

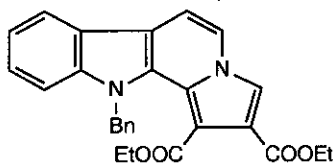
SYNTHESIS OF FUNCTIONALIZED INDOLIZINO[8,7-*b*]-  
INDOLES VIA 1,3-DIPOLAR CYCLOADDITION REACTIONS OF  
3,4-DIHYDRO- $\beta$ -CARBOLINE AZOMETHINE YLIDES WITH  
OLEFINIC DERIVATIVES

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**Abstract** - The 1,3-dipolar cycloaddition reaction of 3,4-dihydro- $\beta$ -carboline azomethine ylide (**4**) with dimethyl fumarate (**5**) and fumaronitrile (**5'**) is described. The resulting hexahydroindolizine products (**6**) and (**6'**) were dehydrogenated stepwise (- H<sub>2</sub>, - 2H<sub>2</sub>, - 3H<sub>2</sub>) using KMnO<sub>4</sub>, MnO<sub>2</sub> and DDQ as oxidants.

As part of a program aimed at the development of multifunctional anticancer agents, we recently synthesized 11*H*-indolizino[8,7-*b*]indoles (**1**) *via* reaction of acetylenic di- (and mono-) carboxylates with

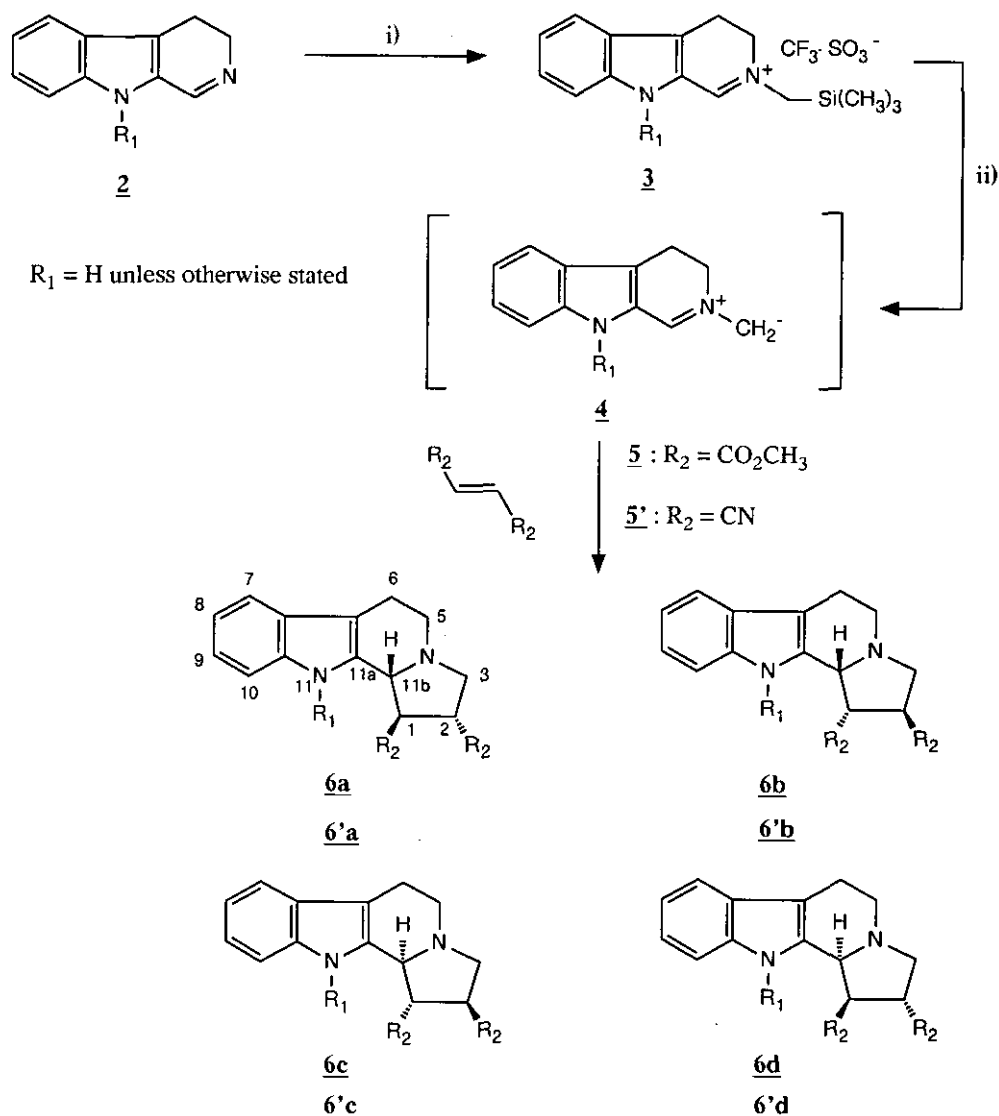


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$\beta$ -carboline azomethine ylides (**4**,  $R^1 = \text{Bn}$ , Scheme 1).<sup>1</sup> The latter were generated from the trimethylsilylmethyl triflate salts (**3**) ( $R^1 = \text{Bn}$ ) of 3,4-dihydro- $\beta$ -carbolines (**2**) ( $R^1 = \text{Bn}$ ). In this communication, we now wish to report the 1,3-dipolar cycloaddition reactions of unprotected ylide (**4**) ( $R^1 = \text{H}$ ) with ethylenic dipolarophiles (**5**) (dimethyl fumarate) and (**5'**) (fumaronitrile), allowing entry into the hexahydroindolizine analogues of **1**.

Scheme 1



i)  $(\text{CH}_3)_3\text{SiCH}_2\text{OSO}_2\text{CF}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $25^\circ\text{C}$ ; ii)  $\text{CsF}$ ,  $\text{DME}$ , reflux, olefin **5** or **5'**

Alkylation of unprotected 3,4-dihydro- $\beta$ -carboline (**2**) ( $R^1 = H$ ) with trimethylsilylmethyl trifluoromethanesulfonate<sup>2</sup> in dichloromethane at room temperature gave exclusively the quaternized  $\beta$ -carboline derivative (**3**) ( $R^1 = H$ ) (73% ; mp 136°C (EtOH)).<sup>3</sup> No alkylation of the indolic N-H by the silyl reagent was observed. Treatment of the triflate salt (**3**) with cesium fluoride in anhydrous dimethoxyethane<sup>2</sup> produced the azomethine ylide (**4**) ( $R^1 = H$ ). The latter was trapped *in situ* with dimethyl fumarate (**5**) yielding the 1,2,3,5,6,11b-hexahydroindolizino[8,7-*b*]indoles (**6a-d**) as a diastereomeric pair of enantiomers (87% overall yield). A mixture of the enantiomers (**6a**) and (**6c**) was obtained by fractional crystallization of the crude reaction mixture from ethanol (mp 169°C ; 51%). Chromatography of the mother liquor on silica gel using dichloromethane - ethyl acetate (7:3) as developer provided a mixture of **6b** and **6d** in the form of a yellow oil (36% yield).

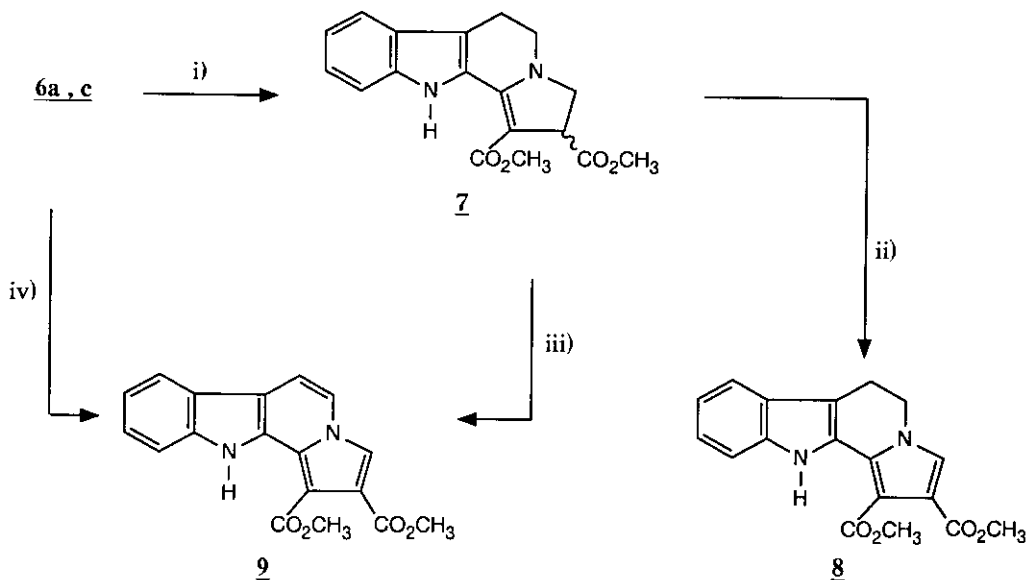
As has been amply demonstrated<sup>2,4</sup> 1,3-dipolar cycloaddition reactions of non-stabilized azomethine ylides with electron-deficient ethylenic dipolarophiles are highly stereospecific, the *cis* (or *trans*) relationship of the latter being maintained in the final products. The reaction of the  $\beta$ -carboline ylide (**4**) with fumarate (**5**) follows this rule, a *trans* arrangement of the ester groups being conserved in the reaction products (**6a-d**). This was evident from the <sup>1</sup>H-<sup>1</sup>H two-dimensional nmr spectrum of the enantiomeric mixture (**6a**) + (**6c**), in which  $J_{1,2} = 7$  Hz.<sup>5</sup> A  $H_{11b,1}$  coupling constant of 7 Hz was also consistent with a *trans* arrangement of these protons. In the case of **6b** + **6d**,  $J_{11b,1}$  was of the order of 9 Hz, indicating a *cis* geometry at these positions while a  $J_{1,2}$  value of 7 Hz again pointed to a *trans* relationship of H-1 and H-2.

In similar fashion, reaction of ylide (**4**) ( $R^1 = H$ ) with fumaronitrile (**5'**) in DME gave the mixture of isomers (**6'a-d**) in 64% overall yield. The enantiomeric pair (**6'a**) and (**6'c**) (48%) was separated from their diastereomers (**6'b**) and (**6'd**) (16%) by hplc.<sup>6</sup> The relative configurations of each pair of enantiomers were assigned by 2-D <sup>1</sup>H-nmr spectroscopy as for the diester analogues.

The hexahydroindolizines (**6**) and (**6'**) could be dehydrogenated progressively (- H<sub>2</sub>, - 2H<sub>2</sub>, - 3H<sub>2</sub>) and selectively by use of different oxidants. Thus, treatment of (**6a,c**) with excess potassium permanganate in anhydrous THF<sup>7</sup> for 1 h at 0°C gave the tetrahydro derivative (**7**) (Scheme 2) which was isolated as an oil

in 84% yield after chromatography on silica gel. The pyrroline ring of (**7**) was then transformed, albeit

Scheme 2



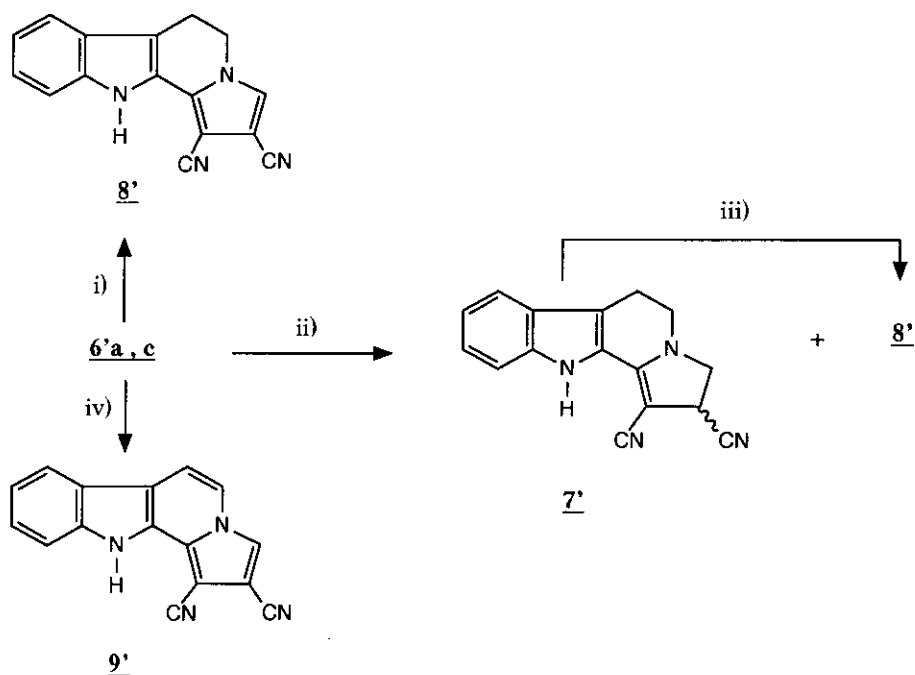
- i)  $\text{KMnO}_4$ , THF,  $0^\circ\text{C}$ , 1 h; ii) 1 eq. DDQ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ ; iii) 2 eq. DDQ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ ;  
 iv) 3 eq. DDQ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$  or  $\text{MnO}_2$ , THF, reflux

in low yield (15%), into the pyrrolidine derivative (**8**) (mp  $193^\circ\text{C}$ ) by use of 1 eq. of DDQ in dichloromethane at  $0^\circ\text{C}$ . The low yield of this reaction is attributable to incomplete reaction; starting material (**7**) could, however, be isolated by chromatography on silica gel and then recycled. Finally, treatment of **7** with 2 eq. of DDQ or of **6a,c** with 3 eq. of DDQ in THF at  $0^\circ\text{C}$  (or with active manganese dioxide in refluxing THF) gave the completely unsaturated derivative (**9**) (mp  $163^\circ\text{C}$ ) in 70% yields. Compounds (**7**), (**8**) and (**9**) were characterized by comparison of their spectral properties (uv, ir,  $^1\text{H}$ -nmr) with those of the previously described<sup>1</sup> N-protected diethyl ester analogues produced by reaction of  $\beta$ -carboline ylides with diethyl acetylenedicarboxylate. In the latter case, the highly electrophilic character of the acetylenic dipolarophiles necessitated protection of the nucleophilic  $\beta$ -carboline N-H

function to avoid competing reactions. The present step-wise oxidation of **6** now allows direct access to the unprotected derivatives.

Stepwise dehydrogenation of the dicyanohexahydroindolizine compounds (**6'a,c**) proved to be more delicate than that of the diester analogues. Thus, under conditions identical to those which led to **7** ( $\text{KMnO}_4$ , THF,  $0^\circ\text{C}$ , 1 h), the dicyano derivative (**6'a,c**) gave only the product resulting from loss of  $2\text{H}_2$ , **8'** (65% ; mp  $245^\circ\text{C}$  ; Scheme 3). Although **7'** could be detected by tlc when **6'a,c** was treated with 0.5 eq. of DDQ in dichloromethane at  $0^\circ\text{C}$ , all attempts to isolate this compound invariably led to formation of **8'** due to air oxidation. The fully aromatic (**9'**) could be obtained by treatment of **6'a,c** with 3 eq. of DDQ (60% ; mp  $295^\circ\text{C}$ ).

Scheme 3



i)  $\text{KMnO}_4$ , THF,  $0^\circ\text{C}$ , 1 h ; ii) 0.5 eq. DDQ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$  ; iii) air ;  
 iv) 3 eq. DDQ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$  .

In conclusion, the reaction of unprotected 3,4-dihydro- $\beta$ -carboline azomethine ylides (**4**) ( $\text{R}^1 = \text{H}$ ) with olefinic dipolarophiles (**5**) and (**5'**) allows direct access to the new class of hexahydroindolizino[8,7-*b*]indole derivatives in a stereospecific fashion. The ability of the products (**6**) and (**6'**) to undergo

controlled, stepwise dehydrogenation will allow evaluation of the optimal geometry necessary to ensure cytotoxic activity.

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