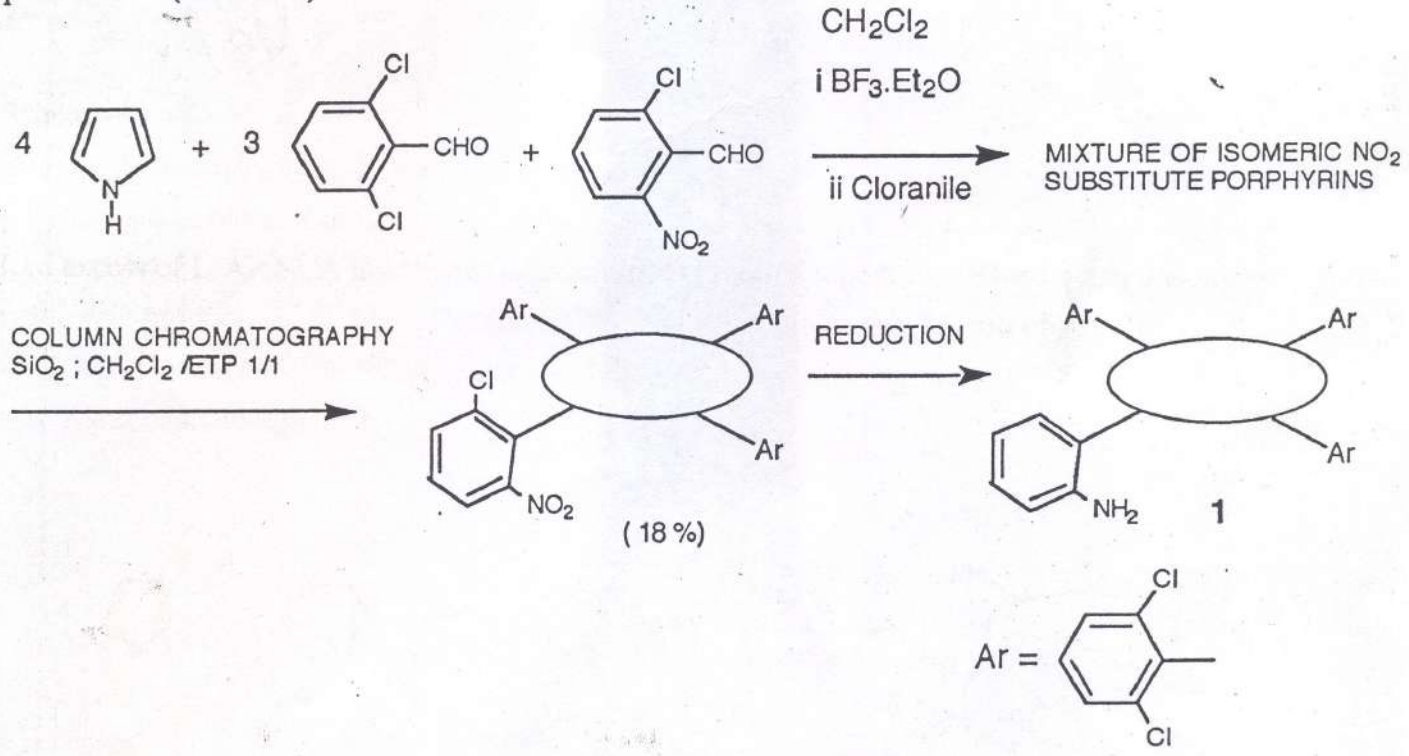
COOPERATION IN SCIENCE AND TECHNOLOGY WITH CENTRAL AND EASTERN COUNTRIES.
RESEACH FELLOWSHIPS : contract NR. ERB-CIPA-CT-92-2257 (proposal NR. 12588).
FELLOW: Dr. ARTAN TREBICKA

FINAL REPORT.

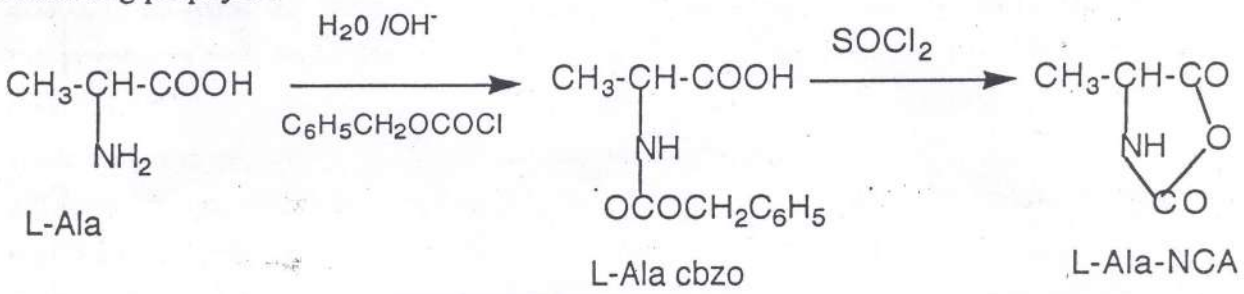
The research accomplished by Dr. Artan Trebicka throughout his stage of three months (from 26 June to 30 October 1993) at the Department of Organic and Industrial Chemistry of Milano University can be devided in two parts: i) synthesis of tetraarylporphyrin featuring an amino group and its reaction with aminoacid N-carboxyanhydride (aminoacidNCA); ii) synthesis of β-alkyl substituted tetraarylporphyrins *via* dipyrril aryl methane building blocks.
The first part concerns with the synthesis of H_2-tri(2,6-dichloro phenyl) -mono(2-chloro 6-amino phenyl) porphyrin **1** startig from pyrrole and aromatic aldehydes following the Lindsey procedure [1] (scheme 1).

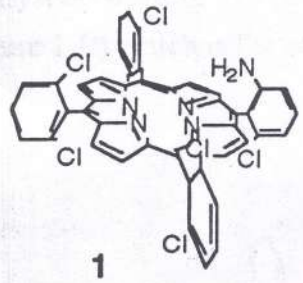


Scheme 1

About the synthesis of **1**, the step of reduction of the nitro group to amino was found to be particularly difficult and the desired product was obtained in very poor yields, although different tecniques were used.(i.e. $SnCl_2$/AcOEt,rt; $SnCl_2$/HCl, reflux; H_2/Pd). This problem was unexpected because the analogous reaction on H_2-tri(2,6-dichlorophenyl)-mono(2,6 dichloro 3-nitrophenyl) porphyrin gave the corresponding amino compound in good yields, as it was previously observed.[2] Furthermore it was found that the reaction of **1** with L-AlaNCA, prepared following known procedures [3] reported in scheme 2, did not afford the polypeptide

linked porphyrin, probably due to the low nucleophilicity of the amino group of the chloro containing porphyrin.





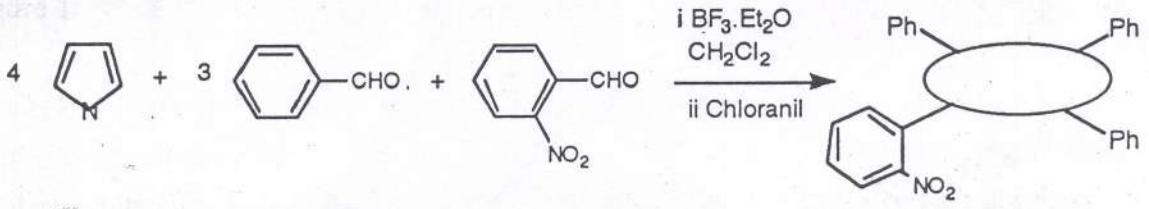
1

+ L-Ala-NCA ⟶ NO REACTION

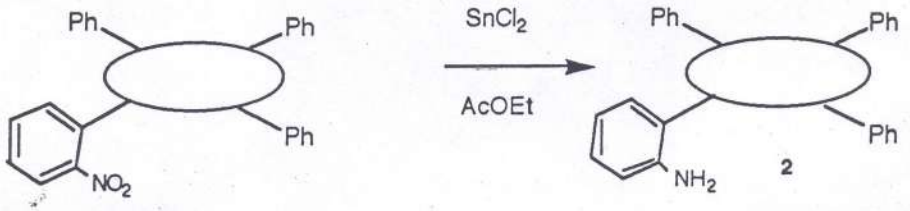
Scheme 2

The low reactivity of porphyrin **1** led us to check the capacity of a substituted aniline to act as polymerisation initiator of L-AlaNCA, thus *ortho* toluidine was stirred for 4 days with a twenty fold excess of L-AlaNCA in anhydrous acetonitrile at room temperature, affording an unsoluble polymeric product which, by NMR, showed an aniline -alanine average ratio of ten.

For this reason it was decided to synthetize the H_2-triphenyl-mono(2-aminophenyl)porphyrin **2** which was obtained in 16 % yields from pyrrole (scheme 3).



Isolated in 16 % yields after chromatography



2

75 % Yields from nitro porphyrins

Scheme 3

This compound, as Zn complex, was reacted with L-AlaNCA under the condition described above, in this case obtaining a thiny amount of the possible product of condensation between the porphyrin and the L-AlaNCA. Unfortunately the yields could not be improved and the correct ratio of polypeptide linked to the porphyrin has not been determined.(By MS-FAB$^+$ it could be in the range of 4 - 5 units of aminoacid *per* porphyrin).

All these unconfortable results, together with the known difficulties to isolate the porphyrin regioisomer only featuring amino groups on the phenyl rings in positions 5, 15 as **3a** prompted us to find an alternative synthetic way to reach the desired structure of biomimethic catalyst **3b** bearing two polypeptide chains on the opposite faces of the tetrapyrrolic macroring (figure 1-B) which is the actual target of this research project (figure 1).

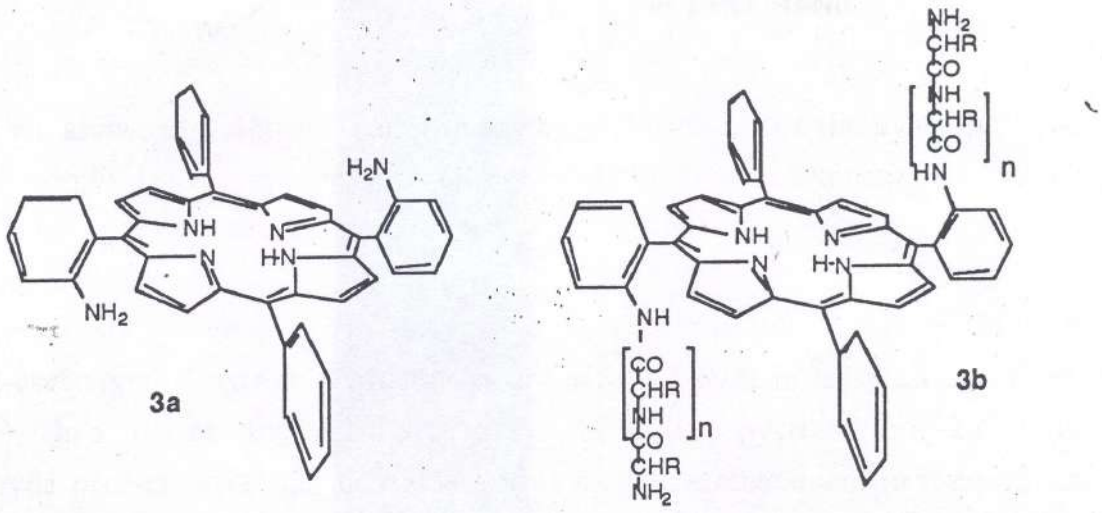
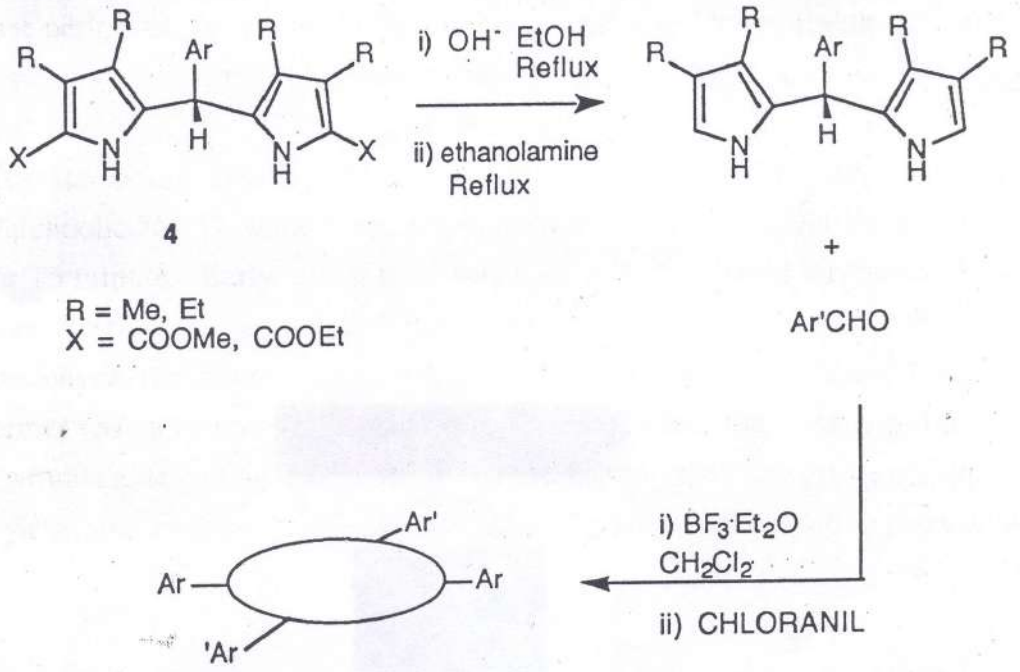


Figure 1

One synthetic pathway was envisaged in the use of dipyrrilarylmethane **4** as intermediate for the synthesis of tetraarylporphyrins showing differently substituted phenyl rings in the meso positions; indeed the condensation of two molecules of **4** with two aromatic aldehydes would produce tetraarylporphyrins of the type represented below (scheme 4).



Scheme 4

As far as we know, this sinthetic pathway has been only used for the synthesis of diaryl substituted porphyrins *via* condensation of dipirrylmethanes with aromatic aldehydes or of aryldipirrylmethanes with formaldehyde or orthoformiates.

It is known that chemically stable dipyrrilarylmethanes are those bearing alkyl substituents on pyrrole β-positions and are quite easily sinthetized by condensations of two molecules of 3,4 dialkyl -2-carboxyethyl pyrrole [4] with one of aromatic aldehyde in the presence of an acid catalyst.[5] Thus by reacting 3,4-dimethyl-2-carboxyethyl pyrrole with 2,6-dichloro benzaldehyde or 2-chloro,6-nitrobenzaldehyde in dichloromethane and in the presence of $BF_3{\cdot}Et_2O$ as catalyst, the corresponding dipirrylmethanes (**4a** ,**4b**) were obtained in 65 and 60% yields respectively. It must be pointed out that the same reaction performed in EtOH and HCl as catalyst, as generally reported in the literature,[6] gave the mono adduct **5** as the main product (figure 2).

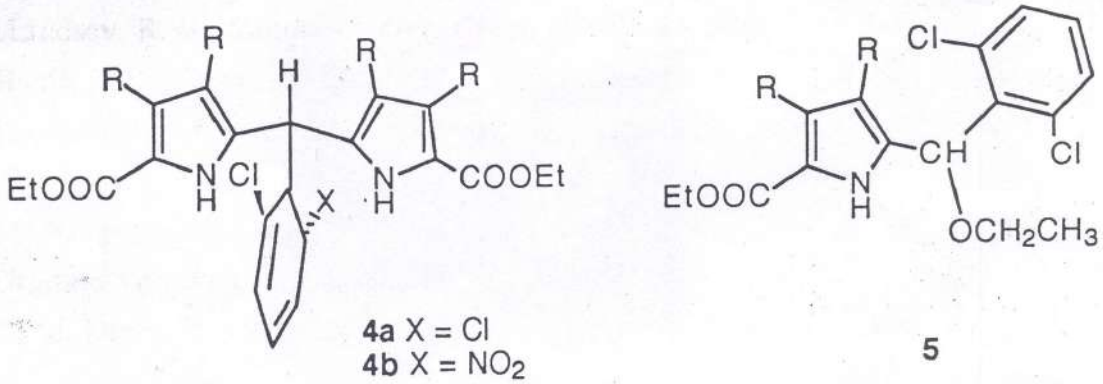


Figure 2

In the last period of the stage the final condensation of dipirrylmethanes with aromatic aldehydes to give the porphyrin was attempted. This reaction can be carried out either starting from the diacid derivative **6** [5a] or by using the decarboxylated dipyrrilmethane **7** [5b] (figure 3),the former being easily obtained by hydrolisis of the ester functions of **4** in aqueous/alchoolic NaOH, while **7** was prepared from **6** by decarboxylation in ethanolamine at reflux for 15 minutes. Early attempts to obtain octaalkyl-tetraarylporphyrins from **6** failed. Better results gave the reaction of **7** either with 2,6-dichlorobenzaldehyde or 2-chloro,6-nitrobenzadehyde, the corresponding porphyrins being obtained in 16% and 20% respectively. In the former case a symmetric porphyrin is obtained, while the condensation of **7** with the nitro substituted aldehyde give only the porphyrin bearing the nitro group on opposite phenyl rings in yields much higher than those obtained by the mixed condensation procedure.

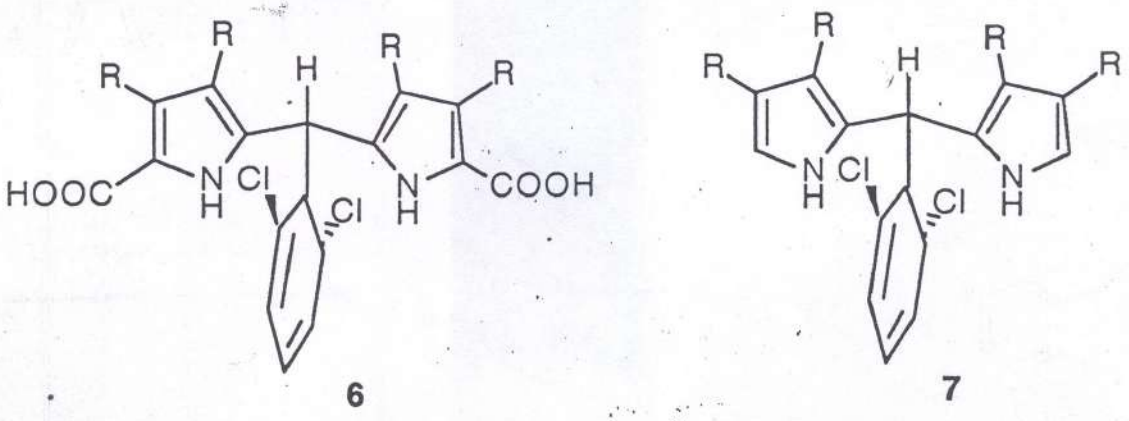


Figure 3

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