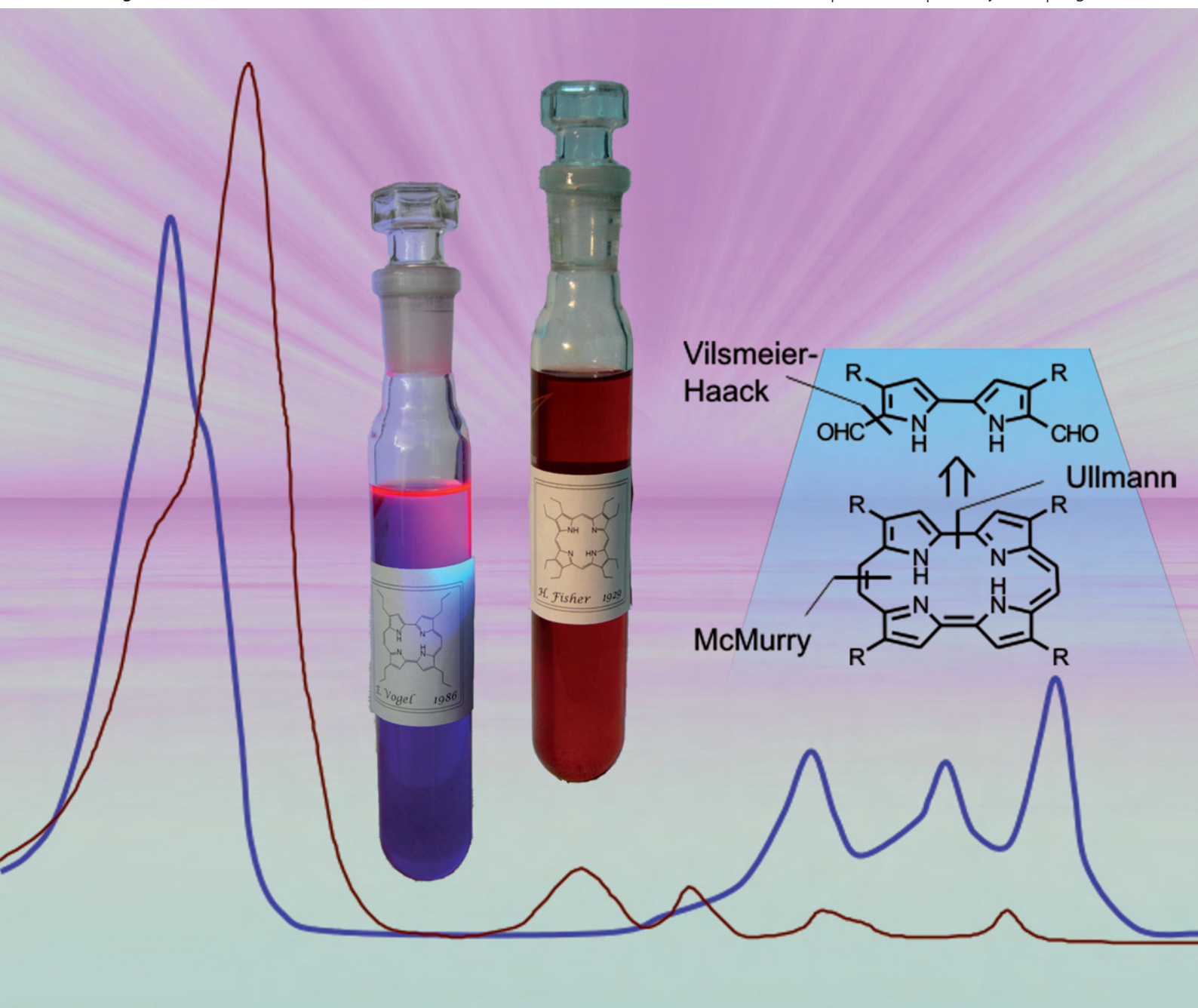


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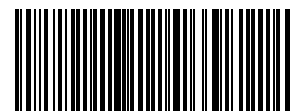
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Porphycenes: synthesis and derivatives†

David Sánchez-García^{ab} and Jonathan L. Sessler^{*a}

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Porphycene is an aromatic macrocycle and a constitutional isomer of porphyrin. It and its derivatives display unique physical and optical properties, including strong absorptions in the red region of the UV-vis spectrum. These features have made porphycene and porphycene analogues appealing molecules for use in biomedical applications and in the design of new materials. This *critical review* provides a concise overview of the most important syntheses of porphycenes, as well as those of various functionalized derivatives and heteroatom containing analogues. (95 references.)

Introduction

Over the years, porphyrins, the so-called pigments of life, have attracted the interest of organic chemists because of their

critical role in biological processes and their structural and aesthetic appeal. Impelled, in part, by this fascination, the synthetic chemistry of porphyrins has developed almost exponentially in recent decades. This has helped provide explanations for a number of biological phenomena while, at the same time, giving access to a plethora of new compounds with applications in fields that range from material chemistry to biomedicine. Three main features characterize porphyrins: They are macrocyclic, highly colored, and aromatic. A desire to understand and extend these characteristics has inspired considerable interest in the preparation of new porphyrin analogues. One of the most important of these is the so-called porphyrin isomers.

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† This work is dedicated to Prof. Emanuel Vogel in commemoration of the 20th anniversary of the first porphycene synthesis.



David Sánchez-García

David Sánchez García was born in Barcelona, Catalonia, Spain. He studied chemistry at the Institut Químic de Sarrià (Universitat Ramon Llull) in Barcelona and received his PhD in 2003 for research on the chemistry of 2,2'-biimidazole and the synthesis of tetraazaporphycenes. He carried out his postdoctoral research (2004–2006) with Professor Jonathan L. Sessler (University of Texas at Austin) developing new strategies for the synthesis of pyrrolic macrocycles. He is currently working with Dr Ivan Huc (Institut Européen de Chimie et Biologie, France) on foldamer chemistry. In addition to chemistry, he enjoys playing the violin.

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Professor Jonathan L. Sessler was born in Urbana, Illinois, USA on May 20, 1956. He received a BS degree (with highest honors) in chemistry in 1977 from the University of California, Berkeley. He obtained a PhD in organic chemistry from Stanford University in 1982 (supervisor: Professor James P. Collman). He was an NSF-CNRS and NSF-NATO Postdoctoral Fellow with Professor Jean-Marie Lehn at L'Université Louis Pasteur de Strasbourg, France. He was then a JSPS Visiting Scientist in Professor Iwao Tabushi's group in Kyoto, Japan. In September 1984 he accepted a position as an Assistant Professor of



Jonathan L. Sessler

Chemistry at the University of Texas at Austin, where he is currently the Roland K. Pettit Professor. Dr Sessler has authored or co-authored over 400 research publications, written two books (with Dr Steven J. Weighorn, and Drs Won-Seob Cho and Philip A. Gale, respectively) and edited a third (with Drs Susan Doctrow, Tom McMurry, and Stephen J. Lippard). He is the inventor of record on more than 70 issued US Patents. Dr Sessler is also a

co-founder (with Dr Richard A. Miller, MD) of Pharmacyclics, Inc., a publicly traded company (pcyc; NASDAQ) dedicated to developing biomedical applications of expanded porphyrins. In conjunction with Dr Martin R. Johnson, Dr Sessler has recently co-founded a second company, Anionics, Inc., that is targeting various commercial opportunities associated with anion recognition chemistry. Dr Sessler has served as the co-organizer of several international conferences and numerous symposia at ACS meetings, including, recently, the 3rd International Conference on Porphyrins and Phthalocyanines that was held in July of 2004. In addition to English, he speaks French, German, Spanish, and Hebrew and can get by in Japanese. He serves as Editor of *Supramolecular Chemistry* and is an Associate Editor for *ChemComm*.

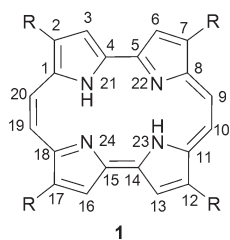


Fig. 1 Core structure of porphycene.

The first constitutional isomer of porphyrin and the focus of this review is porphycene (Fig. 1). It was prepared in 1986 by Vogel and coworkers.¹ Structurally, this new compound consists of two 2,2'-bipyrrole subunits linked by two double bonds. The result is a planar, aromatic macrocycle formally known as [18]porphyrin-(2.0.2.0).² In fact, the name porphycene was suggested because this compound possesses structural features of both porphyrins and acenes. Porphycene is not only the first porphyrin isomer to be reported, it is also the most stable,^{3,4} at least among those systems with an N-four central core (as opposed, *e.g.*, to containing N-confused pyrrolic subunits). Hence, its chemistry has been closely studied, especially as a ligand to form metal complexes.⁵ These complexes have been investigated in the context of many applications, including catalysis,⁶ protein mimicry,⁷ and material chemistry.⁸ They have also attracted interest because of their unique optical properties. As a consequence of their lower symmetry relative to porphyrins, porphycenes generally display strong absorbance bands in the far-red portion of the visible spectrum (depending on the porphycene in question, the lowest energy λ_{max} is found anywhere from 620–760 nm). These spectral characteristics have made functionalized porphycenes attractive for use in photodynamic therapy (PDT).^{9,10} Another biomedical application that has emerged recently involves the use of porphycenes in the photoinactivation of viruses and bacteria.¹¹ However, in addition to their potential practical utility, porphycenes remain objects of fascination because of their relationship to porphyrins and because they provide experimental test beds for theoretical studies focused on electronic structure, aromaticity,¹² and proton exchange,¹³ to name a few.

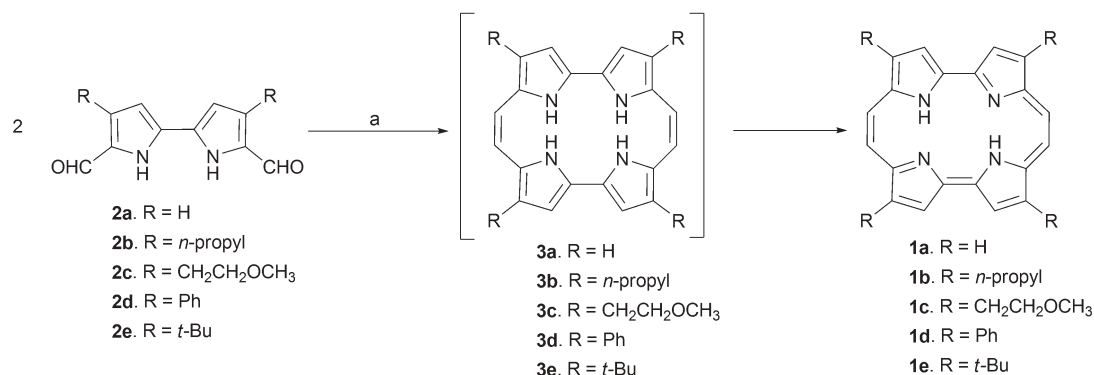
Preparation of porphycenes

In Vogel's seminal paper,¹ porphycene **1** was obtained by using McMurry-type coupling conditions to effect the reductive dimerization^{14,15} of diformyl-2,2'-bipyrrole **2a** (Scheme 1; R = H), followed by spontaneous oxidation with atmospheric O₂. This coupling, which is thought to proceed through the 20 π -electron intermediate **3**, can be regarded as the key step that enabled the synthesis of porphycenes. Although effective, the requisite McMurry reaction demands some precautions from an experimental point of view, especially pure reagents and anhydrous conditions. On the other hand, the starting material for the coupling reaction, the dialdehyde **2a** can be obtained by subjecting 2,2'-bipyrrole¹⁶ to formylation under Vilsmeier–Haack¹⁷ conditions (Scheme 1).

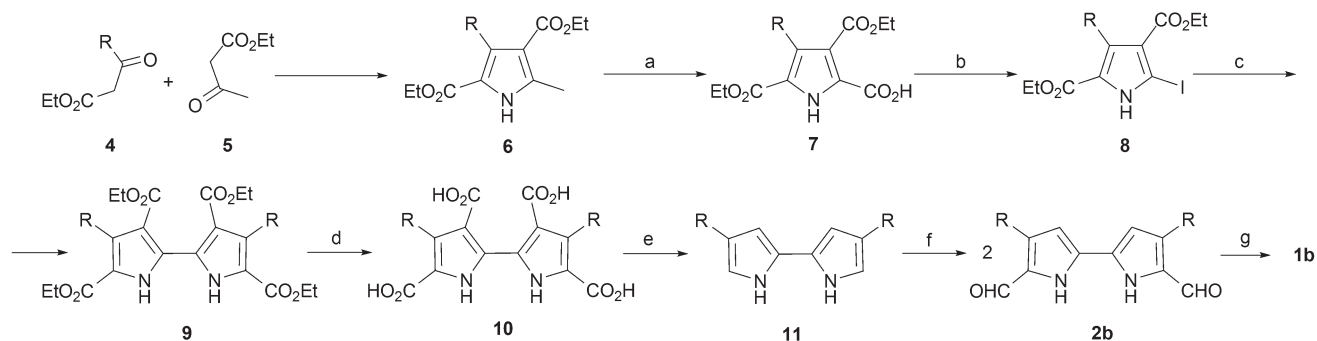
In order to enhance the solubility and crystallinity of porphycene, Vogel and coworkers also prepared derivatives bearing substituents in the 2,7,12 and 17 positions. In particular, tetrasubstituted porphycenes of general structure **1** bearing methyl, ethyl, *tert*-butyl, *n*-propyl (**1b**),¹⁸ and β -methoxyethyl groups (**1c**)¹⁹ were synthesized and characterized early on. Subsequently, derivatives bearing a greater number of substituents on the β -pyrrolic positions, the bridging meso-like alkylidene bridges, or both were prepared and studied. These latter systems are discussed later on in this review.

The general strategy introduced by Vogel remains the method of choice for preparing porphycenes. It takes advantage of the symmetry of the macrocycle and involves two coupling reactions, namely an Ullmann coupling and a subsequent McMurry coupling (Scheme 2). The first coupling provides the requisite substituted 2,2'-bipyrrole moiety,²⁰ whereas the second serves to close the ring.

Although, many methods have been described for the preparation of 2,2'-bipyrroles,²¹ the Ullmann coupling²² of iodopyrroles was, and remains, a particularly attractive choice. This is because, in contradistinction with some other methods, it provides the synthetic flexibility needed to incorporate a large range of substituents on the β -pyrrolic positions. In general, the starting iodopyrrole required for the bipyrrole-forming Ullmann coupling (**8**) is prepared *via* the decarboxylative iodination²³ of a pyrrole monacid, such as **7**. Such acids can, in turn, be prepared by oxidation of the corresponding α -methylpyrrole **6**. Typically, these latter species are obtained



Scheme 1 Vogel's synthesis of porphycene (**1a**, R = H; **1b**, R = *n*-propyl; **1c**, R = CH₂CH₂OCH₃; **1d**, R = Ph). Reaction conditions (yields in parentheses): a) TiCl₄/Zn/pyridine, THF, reflux (R = H, (2%); R = *n*-propyl, (10%); R = CH₂CH₂OCH₃, (25%); R = Ph (30%)).



Scheme 2 Synthesis of β -alkyl substituted porphycenes. The specific conditions and yields (in parentheses) are for R = *n*-propyl, yielding **1b**. a) Br₂, SO₂Cl₂, AcOH/HCOOH, 0 °C, 4 h (50–58%). b) KI/I₂, EtOH/H₂O, 75 °C, (75–77%). c) Cu, dimethylformamide (DMF), 20 °C, 17 h (67–71%). d) NaOH, EtOH/H₂O, 15 h, reflux (96%). e) Sublimation at 230 °C, 0.2 torr (89%). f) POCl₃/DMF then NaOAc/H₂O (86%). g) TiCl₄/Zn/pyridine, THF, reflux, 0.5 h (10%).

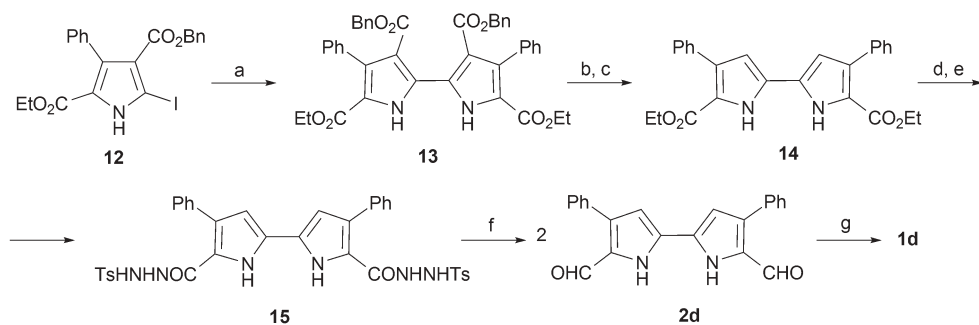
by means of a classical Knorr²⁴ reaction involving the appropriate β -ketoesters (**4**, **5**). Once the coupling is complete, to give a tetraester, such as **9**, further transformations, involving intermediates **10** and **11**, provide the requisite diformyl species **2**.

As noted above, the second dimerization serves to close the ring. It is based on a McMurry-type reductive coupling that is followed presumably by a spontaneous, *in situ* oxidation process. This gives the porphycene in variable yields. While the unsubstituted parent compound **1a** is obtained in only *ca.* 2% yield, the more substituted porphycenes are routinely obtained in yields on the order of 10–25% (**1**; R = alkyl). This is ascribed to the greater solubility of the latter species and the corresponding intermediates during synthesis.

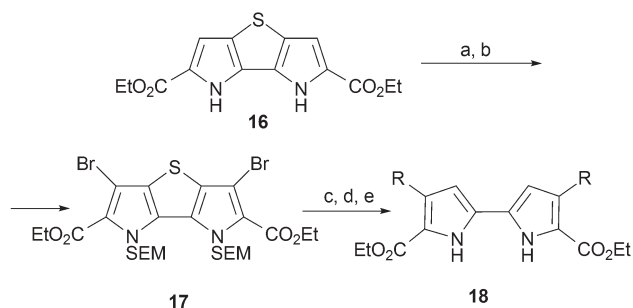
Porphycenes bearing aromatic groups have been investigated, with the 2,7,12,17-phenyl derivative (**1d**) being prepared by the groups of Vogel²⁵ and Nonell.²⁶ The main difference in the synthetic approaches used by these two researchers lies in the conversion of the tetraester **9** (R = Ph) into the 2,2'-bipyrrrole **11** (R = Ph). Specifically, Nonell avoids the sublimation step present in Vogel's preparation; this is done by converting the tetraester into the corresponding 2,2'-bipyrrrole in a single step by treatment with NaOH/ethylene glycol at reflux.²⁷ In principle, the suppression of the sublimation step should facilitate the scale up of the synthesis, thereby making this series of compounds more accessible to those interested in studying their chemical and spectroscopic properties. With this

same goal in mind, Nonell's group reported²⁸ a non-decarboxylative procedure based on 2,2'-bipyrrroles bearing two sets of orthogonal esters (*e.g.*, **13**; Scheme 3). Thus, the use of this kind of tetraester, prepared from iodopyrrole **12**, allows the diester **14** to be prepared under readily accessible conditions (*i.e.*, *via* intermediate **13**). The result is a species that, it was envisioned, could be subsequently reduced selectively to afford the corresponding dialdehyde **2d**. Unfortunately, this planned reduction proved difficult to achieve using conventional reductants. Nonetheless, the desired dialdehyde (**2d**) could be obtained in good yield by use of a MacFayden–Stevens reaction sequence (Scheme 3).²⁹

The introduction of phenyl groups in positions 2,7,12 and 17 leads to a dramatic bathochromic shift (30 nm) compared with the unsubstituted porphycene. It has been suggested that the presence of aromatic rings could modify the position of the Q bands, thereby allowing an optimization of those optical properties considered desirable for applications such as PDT.^{9,30} With these objectives in mind, and cognizant of the emerging concepts of combinatorial chemistry, Borrell and Nonell³¹ reported a new strategy for preparing substituted bipyrrroles. It is based on the use of palladium chemistry and relies on the thienobipyrrrole **16**.³² This precursor acts as a masked bipyrrrole with positions 3 and 3' blocked. It thus allows the remaining positions to be halogenated readily. After SEM protection (SEM = [β -(trimethylsilyl)ethoxy]methyl) the resulting dibrominated compound **17** can participate in Suzuki



Scheme 3 Non-decarboxylative synthesis of tetraphenylporphycene, **1d**. Reaction conditions (yields in parentheses): a) Cu, DMF, 23 °C, 20 h (89%). b) Pd/C, HCOOH/HCOONH₄, reflux, 4 h (100%). c) ethylene glycol, 170 °C, 5 h (93%). d) NH₂NH₂, EtOH, reflux, 48 h, (93%). e) TSCl, pyridine, 23 °C, 1 h (96%). f) diethylene glycol, Na₂CO₃, 170 °C (92%). g) TiCl₄/Zn/CuCl, THF, reflux, 3 h (30%).



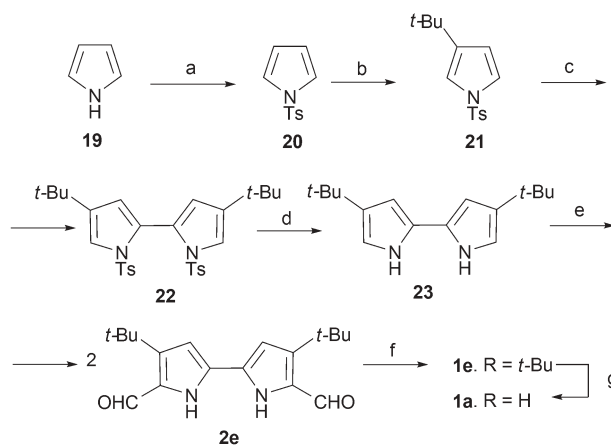
Scheme 4 Reaction conditions (yields in parentheses): a) Br₂, AcOH/AcOEt (89%). b) SEMCl, NaH, THF (94%). c) RB(OH)₂, Pd(PPh₃)₄, Na₂CO₃, 1,4-dioxane; R = Ph (100%), R = C₅H₄N (95%), R = *p*-MeOC₆H₄ (100%). d) Ni Raney, EtOH; R = Ph (100%), R = C₅H₄N (100%), R = *p*-MeOC₆H₄ (94%). e) TBAF (1 M in THF), 1,4-dioxane; R = Ph (93%), R = C₅H₄N (89%), R = *p*-MeOC₆H₄ (91%).

couplings. This permits a higher level of functionalization if so desired. Once such further chemistry is effected, the final substituted 2,2'-bipyrrole **18** is obtained following first removal of the sulfur atom and then the SEM protecting group. This is done by treating with Raney Ni followed by tetra-*n*-butylammonium fluoride (TBAF) (Scheme 4).

Although the McMurry coupling is a well-established efficient reaction, and is one that has been used to effect other kinds of macrocyclizations, in the context of porphycene syntheses yields are only modest. On the basis of the experimental observations noted above, it was concluded that a lack of solubility is largely responsible for the low yields. Predicated on this assumption, an improved method for preparing unsubstituted porphycene **1a** was developed by Waluk and coworkers; this procedure, reported at the 4th International Conference on Porphyrins and Phthalocyanines (ICPP-4),³³ involves using *tert*-butyl substituents as temporary solubilizing groups.

Thus, starting with pyrrole **19**, tosylation and functionalization gives **21**, which is coupled to provide bipyrrole **22** that, after deprotection (**23**) and formylation, yields the key intermediate **2e** (R = *tert*-butyl) required for reductive cyclization. After cyclization, the *tert*-butyl substituents may be removed in 65% yield by heating in H₂SO₄ (Scheme 5). Another novel aspect of this synthesis is that as actually implemented it involved a replacement of the Ullmann reaction used to prepare bipyrrole **22** by an oxidative coupling process.^{34,35}

In 2006, Sessler and Sánchez-García³⁶ reported at the ICPP-4 a simplification of the classic porphycene synthesis that is based on the use of a new protocol for preparing the requisite iodopyrroles (**26**) from simple aldehydes, such as **24**. It takes advantage of the recognition by Suzuki *et al.*³⁷ that α -free pyrrole diesters, such as **25**, can be prepared *via* the reaction of an aldehyde with an alkyl isocynoacetate in the presence of DBU. This preparation furnishes both alkylic and aromatic pyrroles of general structure **25** in good yields (50–71%). Treatment with iodine in a biphasic DCM–water mixture then furnishes the iodopyrroles **26** (Scheme 6). Ullmann coupling (to give **27**) and removal of the ester functionality then provides a disubstituted bipyrrole (**11**) suitable for formylation and cyclization.

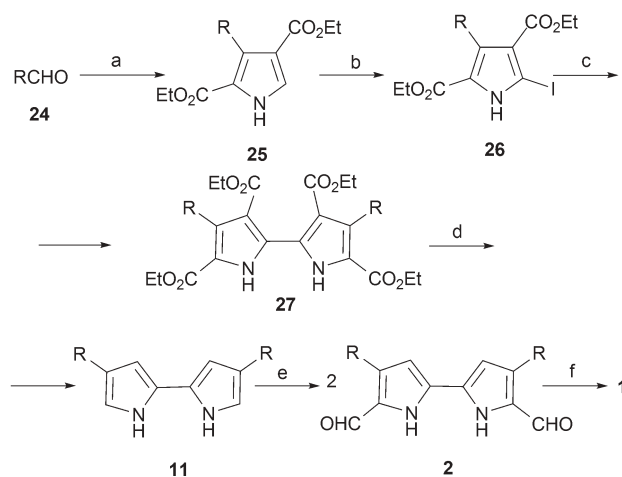


Scheme 5 Improved synthesis of porphycene **1a** of Waluk and coworkers. Reaction conditions (yields in parentheses): a) TsCl, NaOH. b) *t*-BuCl, AlCl₃, CH₂Cl₂. c) *n*-BuLi, TMP, CuCl₂, THF. d) KOH, CH₃OH. e) POCl₃/DMF, CHCl₃. f) TiCl₄/Zn/CuCl, THF. g) H₂SO_{4(aq)}, 15 min (65%).

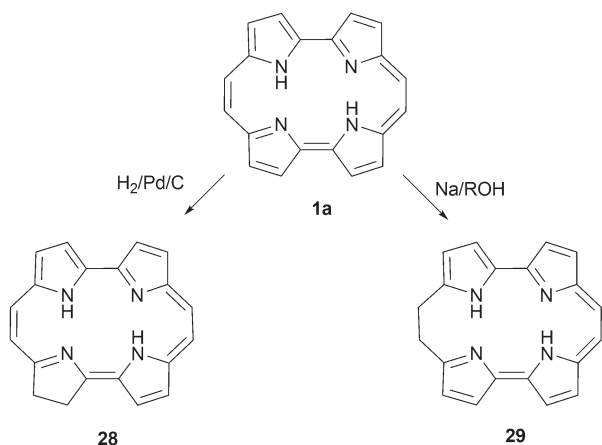
The main features of this new protocol are 1) a reduction in the number of steps (from 8 to 6) compared with the traditional synthesis and 2) the considerable flexibility permitted in terms of the substituents, alkyl or aryl, that can be introduced in positions 2, 7, 12 and 17. In support of this latter assertion, two new porphycenes of general structure **1** were prepared, namely those with R = C₇H₁₅ and R = *p*-MePh.

Reactivity and functionalization of porphycenes

As illustrated in Scheme 7, the double bonds in porphycene undergo selective reduction when treated with H₂ or Na/ROH;



Scheme 6 Simplified synthesis of porphycenes developed by Sánchez-García and Sessler. Reaction conditions (R = C₇H₁₅ and *p*-MePh) (yields in parentheses): a) ethyl isocynoacetate (2 equiv.), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (2 equiv.), 50 °C (75%, 51%). b) I₂/NaI, dichloroethane, 100 °C, (71%, 63%). c) (BOC)₂O, DCM, 23 °C, filtration through a short pad of Celite™ and then Cu, DMF, 110 °C (43%, 35%). d) NaOH, deoxygenated ethylene glycol, 180 °C (60%, 70%). e) POCl₃, DMF, 60 °C, then NaOAc, 100 °C (86%, 79%). f) TiCl₄/Zn/CuCl, THF, reflux (24, 16%).



Scheme 7 Hydrogenation and metal-based reduction of porphycene **1a**.

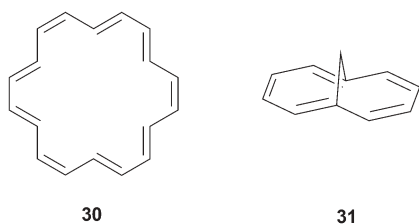
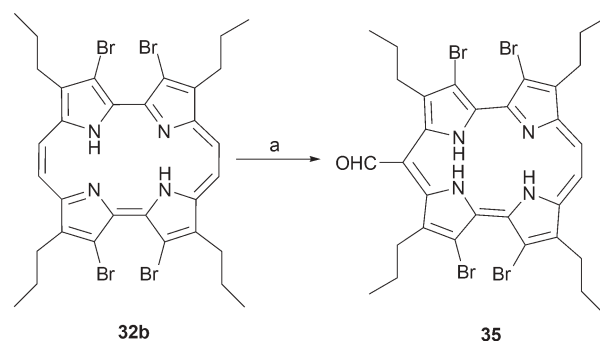


Fig. 2 Structures of Sondheimer's [18]annulene and Vogel's 1,6-methano[10]annulene.

this yields the reduced analogues **28** and **29**.³⁸ Based on this reactivity, porphycenes can be regarded as aza polyenes,³⁹ nitrogenated counterparts of the aromatic [18]annulene **30**¹² (Fig. 2).

One of the characteristics of [18]annulene **30** is that it is more prone to polymerize than to undergo electrophilic substitution, a finding that is ascribed to its conformational freedom. In porphycenes, the rigidity imposed by the pyrrolic



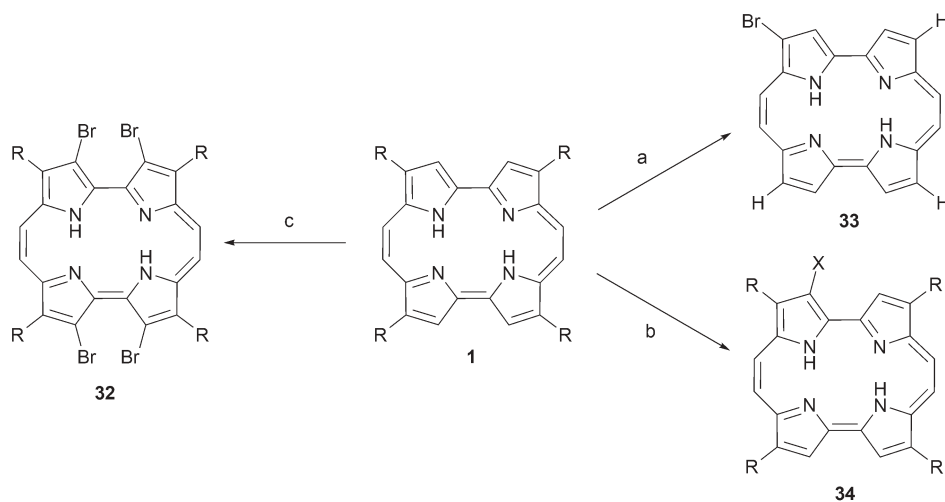
Scheme 9 Contraction of porphycene **32b** observed in basic media. a) K_2CO_3 , DMF/ H_2O , 120 °C, 4 h, (34%).

nitrogens, gives rise to benzenoid reactivity similar to that observed in the case of 1,6-methano[10]annulene **31**.⁴⁰

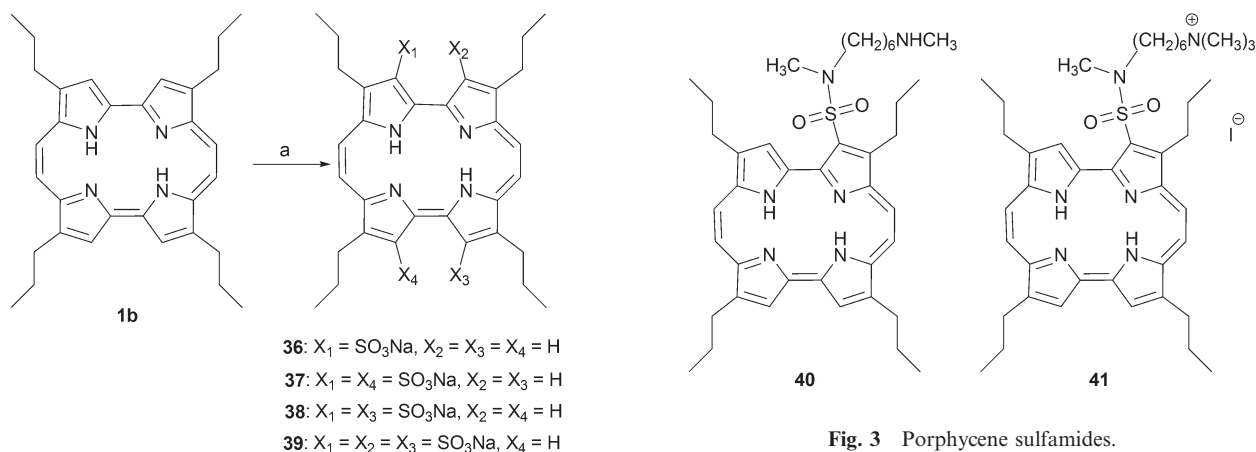
Thus, halogenation of porphycene can be achieved by direct reaction with Br_2 or I_2 .^{41–43} When the porphycene substrate is unsubstituted, attack of the halogen takes place exclusively at position 2 to give **33**, whereas for 2,7,12,17 substituted porphycenes, halogenation takes place at the remaining β -pyrrolic positions. In general, two compounds can be isolated readily, namely the tri- and tetrabrominated porphycene species (*e.g.*, **32**). The use of bromine on a polymeric support has, however, been used to effect mono substitution in position 3 (**34**) (Scheme 8).⁴¹

Brominated pyrroles are not prone to react with nucleophiles. However, an unexpected rearrangement, resulting in the formation of the isocorrole **35** (Scheme 9), takes place when tetrabrominated porphycene **32b** is heated under basic conditions.^{41,44}

Treatment of **1b** with fuming sulfuric acid affords a mixture of mono, di, and tri- β -sulfonated porphycenes (shown in Scheme 10 in the form of their sodium salts, **36–39**).⁴⁵ The mono and tri-substituted products can be isolated and purified from the crude reaction mixture using simple



Scheme 8 Halogenation of porphycenes. Reaction conditions (yields in parentheses): a) ($\text{R} = \text{H}$) *N*-bromosuccinimide (NBS), CHCl_3 , 10 °C, 10 min (23%). b) ($\text{R} = n$ -propyl, $\text{X} = \text{Br}$) Amberlyst A-26, Br_3 -form, CH_2Cl_2 , AcOH, 0 °C, 2 h (80%). ($\text{R} = n$ -propyl, $\text{X} = \text{I}$) I_2 , 0 °C, 2 min (80%). c) ($\text{R} = n$ -propyl) Br_2 , CCl_4 , NaAcO/ H_2O , 23 °C, 1 h (40%).



Scheme 10 Sulfonated porphycenes. Reaction conditions (yields in parentheses): a) H_2SO_4 (SO_3) 25%, CH_2Cl_2 , 25 °C, 25 min, **36** (3%), **37** and **38** (29%), **39** (40%).

extraction methods. In contrast, the difunctionalized compounds are obtained as an inseparable mixture. The sodium salts of most of these sulfonated porphycenes are water-soluble, something that has made them attractive for use in biological applications.

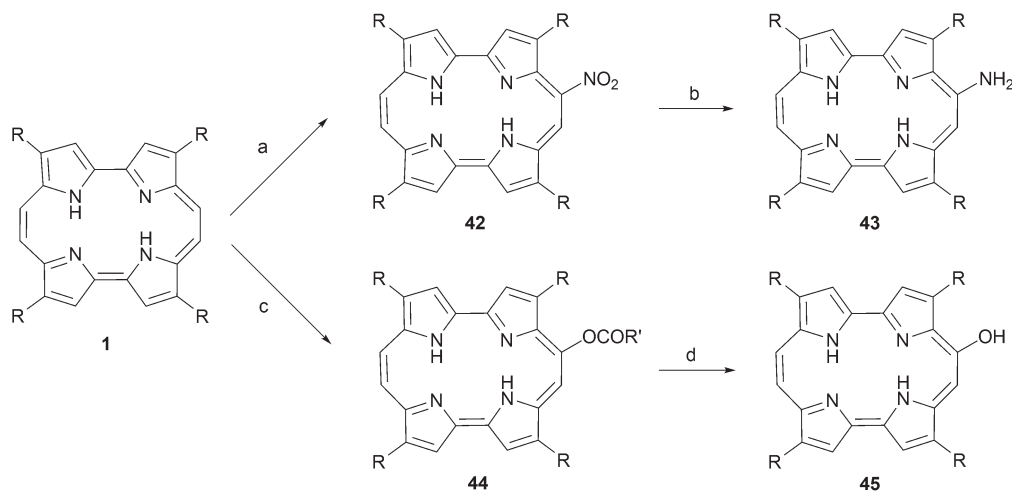
Similarly, the Mak group have synthesized the 3-sulfonyl chloride derivative in 95% by reacting **1b** with chlorosulfonic acid at room temperature.⁴⁶ The resulting acid chloride reacts with amines to give sulfonamides **40** and **41** (Fig. 3). In the same report the authors showed that water-soluble cationic sulfonamides are effective mitochondrial localizers. An alternative means of placing a cationic amine ($-\text{CH}_2\text{N}(\text{CH}_3)_2\cdot\text{HCl}$) onto the periphery of the porphycene core (at position 3) has been disclosed; however, details of the methodology employed are lacking.⁴⁷

Whereas halogens and SO_3 react at the pyrrolic positions, the treatment of porphycenes with fuming HNO_3 yields the 9-nitro substituted macrocycle **42** (Scheme 11).⁴⁸ An alternative means of effecting this nitration involves reacting

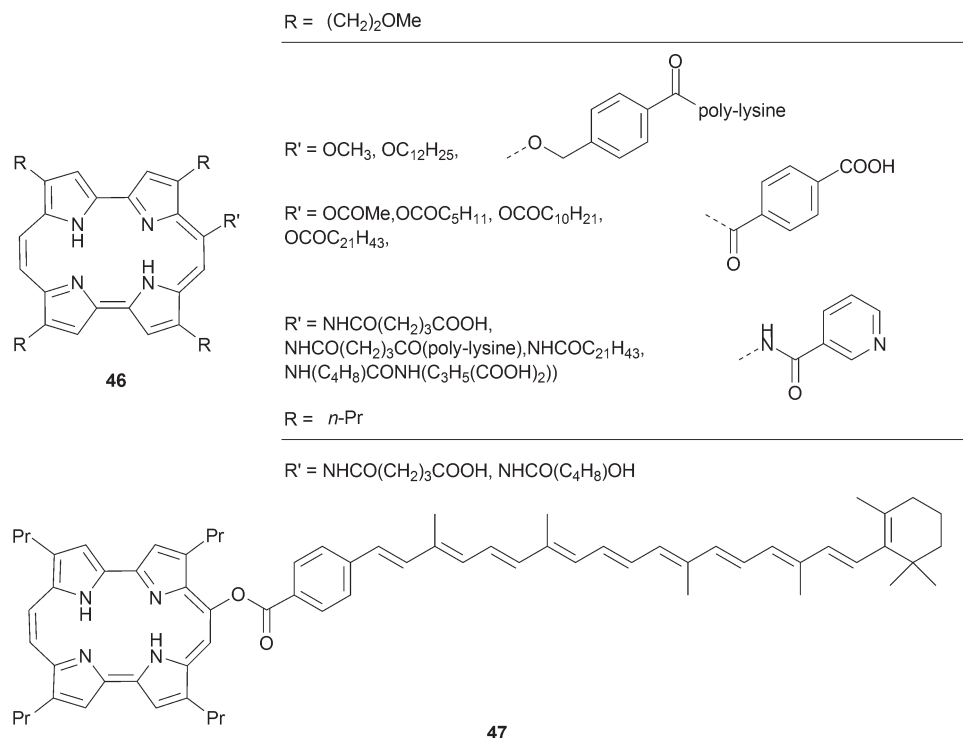
porphycene **1b** with AgNO_3 /acetic acid in dichloromethane. The resulting 9-nitro group can then be reduced selectively to the corresponding amine (**43**) via the Zinin reduction,⁴⁹ or by treatment with Raney Ni and hydrazine.

A different approach to functionalizing the 9 position involves forming the acyloxy derivatives (e.g., **44**) by treatment with a Pb(IV) salt (PbO_2 or $\text{Pb}(\text{OAc})_4$) in the presence of a carboxylic acid (e.g., acetic acid). The free 9-hydroxyporphycene **45** can then be easily prepared by subjecting the resulting acyloxy derivative to hydrolysis in basic media (Scheme 11).⁴⁸

The 9-substituted porphycenes described above provide an important starting point for the preparation of a range of derivatives and conjugates.⁵⁰ For instance, porphycenes bearing 9-hydroxyl groups can be used to prepare ethers, esters, and sulfonic acid esters, whereas 9-amino derivatives can be transformed into amido conjugates when treated with acid chlorides (*cf.* generic structures **46** and **47**; Scheme 12). Many of the resulting systems have proved water soluble, and have attracted attention as possible photodynamic therapy photosensitizers. Not surprisingly, therefore, the basic physical parameters relevant to PDT have been published for many of these elaborated 9-substituted porphycene derivatives.⁴⁷



Scheme 11 Nitration and dehydroacyloxylation of porphycenes: Reaction conditions (yields in parentheses): ($\text{R} = n$ -propyl) a) AgNO_3 , HOAc , CH_2Cl_2 , 60 °C, 15 min. (85%). b) $\text{Na}_2\text{S}_2\text{O}_4$, NaOH , H_2O , reflux, 1 h (50%). c) ($\text{R} = n$ -propyl, $\text{R}' = \text{Me}$) $\text{Pb}(\text{OAc})_4$, THF , reflux, 10 min (30%). ($\text{R}' = (\text{CH}_2)_3\text{CO}_2t\text{-Bu}$) PbO_2 , $\text{HO}_2\text{C}(\text{CH}_2)_3\text{CO}_2t\text{-Bu}$, CH_2Cl_2 , 23 °C, 24 h (23%). d) ($\text{R} = n$ -propyl, $\text{R}' = \text{Me}$) NaOMe , MeOH , 23 °C, 5 min (89%).



Scheme 12 Selected derivatives generated from 9-amino and 9-hydroxy substituted porphycenes.⁴⁷

Functionalization of positions 2, 7, 12 and 17

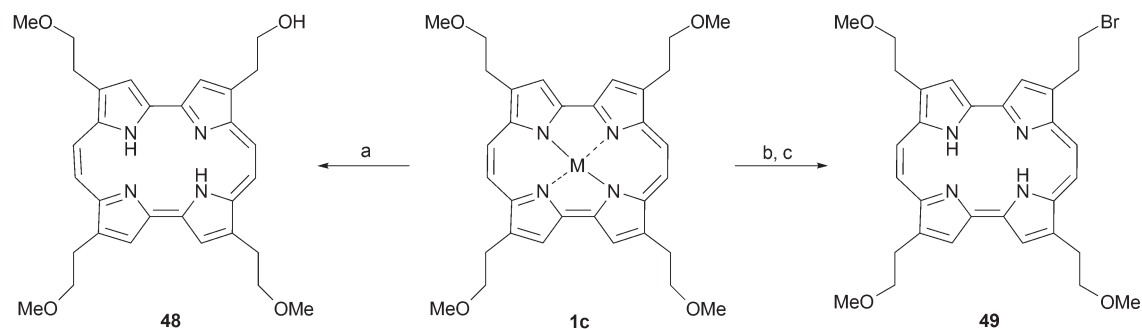
The β -methoxyethyl substituted porphycene **1c** may be regarded as a pivotal compound in the preparation of a large number of peripherally functionalized derivatives. Removal of the methyl ether “protecting group” with a Lewis acid, such as BBr₃, provides the corresponding alcohols. The availability of these latter species, in turn, allows several functional group interconversions, including, for instance, the preparation of other ether derivatives. It is noteworthy that demethylation of **1c** can be carried out stepwise, allowing the preparation of mono, di and tri hydroxy derivatives.¹⁹

Mixed McMurry couplings involving dialdehydes **2** bearing different substituents (*e.g.*, R = CH₂CH₂OMe and R = *n*-propyl) provide access to amphiphilic porphycenes after deprotection. Interestingly, exposure of the Ni complex of **1c** to BBr₃ in the presence of boric acid yields

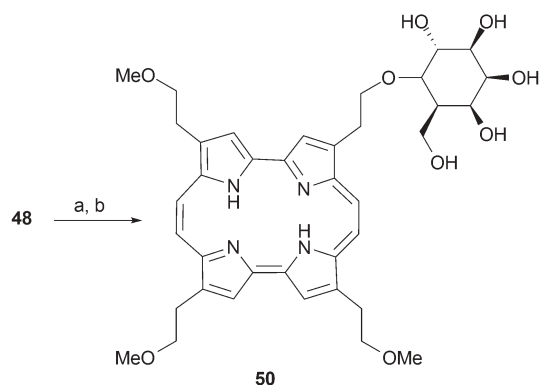
the mono-brominated derivative **49** instead of the corresponding alcohol, **48** (Scheme 13). This latter species can be obtained by treating **1c** with 1 equiv. of BBr₃. The utility of this monohydroxy product as an intermediate in its own right has been demonstrated *via*, for instance, its conversion to porphycene sugar derivatives, such as **50** (Scheme 14).⁵¹

β -Hydroxyethyl chains are versatile substituents that can be transformed into the corresponding chloride, acetate, or mesylate derivatives, as well as the bromides as described above. Both the bromide **49**, as well as the mesylate **51** produced from **48** (Scheme 13), undergo substitution with NaCN to afford the corresponding cyano derivative **52**. Treatment with HCl in methanol then yields the carboxylic ester, which after saponification gives the acid derivative **53** in good yield (Scheme 15).⁵¹

On the other hand, full deprotection of **1c** with BBr₃ in the presence of boric acid affords the tetrabrominated derivative



Scheme 13 Transformations of porphycene (**1c**) effected by BBr₃. Reaction conditions (yields in parentheses): a) (M = H₂) BBr₃, CH₂Cl₂, -30 °C, 16 h (18%). b) (M = Ni) BBr₃, B(OH)₃, CH₂Cl₂, -78 °C, 8 h (35%). c) (M = Ni) H₂SO₄, 10 min (90%).



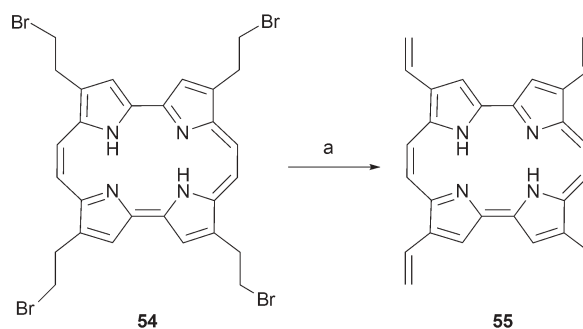
Scheme 14 Synthesis of β -D-galactopyranoside of 2-hydroxyethyl-7,12,17-tris(methoxyethyl)-porphycene. Reaction conditions: a) AgCO_3 , Na_2SO_4 , 2,3,4,6-tetra-*O*-acetyl- α -D-galactopyranosyl bromide, CH_2Cl_2 , 23 °C, 3 d. b) NaOMe , THF, 23 °C, 2 h.

54, which can be converted into 2,7,12,17-tetravinylporphycene **55** by treatment with DBU in 20% yield (Scheme 16).⁵¹

Meso and etio substituted porphycenes

The geometry of the porphycene core is dependent on the peripheral substituents. As a consequence, the metal cation coordination properties of this tetrapyrrolic ligand can be modified by changing the substituents on the periphery of the macrocycle.¹² With a view to mapping out the effect of such modifications on the complexation properties of porphycene, derivatives such as **56** and **57** were prepared that bear different substituents in positions 9, 10, 19 and 20 (*meso* positions),^{52–54} as well as positions 3, 6, 13 and 16 (β -pyrrolic positions); the latter species bear a structural resemblance to the etioporphyrins and are referred to generically as etioporphycenes (Fig. 4).^{55,56}

Meso substituted porphycenes have generally been prepared from 5,5'-acyl substituted bipyrroles using the basic reductive coupling strategy introduced early on by Vogel. In this case, the requisite bipyrroles are usually obtained by treating an α,α' -unsubstituted bipyrrole with a Vilsmeier-type electrophile obtained by reacting the proper alkyl *N,N'*-amide with POCl_3 .⁵⁷ Interestingly, oxidation of the intermediate annulene **58** (to produce the porphycene product **56**) is relatively difficult to effect as compared to the analogous non-*meso*



Scheme 16 Preparation of 2,7,12,17-tetra-vinylporphycene **55**. Reaction conditions: a) DBU, THF, 23 °C, 2 d followed by HCl (20%).

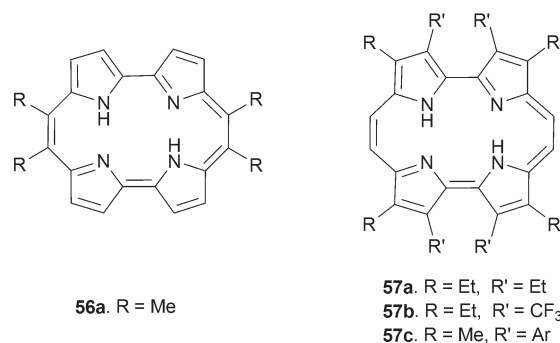
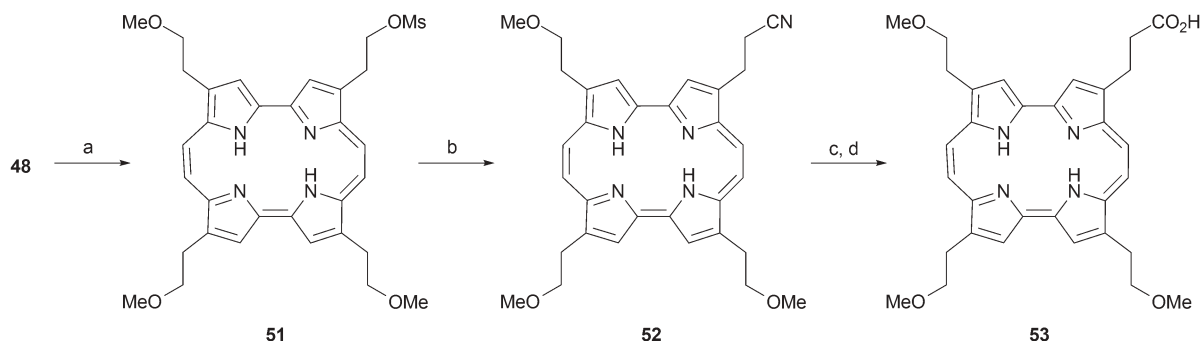


Fig. 4 *Meso* and etio substituted porphycenes.

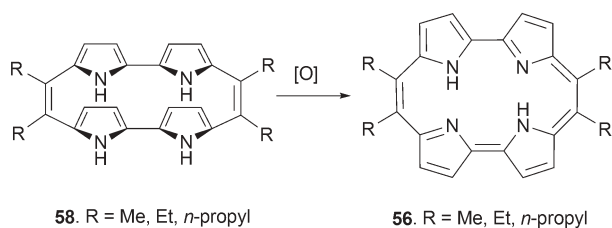
substituted porphycene precursor **3** (*cf.* Scheme 1). As a result, it can be isolated in the form of colorless crystals. It has been suggested that the alkyl chains on the alkene bridges slow down the rate of conformational motion and that this retardation, in turn, makes it difficult to access the near-planar geometry required for oxidation and aromatization (Scheme 17).

An example of an asymmetric porphycene **60** bearing methyl groups in two of the four *meso* positions has been reported recently.³³ It was synthesized *via* the cross coupling of the diformyl and diacetyl bipyrroles **2e** and **59**, respectively. This preparative chemistry, for which a yield was not reported, is summarized in Scheme 18.

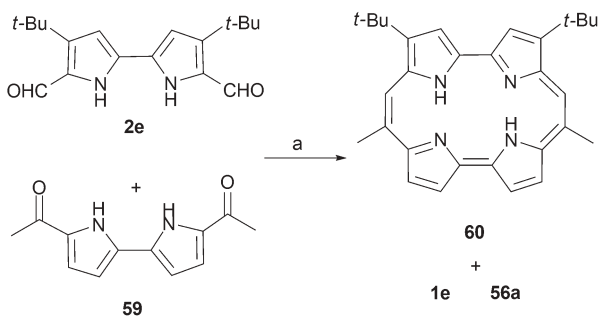
In the solid state, the cavity of 2,7,12,17-tetrasubstituted porphycenes are seen to be slightly rectangular. This geometry



Scheme 15 Functional groups interconversions. Reaction conditions (yields in parentheses): a) MsCl , pyridine, CH_2Cl_2 , 2 h (91%). b) NaCN , DMSO, 3 h, (75%). c) $\text{MeOH}/\text{HCl}(\text{sat})$, 18 h, (81%). d) KOH , THF/ H_2O , 40 h then HCl (72%).



Scheme 17 Reaction sequence meant to underscore the relative stability of *meso* substituted annulenes **58**.



Scheme 18 Synthesis of dimethyl *meso*-substituted porphycene **60**. a) $\text{TiCl}_4/\text{Zn}/\text{CuCl}$, THF, reflux.

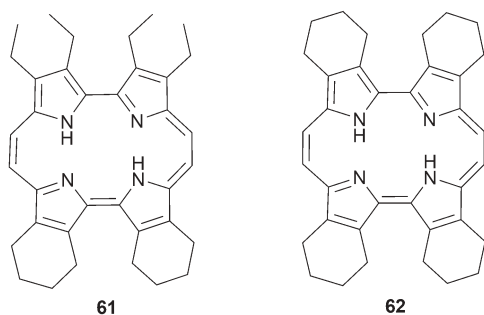
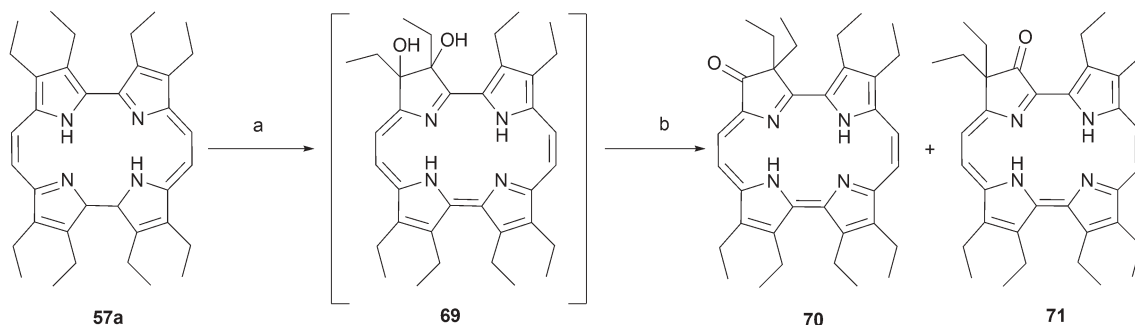
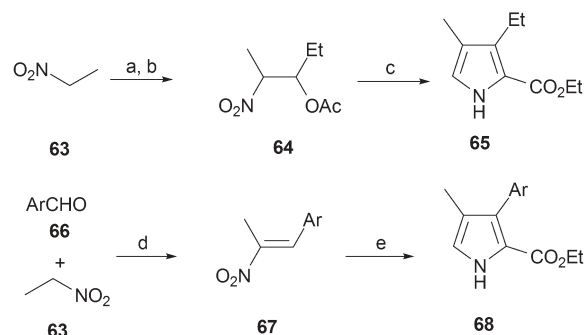


Fig. 5 Etioporphycenes.

favors the formation of metal complexes with small cations. However, etioporphycenes (Fig. 5) have a larger cavity and are thus able to accommodate bigger cations. The more open cavity of etioporphycenes is rationalized in terms of the steric interactions of the alkyl chains in the β -positions that force the molecule to adopt a more square-like geometry.



Scheme 20 Preparation of octaethyl-2-oxoporphycene and octaethyl-3-oxoporphycene. Reaction conditions: a) H_2O_2 . b) H_2SO_4 .



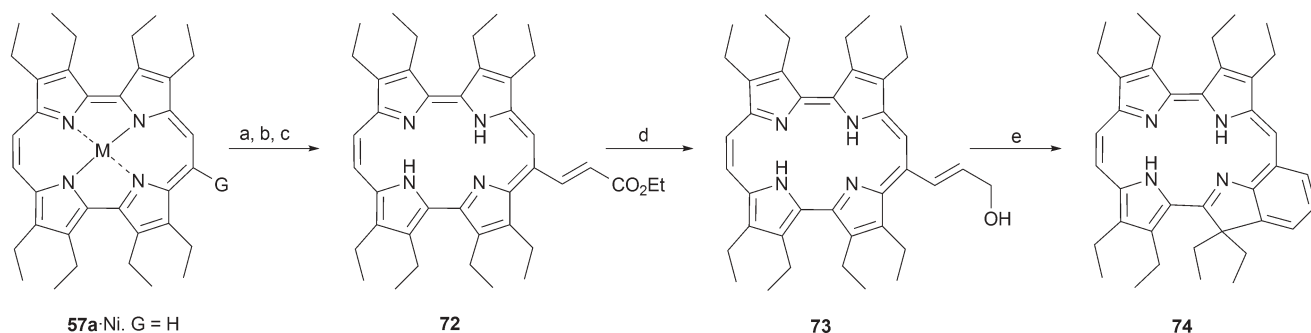
Scheme 19 Zard-Barton synthesis of 3,4-substituted pyrroles. Reaction conditions (yields in parentheses): a) $\text{CH}_3\text{CH}_2\text{CHO}$, KF, *i*-PrOH, 24 h (80%). b) Ac_2O , H_2SO_4 , 1 h, (89%). c) $\text{CNCH}_2\text{CO}_2\text{Et}$, THF, *i*-PrOH, DBU, 4 h, 23 °C, (65%). d) (Ar = (*p*- $\text{H}_{21}\text{C}_{10}\text{O}$ Ph)) AcONH_4 (70%). e) $\text{CNCH}_2\text{COOEt}$, THF/*i*-PrOH, DBU (46%).

To prepare etioporphycenes a route to β, β' -substituted pyrroles is required. The most versatile and efficient approach to these latter intermediates is *via* the Zard-Barton reaction.^{58–60} In this procedure, the pyrrole is prepared from the condensation of ethyl isocyanate with a nitro compound (**64**, prepared from **63**, or **67**, prepared from **66** and **63**) in the presence of DBU; this provides an ethyl β, β' -disubstituted pyrrole 2-carboxylate (*i.e.*, a pyrrole such as **65** or **68**) bearing an ethyl ester group in position 2) (Scheme 19).^{61,62}

Subsequent iodination affords the starting material required for the Ullmann coupling used to produce a tetra- β -substituted bipyrrole. N-protection of the iodopyrroles as the BOC (*tert*-butoxycarbonyl) derivatives allows (Scheme 6) the yield of the dimerization to be increased up to 20% compared with the coupling of unprotected iodopyrroles.⁶³

Although the pyrrolic positions in etioporphycenes are substituted by alkyl chains, some interesting chemistry involving these positions has been reported. In a few cases the result is the production of a new aromatic system. For instance, the two isomeric oxo porphycene derivatives **70** and **71** were prepared by treating octaethylporphycene **57a** with H_2O_2 in acidic media.⁶⁴ The final oxygenated products are believed to arise *via* rearrangement of a dihydroxylated intermediate such as **69** (Scheme 20).

The nickel complex of octaethylporphycene **57a** undergoes mono-formylation under Vilsmeier-Haack conditions.⁶⁵ The aldehyde produced in this way was used by Kister and Vogel to



Scheme 21 Synthesis of octaethylbenzochloracene. Reaction conditions (yields in parentheses): a) (M = Ni, G = H) DMF, POCl₃, dichloroethane, 50 °C, 2 h, then NaOAc/H₂O, 50 °C, 30 min (98%). b) (M = Ni, G = CHO) (carbethoxymethylene)triphenyl phosphorane, xylenes, reflux, 3.5 h (92%). c) H₂SO₄, CH₂Cl₂, 2.5 h, 23 °C, (97%). d) DIBALH, toluene, -78 °C, 1.5 h, (65%). e) phosphoric acid 85%, 23 °C, 3.5 h (45%).

prepare the porphycene analogue of benzochlorin **74** via intermediates **72** and **73** (Scheme 21).⁶⁴ This macrocycle, which was subsequently prepared by Robinson,⁶⁶ was termed octaethylbenzochloracene by these latter researchers.

In 2002, Hayashi reported the reconstitution of myoglobin using a substituted etioporphycene (**75**).⁷ The ligand was designed to mimic the native protoporphyrin IX heme group (**76**) with two acid functions pendant from the macrocycle (Fig. 6). The reconstituted myoglobin prepared from the Fe(II) complex is blue and, like the native system, displays a high affinity for oxygen.

Recently, the same group has synthesized an etioporphycene bearing trifluoromethyl groups.⁶⁷ Although the synthetic plan follows the general sequence used by Vogel to prepare his original porphycenes, some modifications were made so as to adapt the synthesis to the fluoromethyl bearing pyrrolic precursor. Thus, starting with pyrrole **77**, the first step involves oxidation of the α -methyl group to provide the corresponding formyl species **78**. This latter group is then protected as an acetal and iodinated (to give **79** and **80**, respectively) prior to carrying out the key bipyrrole-forming Ullmann coupling to provide **81**. Deprotection and reductive coupling then provides the desired product **57b** (Scheme 22).

Aromatic groups have been placed in the β -pyrrolic positions⁶⁸ and even been used to connect adjacent pyrrolic rings^{69,70} (Scheme 23).

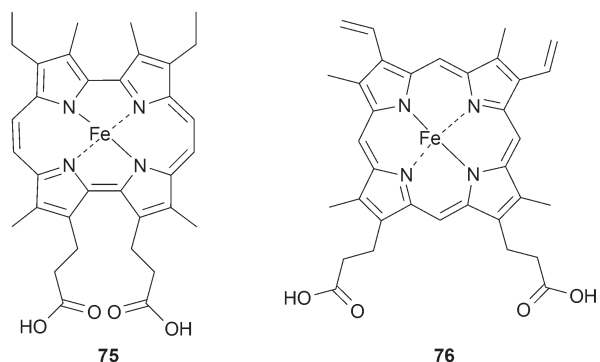
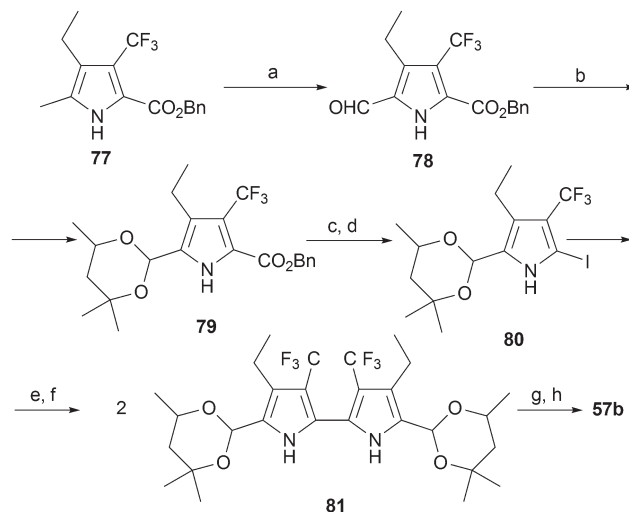
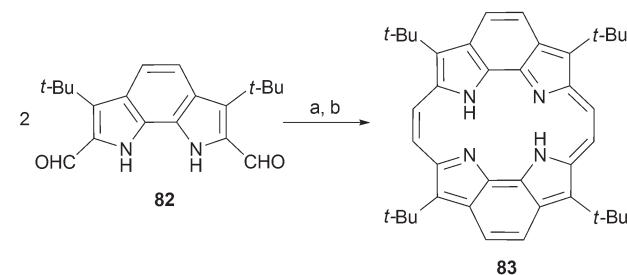


Fig. 6 Artificial Fe(II) porphycene heme group (**75**) and native heme (**76**).

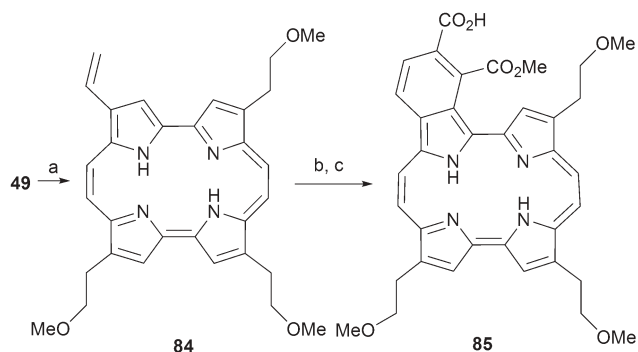
Benzoporphycene **83** was obtained by McMurry coupling of the corresponding aldehyde **82**. As is true for *meso*-substituted porphycenes, such as **56**, the non-aromatic intermediate leading to **83** is stable enough to be isolated. Oxidation of



Scheme 22 Synthesis of **57b**. Reaction conditions: a) Br₂, SO₂Cl₂, AcOH, trifluoroacetic acid, Ac₂O, 0 °C, 3 h (84%). b) Hexylene glycol, *p*-TsOH, benzene (100%). c) Pd/C, H₂, Et₃N, THF (100%). d) KI, I₂, NaHCO₃, 50 °C, 2 h, H₂O (80%). e) Boc₂O, *N,N*-dimethylaminopyridine, CH₂Cl₂ (79%). f) Cu, DMF, 18 h, 23 °C, (64%). g) HCl(_c), AcOH, 50 °C, 10 min (71%). h) TiCl₄/Zn/CuCl, reflux, 3 h, THF then DDQ, CHCl₃ (10%).



Scheme 23 A representative etio-type benzoporphycene. Reaction conditions: a) TiCl₄/Zn. b) DDQ.

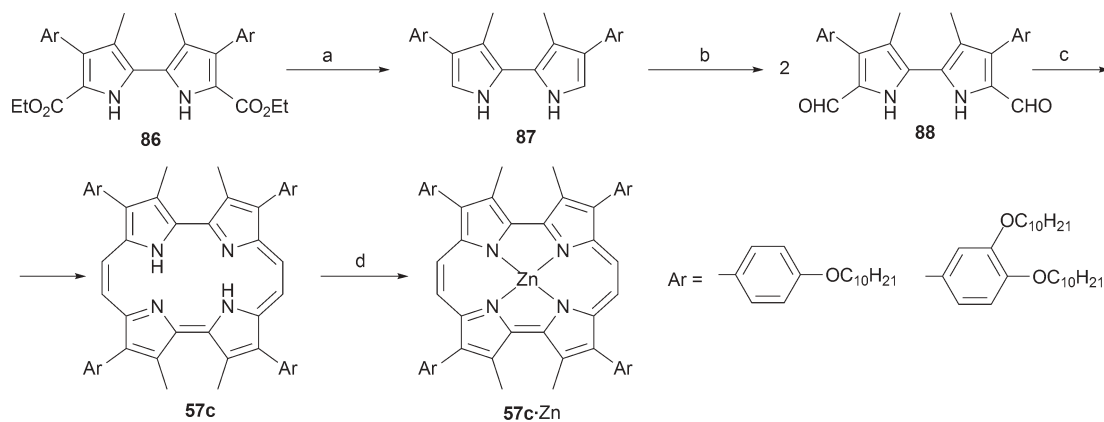


Scheme 24 Synthesis of benzoporphycene **85**. Reaction conditions (yields in parentheses): a) DBU, THF, 40 °C, 90 min (86%). b) dimethyl acetylene carboxylate (DMAD), 75 °C, 90 min (60%) c) LiOH, THF/H₂O (65%).

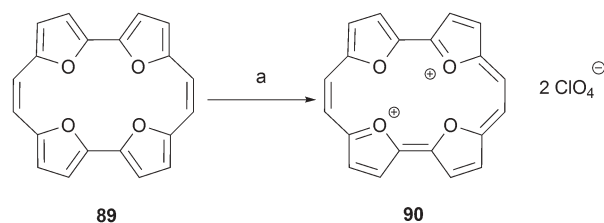
this *N,N'*-dihydroporphycene was effected by treatment with DDQ.

An interesting example, noteworthy because of its potential significance as a PDT photosensitizer, is benzoporphycene **85**.^{19,71} This compound was prepared by a Diels–Alder reaction involving dimethyl acetylene carboxylate (DMAD) and the corresponding vinyl porphycene **84**. The latter light sensitive intermediate can be prepared by subjecting the bromoethyl porphycene **49** to elimination in the presence of DBU (Scheme 24).

In 2007 Sessler and coworkers prepared a series of etioporphycenes bearing aromatic groups in positions 2, 7, 12 and 17 (e.g., **57c**).⁶² These functionalized porphycenes were synthesized in order to study the possible formation of liquid crystals. Accordingly, the aromatic groups on the porphycene core were substituted with –OC₁₀H₂₁ alkoxy chains. Towards this end, β -substituted pyrroles were prepared using the Zard–Barton protocol and carried on to provide the highly organic soluble bipyrrroles **86–88** (Scheme 25). It is noteworthy that the porphycenes in question (**57c**) were obtained in high yield. As in the case of other functionalized porphycene systems, this favorable result can be attributed to the presence of the highly solubilizing substituents.



Scheme 25 Synthesis of aryl substituted etioporphycenes (Ar = *p*-H₂₁C₁₀OPh, *p,m*-H₂₁C₁₀OPh). Reaction conditions (yields in parentheses): a) KOH, ethylene glycol, 200 °C (91%, 90%). b) POCl₃, DMF/DCE, Δ , then AcONa, H₂O, Δ , (82%, 76% two steps). c) TiCl₄, Zn, CuCl, THF, Δ , (41%, 25%). d) Zn(OAc)₂, CHCl₃, MeOH, Δ .



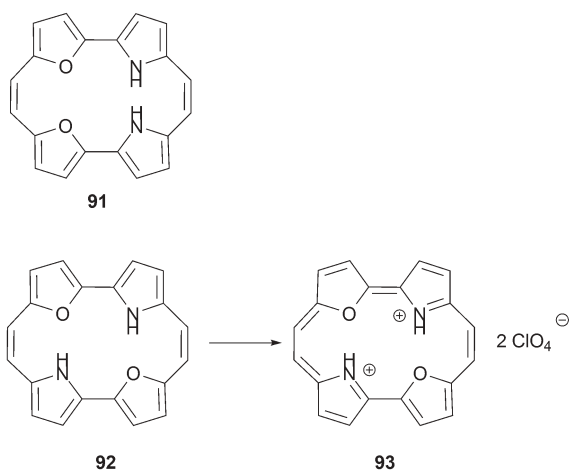
Scheme 26 Synthesis of tetraoxaporphycene dication. Reaction conditions (yields in parentheses): a) Br₂/HClO₄ (90%). The 2-electron oxidation in question is effected using Br₂ dissolved in perchloric acid.

Porphycene analogues containing furan, thiophene, or imidazole subunits

In parallel with recent developments in porphyrin chemistry, structural variations of the tetrapyrrolic porphycene in such a manner that an 18 π -electron conjugation pathway is maintained gives rise to a potentially rich family of neutral as well as charged analogues. So far, efforts have focused on the synthesis of analogues with furan, thiophene, and imidazole subunits.

The field was opened in 1988 by the Vogel group, which brought the furan-based analogue of porphycene, the tetraoxaporphycene dication **90**, to light.⁷² This analogue was obtained in two steps by subjecting 5,5'-bi-2,2-furfuraldehyde⁷³ to reductive coupling followed by oxidation. The coupling affords the cyclophane-type tetraoxa[20]annulene **89** in 16% yield along with smaller amounts of higher order macrocyclic compounds. The tetraoxaannulene **89** is relatively stable in contrast to the corresponding pyrrole-derived 22, 24-dihydroporphycene (compound **3**; Scheme 1). As expected, **89** on reaction with bromine in perchloric acid readily undergoes 2-electron oxidation to give the tetraoxaporphycene dication **90** as its perchlorate salt, a species that exhibits typical aromatic features (Scheme 26).

In 1991, Vogel and Cöln prepared a new porphycene analogue **93** containing two nitrogen and two oxygen atoms within the core.⁷⁴ The starting furan–pyrrole dialdehyde was coupled using Vogel's modified McMurry conditions, a

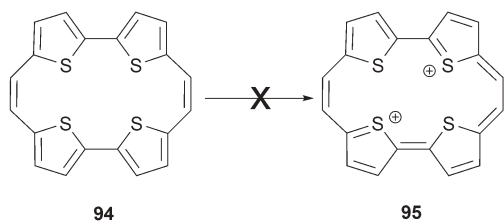


Scheme 27 Oxidation of annulene **92** and synthesis of dioxaporphycene **93**. A mixture of concentrated nitric acid in 70% perchloric acid was used as the oxidant leading to the isolation of **93** in its diprotonated form.

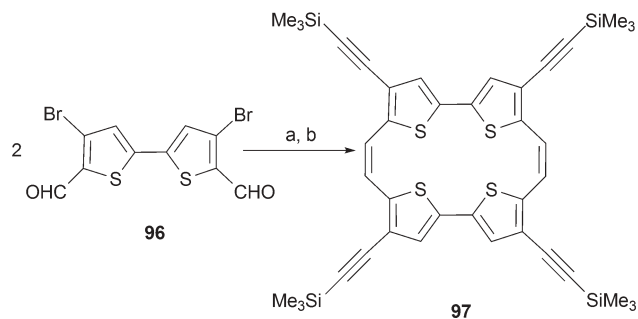
transformation that provided the stable annulene **92**. Interestingly, the symmetric isomer **91** was not formed. However, as expected, oxidation of **92**, using a mixture of concentrated nitric acid and 70% perchloric acid, then provided the 18 π -electron aromatic dioxaporphycene **93** in 94% yield (Scheme 27).

The sulfur analogue of intermediate **3** and annulene **92**, namely **94**, was reported independently by Neidlein (1993) and Cava (1994). As expected based on this analogy, macrocycle **94** was found to be a distorted non-planar 20 π -electron annulene.^{75,76} This sulfur-containing cyclophane was synthesized by heating 2,2'-bithiophene-5,5'-dicarboxaldehyde⁷⁷ at reflux in the presence of the titanium low-valent reagent; this gave **94** in 8–11% yield, along with a 3–14% yield of the corresponding hexathiophene trimer (Scheme 28). There is, however, no evidence that this procedure gave rise to the corresponding aromatic product, **95**, a putative species that would be analogous to the dication **90** or porphycene **1**. Presumably, this reflects an inherent difficulty in carrying out the requisite oxidation.

Neidlein and co-workers⁷⁸ obtained the alkynyl-substituted annulenes **97** *via* Sonogashira coupling⁷⁹ using the corresponding tetrabrominated macrocycle (obtained from the brominated bipyrrrole **96**) as the starting material (Scheme 29). However, there is no report of any successful oxidation to an aromatic species corresponding to the so-far hypothetical dication **95**.



Scheme 28 Presumed resistance towards oxidation inferred for tetrathia[20]annulene **94**.



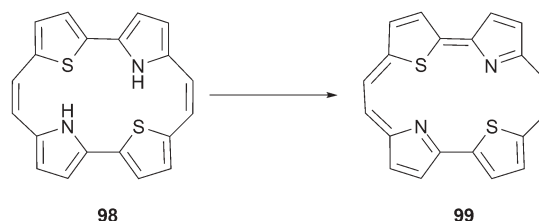
Scheme 29 Synthesis of a tetrakis alkynyl derivative, **97**, of the tetrasulfido[20]annulene **94**. Reaction conditions (yields in parentheses): a) TiCl_4 , Zn/Cu, pyridine, THF, reflux, 72 h followed by hydrolysis (26%). b) $\text{Me}_3\text{Si-C}\equiv\text{CH}$, $\text{Pd}(\text{PhCN})_2\text{Cl}_2$, Ph_3P , CuI, *i*- Pr_2NH , 70 °C, 2 h (76%).

While the tetrathiaporphycene dication **95** defies synthesis, the neutral dithiaporphycene **99**, with the sulfur atoms in a *trans*-like configuration, is found to be a planar aromatic macrocycle, matching the parent porphycene in many respects. It is obtained from the spontaneous oxidation of **98** obtained upon subjecting 2-(2-thienyl)-1*H*-pyrrole to reductive coupling (Scheme 30).⁸⁰

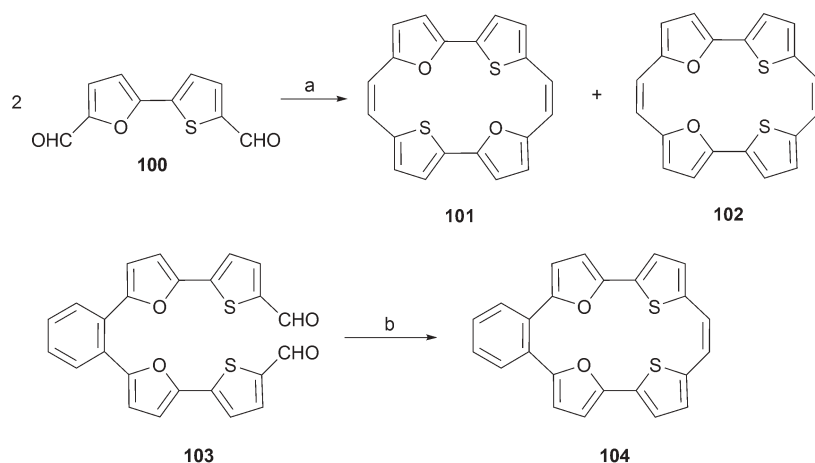
Mixed furan–thiophene porphycene analogues were prepared in 2000 in Dai's laboratory.⁸¹ In this case, McMurry coupling of 5,5'-diformyl-2,2'-furanthiophene **100** in tetrahydrofuran at reflux afforded a separable mixture of the two possible isomers **101** and **102**. Interestingly, isomer **102** (formed in 7.2% yield) is obtained in preference over **101** (generated in 2.6% yield). The authors suggest that the cyclization takes place *via* initial coupling of the furan “sides” of the biaryl precursor reflecting the relatively small size of oxygen compared to sulfur. However, there does not appear to be any independent support for this proposal.

In the same report detailing the synthesis of **101** and **102**, Dai and co-workers disclosed the synthesis of the benzo substituted annulene **104**. The synthesis of this latter product, using Pd-chemistry,⁸² is noteworthy because it provides an exception to the general “rule” wherein a biaryl moiety provides the starting material and a single McMurry coupling serves to close the ring in a “2 + 2” fashion (Scheme 31).

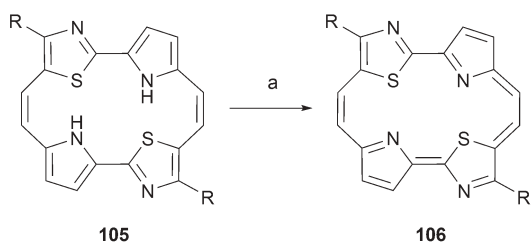
Also in 2000, the first porphycene incorporating nitrogen in its periphery was reported.⁸³ These kinds of compounds, embodied in structures **106**, can be regarded as heteroporphycenes since their UV-vis and NMR spectral data is consistent with an aromatic system (Scheme 32). Again, this kind of



Scheme 30 Thiophene and pyrrole containing annulene **98**, and thiaporphycene **99**.



Scheme 31 Reaction conditions (yields in parentheses): a) $\text{TiCl}_4/\text{Zn}/\text{pyridine}$, reflux, THF, 2.5 h, **101** (2.6%), **102** (7.2%). b) $\text{TiCl}_4/\text{Zn}/\text{pyridine}$, reflux, THF, 5 h (18%).



Scheme 32 Examples of thia and aza porphycenes. Reaction conditions. (R = H, *t*-Bu, Ph) a) DDQ, THF, $-20\text{ }^\circ\text{C}$ to $23\text{ }^\circ\text{C}$, 30 min (17–87%).

porphycene derivative could be obtained by subjecting the appropriate reduced precursor, **105**, to oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).

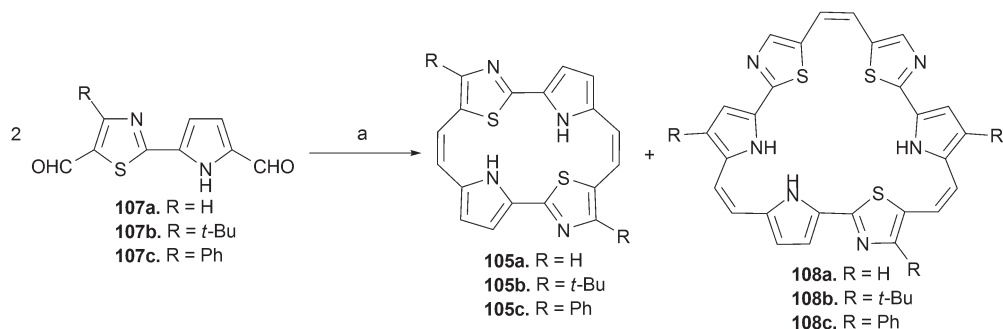
The synthesis of the key, reduced precursor **105** begins with a substituted 2-(1*H*-pyrrol-2-yl)thiazole. This intermediate, in turn, is prepared *via* the cyclocondensation of 1*H*-pyrrole-2-carbothioamide with various α -haloketones. In this latter step, a range of alkyl and aromatic substituents can be introduced. With this precursor in hand, the thiazole ring is formylated *via* selective generation of the anion with *n*-BuLi followed by quenching with *N*-formylmorpholine. Standard Vilsmeier–Haack conditions yield the corresponding dialdehyde **107**. Treatment of these dialdehydes with a low-valent titanium

(McMurry) reagent in THF at reflux, affords the corresponding annulenes **105** and its symmetrical isomer (nitrogens in positions 21 and 24), albeit in low yields (2–3%), along with the trimer **108** (Scheme 33).

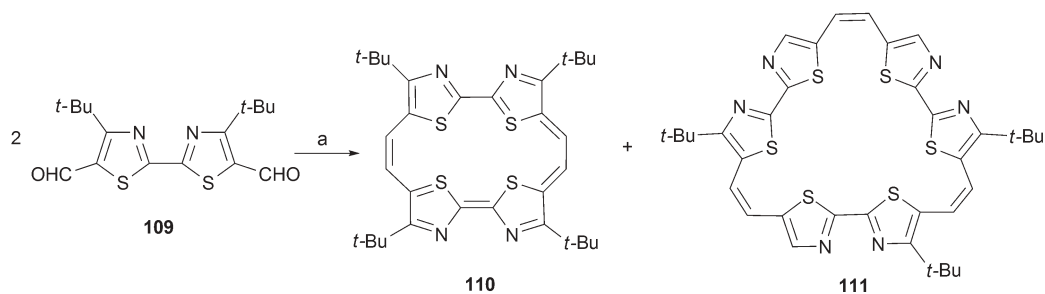
During work-up of the McMurry reaction, the authors noticed some reduction of the porphycene core. However, they found that the removal of any residual Zn species by filtration prior to quenching the reductive coupling reaction obviated this undesirable reduction process, which was ascribed to hydrogenation at the *meso* positions.

In this same year Neidlein reported the preparation of a macrocycle (**110**) containing four thiazole units.⁸⁴ The synthesis is very straightforward and consists of three steps: preparation of the 2-(thiazol-2-yl)thiazole from the double condensation of ethanebis(thioamide) and 1-bromo-3,3-dimethylbuta-2-one followed by formylation (to give **109**), and standard McMurry-type reductive coupling. However, in contrast to what was found in the case of compound **105**, annulene **110** could not be oxidized to produce the corresponding aromatic product (equivalent to the hypothetical species **95**); this proved true in spite of testing a variety of conditions. On the other hand, the preparation was found to yield the corresponding trimer **111** in 10% yield (Scheme 34).

In 2003 the groups of Sessler and Allen⁸⁵ and Teixidó and Nonell⁸⁶ reported independently the preparation of biimidazole-containing tetrazaporphycenes **119**, compounds that have



Scheme 33 Reaction conditions (yields in parentheses): (R = H, R = *t*-Bu, R = Ph) a) $\text{TiCl}_4/\text{Zn}/\text{pyridine}$, reflux, THF, 5 h (7–18%).

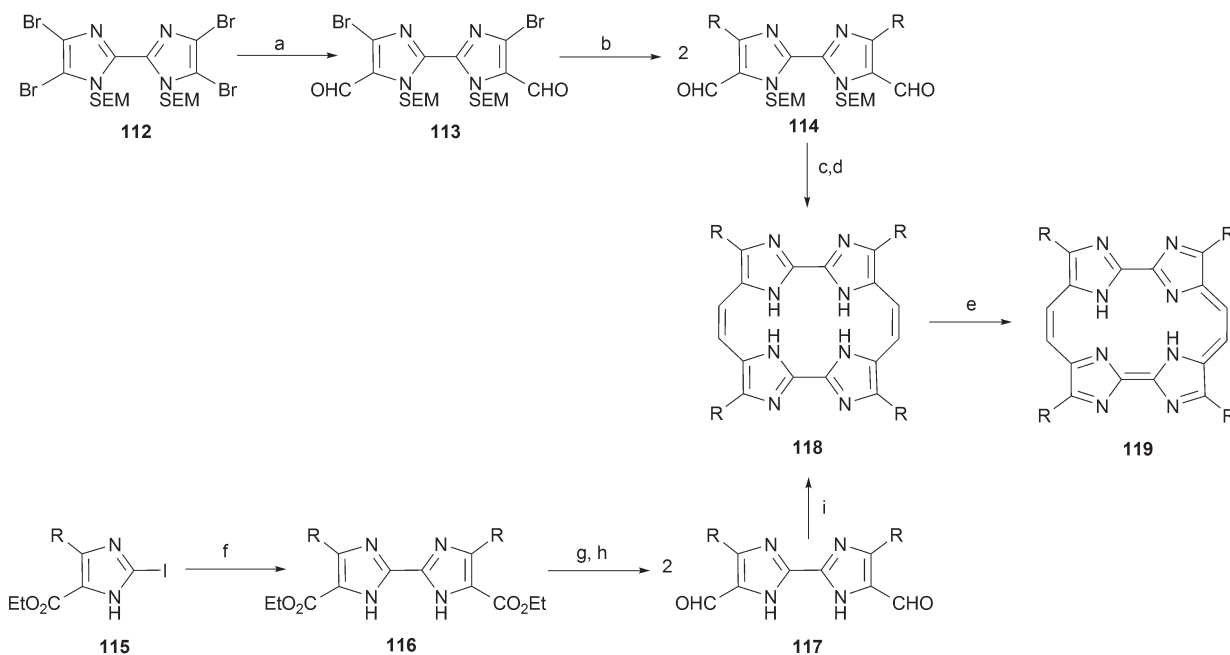


Scheme 34 Reaction conditions (yields in parentheses): a) $\text{TiCl}_4/\text{Zn}/\text{pyridine}$, reflux, THF, 65 h, **110** (6%), **111** (10%).

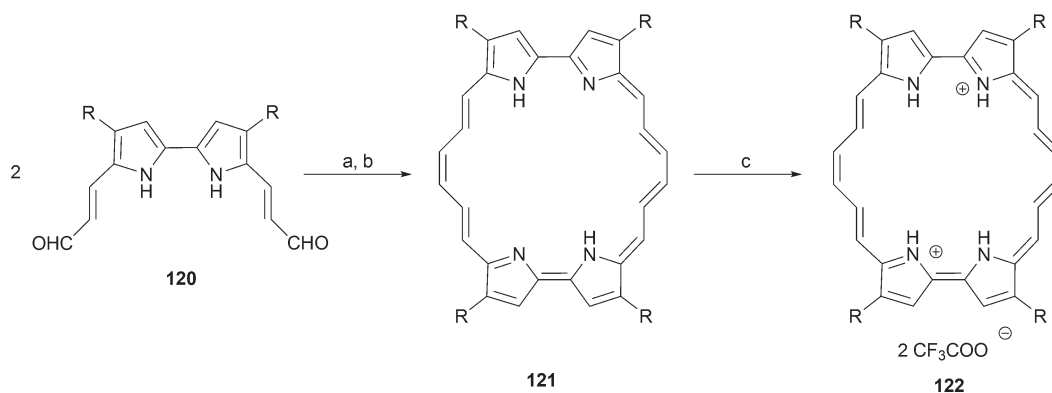
come to be referred to as “imidacenes”. The approach developed by Sessler leads to the alkyl derivatives, whereas that used by Nonell produces the aryl substituted counterpart (Scheme 35). In spite of these differences, in both cases a major effort was required to obtain the requisite 2,2'-bimidazole⁸⁷ precursors.^{88,89} Sessler’s approach to this class of building block involved the dimerization of iodoimidazoles **115** using a Pd-mediated Ullmann-type coupling. This gives a biimidazole **116** that is then formylated (to give **117**) prior to being subject to reductive coupling to produce the annulene species **118**. In contrast, the synthesis of Nonell is predicated on the use of the dibrominated biimidazole **113** (obtained from the tetrabromo species **112**) as a scaffold for further elaboration. This novel strategy is impressive in that it allows for the introduction of aromatic substituents *via* the appropriate use of Pd coupling chemistry. This provides an aryl substituted intermediate (**114**) that is then subject to follow-up reductive coupling. Thus, like Sessler’s approach, Nonell’s strategy is based on the appropriate use of palladium

coupling chemistry,⁹⁰ albeit at a very different point in the synthesis.

As is true for the dioxannulenes discussed above, the reduced synthetic precursor produced after the McMurry ring-forming reductive coupling step (**118**) exhibits unusual stability. Needless to say, this stability stands in stark contrast to what is true in the case of the analogous reduced porphycene precursor **3** (Scheme 1). It is also noteworthy since *a priori* it would be expected that the corresponding oxidized imidacenes **119**, benefiting from [18]annulene-type aromaticity, would be far more stable. To date, the photo-physical properties of the aromatic tetraazaporphycenes (imidacenes), but not those bearing alkyl substituents, have been analyzed in detail.⁹¹ Here, it was noted that the λ_{max} of the imidacene is shifted to the red by *ca.* 100 nm compared to the corresponding porphycene **1d**. This behavior, attributable to the introduction of additional nitrogen atoms into the macrocyclic core, is in agreement with the trend observed for other porphycene analogues.⁸³



Scheme 35 Reaction conditions (yields in parentheses): a) *n*-BuLi, $-78\text{ }^\circ\text{C}$, THF then DMF (71%). b) (R = *p*-BuPh) $\text{RB}(\text{OH})_2$, $\text{Pd}(\text{PPh}_3)_4$, Na_2CO_3 , toluene/EtOH (55%). c) HCl, EtOH/ H_2O (76%). d) $\text{TiCl}_4/\text{Zn}(\text{Cu})/\text{pyridine}$, THF (7%). e) DDQ, THF (60%). f) (R = *n*-propyl) $\text{Pd}(\text{PPh}_3)_4$, Et_3N , toluene, $110\text{ }^\circ\text{C}$ (28%). g) DIBALH, THF (98%). h) DDQ, THF (60%). i) $\text{TiCl}_4/\text{Zn}(\text{Cu})/\text{pyridine}$, THF, (2%).



Scheme 36 Reaction conditions: (R = C₃H₇). a) TiCl₄/Zn, THF. b) air. c) CF₃CO₂H.

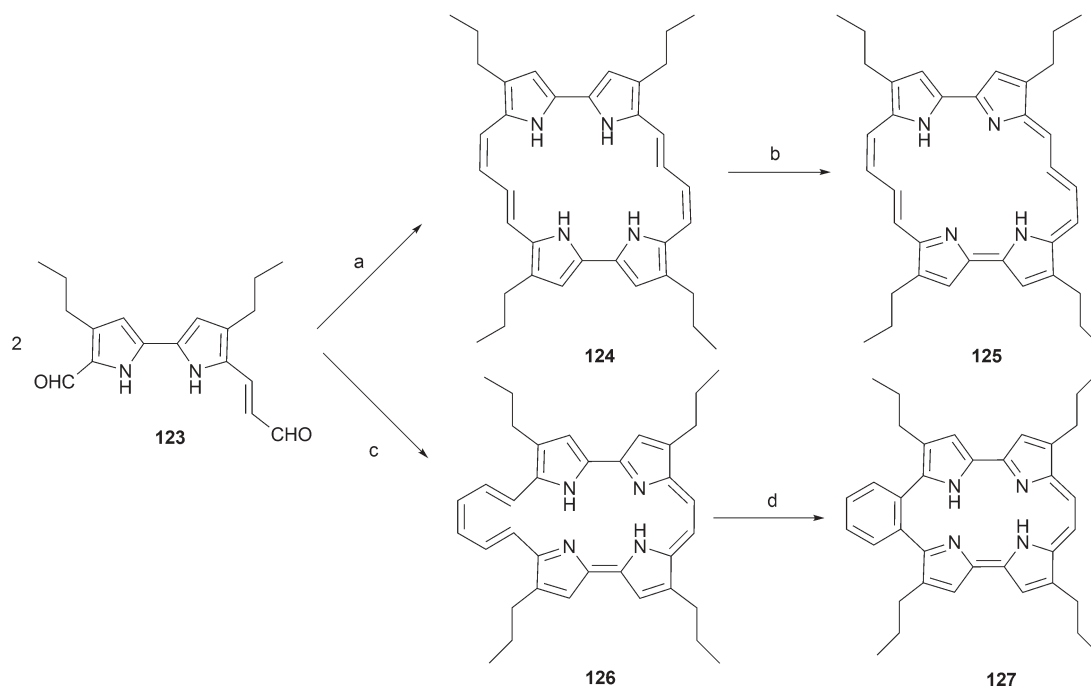
Extended porphycenes

The insertion of an even number of sp or sp² hybridized carbons into the linkers between the pyrrolic units of porphycenes provides an entry into a new class of conjugated macrocycle, the so-called extended porphycenes. The important consequence of this addition is that the main (4*n* + 2) π-electron conjugation pathway is lengthened such that *n* > 4. This leads to chromophores that absorb at longer wavelengths than regular porphycenes of general structure **1**. This feature, in turn, has made extended porphycenes of interest as possible photosensitizers for use in PDT applications.⁹²

As in the case of porphycene, it was the Vogel group that pioneered the synthetic development of extended porphycenes. Towards this end, two general strategies were developed that involve, respectively, the synthetic addition of alkylidene or alkylidene moieties to either the *meso* bridge or between the

2,2' positions of the bipyrrrole subunits. To date, both strategies have been successfully implemented, albeit in neither case has the chemistry of the resulting systems been extensively pursued. The synthesis of the first type of expanded porphycene was achieved by subjecting the vinyllogous dialdehyde **120** to reductive dimerization. The latter intermediate is readily obtained from 4,4'-dipropyl-2,2'-bipyrrrole *via* reaction with 3-(dimethyl-1-amino)acrolein⁷⁰ (Scheme 36).

As an extension of this work, the monovinyllogous diformyl bipyrrrole **123** was subject to reductive coupling under the McMurry conditions followed by exposure to air (Scheme 37). This gave rise to the extended porphycene **124** as the dominant product in 7% yield. Also obtained as a minor by-product was the less symmetric isomer **126**. This latter species could not be isolated. However, after electrocyclicization and spontaneous dehydrogenation it produced **127** in 0.7% yield based on **123**.⁵⁴



Scheme 37 Formation of extended porphycene **125** and 9,10-benzotetrapropylporphycene, **127**, from its putative ring opened precursor **126**. Reaction conditions. a) TiCl₄/Zn, THF. b) air. c) TiCl₄/Zn. d) benzene reflux, 2 days.⁵⁴

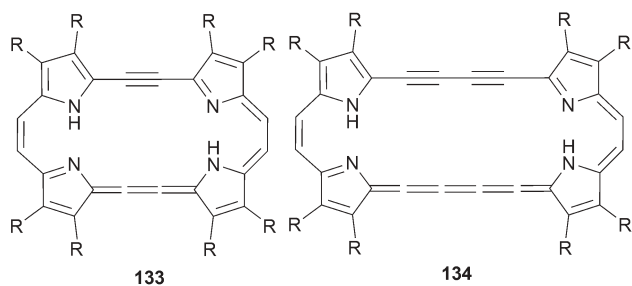


Fig. 7 Extended porphycenes **133** and **134**.

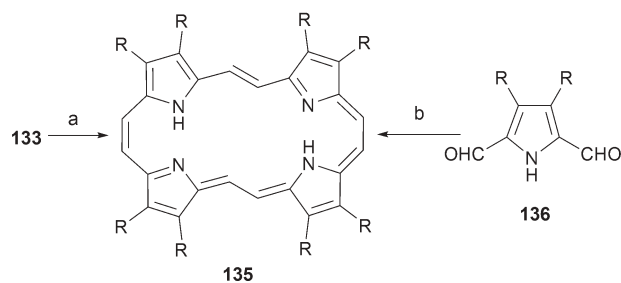
The first example of an expanded porphycene containing triple bonds inserted between the 2,2'-bipyrrole subunits, compound **133**, was reported by Vogel in 1990.⁹³ In this case, the resulting porphycene was found to be a 22 π -electron aromatic macrocycle (Fig. 7). Interestingly, this macrocycle displayed an acetylene-cumulene bonding motif, which is a feature in common with the Sondheimer–Nakagawa $[4n + 2]$ dehydroannulenes.

In 1992 Vogel and coworkers also reported the synthesis of the 26 π -electron homologue, **134**.⁹⁴ In both cases (*i.e.*, **133** and **134**), the synthesis was effected *via* reductive dimerization of the corresponding dialdehyde, **131** or **132**. The requisite acetylene linked bipyrroles were, in turn, prepared from iodopyrrole **128** and an acetylene source with the key bond attachment being made by means of a Sonogashira coupling (to give **129** and then **130** after deprotection). A refined procedure in the case where the β -pyrrolic substituent (R) is methyl was reported by Kim⁹⁵ in 1999 (Scheme 38).

A related class of extended porphycenes, containing “extra” sp^2 hybridized linking atoms between the 2 and 2' positions of the bipyrrole subunit, was obtained *via* hydrogenation of **133**. This yields the 22 π -electron conjugated porphycene homologue **135**. An alternative synthesis of this same macrocycle involves subjecting dialdehyde **136** to reductive oligomerization under McMurry conditions; the desired product **135** is obtained in this way, albeit in low yields (Scheme 39).

Conclusions

The most general method used to prepare porphycenes remains that introduced by Vogel roughly 20 years ago. It

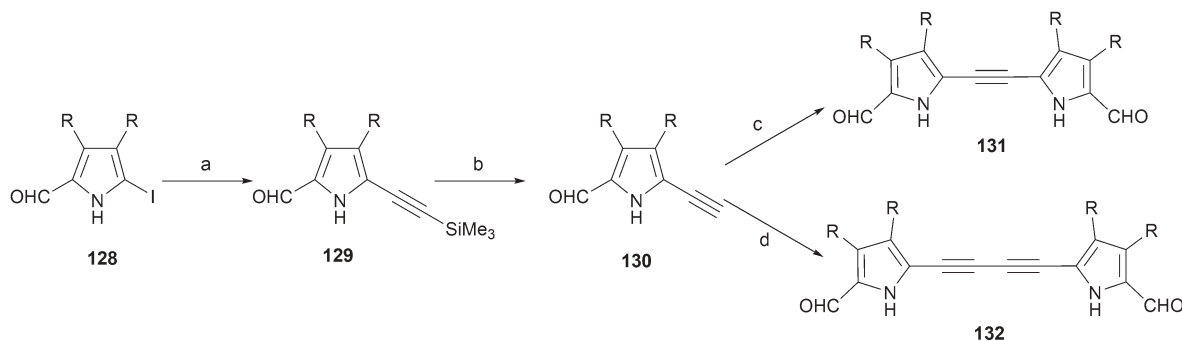


Scheme 39 Reaction conditions: (R = Et). a) H_2/Pd . b) $TiCl_4/Zn$, THF, (2%).

consists of two formal stages, namely the synthesis of a biheteroaryl moiety and dimerization of the corresponding dialdehyde by means of a McMurry coupling. The last step, although low-yielding in the case of less soluble systems is well established and is common to almost all preparations; hence the efforts to build new porphycenes have been focused on the optimization of the 2,2'-bipyrroles synthesis and the production of novel biheteroaryl systems. Nonetheless, the potential utility of new porphycenes and their derivatives provides an incentive to develop new, and more concise preparative methods, in part because such strategies offer a chance to improve the flexibility of current porphycene design strategies.

To achieve these objectives two general approaches are envisioned. The first involves the direct synthesis of substituted porphycenes using appropriate biheteroaryls as the starting materials. This strategy, which is more classical, relies on the design of new preparations of biheteroaryls. Here, new synthetic transformations, including metal-catalyzed cross-coupling reactions, could prove advantageous.

The second strategy is based on the design of easy-to-prepare porphycenes followed by post-synthetic modification. This has the advantage that it could permit access to systems with specific requirements. However, it is unlikely to address the obvious synthetic challenge of finding new ways to make and modify porphycenes using approaches that differ radically from those introduced by Vogel. Nonetheless the current methods have provided a range of interesting structures and have allowed a variety of applications to be pursued. As such, the area of porphycene chemistry continues to attract an ever-larger number of practitioners, including increasingly



Scheme 38 Reaction conditions: (R = CH_3). a) $Pd(PPh_3)_2Cl_2$, CuI, (trimethylsilyl)acetylene, diethylamine, 50 °C, (95%). b) Bu_4NF , THF, 23 °C, 1 h, (99%). c) **128** (0.85. equiv.), $Pd(PPh_3)_2Cl_2$, CuI, diethylamine, 50 °C, 3 h, (65%). d) $(PPh_3)_4Pd$, CuI, Et_3N , chloroacetone, benzene, 23 °C, 16 h, (92%).

researchers outside the synthetic organic chemical field. This attests to the fascination inherent in porphycene as a molecule, ligand, structural motif, and chromophore.

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