Pergamon

Tetrahedron Letters, Vol. 36, No. 15, pp. 2689-2692, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00363-0

A Novel Synthesis of Arcyriaflavin-A†

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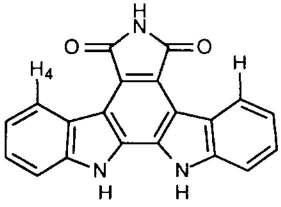
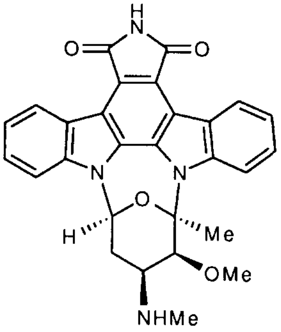
Abstract: 2,3-*Bis* [3'- indolylmercapto]maleimide on treatment with $PdCl_2$ affords arcyriaflavin-A in one step.

Arcyriaflavin-A [1] (**1**), the aglycone of Bmy-41950 [2] (**2**) was first isolated and fully characterised by Steglich.[1] Other related natural products possessing useful and diverse biological activities incorporating the maleimide moiety, such as rebeccamycin,[3] AT 2433-B_1,[4] and AT 2433-B_2[4] were isolated and various syntheses [5] of compounds containing the heterocyclic framework described.



1



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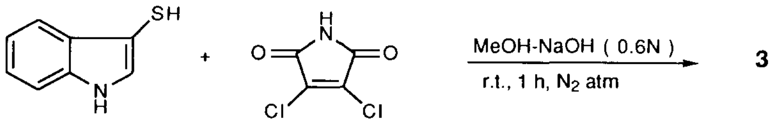
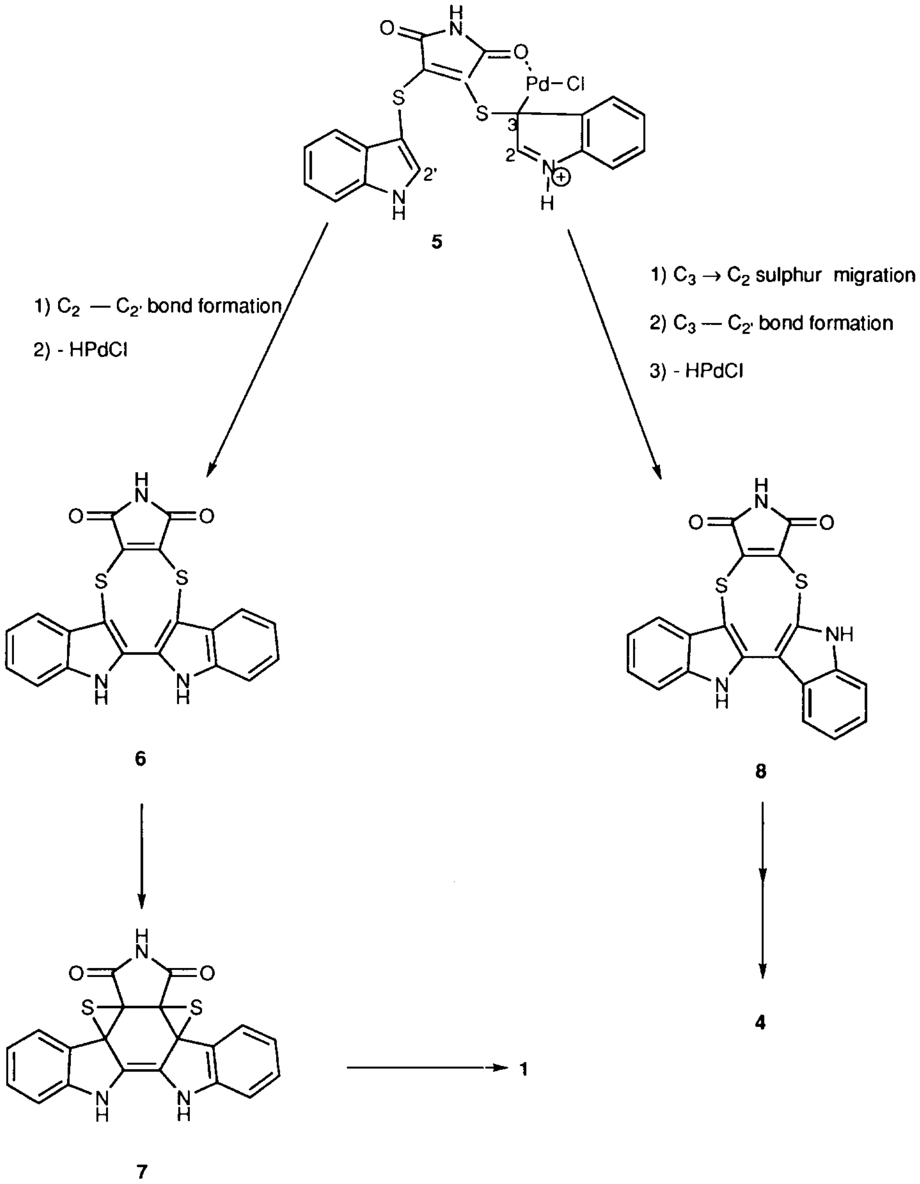
We report here a new, conceptually simple approach to arcyriaflavin-A. The necessary starting material, the *bis*-sulphide **3**, is readily prepared (m.p. 235-237°C ; yield > 85% yield) from dichloromaleimide and 3-mercaptoindole [6] under basic conditions[7] (*Scheme 1*). The compound **3** in *syn*-collidine, a weakly basic



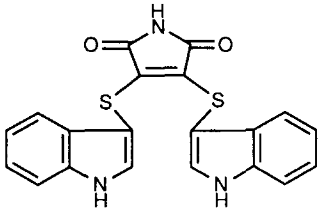
Scheme 1


5
1) C2 — C2' bond formation
2) - HPdCl
1) C3 → C2 sulphur migration
2) C3 — C2' bond formation
3) - HPdCl
6
8
7
1
4

Scheme 2

solvent, under reflux (3 h) gave a complex mixture of products from which the title compound **1** (1%) and its isomer **4** (4%) were isolated by extensive preparative layer chromatography. Change of solvent to acetic acid (80°C; 40 h) did not significantly alter neither the yield nor the proportion of the two isomers formed. However, heating a mixture of **3**, palladium chloride (2 eq) Hünigs' base (2 eq) in benzonitrile (40 h) at 80°C followed by reductive work-up ($NaBH_4$) and chromatographic purification afforded arcyriaflavin **1** (m. p. > 280°C; 10%) and **4** (m.p. > 280°; 1%).[8]

Mechanistically the simultaneous formation of arcyriaflavin-A and its isomer can be rationalised by invoking the involvement of a 3,3-disubstituted chelated organopalladium species **5**[9] (or its equivalent) as the common intermediate. Coupling between C_2 and $C_{2'}$ (*Scheme 2*) followed by loss of HPdCl leads to the new *bis*-sulphide **6**. A (4+2)-cycloaddition and sulphur extrusion from the *bis*-episulphide formed **7** produces **1**.[10] Alternatively, sulphur migration from C_3 to C_2 in **5**, establishment of the C_3-$C_{2'}$ bond and elimination of HPdCl yields the isomeric hexacyclic *bis*-sulphide **8** which subsequently collapses to generate **4**.[11,12]



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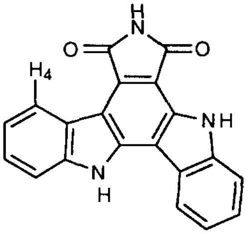

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ACKNOWLEDGMENTS

We thank Professor J. Bergman, Royal Institute of Technology, Sweden, for a sample of arcyriaflavin-A ; Dr. B. C. Ross, Glaxo, U. K., for accurate mass measurements and Junta Nacional de Investigação Científica e Tecnológica (JNICT, Lisbon) for award of a doctoral fellowship to one of us (A. P. F.) and partial financial support.

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8. The low recovery of isolable organic compounds from this reaction (< 40%) is most probably due to occurrence of indiscriminate palladation with attendant formation of oligomers (*cf.* Trost, B. M.; Fortunak, J. M. D., *Organometallics*, **1982**, *1*, 7-13).

9. For an example of a 6-membered chelated Pd-complex involving the carbonyl group see: Harino, H.; Inoue, N. *Tetrahedron Lett.*, **1979**, 2403-2406 .

10. The spectral data (ir, uv, ^{1}H nmr) and the chromatographic behaviour of **1** were identical with those of an authentic sample.

11. The structure **4** was assigned by accurate mass measurement and, more importantly, by ^{1}H nmr spectroscopy. Whereas the symmetrical arcyriaflavin-A molecule contained a low field proton resonance (H_4) at δ 9.155 of 2H intensity (d, J 7.4 Hz), the compound **4** possessed only *one* such hydrogen at δ 9.077 (d, J 7.4 Hz).

12. A blank experiment performed in the absence of $PdCl_2$ showed that the *bis*-sulphide **3** was stable under these conditions.

† This work was presented in part at the annual meeting of the Portuguese Chemical Society held in Aveiro, April 5-8th 1994.

(*Received in UK* 20 *January* 1995; *revised* 23 *February* 1995; *accepted* 24 *February* 1995)