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Total synthesis of bengamide E

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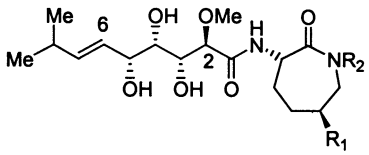
Abstract—A total synthesis of bengamide E is reported. The synthesis includes the utilization of D-tartrate as the chiral building block, construction of the *E*-olefin by the Julia protocol, an *anti*-aldol reaction to generate C-2 and C-3 stereocenters, and coupling of the thioester with caprolactam hydrochloride using sodium 2-ethylhexanoate.

Bengamides (**1a**–**1f**) are a family of compounds isolated from a Choristida sponge from the Fiji Islands.[1] Their structures differ only in the lactam moiety, while a polyhydroxylated C_{10} side chain is the common feature (Fig. 1). They have shown significant cytotoxicity, anthelminthic and antitumor activities.[1,2] Since the discovery of the bengamides, tremendous efforts from different laboratories have resulted in several total syntheses of these biologically important molecules.[3] Recently a chemoenzymatic total synthesis of *ent*-bengamide E has been reported.[4] Herein we report a short total synthesis of bengamide E utilizing inexpensive D-tartrate as the building block to construct the polyhydroxylated C_{10} side chain, followed by coupling with caprolactam hydrochloride in the presence of sodium 2-ethylhexanoate.

The synthesis started with diisopropyl D-tartrate, which resembles the C-4 and C-5 stereocenters in the side chain (Scheme 1).[5] Thus, D-tartrate **2** was dibenzylated using sodium hydride and benzyl bromide in the presence of a catalytic amount of tetrabutylammonium iodide in 60% yield. Treatment of diester **3** with lithium aluminum hydride gave rise to diol **4** in 86% yield after



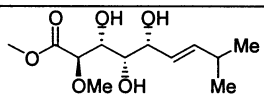
Bengamide	R_1	R_2
A (**1a**)	$OCO(CH_2)_{12}CH_3$	H
B (**1b**)		Me
C (**1c**)		H
D (**1d**)		Me
E (**1e**)	H	H
F (**1f**)	H	Me

Figure 1.

Keywords: bengamide E; Julia olefination; *anti*-aldol; sodium 2-ethylhexanoate.

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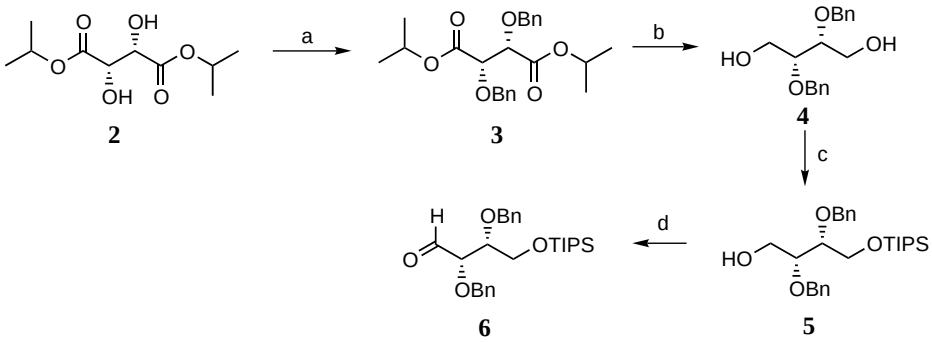
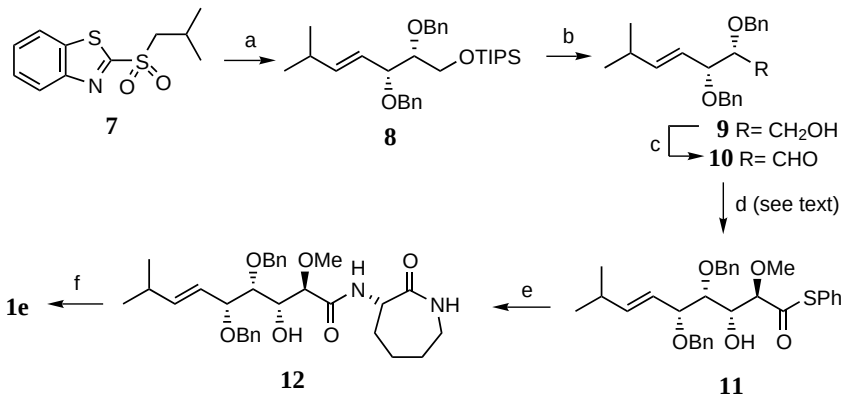


Scheme 1. (a) NaH, BnBr, nBu$_4$NI (cat.), THF, rt, 60%; (b) LAH, THF, rt, 86%; (c) NaH, TIPSCl, nBu$_4$NI (cat.), THF, 92%; (d) ClCOCOCl, DMSO, CH_2Cl_2, −78°C, then Et_3N→rt.

chromatography. The diol **4** was monosilylated to **5** using 1.1 equiv. of sodium hydride and 1.1 equiv. of triisopropylsilyl chloride in the presence of a catalytic amount of tetrabutylammonium iodide (92%). Swern oxidation of alcohol **5** generated aldehyde **6**, which was subsequently subjected to the Julia olefination without further purification.

2-Benzothiazolyl-sulfone **7**[6] was treated with lithium bis(trimethylsilyl)amide in THF at −78°C, and to this lithiated sulfone was added freshly prepared aldehyde **6** (Scheme 2). The reaction mixture was stirred at −78°C for another hour, then gradually warmed up to room temperature. After the reaction was completed, aqueous workup was conducted. ^{1}H NMR of the mixture revealed that the stereoselectivity of the olefination reaction predominantly favored the *E*-olefin (*E*:*Z*= >20:1) as described in the literature.[7] Purification of the mixture over silica gel gave **8** in 92% yield from **5**. Removal of the silyl group in **8** was accomplished using tetrabutylammonium fluoride in THF at 0°C in 83% yield after chromatography. Alcohol **9** was easily converted to its corresponding aldehyde **10** that was used for the subsequent aldol reaction without further purification.

With aldehyde **10** in hand, we were set to explore the crucial aldol reaction with *S*-phenyl methoxythioacetate to construct the C-2 and C-3 *anti*-stereocenters in the side chain. However, extensive efforts using various reaction conditions (nBu$_2$BOTf/iPr$_2$NEt, $SnCl_4$, etc.) were futile. None of those conditions produced significant amount of the desired *anti*-aldol product (2*R*,3*R*). Later, the conditions reported by Annunziata et al.[8] were studied. When the standard conditions ($TiCl_4$, Et_3N) were applied, a pair of *anti*-aldol products was obtained. The desired adduct was the minor isomer (~1:4). However, equal amounts of the two isomers were generated when some modifications were made to the reported reaction conditions. Thus, *S*-phenyl thioacetate (2 equiv.) was treated with titanium tetrachloride (2 equiv.) and *N*,*N*-dimethylethylamine (2 equiv.) in dichloromethane at −78°C, and the resulting dark-red enolate solution was added to the aldehyde premixed with lithium iodide (4 equiv.) at −78°C. After 1 h, most of the aldehyde **10** was consumed and reaction was quenched. ^{1}H NMR of the crude mixture showed the presence of the two *anti*-aldol products. No *syn*-aldol product was observed by ^{1}H NMR. The ratio of the two isomers was 1:1. All of our attempts to



Scheme 2. (a) LHMDS, THF, **6**, −78°C to rt, 92% from **5**; (b) TBAF, THF, 0°C, 83%; (c) ClCOCOCl, DMSO, CH_2Cl_2, −78°C, then Et_3N→rt; (d) *S*-phenyl methoxythioacetate, $TiCl_4$, $EtNMe_2$, LiI, CH_2Cl_2, −78°C, 71% from **9**; (e) L-(−)-α-amino-ε-caprolactam hydrochloride, sodium 2-ethylhexanoate, THF, 87%; (f) Na/NH_3, $(CH_3OCH_2CH_2)_2NH$, THF, −78°C, 87%.

improve upon this selectivity were unsuccessful. Those efforts included the utilization of other Lewis acids ($MgBr_2$, LiCl, Et_2BOMe, $Ti(OiPr)_4$, $SnCl_4$) to complex with the aldehyde **10** in order to distinguish the two benzyl ether groups, and different ratios of $TiCl_4$ and the base. The two isomers can be separated carefully by silica gel chromatography and were obtained in 71% combined yield from alcohol **9**. It nevertheless set the stage for coupling of **11** with the caprolactam moiety to construct the bengamide E molecule.

Treatment of **11** with L-(−)-α-amino-ε-caprolactam hydrochloride in the presence of sodium 2-ethylhexanoate (2 equiv.) in THF produced amide **12** smoothly in 87% yield after chromatographic purification.[9] It is noteworthy that the hydrochloride salt of the caprolactam was used, and that the reaction was carried out at room temperature. These conditions are close to neutral and compatible with a variety of acid/base sensitive substrates,[10] therefore it provides a very mild alternative for preparing amides from thioesters. The mechanism of this coupling reaction of a thioester and a lactam is not clear, but presumably involves the concerted actions of sodium 2-ethylhexanoate and its conjugated acid.[11] Reductive removal (Na/NH_3) of benzyl groups in **12** in the presence of bis(2-methoxyethyl)-amine[12] afforded bengamide E, $[\alpha]_D^{24}$ +33.6 (*c* 1.0, MeOH), lit.[1b] $[\alpha]_D^{20}$ +36.9 (*c* 0.043, MeOH), in 87% yield after purification over silica gel (EtOH/EtOAc). The ^1H and ^{13}C NMR spectra were in excellent accordance with those reported for natural bengamide E.[1b]

In summary, we have achieved a total synthesis of bengamide E. The side chain was constructed from D-tartrate as the chiral building block, with *E*-olefination by the Julia protocol and an *anti*-aldol reaction. Coupling of the side chain with the caprolactam moiety was accomplished using sodium 2-ethylhexanoate.

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9. **12**: $[\alpha]_D^{24}$ −8.3 (*c* 1.0, MeOH); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.84 (d, 1H, $J=6.2$ Hz), 7.18–7.43 (m, 10H), 6.63 (m, 1H), 5.76 (dd, 1H, $J=15.6$, 6.4 Hz), 5.37 (dd, 1H, $J=15.5$, 8.4 Hz), 4.95 (d, 1H, $J=10.9$ Hz), 4.62 (dd, 2H, $J=11.3$, 6.6 Hz), 4.47 (m, 1H), 4.38 (d, 1H, $J=11.9$ Hz), 4.13 (t, 1H, $J=7.8$ Hz), 3.80 (s, 2H), 3.73 (d, 1H, $J=6.8$ Hz), 3.52 (m, 1H), 3.31 (s, 3H), 2.96 (m, 2H), 2.35 (m, 1H), 2.07 (m, 1H), 1.95 (m, 1H), 1.75 (m, 2H), 1.45 (m, 1H), 1.27 (m, 1H), 1.01 (dd, 6H, $J=6.7$, 4.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 171.0, 144.0, 139.1, 139.0, 128.8, 128.7, 128.3, 128.1, 127.8, 123.9, 82.6, 81.6, 80.7, 75.5, 72.2, 70.5, 58.7, 52.4, 42.1, 31.5, 31.3, 29.0, 28.3, 22.7.; MS m/z 561 $(M+Na)^+$, 431; HRMS m/z calcd for $C_{31}H_{43}N_2O_6$ $(M+H)^+$ 539.3121; found 539.3117.
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