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Iminophosphorane-Mediated Synthesis of 1-Substituted-β-Carbolines: Investigative Studies on the Preparation of Alkaloids Lavendamycin and Eudistomins Framework.

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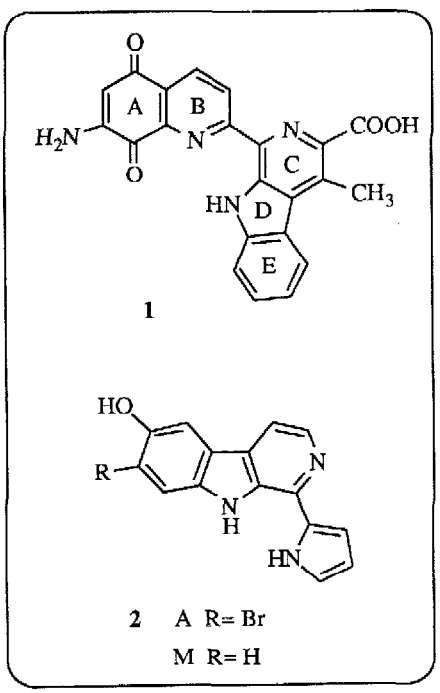
Abstract.- Aza-Wittig reaction of iminophosphorane 3, derived from ethyl α-azido-β-(3-indolyl) propenoate and tri - phenylphosphine, with 2-formylpyrrole and 2-formylquinolines leads to Eudistomins A and M and Lavendamycin derivatives respectively.

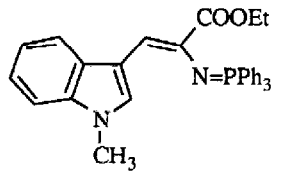
Alkaloids containing a β-carboline ring system substituted at position 1 by a heteroaryl ring represent an important class of compounds which display interesting biological activities. Lavendamycin **1**, isolated from *Streptomyces Lavendulae* and structurally and biogenetically related to Streptonigrin, displays an important antimicrobial and antitumor activity against P-388 and L-1210[1], consequently it has been the focus of synthetic efforts since its initial structural identification. Synthetic approaches towards **1** involve either Bischler-Napieralski reaction between β-methyltryptophan and quinaldic acid derivatives[2] or Pictet-Spengler cyclization reaction between β-methyltryptophan and 8-benzyloxy-2-formylquinoline[3] to construct the ring C. A recent total synthesis of **1** involves formation of the B ring by Friedlander cyclization between an o-aminobenzaldehyde possesing suitable functionality and an 1-acetyl-β-carboline derivative, available by regioselective inverse electron demand [4+2] cycloaddition followed by palladium (0)-mediated β-carboline synthesis[4]. The alkaloids Eudistomins A and M **2** which contain the rare 1-pyrrolinyl-β-carboline ring system, have been isolated[5] from the active antiviral Caribbean tunicate *Eudistoma Olivaceum*. The Eudistomin M has been prepared[6] in five-steps from 6-methoxy-1,2,3,4-tetrahydro-β-carboline-1-carboxylic acid.



In the course of our studies directed towards the synthesis of fused heterocycles based on heterocyclization reaction of unsaturated heterocumulenes, we have developed the so-called tandem aza-Wittig/ electrocyclization strategy for the synthesis of pyridines and

isoquinoline derivatives[7]. We now report a slight modification of this strategy, undertaken in order to prepare some 1-substituted β-carboline derivatives of valuable biological interest. Our approach is centered on the aza Wittig reaction of the iminophosphorane**3** derived from ethyl α-azido-β-(3-indolyl)propenoate with aldehydes to give 2-azahexatrienes which undergo cyclization to give 1-substituted-β-carbolines.

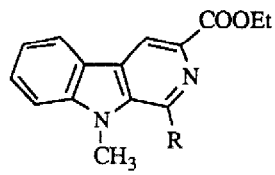
The starting iminophosphorane **3**, easily prepared from 3-formyl-1-methyl indole by sequential treatment with ethyl azidoacetate and triphenylphosphine[8], reacts with aldehydes in toluene at 160°C in a sealed tube to give 1-substituted-β-carbolines **4** in 70-88% yields. The conversion **3**→**4** involves initial aza-Wittig reaction to give a 2-azahexatriene which subsequently undergoes electrocyclic ring-closure[9]. Further dehydrogenation under the reaction conditions leads to the β-carbolines **4** (Scheme 1).



3

+ R-CHO

160 °C
Toluene



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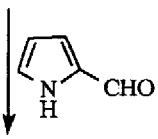
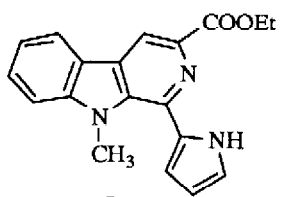




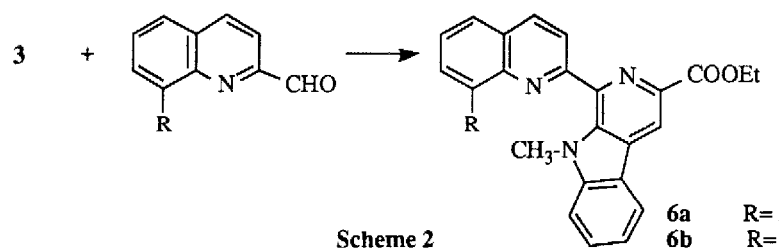
5

4	**R**	Yield (%)
a	4-$H_3C.C_6H_4$	75
b	4-$H_3CO.C_6H_4$	73
c	4-$Cl.C_6H_4$	70
d	2-Pyridyl	88

Scheme 1

In this way, iminophosphorane **3** also reacts with 2-formylpyrrole to give **5** in 70% yield[10] thus completing the assemblage of the carbon skeleton of Eudistomins A and M.

Reaction between iminophosphorane **3** and 2-formylquinoline derivatives is carried out under the same conditions. It is gratifying to note that the reaction goes smoothly to offer **6a** and **6b** , which contain the Lavendamycin ABCDE framework (Scheme 2).

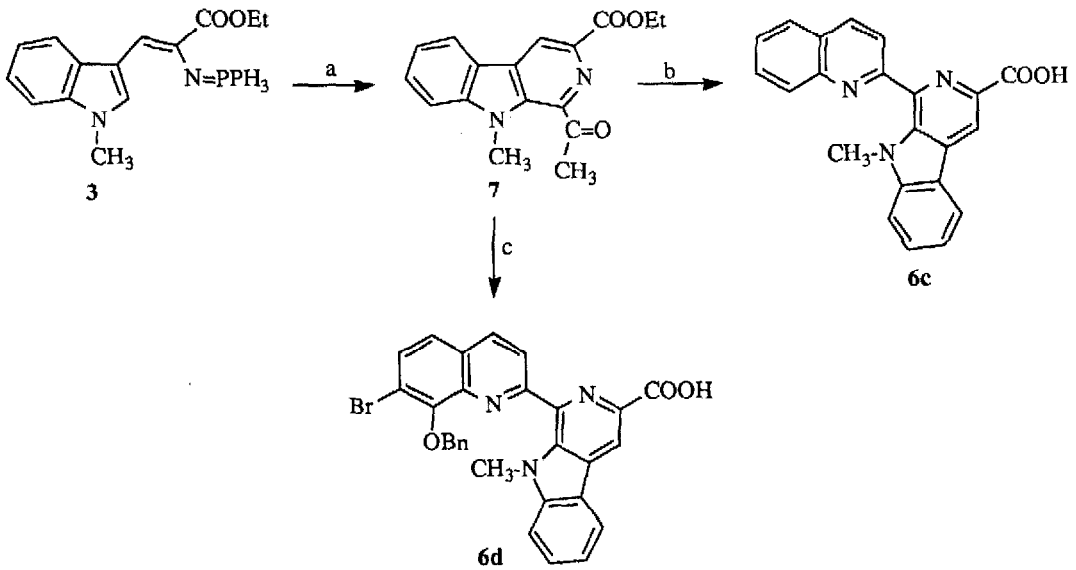


Scheme 2

6a R= H (80%)
6b R= $PhCH_2O$ (75%)

The presence in **6b** of a benzyloxy group at C-8 is exploited to introduce bromine at positions C-5 and C-7 which eventually[3] rendered the aminoquinone ring A.

Finally, iminophosphorane **3** reacts with pyruvaldehyde to give the key intermediate 1-acetyl-β-carboline **7** in 55% yield[11], which undergoes aza-Wittig reaction followed by aldol condensation with concomitant hydrolisis of the ester group by the action of the iminophosphorane derived from o-azidobenzaldehyde[12] in the presence of sodium ethoxide to give **6c** in 75 % yield. Friedlander condensation between **7** and 2-amino-3-benzyloxy-4-bromo benzaldehyde in the presence of benzyltrimethylammonium hydroxide yields **6d** in 61% yields[13] (Scheme 3).



Reagents and conditions: a) pyruvaldehyde, toluene, sealed tube,160°C; b) N-(o-formylphenyl)triphenyliminophosphorane, EtOH-NaOEt, -10°C, 30 min → reflux, 18h ; c) 2-amino-3-benzyloxy-4-bromobenzaldehyde, THF, benzyltrimethylammonium hydroxide, rt, 18h.

Scheme 3

In conclusion the results reported here show that the tandem aza-Wittig/electrocyclic ring-closure strategy affords a new and versatile entry to a variety of 1-substituted-β-carbolines. This method, which is simple and direct, leads from the readily available iminophosphorane **3** to Eudistomin and Lavendamycin derivatives[14]. Further studies are underway in our laboratory which are aimed at the application of this methodology to the formal total synthesis of Eudistomins A and M and Lavendamycin.

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References and Notes

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10. Compound **5**. ^{1}H n.m.r. (200 MHz, $CDCl_3$) δ 1.38 (t, 3H, ^{3}J=7.1Hz), 3.82 (s, 3H, CH_3-N), 4.37 (q, 2H, ^{3}J=7.1Hz), 6.31 (q, 1H, ^{3}J= 3.2Hz, H-4'), 6.52 (m,1H, H-3'), 6.94 (m, 1H, H-5'), 7.35 (t, 1H, ^{3}J=7.4, H-6), 7.47 (d, 1H, ^{3}J=8.3Hz, H-8), 7.63 (td, 1H, ^{3}J=7.4Hz, ^{4}J=0.6Hz, H-7), 8.11 (d, 1H, ^{3}J=7.8, H-5), 8.48 (s, 1H, H-4), 10.32 (s br, 1H, NH); ^{13}C n.m.r. (50 MHz, $CDCl_3$) δ 14.33 (CH_3), 33.11 (CH_3-N), 61.28 (CH_2), 109.06 (C-4'), 110.40(C-8), 111.89 (C-3'), 115,17 (C-5'), 119.78 (C-4), 120.79 (C-5), 121.42 (C-6), 121.56 (C-4a), 128.24 (C-2'), 128.78 (C-7), 130.51 (C-4b), 135.70 (C-9a), 136.50 (C-8a), 136.76 (C-3), 143.68 (C-1), 165.86 (CO); m/z (%) 319 (M+, 26).
11. Compound **7**. ^{1}H n.m.r. (200 MHz, $CDCl_3$) δ 1.51 (t, 3H, ^{3}J=7.1Hz), 3.00 (s, 3H, CH_3-CO), 3.97 (s, 3H,CH_3N), 4.53 (q, 2H, ^{3}J=7.1Hz), 7.39 (t, 1H, ^{3}J=7.4Hz, H-6), 7.54 (d, 1H, ^{3}J=8.2Hz, H-8), 7.68 (t, 1H, ^{3}J=7.4Hz, H-7), 8.20 (d, 1H, ^{3}J=7.7Hz, H-5), 8.96 (s, 1H, H-4); ^{13}C n.m.r. (50 MHz, $CDCl_3$) δ 14.41 (CH_3), 28.34 (CH_3-CO), 34.13 (CH_3-N), 61.61 (CH_2), 110.44 (C-8), 119.77 (C-4), 120.98 (C-4a), 121.23 (C-6), 121.48 (C-5), 129.47 (C-7), 132.26 (C-4b), 135.87 (C-9a), 136.06 (C-8a), 139.26 (C-3), 143.62 (C-1), 165.45 (*C*OOEt), 201.30 (*C*O-CH_3); m/z (%) 269 (M^+, 61).
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13. Compound **6d**. ^{1}H n.m.r. (200 MHz, DMSO-d_6) δ 3.74 (s, 3H, CH_3N), 5.17 (s, 2H, PhCH_2O), 6.90 (d, 2H, ^{3}J=7.6Hz, 2xH_o), 7.10 (t, 1H ,^{3}J=7.3Hz, H_p), 7.31 (d, 2H, ^{3}J=7.6Hz, 2xH_m), 7.40-7.55 (m, 1H, H-6), 7.65-7.76 (m, 2H, H-7 and H-8), 7.80-7.90 (m, 2H, H-6' and H-5'), 8.49 (d, 1H, ^{3}J=8.6Hz, H-3'), 8.56 (d, 1H, ^{3}J= 7.8Hz, H-5), 8.70 (d, 1H, ^{3}J=8.6Hz, H-4'), 9.10 (s, 1H, H-4). ^{13}C n.m.r. (50 MHz, DMSO-d_6) δ 34.69 (CH_3N), 75.90 (PhCH_2O), 111.11 (C-8), 117.03 (C-7'), 117.43 (C-4), 120.83 (C-4a), 121.02 (C-6), 122.23 (C-5), 123.49 (C-3'), 125.10 (C-5'), 128.06 (C_p and C_o), 128.42 (C-4'a), 128.62 (C_m), 129.39 (C-7), 131.05 (C-6 and C_{4b}), 136.57(C-9a), 136.92 (C-8a), 137.05 (C-8'a), 137.57 (C-4'), 141.43 (C-1), 143.44 (C-3), 151.88 (C-8'), 156.72 (C-2')166.60 (CO); m/z (%) 538 (M^+, 5).
14. Satisfactory ^{1}H, ^{13}C n.m.r. (values assigned by decoupling methods and 2D ^{1}H-^{13}C correlation techniques), mass spectra and elemental analyses were obtained for all new compounds.

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