Nucleophilic addition of lithio derivatives to 1-substituted benzo[*c*][2,7]naphthyridines (2,9-diazaphenanthrenes)

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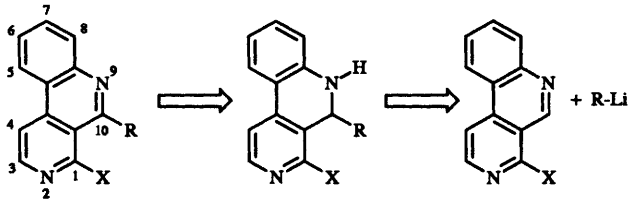
Nucleophilic addition of lithio derivatives to 1-substituted benzo[*c*][2,7]naphthyridines and rearomatization of the intermediate dihydro compounds with MnO_2 gives good overall yields of product.

Introduction

Our group has been long interested in the metallation of π-deficient heterocycles (pyridine, quinoline and diazines),[1] compounds which can, when treated with organolithiums, lead to various dihydro derivatives.[1] This sometimes undesirable reaction can be used to introduce alkyl or aryl groups into an aromatic structure.[1,2]

During the last 10 years, a wide range of polycyclic alkaloids which contain a common benzo[*c*][2,7]naphthyridine (2,9-diazaphenanthrenes) structure have been isolated, from marine organisms.[3] For the synthesis of such compounds, a general and efficient methodology using metallation in connection with cross-coupling has been developed.[4–8] We report here such a route which affords a new synthesis of 1,10-disubstituted benzo[*c*][2,7]naphthyridines based on nucleophilic addition of alkyl- or aryl-lithio derivatives to the corresponding 1-substituted compounds followed by oxidation as shown on the retrosynthetic scheme (Scheme 1).



Scheme 1

Results and discussion

I. Synthesis of 1-substituted benzo[*c*][2,7]naphthyridines 5–7

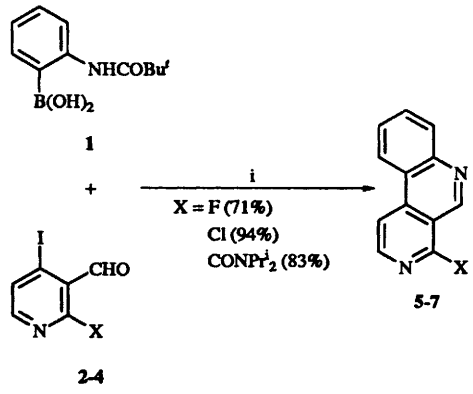
(2-Pivaloylaminophenyl)boronic acid[9] **1** reacted with 2-substituted 4-iodopyridine-3-carbaldehydes **2–4** under Suzuki conditions using $[Pd(PPh_3)_4]$ as catalyst,[10] to give, by way of hetero ring cross-coupling and subsequent cyclization, good yields of the corresponding benzo[*c*][2,7]naphthyridines **5–7** (Scheme 2).

The fluoro compound **5** has already been described[4] and used as a precursor for the synthesis of perlolidine.[11]

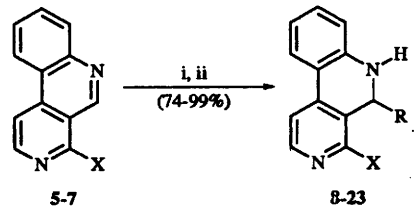
II. Nucleophilic addition of lithio derivatives to compounds 5–7

Chemo- and regio-selective addition in THF at low temperature of alkyl, phenyl and pyridyl-lithiums to compounds **5–7** gave the fluorescent products **8–23** in very good to high yields (Scheme 3 and Table 1).

The behaviour of the 9,10 bond in the benzonaphthyridines ring is very similar to that of a regular imine bond.[12] The nucleophilic addition was affected by steric hindrance since yields were very good with the *ortho*-lithiocarboxamido



Scheme 2 *Reagents and conditions:* i, $[Pd(PPh_3)_4]$, 2 mol dm^{-3} K_2CO_3, EtOH, toluene, reflux under argon, 24 h



Scheme 3 *Reagents and conditions:* i, *x*RLi, THF, heat, 1 h; ii, H_2O

derivatives only at higher temperature (−40 °C) (compounds **17**, **18** and **23**). Surprisingly, it was not possible to carry out the reaction with 4-methoxy-3-pyridyllithium probably because of interaction between the methoxy group and the benzonaphthyridine ring.

Two equivalents of alkyl- or phenyl-lithiums give rise to high yields of addition products. However, addition of pyridyllithiums requires a larger excess of nucleophile because of purification restraints: *viz.*, since it is very difficult to remove the starting benzonaphthyridines from the addition product whatever the flash chromatography conditions, a large excess of pyridyllithiums must be used to consume all the reagent.

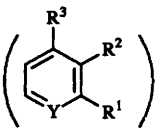
With 3-pyridyllithium, it was impossible to avoid the formation of the re-aromatized product (see Table 1).

III. Oxidation of dihydrobenzo[*c*][2,7]naphthyridines

The previously prepared dihydrobenzonaphthyridines **8–23** were aromatized with manganese dioxide (MnO_2) in refluxed chloroform or toluene,[13] to give compounds **24–31** in good to excellent yields (Scheme 4 and Table 2).

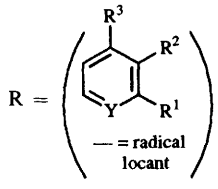
This oxidation is sensitive to steric hindrance. Indeed, if the substituent (R) is a butyl group or a non-bulky aromatic ring (phenyl or pyridyl), yields were very good. However, with

Table 1 Preparation of 1,10-disubstituted 9,10-dihydrobenzo[*c*][2,7]naphthyridines **8–23**

X	RLi	R = 			*x* (equiv.)	Temp. (°C)	Product	Yield (%)[a]
	Y	R^1	R^2	R^3				
F	CH	Li	H	H	2	−75	**8**	74
	N	H	Li	H	4	−75	**9**	99[b]
	N	F	Li	I	4	−75	**10**	77
Cl		MeLi			2	−75	**11**	94
		BuLi			2	−75	**12**	79
	CH	Li	Li	H	2	−75	**13**	94
	N	H	Li	H	4	−75	**14**	99[b]
	N	F	Li	I	4	−75	**15**	74
	N	Cl	Li	I	4	−75	**16**	83
	N	$CONPr^i_2$	H	I	4	−40	**17**	81
	N	$CONPr^i_2$	H	Cl	4	−40	**18**	85
$CONPr^i_2$		BuLi			2	−75	**19**	95
	CH	Li	H	H	2	−75	**20**	81
	CH	Li	H	OMe	4	−75	**21**	92
	N	H	Li	H	4	−75	**22**	99[b]
	N	F	Li	I	4	−40	**23**	83
	N	H	Li	OMe	4	−75 to 0		0

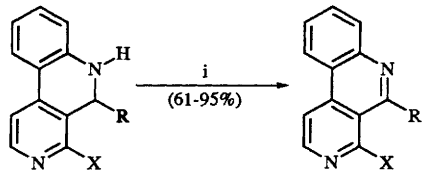
[a] Yields are for isolated products. [b] Yield corresponding to a partly oxidized product (dihydro and aromatized product in a variable ratio varying with air exposure).

Table 2 Preparation of 1,10-disubstituted benzonaphthyridines **24–32**

X	R =  — = radical locant				Solvent	Time (h)	Product	Yield (%)[a]
	Y	R^1	R^2	R^3				
F	N	H	—	H	$CHCl_3$	20	**24**	92
Cl	CH	—	H	H	$CHCl_3$	20	**25**	85
	N	H	—	H	$CHCl_3$	20	**26**	92
	N	F	—	I	$CHCl_3$	48	**27**	84
	N	$CONPr^i_2$	—	Cl	Toluene	72	**28**	61
$CONPr^i_2$		Bu			$CHCl_3$	20	**39**	89
	CH	—	H	H	$CHCl_3$	20	**30**	90
	CH	—	H	OMe	No solvent	30 days	**31**	95[b]
	N	H	—	H	$CHCl_3$	20	**32**	87

[a] Yields are for isolated products. [b] Aerial oxidation at room temperature on the solid compound.

reagents **15** and **18**, the oxidation step, which gives products **27** and **28**, required longer reaction times (see Table 2). It has been shown that aerial oxidation (several days) was efficient for the formation of products **24**, **26**, **31** and **32** which were obtained in good yields (> 80%). Compound **31** has only been obtained under such conditions.



9, 13-15, 18-22 **24-32**

Scheme 4 *Reagents and conditions:* i, MnO_2 (20 equiv.), solvent, time, reflux

Conclusion

1,10-Disubstituted benzo[*c*][2,7]naphthyridines were conveniently obtained by a two-step sequence (addition–oxidation) from the corresponding 1-substituted structures. The high reactivity of the imine moiety allows a full regioselectivity of the addition and very good overall yields. Some of the resulting 10-aryl compounds are potential intermediates for marine alkaloids.[14]

Experimental

General data

Melting points were measured on a Kofler apparatus. ^1H NMR spectra were recorded (in ppm) on a 200 MHz Brücker spectrometer (internal standard: TMS in $CDCl_3$ or HMDS in [$^2H_6$]DMSO) and *J* values are given in Hz. IR spectra were taken on a Beckman IR 4250 spectrometer, and main absorption frequencies (NH, CH, C=O, C=C, C=N) are given

in cm^{-1}. Elementary analyses were performed on a Carlo Erba 1160 apparatus.

Solvent

Tetrahydrofuran (THF) was distilled from benzophenone–sodium. The water content of the solvent was estimated lower than 45 ppm by the modified Karl–Fisher method.[15]

Starting materials

TMEDA and diisopropylamine were distilled from CaH_2 and stored under a dry atmosphere. (2-Pivaloylaminophenyl)-boronic acid[9] **1** was prepared by metallation and boronation of the protected aniline. 2-Substituted 4-iodo-pyridine-3-carboxaldehydes **2–4** were prepared by metallation–isomerization of the corresponding 2-substituted 3-iodopyridines.[4,8] Commercial 2.5 mol dm^{-3} solutions of butyllithium in hexane, 1.4 mol dm^{-3} solutions of *sec*-butyllithium in pentane and 2.0 mol dm^{-3} solutions of phenyllithium in ether–hexane were stored and transferred under a dehydrated and deoxygenated argon atmosphere. Lithium diisopropylamide (LDA) was prepared by reaction of diisopropylamine in THF with butyllithium at −75 °C for 15 min as previously described.[4] Various pyridyllithiums were prepared according to classical procedures.[1,4,8,†]

General procedure A: synthesis of 1-substituted benzo[*c*][2,7]naphthyridines 5–7

The required iodopyridines (1.0 mmol) and (2-pivaloylaminophenyl)boronic acid **1** (1.0 mmol) were added to a solution of potassium carbonate (2 mol dm^{-3}; 1.0 cm^3) and ethanol (1.0 cm^3) in deoxygenated toluene (10 cm^3). The resulting mixture was stirred under an argon atmosphere for 0.5 h, after which tetrakis(triphenylphosphine)palladium(0) (35 mg, 0.030 mmol) was added to it. The reaction mixture was then refluxed for 24 h, cooled, filtered and extracted with toluene. The extract was dried ($MgSO_4$), and evaporated to afford a crude product which was purified by flash chromatography on silica (eluent).

1-Fluorobenzo[*c*][2,7]naphthyridine 5. The general procedure A applied to **2** gave the *title compound* (71%) (diethyl ether–hexane, 25:75), mp 152 °C (Found: C, 72.6; H, 3.5; N, 13.9. $C_{12}H_7FN_2$ requires C, 72.7; H, 3.6; N, 14.1%); ν_{max}(KBr)/cm^{-1} 1620, 1580 and 1420; δ_H(200 MHz; $CDCl_3$) 7.79 (1 H, dt, 6-H), 7.92 (1 H, dt, 7-H), 8.25 (1 H, d, 4-H), 8.30 (1 H, dd, 8-H), 8.50 (1 H, d, 3-H), 8.53 (1 H, dd, 5-H) and 9.58 (1 H, s, 10-H), ($J_{3,4}$ 5.0, $J_{5,6}$ 7.0, $J_{7,8}$ 6.9, $J_{6,7}$ 7.0, $J_{5,7}$ 1.3, $J_{6,8}$ 1.3).

1-Chlorobenzo[*c*][2,7]naphthyridine 6. The general procedure A applied to **3** gave the *title compound* (94%) (diethyl ether–cyclohexane, 5:5), mp 176 °C (Found: C, 67.0; H, 3.4; N, 13.2. $C_{12}H_7ClN_2$ requires C, 67.1; H, 3.3; N, 13.0%); ν_{max}(KBr)/cm^{-1} 1601, 1558 and 1322; δ_H(200 MHz; $CDCl_3$) 7.76 (1 H, dt, 6-H) 7.92 (1 H, dt, 7-H), 8.26 (1 H, dd, 8-H), 8.32 (1 H, d, 4-H), 8.53 (1 H, dd, 5-H), 8.67 (1 H, d, 3-H) and 9.73 (1 H, s, 10-H) ($J_{3,4}$ 5.3, $J_{5,6}$ 7.0, $J_{7,8}$ 6.9, $J_{6,7}$ 7.0, $J_{5,7}$ 1.3, $J_{6,8}$ 1.3).

***N*,*N*-Diisopropylbenzo[*c*][2,7]naphthyridine-1-carboxamide 7.** The general procedure A applied to **4** gave the *title compound* (83%) (diethyl ether), mp 150 °C (Found: C, 74.2; H, 7.1; N, 13.5. $C_{19}H_{21}N_3O$ requires C, 74.2; H, 6.9; N, 13.7%); ν_{max}(KBr)/cm^{-1} 2964, 2926, 1630, 1560, 1474, 1457, 1363 and 1320; δ_H(200 MHz; $CDCl_3$) 1.16 (6 H, 2 d, $2CH_3$), 1.73 (6 H, 2 d, $2CH_3$), 3.54 (1 H, sept, CH), 3.69 (1 H, sept, CH), 7.77 (1 H, dt, 6-H), 7.90 (1 H, dt, 7-H), 8.23 (1 H, dd, 8-H), 8.37 (1 H, d, 4-H), 8.58 (1 H, dd, 5-H), 8.89 (1 H, d, 3-H) and 9.45 (1 H, s, 10-H) (J_{CH,CH_3} 6.9, $J_{3,4}$ 5.8, $J_{5,6}$ 6.9, $J_{7,8}$ 7.0, $J_{6,7}$ 7.0, $J_{5,7}$ 1.3, $J_{6,8}$ 1.3).

General procedure B: synthesis of 1,10-disubstituted 9,10-dihydrobenzo[*c*][2,7]naphthyridines 8–23

The required lithio compound [*x* mmol, THF (10 × cm^3)‡ −75 °C] was added to a cold (−75 °C) solution of the corresponding benzo[*c*][2,7]naphthyridine (1.0 mmol) in THF solution (50 cm^3) under argon; a bright red colour appeared. The resulting mixture was stirred for 1 h at −75 °C before hydrolysis by a mixture of water and THF (2 cm^3; 8 cm^3) and further addition of water (30 cm^3) at room temperature. The mixture was extracted with Et_2O, and the extract dried ($MgSO_4$) and evaporated to afford a crude product (yellow) which was purified by flash chromatography on silica (eluent).

1-Fluoro-10-phenyl-9,10-dihydrobenzo[*c*][2,7]naphthyridine 8. The general procedure B applied to **5** using phenyllithium at −75 °C gave the *title compound* (74%) (diethyl ether–hexane, 5:5), mp 130–132 °C (decomp.) (Found: C, 78.5; H, 4.5; N, 10.3. $C_{18}H_{13}FN_2$ requires C, 78.2; H, 4.7; N, 10.1%); ν_{max}(KBr)/cm^{-1} 3393, 1611, 1558, 1414 and 1353; δ_H(200 MHz; $CDCl_3$) 4.66 (1 H, s, 9-H), 5.76 (1 H, s, 10-H), 6.62 (1 H, dd, 8-H), 6.82 (1 H, dt, 6-H), 7.19–7.31 (6 H, m, 7-H + 5 H_{arom}), 7.50 (1 H, d, 4-H), 7.68 (1 H, dd, 5-H) and 8.10 (1 H, d, 3-H) ($J_{3,4}$ 5.4, $J_{5,6}$ 7.2, $J_{5,7}$ 1.3).

1-Fluoro-10-(3-pyridyl)-9,10-dihydrobenzo[*c*][2,7]naphthyridine 9. The general procedure B applied to **5** using 3-pyridyllithium at −75 °C gave the *title compound* (99%) (diethyl ether). The product was partly oxidized in air (not stable) and it was impossible to separate both products. Only the ^1H NMR spectrum of the *title compound* is given: δ_H(200 MHz; $CDCl_3$) 4.76 (1 H, s, 9-H), 5.82 (1 H, s, 10-H), 6.65 (1 H, d, 8-H), 6.84 (1 H, td, 6-H), 7.12–7.27 (2 H, m, 7-H + 5′-H), 7.49–7.58 (2 H, m, 4-H + 4′-H), 7.69 (1 H, dd, 5-H), 8.12 (1 H, d, 3-H), 8.48 (1 H, d, 6′-H) and 8.59 (1 H, s, 2′-H) ($J_{3,4}$ 5.4, $J_{5,6}$ 7.9, $J_{5,7}$ 1.0).

1-Fluoro-10-(2-fluoro-4-iodo-3-pyridyl)-9,10-dihydrobenzo-[*c*][2,7]naphthyridine 10. The general procedure B applied to **5** using 2-fluoro-4-iodo-3-pyridyllithium at −75 °C gave the *title compound* (77%) (diethyl ether–cyclohexane, 5:5), mp 184–186 °C (Found: C, 48.6; H, 2.5; N, 10.1. $C_{17}H_{10}F_2IN_3$ requires C, 48.5; H, 2.4; N, 10.0%); ν_{max}(KBr)/cm^{-1} 3300, 1607, 1578 and 1415; δ_H(200 MHz; $CDCl_3$) 4.39 (1 H, s, 9-H), 6.48 (1 H, dd, 8-H), 6.50 (1 H, s, 10-H), 6.78 (1 H, td, 6-H), 7.17 (1 H, td, 7-H), 7.52 (1 H, d, 4-H), 7.68 (1 H, dd, 5-H), 7.71 (2 H, s, 5′-H + 6′-H) and 8.10 (1 H, d, 3-H) ($J_{3,4}$ 5.4, $J_{5,6}$ 7.5, $J_{5,7}$ 1.3).

1-Chloro-10-methyl-9,10-dihydrobenzo[*c*][2,7]naphthyridine 11. The general procedure B applied to **6** using methyllithium at −75 °C gave the *title compound* (94%) (methylene dichloride–ethyl acetate, 95:5), mp 70 °C (decomp.) (Found: C, 67.8; H, 4.5; N, 12.4. $C_{13}H_{11}ClN_2$ requires C, 67.7; H, 4.8; N, 12.1%); ν_{max}(KBr)/cm^{-1} 3430, 1611, 1585, 1547 and 1394; δ_H(200 MHz; $CDCl_3$) 1.31 (3 H, d, CH_3), 4.31 (1 H, s, 9-H), 4.84 (1 H, q, 10-H), 6.67 (1 H, dd, 8-H), 6.81 (1 H, td, 6-H), 7.20 (1 H, td, 7-H), 7.47 (1 H, d, 4-H), 7.64 (1 H, dd, 5-H) and 8.26 (1 H, d, 3-H) (J_{10,CH_3} 6.5, $J_{3,4}$ 5.3, $J_{5,6}$ 7.8, $J_{5,7}$ 1.4).

10-Butyl-1-chloro-9,10-dihydrobenzo[*c*][2,7]naphthyridine 12. The general procedure B applied to **6** using butyllithium at −75 °C gave the *title compound* (79%) (diethyl ether–hexane, 25:75), mp 94 °C (decomp.) (Found: C, 70.7; H, 6.0; N, 10.4. $C_{16}H_{17}ClN_2$ requires C, 70.45; H, 6.3; N, 10.3%); ν_{max}(KBr)/cm^{-1} 3450, 2926, 1612, 1584, 1546 and 1394; δ_H(200 MHz; $CDCl_3$) 0.87 (3 H, t, CH_3), 1.27–1.79 (6 H, m, $3CH_2$), 4.57 (1 H, s, 9-H), 4.64 (1 H, dd, 10-H), 6.68 (1 H, dd, 8-H), 6.80 (1 H, td,

† 4-Chloro *N*,*N*-diisopropyl-3-lithiopyridinecarboxamide was prepared by metallation of the corresponding pyridyllithium as previously described for *N*,*N*-diisopropylpyridinecarboxamide.[8] 4-Chloro-*N*,*N*-diisopropylpyridinecarboxamide is a by-product of the formation of *N*,*N*-diisopropylpyridinecarboxamide after chlorination of picolinic acid and treatment with diisopropylamine.

‡ Except for commercial solution where the solvent is generally different.

6-H), 7.20 (1 H, td, 7-H), 7.46 (1 H, d, 4-H), 7.63 (1 H, dd, 5-H) and 8.25 (1 H, d, 3-H) ($J_{3,4}$ 5.3, $J_{5,6}$ 7.9, $J_{5,7}$ 1.25).

1-Chloro-10-phenyl-9,10-dihydrobenzo[*c*]naphthyridine 13. The general procedure B applied to **6** using phenyllithium at −75 °C gave the *title compound* (94%) (diethyl ether–hexane, 5:5), mp 182 °C (decomp.) (Found: C, 74.6; H, 4.3; N, 9.7. $C_{18}H_{13}ClN_2$ requires C, 73.8; H, 4.9; N, 9.6%); ν_{max}(KBr)/cm^{-1} 3259, 1613, 1584, 1543, 1491, 1458 and 1390; δ_H(200 MHz; $CDCl_3$) 4.75 (1 H, s, 9-H), 5.81 (1 H, s, 10-H), 6.58 (1 H, dd, 8-H), 6.62 (1 H, td, 6-H), 7.19 (1 H, td, 7-H), 7.23 (5 H_{arom}, br s), 7.60 (1 H, d, 4-H), 7.70 (1 H, dd, 5-H) and 8.33 (1 H, d, 3-H) ($J_{3,4}$ 5.3, $J_{5,6}$ 6.9, $J_{7,8}$ 7.1, $J_{5,7}$ 1.2).

1-Chloro-10-(3-pyridyl)-9,10-dihydrobenzo[*c*][2,7]naphthyridine 14. The general procedure B applied to **6** using 3-pyridyllithium at −75 °C gave the *title compound* (99%) (diethyl ether). The product was partly oxidized in air (not stable) and it was impossible to separate both products. Only the ^{1}H NMR spectrum of the *title compound* is given: δ_H(200 MHz; $CDCl_3$) 4.82 (1 H, s, 9-H), 5.84 (1 H, s, 10-H), 6.60 (1 H, dd, 8-H), 6.84 (1 H, td, 6-H), 7.15–7.27 (2 H, m, 7-H + 5′-H), 7.47 (1 H, d, 4′-H), 7.60 (1 H, d, 4-H), 7.69 (1 H, dd, 5-H), 8.32 (1 H, d, 3-H), 8.46 (1 H, d, 6′-H) and 8.56 (1 H, s, 2′-H) ($J_{3,4}$ 5.2, $J_{5,6}$ 8.0, $J_{5,7}$ 1.3).

1-Chloro-10-(2-fluoro-4-iodo-3-pyridyl)-9,10-dihydrobenzo-[*c*]naphthyridine 15. The general procedure B applied to **6** using 2-fluoro-4-iodo-3-pyridyllithium at −75 °C gave the *title compound* (74%) (diethyl ether–cyclohexane, 5:5), mp 118 °C (Found: C, 46.9; H, 2.4; N, 9.6. $C_{17}H_{10}ClFIN_3$ requires C, 46.65; H, 2.3; N, 9.6%); ν_{max}(KBr)/cm^{-1} 3276, 2921, 1613, 1577, 1534 and 1389; δ_H(200 MHz; $CDCl_3$) 4.49 (1 H, s, 9-H), 6.34 (1 H, s, 10-H), 6.51 (1 H, dd, 8-H), 6.82 (1 H, td, 6-H), 7.16 (1 H, td, 7-H), 7.60 (1 H, d, 4-H), 7.71 (2 H, s, 5′-H + 6′-H), 7.72 (1 H, dd, 5-H) and 8.33 (1 H, d, 3-H) ($J_{3,4}$ 5.3, $J_{5,6}$ 8.0, $J_{5,7}$ 1.0).

1-Chloro-10-(2-chloro-4-iodo-3-pyridyl)-9,10-dihydrobenzo-[*c*]naphthyridine 16. The general procedure B applied to **6** using 2-chloro-4-iodo-3-pyridyllithium at −75 °C gave the *title compound* (83%) (diethyl ether–cyclohexane, 5:5), mp 94 °C (Found: C, 44.7; H, 2.3; N, 9.0. $C_{17}H_{10}Cl_2IN_3$ requires C, 44.95; H, 2.2; N, 9.25%); ν_{max}(KBr)/cm^{-1} 3276, 2922, 1613, 1581, 1545 and 1388; δ_H(200 MHz; $CDCl_3$) 4.29 (1 H, s, 9-H), 6.45 (1 H, dd, 8-H), 6.71 (1 H, s, 10-H), 6.74 (1 H, td, 6-H), 7.11 (1 H, td, 7-H), 7.56 (1 H, d, 4-H), 7.64 (1 H, dd, 5-H), 7.82 (1 H, d, 5′-H), 7.87 (1 H, d, 6′-H) and 8.30 (1 H, d, 3-H) ($J_{3,4}$ 5.4, $J_{5',6'}$ 5.1, $J_{5,6}$ 7.2, $J_{5,7}$ 1.1).

***N,N*-Diisopropyl-3-(1-chloro-9,10-dihydrobenzo[*c*]naphthyridin-1-yl)-4-iodopyridine-2-carboxamide 17.** The general procedure B applied to **6** using *N,N*-diisopropyl-4-iodo-3-pyridyllithium at −40 °C gave the *title compound* (81%) (methylene dichloride–ethyl acetate, 9:1), mp 202 °C (decomp.) (Found: C, 52.6; H, 4.5; N, 10.3. $C_{24}H_{24}ClIN_4O$ requires C, 52.7; H, 4.4; N, 10.2%); ν_{max}(KBr)/cm^{-1} 3386, 2927, 1609, 1578, 1540, 1388 and 1317; δ_H(200 MHz; $CDCl_3$) 1.23 (3 H, d, CH_3), 1.36 (3 H, d, CH_3), 1.60 (6 H, 2 d, $2CH_3$), 3.62 (1 H, sept, CH), 3.91 (1 H, sept, CH), 5.59 (1 H, s, 9-H), 6.33 (1 H, s, 10-H), 6.51, (1 H, dd, 8-H), 6.66 (1 H, td, 6-H), 7.13 (1 H, td, 7-H), 7.53 (1 H, d, 4-H), 7.57 (1 H, dd, 5-H), 7.81 (1 H, d, 5′-H), 7.97 (1 H, d, 6′-H) and 8.30 (1 H, d, 3-H) ($J_{3,4}$ 5.3, $J_{5',6'}$ 5.1, $J_{5,6}$ 7.2, $J_{5,7}$ 1.3).

4-Chloro-3-(1-chloro-9,10-dihydrobenzo[*c*][2,7]naphthyridin-1-yl)-*N,N*-diisopropylpyridine-2-carboxamide 18. The general procedure B applied to **6** using *N,N*-diisopropyl-4-chloro-3-pyridyllithium at −40 °C gave the *title compound* (85%) (methylene dichloride–ethyl acetate, 9:1), mp 228 °C (Found: C, 63.4; H, 5.2; N, 12.5. $C_{24}H_{24}Cl_2N_4O$ requires C, 63.3; H, 5.3; N, 12.3%); ν_{max}(KBr)/cm^{-1} 3337, 2978, 1610, 1578, 1546, 1444, 1388 and 1320; δ_H(200 MHz; $CDCl_3$) 1.24 (3 H, s, CH_3), 1.37 (3 H, d, CH_3), 1.62 (6 H, 2 d, $2CH_3$), 3.63 (1 H, sept, CH), 3.91 (1 H, sept, CH), 5.64 (1 H, s, 9-H), 6.21 (1 H, s, 10-H), 6.50 (1 H, dd, 8-H), 6.67 (1 H, td, 6-H), 7.10 (1 H, td, 7-H), 7.18 (1 H, d, 5′-H), 7.53 (1 H, d, 4-H), 7.58 (1 H, dd, 5-H) and 8.27–8.31 (2 H, 2 d, 3-H + 6′-H) ($J_{3,4}$ 5.3, $J_{5,6}$ 7.9, $J_{5,7}$ 1.3, $J_{5',6'}$ 5.2).

10-Butyl-*N,N*-diisopropyl-9,10-dihydrobenzo[*c*][2,7]naphthyridine-1-carboxamide 19. The general procedure B applied to **7** using butyllithium at −75 °C gave the *title compound* (95%) (diethyl ether), mp 75 °C (decomp.) (Found: C, 75.8; H, 8.3; N, 11.7. $C_{23}H_{31}N_3O$ requires C, 75.6; H, 8.5; N, 11.5%); ν_{max}(KBr)/cm^{-1} 3323, 2965, 1628, 1581, 1490 and 1348; δ_H(200 MHz; $CDCl_3$) 0.72 (3 H, t, CH_3), 1.18 (6 H, 2 d, $2CH_3$), 1.20 to 1.80 (6 H, m, $3CH_2$), 1.60 (6 H, 2 d, $2CH_3$), 3.59 (2 H, sept, 2CH), 4.42 (1 H, d, 10-H), 4.47 (1 H, s, 9-H), 6.69 (1 H, d, 8-H), 6.83 (1 H, t, 6-H), 7.21 (1 H, t, 7-H), 7.51 (1 H, d, 4-H), 7.70 (1 H, d, 5-H) and 8.47 (1 H, d, 3-H) ($J_{3,4}$ 5.3, $J_{5,6}$ 7.8, $J_{5,7}$ 1.4).

***N,N*-Diisopropyl-10-phenyl-9,10-benzo[*c*][2,7]naphthyridine-1-carboxamide 20.** The general procedure B applied to **7** using phenyllithium at −75 °C gave the *title compound* (81%) (diethyl ether–cyclohexane, 5:5), mp 223 °C (decomp.) (Found: C, 77.7; H, 6.8; N, 10.7. $C_{25}H_{27}N_3O$ requires C, 77.9; H, 7.05; N, 10.9%); ν_{max}(KBr)/cm^{-1} 3317, 2968, 1626, 1584, 1482, 1439, 1370, 1349 and 1325; δ_H(200 MHz; $CDCl_3$) 0.76 (3 H, d, CH_3), 1.08 (3 H, d, CH_3), 1.45 (3 H, d, CH_3), 1.54 (3 H, d, CH_3), 3.05 (1 H, sept, CH), 3.29 (1 H, sept, CH), 4.46 (1 H, s, 9-H), 6.06 (1 H, s, 10-H), 6.48 (1 H, d, 8-H), 6.79 (1 H, t, 7-H), 7.13 (1 H, t, 6-H), 7.19 (5 H_{arom}, m), 7.64 (1 H, d, 4-H), 7.72 (1 H, d, 5-H) and 8.49 (1 H, d, 3-H) ($J_{3,4}$ 5.3, $J_{5,6}$ 7.9, $J_{7,8}$ 8.1).

***N,N*-Diisopropyl-10-(3-methoxyphenyl-9,10-dihydrobenzo-[*c*][2,7]naphthyridine-1-carboxamide 21.** The general procedure B applied to **7** using 3-methoxyphenyllithium at −75 °C gave the *title compound* (92%) (diethyl ether), mp 95 °C (Found: C, 75.4; H, 7.0; N, 10.25. $C_{26}H_{29}N_3O_2$ requires C, 75.15; H, 7.0; N, 10.1%); ν_{max}(KBr)/cm^{-1} 3319, 1967, 1611, 1582, 1487, 1346 and 1316; δ_H(200 MHz; $CDCl_3$) 0.23 (3 H, d, CH_3), 1.10 (3 H, d, CH_3), 1.45 (3 H, d, CH_3), 1.55 (3 H, d, CH_3), 3.10 (1 H, sept, CH), 3.31 (1 H, sept, CH), 3.67 (3 H, s, OCH_3), 4.42 (1 H, s, 9-H), 6.02 (1 H, s, 10-H), 6.49 (1 H, d, 8-H), 6.70–6.82 (4 H, m, 7-H + 3 H_{phenyl}), 6.82–7.17 (2 H, m, 6-H + H_{phenyl}), 7.63 (1 H, d, 4-H), 7.71 (1 H, d, 5-H) and 8.49 (1 H, d, 3-H) ($J_{3,4}$ 5.3, J_{CH,CH_3} 6.5).

***N,N*-Diisopropyl-10-(3-pyridyl)-9,10-dihydrobenzo[*c*][2,7]-naphthyridine-1-carboxamide 22.** The general procedure B applied to **7** using 3-pyridyllithium at −75 °C gave the *title compound* (99%) (diethyl ether). The product was partly oxidized in air (not stable) and it was impossible to separate both products. Only the ^{1}H NMR spectrum of the *title compound* is given; δ_H(200 MHz; $CDCl_3$) 0.33 (3 H, d, CH_3), 1.11 (3 H, d, CH_3), 1.48 (3 H, d, CH_3), 1.55 (3 H, d, CH_3), 3.15 (1 H, sept, CH), 3.35 (1 H, sept, CH), 4.54 (1 H, s, 9-H), 6.05 (1 H, s, 10-H), 6.55 (1 H, d, 8-H), 6.84 (1 H, td, 6-H), 7.10–7.27 (2 H, m, 7-H + 5′-H), 7.45 (1 H, d, 4′-H), 7.65 (1 H, d, 4-H), 7.74 (1 H, dd, 5-H) and 8.40–8.54 (3 H, m, 3-H + 6′-H + 2′-H ($J_{3,4}$ 5.4, $J_{5,6}$ 8.3).

***N,N*-Diisopropyl-10-(2-fluoro-4-iodo-3-pyridyl)-9,10-dihydrobenzo[*c*][2,7]naphthyridine-1-carboxamide 23.** The general procedure B applied to **7** using 2-fluoro-4-iodo-3-pyridyllithium at −40 °C gave the *title compound* (83%) (diethyl ether–cyclohexane, 75:25), mp 248–250 °C (Found: C, 54.6; H, 4.7; N, 10.5. $C_{24}H_{24}FIN_4O$ requires C, 54.35; H, 4.6; N, 10.6%); ν_{max}(KBr)/cm^{-1} 3349, 2966, 1618, 1576, 1535, 1438 and 1397; δ_H(200 MHz; $CDCl_3$) 1.16–1.53 (12 H, m, $4CH_3$), 3.20–3.50 (2 H, m, 2CH), 4.55 (1 H, s, 9-H), 6.51 (1 H, dd, 8-H), 6.61 (1 H, s, 10-H), 6.82 (1 H, td, 6-H), 7.14 (1 H, td, 7-H), 7.62 (1 H, d, 4-H), 7.69 (3 H, m, 5′-H + 6′-H + 5-H) and 8.52 (1 H, d, 3-H) ($J_{3,4}$ 5.7, $J_{5,6}$ 6.9, $J_{5,7}$ 1.3).

General procedure C: oxidation of some 1,10-disubstituted 9,10-dihydrobenzo[*c*]naphthyridines

The required 1,10-disubstituted 9,10-dihydrobenzo[*c*]naphthyridine (5.0 mmol) in solution (solvent, 100 cm^3) with MnO_2

(8.7 g, 100 mmol) was refluxed during t h in a Dean–Stark apparatus. Cooling, filtration through Celite, drying ($MgSO_4$) and solvent removal afforded a crude product (white), which was purified by flash chromatography on silica (eluent).

1-Fluoro-10-(3-pyridyl)benzo[*c*][2,7]naphthyridine 24. The general procedure C applied to **9** using chloroform as solvent (t 20 h) gave the *title compound* (92%) (diethyl ether), mp 196 °C (Found: C, 74.3; H, 3.7; N, 15.5. $C_{17}H_{10}FN_3$ requires C, 74.2; H, 3.7; N, 15.3%); ν_{max}(KBr)/cm^{-1} 2924, 1612, 1552, 1414 and 1353; δ_H(200 MHz; $CDCl_3$) 7.46 (1 H, dd, 5'-H), 7.81 (1 H, dt, 6-H), 7.91–8.03 (2 H, m, 7-H + 4'-H), 8.28 (1 H, dd, 8-H), 8.40 (1 H, d, 4-H), 8.55 (1 H, d, 3-H), 8.58 (1 H, dd, 5-H), 8.76 (1 H, d, 6'-H) and 8.93 (1 H, s, 2'-H) ($J_{3,4}$ 5.7, $J_{5,6}$ 8.0, $J_{5,7}$ 1.2).

1-Chloro-10-phenylbenzo[*c*][2,7]naphthyridine 25. The general procedure C applied to **13** using chloroform as solvent (t 20 h) gave the *title compound* (85%) (diethyl ether–hexane, 6:4), mp 144–146 °C (Found: C, 74.5; H, 3.6; N, 9.8. $C_{18}H_{11}ClN_2$ requires C, 74.4; H, 3.8; N, 9.6%); ν_{max}(KBr)/cm^{-1} 1587, 1541, 1392 and 1324; δ_H(200 MHz; $CDCl_3$) 7.46–7.60 (5 H_{arom}, m), 7.74 (1 H, dt, 6-H), 7.89 (1 H, dt, 7-H), 8.25 (1 H, dd, 8-H), 8.41 (1 H, d, 4-H), 8.53 (1 H, dd, 5-H) and 8.58 (1 H, d, 3-H) ($J_{3,4}$ 5.6, $J_{5,6}$ 7.1, $J_{5,7}$ 1.2, $J_{6,8}$ 1.2).

1-Chloro-10-(3-pyridyl)benzo[*c*][2,7]naphthyridine 26. The general procedure C applied to **14** using chloroform as solvent (t 20 h) gave the *title compound* (92%) (diethyl ether), mp 181–183 °C (Found: C, 70.2; H, 3.6; N, 14.4. $C_{17}H_{10}ClN_3$ requires C, 70.0; H, 3.45; N, 14.4%); ν_{max}(KBr)/cm^{-1} 1593, 1541, 1414 and 1326; δ_H(200 MHz; $CDCl_3$) 7.47 (1 H, dd, 5'-H), 7.80 (1 H, dt, 6-H), 7.90–7.96 (2 H, m, 7-H + 4'-H), 8.26 (1 H, dd, 8-H), 8.47 (1 H, d, 4-H), 8.58 (1 H, dd, 5-H), 8.71 (1 H, d, 3-H), 8.75 (1 H, d, 6'-H) and 8.82 (1 H, s, 2'-H) ($J_{3,4}$ 5.8, $J_{5,6}$ 7.4, $J_{5,7}$ 1.2).

1-Chloro-10-(2-fluoro-4-iodo-3-pyridyl)benzo[*c*][2,7]naphthyridine 27. The general procedure C applied to **15** using chloroform as solvent (t 48 h) gave the *title compound* (84%) (diethyl ether–cyclohexane, 5:5), mp 171 °C (Found: C, 45.2; H, 1.9; N, 9.15. $C_{17}H_8ClFIN_3O$ requires C, 45.2; H, 1.8; N, 9.3%); ν_{max}(KBr)/cm^{-1} 2918, 1591, 1536, 1414 and 1315; δ_H(200 MHz; $CDCl_3$) 7.84 (1 H, d, 5'-H), 7.87 (1 H, dt, 6-H), 7.99 (1 H, dt, 7-H), 8.03 (1 H, d, 6-H), 8.29 (1 H, dd, 8-H), 8.51 (1 H, d, 4-H), 8.65 (1 H, dd, 5-H) and 8.74 (1 H, d, 3-H) ($J_{3,4}$ 5.7, $J_{5',6'}$ 5.2, $J_{5,6}$ 6.0, $J_{5,7}$ 1.2).

4-Chloro-3-(1-chlorobenzo[*c*][2,7]naphthyridin-1-yl)-*N*,*N*-diisopropylpyridine-2-carboxamide 28. The general procedure C applied to **18** using toluene as solvent (t 72 h) gave the *title compound* (61%) (diethyl ether), mp > 260 °C (Found: C, 63.75; H, 4.95; N, 12.55. $C_{24}H_{22}Cl_2N_4O$ requires C, 63.6; H, 4.9; N, 12.35%); ν_{max}(KBr)/cm^{-1} 3448, 2959, 2927, 1630, 1589, 1542, 1466 and 1334; δ_H(200 MHz; $CDCl_3$) 1.24–1.34 (12 H, m, 4CH_3), 3.37 (1 H, sept, CH), 4.10 (1 H, sept, CH), 7.47 (1 H, d, 5'-H), 7.80 (1 H, dt, 6-H), 7.90 (1 H, dt, 7-H), 8.15 (1 H, dd, 8-H), 8.42 (1 H, d, 4-H), 8.57–8.60 (2 H, m, 5-H + 6'-H) and 8.69 (1 H, d, 3-H) ($J_{3,4}$ 5.7, $J_{5',6'}$ 5.3, $J_{5,6}$ 7.9, $J_{5,7}$ 1.3).

10-Butyl *N*,*N*-diisopropylbenzo[*c*][2,7]naphthyridine-1-carboxamide 29. The general procedure C applied to **19** using chloroform as solvent (t 20 h) gave the *title compound* (89%) (diethyl ether), mp 196 °C (Found: C, 76.2; H, 8.0; N, 11.7. $C_{23}H_{29}N_3O$ requires C, 76.0; H, 8.05; N, 11.55%); ν_{max}(KBr)/cm^{-1} 3448, 2958, 1626, 1593, 1560 and 1474; δ_H(200 MHz; $CDCl_3$) 1.03 (3 H, t, CH_3), 1.20 (6 H, d, 2CH_3), 1.16–2.20 (6 H, m, 3CH_2), 1.71 (6 H, d, 2CH_3), 3.51 (1 H, sept, CH), 3.66 (1 H, sept, CH), 7.67 (1 H, dt, 6-H), 7.83 (1 H, dt, 7-H), 8.15 (1 H, dd, 8-H), 8.43 (1 H, d, 4-H), 8.52 (1 H, dd, 5-H) and 8.86 (1 H, d, 3-H) ($J_{3,4}$ 5.6, $J_{5,6}$ 8.0, $J_{5,7}$ 1.3, $J_{6,8}$ 1.3).

***N*,*N*-Diisopropyl-10-phenylbenzo[*c*][2,7]naphthyridine-1-carboxamide 30.** The general procedure C applied to **20** using chloroform as solvent (t 20 h) gave the *title compound* (90%) (diethyl ether), mp 236 °C (Found: C, 78.4; H, 6.4; N, 10.7. $C_{25}H_{25}N_3O$ requires C, 78.3; H, 6.6; N, 10.95%); ν_{max}(KBr)/cm^{-1} 2969, 2364, 1624, 1588, 1444, 1358 and 1318; δ_H(200 MHz; $CDCl_3$) 0.77 (3 H, d, CH_3), 1.16 (3 H, d, CH_3), 1.27 (3 H, d, CH_3), 1.38 (3 H, d, CH_3), 3.27 (1 H, sept, CH), 3.85 (1 H, sept, CH), 7.46 (5 H_{arom}, m), 7.73 (1 H, dt, 6-H), 7.86 (1 H, dt, 7-H), 8.24 (1 H, dd, 8-H), 8.46 (1 H, d, 4-H), 8.58 (1 H, dd, 5-H) and 8.87 (1 H, d, 3-H) ($J_{3,4}$ 5.6, $J_{5,6}$ 8.2, $J_{7,8}$ 8.0, $J_{5,7}$ 1.35, $J_{6,8}$ 1.35).

***N*,*N*-Diisopropyl-10-(3-methoxyphenyl)benzo[*c*][2,7]naphthyridine-1-carboxamide 31.** The general procedure C applied to **21** using aerial oxidation without solvent (t 30 days) gave the *title compound* (95%) (diethyl ether), mp 178 °C (Found: C, 75.7; H, 6.8; N, 10.2. $C_{26}H_{27}N_3O_2$ requires C, 75.5; H, 6.6; N, 10.2%); ν_{max}(KBr)/cm^{-1} 2924, 1629, 1588, 1466 and 1315; δ_H(200 MHz; $CDCl_3$) 0.86 (3 H, d, CH_3), 1.12 (3 H, d, CH_3), 1.25 (3 H, d, CH_3), 1.39 (3 H, d, CH_3), 3.29 (1 H, sept, CH), 3.79 (1 H, m, CH), 3.89 (3 H, s, OCH_3), 7.01–7.55 (4 H_{phenyl}, m), 7.73 (1 H, t, 6-H), 7.87 (1 H, t, 7-H), 8.24 (1 H, d, 8-H), 8.45 (1 H, d, 4-H), 8.59 (1 H, d, 5-H) and 8.87 (1 H, d, 3-H) ($J_{3,4}$ 5.6, $J_{5,6}$ 8.4, J_{CH,CH_3} 6.8).

***N*,*N*-Diisopropyl-10-(3-pyridyl)benzo[*c*][2,7]naphthyridine-1-carboxamide 32.** The general procedure C applied to **22** using chloroform as solvent (t 20 h) gave the *title compound* (87%) (diethyl ether), mp 202–203 °C (Found: C, 74.75; H, 6.15; N, 14.4. $C_{24}H_{24}N_4O$ requires C, 75.0; H, 6.3; N, 14.6%); ν_{max}(KBr)/cm^{-1} 2992, 2850, 1621, 1586, 1458, 1367 and 1318; δ_H(200 MHz; $CDCl_3$) 0.79 (3 H, d, CH_3), 1.21–1.44 (9 H, m, CH_3), 3.32 (1 H, sept, CH), 3.97 (1 H, sept, CH), 7.50 (1 H, m, 5'-H), 7.79 (1 H, td, 6-H), 7.90 (1 H, td, 7-H), 8.18 (1 H, m, 4'-H), 8.23 (1 H, dd, 8-H), 8.49 (1 H, d, 4-H), 8.62 (1 H, dd, 5-H), 8.70 (2 H, m, 2'-H + 6'-H) and 8.90 (1 H, d, 3-H) ($J_{3,4}$ 5.7, $J_{5,6}$ 8.0, $J_{5,7}$ 1.4, J_{CH,CH_3} 6.6).

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