A Concise Synthesis of Bengamide E and Analogues via *E*-Selective Cross-Metathesis Olefination

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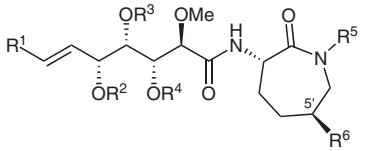
Abstract: A modular, eight-step synthesis of bengamide E and six analogues from a common chiral pool has been developed. The key step in this approach is a cross-metathesis coupling of various commercial terminal olefins and a common alkene bearing the required stereogenic centers of bengamides lateral chain, which was easily derived from α-D-glucoheptonic-γ-lactone. Complete *E*-selectivity, and up to 92% yield were achieved for this crucial cross-metathesis step.

Key words: bengamide, analogues, cross-metathesis, stereoselective olefination, isomerization

Bengamides are sponge-derived natural products of mixed biosynthesis (polyketides and amino acids); the first two members, isolated from Jaspidae sponges in coral surrounding Fiji islands, were reported in 1986 by Crews et al.[1] To this date, 19 members of these natural products have been identified; they share a common *syn*,*syn*,*anti*-polyol-containing C10 side chain. The main structural variation is located on the 3-aminocaprolactam moiety (Figure 1). Beyond the synthetic challenge, some of the known bengamides have a great intrinsic value as they are endowed with nanomolar level of antiproliferative activity against various cancer cell lines, with striking differential cytotoxicity.[2] These interesting biological features, together with their limited supply from natural sources, have made these sponge secondary metabolites popular targets for synthetic chemists.[3]

The significant in vitro and in vivo antitumoral activities observed for bengamides A and B led Kinder et al. to the design and synthesis of a bengamide B analogue LAF389 (Figure 1), which exhibited promising antitumoral activity during preclinical trials.[4]

Recently, Towbin et al.[5] have shown that bengamides target both isoforms of human methionine aminopeptidases (MetAP), resulting in the inhibition of the N-terminal methionine excision, an essential co- or post-translational modification of most nascent proteins in all living organisms.[6] More recently, Hu et al. suggested that inhibition of both MetAP isoforms could indirectly impair the functioning of c-Src and probably that of other oncogenes essential for tumor growth.[7] Therefore, the design and synthesis of new bengamide analogues that can selectively inhibit one of the two human MetAP isoforms is still a challenge.



bengamide A R^1 = *i*-Pr; R^2 = R^3 = R^4 = R^5 = H; R^6 = $OCO(CH_2)_{12}Me$
bengamide B R^1 = *i*-Pr; R^2 = R^3 = R^4 = H; R^5 = Me; R^6 = $OCO(CH_2)_{12}Me$
bengamide E R^1 = *i*-Pr; R^2 = R^3 = R^4 = R^5 = R^6 = H
LAF 389 R^1 = *t*-Bu; R^2 = R^3 = R^4 = R^5 = H; R^6 = OCO-*c*-Hex (5'-*R*)
1 R^1 = R^5 = R^6 = H; R^2, R^3 = CMe_2; R^4 = OTBS (Sarabia's synthon)

Figure 1 Natural bengamides and synthetic analogues

We recently developed a methodology for the synthesis of substituted cyclic L-lysines towards bengamide analogues having structural variations at the caprolactam unit.[8] As all previous strategies,[3] our synthesis relies on the acylation of 3-aminocaprolactam moieties with the C10 polyol side chain. In our initial synthetic plan, we intended to prepare the required acylating polyol moiety according to the most efficient procedure, recently described by Xu et al.[9] for the synthesis of LAF389. The key step of this route relies on a Julia–Kocienski olefination of aldehyde **3** derived in four steps from the commercially available α-D-glucoheptonic-γ-lactone[9] (Scheme 1). In this procedure, the olefination was reported with variable stereoselectivity (3:1 < *E*/*Z* < 10:1) and moderate yields (40–50%), depending on the solvents and additives used. We examined this procedure with 2-(isobutylsulfonyl)benzo[*d*]thiazole (*i*-$BuSO_2$BTS), as well as with 5-(isobutylsulfonyl)-1-phenyl-1*H*-tetrazole (*i*-$BuSO_2$PT). After extensive studies we were able to achieve olefination of **3** with excellent diastereoselectivity (*E*/*Z* up to 20:1) by using a polar solvent system (DMF–HMPA = 4:1); but yields of **5a** were disappointingly poor (20–30%; Scheme 1). Following the same procedure, methylenation compound **4** was obtained with lower yields (6–10%) starting from aldehyde **3** and 5-(methylsulfonyl)-1-phenyl-1*H*-tetrazole.[10] At this point we decided to examine alternative methods for this *E*-olefin installation, both in terms of yield and stereoselectivity. To this end, we directed our attention towards olefin cross metathesis (CM) involving alkene **4** (Scheme 1).

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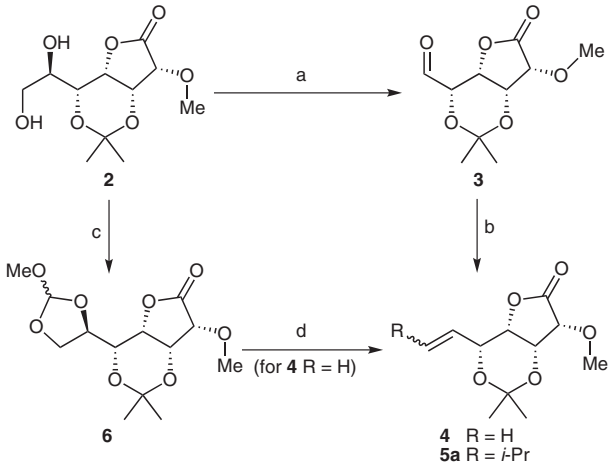


Scheme 1 *Reagents and conditions*: (a) $NaIO_4$, H_2O–MeOH, r.t., 85%; (b) RCH_2SO_2PT, LiHMDS, DMF–HMPA (4:1), –35 °C to 35 °C, 12 h, 6% for **4**, 22% for **5a** (*E*/*Z* = 20:1); (c) $HC(OMe)_3$, PPTS, THF, r.t., 94%; (d) Ac_2O, 150 °C, 93%.

Recently, Sarabia et al.[3e] synthesized bengamide E and two analogues via CM olefination starting from a protected methylene analogue of bengamide E; compound **1** (Figure 1) which was obtained in 17 steps from D-tartrate. The authors reported variable conversions (33–100%) of **1** by using 30 mol% of Hoveyda–Grubbs catalysts; the *E*/*Z* ratios were around 9:1. We hypothesized that this low conversion (observed in the case of styrene and *t*-$BuCH{=}CH_2$) could be due to catalyst inhibition with the substrate amide functionalities. A priori, such inhibition was not expected with olefin **4**, which we were planning to use as a key substrate, and whose synthesis was expected to be significantly shorter than the construction of the key olefin **1** (Figure 1) employed by Sarabia.[3e]

Thus our synthesis commenced from the known vicinal diol **2**, which is routinely obtained in multigram scale from α-D-glucoheptonic-γ-lactone.[4] Diol **2** was converted to the desired key olefin **4**[11] following Eastwood's sequence (Scheme 1).[12] First, **2** was converted to the corresponding 2-methoxy-1,3-dioxolane **6** in 94% yield, as diastereomeric mixture (2:3), by treatment with trimethyl orthoformate in the presence of PPTS;[13] then, pyrolysis of **6** in refluxing acetic anhydride led to the desired olefin **4** in good and reproducible yields (Scheme 1). Once the synthesis of this key synthon was settled up, we selected three of the most common catalysts (Figure 2) in order to examine CM olefination of **4** with various commercially available terminal olefins.

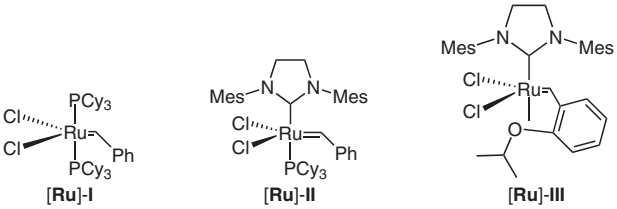
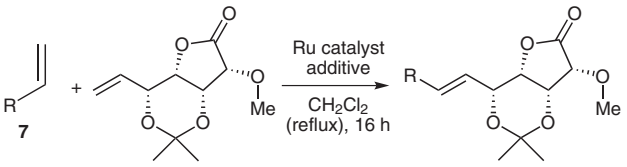


Figure 2 Ru catalysts (Cy = *c*-Hex; Mes = mesityl)

First, we tested the reactivity of **4** in CM reaction towards a model terminal alkene; 3,3-dimethylbut-1-ene **7b** (Table 1), a type III olefin according to Grubbs' olefin categorization.[14] No CM was observed between **4** and **7b** (5 equiv) in presence of first-generation Grubbs catalyst **[Ru]-I** (up to 0.5 equiv), and only moderate conversion was observed when olefin **4** was reacted with *p*-chlorostyrene, **7f** (5 equiv) in the presence of the same catalyst **[Ru]-I**. Using 10 mol% of catalyst **[Ru]-II** (Table 1, entry 1), olefin **7b** and **4** led to the expected cross-metathesis compound **5b**, along with unreacted substrate **4** and its isomerization compound **4′** (Figure 3).

Table 1 Cross-Metathesis of **4** and Olefins **7**



a R = *i*-Pr; **b** R = *t*-Bu; **c** R = *c*-Hex; **d** R = *i*-Bu; **e** R = Ph; **f** R = *p*-ClC_6H_4; **g** R = *p*-FC_6H_4; **h** R = Me_3SiCH_2

Entry	7	Ru cat. (equiv)	Additive (equiv)	Yield of **5** (%)
1	**7b**	**II** (0.1)	none	**5b** (70)[a,b]
2	**7b**	**II** (0.1)	TFQ (0.2)	**5b** (70)[a,c]
3	**7b**	**II** (0.1)	DCQ (0.2)	**5b** (70)[a]
4	**7b**	**II** (0.15)	DCQ (0.3)	**5b** (71)
5	**7b**	**III** (0.15)	none	**5b** (100)[a,d]
6	**7b**	**III** (0.15)	DCQ (0.3)	**5b** (80)
7	**7a**	**III** (0.15)	DCQ (0.3)	**5a** (66)[e]
8	**7c**	**III** (0.15)	DCQ (0.3)	**5c** (86)
9	**7d**	**III** (0.15)	DCQ (0.3)	**5d** (78)
10	**7e**	**III** (0.15)	DCQ (0.3)	**5e** (87)
11	**7f**	**III** (0.15)	DCQ (0.3)	**5f** (92)
12	**7g**	**III** (0.15)	DCQ (0.3)	**5g** (91)
13	**7h**	**III** (0.15)	DCQ (0.3)	**5h** (72)

[a] Conversion.
[b] **5b**:**4′** = 1:0.6 as determined by ^1H NMR.
[c] **5b**:**4′** = 1:0.2.
[d] **5b**:**4′** = 1:0.3.
[e] Performed with large excess of volatile olefin **7a**, in a tight Teflon-capped tube; 85% conversion after 48 h.

Similar results were obtained with other olefins **7a**–**g**, although with less isomerization (1:0.1 < **5**:**4′** < 1:0.3) in the case of styrenes **7e**–**g** (results not shown). These preliminary results were promising in terms of diastereoselectivity since only *E*-isomer was detected in all cases; however, the substrate isomerization rendered the compounds purification very tedious.[15] Alkene isomerization

of both substrates and adducts is a well-known and important side reaction in ruthenium-catalyzed metathesis reactions. It was first reported with the primary metathesis products in presence of catalyst **[Ru]-I**.[16] Fürstner and coworkers reported the first example where the isomerization occurred with the ring-closing metathesis (RCM) substrate prior to its cyclization.[17] It has since been also observed, with both generations of catalysts, on a broad variety of alkenes,[18] particularly those including substrates containing allylic functionalities.[19] Recent mechanistic studies suggest the involvement of ruthenium mono- or dihydride intermediates.[20] Formation of compound **4′**, which was not observed with catalyst **[Ru]-I**, is expected to be thermodynamically irreversible, since **4′** is a conjugated olefin. Recently, Grubbs and coworkers disclosed the advantageous effect of electron-deficient 1,4-benzoquinone additives: since it avoids the generation of ruthenium hydride species, it prevents olefin isomerization.[21] Accordingly, we examined the effect of tetrafluoro-1,4-benzoquinone (TFQ) and 2,6-dichloro-1,4-benzoquinone (DCQ) on the irreversible formation of **4′** (Figure 3).

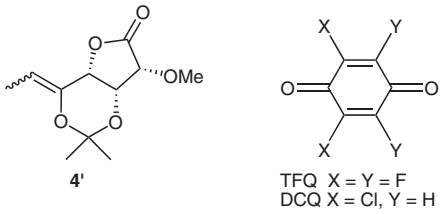


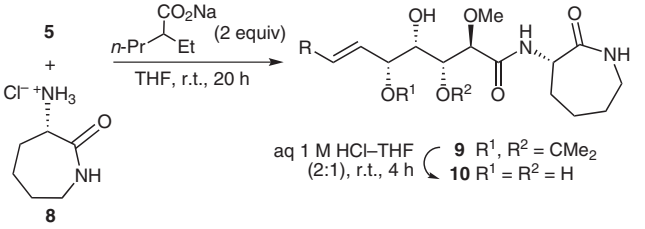
Figure 3 Structure of isomer **4′** and benzoquinones TFQ and DCQ

In order to determine the optimal 1,4-benzoquinone for prevention of olefin **4** isomerization, the latter was first reacted with **7b** in presence of 0.1 equivalents of catalyst **[Ru]-II** and 0.2 equivalents of TFQ in refluxing CH_2Cl_2. Although limited isomerization was observed, this benzoquinone could not totally preclude substrate isomerization (Table 1, entry 2). Using DCQ (0.2 equiv) instead of TFQ completely suppressed the unwanted olefin isomerization reaction; only substrate **4** and its olefin cross-metathesis product **5b** were observed in the crude mixture; no trace of its isomerization compound **4′** was detected after 16 hours (Table 1, entry 3). However, in both cases, the conversion was limited to 70% of substrate **4**. Upon increasing the catalyst loading to 15 mol% – and hence dichloroquinone to 30 mol% – we observed complete conversion providing **5b** in 71% isolated yield (Table 1, entry 4) as a single detectable diastereomer based upon 500 MHz NMR analysis. The optimized procedure thus determined was then applied to CM of substrate **4** with other aliphatic olefins **7a**,**c**,**d** and styrenes **7e**–**g**, as well as allyltrimethylsilane **7h**. Conversion of olefin **4** was generally completed within 16 hours, except with **7a** (R = *i*-Pr), which gave limited conversion; the pure CM compounds **5a**–**h** were isolated in satisfactory to good yields (62–82%, results not shown); moreover, we were pleased to obtain exclusively the *E*-isomer in each case.

Less isomerization was observed when Hoveyda–Grubbs catalyst **[Ru]-III** (15 mol%) was used alone instead of **[Ru]-II** (Table 1, entry 5). In the presence of DCQ (30 mol%), **[Ru]-III** (15 mol%) provided good to excellent yields for CM of **4** with olefins **7a**–**h** (Table 1, entries 6–13); in all examples, only the *trans*-isomer was observed by NMR, and no isomerization compound **4′** was detected.[22] With the polyol side-chain precursors **5** in hand, we proceeded to their coupling with (3*S*)-3-aminocaprolactam **8**,[23] and subsequent cleavage of acetonide, towards the natural bengamide E and analogues (Table 2).

The coupling step was first carried out with **5b** by aminolysis under nearly neutral pH conditions, as described by Liu et al.[24] Lactone **5b** and (*3S*)-3-aminocaprolactam hydrochloride **8** (1.5 equiv) were stirred in the presence of sodium 2-ethylhexanoate (NaEH; 2 equiv) in THF at room temperature for 20 hours to afford amide **9b** as a single diastereomer (75%). Coupling of **8** with other lactones **5**, under the same mild conditions, proceeded smoothly to afford the corresponding amides **9** with good yields (Table 2). Subsequent treatment of acetonides **9a**–**g** with aqueous HCl (1 M) and THF (2:1) mixture, at room temperature, led to the corresponding bengamide analogues **10a**–**g** in satisfactory to good yields (Table 2).

Table 2 Synthesis of Bengamide E and Analogues **10**

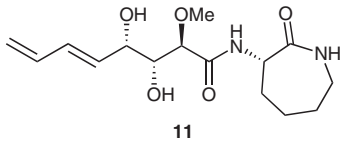


Entry	**5** (R)	Yield of **9** (%)	Yield of **10** (%)
1	**5a** (*i*-Pr)	**9a** 75	**10a** 64
2	**5b** (*t*-Bu)	**9b** 75	**10b** 65
3	**5c** (*c*-Hex)	**9c** 85	**10c** 62
4	**5d** (*i*-Bu)	**9d** 84	**10d** 58
5	**5e** (Ph)	**9e** 89	**10e** 66
6	**5f** (4-ClC_6H_4)	**9f** 79	**10f** 72
7	**5g** (4-FC_6H_4)	**9g** 90	**10g** 70
8	**5h** (Me_3SiCH_2)	**9h** 75	–[a]

[a] Diene **11** (Figure 4) was obtained in 80% yield.

In the case of **9h**, the same acidic conditions led to the conjugated diene **11** (Figure 4) via the acetonide removal and subsequent acid-catalyzed vinylogous Peterson elimination.

In conclusion, we have achieved the synthesis of bengamide E, a natural marine compound, and six analogues, three of them structurally novel (**10d**,**f**,**g**). The synthetic pathway reported here offers an easy access to the polyol



11

Figure 4 Diene **11** obtained from silylated compound **9h**

side chain with different *E*-olefinic moieties, thus introducing structural modification at a position involved in a key noncovalent interaction of bengamides with the active site of MetAP enzymes.[5] We successfully developed synthon **4** as good alternative starting material for olefination; major improvement was made on this step by using cross-metathesis conditions in the presence of 15 mol% of CM catalysts **[Ru]-II** or **[Ru]-III** and 2,6-dichloro-1,4-benzoquinone (0.3 equiv). This procedure offers the key olefins **5** in good to excellent yields for both alkyl- and aryl-substituted alkenes, with complete *E*-selectivity. Unlike aldehyde **3** or Sarabia's synthon **1**, alkene **4** is easy to store and handle and is easily prepared in an efficient five-step sequence from a reasonably priced chiral pool; α-D-glucoheptonic-γ-lactone. The benefits of the present synthesis are threefold: (1) tedious purifications of olefins **5** are avoided due to complete *E*-selectivity in cross-metathesis olefination, (2) good to excellent yields of cross-metathesis olefination improve the overall yield, (3) this modular route is amenable to the preparation of a variety of analogues that could be helpful for bengamides SAR studies.

Supporting Information for this article (preparation of **4** and a typical procedure for its transformation into a bengamide analogue) is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(10) Aldehyde **3** is highly hygroscopic and sensitive to both acid and base; it should be freshly prepared and dehydrated by azeotropic evaporations with *i*-PrOAc prior to its use.

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