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# A versatile new synthesis of 4-aryl- and heteroaryl-[3,4-*c*]pyrrolocarbazoles by [4+2] cycloaddition followed by palladium catalysed cross coupling

Gary McCort,* Olivier Duclos, Caroline Cadilhac and Eric Guilpain

*Department of Medicinal Chemistry, Cardiovascular Research, Synthélabo Recherche, 1 Avenue Pierre Brossolette, 91385 Chilly-Mazarin Cedex, France*

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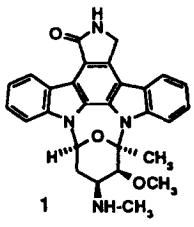
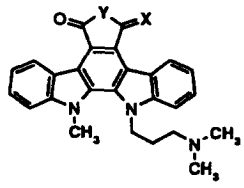
**Abstract**

4-Bromo- and 4-trifluorosulfonyloxypyrrolo[3,4-*c*]carbazoles were prepared in five steps via a [4+2] cycloaddition and were used as key intermediates in palladium-catalysed cross coupling reactions allowing the rapid generation of structurally diverse protein kinase C inhibitors. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Protein phosphorylation is one of the most fundamental mechanisms by which second messengers act to regulate a variety of cellular processes. Protein kinase C (PKC), is of particular interest due to its involvement in cell differentiation, proliferation, secretory processes and gene expression[1–4] and is an actively exploited target for the treatment of diseases such as cancer, inflammatory arthritis, asthma and viral infection.[5] Several natural products such as staurosporine **1**[6] are non-specific PKC inhibitors and much work has been undertaken to induce specificity and reduce structural complexity. Several laboratories have developed indolocarbazole **2**[7,8] and bisindolylmaleimide **3**[9,10] derivatives. More recently, potent aryl- and heteroaryl-pyrrolocarbazole derivatives **4** and **5** have been obtained.[11,12]



**1**



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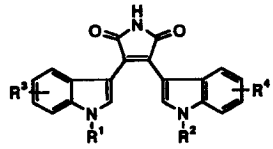

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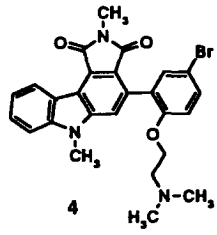
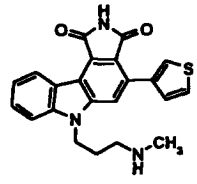


**4**



**5**

* Corresponding author. Fax: 33 (1) 69 79 79 36; e-mail: gmccort@chilly.synthelabo.fr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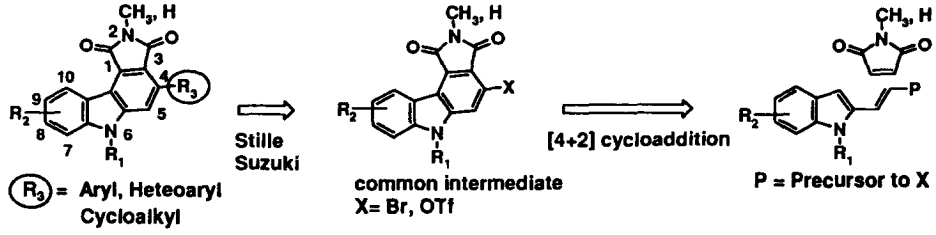
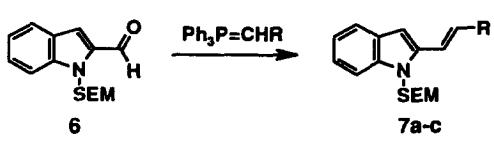
Analogues of **4** and **5** have been previously synthesised by a route involving a Wittig reaction between a phosphonium salt of the indole component and an aromatic aldehyde, forming an aryl-vinylindole. A Diels–Alder reaction between each 2-vinylindole and maleimide forms the compounds **4** and **5**. Although efficient, this approach suffers from the lack of a common intermediate permitting synthetic divergence. To avoid this limitation, we investigated the possibility of preparing a common pyrrolocarbazole intermediate by a [4+2] cycloaddition, adequately functionalised for divergent palladium catalysed cross couplings.



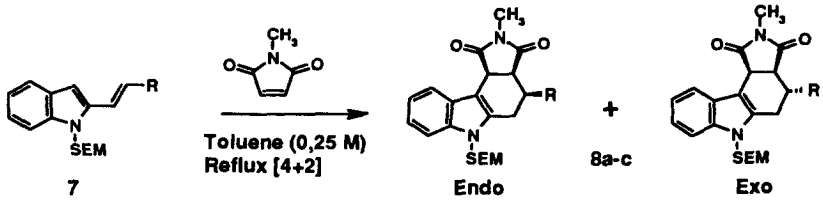

*N*-2-((Trimethylsilyl)ethoxymethyl)indole-2-carboxaldehyde **6** smoothly underwent Wittig reactions with carbomethoxymethylene- and acetylmethylenetriphenyl-phosphoranes, to give the corresponding α,β-unsaturated esters and methyl ketone in quantitative yield with complete *E* stereoselectivity (Scheme 1).




| | R | Solvant ; T |
|---|---|---|
| **7a** | $CO_2Me$ | $CH_2Cl_2$ ; 20°C |
| **7b** | $CO_2Bn$ | $CH_2Cl_2$ ; 20°C |
| **7c** | COMe | Toluene ; 80°C |

Scheme 1.

[4+2] Cycloaddition of the dienes **7a**, **7b** and **7c** with *N*-methylmaleimide in refluxing toluene gave the corresponding cycloadducts **8a–c** in high yield. The inverse *exo* stereoselectivity for ketone **8c** is in agreement with previously reported mechanistic studies (Scheme 2).[13]



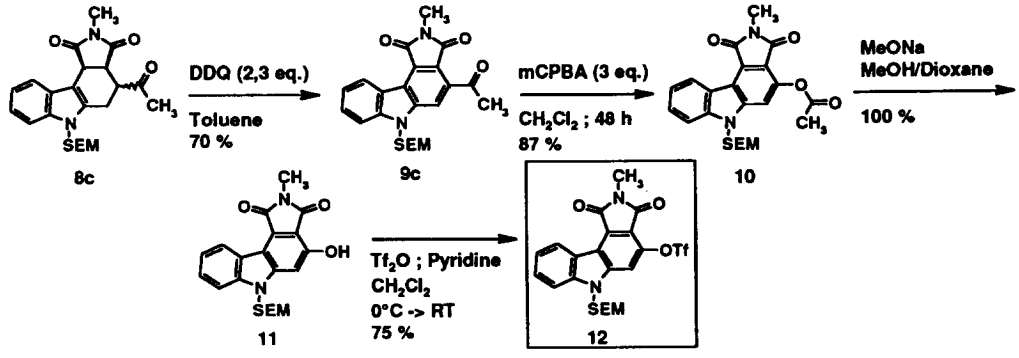

| | R | T | Endo/exo [a] | Yield [b] |
|---|---|---|---|---|
| **8a** | $CO_2Me$ | 72 h | > 95 / 5 | 91 % |
| **8b** | $CO_2Bn$ | 72 h | > 95 / 5 | 88 % |
| **8c** | COMe | 96 h | 15 / 85 | 85 % |

a) determined by $^1H$ NMR
b) after purification by flash-chromatography

Scheme 2.

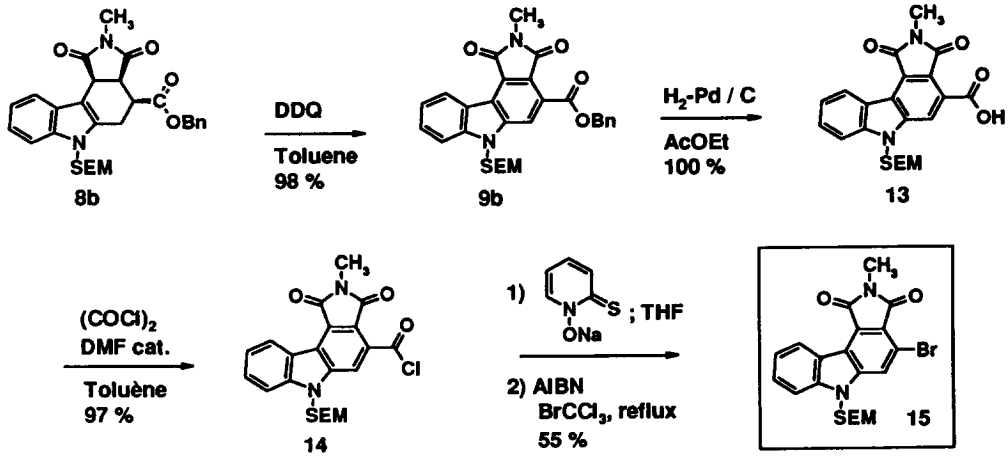
The methyl ketone derivative **8c** was aromatised to the pyrrolocarbazole **9c** with DDQ in 70% yield. After Baeyer–Villiger rearrangement using *m*CPBA, the acetyloxypyrrolocarbazole **10** was obtained in

87% yield. The acetoxy group was then cleaved by sodium methoxide and the phenol **11** was transformed into the triflate **12**, ready for palladium-mediated cross-coupling reactions (Scheme 3).

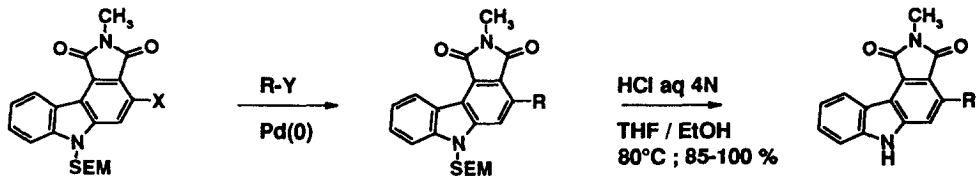


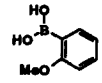
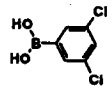
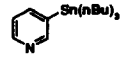
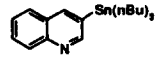

Scheme 3.

Although both the ester adducts **8a** and **8b**, could be aromatised, it proved difficult to saponify the methyl ester without opening the strained maleimide ring. Thus the benzyl ester **8b** was aromatised with DDQ in excellent yield to give **9b** and was then debenzylated by catalytic hydrogenation affording the 4-carboxypyrrolocarbazole **13**. The carboxylic acid was then transformed into the acid chloride **14** which was condensed with the sodium salt of 2-mercaptopyridine *N*-oxide and the thiohydramic ester intermediate was submitted to a Barton radical decarboxylative bromination reaction in presence of 2,2-azabisisobutyronitrile in boiling bromotrichloromethane. The 4-bromopyrrolocarbazole **15** was now ready to undergo cross-coupling reactions.

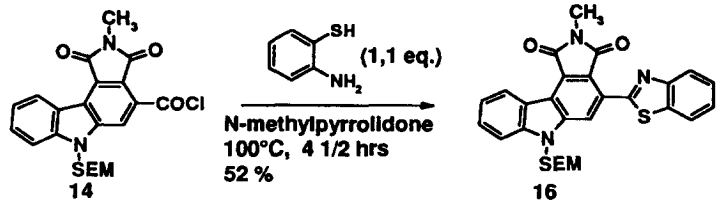



The following are examples of the scope and application of the cross-coupling reactions that can be carried out. Triflate **12** was cross-coupled by a Suzuki reaction with *ortho*-methoxybenzeneboronic acid and 3-thiophene boronic acid, catalysed by $Pd(PPh_3)_4$ with 95% and 88% yields, respectively. The bromo derivative **15** was cross-coupled with the 2,5-dichlorobenzene boronic acid under standard Suzuki conditions in 76% yield. Compound **15** also underwent smooth Stille reactions with 3-(tributylstannyl)pyridine and 3-(tributylstannyl)quinoline by the presence of $Pd(PPh_3)_4$ and CuI with 73 and 67% yields, respectively. The SEM protecting group could be removed from all compounds in high yield by heating at 80°C in THF/EtOH/HCl 4N.




| X | R-Y | Conditions | Time | Yield |
|---|---|---|---|---|
| -OTf |  | $Pd(PPh_3)_4$ Toluene / EtOH aq. $NaHCO_3$, reflux | 4 hrs | 95 % |
| -OTf |  | $Pd(PPh_3)_4$ Toluene / EtOH aq. $NaHCO_3$, reflux | 4 hrs | 88 % |
| -Br |  | $Pd(PPh_3)_4$ Toluene / EtOH aq. $NaHCO_3$ reflux | 3 hrs | 76 % |
| -Br |  | $Pd(PPh_3)_4$ CuI, dioxane, reflux | 15 hrs | 73 % |
| -Br |  | $Pd(PPh_3)_4$ CuI, dioxane, reflux | 48 hrs | 67 % |

It is also of interest that the acid chloride intermediate **14** can itself serve as a platform for heterocyclisation, leading the way towards further structural diversity.




**14** **16**

With the objective of further expanding the scope and application of our approach, we are currently investigating the use of other dienophiles in the Diels–Alder reaction allowing the modulation of the maleimide moiety, as well as other cross-coupling nucleophiles.

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