# Anion recognition and anion-mediated self-assembly with thiourea-functionalised fused [3]polynorbornyl frameworks†

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Three conformationally preorganised host molecules based on the [3]polynorbornyl framework and incorporating di-urea receptors were synthesised and their interaction with a series of anions investigated by $^1$H NMR spectroscopy. A high affinity of each host molecule for dihydrogenphosphate ($H_2PO_4^-$) and dihydrogenpyrophosphate ($H_2P_2O_7^{2-}$) was identified. In addition to binding to the urea receptors of the host molecules, evidence for an interaction involving the non-polar C–H groups within the binding cavity of the framework and guest anions was also discovered. Furthermore, an unusual 2 : 1 host-to-anion stoichiometry was indicated when binding $H_2P_2O_7^{2-}$, and a model for the anion-mediated self-assembly of this complex species is proposed.

## Introduction

In the rapidly maturing fields of anion binding, recognition and sensing[1–4] (and recognition in general) the use of a conformationally rigid host has several major advantages over the use of flexible ones. Firstly, the entropy penalty associated with such an organised bound state is paid during synthesis and *not* during anion binding. Therefore $\Delta G$ for binding will be greater for more rigid hosts.[2,5,6] Secondly, and perhaps more importantly, the receptor geometry is well defined, and a better selectivity for specific anions can be achieved.[7]

We have previously developed several examples of fluorescent and colorimetric anion sensors[3] and recently we have focused on the synthesis of structurally defined hosts for anion recognition.[4] When compared to conformationally rigid scaffolds that have been explored for anion-recognition purposes, such as steroids[8] and calixaranes,[9] the fused [*n*]polynorbornane frameworks (Fig. 1) have been largely overlooked. Nevertheless, this simple system has several features that are desirable for host–guest investigations. For instance, they can: *i*) be synthesised with a wide range of sizes and shapes,[10] and therefore offer the potential to target a variety of guest species selectively; *ii*) be prepared with a high degree of symmetry thereby simplifying characterisation and binding studies employing $^1$H NMR spectroscopy, and; *iii*) be easily functionalised at a variety of framework positions, Fig. 1. Indeed, previous studies on the [*n*]polynorbornane framework have involved the attachment of peptides and DNA-intercalating agents onto the structure at one or both ends of the scaffold.[11,12] The key reaction in the synthesis of the frameworks is a (4π + 2π) 1,3-dipolar cycloaddition reaction in which the thermal (~130 °C) ring opening of a cyclobutane epoxide generates a carbonyl ylide which subsequently cycloadds to the π-bond of a second norbornene.[13] This reaction is tolerant to a wide range of functional groups including esters, amides and carbamates,[11,12] which makes this system extremely attractive for the formation of novel supramolecular hosts. We detail herein the synthesis and use of a symmetric [3]polynorbornane framework, terminally functionalised with thiourea-based receptors, for the purpose of anion recognition.[14] We also investigated this rigid pre-organised structural motif for the development of novel anion-mediated supramolecular self-assembly structures using di-anions such as pyrophosphate, and show that anion-templated dimerisation is possible. Full synthetic details for the receptors are given, as is spectroscopic evaluation (using $^1$H-NMR) of their ability to bind anions and to construct self-assembled structures.

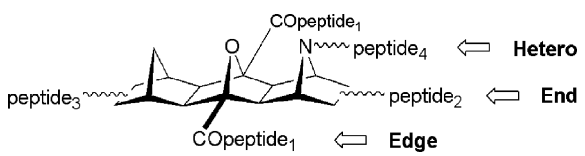


**Fig. 1** Structure and sites for attachment to fused [*n*]polynorbornanes.

## Results and discussion

### Design

Inorganic phosphate and pyrophosphate play key roles in both the environment and molecular biology.[15] It is therefore no surprise that molecules capable of recognising and binding such oxyanions have become the focus of several research groups.[16,17] As phosphate anions are tetrahedral, it is often difficult to recognise them without the use of metal ions such as Zn(II).[16] For a charge-neutral receptor for phosphate, in order to maximise the interaction of the receptor with the target species, a '*staple-like*' design was chosen (Fig. 2), comprised of a polynorbornane backbone to which two thiourea units were attached to form the '*staple*'. This design should enable both recognition motifs to co-operate[6] in binding

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† Electronic supplementary information (ESI) available: Proposed fluoride interaction with **1a** and **1b**; C–H titration curve against $H_2PO_4^-$ and fitplots for all titrations. See DOI: 10.1039/b703208k

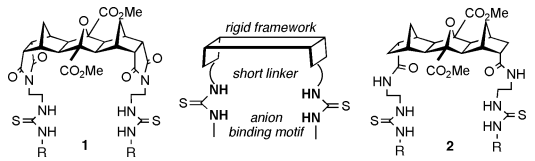



**Fig. 2** New hosts **1** and **2** showing general '*staple-like*' design.

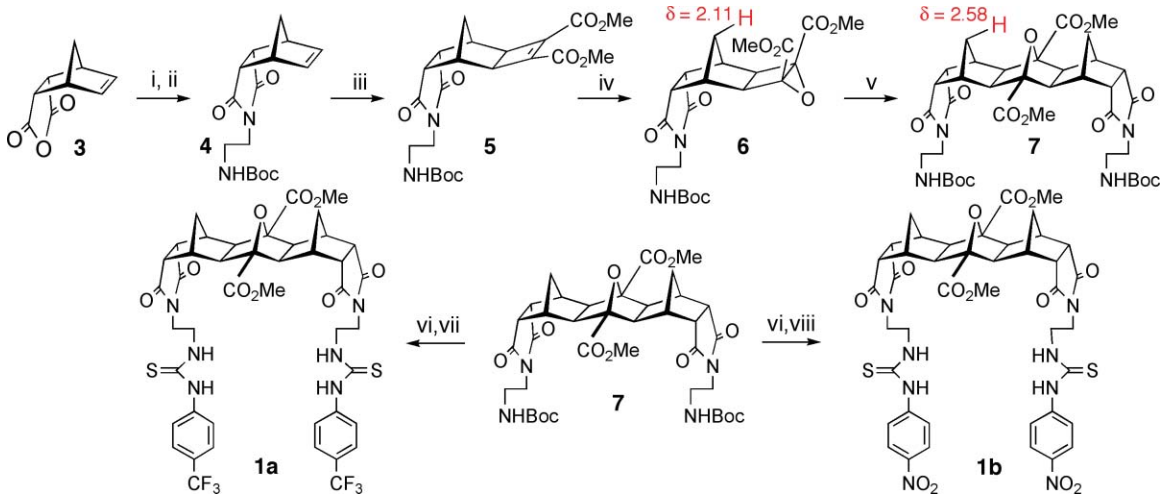
the target. A short, flexible, two-carbon spacer was included in the design in order to allow some '*induced fit*' between the host and the guest. Based on the above, two symmetric targets, **1** and **2** were chosen (Fig. 2). Compound **1** possesses dual $\sigma$ plane and $C_{2v}$ symmetry and 4 H-bond donors whilst compound **2** has only $C_{2v}$ symmetry but offers a total of 6 potential H-bond donors. A qualitative molecular modelling study identified the [3]polynorbornyl system to be of a suitable length (see later discussion) and the $N_{imide}$–$N_{imide}$ distance for **1** was calculated as 7.1 Å; a distance more than sufficient to capture phosphate that has an effective radius of 2.38 Å.[2]

**Synthesis of 1.** Heating *endo*-norbornene-2,3-anhydride **3** with 1,2-diaminoethane overnight afforded an imide in 51% yield, the nitrogen of which was protected with the *tert*-butoxycarbonyl (Boc) group to form **5** in 65% yield (Scheme 1).

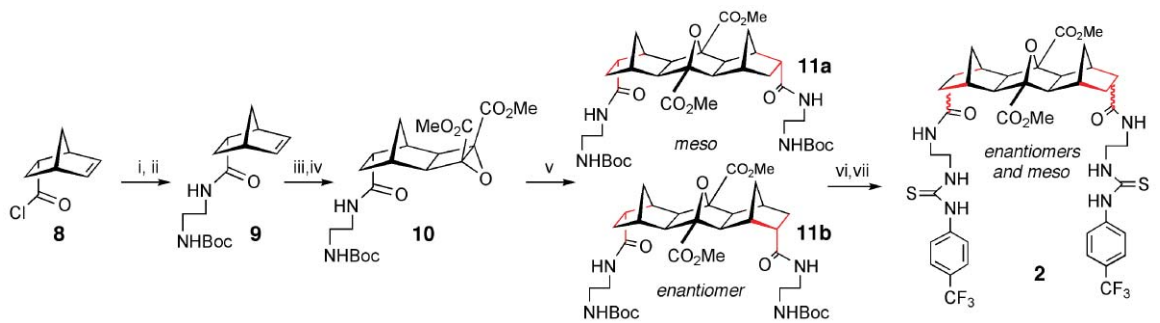
Formation of the cyclobutane epoxide is crucial for the final cycloaddition step to form the fused polynorbornane framework and is achieved in two steps: *i*) the Mitsudo reaction of norbornene with dimethyl acetylenedicarboxylate (DMAD),[18] followed by *ii*) Weitz–Scheffer epoxidation using *tert*butylhydroperoxide (TBHP).[19]

In the current study, the Mitsudo reaction of **4** with DMAD afforded the cyclobutene diester **5** in 67% yield, and epoxidation of this alkene diester using TBHP furnished the requisite epoxide **6** in 45% yield after chromatographic purification. The migration of the resonance assigned to the *syn*-bridgehead proton was indicative of oxirane formation (shown in red, Scheme 2).

The crucial cycloaddition to form the symmetric polynorbornyl framework was accomplished by heating epoxide **6** and the alkene **4** in a sealed tube overnight. The desired compound, **7**, was isolated in 71% yield following flash silica-column chromatographic purification. Once again, the resonance assigned to the bridge proton *syn* to the central oxygen of the framework of **7** was observed downfield ($\delta$ = 2.58 ppm, Scheme 2) from the corresponding proton of epoxide **6** ($\delta$ = 2.11 ppm). For the [3]polynorbornyl framework, the proton is locked into a pseudo H-bonding arrangement with the central oxygen and hence strong deshielding is observed. Removal of the Boc protecting groups




**Scheme 1** Synthesis of hosts **1a** and **1b**. *Reagents and conditions*: (i) 1,2-diaminoethane, 120 °C, 12 h, 51% (ii) di-*tert*-butyldicarbonate, DMAP, $NEt_3$, $CH_2Cl_2$, 12 h, 65% (iii) DMAD, $RuH_2(CO)(PPh_3)$, PhH, 80 °C, 12 h, 67% (iv) TBHP, KO$^t$Bu, THF, 0 °C, 12 h, 45% (v) **4**, $CH_2Cl_2$, sealed tube, 130 °C, 12 h, 71% (vi) 1 : 5 TFA–$CH_2Cl_2$, 12 h, ~100% (vii) *p*-trifluoromethylphenylisothiocyanate, $NEt_3$, 24 h, 70% (viii) *p*-nitrophenylisothiocyanate, $NEt_3$, 24 h, 45%.




**Scheme 2** Synthesis of host **2**. *Reagents and conditions*: (i) 1,2-diaminoethane, DMAP, $NEt_3$, $CH_2Cl_2$, 24 h, 57% (ii) di-*tert*-butyldicarbonate, DMAP, $NEt_3$, $CH_2Cl_2$, 12 h, 34% (iii) DMAD, $RuH_2(CO)(PPh_3)$, PhH, 80 °C, 12 h, 90% (iv) TBHP, KO$^t$Bu, THF, 0 °C, 12 h, 17% (v) **9**, $CH_2Cl_2$, sealed tube, 130 °C, 12 h, 66% (vi) 1 : 5 TFA–$CH_2Cl_2$, 12 h (vii) *p*-trifluoromethylphenylisothiocyanate, $NEt_3$, 24 h, 94%.

was readily achieved using dilute TFA and the resulting diamine, without further purification, was divided into two portions and reacted with *p*-trifluoromethylphenylisothiocyanate and *p*-nitrophenylisothiocyanate, to afford the two new receptors **1a** and **1b** in 70% and 45% yields, respectively. The new compounds were fully characterised and the $^1$H NMR spectrum of compound **1a** (Fig. 3) clearly illustrates the inherent symmetry of the large framework.

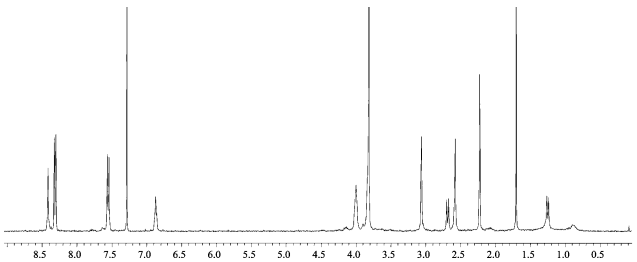



**Fig. 3** Proton NMR spectrum of new host **1a** in $CDCl_3$, showing the high degree of structural symmetry.

**Synthesis of 2.** Hosts **1** and **2** are very similar and hence the required synthetic approach to the construction of **2** was similar to that discussed above for **1a** and **1b**. Methodology to synthesise compounds related to **2** has been previously outlined.[12] Starting with *endo*-norbornene-2-carbonyl chloride **8**,[16] reaction with one equivalent of ethylene diamine followed by Boc protection afforded the mono-amide **9** in 34% yield. The Mitsudo reaction and the epoxidation of **9** was accomplished in exactly the same fashion as that for **1a** and **1b**, and the desired epoxide **10** was isolated in low yield following chromatographic purification. The 1,3 dipolar cycloaddition of this material to alkene **9** afforded an isomeric mixture of the *meso* adduct **11a** and both enantiomers of the $C_{2v}$ adduct **11b**.[21] Whilst formation of such a mixture can be obviated through the use of chiral starting materials[12] the mixture was deemed suitable for further functionalisation and qualitative evaluation. Indeed, whilst the region in the $^1$H NMR spectrum containing the C–H residues contained many overlapping resonances making assignment difficult, the region of interest containing the polar N–H groups was clean and indicated the presence of two sets of isomers (both the *meso* compound and the enantiomers).

**Evaluation of anion recognition for new hosts 1a, 1b and 2.** The ability of **1a**, **1b** and **2** to bind anions was investigated by monitoring the changes in the $^1$H NMR spectra of DMSO-$d_6$ solutions of each host upon addition of $AcO^-$, $F^-$, $Cl^-$, $Br^-$, $H_2PO_4^-$ and $H_2P_2O_7^{2-}$ (as their tetrabutylammonium salts). The addition of $Cl^-$ and $Br^-$ to **1a**, **1b** or **2** afforded only minor changes in the $^1$H NMR spectra and it was concluded that very weak, if any, binding of these anions occurred and they will not be discussed further.

*Acetate, $AcO^-$.* As anticipated, the interaction of $AcO^-$ with the structurally complimentary thiourea receptor[22] was strong, as a significant downfield shift in the resonances of the thiourea protons of each host was observed during the titration, Fig. 4. To exemplify this, the thiourea protons of **1a** shifted by 2.86 and 3.15 ppm respectively, while those for **1b** shifted by 3.04 and 3.16 ppm respectively, whereas for **2** they shifted by ~2.8 ppm.[23]

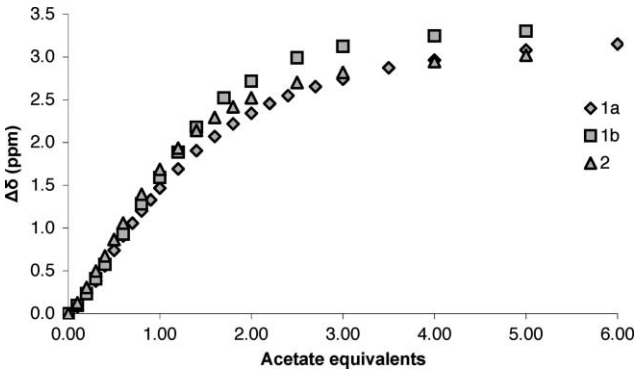



**Fig. 4** Plot of the change in chemical shift of the Ar–NH thiourea protons of **1a**, **1b** and **2** against successive additions of acetate.

The stoichiometry of this binding is worth commenting upon as the combination of the two topographically well-separated thiourea receptors within these structures favours independent thiourea-to-acetate binding *i.e.* 1 : 2 host–$AcO^-$ binding stoichiometry. Such a result is not altogether unexpected given the fact that these compounds were designed to bind larger anions such as $H_2PO_4^-$ and $H_2P_2O_7^{2-}$. From the isotherms, binding constants for the 1 : 2 host–$AcO^-$ complexes were determined as ($\log K_1$ and $\log K_2$): **1a** (3.9 and 2.5); **1b** (3.7 and 2.8), and **2** (~4.1 and ~2.9).[24] Whilst the binding constants are reasonably high for each host, they all show similar affinity for the acetate anion.‡

*Fluoride, $F^-$.* In our experience, fluoride is one of the more difficult anions to reliably investigate using $^1$H NMR spectroscopic techniques due to the potential of fluoride-induced receptor deprotonation.[3,4,25] Indeed, significant changes were seen in the $^1$H NMR spectra of each host upon titration with $F^-$. Unlike those changes induced by acetate, both upfield and downfield shifts were observed with $F^-$, clearly indicating that more complex behaviour than simple 1 : 1 or 1 : 2 host–fluoride interactions were occurring. Moreover, the thiourea N–H proton resonances broadened to the point of being unrecognisable after the addition of *ca.* 1 equivalent of $F^-$. Hence, the only reasonable titration curve was obtained when following one of the aromatic protons. Nevertheless, even this isotherm was unsuitable for calculation of a binding constant. Indeed after 2.5 equivalents of anion had been added, the telltale triplet peak attributed to $[HF_2]^-$ and indicative of deprotonation began to appear and became fully established at 16.13 ppm after 4.0 equivalents had been added.[26] The significant colour changes observed in the NMR tube (Fig. 5) were also consistent with deprotonation, which gives rise to visible colour changes due to the enhancement in the internal charge-transfer (ICT) character of the chromophore.

Some evidence suggesting the cooperative binding of $F^-$ by both thiourea units of **1a** may be gleaned from observing the changes to the resonances assigned to the C–H protons (Fig. 6) at positions 2, 10, 12 and 20 of the framework (*see* Fig. 10). These hydrogen atoms face 'downward' and as such are positioned neatly within the receptor cavity. These resonances experienced a very slight downfield shift before 1 equivalent of $F^-$ was added, although the trend was reversed after the addition of one equivalent of $F^-$, suggesting that until this time the anion was residing within the

‡ Binding constants for **1a** and **1b** were accurate to ±15% whereas those for **2** are approximations only, as **2** was not isomerically pure.

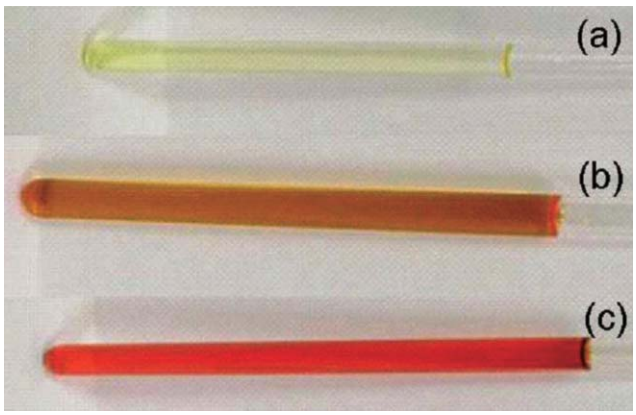



**Fig. 5** The colour changes observed in the NMR tube for **1b** following the addition of 0 (a), 0.5 (b) and 5 (c) equivalents of fluoride.

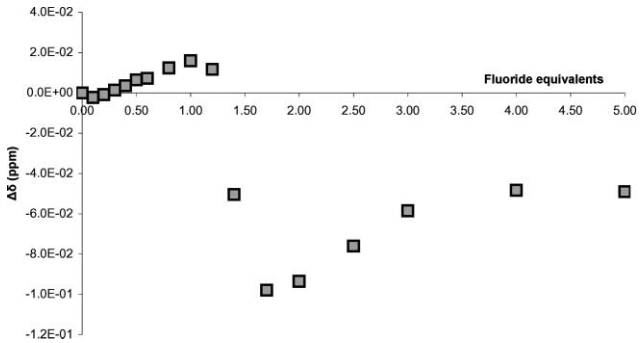



**Fig. 6** Change in chemical shift of the C–H protons of **1a** upon successive additions of fluoride.

binding cleft and both thiourea units participated in the binding event. As a result, the cavity C–H protons were initially slightly deshielded but this trend was subsequently reversed once more than one equivalent of $F^-$ had been added. If two anions were to reside within the cavity, electrostatic repulsion would occur and the more favoured arrangement would be for both thiourea units to function independently and for the fluoride anions to exist outside the cavity (see ESI†). It can also be seen from Fig. 6 that a second change occurs between the addition of 2–4 equivalents of $F^-$ and this reflects the actual deprotonation event and is consistent with the growth of the triplet assigned to $[HF_2]^-$, and the concomitant colour changes shown in Fig. 5.

*Dihydrogenphosphate, $H_2PO_4^-$*. Significant changes were observed in the $^1$H NMR spectra of **1a**, **1b** and **2** upon titration with $H_2PO_4^-$. In particular, substantial shifts of the thiourea-proton resonances were observed and although some broadening occurred, they could be tracked up to the addition of five equivalents of anion, Fig. 7. The thiourea protons of **1a** shifted by 1.82 and 2.26 ppm, respectively, while those for **1b** shifted by 1.77 and 2.07 ppm ,respectively, whereas for **2** the shift was ~2.0 ppm. Inspection of the titration isotherms (Fig. 7) clearly supports 1 : 1 host–$H_2PO_4^-$ stoichiometry for **1a**, **1b** and **2**, and these curves showed excellent agreement with theoretical 1 : 1 models (see ESI†). From these data, binding constants for each host were determined as ($\log K_1$): **1a** (3.9); **1b** (3.6), and **2** (3.1). Whilst these are of similar magnitude to that observed for $AcO^-$, typically binding constants for $H_2PO_4^-$ to simple urea or thiourea receptors are usually *less* than those of $AcO^-$. The binding here is *unusually*

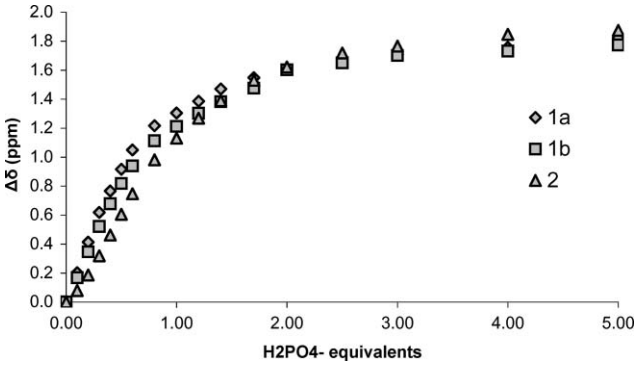



**Fig. 7** Change in chemical shift of the $CH_2NH$ urea protons of **1a**, **1b** and **2** upon successive additions of $H_2PO_4^-$.

*strong* in comparison and attests to our design strategy whereby two receptors are incorporated within the one host molecule and both are utilised in binding the $H_2PO_4^-$ guest. It should also be noted that the non-polar cavity C–H proton resonances also follow similar behaviour upon titration with $H_2PO_4^-$ and support the 1 : 1 host–$H_2PO_4^-$ stoichiometry (see ESI†). These results suggest that a single anion is bound within the cavity from the outset and remains in place throughout the titration.

*Dihydrogenpyrophosphate, $H_2P_2O_7^{2-}$*. As anticipated, large changes were seen in the thiourea protons upon titration with $H_2P_2O_7^{2-}$. However, the thiourea N–H resonances were only discernable up to the addition of 2 equivalents of anion, Fig. 8. Nevertheless, the resultant binding curves clearly indicate the formation of a 2 : 1 host–$H_2P_2O_7^{2-}$ arrangement for both **1a** and **1b**. The isotherms are indicative of strong binding and fitting of these changes gave $\log K_2$ values of 7.4 and 7.8 for **1a** and **1b**, respectively. The binding constants for these hosts to $H_2P_2O_7^{2-}$ are remarkably large, and indicate strong cooperative binding by *two* hosts *i.e.* 2 : 1 host–$H_2P_2O_7^{2-}$. These binding constants are significantly greater then those calculated for $H_2PO_4^-$. This remarkably strong binding is suggestive of additional interactions between host and guest (or host and host) and similarly impressive binding has been observed by Molina *et al.*[27] for the binding of phosphate and also in dynamic combinatorial systems where multiple host units are used.[28] In the case of compound **2**, whilst a 2 : 1 host–$H_2P_2O_7^{2-}$ arrangement was also indicated by the titration data, the strength of binding was orders of magnitude weaker with $\log K_2 \sim 5$. When compared to **1a** and **1b**, the *endo*-functionality of compound **2** has additional flexibility as the link to the framework is a single

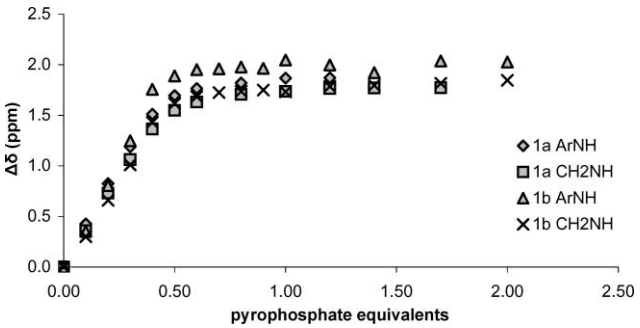



**Fig. 8** Change in chemical shift of the urea protons of **1a** and **1b** upon successive additions of $H_2ppi^{2-}$.

C to amide bond (as opposed to the more rigid imide) and it is this additional flexibility that is thought to be responsible for the differing results observed. Nevertheless, these results clearly illustrate the remarkable affinity of these hosts for the $H_2P_2O_7^{2-}$ anion, and the attractiveness of such preorganised cleft molecules as anion receptors.

To test the feasibility of such a 2 : 1 host–$H_2P_2O_7^{2-}$ complex formation, we performed a qualitative molecular modelling study. To this end, host **1a** was found to minimise with a cleft conformation, as expected given the rigid nature of the [3]polynorbornane framework. Indeed, the flexibility of the 'arms' is then ideal for the complexation of the guest within this cleft. Moreover, when the pyrophosphate anion was placed within the host and it again allowed to minimise, the thiourea receptors were found to converge upon the guest and form the classic 'Y'-shaped H-bond interaction, Fig. 9a. Furthermore, this disposition permits the approach of a second '*staple-like*' molecule, and again subsequent minimisation allowed additional H-bonding to occur between the host and the anion, Fig. 9b. Whilst these models are qualitative, they do show that the 2 : 1 host–$H_2P_2O_7^{2-}$ complex formation is structurally possible and therefore supports the conclusion drawn from the titration study above.

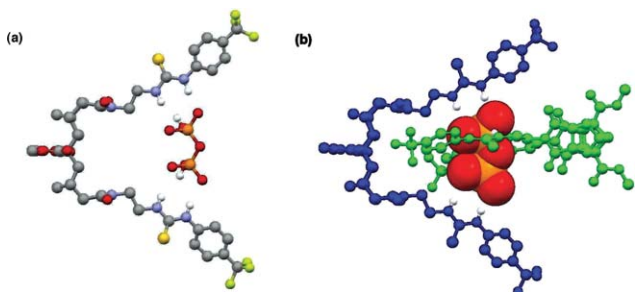



**Fig. 9** Molecular models showing the proposed interaction of $H_2P_2O_7^{2-}$ with **1a** in 1 : 1 (a) and 2 : 1 (b) host–$H_2P_2O_7^{2-}$ stoichiometry.

## Conclusions

A family of fused [3]polynorbornane anion receptors **1a**, **1b** and **2** have been synthesised and characterised. These new hosts show that the binding of phosphate is significantly favoured as a 1 : 1 host–guest binding event and that **1a** and **1b** show remarkably strong 2 : 1 binding to $H_2P_2O_7^{2-}$, as determined from $^1$H NMR titration experiments (Table 1). An organised self-assembled structure is proposed to account for this unusual binding stoichiometry. We are currently investigating structurally related molecules for the use in colorimetric and fluorescence sensing of anions and for transporting anions across cell membranes.

**Table 1** Binding constants (log$\beta$) and host–guest stoichiometry for new hosts against a range of anions[a]

| | host–guest | **1a** | **1b** | **2** |
|---|---|---|---|---|
| $AcO^-$ | 1 : 2 | 3.9, 2.5 | 3.7, 2.8 | 4, 3 |
| $H_2PO_4^-$ | 1 : 1 | 3.9 | 3.6 | 3 |
| $H_2ppi^{2-}$ | 2 : 1 | 7.4 | 7.8 | 5 |

[a] Binding constants determined by WinEQNMR.[20] Errors less than 15% except those for host **2** which are estimates only.[19]

## Experimental

All NMR spectra were recorded on a Bruker Spectrospin DPX-400 spectrometer. Melting points were recorded on a Electrothermal digital melting point apparatus. All solvents were AR grade or higher, reagents were obtained from Aldrich and used as supplied. Dry THF was obtained by distillation from sodium benzophenone ketyl. Thin layer chromatography was performed using aluminium-backed Kieselgel 60 (230–400 mesh), and compounds visualised using a $KMnO_4$ oxidising dip. Compounds were named using the von Baeyer system[29] and numbers correspond to those shown in Fig 10.

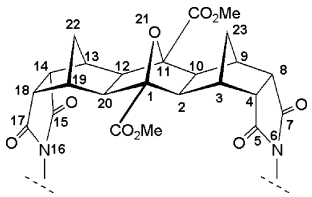



**Fig. 10** Numbering system for frameworks **1a** and **1b**.

### (1α,2α,6α,7α)-4-(2′-*tert*Butoxycarbonylaminoethyl)-4-azatricyclo[5.2.1.0$^{2,6}$]deca-8-ene-3,5-dione (4)[30]

A solution of *endo*-norborn-5-ene-2,3-anhydride **3** (500 mg, 3.0 mmol) and 1,2-diaminoethane was heated at 120 °C overnight. The reaction mix was cooled and diluted with $H_2O$ (10 mL). This aqueous solution was saturated with NaCl and extracted using $CHCl_3$ (4 × 50 mL). The organic extracts were combined, dried ($MgSO_4$) and the solvent removed under reduced pressure. This material was of sufficient quality for the next step. Yield 321 mg (51%).

To a solution of the above amine (321 mg, 1.6 mmol) in $CH_2Cl_2$ (10 mL), the following reagents were added: di-*tert*-butyldicarbonate (500 mg, 2.3 mmol), triethylamine (0.24 g, 0.34 mL, 2.05 mmol) and DMAP (10 mg, 0.08 mmol). The reaction mixture was stirred overnight then washed with 10% citric acid solution (30 mL), and the organic layer separated, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The resultant crude product was subject to column chromatography using 50 : 50 EtOAc–hexane as eluent. Fractions containing the desired product ($R_f$ = 0.45) were combined and the solvent removed under reduced pressure. Complete dryness was attained using high vacuum. Yield 307 mg (65%) of white crystalline material that recrystallised to fluffy, fine needles from EtOAc–hexane. Mp 129.2–131.5 °C; $\delta_H$(400 MHz, $CDCl_3$, $Me_4Si$): 1.43 (9H, s, $^t$Bu), 1.53 (1H, d, *J* 8.6 Hz, H10), 1.72 (1H, d, *J* 8.6 Hz, H10), 3.23 (2H, m, $CH_2$), 3.27 (2H, s, H2,6), 3.39 (2H, s, H1,7), 3.48 (2H, m, $CH_2$), 4.71 (1H, brs, NHBoc), 6.12 (2H, m, H8,9); *m*/*z* (HRES) 329.1484 ([M + Na]$^+$. $C_{16}H_{22}N_2O_4Na$ requires 329.1477).

### Dimethyl(1α,2α,6α,7α,8β,11β)-4-(2′-*tert*butoxycarbonylaminoethyl)-4-azatetracyclo[5.4.1.0$^{2,6}$.0$^{8,11}$]dodeca-9-ene-3,5-dione-9,10-dicarboxylate (5)[30]

A solution of Boc alkene **4** (300 mg, 0.98 mmol), $RuH_2(CO)(PPh_3)$ (30 mg) and dimethyl acetylenedicarboxylate (300 mg, 2.1 mmol)

in benzene was refluxed overnight. The reaction mixture was cooled, filtered (Whatman No. 1) and the solvent removed under reduced pressure. The resulting crude material was purified by column chromatography using 1 : 1 EtOAc–hexane as eluent. The third product ($R_f$ 0.3) to elute was the desired compound (first DMAD ($R_f = 0.7$), second starting alkene ($R_f = 0.4$)). Fractions containing the desired product were combined and the solvent removed under reduced pressure. Complete dryness was obtained using high vacuum. Yield 292 mg (67%) of an extremely viscous oil that crystallised upon standing under vacuum. Mp 152.6–153.9 °C; $\delta_H$(400 MHz, $CDCl_3$, $Me_4Si$) 1.29 (9H, s, $^t$Bu), 1.42 (1H, d, *J* 11.5 Hz, H12), 1.66 (1H, d, *J* 11.4 Hz, H12), 2.71 (2H, s, H8,11), 2.74 (2H, s, H1,7), 3.17 (2H, s, H2,6), 3.19–3.27 (2H, m, $CH_2$), 3.50–3.55 (2H, m, $CH_2$), 3.68 (6H, m, $CO_2Me$), 4.91 (1H, brs, NH); $\delta_C$(100 MHz, $CDCl_3$, $Me_4Si$) 27.87, 33.74, 35.47, 37.79, 38.42, 41.95, 45.32, 47.03, 51.52, 79.01, 140.69, 160.12, 176.51; *m/z* (HRES) 471.1740 ([M + Na]$^+$. $C_{22}H_{28}N_2O_8Na$ requires 471.1743).

**Dimethyl(1α,2α,6α,7α,8α,9α,11β,12β)-4-(2′-*tert*butoxycarbonyl-aminoethyl)-4-aza-10-oxa-pentacyclo[5.5.1.$0^{2,6}$.$0^{8,12}$.$0^{9,11}$]tridecane-3,5-dione-9,11-dicarboxylate (6)[30]**

An argon-flushed solution of alkene diester **5** (292 mg, 0.65 mmol) in dry THF (50 mL) was cooled to 0 °C in an ice bath and *tert*butylhydroperoxide (0.05 mL, 5.5 M in hexanes, 1.0 mmol) was added by syringe with rapid stirring. After a further 10 min. at 0 °C, potassium *tert*butoxide (20 mg, 0.02 mmol) was added in one portion with rapid stirring. After another 10 min., the ice bath was removed and the reaction allowed to stir overnight. After this time, 10% aqueous sodium thiosulfate solution (10 mL) was added and stirring continued for 30 min. The reaction mixture was then concentrated to approx. 1/3 of its volume and extracted with chloroform (3 × 30 mL). The organics were combined, dried ($Na_2SO_4$), filtered and evaporated under reduced pressure. This material was purified by column chromatography using 1 : 1 EtOAc–hexane as eluent. Fractions containing the desired product ($R_f = 0.35$) were combined and the solvent removed under reduced pressure. Complete dryness was attained using high vacuum. Yield 138 mg (45%) of white powder that could be recrystallised from EtOAc–hexane to produce crystals suitable for X-ray crystallographic analysis.[9] Mp 191.2–192.7 °C; $\delta_H$(400 MHz, $CDCl_3$, $Me_4Si$) 1.39 (9H, s, $^t$Bu), 1.73 (1H, d, *J* 11.5 Hz, H13), 2.11 (1H, d, *J* 11.4 Hz, H13), 2.37 (2H, s, H8,12), 3.19 (2H, s, H1,7), 3.22–3.28 (2H, m, $CH_2$), 3.29 (2H, s, H2,6), 3.53–3.56 (2H, m, $CH_2$), 3.79 (6H, s, $CO_2Me$), 4.78 (1H, s, NHBoc); $\delta_C$(100 MHz, $CDCl_3$, $Me_4Si$) 27.85, 36.40, 38.43, 38.56, 38.72, 45.63, 47.11, 52.47, 63.00, 79.05, 155.49, 163.31, 176.21; *m/z* (HRES) 487.1714 ([M + Na]$^+$. $C_{22}H_{28}N_2O_9Na$ requires 487.1693).

**Dimethyl(1α,2β,3α,4α,8α,9α,10β,11α,12β,13α,14α,18α,19α,20β)-6-16-(2′,2″-di*tert*butoxycarbamatoethyl)-6,16-diaza-21-oxaocta-cyclo[9.9.$1^{1,11}$.$1^{3,9}$.$1^{13,19}$.$0^{2,10}$.$0^{4,8}$.$0^{12,20}$.$0^{14,18}$]tricosane-5,7,15,17-tetraone-1,11-dicarboxylate (7)**

A screw-cap pressure vessel was charged with epoxide **6** (73 mg, 0.16 mmol), alkene **4** (50 mg, 0.16 mmol) and $CH_2Cl_2$ (2.0 mL). A stirrer bar was added, the tube sealed then heated for 24 h at 140 °C with stirring. After this time, the tube was cooled, opened and the contents transferred to a round bottom flask and the solvent removed *in vacuo*. This crude material was purified by column chromatography using 1 : 1 EtOAc–hexane as eluent. The third product to elute ($R_f = 0.1$) was the desired material (first is alkene ($R_f = 0.45$), second is epoxide ($R_f = 0.35$)) and fractions containing this product were combined and concentrated to dryness under reduced pressure. Complete dryness was attained using high vacuum. Yield 86 mg (71%) of white powder. Mp >178 °C (slow decomposition); $\delta_H$(400 MHz, $CDCl_3$, $Me_4Si$) 1.19 (2H, d, *J* 10.6 Hz, H22,23), 1.41 (18H, s, $^t$Bu), 2.02 (s, H2,10,12,20), 2.56 (4H, s, H3,9,13,19) 2.58 (2H, d, *J* 10.6 Hz, H22,23), 2.97 (4H, s, H4,8,14,18), 3.25 (4H, m, $CH_2$), 3.59 (4H, m, $CH_2$), 3.84 (6H, s, $CO_2Me$), 4.87 (2H, brs, NHBoc); $\delta_C$(100 MHz, $CDCl_3$, $Me_4Si$): 27.85, 37.44, 38.43, 40.57, 47.71, 49.61, 52.12, 79.18, 89.68, 155.50, 197.20, 176.28; *m/z* (HRES) 793.3291 ([M + Na]$^+$. $C_{38}H_{50}N_4O_{13}Na$ requires 793.3272).

**Dimethyl(1α,2β,3α,4α,8α,9α,10β,11α,12β,13α,14α,18α,19α,20β)-6-16-bis(2′,2″-diaminoethyl)-6,16-diaza-21-oxaoctacyclo-[9.9.$1^{1,11}$.$1^{3,9}$.$1^{13,19}$.$0^{2,10}$.$0^{4,8}$.$0^{12,20}$.$0^{14,18}$]tricosane-5,7,15,17-tetraone-1,11-dicarboxylate (12)**

To a solution of cycloadduct **7** (114 mg, 0.15 mmol) in dry $CH_2Cl_2$ (10 mL), trifluoroacetic acid (2.5 mL) was added and the mixture stirred overnight under an argon atmosphere. After this time, the solvents were removed under reduced pressure and the product dried for a further 24 h under high vacuum. This material was not characterised fully and was used directly in the following steps. Yield 84 mg (~100%) of a glassy, slightly yellow solid; *m/z* (HRES) 571.2411 ([M + H]$^+$. $C_{28}H_{35}N_4O_9H$ requires 571.2404).

**Dimethyl(1α,2β,3α,4α,8α,9α,10β,11α,12β,13α,14α,18α,19α,20β)-6-16-bis((2′,2″-di-(4‴trifluoromethylphenyl)thioureido) ethyl)-6,16-diaza-21-oxa-octacyclo[9.9.1.$1^{3,9}$.$1^{13,19}$.$0^{2,10}$.$0^{4,8}$.$0^{12,20}$.$0^{14,18}$]tricosane-5,7,15,17-tetraone-1,11-dicarboxylate (1a)**

The above amine **12** (56 mg, 0.098 mmol) was dissolved in DMF (10.0 mL) and the following were added: triethylamine (0.27 mL, 0.21 mmol) and 4-trifluoromethylphenylisothiocyanate (44 mg, 0.21 mmol). The reaction was then stirred, under an argon atmosphere, at room temperature, for 24 h. After this time, the solvent was removed under reduced pressure and the crude material purified by column chromatography using EtOAc as eluent. The second product to elute ($R_f = 0.65$) was the desired compound. The fractions containing this product were combined and concentrated to dryness. This material was further dried under high vacuum for 24 h. Yield 67 mg (70%) of a slightly yellow, glassy solid. Mp >300 °C; $\delta_H$(400 MHz, $CDCl_3$, $Me_4Si$) 1.21 (2H, d, *J* 10.2 Hz, H22,23), 2.28 (4H, s, H2,10,12,20), 2.54 (4H, H3,9,13,19), 2.68 (2H, d, *J* 10.2 Hz, H22,23) 3.02 (4H, s, H4,8,14,18), 3.77 (6H, s, $CO_2Me$), 3.76–3.79 (4H, m, $CH_2$), 3.97–4.00 (4H, m, $CH_2$), 6.59 (2H, t, *J* 5.5 Hz, $CH_2NH$), 7.45 (4H, d, *J* 8.8 Hz, $ArH_a$), 7.71 (4H, d, *J* 8.8 Hz, $ArH_b$), 8.37 (2H, s, ArNH); $\delta_C$(100 MHz, $CDCl_3$, $Me_4Si$) 38.72, 38.90, 40.61, 40.75, 43.03, 48.00, 48.16, 48.25, 49.61, 52.02, 90.27, 123.31 (q, *J* 270 Hz), 124.07, 128.11 (q, *J* 33 Hz), 139.02, 167.63, 177.33, 180.31; $\delta_F$(376 MHz, $CDCl_3$,

$Me_4Si$) −62.92; HRMS: 1015.1947 ([M + K]$^+$. $C_{44}H_{42}N_6O_9F_6S_2K$ requires 1015.1996).

**Dimethyl(1α,2β,3α,4α,8α,9α,10β,11α,12β,13α,14α,18α,19α,20β)-6-16-bis((2′,2″-di-(4‴nitrophenyl)thioureido)ethyl)-6,16-diaza-21-oxaoctacyclo[9.9.1.1$^{3,9}$.1$^{13,19}$.0$^{2,10}$.0$^{4,8}$.0$^{12,20}$.0$^{14,18}$]tricosane-5,7,15,17-tetraone-1,11-dicarboxylate (1b)**

Synthesised in an analogous fashion to **1a**. $R_f$ = 0.6, EtOAc; yield 62 mg (45%) of flaky yellow solid. Mp 197 °C (decomposed with evolution of gas bubbles); $\delta_H$(400 MHz, $CDCl_3$, $Me_4Si$) 1.25 (2H, d, *J* 10.8 Hz, H22,23), 2.23 (4H, s, H2,10,12,20), 2.58 (4H, s, H3,9,13,19), 2.68 (2H, d, *J* 10.8 Hz, H22,23), 3.06 (4H, s, H4,8,14,18), 3.81 (6H, s, $CO_2Me$), 3.80–3.84 (4H, m, $CH_2$), 4.10–4.16 (4H, m, $CH_2$), 6.87 (2H, t, *J* 5.4 Hz, N*H*$CH_2CH_2$), 7.55 (4H, d, *J* 8.9, $ArH_a$), 8.31 (4H, d, *J* 8.9 Hz, $ArH_b$), 8.41 (2H, s, ArN*H*C(S)NHCH$_2$); $\delta_C$(100 MHz, $CDCl_3$, $Me_4Si$) 38.54, 38.64, 40.64, 43.46, 48.19, 49.71, 52.17, 90.17, 122.75, 125.17, 142.03, 144.41, 167.57, 177.33, 180.11; *m*/*z* (HRES) 953.2245 ([M + Na]$^+$. $C_{42}H_{42}N_8O_{13}S_2Na$ requires 953.2210).

***Endo*,*exo*-2-(2′-*tert*butoxycarbamatoethyl)-carboxamidonorborn-5-ene (9)**

To an ice cold solution of 1,2-diaminoethane (3.5 g, 3.85 mL, 5.5 mmol), triethylamine (4.4 g, 6.0 mL, 4.2 mmol) and DMAP (10 mg, 0.08 mmol) in dry $CH_2Cl_2$ (20 mL), *endo*,*exo*-norborn-5-ene-2-carbonyl chloride **8** (4.5 g, 2.8 mmol) was added slowly. Visible clouds of HCl were noted during the addition. The reaction mixture was allowed to stir for 24 h whereupon it was diluted with $CHCl_3$ (50 mL), transferred to a separating funnel and washed with $H_2O$ (25 mL). The aqueous layer was extracted with $CHCl_3$ (2 × 30 mL) and all organics combined and washed with brine (10 mL). The organics were separated, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The resulting crude oil (3.0 g, 57%) was not purified but used directly in the following step.

To a solution of the above amine (500 mg, 2.7 mmol) in $CH_2Cl_2$ (10 mL) the following reagents were added: di*tert*butyldicarbonate (500 mg, 2.3 mmol), triethylamine (0.42 g, 0.57 mL, 4.05 mmol) and DMAP (10 mg, 0.08 mmol). The reaction mixture was stirred overnight then washed with 10% citric acid solution (10 mL) and the organic layer separated, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The resultant crude product was subject to column chromatography using EtOAc as eluent. Fractions containing the desired product ($R_f$ *endo* 0.40 $R_f$ *exo* 0.45) were combined and the solvent removed under reduced pressure. Complete dryness was attained using high vacuum. Yield *endo*-isomer 294 mg (34%) and *exo*-isomer 120 mg (20%) both of which were white crystalline material. For the desired *endo* isomer Mp 116–118 °C; $C_{15}H_{24}N_2O_3$ requires C 64.26 H 8.63 N 9.99; found C 64.12 H 8.80 N 9.90; $\delta_H$(400 MHz, $CDCl_3$, $Me_4Si$) 1.27 (1H, d, *J* 8.3 Hz, H7s), 1.29–1.41 (1H, m, H3*endo*), 1.39 (10H, s, $^t$Bu, obscured H7a), 1.89 (1H, ddd, *J* 12.0 Hz, *J* 9.5 Hz, *J* 4.0 Hz, H3*exo*), 2.82–2.87 (2H, m, H2 and H4), 3.12 (1H, s, H1), 3.22–3.32 (4H, m, $NCH_2CH_2N$), 5.06 (1H, br s, NHBoc), 5.93–5.96 (1H, m, H6), 6.18–6.21 (1H, m, H5), 6.24 (1H, br s, NH); $\delta_C$(100 MHz, $CDCl_3$, $Me_4Si$) 28.31, 29.55, 40.21, 40.62, 42.62, 44.66, 46.05, 49.88, 79.54, 132.19, 137.65, 156.92, 175.03.

**Dimethyl-7β-[*N*-(2′*tert*butoxycarbonylaminoethyl)carboxamido]-(1α,2β,5α,6β)tricyclo[4.2.1.0$^{2,5}$]nona-3-ene-3,4-dicarboxylate (13)**

Synthesised in an analogous fashion to **5** starting with the *endo* Boc adduct **9**. Yield 403 mg (89%) of an amorphous solid. $R_f$ = 0.45 (EtOAc); $\delta_H$(400 MHz, $CDCl_3$, $Me_4Si$) 1.14 (1H, d, *J* 10.9 Hz, H9s), 1.34 (9H, s, $^t$Bu), 1.39 (1H, d, *J* 10.9 Hz, H9a), 1.55 (1H, d, *J* 12.3 Hz, H8*endo*), 1.68 (1H, dt, *J* 10.9 Hz, *J* 4.8 Hz, H8*exo*), 2.24 (1H, d, *J* 4.1 Hz, H2), 2.43 (1H, d, *J* 3.4, H5), 2.67–2.74 (2H, m, H1,H7), 2.83 (1H, d, *J* 2.7 Hz, H6), 3.17–3.32 (4H, m, $CH_2CH_2$), 3.68 (6H, s, $CO_2Me$), 5.44 (1H, br s, NHBoc), 6.84 (1H, br s, NH); $\delta_C$(100 MHz, $CDCl_3$, $Me_4Si$) 27.83, 28.99, 31.82, 33.67, 37.58, 39.85, 40.09, 42.37, 45.52, 46.23, 51.32, 51.36, 78.87, 141.11, 141.43, 156.45, 160.81, 160.99, 173.03; *m*/*z* (ES) 845.36 ([M + H]$^+$. $[C_{21}H_{30}N_2O_8]_2H$ requires 845.42).

**Dimethyl-7β-[*N*-(2′*tert*butoxycarbonylaminoethyl)carboxamido]-(1α,2β,3α,5α,6β,7α)-4-oxa-tetracyclo[5.2.1.0$^{2,6}$.0$^{3,5}$]decane-3,5-dicarboxylate (10)**

Synthesised in an analogous fashion to **6** starting with the above alkene diester. Product purified by column chromatography using 1 : 1 EtOAc–hexane as eluent. The third product to elute ($R_f$ = 0.35) was the title compound. Yield 68 mg (17%); $\delta_H$(400 MHz, $CDCl_3$, $Me_4Si$) 1.39 (9H, s, $^t$Bu), 1.46 (1H, d, *J* 11.04 Hz, H9a), 1.54 (1H, d, *J* 10.4 Hz, H9*endo*), 1.69 (1H, td, *J* 11.5 Hz, *J* 4.5 Hz), 1.86 (1H, d, *J* 11.0 Hz, H9s), 2.41 (1H, d, *J* 4.0 Hz, H6), 2.47 (1H, d, *J* 3.5 Hz, H2), 2.68 (1H, dt, *J* 11.5 Hz, *J* 4.5 Hz, H8), 2.75 (1H, d, *J* 4.5 Hz, H1), 2.93 (1H, d, *J* 4.0 Hz, H7), 3.21–3.29 (4H, m, $CH_2CH_2$), 3.75 (6H, s, $CO_2Me$), 5.27 (1H, br s, NHBoc), 6.70 (1H, br s, NH); $\delta_C$(100 MHz, $CDCl_3$, $Me_4Si$) 27.86, 29.07, 34.72, 36.38, 39.95, 40.09, 40.16, 45.26, 45.59, 48.97, 52.16, 63.34, 63.41, 78.99, 156.51, 164.16, 172.75; *m*/*z* (ES) 877.20 ([M + H]$^+$. $[C_{21}H_{30}N_2O_9]_2H$ requires 877.41).

**Mixture of dimethyl-4β,11β-di-[*N*-(2′*tert*butoxycarbonylamino-ethyl)carboxamido]-16-oxa(1α,2β,3α,6α,7β,8α,9β,10α,13α,14β)-hexacyclo[6.6.1.1$^{3,6}$.1$^{10,13}$.0$^{2,7}$.0$^{9,14}$]heptadeca-1,8-dicarboxylate and the 4β,12β-*meso* isomer (11a and 11b)**

Synthesised in an analogous fashion to **7** using epoxide **10** (60 mg, 0.14 mmol) and alkene **9** (50 mg, 0.18 mmol). Crude material was purified by column chromatography using 1 : 1 EtOAc–hexane as eluent. The third product to elute ($R_f$ = 0.2) was the desired material and fractions containing this product were combined and concentrated to dryness under reduced pressure. Complete dryness was attained using high vacuum. Yield 86 mg (66%) of white crystalline solid. Due to the mixture of stereoisomers produced, this material was not fully characterised. $\delta_H$(400 MHz, $CDCl_3$, $Me_4Si$) 0.97 (2H, d, *J* 9.9 Hz, H15,17), 1.42 (18H, s, $^t$Bu), 1.50–1.55 (4H, m, H5*endo*H5*exo*H12*endo*H12*exo*), 2.04–2.06 (2H, br d, H6H13), 2.17 (4H, dd, *J* 13.5 Hz, *J* 6.6 Hz, H2,7,9,14), 2.23–2.25 (2H, br t, H3,10), 2.31 (2H, d, *J* 9.8, H15,17), 2.42–2.47 (2H, br m, H4,11), 3.21–3.45 (8H, m, $CH_2CH_2$), 3.81 (s, $CO_2Me$ *meso*), 3.83 (s, $CO_2Me$ enant.), 3.84 (s, $CO_2Me$ *meso*), 5.34 (2H, br s, NHBoc), 6.32 (br s, NH); 6.37 (br s, NH); *m*/*z* (HRMS) 741.3651 ([M + Na]$^+$. $C_{36}H_{54}N_4O_{11}Na$ requires 741.3687).

**Mixture of dimethyl-4β,11β-di[*N*-(2′aminoethyl)carboxamido-16-oxa(1α,2β,3α,6α,7β,8α,9β,10α,13α,14β)hexacyclo-[6.6.1.1$^{3,6}$.1$^{10,13}$.0$^{2,7}$.0$^{9,14}$]heptadeca-1,8-dicarboxylate and the 4β,12β-*meso* isomer (14)**

Synthesised in an analogous fashion to **12** starting with framework **11**. Slightly yellow glassy solid (62 mg, ~100%) was used directly in the next step; *m/z* (HRES) 519.2813 (M + H$^+$. $C_{28}H_{35}N_4O_9H$ requires 519.2819).

**Mixture of (±) dimethyl-4β,11β-di[*N*-(2′(4″-trifluoromethylphenyl-ureido)ethyl)carboxamido]-16-oxa-(1α,2β,3α,6α,7β,8α,9β,10α,13α,14β)hexacyclo [6.6.1.1$^{3,6}$.1$^{10,13}$.0$^{2,7}$.0$^{9,14}$]heptadeca-1,8-dicarboxylate and the 4β,12β-*meso* isomer[19] (2)**

Synthesised in an analogous fashion to **1a** starting with diamine **14**. $R_f$ = 0.7, EtOAc. Yield 104 mg (94%) of a clear glassy solid. Mp 179.5 °C (decomposed with evolution of gas); $\delta_H$(400 MHz, $CDCl_3$, $Me_4Si$) 0.96 (2H, d, *J* 10.0 Hz, H15,17), 1.39–1.50 (4H, m, H5,12 $C_{2v}$ H5,11 *meso*), 1.53–1.62 (2H, m, H5,12 $C_{2v}$), 1.95 (2H, d, *J* 4.1 Hz, H7,14), 2.03–2.07 (2H, m, H5,11 *meso*), 2.09 (2H, d, *J* 4.1 Hz, H2,9), 2.19 (2H, d, *J* 6.8 Hz, H2,14 *meso*), 2.25 (2H, d, *J* 9.8 Hz, H15,17), 2.27–2.33 (6H, m, H6,13 $C_{2v}$ H4,7,9,12 *meso*), 2.37 (2H, d, *J* 4.1 Hz, H3,10), 2.44–2.57 (2H, m, H4,11), 3.36–3.57 (4H, m, $CH_2$), 3.63–3.76 (2H, m, $CH_2$), 3.81 (6 + 3H, $CO_2Me$ $C_{2v}$ and $CO_2Me$ *meso*), 3.83 (3H, s, $CO_2Me$ *meso*), 4.32 (2H, m, $CH_2$), 6.45 (2H, t, *J* 6.1 Hz, C$H_2$NH $C_{2v}$), 6.59 (2H, t, *J* 4.8 Hz, C$H_2$NH *meso*), 7.07 (2H, t, *J* 4.8 Hz, C$H_2$NH $C_{2v}$), 7.50 (2H, t, *J* 5.5 Hz, NHCH2 *meso*), 7.63 (8H, d, *J* 9.6, ArH *meso*), 7.65 (8H, s, ArH $C_{2v}$), 8.89 (2H, s, ArNH *meso*), 9.22 (2H, s, ArNH $C_{2v}$); $\delta_C$(100 MHz, $CDCl_3$, $Me_4Si$) 28.28, 30.24, 30.39, 35.21, 35.39, 38.51, 38.61, 38.91, 39.49, 42.05, 44.07, 44.17, 46.03, 46.28, 50.15, 51.72, 51.97, 54.72, 54.81, 89.71, 122.13, 89.71, 90.05, 90.33, 123.27, 123.49 (q, *J* 272 Hz), 126.05, 126.09, 126.83 (q, *J* 33 Hz), 145.50, 168.94, 169.97, 170.11, 173.71, 174.04, 180.62, 180.74; $\delta_F$(376 MHz, $CDCl_3$, $Me_4Si$) −62.72; *m/z* (HRES) 947.2656 ([M + Na]$^+$. $C_{42}H_{46}N_6O_7F_6S_2Na$ requires 947.2671).

### Molecular mechanics modelling studies

Molecular mechanics calculations on **1a**, **1a**–$H_2P_2O_7^{2-}$ and (**1a**)$_2$–$H_2P_2O_7^{2-}$ were undertaken with Hyperchem Version 7.52. Molecular mechanics was carried out using MM+ with the Polak–Ribiere algorithm of Hyperchem and guided by the $^1$H NMR spectroscopic data. The target configuration was arranged roughly by eye and the energy minimised at an RMS gradient of 0.01. Molecular dynamics was also used (simulated heating to 3000 K) to ensure that the true energy minima had been reached.

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