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An improved total synthesis of spermatinamine, an inhibitor of isoprenylcysteine carboxy methyltransferase

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ABSTRACT

An improved total synthesis of spermatinamine, an inhibitor of the anticancer target, isoprenylcysteine carboxy methyltransferase (Icmt) was accomplished from the commercially available 3,4-dibromo-4-hydroxybenzaldehyde via a high yielding reaction sequence in an overall yield of 31%.

Protein farnesyltransferase (FTase) or protein geranylgeranyltransferase type I (GGTase-I) mediated protein prenylation, a process initiated by covalent attachment of a 15-carbon farnesyl or a 20-carbon geranylgeranyl isoprenoid to a conserved cysteine residue, is critical for the correct localization and function of many key regulatory proteins in eukaryotic cells.[1,2] The so-called CaaX (*C* = modified cysteine residue, *a* = aliphatic residue, and X can be any of a number of amino acids such as cysteine, serine, methionine, and alanine) motif at the C-terminus of these proteins dictate the modification of the majority of prenylated proteins. After prenylation of cysteine, removal of the aaX residues by the Ras-converting enzyme 1(Rcel)[3,4] generates an exposed carboxyl group on prenylated cysteine, which is then methylated by isoprenylcysteine carboxy methyltransferase (Icmt). These final two processing steps result in a more hydrophobic protein with a distinctive structure at the C-terminus and provide a unique determinant of the protein–protein interaction.[5,6]

The implication of several CaaX proteins, including members of the Ras family of GTPases, in oncogenesis and tumor progression has led to the development of a number of FTase inhibitors (FTIs).[7] The lower efficacy than was expected in patients of FTIs, currently in clinical trials, has been attributed to cross-prenylation whereby, when FTase is inhibited, GGTase-I can modify the proteins at an appreciable rate.[8,9] Consequently, focus has been directed to target the post-prenylation enzymes such as Rce1 and Icmt, and inhibition of the latter, in particular, offers a potential alternative to FTIs.[10]

Spermatinamine (**1**), an inhibitor of Icmt (IC_{50} = 1.9 μM), is a novel alkaloid with a bromotyrosyl-spermine-bromotyrosyl sequence and was isolated from the Australian marine sponge, *Pseudoceratina* sp.[11,12] Garcia et al. reported the first total synthesis of spermatinamine.[13] Their synthetic strategy utilized *O*-methyl-L-tyrosine and spermine as starting materials.

The desired key intermediate, *N*-4,*N*-9-dimethylspermine (**3**), was synthesized from spermine in three steps (67% overall yield) after column purification in each step. Column purification of the final product, spermatinamine, from the polar coupling activating reagents was difficult and required the use of very polar solvent mixtures and rendered an overall yield of 15% from *O*-methyl-L-tyrosine.

In continuation of our ongoing interest in the total synthesis of bio-active natural products,[14] we disclose an improved total synthesis of spermatinamine (**1**). We envisioned accomplishing the synthesis of **1** through a straightforward reaction sequence which would employ cheap chemicals and improve the overall yield of the final target compound. The preparation of the key intermediate **3** was accomplished in two steps with an overall yield of 83%, by the conjugate addition of commercially available *N*,*N*′-dimethyl-1,4-diaminobutane (**2**) to acrylonitrile to afford the corresponding Michael adduct, which was hydrogenated at 50 psi, using Ra-Ni as the catalyst.[15] (Scheme 1).

The other segment of the spermatinamine, benzyloxime acid **7**, was prepared as described in Scheme 1. Alkylation of aldehyde **4** with iodomethane in DMF, using K_2CO_3 as a base afforded aldehyde **5** in quantitative yield.[16] Heating a mixture of aldehyde **5** and *N*-acetylglycine to 120 °C in acetic anhydride for 4 h gave azlactone **6**[17] as a light yellow solid (74%). The hydrolysis of **6** with

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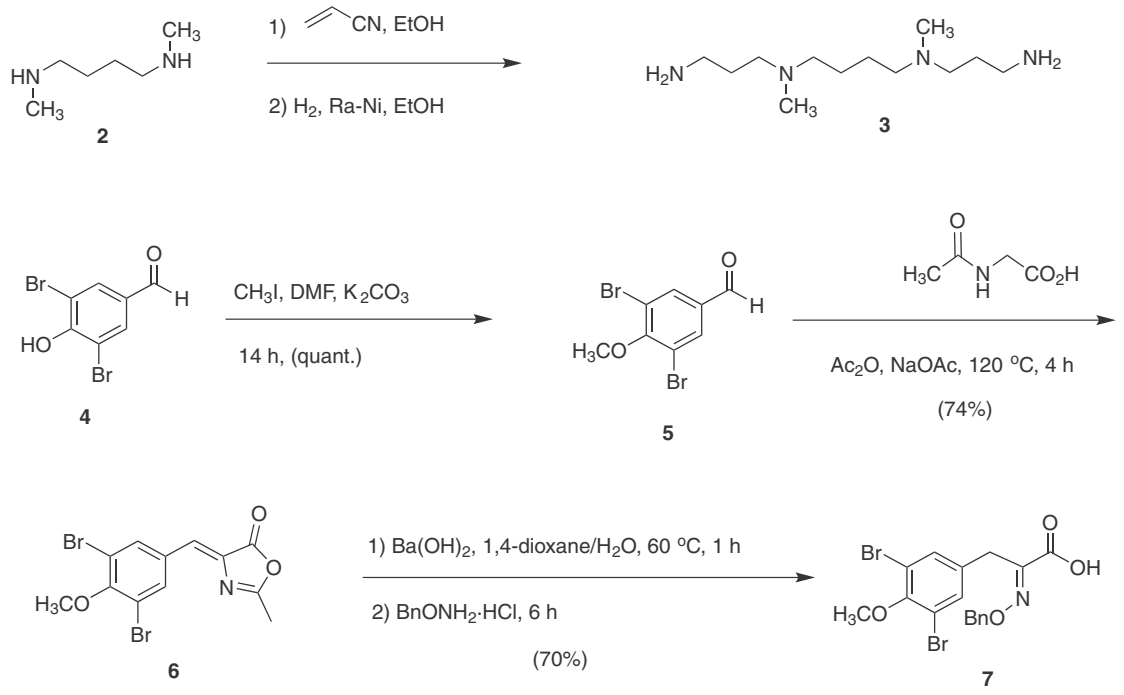
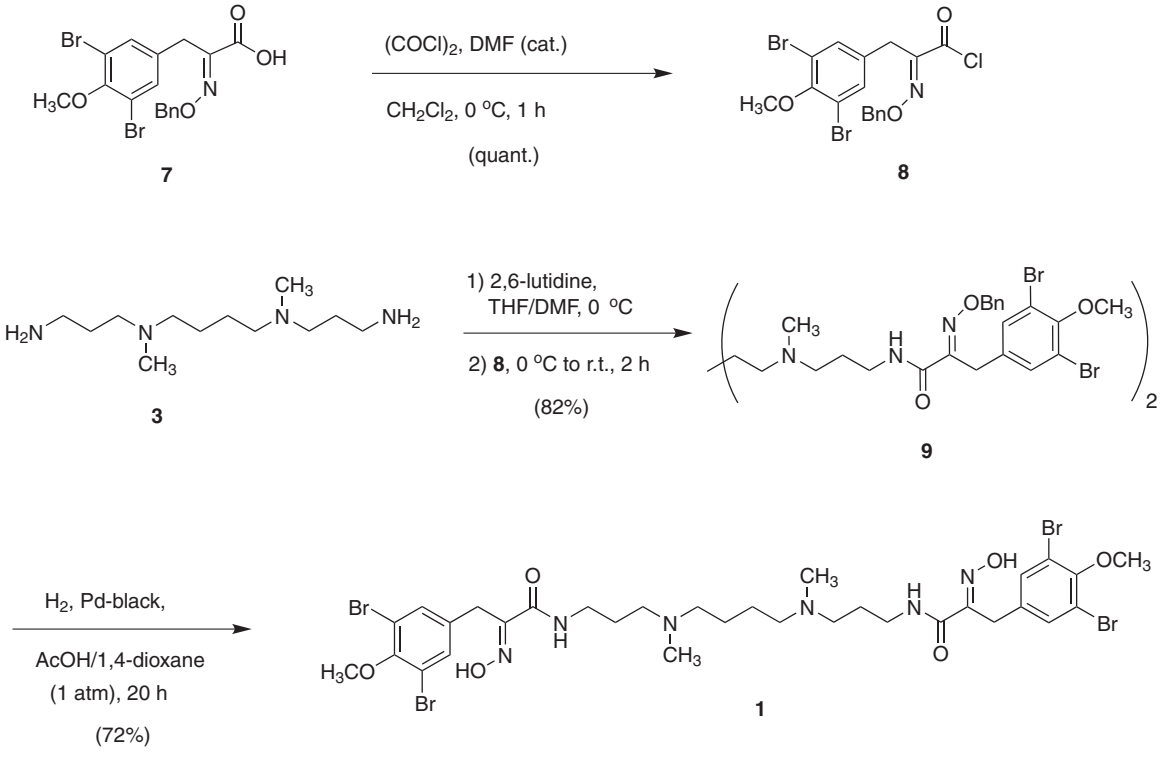


Scheme 1.



Scheme 2.

$Ba(OH)_2$ in a mixture of 1,4-dioxane and water at 60 °C gave the corresponding keto acid, which was condensed in situ with *O*-benzylhydroxylamine hydrochloride to give *E*-benzyloxime acid **7**[13,18] in 70% yield.

Having the desired benzyloxime acid **7** and *N*-4,*N*-9-dimethylspermine (**3**) in hand, we next condensed them to generate the advanced intermediate **9**. To this end, acid **7** was transformed into the corresponding acid chloride **8** using oxalyl chloride in CH_2Cl_2, and DMF as a catalyst. After evaporation of the solvents, a solution of the acid chloride in dry THF was added dropwise to a solution of amine **3** in a mixture of THF and DMF at 0 °C, using 2,6-lutidine as the base to produce the desired coupled product **9**[19] in 82% yield after column purification. Exposure of compound **9** to hydrogenation in a mixture of acetic acid and 1,4-dioxane at 1 atm, using

Pd-black as the catalyst afforded the target compound **1**[20] in 72% yield, after column purification. All the spectral data of **1** matched with those of natural spermatinamine[11] (Scheme 2).

In summary, we have accomplished a facile synthesis of spermatinamine (**1**) in an overall yield of 31% from commercially available 3,4-dibromo-4-hydroxybenzaldehdye.

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Supplementary data

Supplementary data (^{1}H, ^{13}C NMR and DEPT spectra of compound **9**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.164.

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17. Synthesis of azlactone **6**: A mixture of aldehyde **5** (2.94 g, 10 mmol), NaOAc (0.82 g, 10 mmol), and *N*-acetylglycine (1.17 g, 10 mmol) in Ac_2O (20 mL) was stirred at 120 °C for 4 h. The reaction mixture was cooled to room temperature and the yellow solid which precipitated was filtered and washed with cold 1:1 pentane/Et_2O to yield **6** as a yellow solid (2.78 g, 74%); mp: 154–155 °C; IR (neat) (ν_{max}/cm^{-1}) 3233, 2927, 1692, 1662, 1633, 1468, 1416, 1365, 1255, 1201, 981, 902, 721. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.40 (s, 3H), 3.84 (s, 3H), 7.16 (s, 1H), 8.47 (s, 2H). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 15.52, 60.73, 117.90, 125.70, 132.28, 133.88, 135.66, 154.95, 166.88, 168.04. Anal. Calcd for $C_{12}H_9Br_2NO_3$: C, 38.43; H, 2.42; N, 3.73. Found: C, 38.40; H, 2.46; N, 3.70.
18. Synthesis of benzyloxime acid **7**: A suspension of azlactone **6** (1.5 g, 4 mmol) and $Ba(OH)_2$ (4.8 g, 28 mmol) in a mixture of 1,4-dioxane/H_2O (1:1, 56 mL) was stirred at 60 °C for 1 h, followed by the addition of *O*-benzylhydroxylamine hydrochloride (2.05 g, 12.8 mmol) and the mixture stirred vigorously at the same temperature for 6 h. The mixture was cooled to 0 °C, acidified to pH 4 with 10% HCl and extracted with EtOAc (50 mL × 2). The combined organic extracts were washed with H_2O (20 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The yellow oily material was loaded onto a silica column eluting with EtOAc/MeOH (10:1) to afford **7** (as a pale-yellow solid, 1.28 g, 70%); mp: 115–116 °C; IR (neat) (ν_{max}/cm^{-1}) 3060, 2943, 1692, 1589, 1471, 1416, 1259, 1219, 991, 897, 738, 696. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.80 (s, 2H), 3.83 (s, 3H), 5.30 (s, 2H), 7.40–7.26 (m, 7H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 29.13, 78.74, 117.99, 128.56, 128.84, 133.38, 133.59, 135.36, 148.89, 153.03, 163.31. Anal. Calcd for $C_{17}H_{15}Br_2NO_4$: C, 44.67; H, 3.31; N, 3.06. Found: C, 44.64; H, 3.33; N, 3.02.
19. Synthesis of compound **9**: To a solution of **7** (0.1 g, 0.22 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C was added oxalyl chloride (22 μL, 0.26 mmol) dropwise, followed by one drop of DMF and the reaction mixture stirred for 1 h at 0 °C. The solvent was evaporated and the acid chloride **8** was kept under high vacuum for 0.5 h. In another flask, a solution of compound **3** (23 mg, 0.1 mmol) in a mixture of dry THF (3 mL) and DMF (1 mL) was cooled to 0 °C and to the mixture was added 2,6-lutidine (64 mg, 0.6 mmol). After being stirred for 10 min, a solution of acid chloride **8** in dry THF (3 mL) was added dropwise. The mixture was stirred for 2 h at room temperature, diluted with $CHCl_3$ (50 mL) and the organic layer washed with H_2O (25 mL), dried over Na_2SO_4 and evaporated under vacuum. The resulting pale yellow oil was chromatographed on silica gel eluting with EtOAc/MeOH/NH_4OH (6:4:1) to yield **9** as a thick yellow liquid (0.2 g, 82%). IR (neat) (ν_{max}/cm^{-1}) 2941, 2858, 2797, 1664, 1527, 1468, 1420, 1366, 1258, 1203, 996, 906, 726. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.43 (br s, 4H), 1.66 (m, 4H), 2.15 (s, 6H), 2.29 (m, 4H), 2.40 (t, 4H, J = 4.88), 3.37 (q, 4H, J = 6.1), 3.83 (s, 10H), 5.20 (s, 4H), 7.36–7.27 (m, 10H), 7.44 (s, 4H), 7.80 (br s, 2H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 24.96, 26.00, 28.72, 39.12, 41.78, 56.25, 57.82, 60.47, 77.33, 117.62, 127.92, 128.24, 128.57, 133.43, 134.94, 136.39, 152.48, 151.52, 161.91. Anal. Calcd for $C_{46}H_{56}Br_4N_6O_6$: C, 49.84; H, 5.09; N, 7.58. Found: C, 49.80; H, 5.13; N, 7.52.
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