Effect of Conformational Preorganization of a Three-Armed Host on Anion Binding and Selectivity

Frank Hettche, Philipp Reiß, and Reinhard W. Hoffmann*[a]

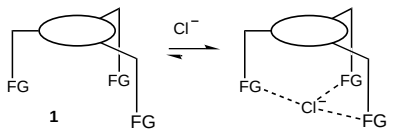
Abstract: A set of three-armed urea-containing anion receptors was prepared. The receptors all have the same binding topology but differ in the level of conformational preorganisation with respect to the arrangement of the side-arms relative to the platform and within the side arms themselves. This is mirrored in a specific increase ($\times 2.5$) in the binding constant for chloride and in a 12-fold increase in the chloride/nitrate-selectivity.

Keywords: anion binding · anions · conformation analysis · host–guest systems · molecular recognition

Introduction

Molecular recognition describes the association between two molecules to form a noncovalently bonded complex.[1] The partners are frequently dubbed as host and guest. Specificity in molecular recognition derives from differences in the free binding energies with respect to the complexation of different guests. Binding enthalpies depend on the kind of interaction (hydrogen bridges, dipolar attractions, Coulomb attractions), binding topology, and desolvation effects. These last factors are reflected in the binding entropies, which also comprise solvation changes and losses of internal motions on complexation. Especially with regard to the latter one tends to use rigid hosts, which suffer less from losses of internal motions on complexation.

Molecular recognition is the key element in nature's binding of effectors to receptors in biology. It is quite evident that nature uses rigid effectors (such as steroids) or rigid receptors only in a few instances, and indeed flexible molecules prevail. However, many biologically active molecules, particularly those of polyketide biogenetic origin show high levels of conformational preorganisation,[2] which may directly augment the binding free energy to the respective host. Conformational preorganisation has thus been recognised as a feature in molecular recognition,[3] since the pioneering studies of Cram.[4] The magnitude of these effects, however, is not easily assessed, because on comparing guests (or hosts) of different conformational preorganisation other structure parameters are likewise changed. This situation, in line with our interest in the benefits of conformational preorganisation, led us to design a series of hosts that have identical binding topology and binding groups, but different degrees of conformational preorganisation. Thus, the idea is to have a tripodal host **1** consisting of a platform and three side arms with urea moieties as sticky groups,[5, 6] see Scheme 1. These were chosen in order to complex spherically symmetrical anions,[6] which do not require a specific coordination geometry.



Scheme 1. Schematic representation of the tripodal host **1** and the complex formation with the spherically symmetrical chloride anion guest. FG = urea.

The distance between the platform and the urea groups is kept constant. The only feature to be changed is the conformational preorganisation of the side arms relative to the platform and within the side arms themselves. We hoped that with a system such as **1** it would be possible to clearly delineate the effects of conformational preorganisation on binding energies and selectivities. Some of the results have been communicated in preliminary form.[7] Here, we detail the whole study.

Design of the receptors: As a central platform we chose a triazine-trione unit,[8, 9] because the arrangement of the bond dipoles should facilitate the positioning of a negatively charged anion on top of the ring. Moreover, triazine-triones are synthetically quite versatile. We envisioned the use of four-carbon chains as side arms; these allow enough conformational diversity, but can in turn be easily conformation-

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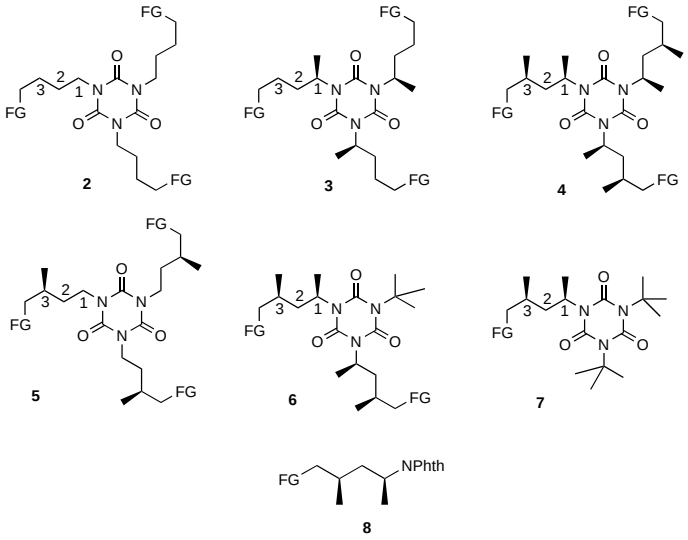
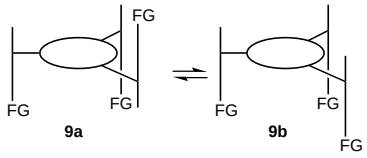
ally controlled,[10] see Scheme 2. Thus, the most flexible host would be compound **2**, in which the side-arms may explore the full conformational space available.



Scheme 2. Different hosts discuused in this paper. FG = NH-CO-NH-pC$_6$H$_4$-nC$_4$H$_9$.

The first restriction we wanted to introduce is illustrated in host **3**. Here, the methyl branches at C-1 cause a folding such that the lateral chains arrange themselves orthogonal to the platform to avoid A^{1,3}-strain.[11] This system can explore the conformations illustrated as **9a** and **9b**, see Scheme 3, with the former being statistically favoured by 3:1.

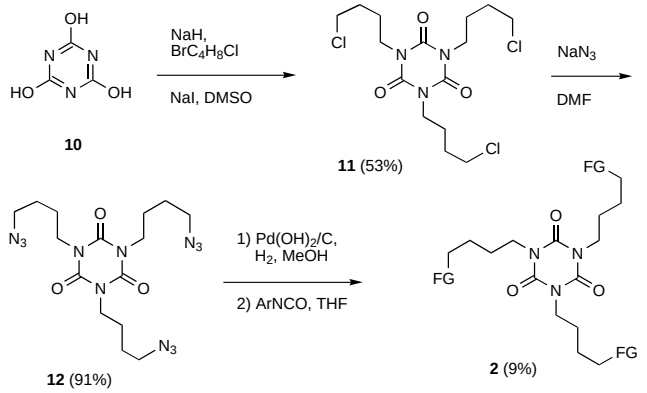


Scheme 3. Different conformations to avoid A^{1,3} strain. FG = urea.

As the next stage of conformational preorganisation we envisioned the receptor **4**, in which the side chains should now each adopt an extended conformation as a result of the additional methyl group at C-3.[10] This set of three compounds should therefore have an identical binding topology towards anions such as chloride, but with various degrees of conformational preorganisation. In the realisation of this plan, it turned out that the solubility of host **2** in $CDCl_3$, as the medium of choice for the binding studies, was very low. Because of this, host **2** was replaced by host **5**; these are equivalent in terms of conformational preorganisation.

The design of the receptors implied that all three arms would simultaneously be involved in the binding of the anion. To verify this premise, a two-armed (**6**) and a mono-armed (**7**) "receptor" were included in the study. Since compound **7** was accessible only in small quantities (see below) we chose the simple phthaloyl derivative **8** as a substitute.

Synthesis of the receptors: The three-fold symmetry of the receptor invited a divergent synthesis from a central triazinetrione unit, as exemplified in the synthesis of the receptors **2** and **5**, cf. Schemes 4–6. To this end, cyanuric acid (**10**) was alkylated[8] to give the tris-chloro compound **11**.

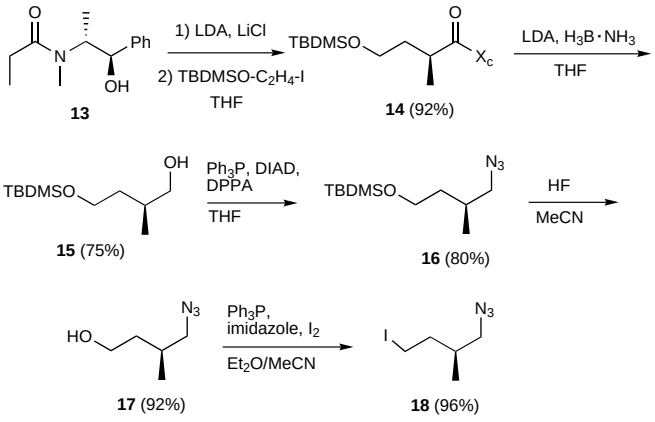


Scheme 4. Synthesis of host **2**. FG = NH-CO-NH-pC$_6$H$_4$-nC$_4$H$_9$.

Nucleophilic displacement of the chloride by azide furnished the tris-azide **12**, which was reduced by hydrogenation and converted into the tris-urea **2**. The last reaction was not optimised, once the poor solubility of **2** in $CDCl_3$ had become apparent.

Instead, we focussed on the methyl-branched compound **5**. The methyl branches constitute stereogenic centres in each chain. To have a constitutionally homogenous receptor, which is necessary for the binding studies by NMR titration, the side chains in **5** have to be homochiral. Therefore, an enantiomerically pure alkylating agent **18** was required to convert **10** into **19**, see Scheme 6.

The synthesis of the alkylating agent **18** emanated from a Myers alkylation of the chiral propionamide **13** to give **14** (Scheme 5).[12] Reductive cleavage of the chiral auxiliary furnished the alcohol **15**. At this stage the azido group was introduced by a Mitsunobu reaction.[13] Finally, removal of the silyl protecting group in **16** gave the alcohol **17**, which was then converted to the alkylating agent **18** by iodination.



Scheme 5. Synthesis of alkylating agent **18**.

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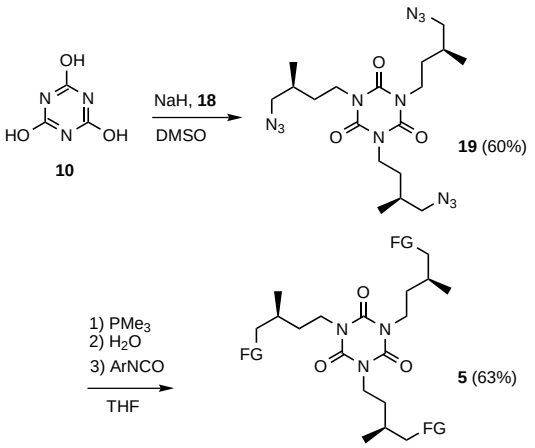
Alkylation of **10** by iodide **18** provided tris-azide **19**, see Scheme 6. Instead of hydrogenation, which had been problematic with the tris-azide **12**, we reduced the azide **19** through a Staudinger procedure[14] using trimethylphosphine. This resulted in 63% of the tris-urea **5**.



Scheme 6. Synthesis of host **5**. Ar = nC_4H_9-pC_6H_4-; FG = NH-CO-NH-pC_6H_4-nC_4H_9.

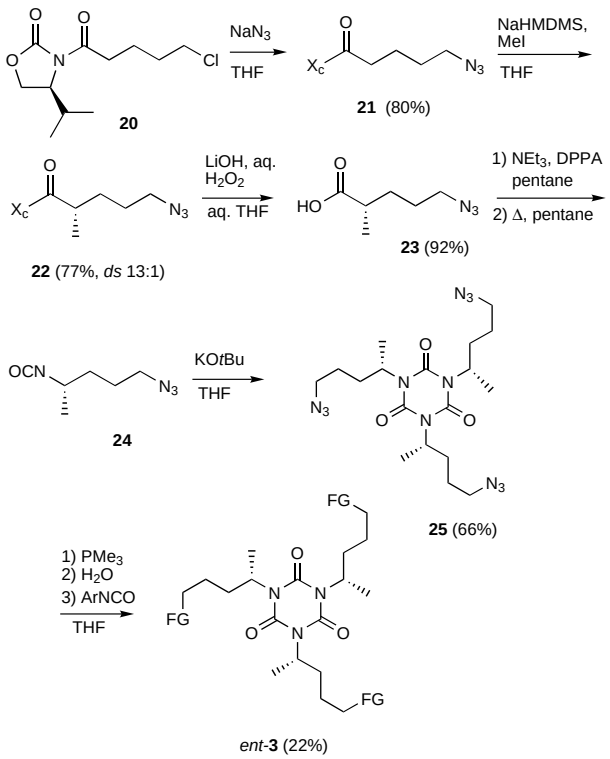
The anion receptors **3** and **4** have stereogenic centres at C-1 of the side chain, that is the attachment point to the platform. One way to create such structures would be by Mitsunobu inversion using cyanuric acid (**10**) as the nucleophile. We had doubts whether substantial yields could be attained in such a three-fold alkylation reaction. For this reason we envisioned a convergent route to compounds **3** and **4** by relying on the cyclotrimerisation of isocyanates,[15] such as **24**, see Scheme 7. The isocyanate **24** was prepared by using an Evans alkylation[16] starting from the chloroacyl-oxazolidinone **20**. First, the azido function was introduced to give **21**. Methylation of **21** could be attained with a 13:1 diastereoselectivity to furnish **22**, from which the chiral auxiliary was removed by a standard method.[16] The resulting acid **23** was then subjected to a Curtius degradation to give the isocyanate **24**, which was immediately subjected to a KO*t*Bu-catalysed cyclotrimerisation.[17]

This afforded the tris-azide **25** in 66% yield. The latter was then converted to the receptor *ent*-**3** as before, albeit in only moderate yield.

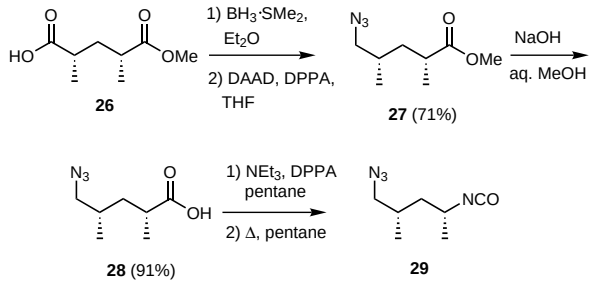
Since the cyclotrimerisation of the isocyanate **24** to **25** was readily achieved, we chose the same route for the preparation of the receptor **4**. The required isocyanate **29** was obtained from **26** as summarized in Scheme 8.

Thus, borane reduction of the half-ester **26** gave a δ-hydroxyester, which was immediately converted to the azido-ester **27** to prevent lactonisation. The ester **27** was saponified to afford the acid **28**. Curtius degradation of the latter furnished the desired isocyanate **29**.

The enantiomerically pure half-ester **26** itself was obtained in a two-step sequence. First, the corresponding *meso*-diester was transformed into enantio-enriched **26**[18] by a chymotrypsin-catalysed hydrolysis.[19] The reaction was performed for six weeks at room temperature to reach an *ee* of 70%. The



Scheme 7. Synthesis of host *ent*-**3**. Ar = nC_4H_9-pC_6H_4-; FG = NH-CO-NH-pC_6H_4-nC_4H_9.



Scheme 8. Synthesis of enantiomerically pure isocyanate **29**.

enantiomeric purity of the resulting half-ester was then upgraded to 98% by recrystallisation of the *R*-(+)-phenylethylammonium salts.[20]

During the optimisation of the synthesis of receptor **4** with racemic starting material, we discovered information, that we could not have gained on cyclotrimerisation of the enantiomerically pure isocyanate **29**: We obtained first experimental indications of the conformational preorganisation within our tailor-made side arms of the receptors of type **4**. The cyclotrimerisation of *rac*-**29** generates a statistical 3:1 mixture of the asymmetric (*rac*-**30**) and the C_3-symmetric (*rac*-**31**) trimer, see Scheme 9.

The presence of a 3:1 product mixture can be deduced from the ^{13}C NMR spectrum (Figure 1), in which several of the signals appear to be split into "triplets".

The "triplet multiplicity" of the individual signals can be rationalised as a combination of a single signal for the homochiral trimer *rac*-**31** and two signals for the heterochiral trimer *rac*-**30**, because in *rac*-**30** the side chains are diastereotopic to one another. The stereochemically distinct side-

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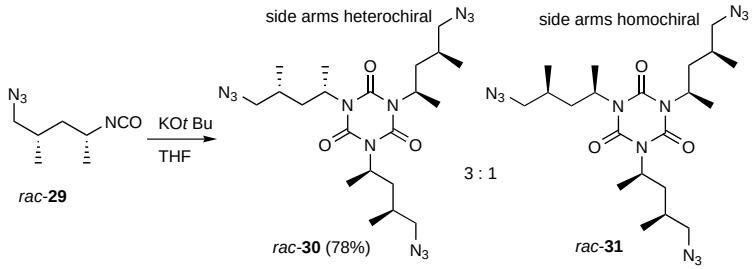


Scheme 9. Cyclotrimerization of *rac*-**29**.

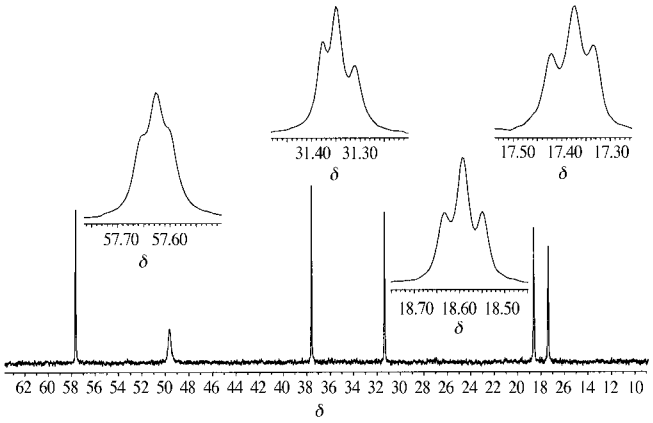


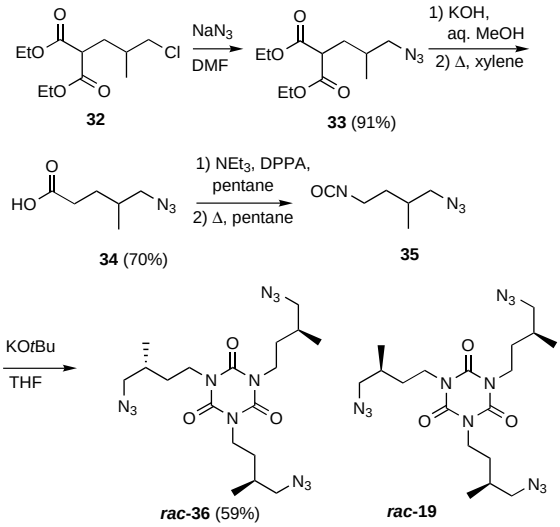
Figure 1. ^{13}C NMR spectrum of the mixture of *rac*-**30** and *rac*-**31**.

chains in *rac*-**30** are present in a 2:1 ratio. Thus, a 1:2:1 intensity ratio within each "triplet" will arise when the isomers *rac*-***30*** and *rac*-**31** are present in approximately 3:1 ratio. As the homochiral trimer **31** is available from the cyclotrimerisation of the enantiomerically pure isocyanate **29**, the signals of the former could readily be identified.

The point to be made about the observed splitting in the ^{13}C NMR spectrum of *rac*-**30** and *rac*-**31** in regards to conformational preorganisation is the following: common experience does not suggest that symmetry-related methyl groups at stereogenic centres separated by four or eight intervening bonds should have detectable differences in chemical shift. Hence, if this is the case, a special situation must prevail in which these stereogenic centres are so close to one another in space that they "talk" to one another. The observed splitting of the ^{13}C NMR signals within the side chains of *rac*-**30** and the differences between the signal positions of *rac*-**30** and *rac*-**31** indicate that a particular folding of these molecules prevails as anticipated in the generalised structure **9**.

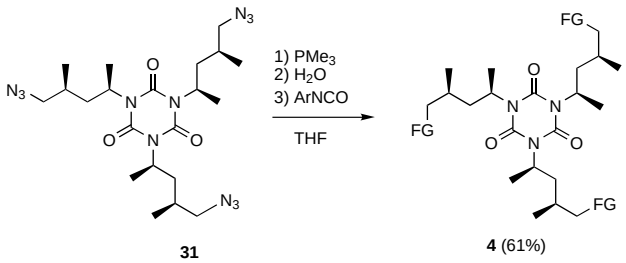
The key to the conformational preorganisation within the compounds *rac*-**30** and *rac*-**31** are the methyl groups at C-1 of the side chains. There are no such methyl groups in the tris-azide **19**. Just as a control, we synthesised *rac*-**19** admixed with its epimer **36** by a cyclotrimerisation of the isocyanate *rac*-**35**, see Scheme 10.

The ^{13}C NMR spectrum of the resulting mixture has only a single set of lines, in contrast to the *rac*-**30**/*rac*-**31** mixture. This indicates that the splitting observed with the *rac*-**30**/*rac*-**31** mixture is genuinely a consequence of the conformational preorganisation prevalent in that system.



Scheme 10. Synthesis of *rac*-**36** and *rac*-**19**.

To conclude the synthesis of **4**, enantiomerically pure tris-azide **31** obtained from enantiomerically pure half-ester **26** was converted to the tris-urea **4** as before, see Scheme 11.

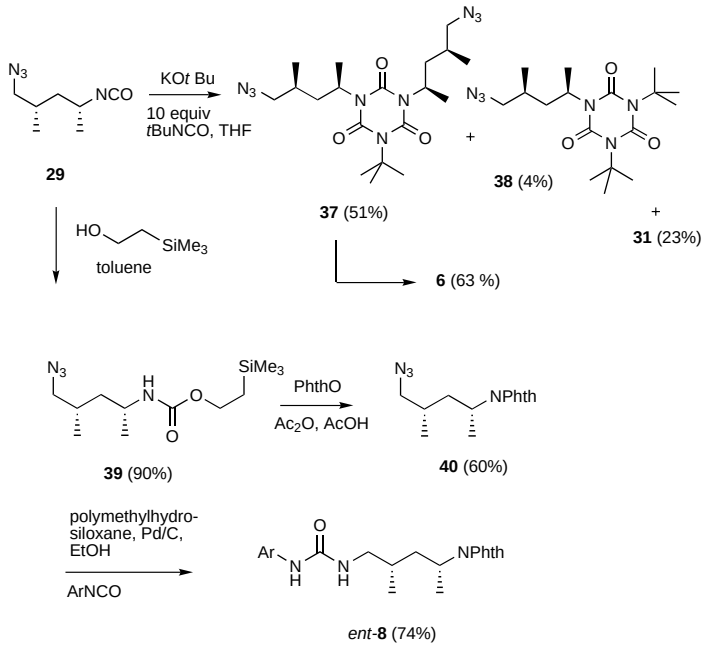


Scheme 11. Assembly of the side chains. Ar = nC$_4$H$_9$-pC$_6$H$_4$-; FG = NH-CO-NH-pC$_6$H$_4$-nC$_4$H$_9$.

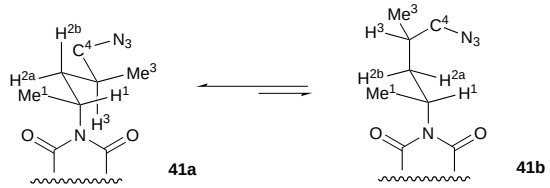
The synthesis of the dipodal receptor **6** and the monopodal "receptor" **8** (cf. Scheme 2) both originated from isocyanate **29**, see Scheme 12. Co-trimerisation of **29** with 10 equivalents of *tert*-butyl isocyanate furnished the bis-azide **37** and mono-azide **38** in a 13:1 ratio. Compound **37** then was converted into the two-armed receptor **6**.

Since only a very small quantitty of the mono-armed azide **38** was obtained, we turned our attention to the phthaloyl-derivative **8** as a model for the mono-armed system. The precursor compound, azide **40**, was obtained by phthaloylation of the trimethylsilylethyl carbamate **39** derived from **29** in 60% yield. The azide **40** was in this case reduced with polymethylhydrosiloxane in the presence of the *p*-butylphenylisocyanate to give the receptor *ent*-**8** in 74% yield.

Conformational analysis of the side chains in the host molecules: The 1,3-dimethylbutyl chains in the azides **31** and **37**–**40** are derivatives of 2,4-di-substituted pentanes and hence have just two low energy conformations, namely **41a** and **41b** as shown in Scheme 13. Such a system can readily be analysed on the basis of ^3J(H,H) coupling constants.[21]



Scheme 12. Side chain modifications. Ar = nC$_4$H$_9$-pC$_6$H$_4$-.



Scheme 13. Conformational equilibrium of **41**.

If one of the conformers is favoured in the conformer equilibrium a large alternation in the magnitude of the coupling constants $J(H^{2a},H^1)$, $J(H^{2a},H^3)$, and $J(H^{2b},H^1)$, $J(H^{2b},H^3)$ should result. The data compiled in Table 1 show that this is indeed the case.[22]

For compound **31** the ^3J(C,H) coupling constants (H^{2a},Me^1: 2.6 ± 0.2; H^{2a},Me^3: 6.8 ± 0.1; H^{2b},Me^3: 3.6 ± 0.2 Hz) reveal[23] that conformation **41a** is the major conformer populated. The observation of a large and a small coupling to Me^3 is uniquely consistent with the prevalence of conformation **41a** in compound **31**.

For the other azido compounds **37**, **38** and **40** we only have soft arguments to support the notion that conformer **41a** is the favoured one: the "slim" imido moieties should prefer the position lateral to the chain, rather than the more bulky C-4 methylene group, in line with previous studies.[10] The large (1 ppm) difference in chemical shift between the two diastereotopic protons H^{2a} and H^{2b} (see Table 1) is a telltale sign of their different disposition relative to the phthalimido group as prevails in conformation **41a**, whereas in conformation **41b** they should be symmetrically disposed.

Table 1. Characteristic coupling constants [Hz, ± 0.1 Hz] for the conformation of the 1,3-dimethylbutyl side chains.

Signal	^3J(H,H)	**40**	**38**	**37**	**31**
H^{2a}: $\delta = \approx 2.35$ ppm	(H^{2a},H^1)	10.9	9.9	10.1	10.3
	(H^{2a},H^3)	4.3	4.0	3.9	3.7
H^{2b}: $\delta = \approx 1.35$ ppm	(H^{2b},H^3)	10.1	9.3	9.3	9.6
	(H^{2b},H^1)	4.3	5.2	5.0	4.9

For the tris-urea **4**, solid evidence for the prevalence of conformation **41a** again comes from determination of the ^3J(C,H) coupling constants. For conformational analysis we had to rely on the latter exclusively, because the ^{1}H NMR signals of **4** are too broad to determine ^3J(H,H) coupling constants. The following ^3J(C,H) coupling constants were obtained: $J(H^{2a},Me^1) = 2.8 \pm 0.2$ Hz; $J(H^{2a},Me^3) = 6.1 \pm 0.1$ Hz, $J(H^{2b},Me^3) = 4.6 \pm 0.2$ Hz; $J(H^{2b},Me^1) = 2.0 \pm 0.1$ Hz. As before, the observation of a large and a small coupling to Me^3 indicates the prevalence of conformation **41a** in compound **4**. In line with this, H^{2b} should show two small ^3J(C,H) coupling constants in conformation **41a** of **4**. However, one of the values (4.6 Hz) is intermediate magnitude.[23] This indicates that the conformational homogeneity of the tris-urea **4** is not as high as in the azido compounds studied before. This could be caused by intra- and intermolecular interactions between the urea end-groups which can be seen in the crystal structure of **4** (cf. Figure 2).

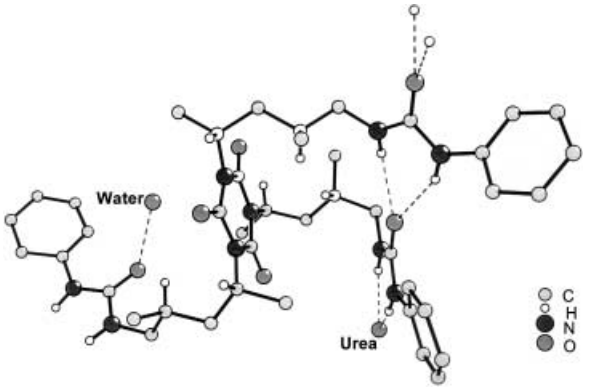


Figure 2. Crystal structure of **4**, butyl groups omitted for clarity.

This X-ray crystal structure confirms our above considerations, as it illustrates nicely the predicted details about the spatial arrangement of the side-chains (in the solid state): thus, they are arranged orthogonal to the platform, and at least one pair of side-chains is so close in space that they may "talk" to one another, as seen in the NMR-spectra of *rac*-**30** and *rac*-**31**. The X-ray structure further shows that each of the side chains adopts an extended conformation.

Complexation studies: The complexation of three representative anions (Cl^-, Br^- and NO_3^- as tetrabutylammonium salts in $CDCl_3$) by the receptors was followed by NMR titration. The complexation was monitored by following the changes in the chemical shifts of the NH protons. In some instances changes in the chemical shifts of the *ortho*-protons on the phenylene units were also used. The resulting curves were simulated with SigmaPlot 2000.[24] The prevalence of 1:1 complexes was secured in all cases by Job plots, again fitted with SigmaPlot 2000. Self-association is quite common for urea containing compounds.[25] (cf. also Figure 2) We therefore determined the self-association constants for some of the

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receptors by dilution experiments, and we fitted the data with HOSTEST.[26] In this way, the following self-association constants were determined: **4**: $16 \pm 4\,\text{M}^{-1}$; **5**: $17 \pm 6\,\text{M}^{-1}$; **6**: $22 \pm 4\,\text{M}^{-1}$. As the complexation constants for the anions (see Table 3) are at least one order of magnitude larger, self-association of the receptors is not a matter of concern.

The receptor design relied on the notion, that each of the tripodal ligands **3** (binding studies were in fact carried out with *ent*-**3**), **4** and **5** uses all three arms cooperatively when complexing an anion, while in principle, each arm could interact with the guest independently. To rule out the latter possibility, we compared the complexing ability of the mono-armed **8**, the bis-armed receptor **6** and the tris-armed receptor **4**. The data are compiled in Table 2.

Table 2. Complexation constants [M^{-1}] for tetrabutylammonium salts in $CDCl_3$ at 300 K.[a]

Guest/Host	*ent*-**8**	**6**	**4**
Bu_4N^+ Cl^-	621 ± 40	2610 ± 50	19500 ± 2100
Bu_4N^+ Br^-	79 ± 5	646 ± 5	2260 ± 100
Bu_4N^+ NO_3^-	103 ± 5	528 ± 7	800 ± 10

[a] The error limits given are standard deviations from nonlinear regression analysis.

If the side arms were functioning completely independently of one another, one would expect an increase in the binding constants in a sequence 1:2:3. The data in Table 2 show that the increase surpasses these values and is, in addition, not uniform for all anions. This indicates a substantial cooperativity of the side arms in forming 1:1 complexes (Job plots) with those anions.

After establishing that the three-armed receptors employ their binding groups in a cooperative manner, we can now identify the effects of conformational preorganisation on the binding constants and selectivities for different anions. These results are compiled in Table 3.

Table 3. Effects of conformational preorganisation on the binding energies [kcal mol^{-1}] and binding constants [M^{-1}] for tetrabutylammonium salts in $CDCl_3$ at 300 K.[a]

Guest/Host	**5**	*ent*-**3**	**4**
Bu_4N^+ Cl^-	-5.27 ± 0.02	-5.80 ± 0.07	-5.84 ± 0.06
	7400 ± 280	18300 ± 2270	19500 ± 2100
Bu_4N^+ Br^-	-4.56 ± 0.02	-4.76 ± 0.03	-4.57 ± 0.03
	1990 ± 50	3100 ± 160	2260 ± 100
Bu_4N^+ NO_3^-	-4.45 ± 0.02	-4.17 ± 0.02	-3.95 ± 0.02
	1840 ± 40	1150 ± 13	800 ± 10

[a] The error limits given are standard deviations from nonlinear regression analysis.

The data in Table 3 show that the binding energies increase in going from bromide to chloride, a feature commonly seen for the binding of different halide ions to urea receptors.[6, 27]

The binding constants react in a diverse manner to the changes in the conformational preorganisation of the hosts. Chloride binding increases by a factor of 2.5 on going from the non-preorganised receptor **5** to the host **3** with a controlled arrangement of the side chains relative to the platform. However, an additional conformational preorganisation within the side chains, that is going from receptor **3** to receptor **4**, is without a pronounced effect on chloride binding. This is not the case for the binding of bromide or nitrate; the latter change results in a significant decrease of the binding constant. It appears that chloride fits quite well into the detailed binding pocket provided by receptor **4**, whereas accommodation of the larger anions (bromide or nitrate), requires some conformational adjustments in the side-arms. These are readily possible in the unorganised receptor **5**, to some extent in **3**, but are opposed by the conformational preferences of the side arms in the most evolved receptor **4**.

Thus, conformational preorganisation may lead to an increase in binding constants (e.g. for chloride), no changes (bromide), or to a decrease (on binding nitrate). Obviously then, the most pronounced effect of conformational preorganisation is on binding selectivities: the chloride/nitrate selectivity increases from two in the case of receptor **5** to 16 for receptor **3** and on to 24 for receptor **4**, which has the strongest conformational preorganisation.[28] One referee raised a question regarding the influence of adventitious amounts of water on binding selectivities. While we did not study this in depth, the chloride/bromide selectivity for host **4** was found to be 5.1 in water-saturated deuterochloroform, compared with 8.6 (cf. Table 3) in commercial deuterochloroform. For host **5** the corresponding values are 2.3 versus 3.7. This indicates that binding selectivities were not oversensitive to changes in the water content even when binding constants were lower in the more aqueous solvent system.

Conclusion

In summary, we have synthesised a set of receptors with the same bond connectivity and the same backbone. They just differ in the level of conformational preorganisation. Detailed binding studies of simple anions revealed a cooperative binding mode and demonstrated that conformational preorganisation leads to strong changes in binding selectivities despite only moderate changes in binding strength. The principles outlined in this study should be applicable to the rational design of a broad range of advanced, conformationally flexible receptor molecules.

Experimental Section

General remarks: All temperatures quoted are uncorrected. ^{1}H NMR, ^{13}C NMR: Bruker ARX-200, AC-300, WH-400, AMX-500. Boiling range of petroleum ether: 40–60 °C. Flash chromatography: Silica gel SI 60, E. Merck KGaA, Darmstadt, 40–63 μm. pH 7 buffer was prepared dissolving : $NaH_2PO_4 \times 2\,H_2O$ (56.2 g) and $Na_2HPO_4 \times 4\,H_2O$ (213.6 g) in water to a final volume of 1 L.

1,3,5-Tris(4-chlorobutyl)-1,3,5-triazine-2,4,6-trione (11): A suspension of sodium hydride in white oil (80%, 1.33 g, 44.3 mmol) was washed with pentane (4×50 mL) and a solution of cyanuric acid (**10**) (1.52 g, 11.8 mmol) in DMSO (115 mL) was added at 0 °C. After stirring for 30 min at 0 °C, 1-bromo-4-chlorobutane (5.11 mL, 44.4 mmol) and sodium iodide (340 mg, 2.27 mmol) were added. After stirring for 1 d at room temperature, saturated aqueous $NaHCO_3$ solution (40 mL) and water

(60 mL) were added dropwise. The resulting solution was extracted with ethyl acetate (450 mL). The combined organic layers were washed with water (4 × 50 mL), brine (10 mL), dried ($MgSO_4$) and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether 3:1 → 1:1 furnished compound **11** (2.76 g, 58%) as a slightly yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.74-1.88$ (m, 12H), 3.50–3.60 (m, 6H), 3.84–3.94 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 25.3$ (3C), 29.6 (3C), 42.2 (3C), 44.2 (3C), 148.8 (3C); HRMS (EI): calcd for $C_{15}H_{24}Cl_3N_3O_3$: 399.0883; found: 399.0884.

1,3,5-Tris(4-azidobutyl)-1,3,5-triazine-2,4,6-trione (12): Sodium azide (4.31 g, 66.3 mmol) was added into a solution of the tris-chloride **11** (1.30 g, 3.24 mmol) in DMF (60 mL). After stirring for 4 d at 65 °C, saturated aqueous $NaHCO_3$ solution (100 mL), water (100 mL) and *tert*-butyl methyl ether (100 mL) were added. The layers were separated and the aqueous layer was extracted with *tert*-butyl methyl ether (5 × 50 mL) The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether 1.5:1 → 1:1 furnished compound **12** (1.25 g, 91%) as a slightly yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.52-1.80$ (m, 12H), 3.30 (t, $J = 6.5$ Hz, 6H), 3.88 (t, $J = 6.5$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 25.1$ (3C), 26.0 (3C), 42.3 (3C), 50.8 (3C), 148.8 (3C); elemental analysis calcd (%) for $C_{15}H_{24}N_{12}O_3$ (420.4): C 42.85, H 5.75, N 39.98; found: C 43.10, H 6.03, N 40.00.

1,3,5-Tris{4-[3-(4-butylphenyl)ureido]-butyl}-1,3,5-triazine-2,4,6-trione (2): Palladium hydroxide (20% on carbon, 39 mg, 56 μmol) was added to a solution of the tris-azide **12** (67 mg, 0.16 mmol) in methanol (11 mL). The suspension was stirred for 3 h under an atmosphere of hydrogen. The catalyst was removed by filtration through a cellulose acetate membrane (Fa. Sartorius), and the filtrate was concentrated. The residue was taken up in THF (4 mL), *p*-(*n*-butyl)-phenylisocyanate (166 mg, 946 μmol) was added and the mixture was stirred for 7 d. Methanol (82 μL) was added to the suspension and stirring was continued for 4 d. The solution was concentrated in vacuo and subsequent flash chromatography of the residue with *tert*-butyl methyl ether/ethyl acetate 2:1 furnished compound **2** (13 mg, 9%) as a slightly yellowish solid. M.p. 94–95 °C; ^{1}H NMR (500 MHz, [D$_6$]DMSO): $\delta = 0.86$ (t, $J = 7.5$ Hz, 9H), 1.25 (sex, $J = 7.5$ Hz, 6H), 1.40 (quin, $J = 7.5$ Hz, 6H), 1.47 (t, $J = 7.5$ Hz, 6H), 1.50–1.59 (m, 6H), 2.45 (t, $J = 7.6$ Hz, 6H), 3.05 (quin, $J = 6.1$ Hz, 6H), 3.73 (t, $J = 7.2$ Hz, 6H), 6.04 (t, $J = 5.7$ Hz, 3H), 6.99 (d, $J = 8.4$Hz, 6H), 7.23 (d, $J = 8.4$ Hz, 6H), 8.26 (s, 3H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): $\delta = 13.8$ (3C), 21.7 (3C), 24.8 (3C), 27.2 (3C), 33.3 (3C), 34.1 (3C), 38.7 (3C), 42.1 (3C), 117.7 (6C), 128.3 (6C), 134.8 (3C), 138.1 (3C), 149.0 (3C), 155.3 (3C); HRMS (ESI): calcd for $C_{48}H_{69}N_9O_6$+H: 868.5449; found: 868.5451.

(3*S*)-4-Azido-1-*tert*-butyldimethylsilyloxy-3-methylbutane (16): A solution of *n*-butyllithium (1.66 M in hexane, 66.7 mL, 111 mmol) was added dropwise at −70 °C to a solution of diisopropylamine (16.8 mL, 119 mmol) in THF (140 mL). After stirring for 10 min at 0 °C the mixture was cooled to −70 °C and $H_3B \cdot NH_3$ (90% by weight, 4.29 g, 125 mmol) was added. The mixture was stirred for 20 min at 0 °C, 20 min at room temperature and then cooled to −10 °C. A solution of (2*S*)-4-*tert*-butyldimethylsilyloxy-*N*-[(1*R*,2*R*)-2-hydroxy-1-methyl-phenylethyl]-*N*,2-dimethylbutanoic amide[12] (**14**) (10.8 g, 28.4 mmol) in THF (150 mL) was added dropwise. After stirring for 75 min at room temperature. The reaction was quenched at 0 °C by the addition of saturated aqueous NH_4Cl (150 mL). After stirring for 20 min the layers were separated. The aqueous layer was extracted with diethyl ether (5 × 20 mL). The combined organic layers were washed with saturated aqueous NH_4Cl (2 × 40 mL), brine (2 × 20 mL), dried ($MgSO_4$) and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether 5:1 furnished compound **15** (4.67 g, 75%) as a colourless oil. $[\alpha]_D^{20} = -7.19$ ($c = 1.39$, Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.05$ (s, 6H), 0.88 (s, 9H), 0.89 (d, $J = 6.9$ Hz, 3H), 1.47–1.58 (m, 2H), 1.72–1.82 (m, 1H), 3.05 (br s, 1H), 3.39 (dd, $J = 10.9$, 6.9 Hz, 1H), 3.47 (dd, $J = 10.9$, 4.8 Hz, 1H), 3.63 (ddd, $J = 10.5$, 7.5, 4.9 Hz, 1H), 3.70–3.76 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = -5.5$ (2C), 17.3, 18.2, 25.8 (3C), 34.3, 37.4, 61.7, 68.1. The NMR data correspond to those given in ref. [29].

Diisopropyl azodicarboxylate (DIAD, 5.40 g, 26.7 mmol) was added at 0 °C into a solution of triphenylphosphane (7.09 g, 27.0 mmol) in THF (160 mL). After stirring for 15 min a solution of the alcohol **15** (4.52 g, 20.7 mmol) in THF (10 mL) and diphenoxyphosphoryl azide (DPPA, 6.83 g, 24.8 mmol) were added. Stirring was continued for 1 d at room temperature and the solution was concentrated. Flash chromatography of the residue with pentane/ether 30:1 followed by bulb-to-bulb distillation (10^{-1} Torr, ≤ 50 °C) furnished compound **16** (4.03 g, 80%) as a colourless oil. $[\alpha]_D^{20} = +2.72$ ($c = 1.47$, Et_2O); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.04$ (s, 6H), 0.88 (s, 9H), 0.96 (d, $J = 6.8$ Hz, 3H), 1.28–1.46 (m, 1H), 1.52–1.73 (m, 1H), 1.80–2.00 (m, 1H), 3.12 (dd, $J = 11.9$, 6.9 Hz, 1H), 3.26 (dd, $J = 11.9$, 5.6 Hz, 1H), 3.55–3.75 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = -5.5$ (2C), 17.6, 18.2, 25.9 (3C), 30.5, 36.9, 57.8, 60.7; elemental analysis calcd (%) for $C_{11}H_{25}N_3OSi$ (243.4): C 54.28, H 10.35, N 17.26; found: C 54.06, H 10.45, N 17.10.

(3*S*)-4-Azido-3-methyl-1-butanol (17): A solution of hydrofluoric acid (5% in acetonitrile, 30 mL) was added to the TBDMS-ether **16** (3.86 g, 15.9 mmol) and the resulting emulsion was stirred for 2.5 h. Solid $NaHCO_3$ was added slowly to saturation, followed by addition of saturated aqueous $NaHCO_3$ (20 mL) and diethyl ether (50 mL). The layers were separated and the aqueous layer was extracted with ether (5 × 50 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and concentrated. Flash chromatography of the residue with pentane/diethyl ether 1:1 furnished compound **17** (1.88 g, 92%) as a colourless oil. $[\alpha]_D^{20} = +11.03$ ($c = 1.36$, diethyl ether); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.98$ (d, $J = 6.6$ Hz, 3H), 1.32–1.55 (m, 2H), 1.57–1.76 (m, 1H), 1.78–1.98 (m, 1H), 3.18 (dd, $J = 12.0$, 6.3 Hz, 1H), 3.26 (dd, $J = 12.0$, 6.2 Hz, 1H), 3.60–3.80 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$):$\delta = 17.7$, 30.5, 36.9, 57.8, 60.5; elemental analysis calcd (%) for $C_5H_{11}N_3O$ (129.2): C 46.50, H 8.58, N 32.53; found: C 46.28, H 8.30, N 32.50.

1,3,5-Tris[(3*S*)-4-azido-3-methylbutyl]-1,3,5-triazine-2,4,6-trione (19): Imidazole (2.49 g, 36.6 mmol) and iodine (5.18 g, 20.4 mmol) were added at 0 °C into a solution of triphenylphosphane (4.77 g, 18.2 mmol) in an ether/acetonitrile solvent mixture (3:1, 90 mL). A solution of the alcohol **17** (1.81 g, 14.0 mmol) in the same solvent mixture (4 mL) was added followed by flask rinsings (3 × 8 mL). After stirring for 2 h at room temperature, the solution was concentrated. Flash chromatography of the residue with pentane/diethyl ether 40:1 was followed by bulb-to-bulb distillation (10^{-1} Torr, ≤ 40 °C) to furnish compound **18** (3.21 g, 96%) as a colourless oil, which was stored over copper turnings. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.96$ (d, $J = 6.8$ Hz, 3H), 1.59–1.76 (m, 1H), 1.78–2.04 (m, 2H), 3.08–3.31 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 4.2$, 17.2, 34.8, 38.1, 57.2.

A suspension of sodium hydride in white oil (60%, containing 217 mg, 9.05 mmol NaH) was washed with pentane (4 × 5 mL) and diluted with DMSO (15 mL). A solution of cyanuric acid (**10**) (323 mg, 2.50 mmol) in DMSO (5 mL) was added at 0 °C. After stirring for 40 min at room temperature, iodide **18** (2.20 g, 9.18 mmol) was added. After stirring for 3 d at room temperature, saturated aqueous $NaHCO_3$ (15 mL) was added dropwise at 0 °C. The resulting solution was extracted with diethyl ether (250 mL). The combined organic layers were washed with water (3 × 10 mL), brine (10 mL), dried (Na_2SO_4) and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether 20:1 → 3:1 furnished compound **19** (846 mg, 60%) as a colourless oil. $[\alpha]_D^{20} = -10.1$ ($c = 1.29$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.03$ (d, $J = 6.4$ Hz, 9H), 1.44–1.55 (m, 3H), 1.67–1.80 (m, 6H), 3.18 (dd, $J = 12.1$, 6.2 Hz, 3H), 3.26 (dd, $J = 12.1$, 5.5 Hz, 3H), 3.84–3.97 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 17.5$ (3C), 31.5 (3C), 32.1 (3C), 41.0 (3C), 57.3 (3C), 148.8 (3C); elemental analysis calcd (%) for $C_{18}H_{30}N_{12}O_3$ (462.5): C 46.74, H 6.54, N 36.34; found: C 46.80, H 6.63, N 36.25.

1,3,5-Tris{(3*S*)-4-[3-(4-butylphenyl)-ureido]-3-methylbutyl}-1,3,5-triazine-2,4,6-trione (5): A solution of trimethylphosphine (1.0 M in THF,1.34 mL, 1.34 mmol) was added at 0 °C into a solution of the tris-azide **19** (173 mg, 374 μmol) in THF (4 mL). After stirring for 2.5 h, water (38 μL, 2.1 mmol) was added and stirring was continued for 12 h at 45 °C. *p*-(*n*-Butyl)-phenylisocyanate (520 mg, 2.97 mmol) was added and the mixture was heated to 80 °C for 6 h. Ethanol (300 μL) was added dropwise and stirring was continued for 14 h at room temp. Pentane (3 mL) was added and the solution was added to a column with silica gel (Ø5 cm, height 13 cm) and eluted with *tert*-butyl methyl ether/ethyl acetate 5:1 → *tert*-butyl methyl ether/chloroform 2:1 → chloroform. The crude product was re-chromatographed to give the tris-urea **5** (215 mg, 63%) as a colourless solid. M.p. 92–93 °C; $[\alpha]_D^{20} = -37$ ($c = 0.19$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.85$ (d, $J = 6.6$ Hz, 9H), 0.90 (t, $J = 7.4$ Hz, 9H), 1.08–1.19 (m, 3H), 1.32 (sex, $J = 7.4$ Hz, 6H), 1.33–1.43 (m, 3H), 1.53 (quin, $J = 7.6$ Hz, 6H), 1.71–1.81 (m, 3H), 2.52 (t, $J = 7.6$ Hz, 6H), 2.84 (dd, $J = 13.3$, 9.1 Hz, 3H), 2.98 (dd, $J = 13.3$, 4.7 Hz, 3H), 3.81–3.96 (m, 6H), 5.62 (br s, 3H), 7.05 (d, $J = 8.2$ Hz, 6H), 7.89 (d, $J = 8.4$ Hz, 6H), 7.47 (br s, 3H); ^{13}C NMR (125 MHz,

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$CDCl_3$): $\delta = 13.9$ (3C), 17.4 (3C), 22.3 (3C), 31.9 (3C), 32.0 (3C), 33.7 (3C), 35.0 (3C), 40.8 (3C), 46.0 (3C), 120.7 (6C), 128.9 (6C), 136.4 (3C), 137.9 (3C), 148.9 (3C), 156.8 (3C); HRMS (FAB): calcd for $C_{51}H_{75}N_9O_6$+H: 910.5919; found: 910.5892.

(4*S*)-3-(5-Chloropentanoyl)-4-isopropyl-oxazolidin-2-one (20): A solution of *n*-butyllithium (1.47 M in hexane, 55.0 mL, 80.9 mmol) was added dropwise at $-78\,^\circ C$ into a solution of the (4*S*)-4-isopropyl-oxazolidinone[30] (9.65 g, 75.3 mmol) in THF (300 mL). After stirring for 1 h a solution of 5-chloro-pentanoyl chloride (12.8 g, 82.9 mmol) in THF (100 mL) was added dropwise. Stirring was continued for 30 min at $-78\,^\circ C$ and 3 h at room temperature. Saturated aqueous $NaHCO_3$ (500 mL) and *tert*-butyl methyl ether (100 mL) were added, the layers were separated and the aqueous layer was extracted with *tert*-butyl methyl ether (4×150 mL). The combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether 3:1 furnished compound **20** (14.2 g, 76%) as a colourless oil. $[\alpha]_D^{20} = +59.4$ ($c = 4.31$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.85$ (d, $J = 6.8$ Hz, 3H), 0.89 (d, $J = 7.1$ Hz, 3H), 1.72–1.90 (m, 4H), 2.26–2.44 (m, 1H), 2.80–3.08 (m, 2H), 3.54 (t, $J = 5.9$ Hz, 2H), 4.15–4.32 (m, 2H), 4.36–4.47 (m, 1H); ^{13}C NMR (500 MHz, $CDCl_3$): $\delta = 14.6$, 17.9, 21.7, 28.4, 31.8, 34.7, 44.5, 58.4, 63.4, 154.1, 172.7; elemental analysis calcd (%) for $C_{11}H_{18}ClNO_3$ (247.7): C 53.33, H 7.32, N 5.65; found: C 53.25, H 7.37, N 5.46.

(4*S*)-3-(5-Azido-pentanoyl)-4-isopropyl-oxazolidin-2-one (21): Chloro-compound **20** (14.9 g, 57.3 mmol) was converted into azido-compound **21** as described for the preparation of **11**. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether 2:1 furnished compound **21** (11.6 g, 80%) as a slightly yellowish oil. $[\alpha]_D^{20} = +74.5$ ($c = 1.06$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.85$ (d, $J = 7.0$ Hz, 3H), 0.89 (d, $J = 7.0$ Hz, 3H), 1.52–1.84 (m, 4H), 2.20–2.48 (m, 1H), 2.77–3.09 (m, 2H), 3.29 (t, $J = 5.9$ Hz, 2H), 4.13–4.31 (m, 2H), 4.35–4.47 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.6$, 17.9, 21.5, 28.2, 28.3, 34.9, 51.1, 58.3, 63.4, 154.0, 172.5; elemental analysis calcd (%) for $C_{11}H_{18}N_4O_3$ (254.3): C 51.96, H 7.13, N 22.03; found: C 51.85, H 6.91, N 21.87.

(4*S*)-3-[(2*S*)-5-Azido-2-methylpentanoyl)-4-isopropyl-oxazolidin-2-one (22): A solution of sodium hexamethyldisilazide (2.0 M in THF, 20.5 mL, 41.0 mmol) was added dropwise at $-78\,^\circ C$ into a solution of the azido-compound **21** (8.71 g, 34.2 mmol) in THF (250 mL). After stirring for 30 min at $-78\,^\circ C$, methyl iodide (6.60 mL, 106 mmol) was added dropwise. After stirring was continued for 1 h at $-78\,^\circ C$, saturated aqueous NH_4Cl (40 mL) was added. After reaching room temperature further saturated aqueous NH_4Cl (40 mL), *tert*-butyl methyl ether (100 mL), and water (100 mL) were added. The layers were separated and the aqueous layer was extracted with *tert*-butyl methyl ether (6×50 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether 5:1 furnished compound **22** (7.08 g, 77%) as a 13:1 diastereomer mixture. Repeated flash chromatography furnished eventually pure **22** (2.93 g, 32%) as a colourless oil. $[\alpha]_D^{20} = +94.8$ ($c = 1.91$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.86$ (d, $J = 6.9$ Hz, 3H), 0.90 (d, $J = 7.0$ Hz, 3H), 1.22 (d, $J = 6.9$ Hz, 3H), 1.41–1.50 (m, 1H), 1.53–1.63 (m, 2H), 1.75–1.85 (m, 1H), 2.28–2.29 (m, 1H), 3.20–3.37 (m, 2H), 3.75 (ψsex, $J = 6.9$ Hz, 1H), 4.19 (dd, $J = 9.1$, 3.0 Hz, 1H), 4.24–4.29 (m, 1H), 4.42–4.48 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 14.6$, 17.8, 17.9, 26.6, 28.4, 30.0, 37.4, 51.3, 58.3, 63.2, 153.6, 176.5; elemental analysis calcd (%) for $C_{12}H_{20}N_4O_3$ (268.3): C 53.72, H 7.51, N 20.88; found: C 53.47, H 7.56, N 20.99.

(2*S*)-5-Azido-2-methylpentanoic acid (23): Aqueous hydrogen peroxide (30%, 5.80 mL, 51.2 mmol) and lithium hydroxide monohydrate (621 mg, 14.8 mmol) were added at $0\,^\circ C$ to a solution of the oxazolidinone **22** (2.08 g, 7.75 mmol) in a THF/water mixture (3:1, 200 mL). After stirring for 1 h at $0\,^\circ C$, a solution of Na_2SO_3 (6.92 g, 54.9 mmol) in water (44 mL) was added dropwise. The pH of the solution was adjusted to 10 by addition of Na_2CO_3 (2 g). The volume of the solution was reduced in vacuo in order to remove most of the THF. The solution was extracted with dichloromethane (4×50 mL). The aqueous layer was acidified with hydrochloric acid to pH 2 and was extracted with ethyl acetate (5×50 mL). The combined extracts were dried (Na_2SO_4), and concentrated. Bulb-to-bulb distillation of the residue (10^{-1} Torr, $\leq 85\,^\circ C$) furnished compound **23** (1.12 g, 92%) as a colourless oil. $[\alpha]_D^{20} = +18.1$ ($c = 1.93$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.23$ (d, $J = 7.0$ Hz, 3H), 1.52–1.61 (m, 1H), 1.66 (quin, $J = 7.0$ Hz, 2H), 1.73–1.82 (m, 1H), 2.55 (sex, $J = 6.9$ Hz, 1H), 3.29 (t, $J = 6.8$ Hz, 2H), 9.40 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 16.9$, 26.7, 30.7, 38.7, 51.4, 179.6. Compare the data given in ref. [31].

1,3,5-Tris[(1*S*)-4-azido-1-methylbutyl]-1,3,5-triazine-2,4,6-trione (25): Triethylamine (552 μL, 3.98 mmol) and diphenoxyphosphoryl azide (DPPA, 933 μL, 4.32 mmol) were added at $0\,^\circ C$ to a solution of the acid **23** (580 mg, 3.69 mmol) in pentane (20 mL). The mixture was stirred for 30 min at $0\,^\circ C$ and for 15 h at $40\,^\circ C$. The supernatant liquid was removed with a cannula and the residue was extracted with pentane (5×5 mL). The combined extracts were concentrated in vacuo and the residue was bulb-to-bulb distilled (10^{-1} Torr, $\leq 45\,^\circ C$). The obtained oily isocyanate **24** (410 mg, 2.66 mmol) was taken up immediately in THF (2 mL) and potassium *tert*-butoxide (16.0 mg, 143 μmol) was added. After stirring for 12 h the suspension was concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether 7.5:1 → 4:1 furnished compound **25** (374 mg, 66%) as a colourless oil. $[\alpha]_D^{20} = +16.7$ ($c = 1.20$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.44$ (d, $J = 7.02$ Hz, 9H), 1.39–1.50 (m, 3H), 1.51–1.61 (m, 3H), 1.74–1.85 (m, 3H), 2.04–2.17 (m, 3H), 3.22–3.34 (m, 6H), 4.78–4.88 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 18.0$ (3C), 25.6 (3C), 30.4 (3C), 51.0 (3C), 51.6 (3C), 148.8 (3C); elemental analysis calcd (%) for $C_{18}H_{30}N_{12}O_3$ (462.5): C 46.74, H 6.54, N 36.34; found: C 46.72, H 6.69, N 36.53.

1,3,5-Tris{(1*S*)-4-[3-(4-butylphenyl)-ureido]-1-methylbutyl}-1,3,5-triazine-2,4,6-trione (*ent*-3): Tris-azide **25** (300 mg, 649 μmol) was converted into tris-urea *ent*-**3** as described for the preapration of **5**. Flash chromatography of the crude product with pentane/*tert*-butyl methyl ether 1:4 → *tert*-butyl methyl ether/chloroform 3:1 furnished compound *ent*-**3** (130 mg, 22%) as a colourless solid. M.p. 90–92 °C; $[\alpha]_D^{20} = +9.1$ ($c = 1.1$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.89$ (t, $J = 7.4$ Hz, 9H), 1.19–1.29 (m, 3H), 1.31 (sex, $J = 7.4$ Hz, 6H), 1.34–1.48 (m, 6H), 1.42 (d, $J = 6.9$ Hz, 9H), 1.51 (quin, $J = 7.6$ Hz, 6H), 2.11–2.23 (m, 3H), 2.49 (t, $J = 7.6$ Hz, 6H), 2.95–3.06 (m, 3H), 3.18–3.28 (m, 3H), 4.78–4.92 (m, 3H), 5.82 (br s, 3H), 7.00 (d, $J = 8.3$ Hz, 6H), 7.14 (d, $J = 8.3$ Hz, 6H), 7.54 (br s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 13.9$ (3C), 18.5 (3C), 22.3 (3C), 27.7 (3C), 30.3 (3C), 33.7 (3C), 34.9 (3C), 39.8 (3C), 51.3 (3C), 120.6 (6C), 128.9 (6C), 136.4 (3C), 137.8 (3C), 148.9 (3C), 156.8 (3C); HRMS (ESI): calcd for $C_{51}H_{75}N_9O_6$+H: 910.5919; found: 910.5890.

Methyl (2*R*,4*S*)-5-azido-2,4-dimethylpentanoate (27): $BH_3 \cdot SMe_2$ (1.60 mL, 16.6 mmol) was added at $0\,^\circ C$ to a solution of the 1-methyl-5-hydrogen (2*R*,4*S*)-2,4-dimethyl-pentanedioate **26** (2.04 g, 11.7 mmol) in diethyl ether (15 mL). The mixture was stirred for 20 min at $0\,^\circ C$ and 1 h at room temperature. $NaHCO_3$ (ca. 10 mg) was added at $0\,^\circ C$ followed by a glycerol/water mixture (3:1, 8 mL). NaCl was added to saturate the aqueous layer. After stirring for 15 min, the layers were separated and the aqueous layer was extracted with diethyl ether (4×10 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The residue was taken up in THF (5 mL). This solution was added at $0\,^\circ C$ to a freshly prepared mixture of triphenylphosphane (3.80 g, 14.5 mmol), diisopropyl azodicaboxylate (DIAD, 2.80 mL, 14.4 mmol) in THF (80 mL). Finally, diphenoxyphosphoryl azide (3.03 mL, 14.1 mmol) was added and the mixture was stirred for 1 d at room temperature. The mixture was concentrated. Two-fold flash chromatography of the residue with pentane/*tert*-butyl methyl ether 5:1 and pentane/*tert*-butyl methyl ether 20:1 followed by bulb-to-bulb distillation (10^{-1} Torr, $\leq 40\,^\circ C$) furnished the azido-ester **27** (1.53 g, 71%) as a colourless oil. $[\alpha]_D^{20} = -26.7$ ($c = 3.64$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.96$ (d, $J = 6.6$ Hz, 3H), 1.15–1.25 (m, 1H), 1.16 (d, $J = 6.9$ Hz, 3H), 1.62–1.79 (m, 2H), 2.49–2.58 (m, 1H), 3.11 (dd, $J = 12.0$, 6.4 Hz, 1H), 3.18 (dd, $J = 12.0$, 5.7 Hz, 1H), 3.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.5$, 18.1, 31.7, 37.1, 38.4, 51.6, 57.8, 176.8; elemental analysis calcd (%) for $C_8H_{15}N_3O_2$ (185.2): C 51.88, H 8.16, N 22.69; found: C 51.74, H 7.95, N 22.90.

(2*R*,4*S*)-5-Azido-2,4-dimethylpentanoic acid (28): Aqueous NaOH (1N, 25.8 mL, 25.8 mmol) was added to a solution of the ester **27** (3.77 g, 20.4 mmol) in methanol (25 mL). After stirring for 41 h, the mixture was concentrated and the residue was washed with *tert*-butyl methyl ether (2×10 mL). Hydrochloric acid (2N) was added to the residue until the pH reached 2. The solution was extracted with diethyl ether (6×10 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated. Bulb-to bulb-distillation at (10^{-1} Torr, $\leq 100\,^\circ C$) furnished the acid **28** (3.19 g, 91%) as a colourless oil. $[\alpha]_D^{20} = -25.4$ ($c = 3.62$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.98$ (d, $J = 6.7$ Hz, 3H), 1.17–1.27 (m, 1H), 1.15 (d, $J = 7.0$ Hz, 3H), 1.73–1.85 (m, 2H), 2.49–2.59 (m,

1H), 3.12 (dd, $J = 12.0$, 6.3 Hz, 1H), 3.20 (dd, $J = 12.0$, 5.7 Hz, 1H), 11.18 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.4$, 17.9, 31.5, 37.1, 38.1, 57.7, 183.0; elemental analysis calcd (%) for $C_7H_{13}N_3O_2$ (171.1): C 49.11, H 7.65, N 24.54; found: C 49.39, H 7.64, N 24.73.

1,3,5-Tris[(1*R*,3*S*)-4-azido-1,3-dimethylbutyl]-1,3,5-triazine-2,4,6-trione (31): The carboxylic acid **28** (782 mg, 4.57 mmol) was converted into the isocyanate and then the triazine-trione as described for the preparation of **25**. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether 10:1 → 4:1 furnished compound **31** (601 mg, 78%) as a colourless oil. $[\alpha]_D^{20} = +22.9$ ($c = 4.28$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.96$ (d, $J = 6.6$ Hz, 9H), 1.35 (ddd, $J = 13.8$, 9.6, 4.9 Hz, 3H), 1.39–1.49 (m, 3H), 1.43 (d, $J = 6.9$ Hz, 9H), 2.35 (ddd, $J = 13.8$, 10.3, 3.7 Hz, 3H), 3.12 (dd, $J = 14.3$, 6.3 Hz, 3H), 3.14 (dd, $J = 14.3$, 6.3 Hz, 3H), 4.90–4.99 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 17.4$ (3C), 18.6 (3C), 31.4 (3C), 37.6 (3C), 49.6 (3C), 57.7 (3C), 148.7 (3C); elemental analysis calcd (%) for $C_{21}H_{36}N_{12}O_3$ (504.6): C 49.99, H 7.19, N 33.31; found: C 49.87, H 7.05, N 33.37.

1,3,5-Tris{(1*R*,3*S*)-4-[3-(4-butylphenyl)-ureido]-1,3-dimethylbutyl}-1,3,5-triazine-2,4,6-trione (4): Tris-azide **31** (219 mg, 430 μmol) was converted into the tris-urea as described for the preparation of **5**. Flash chromatography of the crude product with pentane/*tert*-butyl methyl ether 1:1 → 1:3 furnished compound **4** (250 mg, 61%) as a colourless solid. M.p. 99–100 °C; $[\alpha]_D^{20} = +16.9$ ($c = 1.36$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.79$ (d, $J = 6.3$ Hz, 9H), 0.89 (t, $J = 7.3$ Hz, 9H), 1.06–1.14 (m, 3H), 1.14–1.22 (m, 3H), 1.30 (sex, $J = 7.5$ Hz, 6H), 1.39 (d, $J = 6.9$ Hz, 9H), 1.50 (quin, $J = 7.6$ Hz, 6H), 2.02–2.14 (m, 3H), 2.48 (t, $J = 7.9$ Hz, 6H), 2.68–2.77 (m, 3H), 3.06–3.15 (m, 3H), 4.88–4.99 (m, 3H), 6.08 (br s, 3H), 6.98 (d, $J = 8.2$ Hz, 6H), 7.14 (d, $J = 8.2$ Hz, 6H), 7.66 (br s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 13.9$ (3C), 17.9 (3C), 18.4 (3C), 22.3 (3C), 32.3 (3C), 33.7 (3C), 34.9 (3C), 38.0 (3C), 46.4 (3C), 49.6 (3C), 120.2 (6C), 128.6 (6C), 136.7 (3C), 137.2 (3C), 148.5 (3C), 157.1 (3C); HRMS (FAB): calcd for $C_{54}H_{81}N_9O_6$+Na: 974.6207; found: 974.6207.

Crystallographic data, see also ref. [7] (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as no. CCDC-178240. Copies of the data can be obtained free of charge via www.cdcc.cam.ac.uk/conts/retrieving.html or on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax:(+44) 1233-336033 or e-mail : deposit@ccdc.cam.ac.uk).

1,3-Bis[(1*R,3*S**)-4-azido-1,3-dimethylbutyl]-5-[(1*S**,3*R**)-4-azido-1,3-dimethylbutyl]-1,3,5-triazine-2,4,6-trione (*rac*-30) and 1,3,5-tris[(1*R**,3*S**)-4-azido-1,3-dimethylbutyl]-1,3,5-triazine-2,4,6-trione (*rac*-31)**: The racemic acid *rac*-**28** (820 mg, 4.79 mmol) was converted into the isocyanate and the triazine-trione as described for the preparation of enantiomerically pure material under **31**. Flash chromatography of the crude product with pentane/*tert*-butyl methyl ether 10:1 furnished a 3:1 mixture of the compounds *rac*-**30** and *rac*-**31** (586 mg, 73%) as a colourless oil. This allowed us to record the following spectral data of *rac*-**30**: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.95$ (d, $J = 6.5$ Hz, 3H), 0.95 (d, $J = 6.5$ Hz, 6H), 1.31–1.39 (m, 3H), 1.39–1.49 (m, 3H), 1.42 (d, $J = 6.8$ Hz, 3H), 1.42 (d, $J = 6.9$ Hz, 6H), 2.35 (ψddd, $J = 13.6$, 10.4, 3.5 Hz, 3H), 3.11–3.15 (m, 6H), 4.90–4.99 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 17.3$, 17.4 (2C), 18.5, 18.6 (2C), 31.3, 31.3 (2C), 37.6 (3C), 49.6 (3C), 57.6, 57.6 (2C), 148.7 (3C).

Diethyl 2-(3-chloro-2-methylpropyl)-malonate (*rac*-32): Diethyl malonate (11.4 mL, 75.0 mmol) was added slowly to a suspension of sodium hydride (60% in white oil, 3.11 g, 77.8 mmol) in THF (220 mL) followed by the addition of 1-bromo-3-chloro-2-methyl-propane (9.24 mL, 79.0 mmol). After stirring for 18 h at 80 °C, saturated aqueous $NaHCO_3$ (100 mL), water (100 mL) and *tert*-butyl methyl ether (300 mL) were added. The layers were separated and the aqueous layer was extracted with *tert*-butyl methyl ether (4 × 50 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), and concentrated. Distillation of the residue (10^{-1} Torr, 69–73 °C) furnished compound *rac*-**32** (10.0 g, 53%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.02$ (d, $J = 6.4$ Hz, 3H), 1.24 (d, $J = 7.4$ Hz, 6H), 1.73–1.94 (m, 3H), 2.04–2.15 (m, 1H), 3.37–3.52 (m, 2H), 4.13–4.27 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.0$ (2C), 17.4, 32.8, 33.3, 49.8, 50.3, 61.4 (2C), 169.1, 169.3; elemental analysis calcd (%) for $C_{11}H_{19}ClO_4$ (250.7): C 52.70, H 7.64; found: C 52.69, H 7.58.

Diethyl 2-(3-azido-2-methylpropyl)-malonate (*rac*-33): Chloro-compound *rac*-**32** (2.66 g, 10.6 mmol) was converted into the azide as described for the preparation of compound **11**. Flash chromatography of the crude product with pentane/*tert*-butyl methyl ether = 10:1 → 1:4 furnished compound *rac*-**33** (2.48 g, 91%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.96$ (d, $J = 6.4$ Hz, 3H), 1.19–1.29 (m, 6H), 1.65–1.81 (m, 2H), 1.94–2.08 (m, 1H), 3.16 (dd, $J = 12.1$, 6.0 Hz, 1H), 3.22 (dd, $J = 12.1$, 5.6 Hz, 1H), 3.41 (dd, $J = 8.5$, 6.3 Hz, 1H), 4.12–4.24 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.0$ (2C), 17.3, 31.6, 32.9, 49.8, 57.3, 61.4 (2C), 169.1, 169.3; elemental analysis calcd (%) for $C_{11}H_{19}N_3O_4$ (257.3): C 51.35, H 7.44, N 16.33; found: C 51.10, H 7.48, N 16.16.

5-Azido-4-methylpentanoic acid (*rac*-34): Aqueous KOH (5N, 4.20 mL, 21.0 mmol) was added to a solution of the malonate *rac*-**33** (1.95 g, 7.56 mmol) in ethanol (4.2 mL). The solution was heated for 18 h to 75 °C. After evaporation to dryness the residue was taken up in water (30 mL). The resulting solution was washed with ether (2 × 20 mL). The aqueous layer was acidified with hydrochloric acid to pH 2, saturated with NaCl and extracted with diethyl ether (7 × 20 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was taken up in *o*-xylene (10 mL) and heated for 30 min to 130 °C and 60 min to 150 °C. After evaporation of the solvent flash chromatography with pentane/*tert*-butyl methyl ether 5:1 → 2:1 furnished acid *rac*-**34** (833 mg, 70%) as a slightly yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.96$ (d, $J = 6.6$ Hz, 3H), 1.43–1.61 (m, 1H), 1.67–1.87 (m, 2H), 2.29–2.51 (m, 2H), 3.16 (dd, $J = 12.1$, 6.1 Hz, 1H), 3.21 (dd, $J = 12.1$, 5.9 Hz, 1H), 11.19 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.3$, 28.8, 31.4, 32.9, 57.4, 179.4; elemental analysis calcd (%) for $C_6H_{11}N_3O_2$ (157.2): C 45.85, H 7.05, N 26.74; found: C 45.69, H 6.80, N 26.65.

1,3-Bis[(3*R)-4-azido-3-methylbutyl]-5-[(3*S**)-4-azido-3-methylbutyl]-1,3,5-triazine-2,4,6-trione (*rac*-36) and 1,3,5-tris[(3*R**)-4-azido-3-methylbutyl]-1,3,5-triazine-2,4,6-trione (*rac*-19)**: Acid *rac*-**34** (1.97 g, 12.5 mmol) was converted to the isocyanate **35** and to the triazinetrione as described for the preparation of compound **25**. Flash chromatography of the crude product with pentane/*tert*-butyl methyl ether 4:1 furnished the compounds *rac*-**36** and *rac*-**19** (1.14 g, 59%) as a colourless oil, which showed NMR spectra identical to those recorded for **19**.

1,3-Bis[(1*R*,3*S*)-4-azido-1,3-dimethylbutyl]-5-(*tert*-butyl)-1,3,5-triazine-2,4,6-trione (37): Potassium *tert*-butoxide (74 mg; 655 μmol) was added into a solution of the isocyanate **29** (233 mg, 1.39 mmol) and *tert*-butyl isocyanate (1.303 g, 13.10 mmol) in THF (10 mL). After stirring for 16 h the mixture was concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether 20:1 → 5:1 furnished the bis-azide **37** (153 mg, 51%) as a colourless solid, the tris-azide **31** (53 mg, 23%) as colourless oil, and the mono-azide **38** (22 mg, 4%) as a colourless resin. Bis-azide **37**: m.p. 66–67 °C; $[\alpha]_D^{20} = +7.59$ ($c = 1.58$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.97$ (d, $J = 6.7$ Hz, 6H), 1.34 (ddd, $J = 14.1$, 9.3, 5.0 Hz, 2H), 1.40 (d, $J = 6.9$ Hz, 6H), 1.43–1.52 (m, 2H), 1.62 (s, 9H), 2.32 (ddd, $J = 14.1$, 10.1, 3.9 Hz, 2H), 3.13 (dd, $J = 13.7$, 6.3 Hz, 2H), 3.15 (dd, $J = 13.7$, 6.3 Hz, 2H), 4.88 (dqd, $J = 10.1$, 6.9, 5.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 17.5$ (2C), 18.7 (2C), 29.4 (3C), 31.4 (2C), 37.8 (2C), 49.5 (2C), 57.8 (2C), 62.7, 149.1 (3C); elemental analysis calcd (%) for $C_{19}H_{33}N_9O_3$ (435.5): C 52.40, H 7.64, N 28.94; found: C 52.33, H 7.67, N 28.64.

Mono-azide **38**: $[\alpha]_D^{20} = +8.91$ ($c = 2.02$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.96$ (d, $J = 6.6$ Hz, 3H), 1.35 (ddd, $J = 14.2$, 9.3, 5.2 Hz, 1H), 1.38 (d, $J = 6.9$ Hz, 3H), 1.44–1.54 (m, 1H), 1.60 (s, 18H), 2.28 (ddd, $J = 14.2$, 9.9, 4.0 Hz, 1H), 3.11 (dd, $J = 11.9$, 6.6 Hz, 1H), 3.17 (dd, $J = 11.9$, 6.1 Hz, 1H), 4.88 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 17.5$, 18.8, 29.4 (6C), 31.4, 38.0, 49.0, 57.9, 62.1 (2C), 149.0, 150.6 (2C); elemental analysis calcd (%) for $C_{17}H_{30}N_6O_3$ (366.5): C 55.72, H 8.25, N 22.93; found: C 55.95, H 8.55, N 22.72.

1,3-Bis{(1*R*,3*S*)-4-[3-(4-butylphenyl)-ureido]-1,3-dimethylbutyl}-5-(*tert*-butyl)-1,3,5-triazine-2,4,6-trione (6): Bis-azide **37** (109 mg, 250 μmol) was converted in to the bis-urea **6** as described for the preparation of compound **5**. Flash chromatography of the crude product with pentane/*tert*-butyl methyl ether 1:1 → 1:4 furnished compound **6** (115 mg, 63%) as a colourless solid. M.p. 160–161 °C; $[\alpha]_D^{20} = +32.1$ ($c = 1.34$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.85–0.95$ (m, 12H), 1.10–1.21 (m, 2H), 1.22–1.32 (m, 2H), 1.31 (t, $J = 7.4$ Hz, 4H), 1.42 (d, $J = 6.9$ Hz, 6H), 1.52 (quin, $J = 7.7$ Hz, 4H), 1.58 (s, 9H), 2.24–2.38 (m, 2H), 2.50 (t, $J = 7.7$ Hz, 4H), 2.86 (br s, 2H), 3.15 (br s, 2H), 4.86–4.97 (m, 2H), 5.81 (br s, 2H), 7.02 (d, $J = 8.2$ Hz, 4H), 7.14 (d, $J = 8.2$ Hz, 4H), 7.22 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 13.9$ (2C), 17.6 (2C), 18.8 (2C), 22.3 (2C), 29.5 (3C), 32.0 (2C), 33.7 (2C), 35.0 (2C), 38.1 (2C), 46.4 (2C), 49.4 (2C),

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62.8, 120.6 (4C), 128.9 (4C), 136.4 (2C), 137.9 (2C), 149.1 (3C), 156.7 (2C); HRMS (ESI): calcd for $C_{41}H_{63}N_7O_5$+Na: 756.4788; found 756.4819.

***N*-[(1*R*,3*S*)-4-Azido-1,3-dimethylbutyl]-*O*-[2-trimethylsilylethyl] carbamate (39)**: Triethylamine (845 mg, 0.835 mmol) and diphenoxyphosphoryl azide (DPPA, 2.30 g, 0.835 mmol) were added to a solution of the acid **28** (1.43 g, 0.835 mmol) in toluene (6 mL). After heating for 2 h to 80 °C, 2-trimethylsilylethanol (1.98 g, 1.67 mmol) was added dropwise. After stirring at 80 °C for 6 h, the mixture was concentrated. Flash chromatography of the residue with pentane/diethyl ether 7:1 furnished the carbamate **39** (2.03 g, 90 %) as a colourless liquid. $[\alpha]_D^{20} = +0.54$ ($c = 7.4$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.02$ (s, 9H), 0.92–1.02 (m, 2H), 0.99 (d, $J = 6.6$ Hz, 3H), 1.17 (d, $J = 6.6$ Hz, 3H), 1.17–1.26 (m, 1H), 1.44–1.55 (m, 1H), 1.78–1.90 (m, 1H), 3.17 (d, $J = 6.4$ Hz, 2H), 3.47 (br s, 1H), 4.12 (br d, $J = 7.0$ Hz, 2H), 4.37 (br d, $J = 6.5$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = -1.5$ (3C), 17.5, 17.7, 22.5, 30.7, 42.0, 44.6, 58.0, 62.8, 156.3; elemental analysis calcd (%) for $C_{12}H_{26}N_4O_2Si$ (286.5): C 50.32, H 9.15, N 19.56; found: C 50.25, H 9.10, N 19.82.

***N*-[(1*R*,3*S*)-4-Azido-1,3-dimethylbutyl]-phthalimide (40)**: Phthalic anhydride (148 mg, 1.00 mmol), the carbamate **39** (286 mg, 1.00 mmol), acetic acid (3 mL), and acetic anhydride (1 mL) were heated for 12 h to reflux. After cooling saturated aqueous Na_2CO_3 was carefully added until the pH of the solution was 9. The mixture was extracted with dichloromethane (3×15 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated. Flash chromatography of the residue with pentane/diethyl ether 3:1 furnished compound **40** (163 mg, 60 %) as a colourless oil. $[\alpha]_D^{20} = -6.3$ ($c = 1.1$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.98$ (d, $J = 6.6$ Hz, 3H), 1.40 (ddd, $J = 14.0$, 10.1, 4.3 Hz, 1H), 1.47 (d, $J = 6.9$ Hz, 3H), 1.53 (m, 1H), 2.38 (ddd, $J = 14.0$, 10.9, 4.3 Hz, 1H), 3.11 (dd, $J = 12.0$, 6.6 Hz, 1H), 3.17 (dd, $J = 12.0$, 5.9 Hz, 1H), 4.45–4.50 (m, 1H), 7.69–7.73 (m, 2H), 7.80–7.84 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 17.0$, 19.3, 31.0, 37.8, 44.7, 57.9, 123.1 (2C), 131.8 (2C), 133.9 (2C), 168.4 (2C); elemental analysis calcd (%) for $C_{14}H_{16}N_4O_2$ (272.3): C 61.75, H 5.92, N 20.58; found: C 61.77, H 5.96, N 19.66.

***N*-[(1*R*,3*S*)-4-Phthalimido-1,3-dimethylbutyl]-*N*′-(4-butyl-phenyl)urea (8)**: Palladium on carbon (5 %, 20 mg), 4-butylphenylisocyanate (634 mg, 3.67 mmol), and poly(methylhydrosiloxane) (87 mg, 1.5 mmol) were added sequentially to a solution of the azide **40** (200 mg, 0.734 mmol) in ethanol (2 mL). The mixture was stirred for 12 h and was then filtered through a membrane filter. The filter was washed with methanol (25 mL) and the combined filtrates were concentrated. Flash chromatography of the residue with pentane/diethyl ether 1:1 → 0:1 furnished compound **8** (224 mg, 74 %) as a colourless oil, which solidified on standing. M.p. 85–87 °C; $[\alpha]_D^{20} = +31.6$ ($c = 0.73$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.90$–0.94 (m, 7H), 1.29–1.37 (m, 2H), 1.45 (d, $J = 6.5$ Hz, 3H), 1.44–1.50 (m, 1H), 1.52–1.59 (m, 2H), 2.43 (ddd, $J = 13.8$, 11.3, 2.7 Hz, 1H), 2.57 (t, $J = 7.9$ Hz, 2H), 3.00–3.07 (m, 1H), 3.10–3.16 (m, 1H), 4.47–4.51 (m, 1H), 4.64 (s, 1H; *N*H), 6.03 (s, 1H; *N*H), 7.12 (d, $J = 6.6$ Hz, 2H), 7.16 (d, $J = 6.7$ Hz, 2H), 7.66–7.68 (m, 2H), 7.76–7.78 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 13.9$, 17.4, 22.3, 22.6, 30.0, 33.6, 34.9, 41.8, 43.5, 44.2, 121.2 (2C), 123.2 (2C), 128.8 (2C), 131.9 (2C), 133.9 (2C), 136.5, 137.7, 155.9, 168.7 (2C); elemental analysis calcd (%) for $C_{25}H_{31}N_3O_3$ (421.5): C 71.23, H 7.41, N 9.97; found: C 71.11, H 7.12, N 9.95.

Complexation studies: 15 Incremental amounts of the solution of the tetrabutylammonium salt (26 mM in $CDCl_3$, 100 μL in total) were added with syringe to a solution of the host (1 mM, in $CDCl_3$ Aldrich, 99.6 % D, 600 μL). ^{1}H NMR spectra were recorded at 500 MHz. The signals of the host did not sharpen upon addition of the guest, but instead broadened further (nitrate > bromide ≅ chloride).

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