Tetrahedron Letters, Vol. 34, No. 51, pp. 8361-8364, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

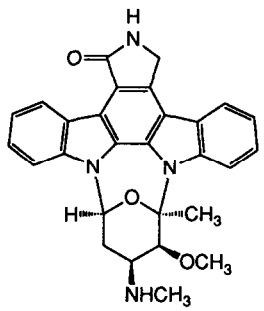
Oxidative Cyclisations with Palladium Acetate. A Short Synthesis of Staurosporine Aglycone.

William Harris, Christopher H. Hill*, Elizabeth Keech and Patrick Malsher.

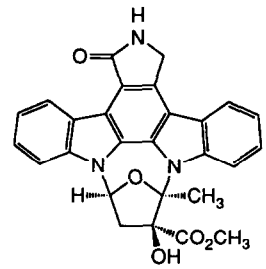
Roche Products Ltd., Research Centre, Broadwater Road, Welwyn Garden City, Herts., AL7 3AY, U.K.

Abstract: A palladium acetate mediated oxidative cyclisation has been used as the key step for the syntheses of staurosporine aglycone and related analogues.

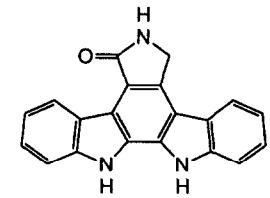
The microbial metabolites staurosporine (**1**)[1] and K252a (**2**)[2] have both been reported as inhibitors of protein kinase C. This family of isoenzymes is believed to control a wide range of physiological processes including cell growth and proliferation.[3] Since the common aglycone portion of these compounds is known to retain much of the activity of the parents[4] we set out to identify the structural elements of **3** required for the inhibition of protein kinase C. Initially we required a route to the indolo[2,3-a]pyrrolo[3,4-c]carbazole ring system which was shorter and potentially more flexible than those already published.[5,6]



1

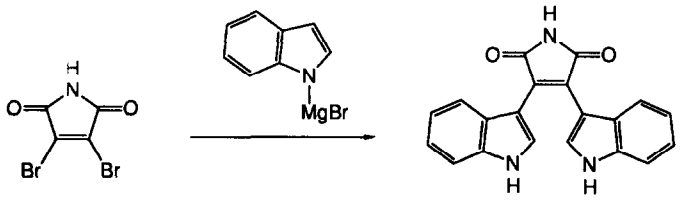


2



3

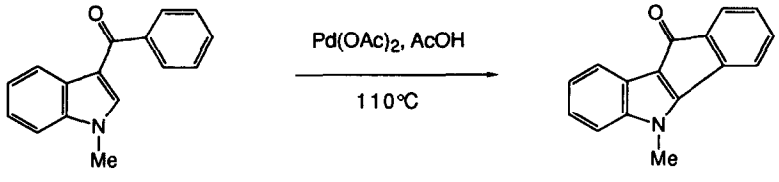
We believed that the most attractive approach to the aglycone would be *via* the bisindolylmaleimide, arcyriarubin A (**4**),[7] which would require only an oxidative cyclisation followed by a reduction to afford the desired lactam **3**. A three step synthesis of arcyriarubin A has been reported by reaction of indolylmagnesium bromide with an N-protected dibromomaleimide,[8] however, we have found it more convenient to avoid protection of the imide nitrogen whilst retaining satisfactory yields in the reaction. Hence, dibromomaleimide was treated directly with four equivalents of indolylmagnesium bromide in benzene at reflux for 18h to afford a 29% yield of **4**[9] as an orange solid, in a single step.



4

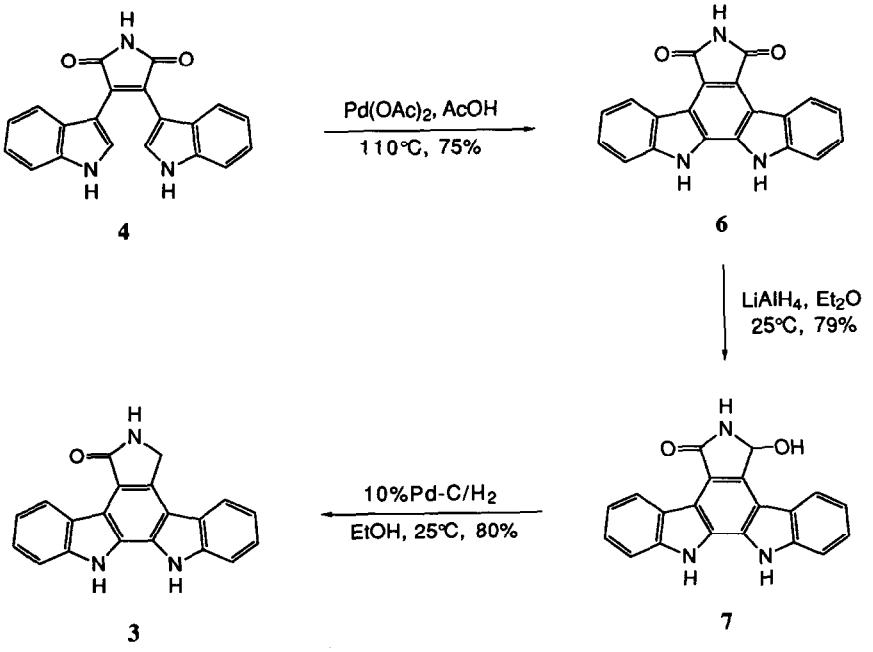
Oxidative cyclisation of bisindolylmaleimides has been achieved with pTSA/DDQ,[6] however, in our hands the product has proved difficult to isolate. We therefore wished to investigate alternative methods.

The direct oxidative cyclisation of diphenyl ethers and diphenylamines is known to proceed readily with palladium acetate to afford the corresponding dibenzofurans and carbazoles.[10] Furthermore, Itahara has reported that palladium acetate successfully promotes the dimerisation of electron deficient pyrroles to afford the corresponding 2,2'-bipyrroles[11] and it also cyclises 3-benzoyl-1-methylindole to 5-methyl-5,10-dihydroindeno[1,2-b]indol-10-one (**5**) in 60% yield.[12]



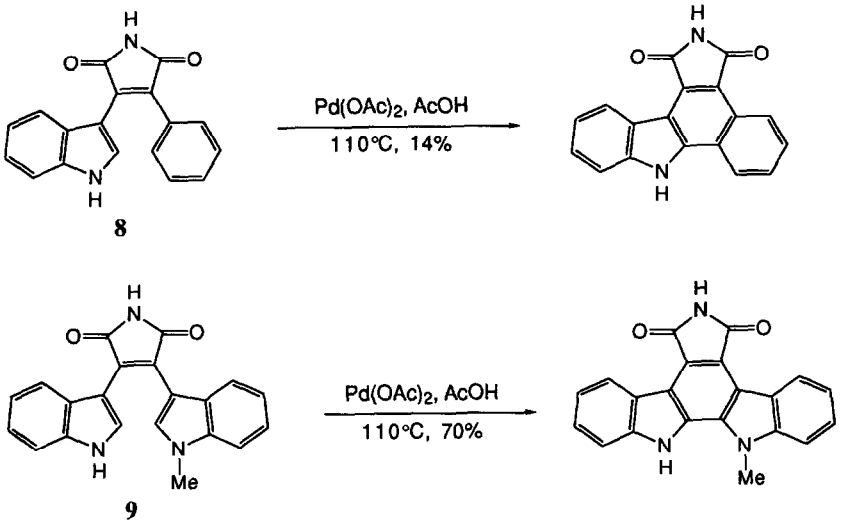
5

Although most of the literature on such oxidative cyclisations reports the formation of a new five membered ring, we were sufficiently encouraged to attempt a palladium mediated cyclisation to construct the central six membered ring of the indolo[2,3-a]carbazole system. Indeed, treatment of arcyriarubin A with one equivalent of palladium acetate in acetic acid at reflux for 18h gave the desired product **6** in 75% yield. Reduction of the imide to the hydroxylactam **7** with lithium aluminium hydride in THF, followed by hydrogenolysis afforded the aglycone **3** in 14% overall yield over four steps from dibromomaleimide. We next examined the cyclisation of other indolylarylmaleimides, since these are now readily available from the corresponding indoles and arylacetonitriles.[13]



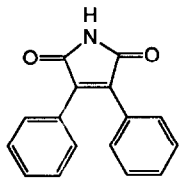
4 6 7 3

It was gratifying to find that palladium acetate was also the method of choice for the oxidative cyclisation of imides **8**[14] and **9**[13]. Indeed, whilst no reaction was observed when 3-indolyl-4 -phenylmaleimide (**8**) was subjected to an oxidative procedure using DDQ as oxidant[6] palladium acetate did effect the oxidative cyclisation, albeit in modest yield.

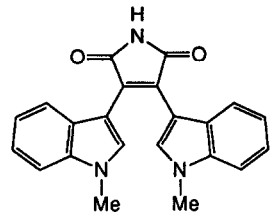


8 9

The reaction was not successful, however, for the cyclisation of diphenylmaleimide (**10**) or imide **11**. The lack of reactivity of the former is consistent with the observation that benzophenone does not undergo cyclisation under the conditions used to cyclise 3-benzoyl-1-methylindole.[11] Presumably, the extra methyl group in **11** precludes cyclisation on steric grounds.



10



11

In conclusion, palladium acetate is a powerful reagent for oxidative cyclisations of indolylarylmaleimides to the corresponding substituted carbazoles[15] and has proved successful for substrates which would not react under alternative conditions. This methodology , when coupled to the novel synthesis of substituted maleimides, should allow rapid access to a large range of analogues of staurosporine aglycone. The protein kinase inhibitory activities of these compounds will be reported elsewhere.

References and Notes:

1. Tamaoki, T.; Nomoto, H.; Takahishi, I.; Kato, Y.; Morimoto, M.; Tomita, F. *Biochem. Biophys. Res. Commun.* **1986**, *135*, 397.
2. Kase, H.; Iwahashi, K.; Matsuda, Y. *J. Antibiotics* **1986**, *39*, 1059.
3. Nishizuka, Y. *Nature* **1984**, *308*, 693.
4. Nakanishi, S.; Matsuda, Y.; Iwahashi, K.; Kase, H. *J. Antibiotics* **1986**, *39*, 1066.
5. Sarstedt, B.; Winterfeldt, E. *Heterocycles* **1983**, *20*, 469; Magnus, P. D.; Sear, N. L. *Tetrahedron* **1984**, *40*, 2795; Kaneko,T.; Wong, H.; Okamoto, K. T.; Clardy, J. *Tetrahedron Lett.* **1985**, *26*, 4015; Bergman, J.; Pelcman, B. *J. Org. Chem.* **1989**, *54*, 824; Hughes, I.; Nolan, W. P.; Raphael, R. A. *J. Chem. Soc. Perkin Trans. I* **1990**, 2475; Gribble, G. W.; Berthel, S. J. *Tetrahedron* **1992**, *48*, 8869; Moody, C. J.; Rahimtoola, K. F.; Porter, B.; Ross, B. C. *J. Org. Chem.* **1992**, *57*, 2105.
6. Joyce, R. P.; Gainor, J. A.; Weinreb, S. M. *J. Org. Chem.* **1987**, *52*, 1177.
7. Gill, M.; Steglich, W. *Progr. Chem. Org. Nat. Prod.* **1987**, *51*, 216.
8. Brenner, M.; Rexhausen, H.; Steffan, B.; Steglich, W. *Tetrahedron* **1988**, *44*, 2887.
9. All compounds had satisfactory microanalytical and spectral data.
10. Akermark, B.; Eberson, L.; Jonsson, E.; Pettersson, E. *J. Org. Chem.* **1975**, *40*, 1365.
11. Itahara, T. *J. Chem. Soc. Chem. Commun.* **1980**, 49.
12. Itahara, T.; Sakakibara, T. *Synthesis* **1978**, 607.
13. Bit, R. A.; Crackett, P. H.; Harris, W.; Hill, C. H. *Tetrahedron Lett.* **1993**, in press.
14. Prepared from phenylsuccinimide by treament with (i) Br_2, 120°C; (ii) NH_4OAc, 200°C; (iii) indolylmagnesium bromide, C_6H_6, reflux.
15. Typical work-up requires removal of metallic palladium by filtration, concentration of the filtrate and flash-chromatography of the residue.

(Received in UK 22 September 1993; accepted 15 October 1993)