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Asymmetric Total Synthesis of the Individual Diastereoisomers of Hypoglycin A.

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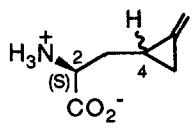
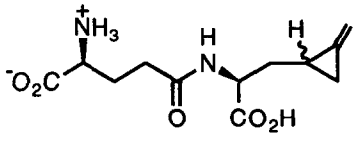
Abstract: *The individual diastereoisomers that constitute the unusual methylenecyclopropane containing α-amino acid hypoglycin A have been synthesised utilising the Sharpless epoxidation to permit an asymmetric methylenecyclopropane synthesis.*

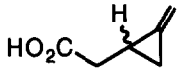
Hypoglycin A **1** is an unusual α-amino acid originally isolated from the arillus and seeds of the unripe fruit of the Jamaican ackee tree (*Blighia sapida*), together with its γ-glutamyl conjugate hypoglycin B **2**.[1] For many years it has attracted considerable attention due to its pronounced physiological effects which manifest themselves in the often fatal condition known as "Jamaican vomiting sickness", its mechanism of action and the synthetic challenge presented by its unusual structure. The biological activity was shown to arise from its metabolite methylenecyclopropane acetic acid (MCPA) **3**, studies on which are currently under active investigation.[2]



Hypoglycin A. **1**

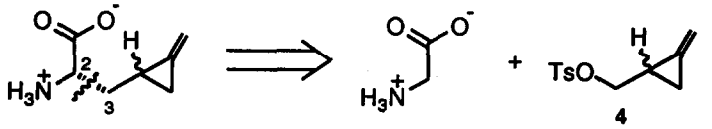


Hypoglycin B. **2**



MCPA **3**

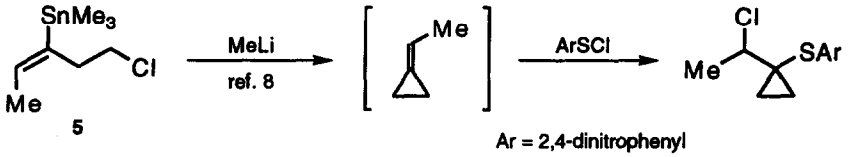
Structural studies have defined the stereochemistry at C-2[3] and subsequently the configuration of the methylenecyclopropane. From Baldwin's reinterpretation of the original degradation studies[4] it is now apparent that hypoglycin A exists as a mixture of diastereoisomers at C-4 with a 17% diastereomeric excess favouring the (2S,4R) isomer.[2h,l] Two syntheses have been reported but neither address the issue of C-4 stereochemistry.[5] We recently reported an asymmetric total synthesis of the individual diastereoisomers of hypoglycin A[6] and now present full details of this work.



Scheme 1

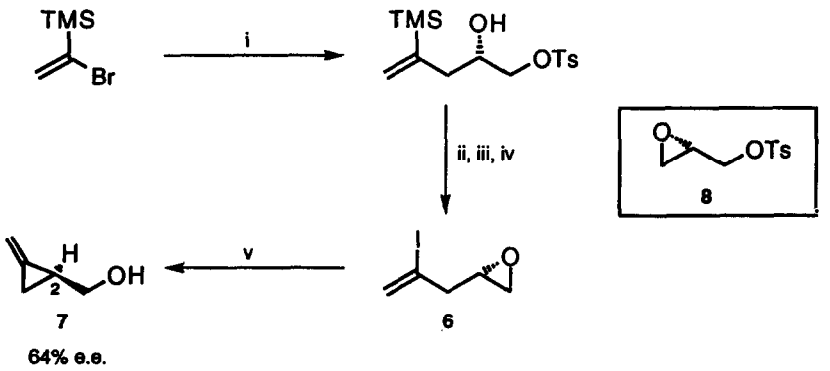
Disconnection of the C-2 to C-3 bond splits the molecule into two components of similar complexity (Scheme 1). As the literature describes a number of alternative chiral glycine enolate equivalents,[7] we chose to investigate an asymmetric synthesis of both antipodes of the methylenecyclopropyl fragment **4** first.

Based on the observation of Piers *et al.* that a methylenecyclopropane is formed and trapped *in situ*, when **5** is reacted with methyllithium[8] (Scheme 2), we initially examined a direct ring closure of **6** to **7** (Scheme 3).



Scheme 2

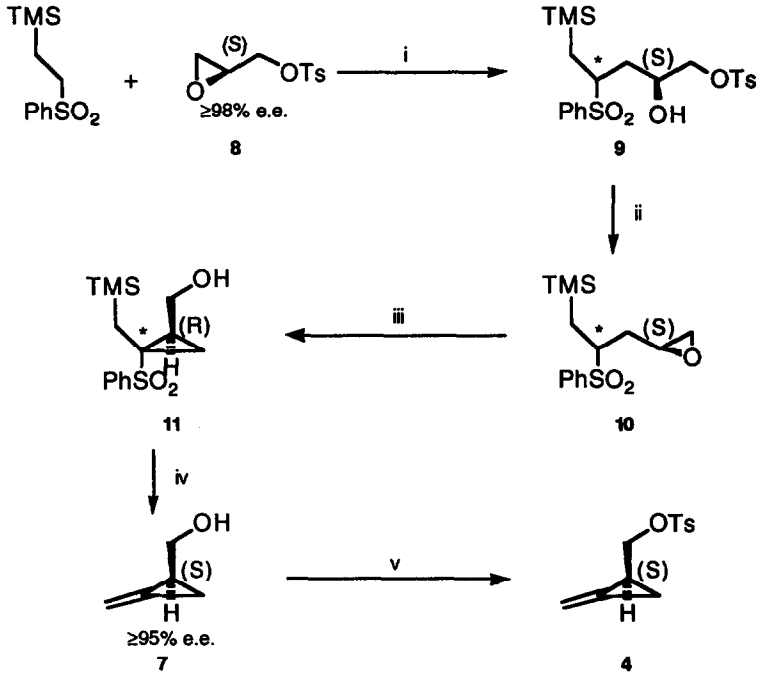
The epoxyvinyliodide **6** was prepared in four steps[9,10] from epoxytosylate **8** (≥98% e.e.)[11]. Despite employing various metallation conditions we found that subsequent cyclisation was always accompanied by some degree of racemisation.[12a,b]



Scheme 3

Reagents and conditions: i, ^{t}BuLi (2eq.), THF, -78°C then $BF_3.OEt_2$ and **8** in THF (21%); ii, K_2CO_3, MeOH (69%); iii, ICl, CCl_4, -23°C (100%); iv, NaOMe, MeOH, CH_2Cl_2 (88%); v, ^{t}BuLi (2eq.), Et_2O, -78°C to 25°C (50%). (Ts = *p*-$MeC_6H_4SO_2$; TMS = $(CH_3)_3Si$).

As no racemisation had been encountered in related cyclisations of saturated substrates[14] it appeared most likely that after cyclisation some of the lithium alkoxide of **7** had suffered further deprotonation at C-2 to give an allylic anion.[15] Consequently we required a cyclisation which would establish the ring prior to introduction of the double bond. As such the methodology of Scheme 3 was abandoned in favour of an approach described by Schecter *et al.* for preparing methylenecyclopropanes.[16,17] Thus treatment of **8** with boron trifluoride etherate and the lithium anion derived from phenyl trimethylsilyl ethyl sulphone gave hydroxy tosylate **9** (60%). Conversion of **9** to the epoxide **10** (93%) was achieved by stirring with K_2CO_3 in THF:MeOH (3:1). Subsequent cyclization of **10** [lithium diisopropylamide (LDA), THF, -78°C] proceeded smoothly to afford cyclopropane **11** (83%). Conversion of **11** to methylenecyclopropane **7** was achieved with anhydrous tetrabutylammonium fluoride (TBAF) and **7**, due to its volatility, was not routinely isolated but taken on as an ethereal solution.[18] (Scheme 4).



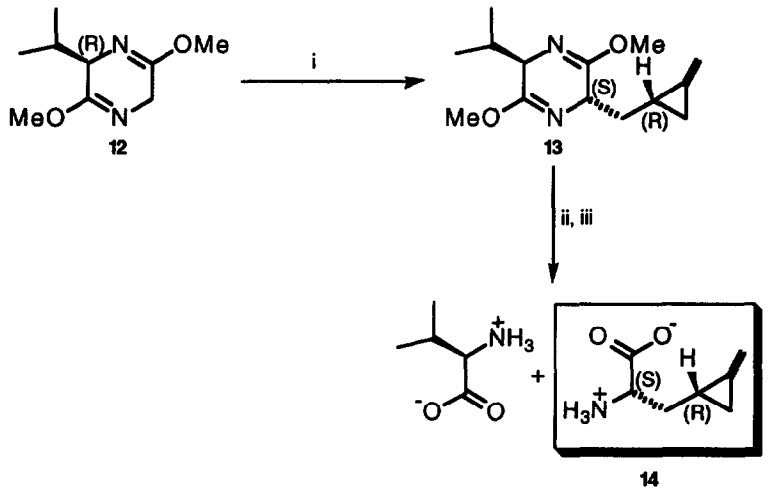
Scheme 4

Reagents and conditions: i, ^nBuLi, -70°C, 25 min., $BF_3.OEt_2$, then **8**, reflux, 1.5 hours, (60%); ii, MeOH-THF, K_2CO_3 (1.1 equiv.), room temp., 4 hours, (93%); iii, LDA (1.5 equiv.), THF, -78°C, 30 min., (83%); iv, anhyd. TBAF (2.5 equiv.), THF, reflux, 85 min.; v, Et_2O, pyridine (3.8 equiv.), TsCl (1.4 equiv.), room temp., 21 hours, DMAPA (2 equiv.), 1 mol dm^{-3} HCl wash (50% from **11**).

An analogous series of transformations starting with the (R) enantiomer of epoxy tosylate **8** provided the antipodal alcohol of **7**. With both enantiomers of **7** available, the enantiomeric purity was confirmed by derivatisation as Mosher esters,[12a,c] the diastereomeric excess of which was found to be ≥95% in each case.

Alcohol **7** was stirred in Et_2O with tosyl chloride and pyridine for 21 hours followed by N,N-dimethylaminopropylamine (DMAPA, 2.0 equiv.) to convert residual tosyl chloride to a basic species, removed by washing with 1M HCl, to give essentially pure tosylate **4** (50% from **11**).[5a,19]

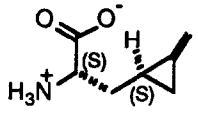
With both enantiomers of the tosylate in hand we next investigated coupling with an asymmetric glycine enolate equivalent and found that the Schöllkopf bis-lactim ether **12** was particularly effective in this case.[20] Thus treatment of tosylate **4** with the lithiated bis-lactim **12** gave, after purification, **13** (90%), ≥95% diastereomerically pure as judged by ^1H NMR (Scheme 5).



Scheme 5

Reagents and conditions: i, ^{n}BuLi, THF, -78°C, 30 min., then **4** (0.5 equiv.), -78°C-room temp., 5 hours, (90%); ii, 0.25 mol dm^{-3} HCl (10 equiv.), 70 hours; iii, LiOH, THF-H_2O (3:1), 0.25 mol dm^{-3} HCl, Dowex, HPLC, (83% from **13**).

Hydrolysis of the alkylated bis-lactim ether **13** proved troublesome under standard conditions.[20] Use of an excess (10.0 equiv.) of 0.25 mol dm^{-3} HCl, however, effected the desired transformation in 73 hours at room temperature to yield the (2S, 4R)-hypoglycin A methyl ester as a mixture with (R)-valine methyl ester in 83% yield. Saponification with LiOH followed by HPLC separation gave pure (2S, 4R)-hypoglycin A **14** in quantitative yield. The analogous series of transformations for the (R) enantiomer of tosylate **4** gave pure (2S, 4S)-hypoglycin A **15** in similar yields. That epimerisation did not occur during the hydrolysis was evident from comparison of the ^1H NMR spectra of the diastereoisomers **14** and **15**. We also performed the saponification with LiOD in D_2O and observed no deuterium incorporation at the α-carbon.



15

It is interesting to note that during initial studies using racemic tosylate (RS-**4**) a degree of kinetic resolution was observed in the alkylation.[21] Using the (R)-Schöllkopf reagent **12** an 83% yield of bis-lactim adduct (cf.**13**) was obtained having approximately a 20% d.e. favouring the (R) configuration at the cyclopropyl centre. After hydrolysis and saponification this gave synthetic hypoglycin A with the same sense of stereochemistry and almost the same diastereomeric ratio observed for the natural material!

Finally the individual diastereoisomers of synthetic hypoglycin A were mixed in turn with a sample of the natural material. Examination of the olefinic region in the ^{1}H NMR (500MHz, D_2O) confirmed the major diastereoisomer of hypoglycin A as (2S, 4R), and the minor diastereoisomer as (2S, 4S).[22] (Fig. 1). Further confirmation of this was obtained by circular dichroism (CD). The CD spectra of **14** showed a positive cotton effect in the 200-230nm region while **15** displayed a smaller negative effect. Proportional combination of **14** and **15** in the same ratio as the natural material gave a positive curve comparable to that of natural hypoglycin A (within experimental error). (Fig. 2).

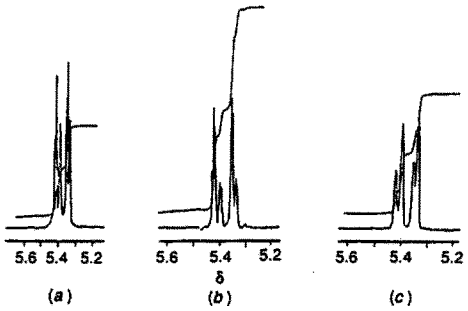


Fig. 1 ^{1}H NMR (500MHz, D_2O) spectra of (a) natural hypoglycin A only; (b) natural hypoglycin A and **14**; (c) natural hypoglycin A and **15**.

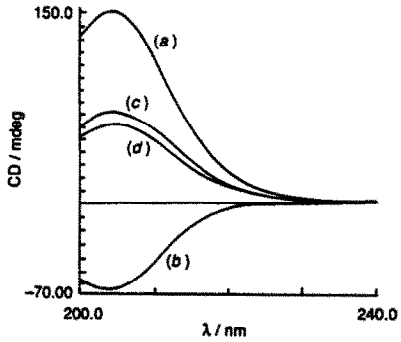


Fig. 2 CD spectra of (a) **14**; (b) **15**; (c) natural hypoglycin A; (d) combination of **14** and **15** in the same ratio as the natural material.

In summary we have described the first asymmetric total synthesis of both diastereoisomers of hypoglycin A and in so doing confirmed its proposed stereochemistry.

EXPERIMENTAL SECTION

All solvents were distilled before use. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone ketyl under argon immediately prior to use. *n*-Butyl lithium was used as bought from Aldrich after standardization with diphenylacetic acid. All other reagents were purified in accordance with D. D. Perrin and W. L. F. Armarego's "Purification of Laboratory Chemicals", 3rd Ed, Pergamon Press, London, 1988, or used as obtained from commercial sources. Reactions were monitered by TLC and/or ^1H NMR prior to workup. Solvents were evaporated from reaction mixtures at ≤30°C on a Büchi RE111 Rotavapor. High boiling solvents were removed on a Büchi RE111 Rotavapor fitted with a dry-ice condenser at <2mmHg.

Flash chromatography was performed on silica gel (Merck Kieselgel 60 F_{254} 230-400 mesh). Thin layer chromatography (TLC) was performed on glass backed plates pre-coated with silica (0.2mm, 60 F_{254}) and visualised using UV fluoresence (254 and 366nm), iodine, then either ninhydrin, ammonium molybdate or anisaldehyde solution followed by heating. Ion exchange chromatography was performed on Dowex 50X8-400 ion exchange resin (activated before use by washing with 1M HCl, followed by distilled water until the eluent reached neutrality).

Melting points were determined on either Büchi 510 or Gallencamp capillary apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. Circular dichroism (CD) was recorded on a JASCO J-720 Spectropolarimeter. Elemental analyses were performed by Mrs. V. Lamburn of the Dyson Perrins Analytical department. Infrared (IR) spectra were recorded on a Perkin Elmer 1750 fourier transform spectrometer with only selected absorptions being recorded. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian Gemini-200 or Brucker AM-500 spectrometer with chemical shifts quoted in parts per million (δ p.p.m.) using the residual solvent peak as an internal reference (except in the case of ^{13}C spectra recorded in D_2O, which were referenced to 1,4-dioxane). Coupling constants (*J*) are quoted to the nearest 0.5Hz. ^{13}C spectra were recorded using DEPT editing, with quarternary carbons being assigned from a broad band proton decoupled analysis used in combination with the DEPT programme. Low resolution mass spectra were recorded on V.G. Micromas ZAB 1F (ACE, FAB, CI^+, DCI^+), V.G. Masslab (CI^+, DCI^+, EI) and V.G. TRIO 1 (GCMS-CI, EI) spectrometers. High resolution mass spectra were recorded on a V.G. Micromas 1F spectrometer.

(2S, 4RS)-2-Hydroxy-4-phenylsulphonyl-5-trimethylsilyl-1-pentyl *p*-toluenesulphonate (9).

^{n}BuLi (0.48cm^3 of 2.6M solution in hexanes, 1.24mmol, 1.0eq) was added dropwise to a suspension of 2-trimethylsilylethyl phenyl sulphone (300mg, 1.24mmol, 1.0eq) in anhydrous Et_2O (6.0cm^3) at -70°C. The white suspension changed to a light yellow solution. After the mixture had been stirred for 25 minutes boron trifluoride etherate (0.15cm^3, 1.24mmol, 1.0eq) was added dropwise followed immediately by a solution of (2S)-glycidyl *p*-toluenesulphonate (**8**) (≥98% e.e.)[9,11] (283mg, 1.24mmol, 1.0eq) in Et_2O (6.0cm^3). The reaction mixture was stirred at -70°C for 5 minutes, allowed to warm to room temperature, then refluxed for a further 1 hour 30 minutes. The reaction was quenched with saturated aqueous $NaHCO_3$ (0.8cm^3) and allowed to cool to room temperature. The layers were separated, and the aqueous phase extracted with Et_2O. The combined ether layers were washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered and reduced *in vacuo* to give 0.50g of crude material which was purified by flash chromatography (SiO_2, 25:75, EtOAc : Pet. Ether (40/60)) to yield

353mg (60%, 75% based on recovered starting material) of (2S, 4RS)-2-hydroxy-4-phenylsulphonyl-5-trimethylsilyl-1-pentyl *p*-toluenesulphonate (**9**) as a clear gum. $R_{f\ Diastereoisomer\ a.}$ 0.30, $R_{f\ Diastereoisomer\ b.}$ 0.25 (30:70, EtOAc : Pet. Ether (40/60)). (Found: C, 53.44; H, 6.54. Calc. for $C_{21}H_{30}O_6S_2Si$: C, 53.59; H, 6.42%). ν_{max} (Thin film) 3 500br m (O-H), 3 066w, 2 954m, 1 599m, 1 448s, 1 451w, 1 363s (S=O), 1 305s, 1 251s, 1 177s, 1 144s (S=O), 1 085s, 1 046m, 981s, 845s, 764m, 740m, 692s, 667s cm^{-1}. δ_H (200MHz, $CDCl_3$) Diastereoisomer a. -0.02 (9H, s, $Si(CH_3)_3$), 0.66 (1H, dd, *J* 12.5, 14.5Hz, $CH_aH_bSiMe_3$), 1.01 (1H, dd, *J* 2.0, 14.5Hz, $CH_aH_bSiMe_3$), 1.64 (1H, ddd, *J* 2.0, 10.5, 15.5Hz, CH_aH_bCHOH), 1.89 (1H, ddd, *J* 2.5, 9.5, 15.5Hz, CH_aH_bCHOH), 2.46 (3H, s, CH_3), 2.78 (1H, br s, OH), 3.47 (1H, ddt, *J* 12.5, 9.5, 2.0Hz, $CHSO_2Ph$), 3.90 (1H, dd, *J* 6.0, 10.0Hz, CH_aH_bOTs), 3.97 (1H, dd, *J* 3.5, 10.0Hz, CH_aH_bOTs), 4.20 to 4.40 (1H, m, CHOH), 7.37 (2H, d, *J* 8.0Hz, 2x tosyl H's), 7.54 to 7.88 (7H, m, 5x Phenyl H's, 2x tosyl H's). Diastereoisomer b. -0.01 (9H, s, $Si(CH_3)_3$), 0.73 (1H, dd, *J* 10.5, 15.0Hz, $CH_aH_bSiMe_3$), 1.05 (1H, dd, *J* 3.0, 15.0Hz, $CH_aH_bSiMe_3$), 1.70 to 1.85 (1H, m, CH_aH_bCHOH), 1.93 to 2.10 (1H, m, CH_aH_bCHOH), 2.46 (3H, s, CH_3), 3.20 to 3.33 (1H, m, $CHSO_2Ph$), 3.35 (1H, d, *J* 4.5Hz, OH), 3.90 to 4.10 (3H, m, CHOH and CH_2OTs), 7.37 (2H, d, *J* 8.0Hz, 2x tosyl H's), 7.55 to 7.89 (7H, m, 5x Phenyl H's and 2x tosyl H's). δ_C (125MHz, $CDCl_3$) Diastereoisomer a. -1.18 (q, $Si(CH_3)_3$), 17.57 (t, CH_2SiMe_3), 21.56 (q, tosyl CH_3), 33.82 (t, CH_2CHOH), 58.27 (d, $CHSO_2Ph$), 66.71 (d, CHOH), 73.17 (t, CH_2OTs), 127.93 (d, ArCH), 129.07 (d, ArCH), 129.13 (d, ArCH), 129.91 (d, ArCH), 132.81 (ArC), 133.70 (d, ArCH), 137.01 (ArC), 145.05 (ArC). Diastereoisomer b. -1.11 (q, $Si(CH_3)_3$), 17.37 (t, CH_2SiMe_3), 21.56 (q, tosyl CH_3), 34.13 (t, CH_2CHOH), 60.14 (d, $CHSO_2Ph$), 67.45 (d, CHOH), 72.83 (t, CH_2OTs), 127.98 (d, ArCH), 129.16 (d, ArCH), 129.22 (d, ArCH), 129.94 (d, ArCH), 132.75 (ArC), 133.82 (d, ArCH), 136.63 (ArC), 145.10 (ArC). m/z (chemical ionization, NH_3) 488 (MNH_4^+, 25%), 471 (MH^+, 3), 439 (41), 316 (MH^+-SO_2Ph, 50), 299 (M^+-OSO_2Ph, 50), 215 (86), 90 (100), 73 ($Si(CH_3)_3^+$, 19).

(2S, 4RS)-1,2-Epoxy-4-phenylsulphonyl-5-trimethylsilylpentane (10).

Anhydrous K_2CO_3 (86.2mg, 0.62mmol, 1.1eq) was added to a solution of (2S, 4RS)-2-hydroxy-4-phenylsulphonyl-5-trimethylsilyl-1-pentyl *p*-toluenesulphonate (**9**) (267mg, 0.57mmol, 1.0eq) in MeOH : THF (50:50) (7.0cm^3) and stirred at room temperature under argon. After 4 hours 10 minutes the mixture was partitioned between CH_2Cl_2 (8.0cm^3) and water (4.5cm^3). The aqueous phase was extracted with CH_2Cl_2 (2x 4.0cm^3) and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to leave 183mg of crude product. This was purified by flash chromatography (SiO_2, 15:85, EtOAc : Pet. Ether (40/60)) to yield 157mg (93%) of (2S, 4RS)-1,2-epoxy-4-phenylsulphonyl-5-trimethylsilylpentane (**10**) as a clear oil. R_f 0.45 (30:70, EtOAc : Pet. Ether (30/40)). (Found: C, 56.55; H, 7.50. Calc. for $C_{14}H_{22}O_3SSi$: C, 56.34; H, 7.43%). ν_{max} (Thin film) 3 062w, 2 953m, 2 898w, 1 481w, 1 447m, 1 417w, 1 306s, 1 252s, 1 185w, 1 146s, 1 085s, 845s, 761m, 734s, 693s cm^{-1}. δ_H (500MHz, $CDCl_3$) 0.00 (9H, s, $Si(CH_3)_3$ of diastereoisomer a.), 0.02 (9H, s, $Si(CH_3)_3$ of diastereoisomer b.), 0.80 (1H, dd, *J* 11.5, 14.5Hz, $CH_aH_bSiMe_3$ of diastereoisomer a.), 0.95 (1H, dd, *J* 11.0, 15.0Hz, $CH_aH_bSiMe_3$ of diastereoisomer b.), 1.10 (1H, dd, *J* 3.0, 14.5Hz, $CH_aH_bSiMe_3$ of diastereoisomer a.), 1.20 (1H, dd, *J* 3.0, 15.0Hz, $CH_aH_bSiMe_3$ of diastereoisomer b.), 1.54 (1H, ddd, *J* 3.0, 7.5, 15.5Hz, $CHCH_aH_b(C_2H_3O)$ of diastereoisomer a.), 1.87 (1H, dt, *J* 5.0, 15.0Hz, $CHCH_aH_b(C_2H_3O)$ of diastereoisomer b.), 2.02 (1H, dt, *J* 6.0, 15.0Hz, $CHCH_aH_b(C_2H_3O)$ of diastereoisomer b.), 2.25 (1H, ddd, *J* 4.0, 8.5, 15.5Hz, $CHCH_aH_b(C_2H_3O)$ of diastereoisomer a.), 2.44 (1H, dd, *J* 2.5, 5.0Hz, epoxide CH_aH_b of diastereoisomer a.), 2.47 (1H, dd, *J* 2.5, 5.0Hz, epoxide CH_aH_b of diastereoisomer b.), 2.77 (1H, dd, *J* 4.0,

5.0Hz, epoxide CH_aH_b of diastereoisomer a.), 2.78 (1H, t, *J* 5.0Hz, epoxide CH_aH_b of diastereoisomer b.), 3.09 to 3.13 (1H, m, epoxide CH of diastereoisomer a.), 3.16 to 3.22 (1H, m, $CHSO_2Ph$ and epoxide CH of diastereoisomer b.), 3.34 (1H, tdd, *J* 3.0, 8.5, 11.5Hz, $CHSO_2Ph$ of diastereoisomer a.), 7.57 to 7.60 (2H, m, 2x ArH's), 7.65 to 7.69 (1H, m, ArH), 7.89 to 7.93 (2H, m, 2x ArH's). δ_C (125MHz, $CDCl_3$) -1.11 and -1.21.(q, $Si(CH_3)_3$ of both diastereoisomers), 15.54 and 16.89 (t, CH_2SiMe_3 of both diastereoisomers), 33.20 and 34.21 (t, $CHCH_2(C_2H_3O)$ of both diastereoisomers), 47.15 and 48.23 (t, epoxide CH_2 of both diastereoisomers), 48.67 and 50.27 (d, epoxide CH of both diastereoisomers), 59.94 and 60.20 (d, $CHSO_2Ph$ of both diastereoisomers), 129.08 (d, ArCH of both diastereoisomers), 129.12 (d, ArCH of both diastereoisomers), 137.41 and 137.59 (ArC of both diastereoisomers). m/z GCMS (chemical ionization, NH_3) 316 (MNH_4^+, 11%), 299 (MH^+, 9), 216 (9), 215 (61), 199 (10), 166 (13), 157 (M^+-SO_2Ph, 20), 141 (SO_2Ph^+, 6), 135 (16), 125 (8), 110 (10), 91 (10), 90 (70), 77 (10), 75 (14), 74 (22), 73 ($Si(CH_3)_3^+$, 100), 67 (22), 59 (6).

(1R, 2RS)-[2-Phenylsulphonyl-2-[(trimethylsilyl)methyl]cyclopropyl]methanol (11).

Lithium diisopropylamide (LDA) (0.79mmol, 1.5eq) was prepared by adding ^{n}BuLi (0.3cm^3 of 2.6M solution in hexanes, 0.79mmol, 1.5eq) dropwise to a solution of diisopropylamine (88.0mg, 121.9µl, 0.87mmol, 1.65eq) in THF (3.8cm^3) at 0°C, under argon. This mixture was stirred at 0°C for 30 minutes then cooled to -78°C. A solution of (2S, 4RS)-1,2-epoxy-4-phenylsulphonyl-5-trimethylsilylpentane (10) (157mg, 0.53mmol, 1.0eq) in THF (2.5cm^3) was added to the LDA solution, which immediately turned bright yellow. After 30 minutes the reaction, now a brown/yellow colour, was quenched with saturated aqueous NH_4Cl (1.0cm^3) then warmed to room temperature. The mixture was extracted with Et_2O, and the remaining aqueous layer extracted twice more with Et_2O. The combined organic layers were reduced *in vacuo* to leave a oily residue, this was taken up in Et_2O, washed with saturated aqueous NaCl , dried ($MgSO_4$), filtered and reduced *in vacuo* to leave 0.16g of crude product. This was purified by flash chromatography (SiO_2, 35:65, EtOAc : Pet. Ether (40/60)) to give 130mg (83%, 98% based on recovered starting material) of (1R, 2RS)-[2-phenylsulphonyl-2-[(trimethylsilyl)methyl]cyclopropyl]methanol (11) as a clear viscous oil. R_f 0.20 (30:70, EtOAc : Pet. Ether (30/40)). (Found: C, 56.66; H, 7.74. Calc. for $C_{14}H_{22}O_3SSi$: C, 56.34; H, 7.43%). ν_{max} (Thin film) 3 513br s (O-H), 3 068w, 2 953s, 2 897m, 1 586w, 1 479w, 1 447s, 1 415m, 1 303s (S=O), 1 250s, 1 143s (S=O), 1 085s, 1 026s, 844s, 759s, 730s, 692s, 639s, 609s, 483s cm^{-1}. δ_H (500MHz, $CDCl_3$) 0.02 (9H, s, $Si(CH_3)_3$ of diastereoisomer a.), 0.07 (9H, s, $Si(CH_3)_3$ of diastereoisomer b.), 0.73 (1H, d, *J* 15.5Hz, $CH_aH_bSiMe_3$ of diastereoisomer b.), 0.77 (1H, dd, *J* 6.0, 6.5Hz, cyclopropyl CH_aH_b of diastereoisomer a.), 0.78 (1H, d, *J* 16.5Hz, $CH_aH_bSiMe_3$ of diastereoisomer a.), 1.11 (1H, dd, *J* 1.0, 16.5Hz, $CH_aH_bSiMe_3$ of diastereoisomer a.), 1.16 (1H, dd, *J* 5.0, 9.0Hz, cyclopropyl CH_aH_b of diastereoisomer b.), 1.25 (1H, d, *J* 15.5Hz, $CH_aH_bSiMe_3$ of diastereoisomer b.), 1.56 (1H, br s, OH of diastereoisomer a.), 1.70 to 1.76 (1H, m, cyclopropyl CH of diastereoisomer b.), 1.79 (1H, dd, *J* 5.0, 8.0Hz, cyclopropyl CH_aH_b of diastereoisomer b.), 1.86 (1H, ddd, *J* 1.0, 6.0, 10.5Hz, cyclopropyl CH_aH_b of diastereoisomer a.), 2.10 to 2.12 (1H, m, cyclopropyl CH of diastereoisomer a.), 2.47 (1H, t, *J* 6.0Hz, OH of diastereoisomer b.), 3.44.(1H, t, *J* 10.5Hz, CH_aH_bOH of diastereoisomer a.), 3.80 to 3.83 (1H, m, CH_aH_bOH of diastereoisomer a.), 4.17 to 4.21 (2H, m, CH_2OH of diastereoisomer b.), 7.54 to 7.67 (3H, m, 3x ArCH's of diastereoisomer a. and b.), 7.89 to 7.91 (2H, m, 2x ArCH's of diastereoisomer a. and b.). δ_C (125MHz, $CDCl_3$) -0.14 and -0.33 (2x q, Si (CH_3)$_3$ of both diastereoisomers), 13.32 and 15.41 (2x t, CH_2TMS of both diastereoisomers), 19.01 and 21.52 (2x t, cyclopropyl CH_2 of both diastereoisomers),

25.34 and 31.28 (2x d, cyclopropyl CH of both diastereoisomers), 60.48 and 60.99 (2x t, CH_2OH of both diastereoisomers), 128.57, 128.87, 128.99, 129.01, 133.24, and 133.34 (6x d, ArCH of both diastereoisomers), 138.60 and 133.25 (ArC of both diastereoisomers). m/z GCMS (chemical ionization, NH_3) 316 (MNH_4^+, 77%), 283 (49), 281 (33), 157 (M^+-SO_2Ph, 34), 141 (SO_2Ph^+, 38), 94 (30), 92 (28), 90 (100), 78 (38), 73 ($Si(CH_3)_3^+$, 28).

(S)-(+)-Methylenecyclopropanemethanol (7).

A mixture of (1R, 2RS)-[2-Phenylsulphonyl-2-[(trimethylsilyl)methyl]cyclopropyl]methanol (11) (130mg, 0.44mmol, 1.0eq), anhydrous THF (0.8cm^3) and tetrabutylammonium fluoride (1.08cm^3 of 1.0M solution in THF predried over 4Å molecular sieves, 1.08mmol, 2.46eq) was refluxed for 1 hour 25 minutes. The resulting solution was purified by flash chromatography (SiO_2, 7.0g), initially eluting with Pet. Ether (30/40) to remove the THF, then with 50:50 Et_2O : Pet. Ether (30/40) to elute the (S)-(+)-methylenecyclopropanemethanol. The majority of the solvent was removed by careful distillation at <50°C using a vigreux column to leave approximately 28.4mg (77% yield, as estimated by ^1H NMR) of (S)-(+)-methylenecyclopropanemethanol (7) in a small amount of Et_2O/Pet. Ether. For characterisation purposes, (7) was separated from the Et_2O by preparative gas chromatography (column type:- 15% PEG Chromosorb A. length:- 5.5m. diameter:- 1.0cm) at 150°C to give (7) as a clear oil, with a retention time of 14.5 minutes. R_f 0.20 (50:50, Et_2O : Hexane). $[\alpha]_D^{20}$ +47.8° (*c* 0.95, Et_2O). (≥95% e.e.)[12]. (Found: M (High Resolution E.I. Mass Spectrum), 84.0575. C_5H_8O requires M, 84.0575). ν_{max} (Thin film) 3 320br s (O-H), 2 985m, 2 870m, 1 135m, 1 095m, 1 015s, 885s cm^{-1}. δ_H (500MHz, $CDCl_3$) 0.96 to 0.99 (1H, m, cyclopropyl CH_aH_b), 1.33 (1H, tt, *J* 9.0, 2.0Hz, cyclopropyl CH_aH_b), 1.75 (1H, obscurred br s, OH), 1.77 to 1.83 (1H, m, cyclopropyl CH), 3.51 (1H, dd, *J* 11.0, 6.5Hz, CH_aH_bOH), 3.62 (1H, dd, *J* 11.0, 7.5Hz, CH_aH_bOH), 5.436 to 5.439 (1H, m, $C=CH_aH$), 5.482 to 5.487 (1H, m, $C=CHH_b$). δ_C (50MHz, $CDCl_3$) 7.71 (t, cyclopropyl CH_2), 17.92 (d, cyclopropyl CH), 65.14 (t, CH_2OH), 103.76 (t, $C=CH_2$), 133.52 ($C=CH_2$). m/z GCMS (chemical ionization, NH_3) 102 (MNH_4^+, 51%), 85 (MH^+, 27), 84 (61), 83 (33), 82 (25), 81 (13), 67 (M-OH^+, 100).

(S)-(Methylenecyclopropyl)methyl *p*-toluenesulphonate (4).

Dry pyridine (99.7mg, 0.102cm^3, 1.26mmol, 3.8eq), *p*-toluenesulphonyl chloride (88.0mg, 0.46mmol, 1.4eq), carbon tetrachloride (0.5cm^3) and (S)-(+)-methylenecyclopropanemethanol (7) (~28.0mg, ~0.33mmol, ~1.0eq) in Et_2O (1.0cm^3) were injected *via* syringe into a 5cm^3 round bottom flask, in the above order, under argon, at 0°C. The reaction was warmed to room temperature and stirred for 21 hours. The reaction was diluted with Et_2O, then excess 3-dimethylamino-1-propylamine (DMAPA) (83µl, 68.0mg, 0.66mmol, 2.0eq) was added and the mixture stirred for 10 minutes, at which time no more *p*-toluenesulphonyl chloride remained as evidenced by TLC. It was then diluted with Et_2O, washed with cold 1M HCl, cold saturated aqueous Na_2CO_3 and saturated aqueous NaCl, then dried ($MgSO_4$), filtered and reduced *in vacuo* to give 51mg (65%, 50% from 11) of the title compound (4) essentially pure as a clear oil.[19] R_f 0.20 (10:90, Et_2O : Hexane). ν_{max} (Thin film) 3 175w, 2 996w, 1 599m, 1 359s, 1 189m, 1 177s, 1 097m, 937s, 813s, 664s cm^{-1}. δ_H (200MHz, $CDCl_3$) 0.95 to 1.05 (1H, m, cyclopropyl CH_aH_b), 1.32 to 1.48 (1H, m, cyclopropyl CH_aH_b), 1.72 to 1.90 (1H, m, cyclopropyl CH), 2.46 (3H, s, CH_3), 3.82 (1H, dd, *J* 9.0, 10.5Hz, CH_aH_bOTs), 4.09 (1H, dd, *J* 6.5, 10.5Hz, CH_aH_bOTs),

5.40 to 5.50 (2H, m, C=C$\underline{H}_2$), 7.36 (2H, d, *J* 8.0Hz, Ar$\underline{H}$'s), 7.87 (2H, d, *J* 8.0Hz, Ar$\underline{H}$'s). δ_C (50MHz, $CDCl_3$) 8.92 (t, cyclopropyl $\underline{C}H_2$), 13.95 (d, cyclopropyl $\underline{C}H$), 21.46 (q, $\underline{C}H_3$), 73.42 (t, $\underline{C}H_2OTs$), 105.77 (t, C=$\underline{C}H_2$), 127.96 (d, H$\underline{C}$CMe$\underline{C}$H), 129.97 (d, H$\underline{C}$C$\underline{C}SO_3\underline{C}$H), 130.99 ($\underline{C}$=$CH_2$), 133.47 ($\underline{C}$-Me), 144.90 ($\underline{C}$-$SO_2$). m/z GCMS (chemical ionization, NH_3) 238 (M^+, 3.4%), 217 (10) 155 ($CH_3C_6H_4SO_2^+$, 59), 91 ($CH_3C_6H_4^+$, 100), 83 ($C_5H_7O^+$, 23), 65 (20), 55($C_4H_7^+$, 16).

(3R, 6S, 2"R)-(+)-3,6-Dihydro-2,5-dimethoxy-3-isopropyl-6-[(methylenecyclopropyl)methyl] pyrazin (13).

^{n}BuLi (0.28cm^3 of 1.6M soln. in hexanes, 0.45mmol, 2.0eq) was added to a stirred solution of (3R)-3,6-dihydro-2,5-dimethoxy-3-isopropyl pyrazin (12) (83.3mg, 0.45mmol, 2.0eq) in THF (1.1cm^3) at -78°C. The mixture was stirred at -78°C for 30 minutes and then treated dropwise with a solution of (S)-(methylenecyclopropyl)methyl *p*-toluenesulphonate (4) (53.9mg, 0.226mmol, 1.0eq) in THF (0.6cm^3), upon which the reaction mixture turned yellow. This was kept stirring at -78°C, under argon, for 2 hours 25 minutes, then allowed to warm to room temperature and stirred for a further 2 hours 25 minutes, and then worked up by adding water (1.0cm^3) and stirring for 5 minutes. The THF was then removed *in vacuo* and the residue taken up in water and extracted four times with Et_2O. The combined organic layers were dried ($MgSO_4$), filtered, and the Et_2O removed *in vacuo* to yield 99.2mg of crude product as a yellow oil. This was purified by flash chromatography (SiO_2, 7.5:92.5, Et_2O : Hexane) to yield 50.8mg, 0.20mmol (90%) of (3R, 6S, 2"R)-(+)-3,6-dihydro-2,5-dimethoxy-3-isopropyl-6-[(methylenecyclopropyl)methyl] pyrazin (13) as a clear oil. R_f 0.30 (7.5:92.5, Et_2O : Hexane), 0.40 (20:80 Et_2O : Hexane). $[\alpha]_D^{20}$ +39.1° (*c* 0.37, Et_2O). (Found: C, 67.22, H, 9.16, N, 10.88. $C_{14}H_{22}N_2O_2$ requires C, 67.16, H, 8.86, N, 11.19%). ν_{max} (Thin film) 2 945m, 1 696s (C=N), 1 452w, 1 436m, 1 309w, 1 236s, 1 197m, 1 142w, 1 012m, 886m cm^{-1}. δ_H (200MHz, $CDCl_3$) 0.71 (3H, d, *J* 7.0Hz, $\underline{C}H_3$), 0.70 to 0.85 (1H, obscurred m, cyclopropyl C$\underline{H}$), 1.08 (3H, d, *J* 7.0Hz, $\underline{C}H_3$), 1.10 to 1.30 (1H, obscurred m, cyclopropyl C$\underline{H}$), 1.32 to 1.50 (1H, m, cyclopropyl C$\underline{H}$), 1.70 to 2.02 (2H, m, $\underline{C}H_2$), 2.31 (1H, d septet, *J* 3.5, 7.0Hz, C$\underline{H}$Me$_2$), 3.71 (3H, s ,O$\underline{C}H_3$), 3.72 (3H, s, O$\underline{C}H_3$), 4.02 (1H, t, *J* 3.5Hz, C$\underline{H}$CHMe$_2$), 4.14 (1H, dt, *J* 3.5, 5.0Hz, 6-$\underline{H}$), 5.32 to 5.40 (2H, m, C=C$\underline{H}_2$). δ_C (50MHz, $CDCl_3$), 8.89 (t, cyclopropyl $\underline{C}H_2$), 11.40 (d, cyclopropyl $\underline{C}H$), 16.32 (q, $\underline{C}H_3$) 18.94 (q, $\underline{C}H_3$), 31.50 (d, $\underline{C}$HMe$_2$), 37.09 (t, $\underline{C}H_2$), 52.09 (q, O$\underline{C}H_3$), 52.31 (q, O$\underline{C}H_3$), 55.43 (d, $\underline{C}$HCH$_2$), 60.64 (d, $\underline{C}$HCHMe$_2$), 103.06 (t, C=$\underline{C}H_2$), 136.13 ($\underline{C}$=CH$_2$), 168.82 (2x $\underline{C}$OMe). m/z GCMS (chemical ionization, NH_3) 252 (13%), 251 (MH^+, 100), 225 (12), 207 (7), 183 (5), 141 (14).

(2S, 4R) α-[(Methylenecyclopropyl)methyl] glycine. [(2S,4R)-Hypoglycin A] (14).

(3R, 6S, 2"R)-(+)-3,6-dihydro-2,5-dimethoxy-3-isopropyl-6-[(methylenecyclopropyl) methyl] pyrazin (13) (50.8mg, 0.2mmol, 1.0eq) was stirred vigorously with 0.25M HCl (8.12cm^3, 2.0mmol, 10.0eq) for 70 hours at room temperature. The mixture was extracted with Et_2O, the ether layer dried ($MgSO_4$), filtered and reduced *in vacuo* to leave an oily residue. The residue was dissolved in water, covered in excess Et_2O and vigorously shaken with concentrated ammonia solution until pH 8-10. The ether phase was separated, and the aqueous phase was further extracted with Et_2O (x 4). The ether phases were recombined, dried ($MgSO_4$), filtered and reduced *in vacuo* to leave an inseperable 1:1 mixture of (R)-valine methyl ester and (2S,4R)-hypoglycin A

methyl ester (47.5mg) as a white solid. R_f 0.40 (90:10, EtOAc : MeOH). δ_H (200MHz, $CDCl_3$) 0.75 to 0.88 (1H, m, cyclopropyl C<u>H</u>), 0.91 (3H, d, *J* 7.0Hz, C<u>H</u>$_3$ of Val methyl ester), 0.98 (3H, d, *J* 7.0Hz, C<u>H</u>$_3$ of Val methyl ester), 1.22 to 1.38 (1H, m, cyclopropyl C<u>H</u>), 1.40 to 1.60 (1H, obscured m, cyclopropyl C<u>H</u>), 1.66 (4H, br s, 2x N<u>H</u>$_2$), 1.70 to 1.80 (2H, obscured m, C<u>H</u>$_2$), 1.95 to 2.15 (1H, m, C<u>H</u>Me$_2$ of Val methyl ester), 3.32 (1H, d, *J* 5.0Hz, α-<u>H</u> of Val methyl ester), 3.61 (1H, t, *J* 6.0Hz, α-<u>H</u>), 3.74 (3H, s, OC<u>H</u>$_3$ of Val methyl ester), 3.75 (3H, s, OC<u>H</u>$_3$), 5.40 to 5.50 (2H, m, C=C<u>H</u>$_2$).

The 1:1 mixture of (R)-valine methyl ester and (2S,4R)-hypoglycin A methyl ester (45.4mg, 2x 0.16mmol) was dissolved in THF/water 3:1 (47cm^3). LiOH.H_2O (14.0mg, 0.33mmol, 1.05eq) was added to the stirred solution and allowed to stir at room temperature for 24 hours. The reaction was worked up by removing the THF *in vacuo*, then adding 0.25M HCl dropwise to the remaining aqueous phase until pH 1-2. The water was then removed under high vacuum and the resulting residue was columned on Dowex 50X8-400, initially washing with water followed by eluting with 1M NH_4OH to elute the desired product, then lyophilised to leave a crude 1:1 mixture of (R)-valine and (2S,4R)-hypoglycin A (50.0mg) as a white solid. The (2S,4R)-hypoglycin A was then separated from the (R)-valine by HPLC using a Hypersil ODS silica gel column (1 x 25cm), eluted with MeOH : 25mM aqueous NH_4HCO_3 (10:90) (flow rate 4cm^3/min, monitoring wavelength 220nm). After evaporation the resulting residue was acidified to pH 1-2, columned on Dowex 50X8-400, initially washing with water followed by eluting with 1M NH_4OH to elute the desired product, then lyophilised to leave pure (2S,4R)-hypoglycin A (**14**) (22.4mg, 83% from **13**) as a white solid. R_f 0.75 (H_2O, reverse phase SiO_2). m.p. Decomposed above 215°C. $[\alpha]_D^{22}$ +12.4° (*c* 0.16, H_2O). CD (*c* 0.12, H_2O) λnm (θ) 200-230 (+150). ν_{max} (KBr Disc) 3 431br m, 3 049br m, 1 585br m, 1 516s, 1 440m, 1 406m, 1 349w, 1 318m, 1 178w, 889m, 844w cm^{-1}. δ_H (500MHz, D_2O) 0.77 to 0.83 (1H, m, cyclopropyl C<u>H</u>$_a$H$_b$), 1.29 (1H, tt, *J* 2.0, 9.0Hz, cyclopropyl CH$_a$<u>H</u>$_b$), 1.38 to 1.45 (1H, m, cyclopropyl C<u>H</u>), 1.76 to 1.90 (2H, m, C<u>H</u>$_2$), 3.72 (1H, broad t, *J* 6.0Hz, α-<u>H</u>), 5.368 to 5.371 (1H, m, C=C<u>H</u>$_a$H$_b$), 5.433 to 5.438 (1H, m, C=CH$_a$<u>H</u>$_b$).[23] δ_C (125MHz, D_2O) 9.81 (t, cyclopropyl <u>C</u>H$_2$), 11.71 (d, cyclopropyl <u>C</u>H), 34.51 (t, <u>C</u>H$_2$), 55.85 (d, α-<u>C</u>H), 104.61 (t, C=<u>C</u>H$_2$), 135.50 (<u>C</u>=CH$_2$), 175.08 (<u>C</u>=O). m/z (chemical ionization, NH_3) 142 (MH^+, 100%), 96 (M^+-CO_2H, 15).

(2S, 4S) α-[(Methylenecyclopropyl)methyl] glycine. [(2S,4S)-Hypoglycin A] (15).

(R)-(Methylenecyclopropyl)methyl p-toluenesulphonate (R-4):-

Starting from the (R) enantiomer of glycidyl *p*-toluenesulphonate **8**,[9,11] an identical set of procedures as for the preparation of **4** delivered (R)-(methylenecyclopropyl)methyl p-toluenesulphonate (R-**4**). The spectroscopic data for R-**4** and the preceding compounds was in agreement with that obtained for compounds in the other enantiomeric series (see above). In addition R-**7** $[\alpha]_D^{20}$ -44.9° (*c* 0.95, Et_2O). (≥95% e.e.)[12].

(3R, 6S, 2"S)-(+)-3,6-Dihydro-2,5-dimethoxy-3-isopropyl-6-[(methylenecyclopropyl)methyl] pyrazin:-

Using (R)-(methylenecyclopropyl)methyl p-toluenesulphonate (R-**4**) an identical procedure as for the preparation of **13** delivered <u>(3R, 6S, 2"S)-(+)-3,6-dihydro-2,5-dimethoxy-3-isopropyl-6-[(methylenecyclopropyl)methyl] pyrazin</u> as a clear oil (74%). R_f 0.30 (7.5:92.5, Et_2O : Hexane), 0.40 (20:80 Et_2O : Hexane). $[\alpha]_D^{20}$ +89.5° (*c* 1.91, Et_2O). δ_H (200MHz, $CDCl_3$) 0.71 (3H, d, *J* 7.0Hz, C<u>H</u>$_3$), 0.70 to 0.90 (1H, obscurred m, cyclopropyl C<u>H</u>), 1.08 (3H, d, *J* 7.0Hz, C<u>H</u>$_3$), 1.15 to 1.30 (1H, obscured m, cyclopropyl

CH), 1.35 to 1.55 (1H, m, cyclopropyl CH), 1.80 to 1.95 (2H, m, CH_2), 2.31 (1H, d septet, *J* 3.5, 7.0Hz, $CHMe_2$), 3.70 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 4.00 (1H, t, *J* 3.5Hz, $CHCHMe_2$), 4.13 (1H, dt, *J* 3.5, 5.0Hz, 6-H), 5.32 to 5.40 (2H, m, $C=CH_2$). δ_C (50MHz, $CDCl_3$) 9.22 (t, cyclopropyl CH_2), 11.54 (d, cyclopropyl CH), 16.34 (q, CH_3) 18.93 (q, CH_3), 31.39 (d, $CHMe_2$), 37.42 (t, CH_2), 52.05 (q, OCH_3), 52.27 (q, OCH_3), 55.61 (d, $CHCH_2$), 60.57 (d, $CHCHMe_2$), 103.19 (t, $C=CH_2$), 135.90 ($C=CH_2$), 163.68 (COMe), 163.97 (COMe). m/z GCMS (chemical ionization, NH_3) 252 (13%), 251 (MH^+, 100).

(2S,4S)-Hypoglycin A (**15**):-

Using (3R, 6S, 2"S)-(+)-3,6-dihydro-2,5-dimethoxy-3-isopropyl-6-[(methylenecyclopropyl)methyl] pyrazin an identical procedure as for the preparation of **14** delivered (2S,4S)-hypoglycin A **15** as a white solid (62%). R_f 0.75 (H_2O, reverse phase SiO_2). m.p. Decomposed above 215°C. $[\alpha]_D^{22}$ +9.1° (*c* 0.11, H_2O). CD (*c* 0.12, H_2O) λnm (θ) 200-230 (-70). ν_{max} (KBr Disc) 3 430br m, 3 050br m, 1 585br m, 1 516s, 1 440m, 1 406m, 1 349w, 1 318m, 1 178w, 889m, 845w cm^{-1}. δ_H (500MHz, D_2O) 0.81 to 0.86 (1H, m, cyclopropyl CH_aH_b), 1.31 (1H, tt, *J* 2.0, 9.0Hz, cyclopropyl CH_aH_b), 1.38 to 1.45 (1H, m, cyclopropyl CH), 1.83 to 1.93 (2H, m, CH_2), 3.67 (1H, broad t, *J* 6.0Hz, α-H), 5.378 to 5.381 (1H, m, $C=CH_aH_b$), 5.438 to 5.441 (1H, m, $C=CH_aH_b$).[23] δ_C (125MHz, D_2O) 9.65 (t, cyclopropyl CH_2), 11.61 (d, cyclopropyl CH), 34.62 (t, CH_2), 55.78 (d, α-CH), 104.61 (t, $C=CH_2$), 135.63 ($C=CH_2$), 175.17 (C=O). m/z (chemical ionization, NH_3) 142 (MH^+, 100%), 96 (M^+-CO_2H, 15).

Analysis of Natural Hypoglycin A.

Natural hypoglycin A was shown to be a mixture of two diastereoisomers, with the (S, R) diastereoisomer being in 17% excess over the (S,S) diastereoisomer.[22] R_f 0.75 (H_2O, reverse phase SiO_2). m.p. Decomposed above 220°C (lit.,[1b] 280-284°C; lit.,[5a] "darkens above 200°C and does not melt to 300°C"). $[\alpha]_D^{22}$ +11.8° (*c* 0.16, H_2O) (lit.,[3b] $[\alpha]_D^{26}$ +11°±1° (*c* 1.0, H_2O)). CD (*c* 0.12, H_2O) λnm (θ) 200-230 (+70). ν_{max} (KBr Disc) 3 434br m, 3 050br m, 1 580br m, 1 514s, 1 440m, 1 400m, 1 349w, 1 318m, 1 175w, 885m, 840w cm^{-1}. δ_H (500MHz, D_2O) 0.79 to 0.87 (1H, m, cyclopropyl CH_aH_b), 1.26 to 1.31 (1H, m, cyclopropyl CH_aH_b), 1.36 to 1.44 (1H, m, cyclopropyl CH), 1.76 to 1.90 (2H, m, CH_2), 3.70 to 3.74 (1H, m, α-H), 5.347 to 5.350 (1H, fine m, $C=CH_aH_b$ of (S, S) diastereoisomer), 5.364 to 5.367 (1H, fine m, $C=CH_aH_b$ of (S, R) diastereoisomer), 5.405 to 5.408 (1H, fine m, $C=CH_aH_b$ of (S, S) diastereoisomer), 5.430 to 5.433 (1H, fine m, $C=CH_aH_b$ of (S, R) diastereoisomer).[23] δ_C (125MHz, D_2O) 9.61 (t, cyclopropyl CH_2 of (S, S) diastereoisomer), 9.80 (t, cyclopropyl CH_2 of (S, R) diastereoisomer), 11.48 (d, cyclopropyl CH of (S, S) diastereoisomer), 11.70 (d, cyclopropyl CH of (S, R) diastereoisomer), 34.50 (t, CH_2), 55.83 (d, α-CH), 104.61 (t, $C=CH_2$), 135.48 ($C=CH_2$), 175.09 (C=O). m/z (chemical ionization, NH_3) 142 (MH^+, 100%), 96 (M^+-CO_2H, 15).

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11. The optical purity of **8** was determined using the procedure of Sharpless *et al.*[9c]
12. (*a*) The optical purity of **7** was established by derivatisation with (S)-(+)-Moshers acid chloride.[13] The resulting esters were examined by ^{1}H NMR in the prescence of Eu(fod)$_3$ [Hfod = 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dione] comparison being made to the Moshers esters derived from racemic **7** which showed clearly distinguishable peaks for the two diastereoisomers; (*b*) Further conformation of optical purity was obtained from specific rotations by comparison with a sample of **7** produced by resolution;[2m] (*c*) Equivalent results were obtained by Mosher ^{1}H NMR analysis of alcohol **7** and its enantiomer obtained by a literature resolution route.[2m]

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22. Calculated by ^{1}H NMR integration to be a 17% d.e., in accordance with Baldwin.[21]
23. Minor variations in the ^{1}H NMR chemical shift values for both synthetic and natural hypoglycin A were observed, depending on the sample concentration. However, the relative positions of peaks from the individual diastereoisomers were not effected.

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