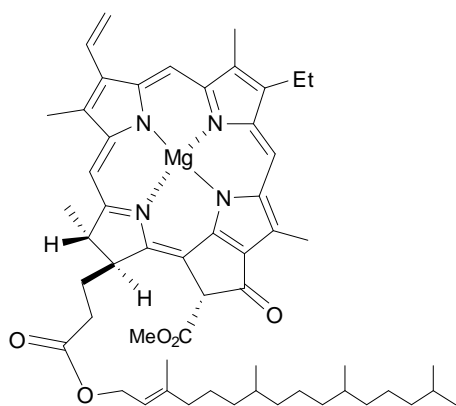


The Total Synthesis of Chlorophyll

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Fresh from his dramatic conquest of the blood pigment, Fischer hurdled his legions in the attack on chlorophyll, and during a period of approximately 15 years, built a monumental corpus of fact. As this chemical record, almost unique in the scope and depth, was constructed, the molecule was transformed and rent asunder in innumerable directions, and the fascination and intricacy of the chemistry of chlorophyll and its congeners was fully revealed. These massive contributions were crowned by the proposal, in 1940 of a structure which was complete except for stereochemical detail.

– R B Woodward

Ping-pong is played by the proton on the Chlorophyll table!

– S Ranganathan

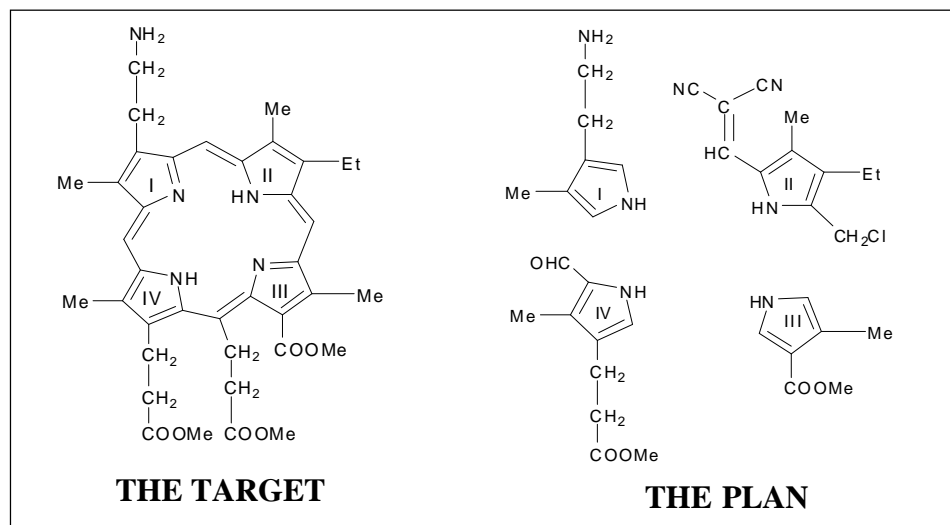
The four simple building blocks, two of which were known and others easily made must now be united in a specific manner. The control of the nature of the ring nitrogen presented a formidable challenge in this endeavour.

Ring II + III

Ring II is notable because the α -carbonyl needed, is protected with malanonitrile (1). This condensed readily with 2 to specifically provide 3, which was functionalized with β -carbomethoxy propionyl chloride to provide 4. Aq NaOH removed the protecting group to generate the aldehyde which on esterification afforded the

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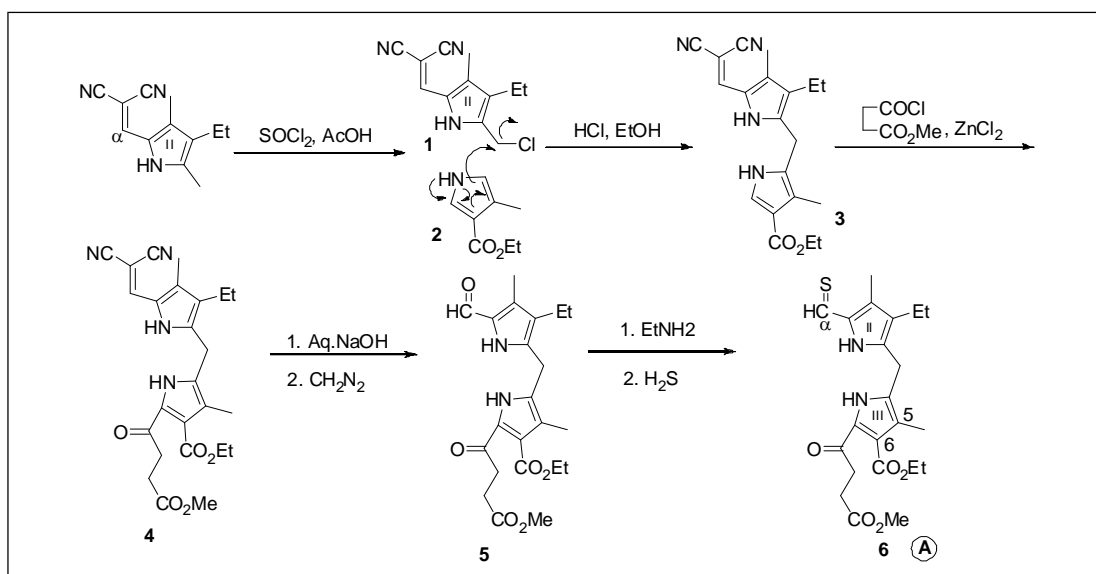


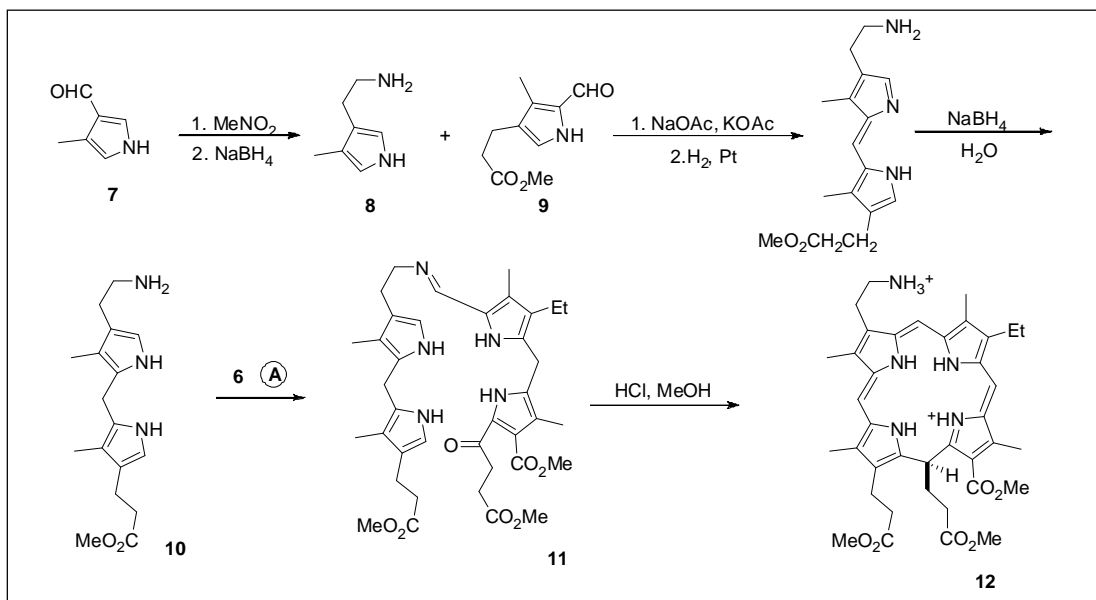
methylester **5** which was transformed to the thio aldehyde **6** (Scheme 1) via the Schiff's base from EtNH₂.

Ring I + IV

4-methyl pyrrole 3-carboxaldehyde (**7**) was transformed to **8** coupled with aldehyde **9** and the resulting product reduced to give the key intermediate **10** (Scheme 2) which on treatment with **6** (A), gave the sensitive Schiff's base **11** which was introduced into

Scheme 1.



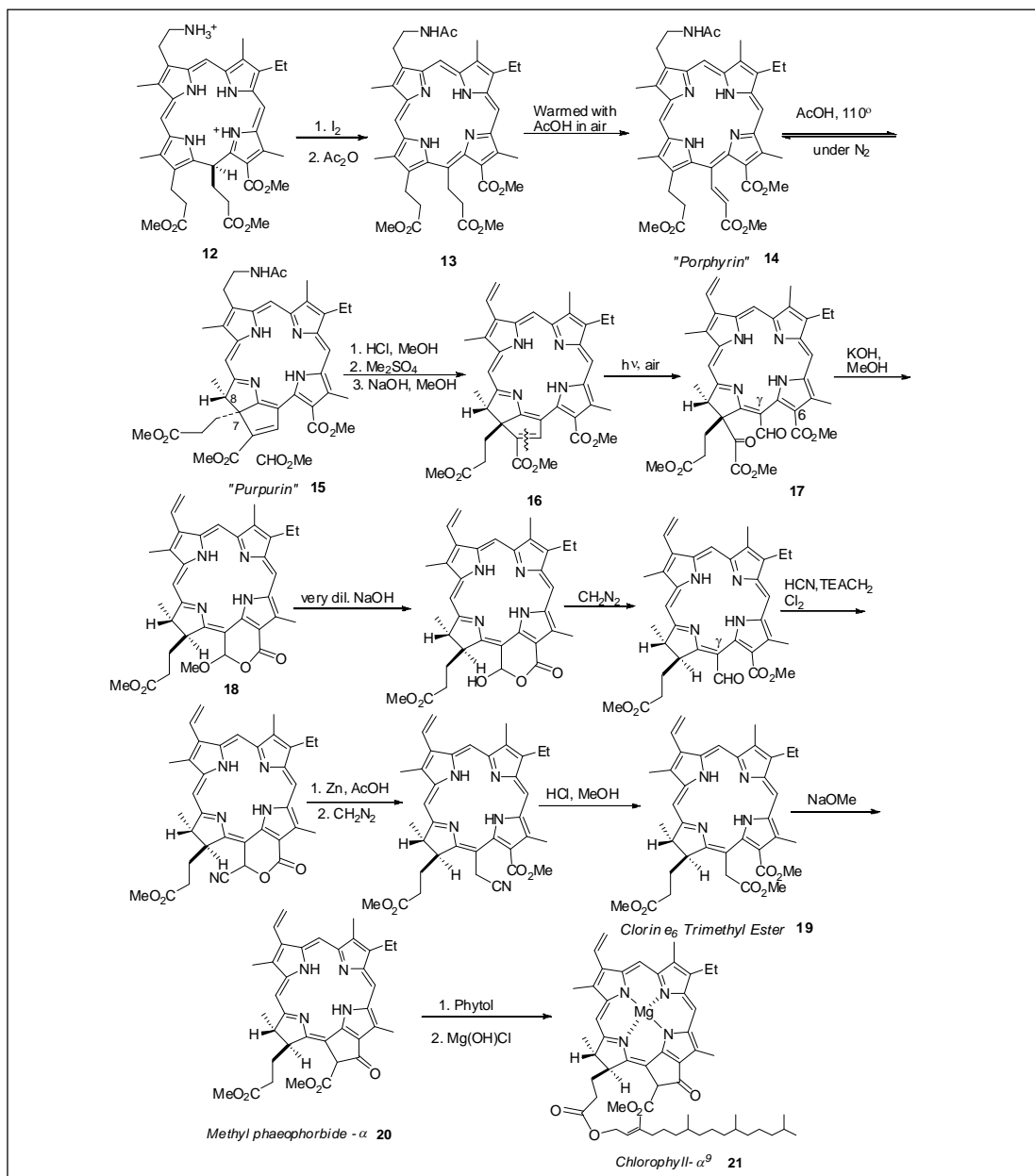


CH_2Cl_2 , evaporated and immediately introduced into MeOH.HCl to give the stable **12**. It may be noted that in the formation of **12** both the bridges connecting all the four rings were simultaneously formed.

Scheme 2.

Compound **12** was oxidized with I_2 and the product isolated to give **13**. This crystalline porphyrin can be isolated in gram quantities! The next task would be the proper placement of the only chiral centres at 7 and 8. Treatment of **13** with AcOH in air on steam bath led to the porphyrin **14**, which when held at 110°C in AcOH afforded the purpurin **15**. This is the first example of porphyrin \rightarrow purpurin change. Indeed Woodward anticipated this because such a change not only makes 7 and 8 tetrahedral, but also relieves the strain around the lower bridge! As the next step, the $\text{CH}_2\text{CH}_2\text{NHAc}$ of **15** was transformed to the $-\text{CH}=\text{CH}_2$ group by a sequence of hydrolysis, methylation and Hoffmann elimination to **16**. When **16** was exposed to strong visible light in the presence of air, it was transformed to **17**. It is most appropriate that the key reaction in this synthesis is the one brought about by oxygen! Treatment of **17** with MeOH/KOH , the methoxy group was cleaved and replaced. The hydrolysed acrylic acid interacted with proximate CHO , eventually leading to **18** (Scheme 3). The maverick nature of the lactoether in **18** has been beneficially taken advantage by Woodward in reaching **19**! Dieckman





cyclization of **19** afforded methyl pheaphorbide α (**20**; R = Me). **Scheme 3.**

The ester at the chiral centre was replaced by phytol and the magnesium introduced to yield **21**, chlorophyll- α^9 .

Suggested Reading

[1] R B Woodward, The Total Synthesis of Chlorophyll, *Pure and Appl. Chem.*, Vol.2, pp.383–404, 1961.