Efficient Preparation of Alkaloids Polycarpine and Polycarpaurines A and C

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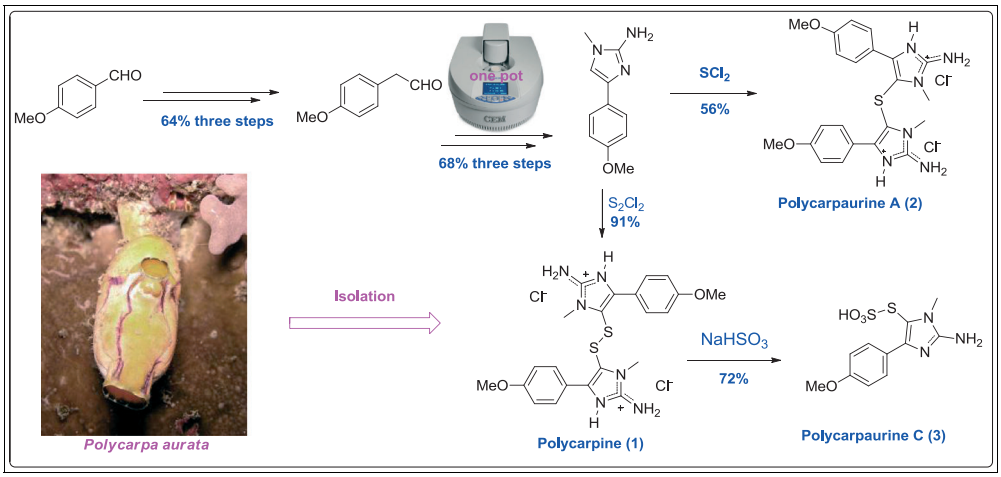


An efficient method for the preparation of alkaloids polycarpine and polycarpaurines A and C via microwave-assisted three-step one-pot reaction as the key step has been developed. This is the first report about the synthesis of polycarpaurines A and C. Starting from commercially available *p*-methoxy benzaldehyde, polycarpine and polycarpaurine A were obtained over seven steps with 40 and 24 % overall yield, respectively. Polycarpine could convert to polycarpaurine C in 72% yield in the presence of $NaHSO_3$. The structure of polycarpine and polycarpaurines A and C was confirmed by ^{1}H NMR, ^{13}C NMR, and HRMS.

INTRODUCTION

Marine natural products are important lead compounds for the development of novel drugs. The natural product-based drugs can sometimes be specific to a target species and have unique mode of action with low toxicity in mammalian [1–3]. Many interesting sulfur-containing marine alkaloids have been isolated from ascidians [4]. These compounds displayed various biological activities, such as cytotoxicity [5,6], anti-HIV activity [7], immunosuppressive activity [8], antibacterial activity [9], antifungal activity [10], and enzyme inhibitory activity [11,12]. One of such promising alkaloids is polycarpine (**1**, Fig. 1), isolated from the ascidian *Polycarpa aurata* collected at Flinders Reef (Coral Sea) [13]. This compound was previously found to be active in vitro and in vivo against a wide range of human and murine tumors [14,15]. Polycarpaurines A and C (**2** and **3**, Fig. 1), isolated from an Indonesian ascidian *P. aurata*, are another two interesting sulfur-containing 2-aminoimidazole alkaloids [15].

Polycarpine (**1**) is attracting considerable interest, not only because of its high biological activity but also as the first representative of a new structural type of alkaloid from an ascidian. In spite of a wide variety of metabolites isolated earlier from different ascidians, compounds containing 2-aminoimidazole cycles linked by a disulfide bridge were not among the sulfur-containing metabolites.

As a continuation of the previous work for discovery of bioactive compounds from nature product, polycarpine (**1**) and polycarpaurines A (**2**) and C (**3**) were selected as interesting lead compounds. Only one route for the synthesis of polycarpine (**1**) has been reported till now [14]. However, the given report had no experiment details. Although a high yield was given, it is difficult to repeat. There is no report about the synthesis of polycarpaurines A (**2**) and C (**3**) as far as we know.

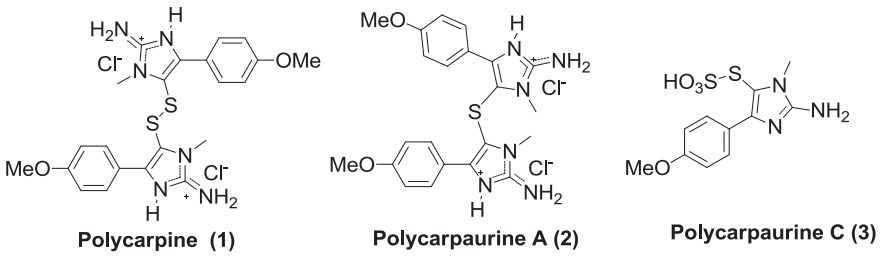


Figure 1. Structures of alkaloids polycarpine (**1**), polycarpaurines A (**2**) and C (**3**).

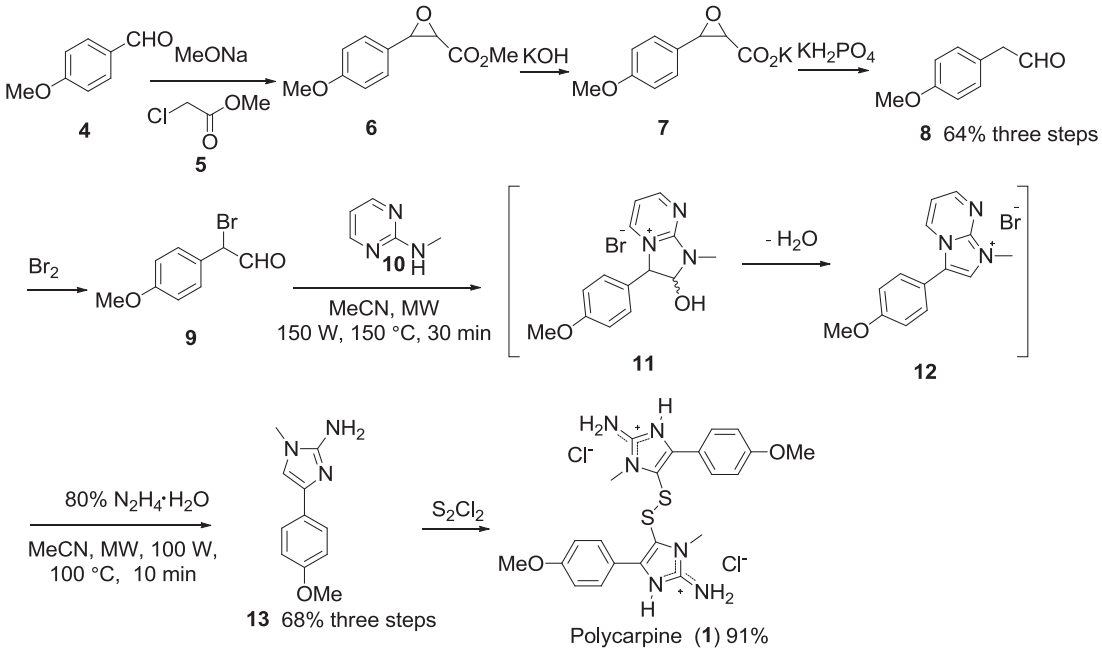
Using microwave irradiation to carry out reactions is a growing popularity and hence becoming an attractive method for chemical synthesis [16–20]. It involves neat reactants to be exposed to microwave irradiation so as to acquire greater selectivity and achieve high yields within a short reaction time and with ease in experimentation.

Here, we report the efficient method for the preparation of alkaloids polycarpine and polycarpaurines A and C via microwave assisted three-step one-pot reaction as the key step.

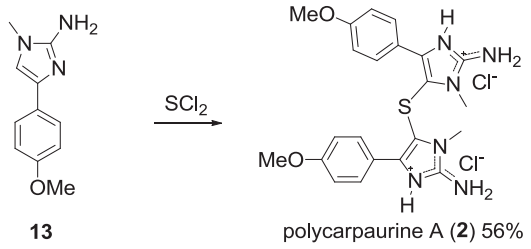
RESULTS AND DISCUSSION

As shown in Scheme 1, following Darzens reaction, hydrolysis reaction, and decarboxylation reaction, 4-meth oxyphenylacetaldehyde (**8**) was obtained with 64% yield over three steps from *p*-methoxybenzaldehyde (**4**). The bromination of **8** was carried out under numerous conditions with GC as the detector. The bromide **9** was obtained in higher yield when the reaction was carried out at 0°C for 1.5 h with Br_2 as the bromination agent and 1,4-dioxane and dichloromethane (v/v, 1/2) as the solvents. The addition of concentrated HCl can efficiently inhibit further bromination of bromide **9**. As bromide **9** is unstable at room temperature, it was used for the next step directly with no further separation. Condensation of **9** and pyrimidine **10** [21] under microwave condition gave intermediate **11**, which was converted to **12** rapidly. Then hydrolysis of **12** with 80% $N_2H_4 \cdot H_2O$ gave 2-aminoimidazole **13** in 68% yield over three steps from aldehyde **8**. Oxidative coupling of **13** gave the alkaloid polycarpine (**1**) in 91% yield. Although this step has been reported by Novikov and co-authors [14], the experiment details were not given. The ratio of S_2Cl_2 and 2-aminoimidazole **13** is the critical factor of the reaction. When the ratio of S_2Cl_2 and 2-aminoimidazole **13** is lower than 1/2, polycarpaurine A (**2**) was detected as byproduct by ^{1}H NMR and HRMS. As the molecular polarity of polycarpine (**1**) and polycarpaurine A (**2**) is similar, they cannot be separated

Scheme 1. Synthesis of polycarpine (**1**).



Scheme 2. Synthesis of polycarpaurine A (**2**).



by column chromatography on silica gel. When the ratio of S_2Cl_2 and 2-aminoimidazole **13** is more than 1/2, the byproduct polycarpaurine A (**2**) can be avoid. When the ratio rises to 0.55, polycarpine (**1**) was obtained in 91% yield. As shown in Scheme 2, replacing of S_2Cl_2 with SCl_2, polycarpaurine A (**2**) was obtained in 56% yield by using similar procedure for the preparation of polycarpine (**1**). The introduction of S_2SO_3H group is very difficult. For the preparation of polycarpaurine C (**3**), we found that $NaHSO_3$ can efficiently disrupt the SS bond of polycarpine (**1**) to give polycarpaurine C (**3**) in 72% yield (Scheme 3).

In summary, the efficient preparation of alkaloids polycarpine and polycarpaurines A and C has been accomplished. This is the first report about the synthesis of polycarpaurines A and C. Polycarpine can convert to polycarpaurine C in 72% yield in the presence of $NaHSO_3$. The structure of polycarpine and polycarpaurines A and C were confirmed by ^{1}H NMR, ^{13}C NMR, and HRMS. Present study provides fundamental support for the further SAR studies of these alkaloids.

EXPERIMENTAL

Reagents were purchased from commercial sources and were used as received. Reaction progress was monitored by GC or thin-layer chromatography on silica gel GF-254 with detection by UV. Melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments Co., Beijing, China) and were uncorrected. ^{1}H NMR spectra were obtained by using Bruker AV 400 spectrometer. Chemical shifts (δ) were given in parts per million (ppm) and were measured downfield from internal tetramethylsilane. High-resolution mass spectra were obtained with an FT-ICR MS spectrometer (Ionspec, 7.0 T). Microwave instrument: CEM Focused Microwave™ Synthesis System, Discover, S-Class.

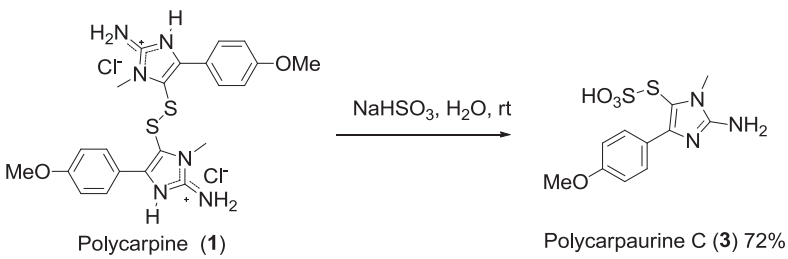
Synthesis of 4-methoxyphenylacetaldehyde (8). To the solution of *p*-methoxybenzaldehyde (**4**, 13.6 g, 0.10 mol) and methyl chloroacetate (**5**, 16.3 g, 0.15 mol) in ethyl alcohol (70 mL) was added dropwise the solution of sodium methylate (30%, 27.0 g, 0.15 mol) in ethyl alcohol (70 mL) at 15°C, and the mixture was stirred for 4 h. Then, the reaction mixture was added to the solution of KOH (8.4 g, 0.15 mol) in ethyl alcohol (100 mL) at 15°C, and the mixture was stirred for further 5 h at 15°C and stood for 3 h at 0°C. The mixture was filtered to give potassium salt **7** as a white solid.

To the solution of the mentioned potassium salt **7** earlier in H_2O (150 mL) and dichloromethane (150 mL) was added KH_2PO_4 (14.0 g, 0.10 mol), and the mixture was stirred at room temperature for 4 h and separated. The aqueous phase was washed with dichloromethane (3 × 80 mL). The combined organic phase was washed with H_2O (3 × 100 mL) and brine (3 × 100 mL), dried over $MgSO_4$, and concentrated to afford 4-methoxyphenylacetaldehyde (**8**, 9.6 g, 64% yield over three steps from **4**) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.72 (s, 1H, CHO), 7.13 (d, J = 8.7 Hz, 2H, Ar-H), 6.90 (d, J = 8.7 Hz, 2H, Ar-H), 3.80 (s, 3H, OMe), 3.62 (d, J = 2.3 Hz, 2H, Ar-CH_2) ppm.

Synthesis of 4-(4-methoxyphenyl)-1-methyl-1*H*-imidazol-2-amine (13). To the solution of aldehyde (**8**, 2.0 g, 13.3 mmol), concentrated HCl (1 d) in 1,4-dioxane (15 mL) and dichloromethane (15 mL) was added the solution of Br_2 (2.13 g, 13.3 mmol) in dichloromethane (15 mL) at 0°C (about 1 h complete the addition), and the mixture was stirred at 0°C for further 0.5 h. Dichloromethane (80 mL) was added, and the mixture was washed with saturated $NaHCO_3$ solution (100 mL), saturated $Na_2S_2O_3$ solution (100 mL), and brine (100 mL); then dried with anhydrous $MgSO_4$; and concentrated in vacuo to give bromide **9**.

To a 35-mL vessel was added the aforementioned bromide **7**, 2-methylaminopyrimidine (**9**, 1.45 g, 13.3 mmol) and acetonitrile (15 mL). The reaction vessel was sealed

Scheme 3. Synthesis of polycarpaurine C (**3**).



and placed into microwave instrument and stirred under the conditions of 150 W and 150°C for 30 min and then cooled to room temperature and added 80% hydrazine hydrate (4.17 g, 66.7 mmol). The mixture was stirred under the conditions of 100 W and 100°C for further 10 min and concentrated in vacuo. The residue was purified by column chromatography on silica gel (CH_2Cl_2/CH_3OH 20/1 as eluent) to give compound **13** (1.8 g, 68% yield over three steps from **8**) as a slight yellow solid, mp 148–150°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, J = 8.4 Hz, 2H, Ar-H), 6.88 (d, J = 8.4 Hz, 2H, Ar-H), 6.71 (s, 1H, Ar-H), 4.00 (br, 2H, NH_2), 3.81 (s, 3H, OMe), 3.44 (s, 3H, NMe) ppm. HRMS (ESI) Calcd. for $C_{11}H_{14}N_3O$ $(M+H)^+$: 204.1131. Found: 204.1135.

Synthesis of polycarpine (1). The solution of compound **13** (1 g, 4.93 mmol) and S_2Cl_2 (0.37 g, 2.71 mmol) in acetic acid (100 mL) was stirred at room temperature for 10 h and concentrated. The residue was washed with acetone (50 mL) to give polycarpine (**1**, 1.2 g, 91%) as a yellow solid, mp 205–207°C (lit. [14] mp 209–211°C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.43 (s, 2H, HCl), 7.67 (s, 4H, NH_2), 7.46 (d, J = 8.4 Hz, 4H, Ar-H), 7.01 (d, J = 8.9 Hz, 4H, Ar-H), 3.89 (s, 3H, OMe), 3.19 (s, 3H, NMe) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.6, 147.2, 136.9, 127.5, 117.1, 114.1, 108.8, 55.4, 28.7. HRMS (ESI) Calcd. for $C_{22}H_{25}N_6O_2S_2$ $(M\text{-}2HCl+H)^+$: 469.1475. Found: 469.1469.

Synthesis of polycarpaurine A (2). The solution of compound **13** (1 g, 4.93 mmol) and SCl_2 (0.28 g, 2.71 mmol) in acetic acid (100 mL) was stirred at room temperature for 10 h and concentrated. The residue was washed with acetone (50 mL) to give polycarpaurine A (**2**, 0.7 g, 56%) as a white solid, mp 180°C (dec.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.65 (s, 2H, HCl), 7.81 (s, 4H, NH_2), 7.69 (d, J = 8.8 Hz, 4H, Ar-H), 7.11 (d, J = 8.8 Hz, 4H, Ar-H), 3.84 (s, 6H, O-CH_3), 2.90 (s, 6H, N-CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.6, 148.2, 132.6, 130.1, 119.9, 114.7, 110.7, 55.9, 30.2. HRMS (ESI) Calcd. for $C_{22}H_{25}N_6O_2S^+$ $[M+H\text{-}2HCl]^+$: 437.1754. Found: 437.1756.

Synthesis of polycarpaurine C (3). The solution of polycarpine (**1**, 0.5 g, 0.90 mmol) and $NaHSO_3$ (0.32 g, 3.04 mmol) in H_2O (50 mL) was stirred at room temperature for 1 h and concentrated. The residue was filtered to give polycarpaurine C (**3**, 0.5 g, 72%) as a yellow solid, mp 184°C (dec.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.90 (s, 1H, NH), 7.88 (d, J = 8.9 Hz, 2H, Ar-H), 7.72 (s, 2H, NH_2), 7.04 (d, J = 8.9 Hz, 2H, Ar-H), 3.81 (s, 3H, O-CH_3), 3.50 (s, 3H, N-CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.9, 146.9, 131.8, 129.2, 119.8, 114.7, 113.8, 55.2, 29.6. HRMS (ESI) Calcd. for $C_{11}H_{14}N_3O_4S_2^+$ $[M+H]^+$: 316.0420. Found: 316.0410.

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