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An Efficient Synthesis of (-)-Bulgecinine

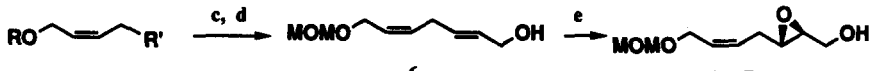
Yoshiro Hirai,[1] Takashi Terada, Yoshiko Amemiya, and Takefumi Momose*

Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani 2630, Toyama 930-01, Japan

Abstract: A highly stereoselective synthesis of (-)-bulgecinine (**1**) *via* the pyrrolido[1,2-*c*]oxazolidin-3-one system (**2**) has been achieved by starting with the asymmetric epoxidation of the twin allyl alcohol system (**6**). The transformation of note includes the palladium-catalyzed $N \rightarrow \pi$ cyclization leading exclusively to a *trans*-2,5-disubstituted pyrrolidine.

The title compound, (-)-bulgecinine (**1**), is a constituent amino acid of the novel glycopeptide bulgecins, potent β-lactam synergists found in the culture broth of *Pseudomonas acidophila* and of *Pseudomonas mesoacidophila*.[2,3] As a consequence of their biological activities and novel structural features, bulgecins have been the subject of synthetic investigations, and the aglycon bulgecinine (**1**) has been synthesized from chiral pools.[4] In connection with our current studies[5] directed towards the construction of chiral building blocks for nitrogen-containing natural products, we have focussed our attention to the asymmetric construction of an oxazolidinone [(+)-**2**] which is expected to provide a new synthetic method for carbapenems and for **1**. In this paper we report facile preparation of the chiral oxazolidinone (+)-**2** from an achiral allylic alcohol and its highly stereoselective conversion to **1**.

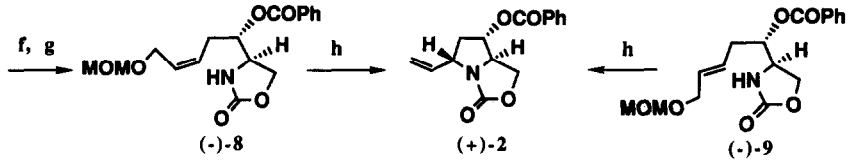
The synthesis was commenced with *(Z)*-2-buten-1,4-diol (**3**), which was first converted to the half ether **4** and subsequently to the allylic chloride **5** by treatment with methanesulfonyl chloride. The C-C coupling reaction[6] of **5** with propargyl alcohol and subsequent reduction with lithium aluminum hydride gave the requisite substrate **6** in 45% yield. The asymmetric epoxidation[7] of **6** afforded the 2,3-epoxy alcohol (-)-**7** [$[\alpha]_D$ -24.7° (*c* 0.9, $CHCl_3$)]. The treatment of (-)-**7** with benzoyl isocyanate[8] followed by cyclization with migration of the *N*-benzoyl group over K_2CO_3 in acetonitrile afforded the 2-oxazolidinone (-)-**8** in quantitative yield. The intramolecular cyclization of (-)-**8** was effected by treatment with bis(acetonitrile)palladium (II) chloride (30 mol %) [$PdCl_2(CH_3CN)_2$][9] in tetrahydrofuran to give an oxazolidinone [(+)-**2**, $[\alpha]_D$ +26.7°(*c* 1.1, $CHCl_3$)] in 70% yield (96% ee)[10] as a single diastereoisomer. In order to examine the effect of the double bond geometry on the stereochemical outcome of this cyclization, the *E*-isomer of (-)-**8** was prepared from 2-butyn-1,4-diol. The palladium-catalyzed cyclization of the isomer (-)-**9** resulted in formation of the same product, (+)-**2**, in 85% yield



a 3 R = H, R' = OH
a 4 R = MOM, R' = OH
b 5 R = MOM, R' = Cl

6

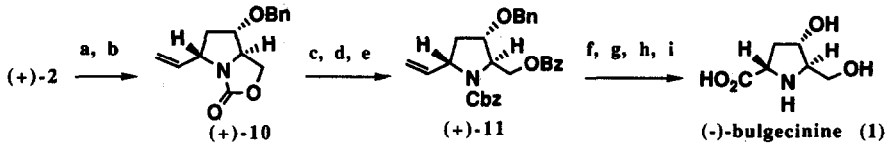
(-)-7



a) MOMCl, NaH, THF, 64%; b) MsCl, pyridine, 87%; c) propargyl alcohol, DBU, CuI, $NH_2OH.HCl$, phenothiazine, THF-HMPA, 60°C, 60%; d) $LiAlH_4$, Et_2O, 76%; e) L-DIPT, Ti(*i*-PrO)$_4$, TBHP, -23°C, 57%; f) benzoyl isocyanate, CH_2ClCH_2Cl; g) K_2CO_3, CH_3CN, 93% in 2 steps; h) 30 mol%-$PdCl_2(MeCN)_2$, THF, rt.

The oxazolidinone (+)-**2** thus obtained is a useful precursor for the preparation of nitrogen-containing natural products, and its versatility was demonstrated by its transformation into (-)-bulgecinine (**1**).

The debenzoylation of (+)-**2** followed by benzylation gave a benzyl ether [(+)-**10**]. The cleavage of the oxazolidinone ring in (+)-**10** was effected by treatment with 1N-KOH to give a pyrrolidine derivative, which was subjected to sequential *N*-benzyloxycarbonylation and *O*-benzoylation to afford the pyrrolidine (+)-**11**. Finally, the conversion of (+)-**11** to **1** was achieved in four steps: ozonolysis, oxidation of the resulting aldehyde with $KMnO_4$,[11] debenzylation, and acid hydrolysis of the carbamate and benzoate moiety. The physical data for the synthetic product [$[\alpha]_D$ -12.7° (*c* 0.1, H_2O)] were in accordance with those reported for natural (-)-bulgecinine.[2c]



a) 1N-KOH, MeOH, rt, 86%; b) BnBr, NaH, 96%; c) 1N-KOH, MeOH, reflux, 100%; d) CbzCl, $NaHCO_3$, H_2O-CH_2Cl_2, 90%; e) BzCl, pyridine, THF, 97%; f) O_3 and then Me_2S, 99%; g) $KMnO_4$, *t*-BuOH, 80%; h) H_2, Pd/C, 81%; i) 5N-HCl, MeOH, reflux, 64%.

References and Notes

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