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Total Synthesis of Bengamide E and Analogues by Modification at C-2 and at Terminal Olefinic Positions

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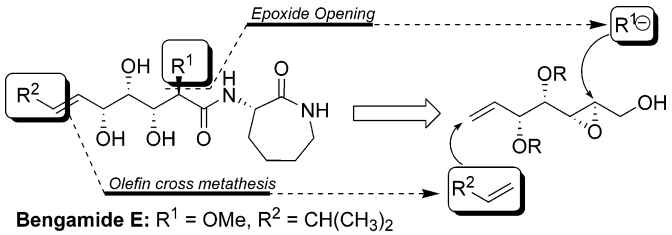

The total synthesis of the natural product Bengamide E, one of the members of a new class of antitumor natural products of marine origin, is reported based on a convergent and flexible synthetic route featuring an oxirane ring-opening reaction and an olefin cross metathesis. In a similar way, analogues structurally modified at C-2 and at the terminal vinyl positions were prepared by introduction of various nucleophiles and alkyl substituents during the epoxide opening and the olefin cross metathesis steps, respectively. These studies demonstrate the validity of our synthetic strategy, although they reveal some problems associated with the olefin cross metathesis, whose efficiency depends on the substituent at the C-2 position as well as the steric environment of the alkene.

Introduction

The bengamides represent an interesting and promising family of marine natural products, isolated from sponges of the Jaspidae family,[1] with unique molecular structures and a broad array of biological activities that include antitumor, antibiotic, and antihelmintic properties.[2] According to recent biological investigations,[3] the bengamides possess an intriguing mode of action characterized by their binding to methionine aminopeptidases type 2 (MetAp2),[4] enzymes that are involved in the cell cycle of endothelial cells and angiogenesis.[5] This mode is similar to those of fumagillin and ovalicin, despite their structural differences.[6] All these biological features in conjuction with their molecular architectures have elicited great interest among chemists[7] and biologists.[8] Our group engaged recently in a research program directed toward the total syntheses of these naturally occurring cytotoxic molecules, of which six representative members are depicted in Figure 1.

Our early synthetic studies were conducted according to a synthetic strategy utilizing sulfur ylides to construct an oxirane ring as a means for the introduction of the

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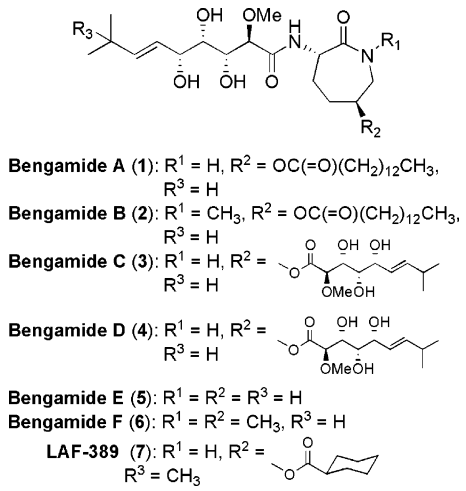
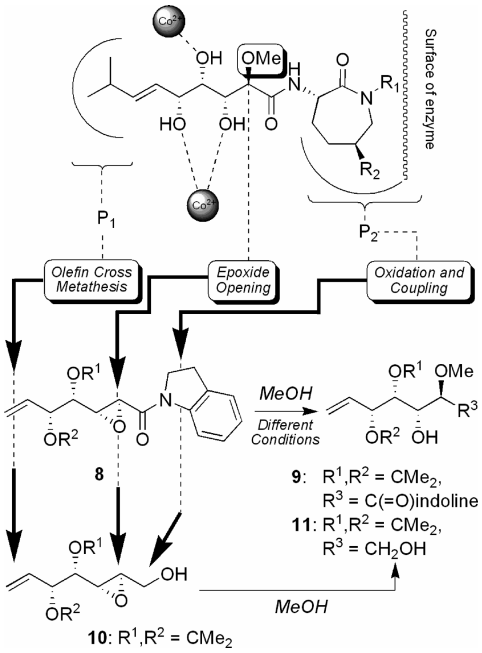


FIGURE 1. Molecular structures of bengamides.

methoxide group at the C-2 position via a regioselective oxirane ring-opening reaction,[9] and an olefin cross metathesis reaction for the introduction of the terminal alkyl group.[10] Our synthetic course offered the possibility of introducing structural modifications at key positions involved in the interaction of the molecule with the methionine aminopeptidases, leading us to epoxy amide **8**, prepared by reacting the corresponding aldehyde with the stabilized sulfur ylide derived from the indoline amide, as the key suitable precursor. As depicted in Scheme 1, the highly specific affinity of the bengamides toward methionine aminopeptidases is the result of multiple interactions that include hydrophobic and polar interactions of the terminal alkyl group of the olefin and

SCHEME 1. Interaction of Bengamides with Methionine Aminopeptidases and Synthetic Strategy



the caprolactam moiety with the P1 pocket and the solvent-exposed P2 region, respectively, together with a coordination of the cobalt ions, present at the active site, with the hydroxyls at the C-3, C-4, and C-5 positions. An example of the biological importance of the terminal alkyl group is the synthetic *tert*-butyl analogue LAF-389 (**7**), which displays greater antitumor activity compared with its natural counterpart.[11] On the basis of these precedents, we demonstrated the efficiency of this strategy for the preparation of 2-amino analogues of bengamides. Unfortunately, we were unable to introduce the requisite methoxyl group at C-2 to give the 2-methoxy derivative **9** when **8** was treated with methanol under a wide array of reaction conditions. In light of this unsuccessful result, we decided to modify the original synthetic strategy, figuring that epoxy alcohol **10** could represent an alternative for the preparation of **11**. This slight modification in our synthesis would allow us to surmount the synthetic hurdle imposed by the lack of reactivity of epoxy amides toward alcohols, and would allow us to maintain a synthetic strategy capable of rendering a variety of analogues, modified at key regions, that are involved in the biological interactions with the active site of enzymes, as illustrated in Scheme 1.

Results and Discussion

The synthesis of epoxy alcohol **10** was efficiently accomplished from aldehyde **12**, as previously described by our laboratory.[10] The regioselective opening of the epoxy alcohol with methanol represented a key reaction for the construction of the complete framework contained in the bengamides, which previously had failed in the epoxy amide case. An extensive search of the literature

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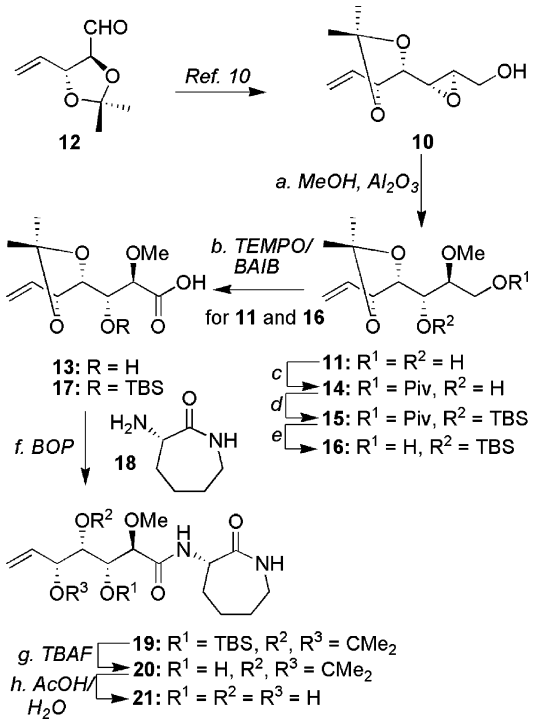
revealed the difficulty of such a task given the scarcity of described methods.[12] Among them, the neutral conditions employed by Hudlicky[13] seemed to be the most adequate procedure, taking into account the acidic lability of the acetal present in **10**. Thus, treatment of **10** with neutral alumina in refluxing methanol proceeded smoothly, to provide the opening product **11** in 57% yield and complete regioselectivity.[14] The oxidation of the resulting diol **11** was attempted in a straightforward manner, via TEMPO oxidation[15] followed by $NaClO_2$/NaH_2PO_4 treatment[16] in the presence of an excess of 2-methylbutene.[17] Disappointingly, the second oxidation afforded a complex mixture of products, prompting us to investigate other methods. This resulted in the identification of a TEMPO/BAIB[18] system in the presence of water, which provided the acid in quantitative yield. The crude acid **13** was then coupled with the commercially available aminolactam **18**[19] mediated by the action of (benzotriazol-1-yloxy) tris(dimethylamino)phosphonium hexafluorophosphate (BOP) to furnish the corresponding amide **20**, together with its 2-epimer, in 25% yield. The epimerization was circumvented by protection of the secondary hydroxyl group of **11** as the *tert*-butyldimethylsilyl ether. This was achieved by selective protection of the primary hydroxyl group of **11** as its pivaloate **14**, followed by silylation of the secondary hydroxyl to give the silyl ether **15**, which was treated with DIBAL to give the alcohol **16**. Thus, oxidation of **16** with TEMPO/BAIB, in a way similar to that for **11**, afforded acid **17**, which was reacted with aminolactam **18** under the influence of BOP to give compound **19** in 50% overall yield from alcohol **16** and no detectable epimerization according to ^{1}H NMR. Removal of the protecting groups of **19** was achieved in two steps (TBAF treatment, followed by reaction with acetic acid in H_2O) to provide the methylene analogue of Bengamide E, compound **21** (Scheme 2).

SCHEME 2. Synthesis of Bengamide E Precursor 19 and Analogue 21[a]



[a] Reagents and conditions: (a) Al_2O_3 (large excess), MeOH, reflux, 3 days, 57%; (b) 0.3 equiv of TEMPO, 3.0 equiv of BAIB, 1:1 CH_3CN:H_2O, 25 °C, 2.0 h; (c) 1.3 equiv of PivCl, 2:1 pyr:CH_2Cl_2, −20 °C, 0.5 h, 96%; (d) 1.2 equiv of TBSOTf, 1.5 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 15 min, 93%; (e) 2.2 equiv of DIBAL-H, CH_2Cl_2, −78 °C, 20 min, 90%; (f) 1.5 equiv of **18**, 1.2 equiv of BOP, 2.0 equiv of DIPEA, DMF, 25 °C, 3.0 h, 50% for **20** together with its 2-epimer (ca. 25% epimerization) from **11**, 50% for **19** from **16**; (g) 1.5 equiv of TBAF, THF, 25 °C, 0.5 h; (h) 70% AcOH in H_2O, 50 °C, 8 h, 45% over two steps from **19**.

In our pursuit of the natural product, Bengamide E (**5**), we initiated studies on the olefin cross metathesis[20] in order to introduce the terminal isopropyl group. Our preliminary results obtained in this reaction with epoxy amide derivatives represented promising precedent for surmising that this reaction would proceed in a similar fashion for compound **19**. However, when a solution of olefinic compound **19** in DCM with 3-methyl-1-butene as cosolvent was exposed to the action of the second-generation Grubbs catalyst **22**[21] at 40 °C, the reaction did not proceed as expected. This resulted in no detection of the coveted alkene **24**, even after a long reaction time with the recovery of the starting olefin. The lack of reactivity found for this substrate toward the catalytic action of **22** was overcome by use of the more reactive second-generation Hoveyda−Grubbs catalyst (**23**),[22] which promoted olefin cross metathesis of **19** in the presence of 3-methyl-1-butene, to furnish compound **24** in 89% yield and with excellent selectivity (9:1 mixture of *E*:*Z* isomers, as determined by ^{1}H NMR spectroscopy). For the unprotected olefin **20**, the result was discouraging; utilization of either catalyst **22** or **23** resulted in no formation of the expected cross olefin product **25**. In light of these results, the introduction of different terminal alkyl substituents was undertaken from the precursor **19**, using **23** as the catalyst. Thus, in a way similar to that for **24**, the reaction of **19** with 3,3-dimethyl-1-butene provided the corresponding *tert*-butyl-substituted alkene **26**, albeit in poor conversion (90% for a 33% conversion, 9:1 *E*:*Z* mixture). On the other hand, treatment of **19** with styrene under the influence of **23** provided in a reason-

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(14) The complete regioselectivity found with this reaction was ascribed to a mixed aluminate formation between Al_2O_3 with methanol and epoxy alcohol **10** that led to a regioselective attack of a methoxyl group at the C-2 position of **10** in an intramolecular opening process.

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(19) L-(−)-α-Amino-ϵ-caprolactam hydrochloride **18** was purchased from Fluka.

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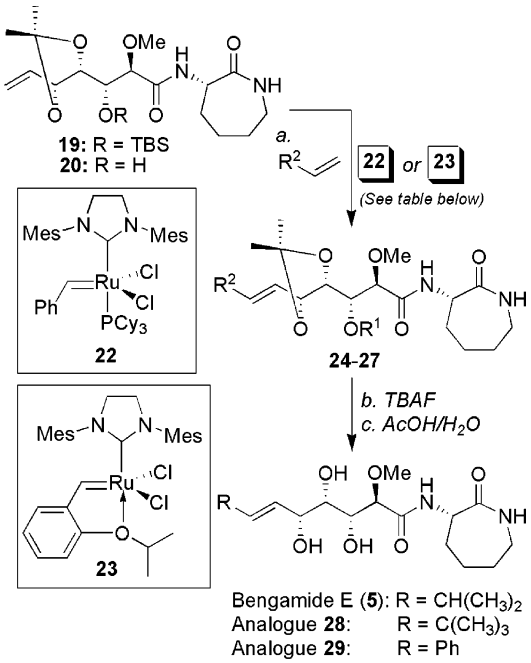
SCHEME 3. Synthesis of Bengamide E (5) and Analogues 28 and 29[a]



Product	Catalyst	R^1	R^2	Yield (%)
24:	**22**	TBS	*i*-Pr	---
24:	**23**	TBS	*i*-Pr	89
25:	**22 or 23**	H	*i*-Pr	---[a]
26:	**23**	TBS	*t*Bu	90[a]
27:	**23**	TBS	Ph	94[b]

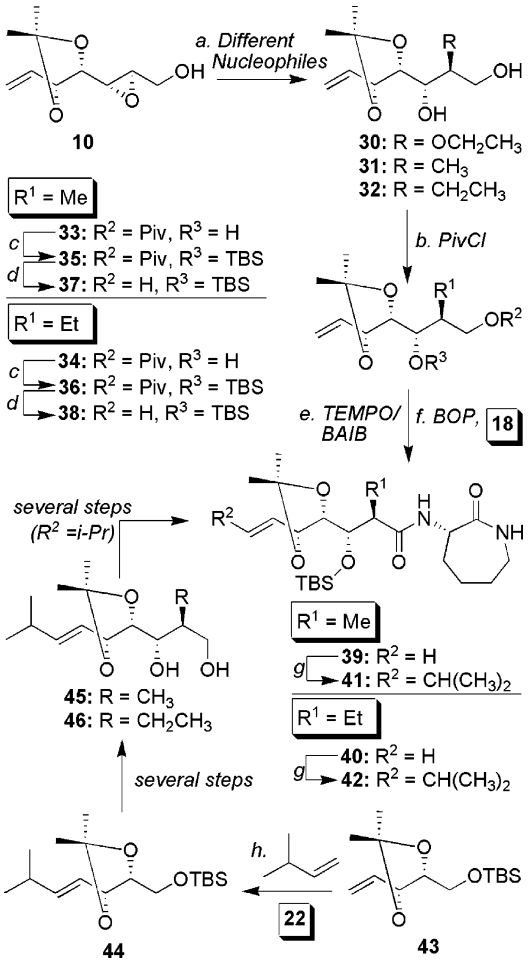
[a] *Yield after a 33% conversion.* [b] *Yield after a 66% conversion*

[a] Reagents and conditions: (a) all the metathesis reactions were performed in 2:1 alkene:CH_2Cl_2, 40 °C for 6−72 h (for yields see table); (b) 1.5 equiv of TBAF , THF, 25 °C, 0.5 h; (c) 70% AcOH, 50 °C, 0.5 h, 62% over 2 steps for Bengamide E (**5**), 43% for **28**, 60% for **29**.

able conversion the phenyl analogue **27** (94% for a 66% conversion, 9:1 *E*:*Z* mixture). Finally, the cleavage of protecting groups of the olefin cross metathesis products **24**, **26**, and **27** was performed as described previously for **19** to obtain Bengamide E (**5**) and its *tert*-butyl and phenyl analogues **28** and **29** (Scheme 3).

Another structural point amenable to modification is the C-2 position, which takes advantage of the reactivity of the oxirane ring. Thus, epoxy alcohol **10** was subjected to the action of various nucleophiles to obtain the corresponding opened products in a wide range of yields depending on the nature of the nucleophile. In particular, the introduction of different alcohols such as ethanol was achieved as previously described for methanol, providing a poor yield of the corresponding 2-ethoxy derivative **30**. In contrast, the treatment of **10** with organocuprate reagents yielded the 2-alkyl opening compounds in good yields, 60% and 65% for 2-methyl **31** and 2-ethyl **32**, respectively.[23] Other nucleophiles such as sulfides were more problematic, yielding a mixture of compounds,

SCHEME 4. Synthesis of 2-C-Modified Bengamide Analogues from Epoxy Alcohol 10[a]



[a] Reagents and conditions: (a) (i) Al_2O_3 (large excess), EtOH, reflux, 3 days, 20% for **30**; (ii) 10.0 equiv of Me_2CuLi, THF, 25 °C, 3 h, 60% for **31**; (iii) 6.0 equiv of EtMgBr, 2.0 equiv of CuI, THF, 25 °C, 3 h, 65% for **32**; (b) 1.3 equiv of PivCl, 2:1 pyr:CH_2Cl_2, −20 °C, 0.5 h, 90% for **33**, 72% for **34**; (c) 1.7 equiv of TBSOTf, 2.0 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 15 min, 86% for **35**, 85% for **36**; (d) 2.2 equiv of DIBAL-H, CH_2Cl_2, −78 °C, 0.5 h, 96% for **37**, 97% for **38**; (e) 0.3 equiv of TEMPO, 8.0 equiv of BAIB, CH_3CN/H_2O (1:1), 25 °C, 3.0 h; (f) 1.5 equiv of **18**, 1.2 equiv of BOP, 2.0 equiv of DIPEA, DMF, 25 °C, 1.5 h, 58% for **39** overall yield from **37**, 63% for **40** overall yield from **38**; (g) 0.3 equiv of **23**, 1:2 CH_2Cl_2:2-methyl-2-butene, 40 °C, 6−48 h, 22% for **41** (*E*:*Z* ≈ 9:1); 12% for **42** (*E*:*Z* ≈ 9:1); (h) 0.3 equiv of **22**, 1:2 CH_2Cl_2:2-methyl-2-butene, 40 °C, 38 h, 94%.

probably through Payne rearrangement processes.[24] For compounds **31** and **32**, we proceeded in a similar synthetic sequence as described before for Bengamide E (**5**), to obtain the 2-C-alkyl analogues of bengamides **39** and **40**, through compounds **33**, **35**, and **37**, and **34**, **36**, and **38**, respectively. With the key products for the final olefin cross metathesis in hand, we proceeded with the reaction under similar conditions as before; however, unlike with the 2-methoxy derivative **24**, on this occasion the reactions were not so efficient, providing the targeted prod-

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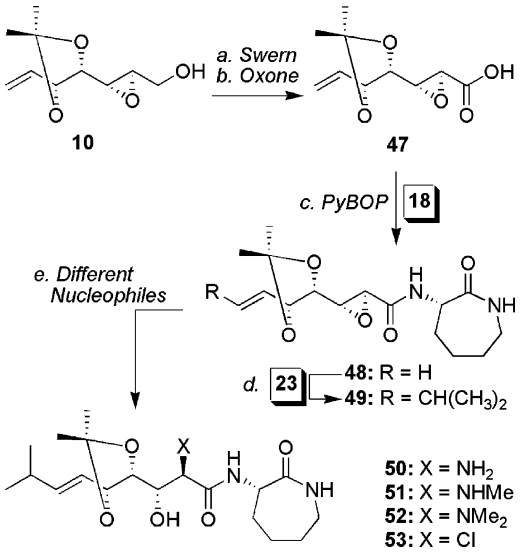
SCHEME 5. Synthesis of 2-C-Modified Bengamide Analogues from Epoxy Amide 49[a]



[a] Reagents and conditions: (a) 1.8 equiv of $(COCl)_2$, 1.8 equiv of DMSO, CH_2Cl_2, −78 °C, 0.5 h, then 5.4 equiv of Et_3N, 10 min; (b) 1.0 equiv of Oxone, DMF, 25 °C, 1 h; (c) 1.5 equiv of **18**, 1.2 equiv of PyBOP, 2.0 equiv of DIPEA, DMF, 25 °C, 8 h, 38% overall yield from **10**; (d) 0.3 equiv of **23**, 1:1 CH_2Cl_2:2-methyl-2-butene, 40 °C, 38 h, 78% (*E*:*Z* ≈ 9:1); (e) (i) RNH_2 (excess), MeOH, 25 °C, 12 h, 95% for **50**, 97% for **51**, 95% for **52**, (ii) 1.5 equiv of LiCl, 1.5 equiv of AcOH, THF, reflux, 12 h, 60%.

ucts **41** and **42** in low yields and overall conversions. These unexpected results seem to demonstrate the influence of the substituent at the C-2 position in the course of the metathesis process. To overcome this inconvenience, we decided to introduce the terminal isopropyl group earlier in the synthetic sequence, prior to the incorporation of the alkyl groups. Thus, olefin cross metathesis of the earlier precursor **43** delivered the corresponding *E*-alkene **44** in excellent yield (94%, after a 100% conversion) by the action of the second-generation Grubbs catalyst **22**. From compound **44**, we prepared the targeted 2-alkyl analogues **41** and **42** through intermediates **45** and **46** following the same synthetic pathway as described for **31** and **32**, encountering no significant difficulties along the synthetic course, and obtaining yields similar to those of the corresponding methylene derivatives (Scheme 4).

On the other hand, 2-amino derivatives of bengamides represent very interesting 2-C-modified analogues because of a potential strong coordination with the cobalt ions present at the active site of aminopeptidases. To this end, epoxy amide **48** was prepared from epoxy alcohol **10**, involving a two-step oxidation to the epoxy acid **49**, and coupling with L-Lys-ϵ-caprolactam **18**, by the action of PyBOP, in a 38% overall yield. The epoxy amide was treated with 3-methyl-1-butene under the influence of Grubbs catalyst **23** to obtain in a very gratifying yield (78%) the corresponding *E*-olefin **49**. The treatment of the resulting epoxy amide **49** with different amines, including ammonia, *N*-methylamine, and *N*,*N*-dimethylamine, provided the corresponding 2-amino derivatives **50**−**52** in very high yields (95−97%) and with complete regio- and stereoselectivities. The introduction of different heteroatoms, such as halogens, proved to be efficient for chloride, obtaining 2-chlorohydrine **53** in a 60% yield by treatment with lithium chloride in the presence of acetic acid.[9c] This is in contrast to other halogens, such as fluoride, in which, after different reagents and reaction conditions were used, the starting material was recovered, or to sulfides, in which elimination products were obtained[10] (Scheme 5).

Conclusions

In conclusion, a new synthetic route has been established for the bengamides capable of generating a variety of bengamide analogues, providing significant advantages over previous reported syntheses. Particularly, this new strategy proved to be efficient for the synthesis of Bengamide E (**5**), as well as terminal alkyl-modified analogues such as **21**, **28**, and **29**. On the other hand, the modifications at the C-2 position were also possible by opening of the oxirane ring with different nucleophiles (alcohols and organometallics for epoxy alcohol **10**, and nitrogen- or halide-type nucleophiles for epoxy amide **49**). However, the results obtained during the cross metathesis reactions revealed that the substituent at C-2 might play an important role in this reaction, probably because of steric reasons, which requires a more thorough mechanistic investigation. The biological evaluation of these compounds will allow for the establishment of a pharmacophore model for the molecule and, consequently, a refined design of new analogues, which will allow for the discovery of biologically active compounds with potential therapeutic applications. All these items represent our priorities in current and future investigations.

Experimental Section

Epoxy Alcohol 10. A suspension of 4 Å molecular sieves (1.15 g) in CH_2Cl_2 (39 mL) was cooled to −20 °C, followed by the addition of $Ti(O^iPr)_4$ (0.15 mL, 0.5 mmol, 0.1 equiv) and D-(−)-DET (0.084 mL, 0.5 mmol, 0.1 equiv). The reaction mixture was stirred for 30 min at −20 °C, and after that time a solution of the corresponding allylic alcohol (see Supporting Information) (0.91 g, 5 mmol, 1.0 equiv) in CH_2Cl_2 and TBHP (1.8 mL of a 5.5 M solution in decane, 2.0 equiv) was sequentially added. The reaction mixture was stirred at −20 °C for 48 h, after which the crude mixture was filtered through Celite, concentrated under reduced pressure, and purified by flash column chromatography (silica gel, 30% AcOEt in hexanes) to obtain epoxy alcohol **10** (666 mg, 86% based on the reacted material) together with unreacted allylic alcohol (197 mg) as a colorless oil: R_f = 0.16 (silica gel, 30% AcOEt in hexanes); $[\alpha]^{25}_D$ = +2.39 (*c* 0.23, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 3H), 1.40 (s, 3H), 1.76 (bs, 1H), 3.09−3.19 (m, 2H), 3.61 (dd, *J* = 4.3, 8.6 Hz, 1H), 3.65 (dd, *J* = 3.7, 12.9 Hz, 1H), 3.93 (dd, *J* = 2.2, 12.9 Hz, 1H), 4.33 (t, *J* = 8.1 Hz, 1H), 5.28 (d, *J* = 10.2 Hz, 1H), 5.40 (d, *J* = 17.2 Hz, 1H), 5.78−5.87 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.5, 26.9, 53.4, 55.3, 60.6, 79.5, 79.9, 109.9, 119.6, 134.6.

Diol 11. To a solution of epoxy alcohol **10** (50 mg, 0.25 mmol, 1.0 equiv) in MeOH (50 mL) was added neutral Al_2O_3 (2.5 g), and the resulting suspension was refluxed for 3 days. After that time, the Al_2O_3 was filtered off and washed with hot MeOH (3 × 10 mL). The filtrate was evaporated, and the crude was purified by flash column chromatography (silica gel, 60% AcOEt in hexanes) to afford diol **11** (24.4 mg, 57% based on recovered starting material) as a clear oil: R_f = 0.18 (silica gel, 60% AcOEt in hexanes); $[\alpha]^{25}_D$ = +11.3 (*c* 0.16, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 6H), 3.14−3.18 (m, 1H),

3.41 (s, 3H), 3.57 (dd, J = 1.6, 8.1 Hz, 1H), 3.77 (dd, J = 3.7, 11.8 Hz, 1H), 3.86 (dd, J = 4.8, 11.8 Hz, 1H), 3.88 (dd, J = 1.6, 8.1 Hz, 1H), 4.42 (t, J = 8.1 Hz, 1H), 5.26 (d, J = 9.6 Hz, 1H), 5.38 (d, J = 17.2 Hz, 1H), 5.76−5.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.8, 27.1, 57.9, 60.7, 67.5, 78.6, 79.3, 81.5, 109.4, 119.7, 134.7; FAB HRMS (NBA) *m/e* 255.1210, $[M + Na]^+$ calcd for $C_{11}H_{20}O_5$ 255.1208.

Acid 13. Diol **11** (20 mg, 0.073 mmol, 1.0 equiv) was dissolved in a 1:1 CH_3CN/H_2O mixture (0.12 mL). BAIB (70.8 mg, 0.22 mmol, 3 equiv) and TEMPO (3.42 mg, 0.022 mmol, 0.3 equiv) were added at rt, and the reaction was monitored by TLC (60% AcOEt in hexanes) to detect depletion of the starting material and formation of the intermediate aldehyde (step 1, R_f = 0.6, 1 h approximately), followed by the disappearance of this aldehyde and formation of the desired acid **13** (step 2, R_f = 0.17) after an additional 1 h. The reaction was then quenched by the addition of saturated aqueous $Na_2S_2O_3$ solution (2 mL); the aqueous phase was then extracted with AcOEt (3 × 5 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The crude was employed in the next step without purification.

Amide 20. Coupling of Acid 13 with L-Lys-Lactam. To a solution of crude acid **13** (21 mg, 0.073 mmol, 1.0 equiv) in DMF (2 mL) were added Hünig's base (0.025 mL, 0.16 mmol, 2.2 equiv) and L-Lys-caprolactam **18** (17.7 mg, 0.11 mmol, 1.5 equiv). When the solution was homogeneous, BOP (44.3 mg, 0.087 mmol, 1.2 equiv) was added in one portion, and the reaction mixture was stirred for 3 h at rt. After this time, Et_2O (10 mL) was added, and the organic phase was washed with saturated aqueous NH_4Cl solution (2 × 5 mL); the organic extracts were dried with $MgSO_4$, and the solvent was evaporated. The crude product was subjected to flash column chromatography (silica gel, 100% AcOEt) to yield coupling product **20** (13.3 mg, 50% over 3 steps) as a white solid, which was accompanied with its 2-epimer in a 25% yield according to its ^{1}H NMR spectra.

Pivaloyl Ester 14. Diol **11** (100 mg, 0.37 mmol, 1.0 equiv) was dissolved in a 2:1 pyridine/CH_2Cl_2 mixture (0.78 mL), and cooled to −20 °C. Pivaloyl chloride (0.06 mL, 0.48 mmol, 1.3 equiv) was added, and the reaction mixture was stirred at this temperature until the starting material was depleted (ca. 20 min). The mixture was then diluted with CH_2Cl_2 (10 mL), and the organic phase was washed with saturated aqueous $NaHCO_3$ solution (2 × 5 mL), dried ($MgSO_4$), and concentrated. After flash column chromatography (silica gel, 20% AcOEt in hexanes), pure pivaloate ester **14** (125 mg, 96%) was obtained as a colorless oil: R_f = 0.25 (silica gel, 20% AcOEt in hexanes); $[\alpha]^{25}_D$ = +7.69 (*c* 0.20, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (s, 9H), 1.43 (s, 6H), 3.30−3.60 (m, 1H), 3.40−3.42 (m, 1H), 3.42 (s, 3H), 3.94 (bd, J = 8.6 Hz, 1H), 4.10−4.16 (m, 1H), 4.42 (t, J = 8.6 Hz, 1H), 4.55 (dt, J = 2.2, 12.4 Hz, 1H), 5.26 (d, J = 10.2 Hz, 1H), 5.38 (d, J = 17.2 Hz, 1H), 5.77−5.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.9, 27.2, 38.7, 58.6, 63.3, 67.0, 78.6, 78.8, 80.1, 109.4, 119.6, 134.8, 178.5; FAB HRMS (NBA) *m/e* 339.1783, $[M + Na]^+$ calcd for $C_{16}H_{28}O_6$ 339.1784.

Silyl Ether 15. To a solution of **14** (125 mg, 0.035 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) and 2,6-lutidine (0.06 mL, 0.053 mmol, 1.5 equiv) was added at 0 °C TBSOTf (0.096 mL, 0.042 mmol, 1.2 equiv). Monitoring of the reaction by TLC showed that it was complete in 15 min. The mixture was then diluted with Et_2O (10 mL), and washed with saturated aqueous NH_4Cl solution (2 × 4 mL). After drying ($MgSO_4$) and solvent evaporation, the crude product was subjected to purification by flash column chromatography (silica gel, 5% AcOEt in hexanes) to yield pure **15** (135 mg, 93%) as a colorless oil: R_f = 0.23 (silica gel, 5% AcOEt in hexanes); $[\alpha]^{25}_D$ = −7.63 (*c* 0.20, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 1.18 (s, 9H), 1.38 (s, 3H), 1.41 (s, 3H), 3.37 (s, 3H), 3.37−3.40 (m, 1H), 3.78 (dd, J = 4.3, 8.6 Hz, 1H), 3.83 (t, J = 4.3 Hz, 1H), 4.01 (dd, J = 6.9, 11.8 Hz, 1H), 4.33 (t, J = 8.1 Hz, 1H), 4.50 (dd, J = 2.7, 12.4 Hz, 1H), 5.25 (d, J = 10.7 Hz, 1H), 5.37 (d, J = 17.2 Hz, 1H), 5.77−5.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.4, 25.9, 26.9, 26.96, 27.2, 38.7, 58.1, 64.1, 71.6, 78.2, 81.2, 81.7, 108.8, 119.0, 135.7, 178.3; FAB HRMS (NBA) *m/e* 453.2654, $[M + Na]^+$ calcd for $C_{22}H_{42}O_6Si$ 453.2648.

Alcohol 16. A solution of **15** (135 mg, 0.32 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was cooled at −78 °C, and then treated with DIBAL (0.74 mL of a 1 M solution in CH_2Cl_2, 2.3 equiv). After 20 min, the reaction was quenched by adding AcOEt (10 mL) at −78 °C, and the mixture was allowed to reach room temperature and was then treated with saturated aqueous Na^+/K^+-tartrate solution (5 mL). 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 saturated aqueous Na/K-tartrate solution (5 mL) and dried ($MgSO_4$), and the solvents were evaporated. The crude was purified by flash column chromatography (silica gel, 20% AcOEt in hexanes) to yield **16** (110 mg, 90%) as a clear oil: R_f = 0.12 (silica gel, 20% AcOEt in hexanes); $[\alpha]^{25}_D$ = −1 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.09 (s, 3H), 0.89 (s, 9H), 1.39 (s, 3H), 1.41 (s, 3H), 3.18−3.22 (m, 1H), 3.37 (s, 3H), 3.63 (dd, J = 4.8, 11.8 Hz, 1H), 3.72 (dd, J = 3.2, 8.6 Hz, 1H), 3.82 (dd, J = 5.4, 11.8 Hz, 1H), 3.90 (t, J = 3.2 Hz, 1H), 4.36 (t, J = 8.1 Hz, 1H), 5.28 (d, J = 10.7 Hz, 1H), 5.38 (d, J = 17.2 Hz, 1H), 5.76−5.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.3, 18.4, 25.9, 26.9, 27.0, 57.2, 59.9, 70.8, 78.4, 81.2, 83.4, 109.1, 119.6, 135.3; FAB HRMS (NBA) *m/e* 369.2085, $[M + Na]^+$ calcd for $C_{17}H_{34}O_5Si$ 369.2073.

Acid 17. A solution of alcohol **16** (23.5 mg, 0.07 mmol, 1.0 equiv) in a 1:1 CH_3CN/H_2O mixture (0.12 mL) was treated with BAIB (84.0 mg, 0.28 mmol, 4.0 equiv) and TEMPO (3.8 mg, 0.021 mmol, 0.3 equiv) under conditions similar to those described for **11**, to obtain crude acid **17**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.11 (s, 3H), 0.87 (s, 9H), 1.41 (s, 3H), 1.43 (s, 3H), 3.45 (s, 3H), 3.84 (d, J = 2.2 Hz, 1H), 3.90 (dd, J = 4.8, 8.1 Hz, 1H), 4.06 (dd, J = 2.2, 4.8 Hz, 1H), 4.42 (t, J = 8.1 Hz, 1H), 5.30 (d, J = 10.2 Hz, 1H), 5.40 (d, J = 17.2 Hz, 1H), 5.81−5.89 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7, −4.6, 18.2, 25.7, 26.6, 26.9, 58.7, 72.9, 78.3, 81.8, 82.7, 109.5, 119.7, 135.0, 170.1.

Amide 19. The coupling of crude acid **17** (24.6 mg, 0.07 mmol, 1.0 equiv) with L-Lys-caprolactam **18** (17 mg, 0.11 mmol, 1.5 equiv) was carried out under exactly the same conditions as before for **20** to obtain amide **19**, which was subjected to flash column chromatography (silica gel, 50% AcOEt in hexanes) to afford pure **19** (16 mg, 50% over 3 steps) as a white solid: R_f = 0.33 (silica gel, 50% AcOEt in hexanes); $[\alpha]^{25}_D$ = +50.3 (*c* 0.06, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.09 (s, 3H), 0.82 (s, 9H), 1.34 (s, 3H), 1.37 (s, 3H), 1.40−1.67 (m, 2H), 1.75−2.16 (m, 4H), 3.22 (m, 2H), 3.43 (s, 3H), 3.70 (d, J = 1.6 Hz, 1H), 4.29 (t, J = 7.5 Hz, 1H), 4.42 (dd, J = 5.4, 10.2 Hz, 1H), 5.24 (d, J = 10.2 Hz, 1H), 5.34 (d, J = 17.2 Hz, 1H), 5.92−6.00 (m, 1H), 6.00 (bs, 1H), 7.87 (bd, J = 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7, −4.6, 18.2, 25.7, 26.8, 27.0, 27.9, 28.9, 31.4, 42.1, 51.9, 58.8, 74.4, 79.3, 80.8, 83.8, 108.6, 118.6, 136.6, 168.8, 174.8; FAB HRMS (NBA) *m/e* 493.2715, $[M + Na]^+$]calcd for $C_{23}H_{42}N_2O_6Si$ 493.2710.

Hydroxy Amide 20. To a solution of **19** (8 mg, 0.0017 mmol, 1.0 equiv) in THF (1 mL) was added TBAF (0.026 mL of a 1 M solution in THF, 1.5 equiv) at rt. After being stirred for 30 min, the reaction mixture was diluted with Et_2O (5 mL) and washed with saturated aqueous NH_4Cl solution (2 mL). The organic phase was dried ($MgSO_4$), and the solvent evaporated. The crude product **20** (6 mg, clear oil) was used without further purification in the next step: R_f = 0.07 (silica gel, 100% AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 3H), 1.43 (s, 3H), 1.42−1.59 (m, 2H), 1.78−1.88 (m, 2H), 1.97−2.11 (m, 2H), 3.22−3.30 (m, 2H), 3.47 (s, 3H), 3.62 (dd, J = 1.6, 8.1 Hz, 1H), 3.70 (d, J = 8.1 Hz, 1H), 3.86 (dd, J = 1.6, 8.6 Hz,

1H), 4.48 (t, J = 7.5 Hz, 1H), 4.53 (dd, J = 6.4, 11.3 Hz, 1H), 5.23 (d, J = 10.2 Hz, 1H), 5.36 (d, J = 17.2 Hz, 1H), 5.76−5.84 (m, 1H), 6.11 (bt, J = 5.9 Hz, 1H), 7.83 (bd, J = 5.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 171.1, 134.9, 119.5, 109.3, 81.5, 79.1, 78.1, 69.1, 59.6, 51.8, 42.1, 31.3, 28.8, 27.9, 27.2, 26.7.

Methylene Analogue of Bengamide E 21. A solution of alcohol **20** (6 mg, 0.00175 mmol, 1.0 equiv) in AcOH (0.5 mL of a 70% aqueous solution) was heated at 50 °C. When the reaction was complete, the solvent was evaporated, and the crude residue was purified by flash column chromatography (silica gel, 10% MeOH in AcOEt) to yield the methylene analogue of Bengamide E **21** (2.3 mg, 45% over 2 steps) as a white solid: R_f = 0.27 (silica gel, 10% MeOH in AcOEt); $[\alpha]^{25}_D$ = +23.7 (*c* 0.11, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33−1.47 (m, 1H), 1.50−1.62 (m, 1H), 1.73−1.90 (m, 3H), 1.98−2.08 (m, 1H), 2.91−3.17 (bm, 3H), 3.24−3.31 (m, 2H), 3.52 (s, 3H), 3.63 (dd, J = 1.1, 4.8 Hz, 1H), 3.78 (d, J = 6.9 Hz, 1H), 3.83 (dd, J = 1.1, 6.9 Hz, 1H), 4.28 (t, J = 4.8 Hz, 1H), 4.52 (dd, J = 6.4, 10.7 Hz, 1H), 5.23 (d, J = 10.2 Hz, 1H), 5.38 (d, J = 17.2 Hz, 1H), 5.83−5.91 (m, 1H), 6.21 (bs, 1H), 7.96 (bd, J = 5.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.9, 28.7, 30.9, 42.1, 51.9, 60.1, 71.8, 73.1, 74.3, 80.6, 117.5, 136.7, 172.1, 174.7.

Amide 24. Cross Metathesis of 19. Amide **19** (10.3 mg, 0.022 mmol, 1.0 equiv) was dissolved in a 1:2 CH_2Cl_2/3-methyl-1-butene mixture (3 mL), and Hoveyda−Grubbs catalyst **23** (4.1 mg, 0.0066 mmol, 0.3 equiv) was added. The flask was then capped and heated at 40 °C overnight, after which the crude mixture was concentrated and purified by flash column chromatography (silica gel, 40% AcOEt in hexanes) to yield **24** (10 mg, 89%) as a brown foamy solid: R_f = 0.43 (silica gel, 50% AcOEt in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.07 (s, 3H), 0.82 (s, 9H), 0.96 (d, J = 3.2 Hz, 3H), 0.98 (d, J = 3.2 Hz, 3H), 1.34 (s, 3H), 1.35 (s, 3H), 1.35−1.52 (m, 2H), 1.76−1.89 (m, 2H), 1.91−2.03 (m, 1H), 2.05−2.15 (m, 1H), 2.26−2.37 (m, 1H), 3.17−3.27 (m, 2H), 3.40 (s, 3H), 3.72 (d, J = 1.6 Hz, 1H), 4.00 (t, J = 6.9 Hz, 1H), 4.04 (dd, J = 1.6, 6.9 Hz, 1H), 4.24 (t, J = 8.1 Hz, 1H), 4.43 (dd, J = 5.4, 10.7 Hz, 1H), 5.50 (dd, J = 8.1, 15.0 Hz, 1H), 5.71 (dd, J = 6.5, 15.0 Hz, 1H), 5.94 (bs, 1H), 7.83 (bd, J = 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.7, 21.9, 22.0, 25.6, 25.65, 26.8, 26.9, 27.7, 28.8, 28.9, 30.2, 30.8, 31.3, 42.0, 51.8, 58.5, 68.0, 79.4, 80.7, 83.1, 108.0, 125.2, 143.3, 168.6, 174.8; FAB HRMS (NBA) *m/e* 535.3186, $[M + Na]^+$ calcd for $C_{26}H_{48}N_2O_6Si$ 535.3179.

Bengamide E (5). Alkene **24** (10 mg, 0.002 mmol, 1.0 equiv) was dissolved in THF (1 mL), and treated with TBAF (0.03 mL of a 1 M solution in THF, 1.5 equiv) at 25 °C for 30 min. After this time, the reaction mixture was diluted with Et_2O (5 mL), and washed with saturated aqueous NH_4Cl solution (2 mL). The organic phase was separated and dried ($MgSO_4$), and the solvent was evaporated. The crude product corresponding to the alcohol (7 mg) was used without further purification in the next step: R_f = 0.09 (silica gel, 100% AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, J = 3.2 Hz, 3H), 0.97 (d, J = 3.2 Hz, 3H), 1.41 (s, 6H), 1.44 (m, 1H), 1.72−1.89 (m, 3H), 1.97−2.12 (m, 2H), 2.23−2.32 (m, 1H), 3.21−3.31 (m, 2H), 3.47 (s, 3H), 3.57 (dd, J = 1.6, 8.6 Hz, 1H), 3.69 (d, J = 8.6 Hz, 1H), 3.82 (dd, J = 1.6, 8.6 Hz, 1H), 4.45 (t, J = 8.6 Hz, 1H), 4.53 (dd, J = 5.4, 11.3 Hz, 1H), 5.34 (ddd, J = 1.6, 8.1, 15.6 Hz, 1H), 5.79 (dd, J = 6.5, 15.6 Hz, 1H), 6.05 (bs, 1H), 7.84 (bd, J = 6.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.7, 27.3, 27.9, 28.9, 29.7, 30.8, 31.3, 42.1, 51.8, 52.1, 59.6, 68.9, 78.0, 79.1, 81.4, 108.5, 123.2, 144.5, 171.3, 174.9.

The resulting alcohol (7 mg, 0.00175 mmol, 1.0 equiv) was treated with AcOH (0.5 mL of a 70% aqueous solution) at 50 °C for 30 min. After this time, the solvent was removed by evaporation under high vacuum, and the crude product was purified by flash column chromatography (silica gel, 10% MeOH in AcOEt) to yield Bengamide E (**5**) (4.3 mg, 62% over 2 steps) as a white solid whose physical and spectroscopic properties were identical to those reported in the literature:[1] R_f = 0.28 (silica gel, 10% MeOH in AcOEt); $[\alpha]^{25}_D$ = +35 (*c* 0.22, $CHCl_3$) ($[\alpha]^{lit.}$ = +32 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (d, J = 2.2 Hz, 3H, $(CH_3)_2CH$), 0.98 (d, J = 2.2 Hz, 3H, $(CH_3)_2CH$), 1.33−1.47 (m, 2H, $-CH_2$-), 1.50−1.62 (m, 1H, $-CH_2$-), 1.71−1.90 (m, 3H, $-CH_2$-), 2.24−2.34 (m, 1H, $CH(CH_3)_2$), 3.21−3.32 (m, 2H, $-CH_2-NH$), 3.52 (s, 3H, OMe), 3.59 (m, 1H, C*H*-OH), 3.76 (d, J = 7.5 Hz, 1H, C*H*-OMe), 3.81 (bd, J = 7.5 Hz, 1H, C*H*-OH), 4.21 (bt, J = 5.9 Hz, 1H, C*H*-OH), 4.52 (dd, J = 6.5, 10.2 Hz, 1H, C*H*-CON), 5.43 (dd, J = 6.91, 15.6 Hz, 1H, =C*H*-), 5.76 (dd, J = 6.5, 15.6 Hz, 1H, $-CH$=), 6.12 (bs, 1H, N*H*), 7.97 (bd, J = 6.5 Hz, 1H, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1, 22.2, 27.9, 28.8, 30.8, 31.0, 42.1, 51.9, 59.9, 72.3, 72.8, 74.3, 80.8, 125.3, 141.9, 172.4, 174.7; FAB HRMS (NBA) *m/e* 381.2008, $[M + Na]^+$ calcd for $C_{17}H_{30}N_2O_6$ 381.2002.

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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.

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