

Epoxy-bridged [19]- and [21]-Annulenones

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Wittig reaction between carbonyldi(furan-2,5-diyl)dimethylenebis(triphenylphosphonium chloride) (1) and 2,5-bis-(β -formylvinyl)furan (2) gave chiefly (6*Z*,8*E*,14*E*,16*Z*)-2,5:10,13:18,21-triepoxy[21]annulenone (4). Although the inner protons of annulenone (4) resonate at low field this is shown to be due to mutual steric compression rather than a paramagnetic ring current. A synthesis of 1,4-bis-(2-formylcyclohex-1-enyl)buta-1,3-diyne (20) is described. This on reaction with the salt (1) gave (6*E*,16*E*)-2,5:18,21-diepoxy-8,9:14,15-bis(tetramethylene)-10,11,12,13-tetrahydro[21]annulenone (24), which was also atropic. Wittig reaction between the salt (1) and 5-(β -formylvinyl)-2-furaldehyde (33) gave (6*Z*,12*E*,14*Z*)-2,5:8,11:16,19-triepoxy-[19]annulenone (34) which is diatropic.

In a previous paper¹ we explored the paratropicity of heteroatom-bridged [17]annulenones. We now describe extensions of this work, which has already appeared in

¹ T. M. Cresp and M. V. Sargent, *J.C.S. Perkin I*, 1973, 2961.

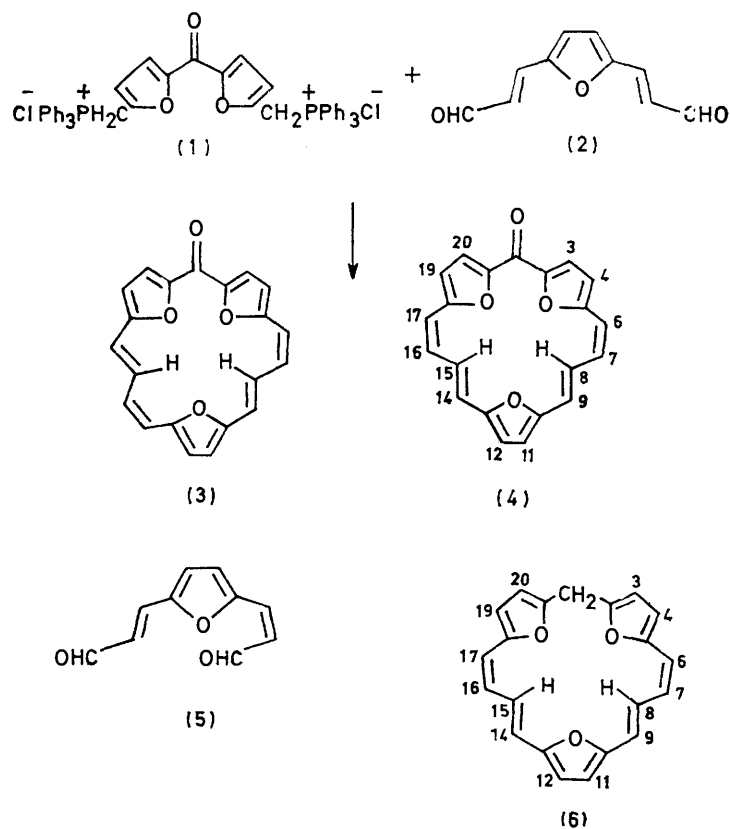
² T. M. Cresp and M. V. Sargent, *J.C.S. Chem. Comm.*, 1974, 101.

preliminary form,² to epoxy-bridged [19]- and [21]-annulenones.

It has been predicted³ that the limiting ring size for aromaticity in the ($4n + 2$) annulene series would be

³ M. J. S. Dewar and G. J. Gleicher, *J. Amer. Chem. Soc.*, 1965, **87**, 685.

reached at [26]annulene although doubt has been cast on this prediction by the synthesis of a diatropic dihydro[26]annulene^{4,*} and an allegedly diatropic tetrahydro[30]annulene.⁵ Similarly the question of limiting ring size for the paratropicity of $4n$ annulenes has yet to be resolved. Since little theoretical work⁶ has been reported on the ring size limitation for diatropicity and paratropicity in annulenones we decided to extend our previous work to epoxy-bridged [19]- and [21]-annulenones.



Wittig reaction between carbonyldi(furan-2,5-diyl)-dimethylenebis(triphenylphosphonium chloride) (1)¹ and 2,5-bis-(β -formylvinyl)furan (2)⁷ gave a 15% yield of mixture of two [21]annulenones. By crystallisation of the mixture from ethanol a [21]annulenone was isolated as purple needles, m.p. 218–221°, in 1.2% yield. The n.m.r. spectrum of this isomer, which was only sparingly soluble in most organic solvents, was determined in [²H₆]dimethyl sulphoxide, and exhibited a 2H multiplet at τ -1.2 to -0.8 and a 12H multiplet at 2.7–4.7. The insolubility of this isomer prevented any analysis of its spectrum by decoupling or by the INDOR technique. The complexity of the n.m.r. spectrum indicated an unsymmetrical structure. The 2H low field multiplet is best ascribed to two internal protons located on two *trans*-double bonds which is most readily accommodated

* The term 'dehydro' is used to denote loss of one hydrogen atom.

⁴ B. W. Metcalf and F. Sondheimer, *J. Amer. Chem. Soc.*, 1971, **93**, 5271.

by structure (3). The material left after removal of the isomer (3) failed to crystallise and was obtained as a red gum which was apparently homogeneous, since its n.m.r. spectrum indicated the symmetrical structure (4) (see below). The unsymmetrical isomer (3) must have arisen before chromatography since on re-chromatography the pure symmetrical isomer (4) was recovered unchanged even after 60 h on the column. The n.m.r. spectrum of the diacrolein (2) used in the reaction did not have any signals attributable to the *cis,trans*-isomer (5).

In a subsequent Wittig reaction between the salt (1) and a different batch of the diacrolein (2) none of the unsymmetrical isomer (3) was obtained. This suggests that in the initial Wittig reaction the diacrolein (2) was contaminated by its isomer (5) present in smaller amount than was detectable by n.m.r. spectroscopy. As the yield of the macrocycle (3) was only 7.9% of the total yield of macrocyclic material isolated from the Wittig reaction this does not appear unlikely. On attempted photoisomerisation the diacrolein (2) decomposed.

The very low field resonance of the internal protons of the unsymmetrical [21]annulenone (3) indicates that it may be paratropic but in the absence of any other n.m.r. data no firm conclusion can be drawn.

Reduction of the symmetrical [21]annulenone (4) with

⁵ M. Iyoda and M. Nakagawa, *Tetrahedron Letters*, 1973, 4743.

⁶ B. A. Hess, jun., L. J. Schaad, and C. W. Holyoke, jun., *Tetrahedron*, 1972, **28**, 5299.

⁷ T. M. Cresp, M. V. Sargent, and P. Vogel, *J.C.S. Perkin I*, 1974, 37.

lithium aluminium hydride and aluminium chloride gave the homoannulene (6) as orange needles, m.p. 142–144°. Analysis of the n.m.r. spectrum of annulene (4) confirmed the (6*Z*,8*E*,14*E*,16*Z*)-stereochemistry* of the diene systems. The furan protons 4- and 19-H are coupled to 6- and 17-H (J 1.0 Hz), and these latter protons are *cis*-coupled to 7- and 16-H (J 11.7 Hz). The internal protons 8- and 15-H are at different field from the other olefinic protons and resonate as a doublet of doublets coupled with 9- and 14-H (J_{trans} 15.3 Hz), and 7- and 16-H (J_{vic} 10.6 Hz).

If the [21]annulene (4) is paratropic then in its n.m.r. spectrum the internal protons should resonate at low field and the external protons at high field. The internal protons 8- and 15-H resonate at significantly lower field than the external protons (Table 1). That the low field

TABLE 1

Chemical shifts (τ ; CDCl₃, 90 MHz) of annulene (4) and homoannulene (6)*

| Compound | 3-, 20-H | 4-, 19-H | 6-, 17-H | 7-, 16-H | 8-, 15-H | 9-, 14-H | 11-, 12-H |
|----------|----------|----------|----------|----------|----------|----------|-----------|
| (4) | 2.60 | 3.44 | 3.97 | 3.77 | 1.95 | 3.96 | 3.95 |
| (6) | 4.04 | 4.04 | 4.34 | 4.12 | 0.89 | 4.03 | 4.28 |

* For convenience the numbering system of the annulene (4) has been used in the assignment of the chemical shifts of the homoannulene (6).

resonance of the internal protons is not due to a paramagnetic ring current in annulene (4) is apparent from the n.m.r. spectrum of the homoannulene (6), in which the internal protons 8- and 15-H resonate at even lower field than those of the annulene (4), and all the external protons resonate at higher field than the analogous protons of (4) (Table 1). The low field resonance of the internal protons of (4) and (6) is presumably due to the mutual steric compression of the internal protons^{8,9} and/or the deshielding effect of the furan oxygen atoms.¹

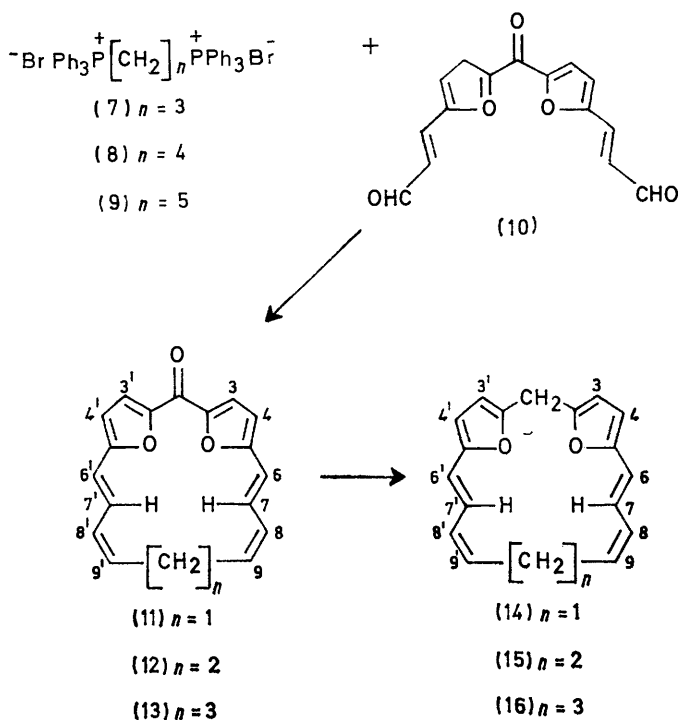
To investigate further the deshielding of the internal protons a series of macrocyclic non-conjugated ketones and alkanes was prepared. Wittig reaction of bis-5-(β -formylvinyl)-2-furyl ketone (10)⁷ with the phosphonium salts (7),¹⁰ (8),¹¹ and (9)¹¹ gave the ketones (11)–(13) respectively. Reduction of the ketones (11)–(13) with lithium aluminium hydride and aluminium chloride then gave the corresponding alkanes (14)–(16).

Examination of molecular models of these compounds indicated that the internal proton–furan oxygen distance remains approximately constant throughout each of the series but that the distance between the two internal hydrogen atoms increases as n increases. This is reflected in the n.m.r. spectra of the macrocycles (Table 2). As n increases the resonances of the internal protons 7- and 7'-H are shifted to higher field but the

* For convenience, the annulene numbering system [*e.g.* as in (4)] is used for macrocycles throughout the Discussion section: this differs from the numbering given in the systematic names in the Experimental section.

⁸ S. Winstein, P. Carter, F. A. L. Anet, and A. J. R. Bourn, *J. Amer. Chem. Soc.*, 1965, **87**, 5247.

external protons remain at fairly constant field. Although these arguments can only be applied qualitatively they support the conclusion that the low field resonance of 8- and 15-H in the annulene (4) is due to steric



compression rather than to a paramagnetic ring current. The chemical shifts of the furan protons adjacent to the carbonyl group are very sensitive to the effect of a paramagnetic ring current as is evident from the n.m.r.

TABLE 2

Chemical shifts (τ ; CDCl₃, 90 MHz) for ketones (11)–(13) and alkanes (14)–(16)

| Protons* | Chemical shift | | | | | |
|----------|----------------|------|------|---------|------|------|
| | Ketones | | | Alkanes | | |
| | (11) | (12) | (13) | (14) | (15) | (16) |
| 3, 3' | 2.70 | 2.64 | 2.48 | 3.97 | 3.93 | 3.98 |
| 4, 4' | 3.76 | 3.71 | 3.56 | 4.04 | 3.93 | 3.98 |
| 6, 6' | 3.73 | 3.78 | 3.54 | 3.83 | 3.74 | 3.82 |
| 7, 7' | 1.49 | 1.94 | 2.87 | 2.17 | 2.67 | 2.72 |
| 8, 8' | 3.94 | 3.95 | 3.77 | 3.92 | 3.85 | 3.92 |
| 9, 9' | 4.39 | 4.24 | 4.22 | 4.41 | 4.33 | 4.36 |

* For ease of comparison a similar numbering system to the annulene (4) has been adopted.

spectra of the heteroatom-bridged [17]annulenes.¹ In annulene (4) the chemical shifts of these furan protons, 3-, 20-, 4-, and 19-H are comparable to those of the similar protons 3-, 3', 4-, and 4'-H in the atropic ketones (11)–(13). Thus the [21]annulene is atropic.

To investigate further the possible paratropicity of [21]annulenes the tetrahydro[21]annulene (24)

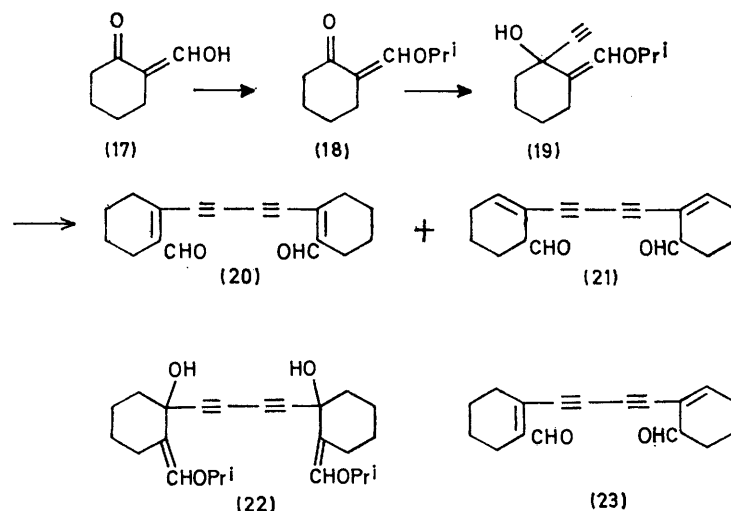
⁹ E. Vogel, R. Feldmann, H. Düwel, H.-D. Cremer, and H. Gunther, *Angew. Chem. Internat. Edn.*, 1972, **11**, 217.

¹⁰ K. Friedrich and H.-G. Henning, *Chem. Ber.*, 1959, **92**, 2756.

¹¹ L. Horner, H. Hoffmann, W. Klink, H. Ertel, and V. G. Toscano, *Chem. Ber.*, 1962, **95**, 581.

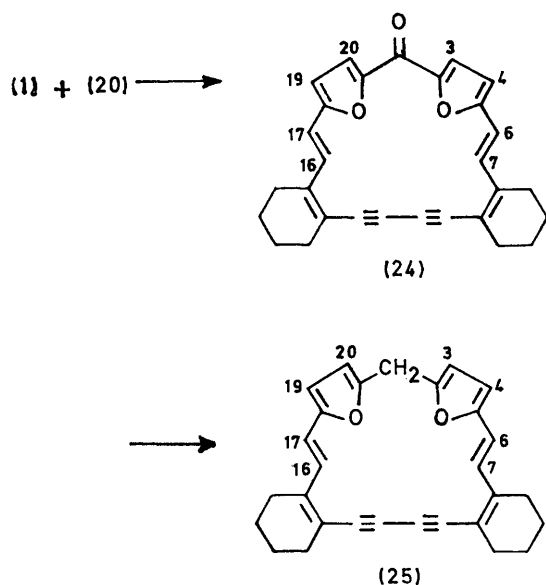
was synthesised. Treatment of 2-hydroxymethylencyclohexanone (17)¹² with 2-bromopropane and potassium carbonate in *NN*-dimethylformamide (DMF) gave 2-isopropoxymethylencyclohexanone (18) in 72% yield. This on reaction with lithium acetylide-ethylenediamine

can either undergo dehydration followed by removal of the protecting groups leading to dicarbaldhyde (21), or undergo removal of the protecting groups followed by dehydration leading to either of the isomeric dicarbaldhydes (20) or (21). That both (20) and (21) did not

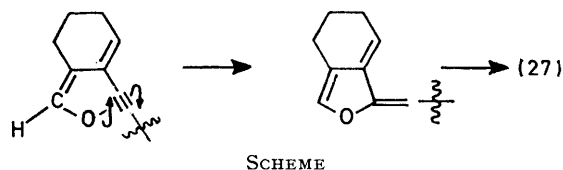


complex¹³ gave the acetylenic alcohol (19). Oxidative coupling of compound (19) by using copper(II) acetate monohydrate in pyridine at 60° followed by treatment with dilute sulphuric acid gave the fully conjugated dicarbaldhyde (20) (37%) and its isomer (21) (8%).

interconvert under the reaction conditions was established by treating the pure isomers separately with dilute sulphuric acid under the same conditions as before, from which they were recovered unchanged. As none of the half-conjugated isomer (23) was detected it must be assumed that if formed it undergoes isomerisation to either or both the observed products. After our preliminary communication was submitted Muneyuki *et al.*¹⁵ independently described the same synthesis of the dicarbaldhyde (20); however these authors did not report the isolation of the minor isomeric product (21).



Wittig reaction of the bisphosphonium salt (1) and the dicarbaldhyde (20) in DMF with lithium methoxide as base gave the [21]annulene (24) (2%) but the major product (26) (6%) arose by nucleophilic addition of methanol to the dicarbaldhyde. With the weak nucleophile 1,5-diazobicyclo[4.3.0]non-5-ene as base¹⁶ a 12% yield of the macrocycle (24) was obtained together with 6% of the difurylacetylene (27). The structure of the latter followed from its spectroscopic properties and



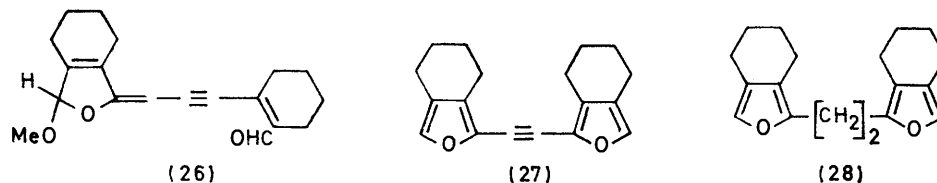
A low yield of (20) + (21) could also be obtained by the reaction of the ketone (18) with 1,4-disodiobuta-1,3-diyne in a similar manner to the reaction of the latter with cyclohexanone.¹⁴ The intermediate (22) involved in the formation of the isomeric dicarbaldhydes (20) and (21)

its reduction to the difurylethane (28). The formation of the difurylacetylene (27) probably involves a base catalysed reaction in which the tautomeric form of the

¹² C. Ainsworth, *Org. Synth.*, Coll. Vol. IV, 1963, p. 536.
¹³ G. M. Pilling and F. Sondheimer, *J. Amer. Chem. Soc.*, 1971, **93**, 1977.
¹⁴ J. B. Armitage, E. R. H. Jones, and M. C. Whiting, *J. Chem. Soc.*, 1951, 44.

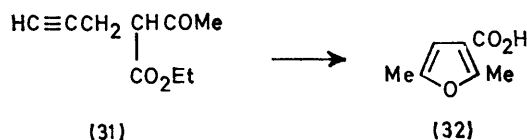
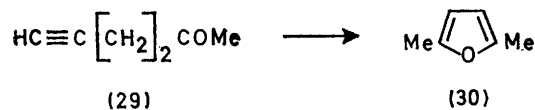
¹⁵ R. Muneyuki, M. Morimoto, M. Tanaka, T. Katakami, T. Kashitani, M. Iyoda, and M. Nakagawa, *Bull. Chem. Soc. Japan*, 1973, **46**, 2565.
¹⁶ H. Oediger, H.-J. Kabbe, F. Möller, and K. Eiter, *Chem. Ber.*, 1966, **99**, 2012.

dicarbalddehyde (20) undergoes cyclisation with subsequent rearrangement of the intermediate (see Scheme). Analogous reactions are known which involve the similar cyclisation of the tautomers of acetylenic ketones,



viz. production of the furans (30) and (32) by acid treatment of propargylacetone (29) and base treatment of ethyl propargylacetoacetate (31), respectively.¹⁷

Muneyki *et al.*¹⁵ observed that heating the dicarbalddehyde (20) in xylene at 120° gave the difurylacetylene



(27): this reaction also occurs on heating the dicarbalddehyde (20) in DMF. Muneyki *et al.* regard their reaction as 'a symmetry allowed thermal process.' This view is based on a misconception of orbital symmetry controlled processes since a neutral species cannot cyclise to an odd-membered ring. It is probable that this apparently thermal reaction arises by catalysis by adventitious acid or base.

The [21]annulenone (24) formed maroon prisms, which decomposed at >270° without melting. Lithium aluminium hydride-aluminium chloride reduction of (24) gave the homoannulene (25) as yellow prisms, m.p.

atropicity of the [21]annulenone (24) follows from the lower field resonance of the internal protons 7- and 16-H of the homoannulene (25) compared with the analogous protons of the annulenone (24) (see Table 3). Further-

more the external protons 3-, 20-, 4-, and 19-H are at similar chemical shifts to those of the analogous protons 3-, 3'-, 4-, and 4'-H of the atropic ketones (11)–(13).

The atropicity of both [21]annulenones (4) and (24) suggests that in the (4*n* + 1) membered-ring, or 4*n*π electron annulenones, the ring size becomes important at *n* = 5.

TABLE 3

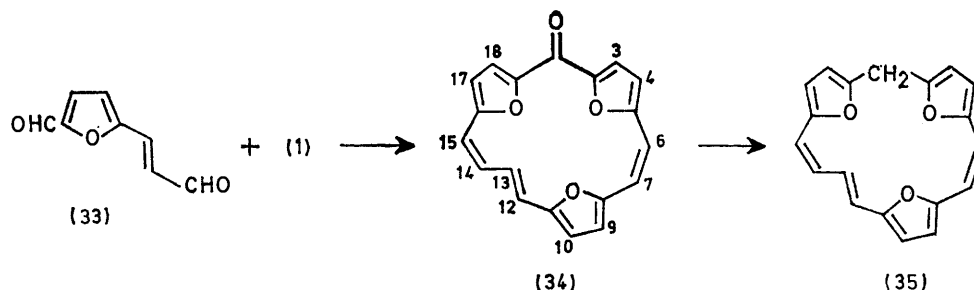
Chemical shifts (τ ; CDCl₃, 90 MHz) for annulenone (24) and homoannulene (25)^a

| Compound | Chemical shift | | | |
|----------|----------------|----------|-------------------|-------------------|
| | 3-, 20-H | 4-, 19-H | 6-, 17-H | 7-, 16-H |
| (24) | 2.76 | 3.68 | 2.27 ^b | 2.33 ^b |
| (25) | 3.99 | 3.99 | 3.85 | 1.86 |

^a For convenience the numbering system of the annulenone (24) has been used in the assignment of the chemical shifts of the homoannulene (25). ^b These assignments may be reversed.

The largest known examples in the (4*n* + 3) membered-ring, or (4*n* + 2)π electron annulenones, contain fifteen carbon atoms,^{18,19} and as expected they are diatropic. It was of interest to determine whether larger (4*n* + 3) membered-ring annulenones exhibit diatropicity and towards this end the synthesis of a [19]annulenone was investigated.

Wittig reaction between the phosphonium salt (1) and 5-(β-formylvinyl)-2-furaldehyde (33)⁷ gave the [19]-annulenone (34) in 3% yield as small red prisms, m.p. 208–209° (from ethanol). The 90 MHz n.m.r. spectrum



of annulenone (34) was very complex and a partial first order analysis was made by the INDOR technique, monitoring at the frequencies of the protons 3-, 18-, and 13-H. It was not possible to assign definite signals to the protons 6-, 7-, 9-, 10-, and 15-H. The spectrum (CDCl₃) exhibited a 2H AB pattern (*J*_{3,4} or *J*_{17,18} 3.8 Hz)

¹⁷ J. Cologne and R. Gelin, *Compt. rend.*, 1953, **237**, 393.

¹⁸ C. P. Cotterell, G. H. Mitchell, F. Sondheimer, and G. M. Pilling, *J. Amer. Chem. Soc.*, 1971, **93**, 259.

¹⁹ H. Ogawa, M. Yoshida, and H. Saikachi, *Tetrahedron Letters*, 1972, 153.

centred at τ 1.86 and 2.87 (3- and 4-H or 18- and 17-H), a 2H AB pattern ($J_{3,4}$ or $J_{17,18}$ 3.8 Hz) at 2.07 and 2.95 (3- and 4-H or 18- and 17-H), a 1H doublet ($J_{12,13}$ 15.0 Hz) at 2.61 (12-H), a 5H multiplet at 2.63–3.02 (6-, 7-, 9-, 10-, and 15-H), a 1H doublet of doublets ($J_{13,14}$ 11.5, $J_{14,15}$ 11.2 Hz) at 3.01 (14-H), and a 1H doublet of doublets ($J_{13,14}$ 11.5, $J_{12,13}$ 15.0 Hz) at 4.88 (13-H). The addition of the lanthanide shift reagent $\text{Eu}(\text{fod})_3$ produced line broadening at a concentration which shifted significantly only protons 3- and 18-H. The use of solvents other than deuteriochloroform also failed to simplify the spectrum. From the coupling constants obtained by INDOR experiments monitoring at the frequency of the proton 13-H the 12,13,14,15-diene system is *trans,cis* or *cis,trans*. If the acrolein (33) retains its stereochemical identity in Wittig reactions as was observed for the diacrolein (2) then the stereochemistry of the 12,13,14,15-diene system is *trans,cis*. Should this stereochemistry be reversed then the conclusions (see below) concerning the diatropicity of annulenone (34) are unaltered. It is also assumed that the stereochemistry of the 6,7-double bond is *cis* since molecular models indicate that a cyclic molecule cannot be obtained if this bond is *trans*. Furthermore in the n.m.r. spectrum of (34) only one olefinic proton occurs at very different field from the others.

Lithium aluminium hydride–aluminium chloride reduction of annulenone (34) gave the homoannulene (35) as a yellow gum. The highly complex n.m.r. spectrum (CDCl_3 , 90 MHz) was not amenable to analysis and exhibited a 12H multiplet at τ 3.22–3.67 (furan and olefinic H), and a 2H singlet at 5.95 (CH_2).

That the [19]annulenone (34) is diatropic is demonstrated by the high field resonance of the internal proton 13-H compared to the adjacent protons 12- and 14-H external to the ring, and to all the olefinic protons of the homoannulene (34). Any effect due to the proximity of the internal protons to the furan oxygen atoms in annulenone (34) would deshield the internal proton. Further evidence for the diatropicity of (34) is the significantly lower field resonance of the protons 3-, 4-, 17-, and 18-H when compared with the chemical shifts of the similar protons 3-, 3', 4-, and 4'-H in the atropic ketones (11)–(13).

It is therefore concluded that the ring size limitation for diatropicity in the $(4n + 3)$ membered-ring annulenes lies beyond $n = 4$.

EXPERIMENTAL

General details have been given previously.¹ Unless stated otherwise n.m.r. spectra were determined at 90 MHz for deuteriochloroform solutions. Where appropriate assignments were assisted by decoupling or INDOR experiments. Wittig reactions were performed with stirring under dry nitrogen at 90° (bath temperature), unless stated otherwise. After the addition of the base the cooled mixture was poured into water and then extracted exhaustively with ethyl acetate or ether, and any insoluble material was separated by filtration through kieselguhr. The combined extracts were washed with water (4 \times) and

then with saturated brine, and dried (Na_2SO_4). The crude product was then pre-adsorbed from dichloromethane on the stated adsorbent and chromatographed over the same adsorbent (total 3.5 \times 40 cm) with ethyl acetate–light petroleum of an appropriate polarity as eluant.

Wittig Reaction between Carbonylidi(furan-2,5-diyl)dimethylenebis(triphenylphosphonium chloride) (1) and 2,5-Bis-(β -formylvinyl)furan (2).—Lithium methoxide [from lithium (69.4 mg)] in absolute methanol (21.3 ml) was added over 5 h to the salt (1) (3.93 g) and the dicarbaldehyde (2) (880 mg) in dry DMF (160 ml). Chromatography over Woelm basic alumina (activity I) yielded a red gum (224 mg, 15.2%). This gave (6Z,8E,14Z,16E)-2,5:10,13:18,21-triepoxy[21]annulenone (3) (17.6 mg), as purple needles, m.p. 218–221° (from ethanol) (Found: M^+ , 330.0877. $^{12}\text{C}_{21}^1\text{H}_{14}^{16}\text{O}_4$ requires M , 330.0892), λ_{max} (EtOH) 275sh (ϵ 21,700), 298sh (27,300), 328 (62,100), 350 (52,400), and 535 nm (850), n.m.r., see Discussion section. From the mother liquors (6Z,8E,14E,16Z)-2,5:10,13:18,21-triepoxy-[21]annulenone (4) was obtained as a red gum which failed to crystallise from a variety of solvents (Found: M^+ , 330.0897. $^{12}\text{C}_{21}^1\text{H}_{14}^{16}\text{O}_4$ requires M , 330.0892), λ_{max} (Et_2O) 284sh (ϵ 34,500), 315sh (52,100), 326 (57,200), 440 (5400), and 462sh nm (5000), τ 1.95 (2H, dd, $J_{8,9} = J_{14,15}$ 15.3, $J_{7,8} = J_{15,16}$ 10.6 Hz, 8- and 15-H), 2.60 (2H, d, $J_{3,4} = J_{19,20}$ 3.5 Hz, 3- and 20-H), 3.44 (2H, dd, $J_{4,6} = J_{17,19}$ 1.0, $J_{3,4} = J_{19,20}$ 3.5 Hz, 4- and 19-H), 3.77 (2H, dd, $J_{6,7} = J_{16,17}$ 11.7, $J_{7,8} = J_{15,16}$ 10.6 Hz, 7- and 16-H), 3.96 (2H, d, $J_{8,9} = J_{14,15}$ 15.3 Hz, 9- and 14-H), 3.97 (2H, dd, $J_{6,7} = J_{16,17}$ 11.7, $J_{4,6} = J_{17,19}$ 1.0 Hz, 6- and 17-H), and 3.95 (2H, s, 11- and 12-H).

(5Z,7E,13E,15Z)-1,4:9,12:17,20-Trieopoxycycloheptacosane-1,3,5,7,9,11,13,15,17,19-decaene (6).—The annulenone (4) (226.9 mg) in a little dry ether was added to a stirred mixture of lithium aluminium hydride (500 mg) and aluminium chloride (30 mg) in dry ether (50 ml). The mixture was then stirred for 15 min and cooled in ice, and enough saturated ammonium chloride solution was added to promote coagulation. The coagulate was filtered off and washed well with ether. The ethereal filtrate was washed with saturated brine and dried (Na_2SO_4). Removal of the solvent left the homoannulene (6) which crystallised from light petroleum as orange needles (182.9 mg, 84.2%), m.p. 142–144° (Found: C, 79.85; H, 5.15. $\text{C}_{21}\text{H}_{16}\text{O}_3$ requires C, 79.75; H, 5.1%. Found: M^+ , 316.1102. $^{12}\text{C}_{21}^1\text{H}_{16}^{16}\text{O}_3$ requires M , 316.1099), τ^* 0.89 (2H, ddd, $J_{7,8} = J_{15,16}$ 9.8, $J_{6,8} = J_{15,17}$ 1.7, $J_{8,9} = J_{14,15}$ 14.8 Hz, 8- and 15-H), 4.03 (2H, d, $J_{8,9} = J_{14,15}$ 14.8 Hz, 9- and 14-H), 4.04br (4H, s, 3-, 4, 19-, and 20-H), 4.12 (2H, dd, $J_{7,8} = J_{15,16}$ 9.8, $J_{6,7} = J_{16,17}$ 11.2 Hz, 7- and 16-H), 4.28 (2H, s, 11- and 12-H), 4.34 (2H, dd, $J_{6,8} = J_{15,17}$ 1.7, $J_{6,7} = J_{16,17}$ 11.2 Hz, 6- and 17-H), and 5.95br (2H, s, CH_2).

(6E,8Z,11Z,13E)-2,5:15,18-Dieopoxycyclo-octaenone-2,4,6,8,11,13,15,17-octaenone (11).—Lithium ethoxide [from lithium (69.4 mg)] in absolute ethanol (15.8 ml) was added over 6 h to bis-5-(β -formylvinyl)-2-furyl ketone (10) (1.35 g) and the phosphonium salt (7) (3.63 g) in dry DMF (120 ml). Chromatography over silica gel gave the ketone (11) (206.6 mg, 14.9%) which crystallised from methanol as orange blades, m.p. 171–174°, which rapidly decomposed, m/e 278 (M^+), λ_{max} (Et_2O) 258sh (ϵ 29,200), 277 (36,400), 298 (36,600), and 350sh nm (19,500) with tailing into the

* For convenience the numbering system used in spectral assignments marked with a dagger (\dagger) is that shown in the structural diagram and not that used in the systematic name.

visible region, τ † 1.49 (2H, dd, $J_{6,7} = J_{6',7'} 15.8$, $J_{7,8} = J_{7',8'} 11.0$ Hz, 7- and 7'-H), 2.70 and 3.76 (4H, ABq, $J_{3,4} = J_{3',4'} 3.5$ Hz, 3-, 3'-, 4-, and 4'-H), 3.73 (2H, d, $J_{6,7} = J_{6',7'} 15.8$, 6- and 6'-H), 3.94 (2H, dd, $J_{8,9} = J_{8',9'} 10.2$, $J_{7,8} = J_{7',8'} 11.0$ Hz, 8- and 8'-H), 4.39 (2H, dt, $J_{8,9} = J_{8',9'} 10.2$, $J_{9,CH_2} = J_{9',CH_2} 9.8$ Hz, 9- and 9'-H), and 6.61br (2H, m, CH₂); in addition fine coupling was observed between 7- and 7'-H, and 9- and 9'-H.

(6E,8Z,12Z,14E)-2,5:16,19-Diepoxy cyclononadeca-2,4,6,8,12,14,16,18-octaenone (12).—Lithium ethoxide [from lithium (69.4 mg)] in absolute ethanol (19.2 ml) was added over 1.5 h to the diacrolein (10) (1.35 g) and the phosphonium salt (8) (3.70 g) in dry DMF (120 ml). Chromatography over silica gel yielded the ketone (12) (259.6 mg, 17.7%) which crystallised from light petroleum as orange prisms, m.p. 165–168° (Found: M^+ , 292.1096. $^{12}C_{19}^{1}H_{16}^{16}O_3$ requires M , 292.1099), λ_{max} (Et₂O) 258sh (ϵ 29,200), 280 (45,900), 298 (38,300), 345 (17,100), 413 (3400), and 430 nm (3300), τ † 1.94 (2H, dd, $J_{6,7} = J_{6',7'} 15.0$, $J_{7,8} = J_{7',8'} 11.0$ Hz, 7- and 7'-H), 2.64 and 3.71 (4H, ABq, $J_{3,4} = J_{3',4'} 3.6$ Hz, 3-, 3'-, 4-, and 4'-H), 3.95 (2H, dd, $J_{8,9} = J_{8',9'} 10.5$, $J_{7,8} = J_{7',8'} 11.0$ Hz, 8- and 8'-H), 3.78 (2H, d, $J_{6,7} = J_{6',7'} 15.0$ Hz, 6- and 6'-H), 4.24br (2H, m, 9- and 9'-H), and 7.51br (2H, m, CH₂); in addition fine coupling was observed between 7- and 7'-H and 9- and 9'-H.

(6E,8Z,13Z,15E)-2,5:17,20-Diepoxy cycloicosadeca-2,4,6,8,13,15,17,19-octaenone (13).—Lithium ethoxide [from lithium (69.4 mg)] in absolute ethanol (21.3 ml) was added over 1.5 h to the diacrolein (10) (1.35 g) and the phosphonium salt (9) (3.77 g). Chromatography over silica gel gave the ketone (13) (315.0 mg, 20.6%). It failed to crystallise from a variety of solvents and precipitated from cold methanol as a yellow amorphous solid, m.p. 114–120° (Found: M^+ , 306.1260. $^{12}C_{20}^{1}H_{18}^{16}O_3$ requires M , 306.1256), λ_{max} (Et₂O) 286sh (ϵ 16,500), 297 (45,000), and 310sh nm (30,300) with tailing into the visible region, τ † 2.87 (2H, dd, $J_{7,8} = J_{7',8'} 10.3$, $J_{6,7} = J_{6',7'} 15.8$ Hz, 7- and 7'-H), 2.48 and 3.56 (4H, ABq, $J_{3,4} = J_{3',4'} 3.5$ Hz, 3-, 3'-, 4-, and 4'-H), 3.54 (d, 2H, $J_{6,7} = J_{6',7'} 15.8$ Hz, 6- and 6'-H), 3.77 (2H, dd, $J_{7,8} = J_{7',8'} 10.3$, $J_{8,9} = J_{8',9'} 11.0$ Hz, 8- and 8'-H), 4.22br (2H, dt, $J_{8,9} = J_{8',9'} 11.0$, $J_{9,CH_2} = J_{9',CH_2} 9.0$ Hz, 9- and 9'-H), 7.87 (4H, m, allylic CH₂), and 8.36 (2H, m, homoallylic CH₂); in addition there was fine coupling between 8- and 8'-H, and the allylic protons, and between 7- and 7'-H, and 9- and 9'-H.

(5E,7Z,10Z,12E)-1,4:14,17-Diepoxy cyclo-octadeca-1,3,5,7,10,12,14,16-octaene (14).—The ketone (11) (14.1 mg) was reduced with lithium aluminium hydride (70 mg) and aluminium chloride (10 mg) in the usual way. The alkane (14) (10.0 mg, 74.7%) precipitated from pentane at –78°, as an amorphous cream solid, m.p. 130–133° (Found: M^+ , 264.1151. $^{12}C_{18}^{1}H_{16}^{16}O_2$ requires M , 264.1150), λ_{max} (Et₂O) 284sh (ϵ 39,600), 294 (45,900), and 335sh nm (7900), τ † 2.17 (2H, dd, $J_{6,7} = J_{6',7'} 15.4$, $J_{7,8} = J_{7',8'} 11.5$ Hz, 7- and 7'-H), 3.92 (2H, dd, $J_{7,8} = J_{7',8'} 11.5$, $J_{8,9} = J_{8',9'} 10.5$ Hz, 8- and 8'-H), 3.97 and 4.04 (4H, ABq, $J_{3,4} = J_{3',4'} 3.5$ Hz, 3-, 3'-, 4-, and 4'-H), 4.41 (2H, dt, $J_{9,CH_2} = J_{9',CH_2} 9.0$, $J_{8,9} = J_{8',9'} 10.5$ Hz, 9- and 9'-H), 6.07br (2H, s, CH₂ between furan rings), and 6.72br (2H, m, CH₂ remote from furan rings); in addition there was fine coupling between 3- and 3'-H, and the methylene protons, and between 7- and 7'-H, and 9- and 9'-H.

(5E,7Z,11Z,13E)-1,4:15,18-Diepoxy cyclononadeca-1,3,5,7,11,13,15,17-octaene (15).—The ketone (12) (86.9 mg) was reduced with lithium aluminium hydride (220 mg) and

aluminium chloride (100 mg) in the usual way. The alkane (15) (50.5 mg, 61.0%) crystallised from light petroleum at –78° as cream prisms, m.p. 141–143° (Found: M^+ , 278.1307. $^{12}C_{19}^{1}H_{18}^{16}O_2$ requires M , 278.1307), λ_{max} (Et₂O) 286 (ϵ 55,600), 297 (71,500), and 340 nm (10,200), τ † 2.67 (2H, dd, $J_{7,8} = J_{7',8'} 10.3$, $J_{6,7} = J_{6',7'} 15.1$ Hz, 7- and 7'-H), 3.74 (2H, d, $J_{6,7} = J_{6',7'} 15.1$ Hz, 6- and 6'-H), 3.85 (2H, dd, $J_{7,8} = J_{7',8'} 10.3$, $J_{8,9} = J_{8',9'} 11.7$ Hz, 8'- and 8'-H), 3.93br (4H, s, 3-, 3', 4-, and 4'-H), 4.33 (2H, m, 9- and 9'-H), 6.03br (2H, s, CH₂ between furan rings), and 7.70 (4H, m, CH₂ remote from furan rings); in addition fine coupling was observed between the 3- and 3'-H, and the methylene protons, and between 7- and 7'-H, and 9- and 9'-H.

(5E,7Z,12Z,14E)-1,4:16,19-Diepoxy cycloicosadeca-1,3,5,7,12,14,16,18-octaene (16).—The ketone (13) (101.0 mg) was reduced with lithium aluminium hydride (300 mg) and aluminium chloride (60 mg) in the usual way. The alkane (16) (71.8 mg, 74.5%) crystallised from light petroleum as cream prisms which changed to long needles at >150°, m.p. 173–177° (Found: M^+ , 292.1168. $^{12}C_{20}^{1}H_{20}^{16}O_2$ requires M , 292.1163), λ_{max} (Et₂O) 275sh (ϵ 27,800), 287 (59,400), 298 (83,300), and 330sh nm (10,700), τ † 2.72 (2H, dd, $J_{6,7} = J_{6',7'} 15.0$, $J_{7,8} = J_{7',8'} 11.0$ Hz, 7- and 7'-H), 3.82 (2H, d, $J_{6,7} = J_{6',7'} 15.0$ Hz, 6- and 6'-H), 3.92 (2H, dd, $J_{8,9} = J_{8',9'} 11.0$, $J_{7,8} = J_{7',8'} 11.0$ Hz, 8- and 8'-H), 3.98br (4H, s, 3-, 3'-, 4-, and 4'-H), 4.36 (2H, dd, $J_{8,9} = J_{8',9'} 11.0$, $J_{9,CH_2} = J_{9',CH_2} 9.0$ Hz, 9- and 9'-H), 6.08br (2H, s, CH₂ between furan rings), 7.70 (4H, m, allylic CH₂), and 8.42 (2H, m, homoallylic CH₂); in addition there was fine coupling between 3- and 3'-H, and the methylene protons, and between 7- and 7'-H and 9- and 9'-H.

2-Isopropoxymethylenecyclohexanone (18).—A mixture of 2-hydroxymethylenecyclohexanone (17) (50 g), dry potassium carbonate (100 g), dry DMF (150 ml), and 2-bromopropane (49 g) was heated on a steam-bath for 7 h with periodic shaking. After cooling, the salts were filtered off and washed with ether (600 ml). The filtrate was washed with water, ice-cold, dilute sodium hydroxide solution (2×), and saturated brine, and dried (Na₂SO₄). The residue left on removal of the solvent was fractionated under diminished pressure and gave the ketone (18) (47.8 g, 71.7%) as a pale yellow liquid, b.p. 82–84° at 0.4 mmHg (lit.²⁰ 64–65° at 0.2 mmHg).

1-Ethynyl-2-isopropoxymethylenecyclohexanol (19).—The foregoing ketone (18) (63 g) was treated with lithium acetylide–ethylenediamine after the manner of Pilling and Sondheimer.¹³ The ethereal extract was washed with water (2×), and with saturated brine, and then dried (Na₂SO₄). The residue left on removal of the solvent was fractionated under reduced pressure and afforded the alcohol (19) (32.0 g, 44.0%) as a pale yellow oil, b.p. 77–79° at 0.2 mmHg, which solidified on cooling below room temperature (Found: C, 74.35; H, 9.25%; M^+ , 194. $C_{12}H_{18}O_2$ requires C, 74.2; H, 9.35%; M , 194), τ (60 MHz, CCl₄) 3.57br (1H, s, olefinic H), 6.08 (1H, sept, Me₂CH), 7.50 (1H, s, acetylenic H), and 7.70 (5H, m, CH₂ and D₂O-exchangeable OH), 8.28 (4H, m, CH₂), and 8.70 (6H, d, Me).

Oxidative Coupling of the Ethynyl-alcohol (19).—A stirred suspension of copper(II) acetate monohydrate (40 g) in pyridine (150 ml) at 60° (bath temperature) was treated over 10 min with a solution of the alcohol (19) (6.7 g) in pyridine (50 ml). After 3 h the cooled mixture was filtered

²⁰ R. B. Woodward and W. M. McLamore, *J. Amer. Chem. Soc.*, 1949, **71**, 379.

and the separated salts were washed with ether (800 ml). The filtrate was added to 10% hydrochloric acid (1 l) and it was extracted with the ether washings. The extract was added to *m*-sulphuric acid (1.5 l) and the mixture was stirred rapidly for 17 h. The separated aqueous layer was extracted with ether (2×), and the combined ethereal layers were washed with water (2×), and with saturated brine, and dried (Na₂SO₄). The residue left on removal of the solvent was pre-adsorbed from ether on silica gel and chromatographed over a column of silica gel (total 4 × 45 cm) with 0–5% ethyl acetate–light petroleum. Early fractions gave 1,4-bis-(2-formylcyclohex-1-enyl)buta-1,3-diyne (20) (1.386 g, 30.2%) which crystallised from light petroleum as prisms, m.p. 91–92.5° (Found: C, 80.95; H, 6.85. C₁₈H₁₈O₂ requires C, 81.15; H, 6.8%), λ_{max.} (Et₂O) 228sh (ε 15,000), 236 (16,000), 253sh (13,600), 265 (15,800), 278sh (18,000), 285 (18,200), 308 (17,000), 327 (19,200), and 352 nm (14,800), τ (60 MHz) –0.10 (2H, s, CHO), 7.67 (8H, m, allylic H), and 8.33 (m, homoallylic H). Later fractions gave 1,4-bis-(6-formylcyclohex-1-enyl)buta-1,3-diyne (21) (675.7 mg) mixed with a trace of the isomer (20), which was easily removed by crystallisation. The cross-conjugated dicarbaldehyde (21) crystallised from light petroleum as yellow blades, m.p. 109–110° (Found: M⁺, 266.1304. ¹²C₁₈¹H₁₈¹⁶O₂ requires M, 266.1307), λ_{max.} (Et₂O) 234 (ε 16,000), 282 (19,200), 288 (18,200), 315sh (18,200), 334 (21,000), and 358 nm (16,000), τ –0.13 (2H, s, CHO), 3.46 (2H, distorted t, J 2.5 Hz, olefinic H), 7.19 (4H, m, allylic H), and 7.39–8.44 (10H, homoallylic and methine H).

Reaction of 1,4-Disodiobuta-1,3-diyne with 2-Isopropoxy-methylenecyclohexanone (18).—A stirred suspension of sodamide [from sodium (1.2 g) and iron(III) nitrate (20 mg)] in boiling liquid ammonia (50 ml) was treated with 1,4-dichlorobut-2-yne²¹ (1.48 g), followed after 1 min by the cyclohexanone (18) (4.0 g). After 1 h the dark mixture was diluted with tetrahydrofuran (110 ml) and the ammonia was allowed to evaporate. Water (100 ml) was then added and the mixture extracted with ether (2×). The extracts were added to sulphuric acid (0.75M; 1 l) and the mixture was stirred for 2 h. The crude oily product obtained as before was distilled at 100° (bath temperature) and 0.05 mmHg and the distillate was passed through a short column of silica gel with 10% ethyl acetate–light petroleum as eluant. This gave a mixture of the isomeric aldehydes (20) and (21) (300 mg) as indicated by t.l.c. and n.m.r. spectroscopy. Extending the reaction time failed to improve the yield.

(6E,16E)-2,5:18,21-Diepoxy-8,9:14,15-bis(tetramethylene)-10,11,12,13-tetrahydro[21]annulenone (24).—(a) *With lithium methoxide as base.* Lithium methoxide [from lithium (13.9 mg)] in absolute methanol (12.8 ml) was added over 2 h to the salt (1) (785 mg) and the dicarbaldehyde (20) (226 mg) in dry DMF (60 ml) at 80° (bath temperature). The solution was stirred for a further 0.5 h. Early fractions from chromatography over silica gel were combined and applied in dichloromethane to 2 preparative t.l.c. (p.l.c.) plates which were developed once with 10% ethyl acetate–light petroleum. The most intense band yielded 2-[3-(3-methoxy-1,3,4,5,6,7-hexahydrobenzofuran-1-ylidene)prop-1-ynyl]cyclohex-1-enecarbaldehyde (26) (18.9 mg, 6.3%) as a yellow gum (Found: M⁺, 298.1557. ¹²C₁₉¹H₂₂¹⁶O₃ requires M, 298.1569), τ (60 MHz) –0.28 (1H, s, CHO), 4.17br (1H, s, methine H), 5.32 (1H, s, olefinic H), 6.52 (3H, s, Me), 7.73 (8H, m, allylic H), and 8.30 (8H, homoallylic H).

²¹ A. W. Johnson, *J. Chem. Soc.*, 1946, 1009.

Later fractions were combined and applied in dichloromethane to 2 p.l.c. plates which were developed once with 15% ethyl acetate–light petroleum. The red band afforded the macrocycle (24) (8.9 mg, 2.1%), identical with that described below.

(b) *With 1,5-diazabicyclo[4.3.0]non-5-ene as base.*—A solution of 1,5-diazabicyclo[4.3.0]non-5-ene (124 mg) in dry DMF (15 ml) was added dropwise over 2.5 h to a stirred solution of the salt (1) (394 mg) and the dicarbaldehyde (20) (133 mg) in dry DMF (80 ml) at 70° (bath temperature). The solution was stirred at 70° (bath temperature) for a further 1 h. Early fractions from chromatography over silica gel afforded bis-(4,5,6,7-tetrahydroisobenzofuran-1-yl)-acetylene (27) (22 mg, 16.5%) which crystallised from dichloromethane–light petroleum as pale yellow needles, m.p. 149–151.5° (Found: M⁺, 266.1304. ¹²C₁₈¹H₁₈¹⁶O₂ requires M, 266.1307), λ_{max.} (Et₂O) 265 (ε 13,800), 296sh (18,400), 306 (20,000), 315sh (17,000), and 328 nm (13,600), ν_{max.} (CCl₄) 2180, 1020 (furan ring breathing), and 918 cm⁻¹, τ (60 MHz) 2.98br (2H, s, furan H), 7.45 (8H, m, allylic H), and 8.30 (8H, m, homoallylic H). Later fractions afforded the [21]annulenone (24) (25.3 mg, 12.0%) which crystallised from dichloromethane–light petroleum as maroon prisms, decomp. >270° without melting (Found: M⁺, 420.1727. ¹²C₂₉¹H₂₄¹⁶O₃ requires M, 420.1725), λ_{max.} (Et₂O) 325sh (ε 64,500), 338 (84,000), and 394sh nm (8400) with tailing into the visible region; τ 2.27 and 2.33 (4H, ABq, J_{6,7} = J_{16,17} 17.0 Hz, 6-, 7-, 16-, and 17-H), 2.76 and 3.68 (4H, ABq, J_{3,4} = J_{19,20} 3.8 Hz, 3-, 20-, 4-, and 19-H), 7.87 (8H, m, allylic H), and 8.40 (8H, m, homoallylic H).

1'-Ethylenebis-(4,5,6,7-tetrahydroisobenzofuran) (28).—The foregoing acetylene (27) (123 mg) was hydrogenated over 10% palladised charcoal (15 mg) in ethanol. After the rapid uptake of 2 mol. equiv. of hydrogen the catalyst was filtered off and washed with ethyl acetate (100 ml). The total filtrate was washed with water and with saturated brine, and dried (Na₂SO₄). The residue left after removal of the solvent was applied in dichloromethane to a p.l.c. plate which was developed once with light petroleum. The most intense band yielded the alkane (28) (34.5 mg, 32.4%) which crystallised from light petroleum as prisms, m.p. 97–98° (Found: C, 80.2; H, 8.0%; M⁺, 270. C₁₈H₂₂O₂ requires C, 79.95; H, 8.2%; M, 270), τ (60 MHz) 3.12br (2H, s, furan H), 7.30 (4H, s, ethane H), 7.72 (8H, m, allylic H), and 8.45 (8H, m, homoallylic H).

(5E,15E)-1,4:17,20-Diepoxy-7,8:13,14-bis(tetramethylene)-cyclohexeneicoso-1,3,5,7,13,15,17,19-octaene-9,11-diyne (25).—The annulenone (24) (17.8 mg) was reduced with lithium aluminium hydride (50 mg) and aluminium chloride (20 mg) in the usual way. The homoannulene (25) (16.6 mg, 96.5%) crystallised from cold light petroleum as small, yellow prisms, m.p. 270–271° (decomp.) (Found: M⁺, 406.1928. ¹²C₂₉¹H₂₈¹⁶O₂ requires M, 406.1933), τ† 1.86 and 3.85 (4H, ABq, J_{6,7} = J_{16,17} 16.0 Hz, 7-, 16-, 6-, and 17-H), 3.99br (4H, s, 3-, 4-, 19-, and 20-H), 6.00br (2H, s, CH₂), 7.79 (8H, m, allylic CH₂), and 8.38 (8H, m, homoallylic H).

(6Z,12E,14Z)-2,5:8,11:16,19-Triepoxy[19]annulenone (34).—Lithium methoxide [from lithium (69.4 mg)] in absolute methanol (17.1 ml) was added over 2.5 h to the salt (1) (3.93 g) and the acrolein (33) (750 mg) in dry DMF (120 ml) at 90° (bath temperature). The solution was then stirred for a further 0.75 h. Chromatography over silica gel gave the [19]annulenone (34) (36.3 mg, 3.1%) which crystallised from ethanol as small, brick-red prisms (Found: M⁺, 304.0732. ¹²C₁₉¹H₁₂¹⁶O₄ requires M, 304.0736), λ_{max.} (Et₂O)

267 (ϵ 31,000), 287sh (30,000), 328 (38,000), 385 (20,000), 440 (20,000), 487 (13,000), and 530 nm (3700); n.m.r., see Discussion section.

(5Z,11E,13Z)-1,4:7,10:15,18-Triepoxycyclononadeca-1,3,5,7,9,11,13,15,17-nonaene (35).—The annulenone (34) (39.2 mg) was reduced with lithium aluminium hydride (100 mg) and aluminium chloride (10 mg) in the usual way.

The *homoannulene* (35) (34.7 mg, 92.8%) was obtained as a yellow gum (Found: M^+ , 290.0949. $^{12}C_{19}H_{14}^{16}O_3$ requires M , 290.0943); n.m.r., see Discussion section.

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