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TOTAL SYNTHESIS OF BENGAMIDE E

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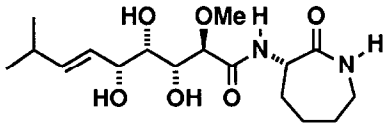
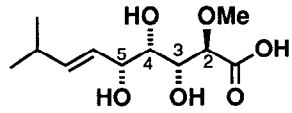
Summary: The first total synthesis of bengamide E (**1**), a novel sponge-derived amino acid, is described. The side chain of bengamide E (**2**) possessing four contiguous chiral centers was prepared in a stereoselective manner starting from naturally abundant cyclitol, L-quebrachitol.

In 1986, Crews and his co-workers isolated bengamides, novel non-alkaloidal natural products which showed anti infectious disease activities, from an undescribed Jaspidae sponge collected in Fiji Islands.[1a] Spectral analyses and degradation study showed that bengamide E (**1**), one of the members of bengamide family, has a unique structure which contains cyclo-L-lysine and C-10 side chain (**2**) possessing four contiguous hydroxyl groups as well as *E*-olefin (Scheme 1). The hydroxyl acid moiety (**2**) is a common unit in bengamide family.[1b, 1c] The absolute configuration of the side chain of bengamides (**2**) has been tentatively assigned as 2*R*, 3*R*, 4*S*, and 5*R* by ^{1}H NMR behavior of its *O*-methylmandelate derivatives.[1c] The novel and intriguing structure of **1**, whose biogenesis is considered to involve the union of C4-diketide and amino acids,[1b] led us to explore the synthesis of bengamide family. In this communication, we wish to report the first total synthesis of bengamide E (**1**), which fully confirmed the proposed absolute stereochemistry of the natural product.



Bengamide E (**1**)



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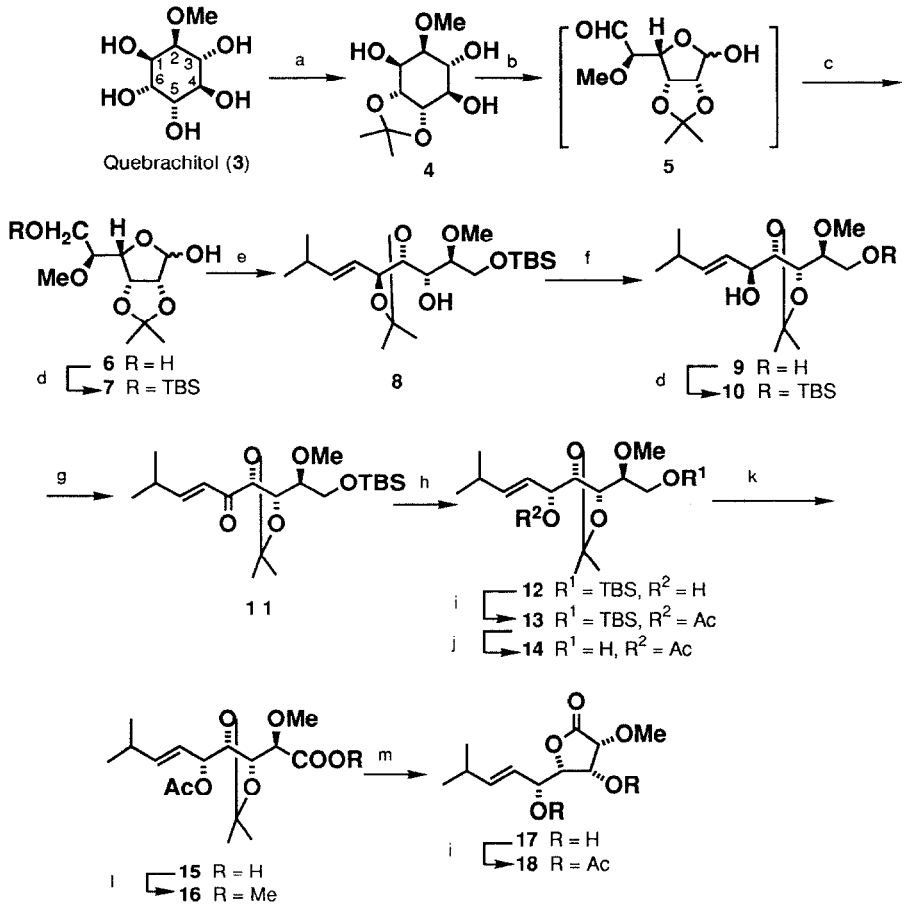
Scheme 1

Our synthetic plan is based on utilization of naturally abundant, optically active cyclitol, L-quebrachitol (**3**)[2] as a chiral starting material and three asymmetric centers (C-2, 1 and 6) of L-quebrachitol were envisioned to correlate with C-2,3 and 4 of the side chain (**2**) of bengamide E.

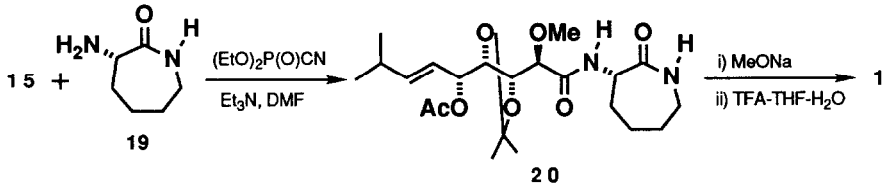
Periodate oxidation of the known triol (**4**),[2d] prepared in one step from L-quebrachitol gave **5**, and, without isolation, the aldehyde group in **5** was reduced with $NaBH_4$ to give 2,3-*O*-isopropylidene-5-*O*-methyl-L-mannofuranose (**6**) in 60% yield from **4** (Scheme 2). The primary hydroxyl group in **6** was protected as *t*-butyldimethylsilyl (TBS) ether to afford **7** (73 %), which was then submitted to Wittig olefination with



Scheme 2: TBS = *t*-BuMe$_2$Si, a, see ref 2d; b, $NaIO_4$ (4.8 mol. eq.), acetone-H_2O (5:1), 0 °C, 2.5 h; c, $NaBH_4$ (0.7 mol. eq.), MeOH, 0 °C, 1 h; d, TBSCl (1.9 mol. eq.), Et_3N (2.8 mol. eq.), 4-dimethylaminopyridine (0.25 mol. eq.), CH_2Cl_2, rt, 20 h; e, $Me_2CHCH_2P^+Ph_3Br^-$ (10 mol. eq.), *n*-BuLi (9 mol. eq.), benzene, rt, 4 h; f, *p*-TsOH (0.05 mol. eq.), CH_3CN, 0 °C, 8 h; g, MnO_2 (30 mol. eq.), CH_2Cl_2, rt, 16 h; h, $Zn(BH_4)_2$ (7 mol. eq.), ether-toluene (1:1), -78 ~ 0 °C, 1 h; i, Ac_2O, pyridine, rt, 15 h; j, *n*-Bu_4NF (10 mol. eq.), AcOH (20 mol. eq.), THF, 0 °C ~ rt, 12 h; k, Jones reagent (3 mol. eq.), acetone, 0 °C, 2 h; l, excess CH_2N_2 , ether, 0 °C, 5 min.; m, TFA-THF-H_2O (1.8:1:1.2), 50 °C, 2 h.

$Me_2CHCH{=}PPh_3$. Among various conditions attempted, the use of *n*-BuLi as a base and benzene as a solvent gave a good result, and the desired **8** was obtained in 76% yield along with its *Z*-isomer (14 %). Mild acid treatment of **8** (*p*-TsOH, acetonitrile, 0 °C) caused the migration of *O*-isopropylidene group, as well as partial deprotection of TBS group and compound **10** was obtained in 59% yield from **8** after re-silylation of the primary hydroxyl group. Since attempted inversion of configuration at the C-5 position in **10** using Mitsunobu reaction[3] resulted in a recovery of the starting material, we next tried oxidation-reduction procedures. Thus, compound **10** was oxidized with MnO_2 to give the enone (**11**) in 74% yield, which was then reduced with $Zn(BH_4)_2$[4] in ether-toluene (1:1, -78 ~ 0 °C) to afford a mixture of the inverted alcohol (**12**) and **10** in 66 and 10% isolated yields, respectively.[5] After acetylation, *O*-TBS group in **13** was removed with *n*-

Bu_4NF-AcOH[6] to give **14** in 96% yield from **12**. The primary hydroxyl group in **14** was oxidized with Jones reagent to afford **15**, which was esterified with diazomethane to give the ester (**16**) in 85% yield from **14**. Treatment of **16** with TFA-THF-H_2O provided the γ-lactone (**17**), which was acetylated to provide **18** in 64% yield from **16**. The ^1H and ^{13}C NMR data of lactone **18** [7] were in good accordance with those reported for authentic **18** prepared from natural product,[1b] and the sign of optical rotations of synthetic **18** was the same as that reported in the literature.[1b,7] Therefore, the absolute configuration of the side chain of bengamides was concluded as 2*R*, 3*R*, 4*S*, and 5*R*.



Scheme 3

With the side chain of bengamides possessing correct stereochemistry in hand, we then turned our attention to the total synthesis of bengamide E (Scheme 3). Thus, condensation of the carboxylic acid (**15**) and cyclo-L-lysine (**19**), prepared by the known method from L-lysine,[8] was performed under the conditions of Shioiri's protocol [$(EtO)_2P(O)CN$ (1.3 mol. eq.), Et_3N (2.2 mol. eq.), DMF, 0 °C, 2 h],[9] and the condensate (**20**) was obtained in 88% yield. Deacetylation [MeONa (1 mol. eq.), MeOH-THF (5:1), 5 °C, 14 h] and subsequent acid hydrolysis of *O*-isopropylidene group [TFA-THF-H_2O (3:3:2), 0 °C ~ rt] afforded bengamide E (**1**) in 50 % yield. The ^1H and ^{13}C NMR data, as well as physical properties of the synthetic specimen were in good accordance with those reported for natural bengamide E.[1b, 7]

In summary, the first total synthesis of bengamide E (**1**), starting from L-quebrachitol and L-lysine has been achieved, confirming the assigned structure and absolute stereochemistry. This synthesis also revealed that cyclitols should be useful starting materials for the synthesis of optically active natural products.

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References and Notes

1. a) E. Quiñoá, M. Adamczeski, P. Crews, G. J. Bakus, *J. Org. Chem.*, **51**, 4497 (1986); b) M. Adamczeski, E. Quiñoá, P. Crews, *J. Am. Chem. Soc.*, **111**, 647 (1989); c) M. Adamczeski, E. Quiñoá, P. Crews, *J. Org. Chem.*, **55**, 240 (1990).
2. Isolation of L-quebrachitol, see: a) J. van Alphen, *Ind. Eng. Chem.*, **43**, 141 (1951); b) N. Chida, M. Suzuki, M. Suwama, S. Ogawa, *J. Carbohydr. Chem.*, **8**, 319 (1989). Syntheses of natural products utilizing L-quebrachitol as a chiral starting material, see c) S. J. Angyal, R. M. Hoskinson, *Methods*

in Carbohydr. Chem., **2**, 87 (1963); d) H. Paulsen, F. R. Heiker, *Liebigs Ann. Chem.*, 2180 (1981); e) H. Paulsen, W. von Deyn, *ibid.*, 133 (1987); f) T. Akiyama, N. Takeuchi, S. Ozaki, *Tetrahedron Lett.*, **31**, 1433 (1990); g) A. P. Kozikowski, A. H. Fauq, G. Powis, D. C. Meilder, *J. Am. Chem. Soc.*, **112**, 4528 (1990); h) N. Chida, T. Tobe, M. Suwama, M. Ohtsuka, S. Ogawa, *J. Chem. Soc., Chem. Commun.*, 994 (1990).

3. O. Mitsunobu, *Synthesis*, 1 (1981).
4. T. Oishi, T. Nakata, *Acc. Chem. Res.*, **17**, 338 (1984) and references therein.
5. Results of reduction of **11** with various reducing reagents were as follows: $NaBH_4$-$CeCl_3 \cdot 7H_2O$ in MeOH-CH_2Cl_2 (5:1) at 0 °C, **12:10** = 68:32 (99% combined yield); $LiBEt_3H$ in THF at -78 °C, **12:10** = 29:71 (96%); L-Selectride® in THF at -78 °C, **12:10** = 47:53 (81%); DIBAL in CH_2Cl_2 at -78 °C, **12:10** = 41:59 (46%).
6. B. J. Fitzsimmons, J. Rokach, *Tetrahedron Lett.*, **25**, 3043 (1984). When desilylation reaction was carried out in the absence of acetic acid, complete migration of *O*-acetyl group to the primary position was observed.
7. Selected spectral and physical data.
15: $[\alpha]_D^{22}$ - 10 ° (c 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.00 (d, 6H, J = 6.7 Hz), 1.41 (s, 3H), 1.42 (s, 3H), 2.09 (s, 3H), 2.31 (m, 1H), 3.50 (s, 3H), 3.96 (d, 1H, J = 3.4 Hz), 4.16 (dd, 1H, J = 7.3 and 3.4 Hz), 4.30 (dd, 1H, J = 7.3 and 4.9 Hz), 5.33 (dd, 1H, J = 7.8 and 4.9 Hz), 5.39 (ddd, 1H, J = 14.9, 7.8 and 1.0 Hz), 5.83 (dd, 1H, J = 14.9 and 6.7 Hz), 6.22 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 21.8, 24.7, 27.0, 27.1, 29.7, 30.8, 59.3, 74.1, 77.5, 78.0, 80.7, 110.6, 120.9, 144.4, 170.3, 172.5. **18**: mp 178-179 °C, $[\alpha]_D^{22}$ - 40 ° (c 0.78, $CHCl_3$), {lit.[1b] $[\alpha]_D^{20}$ - 14.9 ° (c 0.026, $CHCl_3$)}; ^1H NMR ($CDCl_3$) δ 0.96 (d, 3H, J = 6.8 Hz), 0.97 (d, 3H, J = 6.8 Hz), 2.09 (s, 3H), 2.13 (s, 3H), 2.28 (m, 1H), 3.55 (s, 3H), 4.11 (d, 1H, J = 4.4 Hz), 4.48 (dd, 1H, J = 8.8 and 3.2 Hz), 5.21 (ddd, 1H, J = 15.6, 8.3 and 1.2 Hz), 5.54 (dd, 1H, J = 8.8 and 8.3 Hz), 5.65 (dd, 1H, J = 4.4 and 3.2 Hz), 5.88 (dd, 1H, J = 15.6 and 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 20.5, 21.1, 21.5, 21.8, 30.9, 60.0, 68.3, 72.7, 77.7, 78.0, 118.3, 146.9, 169.2, 169.5, 171.3. **20**: $[\alpha]_D^{27}$ +18 ° (c 0.82, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.98 (d, 3H, J = 6.5 Hz), 0.99 (d, 3H, J = 6.5 Hz), 1.37 (s, 3H), 1.41 (s, 3H), 1.43-1.61 (m, 2H), 1.81-1.91 (m, 2H), 1.97-2.15 (m, 2H), 2.06 (s, 3H), 2.29 (m, 1H), 3.24-3.34 (m, 2H), 3.48 (s, 3H), 3.84 (d, 1H, J = 3.1 Hz), 4.16 (dd, 1H, J = 7.3 and 3.1 Hz), 4.27 (dd, 1H, J = 7.3 and 4.9 Hz), 4.54 (ddd, 1H, J = 11.1, 6.2 and 1.6 Hz), 5.21 (dd, 1H, J = 7.8 and 4.9 Hz), 5.38 (ddd, 1H, J = 15.5, 7.8 and 1.3 Hz), 5.79 (dd, 1H, J = 15.5 and 6.5 Hz), 6.09 (t, 1H, J = 6.1 Hz), 7.81 (d, 1H, J = 6.2 Hz); ^{13}C NMR ($CDCl_3$) δ 16.0, 21.2, 21.8, 22.0, 27.0, 27.9, 28.9, 30.8, 31.5, 42.0, 51.8, 59.4, 73.9, 77.5 (two carbons), 82.0, 109.9, 121.4, 143.9, 168.1, 169.9, 174.9. **1**: $[\alpha]_D^{29}$ + 25 ° (c 0.29, MeOH), {lit.[1b] $[\alpha]_D^{20}$ + 37 ° (c 0.043, MeOH)}; ^1H NMR ($CDCl_3$) δ 0.99 (d, 3H, J = 6.4 Hz), 1.00 (d, 3H, J = 6.4 Hz), 1.22-1.68 (m, 4H), 1.76-1.94 (m, 2H), 2.31 (m, 1H), 3.26-3.32 (m, 2H), 3.54 (s, 3H), 3.61 (dd, 1H, J = 5.4 and 1.1 Hz), 3.78 (d, 1H, J = 6.8 Hz), 3.86 (dd, 1H, J = 6.8 and 1.1 Hz), 4.23 (dd, 1H, J = 7.1 and 5.4 Hz), 4.54 (ddd, 1H, J = 10.3, 5.9 and 1.0 Hz), 5.46 (ddd, 1H, J = 15.6, 7.1 and 1.2 Hz), 5.78 (dd, 1H, J = 15.6 and 6.4 Hz), 6.21 (bs, 1H), 7.97 (bd, 1H, J = 5.9 Hz); ^{13}C NMR ($CDCl_3$) δ 22.1, 22.2, 28.0, 28.8, 30.8, 30.9, 42.1, 52.1, 59.9, 72.5, 72.7, 74.3, 81.1, 125.4, 141.9, 172.2, 174.8.
8. R. Pellegate, M. Pinza, G. Pifferi, *Synthesis*, 614 (1978).
9. S. Yamada, Y. Kasai, T. Shioiri, *Tetrahedron Lett.*, 1595 (1973).

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