

Total Synthesis of the Marine Bromotyrosine Alkaloid Moloka'iakitamide

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The first total synthesis of moloka'iakitamide (1), a recently reported bromotyrosine alkaloid from *Pseudoceratina arabica* with oxalamide moiety, was achieved in 7 steps from commercially available tyramine (26% overall).

Key words total synthesis; bromotyrosine alkaloid; marine sponge; moloka'iakitamide; tyramine; 2-chloro-1,3-dimethylimidazolinium chloride

Bromotyrosine alkaloids, well known as one of biologically active substances, possess a wide range of biological activities including anti human immunodeficiency virus 1 (HIV-1) activity,¹⁾ anti methicillin-resistant *Staphylococcus aureus* (MRSA) activity,²⁾ anti multidrug-resistant *Mycobacterium tuberculosis* activity,³⁾ and anti-angiogenic activity.⁴⁾ These are also known as therapeutically important G protein-coupled receptors, the histamine H₂ and H₃ receptors^{5,6)} and the adrenergic α_{1D} and α_{2A} receptors⁶⁾ antagonist. Because of these interesting activities, a number of synthetic studies on these alkaloids have been reported.^{6–16)} Moloka'iakitamide (1)¹⁷⁾ has been isolated from the Red Sea sponge *Pseudoceratina arabica* (Pseudoceratinidae) and shows significant parasympatholytic effects on isolated rabbit heart and jejunum, and weakly antifungal activity, contains one bromotyrosine unit and oxalamide moiety (Fig. 1). In this paper we present the first total synthesis of moloka'iakitamide (1).

Results

As outlined in Chart 1, retrosynthetic analysis of moloka'iakitamide (1) envisaged an alkylation of brominated tyramine (2) with protected amine derivative (3), followed by an amide coupling between oxamic acid (4).

Our synthesis began with commercially available tyramine (5). Introduction of a bromine atom at 5 was carried out by reported method in 2 steps.¹⁵⁾ Di-brominated phenol (6) was treated with iodide (8), which was prepared from *N*-(3-hydroxypropyl)phthalimide (7),¹⁸⁾ in the presence of potassium carbonate (K₂CO₃) and benzyltriethylammonium chloride (BTAC) provided ether (9) in high yields (Chart 2).

After dephthalimidation of 9 with hydrazine monohydrate in ethanol to give amine (10), followed by coupling with oxamic acid (4) using 2-chloro-1,3-dimethylimidazolinium chloride (DMC) as a dehydrating agent,¹⁹⁾ the *N*-Boc-moloka'iakitamide (11) was afforded in moderate yield. Deprotection of *N*-Boc function in 11 with acidic condition, and the residue was made alkaline to give moloka'iakitamide (1)

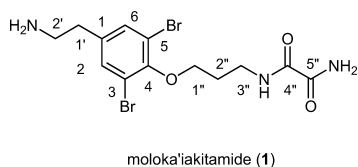


Fig. 1. Structure of Moloka'iakitamide (1), a Bromotyrosine Alkaloid from *Pseudoceratina arabica*

(Chart 3). Thus, the first total synthesis of moloka'iakitamide (1) was completed.

The ¹H- and ¹³C-NMR data of our synthetic moloka'iakitamide (1) were not in complete accordance with those re-

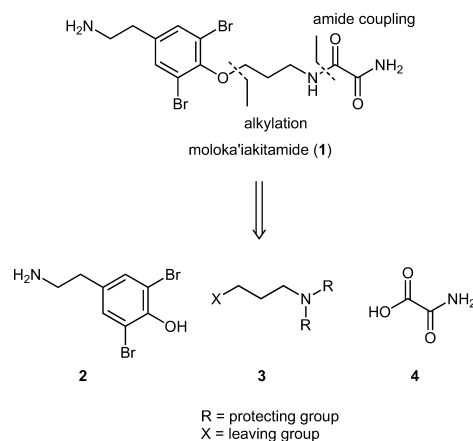
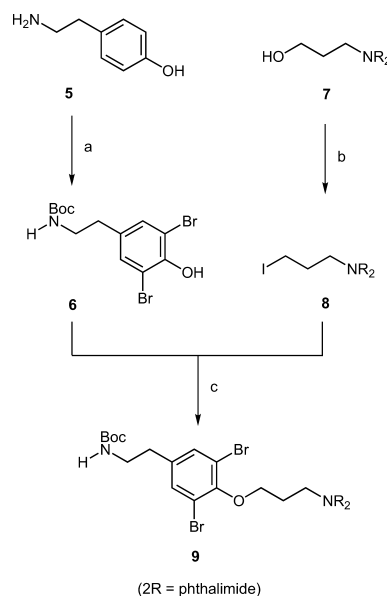


Chart 1. Retrosynthetic Analysis of Moloka'iakitamide (1)



Reagent and conditions: (a) see ref. 15, 63% in 2 steps; (b) see ref. 18, 78%; (c) K₂CO₃, BTAC, CH₃CN, rt, 48 h, quant.

Chart 2. Synthesis of Moloka'iakitamide (1) Part 1: Alkylation of Tyramine Derivative

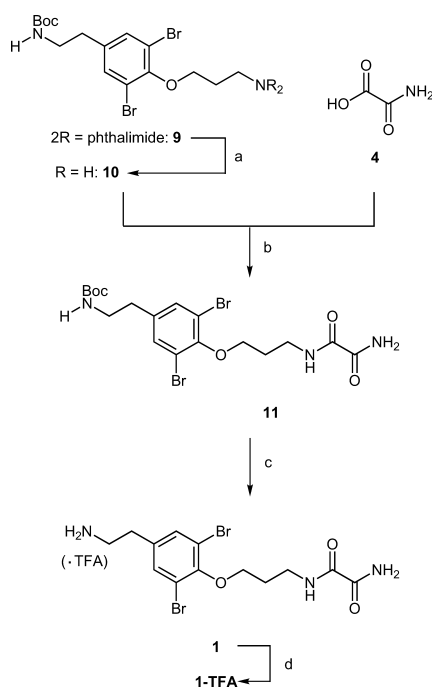
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ported for natural moloka'iakitamide (**1**) by Badr *et al.*¹⁷⁾ On the other hand, moloka'iakitamide trifluoroacetate (**1-TFA**), which was prepared from **1** and trifluoroacetic acid, were spectroscopically identical with reported data (Table 1). Thus, the original report of natural moloka'iakitamide (**1**) by Badr *et al.*,¹⁷⁾ characterized a protonated salt form, such as **1-TFA**, and not the free-base **1**.

In conclusion, we succeeded in the first total synthesis of moloka'iakitamide (**1**) from commercially available tyramine as a starting material. The overall yield was 26% for moloka'iakitamide (**1**) from tyramine (**5**) in 7 steps.

Experimental

All manipulations were carried out under air atmosphere. IR spectra were recorded on a JASCO FT/IR-6300 spectrophotometer; ATR=attenuated total reflectance system. NMR spectra were recorded on a JEOL JNM-ECX400 (400 MHz for ¹H and 100 MHz for ¹³C). Using tetramethylsilane



Reagent and conditions: (a) $\text{H}_2\text{NNH}_2 \cdot \text{H}_2\text{O}$, EtOH, rt, 24 h, 93%; (b) DMC, Et_3N , DMF, rt, 2 h, 61%; (c) CF_3COOH , CH_2Cl_2 , rt, 18 h, then NaOH aq., 72%; (d) CF_3COOH , CH_2Cl_2 , rt, 1 h, quant.

Chart 3. Synthesis of Moloka'iakitamide (**1**) Part 2: Formation of Oxalamide Moiety

(0.00 ppm) in CDCl_3 or residual methanol (CH_3OH) (3.31 ppm) in CD_3OD as internal standard for ¹H-NMR. Using the middle resonance of CDCl_3 (77.0 ppm) or CD_3OD (49.0 ppm) as an internal standard for ¹³C-NMR. ESI-MS were recorded on a JEOL JMS-T100LC mass spectrometer. There used for TLC Silica gel 60 F₂₅₄ plates (Merck No. 5715) and for column chromatography spherical Silica gel 60, particle size 63–210 mm (Kanto Chemical No. 37564-85 for normal, No. 37565-84 for neutral). All reagents and solvents are available from commercial sources and were used as received. 2-Chloro-1,3-dimethylimidazolinium chloride (DMC) was purchased from Tokyo Kasei Co. Inc. Compound **6** and **8** were prepared according to the literature procedure.^{15,18)}

Synthesis of Ether (9) A mixture of phenol (**6**) (410 mg, 1.04 mmol), iodide (**8**) (325 mg, 1.03 mmol), BTAC (24 mg, 0.105 mmol), and K_2CO_3 (290 mg, 2.10 mmol) in CH_3CN (6.0 ml) was stirred at rt for 48 h. The reaction mixture was poured into water, and extracted with AcOEt. The organic layer was washed with water and brine, dried over Na_2SO_4 , and evaporated. The residue was purified by SiO_2 -column chromatography (eluent: toluene/AcOEt=22:1) to give **9** as a colorless amorphous (602 mg, quant.). IR (ATR) ν : 3332, 1775, 1706, 1673 cm^{-1} . ¹H-NMR (400 MHz, CDCl_3) δ : 1.44 (9H, s), 2.27 (2H, m), 2.71 (2H, t, $J=6.7$ Hz), 3.31 (2H, dt, $J=6.7$, 6.6 Hz), 3.99 (2H, t, $J=7.3$ Hz), 4.08 (2H, t, $J=6.2$ Hz), 4.58 (1H, br), 7.31 (2H, s), 7.71 (2H, m), 7.86 (2H, m). ¹³C-NMR (100 MHz, CDCl_3) δ : 28.4 (CH_3), 29.1 (CH_2), 34.9 (CH_2), 35.5 (CH_2), 41.4 (CH_2), 70.9 (CH_2), 79.5 (C), 118.2 (C), 123.2 (CH), 132.1 (C), 132.9 (CH), 133.9 (CH), 137.8 (C), 151.7 (C), 155.7 (C), 168.3 (C). ESI-MS m/z : 603 [$\text{C}_{24}\text{H}_{26}\text{Br}_2^{79}\text{N}_2\text{O}_5 + \text{Na}$]⁺, 605 [$\text{C}_{24}\text{H}_{26}\text{Br}^{79}\text{Br}^{81}\text{N}_2\text{O}_5 + \text{Na}$]⁺, 607 [$\text{C}_{24}\text{H}_{26}\text{Br}_2^{81}\text{N}_2\text{O}_5 + \text{Na}$]⁺. HR-ESI-MS m/z : 605.00907 (Calcd for [$\text{C}_{24}\text{H}_{26}\text{Br}^{79}\text{Br}^{81}\text{N}_2\text{O}_5 + \text{Na}$]⁺, 605.00857).

Synthesis of Amine (10) To a solution of ether (**9**) (140 mg, 0.24 mmol) in EtOH (1.5 ml) hydrazine monohydrate (0.40 g) was added, and the mixture was stirred at rt for 24 h. The reaction mixture was diluted with AcOEt, washed with water and brine, dried over K_2CO_3 , and evaporated to yield **10** as a pale brown oil (101 mg, 93%). IR (ATR) ν : 3365, 1697 cm^{-1} . ¹H-NMR (400 MHz, CD_3OD) δ : 1.40 (9H, s), 1.99 (2H, m), 2.69 (2H, t, $J=6.9$ Hz), 2.95 (2H, t, $J=6.9$ Hz), 3.22 (2H, t, $J=6.9$ Hz), 4.03 (2H, t, $J=6.0$ Hz), 7.42 (2H, s). ¹³C-NMR (100 MHz, CD_3OD) δ : 28.8 (CH_3), 33.8 (CH_2), 35.8 (CH_2), 39.9 (CH_2), 42.4 (CH_2), 72.5 (CH_2), 80.0 (C), 118.8 (C), 134.6 (CH), 140.0 (C), 152.7 (C), 158.3 (C). ESI-MS m/z : 451 [$\text{C}_{16}\text{H}_{24}\text{Br}_2^{79}\text{N}_2\text{O}_3 + \text{H}$]⁺, 453 [$\text{C}_{16}\text{H}_{24}\text{Br}^{79}\text{Br}^{81}\text{N}_2\text{O}_3 + \text{H}$]⁺, 455 [$\text{C}_{16}\text{H}_{24}\text{Br}_2^{81}\text{N}_2\text{O}_3 + \text{H}$]⁺. HR-ESI-MS m/z : 451.02582 (Calcd for [$\text{C}_{16}\text{H}_{24}\text{Br}_2^{79}\text{N}_2\text{O}_3 + \text{H}$]⁺, 451.02319).

Synthesis of N-Boc-moloka'iakitamide (11) To a solution of amine (**10**) (80 mg, 0.18 mmol), oxamic acid (**4**) (18 mg, 0.20 mmol), and Et_3N (0.10 ml, 0.72 mmol) in N,N -dimethylformamide (DMF) (1.5 ml) 2-chloro-1,3-dimethylimidazolinium chloride (DMC, 34 mg, 0.20 mmol) was added, and the mixture was stirred at rt for 2 h. The reaction mixture was poured into water, and extracted with AcOEt. The organic layer was washed with water and brine, dried over Na_2SO_4 , and evaporated. The residue was purified by SiO_2 -column chromatography (eluent: $\text{CHCl}_3/\text{AcOEt}=7:2$) to give **11** as a colorless amorphous (56 mg, 61%). IR (ATR) ν : 3381, 3356, 3311, 3222, 1681, 1652 cm^{-1} . ¹H-NMR (400 MHz, CDCl_3) δ : 1.44 (9H, s), 2.11 (2H, m), 2.72 (2H, t, $J=6.9$ Hz), 3.33 (2H, dt, $J=6.7$, 6.4 Hz), 3.68 (2H, dt, $J=6.5$, 6.4 Hz), 4.07 (2H, t, $J=6.8$ Hz), 4.57 (1H, br), 5.59 (1H, br), 7.32 (1H, br), 7.34 (2H, s), 7.85 (1H, br). ¹³C-NMR (100 MHz, CDCl_3) δ : 28.3

Table 1. ¹H- and ¹³C-NMR Spectroscopic Data for Moloka'iakitamide (**1**)^{a)}

Position	Synthetic 1		1-TFA		Natural 1 ^{b)}	
	δ_{H} (J in Hz)	δ_{C}	δ_{H} (J in Hz)	δ_{C}	δ_{H} (J in Hz)	δ_{C}
1		139.2		136.8		137.5
2, 6	7.43 s	132.9	7.57 s	132.9	7.57 s	132.9
3, 5		117.7		118.0		118.1
4		151.3		152.0		152.1
1'	2.67 t (7.1)	36.8	2.95 t (7.4)	31.7	2.93 t (7.5)	31.7
2'	2.82 t (7.1)	42.6	3.21 t (7.4)	39.9	3.19 t (7.5)	40.0
1''	4.02 t (6.0)	70.8	4.09 t (6.0)	70.7	4.10 t (6.5)	70.7
2''	2.08 m	29.1	2.15 m	28.9	2.14 quin. (6.5)	28.9
3''	3.55 t (6.9)	37.4	3.61 t (6.8)	36.6	3.60 t (6.5)	36.5
4''		160.5		160.4		160.4
5''		162.7		162.5		162.5

a) The NMR data were obtained at 400/100 MHz for ¹H/¹³C. b) Reported by Badr *et al.*¹⁷⁾

(CH₂), 29.1 (CH₂), 34.8 (CH₂), 37.1 (CH₂), 41.4 (CH₂), 70.5 (CH₂), 79.5 (C), 118.0 (C), 132.9 (CH), 138.0 (C), 151.2 (C), 155.9 (C), 159.5 (C), 161.9 (C). ESI-MS *m/z*: 544 [C₁₈H₂₅Br⁷⁹N₃O₅+Na]⁺, 546 [C₁₈H₂₅Br⁷⁹Br⁸¹N₃O₅+Na]⁺, 548 [C₁₈H₂₅Br⁸¹N₃O₅+Na]⁺. HR-ESI-MS *m/z*: 546.00479 (Calcd for [C₁₈H₂₅Br⁷⁹Br⁸¹N₃O₅+Na]⁺, 546.00382).

Synthesis of Moloka'iakitamide (1) To a solution of *N*-Boc-moloka'iakitamide (**11**) (56 mg, 0.11 mmol) in CH₂Cl₂ (1.0 ml) trifluoroacetic acid (0.1 ml) was added, and the mixture was stirred at rt for 18 h. The reaction mixture was poured into water, and washed with Et₂O. The aqueous layer was alkalized with 20% NaOH aq. and extracted with CHCl₃. The organic layer was washed with water and brine, dried over K₂CO₃, and evaporated to afford **1** as a colorless amorphous (32 mg, 72%). IR (ATR) *v*: 3367, 3341, 3301, 1641 cm⁻¹. ¹H-NMR (400 MHz, CD₃OD) δ : 2.08 (2H, m), 2.67 (2H, t, *J*=7.1 Hz), 2.82 (2H, t, *J*=7.1 Hz), 3.55 (2H, t, *J*=6.9 Hz), 4.02 (2H, t, *J*=6.0 Hz), 7.43 (2H, s). ¹³C-NMR (100 MHz, CD₃OD) δ : 29.1 (CH₂), 36.8 (CH₂), 37.4 (CH₂), 42.6 (CH₂), 70.8 (CH₂), 117.7 (C), 132.9 (CH), 139.2 (C), 151.3 (C), 160.5 (C), 162.7 (C). ESI-MS *m/z*: 422 [C₁₃H₁₇Br⁷⁹N₃O₃+H]⁺, 424 [C₁₃H₁₇Br⁷⁹Br⁸¹N₃O₃+H]⁺, 426 [C₁₃H₁₇Br⁸¹N₃O₃+H]⁺. HR-ESI-MS *m/z*: 423.96916 (Calcd for [C₁₃H₁₇Br⁷⁹Br⁸¹N₃O₃+H]⁺, 423.96945).

Synthesis of Moloka'iakitamide Trifluoroacetate (1-TFA) To a solution of moloka'iakitamide (**1**) (30 mg, 0.071 mmol) in CH₂Cl₂ (1.0 ml) trifluoroacetic acid (0.1 ml) was added, and the mixture was stirred at rt for 1 h. The reaction mixture was evaporated to yield **1-TFA** as a colorless amorphous (39 mg, quant.). IR (ATR) *v*: 3392, 3276, 1682, 1652 cm⁻¹. ¹H-NMR (400 MHz, CD₃OD) δ : 2.15 (2H, m), 2.95 (2H, t, *J*=7.4 Hz), 3.21 (2H, t, *J*=7.4 Hz), 3.61 (2H, t, *J*=6.8 Hz), 4.09 (2H, t, *J*=6.0 Hz), 7.57 (2H, s). ¹³C-NMR (100 MHz, CD₃OD) δ : 28.9 (CH₂), 31.7 (CH₂), 36.6 (CH₂), 39.9 (CH₂), 70.7 (CH₂), 118.0 (C), 132.9 (CH), 135.8 (C), 152.0 (C), 160.4 (C), 162.5 (C). ESI-MS *m/z*: 422 [C₁₃H₁₇Br⁷⁹N₃O₃+H]⁺, 424 [C₁₃H₁₇Br⁷⁹Br⁸¹N₃O₃+H]⁺, 426 [C₁₃H₁₇Br⁸¹N₃O₃+H]⁺, 444 [C₁₃H₁₇Br⁷⁹N₃O₃+Na]⁺, 446 [C₁₃H₁₇Br⁷⁹Br⁸¹N₃O₃+Na]⁺, 448 [C₁₃H₁₇Br⁸¹N₃O₃+Na]⁺. HR-ESI-MS *m/z*: 445.95558 (Calcd for [C₁₃H₁₇Br⁷⁹Br⁸¹N₃O₃+Na]⁺, 445.95139).

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