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A New Approach To The Synthesis Of Lavendamycin Analogues.

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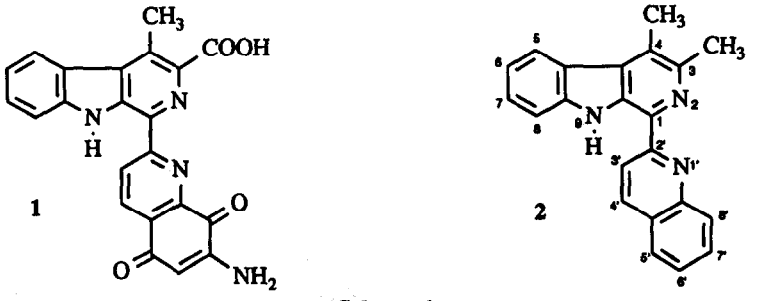
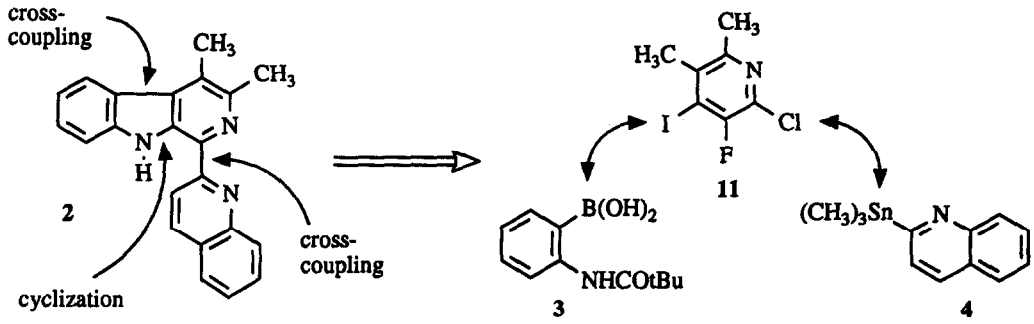
Abstract: *A three-steps approach to the lavendamycin skeleton from benzene, pyridine and quinoline blocks is described. It is based on a new synthetic methodology for the preparation of α-substituted β-carbolines which involves such reactions as Directed Ortho Metalation and Heteroring Cross-Coupling.*

Lavendamycin (1) (scheme 1) was isolated and characterized in 1981 by Doyle from the fermentation broths of *Streptomyces lavendulae*.[1-2] Some syntheses of this antitumor antibiotic or analogues have been afterwards reported.[3-7] They are mainly based on Bischler-Napieralski[4-5,7] or Pictet-Spengler[3] reactions excepted for that of Boger.[6] Our group recently published a new convergent route to α-substituted β-carbolines starting from simple benzene and pyridine reagents.[8] We wish to report here on the extension of this fruitful strategy to the construction of the Lavendamycin skeleton (2).



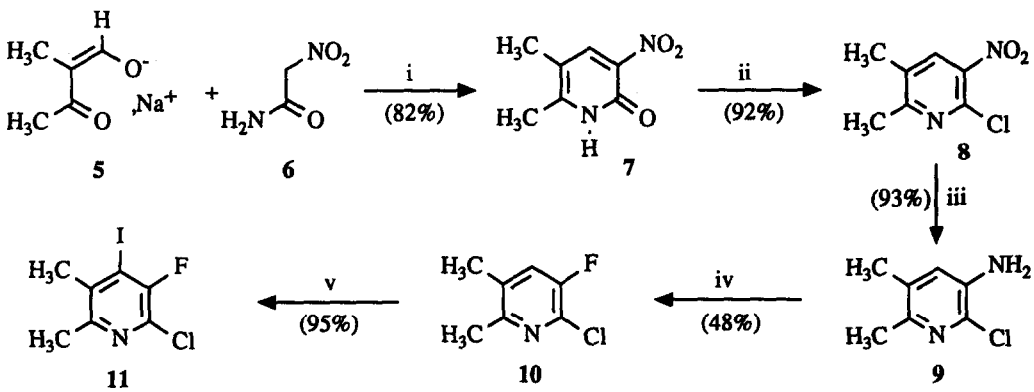
Scheme 1

A retrosynthetic analysis of 3,4-dimethyl-1-(2-quinolyl)-β-carboline (2) (a model of lavendamycin) shows that it could be obtained from benzene, pyridine and quinoline building blocks via three key-steps: a cyclization[9] and two heteroring cross-couplings[10] (scheme 2). This was successfully achieved after synthesis of the required aromatics by directed ortho metalation.[11]



Scheme 2

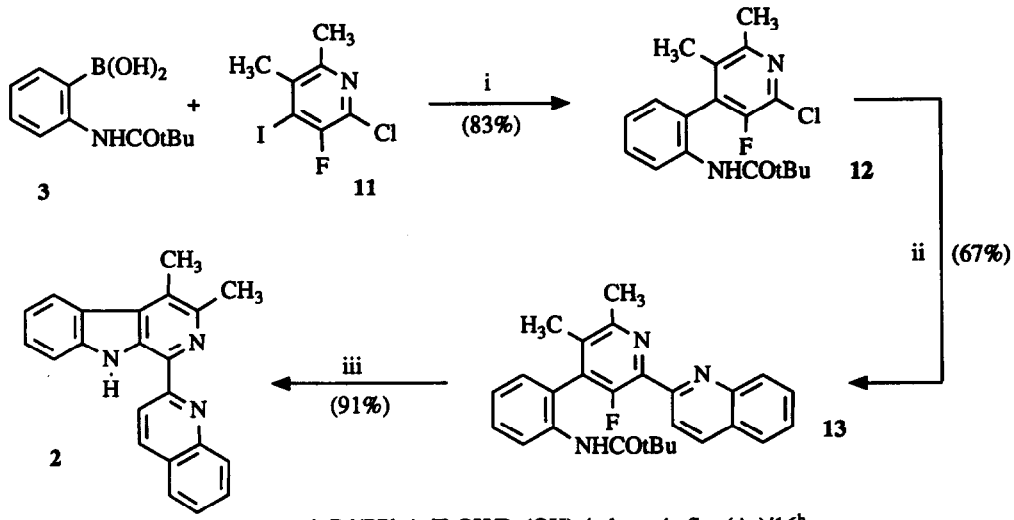
Thus, boronic acid **3** was prepared by metalation-boronation[9] of pivaloylaminobenzene in 58% yield. 2-Trimethylstannylquinoline (**4**) was obtained in 83% yield by bromine-lithium exchange and transmetalation on the corresponding 2-bromoquinoline.[8] The pentasubstituted pyridine **10** could be synthetized in four steps from pyridone **7**. This last compound was previously obtained in good yield from the sodium salt **5** and nitroacetamide (**6**) according to the Mariella procedure[12] (scheme 3). Chloration of the nitropyridone **7** with $POCl_3$ in chlorobenzene at 130°C[13] afforded the chloro compound **8** which was reduced to the desired aminochloropyridine **9**. Diazotation of the amino group with ethylnitrite in tetrafluoroboric acid[14] yielded the fluorocompound **10**. In a last step, metalation of the fluoropyridine **10** by LDA in THF at low temperature and reaction of the resulting lithio derivative with iodine afforded the corresponding iodo compound **11** in excellent yield (95%). No lithiation was observed on the acidic 6-methyl group which proves that metalation is regioselectively directed by the fluoro substituent (scheme 3).



i: piperazine,AcOH/H_2O/70°C/1^h30 ; ii: $POCl_3$/PhCl/reflux 1^h ;
iii: Fe/HCl/EtOH/H_2O/70°C/1^h ; iv: 1) EtONO/Et_2O/HBF_4 2) Hexane/ 60°C ;
v: 1) LDA/THF/-78°C/4^h 2) I_2 3) H_3O^+.

Scheme 3

Palladium-catalyzed cross-coupling between boronic acid **3** and iodopyridine **11** using a new Suzuki procedure[15] ($Ba(OH)_2$ instead of Na_2CO_3) afforded the biaryl **12** in high yield. Reaction of 2-trimethylstannylquinoline (**4**) with the biaryl **12** under the influence of catalytic $Pd(PPh_3)_4$ in refluxing toluene led to the polysubstituted triaryl **13**. Cyclization of **13** to the β-carboline **2**[16] was best achieved by treatment with boiling pyridinium chloride at 215°C (scheme 4).



i: $Pd(PPh_3)_4$/EtOH/$Ba(OH)_2$/toluene/reflux(Ar)/16[h]
ii: 2-Trimethylstannylquinoline/toluene/reflux(Ar)/60[h]
iii: 1) Pyridinium chloride/215°C/15 mn 2) NH_4OH

Scheme 4

In summary, the described strategy allows the synthesis of the lavendamycin skeleton using selective key steps.The overall approach shows a good convergence and is currently being extended to the synthesis of lavendamycin and analogues starting from conveniently functionalized benzene, pyridine and quinoline building blocks.

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16. Main physical data of this product are: mp: 201-202°C; IR (KBr) 3360, 3040, 1630, 1590, 1500, 1240, 1220, 1150, 760, 740 cm^{-1}. UV (EtOH) $\lambda_{max}(\log \varepsilon)$: 393(4.30), 278(4.36), 240(4.55), 232(4.63), 211(4.63) nm. ^1H NMR (DMSO-d^6) δ (ppm) 2.75 (s, 3H, CH_3); 2.86 (s, 3H, CH_3); 7.29 (t, 1H, H_6); 7.60 (t, 1H, H_7); 7.64 (t, 1H, H'_7); 7.86 (t, 1H, H'_6); 8.01 (m, 2H, H_8 and H'_8); 8.33 (d, 1H, H_5); 8.50 (d, 1H, H'_3); 8.69 (d, 1H, H'_5); 8.81 (d, 1H, H'_4); 10.95 (s, 1H, NH); $J_{3',4'}$= 8.7 Hz; $J_{5',6'}$= 8.5 Hz; $J_{6',7'}$= 7.4 Hz; $J_{5,6}$= 7.7 Hz; $J_{6,7}$= 7.9 Hz; ^{13}C NMR (DMSO-d^6) δ 21.67; 27.85; 118.65; 121.72; 124.39; 125.36; 126.65; 129.13; 132.41; 132.89; 133.31; 133.50; 134,96; 135.30; 138.71; 139.48; 142.34; 142.55; 147.06; 150.04; 152.92; 163.19. Anal. Calcd for $C_{22}H_{17}N_3$ (323.40): C, 81.70; H, 5.30; N, 13.00. Found: C, 81.62; H, 5.40; N, 12.85.

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