Tetrahedron Vol. 48, No. 20, pp. 4123-4134, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00

CONVERGENT SYNTHESIS OF THE STREPTONIGRIN ALKALOID SKELETON. DIRECTED ORTHOMETALATION CONNECTION TO ARYL-ARYL CROSS-COUPLING

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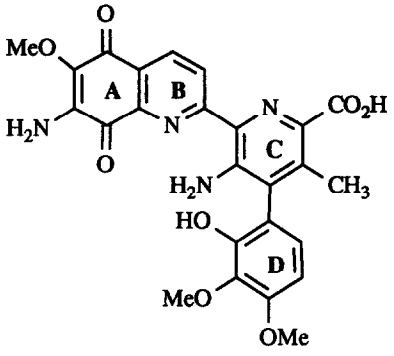
(*Received in Belgium* 13 *March* 1992)

Key Words: Streptonigrin; Alkaloid; Metalation; Palladium; Coupling.

Abstract: A convergent synthesis of 2-[2-(4-phenyl-3-pivaloylamino) pyridyl]quinolines, the streptonigrin alkaloid skeleton, is reported. The methodology involves independent elaboration of the three main building blocks by metalation and two coupling reactions catalyzed by palladium.

Streptonigrin (**1**) is an antitumor antibiotic produced by Streptomyces flocculus.[1] This compound has been shown to possess antitumor and antiviral activity.[2] Its structure incorporates a highly substituted 2-(2-pyridyl)quinoline-5,8-dione.[3] The biological properties and potential applications of this alkaloid **1** has led to many studies on its synthesis as well as of analogues.[4] This research have resulted in three elegant total syntheses [5] which involve multistep routes with poor over-all yields. Thus we have investigated a new approach to streptonigrin using palladium catalyzed biaryl cross-coupling reactions.

We report here new and more convergent synthetic approaches toward 2-[2-(4-phenyl-3-amino)-pyridyl]quinoline derivatives **2** as models of streptonigrin.[6,7]



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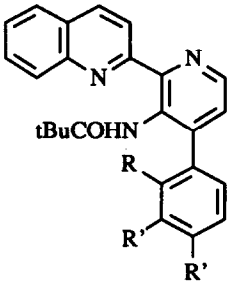

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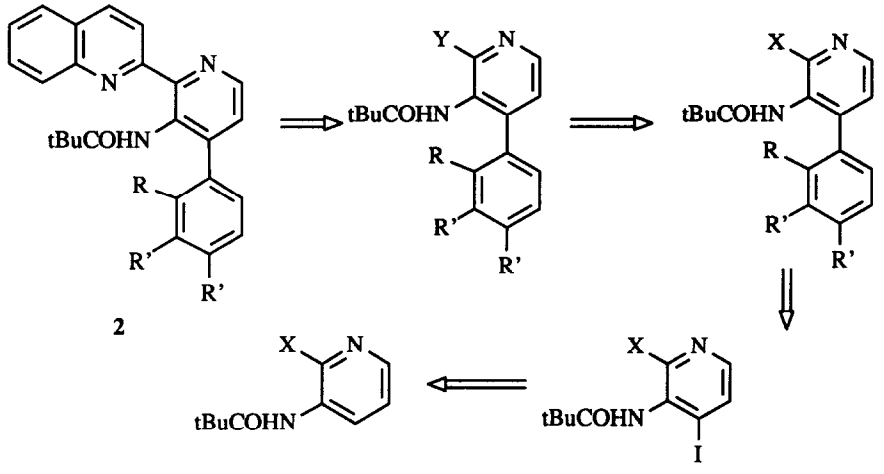
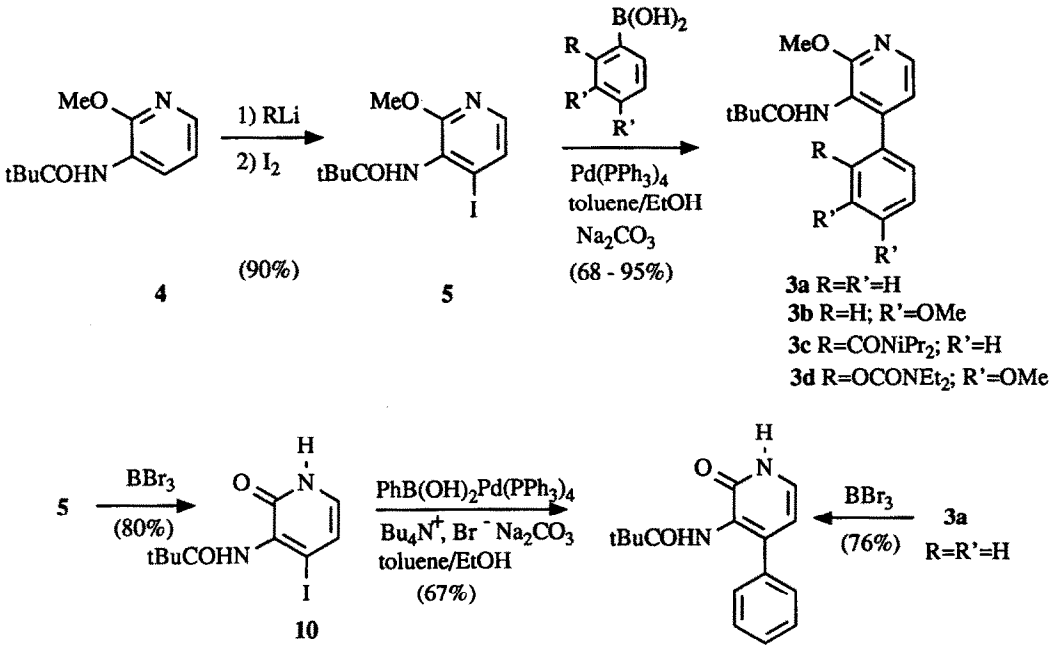
The first retrosynthetic route to structure **2** involves four main steps (scheme 1): (1) the functionalization of 2-substituted-3-pivaloylamino pyridine at C-4 by metalation; (2) a first coupling reaction with a suitable functionalized phenyl group; [6,8] (3) the transformation of substituent X into Y; (4) the construction of an α,α'-quinoline/pyridine bond through a second cross-coupling reaction.[9]



scheme 1

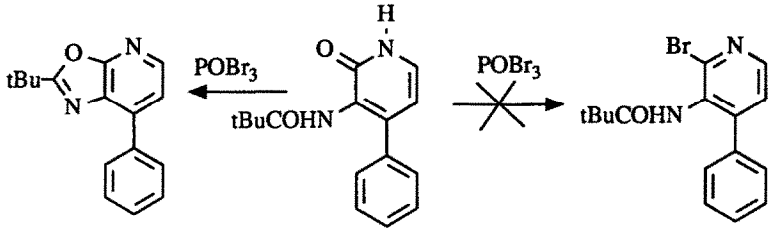
We have recently described the synthesis of 2-substituted- 4-phenyl-3-pivaloylaminopyridines.[6] We were interested in the extension of this work to 2-methoxypyridine derivatives for possible conversion of the methoxy group into suitable substituent for heteroring cross-coupling. Lithiation of 2-methoxy-3-pivaloylaminopyridines (**4**) with n-butyllithium at -10°C followed by reaction with iodine afforded 4-iodo-2-methoxy- 3-pivaloylaminopyridines (**5**) in 90% yield. Palladium catalyzed coupling of the latter with phenylboronic acids under Suzuki's conditions[10] gave the expected 4-phenylpyridines **3a-d** (yields: 68% to 95%)(scheme 2).



scheme 2

The methoxy group of **3a** (R=R'=H) was cleaved by BBr_3 to yield 4-phenyl-2-pyridone **9** (76%). Pyridone **9** could also be obtained by the following sequence: treatment of 4-iodo-2-methoxy-3-pivaloylamino pyridine **5** with BBr_3 to give the corresponding 4-iodo-2-pyridone **10** (80%), followed by cross-coupling with phenylboronic acid to yield **9** (67%)(scheme 2).

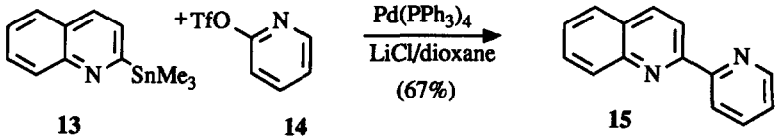
Unfortunately, the treatment of **9** with $POBr_3$ under various conditions did not give the expected 2-bromopyridine derivative **12** but rather 7-phenyl-2-tert-butyloxazolo[5,4-b] pyridine **11** (scheme 3).



11 9 12

scheme 3

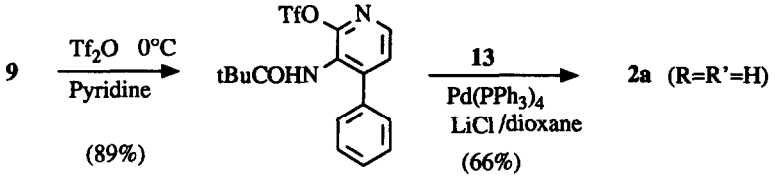
The cross-coupling methodology of Stille[11] involves the reaction of aryltriflates with arylstannanes. It could be readily applied to our synthesis since the 2-pyridone moiety of **9** is a convenient precursor of the corresponding (2-pyridyl)triflate. The facile coupling of (2-pyridyl)triflate (**14**) and (2-quinolyl)trimethylstannane (**13**) giving 2-(2-Pyridyl)quinoline (**15**) in 67% yield (scheme 4) demonstrates the feasibility of this approach.



13 **14** **15**

scheme 4

2-(4-Phenyl-3-pivaloylamino)pyridyltriflate **16** was prepared by treatment of 2-pyridone **9** with triflic anhydride at 0°C. Triflate **16** reacted with (2-quinolyl)trimethylstannane (**13**) to give the expected 2-[2-(4-phenyl-3-pivaloylamino)pyridyl]quinoline (**2a**) (R=R'=H) in 66% yield (scheme 5).



16

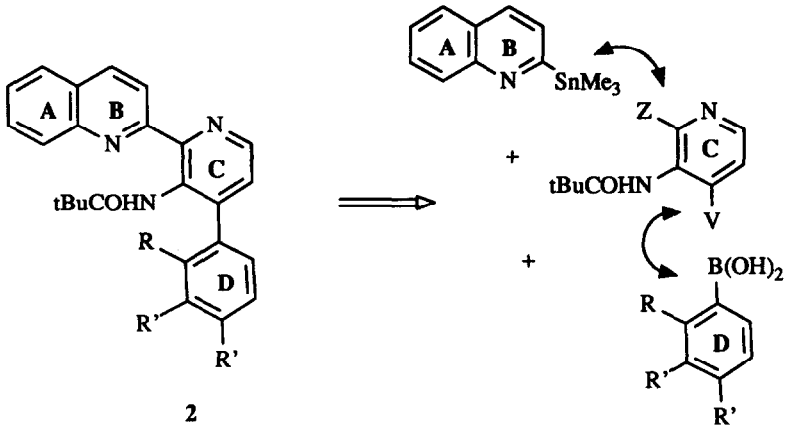
scheme 5

Thus the synthesis of a model **2a** (R=R'=H) from a simple 3-aminopyridine derivative **4** for streptonigrin was carried out in five steps in 38% over-all yield.

The extension of the previous strategy to the synthesis of streptonigrin itself requires the selective cleavage of the C-2 methoxy group on the pyridine ring in the presence of a polymethoxylated benzene ring. Unfortunately this could not be achieved either by BBr_3 or by NaSEt or by LiI. The reactivities of methoxy groups at C-2 on the pyridine ring or on the benzene ring are too close. In each case it is probably increased by the presence of an electro negative atom in the ortho position.[12]

It was thus necessary to develop another method to avoid this problem of selective cleavage of methoxy groups. This methodology was found and based on a convergent route.

The over-all strategy involves the elaboration of three main building blocks: (1) 3-pivaloylaminopyridines bearing substituents at C-2 and C-4 positions capable of selective cross-coupling reactions with aromatic reagents; (2) 2-(Quinolyl)trimethylstannane; (3) derivatives of 3,4-dimethoxy-2-hydroxyphenylboronic acids (scheme 6).

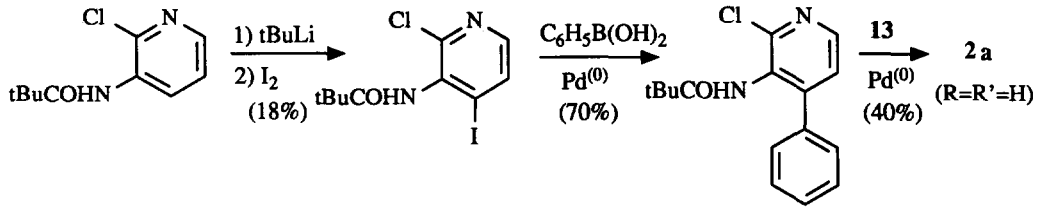


2

scheme 6

The above strategy requires the preparation of a polysubstituted pyridine bearing substituents at C-2 and C-4 for selective cross-coupling. Our first target was 2-chloro-4-iodo-3-pivaloyl aminopyridine (**17**). The chlorine atom at C-2 on a pyridine ring has been shown to allow the cross-coupling reaction albeit with a lower reactivity than the iodine atom.

2-Chloro-3-pivaloylaminopyridine (**18**) was selectively functionalized by way of a lithiation-iodination sequence using tert-butyllithium as the metalation reagent at -70°C. Unfortunately the yield of **17** was low (18%).[6] Coupling of **17** with phenylboronic acid afforded 4-phenylpyridine **19** in 70% yield. Compound **19** was then reacted with 2-(quinolyl)trimethyl stannane in the presence of $Pd(PPh_3)_4$ to give **2a** (R=R'=H) (40%) (scheme 7).

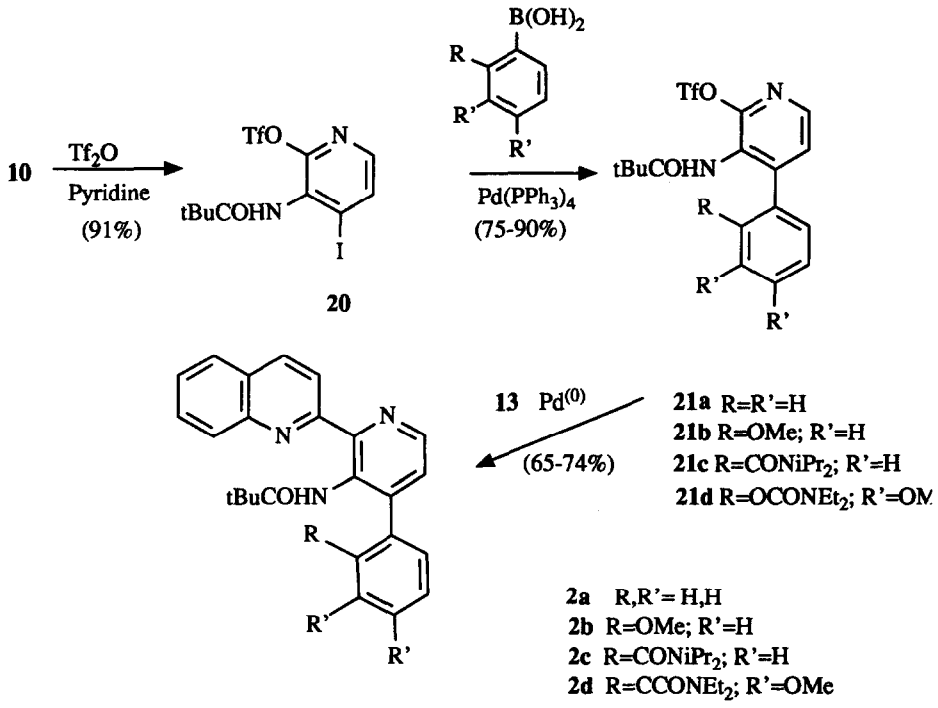


18 **17** **19**

scheme 7

The low over-all yield (5%) made it necessary to look for another C-2 substituted pyridine ring. Thus 2-(4-iodo-3-pivaloylamino)pyridyl triflate **20** was synthesized from pyridone **10** by reaction with triflic anhydride (91%). Reaction of **20** with different phenylboronic acids under Suzuki's conditions afforded 2-(4-phenyl-3-pivaloylaminopyridyl)triflates **21a,b,c,d** in 75% to 90% yield. It should be noted that phenylboronic acid itself gave 84% of the expected 2-(4-phenyl)pyridyltriflate **21a** (R=R'=H), together with 13% of 2,4-diphenyl-3-pivaloylaminopyridine **22**. The formation of compound **22** shows the possibility of coupling an aryltriflate with arylboronic acid.[13] Reaction of intermediate triflates **21** with 2-(quinolyl)trimethylstannane yielded the expected streptonigrin models **2a,b,c,d** in 65% to 74% yield.

The synthesis comprises five steps from easily available 2-methoxy-3-pivaloylaminopyridine **4** with over-all yield between 25% and 39% (scheme 8).



scheme 8

In conclusion, a convergent pathway using a 2-(4-iodo)pyridyl triflate as the key intermediate was developed for the synthesis of streptonigrin models. Syntheses of correctly substituted pyridines and quinolines are currently being carried out for the access to streptonigrin itself as well as its analogues.

Experimental Section

Melting points are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$ or in d_6-DMSO. Chemical shifts are reported in ppm from internal TMS or hexamethyldisiloxane (d_6-DMSO) or residual chloroform (7.27 ppm). Elemental analysis were performed on a Carlo Erba CHNOS 110S apparatus.

4-Iodo-2-methoxy-3-pivaloylaminopyridine (**5**) 2-Methoxy-3-pivaloyl aminopyridine (25 mmol) and TMEDA (9.5 mL, 62.5 mmol) were added to anhydrous THF (150 mL) and the mixture was cooled to -70°C. n-Butyllithium (62,5 mmol, 39 mL of a 1.6 M solution in hexane) was then slowly added. The mixture was stirred for 2 h at -10°C, cooled to -70°C and a solution of iodine (15.9 g, 62.5 mmol) in

anhydrous THF was added dropwise. After 15 min at -70°C, the solution was warmed to -10°C and stirred for 2 h at this temperature. An aqueous solution of saturated sodium thiosulfate was then added at 0°C. Extraction of the reactionmixture with methylene chloride and evaporation in vacuo, gave an oil which was purified by flash chromatography (silica gel). Eluent: hexane/Et_2O 50:50; Yield: 90%; mp 166°C. ^1H NMR ($CDCl_3$, 60 MHz): δ 1.4(s, 9 H), 3.6(s, 3 H), 7.05 (s, 1 H exch), 7.35 (d, *J= 5 Hz*, 1 H), 7.65 (d, *J= 5 Hz*, 1 H). Anal. Calcd for $C_{11}H_{15}IN_2O_2$: C,39.53; H, 4.52; N, 8.38. Found: C, 39.94; H, 4.57; N, 8.30.

2-Chloro-4-iodo-3-pivaloylaminopyridine (17). A solution of 2-chloro- 3-pivaloylaminopyridine (2 g, 9.41 mmol), TMEDA (2.08 g, 17.9 mmol) in ether (100 mL) was cooled to -70°C and t-butyllithium (17.9 mmol, 10.5 mL of a 1.7 M solution in pentane) was added dropwise. The reaction mixture was stirred at -50°C for 2 h and cooled again to -70°C. A solution of iodine (4.6 g, 17.9 mmol) in dry THF was then added at this temperature. The mixture was stirred for 15 min at -70°C, for 2 h at -10°C, and treated as described above. Flash chromatography (silica gel, hexane/AcOEt 80:20) afforded 0.573 g of 2-chloro-4-iodo-3-pivaloylaminopyridine (17) in 18% yield; mp 166°C. ^1H NMR ($CDCl_3$, 60 MHz): δ 1.4 (s, 9 H), 7.4 (s, 1H exch), 7.75 (d, *J= 5 Hz*, 1 H), 7.9 (d, *J= 5 Hz*, 1 H). Anal. Calcd for $C_{10}H_{12}ClIN_2O$: C, 35.47; H,3.57; N, 8.27. Found:C, 35.35; H, 3.57; N, 8.25.

General Procedure for Cross-coupling of Phenylboronic Acids and 4-Iodopyridines Derivatives.

The phenylboronic acid (3.96 mmol) was added to a solution of 3.3 mmol of the corresponding o-iodopivaloylaminopyridine, palladium tetrakis(triphenyl)phosphine (0.115 g, 0.1 mmol), sodium carbonate (3 mL of an aqueous solution (2M)) in 1.7 mL of ethyl alcohol and 30 mL of toluene. The mixture was refluxed under argon for 12 h. 4-Phenyl-3-pivaloylaminopyridines were obtained after extraction with methylene chloride and purified by flash chromatography (silica gel).

2-Methoxy-4-phenyl-3-pivaloylaminopyridine (3a) (R=R'=H). Eluent: hexane/Et_2O 50:50; Yield: 95%; mp 208°C. ^1H NMR ($CDCl_3$, 60 Mz): δ 1.15 (s, 9H), 4.0 (s, 3 H), 6.9 (d, *J= 5 Hz* 1 H), 6.95 (s, 1 H exch), 7.35 (s, 5 H), 8.1 (d, *J= 5 Hz* 1 H). Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.09; N,9.85. Found: C, 72.07; H, 7.36; N, 9.86.

2-Methoxy-4-(3,4-dimethoxyphenyl)-3-pivaloylaminopyridine (3b) (R=H; R'= OMe). Eluent: Et_2O; Yield: 68%; mp 132°C. ^1H NMR ($CDCl_3$,60 MHz): δ 1.2 (s, 9 H), 3.9 (s, 3 H), 3.95 (s, 3 H), 4.05 (s, 3 H), 6.85 (d, *J= 5Hz*, 1 H), 6.95 (m, 3 H and 1 H exch), 8.05 (d, *J= 5 Hz*, 1H). Anal. Calcd for $C_{19}H_{24}N_2O_4$: C, 66.25; H, 7.02; N, 8.13. Found: C, 66.33; H, 6.44; N, 8.25.

2-Methoxy-4-(2-N,N-diisopropylcarbamoylphenyl)-3-pivaloylaminopyridine (3c) (R= $CONiPr_2$; R'= H). Eluent: Et_2O; Yield: 93%; mp 188°C. ^1H NMR ($CDCl_3$, 60 MHz) δ 0.8 to 1.6 (m, 12 H), 1.0 (s, 9 H), 3.1 to 3.9 (m, 2H), 3.95 (s, 3 H), 6.75 (d, *J= 5 Hz*, 1 H), 7.4 (m, 4 H), 8.05 (d, *J= 5Hz*,1H), 8.75 (s, 1 H exch). Anal. Calcd for $C_{24}H_{33}N_3O_3$: C,70.04; H, 8.08; N, 10.21. Found: C, 70.16; H, 8.10; N, 10.06.

2-Methoxy-4-[3,4-dimethoxy-2-(N,N-diethylcarbamoyloxy)phenyl]-3- pivaloylaminopyridine (3d) (R= $OCONEt_2$; R'= OMe). Eluent: hexane/Et_2O 30:70; Yield: 88%; mp 97°C. ^1H NMR ($CDCl_3$, 60 MHz): δ 0.95 (t, *J= 7 Hz*, 6 H), 1.05 (s, 9 H), 3.15 (q, *J= 7 Hz*,4 H), 3.75 (s, 6 H), 3.9 (s, 3 H), 6.7 (d, *J= 5 Hz*,1 H), 6.75 (s, 2 H), 7.55 (s, 1 H exch), 7.95 (d, *J= 5 Hz*,1H). Anal. Calcd for $C_{24}H_{33}N_3O_6$: C, 62.72; H, 7.24; N, 9.14. Found: C, 62.77; H, 7.23; N, 9.05.

2-Chloro-4-phenyl-3-pivaloylaminopyridine (19). Eluent: hexane/ Et_2O 30:70; Yield: 70%; mp 220°C. ^1H NMR ($CDCl_3$, 60 MHz): δ 1.1 (s, 9 H), 7.25 (d, *J= 5 Hz*, 1 H), 7.35 (m, 5 H and 1 H exch), 8.3 (d, *J= 5 Hz*, 1 H). Anal. Calcd for $C_{16}H_{17}ClN_2O$: C, 66.53; H, 5.93; N, 9.70. Found: C, 66.37; H, 5.85; N, 9.67.

Cleavage of Ethers: Synthesis of 2-(1H)Pyridones. General Procedure: 5O mL of a solution of boron tribromide (1M in dichloromethane) was added dropwise to a solution of 2-methoxypyridine derivative (10 mmol) in 100 mL of dry CH_2Cl_2 cooled at -70°. After stirring at -70°C for 15 min and then at room temperature for 15 h, the mixture was hydrolyzed with ice and treated with aqueous sodium carbonate (pH= 7-8). Extraction with $CH_2Cl_2$and evaporation of the solvent gave the pyridone.

4-Iodo-3-pivaloylamino-2-(1H)pyridone (10). The pyridone **10** was synthesized starting from 4-iodo-2-methoxy-3-pivaloylaminopyridine (**5**) and was purified by recrystallization from a mixture of ethanol/ water; yield: 80%; mp 210-212°C. H^1 NMR (DMSO, 60 MHz): δ 1.15 (s, 9H), 6.5 (d, *J= 5 Hz*, 1 H), 6.95 (d, *J= 5 Hz*, 1 H), 8.65 (br s, 1 H exch). Anal. Calcd for $C_{10}H_{13}IN_2O_2$,H2O: C, 35.52; H, 4.47; N, 8.28. Found: C, 35.31; H,4.31; N, 8.11.

4-Phenyl-3-pivaloylamino-2-(1H)pyridone (9). The pyridone **9** was synthesized starting from 2-methoxy-4-phenyl-3-pivaloylaminopyridine (**3**) and was purified by recrystallization in a mixture of ethanol/water; yield: 76%; mp 228°C; ^1H NMR (d_6-DMSO, 60 MHz): δ 0.95 (s, 9H), 6.1 (d, *J= 5 Hz*, 1 H), 7,25 (d, *J= 5 Hz*, 1 H), 7.35 (s, 5 H), 8.35 (br s, 1 H exch). Anal. Calcd for $C_{16}H_{18}N_2O_2$,H_2O: C, 66.64; H, 6.99; N,9.72. Found: C, 66.99; H, 6.91; N, 9.45. (**Note**: 4-Phenyl-3-pivaloylamino-2-(1H)pyridone (**9**) was also obtained using the general procedure described above for coupling of phenylboronic acid with the 4-iodo-2-(1H)pyridone (**10**); yield: 67%).

7-Phenyl-2-tertiobutyloxazolo[5,4-b]pyridine (11). Pyridine (0.121 mL) and 2.2 g of phosphorus trioxybromide (7.7 mmol) were added to a solution of 1.44 g of 4-phenyl-3-pivaloylamino-2-(1H)pyridone **9** (5 mmol) in 50 mL of benzene chloride. The mixture was refluxed for 1 hour, hydrolyzed and neutralized with a solution of sodium carbonate. The oxazolo[5,4-b]pyridine derivative **11** (0.88 g, 0.35 mmol) was recorved by extraction and purified by flash chromatography (eluent: hexane/Et_2O 50:50); Yield: 70%; mp 72°C; ^1H NMR ($CDCl_3$, 200 MHz): 1.54 (s, 9 H), 7.4- 7.6 (m, 3 H), 7.51 (d, *J= 5.3 Hz*, 1 H), 8.17 (dd, *J= 8.1 Hz and 1.5 Hz*, 2 H), 8.34 (d, *J= 5.3 Hz*, 1 H). Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 75.62; H, 6.29; N, 10.87.

Triflates synthesis. General procedure: Trifluoro methanesulfonic anhydride (1.11 mL; 2.2 eq) were added dropwise to a cooled solution of 3 mmol (1 eq) of 2-(1H)pyridone derivative at 0°C. After stirring at 0°C for 5 min and at room temperature for 24 h the reaction mixture was hydrolyzed, treated with sodium carbonate and extracted with methylene chloride to give the corresponding 2-(pyridyl)triflate.

2-(4-Phenyl-3-pivaloylamino)pyridyltriflate (16). This compound was obtained starting from the pyridone **9** and purified by flash chromatography (eluent: hexane/Et_2O 30:70); Yield: 89%; mp 206°C. ^1H NMR ($CDCl_3$, 60MHz): δ 1.15 (s, 9 H), 7.0 (br s, 1 H), 7.75 (d, *J= 5 Hz*, 1 H), 7.4 (m, 4 H), 8.3 (d, *J= 5 Hz*, 1 H). Anal. Calcd for $C_{17}H_{17}F_3N_2O_4S$: C,50.74; H, 4.26; N, 6.96. Found: C, 50.83; H, 4.51; N, 6.83.

2-(4-iodo-3-pivaloylamino)pyridyltriflate (20). This compound was obtained from the iodopyridone **10** and purified by flash chromatography (eluent: hexane/Et_2O 50:50). Yield: 91%; mp 220°C (dec.).^1H NMR(d_6-DMSO, 60 MHz): δ 1.2 (s, 9 H), 7.95 (d, *J= 5 Hz*, 1 H), 8.1 (d, *J= 5 Hz*, 1 H), 9.55 (br s, 1 H). Anal. Calcd for $C_{11}H_{12}F_3IN_2O_4S$: C,29.21; H, 2.67; N, 6.19. Found: C, 29.58; H, 2.55; N, 6.15.

Selective Coupling of 2-(4-Iodo-3-pivaloylamino)pyridyltriflates 20 with Phenylboronic Acids. The procedure described above was used. 3.465 mmol of arylboronic acid was used in place of 3.96 mmol to avoid possible coupling with the triflate function.

2-(4-Phenyl-3-pivaloylamino)pyridyltriflate (21a) (R=R'=H). Phenylboronic acid itself was used as coupling reagent. Compound **21a** was purified by flash chromatography on silica gel (eluent: hexane/Et2O, 30:70); yield: 84%; mp 206°C. ^1H NMR ($CDCl_3$, 60 MHz): δ 1.15 (s, 9 H), 7.0 (br s, 1 H), 7.35 (d, *J= 5 Hz*, 1 H), 7.4 (m, 4 H), 8.3 (d, *J= 5 Hz*, 1 H). Anal. Calcd for $C_{17}H_{17}F_3N_2O_4S$: C, 50.74; H, 4.26; N, 6.96. Found: C, 50.83; H, 4.51; N, 6.83. **2,4-diphenyl-3-pivaloylaminopyridine (22)** was obtained as a side product: yield: 13%; mp >260°C. ^1H NMR ($CDCl_3$, 60 MHz): δ 0.90 (s, 9H), 6.90 (br s, 1 H), 7.25 (d, *J= 5 Hz*, 1 H), 7.4 (m, 10 H), 8.65 (d, J= 5 Hz, 1 H). Anal. Calcd for $C_{22}H_{22}N_2O$: C, 79.96; H, 6.71; N, 8.48. Found: C, 80.26; H, 6.44; N, 8.44. (**Note**: compound **21a** was also obtained by reaction of 4-phenyl-3-pivaloyl- amino-2-(1H)pyridone (**9**) with triflic anhydride following the procedure already described (yield: 89%).

2-[4-(2-Methoxyphenyl)-3-pivaloylamino]pyridyltriflate (21b)(R=OMe; R'=H). Starting material: 2-methoxyphenylboronic acid. Purification by flash chromatography (eluent: hexane/Et_2O, 50:50); yield: 90%; mp 169°C. ^1H NMR ($CDCl_3$, 60 MHz): δ 1.1 (s, 9 H), 3.9 (s, 3 H), 6.9 to 7.65 (m, 5 H), 7.7(br s, 1 H), 8.3 (d, *J= 5 Hz*, 1 H). Anal. Calcd for $C_{18}H_{19}F_3N_2O_5S$: C, 50.00; H, 4.43; N, 6.48. Found: C, 49.93; H, 4.27; N, 6.42.

2-[4-(2-N,N-Diisopropylcarbamoylphenyl)-3-pivaloylamino]pyridyl triflate (21c)(R=$CONiPr_2$; R'=H). Starting material: 2-N,N-diisopropyl- carbamoylphenylboronic acid. Purification by flash chromatography (eluent: hexane/AcOEt, 70:30); yield: 90%; mp 223°C. ^1H NMR ($CDCl_3$, 60MHz): δ 0.75 to 1.65 (m, 21 H), 3.05 to 3.85 (m, 2 H), 7.05 to 7.6 (m, 5 H), 8.25 (d, *J= 5 Hz*, 1 H), 9.3 (br s, 1 H). Anal. Calcd for $C_{24}H_{30}F_3N_3O_5S$: C, 54.43; H, 5.71; N, 7.93. Found: C, 54.56; H, 5.63; N, 7.90.

2-[4-(3,4-Dimethoxy-2-N,N-diethylcarbamoyloxyphenyl)-3-pivaloylamino] pyridyltriflate (21d) (R=$OCONEt_2$; R'=OMe). Starting material: 3,4-dimethoxy 2-N,N-diethylcarbamoyloxyphenylboronic acid. Purification by flash chromatography (eluent: hexane/Et_2O 50:50). Yield: 75%; mp 160-162°C. ^1H NMR ($CDCl_3$, 60MHz): δ 0.75 to 1.3 (m, 15 H), 3 to 3.45 (m, 4 H), 3.85 (s, 3 H), 3.9 (s, 3 H), 6.85 (s, 2 H), 7.25 (d, *J= 5 Hz*, 1 H), 8.15 (br s, 1 H), 8.25 (d, *J= 5 Hz*, 1 H). Anal. Calcd for $C_{24}H_{30}F_3N_3O_8S$: C, 49.90; H, 5.23; N, 7.28. Found: C, 50.04; H, 5.12; N, 7.15.

General Procedure for Cross-coupling of 2-Pyridyltriflates with (2-Quinolyl)trimethylstannane. Argon was bubbled for 1 h in a solution of 2-pyridyltriflate (2 mmol), (2-quinolyl)trimethylstannane (0.7g, 2.4 mmol) and lithium chloride (0.254 g, 6 mmol) in dioxane (50 mL). Palladium tetrakis(triphenyl)phosphine (69 mg, 3%) was added and the mixture refluxed for a time noted t. Hydrolysis, treatment with aqueous ammonium hydroxide (10 mL of a 10% solution) and extraction with CH_2Cl_2 afforded the crude streptonigrin model 2.Purification was carried out by flash chromatography on silica gel.

2-(2-Pyridyl)quinoline (15). Starting material: 2-pyridyltriflate (**14**)(t = 72 h). Eluent: hexane/Et_2O 50:50; yield: 67%; mp 97-98°C. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.35 (dd, *J= 4.4 Hz and 7.4 Hz*, 1 H), 7.55 (dd, *J= 8 Hz and 7.4 Hz*, 1 H), 7.73 (dd, *J= 7.4 Hz and 8.5 Hz*, 1 H), 7.85 (d, *J= 8 Hz*, 1 H), 7.87 (dd, *J= 7.4 Hz and 7.9 Hz*), 8.18 (d, *J= 8.5 Hz*, 1 H), 8.28 (d, *J= 8.6 Hz*, 1 H), 8.56 (d, *J= 8.6 Hz*, 1 H), 8.65 (d, *J= 7.9 Hz*, 1 H), 8.74 (d, *J= 4.4 Hz*, 1 H).Anal. Calcd for $C_{14}H_{10}N_2$: C, 81.52; H, 4.88; N, 13.58. Found C, 81.79; H, 4.86; N, 13.66.

2-[2-(4-Phenyl-3-pivaloylamino)pyridyl]quinoline (2a) (R=R'=H). Starting material 2-(4-phenyl-3-pivaloylamino)pyridyltriflate (**21a**). (t = 36 h). Eluent hexane/Et_2O, 40:60; yield: 66%; mp 170°C. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.03 (s, 9 H), 7.33 (d, *J= 4.8 Hz*, 1 H), 7.35 (dd, *J= 7.6 Hz*, 1 H), 7.44 (dd, *J= 7.6 Hz*, 1 H), 7.58 (d, *J= 7.6 Hz*, 1 H), 7.61 (dd, *J= 7.5 Hz and 8 Hz*, 1 H), 7.78 (dd, *J= 7.5 and 8.5 Hz*, 1 H), 7.9 (d, *J= 8 Hz*, 1 H), 8.13 (d, *J= 8.5 Hz*, 1 H), 8.35 (d, *J= 8.6 Hz*, 1 H), 8.50 (d, *J= 8.6 Hz*, 1 H), 8.6 (d, *J= 4.8 Hz*, 1 H), 11.63 (s, 1 H exch). Anal. Calcd for $C_{25}H_{23}N_3O$: C, 78.71; H, 6.07; N, 11.O2. Found C, 78.39; H, 6.12; N, 10.96.

Note: Cross-coupling of 2-chloro-4-phenyl-3-pivaloylaminopyridine **19** with (2-quinolyl) trimethylstannane **13**:

Argon was bubbled for 1 h into a solution of **19** (140 mg, 0.485 mmol) and 25 mL of xylene. 212 mg of (2-quinolyl)trimethylstannane, 17 mg of tetrakis(triphenyl)phosphine palladium are then added to the reaction mixture. The solution was then refluxed for 12 h. Treatment with NH_4OH (10 mL of a 10% solution) and extraction with methylene chloride afforded 2-[2-(4-Phenyl-3-pivaloylamino)pyridyl]quinoline (**2a**) (R= R'= H) in an estimated yield of 40% (Purity was established by ^1H NMR analysis).

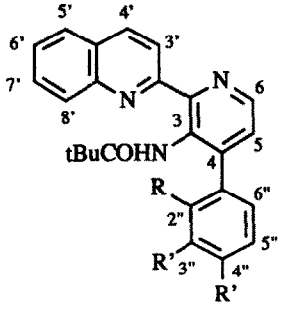
2-[2-(4-(2-methoxyphenyl)-3-pivaloylamino)pyridyl]quinoline (2b) (R= OMe,R'=H) . Starting material: 2-[4-(2-methoxyphenyl)-3-pivaloylamino] pyridyltriflate (**21b**). (t = 20 h). Eluent: hexane/Et_2O, 50:50); yield: 65%; mp 147°C. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.00 (s, 9H), 3.90 (s, 3 H), 7.01 (m, 1 H), 7.09 (m, 1 H), 7.32 (m, 1 H), 7.37 (m, 1 H), 7.38 (d, *J= 4.8 Hz*, 1 H), 7.59 (dd, *J= 8 Hz and 7.5 Hz*, 1 H), 7.76 (dd, *J= 7.5 Hz and 8.4 Hz*, 1 H), 7.89 (d, *J= 8 Hz*, 1 H), 8.11 (d, *J= 8.4 Hz*, 1 H), 8.33 (d, *J= 8.6 Hz*, 1 H), 8.44 (d, *J= 8.6 Hz*, 1 H), 8.58 (d, *J= 4.8 Hz*, 1 H), 11.15 (s, 1 H exch). Anal. Calcd for $C_{26}H_{25}N_3O_2$: C, 75.88; H, 6.12; N, 10.21; Found: C, 75.90; H, 6.27; H, 10.17.

2-[2-(4-(2-N,N-diisopropylcarbamoylphenyl)-3-pivaloylamino) pyridyl] quinoline (2c) (R = $CONiPr_2$; R'= H). Starting material: 2-[4-(2-N,N-diisopropylcarbamoylphenyl)-3-pivaloylamino] pyridyltriflate (**21c**). (t = 20 h). Eluent: Et_2O; yield: 67%; mp 236°C. ^1H NMR ($CDCl_3$, 400 MHz; temperature: 262°K): δ 0.58 (d, *J= 6.5 Hz*, 3 H), 0.90 (s, 9 H), 0.96 (d, *J= 6.4 Hz*, 3 H), 1.24 (d, *J= 6.7 Hz*, 3 H), 1.51 (d, *J= 6.7 Hz*, 3 H), 3.22 (m, 1 H),3.51 (m, 1 H), 7.28 (d, *J= 4.8 Hz*, 1 H), 7.32 (d, *J= 8.4 Hz*, 1 H), 7.4 to 7.5 (m, 3 H), 7.57 (dd, *J= 8 Hz and 7.4 Hz*, 1 H), 7.73 (dd, *J= 7.4 Hz and 8.4 Hz*, 1 H), 7.86 (d, *J= 8Hz*, 1 H), 8.13 (d, *J= 8.4 Hz*, 1 H), 8.19 (d, *J= 8.6 Hz*, 1 H), 8.30 (d, *J= 8.6 Hz*, 1 H), 8.67 (d, *J= 4.8 Hz*, 1 H), 10.32 (br s, 1 H). Anal. Calcd for $C_{32}H_{36}N_4O_2$: C, 75.55; H, 7.13; N, 11.01. Found: C, 75.25; H, 7.42; N, 10.84.

2-[2-(4-(3,4-dimethoxy-2-N,N-diethylcarbamoyloxyphenyl)-3-pivaloylamino) pyridyl]quinoline (2d) (R= $OCONEt_2$; R'= OMe). Starting material: 2-[4-(3,4-dimethoxy-2-N,N-diethylcarbamoyloxyphenyl) -3-pivaloylamino] pyridyltriflate (**21d**). (t= 15 h). Eluent: Et_2O; yield= 74%; mp 163°C. ^1H NMR ($CDCl_3$, 400 MHz; temperature: 318°K): δ 0.99 (s, 9 H), 1.05 (m, 3 H), 1.52 (m, 3 H), 3.28 (m, 4 H), 3.87 (s, 3 H), 3.91 (s, 3 H), 6.91 (d, *J= 8.5 Hz*, 1 H), 7.15 d, *J= 8.5 Hz*, 1 H), 7.31 (d, *J= 4.8 Hz*, 1 H), 7.57 (dd, J= 7.4 Hz *and 8 Hz*, 1 H), 7.73 (dd, *J= 7.4 Hz and 8.4 Hz*, 1 H), 7.88 (d, *J= 8 Hz*, 1 H), 8.03 (d, *J= 8.4 Hz*, 1 H), 8.30 (d, *J= 8.6 Hz*, 1 H), 8.43 (d, *J= 8.6 Hz*, 1 H), 8.57 (d, *J= 4.8 Hz*, 1 H),11.2 (br s, 1 H). Anal. Calcd for $C_{32}H_{36}N_4O_5$: C, 69.04; H, 6.52; N, 10.06. Found: C, 68.84; H, 6.35; N, 9.66.

Compounds **2a,b,c,d** and **15** were subjected to structural confirmation by 2D NMR techniques. COSY provided the ^{1}H-^{1}H scalar coupling relation ships. The linking of protons at carbon positions were established and given in the following table:

Table: chemical shifts of aromatic protons



2a R=R'=H
2b R=OMe; R'=H
2c R=CONiPr$_2$, R'=H
2d R=OCONiPr$_2$; R'=OMe

Compound:		15 [a]	2-a [a]	2-b [a]	2-c [b]	2-d [c]
pyridine	H3	8.65	----	----	----	----
	H4	7.87	----	----	----	----
	H5	7.35	7.33	7.38	7.28	7.31
	H6	8.74	8.60	8.58	8.67	8.57
quinoline	H3'	8.56	8.50	8.44	8.30	8.43
	H4'	8.28	8.35	8.33	8.19	8.3O
	H5'	7.85	7.90	7.89	7.86	7.88
	H6'	7.55	7.61	7.59	7.57	7.57
	H7'	7.73	7.78	7.76	7.73	7.73
	H8'	8.18	8.13	8.11	8.13	8.03
benzene	H2"	----	7.58	----	----	----
	H3"	----	7.44	7.O1	7.4 to 7.5	----
	H4"	----	7.35	7.37		----
	H5"	----	7.44	7.09		6.91
	H6"	----	7.58	7.32	7.32	7.15

a) rt (294°K); b) temperature: 262°K; c) temperature: 318°K

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