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SYNTHESIS OF XESTOMANZAMINES A AND B

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Abstract - Synthetic pathways are described for the synthesis of two naturally occurring β-carbolines, xestomanzamine A and B. The synthesis of aromatic xestomanzamine A was most conveniently achieved by way of a Grignard reaction in dichloromethane. This route is suitable for the synthesis of analogues with modifications in the imidazole ring of xestomanzamine A. Xestomanzamine B, an oxidation-sensitive dihydro-β-carboline, was prepared by Pictet-Spengler condensation of tryptamine with a vicinal tricarbonyl substituted imidazole.

INTRODUCTION

In 1995 four new biologically active β-carbolines were isolated from the Okinawan marine sponge *Xestospongia* sp.[1] Amongst those xestomanzamine A (**1**) and B (**2**) were characterised, the latter exhibiting cytotoxicity against human epidermoid carcinoma (KB) cells.[2] It was found that the 3,4-dihydro-β-carboline system in **2** was gradually converted to β-carboline derivative (**1**) by air-oxidation.

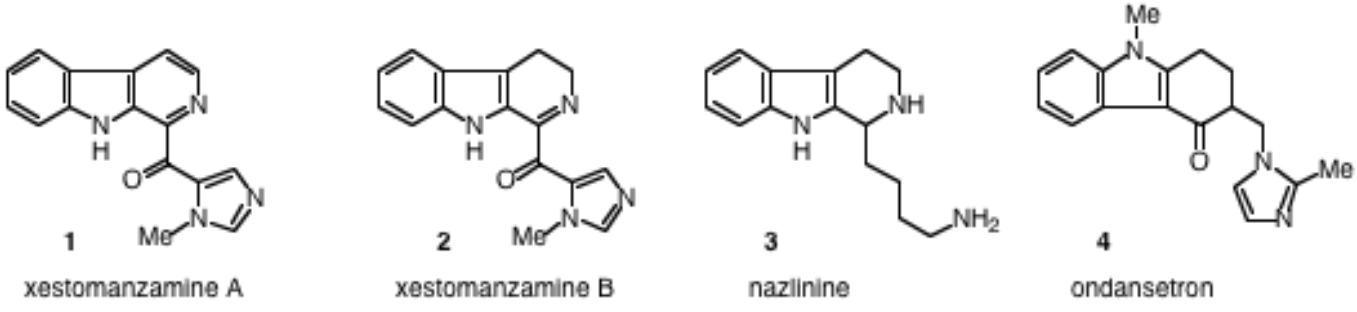

Figure 1. Naturally occurring xestomanzamines A and B and nazlinine and 5-HT_3 antagonist ondansetron.

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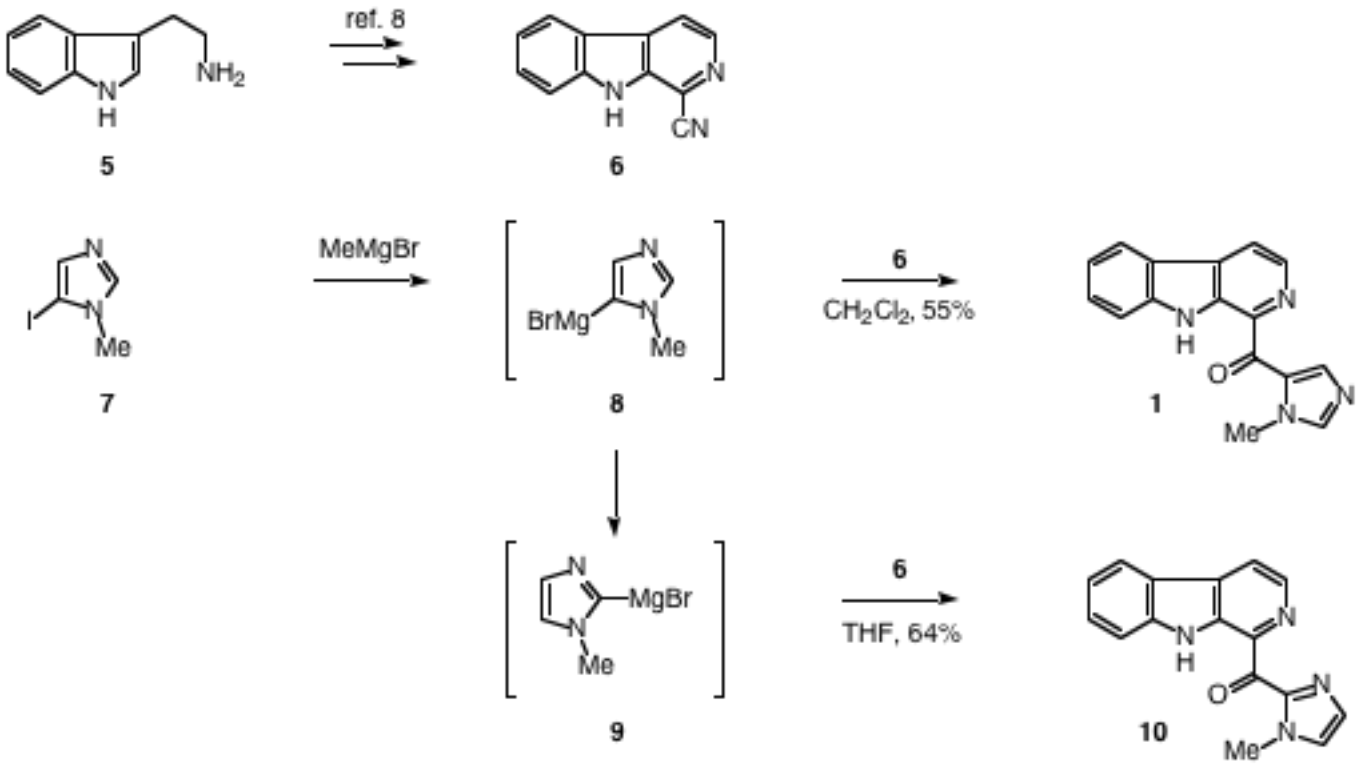
The alkaloid nazlinine (**3**) was isolated and characterised several years ago[3] and has been the subject of synthetic studies in our group[4] and others[5] for some time. In view of the structural similarities among **1**-**3**, **1** and **2** can be regarded as conformationally restricted nazlinine analogues, in which one of the nitrogen atoms is part of the imidazole ring. In addition, there is a resemblance between **1**, **2** and ondansetron (**4**), which is a known 5-HT_3 antagonist.[6]

Untill now only one synthesis of xestomanzamine A (**1**) has been published[7] with as a key step the addition of a C2-protected 5-lithioimidazole to a β-carboline. We wish to report here a new straightforward synthesis of xestomanzamine A (**1**), as well as a strategy to synthesise the air sensitive xestomanzamine B (**2**). Due to the limited stability of **2**, *vide supra*, the imine bond in the 3,4-dihydro-β-carboline system had to be introduced in the last step of the synthesis.

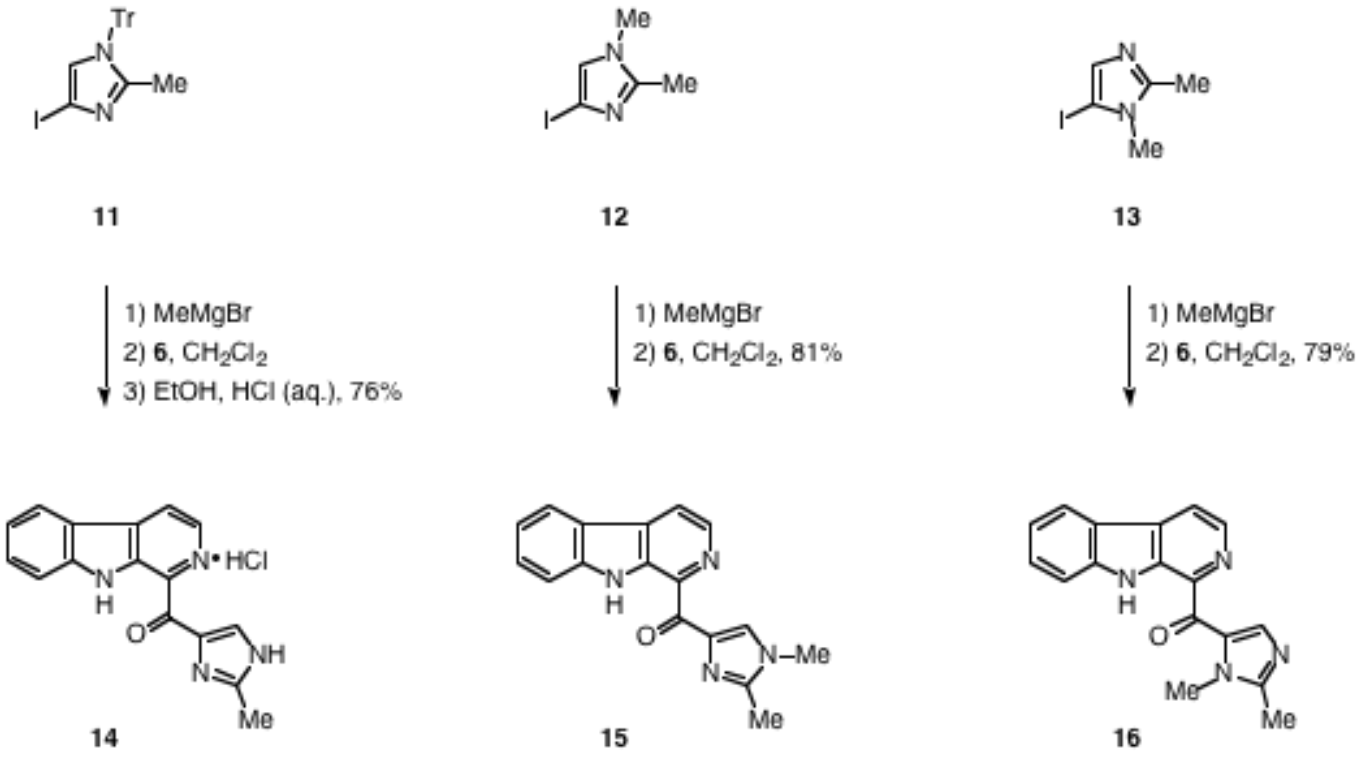
RESULTS AND DISCUSSION

Synthesis of xestomanzamine A and some analogues.

1-Cyano-β-carboline (**6**), which is readily available from tryptamine (**5**),[8] was chosen as electrophile in addition reactions with imidazole anions. A suitable imidazole nucleophile is not found straightforwardly, since the 4(5)-lithium- or magnesiumimidazoles, which are initially formed after halogen/ metal exchange, rearrange to the thermodynamically more stabile 2-metallated isomers. This process can be prevented by blocking the 2-position with a triethylsilyl substituent, as was applied in the xestomanzamine A synthesis of Molina *et al.*[7] We here report an alternative approach that prevents this 5 → 2 organometal rearrangement, the so-called "dance reaction",[10,9] by using Grignard reagent (**8**) in dichloromethane as the solvent instead of the more commonly used ether or THF (Scheme 1). Imidazolemagnesium bromide (**8**) is prepared by an exchange reaction of 5-iodo-1-methylimidazole (**7**) with methylmagnesium bromide[10]. Reaction of a dichloromethane solution of **8** with 1-cyano-β-carboline (**6**) followed by hydrolytic work-up immediately produced xestomanzamine A (**1**) in 55% yield. Due to the acidity of the indole N-H two equivalents of the imidazole anion were necessary to complete the reaction. Indeed when a co-ordinating solvent like THF was used, isomer (**10**) of xestomanzamine A was obtained *via* rearrangement of **8** to **9**. Examples of such a base-catalysed halogen "dance reaction" have been reported for imidazoles,[11,12] but the reaction was first described to occur in aryl halides.[13] Also halogenated thiophenes are known to undergo this rearrangement.[14] In order to demonstrate the general applicability of the route to **1**, three additional analogues (**14**-**16**) of xestomanzamine A (**1**) were synthesised (Scheme 2). Derivative (**14**), in which the imidazole 2-position is substituted with a methyl group, was obtained by Grignard reaction of tritylimidazole (**11**) with 1-cyano-β-carboline (**6**), followed by removal of the trityl-protecting group. The dimethyl-substituted analogues (**15**) and (**16**) were obtained in good yield using the same procedure as described for the synthesis of **1**.



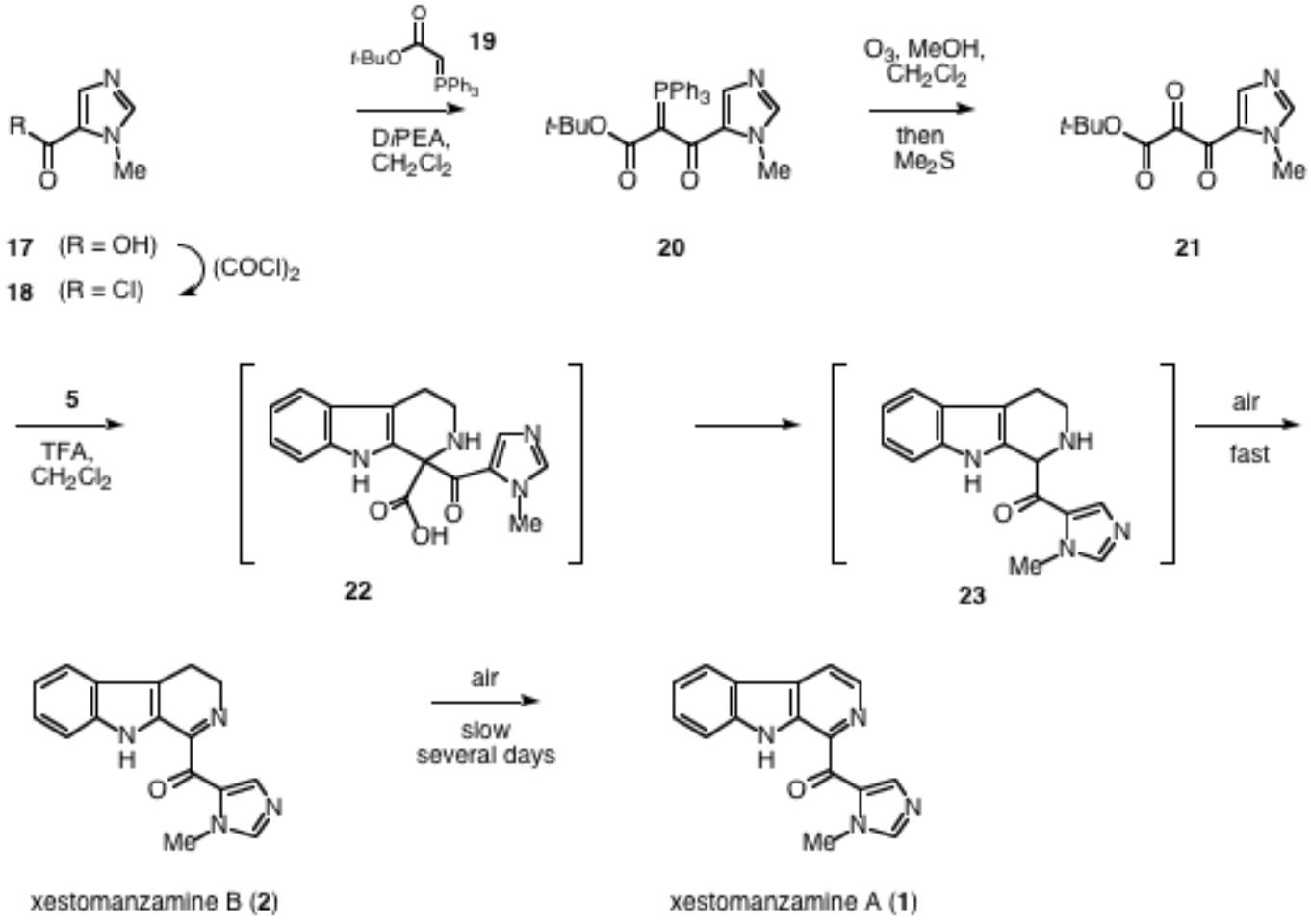
Scheme 1. Synthesis of xestomanzamine A (**1**) and demonstration of the "dance reaction".



Scheme 2. Application of the Grignard reaction in the synthesis of xestomanzamine A analogues (**14** – **16**).

Synthesis of xestomanzamine B.

For the synthesis of the partially reduced xestomanzamine B (**2**) a different strategy had to be employed since selective reduction of the 3,4-double bond in **1** was not succesful. Working with the dihydro-β-carboline ring system should be kept to a minimum, because oxidation by air-oxygen easily gives the fully aromatised **1**. For this reason the sensitive 3,4-dihydro bond in **2** was introduced in the last step of the synthesis. The key reaction of this approach is Pictet-Spengler condensation of tryptamine (**5**) with tricarbonyl substituted imidazole (**21**). Vicinal tricarbonyl compounds have been employed successfully in the syntheses of eudistomins T, I and M,[15] and isoquinoline[16] and vincamine-related alkaloids.[17]
Vicinal tricarbonyl substituted *N*-methylimidazole (**21**) was prepared from *N*-methyl-5-imidazolecarboxylic acid (**17**). A convenient large scale synthesis of the corresponding methyl ester has been described;[18] hydrolysis of the methyl ester and reaction of acid (**17**) with oxalyl chloride afforded the acid chloride (**18**). Condensation of **18** with the stabilised phosphorane (**19**)[19] yielded crystalline ylide (**20**). Ozonolysis of **20** in a mixture of dichloromethane and methanol followed by reductive work-up



Scheme 3. Synthesis of xestomanzamine B (**2**).

furnished the vicinal tricarbonyl derivative (**21**), which was used without further purification in the condensation step with tryptamine (**5**). The central carbonyl group of **21** is activated by the two other carbonyl functions for participation in the Pictet-Spengler condensation catalysed by trifluoroacetic acid. In the same reaction, the *tert*-butyl ester is cleaved to form β-keto acid (**22**) (not isolated), followed by facile decarboxylation to the tetrahydro-β-carboline (**23**). The intermediate (**23**) was oxidised *in situ* by air-oxygen to give the final product xestomanzamine B (**2**) in a yield of 43% starting from ylide (**20**). The reaction time and purification of **2** had to be controlled carefully in order to supress the second oxidation step to the fully aromatised xestomanzamine A (**1**).
Synthetic xestomanzamine A (**1**)‡ and B (**2**) were identical in all aspects (mp, IR, MS, ^{1}H and ^{13}C NMR) with the natural alkaloids.[1]

CONCLUSIONS

New routes were developed for the synthesis of the alkaloids xestomanzamine A (**1**) and B (**2**). A modified Pictet-Spengler reaction between tryptamine and a vicinal tricarbonyl substituted imidazole is a useful strategy for the synthesis of the air-sensitive xestomanzamine B (**2**). A second pathway *via* Grignard reaction of imidazole magnesiumbromide with 1-cyano-β-carboline was more convenient for the synthesis of xestomanzamine A (**1**) and is in particular suitable for the preparation of a variety of analogues **10**, **14**, **15** and **16**.

EXPERIMENTAL

General Remarks: See for general information ref. 20. For ozonolysis a Fischer Ozon-generator 500 was used, which produces 1.2 g ozone per hour at an oxygen flow of 25 Lh^{-1}.
(9*H*-β-Carbolin-1-yl)-(3-methyl-3*H*-imidazol-4-yl)-methanone (Xestomanzamine A) (1): To a solution of 5-iodo-1-methylimidazole (**7**)[21] (0.35 g, 1.68 mmol) in dichloromethane (3.5 mL) was added dropwise at 0 °C a solution of methylmagnesium bromide in ether (0.61 mL, 1.83 mmol, 3 M). After stirring during 30 min the mixture was allowed to warm to rt and slowly added to a solution of 1-cyano-β-carboline[8] (170 mg, 0.86 mmol) in dichloromethane (30 mL). The mixture was stirred during one night at rt and then washed with water. The water layer was extracted with CH_2Cl_2 (3x) and the combined organic layers were washed with water (3x), dried (Na_2SO_4) and evaporated. Crystallisation from methanol gave **1**·MeOH as yellow plates (according to the ^{1}H NMR spectrum these crystals contain one equivalent of methanol, see also footnote ‡ to the text). Alternatively the product could also be purified by flash chromatography (EtOAc) to afford **1** (130 mg, 55%) as yellow needles: mp 185 - 186 °C; ^{1}H NMR

‡ Xestomanzamine A (**1**) was crystallised from methanol as yellow plates and contained one equivalent of methanol according to its ^{1}H NMR spectrum. Upon heating, the methanol evaporated and yellow needles (mp 185 - 186 °C) were formed. Alternatively, purification by flash chromatography (EtOAc) also gave those yellow needles. Kobayashi *et al.*[1] report the isolation of xestomanzamine A (**1**) as yellow needles with mp 185 - 186 °C, although their crystal structure shows the presence of one equivalent of methanol.

($CDCl_3$, 400 MHz) δ 10.42 (br s, 1H, H-9), 8.93 (s, 1H, H-13), 8.59 (d, *J* = 4.9 Hz, 1H, H-3), 8.17 (d, *J* = 6.0 Hz, 1H, H-5), 8.15 (d, *J* = 4.9 Hz, 1H, H-4), 7.67 (s, 1H, H-15), 7.63 - 7.57 (m, 2H, H-7, H-8), 7.36 - 7.32 (m, 1H, H-6), 4.10 (s, 3H, NCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 184.3, 143.4, 143.1, 140.8, 138.0, 136.6, 136.4, 131.5, 129.2, 129.1, 121.7, 120.7, 120.6, 118.5, 111.8, 35.2; IR (KBr) ν 3427, 1612; HRMS (FAB) obs. mass 277.1119, calcd for $C_{16}H_{13}N_4O$ (M + H) 277.1089.

(9*H*-β-Carbolin-1-yl)-(1-methyl-1*H*-imidazol-2-yl)-methanone (10): To a solution of 5-iodo-1-methylimidazole (**7**)[21] (50 mg, 0.24 mmol) in tetrahydrofuran (0.5 mL) a solution of methylmagnesium bromide in ether (0.09 mL, 0.27 mmol, 3 M) was added dropwise at 0 °C. After stirring during 30 min the mixture was allowed to warm to rt and slowly added to a solution of 1-cyano-β-carboline[8] (20 mg, 0.11 mmol) in tetrahydrofuran (4 mL). The mixture was stirred during one night at rt and then concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (6 mL) and water (10 mL) was added. The layers were separated and the water layer extracted with CH_2Cl_2 (2x). The combined organic layers were dried (Na_2SO_4) and evaporated. Flash chromatography (EtOAc) afforded **10** (20 mg, 64%) as a foam: ^1H NMR ($CDCl_3$, 400 MHz) δ 10.91 (br s, 1H, H-9), 8.52 (d, *J* = 5.1 Hz, 1H, H-3), 8.18 (d, *J* = 7.8 Hz, 1H, H-5), 8.08 (d, *J* = 5.1 Hz, 1H, H-4), 7.62 - 7.57 (m, 2H, H-7, H-8), 7.57 (br s, 1H, H-14), 7.42 (br s, 1H, H-13), 7.34 - 7.32 (m, 1H, H-6), 3.66 (s, 3H, NCH_3); IR ($CHCl_3$) ν 3460, 1618; HRMS (FAB) obs. mass 277.1084, calcd for $C_{16}H_{13}N_4O$ (M + H) 277.1089.

(9*H*-β-carbolin-1-yl)-(2-methyl-3*H*-imidazol-4-yl-methanone (14): The same procedure was used as described for the synthesis of xestomanzamine A, using **11** (900 mg, 2.0 mmol), 1.1 eq. of MeMgBr and **6** (100 mg, 0.52 mmol). After work-up, the remaining residue was redissolved in ethanol (15 mL) and concd hydrogen chloride (50 mL) was added. The mixture was stirred at rt during 3 h and subsequently washed with ether and concentrated under reduced pressure. The residue was dissolved in a saturated, aqueous K_2CO_3 solution which was extracted with EtOAc (3x). The combined organic layers were dried (Na_2SO_4) and evaporated. Flash chromatography (EtOAc/ NEt_3 90/ 10) afforded **14** (109 mg, 76%). Crystallisation of the HCl salt from EtOH/ HCl gave a solid white material: mp 246 - 248 ºC; ^1H NMR (DMSO-d_6, 400 MHz) δ 12.09 (br s, 1H, H-9), 8.94 (s, 1H, H-15), 8.62 (d, *J* = 4.9 Hz, 1H, H-3), 8.55 (d, *J* = 4.9 Hz, 1H, H-4), 8.35 (d, *J* = 7.8 Hz, 1H, H-5), 7.88 (d, *J* = 8.2 Hz, 1H, H-8), 7.67 - 7.63 (m, 1H, H-7), 7.37 - 7.34 (m, 1H, H-6), 2.73 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 180.4, 147.4, 141.9, 138.0, 135.3, 134.2, 131.6, 129.3, 129.2, 127.7, 122.0, 120.6, 120.1, 119.9, 113.2, 11.5; IR (KBr) ν 3347, 1621; HRMS (FAB) obs. mass 277.1086, calcd for $C_{16}H_{13}N_4O$ (M + H) 277.1089.

(9*H*-β-Carbolin-1-yl)-(1,2-dimethyl-1*H*-imidazol-4-yl)-methanone A (15): The same procedure was used as described for the synthesis of xestomanzamine A, using **12** (444 mg, 2.0 mmol), 1.1 eq. of MeMgBr and **6** (100 mg, 0.52 mmol). Flash chromatography (EtOAc/ NEt_3 95/ 5) afforded **15** (122 mg, 81%) as a yellow solid: mp 200 - 204 ºC; ^1H NMR (DMSO-d_6, 400 MHz) δ 11.82 (br s, 1H, H-9), 8.53 (d, *J* = 4.7 Hz, 1H, H-3), 8.31 - 8.29 (m, 3H, H-4, H-5, H-15), 7.87 (d, *J* = 8.2 Hz, 1H, H-8), 7.59 - 7.55 (m, 1H, H-7), 7.30 - 7.27 (m, 1H, H-6), 3.68 (s, 3H, NCH_3), 2.41 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 167.1, 145.4, 140.9, 137.5, 137.0, 134.7, 134.3, 133.4, 129.5, 128.3, 121.6, 120.3, 119.7, 116.5,

113.0, 32.7, 12.5; IR (KBr) ν 3356, 1593; HRMS (FAB) obs. mass 291.1240, calcd for $C_{17}H_{15}N_4O$ (M + H) 291.1246.

(9*H*-β-Carbolin-1-yl)-(2,3-dimethyl-3*H*-imidazol-4-yl)-methanone (16): The same procedure was used as described for the synthesis of xestomanzamine A, using **13** (444 mg, 2.0 mmol), 1.1 eq. of MeMgBr and **6** (100 mg, 0.52 mmol). Flash chromatography (EtOAc/ NEt_3 95/ 5) afforded **16** (118 mg, 79%) as a yellow solid: mp 264 - 267 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.99 (br s, 1H, H-9), 8.56 - 8.54 (m, 2H, H-3, H-15), 8.43 (d, *J* = 4.4 Hz, 1H, H-4), 8.32 (d, *J* = 7.6 Hz, 1H, H-5), 7.83 (d, *J* = 8.0 Hz, 1H, H-8), 7.63 - 7.61 (m, 1H, H-7), 7.33 - 7.32 (m, 1H, H-6), 4.00 (s, 3H, NCH_3), 2.47 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 182.3, 151.4, 141.9, 141.6, 137.2, 137.0, 135.2, 131.0, 129.6, 128.8, 121.7, 120.1, 120.0, 118.6, 113.0, 33.0, 13.2; IR (KBr) ν 3244, 1609; HRMS (FAB) obs. mass 291.1276, calcd for $C_{17}H_{15}N_4O$ (M + H) 291.1246.

3-Methyl-3*H*-imidazole-4-carbonyl chloride•HCl (18): A suspension of **17**[18,¶] (0.74 g, 5.8 mmol), oxalyl chloride (5.4 mL, 60 mmol) and dimethylformamide (1 drop) in dichloromethane (10 mL) was stirred vigorously during one night at rt. The suspension was filtered and the residue was washed with dry CH_2Cl_2 to give **18** (0.90 g, 85%) as its solid hydrogen chloride salt which was immediately used in the next step: IR (KBr) ν 2991, 2749, 2597, 1774, 1561, 1457.

3-(3-Methyl-3*H*-imidazol-4-yl)-3-oxo-2-(triphenyl-λ^5-phosphanylidene)-propionic acid *tert*-butyl ester (20): To a solution of *tert*-butyl(triphenylphosphoranylidene)acetate (**19**)[19] (1.82 g, 4.83 mmol) and *N*,*N*-di*iso*propylethylamine (2.18 mL, 15 mmol) in dichloromethane (25 mL), **18** (0.88 g, 4.83 mmol) was added at 0 °C. The solution was subsequently stirred during 30 min at 0 °C and 4 h at rt. An saturated aqueous Na_2CO_3 solution was added and the layers were separated. The water layer was extracted with CH_2Cl_2 (3x) and the combined organic layers were dried (Na_2SO_4) and evaporated. Crystallisation from EtOAc gave a first crop of **20**. By flash chromatography (EtOAc/ EtOH 90/ 10) of the motherliquor followed by crystallisation from EtOAc, **20** (1.12 g, 2.41 mmol) was obtained in a total yield of 41%: mp 168 - 169 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77 - 7.72 (m, 6H, Ar-H), 7.57 (s, 1H, H-2), 7.56 - 7.51 (m, 3H, Ar-H), 7.48 - 7.44 (m, 6H, Ar-H), 7.33 (s, 1H, H-4), 3.69 (s, 3H, NCH_3), 1.03 (s, 9H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.2 (C-6, $^2J_{CP}$ = 8.0 Hz), 166.6 (C-8, $^2J_{CP}$ = 12.4 Hz), 139.4, 134.2, 133.5, 133.1 (Ar-C) 131.6 (Ar-C, $^4J_{CP}$ = 3.0 Hz), 128.4 (Ar-C, $^2J_{CP}$ = 13.1 Hz), 126.3 (Ar-C, $^2J_{CP}$ = 92.6 Hz), 78.5 ($C(CH_3)_3$), 69.7 (C-7, $^1J_{CP}$ = 111 Hz), 33.0 (NCH_3), 27.9 ($C(CH_3)_3$); IR (KBr) ν 1669, 1657; HRMS (EI) obs. mass 484.1902 calcd for $C_{29}H_{29}N_2O_3P$ 484.1916.

Ozonolysis of phosphorane (20) to 3-(3-methyl-3*H*-imidazol-4-yl)-2,3-dioxo-propionic acid *tert*-butyl ester (21): Ozone was passed through a solution of **20** (98 mg, 0.2 mmol) in a mixture of methanol (2 mL) and dichloromethane (6 mL) at -60 °C until the starting material had disappeared according to TLC analysis (about 10 min). Nitrogen gas was bubbled through the solution during 15 min at -60 °C to

¶ 1-Methyl-5-imidazolecarboxylic acid (**17**) was synthesised by hydrolysis (6 M NaOH, 80 °C, 18 h) of the corresponding methyl ester[18] and obtained by crystallisation after adjusting the pH to 2 (concd HCl): mp 256 - 258 °C; ^{1}H NMR (D_2O, 400 MHz) δ 7.63 (s, 1H, H-2), 7.43 (s, 1H, H-4), 3.85 (s, 3H, NCH_3); ^{13}C NMR (D_2O, 100 MHz) δ 170.6 (C-6), 144.4 (C-5), 135.9 (C-4), 132.1 (C-2), 36.4 (NCH_3); IR (KBr) ν 1699.

remove excess ozone and the reaction was quenched with an excess of dimethyl sulfide. The reaction mixture was concentrated *in vacuo* at rt to afford **21** which was immediately used in the Pictet-Spengler condensation.

(4,9-Dihydro-3*H*-β-carbolin-1-yl)-(3-methyl-3*H*-imidazol-4-yl)-methanone (Xestomanzamine B) (2): Freshly prepared **21** (from **20**: 98 mg, 0.2 mmol) was dissolved in dichloromethane (5 mL) and a solution of tryptamine (40 mg, 0.25 mmol) in dichloromethane (4 mL) was added. The reaction mixture was stirred during 4 h at rt under nitrogen atmosphere. Trifluoroacetic acid (1 mL) was added and this solution was stirred during 4 h in an open vessel. Saturated aqueous Na_2CO_3 solution (5 mL) and water (5 mL) were added, the product was extracted with CH_2Cl_2 (3x) and the combined organic layers were dried (Na_2SO_4) and evaporated. Flash chromatography (EtOAc/ EtOH 90/ 10 → 75/ 25) gave **2** (24 mg, 43%) as a glass. The product had to be purified fast and kept strictly under a nitrogen atmosphere, otherwise air-oxidation resulted in the formation of substantial amounts of the fully aromatised **1**. In a separate experiment following the same procedure, omitting the nitrogen atmosphere, **1** (20 mg, 0.06 mmol, 28%) was isolated as a yellow crystalline compound. The spectral data of **1** were identical to those obtained from the synthesis of **1** *via* the Grignard exchange reaction.

2: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.53 (br s, 1H, H-9), 8.37 (s, 1H, H-13), 7.63 (s, 1H, H-15), 7.60 (d, *J* = 8.0 Hz, 1H, H-5), 7.40 (d, *J* = 8.3 Hz, 1H, H-8), 7.29 (dd, *J* = 8.3 Hz, *J* = 7.1 Hz, 1H, H-7), 7.14 (dd, *J* = 8.0 Hz, *J* = 7.1 Hz, 1H, H-6), 4.16 (dd, *J* = 8.9 Hz, *J* = 8.7 Hz, 2H, H-3), 4.00 (s, 3H, NCH_3), 2.98 (dd, *J* = 8.9 Hz, *J* = 8.7 Hz, 2H, H-4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.7, 155.7, 144.1, 144.0, 136.8, 128.5, 126.2, 125.0, 124.6, 120.2, 119.8, 117.9, 112.1, 49.0, 35.0, 18.7; IR ν 3459, 1641; HRMS (FAB) obs. mass 279.1245 calcd for $C_{16}H_{15}N_4O$ (M + H) 279.1246.

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