Constructing a Molecular LEGO Set

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1 Introducing the Science and the Scientists (JFS)

In academic circles, science is just as much about training, learning, and understanding as it is about discovery, innovation, and invention. The primary responsibility of a research supervisor is to capture the imaginations of young scientists who have found themselves – for whatever reasons – attracted to the prospect of tackling contemporary problems in science. More often than not, it is for the advisor to identify and define the research problem. This task is by no means an easy one, particularly since anything approaching unanimous agreement on the definition and identification of an important problem is unlikely ever to be forthcoming at the time of its conception. We can only be guided ultimately by the reception the scientific community extends to the science when it reaches the light of day from platforms at conferences and from the pages of the journals. This story, which will be told here alternately by advisor (JFS) and student (JPM), is about how a molecular LEGO set was conceived and constructed. We shall try to communicate how we responded to the disappointments and triumphs during the execution of a research programme that produced more than its fair share of setbacks and rewards.

The tale behind the making of kohnkene (Figure 1) at Sheffield University in the mid 1980s by Franz Kohnke has been related at length elsewhere.[1-8] This interesting macropolycyclic belt-like compound (5) had been targeted for synthesis (Scheme 1) for a variety of reasons. For example, it could be viewed as a precursor to novel hydrocarbons, such as [12]beltene (6) and [12]cyclacene (7) or it might be regarded as a potential molecular receptor towards appropriate substrates with complementary structures. Retrosynthetic analysis of kohnkene (5) indicates that four repetitive stereoselective Diels–Alder reactions, involving the bisdiene (1) and the bisdienophile (2), are all that are required to construct (5). This approach to the synthesis of (5) relies heavily upon the precise stereoelectronic control[3,4,7,8] and remarkable efficiency that can be imposed on this series of step-wise cycloadditions which occurs when the bisdiene (1) reacts with the bisdienophile (2). On heating two molar equivalents of (1) with one molar equivalent of (2) under reflux in toluene, the 2:1 adduct (3) was isolated in 68% yield.[1,3,7,8] Macropolycyclization of (3) with a further molar equivalent of (2) was achieved most easily and efficiently (48%) inside a high pressure reaction vessel at 18 kbars in dichloromethane.

Following the successful construction of (5), the question immediately arose as to whether the formation of this belt-like

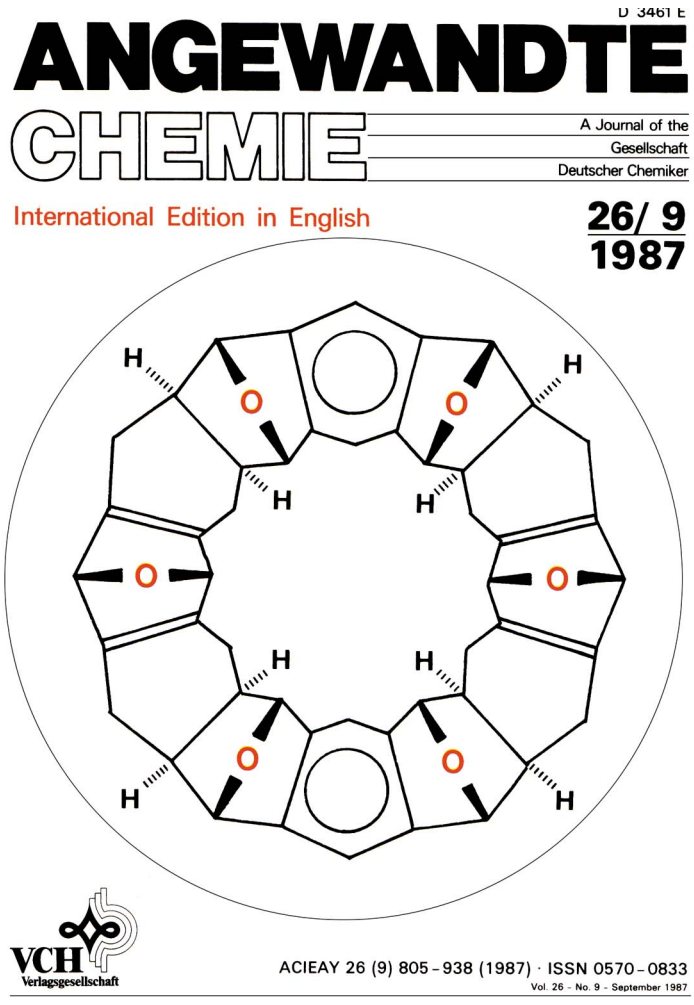

Figure 1 Kohnkene (5) on the cover of the September 1987 issue of *Angewandte Chemie*.
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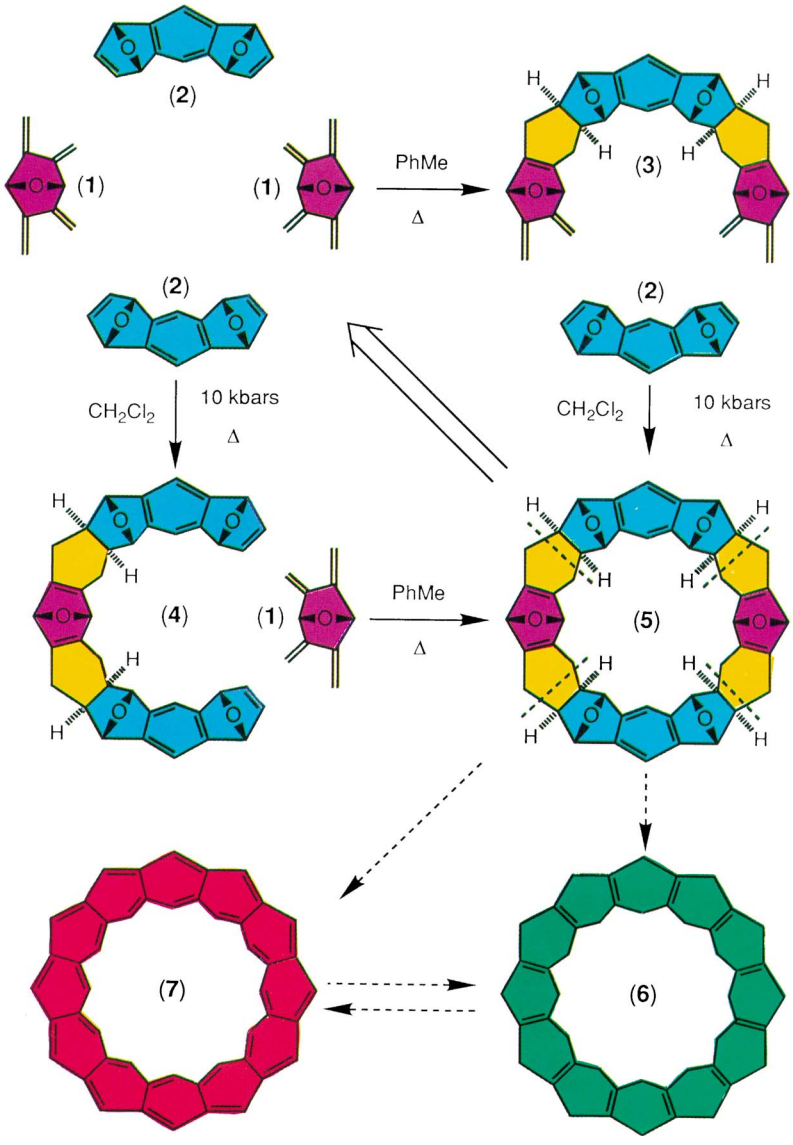
John Mathias was born in Stockport, England. He has B.Sc. (1987) and Ph.D. (1990) degrees from Sheffield University. Presently, he is carrying out postdoctoral work on an SERC NATO Fellowship with Professor G. M. Whitesides at Harvard University. His research interests encompass the general areas of synthetic and physical organic chemistry, with particular emphasis on the design and synthesis of supramolecular assemblies and nanoscale systems.

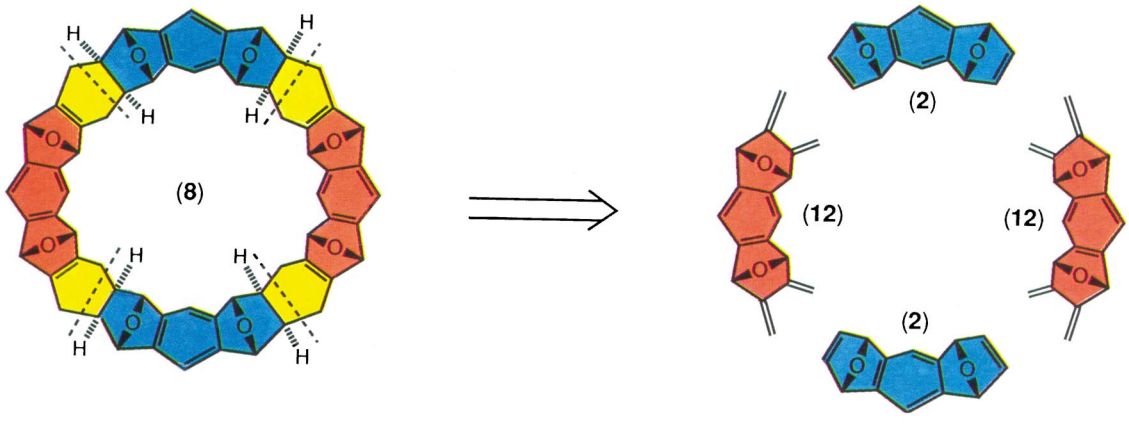
Fraser Stoddart (b. 1942) is a graduate (BSc./Ph.D./D.Sc.) of Edinburgh University where he carried out Postgraduate Research between 1964 and 1966 on polysaccharides in the Carbohydrate Chemistry School headed by Professor Sir Edmund Hirst F.R.S. After three years as an NRC Postdoctoral Fellow at Queen's University in Kingston (Canada) with Professor J. K. N. Jones F.R.S., he returned to Sheffield University in the U.K. as an ICI Postdoctoral Fellow with Professor W. D. Ollis F.R.S. There, he was appointed to a Lectureship in 1970 and subsequently to a Readership in 1982. During the three-year period from 1978–1981, he was seconded to the ICI Corporate Laboratory in Runcorn. In 1990, he moved to Birmingham University to the Chair of Organic Chemistry. His research interests lie in the broad areas of unnatural product synthesis, supramolecular chemistry, and functioning molecular systems and materials. He has been the recipient worldwide of numerous awards, fellowships, and lectureships, and is the author of over 300 scientific publications.



Scheme 1 Kohnkene (5) – its retrosynthesis and synthesis, as well as its key position as a potential precursor of [12]beltene (6) and [12]cyclacene (7).

compound, with 12 laterally-fused six-membered rings, was a unique process. John Mathias had heard about the challenges surrounding the synthesis of kohnkene (5) as an undergraduate student while attending my tutorials in organic chemistry. His interest was heightened further by spending a summer as a vacation student in my laboratories during 1986. At that time, Franz was grappling with the final stages of the synthesis of (5). When John joined my research group at Sheffield in September of the following year, the scene was set to see if we could build a [16]cyclacene derivative (8), analogous to (5), using the repetitive stereoselective Diels–Alder methodology (Scheme 2) between the larger *syn*-bisdiene (12) and the original bisdienophile (2). John will now take up the story of how this problem was tackled

Scheme 2 The retrosynthesis of the proposed [16]cyclacene derivative (8), identifying the *syn*-bisdiene (12) as the required precursor in combination with the *syn*-bisdienophile (2).



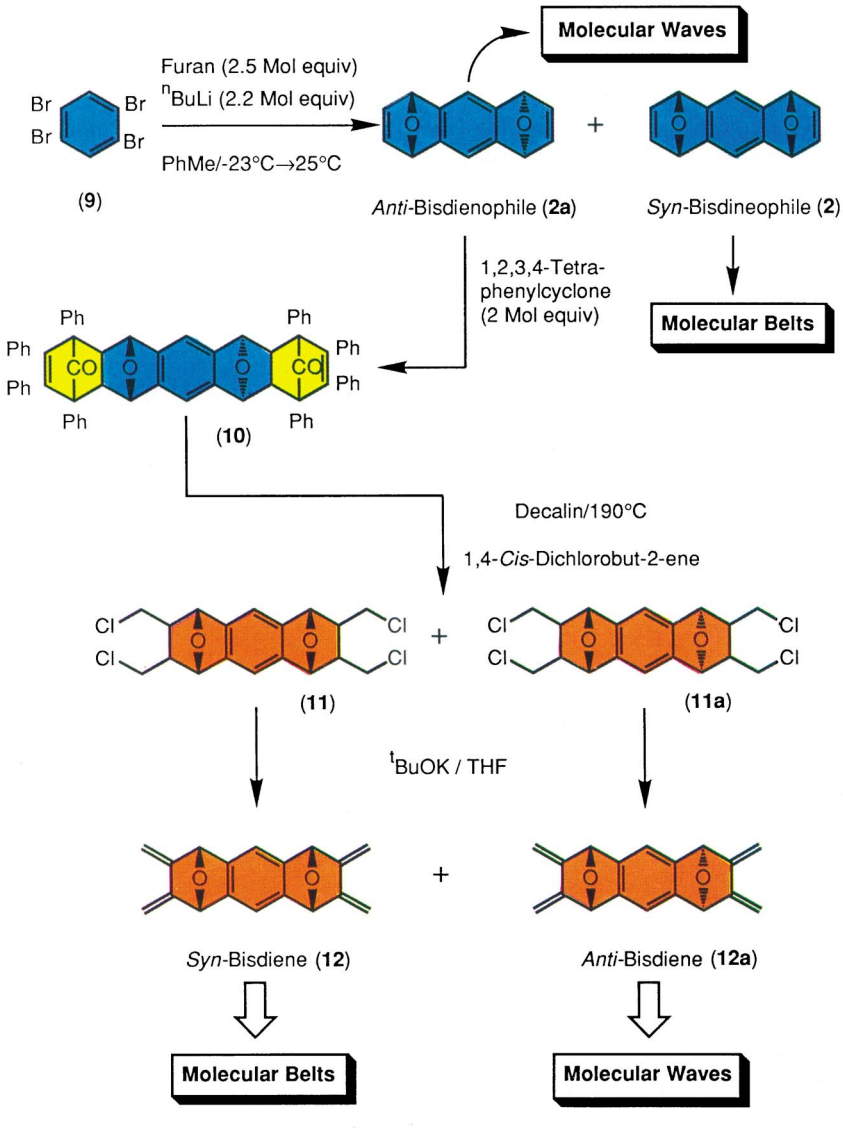
and how the ideas that grew out of the research project were pursued. The results which emerged were certainly not those which were anticipated at the outset!

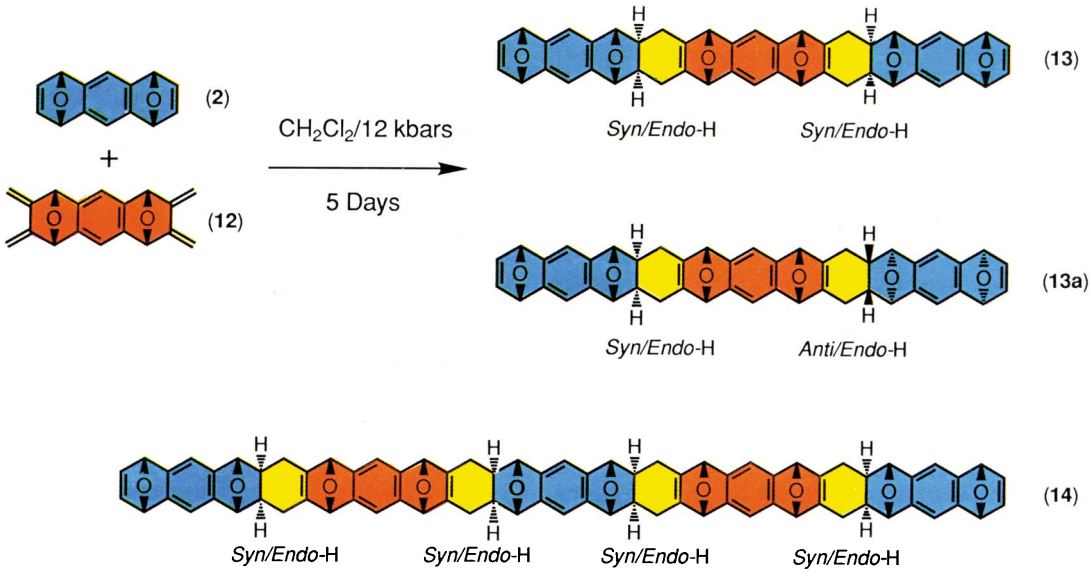
2 Making Molecular Belts and Coils (JPM)

The first objective following the synthesis of kohnkene (5) was to try and extend the Diels–Alder methodology in a way that would (i) probe the generality or otherwise of the treble diastereoselectivity that was evident in the repetitive cycloadditions leading to (5) and (ii) provide access to molecular belts with large diameters and novel topologies. A synthesis (Scheme 2) of the [16]cyclacene derivative (8) would not only afford a compound with a larger cavity size than that of (5) – an important consideration if we want ultimately to study molecular recognition of any sort – but would also allow us to assess whether the *syn*-bisdiene (12) would react with dienophiles with the same treble diastereoselectivity[1–8] as did the original bisdiene (1).

After some preliminary work, the *syn*-bisdiene (12) was obtained in good yields from the *anti*-bisdienophile (2a) using some bisisobenzofuran chemistry[9] that was communicated privately to us by Professor Harold Hart of Michigan State University. The readily available *anti*-bisdienophile (2a) was converted (Scheme 3) into the bisisobenzofuran precursor (10) by cycloaddition with two molar equivalents of 1,2,3,4-tetraphenylcyclone. This product can be decomposed thermolytically and was trapped with *cis*-1,4-dichlorobut-2-ene, affording an equimolar ratio of the *syn*- and *anti*-tetrachlorides, (11) and (11a), respectively, in 57% yield overall.[10] The *syn*-tetrachloride (11) was then converted stereospecifically[11] into the *syn*-bisdiene (12) by treatment with potassium t-butoxide in tetrahydrofuran. This solution to the synthesis of (12) meant that both precursors of the anticipated [16]cyclacene derivative (8) were obtained from the same original reaction in a satisfying and resourceful manner. The next step in the proposed synthesis of (8) was the cycloaddition between two molar equivalents of the *syn*-bisdienophile (2) and one molar equivalent of the *syn*-bisdiene (12) to produce a 2:1 adduct (13). Franz's experience in the synthesis of (5) suggested that this reaction would require high pressure in order to proceed, because of the low reactivities associated with the diene units in (12). Indeed, after 5 days at 10 kbars pressure in an ultra-high pressure vessel at the University of Reading, we were able to isolate (Scheme 4) the 2:1 adduct (13) in 30% yield.[7,8,12] The most important feature of the 2:1 adduct (13) was that *syn*/*endo*-H stereochemistry had resulted across both of the newly-formed cyclohexene rings. The remarkable stereoselectivities that were the hallmark of the cycloadditions between bisdiene and bisdienophilic molecules in the synthesis of (5) had, therefore, been retained in the reaction of the *syn*-bisdienophile (2) with the new *syn*-bisdiene (12). This feature dictates that the gross conformation of the 2:1 adduct (13) is the horseshoe-like

Scheme 3 The synthesis of the *syn*-bisdiene (12) and the *anti*-bisdiene (12a) from the *anti*-bisdienophile (2a).





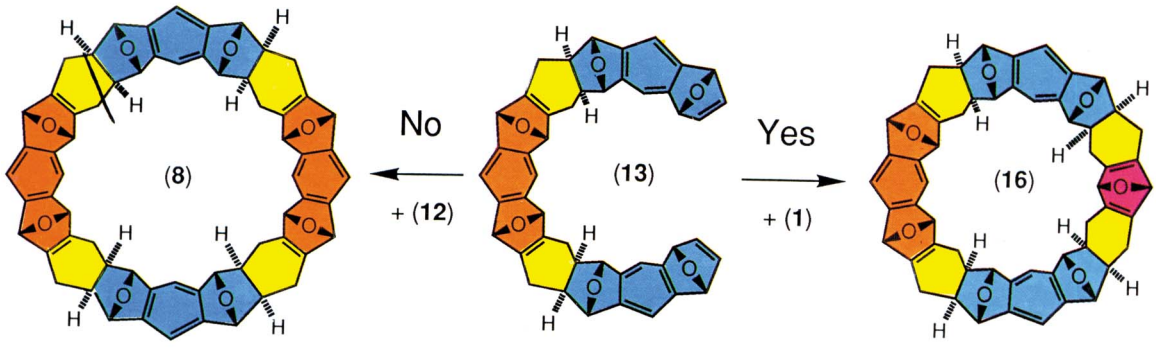
Scheme 4 Reaction of the *syn*-bisdienophile (2) with the *syn*-bisdiene (12) under ultra high pressure to give the 2:1 adducts (13) and (13a) – and the 3:2 adduct (14).

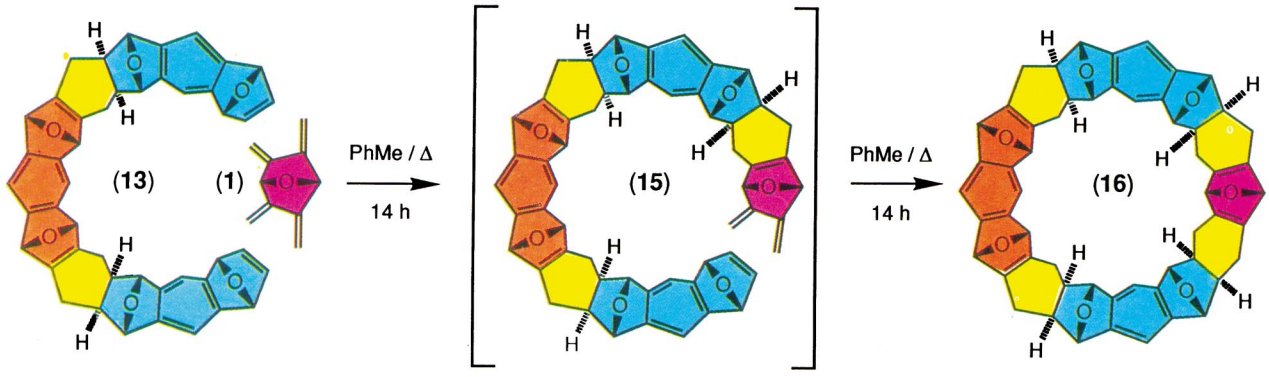
one that we required for the subsequent preparation of any closed macropolycyclic derivatives. In addition to the 2:1 adduct (13), however, we also isolated a small amount (2%) of the nonadecacene derivative (14) from this high pressure reaction.[7,8,12] This product is the result of the cycloaddition of three molar equivalents of (2) with two molar equivalents of (12) – it is a 3:2 adduct. The curvature that is inherent in each of the five constituent pieces of (14) means that the conformation of this molecule is that of a coil in which the two ends are overlapping. This suspicion was confirmed by ^{1}H NMR spectroscopy. Small quantities of a third compound were also isolated from the high pressure reaction between (2) and (12). Initially, we hoped that this compound might be the [16]cyclacene derivative (8). These hopes were dashed, however, by the FABMS performed by Peter Ashton. He showed[7,8,12] that this product was, in fact, a diastereoisomer of the 2:1 adduct (13). ^{1}H NMR Spectroscopy allowed us to identify the product as (13a). Intriguingly, a different stereochemistry from that observed in the major diastereoisomer (13) had been generated across one of the two newly-formed cyclohexene rings in (13a). Analysis by HPLC revealed that (13) and (13a) are produced in a ration of 18:1, respectively. We shall return to addressing the reasons for the appearance of this diastereoisomer shortly. All our attempts to isolate the [16]cyclacene derivative (8) from this reaction, as well as from reactions between (13) and a further molar equivalent of (12) under high pressure, were to prove unsuccessful. All that resulted were polymeric products in addition to the unchanged starting materials.

Scheme 5 The synthetic elaboration of the 2:1 adduct (13) to give the [16]cyclacene derivative (8) could not be effected. On the other hand, the formation of the [14]cyclacene derivative (16) from (13) is an extremely facile process.

Undaunted by the failure to isolate the [16]cyclacene derivative (8), our attention turned to the attempted preparation (Scheme 5) of a smaller [14]cyclacene derivative (16) from the 2:1 adduct (13). We anticipated that reaction of (13) with the original bisdiene (1) in equimolar proportions would proceed (Scheme 6) under reflux in toluene to afford the acyclic reaction product (15). Final closure of (15) to give the macropolycycle (16) would then be achieved, we reasoned, under high pressure. In the event, the thermally-promoted cycloaddition between (1) and (13) proceeded much more easily than we had expected. Indeed, we were able to isolate[7,8,12] the [14]cyclacene derivative (16) in 78% yield directly without the use of high pressure at all! At the time, our amazement at the extremely facile nature of the macropolycyclic ring closure was revealed by the fact that we dispatched a sample of the product obtained from the thermally-promoted reaction between (1) and (13) to Reading for macropolycyclization under high pressure. Only when this material came back to Sheffield unchanged – after 5 days at 12 kbars – did we consider the possibility that the macropolycyclic ring closure happens simply on heating! With hindsight, we can ascribe the remarkable acceleration of the ring-closure step to the high degree of stereoelectronic complementarity between the diene and dienophilic components of (15) immediately prior to the final cycloaddition. Clearly, the bisdiene (1) is just the right size and shape to bridge the ends of the 2:1 adduct (13) and give the [14]cyclacene derivative (16).

In summary, the synthesis of the [14]cyclacene derivative (16)





Scheme 6 The synthesis of the [14]cyclacene derivative (16) from the 2:1 adduct (13) and the bisdiene (1) under mild thermal conditions *via* a presumed intermediate (15) which could not be isolated or detected.

illustrated that (i) the high stereoselectivity, which is evident[1–8] in the synthesis of kohnkene (5), is not a unique event and can be extended to the synthesis of homologous systems, and that, in this approach to macropolycyclic structures, (ii) the size of the cavity that can be obtained is governed rather precisely by the curvatures inherent in the constituent pieces.

3 The Elusive Search for the Precursor to Kohnkene (JFS)

The ease with which John obtained[7,8,12] the [14]cyclacene derivative (16) from the thermally-promoted cycloaddition (Scheme 6) between (1) and (13) was to plague us later on in another series of experiments. Diane Smith, who joined my research group in the year after John, decided to see if she could isolate and characterize the immediate precursor of kohnkene (5) – a 2:2 adduct which we expected would require high pressure in order to induce it to undergo macropolycyclization. The problem with the first route {2 × (1) + (2) → (3)[+ (2)] → (5)} to kohnkene (5), shown in Scheme 1, is that the formation of the 2:2 adduct also has to be promoted by high pressure. Diane realized, however, that the alternate route {2 × (2) + (1) → (4)[+ (1)] → (5)} to (5), also shown in Scheme 1, avoided the problem of having to form the 2:2 adduct under high pressure. In principle, the 2:1 adduct (4) should be convertible into the 2:2 adduct thermally in toluene solution. In practice, all of Diane's attempts to isolate this 2:2 adduct were in vain. It would appear that, even under the mildest possible thermal conditions we could employ to make the 2:2 adduct, it undergoes macropolycyclization to give kohnkene (5) very much faster than it is formed from the 2:1 adduct (4) and the bisdiene (1). You win some and you lose some!

4 Kinetic Control *versus* Thermodynamic Control (JPM)

The isolation of a minor diastereoisomer (13a) in addition to the major 2:1 adduct (13) during the synthesis (Schemes 4 and 6) of the [14]cyclacene derivative (16) presented the first experimental evidence for the lack of total treble diasteroselectivity in the repetitive Diels–Alder reactions. This observation focused our minds on the factors that might be responsible for the high treble diastereoselectivity that usually characterizes these cycloadditions. It also encouraged us to ask whether the reactions were proceeding under kinetic or thermodynamic control. After all, Diels–Alder reactions can be either reversible or irreversible processes.[13] We have described these cycloadditions as being trebly diastereoselective.[3,4,7,8,12] This description is derived from the fact that there are three levels of diastereoselectivity associated with each cycloaddition: (i) one involving the two faces [*exo*-(1) or *endo*-(1)] of the bisdienophiles; (ii) another involving the two faces [*exo*-(2) or *endo*-(2)] of the bisdienes; (iii) and yet another involving the relative orientations (*syn* or *anti*) of the endoxide bridges across each of the newly-formed cyclohexene rings. On account of the constitutional symmetry of the 2:1 adducts formed when two molar equivalents of (2) react with one molar equivalent of (12) there are 10 possible diastereoisomeric compounds with this constitution. These 10 diastereoisomers are shown in Figure 2. Given all the possible products, the isolation[7,8,12] of only two, a major one, (13), and a minor one, (13a), in the ratio 18:1, indicates that both cycloadditions are remarkably stereoselective. The rationale that we have developed to account for this stereoselectivity is based on both steric factors, involving the endoxide bridges in the approaching reactants, and stereoelectronic features, associated with the π-systems of the diene and dienophilic units that undergo cycloaddition. A detailed discussion of these issues has been presented elsewhere.[3,4,7,8] Suffice it to say here, that precedents in the literature indicated[14] that dienophilic units, such as those present in the bicyclic dienophile (2), prefer to react at their top (*exo*-1) faces, while diene units, such as those present in the bicyclic diene molecule (12), prefer[15] to react at their bottom (*endo*-2) faces. In addition, the steric bulk on the reactants dictates that they must dock by a side-ways approach rather than by a trajectory which would require their stacking one on top of the other. The highly preferred pathway for the Diels–Alder reactions, that reflects their treble diastereoselectivity, is shown in Figure 3. The arguments I have just presented, however, are based on the relative energies of different transition states. They imply that the reaction sequences are proceeding under kinetic control. We had no direct evidence that this was the case. It was therefore important to establish that the 2:1 adducts (13) and (13a) are indeed formed under kinetic control and do not constitute a system that is equilibrating. To resolve this matter, we subjected (Scheme 7) the minor 2:1 adduct (13a) to the original high pressure conditions from which it had emerged in the first place. If it was able to undergo thermodynamic equilibration with the major isomer (13), then the 18:1 equilibrium mixture of diastereoisomers should be re-established.[7,8] In the event, the minor isomer (13a) was isolated unchanged from this reaction. This observation effectively ruled out any notion of thermodynamic control being responsible for the formation of these adducts and, therefore, established that kinetic control was, indeed, responsible for the outcome of these reactions. This conclusion was confirmed beyond any doubt in another independent experiment (Scheme 8) involving deuterium-labelled compounds. In this experiment, the hexadecadeuterio analogue (17) of the 2:1 adduct (3) involved in the synthesis of kohnkene (5) was heated under reflux in toluene with 10 molar equivalents of the bisdiene (1). If (17) was able to undergo thermodynamic equilibration with the bisdiene (1) then the deuterium atoms in (17) should be replaced as the bisdiene (1) becomes incorporated into the structure of the 2:1 adduct. In the event, the hexadecadeuterio derivative (17) was isolated unchanged from the reaction mixture and no evidence for the incorporation of (1) into the structure of the 2:1 adduct was evident.[7,8] This observation

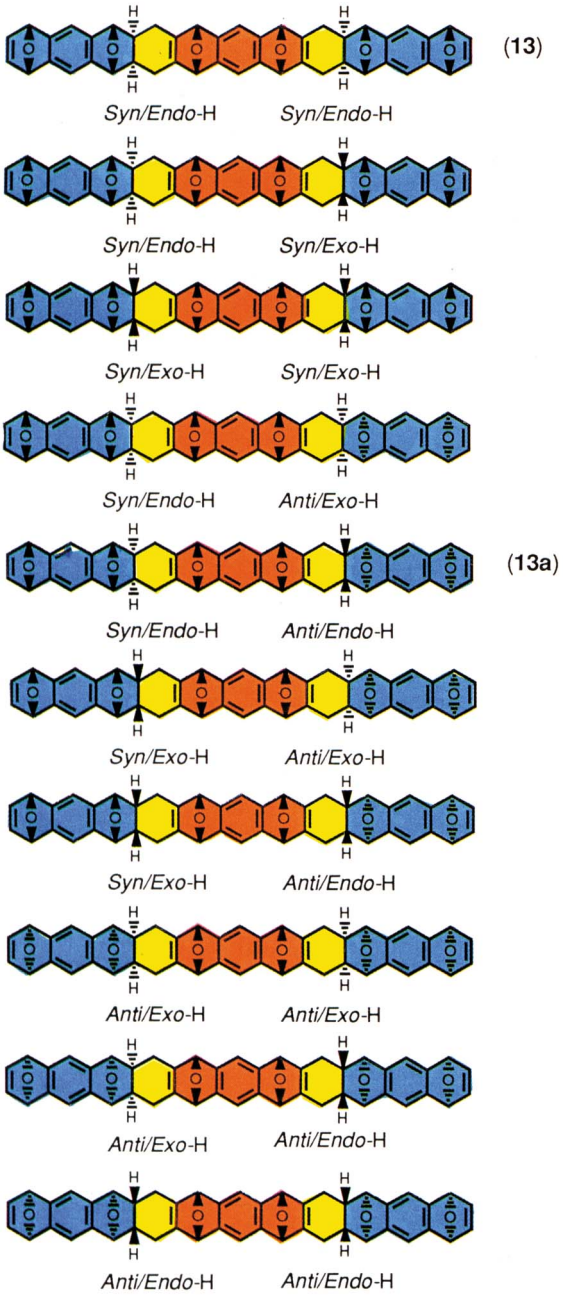
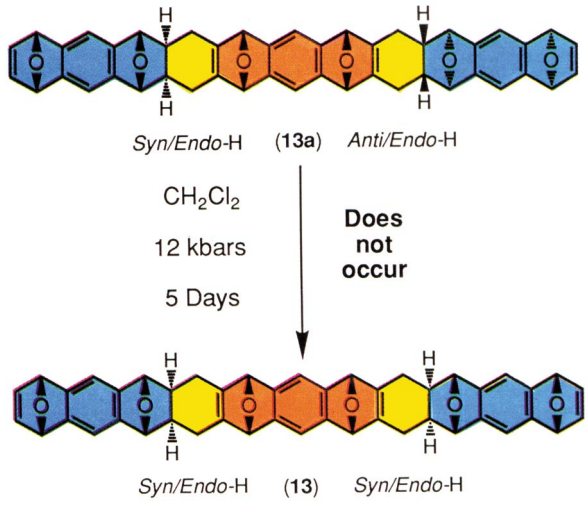


Figure 2 The 10 diastereoisomeric 2:1 adducts which can be formed from two equivalents of the *syn*-bisdieneophile (2) and a single equivalent of the *syn*-bisdiene (12).



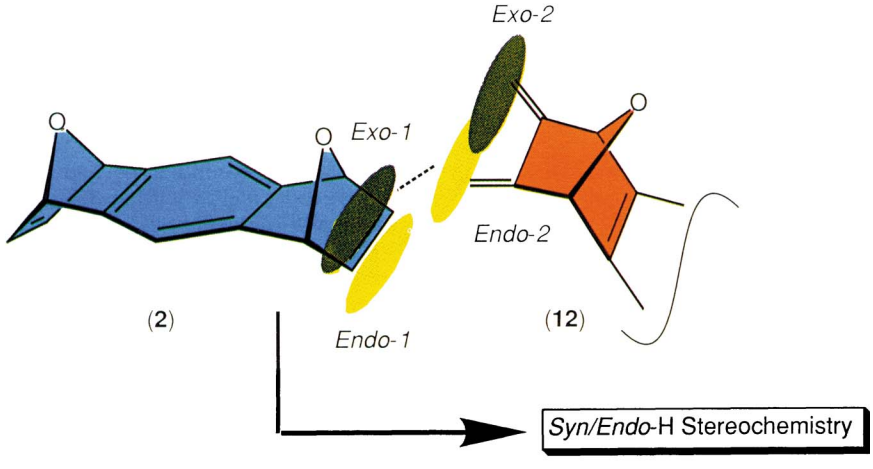
Scheme 7 The attempted equilibration of the diastereoisomeric 2:1 adducts (13) and (13a), which provides evidence for the operation of kinetic control in the cycloadditions.

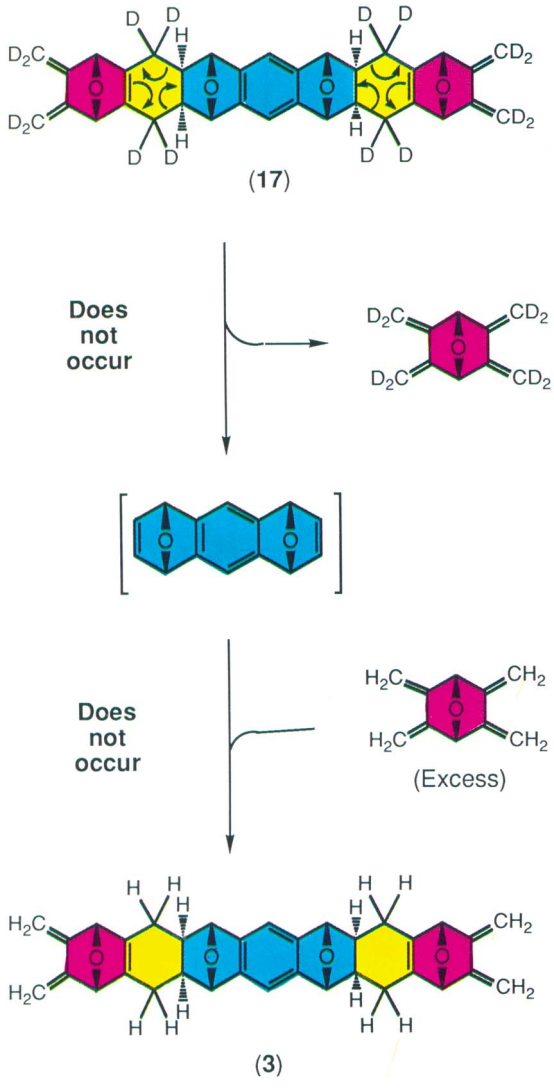
clinches the argument. Kinetic control it is in all these trebly diastereoselective Diels–Alder reactions.

5 Tooling up for the Job (JFS)

By the end of John's first year as a research student, it was becoming increasingly clear that our demands on the SERC High Pressure Facility at the University of Reading were mushrooming to a point that we were in danger of monopolizing the excellent service provided there by Neil Isaacs. The prospect of the arrival in October 1988 of another three research students – Shaid Mahmood and Michael Thompson, in addition to Diane Smith – to carry out research on the synthesis of cyclacene and polyacene derivatives persuaded me that the time was fast approaching when we had to be self-sufficient in ultra-high pressure reaction equipment. Fortunately, it was about this time that the University of Sheffield established a Research Fund on a scale that was not inappropriate to commission the building of a high pressure press by Ken Ashcroft of PSIKA in Glossop. An application to the fund was successful and, on a glorious Sunday afternoon in June 1989, the equipment was hoisted into its new

Figure 3 A graphical representation of the cause and effect of treble diastereoselectivity.





Scheme 8 This attempt to equilibrate the hexadeuterio derivative (17) with its preprotio analogue (3) which provides further evidence for the absence of any reversibility operating during these cycloadditions.

home on the roof of the Chemistry Department at Sheffield University.

Little did I appreciate at the time that I would be living through the same experience at the University of Birmingham two years later. However, on the second occasion, it took many weeks to convince the Safety Unit here that there was no need to build a bunker in the middle of a field to house a high pressure reaction vessel! The problem was a reluctance to recognize the basic difference between compressing gases and compressing liquids. The former can, indeed, be dangerous. The latter is no more than hydraulics in action. Indeed, we are surrounded by them in everyday life. Eventually, a home was sanctioned in an outside store room in a courtyard adjoining the Haworth Building.

6 Going from Two to Three Dimensions (JFS)

I recall how Franz Kohnke and I had spent a day in early June 1987 at Imperial College London with David Williams writing the paper to *Angewandte Chemie* that was to appear (Figure 1) in September of that year. On the train journey from London back to Sheffield, ideas concerning our next objectives started to surface. One of these envisaged (Figure 4) a conceptual jump in structural terms from two to three dimensions, akin to that which led[16,17] to [2.2.2]cryptand from 18-crown-6. Just as a

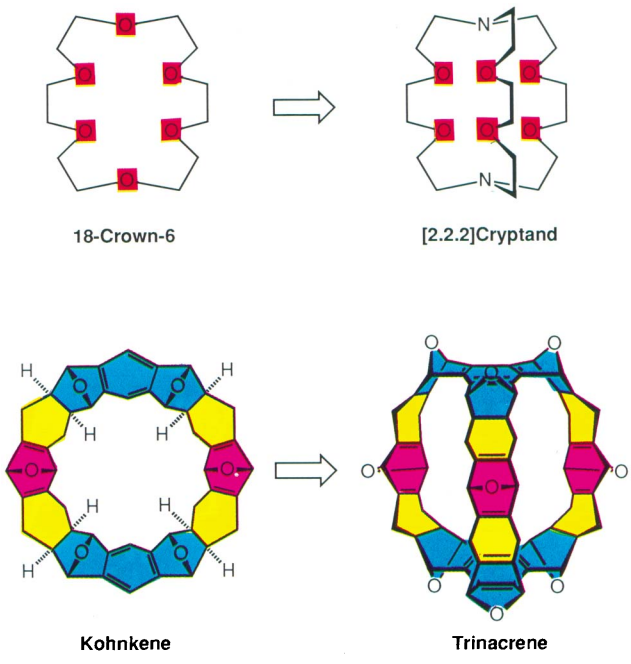


Figure 4 A conceptual comparison between two different classes of monocycles and bicycles.

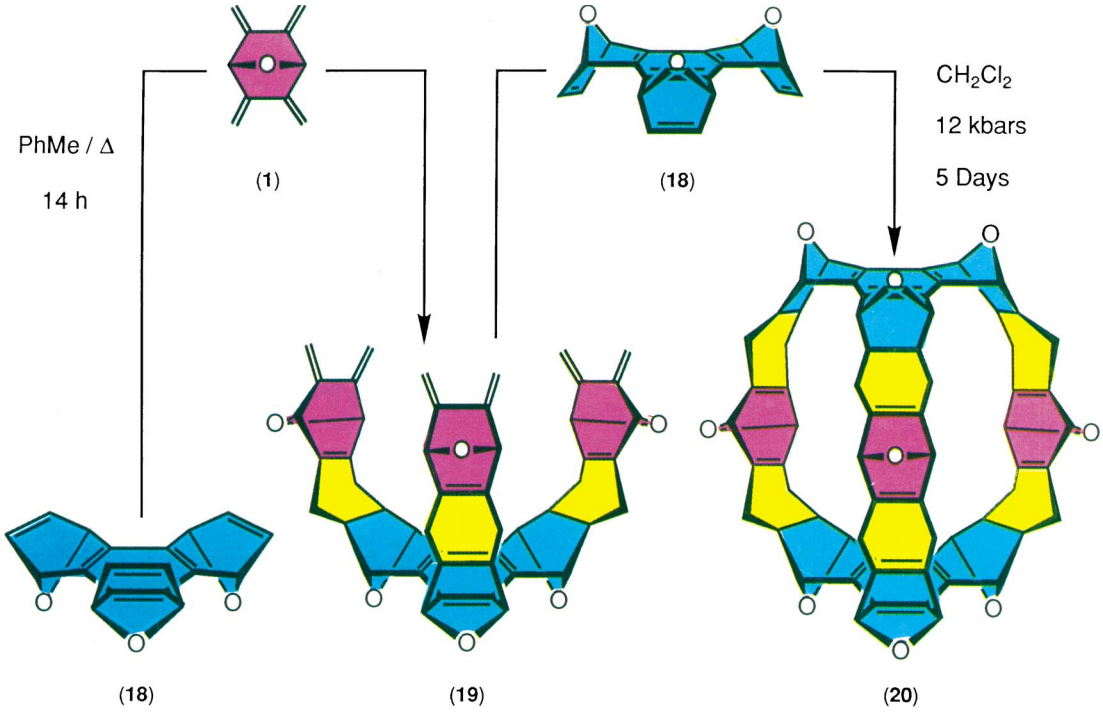
divalent oxygen atom can be replaced by a trivalent nitrogen atom, so a 'divalent' [*a,d*]-fused benzene ring can be replaced by a 'trivalent' (*a,c,e*]-fused benzene ring. This alteration permits the structural progression from a belt-like compound, such as (5), to a cage-like compound,[18] such as (20). We have called this molecular cage trinacrene after an old name (Trinacria) for Sicily where Franz was born and brought up. By the end of the year, Franz had transformed[19,20] this idea, that came to us on British Rail, into reality. He managed to synthesize (Scheme 9) trinacrene (20) – albeit in a low yield – from the bisdiene (1) and the all-*syn*-trisdienophile (18) by a two-step sequence of trebly diastereoselective Diels–Alder reactions promoted, firstly by heat to afford the 3:1 adduct (19) and finally by high pressure to generate trinacrene (20). A logical train of thought had literally reached its destination!

7 Hydrocarbons and Aromaticity (JFS)

All our attempts so far to convert (Scheme 1) kohnkene (5) into [12]cyclacene (7) have been unsuccessful.[21,22] This is hardly surprising when one considers that, not only is [12]cyclacene a $4n$ π-electron system overall, but it may also be regarded (Figure 5) as two antiaromatic [24]annulenes linked to each other by σ-bonds attached to every other carbon atom around the macro-ring. The second of these undesirable features can be avoided by introducing two [*a,c*]-fused rings at diametrically-opposite positions in the [12]cyclacene constitution. This feature produces (Figure 5) the isomeric hydrocarbon (21) comprising two macro-rings containing 22 π and 26 π electrons, *i.e.* they both constitute [$4n + 2$]annulenes. They might, therefore, be expected to display some aromaticity and so be more stable than their purely [*a,d*]-fused counterparts. It followed that if we wanted to begin to probe these ideas, we needed to make the angular belt-like compound (31), an interesting structural intermediate between the molecular belt molecule kohnkene (5) and the molecular cage molecule trinacrene (20). This was one of the challenges John took up in collaboration with Daniele Guiffrida from Messina.

8 Making an Angular Molecular Belt (JPM)

The synthesis of the angular molecular belt compound (24)



Scheme 9 The two-step synthesis of trinacrene (20) from the bisdiene (1) and the triadienophile (25).

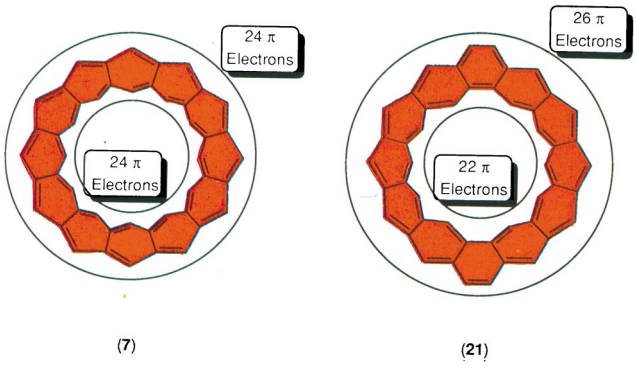


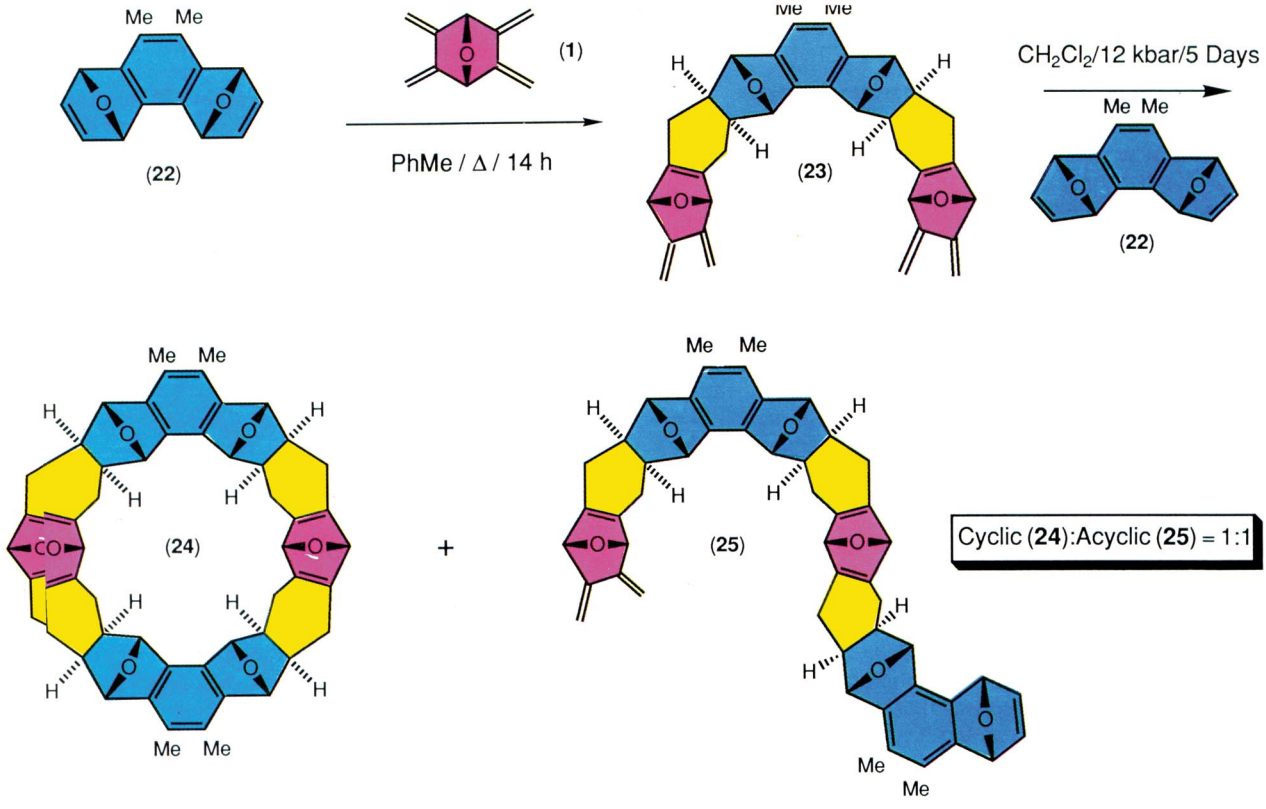
Figure 5 Counting π-electrons in [12]cyclacene (7) and its constitutional isomer (21) which contains two [*a*,*c*]-fused rings.

posed two new problems. Firstly, could we synthesize the phenanthrene-based *syn*-bisdienophile (22) and secondly, would the loss in the constitutional symmetry of the dienophilic π-systems in (22) as a consequence of the [*a*,*c*]-fusion, result in the impairment of treble diastereoselectivity during their cycloadditions with dienes? The synthesis of the angular *syn*-bisdienophile (22) turned out to be a straightforward matter[23,24] and, furthermore, heating of (22) with 2.5 molar equivalents of the bisdiene (1) under reflux in toluene afforded (Scheme 10) the 2:1 adduct (23), in 91% yield.[19,20] The same *syn*/*endo*-H stereochemistry that had been observed overwhelmingly in the cycloadditions of [*a*,*d*]-fused bisdienophiles, was clearly maintained in the cycloadditions between the dienophilic units in the angular *syn*-bisdienophile (22) and the bisdiene (1). In fact, the [*a*,*c*]-fused *syn*-bisdienophile (22) appears to exercise, not only the same high degree of treble diastereoselectivity in cycloadditions, but also at an accelerated rate compared to that exhibited by its [*a*,*d*]-fused analogue (2). A high pressure-promoted reaction of (23) with a further equivalent of the angular *syn*-bisdienophile (22) gave (Scheme 10) two products in the ratio of 1:1. One was the expected angular molecular belt compound (24) and the other was the novel acyclic product (25). The explanation for the formation of two products lies in the angular nature of the *syn*-bisdienophile (22). This feature means that there are two possible modes (Scheme 11) for the initial intermolecular Diels–Alder reaction between (22) and (23) that are constitutionally different. The regiochemistry shown in pathway A brings the two remaining reactive termini close together in the intermediate 2:2 adduct (26). This mode is followed by intramolecular macropolycyclization to afford the angular molecular belt compound (24). The regiochemistry shown in pathway B places the remaining reactive termini too far apart after the initial cycloaddition between (22) and (23) for any subsequent intramolecular cycloaddition to be possible. This mode of cycloaddition is responsible for the formation of the novel acyclic product (25).

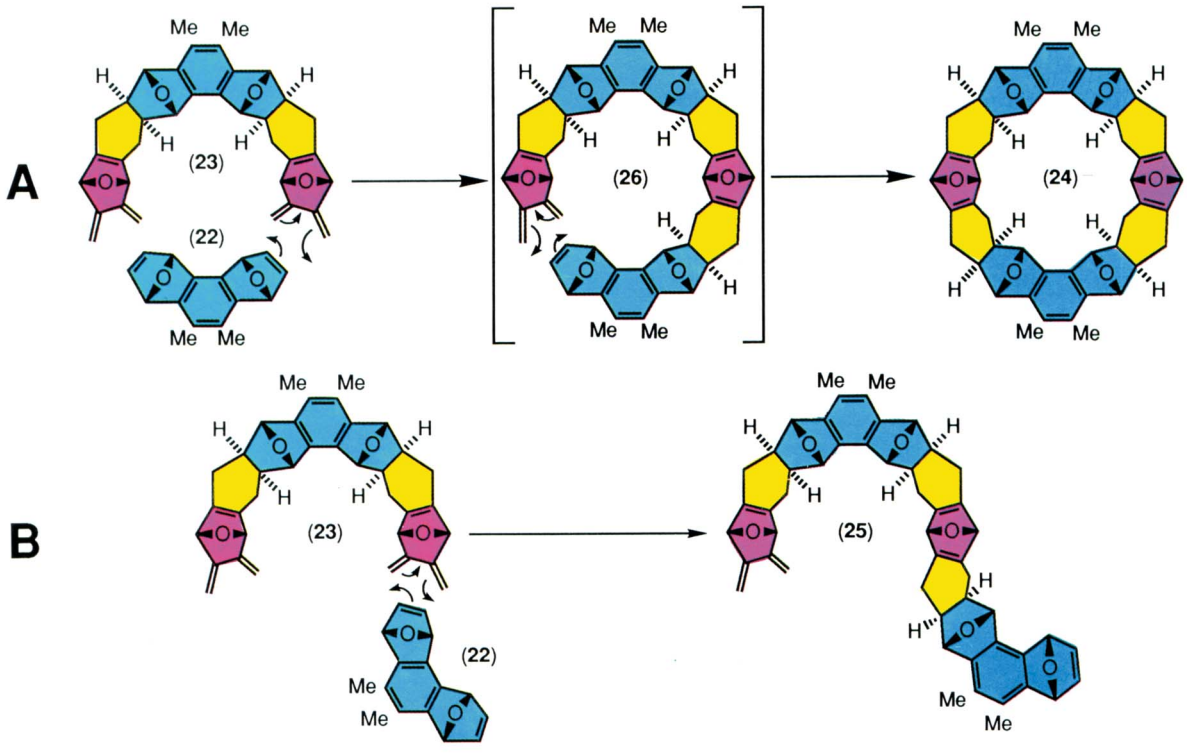
The molecular belt compound (24) is an obvious precursor to derivatives of hydrocarbon (21) shown in Figure 5. This challenge was taken up[22] subsequently by Ulrich Girreser on my leaving Sheffield at the beginning of 1991.

9 The Prospect of Chiral Diels–Alder Building Blocks (JFS)

It did not escape our attention that the *anti*-isomer of the angular *syn*-bisdienophile (22) that was employed by John and Daniele in the synthesis (Scheme 10) of the angular molecular belt compound (24) is chiral. Unfortunately, although this compound can be separated[25] on an analytical scale by both chiral GLC and chiral HPLC, samples of the enantiomerically-pure compounds are not available to us on a preparative scale. If they had been easy to obtain, then the opportunity would have existed to construct chiral molecular snake-like oligomers by carrying out repetitive Diels–Alder reactions on the optically-active bisdienophiles (+)-(22a) and (−)-(22a) with the appropriate bisdienes. It was still of great interest to us to go ahead, however, and establish the synthetic methodology for constructing linear molecular wave-like compounds in a highly controlled manner using the *anti*-fused building blocks rather than the *syn*-fused compounds that we had employed to date. We expected that this progression would allow us to create access to a range of compounds with very different gross conformations compared with the macropolycyclic compounds that had been our initial



Scheme 10 The synthesis of the angular molecular belt compound (24) and its acyclic cousin (25) from the bisdiene (1) and the angular *syn*-bisdienophile (22).



Scheme 11 The two pathways available to the reaction between the angular *syn*-bisdienophile (22) and the 2:1 adduct (23) which lead to the production of (A) the angular molecular belt (24) and (B) the novel acyclic product (25).

targets. This topic was the final area John was to explore while in my laboratories.

10 Molecular Waves under Construction (JPM)

The syntheses of kohnkene (5) (Scheme 1),[1–8] the [14]cyclacene derivative (16) (Scheme 6),[7,8,12] trinacrene (20) (Scheme 9),[19,20] and the angular molecular belt compound (24) (Scheme 10)[19] illustrated that the repetitive Diels–Alder methodology offered us a flexible approach to a range of macropolycyclic compounds. These syntheses, however, were all based upon the combination of exclusively *syn*-fused bisdienes and bisdienophiles. An extension to this methodology in which we used *anti*-fused building blocks to prepare extended polyacene derivatives, with gross conformations resembling molecular waves rather than molecular belts was a logical progression. In particular, the different rates of mono- and bis-addition[26] of dienophiles to the bisdiene (1) that we had exploited to control the syntheses of the macropolycyclic derivatives could, we reasoned, be used to develop a reaction sequence to obtain polyacene derivatives with complete oligoselectivity, by making use alternately of thermally-promoted and high pressure-promoted cycloadditions. Indeed, when the *anti*-bisdienophile (2a) was heated (Scheme 12) under reflux in toluene with 2.5 molar equivalents of the bisdiene (1), the expected 2:1 adduct (27) was obtained in 81% yield.[27] As we had anticipated, the reaction ceases completely upon formation of this product. We appreciated that further cycloaddition of the *anti*-bisdienophile (2a) to the diene units in (27) would require high pressure. Importantly, in both cycloadditions between (1) and (2a), *syn*/*endo*-H stereochemistry results across the newly-formed cyclohexene rings. The treble diastereoselectivity that was exhibited in cycloadditions involving the *syn*-fused building blocks was, therefore, retained in the corresponding reactions of the *anti*-fused building blocks. High pressure-promoted cycloaddition of two molar equivalents of the *anti*-bisdienophile (1a) to the 2:1 adduct (27) afforded (Scheme 12) the pentadecacene derivative (28) in 49% yield. Again, both the cycloadditions between (1a) and (27) proceed with complete treble diastereoselectivity and, furthermore, the low reactivity of the diene units in (27) serves to inhibit any additional reaction between (27) and the product (28). The reaction stopped just where we had expected it to stop!

Scheme 12 A stepwise synthetic approach to the molecular wave compounds (27) and (28) which makes alternate use of thermally-promoted and high pressure-promoted cycloadditions in reactions involving the bisdiene (1) and the *anti*-bisdienophile (2a).

The success of these step-wise syntheses[28] suggest that it should be possible to construct extended polyacene derivatives from bisdienophilic building blocks containing the *anti*-configuration in a manner that is both highly stereoregular and precisely controlled. The very different gross conformations – and hence potential applications – of these molecular wave compounds, compared to those of the compounds constructed using exclusively *syn*-fused building blocks, provides yet another opportunity for further research. Indeed, the ability to construct highly-ordered rod-like molecules by a controlled, stepwise synthetic procedure opens up the possibility of producing well-defined, rigid structures on the nanometer scale[29] which could have important functions.[30]

11 The State of the Science and the Scientists (JFS)

By the end of John's 'Ph.D.' he had raised just as many new questions as he had provided answers to old questions. This is a situation that is all too familiar to those of us who have been engaged in scientific research for any length of time. Nonetheless, we could argue that, even although the construction of a molecular LEGO set is – by definition – an open ended pursuit, it has been recognized as a research activity worthy of some artistic licence (Figure 6) when it was released at Christmas 1988 to a wider than usual chemical audience. It is well to try and keep a sense of proportion in all that we achieve in an academic research laboratory. Occasionally, a discovery is made, or innovation is recognized, or an invention is recorded, but most of the time supervisor and research student are involved in the crucial and fundamentally-important exercises of training, learning, and understanding. So it was for John and I at Sheffield before we went our separate ways – he to Harvard and I to Birmingham – in 1991.

Acknowledgements. Many different opportunities are available to potential academic supervisors in the United Kingdom for the support of fundamental research in Chemistry. In this instance, it was the Chemical Defence Establishment of the Ministry of Defence who sponsored the research when the original project

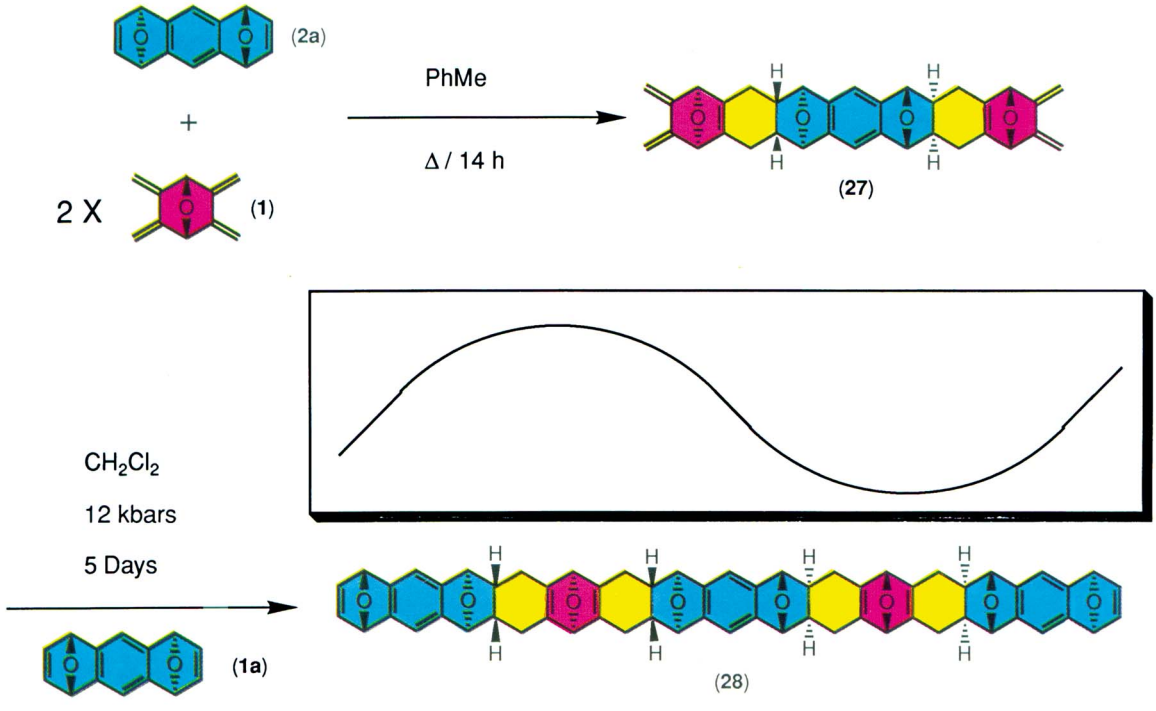


Figure 6 The lonely water molecule inside dideoxykohnkene, obtained on deoxygenation of kohnkene (5) at 3 and 9 o'clock, as portrayed on the cover of the December 1988 issue of *Chemistry in Britain*.
(Reproduced by kind permission of the Editor, Mr. Richard Stevenson, and the Illustrator, Gillian Martin.)

they agreed to fund was less than successful in our hands. John and I thank Drs. Robin Black and Derek Anderson at Porton Down for the flexibility of minds and purpose they brought to their professional relationship with us.

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