

V. Pomel, J. C. Rovera, A. Godard, F. Marsais and G. Quéguiner*

Laboratoire de Chimie Organique Fine et Hétérocyclique (URA du CNRS 1429), Laboratoire de l'IRCOF,
INSA de Rouen BP08, 76131 Mont Saint-Aignan Cedex, France

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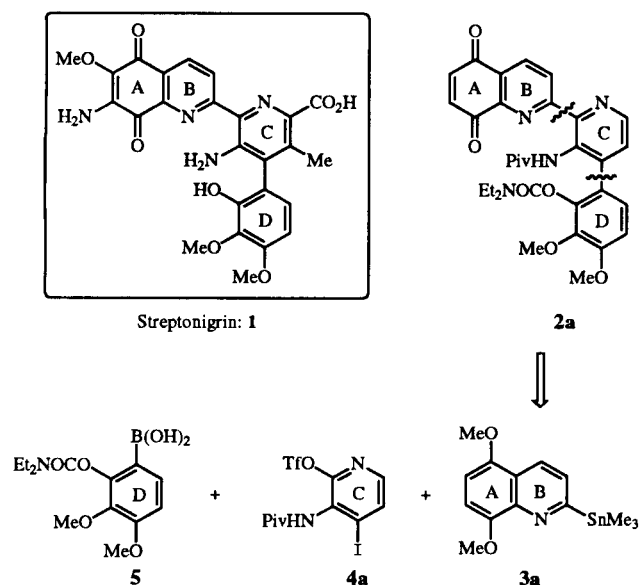
Starting from available 2-amino-6-chloro-3-nitropyridine, synthesis of 3-amino-6-pyridinecarboxylic acid derivatives precursor for pyridine ring C of streptonigrin analogues is described.

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Streptonigrin **1** has been reported as possessing interesting biological properties as antitumor and anti HIV agents [1]. According to this, synthesis of streptonigrin and analogues has been widely studied [2]. Three elegant total syntheses have particularly been described by Weinreb [2a], Kende [2b] and Boger [2c]. Unfortunately, the synthesis of such a highly substituted molecule by a multistepsequence afforded low overall yields.

In order to obtain streptonigrin analogues and later provide a total synthesis of this alkaloid a more convergent route has been carried out in our laboratory [3]. The methodology involves the independent synthesis of the three moieties and two selective biaryl cross-couplings as shown on the retrosynthetic scheme depicted below for the synthesis of **2a** (Scheme 1).

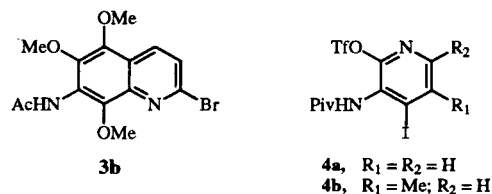
Scheme 1



In the field of our investigations for a total synthesis of streptonigrin **1**, suitably substituted quinoline **3b** [3a] and benzene **5** [3b] precursors, have already been prepared. Moreover, some 2-(4-iodopyridyl) triflates intermediates **4a** and **4b** were also prepared [3c] (Scheme 2). Our aim

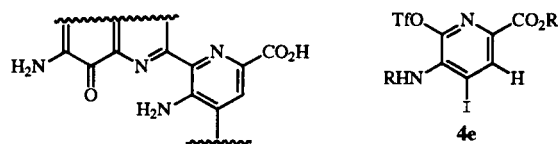
was now to synthesize a suitably substituted pyridine intermediate bearing the carboxylic acid function at C-6 necessary for biological activity.

Scheme 2



In a preliminary approach the synthesis of pyridine **4e** bearing a hydrogen at C-5 in place of a methyl group ($R_1 = H$, $R_2 = CO_2R$) was studied. On one hand, the lack of a methyl group at C-5 does not play an important role since the pharmacophore for biological activity has been studied and does not involve this group [4]. On the other hand, generally low yields of the C and D ring systems were obtained when 3,5-disubstituted pyridines were reacted with 2-substituted phenylboronic acids under standard Suzuki's cross-coupling conditions [5].

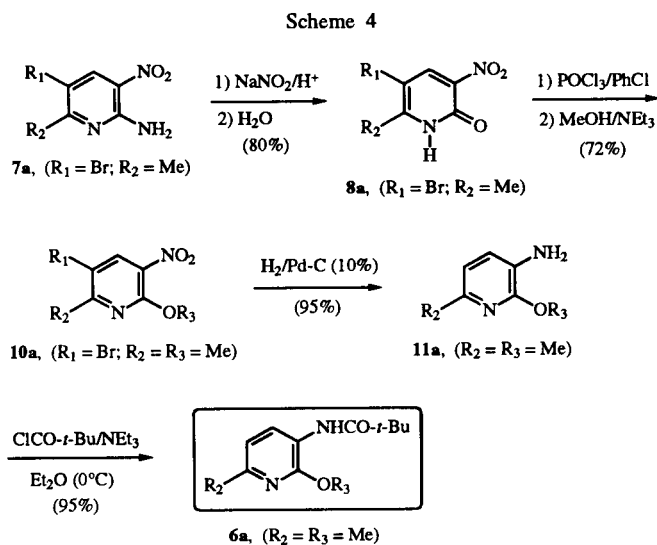
Scheme 3



A) Synthesis and Oxidation of 6-Methylpyridine Derivatives.

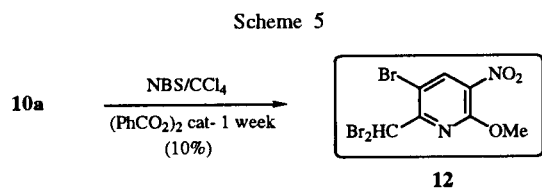
In a first approach, the synthesis of 2-methoxy-6-methylpyridine derivatives was carried out and then conversion into suitable carbonyl derivatives by oxidation of the methyl group was studied. The strategy we used previously, for the synthesis of 2-(4-iodopyridyl) triflates **4a** and **4b**, involved the elaboration of the corresponding 2-methoxy-3-pivaloylaminopyridine derivatives. Iodine is introduced at C-4 by metalation and the triflate results from the cleavage of the methoxy group followed by reaction with triflic anhydride. This strategy was applied for the

synthesis of 2-(4-iodo-2-methoxy-6-methyl-3-pivaloylaminopyridyl)triflate (**4c**) (Scheme 11). The required 2-methoxy-6-methyl-3-pivaloylaminopyridine (**6a**) ($R_2 = R_3 = \text{Me}$) was synthesized by a standard multistep sequence from 2-amino-5-bromo-6-methyl-3-nitropyridine (**7a**) readily prepared by Fox and Threlfall [6].



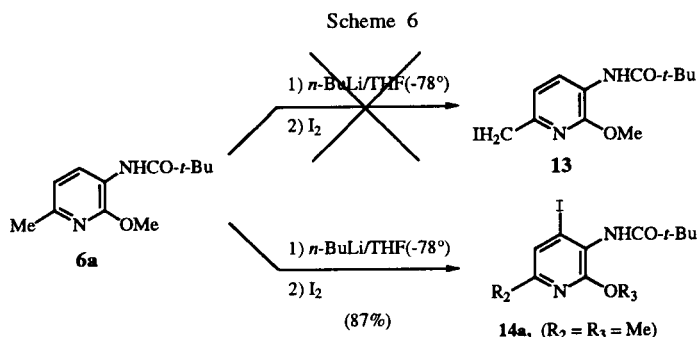
Diazotation of **7a** followed by hydrolysis, according to the Baumgarten's procedure [7] afforded the pyridone **8a** ($R_1 = \text{Br}, R_2 = \text{Me}$) in 80% yield. Substitution of the hydroxy group by a chloride and then action of refluxing methanol gave the 2-methoxy-3-nitropyridine (**10a**) in 72% yield (two steps). Treatment of **10a** with hydrogen with palladium (Pd/C (10%)) at atmospheric pressure afforded the 3-aminopyridine **11a** ($R_2 = R_3 = \text{Me}$) in 95% yield. It should be noted that reduction of the nitro group and debromination took place in the same reaction. The 3-aminopyridine **11a** was reacted with pivaloyl chloride to give the expected 2-methoxy-6-methyl-3-pivaloylaminopyridine (**6a**) in 95% yield (overall yield: 52%, 5 steps).

A methyl group of α -picoline is usually well-known for its easy oxidation to the corresponding α -formyl or α -carboxylic acid [8]. Then compounds **10a** and **6a** could be convenient precursors of α -pyridine carbonylated derivatives.



Surprisingly, none of the oxidizing reagents used, afforded the expected carbonylated compounds in suitable yields. Most of the oxidation reactions we carried out, afforded either the reagent or unidentified products.

However it could be noted that substitution of the methyl group by NBS under radical conditions afforded the 5-bromo-6-dibromomethyl-2-methoxy-3-nitropyridine (**12**), in a poor yield of 10%.



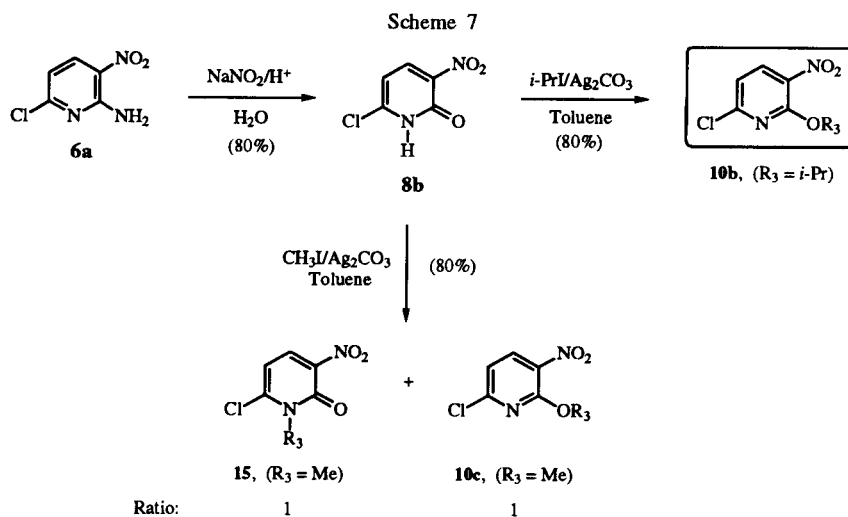
In order to synthesize α -pyridine carbonylated compounds from the corresponding α -methylpyridine, another pathway could involve a metalation of the methyl group and reaction of the intermediary lithio species with electrophiles. On one hand, reaction of the 6-methyl-3-nitropyridine **10a** with *n*-butyllithium at low temperature (-78°) led to a residual tar. On the other hand, metalation of 2-methoxy-6-methyl-3-pivaloylaminopyridine (**6a**) followed by reaction with iodine did not give the expected compound **13** but 4-iodo-2-methoxy-6-methylpyridine-3-pivaloylaminopyridine (**14a**). Attempts for subsequent metalation of the methyl group of compound **14a** were unsuccessful.

In conclusion, neither metalation nor oxidation of the methyl group of compound **6a** occurred. It could be explained by relatively high electron density of this substrate in comparison with α -picoline. However, nonreactivity of the methyl group towards strong bases allowed the synthesis of 4-iodo-2-methoxy-6-methylpyridine-3-pivaloylaminopyridine (**14a**). This compound has been used in a later step of the synthesis (Scheme 11).

B) Synthesis of 6-Carbonylpyridine Derivatives from 6-Chloropyridine.

Difficulties encountered in the transformation of the methyl group led us to choose another pathway and eventually a different starting material. In place of the 6-methylpyridine derivatives, 6-chloro analogues were used. Such a chloropyridine could be transformed to corresponding carbonyl compounds by nucleophilic substitution or cross-coupling reactions.

Commercial 2-amino-6-chloro-3-nitropyridine (**7b**) was chosen as the starting material for the synthesis of our target molecules. In this series, the 2-methoxy and the 2-isopropoxy derivatives were synthesized. Indeed, the latter could probably be more easily cleaved than a methoxy group in a subsequent step of the synthesis.



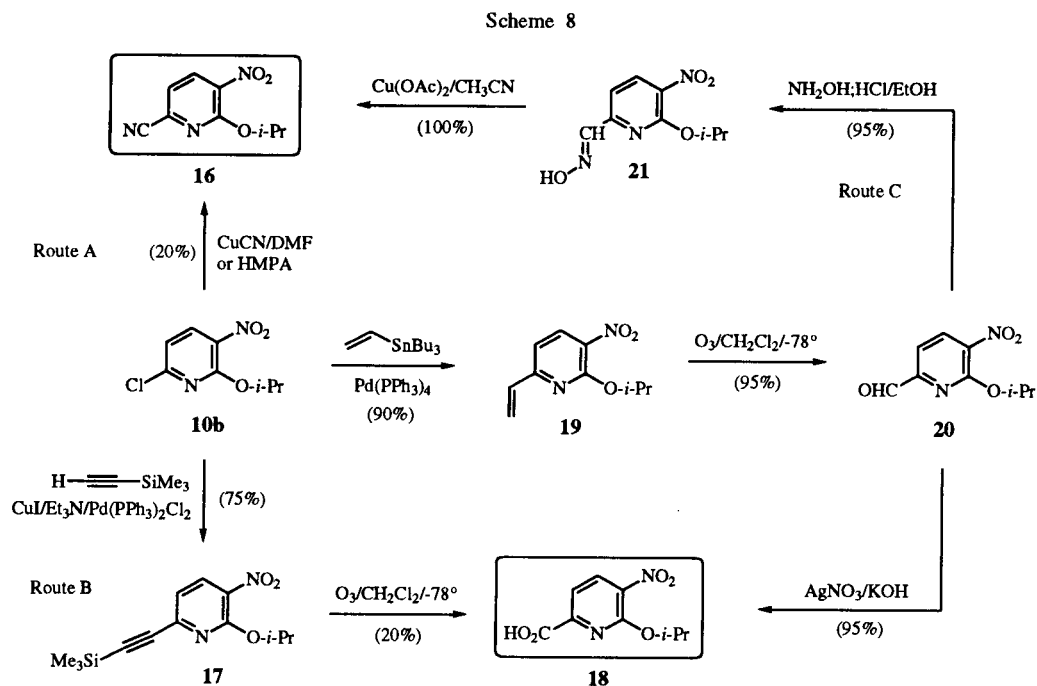
Diazotation of **7b** afforded the corresponding pyridone **8b** in 80% yield. Protection of the pyridone **8b** by *O*-alkylation was then studied. As commonly accepted this reaction allows both nitrogen and/or oxygen alkylation and the presence of a silver cation usually favors oxygen alkylation [9]. In our case, the reaction was carried out with an alkyl iodide in toluene in the presence of silver carbonate. Oxygen alkylation predominated when isopropyl iodide was used as the electrophile and compound **10b** ($R_3 = i\text{-Pr}$) was obtained in 80% yield, while nitrogen and oxygen alkylation occurred together with methyl iodide, and pyridone **15** and 2-methoxypyridine **10c** ($R_3 = \text{Me}$) were obtained in a 1/1 ratio (80% yield). These results are consistent with Hopkin's proposal [10].

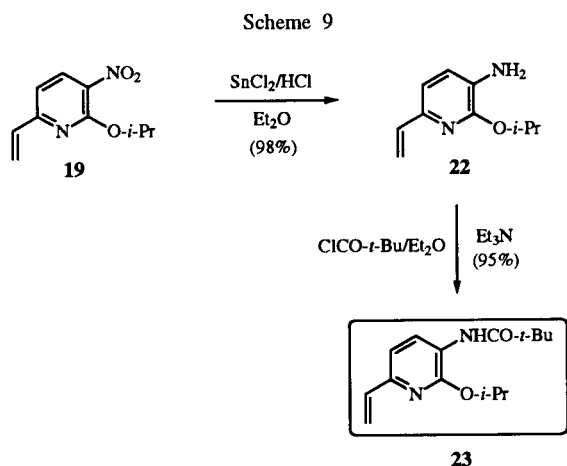
This author suggests that steric hinderance around nitro- gen is an important factor which led preferentially to *O*-alkylation as observed in alkylation of **8b**.

Several attempts were carried out to transform the 6-chloro group of **10b** into precursors of carbonylated functions.

Route A.

Aromatic nucleophilic substitution of halides by cuprous cyanide is a convenient method to convert aromatic halides to aromatic carbonitriles [11]. Direct cyana- tion of the 6-chloro-3-nitropyridine **10b** by cuprous cyanide was studied. Unfortunately a low yield (20%) of the expected compound **16** was obtained. Takemoto and





co-workers [12] described the cyanation of a 2-bromo-5-nitropyridine using palladium(0) as the catalyst in the presence of cuprous cyanide in 50% yield. The similarity of both molecules led us to apply this methodology, but only low yields were obtained.

These results led us to carry out another strategy involving an oxidative cleavage of 6-vinyl and 6-ethynylpyridines, which were obtained by palladium-catalyzed cross-coupling reactions.

Route B.

6-Chloro-2-isopropoxy-3-nitropyridine (**10b**) was submitted to cross-coupling reaction with trimethylsilylacetylene under Heck conditions [13]. This reaction led to 2-isopropoxy-3-nitro-6-trimethylsilylethynylpyridine (**17**) in 75% yield. Oxidative cleavage of the triple bond has been performed with ozone at low temperature (-78°) and 2-isopropoxy-3-nitro-6-pyridinecarboxylic acid (**18**) was obtained in 20% yield. This low yield led us to replace the triple bond at C-6 by a double bond.

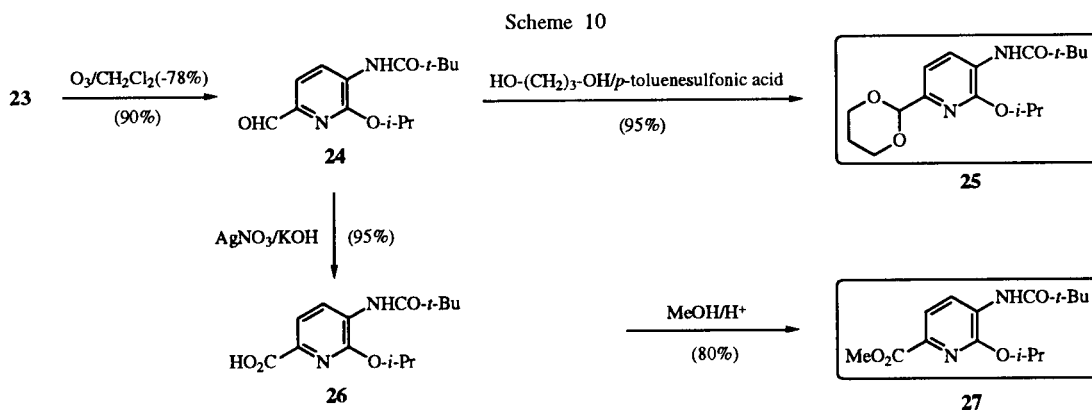
Route C.

Cross-coupling reaction between compound **10b** and vinyltributyltin under Stille conditions [14] led to 2-isopropoxy-3-nitro-6-vinylpyridine (**19**) in 90% yield.

Treatment of the 6-vinylpyridine **19** with ozone afforded the desired 6-pyridinecarboxaldehyde **20** in 95% yield. These results are in agreement with the fact that ozonolysis proceeded less easily when ozone was reacted with triple bonds than double bonds, since ozone is an electrophilic agent and therefore prefers double to triple bonds [15]. Oxidation of the 6-formyl group with silver nitrate afforded the expected 2-isopropoxy-3-nitro-6-pyridinecarboxylic acid (**18**) (95%). It could be noted that direct oxidation of the double bond with potassium permanganate only led to traces of **18**. Taking into account that 6-formylpyridine **20** could be easily obtained, the 6-cyanopyridine **16** was prepared in good yield by an oxime dehydration sequence (overall yield, 81% (4 steps)). Therefore, it has been shown that 6-pyridinecarbonitrile **16**, 6-pyridinecarboxaldehyde **20** and 6-pyridinecarboxylic acid **18** could be obtained by a coupling oxidation sequence in good yields. This methodology was applied to the synthesis of our target molecules (Scheme 9 and 10).

2-Isopropoxy-3-pivaloylamino-6-vinylpyridine (**23**) was synthesized in two steps in fairly good yields, starting from the 6-vinylpyridine **19**. The controlled reduction of the 3-nitro group was achieved selectively with tin chloride under acidic conditions to give the expected 3-aminopyridine **22**. Then protection of the amino group with pivaloyl chloride afforded compound **23** in 95% yield.

A similar pathway, as described before in Scheme 8, in the 3-nitropyridine series, was used to convert the 3-pivaloylamino-6-vinylpyridine **23** to 6-pyridine carbonylated derivatives **24** and **26**. Ozonolysis of the double bond at low temperature (-78°), followed by oxidation of the 6-formylpyridine **24** afforded 2-isopropoxy-3-pivaloylamino-6-pyridinecarboxylic acid (**26**) in 81% yield (2 steps). Then, protection of the carboxylic acid or formyl functions were achieved by standard methods. On one hand, protection of 6-pyridinecarboxaldehyde **24** as a cyclic acetal was obtained, when **24** was treated with 1,3-propanediol in the presence of *p*-toluenesulfonic acid as the catalyst to give 6-(1,3-dioxan-6-yl)-2-isopropoxy-3-

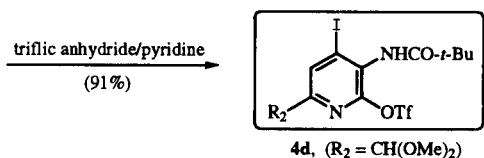
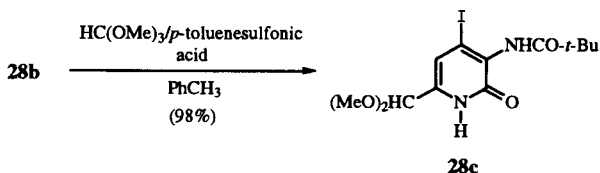
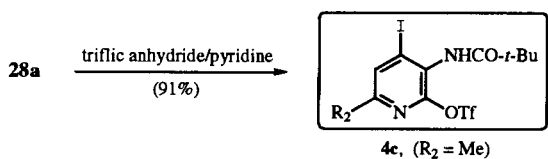
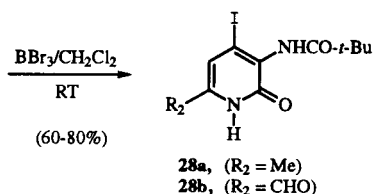
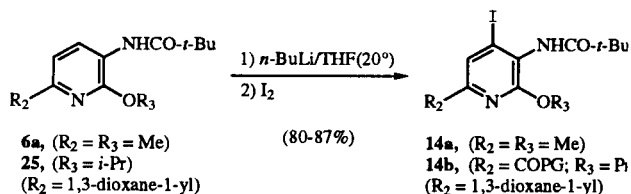


pivaloylaminopyridine (**25**) in 95% yield. On the other hand, protection of 6-pyridinecarboxylic acid **26** as the methyl carboxylate was performed in methanol refluxed in the presence of a few drops of sulfuric acid as the catalyst to give methyl 2-isopropoxy-3-pivaloylamino-6-pyridinecarboxylate (**27**) in 80% yield.

Our strategy requires the preparation of a polysubstituted pyridine bearing substituents at the C-2 and C-4 positions allowing selective cross-coupling reactions with 2-(quinolyl)trimethylstannane **3c** and 2-*N,N*-diethylcarbamoyloxy-3,4-dimethoxyphenylboronic acid (**5**) respectively (Scheme 1). We previously reported [3] that triflate function at C-2 reacts with lower reactivity than the iodine group at C-4. Iodination at C-4 was performed by a metalation electrophilic substitution sequence and triflic function at C-2 by cleavage of the alkoxy function, followed by treatment with triflic anhydride.

Moreover, it is well known that an aromatic ester is very sensitive towards aromatic nucleophilic addition. So lithiation at C-4 was not performed with methyl carboxylate **27**, but with acetal **25** which could be easily converted to the carboxylic acid in a subsequent step.

Scheme 11

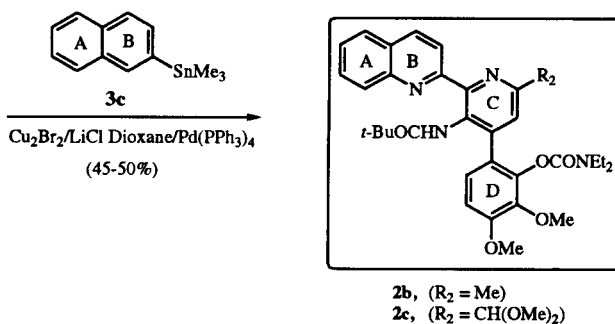
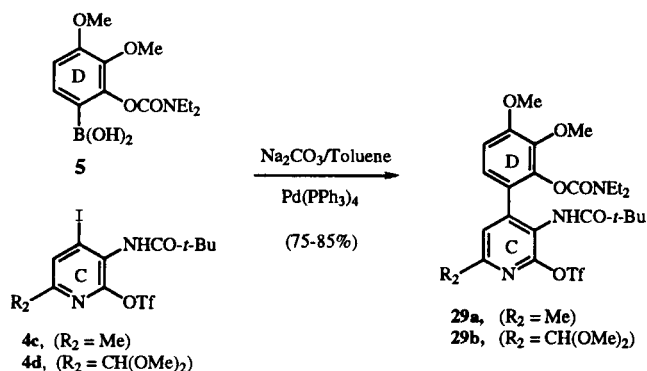


Lithiation of the suitable 3-pivaloylaminopyridines **6a** and **25** with *n*-butyllithium at -20° , followed by reaction with iodine as the electrophile at -10° , allowed selective iodination at C-4 to give the expected 4-iodopyridines **14** in fairly good yields (80-87%). Treatment of the 2-alkoxy-pyridines **14** with boron tribromide gave the corresponding pyridones **28a** ($R_2 = \text{Me}$) and **28b** ($R_2 = \text{CHO}$) in 80 and 60% yields respectively. Treatment of **28a** with triflic anhydride afforded the corresponding 2-(pyridyl)triflate **4c** ($R_2 = \text{Me}$) in 91% yield. In contrast, treatment of **28b** under similar conditions gave only residual tar. The functionalization with triflic anhydride at C-2, required further protection of the formyl group (98%) to give **28c** which was easily transformed into the expected compound **4d** ($R_2 = \text{CH}(\text{OMe})_2$) in 91% yield.

C) Synthesis of 4-Phenyl-2-(2-quinolyl)pyridines.

In order to limit the number of steps of our synthetic route, conversion of 6-pyridinecarboxaldehyde to 6-pyridinecarboxylic acid (as preliminarily studied in Scheme 8 and 10) would be attempted in the final deprotecting steps.

Scheme 12



Cross-coupling of 4-iodopyridines **4** with phenylboronic acid **5** under Suzuki's conditions afforded the corresponding 4-phenylpyridines **29** with high selectivity (75-85% yields). Coupling of triflates **29** with 2-(quinolyl)trimethylstannane (**3c**) gave the tetracyclic compounds **2c** and **2b** in 50% and 45% yields respectively.

Conclusion.

Our strategy for the synthesis of biologically active streptonigrin and its analogues requires the preparation of suitably substituted pyridines bearing more specially a carbonylated function at C-6. It was accomplished efficiently by oxidation of a vinylpyridine obtained by a Stille cross-coupling reaction. The synthesis of streptonigrin or its potentially active analogues is currently under investigation.

EXPERIMENTAL

Tetrahydrofuran (THF) was distilled from benzophenone/sodium and used immediately (water content <40 ppm). The ir spectra were obtained as potassium bromide pellets for solids and as films for liquids or oils with a Perkin-Elmer FMR 1650 spectrometer. The nmr spectra were recorded on a JEOL JNM-PMX 60 SI (60 MHz) or a Bruker 200 MHz spectrometer. All nmr spectra were carried out with deuteriochloroform solutions or dimethyl sulfoxide- d_6 and δ are given in ppm. Microanalysis were performed with a Carlo Erba 1106 apparatus. Melting points were determined with a Kofler hot-stage and are uncorrected. 2-Amino-6-chloro-3-nitropyridine (**7b**) is a commercial product, but can also be synthesized starting from 2,6-dichloro-3-nitropyridine [16]. 2-Amino-5-bromo-3-nitro-6-methylpyridine (**7a**) has been synthesized in two steps starting from 2-amino-6-methylpyridine [6]

General Procedure for the Preparation of Nitropyridones **8**.

To a solution of the corresponding 2-aminopyridine **7** (45 mmoles) in concentrated sulfuric acid (25 ml), was added a solution of sodium nitrite (6 g, 90 mmoles) at 0°. After 30 minutes of reaction at low temperature, the mixture was hydrolyzed slowly with 150 ml of water and the nitropyridones were collected by filtration *in vacuo*. Crude products were purified by sublimation under reduced pressure.

5-Bromo-6-methyl-3-nitro-2(1H)-pyridone (**8a**).

This compound was obtained in a yield of 80% as a white solid, mp 221°; ^1H nmr (dimethyl sulfoxide- d_6): δ 2.35 (s, 3H, CH_3), 8.45 (s, 1H, 4-H); ir: 3410, 2860, 1685, 1660, 1590 cm^{-1} .

Anal. Calcd. for $\text{C}_6\text{H}_5\text{N}_2\text{O}_3\text{Br}$: C, 30.93; H, 2.16; N, 12.02. Found: C, 30.64; H, 2.14; N, 12.31.

6-Chloro-3-nitro-2(1H)-pyridone (**8b**).

This compound was obtained in a yield of 80% as a white solid, mp 192°; ^1H nmr: (dimethyl sulfoxide- d_6): δ 7.10 (d, 1H, 5-H, $J_{5,4} = 8$ Hz), 8.45 (d, 1H, 4-H, $J_{4,5} = 8$ Hz); ir: 3420, 3107, 2771, 1654, 1585 cm^{-1} .

Anal. Calcd. for $\text{C}_5\text{H}_3\text{N}_2\text{O}_3\text{Cl}$: C, 34.40; H, 1.70; N, 16.04. Found: C, 34.51; H, 1.61; N, 15.94.

5-Bromo-2-chloro-6-methyl-3-nitropyridine (**9a**).

A mixture of 5-bromo-6-methyl-3-nitro-2(1H)-pyridone (**8a**) (4.6 g, 20 mmoles), phosphorus oxychloride (4.7 g, 30.8 mmoles) and pyridine (0.47 g, 30.8 mmoles) was refluxed in chlorobenzene (50 ml) over a period of 1 hour. The solution was then hydrolyzed with 20 ml of water and neutralized with a

sodium carbonate solution. Extraction with methylene chloride, drying over magnesium sulfate and evaporation *in vacuo* gave 3.7 g (75%) of the expected compound **9a** as a solid which was purified by flash chromatography on silica gel (eluent:cyclohexane/ethyl ether (8:2)), mp 63°; ^1H nmr (deuteriochloroform): δ 2.75 (s, 3H, CH_3), 8.35 (s, 1H, 4-H); ir: 3040, 1585, 1565, 1525, 1440 cm^{-1} .

Anal. Calcd. for $\text{C}_6\text{H}_4\text{N}_2\text{O}_2\text{BrCl}$: C, 28.62; H, 1.60; N, 11.14. Found: C, 28.70; H, 1.57; N, 11.06.

5-Bromo-2-methoxy-6-methyl-3-nitropyridine (**10a**).

A mixture of 5-bromo-2-chloro-6-methyl-3-nitropyridine (**9a**) (1 g, 4 mmoles) and triethylamine (5.55 ml, 40 mmoles) was refluxed in methanol (50 ml) over a period of 6 days. Methanol was evaporated *in vacuo*, water (5 ml) was added to the residue and the solution was extracted with methylene chloride. The combined extracts were dried over anhydrous magnesium sulfate and then evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluent:cyclohexane/ethyl acetate (9:1)) to give 895 mg (90%) of the expected compound **10a** as a yellow solid, mp 70°; ^1H nmr (deuteriochloroform): δ 2.65 (s, 3H, CH_3), 4.10 (s, 3H, OMe), 8.45 (s, 1H, 4-H); ir: 3000, 2980, 1600, 1580, 1520, 1470 cm^{-1} .

Anal. Calcd. for $\text{C}_7\text{H}_7\text{N}_2\text{O}_3\text{Br}$: C, 34.03; H, 2.84; N, 11.34. Found: C, 33.90; H, 2.82; N, 11.32.

General Procedure for *O*-Alkylation of Nitropyridones **8b**.

A suspension of 6-chloro-3-nitro-2(1H)-pyridone (**8b**) (1.4 g, 8 mmoles), silver carbonate (1.33 g, 4.8 mmoles) and 2-iodopropane (1.64 g, 9.63 mmoles) or methyl iodide (1.5 ml, 24 mmoles) in dry toluene was stirred at room temperature in darkness over two weeks. The precipitate of the corresponding silver iodide was filtered and washed with an aqueous solution of hydrogen carbonate. Extraction with methylene chloride, drying over magnesium sulfate and solvent removal afforded a crude product, which was purified on silica gel (eluent:cyclohexane/ethyl acetate (9:1)).

6-Chloro-2-isopropoxy-3-nitropyridine (**10b**).

This compound was obtained as a white solid to give 1.38 g (80%) of the expected compound **10b**, mp 70°; ^1H nmr (deuteriochloroform): δ 1.40 (d, 6H, CH_3 -*i*-Pr, $J = 8$ Hz), 5.50 (h, 1H, CH-*i*-Pr, $J = 8$ Hz), 7.0 (d, 1H, 5-H, $J_{5,4} = 8.5$ Hz), 8.25 (d, 1H, 4-H, $J_{4,5} = 8.5$ Hz); ir: 2988, 2950, 1593 cm^{-1} .

Anal. Calcd. for $\text{C}_8\text{H}_9\text{N}_2\text{O}_3\text{Cl}$: C, 44.30; H, 4.16; N, 12.93. Found: C, 44.53; H, 4.18; N, 12.85.

6-Chloro-2-methoxy-3-nitropyridine (**10c**).

This compound was obtained as a yellow solid to give 0.605 g (40%) of the expected compound **10c**, mp 80°; ^1H nmr (deuteriochloroform): δ 4.15 (s, 3H, OMe), 7.10 (d, 1H, 5-H, $J_{5,4} = 8.5$ Hz), 8.40 (d, 1H, 4-H, $J_{4,5} = 8.5$ Hz); ir: 2800, 1592 cm^{-1} .

Anal. Calcd. for $\text{C}_6\text{H}_5\text{N}_2\text{O}_3\text{Cl}$: C, 38.20; H, 2.65; N, 14.85. Found: C, 38.37; H, 2.60; N, 14.64.

6-Chloro-3-nitro-2-oxo-*N*-methylpyridine (**15**).

This compound was obtained as a yellow solid to give 0.605 g (40%) of the expected compound **15**, mp 162°; ^1H nmr (deuteriochloroform): δ 3.90 (s, 3H, NMe), 6.50 (d, 1H, 5-H, $J_{5,4} = 8.5$ Hz), 8.30 (d, 1H, 4-H, $J_{4,5} = 8.5$ Hz); ir: 3400, 3092, 1680, 1586 cm^{-1} .

Anal. Calcd. for $\text{C}_6\text{H}_5\text{N}_2\text{O}_3\text{Cl}$: C, 38.20; H, 2.65; N, 14.85. Found: C, 38.35; H, 2.62; N, 14.74.

Reduction of 3-Nitropyridines to the Corresponding 3-Aminopyridines.

3-Amino-2-methoxy-6-methylpyridine (11a).

5-Bromo-2-methoxy-6-methyl-3-nitropyridine (**10a**) (5.0 g, 20 mmoles) was dissolved in dry ethanol (50 ml) and hydrogenated over Pd/C (10%, 0.5 g) at atmospheric pressure. After absorption of the calculated quantity of hydrogen, the solution was filtered through celite and the solvent removed by evaporation. The crude product was purified by distillation under reduced pressure to give 2.63 g of compound **11a** in a yield of 95%, (bp 102°/15 mm Hg); ¹H nmr (deuteriochloroform): δ 2.35 (s, 3H, CH₃), 3.55 (m, 2H, NH₂), 3.95 (s, 3H, OCH₃), 6.50 (d, 1H, 4-H, J_{4,5} = 8 Hz), 6.75 (d, 1H, 5-H, J_{5,4} = 8 Hz); ir: 3450, 3350, 2980, 2950, 2920, 1620 cm⁻¹.

Anal. Calcd. for C₇H₁₀N₂O: C, 60.85; H, 7.29; N, 20.27. Found: C, 60.74; H, 7.39; N, 20.47.

3-Amino-2-isopropoxy-6-vinylpyridine (22).

To a solution of 6-vinyl-2-isopropoxy-3-nitropyridine (**19**) (1 g, 4.8 mmoles) in anhydrous ether (25 ml) was added a solution of stannous chloride dihydrate (4.2 g, 18 mmoles) in concentrated hydrochloric acid (25 ml) at 0°. The reaction mixture was allowed to stir at room temperature for 1 hour and then hydrolyzed and neutralized with a solution of sodium hydroxide to pH 10-12 at 0°. Extraction with ethyl acetate, drying over magnesium sulfate and solvent removal afforded 0.85 g (98%) of the expected compound **22** as an oil, which was purified on silica gel (eluent:cyclohexane/ethyl ether (8:2)); ¹H nmr (deuteriochloroform): δ 1.40 (d, 6H, CH₃-i-Pr, J = 8 Hz), 3.80 (m, 2H, NH₂), 5.15 (dd, 1H, H_{vinyl}, J_{cis} = 10.5 Hz, J_{gem} = 1.5 Hz), 5.50 (h, 1H, CH-i-Pr, J = 8 Hz), 6.20 (dd, 1H, H_{vinyl}, J_{trans} = 17 Hz, J_{gem} = 1.5 Hz), 6.40 (dd, 1H, H_{vinyl}, J_{trans} = 17 Hz, J_{cis} = 10.5 Hz), 6.70 (d, 1H, 4-H, J_{4,5} = 8 Hz), 6.75 (d, 1H, 5-H, J_{5,4} = 8 Hz); ir: 3382, 2975, 2931, 1578, 1470 cm⁻¹.

Anal. Calcd. for C₁₀H₁₄N₂O: C, 67.40; H, 7.86; N, 15.70. Found: C, 67.39; H, 7.74; N, 15.52.

General Procedure for the Preparation of 3-Pivaloylaminopyridines.

A solution of the corresponding 3-aminopyridine, **11a** and **22**, (0.27 mole) and triethylamine (27 g, 0.27 mole) in anhydrous ether (150 ml) was cooled to 0°. Trimethylacetylchloride (33 g, 0.29 mole) was added dropwise into the solution so that the temperature did not rise above 5°. The mixture was stirred at room temperature over 1 hour, water (100 ml) was added and the solution neutralized to pH 8-9 with an aqueous solution of hydrogen carbonate. Extraction with methylene chloride, drying over magnesium sulfate and evaporation *in vacuo* gave a crude product which was purified by flash chromatography on silica gel (eluent).

2-Methoxy-6-methyl-3-pivaloylaminopyridine (6a).

This compound was obtained in a yield of 95% as an oil (eluent:cyclohexane/ethyl ether (8:2)); ¹H nmr (deuteriochloroform): δ 1.30 (s, 9H, *t*-Bu), 2.40 (s, 3H, CH₃), 4.0 (s, 3H, OMe), 6.70 (d, 1H, 5-H, J_{5,4} = 7 Hz), 7.90 (m, 1H, NH), 8.50 (d, 1H, 4-H, J_{4,5} = 7 Hz); ir: 3450, 2960, 2870, 1685, 1595 cm⁻¹.

Anal. Calcd. for C₁₂H₁₈N₂O₂: C, 64.83; H, 8.16; N, 12.60. Found: C, 64.65; H, 7.90; N, 12.48.

2-Isopropoxy-3-pivaloylamino-6-vinylpyridine (23).

This compound was obtained in a yield of 95% as an oil (eluent:cyclohexane/ethyl ether (9:1)); ¹H nmr (deuteriochloroform):

δ 1.30 (s, 9H, *t*-Bu), 1.35 (d, 6H, CH₃-i-Pr, J = 8 Hz), 5.30 (dd, 1H, H_{vinyl}, J_{cis} = 10.5 Hz, J_{gem} = 1.5 Hz), 5.42 (h, 1H, CH-i-Pr, J = 8 Hz), 6.15 (dd, 1H, H_{vinyl}, J_{trans} = 17 Hz, J_{gem} = 1.5 Hz), 6.60 (dd, 1H, H_{vinyl}, J_{trans} = 17 Hz, J_{cis} = 10.5 Hz), 6.80 (d, 1H, 5-H, J_{5,4} = 8 Hz), 8.10 (m, 1H, NH), 8.55 (d, 1H, 4-H, J_{4,5} = 8 Hz); ir: 3444, 2960, 2871, 1809, 1741, 1686 cm⁻¹.

Anal. Calcd. for C₁₅H₂₂N₂O₂: C, 68.70; H, 8.39; N, 10.68. Found: C, 68.75; H, 8.50; N, 10.80.

5-Bromo-6-dibromomethyl-2-methoxy-3-nitropyridine (12).

A mixture of carbon tetrachloride (10 ml), 5-bromo-2-methoxy-6-methyl-3-nitropyridine (**10a**) (405 mg, 1.62 mmoles), *N*-bromosuccinimide (1.40 g, 8.0 mmoles) and benzoyl peroxide (20 mg) as the catalyst was refluxed over a period of 1 week. After cooling the reaction mixture, the precipitate of succinimide was filtrated and the filtrate neutralized to pH 8-9 with a hydrogen carbonate solution (benzoyl peroxide was also allowed to be neutralized by a thiosulfate solution). Extraction with methylene chloride and drying over magnesium sulfate, afforded a crude product which was purified by recrystallization (ethanol) to give 66 mg (10%) of compound **12** as a yellow solid, mp 110°; ¹H nmr (deuteriochloroform): δ 4.0 (s, 3H, OMe), 6.95 (s, 1H, CH), 7.75 (s, 1H, 4-H); ir: 2950, 1565, 1542, 1463, 1400 cm⁻¹.

Anal. Calcd. for C₇H₅N₂O₃Br₃: C, 20.77; H, 1.24; N, 6.92. Found: C, 20.55; H, 1.25; N, 7.01.

Route A.

2-Isopropoxy-3-nitro-6-pyridinecarbonitrile (16).

Method A.

A mixture of 6-chloro-2-isopropoxy-3-nitropyridine (**10b**) (265 mg, 1.22 mmoles) and cuprous cyanide (115 mg, 1.27 mmoles) was refluxed in *N,N*-dimethylformamide (20 ml) (or HMPA) over 24 hours. The mixture was then neutralized and extracted with methylene chloride. Drying over magnesium sulfate and evaporation *in vacuo* afforded a crude product which was purified on silica gel (eluent:cyclohexane/ethyl acetate (8:2)) to give 50 mg (20%) of the expected compound **16**.

Route C.

Method B.

2-Isopropoxy-3-nitro-6-pyridinealdehyde (21, intermediate to 16).

A mixture of 2-isopropoxy-3-nitro-6-pyridinecarboxaldehyde (**20**) (230 mg, 1.0 mmole), hydroxylamine sulfate (1.5 g, 11 mmoles), and pyridine (2 ml) was refluxed in ethanol (25 ml) over 2 hours. The mixture was then concentrated *in vacuo* and the residue washed with a solution of methylene chloride and water (1/1). Extraction of the organic layers, drying over magnesium sulfate and evaporation *in vacuo* afforded 225 mg (95%) of the expected compound **21** which was purified on silica gel (eluent:cyclohexane/ethyl acetate (8:2)), mp 136°, ¹H nmr (deuteriochloroform): δ 1.45 (d, 6H, CH₃-i-Pr, J = 8 Hz), 5.60 (h, 1H, CH-i-Pr, J = 8 Hz), 7.40 (d, 1H, 5-H, J_{5,4} = 8.5 Hz), 8.10 (s, 1H, CH), 8.30 (d, 1H, 4-H, J_{4,5} = 8.5 Hz); ir: 3208, 3079, 2978, 2933, 1647 cm⁻¹.

Anal. Calcd. for C₉H₁₁N₃O₄: C, 48.0; H, 4.89; N, 18.67. Found: C, 48.05; H, 4.95; N, 18.70.

2-Isopropoxy-3-nitro-6-pyridinecarbonitrile (16).

Copper(II) acetate monohydrate (70 mg, 0.387 mmole) was dissolved in acetonitrile (20 ml) and added to a solution of 2-iso-

propoxy-3-nitro-6-pyridinealdehyde (21) (160 mg, 0.71 mmole) in acetonitrile (5 ml). The mixture was heated under gentle reflux until the reaction was completed (monitored by silica gel TLC (3 hours)). The solvent was then removed under reduced pressure and the residue hydrolyzed and extracted with methylene chloride. Drying over magnesium sulfate and evaporation *in vacuo*, afforded a crude product which was purified on silica gel (eluent:cyclohexane/ethyl acetate (8:2)), to give 150 mg (100%) of the expected compound **16** as an oil; ^1H nmr (deuteriochloroform): δ 1.40 (d, 6H, CH_3 -*i*-Pr, $J = 8$ Hz), 5.50 (h, 1H, CH-*i*-Pr, $J = 8$ Hz), 7.40 (d, 1H, 5-H, $J_{5,4} = 8.5$ Hz), 8.25 (d, 1H, 4-H, $J_{4,5} = 8.5$ Hz); ir: 3080, 2926, 2235, 1602 cm^{-1} .

Anal. Calcd. for $\text{C}_9\text{H}_9\text{N}_3\text{O}_3$: C, 52.17; H, 4.35; N, 20.29. Found: C, 52.23; H, 4.45; N, 20.10.

Procedures for Cross-coupling Reactions.

Route B.

6-Ethynyl-2-isopropoxy-3-nitropyridine (17).

To a 250 ml round-bottom flask were added triethylamine (30 ml), 6-chloro-2-isopropoxy-3-nitropyridine (**10b**) (5 g, 28.70 mmoles) and cuprous iodide (537 mg, 2.83 mmoles). The mixture was then gently warmed to 30° under argon. Then trimethylsilylacetylene (6.25 ml, 42.5 mmoles) was added, followed by bis(triphenylphosphine)palladium(II) chloride (1 g, 1.437 mmoles) under argon. The mixture was then refluxed at 80° over 12 hours and hydrolyzed with 20 ml of water. Extraction with methylene chloride, and drying over magnesium sulfate afforded a crude product which was purified by recrystallization (ethanol/water (1:1)) to give 5.10 g (75%) of compound **17** as a yellow solid, mp 161°; ^1H nmr (deuteriochloroform): δ 0.25 (s, 9H, SiMe₃), 1.45 (d, 6H, CH_3 -*i*-Pr), 5.50 (m, 1H, CH-*i*-Pr), 6.88 (d, 1H, 5-H, $J_{5,4} = 8.5$ Hz), 8.40 (d, 1H, 4-H, $J_{4,5} = 8.5$ Hz); ir: 3471, 3143, 2960, 2200 cm^{-1} .

Anal. Calcd. for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_3\text{Si}$: C, 56.11; H, 6.52; N, 10.07. Found: C, 56.35; H, 6.32; N, 10.20.

Route C.

2-Isopropoxy-3-nitro-6-vinylpyridine (19).

6-Chloro-2-isopropoxy-3-nitropyridine (**10b**) (0.4 g, 1.85 mmoles), vinyltributylstannane (0.54 g, 1.85 mmoles) and tetrakis(triphenylphosphine)palladium(0) (0.07 g, 0.06 mmoles) were refluxed over 12 hours in deoxygenated toluene (15 ml). The solvent was removed and the crude product was treated with 5 ml of water and then extracted with dichloromethane (2 x 20 ml). Solvent removal afforded a crude product which was purified by flash chromatography on silica gel (eluent:cyclohexane/ethyl ether (9.5:0.5)) to give 0.35 g (90%) of the expected vinyl compound **19** as an oil; ^1H nmr (deuteriochloroform): δ 1.40 (d, 6H, CH_3 -*i*-Pr, $J = 8$ Hz), 5.55 (h, 1H, CH-*i*-Pr, $J = 8$ Hz), 5.60 (dd, 1H, H_{vinyl} , $J_{\text{cis}} = 10.5$ Hz, $J_{\text{gem}} = 1.5$ Hz), 6.35 (dd, 1H, H_{vinyl} , $J_{\text{trans}} = 17$ Hz, $J_{\text{gem}} = 1.5$ Hz), 6.70 (dd, 1H, H_{vinyl} , $J_{\text{trans}} = 17$ Hz, $J_{\text{cis}} = 10.5$ Hz), 6.85 (d, 1H, 5-H, $J_{5,4} = 8$ Hz), 8.20 (d, 1H, 4-H, $J_{4,5} = 8$ Hz); ir: 2981, 2933, 2871, 1632, 1575 cm^{-1} .

Anal. Calcd. for $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_3$: C, 57.70; H, 5.80; N, 13.50. Found: C, 57.60; H, 5.85; N, 13.64.

General Procedure for Ozonolysis of Unsaturated Bonds.

Ozonized oxygen was bubbled through a cooled solution (-78°) of vinylpyridine, **19** and **23**, (141 mmoles) or ethynylpyridine (41 mmoles) in methylene chloride (50 ml) with acetic acid (1.5 ml)

for about 25 minutes (until the colour changed from yellow to blue). The reaction mixture was then allowed to stir at room temperature for 10 minutes and neutralized to pH 7-8 with an aqueous solution of hydrogen carbonate. Extraction with methylene chloride, drying over magnesium sulfate and evaporation *in vacuo* gave a crude product which was purified by flash chromatography on silica gel (eluent:cyclohexane/ethyl ether (8:2)).

2-Isopropoxy-3-nitro-6-pyridinecarboxaldehyde (20).

This compound was obtained in a yield of 95% as an oil; ^1H nmr (deuteriochloroform): δ 1.45 (d, 6H, CH_3 -*i*-Pr, $J = 8$ Hz), 5.60 (h, 1H, CH-*i*-Pr, $J = 8$ Hz), 7.70 (d, 1H, 5-H, $J_{5,4} = 8.5$ Hz), 8.30 (d, 1H, 4-H, $J_{4,5} = 8.5$ Hz), 9.90 (s, 1H, CHO); ir: 3414, 3085, 2984, 1718, 1602 cm^{-1} .

Anal. Calcd. for $\text{C}_9\text{H}_{10}\text{N}_2\text{O}_4$: C, 51.43; H, 4.76; N, 13.33. Found: C, 51.34; H, 4.53; N, 13.42.

2-Isopropoxy-3-pivaloylamino-6-pyridinecarboxaldehyde (24).

This compound was obtained in a yield of 90% as a white solid, mp 84°; ^1H nmr (deuteriochloroform): δ 1.35 (s, 9H, *t*-Bu), 1.50 (d, 6H, CH_3 -*i*-Pr, $J = 8$ Hz), 5.50 (h, 1H, CH-*i*-Pr, $J = 8$ Hz), 7.60 (d, 1H, 5-H, $J_{5,4} = 8.5$ Hz), 8.20 (m, 1H, NH), 8.70 (d, 1H, 4-H, $J_{4,5} = 8.5$ Hz), 9.85 (s, 1H, CHO); ir: 3430, 2957, 2874, 2870, 1690 cm^{-1} .

Anal. Calcd. for $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_3$: C, 63.63; H, 7.57; N, 10.61. Found: C, 63.65; H, 7.67; N, 10.65.

General Procedure for Oxidation of 6-Pyridinecarboxaldehydes.

To a solution of 6-pyridinecarboxaldehyde, **20** and **24** (1.0 mmole) in ethanol (10 ml), was added a solution of silver nitrate (434 mg, 2.56 mmoles) in distilled water (1.5 ml). To this, was added dropwise with stirring 20 ml of a potassium carbonate solution (1.20 g dissolved in 15 ml of water). The heterogeneous mixture was stirred an additional 2 hours. The silver salts were filtrated *in vacuo*, washed with an equal volume of water and the basic filtrate washed several times with methylene chloride. The solution was now made acidic with hydrochloric acid to pH 3-4 and then extracted with methylene chloride. Drying over magnesium sulfate and evaporation *in vacuo* afforded purified product in 95% yields.

2-Isopropoxy-3-nitro-6-pyridinecarboxylic Acid (18).

This compound was obtained as a yellow solid, mp 128°; ^1H nmr (deuteriochloroform): δ 1.45 (d, 6H, CH_3 -*i*-Pr, $J = 8$ Hz), 5.50 (h, 1H, CH-*i*-Pr, $J = 8$ Hz), 7.80 (d, 1H, 5-H, $J_{5,4} = 8.5$ Hz), 8.30 (d, 1H, 4-H, $J_{4,5} = 8.5$ Hz), 9.15 (m, 1H, CO₂H); ir: 3083, 2980, 2614, 1948, 1723, 1601 cm^{-1} .

Anal. Calcd. for $\text{C}_9\text{H}_{10}\text{N}_2\text{O}_5$: C, 47.48; H, 4.42; N, 12.38. Found: C, 47.75; H, 4.47; N, 12.38.

2-Isopropoxy-3-pivaloylamino-6-pyridinecarboxylic Acid (26).

This compound was obtained as a white solid, mp 98°; ^1H nmr (deuteriochloroform): δ 1.45 (s, 9H, *t*-Bu), 1.50 (d, 6H, CH_3 -*i*-Pr, $J = 8$ Hz), 5.40 (h, 1H, CH-*i*-Pr, $J = 8$ Hz), 7.80 (d, 1H, 5-H, $J_{5,4} = 8.5$ Hz), 7.85 (m, 1H, CO₂H), 8.20 (m, 1H, NH), 8.75 (d, 1H, 4-H, $J_{4,5} = 8.5$ Hz); ir: 3436, 2968, 1689, 1595 cm^{-1} .

Anal. Calcd. for $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_4$: C, 60.0; H, 7.14; N, 10.0. Found: C, 60.05; H, 7.10; N, 10.10.

Protection of 6-Pyridinecarboxaldehydes such as Acetals.

6-(1,3-Dioxan-6-yl)-2-isopropoxy-3-pivaloylamino-6-pyridine (25).

To 2-isopropoxy-3-pivaloylamino-6-pyridinecarboxaldehyde (**24**) (300 mg, 1.14 mmoles) in toluene (25 ml) was

added *p*-toluenesulfonic acid (15 mg, 0.08 mmoles (7.5%)) and 1,3-propanediol (0.10 ml, 1.68 mmoles). The reaction mixture was refluxed over 12 hours with stirring, and a dean stark trap was used to remove the water formed during condensation. The mixture was then cooled and washed with 15 ml of an aqueous solution of hydrogen carbonate, followed by 20 ml of water. The aqueous layer was extracted with methylene chloride and dried over anhydrous sulfate magnesium. Solvent removal under reduced pressure and purification of the residue by chromatography on silica gel (eluent:cyclohexane/ethyl ether (5:5)) give 340 mg (95%) of the expected compound **25** as yellow crystals, mp 77°; ¹H nmr (deuteriochloroform): δ 1.35 (s, 9H, *t*-Bu), 1.40 (d, 6H, CH₃-*i*-Pr, *J* = 8 Hz), 2.25 (m, 2H, CH₂), 4.10 (m, 4H, CH₂), 5.45 (m, 2H, CH), 7.10 (d, 1H, 5-H, *J*_{5,4} = 8 Hz), 8.05 (m, 1H, NH), 8.60 (d, 1H, 4-H, *J*_{4,5} = 8 Hz); ir: 3322, 2973, 2848, 1669, 1605, 1108 cm⁻¹.

Anal. Calcd. for C₁₇H₂₆N₂O₄: C, 63.35; H, 8.07; N, 8.70. Found: C, 63.35; H, 8.10; N, 8.45.

6-(Dimethylacetal-6-yl)-4-iodo-3-pivaloylamino-2(1*H*)-pyridone (**28c**).

To 6-formyl-4-iodo-3-pivaloylamino-2(1*H*)-pyridone (**28b**) (250 mg, 0.72 mmole) in methanol (25 ml) was added methyl orthoformate (0.31 ml, 2.84 mmoles) under acidic conditions (two drops of hydrochloric acid). The mixture was refluxed over 6 hours and then cooled, concentrated *in vacuo*, neutralized to pH 8-9 with an aqueous solution of hydrogen carbonate, and extracted with methylene chloride (3 x 25 ml). The organic layers were dried over magnesium sulfate and evaporated under reduced pressure. The residue was then purified on silica gel (eluent:cyclohexane/ethyl acetate (2:8)) to give 280 mg (98%) of a white solid, mp 230°; ¹H nmr (deuteriochloroform): δ 1.30 (s, 9H, *t*-Bu), 3.35 (s, 6H, OMe), 5.15 (s, 1H, CH_{acetal}), 6.80 (s, 1H, 5-H), 7.50 (m, 1H, NH); ir: 3300, 2900, 1780, 1600 cm⁻¹.

Anal. Calcd. for C₁₃H₁₉N₂O₄I: C, 39.59; H, 4.82; N, 7.11. Found: C, 39.68; H, 4.95; N, 7.25.

Methyl 2-Isopropoxy-3-pivaloylamino-6-pyridinecarboxylate (**27**).

2-Isopropoxy-3-pivaloylamino-6-pyridinecarboxylic acid (**26**) (225 mg, 0.8 mmole) was refluxed in hot methanol (250 ml) over 48 hours. The mixture was then cooled and concentrated under reduced pressure. The residue was neutralized to pH 10 and extracted with methylene chloride. The organic layers were washed with sodium hydroxide and then dried over magnesium sulfate. Evaporation *in vacuo*, afforded 190 mg (80%) of the expected product **27**, as an oil; ¹H nmr (deuteriochloroform): δ 1.35 (s, 9H, *t*-Bu), 1.45 (d, 6H, CH₃-*i*-Pr, *J* = 8 Hz), 3.90 (s, 3H, OMe), 5.50 (h, 1H, CH-*i*-Pr, *J* = 8 Hz), 7.90 (d, 1H, 5-H, *J*_{5,4} = 8.5 Hz), 8.20 (m, 1H, NH), 8.85 (d, 1H, 4-H, *J*_{4,5} = 8.5 Hz); ir: 3438, 2975, 2871, 1739, 1719, 1517, 1207 cm⁻¹.

Anal. Calcd. for C₁₅H₂₂N₂O₄: C, 61.22; H, 7.48; N, 9.52. Found: C, 61.20; H, 7.50; N, 9.50.

General Procedure for the Synthesis of 4-Iodo-3-pivaloylamino-pyridines **14**.

A solution of the corresponding 3-pivaloylamino-pyridine **6a** and **25**, (25 mmoles) and tetramethylethylenediamine (7.25 g, 62.5 mmoles) in anhydrous tetrahydrofuran (150 ml) was cooled to -78°. *n*-Butyllithium (62.5 mmoles, 39 ml of a 1.6 *M* in hexane) was added slowly. After 15 minutes at -78°, the mixture

was stirred at -25° over a period of 45 minutes. A solution of iodine (62.5 mmoles, 15.9 g) in anhydrous tetrahydrofuran (15 ml) was added dropwise at -78°. After 15 minutes at this temperature, the solution was heated at -25° and stirred over 3 hours at this temperature. A few drops of a saturated aqueous solution of sodium thiosulfate was then added at 0° to remove excess iodine. Extraction of the reaction mixture with methylene chloride and evaporation *in vacuo*, gave an oil which was purified by flash chromatography on silica gel (eluent).

4-Iodo-2-methoxy-6-methyl-3-pivaloylamino-pyridine (**14a**).

This compound was obtained in a yield of 87% as a white solid (eluent:cyclohexane/ethyl ether (7:3)), mp 136°; ¹H nmr (deuteriochloroform): δ 1.35 (s, 9H, *t*-Bu), 2.40 (s, 3H, CH₃), 3.90 (s, 3H, OMe), 6.95 (m, 1H, NH), 7.20 (s, 1H, 5-H); ir: 3290, 2960, 2860, 1660, 1560 cm⁻¹.

Anal. Calcd. for C₁₂H₁₇N₂O₂I: C, 41.39; H, 4.92; N, 8.04. Found: C, 41.60; H, 5.01; N, 7.90.

6-(1,3-Dioxan-6-yl)-4-iodo-2-isopropoxy-3-pivaloylamino-pyridine (**14b**).

This compound was obtained in a yield of 80% as a white solid (eluent:cyclohexane/ethyl ether (8:2)), mp 186°; ¹H nmr (deuteriochloroform): δ 1.35 (s, 9H, *t*-Bu), 1.40 (d, 6H, CH₃-*i*-Pr, *J* = 8 Hz), 2.20 (m, 2H, CH₂), 4.10 (m, 4H, CH₂), 5.30 (m, 2H, CH), 6.95 (m, 1H, NH), 7.55 (s, 1H, 5-H); ir: 3274, 2974, 2855, 1665, 1570, 1103 cm⁻¹.

Anal. Calcd. for C₁₇H₂₅N₂O₄I: C, 45.50; H, 5.58; N, 6.25. Found: C, 45.56; H, 5.69; N, 6.15.

General Procedure for the Cleavage of Alkoxy Groups.

To alkoxyaryls **14** (10 mmoles) dissolved in methylene chloride (100 ml), was added slowly under argon, a solution of boron tribromide (50 mmoles, 50 ml of a 1.0 *M* in methylene chloride) at -78°. The mixture was allowed to stir at room temperature over 10 hours and then hydrolyzed at 0° with 30 ml of water. The aqueous layer was neutralized first with an aqueous solution of sodium hydroxide and finally with hydrogen carbonate 10% to pH 7-8. Extraction of the reaction mixture with methylene chloride and evaporation *in vacuo*, gave a crude solid which was purified by flash chromatography on silica gel (eluent).

4-Iodo-6-methyl-3-pivaloylamino-2(1*H*)-pyridone (**28a**).

This compound was obtained in a yield of 80% as a solid (eluent:acetone), mp 249°; ¹H nmr (deuteriochloroform): δ 1.35 (s, 9H, *t*-Bu), 2.25 (s, 3H, CH₃), 6.50 (s, 1H, 5-H), 7.35 (m, 1H, NH); ir: 3215, 2960, 1665, 1500, 1475, 1400, 1290 cm⁻¹.

Anal. Calcd. for C₁₁H₁₅N₂O₂I: C, 39.54; H, 4.52; N, 8.38. Found: C, 39.43; H, 4.40; N, 8.25.

4-Iodo-3-pivaloylamino-2(1*H*)-6-pyridonecarboxaldehyde (**28b**).

This compound was obtained in a yield of 60% as a solid (eluent:cyclohexane/ethyl acetate (3:7)), mp 210°; ¹H nmr (deuteriochloroform): δ 1.35 (s, 9H, *t*-Bu), 7.25 (s, 1H, 5-H), 8.05 (m, 1H, NH), 9.45 (s, 1H, CHO); ir: 3280, 2962, 1702, 1675, 1500 cm⁻¹.

Anal. Calcd. for C₁₁H₁₃N₂O₃I: C, 38.01; H, 3.74; N, 8.07. Found: C, 38.25; H, 3.64; N, 8.02.

General Procedure for the Synthesis of 2-(4-Iodo-3-pivaloylamino-pyridyl) Triflates **4**.

The corresponding pyridone, **28a** and **28c**, (3.0 mmoles) was dissolved in dry pyridine (15 ml). Trifluoromethanesulfonic anhydride (2.52 ml, 15 mmoles) was added dropwise to the cooled

solution at 0°. After stirring at room temperature for 25 hours, the mixture was hydrolyzed in an ice bath, neutralized with an aqueous solution of hydrogen carbonate and extracted with methylene chloride. The organic layers were dried with magnesium sulfate and evaporated *in vacuo* to give a residue, which was purified by flash chromatography on silica gel (eluent).

2-(4-Iodo-6-methyl-3-pivaloylamino-2-pyridyl) Triflate (4c).

This compound was obtained in a yield of 91% as a solid (eluent:cyclohexane/ethyl ether (7:3)), mp 152°; ¹H nmr (deuteriochloroform): δ 1.35 (s, 9H, *t*-Bu), 2.50 (s, 3H, CH₃), 7.25 (m, 1H, NH), 7.70 (s, 1H, 5-H); ir: 3320, 2980, 2930, 1680, 1535 cm⁻¹.

Anal. Calcd. for C₁₂H₁₄N₂O₄ISF₃: C, 30.92; H, 3.03; N, 6.01. Found: C, 30.92; H, 2.77; N, 5.97.

2-(6-(Dimethylacetal-6-yl)-4-iodo-3-pivaloylamino-2-pyridyl) Triflate (4d).

This compound was obtained in a yield of 91% as a solid (eluent:cyclohexane/ethyl acetate (9:1)), mp 152°; ¹H nmr (deuteriochloroform): δ 1.40 (s, 9H, *t*-Bu), 3.40 (s, 6H, OMe), 5.20 (s, 1H, CH_{acetal}), 7.10 (m, 1H, NH), 8.10 (s, 1H, 5-H); ir: 3294, 2971, 2834, 1664, 1496 cm⁻¹.

Anal. Calcd. for C₁₄H₁₈N₂O₆ISF₃: C, 31.94; H, 3.43; N, 5.33. Found: C, 31.87; H, 3.26; N, 5.39.

Preparation of 2-Trimethylstannylquinoline 3c.

A solution of chlorotrimethylstannane (19.9 g, 100 mmoles) in freshly distilled 1,2-dimethoxyethane (20 ml) was added dropwise to a stirred suspension of small cubes of sodium metal (11.5 g, 500 mmoles) in dimethoxyethane (50 ml) under an argon stream in an ice salt bath for three hours (the color changes from white to green). The unreacted sodium was removed by filtration through a fritted-glass filter funnel under an argon stream. A solution of 2-chloroquinoline (10.64 g, 80 mmoles) in dimethoxyethane was added dropwise to the above filtrate in an ice-salt bath. The reaction mixture was stirred for two hours at the same temperature and then allowed to warm to room temperature. After removal of the solvent *in vacuo*, the residue was extracted with ethyl ether and dried over magnesium sulfate. The residue was purified by distillation to give 18.1 g (78%) of compound 3c as a colorless liquid, (bp 125°/1 torr); ¹H nmr (deuteriochloroform): δ 0.46 (s, 9H, CH₃), 7.45 to 7.62 (m, 2H), 7.66 to 7.79 (m, 2H), 7.98 (d, 1H, 3-H, J_{3,4} = 8 Hz), 8.19 (d, 1H, 4-H, J_{4,3} = 8 Hz); ir: 3050, 2990, 2920, 1620, 1585 cm⁻¹.

Anal. Calcd. for C₁₂H₁₅NSn: C, 49.36; H, 5.18; N, 4.80. Found: C, 49.23; H, 4.91; N, 5.05.

General Procedure for Cross-coupling Reactions under Suzuki's Conditions.

4-Iodopyridine, 4c and 4d, (0.50 mmole) and phenylboronic acid 5 (150 mg, 0.50 mmole) were added to a solution of potassium carbonate (2M, 0.5 ml) and ethanol (0.25 ml) in deoxygenated toluene (20 ml). The resulting mixture was stirred under an argon atmosphere for 10 minutes. Tetrakis(triphenylphosphine)palladium(0) (17.5 mg, 0.015 mmole) was added and the reaction mixture was warmed under inert atmosphere at 110° for 12 hours. The solvent was removed and the crude product was treated with 5 ml of water, then extracted with methylene chloride. The solvent removal afforded a crude product which was purified by flash chromatography on silica gel (eluent).

2-(4-(2'-*N,N*-Diethylcarbamoyloxy-3',4'-dimethoxyphenyl)-6-methyl-3-pivaloylamino-2-pyridyl) Triflate (29a).

This compound was obtained in a yield of 85% as a white solid (eluent:cyclohexane/ethyl ether (5:5)), mp 100°; ¹H nmr (deuteriochloroform): δ 1.0 to 1.10 (m, 15H, *t*-Bu and CH₃), 2.53 (s, 3H, CH₃), 3.24 (m, 4H, CH₂), 3.87 (s, 3H, OMe), 3.91 (s, 3H, OMe), 6.83 (s, 2H, H-Ar), 7.11 (s, 1H, 5-H), 8.03 (m, 1H, NH); ir: 3250, 2980, 2860, 1710, 1680, 1620 cm⁻¹.

Anal. Calcd. for C₂₅H₃₂N₃O₈SF₃: C, 50.76; H, 5.45; N, 7.10. Found: C, 50.64; H, 5.45; N, 7.18.

2-(4-(2'-*N,N*-Diethylcarbamoyloxy-3',4'-dimethoxyphenyl)-6-(dimethylacetal-6-yl)-3-pivaloylamino-2-pyridyl) Triflate (29b).

This compound was obtained in a yield of 75% as an oil (eluent:cyclohexane/ethyl acetate (5:5)); ¹H nmr (deuteriochloroform): δ 1.05 to 1.10 (m, 15H, CH₃ and *t*-Bu), 3.20 (m, 4H, CH₂), 3.40 (s, 6H, OMe), 3.85 (s, 3H, OMe-Ar), 3.90 (s, 3H, OMe-Ar), 5.25 (s, 1H, CH), 6.80 (s, 2H, H-Ar), 7.55 (s, 1H, 5-H), 8.20 (m, 1H, NH); ir: 3230, 2985, 2875, 1720, 1610 cm⁻¹.

Anal. Calcd. for C₂₇H₃₆N₃O₁₀SF₃: C, 49.73; H, 5.52; N, 6.44. Found: C, 49.73; H, 5.74; N, 6.52.

General Procedure for Cross-coupling Reactions Between 2-Pyridyltriflates 29 and 2-Trimethylstannylquinoline (3c).

To 2-pyridyltriflate 29 (2.0 mmoles) and 2-trimethylstannylquinoline (3c) (2.40 mmoles, (1.2 equivalents)) in deoxygenated dioxane (50 ml), lithium chloride was added (255 mg, 6 mmoles, 3 equivalents). The mixture was stirred under an argon atmosphere over 10 minutes, then copper(II) bromide (14 mg (5%)) and tetrakis(triphenylphosphine)palladium(0) (70 mg (3%)) were added to the solution. The reaction mixture was refluxed over 48 hours under argon and then cooled at room temperature and hydrolyzed with 10 ml of ammonia (10%). Extraction with methylene chloride, drying over magnesium sulfate and solvent removal afforded crude solids which were purified on silica gel (eluent).

4-(2'-*N,N*-Diethylcarbamoyloxy-3',4'-dimethoxyphenyl)-6-methyl-3-pivaloylamino-2-(2"-quinolyl)pyridine (2b).

This compound was obtained in a yield of 45% as a white solid (eluent:cyclohexane/ethyl ether (2:8)), mp 160°; ¹H nmr (deuteriochloroform): δ 0.99 (s, 9H, *t*-Bu), 1.00 (m, 3H, CH₃), 1.17 (m, 3H, CH₃), 3.22 (s, 3H, CH₃), 3.28 (m, 4H, CH₂), 3.89 (s, 3H, OMe), 3.91 (s, 3H, OMe), 6.92 (d, 1H, 5'-H, J_{5',6'} = 8.8 Hz), 7.18 (d, 1H, 6'-H, J_{6',5'} = 8.8 Hz), 7.20 (s, 1H, 5-H), 7.57 (dd, 1H, 6"-H, J = 8.3 Hz and J = 7.2 Hz), 7.73 (dd, 1H, 7"-H, J = 8.3 Hz and J = 7.2 Hz), 7.88 (d, 1H, 5"-H, J = 8.3 Hz), 8.01 (d, 1H, 8"-H, J = 8.3 Hz), 8.30 (d, 1H, 4"-H, J = 8.7 Hz), 8.45 (d, 1H, 3"-H, J = 8.7 Hz), 10.93 (m, 1H, NH); ir: 3500, 3230, 2960, 2860, 1710, 1610 cm⁻¹.

Anal. Calcd. for C₃₃H₃₈N₄O₅: C, 69.45; H, 6.71; N, 9.82. Found: C, 69.64; H, 6.70; N, 9.60.

4-(2'-*N,N*-Diethylcarbamoyloxy-3',4'-dimethoxyphenyl)-6-(dimethylacetal-6-yl)-3-pivaloylamino-2-(2"-quinolyl)pyridine (2c).

This compound was obtained in a yield of 50% as an oil (eluent:cyclohexane/ethyl acetate (7:3)); ¹H nmr (deuteriochloroform): δ 0.99 (s, 9H, *t*-Bu), 1.05 (m, 3H, CH₃), 1.15 (m, 3H, CH₃), 3.30 (m, 4H, CH₂), 3.90 (s, 6H, OMe), 3.95 (s, 6H, OMe), 5.20 (s, 1H, CH_{acetal}), 6.90 (d, 1H, 5'-H, J_{5',6'} = 8.8 Hz), 7.20 (d, 1H, 6'-H, J_{6',5'} = 8.8 Hz), 7.25 (s, 1H, 5-H), 7.57 (dd, 1H, 6"-H, J = 8.3 Hz and J = 7.2 Hz), 7.75 (dd, 1H, 7"-H, J = 8.3 Hz

and J = 7.2 Hz), 7.80 (d, 1H, 5"-H, J = 8.3 Hz), 8.05 (d, 1H, 8"-H, J = 8.3 Hz), 8.32 (d, 1H, 4"-H, J = 8.7 Hz), 8.48 (d, 1H, 3"-H, J = 8.7 Hz), 10.80 (m, 1H, NH); ir: 3450, 3200, 2980, 2870, 1710, 1620 cm⁻¹.

Anal. Calcd. for C₃₅H₄₂N₄O₇: C, 66.66; H, 6.66; N, 8.88. Found: C, 66.85; H, 6.70; N, 8.60.

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