantly less active. Salicylihalamide A ((***E*)-2**) turned out to be quite potent in the KB cell lines. The assay was also extended to the multiply drug-resistant cell line KB-V1, in which the P-glycoprotein (Pgp) transporter is overexpressed. In this case it is striking that 11-deoxy-api (**21**) is the most active compound. Thus, removal of the 11-hydroxy group seems to reduce affinity to the compound pump. The assay in the presence of verapamil reveals the affinity of the test compounds to the Pgp. Similar values indicate a low affinity.

Studies with living KB-3–1 cells and use of the acidotropic reagent LysoTracker Red DND-99 showed that all benzolactone enamides of Table 1 inhibited the acidification of lysosomes when given in amounts above the IC_{50} values.

Conclusions

As a general conclusion, it can be said that the macrocyclic ring does tolerate modifications to some degree, whereas even small modifications on the enamide reduce the activity significantly. The results show that the 11-OH is not responsible for cytotoxicity, whilst the THP ring in the macrolactone seems to be important. It was also found that removal of the 11-hydroxy group increases the biological activity against multiply drug-resistant cell lines. The sensitivity of the enamide binding site might be exploitable to steer benzolactone macrocycles to a completely different molecular target. Studies along these lines are currently underway in our laboratory.

Experimental Section

General: ^1H and ^{13}C NMR: Bruker Avance 400, spectra were recorded at 295 K in $CDCl_3$, C_6D_6, or [D_6]acetone; chemical shifts are calibrated to the residual proton and carbon resonance of the solvent: $CDCl_3$ (δH, 7.25, δC 77.0 ppm), C_6D_6 (δH, 7.16, δC 128.0 ppm) or [D_6]acetone (δH, 2.04, δC 29.8, 206.7 ppm). Melting points: Büchi Melting Point B-540, uncorrected. IR: Jasco FT/IR-430. Optical rotation: Jasco polarimeter P-1020, reported in degree $[\alpha]_D$ (c [g/100 mL], solvent). HRMS (FT-ICR): Bruker Daltonic APEX 2 with electron spray ionization (ESI). Semipreparative HPLC: Varian ProStar with Dynamax UV-1 UV-detector. Flash chromatography: J. T. Baker silica gel 43–60 μm. Thin-layer chromatography: Polygram Sil G/UV_{254} from Macherey-Nagel. All solvents used in the reactions were purified before use. Dry diethyl ether, tetrahydrofuran, and toluene were distilled from sodium and benzophenone, whereas dry dichloromethane, dimethylformamide, pyridine, and triethylamine were distilled from CaH_2. Petroleum ether with a boiling range of 40–60 °C was used. Reactions were generally run under an argon or nitrogen atmosphere. All commercially available compounds (Acros, Aldrich, Fluka, Merck) were used as received unless stated otherwise. NMR peaks were assigned according to the numbering by Jansen et al.[4]

General Procedure A: Oxidation of Primary Alcohols to Aldehydes: NMO (1.5 equiv.) and powdered molecular sieves (4 Å, 500 mg $mmol^{-1}$), followed by TPAP (0.15 equiv.) in one portion, were added at 0 °C to a solution of primary alcohol (0.01 M, 1.0 equiv.) in dry CH_2Cl_2 . After stirring for 1 h at 0 °C, the reaction mixture was filtered through a short pad of silica and the pad was washed with a solution of petroleum ether/EtOAc (1:1). The resulting solution was concentrated in vacuo to yield the aldehyde, which was used directly in the next step. For analytical purposes, a small portion was purified by flash chromatography on silica gel.

General Procedure B: Coupling of Amides and Aldehydes to Afford Hemiaminals: DIBAL (1.0 M in hexanes, 2.1 equiv.) was added dropwise at 0 °C to a well stirred solution of amide (0.06 M, 2.4 equiv.) in dry THF. After the mixture had been stirred for 30 min at 0 °C, a solution of aldehyde (0.08 M, 1.0 equiv.) in dry THF was added dropwise. The resulting solution was stirred for 16 h at 0 °C, after which it was quenched with pH 7 buffer at 0 °C and diluted with EtOAc. After separation of the layers, the aqueous layer was extracted four times with EtOAc. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel gave the hemiaminals as mixtures of diastereomers.

General Procedure C: Dehydration of Hemiaminals to Afford Enamides: Dry pyridine (30 equiv.) and dry acetic anhydride (15 equiv.) were added at room temperature to a stirred solution of hemiaminal (0.05 M, 1.0 equiv.) in dry THF. The resulting mixture was stirred for 40 h at room temperature, followed by heating at reflux for 48 h. After the solution had cooled to room temperature, it was treated with pH 7 buffer and the aqueous layer was extracted

four times with Et_2O. The combined organic layers were washed with saturated $NaHCO_3$ solution and pH 7 buffer, dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by rapid flash chromatography on silica gel gave the desired enamides in varying ratios of separable *E*/*Z* isomers.

General Procedure D: Final *tert*-Butyl(dimethyl)silyl Removal: TASF (5.0 equiv.) was added at room temperature to a solution of TBDMS-protected enamide (0.04 M, 1.0 equiv.) in dry DMF. The reaction mixture was stirred for 21 h at room temperature and was then quenched with pH 7 buffer and extracted three times with Et_2O. The combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The product was purified by flash chromatography on silica gel to give the apiculaaren A analogue.

11-Deoxy Diol 14: 9-Iodo-9-BBN (1 M solution in hexanes, 1.42 mL, 1.42 mmol) was added at room temperature to a solution of *trans*-pyran[14] **13** (150 mg, 0.35 mmol) in dry CH_2Cl_2 (14 mL). The reaction mixture was stirred for 20 seconds at room temperature, followed by quenching with ethanolamine (1.1 M in THF, 3.22 mL, 3.54 mmol). The resulting mixture was stirred for 1 h at room temperature, after which it was filtered. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 1:2) to yield diol **14** (104 mg, 92%) as a colorless solid, m.p. 47–49 °C. R_f = 0.35 (petroleum ether/EtOAc, 1:2). $[\alpha]_D^{20}$ = +37.4 (*c* = 1.8, CH_2Cl_2). ^{1}H NMR (400 MHz, C_6D_6): δ = 7.02 (dd, *J* = 8.1, 7.6 Hz, 1 H, 5-H), 6.88 (d, *J* = 8.1 Hz, 1 H, aromatic H), 6.54 (d, *J* = 7.6 Hz, 1 H, aromatic H), 5.60–5.48 (m, 1 H, 15-H), 4.38 (s, 1 H, OH), 4.29 (s, 1 H, OH), 4.07–3.93 (m, 1 H, 13-H), 3.85–3.75 (m, 1 H, 9-H), 3.67–3.54 (m, 3 H, 18-H, 8a-H), 2.09 (d, *J* = 13.9 Hz, 1 H, 8b-H), 1.78–1.58 (m, 4 H, 14a-H, 16a-H, 17-H), 1.44–1.25 (m, 5 H, 16b-H, 10a-H, 11-H, 12a-H), 1.24–1.06 (m, 2 H, 12b-H, 10b-H), 1.06 (d, *J* = 13.1 Hz, 14b-H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 170.2 (C-1), 153.8 (C-3), 139.7 (aromatic C), 130.2 (C-5), 124.8 (aromatic C), 122.1 (aromatic CH), 114.8 (aromatic CH), 75.3 (C-9), 74.7 (C-15), 68.8 (C-13), 61.8 (C-18), 40.3 (C-14), 38.2 (C-8), 30.7 (C-16), 30.4 (C-12), 29.2 (C-10), 29.0 (C-17), 19.7 (C-11) ppm. HRMS (ESI): $[M + Na]^+$ calcd. for $C_{18}H_{24}O_5Na$ 343.15159; found 343.15141.

11-Deoxy Silyl Ether 15: TBDMS chloride (152 mg, 1.0 mmol), DMAP (6 mg, 0.05 mmol), and imidazole (137 mg, 2.0 mmol) were added at room temperature to a solution of diol **14** (81 mg, 0.25 mmol) in dry CH_2Cl_2 (5.6 mL). The reaction mixture was stirred for 16 h at room temperature, after which the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 9:1) to yield silyl ether **15** (129 mg, 93%) as a colorless oil. R_f = 0.59 (petroleum ether/EtOAc, 9:1). $[\alpha]_D^{20}$ = +30.9 (*c* = 3.1, CH_2Cl_2). ^{1}H NMR (400 MHz, C_6D_6): δ = 6.97 (dd, *J* = 8.1, 7.6 Hz, 1 H, 5-H), 6.70 (d, *J* = 8.1 Hz, 1 H, aromatic H), 6.59 (d, *J* = 7.6 Hz, 1 H, aromatic H), 5.78–5.70 (m, 1 H, 15-H), 4.02–3.87 (m, 2 H, 13-H, 9-H), 3.71–3.61 (m, 2 H, 18-H), 3.50 (dd, *J* = 14.4, 10.4 Hz, 1 H, 8a-H), 2.10 (d, *J* = 14.4 Hz, 1 H, 8b-H), 1.89–1.64 (m, 5 H, 14a-H, 17-H, 16-H), 1.44–1.25 (m, 4 H, 10a-H, 11-H, 12a-H), 1.20–1.03 (m, 3 H, 10b-H, 14b-H, 12b-H), 1.05 (s, 9 H, $C(CH_3)_3$), 1.01 (s, 9 H, $C(CH_3)_3$), 0.23 (s, 3 H, $SiCH_3$), 0.16 (s, 3 H, $SiCH_3$), 0.11 (s, 3 H, $SiCH_3$), 0.10 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 169.5 (C-1), 152.5 (C-3), 140.1 (aromatic C), 129.8 (aromatic C), 129.2 (C-5), 123.5 (aromatic CH), 117.5 (aromatic CH), 74.4 (C-9), 73.7 (C-15), 69.2 (C-13), 63.2 (C-18), 38.9 (C-14), 38.8 (C-8), 32.1 (C-16), 30.4 (C-12), 30.1 (C-10), 29.0 (C-17), 26.2 ($C(CH_3)_3$), 26.1 ($C(CH_3)_3$), 20.0 (C-11), 18.6 ($C(CH_3)_3$), 18.5 ($C(CH_3)_3$), –4.0 (two peaks, $SiCH_3$), –5.2 ($SiCH_3$) ppm. HRMS (ESI): $[M + Na]^+$ calcd. for $C_{33}H_{52}O_5Si_2Na$ 571.32455; found 571.32464.

11-Deoxy Primary Alcohol 16: Water (19 μL, 1.06 mmol) and $Sc(OTf)_3$ (0.5 mg, 1 μmol) were added at room temperature to a solution of silyl ether **15** (115 mg, 0.21 mmol) in CH_3CN (8 mL). The reaction mixture was stirred for 1 h at room temperature, and then CH_2Cl_2 (75 mL) and saturated $NaHCO_3$ solution (10 mL) were added. After separation of the layers, the aqueous layer was extracted with CH_2Cl_2 (1 × 20 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 2:1) to yield primary alcohol **16** (80 mg, 88%) as a colorless oil. R_f = 0.37 (petroleum ether/EtOAc, 2:1). $[\alpha]_D^{20}$ = +43.0 (*c* = 2.0, CH_2Cl_2). ^{1}H NMR (400 MHz, C_6D_6): δ = 6.97 (dd, *J* = 8.1, 7.6 Hz, 1 H, 5-H), 6.71 (d, *J* = 8.1 Hz, 1 H, aromatic H), 6.57 (d, *J* = 7.6 Hz, 1 H, aromatic H), 5.72–5.65 (m, 1 H, 15-H), 4.29 (s, 1 H, OH), 4.02–3.87 (m, 2 H, 13-H, 9-H), 3.53–3.42 (m, 3 H, 8a-H, 18-H), 2.11 (d, *J* = 14.4 Hz, 1 H, 8b-H), 1.86–1.77 (m, 1 H, 14a-H), 1.71–1.54 (m, 4 H, 17-H, 16-H), 1.46–1.24 (m, 4 H, 10a-H, 11-H, 12a-H), 1.23–1.13 (m, 1 H, 10b-H), 1.13–1.03 (m, 2 H, 12b-H, 14b-H), 1.04 (s, 9 H, $C(CH_3)_3$), 0.22 (s, 3 H, $SiCH_3$), 0.15 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 169.5 (C-1), 152.3 (C-3), 140.0 (aromatic C), 129.8 (aromatic C), 129.2 (C-5), 123.6 (aromatic CH), 117.5 (aromatic CH), 74.3 (C-9), 73.7 (C-15), 69.3 (C-13), 62.4 (C-18), 38.8 (C-8), 38.6 (C-14), 31.7 (C-16), 30.3 (C-12), 30.1 (C-10), 28.7 (C-17), 26.0 ($C(CH_3)_3$), 20.0 (C-11), 18.6 ($C(CH_3)_3$), –4.0 ($SiCH_3$), –4.1 ($SiCH_3$) ppm. HRMS (ESI): $[M + Na]^+$ calcd. for $C_{24}H_{38}O_5SiNa$ 457.23807; found 457.23792.

11-Deoxy Aldehyde 17: Primary alcohol **16** (47 mg, 0.108 mmol) was oxidized according to General Procedure A to yield aldehyde **17** (44 mg, 95%) as a colorless oil; an analytical sample was purified by flash chromatography (petroleum ether/EtOAc, 4:1). R_f = 0.40 (petroleum ether/EtOAc, 4:1). $[\alpha]_D^{20}$ = +43.6 (*c* = 0.7, CH_2Cl_2). ^{1}H NMR (400 MHz, C_6D_6): δ = 9.48 (s, 1 H, 18-H), 6.96 (dd, *J* = 8.1, 7.6 Hz, 1 H, 5-H), 6.70 (d, *J* = 8.1 Hz, 1 H, aromatic H), 6.57 (d, *J* = 7.6 Hz, 1 H, aromatic H), 5.58–5.53 (m, 1 H, 15-H), 3.95–3.83 (m, 2 H, 13-H, 9-H), 3.43 (dd, *J* = 14.4, 10.1 Hz, 1 H, 8a-H), 2.24 (t, *J* = 3.6 Hz, 2 H, 17-H), 2.09 (d, *J* = 14.5 Hz, 1 H, 8b-H), 1.76–1.64 (m, 3 H, 16-H, 14a-H), 1.47–1.13 (m, 5 H, 10-H, 11-H, 12a-H), 1.11–1.02 (m, 1 H, 12b-H), 0.99 (s, 9 H, $C(CH_3)_3$), 0.95–0.85 (m, 1 H, 14b-H), 0.18 (s, 3 H, $SiCH_3$), 0.12 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 199.9 (C-18), 169.2 (C-1), 152.3 (C-3), 140.0 (aromatic C), 129.4 (aromatic C), 129.3 (C-5), 123.6 (aromatic CH), 117.5 (aromatic CH), 74.2 (C-9), 72.7 (C-15), 69.2 (C-13), 39.8 (C-17), 38.9 (C-8), 38.3 (C-14), 30.1 (two peaks, C-12, C-10), 27.3 (C-16), 25.9 ($C(CH_3)_3$), 19.9 (C-11), 18.6 ($C(CH_3)_3$), –4.0 ($SiCH_3$), –4.1 ($SiCH_3$) ppm. HRMS (ESI): $[M + Na]^+$ calcd. for $C_{24}H_{36}O_5SiNa$ 455.22242; found 455.22358.

11-Deoxy Hemiaminal 19: This compound was prepared from amide **18** (30 mg, 0.24 mmol) and aldehyde **17** (43 mg, 0.10 mmol) according to General Procedure B; purification of the crude product by flash chromatography (petroleum ether/EtOAc, 2:1) gave hemiaminal **19** (51 mg, 92%) as a slightly yellow oil, ca. 1:1 mixture of diastereomers. R_f = 0.25 (petroleum ether/EtOAc, 2:1). ^{1}H NMR (400 MHz, C_6D_6): δ = 7.93 (t, *J* = 11.6 Hz, 1 H, 22-H), 6.97 (dd, *J* = 8.3, 7.6 Hz, 1 H, 5-H), 6.72 (d, *J* = 8.3 Hz, 1 H, aromatic H), 6.71–6.62 (m, 2 H, 21-H, OH), 6.58 (d, *J* = 7.6 Hz, 1 H, aromatic H), 5.72–5.51 (m, 4 H, 23-H, 15-H, 18-H, 20-H), 4.74 (2 d, *J* = 3.7 Hz, 1 H, NH), 3.99–3.85 (m, 2 H, 13-H, 9-H), 3.50–3.39 (m, 1 H, 8a-H), 2.12 (d, *J* = 14.6 Hz, 1 H, 8b-H), 2.06–1.96 (m, 2 H, 24-H), 1.93–1.75 (m, 4 H, 11-H, 14a-H, 16a-H), 1.72–1.61 (m, 1 H,

16b-H), 1.46–1.27 (m, 4 H, 17-H, 10a-H, 12a-H), 1.24–1.08 (m, 3 H, 12b-H, 10b-H, 14b-H), 1.04 (s, 9 H, $C(CH_3)_3$), 0.81 (2 t, J = 7.5 Hz, 3 H, 25-H), 0.25 (s, 3 H, $SiCH_3$), 0.17 (2 s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 169.8 (C-1), 167.3 (C-19), 167.2 (C-19), 152.5 (C-3), 152.4 (C-3), 141.3 (C-23), 141.2 (C-23), 140.0 (aromatic C), 139.9 (aromatic C), 136.4 (two peaks, C-21), 129.5 (aromatic C), 129.4 (aromatic C), 129.3 (two peaks, C-5), 125.0 (C-22), 123.6 (two peaks, aromatic CH), 120.6 (C-20), 120.5 (C-20), 117.6 (aromatic CH), 117.5 (aromatic CH), 75.0 (C-18), 74.4 (C-15), 74.3 (C-15), 74.2 (two peaks, C-9), 73.8 (C-18), 69.6 (C-13), 69.4 (C-13), 39.1 (C-8), 38.9 (C-8), 38.6 (C-14), 38.2 (C-14), 31.6 (C-17), 31.0 (C-17), 30.7 (C-10), 30.6 (C-10), 30.2 (C-12), 30.1 (three peaks, C-12, 2×C16), 26.1 (two peaks, $C(CH_3)_3$), 20.8 (C-24), 20.0 (C-11), 18.7 (two peaks, $C(CH_3)_3$), 14.1 (C-25), –3.8 (two peaks, $SiCH_3$), –3.9 ($SiCH_3$), –4.0 ($SiCH_3$) ppm. IR (film): $\tilde{\nu}$ = 3311, 2933, 2858, 1715, 1660, 1593, 1525, 1463, 1261, 1095 cm^{-1}. HRMS (ESI): $[M + Na]^+$ calcd. for $C_{31}H_{47}NO_6SiNa$ 580.30649; found 580.30668.

(*E*)-11-Deoxy Enamide 20: The enamide **20** was prepared from hemiaminal **19** (49 mg, 0.088 mmol) according to General Procedure C; purification of the crude product by rapid flash chromatography (petroleum ether/EtOAc, 5:1, containing 0.2% NEt_3) gave, in order of elution, the (*Z*)-enamide (7.4 mg, 16%) and the (*E*)-enamide **20** (25 mg, 53%) as colorless, highly viscous oils. Data for (*E*)-**20**: R_f = 0.60 (petroleum ether/EtOAc, 2:1). $[\alpha]_D^{24}$ = +97.6 (c = 1.0, acetone). ^1H NMR (400 MHz, C_6D_6): δ = 8.00 (t, J = 11.5 Hz, 1 H, 22-H), 7.22–7.12 (m, 1 H, 18-H), 6.99 (dd, J = 8.1, 7.6 Hz, 1 H, 5-H), 6.84 (d, J = 10.7 Hz, 1 H, NH), 6.72 (d, J = 8.1 Hz, 1 H, aromatic H), 6.63 (t, J = 11.5 Hz, 1 H, 21-H), 6.58 (d, J = 7.6 Hz, 1 H, aromatic H), 5.78–5.70 (m, 1 H, 15-H), 5.67–5.59 (m, 1 H, 23-H), 5.24 (d, J = 11.5 Hz, 1 H, 20-H), 5.05 (ddd, J = 14.6, 8.2, 6.3 Hz, 1 H, 17-H), 4.02–3.94 (m, 1 H, 13-H), 3.90–3.82 (m, 1 H, 9-H), 3.51 (dd, J = 14.5, 10.6 Hz, 1 H, 8a-H), 2.49 (dt, J = 14.5, 6.3 Hz, 1 H, 16a-H), 2.22–2.12 (m, 1 H, 16b-H), 2.06 (d, J = 14.5 Hz, 1 H, 8b-H), 2.01 (qd, J = 7.6, 1.4 Hz, 2 H, 24-H), 1.96–1.84 (m, 1 H, 14a-H), 1.47–1.38 (m, 1 H, 10a-H), 1.37–1.22 (m, 3 H, 11-H, 12a-H), 1.21–1.07 (m, 3 H, 10b-H, 12b-H, 14b-H), 1.05 (s, 9 H, $C(CH_3)_3$), 0.80 (t, J = 7.5 Hz, 3 H, 25-H), 0.20 (s, 3 H, $SiCH_3$), 0.17 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 169.4 (C-1), 162.8 (C-19), 152.2 (C-3), 141.4 (C-23), 140.3 (aromatic C), 136.7 (C-21), 129.8 (aromatic C), 129.4 (C-5), 126.0 (C-18), 125.1 (C-22), 123.6 (aromatic CH), 120.0 (C-20), 117.3 (aromatic CH), 106.9 (C-17), 74.9 (C-15), 73.1 (C-9), 69.0 (C-13), 38.2 (C-8), 37.6 (C-14), 35.4 (C-16), 30.6 (C-12), 29.9 (C-10), 25.9 ($C(CH_3)_3$), 20.8 (C-24), 20.0 (C-11), 18.4 ($C(CH_3)_3$), 14.1 (C-25), –3.8 ($SiCH_3$), –4.6 ($SiCH_3$) ppm. IR (film): $\tilde{\nu}$ = 3293, 3064, 2933, 2858, 1715, 1654, 1593, 1517, 1463, 1362, 1262, 1058 cm^{-1}. HRMS (ESI): $[M + Na]^+$ calcd. for $C_{31}H_{45}NO_5SiNa$ 562.29592; found 562.29621.

11-Deoxy-apicularen Analogue 21: TASF (30 mg, 0.11 mmol) was added at room temperature to a solution of enamide (*E*)-**20** (23.7 mg, 0.044 mmol) in dry DMF (550 μL). The reaction mixture was stirred for 1 h at room temperature, and was then quenched with pH 7 buffer (5 mL) and extracted with Et_2O (3×5 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 2:1) to give apicularen analogue **21** (17.2 mg, 92%) as a highly viscous, colorless oil. R_f = 0.45 (petroleum ether/EtOAc, 1:1). $[\alpha]_D^{25}$ = +1.6 (c = 1.0, acetone). ^1H NMR (400 MHz, [D$_6$]acetone): δ = 9.12 (d, J = 10.4 Hz, 1 H, NH), 8.48 (br. s, 1 H, OH), 7.50 (t, J = 11.5 Hz, 1 H, 22-H), 7.10 (dd, J = 8.2, 7.5 Hz, 1 H, 5-H), 6.88 (dd, J = 14.4, 10.5 Hz, 1 H, 18-H), 6.84 (t, J = 11.6 Hz, 1 H, 21-H), 6.76 (d, J = 8.2 Hz, 1 H, aromatic H), 6.70 (d, J = 7.5 Hz, 1 H, aromatic H), 5.83–5.74 (m, 1 H, 23-H), 5.74 (d, J = 11.7 Hz, 1 H, 20-H), 5.47–5.38 (m, 1 H, 15-H), 5.24 (dt, J = 14.4, 7.4 Hz, 1 H, 17-H), 3.98–3.90 (m, 1 H, 13-H), 3.86–3.78 (m, 1 H, 9-H), 3.28 (dd, J = 14.1, 10.7 Hz, 1 H, 8a-H), 2.35–2.28 (m, 3 H, 16-H, 8b-H), 2.26 (qd, J = 7.6, 1.4 Hz, 2 H, 24-H), 1.80–1.43 (m, 7 H, 14a-H, 10a-H, 11-H, 12a-H, 14b-H, 10b-H), 1.33–1.23 (m, 1 H, 12b-H), 0.99 (t, J = 7.5 Hz, 3 H, 25-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 169.9 (C-1), 163.6 (C-19), 154.1 (C-3), 141.5 (C-23), 140.3 (aromatic C), 136.8 (C-21), 130.3 (C-5), 126.2 (C-18), 125.6 (aromatic C), 125.3 (C-22), 122.2 (aromatic CH), 120.8 (C-20), 114.4 (aromatic CH), 108.1 (C-17), 75.8 (C-9), 74.4 (C-15), 69.2 (C-13), 39.7 (C-14), 38.1 (C-8), 36.2 (C-16), 31.0 (C-12), 30.4 (C-10), 21.0 (C-24), 20.3 (C-11), 14.3 (C-25) ppm. IR (film): $\tilde{\nu}$ = 3285, 3064, 2935, 2871, 1713, 1643, 1585, 1522, 1464, 1363, 1289, 1216, 1065 cm^{-1}. HRMS (ESI): $[M + Na]^+$ calcd. for $C_{25}H_{31}NO_5Na$ 448.20944; found 448.20943.

Open Silyl Ether 24: 9-Iodo-9-BBN (1 M solution in hexanes, 1.15 mL, 1.15 mmol) was added at room temperature to a solution of macrolactone **22** (102 mg, 0.19 mmol) in dry CH_2Cl_2 (7.7 mL). The reaction mixture was stirred for 150 seconds at room temperature, followed by quenching with MeOH (5 mL). The resulting mixture was stirred for 30 min at room temperature, after which it was concentrated under reduced pressure. The residue was redissolved in MeOH (5 mL) and stirred for 30 min at room temperature, and the solvent was removed in vacuo. This procedure was repeated once more, and the residue was dried under high vacuum for 1 h to remove remaining 9-OMe-9-BBN. The obtained crude tetraol **23** was dissolved in dry DMF (4.3 mL) and treated at room temperature with imidazole (183 mg, 2.69 mmol), DMAP (19 mg, 0.15 mmol), and TBDMS chloride (348 mg, 2.31 mmol). After stirring for 72 h at room temperature, the mixture was poured into water (40 mL) and extracted with Et_2O (3×15 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo, and the residue was purified by flash chromatography (petroleum ether/EtOAc, 29:1) to yield the silyl ether **24** (104 mg, 68% over 2 steps) as a slightly yellow oil. R_f = 0.46 (petroleum ether/EtOAc, 29:1). $[\alpha]_D^{25}$ = +73.3 (c = 1.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.15 (dd, J = 8.2, 7.5 Hz, 1 H, 5-H), 6.75 (d, J = 7.5 Hz, 1 H, aromatic H), 6.72 (d, J = 8.2 Hz, 1 H, aromatic H), 6.46 (d, J = 15.9 Hz, 1 H, 8-H), 5.86 (ddd, J = 15.9, 8.8, 5.8 Hz, 1 H, 9-H), 5.25–5.15 (m, 1 H, 15-H), 4.04–3.88 (m, 2 H, 13-H, 11-H), 3.65–3.52 (m, 2 H, 18-H), 2.52–2.42 (m, 1 H, 10a-H), 2.40–2.30 (m, 1 H, 10b-H), 1.95–1.83 (m, 2 H, 14a-H, 12a-H), 1.76–1.48 (m, 6 H, 16-H, 14b-H, 17-H, 12b-H), 0.98 (s, 9 H, $C(CH_3)_3$), 0.88 (s, 9 H, $C(CH_3)_3$), 0.87 (s, 9 H, $C(CH_3)_3$), 0.87 (s, 9 H, $C(CH_3)_3$), 0.26 (s, 3 H, $SiCH_3$), 0.23 (s, 3 H, $SiCH_3$), 0.06–0.02 (m, 12 H, $SiCH_3$), 0.01 (s, 3 H, $SiCH_3$), 0.00 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6 (C-1), 152.6 (C-3), 138.0 (aromatic C), 131.2 (C-8), 131.1 (C-9), 129.6 (C-5), 125.9 (aromatic C), 120.4 (aromatic CH), 117.5 (aromatic CH), 72.1 (C-15), 68.3 (C-11), 66.8 (C-13), 63.0 (C-18), 42.3 (C-12), 41.6 (C-14), 41.4 (C-10), 32.4 (C-16), 28.4 (C-17), 26.0 ($C(CH_3)_3$), 25.9 (two peaks, $C(CH_3)_3$), 25.8 ($C(CH_3)_3$), 18.3 (two peaks, $C(CH_3)_3$), 18.1 ($C(CH_3)_3$), 18.0 ($C(CH_3)_3$), –3.9 ($SiCH_3$), –4.1 ($SiCH_3$), –4.3 ($SiCH_3$), –4.5 ($SiCH_3$), –4.6 ($SiCH_3$), –4.7 ($SiCH_3$), –5.3 (two peaks, $SiCH_3$) ppm. IR (film): $\tilde{\nu}$ = 2955, 2929, 2886, 2858, 1729, 1575, 1463, 1255, 1100 cm^{-1}. HRMS (ESI): $[M + Na]^+$ calcd. for $C_{42}H_{80}O_6Si_4Na$ 815.49242; found 815.49236.

Open Primary Alcohol 25: CSA (6.1 mg, 0.026 mmol) was added at 0 °C to a solution of the silyl ether **24** (104 mg, 0.13 mmol) in CH_2Cl_2/MeOH (2:1 v/v, 8.7 mL). The reaction mixture was stirred for 3 h at 0 °C, quenched with saturated $NaHCO_3$ solution

(10 mL), and allowed to warm to room temperature. The resulting mixture was extracted with Et_2O (3 × 10 mL), and the combined organic layers were washed with brine, dried with Na_2SO_4, and filtered. Removal of the solvent in vacuo and flash chromatography (petroleum ether/EtOAc, 15:1) yielded the primary alcohol **25** (62 mg, 70%) as a colorless oil. R_f = 0.29 (petroleum ether/EtOAc, 9:1). $[\alpha]_D^{23}$ = +96.7 (c = 1.0, acetone). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 (dd, J = 8.3, 7.6 Hz, 1 H, 5-H), 6.75 (d, J = 7.6 Hz, 1 H, aromatic H), 6.73 (d, J = 8.3 Hz, 1 H, aromatic H), 6.46 (d, J = 16.0 Hz, 1 H, 8-H), 5.85 (ddd, J = 16.0, 8.8, 5.9 Hz, 1 H, 9-H), 5.25–5.15 (m, 1 H, 15-H), 4.02–3.88 (m, 2 H, 13-H, 11-H), 3.68–3.61 (m, 2 H, 18-H), 2.51–2.42 (m, 1 H, 10a-H), 2.39–2.30 (m, 1 H, 10b-H), 1.95–1.83 (m, 2 H, 14a-H, 12a-H), 1.82–1.74 (m, 1 H, 16a-H), 1.70–1.59 (m, 2 H, 16b-H, 14b-H), 1.58–1.47 (m, 2 H, 17-H), 1.44–1.36 (m, 1 H, 12b-H), 0.97 (s, 9 H, $C(CH_3)_3$), 0.87 (s, 9 H, $C(CH_3)_3$), 0.86 (s, 9 H, $C(CH_3)_3$), 0.25 (s, 3 H, $SiCH_3$), 0.23 (s, 3 H, $SiCH_3$), 0.04 (s, 3 H, $SiCH_3$), 0.04 (s, 3 H, $SiCH_3$), 0.03 (s, 3 H, $SiCH_3$), 0.00 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8 (C-1), 152.6 (C-3), 138.0 (aromatic C), 131.2 (C-8), 131.1 (C-9), 129.7 (C-5), 125.6 (aromatic C), 120.5 (aromatic CH), 117.6 (aromatic CH), 71.9 (C-15), 68.3 (C-11), 66.7 (C-13), 62.7 (C-18), 42.3 (C-12), 41.6 (C-14), 41.4 (C-10), 32.3 (C-16), 28.1 (C-17), 25.9 ($C(CH_3)_3$), 25.8 ($C(CH_3)_3$), 25.7 ($C(CH_3)_3$), 18.3 ($C(CH_3)_3$), 18.1 ($C(CH_3)_3$), 18.0 ($C(CH_3)_3$), –3.9 ($SiCH_3$), –4.1 ($SiCH_3$), –4.3 ($SiCH_3$), –4.5 ($SiCH_3$), –4.7 (two peaks, $SiCH_3$) ppm. IR (film): $\tilde{\nu}$ = 3480, 2954, 2929, 2858, 1728, 1575, 1464, 1292, 1256, 1061 cm^{-1}. HRMS (ESI): $[M + Na]^+$ calcd. for $C_{36}H_{66}O_6Si_3Na$ 701.40594; found 701.40660.

Open Aldehyde 26: Primary alcohol **25** (61 mg, 0.090 mmol) was oxidized according to General Procedure A to yield aldehyde **26** (60 mg, 98%) as a colorless, viscous oil; an analytical sample was purified by flash chromatography (petroleum ether/EtOAc, 20:1). R_f = 0.65 (petroleum ether/EtOAc, 9:1). $[\alpha]_D^{23}$ = +98.5 (c = 1.0, acetone). ^{1}H NMR (400 MHz, C_6D_6): δ = 9.43 (s, 1 H, 18-H), 6.96 (dd, J = 8.2, 7.7 Hz, 1 H, 5-H), 6.75 (d, J = 7.7 Hz, 1 H, aromatic H), 6.69 (d, J = 8.2 Hz, 1 H, aromatic H), 6.55 (d, J = 15.9 Hz, 1 H, 8-H), 6.04 (ddd, J = 15.9, 8.4, 6.2 Hz, 1 H, 9-H), 5.30–5.21 (m, 1 H, 15-H), 4.20–4.04 (m, 2 H, 13-H, 11-H), 2.56–2.46 (m, 1 H, 10a-H), 2.41–2.32 (m, 1 H, 10b-H), 2.20–2.12 (m, 2 H, 17-H), 2.10–2.02 (m, 1 H, 12a-H), 1.93–1.80 (m, 3 H, 14a-H, 16-H), 1.79–1.70 (m, 1 H, 12b-H), 1.54–1.45 (m, 1 H, 14b-H), 1.01 (s, 9 H, $C(CH_3)_3$), 1.00 (s, 9 H, $C(CH_3)_3$), 0.98 (s, 9 H, $C(CH_3)_3$), 0.23 (s, 3 H, $SiCH_3$), 0.15 (s, 3 H, $SiCH_3$), 0.13 (s, 3 H, $SiCH_3$), 0.12 (s, 3 H, $SiCH_3$), 0.07 (s, 3 H, $SiCH_3$), 0.03 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 199.4 (C-18), 167.7 (C-1), 153.0 (C-3), 138.4 (aromatic C), 131.8 (C-8), 131.5 (C-9), 129.9 (C-5), 126.8 (aromatic C), 120.8 (aromatic CH), 118.2 (aromatic CH), 71.2 (C-15), 68.7 (C-11), 67.1 (C-13), 43.2 (C-12), 42.2 (C-14), 41.9 (C-10), 39.8 (C-17), 28.4 (C-16), 26.1 ($C(CH_3)_3$), 26.0 ($C(CH_3)_3$), 25.9 ($C(CH_3)_3$), 18.5 ($C(CH_3)_3$), 18.2 (two peaks, $C(CH_3)_3$), –3.8 ($SiCH_3$), –4.2 (two peaks, $SiCH_3$), –4.3 ($SiCH_3$), –4.4 ($SiCH_3$), –4.5 ($SiCH_3$) ppm. IR (film): $\tilde{\nu}$ = 2929, 2857, 2713, 2359, 1733, 1575, 1464, 1388, 1256, 1106 cm^{-1}. HRMS (ESI): $[M + Na]^+$ calcd. for $C_{36}H_{64}O_6Si_3Na$ 699.39029; found 699.39067.

Open Hemiaminal 27: The hemiaminal **27** was prepared from amide **18** (26 mg, 0.21 mmol) and aldehyde **26** (59 mg, 0.087 mmol) according to General Procedure B; purification of the crude product by flash chromatography (petroleum ether/EtOAc, 9:1) gave hemiaminal **27** (40 mg, 57%) as a slightly yellow oil, ca. 1:1 mixture of diastereomers. R_f = 0.12 (petroleum ether/EtOAc, 9:1). ^{1}H NMR (400 MHz, C_6D_6, two isomers): δ = 7.90 (t, J = 11.6 Hz, 1 H, 22-H), 6.97 (dd, J = 8.4, 7.5 Hz, 1 H, 5-H), 6.75 (2 d, J = 7.5 Hz, 1 H, aromatic H), 6.71 (2 d, J = 8.4 Hz, 1 H, aromatic H), 6.65 (2 d, J = 11.6 Hz, 1 H, 21-H), 6.58 (d, J = 16.0 Hz, 1 H, 8-H), 6.29 (2 d, J = 7.7 Hz, 1 H, NH), 6.10–5.99 (m, 1 H, 9-H), 5.71–5.63 (m, 1 H, 23-H), 5.57–5.48 (m, 1 H, 18-H), 5.41 (2 d, J = 11.6 Hz, 1 H, 20-H), 5.38–5.28 (m, 1 H, 15-H), 4.26 (br. s, 1 H, OH), 4.21–4.13 (m, 1 H, 13-H), 4.13–4.05 (m, 1 H, 11-H), 2.58–2.48 (m, 1 H, 10a-H), 2.43–2.33 (m, 1 H, 10b-H), 2.15–1.89 (m, 4 H, 12a-H, 24-H, 14a-H), 1.88–1.51 (m, 6 H, 16a-H, 12b-H, 17-H, 14b-H, 16b-H), 1.04 (2 s, 9 H, $C(CH_3)_3$), 1.01 (2 s, 9 H, $C(CH_3)_3$), 0.98 (2 s, 9 H, $C(CH_3)_3$), 0.81 (t, J = 7.5 Hz, 3 H, 25-H), 0.31 (s, 1.5 H, $SiCH_3$), 0.26 (s, 1.5 H, $SiCH_3$), 0.17 (s, 3 H, $SiCH_3$), 0.16 (s, 1.5 H, $SiCH_3$), 0.15 (s, 1.5 H, $SiCH_3$), 0.13 (s, 1.5 H, $SiCH_3$), 0.12 (s, 1.5 H, $SiCH_3$), 0.09 (s, 1.5 H, $SiCH_3$), 0.07 (s, 1.5 H, $SiCH_3$), 0.04 (s, 1.5 H, $SiCH_3$), 0.03 (s, 1.5 H, $SiCH_3$) ppm. ^{13}C NMR (100 MHz, C_6D_6, two isomers): δ = 168.3 (C-1), 168.2 (C-1), 167.2 (two peaks, C-19), 153.1 (C-3), 152.9 (C-3), 141.3 (two peaks, C-23), 138.5 (two peaks, aromatic C), 136.5 (two peaks, C-21), 131.9 (two peaks, C-8), 131.5 (two peaks, C-9), 129.9 (C-5), 126.9 (aromatic C), 126.8 (aromatic C), 124.9 (C-22), 120.8 (aromatic CH), 120.3 (two peaks, C-20), 118.3 (two peaks, aromatic CH), 75.1 (C-18), 74.6 (C-18), 72.6 (C-15), 72.2 (C-15), 68.8 (C-11), 68.6 (C-11), 67.2 (C-13), 43.5 (C-12), 43.2 (C-12), 42.6 (C-14), 42.5 (C-14), 42.2 (C-10), 41.9 (C-10), 31.8 (C-17), 31.7 (C-17), 31.3 (C-16), 30.7 (C-16), 26.1 (three peaks, $C(CH_3)_3$), 20.8 (C-24), 18.7 ($C(CH_3)_3$), 18.6 ($C(CH_3)_3$), 18.2 (four peaks, $C(CH_3)_3$), 14.1 (C-25), –3.8 (two peaks, $SiCH_3$), –3.9 ($SiCH_3$), –4.1 (two peaks, $SiCH_3$), –4.2 (two peaks, $SiCH_3$), –4.3 ($SiCH_3$), –4.4 (two peaks, $SiCH_3$), –4.5 (two peaks, $SiCH_3$) ppm. IR (film): $\tilde{\nu}$ = 3339, 2955, 2929, 2857, 1728, 1661, 1575, 1526, 1464, 1255, 1063 cm^{-1}. HRMS (ESI): $[M + Na]^+$ calcd. for $C_{43}H_{75}NO_7Si_3Na$ 824.47435; found 824.47456.

Open (*E*)-Enamide 28: The enamide **28** was prepared from hemiaminal **27** (38 mg, 0.047 mmol) according to General Procedure C; purification of the crude product by rapid flash chromatography (petroleum ether/EtOAc, 16:1, containing 0.2% NEt_3) gave, in order of elution, the (*Z*)-enamide (1.1 mg, 3%) and the (*E*)-enamide **28** (14.1 mg, 38%) as colorless, highly viscous oils. Data for (*E*)-**28**: R_f = 0.40 (petroleum ether/EtOAc, 9:1). $[\alpha]_D^{24}$ = +85.9 (c = 1.0, acetone). ^{1}H NMR (400 MHz, C_6D_6): δ = 7.94 (t, J = 11.5 Hz, 1 H, 22-H), 7.21–7.13 (m, 1 H, 18-H), 6.98 (dd, J = 8.1, 7.6 Hz, 1 H, 5-H), 6.77 (d, J = 7.6 Hz, 1 H, aromatic H), 6.72 (d, J = 8.1 Hz, 1 H, aromatic H), 6.62 (t, J = 11.5 Hz, 1 H, 21-H), 6.57 (d, J = 15.5 Hz, 1 H, 8-H), 6.19 (d, J = 10.9 Hz, 1 H, NH), 6.06 (ddd, J = 15.5, 8.2, 6.7 Hz, 1 H, 9-H), 5.66–5.58 (m, 1 H, 23-H), 5.42–5.32 (m, 1 H, 15-H), 5.04 (d, J = 11.5 Hz, 1 H, 20-H), 4.84 (dt, J = 14.2, 7.6 Hz, 1 H, 17-H), 4.24–4.15 (m, 1 H, 13-H), 4.13–4.05 (m, 1 H, 11-H), 2.57–2.43 (m, 3 H, 10a-H, 16-H), 2.43–2.33 (m, 1 H, 10b-H), 2.17–2.09 (m, 1 H, 12a-H), 2.08–1.88 (m, 3 H, 14a-H, 24-H), 1.83–1.74 (m, 1 H, 12b-H), 1.72–1.64 (m, 1 H, 14b-H), 1.07 (s, 9 H, $C(CH_3)_3$), 1.00 (s, 9 H, $C(CH_3)_3$), 0.97 (s, 9 H, $C(CH_3)_3$), 0.78 (t, J = 7.5 Hz, 3 H, 25-H), 0.26 (s, 3 H, $SiCH_3$), 0.20 (s, 3 H, $SiCH_3$), 0.15 (s, 3 H, $SiCH_3$), 0.12 (s, 3 H, $SiCH_3$), 0.09 (s, 3 H, $SiCH_3$), 0.06 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 167.5 (C-1), 162.3 (C-19), 153.1 (C-3), 141.6 (C-23), 138.5 (aromatic C), 136.8 (C-21), 131.9 (C-8), 131.3 (C-9), 130.0 (C-5), 127.0 (aromatic C), 126.0 (C-18), 125.0 (C-22), 120.9 (aromatic CH), 119.6 (C-20), 118.1 (aromatic CH), 106.2 (C-17), 71.8 (C-15), 68.9 (C-11), 67.4 (C-13), 43.4 (C-12), 42.1 (C-10), 41.1 (C-14), 36.5 (C-16), 26.1 ($C(CH_3)_3$), 26.0 (two peaks, $C(CH_3)_3$), 20.8 (C-24), 18.5 ($C(CH_3)_3$), 18.2 (two peaks, $C(CH_3)_3$), 14.0 (C-25), –3.8 ($SiCH_3$), –3.9 ($SiCH_3$), –4.3 ($SiCH_3$), –4.4 (two peaks, $SiCH_3$), –4.5 ($SiCH_3$) ppm. IR (film): $\tilde{\nu}$ = 3297, 2955, 2929, 2857, 1727, 1654, 1522, 1464, 1255, 1105, 1065 cm^{-1}. HRMS (ESI): $[M + Na]^+$ calcd. for $C_{43}H_{73}NO_6Si_3Na$ 806.46379; found 806.46409.

Open Apicularen Analogue 29: TASF (42 mg, 0.15 mmol) was added at room temperature to a solution of enamide **28** (12 mg, 0.015 mmol) in dry DMF (380 μL). The reaction mixture was stirred for 36 h at room temperature, after which it was treated with pH 7 buffer (400 μL). The resulting mixture was injected without further processing in four portions onto a RP-HPLC column (Grom-Sil 120 ODS-4 HE, 5 μm, 250 × 10 mm ID, solvent 30% acetonitrile in water, flow rate 4 mL min^{-1}, detection UV absorption at 210 nm). The fractions eluting at 19–22 min were combined and lyophilized to yield apicularen analogue **29** (4.3 mg, 64%) as a white solid. R_f = 0.42 ($CHCl_3$/MeOH, 9:1). $[a]_D^{25}$ = –121.8 (*c* = 0.25, acetone). ^{1}H NMR (400 MHz, [D_6]acetone): δ = 10.58 (br. s, 1 H, OH), 9.18 (d, *J* = 10.4 Hz, 1 H, NH), 7.47 (t, *J* = 11.4 Hz, 1 H, 22-H), 7.35 (dd, *J* = 8.3, 7.6 Hz, 1 H, 5-H), 6.91 (dd, *J* = 14.5, 10.4 Hz, 1 H, 18-H), 6.87–6.80 (m, 1 H, 21-H), 6.83 (d, *J* = 8.3 Hz, 1 H, aromatic H), 6.82 (d, *J* = 7.6 Hz, 1 H, aromatic H), 6.81–6.75 (m, 1 H, 8-H), 5.83–5.68 (m, 3 H, 23-H, 9-H, 20-H), 5.28–5.17 (m, 2 H, 17-H, 15-H), 4.17–4.06 (m, 2 H, 13-H, 11-H), 3.81 (br. s, 1 H, OH), 3.66 (br. s, 1 H, OH), 2.66–2.60 (m, 1 H, 10a-H), 2.57 (t, *J* = 6.9 Hz, 2 H, 16-H), 2.47–2.39 (m, 1 H, 10b-H), 2.25 (qd, *J* = 7.6, 1.4 Hz, 2 H, 24-H), 2.02–1.94 (m, 1 H, 14a-H), 1.90–1.78 (m, 2 H, 12a-H, 14b-H), 1.64–1.54 (m, 1 H, 12b-H), 0.98 (t, *J* = 7.5 Hz, 3 H, 25-H) ppm. ^{13}C NMR (100 MHz, [D_6]acetone): δ = 171.0 (C-1), 163.7 (C-19), 161.2 (C-3), 142.5 (aromatic C), 141.6 (C-23), 136.9 (C-21), 135.3 (C-8), 134.3 (C-5), 129.6 (C-9), 126.9 (C-18), 125.3 (C-22), 120.7 (C-20), 120.4 (aromatic CH), 116.4 (aromatic CH), 114.5 (aromatic C), 107.3 (C-17), 75.0 (C-15), 68.5 (C-13), 65.1 (C-11), 44.9 (C-12), 41.6 (C-14), 39.6 (C-10), 35.3 (C-16), 21.0 (C-24), 14.3 (C-25) ppm. IR (film): $\tilde{\nu}$ = 3285, 2931, 1652, 1602, 1524, 1450, 1367, 1250, 1216, 1116, 1060 cm^{-1}. HRMS (ESI): [*M* + Na]$^+$ calcd. for $C_{25}H_{31}NO_6Na$ 464.20436; found 464.20433.

Enyne Hemiaminal 32: The hemiaminal **32** was prepared from enynamide **31** (22 mg, 0.18 mmol) and aldehyde **30** (42 mg, 0.075 mmol) according to General Procedure B; purification of the crude product by flash chromatography (petroleum ether/EtOAc, 3:1) gave hemiaminal **32** (35 mg, 68%) as a colorless, viscous oil, ca. 1:1 mixture of diastereomers. R_f = 0.71 (petroleum ether/EtOAc, 1:1). ^{1}H NMR (400 MHz, C_6D_6): δ = 7.82 (2 d, *J* = 11.5 Hz, 1 H, NH), 6.96 (2 dd, *J* = 8.2, 7.6 Hz, 1 H, 5-H), 6.69 (2 d, *J* = 8.2 Hz, 1 H, aromatic H), 6.58 (d, *J* = 7.6 Hz, 1 H, aromatic H), 5.98 (2 d, *J* = 12.0 Hz, 1 H, 20-H), 5.72–5.50 (m, 3 H, 18-H, 21-H, 15-H), 4.37–4.21 (m, 2 H, 13-H, OH), 3.97–3.88 (m, 1 H, 9-H), 3.88–3.80 (m, 1 H, 11-H), 3.69 (dd, *J* = 14.7, 10.4 Hz, 1 H, 8a-H), 2.25 (d, *J* = 14.7 Hz, 1 H, 8b-H), 2.18–1.93 (m, 3 H, 24-H, 16a-H), 1.92–1.55 (m, 5 H, 16b-H, 17-H, 10a-H, 14a-H), 1.47–1.36 (m, 3 H, 12-H, 10b-H), 1.07–1.02 (m, 10 H, 14b-H, $C(CH_3)_3$), 1.01 (s, 9 H, $C(CH_3)_3$), 0.91–0.83 (m, 3 H, 25-H), 0.26 (s, 1.5 H, $SiCH_3$), 0.21 (s, 1.5 H, $SiCH_3$), 0.13 (2 s, 3 H, $SiCH_3$), 0.06 (s, 3 H, $SiCH_3$), 0.04 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 169.3 (C-1), 169.2 (C-1), 165.6 (C-19), 165.5 (C-19), 152.3 (C-3), 140.2 (two peaks, aromatic C), 133.2 (two peaks, C-20), 129.8 (aromatic C), 129.7 (aromatic C), 129.2 (C-5), 123.5 (aromatic CH), 117.7 (aromatic CH), 117.6 (aromatic CH), 117.0 (C-21), 105.4 (alkyne C), 105.2 (alkyne C), 77.0 (two peaks, alkyne C), 74.9 (two peaks, C-18), 73.6 (C-9), 73.5 (C-9), 73.4 (C-15), 66.4 (C-13), 66.2 (C-13), 66.0 (C-11), 39.9 (two peaks, C-8), 39.7 (C-10), 39.2 (C-12), 39.1 (C-12), 39.0 (C-14), 38.9 (C-14), 32.2 (C-16), 31.5 (C-16), 31.0 (C-17), 30.1 (C-17), 26.1 (C(CH_3)$_3$), 26.0 (C(CH_3)$_3$), 18.7 (C(CH_3)$_3$), 18.6 (C(CH_3)$_3$), 18.1 (C(CH_3)$_3$), 13.4 (C-24), 13.2 (two peaks, C-25), –3.7 ($SiCH_3$), –4.0 ($SiCH_3$), –4.1 ($SiCH_3$), –4.2 ($SiCH_3$), –4.6 ($SiCH_3$), –4.7 ($SiCH_3$) ppm. IR (film): $\tilde{\nu}$ = 3378, 2929, 2857, 2208, 1719, 1656, 1578, 1527, 1463, 1254, 1069 cm^{-1}. HRMS (ESI): [*M* + Na]$^+$ calcd. for $C_{37}H_{59}NO_7Si_2Na$ 708.37223; found 708.37261.

Enyne (*E*)-Enamide 33: The enamide **33** was prepared from hemiaminal **32** (33.6 mg, 0.049 mmol) according to General Procedure C; purification of the crude product by rapid flash chromatography (petroleum ether/EtOAc, 7:1, containing 0.2% NEt_3) gave, in order of elution, the (*Z*)-enamide (3.0 mg, 9%) and the (*E*)-enamide **33** (9.5 mg, 29%) as a slightly yellow, viscous oil. Data for (*E*)-**33**: R_f = 0.57 (petroleum ether/EtOAc, 2:1). $[a]_D^{29}$ = +56.6 (*c* = 0.5, acetone). ^{1}H NMR (400 MHz, C_6D_6): δ = 8.38 (d, *J* = 10.6 Hz, 1 H, NH), 7.25 (dd, *J* = 14.3, 10.6 Hz, 1 H, 18-H), 6.98 (dd, *J* = 8.1, 7.6 Hz, 1 H, 5-H), 6.69 (d, *J* = 8.1 Hz, 1 H, aromatic H), 6.60 (d, *J* = 7.6 Hz, 1 H, aromatic H), 5.88 (d, *J* = 12.0 Hz, 1 H, 20-H), 5.76–5.68 (m, 1 H, 15-H), 5.48 (dt, *J* = 12.0, 2.4 Hz, 1 H, 21-H), 5.16 (ddd, *J* = 14.3, 7.9, 6.5 Hz, 1 H, 17-H), 4.40–4.32 (m, 1 H, 13-H), 3.96–3.88 (m, 1 H, 9-H), 3.88–3.81 (m, 1 H, 11-H), 3.77 (dd, *J* = 14.5, 10.6 Hz, 1 H, 8a-H), 2.50–2.40 (m, 1 H, 16a-H), 2.28–2.17 (m, 2 H, 8b-H, 16b-H), 1.94–1.83 (m, 3 H, 24-H, 14a-H), 1.71–1.63 (m, 1 H, 10a-H), 1.49–1.34 (m, 3 H, 12-H, 10b-H), 1.15–1.06 (m, 1 H, 14b-H), 1.03 (s, 9 H, $C(CH_3)_3$), 1.01 (s, 9 H, $C(CH_3)_3$), 0.81 (t, *J* = 7.5 Hz, 3 H, 25-H), 0.17 (s, 3 H, $SiCH_3$), 0.15 (s, 3 H, $SiCH_3$), 0.04 (s, 3 H, $SiCH_3$), 0.02 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 169.2 (C-1), 161.3 (C-19), 152.2 (C-3), 140.5 (aromatic C), 133.1 (C-20), 129.9 (aromatic C), 129.4 (C-5), 125.7 (C-18), 123.5 (aromatic CH), 117.3 (aromatic CH), 116.6 (C-21), 107.2 (C-17), 104.7 (alkyne C), 77.0 (alkyne C), 73.7 (C-9), 72.9 (C-15), 66.0 (C-11), 65.8 (C-13), 39.8 (C-12), 39.7 (C-8), 38.7 (C-10), 38.0 (C-14), 35.4 (C-16), 26.0 (C(CH_3)$_3$), 25.9 (C(CH_3)$_3$), 18.4 (C(CH_3)$_3$), 18.1 (C(CH_3)$_3$), 13.3 (two peaks, C-24, C-25), –3.9 ($SiCH_3$), –4.6 ($SiCH_3$), –4.7 (two peaks, $SiCH_3$) ppm. IR (film): $\tilde{\nu}$ = 3285, 2929, 2857, 2209, 1717, 1661, 1463, 1284, 1254, 1105, 1061 cm^{-1}. HRMS (ESI): [*M* + Na]$^+$ calcd. for $C_{37}H_{57}NO_6Si_2Na$ 690.36166; found 690.36173.

Enyne Apicularen Analogue 34: The analogue **34** was prepared by deprotection of enamide **33** (7.9 mg, 0.012 mmol) according to General Procedure D; purification of the crude product by flash chromatography (petroleum ether/EtOAc, 1:3) gave apicularen analogue **34** (3.0 mg, 58%) as a colorless solid. R_f = 0.42 ($CHCl_3$/MeOH, 9:1). $[a]_D^{29}$ = +5.3 (*c* = 0.2, acetone). ^{1}H NMR (400 MHz, [D_6]acetone): δ = 9.08 (d, *J* = 10.2 Hz, 1 H, NH), 8.50 (br. s, 1 H, OH), 7.09 (dd, *J* = 8.2, 7.5 Hz, 1 H, 5-H), 6.88 (dd, *J* = 14.4, 10.5 Hz, 1 H, 18-H), 6.76 (d, *J* = 8.2 Hz, 1 H, aromatic H), 6.68 (d, *J* = 7.5 Hz, 1 H, aromatic H), 6.13–6.04 (m, 2 H, 20-H, 21-H), 5.48–5.38 (m, 1 H, 15-H), 5.31 (dt, *J* = 14.4, 7.4 Hz, 1 H, 17-H), 4.30–4.20 (m, 1 H, 13-H), 4.03–3.93 (m, 1 H, 11-H), 3.90–3.80 (m, 2 H, 9-H, OH), 3.32 (dd, *J* = 14.7, 9.8 Hz, 1 H, 8a-H), 2.47–2.40 (m, 3 H, 24-H, 8b-H), 2.34 (t, *J* = 6.8 Hz, 2 H, 16-H), 1.98–1.78 (m, 2 H, 10a-H, 14a-H), 1.72–1.63 (m, 1 H, 12a-H), 1.62–1.42 (m, 3 H, 14b-H, 12b-H, 10b-H), 1.16 (t, *J* = 7.5 Hz, 3 H, 25-H) ppm. ^{13}C NMR (100 MHz, [D_6]acetone): δ = 169.3 (C-1), 161.8 (C-19), 154.3 (C-3), 140.2 (aromatic C), 132.3 (C-21), 130.2 (C-5), 125.8 (C-18), 125.4 (aromatic C), 122.2 (aromatic CH), 119.4 (C-20), 114.4 (aromatic CH), 108.7 (C-17), 104.5 (alkyne C), 77.9 (alkyne C), 74.1 (C-15), 73.6 (C-9), 68.1 (C-13), 64.8 (C-11), 40.3 (C-8), 39.9 (C-12), 39.6 (C-10), 38.8 (C-14), 36.3 (C-16), 13.9 (C-25), 13.8 (C-24) ppm. IR (film): $\tilde{\nu}$ = 3285, 2924, 2207, 1713, 1652, 1583, 1531, 1464, 1360, 1290, 1220, 1076 cm^{-1}. HRMS (ESI): [*M* + Na]$^+$ calcd. for $C_{25}H_{29}NO_6Na$ 462.18871; found 462.18880.

Oxime Hemiaminal 36: The hemiaminal **36** was prepared from amide **35** (27 mg, 0.21 mmol) and aldehyde **30** (50 mg, 0.089 mmol) according to General Procedure B; purification of the crude product by flash chromatography (petroleum ether/EtOAc, 2:1) gave hemiaminal **36** (50 mg, 82%) as a colorless viscous oil, ca. 1:1 mixture of diastereomers. R_f = 0.48 (petroleum ether/EtOAc, 1:1). ^{1}H NMR (400 MHz, C_6D_6): δ = 7.76–7.55 (m, 2 H, 22-H, 21-H), 7.01–

6.85 (m, 2 H, 5-H, NH), 6.73 (d, J = 8.2 Hz, 1 H, aromatic H), 6.59 (d, J = 7.6 Hz, 1 H, aromatic H), 5.87 (2 d, J = 15.1 Hz, 1 H, 20-H), 5.71–5.56 (m, 2 H, 18-H, 15-H), 5.05–4.87 (m, 1 H, OH), 4.35–4.26 (m, 1 H, 13-H), 4.00–3.91 (m, 1 H, 9-H), 3.90–3.81 (m, 1 H, 11-H), 3.72 (s, 3 H, OCH_3), 3.70–3.60 (m, 1 H, 8a-H), 2.27 (d, J = 14.6 Hz, 1 H, 8b-H), 1.98–1.76 (m, 4 H, 16a-H, 17-H, 14a-H), 1.76–1.57 (m, 2 H, 10a-H, 16b-H), 1.54–1.37 (m, 3 H, 12-H, 10b-H), 1.15–1.05 (m, 1 H, 14b-H), 1.05–0.99 (m, 18 H, $C(CH_3)_3$), 0.26–0.23 (m, 3 H, $SiCH_3$), 0.18–0.14 (m, 3 H, $SiCH_3$), 0.08–0.06 (m, 3 H, $SiCH_3$), 0.06–0.04 (m, 3 H, $SiCH_3$) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 169.7 (C-1), 169.6 (C-1), 165.5 (two peaks, C-19), 152.5 (C-3), 152.4 (C-3), 148.1 (C-22), 140.0 (two peaks, aromatic C), 134.7 (C-21), 134.6 (C-21), 130.0 (aromatic C), 129.9 (aromatic C) 129.5 (C-20), 129.4 (three peaks, C-20, 2×C-5), 123.7 (aromatic CH), 123.6 (aromatic CH), 117.7 (two peaks, aromatic CH), 75.1 (C-18), 74.5 (C-18), 74.1 (C-15), 73.8 (C-15), 73.1 (C-9), 73.0 (C-9), 67.1 (C-13), 66.0 (C-11), 62.2 (OCH_3), 40.2 (C-8), 39.6 (C-10), 39.4 (C-12), 38.6 (C-14), 38.4 (C-14), 31.6 (C-17), 31.0 (C-17), 30.5 (C-16), 26.2 ($C(CH_3)_3$), 26.1 ($C(CH_3)_3$), 26.0 ($C(CH_3)_3$), 18.7 (two peaks, $C(CH_3)_3$), 18.2 ($C(CH_3)_3$), –3.7 ($SiCH_3$), –3.8 ($SiCH_3$), –4.0 ($SiCH_3$), –4.1 ($SiCH_3$), –4.6 (two peaks, $SiCH_3$) ppm. IR (film): $\tilde{\nu}$ = 3309, 3059, 2930, 2858, 2280, 1719, 1663, 1534, 1463, 1362, 1255, 1045 cm^{-1}. HRMS (ESI): [M + Na]$^+$ calcd. for $C_{35}H_{58}N_2O_8Si_2Na$ 713.36239; found 713.36206.

Oxime (*E*)-Enamide 37: The enamide **37** was prepared from hemiaminal **36** (48 mg, 0.069 mmol) according to General Procedure C; purification of the crude product by rapid flash chromatography (petroleum ether/EtOAc, 6:1, containing 0.2% NEt_3) gave, in order of elution, the (*Z*)-enamide (13.7 mg, 29%) and the (*E*)-enamide **37** (17.3 mg, 37%) as a slightly yellow wax. Data for (*E*)-**37**: R_f = 0.51 (petroleum ether/EtOAc, 2:1). $[\alpha]_D^{27}$ = +61.2 (c = 1.0, acetone). ^1H NMR (400 MHz, C_6D_6): δ = 7.64–7.52 (m, 2 H, 22-H, 21-H), 7.09 (dd, J = 14.3, 10.6 Hz, 1 H, 18-H), 6.99 (dd, J = 8.1, 7.7 Hz, 1 H, 5-H), 6.72 (d, J = 8.1 Hz, 1 H, aromatic H), 6.61 (d, J = 7.7 Hz, 1 H, aromatic H), 6.55 (d, J = 10.6 Hz, 1 H, NH), 5.76–5.69 (m, 1 H, 15-H), 5.40 (d, J = 14.4 Hz, 1 H, 20-H), 5.09 (ddd, J = 14.3, 8.3, 6.6 Hz, 1 H, 17-H), 4.46–4.37 (m, 1 H, 13-H), 3.98–3.84 (m, 2 H, 9-H, 11-H), 3.80 (dd, J = 14.4, 10.8 Hz, 1 H, 8a-H), 3.70 (s, 3 H, OCH_3), 2.50–2.41 (m, 1 H, 16a-H), 2.25 (d, J = 14.4 Hz, 1 H, 8b-H), 2.18–2.09 (m, 1 H, 16b-H), 1.94–1.82 (m, 1 H, 14a-H), 1.74–1.64 (m, 1 H, 10a-H), 1.55–1.37 (m, 3 H, 12a-H, 10b-H, 12b-H), 1.16–1.07 (m, 1 H, 14b-H), 1.05 (s, 9 H, $C(CH_3)_3$), 1.02 (s, 9 H, $C(CH_3)_3$), 0.20 (s, 3 H, $SiCH_3$), 0.15 (s, 3 H, $SiCH_3$), 0.05 (s, 3 H, $SiCH_3$), 0.03 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 169.4 (C-1), 161.1 (C-19), 152.1 (C-3), 148.0 (C-22), 140.5 (aromatic C), 134.6 (C-21), 129.8 (aromatic C), 129.6 (C-5), 129.3 (C-20), 125.8 (C-18), 123.6 (aromatic CH), 117.4 (aromatic CH), 108.0 (C-17), 74.1 (C-9), 72.8 (C-15), 65.9 (C-11), 65.5 (C-13), 62.2 (OCH_3), 39.9 (C-12), 39.5 (C-8), 38.5 (C-10), 37.9 (C-14), 35.1 (C-16), 26.0 ($C(CH_3)_3$), 25.9 ($C(CH_3)_3$), 18.4 ($C(CH_3)_3$), 18.1 ($C(CH_3)_3$), –3.8 ($SiCH_3$), –4.7 (three peaks, $SiCH_3$) ppm. IR (film): $\tilde{\nu}$ = 3286, 2930, 2857, 1716, 1657, 1525, 1463, 1360, 1254, 1105, 1044 cm^{-1}. HRMS (ESI): [M + Na]$^+$ calcd. for $C_{35}H_{56}N_2O_7Si_2Na$ 695.35183; found 695.35115.

Oxime Apicularen Analogue 38: The analogue **38** was prepared by deprotection of enamide **37** (16.5 mg, 0.025 mmol) according to General Procedure D; purification of the crude product by flash chromatography (CH_2Cl_2/acetone, 2:1) gave apicularen analogue **38** (8.2 mg, 75%) as a colorless solid. R_f = 0.43 (CH_2Cl_2/acetone, 1:1). $[\alpha]_D^{24}$ = –13.4 (c = 0.5, acetone). ^1H NMR (400 MHz, [D_6]acetone): δ = 9.36 (d, J = 10.2 Hz, 1 H, NH), 8.53 (br. s, 1 H, OH), 7.88 (d, J = 10.3 Hz, 1 H, 22-H), 7.14 (dd, J = 15.5, 10.3 Hz, 1 H, 21-H), 7.09 (dd, J = 8.2, 7.6 Hz, 1 H, 5-H), 6.90 (dd, J = 14.4, 10.3 Hz, 1 H, 18-H), 6.76 (d, J = 8.2 Hz, 1 H, aromatic H), 6.68 (d, J = 7.6 Hz, 1 H, aromatic H), 6.40 (d, J = 15.5 Hz, 1 H, 20-H), 5.46–5.38 (m, 1 H, 15-H), 5.33 (dt, J = 14.4, 7.5 Hz, 1 H, 17-H), 4.29–4.20 (m, 1 H, 13-H), 4.02–3.93 (m, 1 H, 11-H), 3.92–3.82 (m, 5 H, 9-H, OCH_3, OH), 3.32 (dd, J = 14.7, 9.9 Hz, 1 H, 8a-H), 2.42 (d, J = 14.7 Hz, 1 H, 8b-H), 2.34 (t, J = 7.0 Hz, 2 H, 16-H), 1.95–1.87 (m, 1 H, 10a-H), 1.86–1.78 (m, 1 H, 14a-H), 1.71–1.63 (m, 1 H, 12a-H), 1.60–1.42 (m, 3 H, 14b-H, 12b-H, 10b-H) ppm. ^{13}C NMR (100 MHz, [D_6]acetone): δ = 169.3 (C-1), 162.2 (C-19), 154.3 (C-3), 149.1 (C-22), 140.1 (aromatic C), 134.3 (C-21), 130.9 (C-20), 130.2 (C-5), 126.1 (C-18), 125.4 (aromatic C), 122.2 (aromatic CH), 114.4 (aromatic CH), 109.5 (C-17), 74.1 (C-15), 73.6 (C-9), 68.1 (C-13), 64.8 (C-11), 62.5 (OCH_3), 40.3 (C-8), 39.8 (C-12), 39.6 (C-10), 38.8 (C-14), 36.3 (C-16) ppm. IR (film): $\tilde{\nu}$ = 3285, 2938, 1713, 1652, 1582, 1532, 1463, 1354, 1259, 1040 cm^{-1}. HRMS (ESI): [M + Na]$^+$ calcd. for $C_{23}H_{28}N_2O_7Na$ 467.17887; found 467.17883.

***N*-Methyl (*E*)-Enamide 40:** NaH (0.33 mg, 0.014 mmol, suspended in THF (70 μL)) was added at 0 °C to a solution of enamide **39** (8.7 mg, 0.013 mmol) in dry THF (90 μL). After being stirred for 1 h at 0 °C, the reaction mixture was treated with methyl iodide (0.9 μL, 0.014 mmol). The reaction mixture was allowed to warm to room temperature, stirred for 16 h at room temperature, and then quenched with pH 7 buffer (3 mL). The resulting mixture was extracted with Et_2O (3×5 mL). The combined organic layer was washed with brine, dried with Na_2SO_4, and filtered. Removal of the solvent in vacuo and rapid flash chromatography (petroleum ether/EtOAc, 9:1, containing 0.2% NEt_3) yielded the *N*-methyl-(*E*)-enamide **40** (7.1 mg, 80%) as a colorless oil. NMR analysis in C_6D_6 indicated that compound **40** consists of a 6:4 mixture of rotamers. R_f = 0.46 (petroleum ether/EtOAc, 4:1). $[\alpha]_D^{25}$ = +46.1 (c = 0.5, acetone). ^1H NMR (400 MHz, C_6D_6, data for major rotamer): δ = 7.23–7.04 (m, 1 H, 22-H), 7.00–6.93 (m, 1 H, 5-H), 6.74–6.66 (m, 2 H, 18-H, aromatic H), 6.64–6.47 (m, 2 H, 21-H, aromatic H), 5.85–5.74 (m, 2 H, 15-H, 23-H), 5.58–5.48 (m, 1 H, 20-H), 4.68 (dt, J = 14.5, 7.7 Hz, 1 H, 17-H), 4.50–4.37 (m, 1 H, 13-H), 4.03–3.94 (m, 1 H, 9-H), 3.92–3.76 (m, 2 H, 11-H, 8a-H), 2.39 (s, 3 H, *N*-Methyl), 2.03–1.82 (m, 3 H, 16a-H, 8b-H, 16b-H), 1.74–1.65 (m, 1 H, 14a-H), 1.56–1.38 (m, 3 H, 10a-H, 12a-H, 12b-H), 1.36–1.19 (m, 2 H, 24-H), 1.06 (s, 9 H, $C(CH_3)_3$), 1.01 (s, 9 H, $C(CH_3)_3$), 0.95–0.82 (m, 2 H, 10b-H, 14b-H), 0.79 (t, J = 7.5 Hz, 3 H, 25-H), 0.18 (s, 3 H, $SiCH_3$), 0.17 (s, 3 H, $SiCH_3$), 0.04 (s, 3 H, $SiCH_3$), 0.03 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (100 MHz, C_6D_6, data for major rotamer): δ = 170.2 (C-1), 169.3 (C-19), 152.2 (C-3), 140.5 (C-23), 140.0 (aromatic C), 133.7 (C-21), 131.8 (aromatic C), 129.4 (C-5), 127.3 (C-18), 125.0 (C-22), 123.5 (aromatic CH), 120.3 (C-20), 117.3 (aromatic CH), 104.6 (C-17), 73.9 (C-9), 73.1 (C-15), 66.0 (two peaks, C-11, C-13), 40.0 (C-12), 39.7 (C-8), 38.7 (C-10), 36.3 (C-14), 34.1 (C-16), 29.1 (*N*-Methyl), 26.0 ($C(CH_3)_3$), 25.9 ($C(CH_3)_3$), 21.0 (C-24), 18.4 ($C(CH_3)_3$), 18.1 ($C(CH_3)_3$), 14.1 (C-25), –3.9 ($SiCH_3$), –4.5 ($SiCH_3$), –4.7 (two peaks, $SiCH_3$) ppm. IR (film): $\tilde{\nu}$ = 2929, 2857, 1716, 1644, 1578, 1463, 1381, 1286, 1254, 1102, 1061 cm^{-1}. HRMS (ESI): [M + Na]$^+$ calcd. for $C_{38}H_{61}NO_6Si_2Na$ 706.39296; found 706.39392.

***N*-Methyl-apicularen Analogue 41:** The analogue **41** was prepared by deprotection of enamide **40** (5.4 mg, 0.008 mmol) according to General Procedure D; purification of the crude product by flash chromatography (petroleum ether/EtOAc, 1:3) gave apicularen analogue **41** (2.7 mg, 75%) as a colorless, highly viscous oil. NMR analysis in [D_6]acetone indicated that compound **41** consists of a 7:3 mixture of rotamers. R_f = 0.32 (petroleum ether/EtOAc, 1:9). $[\alpha]_D^{29}$ = –31.6 (c = 0.22, acetone). ^1H NMR (400 MHz, [D_6]acetone, data for major rotamer): δ = 8.58 (br. s, 1 H, OH), 7.09 (t, J = 8.0 Hz, 1 H, 5-H), 6.93 (d, J = 13.9 Hz, 1 H, 18-H), 6.86–6.74 (m,

2 H, 21-H, aromatic H), 6.67 (d, J = 7.6 Hz, 1 H, aromatic H), 6.63 (t, J = 11.6 Hz, 1 H, 22-H), 6.16 (d, J = 11.3 Hz, 1 H, 20-H), 5.79–5.66 (m, 1 H, 23-H), 5.49–5.39 (m, 1 H, 15-H), 5.25–5.10 (m, 1 H, 17-H), 4.33–4.21 (m, 1 H, 13-H), 4.03–3.87 (m, 2 H, 11-H, 9-H), 3.82 (br. s, 1 H, OH), 3.32–3.23 (m, 1 H, 8a-H), 3.05 (s, 3 H, *N*-methyl), 2.45 (d, J = 14.9 Hz, 1 H, 8b-H), 2.42–2.31 (m, 2 H, 16-H), 2.31–2.21 (m, 2 H, 24-H), 1.97–1.84 (m, 2 H, 10a-H, 14a-H), 1.73–1.39 (m, 4 H, 12a-H, 14b-H, 12b-H, 10b-H), 0.99 (t, J = 7.5 Hz, 3 H, 25-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]acetone, data for major rotamer): δ = 169.0 (C-1), 162.7 (C-19), 154.3 (C-3), 140.3 (C-23), 139.3 (aromatic C), 133.8 (C-21), 131.8 (aromatic C), 130.1 (C-5), 125.2 (C-18), 122.3 (two peaks, C-22, aromatic CH), 121.3 (C-20), 114.3 (aromatic CH), 107.0 (C-17), 74.2 (C-15), 73.1 (C-9), 68.9 (C-13), 64.8 (C-11), 40.7 (C-8), 40.2 (C-12), 39.7 (C-10), 38.4 (C-14), 36.5 (C-16), 29.1 (*N*-Methyl), 21.3 (C-24), 14.3 (C-25) ppm. IR (film): $\tilde{\nu}$ = 3286, 2924, 1714, 1634, 1582, 1463, 1387, 1289, 1098 cm^{-1}. HRMS (ESI): [M + Na]$^+$ calcd. for $C_{26}H_{33}NO_6Na$ 478.22001; found 478.22017.

Biological Assays: The biological activities of the compounds were tested by a growth inhibition assay with different mammalian cell lines from DSMZ. Cell line 3Y1 was a generous gift from Dr. S. Miyamoto, Fukuoka, Japan. All cell lines were cultivated in Dulbeco's modified Eagle medium with high glucose and 10% fetal calf serum. Aliquots of 120 µL of suspended cells (50000/mL) were given to 60 µL of a serial dilution of the compounds. After 5 days the reduction of MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) was measured as a parameter of growth and metabolic activity of the cells.

LysoTracker Red DND-99 from Molecular Probes was used to trace acidic organelles in living cells.

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