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LETTERS

A Diels-Alder, Retro-Diels-Alder Approach to Arcyriaflavin-A

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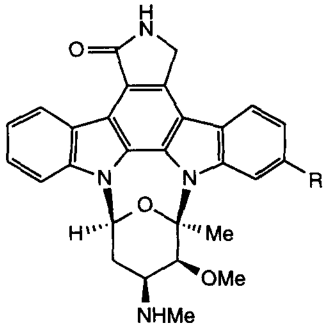
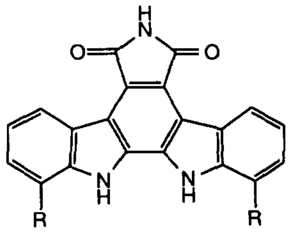
Abstract: 2,2'-Bi-indolyl-3,3'-dithiete and maleimide participate in a [4 + 2] cycloaddition reaction to provide arcyriaflavin-A.

Keywords: Alkaloids, Diels-Alder reactions, dithietes, extrusions.

Indolo [2,3-*a*]carbazole alkaloids such as staurosporin (**1**) [1], Tan-999 (**2**) [2] and the structurally related bi-indolylmaleimides as exemplified by arcyriaflavin-A (**3**) [3], BE-13793 C (**4**) [4] and the aglycone of rebeccamycin (**5**) [5] have, since their isolation, been the target of synthesis owing to their important biological properties [6], such as antimicrobial, hypotensive, cell cytotoxic activity and also inhibition of protein kinase C and platelet aggregation.

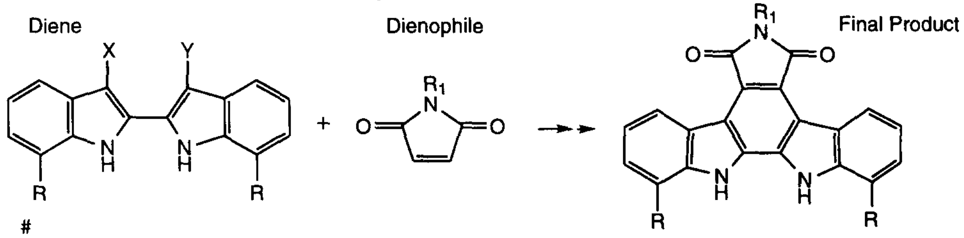


staurosporin (**1**) R = H
TAN-999 (**2**) R = OMe



arcyriaflavin-A (**3**) R = H
BE-13793 C (**4**) R = OH
rebeccamycin aglycone (**5**) R = Cl

Of the many synthetic methods [6] devised for these alkaloids, perhaps conceptually the most direct route to the bi-indolylmaleimide alkaloids is the one that involves a [4 + 2] cycloaddition of appropriate 2,2'-bi-indoles with maleimide. In fact two such bi-indolyl based approaches [7,8] (Scheme 1 ; # a, b) have been reported, both involving N-protected maleimide as the dienophile.



#					
a		R = X = Y = H	R_1 = Me		R = H ; R_1 = Me (7% ; ref. 7)
b		R = Cl ; X = H ; Y =OAc	R_1 = CH_2OCH_2Ph		R = Cl ; R_1 = CH_2OCH_2Ph (22% ; ref. 8)
c	**6**	R = H ; X-Y = S-S	R_1 = H	**3**	R = R_1 = H *(36% ; present work)*

Scheme 1

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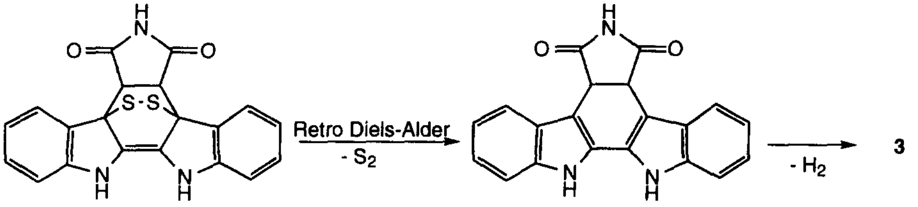
We describe herein a new method consisting of heating the conformationally rigid dithiete (**6**)[1] [9] (*cf.* Scheme 1; # c) and maleimide in *o*-dichlorobenzene which furnished[2] an improved yield (36%) of arcyriaflavin-A[3] identical with an authentic sample [10].

The formation of **3** (*cf.* Scheme 2) is believed to occur *via* the [4 + 2] adduct **7**, undergoing a retro Diels-Alder reaction to yield singlet S_2 [11], and dihydroarcyriaflavin-A (**8**) [12]. The latter, on dehydrogenation presumably effected by dissolved oxygen and/or extruded sulfur, would lead to the alkaloid **3**.



7 **8**

Scheme 2

Since the aglycone of staurosporin (staurosporinone) has been obtained [13,14] by reduction of arcyriaflavin-A, the work described above constitutes, in a formal sense, a synthesis of staurosporinone.

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[1] The dithiete **6** was obtained in 86% yield by dithiation of bis-indole.

[2] The dithiete **6** (45 mg), and maleimide (14.7 mg) in *o*-dichlorobenzene (5 mL) were heated to 188°C in a sealed tube, previously washed with dilute ammonium hydroxide solution, for 15 days. No special precaution was taken to exclude oxygen from the system. The mixture was cooled to room temperature and filtered from the insoluble material. The residue obtained on evaporation of the solvent was purified by preparative tlc to afford arcyriaflavin-A (18 mg ; 36%) identical with an authentic sample (tlc, ^1H NMR, IR).

[3] It is of interest that the dithiete **6** and dibromomaleimide in CH_3CN on treatment with n-Bu_3P also yielded arcyriaflavin-A. However, it was found very difficult to purify it from phosphorus containing substances.