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Acenaphane Derivatives from Furan Macrocycles

Franz H. Kohnke,* Melchiorre F. Parisi and Françisco M. Raymo

Dipartimento di Chimica Organica e Biologica, Università di Messina, Salita Sperone 31, 98166 - S. Agata - Messina, Italy

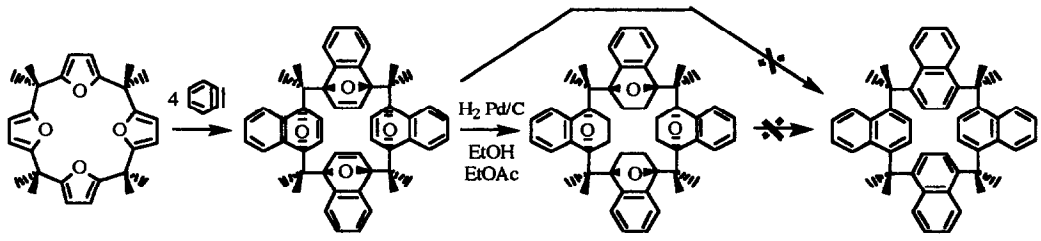
Paul A. O'Neil and David J. Williams

Department of Chemistry, Imperial College, London SW7 2AY, United Kingdom

Abstract: *The macrocycle 1 reacts with benzynes to give the Diels-Alder tetra-adduct 11 as a single isomer in good yields. Its mode of formation has now been investigated and its stereochemistry confirmed by X-ray crystallographic analysis. Benzynes react with 1 stepwise with high regio and facial selectivity. Only the mono-adduct 2 could be aromatised to the furanaphthaphane 17, and its conformational behaviour has been investigated by means of dynamic ^1H NMR spectroscopy and by single crystal X-ray analysis. The tetra-adduct 11 exhibits molecular recognition in the solid state selectively entrapping p-xylene when crystallised from a mixture of xylenes.*

INTRODUCTION

Macrocycles containing furan units are potentially useful precursors for the synthesis of cyclophanes and acenophanes by means of their Diels-Alder reactions with suitable dienophiles, followed by aromatisation of the initial adducts. This strategy has been successfully exploited in the case of 3,4-furaphanes.[1] However, Hart reported[2] that the readily accessible octamethyltetraoxaquaterene **1**[3] reacts with benzynes to give the tetra-adduct **11** as a single isomer which could not be converted into the corresponding [1.1.1.1]paranaphthalenaphane **15** either by direct deoxygenation or *via* the hydrogenated derivative **14** (Scheme 1).



1 **11** **14** **15**

Scheme 1

The remarkable facial diastereoselectivity of benzyne cycloaddition to **1** was rather intriguing. Moreover, the products of mono-, bis-, and tris-addition had not been isolated and characterised. We thus decided to re-investigate the reaction of **1** with benzynes in order to gain some understanding on the selective mode of formation of the tetra-adduct **11** and to explore the use of mono-, bis-, and tris-addition products as synthetic precursors of novel furanaphthaphanes.

RESULTS AND DISCUSSION

It seems reasonable to assume that benzynes react with **1** in a stepwise fashion. These cycloadditions can in principle lead to the formation (Scheme 2) of the mono-adduct **2**, the four bis-adducts **3-6**, the three tris-adducts **7-9**, and the four tetra-adducts **10-13**, differing in respect to the relative configuration of the endoxide bridges.[4] However, when **1** was treated with various stoichiometric proportions of benzyne (generated by pyrolysis of benzenediazonium-2-carboxylate hydrochloride in refluxing THF),[5] single adducts were produced in all cases.

The ^{1}H NMR spectrum of the mono-adduct **2** shows four signals for each set of heterotopic methyl groups, one AB system for the two pairs of protons of the furan residues closer to the newly formed 1,4-epoxynaphthalene residue, one singlet for the pair of protons of the third furan ring, and one singlet for the pair of olefinic protons. The ^{13}C NMR spectrum shows seventeen resonances for each pair of heterotopic carbon atoms present in **2**.

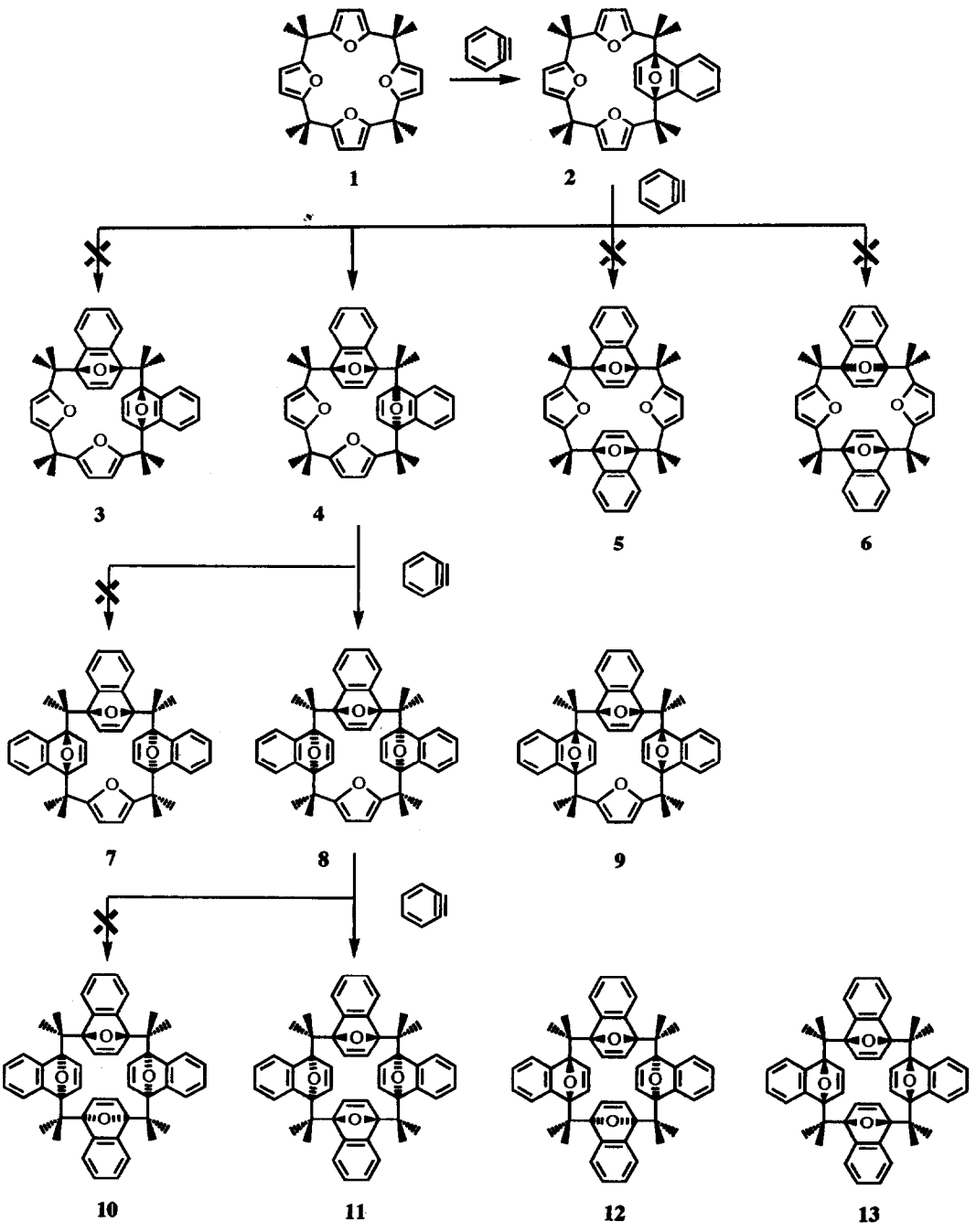
The presence of four signals for the methyl groups and of two AB systems, arising from (1) the furan ring protons and (2) the olefinic protons, in the ^{1}H NMR spectrum of the bis-adduct rules out structures **5** and **6**, which contain only two sets of heterotopic methyl groups and which do not contain protons that can resonate as AB systems. On the other hand, structure **3** is ruled out because its ^{1}H NMR spectrum should show six signals for each pair of heterotopic methyl groups. Thus, the bis-adduct must have structure **4**. This conclusion is also confirmed by the presence of twenty-one resonances in its ^{13}C NMR spectrum.

The reaction of **4** with a third benzyne can lead to the tris-adducts **7** and **8**. The tris-adduct **9** is obviously excluded because it can only derive from **5** and **3**, which are not formed. However, the ^{1}H NMR spectrum of the only isolated isomer shows four discrete signals for the methyl protons and one AB system for the two pairs of olefinic protons of the 1,4-epoxyanaphthalene units closer to the furan ring. These data are consistent with the isomer **8** and rule out **7** which should show eight discrete resonances for the methyl protons and four AB systems in its ^{1}H NMR spectrum. This conclusion is also supported by the ^{13}C NMR spectrum which contains twenty-three discrete resonances corresponding to each pair of heterotopic carbon atoms present in **8**.

The reaction of **8** with the fourth benzyne could give the tetra-adducts **10** and **11**. The stereoisomers **12** and **13** are obviously ruled out because their precursors - **7** and **9** respectively - are not formed.

The spectroscopic characteristics of the tetra-adduct were consistent with structure **11** and with those reported in the literature[2] for this compound.

These results indicate that *there is only one pathway* leading to the formation of the tetra-adduct **11**, as indicated in Scheme 2. Benzyne and **1** have homotopic faces.[6] The first cycloaddition leads to the formation of **2** which has two diastereotopic faces. This initial event determines the *regio* and *facial* selectivity of the second benzyne addition, which only takes place on a furan unit adjacent to the 1,4-epoxynaphthalene moiety and on the face *anti* to the endoxide bridge. The formation of two enantiomers arises from the cycloaddition to one or the



Scheme 2

other of the two reactive furan units. The bis-adduct **4** has two diastereotopic faces, and its furan residues react with the benzyne only with the face *anti* to the closer endoxide bridge. The tris-adduct **8** thus formed has two diastereotopic faces and its furan residue reacts only with the face *anti* to the two closest endoxide bridges.

In agreement with the results obtained by Hart,[2] all our attempts to convert **11** into the [1.1.1.1]naphthalenophane **15** (Scheme 1), either by direct deoxygenation or by hydrogenation followed by acid catalysed aromatisation,[7] were not successful. This failure has been ascribed[2] to the rigidity of the molecule and/or to steric hindrance of the oxygen atoms. We therefore decided to investigate the structural features of **11** by means of X-ray crystallography. Suitable single crystals were obtained from toluene.

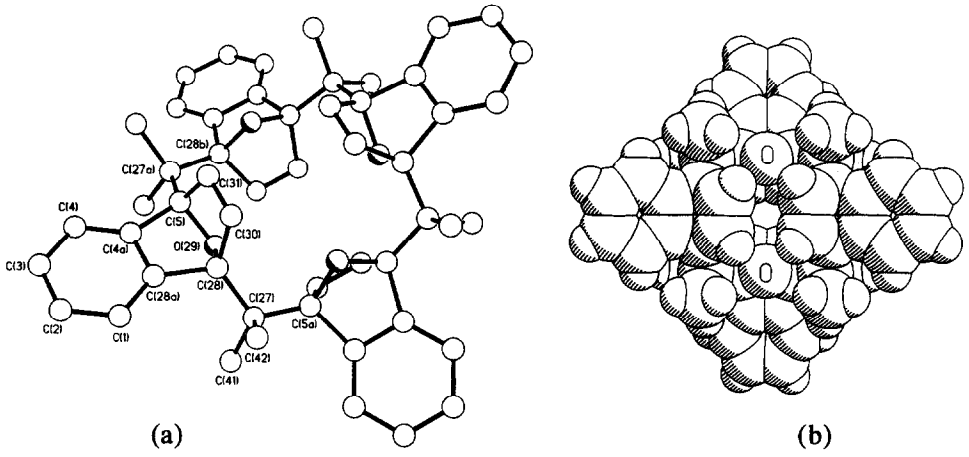


Figure 1. The X-ray crystal structure of **11**. (a) Framework and (b) space-filling representations. With the exception of C(5a), C(27a), and C(28b) whose formal numbers should be C(26), C(6), and C(7) respectively, the atom numbering corresponds to the IUPAC nomenclature. The changes are the consequence of the crystallographic S_4 symmetry.

The X-ray crystal structure of **11** is shown in Figure 1. The relative orientation of the oxygen atoms is consistent with that assigned on the basis of ^1H and ^{13}C NMR spectroscopic data. The molecule has crystallographic S_4 and molecular D_{2d} symmetries. The oxygen atoms and the olefinic double bonds lie alternately above and below the mean plane of the macrocycle. However, inspection of space-filling drawings shows the oxygen atoms to be partially shielded by the diene units. The planes of the aryl rings are tilted alternately above and below the mean plane of the macrocycle as defined by the four isopropylidene carbon atoms, by *ca.* 18°. The distance between the two oxygen atoms on the same face of the molecule is 4.86 Å and the distance between each pair of parallel olefinic bonds is 3.50 Å. The distance between the molecular centre and the vertices of the tetrahedron defined by the mid-points of each olefinic bond is 2.50 Å.[8] Overall the molecule appears to be remarkably rigid and strain-free, there being only small departures from the tetrahedral geometry [112.5° for C(41)-C(27)-C(42) and 112.8° for C(28)-C(27)-C(5a)] at each of the bridging isopropylidene carbon atoms. These distortions correspond to a slight flattening of the tetrahedrons. The geometry of the 7-oxanorbornadiene moiety appears unchanged on incorporation with the macrocycle.[9]

The crystals studied were solvated with two molecules of toluene for each molecule of **11**. As shown in the packing diagram (Figure 2) the toluene molecules lie in channels that extend through the crystals in both the *a* and the *b* directions, thus permitting their slow diffusion out of the lattice. The guest molecules are located in

regions adjacent to the periphery of the cyclophane there being no significant short host-guest contacts. The toluene molecules are disordered about a crystallographic centre of symmetry, thus mimicking the trapping of a *p*-xylene molecule.

This suggested to us that *p*-xylene should also be trapped well - perhaps even better - within the lattice. When **11** was crystallised from a commercial mixture of xylenes (*o*-: *m*-: *p*- / 26 : 58 : 16) the ^{1}H NMR spectrum of the crystals showed, in addition to the resonances of **11**, only signals due to *p*-xylene. When crystals of **11** were grown from *p*-xylene, these were found to be isomorphous with those obtained from toluene. Thus the tetra-adduct **11** is capable of solid-state molecular recognition[10] of xylene isomers.[11] However, this property is lost upon hydrogenation of the olefinic bonds, and **14** does not clathrate either toluene or xylenes. The crystalline host properties of **11** are commensurate with the demonstrated behaviour of *roof-shaped* hosts, and in particular with those that possess a secondary C_2 axis.[10-12]

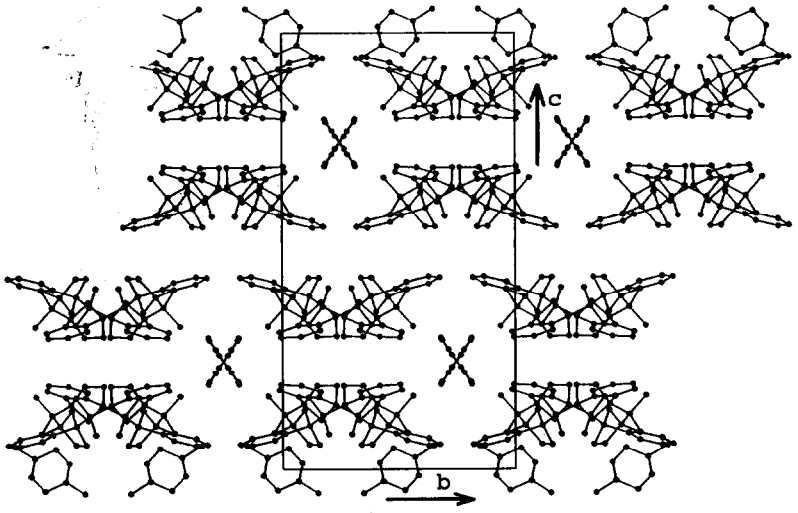
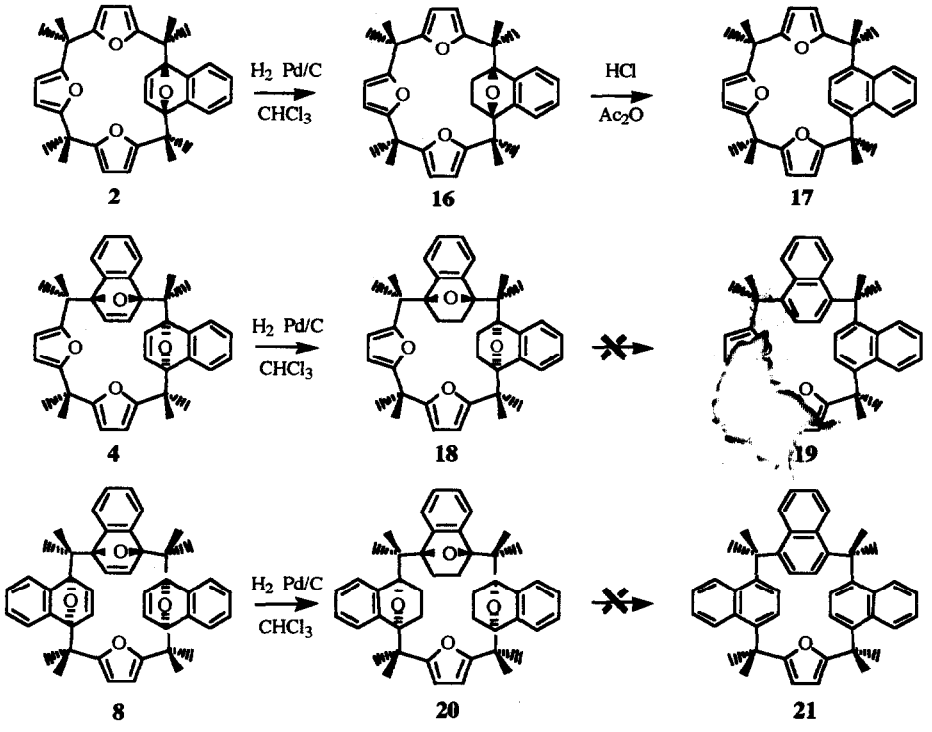


Figure 2. Packing diagram of **11** showing toluene molecules entrapped within channels that extend along the *a* and *b* axes. The symmetry centres result in the toluene molecules appearing as *p*-xylenes.

The aromatisation of **11** either by direct deoxygenation or by dehydration of **14** requires the initial opening of the epoxy bridge. However, this process would introduce considerable strain in the molecule that could not be relieved by means of conformational changes. Encouraged by the successful synthesis of the furanaphthaphane **22** by an alternative route,[2] which still employs as a key step the aromatisation of 1,4-epoxynaphthalene residues, we investigated the possibility of aromatisation of the more flexible mono-, bis-, and tris- adducts . However, none of these compounds could be directly deoxygenated with any of a variety of reagents including $LiAlH_4$-$TiCl_4$[1b, 6b,g,f] and trimethylsilyl iodide.[6a]

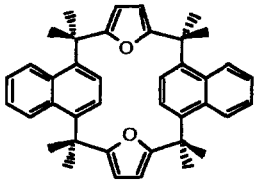
The hydrogenation of **2**, **4**, and **8** (Scheme 3) using Pd/C as catalyst gave quantitative yields of **16**, **18**, and **20** respectively. However, only **16** could be dehydrated to give the furanaphthaphane **17**.

The ^{1}H NMR spectrum of **17** recorded at 300 MHz in $CDCl_3$ at 20 °C shows a sharp signal of 12 protons (δ 1.36) and two broad singlets of six protons each (δ 1.79 and 1.90) for the methyl groups. These signals are temperature dependent. The results of a dynamic ^{1}H NMR study indicate that **17** is in equilibrium between two degenerate non-planar conformations as shown in Figure 3. This process exchanges the methyl groups of the



Scheme 3

isopropylidene units adjacent to the naphthalene moiety and those adjacent to the diametrically opposite furan ring between the sites A/A' and B/B' respectively (the relative assignment of the sites A/A' and B/B' for each of the two pairs of methyl groups is arbitrary). On heating the solution, the two broad signals coalesced at $T_{c(A/A')} = 30\pm3$ °C to give a sharp signal at δ 1.84 at 50 °C. The frequency separation at the coalescence temperature $\Delta\nu_{c(A/A')} = 33$ Hz was obtained from ν_A and $\nu_{A'}$ below $T_{c(A/A')}$ as these values show no relevant temperature dependence. An approximate treatment of these data gave the rate constant for the exchange at the coalescence temperature $k_{c(A/A')} = 73$ s^{-1} (calculated from the expression $k_c = \pi\Delta\nu_c/(2)^{1/2}$) and the corresponding free energy of activation $\Delta G_c^{\neq}{}_{(A/A')} = 15.1\pm0.5$ Kcal/mol (calculated from the Eyring[13] equation). On cooling the solution, the two broad signals became sharper whilst the sharp 12 protons signal broadened until, by -20 °C it appeared well separated into two signals of equal intensity (δ 1.36 and 1.38). The coalescence temperature was $T_{c\ (B/B')} = 10\pm3$ °C. A treatment of these data analogous to the one described above for the A/A' site exchange gave: $\Delta\nu_{c(B/B')} = 6$ Hz, $k_{c(B/B')} = 13$ s^{-1}, $\Delta G_c^{\neq}{}_{(B/B')} = 15.0\pm0.5$ Kcal/mol.



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The conformational behaviour of **17** is similar to that observed[2,14] for the furanaphthaphane **22**. The protons of the furan ring opposite to the naphthalene unit resonate at δ 4.86. This value is consistent with the furan ring being tilted with the hydrogen atoms pointing towards the unsubstituted benzo ring of the naphthalene. These furan protons give only one signal even at low temperature, therefore, the conformational flipping of the naphthalene moiety must be concerted with the one of the diametrically opposite furan ring. The molecular models show that the furan units adjacent to the naphthalene must also be tilted. Their relative orientations[15] should be related by approximate mirror symmetry because, regardless of the temperature, i) the naphthalene protons resonate as only three discrete signals and ii) the signal at δ 4.86 is a singlet. Thus the conformational inversion of **17** must involve the flipping of all the aromatic units in a concerted fashion.

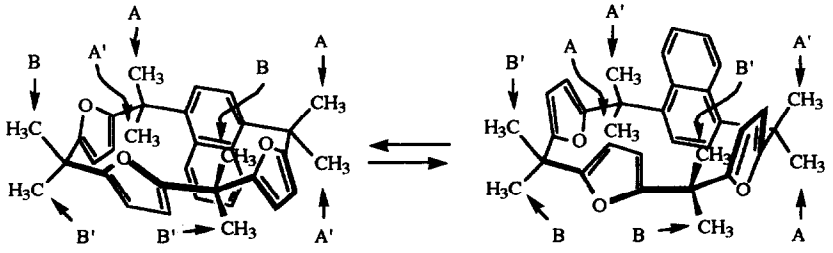

Figure 3. The conformational inversion of **17** exchanging the methyl groups betwen the sites A/A'and B/B'.

With the objective of synthesising acenaphanes possessing cavities as a result of their non-planar conformations, we considered it important to investigate the structure of the furanaphthaphane **17** in the solid state. Single crystals of **17** were obtained by slow cooling of a toluene solution. The X-ray structure (Figure 4)

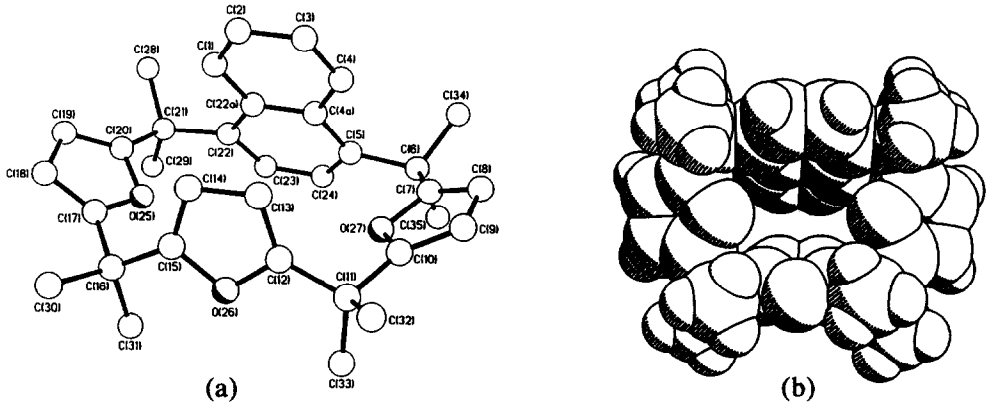

Figure 4 .The X-ray crystal structure of **17**. (a) Framework and (b) space-filling representations (one viewed essentially from above and the other from underneath).

shows the molecule to adopt a conformation very different from that of **11** in the solid state. Here all three oxygen atoms lie on one face. The diametrically opposite furan rings are inclined by *ca.* 28° and 32° respectively to the main plane of the macrocycle (as defined by the four bridging isopropylidene carbon atoms), with the oxygen atoms directed inwards. The remaining furan ring and the naphthalene unit are both inclined steeply

with the pair of furan protons directed inwards towards the face of the unsubstituted benzo ring of the naphthalene. The distances between the C(13) and C(14) protons from C(4) and C(1) are 3.49 and 3.35 Å respectively. This is reflected in the up-field shift (δ 4.86 ppm) of these furan protons observed in the ^{1}H NMR spectrum. The dihedral angle between the naphthalene and the opposite furan ring-planes is 35°. [16] The molecule is essentially strain-free with only very minor deviations from the tetrahedral geometry at each of the isopropylidene carbon centres. The only noticeable deformations are a slight pyramidalisation at C(5) and C(22) and a slight boat deformation of the substituted benzo ring of the naphthalene. As a result the bonds between the naphthalene and the adjacent isopropylidene carbon atoms are inclined by 8° with respect to each other. The trans-annular O(25)-O(26), O(26)-O(27), and O(25)-O(27) distances are 3.73, 3.59, and 5.31 Å respectively. An inspection of the packing of the molecules in the crystal does not reveal any significant intermolecular interactions.

CONCLUSIONS

The attainment of **17** from **2** and the impossibility to aromatise **4**, **8**, and **11**, points to the importance of steric factors, which are probably also responsible for the remarkable *facial* and *regio* selectivity of the mode of formation of **11** outlined in Scheme 2. These conclusions are further supported by the analysis of the X-ray crystal structure of **11**. We have also uncovered the remarkable selectivity of **11** as crystalline host. An examination of molecular models indicates that larger macrocycles containing five or six furan units[17] should be better suited than **1** for the syntheses of furanaphthaphanes and naphthaphanes *via* multiple aryne cycloaddition followed by aromatisation of the adducts. In fact, these adducts would be less sterically constrained than those discussed in this paper. The preferred cone-shaped conformation of cyclophanes such as the calixarenes[18] has been the basis for the development of a vast class of molecular receptors. Thus furan macrocycles appear very attractive precursors of novel molecular receptors. We are currently exploring this possibility.

Acknowledgements. This research was supported by the Ministry of Universities and of Scientific and Technological Research (Italy), and the Science and Engineering Research Council (UK).

EXPERIMENTAL

General. Tetrahydrofuran (THF) was distilled from the sodium ketyl of benzophenone. Furan was distilled from CaH_2. All other chemicals were standard reagent grade and were used without further purification. All air-sensitive and/or moisture sensitive reactions were conducted under a dry argon atmosphere. Thin layer chromatography (TLC) was carried out on either glass or aluminium SiO_2 Carlo Erba Stratocrom SIF 254 or Al_2O_3 Carlo Erba Stratocrom ALF plates. Compounds were visualised with iodine or by examination under UV light. Column chromatography was conducted on Aldrich Si gel 230-400 mesh, 60Å. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 spectrometer in $CDCl_3$ using $(CH_3)_4Si$ as internal standard. Mass spectra were measured by electron impact (EI) or fast atom bombardment (FAB) on a Finnigan Mat 90 spectrometer operated by Dr. Marcello Saitta. Melting points were determined on a Kofler hot stage apparatus, and are not corrected.

Crystal data. **11**·2(C_7H_8), $C_{66}H_{64}O_4$, M = 921.2, tetragonal, a = 13.911(3), c = 26.310(5) Å, U = 5091(2) Å^3, space group $I4_1/a$, Z = 4, (the molecule has S_4 crystallographic symmetry) D_c = 1.20 g·cm^{-3}, μ(Mo-K$_\alpha$) = 0.73 cm^{-1}, F(000) = 1968. **17**, $C_{34}H_{36}O_3$, M = 492.6, monoclinic,

a = 14.833(14), b = 13.489(16), c = 14.954(13) Å, β = 113.03(2)°, U = 2753(5) Å^3, space group $P2_1/c$, Z = 4, D_c = 1.19 g·cm^{-3}, μ(Mo-K$_\alpha$) = 0.74 cm^{-1}, F(000) = 1056. Data for both compounds were measured on a Siemens P4/PC diffractometer ($2\theta < 50°$) with Mo-K$_\alpha$ radiation (graphite monochromator) using the ω-scans. For compounds **11** and **17**, 2692 and 4847 independent reflections respectively were measured and of these 1495 and 2719 respectively had $|F_o| > 4\sigma(|F_o|)$ and were considered to be observed. The data were corrected for Lorentz and polarization factors: no absorption corrections were applied. The structures were solved by direct methods and the non-hydrogen atoms were refined anisotropically. In compound **11** a ΔF map revealed the presence of an included molecule of toluene disordered about a centre of symmetry. The positions of the methyl hydrogen atoms in **11** were observed to adopt two discrete orientations each of estimated occupancy of 0.5. The positions of all the hydrogen atoms were optimised, C-H = 0.96 Å, assigned isotropic thermal parameters U(H) = 1.2 Ueq(C), and allowed to ride on their parent carbon atoms. Refinement was by full-matrix least-squares to give for **11** R = 0.061, R_w = 0.063 ($w^{-1} = \sigma^2(F) + 0.0005\,F^2$), for **17** R = 0.055, R_w = 0.052 ($w^{-1} = \sigma^2(F) + 0.0006\,F^2$). The maximum residual electron densities in the final ΔF maps were 0.22 and 0.23 e Å^{-3} for **11** and **17** respectively. Computations were carried out on a 486 PC using the SHELXTL-PC™ program[19] system. Atomic coordinates and the bond lengths and angles, also the thermal parameters, have beeen deposited at the Cambridge Crystallographic Data Centre.

Crystal data for the isomorphous p-xylene solvate of **11**: **11**·2[*p*-$(CH_3)_2C_6H_4$], $C_{68}H_{68}O_4$, M = 949.3, tetragonal, a = 14.086(8), c = 25.926(10) Å, U = 5144(4) Å^3, space group $I4_1/a$

(5R,7R*,12S*,14S*,19R*,21R*,26S*,28S*)-6,6,13,13,20,20,27,27-Octamethyl-6H,13H,20H,27H-5,28:7,12:14,19:21,26-tetraepoxy-5,28:7,12:14,19:21,26-tetraethenotetrabenzo[a,f,k,p]cycloeicosene* **11**.

Benzenediazonium-2-carboxylate hydrochloride (8.0 g, 43.4 mmol) was added to a solution of **1** (3.0 g, 6.9 mmol) and propylene oxide (6 ml) in THF (300 ml). The mixture was heated under reflux until clear (2 h). The solvent was evaporated under reduced pressure and the residue extracted with DCM / H_2O. The organic phase was dried ($MgSO_4$) and concentrated. The oily residue was crystallised from toluene to give clear prisms of **11** (4.0 g, solvated with two molar equivalents of toluene) which did not melt but decomposed slowly above 280°C. The net yield of **11** was 63%. ^{1}H NMR: δ 1.80 (s, 24H), 6.64 (s, 8H), 6.90 (m, 8H), 7.47 (m, 8H); ^{13}C NMR: δ 21.4, 37.5, 97.3, 121.5, 123.1, 141.7, 154.2; EIMS, m/z (rel. int.): 736 (M^+, 8), 721 (14), 340 (9), 325 (10), 297 (19), 269 (36), 185(100), 157 (34), 141 (23).

6,11,16,21-Tetrahydro-6,6,11,11,16,16,21,21-octamethyl-5,22:7,10:12,15:17,20-tetraepoxy-5,22-ethenobenzocycloeicosene **2** and *(5R*,17R*,22S*,24S*)-11,16-Dihydro-6,6,11,11,16,16,23,23-octamethyl-6H,23H-5,24:7,10:12,15:17,22-tetraepoxy-5,24:17,22-diethenodibenzo [a,f]cycloeicosene* **4**.

Benzenediazonium-2-carboxylate hydrochloride (1.4 g, 7.5 mmol) was added to a solution of **1** (4.0 g, 9.2 mmol) and propylene oxide (5 ml) in THF (500 ml). The mixture was heated under reflux until clear (2 h) and allowed to stand at room temperature for two days. The solvent was removed under reduced pressure and the residue extracted with DCM / H_2O. The organic phase was dried ($MgSO_4$) and concentrated. Fractional crystallisation of the residue with toluene afforded unreacted **1**, (2.0 g). The mother liquor was concentrated and subjected to column chromatography (SiO_2, toluene:hexane / 30:70) to give, in order of eluition, two fractions which were characterised as **4** and **2**.

4: 427 mg, 8%, m.p. 249 °C, white crystals from MeOH/toluene; ^{1}H NMR: δ 1.45 (s, 6H), 1.63 (s, 12H), 1.72 (s, 6H), 5.83 (d, A part of AB system, J_{AB}=3.1 Hz, 2H), 5.98 (d, B part of AB system, J_{AB}=3.1 Hz, 2H), 6.50 (d, A part of AB system, J_{AB}=5.6 Hz, 2H), 6.54 (d, B part of AB system, J_{AB}=5.6 Hz, 2H), 6.89 (m, 4H), 7.35 (m, 4H); ^{13}C NMR: δ 20.6, 21.2, 23.7, 24.4, 36.8, 37.7, 37.8, 95.3, 97.2, 102.9, 104.0., 120.5, 120.9, 123.3, 123.4, 139.3, 143.0., 152.6, 154.2, 157.9, 159.1; EIMS, m/z (rel. int.): 584 (M^+, 100), 569 (90), 541 (39), 385 (51), 357 (23), 293 (38), 257 (90), 185 (50), 149 (30); HRMS calculated for $C_{40}H_{40}O_4$ 584.2926, found 584.2923.

2: 753 mg, 16%, m.p. 239 °C, white crystals from MeOH/toluene; ^{1}H NMR: δ 1.41 (s, 6H), 1.51 (s 6H), 1.55 (s, 6H), 1.65 (s, 6H), 5.76 (d, A part of AB system, J_{AB}=3.1 Hz, 2H), 5.87 (d, B part of AB system, J_{AB}=3.1 Hz, 2H), 5.92 (s, 2H), 6.72 (s, 2H), 6.90 (m, 2H), 7.32 (m, 2H); ^{13}C NMR: δ 21.3, 23.9, 24.7, 25.1, 36.6, 37.7, 76.6, 102.6, 103.1, 104.4, 120.7, 123.6, 142.2, 152.6, 157.8, 158.4, 158.8; EIMS, m/z (rel. int.): 508 (M^+,95), 493 (100), 465 (85), 365 (37), 257 (24), 149 (10); HRMS calculated for $C_{34}H_{36}O_4$ 508.2613, found 508.2608.

(5R,7R*,12S*,19R*,24S*,26S*)-13,18-Dihydro-6,6,13,13,18,18,25,25-octamethyl-6H,25H-5,26:7,12:14,17:19,24-tetraepoxy-5,26:7,12:19,24-triethenotribenzo[a,f,k]cycloeicosene* **8**.

The reaction between benzyne generated from benzenediazonium-2-carboxylate hydrochloride (2.5 g, 13.8 mmol) and **1** (2.0 g, 4.6 mmol) was conducted as for the synthesis of **2** and **4**. Treatment with methanol (10 ml) of the crude oil obtained after the work-up gave unreacted **1** (615 mg, 18%) as a white precipitate. The mother liquor was concentrated and subjected to column chromatography (SiO_2, toluene:hexane / 20:80) to give, in order of eluition, two fractions which were characterised as **4** (360 mg, 13%) and **8**: 384 mg, 13%, m.p. 315 °C, white solid from MeOH/THF; ^{1}H NMR: δ 1.54 (s, 6H), 1.70 (s, 6H), 1.72 (s, 6H), 1,82 (s, 6H), 5.92 (s, 2H), 6.40 (s, 2H), 6.73 (d, A part of AB system, J_{AB}=5.5 Hz, 4H), 6.98 (d, B part of AB system, J_{AB}=5.5 Hz, 4H), 6.91 (m, 4H), 7.38 (m, 4H), 7.50 (m, 4H); ^{13}C NMR: δ 20.7, 21.3, 22.1, 23.4, 37.6, 37.8, 95.6, 97.3, 97.4, 105.1, 120.7, 121.2, 121.3, 123.1, 123.3, 123.5, 140.5, 141.2, 143.9, 152.6, 154.0, 154.5, 158.9; FABMS, m/z (rel. int.): 660 (M^+, 17), 646 (8), 417 (19), 239 (35), 185 (60), 149 (100), 135 (70), 115 (59); HRMS calculated for $C_{46}H_{44}O_4$ 660.3239, found 660.3231.

General procedure for the hydrogenation of ***2, 4, 8*** *,and* ***11***.

The adducts were dissolved in $CHCl_3$, and added to a suspension of Pd/C (5% Pd) in the same solvent. The mixture was degassed and vigorously stirred under a hydrogen atmosphere at room temperature and pressure. The course of the reaction was monitored by TLC (SiO_2, toluene:hexane / 30:70). When no further change in the composition of the reaction mixture could be observed (1-2 days), this was filtered and concentrated to give quantitative yields of **16**, **18**, **20**, and **14** respectively.

6,11,16,21-Tetrahydro-6,6,11,11,16,16,21,21-octamethyl-5,22:7,10:12,15:17,20-tetraepoxy-5,22-ethanobenzocycloeicosene **16**: m.p. 240°C, white solid from MeOH/toluene; ^{1}H NMR: δ 1.10 (d, A part of AB system, J_{AB}=7.0 Hz, 2H), 1.39 (s, 6H), 1.54 (s, 6H), 1.56 (s, 6H), 1.59 (s, 6H), 2.2 (d, B part of AB system, J_{AB}=7.0 Hz, 2H), 5.83 (d, A part of AB system, J_{AB}=3.1 Hz, 4H), 5.98 (d, B part of AB system, J_{AB}=3.1 Hz, 4H), 5.99 (s, 2H), 7.13 (m, 2H), 7.34 (m, 2H); ^{13}C NMR: δ 23.0, 23.8, 24.4, 25.0, 29.6, 36.7, 38.3, 90.6, 102.8, 103.4, 104.8, 119.9, 125.4, 147.8, 157.7, 158.6, 159.3; EIMS, m/z (rel. int.): 510

(M^+, 50), 482 (100), 467 (75), 437 (8), 338 (7), 323 (21), 226 (18), 149 (8); HRMS calculated for $C_{34}H_{38}O_4$ 510.2669, found 510.2661.

(5R,17R*,22S*,24S*)-11,16-Dihydro-6,6,11,11,16,16,23,23-octamethyl-6H,23H-5,24:7,10:12,15:17,22-tetraepoxy-5,24:17,22-diethanodibenzo[a,f]cycloeicosene* **18**: m.p. 290°C, white solid from MeOH/THF; ^{1}H NMR: δ 0.92 (m, 2H), 1.14 (m, 2H), 1.53 (s, 6H), 1.56 (s, 6H), 1.65 (s, 6H), 1.71 (s, 6H), 2.19 (m, 2H), 2.47 (m, 2H), 5.89 (d, A part of AB system, J_{AB}=3.15 Hz), 6.09 (d, B part of AB system, J_{AB}=3.08 Hz, 4H), 7.13 (m, 4H), 7.40 (m, 4H); ^{13}C NMR: δ 21.9, 23.1, 23.6, 24.1, 29.4, 29.5, 37.0, 37.7, 38.5, 91.5, 94.3, 103.3, 104.7, 120.1, 120.4, 125.1, 146.6, 149.7, 157.8, 159.9; EIMS, m/z (rel. int.): 588 (M^+, 19), 560 (100), 545 (20), 532 (10), 373 (4), 250 (4), 149 (3); HRMS calculated for $C_{40}H_{44}O_4$ 588.3083, found 588.3075.

(5R,7R*,12S*,19R*,24S*,26S*)-13,18-Dihydro-6,6,13,13,18,18,25,25-octamethyl-6H,25H-5,26:7,12:14,17:19,24-tetraepoxy-5,26:7,12:19,24-triethanotribenzo[a,f,k]cycloeicosene* **20**: m.p. 322 °C, white solid from toluene; ^{1}H NMR: δ 0.96 (m, 2H), 1.21 (m, 2H), 1.42 (m, 2H), 1.59 (s, 6H), 1.62 (s, 6H), 1.65 (s, 6H), 1.78 (s, 6H), 2.57 (m, 2H), 2.81 (m, 2H), 6.03 (s, 2H), 7.12 (m, 4H), 7.18 (m, 4H), 7.47 (m, 4H); ^{13}C NMR: δ 22.1, 22.8, 23.3, 24.2, 29.3, 30.5, 31.1, 38.1, 38.6, 92.1, 94.2, 95.2, 105.9, 120.1, 120.7, 121.0, 125.0, 125.3, 125.4, 146.6, 148.6, 149.4, 159.6; FABMS, m/z (rel. int.): 666 (M^+, 8), 638 (100), 595 (10), 567 (3), 419 (3), 293 (10), 215 (15), 185 (19), 154 (50), 77 (42), 39 (19). HRMS calculated for $C_{46}H_{50}O_4$ 666.3709, found 666.3699.

(5R,7R*,12S*,14S*,21R*,26R*,28S*)-6,6,13,13,20,20,27,27-Octamethyl-6H,13H,20H,27H-5,28:7,12:14,19:21,26-tetraepoxy-5,28:7,12:14,19:21,26-tetraethanotetrabenzo[a,f,k,p]cycloeicosene* **14.**: gradually decomposes above 295 °C, white solid from MeOH/toluene; ^{1}H NMR: δ 1.26 (d, A part of AB system, J_{AB}=6.6 Hz, 8H), 1.75 (s, 24H), 3.00 (d, B part of AB system, J_{AB}=6.6 Hz, 8H), 7.18 (m, 8H), 7.54 (m, 8H); ^{13}C NMR δ 23.0, 30.5, 38.4, 95.3, 121.1, 125.1, 148.6; EIMS, m/z (rel. int.): 744 (M^+, 1), 718 (14), 716 (100), 714 (18), 688 (8), 673 (3), 645 (3), 344 (27), 200 (8), 187 (17).

6,11,16,21-Tetrahydro-6,6,11,11,16,16,21,21-octamethyl-7,10:12,15:17,20-triepoxy-5,22-etheno-benzocycloeicosene **17.**

Concentrated HCl (37%, 1.5 ml) was added to a suspension of **16** (384 mg, 0.753 mmol) in acetic anhydride (7.5 ml). The mixture was heated under reflux for two days, cooled, neutralised with a saturated solution of $NaHCO_3$ and extracted with DCM (3 x 10 ml). The organic extracts were combined, washed with H_2O, dried (Mg_2SO_4), and concentrated to give a residue (344 mg) which was subjected to column chromatography (SiO_2, toluene:hexane / 30:70). The first fraction to be eluted was characterised as **17**: 56.5 mg, 15%, m.p. 265-266 °C, white solid from toluene; ^{1}H NMR (20 °C): δ 1.36 (s, 12H), 1.79 (bs, 6H), 1.90 (bs, 6H), 4.86 (s, 2H), 5.99 (d, A part of AB system, J_{AB}=2.9, 2H), 6.14 (d, B part of AB system, J_{AB}=2.9, 2H), 7.00 (m, 2H), 7.47(s, 2H), 7.90 (m, 2H); ^{13}C NMR: 23.9, 24.0, 27.6, 27.9, 28.0, 32.2, 32.3, 36.8, 40.2, 96.1, 101.3, 102.2, 105.2, 122.4, 123.2, 126.6, 132.5, 141.3, 156.1, 160.2, 162.7; EIMS, m/z (rel. int.): 492 (M^+, 49), 477 (100), 447 (8), 231 (10), 216 (5); HRMS calculated for $C_{34}H_{36}O_3$ 492.2662, found 492.2659.

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4. The bis-adduct **4** and the tris-adduct **7** can exist as pairs of enantiomers.
5. This is a modification of the reaction conditions previously used by Hart: see ref. 2.
6. Compound **1** has S_4 symmetry in the solid state, with the furan ring-planes tilted steeply with respect to the mean plane of the macrocycle: Hazel A. Acta Cryst. **1989**, *C45*, 137-140. However, our considerations are equally valid whether the S_4 symmetry is maintained in solution or assuming an averaged planar arrangement of the furan rings.
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