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A diversity-oriented synthetic approach to bengamides

Francisco Sarabia* and Antonio Sánchez-Ruiz

Departamento de Bioquímica, Biología Molecular y Química Orgánica, Facultad de Ciencias, Universidad de Málaga, 29071 Málaga, Spain

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Abstract—A new approach to the bengamides, a new class of antitumor natural products of marine origin, is reported from epoxyamides, prepared by reaction of aldehydes with sulfur ylides. The synthetic strategy has been designed for the delivery of a wide array of analogues. Thus, the terminal alkyl substituent is introduced by a cross olefin metathesis from the corresponding terminal olefin. The combination of cross olefin metathesis, introduction of different nucleophiles by the oxirane ring opening and the introduction of different amines via amide bond formation, can produce a wide array of bengamides analogues. © 2004 Elsevier Ltd. All rights reserved.

The bengamides (1-6) (Fig. 1) comprise a family of natural products isolated from marine sponges of the Jaspidae family (order Choristida = Astrophorida)¹ that display a wide and interesting range of biological activities, including antitumor, antibiotic, and antihelmintic properties.² Particularly striking and attractive are their antitumor properties,³ which have stimulated intense re-search activity, covering synthetic⁴ and biological aspects.^{2,3} Recent proteomic investigations have cast some light on the mode of action of the bengamides,⁵ revealing that they may be involved in the inhibition of methionine aminopeptidases (types 1 and 2, MetAp1 and MetAp2).⁶ These enzymes are proposed to play important roles in endothelial cell proliferation and other sensitive cell types prior to cdk activation, thereby mediating the cell cycle progression of such cells, and may serve as a target for the identification of novel inhibitors of angiogenesis. In contrast to the other known MetAp2 inhibitors such as fumagillin or ovalicin,⁷ in which the mode of inhibition is due to a covalent bond formed from the amine group of a histidine aminoacid residue, located at the active site, with the oxirane ring of these compounds; the bengamides exert their inhibition as a result of multiple highly specific interactions. In particular, these molecules are embedded at the active site of the enzyme due to a hydrophobic

interaction between the terminal alkyl group of the olefin in the P1 pocket, a polar interaction of the caprolactam moiety in the solvent exposed P2 region and coordination of the cobalt ion via the hydroxyls at C-3, C-4, and C-5. These biological observations have been performed with a more soluble analogue of the natural bengamides, the compound LAF-389 (7),⁸ which possesses improved bioavaliability over the natural products. Nevertheless, all these valuable biological disclosures do not permit the establishment of a direct effect of the inhibition of MetAp on the protein regulation, and, consequently, with the antiproliferative properties of the bengamides. All these outstanding biological properties, in conjuction with the attractive molecular structures of the bengamides, encouraged us to design a synthesis that would allow access to a wide family of analogues, including the natural congeners. To this aim, and after careful chemical inspection of their molecular structures, we devised a synthetic strategy involving three key steps into a synthetic scheme capable of reaching either the natural bengamides or analogues by modification of the building blocks employed in each one of these key steps. In particular, these three steps are: (a) a cross olefin metathesis for the stereoselective introduction of the terminal alkyl group; (b) an epoxide ring opening reaction, that would allow the introduction of various nucleophiles; and, (c) an amide bond formation by displacement of a suitable leaving group by different nitrogen nucleophiles, including the lactams found in the natural compounds. The introduction of structural modifications along the proposed synthesis would provide a diverse set of bengamide

Keywords: Bengamides; LAF-389; Methionine aminopeptidase inhibitors; Sulfur ylides; Epoxyamides; Cross metathesis; Stereoselective synthesis.

^{*} Corresponding author. Tel.: +34 952134258; fax: +34 952131941; e-mail: frsarabia@uma.es

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Figure 1. Molecular structures of bengamides and retrosynthetic analysis.

analogues, modified in key regions where interaction with the enzyme seems to be essential. According to this synthetic strategy, the epoxyamide **8**, which can be prepared via reaction of aldehydes with a sulfur ylide,⁹ would represent the suitable precursor to initiate this research. In fact, analogues containing the oxirane ring functionality promise to be especially interesting as they could interact in a fumagillin mode of action by covalently interacting with the enzyme through an oxirane ring opening reaction.

The synthesis of the synthetic subtarget 8 commenced with the reaction of aldehyde 9^{10} with the in situ generated sulfur ylide from sulfonium salt 10, providing a diastereomic mixture of epoxyamides 8 and 11 in a 59% combined yield (4:1 proportion in favor of the undesired epoxyamide 11). After separation by flash column chromatography, the minor isomer, compound 8, was transformed into the more reactive indole derivative 12, which is potentially susceptible to direct displacement¹¹ by the aminolactam 13.¹² However, after obtaining 12 in a very good yield (83%), the reaction with the aminolactam 13 failed to provide the desired result, under a wide variety of reaction conditions. The lack of reactivity of 12 toward 13 prompted us to modify the straightforward preparation of 14, resulting in the introduction

of an additional step of hydrolysis to the acid¹³ and subsequent coupling with 13 mediated by the action of (benzotriazol-1-yloxy) tris-(dimethylamino)phosphonium hexafluorophosphate (BOP) to afford compound 14 in a 65% yield. At this stage, we decided to tackle the cross-olefin metathesis in order to test the synthetic strategy devised for the bengamides. Thus, exposure of a solution of olefinic epoxyamide 14 in DCM and 3methyl-1-butene as cosolvent to the second generation Grubbs catalyst 15^{14} at 40 °C for 38 h, yielded the alk-ene 16 in a 76% yield (9:1 mixture of *E:Z* isomers). In a similar way, the reaction of 14 with 3,3-dimethyl-1-butene provided the corresponding tert-butyl substituted alkene 17 in similar diastereomeric proportion but in much lower yield (28%, 9:1 E:Z mixture). The hydrolysis of 16 by the action of Amberlyst-15 afforded the dihydroxy epoxy-bengamide analogue 18 in a quantitative yield (Scheme 1).



Scheme 1. Synthesis of the bengamide precursors 16 and 17 and bengamide analogue 18. Reagents and conditions: (a) 1.5 equiv 10, 1.5 equiv NaOH, CH₂Cl₂/H₂O, 0 °C, 12 h, 59% (4:1 mixture of 11:8). (b) 4.0 equiv DDQ, C₆H₆, reflux, 8 h, 83%. (c) 2.0 equiv LiOH (0.1 M), THF/H₂O, 0 °C, 0.5 h, 67%. (d) 1.5 equiv 13, 1.2 equiv BOP, 2.2 equiv DIEA, DMF, 25 °C, 8 h, 65%. (e) 0.1 equiv 15, CH₂Cl₂/Alkene (4/1), 40 °C, 38 h, 76% for 16 ($E/Z \approx 9/1$); 28% for 17 ($E/Z \approx 9/1$). (f) Amberlyst-15, MeOH, 8 h, 25 °C, 99%.

Since the reaction of aldehyde 9 with the sulfur ylide did not supply sufficient amounts of the correct epoxide, we decided to stereoselectively prepare the epoxide via Sharpless asymmetric epoxidation. Accordingly, the α,β -unsaturated ester 19, prepared in a 80% yield from aldehyde 9 by reaction with the corresponding phosphorous ylide, was transformed into the allylic alcohol 20 by treatment with DIBAL-H, and subjected to the Sharpless asymmetric epoxidation, using (-)-DET, to provide epoxyalcohol 21 in 87% yield and excellent diastereoselectivity. The oxidation to the epoxyacid 23 was undertaken in two steps, through aldehyde 22, obtained via Swern oxidation of alcohol 21, followed by treatment with Oxone[®].¹⁵ The preparation of epoxyamide **16** was then carried out as described before in Scheme 1. With the construction of the main backbone of the bengamides complete, the oxirane ring contained in these products represented a suitable functionalization point amenable to the final introduction of the requisite methoxyl group. Thus, we attempted this final key step by exploring an extensive set of reaction conditions that included either basic or acidic conditions, resulting in no formation of the coveted product 24. Despite being an important synthetic hurdle for the total synthesis of the bengamides, this epoxide offers the opportunity of preparing a series of 2-C-modified analogues of the bengamides via oxirane ring opening with various nucleophiles.¹⁶ In fact, the 2-amino derivatives 25-27 were efficiently prepared, providing interesting biological probes for the aminopeptidase enzymes with a potentially strong coordination with the cobalt ions present at the active site. With the objective of broadening the structural diversity of the bengamide analogues, we undertook the opening reaction with other nucleophiles including alkyl organometallics and sulfur nucleophiles.¹⁷ However, in both cases, the elimination products, for example, 28 were obtained as the main products. On the other hand, proceeding in the manner described above for 16, the 2,3-epimeric compound 29 was easily prepared from epoxyamide 11 and reacted with nitrogen nucleophiles to obtain the 2-amino derivatives **30–32** in excellent yields (Scheme 2).

Owing to the problems that arose in the oxirane ring opening with alcohols, we opted to work with the more robust O-benzyl protected aldehyde 33¹⁸ in order to expand the reaction conditions for the epoxide opening process. Then, 33 was reacted with the sulfur ylide under similar conditions as for 9, to obtain a 1:1 mixture of epoxyamides 34 and 35. This lower stereoselectivity compared with aldehyde 9 was considered satisfactory since it was secured adequate supplies of both diastereoisomers. After separation of both isomers by flash column chromatography, the desired isomer 35 was subjected to a wide variety of catalysts (TiCl₄, Ti(Oi-Pr)₄, ZrCl₄, Zn(OTf)₂, Sc(OTf)₃, Yb(OTf)₃, Cu(BF₄)₂, BF₃, CSA, H₂SO₄, etc.)¹⁹ and reaction conditions (solvents and temperatures) with the objective of introducing the alkoxyl group. Unfortunately, this extensive exploration was not successful in providing the compound 36, recovering starting material or obtaining the chlorhydrine 37 when ZrCl₄ was employed as catalyst, probably through the intermediate A^{20} The cross-olefin

32: X = N(CH₃)₂ **32**: X = N(CH₃)₂ **33**: X = N(CH₃)₂ **35**: X = N(CH₃)₂ **35**: X = N(CH₃)₂ **37**: X = N(CH₃)₃ **37**: X = N(CH₃)₃

metathesis of epoxyamide **35** was similarly disappointing, because of the poor yields obtained for **38** (50%) and **39** (29%), ascribed to steric reasons, which devaluated the synthetic interest of this olefin metathesis approach (see Scheme 3).

In conclusion, a new synthetic approach to the bengamides has been described based on the chemistry of sulfur ylides, according to a synthetic scheme capable of generating a variety of bengamide analogues.²¹ The extension of this synthetic strategy to the natural bengamides will require some modifications in order to introduce the methoxyl group. These synthetic efforts as well as biological evaluations of the described bengamide analogues are currently in progress and will be presented in the due course.





Scheme 3. Synthesis of bengamides from O-benzyl aldehyde (33). Reagents and conditions: (a) 1.5 equiv 10, 1.5 equiv NaOH, CH_2Cl_2/H_2O , 0 °C, 12 h, 62% (1:1 mixture of 34:35). (b) See text for more experimental details. (c) 1.2 equiv ZrCl₄, $CH_2Cl_2/MeOH$, 25 °C, 6 h, 85%. (d) 0.1 equiv 15, $CH_2Cl_2/Alkene$ (4/1), 40 °C, 38 h, 50% for 38 (*E*/*Z* ≈ 9/1); 29% for 39 (*E*/*Z* ≈ 9/1).

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