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# 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, Tanabe-dori, 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[1] 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

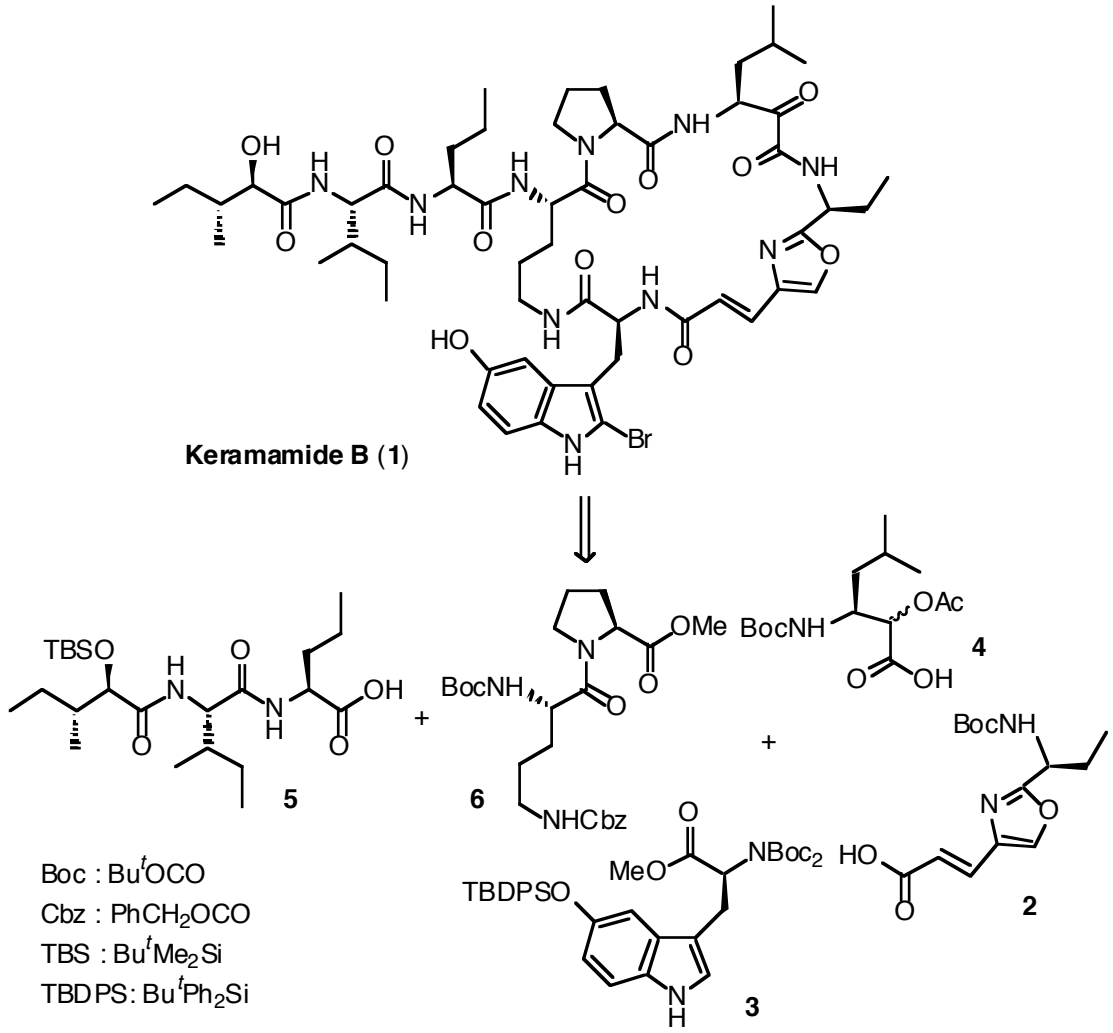
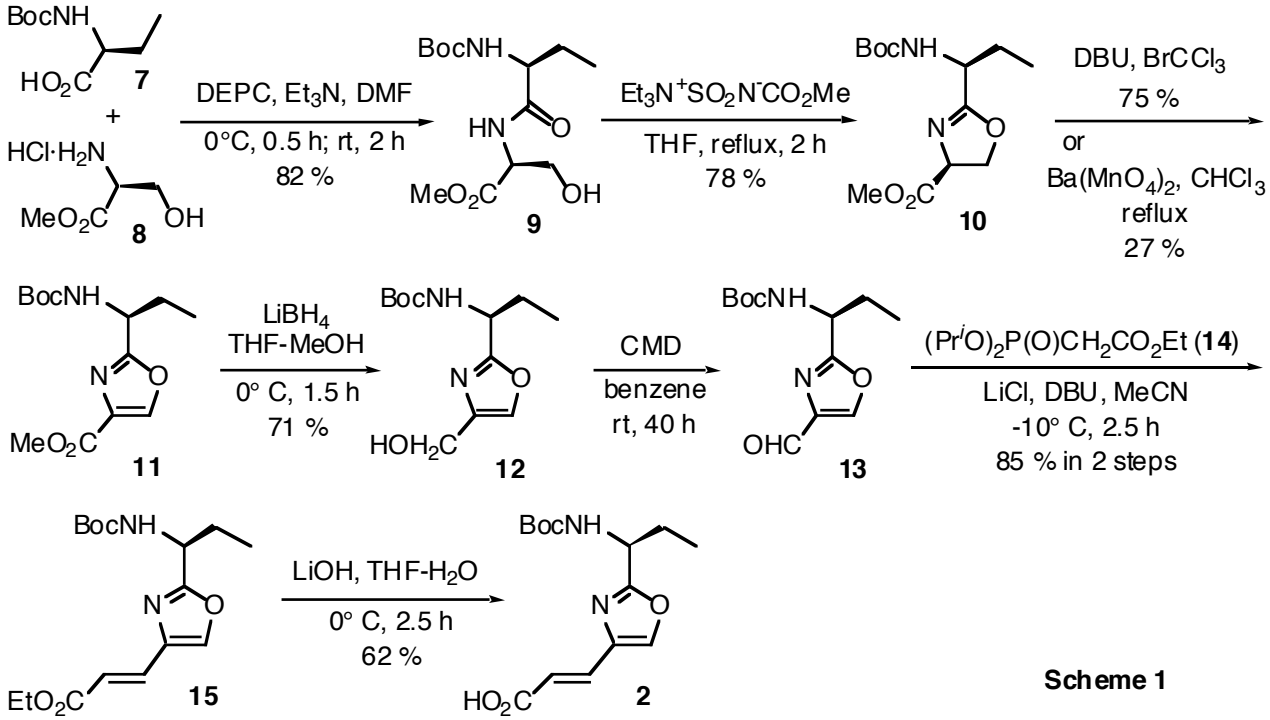


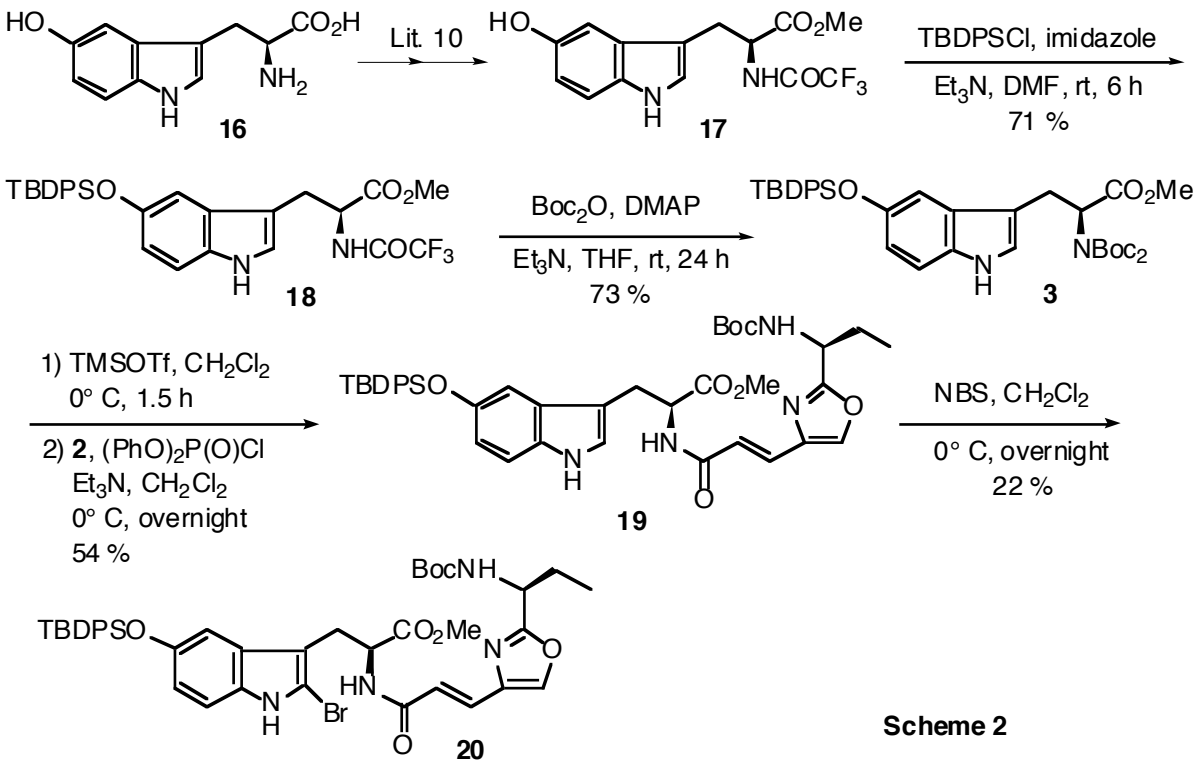

Figure 1 The Structure and Retrosynthesis of Keramamide B (**1**)

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, $[\alpha]_D$ –51.5 ° (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*)-$\alpha,\beta$-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 ° (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

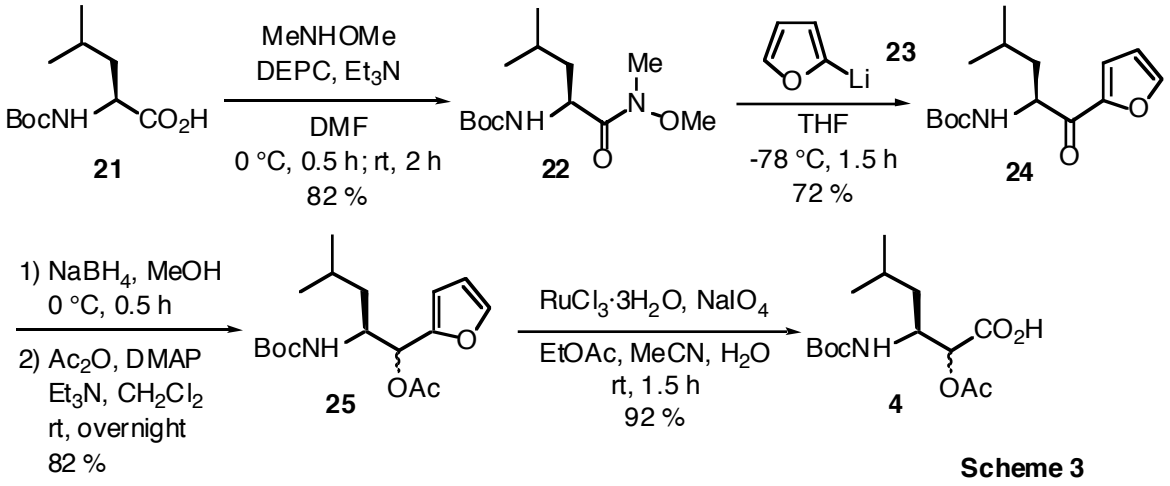



Scheme 2. The direct displacement of the trifluoroacetyl group from the TBDPS derivative (**18**) with the di-*tert*-butyloxycarbonyl (di-Boc) group was smoothly carried out with $Boc_2O$-4-dimethylaminopyridine (DMAP)-triethylamine to give the required 5-hydroxytryptophan fragment (**3**) as an oil, $[\square]_D$ +6.2 ° (c 0.27, $CHCl_3$).



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**).

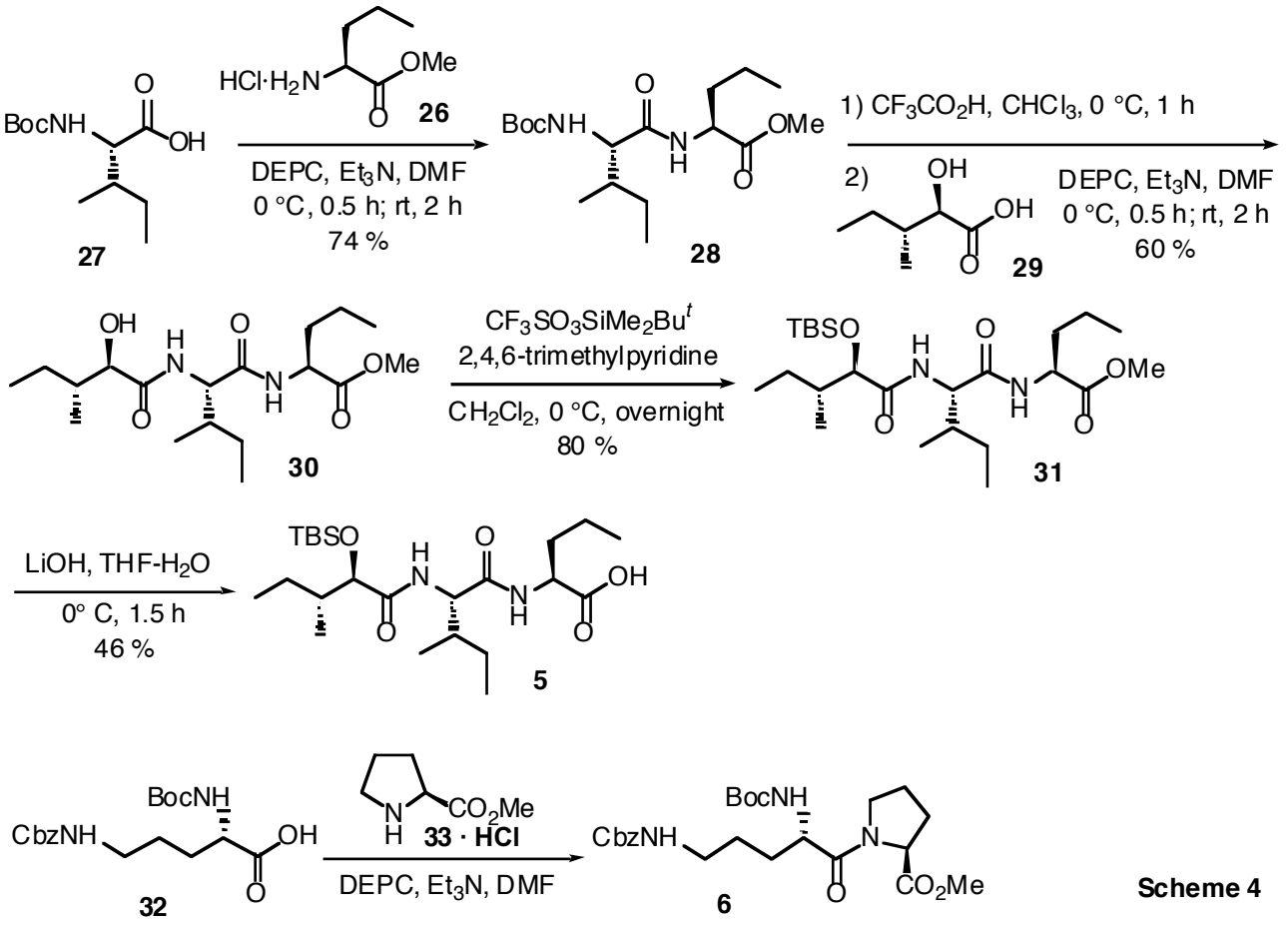
Synthesis of the α-keto-β-amino acid unit (**4**) was straightforwardly accomplished by use of the furyl group as the carboxyl synthon,[14] shown in Scheme 3. Boc-(*S*)-leucine (**21**) was converted to the corresponding Weinreb amide (**22**), which was treated with 2-lithiofuran (**23**), prepared 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 $RuCl_3 \cdot 3H_2O$-$NaIO_4$ gave the required α-keto-β-amino acid unit (**4**) as a diastereoisomeric mixture (59:41), $[\alpha]_D$ –33.4 ° (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, $[\alpha]_D$ –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.




**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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7. This will be the first attempt of the application of $Ba(MnO_4)_2$ to the dehydrogenation of the oxazoline.
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10. The corresponding (*Z*)-isomer was also isolated in 3% yield.
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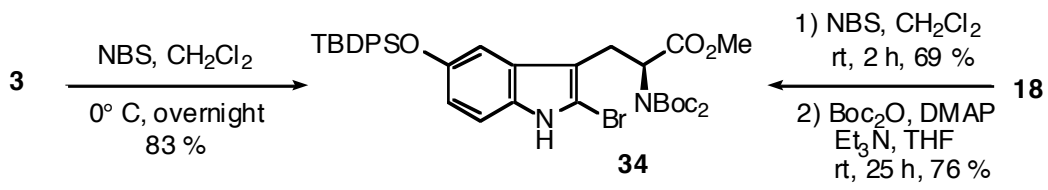
12. In this particular case, the use of DEPC and BopCl (bis(2-oxo-3-oxazolidinylphosphinic chloride) failed to give any coupling product.
13. Incidentally, the di-Boc tryptophan derivative (**3**) and the trifluoroacetyl derivative (**18**) were respectively converted to the bromo-di-Boc derivative (**34**). Initial attempt to cleave the



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

14. (a) T. Shioiri, Y. Hamada, and F. Matsuura, *Pure Applied Chem.*, 1994, **66**, 2151 and references therein. (b) J. Deng, Y. Hamada, T. Shioiri, S. Matsunaga, and N. Fusetani, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1729. (c) T. Shioiri, Y. Hamada, and F. Matsuura, *Tetrahedron*, 1995, **51**, 3939. (d) J. Deng, Y. Hamada, and T. Shioiri, *Tetrahedron Lett.*, 1996, **37**, 2261. (e) S. Sasaki, Y. Hamada, and T. Shioiri, *Tetrahedron Lett.*, 1997, **38**, 3013. (f) H. Fujiwara, K. Tojiki, F. Yokokawa, and T. Shioiri, *Peptide Science 1999*, 2000, 123.
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: $\delta$ (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 $CH_3CO_2$.