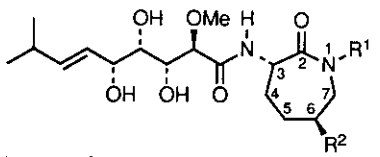
STEREOSELECTIVE CONVERSION OF L-QUEBRACHITOL INTO A NOVEL HYDROXYLATED CAPROLACTAM: TOTAL SYNTHESIS OF BENGAMIDE B

Noritaka Chida,* Takahiko Tobe, Katsuyuki Murai, Kaori Yamazaki, and Seiichiro Ogawa*

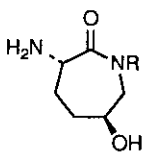
Department of Applied Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Kohoku-ku, Yokohama 223, Japan

Abstract- The stereoselective synthesis of the novel marine natural product, bengamide B (**1**), starting from L-quebrachitol (**3**) is described. The hydroxylated caprolactam portion (**2a**) in **1** was prepared from (+)-conduramine derivative (**7**), whose amino functionality was introduced stereoselectively by means of palladium-catalyzed azidation of a chiral cyclohexene (**6**) derived from **3**.

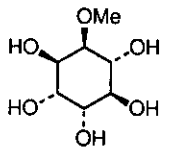
The bengamide family, first isolated from a choristid sponge by Crews, is a new category of amino acid derivatives, and reported to show anti-infectious disease activities.[1] The unique structure of the bengamide family,[1] which contains a caprolactam moiety and a polyhydroxylated C_{10} side chain, attracted the synthetic interest and a number of reports on the synthesis of this family have appeared.[2] However, synthetic studies toward the novel hydroxylated caprolactams (**2a** and **2b**) found in bengamides B and A, respectively, are limited, and only two approaches to the caprolactams (**2a**) starting from (*S*)-butanetriol[2a] and (**2b**) from L-glutamic acid[2b] have been reported to date. In this communication, as a part of our continuous study to utilize cyclitols as the chiral building block for natural product synthesis,[3] we wish to report the stereoselective total synthesis of bengamide B (**1**), a representative component of the bengamide family. Our synthetic tactic is based on the utilization of L-quebrachitol (**3**), an optically active cyclitol readily obtained from the serum of the rubber tree,[4] as the sole chiral building block, and both components of bengamide B [the novel hydroxylated



R^1 = Me, R^2 = $OC(O)(CH_2)_{12}Me$: Bengamide B (**1**)
R^1 = H, R^2 = $OC(O)(CH_2)_{12}Me$: Bengamide A
R^1 = R^2 = H: Bengamide E

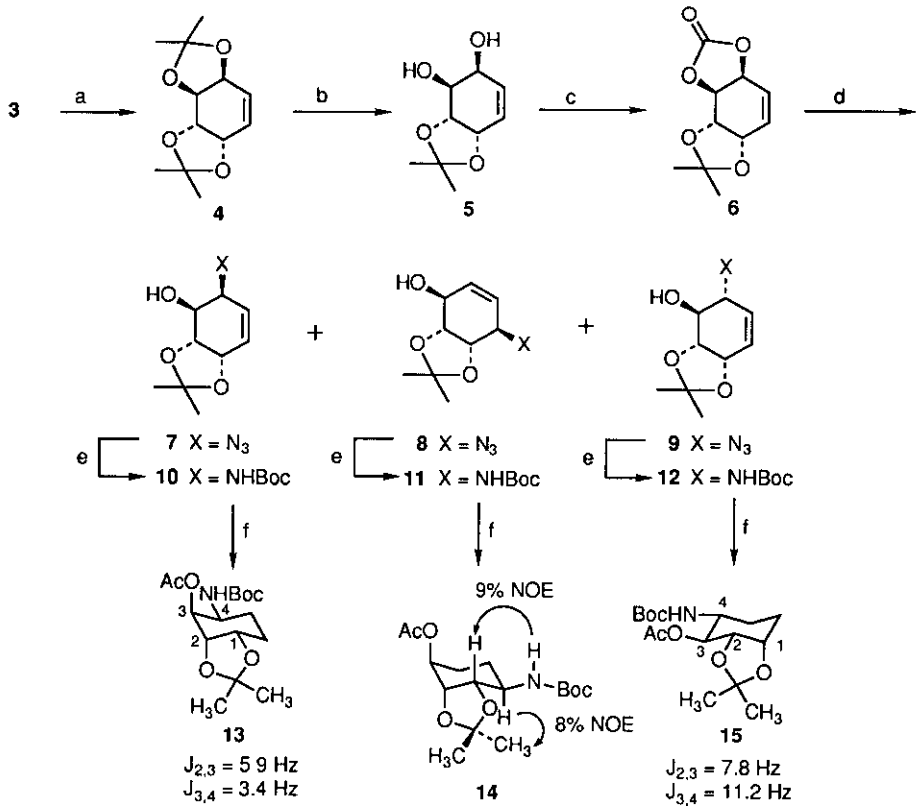


2a R = Me
2b R = H



L-Quebrachitol (**3**)

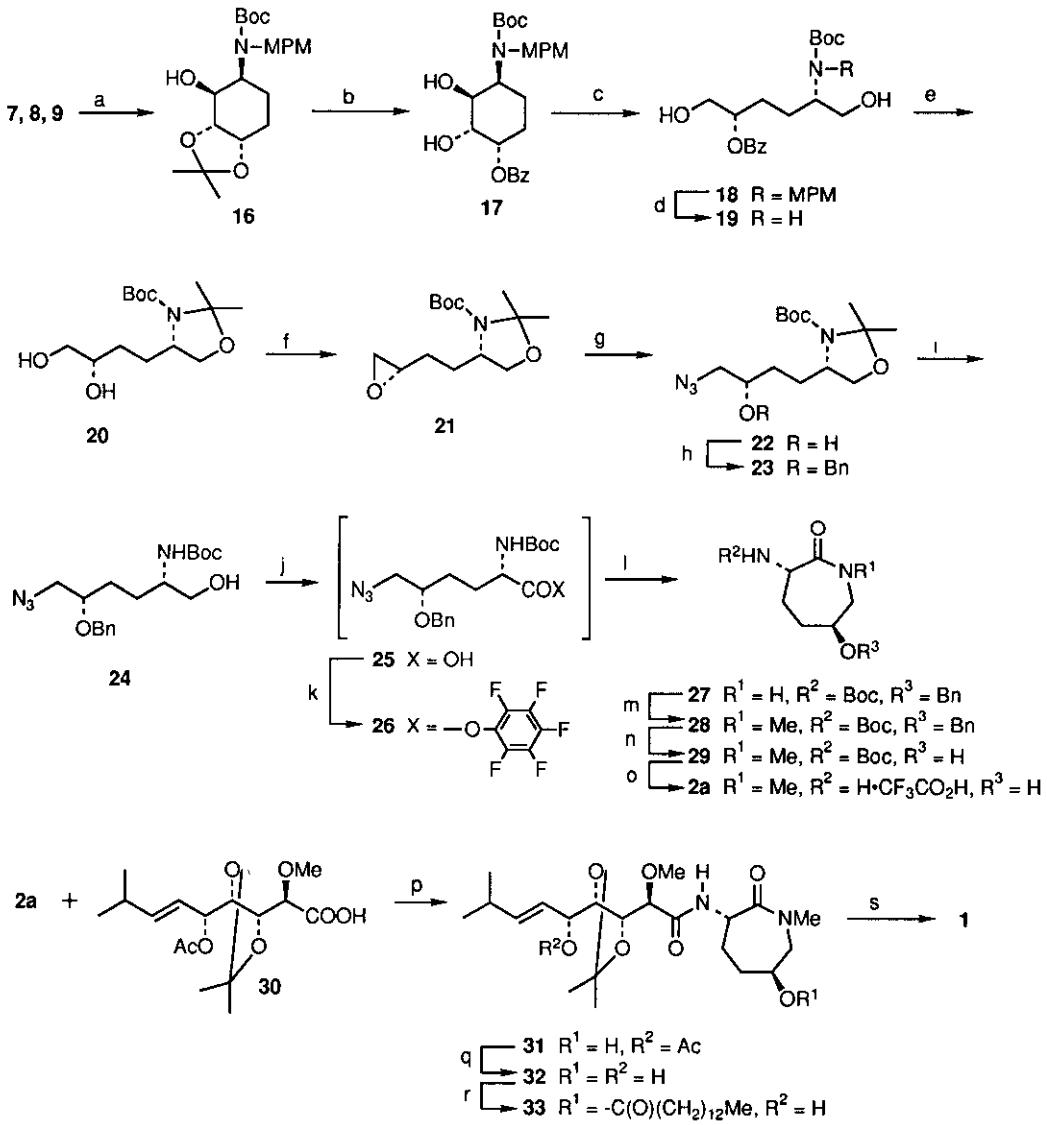
caprolactam (**2a**) and the protected C_{10} side chain (**30**)] were planned to be prepared starting from **3**. The known di-*O*-isopropylidene derivative of conduritol E (**4**),[5] prepared from L-quebrachitol (**3**) in 3 step reactions, was converted into diol (**5**) (60% yield). Treatment of **5** with 1,1'-carbonyldiimidazole provided



Scheme 1. Boc= -C(O)OCMe$_3$, *Reagents and Conditions*: a, see ref. 5; b, IR-120 resin (H^+ form), THF-MeOH (10 1), room temperature; c, 1,1'-carbonyldiimidazole, toluene, 50 °C, d, NaN_3, $(PPh_3)_4Pd$ (3 mol%), THF-H_2O (5:1), room temperature; e, $LiAlH_4$, THF, 0 °C ~ room temperature, then $(Boc)_2O$, room temperature; f, H_2, $Pd(OH)_2$, EtOH, then Ac_2O, pyridine

cyclic carbonate (**6**) in 94% yield. Palladium catalyzed azidation of **6** under the conditions developed by Murahashi[6] [NaN_3 (1.1 equiv), $Pd(PPh_3)_4$ (3 mol%), tetrahydrofuran (THF)–H_2O (5:1), room temperature] afforded an inseparable mixture of allylic azides (**7**, **8**, and **9**) in a ratio of 86:8:6 (determined with 270 MHz ^1H nmr) in 97% yield.[7] Using other solvents (*N*,*N*-dimethylformamide (DMF), acetonitrile or ether) or other catalysts ($Pd_2(dba)_3CHCl_3$ or $Pd(PPh_3)_4$-2dppb)[8] dramatically reduced the yield of the products. To clarify the structures of **7**, **8**, and **9**, the mixture was reduced with lithium aluminium hydride and then transformed into *tert*-butyl carbamates. The products were cleanly separated by silica gel chromatography to provide **10**, **11** and **12** in 78, 7, and 5% isolated yields, respectively. The ^1H nmr analyses of their saturated derivatives (**13**, **14** and **15**) with spin-spin decoupling experiments and NOE measurement successfully assigned their structures (Scheme 1).

The mixture of compounds (**7**, **8**, and **9**) was hydrogenolyzed in the presence of palladium catalyst to give corresponding saturated amines. Reductive alkylation of these amines with anisaldehyde and sodium borohydride, and subsequent treatment of the products with di-*tert*-butyl dicarbonate gave a mixture of **16** and its diastereoisomers. Chromatographic separation of the mixture provided pure **16** in 72% isolated yield from **6** (Scheme 2). After removal of the acetonide group, the equatorial hydroxy group in the resulting triol was selectively acylated with benzoyl chloride to afford **17** in 92% yield. Glycol cleavage of **17** with lead tetraacetate, followed by reductive workup gave **18**, whose *N*-MPM group was cleanly detached by the action of cerium (IV) ammonium nitrate (CAN)[9] to provide **19** in 47% yield from **17**. *N*,*O*-Acetalization of **19** and subsequent deprotection of *O*-benzoyl group afforded **20** (82% yield), which was transformed into epoxide (**21**) by means of Mitsunobu reaction[10] in 76% yield. Introduction of the azide group into **21** (80% yield) followed by *O*-benzylation provided **23**, whose *N*,*O*-acetal was removed to afford **24** in 77% yield from **21**. The physical and spectral properties of **24** were fully identical with those of the authentic sample, previously prepared in non-stereoselective manner from L-glutamic acid,[2b] confirming the assigned structure. Jones oxidation of **24** gave **25**, which was treated with pentafluorophenol[11] and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSC) to give an activated ester (**26**). Hydrogenolysis of **26** in the presence of Raney Ni in THF caused the reduction of azido function as well as spontaneous cyclization of the resulting amino ester to provide the caprolactam (**27**) in 62% yield from **24**. Treatment of **27** with MeI in the presence of Ag_2O in DMF afforded the *N*-Me derivative (**28**), whose *O*-benzyl group was removed by hydrogenolysis with $Pd(OH)_2$-C to give **29** (87% yield). Removal of the *N*-Boc group with trifluoroacetic acid (TFA) gave **2a**



Scheme 2. MPM = -$CH_2C_6H_4$(*p*-OMe), Bz = -C(O)Ph, Bn = -CH_2Ph, *Reagents and Conditions*: a, (i) H_2, $Pd(OH)_2$-C, EtOH, (ii) anisaldehyde, toluene-pyridine (10:1), reflux, (iii) $NaBH_4$, MeOH-THF, 0 °C, (iv) $(Boc)_2O$, THF-MeOH-H_2O (1:1:2), room temperature; b, camphorsulfonic acid (CSA) (2 mol%), MeOH, room temperature, then BzCl, pyridine, 0 °C; c, $Pb(OAc)_4$, pyridine, room temperature, then $NaBH_3CN$, d, CAN, MeCN-H_2O (4:1), room temperature; e, (i) $Me_2C(OMe)_2$, CSA, PhMe, 70 °C, (ii) pyridinium *p*-toluenesulfonate, MeOH-THF, room temperature, (iii) MeONa, MeOH, room temperature; f, PPh_3, diethyl azodicarboxylate, PhMe, reflux; g, NaN_3, NH_4Cl, 2-methoxyethanol-H_2O (9:1), 50 °C; h, NaH, BnBr, n-Bu_4NI, THF, room temperature, i, *p*-TsOH (5 mol%), MeOH, room temperature; j, Jones reagent, acetone, 0 °C; k, pentafluorophenol, WSC, CH_2Cl_2, 0 °C ~ room temperature; l, H_2, Raney Ni, THF, room temperature; m, Ag_2O, MeI, DMF, room temperature; n, H_2, $Pd(OH)_2$, EtOH, room temperature; o, trifluoroacetic acid, CH_2Cl_2, 0 °C, p, $(EtO)_2P(O)CN$, Et_3N, DMF, room temperature; q, MeONa, MeOH, room temperature; r, myristic acid, WSC, DMAP, CH_2Cl_2-THF, -50 ~ -15 °C; s, TFA-THF-H_2O (1:1:1), -15°C ~ room temperature.

(as its trifluoroacetate salt) in quantitative yield. Having established the stereoselective preparation of the caprolactam moiety, total synthesis of **1** using the essentially same approach which had been employed in the synthesis of bengamide A[2b] was next explored. Thus, condensation of **2a** with the protected C_{10} side chain (**30**) which had been prepared stereoselectively from L-quebrachitol (**3**) by our group,[2c] under the conditions of Shioiri[12] successfully afforded the condensate (**31**) in 67% yield. Removal of the *O*-acetyl group in **31** gave **32** (93% yield), which was treated with myristic acid (3.5 equiv.) in the presence of WSC and 4-dimethylaminopyridine (DMAP) in CH_2Cl_2–THF (–50 ~ –15 °C) to afford **33** in 33% yield, along with di-*O*-acylated product (40%). Treatment of **33** with aqueous TFA provided **1** as a syrupy product in 50% yield. The spectral (^1H and ^{13}C nmr) data and specific rotational value {$[\alpha]_D^{22}$ +36° (*c* 0.25, MeOH), lit.,[1a] $[\alpha]_D^{20}$ +34.6° (*c* 0.075, MeOH)} of synthetic **1** showed a good accord with those reported in the literature.[1a]

In summary, total synthesis of bengamide B starting from L-quebrachitol *via* stereoselective introduction of the azide group has been achieved. This success proved that cyclitol derivatives should be efficient starting material for the chiral synthesis of complex natural products.

ACKNOWLEDGMENT

We thank Yokohama Rubber Co. Ltd., (Tokyo, Japan) for the generous gift of L-quebrachitol. This work was supported in part by the Sasakawa Scientific Research Grant from the Japan Science Society.

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Received, 20th July, 1994