Asymmetric Total Synthesis of the Individual Diastereoisomers of Hypoglycin A

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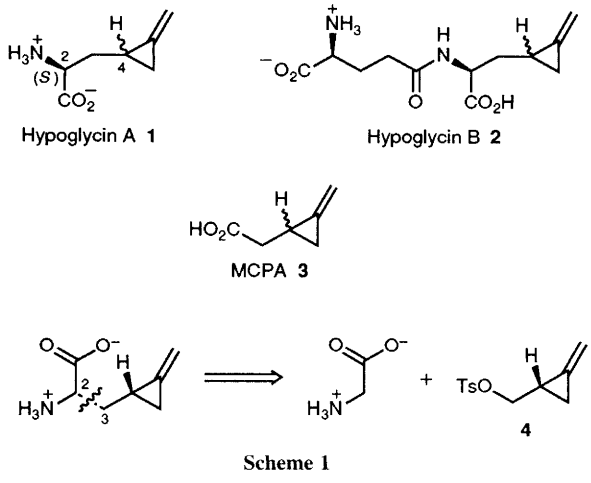
The individual diastereoisomers that constitute the unusual methylenecyclopropane containing α-amino acid hypoglycin A have been synthesised utilising the Sharpless epoxidation to permit an asymmetric methylene cyclopropane synthesis.

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 owing 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]

Structural studies have defined the stereochemistry at C-2[3]



Scheme 1

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% diastereoisomeric excess (d.e.) favouring (*R*).[2h,l] Two syntheses have been reported but neither address the issue of C-4 stereochemistry.[5] We now report an asymmetric total synthesis of the individual diastereoisomers of hypoglycin A.

Disconnection of the C-2 to C-3 bond splits the molecule into two components of similar complexity (Scheme 1). Hence, we initially chose to investigate an asymmetric synthesis of the methylenecyclopropyl fragment **4**, based on a reported method.[6,7]

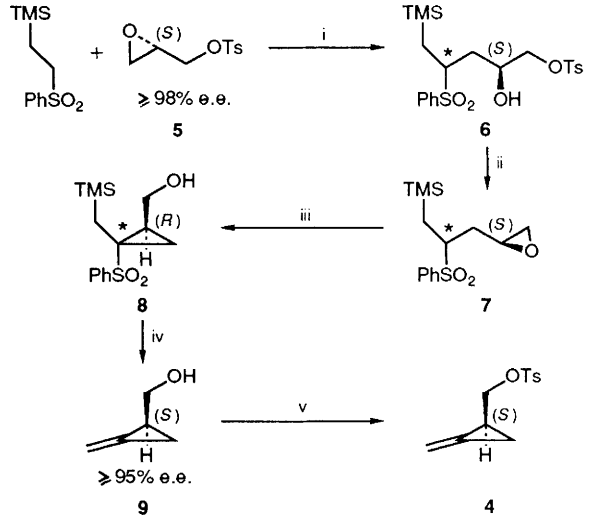
Epoxy toluene-*p*-sulfonate (tosylate) **5** [≥98% enantiomeric excess (e.e.)] was obtained *via* Sharpless asymmetric epoxidation of allyl alcohol followed by *in situ* tosylation.[8] Treatment of **5** with boron trifluoride etherate and the lithium anion derived from phenyl trimethylsilylethyl sulfone gave hydroxy tosylate **6** (60%). Conversion of **6** into the epoxide **7** (93%) was achieved by stirring with K_2CO_3 in tetrahydrofuran (THF)–MeOH (3:1). Subsequent cyclization of **7** [lithium diisopropylamide (LDA), THF, −78 °C] proceeded smoothly to afford cyclopropane **8** (83%). Conversion of **8** into methylenecyclopropane **9** was achieved with anhydrous tetrabutylammonium fluoride (TBAF) and **9**, due to its volatility, was not routinely isolated but taken on as an ethereal solution.† (Scheme 2).

An analogous series of transformations starting with the (*R*) enantiomer of epoxy tosylate **5** provided the antipodal alcohol of **9**. With both enantiomers of **9** available, confirmation of the enantiomeric purity was achieved by derivatisation with (*R*)-Mosher's acid chloride. The resulting esters were individually examined by ^{1}H NMR in the presence of Eu(fod)$_3$ (Hfod = 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dione) and each found to be in ≥95% diastereoisomeric excess (d.e.),‡ comparison being made to the Mosher esters derived from racemic **9** which showed clearly distinguishable peaks for the two diastereoisomers.[9]

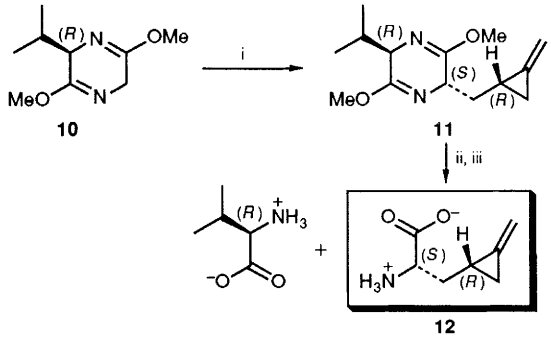
Alcohol **9** was stirred in Et_2O with tosyl chloride and pyridine for 21 h followed by *N*,*N*-dimethylaminopropylamine

† For characterisation purposes **9** was isolated by preparative gas chromatography.

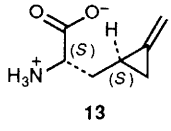
‡ Equivalent results were obtained by Mosher ^{1}H NMR analysis of alcohol **9** and its enantiomer obtained by a literature resolution route.[2m]



Scheme 2 Ts = *p*-MeC$_6$H$_4$SO$_2$. *Reagents and conditions*: i, Bu^{n}Li, −70 °C, 20 min, BF_3·OEt$_2$, then **5**, reflux, 4 h, (60%); ii, MeOH–THF, K_2CO_3 (1.1 equiv.), room temp., 4 h, (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 h, DMAPA (2 equiv.), 1 mol dm^{-1} HCl wash (50% from **8**)



Scheme 3 *Reagents and conditions*: i, Bu^{n}Li, THF, −78 °C 30 min, then **4** (0.5 equiv.), −78 °C–room temp., 5 h (90%); ii, 0.25 mol dm^{-3} HCl (10 equiv.), 73 h (83%); iii, LiOH, THF–H_2O (3:1), 0.25 mol dm^{-3} HCl, Dowex, HPLC (100%)



(DMAPA, 2.0 equiv.) to convert residual tosyl chloride to a basic species, removed by washing with 1 mol dm^{-1} HCl, to give essentially pure tosylate **4** (50% from **8**).[5a,10]

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 **10** was particularly effective in this case.[11] Thus, treatment of tosylate **4** with the lithiated bis-lactim **10** gave, after purification, **11** (90%), ≥95% diastereomerically pure as judged by ^{1}H NMR (Scheme 3).

Hydrolysis of the alkylated bis-lactim ether **11** proved troublesome under standard conditions.[11] Use of an excess (10 equiv.) of 0.25 mol dm^{-3} HCl however, effected the desired transformation in 73 h at room temperature to yield the (2*S*,4*R*)-hypoglycin A methyl ester as a mixture with (*R*)-valine methyl ester in 83% yield. Saponification with LiOH followed by HPLC separation gave pure (2*S*,4*R*)-hypoglycin

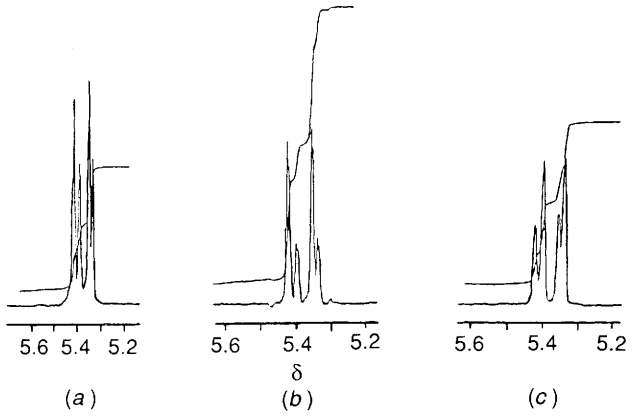


Fig. 1 ^{1}H NMR (500 MHz, D_2O) spectra of (*a*) natural hypoglycin A only; (*b*) natural hypoglycin A and **12**; (*c*) natural hypoglycin A and **13**

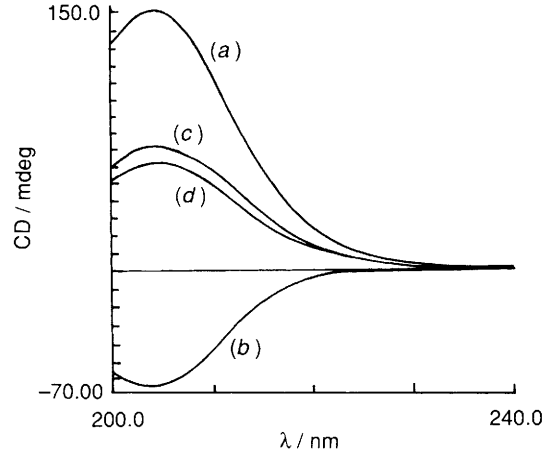


Fig. 2 CD spectra of (*a*) **12**; (*b*) **13**; (*c*) natural hypoglycin A; (*d*) combination of **12** and **13** in the same ratio as the natural material

A **12** in quantitative yield. That epimerisation did not occur during the hydrolysis was evident from comparison of the ^{1}H NMR spectrum with that of the diastereoisomer derived from the (*R*) enantiomer of tosylate **4**. We also performed the saponification with LiOD in D_2O and observed no deuterium incorporation at the α-carbon.

The analogous series of transformations for the (*R*) enantiomer of tosylate **4** gave pure (2*S*,4*S*)-hypoglycin A **13** in similar yields.

It is interesting to note that during initial studies using racemic tosylate a degree of kinetic resolution was observed in the alkylation.[12] Using the (*R*)-Schöllkopf reagent **10** an 83% yield of bis-lactim adduct 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 alkenic region in the ^{1}H NMR (500 MHz, D_2O) confirmed the major diastereoisomer of hypoglycin as (2*S*,4*R*), and the minor diastereoisomer as (2*S*,4*S*).¶ (Fig. 1). Further confirmation of this was obtained by circular dichroism (CD). The CD spectra of **12** showed a positive cotton effect in the 200–230 nm region while **13** displayed a smaller negative effect. Mathematical combination of **12** and **13** in the same ratio as the natural material gave a positive peak the same as that of natural hypoglycin A (within experimental error) (Fig. 2).

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

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§ The natural sample of hypoglycin A was kindly donated by Professor C. H. Hassall.

¶ Calculated by ^{1}H NMR integration to be a 17% d.e., in accordance with Baldwin.[2l]

‖ All new compounds have been fully characterized by IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and possess satisfactory elemental analysis or high resolution mass spectrometry. Full details of the synthesis of these individual diastereoisomers will be reported later.