Epi-, Epoxy- and C2-Modified Bengamides: Synthesis and Biological Evaluation

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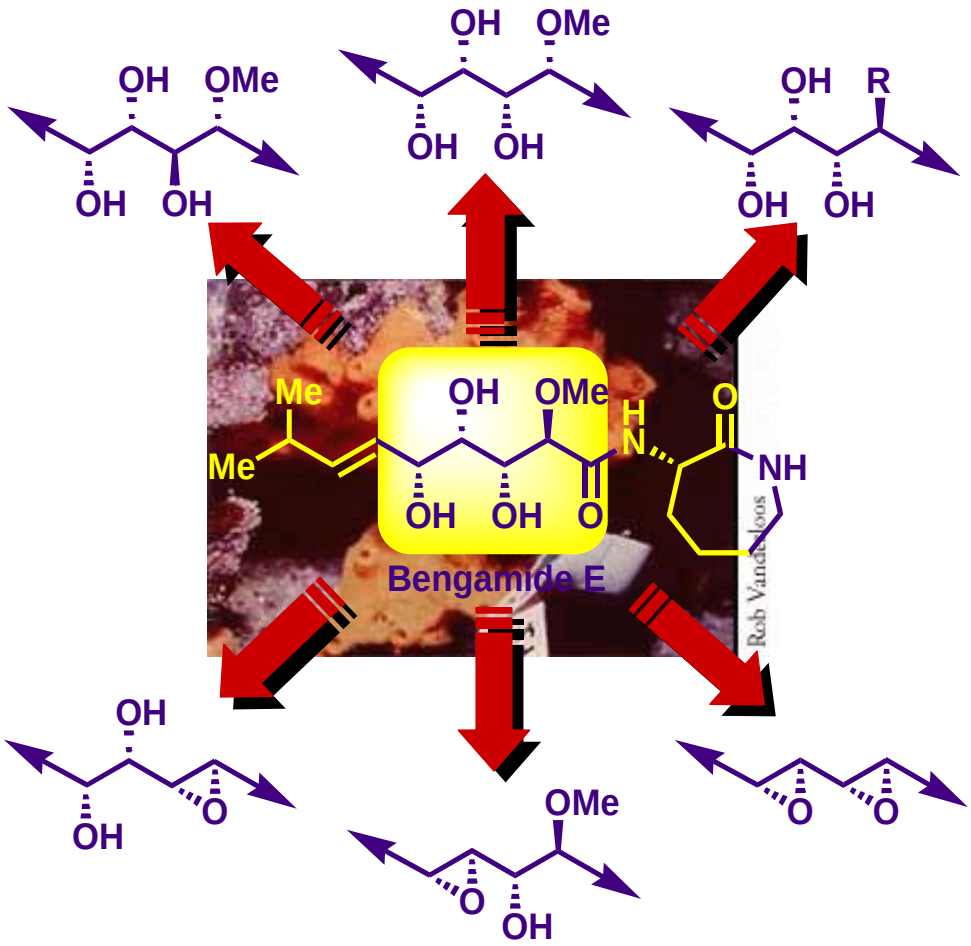


Abstract: With the objective of investigating the influence of structural modifications of the polyketide chain of the bengamides upon their antitumoral activities, we targeted the preparation of bengamide E analogues with modification of the stereochemistry at C-2 and at C-3, the substituent at the C-2 position, as well as the presence of oxirane rings. For the synthesis of these analogues, a new synthetic method for asymmetric epoxidation, developed in our laboratories, was employed utilizing the chiral sulfonium salts **22** and **23**. In order to access 2-*epi*-Bengamide E from these epoxy amides, a synthetic methodology, developed by Miyashita, allowed an oxirane-ring opening reaction with a double inversion of the configuration. Alternatively, an aldol reaction provided access to the same analogue in a shorter and more efficient manner. Finally, biological evaluation of all these bengamide E analogues demonstrated that the polyketide chain is essential for the antitumor activity of these natural products, not being amenable of structural or configurational modifications.

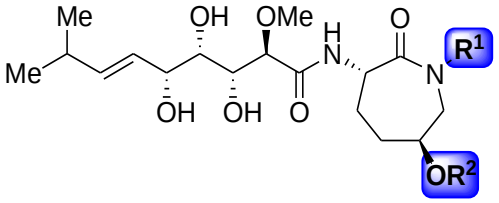
Introduction

The bengamides (**1**-**21**), a family of marine natural products isolated from sponges of the *Jaspidae* family (Figure 1),[1] have elicited widespread interest in both biological and chemical circles due to their prominent antitumor, antihelmintic and antibiotic properties.[2] Interestingly, the bengamides were found to bind the methionine aminopeptidases (MetAp1 and MetAp2),[3] enzymes responsible of the cleavage of the *N*-terminal initiator methionine residue during protein synthesis.[4] A similar mode of action is displayed by the anti-angiogenic agents fumagillin and ovalicin despite their structural differences.[5] As a consequence of the inhibition of these enzymes, there is a blockade of the cell cycle division of endothelial cells at the G1 and G2 phases[6] as well as anti-angiogenic effect in epithelial cells.[7] Additional biological studies demonstrated that bengamide A altered the subcellular distribution of the proto-oncogene *c*-Src, a substrate of both MetAp, that allowed to establish a link between these enzymes and oncogenes involved in tumor growth.[8] More recently, Crews et al. discovered that the bengamides were capable of inhibiting the nuclear factor κB (NF-κB).[9] This inhibition ability render bengamides as potential leads for the treatment of diseases involving inflammation. In conjuction with this valuable finding, Crews and coworkers isolated bengamide E (**15**) and two new congeners of this family, bengamides E' (**17**) and F' (**18**) from *Myxobacteria virescens* in the course of this investigation. Curiously, we reported the synthesis of bengamide E' (**17**) before its discovery from natural sources.[10] All these biological properties displayed by the bengamides, coupled with their appealing molecular structures explain the flurry of activity directed toward their total synthesis[11] and analogues design.[12] Among the most prominent analogues synthesized so far, it is important to highlight compound LAF389[12a-b] and other bengamide analogues modified at the caprolactam unit, which exhibited cytotoxicities in the low nM range and improved solubilities in water with

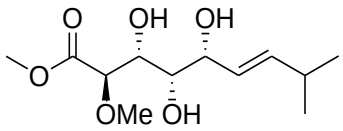
respect to the displayed by the natural counterparts.[12c-d] On the other hand, the ability of the bengamides of inhibiting methionine aminopeptidase has been exploited in the design of new potential leads for the tuberculosis treatment.[13]

Figure 1. Molecular Structures of Bengamides.

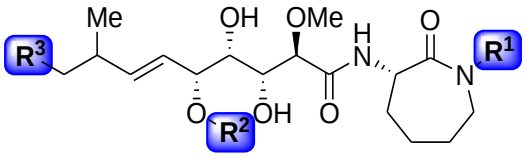
Bengamides Type I



Bengamide A (**1**): R^1 = H, R^2 = $C(=O)(CH_2)_{12}CH_3$
Bengamide B (**2**): R^1 = CH_3, R^2 = $C(=O)(CH_2)_{12}CH_3$
Bengamide G (**3**): R^1 = H, R^2 = $C(=O)(CH_2)_{11}CH_3$
Bengamide H (**4**): R^1 = CH_3, R^2 = $C(=O)(CH_2)_{11}CH_3$
Bengamide I (**5**): R^1 = H, R^2 = $C(=O)(CH_2)_{13}CH_3$
Bengamide J (**6**): R^1 = CH_3, R^2 = $C(=O)(CH_2)_{13}CH_3$
Bengamide L (**7**): R^1 = H, R^2 = $C(=O)(CH_2)_{11}CH(CH_3)_2$
Bengamide M (**8**): R^1 = CH_3, R^2 = $C(=O)(CH_2)_{11}CH(CH_3)_2$
Bengamide N (**9**): R^1 = H, R^2 = $C(=O)(CH_2)_{10}CH(CH_3)_2$
Bengamide O (**10**): R^1 = CH_3, R^2 = $C(=O)(CH_2)_{10}CH(CH_3)_2$
Bengamide Y (**11**): R^1 = R^2 = H
Bengamide Z (**12**): R^1 = CH_3, R^2 = H
Bengamide C (**13**): R^1 = H, R^2 =
Bengamide D (**14**): R^1 = CH_3, R^2 =



Bengamides Type II

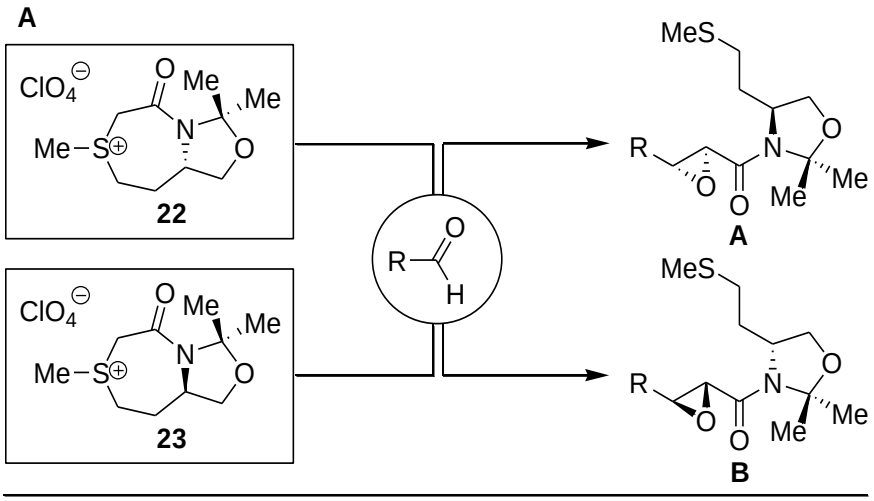


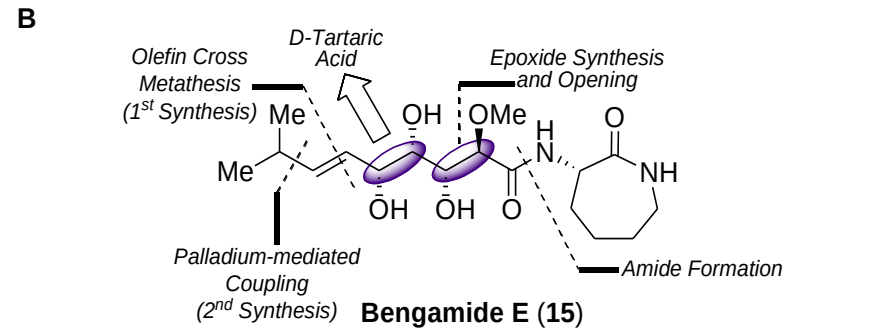
Bengamide E (**15**): R^1 = R^2 = R^3 = H
Bengamide F (**16**): R^1 = CH_3, R^2 = R^3 = H
Bengamide E' (**17**): R^1 = R^2 = H, R^3 = CH_3
Bengamide F' (**18**): R^1 = R^3 = CH_3, R^2 = H
Bengamide P (**19**): R^1 = R^3 = H, R^2 = $C(=O)(CH_2)_{12}CH_3$
Bengamide Q (**20**): R^1 = CH_3, R^3 = H, R^2 = $C(=O)(CH_2)_{12}CH_3$
Bengamide R (**21**): R^1 = R^3 = H, R^2 = $C(=O)(CH_2)_{14}CH_3$

As part of a research programme engaged in the development of new asymmetric methodologies of epoxidation, we recently designed and synthesized a new class of chiral sulfonium salts,[14] for example **22** and **23**, which haven proven to be efficient and high-yielding tools for the asymmetric synthesis of epoxy amides, types **A** and **B** (Scheme 1, A). Encouraged by these results, we decided to exploit these synthetic tools for the synthesis of various bioactive compounds.[15,16] Thus, based on our delineated synthetic strategy for bengamides (Scheme 1, B), which relied on the construction of an oxirane-ring and subsequent opening to generate the C2/C3 system,[17,18] we applied this novel asymmetric epoxidation for the synthesis of bengamides.[10] From epoxy amides **24** and **25**, prepared in good yields and excellent stereoselectivities according to this new epoxidation methodology, we were able to prepare bengamide E (**15**) and a wide array of analogues, such as **26a**-**c**, via olefin cross metathesis or via palladium-mediated couplings for the stereoselective installation of the substituyent at the terminal olefinic position (Scheme 1, C).

Despite all the synthetic efforts by us and others directed towards the bengamides and analogues thereof, little has been reported regarding the effect of the polyketide chain towards biological activity. Among the possible modifications of the polyketide chain of the bengamides, we initially paid attention to the stereochemistry of the two chiral centres at C2 and at C3 positions. On the other hand, we were intrigued with the biological role of the methoxyl group at the C2 position, which apparently is not involved in the coordination with the cobalt ions present at the enzyme active site, as the rest of the polyol system. In addition, inspired by the mode of action of fumagillin (**27**), depicted in figure 2, which is characterized by irreversible inhibition of methionine aminopeptidase via a nuclepohilic attack of a histidine residue onto the oxirane ring of the natural product, we considered the introduction of oxirane rings along the polyketide chain of the bengamides, which could lead to a fumagillin-like interaction with methionine aminopeptidase (Figure 2).

Scheme 1. Synthetic Strategy for Bengamides based on Chiral Sulfur Ylides: A) Synthetic Tools. B) Synthetic Strategy. C) Synthesized Bengamides





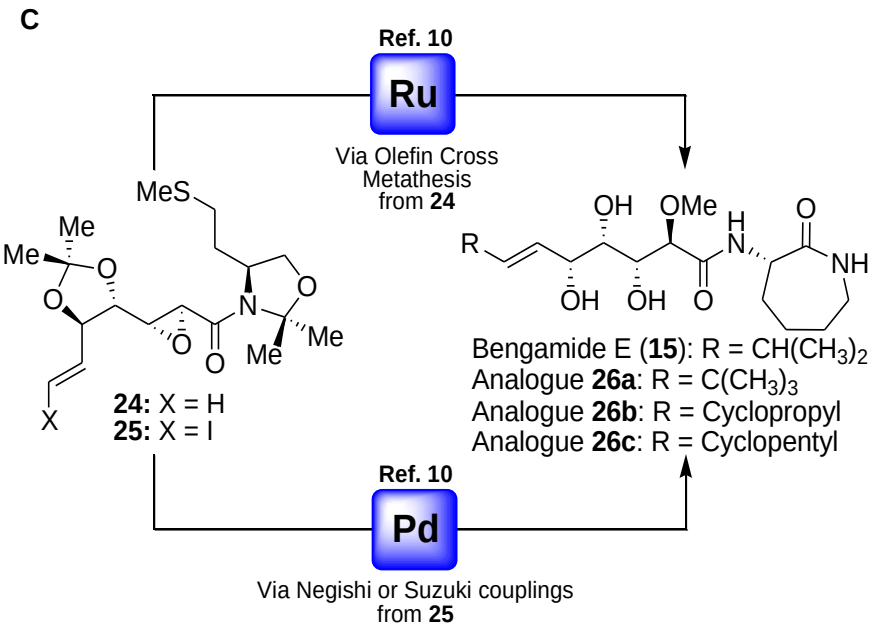
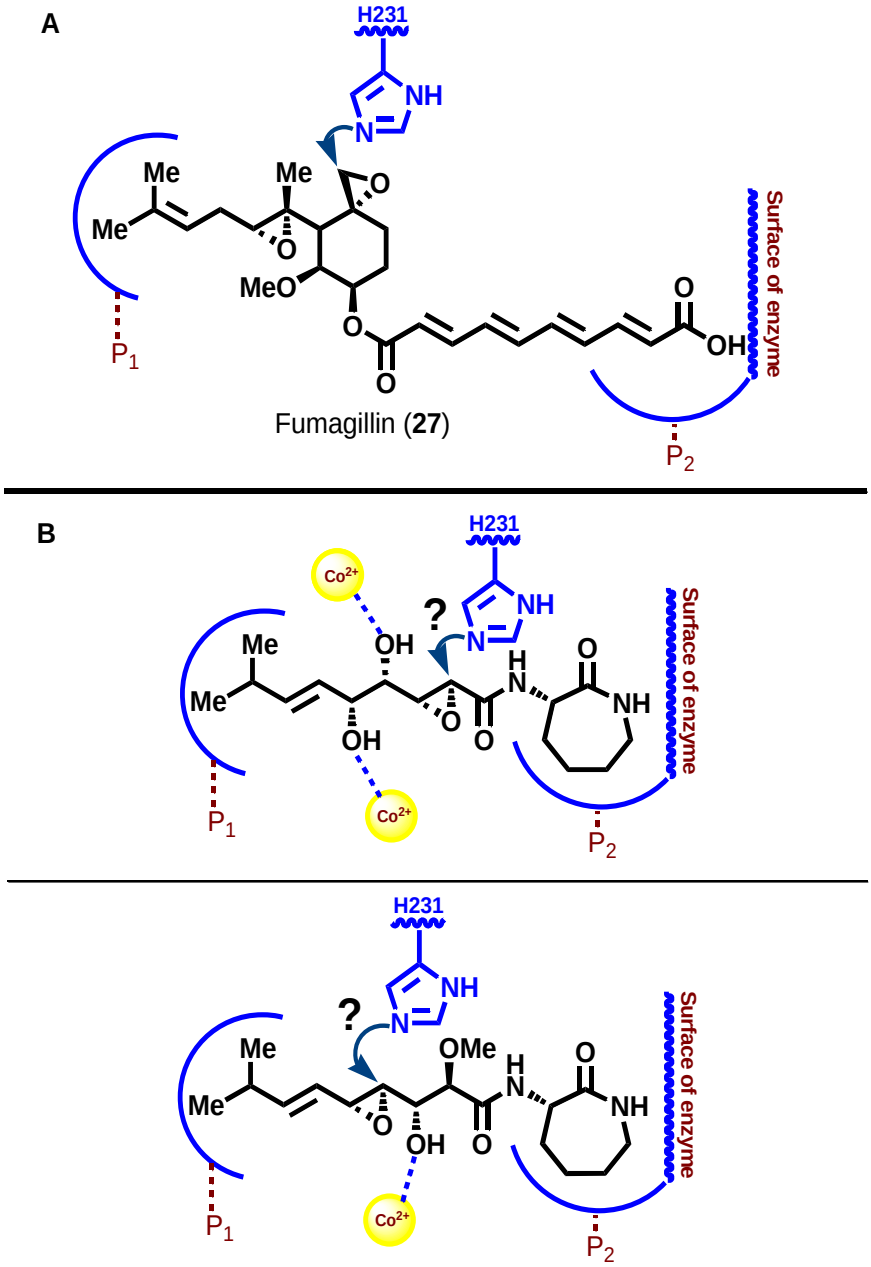


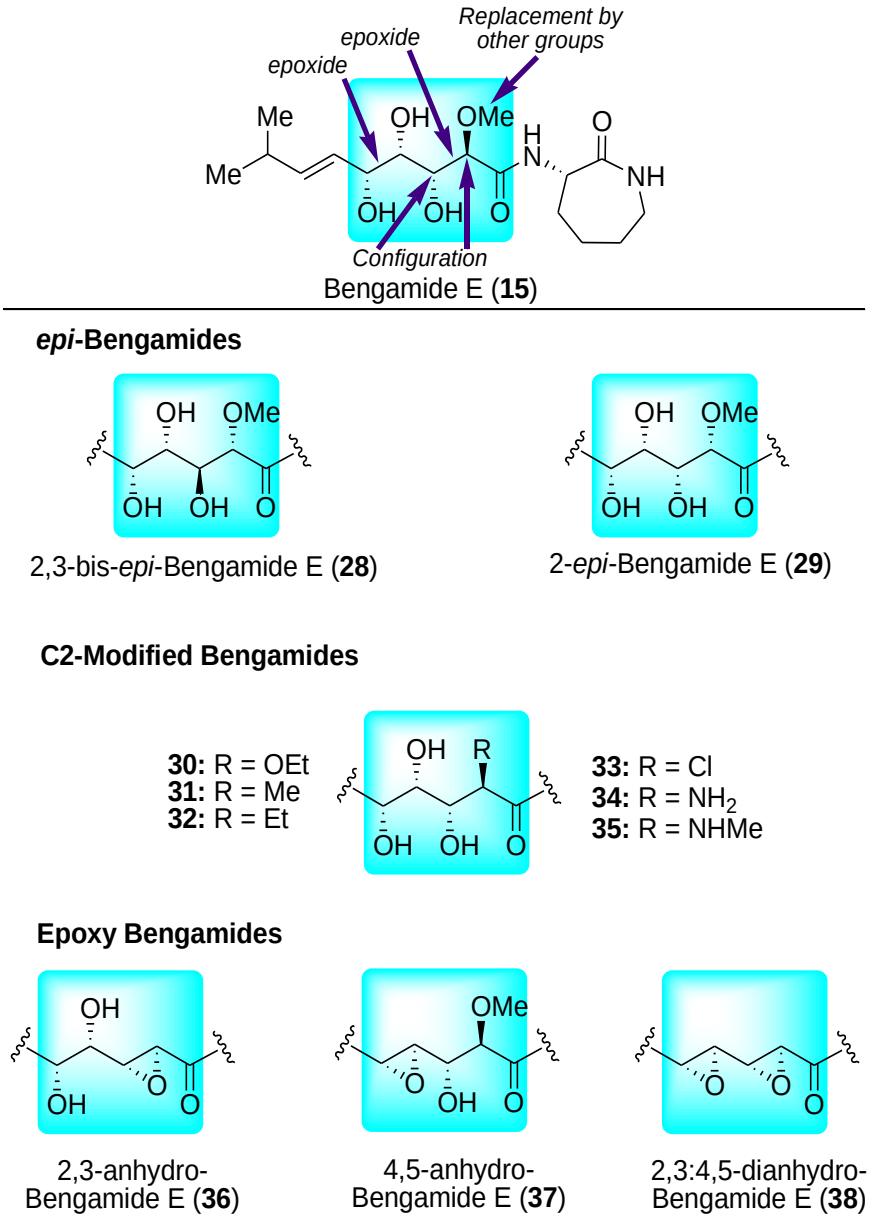
Figure 2. (A) Mode of Action of Fumagillin with Methionine Aminopeptidases. (B) Epoxy Bengamides as New Potential Fumagillin-like inhibitors



Consequently, in order to probe the effect of the stereochemistry as well as the biological significance of the methoxyl group and the presence of oxirane rings along the polyketide chain on their cytotoxic potency, we targeted the bengamide E analogues **28**-**35** and the epoxy derivatives **36**-**38** as potential fumagillin-bengamide hybrids (Figure 3). To

accomplish this goal, we decided to extend our synthetic strategy utilizing chiral sulfonium salts for their preparation.

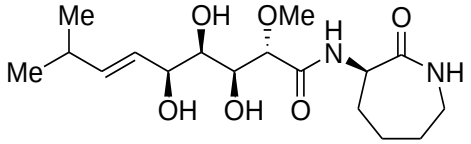
Figure 3. Programmed Modifications of Bengamide E and Targeted Analogues.



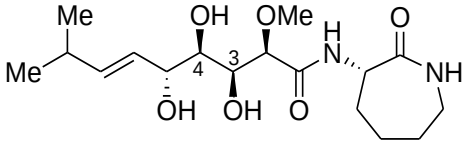
During these synthetic studies, Zhou et at. reported the synthesis of the 3,4-bis-*epi*-bengamide E (**39**),[19] revealing that these stereochemical changes resulted in a complete loss of antitumor activity. Previously, Banwell and coworkers described the synthesis of the enantiomer of bengamide E (***ent*-15**),[20,21] which also resulted in a completely inactive

compound. More recently, during the preparation of the present manuscript, Li and coworkes have described the synthesis of the 2-epimer of bengamide E and the desmethyl derivative **40** (Figure 4), together with a series of truncated bengamides.[22] In this study, Li et al. checked that whereas the 2-epimer and the truncated series of bengamides were completely inactive against different tumor cell lines, the 2-hydroxy derivative **40** retained certain cytotoxicity compared with bengamide E.

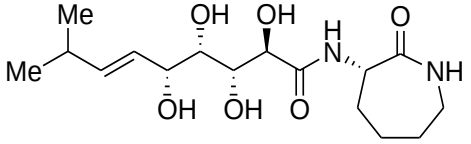
Figure 4. Precedents in Bengamide Analogues Modified at the Polyketide Chain.



ent-Bengamide E (***ent*-15**)
(Banwell, 2001, inactive)



3,4-bis-*epi*-Bengamide E (**39**)
(Zhou, 2010, inactive)



Desmethyl Bengamide E (**40**)
*(Li, 2013, 2 fold less active than **15**)*

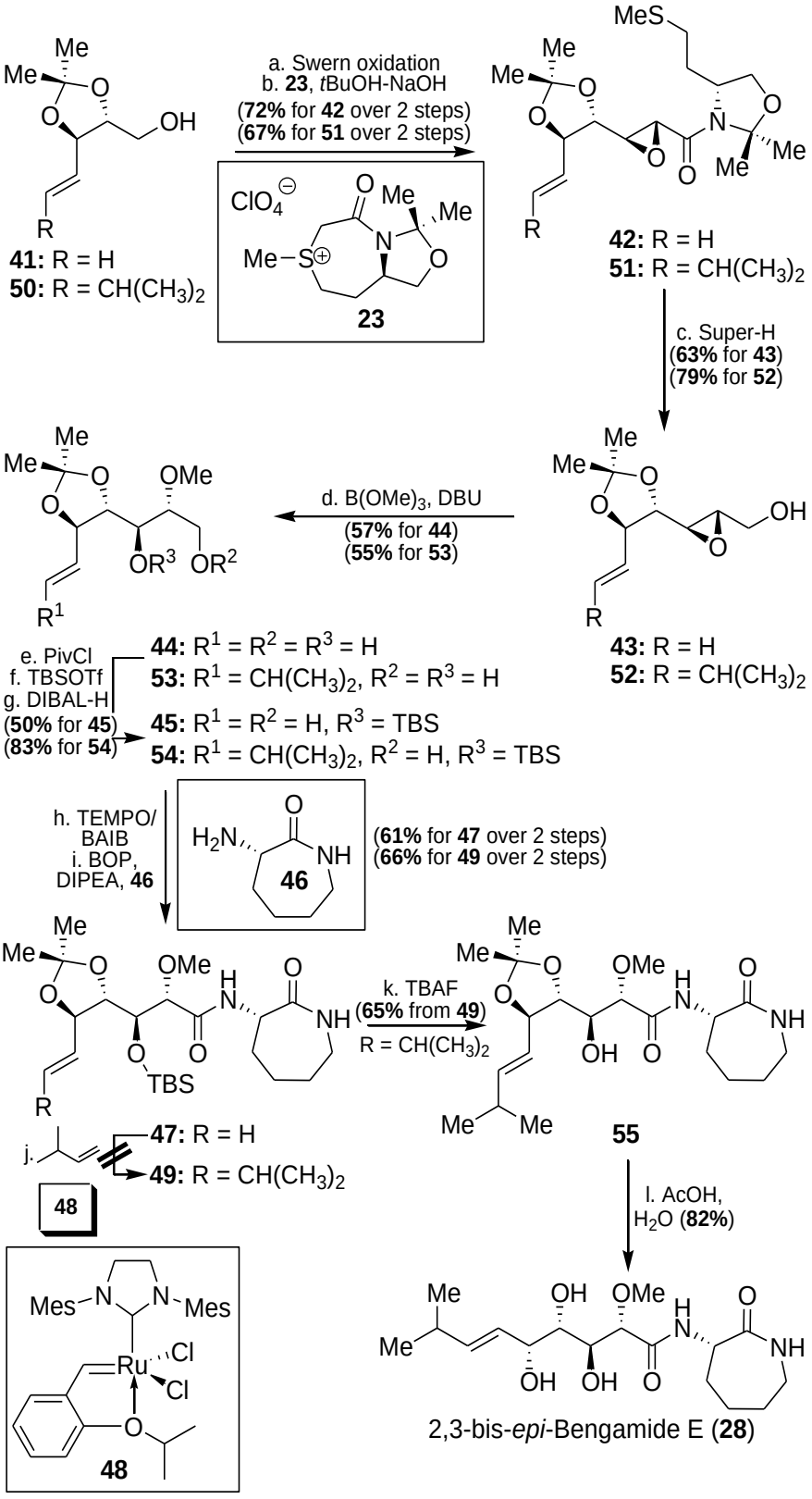
Results and Discussion

Synthesis of 2,3-bis-*epi*- and 2-*epi*-Bengamide E. For the synthesis of the 2,3-bis-epimer of bengamide E, compound **28**, we utilized our synthetic strategy for bengamide E by

use of the chiral sulfonium salt **23** prepared from D-methionine. Thus, starting from alcohol **41**,[18] its transformation into the aldehyde, via Swern oxidation,[23] was followed by the reaction with sulfonium salt **23**, under the same conditions reported by us for bengamide E. As a result, epoxy amide **42** was obtained in a reasonable good yield over 2 steps and complete stereoselectivity. The synthesis continued with the reduction of epoxy amide **42** to the corresponding epoxy alcohol **43** by treatment with lithium triethylborohydride (Super-H®)[24] and then, oxirane-ring opening reaction with MeOH in the presence of trimethyl borate [$(MeO)_3B$] and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU),[25] to provide the corresponding 2-methoxyl opened product **44** in 57% yield. Compound **44** was transformed into the olefin cross metathesis precursor **47** without major difficulties via the chemistry already described, involving selective protections and deprotections of the primary and secondary hydroxyl groups, oxidation and amide coupling with caprolactam **46**. Having prepared compound **47**, we proceeded with the olefin cross metathesis reaction by treatment with 3-methyl-1-butene in the presence of the 2nd generation Hoveyda-Grubbs catalyst **48**.[26] Unfortunately, this reaction did not work at all resulting in only recovered starting material and no detection of the desired compound **49**. Even though the olefin cross metathesis reaction was proven to be efficient for installation of the terminal olefinic substituent in the bengamide derivatives with the correct configuration at the C-2 and C-3 positions, the failure for other bengamide precursors, in particular the 2-C-alkyl analogues, as we reported in our previous article,[18] led to uncertainty as in the case of **47**. Consequently, as in previous cases, we sought to install the terminal isopropyl substituent earlier in the synthesis. As described in our previous work,[18] we efficiently prepared alcohol **50** via metathesis and then proceeded towards the synthesis of the targeted 2,3-bis-epimer. The synthetic sequence leading to the desired compound **49** was carried out without issue, according to the same synthetic sequence as before for **47** and through compounds **51**-**54**. Finally, the protecting groups were removed in two steps,

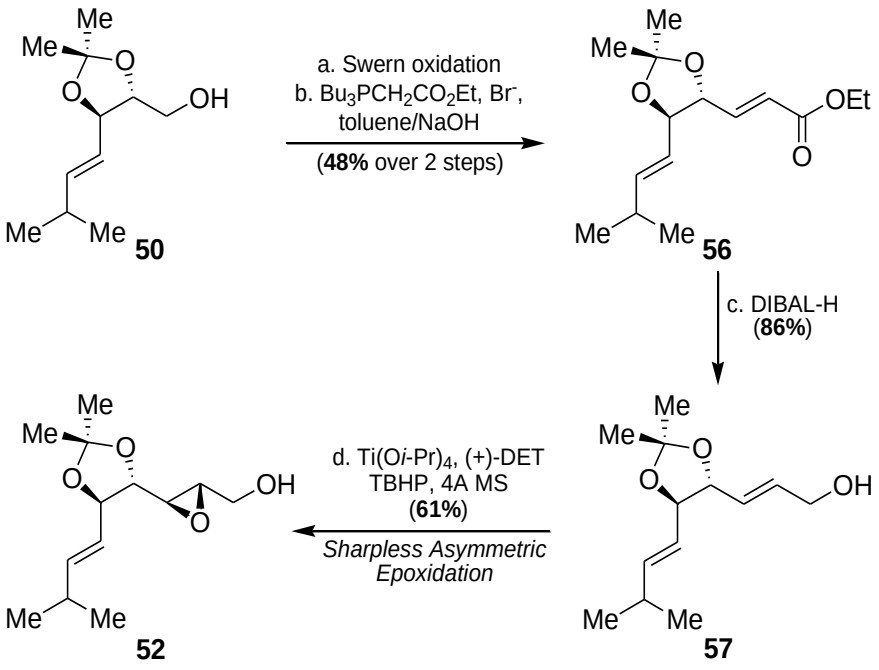
consisting of a TBAF treatment to obtain **55**, followed by acidic hydrolysis to afford the targeted 2,3-bis-epimer analogue of bengamide E, compound **28** (Scheme 2).

Scheme 2. Synthesis of 2,3-bis-*epi*-Bengamide E (**28**).



As a comparison, we decided to assess the Sharpless asymmetric epoxidation[27] as an alternative methodology to obtain epoxy alcohol **52**. Towards this aim, the starting alcohol **50** was subjected again to a Swern oxidation, and the resulting aldehyde transformed into the α,β-unsaturated ester **56** by reaction with the *in situ* ylide prepared from the phosphonium salt as depicted in Scheme 3.[28] The resulting α,β-unsaturated ester, formed in 48% overall yield from **50**, was then treated with diisobutylaluminum hydride (DIBAL-H) to provide the allylic alcohol **57** in 86% yield. Sharpless asymmetric epoxidation of **57** by use of (+)-Diethyl L-tartrate (DET) afforded the corresponding epoxy alcohol **52** in 61% yield and in excellent stereoselectivity (Scheme 3). The subsequent balance of both linear sequences led us to conclude that the sulfur ylide-based methodology was more efficient when compared to the Sharpless methodology, at least for this case.

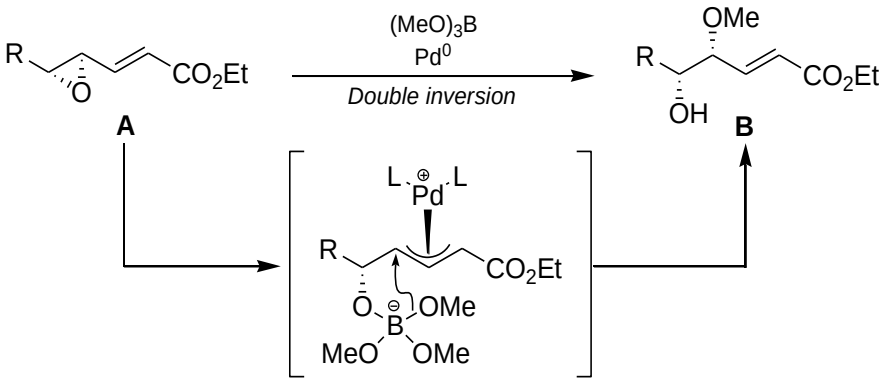
Scheme 3. Sharpless Asymmetric Epoxidation for the Synthesis of Epoxy Alcohol **52**.



Epoxy alcohol **52** via Sulfur Ylides from **50**: 3 steps, 40% overall yield
Epoxy alcohol **52** via Sharpless Epoxidation from **50**: 4 steps, 25% overall yield

The synthesis of the 2-epimer analogue of bengamide E by means of the epoxide chemistry presents an important stereochemical problem since a *trans* epoxide should deliver an *anti* opened product. The required *syn* stereochemistry for the 2-epimer would require either the generation of a *cis* epoxide[29] and subsequent oxirane-opening or an opening process from a *trans* epoxide via a substitution reaction with a double inversion of configuration, thus resulting with retention of configuration.[30] Since the chemistry of amide-stabilized sulfur ylides generate in all cases *trans* epoxides, we focused on the possibility of undertaking an oxirane-ring opening process capable of delivering the *syn*-opened product. Recently, Miyashita et al. described the opening of *trans*-γ,δ-epoxy-α,β-unsaturated esters (compounds type **A**) with alkylborates catalyzed by palladium (0) to yield the corresponding ring-opened products with *syn* relative configuration (compounds type **B**).[31] This stereochemical result can be rationalized according to Scheme 4.

Scheme 4. Stereochemical Rationale of the Double Inversion of Configuration of Substitution Reaction of Unsaturated *trans*-epoxy Esters.

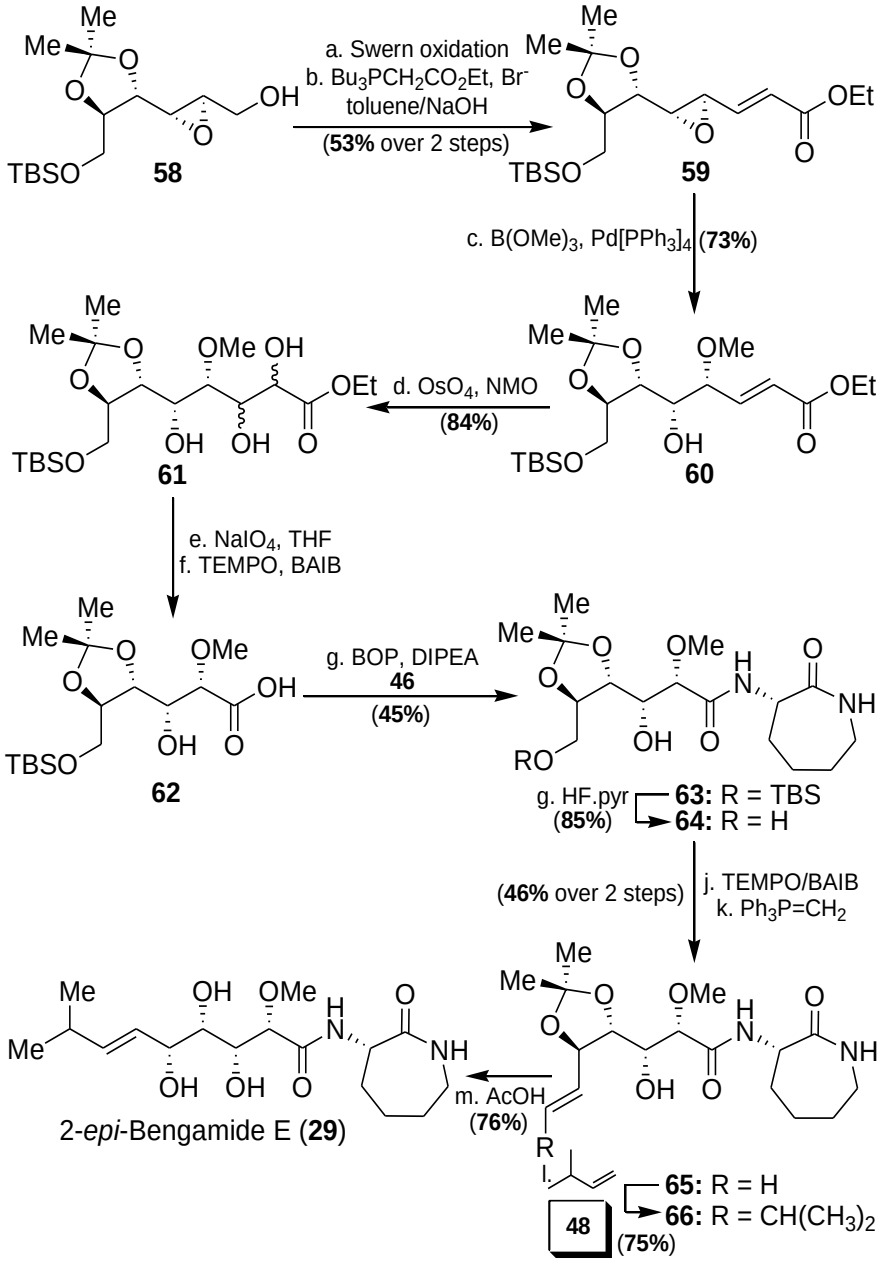


Inspired by this reaction, we proceeded to extend it to our synthetic endeavour. For this purpose, we prepared compound **59** via oxidation of epoxy alcohol **58**[32] followed by a Wittig

reaction. Then, **59** was subjected to the action of trimethylborate in the presence of tetrakis(triphenylphosphine)palladium (0) to obtain, in good yield and as a only one diastereoisomer, the targeted *syn* opened product **60**. Having installed the C2/C3 system with the required functionality and stereochemistry, the next step was to remove the α,β-unsaturated ester appendage. To achieve this transformation, dihydroxylation of **60** by treatment with catalytic osmium tetroxide[33] afforded the corresponding 1,2-diol product **61**. Subsequently, oxidative cleavage of the 1,2-diol with sodium periodate provided the aldehyde, which was converted to the acid **62** by treatment with 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and (diacetoxyiodo)benzene (BAIB).[34] Coupling of acid **62** with lactam **46** under the same conditions as before for **45** or **54** resulted in the formation of the lactam derivative **63**. Surprisingly, the deprotection of the silyl group of **63** by treatment with TBAF proceeded in a meager 5% yield for **64**. Fortunately, the silylether deprotection by treatment with HF.pyr resulted in a satisfactory 85% yield for **64**. This deprotection allowed a clear path towards the synthesis of the targeted 2-*epi*-bengamide E. To this end, compound **64** was selectively oxidized by the action of TEMPO/BAIB[35] and immediately treated with freshly prepared methylene triphenylphosphorane to provide the terminal alkene **65** albeit in a poor 46% overall yield. Finally, olefin cross metathesis under conventional conditions afforded the corresponding *trans* disubstituted olefin **66** in a good 75% yield, which was subjected to a final acetal deprotection step to furnish 2-*epi*-bengamide E (**29**) in 76% yield (Scheme 5).

Taking into account that the construction of the epimer at C2 of bengamide E through *trans*-epoxide chemistry required a synthetic detour that made its synthesis too long for practical supply of material, we considered an aldol reaction as a shorter synthetic alternative. To secure the desired absolute and relative configuration, the Evans methodology[36] was selected for this purpose.

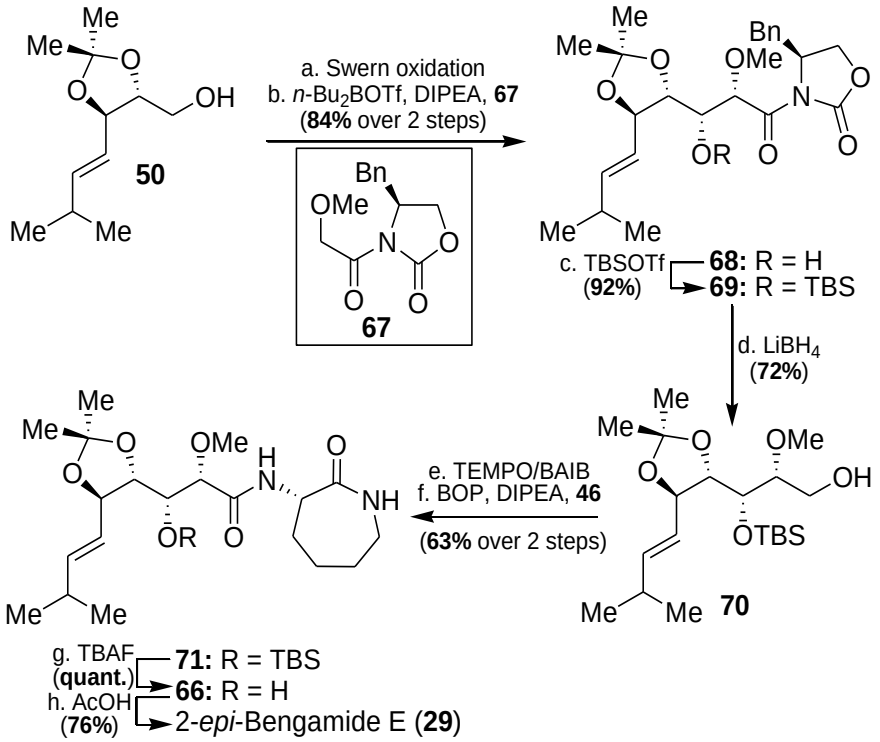
Scheme 5. Synthesis of 2-*epi*-Bengamide E (**29**) via Epoxide Chemistry.



Thus, aldol reaction of the (*Z*)-boron enolate of oxazolidinone **67**,[37] prepared by reaction with dibutylboron triflate (*n*-Bu_2BOTf) and *N*,*N*-diisopropylethylamine (DIPEA), with the aldehyde obtained from alcohol **50**, provided the *syn*-aldol product **68** as a single diastereoisomer in an excellent 84% yield. Silylation of **68**, followed by $LiBH_4$ reduction of the resulting silyl ether **69** provided alcohol **70** in very high yields. Oxidation of alcohol **70** to the acid, followed by coupling with **46** by the action of (benzotriazol-1-

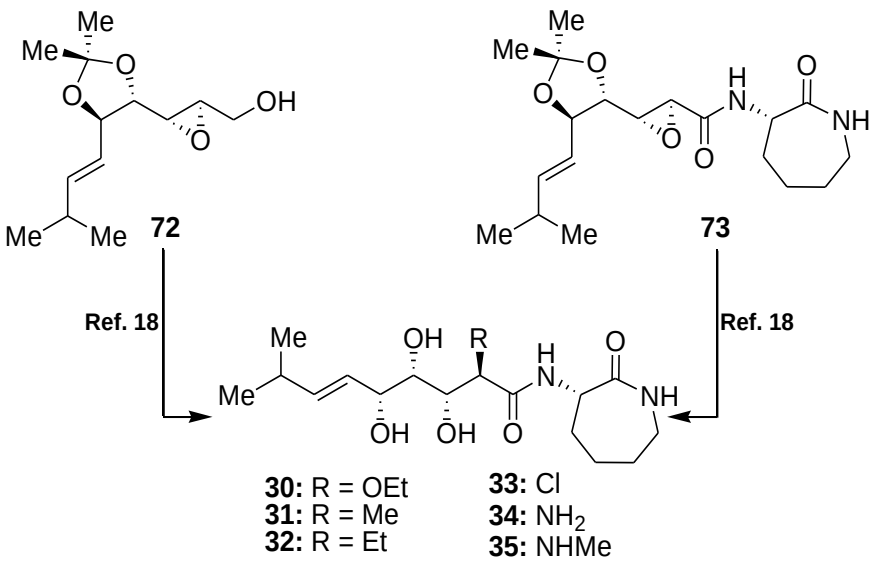
yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP), provided the precursor of 2-*epi*-bengamide E, compound **71**. The deprotection steps were carried out without any difficulty to obtain 2-*epi*-bengamide E (**29**) in a straightforward and efficient manner (Scheme 6).

Scheme 6. Synthesis of 2-*epi*-Bengamide E via Aldol Reaction.



Synthesis of C2-Modified Bengamides. The synthesis of the series of C2-modified bengamides (**30**-**35**) was achieved via oxirane-ring opening reactions of either epoxy alcohol **72** (compounds **30**-**32**) or epoxy amide **73** (compounds **33**-**35**) as previously described by us elsewhere[18] (Scheme 7).

Scheme 7. Synthesis of C2-Modified Bengamides.

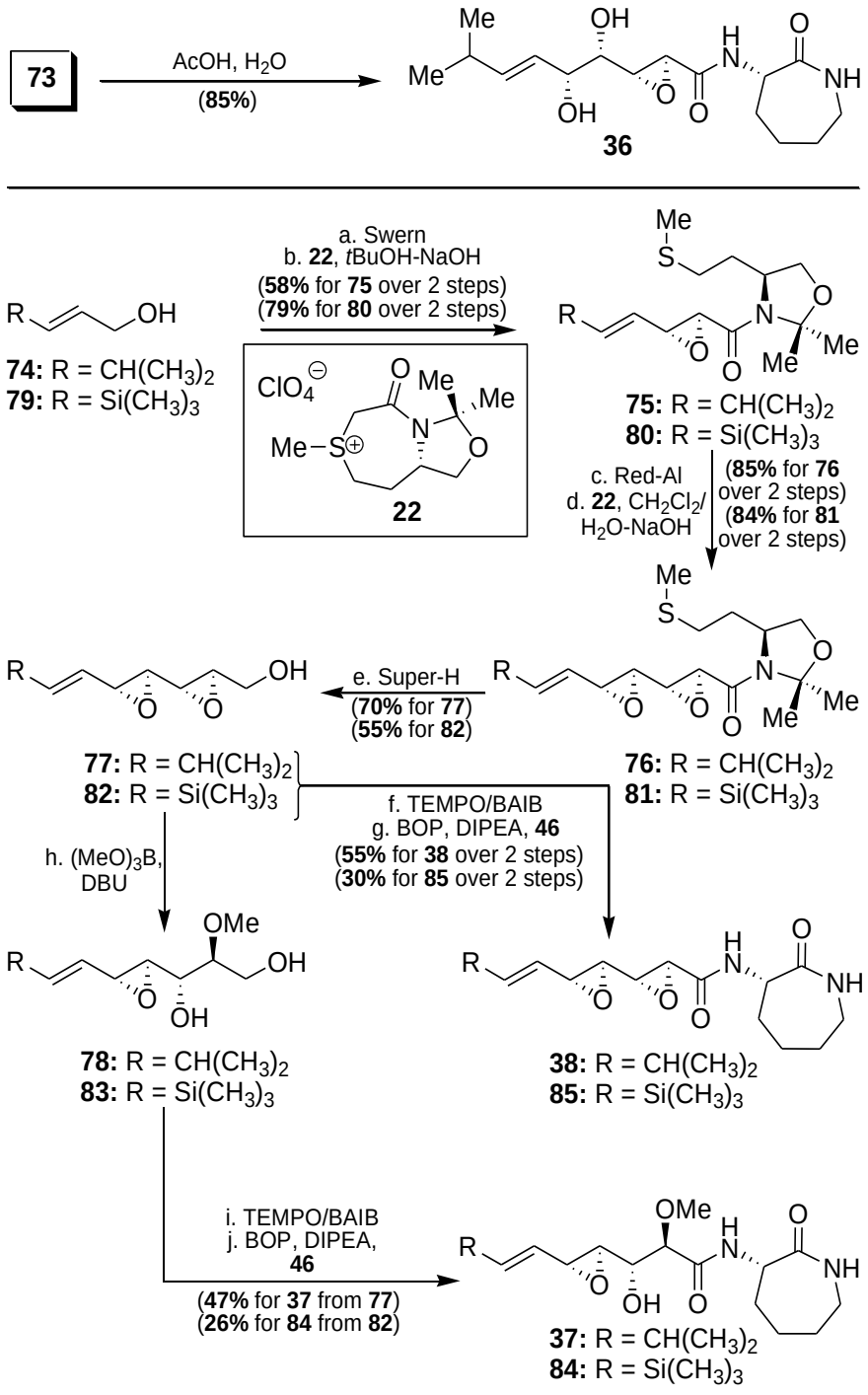


Synthesis of Epoxy Bengamides. For the synthesis of the series of anhydro derivatives of bengamide E, we commenced with the synthesis of the 2,3-epoxy analogue, compound **36**, which was achieved by acidic treatment of epoxy amide **73**, previously described by us. For the preparation of 4,5-epoxy or 2,3:4,5-diepoxy analogues, a different strategy was required. Thus, starting from allylic alcohol **74**,[38] its oxidation to the corresponding α,β-unsaturated aldehyde, followed by the reaction with the sulfonium salt **22** under basic conditions, afforded the corresponding epoxy amide **75** in good overall yield. Once the first oxirane ring was installed in a stereoselective fashion, the construction of a second oxirane group was undertaken via direct reduction of **75** to the epoxy aldehyde by the action of sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al),[39] followed by a second reaction with sulfonium salt **22**, according to our two-phase method,[40] to obtain diepoxy amide **76** in an excellent 85% overall yield from **75**. Reduction of **76** with Super-H yielded the expected diepoxy alcohol **77** which was considered a key product for the consecution of both coveted epoxy analogues of bengamide E. In a first set, diepoxy alcohol **77** was oxidized to the corresponding diepoxy acid and coupled with lactam **46**, as previously described, to

furnish the diepoxy bengamide E analogue **38**. On the other hand, **77** was treated with methanol in the presence of $B(OMe)_3$ and DBU to yield the corresponding 2-methoxyl derivative **78** in both chemo- and regioselective manners. Selective oxidation and coupling with amino lactam **46** were carried out without problems to obtain the desired 5,6-epoxy bengamide E **37** (Scheme 8). Given the positive results obtained in the synthesis of the epoxy and diepoxy bengamide analogues, we deemed it of interest to extend this chemistry to the trimethyl silyl derivative **79**[41] because the presence of this trimethylsilyl moiety can serve as an isostere for the isopropyl group found in the natural bengamides, as well as a handle to expand the synthetic possibilities for further structural modifications at the terminal olefinic position in virtue of the reactivity of vinylsilanes.[42] Thus, proceeding in a similar manner as for **74**, **79** was converted to epoxy and diepoxy bengamides **84** and **85**, through compounds **80**-**83**, in similar, or even better yields compared with the isopropyl series (Scheme 8).

Biological Evaluation of Bengamide E and Analogues. Having prepared the analogues of bengamide E, compounds **28**-**38**, **84** and **85**, our next goal in this research was to evaluate their antitumor properties to determine the influence of the described structural modifications against the antiproliferative potency. The determination of the cytotoxic properties of all these compounds was performed by measuring their IC_{50} values against a panel of different tumor cell lines using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) dye reduction assay.[43] This cytotoxicity was examined in four different cancer cell lines, namely HL 60 (human promyelocytic leukemia), MDA-MB-231 (human breast carcinoma), HT1080 (human fibrosarcoma), and HT29 (human colon adenocarcinoma), and in a primary culture of non transformed bovine aorta endothelial (BAE) cells. Bengamide E and fumagillin were used as controls to compare the activity of the new synthesized analogues. The results of this investigation are summarized in table 1.[44]

Scheme 8. Synthesis of Epoxy and Diepoxy Bengamides **37**, **38**, **84** and **85**.



Bengamide E (**15**) has previously been described to inhibit the in vitro growth of a tumor cell line at micromolar concentrations (3.3 μM against MDA-MB-435).[2a] A more detailed characterization of its activity and selectivity profile, however, is missing with the exceptions of the in vitro antitumor studies carried out by Banwell[20] and Li[22] who reported activity

against three tumor cell lines. The antiproliferative activity obtained for bengamide E in our biological assays are in agreement with the previously reported cytotoxic activity, since IC_{50} values obtained for bengamide E in the 5 cell types were in the low micromolar range. On the other hand, fumagillin (**27**), a fungal metabolite that potently inhibits angiogenesis by blocking endothelial cell proliferation and has advanced into clinical trials for multiple cancers, showed a biphasic effect on the growth of proliferating endothelial cells. At lower concentrations there is a first decrease in cell number, probably due to a cytostatic effect and, after a plateau covering several orders of concentration, a second cytotoxic effect is observed. This biphasic dosic-response curves, typical of fumagillin and its derivatives, were obtained with the tumor cell lines studied, indicating that fumagillin antiproliferative activity is not endothelial specific, which is in agreement with previously reported data (Table 1).[45]

In contrast to fumagillin, bengamide E and its analogues displayed well-defined cytotoxic activity in tumor cells as well as in endothelial cells. This is in agreement with previous observations indicating that inhibition of MetAp2 by the bengamides does not result in selective inhibition of endothelial cell proliferation.[46] Dose-response curves obtained with bengamide E and its epimeric analogues showed a sharp decrease in cell survival at concentrations that are around the IC_{50}. Thus, as these IC_{50} values reflect, it was quite clear that configurational changes in the polyketide chain led to a complete loss of cytotoxic activity, over 2-fold compared with bengamide E. These data, together with that reported by Zhou regarding the biological activity of the 3,4-bis-epimer,[19] reveal that modifications of the configuration of the polyketide chain severely impact the biological activity, demonstrating that the configuration of the polyketide chain is essential for recognition and binding to the biological target. Furthermore, it was observed that the 2-epimer of bengamide E was slightly more active than its 2,3-bis-epimer, indicating that the methoxyl group plays an important role

in the interaction with the active site of the enzyme, although probably not to the degree of the hydroxyl groups at C3, C4 and C5 positions, which seem to be involved in the coordination with cobalt ions present at the active site of the enzymes. Anyway, it is possible that the modification of the configuration at C2 position leads to a distorsion of the normal conformation of the bengamide framework, thereby preventing the molecule from adopting the required shape for binding to the methionine aminopeptidases. In order to more fully comprehend the role of the methoxyl group upon the antitumor potency, we resorted to the biological evaluation of the analogues **30**-**35**. The obtained cytotoxicities for these compounds clearly showed that the replacement of the methoxyl group with other functionalities resulted in a severe effect on activity. Thus, whereas the replacement of the methoxyl group by a *N*-methylamino system (compound **35**) led to a loss of activity of 10-20 fold with respect to bengamide E, the substitution of this group by others (compounds **30**-**34**) resulted in a total loss of antitumor activity. In a similar way, the epoxy and diepoxy bengamide E analogues (**36**-**38** and **85**) were completely inactive in the cytotoxic studies, indicating that the replacement of the 1,2-hydroxyl systems by an oxirane ring produced a complete lack of interaction with the active site of the enzymes and not resulting in a fumagillin-like interaction as we initially surmised.

Table 1. In vitro Antitumor Activities of Bengamide E, Bengamide E Analogues **28**-**38**, **85** and Fumagillin (**27**) against Different Tumor Cell Lines and BAEC (IC_{50}, μM)*

Compound	Tumor Cell Lines				
	MDA-MB-435[a]				
Bengamide E (**15**)[1]	3.3				
	A549[b]	**HCT116**[c]	**HUVEC**[d]		
Bengamide E (**15**)[2]	1.9	0.6	0.3		
	MDA-MB-435[a]	**HCT116**[c]	**MCF-7**[e]		
Bengamide E (**15**)[3]	6.71	9.02	3.36		
	MDA-MB-231[f]	**HT29**[g]	**HT1080**[h]	**HL60**[i]	**BAEC**[j]
Bengamide E (**15**)[4]	1.64 ± 0.54	0.95 ± 0.16	0.29 ± 0.03	0.68 ± 0.10	0.28 ± 0.03
2,3-bis-*epi*-Bengamide E (**28**)	100	89	> 100	81	100
2-*epi*-Bengamide E (**29**)	100.2 ± 13.3	85.2 ± 17.0	93.2 ± 8.1	60.3 ± 15.1	69.7 ± 3.2
Bengamide E Analogue **30**	100	100	> 100	68	75
Bengamide E Analogue **31**	> 100	> 100	n.d.	> 100	n.d.
Bengamide E Analogue **32**	> 100	> 100	n.d.	> 100	n.d.
Bengamide E Analogue **33**	> 100	> 100	89	n.d.	n.d.
Bengamide E Analogue **34**	38.5 ± 4.8	70.7 ± 12.0	30.2 ± 6.1	25.3 ± 5.2	28.9 ± 7.2
Bengamide E Analogue **35**	12.5 ± 3.0	10.6 ± 1.2	5.8 ± 0.1	9.2 ± 0.6	4.1 ± 1.3
Epoxy Bengamide **36**	100	79	> 100	n.d.	100
Epoxy Bengamide **37**	100	100	> 100	n.d.	100
Diepoxy Bengamide **38**	100	100	> 100	n.d.	100
TMS Epoxy Bengamide **85**	100	100	> 100	72	78
Fumagillin	54.3 ± 10.2	38.3 ± 12.5	Biphasic curve	36 ± 7.5	Biphasic curve

* In vitro cytotoxicities were determined according to the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide dye reduction assay as detailed in experimental part. The IC_{50} values were obtained from semilogarithmic dose-response plots as the concentration of compound yielding a 50% of cell survival.
[1] IC_{50} determined by Crews et al. (Ref. 2a)
[2] IC_{50} determined by Banwell et al. (Ref. 20)
[3] IC_{50} determined by Li et al. (Ref. 22)
[4] IC_{50} determined in our laboratories
[a] MDA-MB-435: Human breast carcinoma. [b] A549: Nonsmall cell lung cancer. [c] HCT116: Colon cancer cells. [d] HUVEC: Primary human umbilical vein endothelial cells. [e] MCF-7: Human breast adenocarcinoma. [f] MDA-MB-231: Human breast carcinoma. [g] HT29: Human colon adenocarcinoma. [h] HT1080: Human fibrosarcoma. [i] HL60: Human promyelocytic leukemia. [j] BAEC: Non transformed bovine aorta endothelial cells
n.d.: Not Determined

Conclusions

In conclusion, we have described the synthesis of two stereoisomers of Bengamide E, the 2,3-bis-*epi*- and the 2-*epi*- analogues, a collection of C2-modified analogues and various epoxy bengamides. Their syntheses were based on our synthetic methodology of epoxide formation via chiral sulfur ylides. Whereas this strategy proved to be efficient for the synthesis of the 2,3-bis-epimer, the C2-modifed analogues and the epoxy and diepoxy bengamides, the synthesis of the 2-epimer by means of the formation of *trans* epoxides was envisioned more problematic. To outcome this problem, the Miyashita methodology proved to be a valid and efficient method, representing the first synthetic application of this strategy in the synthesis of a bioactive compound. Alternatively, this 2-epimer was also prepared via aldol reaction. The biological activities of all these compounds against a panel of different tumor cell lines revealed that the stereochemistry at C2 and at C3 positions and the methoxyl group at C2 are essential for retaining the cytotoxic potency. These biological findings are in accordance with the proposed interaction of the bengamides with methionine aminopeptidases in which, the hydroxyl groups at C-3, C-4 and C-5 positions are involved in coordination with Co ions at the active site. Less clear is the importance of the methoxyl group at the C-2 position. Nonetheless, the lack of notable activity for either the 2-*epi*-bengamide E or the other C2-modified analogues indicates that this methoxyl group plays an important role in the binding of the compound to the active site of methionine aminopeptidases. All together, we have successfully demonstrated the utility and applicability of chiral sulfonium salts for the synthesis of bengamide analogues modified at the polyketide chain. In contrast, biological evaluation indicated that the polyol system is not amenable to modification due to the strong involvement that the polyketide chain has in its binding with the active site of the targeted enzymes. These results provide further support for the limited tolerance of the bengamide pharmacophore and its highly specific binding to the enzyme.

Experimental

General Techniques. All reactions were carried out under argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF) was distilled from sodium benzophenone, and methylene chloride (CH_2Cl_2) and benzene (PhH) from calcium hydride. Yields refer to chromatoghraphically and spectroscopically (1H NMR) homogeneous materials, unless otherwise stated. All solutions used in workup procedures were saturated unless otherwise noted. All reagents were purchased at highest commercial quality and used without further purification unless otherwise stated. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm silica gel plates (60F-254) using UV light as visualizing agent and 7% ethanolic phosphomolybdic acid or *p*-anisaldehyde solution and heat as developing agents. 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, 0.50 or 1 mm silica gel plates (60F-254). NMR spectra were recorded on a 400 MHz instrument and calibrated 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; band, several overlapping signals; b, broad. Optical rotations were recorded on a polarimeter. High resolution mass spectra (HRMS) were recorded on an ESI-TOF mass spectrometer in positive mode. Analytical and preparative HPLC were carried out in a reversed-phase using a reflection index detector. For preparative HPLC, a C8 5μm column (250 x 10.00 nm) was employed with a flow rate of 4.7 mL/min.

Biological Material and Methods. Cell culture media were purchased from Grand Island (NY, USA) and Walkersville (MD, USA). Fetal bovine serum (FBS) was a product from Belton (U.K.). Supplements and other chemicals not listed in this section were obtained from

St. Louis (Mo, USA). Plastics for cell culture were supplied by a company from Roskilde (Denmark). Bovine aortic endothelial (BAE) cells were obtained by collagenase digestion and maintained in Dulbecco´s modified Eagle´s medium (DMEM) containing glucose (1 g/L), glutamine (2 mM), penicillin (50 IU/mL), streptomycin (50 μg/mL), and amphotericin (1.25 μg/mL) supplemented with 10% FBS. All the cancer cell lines used in this study were obtained from the American Type Culture Collection (ATCC). Human fibrosarcoma HT1080 cells were maintained in DMEM containing glucose (4.5 g/L), glutamine (2 mM), penicillin (50 IU/mL), streptomycin (50 μg/mL), and amphotericin (1.25 μg/mL) supplemented with 10% FBS. Human colon adenocarcinoma HT29 cells were maintained in McCoy´s 5A medium containing glutamine (2 mM), penicillin (50 IU/mL), streptomycin (50 μg/mL), and amphotericin (1.25 μg/mL) supplemented with 10% FBS. Human breast cancer carcinoma MDA-MB-231 and human promyelocytic leukemia HL60 cells were maintained in RPMI1640 medium containing glutamine (2 mM), penicillin (50 IU/mL), streptomycin (50 μg/mL), and amphotericin (1.25 μg/mL) supplemented with 10 and 20% FBS, respectively.

Epoxy Amide 42. To a solution of sulfonium salt **23** (472 mg, 1.49 mmol, 1.1 equiv) in *t*BuOH (10 mL) was added a 3.0 M aqueous NaOH solution (0.49 mL, 1.49 mmol, 1.1 equiv). After 15 min at 25 ºC, a solution of crude aldehyde, obtained from alcohol **41** via Swern oxidation (1.36 mmol, 1.0 equiv), in *t*BuOH (4 mL) was added and the crude reaction mixture was stirred overnight at 25 ºC. After this time, the crude was diluted with EtOAc. The resulting organic solution was then sequentially washed with water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The resulting crude was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to obtain epoxy amide **42** (366 mg, 72% over two steps) as a yellow foam: R_f = 0.48 (silica gel, 20% EtOAc in hexanes); $[\alpha]^{25}_D$ = - 22.1 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.40 (s, 3 H), 1.44 (s, 3H),

1.52 (s, 3 H), 1.64 (s, 3 H), 1.84-1.92 (m, 1 H), 2.01-2.09 (m, 1 H), 2.10 (s, 3 H), 2.42-2.50 (m, 1 H), 2.53-2.58 (m, 1 H), 3.32 (dd, *J* = 5.9, 1.9 Hz, 1 H), 3.52-3.54 (m, 1 H), 3.56 (d, *J* = 1.9 Hz, 1 H), 3.91 (d, *J* = 9.2 Hz, 1 H), 4.01 (ddd, *J* = 9.2, 5.2, 1.3 Hz, 1 H), 4.27 (ddd, *J* = 10.3, 4.9, 3.4 Hz, 1 H), 4.42 (dd, *J* = 7.9, 6.9 Hz, 1 H), 5.29 (dt, *J* =10.3, 1.0 Hz, 1 H), 5.46 (dt, *J* = 17.2, 1.1 Hz, 1 H), 5.86 (ddd, *J* = 17.1, 10.4, 6.7 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 16.1, 23.3, 26.6, 27.1, 27.3, 31.2, 34.5, 52.1, 56.5, 57.4, 67.3, 80.1, 81.0, 96.3, 110.6, 119.6, 134.6, 163.3; HRMS (ESI-TOF) *m/e* 372.1852, $M+H^+$ calcd for $C_{18}H_{29}NO_5S$ 372.1845.

Epoxy Alcohol 43. Epoxy amide **42** (70 mg, 0.188 mmol, 1.0 equiv) in THF (2.0 mL) was treated with Super-H® (0.50 mL, 0.47 mmol, 2.5 equiv) at 0 ºC. After 1 h at this temperature, the reaction mixture was diluted with Et_2O and washed with a saturated aqueous NH4Cl solution. The aqueous phase was separated, extracted with Et_2O twice and the combined organic phase were washed with water and brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 40% EtOAc in hexanes) of the obtained crude product provided epoxy alcohol **43** (24 mg, 63%) as a yellow oil: R_f = 0.38 (silica gel, 50% EtOAc in hexanes); $[\alpha]^{25}_D$ = - 8.5 (*c* 0.4, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ =1.42 (s, 3 H), 1.43 (s, 3 H), 3.05-3.17 (m, 2 H), 3.65 (dt, *J* = 8.3, 4.2 Hz, 1 H), 3.81 (dd, *J* = 12.4, 4.9 Hz, 1 H), 4.14 (dd, *J* = 12.4, 2.6 Hz, 1 H), 4.35 (t, *J* = 7.4 Hz, 1 H), 5.28 (d, *J* = 10.3 Hz, 1 H), 5.43 (d, *J* = 17.1 Hz, 1 H), 5.86 (ddd, *J* = 17.1, 10.3, 6.9 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 27.1, 27.2, 54.9, 55.9, 62.9, 79.9, 80.5, 110.3, 119.4, 135.3; HRMS (ESI-TOF) *m/e* 201.1135, $M+H^+$ calcd for $C_{10}H_{16}O_4$ 201.1127.

Diol 44. Epoxy alcohol **43** (24 mg, 0.12 mmol, 1.0 equiv) was dissolved in a 1:1 mixture of MeOH/$B(OMe)_3$ (3.0 mL) and the resulting solution was treated with DBU (18 μL, 0.12

mmol, 1.0 equiv) and heated at 70 ºC for 12 hours. After this time, the reaction mixture was allowed to reach room temperature, cooled to 0 ºC, and then treated with a saturated aqueous $NaHCO_3$ solution. After the mixture was stirred for 30 min at 0 ºC, EtOAc was added and both phases were separated. The aqueous phase was extracted with EtOAc and the combined organic extracts were washed with water and brine then dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The resulting crude product was purified by flash column chromatography (silica gel, 60% EtOAc in hexanes) to afford diol **44** (16 mg, 57%) as a yellow oil: R_f = 0.21 (silica gel, 60% EtOAc in hexanes); $[\alpha]^{25}_D$ = - 2.1 (*c* 1.7, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.41 (s, 3 H), 1.43 (s, 3 H), 2.60 (bs, 2 H), 3.30-3.34 (m, 1 H), 3.38 (s, 3 H), 3.82 (dd, *J* = 12.1, 3.5 Hz, 1 H), 3.87 (dd, *J* = 12.1, 4.3 Hz, 1 H), 3.94 (dd, *J* = 7.7, 5.6 Hz, 1 H), 3.99 (t, *J* = 5.9 Hz, 1 H), 4.47 (dd, *J* = 7.5, 7.3 Hz, 1 H), 5.24-5.26 (m, 1 H), 5.41-5.45 (m, 1 H), 5.91 (ddd, *J* = 17.2, 10.2, 7.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 26.8, 27.1, 58.0, 60.8, 67.5, 78.6, 79.5, 81.6, 109.4, 119.5, 135.0; HRMS (ESI-TOF) *m/e* 233.1395, $M+H^+$ calcd for $C_{11}H_{20}O_5$ 233.1389.

Alcohol 45. Diol **44** (43 mg, 0.185 mmol, 1.0 equiv) was dissolved in a 2:1 pyridine/CH_2Cl_2 (1.75 mL) and cooled to 0 ºC. Pivaloyl chloride (28 μL, 0.22 mmol, 1.2 equiv) was added and the reaction mixture was stirred at this temperature for 90 min, then the mixture was diluted with CH_2Cl_2, and the organic phase was washed with a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The resulting crude was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to afford the corresponding pivaloate ester (33 mg, 67%) as a yellow oil. To a solution of pivaloate ester (33 mg, 0.104 mmol, 1.0 equiv) in CH_2Cl_2 (2.0 mL) was added 2,6-lutidine (24 μL, 0.21 mmol, 2.0 equiv) and TBSOTf (36 μL, 0.16 mmol, 1.5 equiv) at 0 ºC. After 1 hour at this temperature, the mixture was quenched with MeOH, diluted with Et_2O and washed with a saturated aqueous NH_4Cl solution. The aqueous phase was extracted with Et_2O and the

organic layers were washed with brine, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was subjected to purification by flash column chromatography (silica gel, 5% EtOAc in hexanes) to yield the corresponding silyl ether (39 mg, 87%) as a yellow oil. A solution of silyl ether (32 mg, 0.075 mmol, 1.0 equiv) in CH_2Cl_2 (2.0 mL) was cooled at -78 ºC and then treated with DIBAL (164 μL of a 1.0 M solution in toluene, 0.164 mmol, 2.2 equiv). After 40 min, the reaction was quenched by adding of AcOEt at -78 ºC, the resulting mixture was treated with a saturated aqueous Na^+/K^+ tartrate solution and allowed to reach room temperature. The resulting mixture was vigorously stirred until a clear separation of both organic and aqueous phases. The aqueous phase was then separated, the organic extract was washed with water and brine, dried ($MgSO_4$) and the solvent was evaporated. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to yield alcohol **45** (24 mg, 92%, 50% overall yield from **44**) as a yellow oil: R_f = 0.30 (silica gel, 20% EtOAc in hexanes); $[\alpha]^{25}_D$ = +30.4 (*c* 0.9, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.11 (s, 3 H), 0.12 (s, 3 H), 0.90 (s, 9 H), 1.39 (s, 3 H), 1.44 (s, 3 H), 1.95 (bs, 1 H), 3.35 (q, *J* = 4.5 Hz, 1 H), 3.40 (s, 3 H), 3.70 (dd, *J* = 11.9, 4.8 Hz, 1 H), 3.77 (dd, *J* = 11.9, 4.0 Hz, 1 H), 3.93-3.99 (m, 2 H), 4.42-4.46 (m, 1 H), 5.23 (dt, *J* = 10.3, 1.3 Hz, 1 H), 5.38 (dt, *J* = 17.1, 1.3 Hz, 1 H), 5.90 (ddd, *J* = 17.1, 10.4, 6.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.1,-3.8, 18.6, 26.4, 27.2, 27.5, 57.9, 60.5, 72.2, 79.0, 81.4, 82.4, 109.3, 118.2, 137.3; HRMS (ESI-TOF) *m/e* 347.2238, $M+H^+$ calcd for $C_{17}H_{34}O_5Si$ 347.2254.

Amide 47. Alcohol **45** (24 mg, 0.07 mmol, 1.0 equiv) was dissolved in a 1:1 mixture of CH_3CN:H_2O (2.0 mL) and the resulting solution was treated with BAIB (136 mg, 0.415 mmol, 6.0 equiv) followed by TEMPO (6.0 mg, 0.035 mmol, 0.5 equiv) at 25 ºC. After 5 h, the crude mixture was diluted with EtOAc, quenched by the addition of a saturated aqueous $Na_2S_2O_3$ solution and, after separation of both layers, the aqueous phase was then extracted

with EtOAc. The organic solution was washed with a saturated aqueous $Na_2S_2O_3$ solution, then dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude acid (0.07 mmol) was dissolved in DMF (1.0 mL) and treated with DIPEA (24 μL, 0.14 mmol, 2.0 equiv), L-Lys-Lactam **46** (17 mg, 0.104 mmol, 1.5 equiv) and BOP (38 mg, 0.08 mmol, 1.2 equiv) at 25 ºC. After being stirred at this temperature overnight, the crude mixture was diluted with Et_2O and washed with a saturated aqueous NH_4Cl solution. The aqueous phase was washed with Et_2O and the combined organic phases were washed with brine then dried over anhydrous $MgSO_4$ and the solvent was evaporated under vacuum. Purification of the obtained crude product by flash column chromatography (silica gel, 70% EtOAc in hexanes) provided amide **47** (20 mg, 61% over two steps) as a yellow foam: R_f = 0.30 (silica gel, 80% EtOAc in hexanes); $[\alpha]^{25}_D$ = +6.5 (*c* 0.8, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.12 (s, 3 H), 0.17 (s, 3 H), 0.89 (s, 9 H), 1.34 (s, 3 H), 1.37 (s, 3 H), 1.41-1.51 (m, 2 H), 1.76-1.87 (m, 2 H), 1.97-2.08 (m, 2 H), 3.23-3.30 (m, 2 H), 3.52 (s, 3 H), 3.82 (d, *J* = 2.1 Hz, 1 H), 4.03 (dd, *J* = 7.1, 7.0 Hz, 1 H), 4.27 (dd, *J* = 7.2, 2.1 Hz, 1 H), 4.43 (ddt, *J* = 7.0, 5.4, 1.4 Hz, 1 H), 4.53 (ddd, *J* = 11.2, 6.7, 1.5 Hz, 1 H), 5.17 (dt, *J* = 10.5, 1.4 Hz, 1 H), 5.40 (dt, *J* = 17.2, 1.5 Hz, 1 H), 5.95 (ddd, *J* = 17.2, 10.5, 5.4 Hz, 1 H), 6.03-6.05 (m, 1 H), 7.76 (d, *J* = 6.7 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ =-4.1, -3.7, 18.4, 26.4, 27.4, 27.5, 28.4, 29.3, 31.6, 42.6, 52.2, 60.3, 75.8, 79.8, 80.0, 85.0, 109.4, 116.7, 137.5, 169.1, 175.6; HRMS (ESI-TOF) *m/e* 471.2892, M+H$^+$ calcd for $C_{23}H_{42}N_2O_6Si$ 471.2890.

Epoxy amide 51. Epoxy amide **51** (725 mg, 67% over two steps) was prepared from alcohol **50** (534 mg, 2.66 mmol) by a Swern oxidation, followed by reaction with sulfonium salt **23** (1.01 g, 3.20 mmol, 1.20 equiv) according to the same procedure described above for the preparation of **42**. **[51]:** yellow oil; R_f = 0.52 (silica gel, 20% EtOAc in hexanes); $[\alpha]^{25}_D$ = -11.5 (*c* 0.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.96 (d, *J* = 6.7 Hz, 3 H), 0.97 (d, *J* = 6.7 Hz, 3 H), 1.30 (s, 3 H), 1.35 (s, 3 H), 1.49 (s, 3 H), 1.59 (s, 3 H), 1.73-1.83 (m, 1 H), 1.95-

2.05 (m, 1 H), 2.08 (s, 3 H), 2.28 (do, *J* = 6.7, 1.3 Hz, 1 H), 2.38-2.48 (m, 1 H), 2.54 (ddd, *J* = 13.1, 7.9, 5.0 Hz, 1 H), 3.25 (dd, *J* = 2.1 Hz, 1 H), 3.64 (d, *J* = 2.0 Hz, 1 H), 3.82 (dd, *J* = 8.5, 2.2 Hz, 1 H), 3.86 (d, *J* = 9.2 Hz, 1 H), 3.97 (ddd, *J* = 9.2, 5.2, 1.3 Hz, 1 H), 4.30 (ddd, *J* = 8.5, 4.6, 3.3 Hz, 1 H), 4.38 (dd, *J* = 8.3 Hz, 1 H), 5.37 (ddd, *J* = 15.4, 8.1, 1.4 Hz, 1 H), 5.87 (dd, *J* = 15.5, 6.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.8, 22.0, 25.4, 26.1, 26.3, 30.8, 30.9, 52.9, 57.3, 63.2, 78.4, 79.1, 82.6, 84.5, 111.1, 125.9, 142.2, 176.5; HRMS (ESI-TOF) *m/e* 414.2321, M+H$^+$ calcd for $C_{21}H_{35}NO_5S$ 414.2314.

Epoxy Alcohol 52. Epoxy amide **51** (551 mg, 1.33 mmol, 1.0 equiv) was reduced by treatment with Super-H® (3.40 mL, 1.0 M in THF, 2.5 equiv) according to the procedure described above for **42** to yield epoxy alcohol **52** (255 mg, 79%) as a yellow oil: R_f = 0.59 (silica gel, 50% EtOAc in hexanes); $[\alpha]^{25}_D$ = -18.4 (*c* 0.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.98 (d, *J* = 6.9 Hz, 6 H), 1.39 (s, 3 H), 1.40 (s, 3 H), 1.87 (bs, 1 H), 2.27- 2.38 (m, 1 H), 3.12-3.14 (m, 1 H), 3.15-3.18 (m, 1 H), 3.63-3.68 (m, 2 H), 3.94 (ddd, *J* = 12.7, 4.6, 2.3 Hz, 1 H), 4.29 (t, *J* = 8.0 Hz, 1 H), 5.38 (dd, *J* = 15.6, 7.5 Hz, 1 H), 5.82 (dd, *J* = 15.6, 6.9 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.8, 22.0, 26.5, 27.0, 31.0, 54.5, 56.0, 61.0, 79.0, 80.0, 109.5, 123.0, 144.0; HRMS (ESI-TOF) *m/e* 243.1602, M+H$^+$ calcd for $C_{13}H_{22}O_4$ 243.1596.

Diol 53. Diol **53** (129 mg, 55%) was prepared from epoxy alcohol **52** (209 mg, 0.863 mmol) by treatment with MeOH/$B(OMe)_3$ and DBU according to the same procedure described above for the preparation of **44**. **[53]:** yellow oil; R_f = 0.30 (silica gel, 50% EtOAc in hexanes); $[\alpha]^{25}_D$ = + 2.6 (*c* 0.4, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.99 (d, *J* = 6.4 Hz, 3 H), 1.00 (d, *J* = 6.4 Hz, 3 H), 1.41 (s, 6 H), 2.14 (bs, 2 H), 2.28-2.36 (m, 1 H), 3.26-3.30 (m, 1 H), 3.35 (s, 3 H), 3.81 (dd, *J* = 12.0, 3.4 Hz, 1 H), 3.86 (dd, *J* = 12.0, 4.5 Hz, 1 H), 3.91-3.98 (m, 2 H), 4.43 (dd, *J* = 8.1, 7.5 Hz, 1 H), 5.44 (ddd, *J* = 15.6, 8.1, 1.6 Hz, 1 H), 5.83 (dd, *J* =

15.6, 5.9 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.8, 21.9, 27.1, 30.7, 56.9, 60.4, 71.1, 78.6, 79.9, 108.6, 124.9, 143.4; HRMS (ESI-TOF) *m/e* 275.1852, M+H$^+$ calcd for $C_{14}H_{26}O_5$ 275.1858.

Alcohol 54. Alcohol **54** (128 mg, 83% over three steps) was prepared from diol **53** (113 mg, 0.41 mmol) by sequential treatment with pivaloyl chloride, TBSOTf and DIBAL-H according to the same procedure described above for the preparation of **45**. **[54]:** yellow oil; R_f = 0.59 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}_D$ = + 6.5 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.09 (s, 3 H), 0.10 (s, 3 H), 0.88 (s, 9 H), 0.97 (d, *J* = 6.4 Hz, 3 H), 0.99 (d, *J* = 6.4 Hz, 3 H), 1.37 (s, 3 H), 1.40 (s, 3 H), 1.90 (bs, 1 H), 2.26-2.34 (m, 1 H), 3.29-3.33 (m, 1 H), 3.37 (s, 3 H), 3.68 (dd, *J* = 11.8, 4.3 Hz, 1 H), 3.77 (dd, *J* = 11.8, 4.3 Hz, 1 H), 3.90 (dd, *J* = 8.1, 3.8 Hz, 1 H), 3.95 (dd, *J* = 5.9, 3.8 Hz, 1 H), 4.37 (dd, *J* = 8.1, 7.5 Hz, 1 H), 5.41 (ddd, *J* = 15.6, 7.5, 1.1 Hz, 1 H), 5.75 (dd, *J* = 15.6, 5.9 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ =-4.6, -4.2, 18.1, 21.9, 22.0, 26.0, 27.0, 27.1, 30.7, 57.3, 59.9, 71.2, 78.4, 81.5, 81.6, 108.4, 125.4, 142.6; HRMS (ESI-TOF) *m/e* 389.2718, M+H$^+$ calcd for $C_{20}H_{40}O_5Si$ 389.2723.

Amide 49. The oxidation of alcohol **54** (128 mg, 0.33 mmol) and subsequent coupling with L-Lys-Lactam **46** (84 mg, 0.49 mmol, 1.5 equiv) was carried out exactly as described above for **45** to yield amide **49** (112 mg, 66% over two steps) as a white foam: R_f = 0.20 (silica gel, 70% EtOAc in hexanes); $[\alpha]^{25}_D$ = +9.2 (*c* 0.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.08 (s, 3 H), 0.12 (s, 3 H), 0.84 (s, 9 H), 0.96 (d, *J* = 6.9 Hz, 6 H), 1.31 (s, 6 H), 1.34-1.47 (m, 3 H), 1.75-1.82 (m, 1 H), 1.93-2.04 (m, 2 H), 2.22- 2.28 (m, 1 H), 3.18-3.25 (m, 2 H), 3.47 (s, 3 H), 3.79 (d, *J* = 2.1 Hz, 1 H), 3.95 (dd, *J* = 6.9, 5.4 Hz, 1 H), 4.20 (dd, *J* = 6.9, 2.1 Hz, 1 H), 4.36 (dd, *J* = 6.5, 5.4 Hz, 1 H), 4.47-4.51 (m, 1 H), 5.43 (ddd, *J* = 15.6, 6.4, 1.6 Hz, 1 H), 5.71 (dd, *J* = 15.6, 6.4 Hz, 1 H), 6.37-6.44 (m, 1 H), 7.71 (d, *J* = 6.9 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.6, -4.2, 17.9, 21.9, 22.0, 25.9, 27.0, 27.2, 27.9, 28.8, 30.6, 31.2, 42.1, 51.7,

59.7, 75.2, 79.4, 79.9, 84.5, 108.5, 125.7, 140.8, 168.7, 175.3; HRMS (ESI-TOF) *m/e* 513.3364, M+H$^+$ calcd for $C_{26}H_{48}N_2O_6Si$ 513.3360.

Hydroxy Amide 55. To a solution of silylether amide **49** (52 mg, 0.10 mmol, 1.0 equiv) in THF (3.0 mL) was added TBAF (0.13 mL, 1.0 M in THF, 0.12 mmol, 1.2 equiv) at 25 ºC. After 50 min, the reaction mixture was diluted with Et_2O and washed with a saturated aqueous NH_4Cl solution. The aqueous phase was extracted with Et_2O and the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was then purified by flash column chromatography (silica gel, 6% MeOH in CH_2Cl_2) to obtain alcohol **55** (26 mg, 65%) as a white foam: R_f = 0.53 (silica gel, 8% MeOH in CH_2Cl_2); $[\alpha]^{25}_D$ = -13.3 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.97 (d, *J* = 6.9 Hz, 3 H), 0.98 (d, *J* = 6.9 Hz, 3 H), 1.38 (s, 6 H), 1.43-1.53 (m, 3 H), 1.75-1.85 (m, 1 H), 1.97-2.05 (m, 2 H), 2.25-2.33 (m, 1 H), 2.48 (bs, 1 H), 3.23-3.31 (m, 2 H), 3.43 (s, 3 H), 3.74 (d, *J* = 5.4 Hz, 1 H), 3.91 (dd, *J* = 7.7, 5.4 Hz, 1 H), 3.97 (t, *J* = 5.4 Hz, 1 H), 4.47 (t, *J* = 7.8 Hz, 1 H), 4.51-4.57 (m, 1 H), 5.41 (ddd, *J* = 15.6, 7.5, 1.1 Hz, 1 H), 5.83 (dd, *J* = 15.6, 6.4 Hz, 1 H), 6.15-6.19 (bs, 1 H), 7.72 (d, *J* = 6.7 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.8, 22.0, 26.8, 27.2, 27.9, 28.8, 30.7, 31.3, 42.1, 51.8, 59.1, 72.3, 79.1, 80.0, 82.0, 108.7, 124.8, 143.1, 169.6, 175.1; HRMS (ESI-TOF) *m/e* 399.2499, M+H$^+$ calcd for $C_{20}H_{34}N_2O_6$ 399.2495.

2,3-bis-*epi*-bengamide E (28). A solution of alcohol **55** (26 mg, 0.065 mmol, 1.0 equiv) in MeOH (0.5 mL) was treated with a 70% aqueous AcOH solution (2.0 mL) at 70 ºC for 1 h. After this time, the solvent was removed by evaporation under reduced pressure. Purification by flash column chromatography (silica gel, 6% MeOH in CH_2Cl_2) afforded the 2,3-bis-epimer of Bengamide E (**28**) (14 mg, 82%) as a white foam: R_f = 0.29 (silica gel, 8% MeOH in CH_2Cl_2); $[\alpha]^{25}_D$ = -24.6 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.97 (d, *J* = 6.5

Hz, 3 H), 0.98 (d, *J* = 6.5 Hz, 3 H), 1.36-1.44 (m, 1 H), 1.49-1.65 (m, 2 H), 1.74-1.86 (m, 2 H), 2.25-2.34 (m, 1 H), 2.78 (bs, 3 H), 3.25-3.27 (m, 2 H), 3.49 (s, 3 H), 3.55-3.57 (m, 1 H), 3.91 (d, *J* = 3.8 Hz, 1 H), 4.09 (dd, *J* = 7.0, 3.8 Hz, 1 H), 4.23-4.25 (m, 1 H), 4.55 (dd, *J* = 10.2, 7.0 Hz, 1 H), 5.53 (ddd, *J* = 15.6, 6.9, 1.1 Hz, 1 H), 5.75 (dd, *J* = 15.6, 5.9 Hz, 1 H), 6.15-6.22 (m, 1 H), 7.91 (d, *J* = 6.9 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 22.1, 22.2, 27.9, 28.8, 30.8, 31.4, 42.1, 52.0, 59.1, 71.7, 72.8, 74.2, 82.1, 126.0, 140.9, 170.0, 174.9; HRMS (ESI-TOF) *m/e* 359.2178, $M+H^+$ calcd for $C_{17}H_{30}N_2O_6$ 359.2182.

α,β-Unsaturated Ester 56. A solution of oxalyl chloride (0.80 mL, 9.10 mmol, 2.5 equiv) in CH_2Cl_2 (20.0 mL) was cooled to -78 ºC, and DMSO (1.3 mL, 18.20 mmol, 5.0 equiv) was added dropwise. After 10 min, a solution of alcohol **50** (729 mg, 3.64 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added. The reaction mixture was stirred at -78 ºC for 40 min, and then TEA (3.8 mL, 27.30 mmol, 7.5 equiv) was added at this temperature. After 10 min at -78 ºC, the reaction was allowed to reach room temperature and then diluted with Et_2O and washed with a saturated aqueous NH_4Cl solution. The aqueous phase was washed with water and brine, dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude aldehyde obtained was used in the next step without purification. A solution of tributyl(methoxycarbonylmethylene)phosphonium bromide (1.70 g, 4.55 mmol, 1.25 equiv) in CH_2Cl_2 (5.0 mL) was washed with a 1.0 M aqueous NaOH solution (2 x 4.6 mL), dried ($MgSO_4$), and diluted with toluene (4.0 mL). The CH_2Cl_2 was evaporated and the resulting solution was then added to a stirred solution of crude aldehyde (~ 3.64 mmol, 1.0 equiv) and benzoic acid (89 mg, 0.73 mmol, 0.2 equiv) in toluene (16 mL) at 90 ºC. After 30 min, the solvent was evaporated and the residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to provide α,β-unsaturated ester **56** (466 mg, 48% over two steps) as a colorless oil: R_f = 0.32 (silica gel, 10% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.00 (d, *J* = 6.7 Hz, 3 H), 1.01 (d, *J* = 6.7 Hz, 3 H), 1.30 (t, *J* = 7.1 Hz, 3 H),

1.43 (s, 3 H), 1.46 (s, 3 H), 2.32 (od, *J* = 6.7, 1.3 Hz, 1 H), 4.08 (dd, *J* = 8.2, 8.1 Hz, 1 H), 4.17-4.24 (m, 1 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 5.38 (ddd, *J* = 15.5, 7.9, 1.3 Hz, 1 H), 5.81 (dd, *J* = 15.5, 6.4 Hz, 1 H), 6.11 (dd, *J* = 15.6, 1.5 Hz, 1 H), 6.84 (dd, *J* = 15.6, 5.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.2, 21.8, 22.0, 26.7, 27.1, 30.8, 60.6, 79.8, 82.1, 109.5, 122.0, 122.4, 143.1, 144.8, 166.1; HRMS (ESI-TOF) *m/e* 269.1736, $M+H^+$ calcd for $C_{15}H_{24}O_4$ 269.1753.

Allylic Alcohol 57. A solution of α,β-unsaturated ester **56** (466 mg, 1.74 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was cooled at -78 ºC and then treated with DIBAL-H (4.4 mL of a 1.0 M solution in toluene, 4.34 mmol, 2.5 equiv). After 40 min, the reaction was quenched by adding of EtOAc at -78 ºC and the mixture was allowed to reach room temperature and treated with a saturated aqueous Na^+/K^+ tartrate solution. The resulting mixture was vigorously stirred until a clear separation of both organic and aqueous phases. The aqueous phase was then separated, the organic extracts were washed with water and brine, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The crude product was then purified by flash column chromatography (silica gel, 30% EtOAc in hexanes) to yield allylic alcohol **57** (338 mg, 86%) as a yellow oil: R_f = 0.20 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}_D$ = -32.9 (*c* 0.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.99 (d, *J* = 6.7 Hz, 3 H), 1.00 (d, *J* = 6.7 Hz, 3 H), 1.43 (s, 3 H), 1.44 (s, 3 H), 1.54 (bs, 1 H), 2.31 (od, *J* = 6.7, 1.1 Hz, 1 H), 4.03-4.14 (m, 2 H), 4.17 (dd, *J* = 5.2, 1.6 Hz, 2 H), 5.35 (ddd, *J* = 15.4, 7.4, 1.3 Hz, 1 H), 5.69 (ddt, *J* = 15.5, 6.6, 1.6 Hz, 1 H), 5.76 (dd, *J* = 15.1, 6.5 Hz, 1 H), 5.95 (dtd, *J* = 15.5, 5.1, 0.7 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.9, 22.2, 26.8, 30.6, 63.2, 80.1, 82.2, 109.3, 119.0, 126.7, 134.5, 135.8; HRMS (ESI-TOF) *m/e* 227.1628, $M+H^+$ calcd for $C_{13}H_{22}O_3$ 227.1647.

Epoxy Alcohol 52. To a suspension of titanium tetraisopropoxide (180 μL, 0.59 mmol, 0.4 equiv) and 4 Å molecular sieves (500 mg) in CH_2Cl_2 (5.0 mL) was added (+)-DET (110 μL,

0.59 mmol, 0.4 equiv) at -23 ºC. After 15 min at this temperature, a solution of allylic alcohol **57** (338 mg, 1.49 mmol, 1.0 equiv) in CH_2Cl_2 (3.0 mL) was added dropwise, followed by the addition, after 30 min, of *tert*-butyl hydroperoxide (TBHP) (980 μL, 5.5 M in decane, 5.38 mmol, 3.9 equiv) at -23 ºC. After 8 h at this temperature, the reaction mixture was quenched by addition of Me_2S (0.5 mL) at 0 ºC and then, the solution was filtered and the filtrate was evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 30% EtOAc in hexanes) to obtain epoxy alcohol **52** (222 mg, 61%) whose spectroscopic and physical properties were identical to those obtained from epoxy amide **51**.

α,β-Unsaturated Epoxy Ester 59. A solution of oxalyl chloride (0.10 mL, 1.18 mmol, 2.0 equiv) in CH_2Cl_2 (5.0 mL) was cooled to -78 ºC, and DMSO (0.17 mL, 2.36 mmol, 4.0 equiv) was added dropwise. After 10 min, a solution of alcohol **58** (187 mg, 0.59 mmol, 1.0 equiv) in CH_2Cl_2 was added. The reaction mixture was stirred at -78 ºC for 40 min, and then TEA (0.49 mL, 3.54 mmol, 6.0 equiv) was added at this temperature. After 10 min at -78 ºC, the reaction was allowed to reach room temperature and then diluted with Et_2O and washed with a saturated aqueous NH_4Cl solution. The aqueous phase was washed with water and brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude aldehyde obtained was used in the next step without purification. A solution of tributyl(methoxycarbonylmethylene)phosphonium bromide (275 mg, 0.74 mmol, 1.25 equiv) in CH_2Cl_2 (5.0 mL) was washed with a 1.0 M aqueous NaOH solution (twice), dried ($MgSO_4$), and diluted with toluene. The CH_2Cl_2 was then evaporated under vacuum. The resulting solution was then added to a stirred solution of crude aldehyde (~ 0.59 mmol, 1.0 equiv) and benzoic acid (18 mg, 0.15 mmol, 0.25 equiv) in toluene at 95 ºC. After 30 min, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel, 10%→20% EtOAc in hexanes) to provide α,β-unsaturated epoxy

ester **59** (120 mg, 53% over two steps) as a yellow oil: R_f = 0.28 (silica gel, 10% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.08 (s, 6 H), 0.90 (s, 9 H), 1.29 (t, *J* = 7.2 Hz, 3 H), 1.40 (s, 6 H), 3.06 (dd, *J* = 3.8, 2.0 Hz, 1 H), 3.53 (dd, *J* = 7.3, 1.9 Hz, 1 H), 3.72 (dd, *J* = 10.5, 6.1 Hz, 1 H), 3.85 (dd, *J* = 10.6, 2.9 Hz, 1 H), 3.99 (dd, *J* = 7.7, 3.9 Hz, 1 H), 4.05 (ddd, *J* = 7.7, 6.1, 3.8 Hz, 1 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 6.15 (d, *J* = 15.7, 1 H), 6.67 (dd, *J* = 15.7, 7.3 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -5.40, -5.39, 14.1, 18.3, 25.8, 26.4, 27.0, 53.6, 60.1, 60.6, 63.4, 77.6, 77.9, 110.0, 124.4, 143.6, 165.4; HRMS (ESI-TOF) *m/e* 387.2212, $M+H^+$ calcd for $C_{19}H_{34}O_6Si$ 387.2203.

α,β-Unsaturated-γ-Methoxy-δ-Hydroxy Ester 60. To a solution of α,β-unsaturated-γ,δ-epoxy ester **59** (73 mg, 0.19 mmol, 1.0 equiv) in THF (5.0 mL) was added at 0 ºC trimethyl borate (19 μL, 0.25 mmol, 1.3 equiv) and $Pd(PPh_3)_4$ (22 mg, 0.019 mmol, 0.1 equiv) and the mixture was stirred at 0 ºC for 30 min. After this time, the reaction mixture was passed through a silica gel column by the aid of EtOAc and the eluate was concentrated in vacuo to obtain a crude product which was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to afford γ-methoxy-δ-hydroxy ester **60** (58 mg, 73%) as a yellow oil: R_f = 0.30 (silica gel, 20% EtOAc in hexanes); $[\alpha]^{25}_D$ = -10.6 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.04 (s, 3 H), 0.05 (s, 3 H), 0.87 (s, 9 H), 1.30 (t, *J* = 7.1 Hz, 3 H), 1.38 (s, 3 H), 1.43 (s, 3 H), 2.71 (d, *J* = 5.9 Hz, 1 H), 3.36 (s, 3 H), 3.62 (dt, *J* = 6.9, 1.8 Hz, 1 H), 3.67 (dd, *J* = 10.7, 5.9 Hz, 1 H), 3.80 (dd, *J* = 10.6, 4.1 Hz, 1 H), 3.91 (dt, *J* = 6.9, 1.0 Hz, 1 H), 3.94 (dd, *J* = 8.1, 1.9 Hz, 1 H), 4.14-4.20 (m, 1 H), 4.21 (dc, *J* = 7.1, 1.4 Hz, 2 H), 6.10 (dd, *J* = 15.8, 1.1 Hz, 1 H), 6.82 (dd, *J* = 15.8, 7.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -5.6, -5.5, 14.1, 18.2, 25.8, 26.7, 27.0, 57.4, 60.4, 63.2, 71.6, 76.7, 77.4, 82.3, 109.2, 124.6, 143.9, 165.5; HRMS (ESI-TOF) *m/e* 419.2472, $M+H^+$ calcd for $C_{20}H_{38}O_7Si$ 419.2465.

Trihydroxy Ester 61. OsO_4 (2.5 wt.-% solution in *t*BuOH, 66 μL, 0.0065 mmol, 0.05 equiv) was added to a stirred solution of *N*-methylmorpholine *N*-oxide (46 mg, 0.39 mmol, 3.0 equiv) and γ-methoxy-α,β-unsaturated ester **60** (55 mg, 0.13 mmol, 1.0 equiv) in THF (5.0 mL). When the reaction was complete (6-8 h), the reaction mixture was diluted with EtOAc and treated with a saturated aqueous Na_2SO_3 solution. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$, and the solvent evaporated under reduced pressure to afford the crude compound which was purified by flash column chromatography (silica gel, 40% EtOAc in hexanes) to obtain trihydroxy ester **61** (50 mg, 84%) as a yellow oil: R_f = 0.28 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$ = +1.97 (*c* 0.4, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.06 (s, 6 H), 0.88 (s, 9 H), 1.30 (t, *J* = 7.7 Hz, 3 H), 1.39 (s, 3 H), 1.42 (s, 3 H), 3.02-3.05 (m, 2 H), 3.24-3.27 (m, 1 H), 3.42-3.44 (m, 1 H), 3.47 (d, *J* = 0.9 Hz, 3 H), 3.73 (dd, *J* = 10.7, 5.4 Hz, 1 H), 3.82-3.86 (m, 1 H), 3.91 (d, *J* = 9.6 Hz, 1 H), 4.06-4.15 (m, 3 H), 4.25-4.31 (m, 2 H), 4.39 (d, *J* = 6.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -5.5, -5.4, 14.1, 18.3, 25.9, 26.9, 27.2, 59.3, 62.0, 63.5, 68.1, 70.6, 72.3, 78.8, 80.7, 109.4, 173.7; HRMS (ESI-TOF) *m/e* 453.2526, $M+H^+$ calcd for $C_{20}H_{40}O_9Si$ 453.2520.

Acid 62. $NaIO_4$ (24 mg, 0.11 mmol, 1.1 equiv) was added to a solution of trihydroxy ester **61** (46 mg, 0.10 mmol, 1.0 equiv) in a 1:1 THF:H_2O mixture (4.0 mL). The mixture was stirred during 8 h, then was diluted with Et_2O and washed with water. The aqueous layer was extracted with Et_2O and the combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution, dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The crude aldehyde obtained was used in the next step without purification. The crude aldehyde (~ 0.11 mmol, 1.0 equiv) was dissolved in a 1:1 mixture of CH_3CN/H_2O (5.0 mL) and the resulting solution was treated with BAIB (193 mg, 0.60 mmol, 6.0 equiv) followed by TEMPO (4.7 mg, 0.03 mmol, 0.3 equiv) at 25 ºC. After 6 h, the crude mixture was diluted

with EtOAc, quenched by the addition of a saturated aqueous $Na_2S_2O_3$ solution and, after separation of both layers, the aqueous phase was then extracted with EtOAc. The combined organic solution was washed with a saturated aqueous $Na_2S_2O_3$ solution again, then dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure to obtain crude acid **62** which was used for the next step without further purification.

Amide 63. Crude acid **62** (~ 0.10 mmol, 1.0 equiv) was coupled with L-Lys-Lactam **46** (19 mg, 0.15 mmol, 1.5 equiv) in the same manner as described above for **47** to yield amide **63** (21 mg, 45% over three steps) as a yellow oil: R_f = 0.36 (silica gel, EtOAc); $[\alpha]^{25}_D$ = -0.26 (*c* 0.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.06 (s, 6 H), 0.90 (s, 9 H), 1.33 (s, 3 H), 1.37 (s, 3 H), 1.40-146 (m, 2 H), 1.77-1.88 (m, 2 H), 1.97-2.02 (m, 1 H), 2.15-2.18 (m, 1 H), 3.24-3.31 (m, 2 H), 3.50 (s, 3 H), 3.70 (dd, *J* = 10.5, 6.2 Hz, 1 H), 3.80 (d, *J* = 6.3 Hz, 1 H), 3.83 (dd, *J* = 10.5, 4.1 Hz, 1 H), 3.92 (dd, *J* = 4.8, 1.7 Hz, 1 H), 4.05 (dd, *J* = 8.1, 1.6 Hz, 1 H), 4.14-4.18 (m, 1 H), 4.55 (ddd, *J* = 11.2, 7.0, 1.7 Hz, 1 H), 6.06-6.10 (m, 1 H), 7.86 (d, *J* = 6.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -5.5, -5.4, 18.3, 25.9, 26.8, 27.3, 27.9, 28.9, 30.7, 42.0, 51.6, 53.4, 59.1, 63.7, 69.4, 77.9, 81.0, 109.3, 170.1, 175.4; HRMS (ESI-TOF) *m/e* 475.2842, $M+H^+$ calcd for $C_{22}H_{42}N_2O_7Si$ 475.2839.

Diol 64. A solution of silyl ether **63** (20 mg, 0.042 mmol, 1.0 equiv) in THF (2.0 mL) was treated with HF•pyr (70% solution, 25 μL) at 0 ºC. After stirring for 1 h at this temperature, the reaction mixture was quenched by addition of a saturated aqueous $NaHCO_3$ solution and diluted with CH_2Cl_2. After separation of both layers, the aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$, and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 70% EtOAc in hexanes) to obtain diol **59** (13 mg, 85%) as a yellow oil: R_f = 0.26 (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]^{25}_D$ = -15.6 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz,

$CDCl_3$) δ = 1.37 (s, 3 H), 1.40 (s, 3 H), 1.80-1.90 (m, 3 H), 1.95-2.10 (m, 2 H), 2.15-2.20 (m, 1 H), 3.23-3.36 (m, 2 H), 3.52 (s, 3 H), 3.66 (dd, *J* = 12.0, 3.8 Hz, 1 H), 3.81-3.86 (m, 3 H), 4.07 (d, *J* = 8.5 Hz, 1 H), 4.22 (dd, *J* = 8.1, 3.9 Hz, 1 H), 4.56 (dd, *J* = 10.4, 7.1 Hz, 1 H), 6.02 (t, *J* = 6.8 Hz, 1 H), 7.86 (d, *J* = 6.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 26.8, 27.4, 28.0, 29.0, 29.7, 30.8, 42.2, 51.8, 59.3, 61.6, 69.4, 76.2, 81.0, 109.5, 170.1, 175.1; HRMS (ESI-TOF) *m/e* 361.1958, $M+H^+$ calcd for $C_{16}H_{28}N_2O_7$ 361.1975.

Alkene 65. To a solution of diol **64** (10 mg, 0.03 mmol, 1.0 equiv) in CH_2Cl_2 (2.0 mL) was added BAIB (29 mg, 0.09 mmol, 3.0 equiv) and TEMPO (1.4 mg, 0.009 mmol, 0.3 equiv) at 0 ºC. After 0.5 h at this temperature, the crude mixture was diluted with Et_2O, quenched by the addition of a saturated aqueous $Na_2S_2O_3$ solution and, after separation of both layers, the aqueous phase was then extracted with Et_2O twice. The organic solution was washed again with a saturated aqueous $Na_2S_2O_3$ solution, then dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude aldehyde (~ 0.03 mmol) was dissolved in THF (2.0 mL) and added dropwise to a freshly prepared solution of methylenetriphenylphosphorane ($Ph_3P=CH_2$) [Sodium hexamethyldisilylamide (NaHMDS, 0.12 mL, 0.12 mmol, 1.0 M solution in THF, 4.0 equiv) was slowly added to a suspension of methyltriphenylphosphonium bromide (44 mg, 0.12 mmol, 4.0 equiv) in THF (4.0 mL) at 0 ºC and stirring at this temperature for 15 min] at 0 ºC. After being stirred for 0.5 h, the reaction mixture was diluted with Et_2O and washed with a saturated aqueous NH_4Cl solution. The aqueous phase was washed with Et_2O and the combined organic phases were washed with brine, then dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. Purification of the obtained crude product by flash column chromatography (silica gel, 30% EtOAc in hexanes) provided alkene **65** (5.0 mg, 46% over two steps) as a pale yellow oil: R_f = 0.25 (silica gel, 20% EtOAc in hexanes); $[\alpha]^{25}_D$ = -5.4 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.43 (s, 3 H), 1.44 (s, 3 H), 1.42-1.57 (m, 2 H), 1.79-1.90 (m, 2

H), 1.95-2.11 (m, 2 H), 3.23-3.32 (m, 2 H), 3.48 (s, 3 H), 3.63 (ddd, *J* = 7.7, 5.8, 1.7 Hz, 1 H), 3.70 (dd, *J* = 11.1, 6.8 Hz, 1 H), 3.88 (dd, *J* = 8.5, 1.7 Hz, 1 H), 4.47-4.53 (m, 1 H), 4.53-4.58 (m, 1 H), 5.24 (dd, *J* = 10.3, 0.7 Hz, 1 H), 5.37 (d, *J* = 17.1 Hz, 1 H), 5.82 (ddd, *J* = 17.5, 10.3, 7.4 Hz, 1 H), 6.36 (t, *J* = 6.2 Hz, 1 H), 7.84 (d, *J* = 6.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 26.6, 27.0, 27.7, 28.1, 31.8, 41.9, 51.2, 61.4, 71.3, 77.6, 78.2, 81.3, 108.9, 119.9, 135.0, 172.4, 174.9; HRMS (ESI-TOF) *m/e* 357.2018, M+H$^+$ calcd for $C_{17}H_{28}N_2O_6$ 357.2026.

***E*-Alkene 66.** To a solution of alkene **65** (4.3 mg, 0.012 mmol, 1.0 equiv) in a 1:2 CH_2Cl_2/3-methyl-1-butene mixture (3.0 mL) was added 2nd generation Hoveyda-Grubbs catalyst **48** (2.3 mg, 0.0036 mmol, 0.3 equiv). The flask was then capped and heated at 40 ºC overnight. After this time, the reaction mixture was allowed to reach room temperature and the solvents were removed by concentration under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 6% MeOH in CH_2Cl_2) to obtain alcohol *E*-alkene **66** (3.6 mg, 75%) as a yellow oil: R_f = 0.30 (silica gel, 20% EtOAc in hexanes); $[\alpha]^{25}_D$ = -9.8 (*c* 0.4, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.98 (d, *J* = 6.7 Hz, 3 H), 1.01 (d, *J* = 6.7 Hz, 3 H), 1.39 (s, 6 H), 1.41-1.52 (m, 2 H), 1.77-1.89 (m, 2 H), 1.99-2.04 (m, 1 H), 2.16 (dd, *J* = 1.4, 1.2 Hz, 1 H), 2.32 (od, *J* = 6.7, 1.5 Hz, 1 H), 3.24-3.26 (m, 2 H), 3.48 (s, 3 H), 3.60 (d, *J* = 9.5 Hz, 1 H), 3.75-3.79 (m, 1 H), 3.81 (ddd, *J* = 9.5, 4.4, 2.0 Hz, 1 H), 4.42 (dd, *J* = 8.5, 8.4 Hz, 1 H), 4.56 (ddd, *J* = 11.1, 7.0 Hz, 1 H), 5.38 (ddd, *J* = 15.4, 8.3, 1.3 Hz, 1 H), 5.85 (dd, *J* = 15.4, 6.5 Hz, 1 H), 6.26 (t, *J* = 6.2 Hz, 1 H), 7.86 (d, *J* = 7.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.9, 22.1, 26.7, 27.4, 27.9, 28.9, 30.8, 30.9, 42.1, 51.7, 59.1, 68.3, 78.8, 79.6, 81.3, 109.1, 123.5, 144.6, 169.8, 175.2; HRMS (ESI-TOF) *m/e* 399.2487, M+H$^+$ calcd for $C_{20}H_{34}N_2O_6$ 399.2495.

2-*epi*-bengamide E (29). A solution of hydroxyl amide **66** (3.5 mg, 0.009 mmol, 1.0 equiv) in MeOH (2.0 mL) was treated with a 70% aqueous AcOH solution (1.5 mL) at 70 ºC for 1 h.

After this time, the solvent was removed by evaporation under reduced pressure. Purification of the crude product by flash column chromatography (silica gel, 6% MeOH in CH_2Cl_2) afforded the 2-epimer of Bengamide E, compound **29** (2.5 mg, 76%) as a white solid: R_f = 0.36 (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]^{25}_D$ = -7.5 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.98 (d, *J* = 6.7 Hz, 3 H), 1.00 (d, *J* = 6.7 Hz, 3 H), 1.36-1.43 (m, 1 H), 1.51-1.57 (m, 1 H), 1.74-1.88 (m, 2 H), 1.99-2.08 (m, 2 H), 2.30 (od, *J* = 6.7, 1.2 Hz, 1 H), 3.06 (bs, 2 H), 3.25-3.31 (m, 2 H), 3.51 (s, 3 H), 3.58-3.59 (m, 1 H), 3.81 (d, *J* = 5.5 Hz, 1 H), 3.94-3.95 (m, 1 H), 4.00 (bs, 1 H), 4.23 (dd, *J* = 6.3, 6.2 Hz, 1 H), 4.56 (ddd, *J* = 11.2, 7.1, 1.4 Hz, 1 H), 5.42 (ddd, *J* = 15.5, 7.2, 1.4 Hz, 1 H), 5.79 (ddd, *J* = 15.5, 6.5, 0.9 Hz, 1 H), 6.28 (t, *J* = 5.3 Hz, 1 H), 7.85 (d, *J* = 6.7 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 22.1, 22.2, 28.0, 28.9, 30.8, 31.1, 42.1, 51.7, 59.2, 72.0, 72.9, 74.0, 81.9, 125.4, 141.9, 170.2, 175.1; HRMS (ESI-TOF) *m/e* 359.2175, M+H$^+$ calcd for $C_{17}H_{30}N_2O_6$ 359.2182.

Aldol Product 68. To a stirred solution of oxazolidinone **67** (257 mg, 1.03 mmol, 1.0 equiv) in CH_2Cl_2 (5.0 mL) at 0 ºC was added a freshly prepared 1.0 M solution of *n*-Bu_2BOTf in CH_2Cl_2 (1.23 mL, 1.23 mmol, 1.2 equiv) dropwise followed by freshly distilled Hunig's base (269 μL, 1.54 mmol, 1.5 equiv), and the mixture was stirred for 1 h at 0 ºC. This mixture was cooled to -78 ºC and a solution of crude aldehyde, obtained by oxidation of alcohol **50** (226 mg, 1.13 mmol, 1.1 equiv), in CH_2Cl_2 (3.0 mL) was added. The resulting solution was then stirred for 8 h while gradually being warmed to 25 ºC. An aqueous phosphate buffer solution (pH = 7.0, 3.0 mL) was added and the mixture was stirred for 30 min. The aqueous phase was separated and extracted with CH_2Cl_2 twice. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 50%→70% EtOAc in hexanes) to afford oxazolidinone **68** (386 mg, 84%) as a yellow oil: R_f = 0.23 (silica gel, 60% EtOAc in hexanes); $[\alpha]^{25}_D$ = +12.7 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.05 (d, *J* = 6.8 Hz, 3 H), 1.06 (d, *J* = 6.8

Hz, 3 H), 1.44 (s, 3 H), 1.47 (s, 3 H), 2.37 (od, *J* = 6.6, 1.0 Hz, 1 H), 2.89 (dd, *J* = 13.5, 9.2 Hz, 1 H), 3.31 (dd, *J* = 13.6, 3.2 Hz, 1 H), 3.40 (s, 3 H), 3.96-4.04 (m, 2 H), 4.22 (dd, *J* = 9.1, 2.2 Hz, 1 H), 4.36-4.42 (m, 2 H), 4.79-4.85 (m, 1 H), 4.96 (d, *J* = 1.2 Hz, 1 H), 5.43 (ddd, *J* = 15.4, 8.6, 1.4 Hz, 1 H), 5.99 (dd, *J* = 15.4, 6.3 Hz, 1 H), 7.20 (d, *J* = 7.5 Hz, 2 H), 7.30-7.35 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.8, 21.9, 26.7, 27.0, 30.9, 37.7, 55.5, 58.3, 67.6, 72.2, 79.3, 79.9, 80.6, 109.3, 123.9, 127.6, 129.1, 129.5, 134.9, 145.2, 153.6, 170.6; HRMS (ESI-TOF) *m/e* 448.2329, $M+H^+$ calcd for $C_{24}H_{33}NO_7$ 448.2335.

Silyl Ether 69. To a solution of compound **68** (197 mg, 0.44 mmol, 1.0 equiv) in CH_2Cl_2 (5.0 mL) was added 2,6-lutidine (108 μL, 0.924 mmol, 2.0 equiv) and TBSOTf (162 μL, 0.704 mmol, 1.6 equiv) at 0 ºC. After 1 h at this temperature, the mixture was quenched by addition of MeOH, diluted with Et_2O and washed with a saturated aqueous NH_4Cl solution. The aqueous phase was extracted with Et_2O and the organic layers were washed with brine, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was then subjected to purification by flash column chromatography (silica gel, 20% EtOAc in hexanes) to yield silyl ether **69** (227 mg, 92%) as a yellow oil: R_f = 0.31 (silica gel, 20% EtOAc in hexanes); $[\alpha]^{25}_D$ = +41.0 (*c* 0.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.11 (s, 3 H), 0.22 (s, 3 H), 0.92 (s, 9 H), 1.02 (d, *J* = 6.8 Hz, 6 H), 1.40 (s, 3 H), 1.41 (s, 3 H), 2.34 (od, *J* = 6.7, 1.3 Hz, 1 H), 2.88 (dd, *J* = 13.4, 9.4 Hz, 1 H), 3.34 (s, 3 H), 3.31-3.37 (m, 1 H), 3.92 (dd, *J* = 8.3, 6.7 Hz, 1 H), 4.08 (dd, *J* = 6.7, 2.9 Hz, 1 H), 4.19 (dd, *J* = 9.0, 7.2 Hz, 1 H), 4.24 (dd, *J* = 9.1, 2.0 Hz, 1 H), 4.37 (dd, *J* = 8.3 Hz, 1 H), 4.62 (ddt, *J* = 11.1, 7.7, 3.5 Hz, 1 H), 4.92 (d, *J* = 2.9 Hz, 1 H), 5.42 (ddd, *J* = 15.4, 8.5, 1.5 Hz, 1 H), 5.91 (dd, *J* =15.4, 6.0 Hz, 1 H), 7.23-7.26 (m, 2 H), 7.28-7.37 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ =-4.9, -3.7, 18.5, 22.0, 22.1, 26.1, 27.1, 27.2, 30.9, 37.8, 55.7, 58.0, 66.8, 71.9, 78.3, 81.5, 81.6, 108.4, 123.8, 127.2, 128.9, 129.0, 129.2, 136.0, 144.1, 153.6, 169.0; HRMS (ESI-TOF) *m/e* 562.3186, $M+H^+$ calcd for $C_{30}H_{47}NO_7Si$ 562.3200.

Alcohol 70. To a solution of oxazolidinone **69** (62 mg, 0.11 mmol, 1.0 equiv) in THF (3.0 mL) was added $LiBH_4$ (276 μL, 2.0 M in THF, 0.55 mmol, 5.0 equiv) at 0 ºC. The reaction was allowed to reach room temperature. After 6 h at this temperature, the reaction mixture was diluted with EtOAc and quenched with a saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The obtained crude product was purified by flash column chromatography (silica gel, 25% EtOAc in hexanes) to afford alcohol **70** (31 mg, 72%) as a yellow oil: R_f = 0.27 (silica gel, 20% EtOAc in hexanes); $[\alpha]^{25}_D$ = +31.8 (*c* 0.9, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.14 (s, 6 H), 0.96 (s, 9 H), 1.01 (d, *J* = 6.7 Hz, 3 H), 1.02 (d, *J* = 6.7 Hz, 3 H), 1.41 (s, 3 H), 1.42 (s, 3 H), 2.34 (od, *J* = 6.7, 1.3 Hz, 1 H), 3.30 (dt, *J* = 5.0, 4.1 Hz, 1 H), 3.41 (s, 3 H), 3.75 (dd, *J* = 5.3, 1.6 Hz, 1 H), 3.81 (t, *J* = 4.4 Hz, 2 H), 3.87 (dd, *J* = 8.7, 1.5 Hz, 1 H), 4.36 (dd, *J* = 8.5, 8.4 Hz, 1 H), 5.40 (ddd, *J* = 15.5, 8.2, 1.3 Hz, 1 H), 5.80 (ddd, *J* = 15.5, 6.6, 0.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.5, -4.0, 18.2, 22.0, 22.1, 25.9, 26.8, 27.3, 31.0, 57.3, 58.9, 68.4, 78.2, 78.9, 82.1, 108.8, 123.6, 144.6; HRMS (ESI-TOF) *m/e* 389.2718, $M+H^+$ calcd for $C_{20}H_{40}O_5Si$ 389.2723.

Amide 71. The oxidation of alcohol **70** (62 mg, 0.159 mmol, 1.0 equiv) and subsequent coupling with L-Lys-Lactam **46** (39 mg, 0.239 mmol, 1.5 equiv) was carried out exactly as described for **45** above to yield amide **71** (51 mg, 63% over two steps) as a yellow oil: R_f = 0.32 (silica gel, EtOAc); $[\alpha]^{25}_D$ = +5.6 (*c* 0.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.07 (s, 3 H), 0.08 (s, 3 H), 0.90 (s, 9 H), 0.97 (d, *J* = 6.8 Hz, 3 H), 0.98 (d, *J* = 6.8 Hz, 3 H), 1.39 (s, 3 H), 1.41 (s, 3 H), 1.45-1.60 (m, 2 H), 1.76-1.87 (m, 3 H), 2.00-2.10 (m, 1 H), 2.30 (od, *J* = 6.6, 1.3 Hz, 1 H), 3.20-3.33 (m, 2 H), 3.37 (s, 3 H), 3.61 (d, *J* = 3.9 Hz, 1 H), 3.83 (dd, *J* = 8.3, 5.4 Hz, 1 H), 3.97 (dd, *J* = 5.4, 3.9 Hz, 1 H), 4.30 (t, *J* = 8.3 Hz, 1 H), 4.55 (ddd, *J* = 11.3,

6.7, 1.4 Hz, 1 H), 5.40 (ddd, *J* = 15.5, 8.3, 1.4 Hz, 1 H), 5.80 (ddd, *J* = 15.5, 6.2, 0.4 Hz, 1 H), 6.14-6.17 (m, 1 H), 7.60 (d, *J* = 6.7 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.3, -4.0, 18.5, 21.8, 21.9, 26.2, 27.0, 27.1, 27.9, 28.9, 30.7, 31.4, 42.0, 51.9, 58.5, 73.1, 78.8, 81.0, 83.5, 108.4, 124.5, 144.1, 169.8, 175.2; HRMS (ESI-TOF) *m/e* 513.3365, $M+H^+$ calcd for $C_{26}H_{48}N_2O_6Si$ 513.3360.

Hydroxy Amide 66. The treatment of silyl ether **71** (28 mg, 0.055 mmol, 1.0 equiv) with TBAF (81 μL, 1.0 M in THF, 0.082 mmol, 1.5 equiv) was carried out exactly as described before for **49** to obtain alcohol **66** (22 mg, 100%) whose physical and spectroscopic properties were identical to those obtained from alkene **65**.

2-*epi*-bengamide E (29). Treatment of hydroxyl amide **66** (22 mg, 0.055 mmol, 1.0 equiv) with a 70% aqueous AcOH solution was carried out exactly as described above to obtain 2-*epi*-Bengamide E (**29**) (15 mg, 76%).

2,3-Epoxy Bengamide 36. The treatment of acetal **73** (22 mg, 0.060 mmol, 1.0 equiv) with AcOH was carried out exactly as described before for **29** to obtain 2,3-epoxy bengamide E **36** (17 mg, 85%) as a white foam: R_f = 0.34 (silica gel, 10% MeOH in EtOAc); $[\alpha]^{25}_D$ = -15.3 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.98 (d, *J* = 6.9 Hz, 3 H), 0.99 (d, *J* = 6.9 Hz, 3 H), 1.31-1.51 (m, 2 H), 1.72-2.08 (m, 4 H), 2.27-2.37 (m, 1 H), 3.17 (t, *J* = 2.2 Hz, 1 H), 3.21-3.28 (m, 2 H), 3.49 (s, 1 H), 3.58-3.64 (m, 1 H), 4.15 (t, *J* = 6.5 Hz, 1 H), 4.49 (dd, *J* = 10.2, 5.9 Hz, 1 H), 5.47 (dd, *J* = 15.6, 7.5 Hz, 1 H), 5.82 (dd, *J* = 15.6, 6.5 Hz, 1 H), 6.03-6.19 (m, 1 H), 7.43-7.49 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.9, 22.1, 27.8, 28.8, 30.8, 31.4, 42.1, 51.7, 52.2, 58.7, 71.7, 74.3, 124.6, 143.2, 167.2, 174.8; HRMS (ESI-TOF) *m/e* 327.1908, $M+H^+$ calcd for $C_{16}H_{26}N_2O_5$ 327.1920.

Epoxy Amide 75. To a solution of allylic alcohol **74** (102 mg, 1.0 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added MnO_2 (14.0 g, 16.3 mmol, 16.0 equiv). After stirring for 12 h at 25 ºC, the crude mixture was filtered through celite and the resulting clear solution was concentrated under reduced pressure at 20 ºC, to obtain the corresponding α,β-unsaturated aldehyde which was employed for the next step without further purification. This aldehyde was reacted with sulfonium salt **22** (350 mg, 1.12 mmol, 1.1 equiv) and NaOH (3.0 M aqueous solution, 0.34 mL, 1.02 mmol, 1.0 equiv) according to the procedure described above for **42** to yield epoxy amide **75** (184 mg, 58% over 2 steps) as a yellow oil: R_f = 0.18 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}_D$ = +15.9 (*c* 0.4, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.98 (d, *J* = 6.7 Hz, 3 H), 0.99 (d, *J* = 6.7 Hz, 3 H), 1.53 (s, 3 H), 1.63 (s, 3 H), 1.72-1.80 (m, 1 H), 1.97-2.05 (m, 1 H), 2.07 (s, 3 H), 2.28-2.37 (m, 1 H), 2.37-2.46 (m, 1 H), 2.51-2.59 (m, 1 H), 3.49-3.54 (m, 2 H), 3.88 (d, *J* = 9.3 Hz, 1 H), 4.01 (ddd, *J* = 9.1, 5.3, 1.4 Hz, 1 H), 4.27 (ddd, *J* = 8.5, 4.8, 3.2 Hz, 1 H), 5.13 (ddd, *J* = 15.7, 8.0, 1.4 Hz, 1 H), 6.02 (dd, *J* = 15.6, 6.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 15.8, 21.7, 21.8, 23.0, 26.3, 30.8, 30.9, 34.3, 55.5, 55.8, 58.5, 67.0, 95.9, 122.5, 146.1, 163.6; HRMS (ESI-TOF) *m/e* 314.1784, $M+H^+$ calcd for $C_{16}H_{27}NO_3S$ 314.1790.

Diepoxy Amide 76. To a solution of epoxy amide **75** (320 mg, 1.02 mmol, 1.0 equiv) in THF (20 mL) was added dropwise Red-Al (0.7 mL, 70% w/v in toluene, 2.24 mmol, 2.2 equiv) at 0 ºC. After 1 h at 0 ºC, the reaction mixture was quenched by addition of a saturated aqueous NH_4Cl solution. After separation of both layers, the aqueous phase was extracted with EtOAc and the organic extracts were washed with brine, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude epoxy aldehyde was used for the next step without further purification. To a solution of sulfonium salt **22** (350 mg, 1.12 mmol, 1.1 equiv) in H_2O (15 mL) was added a 5.0 M aqueous NaOH solution (0.20 mL, 1.02 mmol, 1.0

equiv). Then, a solution of crude epoxy aldehyde (~ 1.02 mmol) in CH_2Cl_2 (10 mL) was added and the reaction mixture was vigorously stirred overnight at 25 ºC. After this time, both phases were separated and the aqueous layer was extracted with CH_2Cl_2 twice. Combined organic extracts were then washed with water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. Purification of the crude product by flash column chromatography (silica gel, 20% EtOAc in hexanes) provided diepoxy amide **76** (310 mg, 85% over 2 steps) as a yellow oil: R_f = 0.37 (silica gel, 40% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.99 (d, J = 6.8 Hz, 6 H), 1.52 (s, 3 H), 1.63 (s, 3 H), 1.76-1.86 (m, 1 H), 2.01-2.09 (m, 1 H), 2.11 (s, 3 H), 2.27-2.37 (m, 1 H), 2.47 (ddd, J = 13.2, 8.4, 7.2 Hz, 1 H), 2.57 (ddd, J = 13.0, 7.7, 5.1 Hz, 1 H), 3.01 (dd, J = 3.5, 2.1 Hz, 1 H), 3.34 (dd, J = 3.6, 1.9 Hz, 1 H), 3.36 (dd, J = 8.3, 1.7 Hz, 1 H), 3.58 (d, J = 2.0 Hz, 1 H), 3.90 (dd, J = 9.2, 0.6 Hz, 1 H), 4.00 (ddd, J = 9.2, 5.2, 1.4 Hz, 1 H), 4.31 (ddd, J = 8.5, 4.8, 3.3 Hz, 1 H), 5.09 (ddd, J = 15.6, 8.3, 1.4 Hz, 1 H), 5.92-6.00 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 15.9, 21.8, 21.9, 23.0, 26.2, 30.7, 30.9, 34.5, 51.2, 55.6, 56.0, 56.4, 56.5, 67.1, 95.9, 122.8, 145.4, 163.0; HRMS (ESI-TOF) *m/e* 356.1872, $M+H^+$ calcd for $C_{18}H_{29}NO_4S$ 356.1896.

Diepoxy Alcohol 77. Diepoxy amide **76** (100 mg, 0.28 mmol, 1.0 equiv) was reduced by treatment with Super-H® (0.70 mL, 1.0 M in THF, 2.5 equiv) according to the procedure described above for **42** to yield diepoxy alcohol **78** (36 mg, 70%) as a yellow oil: R_f = 0.26 (silica gel, 40% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.00 (d, J = 6.8 Hz, 6 H), 2.27-2.40 (m, 1 H), 2.91 (dd, J = 4.6, 2.1 Hz, 1 H), 2.97-3.09 (m, 1 H), 3.16-3.20 (m, 1 H), 3.33 (dd, J = 8.2, 2.0 Hz, 1 H), 3.65-3.75 (m, 1 H), 3.93-4.01 (m, 1 H), 5.10 (ddd, J = 15.6, 8.3, 1.3 Hz, 1 H), 5.95 (ddd, J = 15.6, 6.5, 3.3 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.8, 21.9, 30.9, 53.5, 55.7, 56.3, 57.9, 60.6, 123.2, 145.1; HRMS (ESI-TOF) *m/e* 185.1206, $M+H^+$ calcd for $C_{10}H_{16}O_3$ 185.1178.

Epoxy Bengamide E Analogue 37. Diepoxy alcohol **77** (15 mg, 0.08 mmol, 1.0 equiv) was treated with MeOH/$B(OMe)_3$ and DBU according to the same procedure described above for the preparation of **44**. Crude opening product **78** (~ 0.08 mmol) was oxidized with TEMPO/BAIB and coupled with L-Lys-Lactam **46** (20 mg, 0.12 mmol, 1.5 equiv) exactly as described above for **47** to yield epoxy amide **37** (13.0 mg, 47% over 3 steps) as a colorless oil: R_f = 0.21 (silica gel, EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.02 (d, J = 6.8 Hz, 6 H), 1.56-1.67 (m, 2 H), 1.79-1.91 (m, 2 H), 1.95-2.09 (m, 2 H), 2.30-2.39 (m, 1 H), 3.19-3.40 (m, 4 H), 3.86 (s, 3 H), 4.02-4.05 (m, 1 H), 4.50-4.59 (m, 2 H), 5.36 (ddd, J = 15.5, 7.1, 1.4 Hz, 1 H), 5.84 (ddd, J = 15.5, 6.5, 1.0 Hz, 1 H), 5.87-5.94 (m, 1 H), 7.78 (d, J = 12.3 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 22.0, 22.1, 27.9, 28.9, 30.2, 31.4, 42.1, 51.6, 52.1, 53.4, 57.0, 57.8, 82.9, 122.4, 143.4, 175.2, 175.6; HRMS (ESI-TOF) *m/e* 341.2058, $M+H^+$ calcd for $C_{17}H_{28}N_2O_5$ 341.2077.

Diepoxy Amide 38. The oxidation of diepoxy alcohol **77** (50 mg, 0.27 mmol, 1.0 equiv) and subsequent coupling with L-Lys-Lactam **46** (67 mg, 0.41 mmol, 1.5 equiv) was carried out exactly as described above for **45** to yield diepoxy amide **38** (46 mg, 55% over two steps) as a white solid: R_f = 0.43 (silica gel, EtOAc); $[\alpha]^{25}_D$ = +49.4 (*c* 0.2, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.00 (d, J = 6.8 Hz, 6 H), 1.36-1.50 (m, 2 H), 1.79-1.90 (m, 2 H), 1.96-2.04 (m, 2 H), 2.28-2.38 (m, 1 H), 2.90 (dd, J = 4.5, 2.1 Hz, 1 H), 3.05 (dd, J = 4.5, 2.1 Hz, 1 H), 3.24-3.30 (m, 2 H), 3.35 (dd, J = 8.2, 1.8 Hz, 1 H), 3.45 (d, J = 2.1 Hz, 1 H), 4.50 (ddd, J = 11.4, 6.0, 1.4 Hz, 1 H), 5.09 (ddd, J = 15.6, 8.2, 1.4 Hz, 1 H), 5.95 (dd, J = 15.6, 6.6 Hz, 1 H), 6.10 (t, J = 6.0 Hz, 1 H), 7.46 (d, J = 5.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.8, 27.9, 28.9, 30.9, 31.4, 42.2, 51.7, 52.7, 56.4, 57.0, 57.2, 122.7, 145.4, 166.8, 174.6; HRMS (ESI-TOF) *m/e* 309.1802, $M+H^+$ calcd for $C_{16}H_{24}N_2O_4$ 309.1814.

Epoxy Amide 80. Epoxy amide **80** (1.82 g, 79% over two steps) was prepared from allylic alcohol **79** (880 mg, 6.70 mmol, 1.0 equiv) by oxidation with MnO_2, followed by reaction with sulfonium salt **22** (1.90 g, 6.70 mmol, 1.0 equiv) according to the same procedure described above for the preparation of **75**. **[80]:** yellow oil; R_f = 0.44 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$ = +25.1 (*c* 0.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.03 (s, 9 H), 1.49 (s, 3 H), 1.59 (s, 3 H), 1.69-1.75 (m, 1 H), 1.94-2.01 (m, 1 H), 2.02 (s, 3 H), 2.38 (ddd, *J* = 13.4, 8.9, 6.7 Hz, 1 H), 2.52 (ddd, *J* = 13.2, 7.0, 5.1 Hz, 1 H), 3.48-3.53 (m, 2 H), 3.85 (d, *J* = 9.2 Hz, 1 H), 3.98 (ddd, *J* = 9.1, 5.2, 1.4 Hz, 1 H), 4.25 (ddd, *J* = 10.2, 4.9, 3.2 Hz, 1 H), 5.65-5.72 (m, 1 H), 6.24-6.30 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -1.6, 15.7, 22.9, 26.2, 30.7, 55.7, 55.8, 59.5, 67.0, 68.7, 95.8, 138.6, 140.4, 166.1; HRMS (ESI-TOF) *m/e* 344.1709, $M+H^+$ calcd for $C_{16}H_{30}NO_3SSi$ 344.1716.

Diepoxy amide 81. Diepoxy amide **81** (104 mg, 84% over two steps) was prepared from epoxy amide **80** (110 mg, 0.32 mmol, 1.0 equiv) by reduction with Red-Al, followed by reaction with sulfonium salt **22** (111 mg, 0.35 mmol, 1.1 equiv) according to the same procedure described above for the preparation of **76**. **[81]:** yellow oil; R_f = 0.19 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$ = +31.4 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.06 (s, 9 H), 1.52 (s, 3 H), 1.63 (s, 3 H), 1.76-1.85 (m, 1 H), 2.02-2.08 (m, 1 H), 2.10 (s, 3 H), 2.46 (ddd, *J* = 13.3, 8.4, 7.2 Hz, 1 H), 2.58 (ddd, *J* = 13.0, 7.5, 5.1 Hz, 1 H), 3.03 (dd, *J* = 3.6, 2.0 Hz, 1 H), 3.35 (dd, *J* = 3.6, 2.0 Hz, 1 H), 3.36-3.40 (m, 1 H), 3.58 (d, *J* = 1.9 Hz, 1 H), 3.89 (d, *J* = 9.2 Hz, 1 H), 4.00 (ddd, *J* = 9.1, 5.2, 1.2 Hz, 1 H), 4.28-4.34 (m, 1 H), 5.67 (dd, *J* = 18.7, 7.6 Hz, 1 H), 6.23 (dd, *J* = 18.7, 0.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -1.6, 15.9, 22.9, 26.2, 30.7, 34.4, 51.2, 55.5, 56.0, 56.7, 57.6, 67.0, 95.9, 137.9, 140.9, 162.9; HRMS (ESI-TOF) *m/e* 386.1820, $M+H^+$ calcd for $C_{18}H_{31}NO_4SSi$ 386.1821.

Diepoxy Alcohol 82. Diepoxy amide **81** (50 mg, 0.13 mmol, 1.0 equiv) was reduced by treatment with Super-H® (0.33 mL, 1.0 M in THF, 2.5 equiv) according to the procedure described above for **42** to yield diepoxy alcohol **82** (15 mg, 55%) as a yellow oil: R_f = 0.22 (silica gel, 60% EtOAc in hexanes); $[\alpha]^{25}_D$ = +16.4 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.08 (s, 9 H), 2.93 (dd, *J* = 4.7, 2.1 Hz, 1 H), 3.08 (dd, *J* = 4.7, 2.2 Hz, 1 H), 3.19 (dd, *J* = 5.7, 2.3 Hz, 1 H), 3.33-3.38 (m, 1 H), 3.67-3.75 (m, 1 H), 3.94-4.00 (m, 1 H), 5.69 (dd, *J* = 18.7, 7.6 Hz, 1 H), 6.23 (d, *J* = 18.7 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -1.6, 53.4, 55.7, 57.5, 58.0, 60.4, 137.5, 141.2; HRMS (ESI-TOF) *m/e* 215.1112, M+H$^+$ calcd for $C_{10}H_{18}O_3Si$ 215.1104.

Epoxy Bengamide E Analogue 84. Diepoxy alcohol **82** (45 mg, 0.21 mmol, 1.0 equiv) was treated with MeOH/$B(OMe)_3$ and DBU according to the same procedure described above for the preparation of **44**. Crude opening product **83** (~ 0.21 mmol) was oxidized with TEMPO/BAIB and coupled with L-Lys-Lactam **46** (52 mg, 0.32 mmol, 1.5 equiv) exactly as described above for **47** to yield epoxy amide **84** (20 mg, 26% over 3 steps) as a colorless oil: R_f = 0.21 (silica gel, EtOAc); $[\alpha]^{25}_D$ = +11.0 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.08 (s, 9 H), 1.35-1.55 (m, 2 H), 1.74-1.91 (m, 2 H), 1.95-2.04 (m, 2 H), 2.18-2.24 (m, 1 H), 3.19-3.37 (m, 4 H), 3.42 (s, 3 H), 4.10 (dd, *J* = 4.9, 1.2, 0.5 Hz, 1 H), 4.52-4.58 (m, 1 H), 5.88-5.96 (m, 1 H), 6.00 (dd, *J* = 18.7, 4.9 Hz, 1 H), 6.10 (dd, *J* = 18.8, 1.2 Hz, 1 H), 7.74 (d, *J* = 7.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -1.4, 14.1, 28.0, 29.0, 29.7, 31.6, 42.2, 51.6, 57.7, 77.2, 84.5, 133.8, 140.2, 169.7, 175.2; HRMS (ESI-TOF) *m/e* 371.1986, M+H$^+$ calcd for $C_{17}H_{30}N_2O_5Si$ 371.2002.

Diepoxy Amide 85. The oxidation of diepoxy alcohol **82** (40 mg, 0.20 mmol, 1.0 equiv) and subsequent coupling with L-Lys-Lactam **46** (46 mg, 0.27 mmol, 1.5 equiv) was carried out exactly as described above for **77** to yield diepoxy amide **85** (20 mg, 30% over 2 steps) as a

colorless oil: R_f = 0.33 (silica gel, EtOAc); $[\alpha]^{25}_D$ = +33.1 (*c* 0.4, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.08 (s, 9 H), 1.55-1.70 (m, 2 H), 1.78-1.91 (m, 2 H), 1.95-2.07 (m, 2 H), 2.93 (dd, *J* = 4.5, 2.0 Hz, 1 H), 3.06 (dd, *J* = 4.5, 2.0 Hz, 1 H), 3.23-3.30 (m, 2 H), 3.37 (ddd, *J* = 7.5, 2.0, 0.5 Hz, 1 H), 3.46 (d, *J* = 2.1 Hz, 1 H), 4.50 (ddd, *J* = 11.4, 5.8, 1.3 Hz, 1 H), 5.67 (dd, *J* = 18.7, 7.5 Hz, 1 H), 6.17 (t, *J* = 7.2 Hz, 1 H), 6.23 (dd, *J* = 18.7, 0.6 Hz, 1 H), 7.46 (d, *J* = 5.9 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -1.6, 27.9, 28.8, 31.4, 42.1, 51.7, 52.7, 56.8, 57.3, 57.5, 137.9, 140.6, 162.5, 174.6; HRMS (ESI-TOF) *m/e* 339.1725, $M+H^+$ calcd for $C_{16}H_{26}N_2O_4Si$ 339.1740.

Cytotoxicity Assay. The 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) dye reduction assay in 96-well microplates was performed according to the Mossman method. 3.10^3 BAE or 2.10^3 tumor cells in a total volume of 100 μL of their respective growth media were incubated with serial dilutions of the tested compounds. After 3 days of incubation (37 ºC, 5% CO_2 in a humid atmosphere), 10 μL of MTT (5 mg/mL in PBS) were added to each well and the plate was incubated for a further 4 h (37 ºC). The resulting formazan was dissolved in 150 μL of 0.04 N HCl/2-propanol and read at 550 nm. All determinations were carried out in triplicate. IC_{50} value was calculated from semilogarithmic dose-response plots as the concentration of compound yielding a 50% of cell survival.

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Supporting Information Available

^{1}H- and ^{13}C-NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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