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Design and sterospecific synthesis of modular ligands based upon *cis*-1,3-*trans*-5-substituted cyclohexanes

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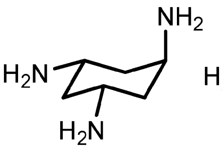
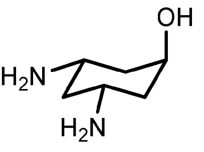
A range of eight novel ligands, based on the *cis*-1,3-*trans*-5-substituted cyclohexane framework, have been synthesized by a stereospecific route starting from *cis*-1,3,5-cyclohexanetriol. This route depends on the use of efficient *mono*-silylation and *mono*-tosylation procedures, is well optimised, and due to isolation of the diazido alcohol precursor *cis*-3,5-diazido-*trans*-hydroxycyclohexane readily allows the synthesis of a sizeable family of related ligands *via* O-derivatisation. Such derivatisations allow systematic changes between various coordinating, hydrogen bonding and lipophilic groups, allowing potential for this ligand system to be utilised in supramolecular coordination chemistry.

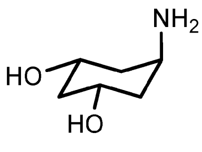
Introduction

Development of novel ligand systems is an important problem for inorganic and supramolecular chemists, as highlighted in recent years by the use of ligand directed "rational design" strategies, where the choice of suitable rigid ligands can control the shape and size of multimetallic complexes.[1–3] Ligands play an equally important role in other areas of coordination chemistry; for example helping mimic protein environments,[4–7] adjusting the magnetism of multimetallic clusters,[8] and influencing the reactivity of complexes, including catalysts.[9,10] Furthermore, ligand design can be used to control the intermolecular interactions between discrete complexes in the assembly of supramolecular arrays.[11,12]

While many large, frequently aromatic, ligands have been synthesized for use in ligand directed strategies,[1–3] rather less attention has been paid to the design and synthesis of smaller, non-aromatic building blocks. However, such ligands, by both organic derivatisation and variation of complexation conditions, can quickly provide access to a wide range of novel metal complexes. One such example is provided by the two stereo isomers of 1,3,5-triaminocyclohexane (*cis*-TACH and *trans*-TACH), which have been used to synthesise a range of mono and multinuclear coordination complexes,[13–17] with further variety yielded by the derivatisation of *cis*-TACH with carboxylate donors.[18] The *trans*-TACH ligand has proved particularly interesting because of its combination of a potentially chelating diamino "head" group with a non-interacting amino "tail" which may either coordinate or participate in hydrogen bonding interactions. Furthermore, the coordination behaviour (chelating or bridging) of the diamine group appears to be controlled by the nature of the metal centre; "closed shell" d^{10} metal centres such as Ag(I) give bridged structures, while "open shell" transition metals such as copper(II) prefer chelation.


***trans*-TACH**


***cis,trans*-DAHC**


***cis,trans*-DHAC**

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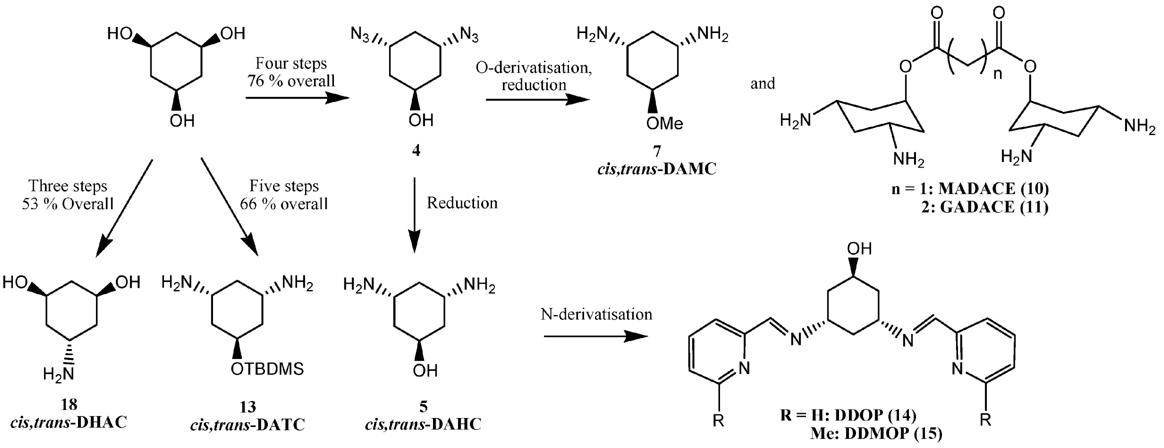
Herein, we present synthetic routes to the novel ligands *cis*-3,5-diamino-*trans*-hydroxycyclohexane (*cis,trans*-DAHC) and *cis*-1,3-dihydroxy-*trans*-5-aminocyclohexane (*cis,trans*-DHAC). These ligands were designed with the aim of incorporating heteroleptic donor sets while preserving the molecular shape of *trans*-TACH. However, the route chosen to *cis,trans*-DAHC has allowed a new family of ligands promising diverse and interesting coordination chemistry.[19]

Results and discussion

An overview of the family of ligands and the routes used in their synthesis is presented as an abridged reaction scheme in Scheme 1. This family comprises the three diamines *cis*-3,5-diamino-*trans*-hydroxycyclohexane (*cis,trans*-DAHC, **5**), *cis*-3,5-diamino-*trans*-methoxycyclohexane (*cis,trans*-DAMC, **7**) and *cis*-3,5-diamino-*trans*-*tert*-butyldimethylsilylanyloxycyclohexane (*cis,trans*-DATC, **13**); the diol *cis*-1,3-dihydroxy-*trans*-5-aminocyclohexane (*cis,trans*-DHAC, **18**); and the four tetradentate/*bis*bidentate *cis,trans*-DAHC derivatives; malonic acid *bis*-(*cis*-3,5-diaminocyclohexyl) ester (MADACE, **10**), glutaric acid *bis*-(*cis*-3,5-diaminocyclohexyl) ester (GADACE, **11**), *cis*-3,5-*bis*[(2-pyridinyleneamin]-*trans*-hydroxycyclohexane (DDOP, **14**), and *cis*-3,5-*bis*[6-methyl-2-pyridinyleneamin]-*trans*-hydroxycyclohexane (DDMOP, **15**). It can be seen that synthesis of this wide range of products is greatly facilitated by the possibility of performing imine condensations on the amines without reacting the alcohols, and by use of the precursor **4** as a "pro-amine" whereby the alcohol group can be reacted prior to reduction of the azide to the amine.

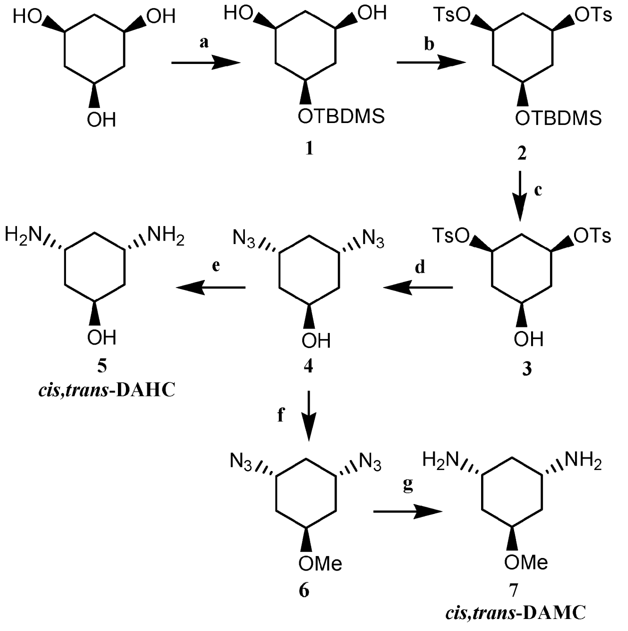
The first target ligand, *cis,trans*-DAHC (**5**), was previously synthesised, though not isolated, in 1972 as a by-product in the synthesis of the *cis*-isomer from 3,5-dinitrophenol.[20] Its diacetamide derivative co-crystallised with the diacetamide of the third, *trans*-isomer in a combined overall yield of 25%. Although the poor yield is counterbalanced the relatively low cost of the 3,5-dinitrophenol precursor, this method was not considered suitable owing to the difficulty of separating the desired isomer. However, discovery in the literature of a highly effective *mono*-TBDMS protection protocol for *cis*-1,3,5-cyclohexanetriol (Scheme 2)[21,22] inspired the use of a tosylation and stereospecific, S_N2 azide reaction to yield the desired *cis,trans*



Scheme 1 Abridged reaction scheme summarising the *cis,trans*-DAHC and *cis,trans*-DHAC ligand family.

diamino alcohol as the exclusive product in an overall yield of 69%. The extremely specific and high yielding nature of the *mono*-TBDMS protection is vital to the viability of this route, as it allows the tosylation and subsequent inversion of only two of the three alcohols.

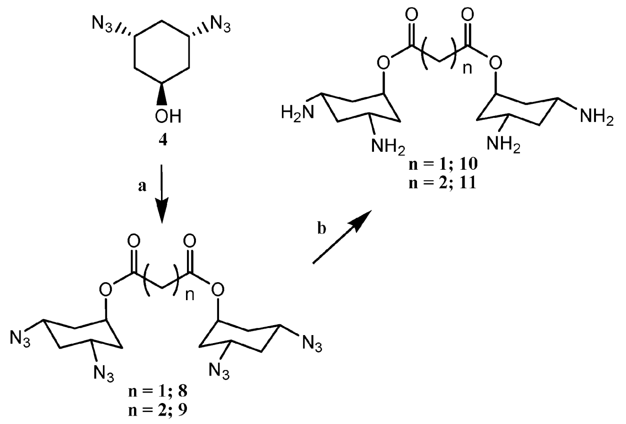
In the first, mono silylation step (Scheme 2) it was found that extension of the published reaction time from 2[22] to 18 h was necessary to achieve the published, or better than published, yield of **1**. The subsequent tosylation of the unprotected alcohols was found to proceed best at low temperatures with a relatively small excess (1.8 equivalents per alcohol) of *recrystallised* tosyl chloride, giving a 95% yield of the desired *bis*-tosylate **2**. Larger quantities of tosyl chloride at higher temperatures gave yields of only 40–70% due to a side reaction forming the *mono*-chloro, *mono*-tosyl derivative *trans*-3-*tert*-butyldimethylsilanyloxy-5-chlorotosyloxycyclohexane. Indeed, direct conversion of alcohols to alkyl halides has been reported in similar conditions.[23] Removal of the TBDMS group to form **3** was carried out directly after the tosylation to avoid potential problems with partial deprotection during the azide step,[24] with an HF protocol[25] being preferred to TBAF as its volatility and water solubility eliminated the need for chromatographic purification. The critical azide step to form **4** was performed according to published methods,[26] using a large excess of sodium azide in DMF (CAUTION–azides can be explosive), while the subsequent catalytic hydrogenation allowed isolation of the target material **5** in adequate purity simply by filtration of the catalyst.



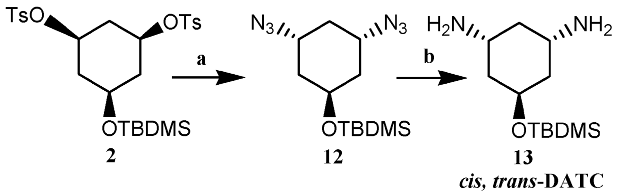
Scheme 2 Route to *cis,trans*-DAHC (**5**) and *cis,trans*-DAMC (**7**); reagents, conditions and yields: (a) TBDMSCl, NEt_3, NaH, THF, 40 °C, 20 h, 97%; (b) TsCl, pyridine, 0 °C, 48 h, 95%; (c); HF, CH_3CN, 45 °C, 18 h, 95%; (d) NaN_3, DMF, 70 °C, 24 h, 87%; (e) H_2, Pd/C, EtOH, rt, 18 h, 90%; (f) MeI, KOH, DMSO, rt, 6 h, 87%; (g) H_2, Pd/C, MeOH, rt, 20 h, 89%.

In addition to efficiency, selectivity and synthetic ease, this route has the advantage of isolating the diazido precursor **4**. The non-nucleophilic character of alkyl azides allows them to act as "pro-amines", so that derivatisation of the alcohol group can be performed without the need for protection and deprotection of the amine groups. In this way the methyl derivative *cis,trans*-DAMC (**7**) could be obtained *via* a simple etherification protocol,[27] followed by hydrogenation.

Isolation of precursor **4** also opens the possibility of linking two *cis,trans*-DAHC units to form a tetradentate ligand, with the wide range of commercially available alkyl halides and alkanoyl chlorides expected to allow a wide variety of lengths and rigidities in the linker. While attempts to form a *bis*-ether linkage failed due to elimination at the second centre, changing to an ester linkage permitted the synthesis of MADACE (**10**) and GADACE (**11**) by reaction with malonyl and glutaryl dichloride respectively (Scheme 3). Relatively long reaction times (48 h) were necessary in the initial esterification step, while reduction of the resulting tetrazides proceeded better using the more active Rh/C catalyst in place of Pd/C, perhaps due to the presence of four, rather than two azide groups per molecule. Ethanol and methanol proved to be the best solvents despite the low solubility of the substrates in such polar



Scheme 3 Synthesis of MADACE (**10**) and GADACE (**11**); reagents, conditions and yields: (a) malonyl/glutaryl dichloride, DMAP, DCM, 0 °C then rt, 48 h, 65%; (b) H_2, Rh/C, EtOH, rt, 48 h, ~90%.

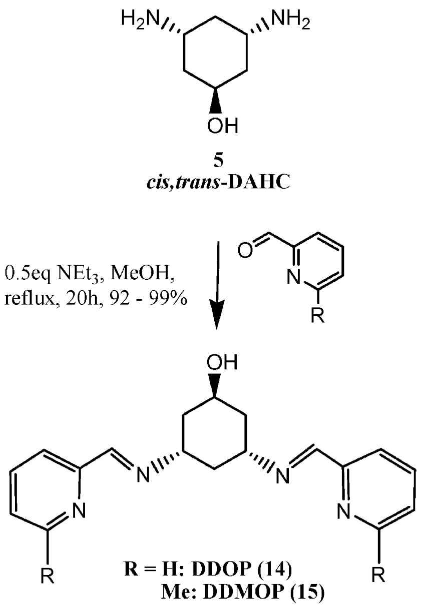


Scheme 4 Route to *cis,trans*-DATC, **13**; reagents, conditions and yields: (a) NaN_3, DMF, 70 °C, 24 h, 77%; (b) (i) $(Bu_3Sn)_2O$, PMHS, AIBN, *n*-PrOH, 85 °C, 2.5 h then HCl, 98%; (ii) NaOH, H_2O, MeOH, rt, 1 h, 66% (65% overall); or H_2, Rh/C, MeOH, rt, 60 h, 93%.

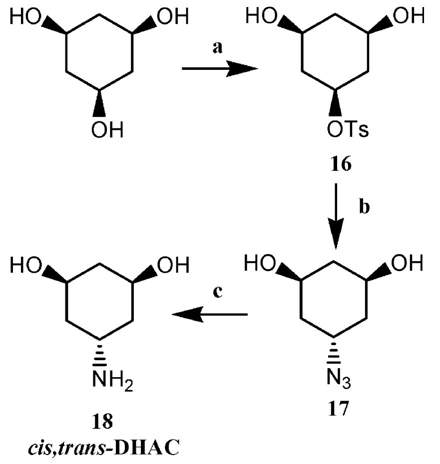
solvents. When a 1 : 1 mixture of ethanol and ethyl acetate was used to better dissolve the starting material, partly reduced substrate would precipitate preventing complete reaction.

Having synthesised *cis,trans*-DAHC (**5**) and its methylated analogue *cis,trans*-DAMC (**7**), the next logical step was to derivatise the alcohol with a bulkier and more hydrophobic group so that potential ligands with varying degrees of lipophilicity could be accessed. Consequently, the TBDMS derivative *cis,trans*-DATC (**13**) was synthesised (Scheme 4). To avoid unnecessary desilylation and resilylation of the oxygen, only the first two steps of the route to **5** were followed. The azide reaction was therefore performed on **2** resulting in a slight loss of yield due to partial deprotection, with the target material **12** being recovered in yields of 68 to 77%, and the deprotected product **4** in a yield of around 15%. A similar cleavage of methyldiphenylsilyl ethers at room temperature with one equivalent of sodium azide in DMF has been documented,[24] and although TBDMS ethers resisted these conditions it appears that the higher temperatures and concentrations of azide utilised here are capable of slowly cleaving the TBDMS ether.

The following reduction step to yield **13** was also complicated by the presence of the TBDMS protecting group. Poor results were obtained using hydrogenation with Pd/C, which has been shown to be capable of cleaving of silyl ethers.[28] While a catalytic free radical reduction[29] mediated by *bis*-(tributyltin) oxide, AIBN, poly(methylhydrosiloxane)(PMHS) and *n*-propanol gave satisfactory results, the acid work up is likely to have caused some cleavage of the silyl group.[30] Furthermore, a certain amount of product was lost in producing the free amine. Ultimately, the simplest and highest yielding method proved to be hydrogenation with Rh/C as the catalyst.



Scheme 5 Synthesis of DDOP (**14**) and DDMOP (**15**). Yields are calculated by ^{1}H-NMR integration from impure material.



Scheme 6 Synthesis of *cis,trans*-DHAC, reagents, conditions and yields: (a) *n*-BuLi, pyridine, TsCl, THF, 40 °C then rt, 15 h, 70%; (b) NaN_3, DMF, 70 °C, 16 h, 80%; (c) H_2, Pd/C, EtOH, 18 h, 95%.

An alternative to derivatisation of the azide precursor **4** in the synthesis of new *cis,trans*-DAHC based ligands is reaction of the amines with aldehydes, for example 2-pyridinecarbaldehyde (Scheme 5). In this way, the *bis*-bidentate chelating ligands DDOP (**14**) and DDMOP (**15**) can be synthesised by a simple, high yielding procedure where *cis,trans*-DAHC is refluxed in methanol with the appropriate aldehyde and 0.5 equivalents of triethylamine. A certain amount of unreacted aldehyde remained which could not be removed owing to the instability of imines to column chromatography, thus preventing the isolation of an analytical grade sample. However, the presence of the aldehyde impurity is unlikely to cause significant issues with complex formation.

The last ligand, *cis,trans*-DHAC (**18**), shares the same geometry as *cis,trans*-DAHC (**5**) and *trans*-TACH, but the bidentate chelating diamine group is replaced with a diol and the *trans* substituent is an amine. The change of chelating group is designed to adjust the coordination, hydrogen bonding and solubility properties of the ligand. While derivatisation of this molecule remains unexplored, the route through azido diol **17** should provide similar possibilities to the *cis,trans*-DAHC (**5**) synthesis for the generation of new, related ligands.

The synthesis of *cis,trans*-DHAC (Scheme 6) was approached in a similar way to that of DAHC, but in this case inversion of only one of the substituents of *cis*-1,3,5-cyclohexanetriol was required. To this end it was necessary to develop a monotosylation strategy, based on a literary precedent with a large diol.[31] This *mono*-tosylation of *cis*-1,3,5-cyclohexane triol proceeds with reasonable selectivity, producing the desired product in a 70% yield. Butyllithium is added prior to the tosyl chloride in an effort to activate one alcohol towards tosylation, but the selectivity is not nearly so impressive as that seen in the *mono*-silylation, with *bis* and *tris*-tosylated products also recovered during the chromatographic separation. Nonetheless, the ability to carry out a *mono*-tosylation, albeit imperfectly, is essential to the viability of the route. The subsequent azide reaction and catalytic hydrogenation are essentially the same as the steps used in the synthesis of *cis,trans*-DAHC (**5**). Overall, the efficiency of conversion of *cis*-1,3,5-cyclohexane triol to *cis,trans*-DHAC is 53%.

Conclusions

The modular synthetic approach outlined above has so far allowed access to eight different, novel ligands. It is to be anticipated that many more may be synthesized *via* relatively simple etherification, esterification, imination and amide forming reactions. The *cis,trans*-DAHC and *cis,trans*-DHAC systems therefore represent a useful tool both for synthesis of new coordination compounds, and studying the effect of systematic changes in ligand substituents on complex size, shape and properties. In addition, the *cis,trans* cyclohexane geometry, as seen with TACH, provides an unusual angle between the chelating and pendant groups, and hence should allow access to interesting coordination and supramolecular chemistry, and we are currently conducting investigations in these areas using these ligands as a basis.

Experimental

cis-1,3,5-cyclohexanetriol dihydrate (Aldrich/Fluka) was dried under high vacuum (Schlenk line) at 50 °C. Tosyl chloride (Lancaster) was recrystallised from ethyl acetate after washing with 10% NaOH solution. THF (Fisher) was distilled over sodium wire under nitrogen; pyridine (Lancaster) was distilled and stored over NaOH under nitrogen; and triethylamine (Lancaster) was distilled at reduced pressure over NaOH and stored over NaOH under nitrogen. Water was purified with an Elga *Option 3* water purifier. Anhydrous DMF was supplied by Aldrich. All other reagents and solvents (Fisher/Lancaster/Riedel-de Haën/Avocado/Aldrich/BDH) and gases (BOC) were used as received. Deuterated solvents were obtained from Aldrich, Avocado and Goss Scientific.

With the exception of the desilylations, hydrogenations and *O*-methylation, all syntheses were carried out under an atmosphere of calcium chloride dried oxygen-free nitrogen using standard Schlenk techniques. TLC plates were developed using an ultraviolet lamp, iodine chamber, $KMnO_4$ dip (alcohols), ninhydrin (amines), or phosphomolybdic acid in ethanol.

Kugelrohr sublimations were performed using a Büchi *Glass Oven B-580*. Melting points (given uncorrected) were recorded with an Electrothermal *IA 9000* digital melting point apparatus. NMR measurements were performed using Bruker *DRX-500* (500 MHz ^{1}H, 2D experiments), *DPX-400* and *Avance-400* (400 MHz ^{1}H, 100 MHz ^{13}C, 2D experiments) and *AC-300* (300 MHz ^{1}H) spectrometers. Mass spectra were acquired with LCT Micromass *TOF* (ES), Micromass *Prospec* (CI/EI) and JEOL *JMS-700* (FAB/CI/EI) mass spectrometers. Infra-red measurements were taken using Shimadzu *FTIR-8300* and Jasco *FTIR-410* spectrometers, and elemental analysis was performed with an *EA 1110 CHNS, CE-440* Elemental Analyser.

Syntheses

***cis*-5-(*tert*-Butyldimethylsilanyloxy)cyclohexane-1,3-diol (1).** *tert*-Butyldimethylsilyl chloride (2.584 g, 16.6 mmol), followed by NEt_3 (1.68 g, 16.6 mmol), were added to a suspension of anhydrous *cis*-1,3,5-cyclohexanetriol (1.999 g, 15.1 mmol) in dry THF (40 ml). The mixture was stirred for half an hour before the addition of one equivalent NaH (0.666 g, 60% in oil, 16.6 mmol), whereupon the suspension fizzed and evolved heat. A temperature of *ca.* 45 °C was maintained for 2.5 hours, when TLC showed the reaction to be incomplete. Heating and stirring were continued for 18 h before the suspension was cooled to 10 °C and filtered to remove sodium chloride. The filtrate was evaporated and then triturated with 40 ml *n*-hexane, affording the pure title compound **1** (3.613 g, 14.7 mmol, 96.7% yield) as a white solid. m.p. 122.7–125 °C (lit. value 120–122 °C). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.78 (m, 3H, 2*H*COH + *H*COTBDMS), 2.28–1.93 (m, 5H, 3*H*CH eq. + 2*H*OCH), 1.55 (m, 3H, 3*H*CH ax.), 0.89 (s, 9H, TBDMS *tert*-butyl group), 0.08 (s, 6H, TBDMS methyl groups). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 67.1 (CH), 66.2 (CH), 42.7 (CH_2), 42.5 (CH_2), 25.8 (CH_3), 18.1 (C), −4.8 (CH_3). ES-MS: *m/z* 269.1 $[M + Na]^+$. IR (diamond anvil) cm^{-1}: 3406 m, 3271 w, 3136 sh (OH); 2928 m, 2858 m (CH); 1250 m (Si–C); 1099 s, 1045 s (C–O). Elemental analysis for $C_{12}H_{26}O_3Si$, actual (expected) %: C 58.36 (58.49), H 10.80 (10.63).

***cis*-1,3-Ditosyloxy-5-(*tert*-butyldimethylsilanyloxy)cyclohexane (2).** Tosyl chloride (19.41 g, 101.9 mmol) was added to a solution of *cis*-(5-*tert*-butyldimethylsilanyloxy)cyclohexane-1,3-diol (**1**) (6.942 g, 28.2 mmol) in distilled pyridine (70 ml), with stirring at 0 °C. A change from a clear colourless solution to an orange-pink suspension was observed. Stirring was continued for 48 hours at 0 °C, before the suspension was decanted into 100 ml water and 100 ml EtOAc and shaken. The organic layer was recovered and washed with 3 × 80 ml portions of brine, and the aqueous layer washed with 2 × 80 ml portions of EtOAc. The organic layers were combined and reduced to *ca.* 50 ml on the rotary evaporator, before water was added to precipitate the crude product overnight as a white solid (14.775 g, 26.6 mmol, 94.5% yield after drying under vacuum). NMR and MS showed that no further purification was necessary for further reaction, a small sample was recrystallised from acetone for melting point and elemental analysis. m.p. 112–114 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.75 (d, 4H, 4Ar*H*), 7.34 (d, 4H, 4Ar*H*), 4.29 (*ptpt*, 2H, 2*H*COTs), 3.40 (tt, 1H, *H*COTBDMS), 2.47 (s, 6H, 2H_3CAr), 2.17 (m, 1H, *H*CH eq.), 1.99 (m, 2H, 2*H*CH eq.), 1.54 (*pq*, 1H, *H*CH ax.), 1.46 (*pq*, 2H, 2*H*CH ax.), 0.78 (s, 9H, TBDMS *tert*-butyl group), −0.08 (s, 6H, TBDMS methyl groups). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 145.1 (Ar, C), 134.0 (Ar, C), 130.0 (Ar, CH), 127.7 (Ar, CH), 74.3 (CH), 64.9 (CH), 41.0 (CH_2), 37.8 (CH_2), 25.6 (CH_3), 21.7 (CH_3), 18.0 (C), −4.9 (CH_3). ES-MS: *m/z* 577.2, 578.2, 579.2 $[M + Na]^+$; 405.1. IR (diamond anvil) cm^{-1}: 2955 m, 2936 m, 2858 m (CH); 1597 m, 1493 w (aromatic); 1342 s, 1173 s (-SO_2–O); 1258 m (Si–C). Elemental analysis for $C_{26}H_{38}O_7S_2Si$, actual (expected)%: C 56.21 (56.29), H 7.01 (6.90).

***cis*-3,5-Ditosyloxycyclohexanol (3).** *cis*-1,3-ditosyloxy-5-(*tert*-butyldimethylsilanyloxy)cyclohexane (**2**) (12.234 g, 22.05 mmol) was added to a 5% volume solution of 40% aqueous HF in acetonitrile. After stirring for 17 hours at 40 °C, water (150 ml) was added and the mixture extracted with chloroform (3 × 150 ml). The combined organic layers were washed with water (150 ml) and saturated brine (100 ml), before drying over $MgSO_4$ and evaporation of the solvent to yield the title compound **3** (9.204 g, 20.9 mmol, 95%) as a white solid. A small portion was recrystallised from hot Et_2O/ethanol for melting point and elemental analysis, yielding a white solid. m.p. 127–129 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.70 (d, 4H, 4Ar*H*), 7.28 (d, 4H, 4Ar*H*), 4.28 (*ptpt*, 2H, 2*H*COTs), 3.49 (m, 1H, *H*COH), 2.40 (s, 6H, 2H_3CAr), 2.14 (m, 3H, 3*H*CH eq.), 1.53 (*pq*, 1H, *H*CH ax.), 1.37 (*pq*, 2H, 2*H*CH ax.). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 145.2 (Ar, C), 133.8 (Ar, C), 130.0 (Ar, CH), 127.6 (Ar, CH), 74.1 (CH), 64.4 (CH), 40.3 (CH_2), 37.7 (CH_2), 21.7 (CH_3). FAB$^+$-MS: *m/z* 441.1 $[M + H]^+$, 401.0, 360.2, 327.0, 281.0, 251.0, 207.0, 173.0 $[TsOH_2]^+$, 147.0, 97.4, 73.7. IR (KBr disc) cm^{-1}: 3428 s (OH); 2962 m, 2890 w (CH); 1599 m, 1496 w (aromatic); 1355 s, 1178 s (SO_2–O); 1097 m (C–O) Elemental analysis for $C_{20}H_{24}O_7S_2$, actual (expected) %: C 54.49 (54.53), H 5.51 (5.49).

***cis*-3,5-Diazido-*trans*-hydroxycyclohexane (4).** To *cis*-1,3-ditosyloxy-5-hydroxycyclohexane (**3**) (11.985 g, 27.21 mmol) in anhydrous DMF was added sodium azide (17.70 g, 272.3 mmol). The resulting suspension was stirred at 70 °C for 16 hours before cooling, addition of EtOAc (80 ml) and removal of salts by filtration. The salts were washed with EtOAc, the washings combined with the filtrate and washed with water (3 × 80 ml), and the aqueous layer back extracted with EtOAc (2 × 50 ml). Combination of the organic layers, drying over $MgSO_4$ and reduction on the rotary evaporator, followed by column chromatography on silica (37.5% to 75% EtOAc in hexane) afforded the title compound **4** as a pale yellow oil (4.291 g, 23.6 mmol, 87% yield). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.27 (m, 1H, *H*COH), 3.70 (*ptpt*, 2H, 2*H*CN_3), 2.23 (m, 1H, *H*CH eq.), 1.99 (m, 2H, 2*H*CH eq.), 1.36 (*p*td, 2H, 2*H*CH ax.), 1.28 (*p*q, 1H, *H*CH ax.). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 65.7 (CH), 54.1 (CH), 37.5 (CH_2), 37.0 (CH_2). EI$^+$-MS: 182.2 $[M]^+$, 179.1, 112.1, 93.0, 67.1, 55.1. IR (diamond anvil) cm^{-1}: 3383 m (OH); 2933 m, 2903 sh, 2852 w (CH); 2083 *vs*., 1234 s (N_3); 1126 s (C–O). Elemental analysis for $C_6H_{10}N_6O$, actual (expected) %: C 39.42 (39.56), H 5.55 (5.53), N 45.21 (46.13).

***cis*-3,5-Diamino-*trans*-hydroxycyclohexane (5).** To *cis*-3,5-diazido-*trans*-hydroxycyclohexane (**4**) (0.611 g, 3.35 mmol) in ethanol (20 ml) was added 10% Pd/C catalyst (0.025 g). The mixture was agitated for 18 hours at 25 °C, under a hydrogen atmosphere of 6 bar before the catalyst was removed by gravity filtration. Evaporation of the solvent yielded **5** as a white solid (0.393 g, 3.02 mmol, 90% yield). ^{1}H-NMR (400 MHZ, D_2O): δ 4.17 (*p*qi, 1H, *H*COH), 2.93 (*p*t*p*t, 2H, *H*CNH_2), 1.95 (m, 1H, *H*CH eq.), 1.83 (m, 2H, 2*H*CH eq.), 1.18 (*p*td, 2H, 2*H*CH ax.), 0.88 (*p*q, 1H, *H*CH ax.). ^{13}C-NMR (100 MHz, D_2O): δ 67.0 (CH), 43.7 (CH), 43.5 (CH_2), 39.7 (CH_2). CI$^+$-MS: *m*/*z* 130.2 $[M]^+$, 113.2 $[M - OH]^+$, 97.1 $[M - OH - NH_2]^+$. IR (KBr disc) cm^{-1}: 3346 s, 3282 w, 3176 sh (OH and NH_2); 2925 s, 2853 sh (CH); 1609 s (NH_2). Elemental analysis for the dihydrochloride salt, $C_6H_{16}Cl_2N_2O$, actual (expected) %: C 34.98 (35.48), H 8.04 (7.94), N 13.50 (13.79).

***cis*-3,5-Diazido-*trans*-methoxycyclohexane (6).** To ground KOH (1.16 g, 20.67 mmol) in DMSO (9 ml) was added *cis*-1,3-diazido-*trans*-5-hydroxycyclohexane (**4**) (1.00 g, 5.49 mmol), followed by iodomethane (3.70 g, 26.06 mmol). The mixture became brown and was stirred at room temperature for six hours before it was poured into 30 ml water. This yellow, cloudy aqueous mixture was extracted with dichloromethane (3 × 30 ml), the organic layers combined and washed with water (2 × 60 ml) then brine (1 × 60 ml) before drying over $MgSO_4$ and removal of solvent *in vacuo* yielded the title compound as a yellow oil (0.886 g, 4.52 mmol, 87% yield). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.67 (m, 1H, *H*COMe), 3.57 (*p*t*p*t, 2H, 2*H*CN_3), 3.24 (s, 3H, H_3COCH), 2.25 (m, 1H, *H*CH eq.), 2.17 (m, 2H, *H*CH eq.), 1.35–1.20 (m, 3H, 3*H*CH ax.). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 74.3 (CH), 56.3 (CH_3), 54.2 (CH), 36.9 (CH_2), 34.2 (CH_2). CI$^+$-MS: *m*/*z* 197.2 $[M + H]^+$, 169.2 $[MH - N_2]^+$, 126.1, 109.1. IR (KBr disc) cm^{-1}: 2933 m, 2886 w, 2827 w (CH); 2082 *vs*. (N_3), 1247 s (N_3), 1081 s (C–O). Elemental analysis for $C_7H_{12}N_6O$, actual (expected) %: C 42.74 (42.85), H 6.18 (6.16), N 42.61 (42.85).

***cis*-3,5-Diamino-*trans*-methoxycyclohexane (7).** *cis*-3,5-Diazido-*trans*-methoxycyclohexane (**6**) (0.6 g, 0.003 mol) in methanol (30 ml) was added to 10% Pd/C catalyst (0.07 g) and hydrogenated (25 °C, 7 bar, 20 h). The reaction mixture was filtered to remove the catalyst and the solvent removed *in vacuo* producing the title compound as a yellow oil (0.39 g, 2.70 mmol, 89% yield). ^{1}H-NMR (400 MHz, D_2O): δ 3.70 (m, 1H, *H*COMe), 3.20 (s, 3H, H_3COCH), 2.82 (*p*t*p*t, 2H, 2*H*CNH_2), 1.98 (m, 2H, 2*H*CH eq.), 1.93 (m, 1H, *H*CH eq.), 1.08 (*p*dt, 2H, 2*H*CH ax.), 0.87 (*p*q, 1H, *H*CH ax.). ^{13}C-NMR (100 MHz, D_2O): δ 76.2 (CH), 55.10 (CH_3), 43.6 (CH), 43.4 (CH_2), 36.7 (CH_2). CI$^+$-MS: *m*/*z* 145.2 $[M + H]^+$, 113.2. IR (NaCl disc) cm^{-1}: 3342 m (NH_2), 2925 m (CH), 1571 (NH_2), 1073 m (C–O). Elemental analysis as dihydrochloride salt, $C_7H_{16}Cl_2N_2O$, actual (expected) %: C 38.11 (38.72), H 8.67 (8.36), N 13.10 (12.90).

Malonic acid *bis*-(*cis*-3,5-diazidocyclohexyl) ester (8). *cis*-3,5-diazido-*trans*-hydroxycyclohexane (**4**) (0.505 g, 2.77 mmol) and DMAP (0.170 g, 1.39 mmol) in dry dichloromethane (10 ml) were added dropwise over 30 min to a stirred, ice-cooled solution of malonyl dichloride (0.183 g, 1.30 mmol) in dry dichlormethane (15 ml). After further stirring at 0 °C for 20 minutes, the ice bath was removed and reaction continued at room temperature for 48 hours. Saturated sodium hydrogen carbonate (20 ml) was added, the layers separated, and the aqueous layer extracted with dichloromethane (2 × 20 ml). The combined organic layers were then washed with water (2 × 20 ml) and saturated brine (20 ml) before drying over $MgSO_4$ and evaporation of solvent *in vacuo*. Column chromatography on silica (20% EtOAc in hexane) yielded the title compound as a pale yellow oil (0.382 g, 0.883 mmol, 67%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.29 (t, 2H, 2*H*COCOR), 3.58 (*p*t*p*t, 4H, 4*H*CN_3), 3.32 (s, 2H, malonyl H_2C), 2.32 (m, 2H, 2*H*CH eq.), 2.24 (m, 4H, 4*H*CH eq.), 1.44 (*p*td, 4H, 4*H*CH ax.), 1.36 (*p*q, 2H, 2*H*CH ax.). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 165.2 (CO), 70.0 (CH), 54.1 (CH), 41.5 (CH), 36.5 (CH_2), 34.5 (CH_2). CI$^+$-MS: *m*/*z* 433.3 $[M + H]^+$, 405.2 $[MH - N_2]^+$, 362.2 $[M - N_5]^+$, 326.3, 269.2, 225.2, 199.2. 137.1, 94.1. IR (diamond anvil) cm^{-1}: 2952 w (CH_2), 2087 *vs*. (N_3), 1729 s (C=O), 1249 (N_3), 1110 s (C–O).

Glutaric acid *bis*-(*cis*-3,5-diazidocyclohexyl) ester (9). *cis*-3,5-Diazido-*trans*-hydroxycyclohexane (**4**) (0.504 g, 2.76 mmol) and DMAP (0.170 g, 1.39 mmol) in dry dichloromethane (9 ml) were added dropwise over 30 minutes to a stirred, ice-cooled solution of glutaryl dichloride (0.223 g, 1.32 mmol) in dry dichloromethane (15 ml). After further stirring at 0 °C for 20 min, the ice bath was removed and reaction allowed to proceed at room temperature for 4 days. Thin layer chromatography showed that the reaction was incomplete, so the reaction mixture was refluxed for a further 24 hours. Saturated sodium hydrogen carbonate (20 ml) was added, the layers separated, and the aqueous layer extracted with dichloromethane (2 × 20 ml). The combined organic layers were then washed with water (2 × 20 ml) and saturated brine (20 ml) before drying over $MgSO_4$ and evaporation of solvent *in vacuo*. Column chromatography on silica (30% EtOAc in hexane) yielded the title compound as a pale yellow oil (0.378 g, 0.821 mmol, 63%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.21 (*t*, 2H, 2*H*COCOR), 3.54 (*p*t*p*t, 4H, 4*H*CN_3), 2.28 (t, 4H, 2 glutaryl H_2C), 2.07 (m, 6H, 6*H*CH eq.), 1.86 (qi, 2H, glutaryl H_2C), 1.38 (*p*td, 4H, 4*H*CH ax.), 1.31 (*p*q, 2H, 2*H*CH ax.). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.6 (CO), 68.4 (CH), 54.2 (CH), 36.7 (CH_2), 34.7 (CH_2), 33.3 (CH_2), 20.0 (CH_2). CI$^+$-MS: *m*/*z* 461.2 $[M + H]^+$, 433.2 $[M + H - N_2]^+$, 390.2 $[M - N_5]^+$, 375.2 $[M - H - 3N_2]^+$, 297.2, 271.2, 242.2, 137.1, 94.1. IR (diamond anvil) cm^{-1}: 2955 m, 2865 w (CH); 2094 s (N_3), 1735 s (C=O), 1254 s (N_3).

Malonic acid *bis*-(*cis*-3,5-diaminocyclohexyl) ester (MADACE, 10). Malonic acid *bis*-(*cis*-3,5-diazidoocyclohexyl) ester (**8**) (0.368 g, 0.85 mmol) in EtOH 1 : 1 EtOAc (20 ml) was hydrogenated (25 °C, 7 bar) over 5% Rh/C catalyst (0.035 g), with agitation, for 18 hours. Removal of the catalyst by filtration and evaporation of solvent *in vacuo* afforded the title compound as a sticky yellow solid (0.279 g, 0.850 mmol, 85%). ^{1}H-NMR (400 MHz, CD_3OD): δ 5.24 (*p*qi, 2H, 2*H*COCOR), 3.36 (s, 2H, malonyl H_2C), 3.00 (*p*t*p*t, 4H, 4*H*CNH_2), 2.09 (m, 6H, 6*H*CH eq.), 1.30 (*p*td, 4H, 4*H*CH ax.), 1.04 (*p*q, 2H, 2*H*CH ax.). CI$^+$-MS: *m*/*z* 329.2 $[M + H]^+$, 287.3, 231.2, 173.2, 131.2 (unassigned). IR (diamond anvil) cm^{-1}: 3272 m (NH_2), 2921 m (CH_2), 1728 m (CO_2R), 1585 s (NH_2), 1244 m (C–OR), 1140 m (C–OR).

Glutaric acid *bis*-(*cis*-3,5-diaminocyclohexyl) ester (GADACE, 11). Glutaric acid *bis*-(3,5-diazidocyclohexyl) ester (**11**) (0.266 g, 0.578 mmol) in EtOH (40 ml) was hydrogenated (25 °C, 7 bar H_2) over 5% Rh/C catalyst (0.060 g), with agitation, for 24 hours. Removal of the catalyst by filtration and evaporation of solvent *in vacuo* afforded the title compound as a slightly yellow, highly viscous oil (0.190 g, 0.533 mmol, 92%). ^{1}H-NMR (400 MHz, D_2O): δ 5.10 (*p*qi, 2H, 2*H*COCOR), 3.00 (*p*t*p*t, 4H, 4*H*CNH_2), 2.31 (t, 4H, 2 glutaryl H_2C), 2.00–1.87 (m, 6H, 6*H*CH eq.), 1.80 (qi, 2H, glutaryl H_2C), 1.20 (*p*td, 4H, 4*H*CH ax.), 0.93 (*p*q, 2H, 2*H*CH ax.). ^{13}C-NMR (100 MHz, D_2O): δ 175.1 (CO), 71.0 (CH), 44.1 (CH), 38.4 (CH_2), 36.5 (CH_2), 33.4 (CH_2), 19.9 (CH_2). FAB$^+$-MS: *m*/*z* 357.2 $[M + H]^+$, 259.1, 131.1, 96.4. IR (NaCl disc) cm^{-1}: 3356 m (NH_2), 2927 m (CH_2), 1725 (CO_2R), 1572 s (NH_2), 1260 m (C–OR), 1155 m (C–OR).

***cis*-3,5-Diazido-*trans*-(*tert*-butyldimethylsilanyloxy)cyclohexane (12).** Sodium azide (2.72 g, 41.8 mmol) was added to *cis*-1,3-ditosyloxy-5-*tert*-butyldimethylsilanyloxycyclohexane (**2**) (2.259 g, 4.08 mmol) in anhydrous DMF (30 ml). The resulting suspension was stirred at 70 °C for 24 hours before it was allowed to cool and the salts were filtered off and washed with ether. The filtrate and washings were combined and washed with 3 × 20 ml portions of brine, and the brine washed with 2 × 20 ml portions of ether, before the organic layers were combined, dried over $MgSO_4$ and reduced on the rotary evaporator. The target compound **12** was isolated as a pale yellow oil (0.917 g, 3.09 mmol, 77%) by column chromatography on silica, using 5% ether in hexane as eluent. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.26 (m, 1H, *H*COTBDMS), 3.71 (*p*t*p*t, 2H, 2*H*CN_3), 2.33 (dt, 1H, *H*CH eq.), 1.97 (d, 2H, 2*H*CH eq.), 1.36 (*p*td, 2H, 2*H*CH ax.), 1.34 (*p*q, 1H, *H*CH ax.), 0.89 (s, 9H, TBDMS *tert*-butyl group), 0.06 (s, 6H, TBDMS methyl groups). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 66.2 (CH), 54.3 (CH), 38.1 (CH_2), 37.0 (CH_2), 25.7 (CH_3), 17.9 (C), −5.0 (CH_3). EI-MS: *m*/*z* 296 $[M]^+$; 281 $[M - CH_3]^+$; 239 $[M - C_4H_9]^+$; 211 $[(M - C_4H_9) - N_2]^+$; 196 $[(M - C_4H_9 - N_2) - CH_3]^+$, 168 $[(M - C_4H_9 - N_2 - CH_3) - N_2]^+$, 141, 128, 115 $[Si(CH_3)_2(C_4H_9)]^+$, 101, 82, 75 $[(CH_3)_2SiOH]^+$, 59, 41. IR (diamond anvil) cm^{-1}: 2952 m, 2932 m, 2855 m (CH); 2091 *vs.* (N_3); 1250 *vs.* (N_3 and Si–C); 1042 s (C–O). Elemental analysis for $C_{12}H_{24}N_6OSi$, actual (expected) %: C 49.10 (48.62), H 8.34 (8.17), N 27.57 (28.36).

***cis*-3,5-Diamino-*trans*-(*tert*-butyldimethylsilanyloxy)cyclohexane (13). (a) Free radical reduction.** AIBN (0.050 g, 0.26 mmol), *n*-PrOH (1.738 ml, 23.25 mmol), PMHS (2.08 ml, 1.10 mmol) and $(Bu_3Sn)_2O$ (0.150 ml, 0.29 mmol) were added to *cis*-1,3-diazido-*trans*-5-*tert*-butyldimethylsilanyloxycyclohexane (**12**) (1.733 g, 5.85 mmol). After 20 minutes stirring at 85 °C the mixture started to bubble due to release of N_2, and after 1 hour the colour changed from yellow to black and the bubbling slowed. After 2.5 hours the mixture was allowed to cool, before addition of anhydrous HCl (2.0 M in ether, 10 ml) and a small amount of hexane resulted in formation of a white precipitate. This was washed with hexane and dried under vacuum to yield the title compound **13** as the dihydrochloride salt (**13a**) (1.822 g, 5.74 mmol, 98.2% yield). ^{1}H-NMR (400 MHz, D_2O): δ 4.35 (m, 1H, *H*COTBDMS), 3.55 (*p*t*p*t, 2H, 2*H*CNH_3^+), 2.28 (dt, 1H, *H*CH eq.), 2.00 (m, 2H, 2*H*CH eq.), 1.46 (*p*td, 2H, 2*H*CH ax.), 1.42 (*p*q, 1H, *H*CH ax.), 0.78 (s, 9H, TBDMS *tert*-butyl group), 0.00 (s, 6H, TBDMS methyl groups). FAB$^+$-MS: *m*/*z* 525.1 $[(M + H)_2Cl]^+$, 321.0, 287.1, 245.1 $[M + H]^+$, 185.1, 73.3, 70.3. IR (KBr disc) cm^{-1}: 3434 s (NH_3^+, water and deprotected OH), 1612 (NH_3^+), 1261 m (Si–C), 1068 m (C–O). This dihydrochloride salt **13a** (2.06 g, 6.48 mmol) in 130 ml methanol was then treated with NaOH (1.20 g, 15.04 mmol) and water (15 ml) and stirred until the cloudy mixture became a clear solution. After reduction to dryness at the rotary evaporator, the title compound **13** (1.050 g, 4.30 mmol, 66%) was recovered from the residue by Kugelrohr sublimation under vacuum (high vac pump) in the temperature range 110–150 °C. ^{1}H-NMR (400 MHz, D_2O): δ 4.23 (m, 1H, *H*COTBDMS), 3.04 (*p*t*p*t, 2H, 2*H*CNH_2), 1.94 (dt, 1H, *H*CH eq.), 1.81 (m, 2H, 2*H*CH eq.), 1.16 (*p*td, 2H, 2*H*CH ax.), 0.90 (*p*q, 1H, *H*CH ax.), 0.78 (s, 9H, TBDMS *tert*-butyl group), 0.00 (s, 6H, TBDMS methyl groups). ^{13}C-NMR (100 MHz, MeOD): δ 68.8 (CH), 46.4 (CH), 45.6 (CH_2), 43.0 (CH_2), 26.3 (CH_3), 18.9 (C), −4.8 (CH_3). FAB$^+$-MS: *m*/*z* 245.2 $[MH]^+$, 185.1, 73.7, 70.8. IR (KBr disc) cm^{-1}: 3432 s (NH_2); 2929 m, 2854 m (CH); 1574 m (NH_2),1257 m (Si–C), 1055 s (C–O).

(b) Hydrogenation over Rh/C. A solution of *cis*-3,5-diazido-*trans*-(*tert*-butyldimethylsilanyloxy)cyclohexane (**12**, 0.500 g, 1.69 mmol) in methanol (30 ml) was added to 5% Rh/C (0.060 g) and hydrogenated at 7 bar, 25 °C, for 60 hours. Removal of the catalyst by filtration and evaporation of the solvent *in vacuo* isolated the title compound **13** as a white waxy solid (0.384 g, 1.57 mmol, 93%).

***cis*-3,5-*bis*[(2-Pyridinyleneamin]-*trans*-hydroxycyclohexane (DDOP, 14).** A methanolic solution (2 ml) of 2-pyridinecarboxaldehyde (0.587 g, 5.48 mmol) was added to a solution of *cis*-3,5-diamino-*trans*-hydroxycyclohexane (**5**) (0.300 g, 2.27 mmol) and triethylamine (0.115 g, 1.14 mmol) in methanol (50 ml). The mixture was refluxed under nitrogen for 20 hours and the volume was then reduced giving a brown oil. This was extracted from water with chloroform (3 × 25 ml), the organic layer back-extracted with water (3 × 25 ml) and dried over $MgSO_4$ before evaporation of solvent yielded **14** (0.685 g, 94% pure by NMR, 2.09 mmol, 92% yield) as a brown oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.58 (m, 2H, 2Ar*H*), 8.41 (s, 2H, 2*H*C═N), 7.92 (m, 2H, 2Ar*H*), 7.67 (*p*td, 2H, 2Ar*H*), 7.24 (m, 2H, 2Ar*H*), 4.40 (*p*qi, 1H, *H*COH), 3.90 (*p*t*p*t, 2H, 2*H*C-N), 2.01–1.80 (m, 6H, 3H_2C). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 160.6 (HC═N), 154.6 (Ar, C), 149.4 (Ar, CH), 136.6 (Ar, CH), 124.8 (Ar, CH), 121.6 (Ar, CH), 66.6 (CH), 62.8 (CH), 41.09 (CH_2), 39.70 (CH_2). EI$^+$-MS: *m*/*z* 308.2 $[M]^+$, 202.1 $[M - C_6N_2H_5]^+$, 183.1, 158.1, 119.0. IR (diamond anvil) cm^{-1}: 3278 m (OH); 2926 m, 2858 m (CH); 1643 s (C═N); 1130 s (C–O).

***cis*-3,5-*bis*[6-Methyl-2-pyridinyleneamin]-*trans*-hydroxycyclohexane (DDMOP, 15).** A methanolic solution (2 ml) of 2-pyridinecarboxaldehyde (0.516 g, 4.26 mmol) was added to a solution of *cis*-3,5-diamino-*trans*-hydroxycyclohexane (**15**) (0.252 g, 1.94 mmol) and triethylamine (0.097 g, 0.97 mmol) in methanol (50 ml). The mixture was refluxed under nitrogen for 22 hours and the volume was then reduced giving a brown oil. This was extracted from water with chloroform (4 × 20 ml), the organic layer back-extracted with water (1 × 30 ml) and dried over $MgSO_4$ before evaporation of solvent yielded **15** (0.72 g, 89% pure by NMR, 1.92 mmol, 99% yield) as a brown oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.39 (s, 2H, 2*H*C═N), 7.74 (d, 2H, 2Ar*H*), 7.56 (*p*t, 2H, 2Ar*H*), 7.10 (d, 2H, 2Ar*H*), 4.38 (*p*qi, 1H, *H*COH), 3.88 (*p*t*p*t, 2H, 2*H*C–N), 2.52 (s, 6H, H_3CAr), 1.99 − 1.79 (m, 6H, 3H_2C). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 161.0 (HC═N), 158.1 (Ar, C), 154.2 (Ar, C), 136.9 (Ar, CH), 124.4 (Ar, CH), 118.6 (Ar, CH), 66.5 (CH), 62.7 (CH), 41.1 (CH_2), 39.7 (CH_2), 24.4 (CH_3). EI$^+$-MS: *m*/*z* 336.2 $[M]^+$, 216.2 $[M - C_7N_2H_7 - H]^+$, 172.1, 147.1. IR (diamond anvil) cm^{-1}: 3356 m (OH); 2925 m, 2860 m (CH); 1645 s (C═N).

***cis*-1,3-Dihydroxy-5-tosyloxycyclohexane (16).** To a suspension of anhydrous *cis*-1,3,5-cyclohexanetriol (1.855 g, 14.04 mmol) in dry THF (15 ml) was added *n*-butyllithium (2.5 M in hexanes, 5.62 ml, 14.05 mmol). After stirring at 40 °C for 10 minutes dry pyridine (6.5 ml) was added, causing a colour change to orange, and the suspension was stirred at 40 °C for a further 30 minutes before cooling and addition of tosyl chloride (2.950 g, 15.47 mmol). The resulting clear brown solution was stirred at room temperature for 15 hours, whereupon TLC showed that all the tosyl chloride had been consumed. The reaction was quenched with water, the mixture added to 20 ml EtOAc and washed with 3 × 20 ml portions of water. The aqueous layers were washed with 2 × 20 ml EtOAc and the organic layers combined, dried over $MgSO_4$ and reduced. Purification by column chromatography on silica (1 : 1 EtOAc /hexane, then 100% EtOAc, then 15% i-PrOH in EtOAc) yielded the title compound **16** as an oily orange solid (2.832 g, 9.89 mmol, 70% yield). A small portion was recrystallised from hot Et_2O/EtOH, yielding a white crystalline solid for melting point and elemental analysis. m.p. 94–97 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.71 (d, 2H, 2Ar*H*), 7.26 (d, 2H, 2Ar*H*), 4.40 (*ptpt* 1H, *H*COTs), 3.60 (m, 2H, 2*H*COH), 2.37 (s, 3H, H_3CAr), 2.10 (m, 3H, 3*H*CH eq.), 1.50 (*p*q, 2H, 2*H*CH ax.), 1.32 (*p*q, 1H, *H*CH ax.). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 144.9 (Ar, C), 134.0 (Ar, C), 130.0 (Ar, CH), 127.7 (Ar, CH), 75.8 (CH), 65.2 (CH), 42.4 (CH_2), 40.2 (CH_2), 21.7 (CH_3). EI-MS: m/z 286.2 $[M]^+$, 245.1, 173.1 $[TsOH_2]^+$, 155.1 $[Ts]^+$, 91.1, 73.1, 68.1. IR (KBr disc) cm^{-1}: 3340 s (OH); 2953 m, 2909 m (CH); 1599 m (aromatic); 1360 s, 1176 s (SO_2–O). Elemental analysis for $C_{13}H_{18}O_5S$, actual (expected) %: C 54.38 (54.53), H 6.37 (6.34).

***cis*-1,3-Dihydroxy-*trans*-5-azidocyclohexane (17).** Sodium azide (1.24 g, 19.1 mmol) was added to a solution of *cis*-1,3-dihydroxy-5-tosyloxycyclohexane (**16**) (1.088 g, 3.80 mmol) in dry DMF (10 ml). The resulting suspension was stirred at 70 °C for 16 hours before it was allowed to cool and acetone (25 ml) was added to precipitate the salts. The salts were filtered off and washed with acetone (3 × 20 ml), and the filtrate reduced under vacuum before purification by column chromatography on silica (EtOAc, then 10%–30% ^{i}PrOH in EtOAc) yielded the title compound as a yellowish crystalline solid (0.473 g, 3.01 mmol, 80% yield). A small amount was recrystallised from Et_2O/EtOH, to give a paler yellow solid for melting point and elemental analysis. m.p. 96–98 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.17 (m, 2H, 2*H*COH), 4.02 (m, 1H, *H*CN_3), 2.02 (*p*dt, 2H, 2*H*CH eq.), 1.86 (dt, 1H, *H*CH eq.), 1.70 (dt, 1H, *H*CH ax.), 1.60 (m, 2H, 2*H*CH ax.). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 67.3 (CH), 52.6 (CH), 38.3 (CH_2), 37.9 (CH_2). CI$^+$-MS: m/z 158 $[M + H]^+$, 130 $[MH - N_2]^+$, 112 $[M - N_2 - OH]^+$, 97, 79. IR (KBr disc) cm^{-1}: 3289 s (OH); 2941 m, 2854 w (CH); 2103 s, 1245 s (N_3). Elemental analysis for $C_6H_{11}N_3O_2$, actual (expected) %: C 46.11 (45.85), H 7.105 (7.05), N 25.88 (26.73).

***cis*-1,3-Dihydroxy-*trans*-5-aminocyclohexane (18).** A solution of *cis*-1,3-dihydroxy-*trans*-5-aminocyclohexane (**11**) (0.359 g, 2.28 mmol) in ethanol (20 ml) was added to 10% Pd/C catalyst (0.027 g). The mixture was agitated at 25 °C, under a hydrogen atmosphere of 6 bar before the catalyst was removed by gravity filtration. Evaporation of the solvent followed by a Kugelrohr sublimation under high vacuum yielded **18** as a white solid (0.285 g, 2.17 mmol, 95% yield). m.p. 146.5–148.5 °C. ^{1}H-NMR (400 MHz, D_2O): δ 3.97 (tt, 2H, 2*H*COH), 3.31 (*p*qi, 1H, *H*CNH_2), 2.05 (m, 1H, *H*CH eq.), 1.70 (*p*dt, 2H, 2*H*CH eq.), 1.49 (m, 2H, 2*H*CH ax.), 1.33 (m, 1H, *H*CH ax.). ^{13}C-NMR (100 MHz, D_2O): δ 65.1 (CH), 43.7 (CH), 41.2 (CH_2), 39.4 (CH_2). CI$^+$-MS: m/z 132.2 $[M + H]^+$, 114.1 $[M - OH]^+$. IR (KBr disc) cm^{-1}: 3342 s, 3273 m (OH and NH_2); 2929 m, 2852 m (CH); 1626 m (NH_2). Elemental analysis for $C_6H_{13}NO_2$, actual (expected): C 55.16 (54.94), H 10.15 (9.99), N 10.44 (10.68).

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