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Chiral Sulfur Ylides for the Synthesis of Bengamide E and Analogues

Francisco Sarabia,* Francisca Martín-Gálvez, Samy Chammaa, Laura Martín-Ortiz, and Antonio Sánchez-Ruiz

Department of Organic Chemistry, Faculty of Sciences, University of Malaga, Campus de Teatinos s/n 29071, Malaga, Spain

frsarabia@uma.es

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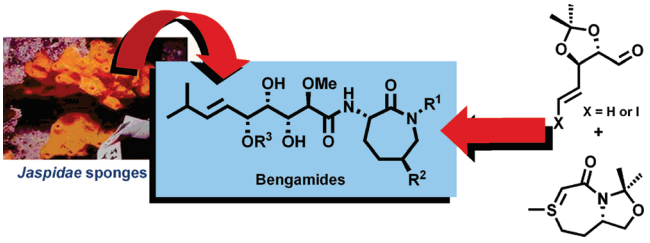

A new synthetic methodology of asymmetric epoxidation developed in our laboratories has been employed for the stereoselective synthesis of bengamide E (**16**) and analogues at the terminal olefinic position. In the event, the chiral sulfonium salt **30** was transformed into its corresponding sulfur ylide and reacted with aldehydes **21** and **44** to efficiently provide epoxy amides **31** and **45**, respectively. To access the bengamides from these epoxy amides, we combined a synthetic strategy previously reported by us, using an olefin cross metathesis reaction to introduce various alkyl substituents at the terminal olefinic position of amide **33**, with reactions mediated by palladium (Negishi or Suzuki couplings) from amide **49**. This latter route of introduction of alkyl groups proved to be more efficient than the metathesis approach and allowed access to the generation of a wide array of new bengamide analogues.

Introduction

The bengamides A−F were discovered and isolated between 1986[1] and 1989[2] by the research group of Professor Crews from an undescribed member of an orange sponge belonging to the Jaspidae family. Following these discoveries, the isolation of new members, such as the bengamides G−J,[3] L,[4] and M−R[5] (Figure 1), together with bengamides Z and Y,[6] K[3] and isobengamide E,[2] were described. Rapidly, these natural products were recognized as interesting bioactive compounds possessing potent cytotoxic activity against larynx epithelial carcinoma (1.0 μg/mL) as well as prominent antibiotic and antihelmintic properties.[7] More recently, the biological mode of action of the bengamides has been disclosed,[8] revealing an intriguing mechanism characterized by their binding to either methionine aminopeptidase type 1 (MetAp1) or type 2 (MetAp2),[9] enzymes involved in the cell cycle of endothelial cells and angiogenesis.[10] Interestingly, this is a mode of action similar to

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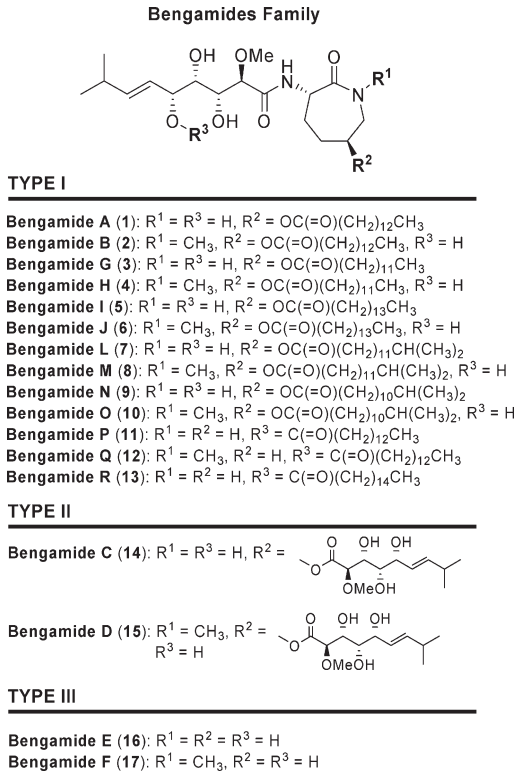

FIGURE 1. Molecular structures of bengamides.

that of fumagillin and ovalicin despite their structural differences.[11] These biological features render the bengamides as promising new anticancer compounds and subsequently have elicited intense research activity in biology and chemistry, including the total syntheses of natural bengamides[12] and the

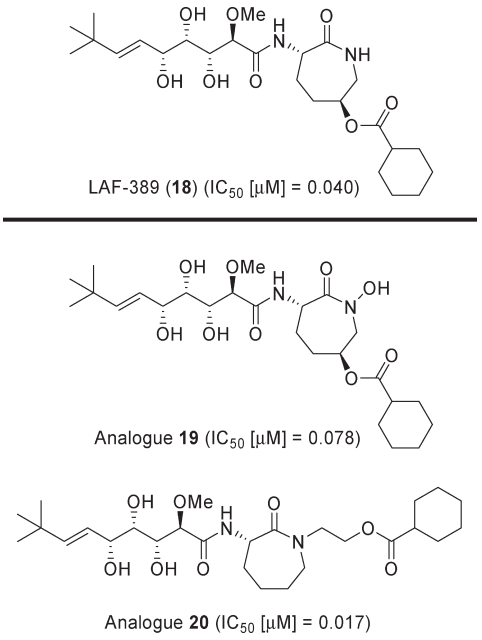

FIGURE 2. Potent bioactive analogues of bengamides.

design and syntheses of analogues[13] for biological evaluations.[13,14] A particularly important structural feature is the terminal olefinic group as it has been demonstrated with the synthetic *tert*-butyl analogue LAF-389 (**18**),[12f] which displays greater antitumor activity versus the natural members.[15] Similarly, modifications of the caprolactam moiety have led to potent antitumor analogues with promising pharmacokinetic properties, such as compounds **19** and **20**[13d] (Figure 2).

Early on our research group became interested by the biological potential of these natural products, and thus initiated a research program directed toward the total syntheses of this class of natural products, recently culminating with the total synthesis of bengamide E (**16**) and a series of analogues.[16] Our synthetic strategy for the bengamides consisted of three key steps: (1) an epoxide opening for the introduction of the methoxyl group at the C-2 position, (2) an olefin cross metathesis, as a means for the introduction of the isopropyl substituent of the olefin, and (3) an amide coupling for the incorporation of the ε-caprolactam residue. Interestingly, this strategy was envisioned as a diversity-oriented synthetic approach,[17] capable of delivering a wide array of analogues, allowing the incorporation of structural modifications at positions essential in the interaction of the molecule with the active site of methionine aminopeptidases.[18]

The development of this strategy provided ready access to a set of analogues by modifications at C-2 and olefinic positions, as well as modification of the lactam residue. Initially, we achieved the construction of the oxirane ring by reaction of aldehyde **21**[19] with the sulfur ylide derived from sulfonium

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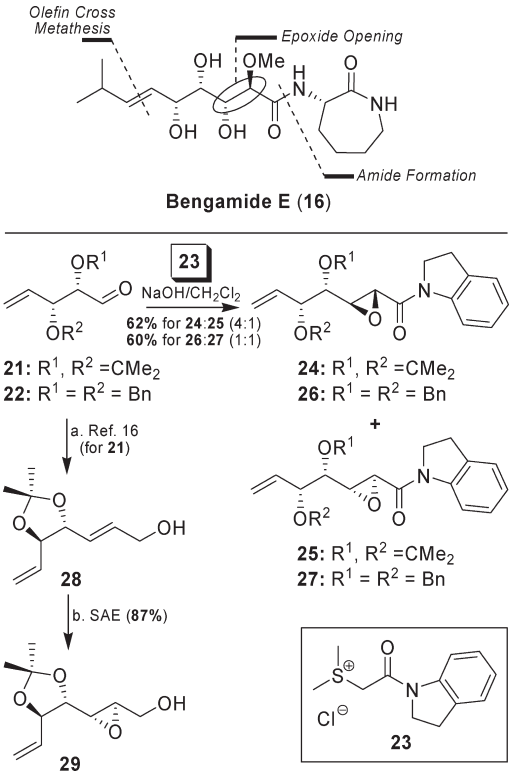
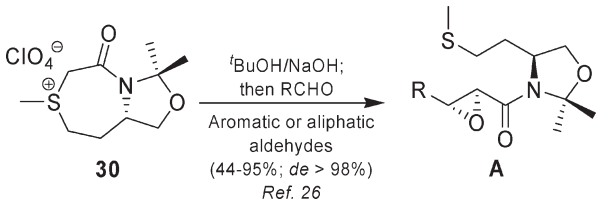
SCHEME 1. Divergent Strategy to Bengamides via Sulfur Ylides



salt **23**.[20] However, this reaction delivered a 4:1 mixture of epoxy amides **24**:**25** in favor of the epoxide with the undesired stereochemistry, as the Felkin−Ahn model predicts.[21] The use of the benzylated aldehyde **22**[22] provided a 1:1 mixture of epoxy amides **26** and **27**. Consequently, we employed a Sharpless asymmetric epoxidation[23] to prepare stereoselectively the epoxy alcohol **29** from the allylic alcohol **28**, a common precursor for the preparation of the natural bengamides and analogues thereof (Scheme 1).

SCHEME 2. Chiral Sulfonium Salt 30 and Its Reactions with Aldehydes



As an alternative to the Sharpless methodology, and as a continuation of our efforts in the chemistry of sulfur ylides,[24] we recently designed a new class of chiral ylides[25] that provides the epoxide in excellent chemical and stereochemical yields.[26] In particular, this class of new chiral ylides, represented by the sulfonium salt precursor **30**, readily prepared from L-methionine, smoothly reacted with aldehydes under basic conditions to yield epoxy amides of type A (Scheme 2).

In the present article, we wish to report the use of this new methodology of asymmetric epoxidation for the stereoselective preparation of bengamide E and analogues at the terminal olefinic position using an olefin cross metathesis reaction as described in our first total synthesis of bengamide E.

Results and Discussion

This new synthetic strategy to the bengamides was based on the use of the cyclic sulfonium salt **30** as precursor of its corresponding ylide and source of asymmetric induction for the stereoselective generation of an oxirane ring with a desired stereochemistry. To this aim, aldehyde **21** was reacted with the sulfur ylide, generated from its corresponding sulfonium salt **30**, to provide epoxy amide **31** in a 72% yield and excellent diastereoselectivity estimated to be greater than 98% according to NMR and GC-MS analyses. Treatment of this epoxy amide with Super-H[27] afforded the corresponding epoxy alcohol **29**, from which one could prepared the natural bengamide E (**16**) via the synthetic route previously described by us.[16] Nevertheless, we wished to improve upon the oxirane-ring-opening reaction, which was previously achieved by treatment of **29** with neutral alumina in refluxing methanol,[28] providing the ring-opened product **32** in a moderate 57% yield and complete regioselectivity. Our efforts toward improving the reaction with respect to chemical yield and development of a more efficient procedure led us to the methodology described by Miyashita et al.[29] In their work, they employed trimethyl borate for the activation of epoxy alcohols in their regioselective opening with nitrogen or sulfur nucleophiles. Taking into account the reduced nucleophilic character of alcohols, we decided to modify the original Miyashita procedure by the addition of DBU to enhance the nucleophilicity of the alcohol. Thus, epoxy alcohol **29** was treated with methanol in the presence of trimethyl borate and DBU to obtain the corresponding 2-methoxyl opening product **32** in an improved 70% yield. Compound **32** was

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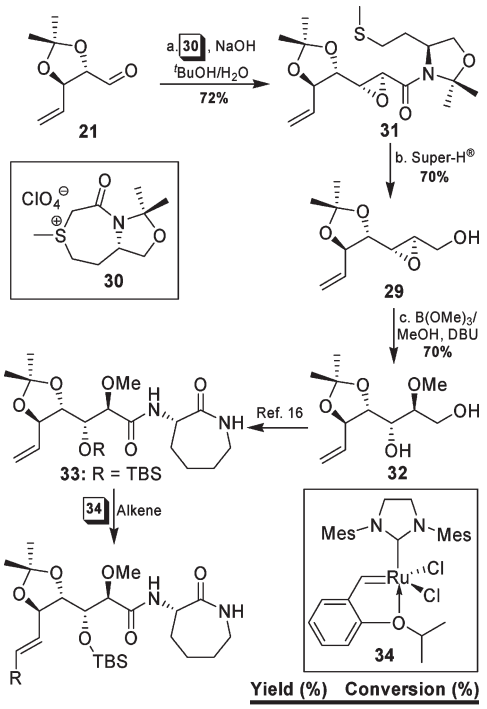
SCHEME 3. Synthesis of Bengamides E and Analogues via a New Asymmetric Methodology of Epoxidation



	Yield (%)	Conversion (%)	
35: R = $CH(CH_3)_2$	89	100	
36: R = $C(CH_3)_3$	90	33	Ref. 16
37: R = Ph	94	66	
38: R = $CH_2CH(CH_3)_2$	80	85	
39: R = $CH_2C(CH_3)_3$	74	71	
40: R = $CH(CH_3)CH_2CH_3$	26	71	
41: R = Chx	77	72	

transformed into the olefin cross metathesis precursor **33** without major difficulties via the chemistry already described. To complete the synthesis of the terminal alkyl olefinic analogues, we used the olefin cross metathesis reaction as described for compounds **35**−**37**[16] to prepare other analogues via reaction of **33** with various commercially available alkenes in the presence of the second generation Hoveyda−Grubbs catalyst (**34**).[30] Thus, the homologue series of bengamides E and its *tert*-butyl analogue (compounds **38** and **39**), branched aliphatic analogue **40**, and the cyclohexyl derivative **41** were prepared (Scheme 3). The results of all these metathesis reactions were reasonable in terms of chemical yields, with the exception of compound **40**. Furthermore, the preparation of trisubstituted derivatives via this cross metathesis reaction was attempted. However, this strategy failed to give the desired bengamide analogue with an additional methyl group when **33** reacted with 2,3-dimethyl-1-butene in the presence of **34**, instead giving compound **35**, with no detection of the expected trisubstituted derivative.

Even though the olefin cross metathesis reaction is efficient for installation of the terminal olefinic substituent, the moderate to poor conversion observed for some cases and failure for other bengamide precursors, in particular the 2-C-alkyl analogues, as we reported in our previous article,[16] or for the synthesis of trisubstituted olefinic derivatives, as described above, led to uncertainty. This observed unpredictability made the reaction unsuitable as a general method for the generation of libraries of bengamide analogues. In pursuit of an alternative route that would allow the introduction of different substituents at the terminal olefinic position in a stereoselective manner, we devised vinyl iodide **42**[31] as an intermediate for the construction of the ketide chain of bengamides and allowing the opportunity to incorporate various alkyl groups at the terminal olefinic position via a palladium-mediated reaction.

To determine the viability of this new route, we initially targeted the natural compound bengamide E. The vinyl iodide **42** was transformed into the aldehyde **44** by oxidation of alcohol **43**, prepared by treatment of **42** with TBAF. This aldehyde **44** was reacted with the chiral sulfonium salt **30** under biphasic conditions[32] to afford surprisingly a 4:1 mixture of epoxy amides in a 62% combined yield which, after separation by flash column chromatography and spectroscopic analyses, were identifed as *trans* epoxy amides **45** and its *cis* isomer, respectively. The unexpected formation of this *cis* epoxy amide, not previously observed in reactions involving sulfonium salt **30** with aldehydes,[26] likely is due to steric factors present in the starting aldehyde that could block the thermodynamic equilibrium that leads to the predominant formation of the *trans* isomer.[33] With epoxy amide **45** in hand, the synthesis toward lactam **49** was conducted in a more straightforward manner versus our previous route.[16] Thus, epoxy amide **45** was subjected to reduction by treatment with Super-H to obtain epoxy alcohol **46**, which was converted into diol **47** by treatment with MeOH in the presence of trimethylborate. From **47**, we then decided to attempt selective oxidation of the primary alcohol to the acid by treatment with TEMPO/BAIB,[34] followed by coupling with the amino lactam **48**, which was already attempted with diol **32**. In that case, we found 25% epimerization at C-2 of the resulting coupling product, which could be avoided by protection of the secondary alcohol. To our delight, in contrast to that diol case, lactam **49** was obtained in 63% overall yield with no detectable epimerization at C-2. Finally, the introduction of the isopropyl group was achieved by a Negishi reaction,[35] using diisopropyl zinc and Pd(dpephos)-Cl_2 in a DMF:THF mixture to give **50** in 67% yield, which after acidic hydrolysis provided natural bengamide E (**16**) in 85% yield (Scheme 4).

On the other hand, hydroxy amide **49** is a useful intermediate for the incorporation of various alkyl, alkenyl, or alkynyl groups via Negishi, Suzuki, or Sonogashira couplings, respectively.[36] Given the range of possibilities, we decided to initially carry out Suzuki couplings[37] with alkenyl pinacol esters **51** and **52**, which gave in modest yields coupling products **53** and **54** in 42% and 41% yields, respectively. The extension of the Negishi reaction by using alkylzinc bromides[38] with **49** was unsuccessful, thus the alcohol was protected as its silyl ether **55**. Subsequently, the ether was

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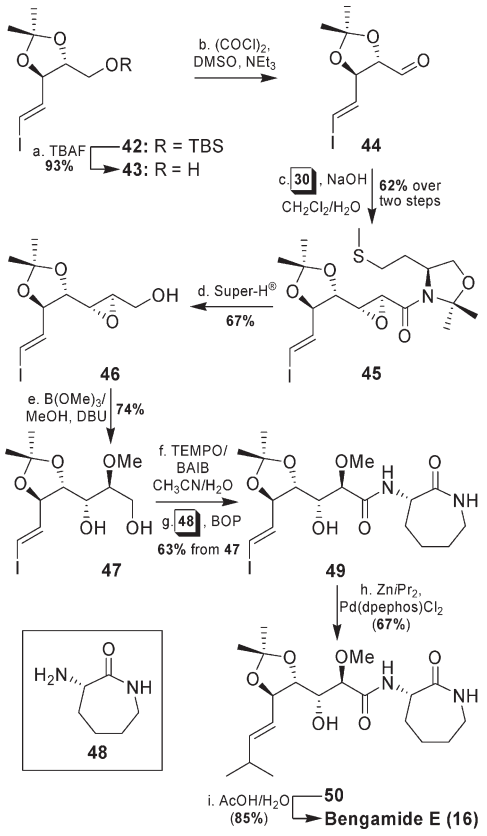
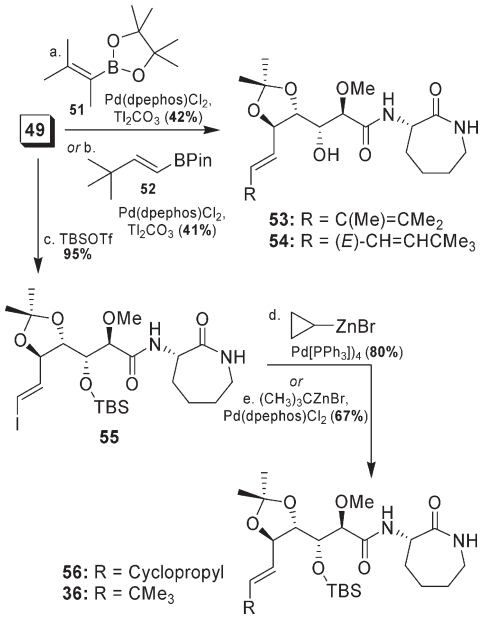
SCHEME 4. Synthesis of Bengamide E through Vinyl Iodide 42

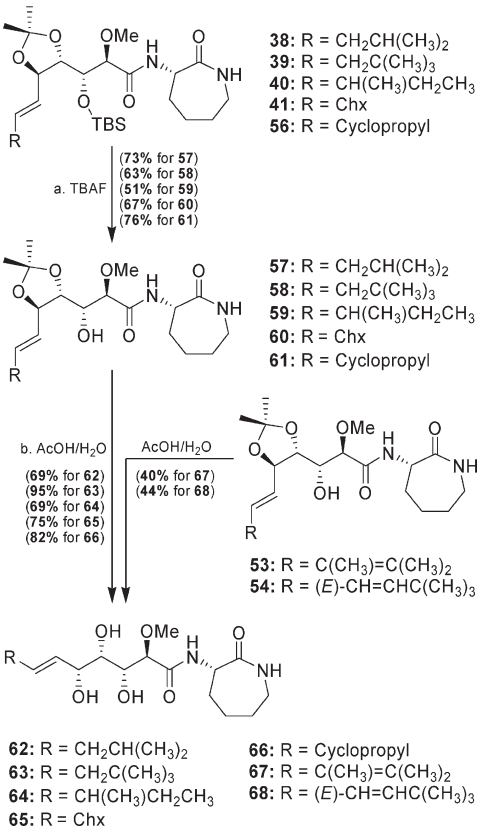


SCHEME 5. Synthesis of Bengamide E Analogues at the Terminal Olefinic Position via Suzuki and Negishi Couplings



reacted with different alkylzinc bromides, such as commercially available cyclopropyl- or *tert*-butylzinc bromides, in the presence of tetrakistriphenylphosphine palladium(0) to provide in good yields alkyl analogues **56** and **36**, respectively (Scheme 5). These examples are representative and reflect the potential of vinyl iodides **49** and its silyl ether derivative **55** for the generation of a wide array of bengamide analogues at the terminal olefinic position.

SCHEME 6. Removal of Protecting Groups of Bengamide Derivatives: Synthesis of New Bengamide E Analogues



Finally, removal of the protective groups by acidic hydrolysis of **53** and **54**, or by sequential desilylation with TBAF followed by acidic hydrolysis for **38**−**41** and **56**, provided bengamide analogues **62**−**68** (Scheme 6). Thus, together with the previously synthesized *tert*-butyl and phenyl derivatives obtained from **36** and **37**, the current set of compounds represent an interesting group of bengamide E analogues to evaluate the role of the terminal alkyl group toward antitumoral activity for this class of compounds.

Conclusions

In conclusion, we have described a new synthesis of bengamide E and analogues at the terminal olefinic position. This route utilizes our synthetic methodology of epoxide formation with chiral sulfur ylides for the preparation of key intermediates. As an alternative to the strategy described by us in a previous synthesis of the bengamides, we have developed a modified synthesis of the bengamide analogues, from vinyl iodide **42**. The route improves upon the previous syntheses in terms of chemical efficiency and gives access to a larger variety of analogues by modifications at the terminal olefinic position by using palladium chemistry. The generation of a broad library of bengamides as well as their biological evaluations[39] represent our focus in current and future investigations.

(39) Biological evaluations are being conducted by Dr. Frederick Valeriote from Henry Ford Health System (Detroit, MI).

Experimental Section[40]

Alcohol 43. To a solution of silyl ether **42**[31] (1.72 g, 4.32 mmol) in THF (22 mL) was added TBAF (5.2 mL, 5.18 mmol, 1.2 equiv) at 25 °C. After 30 min, the reaction mixture was diluted with Et_2O and washed with saturated aqueous NH_4Cl solution. The aqueous phase was washed with Et_2O and the combined organic phases were washed with brine and dried over anhydrous $MgSO_4$ and the solvent was evaporated. The crude product was then purified by flash column chromatography (silica gel, 25% AcOEt in hexanes) to obtain alcohol **43** (1.15 g, 94%) as a yellow oil: R_f 0.43 (silica gel, 30% AcOEt in hexanes); $[\alpha]^{25}_D$ +14.5 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 6 H), 2.10 (br s, 1 H), 3.54 (dd, J = 12.9, 4.4 Hz, 1 H), 3.78−3.83 (m, 2 H), 4.29 (ddd, J = 8.3, 3.1, 3.0 Hz, 1 H), 6.56 (d, J = 3.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.8, 26.9, 60.5, 79.0, 80.1, 80.9, 109.6, 142.4.

Aldehyde 44. A solution of oxalyl chloride (0.69 mL, 7.96 mmol, 2.0 equiv) in CH_2Cl_2 (10.0 mL) was cooled to −78 °C, and DMSO (1.13 mL, 15.91 mmol, 4.0 equiv) was added dropwise. After 5 min, a solution of alcohol **43** (1.13 g, 3.98 mmol) in CH_2Cl_2 (15 mL) was added. The reaction mixture was stirred at −78 °C for 40 min, and then TEA (3.32 mL, 23.87 mmol, 6.0 equiv) was added at this temperature. After 10 min at −78 °C, the reaction was allowed to reach room temperature and was then diluted with Et_2O and washed with saturated aqueous NH_4Cl solution. The aqueous phase was washed with Et_2O and the combined organic phases were washed with water and brine, dried over anhydrous $MgSO_4$, and filtered and the solvent was evaporated. The crude aldehyde obtained was used in the next step without purification.

Epoxy Amide 45. To a solution of sulfonium salt **30** (1.60 g, 5.17 mmol, 1.3 equiv) in H_2O (8.0 mL) was added a solution of NaOH 3.0 M in H_2O (1.32 mL, 4.77 mmol, 1.2 equiv). After 1 h at 25 °C, a solution of crude aldehyde **44** (∼3.98 mmol) in CH_2Cl_2 (8.0 mL) was added and the reaction mixture was vigorously stirred overnight at 25 °C. 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, filtered, and concentrated. Purification by flash column chromatography (silica gel, 30% AcOEt in hexanes) provided epoxy amides **45** (958 mg, 49.5%) together with its *cis* epoxy amide (242 mg, 12.5%) (62% combined yield, 4:1 proportion) as colorless oils. **45:** yellow oil; R_f 0.53 (silica gel, 40% AcOEt in hexanes); $[\alpha]^{25}_D$ +50.0 (*c* 0.9, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 3 H), 1.37 (s, 3 H), 1.51 (s, 3 H), 1.61 (s, 3 H), 1.75−1.81 (m, 1 H), 2.00−2.08 (m, 1 H), 2.10 (s, 3 H), 2.45 (ddd, J = 13.3, 8.5, 7.2 Hz, 1 H), 2.59 (ddd, J = 12.8, 7.6, 5.0 Hz, 1 H), 3.31 (dd, J = 2.6, 2.1 Hz, 1 H), 3.66 (d, J = 2.0 Hz, 1 H), 3.88 (dd, J = 8.4, 2.6 Hz, 1 H), 3.90 (d, J = 9.2 Hz, 1 H), 3.99 (ddd, J = 9.2, 5.2, 1.3 Hz, 1 H), 4.32 (ddd, J = 10.2, 4.8, 3.3 Hz, 1 H), 4.41 (dd, J = 8.2, 7.2 Hz, 1 H), 6.57 (dd, J = 14.6, 7.1 Hz, 1 H), 6.66 (d, J = 14.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8, 22.8, 26.1, 26.2, 27.0, 30.8, 34.3, 51.3, 55.4, 55.9, 66.9, 76.7, 80.3, 82.1, 95.9, 110.3, 141.3, 163.0; FAB HRMS (NBA) *m*/*e* 498.0802, M + H$^+$ calcd for $C_{18}H_{28}INO_5S$ 498.0811. ***cis*-Epoxy amide:** yellow oil; R_f 0.43 (silica gel, 40% AcOEt in hexanes); $[\alpha]^{25}_D$ −12.5 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (s, 3 H), 1.39 (s, 3 H), 1.52 (s, 3 H), 1.60 (s, 3 H), 1.89−2.05 (m, 2 H), 2.10 (s, 3 H), 2.37−2.46 (m, 1 H), 2.55−2.60 (m, 1 H), 3.23 (dd, J=7.9, 4.3 Hz, 1 H), 3.67 (dd, J = 7.8 Hz, 1 H), 3.74 (d, J=4.3 Hz, 1 H), 3.87 (d, J=9.1 Hz, 1 H), 3.99 (dd, J= 9.1, 5.1 Hz, 1 H), 4.24−4.28 (m, 1 H), 4.41 (dd, J=7.7, 3.9 Hz, 1 H), 6.60 (d, J=3.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.7, 22.9, 26.0, 26.6, 26.8, 30.8, 33.2, 52.5, 55.9, 56.3, 67.3, 75.9, 80.6, 82.1, 96.1, 110.4, 141.6, 161.7; FAB HRMS (NBA) *m*/*e* 498.0815, M + H$^+$ calcd for $C_{18}H_{28}INO_5S$ 498.0811.

(40) See the Supporting Information for General Techniques.

Epoxy Alcohol 46. A solution of epoxy amide **45** (899 mg, 1.86 mmol) in THF (10.0 mL) was treated with Super-H (4.7 mL 1.0 M in THF, 2.5 equiv) at 0 °C. After 1.0 h at this temperature, the reaction mixture was treated with MeOH at 0 °C and quenched by the addition of saturated aqueous NH_4Cl solution. The aqueous phase was washed with Et_2O and the combined organic extracts were washed with water and brine then dried over anhydrous $MgSO_4$ and the solvent was evaporated. The resulting crude product was purified by flash column chromatography (silica gel, 10% AcOEt in hexanes) to provide epoxy alcohol **46** (386 mg, 67%) as a yellow oil: R_f 0.23 (silica gel, 30% AcOEt in hexanes); $[\alpha]^{25}_D$ +52.4 (*c* 0.4, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (s, 3 H), 1.39 (s, 3 H), 3.11 (dd, J = 4.2, 2.3 Hz, 1 H), 3.15−3.18 (m, 1 H), 3.65−3.72 (m, 1 H), 3.93 (dd, J = 12.9, 2.3 Hz, 1 H), 4.05 (dd, J = 12.4, 3.4 Hz, 1 H), 4.32 (ddd, J = 8.2, 6.5, 1.5 Hz, 1 H), 6.54 (dd, J = 14.6, 6.6 Hz, 1 H), 6.61 (d, J = 14.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.5, 26.9, 53.0, 55.3, 60.4, 78.7, 80.1, 81.4, 110.3, 141.7; FAB HRMS (NBA) *m*/*e* 327.0105, M + H$^+$ calcd for $C_{10}H_{15}IO_4$ 327.0093.

Diol 47. Epoxy alcohol **46** (345 mg, 1.06 mmol) was dissolved in a 1:1 mixture of MeOH/$B(OMe)_3$ (10 mL) and the resulting solution was treated with DBU (0.16 mL, 1.06 mmol, 1.0 equiv) and heated at 70 °C for 1 day. After this time, the reaction mixture was allowed to reach room temperature, cooled to 0 °C, and then treated with a saturated aqueous $NaHCO_3$ solution. After the mixture was stirred for 30 min at 0 °C, AcOEt was added and both phases were separated. The aqueous phase was extracted with AcOEt 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, 40% AcOEt in hexanes) to afford diol **47** (281 mg, 74%) as a yellow oil: R_f 0.25 (silica gel, 60% AcOEt in hexanes); $[\alpha]^{25}_D$ +46.2 (*c* 0.03, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 6 H), 2.20 (br s, 2 H), 3.16 (ddd, J = 8.2, 3.9, 3.3 Hz, 1 H), 3.41 (s, 3 H), 3.58 (dd, J = 8.2, 1.5 Hz, 1 H), 3.79 (dd, J = 11.9, 3.3 Hz, 1 H), 3.88 (dd, J = 11.9, 3.9 Hz, 1 H), 3.93 (dd, J = 8.5, 1.6 Hz, 1 H), 4.42 (ddd, J = 8.4, 4.7, 1.6 Hz, 1 H), 6.54 (d, J = 4.7 Hz, 1 H), 6.55 (d, J = 1.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.8, 27.0, 58.0, 60.6, 67.6, 78.8, 79.3, 81.40, 81.43, 109.7, 142.2; FAB HRMS (NBA) *m*/*e* 359.0363, M + H$^+$ calcd for $C_{11}H_{19}IO_5$ 359.0355.

Amide 49. Diol **47** (43 mg, 0.12 mmol) was dissolved in a mixture of CH_3CN/H_2O (2.0 mL, 1/1) and the resulting solution was treated with BAIB (237 mg, 0.72 mmol, 6.0 equiv) followed by TEMPO (9.8 mg, 0.06 mmol, 0.5 equiv) at 25 °C. After 5 h, the crude mixture was diluted with AcOEt, 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 AcOEt. The combined organic solution was washed with saturated aqueous $Na_2S_2O_3$ solution again then dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude acid (∼0.12 mmol) was dissolved in DMF (1.5 mL) and treated with DIPEA (41 μL, 0.24 mmol, 2.0 equiv), L-Lys-Lactam **48** (30 mg, 0.18 mmol, 1.5 equiv), and BOP (65 mg, 0.14 mmol, 1.20 equiv) at 25 °C. 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, 90% AcOEt in hexanes) provided amide **49** (30 mg, 63% over 2 steps) as a white solid: R_f 0.29 (silica gel, 70% AcOEt in hexanes); mp 90−95 °C; $[\alpha]^{25}_D$ +61.4 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 3 H), 1.42 (s, 3 H), 1.47−1.61 (m, 2 H), 1.76−1.88 (m, 2 H), 1.97−2.12 (m, 2 H), 3.23−3.33 (m, 2 H), 3.48 (s, 3 H), 3.61 (dd, J=8.3, 1.8 Hz, 1 H), 3.70 (d, J = 8.3 Hz, 1 H), 3.90 (dd, J = 8.4, 1.7 Hz, 1 H), 4.48−4.55 (m, 2 H), 6.11 (t, J = 6.0 Hz, 1 H), 6.52 (d, J = 2.7 Hz, 1 H), 6.53

(d, J=3.7 Hz, 1 H), 7.90 (d, J = 6.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.7, 27.1, 27.9, 28.8, 31.2, 42.1, 51.9, 59.8, 69.1, 78.5, 78.6, 81.1, 81.2, 109.6, 142.4, 171.3, 174.8; FAB HRMS (NBA) m/e 483.0985, M + H$^+$ calcd for $C_{17}H_{27}IN_2O_6$ 483.0992.

Amide 50. To a solution of vinyl iodide **49** (20.0 mg, 0.04 mmol) in a 1:1 mixture of DMF:THF (1.0 mL) was added Pd(dpephos)Cl_2 (3.0 mg, 0.004 mmol, 0.1 equiv), followed by diisopropylzinc (27 μL, 1 M solution in THF, 0.027 mmol, 0.65 equiv) at 25 °C. After being stirred for 2.5 h at 25 °C, the crude mixture was treated with water, diluted with Et_2O and, after separation of both layers, the aqueous phase extracted with Et_2O twice. The resulting organic solution was then washed with brine, dried ($MgSO_4$), filtered, and concentrated. Purification by flash column chromatography (silica gel, AcOEt) provided compound **50** (11.0 mg, 67%) whose physical and spectroscopic properties were identical with those reported elsewhere.[16]

Amide 53. A solution of vinyl iodide **49** (22.0 mg, 0.046 mmol) and pinacol boronic ester **51** (12 μL, 0.050 mmol, 1.1 equiv) in a 3:1 mixture of THF:H_2O (2.0 mL) was treated with Pd(dpephos)Cl_2 (3.2 mg, 0.0046 mmol, 0.1 equiv) and Tl_2CO_3 (43 mg, 0.09 mmol, 2.0 equiv). After being stirred overnight at 25 °C, the crude mixture was diluted with Et_2O and washed with a saturated aqueous $KHSO_4$ 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. The crude product was purified by flash column chromatography (silica gel, AcOEt) to afford compound **53** (8.0 mg, 42%) as a pale yellow solid: R_f 0.22 (silica gel, AcOEt); mp 110−113 °C; $[\alpha]^{25}_D$ +70.0 (c 2.4, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 6 H), 1.47−1.50 (m, 2 H), 1.73 (s, 3 H), 1.75 (s, 3 H), 1.78 (s, 3 H), 1.75−1.88 (m, 2 H), 1.97−2.10 (m, 2 H), 3.22−3.32 (m, 2 H), 3.47 (s, 3 H), 3.60 (dd, J = 8.3, 1.6 Hz, 1 H), 3.69 (d, J = 8.3 Hz, 1 H), 3.88 (dd, J = 8.6, 1.6 Hz, 1 H), 4.50−4.54 (m, 1 H), 4.57 (dd, J = 8.5 Hz, 1 H), 5.45 (dd, J = 15.4, 8.3 Hz, 1 H), 5.98−6.01 (m, 1 H), 6.79 (d, J = 15.4 Hz, 1 H), 7.82 (d, J = 6.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 20.4, 21.9, 26.8, 27.4, 27.9, 28.9, 31.3, 42.1, 51.9, 59.6, 69.0, 78.8, 79.4, 81.5, 81.2, 108.9, 122.2, 125.6, 134.7, 171.2, 174.9; FAB HRMS (NBA) m/e 425.2647, M + H$^+$ calcd for $C_{22}H_{36}N_2O_6$ 425.2652.

Amide 54. A solution of vinyl iodide **49** (32.0 mg, 0.066 mmol) and pinacol boronic ester **52** (15 mg, 0.073 mmol, 1.1 equiv) in a 3:1 mixture of THF:H_2O (2.0 mL) was treated with Pd(dpephos)Cl_2 (5.0 mg, 0.0066 mmol, 0.1 equiv) and Tl_2CO_3 (62 mg, 0.13 mmol, 2.0 equiv). The reaction mixture was then heated at 60 °C for 4 h, after which it was left to reach room temperature, diluted with Et_2O, and washed with a saturated aqueous $KHSO_4$ 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. The crude product was purified by flash column chromatography (silica gel, 10% MeOH and 45% AcOEt in hexanes) to afford compound **54** (12.0 mg, 41%) as a pale yellow solid: R_f 0.23 (silica gel, AcOEt); mp 122−125 °C; $[\alpha]^{25}_D$ +58.8 (c 1.6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (s, 9 H), 1.41 (s, 3 H), 1.42 (s, 3 H), 1.49−1.52 (m, 2 H), 1.72−1.90 (m, 2 H), 1.98−2.10 (m, 2 H), 3.22−3.32 (m, 2 H), 3.46 (s, 3 H), 3.59 (dd, J = 8.3, 1.6 Hz, 1 H), 3.68 (d, J = 8.3 Hz, 1 H), 3.85 (dd, J = 8.6, 1.5 Hz, 1 H), 4.49−4.55 (m, 1 H), 4.50 (dd, J = 8.5 Hz, 1 H), 5.50 (dd, J = 15.2, 8.1 Hz, 1 H), 5.70 (d, J = 15.5 Hz, 1 H), 5.93 (dd, J = 15.5, 10.3 Hz, 1 H), 6.07−6.10 (m, 1 H), 6.27 (dd, J = 15.2, 10.3 Hz, 1 H), 7.83 (d, J = 6.3 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.8, 27.3, 27.9, 28.9, 29.4, 31.3, 33.2, 42.1, 51.9, 59.6, 69.0, 78.8, 79.3, 81.5, 109.0, 124.1, 126.4, 135.9, 147.5, 171.3, 174.9; FAB HRMS (NBA) m/e 439.2787, M + H$^+$ calcd for $C_{23}H_{38}N_2O_6$ 439.2808.

Silyl Ether 55. A solution of hydroxy amide **49** (21 mg, 0.044 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) (15 μL, 0.065 mmol, 1.5 equiv) at 0 °C in the presence of 2,6-lutidine (10 μL, 0.088 mmol, 2.0 equiv). After 0.5 h at 0 °C, the reaction mixture was quenched by addition of MeOH (0.1 mL), followed by addition of aqueous saturated NH_4Cl solution and dilution with Et_2O (2 mL). After separation of both phases, the aqueous phase was extracted with Et_2O (2 × 10 mL), then the combined organic layers were washed with brine and dried with $MgSO_4$. After filtration, the solvents were removed by reduced pressure to obtain a crude product that was purified by flash column chromatography (silica gel, 50% EtOAc in hexanes) to afford silyl ether **55** (25 mg, 95%) as a yellow foam: R_f 0.49 (silica gel, 60% AcOEt in hexanes); $[\alpha]^{25}_D$ +20.0 (c 0.8, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 3 H), 0.08 (s, 3H), 0.84 (s, 9 H), 1.34 (s, 3 H), 1.33 (s, 3 H), 1.37−1.52 (m, 1 H), 1.71 (br s, 1 H), 1.77−1.88 (m, 2 H), 1.96−2.04 (m, 2 H), 3.21−3.26 (m, 2 H), 3.47 (s, 3 H), 3.73 (d, J = 2.0 Hz, 1 H), 3.91 (dd, J = 8.1, 6.3 Hz, 1 H), 4.27 (dd, J = 6.3, 2.0 Hz, 1 H), 4.41 (ddd, J = 11.1, 5.6, 1.5 Hz, 1 H), 4.55 (ddd, J = 8.0, 6.1, 1.0 Hz, 1 H), 6.15 (t, J = 5.9 Hz, 1 H), 6.46 (dd, J = 14.5, 1.1 Hz, 1 H), 6.64 (dd, J = 14.5, 6.1 Hz, 1 H), 7.87 (d, J = 5.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.6, 18.1, 25.8, 26.7, 26.8, 27.9, 28.9, 31.4, 42.1, 52.0, 59.5, 73.9, 79.5, 79.6, 80.7, 83.9, 108.9, 143.9, 168.7, 174.9; FAB HRMS (NBA) m/e 597.1843, M + H$^+$ calcd for $C_{23}H_{41}IN_2O_6Si$ 597.1857.

Amide 56. To a solution of silyl ether **55** (18.0 mg, 0.032 mmol) in THF (1.0 mL) was added cyclopropylzinc bromide (318 μL, 0.5 M solution in THF, 0.16 mmol, 5.0 equiv) followed by Pd[PPh_3]$_4$ (4.0 mg, 0.0032 mmol, 0.1 equiv) at 25 °C. After 1 h at 25 °C, the crude mixture was diluted with Et_2O then washed with a saturated aqueous NH_4Cl solution and the aqueous phase was extracted with Et_2O twice. The combined organic phases were washed with brine then dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. Purification by flash column chromatography (silica gel, 50% AcOEt in hexanes) of the resulting crude product provided amide **56** (12.0 mg, 80%) as a colorless oil: R_f 0.34 (silica gel, 50% AcOEt in hexanes); $[\alpha]^{25}_D$ +30.0 (c 0.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 3 H), 0.07 (s, 3 H), 0.30−0.39 (m, 2 H), 0.67−0.69 (m, 2 H), 0.82 (s, 9 H), 1.34 (s, 6 H), 1.45−1.51 (m, 2 H), 1.69−1.89 (m, 2 H), 1.98−2.14 (m, 2 H), 3.19−3.28 (m, 2 H), 3.41 (s, 3 H), 3.72 (d, J = 1.9 Hz, 1 H), 3.98 (dd, J = 8.2, 6.8 Hz, 1 H), 4.08 (dd, J = 6.8, 1.9 Hz, 1 H), 4.27 (dd, J = 8.0 Hz, 1 H), 4.43 (dd, J = 10.1, 6.0 Hz, 1 H), 5.25 (dd, J = 15.2, 9.0 Hz, 1 H), 5.60 (dd, J = 15.2, 8.1 Hz, 1 H), 6.03−6.11 (m, 1 H), 7.85 (d, J = 5.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7, −4.6, 6.8, 6.9, 13.6, 18.2, 25.8, 26.9, 27.0, 27.9, 29.0, 31.4, 42.1, 51.9, 58.7, 74.3, 79.2, 80.7, 83.5, 108.1, 125.3, 140.5, 169.3, 174.9; FAB HRMS (NBA) m/e 511.3195, M + H$^+$ calcd for $C_{26}H_{46}N_2O_6Si$ 511.3203.

Amide 36. Amide **55** (20.0 mg, 0.035 mmol) was converted into amide **36** (12.4 mg, 67%) according to the procedure described above for **56** with Pd(dpephos)Cl_2 (3.0 mg, 0.004 mmol, 0.1 equiv) as catalyst and *tert*-butylzinc bromide (360 μL, 0.5 M solution in THF, 0.18 mmol, 5.0 equiv). Amide **36** displayed identical physical and spectroscopic properties to those reported elsewhere.[16]

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Supporting Information Available: Experimental procedures and spectroscopic data of all new compounds, as well as ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.