The synthesis of 3-phosphonocyclobutyl amino acid analogues of glutamic acid *via* diethyl 3-oxycyclobutylphosphonate, a versatile synthetic intermediate

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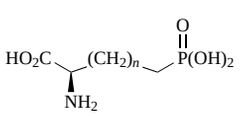
A range of novel 3-phosphonocyclobutyl amino acids have been prepared *via* the versatile synthetic intermediate, diethyl 3-oxocyclobutylphosphonate, which is prepared in three steps from diethyl methylphosphonate. Elaboration of the 3-oxo functionality readily facilitates the synthesis of the 3-phosphonocyclobutyl amino acids.

Introduction

There is much interest in phosphono amino acid analogues **1**–**4** of both natural and synthetic amino acids. These phosphono amino acids are known to have interesting biological activity, in particular, various phosphonic acid analogues of L-aspartic acid **5** and L-glutamic acid **6** act as antagonists at excitatory amino acid (EAA) receptors in the central nervous system (CNS),[1] at which L-aspartic acid **5** and L-glutamic acid **6** are thought to be endogenous neurotransmitters. EAA receptors are now accepted to be the main transmitter receptors mediating synaptic excitation in the mammalian CNS. They are involved with many physiological phenomena, ranging from the processing of sensory information through coordinated movement patterns, to cognitive processes such as learning and memory.[1,2] Dysfunction of these systems leads to various neurological disorders, including memory disorders, epilepsy and spasticity. There is also considerable evidence to indicate that EAA receptors play a role in neurodegenerative conditions such as those associated with Huntington's disease, stroke, schizophrenia and Alzheimer's disease.[3]



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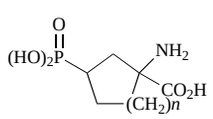

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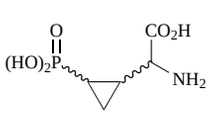

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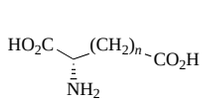

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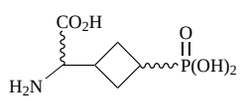

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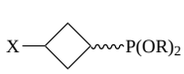

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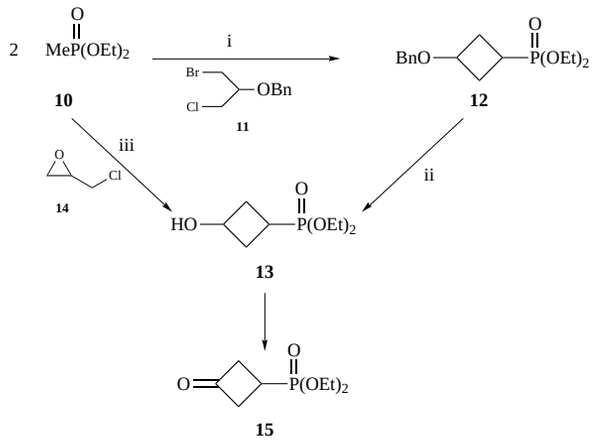
Phosphono amino acids have facilitated the pharmacological characterisation of excitatory amino acid receptors. In particular, the conformationally restrained cyclic phosphono amino acids **2**–**4** have provided much structure–activity information about the various sub-classes of receptors.[4–6] Notably absent from the cyclic phosphono amino acids that have been investigated are the cyclobutane analogues **7** and **8**. This is despite the fact that the severely conformationally restrained cyclobutane offers the promise of much important structure–activity information.

The failure to study the cyclobutane analogues is, primarily due to the lack of synthetic methodology for preparing 3-substituted cyclobutylphosphonates **9**, with functionality at the 3-position suitable for further elaboration. In fact, it is only recently that syntheses of any phosphono-substituted cyclobutanes have been reported. We have reported the synthesis of a range of cyclic bisphosphonate and carboxyphosphonate compounds, including the cyclobutane compounds, using phase transfer methodology[7] and a recent paper has reported the synthesis of dialkyl 1-trimethylsilylcyclobutylphosphate from dialkyl trichloromethylphosphonate.[8] We now describe the synthesis of the versatile intermediate diethyl 3-oxocyclobutylphosphonate **15** from diethyl methylphosphonate, and the elaboration of this intermediate into a range of 3-phosphonocyclobutyl amino acids.

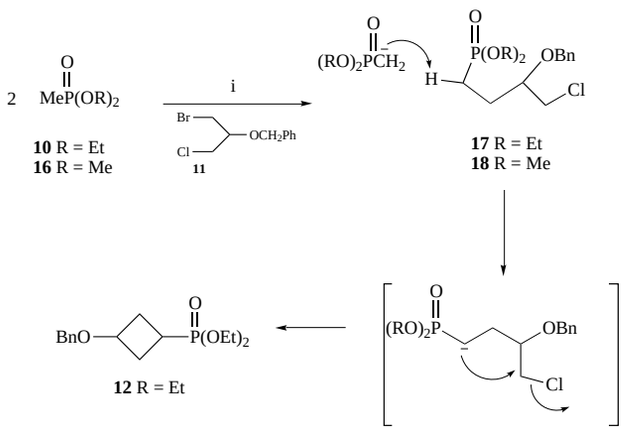
Results and discussion

Reaction of 2 equiv. of diethyl methylphosphonate **10** (Scheme 1) with 2 equiv. of butyllithium and 1 equiv. of 1-chloro-2-benzyloxy-3-bromopropane[9] **11** results in the formation of diethyl 3-(benzyloxy)cyclobutylphosphonate **12** in good yields (*ca.* 50%) for this type of cyclisation reaction. The reaction of 1 equiv. of diethyl methylphosphonate with 2 equiv. of butyllithium results only in monoalkylated products. This cyclisation is also successful in the diisopropyl phosphonate ester analogue is used, although the yield is slightly lower. However, if dimethyl methylphosphonate is used, only the monoalkylated intermediate, dimethyl 3-(benzyloxy)-4-chlorobutylphosphonate **18** and some dimethyl 3-(benzyloxy)butylphosphonate are obtained (Scheme 2).

Thus we suggest that the mechanism of the reaction is as follows: the addition of butyllithium results in the formation of the lithiophosphonate, which displaces the bromide to form a carbon–carbon bond. The second equivalent of the lithiophosphonate then acts as a base, removing a proton from **17** and completing the cyclisation. In the case of dimethyl methylphosphonate, the smaller ester groups allow greater aggregation of



Scheme 1 *Reagents and conditions:* i, BuLi (2 equiv.), THF, −78 °C, 30 min, then **11** (1 equiv.), 2 h, −78 °C to room temp.; ii, H_2, 10% Pd–C, MeOH; iii, BuLi (2 equiv.), THF, −78 °C, 30 min, then **14** (1 equiv.), 2 h, −78 °C to room temp.; iv, cat. $RuCl_3$, CH_2Cl_2, $NaIO_4$, H_2O



Scheme 2 *Reagents and conditions:* i, BuLi (2 equiv.), THF, −78 °C, 30 min, then **11** (1 equiv.), 2 h, −78 °C to room temp

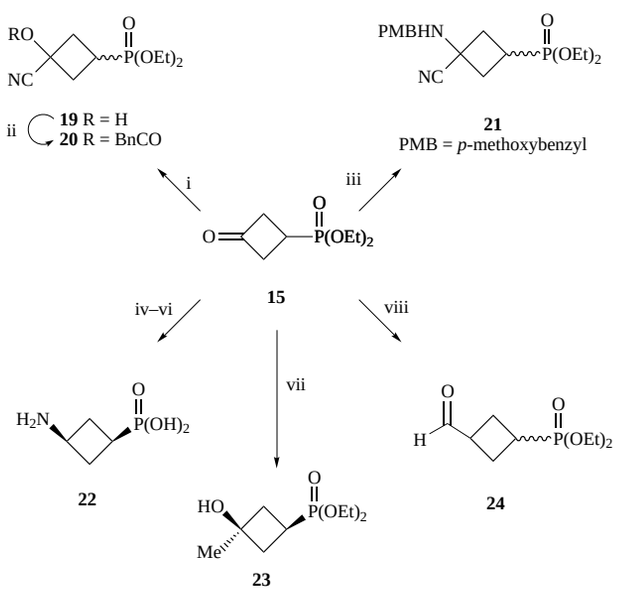
the dimethyl lithiomethylphosphonate, making it more stable than the diethyl lithiomethylphosphonate and thus not able to abstract the second proton from **18**.

The cyclobutylphosphonate **12** is formed as a 2:1 mixture of the two diastereoisomers. The stereochemistry is thought to be directed mainly by the steric interaction of the bulky substituents, thus the major isomer is most likely to be the *trans*-isomer with the phosphonate and the benzyloxy substituents on opposite sides of the ring. Diethyl 3-(benzyloxy)cyclobutylphosphonate **12** was purified by distillation under reduced pressure. The benzyl protecting group was removed in quantitative yield by hydrogenolysis over palladium on carbon. The alcohol was oxidised without further purification to give the desired diethyl 3-oxocyclobutylphosphonate **15** in high yields.

Due to the success of the reaction between the anion of diethyl methylphosphonate **10** and 1-chloro-2-benzyloxy-3-bromopropane **11** we decided to investigate the reaction between the anion of diethyl methylphosphonate and epichlorohydrin **14** (Scheme 1) as a simpler procedure for the preparation of diethyl 3-hydroxycyclobutylphosphonate **13**. Again, 2 equiv. of diethyl methylphosphonate and butyllithium were required to react with 1 equiv. of epichlorohydrin. Diethyl 3-hydroxycyclobutylphosphonate **13** was produced in one step in approximately 25–30% yield. Unfortunately, we were unable to separate **13** from monosubstituted diethyl 3-hydroxy-4-chlorobutylphosphonate by distillation. Thus, we suggest that the use of reagent **11** followed by deprotection is the method of choice for the preparation of **13**.

In contrast to the use of **11**, the reaction with epichlorohydrin **14** produced only one diastereoisomer. The signals in the ^{13}C NMR spectrum of this compound corresponded to the signals that we had assigned to the minor *cis*-isomer of diethyl 3-hydroxycyclobutylphosphonate produced by hydrogenolysis of **12**. This can be explained by chelation of the lithium in the intermediate by both the alkoxide and the phosphonate, holding these two groups *cis* to each other. A similar situation has been described in the reaction of 4-phenyl-4-(phenylsulfonyl)-1,2-epoxybutane with 2 equiv. of methylmagnesium bromide. This reaction produces only one isomer of phenyl 3-phenyl-1-hydroxycyclobutanesulfonate, which has been unambiguously shown to be the *cis*-isomer by X-ray structure determination. In this case the *cis* relationship is proposed to occur due to chelation of the magnesium by the alkoxide ion and the sulfone, in a system that is analogous to the alkoxide–lithium–phosphonate system described above.[10]

Under standard Strecker reaction conditions compound **15** yielded a complex mixture of cyanohydrin, amino nitriles and condensation products. Our attention therefore turned to literature reports of high yielding modifications of the Strecker synthesis using ultrasonic irradiation (Scheme 3).[11] A procedure



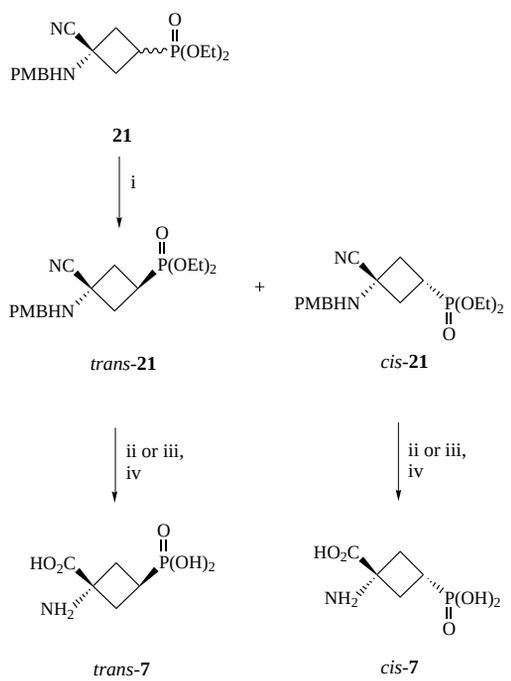
Scheme 3 *Reagents and conditions:* i, NaCN, NH_4Cl, Al_2O_3, MeCN, ultrasound; ii, BnCOCl, Et_3N, CH_2Cl_2; iii, PMB–NH_2, AcOH, MeOH, NaCN; iv, $NH_2OH{\cdot}HCl$, H_2O reflux; v, H_2, Rh–Al_2O_3, MeOH; vi, H^+, H_2O, reflux, Dowex 50W (H^+) ion exchange column; vii, MeMgBr, THF, −78 °C; viii, $CNCH_2P(O)(OEt)_2$, BuLi, THF, −78 °C to room temp., then 6 M HCl

which involves the heterogeneous reaction of a ketone with potassium cyanide, ammonium chloride and alumina in MeCN under ultrasonic irradiation has been reported to give high yields of amino nitriles, while suppressing the formation of cyanohydrins and condensation products.[12] Reaction of **15** with sodium cyanide, ammonium chloride and alumina in MeCN under ultrasonic irradiation for 12 h resulted only in the formation of the cyanohydrins **19** in high yields.

Separation of the *cis*- and *trans*-cyclobutyl cyanohydrins **19** was achieved by chromatography of the *N*-phenylacetyl derivatives **20** on silica gel, allowing assignment of the configurations using ^{13}C NMR spectroscopy and X-ray crystallography. The major isomer from the crude reaction mixture, which eluted first from the column, was identified as the *cis*-isomer *cis*-**20** [Fig. 1(*a*)] and the minor component as the *trans*-isomer. Comparison of the ^{13}C NMR spectra of the two isomers showed a singlet for the peak at δ 117.93 for *cis*-**20**, and a doublet (J = 3.2 Hz) at δ 117.12 for *trans*-**20**. These peaks correspond to the signal from the nitrile carbon of the *trans*-isomer (in which the nitrile and phosphonate functionalities are *cis* to one

another) exhibiting long-range 'w-coupling' [NC–C(3)–C(2)–C(1)–P] between the phosphorus and the nitrile carbon. This long-range coupling is diagnostic of these phosphorus substituted *trans* isomers.

Reaction of **15** with *p*-methoxybenzylamine (or benzylamine), sodium cyanide in MeOH and acetic acid at reflux for 15 h was successful as a method of forming diethyl 3-(*p*-methoxybenzylamino)-3-cyanocyclobutylphosphonate **21** (Scheme 3).[13] Analysis of the ^{31}P and ^{13}C NMR spectra of the crude reaction mixture indicated the formation of just two products, which were identified as the two isomers (3:2 ratio). Separation of the isomers of diethyl 3-(*p*-methoxybenzylamino)-3-cyanocyclobutylphosphonate **21** was achieved by careful silica gel chromatography with hexane–Pr^{i}OH as eluent (Scheme 4). *p*-Methoxybenzylamine was used in preference to benzylamine as the *N*-benzyl group could not be removed from *N*-benzyl analogues of **21** by hydrogenolysis or transfer hydrogenolysis. In contrast, the *p*-methoxybenzyl (PMB) group was easily removed under mild oxidative conditions, using ceric ammonium nitrate,[14,15] or by hydrogenolysis. The crude amino nitriles were hydrolysed to give the amino phosphonic acids *cis*-**7** and *trans*-**7** which were purified by ion exchange chromatography.



Scheme 4 *Reagents and conditions:* i, flash silica chromatography (hexane–Pr^{i}OH, 85:15); ii, CAN, MeCN, H_2O; iii, H_2, 10% Pd–C, MeOH; iv, H^+, H_2O, reflux, Dowex 50W (H^+) ion exchange column

The configuration of the isomers was again assigned using ^{13}C NMR spectroscopy and X-ray crystallography of *trans*-**21**. The signal at δ 121.36 in the ^{13}C NMR spectrum due to the nitrile carbon of the *cis*-isomer is a singlet, whereas the signal due to the nitrile carbon of the *trans*-isomer at δ 120.26 is a doublet (J = 4.8 Hz) due to the long range 'w-coupling' of the nitrile carbon to the phosphorus. It is interesting to note that this long-range coupling between the phosphorus and the nitrile carbon is not seen in the ^{13}C NMR spectrum of either diethyl 3-(acetylamino)-3-cyanocyclopentylphosphonate or 3-(acetylamino)-3-cyanocyclohexylphosphonate.[6] Presumably this is because the cyclobutane bond angle of approximately 90° is exactly right to allow backside interaction of the C(1)–P and C(3)–CN orbitals, whereas the bond angles of the cyclopentane and cyclohexane compounds prevent interaction of their equivalent orbitals.

The *trans*-isomer of diethyl 3-(*p*-methoxybenzylamino)-3-cyanocyclobutylphosphonate *trans*-**21** was isolated as colourless crystals. Slow recrystallisation from a mixture of diethyl ether, toluene and pentane provided crystals suitable for X-ray diffraction. The X-ray structure of *trans*-diethyl 3-(*p*-methoxybenzylamino)-3-cyanocyclobutylphosphonate *trans*-**21** [Fig. 1(*b*)] was obtained. The dihedral angle C(1)–C(2)–C(3)–C(4) is −5.7°, which is considerably less than that of *cis*-diethyl 3-(phenhylacetoxy)-3-cyanocyclobutylphosphonate *cis*-**20**. However, it has been reported that this folding can be significantly affected by solid-state effects, with different crystals of the same compound showing different amounts of ring puckering.[16] The ^{13}C NMR spectra of the free amino acids **7** show similar shifts and coupling constants for the signals due to the cyclobutane ring to those in the spectra of the protected amino nitriles. The signal due to the carboxylic acid functionality of the *trans*-isomer at δ 176.94 is a doublet (J = 2.9 Hz) due to the long-range coupling with the phosphorus.

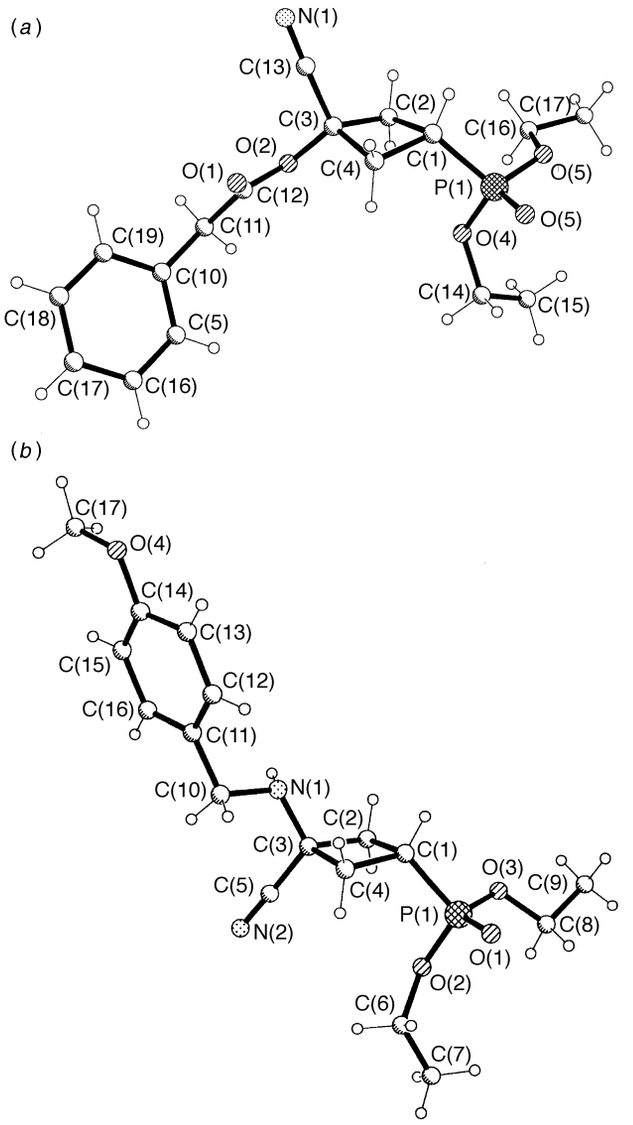


Fig. 1

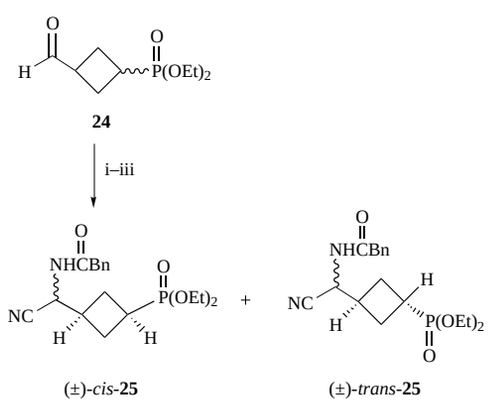
Diethyl 3-oxocyclobutylphosphonate **15** can be rapidly converted to 3-aminocyclobutylphosphonic acid **22** (Scheme 3) by treatment with hydroxylamine hydrochloride in water at reflux for 12 h, which produces the oxime in good yield with a small amount (*ca.* 10%) of starting material remaining.[17] The crude oxime was converted to the amine by hydrogenolysis at 3 atmospheres of hydrogen with rhodium on alumina as the catalyst. The crude amine was hydrolysed to the phosphono amino acid **22** and purified by ion exchange chromatography (Dowex-50 H^+ form).

The ^{13}C NMR spectrum of the crude reaction mixture indicated that only one of the two possible diastereoisomers is formed. We propose this to be the *cis*-isomer by the following argument. The carbonyls of cyclobutanones, *e.g.* **15**, are known to prefer to be distorted toward the inner *endo* face.[18,19] Thus it is plausible to assume that the oxime will adopt a similar conformation. It is also likely that the bulky phosphonate group will prefer to be in the pseudo-axial position to minimise steric interactions. In this conformation it is likely that hydrogenation will occur from the substantially less hindered top side of the cyclobutane ring rather than from the more hindered bottom side, leading to the *cis*-isomer.

This proposition was supported by treatment of diethyl 3-oxocyclobutylphosphonate **15** with methylmagnesium bromide at −78 °C, resulting in the formation of only the *cis*-isomer of diethyl 3-hydroxy-3-methylcyclobutylphosphonate **23**. The *cis*-isomer was identified by the lack of coupling between the methyl carbon and the phosphorus in the ^{13}C NMR spectrum. No evidence of the other diastereoisomer was found. Molecular modelling studies using QUANTA indicate that the lower energy conformation of the cyclobutanone is the one in which the ketone is distorted toward the inner *endo* face and the phosphonate is in the pseudo-axial position with approximately a 19 kJ difference between the two possible conformations (256 kJ *versus* 237 kJ), indicative of a ratio in the region of 99:1. Thus the nucleophilic attack occurs at the requisite angle ($Ø = ca.$ 110°) from the *exo*-face to provide a *trans*-selective addition. A similar selective addition has been observed in the addition of (1-phenylvinyl)lithium to a substituted cyclobutanone.[20] Similar selectivity has also recently been noted in the reduction of *N*-[(3-chloromethyl)cyclobut-1-ylidene]amines by lithium aluminium hydride. This reduction results in subsequent nucleophilic displacement of the chloride, forming 2-alkyl-2-azabicyclo[2.1.1]hexanes, which would only be possible if the reduction occurred to give the *cis*-isomer.[21]

The versatile 3-oxocyclobutylphosphonate **15** also facilitates access to the homologous diethyl 3-formylcyclobutylphosphonate **24** (Scheme 3), which was successfully prepared by reaction of the anion of diethyl isocyanomethylphosphonate[22] with diethyl 3-oxocyclobutylphosphonate **15** and subsequent hydrolysis with 6 M HCl. Diethyl 3-formylcyclobutylphosphonate **24** was isolated in good yield as a 1:1 mixture of the two isomers as determined by ^{31}P NMR. The two isomers were inseparable by chromotography, so the mixture was carried though to the next stage, when separation of the diastereoisomers was likely to be easier.

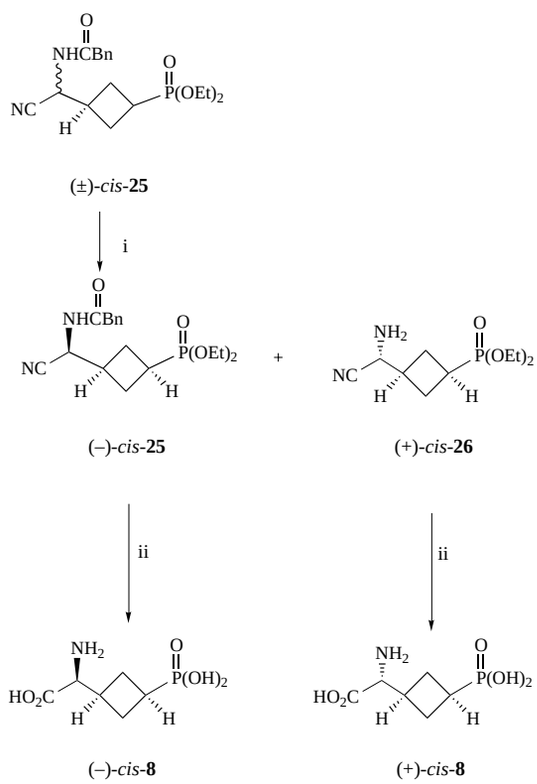
Reaction of diethyl 3-formylcyclobutylphosphonate **24** with sodium cyanide and ammonium chloride in ammonium hydroxide for 12 h, with light excluded, produced a high yield of the desired amino results (Scheme 5). Little or no formation of condensation products occurred under these conditions. Longer reaction times resulted in hydrolysis of the phosphonate esters.



Scheme 5 *Reagents and conditions:* i, NaCN, NH_4Cl, NH_4OH, room temp.; ii, BnCoCl, Et_3N, CH_2Cl_2; iii, flash silica chromatography (hexane–Pr^{i}OH, 7:3)

The amino nitriles were converted directly to the *N*-phenylacetyl derivatives **25** and the diastereoisomers were easily separated by silica gel chromatography using hexane–Pr^{i}OH as eluent. The assignment of the isomers was again made using the characteristic coupling of the phosphorus to the carbon attached to the C-3 position of the *cis*-isomer, which was found to be the second isomer that eluted from the column.

Enzymatic hydrolyses of racemic *trans*-**25** and *cis*-**25** (as shown in Scheme 6 for *cis*-**25**) using penicillinacylase (EC 3.5.1.11) from *Escherichia coli* provided a mild, highly enantioselective, high yielding method of resolution. The hydrolyses were carried out using penicillinacylase immobilised on Eupergit under the conditions described by Rossi.[23] The reactions were monitored by thin layer chromatography (TLC) until there ceased to be an obvious increase in the amount of phenylacetic acid produced (approximately 6 h).



Scheme 6 *Reagents and conditions:* i, Penicillinacylase (immobilised on Eupergit), phosphate buffer pH 7, MeOH, 27 °C; ii, H^+, H_2O, reflux, Dowex 50W (H^+) ion exchange column

The absolute configuration of the isomers is not known. However, it is likely that the isomer hydrolysed by the enzyme has *R* stereochemistry. Penicillinacylase is known to preferentially hydrolyse the L-isomer of amino acids and extensive efforts have been made to determine factors that influence the stereoselectivity of the hydrolysis of other phenylacetylamino compounds.[23] These studies have shown that when a nitrile, rather than a carboxylic acid functionality, is present on the carbon α to the phenylacetylamino group and the third substituent is larger than an ethyl group, *e.g.* an isopropyl or phenyl group, then the *R*-isomer is the one which is preferentially hydrolysed. As the cyclobutane ring can be thought of as isopropyl group that has a carbon joining the two methyl groups together, then it is plausible to expect a similar stereoselectivity in the hydrolysis of these cyclobutane compounds.

The amino nitriles **26** and phenylacetylamino nitriles **25** were hydrolysed to the corresponding aminophosphine acids **8** and purified by ion exchange chromatography (Dowex 50W, H^+

form) yielding the enantiomerically pure aminophosphonic acids.

Conclusion

The synthesis of the key intermediate diethyl 3-oxocyclobutylphosphonate **15** has facilitated the synthesis of a variety of novel, biologically interesting 3-phosphonocyclobutyl amino acids. Both diastereoisomers of 3-amino-3-carboxycyclobutylphosphonic acid **7** have been prepared *via* a modified Strecker reaction. In the synthesis of 3-aminocyclobutylphosphonic acid **22**, the cyclobutylphosphonic acid analogue of γ-aminobutyric acid (GABA), only the *cis*-isomer was obtained due to a diastereoselective hydrogenation of the intermediate hydroxylamine. The synthesis of *trans*- and *cis*-diethyl 3-formylcyclobutylphosphonates **24** was also carried out and the products were transformed into *trans*- and *cis*-3-[amino(carboxy)methyl]cyclobutylphosphonic acid **8**, the homologue of 3-amino-3-carboxycyclobutylphosphonic acid. In all cases the diastereoisomers were separable at the N-protected amino nitrile stage by column chromatography. The enantiomers of 3-[amino(carboxy)methyl]cyclobutylphosphonic acids **8** were separated by enantioselective enzymatic hydrolysis of the intermediate diethyl 3-[(phenylacetylamino)cyanomethyl]cyclobutylphosphonates **25**. Using this method of resolution, high enantioselectivities were obtained. Thus, diethyl 3-oxocyclobutylphosphonate **15** is a versatile intermediate in the synthesis of diastereomerically and enantiomerically pure cyclobutylphosphonic acid analogues of amino acids.

Experimental

Optical rotations were recorded on an Optical Activity Ltd model AA-1000 polarimeter at 589 nm (Na D-line) with a path length of 2 dm. Concentrations (*c*) are quoted in g 100 cm^{-3}. Microanalyses were performed at the Univeristy of Warwick. Infrared spectra were recorded neat, in solution or as Nujol mulls on a Perkin-Elmer 1720X Fourier transform spectrometer using sodium chloride plates. Only selected absorbances (ν_{max}) are reported. ^{1}H NMR spectra were recorded at either 250 or 400 MHz on Bruker ACF 250 or Bruker ACP 400 instruments respectively. ^{13}C NMR spectra were recorded at 62.9 MHz on a Bruker ACF 250 instrument or 100.6 MHz on a Bruker ACP 400 instrument. ^{31}P NMR spectra were recorded at 162 or 101 MHz on a Bruker ACP 400 or Bruker ACF 250 instrument, respectively. ^{19}F NMR spectra were recorded at 376.3 MHz on a Bruker ACP 400 instrument. Chemical shifts (δ) are quoted in parts per million (ppm), referenced externally to $SiMe_4$ (^{1}H, ^{13}C), 85% phosphoric acid (^{31}P) or F_3CCO_2H (^{19}F); *J* values are given in Hz. All mass spectra were recorded on a Kratos MS 90 spectrometer, with only molecular ions (M^+) and major peaks being reported, with intensities quoted as percentages of the base peak. Chemicals were purchased from Aldrich, Fluka or Sigma at the highest available grade. Penicillin G acylase, immobilised on Eupergit (10 000 units per 100 g wet weight) was purchased from Rohm-Pharm GMBH, Weiterstadt. All solvents were purchased from Fisons Scientific Equipment at SLR grade and purified, when required, by literature methods.[24] Thin layer chromatography (TLC) was performed on aluminium-backed plates pre-coated with silica (0.2 mm, $60F_{254}$) which were developed using one or more of the following agents: UV fluorescence (254 nm), iodine vapour, potassium permanganate solution (0.5% v/v), ammonium molybdate (2.5% w/v), *p*-anisaldehyde (2.5% v/v) or ninhydrin (0.2% w/v). Flash chromatography was performed on silica gel (Merck Kieselgel $60F_{254}$, 230–400 mesh).

X-Ray crystallographic measurements were made with a Siemens P3R3 four-circle diffractometer equipped with an Oxford Cryosystems Cooler (version 2.4). Graphite monochromated Mo-Kα radiation ($\lambda = 0.710\ 73$ Å) was used to collect the intensity data in the ω–2θ mode. Unit cell parameters and orientation were obtained by least-squares refinement of the setting angles of 20 high angle reflections. The structures were solved by direct methods (using SHELXTL-Plus) and refined using full-matrix least-squares on F^2 (using SHELXL93).[25] All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were given isotropic thermal parameters equal to 1.2 (or 1.5 for methyl groups) times the equivalent isotropic displacement parameter of the atom to which it is attached.

The enantiomeric purities of the compounds were determined by ^{19}F NMR analysis of the Mosher's amides.[26] Reaction of samples of the hydrolysed isomer with α-methoxy-α-trifluoromethylphenylacetyl chloride provided the Mosher's amide of the amino nitrile. On comparison of the ^{19}F NMR spectrum of the single enantiomer from the enzymatic hydrolysis with the ^{19}F NMR spectrum of a sample of the Mosher's amide of the racemic compound, no evidence of a signal in the ^{19}F NMR spectrum corresponding to the opposite enantiomer was found in either of the two diastereoisomers. However, given that the sample converted to the Mosher's amide was in the region of 3–4 mg, it would be unwise to say that the enantiomeric purity was greater than 95%.

Diethyl 3-(benzyloxy)cyclobutylphosphonate 12

Diethyl methylphosphonate (5 g, 32.9 mmol), as a solution in anhydrous THF (150 cm^3) at −78 °C under an atmosphere of nitrogen, was treated with butyllithium (13.2 cm^3, 33 mmol). The solution was stirred at −78 °C for 30 min and then 1-chloro-2-benzyloxy-3-bromopropane (4.3 g, 16.45 mmol) was added. The reaction mixture was stirred at −78 °C for 1 h and then warmed to room temperature and stirred for a further 1 h. The reaction was quenched by the addition of saturated ammonium chloride. The THF was removed *in vacuo* and the aqueous layer extracted with CH_2Cl_2 (4 × 40 cm^3. The organic fractions were combined, washed with water (2 × 40 cm^3) and brine (2 × 30 cm^3), dried over anhydrous $MgSO_4$ and filtered, and the solvent removed under reduced pressure. The excess diethyl methylphosphonate (40 °C, 0.1 mmHg), unreacted 1-chloro-2-benzyloxy-3-bromopropane (100 °C, 0.1 mmHg) and some mono-substituted product (120–135 °C, 0.1 mmHg) were removed by distillation under reduced pressure. The residue was purified by Kugelrohr distillation (200–205 °C, 0.1 mmHg) to yield the desired products **12** as a colourless oil (2.4 g, 49% yield) as a mixture of *trans*- and *cis*-isomers in a 2:1 ratio; δ_H(250 MHz; $CDCl_3$) 1.23 (6 H, t, *J* 7.3, OCH_2CH_3), 2.84–3.83 [5 H, br m, C(1)-H, C(2)-H and C(4)-H], 4.11 [4.7 H, m, OCH_2CH_3 and C(3)-H of *trans*-isomer], 4.25 [0.3 H, m, C(3)-H of *cis*-isomer], 4.35 (2 H, br s, $PhCH_2O$), 7.33 (5 H, br s, ArH); δ_C(63 MHz; $CDCl_3$) 16.41 (d, $^3J_{CP}$ 5.9, 2 × OCH_2CH_3), 20.9 (d, J_{CP} 154.5, C-1 *trans*-isomer), 22.6 (d, J_{CP} 149.6, C-1 *cis*-isomer), 30.67 (d, $^2J_{CP}$ 5.9, C-2 and C-4 *cis*-isomer), 31.68 (d, $^2J_{CP}$ 4.9, C-2 and C-4 *trans*-isomer), 61.57 (d, $^2J_{CP}$ 7.9, 2 × OCH_2CH_3), 69.81 ($PhOCH_2$), 70.13 (d, $^3J_{CP}$ 35.4 C-3 *trans*-isomer), 71.37 (d, $^3J_{CP}$ 4.9 C-3 *cis*-isomer), 127.57, 127.68, 128.27 and 137.79 (6 C, Ar); δ_P(162 MHz; $CDCl_3$) 33.17 (*trans*-isomer), 36.59 (*cis*-isomer); MS (NH_3 CI) *m/z* 299 ([M + H]$^+$, 40%), 209 (13), 192 (12), 163 (10), 91 (100), 79 (20) (HRMS: calc. for $C_{15}H_{24}O_4P$ [M + H], 299.1412. Found, 299.1410).

Diethyl 3-hydroxycyclobutylphosphonate 13

A solution of diethyl 3-(benzyloxy)cyclobutylphosphonate **12** (20 g, 67.1 mmol) in MeOH (150 cm^3) was hydrogenated (3 atm) over palladium on carbon (200 mg) until the uptake of hydrogen ceased (*ca.* 3 h). The catalyst was removed by filtration through Celite, which was washed with MeOH (3 × 20 cm^3). Removal of the solvent *in vacuo* yielded the alcohols **13** as a colourless oil (13.9 g, 100% yield) which was used without further purification; ν_{max}(neat)/cm^{-1} 3382, 2995, 2910, 1445, 1235, 1163; δ_H(250 MHz; $CDCl_3$) 1.25 (6 H, m, OCH_2CH_3), 1.9–2.55

[5 H, m, C(1)-H, C(2)-H and C(4)-H], 4.05 (4 H, m, OCH_2CH_3), 4.25 [0.7 H, m, C(3)-H *trans*-isomer], 4.45 [0.3 H, m, C(3)-H *cis*-isomer]; δ_C(63 MHz; $CDCl_3$) 16.31 (d, $^3J_{CP}$ 5.6, 2 × OCH_2CH_3), 19.14 (d, J_{CP} 154, C-1 *trans*-isomer), 20.71 (d, J_{CP} 151, C-1 *cis*-isomer), 33.35 ($^2J_{CP}$ 6.2, C-2 and C-4 *cis*-isomer), 34.26 ($^2J_{CP}$ 5.3, C-2 and C-4 *trans*-isomer), 61.61 (d, $^3J_{CP}$ 5.4, 2 × OCH_2CH_3), 64.28 (d, $^3J_{CP}$ 33, C-3 *trans*-isomer), 65.00 (d, $^3J_{Cp}$ 5.6, C-3 *cis*-isomer); δ_P(162 MHz; $CDCl_3$) 32.2 (*trans*-isomer), 35.0 (*cis*-isomer); MS (EI) *m/z* 208 (M^+, 10%), 195 (10), 165 (25), 138 (45), 109 (60), 91 (30), 83 (100) (HRMS: calc. for $C_8H_{18}O_4P$ [M + H], 209.0943. Found, 209.0942).

Diethyl 3-oxocyclobutylphosphonate 15

To a solution of $RuCl_3$ (150 mg) in CH_2Cl_2 (50 cm^3) was added a solution of $NaIO_4$ (2 g) in water (50 cm^3). The biphasic mixture was stirred at room temperature for 12 h. The aqueous layer was separated and extracted with CH_2Cl_2, (2 × 10 cm^3). The combined yellow organic layers were added to a solution of diethyl 3-hydroxycyclobutylphosphonate **13** (12 g, 57.7 mmol) in CH_2Cl_2 (20 cm^3) and a solution of $NaIO_4$ (24.7 g, 115.4 mmol) in water (100 cm^3). The biphasic mixture was stirred vigorously (*ca.* 16 h) until the yellow colour persisted on standing. Sufficient water to dissolve the $NaIO_3$ was added to the reaction mixture. The two layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 × 30 cm^3). The combined organic layers were washed with water (2 × 50 cm^3) and brine (2 × 40 cm^3), dried over anhydrous magnesium sulfate and filtered, and the solvent evaporated *in vacuo*. The crude ketone containing $RuCl_3$ was purified by Kugelrohr distillation (160–165 °C, 0.1 mmHg) to yield the pure ketone **15** (10.8 g, 90%); ν_{max}(neat)/cm^{-1} 2985, 1785, 1228, 1054; δ_H(250 MHz; $CDCl_3$) 1.21 (6 H, t, *J* 7.3, OCH_2CH_3), 2.55 [1 H, m, C(1)-H], 3.11–3.37 [4 H, m, C(2)-H and C(4)-H], 4.01 (4 H, q, *J* 7.3 OCH_2CH_3); δ_C(63 MHz; $CDCl_3$) 16.31 (d, $^3J_{CP}$ 5.6, OCH_2CH_3), 20.47 (d, J_{CP} 157.9, C-1), 49.15 (d, $^2J_{CP}$ 4.6, C-2 and C-4), 62.13 (d, $^2J_{CP}$ 6.6, OCH_3CH_3), 202.8 (d, $^3J_{CP}$ 18.4, C=O); δ_P(162 MHz; $CDCl_3$) 30.2; MS (NH_3 CI) *m/z* 224 ([M + 18]$^+$, 22%), 206 ([M + H]$^+$, 100), 178 (32), 165 (43), 138 (25), 109 (29) (HRMS: calc. for $C_8H_{16}O_4P$ [M + H], 207.0786. Found, 207.0789).

***cis*/*trans*-Diethyl 3-cyano-3-hydroxycyclobutylphosphonate 19**

Ammonium chloride (1.09 g, 20 mmol), sodium cyanide (1 g, 20 mmol) and alumina (2.8 g, 34 mmol) were suspended in MeCN (60 cm^3). The suspension was sonicated for 10 min and then a solution of diethyl 3-oxocyclobutylphosphonate **15** (3.5 g, 17 mmol) in MeCN (5 cm^3) was added and the reaction was sonicated for 15 h. The reaction mixture was filtered through a pad of Celite which was washed with MeCN (50 cm^3). The combined MeCN fractions were evaporated *in vacuo* and then taken up in CH_2Cl_2 (40 cm^3) and washed with water (2 × 20 cm^3) and brine (2 × 20 cm^3), dried over anhydrous magnesium sulfate and filtered, and evaporated to dryness to yield a colourless oil which was identified as a mixture of the two isomers of diethyl 3-cyano-3-hydroxycyclobutylphosphonate **19** (3.14 g, 79%); ν_{max}(neat)/cm^{-1} 3382, 2221, 1164, 1052, 1023; δ_H(250 MHz; $CDCl_3$) 1.24 (6 H, t, *J* 7.2, OCH_2CH_3), 2.39–2.89 [5 H, br m, C(1)-H, C(2)-H and C(4)-H], 4.08 (4 H, m, OCH_2CH_3); δ_C(63 MHz; $CDCl_3$) 16.23 (d, $^3J_{CP}$ 5.6, 2 × OCH_2CH_3), 21.61 (d, J_{CP} 158.6, C-1 minor isomer), 24.74 (d, J_{CP} 156.1, C-1 major isomer), 36.23 (d, $^2J_{CP}$ 5.7, C-2 and C-4 minor isomer), 37.56 (d, $^2J_{CP}$ 4.9, C-2 and C-4 major isomer), 62.28 (d, $^2J_{CP}$ 6.7, 2 × OCH_2CH_3), 63.26 (d, $^3J_{CP}$ 23.5, C-3 minor isomer), 64.35 (d, $^3J_{CP}$ 33.7, C-3 major isomer), 121.71 (*C*N); MS (NH_3 CI) *m/z* 233 ([M + H]$^+$, 16%), 205 (83), 165 (81), 138 (100), 111 (69).

***cis*-Diethyl 3-(phenylacetoxy)-3-cyanocyclobutylphosphonate *cis*-20**

To a solution of the crude cyanohydrin **15** (3.0 g, 12.9 mmol) in CH_2Cl_2 (40 cm^3) at 0 °C was added triethylamine (2.73 g, 27 mmol) and phenylacetyl chloride (2.1 g, 13.4 mmol). The reaction mixture was stirred at room temperature for 12 h, after which time the solution as diluted to CH_2Cl_2 (100 cm^3) and washed with water (3 × 20 cm^3), dilute hydrochloric acid (2 × 20 cm^3), saturated sodium hydrogen carbonate (3 × 20 cm^3), water (2 × 20 cm^3) and brine (2 × 20 cm^3). The organic solution was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to yield the crude product as an orange oil. Separation of the isomers was achieved using silica gel chromatography (CH_2Cl_2–MeOH, 99:1) to give each isomer as a colourless oil. The isomer with the higher R_f value was crystallised by cooling an Et_2O solution of the compound to −100 °C to given an off white solid (2.4 g, 54%); R_f 0.65 (99:1 CH_2Cl_2–MeOH); mp 43 °C (Found: C, 57.76; H, 6.28; N, 3.89; $C_{17}H_{22}NO_5P$ requires C, 58.12; H, 6.31; N, 3.99%); ν_{max}(CH_2Cl_2)/cm^{-1} 3075, 3068, 3039, 2140, 1752; δ_H(250 MHz; $CDCl_3$) 1.24 (6 H, t, *J* 7.7, OCH_2CH_3), 2.55–2.71 [3 H, m, C(1)-H, C(2)-H and C(4)-H], 2.85–2.95 [2 H, m, C(2)-H and C(4)-H], 3.64 (2 H, s, $PhCH_2CO$), 4.01 (4 H, m, OCH_2CH_3), 7.21 and 7.32 (5 H, m, Ar-H); δ_C(63 MHz; $CDCl_3$) 16.33 (d, $^3J_{CP}$ 5.9, OCH_2CH_3), 21.05 (d, J_{CP} 154.8, C-1), 35.48 (d, $^2J_{CP}$ 4.9, C-2 and C-4), 40.33 ($PhCH_2$), 62.12 (d, $^2J_{CP}$ 6.9, OCH_2CH_3), 65.48 (d, $^3J_{CP}$ 20.95, C-3), 117.96 (CN), 127.41, 128.65, 129.06, 132.25 (6 C, Ar), 169.18 (C=O); δ_P(162 MHz; $CDCl_3$) 27.62; MS (EI) *m/z* 351 (M^+, 27%), 205 (46), 181 (31), 169 (40), 118 (96), 91 (50), 83 (100).

X-Ray crystallography. Crystals were colourless plates of formula $C_{17}H_{22}NO_5P$ grown from a saturated solution in pentane–diethyl ether–toluene at ambient temperature; orthorhombic, $a = 9.991(5)$, $b = 12.885(8)$, $c = 28.39(2)$ Å, $\alpha = 90$, $\beta = 90$, $\gamma = 90°$, space group *Pcba*, $U = 3655(4)$ Å^3, $Z = 8$, $D_c = 1.277$ mg dm^{-3}, Mo-Kα radiation ($\lambda = 0.710\,69$ Å), μ(Mo-Kα) = 0.84 mm^{-1}, $T = 220$ K, $R = 0.0366$ for 2405 unique reflections observed [$I/\sigma(I) \geq 2.0$] reflections.†

***trans*-Diethyl 3-(phenylacetoxy)-3-cyanocyclobutylphosphonate *trans*-20**

The lower R_f isomer from above was isolated (1.3 g, 30%), R_f 0.55 (99:1 CH_2Cl_2–MeOH) (Found: C, 57.92; H, 6.38; N, 3.87; $C_{17}H_{22}NO_5P$ requires C, 58.12; H, 6.31; N, 3.99%); ν_{max}(CH_2Cl_2)/cm^{-1} 2984, 2909, 2235, 1754; δ_H(250 MHz; $CDCl_3$) 1.30 (6 H, t, OCH_2CH_3), 2.62 [3 H, m, C(1)-H, C(2)-H and C(4)-H], 2.94 [2 H, m, C(2)-H and C(4)-H], 3.63 (2 H, s, $PhCH_2$), 4.07 (4 H, m, OCH_2CH_3), 7.21–7.36 (5 H, m, Ar-H); δ_C(63 MHz; $CDCl_3$) 16.27 (d, $^3J_{CP}$ 5.9, OCH_2CH_3), 23.76 (d, J_{CP} 155.5, C-1), 34.27 (d, $^2J_{CP}$ 4, C-2 and C-4), 40.53 ($PhCH_2$), 62.20 (d, $^2J_{CP}$ 6.9, OCH_2CH_3), 66.47 (d, $^3J_{CP}$ 12, C-3), 117.13 (d, $^4J_{CP}$ 2.9, CN), 127.41, 128.48, 129.00 and 132.31 (6 C, Ar), 162.32 (C=O); δ_P(162 MHz; $CDCl_3$) 28.25; MS (EI) *m/z* 351 (M^+, 31%), 205 (38), 181 (32), 169 (48), 118 (93), 91 (62), 83 (100).

***cis*/*trans*-Diethyl 3-(*p*-methoxybenzylamino)-3-cyanocyclobutylphosphonate 21**

To a solution of diethyl 3-oxocyclobutylphosphonate **15** (1.5 g, 7.3 mmol) and sodium cyanide (430 mg, 8.74 mmol) in dry MeOH was added *p*-methoxybenzylamine (1.2 g, 9.7 mmol). The solution was cooled to 0 °C and glacial acetic acid (1 cm^3) was added in a dropwise fashion. The reaction mixture was heated gradually with stirring to 60 °C for 20 h. After cooling to room temperature the solution was neutralised with saturated sodium hydrogen carbonate (5 cm^3), the solvent was removed under reduced pressure and the residue taken up in CH_2Cl_2 (30 cm^3) and water (20 cm^3). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 cm^3). The

† Atomic coordinates, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/75.

combined organic layers were washed with water (2 × 20 cm^3) and brine (2 × 20 cm^3), dried over anhydrous magnesium sulfate and filtered, and the solvent removed *in vacuo* yielding the crude α-(*p*-methoxybenzylamino) nitrile **21** as a mixture of the two isomers in a 3:2 ratio. The crude product was purified by silica gel chromatography (CH_2Cl_2–MeOH, 95:5). Separation of the isomers was achieved by silica gel chromatography (3 times) (hexane–Pr^iOH, 85:15) to afford pure *cis*-diethyl 3-(*p*-methoxybenzylamino)-3-cyanocyclobutylphosphonate (1.37 g, 53%), R_f 0.52 (hexane–Pr^iOH, 8:2) (Found: C, 57.82; H, 7.08; N, 7.85; $C_{17}H_{25}N_2O_4P$ requires C, 57.95; H, 7.15; N, 7.95%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3278, 2982, 2839, 2221, 1795, 1686; δ_H(400 MHz; $CDCl_3$) 1.23 (6 H, t, *J* 7.0, OCH_2CH_3), 2.06 (1 H, br s, NH), 2.32 [2 H, m, C(2)-H and C(4)-H], 2.59 [3 H, m, C(1)-H, C(2)-H and C(4)-H], 3.68 (2 H, s, $PhCH_2$), 3.73 (3 H, s, OCH_3), 4.00 (4 H, m, OCH_2CH_3), 6.78 (2 H, d, *J* 8.7, Ar-H), 7.20 (2 H, d, *J* 8.7, Ar-H); δ_C(100 MHz; $CDCl_3$) 16.31 (d, $^3J_{CP}$ 4.8, OCH_2CH_3), 22.20 (d, J_{CP} 154.8, C-1), (d, $^2J_{CP}$ 6.4, C-2 and C-4), 48.29 ($PhCH_2$), 52.44 (d, $^3J_{CP}$ 27.1, C-3), 55.10 (OCH_3), 61.92 (d, $^2J_{CP}$ 6.4, OCH_2CH_3), 113.73 (2 C, Ar), 121.35 (CN), 129.50, 130.31 and 158.85 (4 C, Ar); δ_P(162 MHz; $CDCl_3$) 29.17; MS (NH_3 CI) *m/z* 353 ([M + H]$^+$, 5%), 326 (71), 207 (20), 136 (12), 121 (100).

trans-Diethyl 3-(*p*-methoxybenzylamino)-3-cyanocyclobutylphosphonate *trans*-21

The lower R_f isomer from above was isolated as an off white solid (801 mg, 31%), R_f 0.43 (hexane–Pr^iOH, 85:15) mp 45 °C (Found: C, 57.87; H, 7.19; N, 8.03; $C_{17}H_{25}N_2O_4P$ requires C, 57.95; H, 7.15; N, 7.95%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3276, 2982, 2909, 2221, 1795, 1613, 1249, 1176; δ_H(400 MHz; $CDCl_3$) 1.33 (6 H, t, *J* 7.0, OCH_2CH_3), 1.63 (1 H, br, s, NH), 2.22 [2 H, m, C(2)-H and C(4)-H], 2.68 [2 H, m, C(2)-H and C(4)-H], 2.91 [1 H, m, C(1)-H], 3.72 (2 H, br d, *J* 4.9, $PhCH_2$), 3.76 (3 H, s, OCH_3), 4.07 (4 H, m, OCH_2CH_3), 6.83 (2 H, d, *J* 8.8, Ar-H), 7.23 (2 H, d, *J* 8.8, Ar-H); δ_C(100 MHz; $CDCl_3$) 16.36 (d, $^3J_{CP}$ 4.8, OCH_2CH_3), 24.58 (d, J_{CP} 154.8, C-1), 33.12 (d, $^2J_{CP}$ 6.4, C-2 and C-4), 48.38 ($PhCH_2$), 50.60 (d, $^3J_{CP}$ 23.9, C-3), 55.13 (OCH_3), 61.89 (d, $^2J_{CP}$ 6.4, OCH_2CH_3), 113.84 (2 C, Ar), 120.21 (d, $^4J_{CP}$ 4.8, CN), 129.96, 130.36 and 158.92 (4 C, Ar); δ_P(162 MHz; $CDCl_3$) 29.49; MS (NH_3 CI) *m/z* 353 ([M + H]$^+$, 6%), 326 (28), 165 (13), 136 (22), 121 (100), 95 (11), 81 (12).

X-Ray crystallography. Crystals were colourless plates of formula $C_{17}H_{22}NO_5P$ grown from a saturated solution in pentane–diethyl ether–toluene at ambient temperature; triclinic, $a = 7.630(3)$, $b = 9.882(5)$, $c = 13.604(6)$ Å, $\alpha = 94.09(4)$, $\beta = 104.07(3)$, $\gamma = 99.27(4)°$, space group *P*1, $U = 975.4(8)$ Å^3, $Z = 2$, $D_c = 1.200$ mg dm^{-3}, Mo-Kα radiation ($\lambda = 0.710\,69$ Å), μ(Mo-Kα) = 0.84 mm^{-1}, $T = 220$ K, $R = 0.0548$ for 3443 unique reflections observed [$I/\sigma(I) \geq 2.0$] reflections.†

Deprotection of compound 21

Oxidative removal of the *N*-*p*-methoxybenzyl group. Ceric ammonium nitrate (822 mg, 1.5 mmol) was added to a solution of the *p*-methoxybenzylamino nitrile **21** (80 mg, 0.23 mmol) in MeCN and water (6 cm^3, 9:1). The reaction was monitored by TLC(CH_2Cl_2–MeOH, 19:1). After 2 h no starting material remained. The reaction mixture was diluted by the addition of water (20 cm^3) and extracted with CH_2Cl_2 (3 × 15 cm^3). The organic fractions were then extracted with dilute hydrochloric acid (1 M, 2 × 15 cm^3) and the acidic fractions were adjusted to pH 8 and extracted with CH_2Cl_2 (3 × 10 cm^3). The CH_2Cl_2 fractions were washed with water (2 × 10 cm^3) and brine (2 × 10 cm^3), dried over anhydrous magnesium sulfate and filtered, and the solvent evaporated *in vacuo* to afford the deprotected α-amino nitrile compound as a crude oil which was used in the next step without further purification.

Removal of the *N*-*p*-methoxybenzyl group by hydrogenation. A solution of the *p*-methoxybenzylamino nitrile **21** (100 mg, 0.29 mmol) in MeOH (15 cm^3) was hydrogenated (3 atm) over palladium on carbon for 4 h. The reaction mixture was filtered through a pad of Celite, which was then washed with MeOH (2 × 10 cm^3). The combined filtrates were evaporated to dryness under reduced pressure. The residue was dissolved in dilute hydrochloric acid (1 M, 15 cm^3) and extracted with CH_2Cl_2 (2 × 10 cm^3). The aqueous fraction was adjusted to pH 8 with aqueous sodium hydroxide (1 M) and extracted with CH_2Cl_2 (3 × 15 cm^3). The CH_2Cl_2 fractions were washed with water (2 × 10 cm^3) and brine (2 × 10 cm^3), dried over anhydrous magnesium sulfate and filtered, and the solvent evaporated *in vacuo* to afford diethyl 3-amino-3-cyanocyclobutylphosphonate as a crude oil which was used in the next step without further purification.

cis-3-Amino-3-carboxycyclobutylphosphonic acid *cis*-7

cis-Diethyl3-(*p*-methoxybenzylamino)-3-cyanocyclobutylphosphonate **21** was deprotected by either of the methods described above to afford *cis*-diethyl 3-amino-3-cyanocyclobutylphosphonate; δ_H(250 MHz; $CDCl_3$) 1.279 (6 H, t, *J* 6.8, OCH_2CH_3), 2.16 (2 H, br s, NH_2), 2.24 [2 H, m, C(2)-H and C(4)-H], 2.32 [3 H, br m, C(1)-H, C(2)-H and C(4)-H], 4.03 (4 H, m, OCH_2CH_3); δ_C(63 MHz; $CDCl_3$) 16.23 (d, $^3J_{CP}$ 6.4, OCH_2CH_3), 22.51 (d, J_{CP} 143, C-1), 34.25 (d, $^2J_{CP}$ 6.3, C-2 and C-4), 51.78 (d, $^3J_{CP}$ 24, C-3), 61.92 (d, $^2J_{CP}$ 6.5 OCH_2CH_3), 121.25 (CN). Crude *cis*-diethyl 3-amino-3-cyanocyclobutylphosphonate (100 mg, 0.43 mmol) was dissolved in hydrochloric acid (6 M, 10 cm^3) and the solution was heated to reflux for 48 h. After cooling the solution was evaporated to dryness under reduced pressure. The residue was dissolved in water (2 cm^3) and applied to an ion exchange column (Dowex 50W, H^+ form). The column was washed with water (100 cm^3) and then eluted with aqueous pyridine (1 M, 200 cm^3). Ninhydrin active fractions were combined and evaporated to dryness under reduced pressure. Residual traces of pyridine were removed by repeatedly dissolving the compound in water (10 cm^3) and re-evaporating (3 times), affording the title compound *cis*-**7** as an off-white solid (62 mg, 74%); δ_H(400 MHz; D_2O) 2.28 [2 H, m, C(2)-H and C(4)-H], 2.56 [1 H, m, C(1)-H], 2.73 [2 H, M, C(2)-H and C(4)-H]; δ_C(101 MHz; D_2O) 25.10 (d, J_{CP} 142, C-1), 31.65 (d, $^2J_{CP}$ 4.8, C-2 and C-4), 57.28 (d, $^3J_{CP}$ 14.5, C-3), 176.40 (C=O); δ_P(162 MHz; D_2O) 26.51 [HRMS (FAB): calc. for $C_5H_{10}NO_5P$, 195.0296. Found, 195.0294].

trans-3-Amino-3-carboxycyclobutylphosphonic acid *trans*-7

trans-Diethyl 3-(*p*-methoxybenzylamino)-3-cyanocyclobutylphosphonate **21** was deprotected by either of the methods described above to afford *trans*-diethyl 3-amino-3-cyanocyclobutylphosphonate; δ_H(250 MHz; $CDCl_3$) 1.27 (6 H, t, *J* 6.8, OCH_2CH_3), 2.18 (2 H, br s, NH_2), 2.35 [3 H, m, C(1)-H, C(2)-H and C(4)-H], 2.68 [2 H, m, C(2)-H and C(4)-H], 4.03 (4 H, m, OCH_2CH_3); δ_C(63 MHz; $CDCl_3$) 16.33 (d, $^3J_{CP}$ 6.4, OCH_2CH_3), 24.02 (d, J_{CP} 144, C-1), 32.85 (d, $^2J_{CP}$ 6.3, C-2 and C-4), 50.01 (d, $^3J_{CP}$ 17, C-3), 61.82 (d, $^2J_{CP}$ 6.5 OCH_2CH_3), 120.06 (d, $^4J_{CP}$ 3.9, CN). Crude *trans*-diethyl 3-amino-3-cyanocyclobutylphosphonate (100 mg, 0.43 mmol) was dissolved in hydrochloric acid (6 M, 10 cm^3) and the solution was heated to reflux for 48 h. After cooling the solution was evaporated to dryness under reduced pressure. The residue was dissolved in water (2 cm^3) and applied to an ion exchange column (Dowex 50W, H^+ form). The column was washed with water (100 cm^3) and then eluated with aqueous pyridine (1 M, 200 cm^3). Ninhydrin active fractions were combined and evaporated to dryness under reduced pressure. Residual traces of pyridine were removed by repeatedly dissolving the compound in water (10 cm^3) and re-evaporating (3 times) affording the title compound *trans*-**7** as an off-white solid (67 mg, 76%); δ_H(400 MHz; D_2O) 2.33 [3 H, m, C(1)-H, C(2)-H and C(4)-H], 2.46 [2 H, m, C(2)-H and C(4)-H]; δ_C(101 MHz; D_2O) 22.76 (d, J_{CP} 141, C-1), 31.77 (d $^2J_{CP}$ 4.8, C-2 and C-4), 55.18 (d, $^3J_{CP}$ 16, C-3), 175.22 (d, $^4J_{CP}$ 3.1, C=O). δ_P(162

MHz; D_2O) 25.70 [HRMS (FAB): calc. for $C_5H_{10}NO_5P$, 195.0296. Found 195.0293].

cis-3-Aminocyclobutylphosphonic acid 22

Hydroxylamine hydrochloride (520 mg, 8.1 mmol) was added to a solution of diethyl 3-oxocyclobutylphosphonate (500 mg, 2.43 mmol) in water (10 cm^3) and the pH of the solution was adjusted to 4 (1 M HCl). The reaction mixture was heated to reflux for 15 h. After cooling the solution was adjusted to pH 8 (1 M NaOH) and extracted with CH_2Cl_2 (3 × 10 cm^3). The organic extracts were washed with water (2 × 10 cm^3) and brine (2 × 10 cm^3), dried over anhydrous magnesium sulfate and filtered, and the solvent removed *in vacuo* to afford *cis*-diethyl 3-hydroxyiminocyclobutylphosphonate (455 mg, 85%); ν_{max}(neat)/cm^{-1} 3851, 3274, 2965, 2359, 1651; δ_H(250 MHz; $CDCl_3$) 1.18 (m, 6 H, OCH_2CH_3), 1.75 (1 H, s, NOH), 2.25 [1 H, m, C(1)-H], 2.97–3.30 [4 H, m, C(2)-H and C(4)-H], 3.99 (4 H, m, OCH_2CH_3); δ_C(63 MHz; $CDCl_3$) 16.21 (d, $^3J_{CP}$ 5.9, OCH_2CH_3), 21.51 (d, J_{CP} 152.6, C-1), 31.91 (d, $^2J_{CP}$ 5.9, C-2 or C-4), 32.76 (d, $^2J_{CP}$ 4.9, C-2 or C-4), 62.20 (d, $^2J_{CP}$ 5.9 OCH_2CH_3), 152.30 (d, $^3J_{CP}$ 15.8, C-3); MS (NH_3 CI) *m/z* 222 ([M + H]$^+$, 16%), 204 (18), 191 (100), 165 (43).

A solution of crude diethyl 3-hydroxyiminocyclobutylphosphonate (400 mg, 1.81 mmol) in MeOH (containing 4 drops of concentrated hydrochloric acid) was hydrogenated (3 atm) over rhodium on alumina (30 mg) for 15 h. The reaction mixture was filtered through a pad of Celite, which was then washed with MeOH (3 × 10 cm^3). The combined filtrates were evaporated to dryness under reduced pressure. The residue was dissolved in water (3 cm^3) and applied to an ion exchange column (Dowex 50W, H^+ form). The column was washed with water (100 cm^3) and eluted with pyridine (200 cm^3). The ninhydrin positive fractions were combined and evaporated to dryness under reduced pressure, residual traces of pyridine were removed by repeated addition of water (5 cm^3) and re-evaporation (3 times) to afford the title compound **22** (169 mg, 62%); δ_H(250 MHz; D_2O) 2.26 [2 H, m, C(2)-H and C(4)-H], 2.49 [1 H, m, C(1)-H], 2.63 [2 H, m, C(2)-H and C(4)-H], 3.03 [1 H, m, C(3)-H]; δ_C(64 MHz; D_2O) 24.32 (d, J_{CP} 144, C-1), 28.41 (d, $^2J_{CP}$ 4.8, C-2 and C-4), 39.38 (d, $^3J_{CP}$ 4.8, C-3); δ_P(162 MHz; D_2O) 26.32; MS (NH_3 CI) *m/z* 169 ([M + 18]$^+$, 24%), 152 ([M + H]$^+$, 16), 135 (12), 118 (16), 107 (100).

cis-Diethyl 3-hydroxy-3-methylcyclobutylphosphonate *cis*-23

A solution of diethyl 3-oxocyclobutylphosphonate **15** (100 mg, 0.49 mmol) in anhydrous THF (15 cm^3) at −78 °C under an atmosphere of nitrogen, was treated with a solution of methylmagnesium bromide (0.17 cm^3, 3 M in diethyl ether). The reaction mixture was stirred for 2 h at −78 °C then allowed to warm to room temperature and quenched with saturated aq. ammonium chloride (15 cm^3). The THF was removed *in vacuo* and the aqueous residue was extracted with CH_2Cl_2 (3 × 15 cm^3). The combined organic fractions were washed with water (2 × 15 cm^3) and brine (2 × 15 cm^3), dried over anhydrous magnesium sulfate and filtered, and the solvent evaporated *in vacuo* to afford the title compound *cis*-**23** as a colourless oil (88 mg, 81%); δ_H(250 MHz; $CDCl_3$) 1.24 (6 H, t, *J* 6.9, OCH_2CH_3), 1.33 (3 H, s, CH_3), 2.20 [3 H, m, C(1)-H, C(2)-H and C(4)-H], 2.68 [2 H, m, C(2)-H and C(4)H], 4.01 (4 H, m, OCH_2CH_3); δ_C(63 MHz; D_2O) 16.32 (d, $^3J_{CP}$ 6.9, OCH_2CH_3), 18.86 (d, J_{CP} 152, C-1), 26.36 (CH_3), 38.30 (d, $^2J_{CP}$ 4.9, C-2 and C-4), 61.82 (d, $^2J_{CP}$ 5.9, OCH_2CH_3), 70.27 (d, $^3J_{CP}$ 24.6, C-3); δ_P(101 MHz; $CDCl_3$) 32.15; MS (NH_3 CI) *m/z* 223 ([M + H]$^+$, 32%), 205 (63), 177 (24), 149 (27), 122 (100), 107 (21) (HRMS: calc. for $C_9H_{20}O_4P$ [M + H], 223.1099. Found, 223.1094).

cis/*trans*-Diethyl 3-formylcyclobutylphosphonate 24

A solution of diethyl isocyanomethylphosphonate (850 mg, 4.8 mmol) in anhydrous THF (25 cm^3) at −78 °C was treated with butyllithium (1.92 cm^3, 4.8 mmol). The solution was stirred at this temperature for 30 min and then a solution of diethyl 3-oxocyclobutylphosphonate **15** (900 mg, 4.4 mmol) in anhydrous THF (5 cm^3) was added. The reaction mixture was stirred for a further 2 h at −78 °C and then warmed to room temperature and quenched with water (5 cm^3). The THF was removed *in vacuo* and the residue redissolved in diethyl ether (20 cm^3) and hydrochloric acid (6 M, 10 cm^3). The biphasic solution was stirred at ambient temperature for 15 h. The diethyl ether was removed by evaporation under reduced pressure and the aqueous residue was extracted with CH_2Cl_2 (3 × 20 cm^3). The combined organic extracts were washed with water (2 × 15 cm^3) and brine (2 × 15 cm^3), dried over anhydrous magnesium sulfate and filtered, and the solvent removed under reduced pressure to afford a 1:1 mixture of the two diastereoisomers of the title compound **24** as a colourless oil (795 mg, 83%); ν_{max}(neat)/cm^{-1} 2984, 2724, 1719, 1480, 1444, 1292, 1226; δ_H(250 MHz; $CDCl_3$) 1.14 (6 H, m, OCH_2CH_3), 2.20–2.63 [5 H, br m, C(1)-H, C(2)-H and C(4)-H], 3.00 [1 H, m, C(3)-H], 3.94 (4 H, m, OCH_2CH_3), 9.54 (*ca.* 0.5 H, t, *J* 1.75, HC=O, *cis*-isomer), 9.62 (*ca.* 0.5 H, d, *J* 1.2, HC=O, *trans*-isomer); δ_C(63 MHz; $CDCl_3$) 16.23 (d, $^3J_{CP}$ 5.9, 2 × OCH_2CH_3, 21.76 (d, $^2J_{CP}$ 5.9, C-2 and C-4 of one isomer), 22.41 (d, $^2J_{CP}$ 5.9, C-2 and C-4 of other isomer), 24.59 (d, J_{CP} 133, C-1 of one isomer), 24.59 (J_{CP} 151, C-1 of other isomer), 42.09 ($^3J_{CP}$ 17.7, C-3 of one isomer), 42.67 (d, $^3J_{CP}$ 11.8 of other isomer), 61.79 (d, $^2J_{CP}$ 5.9, 2 × OCH_2CH_3), 200.99 (d, $^4J_{CP}$ 2.9, C=O *cis*-isomer), 201.11 (C=O *trans*-isomer); δ_P(162 MHz; $CDCl_3$) 29.99, 31.98; MS (NH_3 CI) *m/z* 221 ([M + H]$^+$, 100%), 191 (32), 165 (40), 152 (65), 138 (70), 109 (42), 55 (31) (HRMS: calc. for $C_9H_{18}O_4P$ [M + H], 221.0943. Found, 221.0942).

(±)-*cis*/*trans*-Diethyl 2-(aminocyanomethyl)cyclobutylphosphonate

To a solution of aldehyde **24** (400 mg, 1.8 mmol) in dry MeOH (20 cm^3) was added sodium cyanide (135 mg, 2.7 mmol) and ammonium chloride (244 mg, 4.6 mmol). The reaction was stirred at ambient temperature with light excluded for 15 h. The MeOH was removed under reduced pressure and the residue dissolved in CH_2Cl_2 (20 cm^3) and water (20 cm^3). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 20 cm^3). The combined organic layers were washed with water (2 × 15 cm^3) and brine (2 × 15 cm^3), dried over anhydrous magnesium sulfate and filtered, and the solvent removed *in vacuo* to yield the title compound as a pale orange oil which was used in the next step without any further purification (385 mg, 91%); δ_H(250 MHz; $CDCl_3$) 1.21 (6 H, m, OCH_2CH_3), 1.56 (2 H, br s, NH_2), 2.11–2.74 [6 H, br m, C(1)-H, C(2)-H, C(3)-H and C(4)-H], 3.61 [1 H, m, $HC(CN)NH_2$], 3.99 (4 H, m, OCH_2CH_3); δ_C(63 MHz; $CDCl_3$) 16.36 ($^3J_{CP}$ 5.9, 2 × OCH_2CH_3), 23.79 (d, $^2J_{CP}$ 7.9, C-2 or C-4 of one isomer), 24.01 (d, J_{CP} 137, C-1 of one isomer), 24.09 (d, J_{CP} 149, C-1 of other isomer), 24.51 (d, $^2J_{CP}$ 5.9, C-2 or C-4 of one isomer and C-2 or C-4 of other isomer), 25.36 (d, $^2J_{CP}$ 5.9, C-2 or C-4 or other isomer), 36.67 (d, $^3J_{CP}$ 21.7, C-3 of one isomer), 36.39 (d, $^3J_{CP}$ 29, C-3 of other isomer), 47.55 [$C(CN)NH_2$, *trans*-isomer], 47.56 [d, $^4J_{CP}$ 3.2, $C(CN)NH_2$, *cis*-isomer], 61.64 (d, $^2J_{CP}$ 6.9, 2 × OCH_2CH_2), 120.62 (CN of one isomer), 120.67 (CN of other isomer); δ_P(250 MHz; $CDCl_3$) 30.52, 32.28.

(±)-*trans*-Diethyl 3-[(phenylacetylamino)cyanomethyl]cyclobutylphosphonate (±)-*trans*-25

Triethylamine (1.5 cm^3) was added dropwise to a solution of (±)-*cis*/*trans*-diethyl 3-(aminocyanomethyl)cyclobutylphosphonate (360 mg, 1.46 mmol) and phenylacetyl chloride (250 mg, 1.6 mmol) in dry CH_2Cl_2 (20 cm^3) at room temperature. The reaction was stirred for 15 h and then poured into water (20 cm^3). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 cm^3). The combined organic extracts were washed with water (2 × 15 cm^3) and brine (2 × 15 cm^3), dried over anhydrous magnesium sulfate and filtered, and

the solvent removed *in vacuo* to afford a crude product. The diastereosiomers were separated by silica gel chromatography to yield the title compound (±)-*trans*-**25** (214 mg, 80.5%); R_f 0.48 (hexane–Pr^{i}OH, 7:3) (Found: C, 59.29; H, 6.89; N, 7.69. $C_{18}H_{25}N_2O_4P$ requires C, 59.31; H, 6.92; N, 7.72%); ν_{max}(neat)/cm^{-1} 3295, 2865, 2898, 2960, 2222, 1655, 1490, 1465, 1045; δ_H(400 MHz; $CDCl_3$) 1.26 (6 H, dt, *J* 7.0, 2.8, OCH_2CH_3), 1.96 (1 H, br s, NH), 2.04 [2 H, m, C(2)-H and C(4)-H], 2.27 [2 H, m, C(2)-H and C(4)-H], 2.49 [1 H, m, C(1)-H], 2.79 [1 H, m, C(3)-H], 3.57 (2 H, s, $PhCH_2$), 4.00 (4 H, m, OCH_2CH_3), 4.9 [1 H, t, *J* 8.8, *H*C(CN)NHCOCH$_2$Ph], 7.23 (3 H, m, Ar-H), 7.29 (2 H, m, Ar-H); δ_C(101 MHz; $CDCl_3$) 16.33 (d, $^3J_{CP}$ 6.4, OCH_2CH_3), 24.02 (d, J_{CP} 150, C-1), 24.10 (d, $^2J_{CP}$ 4.8, C-2 or C-4), 24.30 (d, $^2J_{CP}$ 6.4, C-2 or C-4), 34.99 (d, $^3J_{CP}$ 9.7, C-3), 42.78 ($PhCH_2$), 44.17 [C(CN)NHCOCH$_2$Ph], 61.97 (d, $^2J_{CP}$ 4.8, OCH_2CH_3), 117.35 (CN), 127.31, 128.81, 128.96 and 134.19 (6 C, Ar), 170.94 (C=O); δ_P(162 MHz; $CDCl_3$) 32.42; MS (NH_3 CI) *m/z* 365 ([M + H]$^+$, 100%), 338 (8), 273 (19), 165 (12), 136 (22), 91 (32).

(±)-*cis*-Diethyl 3-[(phenylacetylamino)cyanomethyl]cyclobutylphosphonate (±)-*cis*-25

The lower R_f isomer from above was isolated (228 mg, 86%); R_f 0.40 (hexane–Pr^{i}OH, 7:3) (Found: C, 59.28; H, 6.96; N, 7.77; $C_{18}H_{25}N_2O_4P$ requires C, 59.31; H, 6.92; N, 7.69%); ν_{max}(neat)/cm^{-1} 3295, 2865, 2898, 2960, 2222, 1655, 1490, 1465, 1045; δ_H(400 MHz; $CDCl_3$) 1.28 (6 H, dt, *J* 7.0 and 2.8, OCH_2CH_3), 2.06 (1 H, br s, NH), 2.11–2.46 [4 H, br m, C(2)-H and C(4)-H], 2.54 [1 H, m, C(1)-H], 2.81 [1 H, m, C(3)-H], 3.62 (2 H, s, $PhCH_2$), 4.04 (4 H, m, $OCH_2C H_3$), 4.78 [1 H, dd, *J* 6.7 and 7.7, *H*C(CN)NHCOCH$_2$Ph], 7.24 (3 H, m, Ar), 7.29 (2 H, m, Ar-H); δ_C(101 MHz; $CDCl_3$) 16.36 (d, $^3J_{CP}$ 6.4, OCH_2CH_3), 22.94 (d, $^2J_{CP}$ 6.5, C-2 or C-4), 23.19 (d, J_{CP} 148, C-1), 23.63 (d, $^2J_{CP}$ 4.8, C-2 or C-4), 33.30 (d, $^3J_{CP}$ 17.7, C-3), 42.60 ($PhCH_2$), 43.55 [d, $^4J_{CP}$ 3.2, *C*(CN)NHCOCH$_2$Ph], 62.07 (d, $^2J_{CP}$ 4.8, $POCH_2CH_3$), 117.29 (CN), 127.04, 128.61, 129.10 and 134.32 (6 C, Ar), 171.33 (C=O); δ_P(162 MHz, $CDCl_3$) 32.24; MS (NH_3, CI) *m/z* 365([M + H]$^+$, 100%), 338 (11), 273 (22), 165 (17), 136 (34), 91 (37).

Enantioselective enzyme hydrolysis, general procedure

(±)-*cis*-Diethyl 3-[(phenylacetylamino)cyanomethyl]cyclobutylphosphonate **25** (150 mg, 0.41 mmol) was dissolved in MeOH (3 cm^3) and phosphate buffer (8 cm^3, 0.01 M, pH 7). Penicillinacylase immobilised on Eupergit (*ca.* 20 units) was added. The reaction mixture was incubated at 27 °C and monitored by TLC (hexane–Pr^{i}OH, 7:3). After conversion had ceased (*ca.* 6 h), the reaction mixture was filtered, adjusted to pH 4 (1 M HCl) and extracted with CH_2Cl_2 (3 × 10 cm^3). The combined organic fractions were washed with saturated sodium hydrogen carbonate (2 × 10 cm^3), water (2 × 10 cm^3) and brine (2 × 10 cm^3), dried over anhydrous magnesium sulfate and filtered, and the solvent removed *in vacuo* to yield crude (−)-*cis*-diethyl 3-[(phenylacetylamino)cyanomethyl]cyclobutylphosphonate (−)-*cis*-**25** (67 mg, 45%). The acidic fraction from above was adjusted to pH 7 (1 M NaOH) and extracted with CH_2Cl_2 (3 × 10 cm^3). The combined organic fractions were washed with saturated aqueous sodium hydrogen carbonate (2 × 10 cm^3), water (2 × 10 cm^3) and brine (2 × 10 cm^3), dried over anhydrous magnesium sulfate and filtered, and the solvent removed *in vacuo* to yield crude (+)-*cis*-diethyl 3-(aminocyanomethyl)-cyclobutylphosphonate (+)-*cis*-**26** (42 mg, 41%).

A similar procedure yielded (−)-*trans*-diethyl 3-[(phenylacetylamino)cyanomethyl]cyclobutylphosphonate (−)-*trans*-**25** (67 mg, 42%) and (+)-*trans*-diethyl 3-(aminocyanomethyl)cyclobutylphosphonate (+)-*trans*-**26** (41 mg, 40%).

(+)-*trans*-3-[Amino(carboxy)methyl]cyclobutylphosphonic acid (+)-*trans*-8

(+)-*trans*-Diethyl3-(aminocyanomethyl)cyclobutylphosphonate (+)-*trans*-**26** (35 mg, 0.14 mmol) was dissolved in hydrochloric acid (6 M, 5 cm^3) and the reaction mixture heated to reflux for 36 h. After cooling the solvent was removed by evaporation under reduced pressure and the residue dissolved in water (1 cm^3), applied to an ion exchange column and washed with water (40 cm^3). The column was eluted with pyridine (1 M, 90 cm^3) and the ninhydrin active fractions were combined and evaporated to dryness. Residual traces of pyridine were removed by re-evaporation (3 times) to afford (+)-*trans*-3-[amino(carboxy)methyl]cyclobutylphosphonic acid (+)-*trans*-**8** (19 mg, 64%); $[a]_D^{20}$ +18.7 (*c* 0.8 in 1 M HCl); δ_H(400 MHz; D_2O) 2.09–2.27 [2 H, br m, C(2)-H and C(4)-H], 2.30–2.62 [3 H, br m, C(1)-H, C(2)-H and C(4)-H], 2.79 [1 H, m, C(3)-H], 4.14 [1 H, m, C*H*(NH$_2$)CO$_2$H]; δ_C(101 MHz; D_2O) 22.45 (d, $^2J_{CP}$ 5.9, C-2 or C-4), 22.62 (d, $^2J_{CP}$ 5.2, C-2 or C-4), 23.32 (d, J_{CP} 143, C-1), 33.28 (d, $^2J_{CP}$ 15.2, C-3), 49.29 [*C*(NH$_2$)CO$_2$H], 176.38 (C=O); δ_P(162 MHz; D_2O) 25.26 [HRMS (FAB): calc. for $C_6H_{12}NO_5P$, 209.0452. Found, 209.0454].

(−)-*trans*-3-[Amino(carboxy)methyl]cyclobutylphosphonic acid (−)-*trans*-8

(−)-*trans*-Diethyl 3-[(phenylacetylamino)cyanomethyl]cyclobutylphosphonate (−)-*trans*-**25** (67 mg, 0.18 mmol) was dissolved in hydrochloric acid (6 M, 5 cm^3) and the reaction mixture heated to reflux for 36 h. After cooling the solvent was removed by evaporation under reduced pressure and the residue dissolved in water (1 cm^3), applied to an ion exchange column and washed with water (40 cm^3). The column was eluted with pyridine (1 M, 90 cm^3) and the ninhydrin active fractions were combined and evaporated to dryness. Residual traces of pyridine were removed by repeated dissolution in water and re-evaporation (3 times) to afford (−)-*trans*-3-[amino(carboxy)methyl]cyclobutylphosphonic acid (−)-*trans*-**8** (24 mg, 62%) $[a]_D^{20}$ −17.9 (*c* 0.8 in 1 M HCl); δ_H(400 MHz; D_2O) 2.09–2.27 [2 H, m, C(2)-H and C(4)-H], 2.30–2.62 [3 H, br m, C(1)-H, C(2)-H and C(4)-H], 2.79 [1 H, m, C(3)-H], 4.14 [1 H, m, C*H* (NH$_2$)CO$_2$H]; δ_C(101 MHz; D_2O) 22.45 (d, $^2J_{CP}$ 5.9, C-2 or C-4), 22.62 (d, $^2J_{CP}$ 5.2, C-2 or C-4), 23.32 (d, J_{CP} 143, C-1), 33.28 (d, $^2J_{CP}$ 15.2, C-3), 49.29 [*C*(NH$_2$)CO$_2$H], 176.38 (C=O); δ_P(162 MHz; D_2O) 25.26 [HRMS (FAB): calc. for $C_6H_{12}NO_5P$, 209.0452. Found, 209.0454].

(+)-*cis*-3-[Amino(carboxy)methyl]cyclobutylphosphonic acid (+)-*cis*-8

(+)-*cis*-Diethyl 3-(aminocyanomethyl)cyclobutylphosphonate (+)-*cis*-**26** (35 mg, 0.14 mmol) was hydrolysed as described above to afford (+)-*cis*-3-[amino(carboxy)methyl]cyclobutylphosphonic acid (+)-*cis*-**8** (18 mg, 61%); $[a]_D^{20}$ +13.6 (*c* 1 in 1 M HCl), δ_H(400 MHz; D_2O) 2.23–2.48 [4 H, br m, C(2)-H and C(4)-H], 2.55 [1 H, m, C(1)-H], 2.87 [1 H, m, C(3)-H], 4.21 [1 H, C*H*(NH$_2$)CO$_2$H]; δ_C(101 MHz; D_2O) 22.61 (d, $^2J_{CP}$ 4.8, C-2 or C-4), 22.87 (d, $^2J_{CP}$ 4.2, C-2 or C-4), 25.15 (d, J_{CP} 142, C-1), 31.43 (d, $^3J_{CP}$ 13.8, C-3), 48.92 [d, $^4J_{CP}$ 2.8, *C*(NH$_2$)CO$_2$H], 176.21 (C=O); δ_P(162 MHz; D_2O) 26.48 [HRMS (FAB): calc. for $C_6H_{12}NO_5P$, 209.0452. Found, 209.0453].

(−)-*cis*-3-[Amino(carboxy)methyl]cyclobutylphosphonic acid (−)-*cis*-8

(−)-*cis*-Diethyl 3-[(phenylacetylamino)cyanomethyl]cyclobutylphosphonate (−)-*cis*-**25** (63 mg, 0.18 mmol) was treated as described above to afford (−)-*cis*-3-[amino(carboxy)methyl]-cyclobutylphosphonic acid (−)-*cis*-**8** (24 mg, 63%); $[a]_D^{20}$ −12.9 (*c* 9 in 1 M HCl); δ_H(400 MHz; D_2O) 2.23–2.48 [4 H, br m, C(2)-H and C(4)-H], 2.55 [1 H, m, C(1)-H], 2.87 [1 H, m, C(3)-H], 4.21 [1 H, C(NH$_2$)CO$_2$H]; δ_C(101 MHz; D_2O) 22.61 (d, $^2J_{CP}$ 4.8, C-2 or C-4), 22.87 (d, $^2J_{CP}$ 4.2, C-2 or C-4), 25.15 (d, J_{CP} 142, C-1), 31.43 (d, $^3J_{CP}$ 13.8, C-3), 48.92 [d, $^4J_{CP}$ 2.8, *C*(NH$_2$)CO$_2$H], 176.21 (C=O); δ_P(162 MHz; D_2O) 26.48 [HRMS (FAB): calc. for $C_6H_{12}NO_{56}P$, 209.0452. Found, 209.0454].

Preparation of 2-methoxy-2-trifluoromethyl-2-phenylacetylamine derivatives

General procedure. To a sample of diethyl 3-(aminocyanomethyl)cyclobutylphosphonate (5 mg, 20 μmol) in CH_2Cl_2 (1 cm^3) was added triethylamine (50 mm^3) and 2-methoxy-2-trifluoromethyl-2-phenylacetyl chloride (240 mm^3 of a 0.1 M solution in CH_2Cl_2). The reaction mixture was stirred for 12 h at room temperature and then the solvent removed by evaporation under reduced pressure. The residue was dissolved in $CDCl_3$ and the sample analysed by ^{19}F NMR spectroscopy. The spectra of the enantiomerically pure samples were compared with the spectra of the racemic samples and in all cases no evidence of a second isomer was detected.

(±)-*trans*-Diethyl 3-[(2-methoxy-2-trifluoromethyl-2-phenylacetylamino)carboxymethyl]cyclobutylphosphonate. δ_F(376 MHz; $CDCl_3$) −71.89 and −7.84.

(+)-*trans*-Diethyl 3-[(2-methoxy-2-trifluoromethyl-2-phenylacetylamino)carboxymethyl]cyclobutylphosphonate. δ_F(376 MHz; $CDCl_3$) −71.89.

(±)-*cis*-Diethyl 3-[(2-methoxy-2-trifluoromethyl-2-phenylacetylamino)carboxymethyl]cyclobutylphosphonate. δ_F(376 MHz; $CDCl_3$) −69.85 and −71.91.

(+)-*cis*-Diethyl 3-[(2-methoxy-2-trifluoromethyl-2-phenylacetylamino)carboxymethyl]cyclobutylphosphonate. δ_F(376 MHz; $CDCl_3$) −71.91.

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