Incorporation of a Molecular Hinge into Molecular Tweezers by Using Tandem Cycloadditions onto 5,6-Dimethylenenorbornene

Ronald N. Warrener,*[a] Douglas N. Butler,[a] Ligong Liu,[a] Davor Margetic,[a] and Richard A. Russell[b]

Abstract: Site-selective 1,3-dipolar coupling at the norbornene π-bond of 5,6-dimethylenenorbornene **1** yields cycloadducts with an end-fused 1,3-diene system which have been reacted with N=N (or C=C) dienophiles to produce ribbon molecules, in which the internal diazacyclohexene (or cyclohexene) subunits are capable of acting as conformational hinges. Direct coupling of 5,6-dimethylenenorbornene with 1,3,4-oxadiazoles or dual coupling with bis(cyclobutene epoxides) afforded bis(1,3-dienes) that diastereoselectively react with dienophiles to produce new, conformationally mobile, molecular tweezers.

Keywords: conformational mobility · crown compounds · cycloaddition · molecular modeling · phthalazine diones

Introduction

Rigid assemblies of defined geometry have many positive attributes as spacers or hosts for guest complexation, yet it is often difficult to find ring systems which provide exactly the correct distances for optimum binding. In an excellent review on rods and spacers in chemistry, Michl et al.[1] have collated the different types of σ-linked spacers, for which some representatives, as well as the fused benzenoids, are shown in Figure 1a. These systems have different repeat units, ranging from the polyacetylenes at 2.66 Å to the *para*-linked benzene rings which have repeat units of 4.28 Å. Within the context of using molecular tweezers as hosts for guest complexation,[2] however, none may be suitable for optimum complexation with a particular guest, since one may be too small and the next member may be too big, as illustrated in principle for the polyacetylene series in Figure 1b. One solution to this problem is to introduce conformational mobility into some section(s) of the host frame, thereby retaining the spacer for gross separation and allowing the hinges to provide the optimum distances for fine tuning (Figure 1c). In early work which is pertinent to the present study, Stoddart et al. have used cyclohexene rings to provide conformational flexibility. This concept has been used in the synthesis of beltanes,[3] in which the precursor must attain a cavity conformation to allow the final cap to be attached (Figure 1d); indeed the cavity precursors have themselves been used as host systems.[4] These applications rely on the conformational flexibility of cyclohexene rings integrated into an otherwise rigid framework of the alicyclic precursor as an essential design feature, in order to attain the transition-state geometry required for belt formation. This same concept has been employed subsequently in the design of molecular tweezers using the conformational mobility of the 1,4-dioxacycloocta-2,6-diene ring (dioxa[2.2]orthocyclophane),[5] while others have used the conformational flexibility of carbocyclic variants such as bicyclo[3.3.1]nonanes to form cavity systems.[6] In other applications, the 4,5-diazacyclohexene ring served a similar role when the carbocyclic frame of a space-separated bis-glycoluril monomer was required to adopt a concave geometry in order to allow effective self-assembly (dimerisation) (Figure 1e) to form "tennis ball", "softball" or similar structures.[7]

Taking this lead, we set out to develop a general synthetic strategy that could be used to incorporate a cyclohexene (or diazacyclohexene) ring as part of a fused carbo-alicyclic [*n*]polynorbornane frame. Our objective was to provide a flexibile element (a molecular hinge, Figure 1c) which would allow conformational movement within the long axis of the rigid frame, thereby retaining the C_2 symmetry of the overall structure and these became our target molecules.

In this paper, we report on the use of 5,6-dimethylenenorbornene (DMN, **1**)[8, 9] to introduce the molecular hinge as part of a "Lego" BLOCK[10–12] approach to the construction of molecular tweezers (Scheme 1). Alder and co-workers

[a] Prof. Dr. R. N. Warrener, Prof. Dr. D. N. Butler, Dr. L. Liu
Dr. D. Margetic
Centre for Molecular Architecture
Central Queensland University, North Rockhampton
Queensland, 4702 (Australia)
Fax: (+61) 749-309-919
E-mail: r.warrener@cqu.edu.au

[b] Prof. Dr. R. A. Russell
Centre for Chiral and Molecular Technologies
Deakin University, Geelong, Victoria, 3217 (Australia)

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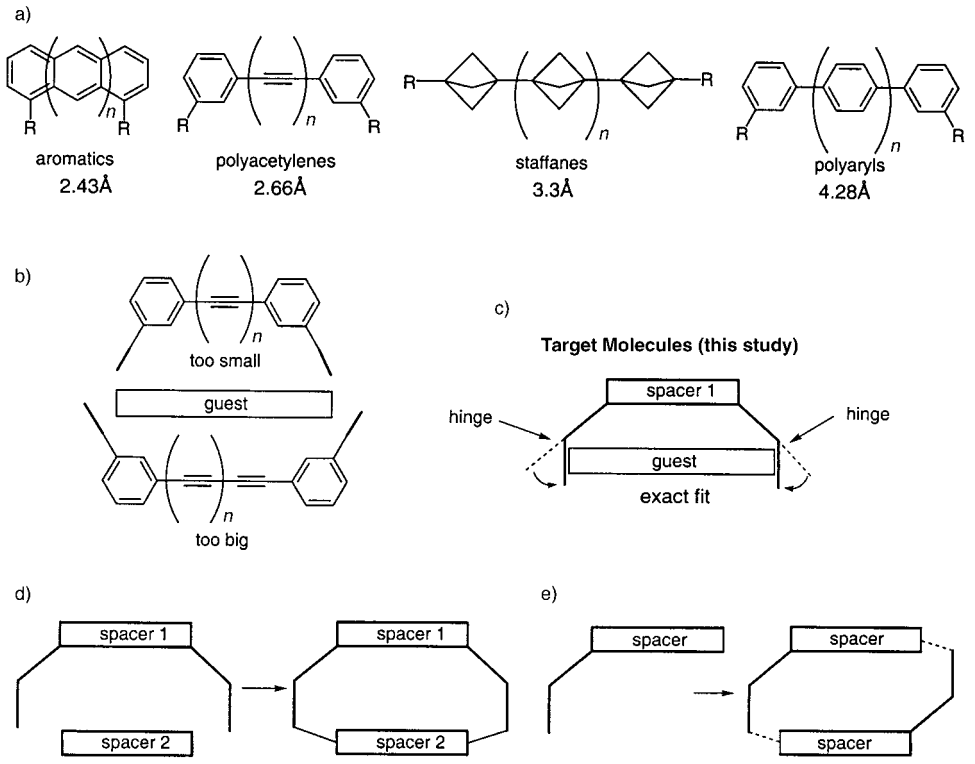
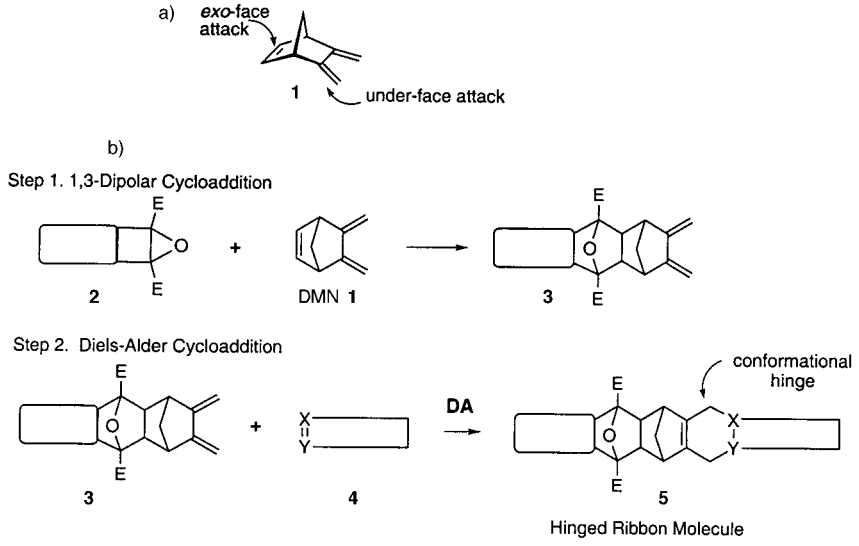


Figure 1. a) Representative spacer units showing the repeat spacer distances for each system (R = effector, n = integer); b) Diagram illustrating the difficulty in obtaining exact matching between guest and fixed length hosts (n = integer); c) Diagram showing the advantage of having flexi-armed hosts to fit guest dimensions; d) Diagram illustrating the role of flexi-armed hosts in belt formation; e) Diagram illustrating the use of flexi-armed structures in self-assembly to cyclic products.

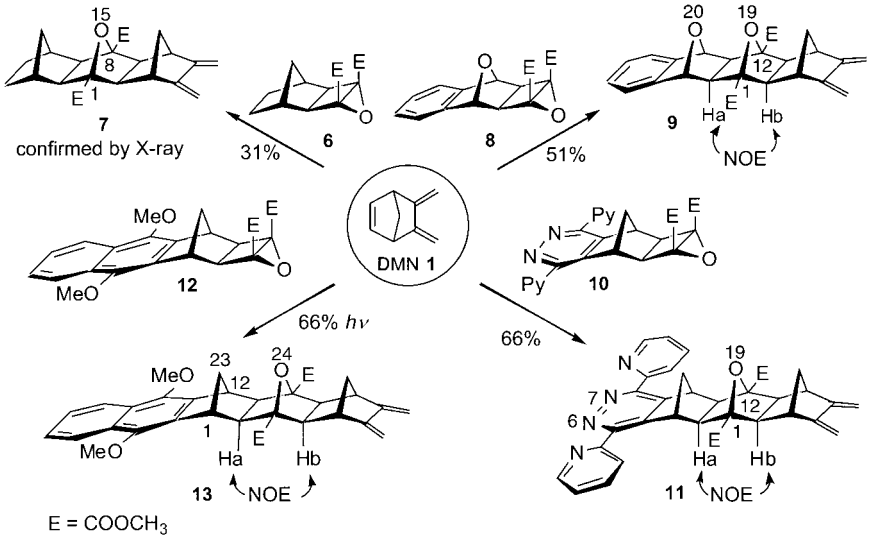


Scheme 1. a) Facial stereoselectivity for attack at the 2π-alkene (1,3-dipolar) and 4π-diene (Diels–Alder) sites of DMN **1**; b) Cycloaddition protocols used in the building of the hinged ribbon molecule **5** (E = CO_2Me, X = Y = CH, N).

offered excellent foresight in their 1957 paper, in which they reported that DMN (**1**) reacted with phenylazide (1,3-dipolar cycloaddition) at the norbornene π-bond and that maleic anhydride reacted at the 1,3-diene component. This work sets the stage for the present study, since we have used a two-stage protocol; the first effectors are introduced as functionalised norbornane-fused cyclobutene epoxides in a 1,3-dipolar cycloaddition (ACE coupling)[10] onto the norbornene π-centre of **1** to form a functionalised BLOCK **3** with terminal *exo*-cyclic dimethylene units. The second effector group is attached by way of dienophilic BLOCK **4** in a Diels–Alder cycloaddition onto the exocyclic 1,3-diene which effects ribbon molecule extension, and concomitantly produces the conformation hinge via the cyclohexene ring formed in the cycloaddition step. There may be applications for which it is beneficial to reverse the order of cycloaddition. The facial and diasteroselectivities of both the 1,3-dipolar cycloaddition and the effect of structure on Diels–Alder reaction rates[13] are well established (Scheme 1a), so this allows the protocol to be used in molecular design with reliable forecasts of shape and size.[3, 11, 14]

Results and Discussion

Site-selective addition at the norbornene π-bond of the title triene 1: There are several reports on the 1,3-diene reactivity[14, 15] of 5,6-dimethylenenorbornene **1**[8] and we have exploited this property for the synthesis of aryl-substituted benzonorbornadienes by the reaction of activated acetylenes to DMN **1**, followed by dehydrogenation of the dihydrobenzene adducts so formed (Scheme 4a).[15] In contrast, there has been essentially no comment on cycloadditions at the norbornene π-bond. In the first phase of this project, we established that cyclobutene epoxides reacted site-selectively and *exo*,*exo*-stereoselectively at the norbornene π-bond of DMN **1** to produce end-fused norbornane 1,3-dienes in 38–87% yield.[16] Typically, reaction of DMN **1** with ester-activated[20] cyclobutene epoxide **6** occurred on heating in dichloromethane (sealed tube, 140 °C, two hours) to yield a single adduct **7** (Scheme 2), the



Scheme 2. Thermal and photochemical addition of cyclobutene epoxides to the alkene π-bond of DMN **1**. General reaction conditions: thermal, CH_2Cl_2, sealed tube, 140 °C, 2–3 h; photochemical, acetone, quartz, 300 nm, RT, 2 h.

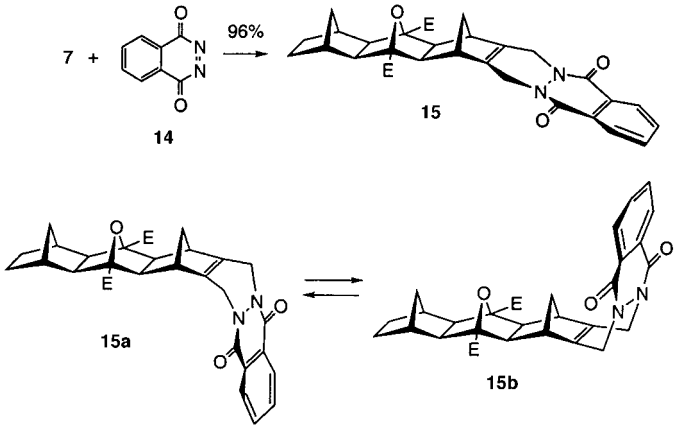
structure of which was confirmed by X-ray single-crystal analysis.[21]

Similar selectivities were observed in the reaction of DMN **1** with aromatic-fused cyclobutene epoxide **8**. The reaction of fused-norbornene **10** with DMN **1** illustrated the delivery of the 3,6-di(pyridyl)pyridazine (dpp) ligand by formation of the ligand-functionalised 1,3-diene **11**. The reaction of epoxide BLOCK **12** demonstrated that the 1,4-dimethoxynaphthalene functionality could be delivered to the 1,3-diene BLOCK **13**, and potentially to the ribbon molecule, by suitable modification of the aromatic ring. Furthermore, the fact that the addition could be achieved under photochemical conditions without affecting the diene component was especially significant as this process was achieved at ambient, rather than the high temperature (140 °C) required for the other cycloadditions.

The structures of these adducts were supported by spectroanalytical data, especially the NOE (Nuclear Overhauser Effect) exhibited between protons Ha and Hb, which served to establish the stereochemistry of the coupling process. The ^{1}H NMR spectra of the various 1,3-dienes, like that of the starting DMN **1**, all showed two characteristic finely coupled vinylic resonances at about $\delta = 5.1$ and 4.8, corresponding to external and internal olefin protons of the exocyclic 1,3-dienes, respectively.

The potential for the second step in the cycloaddition strategy has been illustrated by the Diels–Alder reaction of activated acetylenes with the 1,3-diene component of DMN **1** to form dihydroaromatics en route to benzonorbornadienes (Scheme 4a),[15] and the established use of 5,6-dimethylenebicyclo[2.2.2]octanes to couple to C_{60}.[22] However, we have chosen to employ the highly reactive phthalazine dione **14** in the second step in the tandem coupling with triene DMN **1** (Scheme 4b), illustrated by reaction of **14** with the diene **7**, which at room temperature produced the adduct **15** in 96% yield. A significant feature of this cycloaddition is that the resultant adduct contains a tetrahydropyridazine ring that fuses the two rigid sections of the molecule together. Accordingly, it has conformational flexibility in that region and can flip from one boat conformation to the other. This change in geometry causes significant reorientation of the alkylated phthalhydrazide component from below the plane of the carbocyclic molrac, for example, conformation **15a**, to a position above it, for example, conformation **15b**, in a motion that resembles the movement of a whale's tail (Scheme 3).

In determining the topology of the conformational alternatives **15a** and **15b**, it should be noted that the stereochemistry of the nitrogen atom has been set as trigonal (sp^2 hybridisation) and this is justified by X-ray data reported by Agmon et al.[23]



Scheme 3. Reaction of the ribbon 1,3-diene **7** with phthalazinedione **14** to form hinged product **15** and conformational alternatives **15a** and **15b** (E = CO_2Me).

The advantage of using phthalazine diones as dienophiles in our tandem cycloaddition protocol is that it provides rapid entry to compounds containing the octahydro-methanodiazanaphthacene ring **22** (Scheme 4d). Using the phthalazine dione **14** also introduces carbonyl groups as part of the amide in ring C and ensures planarity of that ring. This cycloaddition

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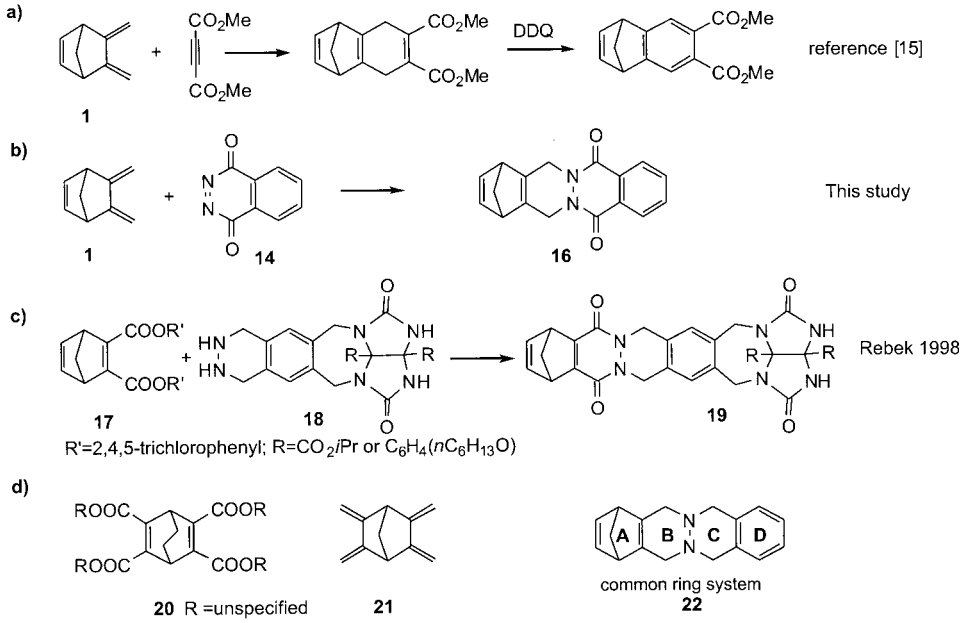
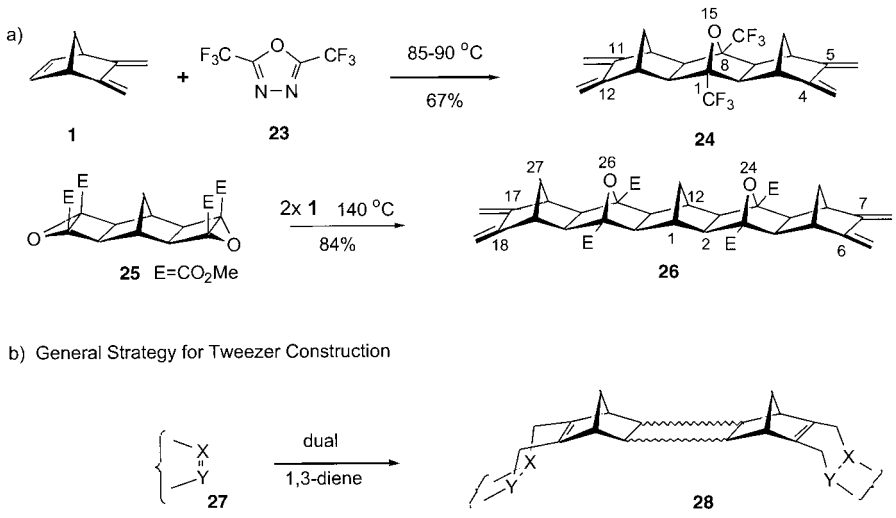
methodology complements work described in recent reports by Rebek and co-workers[7] who used displacement chemistry to gain access to the same basic octahydromethano-diazanaphthacene ring, except that their system has the amide in the B-ring of **22**. These workers utilise the bent stereochemistry of the tetrahydropyridazine component (ring C in their case) to achieve the C-shaped topology required for "tennis ball" self-assembly processes. Construction of their C-shaped (or W-shaped or S-shaped) systems is achieved by dual application of their condensation procedure on the alicyclic tetraester **20**. As discussed below, our protocol also provides access to cavity systems containing flexible tetrahydropyridazine links (ring B in our case) by employing cycloadditions onto dual 1,3-dienes of type **24** (Scheme 5a). Access to simpler systems should also be available by cycloaddition onto alicyclic tetraene **21**[24] for which carbon dienophilic addition has been used many times in the preparation of spacer and cavity systems.[25]



Scheme 4. a) Formation of a hinged adduct from DMN **1** as an intermediate in the preparation of benzonorbornadienes; b) The cycloaddition of phthalazinedione with DMN **1** to form the tetracyclic ring system **16**; c) The ester, amine condensation route to hinged ribbon molecules containing common ring system **22**; d) Doubly functionalised reagents **20** (condensation route) and **21** (cycloaddition route) for dual coupling protocols.

Preparation and reactions of molrac dual 1,3-diene systems 24: We have investigated the coupling of two DMN **1** units together through the norbornene π-bond as a route to space-separated 1,3-diene systems; this was with the aim of using such dual 1,3-dienes as the central unit in flexible cavity molecule formation (Scheme 5b). To this end, DMN **1** was treated with 2,5-bis(trifluoromethyl)-1,3,4-oxadiazole **23** to form the dual 1,3-diene BLOCK **24**. The reaction was carried out in a sealed tube with a solution in benzene and slowly afforded **24** at 85–90 °C; attempts to speed up the reaction at higher temperature (120–140 °C) produced only polymeric material. Accordingly, the dual 1,3-diene **24** was isolated from the lower temperature cycloaddition (67% yield after 24 h) and fully characterised.

Reaction of DMN **1** with the bis-cyclobutene epoxide **25** (Scheme 5a) furnished the spacer tetraene **26** in excellent yield (84%) by site-selective 1,3-dipolar cycloaddition of DMN **1** at each of the cyclobutene epoxide sites. This was a particularly important result since there is a whole range of bis-epoxides available in different topologies;[11e, 26] this thereby opens the way to modify the distance between the terminal 1,3-diene units and also presents an opportunity to modify their relative orientation. The structure of **26** was readily deduced by using ^{1}H NMR spectroscopy, from which the C_{2v} symmetry was apparent in the spectrum, for example, only a



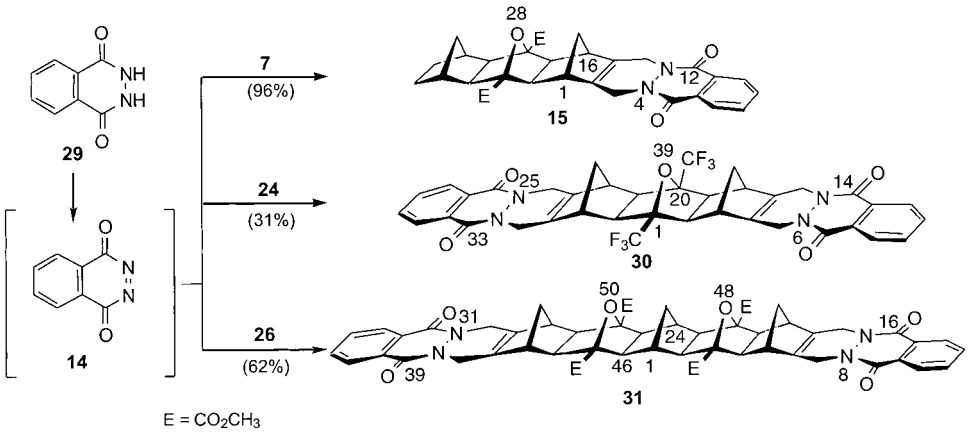
Scheme 5. a) Preparation of doubly functionalised 1,3-dienes; b) Schematic representation for the preparation of large ribbon molecules containing two molecular hinges (E = CO_2Me).

single ester methyl resonance was observed; there were two types of bridge methano groups, the central one a singlet (2H) whereas the outer ones were split into a pair of doublets (typically the inner H is sterically compressed and occurs at low field $\delta = 2.36$, whereas the outer resonance occurs at $\delta = 1.03$); a single set of finely coupled vinylic protons and four other uncoupled methine singlets were also apparent from the spectrum (ratio 1:2:2:2).

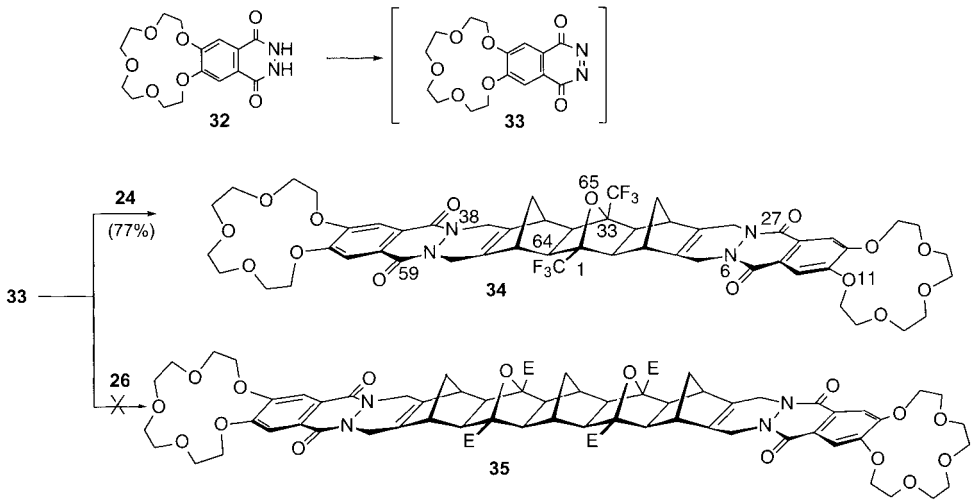
The dual 1,3-dienes **24** and **26** were not stable and underwent polymerisation when left to stand at room temperature forming insoluble polymeric solids, which contrasted with the good stability exhibited by the mono-1,3-dienes **7**, **9**, **11** and **13**. Cycloaddition reactions needed to be conducted soon after dual 1,3-diene generation and cycloaddition products were often contaminated by polymeric by-products.

Formation of molecular tweezers: 1,4-Phthalazinedione **14** was generated by lead tetraacetate oxidation of phthalhydrazide **29**[27] and trapped in situ with different norbornane exocyclic 1,3-dienes. The results are summarised in Scheme 6. Reaction with the simple 1,3-diene **7** gave an almost quantitative yield of the adduct **15**. As a result of the instability of the dual 1,3-dienes **24** and **26**, their reactions gave lower yields of adducts **30** and **31** with phthalazine dione **14**, together with substantial amounts of polymeric by-products. From the ^{1}H NMR spectra, the products **15**, **30**, and **31** all showed, diagnostically, two broadened doublets at $\delta = 4.4 - 4.9$, which correspond to the magnetically nonequivalent methylene protons of the newly formed tetrahydropyridazine ring.

With this success, an extension of the method to include reaction of a functionalised phthalazine dione was pursued using the benzo-15-crown-5 fused phthalazinedione **33** (Scheme 7). Reaction of dual 1,3-diene **24** with the 15-crown-5 substituted phthalazine dione **33**[28] gave the desired bis-crown product **34** in good yield (77%). During the reaction, ultrasonication was used at the beginning of the addition of lead tetraacetate in order to improve the reactivity because the reactant **32** had low solubility in the reaction media (AcOH/DCM). Like other adducts, the bis-crown ether **34** also showed two diagnostically broadened doublets at $\delta = 4.4 - 4.9$ in the ^{1}H NMR spectrum. In the present study, none



Scheme 6. Examples of mono-adducts, for example, **15**, and dual-coupled systems, for example, **30** and **31**, available from the Diels – Alder cycloaddition of polyalicyclic 1,3-dienes with diaza-dienophiles.



Scheme 7. Application of the coupling technique to the preparation of hinged crown ether **34** and the unexpected failure to produce the higher polynorbornane analogue **35** (E = CO_2Me).

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of the desired bis-crown adduct **35** was obtained in the reaction of the crown-phthalazine dione **33** with the dual 1,3-diene **26**.

Molecular modelling: Molecular modelling (Sybyl) was used to predict the possible geometrical change for the phthalazine dione adducts **30** and **31** caused by conformational change in the tetrahydropyridazine rings (Figure 1). The substituents at the bridgehead positions were removed from the molecules in order to simplify the calculations, especially as the separate mobility of the ester substituents causes problems because of the possible formation of local minima. For the same reason, the crown ether rings were not included in these calculations. The stripped down versions are given numbers within inverted commas, for example, **′30′** and **′31′** to distinguish them from the actual molecules (Figure 2).

In the **A**-series, no constraints were placed on the system. In the resultant optimised geometries, the tetrahydropyridazine rings have adopted a twist-boat conformation, the pyridazine dione rings are planar and a U-shaped product is obtained. The distances between two ends of the molecule are 19.62 Å for **′30′** and 17.59 Å for **′31′**.

In the **B**-series, constraints have been placed on the tetrahydropyridazine ring, such that the CCCC atoms are coplanar and the CCNN atoms are coplanar; no constraints are placed on the CCNC atoms. In these cases, the dihydropyridazine ring becomes essentially planar and a U-shaped product is obtained, which is very similar in many dimensions to the **A**-series. The main feature is the near C_{2v} symmetry of the molecules and separations of the terminal benzene rings comparable with the unconstrained model (19.56 Å for **′30′**; 17.17 Å for **′31′**).

When the conformation of the tetrahydropyridazine ring is constrained into an inward-directed boat conformation (conformation **C**), the two ends of the molecules are brought towards each other. In **′31′C**, the termini close to within 6.86 Å, which would be too close to accommodate terminally fused crown ether rings. However, it was very interesting to note that in the system with the shorter frame, **′30′C**, the two ends hold a parallel geometry and should be a good model for face-to-face bis-crown ether alignment.

In conformation **D**, the boat configuration of the tetrahydropyridazine rings is bent outwards and the resultant structures are far different from those conformations with U-shape geometry. The extended conformations present in

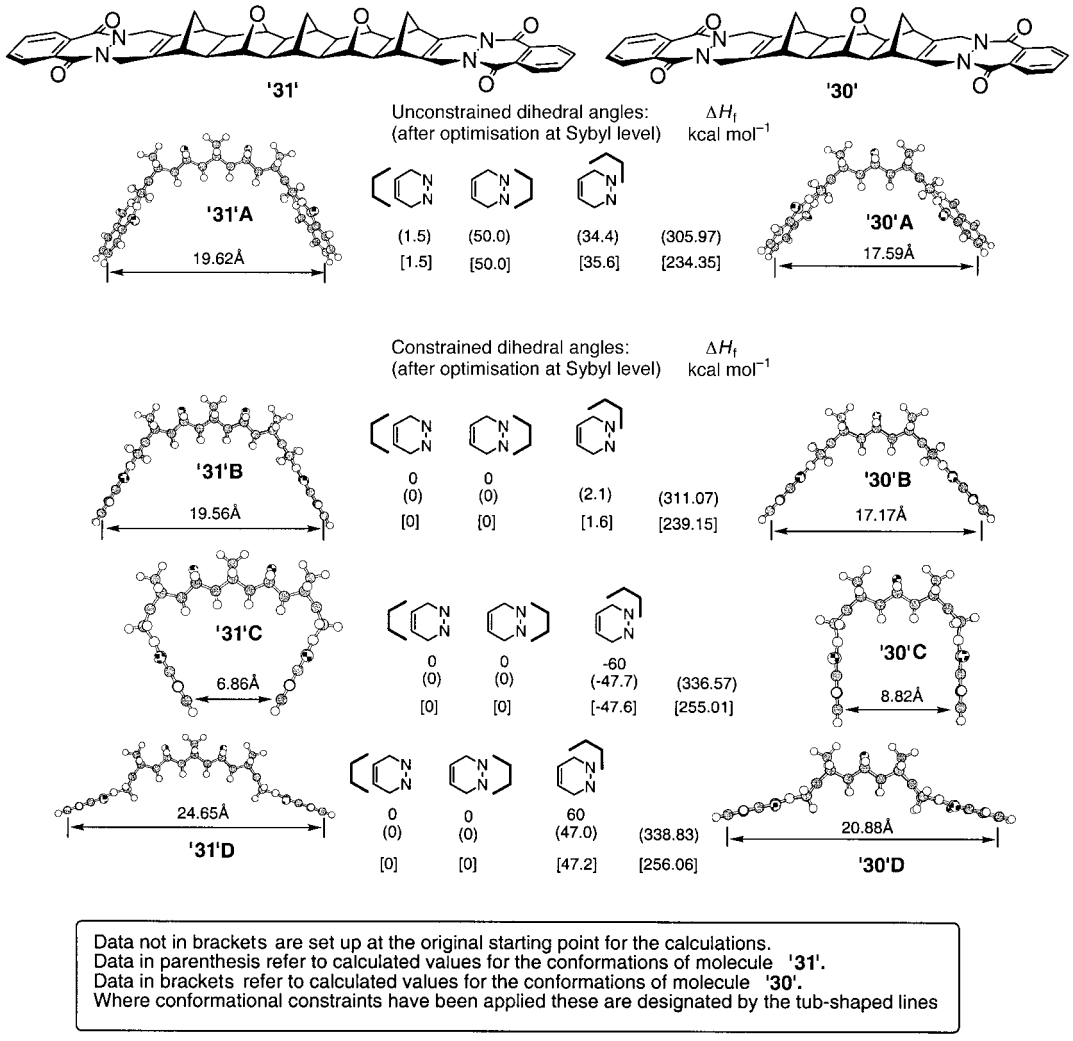


Figure 2. Molecular topologies for "stripped down" systems **′30′** and **′31′** associated with conformational changes in the tetrahydropyridazine ring.

this topology make them excellent candidates for the formation of intermolecular sandwich-like compounds using metal complexation of the crown ethers.

The calculated heats of hydrogenation of the various conformers indicate that conformers **A** and **B** are of the lowest energy and that conformers **C** and **D**, while of similar energy to one another, are more than 20 Kcal mol^{-1} higher in energy. This indicates that conformers **C** and **D** are likely to be only minor components under equilibrium conditions in solution. The importance of minor conformations in solution is demonstrated by the findings of Rebek and his co-workers for the related bis-glycoluril compounds (see above), where the presence of conformers of type **C** is imperative for the attainment of the C-shaped geometry required to allow formation of the "tennis ball" self-assemblies.

Conclusion

The use of 1,3-dipolar cycloadditions at the norbornene π-bond of 5,6-dimethylenenorbornene **1** combined with Diels–Alder cycloaddition at the 1,3-diene site has provided a versatile route to rigid ribbon frameworks containing a conformational hinge. Each cycloaddend can carry its own auxiliary, so the method is extremely versatile and has the additional features of synthetic brevity and high yields. Dual application of this strategy has led to a short route to flexible molecular tweezers.

Experimental Section

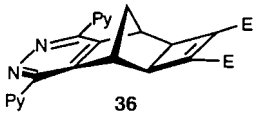
General methods: Melting points, which were uncorrected, were obtained on a Reinhart Micro hot stage melting point apparatus Model YOSCO No. 67885. ^{1}H NMR spectra were recorded at 300 or 400 MHz. ^{13}C NMR spectra were recorded by using an inverse gated sequence at 75.4 MHz. Unless otherwise stated all data were acquired using solutions in $CDCl_3$ with TMS as an internal standard and are reported on the appropriate ^{1}H NMR δ and ^{13}C NMR δ scales. Coupling constants are reported in Hz. Silica gel 60 (230–400 mesh) was used for column chromatography. TLC was performed on Merck aluminium sheets coated with silica gel 50 F_{254}. Centrifugal radial chromatography was carried out with a Chromatotron, Model No. 7924T, using plates (1 mm) coated with silica gel 60 F_{254}.

Mass spectra were obtained by EI or PCI (photochemical ionisation) on a Hewlett Packard 5988A spectrometer or by EI or ESMS (electrospray mass spectrometry) on a Micromass Platform II single quadripole mass spectrometer.

(1*R*,2*S*,3*R*,5*S*,6*R*,7*S*)-Dimethyl-4,6-dioxatetracyclo[5.2.1.0^{2,6}.0^{3,5}]deca-3,5-dicarboxylate (6): *t*BuOOH (0.6 mL, 2.28 mmol), followed by a solution of MeLi in diethyl ether (0.6 mL, 0.95 mmol), was added with stirring to a stirred solution of dimethyl-tricyclo[4.2.1.0^{2,5}]nona-3-ene-3,4-dicarboxylate[33] (0.20 g, 0.85 mmol) in dry THF (2 mL), which had been cooled to −78 °C . The solution turned deep yellow and after stirring for 2 h the temperature was allowed to rise to RT. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous Na_2SO_3 (5%), water and dried over sodium sulfate. Evaporation of solvent yielded an opaque oil, which was titurated with EtOAc/hexane and recrystallised from CH_2Cl_2/ether to yield the title compound **6** (128 mg, 60%) as white needles (m.p. 197–199 °C).

^{1}H NMR (300 MHz, $CHCl_3$, 25 °C, TMS): δ = 3.79 (s, 6H; 2 × CH_3), 2.72 (br s, 2H; 2 × CH), 2.31 (s, 2H; 2 × CH), 1.76 (d, ^3J(H,H) = 11 Hz, 1H; bridge CH_2), 1.58 (m, 2H; CH_2), 1.34 (d, ^3J(H,H) = 11 Hz, 1H; bridge CH_2), 1.08 (m, 2H; CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C, TMS): δ = 165.1, 64.6, 52.9, 50.5, 36.6, 33.7, 28.0; LRMS (PCI, CH_4): *m*/*z* (%): 253 (100) [M^++1], 221 (19), 207 (12), 193 (17), 165 (59); HRMS (EI): *m*/*z* (%): calcd for $C_{13}H_{16}O_5$ 252.0998; found 252.0991.

(1*R*,2*S*,7*R*,8*S*,9*R*,10*S*,12*R*,13*S*)-Dimethyl-3,5-di(2-pyridyl)-4,5-diaza-11,14-dioxapentacyclo[6.5.1.0^{2,7}.0^{9,13}.0^{10,12}]tetradeca-2,4,6-triene-10,12-dicarboxylate (10): The cyclobutene diester **36**[29] E = CO_2Me, 1.0 g, 2.273 mmol) was placed in a two-neck flask, fitted with septum, under a nitrogen atmosphere, and dissolved in dry THF (20 mL). The solution was then cooled to −78 °C using a dry-ice/acetone bath. Anhydrous[30] *t*BuO_2H (1.0 mL, 2.97 mmol, 3 M in toluene, 1.25 equivalent) was added using a syringe. After 5–10 min, MeLi (2.36 mL, 3.30 mmol, 1.4 M solution in diethyl ether, 1.4 equivalent) was added using a syringe, which caused the colour to change. After stirring for an additional 15–20 min, the dry-ice bath was removed and the solution was stirred at room temperature for three hours. During that period, the solution became less yellow in colour. Dichloromethane was added to the flask and the contents were transferred to a separating funnel, washed with sodium sulfite (10%), water and dried ($MgSO_4$). Removal of the solvent under vacuum yielded the crude epoxide **10**, which was purified by recrystallisation from ethyl acetate (0.210 g, 27.6%, m.p. 152–154 °C).



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^{1}H NMR (300 MHz, $CHCl_3$, 25 °C, TMS): δ = 8.66 (d, ^3J(H,H) = 4.0 Hz, 2H), 8.46 (d, J = 8.0 Hz, 2H), 7.77 (dd, ^3J(H,H) = 7.7, ^3J(H,H) = 1.6 Hz, 2H), 7.26 (t, J = 6.6 Hz, 2H), 4.84 (s, 2H), 3.87 (s, 6H), 2.64 (s, 2H), 2.10 (d, ^3J(H,H) = 10.8 Hz, 2H), 1.85 (d, ^3J(H,H) = 10.8 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C, TMS): δ = 164.28, 155.10, 152.78, 149.27, 147.41, 136.70, 123.85, 122.69, 65.38, 52.80, 52.50, 48.89, 42.75, 41.59; LRMS (EI): *m*/*z* (%): 456 [M]$^+$ (3.9), 272 (100.0), 243 (21.1), 242 (22.6), 153 (48.1), 44 (49.5); HRMS: *m*/*z* (%): calcd for $C_{25}H_{20}0_4N_4$ 440.1484; found 440.1485.

General procedure for ACE coupling reactions of 5,6-dimethylenenorbornene 1

a) *Thermal route*: A solution of the epoxide (0.1 mmol) and 5,6-dimethylenenorbornene **1** (0.1 mmol) in dichloromethane (0.16 mL) was heated in a sealed tube at 140 °C in an oven for 2–3 h. Purification by chromatotron (eluted with petrol/EtOAc) followed by recrystallisation provided the desired adduct.

b) *Photochemical route*: A solution of epoxide and the dipolarophile in acetone was irradiated for two hours at 300 nm in a quartz tube, the solvent removed under vacuum and purified by chromatography or recrystallisation.

(1*SR*,2*RS*,3*RS*,6*SR*,7*SR*,8*RS*,9*RS*,10*SR*,13*RS*,14*SR*)-Dimethyl-4,5-bismethylene-15-oxahexacyclo[6.6.1.1^{3,6}.1^{10,13}.0^{2,7}.0^{9,14}]heptadecane-1,8-dicarboxylate (7): The compound was prepared by the reaction of DMN **1** with epoxide **6** (m.p. 186–189 °C, white rods, EtOAc/petrol, stereochemistry was confirmed by X-ray single-crystal analysis).[21] The yield was 31%.

^{1}H NMR (400 MHz, $CHCl_3$, 25 °C, TMS): δ = 5.09 (s, 2H), 4.82 (s, 2H), 3.87 (s, 6H), 2.64 (br s, 2H), 2.43 (dt, J = 10.0, 1.5 Hz, 1H), 2.26 (d, ^3J(H,H) = 1.0 Hz, 2H), 2.19 (dm, ^3J(H,H) = 10.0 Hz, 1H), 2.06 (br s, 4H), 1.34–1.42 (m, 2H), 1.03–1.11 (m, 3H), 0.83 (dm, ^3J(H,H) = 10.0 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C, TMS): δ = 170.52, 151.25, 101.78, 91.12, 56.48, 55.34, 52.69, 48.25, 38.96, 34.64, 34.60, 29.49; MS (EI, 70 eV): *m*/*z* (%): 370 [M]$^{+\bullet}$ (21), 311 (8), 279 (9), 253 (8), 251 (13), 189 (10), 153 (15), 129 (14); HRMS: *m*/*z* (%): calcd for $C_{22}H_{26}O_5$ 370.1780; found 370.1781.

(1*RS*,2*RS*,3*RS*,10*SR*,11*SR*,12*SR*,13*SR*,14*SR*,17*RS*,18*RS*)-Dimethyl-15,16-bismethylene-19,20-dioxaheptacyclo[10.6.1.13,10.114,7.02,11.04,9.013,18]-heneicosa-4,6,8-trien-1,12-dicarboxylate (9): The compound was prepared by the reaction of DMN **1** with epoxide **8**[34] (m.p. 250 °C (dec), white solid, EtOAc/petrol). The yield was 51%.

^{1}H NMR (300 MHz, $CHCl_3$, 25 °C, TMS): δ = 7.22 (dd, ^3J(H,H) = 5.4, 3.0 Hz, 2H), 7.12 (dd, ^3J(H,H) = 5.4, 3.0 Hz, 2H), 5.22 (s, 2H), 5.08 (s, 2H), 4.81 (s, 2H), 3.97 (s, 6H), 2.69 (t, ^3J(H,H) = 1.3 Hz, 2H), 2.55 (dt, ^3J(H,H) = 10.0, 1.2 Hz, 1H), 2.37 (s, 2H), 2.21 (d, ^3J(H,H) = 0.9 Hz, 2H), 1.12 (dm, ^3J(H,H) = 10.0 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C, TMS): δ = 170.40, 150.84, 146.05, 127.68, 120.01, 102.17, 89.88, 81.13, 55.54, 55.16, 53.15, 48.22, 34.87; HRMS: *m*/*z* (%): calcd for $C_{25}H_{24}O_6$ 420.1573; found 420.1573.

(1*SR*,2*SR*,3*RS*,10*SR*,11*RS*,12*RS*,13*SR*,14*SR*)-Dimethyl-15,16-bismethylene-5,8-di(2-pyridyl)-6,7-diaza-19-oxaheptacyclo[10.6.1.1.^{3,10}.1^{14,17}.0^{2,11}.0^{4,9}.

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$0^{13,8}$]heneicosa-4,6,8-trien-1,12-dicarboxylate (11): The compound was prepared by the reaction of DMN **1** with epoxide **10** (m.p. 251 °C (dec), white crystals, EtOAc/petrol). The yield was 66 %.

^{1}H NMR (400 MHz, $CHCl_3$, 25 °C, TMS): $\delta = 8.75$ (dm, $^3J(H,H) = 4.8$ Hz, 2H), 8.58 (d, $^3J(H,H) = 8.0$ Hz, 2H), 7.89 (td, $^3J(H,H) = 7.8$, 1.8 Hz, 2H), 7.37 (ddd, $^3J(H,H) = 7.5$, 4.8, 1.0 Hz, 2H), 5.06 (s, 2H), 4.80 (s, 2H), 4.40 (s, 2H), 4.04 (s, 6H), 2.88 (d, $^3J(H,H) = 10.1$ Hz, 1H), 2.75 (s, 2H), 2.53 (d, $^3J(H,H) = 10.1$ Hz, 1H), 2.49 (s, 2H), 2.33 (s, 2H), 1.38 (d, $^3J(H,H) = 10.1$ Hz, 1H), 1.12 (d, $J = 10.1$ Hz, 1H); HRMS: *m*/*z* (%): calcd for $C_{34}H_{30}N_4O_5$ 574.2216; found 574.2216.

(1*RS*,12*SR*,13*RS*,14*SR*,15*SR*,16*SR*,19*RS*,20*RS*,21*RS*,22*SR*)-Dimethyl-17,18-bismethylene-4,10-dimethoxy-24-oxa-octacyclo[10.10.1.1^{14,21}.1^{16,19}.0^{2,11}.0^{4,9}.0^{13,22}.0^{15,20}]pentacosa-2,4,6,8,10-pentaen-14,21-dicarboxylate (13): A solution of epoxide **12** (60 mg, 0.146 mmol) and DMN **1** (160 mg, excess) in acetone (1 mL) was irradiated at 300 nm in a quartz NMR tube for two hours. Solvent and excess of DMN **1** were removed under vacuum and the solid residue was recrystallised from methanol to afford the adduct **13** as a colourless solid (51 mg, m.p. 291–293 °C). The yield was 66 %.

^{1}H NMR (400 MHz, $CHCl_3$, 25 °C, TMS): $\delta = 8.05$–8.09 (m, 2H), 7.43–7.46 (m, 2H), 5.08 (s, 2H), 4.82 (s, 2H), 3.99 (s, 6H), 3.98 (s, 6H), 3.64 (s, 2H), 2.75 (d, $^3J(H,H) = 9.6$ Hz, 1H), 2.71 (s, 2H), 2.51 (d, $^3J(H,H) = 10.0$ Hz, 1H), 2.39 (s, 2H), 2.29 (s, 2H), 1.43 (d, $^3J(H,H) = 9.6$ Hz, 1H), 1.12 (d, $^3J(H,H) = 10.0$ Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C, TMS): $\delta =$ 169.9, 150.5, 144.5, 134.7, 128.4, 125.9, 122.6, 101.9, 90.2, 61.8, 55.7, 55.4, 52.8, 47.9, 43.3, 42.3, 34.5; HRMS: *m*/*z* (%): calcd for $C_{32}H_{32}O_7$ 528.2148; found 528.2138.

(2*RS*,3*RS*,6*SR*,7*SR*,9*RS*,10*RS*,13*SR*,14*SR*)-1,8-Bis(trifluoromethyl)-4,5,11,12-tetramethylene-hexacyclo[6.6.1.1^{3,6}.1^{10,13}.0^{2,7}.0^{9,14}]heptadecane (24): A mixture of 2,5-bis(trifluoromethyl)-1,3,4-oxadiazole[31] (65 mg, 0.314 mmol) and **1** (186 mg, 0.629 mmol) in benzene (0.4 mL) was heated in a sealed tube in an oven (90 °C) for five days. Concentration of the resulting solution afforded a gum, which crystallised from methanol to give the bis-1,3-diene **27** as white crystals (m.p. > 400 °C).

^{1}H NMR (400 MHz, $CHCl_3$, 25 °C, TMS): $\delta = 5.11$ (s, 4H), 4.85 (s, 4H), 3.09 (br s, 4H), 2.24 (s, 4H), 2.14 (d, $^3J(H,H) = 10.0$ Hz, 2H), 1.22 (dm, $^3J(H,H) = 10.0$ Hz, 2H); HRMS: *m*/*z* (%): calcd for $C_{22}H_{20}F_6O$ 414.1418; found 414.1418.

(2*SR*,3*SR*,4*RS*,5*RS*,8*SR*,9*SR*,10*RS*,11*RS*,13*SR*,14*SR*,15*RS*,16*RS*,19*SR*,20*SR*,21*RS*,22*RS*)-Tetramethyl-6,7,17,18-tetramethylene-24,26-dioxadeca-cyclo[10.10.1.1^{3,10}.1^{5,8}.1^{14,21}.1^{16,19}.0^{2,11}.0^{4,9}.0^{13,22}.0^{15,20}]-heptacosan-3,10,14,21-tetracarboxylate (26): The bis-diene **26** was obtained by following the general thermal ACE coupling procedure, employing a 2:1 ratio of 5,6-dimethylenenorbornene **1** with bis-epoxide **25**[10, 32] (m.p. > 400 °C, white solid, low solubility in $CDCl_3$ or DMSO). The yield was 84 %.

^{1}H NMR (400 MHz, $CHCl_3$-[D_6]DMSO (3:1), 25 °C, TMS): $\delta = 5.08$ (s, 4H), 4.81 (s, 4H), 3.85 (s, 12H), 3.82 (s, 4H), 2.61 (s, 4H), 2.36 (d, $J =$ 9.8 Hz, 2H), 2.20 (s, 4H), 1.03 (d, $^3J(H,H) = 9.3$ Hz, 2H), 0.83–0.95 (m, 4H) (easily polymerised in solution); LRMS (EI, 70 eV): *m*/*z* (%): 644 $[M]^{+\cdot}$ (67), 55 (16), 44 (100).

Diels–Alder reaction of norbornane exocyclic dienes with phthalazine-dione 16, general procedure: A mixture of norbornane exocyclic diene (0.1 mmol) and phthalhydrazide (0.15 mmol) in acetic acid (1.4 mL) or acetic acid/DCM (1.0 mL/0.5 mL) was treated with lead tetraacetate (0.15 mmol). The mixture was stirred in darkness overnight (to improve the contact of the reagents, the mixture was ultrasonicated for a few minutes at the beginning of the reaction). The mixture was filtered through a plug of supercell and the flask rinsed with DCM. The combined filtrates were washed with saturated K_2CO_3 solution, brine and dried ($MgSO_4$). Concentration gave the solid product, which was further purified by recrystallisation.

(1*RS*,16*SR*,17*RS*,18*SR*,19*SR*,20*RS*,23*SR*,24*RS*,25*RS*,26*SR*)-Dimethyl-4,13-diaza-28-oxa-nonacyclo[14.10.1.1^{18,25}.1^{20,23}.0^{2,5}.0^{4,13}.0^{6,11}.0^{17,26}.0^{19,24}]nona-cosa-2(15),6,8,10-tetraen-5,12-dione-18,25-dicarboxylate (15): The compound was produced from the cycloaddition of phthalazine dione **14** with diene **7** (m.p. 288–290 °C, white needles, CH_2Cl_2/MeOH). The yield was 96 %.

^{1}H NMR (300 MHz, $CHCl_3$, 25 °C, TMS): $\delta = 8.31$ (dd, $^3J(H,H) = 5.9$, 3.3 Hz, 2H; H7/H10), 7.80 (dd, $^3J(H,H) = 5.9$, 3.3 Hz, 2H; H8/H9), 4.77 (dm, $^3J(H,H) = 15.6$ Hz, 2H; equatorial H3/H14), 4.51 (dm, $^3J(H,H) =$ 15.6 Hz, 2H; axial H3/H14), 3.89 (s, 6H; 2 × $COOCH_3$), 2.79 (s, 2H; H1/H16), 2.56 (dm, $^3J(H,H) = 9.1$ Hz, 1H; 27-Ha), 2.23 (dm, $^3J(H,H) = 9.7$ Hz, 1H; 29-Ha), 2.21 (s, 2H; H17/H26), 2.10 (br s, 2H; H20/H23), 2.06 (s, 2H; H19/H24), 1.41 (br d, $^3J(H,H) = 7.5$ Hz, 2H; H21/H22), 1.22 (d, $^3J(H,H) =$ 9.1 Hz, 1H; 27-Hb), 1.07 (br d, $^3J(H,H) = 7.0$ Hz, 2H; H21/H22), 0.87 (d, $^3J(H,H) = 9.7$ Hz, 1H; 29-Hb), (Ha pointing to oxygen atom and Hb to the other side); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 170.13$ ($COOCH_3$), 159.61 (C 5/12), 136.98 (C 2/15), 134.24 (C 8/9), 129.44 (C 6/11), 128.32 (C 7/10), 89.73 (C 18/25), 56.91 (C 19/24), 55.87 (*C* 17/26), 52.81 (2 × $COOCH_3$), 46.58 (C 1/16), 45.79 (C 3/14), 41.24 (C 27) 38.91 (C 20/23), 34.62 (C 29), 29.47 (C 21/22); HRMS: *m*/*z* (%): calcd for $C_{30}H_{30}N_2O_7$ 530.2053; found 530.2050.

(2*RS*,3*RS*,18*SR*,19*SR*,21*RS*,22*RS*,37*SR*,38*SR*)-1,20-Bis(trifluoromethyl)-6,15,25,34-tetraaza-39-oxadodecacyclo[18.18.1.1^{3,18}.1^{22,37}.0^{2,10}.0^{4,17}.0^{6,15}.0^{8,13}.0^{21,38}.0^{22,36}.0^{25,34}.0^{27,32}]hentetraconta-4(17),8,10,12,23(36),27,29,31-octaen-7,14,26,33-tetraone (30): The compound was prepared from dual-cycloaddition of phthalazine dione **14** with tetraene **24** (m.p. > 350 °C, pale yellow solid). The yield was 31 %.

^{1}H NMR (400 MHz, $CHCl_3$, 25 °C, TMS): $\delta = 8.25$ (dd, $J = 5.9$, 3.3 Hz, 4H), 7.79 (dd, $J = 5.9$, 3.3 Hz, 4H), 4.77 (dm, $^3J(H,H) = 15.7$ Hz, 4H), 4.48 (dm, $^3J(H,H) = 15.7$ Hz, 4H), 3.26 (br s, 4H), 2.32 (d, $^3J(H,H) = 9.9$ Hz, 2H), 2.29 (s, 4H), 1.49 (d, $^3J(H,H) = 9.9$ Hz, 2H).

(2*RS*,3*RS*,4*RS*,5*RS*,20*SR*,21*SR*,22*SR*,23*SR*,25*RS*,26*RS*,27*RS*,28*RS*,43*SR*,44*SR*,45*SR*,46*SR*)-Tetramethyl-8,17,31,40-tetraaza-48,50-dioxa-hexadeca-cyclo[22.22.1.1^{3,22}.1^{5,20}.1^{26,45}.1^{28,43}.0^{2,23}.0^{4,20}.0^{6,19}.0^{8,17}.0^{19,15}.0^{25,46}.0^{27,44}.0^{29,42}.0^{31,40}.0^{33,38}]henpentaconta-6(19),10,12,14,29(42),33,35,37-octaen-9-16,32,39-tetra-one-3,21,25,45-tetracarboxylate (31): The compound was prepared from dual-cycloaddition of phthalazine dione **14** with tetraene **26** (m.p. > 350 °C, white solid). The yield was 62 %.

^{1}H NMR (400 MHz, $CHCl_3$, 25 °C, TMS): $\delta = 8.28$ (dd, $J = 5.9$, 3.3 Hz, 4H), 7.79 (dd, $^3J(H,H) = 5.9$, 3.3 Hz, 4H), 4.75 (dm, $^3J(H,H) = 15.6$ Hz, 4H), 4.47 (dm, $^3J(H,H) = 15.6$ Hz, 4H), 3.88 (s, 12H), 2.76 (s, 4H), 2.49 (d, $^3J(H,H) =$ 8.9 Hz, 2H), 2.14 (s, 4H), 2.06 (s, 2H), 2.04 (s, 2H), 1.95 (s, 4H), 0.87 (d, $^3J(H,H) = 8.9$ Hz, 2H).

(2*RS*,3*RS*,31*SR*,32*SR*,34*RS*,35*RS*,63*SR*,64*SR*)-1,33-Bis(trifluoromethyl)-6,28,38,60-tetraaza-11,14,17,20,23,43,46,49,52,55,65-undecaoxa-tetradeca-cyclo[31.31.1.1^{3,31}.1^{35,63}.0^{2,32}.0^{4,30}.0^{6,28}.0^{8,26}.0^{10,24}.0^{34,64}.0^{36,62}.0^{38,60}.0^{40,58}.0^{42,56}]hep-tahexaconta-4(30),8,10(24),25,36(62),40,42(56),57-octaen-7,27,39,59-tetra-one (34): The compound was prepared from dual-cycloaddition of crown phthalazine dione **33** with tetraene **24** (m.p. 274–276 °C, pale yellow solid). The yield was 77 %.

^{1}H NMR (400 MHz, $CHCl_3$, 25 °C, TMS): $\delta = 7.47$ (s, 4H), 4.73 (dm, $^3J(H,H) = 16.2$ Hz, 4H), 4.44 (dm, $^3J(H,H) = 16.2$ Hz, 4H), 4.22 (m, 8H), 3.92 (m, 8H), 3.73 (m, 16H), 3.25 (br s, 4H), 2.35 (d, $^3J(H,H) = 8.4$ Hz, 2H), 2.31 (s, 4H), 1.47 (d, $^3J(H,H) = 8.4$ Hz, 2H).

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