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Sapphyrin Total Synthesis: The Persistent Trade-off Between Precursor Preorganisation and Step Economy

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Abstract. Porphyrins and expanded porphyrins are important macrocycles with applications in catalysis, molecular recognition, metal coordination, nonlinear optics, magnetic resonance imaging, and photodynamic therapy. Among them, sapphyrins are 22π-electron expanded porphyrins composed of five pyrrolic or heterocyclic units connected by four meso-carbon bridges and one direct pyrrole–pyrrole bond. Their distinctive structure, extended aromaticity, large central cavity, and red-shifted optical absorption have stimulated the development of increasingly efficient synthetic methods. This Review summarizes the major strategies used for sapphyrin construction, with particular emphasis on MacDonald-type fragment condensations, Lindsey-type multicomponent reactions, and Rothemund-type statistical condensations. Representative syntheses are compared in terms of precursor design, macrocyclization mechanism, oxidation step, product yield, substrate scope, and practical limitations. This discussion takes a traditional mechanistic organic chemistry view, and it highlights how the formation of the 22π-electron macrocycle is controlled by several processes, namely acid-catalysed pyrrole–aldehyde condensation, precursor preorganization, direct pyrrole–pyrrole bond formation, and oxidative aromatization. This Review is meant to serve as an accessible introduction for students and researchers who are new to sapphyrin chemistry.

Keywords: sapphyrin, expanded porphyrins, total synthesis, macrocyclization, precursor preorganisation

1. Introduction

Porphyrins are often called the "pigments of life," and they play indispensable roles in basic biological processes such as oxygen transport, cellular respiration, photosynthetic light harvesting, and enzymatic catalysis. Building on the remarkable structural and functional versatility of porphyrins, researchers began to explore larger macrocyclic analogues, which are now referred to as expanded porphyrins. Sapphyrin was the first member of this class to be reported. Its name comes from the Greek word sappheiros ("sapphire"), reflecting its characteristic deep-blue color [1–3].

The first sapphyrin was obtained by R. B. Woodward and co-workers during studies connected with the total synthesis of vitamin B12. In an attempt to convert a tetrapyrrolic intermediate into the corresponding corrole, the precursor was treated with formic acid and hydrogen bromide. Instead of forming the expected tetrapyrrolic macrocycle, the reaction gave a pentapyrrolic product in low

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yield, and this product appeared as an intensely blue material, Woodward first reported this finding at the Aromaticity Conference held in Sheffield in 1966, and he proposed the name "sapphyrin" because of its sapphire-like color, although the full synthetic and structural details were not published until 1983, this unexpected result already showed that a stable aromatic macrocycle made of five pyrrole rings could indeed be formed [4, 5].

During the 1980s and 1990s, Jonathan L. Sessler and his coworkers developed practical synthetic routes to sapphyrins, and they also demonstrated that these compounds have an exceptional ability to act as anion receptors for both neutral and protonated species, these pioneering studies established sapphyrins as one of the most important classes of expanded porphyrins, and they also stimulated extensive research into their synthesis, coordination chemistry, and functional applications [7, 8].

As a key member of the expanded porphyrin family, sapphyrin has drawn considerable interest because of its unique macrocyclic structure, structurally, it can be seen as an expanded analogue of porphyrin, and it consists of five pyrrole rings connected by four meso-carbon bridges plus one direct α–α pyrrole–pyrrole bond, this arrangement creates a 22π-electron aromatic pathway and gives a central cavity that is larger than that of a regular porphyrin, as shown in Figure 1, sapphyrin thus combines structural features from both porphyrin and corrole, like porphyrin, it has four meso-carbon bridges, and like corrole, it contains a direct pyrrole–pyrrole linkage, in this sense, it sits between conventional porphyrins and larger pentapyrrolic macrocycles, because it satisfies Hückel's 4n+2 rule (with n=5) and shows aromatic character, whereas porphyrin and corrole both have 18π-electron aromatic cores, sapphyrin and pentaphyrin each contain five pyrrole units and a 22π-electron conjugated pathway, but they differ in the number and arrangement of meso-carbon bridges and also in where the direct pyrrole–pyrrole bond is located, this distinction should be understood together with Figure 2 [2, 3, 5].

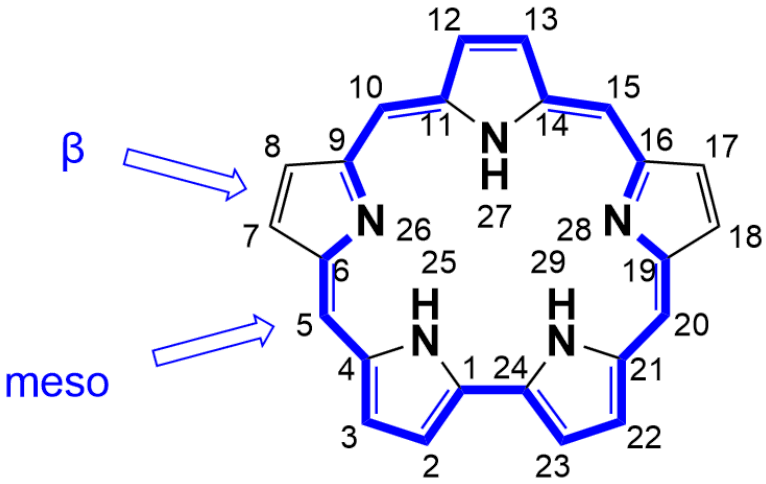

Figure 1. Molecular structure and atom-numbering scheme of sapphyrin [3]

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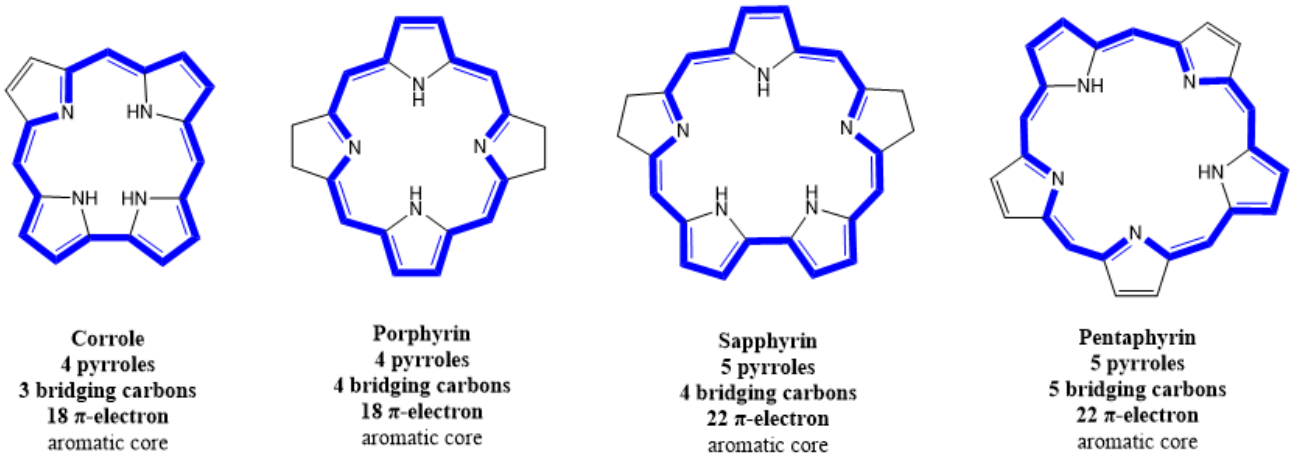

Figure 2. A comparison of the core structures of corrole, porphyrin, and sapphyrin, with the shortest π-electron conjugation pathway of each macrocycle shown in bold [3]

The structural features of sapphyrin give rise to distinct electronic and functional properties, its five-heterocycle, 22π-electron conjugated framework provides a larger and more donor-rich central cavity compared with that of a regular porphyrin, and this enables unique protonation behavior, anion-binding ability, and metal-coordination performance, its extended π-conjugated pathway also leads to characteristic spectral and redox properties, for example, its absorption occurs at wavelengths that are red-shifted relative to those of porphyrins [2, 3].

These properties have supported the investigation of sapphyrins as anion receptors and sensors, transmembrane carriers, DNA-binding and photocleaving agents, components of supramolecular and nanostructured assemblies, and photosensitizers for photodynamic therapy [2, 3, 8].

Importantly, these properties are not fixed by the parent macrocyclic framework. Peripheral substitution at the β- and meso-positions, together with core modification through replacement of pyrrole units with other heterocycles, provides direct means of tuning aromaticity, binding affinity, redox behaviour, and photophysical properties. Such structural modifications therefore establish a direct connection between molecular design and functional applications. At the same time, they place additional demands on synthetic methodology, since access to different substitution patterns and core architectures depends critically on the availability of appropriately functionalised precursors and on the selectivity of macrocyclization reactions. Consequently, the development of efficient and structurally versatile synthetic routes is essential for expanding the chemical diversity and functional scope of sapphyrin-based systems [2, 3, 8].

This review gave a focused, reaction-centred account of the landmark strategies that have been developed for constructing the sapphyrin framework. Earlier reviews surveyed expanded porphyrins as a broad class, or discussed sapphyrins together with smaragdyrins across synthesis, characterization, coordination chemistry, anion recognition, and applications; in contrast, the present Review concentrates specifically on the synthetic logic behind classical sapphyrin formation. Particular emphasis is placed on the MacDonald-type [3+2] condensation, Lindsey-type multicomponent synthesis, Rothemund-type statistical condensation, and representative [4+1] approaches. These routes are not catalogued simply according to the substitution patterns or functional properties of sapphyrin derivatives; instead, they are organized and compared according to their bond-forming strategies, precursor design, proposed mechanisms, macrocyclization selectivity, oxidation conditions, isolated yields, substrate scope, and practical limitations. By reassessing these landmark reactions from a mechanistic organic chemistry perspective, this Review

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clarifies how sapphyrin synthesis moved forward from Woodward's serendipitous discovery to increasingly rational and versatile synthetic methods, while also identifying precursor accessibility, selective macrocyclization, and oxidative aromatization as persistent challenges that continue to shape the development of the field [2, 3].

2. Major synthetic strategies for sapphyrin construction

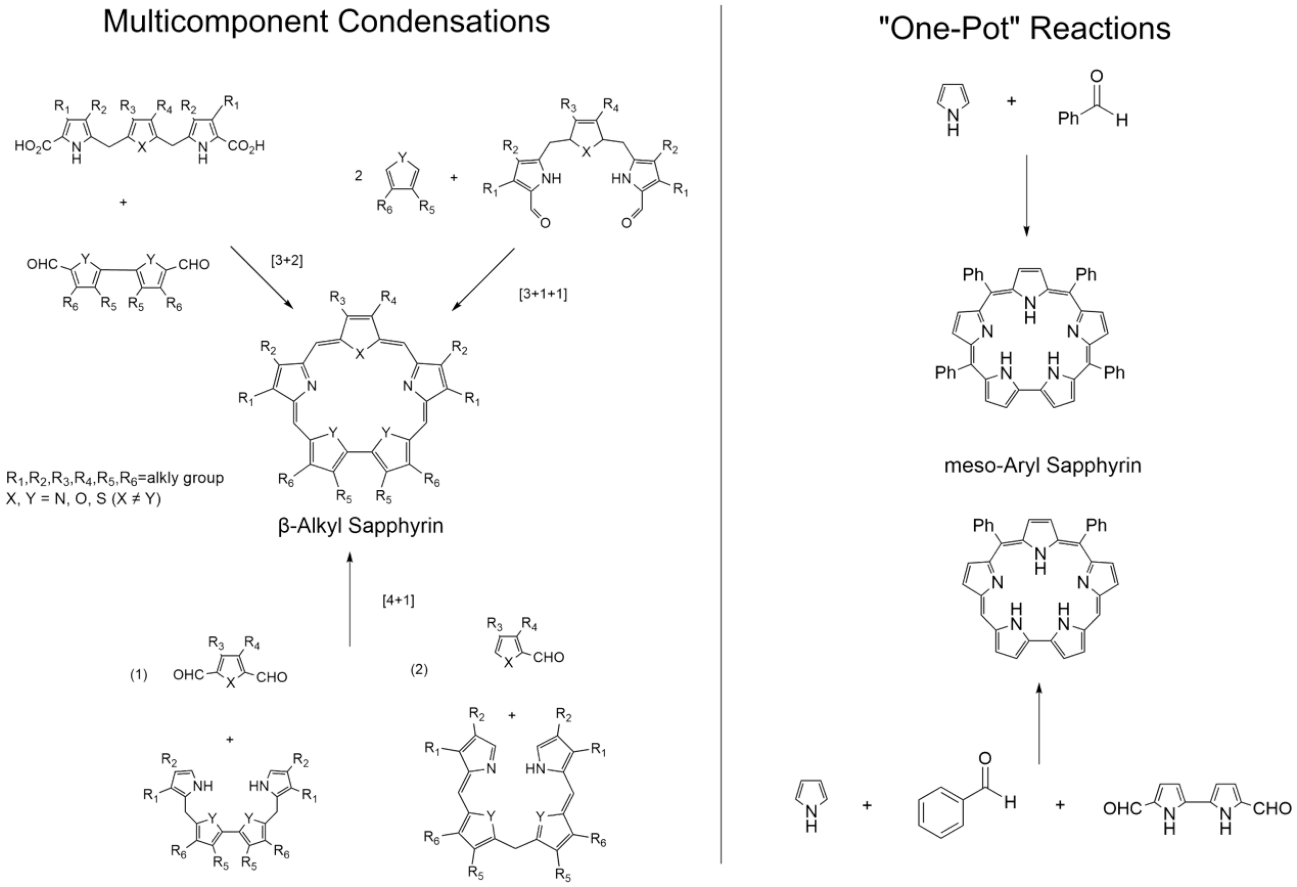

Figure 3. Some of the approaches used to build up sapphyrins [3]

As summarized in Figure 3, the principal synthetic strategies for sapphyrins, many of which were adapted from established porphyrin chemistry, can be broadly divided into multicomponent condensations and one-pot approaches. Multicomponent strategies use appropriately functionalized oligopyrrolic fragments, and these fragments are assembled through combinations such as [3+2] or [4+1] condensations to form the sapphyrin macrocycle. The precise route is largely determined by the availability and accessibility of the required pyrrolic building blocks. Nevertheless, the use of prefunctionalized intermediates provides considerable structural control: substituents can be introduced at the β-positions before macrocyclization, and individual pyrrole units may be replaced by other heterocycles containing atoms such as oxygen or sulfur. Although Sessler and co-workers substantially improved these fragment-based routes and achieved relatively high yields, the multistep preparation and subsequent coupling of oligopyrrolic precursors remain among the most demanding and potentially optimizable stages of sapphyrin synthesis [2, 3].

In contrast, one-pot approaches try to construct the sapphyrin framework from simpler starting materials with fewer isolated intermediates. As illustrated in Figure 3, this category includes the

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direct condensation of pyrrole with aldehydes to produce meso-aryl sapphyrins, and it also includes routes that involve the formation of an open-chain pentapyrrolic precursor followed by macrocyclization. However, the assembly of the linear pentapyrrole remains difficult to control; even in a method optimized by a French research group in 2025 [9], this step proceeded in relatively low yield, primarily because both the sequence and the number of heterocyclic units incorporated during oligomerization are difficult to regulate. Such statistical assembly also provides less control over the heteroatom composition of the macrocyclic core. Although combining different heterocycles, such as pyrroles and furans, could increase structural diversity, the larger number of possible products would further reduce selectivity and isolated yield. Therefore, substantial opportunities remain to improve both the controlled preparation of linear pentapyrrolic intermediates and their subsequent ring closure. Compared with the well-established synthetic chemistry of porphyrins, sapphyrin synthesis remains less mature and consequently offers greater scope for methodological innovation and future breakthroughs [3, 9].

2.1. MacDonald-type approaches to the synthesis of sapphyrins

The classical MacDonald synthesis of porphyrins is based on an acid-catalysed [2+2] condensation between an α,α′-diunsubstituted dipyrrylmethane and a diformyl dipyrrolic component. Alternatively, an α,α′-dicarboxyl-substituted dipyrrylmethane may be used because the terminal carboxyl groups undergo rapid decarboxylation under the acidic reaction conditions, generating the reactive α-positions required for macrocyclisation. The resulting reduced macrocyclic intermediate is subsequently oxidised to afford the aromatic porphyrin, as illustrated in Figure 4 [1].

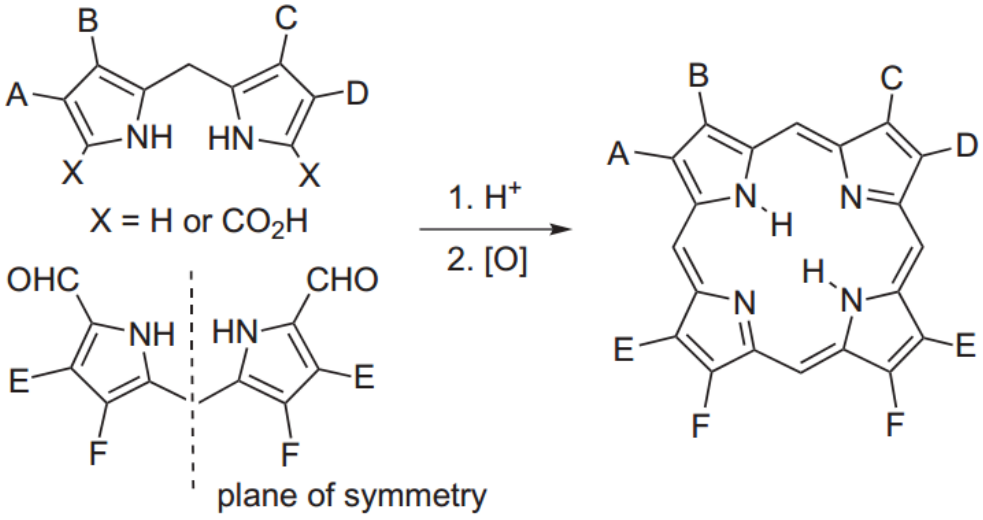

Figure 4. General porphyrin synthesis using MacDonald's method [1]

2.2. Johnson's rational [3+2] MacDonald-type synthesis of sapphyrins

This modular strategy was later extended by Johnson and co-workers to the synthesis of sapphyrin-type macrocycles. Their work represented a direct adaptation of the classical MacDonald porphyrin synthesis: instead of combining two dipyrrolic fragments in a [2+2] process, they condensed a two-ring component with a tripyrrane dicarboxylic acid in a [3+2] assembly. Under acidic conditions, the terminal carboxyl groups of the tripyrrane undergo decarboxylation, generating reactive α-positions that attack the protonated aldehyde groups of the diformyl bipyrrole. Two successive condensations

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establish the new meso-carbon linkages and close the pentapyrrolic ring, after which oxidation with air or iodine produces the aromatic 22π-electron sapphyrin framework shown in Figure 5 [6].

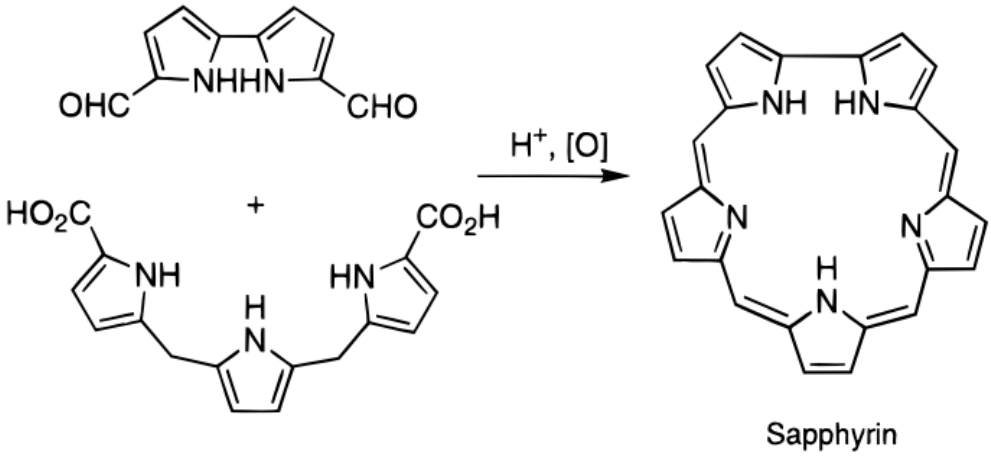

Figure 5. MacDonald "3+2" synthesis of sapphyrins [6]

Johnson's initial studies focused on the synthesis of a dioxasapphyrin in order to confirm the proposed structure of a by-product previously isolated during investigations of dioxacorroles. To achieve this, a diformyl two-ring component was subjected to acid-catalysed condensation with a bis(pyrrolylmethyl)pyrrole diacid, followed by oxidation with either air or iodine. The resulting dioxasapphyrin was obtained as a single isomer, as established by NMR spectroscopy. The same general strategy was subsequently applied to an all-aza sapphyrin, which was isolated in 46% yield, demonstrating that the MacDonald-type fragment-condensation approach could serve as a general method for constructing sapphyrin-type expanded porphyrins [5, 6].

Despite the conceptual elegance and useful macrocyclisation yields of the [3+2] route, its practical application was limited by the preparation of the two pyrrolic precursors. Both the diformyl bipyrrole and the tripyrrane dicarboxylic acid required lengthy, multistep syntheses involving carefully controlled functional-group transformations, and some intermediates showed limited stability and solubility. Consequently, although Johnson established the fundamental synthetic logic of the [3+2] MacDonald-type approach, the overall preparation remained long and tedious, creating an important need for later improvements in precursor synthesis [2, 3, 5, 6].

2.3. Sessler's rational [3+2] MacDonald-type synthesis of sapphyrins

Johnson established the conceptual [3+2] MacDonald-type disconnection, whereas Sessler improved the preparative practicality of this strategy by simplifying access to the tripyrrane and bipyrrole components and demonstrating the synthesis of sapphyrin in useful quantities. Their approach relied on a [3+2] MacDonald-type condensation between a dicarboxyl-substituted tripyrrane 9 and a diformyl-substituted bipyrrole 15. This strategy addressed one of the major limitations of earlier syntheses, namely the long and tedious preparation of the required pyrrolic precursors [7].

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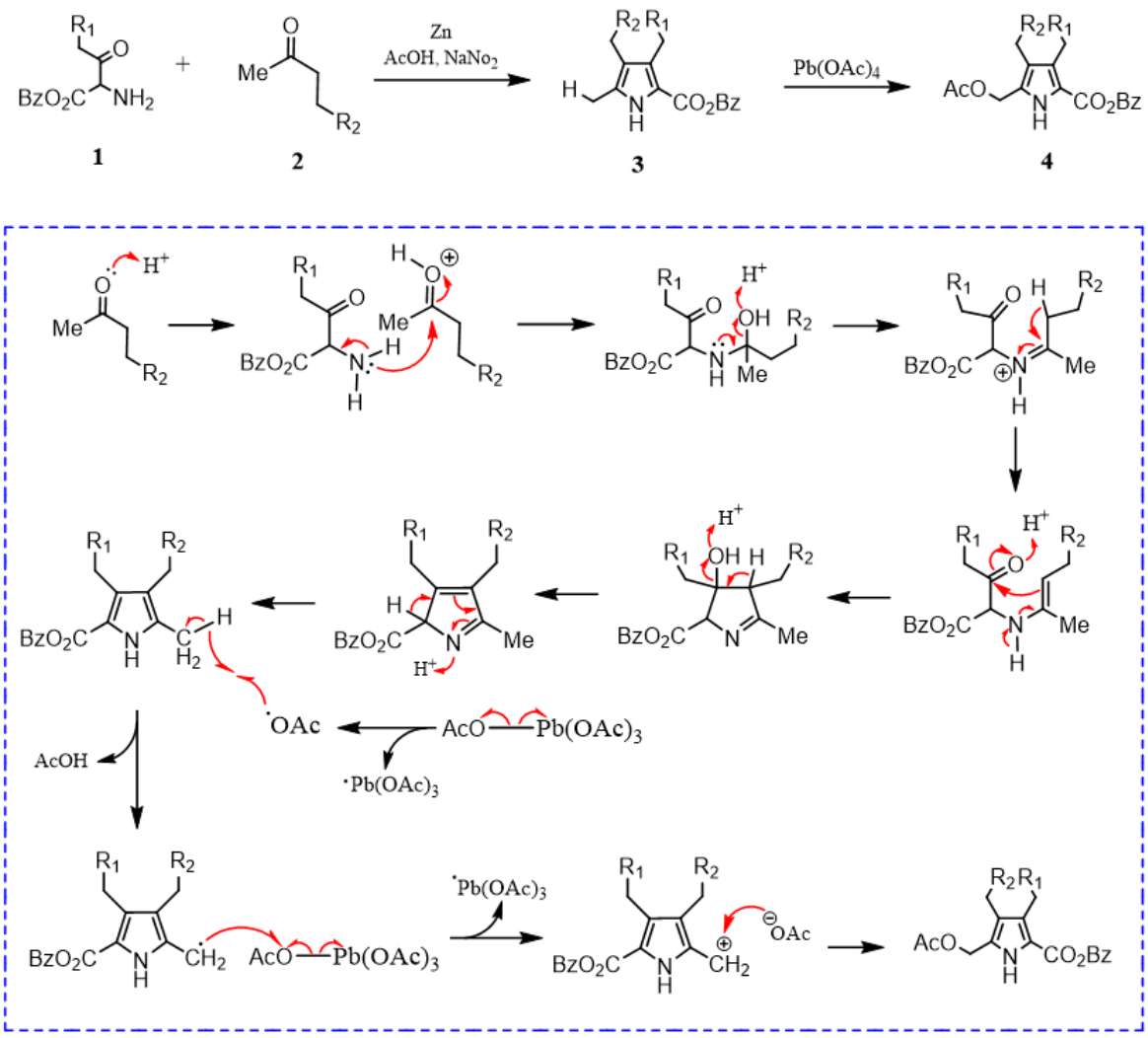

Figure 6. Proposed mechanisms for (left to right) the conversion of α-amino carbonyl compound 1 into pyrrole 3 with $Pb(OAc)_4$-mediated formation of acetoxymethyl-pyrrole 4

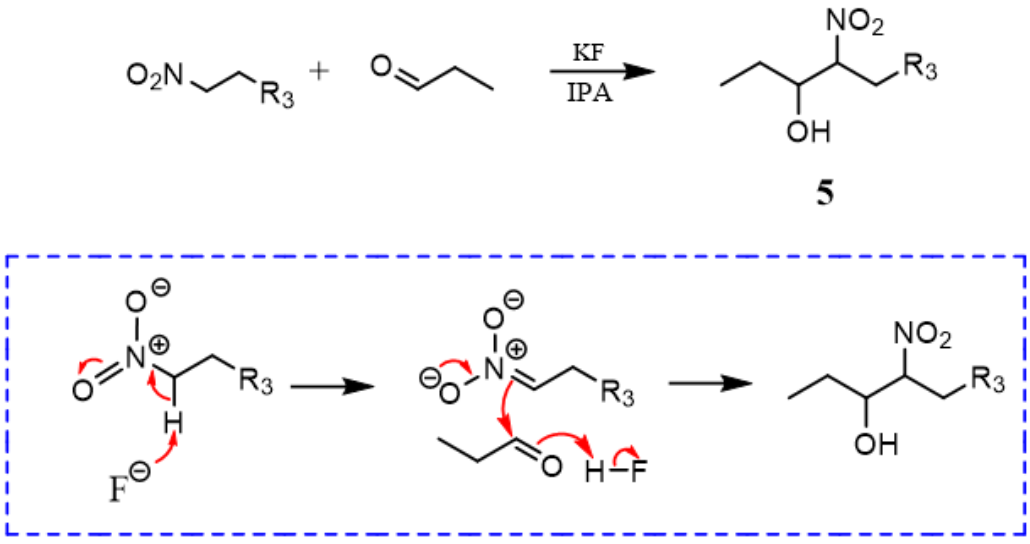

Figure 7. KF-promoted Henry reaction to β-nitro alcohol 5

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In this improved route, tripyrrane 9 was prepared in a simple, high-yielding sequence from pyrrole building blocks 4 and 8. Mechanistically, acid-promoted activation of the acetoxymethyl substituent in 4 generates an electrophilic methylene intermediate, which undergoes sequential electrophilic substitution with pyrrole 8 to form the linear tripyrrane framework. Subsequent hydrogenolysis removed the benzyl ester groups to furnish 9. The required pyrrole building blocks 4 and 8 were themselves obtained by established methods (Figure 6–8): pyrrole 4 from the $Pb(OAc)_4$-mediated acetoxymethylation of the α-methylpyrrole 3, and the α-free pyrrole 8 via a fluoride-promoted Henry reaction and a Barton–Zard pyrrole synthesis followed by hydrolysis and thermal decarboxylation [7, 10].

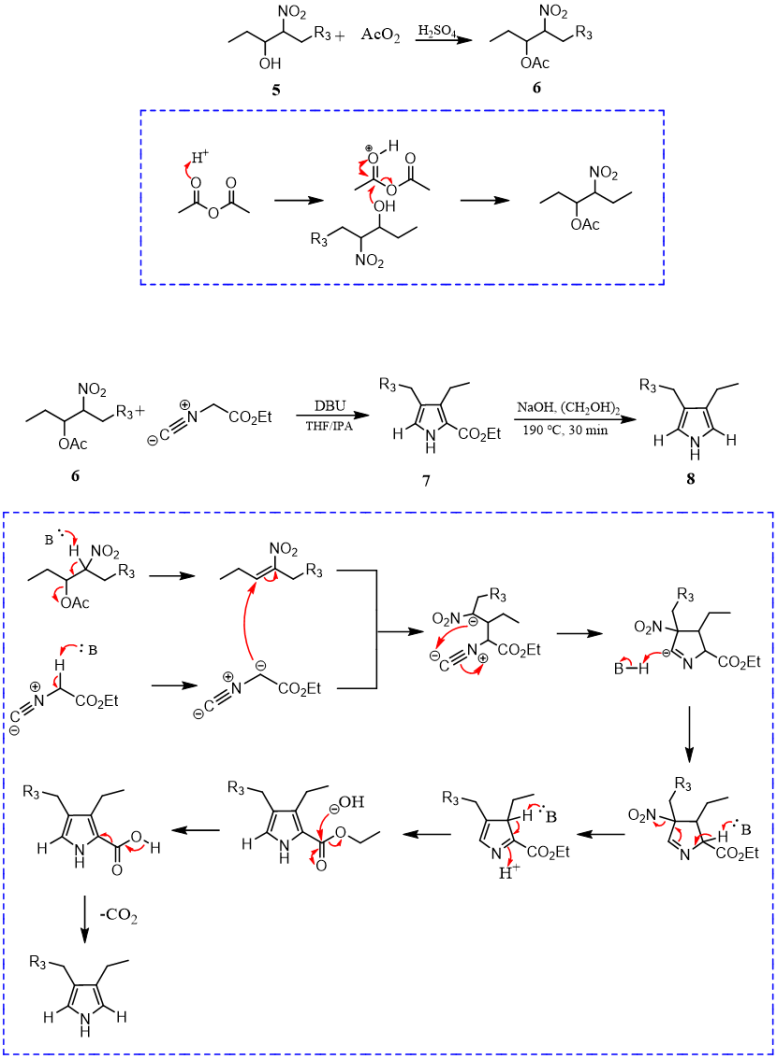

Figure 8. Barton–Zard synthesis of α-free pyrrole 8 [7, 10]

Sessler and co-workers also improved access to the bipyrrolic component. Through the Barton–Zard pyrrole synthesis they obtained the required α-free pyrrole 10, which, after N-Boc protection and copper-mediated Ullmann homocoupling, gave a bipyrrole that was converted by thermolysis, hydrolysis/decarboxylation, and Vilsmeier formylation into the key diformyl bipyrrole 15. Final acid-catalysed condensation of 9 and 15, followed by oxidative cyclization, afforded sapphyrin 16 (Figure 9-11) [7, 10].

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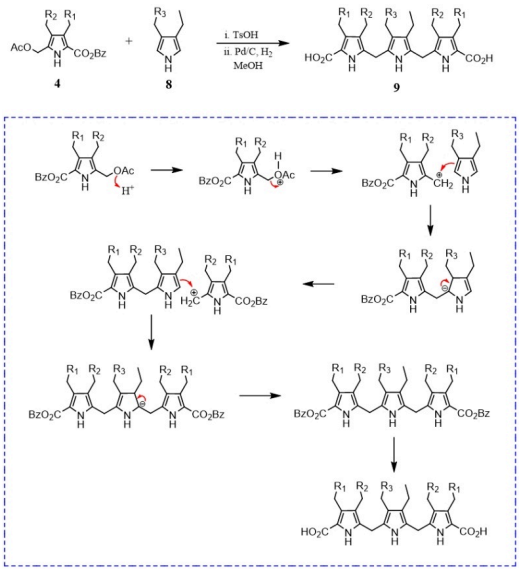

Figure 9. Proposed mechanism for the acid-promoted formation of tripyrrane 9 from pyrroles 4 and 8, followed by hydrogenolytic debenzylation

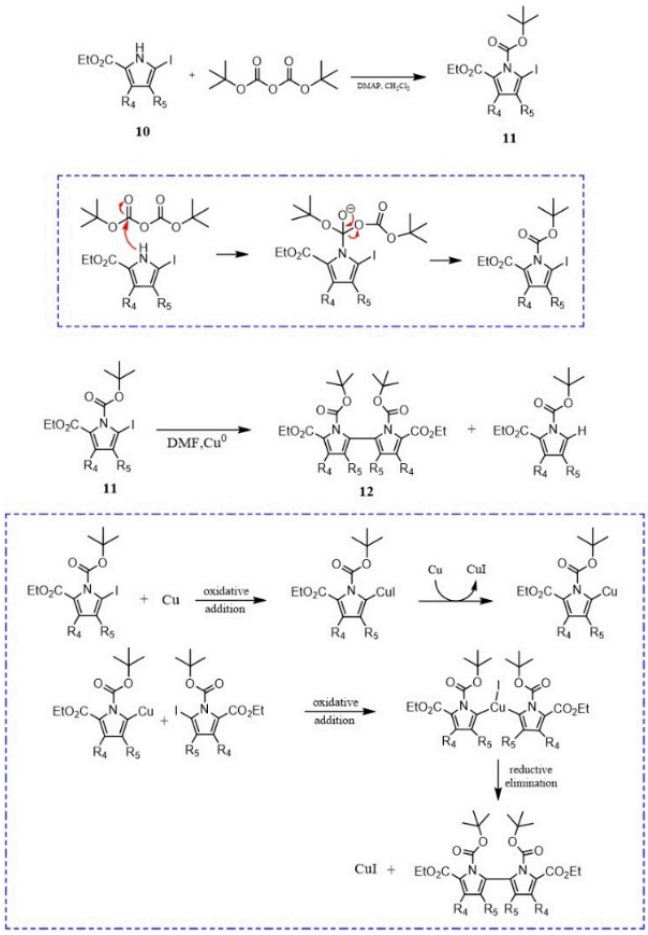

Figure 10. Proposed mechanisms for the N-Boc protection of iodopyrrole 10 and the subsequent copper-mediated Ullmann homocoupling of 11 to form bipyrrole 12

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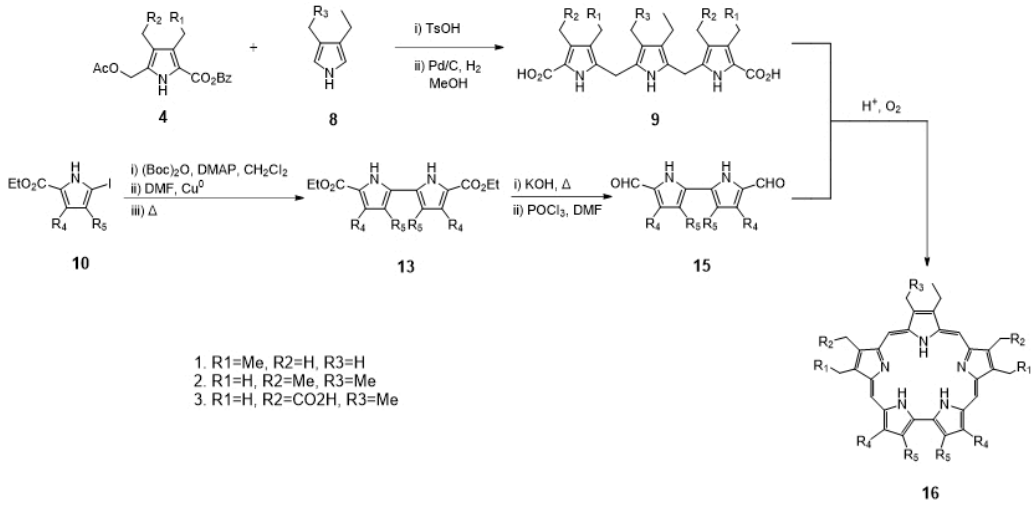

Figure 11. Sessler's improved MacDonald-type [3+2] synthesis of sapphyrin 16 from tripyrrane dicarboxylic acid 9 and diformyl bipyrrole 15

This work marked a turning point in sapphyrin synthesis, because it combined a rational fragment-coupling strategy with better precursor accessibility, and this greatly improved the practical usefulness of the [3+2] MacDonald-type approach for preparative purposes [7, 8].

2.4. Woodward's rational [4+1] and lash [4+1] MacDonald-type synthesis of sapphyrins

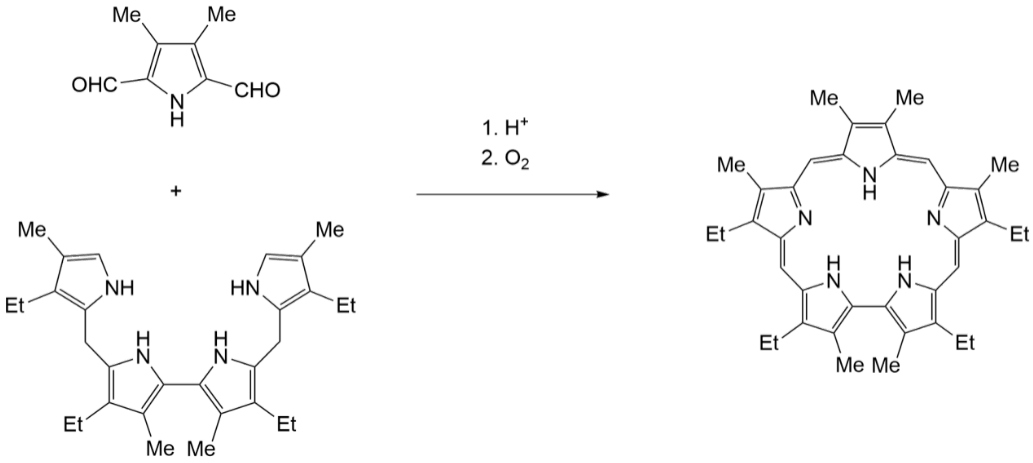

Figure 12. "4+1" synthesis of a sapphyrin [5].

In the [4+1] approach, a preformed linear tetrapyrrolic precursor was condensed with 2,5-diformyl-3,4-dimethylpyrrole under acidic conditions, followed by oxidation to afford the aromatic sapphyrin. The [4+1] designation reflects the combination of a linear tetrapyrrole and a monopyrrolic dialdehyde. Unlike statistical pyrrole–aldehyde condensations, the tetrapyrrolic precursor already contained the characteristic direct pyrrole–pyrrole linkage, thereby predetermining the number and sequence of pyrrolic units and allowing the final macrocyclisation to form only the two remaining meso linkages. This structure-directed strategy provided a rational alternative to the classical [3+2] MacDonald-type approach(Figure 12) [5].

Despite its conceptual advantages, Woodward's [4+1] route was limited by the difficult preparation of the required linear tetrapyrrolic precursor. The precursor required multiple protection,

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reduction, oxidation, and functional-group interconversion steps, while several intermediates were sensitive to acid, air, or light. The final macrocyclisation also proceeded in only modest yield and required strong acid, controlled oxidation, and extensive purification. Consequently, Woodward's approach was less widely adopted than the more practical [3+2] MacDonald-type strategy [2, 3, 5].

A more accessible tetrapyrrolic precursor was later developed by Sessler and co-workers during their studies of rubyrins. As shown in figure 13, acid-promoted condensation of a dipyrrolic component with two equivalents of a functionalised pyrrole in an acetic acid–ethanol mixture provided tetrapyrrole 11, making the [4+1] strategy more accessible for subsequent development [11].

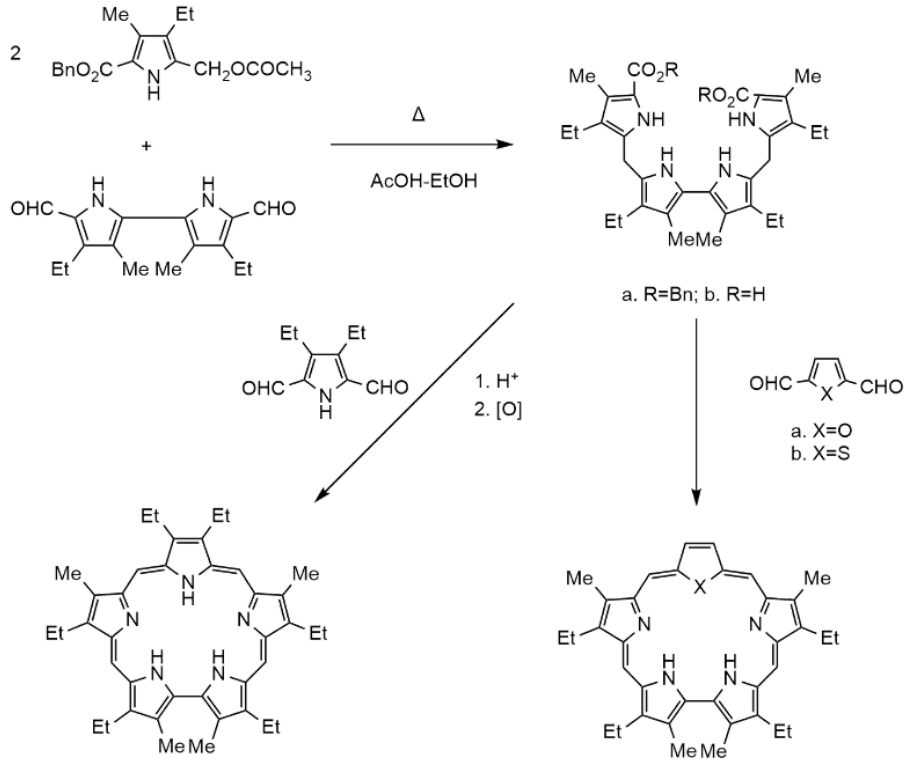

Figure 13. Preparation of tetrapyrrole 11 and its acid-catalyzed "4 + 1" condensation with heterocyclic dialdehydes to give sapphyrin 14, oxasapphyrin 16, and thiasapphyrin 17 [11]

Building on this improved precursor, Lash and co-workers revived and extended the [4+1] strategy. Tetrapyrrole 11 was condensed with pyrrole-2,5-dialdehyde 15 under acidic conditions, followed by oxidation to give sapphyrin 14, isolated as 14·2HCl. Replacement of the pyrrole dialdehyde with furan- and thiophene-derived dialdehydes 18a and 18b further afforded oxasapphyrin 16·2HCl and thiasapphyrin 17·2HCl, respectively. The modularity of the approach was subsequently demonstrated through the synthesis of additional expanded macrocycles, including systems containing fused phenanthrene and acenaphthylene units, as well as carbasapphyrins and an azulisapphyrin [11].

Lash and co-workers therefore did not introduce a fundamentally new macrocyclisation mode, but rather revived, refined, and broadened Woodward's [4+1] strategy, demonstrating its potential for the synthesis of structurally diverse sapphyrin and related expanded porphyrinoids [11].

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2.5. Paolesse MacDonald-related "4+1" cyclization

Paolesse and co-workers developed a new biladiene–formylpyrrole "4+1" route to sapphyrins in order to overcome the limitations of the classical Woodward–Sessler syntheses. The traditional MacDonald-type "3+2" approach required the preparation of a tripyrrane dicarboxylic acid and a bipyrrole dialdehyde, while the earlier "4+1" route relied on an even less accessible bipyrryldipyrromethene precursor. In both cases, the direct pyrrole–pyrrole linkage required in the sapphyrin skeleton had already been introduced at an early stage of the synthesis. This dependence on structurally elaborate oligopyrrolic intermediates made the routes lengthy and restricted the range of peripheral substitution patterns that could be obtained [12].

Paolesse's strategy reversed this conventional bond-forming sequence. As shown in Figure 14, a preformed 1,19-diunsubstituted a,c-biladiene was used as the tetrapyrrolic "4" component and condensed with a 2-formylpyrrole as the monopyrrolic "1" component under acidic conditions, following the same condensation–dehydration sequence described above. Protonation of the aldehyde activates it towards attack by one terminal α-position of the biladiene, generating an open-chain pentapyrrolic intermediate that folds to bring its two remaining terminal α-positions into proximity; a late-stage intramolecular α–α bond formation then closes the macrocycle, and subsequent oxidation establishes the fully conjugated sapphyrin system. Thus, unlike the classical routes, the direct pyrrole–pyrrole bond is formed during the final macrocyclization step rather than being preassembled in one of the starting fragments [12].

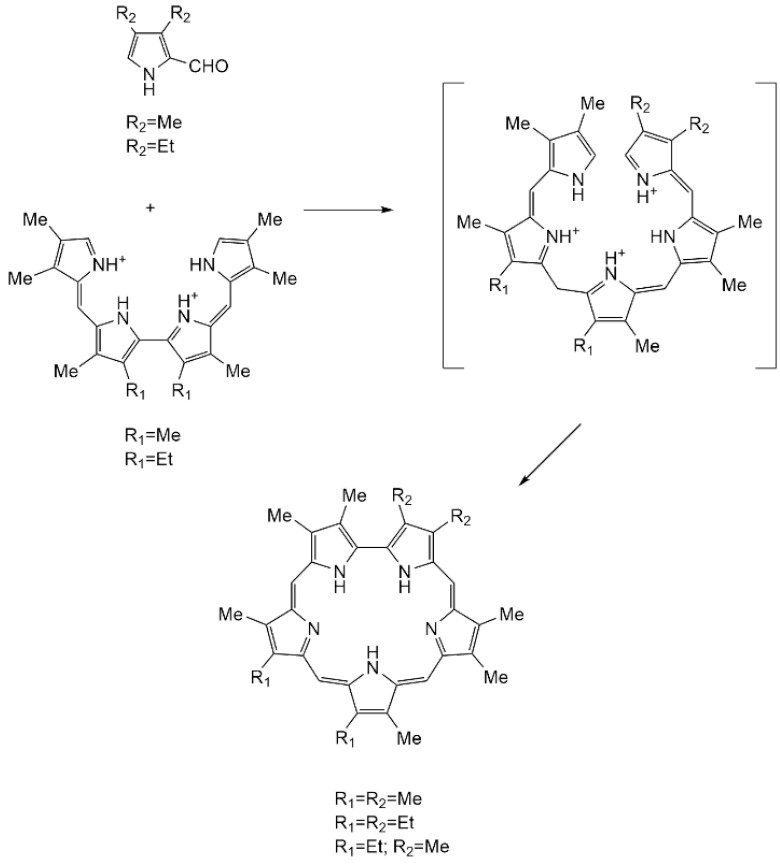

Figure 14. Paolesse's acid-catalysed [4+1] synthesis of substituted sapphyrins from an a,c-biladiene and a formylpyrrole

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The principal advantage of this approach is its greater control over peripheral substitution. Because the four-pyrrole sequence is already defined in the a,c-biladiene and the fifth pyrrole is introduced independently as a formylpyrrole, the method permits the construction of less symmetrical sapphyrins that would be difficult to obtain from symmetrically substituted tripyrrane and bipyrrole precursors. It also avoids the separate preparation of the bipyrrole dialdehydes required in the classical "3+2" synthesis. Nevertheless, the route does not eliminate the need for a structurally complex oligopyrrolic precursor, since the a,c-biladiene must still be prepared in advance. In addition, the late-stage direct α–α coupling is likely to be highly dependent on the conformation, substitution pattern and steric environment of the pentapyrrolic intermediate. The method should therefore be regarded as a strategically important route to peripherally unsymmetrical sapphyrins rather than as a universally superior replacement for the established Sessler synthesis. Paolesse's principal innovation was not simply the use of a "4+1" fragment combination, but the transfer of the direct pyrrole–pyrrole bond-forming event from precursor synthesis to the final macrocyclization step, thereby enabling greater control over unsymmetrical peripheral substitution [12].

2.6. LatosGrażyński identified tetraphenylsapphyrin in a Rothemund-type synthesis

In 1995, Chmielewski, Latos-Grażyński, and Rachlewicz identified 5,10,15,20-tetraphenylsapphyrin as a very minor product of the Rothemund-type acid-catalysed condensation of pyrrole and benzaldehyde. The same reaction also produced tetraphenylporphyrin and N-confused tetraphenylporphyrin, which shows that pyrrole–aldehyde self-assembly can follow alternative cyclooligomerisation pathways to form expanded macrocycles, not only the conventional four-pyrrole porphyrins. Structurally, tetraphenylsapphyrin can be seen as an enlarged porphyrin framework that contains an extra pyrrole unit and a direct pyrrole–pyrrole linkage, and this arrangement gives rise to an aromatic 22π-electron pentapyrrolic system. The Rothemund-type condensation used simple, readily available starting materials and did not require the preparation of preassembled bipyrrole and tripyrrane intermediates, so the approach was conceptually attractive. However, Chmielewski, Latos-Grażyński, and Rachlewicz obtained tetraphenylsapphyrin in only about 1% yield; subsequent systematic studies by Geier and Lindsey showed maximum yields of around 1.2%, and the yields were generally below 1% across a wider range of acid conditions. The same condensation also generated tetraphenylporphyrin, N-confused porphyrin, and oligomeric by-products, which made it difficult to control oligomer length, macrocycle size, and substituent arrangement; moreover, the resulting porphyrinoids exhibited similar chromatographic behaviour, so purification was difficult. The Rothemund-type condensation was therefore primarily important as a discovery route rather than as an efficient preparative method for sapphyrins. The Rothemund-type condensation revealed a previously unrecognised cyclooligomerisation pathway in pyrrole–aldehyde condensation and inspired more rational sapphyrin syntheses, in which formation of the direct pyrrole–pyrrole bond could be controlled during the final macrocyclisation step. The Rothemund synthesis is therefore best regarded as a discovery route that revealed the possibility of pentapyrrolic macrocycle formation, rather than as a generally efficient preparative method [13, 14].

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2.7. Brückner's non-decarboxylative, acid-catalysed [3+2] condensation of a preformed tripyrrane with a bipyrrole dialdehyde.

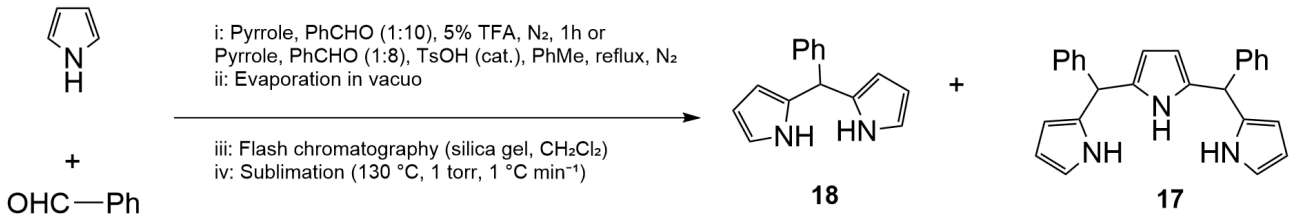

Figure 15. Proposed acid-catalysed formation of 5-phenyldipyrromethane 18 and 5,10-diphenyltripyrrane 17 from pyrrole and benzaldehyde [15]

In 1997, Brückner, Sternberg, Boyle and Dolphin developed a precursor-directed approach to meso-phenyl-substituted sapphyrins based on the readily accessible 5,10-diphenyltripyrrane. As illustrated in Figure 15, acid-catalysed condensation of commercially available pyrrole and benzaldehyde initially produces 5-phenyldipyrromethane 18. Mechanistically, protonation of the benzaldehyde carbonyl increases its electrophilicity, allowing nucleophilic attack by the electron-rich α-position of pyrrole. Subsequent dehydration and addition of a further pyrrole unit generate tripyrrane 17. Because these successive electrophilic substitutions are not completely selective, dipyrromethene 18 is formed alongside the desired tripyrrane 17 and must be separated. Nevertheless, this preparation is considerably simpler than that of the highly functionalised β-alkyltripyrrane precursors used in the classical Sessler–MacDonald [3+2] synthesis, which generally requires multiple steps from less readily available substituted pyrroles [15].

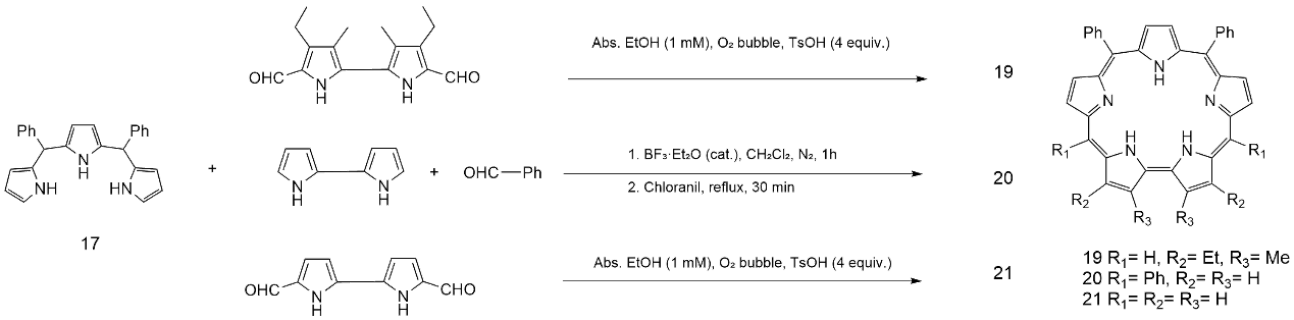

Figure 16. Proposed non-decarboxylative, acid-catalysed [3+2] condensation of tripyrrane 17 with a bipyrrole dialdehyde, followed by oxidation to form the aromatic sapphyrin macrocycle [15]

The subsequent formation of the sapphyrin macrocycle is shown in Figure 16. Under acidic conditions, protonation of the two aldehyde groups of the bipyrrole dialdehyde activates them towards nucleophilic attack by the two free terminal α-positions of tripyrrane 17. Two successive carbon–carbon bond-forming condensations connect the three-pyrrole and two-pyrrole fragments, producing a cyclic pentapyrrolic intermediate; dehydration followed by oxidation establishes the fully conjugated 22π-electron sapphyrin system. This reaction is therefore best described as a non-decarboxylative, acid-catalysed [3+2] condensation using a preformed tripyrrolic precursor. The same building block also enabled a four-component Rothemund-type condensation with bipyrrole and benzaldehyde to afford meso-tetraphenylsapphyrin 20. Preorganisation of three pyrrole units within 17 improved macrocycle-size selectivity: under the optimized conditions (tripyrrane 17, 1.0 equiv; bipyrrole dialdehyde, 2.0 equiv; p-TsOH, 10 mol%; CH_2Cl_2, rt, 4 h), sapphyrin 19 was

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isolated in up to 39% yield (Scheme 14). In parallel, Sessler's Lindsey-type approach afforded the corresponding diarylsapphyrin in ~10% under similar conditions but with a more tedious purification protocol [15, 16].

Moreover, the absence of competing porphyrinoid products substantially reduced the chromatographic work-up. However, the statistical formation of dipyrromethane , together with the presence of three stereoisomers and the instability of tripyrrane 17 as an oil, complicated its isolation and handling. Thus, Brückner's main contribution was not a fundamentally new [3+2] disconnection, but a more accessible preformed tripyrrolic building block for the selective preparation of meso-phenyl-substituted sapphyrins [15, 16].

Sessler's Lindsey-type multicomponent synthesis and Brückner's precursor-directed route represent two distinct strategies for preparing meso-diarylsapphyrins. In Sessler's method, the required pyrrolic components and aromatic aldehyde undergo acid-catalysed condensation under mild Lindsey-type conditions, followed by oxidation to generate the aromatic sapphyrin macrocycle. Although this approach avoids the lengthy preparation of the highly functionalised precursors required in classical MacDonald syntheses, the five-pyrrole framework is assembled largely in situ. Consequently, competing oligomerisation and the formation of porphyrinoids of different ring sizes limit macrocycle-size selectivity, giving the diarylsapphyrin in only approximately 9.5–10% yield and necessitating extensive chromatographic purification. In contrast, Brückner's method employs the preformed 5,10-diphenyltripyrrane 4, in which three pyrrole units and two meso-phenyl substituents are already incorporated before macrocyclisation. Acid-catalysed, non-decarboxylative [3+2] condensation of 4 with a bipyrrole dialdehyde, followed by oxidation, afforded the corresponding sapphyrin in yields of up to 39%. Preorganisation of the tripyrrolic fragment therefore suppressed the formation of competing porphyrinoid products and simplified purification. However, this improvement required the separate preparation of 4, whose statistical formation alongside 5-phenyldipyrromethane, stereoisomerism and limited stability complicated its isolation and handling. Overall, Sessler's route offered greater operational directness, whereas Brückner's route achieved superior selectivity and yield by introducing a preassembly step [15, 16].

3. Conclusion and outlook

Table 1. Comparison of representative synthetic strategies for sapphyrin construction

Synthetic strategy	Representative precursor type	Stage of direct α–α bond formation	Representative yield	Core advantage	Major limitation
MacDonald-type [3+2]	Tripyrrane dicarboxylic acid + diformyl bipyrrole	Precursor stage; direct pyrrole–pyrrole linkage is preassembled	Up to 46%	High structural control; modular fragment coupling; reliable macrocyclization	Multistep preparation of highly functionalized precursors; precursor stability and accessibility can be limiting
Woodward/Lash [4+1]	Linear tetrapyrrole + pyrrole/heterocyclic dialdehyde	Precursor stage; α–α linkage incorporated in tetrapyrrolic fragment	Modest (not specified)	Clear structure-directed assembly; modular access to hetero-, carbo-, and fused sapphyrins	Difficult preparation of linear tetrapyrrolic precursor; strong acid, controlled oxidation, and purification required
Paolesse [4+1]	a,c-Biladiene + formylpyrrole	Late-stage macrocyclization	Not specified	Late formation of α–α bond enables greater control over unsymmetrical peripheral substitution	Complex biladiene precursor still required; late α–α coupling is conformation- and sterically dependent

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Table 1. (continued)

Lindsey-type multicomponent	Pyrrolic components + aromatic aldehyde	During macrocycle assembly; largely formed in situ	~9.5–10%	Simple and operationally direct; avoids lengthy preparation of highly functionalized oligopyrroles	Competing oligomerization and different macrocycle sizes; poor selectivity and extensive purification
Rothemund-type statistical condensation	Pyrrole + aldehyde	During statistical cyclooligomerization	~1–1.2%	Very simple, readily available starting materials; one-flask assembly	Poor control of oligomer length, macrocycle size and substitution pattern; porphyrin/N-confused and oligomeric by-products

Table 1 summarizes the representative synthetic strategies, precursor types, bond-forming stages, yields, advantages, and limitations discussed above. Sapphyrin synthesis has developed from Woodward's serendipitous discovery into an increasingly rational and versatile branch of expanded-porphyrin chemistry. The classical reactions examined in this Review demonstrate that successful construction of the 22π-electron pentapyrrolic framework depends on several closely related factors: the accessibility and preorganisation of the oligopyrrolic precursors, control over the formation of the direct pyrrole–pyrrole bond, efficient macrocyclisation, and final oxidative aromatisation. Although the major approaches share acid-catalysed carbon–carbon bond formation at reactive pyrrolic α-positions, they differ substantially in the stage at which the five-pyrrole sequence and the characteristic direct α–α linkage are established.

Among these methods, the MacDonald-type [3+2] condensation remains one of the most reliable and structurally controlled strategies because the identities and sequence of the pyrrolic units are largely predetermined before macrocyclisation. Sessler's improvements greatly increased the practical accessibility of the required tripyrrane and bipyrrole components, allowing sapphyrins to be prepared in useful quantities. The Woodward–Lash [4+1] approach provided an alternative modular disconnection and was successfully extended to heterosapphyrins, carbasapphyrins, and fused derivatives. Paolesse's biladiene–formylpyrrole route further altered the synthetic logic by transferring direct pyrrole–pyrrole bond formation to the final ring-closing stage, thereby improving access to less symmetrical substitution patterns. By contrast, Rothemund- and Lindsey-type reactions reduced the need for elaborate preformed intermediates but generally suffered from competing oligomerisation, poor macrocycle-size selectivity, low isolated yields, and difficult purification. Brückner's precursor-directed synthesis illustrates an important compromise between these extremes: the introduction of a preformed tripyrrane increased yield and selectivity, although it required an additional precursor-preparation step.

Taken together, these studies reveal a persistent trade-off in sapphyrin synthesis. Greater precursor preorganisation usually improves structural control, macrocycle selectivity, and isolated yield, but increases the number of synthetic operations. More direct multicomponent reactions simplify the starting-material requirements but provide less control over oligomer length, substitution pattern, and product distribution. Future progress will therefore depend on combining the advantages of both approaches. Particularly valuable developments would include shorter and more scalable routes to stable oligopyrrolic building blocks, selective formation of linear pentapyrrolic intermediates, improved control over late-stage α–α coupling, and milder or more sustainable oxidative aromatisation methods. Such advances would not only improve the preparation of known sapphyrins but also facilitate access to previously inaccessible substitution patterns and core-modified analogues. The history of sapphyrin synthesis thus shows that classical porphyrin-forming reactions remain highly relevant, while continuing to provide opportunities for mechanistic refinement and methodological innovation.

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