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Synthesis of naphthopyrrolo[3,4-*c*]carbazoles

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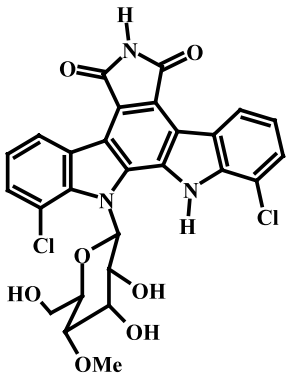
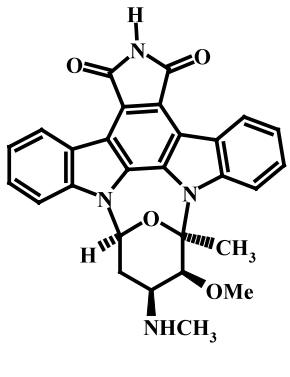
Abstract—New naphthocarbazoles **1** were built from protected 3-(3-indolyl)-4-bromo-*N*-methylmaleimide in four steps using palladium-catalysed cross-coupling reactions such as Suzuki reaction of 3-methoxy-2-boronic acid and Heck cyclisation of triflate.

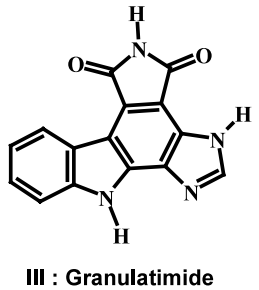
Indolocarbazoles represent an important class of anti-tumour antibiotics.[1,2] Rebeccamycin **I** weak inhibitor of topoisomerase **I** and staurosporin **II** a non-specific protein kinase C (PKC) inhibitor are the most representative compounds of this family. Recently it has been reported than extracts of Brazilian ascidian '*Didemnum granulatum*' showed strong activity as G_2 checkpoint inhibitors in the cell cycle due to the presence of two compounds granulatimide **III** and isogranulatimide **IV** (Fig. 1).[3,4]



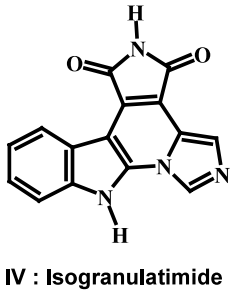
I : Rebeccamycin



II : Staurosporine



III : Granulatimide



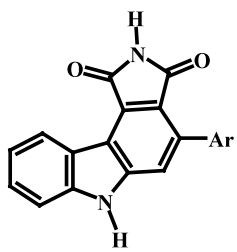
IV : Isogranulatimide

Figure 1.

These compounds, even if they lack the second indole unit which is replaced by an imidazole moiety, are potential candidates for cancer treatment. Numerous potent aryl and heteroarylpyrrolocarbazoles of type **V** have also been described (Fig. 2).[5]

Common methods to construct symmetric or non-symmetric bisindolylmaleimides employed indolyl Grignard reagents in reaction with dibromomaleimides.[6–8]

Direct formation of the maleimide framework through reaction of indole-3-acetimidate[9] or by oxidative coupling of indolyl acetate dianion[10,11] have been used. Generation of the second indole moiety via nitrene insertion,[12,13] use of 2,2′-bisindole and diazolactam[14] or dimethyl acetylene dicarboxylate[15] were also tested as alternative approaches to indolocarbazoles. By contrast the use of palladium-catalysed cross-coupling reactions in the construction of indolocarbazoles is scarcely



V

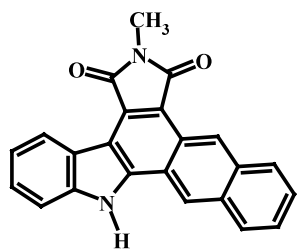


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Figure 2.

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described;[5] Suzuki reaction of triflate derivative with 3-indoleboronic acid has been reported.[16]

The huge synthetic effort developed in this area prompted us to report our own work about new series of related derivatives **1** lacking an indolo group but containing a naphtho group. The well-known indole/naphthalene bioisostery,[17] and the exploration of the DNA intercalative binding properties[18] prompted us to replace the indole by a naphthalene group.

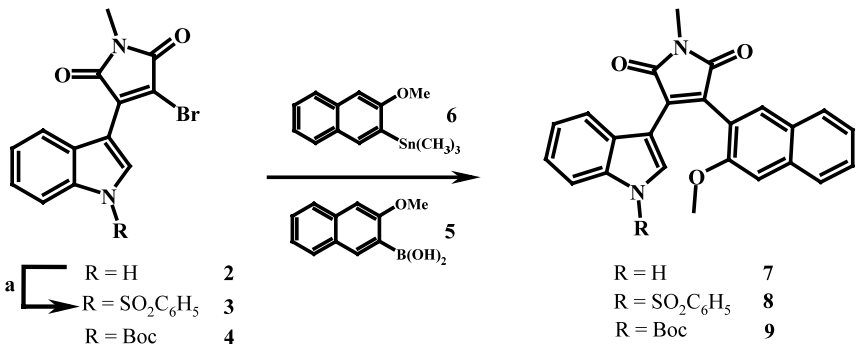
For the first time, introduction of the naphthalene group on compounds **2**, **3** and **4** was carried out using the 3-methoxynaphthalene-2-boronic acid **5** or 3-methoxy-2-trimethylstannyl naphthalene **6** (Scheme 1). These compounds were obtained by regioselective lithiation of 2-methoxynaphthalene using *n*-BuLi[19] followed by addition of the appropriate electrophile. Thus trimethylborate afforded compound **5** in 78% yield after hydrolysis and trimethylstannylchloride gave compound **6** in 95% yield.

Optimisation of the cross-coupling reaction was performed on **2**[20] with the stannyl derivative **6** in dioxane using $Pd(PPh_3)_4$ as catalyst and CuI or LiCl as additives (Table 1). Addition of CuI gave a poor yield of **7** (10%) even by changing the solvent and the amount of **6**. LiCl instead of CuI increased the yield from 10 to 53%. The same behaviour (entries 3 and 5 compared to entries 8 and 9) was observed with the Boc derivative **4**.[20] Use of $Pd_2(dba)_3$ as catalyst and triphenylarsine did not improve the yield of the coupling reaction despite the increase of the amount of catalyst (entry 6).

Boronic acid **5** gave better results than the stannyl derivative **6** in the cross-coupling reaction. Suzuki reaction was performed by heating for 12 h the boronic acid **5** (1.5 equiv.), compounds **2**, or **4** and palladium acetate (10%) at 100°C in dioxane in the presence of triphenylphosphine (20%) and potassium carbonate (2 equiv.). The non-similar behaviour of compounds **3** and **4** could be explained by the cleavage of the Boc protective group observed in all cases. This reaction was inhibited by this cleavage (entries 5 and 9; yields 54 or 55% for **7**). The benzenesulfonyl protective group was not affected by conditions of the reaction. The coupling reaction of **5** with compound **3** was more efficient (2 h compared to 12 h) and the yield for **8** was up to 80% (entry 7).

Deprotection of the hydroxy group was performed with BBr_3 in dichloromethane either on **7** or **8** (Scheme 2). The hydroxy derivatives **10** and **11** were obtained in 72 and 98% yield, respectively. These compounds were then converted into triflates **12** and **13**, respectively, in 88 and 98% yield by reaction with triflic anhydride in the presence of triethylamine at room temperature for 3 h. Treatment of **12** with Boc_2O in THF at room temperature gave **14** in 81% yield.

The final key-step of the synthesis was the cyclisation of **12**–**14** into **1**. Numerous methods to perform this reaction have been reported for indolocarbazoles with limitations.[21] Recently, intramolecular cyclisation of bisindole maleimides was performed using phenyliodine(III)diacetate (PIFA), but this approach was unsuccessful with a naphthalene group.[22]

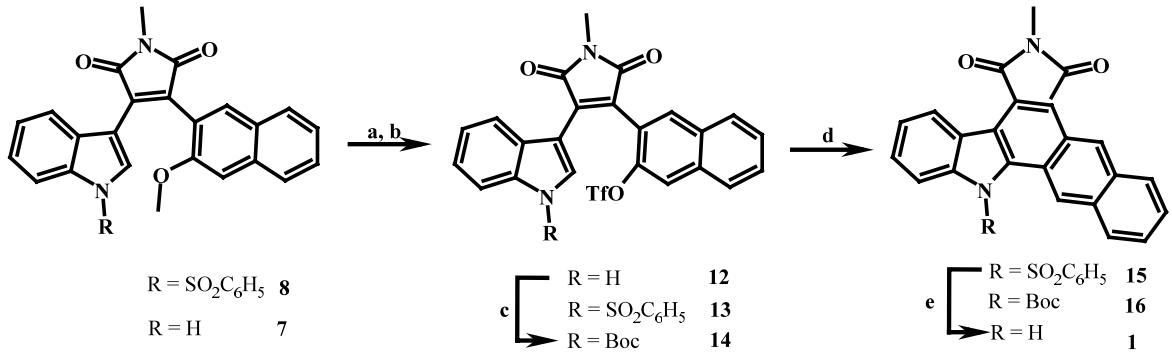


Scheme 1. *Reagents and conditions*: (a) $C_6H_5SO_2Cl$, NaH, THF, 0°C then rt, 80%.

Table 1. Stille and Suzuki cross-coupling reactions of derivatives **2**–**4**

Entry	Reactant (equiv.)	Coupling agent	Conditions[a]	Product (yield %)
1	**2** (1.3)	**6**	$Pd(PPh_3)_4$ 10%, CuI 20%, dioxane, 12 h	**7** (10)
2	**2** (1.3)	**6**	$Pd(PPh_3)_4$ 10%, CuI 20%, DMF, 12 h	**7** (10)
3	**2** (2.0)	**6**	$Pd(PPh_3)_4$, 10%, CuI 20%, DMF, 12 h	**7** (10)
4	**2** (1.3)	**6**	$Pd(PPh_3)_4$ 10%, LiCl (3 equiv.), dioxane, 12 h	**7** (53)
5	**2** (1.5)	**5**	$Pd(OAc)_2$ 10%, PPh_3 20%, K_2CO_3, 100°C, dioxane/water, 12 h	**7** (55)
6	**2** (1.3)	**6**	$Pd_2(dba)_3$ 30%, $AsPh_3$ 40%, LiCl (3 equiv.), K_2CO_3, dioxane/water, 24 h	**7** (56)
7	**3** (1.5)	**5**	$Pd(OAc)_2$ 10%, PPh_3 20%, K_2CO_3, dioxane/water, 2 h	**8** (80)
8	**4** (1.3)	**6**	$Pd(PPh_3)_4$ 10%, CuI 20%, dioxane, 10 h	**9** (12)
9	**4** (1.5)	**5**	$Pd(OAc)_2$ 10%, PPh_3 20%, K_2CO_3, dioxane/water, 12 h	**7** (54)

[a] Reactions at 100°C.



Scheme 2. *Reagents and conditions*: (a) BBr_3 (6 equiv.), CH_2Cl_2, 0°C to rt, 1 h; (b) Tf_2O (3 equiv.), NEt_3 (3.1 equiv.), THF, 0°C to rt, 3 h; (c) Boc_2O (2 equiv.), THF, rt, 3 h, 81%; (d) see Table 2; (e) TBAF, THF, reflux, 2 h.

Table 2. Intramolecular cyclisation

Entry	Compound	Solvent	Time (h)	*T* (°C)	$Pd(OAc)_2$ (%)	Yield of **15** or **16** (%)	Yield of **1** (%)
1	**12**	DMA	12	100	10	–	40
2	**14**	Dioxane	7	100	10	20	10
3	**13**	Dioxane	16	100	10	10	51
4	**13**	Dioxane	72	100	30	–	63
5	**13**	Dioxane	3	100	100	–	91[a]

[a] After TBAF treatment.

Attempts for this cyclisation via a Heck reaction are summarised in Table 2. This reaction was performed using $Pd(OAc)_2$ as catalyst, NaOAc as base (2 equiv.) and Bu_4NCl (1 equiv.) as transfer agent. The lack of protective group on the nitrogen atom stopped the coupling reaction as described for Stille or Suzuki reactions. The phenylsulfonyl group which partially survive the experimental conditions afforded a mixture of cyclised compounds **15** and **1** (entry 3). Increasing the amount of palladium acetate, decreases reaction time (entries 4 and 5) and so gave a higher yield of the required cyclised derivative **15**, which was then converted into **1** by TBAF treatment.

This result indicated a non-catalytic reaction such as described when indolocarbazoles were built using a large excess of catalyst to perform the final intramolecular cyclisation.[21,23] Treatment of compound **13** with 1 equiv. of palladium acetate for 2 h in dioxane followed by a treatment of the crude product by TBAF for 3 h, afforded exclusively compound **1**[24] in 91% global yield.

In this paper we have described a straightforward and efficient preparation of a new naphthocarbazole. The reactivity of both the maleimide moiety and the free nitrogen atom are under progress.

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23. Ohkubo, M.; Nishimura, T.; Jona, H.; Honma, T.; Ito, S.; Morishima, H. *Tetrahedron* **1997**, *53*, 5937–5950.
24. *Synthesis of **1***: A solution containing compound **13** (1 g, 1.56 mmol), Bu_4NCl (433 mg, 1.56 mmol), NaOAc (256 mg, 3.12 mmol) and triphenylphosphine (818 mg, 3.12 mmol), $Pd(OAc)_2$ (350 mg, 1.56 mmol) in dry dioxane (10 mL) was heated to 90°C. After 3 h, CH_2Cl_2 (100 mL) was added and the solution was filtered off. The organic layers were washed with water, dried with Na_2SO_4 and the solvents were removed under reduced pressure. Dry THF (30 mL) was then added to the crude residue and a solution of Bu_4NF in THF (2 mL, 2 mmol, 1 M) was added. The solution was heated to reflux for 1 h. After addition of water (30 mL) and extraction with CH_2Cl_2 (150 mL), the organic layers were washed with brine (50 mL), dried under Na_2SO_4, filtered and the solvents were removed under reduced pressure. Product **1** was precipitated using EtOAc, filtered, washed with EtOAc and dried (457 mg, 91%): mp 250°C (dec.); IR (KBr, cm^{-1}) ν 1381, 1443, 1680, 1748, 2925, 3052, 3552 (NH). ^1H NMR (DMSO-d_6) δ 3.00 (s, 3H), 7.34 (t, 1H, $J=10$ Hz), 7.62 (t, 1H, $J=7.5$ Hz), 7.57–7.68 (m, 3H), 8.04 (d, 1H, $J=7.5$ Hz), 8.13 (d, 1H, $J=10$ Hz), 8.78 (d, 1H, $J=10$ Hz), 9.08 (s, 1H), 9.36 (s, 1H), 13.01 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 25.7 (CH_3), 110.2 (Cq), 112.6 (CH), 118.8 (Cq), 121.7 (CH), 121.8 (Cq), 112.2 (CH), 122.5 (Cq), 124.3 (CH), 124.9 (CH), 126.5 (CH), 127.5 (CH), 127.8 (CH), 128.9 (CH), 129.5 (Cq), 132.1 (CH), 132.4 (Cq), 132.6 (Cq), 140.0 (Cq), 140.8 (Cq), 169.9 (Cq), 170.8 (Cq). MS (IS) 351 $(M+H)^+$.