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The Synthesis of U-Shaped Cavity Molecules with "Inner-Surface" Functionality

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Abstract: New U-shaped cavity molecules with inner-surface functionalisation, eg **19** and **20**, have been prepared by stereoselective reaction of cyclopentadiene onto linear *bis*-(7-oxanorbornenes) **18** and **17** respectively. The norbornene π-centres of cavity molecules **19, 20** are reacted with DMAD/Ru to yield rigid *bis*-cyclobutenes **21** and **22** which serve as a common entry point to advanced cavity systems with further inner-surface functionalisation (CO, O, alkene). This is achieved by reaction of **21** or **22** with appropriate cyclic dienes (cyclopentadienones, isobenzofurans, furan and 6,6-dimethylfulvene) in highly specific cycloaddition reactions.

There are now several techniques which are available for the preparation of U-shaped cavity molecules and molecular belts based on a rigid or semi-rigid alicyclic framework.[1] Almost without exception, however, the inner face of such systems are free of functionalisation. The ability to incorporate inner-functionality improves the specificity of such systems when being designed as hosts to provide enzyme-like pockets or best-fit host-guest systems which depend on self-assembly using non-covalent bonding interactions. While one of the long-term objectives of our synthetic program in this area is to prepare molecular belts functionalised on the inner-surface (Fig. 1), this report addresses only the first two stages of the program.[2]

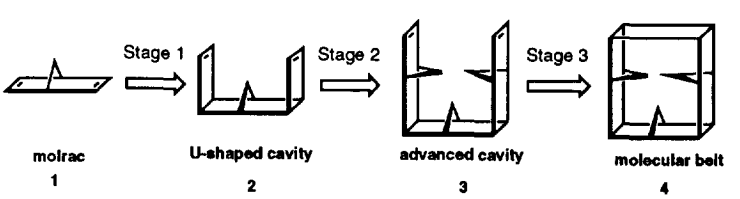
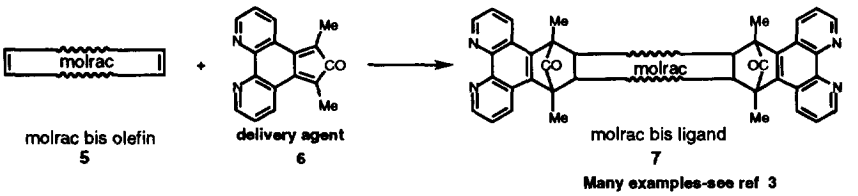


Figure 1: Building hierarchy for the construction of inner functionalised Molecular Belts

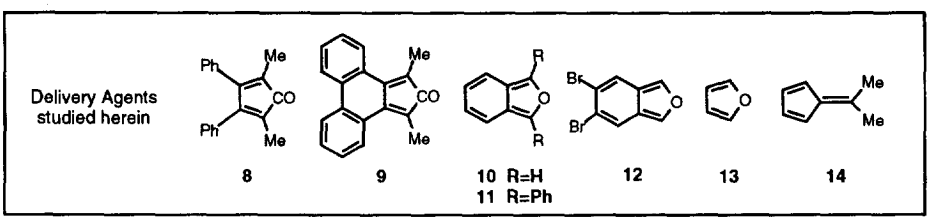
We have previously demonstrated that molrac *bis*-alkenes **1** can be functionalised through the dual application of a cycloaddition reaction (Scheme 1) using the dienone **6** to deliver the functionality (delivery agents) and this approach forms the core of our current strategy.[3] In the present case, we have chosen to use *bis*-alkenes **20-22** to provide ether oxygens on the inner-surface of the cavity (stage 1).

This paper is dedicated to Professor Arthur J. Birch, who, as a cofounder of the Research School of Chemistry at the Australian National University, fostered the careers and inspired the minds of many destined to become Australia's leading chemists.



Scheme 1

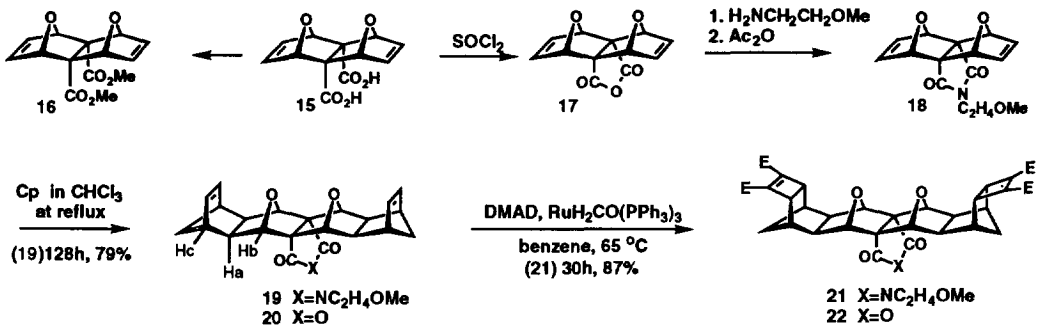
Additional functionality is then added in stage 2 through the cycloaddition step with a diene chosen from the selection **8-14** (Scheme 2). This bilateral construction methodology substantially increases the efficiency of the synthesis.



Scheme 2

Foremost in this study, was a requirement to determine cycloaddition specificities with these different dienes so that, in combination with the shape of the starting molrac *bis*-alkene, these factors could be used to forecast the final geometry of the cavity molecule. An additional factor was to help decide which types of cyclic 1,3-dienes might be embellished with specific functionality and act as new delivery agents. In selecting the route outlined in Scheme 3, we appreciated that the bridge oxygens would not only provide inner-surface functionality but they would provide a key element in governing reactivity and stereoselectivity in the assembly of the host.

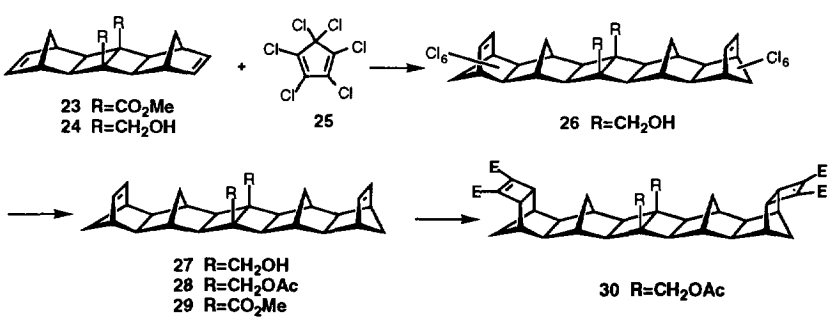
Tetracyclic *bis*-alkene **15** (Scheme 3) is used as our entry point for this work since it is available in one step from furan and acetylene dicarboxylic acid according to Alder's original report.[4] From earlier work in this area using the derived diester **16**,[5] we noted its propensity to undergo retro-Diels-Alder fragmentation at quite low temperatures. Accordingly, **16** was rejected and we turned our attention to the use of the related anhydride **17** and imide **18**, each of which exhibit significantly higher thermal stability. Anhydride **17** was prepared from the diacid **15** by treatment with thionyl chloride following the work of others.[6] Conversion of **17** to the succinimide **18** was achieved in two steps by reaction with 2-methoxyethylamine in chloroform at reflux and cyclisation of the resultant amic acid with sodium acetate in acetic anhydride. Conversion to the *N*-substituted imide series provided molecules with better solubility and chromatographic characteristics than the corresponding anhydrides.



Scheme 3

The addition of cyclopentadiene onto the π-bonds of 7-oxonorbornenes **17** and **18** occurred in high yield to form the U-shaped cavity molecules **19** and **20** respectively. The high selectivity observed in these cycloadditions is a direct consequence of the interaction of the lone pair electrons of the oxygen bridges, first by interaction with the adjacent π bond which lowers their LUMO energy and accounts for the increased reactivity, and secondly by interaction with the incoming diene in the transition state leading to adduct formation which dictates the stereoselectivity.

The relatively mild conditions (56 °C, 128 h) used in the conversion of *bis*-(7-oxanorbornenes) **17**, **18** to the U-shaped cavity molecules **19** and **20** respectively, contrast sharply with existing methods for the preparation of U-shaped cavity molecules from alicyclic precursors containing norbornene end-groups. The preparation of *bis*-norbornene **28** *en route* to cavity *bis*-cyclobutene **30**, described by us elsewhere,[7] typifies the alternative methodology and one of its major limitations (Scheme 4). Thus the ester groups in **23** could not be retained in the process to form **29** directly and required prior reduction to the diol **24** prior to high temperature (140 °C, 24 h) cycloaddition with perchlorocyclopentadiene **25** to achieve the desired bent geometry present in **26** and this was followed by vigorous reductive dechlorination (hence the need for prior reduction of the ester groups) to return to the carbocyclic product **27**. Conversion of the diacetate **28** to *bis*-cyclobutene **30** by reaction with dimethyl acetylenedicarboxylate proceeded smoothly under Mitsudo conditions (Ru catalyst) and these same conditions were used in the transformation of *bis*-norbornenes **19**, **20** to the respective *bis*-cyclobutenes **21** or **22** (see below).

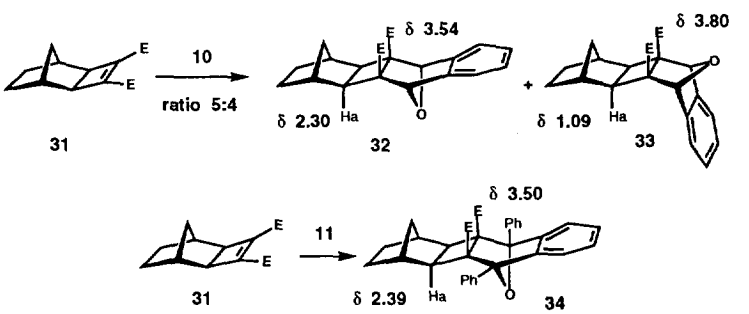


Scheme 4

The structure assigned to *bis*-adducts **19, 20** follows from the C_{2v} symmetry evident in the ^1H NMR whilst the stereochemistry follows from the lack of coupling between Ha and the oxygen bridgehead proton Hb which indicates that *exo*-attack has occurred on the π-bond of **17, 18.** Equally diagnostic is the coupling of Ha with the allylic bridgehead proton Hc of the newly formed norbornene which indicates the *endo*-fusion of this group.

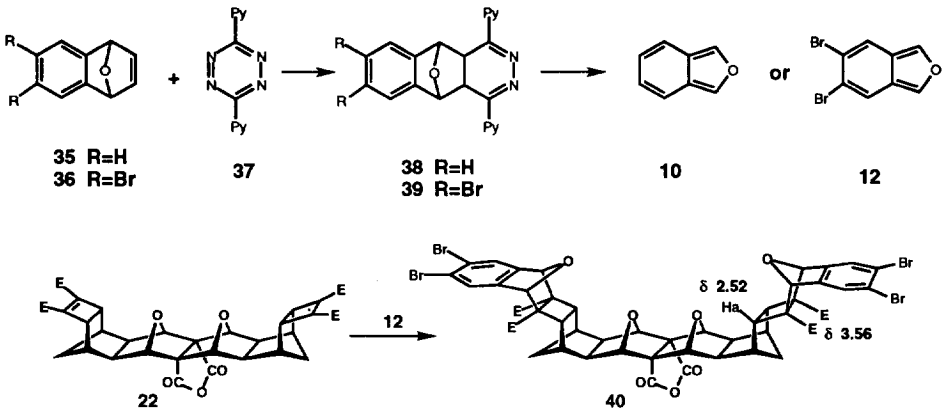
Extending the cavity walls requires reactions which exhibit high and predictable facial selectivity. In the first step of this process the norbornene π-bonds of **19, 20** are subjected to a [2π+2π] Ru-catalysed addition to DMAD in which steric constraints dictate a single stereochemical outcome, ie formation of **21** and **22** exclusively.[8] This reaction incorporates into the growing cavity two highly dienophilic double bonds each of which have one face screened by a methylene bridge. Consequently, [4π+2π] cycloadditions of dienes to these dienophiles deepen the cavity in the desired fashion.

The availability of both stereoisomers **32** and **33**,[5] formed in the reaction of isobenzofuran **10** with cyclobutene **31**, provides standard chemical shift data to help assign stereochemistry to other isobenzofuran cycloadducts (Scheme 5). The anisotropy of the aromatic ring holds the key: where there is a *syn*-relationship between the ester groups and the aromatic ring, as in the extended isomer **32**, this is reflected in an upfield shift of the ester methyl protons relative to those in **33** (Δ = 0.26 ppm); similarly when the aromatic ring is proximate to the bridgehead protons Ha, there is an upfield shift , eg those in **33** are significantly shifted relative to those in **32** (Δ = 1.21 ppm). Thus, the single adduct formed from the reaction of 1,3-diphenylisobenzofuran **11** with **31** is readily assigned the extended stereochemistry **34** by comparison of the relevant Ha proton shifts and the ester resonances with those in **32** (see annotated shifts in Scheme 5).



Scheme 5

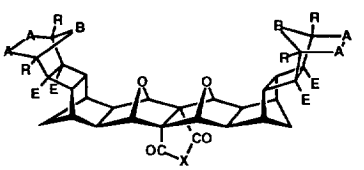
Reaction of 4,5-dibromoisobenzofuran **12** (formed by the *s*-tetrazine route shown in Scheme 6)[9] with the *bis*-cyclobutene anhydride **22** afforded exclusively the *bis*-adduct **40.** This stereochemical assignment again followed from comparison of the chemical shifts for **40** (Ha δ 2.52, ester methyl δ 3.56) with models **32** and **33.** Similar exclusive formation of a single adduct is exhibited by reaction of isobenzofuran **12**, also formed *in situ* by the *s*-tetrazine method, with anhydride **22** *en route* to *bis*-adduct **41.** These results highlight an important difference between U-shaped cavity structures where single isomers are formed and the simple cyclobutene **31** where stereoisomeric mixtures are produced. This difference in stereospecificity for cavity structures **21** and **22** may well indicate yet another strategic role for the oxygen bridges at the base of the cavity.



Scheme 6

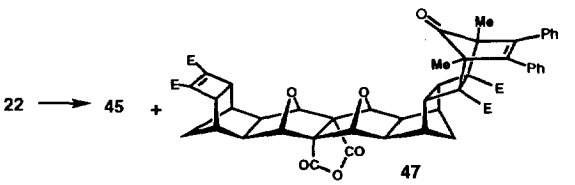
The preference for the Alder-transition state products (ester groups proximate to the π-system) is followed without exception for reactions of cyclic dienes **8-14** with *bis*-cyclobutenes **21** or **22**, for example 6,6-dimethylfulvene **14** reacts with **22** to produce *bis*-adduct **44**, hemicyclone **8** gives **45** (a 1:1 adduct **47** is also isolated; cf Scheme 7) and phencyclone **9** affords **46**. The reaction of furan **13** with imide **21** requires special mention as it only occurs under high pressure conditions[10] and the resultant product **43** is unstable at ambient temperature, rapidly reverting to its precursors in a retro-Diels-Alder reaction. In all cases the high-field shift for the chemical shift of the ester groups (see Table 1, final column) are diagnostic of structure.

Table 1. The physical properties of representative cavity molecules **40-46.**



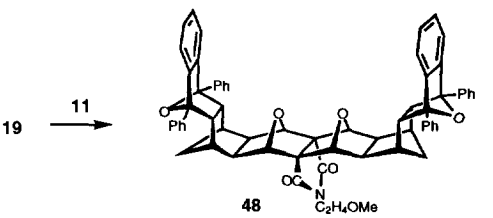
structure number	B	A-A	X	R	yield (%)	mp (°C)	δ(ester)
40	O		O	H	43	326	3.56
41	O		NC_2H_4OMe	H	65	314-316	3.49
42	O		NC_2H_4OMe	Ph	81	154-156	3.43
43	O	C=C	NC_2H_4OMe	H	*	*	3.60
44	$C=C(Me)_2$	C=C	NC_2H_4OMe	H	34	152-154	3.61
45	CO		O	Me	78	223-225	3.51
46	CO		O	Me	44	246(dec)	3.04

* compound unstable



Scheme 7

Isobenzofuran **10** cannot be made to react with the U-shaped cavity molecule **19** as cycloaddition does not occur when **10** is generated at room temperature *via* the *s*-tetrazine reaction (Scheme 6) and attempts to prepare the adduct under high temperatures (refluxing diglyme) using the Fieser method for generating **10**,[11] are frustrated by the decomposition of **19** under these conditions. In contrast, the stable 1,3-diphenylisobenzofuran **11** does react with **19** (in benzene at reflux) and stereoselective entry to the U-shaped cavity molecule **48** can be obtained (Scheme 8). No high field resonance for the methylene bridge protons appears in ^{1}H NMR spectrum for **48** and this forms the basis for the assigned U-shaped geometry.



Scheme 8

Molecular Modelling

Molecular modelling has been conducted on all systems to assess their geometry and the separation of the wall components shown in the diagram for U-shaped cavity molecule **48** has been calculated using SPARTAN's SYBYL forcefield. This datum has been provided to indicate a typical dimension of this class of compound. The calculated structure for **48** is shown in Fig. 2.

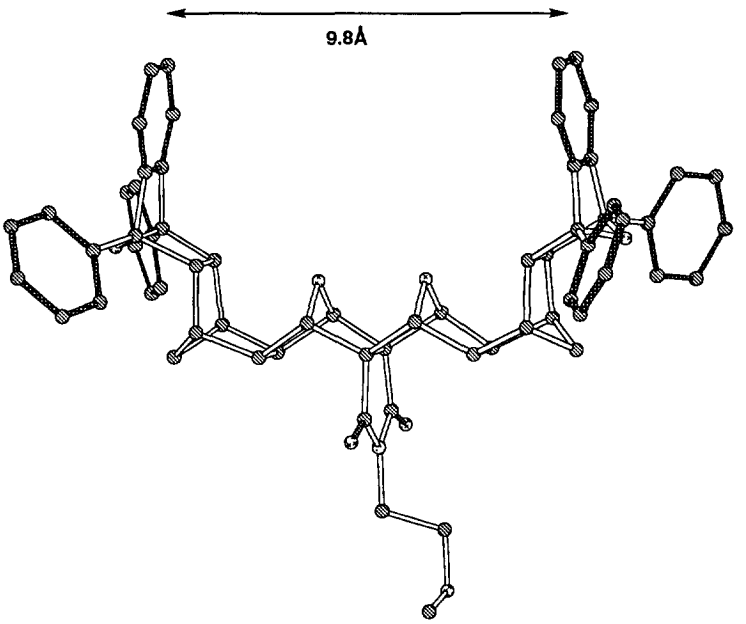


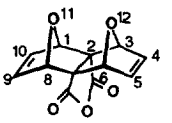
Figure 2: The structure for U-shaped cavity molecule **48** based on SYBYL calculations.

Acknowledgements

We thank Dr D Margetic for making the preparation of anhydride **17** available prior to publication. RNW acknowledges the award of a senior ARC Fellowship (1992-1996). SW thanks the Centre for Molecular Architecture for the award of CMA Postgraduate Scholarship.

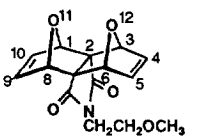
Experimental

Melting points were determined on a GALLENKAMP Melting Point Apparatus and were uncorrected. Microanalyses were performed by either the Australian Microanalytical Service or Central Queensland University. ^{1}H NMR spectra were recorded using 300 MHz, Bruker AM300. All ^{1}H NMR spectra were recorded in deuterchloroform solution unless otherwise stated with deuterchloroform as internal standard (δ = 7.26 ppm). The multiplicity of the signals was described as either s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or br (broad). ^{13}C NMR spectra were recorded in deuterochloroform solution using a Bruker AM300 (operating at 75.5 MHz) instrument. Chemical shifts were measured relative to deuterchloroform (δ = 77.00 ppm). Analytical TLC was carried out using Merck (A.T. 5554) silica gel 60 F_{254} precoated on aluminium sheets. Chromatograms were visualised using UV light (254 nm and 365 nm). Preparative radial chromatography was carried out using a Chromatotron Model 7924T (Harrison Research, Palo Alto, California) with Silica gel 60 PF_{254} gipshaltig (Merck Art. 7749) as absorbent. High pressure reactions were carried out using an HOFER High Pressure Apparatus Model HP14 at room temperature. Light petroleum (PE) refers to the fraction b.p. 65-75 °C. All organic extracts were dried with anhydrous magnesium sulphate.



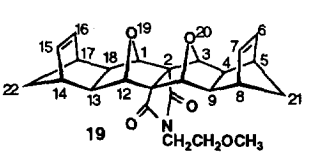
1α,2β,3α,6α,7β,8α-11,12-dioxatetracyclo[6.2.1.1^{3,6}.0^{2,7}]dodeca-4,9-dien-2,7-dicarboxylic anhydride (17)

A solution of **15** (5.00 g, 20 mmol) in thionyl chloride (20 ml) was heated at 85-90 °C for 2 h under N_2. The excess thionyl chloride was evaporated off under reduced pressure. The resultant dark brown solid was recrystallised from a minimum amount of EtOAc to give **17** as light yellow-coloured needles (1.98 g, 43%). m.p. 184-185 °C (lit[6] m.p. 184-185 °C) ^{1}H NMR ($CDCl_3$) δ 5.30 (4H, t, J = 0.9 Hz), 6.78 (4H, t, J = 0.9 Hz); ^{13}C NMR ($CDCl_3$) δ 78.01, 81.52, 139.92, 167.30.



1α,2β,3α,6α,7β,8α-*N*-(2-methoxyethyl)-11,12-dioxatetracyclo[6.2.1.1^{3,6}.0^{2,7}]dodeca-4,9-dien-2,7-carboximide (18)

2-Methoxyethylamine (7 ml) was added dropwise to an ice-cooled solution of anhydride **17** (8.20 g, 35.34 mmol) in $CHCl_3$ (40 ml). The solution was allowed to stir while heating under reflux for 4 days. The solvent and excess of amine starting material were evaporated off under reduced pressure to give the intermediate amic acid as a brown oil. ^{1}H NMR (D_2O) δ 3.27 (2H, t, J = 5.5 Hz), 3.40 (3H, s), 3.50 (2H, t, J = 5.5 Hz), 5.13 (2H, sbr), 5.16 (2H, sbr), 6.62 (2H, dd, J = 5.8, 1.6 Hz), 6.73 (2H, dd, J = 5.8, 1.6 Hz); ^{13}C NMR (D_2O) δ: 41.28, 60.68, 72.49, 72.78, 73.68, 87.12, 87.48, 141.33, 143.28, 175.85, 179.62. Without further purification, this oil was treated with Ac_2O-NaOAc (50 ml), and the mixture was allowed to stir at 60 °C for 3 days. The mixture was poured onto ice-water, and extracted with $CHCl_3$ (5 x 50 ml). The organic layers were combined and washed with water, dried over $MgSO_4$ and the solvent was evaporated off to produce solid material which was recrystallised from EtOAc to yield colourless crystals of product **18** (6.01 g, 60%), m.p. 221-222 °C. Anal. Calc. $C_{15}H_{15}O_5N$ requires C, 62.28, H, 5.23, N, 4.84; found C, 62.05, H, 5.16, N, 4.57. ^{1}H NMR ($CDCl_3$) δ: 3.28 (3H, s), 3.34 (2H, m), 3.42 (2H, m), 5.24 (4H, sbr), 6.58 (4H, m); ^{13}C NMR ($CDCl_3$) δ 37.74, 58.36, 68.41, 69.29, 81.30, 138.95, 174.12.



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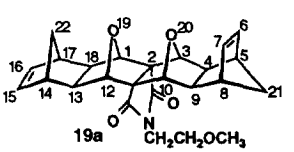
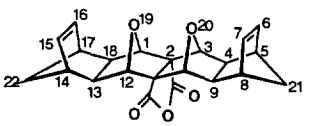


19a

(1α,2β,3α,4β,5β,8β,9β,10α,11β,12α,13β,14β,17β,18β) *N*-(2-methoxyethyl)-19,20-dioxaocta cyclo[10.6.1.1^{3,10}.1^{5,8}.1^{14,17}.0^{2,11}.0^{4,9}.0^{13,18}]docosa-6,15-dien-2,11-dicarboximide (19) and (1α,2β,3α,4β,5β,8β,9β,10α,11β,12α,13β,14α,17α,18β) *N*-(2-methoxyethyl)-19,20-dioxaoctacyclo[10.6.1.1^{3,10}.1^{5,8}.1^{14,17}.0^{2,11}.0^{4,9}.0^{13,18}]docosa-6,15-dien-2,11-dicarboximide (19a)

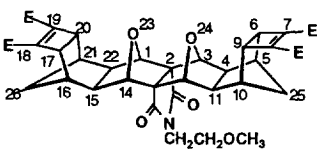
A solution of imide **18** (0.38 g, 1.31 mmol) and cyclopentadiene (4 ml) in $CHCl_3$ (5 ml) was stirred at 60 °C in a sealed container for 128 h. The solvent was removed and the residue was chromatographed (silica gel, EtOAc/PE, 1:5, v/v) to provide a light yellow-coloured oil which slowly solidified. Recrystallisation of this material from EtOAc/PE yielded the *bis*-adduct **19** as colourless crystals (0.437 g, 79 %), m.p. 169-170 °C; Anal. Calc. $C_{25}H_{27}O_5N$ requires C, 71.23, H, 6.46, N, 3.32; found C, 70.88, H, 6.48, N, 3.32. ^{1}H NMR ($CDCl_3$) δ 0.98 (2H, d, *J* = 8.1 Hz), 1.12 (2H, m), 2.27 (4H, m), 2.82 (4H, m), 3.26 (3H, s), 3.54 (2H, m), 3.63 (2H, s), 4.31 (4H, s), 5.81 (4H, dd, *J* = 3.42 Hz, 1.71 Hz); ^{13}C NMR ($CDCl_3$) δ 37.70, 45.15, 46.39, 50.39, 58.30, 68.18, 73.46, 81.37, 133.25, 174.98.

A small amount of the unsymmetrical isomer **19a** observed in one reaction, but not in subsequent experiments, was separated by chromatography and recrystallised from EtOAc/PE as colourless crystals, m.p. 213-214 °C; Anal. Calc. $C_{25}H_{27}O_5N$ requires C, 71.23, H, 6.46; found C, 71.26, H, 6.33. ^{1}H NMR ($CDCl_3$) δ 0.94 (1H, d, *J* = 8.2 Hz), 1.03 (1H, d, *J* = 8.0 Hz), 1.23 (1H, d, *J* = 8.2 Hz), 1.75 (2H, s), 2.30 (1H, d, *J* = 8.0 Hz), 2.34 (2H, m), 2.74 (2H, sbr), 2.89 (2H, sbr), 3.25 (2H, s), 3.50 (2H, m), 3.62 (2H, s), 4.42 (2H, s), 4.58 (2H, s), 5.89 (2H, sbr), 6.06 (2H, sbr); ^{13}C NMR ($CDCl_3$) δ 38.23, 42.85, 45.45, 45.51, 46.72, 47.75, 50.77, 58.89, 68.55, 73.30, 81.84, 83.39, 133.62, 138.79, 175.31.



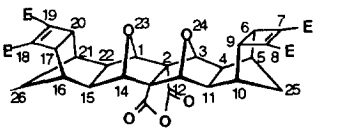
1α,2β,3α,4β,5β,8β,9β,10α,11β,12α,13β,14β,17β,18β-19,20-dioxaoctacyclo[10.6.1. 1^{3,10}.1^{5,8}.1^{14,17}.0^{2,11}.0^{4,9}.0^{13,18}]docosa-6,15-dien-2,11-dicarboxylic anhydride (20)

Cyclopentadiene (5 ml) was added to a solution of anhydride **17** (0.32 g, 1.38 mmol) in $CHCl_3$ (5 ml) and the mixture heated under reflux for 24 h. The solvent was removed and the residue was chromatographed (silica gel, CH_2Cl_2/hexane, 5:1 v/v) to provide the *bis*-adduct **17** as colourless crystals (0.46 g, 92%), m.p. 279-180 °C. Anal. Calc. $C_{22}H_{20}O_5$ requires C, 72.50, H, 5.53; found C, 72.70, H, 5.37. ^{1}H NMR ($CDCl_3$) δ 1.13 (2H, d, *J* = 8.3 Hz), 1.30 (2H, dt, *J* = 8.3, 1.6 Hz), 2.50 (4H, dd, *J* = 1.4 Hz, 2.4 Hz), 2.94 (4H, m), 4.43 (4H, s), 5.90 (4H, t, *J* = 1.6 Hz); ^{13}C NMR ($CDCl_3$) δ 45.52, 46.96, 50.70, 76.52, 82.12, 133.61, 169.01.



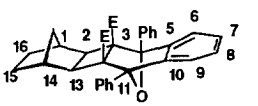
(1α,2β,3α,4β,5β,6α,9α,18β,11β,12α,13β,14α,15β,16β,17α,20α) 7,8,18,19-tetramethoxy carbonyl-*N*-(2-methoxyethyl)-23,24-dioxadecacyclo[12.8.1.1^{3,12}1^{5,10}.1^{16,21}.0^{2,13}.0^{4,11}.0^{6,9}.0^{15,22}.0^{17,20}]tetracosa-7,18-dien-2,13-dicarboximide (21)

A solution of *bis*-alkene **19** (0.408 g, 0.968 mmol) and DMAD (3 ml) in benzene (5 ml) containing a catalytical amount of $RuH_2CO(PPh_3)_3$ was stirred at 65 °C for 30 h. The solvent was removed and the resulting dark brown-coloured residue was chromatographed (silica gel, EtOAc/PE, 1:1, v/v) to provide a colourless solid which was recrystallised from $CHCl_3$/PE to afford the product **21** (0.69 g, 87 %), m.p. 278 °C (dec.). Anal. Calc. $C_{37}H_{39}O_{13}N_1$ requires C, 62.97, H, 5.57, N, 1.98; found C, 62.93, H, 5.71, N, 1.98. ^{1}H NMR ($CDCl_3$) δ 0.95 (2H, d, *J* = 10.9 Hz), 1.42 (2H, d, *J* = 10.9 Hz), 2.19 (4H, m), 2.43 (4H, sbr), 2.95 (4H, s), 3.28 (3H, s), 3.55 (2H, m), 3.62 (2H, m), 3.74 (12H, s), 4.74 (4H, s); ^{13}C NMR ($CDCl_3$) δ 32.44, 36.79, 38.07, 42.96, 46.35, 51.76, 58.54, 68.28, 71.68, 81.26, 141.29, 161.33, 174.50.



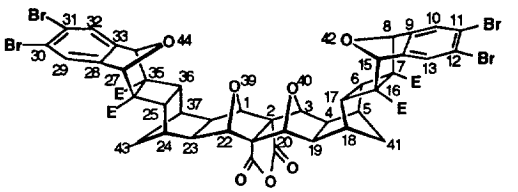
1α,2β,3α,4β,5β,6α,9α,10β,11β,12α,13β,14α,15β,16β,17α,20α,21β,22β-tetramethyl-23, 24-dioxadecacyclo[12.8.1.1^{3,12}.1^{5,10}.1^{16,21}.0^{2,13}.0^{4,11}.0^{6,9}.0^{15,22}.0^{17,20}] hexacosa-7,18-dien-7,8,18,19-tetracarboxyl-2,13-dicarboxylic anhydride (22)

DMAD (2 ml) was added to a mixture of anhydride **20** (0.138 g, 0.379 mmol) and $RuH_2CO(PPh_3)_3$ (0.06 g, 0.065 mmol) in benzene (5 ml) under N_2. The reaction was stirred at room temperature for 143 h, followed by heating at 60 °C for 5 h. The solvent was removed under reduced pressure and the residue chromatographed (silica gel, EtOAc/hexane, 10:3 v/v) to give the product, which was recrystallised from CH_2Cl_2 (0.228 g, 93%). m.p. 324 °C (dec.); Anal. Calc. $C_{34}H_{32}O_{13}$ requires C, 62.96, H, 4.97, found C, 62.45, H, 4.81; ^{1}H NMR ($CDCl_3$) δ 1.06 (2H, m); 1.49 (2H, m); 2.37 (4H, m); 2.52 (4H, m); 2.94 (4H, s); 3.76 (12H, s); 4.82 (4H, s); ^{13}C NMR ($CDCl_3$) δ 32.49, 36.89, 42.78, 46.64, 51.85, 74.36, 81.71, 141.12, 161.20, 168.12.



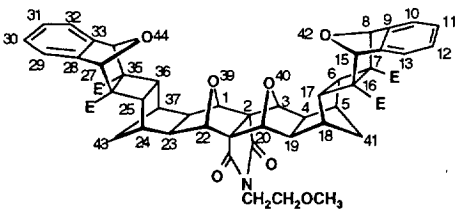
1α,2β,3α,4β,11β,12α,13β,14α-dimethyl-4,11-diphenyl-18-oxahexacyclo[12.2.1.1^{4,11}. 0^{2,13}.0^{3,12}.0^{5,10}]octadeca-5,7,9-trien-3,12-dicarboxylate (34)

A solution of cyclobutene **31** (0.316 g, 1.34 mmol) and 1,3-diphenylisobenzofuran **11** (0.362 g, 1.34 mmol) in $CHCl_3$ (2 ml) was heated under reflux for 16 h. The solvent was removed and the crude product was crystallised from EtOAc/PE and then recrystallised from EtOAc to yield light yellow-coloured crystals of the adduct **34** (0.43 g, 63%), m.p. 153-154 °C. Anal. Calc. $C_{33}H_{30}O_5$ requires C, 78.24, H, 5.94; found C, 78.20, H, 5.98. ^{1}H NMR ($CDCl_3$) δ 0.96 (2H, m), 1.30 (1H, d, *J* = 5.5 Hz), 1.46 (2H, m), 2.24 (1H, d, *J* = 5.5 Hz), 2.39 (2H, s), 2.52 (2H, br), 3.50 (6H, s), 7.03-7.63 (14H, m)



(1α, 2β, 3α, 4β, 5β, 6α, 7β, 8α, 15α, 16β, 17α, 18β, 19β, 20α, 21β, 22α, 23β, 24β, 25α, 26β, 27α, 34α, 35β, 36α, 37β, 38β) 11,12,30,31-Tetrabromo-7,16,26,35-tetra methoxycarbonyl-39,40,42,44-tetraoxahexadecacyclo[20.16.1.1^{3,20}.1^{5,18}.1^{8,15}.1^{24,37}.1^{27,34}.0^{2,21}.0^{4,19}.0^{6,17}.0^{9,14}.0^{23,38}.0^{25,36}.0^{26,35}.0^{28,33}]tetratetraconta-9,11,13,28, 30,32-hexaen-2,21-dicarboxylic anhydride (40)

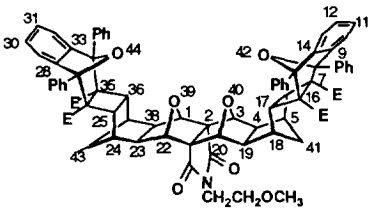
To a solution of the *bis*-cyclobutene anhydride **22** (0.375 g, 0.578 mmol) in $CHCl_3$ (20 ml) was added 4,5-dibromo-11-oxatricyclo[6.2.1.0^{2,7}]undeca-2,4,6,9-tetraene **36** (0.343g, 1.136 mmol) and 3,6-di(2-pyridyl)-*s*-tetrazine[12] (0.268g, 1.136 mmol). The mixture was allowed to stir at room temperature for 12 h, acidified with hydrochloric acid, washed with water, dried with anhydrous magnesium sulphate and the solvent evaporated to yield the title compound **40** as a colourless solid which was recrystallised from $CHCl_3$ (0.30g, 43%), m.p. 326 °C (dec.); Anal. Calc. $C_{50}H_{40}O_{15}Br_4 \cdot H_2O$ requires C, 49.29, H, 3.47; found C, 49.64, H 3.13; ^{1}H NMR ($CDCl_3$) δ 1.24 (2H, m), 2.24 (2H, m), 2.30 (4H, m), 2.52 (8H, br), 3.56 (12H, s), 4.79 (4H, s), 5.13 (4H, s), 7.40 (4H, s). ^{13}C NMR δ 36.94, 40.62, 43.24, 47.44, 51.45, 59.09, 74.84, 81.71, 84.66, 123.35, 126.12, 143.20, 168.02, 173.05.



(1α,2β,3α,4β,5β,6α,7β,8α,15α,16β,17α,18β,19β,20α,21β,22α,23β,24β,25α,26β,27α ,34α,35β,36α,37β,38β) 7,16,26,35-Tetramethoxycarbonyl-*N*-(2-methoxyethyl)-7,16, 26,35-tetramethyl-39,40,42,44-tetraoxahexadecacyclo [20.16.1.1^{3,20}.1^{5,18}.1^{8,15}. 1^{24,37}.1^{27,34}.0^{2,21}.0^{4,19}.0^{6,17}.0^{9,14}.0^{23,38}.0^{25,36}.0^{26,35}.0^{28,33}]tetratetraconta-9,11, 13,28,30,32-hexaen-2,21-dicarboximide (41)

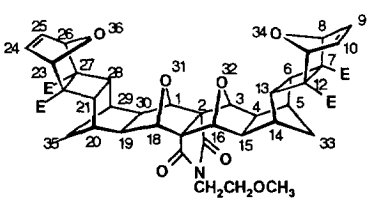
To a solution of *bis*-alkene **21** (0.055 g, 0.078 mmol) in $CHCl_3$ (20 ml) was added 11-oxatricyclo[6.2.1.0^{2,7}]undeca-2,4,6,9-tetraene **35** (0.022g, 0.156 mmol) and 3,6-di(2'-pyridyl)-s-tetrazine **37** (0.0368g, 0.156 mmol). The mixture was allowed to stir at room temperature for 3 h, acidified with hydrochloric acid, washed with water, dried with anhydrous magnesium sulphate and the solvent was evaporated to yield a mixture of the product **41** and recovered starting material **35**. This mixture was separated by radial chromatography (silica gel; EtOAc/PE; 1:5, v/v) to yield a light yellow solid which was recrystallised from EtOAc (0.045g, 65%), m.p. 314-316 °C; ^{1}H NMR ($CDCl_3$) δ 1.05 (2H, d, J = 9.2 Hz), 2.14 (4H, br),

2.17 (2H, d, J = 9.2 Hz), 2.42 (4H, br), 2.56 (4H, s), 3.24 (3H, s), 3.49 (6H, s), 3.56 (4H, m), 4.72 (4H, s), 5.17 (4H, s), 7.12 (8H, br).



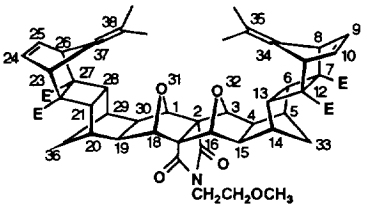
(1α, 2β, 3α, 4β, 5β, 6α, 7β, 8α, 15α, 16β, 17α, 18β, 19β, 20α, 21β, 22α, 23β, 24β, 25α, 26β, 27α, 34α, 35β, 36α, 37β, 38β) 7,16,26,35-Tetramethoxycarbonyl-*N*-(2-methoxyethyl) -8,15,27,34-tetraphenyl--39,40,42,44-tetraoxahexadeca [20.16.1.1^{3,20}.1^{5,18}.1^{8,15}.1^{24,37}. 1^{27,34}.0^{2,21}.0^{4,19}.0^{6,17}.0^{7,16}.0^{9,14}.0^{23,38}.0^{25,36}.0^{26,35}.0^{28,33}]dotetraconta-9,11,13,28,30, 32-hexaen-2,21-carboximide (42)

A solution of *bis*-cyclobutene **21** (0.091 g, 0.130 mmol) and 1,3-diphenylisobenzofuran **11** (0.070 g, 0.259 mmol) in $CHCl_3$ (2 ml) was refluxed for 20 h. The solvent was evaporated off and the residue was chromatographed (silica gel), using solvent EtOAc/PE (1:5, v/v) to wash off the excess starting material **11**, followed by EtOAc/MeOH (3:1, v/v) to elute the crude product, which was recrystallised from EtOAc to give **42** as colourless crystals (0.13 g, 81 %), m.p. 154-156 °C; Anal. Calc. $C_{77}H_{67}O_{15}N{\cdot}H_2O$ requires C 73.15, H 5.50, N 1.11; found C, 73.06, H, 5.30, N 1.20; ^{1}H NMR ($CDCl_3$) δ 1.16 (2H, d, J = 11.4 Hz), 2.01 (4H, m), 2.18 (2H, d, J =11.4 Hz), 2.62 (8H, s), 3.26 (3H, s), 3.43 (12H, s), 3.50 (4H, m), 4.33 (4H, s), 7.00-7.55 (28H, m). ^{13}C NMR ($CDCl_3$) δ 37.93, 38.64, 40.79, 47.76, 50.78, 50.82, 58.57, 64.91, 68.32, 72.58, 80.72 , 92.19, 121.56, 126.21, 127.81, 127.99, 128.52, 134.91, 146.71, 169.60, 175.04.



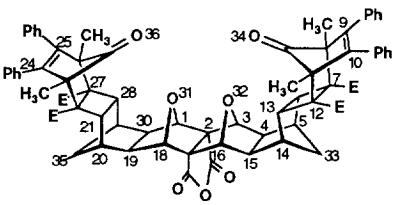
1α, 2β, 3α, 4β, 5β, 6α, 7β, 8α, 11α, 12β, 13α, 14β, 15β, 16α, 17β, 18α, 19β, 20β, 21α, 22β, 23α, 26α, 27β, 28α, 29β, 30β-7,12,22,27-Tetramethoxycarbonyl-*N*-(2-methoxyethyl)-31,32-dioxatetradecacyclo[16.12.1.1^{3,16}.1^{5,14}.1^{8,11}.1^{20,29}.1^{23,26}.0^{2,17}.0^{4,15}.0^{6,13}.0^{7,12}.0^{19,30}. 0^{21,28}.0^{22,27}]hexatriaconta-9,24-dien-2,17-carboximide (43)

A mixture of *bis*-cyclobutene **21** (0.100 g, 0.142 mmol) and furan **13** (3 g, 4.41 mmol) was reacted under high pressure (10 kbar) for 24 h. The excess furan was evaporated off under reduced pressure below 30 °C and the residual solid crystallised from EtOAc to afford *bis*-adduct **43** as colourless crystals. This compound was too unstable for further characterisation as *retro*-Diels-Alder reaction occurred. ^{1}H NMR ($CDCl_3$) δ 1.03 (2H, d, J = 8.8 Hz), 2.08 (4H, br), 2.13 (2H, d, J = 11.0 Hz), 2.33 (4H, s), 2.42 (4H, br), 3.26 (3H, s), 3.60 (12H, s), 3.50-3.56 (4H, m), 4.60 (4H, s), 6.37 (4H, m). ^{13}C NMR unavailable.



(1α, 2β, 3α, 4β, 5β, 6α, 7β, 8α, 11α, 12β, 13α, 14β, 15β, 16α, 17β, 18α, 19β, 20β, 21α, 22β, 23α, 26α, 27β, 28α, 29β, 30β) 7,12,22,27--*N*-(2-methoxyethyl)-34,37-bis(isopropyliden)-31,32-dioxatetradecacyclo[16.12.1.1^{3,16}.1^{5,14}.1^{8,11}.1^{20,29}.1^{23,26}.0^{2,17}.0^{4,15}.0^{6,13}.0^{7,12}.0^{19,30}.0^{22,27}]hexatriaconta-9,24-diene-2,17-carboximide (44)

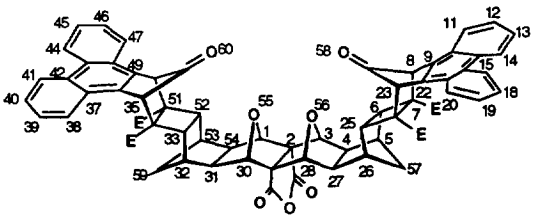
A solution of *bis*-cyclobutene **21** (0.132 g, 0.187 mmol) and dimethylfulvene **14** (0.500 g, 4.72 mmol) in CH_2Cl_2 (5 ml) was stirred at 60 °C for 66 h. The solvent was removed and the residue was chromatographed (silica gel), using EtOAc/PE (1:10, v/v) to remove excess dimethyl fulvene. Elution of the column with methanol provided the more polar **34**, admixed with recovered starting cyclobutene **21**. This mixture was separated by radial chromatography (silica gel; EtOAc/PE, 10:7 v/v) to give a light yellow solid which was recrystallised from $CHCl_3$ to yield the title compound **44** (0.057 g, 34%), m.p. 152-154 °C; ^{1}H NMR ($CDCl_3$) δ 1.03 (2H, d, *J* = 10.5 Hz), 1.64 (12H, s), 1.91 (4H, s), 2.01 (4H, m), 2.05 (2H, d, *J* = 10.5 Hz), 2.41 (4H, sbr), 3.26 (3H, s), 3.46 (4H, t, *J* = 1.8 Hz), 3.48-3.56 (4H, m), 3.61 (12H, s), 4.42 (4H, s), 6.23 (4H, t, *J* = 1.8 Hz, 3.7 Hz). ^{13}C NMR ($CDCl_3$) δ 19.88, 37.18, 38.03, 40.38, 43.86, 46.97, 51.13, 52.88, 58.65, 59.16, 68.41, 72.16, 81.27, 114.96, 135.14, 142.11, 171.48, 174.90.



(1α, 2β, 3α, 4β, 5β, 6α, 7β, 8α, 11α, 12β, 13α, 14β, 15β, 16α, 17β, 18α, 19β, 20β, 21α, 22β, 23α, 26α, 27β, 28α, 29β, 30β) 7,12,22,27-Tetramethoxycarbonyl 8,11,23,26-tetra methyl-9,10,24,25-tetraphenyl-31,32-dioxatetradecacyclo-[16.12.1.1^{3,16}.1^{5,14}.1^{8,11}.1^{20,29}.1^{23,26}.0^{2,17}.0^{4,15}.0^{6,13}.0^{7,12}.0^{19,30}.0^{21,28}.0^{22,27}]-hexatriaconta-9,14-dien-34,36-dione-2,17-dicarboxylic anhydride (45)

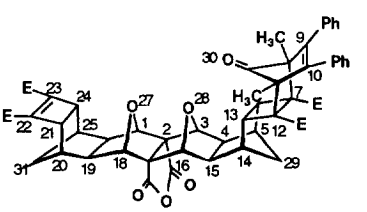
A solution of *bis*-cyclobutene anhydride **22** (0.030 g, 0.0462 mmol) and hemicyclone **9** (0.048 g, 0.185 mmol) in toluene (5 ml) was heated under reflux for one week. The solvent was evaporated off to give a light yellow coloured oil, which was separated by radial chromatography (silica gel, EtOAc/PE 1:2, v/v) into a mixture of *bis*-adduct **45** (more mobile) and monoadduct **47** (less mobile). The *bis*-adduct **45** was isolated as a light yellow solid which was recrystallised from EtOAc (0.042 g, yield 78%), m.p. 223-225 °C; Anal. Calc. $C_{72}H_{64}O_{15}$ 0.25 $CHCl_3$, C, 72.37, H 5.40; found C, 72.53, H, 5.02. ^{1}H NMR ($CDCl_3$) δ 1.26 (2H, d, *J* = 12.0 Hz), 1.34 (12H, s), 2.00 (2H, d, *J* = 12.0 Hz), 2.24 (4H, s), 2.27 (4H, m), 2.75 (4H, br), 3.51 (12H,

s), 4.74 (4H, s), 6.86-7.25 (20H, m). ^{13}C NMR ($CDCl_3$) δ 7.69, 37.20, 39.22, 41.03, 47.52, 51.22, 60.89, 61.24, 74.98, 81.29, 127.11, 127.65, 129.85, 134.46, 142.37, 168.56, 169.63, 199.87.



(1α, 2β, 3α, 4β, 5β, 6α, 7β, 8α, 23α, 24β, 25α, 26β, 27β, 28α, 29β, 30α, 31β, 32β, 33α, 34β, 35α, 50α, 51β, 52α, 53β, 54β) 7,24,34,51-Tetramethoxycarbonyl-8,23,35,50-tetramethyl-55,56-dioxaeicosacyclo[28.24.1.1^{3,28}.1^{5,26}.1^{8,23}.1^{32,53}.1^{35,50}.0^{2,29}.0^{4,27}.0^{6,25}.0^{7,24}.0^{9,22}.0^{10,15}.0^{16,21}.0^{31,54}.0^{33,52}.0^{34,51}.0^{36,49}.0^{37,42}.0^{43,48}]hexaconta-9,11,13,15,17,19,21,36,38,40,42,44,46,48-tetradecen-58,60-dione-tetracarboxylate-2,29-dicarboxylic anhydride (46)

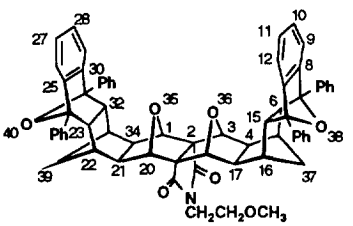
A solution of *bis*-cyclobutene anhydride **22** (0.019 g, 0.029 mmol) and phencyclone **9** (0.031 g, 0.06 mmol) in toluene (2 ml) was heated under reflux for 70 h. The solvent was evaporated off under reduced pressure to produce a brown-coloured solid which was recrystallised from benzene to give *bis*-adduct **46** as a colourless powder (0.015 g, 44 %), m.p. 246 °C (dec.); ^{1}H NMR ($CDCl_3$) δ 1.13 (2 H, d, J = 11.0 Hz), 1.75 (2H d, J = 11.0 Hz), 1.95 (12H, s), 2.21 (4H, br), 2.33 (4H, s), 2.73 (4H, br), 3.04 (12H, s), 4.73 (4H, s), 7.16-8.65 (16H, m). ^{13}C NMR δ 9.93, 36.90, 38.26, 41.00, 47.58, 51.10, 59.33, 62.18, 75.06, 81.38, 123.54, 124.54, 126.20, 126.46, 128.17, 130.55, 134.93, 168.58, 169.22, 200.73.



(1α, 2β, 3α, 4β, 5β, 6α, 7β, 8α, 11α, 12β, 13α, 14β, 15β, 16α, 17β, 18α, 19β, 20β, 21α, 24α, 25β, 26β) Tetramethyl 8,11-dimethyl-9,10-diphenyl-27,28-dioxadodecacyclo-[16.8.1.1^{3,16}.1^{5,14}.1^{8,11}.1^{20,25}.0^{2,17}.0^{4,15}.0^{6,13}.0^{7,12}.0^{19,26}.0^{21,24}]hexatriaconta-10,22-dien-30-one-7,12,22,23-tetracarboxylate-2,17-dicarboxylic anhydride (47)

Mono-adduct **47** (0.021 g), obtained from the above reaction, was isolated from the less mobile fraction from radial chromatography as a light yellow coloured solid. m.p. 246-247 °C. Anal. Calc. $C_{53}H_{48}O_{14}$•H_2O requires C, 68.67, H, 5.44, found C 68.99, H, 5.12. ^{1}H NMR ($CDCl_3$) δ 1.04 (1H, d, J = 11.0 Hz), 1.48 (1H, d, J = 11.0 Hz), 1.25 (1H, d, J = 11.0 Hz), 2.00 (1H, d, J = 11.0 Hz), 2.25 (2H, s), 2.29 (2H, dd, J = 2.9 Hz), 2.34 (2H, dd, J = 2.9 Hz), 2.50 (2H, sbr), 2.76 (2H, sbr), 2.94 (2H, s), 3.51 (6H, s), 3.77 (6H, s), 4.75 (2H, s), 4.80 (2H, s). ^{13}C NMR ($CDCl_3$) δ 7.69, 32.49, 36.91, 37.17, 39.03, 41.07, 42.87, 46.70,

47.55, 51.25, 51.86, 60.35, 74.73, 54.54, 81.43, 81.51, 127.16, 127.68, 129.83, 134.41, 141.16, 142.45, 161.25, 168.39, 169.60, 199.38.



(1α, 2β, 3α, 4β, 5β, 6α, 7β, 14β, 15α, 16β, 17β, 18α, 19β, 20α, 21β, 22β, 23α, 24β, 31β, 32α, 33β, 34β) *N*-(2-methoxyethyl)-7,14,24,31-tetraphenyl-35,36,38,40-tetraoxatetradeca cyclo [18.14.1.1^{3,18}.1^{5,16}.1^{7,14}.1^{22,33}.1^{24,31}.0^{2,19}.0^{4,17}.0^{6,15}.0^{8,13}.0^{21,34}.0^{23,32}.0^{25,30}] tetraconta-8,10,12,25,27,29-hexaen-2,19-dicarboximide (48)

A solution of *bis*-norbornene **19** (0.30 g, 0.713 mmol) and 1,3-diphenylisobenzofuran **11** (0.38 g, 1.41 mmol) in $CHCl_3$ (3 ml) was refluxed for 16 h. The solvent was evaporated off and the resulting crude product was recrystallised from EtOAc/$CHCl_3$ to produce the *bis*-adduct **48** (0.60 g, 88 %), m.p. 285-286 °C; Anal. Calc. $C_{65}H_{55}O_7N{\cdot}2H_2O$ requires C, 78.21, H, 5.96, N, 1.40; found C, 78.54, H,5.81, N, 1.46; ^{1}H NMR ($CDCl_3$) δ 0.51 (2H, d, J = 9.8 Hz), 1.91 (4H, br), 2.15 (4H, br), 2.47 (2H, d, J = 9.8 Hz), 2.50 (4H, s), 3.10 (3H, s), 3.36 (2H, m), 3.46 (2H, m), 4.59 (4H, s), 6.99-7.60 (28H, m). ^{13}C NMR ($CDCl_3$) δ 35.87, 38.03, 41.05, 47.70, 50.30, 58.46, 68.27, 72.26, 81.39, 90.07, 117.87, 125.84, 126.34, 127.15, 128.39, 137.59, 148.89, 174.42.

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