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Iminophosphorane-Mediated Synthesis of 1-Acyl-β-Carbolines : A New Access to the Alkaloids Eudistomin T, S and Xestomanzamine A of Marine Origin .

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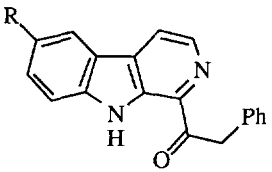
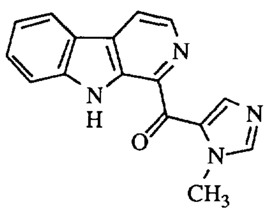
Abstract: *New syntheses of the alkaloids eudistomin T and S are described. The key step, formation of the 1-phenylacetyl β- carboline, involves a tandem aza Wittig / electrocyclic ring closure process. The first synthesis of the alkaloid xestomanzamine A is achieved by coupling of a N-protected harmane, now available via aza Wittig / electrocyclic ring closure process, with a 5-lithioimidazole derivative.*

In 1984 Rinehart et al[1] reported the isolation of seventeen indole containing alkaloids named eudistomins, from the active Caribbean colonial tunicate *Eudistoma olivaceum* . Twelve are β-carbolines either unsubstituted at C-1 or with a heteroaromatic substituent at C-1.Contemporaneously, Cardenilla et al[2] reported the isolation from these species of three new β-carbolines bearing a phenylacetyl group at C-1, eudistomins R, S and T, which display antimicrobial activity. Recently,[3] two new β-carboline alkaloids, which contain a heteroaroyl substituent at C-1, xestomanzamine A and xestomanzamine B, have been isolated as cytotoxic constituents from an Okinawan marine sponge *Xestopongia sp* . In 1996, hyrtiomanzamine, a β-carboline alkaloid closely related to xestomanzamine A which displays immunosuppressive activity has been isolated from the marine sponge *Hyrtios erecta* collected in the Red Sea.[4] Synthetic approaches towards eudistomin T involve either acylation of 2-(3-indolyl) ethyl isocyanide with phenylacetyl chloride followed by cyclization and further aromatization,[5] or Pictet-Spengler cyclization reaction between tryptamine and the appropriate 1, 2, 3 -tricarbonyl compounds [6] or glyoxylic acid.[7] The only reported synthesis of the eudistomin S is based on the 1, 2, 3-tricarbonyl compound approach. To the best of our knowledge no synthesis of the xestomanzamine A **3** has been previously reported.

In the course of our studies directed towards the synthesis of nitrogen heterocyclic compounds based on the heterocyclization reactions of azahexatriene system, we have developed the so-called aza Wittig/ electrocyclic ring-closure strategy for the synthesis of fused pyridines.[8] This methodology has been successfully applied to the synthesis of eudistomin U, [9] a β-carboline alkaloid with a 3-indolyl substituent at C-1. We have been interested in developing a reliable general route to β-carboline alkaloids with an acyl substituent at C-1 following the aza Wittig / electrocyclic ring-closure strategy.



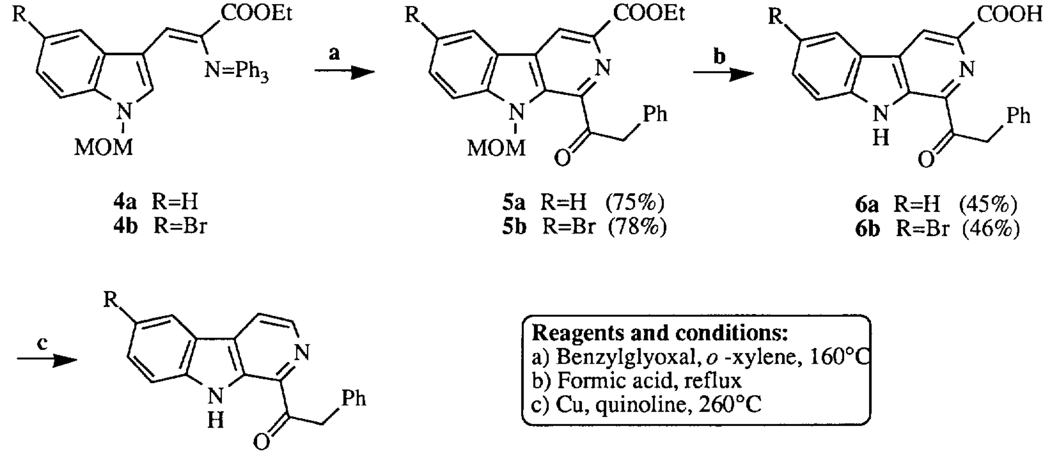
1 R=H Eudistomin T
2 R=Br Eudistomin S



3 Xestomanzamine A

Herein, we want to report the synthesis of the antibacterial compound eudistomin T **1**, eudistomin S **2** and the first synthesis of the xestomanzamine A **3**.

The formation of eudistomin T **1** illustrates the procedure used in this work. Iminophosphorane **4a**, available from N-methoxymethyl-3-formylindole by sequential treatment with ethyl azidoacetate and triphenylphosphine,[10] reacted with benzylglyoxal[11] in *o* -xylene at 160°C to give the 1-phenylacetyl β -carboline **5a** in 75% yield thus completing the assemblage of the carbon skeleton of eudistomin T. Compound **5a** was converted into the eudistomin T in a straighforward manner: (a) deprotection of the N-methoxymethyl substituent and hydrolysis of the ester group with formic acid at reflux temperature (45%) and finally (b) decarboxylation with copper/ quinoline at 260°C (44%). For the synthesis of eudistomin S **2** we used the iminophosphorane **4b** as a precursor of the β-carboline ring. Iminophosphorane **4b** was available from 5-bromo-3-formylindole by the three-step sequence : (a) N-protection with chloromethylmethyl ether (56%), (b) condensation with ethyl azidoacetate (75%) and (c) Staudinger reaction with triphenylphosphine (85%). Aza Wittig reaction of **4b** with benzylglyoxal, treatment of the resulting β-carboline **5b** with formic acid followed by decarboxylation, produced the desired eudistomin S **2**.



4a R=H
4b R=Br

5a R=H (75%)
5b R=Br (78%)

6a R=H (45%)
6b R=Br (46%)

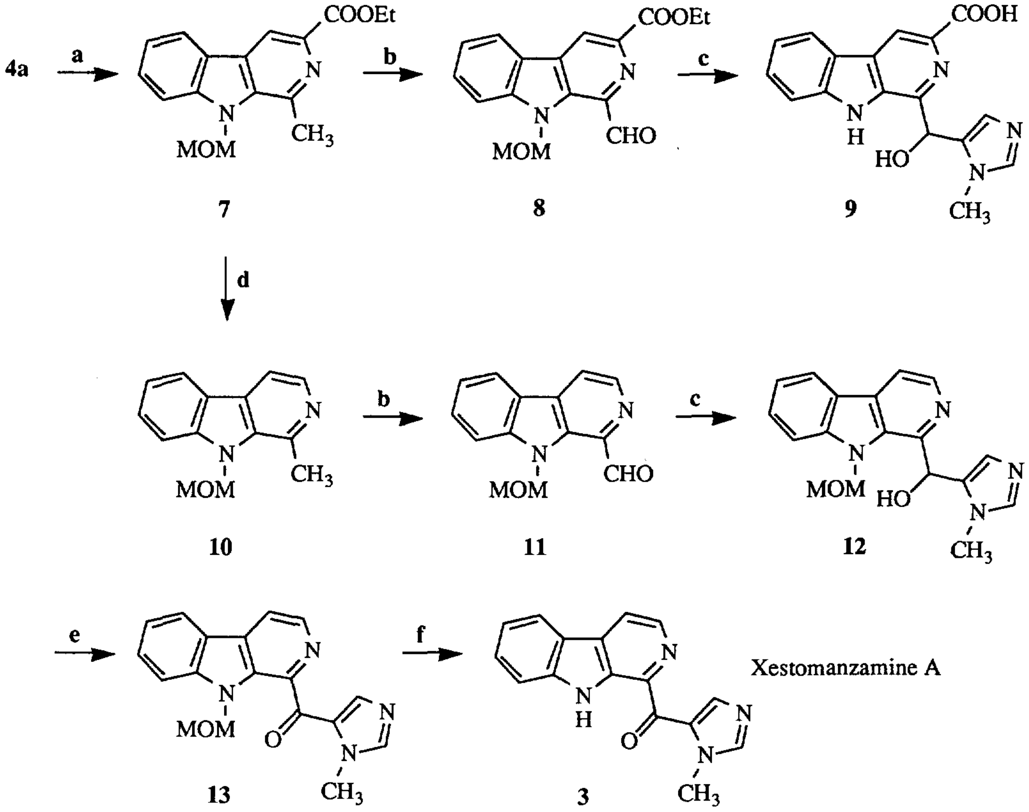
Reagents and conditions:
a) Benzylglyoxal, *o* -xylene, 160°C
b) Formic acid, reflux
c) Cu, quinoline, 260°C

1 R=H Eudistomin T (44%)
2 R=Br Eudistomin S (45%)

Compounds **1** and **2** were identical in all aspects (IR, MS, ^{1}H and ^{13}C n.m.r.) with the natural products.

Iminophosphorane **4a** has also been used as starting material in the synthesis of the xestomanzamine A. Thus compound **4a** reacted with acetaldehyde in *o* -xylene at 160°C in the presence of palladium on charcoal to give the 1-methyl-β-carboline **7** in 76% yield, which was converted into the 1-formyl-β-carboline **8** in 87% yield by oxidation with SeO_2. Reaction of compound **8** with 5-lithio-1-methyl-2-triethylsilylimidazole[12] in THF at -78°C gave the 1-substituted β-carboline **9** in 48%. One - flask conversion of compound **9** into the target compound **3** was achieved by oxidation with freshly made Jones reagent followed by decarboxylation, albeit in lower yield than 15%. This frustrating result led us to reexamine the reaction sequence. Thus, hydrolysis, deprotection and finally decarboxylation of compound **7** provided the N-methoxymethyl harmane **10** in an overall yield of 68%, this compound can also be prepared from harmane in 66% yield. Conversion of **10** into xestomanzamine **3** was achieved following the above described sequence: (a) oxidation with SeO_2 (80%), (b) coupling with 5-lithio-1-methyl-2-triethylsilylimidazole (47%) and finally (c) oxidation with Jones reagent and deprotection (94%).[14]

In conclusion, we have developed the first synthesis of the β-carboline alkaloid xestomanzamine A by a six-step sequence and new syntheses of eudistomin T and S by a three-step sequence, in which the key step, formation of the 1-phenylacetyl-β-carboline ring involves an aza Wittig/electrocyclic ring-closure process, demonstrating the usefulness of this approach.



Reagents and conditions: a) Acetaldehyde,*o* -xylene, Pd/C, 160°C; SeO_2, dioxane , reflux; c) 5-lithio-1-methyl-2-triethylsilylimidazole, THF, -78°C d) LiOH, THF / H_2O → formic acid, reflux → Cu / quinoline; e) Jones reagent, acetone, r.t.; f) formic acid, reflux.

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11. Bestmann, H.J.; Klein, O. ; Göthlich, L.; Buckschewski, H. *Chem. Ber.* **1963**, 2259.
12. Preparation of 5-lithio-1-methyl-2-triethylsilylimidazole has been carried out using the same method that described[13] for the preparation of 5-lithio-2-triethylsilyl-N,N-dimethylimidazole-1-sulphonamide: 2-metalation of 1-methylimidazole with nBuLi, blocking of this position with the triethylsilyl group and regioselective 5-metallation with SecBuLi.
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14. *Typical procedure:* To a mixture of **7** (0.5, 1.67 mmol), water (5 ml) and THF (20 ml), was added LiOH (0.12 g, 5 mmol), the solution was stirred at room temperature for 14 h. The corresponding N-protected carboxylic acid (90%) was isolated after acidification with concentrated hydrochloric acid. A solution of the carboxylic acid (0.5 g, 1.8 mmol) in 85% formic acid (30 ml) was refluxed for 12 h. After cooling , the solution was concentrated to dryness and the residue was chromatographed on a silica gel column (dichloromethane/ethanol 9:1) to give the N-deprotected carboxylic acid (85%). A mixture of this compound (0.1g, 0.4 mmol), copper (3 mg) and dry quinoline (2 ml) was heated at 240°C under nitrogen for 1 h. After filtration, the solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column, with dichloromethane/ethanol (9:1) as eluent to give **10** (88%), m.p. 60-61°C. To a solution of compound **10** (0.4 g, 1.7 mmol) in dioxane (20 ml), SeO_2 (0.44 g, 3.9 mmol) was added. The resultant solution was refluxed for 4 h. After cooling, the solvent was removed under reduced pressure and the residual material was chromatographed on a silica gel column, with ethyl acetate/ n-hexane (3:4) as eluent to give **11** (80%, m.p. 104-106°C). To a cooled at -78°C solution of 5-lithio-1-methyl-2-triethylsilylimidazole (0.63g, 3.12 mmol) in THF (20 ml), a solution of compound **11** (0.24 g, 1 mmol) in the same solvent (5 ml) was added. The resultant solution was stirred at that temperature for 30 min and then allowed to warm to room temperature and stirred for an additional 3 h. The solvent was removed under reduced pressure and the residual material was slurried with 2N hydrochloric acid (30 ml) for 16 h. The solution was extracted with n-hexane (2x10 ml), and a 40% NaOH solution was added until pH=8. The resultant mixture was extracted with ethyl acetate (6x20 ml) and the organic layers were dried on anhydrous $MgSO_4$. Filtration and elimination of the solvent gave a crude which was chromatographed on a silica gel column, using ethanol as eluent, to give **12** (47%, m.p. 141-142°C). ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 3.15 (s, 3H, CH_3O), 3.86 (s, 3H, CH_3N), 5.17 (d, 1H, J=12Hz, CH_2O), 5.38 (d, 1H, J=12Hz, CH_2O), 6.05 (s, 1H, *CH* OH), 6.57 (s, 1H, imidazole proton), 7.29 (dd, 1H, J=6.8, 7.8Hz, H-6), 7.43 (s, 1H, imidazole proton), 7.47-7.55 (m, 2H, H-7 + H-8), 7.98 (d, 1H, J=5.0Hz, H-3), 8.11 (d, 1H, J=7.1Hz, H-5), 8.48 (d, 1H, J=5.0 Hz, H-4). ^{13}C n.m.r. (75 MHz, $CDCl_3$) δ 31.9 (CH_3N), 55.8 (CH_3O), 62.7 (*CH* OH), 74.9 (OCH_2N), 109.6 (C-8), 114.6 (C-4), 120.9 (C-6), 121.3 (C-4b), 121.7 (C-5), 127.8 (C-4 imidazole ring), 128.9 (C-7), 131.1 (C-4a), 133.0 (q), 134.5 (q), 137.9 (C-3), 139.2 (C-2 imidazole ring), 142.1(q), 142.3 (q); m/z (%) 322 (M^+, 32), 181 (100). To a solution of compound **12** (46 mg, 0.14 mmol) in acetone (7 ml), freshly made Jones reagent (3 ml) was added. The mixture was stirred at room temperature for 48 h. An aqueous solution of K_2CO_3 was added until pH=7 and then extracted with dichloromethane (3x10 ml). The combined organic layers were concentrated to dryness and the crude product **13** was dissolved in 85% formic acid (20 ml) and refluxed for 4 h. After cooling, the solvent was removed and the crude product was chromatographed on a silica gel column with methanol/chloroform (1:1) to give **3** (94%, m.p. 185°C). The physical data (IR, MS, ^{1}H and ^{13}C n.m.r.) of **3** are identical to those of the natural product.

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