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TOWARD A TOTAL SYNTHESIS OF KERAMAMIDE B

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In congratulation of the 30th Anniversary of Heterocycles

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

Keramamide B is a member of keramamides¹ found in the *Theonella* sponge off the Kerama islands of Okinawa, Japan, by J. Kobayashi and co-workers.^{1a} Most of keramamides^{1b,c} show cytotoxic activity while keramamide B does not show any cytotoxicity but inhibits super oxide formation.^{1a} 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,² the interesting structural features of keramamide B (**1**) as well as its unique biological activities stimulated us to commence synthesizing **1**.³ 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)⁴ together with triethylamine to give the dipeptide (**9**). Dehydration with the Burgess reagent ((carbomethoxysulfamoyl)triethylammonium inner salt)⁵ afforded the oxazoline (**10**), which

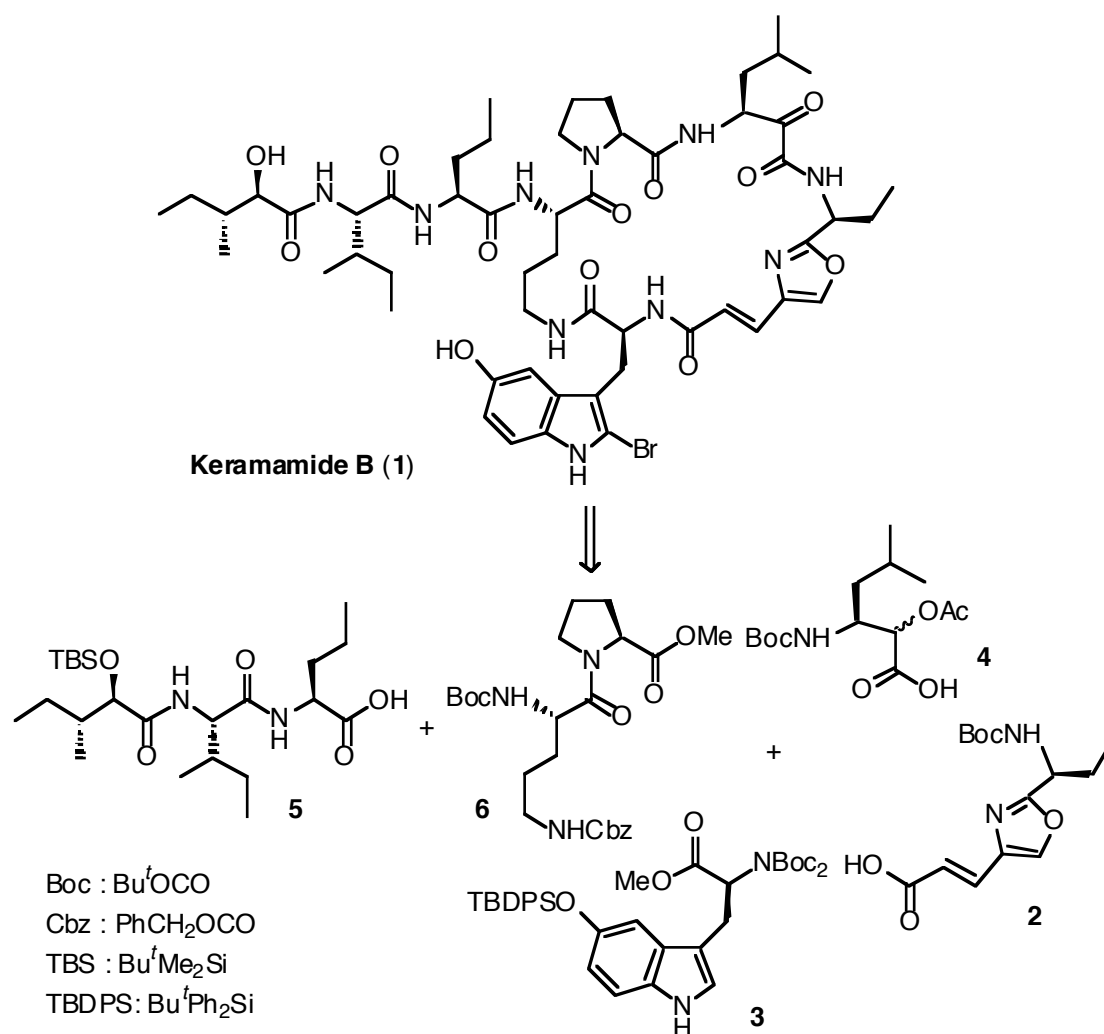
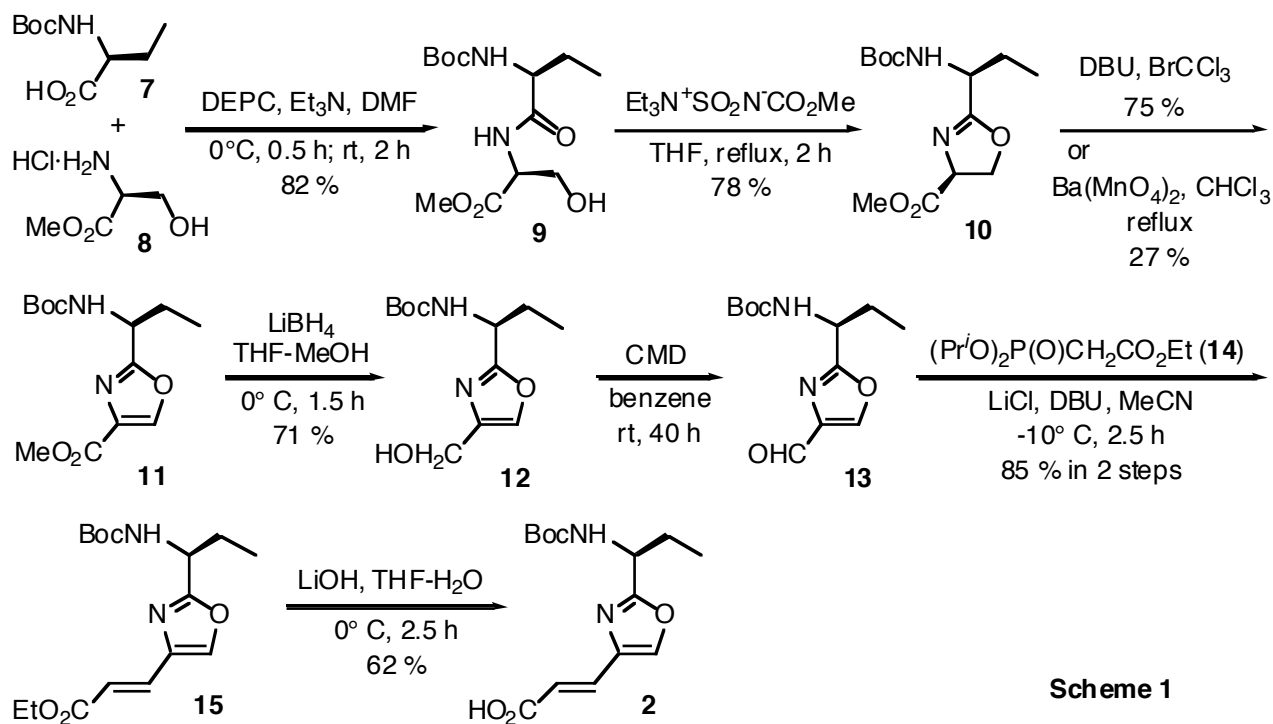


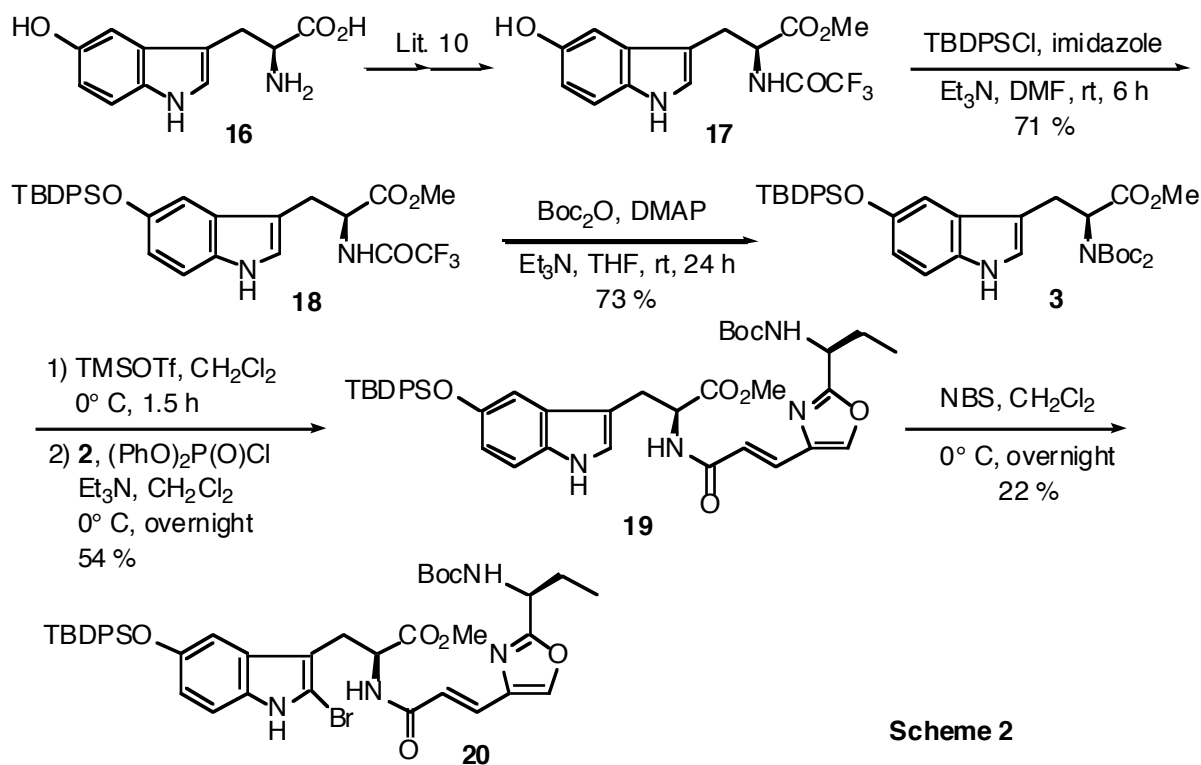
Figure 1 The Structure and Retrosynthesis of Keramamide B (1)

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, $[\alpha]_D^{25}$ -51.5 ° (c 0.9, CHCl₃)), 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*)- α,β -unsaturated ester (**15**) as the major product in 85% yield.¹⁰ Alkaline hydrolysis of **15** afforded the oxazole fragment (**2**) (mp 153 °C, $[\alpha]_D^{25}$ -98.4 ° (c 1.1, CHCl₃)).

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

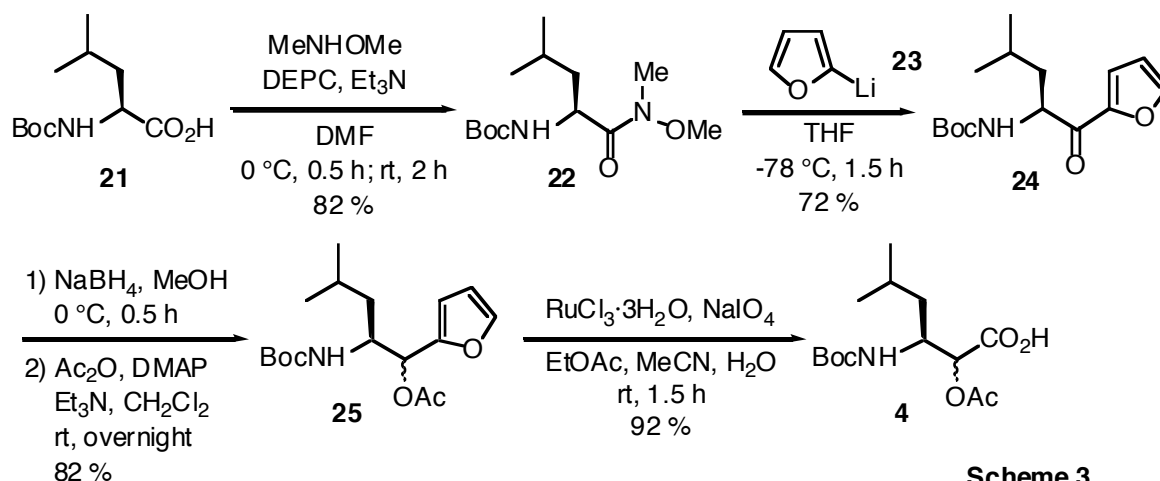


Scheme 2. The direct displacement of the trifluoroacetyl group from the TBDPS derivative (**18**) with the di-*tert*-butyloxycarbonyl (di-Boc) group was smoothly carried out with Boc₂O-4-dimethylaminopyridine (DMAP)-triethylamine to give the required 5-hydroxytryptophan fragment (**3**) as an oil, $[\alpha]_D^{20} +6.2^\circ$ (c 0.27, CHCl₃).



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**), $[\alpha]_D^{25} +26.4^\circ$ (c 2.6, CHCl_3), in 54 % yield.¹² Bromination of **19** with *N*-bromosuccinimide¹³ afforded the desired oxazolyl-2-bromo-tryptophan unit (**20**).

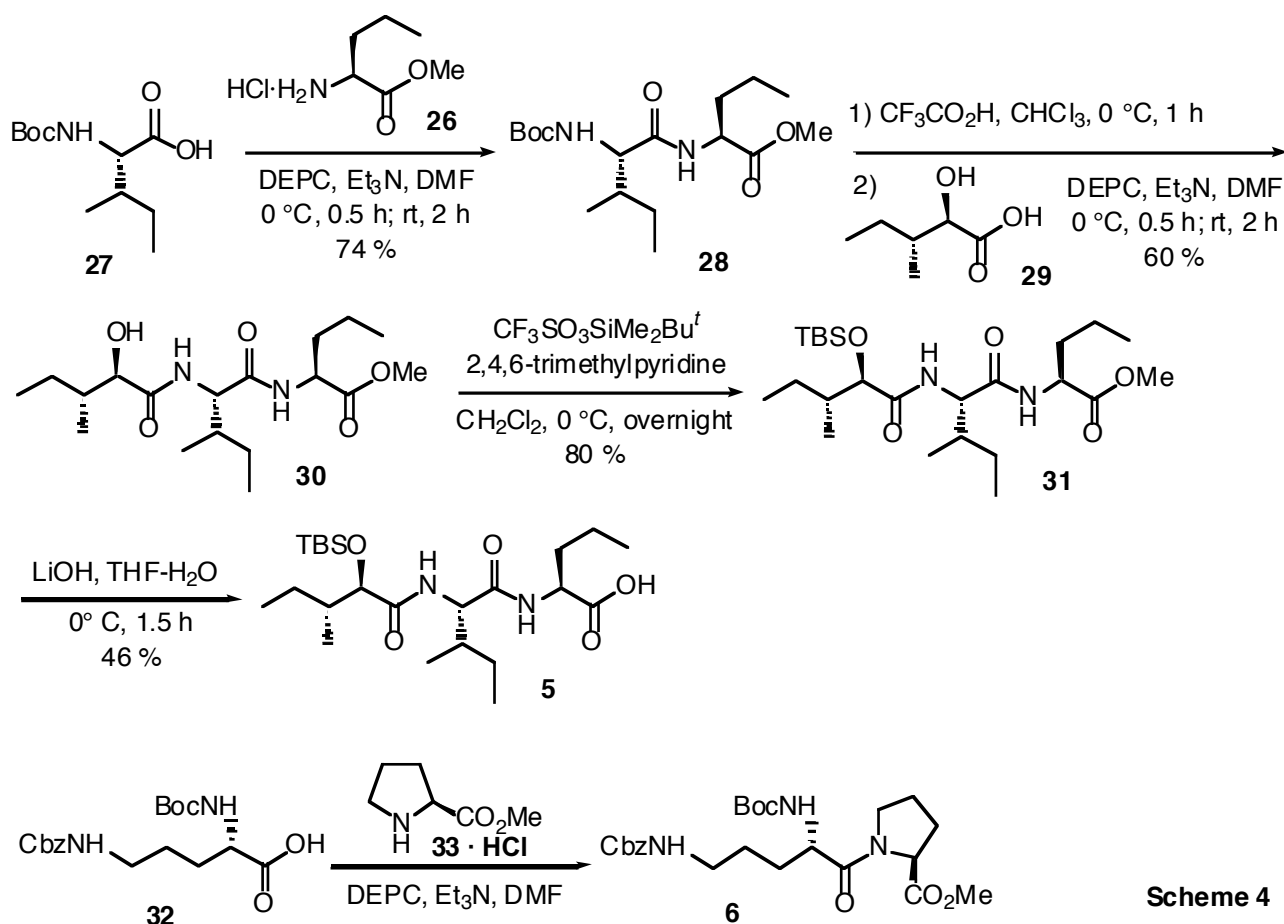
Synthesis of the α -keto- β -amino acid unit (**4**) was straightforwardly accomplished by use of the furyl group as the carboxyl synthon,¹⁴ shown in Scheme 3. Boc-*(S)*-leucine (**21**) was converted to the corresponding Weinreb amide (**22**), which was treated with 2-lithiofuran (**23**), prepared 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 $\text{RuCl}_3 \cdot 3\text{H}_2\text{O} \cdot \text{NaIO}_4$ gave the required α -keto- β -amino acid unit (**4**) as a diastereoisomeric mixture (59:41), $[\alpha]_D^{25} -33.4^\circ$ (c 0.59, MeOH).



Scheme 3

The side chain fragment (**5**) of keramamide B was prepared from norvaline methyl ester hydrochloride (**26**), to which Boc-*(S)*-isoleucine (**27**) and (2*S*,3*S*)-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 (TBSCl-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 , $[\alpha]_D^{25} -37.5^\circ$ (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.



Scheme 4

ACKNOWLEDGEMENTS

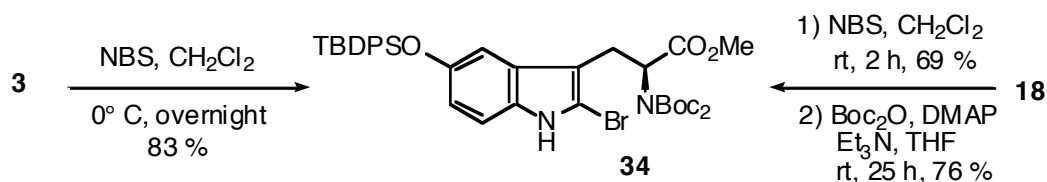
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This paper is dedicated to the memory of the late Dr. Robert John Hughes who died on 16 March, 2003.

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



trifluoroacetyl group of the bromo derivative derived from **18** with base resulted in the decomposition.

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15. The *syn* isomer will be formed in preference of the *anti* one (see ref. 14b and 14f). The ratio was determined by ¹H nmr spectrum: □ (ppm) 1.42 (s, minor) and 1.45 (s, major) for (CH₃)₃C; 2.05 (s, minor) and 2.17 (s, major) for CH₃CO₂.