1560, 1225, 1090, 1050, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.85 (s, 1 H, 4-NCHO), 8.5 (s, 1 H, 5-N=CH), 5.0–6.1 (m, 4 H, sugar), 3.8–4.4 (m, 3 H, sugar), 4.1 (s, 3 H, OCH_3), 3.45 (s, 3 H, 3-CH_3), 2.95 (br s, 6 H, $N(CH_3)_2$), 1.8–2.1 (4 s, 12 H, acetates).

Anal. Calcd for $C_{22}H_{33}N_5O_{12}$ (583.55): C, 49.40; H, 5.70; N, 12.00. Found: C, 49.39; H, 5.85; N, 11.75.

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Registry No. **1a**, 125162-88-1; **1b**, 124516-16-1; **1c**, 125172-02-3; **1d**, 125162-90-5; **1f**, 125162-92-7; **1g**, 125162-91-6; **2a**, 137363-03-2; **2b**, 137363-04-3; **2d**, 137363-05-4; **2e**, 137363-06-5; **2f**, 137363-07-6; **2g**, 137363-08-7; **3a**, 137393-24-9; **3b**, 137393-25-0; **3c**, 137363-09-8; **3d**, 137433-68-2; **3e**, 137363-10-1; **3f**, 137393-26-1; **3g**, 137363-11-2; **4a**, 124516-17-2; **4b**, 124516-18-3; **5**, 124516-20-7; **6**, 137363-12-3; **7**, 97442-99-4; **8**, 95965-90-5; **9**, 137363-13-4; **10**, 137393-27-2; **11**, 137363-14-5.

A New Convergent Route to 1-Substituted Ellipticines

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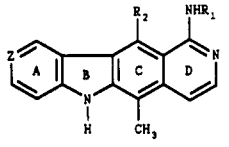
1-(2-Fluoro-4-pyridyl)ethanone was synthesized from 2-fluoropyridine and was ortho-lithiated after activation as the propylene glycol ketal. The resulting 3-lithio derivative was trapped by various electrophiles but reacted in low yield with N-protected 3-indolecarbaldehyde. Model compounds 1-[[[2-(diethylamino)ethyl]amino]-3-pyridyl]ethanol and -ethanone were prepared and selectively condensed with indole. 1-[[[2-(Diethylamino)-ethyl]amino]-3-pyridyl]ethanol and -ethanone bearing a ketal-protected acetyl moiety at the C-4 position have been obtained in high yields starting from the propylene glycol ketal of 1-(2-fluoro-4-pyridyl)ethanone. These reagents could not be condensed with indole either due to side reactions between the C-3 and C-4 functions or to steric hindrance. 1-(2-Substituted-4-bromo-3-pyridyl)ethanols were synthesized via a metalation/halogen-dance strategy starting from 2-fluoropyridine. 1-(2,4-Dihalo-3-pyridyl)-1-chloroethane could be prepared and condensed with 1-indolylmagnesium iodide, which allowed the construction of the expected 3-[1-(3-pyridyl)ethyl]indole skeleton. Functionalization of the pyridine C-4 bromo position was achieved by a vinylstannane cross-coupling reaction using a palladium(0) catalyst. Acidic treatment of the resulting 4-(1-ethoxyethenyl)pyridine led to 1-fluoroellipticine. The whole sequence requires six steps from indole and 2-fluoropyridine and allows an attractive overall yield.

Introduction

In the field of antitumor compounds, much interest has been focused by chemists on the ellipticine series.[1] Some ellipticine derivatives, such as 9-hydroxyellipticine[2] and the derived acetate of 9-hydroxy-2-methylellipticium (Celiptium),[3] have proved to be powerful anticancer agents but exhibit a high toxicity. 9-Aza and 9-methoxy derivatives of 5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole bearing a [(dialkylamino)propyl]amino moiety at the C-1 position show a high anticancer activity against myeloblastic leukemias as well as solid tumors[4-6] with lower cardiovascular effects compared with the parent ellipticines.



Z = CH, C-OCH_3, N ; R_2 = H, CH_3 ; R_1 = $(CH_2)_nNEt_2$

General and convenient procedures for the synthesis of such 1,9-difunctionalized ellipticines were not available and tedious multistep strategies were required.[7,8] A general pathway to 1,9-disubstituted ellipticines soon appeared as an attractive challenge for our laboratory. The chosen synthetic strategy was the construction of the C-ring of the ellipticine skeleton by means of indole and polyfunctionalized pyridine building blocks, which could be prepared by such selective reactions as directed ortho metalation,[10] halogen-dance,[18] Cross-Coupling reaction...[12]

Among the numerous syntheses of ellipticines or analogues based on the construction of the C-ring,[13] some involve reaction between a 4-substituted 3-lithiopyridine and an indole derivative bearing a 3-carbonyl function. At the beginning of the 1980s, the only reported results in this field were those of Snieckus who prepared ellipticine by a tandem lithiation strategy of both pyridine and indole.[14]

Bisagni was later interested in such a route to ellipticine analogues and for this purpose he succeeded in lithiating 2-(2-methoxy-4-pyridyl)-4,4-dimethyl-2-oxazoline[15] and

(1) Goodwin, S.; Smith, A. F.; Horning, E. C. *J. Am. Chem. Soc.* **1959**, *81*, 1903. Dalton, L. K.; Demerac, S.; Elmes, B. C.; Loder, J. W.; Swan, J. M.; Teitei, T. *Aust. J. Chem.* **1967**, *20*, 2715. Hewlins, M. J. E.; Oliveira-Campos, A. M.; Shannon, P. V. R. *Synthesis* **1984**, 289. Gribble, G. W.; Saulnier, M. G. *Heterocycles* **1985**, *23*, 1277. Gribble, G. W. In *Synthesis and antitumor activity of ellipticine alkaloids and related compounds, Alkaloids*; Academic Press: New York, 1990; Vol. 39, p 239.

(2) Le Pecq, J. B.; Gosse, C.; Dat-Xuong, N.; Paoletti, C. *C. R. Acad. Sci., Ser. D* **1973**, *277*, 2289.

(3) Paoletti, C.; Le Pecq, J. B.; Dat-Xuong, N.; Huret, P. J.; Garnier, H.; Amiel, J. L.; Rouesse, J. *Recent Results Cancer Res.* **1980**, *74*, 107.

(4) Lidereau, C.; Chermann, J.-C.; Gruest, J.; Montagnier, L.; Ducrocq, C.; Rivalle, C.; Bisagni, E. *Bull. Cancer* **1980**, *67*, 1.

(5) Ducrocq, C.; Wendling, F.; Tourbez-Perrin, M.; Rivalle, C.; Pochon, F.; Bisagni, E.; Chermann, J.-C. *J. Med. Chem.* **1980**, *23*, 1212.

(6) Rivalle, C.; Wendling, F.; Tambourin, P.; Lhoste, J.-M.; Bisagni, E.; Chermann, J.-C. *J. Med. Chem.* **1983**, *26*, 181.

(7) Bisagni, E.; Ducrocq, C.; Lhoste, J. M.; Rivalle, C.; Civier, A. *J. Chem. Soc., Perkin Trans. I* **1979**, 1706.

(8) Rivalle, C.; Ducrocq, C.; Lohste, J. M.; Wendling, F.; Bisagni, E.; Chermann, J.-C. *Tetrahedron* **1981**, *37*, 2097.

(9) Bisagni, E.; Rautureau, M.; Huel, C. *Heterocycles* **1988**, *27*, 1671.

(10) For a comprehensive review on directed ortho metalation, see: Gschwend, H. W.; Rodriguez, H. R. *Org. React. (N.Y.)* **1979**, *26*, 1. For a review on lithiation of π-deficient heterocycles, see: Marsais, F.; Queguiner, G. *Tetrahedron* **1983**, *39*, 2009. For a recent review on directed ortho metalation of π-deficient azaaromatics, see: Marsais, F.; Queguiner, G.; Snieckus, V.; Epsztajn, J. *Adv. Heterocycl. Chem.* In press.

(11) Bunnett, J. F.; Moyer, E. *J. Am. Chem. Soc.* **1971**, *93*, 1183.

(12) Beletskaya, I. P. *J. Organomet. Chem.* **1983**, *250*, 551.

(13) Sainsbury, M. *Synthesis* **1977**, 437. Kansal, V. K.; Potier, P. *Tetrahedron* **1986**, *42*, 2389.

(14) Watanabe, M.; Snieckus, V. *J. Am. Chem. Soc.* **1980**, *102*, 1457.

(15) Bisagni, E.; Rautureau, M. *Synthesis* **1987**, 142.

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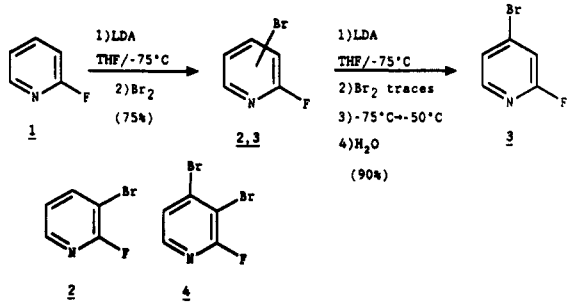
Scheme I

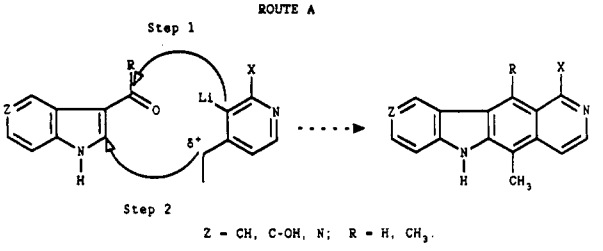


1-(2-chloro-4-pyridyl)ethanone ethylene glycol ketal.[9] This last reaction allowed him to prepare 9-aza and 9-methoxy derivatives of 5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole bearing a [(dialkylamino)propyl]amino moiety at the C-1 position. Unfortunately, he was not able to obtain the N-6 unsubstituted ellipticine derivatives, mostly due to the poor reactivity of the intermediary 3-lithiopyridine toward otherwise N-protected 3-indolecarbaldehydes.

We wish to report in the present paper on the attempted synthesis of 1-haloellipticine via three different routes, each resulting from modifications of the previous strategy due to the chemical dead-locks encountered.

Results

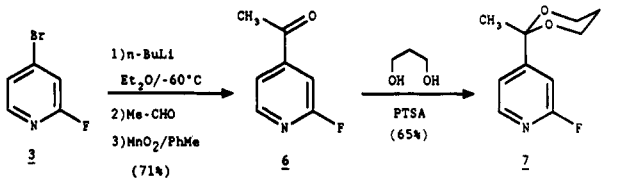
I. Synthesis and Lithiation of Ketal Derived from 1-(2-Fluoro-4-pyridyl)ethanone. As early as 1986 we reported[16] on the synthesis and lithiation of 2-(2-fluoro-4-pyridyl)-2-methyl-1,3-dioxane (as well as the 2-chloro-isomer). We were interested in the reaction of the resulting 3-lithio derivatives with N-protected 3-formyl- or 3-acetylindole, which was the key step in the following route to 1-haloellipticine (route A).



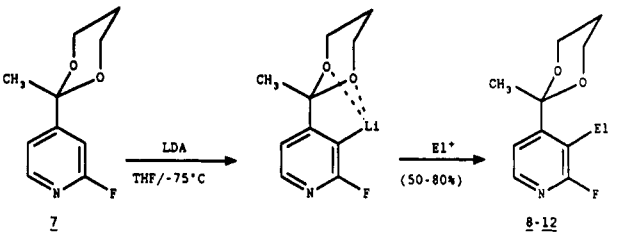
1-(2-Fluoro-4-pyridyl)ethanone (6) was prepared in four steps from 2-fluoropyridine (1) via 4-bromo-2-fluoropyridine (3). Directed lithiation of 2-fluoropyridine (1) by lithium diisoproylamide (LDA) at −75 °C[17] followed by reaction of bromine gave 3-bromo-2-fluoropyridine (2). This derivative was isolated together with 4-bromo-2-fluoropyridine (3) and traces of 3,4-dibromo-2-fluoropyridine (4) in a 75% overall yield. The crude 3-bromo-2-fluoropyridine (2) was lithiated, isomerized by LDA between −75 and −50 °C in the presence of small amounts of bromine, and hydrolyzed to 4-bromo-2-fluoropyridine (3)[18] (Scheme I).

Bromine–lithium exchange on 3 using *n*-butyllithium, followed by reaction of acetaldehyde, gave the expected secondary alcohol, which was oxidized with manganese dioxide[19] to ketone 6. This fluoro ketone was then

Scheme II



Scheme III

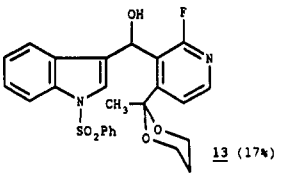


El	D	I	CHO	Ph-CH(OH)	Me-CH(OH)
Cmpd	8	9	10	11	12
Yield	80%	60%	50%	75%	80%

transformed into the corresponding 1,3-propylene glycol ketal 7 (Scheme II).

Fluoro ketal 7 was selectively lithiated by LDA in THF at −75 °C and the resulting 3-lithiopyridine derivative could be trapped by various electrophiles to give the C-3-functionalized products (Scheme III).

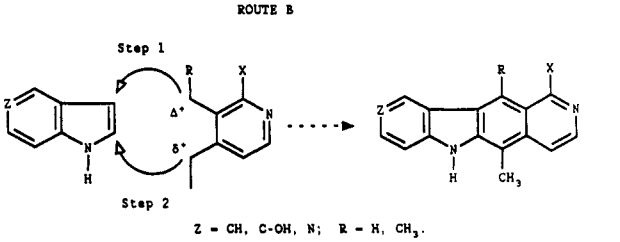
The 3-lithio derivative of fluoro ketal 7 failed to react with *N*-(phenylsulfonyl)-3-indolecarbaldehyde at low temperature, but the addition product 13 could be obtained in a low 17% yield when working at room temperature.



13 (17%)

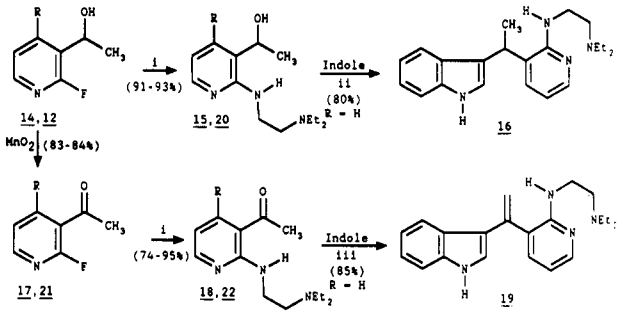
This key reaction for the construction of the ellipticine C-ring (route A) could not be improved, which made it necessary to change the initial strategy, especially since a 3-acetylindole reagent was suspected of giving a still lower yield than the corresponding aldehyde.

II. Synthesis of 1-(3-Pyridyl)ethanols and -ethanones and Coupling with Indole. As the introduction of the ellipticine C-ring C_{11}-CH_3 moiety by means of the indole building block could not be conveniently achieved, a modified strategy (route B) was then proposed employing the synthesis of 2,3,4-trifunctionalized pyridines and their coupling with indole.



(16) Marsais, F.; Pineau, Ph.; Queguiner, G. Poster Communication, 12th European Congress of Heterocyclic Chemistry, Reims, France, 1986.
(17) Güngör, T.; Marsais, F.; Queguiner, G. *J. Organomet. Chem.* **1981**, *215*, 139.
(18) Mallet, M.; Queguiner, G. *Tetrahedron* **1979**, *35*, 1625. Mallet, M.; Queguiner, G. *Tetrahedron* **1982**, *38*, 3035. Mallet, M.; Marsais, F.; Branger, G.; Queguiner, G. *J. Organomet. Chem.* **1990**, *382*, 319.
(19) Attenburrow, J.; Cameron, A. F. B.; Chapman, J. H.; Evans, R. M.; Hems, B. A.; Jansen, A. B. A.; Walker, T. *J. Chem. Soc.* **1952**, 1094.

Scheme IV



R = H (14,15,17,18); 2-methyl-1,3-dioxan-2-yl(12,20,21,22).
i = refluxing NH_2-$(CH_2)_2$-NEt_2 ; ii = PTSA/AcOH ; iii = HCl_g/MeOH.

Such pyridines require two proelectrophilic centers at the C_α positions of the C-3 and C-4 lateral chains. The electrophilic character of these two positions must be well differentiated to allow regioselective couplings with the indole C-3 and C-2 positions, respectively. A pyridine C-4 ketal moiety (route A) was used as a masked electrophilic center (δ^+). Among the possible proelectrophilic C_α centers for the second pyridine C-3 substituent were the C—OH and C=O moieties,[20,21] which led us to propose pyridines **20** and **22** as target molecules (Scheme IV).

Selective condensation conditions were first checked on pyridine models.

1-[[[2-(Diethylamino)ethyl]amino]-3-pyridyl]ethanol (**15**) and -ethanone (**18**) were synthesized from the corresponding fluoro derivatives **14** and **17**[17] in high yields (Scheme IV).

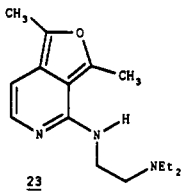
Condensation of secondary alcohol **15** with indole was best achieved under acidic catalysis (*p*-toluenesulfonic acid in refluxing acetic acid) to yield 80% of the 3-[1-(3-pyridyl)ethyl]indole (**16**).

Ethanone **18** was successfully coupled with indole in refluxing 2 N hydrogen chloride in anhydrous methanol to give the expected vinyl derivative **19** (Scheme IV).

These promising methods were then extended to pyridines bearing the required ketal moiety at the C-4 position. Thus, 1-[[[2-(diethylamino)ethyl]amino]-3-pyridyl]ethanol (**20**) and -ethanone (**22**) were prepared from the previously obtained fluoro alcohol **12** and its corresponding ketone **21**, respectively (Scheme IV).

Ethanone **22** could not be condensed with indole under Sainsbury's conditions[20] and was recovered almost unchanged.

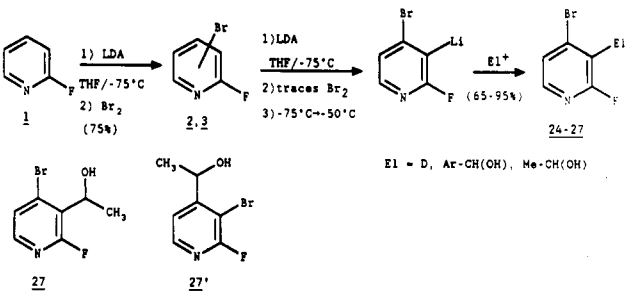
Reaction of 1-(3-pyridyl)ethanol **20** with indole under the previously defined conditions (*p*-toluenesulfonic acid in refluxing acetic acid) did not lead to the expected condensation product but to 42% of the furo[3,4-*c*]pyridine **23**. This compound proved to be highly unstable, but could be characterized via its ^{1}H-NMR spectrum.



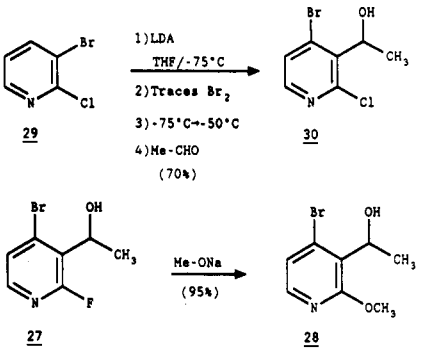
23

III. Functionalization of Halopyridines and Coupling with Indole. The previous route to 1-substituted ellipticines had to be modified by searching for new pyridines which would be capable of inducing selective formation of the ellipticine C-ring. The main idea was to use pyridines bearing a precursor of the required two-carbon chain at the C-4 position (route C).

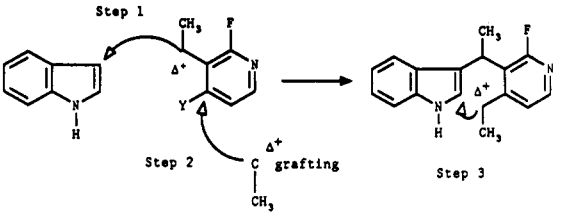
Scheme V



Scheme VI



ROUTE C



One of the possible ways was to use a 4-bromopyridine (Y = Br) and to achieve step 2 via an organometallic or a cross-coupling pathway.

Directed lithiation of 2-fluoropyridine (**1**) by LDA at −78 °C[17] followed by reaction of bromine gave 3-bromo-2-fluoropyridine (**2**). This crude compound was lithiated and isomerized by LDA at −78 °C to give 4-bromo-2-fluoro-3-lithiopyridine, as proved by reaction with such electrophiles as CH_3OD, benzaldehyde, 1-(phenylsulfonyl)-3-indolecarbaldehyde, and acetaldehyde.

This last reagent had to be added as fast as possible to the lithiation mixture in order to avoid competitive formation of 1-(3-bromo-2-fluoro-4-pyridyl)ethanol (**27′**) (slow addition of acetaldehyde led to **27′** in a 5–15% yield) (Scheme V).

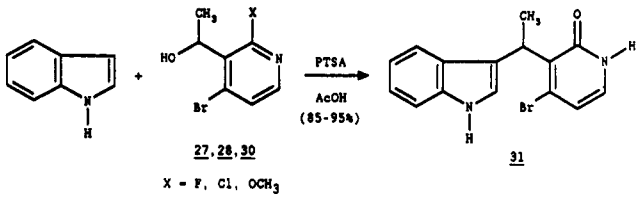
Other 2-substituted 1-(4-bromo-3-pyridyl)ethanols were also prepared. The previously described metalation and isomerization strategy was applied to 3-bromo-2-chloropyridine (**29**) to give 2-chloropyridine **30** after reaction with acetaldehyde. The 2-methoxypyridine **28** was obtained by treating **27** with sodium methylate (Scheme VI).

Unfortunately, substitution of the fluoro group by a [(diethylamino)ethyl]amino moiety could not be achieved selectively due to competitive attack on both halo groups of **27** upon treatment with (diethylamino)ethylamine under reflux.

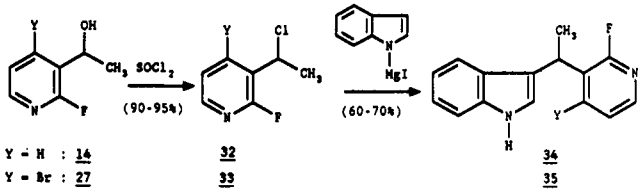
When the 2-substituted 1-(4-bromo-3-pyridyl)ethanols **27**, **28**, and **30** were treated with indole under acidic ca-

(20) Sainsbury, M.; Schinazi, R. F. *J. Chem. Soc., Perkin Trans. I* **1976**, 1155.
(21) Bergman, J.; Carlsson, R. *Tetrahedron Lett.* **1978**, *38*, 4055.

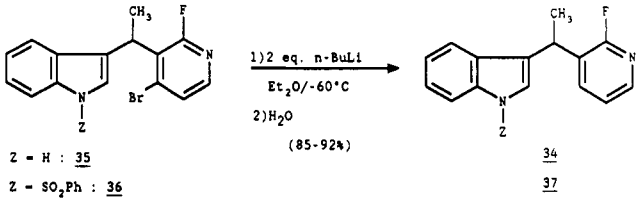
Scheme VII



Scheme VIII



Scheme IX



talysis (PTSA/AcOH), the coupling reaction occurred in high yield, but simultaneous hydrolysis of the C-2 chloro, fluoro, or methoxy group could not be avoided, which led to pyridone **31** being formed (Scheme VII).

Transformation of pyridone **31** to the corresponding C-2 chloropyridine using standard procedures could not be achieved without degradation of the substrate, and it was necessary to look for nonacidic condensation conditions. It was found that the chloro derivatives **32** and **33** of 1-(3-pyridyl)ethanols **14** and **27** (prepared by reaction of $SOCl_2$) reacted with 1-indolylmagnesium iodide in refluxing benzene following DeGraw's procedure[22] to give the expected condensed products **34** and **35** (Scheme VIII).

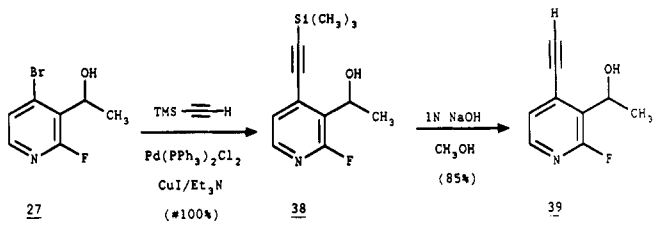
The last part of the synthesis consisted in introducing at the pyridine C-4 bromo site a suitable two-carbon moiety bearing a proelectrophilic α-carbon for the final cyclization step.

The first pathway checked was a bromine–lithium exchange on compound **35**, followed by reaction of the intermediate lithio derivative with acetaldehyde. Bromine–lithium exchange was achieved either on **35** or on its *N*-phenylsulfonyl derivative **36** using a twofold excess of butyllithium in THF at −70 °C, and it occurred almost quantitatively as proved by hydrolysis quenching experiments (Scheme IX).

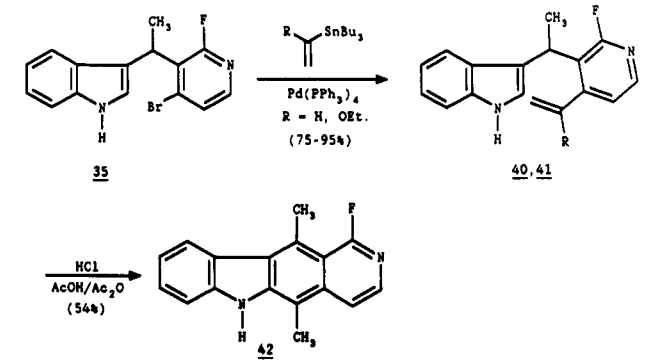
Unfortunately, acetaldehyde failed to react with the lithio derivative of bromopyridine **35** (or **36**). This reaction led mainly to the debrominated compound **34** (or **37**) in a 70% yield.

The cross-coupling strategy between aromatic bromo compounds and alkynes[23] or alkenes[24] offered another route for the functionalization of compound **35** at the pyridine C-4 position and the introduction of a masked electrophilic moiety.

Scheme X



Scheme XI



1-(4-Bromo-2-fluoro-3-pyridyl)ethanol (**27**) as a model molecule was treated with (trimethylsilyl)acetylene in the presence of dichlorobis(triphenylphosphine)palladium(II) and cuprous iodide in catalytic amounts (GC monitoring showed quantitative coupling after 3 h in refluxing triethylamine). The resulting crude product **38** was desilylated under basic conditions to give the expected 4-ethynylpyridine **39** in good yields (Scheme X).

The same reaction could not be applied to bromo compound **35**, which remained unchanged or was destroyed depending on the reaction conditions (triethylamine in a sealed tube, tripropylamine or pyridine, with protected or unprotected indole).

Functionalization of **35** at the pyridine C-4 bromo site was successfully realized by means of tributylvinylstannanes. The coupling reaction was achieved in refluxing toluene with a palladium(0) catalyst to give the expected 4-vinylpyridines **40** and **41** in high yields (Scheme XI).

Acidic treatment of compound **41** (R = OEt) allowed the final C-ring closure and 1-fluoroellipticine (**42**) was isolated in 54% yield (Scheme XI).

Discussion

The main part of this work was dedicated to the search for selective pathways for the synthesis of complex polyfunctionalized pyridines which would be very difficult to obtain via the usual routes.

Synthesis of 1-(2-fluoro-4-pyridyl)ethanone (**5**) was conveniently achieved in four steps (48% overall yield) starting from commercial 2-fluoropyridine.

Lithiation of 1-(2-fluoro-4-pyridyl)ethanone ketal **7** was chemoselectively achieved by LDA. The metalation is regioselectively directed at the C-3 position due to a strong proximity effect of both ketal and halogen (stabilization of the resulting 3-lithio derivative is related to the fluorine electron-withdrawing effect as well as the ketal oxygen chelation). It must be added that the ketal group alone has been proved to be unable to direct an ortho-lithiation whatever the lithiation conditions (this has been demonstrated in the case of 2-methyl-2-[4-pyridyl]-1,3-dioxane).[25]

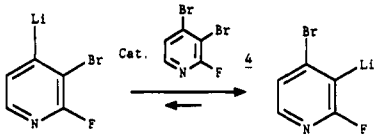
(22) DeGraw, J. I.; Kennedy, J. G.; Skinner, W. A. *J. Heterocycl. Chem.* **1966**, *3*, 67.

(23) Mc Kean, D. R.; Parrinello, G.; Renaldo, A. F.; Stille, J. K. *J. Org. Chem.* **1987**, *52*, 422. Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813.

(24) Sakamoto, T.; Shiraiwa, M.; Kondo, Y.; Yamanaka, H. *Synthesis* **1983**, 312. Sakamoto, T.; Kondo, Y.; Shiraiwa, M.; Yamanaka, H. *Synthesis* **1984**, 245.

(25) Pineau, Ph. University Thesis, Rouen, France, 1989.

Scheme XII



The first route (route A) was based on the reaction of *N*-(phenylsulfonyl)-3-indolecarbaldehyde with the 3-lithio derivative of a 2-fluoropyridine bearing a ketal group at the C-3 position (compound **7**). This pathway was abandoned owing to the low yield of the condensation step. The poor reactivity of the lithio species is more likely related to steric hindrance than to deactivation of the aldehyde by the nitrogen electron-donating effect. Similar difficulties were reported by Bisagni who used *N*-methyl-3-indolecarbaldehyde.[9]

The second route (route B) involved the condensation of a 1-[[[2-(diethylamino)ethyl]amino]-4-pyridyl]ethanone ketal bearing either a 1-hydroxyethyl or an acetyl moiety at the pyridine C-3 position with indole. Good results were obtained on model molecules (compounds **15** and **18**), but difficulties appeared when the condensed pyridines possessed a ketal-protected acetyl function at the C-4 position. Condensation via a picolinic secondary alcohol (compound **20**) could not be realized due to a competitive intramolecular transacetalization between the alcohol and the ketal function. Condensation via an acetyl function (compound **22**) failed, mostly due to steric hindrance in the vicinity of the electrophilic center as Sainsbury previously reported.[26]

Bromination of 2-fluoro-3-lithiopyridine afforded a 70% mixture of 3-bromo- and 4-bromo-2-fluoropyridine, respectively, in a ratio of 7:3. Formation of the 4-bromo derivative results from a combined metalation and isomerization reaction of the 3-bromo product, either by unreacted LDA or 3-lithio-2-fluoropyridine itself in the lithiation mixture. The same reaction was involved during the following step, which leads to 3-functionalized 4-bromo-2-fluoropyridines **24–27**. The isomerization reaction can be understood in terms of an equilibrium between the 3-bromo-2-fluoro-4-lithiopyridine and 4-bromo-2-fluoro-3-lithiopyridine, in favor of the more stabilized 3-lithio species[18] (Scheme XII).

The "halogen-dance" reaction was discovered by Bunnett[11] in the aromatic series and has been widely studied by our team[18] in the pyridine series. It was shown to occur via catalytic amounts of 3,4-dibromo-2-fluoropyridine (**4**) (**4** could be isolated from the reaction mixture).

The previous overall sequence allows a very convenient pathway to complex 2,3,4-trisubstituted pyridines starting from commercial 2-fluoro(or 2-chloro)pyridine.

Bromine–lithium exchange on 3-[1-(4-bromo-3-pyridyl)ethyl]indole **35** (or its N-protected derivative **36**) was effective as proved by hydrolysis experiment. Nevertheless, reaction of the intermediary C-4 lithiopyridine with acetaldehyde failed and hydrolysis was mainly observed.

A cross-coupling reaction between the 4-bromopyridine **27** and (trimethylsilyl)acetylene selectively occurred at the bromo position, but the same reaction could not be extended to the indole-coupled derivative **35**. This can be explained in terms of steric hindrance related to the linear geometry of the coupling moiety. This hypothesis is in keeping with the almost quantitative cross-coupling reaction of the same derivative **35** with tributylvinylstannanes to yield compounds **40** and **41**.

The described route from 2-fluoropyridine to 1-fluoroellipticine (**42**), with a nonoptimized overall yield of 20%, requires only six steps, each being feasible on a multigram scale. The selected strategy has the advantage of being quite general as well as involving a very simple indole building block.

Experimental Section

General Data. Infrared spectra were taken on a Beckman IR 4250 spectrometer, and main absorption frequencies (OH, NH, C=O, C=C, C=N) are given in cm^{-1}. Nuclear magnetic resonance (NMR) spectra were run on a Varian T60 or Brucker AM 400 spectrometer equipped with an Aspect 3000 calculator. Chemical shifts are recorded in ppm downfield from an internal standard, TMS in $CDCl_3$ or HMDS in DMSO-d_6. Unless otherwise noted, pyridine ^1H–^1H coupling constants are in good agreement with the common values (J_{2-3} = 5 Hz; J_{2-4} = 2 Hz; J_{3-4} = 8 Hz) and are not given. Elemental analysis were performed on a Carlo Erba CHNS apparatus.

Starting Materials. Commercial 2-fluoropyridine, TMEDA, (diethylamino)ethylamine, and diisopropylamine were distilled from CaH_2 and stored over CaH_2. Commercial 1.6 M solutions of *n*-butyllithium in hexane were stored and transferred under a dehydrated and deoxygenated argon atmosphere via syringes through septa. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from benzophenone sodium prior to use. Lithium diisopropylamide (LDA) was prepared by addition of *n*-butyllithium (125 mL, 0.2 mol) to a cold (−75 °C) THF (500 mL) solution of diisopropylamine (20.2 g, 0.2 mol) and warming at 0 °C for $^1/_2$ h.

3-Bromo-2-fluoropyridine (2). 2-Fluoropyridine (1) (19.4 g, 0.2 mol) in THF (50 mL) was slowly added to a cold (−75 °C) THF solution of LDA (0.2 mol). The resulting yellow mixture was stirred for 4 h at −75 °C before fast addition of bromine (32 g, 0.2 mol) while holding on the temperature below −35 °C. Stirring was continued for $^1/_2$ h at −75 °C before hydrolysis by a mixture of concentrated HCl (0.2 mol) in THF (50 mL). An excess of water (200 mL) was added at room temperature before basification by K_2CO_3 (pH 10) and extraction by Et_2O (3 × 150 mL). Drying of the combined organic extracts ($MgSO_4$) and solvent removal under vacuum afforded a crude oil which was purified by two vacuum distillations to yield 75% of a mixture of **2** and **3** in a 7:3 ratio: bp 65–70 °C (5 mmHg). **2**: ^1H NMR ($CDCl_3$) δ 7.05–7.35 (m, 1 H, 5-H), 7.80–8.10 (m, 1 H, 4-H), 8.10–8.40 (m, 1 H, 6-H). **3**: ^1H NMR ($CDCl_3$) δ 7.10 (d, 1 H, 3-H, J_{3-F} = 3 Hz), 7.40 (dd, 1 H, 5-H, J_{5-F} = 1.5 Hz), 8.10 (d, 1 H, 6-H).

The end of vacuum distillation afforded a small impure fraction of 3,4-dibromo-2-fluoropyridine (**4**). This unstable derivative has been characterized by its ^1H NMR spectrum: ^1H NMR ($CDCl_3$) δ 7.70 (d, 1 H, 5-H), 8.10 (d, 1 H, 6-H).

4-Bromo-2-fluoropyridine (3). The previous mixture of **2** and **3** (0.1 mol) was slowly (1 h) added to a cold (−75 °C) THF (250 mL) solution of LDA (0.1 mol) after the previous addition of a drop of bromine. The resulting solution was slowly (3 h) warmed up from −75 to −50 °C, cooled, and hydrolyzed at −75 °C by a mixture of concentrated HCl (0.1 mol) and THF (50 mL). An excess of water (100 mL) was added at room temperature before basification by K_2CO_3 (pH 10) and extraction by Et_2O (3 × 100 mL). Drying of the combined organic extracts ($MgSO_4$) and solvent removal under vacuum afforded a crude oil, which was purified by vacuum distillation to yield 90% of **3**: bp 65 °C (5 mmHg); ^1H NMR ($CDCl_3$) δ 7.10 (d, 1 H, 3-H, J_{3-F} = 3 Hz), 7.40 (dd, 1 H, 5-H, J_{5-F} = 1.5 Hz), 8.10 (d, 1 H, 6-H); IR (neat) 2950, 1600, 1585, 1440 cm^{-1}. Anal. Calcd for C_5H_3BrFN (176.0): C, 34.12; H, 1.72; N, 7.96. Found: C, 34.3, H, 1.75; N, 7.99.

1-(2-Fluoro-4-pyridyl)ethanol (5). Compound **3** (17.6 g, 0.1 mol) in an Et_2O solution (50 mL) was slowly added to a cold (−60 °C) Et_2O (250 mL) solution of *n*-butyllithium (69 mL, 0.11 mol) and TMEDA (12.8 g, 0.11 mol). Stirring at −60 °C for $^1/_2$ h afforded a white precipitate, which was cooled to −75 °C before addition of freshly distilled acetaldehyde (6.6 g, 1.5 mol) in Et_2O. The mixture was allowed to react for 2 h at −75 °C before hydrolysis by a mixture of aqueous concentrated HCl (0.1 mol) in THF (50 mL). An excess of water (100 mL) was added at room

(26) Sainsbury, M.; Webb, B.; Schinazi, R. F. *J. Chem. Soc., Perkin Trans. I* **1975**, 289.

temperature before extraction by $CHCl_3$ (3 × 100 mL). Drying of the combined organic extracts ($MgSO_4$) and solvent removal under vacuum afforded a crude oil, which was purified by vacuum distillation to yield 83% of **5**: bp 105 °C (5 mmHg); ^1H NMR ($CDCl_3$) δ 1.50 (d, 3 H, CH_3, J_{CH-CH_3} = 7 Hz), 4.90–5.00 (s + q, 2 H, CH–OH), 7.00 (s, 1 H, 3-H), 7.20 (m, 1 H, 3-H), 8.10 (d, 1 H, 6-H); IR (neat) 3365, 2960, 2930, 1580, 1560, 1430 cm^{-1}. Anal. Calcd for C_7H_8FNO (141.15): C, 59.57; H, 6.71; N, 9.92. Found: C, 59.6; H, 6.77; N, 9.80.

1-(2-Fluoro-4-pyridyl)ethanone (6). Secondary alcohol **5** (28.2 g, 0.2 mol) was added to a mixture of manganese dioxide (174 g, 2 mol) and toluene (400 mL) in a flask fitted with a Dean–Stark apparatus.[27] The reaction mixture was boiled for 8–12 h, while monitoring the oxidation evolution by TLC (SiO_2, C_6H_{12}/Et_2O 5/1). Filtration over asbestos, washing of the manganese oxides cake with $CHCl_3$, removal of the solvents, and vacuum distillation yielded 85% of **6**: bp 108–110 °C (5 mmHg); ^1H NMR ($CDCl_3$) δ 2.70 (s, 3 H, CH_3), 7.40 (s, 1 H, 3-H), 7.65 (dd).

2-(2-Fluoro-4-pyridyl)-2-methyl-1,3-dioxane (7). Ketone **6** (9 g, 0.065 mol) was treated with 1,3-dihydroxypropane (7.6 g, 0.1 mol) in toluene (150 mL) in the presence of *p*-toluenesulfonic acid (0.5 g). The reaction mixture was boiled for 24 h and water was stripped off by means of a Dean–Stark apparatus. After addition of water (100 mL), basification by Na_2CO_3, and extraction by $CHCl_3$, the combined organic extracts were dried ($MgSO_4$). Solvent removal and vacuum distillation yielded 65% of **7**: bp 105 °C (1 mmHg); F <50 °C; ^1H NMR ($CDCl_3$) δ 0.8–2.7 (m, 2 H, CH_2), 1.50 (s, 1 H, CH_3), 3.5–4.4 (m, 4 H, CH_2O), 7.00 (d, 1 H, 3-H, J_{3-F} = 1 Hz), 7.15–7.3 (m, 1 H, 5-H), 8.25 (d, 1 H, 6-H); IR (KBr) 1595 cm^{-1}. Anal. Calcd for $C_{10}H_{12}FNO_2$ (197.2): C, 60.90; H, 6.13; N, 7.10. Found: C, 61.0; H, 6.15; N, 7.05.

General Procedure for Lithiation of 2-(2-Fluoro-4-pyridyl)-2-methyl-1,3-dioxane (7). Fluoro ketal **7** (2 g, 0.01 mol) in a THF solution (10 mL) was slowly added to a cold (–75 °C) solution of LDA (0.01 mol) in THF (50 mL). The resulting solution was stirred at –75 °C for 4 h before addition of the required electrophile (0.01 mol) in a THF solution (10 mL) at –75 °C and further reaction at the same temperature for an additional 3 h. Hydrolysis of the reaction mixture was first achieved at –75 °C by concentrated hydrochloric acid (5 mL) in THF (5 mL) and then by water (10 mL) at room temperature. Standard workup (extraction by methylene chloride, drying over $MgSO_4$, and removal of the solvents) gave rise to the crude products, which were purified by defined procedures.

2-(3-Deuterio-2-fluoro-4-pyridyl)-2-methyl-1,3-dioxane (8). Lithiation of fluoro ketal **7** according to the general procedure and quenching by excess of monodeuteriomethanol (3.3 g, 0.1 mol) afforded a mixture of **7** and **8**. Compound **8** was obtained in a 80% yield as shown by the ^1H NMR spectrum of the crude mixture: ^1H NMR ($CDCl_3$) δ 1.45 (s, 3 H, CH_3), 0.8–2.4 (m, 2 H, CH_2), 3.35–4.15 (m, 4 H, OCH_2), 7.20 (dd, 1 H, 5-H, J_{5-F} = 2 Hz), 8.20 (d, 1 H, 6-H).

2-(2-Fluoro-3-iodo-4-pyridyl)-2-methyl-1,3-dioxane (9). Lithiation of fluoro ketal **7** was achieved according to the general procedure. Reaction of iodine (2.54 g, 0.01 mol), decolorization of the crude reaction mixture by sodium thiosulfate, standard workup, and flash chromatography on silica (Et_2O/hexane 1/1) and washing with Et_2O (1 mL) afforded 60% of **9**: mp 110 °C; ^1H NMR ($CDCl_3$) δ 1.40 (s, 3 H, CH_3), 1.1–2.35 (m, 2 H, CH_2), 3.4–4.1 (m, 4 H, OCH_2), 7.35 (d, 1 H, 5-H, J_{5-F} = 1 Hz), 8.20 (d, 1 H, 6-H); IR (KBr) 2990, 2965, 2930, 2865, 1590, 1375 cm^{-1}. Anal. Calcd for $C_{10}H_{11}FINO_2$ (323.1): C, 37.17; H, 3.43; N, 4.33. Found: C, 37.0; H, 3.40; N, 4.30.

2-Fluoro-4-(2-methyl-1,3-dioxan-2-yl)-3-pyridinecarbaldehyde (10). Lithiation of fluoro ketal **7**, reaction of ethyl formate, and standard workup according to the general procedure afforded a crude product, which was purified by flash chromatography on silica (Et_2O/hexane 1/1) to yield 50% of **10**: mp 95 °C; ^1H NMR ($CDCl_3$) δ 1.70 (s, 3 H, CH_3), 1.1–2.55 (m, 2 H, CH_2), 3.35–4.2 (m, 4 H, OCH_2), 7.40 (d, 1 H, 5-H), 8.40 (d, 1 H, 6-H), 10.35 (s, 1 H, CHO); IR (KBr) 3110, 3000, 2980, 1700, 1600, 1400 cm^{-1}. Anal. Calcd for $C_{11}H_{12}FNO_3$ (225.2): C, 58.66; H, 5.37; N, 6.22. Found: C, 58.6; H, 5.31; N, 6.25.

[2-Fluoro-4-(2-methyl-1,3-dioxan-2-yl)-3-pyridyl]phenylmethanol (11). Lithiation of fluoro ketal **7**, reaction of freshly distilled benzaldehyde, and standard workup according to the general procedure afforded a crude product, which was purified by flash chromatography on silica (Et_2O/hexane 1/1) to yield 75% of **11**: mp 134 °C; ^1H NMR ($CDCl_3$) δ 1.65 (s, 3 H, CH_3), 1.0–2.4 (m, 2 H, CH_2), 3.1–4.0 (m, 4 H, OCH_2), 6.65 (s, 1 H, CH), 7.30 (m, 5 H, phenyl), 7.40 (dd, 1 H, 5-H, J_{5-F} = 1 Hz), 8.20 (d, 1 H, 6-H); IR (KBr) 3380, 3000, 2970, 2880, 1610, 1555, 1415 cm^{-1}. Anal. Calcd for $C_{17}H_{18}FNO_3$ (303.3): C, 67.31; H, 5.98; N, 4.62. Found: C, 67.3; H, 5.60; N, 4.63.

1-[2-Fluoro-4-(2-methyl-1,3-dioxan-2-yl)-3-pyridyl]ethanol (12). Lithiation of fluoro ketal **7**, reaction of freshly distilled acetaldehyde, and standard workup according to the general procedure afforded a crude product, which was crystallized by addition of hexane and washed by Et_2O (1 mL) to yield 80% of **12**: mp 134 °C; ^1H NMR ($CDCl_3$) δ 1.6 (2 s, 6 H, CH_3), 1.15–2.5 (m, 2 H, CH_2), 2.85 (s, 1 H, OH), 3.55–4.2 (m, 4 H, OCH_2), 5.70 (q, 1 H, CH), 7.35 (dd, 1 H, 5-H, J_{5-F} = 2 Hz), 8.10 (d, 1 H, 6-H); IR (KBr) 3470, 2970, 2940, 2890, 1600, 1405 cm^{-1}. Anal. Calcd for $C_{12}H_{16}FNO_3$ (241.3): C, 59.74; H, 6.68; N, 5.80. Found: C, 59.7; H, 6.67; N, 5.81.

[2-Fluoro-4-(2-methyl-1,3-dioxan-2-yl)-3-pyridyl][*N*-(phenylsulfonyl)-3-indolyl]methanol (13). Lithiation of fluoro ketal **7**, reaction of *N*-(phenylsulfonyl)-3-indolecarbaldehyde,[28] warming up to room temperature, and standard workup according to the general procedure afforded a crude product, which was crystallized by addition of hexane and washed by Et_2O (1 mL) to yield 17% of **13**: mp 185 °C; ^1H NMR ($CDCl_3$) δ 0.60 (m, 2 H, CH_2), 1.60 (s, 3 H, CH_3), 3.3–4.0 (m, 4 H, OCH_2), 4.0 (s, 1 H, OH), 6.90 (s, 1 H, CH), 7.0–8.10 (m, 11 H, 5-H + indole), 8.40 (d, 1 H, 6-H); IR (KBr) 3040, 1450, 1360 cm^{-1}. Anal. Calcd for $C_{25}H_{23}FN_2O_5S$ (482.5): C, 62.23; H, 4.80; N, 5.80. Found: C, 62.4; H, 4.76; N, 5.83.

1-(2-Fluoro-3-pyridyl)ethanol (14). Compound **14** was prepared from 2-fluoropyridine (**1**) according to ref 17 in 93% yield: bp 115 °C (13 mmHg); ^1H NMR ($CDCl_3$) δ 1.50 (d, 3 H, CH_3), 4.50 (s, 1 H, OH), 5.10 (q, 1 H, CH), 7.20 (ddd, 1 H, 5-H, J_{5-F} = 7.5 Hz), 8.0 (m, 2 H, 4-H + 6-H).

1-[[[2-(Diethylamino)ethyl]amino]-3-pyridyl]ethanol (15). Fluoro alcohol **14** (14.1 g, 0.1 mol) was boiled with (diethylamino)ethylamine (12.8 g, 0.11 mol) for 20 h. The resulting cooled mixture was hydrolyzed with 0.5 N NaOH (100 mL) and extracted with chloroform (3 × 100 mL). The combined extract was washed with slightly acidic water (HCl), dried over $MgSO_4$, and concentrated, before distillation of the crude oil under vacuum to yield 93% of **15**: bp 170 °C (3 mmHg); ^1H NMR ($CDCl_3$) δ 1.0 (t, 6 H, ethyl CH_3), 1.50 (d, 3 H, CH_3), 2.55 (m, 6 H, $CH_2N(CH_2)_2$), 3.50 (m, 2 H, $NHCH_2$), 4.55 (m, 1 H, OH), 4.75 (q, 1 H, CH), 6.0 (s, 1 H, NH), 6.45 (dd, 1 H, 5-H), 7.30 (d, 1 H, 4-H), 8.00 (d, 1 H, 6-H); IR (KBr) 2970, 2810, 1600, 1505, 1470 cm^{-1}. Anal. Calcd for $C_{13}H_{23}N_3O$ (237.3): C, 65.79; H, 9.77; N, 17.70. Found: C, 65.5; H, 9.93; N, 17.9.

3-[1-[[[2-(Diethylamino)ethyl]amino]-3-pyridyl]ethyl]-indole (16). Amino ethanol **15** (2.37 g, 0.01 mol) and indole (1.17 g, 0.01 mol) were introduced in acetic acid (20 mL) and boiled for 4 h in the presence of *p*-toluenesulfonic acid (0.1 g). Hydrolysis on a mixture of ice (50 g) and concentrated aqueous ammonia (50 mL) afforded a crude powder, which was crystallized from $CHCl_3/Et_2O$ (1/1) to yield 80% of **16**: mp 133 °C; ^1H NMR (DMSO) δ 0.85 (t, 6 H, ethyl CH_3), 1.55 (d, 3 H, CH_3), 2.40 (m, 6 H, $CH_2N(CH_2)_2$), 3.35 (m, 2 H, $NHCH_2$), 4.25 (q, 1 H, CH), 5.70 (m, 1 H, NH), 6.40 (dd, 1 H, pyridine 5-H), 6.7–7.5 (m, 6 H, indole + pyridine 4-H), 7.85 (d, 1 H, pyridine 6-H); IR (KBr) 3370, 2960, 1600, 1580, 1500, 1450 cm^{-1}. Anal. Calcd for $C_{21}H_{28}N_4$ (336.5): C, 74.96; H, 8.39; N, 16.65. Found: C, 74.8; H, 8.25; N, 16.30.

1-(2-Fluoro-3-pyridyl)ethanone (17). Oxidation of fluoro alcohol **14**[17] afforded fluoro ketone **17** in 85% yield: bp 85 °C (10 mmHg); ^1H NMR ($CDCl_3$) δ 2.65 (d, 3 H, CH_3, J_{H-F} = 4.5 Hz), 7.30 (ddd, 1 H, 5-H, J_{5-F} = 2 Hz), 8.2 (m, 1 H, 4-H), 8.35 (m, 1 H, 6-H).

1-[[[2-(Diethylamino)ethyl]amino]-3-pyridyl]ethanone (18). Treatment of compound **17** with (diethylamino)ethylamine

(27) Pratt, E. F.; Van de Castle, J. F. *J. Org. Chem.* **1961**, *26*, 2973.

(28) Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1982**, *47*, 757.

following the same procedure as for compound **15** afforded after vacuum distillation amino ketone **18** in 76% yield (95% on the crude product): bp 160 °C (13 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.05 (t, 6 H, ethyl CH_3), 2.20 (s, 3 H, CH_3), 2.4–3.0 (m, 6 H, $CH_2N(CH_2)_2$), 3.4–3.85 (m, 2 H, $NHCH_2$), 6.45 (m, 1 H, 5-H), 7.70 (dd, 1 H, 4-H), 8.15 (dd, 1 H, 6-H), 10.2 (m, 1 H, NH); IR (KBr) 3250, 2965, 2800, 1648, 1595, 1570, 1385 cm^{-1}. Anal. Calcd for $C_{13}H_{21}N_3O$ (235.3): C, 66.35; H, 8.99; N, 17.86. Found: C, 66.2; H, 9.05; N, 18.1.

3-[1-[[[2-(Diethylamino)ethyl]amino]-3-pyridyl]ethenyl]indole (19). Amino ketone **18** (5 g, 0.021 mol) and indole (2.5 g, 0.021 mol) were boiled for 4 h in a 2 N solution of dry hydrogen chloride in methanol (50 mL). Evaporation to dryness, dissolution in chloroform, washing with 5 N aqueous sodium hydroxyde, drying, and solvent removal afforded a crude oil, which was purified by flash chromatography on silica (Et_3N/Et_2O/hexane 1/5/4) to yield 85% of **19**: mp 63–64 °C; ^{1}H NMR ($CDCl_3$) δ 1.05 (t, 6 H, ethyl CH_3), 2.35–3.15 (m, 6 H, $CH_2N(CH_2)_2$), 5.0–5.35 (m, 2 H, $NHCH_2$), 6.9–8.35 (m, 9 H, vinyl CH_2 + aromatic), 8.70 (d, 1 H, pyridine 6-H); IR (KBr) 3400, 2960, 1635, 1555, 1525, 1485, 1450 cm^{-1}. Anal. Calcd for $C_{21}H_{26}N_4$ (334.5): C, 75.41; H, 7.83; N, 16.75. Found: C, 75.5; H, 7.78; N, 16.8.

1-[2-[[2-(Diethylamino)ethyl]amino]-4-(2-methyl-1,3-dioxan-2-yl)-3-pyridyl]ethanol (20). Reaction of fluoro alcohol **12** (2.4 g, 0.01 mol) with (diethylamino)ethylamine (1.28 g, 0.011 mol) as previously described for compound **15** afforded a crude oil, which was purified by flash chromatography on silica (Et_3N/Et_2O/hexane 5/70/25) to yield 91% of **20** (viscous oil): ^{1}H NMR ($CDCl_3$) δ 1.05 (t, 6 H, ethyl CH_3), 1.3–1.7 (m, 6 H, 2 × CH_3), 1.9–2.3 (m, 2 H, CH_2), 2.3–2.9 (m, 6 H, $CH_2N(CH_2)_2$), 3.3–4.05 (m, 6 H, OCH_2 + $NHCH_2$), 5.95 (q, 1 H, CH), 6.65 (d, 1 H, 5-H), 6.8 (m, 1 H, NH or OH), 8.05 (d, 1 H, 6-H); IR (KBr) 3350, 2950, 1650, 1595, 1500, 1470, 1370 cm^{-1}. Anal. Calcd for $C_{18}H_{31}N_3O_3$ (337.5): C, 67.62; H, 9.26; N, 12.45. Found: C, 67.9; H, 9.32; N, 12.8.

4-[[2-(Diethylamino)ethyl]amino]-1,3-dimethylfuro[3,4-*c*]pyridine (23). Reaction of amino alcohol **20** with indole as previously described for the preparation of compound **16** yielded 42% of a crude oil, which was too unstable to be purified. The structure of a furo[3,4-*c*]pyridine could be assigned to compound **23** on the basis of the ^{1}H NMR spectrum: ^{1}H NMR ($CDCl_3$) δ 1.05 (t, 6 H, ethyl CH_3), 2.35–2.9 (m, 12 H, $CH_2N(CH_2)_2$ + 2 × CH_3), 3.4–3.7 (3 m, 3 H, $NHCH_2$ + NH), 6.20 (d, 1 H, 6-H), 7.20 (d, 1 H, 7-H, J_{6-7} = 6 Hz).

1-[2-Fluoro-4-(2-methyl-1,3-dioxan-2-yl)-3-pyridyl]ethanone (21). Fluoro alcohol **12** (14.1 g, 0.1 mol) was oxidized following the same procedure as for the preparation of **5** and fluoro ketone **21** was obtained in 83% yield after flash chromatography on silica (Et_2O/hexane 6/4): mp 130 °C; ^{1}H NMR ($CDCl_3$) δ 1.60 (s, 3 H, CH_3), 1.2–2.35 (m, 2 H, CH_2), 2.60 (s, 3 H, CO–CH_3), 3.3–4.2 (m, 4 H, OCH_2), 7.45 (d, 1 H, 5-H), 8.45 (d, 1 H, 6-H); IR (KBr) 2980, 2940, 2880, 1700, 1575, 1540, 1375 cm^{-1}. Anal. Calcd for $C_{12}H_{14}FNO_3$ (239.2): C, 60.24; H, 5.90; N, 5.85. Found: C, 60.1; H, 5.88; N, 5.91.

1-[2-[[2-(Diethylamino)ethyl]amino]-4-(2-methyl-1,3-dioxan-2-yl)-3-pyridyl]ethanone (22). Fluoro ketone **21** was treated with (diethylamino)ethylamine following the same procedure as for the synthesis of compound **15**. The crude product was purified by flash chromatography on silica (Et_3N/Et_2O/hexane 5/70/25) to yield 74% of ketone **22** (amorphous solid): ^{1}H NMR ($CDCl_3$) δ 1.10 (t, 3 H, ethyl CH_3), 1.60 (s, 3 H, CH_3), 2.10 (s, 3 H, CO–CH_3), 1.95–2.5 (m, 2 H, CH_2), 2.3–2.8 (m, 6 H, $CH_2N(CH_2)_2$), 3.3–4.15 (m, 6 H, $NHCH_2$ + OCH_2), 7.10 (d, 1 H, 5-H), 8.20 (d, 1 H, 6-H); IR (KBr) 3300, 2985, 2875, 2800, 1655, 1600, 1560, 1510 cm^{-1}. Anal. Calcd for $C_{14}H_{28}N_3O_3$ (286.4): C, 58.71; H, 9.85; N, 14.67. Found: C, 58.5; H, 10.1; N, 14.8.

General Procedure for the Formation of 4-Bromo-2-fluoro-3-lithiopyridine and Its Reaction with Electrophiles. The previously prepared mixture of **2** and **3** (0.1 mol) was slowly (1 h) added to a cold (–75 °C) THF (250 mL) solution of LDA (0.1 mol) after the previous addition of a drop of bromine. The resulting solution was slowly (3 h) warmed up from –75 to –50 °C before cooling to –75 °C and adding the required electrophile. The reaction mixture was stirred for 2 h at –75 °C and hydrolyzed at the same temperature by a mixture of concentrated HCl (0.1 mol) in THF (50 mL). An excess of water (100 mL) was added at room temperature before basification by K_2CO_3 (pH 10) and extraction by Et_2O (3 × 100 mL). Drying of the combined organic extracts ($MgSO_4$) and solvent removal under vacuum afforded crude products, which were purified by crystallization, vacuum distillation, or flash chromatography on silica.

4-Bromo-3-deuterio-2-fluoropyridine (24). After lithiation of the crude 2-bromo-3-fluoropyridine (**2**) according to the general procedure and addition of an excess of monodeuteriomethanol, crude **24** was isolated and characterized by its ^{1}H NMR spectrum ($CDCl_3$): δ 7.35 (dd, 1 H, 5-H, J_{5-F} = 1.5 Hz), 8.05 (d, 1 H, 6-H).

(4-Bromo-2-fluoro-3-pyridyl)phenylmethanol (25). After lithiation of the crude 2-bromo-3-fluoropyridine (**2**) according to the general procedure, addition of freshly redistilled benzaldehyde, and recrystallization of the crude product from a 1/1 mixture of diethyl ether and hexane, secondary alcohol **25** was isolated in 70% yield: mp 95 °C; ^{1}H NMR ($CDCl_3$) δ 3.25 (d, 1 H, OH), 6.30 (d, 1 H, CH), 7.30 (m, 5 H, phenyl), 7.40 (d, 1 H, 5-H), 7.90 (d, 1 H, 6-H); IR (KBr) 3280, 1585, 1550, 1450, 1410 cm^{-1}. Anal. Calcd for $C_{12}H_9BrFNO$ (282.1): C, 51.09; H, 3.21; N, 4.96. Found: C, 51.1; H, 3.17; N, 4.94.

(4-Bromo-2-fluoro-3-pyridyl)[*N*-(phenylsulfonyl)-3-indolyl]methanol (26). Lithiation of the crude 2-bromo-3-fluoropyridine (**2**) according to the general procedure and reaction with *N*-(phenylsulfonyl)-3-indolecarbaldehyde afforded a crude product, which was precipitated by addition of a 1/1 mixture of diethyl ether and hexane. Flash chromatography on silica yielded 65% of **26**: mp 174 °C; ^{1}H NMR ($CDCl_3$) δ 4.25 (s, 1 H, OH), 6.50 (s, 1 H, CH), 7.3–8.3 (m, 12 H, Ar H); IR (KBr) 3400, 1590, 1550, 1450, 1410 cm^{-1}. Anal. Calcd for $C_{20}H_{14}BrFN_2O_3S$ (461.3): C, 52.07; H, 3.06; N, 6.07. Found: C, 51.9; H, 3.12; N, 5.97.

1-(4-Bromo-2-fluoro-3-pyridyl)ethanol (27). After lithiation of the crude 2-bromo-3-fluoropyridine (**2**) (0.1 mol) according to the general procedure, freshly redistilled acetaldehyde was added as fast as possible at –50 °C while cooling the reaction flask with a drug ice/acetone bath. The resulting mixture was stirred for 2 h at –75 °C before hydrolysis at the same temperature by a mixture of concentrated HCl (0.1 mol) in THF (50 mL). An excess of water (100 mL) was added at room temperature before basification by K_2CO_3 (pH 10) and extraction by Et_2O (3 × 100 mL). Drying of the combined organic extracts ($MgSO_4$) and solvent removal under vacuum afforded a crude product, which was purified by vacuum distillation to yield 75% of **27**: bp 115 °C (3 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.60 (d, 3 H, CH_3), 4.20 (m, 1 H, OH), 5.40 (q, 1 H, CH), 7.40 (d, 1 H, 5-H), 7.90 (d, 1 H, 6-H); IR (neat) 3380, 2970, 1640, 1590, 1550, 1450, 1410 cm^{-1}. Anal. Calcd for C_7H_7BrFNO (220.0): C, 38.21; H, 3.20; N, 6.36. Found: C, 38.3; H, 3.16; N, 6.38.

1-(3-Bromo-2-fluoro-4-pyridyl)ethanol (27′). If the synthesis of **27** was achieved as previously described, except for the fact that acetaldehyde was slowly added to the lithiation mixture at –75 °C, compound **27** was isolated together with small amounts (5–15%) of the **27′** isomer. This latter compound could be identified from the ^{1}H NMR spectrum of the crude mixture of **27** and **27′**: ^{1}H NMR ($CDCl_3$) δ 1.60 (d, 3 H, CH_3), 4.20 (m, 1 H, OH), 5.40 (q, 1 H, CH), 7.50 (d, 1 H, 5-H), 8.05 (d, 1 H, 6-H).

1-(4-Bromo-2-chloro-3-pyridyl)ethanol (30). Lithiation[29] and isomerization of 3-bromo-2-chloropyridine (**29**)[30] were achieved according to the general procedure previously described for the 2-fluoro isomer **2**. Reaction of acetaldehyde at –75 °C, standard workup, and vacuum distillation yielded 70% of **30**: bp 120 °C (3 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.70 (d, 3 H, CH_3), 3.45 (s, 1 H, OH), 5.55 (q, 1 H, CH), 7.50 (d, 1 H, 5-H), 8.10 (d, 1 H, 6-H); IR (KBr) 3390, 2975, 1640, 1585, 1550, 1455, 1420 cm^{-1}. Anal. Calcd for $C_7H_7BrClNO$ (236.5): C, 35.55; H, 2.98; N, 5.92. Found: C, 35.7; H, 3.01; N, 5.89.

1-(4-Bromo-2-methoxy-3-pyridyl)ethanol (28). A mixture of fluoro alcohol **27** (2.75 g, 0.025 mol) and sodium methylate (0.62 g, 0.027 mol) in methanol (60 mL) was boiled for 4 h before addition of water (100 mL) and evaporation of methanol under vacuum. Extraction with chloroform, drying over $MgSO_4$, and removal of the solvent afforded a crude oil, which was purified by distillation under vacuum to yield 95% of **28**: bp 135 °C (5 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.55 (d, 3 H, CH_3), 3.70 (s, 1 H, OH),

(29) Gribble, G. W.; Saulnier, M. G. *Tetrahedron Lett.* **1980**, *21*, 4137.
(30) Delarge, J. *Acta Pol. Pharm.* **1977**, *34*, 245.

4.05 (s, 3 H, OCH_3), 5.30 (q, 1 H, CH), 7.10 (d, 1 H, 5-H), 7.85 (d, 1 H, 6-H); IR (neat) 3400, 2950, 1560, 1460, 1380 cm^{-1}. Anal. Calcd for $C_8H_{10}BrNO_2$ (232.7): C, 41.40; H, 4.34; N, 6.04. Found: C, 41.0, H, 4.38; N, 6.10.

3-[1-(4-Bromo-2-oxo-1,2-dihydro-3-pyridyl)ethyl]indole (31). Secondary alcohol **27** (5 g, 0.05 mol) was treated with indole (5.85 g, 0.05 mol) in glacial acetic acid (100 mL) in the presence of *p*-toluenesulfonic acid (0.5 g). The reaction mixture was boiled for 4 h before cooling and slow hydrolysis on a mixture of ice (150 g) and concentrated aqueous ammonia (250 mL). The resulting pale yellow precipitate was filtered off, washed with water, dried over vacuum, and washed with chloroform to yield 85% of **31**: mp >260 °C; ^1H NMR (DMSO) δ 1.60 (d, 3 H, CH_3), 4.70 (q, 1 H, CH), 6.30 (d, 1 H, 5-H), 6.6–7.45 (m, 6 H, indole + pyridine 6-H); IR (KBr) 3250, 2960, 1630, 1605, 1545, 1440 cm^{-1}. Anal. Calcd for $C_{15}H_{13}BrFN_2O$ (317.2): C, 56.80; H, 4.13; N, 8.83. Found: C, 57.2; H, 4.56; N, 8.90.

The same result was obtained when the previous reaction was performed with 2-chloro or 2-methoxy derivative **30** or **28**.

1-(4-Bromo-2-fluoro-3-pyridyl)-1-chloroethane (33). Fluoro alcohol **27** (4.4 g, 0.02 mol) was treated with thionyl chloride (2.6 g, 0.022 mol) in chloroform (50 mL) at room temperature for 1.5 h. Chloroform and an excess of thionyl chloride were removed under vacuum and the resulting brown oil in a chloroform solution was washed with cold water, dried over $MgSO_4$, and concentrated under vacuum. Vacuum distillation of the crude product afforded **33** in 95% yield: bp 72 °C (2 mmHg); ^1H NMR ($CDCl_3$) δ 1.95 (d, 3 H, CH_3), 5.60 (q, 1 H, CH), 7.45 (d, 1 H, 5-H), 8.00 (d, 1 H, 6-H); IR (neat) 2960, 2930, 1585, 1550, 1450, 1410 cm^{-1}; MS (30 eV) calcd for $C_7H_6BrClFN$ (238.5), *m/z* (rel intensity) 240 (80), 238 (62.5), 204 (100), 202 (87.5).

3-[1-(4-Bromo-2-fluoro-3-pyridyl)ethyl]indole (35). Indole (2.11 g, 0.018 mol) was added to a solution of methylmagnesium iodide (0.027 mol) in diethyl ether (50 mL) and the resulting mixture was refluxed for 1.5 h. A benzene (20 mL) solution of chloroethane **33** was slowly added while distilling off diethyl ether. The temperature of the reaction mixture thus varied from 40 to 50 °C at the end of the addition and to 80 °C at the end of the distillation. After a 2-h reflux at 80 °C and cooling on ice bath, the mixture was hydrolyzed with diluted hydrochloric acid (3 N, 50 mL). Extraction with chloroform, washing with aqueous 10% $NaHCO_3$, drying over $MgSO_4$, and solvent removal afforded a crude solid, which was purified by flash chromatography on silica (6/4 Et_2O/hexane) to yield 65% of **35**: mp 153 °C; ^1H NMR ($CDCl_3$) δ 1.75 (d, 3 H, CH_3), 5.00 (q, 1 H, CH), 6.9–7.55 (m, 5 H, Ar H), 7.80 (d, 1 H, pyridine 6-H), 8.20 (s, 1 H, indole 2-H); IR (KBr) 3460, 3240, 2970, 1580, 1540, 1400 cm^{-1}. Anal. Calcd for $C_{15}H_{12}BrFN_2$ (319.2): C, 56.44; H, 3.79; N, 8.77. Found: C, 56.3; H, 3.81; N, 8.75.

1-(2-Fluoro-3-pyridyl)-1-chloroethane (32). Compound **32** was prepared from secondary alcohol **14** according to the procedure previously described for compound **33** in 93% yield: bp 61 °C (5 mmHg); ^1H NMR ($CDCl_3$) δ 1.80 (d, 3 H, CH_3), 5.35 (q, 1 H, CH), 7.1–7.3 (m, 1 H, 5-H), 7.85–8.3 (m, 2 H, 4-H + 6-H); IR (neat) 2980, 2910, 1610, 1570, 1450 cm^{-1}. Anal. Calcd for C_7H_7ClFN (159.6): C, 52.68; H, 4.42; N, 8.78. Found: C, 52.5; H, 4.35; N, 8.64.

3-[1-(2-Fluoro-3-pyridyl)ethyl]indole (34). Chloroethane **32** was condensed with 1-indolylmagnesium iodide according to the procedure described for the synthesis of **35**. Compound **34** was isolated in 61% yield: mp 122 °C; ^1H NMR ($CDCl_3$) δ 1.70 (d, 3 H, CH_3), 4.85 (q, 1 H, CH), 6.90 (dd, 1 H, indole 5-H, J_{4-5} = 7.9 Hz, J_{5-6} = 7.3 Hz), 7.05 (dd, 1 H, indole 6-H, J_{6-7} = 8.1 Hz), 7.15 (d, 1 H, indole 4-H), 7.30 (s, 1 H, indole 2-H), 7.35 (d, 1 H, indole 7-H), 7.70 (d, 1 H, pyridine 5-H), 7.95 (d, 1 H, pyridine 6-H), 10.00 (s, 1 H, NH); IR (KBr) 3220, 2980, 1610, 1580, 1460, 1430 cm^{-1}. Anal. Calcd for $C_{15}H_{13}FN_2$ (240.3): C, 74.98; H, 5.45; N, 11.66. Found: C, 74.9; H, 5.39; N, 11.6.

3-[1-(4-Bromo-2-fluoro-3-pyridyl)ethyl]-*N*-(phenylsulfonyl)indole (36). 3-[1-(4-Bromo-2-fluoro-3-pyridyl)ethyl]-indole (**35**) (3.2 g, 0.01 mol) and tetrabutylammonium hydrogen sulfate (0.34 g, 0.001 mol) were dissolved in methylene chloride (50 mL) before addition of 5 N aqueous sodium hydroxide (30 mL). Benzenesulfonyl chloride (2.65 g, 0.015 mol) was slowly introduced and the mixture was stirred at room temperaure for 20 min. The organic layer was washed with water (3 × 25 mL), dried over $MgSO_4$, and concentrated under vacuum. The crude solid was recrystallized from ethanol to yield 85% of **36**: mp 152 °C; ^1H NMR ($CDCl_3$) δ 1.75 (d, 3 H, CH_3), 4.85 (q, 1 H, CH), 7.15–8.2 (m, 12 H, Ar H); IR (KBr) 3400, 3280, 2970, 1585, 1550, 1450, 1405 cm^{-1}. Anal. Calcd for $C_{21}H_{16}BrFN_2O_2S$ (459.3): C, 54.91; H, 3.51; N, 6.09. Found: C, 54.7; H, 3.60; N, 6.17.

Bromine–Lithium Exchange Reaction on Bromopyridine 36. To a cold (−75 °C) of compound **36** (2.3 g, 0.005 mol) in THF (50 mL) was slowly added *tert*-butyllithium (0.01 mol), and the reaction mixture was stirred for 45 min at −75 °C before hydrolysis by a mixture of concentrated hydrochloric acid (5 mL) in THF (10 mL). Excess of water (100 mL) was added at room temperature before basification by K_2CO_3 (pH 10) and extraction by Et_2O (3 × 100 mL). Drying of the combined organic extracts ($MgSO_4$) and solvent removal under vacuum afforded a crude product, which was crystallized from ethanol to yield 81% of 3-[1-(2-fluoro-3-pyridyl)ethyl]-*N*-(phenylsulfonyl)indole (**37**): mp 128–129 °C; ^1H NMR ($CDCl_3$) δ 1.65 (d, 1 H, CH_3), 4.65 (q, 1 H, CH), 8.25–7.0 (m, 13 H, Ar H); IR (KBr) 3275, 2960, 1580, 1460, 1420 cm^{-1}. Anal. Calcd for $C_{21}H_{17}FN_2O_2S$ (380.4): C, 66.30; H, 4.50; N, 7.36. Found: C, 66.4; H, 4.59; N, 7.30.

Bromine–Lithium Exchange Reaction on Bromopyridine 36 and Reaction of Acetaldehyde. To a cold (−75 °C) solution of compound **36** (2.3 g, 0.005 mol) in THF (50 mL) was slowly added *tert*-butyllithium (0.01 mol), and the reaction mixture was stirred for 45 min at −75 °C before addition of acetaldehyde (0.24 g, 0.55 mol). Stirring was continued for 2 h at −75 °C and the reaction mixture was hydrolyzed by a mixture of concentrated hydrochloric acid (5 mL) in THF (10 mL). An excess of water (100 mL) was added at room temperaure before basification by K_2CO_3 (pH 10) and extraction by Et_2O (3 × 100 mL). Drying of the combined organic extracts ($MgSO_4$) and solvent removal under vacuum afforded a crude product, which was purified by flash chromatography on silica (6/4 Et_2O/hexane) to yield an impure fraction which mainly contains 3-[1-(2-fluoro-3-pyridyl)ethyl]-*N*-(phenylsulfonyl)indole (**37**) (70%). Compound **16** was identified by comparison (^1H NMR spectrum and TLC on silica) with an authentic sample prepared as previously described. Besides complex signals of aromatic and methyl protons and the CHMe quadruplet of compound **37** at 4.65 ppm, the ^1H NMR spectrum of the isolated product shows two other quadruplets centered at 3.75 and 5.35 with low intensities compared to those of **37**.

1-[2-Fluoro-4-[2-(trimethylsilyl)ethynyl]-3-pyridyl]ethanol (38). A mixture of 1-(4-bromo-2-fluoro-3-pyridyl)ethanol (**27**) (4.4 g, 0.02 mol), (trimethylsilyl)acetylene (2.36 g, 0.024 mol), cuprous iodide (0.24 g, 1.25 mmol), and tetrakis(triphenylphosphine)-palladium(0) (0.75 g, 0.65 mmol) in triethylamine (25 mL) was boiled for 3 h. Trimethylamine was removed under vacuum and a mixture of diethyl ether (50 mL) and water (20 mL) was added before filtration over Celite. The organic layer was separated, dried over $MgSO_4$, and concentrated under vacuum to afford crude **38**: ^1H NMR ($CDCl_3$) δ 0.30 (s, 9 H, $SiMe_3$), 1.70 (d, 3 H, CH_3), 5.30 (q, 1 H, CH), 7.05–7.4 (m, 1 H, 5-H), 8.05 (d, 1 H, 6-H).

1-(4-Ethynyl-2-fluoro-3-pyridyl)ethanol (39). Crude **38** was reacted for 20 min at room temperature in a mixture of 1 M NaOH in methanol (30 mL). Evaporation of the solvent, hydrolysis (30 mL), extraction with diethyl ether (3 × 30 mL), washing with water (3 × 10 mL), drying over $MgSO_4$, and removal of the solvent afforded a crude product, which was purified by flash chromatography on silica (1/9 Et_2O/hexane). Compound **39** was obtained as a heat-unstable oil in 85% yield: ^1H NMR ($CDCl_3$) δ 1.55 (d, 3 H, CH_3), 4.65 (m, 2 H, acetylenic H + OH), 5.70 (q, 1 H, CH), 7.30 (dd, 1 H, 5-H, J_{5-F} = 2 Hz), 8.05 (d, 1 H, 6-H); IR (neat) 3460, 3270, 2150, 1580, 1400 cm^{-1}. Anal. Calcd for C_9H_8FNO (165.2): C, 65.45; H, 4.88; N, 8.48. Found: C, 65.5; H, 4.95; N, 8.32.

3-[1-(4-Ethenyl-2-fluoro-3-pyridyl)ethyl]indole (40). A mixture of bromo derivative **35** (0.96 g, 3 mmol), tributylvinyltin (1.05 g, 3.3 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.07 g, 0.06 mmol) in toluene (20 mL) was refluxed until precipitation of black palladium. Filtration and evaporation to dryness afforded a crude solid, which was crystallized from diethyl ether/hexane (1/1) to yield 75% of **40**: mp >250 °C; ^1H NMR ($CDCl_3$) δ 1.70 (d, 3 H, CH_3), 4.75 (q, 1 H, CHMe), 5.60 (d, 1 H, vinyl β-H, $J_{\alpha-\beta}$ = 11.1 Hz), 6.00 (d, 1 H, vinyl β-H, $J_{\alpha-\beta}$ = 17.3 Hz), 6.80 (dd, 1 H, indole 5-H, J_{4-5} = 7.9 Hz, J_{5-6} = 7 Hz), 7.00

(d, 1 H, indole 6-H, J_{6-7} = 8.1 Hz), 7.10 (dd, 1 H, indole 4-H), 7.25 (s, 1 H, indole 2-H), 7.30 (d + dd, 2 H, indole 7-H + vinyl α-H), 7.45 (d, 1 H, pyridine 5-H), 8.00 (d, 1 H, pyridine 6-H), 10.95 (s, 1 H, NH); IR (KBr) 3400, 3200, 2980, 2930, 2880, 1610, 1545, 1460, 1410 cm^{-1}; MS (30 eV) calcd for $C_{17}H_{15}FN_2$ (266.32), m/z (rel intensity) 267 (14.6), 266 (M^+, 64.1), 265 (11.0), 252 (19.3), 251 (100), 249 (15.1), 236 (18.8), 144 (15.6), 117 (60.1).

3-[1-[4-(1-Ethoxyethenyl)-2-fluoro-3-pyridyl]ethyl]indole (41). A mixture of (1-ethoxyvinyl)tributyltin (0.95 g, 3 mmol), bromo derivative **35** (1.2 g, 3.3 mmol), and tetrakis(triphenylphospine)palladium(0) (0.07 g, 0.06 mmol) in toluene (20 mL) was refluxed until precipitation of black palladium. Filtration and evaporation to dryness afforded a crude solid, which was crystallized from diethyl ether/hexane (1.1) to yield 95% of **41**: mp >250 °C; ^1H NMR ($CDCl_3$) δ 1.40 (t, 3 H, ethyl CH_3), 1.70 (d, 3 H, CH_3), 3.97 (q, 2 H, CH_2), 4.45 (d, 1 H, vinyl β-H, $J_{\beta-\beta}$ = 2.5 Hz), 4.55 (q, 1 H, CHMe, J = 7 Hz, 4.65 (d, 1 H, vinyl β-H), 6.80 (dd, 1 H, indole 5-H, J_{4-5} = 7.9 Hz, J_{5-6} = 7.3 Hz), 7.00 (dd, 1 H, indole 6-H), 7.10 (d, 1 H, indole 4-H), 7.25 (s + d, 2 H, indole 2-H + pyridine 5-H), 7.30 (d, 1 H, indole 7-H, J_{6-7} = 8 Hz), 8.05 (d, 1 H, pyridine 6-H), 10.65 (s, 1 H, NH); IR (KBr) 3230, 3100, 3050, 3040, 2970, 2930, 1630, 1600, 1550, 1460, 1435, 1410 cm^{-1}; MS (30 eV) calcd for $C_{19}H_{19}FN_2O$ (310.38), m/z (rel intensity) 310 (58.4), 281 (69.8), 264 (100), 249 (56.9), 239 (22.5).

5,11-Dimethyl-1-fluoro-6*H*-pyrido[4,3-*b*]carbazole (42). Ethoxyvinyl derivative **41** (0.5 g, 1.6 mmol) was dissolved in a 1/1 mixture of acetic acid and acetic anhydride (20 mL). A 1/1 solution of aqueous concentrated hydrochloric acid in THF was slowly added under stirring until formation of a white precipitate. The resulting suspension was further stirred at room temperature for 30 min before addition of water in a sufficient amount to dissolve the solid. Neutralization by sodium carbonate, extraction by diethyl ether, drying of the organic extracts over $MgSO_4$, evaporation to dryness, and sublimation (200 °C/1 mmHg) afforded **42** in 54% yield: mp >250 °C; ^1H NMR (DMSO-d_6) δ 2.80 (s, 3 H, Me_5), 3.30 (d, 3 H, Me_{11}, J_{H-F} = 4 Hz), 7.30 (dd, 1 H, 9-H), 7.55 (dd, 1 H, 8-H, J_{7-8} = 8.1 Hz), J_{8-9} = 7.1 Hz), 7.60 (d, 1 H, 7-H), 7.85 (dd, 1 H, 4-H, J_{3-4} = 6.05 Hz, J_{4-F} = 1.3 Hz), 7.95 (dd, 1 H, 3-H, J_{3-F} = 2.1 Hz), 8.40 (d, 1 H, 10-H), 11.70 (s, 1 H, NH); IR (KBr) 3430, 3240, 3180, 3100, 1605, 1470, 1405 cm^{-1}; MS (30 eV) calcd for $C_{17}H_{13}FN_2$ (264.30), m/z (rel intensity) 265 (19.8), 264 (M^+, 100), 263 (29.9), 249 (23.5). Anal. Calcd for $C_{17}H_{13}FN_2$ (264.30): C, 77.57; H, 4.94; N, 10.65. Found: C, 77.6; H, 4.81; N, 10.4.

Registry No. **1**, 372-48-5; **2**, 36178-05-9; **3**, 128071-98-7; **4**, 137718-84-4; **5**, 137718-85-5; **6**, 111887-72-0; **7**, 137718-86-6; **8**, 137718-87-7; **9**, 137718-88-8; **10**, 137718-89-9; **11**, 137718-90-2; **12**, 137718-91-3; **13**, 137718-92-4; **14**, 137718-93-5; **15**, 137718-94-6; **16**, 137718-95-7; **17**, 79574-70-2; **18**, 137718-96-8; **19**, 137718-97-9; **20**, 137718-98-0; **21**, 137718-99-1; **22**, 137742-03-1; **23**, 137719-00-7; **24**, 40247-45-8; **25**, 137719-01-8; **26**, 137719-02-9; **27**, 137719-03-0; **27'**, 137719-04-1; **28**, 137719-05-2; **29**, 52200-48-3; **30**, 137719-06-3; **31**, 137719-07-4; **32**, 137719-08-5; **33**, 137719-09-6; **34**, 137719-10-9; **35**, 137719-11-0; **36**, 137719-12-1; **37**, 137719-13-2; **38**, 137741-91-4; **39**, 137719-14-3; **40**, 137719-15-4; **41**, 137719-16-5; **42**, 137719-17-6; HCO_2Et, 109-94-4; PhCHO, 100-52-7; MeCHO, 75-07-0; TMSC≡CH, 1066-54-2; CH_2=CHSnBu_3, 7486-35-3; CH_2=C(OEt)SnBu_3, 97674-02-7; *N*-(phenylsulfonyl)-3-indolecarbaldehyde, 80360-20-9; indole, 127-72-0.

Radical Cyclization Routes to Bridged Pyranosides as Precursors of Densely Functionalized Cycloalkanes[1]

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Glycals derived from hexopyranoses permit the incorporation of iodine at C-2 as well as elaboration of an olefinic residue via the C-5-hydroxymethyl group. Radical cyclization of these functionalities leads to bicyclic systems whose bridge sizes depend on the lengths of the olefinic appendages. Hydrolysis of the anomeric centers of the [2.2.1] structures leads spontaneously to cyclopentane derivatives. However, with [2.2.2] structures, the hemiacetal intermediates are stable in bicyclic forms but are opened readily upon mcerpatolysis with propane dithiol to give cyclohexane derivatives.

Introduction

In our continuing interest in the development of strategies for carbohydrate → carbocycle transformations,[4] radical cyclization methods have proved valuable as demonstrated by recent syntheses of phyllantocin,[5] pipitzol,[6] and silphiperfolene.[7] In all of these cases the strategy can be symbolized as shown in Scheme Ia, where functionalized branches were installed on a sugar precursor from which the key intermediate I could be generated. Cyclization then led to an annulated sugar, symbolized by II, which could be reduced, or react further in a serial episode.

Notably, the radical center in I is pendant to, rather than directly on, the sugar ring. However, the seminal work of Barton and McCombie on generating carbon-centered radicals on the pyranose ring,[8] coupled with the elegant studies of Giese and co-workers on conformational aspects of pyranosyl radicals,[9] have prompted us to investigate these systems further. For example, the powerful influence

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(4) Fraser-Reid, B., Tsang, R. In *Strategies and Tactics in Organic Synthesis*; Lindberg, T., Ed.; Academic Press: New York, 1989; Vol. 2, pp 123-162.

(5) Bik-Wah, A., Contelles, J. L. M.; Fraser-Reid, B. *J. Chem. Soc., Chem. Comm.* **1989**, 1160.

(6) Pak, H.; Canalda, I. I.; Fraser-Reid, B. *J. Org. Chem.* **1990**, *55*, 3009.

(7) Dickson, J. K., Jr.; Fraser-Reid, B. *J. Chem. Soc., Chem. Comm.* **1990**, 1440.

(8) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

(9) (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon Press: Oxford, 1986. (b) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1989**, 969.

0022-3263/92/1957-0573$03.00/0