Novel peptide isosteres that were designed to inhibit the binding of the HIV surface glycoprotein (gp120) to the T cell surface glycoprotein CD4

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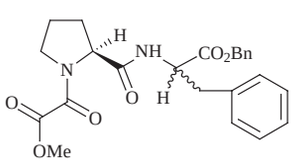
The *cis*- and *trans*-isomers of (2*S*)-2-[3′(*RS*)-3′-benzyl-3′-benzyloxycarbonylprop-1′-enyl]-*N*-methoxycarbonylcarbonylpyrrolidines have been prepared from a Wittig reaction between (*S*)-*N*-Boc-prolinal and the phosphorus ylide from (2*RS*)-3-iodo-2-benzyl-1-triisopropylsilyloxypropane. In addition, (2*S*)-*N*-methoxycarbonylcarbonyl-2-[(3′*RS*)-1-oxo-3′-benzyl-3′-benzyloxycarbonylpropyl]pyrrolidine was prepared from the *cis*-alkene produced in the Wittig reaction. These were intended as peptide isosteres of the known inhibitors of HIV-lymphocyte binding *N*-methoxycarbonylcarbonylprolylphenylalanyl benzyl esters, but did not possess such activity.

There is now a glimmer of hope that chemotherapy will provide a means of eradicating the human immunodeficiency virus (HIV) from infected individuals.[1] However, both the reverse transcriptase inhibitors like AZT, ddC and D4T, and the protease inhibitors like saquinavir and indinavir, interfere with viral reproduction after uptake by T-4 lymphocytes. It would be preferable to have agents that prevented the uptake of the virus by the lymphocyte. A number of such agents are known and these include such diverse substances as heparin, various lectins and derivatives of betulinic acid,[2] but these are too non-specific to consider as drugs.

In 1990, Schreiber and co-workers carried out modelling studies of the interaction between the glycoprotein (so-called gp120) on the surface of HIV with a key glycoprotein (CD4) on the cell surface of the T-4 lymphocyte.[3] Although a further interaction with another lymphocyte factor (either CCR5 or CXCR4)[4] is also required, the initial interaction between gp120 and CD4 is crucial for uptake (internalisation) of the virus. The Schreiber group then synthesised several dipeptides that prevented such binding and subsequently acted to prevent infection of the cells by the virus. The *N*-methoxycarbonylcarbonylprolylphenylalanyl benzyl esters **1** were the most



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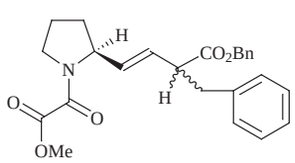
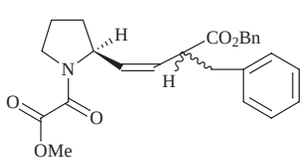
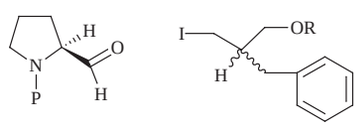


2 *cis* - and *trans*-alkenes



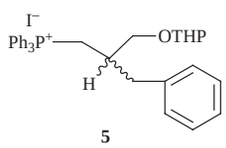
potent and were active at concentrations in excess of 600 μg ml^{-1}. However, no further reports have emanated from this group, though a French group have recently reported similar results.[5] This level of activity is not particularly good and doubt remains whether such dipeptides would have sufficient metabolic stability for drug use. We have used Schreiber's compounds as models for novel peptide isosteres of general structure **2**, which we hoped would have better activity and stability. The synthesis and (preliminary) biological evaluation of such isosteres are the subject of this paper.

An obvious strategy for construction of these compounds was to employ a Wittig reaction between an *N*-protected prolinal **3** and a phosphorus ylide formed from 3-iodo-2-benzyl-1-alkoxypropane **4**. (*S*)-Benzyloxycarbonylproline methyl ester



3a P = Cbz
3b P = Boc

4a R = THP
4b R = TIPS



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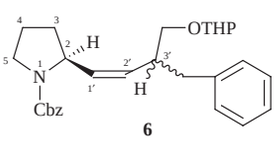

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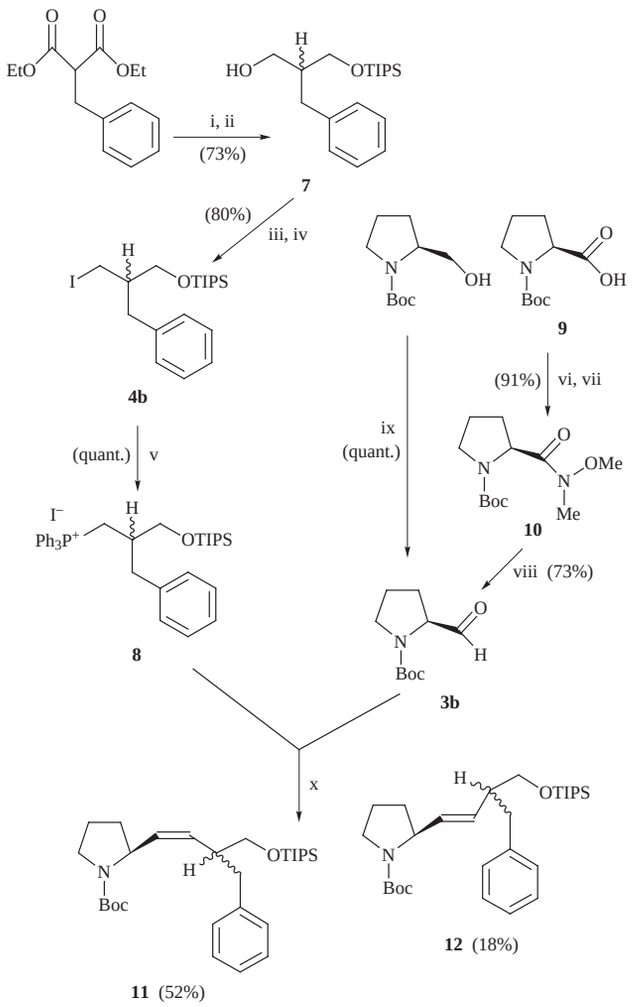
was converted into the desired aldehyde **3a** *via* reduction with $LiBH_4$ followed by Swern oxidation (80% yield overall). The iodopropane derivative **4a** was prepared from diethyl 2-benzylmalonate *via* reduction ($LiBH_4$) to 2-benzylpropane-1,3-diol (55%), followed by formation of the mono-toluene-*p*-sulfonate (toluene-*p*-sulfonyl chloride–pyridine) (55%) and thence the tetrahydropyranyl (THP) derivative (dihydropyran in DCM with toluene-*p*-sulfonic acid as catalyst; essentially quantitative). Finally, the desired iodide **4a** was formed by reaction with sodium iodide in refluxing acetone (95%).

Reaction of this iodide with triphenylphosphine in refluxing acetonitrile provided the desired phosphonium salt **5** as a light yellow foam (quantitative). The phosphorus ylide was generated using butyllithium at −78 °C and the Wittig reaction with aldehyde **3a** proceeded in modest yield (44%) to give what appeared to be two major products. Although these were just separable by flash chromatography, the ^1H NMR spectra of the 'discrete' products were extremely broad, and it seemed likely that they were mixtures of diastereoisomers (not least due to the presence of the THP group). Removal of the THP group from the crude Wittig product mixture (aqueous HCl) produced one major product (*ca.* 20% overall) which was identified as a discrete stereoisomer **6** (but with unknown stereochemistry at C-3′). The other compound appeared to be one of the Wittig products which had not been changed by exposure to the acid.

Clearly the THP group had been an unwise choice for the synthesis, and in an effort to improve the yields and the ease of manipulation of the Wittig products, the alternative route shown in Scheme 1 was investigated.



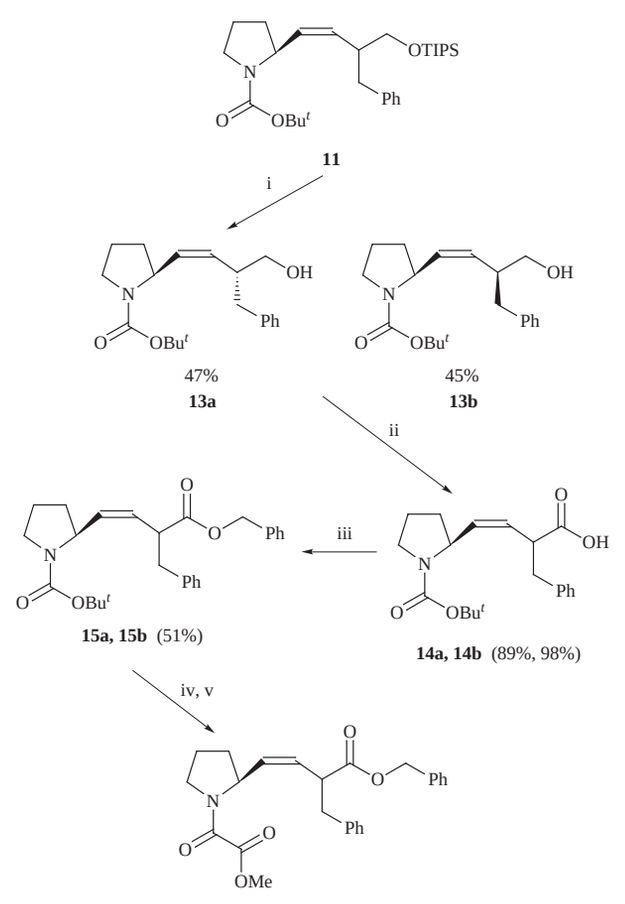
Scheme 1 *Reagents and conditions*: i, $LiAlH_4$, diethyl ether; ii, NaH, TIPSCl, DCM; iii, Et_3N, $MeSO_2Cl$, DCM; iv, NaI, acetone, reflux; v, Ph_3P, MeCN, reflux, 48 h; vi, carbonyldiimidazole, DCM; vii, MeO-NHMe; viii, $LiAlH_4$, diethyl ether; ix, Dess–Martin periodinane; x, BuLi, THF, −78 °C

Diethyl 2-benzylmalonate was converted into 2-benzyl-3-triisopropylsilyloxypropanol **7** *via* reduction to the diol ($LiAlH_4$–diethyl ether) then silyl ether formation with sodium hydride and triisopropylsilyl chloride (73% overall). Conversion into the methanesulfonate (Et_3N–$MeSO_2Cl$–DCM) was followed by displacement of the mesylate group by iodide (NaI in refluxing acetone) (80% overall) to provide the iodide **4b**. Finally, the triphenylphosphonium salt **8** was produced by reaction of the iodide with triphenylphosphine in refluxing acetonitrile (essentially quantitative). It was quite notable that the overall yield for this five-stage process was around 58%, which represented a considerable improvement on the route to phosphonium salt **5**. The compound was a white microcrystalline solid. For this second route we employed Boc-prolinal **3b** and this was prepared *via* the Weinreib amide[6] **10** formed from *N*-Boc-proline **9** (as shown in Scheme 1). Once again, the yields were very good.

To our dismay, the subsequent Wittig reaction between the phosphorus ylide from **8** and aldehyde **3b** proceeded in at best 7% yield! After numerous attempts to improve upon this by changing the nature of the alcohol protecting group or the conditions of the Wittig reaction, we decided to prepare aldehyde **3b** using a Dess–Martin periodinane oxidation[7] of the corresponding prolinol. The ^1H NMR spectrum of this sample of aldehyde was identical in all respects with that obtained with our previous samples, but now the Wittig reaction provided a good yield of two products **11** (52%) and **12** (18%). We believe (although we have no experimental proof) that traces of aluminium salts contaminated the aldehyde produced from the Weinreib amide, and that these led to the very poor yields in the Wittig reaction of aldehyde **3b** prepared by this route.

The major product **11** was clearly a mixture of *cis*-alkenes (*J* around 11 Hz), presumably epimeric at C-3′. Removal of the TIPS group (TBAF–THF) produced a separable mixture of two products **13a** and **13b** whose stereochemistry was subsequently established by X-ray crystallographic studies (ORTEP plots are shown in Figs. 1 and 2). The major differences between **13a** and **13b**, in the X-ray structures, were the stereochemistry at C-3′ and the relative positions of the oxygen atoms of the Boc groups.

The alcohols were then oxidised (Jones' reagent) to yield the discrete acids **14a**,**b** (89 and 98% respectively) (Scheme 2), and



Scheme 2 *Reagents and conditions*: i, TBAF, THF, 25 °C, 60 min; ii, Jones' reagent, Me_2CO, 0 °C, 60 min; iii, CDI, BnOH, DCM, NaOEt, 30 °C, 3 days; iv, TFA, DCM, 25 °C, 5 min; v, MeO_2CCOCl, pyridine, 0 to 25 °C, 60 min

these were converted into the corresponding benzyl esters **15a**,**b** (carbonyldiimidazole then benzyl alcohol and catalytic NaOEt) (51% in each case). Finally, the Boc groups were removed (TFA–DCM) and the products reacted with methyl oxyalyl chloride in pyridine–DCM to provide the desired peptide isosteres **16a** and **16b** (85 and 80% respectively). A problem now arose since the ^1H NMR spectra showed a partial doubling for many of the signals, and it was not initially clear whether we were dealing with rotamers or whether racemisation had occurred during the reaction sequence. Eventually, it was possible to prove

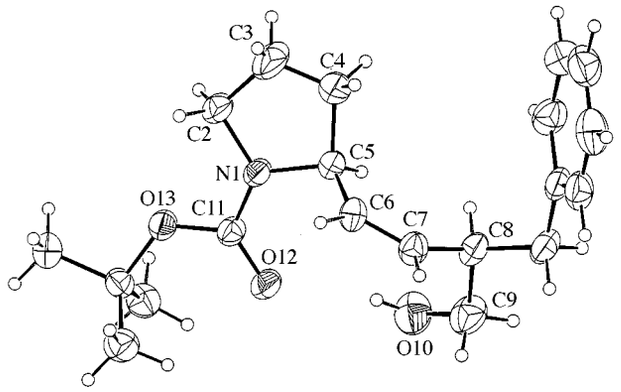


Fig. 1 ORTEP plot of **13a**

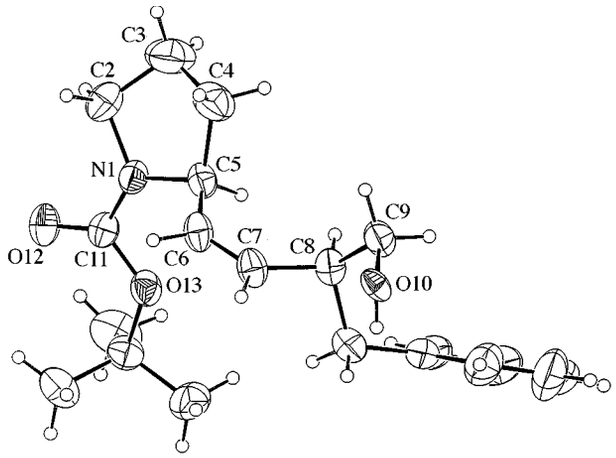
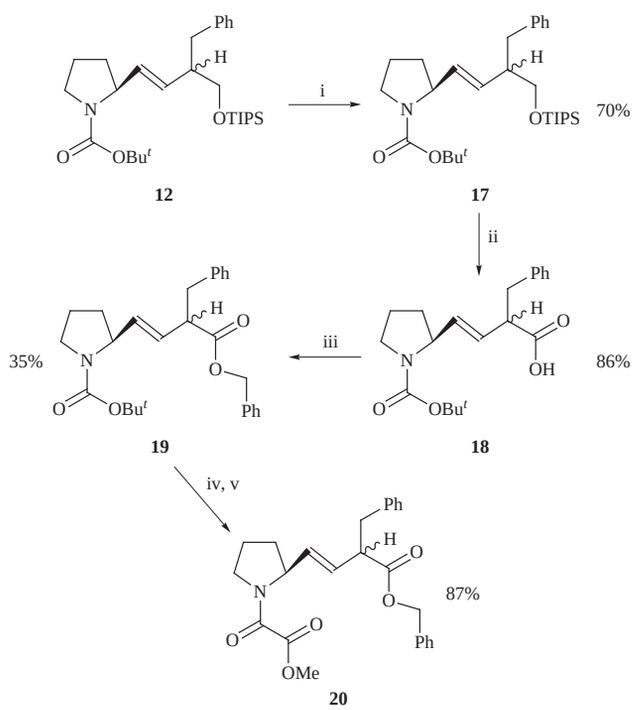


Fig. 2 ORTEP plot of **13b**

definitively by variable temperature NMR studies (at up to 90 °C) that both **16a** and **16b** existed in the form of slowly interconverting rotamers. Their stereochemical homogeneity was evidenced by the fact that the optical rotations of the compounds did not vary between the various preparations that we employed.

The mixture of *trans*-alkenes **12** ($J = 15$ Hz) was converted *via* a similar sequence of reactions (Scheme 3) into the peptide



Scheme 3 *Reagents and conditions*: i, TBAF, THF, 25 °C, 2 h; ii, Jones' reagent, Me_2CO, 0 °C, 60 min; iii, CDI, BnOH, DCM, NaOEt, 30 °C, 3 days; iv, TFA, DCM, 25 °C, 15 min; v, MeO_2CCOCl, pyridine, 0 to 25 °C, 60 min

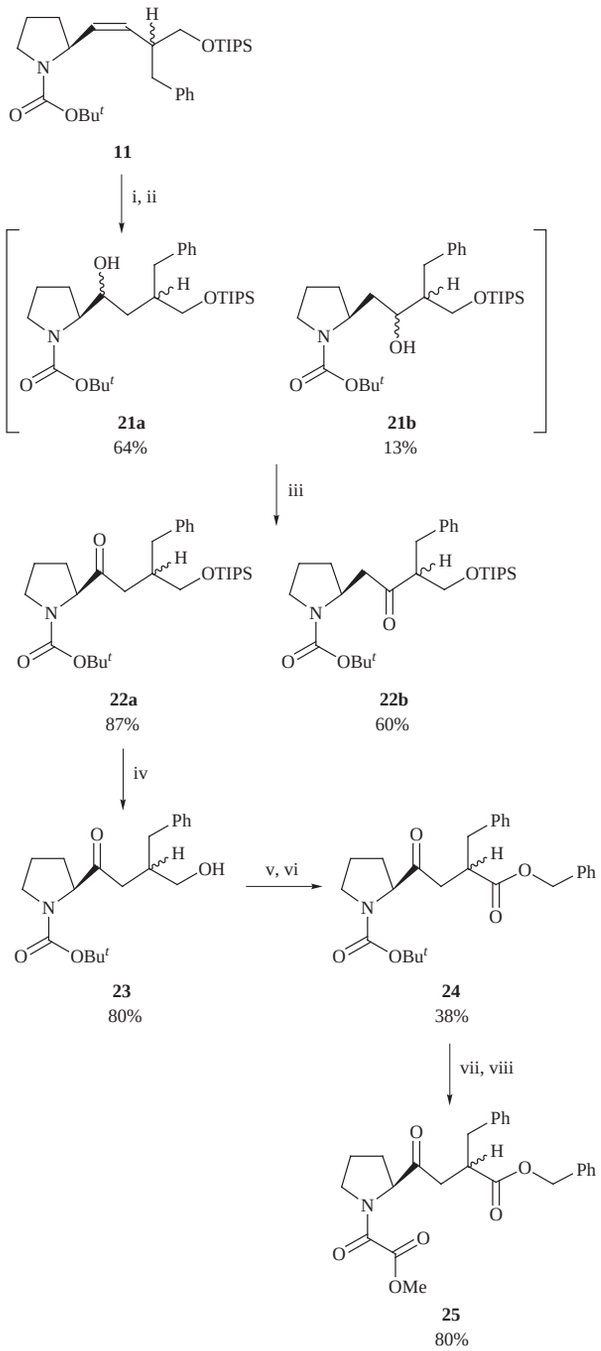
isosteres **20**, though in this series it did not prove possible to separate (at least by flash chromatography) the various stereoisomers. Preliminary biological evaluation (*vide infra*) showed that compounds **16a**, **16b** and **20** did not inhibit binding of gp120 to CD4 at concentrations up to 1 mg ml^{-1}, so the ketomethylene isostere **25** (as a pair of diastereoisomers) was prepared *via* the route shown in Scheme 4, in the hope that this would possess better activity. Of particular note was the regioselectivity of the hydroboration of *cis*-alkene **11** to provide the alcohols **21a** and **21b** in the ratio of around 5 : 1. The remainder of the synthesis was routine. Finally, in order to have a realistic comparison of the biological activities of our peptide isosteres with the dipeptides produced by Schreiber, the dipeptide **1** (as the single *S*,*S*-stereoisomer) was prepared by the route shown in Scheme 5.

Preliminary biological evaluation was carried out [8] according to the method of Weiss and Schreiber.[9] This uses gp120, tethered to an inert support *via* a monoclonal antibody attached to its C-terminal region, and this is then monitored for its ability to bind a CD4–IgG conjugate. The monitoring involves the use of an anti-human IgG-horseradish peroxidase conjugate whose presence is visualised following reaction with 3,3′,5,5′-tetramethylbenzidine (TMB).[10] Our compounds were tested for the ability to prevent the association between gp120 and CD4, but were inactive at concentrations up to 1 mg ml^{-1}. Further biological evaluation is being conducted with other systems and full details will be provided in due course.

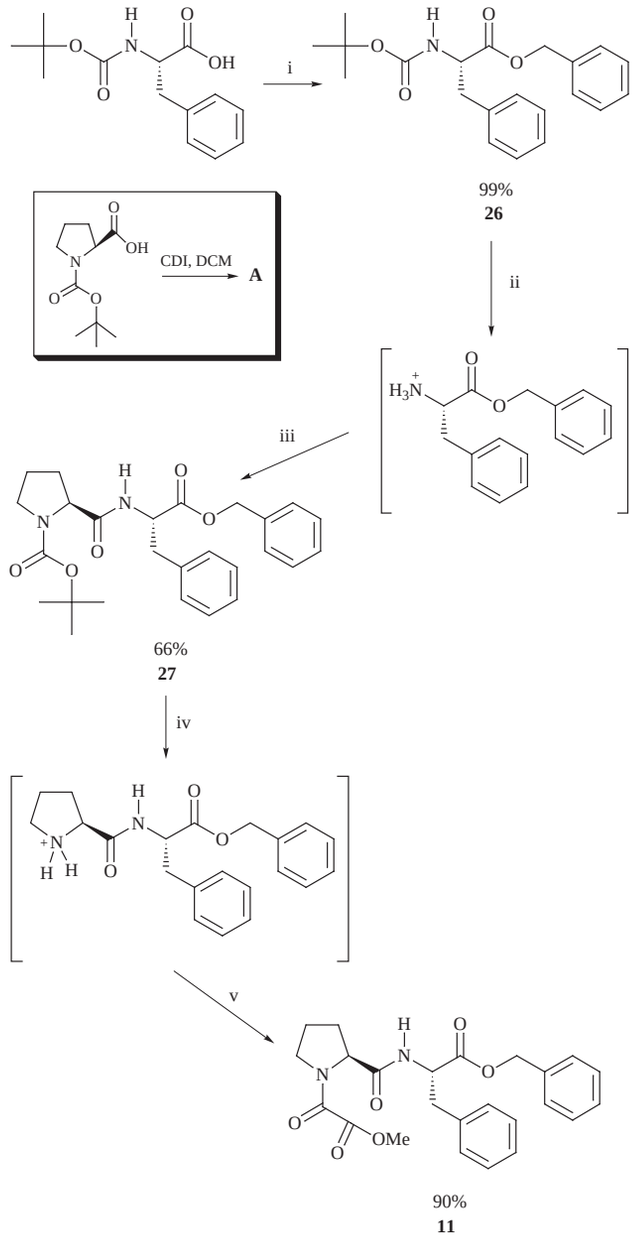
Experimental

IR spectra were recorded using a Perkin-Elmer 881 series double beam spectrophotometer, and samples were run as thin films or in solution using NaCl plates. Low resolution and accurate mass data were recorded on a VG Autospec (Reading) or VG7070F (Swansea: EPSRC facility) spectrometers. Elemental analyses were carried out by Medac Ltd., Brunel University. Optical rotations were measured at room temperature on a Perkin-Elmer 341 polarimeter. NMR spectra were recorded using a JEOL EX400, Bruker DPX 250 or Bruker WM250 spectrometers. Solvents were dried by distillation from calcium hydride (DCM, toluene, benzene, acetonitrile) or from sodium–benzophenone (THF and diethyl ether). Petrol refers to petroleum spirit boiling range 40–60 °C; ether refers to diethyl ether. Most of the compounds were very hygroscopic and it proved difficult to obtain reproducible microanalytical data. However, all pure compounds were homogeneous on TLC in at least three solvent systems and exhibited no spurious signals in their ^{1}H NMR spectra at 400 MHz.

Data for both crystals were collected with Mo-Kα radiation using the MARresearch Image Plate System. The crystals were positioned at 75 mm from the Image Plate and 95 frames were measured at 2° intervals with a counting time of 2 minutes. Data analysis was carried out with the XDS programme.[11] Both structures were solved using direct methods with the SHELX86 programme.[12] In **13a** two positions were refined for C(3) with 50% occupancy. In both structures the non-hydrogen atoms were defined with anisotropic thermal parameters. The hydrogen atoms were included in geometric positions. Both structures were then refined on F2 using SHELX1.[13] All calculations were carried out on a Silicon Graphics R4000 Workstation at the University of Reading. Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the



Scheme 4 *Reagents and conditions*: i, BH_3·DMS, THF, 0 to 40 °C, 18 h; ii, 3 M NaOH, 30% H_2O_2; iii, Dess–Martin periodinane, DCM, 25 °C, 1 h; iv, TBAF, THF, 25 °C, 1 h; v, Jones' reagent, Me_2CO, 0 °C, 1 h; vi, CDI, BnOH, DCM, NaOEt, 40 °C, 3 h; vii, TFA, DCM, 25 °C, 5 min; viii, MeO_2CCOCl, pyridine, 0 to 25 °C, 1 h



Scheme 5 *Reagents and conditions*: i, Carbonyldiimidazole, BnOH, DCM, NaOEt (cat.), 25 °C, 18 h; ii, TFA, DCM, 25 °C, 5 min; iii, **A**, Et_3N, DCM, 25 °C, 18 h; iv, TFA, DCM, 25 °C, 5 min; v, pyridine, MeO_2CCOCl, DCM, 0 °C, 18 h

deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 1*, available *via* RSC Web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/210.

(*S*)-*N*-Benzyloxycarbonyl-2-formylpyrrolidine 3a

To a stirred solution of dry dimethyl sulfoxide (1.81 ml, 25.5 mmol) in dry DCM (35 ml) in a flame-dried flask at −78 °C under N_2 was added oxalyl chloride (8.5 ml, 17.6 mmol) dropwise. The mixture was left stirring for 10 min before a solution of *N*-Cbz-pyrrolidinemethanol (2.0 g, 8.51 mmol) in dry DCM was added dropwise. The mixture was stirred for a further 20 min before triethylamine (4.73 ml, 34 mmol) was added, forming a white precipitate. After warming to room temperature, water was added and the organic layer separated. The aqueous layer was saturated with sodium chloride and extracted three times with ethyl acetate. The combined organic extracts were washed with 1% hydrochloric acid, water and then dried with magnesium sulfate and concentrated to dryness. A yellow oil remained containing some white precipitate. The oil was redissolved in ethyl acetate and the precipitate was filtered off. After rotary evaporating to dryness the crude compound was azeotropically distilled with benzene three times to remove traces of water yielding the desired compound as a light orange oil (1.76 g, 89%) which could not be purified further. Spectroscopic details were consistent with the literature.[14] R_f 0.18 (diethyl ether–light petroleum, 1:1); ν_{max}(thin film)/cm^{-1} 3150–2800s (CH), 2700s, 1736s (aldehyde C=O), 1700s (amide C=O); δ_H(400 MHz; $CDCl_3$; Me_4Si) 1.9 (2H, m, 4-H), 2.1 (2H, m, 3-H), 3.5 (2H, m, 5-H), 4.2–4.3 (1H, m, 2-H), 5.1 (2H, m, 6-H), 7.3 (5H, m, Ph), 9.6 (1H, s, COH); *m*/*z* (CI) 253 (3), 252 (20), 251 (100), 234 (42), 204 (8), 190 (13), 178 (2), 160 (5), 145 (2), 125 (5), 108 (20) (Found: MH^+, 234.1130. $C_{13}H_{15}NO_3$ requires *M*, 233.1052).

1-Iodo-2-benzyl-3-(tetrahydro-2*H*-pyran-2-yloxy)propane 4a

To a stirred solution of the toluene-*p*-sulfonate (0.903 g, 2.23 mmol) in anhydrous acetone (50 ml) in a foil-wrapped flask under N_2 was added sodium iodide (502 mg, 3.36 mmol) all at once. After refluxing for 9 h the mixture was poured into water and extracted with 3 × 30 ml of diethyl ether. The organic extracts were washed with saturated sodium thiosulfate solution, water and then dried with magnesium sulfate. Flash column chromatography (diethyl ether–light petroleum, 1:1) yielded the title compound as a yellow oil (762 mg, 95%); R_f 0.70 (diethyl ether–light petroleum, 1:1) ν_{max}(thin film)/cm^{-1} 3200–3000m (CH), 3000–2800s (CH), 1945w, 1882w, 1806w, 1737w (C=O), 1604m, 1500s, 1460s, 1390m, 1360s, 1300m, 1280m, 1200s; δ_H(400 MHz; $CDCl_3$; Me_4Si) 1.5–1.6 (4H, m, 4′-H and 5′-H), 1.7 (1H, m, 2-H), 1.8 (2H, m, 3′-H), 2.6–2.7 (2H, m, 4-H), 3.2–3.4 (2H, m, 1-H and 3-H isomer) 3.5 (1H, m, 6′a-H), 3.6–3.7 (2H, m, 3-H), 3.8 (1H, m, 6′b-H), 4.6 (1H, m, 2′-H), 7.1–7.3 (5H, m, Ph); δ_C(200 MHz, 0.03% $CDCl_3$) 12 (1-C), 19 (4′-C), 25 (5′-C), 30 (3′-C), 37 (4-C), 41 (2-C), 62 (6′-C), 69 (3-C), 98 and 99 (2′-C diastereomers), 125–130 (Ar-C); *m*/*z* 360 (1), 347 (1), 288 (1), 260 (1), 233 (1), 217 (1), 205 (1), 192 (1), 177 (1), 131 (80), 129 (9), 117 (18), 103 (20), 91 (73), 85 (100), 67 (15) (Found: M$^+$, 360.0586. $C_{15}H_{21}O_2I$ requires *M*, 360.0586).

Synthesis of the phosphonium salt of 1-iodo-2-benzyl-3-(tetrahydro-2*H*-pyran-2-yloxy)propane 5

To a stirred solution of the iodide **4a** (1.0 g, 2.78 mmol) in dry acetonitrile (20 ml) under N_2 was added triphenylphosphine (0.72 g, 2.78 mmol). The yellow solution was heated under reflux for 48 h at which point thin layer chromatography (eluent light petroleum–diethyl ether, 1:1) showed the formation of a baseline spot at the expense of starting material. The compound was rotary evaporated to dryness and dried under high vacuum for 1 day, yielding a light yellow, hygroscopic foam (100%) (1.73 g, 2.78 mmol); R_f 0.00 (diethyl ether–light petroleum, 1:1); δ_H(400 MHz, 0.03% $CDCl_3$) 1.4–1.8 (6H, m, 3′-H, 4′-H and 5′-H), 2.3 (1H, m, 2-H), 2.6–2.9 (2H, m, 4-H), 3.2–4.2 (6H, m, 3-H, 6′-H and 1-H), 4.3–4.5 (1H, m, 2′-H), 7.1–7.4 (5H, m, Ph), 7.6–7.8 (15H, m, 3Ph).

(2*S*)-1-Benzyloxycarbonyl-2-[(*Z*)-3-benzyl-4-(tetrahydro-2*H*-pyran-2-yloxy)but-1-enyl]pyrrolidine 6

To a flame-dried three necked flask under N_2 at −78 °C was added the phosphonium salt **5** (4 g, 6.43 mmol) in dry THF (100 ml). A solution of butyllithium (2.5 M; 2.83 ml, 7.73 mmol) was added dropwise with stirring over 15 min—the solution turned from a pale yellow colour to a deep red. After stirring for a further 30 min a solution of *N*-Cbz-prolinal (2.99 g, 12.8 mmol) in dry THF (150 ml) was added dropwise, the mixture was left to stir at −78 °C for 15 min and then warmed to room temperature and left overnight. The deep yellow solution was then poured into water and extracted three times with ethyl acetate, washed with brine and dried with magnesium sulfate before evaporating to dryness. Flash column chromatography (light petroleum–diethyl ether, 3:1) gave a separable mixture of 2 compounds (R_f = 0.61 and 0.54) as pale yellow oils (41%, 1.18 g) indistinguishable by ^{1}H NMR spectroscopy; R_f 0.61 and 0.54 (light petroleum–diethyl ether, 1:1); δ_H(400 MHz, 0.03% $CDCl_3$) 1.5–1.8 (10H, m, 3″-H, 4″-C and 5″-CH, 3′-H and 4′-H), 2.05 (1H, m, 2-H), 3.0–3.2 (2H, m, C*H*$_2$Ph), 3.3 and 3.6 (6″-H), 3.4 (2H, m, 5′-H), 3.7–3.9 (2H, m, 1-H), 4.4–4.5 (1H, m, 2′-H), 4.6 (1H, m, 2″-H), 5.1 (2H, m, OC*H*$_2$Ph), 5.2 (1H, m, 3-H), 5.4 (1H, m, 4-H), 7.0–7.2 (10H, m, 2Ph); δ_C(200 MHz, 0.03% $CDCl_3$) 23 (4′-C), 38 (2-C), 39 (*C*H$_2$Ph), 40 (3′-C), 47 (5′-C), 54 (2′-C), 67 (1-C), 125–132 (Ar-C), 135 (3-C), 140 (4-C), 170 (C=O).

2-Benzylpropane-1,3-diol

To a slurry of lithium aluminium hydride (4.45 g, 113.9 mmol) in freshly distilled diethyl ether (200 ml) under argon at 0 °C was added, dropwise, diethyl 2-benzylmalonate (15.08 g, 59.9 mmol) in diethyl ether (150 ml). After stirring for 24 hours water (4.5 ml), 15% NaOH (4.5 ml) and water 13.5 ml) were added successively. The resulting white precipitate was removed by filtration and washed with copious amounts of ether. Evaporation under reduced pressure yielded a pink solid. Trituration with hexane to remove starting diester and dibenzyl impurities afforded the title compound as a lustrous white solid. (8.37 g, 50.4 mmol, 84%). Spectroscopic details were consistent with the literature.[15] ν_{max}(film)/cm^{-1} 3200s (OH), 3000–2800s (CH), 1460s, 1380m, 1040m; δ_H(400 MHz; $CDCl_3$; Me_4Si) 2.05 (1H, m, 2-H), 2.5 (2H, br, 2 × OH), 2.6 (2H, d, $J_{4,2}$ 7.7, 4-H), 3.6 (2H, dd, $J_{1a,1b}$ 10.6 $J_{1a,2}$ 7.0, 1a-H), 3.8 (2H, dd, $J_{1b,1a}$ 10.6 $J_{1b,2}$ 7.0, 1b-H), 7.2 (5H, m, Ph); δ_C(100 MHz; $CDCl_3$; Me_4Si) 33.1 (4-C), 43.8 (2-C), 67.3 (1-C, 3-C), 125.1–139.0 (Ph) (Found: M$^+$, 166.0999. $C_{10}H_{14}O_2$ requires *M*, 166.0994).

2-Benzyl-3-triisopropylsilyloxypropanol 7

To a flask containing a slurry of hexane-washed sodium hydride (60% dispersion, 4.62 g, 115 mmol) in THF (300 ml) fitted with an overhead stirrer, was added 2-benzylpropane-1,3-diol (18.2 g, 109 mmol). After 90 minutes a voluminous precipitate had formed. With vigorous stirring, chlorotriisopropylsilane (25.8 ml, 120 mmol) was then added. Once complete dissolution was achieved (2 hours) the solvent was removed and the residue poured on to ether (200 ml). The solution was washed with 10% K_2CO_3 (200 ml) and extracted with ether (2 × 150 ml). The combined organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by flash column chromatography (using 1:1 ether–petrol as eluent) to yield the title compound as a pale yellow oil (29.2 g, 90 mmol, 83%); ν_{max}(film)/cm^{-1} 3700–3300m (OH), 3000–2800s (CH), 1494w, 1462m, 1382w, 1109s, 1053s, 882s; δ_H(400 MHz; $CDCl_3$; Me_4Si) 1.05 (18H, d, $J_{1'2'}$ 4.03, 6 × Me), 1.05–1.2 (3H, m, 3 × 2′-H), 2.0–2.13 (1H, m, 2-H), 2.57–2.67 (2H, m, 4-H), 2.9–2.00 (1H, br, OH), 3.6–3.8 (2H, m, 3-H), 3.83–3.90 (2H, m, 1-H), 7.14–7.32 (5H, m, Ph); δ_C(100 MHz; $CDCl_3$; Me_4Si), 11.7 (2′-C), 17.9 (1′-C), 34.1 (4-C), 44.1 (2-C), 65.7 (3-C), 66.8 (1-C), 125.9–128.9, 140.0 (Ph) (Found: MH$^+$, 323.2411. $C_{19}H_{35}O_2Si$ requires *M*H, 323.2406).

1-Methylsulfonyloxy-2-benzyl-3-triisopropylsilyloxypropane

To a stirred solution of alcohol **7** (35 g, 108.5 mmol), dry DCM (300 ml) and triethylamine (12.34 ml, 119 mmol) at 0 °C was added dropwise methanesulfonyl chloride (9.24 ml, 130 mmol). After 18 hours the mixture was washed with water (200 ml) and the organic phase separated. The aqueous phase was further extracted with ether (2 × 100 ml). The combined organic phases were dried with brine and $MgSO_4$ and evaporated under reduced pressure to yield the title compound as a light yellow oil (42 g, 107 mmol, 99%); ν_{max}(film)/cm^{-1} 3000–2800s (CH), 1500m, 1465s, 1360s and 1178s (SO_2–O–), 960s, 885s, 745m; δ_H(250 MHz; $CDCl_3$; Me_4Si) 0.95–1.15 (21H, m, isopropyl-H), 2.2 (1H, m, 2-H), 2.7 (2H, m, 4-H), 2.95 (3H, s, Me), 3.7 (2H, m, 3-H), 4.25 (2H, m, 1-H), 7.15–7.35 (5H, m, Ph); δ_C(100 MHz; $CDCl_3$; Me_4Si) 11.8 (2′-C), 17.9 (1′-C), 33.6 (4-C), 36.9 (MeS), 43.1 (2-C), 61.8 (3-C), 69.4 (1-C), 126.3–129.0, 138.9 (Ph) (Found: MH$^+$, 401.2208. $C_{20}H_{37}O_4SiS$ requires *M*H, 401.2181).

1-Iodo-2-benzyl-3-triisopropylsilyloxypropane 4b

To a solution of 1-methylsulfonyloxy-2-benzyl-3-triisopropylsilyloxypropane (3.42 g, 8.5 mmol) in freshly distilled AR acetone (50 ml) under argon was added sodium iodide (3.9 g, 25.6 mmol). The flask was wrapped in aluminium foil and the mixture stirred at reflux for 16 hours. The reaction mixture was evaporated under reduced pressure and washed with ether (100 ml) and water (50 ml). The aqueous phase was extracted with ether (3 × 50 ml) and the combined organic extracts dried over anhydrous $MgSO_4$. Evaporation under reduced pressure and purification of the residue by flash column chromatography

(9:1 petrol–ether) afforded iodide **4b** as a colourless oil (2.96 g, 6.85 mmol, 80%); ν_{max}(film)/cm^{-1} 3000–2800s (CH), 1462m, 1248w, 1213w, 1178w, 1107s, 1067m, 882s, 699s; δ_H(250 MHz; $CDCl_3$; Me_4Si) 1.06–1.07 (18H, d, *J* 4.8, isopropyl-CH_3), 1.07–1.09 (3H, m, isopropyl-H), 1.73 (1H, m, 2-H), 2.56–2.62 (1H, dd, $J_{4a,4b}$ 13.5 $J_{4a,2}$ 8.1, 4a-H), 2.7–2.76 (1H, dd, $J_{4b,4a}$ 13.5 $J_{4b,2}$ 6.2, 4b-H), 3.19–3.22 (1H, dd, $J_{1a,1b}$ 9.5 $J_{1a,2}$ 5.8, 1a-H), 3.35–3.38 (1H, dd, $J_{1b,1a}$ 9.8 $J_{1b,2}$ 4.3, 1b-H), 3.57–3.61 (1H, dd, $J_{3a,3b}$ 9.8 $J_{3a,2}$ 6.2, 3a-H), 3.68–3.70 (1H, dd, $J_{3b,3a}$ 9.5 $J_{3b,2}$ 4.7, 3b-H), 7.2–7.3 (5H, m, Ph); δ_C(100 MHz; $CDCl_3$; Me_4Si) 11.8 (1-C), 11.9 (2′-C), 18.0 (1′-C), 37.0 (4-C), 44.5 (2-C), 65.2 (3-C), 126–129.1 and 139.4 (Ph) (Found: MH$^+$, 433.1449. $C_{19}H_{34}IOSi$ requires *M*H, 433.1433).

(2-Benzyl-3-triisopropylsilyloxypropyl)triphenylphosphonium iodide 8

Triphenylphosphine (4.53 g, 17.3 mmol), iodide **4b** (7.37 g, 17.04 mmol) and anhydrous acetonitrile (10 ml) were heated at reflux for 72 hours. The solvent was removed under vacuum and the residue subjected to high vacuum. The resultant foam was then twice triturated with a 9:1 petrol–ether mix (30 ml). This afforded **8** as a microcrystalline solid (11.4 g, 16.4 mmol, 96%); ν_{max}(CH_2Cl_2 solution)/cm^{-1} 3000–2800s (CH), 1605m, 1440s (P–Ph), 1273s, 1112s, 909s; δ_H(250 MHz; $CDCl_3$; Me_4Si) 0.90–1.0 (21H, m, isopropyl-H), 2.2–2.42 (1H, m, 2-H), 2.53–2.65 (1H, m, 4a-H), 2.95–3.10 (1H, m, 4b-H), 3.46–3.95 (4H, m, 3-H and 1-H), 7.0–7.4 (20H, m, 4 × Ph).

N-Boc-Prolinol

To a stirred solution of (*S*)-prolinol (3.02 g, 29.8 mmol) and dry THF (60 ml) at 0 °C was added triethylamine (4.37 ml, 31.36 mmol). After 15 minutes $(Boc)_2O$ (6.39 g, 29.3 mmol) was added as a solution in THF (20 ml). The reaction mixture was concentrated to 20 ml and the residue partitioned between ether (40 ml) and 1 M HCl (60 ml). The aqueous phase was extracted further with ether (2 × 50 ml). The combined organic extracts were washed with $NaHCO_3$ (30 ml), dried with $MgSO_4$ and evaporated under reduced pressure. This yielded a colourless oil which crystallised on cooling (5.96 g, 29.6 mmol, 99%); mp 57 °C (lit.,[16] 57–58 °C); $[\alpha]_D^{25}$ −48.1 (*c* 1.0 in $CHCl_3$) (lit.,[16] −47.3); ν_{max}(film)/cm^{-1} 3400s (OH), 3000–2800s (CH), 1690s (NCO), 1400s, 1260m, 1170s, 1050s, 905m, 780m; δ_H(400 MHz; $CDCl_3$; Me_4Si) 1.47 [9H, s, $C(CH_3)_3$], 1.54–1.56 (1H, m, 3a-H), 1.74–1.87 (2H, m, 4-H), 1.96–2.01 (1H, m, 3b-H), 3.28–3.3 (1H, m, 5a-H), 3.42–3.50 (1H, m, 5b-H), 3.58–3.65 (2H, m, 6-H), 3.9–3.96 (1H, m, 2-H), 4.8 (1H, br, OH); δ_C(100 MHz; $CDCl_3$; Me_4Si) 24.0 (4-C), 28.4 [$C(CH_3)_3$], 28.9 (3-C), 47.5 (5-C), 60.1 (2-C), 67.5 (6-C), 80.1 [$C(CH_3)_3$], 157.0 (NCO) (Found: MH$^+$, 202.1432. $C_{10}H_{20}NO_3$ requires *M*H, 202.1443).

N-Boc-Prolinal 3b

To a stirred solution of Dess–Martin periodinane (27.9 g, 65.8 mmol) in DCM (150 ml) at room temperature was added *N*-Boc-prolinol (12.1 g, 59.8 mmol) as a solution in DCM (50 ml). After 2 hours stirring, the reaction was diluted with ether (200 ml) and washed with 1.3 M NaOH (1 × 200 ml, 1 × 100 ml). The organic layer was washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure to yield a light yellow oil (10.94 g, 54.9 mmol, 92%). Spectroscopic details were consistent with the literature.[17] ν_{max}(film)/cm^{-1} 3000–2800s (CH), 1715s (CHO), 1695s (NCO), 1680m, 1600m, 1520w, 1440m, 1390s, 1160s, 1120m; δ_H(400 MHz; $CDCl_3$; Me_4Si) 1.4–1.5 [9H, 2 × s, $C(CH_3)_3$], 1.8–2.2 (4H, m, 3-H and 4-H), 3.4–3.6 (2H, m, 5-H), 4.0–4.3 (1H, 2 × m, 2-H), 9.45–9.55 (1H, 2 × d, $J_{6,2}$ 2.93, 6-H); δ_C(100 MHz; $CDCl_3$; Me_4Si) 23.9 and 24.6 (4-C), 26.7 (3-C), 28.4 [$C(CH_3)_3$], 46.7 and 46.8 (5-C), 64.8 and 65.0 (2-C), 80.2 [$C(CH_3)_3$], 153.9 (7-C, NCO), 200.4 and 200.6 (6-C, CHO) (Found: MH$^+$, 200.1288. $C_{10}H_{18}NO_3$ requires *M*H, 200.1286).

(*Z*)- and (*E*)-(2*S*)-*N*-Boc-2-(3′-Benzyl-4′-triisopropylsilyloxy-but-1′-enyl)pyrrolidine 11 and 12

To a flame dried flask under argon was added phosphonium salt **8** (5.4 g, 7.76 mmol) and freshly distilled THF (60 ml). After cooling to −78 °C (acetone–CO_2) BuLi (3.1 ml, 2.5 M solution in hexanes, 7.7 mmol) was added dropwise. After 30 minutes and the observance of a deep yellow colour a solution of the aldehyde **3b** (1.7 g, 8.5 mmol) in THF (10 ml) was added by cannula over 40 minutes. The reaction mixture was stirred for 3 hours and gradually allowed to warm to room temperature. Water (30 ml) was added and the mixture extracted with ether (3 × 50 ml). The combined organic extracts were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Flash column chromatography of the residue (9:1 petrol–ether as eluent) afforded the two alkenes as colourless oils: *cis* isomer **11** as a mixture of two diastereoisomers, (1.98 g, 4.1 mmol, 52%); ν_{max}(film)/cm^{-1} 3000–2800s (CH), 1699s (N*CO*), 1456m, 1390s, 1365m, 1254w, 1170s, 1106s; δ_H(400 MHz; $CDCl_3$; Me_4Si) 0.94 (0.5H, m, 0.5 3a-H), 1.03–1.09 (21H, m, isopropyl-H), 1.41–1.43 [9.5H, m, $C(CH_3)_3$ and 0.5 3a-H], 1.5–2.15 (3H, m, 4-H and 3b-H), 2.37–2.46 (0.5H, dd, $J_{5'a,5'b}$ 12.9 $J_{5'a,3'}$ 9.3, 5′a-H), 2.8 (1H, m, 5′b-H), 2.82–2.93 (1H, m, 3′-H), 3.1–3.17 (0.5H, dd, $J_{5'a,5'b}$ 12.9 $J_{5'a,3'}$ 4.5, 5′a-H), 3.22–3.57 (3.5H, m, 5-H, 4′a-H and 0.5 4′b-H), 3.78–3.82 (0.5H, m, 4′b-H), 4.13–4.2 (0.5H, m, 2-H), 4.5–4.58 (0.5H, m, 2-H), 5.2–5.45 (2H, overlapping dd, $J_{2',1'}$ 11.0, 1′-H and 2′-H), 7.15–7.3 (5H, m, Ph); δ_C(100 MHz; $CDCl_3$; Me_4Si) 11.9 and 12.0 (2″-C), 18.0 (1″-C), 23.5 and 23.7 (4-C), 28.5 [$C(CH_3)_3$], 32.6 and 33.9 (3-C), 37.1 and 38.2 (5′-C), 41.5 and 43.0 (3′-C), 46.3 and 46.4 (5-C), 54.5 and 54.7 (2-C), 65.0 and 65.8 (4′-C), 78.8 and 79.0 [$C(CH_3)_3$], 125.6, 128.0, 129.5, 140.0 and 140.9 (Ph), 128.9 and 130.8 (2′-C), 132.9 (1′-C), 154.3 and 154.5 (NCO) (Found: MH$^+$, 488.3533. $C_{29}H_{49}NO_3Si$ requires *M*H, 488.3559); *trans* isomer **12** (0.65 g, 1.33 mmol, 18%); ν_{max}(film)/cm^{-1} 3000–2800s (CH), 1699s (NCO), 1456w, 1394s, 1364m, 1256w, 1170s, 1106s, 882m; δ_H(400 MHz; $CDCl_3$; Me_4Si) 0.8–0.99 (1H, m, 3a-H), 1.06–1.1 (21H, m, 6 × isopropyl-H), 1.44 [9H, 2 × s, diastereoisomers, $C(CH_3)_3$], 1.5–1.97 (3H, m, 3b-H and 4-H), 2.4–2.59 (2H, m, 5′a-H and 3′-H), 2.95–3.02 (1H, dd, $J_{5'b,5'a}$ 12.1 $J_{5'b,3'}$ 4.2, 5′b-H), 3.25–3.38 (2H, m, 5-H), 3.45–3.69 (2H, m, 4′-H), 4.2 (1H, m, 2-H), 5.18–5.47 (2H, overlapping dd, $J_{1',2'}$ 15.9 $J_{2',1'}$15.9, 1′-H and 2′-H), 7.13–7.3 (5H, m, Ph); δ_C(100 MHz; $CDCl_3$; Me_4Si) 11.9 (2″-C), 18.0 (1″-C), 23.2 and 23.5 (4-C), 28.5 [$C(CH_3)_3$], 29.7 and 30.3 (3-C), 37.6 and 37.7 (5′-C), 41.2 and 43.1 (3′-C), 46.0 and 46.9 (5-C), 58.2 (2-C), 66.2 (4′-C), 78.8 [$C(CH_3)_3$], 125.6–132.3 (Ph and 1′-C and 2′-C), 140.6 (quat-C), 154.1 (NCO) (Found: MH$^+$, 488.3555. $C_{29}H_{49}NO_3Si$ requires *M*H, 488.3559).

(*Z*)-*N*-Boc-(2*S*)-2-[(3′*R* and 3′*S*)-3′-benzyl-4′-hydroxybut-1′-enyl]pyrrolidines 13a and 13b

To a solution of alkene **11** (2.28 g, 4.68 mmol) in dry THF (35 ml) at room temperature was added tetrabutylammonium fluoride (5.15 ml, 1 M solution in THF, 5.15 mmol). After 2 hours solvent was removed under vacuum and the residue purified by flash column chromatography (6:4 ether–petrol as eluent) to yield the two isomers as colourless oils. The oils crystallised on prolonged standing. **13a** (0.73 g, 2.2 mmol, 47%); $[\alpha]_D^{25}$ +54.9 (*c* 6.9 in $CHCl_3$); mp 65–66 °C; ν_{max}(film)/cm^{-1} 3450s (OH), 3000–2800s (CH), 1676s (NCO), 1400s, 1167s; δ_H(400 MHz; $CDCl_3$; Me_4Si) 1.05 (1H, m, 3a-H), 1.4 [9H, s, $C(CH_3)_3$], 1.43–1.55 (1H, m, 3b-H), 1.6–1.7 (1H, m, 4a-H), 1.7–1.8 (1H, m, 4b-H), 2.30–2.36 (1H, dd, $J_{5'a,5'b}$ 13.2 $J_{5'a,3'}$ 10.3, 5′a-H), 2.69–2.73 (1H, dd, $J_{5'b,5'a}$ 13.2 $J_{5'b,3'}$ 4.03, 5′b-H), 3.19 (1H, m, 3′-H), 3.24–3.27 (2H, m, 5-H), 3.38–3.43 (1H, m, 4′a-H), 3.8–3.83 (1H, m, 4′b-H), 4.13–4.19 (1H, br, OH), 4.2–4.22 (1H, m, 2-H), 5.19–5.31 (2H, m, 2′-H and 1′-H), 7.11–7.26 (5H, m, Ph); δ_C100 MHz; $CDCl_3$; Me_4Si) 23.9 (4-C), 28.5 [$C(CH_3)_3$], 31.5 (3-C), 38.0 (5′-C), 43.0 (3′-C), 46.5 (5-C), 54.0 (2-C), 66.6 (4′-C), 79.7 [$C(CH_3)_3$], 125.8–129.1 (Ph), 132.2 and 132.4 (1′-C and 2′-C),

155.0 (NCO) (Found: MH^+, 322.2210. $C_{19}H_{30}NO_3$ requires *M*H, 332.2225). **13b** (0.697 g, 2.10 mmol, 45%); $[a]_D^{25}$ +31.7 (*c* 2.0 in $CHCl_3$); mp 82 °C; ν_{max}(film)/cm^{-1} 3430s (OH), 3000–2800s (CH), 1693s (NCO), 1495w, 1477m, 1454m, 1365s, 1167s, 1110; δ_H(400 MHz; $CDCl_3$; Me_4Si) 1.45 [9H, s, $C(CH_3)_3$], 1.58–2.10 (4H, m, 4-H and 3-H), 2.11 (1H, m, 3′-H), 2.6–2.7 (1H, dd, $J_{5'a,5'b}$ 13.6 $J_{5'a,3'}$ 8.5, 5′a-H), 2.77–2.85 (1H, dd, $J_{5'b,5'a}$ 13.6 $J_{5b,3'}$ 5.4, 5′b-H), 2.9–3.1 (1H, br s, OH), 3.2–3.5 (3H, m, 5-H and 4′b-H), 3.51–3.57 (1H, dd, J_{gem} 10.6 $J_{4'a,3'}$ 4.9, 4′a-H), 4.5–4.62 (1H, m, 2-H), 5.23 (1H, dd, $J_{2',1'}$ 11.0 $J_{2',3'}$ 9.9, 2′-H), 5.45–5.5 (1H, dd, $J_{1',2'}$ 11.0 $J_{1',2}$ 8.2, 1′-H), 7.15–7.35 (5H, m, Ph); δ_C(100 MHz; $CDCl_3$; Me_4Si) 23.7 (4-C), 28.4 [$C(CH_3)_3$], 28.6 (3-C), 38.0 (5′-C), 42.0 (3′-C), 46.5 (5-C), 55.0 (2-C), 64.9 (4′-C), 79.2 [$C(CH_3)_3$], 126.0–129.1 (Ph), 131.1 (2′-C), 136.5 (1′-C), 154.6 (NCO) (Found: MH^+, 332.2234. $C_{20}H_{30}NO_3$ requires *M*H, 332.2225).

(*Z*)-(2*S*)-*N*-Boc-2-[(3′*R*)-3′-benzyl-3′-carboxyprop-1′-enyl]-pyrrolidine 14a

To a solution of alcohol **13a** (0.75 g, 2.26 mmol) in acetone (25 ml) at 0 °C was slowly added a solution of Jones' reagent (2 ml, 2.76 M CrO_3 in H_2SO_4). After 1 hour the supernatant liquor was decanted, washed with water (10 ml) and extracted with ether (3 × 15 ml). The combined organic extracts were dried with $MgSO_4$ and filtered through a short pad of silica. Evaporation *in vacuo* yielded **14a** as a light yellow oil (0.698, 2.02 mmol, 89%); ν_{max}(film)/cm^{-1} 3400–2700s (CH and H-bonded OH of CO_2H), 1730s (CO_2H), 1690s, 1477w, 1420s, 1367m, 1165s, 750w; δ_H(400 MHz; $CDCl_3$; Me_4Si) 0.95–1.02 (1H, m, 3a-H), 1.4 [9H, s, $C(CH_3)_3$], 1.40–1.85 (3H, m, 3b-H and 4-H), 2.68–2.74 (1H, dd, J_{gem} 13.6 $J_{5'a,3'}$ 10.6, 5′a-H), 3.3 (3H, m, 5-H and 5′b-H), 3.9–4.03 (2H, m, 3′-H and 2-H), 5.25–5.3 (1H, dd, $J_{1',2'}$10.6 $J_{1',2}$ 9.9, 1′-H), 5.3–5.4 (1H, overlapping dd, $J_{2',1'}$ 10.6 $J_{2',3'}$ 10.6, 2′-H), 7.1–7.3 (5H, m, Ph) (Found: MH^+, 346.2035. $C_{20}H_{28}NO_4$ requires *M*H, 346.2018).

(*Z*)-(2*S*)-*N*-Boc-2-[(3′*S*)-3′-benzyl-3′-carboxyprop-1′-enyl]-pyrrolidine 14b

To a solution of alcohol **13b** (0.60 g, 1.83 mmol) in acetone (25 ml) at 0 °C was slowly added a solution of Jones' reagent (2 ml, 2.76 M CrO_3 in H_2SO_4). After 1 hour the supernatant liquor was decanted, washed with water (10 ml) and extracted with ether (3 × 15 ml). The combined organic extracts were dried with $MgSO_4$ and filtered through a short pad of silica. Evaporation *in vacuo* yielded **14b** as a light yellow oil (0.62, 1.72 mmol, 98%); ν_{max}(film)/cm^{-1} 3400–2700s (CH and H-bonded OH of CO_2H), 1730s (CO_2H), 1694s (NCO), 1392s, 1366s, 1163s, 749w; δ_H(400 MHz; $CDCl_3$; Me_4Si) 1.46 [9H, s, $C(CH_3)_3$], 1.55–2.15 (4H, m, 3-H and 4-H), 2.85–2.95 (1H, dd unresolved, 5′a-H), 3.05–3.15 (1H, dd, J_{gem} 10.7 $J_{5'b,3'}$ 9.5, 5′b-H), 3.28–3.4 (2H, m, 5-H), 3.7–3.8 (1H, m, 3′-H), 4.55–4.65 (1H, m, 2-H), 5.36–5.44 (1H, overlapping dd, $J_{1',2'}$ 10.2, $J_{1',2}$ 10.2, 1′-H), 5.5–5.59 (1H, dd unresolved, 2′-H), 7.18–7.3 (5H, m, Ph) (Found: MH^+, 346.2031. $C_{20}H_{28}NO_4$ requires *M*H, 346.2018).

(*Z*)-(2*S*)-*N*-Boc-2-[(3′*S*)-3′-benzyl-3′-benzyloxycarbonylprop-1′-enyl]pyrrolidine 15b

To a flask under argon at room temperature containing carbonyldiimidazole (0.32 g, 1.98 mmol) was added a solution of acid **14b** (0.62 g, 1.8 mmol) in DCM (5 ml). After 5 minutes, benzyl alcohol (0.30 g, 2.7 mmol) was added. Sodium ethoxide (5 mg, catalytic) was added and the reaction stirred for 72 hours. The solvent was removed under vacuum and the residue purified by flash chromatography (7:3 petrol–ether as eluent). This afforded **15b** as a viscous colourless oil (0.40 g, 0.92 mmol, 51%); $[a]_D^{22}$ +134.6 (*c* 1.8 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3200–2800s (CH), 1733s (CO_2Bn), 1695s (NCO), 1456m, 1390s, 1256m, 1162s, 698m; δ_H(250 MHz; $CDCl_3$; Me_4Si) 1.45 [9H, s, $C(CH_3)_3$], 1.45–1.55 (1H, m, 3a-H), 1.64–1.9 (2H, m, 4-H), 1.9–2.05 (1H, m, 3b-H), 2.9–3.05 (1H, m, 5′a-H), 3.05–3.2 (1H, dd, J_{gem} 13.6 $J_{5'b,3'}$ 10.1, 5′b-H), 3.3–3.5 (2H, m, 5-H), 3.9 (1H, br s, 3′-H), 4.6 (1H, br, 2-H), 4.98 (1H, d, J_{gem} 12.3, 6′a-H), 5.01 (1H, d, J_{gem} 12.3, 6′b-H), 5.4–5.5 (2H, pseudo quintet, $J_{1',2'}$ 10.3 $J_{2',1'}$ 10.3, 1′-H, 2′-H), 7.13–7.36 (10H, m, 2 × Ph); δ_C(100 MHz; $CDCl_3$; Me_4Si) 24.2 (3-C), 24.3 (4-C), 28.9 [$C(CH_3)_3$], 39.2 (5′-C), 46.7 (5-C), 46.9 (3′-C), 54.9 (2-C), 66.6 (6′-C), 79.6 [$C(CH_3)_3$], 126.8–128.8 and 139.1 (Ph), 129.4 (2′-C), 136.1 (1′-C), 154.8 (NCO), 173.6 (4′-C, CO_2Bn) (Found: MH^+, 436.2492. $C_{27}H_{34}NO_4$ requires *M*H, 436.2487).

(*Z*)-(2*S*)-*N*-Boc-2-[(3′*R*)-3′-benzyl-3′-benzyloxycarbonylprop-1′-enyl]pyrrolidine 15a

To a flask under argon at room temperature containing carbonyldiimidazole (0.35 g, 2.15 mmol) was added a solution of acid **14a** (0.675 g, 1.95 mmol) in DCM (5 ml). After 5 minutes, benzyl alcohol (0.32 g, 2.96 mmol) was added. Sodium ethoxide (5 mg, catalytic) was added and the reaction stirred for 72 hours. The solvent was removed under vacuum and the residue purified by flash chromatography (2:1 petrol–ether as eluent). This yielded **15a** as a viscous colourless oil (0.44 g, 1.00 mmol, 51%); $[a]_D^{25}$ +30.9 (*c* 1.3 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3200–2800 (CH), 1732s (CO_2Bn), 1694s (NCO), 1496w, 1455m, 1392s, 1365m, 1105w; δ_H(400 MHz; $CDCl_3$; Me_4Si) 0.9–1.05 (1H, m, 3a-H), 1.35 [9H, s, $C(CH_3)_3$], 1.4–1.6 (1H, m, 3b-H), 1.6–1.8 (2H, m, 4-H), 2.67–2.8 (1H, dd, J_{gem} 13.3, $J_{5'a,3'}$ 8.5, 5′a-H), 3.05–3.15 (1H, dd, J_{gem} 13.3 $J_{5'b,3'}$ 6.35, 5′b-H), 3.23 (2H, m, 5-H), 3.65–3.85 (1H, br s, 3′-H), 4.15–4.25 (1H, m, 2-H), 5.05 (1H, d, J_{gem} 12.3, 6′a-H), 5.12 (1H, d, J_{gem} 12.3, 6′b-H), 5.35–5.45 (1H, dd, $J_{1',2}$ 8.7 $J_{1',2'}$ 10.9, 1′-H), 5.5–5.6 (1H, dd, $J_{2',3'}$ 10.8 $J_{2',1'}$ 10.8, 2′-H), 7.1–7.4 (10H, m, 2 × Ph); δ_C(100 MHz; $CDCl_3$; Me_4Si) 23.6 (3-C), 28.4 [$C(CH_3)_3$], 32.7 (4-C), 39.8 (5′-C), 46.3 (5-C), 46.4 (3′-C), 54.3 (2-C), 66.4 (6′-C), 79.1 [$C(CH_3)_3$], 126.5–128.3 and 129.3 (Ph), 128.1 (2′-C), 128.4 (1′-C), 154.3 (NCO), 173.5 (CO_2Bn) (Found: MH^+, 436.2496. $C_{27}H_{34}NO_4$ requires *M*H, 436.2487).

(2*S*)-*N*-Methoxycarbonylcarbonyl-2-[(3′*R*)-3′-benzyl-3′-benzyloxycarbonylprop-1′-enyl]pyrrolidine 16a

To a stirred solution of **15a** (396 mg, 0.91 mmol) in DCM (2 ml) at room temperature was added trifluoroacetic acid (1 ml). After 20 minutes, solvent and TFA were removed under vacuum and the residue dissolved in DCM (4 ml). The reaction was cooled to 0 °C (ice bath) and pyridine (0.22 ml, 2.73 mmol) and methyl oxalyl chloride (0.09 ml, 1.00 mmol) were added. The reaction was stirred for 1 hour at 0 °C, poured into 1 M HCl (5 ml) and extracted with ether (3 × 10 ml). The combined organic extracts were dried with $MgSO_4$ and evaporated under reduced pressure. Flash column chromatography of the residue (ether as eluent) afforded **16a** as a light orange oil (0.32 g, 0.77 mmol, 85%) (Found: C, 70.5; H, 6.4; N, 3.3; $C_{25}H_{27}NO_5$ requires C, 71.2; H, 6.5; N, 3.3%); $[a]_D^{23}$ +20.3 (*c* 1.8 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3200–2800s (CH), 1734s (CO_2Me and CO_2Bn), 1655s (NCO), 1497m, 1455s, 1378w, 1161s, 917w; δ_H(400 MHz; $CDCl_3$; Me_4Si) (as a mixture of rotamers) 0.9–1.17 (2H, m, 4-H), 1.19–1.75 (2H, m, 3-H), 2.65–2.68 (1H, dd, J_{gem} 13.2 $J_{5'a,3'}$ 10.3, 5′a-H), 3.13–3.17 (1H, dd, J_{gem} 13.2 $J_{5'b,3'}$ 5.13, 5′b-H), 3.39–3.58 (2H, m, 5-H), 3.5 (2.25H, s, OMe), 3.58–3.7 (0.75H, m, 3′-H), 3.8 (0.75H, s, OMe), 3.98–4.06 (0.25H, m, 3′-H), 4.3–4.39 (0.25H, m, 2-H), 4.39–4.45 (0.75H, m, 2-H), 5.07–5.21 (2H, d, J_{gem} 12.1, 6′-H), 5.21–5.28 (1H, m, 1′-H), 5.66–5.71 (1H, dd, $J_{2',1'}$ 10.62 $J_{2',3'}$ 10.63, 2′-H), 7.11–7.37 (10H, m, 2 × Ph); δ_C(100 MHz; $CDCl_3$; Me_4Si) 22.6 and 24.4 (3-C), 30.5 and 33.0 (4-C), 39.3 and 39.5 (5′-C), 46.1 and 46.2 (5-C), 46.6 and 47.5 (3′-C), 52.3 and 52.5 (OMe), 54.8 and 55.4 (2-C), 66.5 and 66.7 (6′-C), 126.4 and 126.7 (Ph), 127.9 and 128.0 (2′-C), 128.2–129.5 (Ph), 130.5 and 131.5 (1′-C), 135.7 and 135.9 (quat-C), 138.1 and 138.4 (quat-C), 159.6 (NCO), 162.5 (CO_2Me), 173.1 and 173.2 (CO_2Bn) (Found: MH^+, 422.1986. $C_{25}H_{28}NO_5$ requires *M*H, 422.1967).

(2*S*)-*N*-Methoxycarbonylcarbonyl-2-[(3′*S*)-3′-benzyl-3′-benzyloxycarbonylprop-1′-enyl]pyrrolidine 16b

To a stirred solution of **15b** (332 mg, 0.76 mmol) in DCM (2 ml) at room temperature was added trifluoroacetic acid (1 ml). After 20 minutes the solvent and TFA were removed under vacuum and the residue dissolved in DCM (4 ml). The reaction was cooled to 0 °C (ice bath) and pyridine (0.185 ml, 2.29 mmol) and methyl oxalyl chloride (0.077 ml, 0.84 mmol) were added. The reaction was stirred for 1 hour at 0 °C, poured into 1 M HCl (5 ml) and extracted with diethyl ether (3 × 10 ml). The combined organic extracts were dried with $MgSO_4$ and evaporated under reduced pressure. Flash column chromatography of the residue (diethyl ether as eluent) afforded **16b** as a light orange oil (0.257 g, 0.61 mmol, 80%) (Found: C, 71.1; H, 6.5; N, 3.5; $C_{25}H_{27}NO_5$ requires C, 71.2; H, 6.5; N, 3.3%); $[\alpha]_D^{26}$ +166.7 (*c* 0.8 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3200–2800 (CH), 1733s (CO_2Me and CO_2Bn), 1635s (NCO), 1515m, 1418m, 1242s, 1139s; δ_H(400 MHz; $CDCl_3$; Me_4Si) (as a mixture of rotamers) 1.5–2.0 (4H, m, 3-H and 4-H), 2.84–2.88 (0.5H, dd, J_{gem} 13.9 $J_{5'a,3'}$ 4.7, 5′a-H), 3.05–3.11 (1.5H, m, 0.5 5′a-H and 5′b-H), 3.47–3.54 (1H, m, 5a-H), 3.63–3.75 (1.5H, m, 5b-H and 0.5 3′-H), 3.69 (1.5H, s, 1.5 O-Me), 3.85 (1.5H, s, 1.5 O-Me), 4.03–4.1 (0.5H, m, 3′-H), 4.86–4.92 (0.5H, m, 2-H), 4.92–5.02 (2.5H, m, 0.5 2-H and 6′-H), 5.34–5.4 (1H, overlapping dd, $J_{1',2'}$ 10.3 $J_{1',2}$ 10.3, 1′-H), 5.5–5.6 (1H, overlapping dd, $J_{2',1'}$ 10.3 $J_{2',3'}$ 10.3, 2′-H), 7.11–7.3 (10H, m, 2 × Ph); δ_C(100 MHz; $CDCl_3$; Me_4Si) 22.8 and 24.7 (3-C), 31.2 and 33.8 (4-C), 38.4 and 38.5 (5′-C), 46.5 and 46.6 (5-C), 46.8 and 47.7 (3′-C), 52.4 and 52.7 (OMe), 54.9 and 55.8 (2-C), 66.2 and 66.5 (6′-C), 126.3–129.2, 135.5 and 138.3 (Ph), 130.6 (2′-C), 132.8 (1′-C), 158.3 and 159.3 (NCO), 162.5 and 162.7 (CO_2Me), 172.4 and 173.1 (CO_2Bn) (Found: MH$^+$, 422.1959. $C_{25}H_{28}NO_5$ requires *M*H, 422.1967).

(*E*)-(2*S*)-*N*-Boc-2-[(3′*RS*)-3′-benzyl-4′-hydroxybut-1′-enyl]-pyrrolidine 17

To a solution of alkene **12** (0.67 g, 1.38 mmol) in dry THF (15 ml) at room temperature was added tetrabutylammonium fluoride (1.6 ml, 1 M solution in THF, 1.6 mmol). After 2 hours the solvent was removed under vacuum and the residue purified by flash column chromatography (2:1 ether–petrol as eluent) to yield the two inseparable diastereoisomers **17** as a colourless oil (0.32 g, 0.96 mmol, 70%); ν_{max}(film)/cm^{-1} 3400bs (OH), 3000–2800s (CH), 1691 (NCO), 1401s, 1365, 1254w, 1170s, 1119m, 966m, 744m, 700s; δ_H(400 MHz; $CDCl_3$; Me_4Si) 0.8–0.9 (1H, m, 3a-H), 1.42 [9H, 2 × s, diastereoisomers, $C(CH_3)_3$], 1.45–1.62 (1H, m, 3b-H), 1.67–1.8 (2H, m, 4-H), 1.99 (1H, br s, OH), 2.49–2.68 (2H, m, 3′-H and 5′a-H), 2.71–2.76 (1H, dd, J_{gem} 13.2 $J_{5'b,3'}$ 6.6, 5′b-H), 3.3–3.41 (3H, m, 5-H and 4′a-H), 3.55–3.6 (1H, m, 4′b-H), 4.1–4.15 (0.5H, m, 2-H), 4.2–4.24 (0.5H, m, 2-H), 5.27–5.36 (1H, m, 2′-H), 5.38–5.4 (1H, dd, $J_{1',2'}$ 15.4 $J_{1',2}$ 5.5, 1′-H), 7.13–7.27 (5H, m, Ph); δ_C(100 MHz; $CDCl_3$; Me_4Si) 22.8 and 23.3 (4-C), 28.4 [C(CH_3)$_3$], 31.8 and 32.2 (3-C), 37.4 (5′-C), 46.3 (3′-C), 46.5 (5-C), 58.2 (2-C), 64.7 (4′-C), 79.2 [$C(CH_3)_3$], 125.8–130.2 and 140.0 (Ph), 133.7 (2′-C), 139.7 (1′-C), 154.3 and 154.6 (NCO) (Found: MH$^+$, 332.2240. $C_{20}H_{30}NO_3$ requires *M*H, 332.2225).

(*E*)-(2*S*)-*N*-Boc-2-[(3′*RS*)-3′-benzyl-3′-benzyloxycarbonylprop-1′-enyl]pyrrolidine 19

To a solution of alcohol **17** (1.37 g, 4.1 mmol) in acetone (65 ml) at 0 °C was slowly added a solution of Jones' reagent (3 ml, 2.76 M CrO_3 in H_2SO_4). After 1 hour the supernatant liquor was decanted, washed with water (30 ml) and extracted with ether (3 × 45 ml). The combined organic extracts were dried with $MgSO_4$ and filtered through a short pad of silica. Evaporation *in vacuo* yielded the acid **18** as a light yellow oil (1.22 g, 3.54 mmol, 86%). Without further purification **18** (0.40 g, 1.16 mmol) as a solution in DCM (5 ml), was added to a flask under argon at room temperature containing carbonyldiimidazole (0.20 g, 1.22 mmol) and DCM (10 ml). After 5 minutes, benzyl alcohol (0.14 ml, 1.4 mmol) was added. Sodium ethoxide (10 mg, catalytic) was added and the reaction stirred for 72 hours. The solvent was removed under vacuum and the residue purified by flash chromatography (3:2 petrol–ether as eluent). This yielded **19** as a colourless oil (0.18 g, 0.4 mmol, 35%); ν_{max}(film)/cm^{-1} 3200–2800s (CH), 1735s (CO_2Bn), 1694s (NCO), 1497w, 1393s, 1364m, 1269m, 1159s, 746m, 699m; δ_H(400 MHz; $CDCl_3$; Me_4Si) 1.39 [9H, 2 × s, diastereoisomers, $C(CH_3)_3$], 1.39–1.9 (4H, m, 4-H and 3-H), 2.78–2.9 (1H, m, 5′a-H), 3.04–3.15 (1H, m, 5′b-H), 3.27–3.43 (3H, m, 5-H and 3′-H), 4.15–4.35 (1H, br m, 2-H), 5.04 (2H, s, 6′-H), 5.36–5.41 (1H, dd, $J_{1',2'}$ 15.4 $J_{1',2}$ 5.5, 1′-H), 5.51–5.57 (1H, dd, $J_{2',1'}$ 15.7 $J_{2',3'}$ 8.5, 2′-H), 7.1–7.4 (10H, m, 2 × Ph); δ_C(100 MHz; $CDCl_3$; Me_4Si) 22.9 (3-C), 28.5 [C(CH_3)$_3$], 34.0 (4-C), 38.9 (5′-C), 46.1 (5-C), 50.6 (3′-C), 57.9 (2-C), 66.3 (6′-C), 79.1 [$C(CH_3)_3$], 126.4–129.1 (2 × Ph and 1′-C, 2′-C), 135.8 and 138.6 (quat-C), 154.5 (NCO), 173.3 (CO_2Bn) (Found: MH$^+$, 436.2472. $C_{27}H_{34}NO_4$ requires *M*H, 436.2487).

(2*S*)-*N*-Methoxycarbonylcarbonyl-2-[(3′*RS*)-3′-benzyl-3′-benzyloxycarbonylprop-1′-enyl]pyrrolidine 20

To a stirred solution of **19** (175 mg, 0.4 mmol) in DCM (3 ml) at room temperature was added trifluoroacetic acid (1 ml). After 15 minutes the solvent and TFA were removed under vacuum and the residue dissolved in DCM (4 ml). After cooling the reaction to 0 °C (ice bath) pyridine (0.1 ml, 1.21 mmol) and methyl oxalyl chloride (0.041 ml, 0.44 mmol) were added. The reaction was stirred for 1 hour at 0 °C, poured into 1 M HCl (5 ml) and extracted with diethyl ether (3 × 15 ml). The combined organic extracts were dried with $MgSO_4$ and evaporated under reduced pressure. Flash column chromatography of the residue (diethyl ether as eluent) afforded **20** as a colourless oil which crystallised as a mixture of isomers on standing (0.15 g, 0.35 mmol, 87%) (Found: C, 70.8; H, 6.45; N, 3.3; $C_{25}H_{27}NO_5$ requires C, 71.2; H, 6.5; N, 3.3%); mp 69 °C; ν_{max}(film)/cm^{-1} 3200–2900s (CH), 1734s (CO_2Me and CO_2Bn), 1652s (NCO), 1495w, 1456m, 1423m, 1252s, 1150s, 1029w, 747m, 699m; δ_H(400 MHz; $CDCl_3$; Me_4Si) 1.55–2.11 (4H, m, 3-H and 4-H), 2.75–2.9 (1H, m, 5′a-H), 3.05 (1H, m, 5′b-H), 3.3–3.4 (1H, m, 3′-H), 3.48–3.6 (2-H, m, 5-H), 3.67 and 3.71 and 3.86 and 3.87 (3H, 4 × s, rotamers and diastereoisomers, OMe), 4.6–4.73 (1H, m, 2-H), 5.05 (2H, m, 6′-H), 5.26–5.41 (1H, m, 1′-H), 5.5–5.6 (1H, overlapping dd, $J_{2',1'}$ 15.4 $J_{2',3'}$ 8.4, 2′-H, 7.1–7.3 (10H, m, 2 × Ph); δ_C(100 MHz; $CDCl_3$; Me_4Si) 21.5, 21.8, 23.5 and 23.6 (3-C), 30.1, 30.2, 32.6 and 32.8 (4-C), 38.5 and 38.6 (5′-C), 46.2, 46.3 and 47.3 (5-C), 50.2, 50.4 and 50.6 (3′-C), 52.4 and 52.6 (OMe), 58.1, 58.3, 59.1 and 59.3 (2-C), 66.3, 66.5 and 66.6 (6′-C), 126.3–132.8 and 141.1 (Ph), 135.4, 135.5 and 135.7 (2′-C), 138.0, 138.1 and 138.3 (1′-C), 158.0 and 159.5 (N*C*O), 162.5 (CO_2Me), 172.5, 172.7 and 173.0 (CO_2Bn) (Found: MH$^+$, 422.1977. $C_{25}H_{28}NO_5$ requires *M*H, 422.1967).

(2*S*)-*N*-Boc-2-[(3′*R* and 3′*S*)-1-Oxo-3′-benzyl-4′-triisopropylsilyloxybutyl]pyrrolidine 22a

To a stirred solution of alkene **11** (0.51 g, 1.05 mmol) in THF (10 ml) at 0 °C was added BH_3·DMF (0.50 ml, 1 M in THF, 0.50 mmol) dropwise. The reaction was warmed to 40 °C and stirred for 18 hours. 3 M NaOH (3 ml) was added followed by H_2O_2 (30%, 2 ml) and the mixture stirred for 3 hours. The aqueous mixture was treated with brine (20 ml) and extracted with diethyl ether (3 × 50 ml). The combined organic extracts were washed with brine, dried with $MgSO_4$ and evaporated to dryness. Flash column chromatography (1:1 diethyl ether–petrol as eluent) of the residue afforded the intermediate 1′-hydroxy (**21a**) (0.34 g, 0.67 mmol, 64%) and the 2′-hydroxy (**21b**) (0.069 g, 0.136 mmol, 13%) regioisomers as colourless oils. To a stirred solution of Dess–Martin periodinane (0.220 g, 0.52 mmol) in DCM (2 ml) at room temperature was added the 1′-hydroxy regioisomer (**21a**) (0.24 g, 0.47 mmol). After 1 hour, diethyl

ether (15 ml) was added and the suspension treated with 1.3 M NaOH (4 ml). After 10 minutes stirring the mixture was washed further with NaOH (2 × 4 ml) and water (1 × 5 ml). The organic phase was dried ($MgSO_4$) and evaporated. Flash column chromatography of the residue (8:2 petrol–ether as eluent) afforded **22a** as an inseparable diastereomeric mixture (210 mg, 0.41 mmol, 87%); ν_{max}(film)/cm^{-1} 3000–2800s (CH), 1702s (NCO and C=O), 1463m, 1393s, 1366s, 1166s, 995w, 882m, 700m; δ_H(400 MHz; $CDCl_3$; Me_4Si) 1.05 (21H, m, isopropyl), 1.30 and 1.45 [9H, 2 × s, 1.5:1 rotameric mixture, $C(CH_3)_3$], 1.7–1.88 (3H, m, 4-H and 3a-H), 2.1 (1H, m, 3b-H), 2.3–2.8 (5H, m, 2′-H, 5′-H and 3′-H), 3.4–3.65 (4H, m, 5-H and 4′-H), 4.15 and 4.3 (1H, 2 × m, 1.5:1 rotameric mixture, 2-H), 7.13–7.3 (5H, m, Ph) (Found: MH$^+$, 504.3490. $C_{29}H_{50}NO_4Si$ requires *M*H, 504.3409).

(2*S*)-*N*-Boc-2-[(3′*RS*)-1-Oxo-3-benzyl-4′-hydroxybutyl]-pyrrolidine 23

To a solution of **22a** (1.6 g, 3.17 mmol) in THF (35 ml) at room temperature was added TBAF (3.35 ml, 1 M in THF, 3.35 mmol). After 1 hour the mixture was rotary evaporated to dryness and the residue purified by flash column chromatography (9:1 diethyl ether–petrol as eluent). This afforded **23** as a colourless oil (0.873 g, 2.52 mmol, 80%); ν_{max}(film)/cm^{-1} 3445s (OH), 3000–2800s (CH), 1700s (C=O), 1690s (NCO), 1455m, 1403s, 1255w, 1166s, 1030m; δ_H(400 MHz; $CDCl_3$; Me_4Si) 1.42 [9H, 4 × s, diastereomeric and rotameric mixture, $C(CH_3)_3$], 1.7–2.1 (5H, m, 4-H, 3-H and 3′-H), 2.3–3.0 (5H, m, 2′-H, 6′-H and OH), 3.2–3.8 (4H, m, 5-H and 4′-H), 4.1–4.4 (1H, m, 2-H), 7.1–7.3 (5H, m, Ph) (Found: MH$^+$, 348.2170. $C_{20}H_{30}NO_4$ requires *M*H, 348.2174).

(2*S*)-*N*-Boc-2-[(3′*RS*)-1-Oxo-3-benzyl-3′-benzyloxycarbonyl-propyl]pyrrolidine 24

To a solution of alcohol **23** (0.19 g, 0.55 mmol) in acetone (10 ml) at 0 °C was added dropwise a solution of Jones' reagent (0.5 ml, 2.76 M CrO_3 in H_2SO_4). After 1 hour, the supernatant liquor was decanted, washed with water (3 ml) and extracted with ether (3 × 15 ml). The combined organic extracts were dried ($MgSO_4$) and filtered through a short pad of silica. Evaporation *in vacuo* afforded the intermediate acid as a light yellow oil (0.174 g, 0.48 mmol, 87%). Without further purification the acid (0.150 g, 0.44 mmol), as a solution in DCM (2 ml), was added to a flask under argon at room temperature containing carbonyldiimidazole (77 mg, 0.46 mmol) and DCM (3 ml). After 5 minutes benzyl alcohol (0.05 ml, 0.5 mmol) and sodium ethoxide (1 mg, catalytic) were added. After stirring for 72 hours the solvent was removed under vacuum and the residue purified by flash chromatography (1:1 petrol–ether as eluent). This afforded the benzyl ester **24** as a colourless oil (74 mg, 0.16 mmol, 38%); ν_{max}(film)/cm^{-1} 3000–2800s (CH), 1730s (CO_2Bn), 1700s (CO), 1690s (NCO), 1455m, 1400s, 1165s, 1118m, 699m; δ_H(400 MHz; $CDCl_3$; Me_4Si) 1.25 and 1.45 [9H, 4 × s, diastereomeric and rotameric mixture, $C(CH_3)_3$], 1.63–2.15 (4H, m, 3-H and 4-H), 2.32–3.17 (5H, m, 2′-H, 3′-H and 5′-H), 3.17–3.6 (2H, m, 5-H), 4.05–4.35 (1H, m, 2-H), 4.95–5.15 (2H, m, 6′-H), 7.1–7.3 (10H, m, 2 × Ph) (Found: MH$^+$, 452.2428. $C_{27}H_{34}NO_5$ requires *M*H, 452.2437).

(2*S*)-*N*-Methoxycarbonylcarbonyl-2-[(3′*RS*)-1-oxo-3′-benzyl-oxycarbonylpropyl]pyrrolidine 25

To a stirred solution of benzyl ester **24** (58 mg, 0.128 mmol) in DCM (2 ml) at room temperature was added trifluoroacetic acid (0.5 ml). After 25 minutes the solvent and TFA were removed under vacuum and the residue dissolved in DCM (2 ml). The reaction mixture was cooled to 0 °C (ice bath) where pyridine (31 µl, 0.38 mmol) and methyl oxalyl chloride (13 µl, 0.14 mmol) were added. The reaction was stirred for 1 hour at 0 °C, poured onto 1 M HCl (5 ml) and extracted with ether (3 × 10 ml). The combined organic extracts were dried with $MgSO_4$ and evaporated under reduced pressure. Flash column chromatography of the residue (diethyl ether as eluent) afforded the desired oxalate **25** as a light yellow oil (45 mg, 0.103 mmol, 80%); $[\alpha]_D^{23}$ −35.1 (*c* 1.8 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3000–2800s (CH), 1740s (CO_2Bn and CO_2Me), 1661s (NCO), 1456s, 1423m, 1251s, 1097w, 744m; δ_H(400 MHz; $CDCl_3$; Me_4Si) 2.01–2.1 (0.5H, m, 3b-H), 2.18–2.3 (0.5H, m, 3a-H), 2.59–2.7 (1H, m, 5′a-H), 2.77–3.09 (3H, m, 5′b-H and 2′-H), 3.25 (0.5H, m, 3′-H), 3.35 (0.5H, m, 3′-H), 3.85 (1H, m, 5a-H), 3.75 (1H, m, 5b-H), 3.69, 3.73, 4.84 and 3.87 (3H, 4 × s, diastereomeric and rotameric mixture, OMe), 4.5 (0.5H, m, 2-H), 4.95 (0.5H, m, 2-H), 5.0–5.12 (2H, m, 6′-H), 7.1–7.3 (10H, m, 2 × Ph); δ_C(100 MHz; $CDCl_3$; Me_4Si) 21.8, 21.9, 24.6 and 24.7 (3-C), 27.2, 27.5, 30.2 and 30.3 (4-C), 37.3, 37.5, 37.6 and 37.7 (2′-C), 39.5, 39.9 and 40.0 (5′-C), 41.1, 41.2, 41.5 and 41.6 (5-C), 47.9, 48.2, 48.3 and 48.4 (3′-C), 52.7 and 52.9 (OMe), 64.5 and 64.8 (2-C), 66.4 (6′-C), 126.5–129.0 and 135.6–138.2 (Ph), 156.8, 157.4 and 157.5 (NCO), 161.6 (CO_2Me), 173.9, 174.0, 174.2 and 174.3 (CO_2Bn), 204.9 and 205.4 (1′-C) (Found: MH$^+$, 438.1910. $C_{25}H_{28}NO_6$ requires *M*H, 438.1916).

***N*-(*tert*-Butoxycarbonyl)-L-phenylalanine benzyl ester 26**

To a flask containing *N*-(*tert*-butoxycarbonyl)phenylalanine (1.02 g, 3.84 mmol) and carbonyldiimidazole (0.66 g, 4.07 mmol) under an atmosphere of argon was added DCM (2 ml). After 5 minutes benzyl alcohol (0.45 g, 4.2 mmol) and sodium ethoxide (2 mg, catalytic) were added. After 18 hours the mixture was evaporated *in vacuo* and the residue purified by flash column chromatography (3:7 diethyl ether–petrol as eluent). This afforded the benzyl ester **26** as white crystalline solid (1.3 g, 3.8 mmol, 99%); mp 62 °C (lit.,[18] 62–63 °C), $[\alpha]_D^{26}$ −10.0 (*c* 1.3 in EtOH) (lit.,[18] $[\alpha]_D^{25}$ −10.0); ν_{max}(film)/cm^{-1} 3370s (NH), 3000–2800s (CH), 1700–1750s (CO_2Bn and NCO), 1500s, 1455s, 1167s, 1055m, 1020m, 751s; δ_H(400 MHz; $CDCl_3$; Me_4Si) 1.4 [9H, s, $C(CH_3)_3$], 3.05 (2H, br, CH_2Ph), 4.6 (1H, m, CHN), 4.95 (1H, d, $J_{NH,CH}$ 7.7, NH), 5.09 (1H, d, J_{gem} 12.2, OCH_2Ph), 7.0–7.38 (10H, m, 2 × Ph); δ_C(100 MHz; $CDCl_3$; Me_4Si) 28.3 [$C(CH_3)_3$], 38.3 (CCH_2Ph), 54.5 (CCH_2Ph), 67.0 (OCH_2Ph), 79.8 [$C(CH_3)_3$], 126.9–129.3 (Ph), 135.2 and 135.9 (quat-C), 155.0 (NCO), 171.6 (CO_2Bn) (Found: [M − Boc]H$^+$ 256.1340. $C_{16}H_{18}NO_2$ requires *M*H, 256.1337).

***N*-[*N*′-(*tert*-Butoxycarbonyl)-L-prolyl]-L-phenylalanine benzyl ester 27**

To a dry flask containing *N*-(*tert*-butoxycarbonyl)proline (0.35 g, 1.61 mmol) and carbonyldiimidazole (0.27 g, 1.69 mmol) was added dry DCM (5 ml). Evolution of CO_2 confirmed the formation of the imidazolide **A**. To a second flask containing Boc-phenylalanine benzyl ester **26** (0.55 g, 1.61 mmol) was added DCM (3 ml) and TFA (1 ml). The solution was stirred for 10 minutes at room temperature and then evaporated to total dryness *in vacuo*. The residue was redissolved in DCM (5 ml) and treated with Et_3N (0.24 ml, 1.69 mmol). This solution was added dropwise to the imidazolide **A**. After 18 hours the mixture was evaporated and the residue purified by flash column chromatography (8:2 diethyl ether–petrol as eluent). This afforded the coupled adduct **27** (0.48 g, 1.06 mmol, 66%) and a highly viscous oil; ν_{max}(film)/cm^{-1} 3320m (NH), 3000–2800s (CH), 1746s (CO_2Bn), 1630s (2 × NCO), 1455m, 1398s, 1167s, 1123m, 1088w; δ_H(400 MHz; $CDCl_3$; Me_4Si) 1.40 [9H, s, $C(CH_3)_3$], 1.6–2.3 (4H, m, 3-H and 4-H), 2.98 (1H, dd, $J_{3'a,3'b}$ 13.8 $J_{3'a,2'}$ 6.6, 3′a-H), 3.14 (1H, dd, $J_{3'b,3'a}$ 13.8 $J_{3'b,2'}$ 5.8, 3′b-H), 3.3 (2H, m, 5-H), 4.2 (1H, m, 2-H), 5.4 (1H, m, 2′-H), 5.13 (2H, s, 4′-H), 6.5 (1H, br, NH), 6.95–7.4 (10H, m, 2 × Ph) (Found: MH$^+$, 453.2402. $C_{26}H_{32}N_2O_5$ requires *M*H, 453.2389).

***N*-[*N*′-(Methoxycarbonylcarbonyl)-L-prolyl]-L-phenylalanine benzyl ester 1**

To a solution of dipeptide **27** (0.43 g, 0.96 mmol) in DCM

(3 ml) at room temperature was added trifluoroacetic acid (1 ml). After 10 minutes the solution was evaporated *in vacuo* to total dryness. The residue was redissolved in DCM (10 ml), cooled to 0 °C and successively treated with pyridine (0.23 ml, 2.87 mmol) and methyl oxalyl chloride (97 μl, 1.06 mmol). After 18 hours the mixture was poured onto 1 M HCl (10 ml) and extracted with diethyl ether (3 × 15 ml). The combined organic phases were dried with $MgSO_4$ and evaporated. Flash column chromatography of the residue (7 : 3 diethyl ether–ethyl acetate as eluent) afforded the desired oxalate **1** as a white crystalline solid (0.38 g, 0.86 mmol, 90%); mp 127–129 °C (lit.,[5] 127 °C); $[\alpha]_D^{25}$ −50.9 (*c* 1.17 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3306s (NH), 3000–2800 (CH), 1738s (CO_2Bn and CO_2Me), 1660s (2 × NCO), 1538s, 1455s, 1426m, 1344w, 1238s, 1177s; δ_H(400 MHz; $CDCl_3$; Me_4Si) 1.65–1.95 (2H, m, 4-H), 1.95–2.32 (2H, m, 3-H), 3.03 (1H, dd, $J_{3'a,2'}$ 6.6 $J_{3'a,3'b}$ 13.7, 3′a-H), 3.16 (1H, dd, $J_{3'b,2'}$ 5.9 $J_{3'b,3'a}$ 13.7, 3′b-H), 3.55–3.7 (2H, m, 5-H), 3.77 (0.9H, s, OMe), 3.9 (2.1H, s, OMe), 4.54 (0.7H, m, 2-H), 4.73 (0.3H, dd, $J_{2,3a}$ 7.3 $J_{2,3b}$ 4.0, 2-H), 4.86–4.91 (1H, ddd, $J_{2',3'a}$ 6.6 $J_{2',3'b}$ 5.9 $J_{2',NH}$ 7.7, 2′-H), 5.12 (2H, overlapping AB system, $J_{4'a,4'b}$ 12.1 $J_{4'b,4'a}$ 12.1, 4′-H), 6.25 (0.3H, d, $J_{NH,2'}$ 7.7, NH), 6.9 (0.7H, d, $J_{NH,2'}$ 7.7, NH), 7.05–7.4 (10H, m, 2 × Ph); δ_C(100 MHz; $CDCl_3$; Me_4Si); 21.9 and 24.8 (3-C), 27.3 and 31.6 (4-C), 37.7 and 37.9 (3′-C), 47.6 and 48.3 (5-C), 52.9 and 53.1 (OMe), 53.2 and 53.4 (2′-C), 60.3 and 61.7 (2-C), 67.2 and 67.4 (4′-C), 126.9–135.7 (Ph), 158.2 and 159.1 (NCO_2Me), 161.6 and 161.7 (CO_2Me), 169.4 (NCO amide), 170.9 (CO_2Bn) (Found: MH^+, 439.2102. $C_{24}H_{26}N_2O_6$ requires *M*H, 439.2090).

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