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Efficient synthesis of protected cyclopropyl β-aspartylphosphates †

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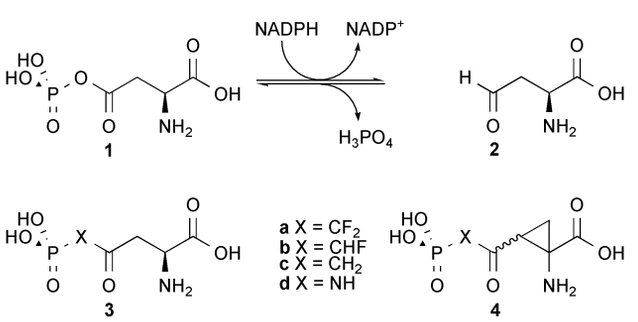
The *in situ* reaction of protected dehydroamino acids with derivatives of vinyldiazomethane leads to good to excellent yields of vinyl cyclopropanes *via* 3 + 2 dipolar cycloaddition followed by N_2 extrusion. Chromatographic separation of the cyclopropane diastereomeric products, followed by characterisation by ^{1}H NMR and X-ray crystallography allowed the *cis* and *trans* diastereomers to be easily identified. Oxidative cleavage of the vinyl moiety then led directly to protected cyclopropane aspartic acid derivatives in three steps from commercially available materials. These compounds were converted to protected methylenephosphonate, difluoromethylenephosphonate and phosphoramidate analogues of β-aspartyl phosphate.

Introduction

Cyclopropane amino acids (2,3-methanoamino acids) are interesting and useful compounds because of their roles in natural compounds and their use in the production of conformationally rigid compounds such as peptides.[1,2] We have an interest in the metabolism of aspartic acid, *via* β-aspartyl phosphate **1**, which is the feedstock in bacteria for protein and cell wall biosynthesis. The enzyme aspartate semi-aldehyde dehydrogenase (ASA-DH), which converts **1** to aspartate semi-aldehyde **2**, is a target for the design and synthesis of potential antimicrobial compounds (Scheme 1).[3] For example, compounds **3a**–**d** mimic **1**, while attenuation of phosphate leaving-group ability makes these compounds reversible inhibitors of ASA-DH. Kinetic and modelling studies suggest that these compounds bind at the active site of ASA-DH, but their conformational flexibility may impede strong binding.[4] For this reason we were interested in investigating more rigid analogues. Modelling studies suggested that cyclopropyl derivatives such as **4a**–**d** would be able to fit into the active site of ASA-DH. Such compounds would provide the rigidity we required, and furthermore, examination of diastereoselectivity in binding could provide additional information about the structure of the active site of ASA-DH.



Scheme 1 Biosynthetic reaction catalysed by ASA-DH and known and potential synthetic inhibitors.

Literature methods for the construction of cyclopropane amino acids tend to be lengthy and low-yielding. One of the better methods is the addition of diazomethane to functionalised dehydroamino acids,[5] leading to dihydropyrazoles which extrude N_2 forming cyclopropanes. However, this method is limited by the complex syntheses of the functionalised olefin. On the other hand, addition of sulfur ylides[6] to simple dehydroamino acids has been explored, but once again significant synthetic challenges are faced in making the functionalised sulfur ylides. Additionally, the synthesis of cyclopropane aspartate derivatives has very rarely been reported. Here we wish to report progress towards the efficient synthesis of cyclopropane aspartic acids in general, and specifically analogues of β-aspartyl phosphate.

Results

Synthesis of cyclopropane amino acids

The synthetic strategy we used to install the acyl phosphate moiety of **3a**–**d** involved the addition of nucleophilic phosphorus-containing species to carbonyls on the amino-acid moiety.[7,8] Thus, we required a synthesis of cyclopropanes with a pendant oxygen or masked carbonyl. Our initial attempts to use ethyldiazoacetate **5** to install a cyclopropyl ester directly onto the protected dehydroamino acid **6** (Scheme 2) resulted in poor yields of the aspartate analogue **7**. Similarly low yields have been reported by Horikawa *et al.* and El Abdioui *et al.* in related systems.[9] In our experience, even lower yields were observed in the presence of metal catalysts such as $Rh_2(OAc)_4$ which are known to mediate carbenoid additions to olefins. Carbene recombination to form diethyl fumarate was the likely cause of the low yields and we identified this as a by-product of the reactions.

We next considered the use of vinyl diazomethane **8** as a masked carbonyl species – oxidation of the vinyl unit at a later stage could expose the required carbonyl. Substituted diazomethanes can undergo 3 + 2 dipolar cycloaddition reactions with olefins to form dihydropyrazoles[9] which extrude N_2 to form cyclopropanes. Vinyl diazomethane **8** can be prepared by the base catalysed rearrangement of *N*-nitroso compounds, but a better method is *in situ* generation from its corresponding tosyl hydrazone salt, as described and used by Aggarwal *et al.*[10] Accordingly, acrolein **9** was treated with tosyl

† Electronic supplementary information (ESI) available: Crystal data and rotatable 3-D crystal structure diagrams for compounds **22** and **24**. See http://www.rsc.org/suppdata/ob/b3/b311322a/

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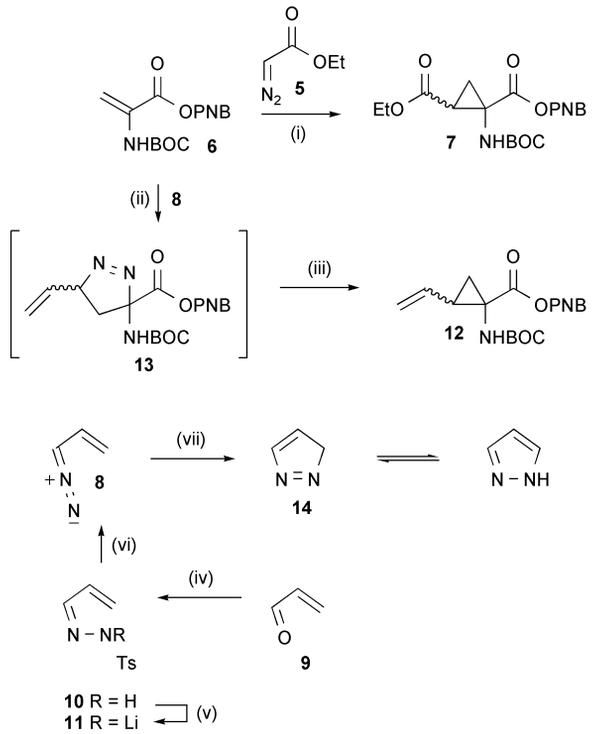
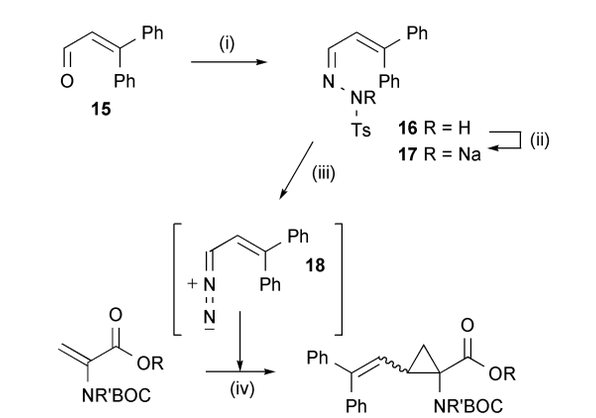


Scheme 2 Access to cyclopropyl aspartate analogues. *Reagents and conditions*: (i) CH_2Cl_2, RT, 35%; (ii)/(iii) toluene, $BnEt_3NCl$, 40 °C, 38%; (iv) $TsNHNH_2$, dioxane, RT, 68%; (v) THF, LiHMDS, −78 °C, 89%; (vi) toluene, $BnEt_3NCl$, 40 °C; (vii) slow *in situ* isomerisation.

hydrazine in dioxane to afford the tosyl hydrazone **10** in good yield (Scheme 2). The tosyl hydrazone salt **11** was then formed by deprotonation of **10** with LiHMDS. Treatment of the salt with **6**, under gentle heating in the presence of a phase transfer catalyst, resulted in a low yield (38%) of the vinyl cyclopropane **12**, formed *via* the dihydropyrazole **13**. The low yield was accompanied by a low diastereomer ratio (73 : 27 *trans* : *cis*, 46% *d.e.*). The low yields are probably due to the known cycloisomerisation of vinyldiazomethane to pyrazole **14** itself.

We reasoned that a more sterically hindered vinyldiazomethane could prevent self-cyclisation. We thus turned to β-phenylcinnamaldehyde **15** which was converted to the corresponding tosyl hydrazone salt **17** by treatment with tosyl hydrazine followed by sodium methoxide (Scheme 3). The corresponding diazo compound **18** was again generated *in situ* in the presence of **6**. This led to excellent yields (88%) of the desired substituted cyclopropane amino acid **19**, again with low



6 R = PNB, R' = H	**19** R = PNB, R' = H	88%	67:33
20 R = Me, R' =BOC	**22** R = Me, R' =BOC	100%	72:28
21 R = PNB, R' = BOC	**23** R = PNB, R' = BOC	42%	55:45

Scheme 3 Access to bisphenylvinyl cyclopropane amino acids. *Reagents and conditions*: (i) MeOH, $TsNHNH_2$, RT, 95%; (ii) MeOH/Na, RT, quant.; (iii)/(iv) toluene, $BnEt_3NCl$, 40 °C.

d.e. (34%). Quantitative yield and better diastereoselectivity (44% *d.e.*) was observed in the conversion of *bis*-Boc methyl ester **20** to cyclopropane **22**, while the *bis*-Boc *p*-nitrobenzyl ester **21** gave a modest yield of cyclopropane **23** in 10% *d.e.*

The diastereomeric cyclopropane products were easily separable by column chromatography in all cases. However, since we wished to study the interactions of both sets of diastereomers with ASA-DH, we decided to continue our syntheses using these mixed diastereomers and separate them nearer the end of the route.

The relative stereochemistry of the cyclopropanes was determined by X-ray crystallography. Treatment of the major diastereomer of **19** with activated Zn powder in phosphate buffered THF (pH 6) led to the formation of the crystalline carboxylic acid **24**. X-ray crystallography revealed this to be the *trans*-isomer (Fig. 1). The minor diastereomer of **22** also crystallised and this proved to be the *cis*-isomer (Fig. 1). ^{1}H NMR analysis of the recovered crystals then enabled us to show that in the *cis*-compounds the γ-vinyl proton resonates at higher field than in the *trans*-compounds, while the cyclopropane β-CH protons resonate at lower field for *cis*-compounds than the corresponding *trans*-compounds (Fig. 1). This pattern was repeated for all the cyclopropanes synthesised here. The apparent shielding of the γ-vinyl proton in the *cis*-compounds may be due to the diamagnetic anisotropy of the cyclopropane ring – in the *cis*-compound H_γ lies in the shielding region of the ring. However the apparent shielding of the cyclopropane H_β in the *trans*-compounds is harder to rationalise, but could be due to differential ring-current effects of the nearby aromatic rings.

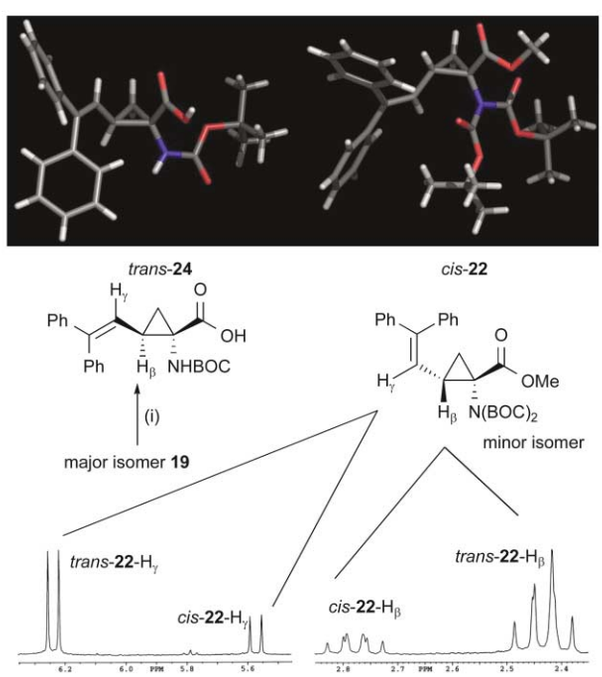
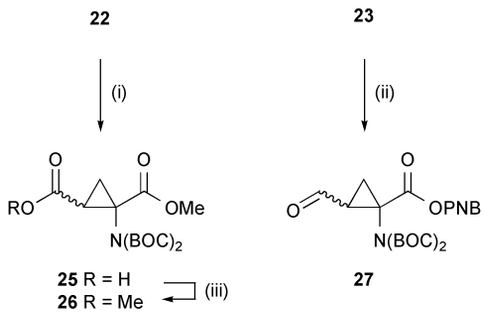


Fig. 1 Relative stereochemistry of cyclopropanation products as determined by X-ray crystallography and ^{1}H NMR. *Reagents and conditions*: (i) Zn, pH 6.0, aq. THF, 80%.

Aspartyl phosphate analogues

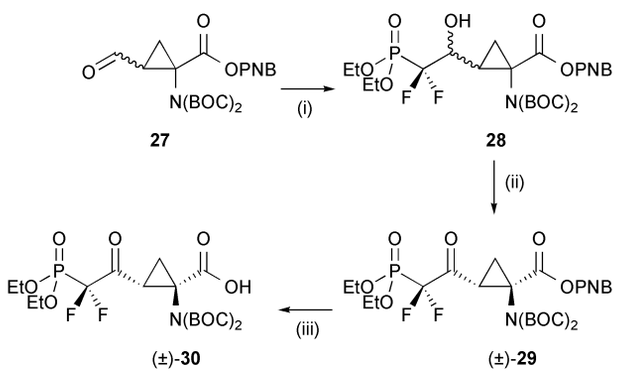
Treatment of **22** with RuO_4 under Sharpless conditions was used to unmask the β-carbonyl (Scheme 4). This reaction cleanly provided the carboxylic acid **25** in 68% yield. The acid was converted to the methyl ester **26** by reaction with ethereal diazomethane. On the other hand, ozonolysis of the diphenylvinyl cyclopropane amino acid **23** followed by reductive work up resulted in a 66% yield of the aldehyde **27**.

We have previously shown that protected aspartyl β-semialdehydes can be converted to substituted difluorophos-



Scheme 4 Synthesis of protected cyclopropyl aspartate derivatives. *Reagents and conditions*: (i) $RuCl_3$ (4.4 mol%), $NaIO_4$, CCl_4, MeCN, H_2O, RT, 68%; (ii) O_3, CH_2Cl_2, −78 °C, then Me_2S, 66%; (iii) CH_2N_2, Et_2O, 88%.

phonates. Thus treatment of a 90 : 10 *trans : cis* mixture of aldehydes **27** with $TMSCF_2P(O)(OEt)_2$ and catalytic TBAF led to a 19% yield of the desired secondary alcohol **28** (Scheme 5). Four diastereomers were isolated in a ratio of 87 : 9 : 4 : <1. Oxidation of this mixture using the Dess–Martin periodinane[11,12] led to the isolation of the desired ketone **29** in 72% yield as a single (*trans*) isomer. It is unlikely that this compound could easily epimerise under the reaction conditions as this would involve formation of an sp^2 hybridised carbon on the cyclopropane, and so the isolation of the *trans*-isomer as the sole product may indicate lack of reactivity of the *cis*-isomers to oxidation, or facile degradation of the *cis*-ketone under the reaction conditions.



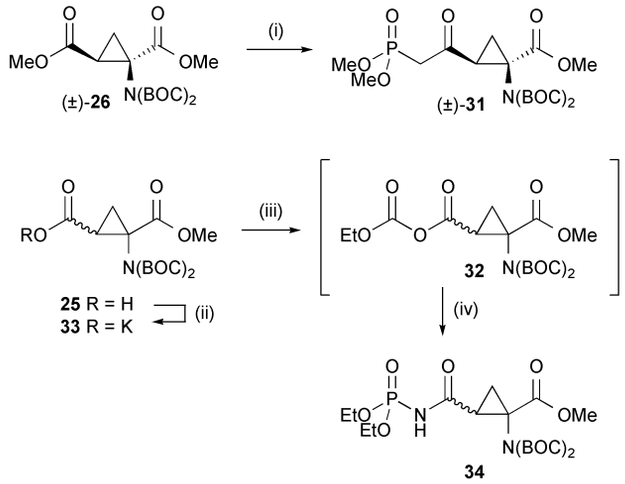
Scheme 5 Synthesis of difluoromethylene phosphonates. *Reagents and conditions*: (i) THF, −60 °C, $TMSCF_2P(O)(OEt)_2$, TBAF, 19%; (ii) Dess–Martin periodinane, CH_2Cl_2, RT, 72%; (iii) Zn, pH 6.0, aq. THF, 67%.

The *cis*-dimethyl ester **26** was treated with the lithium anion derived from methyldimethylphosphonate, to yield the *cis*-methylene phosphonate **31** in 77% yield (Scheme 6). There was no observable (^{1}H NMR) epimerisation under these conditions.

In order to access the phosphoramidate, carboxylic acid **25** (71 : 29 *trans : cis*) was treated with one equivalent of KOH to form the potassium salt **33** which is conveniently soluble in CH_2Cl_2 (Scheme 6). The salt **33** was treated with ethyl chloroformate, forming the mixed anhydride carbonate **32** *in situ*. In parallel, diethylphosphoramidate was deprotonated and the lithium salt added to the preformed mixed anhydride carbonate **32**. This resulted in a moderate yield of the protected *N*-acyl phosphoramidate **34**, this time as a 58 : 42 mixture of *trans* and *cis* isomers which were readily separable by chromatography.

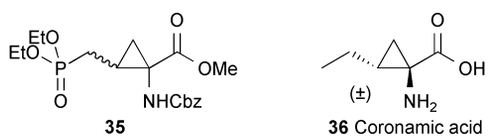
Deprotection

With the three fully protected β-aspartylphosphate analogues in hand, we then set about deprotection. In previous work we have shown that methylene phosphonates are robust and can be deprotected by treatment with refluxing aqueous HCl.[4] However these conditions caused complete decomposition of



Scheme 6 Synthesis of methylene phosphonates and phosphoramidates. *Reagents and conditions*: (i) $(MeO)_2P(O)Me$, BuLi, THF, −78 °C, 77%; (ii) KOH, quant.; (iii) EtOC(O)Cl, CH_2Cl_2; (iv) $(EtO)_2P(O)NH_2$, BuLi, CH_2Cl_2, −78 °C, 45%.

31. Similar compounds such as the *des*-carbonyl analogue **35** are also known to be stable to these conditions,[13] so the instability is unlikely to be due to the cyclopropane *per se*. We also attempted much milder deprotection conditions, for example freshly distilled TMSI (Me_3SiI), or TMSI generated *in situ* from TMSCl and NaI in MeCN can be used to deprotect more delicate compounds such as the phosphoramidate **3d**.[4] However, even these conditions resulted in full decomposition.



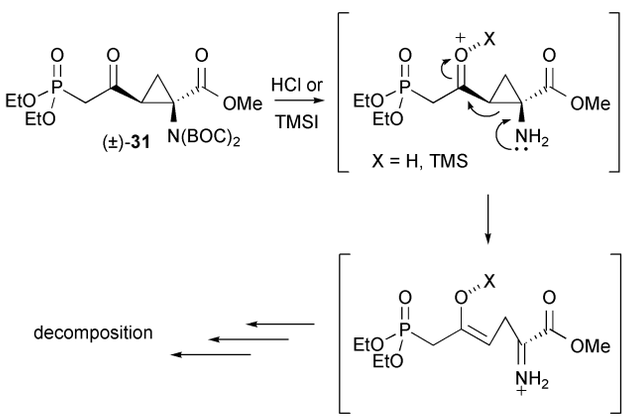
We also tried partial step-wise deprotection. Treatment of the *p*-nitrobenzyl ester **29** with Zn in buffered (pH 6) THF cleanly afforded the carboxylic acid **30** in good yield (Scheme 5). However, once again treatment with either TMSI or TMSCl/NaI/MeCN led to complete decomposition. ^{1}H, ^{19}F and ^{31}P NMR showed the presence of many compounds, despite the fact that similar conditions are known to cleanly deprotect the acyclic analogues. Bearing these results in mind, we were not hopeful about the likelihood of deprotecting the phosphoramidate **34**, and indeed this compound also decomposed under varied reaction conditions.

Discussion

The addition of functionalised diazo compounds to dehydroamino acids provides rapid and efficient access to substituted amino acid cyclopropanes. The use of diphenylvinyldiazomethane **18**, generated *in situ* from the corresponding tosyl hydrazone salt **17**, affords high yields of diphenylvinyl cyclopropanes which are direct precursors of cyclopropane aspartic acid derivatives. Mild oxidation affords the acid, or reductive ozonolysis gives the aldehyde in good yields. For example, the synthesis of the protected cyclopropyl aspartic acid **25** was achieved in 63% yield, over three steps, from commercially available starting materials. This compares with a 15 step synthesis reported by Burgess *et al.*[14] (albeit of enantiomerically pure material) and the six step enantioselective route reported by Ortuno *et al.*[5] Racemic syntheses have also been reported such as the six step route of Tamm *et al.*[15] Other routes to cyclopropane amino acid precursors have been reported such as the reaction of 1-seleno-2-silylethene with methylene malonates.[16] However up to 11 further steps are required to access natural products such as (±) coronamic acid **36**.

This compares with 2 post-cyclopropanation steps using our methodology in the synthesis of **36**.[17]

The cyclopropyl aspartyl derivatives were further reacted to give the conformationally restricted derivatives of β-aspartyl-phosphate, but all attempts to deprotect these compounds failed. Similar reports in the literature probably account for the lack of synthetic work in this area.[18] For example Pyne *et al.* have reported similar decompositions by lone-pair assisted ring-opening only after *N*-deprotection.[6] Our attempts to keep the nitrogen lone-pair protonated under acidic (or Lewis acidic) conditions also failed to prevent decomposition, possibly due to a facile enolic ring-opening route (Scheme 7).



Scheme 7 Decomposition of cyclopropyl aspartates.

Despite the seemingly intractable problem of preparing stable cyclopropyl aspartate derivatives bearing a free amine, the methods presented here give a rapid and high-yielding route to *N*-acylated cyclopropyl aspartate derivatives. Coupled with the simple separation of the *cis* and *trans* diastereomers, and the easy identification of the isomers by ^{1}H NMR, these methods should be useful for the preparation of a range of conformationally restricted aspartate derivatives and peptides.

Experimental

Commercially available reagents were used without further purification except where stated. Thin layer chromatography was performed using 0.25 mm silica gel 60 (F254, Merck) plates visualising at 254 nm, or developed with molybdophosphoric acid, ninhydrin or potassium permanganate solutions by heating with a hot-air gun. Specified products were purified by flash column chromatography using silica gel 60 (230–400 mesh, Merck), by cation exchange chromatography using Dowex AG 50 × 8 or by preparative HPLC using a Gilson system containing a Rheodyne 3098 injection valve. The Gilson system consisted of two 306 pumps, an 806 manometric module, an 811c dynamic mixer, an 819 injection valve actuator, a 215 liquid handler which was responsible for injection and fraction collection and a 119 UV/VIS detector that was set to 254 nm triggered fraction collection. Chromatographic separations were achieved using a Develosil 5 μm normal phase silica (30 Å pore size) column (21.2 × 100 mm) run at 21.2 mL min^{-1}. The mobile phase used an isocratic elution whose composition is specified in the text, *e.g.* 35 : 65 ethyl acetate/hexane. Samples (up to 2.0 mL) of approximately 100 mg mL^{-1} were injected. A typical run lasted approximately 15 min. The void volume of the system was approximately 20.0 mL. The system was controlled by Gilson Unipoint software.

The University of Bristol Structural Chemistry laboratories performed the X-ray crystal structure determinations.§ Melting points were obtained using an Electrothermal melting point apparatus. The University of Bristol microanalytical laboratories performed elemental analyses. IR absorptions on NaCl or as KBr disks run on a Perkin Elmer FT-IR 1600 or samples mounted directly on the diamond cell of a Perkin Elmer FT-IR Paragon 1000 instrument. ^{1}H NMR spectroscopic data was obtained using JEOL Δ 270 MHz, Λ 300 MHz, Eclipse 300 MHz or Δ 400 MHz or Varian Inova 400 MHz or Inova 500 MHz instruments. ^{13}C NMR spectral data was obtained using JEOL Λ 75.5 MHz, Eclipse 75.5 MHz or Δ 101 MHz or Varian Inova 101 MHz spectrometers. ^{19}F and ^{31}P NMR spectroscopic data was obtained using an Eclipse 300 MHz NMR spectrometer operating at 283 MHz and 121 MHz respectively. Samples dissolved in $CDCl_3$ used tetramethylsilane as an internal standard, while samples in CD_3OD, D_2O or DMSO-d_6 are reported downfield from sodium 3-(trimethylsilyl) propionate. ^{19}F and ^{31}P NMR were referenced to trifluoroacetic acid and phosphoric acid respectively. ^{13}C and ^{31}P NMR spectra were obtained under broad-band proton-decoupled conditions {^{1}H}. For all NMR spectra, δ values are given in ppm and J values in Hz.

Mass spectrometry data was obtained from Micromass Autospec mass spectrometers by EI at a potential of 70 eV, by CI, FAB or ES. LCMS data was obtained from a Waters/Micromass system comprising a Waters 600 LC system equipped with both Waters 996 photodiode array and platform MS detectors running in ES$^+$ mode. Chromatographic separations were achieved using a Phenomenex C_8 reverse phase column (4.6 × 250 mm) run at 1 mL min^{-1}. Solvent **A** 0.1% TFA in water. Solvent **B** 0.05% TFA in MeCN. Samples (20 μL) of approximately 1 mg mL^{-1} were injected. The gradient was as follows: 0 min, 0% **B**; 13 min, 99% **B**; 17 min, 99% **B**; 18 min, 0% **B**; 20 min, 0% **B**. The void volume of the system was 540 μL. Data analysis was performed with MassLynx v3.3 software.

N-(*tert*-Butoxycarbonyl)-dehydroalanine *p*-nitrobenzyl ester 6[19]

To a solution of *N*-(*tert*-butoxycarbonyl)-DL-serine *p*-nitrobenzyl ester[19] (25.9 g, 76.1 mmol) in chloroform (700 mL) was added copper(I) chloride (753 mg, 7.61 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (29.2 g, 152 mmol). The mixture rapidly became dark brown in colour and was stirred for 17 h at RT. TLC (50 : 50 ethyl acetate/petrol) showed the protected dehydroalanine **6** (R_f 0.68), UV and potassium permanganate active. The reaction mixture was filtered through Celite and washed with brine (700 mL), the layers were separated and the aqueous layer extracted with chloroform (3 × 500 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure (85 mm Hg, 40 °C), to give the olefin **6** (24.2 g, 99%) as an off colourless solid; ν_{max} (KBr)/cm^{-1} 3426s (N–H), 1735s and 1712s (C=O), 1640m (C=C), 1606m (C=C, Ar), 1515s (N=O), 886m (C–H, alkene) and 840m (C–H, Ar); δ_H(270 MHz; $CDCl_3$) 1.49 (9H, s, C(Me)$_3$), 5.36 (2H, s, CH_2Ar), 5.83 (1H, d, J 1.3, C*H*HC), 6.25 (1H, s, CH*H*C), 6.99 (1H, br s, NH), 7.50–7.58 (2H, m, C(3)H and C(5)H (Ar)) and 8.21–8.29 (2H, m, C(2)H and C(6)H (Ar)); *m*/*z* (CI) 323 (MH$^+$, 2%), 307 (1), 277 (1), 249 (8), 223 (82), 206 (8), 136 (52), 122 (24) and 57 (100); LCMS 19.9 min, *m*/*z* (ES) 323 (MH$^+$, 100%).

cis- and *trans*-(*N*-*tert*-Butoxycarbonyl)-1-amino-1-(*p*-nitrobenzyloxycarbonyl)-2-ethoxycarbonylcyclopropane 7

To a solution of *N*-(*tert*-butoxycarbonyl)-dehydroalanine *p*-nitrobenzyl ester **6** (200 mg, 621 μmol) in dichloromethane (5 mL) was added ethyl diazoacetate (144 μL, 1.37 mmol) dropwise. The yellow solution was stirred at RT for 19 h, then further ethyl diazoacetate (72 μL, 683 μmol) was added dropwise and stirred for 3 days; TLC (40 : 60 ethyl acetate/hexane)

§ CCDC reference numbers 220087 and 220088. See http://www.rsc.org/suppdata/ob/b3/b311322a/ for crystallographic data in.cif or other electronic format.

showed the cyclopropane **7** (R_f 0.29) UV active. Solvent was evaporated under reduced pressure (85 mm Hg, 40 °C) and this crude mixture was dissolved in the minimum amount of dichloromethane and purified by preparative HPLC using 30 : 70 ethyl acetate/hexane as eluent to give *cis-(N-tert-butoxycarbonyl)-1-amino-1-(p-nitrobenzyloxycarbonyl)-2-ethoxycarbonylcyclopropane Z*-**7** (*retention time* 4.71 min) (28 mg, 11%) as a colourless solid; mp 117–119 °C; ν_{max} (solid)/cm^{-1} 1725s (C=O, CO_2), 1689s (C=O, NHCO), 1608w (C=C, Ar), 1507s (N=O), 1185s (C–O, CO_2) and 846s (C–H, Ar); δ_H(300 MHz; $CDCl_3$) 1.29 (3H, t, *J* 7.2, CH_2Me), 1.42 (9H, s, $C(Me)_3$), 1.78 (1H, dd, *J* 8.3 and 5.1, C*H*H (cyclopropane)), 1.87 (1H, dd, *J* 8.3 and 5.1, CH*H* (cyclopropane)), 2.76 (1H, br t, *J* 8.3, $CHCO_2$) 4.05–4.26 (2H, m, CH_2Me) 5.16 (1H, br s, NH), 5.22 (1H, d, *J* 11.8, C*H*HAr), 5.34 (1H, d, *J* 11.8, CH*H*Ar), 7.48–7.56 (2H, m, C(3)H and C(5)H (Ar)) and 8.18–8.26 (2H, m, C(2)H and C(6)H (Ar)); δ_C(75.5 MHz; $CDCl_3$) 14.2 (CH_2*Me*), 22.0 (CH_2 (cyclopropane)), 28.1 (C(*Me*)$_3$), 29.4 (*C*HCO$_2$), 40.1 (*C*CO$_2$), 61.4 (*C*H$_2$Me), 66.1 (CH_2Ar), 80.5 (*C*(Me)$_3$), 123.8 (C(2) and C(6) (Ar)), 128.1 (C(3) and C(5) (Ar)), 142.6 (C(4) (Ar)), 147.7 (C(1) (Ar)), 155.5 (NCO_2), 168.5 (CO_2) and 170.4 (CO_2); HRMS (CI, [M–Boc + H]H$^+$) Found: 309.1085. Calc. for $C_{14}H_{17}N_2O_6$ 309.1087; *m*/*z* (ES) 409 (MH$^+$, 35%), 353 (77) and 309 (100), and *trans-(N-tert-butoxycarbonyl)-1-amino-1-(p-nitrobenzyloxycarbonyl)-2-ethoxycarbonylcyclopropane E*-**7** (*retention time* 5.23 min) (61 mg, 24%) as a colourless oil; ν_{max} (film)/cm^{-1} 1714s (C=O), 1607w (C=C, Ar), 1522m (N=O), 1156s (C–O, CO_2) and 848m (C–H, Ar); δ_H(500 MHz at 55 °C; $CDCl_3$) 1.21 (3H, t, *J* 7.1, CH_2Me), 1.42 (9H, s, $C(Me)_3$), 1.60 (1H, dd, *J* 9.6 and 5.7, C*H*H (cyclopropane)), 2.18 (1H, dd, *J* 7.9 and 5.7, CH*H* (cyclopropane)), 2.31 (1H, dd, *J* 9.6 and 7.9, $CHCO_2$) 4.09 (2H, q, *J* 7.1, CH_2Me), 5.23 (1H, d, *J* 13.4, C*H*HAr), 5.28 (1H, d, *J* 13.4, CH*H*Ar), 5.37 (1H, br s, NH), 7.49–7.57 (2H, m, C(3)H and C(5)H (Ar)) and 8.17–8.25 (2H, m, C(2)H and C(6)H (Ar)); δ_C(101 MHz; $CDCl_3$) 14.0 (CH_2*Me*), 21.2 (CH_2 (cyclopropane)), 28.2 (C(*Me*)$_3$), 31.9 (*C*HCO$_2$), 40.3 (*C*CO$_2$), 61.4 (*C*H$_2$Me), 65.8 (CH_2Ar), 80.8 (*C*(Me)$_3$), 123.7 (C(2) and C(6) (Ar)), 128.2 (C(3) and C(5) (Ar)), 142.7 (C(4) (Ar)), 147.7 (C(1) (Ar)), 155.3 (NCO_2), 167.9 (CO_2) and 169.3 (CO_2); HRMS (CI, [M–Boc + H]H$^+$) Found: 309.1082. Calc. for $C_{14}H_{17}N_2O_6$ 309.1087; *m*/*z* (ES) 409 (MH$^+$, 14%), 394 (14), 353 (100), 309 (39), 287 (58) and 136 (12).

p-Toluenesulfonyl (2-propenylidene)hydrazide 10

The procedure outlined by Aggarwal *et al.*,[20] was adapted for the synthesis of sulfonyl hydrazide **10**. To a solution of acrolein (1 g, 17.8 mmol) in dioxane (25 mL) was added *p*-toluenesulfonyl hydrazide (3.65 g, 19.6 mmol). The clear bright yellow solution was stirred at RT for 1 h, over which time it became orange in colour. TLC (35 : 65 ethyl acetate/petrol) showed allylic hydrazide **10** (R_f 0.29; UV and potassium permanganate active) and precursor hydrazide (R_f 0.09; potassium permanganate and weakly UV active). Solvent was removed under reduced pressure (85 mm Hg, 40 °C) and this crude mixture was purified by column chromatography on silica using 35 : 65 ethyl acetate/petrol as eluent to give *p-toluenesulfonyl (2-propenylidene)hydrazide* **10** (2.70 g, 68%) as a yellow solid; mp 88–90 °C; Found: C, 53.6; H, 5.5; N, 12.4; $C_{10}H_{12}N_2O_2S$ requires C, 53.55; H, 5.4; N, 12.5%; ν_{max} (solid)/cm^{-1} 1597w (C=C, Ar), 1344m and 1158s (N–SO_2), 936m (C–H, alkene) and 809m (C–H, Ar); δ_H(400 MHz; $CDCl_3$) 2.43 (3H, s, Me), 5.52 (1H, d, *J* 17.4, C*H*HCH), 5.59 (1H, d, *J* 9.9, CH*H*CH), 6.40 (1H, dt, *J* 17.4 and 9.9, CHHC*H*), 7.28–7.36 (2H, m, C(3)H and C(5)H (Ar)), 7.41 (1H, d, *J* 9.9, CHN), 7.78–7.86 (2H, m, C(2)H and C(6)H (Ar)) and 8.06 (1H, br s, NH); δ_C(101 MHz; $CDCl_3$) 21.7 (Me), 125.2 (*C*H$_2$CH), 127.9 (C(2) and C(6) (Ar)), 129.8 (C(3) and C(5) (Ar)), 133.2 (CH_2*C*H), 135.3 and 144.3 (C(1) and C(4) (Ar)) and 149.8 (CHN); *m*/*z* (ES) 225 (MH$^+$, 100%).

p-Toluenesulfonyl (2-propenylidene)hydrazide lithium salt 11

Following a modified procedure of Aggarwal *et al.*:[21] to a solution of *p*-toluenesulfonyl (2-propenylidene)hydrazide **10** (1 g, 4.46 mmol) in anhydrous tetrahydrofuran (20 mL) under a nitrogen atmosphere, was added lithium bis(trimethylsilyl)amide (6.70 mL, 6.70 mmol, 1 M solution in tetrahydrofuran) at −78 °C. The clear yellow solution was stirred for 1 h, which resulted in a significant change in colour and formation of the product as a brown precipitate. The mixture was allowed to return to RT and stirred for 1 h. Nitrogen was passed over the precipitate which was collected by filtration and washed with anhydrous diethyl ether (3 × 10 mL). Residual solvent was removed under reduced pressure (85 mm Hg, 40 °C); remaining tetrahydrofuran was removed by azeotroping with toluene, then ethyl acetate, then chloroform under reduced pressure (5 mm Hg, 25 °C) to give *p-toluenesulfonyl (2-propenylidene)hydrazide lithium salt* **11** (911 mg, 89%) as a pale brown hydroscopic solid which was stored under nitrogen at −20 °C prior to use; ν_{max} (solid)/cm^{-1} 3400br w (H_2O), 992s and 906s (C–H, alkene) and 812s (C–H, Ar); δ_H(400 MHz; DMSO) 2.28 (3H, s, Me), 4.96 (1H, d, *J* 9.6, C*H*HCH), 4.99 (1H, d, *J* 17.0, CH*H*CH), 6.24 (1H, dt, *J* 17.0 and 9.6, CHHC*H*), 7.08–7.16 (2H, m, C(2)H and C(6)H (Ar)), 7.30 (1H, d, *J* 9.6, CHN) and 7.44–7.52 (2H, m, C(3)H and C(5)H (Ar)); δ_C(75.4 MHz; CD_3OD) 20.0 (Me), 117.1 (*C*H$_2$CH), 126.8 (C(3) and C(5) (Ar)), 128.5 (C(2) and C(6) (Ar)), 135.4 (CH_2*C*H), 140.6 and 141.7 (C(1) and C(4) (Ar)) and 145.3 (CHN); *m*/*z* (EI) 224 ([M–Li + H]$^+$, 1%), 176 (1), 155 (19), 139 (22), 132 (7), 91 (100) and 68 (84).

cis- and *trans*-(*N-tert*-Butoxycarbonyl)-1-amino-1-(*p*-nitrobenzyloxycarbonyl)-2-ethenylcyclopropane 12

To a mixture of *p-toluenesulfonyl (2-propenylidene)hydrazide lithium salt* **11** (1 g, 4.35 mmol) in anhydrous toluene (15 mL) under a nitrogen atmosphere, was added *N*-(*tert*-butoxycarbonyl)-dehydroalanine *p*-nitrobenzyl ester **6** (2.8 g, 8.70 mmol) followed by benzyltriethylammonium chloride (50 mg, 217 μmol). The cloudy brown mixture was stirred at 40 °C for 3 d. TLC (25 : 75 ethyl acetate/petrol) showed olefin precursor **6** (R_f 0.60), *trans*-**12** (R_f 0.35) and *cis*-**12** (R_f 0.28), all compounds were UV and potassium permanganate active. The reaction was quenched by the addition of water (30 mL) and ethyl acetate (30 mL). The layers were separated and the aqueous further extracted with ethyl acetate (4 × 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure (85 mm Hg, 40 °C) and this crude mixture was purified by column chromatography on silica using 25 : 75 ethyl acetate/petrol as eluent to give *trans-(N-tert-butoxycarbonyl)-1-amino-1-(p-nitrobenzyloxycarbonyl)-2-ethenylcyclopropane E*-**12** (422 mg, 27%) as a colourless solid; mp 69–70 °C; ν_{max} (solid)/cm^{-1} 1710br s (C=O), 1607w (C=C, Ar), 1521s and 1346s (N=O), 1153s (C–O, CO_2), 994m and 912m (C–H, alkene) and 845m (C–H, Ar); δ_H(300 MHz at 55 °C; $CDCl_3$) 1.41 (9H, s, $C(Me)_3$), 1.54 (1H, dd, *J* 8.7 and 5.4, C*H*H (cyclopropane)), 1.83 (1H, dd, *J* 8.7 and 5.4, CH*H* (cyclopropane)), 2.21 (1H, q, *J* 8.7, CH_2CHCH), 5.11 (1H, dd, *J* 10.3 and 1.7, C*H*HCH), 5.22 (1H, br s, NH), 5.22 (1H, d, *J* 13.5, C*H*HAr), 5.28 (1H, d, *J* 13.5, CH*H*Ar), 5.29 (1H, dd, *J* 17.2 and 1.7, CH*H*CH), 5.74 (1H, ddd, *J* 17.2, 10.3 and 8.7, CH_2CH), 7.46–7.54 (2H, m, C(3)H and C(5)H (Ar)) and 8.14–8.22 (2H, m, C(2)H and C(6)H (Ar)); δ_C(101 MHz; $CDCl_3$) 23.9 (CH_2 (cyclopropane)), 28.3 (C(*Me*)$_3$), 34.8 (CH_2CHCH), 40.8 (*C*CO$_2$), 65.5 (*C*H$_2$Ar), 80.3 (*C*(Me)$_3$), 118.2 (*C*H$_2$CH), 123.7 (C(2) and C(6) (Ar)), 128.1 (C(3) and C(5) (Ar)), 133.3 (CH_2*C*H), 143.2 (C(4) (Ar)), 147.8 (C(1) (Ar)), 155.7 (NCO_2) and 170.5 (CO_2); HRMS (ES, [M–C(Me)$_3$ + H]H$^+$) Found: 307.0922. Calc. for $C_{14}H_{15}N_2O_6$ 307.0930; *m*/*z* (ES) 363 (MH$^+$, 41%), 348 (26), 307 (100), 263 (97) and 136 (17), and *cis-(N-tert-butoxycarbonyl)-1-amino-1-(p-nitrobenzyloxycarbonyl)-2-ethenylcyclopropane Z*-**12** (170 mg, 11%) as a colourless solid;

mp 117–119 °C; ν_{max} (solid)/cm^{-1} 1732s (C=O), 1684s (C=O, NHCO), 1608w (C=C, Ar), 1507s and 1339s (N=O), 1157s (C–O, CO_2), 913m (C–H, alkene) and 846m (C–H, Ar); δ_H(300 MHz at 55 °C; $CDCl_3$) 1.27 (1H, dd, *J* 8.4 and 5.1, C*H*H (cyclopropane)), 1.41 (9H, s, $C(Me)_3$), 1.92 (1H, dd, *J* 8.4 and 5.1, CH*H* (cyclopropane)), 2.43 (1H, q, *J* 8.4, CH_2CHCH), 4.91 (1H, br s, NH), 5.21 (1H, d, *J* 13.7, C*H*HAr), 5.24 (1H, d, *J* 9.7, C*H*HCH), 5.27 (1H, d, *J* 13.7, CH*H*Ar), 5.28 (1H, d, *J* 17.2, CH*H*CH), 5.57 (1H, ddd, *J* 17.2, 9.7 and 8.4, CH_2CH), 7.44–7.54 (2H, m, C(3)H and C(5)H (Ar)) and 8.15–8.23 (2H, m, C(2)H and C(6)H (Ar)); δ_C(75.4 MHz; $CDCl_3$) 23.6 (CH_2 (cyclopropane)), 28.3 ($C(Me)_3$), 31.9 (CH_2CHCH), 39.4 (CCO_2), 65.7 (CH_2Ar), 80.4 ($C(Me)_3$), 118.9 (CH_2CH), 123.9 (C(2) and C(6) (Ar)), 128.1 (C(3) and C(5) (Ar)), 133.4 (CH_2CH), 143.1 (C(4) (Ar)), 147.8 (C(1) (Ar)), 156.0 (NCO_2) and 172.2 (CO_2); HRMS (ES, [M–$C(Me)_3$ + H]H$^+$) Found: 307.0922. Calc. for $C_{14}H_{15}N_2O_6$ 307.0930; *m*/*z* (ES) 363 (MH$^+$, 35%), 348 (17), 307 (89), 263 (100), 241 (6) and 136 (15).

p-Toluenesulfonyl (3,3-diphenyl-2-propenylidene) hydrazide 16[20]

The procedure outlined by Aggarwal *et al.*,[20] was followed: dropwise addition of β-phenyl-cinnamaldehyde (5 g, 24.0 mmol) in methanol (20 mL) to a mixture of *p*-toluenesulfonyl hydrazide (4.92 g, 26.4 mmol) in methanol (10 mL) resulted in the formation of a thick colourless precipitate. The mixture was stirred at RT for 1 h, cooled to 0 °C and the precipitate was collected by filtration and washed with methanol (5 mL). The solid was recrystallised from methanol to give the hydrazone **16** (8.56 g, 95%) as colourless crystals; mp 171 °C (from methanol) (lit.,[20] 172–174 °C); δ_H(300 MHz; $CDCl_3$) 2.43 (3H, s, Me), 6.80 (1H, d, *J* 9.7, C*H*CHN), 7.10–7.18 (2H, m, Ar*H*), 7.21–7.42 (11H, m, Ar*H* and CHC*H*N), 7.50 (1H, br s, NH) and 7.79–7.85 (2H, m, Ar*H*); LCMS 17.1 min, *m*/*z* (ES) 377 (MH$^+$, 100%).

p-Toluenesulfonyl (3,3-diphenyl-2-propenylidene)hydrazide sodium salt 17

Following the procedure of Aggarwal *et al.*,[20] for the synthesis of tosylhydrazone sodium salts: a 1 M solution of sodium methoxide was prepared by adding sodium (1 g, 43.5 mmol) to anhydrous methanol (43 mL) at 0 °C. 25 mL of this 1 M sodium methoxide solution was then added to *p*-toluenesulfonyl (3,3-diphenyl-2-propenylidene)hydrazide **16** (8.47 g, 22.5 mmol) under a nitrogen atmosphere. The resultant clear yellow solution was stirred for 15 min at RT and the solvent was removed under reduced pressure (85 mm Hg, 40 °C). Residual methanol was removed by azeotroping with toluene, then ethyl acetate, then chloroform under reduced pressure (5 mm Hg, 25 °C) to give *p-toluenesulfonyl (3,3-diphenyl-2-propenylidene)-hydrazide sodium salt* **17** (10.1 g, 113%) as a pale orange solid, which was kept away from direct sunlight, ground into a fine powder and stored at −20 °C prior to use; ν_{max} (solid)/cm^{-1} 1062s, 811m (C–H, Ts), 764m and 695s (C–H, Ph); δ_H(300 MHz; CD_3OD) 2.30 (3H, s, Me), 6.80 (1H, d, *J* 10.0, C*H*CHN), 7.05–7.34 (10H, m, Ar*H*), 7.43–7.51 (2H, m, Ar*H*), 7.54 (1H, d, *J* 10.0, CHC*H*N) and 7.63–7.74 (2H, m, Ar*H*); δ_C(75.4 MHz; CD_3OD) 20.0 (Me), 123.9 (Ph_2CCH), 126.8 and 126.9 (4C, CH (Ar)), 127.1 and 127.2 (2C, CH (Ar)), 127.9, 128.0, 128.5 and 130.2 (8C, CH (Ar)), 139.6, 140.7, 141.8, 142.0 and 143.4 (5C, 2C(1) (Ph), Ph_2CCH, C(1) and C(4) (Ar, Ts)) and 144.1 (CHN); HRMS (CI, [M–Ph + H]H$^+$) Found: 323.0834. Calc. for $C_{16}H_{16}N_2O_2SNa$ 323.0830; *m*/*z* (CI) 384 ([M–Me]H$^+$, 1%), 323 (1), 307 (3), 221 (41), 206 (17), 193 (100) and 91 (22).

cis- and *trans*-(*N*-*tert*-Butoxycarbonyl)-1-amino-1-(*p*-nitrobenzyloxycarbonyl)-2-(2,2-diphenylethenyl)cyclopropane 19

To a solution of *N*-(*tert*-butoxycarbonyl)-dehydroalanine *p*-nitrobenzyl ester **6** (100 mg, 311 μmol) in anhydrous dioxane (5 mL) under a nitrogen atmosphere, was added benzyltriethylammonium chloride (14 mg, 62.1 μmol) followed by *p*-toluenesulfonyl (3,3-diphenyl-2-propenylidene)hydrazide sodium salt **17** (185 mg, 466 μmol). The clear orange mixture was stirred at 40 °C for 15 h, by which time it had become cloudy and yellow in appearance, it was then allowed to return to RT. TLC (25 : 75 ethyl acetate/petrol) showed *trans*-**19** (R_f 0.32) and *cis*-**19** (R_f 0.22), both compounds were UV and potassium permanganate active. The reaction was quenched by the addition of water (10 mL) and ethyl acetate (10 mL). The layers were separated and the aqueous further extracted with ethyl acetate (4 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure (85 mm Hg, 40 °C) and this crude mixture was purified by column chromatography on silica using 25 : 75 ethyl acetate/petrol as eluent to give *trans-(N-tert-butoxycarbonyl)-1-amino-1-(p-nitrobenzyl-oxycarbonyl)-2-(2,2-diphenylethenyl)cyclopropane E*-**19** (93 mg, 58%) as a yellow solid; mp 146–148 °C; ν_{max} (solid)/cm^{-1} 1731m (CO_2), 1686s (C=O, NHCO), 1607w (C=C, Ar), 1508s (N=O), 1160s (C–O, CO_2), 845s (C–H, PNB), 768m, 739m, 705s and 699s (C–H, Ph); δ_H(300 MHz at 55 °C; $CDCl_3$) 1.41 (9H, s, $C(Me)_3$), 1.55 (1H, dd, *J* 9.3 and 5.4, C*H*H (cyclopropane)), 1.97 (1H, dd, *J* 8.1 and 5.4, CH*H* (cyclopropane)), 2.14 (1H, dd, *J* 9.3 and 8.1, Ph_2CCHCH), 5.00 (1H, br s, NH), 5.19 (1H, d, *J* 13.3, C*H*HAr (PNB)), 5.35 (1H, d, *J* 13.3, CH*H*Ar (PNB)), 5.94 (1H, d, *J* 9.3, Ph_2CCHCH), 7.00–7.42 (10H, m, PhH), 7.41–7.49 (2H, m, C(3)H and C(5)H (Ar, PNB)) and 8.00–8.08 (2H, m, C(2)H and C(6)H (Ar, PNB)); δ_C(75.5 MHz; $CDCl_3$) 25.3 (CH_2 (cyclopropane)), 28.2 ($C(Me)_3$), 32.5 (Ph_2CCHCH), 41.7 (CCO_2), 65.6 (CH_2Ar), 80.4 ($C(Me)_3$), 123.7 (C(2) and C(6) (Ar, PNB)), 124.1 (Ph_2CCHCH), 127.2 (2C, PhCH), 127.5, 127.5, 127.7 and 127.9 (4C, PhCH), 128.1 (C(3) and C(5) (Ar, PNB)), 128.4 (2C, PhCH), 130.1 and 130.1 (2C, PhCH), 139.6 and 141.6 (2C(1) (Ph)), 142.9 (C(4) (Ar, PNB)), 145.2 (Ph_2CCHCH) and 147.5 (C(1) (Ar, PNB)), 155.5 (NCO_2) and 170.8 (CO_2); HRMS (CI, [M–Boc + H]H$^+$) Found: 415.1657. Calc. for $C_{25}H_{23}N_2O_4$ 415.1658; *m*/*z* (CI) 469 ([M–NO_2]H$^+$, 1%), 441 (3), 415 (64), 398 (12), 335 (34), 234 (100), 167 (80), 122 (42) and 57 (66); LCMS 18.5 min, *m*/*z* (ES) 515 (MH$^+$, 100%), 459 (27) and 415 (6), and *cis-(N-tert-butoxycarbonyl)-1-amino-1-(p-nitrobenzyloxycarbonyl)-2-(2,2-diphenylethenyl)cyclopropane Z*-**19** (46 mg, 29%) as a yellow solid; mp 112–113 °C; ν_{max} (solid)/cm^{-1} 1727m (C=O, CO_2), 1693s (C=O, NHCO), 1607w (C=C, Ar), 1510s and 1338s (N=O), 1156s (C–O, CO_2), 844s (C–H, PNB), 762s, 737s and 696s (C–H, Ph); δ_H(300 MHz at 55 °C; $CDCl_3$) 1.42 (10H, s, $C(Me)_3$ and C*H*H (cyclopropane)), 1.98 (1H, dd, *J* 9.2 and 5.1, CH*H* (cyclopropane)), 2.46 (1H, q, *J* 9.2, Ph_2CCHCH), 5.06 (1H, br s, NH), 5.10 (1H, d, *J* 13.6, C*H*HAr (PNB)), 5.26 (1H, d, *J* 13.6, CH*H*Ar (PNB)), 5.69 (1H, d, *J* 9.2, Ph_2CCHCH), 7.15–7.35 (10H, m, PhH), 7.35–7.43 (2H, m, C(3)H and C(5)H (Ar, PNB)) and 8.11–8.19 (2H, m, C(2)H and C(6)H (Ar, PNB)); δ_C(101 MHz; $CDCl_3$) 25.3 (CH_2 (cyclopropane)), 28.1 (CCO_2), 28.3 ($C(Me)_3$), 30.1 (Ph_2CCHCH), 65.5 (CH_2Ar), 80.5 ($C(Me)_3$), 123.8 (C(2) and C(6) (Ar, PNB)), 124.4 (Ph_2CCHCH), 127.6 (PhCH), 127.6 (2C, PhCH), 127.6 (2C, PhCH), 128.1 (PhCH), 128.4, 128.5 and 130.0 (6C, 4PhCH, C(3) and C(5) (Ar, PNB)), 139.5 (2C, C(1) (Ph)), 142.1 (C(4) (Ar, PNB)), 143.1 (Ph_2CCHCH) and 147.7 (C(1) (Ar, PNB)), 156.1 (NCO_2) and 171.7 (CO_2); HRMS (CI, [M–Boc + H]H$^+$) Found: 415.1657. Calc. for $C_{25}H_{23}N_2O_4$ 415.1658; *m*/*z* (CI) 469 ([M–NO_2]H$^+$, 1%), 441 (3), 415 (64), 398 (10), 335 (28), 234 (100), 167 (84), 122 (52) and 57 (84); LCMS 17.9 min, *m*/*z* (ES) 515 (MH$^+$, 68%), 459 (100), 415 (45) and 398 (9).

N,N-Di-(*tert*-butoxycarbonyl)-dehydroalanine *p*-nitrobenzyl ester 21

To a solution of *N*-(*tert*-butoxycarbonyl)-dehydroalanine *p*-nitrobenzyl ester **6** (500 mg, 1.55 mmol) in anhydrous acetonitrile (5 mL) was added 4-(dimethylamino)pyridine (19

mg, 155 μmol) followed by di-*tert*-butyl dicarbonate (746 mg, 3.42 mmol). The yellow solution was stirred under nitrogen at RT for 22 h. Solvent was removed under reduced pressure (85 mm Hg, 40 °C), then diethyl ether (50 mL) and water (25 mL) was added to the resultant residue. The aqueous layer was acidified to pH 1 with saturated aqueous $KHSO_4$ and the layers were separated. The organic was washed sequentially, with water acidified to pH 1 with saturated aqueous $KHSO_4$ (3 × 25 mL), followed by saturated aqueous $NaHCO_3$ (3 × 25 mL), then saturated brine (3 × 25 mL). The organic extract was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure (85 mm Hg, 40 °C) to give *N,N-di-(tert-butoxycarbonyl)-dehydroalanine p-nitrobenzyl ester* **21** (550 mg, 84%) as colourless crystals; mp 64–66 °C; Found: C, 57.15; H, 6.6; N, 6.8; $C_{20}H_{26}N_2O_8$ requires C, 56.9; H, 6.2; N, 6.6%; ν_{max} (solid)/cm^{-1} 1761m, 1728m and 1709s (C=O), 1608m (C=C, Ar), 1522s and 1347s (N=O), 1275s, 1249s, 1156s, 1123s and 1078s (C–O, CO_2), 835m and 815s (C–H, Ar); δ_H(400 MHz; $CDCl_3$) 1.44 (18H, s, 2C(Me)$_3$), 5.34 (2H, s, CH_2Ar), 5.76 (1H, s, C*H*HC), 6.45 (1H, s, CH*H*C), 7.51–7.56 (2H, m, C(3)H and C(5)H (Ar)) and 8.20–8.25 (2H, m, C(2)H and C(6)H (Ar)); δ_C(101 MHz; $CDCl_3$) 27.9 (2C(*Me*)$_3$), 65.5 (CH_2Ar), 83.4 (2*C*(Me)$_3$), 123.8 (C(2) and C(6) (Ar)), 125.9 (*C*H$_2$C), 128.3 (C(3) and C(5) (Ar)), 135.9 (CH_2*C*), 142.8 (C(4) (Ar)), 147.9 (C(1) (Ar)), 150.7 (N(CO_2)$_2$) and 163.1 (CO_2); LCMS 16.7 min, *m/z* (ES) 423 (MH$^+$, 9%), 408 (9), 352 (61), 308 (100), 267 (45) and 223 (3).

cis- and *trans*-*N,N*-Di-(*tert*-butoxycarbonyl)-1-amino-1-methoxycarbonyl-2-(2,2-diphenylethenyl)cyclopropane 22

To a solution of *N,N*-di-(*tert*-butoxycarbonyl)-dehydroalanine methyl ester **20**[22] (3.03 g, 10.1 mmol) in anhydrous dioxane (70 mL) under a nitrogen atmosphere, was added benzyltriethylammonium chloride (458 mg, 2.01 mmol) followed by *p*-toluenesulfonyl (3,3-diphenyl-2-propenylidene)hydrazide sodium salt **17** (6.00 g, 15.1 mmol). The cloudy pale orange mixture was stirred at 40 °C for 24 h, it was then allowed to return to RT. TLC (15 : 85 ethyl acetate/petrol) showed the vinylcyclopropane **22** (R_f 0.32) UV and potassium permanganate active. The reaction was quenched by the addition of water (75 mL) and ethyl acetate (150 mL). The layers were separated and the aqueous further extracted with ethyl acetate (3 × 150 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure (85 mm Hg, 40 °C) and this crude mixture was dissolved in the minimum amount of dichloromethane and purified by filtration through silica using a gradient of ethyl acetate/petrol (5 : 95 ethyl acetate/petrol to 20 : 80 ethyl acetate/petrol) as eluent to give *cis*- and *trans-N,N-di-(tert-butoxycarbonyl)-1-amino-1-methoxycarbonyl-2-(2,2-diphenylethenyl)cyclopropane* **22** (4.47 g, 90%, 71 : 29 *trans*/*cis*) as a yellow oil which solidified upon standing; δ_H(270 MHz; $CDCl_3$) 1.34 (9H, s, C(Me)$_3$ (*cis*)), 1.41 (1H, dd, *J* 7.9 and 5.8, C*H*H (cyclopropane) (*cis*)), 1.43 (19H, br s, 2C(Me)$_3$ and C*H*H (cyclopropane) (*trans*)), 1.51 (9H, s, C(Me)$_3$ (*cis*)), 1.95 (1H, dd, *J* 9.4 and 5.8, CH*H* (cyclopropane) (*trans*)), 1.98 (1H, dd, *J* 9.7 and 5.8, CH*H* (cyclopropane) (*cis*)), 2.43 (1H, q, *J* 9.4, Ph_2CCHC*H* (*trans*)), 2.78 (1H, td, *J* 9.7 and 7.9, Ph_2CCHC*H* (*cis*)), 3.68 (3H, s, OMe (*cis*)), 3.79 (3H, s, OMe (*trans*)), 5.57 (1H, d, *J* 9.7, Ph_2CC*H*CH (*cis*)), 6.24 (1H, d, *J* 9.4, Ph_2CC*H*CH (*trans*)) and 7.08–7.46 (10H, m, PhH); δ_C(101 MHz; $CDCl_3$) 27.0 (CH_2 (cyclopropane) (*trans*)), 27.2 (CH_2 (cyclopropane) (*cis*)), 27.9 (C(*Me*)$_3$ (*cis*)), 28.0 (2C(*Me*)$_3$ (*trans*)), 28.2 (C(*Me*)$_3$ (*cis*)), 30.9 (Ph_2CCH*C*H (*cis*)), 35.2 (Ph_2CCH*C*H (*trans*)), 45.7 (*C*CO$_2$ (*cis*)), 45.9 (*C*CO$_2$ (*trans*)), 52.5 (OMe (*trans*)), 52.5 (OMe (*cis*)), 82.7 (*C*(Me)$_3$ (*trans*)), 82.8 (*C*(Me)$_3$ (*trans*)), 82.8 (*C*(Me)$_3$ (*cis*)), 82.9 (*C*(Me)$_3$ (*cis*)), 124.1 (Ph_2C*C*HCH (*trans*)), 125.3 (Ph_2C*C*HCH (*cis*)), 127.2 (PhCH (*trans*)), 127.3 (PhCH (*cis*)), 127.3 (PhCH (*trans*)), 127.4 (PhCH (*cis*)), 127.5 (2C, PhCH (*trans*)), 127.5 and 128.1 (4C, PhCH (*cis*)), 128.2 and 128.2 (4C, PhCH (*trans*)), 128.3 and 130.3 (4C, PhCH (*cis*)), 130.4 (2C, PhCH (*trans*)), 139.5 (C(1) (Ph) (*cis*)), 139.7 (C(1) (Ph) (*trans*)), 142.4 (C(1) (Ph) (*cis*)), 142.6 (C(1) (Ph) (*trans*)), 144.1 (Ph_2*C*CHCH (*cis*)), 144.2 (Ph_2*C*CHCH (*trans*)), 152.0 (N(CO_2)$_2$ (*trans*)), 152.7 (N(CO_2)$_2$ (*cis*)), 170.8 (CO_2 (*trans*)) and 171.9 (CO_2 (*cis*)), and impure product **22** was then purified by column chromatography on silica using 15 : 85 ethyl acetate/petrol as eluent to give *cis-N,N-di-(tert-butoxycarbonyl)-1-amino-1-methoxycarbonyl-2-(2,2-diphenylethenyl)cyclopropane Z*-**22** (496 mg, 10%) as a yellow solid; mp 155–157 °C; Found: C, 70.9; H, 7.1; N, 2.8; $C_{29}H_{35}NO_6$ requires C, 70.6; H, 7.15; N, 2.8%; ν_{max} (solid)/cm^{-1} 1743m, 1725s and 1702m (C=O), 1600w, 1576w and 1494w (C=C, Ar), 1363s (C–H, C(Me)$_3$), 1271s, 1250s, 1238s, 1162s, 1154s and 1117s (C–O, CO_2), 765s and 697s (C–H, Ar); δ_H(270 MHz; $CDCl_3$) 1.34 (9H, s, C(Me)$_3$), 1.41 (1H, dd, *J* 7.9 and 5.8, C*H*H (cyclopropane)), 1.51 (9H, s, C(Me)$_3$), 1.98 (1H, dd, *J* 9.7 and 5.8, CH*H* (cyclopropane)), 2.78 (1H, td, *J* 9.7 and 7.9, Ph_2CCHC*H*), 3.68 (3H, s, OMe), 5.57 (1H, d, *J* 9.7, Ph_2CC*H*CH) and 7.08–7.46 (10H, m, PhH); δ_C(101 MHz; $CDCl_3$) 27.2 (CH_2 (cyclopropane)), 27.9 (C(*Me*)$_3$), 28.2 (C(*Me*)$_3$), 30.9 (Ph_2CCH*C*H), 45.7 (*C*CO$_2$), 52.5 (OMe), 82.8 (*C*(Me)$_3$), 82.9 (*C*(Me)$_3$), 125.3 (Ph_2C*C*HCH), 127.3 and 127.4 (2C, PhCH), 127.5, 128.1, 128.3 and 130.3 (8C, PhCH), 139.5 and 142.4 (2C(1) (Ph)), 144.1 (Ph_2*C*CHCH), 152.7 (N(CO_2)$_2$) and 171.9 (CO_2); *m/z* (CI) 394 ([M–Boc + H]H$^+$, 1%), 294 (100) and 57 (96).

cis- and *trans*-*N,N*-Di-(*tert*-butoxycarbonyl)-1-amino-1-(*p*-nitrobenzyloxycarbonyl)-2-(2,2-diphenylethenyl)cyclopropane 23

To a solution of *N,N*-di-(*tert*-butoxycarbonyl)-dehydroalanine *p*-nitrobenzyl ester **21** (100 mg, 237 μmol) in anhydrous dioxane (5 mL) under a nitrogen atmosphere, was added benzyltriethylammonium chloride (11 mg, 47.4 μmol) followed by *p*-toluenesulfonyl (3,3-diphenyl-2-propenylidene)hydrazide sodium salt **17** (141 mg, 355 μmol). The cloudy pale brown mixture was stirred at 40 °C for 21 h, it was then allowed to return to RT. TLC (15 : 85 ethyl acetate/petrol) showed *trans*-**23** (R_f 0.32) and *cis*-**23** (R_f 0.25); both compounds were UV active. The reaction was quenched by the addition of water (10 mL) and ethyl acetate (10 mL). The layers were separated and the aqueous further extracted with ethyl acetate (4 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure (85 mm Hg, 40 °C) and this crude mixture was purified by column chromatography on silica using 15 : 85 ethyl acetate/petrol as eluent to give *trans-N,N-di-(tert-butoxycarbonyl)-1-amino-1-(p-nitrobenzyloxycarbonyl)-2-(2,2-diphenylethenyl)cyclopropane trans*-**23** (33 mg, 23%) as a colourless oil; ν_{max} (film)/cm^{-1} 1732m and 1710m (C=O), 1608w (C=C, Ar), 1523m and 1346s (N=O), 1273m, 1243m, 1154s, 1117s and 1095s (C–O, CO_2), 847m (C–H, PNB), 766s and 698s (C–H, Ph); δ_H(300 MHz at 55 °C; $CDCl_3$) 1.40 (18H, s, 2C(Me)$_3$), 1.52 (1H, dd, *J* 9.4 and 5.7, C*H*H (cyclopropane)), 1.95 (1H, dd, *J* 9.4 and 5.7, CH*H* (cyclopropane)), 2.48 (1H, q, *J* 9.4, Ph_2-CCHC*H*), 5.27 (1H, d, *J* 13.7, C*H*HAr (PNB)), 5.34 (1H, d, *J* 13.7, CH*H*Ar (PNB)), 6.17 (1H, d, *J* 9.4, Ph_2CC*H*CH), 7.06–7.38 (10H, m, PhH), 7.48–7.56 (2H, m, C(3)H and C(5)H (Ar, PNB)) and 8.13–8.19 (2H, m, C(2)H and C(6)H (Ar, PNB)); δ_C(101 MHz; $CDCl_3$) 27.2 (CH_2 (cyclopropane)), 28.0 (2C(*Me*)$_3$), 35.5 (Ph_2CCH*C*H), 45.9 (*C*CO$_2$), 65.6 (CH_2Ar), 83.1 (2*C*(Me)$_3$), 123.5 (Ph_2C*C*HCH), 123.8 (C(2) and C(6) (Ar, PNB)), 127.4 and 127.4 (2C, PhCH), 127.5, 128.2, 128.2, 128.2 and 130.4 (10C, 8PhCH, C(3) and C(5) (Ar, PNB)), 139.6 (C(1) (Ph)), 142.4 (C(1) (Ph)), 143.2 (C(4) (Ar, PNB)), 144.6 (Ph_2*C*-CHCH), 147.8 (C(1) (Ar, PNB)), 152.1 (N(CO_2)$_2$) and 170.1 (CO_2); HRMS (CI, [M–2Boc + 2H]H$^+$) Found: 415.1651. Calc. for $C_{25}H_{23}N_2O_4$ 415.1658; *m/z* (CI) 415 ([M–2Boc + 2H]H$^+$, 88%), 398 (12), 234 (100), 122 (22), 78 (6) and 57 (66).

A mixture of *cis- and trans-N,N-di-(tert-butoxycarbonyl)-1-amino-1-(p-nitrobenzyloxycarbonyl)-2-(2,2-diphenylethenyl)-cyclopropane cis*-**23** and *trans*-**23** was then eluted (28 mg, 19%,

61 : 39 *cis*/*trans*) as a colourless solid; δ_H(300 MHz at 55 °C; $CDCl_3$) 1.32 (9H, s, $C(Me)_3$ (*cis*)), 1.40 (18H, s, $2C(Me)_3$ (*trans*)), 1.46 (10H, s, $C(Me)_3$ and C*H*H (cyclopropane) (*cis*)), 1.52 (1H, dd, *J* 9.4 and 5.7, C*H*H (cyclopropane) (*trans*)), 1.95 (1H, dd, *J* 9.4 and 5.7, CH*H* (cyclopropane) (*trans*)), 2.00 (1H, dd, *J* 9.7 and 3.9, CH*H* (cyclopropane) (*cis*)), 2.48 (1H, q, *J* 9.4, Ph_2CCHCH (*trans*)), 2.81 (1H, td, *J* 9.7 and 8.1, Ph_2CCHCH (*cis*)), 5.17 (1H, d, *J* 13.8, C*H*HAr (PNB) (*cis*)), 5.25 (1H, d, *J* 13.8, CH*H*Ar (PNB) (*cis*)), 5.27 (1H, d, *J* 13.7, C*H*HAr (PNB) (*trans*)), 5.34 (1H, d, *J* 13.7, CH*H*Ar (PNB) (*trans*)), 5.58 (1H, d, *J* 9.7, Ph_2CCHCH (*cis*)), 6.17 (1H, d, *J* 9.4, Ph_2CCHCH (*trans*)), 7.08–7.38 (10H, m, PhH), 7.38–7.46 (2H, m, C(3)H and C(5)H (Ar, PNB) (*cis*)), 7.48–7.56 (2H, m, C(3)H and C(5)H (Ar, PNB) (*trans*)) and 8.13–8.19 (2H, m, C(2)H and C(6)H (Ar, PNB)); δ_C(101 MHz; $CDCl_3$) 27.2 (CH_2 (cyclopropane) (*trans*)), 27.5 (CH_2 (cyclopropane) (*cis*)), 27.8 ($C(Me)_3$ (*cis*)), 28.0 ($2C(Me)_3$ (*trans*)), 28.1 ($C(Me)_3$ (*cis*)), 31.3 (Ph_2CCHCH (*cis*)), 35.5 (Ph_2CCHCH (*trans*)), 45.6 (CCO_2 (*cis*)), 45.9 (CCO_2 (*trans*)), 65.5 (CH_2Ar (*cis*)), 65.6 (CH_2Ar (*trans*)), 83.0 ($C(Me)_3$ (*cis*)), 83.1 ($2C(Me)_3$ (*trans*)), 83.2 ($C(Me)_3$ (*cis*)), 123.5 (Ph_2CCHCH (*trans*)), 123.7 (C(2) and C(6) (Ar, PNB) (*cis*)), 123.8 (C(2) and C(6) (Ar, PNB) (*trans*)), 124.7 (Ph_2CCHCH (*cis*)), 127.4, 127.4 and 127.5 (4C, PhCH (*trans*)), 127.5, 127.9 and 128.1 (6C, PhCH (*cis*)), 128.2 (2C, PhCH (*trans*)), 128.2 (C(3) and C(5) (Ar, PNB)), 128.2 (2C, PhCH (*trans*)), 128.3 and 130.2 (4C, PhCH (*cis*)), 130.4 (2C, PhCH (*trans*)), 139.5 (C(1) (Ph) (*cis*)), 139.6 (C(1) (Ph) (*trans*)), 142.2 (C(1) (Ph) (*cis*)), 142.4 (C(1) (Ph) (*trans*)), 143.2 (C(4) (Ar, PNB) (*trans*)), 143.2 (C(4) (Ar, PNB) (*cis*)), 144.6 (Ph_2CCHCH (*trans*)), 144.8 (Ph_2CCHCH (*cis*)), 147.7 (C(1) (Ar, PNB) (*cis*)), 147.8 (C(1) (Ar, PNB) (*trans*)), 152.1 ($N(CO_2)_2$ (*trans*)), 152.1 (NCO_2 (*cis*)), 152.8 (NCO_2 (*cis*)), 170.1 (CO_2 (*trans*)) and 171.0 (CO_2 (*cis*)).

cis- and *trans*-(*N*-*tert*-Butoxycarbonyl)-1-amino-1-carboxyl-2-(2,2-diphenylethenyl)cyclopropane 24

The *p*-nitrobenzyl group was removed using an adaptation of a procedure described by Kumagai *et al.*[23] The zinc powder was activated using the procedure of Shiner and Neumann;[24] zinc powder (16.0 g, 245 mmol) was washed with 1 M HCl (100 mL), the zinc was filtered then further washed with 1 M HCl (100 mL), followed by sequential washing with water (3 × 100 mL), ethanol (2 × 50 mL) and diethyl ether (50 mL), the zinc was filtered between each washing. The phosphate buffer solution was prepared by the addition of a 0.35 M solution of K_2HPO_4 to a 0.35 M solution of KH_2PO_4 until pH 6 was achieved and was stored at RT until required. The freshly activated zinc powder (16.0 g, 245 mmol) was added to a solution of *cis*- and *trans*-(*N*-*tert*-butoxycarbonyl)-1-amino-1-(*p*-nitrobenzyloxycarbonyl)-2-(2,2-diphenylethenyl)cyclopropane **19** (2 g, 3.89 mmol, 77 : 23 *trans*/*cis*) in tetrahydrofuran (120 mL) and 0.35 M phosphate buffer (pH 6) (120 mL). The reaction mixture was stirred at RT in a stoppered flask for 2 d. TLC (70 : 30 ethyl acetate/petrol) showed *trans*-**24** (R_f 0.23) and *cis*-**24** (R_f 0.11); both compounds were UV and potassium permanganate active. The reaction mixture was filtered through Celite, then water (200 mL) and ethyl acetate (200 mL) were passed through the filter. The aqueous layer of the filtrate was acidified (to pH 1) with 2 M HCl, the layers were separated and the aqueous was extracted with ethyl acetate (3 × 200 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure (85 mm Hg, 40 °C) and this crude mixture was purified by column chromatography on silica using 70 : 30 ethyl acetate/petrol as eluent to give *trans-(N-tert-butoxycarbonyl)-1-amino-1-carboxyl-2-(2,2-diphenylethenyl)-cyclopropane* **24** (910 mg, 62%) as a yellow solid; a sample of *trans*-**24** was recrystallised from chloroform/pentane by vapour diffusion to give single crystals suitable for X-ray crystallographic analysis (data presented in ESI †); mp 122–125 °C; ν_{max} (solid)/cm^{-1} 2977w (O–H), 1683br s (C=O), 1598w (C=C, Ar), 1163s (C–O, CO_2), 761s and 700s (C–H, Ar); δ_H(300 MHz at 55 °C; $CDCl_3$) 1.42 (9H, s, $C(Me)_3$), 1.49 (1H, dd, *J* 8.9 and 5.4, C*H*H (cyclopropane)), 1.92 (1H, dd, *J* 8.9 and 5.4, CH*H* (cyclopropane)), 2.16 (1H, q, *J* 8.9, Ph_2CCHCH), 5.03 (1H, br s, NH), 5.98 (1H, d, *J* 8.9, Ph_2CCHCH) and 7.13–7.42 (10H, m, PhH); δ_C(75.5 MHz; $CDCl_3$) 24.3 (CH_2 (cyclopropane)), 28.2 ($C(Me)_3$), 31.5 (Ph_2CCHCH), 42.6 (CCO_2), 80.2 ($C(Me)_3$), 126.1 (Ph_2CCHCH), 126.8 and 127.0 (2C, PhCH), 127.4, 128.0, 128.1 and 130.5 (8C, PhCH), 140.1 and 142.3 (2C(1) (Ph)), 143.2 (Ph_2CCHCH), 157.0 (NCO_2) and 176.3 (CO_2); HRMS (CI, [M–Boc + H]H^+) Found: 280.1336. Calc. for $C_{18}H_{18}NO_2$ 280.1338; *m*/*z* (CI) 324 ([M–^{t}Bu + H]H^+, 6%), 306 (30), 280 (70), 234 (92), 117 (12) and 57 (100); LCMS 16.3 min, *m*/*z* (ES) 380 (MH^+, 88%), 365 (8), 324 (41) and 280 (100), and *cis-(N-tert-butoxycarbonyl)-1-amino-1-carboxyl-2-(2,2-diphenylethenyl)cyclopropane cis*-**24** (268 mg, 18%) as a yellow solid; mp 111–114 °C; ν_{max} (solid)/cm^{-1} 2981w, 2932w and 2576w (O–H), 1701s (C=O, CO_2), 1655m (C=O, NHCO), 1599w (C=C, Ar), 1395m and 1368m (O–H), 1160s (C–O, CO_2), 765m and 698s (C–H, Ar); δ_H(300 MHz at 55 °C; $CDCl_3$) 1.31 (1H, br t, *J* 5.5, C*H*H (cyclopropane)), 1.44 (9H, s, $C(Me)_3$), 1.95 (1H, dd, *J* 9.0 and 5.5, CH*H* (cyclopropane)), 2.46 (1H, q, *J* 9.0, Ph_2CCHCH), 5.12 (1H, br s, NH), 5.66 (1H, d, *J* 9.0, Ph_2CCHCH) and 7.17–7.40 (10H, m, PhH); δ_C(75.5 MHz; $CDCl_3$) 25.3 (CH_2 (cyclopropane)), 28.3 ($C(Me)_3$), 30.3 (Ph_2CCHCH), 33.1 (CCO_2), 80.8 ($C(Me)_3$), 124.2 (Ph_2CCHCH), 127.3 (PhCH), 127.5 and 128.2 (4C, PhCH), 128.2, 128.4, 128.4, 130.1 and 130.3 (5C, PhCH), 139.9 and 142.0 (2C(1) (Ph)), 145.1 (Ph_2CCHCH), 156.7 (NCO_2); HRMS (CI, [M–Boc + H]H^+) Found: 280.1329. Calc. for $C_{18}H_{18}NO_2$ 280.1338; *m*/*z* (CI) 380 (MH^+, 1%), 324 (16), 306 (47), 280 (77), 234 (100), 117 (21) and 57 (85); LCMS 16.2 min, *m*/*z* (ES) 380 (MH^+, 72%), 365 (9), 324 (42) and 280 (100).

cis- and *trans*-*N,N*-Di-(*tert*-butoxycarbonyl)-1-amino-1-methoxycarbonyl-2-carboxycyclopropane 25

To *cis*- and *trans*-*N,N*-di-(*tert*-butoxycarbonyl)-1-amino-1-methoxycarbonyl-2-(2,2-diphenylethenyl)cyclopropane **22** (5 g, 10.1 mmol, 71 : 29 *trans*/*cis*) in carbon tetrachloride (50 mL), acetonitrile (50 mL) and water (75 mL) was added sodium metaperiodate (10.8 g, 50.7 mmol).[25] Ruthenium trichloride hydrate (63 mg, 304 μmol) was added, to initially give a cloudy brown mixture, which was stirred vigorously at RT for 2 h. TLC (40 : 60 ethyl acetate/hexane) showed vinylcyclopropane **22** (R_f 0.29; UV and molybdophosphoric acid active). Therefore further sodium metaperiodate (6.94 g, 32.4 mmol) and ruthenium trichloride hydrate (29 mg, 140 μmol) was added and the reaction was stirred at RT for an additional 1 h. Dichloromethane (250 mL) and water (250 mL) were added, the layers were separated and the aqueous layer extracted with dichloromethane (3 × 250 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure (85 mm Hg, 40 °C). Diethyl ether (250 mL) was added and ruthenium residues were removed by filtration through Celite. Saturated aqueous $NaHCO_3$ (250 mL) was added to the filtrate, the layers were separated and benzophenone was removed by extraction with ethyl acetate (2 × 250 mL). Ethyl acetate (250 mL) was added to the aqueous, which was then acidified to pH 1 conc. HCl, the layers were separated and the aqueous layer extracted with ethyl acetate (3 × 250 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure (85 mm Hg, 40 °C) to give *cis- and trans-N,N-di-(tert-butoxycarbonyl)-1-amino-1-methoxycarbonyl-2-carboxycyclopropane* **25** (2.48 g, 68%, 71 : 29 *trans*/*cis*) as a yellow oil; Found: C, 52.6; H, 7.2; N, 3.6; $4C_{16}H_{25}NO_8.1H_2O$ requires C, 52.8; H, 7.1; N, 3.85%; ν_{max} (film)/cm^{-1} 2980w (O–H), 1737s and 1711s (C=O), 1395m and 1368s (O–H), 1276s, 1252s, 1155s and 1118s (C–O, CO_2); δ_H(400

MHz; $CDCl_3$) 1.44 (9H, s, $C(Me)_3$ (*cis*)), 1.51 (9H, s, $C(Me)_3$ (*cis*)), 1.52 (18H, s, $2C(Me)_3$ (*trans*)), 1.58 (1H, dd, *J* 9.5 and 6.4, C*H*H (cyclopropane) (*trans*)), 1.86 (1H, dd, *J* 8.5 and 6.0, C*H*H (cyclopropane) (*cis*)), 2.11 (1H, dd, *J* 8.5 and 6.0, CH*H* (cyclopropane) (*cis*)), 2.31 (1H, dd, *J* 9.5 and 6.4, CH*H* (cyclopropane) (*trans*)), 2.50 (1H, t, *J* 9.5, $CHCO_2$ (*trans*)), 2.77 (1H, t, *J* 8.5, $CHCO_2$ (*cis*)), 3.73 (3H, s, OMe (*trans*)), 3.75 (3H, s, OMe (*cis*)) and 9.10 (1H, br s, CO_2H); δ_C(75.4 MHz; $CDCl_3$) 22.8 (CH_2 (cyclopropane) (*trans*)), 25.3 (CH_2 (cyclopropane) (*cis*)), 27.8 ($C(Me)_3$ (*cis*)), 28.0 ($2C(Me)_3$ (*trans*)), 28.1 ($C(Me)_3$ (*cis*)), 31.5 ($CHCO_2$ (*cis*)), 35.3 ($CHCO_2$ (*trans*)), 44.1 (CCO_2 (*trans*)), 45.4 (CCO_2 (*cis*)), 53.0 (OMe (*trans*)), 53.2 (OMe (*cis*)), 83.2 ($C(Me)_3$ (*cis*)), 83.3 ($C(Me)_3$ (*cis*)), 84.2 ($2C(Me)_3$ (*trans*)), 151.4 ($N(CO_2)_2$ (*cis*)), 151.9 ($N(CO_2)_2$ (*trans*)), 169.3 (CO_2 (*trans*)), 170.3 (CO_2 (*trans*)), 170.4 (CO_2 (*cis*)) and 174.6 (CO_2 (*cis*)); *m*/*z* (CI) 360 (MH^+, 1%), 304 (12), 260 (10), 84 (100) and 57 (94).

cis- and *trans*-*N,N*-Di-(*tert*-butoxycarbonyl)-1-amino-1,2-dimethoxycarbonylcyclopropane 26

To a solution of *cis*- and *trans*-*N,N*-di-(*tert*-butoxycarbonyl)-1-amino-1-methoxycarbonyl-2-carboxycyclopropane **25** (781 mg, 2.18 mmol, 58 : 42 *trans*/*cis*) in dichloromethane (20 mL) was added an ethereal solution of diazomethane (*ca.* 80 mL); addition was stopped once the reaction mixture acquired the characteristic bright yellow colour of diazomethane. The mixture was stirred for 1 h; TLC (20 : 80 ethyl acetate/petrol) showed *cis*-**26** (R_f 0.30) and *trans*-**26** (R_f 0.23); both compounds were potassium permanganate active. Excess diazomethane was quenched by the addition of acetic acid. The solvent was removed under reduced pressure (85 mm Hg, 40 °C) to give a crude yellow oil. This mixture was purified by column chromatography on silica using 20 : 80 ethyl acetate/petrol as eluent to give *cis-N,N-di-(tert-butoxycarbonyl)-1-amino-1,2-dimethoxycarbonylcyclopropane Z*-**26** (297 mg, 37%) as a colourless solid; mp 93–95 °C; Found: C, 55.0; H, 7.5; N, 3.6; $C_{17}H_{27}NO_8$ requires C, 54.7; H, 7.3; N, 3.75%; ν_{max} (solid)/cm^{-1} 1746s, 1734s and 1707s (C=O), 1394m and 1362s (C–H, $C(Me)_3$), 1272s, 1241s, 1156s, 1120s and 1083s (C–O, CO_2); δ_H(300 MHz; $CDCl_3$) 1.45 (9H, s, $C(Me)_3$), 1.51 (9H, s, $C(Me)_3$), 1.85 (1H, dd, *J* 8.0 and 5.9, C*H*H (cyclopropane)), 2.07 (1H, dd, *J* 9.0 and 5.9, CH*H* (cyclopropane)), 2.79 (1H, dd, *J* 9.0 and 8.0, $CHCO_2$), 3.70 (3H, s, OMe) and 3.74 (3H, s, OMe); δ_C(75.4 MHz; $CDCl_3$) 24.7 (CH_2 (cyclopropane)), 27.9 ($C(Me)_3$), 28.1 ($C(Me)_3$), 31.5 ($CHCO_2$), 44.9 (CCO_2), 52.2 (OMe), 53.1 (OMe), 83.0 ($C(Me)_3$), 83.1 ($C(Me)_3$), 151.9 (NCO_2), 152.1 (NCO_2), 169.3 (CO_2) and 170.6 (CO_2); *m*/*z* (CI) 174 ([M–2Boc + 2H]H^+, 28%) and 57 (100), and *trans-N,N-di-(tert-butoxycarbonyl)-1-amino-1,2-dimethoxycarbonylcyclopropane E*-**26** (412 mg, 51%) as a colourless oil; ν_{max} (film)/cm^{-1} 1737s (C=O), 1393w and 1368m (C–H, $C(Me)_3$), 1274s, 1248s, 1155s, 1117s and 1094s (C–O, CO_2); δ_H(400 MHz; $CDCl_3$) 1.51 (19H, br s, $2C(Me)_3$ and C*H*H (cyclopropane)), 2.27 (1H, dd, *J* 8.7 and 6.4, CH*H* (cyclopropane)), 2.50 (1H, dd, *J* 10.1 and 8.7, $CHCO_2$), 3.72 (3H, s, OMe) and 3.72 (3H, s, OMe); δ_C(101 MHz; $CDCl_3$) 22.8 (CH_2 (cyclopropane)), 28.0 ($2C(Me)_3$), 34.6 ($CHCO_2$), 44.1 (CCO_2), 52.3 (OMe), 52.7 (OMe), 83.4 ($2C(Me)_3$), 151.8 ($N(CO_2)_2$), 167.9 (CO_2) and 169.4 (CO_2); HRMS (CI, [M–2Boc + 2H]H^+) Found: 174.0761. Calc. for $C_7H_{12}NO_4$ 174.0766; *m*/*z* (CI) 359 ([M–Me]H^+, 1%), 274 (30), 218 (96), 174 (100) and 57 (78).

cis- and *trans*-*N,N*-Di-(*tert*-butoxycarbonyl)-1-amino-1-(*p*-nitrobenzyloxycarbonyl)-2-formylcyclopropane 27

A solution of *cis*- and *trans*-*N,N*-di-(*tert*-butoxycarbonyl)-1-amino-1-(*p*-nitrobenzyloxycarbonyl)-2-(2,2-diphenylethenyl) cyclopropane **23** (1.52 g, 2.48 mmol, 93 : 7 *trans*/*cis*) in dichloromethane (40 mL) was cooled to −78 °C. Ozone was passed through the reaction mixture until the solution acquired the characteristic blue colour. Excess ozone was removed by passing oxygen through the mixture. Methyl sulfide (218 μL, 2.97 mmol) was then added. The pale yellow solution was allowed to return to RT; TLC (25 : 75 ethyl acetate/petrol) showed benzophenone (R_f 0.57) and the aldehyde **27** (R_f 0.19); both compounds were UV active. Dichloromethane (50 mL) was then added and the solution washed with water (3 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure (85 mm Hg, 40 °C) and this crude mixture was purified by column chromatography on silica using 25 : 75 ethyl acetate/petrol as eluent to give *cis- and trans-N,N-di-(tert-butoxycarbonyl)-1-amino-1-(p-nitrobenzyloxycarbonyl)-2-formylcyclopropane* **27** (760 mg, 66%, 90 : 10 *trans*/*cis*) as a colourless solid; mp 112–113 °C; ν_{max} (solid)/cm^{-1} 1787m, 1732m and 1710m (C=O), 1526m and 1349m (N=O), 1278m, 1152s and 1094s (C–O, CO_2) and 846m (C–H, Ar); δ_H(400 MHz; $CDCl_3$) 1.40 (9H, s, $C(Me)_3$ (*cis*)), 1.45 (18H, s, $2C(Me)_3$ (*trans*)), 1.50 (9H, s, $C(Me)_3$ (*cis*)), 1.85 (1H, dd, *J* 9.3 and 6.4, C*H*H (cyclopropane) (*trans*)), 1.96 (1H, dd, *J* 7.8 and 6.4, CH*H* (cyclopropane) (*cis*)), 2.19 (1H, dd, *J* 9.3 and 6.4, CH*H* (cyclopropane) (*cis*)), 2.38 (1H, ddd, *J* 9.3, 8.3 and 5.4, C*H*CHO (*trans*)), 2.52 (1H, dd, *J* 8.3 and 6.4, CH*H* (cyclopropane) (*trans*)), 2.94 (1H, ddd, *J* 9.3, 7.8 and 4.4, C*H*CHO (*cis*)), 5.27 (1H, d, *J* 13.7, C*H*HAr), 5.34 (1H, d, *J* 13.7, CH*H*Ar), 7.48–7.54 (2H, m, C(3)H and C(5)H (Ar)), 8.20–8.25 (2H, m, C(2)H and C(6)H (Ar)), 9.30 (1H, d, *J* 4.4, CHO (*cis*)) and 9.48 (1H, d, *J* 5.4, CHO (*trans*)); δ_C(75.5 MHz; $CDCl_3$) 24.5 (CH_2 (cyclopropane)), 27.9 ($2C(Me)_3$), 42.1 ($CHCHO$), 45.7 (CCO_2), 66.2 (CH_2Ar), 83.9 ($2C(Me)_3$), 123.8 (C(2) and C(6) (Ar)), 128.3 (C(3) and C(5) (Ar)), 142.2 (C(4) (Ar)), 147.8 (C(1) (Ar)), 151.5 ($N(CO_2)_2$), 169.4 (CO_2) and 196.7 (CHO); HRMS (CI, [M–2Boc + 2H]H^+) Found: 265.0829. Calc. for $C_{12}H_{13}N_2O_5$ 265.0824; *m*/*z* (CI) 265 ([M–2Boc + 2H]H^+, 100%), 122 (78) and 57 (46).

cis- and *trans*-*N,N*-Di-(*tert*-butoxycarbonyl)-1-amino-1-(*p*-nitrobenzyloxycarbonyl)-2-[2-(diethoxy-phosphoryl)-2,2-difluoro-1-hydroxy-ethyl]-cyclopropane 28

Diethyl [difluoro(trimethylsilyl)methyl]phosphonate (922 μL, 3.82 mmol) was added to a solution of *cis*- and *trans*-*N,N*-di-(*tert*-butoxycarbonyl)-1-amino-1-(*p*-nitrobenzyloxycarbonyl)-2-formylcyclopropane **27** (1.69 g, 3.63 mmol, 90 : 10 *trans*/*cis*) in anhydrous tetrahydrofuran (20 mL). The solution was cooled to −60 °C, tetrabutylammonium fluoride (436 μL, 436 μmol, 1 M solution in tetrahydrofuran) was added and the reaction was stirred for 1 h. Further diethyl [difluoro(trimethylsilyl)methyl]-phosphonate (922 μL, 3.82 mmol) and tetrabutylammonium fluoride (436 μL, 436 μmol, 1 M solution in tetrahydrofuran) were added and the mixture was allowed to return to RT slowly and stirred for an additional 18 h. TLC (25 : 75 ethyl acetate/petrol) showed aldehyde **27** (R_f 0.26; UV and molybdophosphoric acid active), diethyl (difluoromethyl)phosphonate (R_f 0.14; weakly molybdophosphoric acid active) and the difluoromethylene phosphonate **28** (R_f 0.04; UV and weakly molybdophosphoric acid active). Solvent was evaporated under reduced pressure (85 mm Hg, 40 °C) to give a brown oil. This mixture was purified by column chromatography on silica using 25 : 75 ethyl acetate/petrol as eluent to give *trans-N,N-di-(tert-butoxycarbonyl)-1-amino-1-(p-nitrobenzyloxycarbonyl)-2-[2-(diethoxy-phosphoryl)-2,2-difluoro-1-hydroxy-ethyl]-cyclopropane* **28** (442 mg, 19%) as a colourless oil; ν_{max} (film)/cm^{-1} 1736m (C=O, CO_2), 1696m (C=O, NCO_2), 1608w (C=C, Ar), 1525m (N=O), 1367m (O–H), 1348m (N=O), 1272s (P=O), 1158s (C–O, CO_2), 1121s and 1015s (C–F), 846m (C–H, Ar) and 734s (C–F); δ_H(300 MHz; $CDCl_3$) 1.38 (6H, t, *J* 7.2, $2CH_2Me$), 1.46 (9H, s, $C(Me)_3$), 1.47 (9H, s, $C(Me)_3$), 1.62 (1H, dd, *J* 9.5 and 6.2, C*H*H (cyclopropane)), 2.11 (1H, dd, *J* 9.5 and 6.2, CH*H* (cyclopropane)), 2.24 (1H, q, *J* 9.5, C*H*CHOH), 4.04–4.22 (1H, m, C*H*OH), 4.22–4.40 (4H, m, $2CH_2Me$), 5.26

(1H, d, *J* 13.8, C*H*HAr), 5.34 (1H, d, *J* 13.8, CH*H*Ar), 7.46–7.54 (2H, m, C(3)H and C(5)H (Ar)) and 8.16–8.24 (2H, m, C(2)H and C(6)H (Ar)); δ_C(75.4 MHz; $CDCl_3$) 16.5 (CH_2*Me*), 16.6 (CH_2*Me*), 25.0 (CH_2 (cyclopropane)), 28.1 (C(*Me*)$_3$), 28.1 (C(*Me*)$_3$), 33.8 (1C, dd, $^3J_{CF}$ 6.6 and 4.3, *C*HCHOH), 41.9 (*C*CO_2), 64.8 (2C, d, $^2J_{CP}$ 6.9, 2*C*H_2Me), 66.1 (CH_2Ar), 69.6–70.3 (1C, m, *C*HOH), 83.8 (*C*(Me)$_3$), 84.7 (*C*(Me)$_3$), 123.9 (C(2) and C(6) (Ar)), 128.2 (C(3) and C(5) (Ar)), 143.0 (C(4) (Ar)), 147.8 (C(1) (Ar)), 151.9 (N$(CO_2)_2$) and 169.5 (CO_2); δ_F(282 MHz; $CDCl_3$) −122.7 (1F, ddd, $^2J_{FF}$ 305.8, $^2J_{FP}$ 102.6 and $^3J_{FH}$ 14.6, C*F*F) and −117.7 (1F, ddd, $^2J_{FF}$ 305.8, $^2J_{FP}$ 99.6 and $^3J_{FH}$ 9.2, CF*F*); δ_P(121 MHz; $CDCl_3$) 6.86 (dd, $^2J_{PF}$ 102.6 and 99.6); HRMS (CI, [M–2Boc + 2H]H$^+$) Found: 453.1239. Calc. for $C_{17}H_{24}F_2N_2O_8P$ 453.1238; *m*/*z* (CI) 480 ([M–O^{t}Bu–Boc + H]H$^+$, 34%), 454 (34), 345 (76), 301 (76), 217 (6), 188 (6), 154 (78), 138 (36) and 57 (100).

trans-*N*,*N*-Di-(*tert*-butoxycarbonyl)-1-amino-1-(*p*-nitrobenzyloxycarbonyl)-2-[2-(diethoxy-phosphoryl)-2,2-difluoro-1-carbonyl-ethyl]-cyclopropane 29

Under nitrogen, *cis*- and *trans*-*N*,*N*-di-(*tert*-butoxycarbonyl)-1-amino-1-(*p*-nitrobenzyloxycarbonyl)-2-[2-(diethoxy-phosphoryl)-2,2-difluoro-1-hydroxy-ethyl]-cyclopropane **28** (279 mg, 428 μmol) in anhydrous dichloromethane (5 mL) was added to a mixture of Dess–Martin periodinane[26] (454 mg, 1.07 mmol) in anhydrous dichloromethane (5 mL), to give a cloudy pale pink mixture. TLC (40 : 60 ethyl acetate/petrol) showed the α-difluoroketone **29** (R_f 0.22), UV active. The reaction was quenched by the addition of a solution of saturated aqueous $NaHCO_3$ (10 mL) containing $Na_2S_2O_3$ (1.85 g, 11.7 mmol). This biphasic mixture was stirred vigorously for 15 min, the layers were separated and the aqueous further extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (3 × 20 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure (85 mm Hg, 40 °C) and this crude mixture was purified by column chromatography on silica using 40 : 60 ethyl acetate/petrol as eluent to give *trans-N,N-di-(tert-butoxycarbonyl)-1-amino-1-(p-nitrobenzyloxycarbonyl)-2-[2-(diethoxy-phosphoryl)-2,2-difluoro-1-carbonyl-ethyl]-cyclopropane* **29** (202 mg, 72%) as a colourless oil; ν_{max} (film)/cm^{-1} 1745m and 1717m (C=O), 1608w (C=C, Ar), 1524m and 1348s (N=O), 1273s (P=O), 1158s (C–O, CO_2), 1118s, 1095s and 1015s (C–F), 850m (C–H, Ar) and 739m (C–F); δ_H(300 MHz; $CDCl_3$) 1.37 (3H, t, *J* 7.1, CH_2Me), 1.39 (3H, t, *J* 7.1, CH_2Me), 1.46 (18H, s, 2C(Me)$_3$), 1.73 (1H, dd, *J* 9.9 and 6.0, C*H*H (cyclopropane)), 2.51 (1H, dd, *J* 9.9 and 6.0, CH*H* (cyclopropane)), 3.13 (1H, t, *J* 9.9, CHCO), 4.23–4.40 (4H, m, 2C*H*$_2$Me), 5.22 (1H, d, *J* 13.5, C*H*HAr), 5.34 (1H, d, *J* 13.5, CH*H*Ar), 7.48–7.55 (2H, m, C(3)H and C(5)H (Ar)) and 8.17–8.24 (2H, m, C(2)H and C(6)H (Ar)); δ_C(75.4 MHz; $CDCl_3$) 16.3 (CH_2*Me*), 16.4 (CH_2*Me*), 24.1 (CH_2 (cyclopropane)), 27.9 (2C(*Me*)$_3$), 37.0 (*C*HCO), 45.0 (*C*CO_2), 65.6 (2C, d, $^2J_{CP}$ 6.3, 2*C*H_2Me), 66.1 (CH_2Ar), 83.7 (2*C*(Me)$_3$), 123.7 (C(2) and C(6) (Ar)), 128.4 (C(3) and C(5) (Ar)), 142.7 (C(4) (Ar)), 147.7 (C(1) (Ar)), 151.8 (N$(CO_2)_2$), 168.0 (CO_2) and 191.7 (1C, td, $^2J_{CF}$ 24.9 and $^2J_{CP}$ 15.4, CO); δ_F(282 MHz; $CDCl_3$) −117.1 (1F, dd, $^2J_{FF}$ 317.9 and $^2J_{FP}$ 96.0, C*F*F) and −115.3 (1F, dd, $^2J_{FF}$ 317.9 and $^2J_{FP}$ 96.0, CF*F*); δ_P(121 MHz; $CDCl_3$) 3.41 (t, $^2J_{PF}$ 96.0); HRMS (CI, [M–2Boc + 2H]H$^+$) Found: 451.1084. Calc. for $C_{17}H_{22}F_2N_2O_8P$ 451.1082; *m*/*z* (CI) 451 ([M–2Boc + 2H]H$^+$, 52%), 413 (100), 138 (26), 122 (12) and 57 (94); LCMS 4.59 min, *m*/*z* (ES) 692 ([M + MeCN]H$^+$, 40%), 691 (81), 673 (100), 651 (15) and 551 (78).

trans-*N*,*N*-Di-(*tert*-butoxycarbonyl)-1-amino-1-carboxyl-2-[2-(diethoxy-phosphoryl)-2,2-difluoro-1-carbonyl-ethyl]-cyclopropane 30

Freshly activated zinc powder (1.77 g, 27.1 mmol) was added to a vigorously stirred solution of *trans*-*N*,*N*-di-(*tert*-butoxycarbonyl)-1-amino-1-(*p*-nitrobenzyloxycarbonyl)-2-[2-(diethoxy-phosphoryl)-2,2-difluoro-1-carbonyl-ethyl]-cyclopropane **29** (280 mg, 430 μmol) in tetrahydrofuran (20 mL) and 0.35 M phosphate buffer (pH 6) (20 mL). The reaction mixture was stirred at RT for 18 h in a stoppered flask. TLC (10 : 90 methanol/ethyl acetate) showed *trans*-**30** (R_f 0.13) molybdophosphoric acid active. The reaction mixture was filtered through Celite then water (50 mL) and ethyl acetate (50 mL) were passed through the filter. The aqueous layer of the filtrate was acidified (to pH 1) with 2 M HCl, the layers were separated and the aqueous was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure (85 mm Hg, 40 °C) to give an orange oil, which was purified by column chromatography on silica using 10 : 90 methanol/ethyl acetate as eluent to give *trans-N,N-di-(tert-butoxycarbonyl)-1-amino-1-carboxyl-2-[2-(diethoxy-phosphoryl)-2,2-difluoro-1-carbonyl-ethyl]-cyclopropane* **30** (148 mg, 67%) as yellow oil; ν_{max} (film)/cm^{-1} 2982w (O–H), 1806m (C=O, CF_2CO), 1749m (C=O), 1369m (O–H), 1251s (P=O), 1159s (C–O, CO_2), 1122s, 1096s, 1019s and 754m (C–F); δ_H(300 MHz; $CDCl_3$) 1.40 (3H, t, *J* 7.1, CH_2Me), 1.41 (3H, t, *J* 7.0, CH_2Me), 1.52 (18H, s, 2C(Me)$_3$), 1.77 (1H, dd, *J* 8.7 and 6.6, C*H*H (cyclopropane)), 2.01 (1H, t, *J* 6.6, CH*H* (cyclopropane)), 2.61 (1H, br s, CHCO) and 4.22–4.46 (4H, m, 2C*H*$_2$Me); δ_C(101 MHz; $CDCl_3$) 16.3 (CH_2*Me*), 16.3 (CH_2*Me*), 21.6 (CH_2 (cyclopropane)), 28.0 (2C(*Me*)$_3$), 31.5 (*C*HCO), 42.0 (*C*CO_2), 65.4 (1C, br s, *C*H_2Me), 65.7 (1C, d, $^2J_{CP}$ 6.2, *C*H_2Me), 84.9 (2*C*(Me)$_3$), 152.1 (N$(CO_2)_2$) and 169.8 (CO_2); δ_F(282 MHz; $CDCl_3$) −120.5 (1F, dd, $^2J_{FF}$ 313.8 and $^2J_{FP}$ 94.8, C*F*F) and –118.9 (1F, dd, $^2J_{FF}$ 313.8 and $^2J_{FP}$ 94.8, CF*F*); δ_P(121 MHz; $CDCl_3$) 4.37 (t, $^2J_{PF}$ 94.8); HRMS (CI, [M–Boc + H]H$^+$) Found: 416.1311. Calc. for $C_{15}H_{25}F_2NO_8P$ 416.1286; *m*/*z* (CI) 444 ([M–O^{t}Bu + H]H$^+$, 2%), 416 (3), 372 (12), 342 (60), 316 (40), 272 (100), 216 (6), 188 (6) and 57 (66); LCMS 8.66 min, *m*/*z* (ES) 516 (MH$^+$, 7%), 460 (13), 416 (100), 360 (100) and 316 (54).

cis-*N*,*N*-Di-(*tert*-butoxycarbonyl)-1-amino-1-methoxycarbonyl-2-[2-(dimethoxy-phosphoryl)-1-carbonyl-ethyl]-cyclopropane 31

cis-*N*,*N*-di-(*tert*-Butoxycarbonyl)-1-amino-1,2-dimethoxycarbonylcyclopropane **26** (171 mg, 458 μmol) was dissolved in anhydrous tetrahydrofuran (1 mL) and cooled to −78 °C under nitrogen. The lithium salt of dimethyl methylphosphonate was then prepared: to a stirred, cooled (−78 °C) solution of dimethyl methylphosphonate (114 μL, 1.05 mmol) in anhydrous tetrahydrofuran (5 mL), was added butyllithium (403 μL, 1.01 mmol, 2.5 M solution in hexane), which precipitated the lithium salt as a colourless solid after approximately 30 min. The mixture was maintained at −78 °C for 90 min, then the lithiated phosphonate mixture was added slowly *via* cannula to the solution containing the methyl ester. The resultant cloudy yellow mixture was maintained at −78 °C and stirred for a further 1 h. TLC (90 : 10 ethyl acetate/petrol) showed dimethyl ester **26** (R_f 0.81), *cis*-**31** (R_f 0.27) and unreacted dimethyl methylphosphonate (R_f 0.11), all three compounds were potassium permanganate active. The reaction was quenched by the addition of conc. acetic acid (58 μL, 1.01 mmol) and it was subsequently allowed to return to RT. Water (25 mL) and ethyl acetate (25 mL) were added to the reaction mixture, the layers were separated and the aqueous layer extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure (85 mm Hg, 40 °C) to give a colourless oil. This crude mixture was dissolved in the minimum amount of eluting solvent and purified by column chromatography on silica using 90 : 10 ethyl acetate/petrol as eluent to give *cis-N,N-di-(tert-butoxycarbonyl)-1-amino-1-methoxycarbonyl-2-[2-(dimethoxy-phosphoryl)-1-carbonyl-ethyl]-cyclopropane* **31** (164 mg, 77%) as a colourless oil; ν_{max} (film)/cm^{-1} 1737m and 1706s (C=O), 1393m

and 1363m (C–H, $C(Me)_3$), 1248s, 1157s, 1116s and 1091m (C–O, CO_2) and 1025s (P–O); δ_H(300 MHz; $CDCl_3$) 1.45 (9H, s, $C(Me)_3$), 1.50 (9H, s, $C(Me)_3$), 1.93 (1H, dd, *J* 8.3 and 5.7, C*H*H (cyclopropane)), 2.02 (1H, dd, *J* 8.3 and 5.7, CH*H* (cyclopropane)), 3.06 (1H, dd, $^2J_{HP}$ 22.0 and J_{HH} 14.3, PC*H*H), 3.29 (1H, t, *J* 8.3, CHCO), 3.67 (1H, dd, $^2J_{HP}$ 22.0 and J_{HH} 14.3, PCH*H*), 3.74 (3H, s, OMe), 3.78 (3H, d, $^3J_{HP}$ 3.2, POMe) and 3.82 (3H, d, $^3J_{HP}$ 3.2, POMe); δ_C(101 MHz; $CDCl_3$) 23.7 (CH_2 (cyclopropane)), 28.0 ($C(Me)_3$), 28.0 ($C(Me)_3$), 37.8 (*C*HCO), 42.9 (1C, d, $^1J_{CP}$ 129.1, PCH_2), 47.1 (*C*CO_2), 52.9 (1C, d, $^2J_{CP}$ 6.9, POMe), 53.1 (CO_2Me), 53.1 (1C, d, $^2J_{CP}$ 6.9, POMe), 83.1 (*C*$(Me)_3$), 83.4 (*C*$(Me)_3$), 152.3 (NCO_2), 153.3 (NCO_2), 170.2 (CO_2) and 194.4 (1C, d, $^2J_{CP}$ 6.2, CO); δ_P(121 MHz; $CDCl_3$) 23.4; HRMS (CI, $[M-^tBu + H]H^+$) Found: 410.1214. Calc. for $C_{15}H_{25}NO_{10}P$ 410.1216; *m*/*z* (CI) 410 ($[M-^tBu + H]H^+$, 14%), 366 (30), 310 (34), 266 (56), 248 (80), 216 (94), 151 (18) and 57 (100).

cis- and *trans-N,N*-Di-(*tert*-butoxycarbonyl)-1-amino-1-methoxycarbonyl-2-carboxycyclopropane potassium salt 33

A solution of *cis*- and *trans-N,N*-di-(*tert*-butoxycarbonyl)-1-amino-1-methoxycarbonyl-2-carboxycyclopropane **25** (400 mg, 1.11 mmol, 71 : 29 *trans*/*cis*) dissolved in 0.91 M potassium hydroxide (acetonitrile (0.5 mL)/water (0.5 mL)), was stirred for 15 min. Solvent was removed under reduced pressure (85 mm Hg, 40 °C); remaining water was removed by azeotroping with toluene, then ethyl acetate, then chloroform under reduced pressure (5 mm Hg, 25 °C) to give *cis- and trans-N,N-di-(tert-Butoxycarbonyl)-1-amino-1-methoxycarbonyl-2-carboxycyclopropane potassium salt* **33** (444 mg, 100%, 74 : 26 *trans*/*cis*) as a hydroscopic colourless solid; mp 55–58 °C; Found: C, 44.8; H, 6.8; N, 3.1; $3C_{16}H_{24}KNO_8.5H_2O$ requires C, 44.95; H, 6.4; N, 3.3%; ν_{max} (solid)/cm^{-1} 1711m (C=O), 1593m (C=O, CO_2^-), 1393m and 1366s (O–H), 1323m (C=O, CO_2^-), 1274s, 1246s, 1159s and 1107s (C–O, CO_2); δ_H(400 MHz; $CDCl_3$) 1.23 (1H, dd, *J* 9.5 and 5.6, C*H*H (cyclopropane) (*trans*)), 1.41 (9H, s, $C(Me)_3$ (*cis*)), 1.46 (9H, s, $C(Me)_3$ (*cis*)), 1.48 (18H, s, $2C(Me)_3$ (*trans*)), 1.61 (1H, dd, *J* 8.6 and 5.0, C*H*H (cyclopropane) (*cis*)), 1.82 (1H, dd, *J* 8.6 and 5.0, CH*H* (cyclopropane) (*cis*)), 2.04 (1H, dd, *J* 9.5 and 5.6, CH*H* (cyclopropane) (*trans*)), 2.40 (1H, t, *J* 9.5, $CHCO_2$ (*trans*)), 2.54 (1H, t, *J* 8.6, $CHCO_2$ (*cis*)) and 3.68 (3H, s, OMe); δ_C(101 MHz; $CDCl_3$) 23.6 (CH_2 (cyclopropane) (*trans*)), 25.6 (CH_2 (cyclopropane) (*cis*)), 27.6 ($2C(Me)_3$ (*cis*)), 28.1 ($2C(Me)_3$ (*trans*)), 35.3 (*C*HCO_2 (*cis*)), 39.4 (*C*HCO_2 (*trans*)), 44.0 (*C*CO_2 (*cis*)), 44.0 (*C*CO_2 (*trans*)), 52.3 (OMe (*cis*)), 52.8 (OMe (*trans*)), 82.6 (*C*$(Me)_3$ (*cis*)), 82.9 (*C*$(Me)_3$ (*cis*)), 83.0 ($2C(Me)_3$ (*trans*)), 152.3 ($N(CO_2)_2$ (*cis*)), 152.6 ($N(CO_2)_2$ (*trans*)), 171.8 (CO_2 (*cis*)), 172.0 (CO_2 (*trans*)), 172.5 (CO_2 (*trans*)) and 173.3 (CO_2 (*cis*)); *m*/*z* (CI) 260 ($[M-K-Boc + 2H]H^+$, 1%), 186 (18), 160 (28), 142 (30) and 57 (100).

cis- and *trans-N,N*-Di-(*tert*-butoxycarbonyl)-1-amino-1-methoxycarbonyl-2-[1-(diethoxy-phosphoramidate)-1-carbonyl-methyl]-cyclopropane 34

The potassium salt **33** (400 mg, 1.01 mmol, 74 : 26 *trans*/*cis*) was dissolved in anhydrous dichloromethane (9 mL), in the presence of molecular sieves (4 Å, 1.6 mm pellets), subsequent dropwise addition of ethyl chloroformate (693 μL, 7.25 mmol) gave a pale yellow solution which was stirred under nitrogen for 2 h. The lithium salt of diethyl phosphoramidate was then prepared: to a stirred, cooled (−78 °C) solution of diethyl phosphoramidate (895 mg, 5.84 mmol) in anhydrous dichloromethane (4 mL), was added butyllithium (2.34 mL, 5.84 mmol, 2.5 M solution in hexane), which instantaneously precipitated the diethyl phosphoramidate lithium salt as a colourless solid. The mixture was maintained at −78 °C for 30 min, then stirred at RT for 30 min. The solution containing the anhydride was cooled to −78 °C, then the lithiated phosphoramidate mixture was added. The resultant cloudy colourless mixture was allowed to return to RT and stirred for a further 16 h. TLC (85 : 15 ethyl acetate/petrol) showed *trans*-**34** (R_f 0.27), *cis*-**34** (R_f 0.20) and unreacted diethyl phosphoramidate (R_f 0.08), all three compounds were potassium permanganate active. The reaction was quenched by the addition of water (20 mL), the aqueous was subsequently acidified to pH 1 (with 2 M HCl). The layers were separated and the aqueous layer extracted with dichloromethane (4 × 25 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure (85 mm Hg, 40 °C) to give a crude yellow oil. This mixture was dissolved in the minimum amount of ethyl acetate and purified by column chromatography on silica using 85 : 15 ethyl acetate/petrol as eluent to give *trans-N,N-di-(tert-butoxycarbonyl)-1-amino-1-methoxycarbonyl-2-[1-(diethoxy-phosphoramidate)-1-carbonyl-methyl]-cyclopropane* **34** (137 mg, 26%) as a colourless oil; ν_{max} (film)/cm^{-1} 1736s (C=O), 1696m (C=O, NCO), 1272s (P=O), 1247s, 1161s and 1120s (C–O, CO_2) and 1022s (P–O); δ_H(400 MHz; $CDCl_3$) 1.36 (6H, t, *J* 7.2, $2CH_2Me$), 1.52 (19H, br s, $2C(Me)_3$ and C*H*H (cyclopropane)), 2.28 (1H, dd, *J* 9.4 and 6.6, CH*H* (cyclopropane)), 2.43 (1H, t, *J* 9.4, CHCO), 3.72 (3H, s, OMe), 4.19 (2H, q, *J* 7.2, CH_2Me), 4.24 (2H, q, *J* 7.2, CH_2Me) and 8.16 (1H, br d, $^2J_{HP}$ 12.1, NH); δ_C(101 MHz; $CDCl_3$) 16.1 (CH_2Me), 16.2 (CH_2Me), 21.7 (CH_2 (cyclopropane)), 28.0 ($2C(Me)_3$), 37.4 (1C, d, $^3J_{CP}$ 12.3, *C*HCO), 43.7 (*C*CO_2), 52.8 (OMe), 64.0 (1C, d, $^2J_{CP}$ 6.2, *C*H_2Me), 64.1 (1C, d, $^2J_{CP}$ 5.4, *C*H_2Me), 84.2 ($2C(Me)_3$), 167.0 (NHCO) and 169.1 (CO_2); δ_P(121 MHz; $CDCl_3$) −3.10; HRMS (CI, $[M-Boc + H]H^+$) Found: 395.1570. Calc. for $C_{15}H_{28}N_2O_8P$ 395.1583; *m*/*z* (CI) 495 (MH^+, 28%), 395 (22), 295 (24), 278 (56), 180 (84), 154 (88), 142 (80) and 57 (100) and *cis-N,N-di-(tert-butoxycarbonyl)-1-amino-1-methoxycarbonyl-2-[1-(diethoxy-phosphoramidate)-1-carbonyl-methyl]-cyclopropane* **34** (98 mg, 19%) as a colourless oil; ν_{max} (film)/cm^{-1} 1738m and 1708m (C=O), 1273s (P=O), 1244s, 1153s and 1118s (C–O, CO_2) and 1027s (P–O); δ_H(400 MHz; $CDCl_3$) 1.31 (3H, t, *J* 7.7, CH_2Me), 1.33 (3H, t, *J* 7.4, CH_2Me), 1.47 (9H, s, $C(Me)_3$), 1.50 (9H, s, $C(Me)_3$), 1.88 (1H, dd, *J* 8.3 and 5.9, C*H*H (cyclopropane)), 1.99 (1H, dd, *J* 8.3 and 5.9, CH*H* (cyclopropane)), 2.90 (1H, t, *J* 8.3, CHCO), 3.72 (3H, s, OMe), 4.09–4.30 (4H, m, $2CH_2Me$) and 8.85 (1H, br d, $^2J_{HP}$ 8.1, NH); δ_C(101 MHz; $CDCl_3$) 16.1 (CH_2Me), 16.1 (CH_2Me), 24.0 (CH_2 (cyclopropane)), 28.0 ($2C(Me)_3$), 32.8 (1C, d, $^3J_{CP}$ 13.1, *C*HCO), 45.6 (*C*CO_2), 52.9 (OMe), 63.9 (1C, d, $^2J_{CP}$ 5.4, *C*H_2Me), 64.3 (1C, d, $^2J_{CP}$ 6.2, *C*H_2Me), 82.9 (*C*$(Me)_3$), 82.9 (*C*$(Me)_3$), 152.3 (NCO_2), 152.4 (NCO_2), 168.5 (NHCO) and 170.7 (CO_2); δ_P(121 MHz; $CDCl_3$) −2.35; HRMS (CI, $[M-Boc + H]H^+$) Found: 395.1574. Calc. for $C_{15}H_{28}N_2O_8P$ 395.1583; *m*/*z* (CI) 495 (MH^+, 6%), 395 (32), 339 (62), 295 (38), 278 (94), 180 (26) and 57 (100).

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