Total Synthesis and Absolute Configuration of Bengamide A

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The first total synthesis of the novel marine natural product, bengamide A **1** is described, revealing the absolute configuration of this compound.

The bengamide family, a new category of amino acid derivatives, were first isolated from a choristid sponge by Crews and his coworkers, and reported to show anti-infectious disease activities.[1] Spectral analyses and degradation studies revealed that bengamide A **1**, a representative component in the bengamide family, has a quite unique structure which contains a 3-amino-6-hydroxy-hexahydro-2-azepinone derivative and a polyhydroxylated C_{10} side chain.[1] Although the absolute configuration of the C_{10} side chain,[2] a common unit in the bengamide family, was recently confirmed by the total synthesis of bengamide E,[3,4] a C-6 demyristoyloxy analogue of **1**, the proposed stereochemistry (3*S*, 6*S*)[1b] of the hexahydro-2-azepinone portion in bengamide A has not been elucidated synthetically.[4]† In this communication, we report the first total synthesis of **1**, which determined the absolute structure of the natural product.

We chose L-glutamic acid as the chiral starting material for a synthesis of the hexahydro-2-azepinone moiety. Treatment of the known ester **2**,[5] prepared in four steps from L-glutamic acid, with 2,2-dimethoxypropane and toluene-*p*-sulfonic acid (TsOH) afforded **3** in 93% yield (see Scheme 1). Diisobutylaluminium hydride (DIBAL) reduction of **3** gave **4** (88% yield), which was reacted with $Ph_3P{=}CH_2$ to provide the alkene **5** in 86% yield. Epoxidation of **5** with *m*-chloroperbenzoic acid (mCPBA) in 1,2-dichloroethane-phosphate buffer (pH 8)[6] gave **6** as an inseparable mixture of two diastereoisomers in 99% yield. Azidolysis of **6**, followed by separation of the products with silica gel chromatography afforded **7** and **8** in both 48% isolated yields, respectively. The absolute configurations of compounds **7** (2*S*, 5*S*) and **8** (2*S*, 5*R*) were unambiguously determined by conversion of **7** and **8** into the known lactones[7] (**16** and **17**), respectively.‡

The hydroxy group in **7** was benzylated to give **9** (97%), whose acetonide group was removed under acidic conditions to afford **10**§ in 99% yield. Jones oxidation of **10** gave **11**, which was treated with *N*-hydroxysuccinimide in the

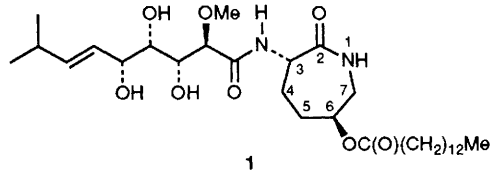

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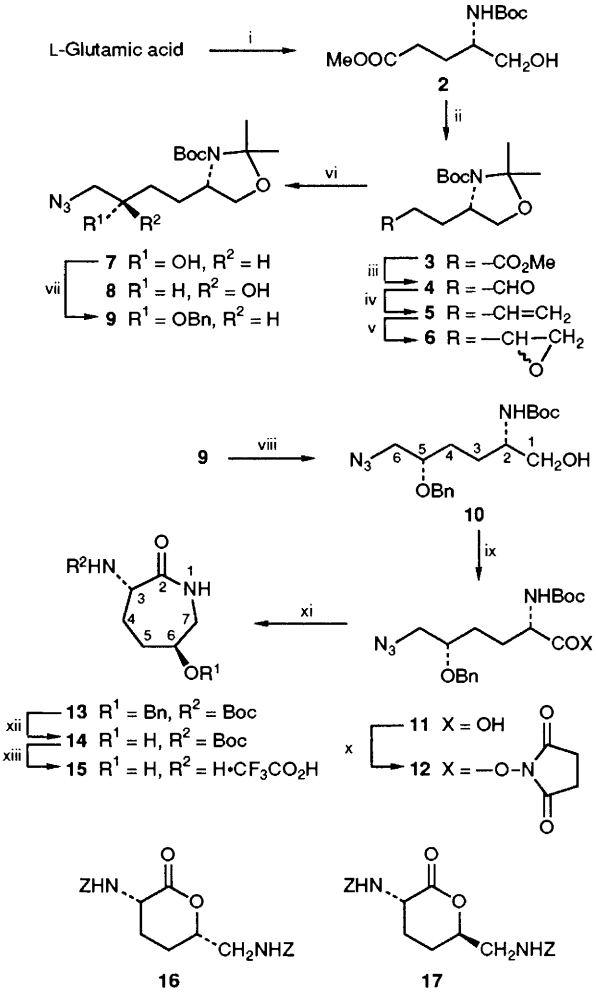
Fig. 1

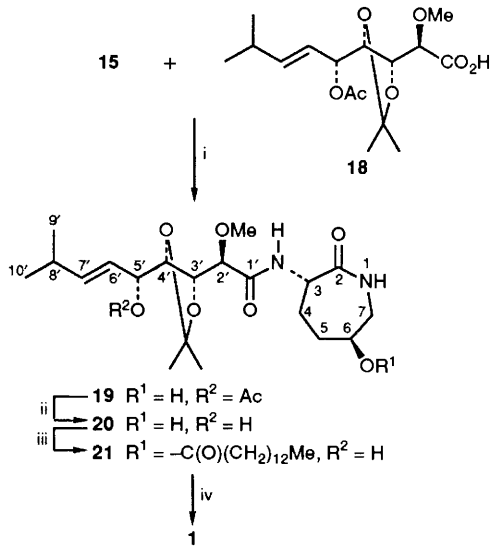
† Quite recently, the total synthesis of bengamide B [*N*(1)-methyl derivative of bengamide A] in an optically active form starting from L-glucose and (*S*)-butanetriol has been accomplished by Broka and Ehrler (see ref. 4).

‡ The carboxylic acid **11**, obtained in three steps from **7** (see text), was transformed into **16** in the following five step reactions (*i*) hydrogenolysis [20% $Pd(OH)_2$, H_2, EtOH–dil.HCl] to reduce azido group as well as remove *O*-benzyl group; (*ii*), protection of the resulting amine with benzyloxycarbonyl chloride [NaOH, H_2O–EtOH–tetrahydrofuran (THF)]; (*iii*), removal of *N*-*tert*-butoxycarbonyl (Boc) group (CF_3CO_2H–CH_2Cl_2); (*iv*), protection of the amino function with benzyloxycarbonyl chloride; (*v*), lactonisation (toluene, reflux). Physical properties of **16** obtained {m.p. 147–148 °C, $[\alpha]_D^{19}$ + 74 (*c* 0.26, $CHCl_3$)} showed a good accordance with those reported in the literature[7] {m.p. 145–146 °C, $[\alpha]_D$ +67 (*c* 1, $CHCl_3$)}. By a similar procedure, compound **8** was converted into another lactone **17** {m.p. 145–148 °C, $[\alpha]_D^{22}$ −8 ±3 (*c* 0.49, $CHCl_3$); lit.[7] m.p. 145–147 °C, $[\alpha]_D$ −18° (*c* 1, $CHCl_3$)}.

§ All new compounds described in this communication were homogeneous on TLC and spectrometric analyses. Selected ^1H NMR ($CDCl_3$, 270 MHz) data for **10**: δ 1.44 (s, 9H, CMe_3), 1.20–1.66 (m, 4 H, 3- and 4-H), 2.12 (br s, OH), 3.28 (dd, 1 H, $J_{5,6}$ 5.6, $J_{6,6'}$ 13.0 Hz, 6-H), 3.38 (dd, 1 H, $J_{5,6'}$ 4.2 Hz, 6-H'), 3.47-3.63 (m, 4 H, 1-H_2, 2- and 5-H), 4.54 and 4.67 (2d, each 1 H, *J* 11.5 Hz, $ArCH_2$), 4.67 (m, 1 H, NH) and 7.28–7.38 (m, 5 H, Ph). For **14**: δ 1.45 (s, 9 H, CMe_3),



Scheme 1 Boc = Bu^{t}OC(O)–, Bn = $PhCH_2$–, Z = $PhCH_2OC(O)$–. *Reagents and conditions*: i, see ref. 5; ii, 2,2-dimethoxypropane, TsOH (5 mol%), PhH, 50 °C; iii, DIBAL (1.7 equiv.), PhMe, −78 °C; iv, Ph_3PCH_3Br, $NaNH_2$, THF, 0 °C; v, mCPBA, $(ClCH_2)_2$–phosphate buffer (pH 8) (1 : 2, v/v), 50 °C; vi, NaN_3, NH_4Cl, 2-methoxyethanol–H_2O (9 : 1, v/v), 50 °C; vii, NaH, BnBr, Bu$^n_4$NI, THF, room temp.; viii, TsOH (5 mol%), MeOH, room temp.; ix, Jones reagent (CrO_3 in dil. H_2SO_4), acetone, 0 °C; x, *N*-hydroxysuccinimide, EDAC, 4-dimethylaminopyridine, DMF, room temp.; xi, H_2 (1 atm), Raney-Ni, THF, room temp.; xii, H_2 (1 atm), $Pd(OH)_2$, EtOH; xiii, CF_3CO_2H–CH_2Cl_2 (1 : 2, v/v), 0 °C.



Scheme 2 *Reagents and conditions*: i, $(EtO)_2P(O)CN$, Et_3N, DMF, room temp.; ii, MeONa–MeOH, room temp.; iii, myristic acid (2.5 equiv.), EDAC (2.5 equiv.), 4-dimethylaminopyridine (1.0 equiv.), CH_2Cl_2, −15 °C–room temp.; iv, CF_3CO_2H–THF–H_2O (3 : 3 : 2, v/v/v), 0 °C–room temp.

1.57–1.93 (m, 2 H, 4- and 5-H), 2.04–2.25 (m, 2 H, 4- and 5-H′), 3.19–3.37 (m, 2 H, 7-H_2), 3.56–3.66 (m, 1 H, 6-H), 4.32 (ddd, 1 H, $J_{3,4}$ 10.8, $J_{3,4'}$ 1.5, $J_{3,NH}$ 5.4 Hz, 3-H), 5.89 (d, 1 H, NH) and 6.09 (br s, 1 H, H-1). For **19**: δ 0.99 and 1.00 (2d, each 3 H, *J* 6.8 Hz, 9′- and 10′-H_3), 1.37 and 1.41 (2s, each 3 H, CMe_2), 1.60–2.36 (m, 5 H, 4-, 5-H_2 and 8′-H), 2.07 (s, 3 H, OAc), 3.22–3.42 (m, 2 H, 7-H_2), 3.48 (s, 3 H, OMe), 3.58–3.68 (m, 1 H, 6-H), 3.85 (d, 1 H, $J_{2',3'}$ 2.9 Hz, 2′-H), 4.15 (dd, 1 H, $J_{3',4'}$ 7.8 Hz, H-3′), 4.26 (dd, 1 H, $J_{4',5'}$ 4.9 Hz, 4′-H), 4.57 (ddd, 1 H, $J_{3,4a}$ 9.8, $J_{3,4b}$ 1.5, $J_{3,NH}$ 5.9 Hz, 3-H), 5.21 (dd, 1 H, $J_{5',6'}$ 7.8 Hz, 5′-H), 5.38 (ddd, 1 H, $J_{6',7'}$ 15.6, $J_{6',8'}$ 1.5 Hz, 6′-H), 5.79 (dd, 1 H, $J_{7',8'}$ 6.4 Hz, 7′-H), 6.11 (br s, 1 H, 1-H) and 7.80 (d, 1 H, NH). For **21**: δ 0.88 (t, 3 H, *J* 6.4 Hz, Me of myristoyl group), 1.00 (d, 6 H, *J* 6.8 Hz, 9′- and 10′-H_3), 1.23–1.33 (m, 20 H, 10 methylenes of myristoyl group), 1.38 and 1.41 (2s, each 3 H, CMe_2), 1.55–2.07 (m, 4 H, 4-, 5-H and methylene of myristoyl group), 2.14–2.38 (m, 3 H, 4-, 5-H′ and 8′-H), 2.30 (t, 2 H, *J* 7.6 Hz, methylene of myristoyl group), 3.16 (ddd, 1 H, $J_{1,7a}$ 7.6, $J_{6,7a}$ 2.0, $J_{7a,7b}$ 14.14 Hz, 7-H^a), 3.37 (ddd, 1 H, $J_{1,7b}$ 5.6, $J_{6,7b}$ 10.0 Hz, 7-H^b), 3.49 (s, 3 H, OMe), 3.85 (d, 1 H, $J_{2',3'}$ 3.4 Hz, 2′-H), 3.99 (dd, 1 H, $J_{4',5'}$ 4.4, $J_{5',6'}$ 6.8 Hz, 5′-H), 4.14 (dd, 1 H, $J_{3',4'}$ 7.3 Hz, 4′-H), 4.25 (dd, 1 H, 3′-H), 4.54–4.67 (m, 2 H, 3- and 6-H), 5.42 (ddd, 1 H, $J_{6',7'}$ 15.6, $J_{6',8'}$ 1.5 Hz, 6′-H), 5.72 (dd, 1 H, $J_{7',8'}$ 6.4 Hz, 7′-H), 6.00 (dd, 1 H, H-1) and 7.80 (d, 1 H, $J_{3,NH}$ 6.4 Hz, NH).

presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDAC) and 4-dimethylaminopyridine to afford an activated ester **12**. Without purification, **12** was hydrogenolysed in the presence of Raney-Ni (atmospheric pressure of H_2, THF). Under these reaction conditions, a reduction of the azido group as well as spontaneous cyclisation of the resulting ε-amino ester took place to provide hexahydro-2-azepinone derivative **13** in 43% yield from **10**. Hydrogenolysis of **13** with $Pd(OH)_2$ removed the *O*-benzyl group to give **14** (97%),§ whose *N*-Boc group was cleanly deprotected by a treatment with CF_3CO_2H–CH_2Cl_2 to provide **15** in quantitative yield. Condensation of **15** with the optically pure polyhydroxylated C_{10} side chain **18** (Scheme 2), which had been prepared from L-quebrachitol,[3a] was successfully achieved under the conditions of Shioiri's protocol [$(EtO)_2P(O)CN$ (1.4 equiv.), Et_3N (2.3 equiv.), *N*,*N*-dimethylformamide (DMF)][8] to afford the condensate **19**§,¶ in 82% yield. After removal of the *O*-acetyl group in **19** (MeONa–MeOH, 97% yield), the resulting compound **20** was treated with myristic acid (2.5 equiv.) in the presence of EDAC and 4-dimethylaminopyridine in CH_2Cl_2 (−15 °C–room temp.) to provide **21**§ in 62% yield, along with the di-*O*-acylated product (20% yield). Finally, the acetonide group in **21** was removed by acidic hydrolysis (CF_3CO_2H–H_2O–THF) to give **1** as an amorphous solid [m.p. 124–126 °C (lit.,[1a] 114–115 °C)] in 53% yield. Although it was impossible for us to make a direct comparison of synthetic **1** with natural bengamide A due to the deficiency of the natural product, the spectral (^{1}H and ^{13}C NMR) data of synthetic **1** were fully identical with those of natural bengamide A, and the sign of optical rotations of synthetic compound was the same as that reported in the literature {$[\alpha]_D^{23}$ + 39 (*c* 0.05, MeOH), lit.,[1a] $[\alpha]_D^{20}$ + 30.3 (*c* 0.081, MeOH)]. From this synthesis, therefore, the absolute configuration of bengamide A was determined as depicted in Fig. 1.

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¶ ^{1}H NMR spectrum (270 MHz) of **19** revealed that this compound consisted of only one diastereoisomer, implying that the amino acid **15** should have high optical purity.

bengamide A. Financial support from Yokohama Rubber Co. Ltd, (Tokyo, Japan) is gratefully acknowledged.

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