Recent Developments in the Synthesis of Biologically Active Indole Alkaloids

A. M. Lobo* and S. Prabhakar¥

Departamento de Química, Centro de Química Fina e Biotecnologia, Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, 2825-114 Monte de Caparica, Portugal

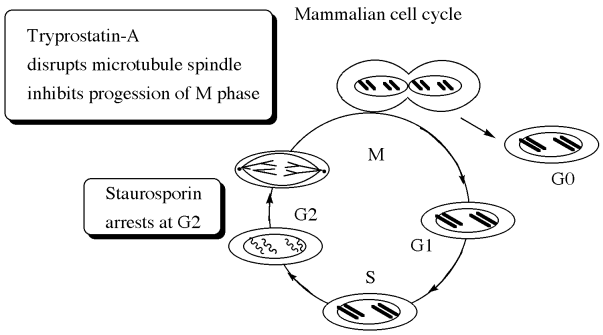
J. Heterocyclic Chem., **39**, 429 (2002).

Cell cycle is a strictly regulated process by which the cells complete the division into daughter cells [1]. It now appears that a universal control mechanism, common to all eukariotic cells, exists and that cellular factors play a crucial function in cell cycle [2]. Molecules that interfere with this process can have far reaching consequences in the control of diseases such as cancer.

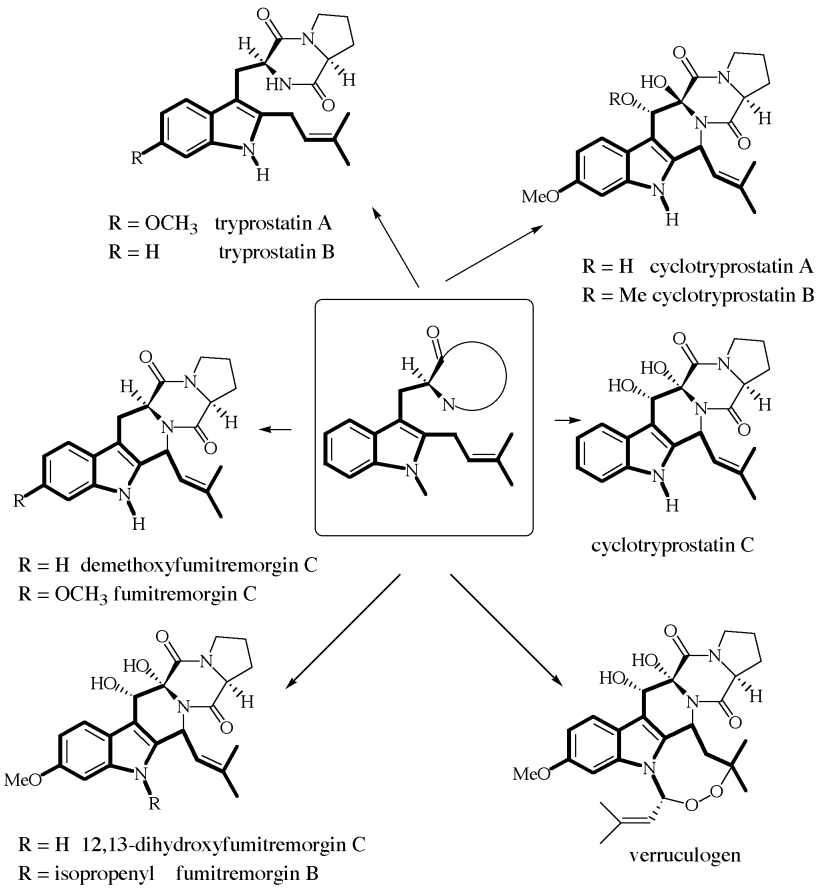
Several alkaloids have been found to interfere with cell division (Scheme 1), notable among them are the G2/M mammalian cell cycle inhibitors such as the tryprostatins [3] and related cyclotryprostratins [4], and the protein kinase C inhibitors, as exemplified by the indolo[2,3-*a*]-pyrrolo[3,4-*c*]carbazole alkaloid staurosporin [5].

We present in this lecture studies directed towards the synthesis of these types of molecules.

Scheme 1



Scheme 2



Tryprostatins.

Tryprostatins, cyclotryprostatins and related alkaloids (Scheme 2) are indole derived compounds which can be biosynthetically interrelated, in as much as they all have the 2-prenyl tryptophane skeleton fused to a diketopiperazine system [4].

In view of their very interesting properties, the tryprostatins have been the focus of recent synthetic efforts by several groups [6,7].

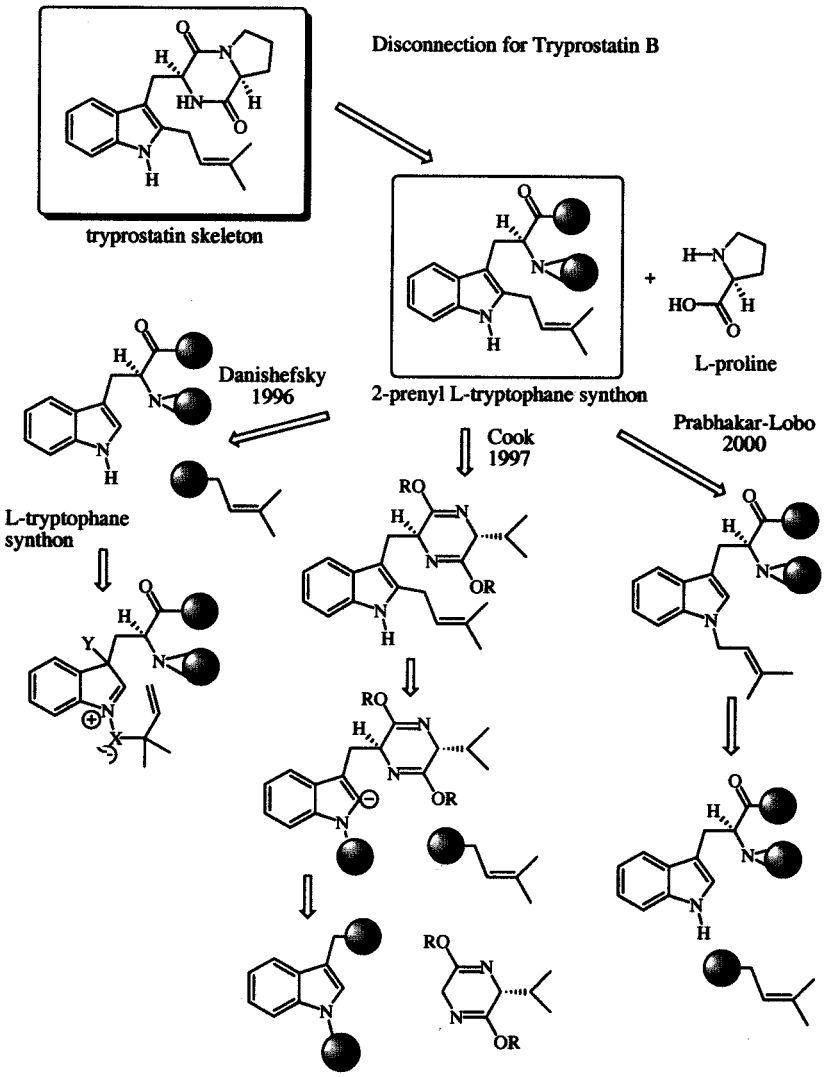
The disconnection processes for the various syntheses of the tryprostatin skeleton are summarized in Scheme 3. While Cook's group [7] used a 2-lithio indole, in a Schöllkopf derived intermediate, to introduce the isoprenoid chain at the indole C-2 position of the L-tryptophane synthon, Danishefsky [6] devised a 3,3-sigmatropic rearrangement of a charged indolenine species, bearing an inverted prenyl group linked to the indole nitrogen, to obtain the same synthon.

In spite of its elegance and high yield, the nature of the reagents and conditions employed in the latter approach (use of prenyl stannane at -78 °C) prompted us to seek an alternative, simpler procedure for the introduction of the C-2 substituent in the tryptophane molecule. Crucial to our approach is a N-1 to C-2 shift of the dimethylallyl group in an appropriately substituted tryptophane derivative (cf. Scheme 3) [8].

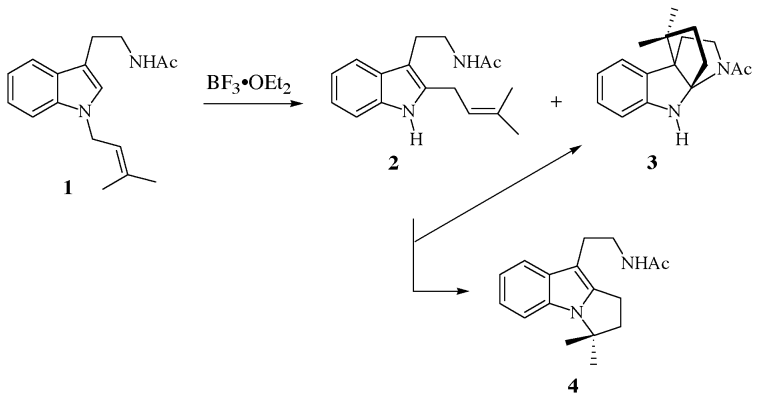
The protic and Lewis acid catalysed rearrangement of *N*-allyl indoles to 2-allyl indoles has been extensively examined by several groups [9]. Preliminary studies [8] with the readily available 1-(3,3-dimethylallyl)-*N*-acetyltryptamine (**1**) showed that $BF_3.Et_2O$ did induced such a shift in an aza-Cope reaction [10] (Scheme 4).

From the mixture of products formed, three isomeric compounds were isolated and structures **2**, **3** and **4** assigned. Exposure of pure **2** to the Lewis acid converted it into **3** and **4**. Their formation is the result of the interaction of the

Scheme 3



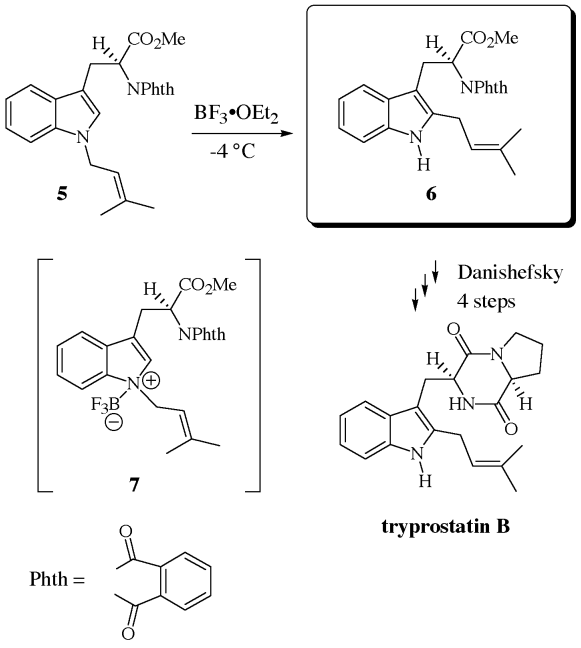
Scheme 4



nitrogen side-chain or that of the indole with the cationic species generated by the Lewis acid with the olefinic bond of **2**. Other acid catalysts studied, such as CF_3CO_2H, $ZnCl_2$ or $AlCl_3$, proved to be much less efficient.

The phthaloyl derivative **5** (Scheme 5) of 1-(3,3-dimethylallyl) L-tryptophane methyl ester, where at least the equivalent cyclisation to a compound akin to **3** was made impossible, was therefore selected next for the synthesis of tryprostatin B. It was easily obtained, without any significant loss of its optical integrity, from the known 1-(3,3-dimethylallyl) L-tryptophane [9d] by methylation (CH_2N_2) followed by phthalimidation of the resulting ester. Exposure of **5** to BF_3-OEt_2 at -4 °C gave **6** in 61% and ee of 95%, *via* a process formally involving consecutive [3,3]-, and [3,5]-sigmatropic shifts from the presumed cationic species **7**. Since the key intermediate **6**, possessing spectral data identical with those recorded earlier [9d], had been converted into tryprostatin by Danishefsky [6], the work constitutes in a formal sense a highly enantioselective synthesis of the latter.

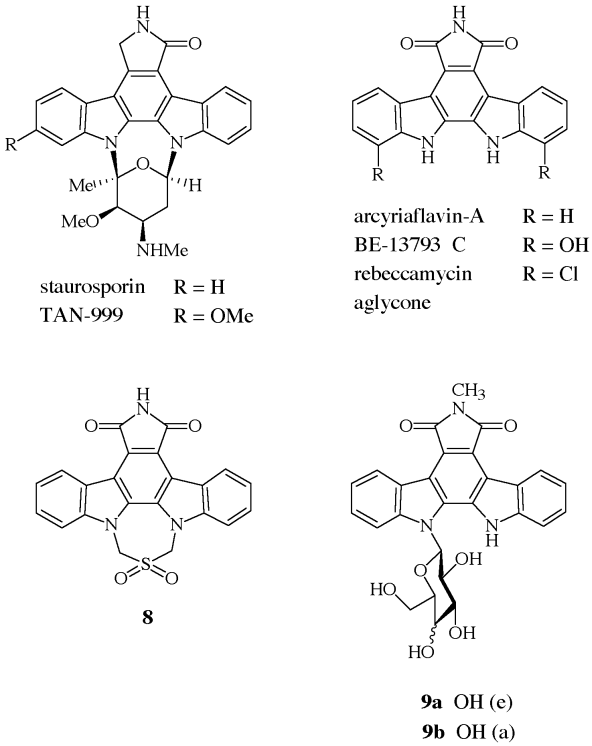
Scheme 5



Indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole and Bisindolylmaleimide Alkaloids.

The indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole alkaloids and the related bisindolylmaleimides are a class of natural products with very interesting activities [5] . For example staurosporin [11], Tan-999 [12], and the structurally related bisindolylmaleimides exemplified by arcyriaflavin-A [13], BE-13793 C [14] and the aglycone of rebeccamycin [15] (Scheme 6), have, since their isolation, been

Scheme 6



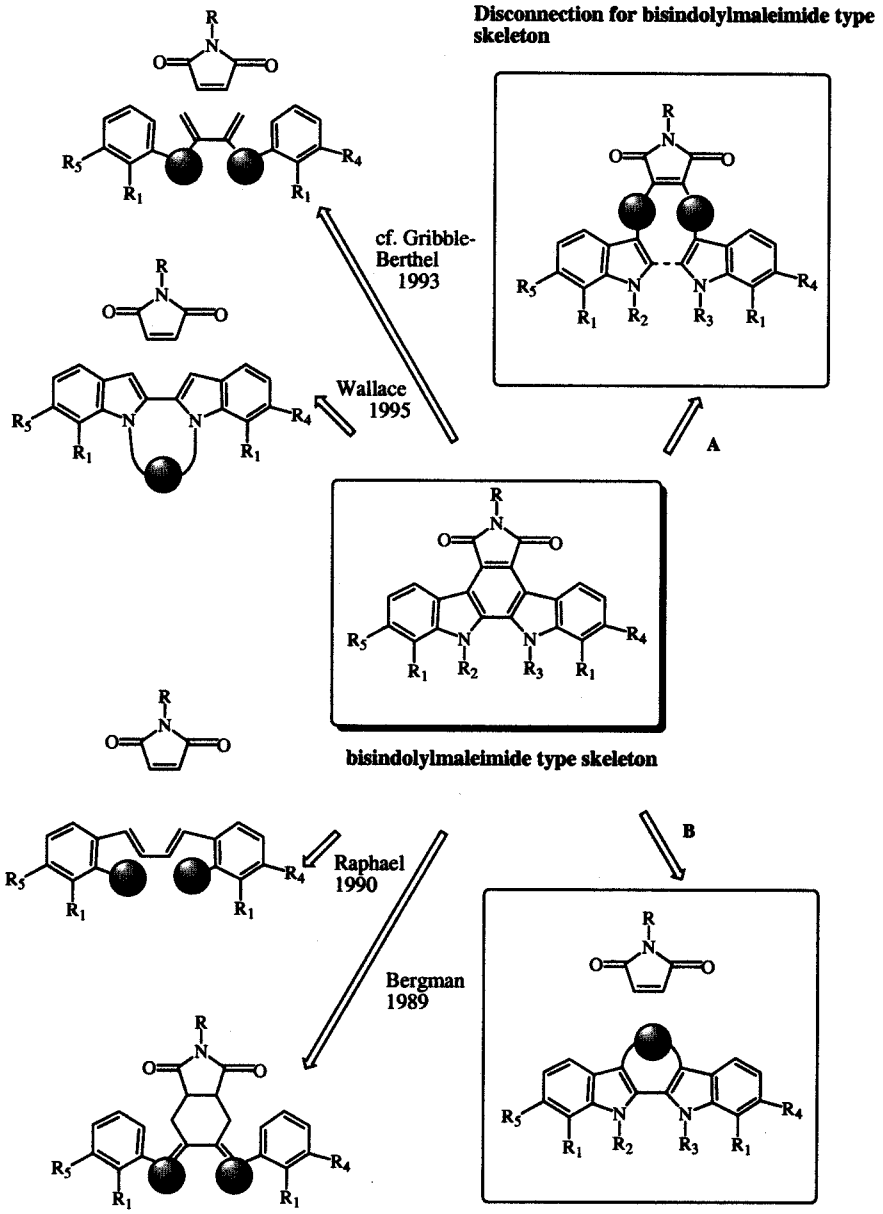
the target of synthesis owing to biological properties [16] such as antimicrobial, hypotensive, platelet aggregation, cell cytotoxicity and also inhibition of protein kinase C (PKC). These properties have also stimulated the development of chemical methods toward obtaining synthetic analogues for pharmaceutical testing. For example whilst **8** is an inhibitor of PKC [5], the DNA intercalating agents **9a** and **9b** are potent topoisomerase inhibitors [17].

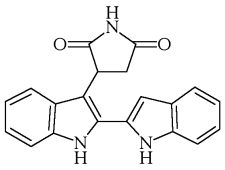
We will describe now our efforts in the synthesis of bisindolylmaleimides such as arcyriaflavin-A. The disconnection for some selected syntheses is summarised in Scheme 7.

The approaches referred to by Gribble and Berthel [16], Wallace [18] and Raphael [19], all make use of [4π+2π] cycloaddition reactions involving the maleimide synthon at advanced stages in the syntheses. Bergman [20], on the other hand, uses a Diels-Alder at an earlier stage to prepare the crucial precursor on which to perform a double Fischer indolization.

Although conceptually simple, a serious drawback in all the [4π+2π] cycloaddition approaches, involving a bis-indolyl and a maleimide, is the significant amount, due to conformational mobility of the dienic system (C-2 ↔ C-2'), of the Michael addition product which is formed.

Scheme 7





Michael addition product

We present our approaches, which sought to minimise such a reaction, by performing the [4π+2π] cycloadditions either in an intermolecular or intramolecular fashion, and using temporary sulfur bridges to lock the reacting elements and thus lower the entropy.

With this end in view (**A** in Scheme 7), the bis-sulfide **10** (Scheme 8) was prepared in near quantitative yield from indole 3-thiolate **12** [21] (obtained *in situ* from the isothiuronium salt **11**) and dichloromaleimide [22].

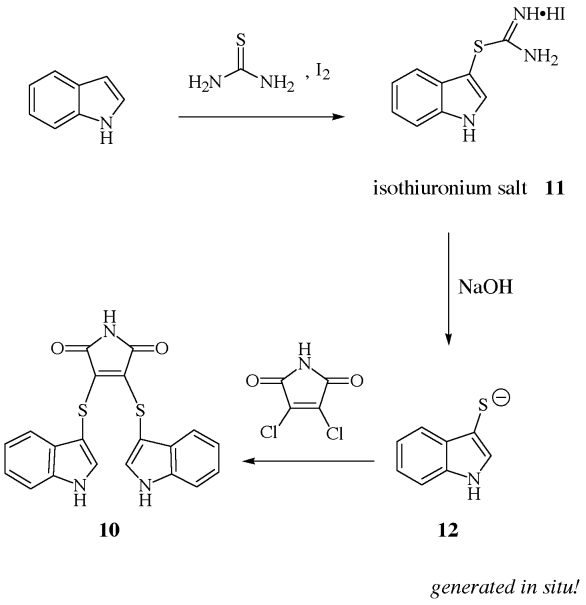
On heating in diphenylether at 210 °C for a short length of time, **10** afforded arcyriaflavin-A in only trace amounts. The other compounds formed in the reaction are shown in Scheme 9.

The use of the weakly basic *sym*-collidine as the solvent furnished arcyriaflavin-A (1%) which was however accompanied by its isomer isoarcyriaflavin-A **13** (4%) (Scheme 10).

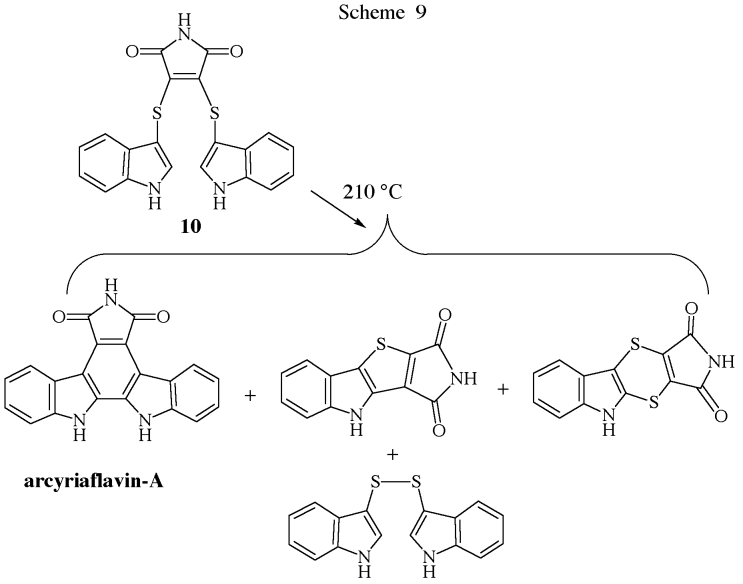
Similar results were obtained when **10** was subjected to the action of a variety of protic acids such as CH_3CO_2H, CF_3CO_2H and *p*-nitrobenzoic acid. Interestingly monochloroacetic acid was found to afford essentially the isoalkaloid **13** in 20%. On the other hand a solution of **10** in PhCN, on heating to *ca.* 130 °C in the presence of $PdCl_2$ and Hünig's base, provided an improved yield of arcyriaflavin-A (10%), along with **13** (1%) [22].

Mechanistically, in the reaction with $PdCl_2$, the simultaneous formation of arcyriaflavin-A and its isomer **13** can be rationalised by invoking a 3,3-disubstituted indolenine organopalladium species **14** (Scheme 11). Coupling between C-2 and C-2', followed by loss of HPdCl, could lead to the new *bis*-sulfide **15**. Then either a [4π+2π] cycloaddition or an iterative Eschenmoser, with sulfur extrusion, could produce the *bis*-episulfide **16**, *en route* to arcyriaflavin-A. Analogously the isomeric *bis*-sulfide **17** would result in the isoalkaloid **13**.

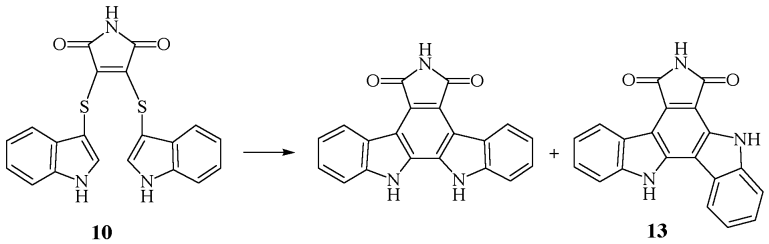
Scheme 8



Scheme 9



Scheme 10



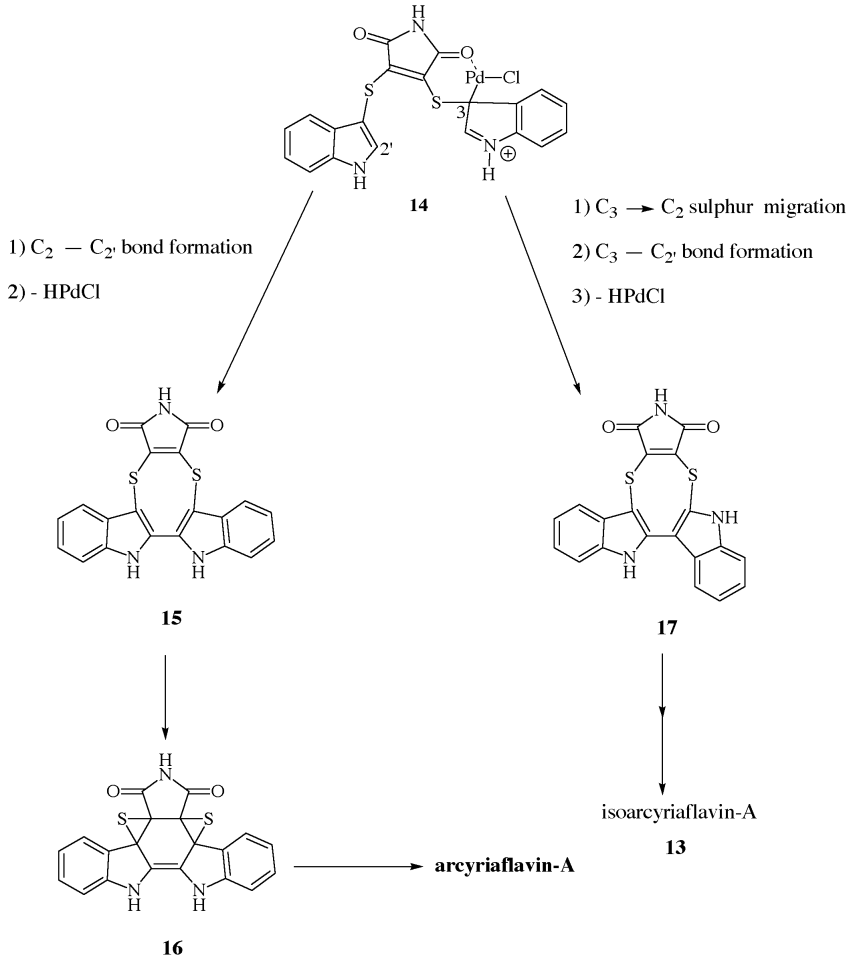
10 | **arcyriaflavin-A** | **13**

sym-collidine, Δ / 3 hr: arcyriaflavin-A 1%; isoarcyriaflavin-A 4%

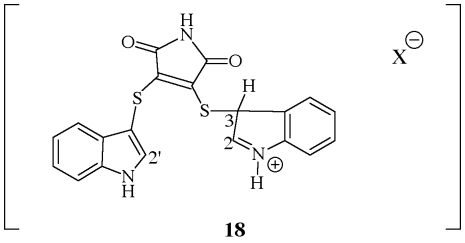
$PdCl_2$ / benzonitrile, Δ / 40 hr: arcyriaflavin-A 10%; isoarcyriaflavin-A 1%

$ClCH_2CO_2H$, Δ / 2 hr: arcyriaflavin-A -; isoarcyriaflavin-A 20%

Scheme 11



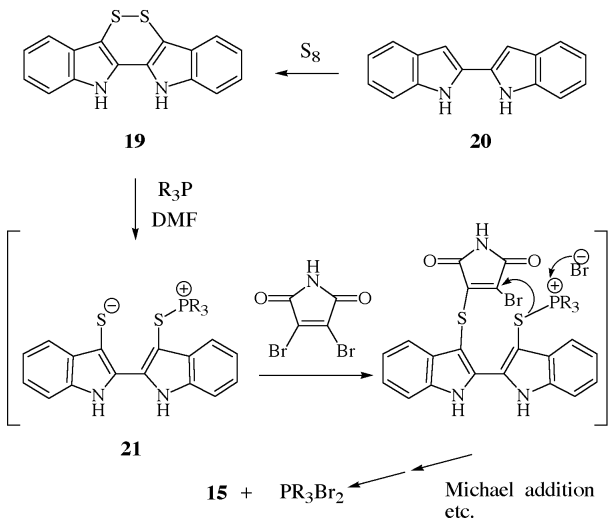
For the reaction with $ClCH_2CO_2H$ the intermediate indolenine **18**, analogous to **14**, is a possibility.



18

On the assumption that the low yield of arcyriaflavin-A could probably reflect the inefficient conversion of the postulated intermediates **14** to **15** or **15** to the alkaloid, the same bis-sulfide **15** was prepared by an independent route. Thus the known disulfide **19** (Scheme 12), obtained by thiation of bi-indolyl **20** [23], on reaction with *n*-Bu_3P, followed by trapping of the presumed intermediate **21** with dibromomaleimide, generated **15** [24].

Scheme 12



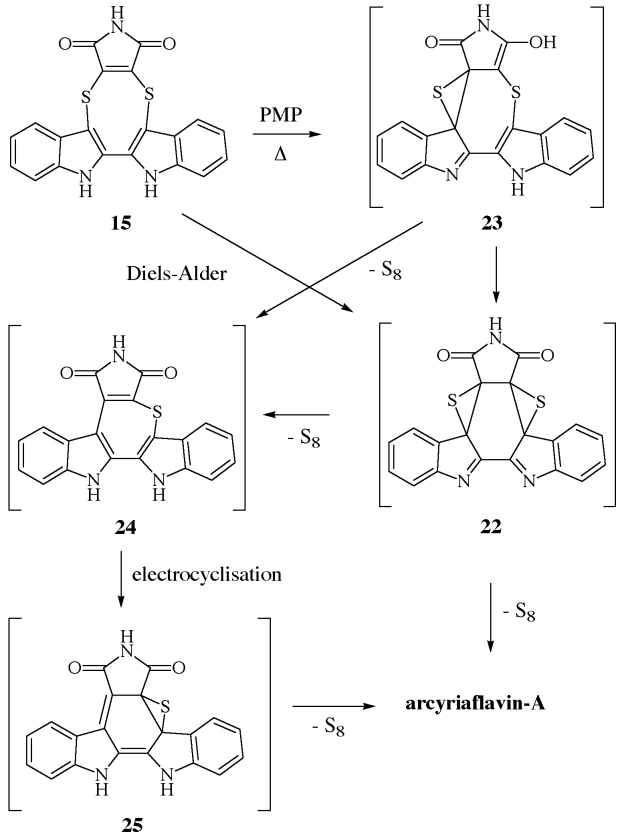
Thermolysis of **15** in DMF, under reflux, did lead to arcyriaflavin-A with an improved yield of 50-60%. The presence of 1,2,2,6,6-pentamethylpiperidine in the reaction mixture, dramatically accelerated the rate of the reaction and provided the alkaloid in 80% yield (Scheme 13) [25].

It seems therefore probable that the formation of arcyriaflavin-A from **15**, in the absence or presence of a base, occurs *via* distinct pathways. In the former it is likely that a true cycloaddition process is in operation, generating the *bis*-episulfide **22**, from which sulfur loss occurs to give arcyriaflavin-A. In the latter case the result could be explained on the basis of *i)* a single, or *ii)* an iterative Eschenmoser type reaction. Whilst process *i)* would originate the *mono*-episulfide-sulfide **23**, which could suffer sulfur extrusion to the *mono*-episulfide **24**, and subsequent electrocyclisation to *mono*-episulfide **25** before generating the alkaloid, process *ii)* would lead to **22** and thence to arcyriaflavin-A. Ready loss of sulfur from *bis*-episulfides or episulfide, leading to fully aromatic substances, has precedent in the literature [26,27].

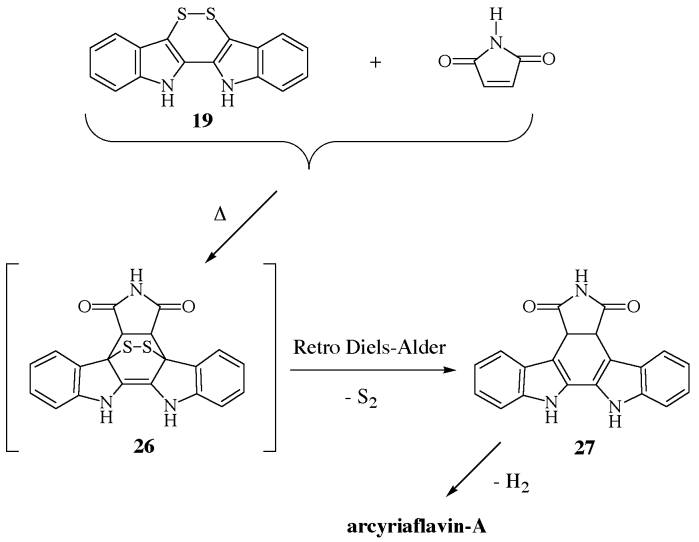
The second and a more concise synthesis (**B** in Scheme 7) involved the conformationally rigid diene **19** and maleimide (Scheme 14) [24] as 4π and 2π participants in an intermolecular Diels-Alder reaction. This, when performed in *o*-dichlorobenzene (190 °C, 2 weeks, sealed tube), produced directly arcyriaflavin-A in 36% yield. It is believed that the reaction occurs *via* the [4π+2π] adduct **26**, formed initially, suffering a sulfur extrusion in a retro Diels-Alder reaction, to provide the dihydroderivative of arcyriaflavin-A **27**. Subsequent dehydrogenation, effected either by sulfur or dissolved oxygen, would lead to the alkaloid **3**.

In conclusion we have provided simple synthetic routes to the skeletons of tryprostatin and bisindolylmaleimide type alkaloids which are of biological importance in the control of cell cycle.

Scheme 13



Scheme 14



Acknowledgments.

The above results of recent efforts are a contribution from Monte de Caparica's dedicated coworkers (namely Prof. P. C. S. Branco) and students (A. S. Cardoso, A. P. Fonseca, M. M. B. Marques and M. M. M. Santos). We are grateful to Fundação para a Ciência e a Tecnologia (Lisbon, Portugal) for financial support.

REFERENCES AND NOTES

[*] aml@mail.fct.unl.pt

[¥] sp@dq.fct.unl.pt

[1] H. Lodish, D. Baltimore, A. Berk, S. L. Zipursky, P. Matsudaira and J. Darnell, Molecular Cell Biology, Scientific American Books, New York, 1995, p. 1066.

[2] P. M. Nurse, *Nature*, **344**, 503 (1990); [b] C. Norbury and P. Nurse, *Ann. Rev. Biochem.*, **61**, 441 (1992); [c] H. Osada, *J. Antib.*, **51**, 973 (1998).

[3a] C.-B. Cui, H. Kakeya, G. Okada, R. Onose, M. Ubukata, I. Takahashi, K. Isono and H. Osada, *J. Antibiot.*, **48**, 1382 (1995); [b] C.-B. Cui, H. Kakeya and H. Osada, *J. Antibiot.*, **49**, 534 (1996); [c] C.-B. Cui, H. Kakeya, G. Okada, R. Onose and H. Osada, *J. Antibiot.*, **49**, 527 (1996); [d] T. Usui, M. Kondoh, C.-B. Cui and H. Osada, *Biochem. J.*, **333**, 543 (1998).

[4] C.-B. Cui, H. Kakeya and H. Osada, *Tetrahedron*, **53**, 59 (1997).

[5] U. Pindur, Y. Kim and F. Mehrabani, *Curr. Med. Chem.*, **6**, 29 (1999).

[6] K. M. Depew, S. J. Danishefsky, N. Rosen and L. Sepp-Lorenzino, *J. Am. Chem. Soc.*, **118**, 12463 (1996).

[7] S. Zhao, T. Gan, P. Yu and J. M. Cook, *Tetrahedron Lett.*, **39**, 7009 (1998); [b] T. Gan, R. Liu, P. Yu, S. Zhao and J. M. Cook, *J. Org. Chem.*, **62**, 9298 (1997).

[8] A. S. Cardoso, A. M. Lobo and S. Prabhakar, *Tetrahedron Lett.*, **41**, 3611 (2000).

[9] G. Casnati, R. Marchelli and A. Pochini, *J. Chem. Soc., Perkin 1*, 754 (1974); [b] S. Inada, K. Nagai, Y. Takayanagi and M. Okazaki, *Bull. Chem. Soc. Jpn.*, **49**, 833 (1976); [c] P. G. Sammes and A. C. Weedon, *J. Chem. Soc., Perkin 1*, 3053 (1979); [d] M. F. Grundon, M. R. Hamblin, D. M. Harrison, J. N. D. Logue, M. Maguire and J. A. McGrath, *J. Chem. Soc., Perkin 1*, 1294 (1980).

[10] R. P. Lutz, *Chem. Rev.*, **84**, 205 (1984).

[11] A. Furusaki, N. Hashiba, T. Matsumoto, A. Hirano, Y. Iwai and S. Omura, *J. Chem. Soc.,Chem. Comm.*, 800 (1978).

[12] S. Tsubotani, S. Tonida and S. Harada. *Tetrahedron*, **47**, 3565 (1991).

[13] W. Steiglich, *Pure Appl. Chem.*, **61**, 281 (1989).

[14] K. Kojiri, H. Kondo, T. Yoshinari, H. Arakawa, S. Nakijima, F. Satoh, K. Kawamura, A. Okura, H. Suda and M. Okanishi, *J. Antib.*, **44**, 723 (1991).

[15] D. E. Nettleton, T. W. Doyle, B. Krishnan, G. K. Matsumoto and J. Clardy, *Tetrahedron Lett.*, **26**, 4011 (1985).

[16] G. W. Gribble and S. J. Berthel, in Studies in Natural Products Chemistry, Vol **12**, Atta-ur-Rahman, ed, Elsevier Science Publishers BV, Amsterdam, 1993, pp. 365-409.

[17] F. Anizon, L. Belin, P. Moreau, M. Sancelme, A. Voldoire, M. Prudhomme, M. Ollier, D. Sevère, J.-F. Riou, C. Bailly, D. Fabbro and T. Meyer, *J. Med. Chem.*, **40**, 3456 (1997).

[18] J. F. Barry, T. W. Wallace and N. D. A. Walshe, *Tetrahedron Lett.*, **51**, 12797 (1995).

[19] I. Hughes, W. P. Nolan and R. A. Raphael, *J. Chem. Soc., Perkin 1*, 2475 (1990).

[20] J. Bergman and B. Pelcman, *J. Org. Chem.*, **54**, 824 (1989).

[21] R. L. N. Harris, *Tetrahedron Lett.*, 4465 (1969).

[22] A. P. Fonseca, A. M. Lobo and S. Prabhakar, *Tetrahedron Lett.*, **36**, 2689 (1995).

[23] J. Bergamn and C. Stälhandske, *Tetrahedron Lett.*, **35**, 5279 (1994).

[24] M. M. B. Marques, A. M. Lobo, S. Prabhakar and P. S. Branco, *Tetrahedron Lett.*, **40**, 3795 (1999).

[25] M. M. B. Marques, M. M. M. Santos, A. M. Lobo and S. Prabhakar, *Tetrahedron Lett.*, **41**, 9835 (2000).

[26] E. Vogel, E. Schimdbauer and H. J. Altenbach, *Angew. Chem. Int. Ed.* **13**, 736 (1974).

[27] G. P. Scott, *J. Am. Chem. Soc.*, **75**, 6332 (1953).