The First Total Synthesis of Racemic Hydroxymoloka'iamine

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Z. Naturforsch. **2009**, *64b,* 879 – 882;
received April 4, 2009

The first total synthesis of racemic hydroxymoloka'iamine, a new brominated metabolite isolated from Red Sea sponge *Pseudoceratna arabica*, was achieved in a high-yield reaction sequence.

Key words: Total Synthesis, Natural Product, Bromination

Introduction

The enormous promise that the sea holds to provide potential lead pharmaceuticals has attracted great interest from the scientific community in the recent years. In an effort to isolate bio-active ingredients from marine sources, investigation of the Red Sea sponge *Pseudoceratna arabica* has led to the isolation and structure elucidation of the new brominated metabolite hydroxymoloka'iamine (**1**) [1]. This compound features a bromotyramine skeleton and has structural resemblance with the known metabolite moloka'iamine [2]. The evaluation of the cytotoxic activity against human colon tumor cells (HCT-116) of **1** has demonstrated that it was not toxic at a test dose of 10 μg mL^{-1}, and such discoveries have important implications for further biological investigations of this class of compounds [1]. As a part of our ongoing research in the total synthesis of bio-active natural products [3, 4], we now wish to report a facile synthesis of racemic hydroxymoloka'iamine (**1**).

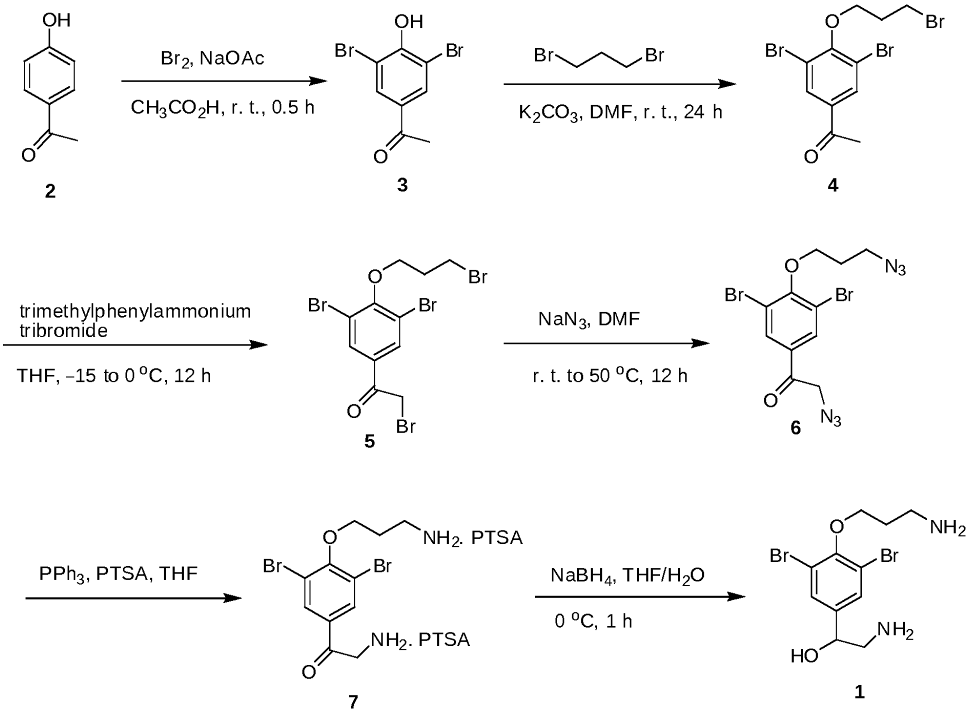
Results and Discussion

The synthesis of hydroxylmoloka'iamine commenced with the bromination of the 4-hydroxyacetophenone with bromine in acetic acid to get the known hydroxyacetophenone dibromide **3** in 93 % yield [5]. The use of sodium acetate as base proved to be effective to improve the yield. The O-alkylation of the latter with an excess of 1,3-dibromopropane in DMF using potassium carbonate as base afforded the desired tribromide **4** in very high yield (97 %). The subsequent reaction of **4** with a stoichiometric amount of trimethylphenylammonium tribromide in THF at 0 °C to r. t. was unclean and gave the desired α-bromoketone **5** in 60 % yield along with a significant amount of unwanted side products. However, the problem was overcome by the addition of trimethylphenylammonium tribromide in portions to a solution of tribromide **4** in THF at -15 °C and aging the reaction overnight at 0 °C, which rendered the desired α-bromoketone **5** in high yield (90 %). At this stage we focused on displacement of the two bromo substituents with azide. To this end, sodium azide was added to a stirred solution of α-bromoketone **5** in a mixture of ethanol and THF (4 : 1). Stirring the mixture first at r. t. followed by heating at 60 °C afforded a low yield of the desired diazide **6** (23 %) along with a few side products which made column chromatography purifications very tedious. In a second attempt the reaction was tried in DMF while the mixture was stirred at 50 °C overnight which gave the desired product **6** in an acceptable yield (49 %). The reduction of the azido group to the amine with triphenylphosphine followed by crystallization to the PTSA salt yielded the aminoketone **7** in 70 % yield [6], which in turn was subjected to reduction with sodium borohydride at 0 °C in a mixture of THF and water to afford the target hydroxylmoloka'iamine in an over all yield of 14 % from **5** (Scheme 1).

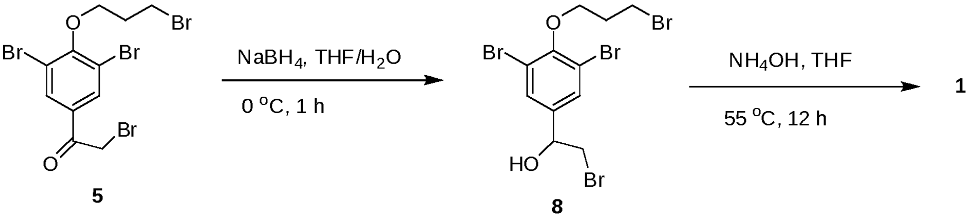
Because of the difficulty in purification by the column chromatography of the diazide **6**, coupled with the low overall yield in the synthesis of **1** from **5**, we envisioned that reducing the α-bromoketone **5** to the α-bromoalcohol, and condensation with ammonia, should give the desired target compound **1**. Thus, ketone **5** was reduced with sodium borohydride at 0 °C in a mixture of THF and water to get the α-bromoalcohol **8**, which was treated with an excess of ammonium hydroxide at 55 °C for 12 h to afford the target compound **1** in an excellent overall yield (54 % from **5**) (Scheme 2). The spectral data of our synthetic **1** coincided with those of the natural material [1].

Conclusion

In conclusion we have accomplished the first synthesis of racemic hydroxylmoloka'iamine (**1**) in an overall high-yield reaction sequence.



Scheme 1. Synthesis of hydroxylmoloka'iamine (**1**) *via* the diazide intermediate **6**.



Scheme 2. Synthesis of hydroxylmoloka'iamine (**1**) *via* the bromoalcohol intermediate **8**.

Experimental Section

*1-(3,5-Dibromo-4-hydroxyphenyl)ethanone (**3**)*

Bromine (3.02 g, 19 mmol) in acetic acid (3 mL) was added dropwise to a mixture of 4-hydroxyacetophenone (1.22 g, 9 mmol) and sodium acetate (2.29 g, 27.9 mmol) in acetic acid (20 mL) at r. t. over 10 min. The reaction mixture was stirred for 0.5 h at r. t., H_2O (20 mL) was added, and the solid was filtered, washed with H_2O and dried under high vacuum to afford the product as a brown solid (2.46 g, 93 %). The physical and spectral data of **3** were identical with those of the literature [5].

*1-(3,5-Dibromo-4(3-bromopropoxy)phenyl)ethanone (**4**)*

To a solution of compound **3** (2 g, 6.8 mmol) in DMF (20 mL) at 5 to 10 °C was added potassium carbonate (1.87 g, 13.6 mmol) in portions, followed by the addition of 1,3-dibromopropane (5.49 g, 27.2 mmol), and the mixture was stirred at r. t. for 24 h. The reaction mixture was taken in ethyl acetate (100 mL) and washed successively with H_2O (25 mL), 1 N HCl (2 × 20 mL), sat. $NaHCO_3$ (20 mL), and brine (15 mL), and dried over sodium sulfate and evaporated. Column chromatography of the light-yellow oily material, eluting with ethyl acetate : hexanes (1 : 9) and then changing to (2 : 8) gave the product as a light-orange thick oil (2.74 g, 97 %). – IR (neat): ν = 3030, 2890, 1692, 1535, 1460, 1365, 1265, 1180, 1010, 910, 735, 630 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 2.36 (m, 2H, 2″-H), 2.57 (s, 3 H, $COCH_3$), 3.73 (t, 2 H, J = 6.7 Hz, 3″-H), 4.20 (t, 2 H, J = 5.8 Hz, 1″-H), 8.10 (s, 2 H, 2′-H, 6′-H). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 26.8 ($COCH_3$), 29.7 (2″-C), 33.3 (3″-C), 71.0 (1″-C), 118.4 (3′-C, 5′-C), 132.9 (2′-C, 6′-C), 135.5 (1′-C), 157.0 (4′-C), 194.2 (CO). – MS

(70 eV): *m/z* (%) = 414 (24), 317 (14), 290 (10), 279 (100). – $C_{11}H_{11}Br_3O_2$ (414.92): calcd. C 31.84, H 2.67; found C 31.81, H 2.70.

*2-Bromo-1-(3,5-dibromo-4-(3-bromopropoxy)phenyl)-ethanone (**5**)*

To a solution of compound **4** (2 g, 4.82 mmol) in THF (30 mL) at −15 °C was added trimethylphenylammonium tribromide (1.9 g, 5.1 mmol), and the mixture was stirred at 0 °C for 12 h. The solid was filtered, and to the filtrate was added ethyl acetate (50 mL). The mixture was washed successively with H_2O (20 mL) and brine (15 mL), and the organic layer was dried over Na_2SO_4 and evaporated to leave a dark-orange oil, which was resolved on a silica column eluting with ethyl acetate : hexanes (1 : 9) to get the product as an off-white crystalline solid (2.14 g, 90 %). M. p. 67 – 68 °C. – IR (neat): ν = 3050, 2937, 2890, 1698, 1540, 1451, 1372, 1280, 1177, 1004, 907, 853, 734, 630 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.43 (m, 2 H, 2″-H), 3.73 (t, 2 H, *J* = 6.4 Hz, 3″-H), 4.22 (t, 2 H, *J* = 5.5 Hz, 1″-H), 4.38 (s, 2 H, 2-H), 8.12 (s, 2 H, 2′-H, H-6′-H). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 29.6 (2″-C), 30.0 (2-C), 33.2 (3″-C), 71.1 (1″-C), 118.9 (3′-C, 5′-C), 131.8 (2′-C, 6′-C), 135.4 (1′-C), 157.3 (4′-C), 188.0 (CO). – MS (70 eV): *m/z* (%) = 494 (20), 399 (26), 372 (9), 279 (100), 121 (20). – $C_{11}H_{10}Br_4O_2$ (493.81): calcd. C 26.75, H 2.04; found C 26.73, H 2.06.

*2-Azido-1-(4-(3-azidopropoxy)-3,5-dibromophenyl)-ethanone (**6**)*

To a solution of compound **5** (1 g, 2.02 mmol) in DMF (15 mL) was added sodium azide (0.27 g, 4.14 mmol) in one portion, and the mixture was heated at 50 °C for 12 h. After addition of H_2O (10 mL), the reaction mixture was extracted with ethyl acetate (25 mL). The organic layer was washed successively with 1 N HCl (2 ×,10 mL), sat. $NaHCO_3$ (15 mL) and brine (10 mL), dried over sodium sulfate and evaporated. Column chromatography of the dark-orange oily material eluting with ethyl acetate : hexanes (1 : 9) gave the product as a dark-orange thick oil (0.41 g, 49 %). – IR (neat): ν = 3073, 2954, 2197, 2104, 1698, 1580, 1539, 1452, 1379, 1250, 1000, 919, 737 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.45 (m, 2 H, 2″-H), 3.83 (t, 2 H, *J* = 6.3 Hz, 3″-H), 4.23 (t, 2 H, *J* = 5.6 Hz, 1″-H), 4.49 (s, 2 H, 2-H), 8.05 (s, 2 H, 2′-H, 6′-H). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 30.0 (2″-C), 48.7 (3″-C), 54.8 (2-C), 71.2 (1″-C), 118.8 (3′-C, 5′-C), 131.9 (2′-C, 6′-C), 135.4 (1′-C), 157.4 (4′-C), 195.2 (CO). – MS (70 eV): *m/z* (%) = 418 (3), 362 (18), 279 (100). – $C_{11}H_{10}Br_2N_6O_2$ (418.04): calcd. C 31.60, H 2.41, N 20.10; found C 31.56, H 2.46, N 20.03.

*2-Amino-1-(4-(3-aminopropoxy)-3,5-dibromophenyl)-ethanone p-toluenesulfonic acid salt (**7**)*

To a solution of compound **6** (0.35 g, 0.84 mmol) in THF (10 mL) was added triphenylphosphine (0.22 g, 0.84 mmol), and when the solution was homogeneous, PTSA (0.8 g, 4.2 mmol) was added in small portions. The reaction mixture was stirred for 24 h. The resulting solid was filtered and allowed to dry under vacuum to get the product as an off-white solid (0.42 g, 70 %). M. p. 264 – 265 °C. – IR (neat): ν = 3070, 2880, 2010, 1690, 1590, 1545, 1451, 1370, 1270, 1170, 1003, 910, 740 cm^{-1}. – ^{1}HNMR (500 MHz, [D_6]DMSO): δ = 2.26 (s, 3 H, CH_3), 2.27 (s, 3 H, CH_3), 2.44 (m, 2 H, 2″-H), 3.88 (t, 2 H, *J* = 6.4 Hz, 3″-H), 4.22 (t, 2 H, *J* = 5.5 Hz, 1″-H), 4.52 (s, 2 H, 2-H), 7.12 (d, 4 H, *J* = 8.0 Hz, aromatic-H), 7.48 (d, 4 H, *J* = 8.0 Hz, aromatic-H), 8.06 (s, 2 H, H-2′, 6′-H), 8.10 (broad s, 3 H), 8.14 (broad s, 3 H). – ^{13}C NMR (125.7 MHz, [D_6]DMSO): δ = 20.7 (CH_3), 29.9 (2″-C), 45.1 (3″-C), 46.2 (2-C), 71.1 (1″-C), 118.8 (3′-C, 5′-C), 125.6 (aromatic-C), 128.2 (aromatic-C), 131.8 (2′-C, 6′-C), 135.5 (aromatic-C), 137.8 (1′-C), 144.9 (aromatic-C), 157.3 (4′-C), 191.4 (CO). – MS (70 eV): *m/z* (%) = 366 (12), 308 (16), 279 (100).

*2-Bromo-1-(3,5-dibromo-4-(3-bromopropoxy)phenyl)-ethanol (**8**)*

To a solution of compound **5** (0.2 g, 0.40 mmol) in a mixture of THF and H_2O (4 : 2, 6 mL) at 0 °C was added sodium borohydride (0.019 g, 0.5 mmol) and after being stirred for 0.5 h, H_2O (5 mL) was added. After extraction of the mixture with ethyl acetate (2 × 15 mL), the organic layer was washed with brine (5 mL), dried over sodium sulfate and evaporated. Column chromatography of the colorless oily material eluting with ethyl acetate : hexanes (1 : 9) gave the product as a colorless thick oil (0.18 g, 90 %). – IR (neat): ν = 3325, 3030, 2937, 2890, 1545, 1450, 1370, 1281, 1175, 1003, 905, 853, 735, 630 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.40 (m, 2 H, 2″-H), 2.69 (d, 1 H, *J* = 3.1 Hz, OH), 3.48 (dd, 1 H, *J* = 10.6, 8.8 Hz, 2-H), 3.60 (dd, 1 H, *J* = 10.3, 3.3 Hz, 2-H), 3.73 (t, 2 H, *J* = 6.4 Hz, 3″-H), 4.13 (t, 2 H, *J* = 5.8 Hz, 1″-H), 4.86 (dd, 1 H, *J* = 8.8, 3.3 Hz, 1-H), 7.55 (s, 2 H, 2′-H, 6′-H). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 29.9 (2″-C), 33.4 (3″-C), 39.5 (2-C), 70.8 (1″-C), 72.1 (1-C), 118.5 (3′-C, 5′-C), 130.3 (2′-C, 6′-C), 138.8 (1′-C), 152.8 (4′-C). – MS (70 eV): *m/z* (%) = 496 (8), 416 (11), 398 (19), 335 (9), 296 (18), 278 (100), 215 (50). – $C_{11}H_{12}Br_4O_2$ (495.83): calcd. C 26.65, H 2.44; found C 26.63, H 2.46.

*Hydroxylmoloka'iamine (**1**)*

*From compound **7**:* Sodium borohydride (0.130 g, 3.36 mmol) was added to a solution of compound **7** (0.4 g, 0.56 mmol) in a mixture of THF and H_2O (4 : 2, 6 mL) at 0 °C, and the reaction mixture was stirred for 1 h at this temperature. The pH of the mixture was adjusted to 9 by 1 N NaOH, the mixture was extracted with ethyl acetate (2 × 10 mL), and the organic layer was washed with brine (5 mL), dried over sodium sulfate and evaporated to get the product as a colorless thick oil, which was purified on a silica column. Elution with MeOH : $CHCl_3$ (5 : 95), then changing to 25 : 75, gave the product as a white solid (0.082 g, 40 %). The physical and spectral data of our synthetic **1** were identical with those of the natural material [1].

From compound 8: To a solution of compound **8** (0.16 g, 0.32 mmol) in THF (1 mL) was added aqueous ammonium hydroxide (3 mL). The reaction mixture was stirred at 55 °C for 12 h, then extracted with ethyl acetate (2 × 10 mL), and the organic layer was washed with brine (5 mL), dried over sodium sulfate, evaporated, and purified on a column as described for compound **7** to get the desired **1** (0.07 g, 60 %).

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Druck: AZ Druck und Datentechnik GmbH, Kempten