Tetrahedron Letters,Vol.28,No.38,pp 4441-4444,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

COUPLING OF INDOLEACETIC ACID TRIANION OR METHYL INDOLEACETIC ACID DIANION. A BIOMIMETIC APPROACH TO INDOLOCARBAZOLE ALKALOIDS.

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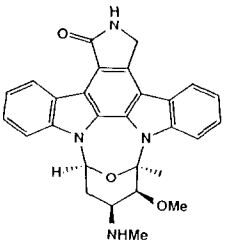
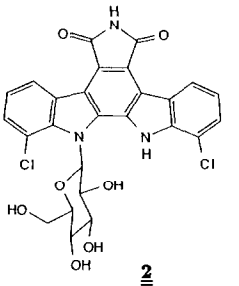
ABSTRACT: The bisindolesuccinic acid ester **8b** was obtained as a mixture of diastereomers by iodine promoted coupling of the dianion **7b** or *via* the trianion **7a**. The diester was converted to the N-benzylimide **10** which was oxidatively cyclized to the indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole compound **13**.

The pronounced physiological activities of indolocarbazole alkaloids have triggered considerable synthetic efforts.[1-7] The active alkaloids include staurosporine (**1**), which is antihypertensive[8] and inhibits platelet aggregation,[9] and the antitumor antibiotic rebeccamycin (**2**).[7,10]



1



2

Although very little is known of the biosynthesis of the indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole skeleton it is reasonable to assume that it is derived from indoleacetic acid or tryptophan moieties. Also, it is likely that the *a* or the *b* bond (Fig 1) is the first to be biosynthetically formed, as suggested by the coexistence of **3** and **4** with **5** in the slime mold *Arcyria denudata*.[11] The formation of the *a* bond was used by Sarstedt and Winterfeldt[1,2] as the first connective step in their bionimetic synthesis of the staurosporine aglycon.

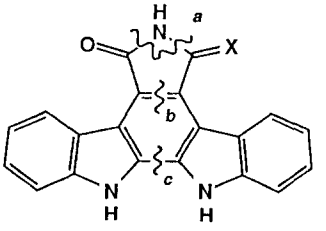
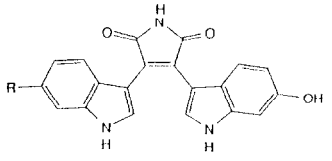
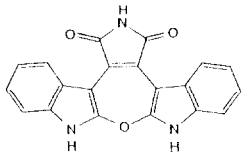


Fig. 1



3 R=H, OH



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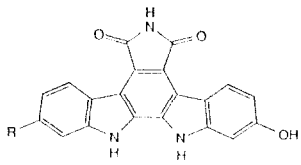
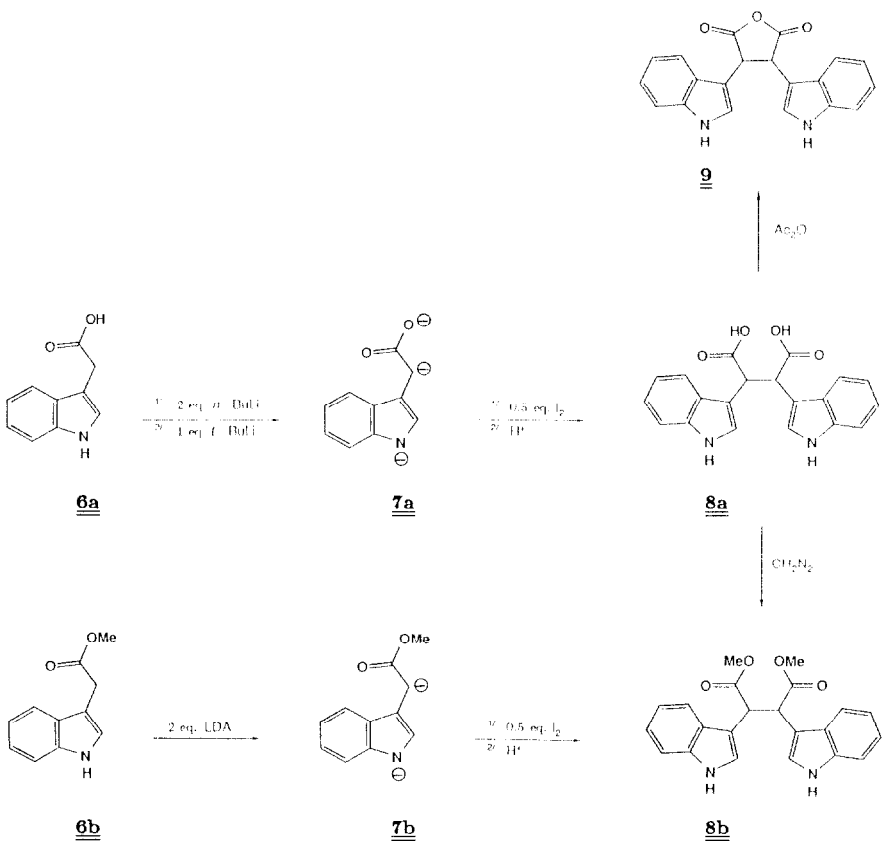


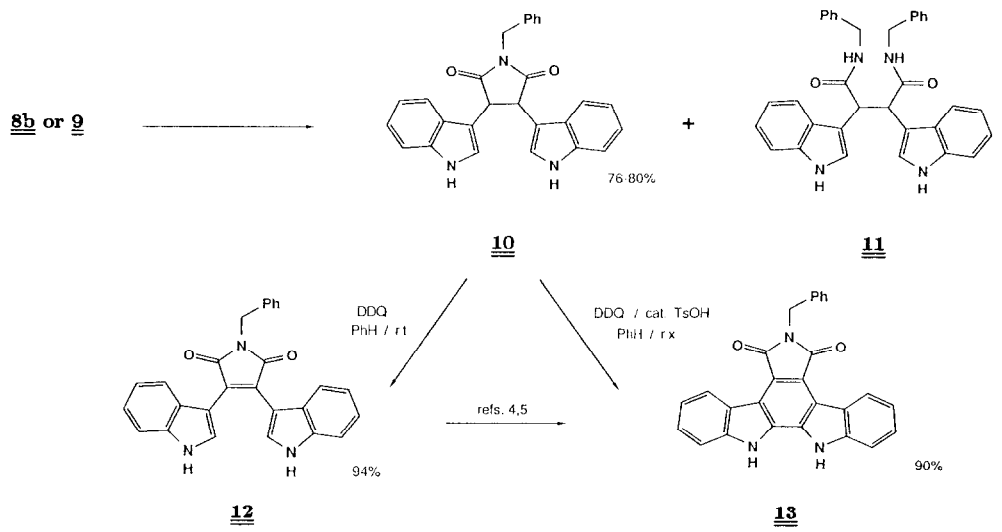
5 R=H, OH

We here present our preliminary results from a biomimetic synthesis of the indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole system where the *b* bond is formed in the first step by oxidative coupling of the indoleacetic acid trianion[12] or the methyl indoleacetate dianion.[13] The trianion **7a** was formed by the sequential addition of *n*-BuLi (2 eq.) and *t*-BuLi (1 eq.) to indoleacetic acid **6a** in THF at -78°C. Coupling with iodine (0.5 eq.) followed by an acidic workup, afforded the bisindolesuccinic acid **8a** which was isolated as the corresponding dimethyl ester **8b** (total yield 38%) or as the anhydride **9** (Scheme 1). A higher yield (85%) of **8b** was obtained by the iodine promoted coupling[13] of the dianion **7b**, prepared from methyl indoleacetate **6b** and LDA.



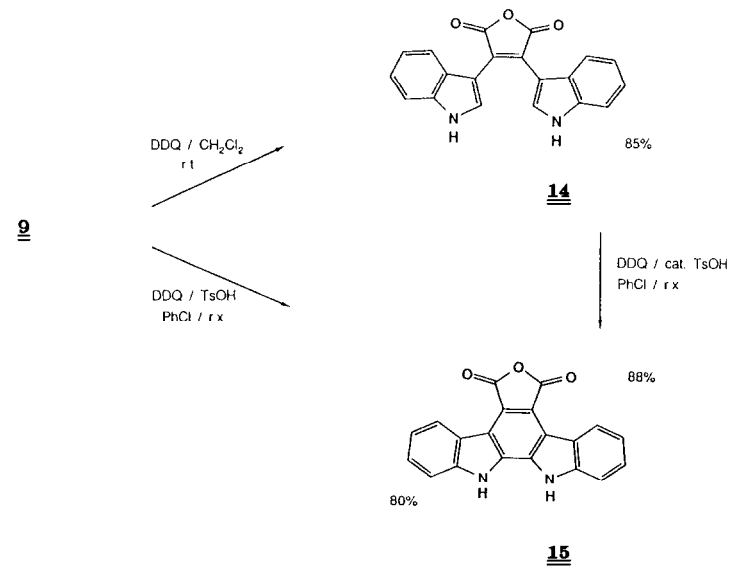
Scheme 1

The diester **8b** was formed as a mixture of *dl* and *meso* forms[14-16] which could easily be separated by crystallization and chromatography. Heating **8b** or **9** with benzylamine gave the succinimide **10** together with small amounts of the bisamide **11** (Scheme 2). Oxidation of **10** with DDQ afforded the maleimide **12** which previously has been transformed to **13** with DDQ/*p*-TsOH.[4,5] By this method it was also possible to convert **10** directly to **13**.



Scheme 2

Similarly, the anhydride **14** was formed from **9** upon treatment with DDQ (Scheme 3). **14** was converted to **15** by DDQ /*p*-TsOH, but the transformation required a higher temperature (130°C) than in the corresponding transformation of **12** to **13**. Compound **15** could also be directly obtained from **9** (Scheme 3).



Scheme 3

In summary the indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole skeleton has been synthesized in three efficient steps from readily available starting materials. We have thus shown that oxidative coupling of anions derived from indoleacetic acid derivatives constitutes a viable route to indolocarbazole alkaloids.[19]

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19. The full details of this investigation will be presented in the near future.

(Received in UK 23 July 1987)