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TETRAHEDRON

Asymmetric Synthesis of (2*R*,5*R*)-2,5-Diaminohexan-1,6-dioic Acid

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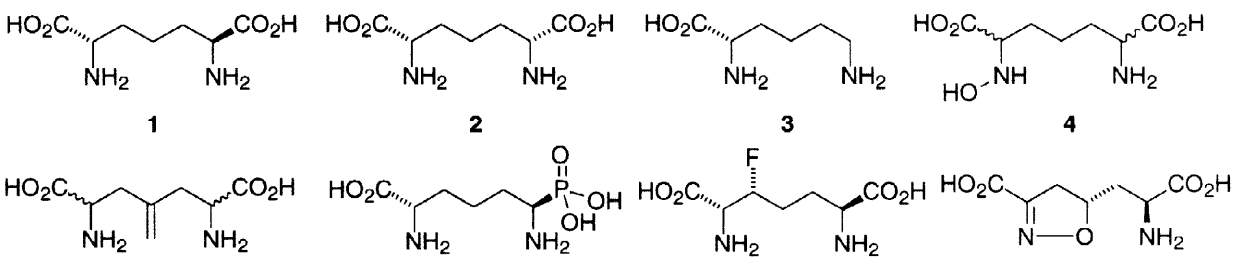
Abstract: Schöllkopf's auxiliary **16** was added to bis-lactim iodide **21** to give 1,2-bis[(3*S*,6*R*)-3,6-dihydro-2,5-dimethoxy-3-isopropylpyrazin-6-yl]ethane **22** in 50% d.e. Dimer **22** was separated from its diastereoisomer **23** and deprotected using 6M HCl to afford homochiral (2*R*,5*R*)-2,5-diaminohexan-1,6-dioic acid **24**.

INTRODUCTION

(*S*,*S*)-Diaminopimelic acid (DAP) **1** plays a key role in bacterial α-amino acid biosynthesis, where it is epimerised by L,L-DAP epimerase to form *meso*-DAP **2** which is then stereoselectively decarboxylated at its (*R*)-stereogenic centre by *meso*-DAP decarboxylase to afford L-lysine **3**.[1] *meso*-Diaminopimelic acid **2** serves a second purpose in bacterial biochemistry as it confers structural rigidity to Gram positive and many Gram negative bacteria by cross-linking the polysaccharides of their cell wall peptidoglycan.[2] Since peptidoglycans and the lysine biosynthetic pathway are foreign to mammalian biochemistry, there has been much interest in employing α,α'-diamino diacids (DADs) as potential antibiotics.[3] Analogues **4-8**, for example, have been shown by Vederas *et al.* to display useful antibacterial activity by selectively inhibiting enzymes of the DAP biosynthetic pathway.[4]



1 **2** **3** **4**

5 **6** **7** **8**

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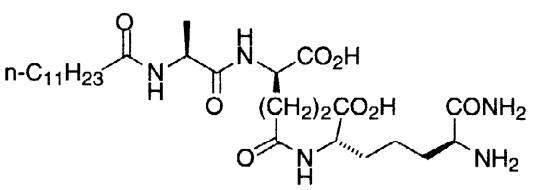
A number of naturally occurring and synthetically derived DAP peptides similar to RP 56124 **9** have been developed as immunostimulants,[5] while the use of DADs as cross-linking agents offers the opportunity of improving the activity, stability and availability of biologically active peptides. DAD **10**, for example, was used to crosslink two haemoregulatory peptides in order to improve their stimulating activity on bone marrow cell division,[6] while the ability of DADs such as **11** to act as crosslinking cystine analogues has great potential in studying the conformation of peptide sequences.[7]



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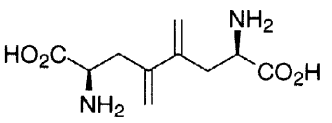

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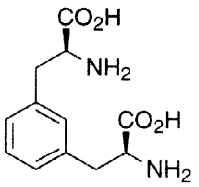

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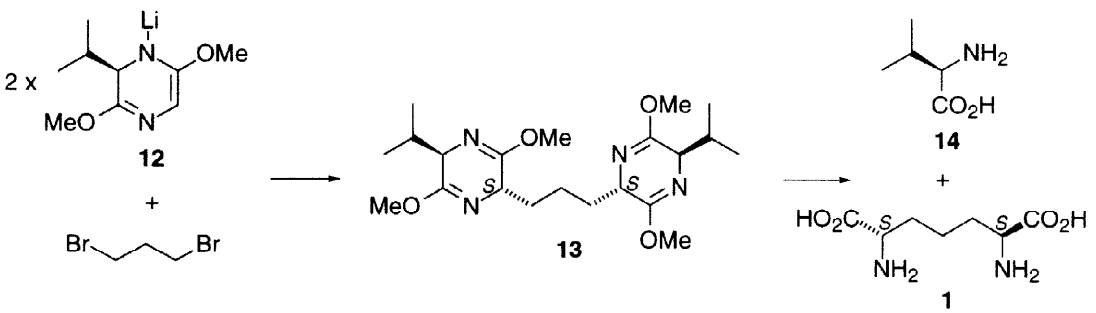
Homochiral DADs are generally prepared by either separation and resolution of a 1:2:1 mixture of the (*S*,*S*), *meso*-(*R*,*S*) and (*R*,*R*) forms,[8] or *via* asymmetric synthesis.[9] An attractive approach to C_2-symmetric α,α'-diamino diacids involves methodology based on the diastereoselective addition of two equivalents of a glycine derived chiral auxiliary to one equivalent of a ω,ω'-dihaloalkane to afford a bridged dimeric species. Subsequent cleavage and purification of the major diastereoisomer arising from this reaction affords the desired homochiral α,α'-diamino diacid. (*S*,*S*)-DAP **1**, for example, can be prepared by the addition of two equivalents of the lithium anion of Schöllkopf's auxiliary **12** to 1,3-dibromopropane in THF at -78°C to give the desired (6*S*,6*S*')-dimer **13** in 60% d.e. Chromatographic purification followed by cleavage of **13** results in a mixture of (*R*)-valine **14** and (*S*,*S*)-DAP **1** which were separated by ion exchange chromatography (Scheme 1).[10]



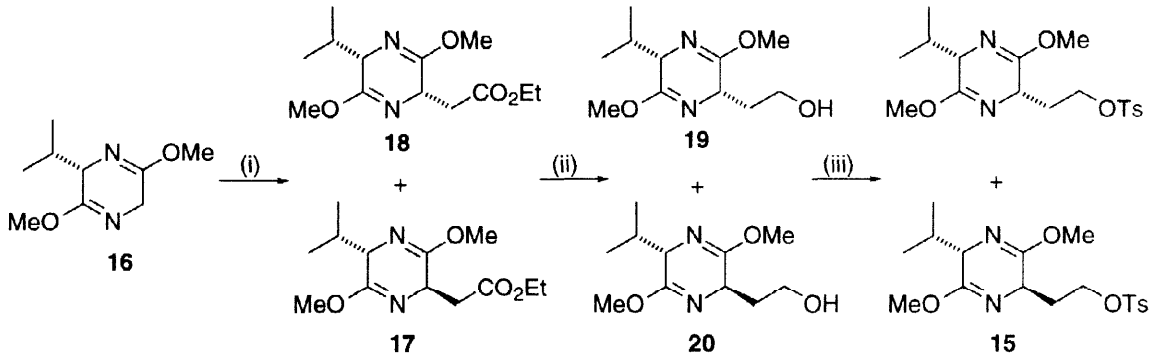
Scheme 1

The use of diiodobutane or diiodopentane as electrophiles *via* this dialkylation protocol enables direct access to the higher homologues of (*S*,*S*)-DAPs (or (*R*,*R*)-DAPs) which contain either tetramethylene or pentamethylene linkers between the α-amino acids functionalities.[6,10,11] This general procedure cannot however be applied to the synthesis of C_2-symmetric DADs comprised of two α-amino acids bridged by a dimethylene linker, because addition of Schöllkopf's anion **12** (or other glycine anion equivalents) to 1,2-dihalo compounds results in nucleophilic elimination of halogen rather than the desired disubstitution pathway.[12]

We wished to prepare homochiral C_2-symmetric 2,5-diaminohexan-1,6-dioic acids and proposed a stepwise approach to this class of compound which involved the diastereoselective addition of the lithium anion of Schöllkopf's auxiliary **12** to bis-lactim ether tosylate **15**. Tosylate **15** was chosen as our initial target, because it had been previously demonstrated by Baldwin *et al.* that primary tosylates were readily displaced by the lithium anion of Schöllkopf's auxiliary **12**.[13]

RESULTS AND DISCUSSION

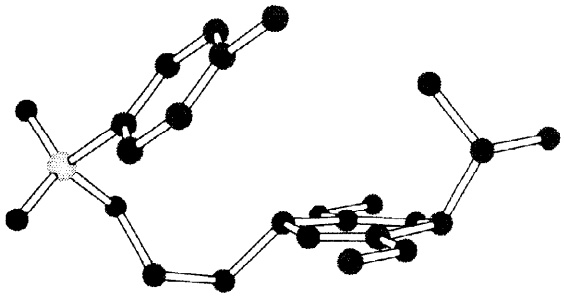
We proposed that tosylate **15** could be readily prepared by alkylation of Schöllkopf's auxiliary **16** with a suitably functionalised electrophile. Investigation into a range of potential electrophiles ($ClCH_2CH_2OTMS$, ethylene oxide, ethylene glycol sulphate, ethylene glycol ditosylate) revealed that ethyl bromoacetate afforded the best yields and highest *trans*-diastereoselectivity. Auxiliary **16** at -78°C was deprotonated in THF with *n*-BuLi and quenched with ethylbromoacetate to afford a 94:6 mixture of *trans* -(3*S*,6*R*)-**17** and *cis*-(3*S*,6*S*)-**18** (88% d.e.). Attempts to purify this mixture of diastereoisomers by distillation or chromatography led to decomposition of product, although a small portion of the crude reaction product was purified by chromatography to confirm the identity of the major diastereoisomer as *trans*-(3*S*,6*R*)-**17**.[14] The mixture of *trans*-**17** and *cis*-**18** esters was reduced with $LiAlH_4$ in THF at -20°C to afford an inseparable mixture of alcohols **19** and **20**. Tosylation of this mixture using pyridine and tosyl chloride at -20°C, followed by chromatographic purification and recrystallisation, afforded *trans*-(3*S*,6*R*)-tosylate **15** in an overall yield of 46% from auxiliary **16** (Scheme 2).



Reagents and Conditions: (i) *n*-BuLi, THF, -78°C; $BrCH_2CO_2Et$; (ii) $LiAlH_4$, THF, -20°C; (iii) TsCl, Pyridine, 0°C.

Scheme 2

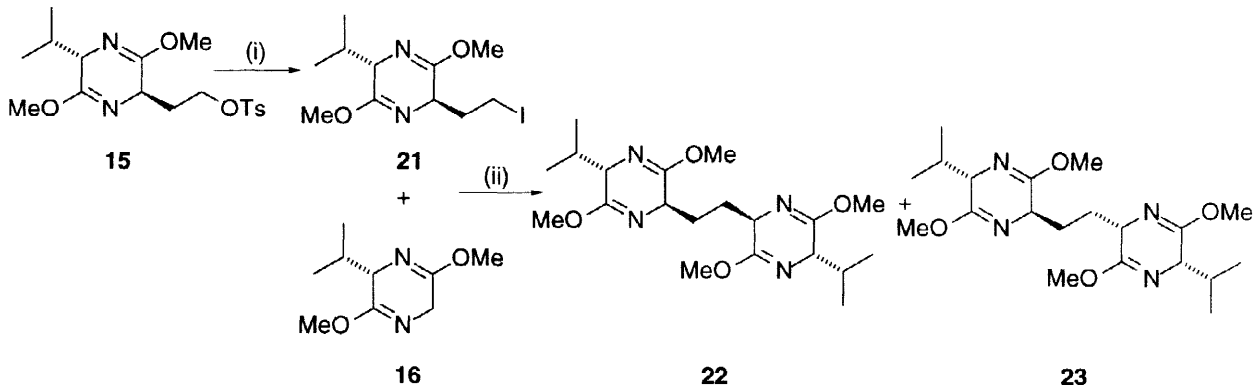
The relative configuration of **15** was confirmed as *trans*- by X-ray crystallographic analysis establishing the planar nature of the dihydropyrazine ring with the C_3-isopropyl and C_6-ethylenetosylate functionalities occupying a *trans* orientation above and below the plane of the pyrazine ring (Figure 1). Assignment of the absolute configuration of **15** as (3*S*,6*R*) follows from the configuration of the starting (*S*)-valine.[15]



X-ray crystal structure of tosylate **15**

Figure 1

Despite the literature precedent,[13] attempts to react the tosylate of **15** with the anion of Schöllkopf's auxiliary (*S*)-**12** were unsuccessful leading to recovery of starting material. Tosylate **15** was therefore converted to iodide **21** using sodium iodide in refluxing acetone. Addition of two equivalents of the anion of Schöllkopf's auxiliary **16** in THF at -78°C to a solution of iodide **21** in THF at -78°C afforded a 75:25 mixture of dimers **22** and **23** (50% d.e.). This mixture was separated by chromatography to afford (6*R*,6'*R*)-dimer **22** and (6*R*,6'*S*)-dimer **23** as low melting point solids and their structures were simply assigned from comparison of their NMR spectra. Dimer **23**, for example, exhibited twenty signals in its ^{13}C NMR spectrum and two sets of resonances in its ^{1}H NMR spectrum while (6*R*,6'*R*)-dimer **22** displayed only ten signals in its ^{13}C NMR spectrum in accordance with its C_2 symmetry. The disappointing 50% d.e. observed for the addition of Schöllkopf's auxiliary **16** to iodide **21** is typical for alkylation of Schöllkopf's auxiliary **16** with linear unactivated electrophiles which generally occurs with much lower selectivity than alkylations with more reactive electrophiles.[16]

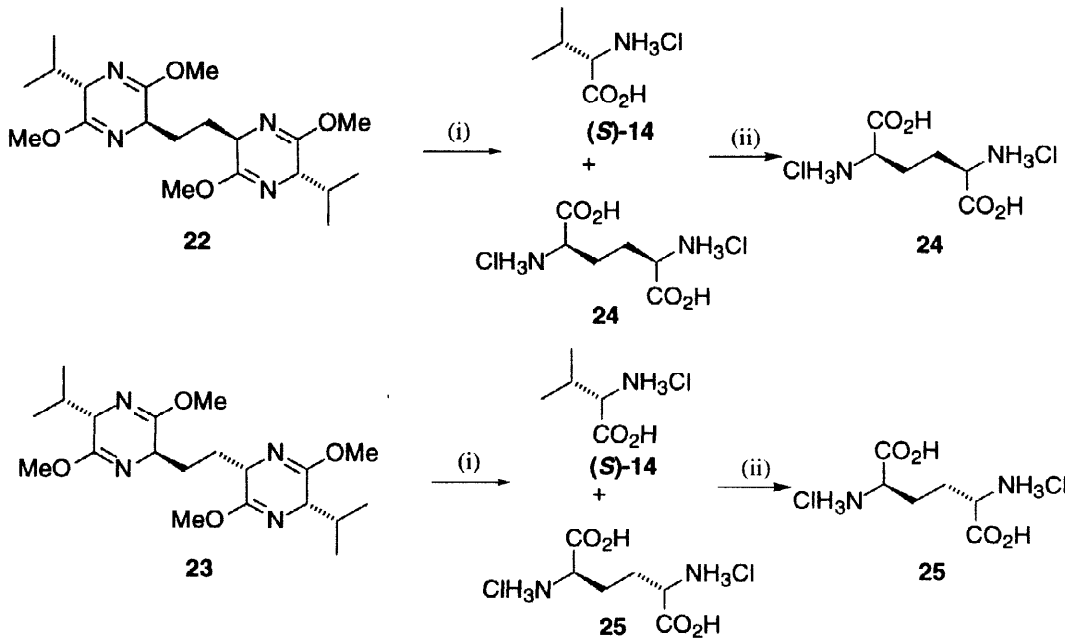


15 **21** **16** **22** **23**

Reagents and Conditions: (i) NaI, acetone, Δ; (ii) *n*-BuLi THF, -78°C.

Scheme 3

(6*R*,6'*R*)-Dimer **22** was deprotected by refluxing in 6M HCl and the resulting mixture of α-amino acids separated by cellulose chromatography to afford L-valine (*S*)-**14** and (2*R*,5*R*)-2,5-diaminohexan-1,6-dioic acid **24** as its bis-HCl salt ($[\alpha]_D^{23}$=-35.2, (*c*=1.0, 6N HCl), Lit[12a] $[\alpha]_D^{23}$ for (*S*,*S*)-DAD=+37.8, (*c*=1.0, 6N HCl); Lit[12b] $[\alpha]_D^{23}$ for (*S*,*S*)-DAD=+26.5, (*c*=5.92, 6N HCl)) in 80 % yield. The corresponding (6*R*,6'*S*)-dimer **23** was also deprotected and purified in a similar manner to afford *meso*-(2*R*,5*S*)-2,5-diaminohexan-1,6-dioic acid **25** as its bis-HCl salt in 80% yield (Scheme 4).[17] ^{1}H and ^{13}C NMR spectroscopic analysis of the crude reaction mixture obtained from hydrolysis of (6*R*,6'*R*)-dimer **22** with 6M HCl revealed that no *meso*-(2*R*,5*S*)-2,5-diaminohexan-1,6-dioic acid **25** could be detected, confirming that no racemisation of (2*R*,5*R*)-2,5-diaminohexan-1,6-dioic acid **24** had occurred under the acidic cleavage conditions.



Reagents and Conditions: (i) 6M HCl, Δ; (ii) cellulose chromatography [*n*-BuOH, H_2O, CH_3CO_2H (4:2:1)].

Scheme 4

CONCLUSION

Schöllkopf's auxiliary **16** has been added to iodide **21** to give 1,2-bis-[(3*S*,6*R*)-3,6-dihydro-2,5-dimethoxy-3-isopropylpyrazin-6-yl]ethane **22** in 50% d.e. Dimer **22** was deprotected using 6M HCl to afford homochiral (2*R*,5*R*)-2,5-diaminohexan-1,6-dioic acid **24** in good yield. Since (3*R*)-Schöllkopf's auxiliary is easily prepared from readily available D-valine, (2*S*,5*S*)-diaminohexan-1,6-dioic acid is also available using this methodology. It is apparent that iodide **21** has potential as a versatile intermediate for the synthesis of γ-substituted α-amino acids and we are currently investigating the functionalisation of this iodide with a wide range of nucleophiles.

EXPERIMENTAL

Melting points were measured on a Gallenkamp hot stage apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker WH 300 and AM 500 and the chemical shifts referenced to $CHCl_3$ (δ 7.27) in $CDCl_3$. IR spectra were recorded on a Perkin Elmer 781 spectrophotometer. Mass spectra were recorded using V.G. MASSLAB VG 20-250 and BIO-Q MICROMASS instruments while HRMS were determined on a VG Autospec. Elemental analyses were performed on a Carlo Erba 1106 elemental analyser. All solvents were purified and dried according to the procedures described in *Purification of Laboratory Chemicals*, D. D. Perrin and W. L. F. Armarego, Pergamon Press, Oxford, 1988. All chemicals used for synthetic procedures were of reagent grade or better. Merck 70-320 mesh silica gel or Fluka cellulose powder (cotton linters) was used for chromatography. Schöllkopf's auxiliary **16** was prepared according to the literature procedure.[15,18]

Ethyl-(3*S*, 6*R*)-3-isopropyl-2,5-dimethoxy-3,6-dihydropyrazin-6-yl-acetate 18

n-BuLi (1.1eq) was added to a solution of Schöllkopf's auxiliary **16** (3.00g, 16.3mmol) in THF (120ml) at -78°C. Ethyl bromoacetate (6ml, 54mmol) was then added dropwise and the reaction mixture stirred at -78°C for 8 hrs. The reaction was allowed to warm to room temperature, quenched with NH_4Cl solution, extracted with ether (3x20ml), dried ($MgSO_4$) and excess electrophile and solvent removed in vacuum to afford the crude product **17** and **18** (3.04g, 11.2 mmol, 88% d.e., 69%) as an unstable oil. A small quantity of the crude reaction product was purified by flash chromatography [silica, petrol/ether (9:1)], to afford ester **18**. $[\alpha]_D^{23}$=+27.3 (*c*=1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 1742 (C=O), 1697 (C=N); δ_H($CDCl_3$) 0.73 (3H, d, *J* 6.9Hz, $CHCH_3$), 1.01 (3H, d, *J* 6.9Hz, $CHCH_3$), 1.27 (3H, t, *J* 7.3Hz, OCH_2CH_3), 2.23 (1H, m, $(CH_3)_2CH$), 2.64 (1H, dd, *J* 13.1 and 5.8Hz, CH'HCO_2Et), 2.85 (1H, dd, *J* 13.1 and 5.8Hz, $CHH'CO_2Et$), 3.66 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 4.02 (1H, t, *J* 3.4Hz, H_3), 4.18 (2H, q, *J* 7.3Hz, OCH_2CH_3), 4.35 (1H, td, *J* 5.8 and 3.4Hz, H_6); δ_C($CDCl_3$) 14.1 (CH_3), 16.8 (CH_3), 18.9 (CH_3), 32.0 (CH), 39.6 (CH_2), 52.4 (C_6), 52.5 (OCH_3), 52.6 (OCH_3), 60.2 (OCH_2), 61.2 (C_3), 162.9 (C=N), 164.6 (C=N), 171.5 (C=O).

(3*S*,6*R*)-3-isopropyl-2,5-dimethoxy-3,6-dihydropyrazine-6-yl ethanol 19

Lithium aluminium hydride (180mg, 5mmol) was added to a solution of esters **17** and **18** (300mg, 1.10mmol) in dry THF (20ml) at -78°C and the reaction left at -20°C overnight. The resultant mixture was quenched with NH_4Cl solution, extracted with diethyl ether (3x20ml), dried ($MgSO_4$), and the solvent removed in vacuum to afford a crude oil which was purified by chromatography [silica, ethyl acetate/petrol (50:50)] to afford alcohols **19** and **20** (203mg, 0.89mmol, 88% d.e., 81% yield). Analysis was carried out on the mixture of coeluting diastereoisomers. ν_{max}(film)/cm^{-1} (film) 3234 (OH, brd), 1696 (C=N), 1670 (C=N); δ_H($CDCl_3$) for major diastereoisomer 0.73 (3H, d, *J* 7.0Hz, $CHCH_3$), 1.01 (3H, d, *J* 7.0Hz, $CHCH_3$), 1.78 (1H, m, CH'CH), 2.20 (2H, m, CH and CHCH'), 3.67 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.86 (2H, m, CH_2OH), 3.98 (1H, t, *J* 3.9 Hz, H_3), 4.10 (1H, m, H_6), 4.45 (1H, broad s, -OH); δ_C($CDCl_3$) for major diastereoisomer 16.8 (CH_3), 18.8 (CH_3), 32.1 (CH), 35.6 (CH_2), 52.6 (2 x OCH_3), 56.5 (C_6), 60.8 (C_3), 62.8 (CH_2OH), 163.3 (C=N), 164.6 (C=N); *m/z* (APCI$^+$, M+1), 229 (100%), (Found 229.1556, $C_{11}H_{21}N_2O_3$ requires 229.1552)

(3*S*,6*R*)-6-(2'-Tosyloxyethyl)-3-isopropyl-2,5-dimethoxy-3,6-dihydropyrazine 15

Tosyl chloride (340mg, 1.78mmol) was added to a solution of alcohols **19** and **20** (194mg, 0.85mmol, 88% d.e.) in pyridine (5ml) at 0°C, and left at -20°C overnight. The reaction was diluted with water (5ml), extracted with ethyl acetate (3 x 10ml), dried ($MgSO_4$), and the solvent removed in vacuum to afford a crude product which was purified by chromatography [silica, petrol:ether (7:3)] and recrystallised from ether to give **15** as a crystalline solid (270mg, 0.71mmol, 83%). m.p. 85°C (ether); $[\alpha]_D^{23}$=+32.5 (*c*=1.2, $CHCl_3$); ν_{max}(film)/cm^{-1} 1695 (C=N), 1329 (S=O), 1176 (S=O); δ_H($CDCl_3$) 0.70 (3H, d, *J* 6.9Hz, $CHCH_3$), 1.01 (3H, d, *J* 6.9Hz, $CHCH_3$), 1.89 (1H, m, CH'HCH_2OTs), 2.21 (1H, m, CHH'CH_2OTs), 2.30 (1H, m, $(CH_3)_2CH$), 2.45 (3H, s, Ar-CH_3), 3.58 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 3.91 (1H, t, *J* 3.4Hz, H_3), 3.98 (1H, td, *J* 6.9 and 3.4Hz, H_6), 4.17 (1H, m, CH_2CH'HOTs), 4.28 (1H, m, CH_2CHH'OTs), 7.34 (2H, d, *J* 8.3Hz, ArH), 7.80 (2H, d, *J* 8.3Hz, ArH); δ_C($CDCl_3$) 16.6 (CH_3), 18.8 (CH_3), 21.4 ($ArCH_3$), 31.9 (CH), 33.1 (CH_2), 51.5 (C_6), 52.2 (OCH_3), 52.4 (OCH_3), 60.9 (C_3), 67.3 (CH_2OTs), 128.0 (ArCH), 129.8 (ArCH), 133.2 (ArCMe), 144.8 ($ArCSO_2$), 163.1 (C=N), 164.3 (C=N); *m/z* (CI^+) 383 (M+1, 100%).

Crystal Data for (3*S*,6*R*)-6-(2'-Tosyloxyethyl)-3-isopropyl-2,5-dimethoxy-3,6-dihydropyrazine 15

$C_{18}H_{26}N_2O_5S$, *M*=382.4, monoclinic, *a*= 8.6223(8), *b*=11.029(2), *c*=11.4260(9) Å, β=111.89(1)°, *U*=1008.2(2) Å, (by the least squares refinement of the diffractometer angles for 24 automatically centred reflections), space group P21, Z=2, D_C=1.26 gcm^{-3}, F(000) = 408, υ=16.38cm^{-1}. Transparent prism. Crystal dimensions 0.16 x 0.48 x 0.58 mm.

Data were measured on an Enraf-Nonius MACH3 diffractometer using graphite monochromated CuKα radiation and an ω-2Ø scan (ω scan width = 0.68 + 0.19tanØ, ω scan speed 1.7-10.1° min^{-1}).[19] Data were corrected for Lorentz and polarisation effects and an empirical absorption correction based on azimuthal scan data applied. A total of 3634 reflections (2 < Ø < 70°, *h*; 0, *k*, -*l*, *l*) were measured, of which 2014 were unique (merging *R*=0.022), and 1987 were observed with I>3σ(*I*).

The crystal structure was refined using full matrix least squares and all hydrogen atoms were located in the difference Fourier maps and included in the final requirement with the fixed positional and thermal parameters. A four term Chebysev weighting[20] scheme was applies which gave satisfactory agreement analysis. At convergence R=0.037 and R'=0.042.

All calculations were carried out using the Oxford Crystals program package on a 486 computer.[21]

(3*S*,6*R*)-6-(2'-Iodoethyl)-3-isopropyl-2,5-dimethoxy-3,6-dihydropyrazine 21

Sodium iodide (904mg, 6.03mmol) was added to a solution of tosylate **15** (223mg, 0.584mmol) in acetone (10ml) and the solution refluxed for 2hrs. The solution was cooled, diluted with water (5ml), extracted with ether (3x5ml), dried ($MgSO_4$), and the solvent removed in vacuum to afford a crude oil , which was purified by chromatography [(silica, petrol/ether (95:5)] to give iodide **21** as a colourless oil (188mg, 0.56mmol, 95%); $[\alpha]_D^{23}$=+18.4 (*c*=0.9, $CHCl_3$); ν_{max}(film)/cm^{-1} 1695 (C=N); δ_H($CDCl_3$) 0.72 (3H, d, *J* 6.8Hz, CH_3), 1.04 (3H, d, *J* 6.8Hz, CH_3), 2.09 (1H, m, CH'H), 2.25 (1H, m, $(CH_3)_2CH$), 2.45 (1H, m, CHH'), 3.25 (1H, m, CH'HI), 3.32 (1H, m, CHH'I), 3.69 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.95 (1H, t, *J* 3.5Hz, H_3), 4.01 (1H, td, *J* 7.9 and 3.5Hz, H_6); δ_C($CDCl_3$) 1.9 (CH_2I), 16.6 (CH_3), 18.9 (CH_3), 31.9 (CH), 38.3 (CH_2), 52.5 (OCH_3), 52.6 (OCH_3), 55.8 (C_6), 60.9 (C_3), 163.1 (C=N), 164.3 (C=N); *m/z* (CI^+), 339 (MH^+, 100%); Found: C 39.4, H 5.7, N 8.3. Calculated for $C_{11}H_{19}IN_2O_2$ C 39.1, H 5.65, N 8.60%,

1,2-bis[3*S*,6*R*)-3,6-Dihydro-2,5-dimethoxy-3-isopropylpyrazin-6-yl]ethane 22 and 1-[3*S*,6*R*)-3,6-Dihydro-2,5-dimethoxy-3-isopropylpyrazin-6-yl]-2-[3'*S*,6'*S*)-3',6'-Dihydro-2',5'-dimethoxy-3'-isopropyl pyrazin-6'-yl]ethane 23

Schöllkopf's auxiliary **16** (184mg, 1mmol) in THF (10ml) at -78°C was deprotonated with *n*-BuLi (1.eq) and transferred *via* cannula into a solution of iodide **21** (170mg, 0.5mmol) in THF at -78°C and the reaction mixture stirred for a further 6hrs at -78°C. After warming to room temperature the reaction mixture was quenched with ammonium chloride solution, extracted with ether (3x20ml), dried ($MgSO_4$), and the solvent removed in vacuum to afford a crude mixture (240mg) containing **16**, **22** and **23** in a ratio of 4:3:1. The mixture was separated by column chromatography [silica, petrol/ether (95:5)] to afford Schöllkopf's auxiliary **16** (74mg, 0.4mmol), (6*R*,6'*R*)-dimer **22** (114mg, 0.29mmol, 58%) and (6*R*,6'*S*)-dimer **23** (38mg, 0.096mmol, 19%).

(6*R*,6'*R*)-dimer 22, m.p. 41°C (pentane); $[\alpha]_D^{23}$=-30.6 (*c*=1.7, $CHCl_3$); ν_{max}(film)/cm^{-1} 1691 (C=N); δ_H($CDCl_3$) 0.69 (6H, d, *J* 6.9Hz, 2 x $CHCH_3$), 1.05 (6H, d, *J* 6.9Hz, 2 x $CHCH_3$), 2.26 (2H, m, 2 x $CH(CH_3)_2$), 3.68 (6H, s, 2 x OCH_3), 3.69 (6H, s, 2 x OCH_3), 3.94 (2H, t, *J* 3.4Hz, 2 x H_3), 4.05 (2H, dt, *J* 3.6 and 3.4Hz, 2 x H_6); δ_C($CDCl_3$) 16.2 (2 x CH_3), 18.4 (2 x CH_3), 29.5 (2 x CH_2), 31.8 (2 x CH), 52.25 (2 x OCH_3), 52.30 (2 x OCH_3), 55.5 (2 x C_6), 60.6 (2 x C_3), 164.05 (2 x C=N), 164.10 (2 x C=N); *m/z* (APCI$^+$, M+1), 395 (100%), (Found 395.2665, $C_{20}H_{35}N_4O_4$ requires 395.2658).

(6*R*,6'*S*)-dimer 23, m.p. 64°C (pentane); $[\alpha]_D^{23}$= -0.8, (*c*=2.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 1692 (C=N); δ_H($CDCl_3$) 0.69 (3H, d, *J* 6.9Hz, CH_3), 0.73 (3H, d, *J* 6.9Hz, CH_3), 1.04 (3H, d, *J* 6.9Hz, CH_3), 1.05 (3H, d, *J* 6.9Hz, CH_3), 1.42-1.50 (1H, m), 1.78-1.87 (3H, m), 2.10 (1H, m), 2.18 (1H, m, $CH(CH_3)_2$), 2.24 (1H, m, $CH(CH_3)_2$), 3.670 (3H, s, OCH_3), 3.676 (3H, s, OCH_3), 3.679 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.65-3.71 (3H, m), 3.92 (1H, t, *J* 4.5Hz, H_3), 3.93 (1H, t, *J* 4.0 Hz, H_3), 3.96 (1H, m, H_6), 4.06 (1H, m, H_6), δ_C($CDCl_3$) 16.6 (CH_3), 17.6 (CH_3), 19.0 (CH_3), 19.5 (CH_3), 30.75 (CH_2), 30.82 (CH_2), 31.4 (CH), 31.8 (CH), 52.2 (2 x OCH_3), 52.3 (2 x OCH_3), 55.2 (C_6), 55.6 (C_6), 60.7 (C_3), 61.0 (C_3), 163.2 (C=N), 163.6 (C=N), 163.8 (C=N), 163.9 (C=N); *m/z* (APCI$^+$, M+1), 395 (100%), (Found 395.2665, $C_{20}H_{35}N_4O_4$ requires 395.2658).

(2*R*,5*R*)-2,5-diaminohexan-1,6-dioic acid 24

(6*R*,6'*R*)-dimer **22** (100mg, 0.25mmol) was dissolved in 6M HCl and the solution refluxed for 2 hrs. The solvent was removed in vacuum to afford a mixture of **24** and (*S*)-valine **14** which was separated by chromatography over cellulose [acetic acid, butanol, water (1:4:2), bed volume=22x3.0cm], acidified with 6M HCl, to afford DAD **24** (50mg, 0.20mmol, 80%) as a pure compound; $[\alpha]_D^{23}$=-35.2 (*c*=1.0, 6M HCl), [Lit[12] $[\alpha]_D^{23}$ for (*S*,*S*)-DAD=+37.8, (*c*=1.0, 6N HCl); Lit[17] $[\alpha]_D^{23}$ for (*S*,*S*)-DAD=+26.5, (*c*=5.92, 6N HCl)]; δ_H(D_2O) 1.88 (2H, m, H_3 and H_4), 1.99 (2H, m, H_3 and H_4), 3.74 (2H, t, *J* 5.6Hz, H_2 and H_5); δ_C(D_2O) 26.4 (C_3 and C_4), 53.0 (C_2 and C_5), 172.2 (C_1 and C_6); *m/z* (ESI$^+$) 174.

(2*R*,5*S*)-2,5-diaminohexan-1,6-dioic acid 25

(6*R*,6'*S*)-dimer **23** (30mg, 0.08mmol) was dissolved in 6M HCl and the solution refluxed for 2 hrs. The solvent was removed in vacuum to afford a mixture of **25** and (*S*)-valine **14** which was separated by

chromatography over cellulose [acetic acid, butanol, water (1:4:2), bed volume=10cmx3.0cm], acidified with HCl, to afford DAD **25** (16mg, 0.064mmol, 80%) as a pure compound; $[\alpha]_D^{23} = 0$ (*c* 1.0, 6M HCl); $\delta_H(D_2O)$ 2.10-2.20 (4H, m, $2xH_3$ and $2xH_4$), 4.18 (2H, br, H_2 and H_5); $\delta_C(D_2O)$ 26.4 (C_3 and C_4), 52.9 (C_2 and C_5), 171.9 (C_1 and C_6); *m/z* (ESI^+) 174.

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