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Asymmetric Synthesis of 3-Carboxyproline and Derivatives Suitable for Peptide Synthesis

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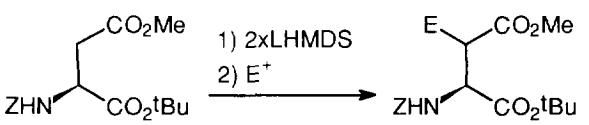
Abstract: *An asymmetric synthesis of both diastereomers of 3-carboxyproline, as well as 5-substituted derivatives and partially protected derivatives suitable for peptide synthesis starting from aspartic acid is reported.*

The asymmetric synthesis of α-amino acids is an area that is currently attracting considerable interest,[1] largely due to the commercial importance of biologically active peptides incorporating unnatural amino acids.[2] To date, the most successful methods for asymmetric amino acid synthesis have involved bond formation at the α-position,[3] though Jackson *et al.* have described methodology for generating a β-anion synthon using organozinc chemistry.[4] Over recent years, we have developed an asymmetric amino acid synthesis based upon the regiospecific deprotonation of aspartic acid as shown in Scheme 1. Thus the β-enolate of aspartic acid derivative (**1**) (and related compounds) can be formed without any loss of stereochemical integrity at the α-centre.[5] The enolate will react with a range of electrophiles to give β-substituted aspartic acid derivatives, and β,γ-unsaturated amino acids. We have also shown that this methodology can be extended to the γ-anion synthon derived from glutamic acid,[6] and similar methodology for the generation of β- and γ-anion synthons has been adopted by other workers.[7] In this paper, we show how this methodology can be used in the asymmetric synthesis of (2**S**,3**R**)-3-carboxyproline (**2**), its diastereomer (**3**), derivatives substituted in the 5-position, and various partially protected derivatives suitable for use in peptide synthesis. Some of these results have been the subject of a preliminary communication.[8]



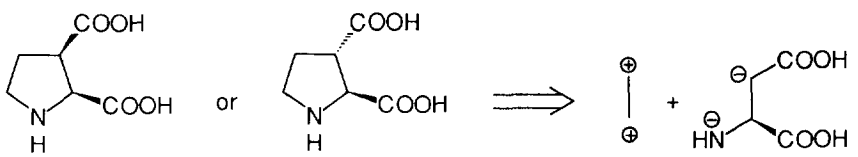
(**1**)

Scheme 1

+Andrew Johnstone was a very talented and promising young chemist who died suddenly in March 1995. The work contained within this paper would have formed part of his PhD thesis.

The two diastereomers of 3-carboxyproline are currently attracting much synthetic attention, with both racemic[9] and asymmetric syntheses being reported in recent years.[10] Much of the interest in these compounds is due to the fact that they contain the features of two naturally occurring amino acids within a single structure, thus they can be considered either as conformationally constrained aspartic acid derivatives, or as a proline analogue with modified electrostatic character.

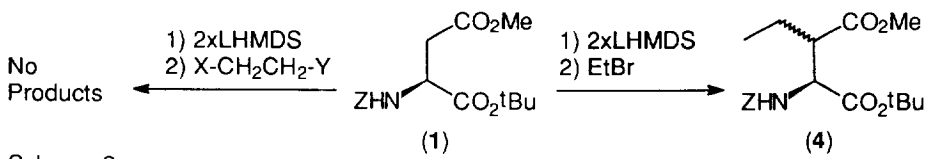
Retrosynthetic analysis of compounds (**2**) and (**3**) revealed that they should be available by reaction of a suitably protected aspartate dianion with a two carbon *bis*-electrophile as shown in Scheme 2. We chose to use the aspartate diester (**1**) as a source of the dianion, as the differential protection of its two carboxylate groups was anticipated to allow their selective deprotection. This would facilitate the further manipulation of compounds (**2**) or (**3**), and in particular their incorporation into biologically active peptides. Previous work[5] on the dianion of compound (**1**), had given good yields of the β-substituted aspartates only with carbonyl compounds, or with reactive benzylic or allylic halides. In addition, reaction of the dianion of compound (**1**) with methyl iodide was known to give a complex mixture of mono and dialkylated products.[5] Thus before investigating the reaction of the dianion of (**1**) with *bis*-electrophiles, its reaction with a simple alkyl halide was investigated.



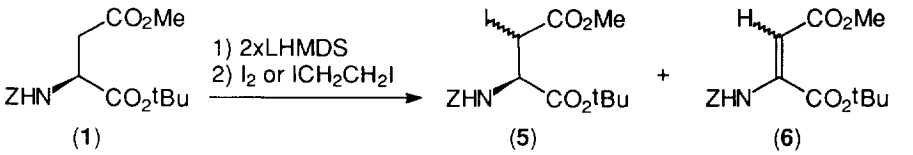
(**2**) (**3**)

Scheme 2

Aspartate (**1**) was prepared by a slight modification of the literature procedure,[5] using Z-OSu in the place of benzyl chloroformate as the latter reagent was found to give highly variable yields (21-75%) for reasons that are not clear. Gratifyingly, reaction of aspartate (**1**) with two equivalents of lithium hexamethyldisilazide in THF, followed by the addition of 4 equivalents of ethyl bromide resulted in formation of the β-ethyl adduct (**4**) in 31% yield as a 4:1 ratio of the two diastereomers as shown in Scheme 3. Given this promising start, the reaction of aspartate (**1**) with a wide variety of 1,2-*bis*-electrophiles was investigated (Scheme 3). Unfortunately, reaction of the dienolate of compound (**1**) with dibromoethane, bromochloroethane, dichloroethane, ethylene oxide, chloroacetyl chloride, ethyl bromoacetate, methyl bromoacetate, bromoethanal diethylacetal, or bromoethanal[11] all failed to gave any identifiable products, as did reaction with 1,3-dibromopropane. Reaction with diiodoethane, gave a mixture of the β-iodoaspartate (**5**), and the α,β-didehydroaspartate (**6**) as shown in Scheme 4. Subsequent investigation showed that this reaction was due to the presence of iodine contaminating the diiodoethane, since pretreatment of the diiodoethane with sodium thiosulphate solution resulted only in the recovery of compound (**1**), whilst reaction of the dienolate of (**1**) with iodine again gave a mixture of aspartates (**5**) and (**6**).

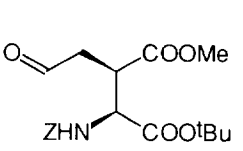


Scheme 3

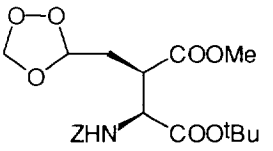


Scheme 4

Given the total lack of success in reacting the *bis*-enolate of compound (**1**) with two carbon *bis*-electrophiles, we turned to the use of allyl bromide as a masked two carbon unit. Previous work[5] had shown that the *bis*-enolate of aspartate (**1**) reacted cleanly with allyl bromide to give the β-allyl adduct (**7a,b**) as a 3:1 ratio of diastereomers at the newly formed chiral centre, though the stereochemistry of the major diastereomer had not been determined. Repetition of this work proceeded smoothly with improved diastereoselectivity (8:1) (Scheme 5) on up to a 26g scale, and the two diastereomers could be easily separated at this stage by flash chromatography. In an attempt to further improve the diastereoselectivity, the reaction conditions were modified (inverse addition of compound (**1**) to the base, use of sodium or potassium hexamethyldisilazide in place of the lithium salt, addition of DMPU to the solvent etc), but always with detrimental effect on the diastereoselectivity. Inverse addition did however result in the preferential formation of the other diastereomer of compound (**7**), though with a modest diastereoselectivity of 3:1 as reported in our earlier communication.[8]



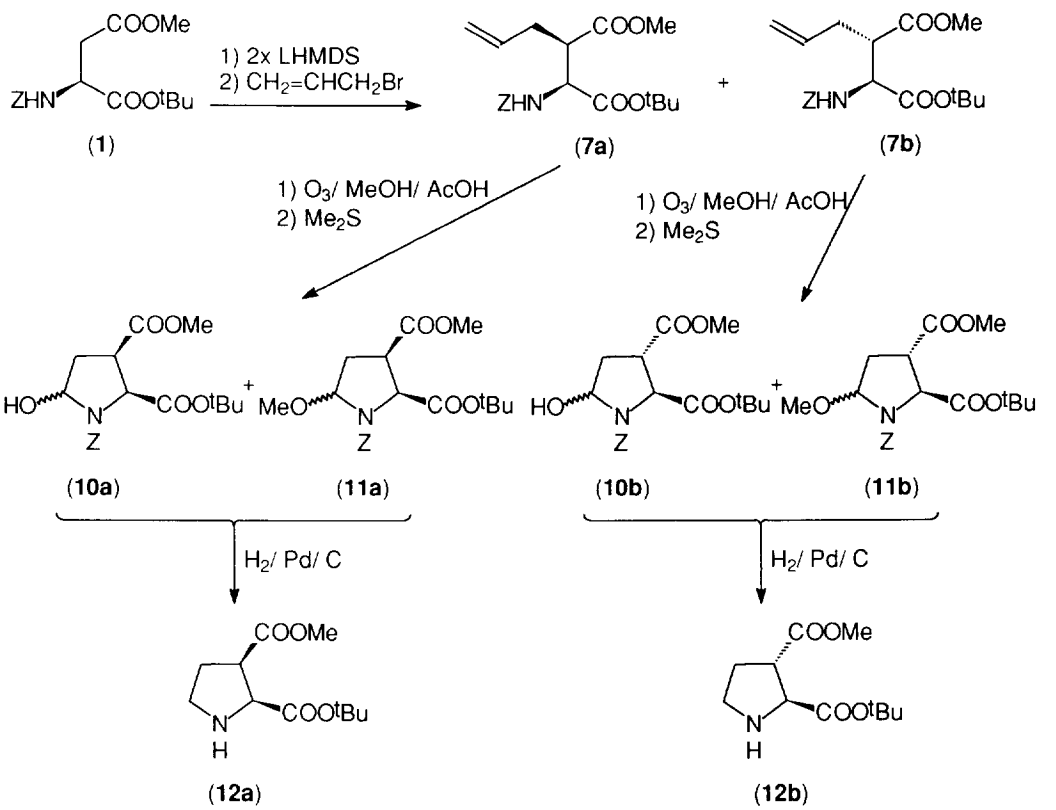
(**8**)



(**9**)

Initial attempts to cleave the carbon-carbon double bond of the major diastereomer of compound (**7**) using osmium tetroxide/ sodium periodate under various conditions[12] were unsuccessful. Ozonolysis of the alkene was also initially largely unsuccessful, giving only very low yields of aldehyde (**8**) or ozonide (**9**). However, ozonolysis in methanol at -78°C in the presence of an equivalent of ethanoic acid, followed by decomposition of the ozonide with excess dimethyl sulphide was eventually found to give a mixture of aminol (**10a**), and methoxyamine (**11a**) in a 91% combined yield as shown in Scheme 5. Compounds (**10a**) and (**11a**)

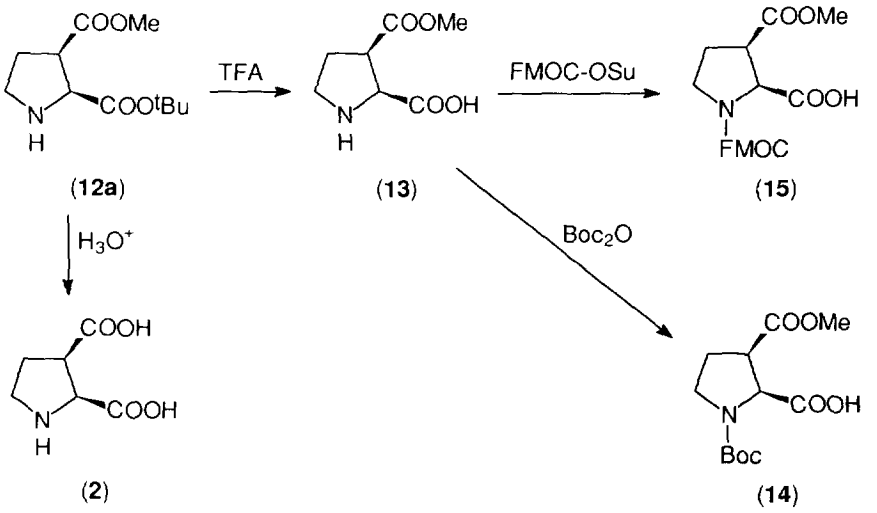
could be separated by flash chromatography if desired, and both were obtained as a 2:1 mixture of stereoisomers at the newly formed chiral centre. The ratio of (**10a**) to (**11a**) was found to be extremely variable, and all attempts to enforce the formation of just one of these products were unsuccessful. The formation of a mixture of compounds (**10a**) and (**11a**) and their stereochemistry at C5 turned out to be irrelevant, since hydrogenation of either or a mixture of these compounds resulted in a tandem hydrogenolysis of the Z-group, elimination of water or methanol to give the corresponding imine, and hydrogenation of the carbon-nitrogen double bond to give proline derivative (**12a**) as the only isolated product (Scheme 5), though at this stage the relative stereochemistry of the two carboxyl groups of (**12a**) was unknown. The same series of reactions were also carried out on the minor diastereomer from the alkylation (**7b**), leading through the aminol (**10b**), and aminoether (**11b**), to 3-carboxyproline derivative (**12b**), as shown in Scheme 5.



Scheme 5

Treatment of compound (**12a**) with 6N HCl at 60°C, resulted in complete deprotection to give (3**R**,2**S**)-3-carboxyproline (Scheme 6), the ^{1}H nmr spectra and optical rotation of which were fully in agreement with those previously reported for the *cis*-isomer[9,10] (**2**) of 3-carboxyproline and different to the reported[10] ^{1}H nmr spectrum and optical rotation of the corresponding *trans*-isomer (**3**). In particular, the magnitude of the coupling constant between the α and β-protons of compounds (**12a**, and **2**) were consistent with the values

previously reported for *cis*-3-carboxyprolines. This result not only established the stereochemistry of the 3-carboxyproline produced by this route, but also established for the first time, the stereochemistry of the alkylation of aspartate (**1**), *ie* the predominant formation of the (**S,R**)-diastereomer. Compound (**12b**), obtained from the minor allyl diastereomer, was also deprotected by treatment with 6N HCl, thus providing a synthesis of (3S,2S)-3-carboxyproline (**3**). The optical rotation and nmr data for compounds (**12b**, and **3**) were entirely consistent with the *trans*-stereochemistry.[10] Compound (**12a**) could also be partially deprotected by treatment with TFA to give ester (**13**), which could be *N*-protected to give the corresponding *N*-Boc (**14**) and *N*-Fmoc (**15**) derivatives (Scheme 6) which are suitable derivatives for use in peptide chemistry.[13] Again, all of the nmr data for compounds (**13-15**) was consistent with a *cis*-configuration of the two carboxyl groups.[10] Starting from (**R**)-aspartic acid, the enantiomers of compounds (**2, 12-15**) were also prepared.



Scheme 6

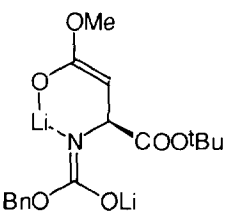
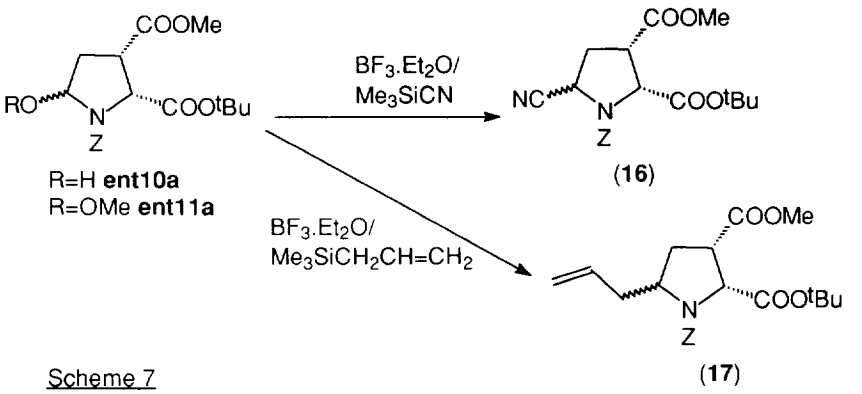


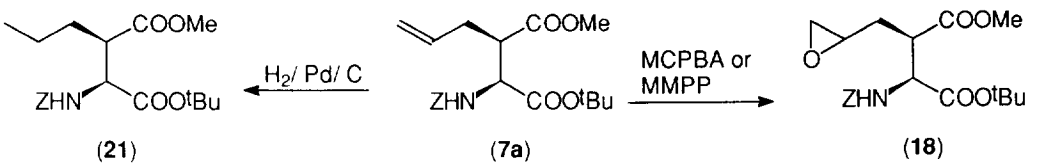
Figure 1

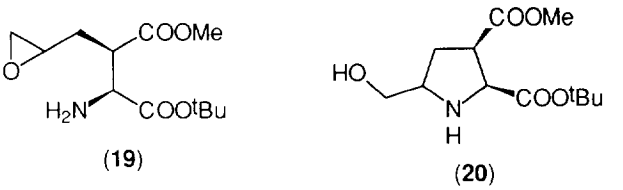
The preferential formation of the (2S,3R)-diastereomer upon alkylation of the enolate of compound (**1**) is consistent with the formation of a chelated enolate intermediate as shown in Figure 1. Alkylation of this chelate from the least hindered face would then lead to the formation of the major diastereomer.

Compounds (**10a/11a**) were also found to be key intermediates in the synthesis of 5-substituted-3-carboxyproline derivatives. Most of these experiments were carried out on the enantiomers of compounds (**10a/11a**) as shown in Scheme 7. Thus treatment of either (**ent10a**), or (**ent11a**), or an unseparated mixture of both compounds with TMS-CN in the presence of $BF_3.Et_2O$ gave a 1:1 mixture of the diastereomeric 5-cyano derivatives (**16**) as shown in Scheme 7. Similar results were obtained using allyl(trimethyl)silane, leading to compound (**17**).



Scheme 7



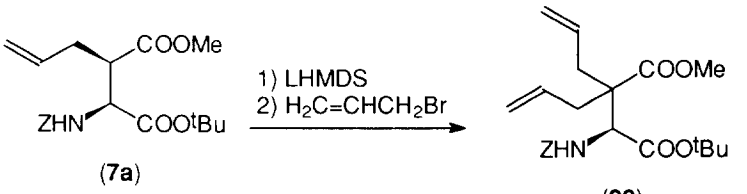


Scheme 8

An alternative route to 5-substituted-3-carboxyproline derivatives was also investigated, utilising allyl adduct (**7a**) directly. Thus epoxidation of compound (**7a**) with either MCPBA or magnesium monoperoxyphthalate (MMPP) gave epoxide (**18**) as a 1:1 mixture of stereoisomers at the new chiral centre in 50-96 and 21% yields respectively as shown in Scheme 8. However, hydrogenation of epoxide (**18**) failed to give either of the expected products epoxide (**19**) or proline derivative (**20**) although mass spectroscopy showed that some species with the correct molecular weight had formed. The use of epoxide (**18**) as a precursor to aldehyde (**8**)/ aminol (**10a**) was also investigated, since periodic acid is known to convert epoxides into aldehydes.[14] However, when this reaction was applied to epoxide (**18**), complete decomposition occurred. Treatment of a urethane protected γ-amino alkene with phenyl selenium bromide has been reported

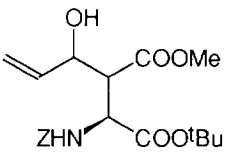
to result in cyclisation to the corresponding phenylselenomethyl pyrrolidine.[15] It was anticipated that this methodology would also allow the synthesis of a variety of 5-substituted derivatives, however compound (**7**) decomposed upon treatment with phenylselenium bromide. Finally, the hydrogenolysis of the urethane protecting group was investigated with a view to obtaining the corresponding amine which it was felt might be more amenable to cyclisation. Unfortunately, all attempts to hydrogenolise the Z-protecting group using molecular hydrogen or a hydrogen donor such as cyclohexadiene resulted instead in preferential hydrogenation of the alkene, giving β-propyl-aspartate derivative (**21**) (Scheme 8).

In an attempt to provide a higher yielding synthesis of (2S,3S)-3-carboxyproline (**3**), the product derived from the minor diastereomer of the allyl adduct (**7b**), the deprotonation and reprotonation of the major allyl adduct (**7a**) was investigated. However, treatment of compound (**7a**) with two equivalents of LHMDS under identical conditions to those used for the deprotonation of compound (**1**) followed by quenching of the reaction mixture with dilute hydrochloric acid lead to the recovery of compound (**7a**) rather than inversion of stereochemistry at the β-position to give (**7b**). That enolate formation had actually occurred under these reaction conditions, was demonstrated by formation of *bis*-allyl adduct (**22**) upon addition of allyl bromide to a solution of the enolate as shown in Scheme 9. Addition of deuterated water to a solution of the enolate formed from allyl adduct (**7a**) however, failed to produce any β-deuterated products.[16]

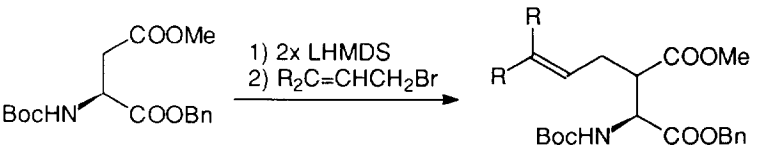


(**7a**) (**22**)

Scheme 9



(**23**)



(**24**) (**25**, R=H; **26**, R=Me)

Scheme 10

The enolate of compound (**1**) was also found to react with propenal, giving adduct (**23**) as a 1:1 mixture of just two stereoisomers as has previously been reported for the reaction of compound (**1**) with other aldehydes.[5] It is anticipated that compound (**23**) will allow the preparation of 4- substituted, and 4,5-disubstituted-3-carboxyproline derivatives. Finally, the generation of a β-enolate of aspartic acid is not restricted to the protecting group combination present in compound (**1**), since treatment of the *N*-Boc derivative (**24**) with LHMDS and either allyl bromide or prenyl bromide gave adducts (**25, 26**), as shown in Scheme 10.

In conclusion, this work has resulted in the development of a short, concise synthesis of both diastereomers of 3-carboxyproline. The ability to prepare a variety of 5-substituted analogues, as well as other β-substituted aspartates has also been demonstrated. In addition, the stereochemistry of the β-substituted aspartates prepared by this methodology has been established for the first time. Our work in this area is continuing, and further results will be resulted in due course.

Experimental

^{1}H NMR spectra were recorded at 250MHz on a Brucker AM250 spectrometer fitted with a ^{1}H-^{13}C dual probe, and were recorded at 293K in $CDCl_3$ unless otherwise stated. Spectra were internally referenced either to TMS or to the residual solvent peak, and peaks are reported in ppm downfield of TMS. Multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q), some combination of these, broad (br), or multiplet (m). ^{13}C NMR spectra were recorded at 62.5MHz on the same spectrometer as ^{1}H NMR spectra, at 293K and in $CDCl_3$ unless otherwise stated. Spectra were referenced to the solvent peak, and are reported in ppm downfield of TMS. Peak assignments were made by DEPT editing of the spectra, and a * indicates that peak assignments may be interchanged. Infra red spectra were recorded on a Perkin Elmer 1600 series FTIR spectrometer, only characteristic absorptions are reported, and peaks are reported as strong (s), moderate (m), weak (w), or broad (br). Mass spectra were recorded using the FAB technique (Cs^+ ion bombardment at 25kV) on a VG Autospec spectrometer, or by chemical ionisation (CI) with ammonia on either a VG model 12-253 quadrupole spectrometer or a VG Quattro II triple quadrupole spectrometer. Only significant fragment ions are reported, and only molecular ions are assigned. High resolution mass measurements were made on a VG ZAB-E spectrometer. Optical rotations were recorded on an Optical Activity Ltd. Polar 2001 polarimeter, and are reported along with the solvent and concentration in g/100ml. Melting points are uncorrected. Elemental analyses were performed within the Chemistry department on a Carlo Erba Model 1106 or Model 1108 analyser.

Flash chromatography[17] was carried out on 40-60μm mesh silica, thin layer chromatography was carried out on aluminium backed silica plates (0.25mm depth of silica containing UV254), and the plates were visualised with u.v. light, and/or dodeçaphosphomolybdic acid as appropriate. All yields refer to isolated, purified material, and are unoptimised. THF was dried by distillation from sodium immediately prior to use, and dichloromethane was dried by distillation from calcium hydride. Other solvents were used as supplied. All reactions involving the generation of enolates were conducted in dry glassware under an inert atmosphere.

β-Methyl N-Z-(S)-aspartate

To β-methyl-(**S**)-aspartate (11.7g, 63.5mmol) dissolved in water (80ml) was added potassium carbonate (13.2g, 95mmol), followed by a solution of Z-OSu (17.4g, 70mmol) in acetone (60ml). The reaction mixture was stirred for 2 hours at room temperature, then washed with ether (2x60ml). The aqueous layer was acidified to pH3 with concentrated hydrochloric acid, and then extracted with ethyl acetate (3x60ml). The combined organic washings were dried ($MgSO_4$), filtered, and the solvent removed *in vacuo* to give β-methyl *N*-Z-(**S**)-aspartate as a white solid. The corresponding (**R**)-enantiomer was prepared from (**R**)-aspartic acid in the same way. Yield 17.8g (99%); physical and spectroscopic data as previously reported.[5]

t-Butyl 2-benzyloxycarbonylamino-3-carbomethoxy-(2S)-pentanoate (4)

To a solution of α-*t*-butyl β-methyl *N*-Z-(**S**)-aspartate (**1**) (0.5g, 1.5mmol) in THF (4ml) at -78°C was added lithium hexamethyldisilizane (3.3ml of a 1M solution in hexanes, 3.3mmol). The resulting solution was allowed to warm up to -30°C, and stirred at between -30 to -40°C for 45 minutes. The solution was recooled to -78°C, and ethyl bromide (0.44ml, 5.9mmol) was added. The resulting solution was allowed to warm to room temperature over a period of 1 hour, then poured onto 1M hydrochloric acid (20ml), and extracted with ether (3x20ml), the combined organic phases were dried ($MgSO_4$) and the solvent removed *in vacuo*. to give a yellow oil. This was purified by flash chromatography (30%ether/ 70%petrol) to give compound (**4**) as a yellow oil. Yield 0.17g (31%); υ_{max} (neat) 3429 m, 3356 m, 2970 s, 2931 s, 1731 s, 1504 s, and 1157cm^{-1} s; δ_H (major diastereomer only) 0.93 (3H, t *J* 7.7Hz, $\underline{CH_3}CH_2$), 1.44 (9H, s, $OC(CH_3)_3$), 1.45-1.8 (2H, m, $CH_3\underline{CH_2}$), 2.8-2.9 (1H, m, βCH), 3.63 (3H, s, OCH_3), 4.42 (1H, dd *J* 10.0, 4.3Hz, NCH), 5.05 (2H, s, $\underline{CH_2}Ph$), 5.57 (1H, d *J* 9.7Hz, NH), 7.2-7.4 (5H, m, ArCH) (Peaks assignments were confirmed by a ^1H-^1H COSY experiment); δ_C 11.83, and 13.92 (2xq, $\underline{CH_3}CH_2$), 21.17, and 21.60 (2xt, $CH_3\underline{CH_2}$), 27.62, and 27.84 (2xq, $OC(\underline{CH_3})_3$), 48.19, and 49.97 (2xd, βCH), 51.55, and 51.65 (2xq, $\underline{OCH_3}$), 54.35, and 55.19 (2xd, NCH), 66.52, and 66.77 (2xt, $\underline{CH_2}Ph$), 82.18, and 82.37 (2xs, $O\underline{C}Me_3$), 127.82, 128.141, and 128.29 (3xd, ArCH), 136.19 (s, ArC), 156.14, and 156.39 (2xs, $\underline{NCO_2}$), 169.35, 169.76, 172.74, and 173.69 (4xd, $\underline{CO_2}$); m/z (CI) 383 (30, $M+NH_4^+$), 366 (40, MH^+), 327 (27), 310 (bp), 266 (41); Found 366.1917 ($C_{19}H_{28}NO_6$) requires: 366.1917.

α-t-Butyl β-methyl N-Z-β-iodo-(S)-Aspartate (5) and α-t-Butyl β-methyl N-Z-didehydroaspartate (6)

To α-*t*-butyl β-methyl *N*-Z-(**S**)-aspartate (**1**) (0.5g, 1.5mmol) dissolved in THF (4ml) at -78°C under nitrogen, lithium hexamethyldisilizane (3.3ml of a 1M solution in hexanes, 3.3mmol) was added. The resulting solution was allowed to warm up to -30°C, and stirred at between -30°C and -40°C for 45 minutes. The solution was recooled to -78°C, and a solution of iodine (1.5g, 5.9mmol) in THF (2ml) was added. The resulting solution was allowed to warm up to room temperature over the course of 1 hour, then poured onto 1M hydrochloric acid (20ml), and extracted with ether (3x20ml). The combined organic phases were dried ($MgSO_4$) and the solvent removed *in vacuo* to leave a dark red oil, which was subjected to flash chromatography (30% Et_2O/petrol), to give compounds (**5**) and (**6**). Data for (**5**): Yield 0.18g (36%); υ_{max} (neat) 3347 br, 3032 m, 2954 s, 1714 s, 1587 s, and 1501cm^{-1} s; δ_H 1.41, and 1.58 (9H, s, $OC(CH_3)_3$), 3.72,

and 3.74 (3H, s, OCH_3), 4.67 (1H, dd *J* 8.5, 3.1Hz, NCH), 5.07 (1H, d *J* 3.1Hz, ICH), 5.69 (2H, s, OCH_2Ph), 6.02 (1H, d *J* 8.5Hz, NH), 7.2-7.4 (5H, m, ArH) (Peaks assignments were confirmed by a ^1H-^1H COSY experiment); δ_C 20.29, and 20.80 (2xd, ICH), 27.73, and 27.80 (2xq, $OC(\underline{C}H_3)_3$), 53.27, and 53.40 (2xq, OCH_3), 57.63 (d, NCH), 67.28, and 68.48 (2xt, OCH_2Ph), 83.73, and 84.58 (2xs, $OCMe_3$), 128.02, 128.16, 128.51, 128.60, 128.69, and 128.75 (6xd, ArCH), 134.86, and 136.19 (2xs, ArC), 151.36, and 156.25 (2xs, NCO_2), 166.51, and 170.02 (2xs, CO_2); m/z (CI) 481, and 479 (60, $M+NH_4^+$), 464 (40, MH^+), 425 (bp), 406 (40), 364 (30); Found 481.0836 ($C_{17}H_{26}N_2O_6I$) requires: 481.0836.

Data for (**6**): Yield 0.19g (28%); υ_{max} (neat) 3291 m, 2978 m, 2930 m, 1750 s, 1688 s, 1633 s, 1585 s, 1454 br, and 1150cm^{-1} s; δ_H 1.60, and 1.71 (9H, s, $C(CH_3)_3$), 3.82 (3H, s, OCH_3), 5.23 (2H, s, CH_2Ph), 5.53 (1H, s, =CH), 7.3-7.4 (5H, m, ArCH); δ_C 27.54, and 27.86 (2xq, $OC(\underline{C}H_3)_3$), 51.44, and 53.56 (2xq, OCH_3), 67.74, and 68.18 (2xt, CH_2Ph), 83.40, and 85.00 (2xs, $OCMe_3$), 99.32, and 100.01 (2xd, =CH), 128.11, 128.19, 128.27, 128.37, and 128.55 (5xd, ArCH), 134.86, and 135.15 (2xs, ArC), 145.63, and 148.81 (2xs, =C), 150.77, and 151.98 (2xs, NCO_2), 161.29, 161.96, 166.60, and 168.12 (4xs, CO_2) (Peak assignments were confirmed by a ^1H-^{13}C correlation experiment); m/z (CI) 353 (4, $M+NH_4^+$), 336 (10, MH^+), 297 (58), 280 (bp), 108 (32); Found 336.1447 ($C_{17}H_{22}NO_6$) requires: 336.1447.

*t-Butyl 2-benzyloxycarbonylamino-3-carbomethoxy-(2**S**,3**R**)-hex-5-enoate (**7a**) and t-Butyl 2-benzyloxycarbonylamino-3-carbomethoxy-(2**S**,3**S**)-hex-5-enoate (**7b**)*

To a solution of α-*t*-butyl β-methyl *N*-Z-(**S**)-aspartate (**1**) (26.85g, 79.6mmol) in THF (45ml) at -78°C under nitrogen was added a 1M solution of lithium hexamethyldisilizane in THF (175ml, 175mmol). The resulting solution was allowed to warm to -30°C, and stirred at between -30 and -40°C for 45 minutes. The solution was recooled to -78°C, and allyl bromide (27.5ml, 318mmol) was added. The resulting solution was allowed to warm up to room temperature over the course of 1 hour, then poured onto 1M hydrochloric acid (500ml), and extracted with ether (3x300ml). The combined organic phases were dried ($MgSO_4$) and the solvent removed *in vacuo* to give a reddish oil, which was subjected to flash chromatography (10% Et_2O/petrol), to give compounds (**7a**) and (**7b**) as pale yellow oils in a combined yield of 17.6g (59%).[5] The (**R**)-enantiomers of compounds (**7a**) and (**7b**), were prepared in the same way. Data for (**7a**): Yield 13.1g (44%); δ_H 1.42 (9H, s, $OC(CH_3)_3$), 2.2-2.4 (1H, m, CH_2CH=), 2.4-2.6 (1H, m, CH_2CH=), 3.12 (1H, td *J* 7.5, 3.8Hz, βCH), 3.65 (3H, s, OCH_3), 4.52 (1H, dd *J* 9.7, 3.8Hz, NCH), 5.0-5.2 (4H, m, $=CH_2+OCH_2Ph$), 5.71 (1H, d *J* 8.8Hz, NH), 5.7-6.0 (1H, m, =CH), 7.3-7.4 (5H, m, ArH); m/z (FAB) 400 (30, $M+Na^+$), 378 (25, MH^+), 344 (10), 322 (bp); other data as previously reported.[5]

Data for (**7b**): Yield 0.6g (2%); δ_H 1.45 (9H, s, $OC(CH_3)_3$), 2.2-2.4 (1H, m, CH_2CH=), 2.4-2.6 (1H, m, CH_2CH=), 2.8-3.0 (1H, m, βCH), 3.66 (3H, s, OCH_3), 4.5-4.6 (1H, m, NCH), 5.0-5.2 (4H, m, $=CH_2+OCH_2Ph$), 5.61 (1H, d *J* 9.8Hz, NH), 5.7-6.0 (1H, m, =CH), 7.3-7.4 (5H, m, ArH); other data as previously reported.[5]

*Ozonide (**9**)*

Ozone was passed through a solution of *t*-butyl 2-benzyloxycarbonylamino-3-carbomethoxy-(2**S**,3**S**)-hex-5-enoate (**7a**) (0.5g, 1.3mmol) in dichloromethane (30ml) at -78°C, until the colour of the solution became steel blue. The reaction was then flushed with oxygen for a further 2 minutes before dimethyl sulphide (3ml, 40mmol) was added. The resulting solution was stirred for 72 hours at room temperature before being poured onto additional dichloromethane (20ml). The reaction mixture was washed with water (8x30ml), the organic phase was dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*. The residue was subjected to flash chromatography (30% Et_2O/petrol) to give ozonide (**9**) as a colourless oil. Yield 0.05g (9%); υ_{max} ($CHCl_3$) 3420 br, 3035 w, 2982 w, and 1738cm^{-1} s; δ_H 1.42 (9H, s, $OC(CH_3)$), 1.8-2.0 (1H, m, γCH_2), 2.1-2.3 (1H, m, γCH_2), 3.3-3.4 (1H, m, βCH), 3.67 (3H, s, OCH_3), 4.59 (1H, dd *J* 9.3, 3.6Hz, NCH), 5.0-5.1 (2H, m, CH_2O_2), 5.11 (2H, s, CH_2Ph), 5.39 (1H, t *J* 5.7Hz, CHO_2), 5.67 (1H, d *J* 7.9Hz, NH), 7.2-7.35 (5H, m, ArCH) (These assignments were confirmed by a ^{1}H-^{1}H COSY experiment); δ_C 27.82 (q, $OC(\underline{C}H_3)$), 30.27 (t, γCH_2), 42.29 (d, βCH), 52.15 (q, OCH_3), 55.23 (d, NCH), 67.23 (t, OCH_2Ph), 83.00 (s, $OCMe_3$), 94.12 (t, CH_2O_2), 101.53 (d, CHO_2), 128.10, 128.20, and 128.53 (3xd, ArCH), 156.50 (s, NCO_2), 170.00, and 172.50 (2xs, CO_2); m/z (FAB) 448 (11, M+Na$^+$), 418 (62), 402 (67), 362 (47), 346 (27), and 262 (bp).

*t-Butyl N-Z-3-carbomethoxy-5-hydroxy-(2**S**,3**R**)-proline (**10a**) and t-Butyl N-Z-3-carbomethoxy-5-methoxy-(2**S**,3**R**)-proline (**11a**)*

To *t*-butyl 2-benzyloxycarbonylamino-3-carbomethoxy-(2**S**,3**R**)-hex-5-enoate (7.0g, 18mmol) dissolved in methanol/dichloromethane (90ml/15ml) was added glacial acetic acid (1.06ml, 18mmol). The solution was cooled to -78°C, and ozone was passed through the solution until the colour of the reaction mixture became steel blue. The reaction was then flushed with oxygen for a further 2 minutes, before dimethyl sulphide (4.15ml, 56mmol) was added. The reaction was stirred for 72 hours at room temperature before being poured onto dichloromethane (50ml). The reaction mixture was washed with sodium carbonate solution (10%w/v, 2x50ml), and water (2x50ml), after which the organic phase was dried ($MgSO_4$), filtered, and the solvent removed *in vacuo* to give a mixture of compounds (**10a**) and (**11a**) as a pale yellow oil. Yield 5.83g. (85%). These compounds could be separated by flash chromatography (40% Et_2O/petrol) to give highly variable amounts of compounds (**10a**) and (**11a**). The (**R**)-enantiomers of compounds (**10a**) and (**11a**), were prepared in the same way. Data for (**10a**); $[\alpha]_D^{21}$ = -29.15° (c= 0.02 in $CHCl_3$); υ_{max} ($CHCl_3$) 3434 br, 3005 m, 2982 m, 17422 s, 1704 s, and 1419cm^{-1} s; δ_H 1.30, and 1.42 (9H, s, $OC(CH_3)_3$), 2.05 (1H, dd *J* 11.4, 6.6Hz, γCH_2), 2.5-2.7 (1H, m, γCH_2), 3.6-3.7 (1H, m, βCH), 3.71, and 3.77 (3H, s, OCH_3), 4.30 (1H, br, OH), 4.54, and 4.58 (1H, d *J* 8.4, and 4.3Hz, αCH), 5.12 (1H, d *J* 11.9Hz, CH_2Ph), 5.29 (1H, d *J* 11.9Hz, CH_2Ph), 5.65, and 5.69 (1H, d *J* 7.0, and 6.6Hz, CH(OH), 7.2-7.4 (5H, m, ArH) (The peak assignments were confirmed by a ^{1}H-^{1}H COSY experiment); δ_C 27.67, and 27.80 (2xq, $OC(\underline{C}H_3)_3$), 33.80, and 34.83 (2xt, γCH_2), 44.48, and 44.64 (2xd, βCH), 52.00, and 52.07 (2xq, OCH_3), 61.28, and 61.62 (2xd, NCH), 67.38, and 67.46 (2xt, CH_2Ph), 81.74, and 82.26 (2xd, CH(OH)), 88.05, and 88.65 (2xs, $OCMe_3$), 127.92, 128.10, 128.19, 128.46 and 128.67 (5xd, ArCH), 135.69, and 135.82 (2xs, ArC), 153.89, and 154.52 (2xs, NCO_2), 168.29, 168.40,

170.17, and 170.27 (4xd, CO_2); m/z (CI) 397 (13, $M+NH_4^+$), 379 (42, M^+), 362 (bp), 323 (71), 306 (41), 262 (55), 108 (41); Found 397.1974 ($C_{19}H_{25}NO_7.NH_4$) requires 397.1974.

Data for (**11a**); $[\alpha]_D^{21}$ -17.1° (c= 0.95 in $CHCl_3$); υ_{max} (neat) 3465 br, 3064 w, 2978 s, 2953 s, 1745 s, and 1405cm^{-1} s; δ_H 1.23, and 1.36 (9H, s, $OC(CH_3)_3$), 1.98 (1H, ddd *J* 12.9, 6.0, 2.9Hz, γCH_2), 2.3-2.5 (1H, m, γCH_2), 3.22, and 3.39 (3H, s, OCH_3), 3.5-3.6 (1H, m, βCH), 3.67, and 3.68 (3H, s, CO_2CH_3), 4.45 (1H, d *J* 8.6Hz, NCH), 5.02 (1H, d *J* 12.4Hz, CH_2Ph), 5.13 (1H, d *J* 12.4Hz, CH_2Ph), 5.18, and 5.30 (1H, d *J* 5.2, and 4.9Hz, NCHO), 7.2-7.3 (5H, m, ArCH) (The peak assignments were confirmed by a COSY experiment); δ_C 27.76, and 27.90 (2xq, $OC(\underline{C}H_3)_3$), 32.96, and 33.78 (2xt, γCH_2), 43.84, and 44.85 (d, βCH), 52.15 (q, OCH_3), 55.92, and 56.67 (2xq, OCH_3), 61.43, and 61.67 (2xd, NCH), 67.55, and 67.65 (2xt, CH_2Ph), 82.18, and 82.32 (2xs, $OCMe_3$), 88.47, and 89.08 (2xd, NCHO), 128.03, 128.10, 128.19, 128.52, and 128.56 (5xd, ArCH), 135.90, and 136.22 (2xs, ArC), 154.39, and 154.83 (2xs, NCO_2), 168.59, 170.28, and 170.48 (3xs, CO_2); m/z (CI) 411 (5, $M+NH_4^+$), 379 (65), 362 (bp), 323 (70), 306 (31), 262 (32), 108 (35); Found 411.2131 ($C_{20}H_{27}NO_7.NH_4$) requires 411.2131.

*t-Butyl 3-carbomethoxy-(2S,3R)-proline (**12a**)*

To a mixture of compounds (**10a**) and (**11a**) (4.85g, 12.3mmol) in propan-2-ol (45ml), was added a suspension of 10% palladium on charcoal (0.3g) in propan-2-ol (5ml). The mixture was stirred under a hydrogen atmosphere for 15 hours, before being filtered through celite and the solvent removed *in vacuo* to give compound (**12a**) as a yellow oil. The compound was characterised as its trifluoroacetate salt, following the addition of excess trifluoroacetic acid, evaporation to dryness, and recrystallisation from chloroform. The (**R**)-enantiomer of compound (**12a**) was prepared in the same way. Yield 2.56g (87%); $[\alpha]_D^{21}$ -29.2° (c= 0.05 in $CHCl_3$); υ_{max} (neat) 3431 br, 3018 m, 2980 m, and 1742.5cm^{-1} s; δ_H 1.47 (9H, s, $OC(CH_3)_3$), 2.25-2.35 (1H, m, γCH_2), 2.35-2.5 (1H, m, γCH_2), 3.5-3.65 (2H, m, NCH_2), 3.65-3.7 (1H, m, βCH), 3.74 (3H, s, OCH_3), 4.51 (1H, d *J* 7.4Hz, αH) (The peak assignments were confirmed by a ^{1}H-^{1}H COSY experiment). δ_C 27.82 (q, $OC(\underline{C}H_3)$), 28.34 (t, γCH_2), 44.76 (t, NCH_2), 45.65 (d, βCH), 52.50 (q, OCH_3), 61.52 (d, NCH), 84.95 (s, $OCMe_3$), 165.89, and 171.22 (2xs, CO_2); m/z (CI) 230 (bp, MH^+), 174 (95), 128 (22); Found 230.1392 ($C_{11}H_{20}NO_4$) requires 230.1392.

*3-Carboxy-(2S,3R)-proline (**2**)*[9,10]

Compound (**12a**) (0.1g, 0.44mmol) was dissolved in 6M hydrochloric acid (2ml), and heated to 60°C for 12 hours. The solvent was removed *in vacuo*, and the crude product was then subjected to ion exchange chromatography (Dowex-50 resin, eluting first with water, then with dilute aqueous ammonia solution), to give compound (**2**).[9,10] Yield 47mg (55%); $[\alpha]_D^{22}$ -40.8° (c= 0.1 in H_2O); υ_{max} (Nujol) 3450 m, 2870 s, 1842 s, and 1771cm^{-1} s; δ_H (D_2O) 2.0-2.4 (2H, m, γCH_2), 3.2-3.3 (1H, m, βCH), 3.4-3.6 (2H, m, NCH_2), 4.53 (1H, d *J* 7.0Hz, αCH); δ_C (D_2O) 23.59 (t, γCH_2) 31.53 (t, NCH_2), 47.06 (d, βCH), 68.96 (d, NCH), 180.09 (s, CO_2); m/z (FAB) 158 (65, M-1$^+$), 151 (9), 127 (6).

3-Carbomethoxy-(2S,3R)-proline (13)

Compound (**12a**) (2.6g, 11mmol) was dissolved in TFA (10ml). The reaction was stirred at room temperature for 2 hours, after which excess TFA was removed *in vacuo*. The product was triturated with ether to give compound (**13**) as a yellow, hygroscopic solid which was used without further purification. The corresponding (**R**)-enantiomer was prepared in the same way. Yield 1.93g (84%); υ_{max} (Nujol) 3372 br, 1736 m, and 1675cm^{-1} s; δ_H (D_2O) 2.5-2.7 (2H, m, γCH_2), 3.6-3.7 (1H, m, βCH), 3.75-3.9 (2H, m, NCH_2), 3.95 (3H, s, OCH_3), 4.64 (1H, d *J* 8.1Hz, αCH); δ_C (CD_3OD) 30.55 (t, γCH_2), 46.69 (t, NCH_2), 47.28 (d, βCH), 54.59 (q, OCH_3), 64.72 (d, αCH), 171.28 and 175.26 (2xd, CO_2).

N-Boc-3-carbomethoxy-(2S,3R)-Proline (14)

To compound (**13**) (2.1g, 11.9mmol) dissolved in water (40ml) was added potassium hydrogen carbonate (5.1g, 51.4mmol). To this, a solution of di-tert-dibutyldicarbonate (3.25g, 14.9mmol) in THF (40ml) was added. The resulting solution was stirred for 14 hours, at room temperature, before being washed with EtOAc (2x80ml). The aqueous layer was acidified to pH3 with concentrated hydrochloric acid, and then extracted with EtOAc (3x80ml). The combined organic extracts were dried ($MgSO_4$), filtered, and the solvent removed *in vacuo* to give compound (**14**) as a yellow oil. Yield 2.3g (68%); $[\alpha]_D^{25}$ -33.8° (c= 0.025 in $CHCl_3$); υ_{max} ($CHCl_3$) 3419 br, 2982 w, 1734 m, 1684 m, 1652 m, and 1404cm^{-1} m;. δ_H (DMSO-d_6 303K) 1.34, and 1.39 (9H, s, $OC(CH_3)_3$), 2.0-2.3 (2H, m, γCH_2), 3.2-3.3 (1H, m, NCH_2), 3.35-3.45 (1H, m, βCH), 3.45-3.5 (1H, m, NCH_2), 3.59 (3H, s, OCH_3), 4.30 (1H, d *J* 9.3Hz, NCH), 12.63 (1H, br, CO_2H); This spectrum was complicated by the presence of rotomers about the urethane bond. By recording the spectrum at 353K, in a DMSO-d_6, CD_3COOD solvent mixture, a well resolved spectrum exhibiting a single set of peaks was observed; δ_C (DMSO-d_6 353K) 25.37 (t, γCH_2), 27.62 (q, $OC(\underline{C}H_3)_3$), 44.78 (t, NCH_2), 46.17 (d, βCH), 51.09 (q, OCH_3), 60.11 (d, NCH), 79.00 (s, $OCMe_3$), 152.81 (s, NCO_2), 170.69, and 171.69 (2xs, CO_2); In spectra recorded at lower temperatures, two sets of peaks were observed due to hindered rotation about the urethane bond: m/z (FAB) 274 (62, MH^+), 218 (bp), 174 (97), 128 (45); Found 274.1290 ($C_{12}H_{20}NO_6$) requires 274.1291.

N-FMOC-3-carbomethoxy-(2S,3R)-Proline (15)

To compound (**13**) (1.9g, 11.1mmol) dissolved in water (20ml) was added sodium carbonate (1.2g, 11.1mmol). To this, a solution of Fmoc-OSu (3.8g, 11.1mmol) in THF/water (40ml/20ml) was added. The pH of the reaction was adjusted to pH8 with sodium carbonate. The solution was stirred for 72 hours at room temperature, before being washed with EtOAc (2x50ml). The aqueous layer was acidified to pH3 with concentrated hydrochloric acid, and then extracted with EtOAc (3x50ml). The combined organic extracts were dried ($MgSO_4$), filtered, and the solvent removed *in vacuo* to leave compound (**15**) as a yellow oil. The corresponding (**R**)-enantiomer was prepared in the same way. Yield 3.5g (80%); $[\alpha]_D^{25}$ +17.8° (c= 0.01 in $CHCl_3$); υ_{max} (neat) 3447 br, 3009 w, 2955 w, 1711 s, 1451 m, and 1422cm^{-1} m; δ_H 2.1-2.3 (1H, m, γCH_2), 2.3-2.5 (1H, m, γCH_2), 3.2-3.35 (1H, m, NCH_2), 3.35-3.5 (1H, m, NCH_2), 3.70 (3H, s, OCH_3), 3.7-3.8 (1H, m, βCH), 4.2-4.3 (1H, m, $CH(Ph)_2$), 4.35-4.55 (2H, m, OCH_2), 4.69 (1H, d *J* 8.4Hz, αCH), 6.82 (1H, br,

CO_2H), 7.3-7.8 (8H, m, ArCH) (These assignments were confirmed by a ^1H-^1H COSY experiment); δ_C 25.30, and 26.70 (t, γCH_2), 34.10 (d, $OCH_2\underline{C}H$), 45.60, and 45.93 (t, NCH_2), 47.04, and 47.10 (d, βCH), 52.38 (q, OCH_3), 60.17, and 60.67 (d, NCH), 67.85, and 68.02 (t, OCH_2), 119.95, 125.00, 127.06, 127.66, and 127.76 (5xd, ArCH), 141.24, and 143.51 (2xs, ArC), 156.29 (s, NCO_2), 170.50, 172.27, 172.88, and 174.15 (4xs, CO_2); m/z (FAB) 396 (19, MH^+), 179 (bp), 174 (23); Found 396.1447 ($C_{22}H_{22}NO_6$) requires 396.1448.

*t-Butyl N-Z-3-carbomethoxy-5-hydroxy-(2S,3S)-Proline (**10b**) and t-Butyl N-Z-3-carbomethoxy-5-methoxy-(2S,3S)-Proline (**11b**)*

To *t*-butyl 2-benzyloxycarbonylamino-3-carbomethoxy-(2**S**,3**R**)-hex-5-enoate (**7b**) (0.6g, 1.7mmol) dissolved in methanol (40ml) and dichloromethane (5ml) was added glacial acetic acid (0.1ml, 1.7mmol). The solution was cooled to -78°C, and ozone (excess) was passed through the solution until the colour of the solution became steel blue. The reaction was then flushed with oxygen for a further 2 minutes before dimethyl sulphide (0.12ml, 5.0mmol) was added. The reaction mixture was stirred for 72 hours at room temperature before being poured onto dichloromethane (30ml). The organic solution was washed with sodium carbonate solution (10%w/v, 2x20ml) and water (2x20ml), dried ($MgSO_4$), filtered, and the solvents removed *in vacuo* to give a mixture of compounds (**10a**) and (**11a**) as a pale yellow oil in a combined yield of 0.2g (34%) which was used without separation of the two components.

*t-Butyl 3-carbomethoxy-(2S,3S)-Proline (**12b**)*

To a mixture of compounds (**10a**) and (**11a**) (0.11g, 0.28mmol,) in ethanol (15ml), was added a suspension of 10% palladium on charcoal (0.05g) in ethanol (5ml). The mixture was stirred under a hydrogen atmosphere for 2 hours, before being filtered through celite and the solvent removed *in vacuo* to give compound (**12b**) as a yellow oil. Yield 0.03g (47%); $[\alpha]_D^{21}$ +4.4° (c=0.01, $CHCl_3$); υ_{max} (neat) 3426 br, 2974 m, and 1732cm^{-1} s; δ_H 1.47 (9H, s, $OC(CH_3)_3$), 1.9-2.15 (2H, m, γCH_2), 2.65 (1H, q *J* 8.3Hz, NCH_2), 2.8-2.9 (1H, m, βCH), 2.9-3.1 (1H, m, NCH_2), 3.52 (1H, d *J* 5.5Hz, NCH), 3.65 (3H, s, OCH_3); δ_C 27.88 (q, $OC(\underline{C}H_3)_3$), 29.59 (t, γCH_2), 47.58 (t, NCH_2), 48.06 (d, βCH), 51.22 (q, OCH_3), 66.11 (d, NCH), 80.82 (s, $OCMe_3$), 172.78 and 174.38 (2xs, CO_2); m/z (CI) 230 (bp, MH^+), 174 (95), 128 (28); Found 230.1392 ($C_{11}H_{20}NO_4$) requires 230.1392.

*3-Carboxy-(2S,3S)-proline (**3**)*

Compound (**12b**) (0.1g, 0.44mmol) was dissolved in 6M hydrochloric acid (2ml), and heated to 60°C for 12 hours. The solvent was removed *in vacuo*., and the crude product was then purified by ion exchange chromatography (Dowex-50 resin, eluting first with water, then with dilute aqueous ammonia solution), to leave compound (**3**). Yield 47mg (55%); $[\alpha]_D^{22}$ +34.0° (c=0.1, H_2O); δ_H (D_2O) 2.05-2.2 (2H, m, γCH_2), 3.1-3.6 (3H, m, βCH, and NCH_2), 4.57 (1H, d *J* 5.2Hz, NCH); δ_C (D_2O) 21.32 (t, γCH_2) 31.50 (t, NCH_2), 53.45 (d, βCH), 72.40 (d, NCH). Other data as previously reported.[9,10]

t-Butyl N-Z-3-carbomethoxy-5-cyano-(2R,3S)-Proline (16)

To **(ent-10a)** (0.1g, 0.25mmol) dissolved in dry dichloromethane (2ml), at -78°C under an argon atmosphere, was added sequentially, trimethylsilyl cyanide (0.1ml, 0.75mmol), and boron trifluoride etherate (0.094ml, 0.762mmol). The reaction was stirred at -78°C for two hours, and was then quenched by the addition of sodium hydrogen carbonate solution (10ml 10%w/v) and allowed to warm to room temperature, before being poured onto ethyl acetate (10ml). The organic layer was washed with brine (2x10ml), dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*. The residue was subjected to flash chromatography (30% Et_2O/petrol), to give compound (**16**) as a colourless oil. The (**2S,3R**)-enantiomer was prepared in the same way. Yield 0.02g (20%); υ_{max} (neat) 2981 w, 2360 w, and 1743cm^{-1} s; δ_H 1.30, and 1.43 (9H, s, $OC(CH_3)_3$), 2.41 (1H, dd *J* 13.2, and 6.3Hz, γCH_2), 2.7-2.9 (1H, m, γCH_2), 3.5-3.7 (1H, m, βCH), 3.76, and 3.79 (3H, s, OCH_3). 4.4-4.6 (1H, m, αCH), 4.8-4.9 (1H, m, CHCN), 5.0-5.2 (2H, m, CH_2Ph), 7.3-7.4 (5H, m, ArCH) (These assignments were confirmed by a ^{1}H-^{1}H COSY experiment); δ_C 27.64, and 27.79 (2xq, $OC(CH_3)_3$), 30.90, and 31.97 (2xt, γCH_2), 44.91, and 46.04 (2xd, βCH), 47.16, and 46.67 (2xd, CHCN), 52.08, and 52.44 (2xq, OCH_3), 60.80, and 61.25 (2xd, NCH), 67.47, and 68.30 (2xt, CH_2Ph), 83.11 (s, $OCMe_3$), 118.09, and 118.28 (2xs, CN), 127.67, 127.94, 128.07, 128.23, 128.42, and 128.53 (6xd, ArCH), 135.25, and 135.45 (2xs, ArC), 153.32, and 153.40 (2xs, NCO_2), 167.85, 168.59, and 168.76 (3xs, CO_2); m/z (FAB) 411 (74, M+Na$^+$), 389 (36, MH$^+$), 362 (47), 306 (17), 262 (bp), 172 (58); Found 389.1713 ($C_{20}H_{25}N_2O_6$) requires 389.1713.

t-Butyl N-Z-3-carbomethoxy-5-(prop-2-enyl)-(2R,3S)-Proline (17)

To aminol **(ent-10a)** (0.1g, 0.25mmol) dissolved in dry dichloromethane (2ml), at -78°C under an argon atmosphere, was added sequentially, allyltrimethylsilane (0.06ml, 0.38mmol) and boron trifluoride etherate (0.094ml, 0.76mmol). The reaction was stirred for two hours, and was then quenched by the addition of sodium hydrogen carbonate solution (10ml, 10%w/v) before being allowed to warm to room temperature and poured onto ethyl acetate (10ml). The organic layer was washed with brine (2x10ml), dried ($MgSO_4$), filtered, the solvent removed *in vacuo*, and the residue subjected to flash chromatography (30% Et_2O/petrol), to give compound (**17**) as a colourless oil. Yield 0.02g (19%); υ_{max} ($CHCl_3$) 2929 m, 1741 m, and 1702cm^{-1} m; δ_H 1.33, and 1.44 (9H, s, $OC(CH_3)_3$), 1.95 (1H, dd *J* 13.1, and 6.9Hz, γCH_2), 2.15-2.3 (1H, m, CH_2CH=), 2.4-2.6 (1H, m, γCH_2), 2.6-2.7 (1H, m, CH_2CH=), 3.3-3.5 (1H, m, βCH), 3.77, and 3.81 (3H, s, OCH_3), 4.2-4.3 (1H, m, NCHCH$_2$), 4.51 (1H, d *J* 7.7Hz, NCHCH), 5.0-5.3 (4H, m, CH_2Ph and CH_2=CH), 5.7-5.9 (1H, m, CH_2=CH), 7.3-7.4 (5H, m, ArCH) (These peak assignments were confirmed by a ^{1}H-^{1}H COSY experiment); δ_C 27.72, and 27.85 (2xq, $OC(CH_3)_3$), 29.41, and 29.71 (2xt, γCH_2), 38.28, and 39.28 (2xt, CH_2CH=), 43.98, and 44.96 (2xd, βCH), 52.10 (q, OCH_3), 56.60, and 57.24 (2xd, NCHCH$_2$), 62.12, and 62.51 (2xd, NCHCH), 67.07, and 67.19 (2xt, CH_2Ph), 82.15 (s, $OCMe_3$), 118.03 (t, CH_2=), 127.83, 127.93, 127.99, 128.39, and 128.46 (5xd, ArCH), 134.18, and 134.34 (2xs, ArC), 136.15 (d, =CH), 156.33 (NCO_2), 168.90, and 170.26 (2xs, CO_2); m/z (CI) 421 (5, M+NH$_4^+$), 404 (21, MH$^+$), 365 (45), 348 (45), 170 (46), 168 (52), 108 (bp); Found 404.2073 ($C_{22}H_{30}NO_6$) requires 404.2073.

t-Butyl 2-Benzyloxycarbonylamino-3-carbomethoxy-5,6-epoxy-(2S)-hexanoate (18)

To alkene (**7**) (5.0g, 0.013mol.) dissolved in THF (20ml), was added a solution of MCPBA (27.5g of 40% purity, excess) in dichloromethane (140ml). The solution was stirred at room temperature for 72 hours, and then poured onto additional dichloromethane (50ml), and washed with 10% sodium metabisulphate solution (2x100ml) and 10% sodium carbonate solution (3x100ml). The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo* to leave epoxide (**18**) as a yellow oil. Yield 4.04g (77%); υ_{max} (neat) 3425 br, 3060 w, 2966 s, 1732 s, and 1513cm^{-1} s; δ_H 1.44, and 1.48 (9H, s, $OC(CH_3)_3$), 1.5-1.7, and 1.8-2.0 (2H, m, $CHCH_2CH$), 2.1-2.3, and 2.3-2.5 (1H, m, OCH_2CH), 2.7-2.8 (1H, m, OCH_2CH), 2.9-3.0, and 3.0-3.1 (1H, m, CH_2CHO), 3.2-3.3 (1H, m, βCH), 3.69, and 3.70 (1H, s, OCH_3), 4.4-4.5, and 4.5-4.6 (1H, m, NCH), 5.12, and 5.13 (2H, s, CH_2Ph), 5.6-5.7 (1H, m, NH), 7.2-7.4 (5H, m, ArCH) (Peak assignments were confirmed by a ^1H-^1H COSY experiment); δ_C 27.67 (q, $OC(\underline{C}H_3)_3$), 29.54, and 31.18 (2xt, $CH\underline{C}H_2CH$), 44.01, and 44.25 (2xd, CHO), 47.45 (t, $O\underline{C}H_2CH$), 49.70, and 50.14 (2xd, βCH), 51.87, and 51.97 (2xq, OCH_3), 54.21, and 55.41 (2xd, NCH), 67.00 (t, CH_2Ph), 82.60, and 82.69 (2xs, $OCMe_3$), 127.87, 127.91, 127.99, 128.33 and 128.43 (5xd, ArCH), 136.00 (s, ArC), 156.14, and 156.47 (2xs, NCO_2), 168.93, 169.19, 172.53, and 172.99 (4xs, CO_2); m/z (CI) 411 (20, $M+NH_4^+$), 394 (56, MH^+), 355 (18), 338 (bp); Found 394.1866 ($C_{20}H_{28}NO_7$) requires: 394.1866.

t-Butyl 2-Benzyloxycarbonylamino-3-carbomethoxy-(2S)-hexanoate (21)

To alkene (**7**) (100mg, 0.26mmol) dissolved in ethyl acetate (10ml), was added 10% palladium on charcoal (30mg). The resulting mixture was stirred under an atmosphere of hydrogen for 18 hours at room temperature. The reaction mixture was diluted with dichloromethane (20ml), and filtered through celite. The solvent was removed from the filtrate *in vacuo*., leaving compound (**21**) as a yellow oil. Yield 67mg (67%); υ_{max} (neat) 3413 m, 2960 s, 2932 s, 1730 s, and 1157cm^{-1} s; δ_H 0.7-0.9 (3H, m, CH_3CH_2), 1.1-1.2 (2H, m, $CH_3\underline{C}H_2CH_2$), 1.35, and 1.38 (9H, s, $OC(CH_3)_3$), 1.5-1.7 (2H, m, $CHC\underline{H}_2$), 2.9-3.0 (1H, m, βCH), 3.61, and 3.65 (3H, s, OCH_3), 4.4-4.5 (1H, m, NCH), 5.05 (2H, s, CH_2Ph), 5.65 (1H, d, *J* 10.3Hz, NH), 7.2-7.3 (5H, m, ArCH) (Peak assignments were confirmed by a ^1H-^1H COSY experiment); δ_C 14.62, and 14.68 (2xq, $\underline{C}H_3CH_2$), 27.98, and 28.06 (2xq, $OC(\underline{C}H_3)_3$), 29.75, and 30.53 (2xt, $CH_3\underline{C}H_2CH_2$), 33.45, and 33.97 (2xt, $CH\underline{C}H_2$), 46.44 (d, βCH), 51.85, and 51.94 (2xq, OCH_3), 54.80, and 58.76 (2xd, NCH), 67.08 (t, CH_2Ph), 82.19 (s, $OCMe_3$), 127.80, 127.90, and 128.29 (3xd, ArCH), 136.10 (s, ArC), 156.15 (s, NCO_2), 169.95, and 170.11 (2xs, CO_2); m/z (CI) 380 (3, MH^+), 324 (60), 280 (22), 108 (bp).

t-Butyl 2-benzyloxycarbonylamino-3-carbomethoxy-3-(2-propenyl)-(2S,3S)-hex-5-enoate (22)

To a solution of compound (**7a**) (0.5g, 1.3mmol,) in THF (4ml), at -78°C under nitrogen, was added lithium hexamethyldisilizane (3.3ml, 3.3mmol,). The resulting solution was allowed to warm to -30°C, and stirred at between -30 and -40°C for 45 minutes. The solution was recooled to -78°C, and allyl bromide (0.5ml, 5.3mmol,) was added. The resulting solution was allowed to warm to room temperature over the course of 1 hour, then poured onto 1M hydrochloric acid (20ml), and extracted with ether (3x20ml). The combined organic phases were dried ($MgSO_4$), and the solvent removed *in vacuo* to leave a reddish oil, which

was subjected to flash chromatography (20% Et_2O/petrol), to give compound (**22**) as a pale yellow oil. Yield 0.24g (44%); $[\alpha]_D^{22}$ +6.2° (c= 1.5 in $CHCl_3$); υ_{max} (neat) 3432 m, 3352 m, 2979 s, 2952 s, and 1731cm^{-1} s; δ_H 1.46 (9H, s, $OC(CH_3)_3$), 2.3-2.6 (4H, m, $=CHC\underline{H}_2$), 3.72 (3H, s, OCH_3), 4.72 (1H, d *J* 10.2Hz, NCH), 5.1-5.2 (6H, m, OCH_2Ph and 2x $=C\underline{H}_2$), 5.65-5.85 (3H, m, NH and 2x =CH), 7.3-7.4 (5H, m, ArH); δ_C 27.85 (q, $OC(\underline{C}H_3)_3$), 35.83, and 36.41 (2xt, $=CH\underline{C}H_2$), 51.94 (q, OCH_3), 58.73 (d, NCH), 65.84 (s, $\beta\underline{C}$), 67.14 (t, CH_2Ph), 82.77 (s, $OCMe_3$), 119.39, and 119.68 (2xt, $=CH_2$), 128.17, and 128.51 (2xd, ArCH), 132.42, and 132.98 (2xd, $=\underline{C}H$), 136.24 (s, ArC), 156.33 (s, NCO_2), 169.25, and 173.86 (2xs, CO_2); m/z (CI) 435 (32, $M+NH_4^+$), 418 (42, MH^+), 379 (90), 362 (bp); Found 418.2230 ($C_{23}H_{32}NO_6$) requires 418.2230.

t-Butyl 2-benzyloxycarbonylamino-3-carbomethoxy-4-hydroxy-(2S)-hex-5-enoate (23)

To a solution of α-*t*-butyl β-methyl *N*-Z-(**S**)-aspartate (**1**) (0.5g, 1.5mmol) in THF (4ml) at -78°C under nitrogen, was added lithium hexamethyldisilizane (3.3ml, 3.3mmol). The resulting solution was allowed to warm up to -30°C, and stirred at between -30°C to -40°C for 45 minutes. The solution was recooled to -78°C, and freshly distiled acrolein (0.4ml, 5.9mmol) was added. The resulting solution was allowed to warm up to room temperature over the course of 1 hour, then poured onto 1M hydrochloric acid (20ml), and extracted with ether (3x20ml). The combined organic phases were dried ($MgSO_4$) and the solvent removed *in vacuo* to give a yellow oil, which was subjected to flash chromatography (30% Et_2O/petrol), to give compound (**23**) as a pale yellow oil. Yield 0.35g (60%); υ_{max} 3358 br, 3066 w, 3034 m, 2954 s, 1790 m, and 1731cm^{-1} s; δ_H 1.45, and 1.48 (9H, s, $OC(CH_3)_3$), 3.02, and 4.06 (1H, t *J* 5.1Hz and 9.7Hz, $CHCO_2Me$), 3.72, and 3.74 (3H, s, OCH_3), 4.45, and 4.58 (1H, t *J* 5.4Hz and dd *J* 10.7, 7.1Hz, NCH), 4.71 (1H, dd *J* 8.6, 5.6Hz, CHO), 5.13 (2H, s, $C\underline{H}_2Ph$), 5.2-5.4 (2H, m, NH + $CH=C\underline{H}_2$), 5.6-5.8 (2H, m, CH= + CH_2=), 7.3-7.4 (5H, m, ArH) (These assignments were confirmed by a ^1H-^1H COSY experiment); δ_C 27.87 (q, $OC(\underline{C}H_3)_3$), 48.87, and 51.79 (2xd, βCH), 52.11, and 52.53 (2xq OCH_3), 52.63, and 54.56 (2xd, NCH), 67.19, and 67.49 (2xt, CH_2Ph), 71.10, and 76.68 (2xd, CHOH), 83.27 (s, $OCMe_3$), 117.00, and 120.35 (2xt, $=CH_2$), 128.10, 128.23, 128.34, and 128.55 (4xd, ArCH), 131.245 (Ar$\underline{C}$), 135.66, and 136.27 (2xs, ArC), 131.22, and 137.80 (2xd, CH=), 156.33 (s, NCO_2), 169.13, 171.74, and 172.11 (3xs, CO_2); m/z (CI) 411 (5, $M+NH_4^+$), 394 (18, MH^+), 355 (21), 337 (bp), 320 (42), 276 (33), 108 (42); Found 394.1866 ($C_{20}H_{28}NO_7$) requires 394.1866.

Benzyl 2-t-butyloxycarbonylamino-3-carbomethoxy-(2S)-hex-5-enoate (25)

To a solution of α-benzyl β-methyl *N*-Boc-(**S**)-aspartate (**24**) (2.0g, 5.9mmol) dissolved in THF (5ml) at -78°C under nitrogen, was added lithium hexamethyldisilizane (13ml, 13mmol). The resulting solution was allowed to warm up to -30°C, and stirred at between -30°C to -40°C for 45 minutes. The solution was recooled to -78°C, and allyl bromide (2.0ml, 23.7mmol) was added. The resulting solution was allowed to warm up to room temperature over the course of 1 hour, then poured onto 1M hydrochloric acid (30ml), and extracted with ether (3x30ml). The combined organic phases were dried ($MgSO_4$) and the solvent removed *in vacuo* to give a yellow oil, which was subjected to flash chromatography (20% Et_2O/petrol), to give compound (**25**) as a colouless oil. Yield 1.6g (72%); υ_{max} (neat) 3422 m, 2982 m, 1724 s, 1641 m, 1488 m, and 1165cm^{-1} s; δ_H 1.54 (9H, s, $OC(CH_3)_3$), 2.3-2.5 (1H, m, CH_2CH=), 2.5-2.8 (1H, m, CH_2CH=), 3.2-3.4

(1H, m, $CHCO_2Me$), 3.68 (3H, s, OCH_3), 4.74 (1H, dd *J* 8.2, and 4.5Hz, NCH), 5.1-5.4 (4H, m, $=CH_2$ + OCH_2Ph), 5.61 (1H, d *J* 8.2Hz, NH), 5.8-6.0 (1H, m, =CH), 7.4-7.5 (5H, m, ArH); δ_C 28.27 (q, $OC(\underline{C}H_3)_3$), 36.33, and 36.52 (2xt, $\underline{C}H_2CH=$), 51.60, and 51.76 (2xd, βCH), 51.76 (q, OCH_3), 57.64 (d, NCH), 67.29 (t, OCH_2Ph), 80.93 (s, $OCMe_3$), 117.07 (t, $=CH_2$), 119.28, and 119.70 (2xd, =CH), 128.43, 128.50, 128.55, and 128.72 (4xd, ArCH), 132.36, and 132.84 (2xs, ArC), 155.62 (s, NCO_2), 171.47 (s, CO_2); m/z (CI) 378 (8, MH^+), 362 (7), 339 (38), 318 (34), 278 (bp).

Benzyl 2-t-butyloxycarbonylamino-3-carbomethoxy-6-methyl-(2S)-hept-5-enoate (26)

To a solution of α-benzyl β-methyl *N*-Boc-(**S**)-aspartate (**24**) (4.0g, 11.8mmol) dissolved in THF (6ml) at -78°C under nitrogen, was added lithium hexamethyldisilizane (26.1ml, 26.1mmol). The resulting solution was allowed to warm up to -30°C, and stirred at between -30°C to -40°C for 45 minutes. The solution was recooled to -78°C, and prenyl bromide (5.5ml, 47.4mmol) was added. The resulting solution was allowed to warm up to room temperature over the course of 1 hour, then poured onto 1M hydrochloric acid (60ml), and extracted with ether (3x50ml). The combined organic phases were dried ($MgSO_4$) and the solvent removed *in vacuo* to give a yellow oil, which was subjected to flash chromatography (20% Et_2O/petrol), to give compound (**26**) as a colouless oil. Yield 1.6g (34%); υ_{max} (neat) 3432 m, 2974 m, 1729 s, 1499 m, and 1166cm^{-1} s; δ_H 1.38 (9H, s, $OC(CH_3)_3$), 1.61, and 1.72 (2x3H, s, $=C(CH_3)_2$), 2.2-2.5 (2H, m, $\underline{C}H_2CH=$), 3.0-3.2 (1H, m, $CHCO_2Me$), 3.58 (3H, s, OCH_3), 4.59 (1H, dd *J* 8.7, and 4.2Hz, NCH), 4.9-5.3 (3H, m, =CH + OCH_2Ph), 5.55 (1H, d *J* 8.7Hz, NH), 7.3-7.4 (5H, m, ArH) (These assignments were confirmed by a ^1H-^1H COSY experiment); δ_C 17.67, 17.85, 25.79, and 26.08 (4xq, $=C(\underline{C}H_3)_2$), 27.28, and 28.25 (2xq, $OC(\underline{C}H_3)_3$), 30.58, and 30.95 (2xt, $\underline{C}H_2CH=$), 46.67 (d, βCH), 51.92 (q, OCH_3), 53.37 (d, NCH), 66.73, and 67.16 (2xt, OCH_2Ph), 79.84 (s, $OCMe_3$), 119.86 (d, =CH), 128.25, 128.47, and 128.55 (3xd, ArCH), 135.41 (s, ArC), 155.89 (s, NCO_2), 171.48, and 173.84 (2xs, CO_2); m/z (FAB) 428 (20, M+Na), 406 (65, MH^+), 338 (58), 284 (57), 260 (51), 216 (bp); Found 406.2230 ($C_{22}H_{32}NO_6$) requires 406.2230.

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