Molecular Belts. 2. Substrate-Directed Syntheses of Belt-Type and Cage-Type Structures†

Peter R. Ashton,‡ Ulrich Girreser,‡ Daniele Giuffrida,‡ Franz H. Kohnke,§,∥ John P. Mathias,§,# Françisco M. Raymo,∥ Alexandra M. Z. Slawin,⊥ J. Fraser Stoddart,*,‡ and David J. Williams⊥

Contribution from the Department of Chemistry, The University, Sheffield S3 7HF, U.K., School of Chemistry, University of Birmingham B15 2TT, U.K., and Chemical Crystallography Laboratory, Department of Chemistry, Imperial College, London SW7 2AY, U.K.

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Abstract: The trebly-diastereoselective synthesis and structural characterization of two macropolycyclic derivatives, which are based upon building blocks incorporating six-membered rings that are both [*a*,*c*]- and [*a*,*d*]-fused, have been achieved by a Diels–Alder oligomerization reaction sequence. The angular syn bisdienophile **3** has been used as a Diels–Alder building block with the bisdiene **12** in a trebly-diastereoselective synthesis of the angular macropolycyclic derivative **5**. The incorporation of two diametrically-opposed [*a*,*c*]-fused units into the skeleton of **5** imposes a conical nature upon the cavity compared with the structures of macropolycyclic compounds such as the cyclacene derivatives **1** and **2**. The construction of the angular macropolycyclic derivative **5** anticipates the use of the C_{3v} trisdienophile **4**, with the bisdiene **12**, in the substrate-directed synthesis of a novel cage-like compound dubbed trinacrene **6**. The structural characterization of both the angular macropolycyclic derivative **5** and trinacrene **6** has been achieved by high-field NMR spectroscopy and FABMS. In each case, the operation of *treble diastereoselectivity* during *each* cycloaddition step dictates the structures of the products, underlining the utility of these stereoregular Diels–Alder oligomerizations to control the formations of molecular structures.

Introduction

Molecules which possess novel belt-like and cage-like structures have played a central role in the development of supramolecular chemistry.[1] Belt-like compounds—such as the cyclodextrins,[2] cyclophanes,[3] calixarenes,[4] spherands,[5] and cavitands[6]—along with cage-like compounds—such as the cryptands,[7] cryptophanes,[8] and carcerands[9]—have provided the basis for many studies of molecular recognition in its widest sense. The interest surrounding the recently-reported[10] isolation of the fullerenes is adequate testament to the growing importance of belt-like and cage-like compounds. Consequently, novel synthetic approaches to the construction of molecular belts and cages are required to sustain new developments in supramolecular chemistry. Here we describe some of our recent research findings in this area.

Results and Discussion

We have demonstrated[11-16] previously a highly selective approach toward the synthesis of complex macropolycyclic compounds, such as the [12]- and [14]cyclacene derivatives **1** and **2**, respectively, which is based upon a stereoregular Diels–

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‡ School of Chemistry, University of Birmingham B15 2TT, U.K.

§ Department of Chemistry, The University, Sheffield S3 7HF, U.K.

⊥ Chemical Crystallography Laboratory, Department of Chemistry, Imperial College, London SW7 2AY, U.K.

∥ Present address: Dipartimento di Chimica Organica e Biologica dell' Università di Messina, Salita Sperone 31-98166, Messina, Italy.

Present address: Department of Chemistry, Harvard University, Cambridge, MA 02138.

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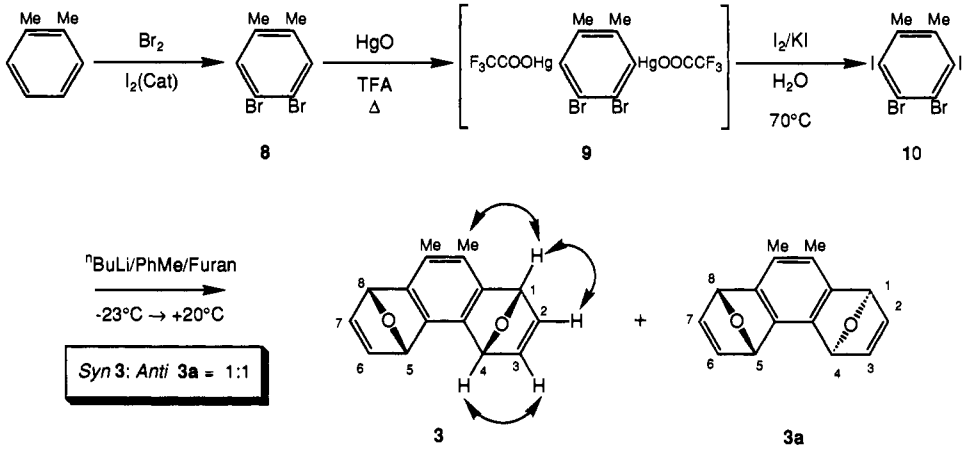
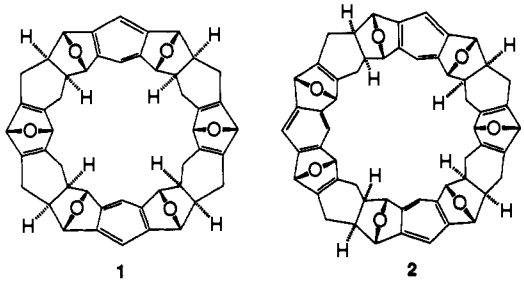
Scheme I. Synthetic Strategy Used To Prepare the Syn and Anti Angular Bisdienophiles **3** and **3a**, Respectively[a]



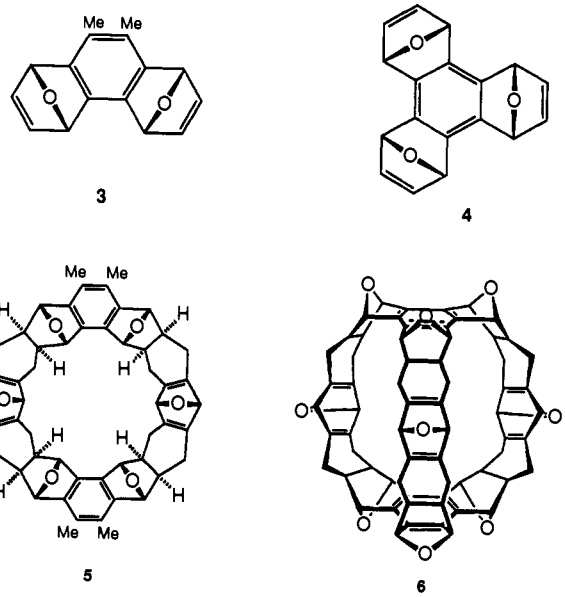
[a] Proximities of the protons that are indicated by arrows on **3** were confirmed by NOE difference spectroscopy.

Alder oligomerization.[12,13] In this procedure, appropriate bisdiene and bisdienophilic building blocks are combined by means of [4 + 2] cycloadditions, under alternate thermally-promoted and high-pressure-promoted conditions, to provide synthetic routes to a range of novel macropolycyclic structures. Moreover, we have demonstrated that each of these cycloadditions proceeds with *treble diastereoselectivity*.[11-16]



1 2

As part of a research program that was designed to increase the scope of this repetitive Diels–Alder methodology, the [*a*,*c*]-fused bisdienophile **3** and the C_{3v} trisdienophile **4** were identified as suitable building blocks to be employed as precursors to the macropolycyclic belt-like and the cage-like molecules, **5** and **6**, respectively, in a series of repetitive trebly-diastereoselective Diels–Alder oligomerizations.



The bicyclic nature of the dienophilic units that we have utilized[11-16] previously in the synthesis of the macropolycyclic compounds **1** and **2** is maintained in the structures of the angular syn bisdienophile **3** and the C_{3v} trisdienophile **4**. The [*a*,*c*]-fusion, which is present in the phenanthrene-based constitution of **3** however, breaks the symmetry of the dienophilic π-systems, i.e. $C_{2,7} \neq C_{3,6}$. The effect of this loss in the symmetry of the dienophilic π-systems in **3**, upon the diastereoselectivities exhibited in cycloadditions involving bisdienes, had to be ascertained in order to extend the generality of substrate-directed synthesis to the preparation of belt-like and cage-like compounds.

The Synthesis of the "Angular" Bisdienophiles. The angular syn and anti bisdienophiles, **3** and **3a**, respectively, can be disconnected to the angular bisaryne equivalent **7**. Hart has shown[17,18] that treatment of 4,5-dibromo-3,6-diiodo-*o*-xylene **10** with 2 molar equiv of *n*-butyllithium, followed by trapping in situ of the bisaryne equivalent **7** with 2 molar equiv of furan, afforded compounds with the phenanthrene bisendoxide skeleton. However, the stereochemical outcome of this synthetic procedure has not been investigated.

7

The synthesis of the angular bisdienophiles **3** and **3a** is outlined in Scheme I. Lithiation of the bisaryne precursor **10** with 3 molar equiv of *n*-butyllithium, followed by trapping in situ of the bisaryne equivalent with 2 molar equiv of furan, afforded an equimolar mixture of the angular syn and anti bisdienophiles, **3** and **3a**, respectively. Fractional crystallization of the crude reaction product from PhMe gave a pure sample of the angular anti bisdienophile **3a**. Column chromatography on the mother liquors was necessary in order to obtain the angular syn bisdienophile **3**.

The unambiguous relative configurational assignments of the syn and anti diastereoisomers, **3** and **3a**, were achieved[19] by X-ray crystallography (Figure 1). The solid-state crystal structures confirmed that the chromatographically least mobile diastereoisomer has the syn configuration. The chromatographically more mobile angular anti bisdienophile **3a** has a C_2 axis as its only

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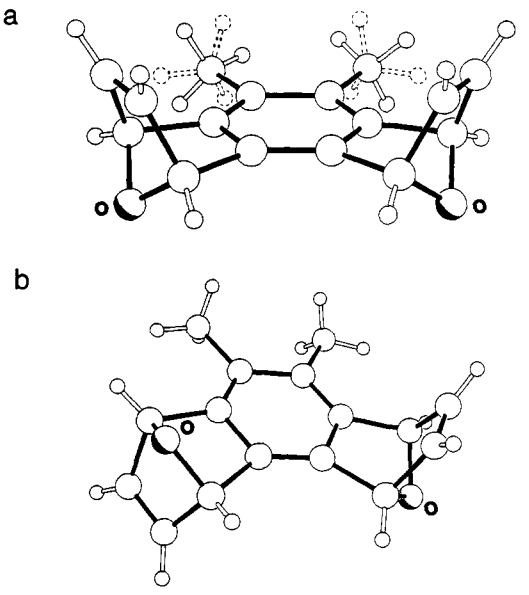
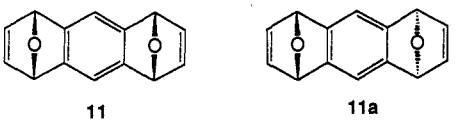


Figure 1. X-ray crystal structure of (a) the syn and (b) the anti angular bisdienophiles, **3** and **3a**, respectively. In compound **3**, the alternative orientations of the two methyl groups are shown with hatched atoms and bonds.

element of symmetry and crystallizes as a racemic mixture. This chiral building block has been resolved at analytical levels by both chiral GLC and HPLC.[20] Thus, if significant quantities of the anti isomer **3a** could be obtained in its optically pure form, the opportunity exists to construct chiral molecular ribbon-like polymers by carrying out repetitive Diels–Alder reactions on the chiral bisdienophles (+)-**3a** and (−)-**3a** with appropriate bisdienes.

The lower C_s and C_2 symmetries of the angular bisdienophiles **3** and **3a**, respectively, compared to their laterally-fused analogs, **11** and **11a**, respectively, is evident from the increased number of signals present in their respective ^1H and ^{13}C NMR spectra. In the ^1H NMR spectra, the signals for the olefinic hydrogen atoms 2,3,6,7-H of the spectroscopically-identical angular bisdienophiles **3** and **3a** both exhibit a vicinal and allylic coupling constant, $J_{1,2} = 2$ Hz, $J_{1,3} = 1$ Hz, respectively, to the bridgehead hydrogen atoms, 1,4,5,8-H. A coupling constant ($J_{2,3} = 6$ Hz)

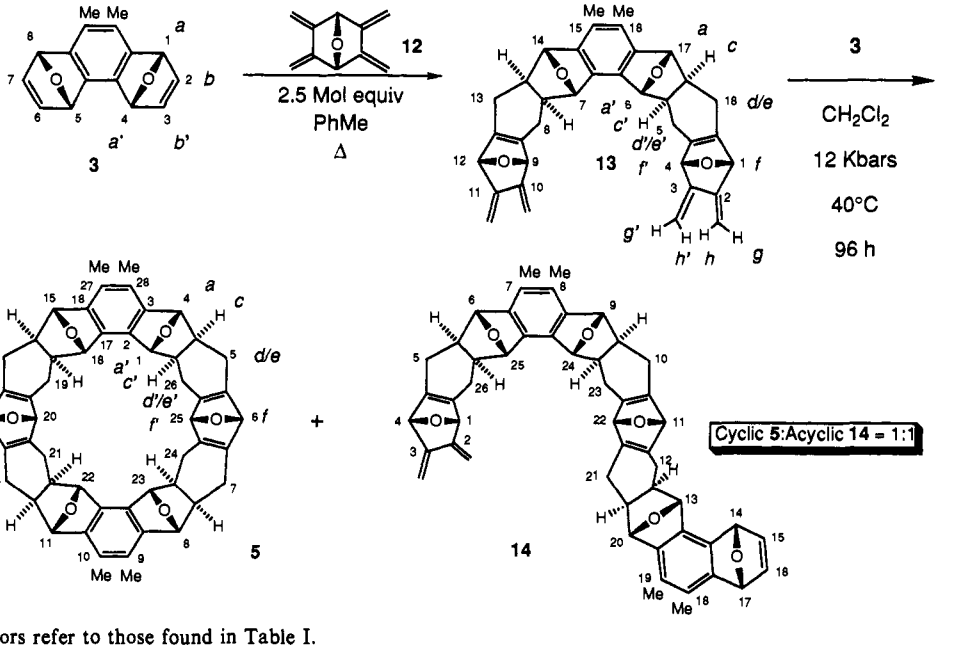


11 **11a**

is also observed between the signals in the ^1H NMR spectrum for the olefinic hydrogen atoms. NOE difference spectroscopy confirmed that the high-field signals in the ^1H NMR spectrum correspond to those hydrogen atoms, 1,2,7,8-H, located on the outer rim of the angular bisdienophile **3**, leaving the hydrogen atoms 3,4,5,6-H located on the inner rim of the dienophiles as the low-field signals (Table I).

Synthesis of the Angular Macropolycycle. Heating the angular syn bisdienophile **3** with 2.5 molar equiv of the bisdiene **12** under reflux in a solution of PhMe for 4 h in the absence of light afforded (Scheme II) a solid which was characterized as the 2:1 adduct **13**. The yield of the 2:1 adduct **13** from this tandem cycloaddition process is 91%. Importantly, in the formation of *both* the newly-formed cyclohexene rings in the 2:1 adduct **13**, syn/endo-H stereochemistry is generated. The treble diasteroselectivity, which characterizes the reactions of [*a*,*d*]-fused bisdienophiles has, therefore, been retained in this series of reactions based upon the [*a*,*c*]-fused angular syn bisdienophile **3**. The structural characterization of the 2:1 adduct **13** is supported by the identification (Table I) of (i) 15 signals in the ^1H NMR spectrum for all 15 sets of heterotopic hydrogen atoms and (ii) 15 observable resonances including three overlapping signals in the broadband-decoupled ^{13}C NMR spectrum which account fully for the 18 types of heterotopic carbon atoms present in **13**. The observation in the ^1H NMR spectrum of the signals associated with the 6,7-H and 14,17-H hydrogen atoms as sharp singlets that show no observable coupling confirms that the adjacent methine hydrogen atoms, 5a,7a-H and 13a,17a-H, respectively, adopt the endo configuration. Moreover, the [*a*,*c*]-fused angular syn bisdienophile **3** appears not only to exercise the same high degree of treble diastereoselectivity in its cycloadditions, compared to that exhibited by the [*a*,*d*]-fused analog **11**, but it also reacts faster with the bisdiene **12**. The configurational assignment to the 2:1 adduct **13** was confirmed by the outcome (Scheme II) of the macropolycyclization carried out between **13** and a further equivalent of the angular syn bisdienophile **3** under high pressure.

Scheme II. Molecular Building Blocks Used for the Synthesis of the Angular Macropolycyclic Derivative **5** and Its Constitutional Isomer **14**[a]



[a] Alphabetic descriptors refer to those found in Table I.

Scheme III. Treble Diastereoselectivity Operating between the Syn Angular Bisdienophile **3** and the 2:1 Adduct **13** in the Absence of Regiochemical Control To Afford the Constitutionally-Isomeric Compounds **5** and **14** via Pathways A and B, Respectively

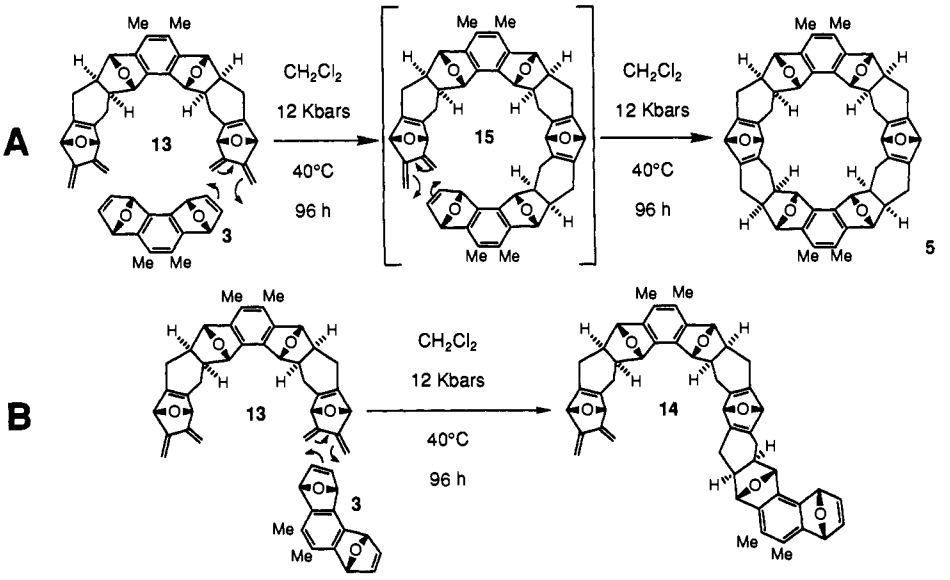


Table I. Comparison of the ^1H NMR Chemical Shifts[a] of Structurally-Related Hydrogen Atoms[b]

	a	*a'*	*b*	*b'*	*c*	*c'*	*d/e*	*d'/e'*	*f*	*f'*	*g*	*g'*	*h*	*h'*
3	5.73 (dd, 2 H)	5.78 (dd, 2 H)	6.84 (ddd, 2 H)	6.96 (ddd, 2 H)										
4	5.73 (dd, 6 H)		6.78 (dd, 6 H)											
5	4.91 (s, 4 H)	4.98 (s, 4 H)			1.37–1.48 (m, 4 H)	1.60–1.71 (m, 4 H)	2.30–2.80 (m, 16 H)	2.30–2.80	5.06 (s, 4 H)	5.06				
6	4.92 (s, 12 H)				1.58–1.62 (m, 12 H)		2.35–2.88 (m, 24 H)		5.10 (s, 6 H)					
13	5.02 (s, 2 H)	5.08 (s, 2 H)			1.70–1.88 (m, 8 H)	1.70–1.88	2.30–2.70 (m, 8 H)	2.30–2.70	4.99–5.00 (s, 2 H)	5.00–4.99 (s, 2 H)	5.10 (s, 4 H)	5.10	5.01 (s, 4 H)	5.01
16	5.30 (s, 4 H)	5.32 (s, 4 H)			1.16–1.38 (m, 8 H)	1.16–1.38	2.65–2.95 (m, 16 H)	2.65–2.95	6.86 (s, 2 H)	6.98 (s, 2 H)				
21	4.98 (s, 6 H)				1.68–1.81 (m, 6 H)		2.28–2.73 (m, 12 H)		5.02 (s, 6 H)		5.10 (br s, 6 H)		4.99 (br s, 6 H)	

[a] The spectra were recorded at ambient temperature on either a Brucker AM250 or WH 400 spectrometer using Me_4Si as the internal standard. The solvent in all cases was $CDCl_3$. [b] This provides a useful means of assessing the structural similarities and differences of the Diels–Alder oligomerization adducts. The alphabetic descriptors correspond with those shown in Schemes II, IV, and VI.

This procedure afforded the angular macropolycyclic derivative **5**, together with the novel acyclic constitutional isomer **14**.

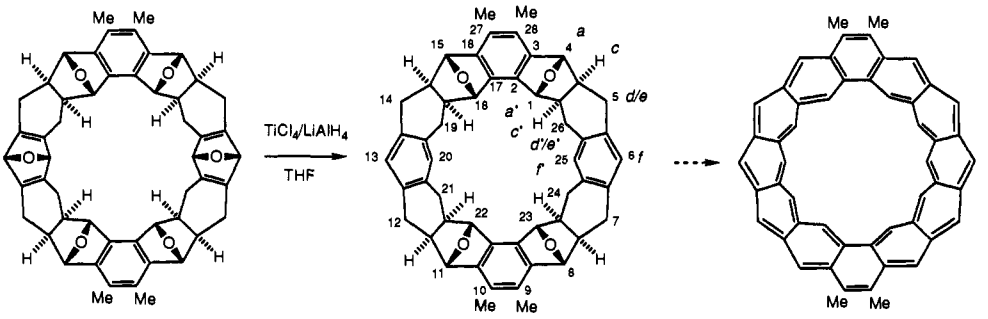
The [*a*,*c*]-fused disposition of the bicyclic dienophilic units in the angular syn bisdienophile **3** means that there are two possible regiochemical outcomes (Scheme III) for the initial intermolecular Diels–Alder reaction between **3** and **13**. Pathway A brings the two remaining reactive termini close together in the intermediate 2:2 adduct **15**. This mode of cycloaddition can be followed by an intramolecular macropolycyclization to afford the angular macropolycyclic derivative **5**. Pathway B locates the reactive termini in **14** too far apart for subsequent intramolecular cycloaddition. Indeed, reaction of the 2:1 adduct **13** with 1 molar equiv of the angular syn bisdienophile **3** under 12 kbar of pressure in CH_2Cl_2 at 40 °C for 96 h afforded (Scheme II) the two constitutionally-isomeric products **5** and **14** in equimolar proportions. The less chromatographically mobile product was characterized as the angular [12]cyclacene derivative **5** by high-field ^1H and ^{13}C NMR spectroscopies and FABMS. This compound revealed a strong molecular ion in the negative-ion FABMS at *m/z* 767 for $[M - H]^-$. The lack of a pronounced fragmentation pattern in the FABMS is consistent with a highly-stable macropolycyclic structure for **5**. Interestingly, replacement of the 15-crown-5/18-crown-6 matrix[21] employed in the FABMS experiment with the more conventional 3-nitrobenzyl alcohol

Table II. Crystal Data and Data Collection Parameters

data	**3**	**3a**
formula	$C_{16}H_{14}O_2$	$C_{16}H_{14}O_2$
formula weight	238.3	238.3
lattice type	monoclinic	monoclinic
space group	$P2_1/n$	$P2_1/n$
T, K	293	293
cell dimensions		
a, Å	9.458(2)	8.134(2)
b, Å	8.782(2)	8.877(3)
c, Å	14.853(4)	16.681(4)
β, deg	93.95(2)	90.77(2)
V, Å^3	1231	1204
Z	4	4
D_c, g cm^{-3}	1.29	1.31
F(000)	504	504
μ, mm^{-1}	0.67	0.65
θ range, deg	58	58
no. of unique reflections		
measd	1655	1620
obsd	1514	1478
no. of variables	180	186
R	0.052	0.049
R_w	0.056	0.059
weighting factor *p*	0.00050	0.00043

(20) We thank Prof. Dr. A. Mannschreck (Regensburg) and Prof. Dr. W. A. Konig (Hamburg) for these results.

Scheme IV. Deoxygenation of the Angular Macropolycyclic Derivative **5** To Afford the Dideoxy Compound **16**[a]



5 16 17

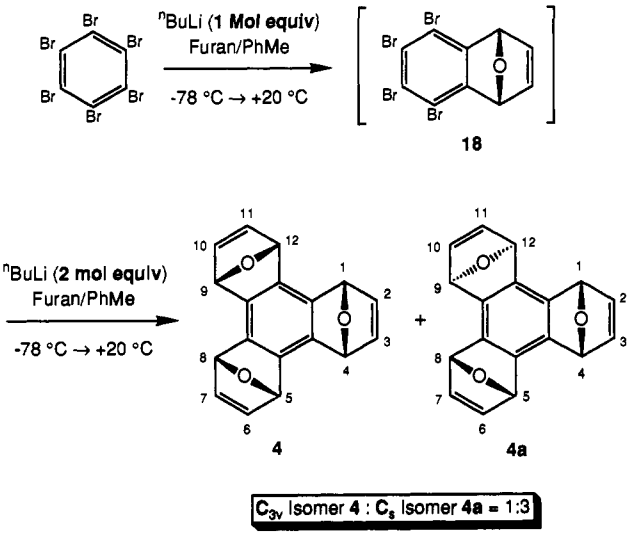
[a] Alphabetic descriptors refer to those found in Table I.

(NOBA) matrix resulted in a very strong pseudomolecular ion at m/z 921 for $[M - H + NOBA]^-$ in the negative-ion FABMS. This observation suggests that a stabilizing interaction[22] may be occurring between the macropolycyclic adduct **5** and the π-electron-deficient NOBA matrix, resulting in the detection of a supramolecular 1:1 complex under the conditions of the FABMS experiment. ^{1}H NMR spectroscopy on an equimolar mixture of **5** and NOBA, however, failed to provide any evidence for the existence of such an interaction in $CDCl_3$. The higher molecular symmetry (C_{2v}) of **5**—compared with that (C_1) of the asymmetric acyclic adduct **14**—is confirmed by the identification of (i) 11 signals in the ^{1}H NMR spectra for the 11 sets of heterotopic hydrogen atoms and (ii) 13 observable resonances including one overlapping signal in the broadband-decoupled ^{13}C NMR spectrum for the 14 types of heterotopic carbon atoms present in **5**. The ^{1}H NMR spectrum of **5** shows the presence of four bridgehead hydrogen atom environments, with signals at δ 4.91, 4.98, 5.06, and 5.06, for 4,8,11,15-H, 1,18,22,23-H, 6,13-H, and 20,25-H, respectively. In sharp contrast with the macropolycyclic derivative **5**, the chromatographically more-mobile product **14**, obtained from the high-pressure reaction, revealed a very weak molecular ion in the positive-ion FABMS at m/z 769 for $[M + H]^+$. This observation is consistent with the constitution we have proposed for the acyclic product **14**. Both the ^{1}H and ^{13}C NMR spectra are consistent with the C_1 symmetry of **14**. The appearance of the signals for the bridgehead hydrogen atoms, 6-H, 9-H, 13-H, 20-H, 24-H, and 25-H, as singlets in the ^{1}H NMR spectrum of **14** confirms that the adjacent methine hydrogen atoms all adopt the endo configuration. In the formation of **14**, syn/endo-H stereochemistry has been generated across *each* of the three newly-formed cyclohexene rings. The presence of both diene and dienophilic units in **14** can be inferred from the appearance in the ^{1}H NMR spectrum of signals associated with these two different termini. The acyclic product **14**—which is potentially a monomer for head-to-tail dimerization or polymerization—is another example of a chiral compound which could be resolved into its enantiomers.

Deoxygenation (Scheme IV) of the angular macropolycyclic derivative **5** afforded the dideoxy compound **16** in 58% yield. The structure of this compound is supported by the identification (Table I) of (i) 11 signals in the ^{1}H NMR spectrum for the 11 sets of heterotopic hydrogen atoms and (ii) 13 observable resonances including one overlapping signal in the broadband decoupled ^{13}C NMR spectrum for the 14 types of heterotopic carbon atoms present in the dideoxy compound **16**. So far, attempts to dehydrate this compound to afford an intermediate en route to the hydrocarbon **17** have not been successful.

The Synthesis of a Cage-like Compound. The successful introduction (Scheme II) of [*a*,*c*]-fused aromatic residues into the angular macropolycyclic derivative **5** raised the possibility that the central benzene ring may be used as a "trivalent" nucleus, supporting three bicyclic dienophilic units in an [*a*,*c*,*e*] relationship. This structural situation is illustrated (Scheme V) in the C_{3v} trisdienophile **4** and in the C_s trisdienophile **4a**. Unfortunately, treatment of hexabromobenzene with 3 molar equiv of *n*-butyllithium did not generate a trisaryne equivalent that would lead to **4** and **4a**. An alternative two-step synthetic procedure, however, was used to prepare small amounts of **4** and **4a**. The monoadduct **18** was produced in situ by the treatment of hexabromobenzene with 1.1 molar equiv of *n*-butyllithium at −78 °C in PhMe before being trapped with excess of furan. Further lithiation of **18** with 2.2 molar equiv of *n*-butyllithium at −78 °C followed by trapping in situ with excess of furan afforded the two diastereoisomeric trisdienophiles **4** and **4a**. Not only were these trisdienophiles produced in the statistically-expected ratio of 1:3 in favor of the C_s isomer **4a**, but the overall yields from the stepwise approach were 0.6% and 1.8%, for **4** and **4a**, respectively.[23,24] The relative configurations of the two trisdienophiles **4** and **4a** can be deduced easily from their ^{1}H and ^{13}C NMR spectra on account of their very different molecular symmetries—namely C_{3v} and C_s, respectively.

Scheme V. Synthetic Strategy Used To Prepare the C_{3v} and C_s Trisdienophiles **4** and **4a**, Respectively



Reaction (Scheme VI) of the C_{3v} trisdienophile **4** with 3.3 molar equiv of the bisdiene **12** in a solution of PhMe heated under

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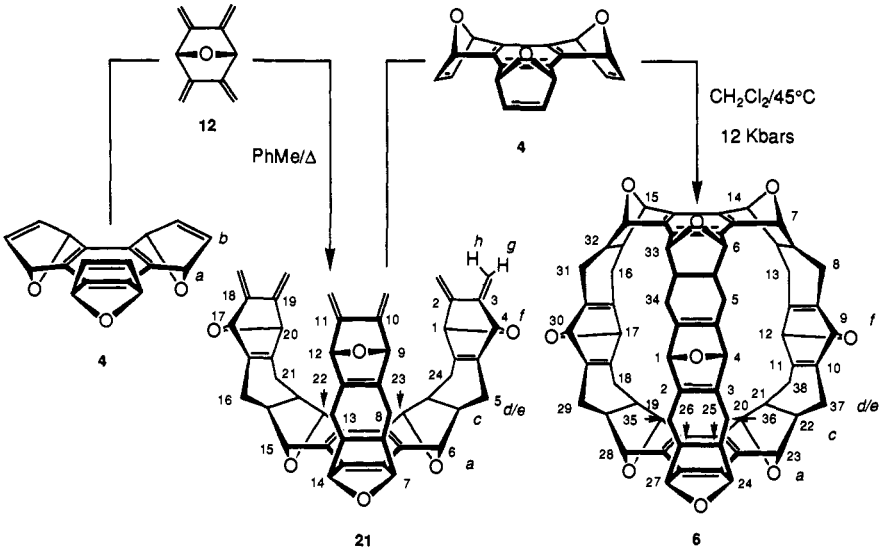
(23) Ashton, P. R.; Isaacs, N. S.; Kohnke, F. H.; D'Alcontres, G. S.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1261–1263.

(24) An alternative approach to the trisdienophiles **4** and **4a** has been described. See: Stringer, M. D.; Wege, D. *Tetrahedron Lett.* **1980**, *21*, 3831–3834. We would like to thank these authors for their comments regarding the possible application of their synthetic procedure to our work. For an improved synthesis of the trisdienophiles **4** and **4a**, see: Raymo, F. M.; Kohnke, F. H.; Cardullo, F.; Girreser, U.; Stoddart, J. F. *Tetrahedron* **1992**, *48*, 6827–6838.

Scheme VI. Molecular Building Blocks Used for the Synthesis of the Molecular Cage Compound Trinacrene **6**[a]



[a] Alphabetic descriptors refer to those found in Table I.

reflux for 14 h afforded the 3:1 adduct **21** in 48% yield.[23] The retention of C_{3v} molecular symmetry on going from **4** to **21** is confirmed by the observation (Table I) of (i) seven signals in the ^{1}H NMR spectrum for the seven sets of heterotopic hydrogen atoms and (ii) eight resonances in the broadband-decoupled ^{13}C NMR spectrum for the eight types of heterotopic carbon atoms present in **21**. The appearance of the signal for the bridgehead hydrogen atoms, 6,7,14,15,22,23-H, in the ^{1}H NMR spectrum as a singlet, indicating no vicinal coupling to the adjacent methine hydrogen atoms, is consistent with the production of syn/endo-H stereochemistry across all the newly-formed cyclohexene rings in **21**. Capping of **21** to give the molecular cage compound **6**, we have called trinacrene, was achieved[23] in a high-pressure reaction of **21** with 1 molar equiv of the C_{3v} trisdienophile **4** in CH_2Cl_2 at 50 °C under 10 kbar of pressure. This reaction afforded the molecular cage compound, trinacrene **6**. The ^{1}H NMR spectrum of **6** exhibits only five signals for the five sets of heterotopic hydrogen atoms present in trinacrene. This observation is consistent with the D_{3h} molecular symmetry of this compound. Further structural characterization of **6** was provided by positive-ion FABMS which revealed an intense molecular ion at m/z 991 for $[M + H]^+$, with very little fragmentation.

Conclusions

The family of Diels–Alder building blocks that we have identified here and elsewhere[11-16] has served as a vehicle for the establishment of a stepwise, highly-controlled synthetic methodology toward the production of several belt-like and cage-like compounds with complex molecular structures. Control of the outcome of these repetitive Diels–Alder reactions has been achieved with a high degree of oligoselectivity—on top of treble diastereoselectivity—by the alternate use of thermally-promoted and high-pressure-promoted cycloadditions. The utilization of the angular syn bisdienophile **3** and the C_{3v} trisdienophile **4** in the synthesis of the novel macropolycyclic derivatives, **5** and **6**, respectively, illustrates a significant extension to our stereoregular Diels–Alder oligomerization methodology. Furthermore, the increased flexibility offered by these new Diels–Alder building blocks anticipates the substrate-directed synthesis of compounds with increasingly novel and functioning molecular structures.

Experimental Section

General. Tetrahydrofuran (THF) was distilled from sodium benzophenone. Benzene, toluene, and hexane were dried using sodium wire prior to use. Decalin and furan were distilled from calcium hydride prior to use. High-pressure reactions were performed using CH_2Cl_2 as a solvent in a PTFE high-pressure reaction vessel. The press was a fully automated 20-kbar reaction system supplied by PSIKA Pressure Systems Limited, Derbyshire, England. Thin-layer chromatography (TLC) was performed on aluminum sheets coated with Merck 5554 Kieselgel 60F, visualization being either by an ultraviolet (UV) lamp, iodine vapor, or $Ce(SO_4)_2$/H_2SO_4 reagent followed by heating to ca. 100 °C in an oven. Column chromatography was performed using Kieselgel 60 (40–63-mm mesh, Merck 9385). Melting points were determined on a Reichart hot stage apparatus and are uncorrected. Microanalyses were performed by the University of Sheffield Microanalytical Service. Mass spectra (MS) were obtained from a Kratos MS80RF instrument. This instrument is equipped with a fast atom bombardment (FABMS) facility, operating at 8 keV using a Xenon primary atom beam. The matrix used was either 3-nitrobenzyl alcohol (NOBA) or a mixture of 15-crown-5 and 18-crown-6. Low-resolution MS were obtained on a Kratos MS 25 mass spectrometer using either electron impact mass spectrometry (EIMS) or chemical ionization mass spectrometry (CIMS), with ammonia as reagent gas. Unless specifically stated, ^{1}H nuclear magnetic resonance (NMR) spectra were recorded with either Bruker WH400 (400 MHz) or Bruker AM 250 (250 MHz) spectrometers, using tetramethylsilane as internal standard. All chemical shifts are quoted in ppm on the δ scale with all coupling constants expressed in hertz (Hz). ^{13}C NMR were recorded with a Bruker AM 250 (63.5-MHz) spectrometer using the JMOD pulse sequence.

X-ray Crystallography. X-ray diffraction measurements were performed on a Siemens P3/PC diffractometer for **3** and on a Nicolet R3m diffractometer for **3a** with graphite monochromated Cu Kα radiation using ω scans. Lattice parameters for both compounds were determined by least squares from 18 centered reflections. Intensities were corrected for the decay of two controlled reflections, measured every 50 reflections, and for Lorentz and polarization factors, but not for absorption. The structures were solved by direct methods and refined with full-matrix least squares. Reflections with $|F_o| > 3\sigma(|F_o|)$ were considered to be observed and were included in the refinements based upon F_o. A weighting function of the form $w^{-1} = \sigma^2(F) + pF^2$ was applied. Leading hydrogen atoms on methyl groups attached to sp^2 carbon atoms were located from ΔF maps. In compound **3**, two orientations, each of 50% occupancy, were identified for both methyl groups. All methyl groups were refined as idealized rigid bodies. The remaining hydrogens were placed in calculated positions (C–H distance 0.96 Å), assigned isotropic thermal parameters (U(H) = 1.2U_{eq}(C)), and allowed to ride on their parent carbon atoms. Parameters refined were the overall scale factor, isotropic extinction parameter g (correction of F_2 where $F^* = F_c[1.0 + 0.002gF^2/\sin(2\theta)]^{0.25}$), and positional and anisotropic thermal parameters for non-hydrogen atoms. Refinements converged with shift/error ratios less than unity for all variables. Final difference Fourier maps showed no significant features. Calculations for compound **3** were carried out using SHELXTL

PLUS (PC-Version)[25] and those for compound **3a** using the SHELXTL program system.[26]

4,5-Dibromo-*o*-xylene[27] (8). I_2 (0.4 g) was added to *o*-xylene (92 mL, 750 mmol). This was followed by dropwise addition of Br_2 (80 mL) over 2 h, maintaining the temperature at 0 °C throughout. The resultant solid cake was left at room temperature overnight before being dissolved in Et_2O (200 mL), washed with 2 N NaOH (2 × 100 mL), H_2O (2 × 100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a faintly pink colored oil which crystallized upon standing. Recrystallization from MeOH gave a white crystalline solid, which was characterized as the product **8** (140.3 g, 530 mmol, 70%): mp 88 °C (from MeOH) (lit.[27] mp 87–88 °C); EIMS *m/z* 264 for $[M]^+$; ^1H NMR (250 MHz, $CDCl_3$) δ 2.22 (6 H, s, 1,2-Me), 7.34 (2 H, s, 3,6-H); ^{13}C NMR (63.5 MHz, $CDCl_3$) δ 19.0 (C-1,2-Me), 121.0 (C-4,5), 134.1 (C-3,6), and 137.5 (C-1,2).

4,5-Dibromo-3,6-diiodo-*o*-xylene[18] (10). A solution of 4,5-dibromo-*o*-xylene (**8**) (2 g, 7.5 mmol) and HgO (5.25 g) in CF_3CO_2H (25 mL) was heated under reflux in an atmosphere of nitrogen for 2 h, during which time a thick white precipitate formed. After the mixture was cooled to room temperature, this precipitate was collected by filtration and suspended in H_2O (150 mL). I_2 (7.5 g) and KI (5 g) were added with further H_2O (100 mL), and the mixture was heated to 75–80 °C, with vigorous stirring, under an atmosphere of nitrogen for 8 h. After cooling, the reaction mixture was filtered, and the residue was dissolved in $CHCl_3$ (400 mL) and washed with $NaHSO_3$ (2 × 75 mL), $NaHCO_3$ (2 × 75 mL), and H_2O (2 × 100 mL). The organic extract was dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a crystalline solid. Recrystallization from MeOH gave a white crystalline solid, which was characterized as the product **10** (2.8 g, 5.4 mmol, 73%): mp 238–240 °C (from MeOH) (lit.[18] mp 239–240 °C); EIMS *m/z* 516 for $[M]^+$; ^1H NMR (250 MHz, $CDCl_3$) δ 2.75 (s, 1,2-Me); ^{13}C NMR (63.5 MHz, $CDCl_3$) δ 32.0 (C-1,2-Me), 110.8 (C-3,6), 129.7 (C-4,5) and 141.4 (C-1,2).

***rel*-(1*R*,4*S*,5*R*,8*S*)-1,4:5,8-Diepoxy-1,4,5,8-tetrahydro-9,10-dimethylphenanthrene (3) and *rel*-(1*R*,4*S*,5*S*,8*R*)-1,4:5,8-Diepoxy-1,4,5,8-tetrahydro-9,10-dimethylphenanthrene (3a).** *n*-Butyllithium (188 mmol, diluted with 500 mL of anhydrous C_6H_{14}) was added dropwise over a period of 5 h to a stirred solution of **10** (32.4 g, 62.8 mmol) and furan (32 mL, freshly distilled from CaH_2) in anhydrous PhMe (2 L) at −23 °C under an atmosphere of argon. Upon completion, the reaction mixture was allowed to warm up to room temperature and stirred overnight. The reaction was quenched with H_2O (25 mL) and stirred vigorously for 30 min. The organic extract was washed with H_2O (3 × 500 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting light brown gum was subjected to column chromatography on silica gel, using $CHCl_3$ containing 1% ^{i}PrOH as eluant, to afford, in order of elution, a white crystalline solid, which was characterized as the anti isomer **3a** (4.65g, 19.5 mmol, 31%), followed by another white crystalline solid, which was characterized as the syn isomer **3** (4.83 g, 20.3 mmol, 32%).

Anti isomer 3a: mp 164–166 °C (from PhMe); EIMS *m/z* 238 for $[M]^+$; ^1H NMR (250 MHz, $CDCl_3$) δ 2.15 (6 H, s, 9,10-Me), 5.71 and 5.73 (2 × 2 H, 2 × dd, $J_{1,2} = J_{3,4} = 2$ Hz, $J_{1,3} = J_{2,4} = 1$ Hz, 1,8-H and 4,5-H), 6.90 and 6.98 (2 × 2 H, 2 × ddd, $J_{2,3} = 6$ Hz, $J_{1,2} = J_{3,4} = 2$ Hz, $J_{1,3} = J_{2,4} = 1$ Hz, 2,7-H and 3,6-H); ^{13}C NMR (63.5 MHz, $CDCl_3$) δ 15.2 (C-9, 10-Me), 80.7 and 81.1 (C-1,4,5,8), 125.7 (C-9,10), 136.3 (C-4a,4b), 141.7 and 141.9 (C-2,3,6,7), and 142.7 (C-8a,10a). Single crystals of **3a** that were suitable for X-ray structural analysis were obtained by vapor diffusion of C_5H_{12} into a $CDCl_3$ solution of **3a** at room temperature.[19]

Syn isomer 3: mp 194–196 °C (from PhMe); EIMS *m/z* 238 for $[M]^+$; ^1H NMR (400 Mhz, $CDCl_3$) δ 2.16 (6 H, s, 9,10-Me), 5.73 (2 H, dd, $J_{1,2} = 2$ Hz, $J_{1,3} = 1$ Hz, 1,8-H), 5.78 (2 H, dd, $J_{3,4} = 2$ Hz, $J_{2,4} = 0.5$ Hz, 4,5-H), 6.84 (2 H, ddd, $J_{2,3} = 6$ Hz, $J_{1,2} = 2$ Hz, $J_{2,4} = 0.5$ Hz, 2,7-H), and 6.96 (2 H, ddd, $J_{2,3} = 6$ Hz, $J_{3,4} = 2$ Hz, $J_{1,3} = 1$ Hz, 3,6-H); ^{13}C NMR (63.5 MHz, $CDCl_3$) δ 15.3 (C-9,10-Me), 80.8 and 80.9 (C-1,4,5,8), 125.5 (C-9,10), 136.3 (C-4a,4b), 141.8 and 142.3 (C-2,3,6,7), and 143.0 (C-8a,10a). Single crystals of **3** that were suitable for X-ray structural analysis were obtained by slow evaporation of a MeOH solution of **3** at room temperature.[19]

***rel*-(1*R*,4*S*,5a*S*,6*S*,7*R*,7a*R*,9*R*,12*S*,13a*S*,14*S*,17*R*,17a*R*)-1,4:6,17:7,14:9,12-Tetraepoxy-1,4,5,5a,6,7,7a,8,9,12,13,13a,14,17,17a,18-hexadecahydro-15,16-dimethyl-2,3,10,11-tetramethylideneheptaphene (13).** A solution of the syn bisdienophile **3** (500 mg, 2.1 mmol) and the bisdiene **12** (766 mg, 5.25 mmol) in anhydrous PhMe (80 mL) was heated under reflux for 4 h in an atmosphere of argon in the absence of light. After cooling to room temperature and removal of solvent in vacuo, the yellow residue was subjected to column chromatography on silica gel, using $CHCl_3$ containing 1.5% MeOH as the eluant, to afford a white solid, which was characterized as the product **13** (1004 mg, 1.9 mmol, 90%): mp >300 °C dec; positive-ion FABMS *m/z* 553 for $[M + Na]^+$, 531 for $[M + H]^+$; ^1H NMR (250 MHz, $CDCl_3$) δ 1.70–1.88 (4 H, m, 5a,7a,13a,17a-H), 2.13 (6 H s, 15,16-Me), 2.30–2.70 (8 H, m, 5,8,13,18-CH_2), 4.99 and 5.00 (2 × 2 H, 2 × s, 1,4,9,12-H), 5.01 (4 H, s, 2a,3a,10a,11a-H_Z), 5.02 and 5.08 (2 × 2 H, 2 × s, 6,7,14,17-H), 5.10 (4 H, s, 2a,3a,10a,11a-H_E); ^{13}C NMR (63.5 MHz, $CDCl_3$) δ 15.3 (C-15, 16-Me), 25.8 and 26.0 (C-5,8,13,18), 42.8 and 43.4 (C-5a,7a,13a,17a), 84.3 and 85.2 (C-1,4,6,7,9,12,14,17), 100.8 and 101.0 (C-2a,3a,10a,11a), 125.5 (C-15,16), 133.1 (C-6a,6b), 143.0, 143.2, 144.3, and 144.4 (C-2,3,4a,8a,10,11,12a,14a,16a,18a). Anal. Calcd for $C_{36}H_{34}O_4$: C, 81.5; H, 6.46. Found: C, 81.6; H, 6.46.

***rel*-(1*R*,4*S*,4a*S*,6*r*,7a*R*,8*R*,11*S*,11a*S*,13*r*,14a*R*,15*R*,18*S*,18a*S*,20*s*,21a*R*,22*R*,23*S*,23a*S*,25*s*,26a*R*)-1,4:6,25:8,23:11,22:13,20:15,18-Hexaepoxy-1,4,4a,5,6,7,7a,8,11,11a,12,13,14,14a,15,18,18a,19,20,21,21a,22,23,23a,24,25,26,26a-octacosahydro-9,10-dimethyl-2,17:3,16-(27,28-dimethyl)ethenoundecaphene (5) and *rel*-(1*S*,4*R*,5a*R*,6*R*,9*S*,9a*S*,11*R*,12a*R*,13*S*,14*R*,17*S*,20*R*,20a*R*,20a*S*,22*S*,23a*R*,24*R*,25*S*,25a*S*)-1,4:6,25:9,24:11,22:13,20:14,17-hexaepoxy-1,2,3,4,5,5a,6,9,9a,10,11,12,12a,13,14,17,20,20a,21,22,23,23a,24,25,25a,26-hexacosahydro-7,8,18,19-tetramethyl-2,3-bismethylenephenanthro[3,2-*f*]octaphene (14).** A solution of the syn bisdienophile **3** (200 mg, 0.95 mmol) and the 2:1 adduct **13** (450 mg, 0.85 mmol) in CH_2Cl_2 was introduced into a PTFE high-pressure reaction vessel and subjected to 12 kbars of pressure for 48 h, with the temperature being maintained at 40 °C. After cooling and depressurization, the solvent was removed in vacuo and the light-brown residue subjected to column chromatography on silica gel, using CH_2Cl_2 containing 3% ^{i}PrOH as the eluant, to yield, in order of elution, a white solid, which was characterized as the acyclic product **14** (41 mg, 0.053 mmol, 6%) followed by another white solid, which was characterized as the macropolycyclic derivative **5** (53 mg, 0.069 mmol, 8.1%).

Acyclic adduct 14: mp >300 °C dec; positive-ion FABMS *m/z* 769 for $[M + H]^+$; ^1H NMR (250 MHz, $CDCl_3$) δ 1.65–1.90 (6 H, m, 5a,9a,12a,20a,23a,25a-H), 2.06, 2.08, 2.09, and 2.14 (4 × 3 H, 4 × s, 7,8,18,19-Me), 2.30–2.66 (12 H, m, 5,10,12,21,23,26-CH_2), 4.92–5.01 (7 × 2 H, 7 × s, 1,2a_Z,2a_E,3a_Z,3a_E,4,6,9,11,13,14,17,20,22,24,25-H), 5.69–5.72 (2 × 1 H, 2 × dd, $J_{14,15} = J_{16,17} = 2$ Hz, $J_{14,16} = J_{15,17} = 1$ Hz, 14,17-H), 6.90 and 6.96 (2 × 1 H, 2 × ddd, $J_{15,16} = 6$ Hz, $J_{14,15} = J_{16,17} = 2$ Hz, $J_{14,16} = J_{15,17} = 1$ Hz, 15,16-H). Anal. Calcd for $C_{52}H_{48}O_6$: C, 81.2; H, 6.29. Found: C, 80.8; H, 6.12.

Macropolycyclic Compound 5: mp >300 °C dec; negative-ion FABMS *m/z* 767 for $[M - H]^-$, 921 for $[M - H +$ nitrobenzyl alcohol$)]^-$; ^1H NMR (250 MHz, $CDCl_3$) δ 1.37–1.48 (4 H, m, 4a,7a,11a,14a-H), 1.60–1.71 (4 H, m, 18a,21a,23a,26a-H), 2.12 (12 H, s, 9,10,27,28-Me), 2.30–2.80 (16 H, m, 5,7,12,14,19,21,24,26-CH_2), 4.91 (4 H, s, 4,8,11,15-H), 4.98 (4 H, s, 1,18,22,23-H), 5.06 (4 H, s, 6,13,20,25-H); ^{13}C NMR (63.5 MHz, $CDCl_3$) δ 15.5 (C-9,10,27,28-Me), 27.1 and 27.2 (C-5,7,12,14,19,21,24,26), 43.6 and 44.3 (C-4a,7a,11a,14a,18a,21a,23a,26a), 83.4 and 83.7 (C-1,4,8,11,15,18,22,23), 86.5 (C-6,13,20,25), 125.2 (C-9,10,27,28), 133.2 (C-2,17,22a,22b), 143.7 (C-3,8a,10a,16), 152.3 and 152.5 (C-5a,6a,12a,13a,19a,20a,24a,25a). Anal. Calcd for $C_{52}H_{48}O_6$: C, 81.2, H, 6.29. Found: C, 81.2; H, 6.19.

***rel*-(1*R*,4*S*,4a*S*,7a*R*,8*R*,11*S*,11a*S*,14a*R*,15*R*,18*S*,18a*S*,21a*R*,22*R*,23*S*,23a*S*,26a*R*)-1,4:8,23:11,22:15,18-Tetraepoxy-1,4,4a,5,7,7a,8,11,11a,12,14,14a,15,18,18a,19,21,21a,22,23,23a,24,26,26a-tetracosahydro-9,10-dimethyl-2,17:3,16-(27,28-dimethyl)ethenoundecaphene (16).** $TiCl_4$ (1.5 mL, 13.7 mmol) was added to THF (50 mL) with vigorous stirring at 0 °C under an atmosphere of nitrogen. After addition of $LiAlH_4$ (300 mg, 7.9 mmol), the reaction mixture was heated to reflux for 5 min. After cooling to 0 °C, a suspension of the macropolycyclic derivative **5** (150 mg, 0.19 mmol) in THF (50 mL) was added dropwise over 20 min. The reaction mixture was stirred at room temperature for 20 H, after which time Et_3N (2 mL, 14 mmol) was added and the mixture was poured into brine (300 mL). After extraction with CH_2Cl_2, the organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was subjected to column chromatography on silica gel, using $CHCl_3$ containing 1% MeOH as eluant, to afford a white solid, which was characterized as the

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dideoxy compound **16** (81 mg, 0.11 mmol, 58%): mp >250 °C dec; Positive-ion FABMS m/z 736 for $[M + H]^+$; ^1H NMR (270 MHz, CD_2Cl_2) δ 1.16–1.38 (8 H, m, 4a,7a,11a,14a,18a,21a,23a,26a-H), 2.26 (12 H, s, 9,10,27,28-Me), 2.65–2.95 (16 H, m, 5,7,12,14,19,21,24,26-CH_2), 5.30 (4 H, s, 4,8,11,15-H), 5.32 (4 H, s, 1,18,22,23-H), 6.86 (2 H, s, 6,13-H), and 6.98 (2 H, s, 20,25-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.8 (C-9,10,27,28-Me), 31.7 and 32.5 (C-5,7,12,14,19,21,24,26), 46.6 (C-4a,7a,11a,14a,18a,21,23a,26a), 82.5 and 82.7 (C-1,4,8,11,15,18,22,-23), 125.2 (C-9,10,27,28), 125.9 and 126.1 (C-6,13,20,25), 134.0 (C-2,17,22a,22b), 138.0 and 138.6 (C-5a,6a,12a,13a,19a,20a,24a,25a), and 145.0 (C-3,8a,10a,16).

***rel*-(1*R*,4*S*,5*R*,8*S*,9*R*,12*S*)-1,4:5,8:9,12-Triepoxy-1,4,5,8,9,12-hexahydrotriphenylene (4) and *rel*-(1*R*,4*S*,5*R*,8*S*,9*S*,12*R*)-1,4:5,8:9,12-Triepoxy-1,4,5,8,9,12-hexahydrotriphenylene (4a).**[24] *n*-Butyllithium (60 mmol, diluted with 60 mL of anhydrous C_6H_{14}) was added dropwise over a period of 4 h to a stirred solution of hexabromobenzene (33 g, 59.8 mmol) and furan (90 mL, freshly distilled from CaH_2) in anhydrous PhMe (1.8 L) at −78 °C under an atmosphere of argon. Upon completion of the addition, the reaction mixture was allowed to warm up to room temperature (16 h) before being cooled again to −78 °C, prior to the addition of further *n*-butyllithium (120 mmol, diluted with 120 mL of anhydrous C_6H_{14}) in a dropwise manner over 8 h. After warming up to room temperature, the reaction mixture was stirred overnight before being quenched by addition of H_2O (50 mL) and stirred vigorously for 30 min. The organic extract was washed with H_2O (3 × 100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was subjected to column chromatography on silica gel, using $CHCl_3$–CH_2Cl_2 (1:1 v/v) as the eluant, to afford, in order of elution, a white crystalline solid, which was characterized as the C_s isomer **4a** (300 mg, 1.1 mmol, 1.8%) and another white crystalline solid which was characterized as the C_{3v} isomer **4** (100 mg, 0.36 mmol, 0.6%).

***C*$_s$ isomer 4a**: mp >250 °C dec; EIMS m/z 276 for M^+; ^1H NMR (400 MHz, $CDCl_3$) δ 5.68 (2 H, m, 1,8-H), 5.69 (2 H, m, 9,12-H), 5.75 (2 H, m, 4,5-H), 6.77 (2 H, m, 3,6-H), 6.88 (2 H, m, 10,11-H), and 6.89 (2 H, m, 2,7-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 79.9, 80.0, and 80.1 (C-1,4,5,8,9,12), 134.0, 134.3, and 134.6 (C-4a,4b,8a,8b,12a,12b), 140.8, 140.9, and 141.1 (C-2,3,6,7,10,11).

***C*$_{3v}$ isomer 4**: mp >250 °C dec; EIMS m/z 276 for M^+; ^1H NMR (400 MHz, $CDCl_3$) δ 5.73 (6 H, m, 1,4,5,8,9,12-H), 6.78 (6 H, m, 2,3,6,7,-10,11-H).

***rel*-(1*R*,4*S*,5a*R*,6*S*,7*R*,7a*S*,9*R*,12*S*,13a*R*,14*S*,15*R*,15a*S*,17*R*,20*S*,21a*R*,-22*S*,23*R*,23a*S*)-1,4:6,23:7,14:9,12:15,22:17,20-Hexaepoxy-1,4,5,5a,6,7,-7a,8,9,12,13,13a,14,15,15a,16,17,20,21,21a,22,23,23a,24-tetracosahydro-2,3,10,11,18,19-hexamethylidenetrianthylene (21).** A solution of the bisdiene **12** (105 mg, 0.73 mmol) and the all-*syn* trisdienophile **3** (61 mg, 0.22 mmol) in anhydrous PhMe (20 mL) was heated under reflux for 16 h under an atmosphere of argon. After removal of the solvent in vacuo, the residue was subjected to column chromatography on silica gel, using CH_2Cl_2–EtOAc as eluant, to afford a crystalline solid after recrystallization from $CHCl_3$, which was characterized as the product **21** (76 mg, 0.1 mmol, 48%): mp >250 °C; positive-ion FABMS m/z 715 for $[M + H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 1.68–1.81 (6 H, m, 5a,7a,13a,-15a,21a,23a-H), 2.28–2.43 and 2.66–2.73 (2 × 6 H, 2 × m, 5,8,13,16,-21,24-CH_2), 4.98 (6 H, s, 6,7,14,15,22,23-H), 4.99 (6 H, br s, 2a,3a,10a,11a,18a,19a-H_Z), 5.02 (6 H, br s, 1,4,9,12,17,20-H), 5.10 (6 H, br s, 2a,3a,10a,11a,18a,19a-H_E).

1,4:6,33:7,14:9,12:15,32:17,30:19,28:20,23:24,27-Nonaepoxy-1,4,5,-5a,6,7,7a,8,9,12,13,13a,14,15,15a,16,17,18,18a,19,20,21,22,23,24,25,26,-27,28,28a,29,30,31,31a,32,33,33a-octatriacontahydro-2,26:3,25:10,22:11,21-tetramethanoanthra[2,3-*f*]triphenyleno[2,3-*f*]octaphene (6). A solution of the C_{3v} trisdienophile **3** (14 mg, 0.05 mmol) and the 3:1 adduct **21** (36 mg, 0.05 mmol) in CH_2Cl_2 (10 mL) was introduced into a PTFE high-pressure reaction vessel, and the reaction mixture was subjected to 10 kbars for 150 h, with the temperature being maintained at 50 °C. After cooling and depressurization, the solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel, using $CHCl_3$ containing 2% MeOH as eluant, to afford the product **6** as a crystalline solid after recrystallization from MeOH (2 mg, 2 μmol, 4%): mp >300 °C dec; positive-ion FABMS m/z 991 for $[M + H]^+$; ^1H NMR (250 MHz, $CDCl_3$) δ 1.58–1.62 (12 H, m, 5a,7a,13a,15a,18a,21,22,25,26,-28a,31a,33a-H), 2.35–2.45 and 2.76–2.88 (2 × 12H, 2 × m, 5,8,13,-16,18,29,31,34,35,36,37,38-CH_2), 4.92 (12 H, s, 6,7,14,15,19,20,23,-24,27,28,32,33-H), 5.10 (6 H, s, 1,4,9,12,17,30-H).

Supplementary Material Available: X-ray crystal structure data for **3** (10 pages); observed and calculated structure factors (4 pages). Ordering information is given on any current masthead page.