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A CONVENIENT SYNTHESIS OF A BROMOTYROSINE DERIVED METABOLITE, PSAMMAPLIN A, FROM PSAMMAPLYSILLA SP.

Osamu Hoshino,* Masatoshi Murakata, and Kohei Yamada
Faculty of Pharmaceutical Sciences, Science University of Tokyo,
12, Ichigaya Funagawara-machi, Shinjuku-ku, Tokyo 162, Japan

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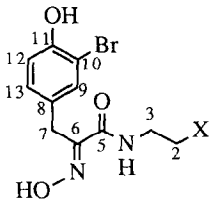
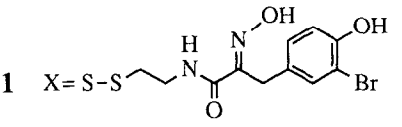
Key words: synthesis; psammaplin A ; bromotyrosine metabolite; marine sponge; *Psammaplysilla sp.*

Abstract: Psammaplin A **1**, one of the bromotyrosine metabolites isolated from marine sponge, Psammaplysilla sp., was synthesized in good yield by direct coupling of phenolic oxime-acid **9** and cystamine using a mixture of DCC and N-hydroxyphthalimide in the presence of Et_3N.

Recently, several bromotyrosine derived metabolites **1-5** have been isolated from *Psammaplysilla sp.*[1] collected in the region of Tonga or from unidentified marine sponge[2] collected in the region of Guam and their structural elucidation as well as evaluation of biological activity has been reported. Among them, psammaplin A **1** has a unique structure, which is a bromotyrosine dimer containing oxime and disulfide moieties. However, synthesis of **1** has been not performed so far. In order to furthermore explore the biological activity caused by the structure having oxime and disulfide groups, developement of the efficient method for synthesis of **1** and its derivatives was of neccesary requirement In this paper, a convenient synthesis of the title compound **1** is described.

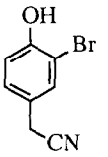


1 X= S-S 

2 X= S-S $NHCO_2Me$

3 X=SCN

4 $X=SO_2NH_2$



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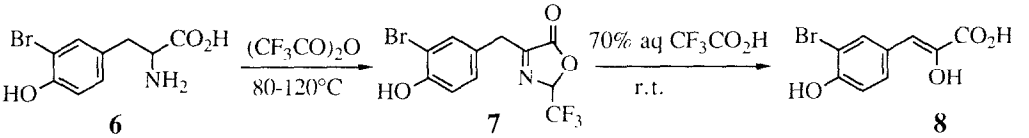
As for a synthetic strategy, direct coupling of phenolic oxime-acid **9** with cystamine was considered, because **9** could be readily prepared from bromotyrosine **6**[3] (Scheme). Therefore, phenolic oxime-acid **9** was synthesized as follows. A mixture of bromotyrosine **6** and $(CF_3CO)_2O$[4] was heated at 80-120°C in sealed tube for 1 h to give the corresponding azlactone **7**[5] in 61% yield. The azlactone **7** was stirred with 70% aqueous CF_3CO_2H[6] at room temperature for 12 h under argon stream to give an arylpyruvic acid **8**[5,7] (enol form) in 97% yield. Treatment of **8** with $HONH_2$·HCl in the usual way gave a phenolic oxime-acid **9**[5,7] in 57% yield.

After several attempts[8] to couple **9** directly with cystamine, a mixture of phenolic oxime-acid **9** (1.0 eq.) and free cystamine (0.5 eq.) in dioxane containing Et_3N (1.0 eq.), DCC (1.0 eq.) and N-hydoxyphthalimide (1.0 eq.) was stirred at room temperature for 12 h to afford, after purification using column chromatography, **1**[5]

in 67% yield, while reaction without Et_3N produced **1** in only 24% yield. Despite using free cystamine, the presence of Et_3N seemed to be essential in the reaction. Spectral data and stereochemistry (*E,E* configuration due to oxime) of the synthetic product were identical with those reported in the literatures.[1,2]



Scheme

Thus, a convenient synthesis of psammaplin A **1** was achieved, which would promise easy supply of the related compounds. Application of the present method to their synthesis and evaluation of biological activity are in progress.

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References and Notes

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4. *Cf* Klein, C.; Schulz, G.; Steglich, W. *Justus Liebigs Ann Chem.* **1983**, 1638; Stein, R.; Englard, S. *Anal. Biochem.* **1981**, *116*, 230; Weygand, F ; Steiglich, W.;Tanner, H. *Justus Liebigs Ann. Chem* **1962**, *658*, 128.
5. **1**: mp 172-174°C (EtOH-H_2O)(lit [2] 172-174°C); ^1H NMR (500 MHz)(CD_3CN) δ 2.77 (4H, t, *J* 6.5, 2 x CH_2S), 3.46 (4H, q, *J* 6.5, 2 x NCH_2), 3.73 (4H, s, 2 x $ArCH_2$), 6.80 (2H, d, *J* 8.2, 2 xArH),7.04(2H,dd, *J* 2.1, 8.2, 2 x ArH), 7.25 (2H, brt, 2 x NH), 7.33 (2H, d, *J* 2.1, 2 x ArH), ^{13}C NMR (125MHz) (DMSO-d_6) δ 27.7 (C_7), 37.0 (C_2), 38.2 (C_3), 108.9 (C_{10}), 116.2 (C_{12}), 128.8 (C_8), 129.2(C_{13}), 132.8(C_9),151.8(C_6), 152.4(C_{11}), 163.3 (C_5); IR (KBr) ν 3600-3000, 1665, 1635, 1540, 1500, 1430, 1025 cm^{-1}, FABMS *m/z* 667, 665, 663. **7**: oil, ^1H NMR ($CDCl_3$) δ 3.90 (2H, d, *J* 2, $ArCH_2$), 5.85-6.32 (1H, m, $CHCF_3$), 6.86(1H, d, *J* 9, ArH), 7.13 (1H, dd, *J* 2, 9, ArH), 7.38 (1H, d, *J* 2, ArH); IR ($CHCl_3$) ν 3530, 3425, 1825, 1495 cm^{-1}; MS *m/z* 339 (M^++1), 337 (M^+-1). **8**. mp 185-187°C (H_2O); ^1H NMR ($CDCl_3$-CD_3OD) δ 6.39 (1H, s, ArCH=), 6.85(1H, d, *J* 8, ArH), 7.51 (1H, dd, *J* 2, 8, ArH), 7.93 (1H, d, *J* 2, ArH); IR (KBr)ν 3550-2800, 1650 cm^{-1}; MS *m/z* 260 (M^++1), 258 (M^+-1) **9**. mp 146-148°C (hexane-AcOEt), ^1H NMR (acetone-d_6) δ3.82 (2H, s, $ArCH_2$), 6.87 (1H, d, *J* 8, ArH), 7.12 (1H, dd, *J* 2, 8, ArH), 7.62 (1H, d, *J* 2, ArH); IR(KBr) ν 3700-2200, 1710 cm^{-1}; MS *m/z* 275 (M^++1), 273 (M^+-1).
6. *Cf* Wilson, M. L.; Coscia, C. J. *J Org Chem.* **1979**, *44*, 301.
7. New compounds described in the text gave satisfactory microanalytical values.
8. Recently, coupling of oxime-acid with amine using a mixture of DCC and N-hydroxysuccinimide has been reported, see Kita, Y; Akai, S; Fujioka, H; Tamura, Y. *Tetrahedron Lett* **1991**, *32*, 6019. However, reaction of phenolic oxime-acid **9** with cystamine in the similar manner was unfruitful.