An efficient route to 5-iodo-1-methylimidazole: synthesis of xestomanzamine A

Francis B. Panosyan and Ian W.J. Still

Abstract: An efficient and practical route to C-5 functionalized *N*-methylated imidazoles is reported. 5-Iodo-1-methylimidazole was synthesized in four steps from imidazole, with complete regiospecificity, in 73% overall yield. The synthesis of xestomanzamine A, a marine natural product isolated in 1995 from an Okinawan sponge of *Xestospongia* sp., has been achieved using 5-iodo-1-methylimidazole in a modified Grignard reaction with a β-carboline ester moiety, in an overall yield of 59% based upon imidazole and 53% based upon tryptamine.

Key words: xestomanzamine A, 5-iodo-1-methylimidazole, methyl β-carboline-1-carboxylate.

Résumé : On propose une méthode efficace et pratique de préparer des imidazoles *N*-méthylés et fonctionnalisés en C-5. On a synthétisé le 5-iodo-1-méthylimidazole en quatre étapes à partir de l'imidazole, avec une régiospécificité complète et un rendement global de 73%. Faisant appel à une réaction de Grignard modifiée entre le 5-iodo-1-méthylimidazole et un ester de la β-carboline, on a réalisé la synthèse de la xestomanzamine A, un produit naturel marin isolé en 1995 à partir de l'éponge d'Okinawa *Xestospongia* sp.; le rendement global est de 59% à partir de l'imidazole et de 53% sur la base de la tryptamine.

Mots clés : xestomanzamine A, 5-iodo-1-méthylimidazole, β-carboline-1-carboxylate de méthyle.

[Traduit par la Rédaction]

Introduction

There has recently been intensive interest in the biological activity of naturally occurring marine alkaloids (for a recent review of marine natural products, see ref. 1). The very prolific β-carboline class of alkaloids has been the focus of particular attention (2, 3). Many of these alkaloids are isolated from sponges and two such compounds are xestomanzamine A (**1**) and its 3,4-dihydro analogue xestomanzamine B (**2**). These cytotoxic constituents of an Okinawan sponge (*Xestospongia* sp.) were first isolated in 1995 (4), and one synthesis of xestomanzamine A has been reported (5). This synthesis required at least eight steps from indole-3-carboxaldehyde, as well as a key coupling reaction with a 5-lithiated 1-methylimidazole, itself requiring three steps for its preparation, which proceeds in a yield of less than 50%. We have developed a considerably shorter, more efficient route to xestomanzamine A, which we now describe.

Results and discussion

A likely biosynthetic route to xestomanzamine A would probably involve condensation of tryptophan **3** with the *N*-methylated histidine-derived aldehyde **4** to produce the tetrahydro-β-carboline[2] intermediate **5**. Decarboxylation, and a series of oxidative steps would then lead to **2** and finally to **1**, Scheme 1. We decided to adopt a similar strategy in our approach but with the initial construction of the β-carboline unit in the form of the 1-carboxylate ester **6**. We then planned to carry out a modified Grignard reaction, using a 5-halo-1-methylimidazole **7**, to lead directly to xestomanzamine A, Scheme 2.

Before we began our approach to **7b** and **7c** we attempted, without success, to form the Grignard reagent from the commercially available 5-chloro-1-methylimidazole **7a**. While the analogous 5-bromo- and 5-iodoimidazoles are not, at first sight, difficult synthetic targets, one well documented complication in imidazole chemistry is the rapid equilibration of 4- and 5-imidazolyl anions to their much more stable 2-imidazolyl anion counterpart (6, 7). Thus, lithiation of *N*-methylimidazole, followed by bromination or iodination, was ruled out. Attempts to carry out regioselective bromination of *N*-methylimidazole with a variety of reagents, including NBS, pyridinium tribromide, 2,4,4,6-tetrabromo-2,5-cyclohexadienone, and dibromotriphenylphosphorane were also unsuccessful. Some conversion (20%) of *N*-methylimidazole to **7b** was achieved using 2,3-dibromo-5,5-dimethylhydantoin (DBDMH) in THF at 0°C (8). The low yield obtained, however, combined with a report (9) of the low reactivity of 5- and 4-bromo-1-methylimidazoles towards magnesium, convinced us to turn our attention to the synthesis of the iodo compound **7c**.

The synthesis of 5-iodo-1-methylimidazole was attempted by the strategy used by Balaban and Pyman (10) and, more recently, by Garegg and Samuelsson (11). We planned to carry out iodination of imidazole at all three carbons, selective deiodination and then regiospecific methylation to afford 5-iodo-1-methylimidazole **7c**, Scheme 3.

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[2]IUPAC name is 1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole.

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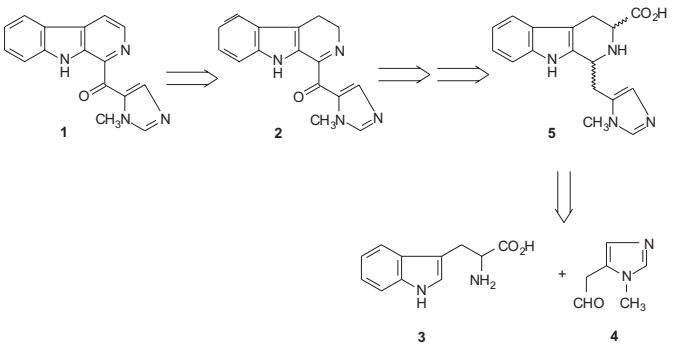
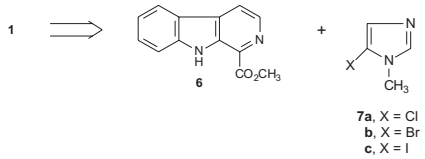
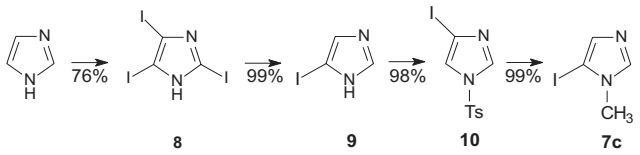
Scheme 1.



Scheme 2.



Scheme 3.



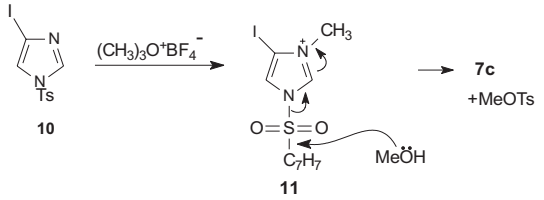
In our hands, the conversion of imidazole to the triiodiomidazole **8** was best achieved with iodine in an aqueous solution of sodium hydroxide, in the presence of potassium iodide (12). 2,4,5-Triiodoimidazole **8** separated from the solution upon neutralization with acetic acid, in 76% yield.

The next step was the selective deiodination of **8** to 4(5)-iodoimidazole **9**. The use of sodium sulfite by Balaban and Pyman (10) for the analogous bromo-series has been extended to the selective deiodination reaction of **8** (13). This reaction, in our hands, afforded **9** in 99% yield, by using 30% ethanol in water as the refluxing solvent, instead of water, to avoid complete deiodination. The ^{1}H NMR spectrum of the reduction product **9** showed the expected signals at δ 7.62 and 7.18, indicative of H(2) and H(4)-(5), respectively.

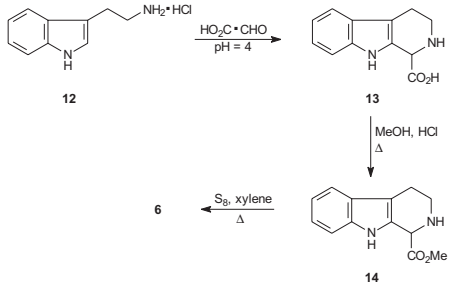
Numerous attempts to regioselectively methylate **9** to produce the desired **7c** were to no avail, under a variety of pH conditions and using both methyl iodide and dimethyl sulfate as methylating agents. Finally, we were able to take advantage of a highly selective two-step procedure that involves the initial, regioselective tosylation (14) of **9** to produce 4-iodo-1-tosylimidazole **10** in 98% yield. This selectivity may be rationalized on steric grounds, although the formation of **10** as a result of a thermodynamic equilibration of two initially formed regioisomers cannot be ruled out.

The final conversion of **10** into the desired 5-iodo-1-methylimidazole **7c** was achieved using trimethyloxonium

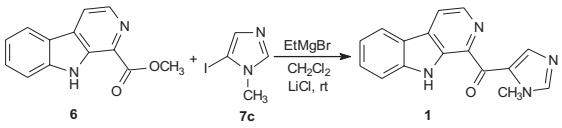
Scheme 4.



Scheme 5.



Scheme 6.



tetrafluoroborate, followed by a methanol quench, in a modification of a recent report by Lindel and Hochgürtel (15). This reaction afforded **7c** in 99% yield. The ^{1}H NMR spectrum had three singlet peaks at δ 3.62, 7.13, and 7.62, for the methyl, H(4), and H(2) protons, respectively. These values were in excellent agreement with the reported literature values (12) for 5-iodo-1-methylimidazole.

This very successful, regioselective methylation at N(3) of **10** using trimethyloxonium tetrafluoroborate presumably proceeds via the 5-iodo-1-methyl-3-tosylimidazolium salt **11**, which is not isolated, Scheme 4.

The sequence of reactions leading to **7c** from imidazole (Scheme 3) does not carry the disadvantages associated with many earlier methods for the synthesis of 5-iodo-1-methylimidazole; namely, low yields, poor reproducibility, and tedious purification methods. The overall yield for the four-step synthesis of **7c** from imidazole was 73%.

The synthesis of the β-carboline ester **6** was much more straightforward, Scheme 5. The initial 1,2,3,4-tetrahydro-β-carboline derivative **13** was obtained through a Pictet–Spengler condensation of tryptamine hydrochloride **12** with glyoxylic acid, forming **13** as a white solid, in 80% yield. The Pictet–Spengler reaction is known to proceed under mildly acidic conditions. This reaction was initiated by the addition of a concentrated solution of potassium hydroxide to solubilize the reagents, and then the pH was adjusted to about 4 with glacial acetic acid. Purification of **13** was readily achieved by simply stirring the product briefly in methanol at 0°C and then filtering. The acid showed the IR bands at ν 3343 (NH) and 1616 (bonded C=O) cm^{-1}, as expected for this compound (16).

Fischer esterification of **13** with methanol gave methyl 1,2,3,4-tetrahydro-β-carboline-1-carboxylate **14**, as its hydrochloride salt (17). The synthesis of **6** was completed by dehydrogenation of **14**, after careful neutralization of the salt with 2,2,6,6-tetramethylpiperidine, using sulfur in refluxing xylene, in 87% yield. The ester showed a carbonyl band in the IR at ν 1678 cm^{-1}, which is attributed to strong intramolecular hydrogen bonding with the indole NH.

Our initial attempt to complete the synthesis of xestomanzamine A was carried out by addition of a solution of EtMgBr and 5-iodo-1-methylimidazole **7c** in THF to a solution of the β-carboline methyl ester **6** in THF, in the presence of excess lithium chloride (17). The indole NH present in **6** was first deprotonated with the addition of one equivalent of EtMgBr, prior to the addition of **7c**. Xestomanzamine A was obtained, but in very low yield. A mild procedure has been reported for metal–halogen exchange with *N*-protected 4-iodoimidazoles (18), using EtMgBr in CH_2Cl_2. Repeating the reaction in CH_2Cl_2 again afforded xestomanzamine A, this time in greatly improved yield. We speculate that the use of dichloromethane may give the Grignard organomagnesium intermediate greater covalent character, thus making the imidazol-5-yl carbanionoid less sensitive to equilibration with its imidazol-2-yl counterpart, Scheme 6.

It was noticed during these initial attempts that the addition of EtMgBr to **7c** produced a white precipitate prior to addition to the β-carboline ester. Grignard reagents are known to exist in equilibrium with the corresponding binary organomagnesium compounds. At low temperatures, and when there is a solvent-induced precipitation of the magnesium salt, there is a shift of the equilibrium towards the organomagnesium species $MgAr_2$. We, thus, decided to direct the equilibrium towards the Grignard reagent ArMgX by warming the solution of EtMgBr and **7c** briefly, prior to addition to the β-carboline methyl ester **6**. In this way the yield of xestomanzamine A was increased finally to 81%.

The physical data (mp, IR, ^{1}H and ^{13}C NMR), which we obtained for xestomanzamine A, are in excellent agreement with those reported for the natural product (4).

Our four-step preparation of 5-iodo-1-methylimidazole in excellent overall yield provides ready access to a synthetic intermediate with the potential to facilitate the synthesis of other natural products with the *N*-substituted, C-5 functionalized imidazole substructure (19). The efficient total synthesis of xestomanzamine A (**1**) has been achieved through a modified Grignard reaction of **7c** with the β-carboline ester **6**, involving a total of four steps from tryptamine (53% overall yield) and five steps from imidazole (59% overall yield).

Experimental

Methanol was dried over magnesium. Xylenes and dichloromethane were distilled over calcium hydride. Tetrahydrofuran and diethyl ether were dried over sodium benzophenone ketyl. Molecular sieves (3 Å) were activated by heating in a furnace to 500°C for 3 h. All glassware for anhydrous reactions was dried overnight prior to use and these reactions were carried out under argon. TLC were run on Merck silica gel 60 F_{254} plates, with detection by means of a 254 nm UV visualizer. Melting points were recorded on a capillary melting point apparatus and are uncorrected. IR spectra reported were recorded on a Nicolet FT-IR spectrophotometer in the form of KBr disks, unless specified otherwise. The ^{1}H NMR spectra (200 MHz) and ^{13}C NMR spectra (125 MHz), unless specified otherwise, were obtained in $CDCl_3$ with an internal standard of TMS.

2,4,5 Triiodoimidazole (8)

Modification of a described procedure (11): a solution of iodine (45.0 g, 0.18 mol) in 20% aqueous potassium iodide (300 mL) was added dropwise to a stirred solution of imidazole (7.06 g, 0.1 mol) in 2 M sodium hydroxide (600 mL) at room temperature and the resulting mixture was stirred overnight. Addition of acetic acid until the mixture was neutral gave a white precipitate, which was filtered off, washed with water, and air dried to give a product sufficiently pure to continue in the next step: (35.4 g, 76%): mp 186–190°C, lit. (11) mp 190–192°C.

4(5)-Iodoimidazole (9)

Modification of a described procedure (13): triiodoimidazole (1.0 g, 2.24 mmol) and sodium sulfite (4.2 g, 33.3 mol) were heated at reflux in 30% ethanol in water solution (50 mL) for 24 h. The ethanol was removed under reduced pressure. The remaining solution was filtered and the filtrate extracted with diethyl ether (3 × 15 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated under reduced pressure to afford the pure product **9** as a white solid (0.43 g, 99%): mp 136 to 137°C, lit. (13) mp 137 to 138°C. ^{1}H NMR δ 7.18 (s, 1H), 7.62 (s, 1H). ^{1}H NMR (DMSO-d_6) δ 7.31 (s, 1H), 7.65 (s, 1H).

4-Iodo-1-*p*-toluenesulfonylimidazole (10)

Compound **10** was prepared from **9** based upon the procedure of Cliff and Pyne (14). White solid (98%): mp 146 to 147°C (EtOH), lit. (14) mp 146 to 147°C; ^{1}H NMR δ 2.46 (s, 3H), 7.37 (s, 1H), 7.40 (d, J = 8.5 Hz, 2H), 7.83 (d, J = 8.5 Hz, 2H), 7.88 (s, 1H).

5-Iodo-1-methylimidazole (7c)

To a solution of **10** (0.94 g, 2.81 mmol) in dry CH_2Cl_2 (30 mL) was added trimethyloxonium tetrafluoroborate (0.46 g, 3.11 mmol). After the mixture was stirred at room temperature for 24 h, methanol (15 mL) was added. The solvent was removed under reduced pressure and the residue was acidified with 1% HCl and extracted with CH_2Cl_2 (2 × 15 mL). The aqueous solution was then basified with 5% $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 × 15 mL). The organic extracts from the basified solution were combined, dried (Na_2SO_4), and the solvent removed under reduced pressure to afford the white product **7c** (0.58 g, 99%): mp 106 to 107°C, lit. (12) mp 102 to 103°C. ^{1}H NMR δ 3.62 (s, 3H), 7.13 (s, 1H), 7.62 (s, 1H).

1,2,3,4-Tetrahydro-β-carboline-1-carboxylic acid (13)

Tryptamine hydrochloride **12** (1.95 g, 9.91 mmol) was dissolved in water (30 mL) while heating. Glyoxylic acid monohydrate (1.10 g, 11.95 mmol) in water (10 mL) was added to this solution, followed by the dropwise addition of potassium hydroxide (0.65 g, 11.58 mmol) in water (10 mL). The pH was adjusted to 4.0 with HOAc and the mixture al-

lowed to stir at room temperature for 2 h. The solution was then chilled and vacuum filtered, giving an impure yellow solid. The solid was dried under vacuum and suspended in methanol at 0°C, then quickly filtered by suction to afford the pure white product (1.99 g, 80%): mp 210 to 211°C, lit. (20) mp 205–208°C. IR (cm^{-1}): 3343 (NH), 1616 (C=O).

Methyl 1,2,3,4-tetrahydro-β-carboline-1-carboxylate (hydrochloride salt) (14)

The carboxylic acid **13** (4.50 g, 20.80 mmol) was stirred in dry methanol (100 mL), while dry HCl gas was bubbled through the mixture for approximately 2 min. The solid dissolved giving a golden yellow solution. The mixture was then brought to reflux through 3 Å sieves in a Soxhlet apparatus for 3 h under argon. Most of the methanol (70 mL) was removed under reduced pressure. The precipitate formed was collected by suction filtration, washed with cold toluene (30 mL), and dried under vacuum, giving the ester hydrochloride as yellow crystals (5.23 g, 94%): mp 205–208°C, lit. (21) mp 212–214°C. IR (cm^{-1}): 3384 (NH), 1757 (C=O). ^{1}H NMR (DMSO-d_6) δ 3.00 (t, J = 6.0 Hz, 2H), 3.54 (t, J = 6.2 Hz, 2H), 3.88 (s, 3H), 5.70 (s, 1H), 7.05–7.20 (m, 2H), 7.44–7.52 (m, 2H), 10.30 (s, 2H), 11.17 (s, 1H).

Methyl β-carboline-1-carboxylate (6)

The ester hydrochloride **14** (4.00 g, 15.02 mmol), precipitated sulfur (1.13 g, 35.15 mmol), and 2,2,6,6-tetramethylpiperidine (2.40 g, 17.03 mmol) were heated at reflux in dry xylenes (200 mL) for 5 h giving a brown solution. Evolution of H_2S could be detected with lead acetate paper. The solution was allowed to cool slowly overnight, forming brown needles. The xylene was removed under reduced pressure and the residual solids were placed in a Soxhlet thimble and extracted with acetone (100 mL) for 3 h. The acetone extracted the ester **6** from the reaction mixture while leaving the insoluble 2,2,6,6-tetramethylpiperidine hydrochloride in the Soxhlet thimble. The acetone was removed under reduced pressure giving a brown solid. Purification of the solid by column chromatography (ethyl acetate) gave **6** as a pale yellow solid (2.94 g, 87%): mp 165 to 166°C, lit. (22) mp 166°C. IR (cm^{-1}): 3378 (NH), 1678 (C=O). ^{1}H NMR δ 4.14 (s, 3H), 7.35–7.63 (m, 3H), 8.15–8.19 (m, 2H), 8.60 (d, J = 4.8 Hz, 1H), 9.90 (s, 1H).

Xestomanzamine A (1)

Ethylmagnesium bromide (1 M in hexane) (0.5 mL, 0.50 mmol) was added dropwise to a solution of 5-iodo-1-methylimidazole **7c** (0.104 g, 0.50 mmol) in dichloromethane (15 mL) under argon at 0°C. After completing the addition, the mixture was warmed briefly with a heat gun to complete the dissolution and then allowed to stir for 1 h at room temperature. In another flask, to a stirring solution of β-carboline ester **6** (0.104 g, 0.46 mmol) and lithium chloride (0.2 g, 4.7 mmol) in dichloromethane (20 mL) under argon at 0°C, ethylmagnesium bromide (1 M in hexane) (0.5 mL, 0.50 mmol) was added dropwise with a syringe. After completion of stirring (1 h), the solution of **7c** and ethylmagnesium bromide was added by cannula dropwise to the β-carboline ester solution at 0°C. The temperature of the reaction flask was allowed to reach 25°C and the mixture was stirred for 24 h. The mixture was quenched (5% $NaHCO_3$) and extracted with dichloromethane (3 × 25 mL). The organic extracts were combined and dried (Na_2SO_4). The dichloromethane was removed under reduced pressure and the resulting solid was purified by column chromatography (ethyl acetate–methanol, 95:5) to give the final product **1** as a yellow solid (0.103 g, 81%): mp 184 to185°C, lit. (4) mp 185 to 186°C. IR (Nujol) (cm^{-1}): 3419, 1606, 1214, 1127 (lit. (4) IR (KBr pellet) (cm^{-1}): 3427, 1612, 1211, 1128). ^{1}H NMR δ 4.11 (s, 3H), 7.35 (dd, J = 7.9, 6.4 Hz, 1H), 7.55 (dd, J = 7.5, 6.4 Hz, 1H), 7.60 (d, J = 7.5 Hz, 1H), 7.69 (s, 1H), 8.17 (d, J = 4.9 Hz, 1H), 8.20 (d, J = 7.9 Hz, 1H), 8.60 (d, J = 4.9 Hz, 1H), 8.94 (s, 1H) (lit. (4) ^{1}H NMR ($CDCl_3$) δ 4.05 (s, 3H), 7.30 (dd, J = 8.2, 6.2 Hz, 1H), 7.55 (dd, J = 7.3, 6.2 Hz, 1H), 7.57 (d, J = 7.3 Hz, 1H), 7.66 (s, 1H), 8.09 (d, J = 5.0 Hz, 1H), 8.12 (d, J = 8.2 Hz, 1H), 8.55 (d, J = 5.0 Hz, 1H), 8.93 (s, 1H)). ^{13}C NMR δ 184.4, 143.8, 143.4, 141.0, 138.2, 136.7, 136.6, 131.7, 129.8, 129.3, 121.8, 120.9, 120.7, 118.6, 111.9, 35.3 (lit.(4) ^{13}C NMR ($CDCl_3$) δ 184.2, 143.6, 143.3, 140.8, 137.9, 136.5, 136.4, 131.5, 129.7, 129.6, 121.7, 120.6, 120.5, 118.4, 111.8, 35.2.

Note added in proof: After this work had been accepted for publication we became aware of a related report on the synthesis of xestomanzamines A and B: B.E.A. Burm, P. Blokker, E. Jongmans, E. van Kampen, M.J. Wanner, and G.-J. Koomen. Heterocycles, **55**, 495 (2001).

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