TOWARD A TOTAL SYNTHESIS OF KERAMAMIDE B

Takayuki Shioiri† and (the late) Robert John Hughes‡

†Graduate School of Environmental and Human Sciences, Meijo University, Shiogamaguchi, Tempaku, Nagoya 468-8502, Japan (Tel. & Fax +81-52-832-1555. E-mail: shioiri@ccmfs.meijo-u.ac.jp)
‡Graduate School of Pharmaceutical Sciences, Nagoya City University, Tanabedori, Mizuho-ku, Nagoya 467-8603, Japan

In congratulation of the 30th Anniversary of Heterocycles

Abstract – Important building blocks, the 2-bromo-5-hydroxytryptophan-oxazole unit, the α-keto-β-amino acid unit, and the side chain units, for the preparation of keramamide B were efficiently synthesized.

Keramamide B is a member of keramamides found in the Theonella sponge off the Kerama islands of Okinawa, Japan, by J. Kobayashi and co-workers. Most of keramamides show cytotoxic activity while keramamide B does not show any cytotoxicity but inhibits super oxide formation. Keramamide B (1) is a 24-membered cyclic peptide containing an oxazoleamino acid, 2-bromo-5-hydroxytryptophan, 3-amino-5-methyl-2-oxohexanoic acid as characteristic features. As a continuation of our interests on the synthetic studies of aquatic natural products, the interesting structural features of keramamide B (1) as well as its unique biological activities stimulated us to commence synthesizing 1. We thought a total synthesis of keramamide B could be achieved by the connection of the five fragments shown in Figure 1. This communication describes the facile synthesis of the requisite building blocks (2-6).

First, the oxazole fragment (2) was synthesized as shown in Scheme 1. Boc-(S)-2-aminobutanoic acid (7) was coupled with (S)-serine methyl ester hydrochloride (8) by use of diethyl phosphorocyanidate (DEPC, (EtO)₂P(O)CN) together with triethylamine to give the dipeptide (9). Dehydration with the Burgess reagent ((carbomethoxysulfamoyl)triethylammonium inner salt) afforded the oxazoline (10), which
underwent the dehydrogenation with bromotrichloromethane and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)\(^6\) to give the oxazoleamino acid derivative (11) (mp 73 °C, [\(\alpha\)]\(_{D}\) \(-51.5 \, ^\circ\) (c 0.9, CHCl\(_3\))), in good yield. Application of barium permanganate to the dehydrogenation resulted in lower yield.\(^7\) The methyl ester (11) was transformed to the corresponding aldehyde (13) via the alcohol (12) by reduction with lithium borohydride and then oxidation with chemical manganese dioxide (CMD).\(^8\) The Horner-Wadsworth-Emmons reaction of the aldehyde (13) with the phosphonate (14)\(^9\) smoothly proceeded to give the (E)-\[\_\]-unsaturated ester (15) as the major product in 85% yield.\(^10\) Alkaline hydrolysis of 15 afforded the oxazole fragment (2) (mp 153 °C, [\(\alpha\)]\(_{D}\) \(-98.4 \, ^\circ\) (c 1.1, CHCl\(_3\))).

The synthesis of the 5-hydroxytryptophan fragment (3) was started from (S)-N-trifluoroacetyl-5-hydroxytryptophan methyl ester (17), which was prepared from (S)-5-hydroxytryptophan (16) according to the method of Schmidt.\(^11\) The hydroxyl group of 17 was protected with the TBDPS group, as shown in
Scheme 2. The direct displacement of the trifluoroacetyl group from the TBDPS derivative (18) with the di-tert-butyloxycarbonyl (di-Boc) group was smoothly carried out with Boc₂O-4-dimethylaminopyridine (DMAP)-triethylamine to give the required 5-hydroxytryptophan fragment (3) as an oil, $[\alpha]_D^{25} +6.2^\circ$ (c 0.27, CHCl₃).

Scheme 1
Treatment of 3 with trimethylsilyl triflate (TMSOTf) removed the di-Boc group, and the resulting amine was coupled with the oxazolecarboxylic acid (2) activated with diphenyl phosphorochloridate in the presence of triethylamine, giving the oxazole-tryptophan derivative (19), $[\alpha]_D +26.4$ ° (c 2.6, CHCl$_3$), in 54 % yield.$^{12}$ Bromination of 19 with N-bromosuccinimide$^{13}$ afforded the desired oxazolyl-2-bromo-tryptophan unit (20).

Synthesis of the $\alpha$-keto-$\beta$-amino acid unit (4) was straightforwardly accomplished by use of the furyl group as the carboxyl synthon,$^{14}$ shown in Scheme 3. Boc-(S)-leucine (21) was converted to the corresponding Weinreb amide (22), which was treated with 2-lithiofuran (23), prepared by treatment of furan with butyllithium, to give the furyl ketone (24). Reduction of 24 with sodium borohydride followed by acetylation afforded the acetate (25) as a diastereoisomeric mixture in a ratio of 62:38.$^{15}$ Oxidation of 25 with RuCl$_3$·3H$_2$O-NaIO$_4$ gave the required $\alpha$-keto-$\beta$-amino acid unit (4) as a diastereoisomeric mixture (59:41), $[\alpha]_D –33.4$ ° (c 0.59, MeOH).

The side chain fragment (5) of keramamide B was prepared from norvaline methyl ester hydrochloride (26), to which Boc-(S)-isoleucine (27) and (2S,3S)-2-hydroxy-3-methylpentanoic acid (29) was sequentially added utilizing DEPC for coupling and trifluoroacetic acid for removal of the Boc group, as shown in Scheme 4. The TBS-protection of the hydroxyl group of 30 sluggishly proceeded under the standard conditions (TBSCI-imidazole-triethylamine), but smoothly afforded 31 by use of TBS triflate-2,4,6-trimethylpyridine. Alkaline hydrolysis of 31 afforded the acid (5), mp 100 °C, $[\alpha]_D -37.5$ ° (c 0.37, CHCl$_3$). The remaining fragment Boc-(S)-Orn(Z)-(S)-Pro-OMe (6) was prepared by the condensation of Boc-(S)-Orn(Z)-OH (32) with H-(S)-Pro-OMe-HCl (33) using DEPC-triethylamine.
In conclusion, synthetic routes to fragments (2-6) required for a total synthesis of keramamide B (1) are now established. Coupling of these fragments and characterization of the final product (1) will be reported in near future.

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REFERENCES AND NOTES

This paper is dedicated to the memory of the late Dr. Robert John Hughes who died on 16 March, 2003.


7. This will be the first attempt of the application of Ba(MnO₄)₂ to the dehydrogenation of the oxazoline.


10. The corresponding (Z)-isomer was also isolated in 3% yield.


12. In this particular case, the use of DEPC and BopCl (bis(2-oxo-3-oxazolidinylphosphinic chloride) failed to give any coupling product.

13. Incidentally, the di-Boc tryptophan derivative (3) and the trifluoroacetyl derivative (18) were respectively converted to the bromo-di-Boc derivative (34). Initial attempt to cleave the

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\begin{align*}
\text{3} & \xrightarrow{\text{NBS, CH₂Cl₂, 0° C, overnight}} \text{TBDPSO} \\
& \xrightarrow{\text{rt, 2 h, 69 %}} \text{NBOc₂Br, rt, 25 h, 76 %} \\
& \xrightarrow{\text{rt, 25 h, 76 %}} \text{18} \\
\end{align*}
\]
trifluoroacetyl group of the bromo derivative derived from 18 with base resulted in the decomposition.


15. The syn isomer will be formed in preference of the anti one (see ref. 14b and 14f). The ratio was determined by $^1$H nmr spectrum: δ (ppm) 1.42 (s, minor) and 1.45 (s, major) for (CH$_3$)$_3$C; 2.05 (s, minor) and 2.17 (s, major) for CH$_3$CO$_2$. 