Synthesis of 4,5-Disubstituted Benzo[*c*][2,7]naphthyridines as Precursors of Pyrido[2,3,4-*kl*]acridones and Related Natural Products

F. Guillier, F. Nivoliers, A. Godard*, F. Marsais and G. Quéguiner

Laboratoire de Chimie Organique Fine et Hétérocyclique, Laboratoire de l'IRCOF associé au CNRS (UPRES-A 6014), INSA de Rouen, BP08 76131 Mont-Saint-Aignan Cedex, France

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A methodical investigation on functionalization by carbonylated groups in position 4 and 5 of the benzo[*c*][2,7]naphthyridine skeleton has been undertaken. In particular the study has shown the complex influence of these two sites on each other. A careful choice of both substituents in 4 and 5 permitted the synthesis of an interesting pyrido[2,3,4-*kl*]acridone tetracyclic structure through an intramolecular Mukayama aldolisation reaction. The structure is supposed to be a potential precursor to various marine alkaloids of the pyridoacridine family.

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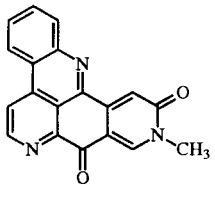
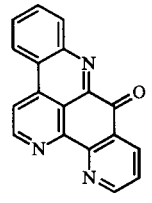
Since amphimedine **1** has been found, in 1983 [1], a wide range of polycyclic alkaloids containing a common benzo[*c*][2,7]naphthyridine unit were isolated from marine organisms [2]. Ascididemine **2**, cystodytins **3**, and meridine **4** are a few examples of this family.

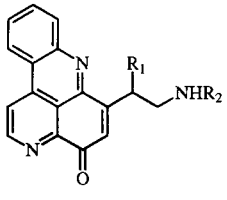
Scheme 1



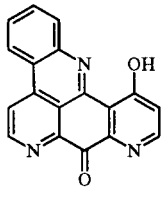
1 (amphimedine)



2 (ascididemine)



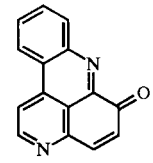
3 (cystodytins)



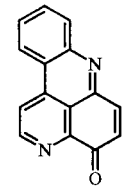
4 (meridine)

Most of these natural products exhibit interesting biological properties (Ca-releasing, antiviral, antimicrobial activities, cytotoxicity to L_{1210} leukemia cells, *etc.*) and several interesting but specific synthetic approaches to these alkaloids have been reported [2]. So it was of interest to explore whether an unified strategy could be applied for the synthesis of a large number of 6*H*-pyrido-[2,3,4-*kl*]acridine-6-ones and 4*H*-pyrido[2,3,4-*kl*]acridin-4-ones alkaloids of type **A** or **B** respectively.

Scheme 2



A

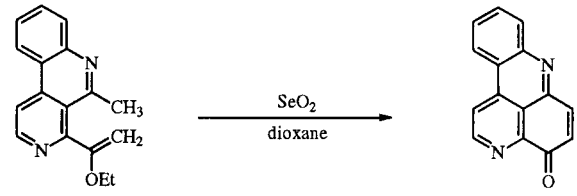


B

Using the first efficient preparation of organometallics of π-deficient heterocycles [3], our laboratory developed many synthetic methodologies based on connection of this reaction with others. It was shown that metalation, in association with transition metal catalyzed coupling reactions, provided a fruitful strategie for the synthesis of natural products [4].

After initial formal synthesis of amphimedine **1** [5], we were more recently interested with the preparation of cystoditins **3**. In this series we published the first synthesis of the unsubstituted 4*H*-pyrido[2,3,4-*kl*]pyridine-4-one **6** [6]. Unfortunately, a low yield was obtained in the last step which uses the cyclization of the 4-(1-ethoxyvinyl)-5-methylbenzo[*c*][2,7]naphthyridine **5** under oxidation conditions. In order to improve the overall yield, we undertook a more systematic study.

Scheme 3

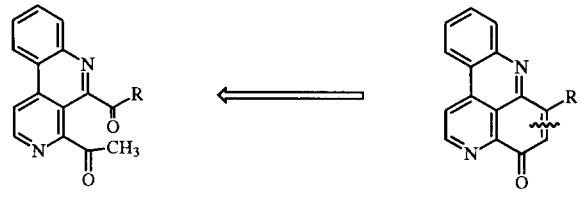


5

6 (11%)

The approach discussed herein was based on the preparation of 4,5-dicarbonylated benzo[*c*][2,7]naphthyridine derivatives **7**, which can afford the expected tetracyclic products upon condensation.

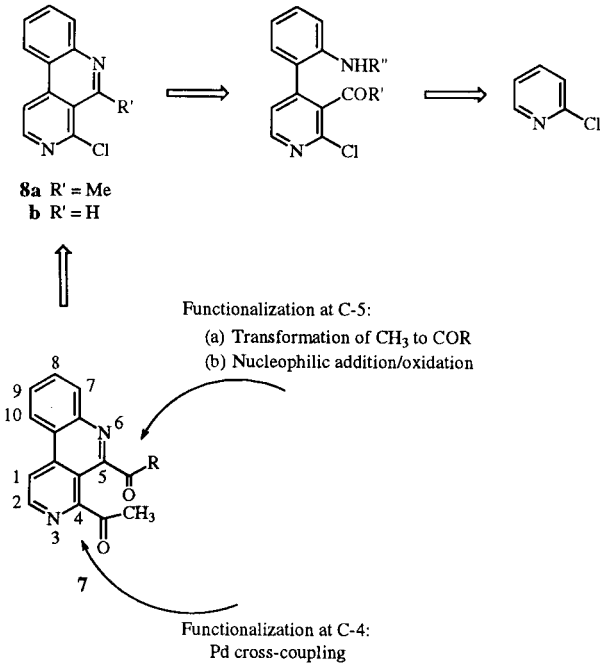
Scheme 4



7

A retrosynthetic analysis, involving the use of 4-chlorobenzo[*c*][2,7]naphthyridines **8** [6] as precursors, required the connection of carbonylated groups to both 4 and 5 positions. The pathway was chosen to take advantage of the straightforward synthesis of the benzo[*c*][2,7]naphthyridine skeleton, largely studied by our group [7], and requiring in some cases no more than 2 steps from a monosubstituted pyridine [5a].

Scheme 5



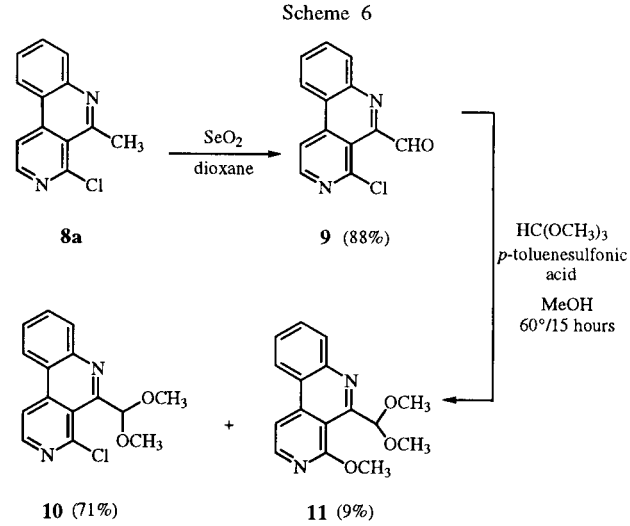
Functionalization at C-4 from a chlorine atom was provided by Stille coupling with tributyl(1-ethoxyvinyl)tin, leading to a protected form of the desired acetyl moiety. Functionalization at C-5 has been investigated following two different strategies: (a) by oxidation of 5-methylbenzonaphthyridine **8a** (R' = Me) into aldehyde or (b) by nuclophilic addition of a carbonylated anion equivalent onto a 5-unsubstituted benzo[*c*][2,7]naphthyridine **8b** (R' = H), then reoxidation into the imine [8].

The stepwise connection of carbonylated groups to peri-position (sites 4 and 5) of benzo[*c*][2,7]naphthyridines and subsequent reactivity and stability is discussed herein. Finally a new approach of 6-alkoxy-4*H*-pyrido-[2,3,4-*kl*]acridin-4-ones, as precursors to alkaloids of the series, is given.

Synthesis of 5-Formyl or 5-Acetyl-4-chlorobenzo[*c*][2,7]-benzonaphthyridines and Related Compounds.

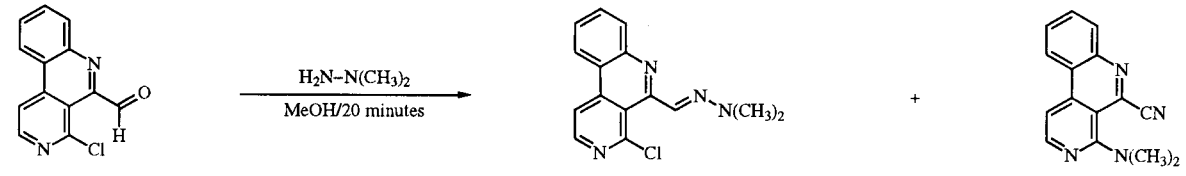
These compounds have been prepared either starting from 4-chloro-5-methylbenzo[*c*][2,7]naphthyridine **8a** [6] or by nucleophilic addition on the imine bond of 4-chlorobenzo[*c*][2,7]naphthyridine **8b** [8]. 4-Chloro-5-benzo[*c*][2,7]-naphthyridinecarbaldehyde **9** was obtained in good yield (88%) by selenium dioxide oxidation of the corresponding 5-methyl derivative **8a**. The protection of the aldehyde group was planed in order to circumvent the supposed thermal low stability of this functionality. Different methods have been attempted but unexpected results were observed, despite the simplicity of such reaction. Unidentified products or decarbonylated **8b** were recovered when degradation did not take place. Satisfactory results were eventually obtained when methyl orthoformate in methanol was used. 4-Chloro-5-benzo[*c*][2,7]naphthyridine-carbaldehyde dimethylacetal **10** was formed in 71% yield along with the product **11** of nucleophilic substitution of the chlorine. The formation of this side product **11** was minimized (9%) by reducing both reaction time and temperature.

Scheme 6



The formation of another side product, characterized as **13** was observed, beside the expected product **12**, in an attempt to improve the formation of a protected aldehyde as the hydrazone derivative.

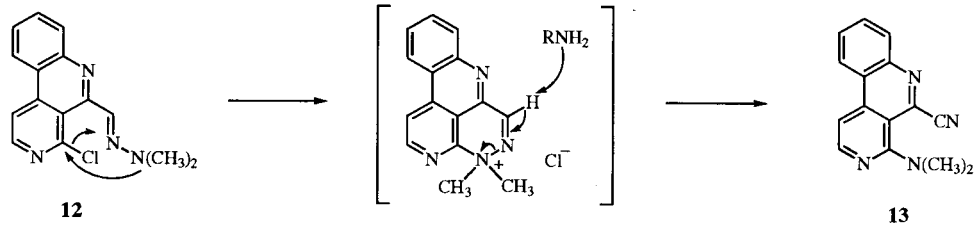
Scheme 7



9 **12** (51%) **13** (39%)

Synthesis of compound **13** can be explained by a nucleophilic substitution of the chlorine atom in the 4-position by the dimethylamino group that is very close. A β-elimination occurring on the intermediate ammonium salt, afforded **13**. A similar mechanism has been suggested by Smith and Walker during the preparation of aromatic nitriles from hydrazones in basic medium [9].

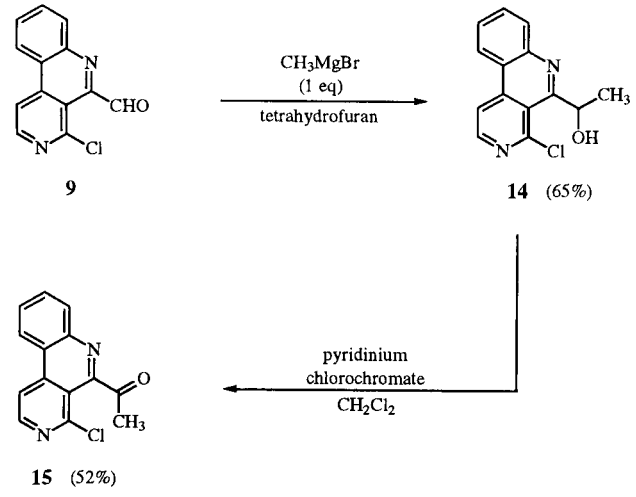
Scheme 8



12 **13**

5-Acetyl-4-chlorobenzo[*c*][2,7]naphthyridine **15** was obtained from the aldehyde **9**, using a nucleophilic alkylation-oxidation sequence. One equivalent of methyl Grignard reagent provided the best conditions as a lower yield was obtained using the lithiated analogous reagent (38%).

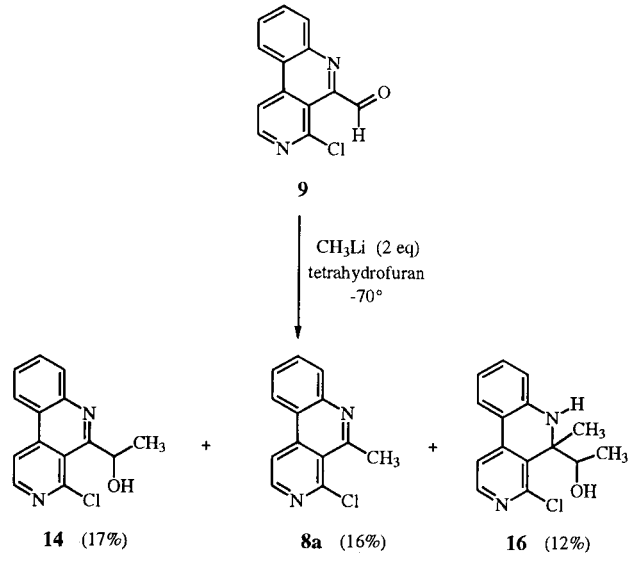
Scheme 9



9 **14** (65%) **15** (52%)

Increasing the number of equivalents of methyllithium led only to a mixture of three compounds. If structures **8a** and **14** could be attributed without ambiguity, structure of compound **16** was attributed by spectroscopy analysis of a mixture. Formation of compound **16** could be explained by a nucleophilic attack of the imine bond, which appears to be facilitated on the lithiated alcoholate of **14** through a double chelation of the lithium cation with the nitrogen and oxygen atoms. No satisfactory explanations have been suggested for the formation of the reduced 4-chloro-5-methylbenzo[*c*][2,7]naphthyridine **8a**.

Scheme 10

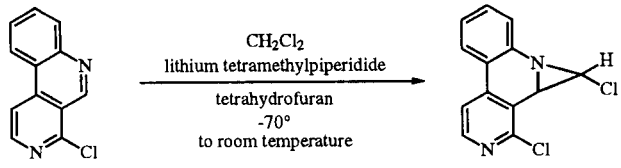


9 **14** (17%) **8a** (16%) **16** (12%)

The particular reactivity of the 5,6-imine bond towards organometallics allowed the synthesis of 5-substituted benzo[*c*][2,7]naphthyridines when further oxidation was possible (*i.e.* the starting imine is an aldimine) [8]. Dichloromethyllithium and 1-ethoxyvinyllithium were used as reagents in order to functionalize the tricyclic structure with an aldehyde or an acetyl group precursor respectively.

Dichloromethyllithium, formed by metallation of dichloromethane with lithium tetramethylpiperidide at -70°, as described by Tagushi [10], was reacted with **8b** at room temperature and afforded the dichlorocarbene adduct instead of the addition product. The aziridine **17** was isolated in 57% yield.

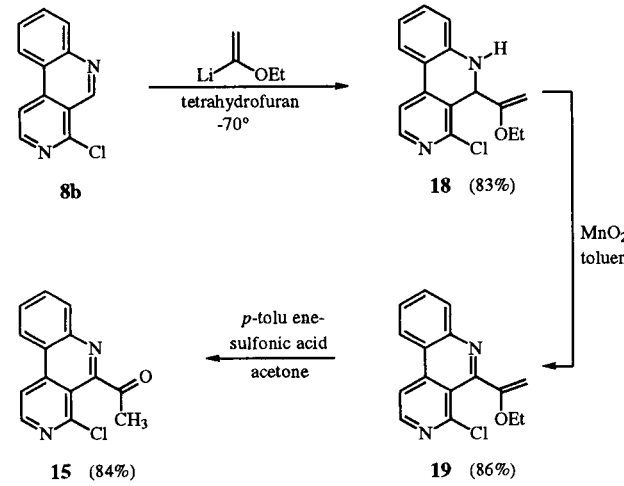
Scheme 11



8b **17** (57%)

More successful was the preparation of the 5-acetyl-4-chlorobenzo[*c*][2,7]naphthyridine **15** which was obtained in 60% overall yield from the aldimine **8b**. Addition of a large excess of 1-ethoxyvinyllithium (4 equivalents), followed by an oxidation step with manganese dioxide, then treatment with *p*-toluenesulfonic acid was required to generate the acetyl group.

Scheme 12

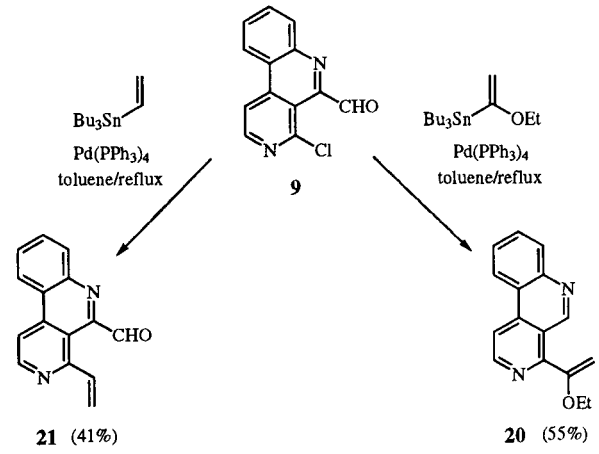


8b **18** (83%) **15** (84%) **19** (86%)

Functionalization of 5-Carbonylated-4-chlorobenzo[*c*][2,7]-naphthyridines by Cross-coupling Reactions at C-4.

Earlier work outlined the reactivity of 4-chlorobenzo-[*c*][2,7]naphthyridine type structures towards either Suzuki or Stille cross-coupling reactions [6]. Having in hands the required 4-chlorobenzo[*c*][2,7]naphthyridines **9**, **10**, **12**, **15** and **19** bearing a carbonyl group or its protected form in C-5, the cross-coupling reactions with tributyl(1-ethoxyvinyl)tin were carried out. As the reaction performed with **9** gave compound **20**, we noticed with disappointment that a decarbonylation of the formyl group occurred beside the coupling reaction. This side reaction is thought to be catalyzed by palladium as this versatile metal plays an important role in various carbonylation and decarbonylation processes [11,12]. However the side reaction was not observed when the tin derivative or the catalyst were omitted. These control experiments suggest that a concomitant action of the ethoxyvinyl group and the palladium catalyst are responsible for the decarbonylation. This is pointed out by the fact that decarbonylation did not occur when coupling was performed with tributylvinyltin. Using these conditions, the aldehyde **21**, bearing a less hindered vinyl group in C-5, was isolated with 41% yield.

Scheme 13

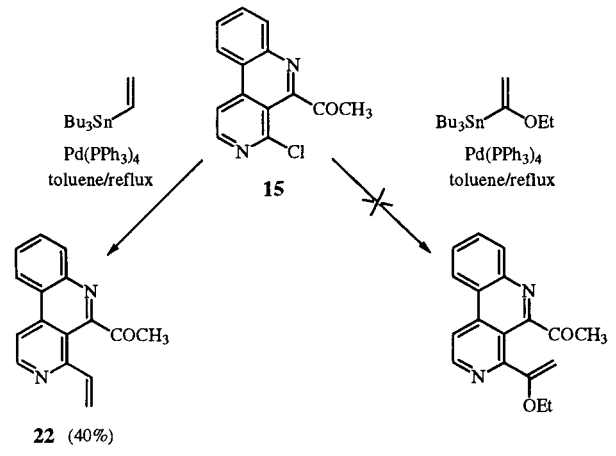


21 (41%) **20** (55%)

Only starting materials with residual tar were partially recovered when the cross-coupling of 5-acetyl-4-chlorobenzo[*c*][2,7]naphthyridine **15** with tributyl(1-ethoxyvinyl)tin was carried out in refluxing toluene for 18 hours. The same reaction carried out with tributylvinyltin gave the expected vinyl derivative **22** in 40% yield.

The different attempts emphasized that groups at C-4 and C-5 are closely related and steric hindrance in these peri-positions makes the synthesis of compounds, bearing simultaneously an ethoxyvinyl group in 4-position and a carbonyl group in 5-position, difficult.

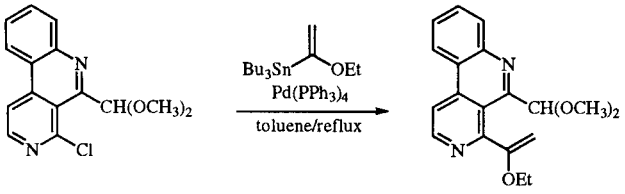
Scheme 14



22 (40%)

Due to the problems encountered with carbonyl groups, the cross-coupling reaction was undertaken with protected derivatives, expecting the energy of rotation around the carbonyl-C4 bond to be reduced. These experiments were carried out with acetal **10**, hydrazone **12** and alcohol **14** but only **10** gave the desired product **23** in 65% yield. Reagents or unidentified tars were recovered in the other cases.

Scheme 15



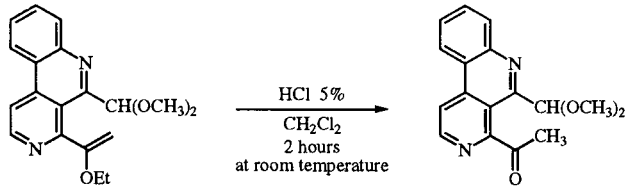
10 **23** (65%)

Stille cross-coupling reaction with 4-chlorobenzo[*c*][2,7]-naphthyridines depends to a large extent on the group at the 5-position. Steric hindrance or complex formation with the Pd catalyst may prevent the reaction. However, formation of the 4-(1-ethoxyvinyl)-5-benzo[*c*][2,7]naphthyridincarbaldehyde dimethylacetal **23,** bearing two protected carbonyl groups at C-4 and C-5, was promising for the synthesis of our target molecules.

Synthesis of 6-Alkoxy-4*H*-pyrido[2,3,4-*kl*]acridin-4-ones.

Hydrolysis of the protected functions of **23** was investigated in order to synthesize the fourth ring. The deprotection of enolethers and acetals were carried out in acidic medium. In most of the reactions either recovered starting material or unidentified products were obtained. Only a low yield (33%) of 4-acetyl-5-benzo[*c*][2,7]naphthyridine-carbaldehyde dimethylacetal **24** was obtained by hydrolysis with dilute hydrochloric acid in dichloromethane. All attempts for subsequent hydrolysis of the acetal group failed. Once again, a model study with the effective hydrolysis of the precursor acetal **10** to aldehyde **9** in standard workup conditions demonstrated the significant role of the group in C-4 on the reactivity of the C-5 function.

Scheme 16

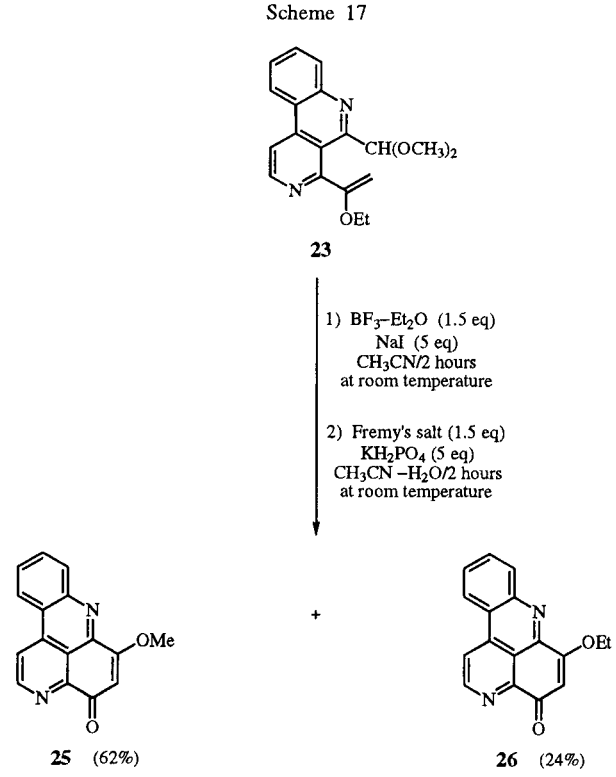


23 **24** (33%)

Because of the failure encountered in the deprotections of the enolether and acetal groups, we chose a more direct route where the cyclization occurred by intramolecular nucleophilic substitution.

As shown by Mukaiyama [13], nucleophilic substitutions by acetyl groups under enolether form are effective if the leaving group is activated by Lewis acids (*e.g.*, titanium tetrachloride). A mixture of the two pyridoacridones **25** and **26** was obtained in 62% and 24% respectively when **23** was treated with boron trifluoride etherate, followed by a rearomatization step with Fremy's salt.

Scheme 17



25 (62%) **26** (24%)

Such compounds are of great interest as precursors to alkaloids of the pyridoacridone series. In particular, it could be anticipated that substitution by alkylation of alkoxy groups (this part of the molecule is considered as an ester vinylogous and supposed to have a similar reactivity) may afford cystodytin derivatives **3** in a straightforward manner. In another way, hetero Diels-Alder reactions may conduct to meridine **4** or other pentacyclic compounds.

In conclusion, we have demonstrated that, if metalation in connection with cross-coupling is a methodology of choice for the synthesis of benzo[*c*][2,7]naphthyridines, further functionalization was difficult, particularly in the 4 and 5 peri-positions. Substituents in these positions 4 and 5 influence each other reactivity. We never succeeded in isolating the tricyclic structure bearing two carbonyl groups in these two positions. Nevertheless, preparation of 4*H*-pyrido[2,3,4-*kl*]acridin-4-ones through an intramolecular Mukayama aldolisation reaction was successful and such compounds constitute potential precursors to various marine alkaloids of the cystodytins **3** family.

EXPERIMENTAL

General Data.

Melting points were determined on Kofler apparatus and are uncorrected. Infrared (ir) spectra were obtained on a Perkin-Elmer FTIR 1650 spectrometer, and main absorption frequencies are given in cm^{-1}. The ^1H nmr spectra were recorded on a 200 MHz AC200F Brücker spectrometer. Chemical shifts (δ) are reported in ppm downfield from an internal standard, tetramethylsilane in deuteriochloroform, or hexamethyldisiloxane in dimethyl-d_6 sulfoxide. Elemental analyses were performed on a Carlo-Erba CHN apparatus. Mass spectra were recorded on a JEOL JMS-AX500 spectrometer.

Tetrahydrofuran was distilled from benzophenone/sodium. The water content was estimated lower than 45 ppm by the modified Karl-Fischer method [14]. The light sensitive tetrakis(triphenylphosphine)palladium(0) catalyst was prepared by hydrazine reduction of palladium chloride, as described by Coulsen [15], and stored under a dehydrated and deoxygenated atmosphere at -10°. Tributylvinyltin was prepared, as described by Seyferth and Stone, by action of vinylmagnesium bromide on tributyltin chloride [16]. Tributyl(1-ethoxyvinyl)tin was prepared by metallation as described by Soderquist [17].

4-Chloro-5-benzo[*c*][2,7]naphthyridinecarbaldehyde (**9**).

A solution of 4-chloro-5-methylbenzo[*c*][2,7]naphthyridine (**8a**) [6] (192 mg, 0.84 mmole) and selenium dioxide (98 mg, 0.88 mmole) was refluxed in distilled dioxane (30 ml) under a nitrogen atmosphere for 8 hours. The solvent was evaporated and the crude product was purified by flash chromatography (diethyl ether/cyclohexane 70:30, R_f = 0.5) to give **9** (179 mg, 88%) as white crystals with mp 162°; ir (potassium bromide): ν 2924, 1692, 1590 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.85 (m, 1H, 9-H), 7.92 (m, 1H, 8-H), 8.26 (d, 1H, 7-H, J_{7-8} = 8 Hz), 8.36 (d, 1H, 1-H, J_{1-2} = 5.6 Hz), 8.50 (d, 1H, 10-H, J_{9-10} = 8 Hz), 8.69 (d, 1H, 2-H, J_{1-2} = 5.6 Hz), 10.79 (s, 1H, CHO).

Anal. Calcd. for $C_{13}H_7ClN_2O$: C, 64.35; H, 2.91; N, 11.54. Found: C, 64.11; H, 2.51; N, 11.52.

4-Chloro-5-benzo[*c*][2,7]naphthyridinecarbaldehyde Dimethylacetal (**10**) and 4-Methoxy-5-benzo[*c*][2,7]naphthyridinecarbaldehyde Dimethylacetal (**11**).

Trimethylorthoformate (55 µl, 0.503 mmole) and *p*-toluenesulfonic acid (9 mg, 0.05 mmole) were added to a solution of 4-chloro-5-benzo[*c*][2,7]naphthyridinecarbaldehyde (**9**) (120 mg, 0.495 mmole) in hot methanol (30 ml). After heating at 60° for 15 hours, the solution was cooled at room temperature. Water (25 ml) was added and the aqueous layer was separated, neutralized and extracted with dichloromethane. The combined organic layers were dried (magnesium sulfate) and evaporated *in vacuo*. Purification by flash chromatography (petroleum ether/diethyl ether, 20:80) afforded **10** (102 mg, 71%, R_f = 0.2) as white crystals with mp 91°; ir (potassium bromide): ν 2925, 1589, 1554 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.61 (s, 6H, OCH_3), 6.70 (s, 1H, CHacetal), 7.70 (dd, 1H, 9-H, J_{8-9} = J_{9-10} = 7.5 Hz), 7.88 (dd, 1H, 8-H, J_{7-8} = J_{8-9} = 7.5 Hz), 8.30-8.35 (m, 2H, 7-H and 1-H), 8.45 (d, 1H, 10-H, J_{9-10} = 7.5 Hz), 8.60 (d, 1H, 2-H, J_{1-2} = 5.5 Hz).

Anal. Calcd. for $C_{15}H_{13}ClN_2O_2$: C, 62.40; H, 4.54; N, 9.70. Found: C, 62.33; H, 4.55; N, 9.76.

The same purification by flash chromatography (petroleum ether/diethyl ether, 20:80) afforded **11** (13 mg, 9%, R_f = 0.3) as yellow crystals with mp 112-115°; ir (potassium bromide): ν 2922, 1600, 1568, 1459 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.65 (s, 6H, OCH_3), 4.27 (s, 3H, OCH_3), 6.55 (s, 1H, CHacetal), 7.70 (dd, 1H, 9-H, J_{8-9} = J_{9-10} = 7.5 Hz), 7.85 (dd, 1H, 8-H, J_{7-8} = J_{8-9} = 7.5 Hz), 8.02 (d, 1H, 1-H, J_{1-2} = 5.5 Hz), 8.35 (d, 1H, 7-H, J_{7-8} = 7.5 Hz), 8.45 (d, 1H, 2-H, J_{1-2} = 5.5 Hz), 8.50 (d, 1H, 10-H, J_{9-10} = 7.5 Hz); ms: 285 ($(M+H)^+$, 100).

4-Chloro-5-benzo[*c*][2,7]naphthyridinecarbaldehyde *N*,*N*-Dimethylhydrazone (**12**) and 5-Cyano-4-dimethylaminobenzo-[*c*][2,7]naphthyridine (**13**).

N,*N*-Dimethylhydrazine (50 µl, 0.658 mmole) was added to a solution of 4-chloro-5-benzo[*c*][2,7]naphthyridinecarbaldehyde (**9**) (142 mg, 0.585 mmole) in hot methanol (40 ml). The mixture was stirred 10 minutes at room temperature before a second addition of *N*,*N*-dimethylhydrazine was performed (50 µl, 0.658 mmole). The stirring was pursued 10 minutes and solvent were finally removal under reduced pressure. The crude resulting product was purified by flash chromatography (diethyl ether) affording **12** (84 mg, 51%, R_f = 0.5) as yellow crystals with mp 120°; ir (potassium bromide): ν 2950, 1586, 1526, 1458 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.27 (s, 6H, $N(CH_3)_2$), 7.64 (ddd, 1H, 9-H, J_{7-9} = 1.5 Hz, J_{8-9} = J_{9-10} = 7.5 Hz), 7.84 (ddd, 1H, 8-H, J_{8-10} = 1.5 Hz, J_{7-8} = J_{8-9} = 7.5 Hz), 8.22 (s, 1H), 8.25 (dd, 1H, 7-H, J_{7-9} = 1.5 Hz, J_{7-8} = 7.5 Hz), 8.33 (d, 1H, 1-H, J_{1-2} = 5.8 Hz), 8.43 (dd, 1H, 10-H, J_{8-10} = 1.5 Hz, J_{9-10} = 7.5 Hz), 8.62 (d, 1H, 2-H, J_{1-2} = 5.7 Hz); ms: 284 (M^+, 22), 214 (100).

The same purification by flash chromatography (diethyl ether) afforded **13** (57 mg, 39%, R_f = 0.9) as yellow crystals with mp 120°; ir (potassium bromide): ν 2950, 1582, 1539, 1486 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.22 (s, 6H, $N(CH_3)_2$), 7.75-7.95 (m, 3H, 9-H, 8-H and 1-H), 8.22 (d, 1H, 7-H, J_{7-8} = 7.5 Hz), 8.47 (d, 1H, 10-H, J_{9-10} = 7.5 Hz), 8.52 (d, 1H, 2-H, J_{1-2} = 5.5 Hz); ms: 248 (M^+, 100).

Anal. Calcd. for $C_{15}H_{12}N_4$: C, 72.56; H, 4.83; N, 22.57. Found: C, 72.43; H, 4.84; N, 22.25.

1-(4-Chloro-5-benzo[*c*][2,7]naphthyridinyl)ethanol (**14**).

A solution of 4-chloro-5-benzo[*c*][2,7]naphthyridinecarbaldehyde (**9**) (85 mg, 0.35 mmole) in dry tetrahydrofuran (15 ml) was placed under a dry argon atmosphere, cooled at 0° and treated with methylmagnesium bromide (3 *M* solution in diethyl ether, 0.13 ml, 0.39 mmole). The mixture was then refluxed for 1 hour, cooled at room temperature and hydrolyzed with cold water. The aqueous layer was separated, neutralized with 5% aqueous hydrochloric acid and extracted with dichloromethane. The combined organic layers were dried (magnesium sulfate) and evaporated *in vacuo*. The crude product was purified by flash chromatography (diethyl ether/petroleum ether 65:35) affording **14** (60 mg, 66%, R_f = 0.6) as yellow crystals with mp 173°; ir (potassium bromide): ν 3370, 2924, 1592, 1552 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.62 (d, 3H, CH_3, J = 6.2 Hz), 5.85 (s, 1H, OH), 6.35 (q, 1H, CH, J = 6.2 Hz), 7.78 (dd, 1H, 9-H, $J_{8-9} = J_{9-10}$ = 8 Hz), 7.92 (dd, 1H, 8-H, $J_{7-8} = J_{8-9}$ = 8 Hz), 8.20 (d, 1H, 7-H, J_{7-8} = 8 Hz), 8.41 (d, 1H, 1-H, J_{1-2} = 5 Hz), 8.55 (d, 1H, 10-H, J_{9-10} = 8 Hz), 8.68 (d, 1H, 2-H, J_{1-2} = 5 Hz).

Anal. Calcd. for $C_{14}H_{11}ClN_2O$: C, 64.98; H, 4.29; N, 10.82. Found: C, 65.00; H, 3.96; N, 10.50.

1-(4-Chloro-6-hydro-5-methyl-5-benzo[*c*][2,7]naphthyridinyl)-ethanol (**16**).

A solution of 4-chloro-5-benzo[*c*][2,7]naphthyridinecarbaldehyde (**9**) (200 mg, 0.825 mmole) in dry tetrahydrofuran (20 ml) was placed under a dry argon atmosphere, cooled at -70° and treated with methyllithium (1.24 *M* solution in diethyl ether, 1.32 ml, 1.65 mmoles). The mixture was stirred for 3 hours at -70°, hydrolyzed with an aqueous solution of tetrahydrofuran (10 ml, water/tetrahydrofuran 20/80, v/v), and warmed to room temperature. After addition of water (20 ml), the aqueous layer was separated, neutralized with 5% aqueous hydrochloric acid and extracted with dichloromethane. The combined organic layers were dried (magnesium sulfate) and evaporated *in vacuo*. The crude product was purified by flash chromatography (diethyl ether/petroleum ether 40:60) affording **8a** (31 mg, 16%, R_f = 0.4) and a mixture (63 mg, R_f = 0.5) of **14** (17%) and **16** (12%) in the molar ratio of 60/40. Structure of **16** was determinated by ^1H nmr analysis in deuteriochloroform: δ 1.18 (d, 3H, CH_3, J = 6.2 Hz), 1.74 (s, 3H, CH_3), 4.90 (s, 1H, OH), 5.02 (q, 1H, CH, J = 6.2 Hz), 6.56 (d, 1H, 7-H, J_{7-8} = 8 Hz), 6.68 (dd, 1H, 9-H, $J_{8-9} = J_{9-10}$ = 8 Hz), 7.13 (dd, 1H, 8-H, $J_{7-8} = J_{8-9}$ = 8 Hz), 7.50 (m, 2H, 10-H and 1-H, J_{1-2} = 5.2 Hz), 8.20 (d, 1H, 2-H, J_{1-2} = 5.2 Hz).

5-Acetyl-4-chlorobenzo[*c*][2,7]naphthyridine (**15**).

This compound was obtained by oxidation of alcohol **14**. Pyridinium chlorochromate (95 mg, 0.44 mmole) was added to a solution of 1-(4-chloro-5-benzo[*c*][2,7]naphthyridinyl)ethanol (**14**) (60 mg, 0.23 mmole) in dichloromethane (25 ml). The mixture was stirred for 15 hours at room temperature. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (diethyl ether/petroleum ether 50:50, R_f = 0.3) affording **15** (31 mg, 52%) as white crystals with mp 151°; ir (potassium bromide): ν 2928, 1702, 1590, 1545 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.94 (s, 3H, CH_3), 7.80 (dd, 1H, 9-H, $J_{8-9} = J_{9-10}$ = 8 Hz), 7.90 (dd, 1H, 8-H, $J_{7-8} = J_{8-9}$ = 8 Hz), 8.20 (d, 1H, 7-H, J_{7-8} = 8 Hz), 8.37 (d, 1H, 1-H, J_{1-2} = 5.7 Hz), 8.55 (d, 1H, 10-H, J_{9-10} = 8 Hz), 8.68 (d, 1H, 2-H, J_{1-2} = 5.7 Hz).

Anal. Calcd. for $C_{14}H_9ClN_2O$: C, 65.51; H, 3.53; N, 10.91. Found: C, 65.83; H, 3.57; N, 10.64.

This compound was also prepared by hydrolysis of enolether **19**. A solution of 4-chloro-5-(1-ethoxyvinyl)benzo[*c*][2,7]naphthyridine (**19**) (410 mg, 1.44 mmoles) in acetone (60 ml) was refluxed for 3 hours with water (40 µl) and *p*-toluenesulfonic acid (275 mg, 1.44 mmoles). Water (30 ml) and dichloromethane (30 ml) were added after cooling at room temperature. The aqueous layer was separated, neutralized then extracted with dichloromethane. The combined organic layers were dried (magnesium sulfate) and evaporated *in vacuo*. Flash chromatography (diethyl ether/petroleum ether 50:50, R_f = 0.3) gave the ketone **15** (311 mg, 84%). Physical data are in agreement with those previously given.

4,6-Dichloroaziridino[1,2][*a*]benzo[*c*][2,7]naphthyridine (**17**).

A solution of 2,2,6,6-tetramethylpiperidine (0.79 ml, 4.68 mmoles) in dry tetrahydrofuran (25 ml) was cooled at -70° under argon, and treated with *n*-butyllithium (2.5 *M* solution in hexane, 1.87 ml, 4.68 mmoles). The mixture was warmed to 0°, stirred for 15 minutes and cooled again to -70°. Anhydrous dichloromethane (0.3 ml, 4.68 mmoles) was added and the mixture stirred for 10 minutes before addition of a solution of 4-chlorobenzo[*c*][2,7]naphthyridine (**8b**) [8] (500 mg, 2.33 mmoles) in anhydrous tetrahydrofuran (15 ml). The mixture was allowed to reach 20°, stirred at this temperature for 6 hours, and hydrolyzed with an aqueous solution of tetrahydrofuran (10 ml, water/tetrahydrofuran 20:80, v/v). The aqueous layer was separated, neutralized and extracted with dichloromethane. The combined organic layers were dried (magnesium sulfate) and evaporated *in vacuo*. Purification by flash chromatography (diethyl ether/petroleum ether 50:50) gave residual starting material **8b** (52 mg, 10%, R_f = 0.35) and aziridine **17** (351 mg, 57%, R_f = 0.5) as white crystals with mp 133°; ir (potassium bromide): ν 2925, 1611, 1582, 1543 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.88 (d, 1H, J_{trans} = 3.8 Hz), 4.88 (d, 1H, J_{trans} = 3.8 Hz), 7.25-7.35 (m, 2H, 9-H and 8-H), 7.38 (d, 1H, 7-H, J_{7-8} = 8 Hz), 7.60 (d, 1H, 1-H, J_{1-2} = 5.3 Hz), 7.80 (d, 1H, 10-H, J_{9-10} = 8 Hz), 8.35 (d, 1H, 2-H, J_{1-2} = 5.3 Hz).

Anal. Calcd. for $C_{13}H_8Cl_2N_2$: C, 59.34; H, 3.06; N, 10.65. Found: C, 59.58; H, 3.32; N, 10.44.

4-Chloro-5-(1-ethoxyvinyl)-5,6-dihydrobenzo[*c*][2,7]naphthyridine (**18**).

A solution of ethyl vinyl ether (0.765 ml, 8 mmoles) in dry tetrahydrofuran (10 ml) was placed at -70° under an argon atmosphere and treated with *tert*-butyllithium (1.3 *M* solution in hexane, 3.1 ml, 4 mmoles). The mixture was stirred at -70° for 15 minutes then at 0° for 1.5 hours before adding a solution of 4-chlorobenzo[*c*][2,7]naphthyridine (**8b**) (214 mg, 1 mmole) in anhydrous tetrahydrofuran (10 ml) at this temperature. The mixture was allowed to reach room temperature, stirred for 1.5 hours and hydrolyzed with a saturated aqueous solution of ammonium chloride (10 ml). After addition of water (20 ml), the aqueous layer was separated and extracted with dichloromethane. The combined organic layers were dried (magnesium sulfate) and evaporated *in vacuo*. Purification by flash chromatography (diethyl ether/petroleum ether 40:60, R_f = 0.55) afforded the dihydro derivative **18** (237 mg, 83%) as yellow crystals with mp 138°; ir (potassium bromide): ν 3302, 2978, 1615, 1584, 1551 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.23 (t, 3H, CH_3, J = 7 Hz), 3.56 (d, 1H, vinyl-H, J = 2.6 Hz), 3.60-3.70 (m, 2H,

CH_2), 3.97 (d, 1H, vinyl-H, J = 2.6 Hz), 4.91 (m, 1H), 5.17 (m, 1H), 6.67 (d, 1H, 7-H, J_{7-8} = 7.5 Hz), 6.80 (dd, 1H, 9-H, J_{8-9} = J_{9-10} = 7.5 Hz), 7.19 (dd, 1H, 8-H, J_{8-9} = J_{9-10} = 7.5 Hz), 7.49 (d, 1H, 1-H, J_{1-2} = 5.2 Hz), 7.62 (d, 1H, 10-H, J_{9-10} = 7.5 Hz), 8.31 (d, 1H, 2-H, J_{1-2} = 5.2 Hz).

Anal. Calcd. for $C_{16}H_{15}ClN_2O$: C, 67.02; H, 5.27; N, 9.77. Found: C, 66.97; H, 5.58; N, 10.05.

4-Chloro-5-(1-ethoxyvinyl)benzo[*c*][2,7]naphthyridine (**19**).

A solution of 4-chloro-5-(1-ethoxyvinyl)-5,6-dihydrobenzo-[*c*][2,7]naphthyridine **18** (510 mg, 1.78 mmoles) in toluene (40 ml) was refluxed with manganese (IV) oxide (3.10 g, 35.6 mmoles) for 20 hours in a Dean-Stark apparatus. Cooling, filtration through celite, drying (magnesium sulfate) and solvent removal afforded a crude product which was purified by flash chromatography (diethyl ether/petroleum ether 40:60, R_f = 0.50) furnishing **19** (434 mg, 86%) as yellow crystals with mp 172°; ir (potassium bromide): ν 2980, 1587, 1546 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.40 (t, 3H, CH_3, J = 7 Hz), 4.04 (q, 1H, CH_2, J = 7 Hz), 4.60 (d, 1H, vinyl-H, J = 2.7 Hz), 4.78 (d, 1H, vinyl-H, J = 2.7 Hz), 7.78 (ddd, 1H, 9-H, J_{8-9} = J_{9-10} = 8 Hz, J_{7-9} = 1.3 Hz), 7.88 (ddd, 1H, 8-H, J_{8-9} = J_{7-8} = 8 Hz, J_{8-10} = 1.3 Hz), 8.26 (dd, 1H, 7-H, J_{7-8} = 8 Hz, J_{7-9} = 1.3 Hz), 8.35 (d, 1H, 1-H, J_{1-2} = 5.6 Hz), 8.49 (dd, 1H, 10-H, J_{9-10} = 8 Hz, J_{8-10} = 1.3 Hz), 8.64 (d, 1H, 2-H, J_{1-2} = 5.6 Hz).

Anal. Calcd. for $C_{16}H_{13}ClN_2O$: C, 67.49; H, 4.60; N, 9.84. Found: C, 67.08; H, 4.91; N, 9.54.

4-(1-Ethoxyvinyl)benzo[*c*][2,7]naphthyridine (**20**).

A solution of 4-chloro-5-benzo[*c*][2,7]naphthyridinecarbaldehyde (**9**) (144 mg, 0.594 mmole) and tributyl(1-ethoxyvinyl)tin (240 µl, 0.713 mmole) in deoxygenated toluene (25 ml) was stirred under an argon atmosphere for 30 minutes before adding tetrakis(triphenylphosphine)palladium(0) (34 mg, 0.03 mmole). The reaction mixture was then refluxed for 72 hours. Cooling at room temperature, filtration through celite and solvent removal *in vacuo* afforded the crude product which was purified by flash chromatography on silica gel (diethyl ether/petroleum ether 75:25, R_f = 0.55) furnishing **20** (82 mg, 55%) as yellow crystals with mp 136°; ir (potassium bromide): ν 2979, 1603, 1561 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.49 (t, 3H, CH_3, J = 7 Hz), 4.14 (q, 2H, CH_2, J = 7 Hz), 4.75 (d, 1H, vinyl-H, J = 2.5 Hz), 4.84 (d, 1H, vinyl-H, J = 2.5 Hz), 7.72 (dd, 1H, 9-H, J_{9-10} = J_{8-9} = 8 Hz), 7.86 (dd, 1H, 8-H, J_{7-8} = J_{8-9} = 8 Hz), 8.20 (d, 1H, 7-H, J_{7-8} = 8 Hz), 8.34 (d, 1H, 1-H, J_{1-2} = 5.7 Hz), 8.54 (d, 1H, 10-H, J_{9-10} = 8 Hz), 8.89 (d, 1H, 2-H, J_{1-2} = 5.7 Hz), 9.78 (s, 1H, 5-H).

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.20. Found: C, 77.07; H, 5.74; N, 10.89.

4-Vinyl-5-benzo[*c*][2,7]naphthyridinecarbaldehyde (**21**).

A solution of 4-chloro-5-benzo[*c*][2,7]naphthyridinecarbaldehyde (**9**) (58 mg, 0.24 mmole) and tributylvinyltin (76 µl, 0.26 mmole) in deoxygenated toluene (20 ml) was stirred under an argon atmosphere for 30 minutes before adding tetrakis(triphenylphosphine)palladium(0) (14 mg, 0.012 mmole). The reaction mixture was refluxed for 16 hours. Cooling at room temperature, filtration through celite and solvent removal *in vacuo* afforded the crude product which was purified by flash chromatography (ethyl acetate/petroleum ether 75:25, R_f = 0.65) yielding **21** (23 mg, 41%) as white crystals; ir (potassium bromide): ν 2957, 1700, 1580 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 5.75 (d, 1H, vinyl β-H, $J_{α-β}$ = 11 Hz), 6.33 (d, 1H, vinyl β-H, $J_{α-β}$ = 16 Hz), 7.30 (dd, 1H, vinyl α-H, $J_{α-β}$ = 11 Hz, $J_{α-β}$ = 16 Hz), 7.80-7.95 (m, 2H), 8.30-8.35 (m, 2H), 8.63 (d, 1H, 10-H, J = 8 Hz), 9.00 (d, 1H, 2-H, J = 5.5 Hz), 10.45 (s, 1H, CHO); ms: 234 (M^+, 52) 205 (100).

5-Acetyl-4-vinylbenzo[*c*][2,7]naphthyridine (**22**).

A solution of 5-acetyl-4-chlorobenzo[*c*][2,7]naphthyridine (**15**) (122 mg, 0.475 mmole) and tributylvinyltin (165 µl, 0.57 mmole) in deoxygenated toluene (30 ml) was stirred under an argon atmosphere for 30 minutes before adding tetrakis(triphenylphosphine)palladium(0) (27 mg, 0.024 mmole). The reaction mixture was then refluxed for 20 hours. Cooling, filtration through celite and solvent removal afforded a crude product which was purified by flash chromatography (diethyl ether/-petroleum ether 75:25, R_f = 0.45) giving **22** (47 mg, 40%) as white crystals with mp 127°; ir (potassium bromide): ν 1704, 1580, 1545 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.89 (s, 3H, CH_3), 5.66 (dd, 1H, vinyl β-H, $J_{α-β}$ = 11 Hz, $J_{β-β}$ = 1.5 Hz), 6.11 (dd, 1H, vinyl β-H, $J_{α-β}$ = 17 Hz, $J_{β-b}$ = 1.5 Hz), 7.16 (dd, 1H, vinyl α-H, $J_{α-β}$ = 11 Hz, $J_{α-β}$ = 17 Hz), 7.74 (ddd, 1H, 9-H, J_{9-10} = J_{8-9} = 7 Hz, J_{7-9} = 1.5 Hz), 7.85 (ddd, 1H, 8-H, J_{7-8} = J_{8-9} = 7 Hz, J_{8-10} = 1.5 Hz), 8.18 (dd, 1H, 7-H, J_{7-9} = 1.5 Hz, J_{7-8} = 7 Hz), 8.26 (d, 1H, 1-H, J = 5.6 Hz), 8.49 (dd, 1H, 10-H, J_{9-10} = 7 Hz, J_{8-10} = 1.5 Hz), 8.87 (d, 1H, 2-H, J = 5.6 Hz).

Anal. Calcd. for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.52; H, 5.19; N, 10.96.

4-(1-Ethoxyvinyl)-5-benzo[*c*][2,7]naphthyridinecarbaldehyde Dimethylacetal (**23**).

A solution of 4-chloro-5-benzo[*c*][2,7]naphthyridinecarbaldehyde dimethylacetal (**10**) (75 mg, 0.26 mmole) and tributyl(1-ethoxyvinyl)tin (200 µl, 0.59 mmole) in deoxygenated toluene (25 ml) was stirred under an argon atmosphere for 30 minutes before adding tetrakis(triphenylphosphine)palladium(0) (14 mg, 0.012 mmole). The reaction mixture was then refluxed for 3 days. Cooling at room temperature, filtration through celite and solvent removal *in vacuo* afforded a crude product which was purified by chromatography (diethyl ether/petroleum ether 80:20, R_f = 0.20) providing **23** (55 mg, 65%) as a colorless oil; ir (film): ν 2924, 1588 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.42 (t, 3H, CH_3, J = 7 Hz), 3.45 (s, 6H, OCH_3), 4.05 (q, 2H, CH_2, J = 7 Hz), 4.63 (d, 1H, vinyl-H, J = 2.5 Hz), 4.71 (d, 1H, vinyl-H, J = 2.5 Hz), 6.23 (s, 1H, CHacetal), 7.67 (dd, 1H, 9-H, J_{8-9} = J_{9-10} = 7 Hz), 7.81 (dd, 1H, 8-H, J_{8-9} = J_{7-8} = 7 Hz), 8.32 (d, 1H, 7-H, J_{7-8} = 7 Hz), 8.35 (d, 1H, 1-H, J = 5.5 Hz), 8.48 (d, 1H, 10-H, J_{9-10} = 7 Hz), 8.82 (d, 1H, 2-H, J = 5.5 Hz).

Anal. Calcd. for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.55; H, 6.30; N, 8.35.

4-Acetyl-5-benzo[*c*][2,7]naphthyridinecarbaldehyde Dimethylacetal (**24**).

A solution of 4-(1-ethoxyvinyl)-5-benzo[*c*][2,7]naphthyridine carbaldehyde dimethylacetal (**23**) (80 mg, 0.247 mmole) in dichloromethane (15 ml) was vigorously stirred at room temperature for 2 hours with 5% hydrochloric acid (5 ml). The aqueous layer was separated, neutralized by a saturated aqueous solution of sodium hydrogenocarbonate and extracted with dichloromethane. The combined organic layers were dried (magnesium sulfate) and evaporated *in vacuo*. Flash chromatography on silica gel (diethyl ether/petroleum ether 60:40) afforded **24** (24 mg, 33%)

as a colorless oil; ir (film): ν 2964, 1698, 1588, 1554 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.90 (s, 3H, CH_3), 3.41 (s, 6H, OCH_3), 5.84 (s, 1H, CHacetal), 7.75 (dd, 1H, 9-H, $J_{9-10} = J_{8-9} = 8$ Hz), 7.88 (dd, 1H, 8-H, $J_{7-8} = J_{8-9} = 8$ Hz), 8.35 (d, 1H, 7-H, $J_{7-8} = 8$ Hz), 8.50 (d, 1H, 1-H, $J_{1-2} = 5$ Hz), 8.55 (d, 1H, 10-H, $J_{9-10} = 8$ Hz), 8.80 (d, 1H, 2-H, $J_{1-2} = 5$ Hz).

Anal. Calcd. for $C_{17}H_{16}N_2O_3$: C, 68.90; H, 5.44; N, 9.45. Found: C, 69.10; H, 5.81; N, 9.09.

6-Methoxy-4*H*-pyrido[2,3,4-*kl*]acridin-4-one (**25**) and 6-Ethoxy-4*H*-pyrido[2,3,4-*kl*]acridin-4-one (**26**).

A solution of 4-(1-ethoxyvinyl)-5-benzo[*c*][2,7]naphthyridinecarbaldehyde dimethyl acetal (**23**) (60 mg, 0.185 mmole) and sodium iodide (130 mg, 0.926 mmole) in dry acetonitrile (10 ml) was treated with boron trifluoride diethyl etherate freshly distilled (35 µl, 0.366 mmole). The mixture was stirred 2 hours at room temperature. To the reaction mixture, a solution of potassium nitrosodisulfonate (Fremy's salt) (248 mg, 0.926 mmole) and potassium dihydrogenophosphate (126 mg, 0.926 mmole) in methanol (5 ml) and water (2 ml) was added. Stirring at room temperature was pursued for 2 hours then water (20 ml) and dichloromethane (20 ml) were added. The aqueous layer was separated, treated with saturated sodium thiosulfate, neutralized and extracted with dichloromethane. The combined organic layers were dried (magnesium sulfate) and evaporated *in vacuo*. Flash chromatography on silica gel (ethyl acetate/ethanol 80:20) gave **25** (30 mg, 62%, $R_f = 0.25$) as yellow crystals with mp >250°; ir (potassium bromide): ν 1640, 1573 cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.15 (s, 3H, OCH_3), 6.43 (s, 1H, 5-H), 7.80-8.00 (m, 2H, 9-H, 10-H), 8.42 (d, 1H, 8-H, $J_{8-9} = 7$ Hz), 8.55 (d, 1H, 1-H, $J_{1-2} = 5.6$ Hz), 8.59 (d, 1H, 11-H, $J_{10-11} = 7$ Hz), 9.22 (d, 1H, 2-H, $J_{1-2} = 5.6$ Hz) ; ms: 262 (M^+,100).

Anal. Calcd. for $C_{16}H_{10}N_2O_2$: C, 73.27; H, 3.84; N, 10.68. Found: C, 73.22; H, 3.79; N, 10.77.

The same purification by flash chromatography on silica gel (ethyl acetate/ethanol 80:20) afforded **26** (12 mg, 24%, R_f = 0.50) as yellow crystals with mp 245° dec; ir (potassium bromide): ν 2925, 1728, 1647, 1578 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.67 (t, 3H, CH_3, J = 7 Hz), 4.38 (q, 2H, CH_2, J = 7 Hz), 6.41 (s, 1H, 5-H), 7.90-8.00 (m, 2H, 9-H, 10-H), 8.49 (d, 1H, 1-H, $J_{1-2} = 5.7$ Hz), 8.61 (m, 2H, 8-H, 11-H), 9.12 (d, 1H, 2-H, $J_{1-2} = 5.7$ Hz); ms: 276 (M^+, 5) 261(100).

Anal. Calcd. for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 74.04; H, 4.62; N, 9.84.

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