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The Synthesis of *N*-Norbornenyl-Amino Acids and Esters: Monomers for the Preparation of Well Defined Polymers+

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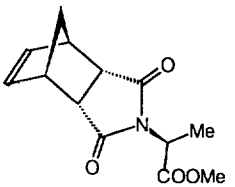
Abstract: *Two routes to the synthesis of various norbornene containing amino acid derivatives are described. The methodology also allows the preparation of the 7-oxonorbornene analogues, and a kinetics study of the racemisation of one of the monomers is reported.*

There is currently considerable interest in the synthesis of new polymeric structures with well defined molecular architectures. In particular, there is a need to exert fine control over factors such as molecular weight, molecular weight distribution, tacticity, and stereochemistry within polymeric molecules. The ring opening metathesis polymerisation (ROMP) of norbornenes and other strained alkenes using well defined transition metal complexes as initiators is one process known to produce polymers with a high degree of control.[1] Recently,[2] we reported the ROMP of amino acid derived monomers (**1,2**), producing homochiral polymers with narrow molecular weight distribution, and good control over double bond geometry. In this paper, full details of the preparation of monomers of type (**1**), and related structures is reported for the first time. In addition to their use as monomers, compounds of type (**1**) have been investigated pharmaceutically as thalidomide analogues.[3]



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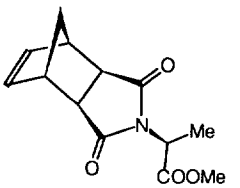

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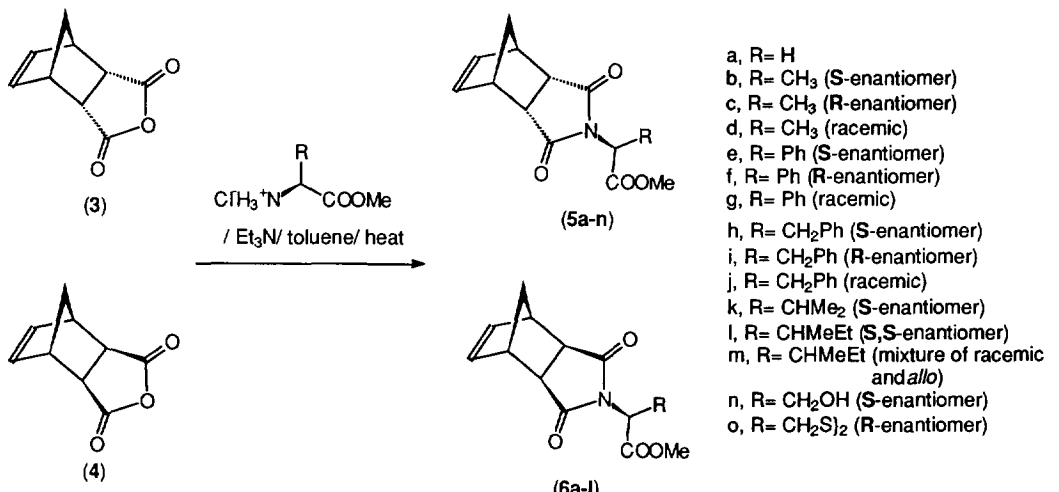
+Dedicated to the memory of Andrew N.C. Johnstone

Route A: The High Temperature Route

Treatment of *endo*-(**3**) or *exo*-himic anhydride[4] (**4**) (*cis*-5-norbornene-2,3-dicarboxylic anhydride) with the hydrochloride salt of an amino acid methyl ester in the presence of triethylamine in toluene at reflux, provided a one-pot synthesis of the desired amino acid derived norbornenes (**5a-n, 6a-l**) as shown in Scheme 1. All of the norbornenes prepared in this way were optically active (except for those derived from glycine[5] (**5,6a**), or racemic amino acids (**5,6d,g,k,m**)), providing a first indication that the relatively harsh reaction conditions had not caused complete racemisation of the amino acid α-centre.



Scheme 1

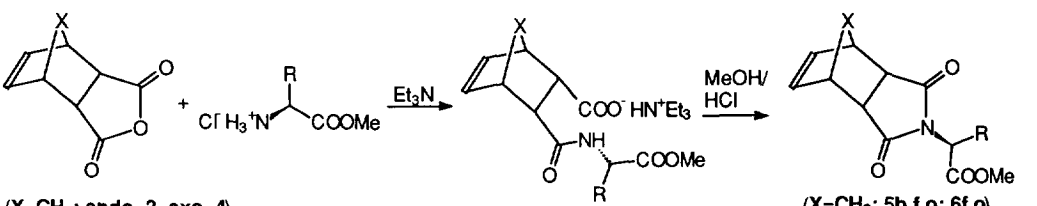
In order to confirm that no racemisation occurred during this process, the synthesis of the isoleucine derived monomers (**5l-m,6l**) was investigated. Any epimerisation of the α-centre of isoleucine would result in the formation of a pair of diastereomers. In the event however, preparation of both the *endo*-(**5l**) and *exo*-(**6l**) monomers derived from (**S,S**)-isoleucine methyl ester gave a single set of peaks by both ^{1}H and ^{13}C nmr. The corresponding monomer (**5m**) derived from racemic isoleucine (commercially available racemic isoleucine is actually a 1:1:1:1 mixture of all four stereoisomers) by comparison showed two sets of peaks in both the ^{1}H and ^{13}C nmr spectra for almost all resonances. These results indicated that the synthetic route shown in Scheme 1 would not cause any racemisation of any of the monomers (**5,6**), with the possible exception of the phenylglycine derived monomers (**5,6e,f**). In this case the α-proton is known to be especially acidic, and the specific rotations of compounds (**5,6e,f**) prepared as shown in Scheme 1 were too low to measure.

That racemisation was a potential problem in difficult cases during the above synthesis was shown by the attempted preparation of the (**R**)-cystine methyl ester derived products (**5,6o**). In this case, the monomer again contains two chiral centres, however this time a mixture of diastereomers (2:1) was obtained during the preparation of both (**5o**) and (**6o**), indicating that substantial racemisation had occurred during the reaction. In the case of the *endo* isomer (**5o**), a small amount of the didehydroalanine derivative (**7**) was also isolated from this reaction.

In order to establish conditions under which this racemisation problem could be circumvented, the racemisation/ decomposition of monomer (**5o**) was studied in more detail. A kinetic study was carried out at constant temperature (boiling toluene), but in the presence of variable concentrations of triethylamine. The racemisation of monomer (**5o**) was conveniently monitored by optical rotation, since all of the reaction products (**rac-5o**) and alkene (**7**) are optically inactive. Plots of the variation of optical rotation with time at three triethylamine concentrations were linear, indicating that the racemisation of compound (**5o**), is first order with respect to (**5o**). Furthermore, a plot of the gradient of these three graphs against triethylamine concentration is also linear, indicating that the racemisation is also first order with respect to triethylamine. These are consistent with a racemisation/ decomposition mechanism in which triethylamine deprotonates the α-carbon of cystine in the rate limiting step. This proton is well known to be more acidic in the case of cystine than for other amino acids.[6] Subsequent reprotonation would give racemic (**5o**), whilst β-elimination of the disulphide would give the didehydroalanine derivative (**7**). Whether or not the latter process is reversible is not apparent from this kinetics study.

Route B: The Low Temperature Route

It was felt that if conditions could be found under which imide formation could be induced at or below room temperature, then racemisation would be negligible. Treatment of *endo*-himic anhydride with (S)-alanine methyl ester hydrochloride and triethylamine in dichloromethane at room temperature, give the amido-acid salt (**8**) as shown in Scheme 2. Compound (**8**) (and related compounds) were found to be unexpectedly soluble in aqueous solution, even at low pH. However, treatment of the crude reaction residue with methanolic HCl resulted in cyclisation to imide (**5b**) as shown in Scheme 2. Application of this methodology to the synthesis of *endo*- and *exo*-cystine derived monomers (**5o, 6o**), gave the desired monomers without causing any racemisation as judged by ^{1}H and ^{13}C nmr. Similarly, starting from (**R**)-phenylglycine monomers (**5f, 6f**) were obtained with significant specific rotations. Thus this two step synthesis provides an attractive alternative to the one step preparation reported above, in cases where racemisation is a potential problem.



(X=CH_2; endo=3, exo=4)

Scheme 2

(X=CH_2; 5b,f,o; 6f,o)
(X=O, R=CH_3, Exo; 11)

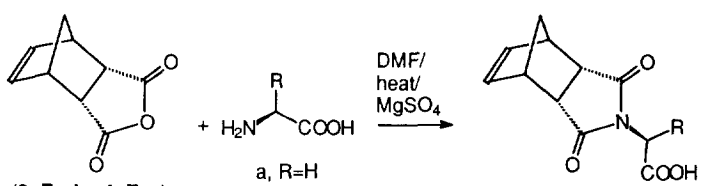
Synthesis of Related Monomers

Using the high temperature route, it has also been possible to prepare the free carboxylic acid derivatives (**endo=9, exo=10**) of compounds (**5**) and (**6**), simply by changing the reaction solvent from toluene to DMF in order to increase the solubility of the zwitterionic amino acids, and adding magnesium sulphate to the reaction mixture to act as a dehydrating agent as shown in Scheme 3. The reaction could also

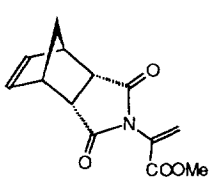
be effected in other highly polar solvents (eg DMSO), or without the addition of magnesium sulphate, but in lower yield. That no racemisation occurred during this process was demonstrated by the subsequent esterification of acid (**9b**) using methanolic HCl, to give ester (**5b**), and comparison of the specific rotations of compound (**5b**) prepared by the two routes. Monomers (**9,10**), are expected to be versatile starting materials for the synthesis of other more sophisticated norbornene derivatives.

Attempts to prepare the 7-oxo analogues (**11**) of compounds (**6**) from the readily available *exo*-Diels Alder adduct of furan and maleic anhydride[7] by the high temperature route were unsuccessful, due to the facile thermal decomposition of these compounds. However, compound (**11**) could be prepared by the low temperature route as shown in Scheme 2. An alternative synthesis of compounds (**11**) was also investigated. Thus reaction of (S)-alanine with maleic anhydride following the high temperature procedure did not give the expected *N*-maleonyl derivative (**12**) directly, rather the intermediate amido acid was obtained. Reaction of the latter compound with oxalyl chloride/ DMF did result in cyclisation to compound (**12**), though in low overall yield. However, the Diels-Alder reaction between alkene (**12**) and furan was found to proceed with little diastereomeric control, giving a mixture of *endo*- and *exo*-isomers.

Similarly, reaction of (S)-phenylalanine methyl ester with acryloyl chloride gave the *N*-acryloyl derivative[8] (**13**). The Diels Alder reaction between compound (**13**) and cyclopentadiene gave a mixture of all four possible stereoisomers of adduct (**14**), which could be separated by flash chromatography into two pairs of diastereomers. In view of the lack of selectivity observed in this Diels Alder reaction, this approach to norbornene derivatives of amino acids was not pursued further.



Scheme 3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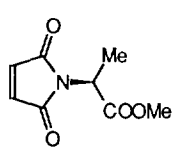
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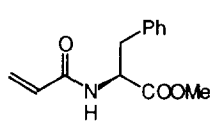
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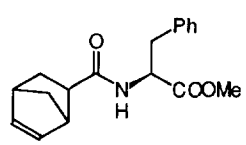
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Conclusions

Two routes for the synthesis of amino acid derived norbornenes which are suitable monomers for ROMP have been developed. Both synthetic approaches are short, use only readily available starting materials and reagents, and are amenable to large scale syntheses. The ROMP of monomers (**5,6b-d**) has already been reported,[1] and the polymerisation of the other monomers will be reported in due course. A kinetics study on

the racemisation of the *endo-cystine* derivative (**5o**), showed the reaction to be first order in both (**5o**) and base, and hence provided an explanation for both the racemisation, and the formation of didehydroalanine derivative (**7**).

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[9] 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 dodecaphosphomolybdic acid as appropriate. All yields refer to isolated, purified material, and are unoptimised. THF was dried by distillation from sodium immediately prior to use. Other solvents were used as supplied.

N-(Endo-Himoyl)-glycine Methyl Ester (5a)

To a solution of *endo*-himic anhydride (7.2g, 44mmol) and triethylamine (11.1ml, 80mmol) in toluene (150ml) was added glycine methyl ester hydrochloride (5.0g, 40mmol). The resulting mixture was heated at reflux for 15 hours, then the cooled reaction mixture was washed with 2M hydrochloric acid (3 x 50ml), and the aqueous phase back-extracted with ethyl acetate (30ml). The combined organic phase was washed with saturated aqueous ammonium carbonate (2 x 50ml), and water (30ml). The organic layer was dried ($MgSO_4$), and the solvent evaporated *in vacuo*., leaving a yellow oil. Trituration with ethyl acetate/ petrol (1:1) gave compound (**5a**) as a white crystalline solid. An analytical sample was obtained by recrystallisation from ether/ petrol. Yield 7.1g (69%); mp 80-82°C; Found: C,61.3; H,5.8; N,6.0. $C_{12}H_{13}NO_4$ requires: C,61.3; H,5.6; N,6.0; υ_{max} ($CHCl_3$) 3019 m, 1756 m, and 1709cm^{-1} s; δ_H 1.54 (1H, d *J* 8.8Hz, CH_2-bridge), 1.71 (1H, d *J* 8.8Hz, CH_2-bridge), 3.3-3.4 (4H, m, CHCH), 3.68 (3H, s, OCH_3), 4.04 (2H, s, NCH_2), 6.10 (2H, d *J* 1.6Hz, =CH); δ_C 38.91 (t, NCH_2), 44.88, and 46.08 (2xd, CHCH), 52.18 (t, CH_2), 52.39 (q, OCH_3), 134.45 (d, =CH), 166.96 (s, CO_2), 176.64 (s, NCO); m/z (CI) 253 (95, $M+NH_4^+$), 236 (bp, MH^+).

N-(Exo-Himoyl)-glycine Methyl Ester (6a)

To a solution of *exo*-himic anhydride (4.8g, 29mmol) and triethylamine (8.9ml, 64mmol) in toluene (100ml) was added glycine methyl ester hydrochloride (4.0g, 32mmol). The resulting mixture was heated at reflux for 15 hours, then the cooled reaction mixture was washed with 2M hydrochloric acid (2 x 50ml), and water (30ml). The organic layer was dried ($MgSO_4$), and the solvent evaporated *in vacuo*. Flash chromatography (ethyl acetate:petrol 1:1) gave compound (**6a**) as a colourless oil which slowly crystallised. An analytical sample was obtained by recrystallisation from ethyl acetate. Yield 5.1g (74%); mp 64-65°C;

Found: C,60.4; H,5.2; N,5.8. $C_{12}H_{13}NO_4.0.1H_2O$ requires: C,60.8; H,5.6; N,5.9; υ_{max} ($CHCl_3$) 3019 m, 1752 m, and 1708cm^{-1} s; δ_H 1.48 (1H, d *J* 9.9Hz, CH_2-bridge), 1.68 (1H, d *J* 10.0Hz, CH_2-bridge), 2.73 (2H, s, CHCO), 3.3-3.4 (2H, m, =CCH), 3.71 (3H, s, OCH_3), 4.20 (2H, s, NCH_2), 6.2-6.3 (2H, m, =CH); δ_C 39.26 (t, NCH_2), 42.81 (t, CH_2), 45.43, and 48.00 (2xd, CHCH), 52.67 (q, OCH_3), 137.99 (d, =CH), 167.40 (s, CO_2), 177.18 (s, NCO); m/z (EI) 235 (3, M^+), 204 (4), 170 (40), 67 (bp).

*N-(Endo-Himoyl)-(S)-Alanine Methyl Ester (**5b**) by the high temperature route*

To a solution of *endo*-himic anhydride (11.7g, 64mmol) and triethylamine (8.7g, 86mmol) in toluene (100ml) was added (**S**)-alanine methyl ester hydrochloride (9.8g, 70mmol). The resulting mixture was heated at reflux for 18 hours, filtered, and the filtrate washed successively with 2M hydrochloric acid (3 x 100ml), saturated aqueous sodium hydrogen carbonate (3 x 100ml), and water (3 x 100ml). The organic layer was dried ($MgSO_4$), and the solvent evaporated *in vacuo*., leaving compound (**5b**) as a white solid. Yield 12.1g (75%); mp 118-119°C; $[\alpha]_D^{22}$ -25.1° (c=5, $CHCl_3$); Found: C,62.6; H,6.2; N,5.8. $C_{13}H_{15}NO_4$ requires: C,62.7; H,6.1; N,5.7; υ_{max} ($CHCl_3$) 2979 m, 1739 s, and 1700cm^{-1} s; δ_H 1.48 (3H, d *J* 7.3Hz, CH_3), 1.53 (1H, d *J* 7.2Hz, CH_2-bridge), 1.69 (1H, dt *J* 7.2, 1.0Hz, CH_2-bridge), 3.2-3.3 (2H, m, COCH), 3.3-3.4 (2H, m, =CHCH), 3.74 (3H, s, OCH_3), 4.67 (1H, q *J* 7.9Hz, NCH), 6.1-6.2 (2H, m, =CH); δ_C 14.22 (q, CH_3), 44.76, 44.89, 45. 39, and 45.55 (4xd, CHCH), 47.19 (t, CH_2), 51.89 (q, OCH_3), 52.20 (d, NCH), 134.03, and 134.15 (2xd, =CH), 170.00 (s, CO_2), 176.30 (s, NCO); m/z (CI) 267 (8, $M+NH_4^+$), 250 (bp, MH^+).

*N-(Exo-Himoyl)-(S)-Alanine Methyl Ester (**6b**)*

To a solution of *exo*-himic anhydride (6.0g, 37mmol) and triethylamine (9ml, 74mmol) in toluene (150ml) was added (**S**)-alanine methyl ester hydrochloride (5.4g, 38mmol). The resulting mixture was heated at reflux for 18 hours, cooled, and washed successively with 2M hydrochloric acid (3 x 50ml), and saturated aqueous sodium hydrogen carbonate (2 x 50ml). The organic layer was dried ($MgSO_4$), and the solvent evaporated *in vacuo*., leaving compound (**5b**) as a white solid, which was recrystallised from 1:1 ether/petrol. Yield 5.8g (62%); mp 117-118°C; $[\alpha]_D^{23}$ -43.2° (c=1, $CHCl_3$); Found C,62.5; H,6.4; N,5.7. $C_{13}H_{15}NO_4$ requires: C,62.7; H,6.1; N,5.7. υ_{max} (Nujol) 1773 m, 1737 s, and 1703cm^{-1} s; δ_H 1.58 (3H, d *J* 7.3Hz, CH_3), 1.5-1.6 (2H, m, CH_2-bridge), 2.7-2.8 (2H, m, =CCH), 3.33 (2H, brs, CHCO), 3.75 (3H, s, OCH_3), 4.80 (1H, q *J* 7.3Hz, NCH), 6.32 (2H, t *J* 1.8Hz, =CH); δ_C 14.12 (q, CH_3), 42.50 (t, CH_2), 45.28 and 45.40 (2xd, CHCO), 47.48, and 47.61 (2xd, =CCH and NCH), 52.60 (q, OCH_3), 137.97 (d, =CH), 170.00 (s, CO_2), 176.42 (s, CON); m/z (CI) 267 (10, $M+NH_4^+$), 250 (bp, MH^+).

*N-(Endo-Himoyl)-(R)-Alanine Methyl Ester (**5c**)*

To a solution of *endo*-himic anhydride (13.5g, 74mmol) and triethylamine (10.0g, 99mmol) in toluene (100ml) was added (**R**)-alanine methyl ester hydrochloride (11.2g, 80mmol). The resulting mixture was heated at reflux for 18 hours, filtered, and the filtrate washed successively with 2M hydrochloric acid (3 x 100ml), saturated aqueous sodium hydrogen carbonate (3 x 100ml), and water (3 x 100ml). The organic layer was dried ($MgSO_4$), and the solvent evaporated *in vacuo*., leaving compound (**5c**) as a white solid. Yield 12.4g (63%); mp 120-121°C; $[\alpha]_D^{23}$ +22.4° (c=1, $CHCl_3$); Found C,62.9; H,6.3; N,5.4. $C_{13}H_{15}NO_4$ requires: C,62.7; H,6.1; N,5.7; other data as reported for compound (**5b**).

*N-(Exo-Himoyl)-(R)-Alanine Methyl Ester (**6c**)*

To a solution of *exo*-himic anhydride (6.0g, 37mmol) and triethylamine (9ml, 74mmol) in toluene (150ml) was added (**R**)-alanine methyl ester hydrochloride (5.4g, 38mmol). The resulting mixture was heated at reflux for 18 hours, cooled, and washed successively with 2M hydrochloric acid (3 x 50ml), and saturated aqueous sodium hydrogen carbonate (2 x 50ml). The organic layer was dried ($MgSO_4$), and the solvent evaporated *in vacuo*., leaving compound (**5b**) as a white solid, which was recrystallised from 1:1 ether/petrol. Yield 4.75g (51%); mp 117-118°C; $[\alpha]_D^{23}$ +42.8° (c=1, $CHCl_3$); Found C,62.9; H,6.1; N,5.5. $C_{13}H_{15}NO_4$ requires: C,62.7; H,6.1; N,5.7; other data as reported for compound (**6b**).

N-(Endo-Himoyl)-(RS)-Alanine Methyl Ester (5d)

To a solution of *endo*-himic anhydride (11.8g, 65mmol) and triethylamine (8.75g, 87mmol) in toluene (100ml) was added (**RS**)-alanine methyl ester hydrochloride (10.0g, 72mmol). The resulting mixture was heated at reflux for 18 hours, filtered, and the filtrate washed successively with 2M hydrochloric acid (3 x 100ml), saturated aqueous sodium hydrogen carbonate (3 x 100ml), and water (3 x 100ml). The organic layer was dried ($MgSO_4$), and the solvent evaporated *in vacuo.*, leaving compound (**5d**) as a white solid. Yield 15.3g (94%); mp 122-123°C; other data as reported for compound (**5b**).

N-(Exo-Himoyl)-(RS)-Alanine Methyl Ester (6d)

To a solution of *exo*-himic anhydride (6.0g, 37mmol) and triethylamine (9ml, 74mmol) in toluene (150ml) was added (**RS**)-alanine methyl ester hydrochloride (5.4g, 38mmol). The resulting mixture was heated at reflux for 18 hours, cooled, and washed successively with 2M hydrochloric acid (3 x 50ml), and saturated aqueous sodium hydrogen carbonate (2 x 50ml). The organic layer was dried ($MgSO_4$), and the solvent evaporated *in vacuo.*, leaving compound (**5b**) as a white solid, which was recrystallised from 1:1 ether/petrol. Yield 6.05g (65%); mp 112-113°C; Found C,62.4; H,6.2; N,5.4. $C_{13}H_{15}NO_4$ requires: C,62.7; H,6.1; N,5.7; other data as reported for compound (**6b**).

N-(Endo-Himoyl)-(S)-Phenylglycine Methyl Ester (5e)

To a stirred solution of *endo*-himic anhydride (12.6g, 76mmol) and triethylamine (8.0ml, 110mmol) in toluene (80ml) was added (**S**)-phenylglycine methyl ester hydrochloride (7.7g, 38mmol). The resulting mixture was stirred at 70°C for 18 hours, washed with 10% hydrochloric acid (3 x 50ml), dried ($MgSO_4$), and the solvents evaporated *in vacuo.*, leaving a light brown oil. The product was purified by flash chromatography (3:2 ether/petrol), giving compound (**5e**) as a colourless oil which crystallised on standing. Yield 7.0g (60%); mp 73-74°C; υ_{max} (neat) 1747 s, and 1712cm^{-1} s; δ_H 1.45 (1H, d *J* 8.7Hz, CH_2-bridge), 1.55 (1H, d *J* 8.7Hz, CH_2-bridge), 3.3-3.4 (2H, m, CHCO), 3.4-3.5 (2H, m, =CCH), 3.73 (3H, s, OCH_3), 5.61 (1H, s, NCH), 5.8-6.0 (2H, m, =CH), 7.2-7.5 (5H, m, ArH); δ_C 45.13, 45.25, 45.67, and 45.76 (4xd, CHCH), 52.01 (t, CH_2), 52.74 (d, NCH), 55.91 (q, OCH_3), 128.25, 128.58, and 129.79 (3xd, ArCH), 134.12, and 134.30 (2xd, =CH), 167.96 (s, CO_2), 176.25, and 176.39 (2xs, NCO); m/z (CI) 329 (10, M+NH_4^+), 312 (bp, MH^+); Found 312.1236 ($C_{18}H_{18}NO_4$ requires 312.1236).

N-(Exo-Himoyl)-(S)-Phenylglycine Methyl Ester (6e)

To a stirred solution of *exo*-himic anhydride (1.5g, 9mmol) and triethylamine (1.9ml, 14mmol) in toluene (50ml) was added (**S**)-phenylglycine methyl ester hydrochloride (1.85g, 9mmol). The resulting mixture was stirred at 70°C for 45 hours, cooled to room temperature, and filtered. The filtrate was washed with 10% hydrochloric acid (3 x 50ml), dried ($MgSO_4$), and the solvents evaporated *in vacuo*. The product was purified by flash chromatography (2:3 ether/petrol) to give compound (**6e**) as a white oil which crystallised on standing. Yield 2.1g (75%); mp 98-100°C; Found C,69.1; H,5.5; N 4.2. $C_{18}H_{17}NO_4$ requires: C,69.4; H,5.5; N,4.5; υ_{max} (neat) 1747 s, and 1703cm^{-1} s; δ_H 1.3-1.5 (2H, m, CH_2-bridge), 2.6-2.8 (2H, m, CHCO), 3.33 (2H, s, =CCH), 3.76 (3H, s, OCH_3), 5.82 (1H, s, NCH), 6.31 (2H, s, =CH), 7.3-7.6 (5H, m, ArH); δ_C 42.69 (t, CH_2), 45.54, 45.70, 47.64, and 47.83 (4xd, CHCH), 52.91 (q, OCH_3), 56.33 (d, NCH), 128.51, 128.73, and 129.87 (3xd, ArCH), 133.89 (s, ArC), 138.03 (d, =CH), 168.09 (s, CO_2), 176.69 (s, NCO); m/z (CI) 329 (8, M+NH_4^+), 312 (bp, MH^+), 182 (30).

N-(Endo-Himoyl)-(R)-Phenylglycine Methyl Ester (5f) by the high temperature route

To a stirred solution of *endo*-himic anhydride (6.7g, 40mmol) and triethylamine (4.0ml, 55mmol) in toluene (80ml) was added (**R**)-phenylglycine methyl ester hydrochloride (7.0g, 35mmol). The resulting mixture was stirred at 70°C for 18 hours, washed with 10% hydrochloric acid (3 x 50ml), dried ($MgSO_4$), and the solvents evaporated *in vacuo.*, leaving a light brown oil. The product was purified by flash

chromatography (3:2 ether/petrol), giving compound (**5f**) as a colourless oil which crystallised on standing. Yield 7.4g (68%); other data as reported for compound (**5e**).

*N-(Exo-Himoyl)-(**R**)-Phenylglycine Methyl Ester (**6f**) by the high temperature route*

To a stirred solution of *exo*-himic anhydride (1.2g, 7mmol) and triethylamine (1.9ml, 14mmol) in toluene (50ml) was added (**R**)-phenylglycine methyl ester hydrochloride (1.3g, 6mmol). The resulting mixture was stirred at 70°C for 45 hours, cooled to room temperature, and filtered. The filtrate was washed with 10% hydrochloric acid (3 x 50ml), dried ($MgSO_4$), and the solvents evaporated *in vacuo*. The product was purified by flash chromatography (2:3 ether/petrol) to give compound (**6f**) as a white oil which crystallised on standing. Yield 1.1g (56%); other data as reported for compound (**6e**).

*N-(Endo-Himoyl)-(**RS**)-Phenylglycine Methyl Ester (**5g**)*

To a stirred solution of *endo*-himic anhydride (2.0g, 12mmol) and triethylamine (1.0ml, 14mmol) in toluene (40ml) was added (**RS**)-phenylglycine methyl ester hydrochloride (2.0g, 10mmol). The resulting mixture was stirred at 70°C for 18 hours, washed with 10% hydrochloric acid (3 x 50ml), dried ($MgSO_4$), and the solvents evaporated *in vacuo*., leaving a light brown oil. The product was purified by flash chromatography (3:2 ether/petrol), giving compound (**5g**) as a colourless oil. Yield 2.3g (74%); other data as reported for compound (**5e**).

*N-(Exo-Himoyl)-(**RS**)-Phenylglycine Methyl Ester (**6g**)*

To a stirred solution of *exo*-himic anhydride (1.0g, 6mmol) and triethylamine (1.3ml, 9mmol) in toluene (50ml) was added (**RS**)-phenylglycine methyl ester hydrochloride (1.3g, 6mmol). The resulting mixture was stirred at 70°C for 45 hours, cooled to room temperature, and filtered. The filtrate was washed with 10% hydrochloric acid (3 x 50ml), dried ($MgSO_4$), and the solvents evaporated *in vacuo*. The product was purified by flash chromatography (2:3 ether/petrol) to give compound (**6g**) as a white oil. Yield 0.78g (41%); other data as reported for compound (**6e**).

*N-(Endo-Himoyl)-(**S**)-Phenylalanine Methyl Ester (**5h**)*

To a stirred solution of *endo*-himic anhydride (9.9g, 60mmol) and triethylamine (6.3ml, 45mmol) in toluene (70ml) was added (**S**)-phenylalanine methyl ester hydrochloride (6.5g, 45mmol). The resulting mixture was stirred at 70°C for 18 hours, washed with 10% hydrochloric acid (3 x 50ml), dried ($MgSO_4$), and the solvents evaporated *in vacuo*. The product (**5h**) was purified by recrystallisation from ethyl acetate, and an analytical sample was obtained by further recrystallisation from ether/ petrol (1:1). Yield 11.1g (76%); mp 125-126°C; $[\alpha]_D^{22}$ -42.3° (c=1, toluene); Found C,70.5; H,5.7; N,4.1. $C_{19}H_{19}NO_4$ requires: C,70.1; H,5.9; N,4.3; υ_{max} (Nujol) 1748 s, and 1697cm^{-1} s; δ_H 1.43 (1H, d *J* 8.7Hz, CH_2-bridge), 1.60 (1H, d, *J* 8.7Hz, CH_2-bridge), 3.0-3.5 (6H, m, CHCH + CH_2Ph), 3.74 (3H, s, OCH_3), 4.96 (1H, dd *J* 9.5, 5.4Hz, NCH), 5.50 (1H, dd *J* 5.6, 3.0Hz, =CH), 5.74 (1H, dd *J* 5.5, 3.1Hz, =CH), 7.0-7.4 (5H, m, ArH); δ_C 33.81 (t, CH_2Ph), 44.65, 44.87, 45.66, and 45.82 (4xd, CHCH), 52.13 (t, CH_2-bridge), 52.61 (d, NCH), 52.70 (q, OCH_3), 126.85, 128.37, and 129.05 (3xd, ArCH), 134.07, and 134.26 (2xd, =CH), 136.48 (s, ArC), 168.90 (s, CO_2), 176.68 and 176.70 (2xs, NCO); m/z (CI) 343 (12, M+NH_4^+), 326 (bp, MH^+).

*N-(Exo-Himoyl)-(**S**)-Phenylalanine Methyl Ester (**6h**)*

To a stirred solution of *exo*-himic anhydride (1.5g, 9mmol) and triethylamine (1.9ml, 14mmol) in toluene (80ml) was added (**S**)-phenylalanine methyl ester hydrochloride (2.0g, 9mmol). The resulting mixture was stirred at 70°C for 40 hours, cooled to room temperature, diluted with ethyl acetate (30ml), and filtered. The filtrate was washed with 10% hydrochloric acid (3 x 50ml), dried ($MgSO_4$), and the solvents evaporated *in vacuo*. The product was purified by flash chromatography (2:3 ether/petrol) to give compound (**6h**) as a yellow oil which crystallised on standing. Yield 2.14g (73%); mp 55-56°C; $[\alpha]_D^{19}$ -107.3° (c=1, $CHCl_3$); υ_{max} (neat) 1773 s, 1746 s, and 1710cm^{-1} s; δ_H 0.93 (1H, d *J* 8.9Hz, CH_2-bridge), 1.28 (1H, d *J* 8.9Hz, CH_2-

bridge), 2.4-2.6 (2H, m, CH_2Ph), 3.17 (2H, s, CHCO), 3.4-3.5 (2H, m, =CCH), 3.79 (3H, s, OCH_3), 5.05 (1H, dd *J* 10.3, 7.9Hz, NCH), 6.20 (2H, s, =CH), 7.0-7.4 (5H, m, ArH); δ_C 33.61 (t, CH_2Ph), 42.38 (t, CH_2-bridge), 45.09, 45.37, 45.44, and 47.48 (4xs, CHCH), 52.81 (d, NCH), 53.14 (q, OCH_3), 126.96, 128.55, and 128.88 (3xd, ArCH), 136.39 (s, ArC), 137.77 and 138.06 (2xd, =CH), 168.91 (s, CO_2), 176.93, and 177.33 (2xs, CON); m/z (CI) 343 (9, $M+NH_4^+$), 326 (bp, MH^+); Found 326.1392 ($C_{19}H_{20}NO_4$ requires 326.1392).

*N-(Endo-Himoyl)-(**R**)-Phenylalanine Methyl Ester (**5i**)*

To a stirred solution of *endo*-himic anhydride (10.0g, 60mmol) and triethylamine (6.3ml, 45mmol) in toluene (70ml) was added (**R**)-phenylalanine methyl ester hydrochloride (6.5g, 45mmol). The resulting mixture was stirred at 70°C for 18 hours, washed with 10% hydrochloric acid (3 x 50ml), dried ($MgSO_4$), and the solvents evaporated *in vacuo*. The product (**5i**) was purified by recrystallisation from ethyl acetate. Yield 11.5g (79%); mp 123-125°C; $[\alpha]_D^{22}$ +42.1° (c=1, toluene); other data as reported for compound (**5h**).

*N-(Exo-Himoyl)-(**R**)-Phenylalanine Methyl Ester (**6i**)*

To a stirred solution of *exo*-himic anhydride (1.5g, 9mmol) and triethylamine (2.0ml, 14mmol) in toluene (60ml) was added (**R**)-phenylalanine methyl ester hydrochloride (2.0g, 9mmol). The resulting mixture was stirred at 70°C for 18 hours, cooled to room temperature, diluted with ethyl acetate (30ml), and filtered. The filtrate was washed with 10% hydrochloric acid (3 x 50ml), dried ($MgSO_4$), and the solvents evaporated *in vacuo*. The product was purified by flash chromatography (2:3 ether/petrol) to give compound (**6i**) as a yellow oil which crystallised on standing. Yield 2.2g (75%); $[\alpha]_D^{19}$ +108.2° (c=1, $CHCl_3$); other data as reported for compound (**6h**).

*N-(Endo-Himoyl)-(**RS**)-Phenylalanine Methyl Ester (**5j**)*

To a stirred solution of *endo*-himic anhydride (10.0g, 60mmol) and triethylamine (6.3ml, 45mmol) in toluene (70ml) was added (**RS**)-phenylalanine methyl ester hydrochloride (6.5g, 45mmol). The resulting mixture was stirred at 70°C for 18 hours, washed with 10% hydrochloric acid (3 x 50ml), dried ($MgSO_4$), and the solvents evaporated *in vacuo*. The product (**5j**) was purified by recrystallisation from ethyl acetate.; Yield 10.2g (70%); mp 112-113°C; other data as reported for compound (**5h**).

*N-(Exo-Himoyl)-(**RS**)-Phenylalanine Methyl Ester (**6j**)*

To a stirred solution of *exo*-himic anhydride (1.5g, 9mmol) and triethylamine (2.0ml, 14mmol) in toluene (60ml) was added (**RS**)-phenylalanine methyl ester hydrochloride (2.0g, 9mmol). The resulting mixture was stirred at 70°C for 18 hours, cooled to room temperature, diluted with ethyl acetate (30ml), and filtered. The filtrate was washed with 10% hydrochloric acid (3 x 50ml), dried ($MgSO_4$), and the solvents evaporated *in vacuo*. The product was purified by flash chromatography (2:3 ether/petrol) to give compound (**6i**) as a colourless oil; Yield 2.3g (78%); other data as reported for compound (**6h**).

*N-(Endo-Himoyl)-(**S**)-Valine Methyl Ester (**5k**)*

Endo-himic anhydride (9.8g, 60mmol) was added to toluene (60ml), and triethylamine (9.1g, 90mmol) was added dropwise. To this, (**S**)-valine methyl ester hydrochloride (5.0g, 30mmol) was added. The resulting mixture was heated at 70°C for 24 hr. The solution was then cooled to room temperature and washed with dilute hydrochloric acid (3 x 50ml). The organic layer was dried with anhydrous magnesium sulphate and filtered. Removal of the solvent *in vacuo* left a yellow oil, which upon flash chromatography (60% diethyl ether, 40% petroleum ether) gave compound (**5k**) as a white solid. Yield 3.6g (43%); mp 59-60°C; $[\alpha]_D^{20}$ -32.3° (c=1.0, $CHCl_3$); Found C,64.95; H,6.6; N,5.1. $C_{15}H_{19}NO_4$ requires: C,64.9; H,6.9; N,5.1; υ_{max} ($CHCl_3$) 1772 m, 1705 s, and 1383cm^{-1} m; δ_H 0.79 (3H, d *J* 7.0Hz, CH_3), 1.01 (3H, d *J* 6.5Hz, CH_3), 1.55 (1H, d *J* 8.8Hz, bridge-CH_2), 1.73 (1H, dt *J* 8.9, 1.5Hz, bridge-CH_2), 2.55 (1H, octet *J* 6.8Hz, $CHMe_2$), 3.3-3.4 (4H, m, CHCHCO), 3.66 (3H, s, OCH_3), 4.24 (1H, d *J* 8.0Hz, NCH), 6.1-6.2 (2H, m, =CH); δ_C 19.21, and 20.67 (2xq, CH_3), 27.82 (d, $CHMe_2$), 44.88, 44.95, 45.67, and 45.78 (4xd, CHCHCO),

51.97 (q, OCH_3), 52.34 (t, CH_2), 57.50 (d, NCH), 134.53, and 134.69 (2xd, =CH), 168.66 (s, CO_2), 176.94 (s, NCO); m/z (CI) 295 (5, $M+NH_4^+$), 278 (bp, MH^+).

N-(Exo-Himoyl)-(S)-Valine Methyl Ester (6k)

Exo-himic anhydride (3.2g, 19mmol) was added to toluene (50ml), and triethylamine (2.9g, 28mmol) was added dropwise. To this, (**S**)-valine methyl ester hydrochloride (3.3g, 19mmol) was added. The mixture was heated at 70°C for 24 hr. The solution was then cooled to room temperature and washed with dilute hydrochloric acid (3 x 50ml). The organic layer was dried with anhydrous magnesium sulphate and filtered. Removal of the solvent *in vacuo* left a yellow oil, which upon chromatography (70% diethyl ether, 30% petroleum ether) yielded compound (**6k**) as a white solid 2.9g (55%); mp 118-119°C; $[\alpha]_D^{20}$ -35.1° (c=1, $CHCl_3$); Found C,65.0; H,6.7; N,5.3. $C_{15}H_{19}NO_4$ requires: C,64.9; H,6.9; N,5.1; υ_{max} ($CHCl_3$) 1745 s, 1703 s, 1385 s, and 1195cm^{-1} s; δ_H 0.85 (3H, d *J* 6.8Hz, CH_3), 1.11 (3H, d *J* 6.5Hz, CH_3), 1.4-1.5 (2H, m, bridge-CH_2), 2.5-2.7 (1H, m, $CHMe_2$), 2.6-2.8 (2H, m, COCH), 3.2-3.3 (2H, m, CH_2CH), 3.68 (3H, s, OCH_3), 4.27 (1H, d *J* 8.2Hz, NCH), 6.2-6.3 (2H, m, =CH); δ_C 19.43, and 21.06 (2xq, CH_3), 27.67 (d, $CHMe_2$), 42.95 (t, CH_2), 45.38, 45.63, 47.42, and 47.89 (4xd, CHCHCO), 57.59 (q, OCH_3), 57.74 (d, NCH), 137.93, and 137.96 (2xd, =CH), 168.79 (CO_2), 177.43, and 177.49 (2xs, NCO); m/z (CI) 295 (15, $M+NH_4^+$), 278 (bp, MH^+), 264 (70).

N-(Endo-Himoyl)-(2S,3S)-Isoleucine Methyl Ester (5l)

To a solution of *endo*-himic anhydride (5.4g, 30mmol) and triethylamine (3.5g, 35mmol) in toluene (200ml) was added (**S**)-isoleucine methyl ester hydrochloride (5.1g, 28mmol). The resulting mixture was heated at reflux for 18 hours, filtered, and the filtrate washed successively with 2M hydrochloric acid (3 x 100ml), and water (3 x 100ml), then dried ($MgSO_4$). The solvent was evaporated *in vacuo*., and the residue redissolved in dichloromethane (50ml) and washed successively with saturated aqueous sodium hydrogen carbonate (3 x 100ml), and water (3 x 100ml). The solvent was evaporated *in vacuo*., to leave compound (**5l**) as a colourless oil. Yield 4.1g (50%); $[\alpha]_D^{22}$ -43.0° (c=0.1, $CHCl_3$); υ_{max} (neat) 1748, and 1704cm^{-1}; δ_H 0.85 (3H, t *J* 7.1Hz, CH_3CH_2), 0.9-1.0 (1H, m, CH_2Me), 1.00 (3H, d *J* 6.7Hz, CH_3CH), 1.3-1.5 (1H, m, CH_2Me), 1.5-1.6 (1H, m, CH_2-bridge), 1.7-1.8 (1H, m, CH_2-bridge), 2.4-2.5 (1H, m, MeCHEt), 3.3-3.4 (2H, m, CHCO), 3.4-3.5 (2H, m, =CCH), 3.65 (3H, s, OCH_3), 4.35 (1H, d *J* 8.0Hz, NCH), 6.0-6.1 (2H, m, =CH); δ_C 10.97, and 16.63 (2xq, CH_3); 25.63 (t, CH_2Me), 34.08 (d, MeCHEt), 45.09, 45.16, 45.81, and 45.91 (4xd, CHCH), 52.06 (d, NCH), 52.47 (t, CH_2-bridge), 57.09 (q, OCH_3), 134.62, and 134.77 (2xd, =CH), 168.89 (s, CO_2), 177.07 (s, NCO); m/z (CI) 292 (bp, MH^+); Found 292.1549 ($C_{16}H_{22}NO_4$ requires 292.1549).

N-(Exo-Himoyl)-(2S,3S)-Isoleucine Methyl Ester (6l)

To a solution of *exo*-himic anhydride (4.6g, 28mmol) and triethylamine (3.5g, 35mmol) in toluene (200ml) was added (**S**)-isoleucine methyl ester hydrochloride (5.2g, 29mmol). The resulting mixture was heated at reflux for 18 hours, filtered, and the filtrate washed successively with 2M hydrochloric acid (3 x 100ml), and water (3 x 100ml), then dried ($MgSO_4$). The solvent was evaporated *in vacuo*., and the residue redissolved in dichloromethane (50ml) and washed successively with saturated aqueous sodium hydrogen carbonate (3 x 100ml), and water (3 x 100ml). The solvent was evaporated *in vacuo*., to leave compound (**6l**) as a colourless oil. Yield 5.5g (67%); $[\alpha]_D^{22}$ -50.9° (c=0.1, $CHCl_3$); υ_{max} (neat) 2963 s, 2879 m, 1730 s, and 1702cm^{-1} s; δ_H 0.85 (3H, t *J* 7.1Hz, CH_3CH_2), 0.9-1.0 (1H, m, $MeCH_2$), 1.05 (3H, d *J* 6.7Hz, CH_3CH), 1.3-1.4 (1H, m, $MeCH_2$), 1.4-1.5 (1H, m, bridge-CH_2), 1.5-1.6 (1H, m, bridge-CH_2), 2.3-2.5 (1H, m, EtCHMe), 2.6-2.8 (2H, m, CHCO), 3.3-3.4 (2H, m, =CCH), 3.70 (3H, s, OCH_3), 4.45 (1H, d *J* 7.9Hz, NCH), 6.3-6.4 (2H, m, =CH); δ_C 10.56, and 16.48 (2xq, CH_3), 25.48 (t, $MeCH_2$), 33.94 (d, MeCHEt), 45.61, 45.75, 47.33, and 47.69 (4xd, CHCH), 51.88 (d, NCH), 52.30 (t, CH_2-bridge), 57.13 (q, OCH_3), 137.92 (d, =CH), 168.81 (s, CO_2), 177.27 (s, NCO); m/z (CI) 309 (27, $M+NH_4^+$), 292 (bp, MH^+); Found 292.1549 ($C_{16}H_{22}NO_4$ requires 292.1549).

N-(Endo-Himoyl)-(2RS,3RS)-Isoleucine Methyl Ester (5m)

To a solution of *endo*-himic anhydride (11.5g, 70mmol) and triethylamine (8.5g, 84mmol) in toluene (200ml) was added (**2RS,3RS**)-isoleucine methyl ester hydrochloride (13.2g, 72.5mmol). The resulting mixture was heated at reflux for 18 hours, filtered, and the filtrate washed successively with 2M hydrochloric acid (3 x 100ml), and water (3 x 100ml), then dried ($MgSO_4$). The solvent was evaporated *in vacuo*., and the residue redissolved in dichloromethane (50ml) and washed successively with saturated aqueous sodium hydrogen carbonate (3 x 100ml), and water (3 x 100ml). The solvent was evaporated *in vacuo*., to leave compound (**5m**) as a colourless oil. Yield 10.8 (53%); υ_{max} (neat) 1744, and 1700cm^{-1}; δ_H 0.7-1.0 (7H, m, CH_3+CH_3+CH_2Me), 1.0-1.5 (1H, m, CH_2Me), 1.5-1.6 (1H, m, CH_2-bridge), 1.7-1.8 (1H, m, CH_2-bridge), 2.2-2.4 (1H, m, MeCHEt), 3.3-3.4 (2H, m, CHCO), 3.4-3.5 (2H, m, =CCH), 3.65, and 3.71 (2x3H, s, OCH_3), 4.35, and 4.42 (2x1H, d *J* 7.8 and 8.0Hz, NCH), 6.0-6.1 (2H, m, =CH); δ_C 10.89, 11.38, 15.75, and 16.63 (4xq, CH_3), 25.57, and 27.11 (2xt, CH_2Me), 34.03, and 34.65 (2xd, MeCHEt), 45.00, 45.03, 45.09, 45.74, 45.78, 45.87, 45.95, and 46.10 (8xd, CHCH), 51.98, and 52.06 (2xd, NCH), 52.04, and 52.40 (2xt, CH_2-bridge), 56.11, and 57.03 (2xq, OCH_3), 134.41, 134.56, 134.65, and 134.74 (4xd, =CH), 168.81, and 168.93 (2xs, CO_2), 177.06 (s, CON); m/z (CI) 292 (bp, MH^+).

N-(Endo-Himoyl)-(S)-Serine Methyl Ester (5n)

To a stirred solution of *endo*-himic anhydride (3.2g, 20mmol) and triethylamine (5.7ml, 42mmol) in toluene (150ml) was added (**S**)-serine methyl ester hydrochloride (3.1g, 20mmol). The resulting mixture was heated at reflux for 24 hours, cooled to room temperature, diluted with ethyl acetate (100ml), and filtered. The filtrate was washed with water (2 x 200ml), dried ($MgSO_4$), and the solvents evaporated *in vacuo*. to leave compound (**5n**) as a white solid which was recrystallised from ethyl acetate. Yield 4.6g (72%); mp 130-131°C; $[\alpha]_D^{22}$ +1.3° (c=1, $CHCl_3$); υ_{max} ($CHCl_3$) 3446 br, 1745 s, and 1702cm^{-1} s; δ_H 1.51 (1H, d *J* 9.3Hz, CH_2-bridge), 1.73 (1H, d *J* 9.3Hz, CH_2-bridge), 3.3-3.5 (4H, m, CHCH), 3.69 (3H, s, OCH_3), 3.92 (2H, d *J* 6.9Hz, CH_2O), 4.63 (1H, t *J* 6.9Hz, NCH), 6.09 (2H, s, =CH), 8.71 (1H, s, OH); δ_C 44.82, 44.95, 45.08, and 45.22 (4xd, CHCH), 52.09, and 52.46 (2xt, CH_2-bridge and CH_2O), 54.35 (d, NCH), 60.06 (q, OCH_3), 134.24, and 134.57 (2xd, =CH), 167.85 (s, CO_2), 177.34, and 177.60 (s, NCO); m/z (CI) 283 (bp, M+NH_4^+), 266 (65, MH^+); Found 266.1028 ($C_{13}H_{16}NO_5$ requires 266.1028).

N-(Endo-Himoyl)-(R)-Cystine Methyl Ester (5o), and N-(Endo-Himoyl)-Didehydroalanine Methyl Ester (7) by the high temperature route

To a solution of *endo*-himic anhydride (5.8g, 32mmol) and triethylamine (5ml, 50mmol) in toluene (200ml) was added (**RR**)-cystine methyl ester dihydrochloride (5.4g, 16mmol). The resulting mixture was heated at reflux for 18 hours, filtered, and the filtrate washed successively with 2M hydrochloric acid (3 x 100ml), and saturated aqueous sodium hydrogen carbonate (2 x 100ml), then dried ($MgSO_4$). The solvent was evaporated *in vacuo*., and the residue purified by flash chromatography (7:3 ether: petrol), to give compounds (**5o**) and (**7**) as white solids. Data for (**5o**): Yield 1.5g (40%); mp 97-100°C; $[\alpha]_D^{25}$ -112° (c=1, $CHCl_3$); Found C,54.8; H,5.2; N,4.8. $C_{26}H_{28}N_2O_8S_2$.(1.5H_2O) requires: C,54.8; H,5.1; N,4.9.; υ_{max} (Nujol) 3019 m, 1730 s, and 1712cm^{-1} s; δ_H 1.56 (1H, d *J* 8.6Hz, CH_2-bridge), 1.75 (1H, d *J* 8.8Hz, CH_2-bridge), 3.1-3.6 (6H, m, CH_2S+CHCH), 3.74, and 3.75 (3H, s, OCH_3), 4.84, and 4.94 (1H, dd *J* 10.4, 4.6Hz, and 10.6, 4.4Hz, NCH), 6.1-6.2 (2H, m, =CH); δ_C 35.41, and 36.53 (2xt, CH_2S), 44.98, 45.06, and 45.98 (3xd, CHCH), 50.81, and 50.94 (2xd, NCH), 51.47 (t, CH_2), 52.29, and 52.70 (2xq, OCH_3), 134.36, and 134.99 (2xd, =CH), 167.84, and 168.00 (2xs, CO_2), 176.68, and 176.73 (2xs, NCO); m/z (CI) 578 (20, M+NH_4^+), 282 (bp). Data for (**7**): Yield 0.18g (2.3%); mp 107-109°C; υ_{max} ($CHCl_3$) 1713 s, and 1600cm^{-1} m; δ_H 1.57 (1H, d *J* 8.8Hz, CH_2-bridge), 1.79 (1H, d *J* 8.8Hz, CH_2-bridge), 3.3-3.5 (4H, m, CHCH), 3.72 (3H, s, OCH_3), 5.75 (1H, s, =CH_2), 6.22 (2H, t *J* 0.8Hz, =CH), 6.54 (1H, s, =CH_2); δ_C 45.34, and 46.24 (2xd, CHCH), 52.27 (t, CH_2-bridge), 52.63 (q, OCH_3), 127.94 (t, =CH_2), 129.48 (s, =C), 134.56 (d, =CH), 162.11 (s, CO_2), 175.78 (s, NCO); m/z (CI) 265 (30, M+NH_4^+), 248 (bp, MH^+); Found 248.0923 ($C_{13}H_{14}NO_4$ requires 248.0923).

N-(Exo-Himoyl)-(R)-Cystine Methyl Ester (6o) by the high temperature route

To a solution of *exo*-himic anhydride (5.8g, 32mmol) and triethylamine (5ml, 50mmol) in toluene (200ml) was added (**RR**)-cystine methyl ester dihydrochloride (5.4g, 16mmol). The resulting mixture was heated at reflux for 18 hours, filtered, and the filtrate washed successively with 2M hydrochloric acid (3 x 100ml), and saturated aqueous sodium hydrogen carbonate (2 x 100ml), then dried ($MgSO_4$). The solvent was evaporated *in vacuo*., and the residue purified by flash chromatography (7:3 ether: petrol), to give compound (**6o**) as an oil. Yield 1.2g (14%); $[\alpha]_D^{20}$ -184.6° (c=1.7, $CHCl_3$); Found C,56.4; H,6.3; N,4.1. $C_{26}H_{28}N_2O_8S_2.Et_2O$ requires: C,56.7; H,6.0; N,4.4.; υ_{max} (Nujol) 1746 s, and 1701cm^{-1} s; δ_H 1.55 (1H, d *J* 8.5Hz, CH_2-bridge); 1.70 (1H, d *J* 8.5Hz, CH_2-bridge), 2.7-3.6 (6H, m, CHCH + CH_2S), 3.76, and 3.77 (3H, s, OCH_3), 4.98, and 5.10 (1H, dd *J* 10.6, 4.3Hz, and 10.5, 4.4Hz, NCH), 6.2-6.4 (2H, m, =CH); δ_C 35.15, and 35.99 (2xt, CH_2), 42.93 (t, CH_2S), 45.35, 45.52, 47.81, and 47.84 (4xd, CHCH), 52.97 (q, OCH_3), 137.94 (d, =CH), 167.90, and 168.08 (2xs, CO_2), 177.07, and 177.24 (2xs, CON); m/z (FAB) 583 (7, M+Na$^+$), 561 (21, MH$^+$), 280 (bp).

N-(Endo-Himoyl)-(S)-Alanine Methyl Ester (5b) by the low temperature route

To a solution of *endo*-himic anhydride (0.66g, 4mmol) and triethylamine (1ml, 8mmol) dissolved in dichloromethane (50ml) was added (**S**)-alanine methyl ester hydrochloride (0.5g, 3.6mmol), and the resulting solution was stirred at room temperature for 18 hours. The solution was evaporated *in vacuo*., and the residue added to a solution of acetyl chloride (2ml) in methanol (20ml) and stirred at room temperature for 18 hours. The solution was evaporated *in vacuo*., the residue redissolved in ethyl acetate (50ml), washed with 10% hydrochloric acid (2 x 50ml) and saturated aqueous sodium hydrogen carbonate (2 x 50ml), dried ($MgSO_4$), and evaporated to leave compound (**5b**) as a white solid. Yield 0.7g (78%); physical data as reported for the high temperature route.

N-(Endo-Himoyl)-(R)-Phenylglycine Methyl Ester (5f) by the low temperature route

To a solution of *endo*-himic anhydride (1.3g, 8mmol) and triethylamine (2ml, 15mmol) dissolved in dichloromethane (20ml) was added (**R**)-phenylglycine methyl ester hydrochloride (1.5g, 7.5mmol), and the resulting solution was stirred at room temperature for 27 hours. The solution was evaporated *in vacuo*., and the residue added to a solution of acetyl chloride (6ml) in methanol (25ml) and stirred at room temperature for 15 hours. The solution was evaporated *in vacuo*., the residue redissolved in ethyl acetate (40ml), washed with 10% hydrochloric acid (2 x 40ml) and saturated aqueous ammonium hydrogen carbonate (2 x 20ml), dried ($MgSO_4$), and evaporated to leave compound (**5f**) as a white solid which was recrystallised from ethyl acetate. Yield 1.6g (69%); $[\alpha]_D^{22}$ +2.6° (c=1, $CHCl_3$); other data as reported for compound (**5f**) prepared by the high temperature route.

N-(Exo-Himoyl)-(R)-Phenylglycine Methyl Ester (6f) by the low temperature route

To a solution of *exo*-himic anhydride (1.3g, 8mmol) and triethylamine (2ml, 15mmol) dissolved in dichloromethane (20ml) was added (**R**)-phenylglycine methyl ester hydrochloride (1.5g, 7.4mmol), and the resulting solution was stirred at room temperature for 27 hours. The solution was evaporated *in vacuo*., and the residue added to a solution of acetyl chloride (6ml) in methanol (25ml) and stirred at room temperature for 15 hours. The solution was evaporated *in vacuo*., the residue redissolved in ethyl acetate (40ml), washed with 10% hydrochloric acid (2 x 40ml) and saturated aqueous ammonium hydrogen carbonate (2 x 20ml), dried ($MgSO_4$), and evaporated to leave compound (**6f**) as a white solid which was recrystallised from ethyl acetate. Yield 1.3g (58%); $[\alpha]_D^{22}$ +10.0° (c=1, $CHCl_3$); other data as reported for compound (**6f**) prepared by the high temperature route.

N-(Endo-Himoyl)-(R)-Cystine Methyl Ester (5o) by the low temperature route

To a solution of *endo*-himic anhydride (3.6g, 22mmol) and triethylamine (5ml, 40mmol) dissolved in dichloromethane (50ml) was added (**R,R**)-cystine dimethyl ester dihydrochloride (3.4g, 10mmol), and the

resulting solution was stirred at room temperature for 72 hours. The solution was evaporated *in vacuo*., and the residue added to a solution of acetyl chloride (5ml) in methanol (50ml) and stirred at room temperature for 18 hours. The solution was evaporated *in vacuo*., the residue redissolved in ethyl acetate (50ml), washed with 10% hydrochloric acid (2 x 50ml) and saturated aqueous sodium hydrogen carbonate (2 x 50ml), dried ($MgSO_4$), and evaporated to leave a colourless oil. The product (**5o**) was crystallised from ether by the addition of hexane. Yield 2.2g (39%); mp 125-126°C; $[\alpha]_D^{20}$ -212° (c=0.1, $CHCl_3$); δ_H 1.51 (1H, d *J* 8.8Hz, CH_2-bridge), 1.71 (1H, d *J* 8.8Hz, CH_2-bridge), 3.1-3.4 (6H, m, CH_2S+CHCH), 3.69 (3H, s, OCH_3), 4.89 (1H, dd *J* 10.5, 4.4Hz, NCH), 6.0-6.2 (2H, m, =CH); δ_H (d_8-toluene) 0.93 (1H, d *J* 8.6Hz, CH_2-bridge), 1.29 (1H, d *J* 8.6Hz, CH_2-bridge), 2.76 (1H, dd *J* 7.7, 4.3Hz, CH_2S), 2.82 (1H, dd *J* 7.7, 4.3Hz, CH_2S), 2.99 (2H, s, CHCO), 3.29 (3H, s, OCH_3), 3.3-3.5 (2H, m, =CCH), 5.05 (1H, dd *J* 9.0, 6.1Hz, NCH), 5.98 (1H, dd *J* 5.6, 2.9Hz, =CH), 6.09 (1H, dd *J* 5.6, 2.9Hz, =CH); δ_C (d_8-toluene) 36.60 (t, CH_2S), 45.12, 45.23, 45.87, and 45.98 (4xd, CHCH), 51.49 (t, CH_2-bridge), 51.96 (d, NCH), 52.16 (q, OCH_3), 134.42, and 135.12 (2xd, =CH), 168.01 (s, CO_2), 176.33 (s, NCO); other data as reported for compound (**5o**) prepared by the high temperature route.

N-(Exo-Himoyl)-(R)-Cystine Methyl Ester (6o) by the low temperature route

To a solution of *exo*-himic anhydride (3.0g, 18mmol) and triethylamine (5ml, 40mmol) dissolved in dichloromethane (50ml) was added (**R,R**)-cystine dimethyl ester dihydrochloride (3.0g, 9mmol), and the resulting solution was stirred at room temperature for 18 hours. The solution was evaporated *in vacuo*., and the residue added to a solution of acetyl chloride (5ml) in methanol (50ml) and stirred at room temperature for 18 hours. The solution was evaporated *in vacuo*., the residue redissolved in ethyl acetate (50ml), washed with 10% hydrochloric acid (2 x 50ml) and saturated aqueous sodium hydrogen carbonate (2 x 50ml), dried ($MgSO_4$), and evaporated to leave compound (**6o**) as a yellow glass. Yield 4.2g (84%); $[\alpha]_D^{20}$ -185° (c=1.7, $CHCl_3$); δ_H 1.46 (1H, d *J* 8.7Hz, CH_2-bridge), 1.65 (1H, d *J* 9.9Hz, CH_2-bridge), 2.6-2.8 (2H, m, CH_2S), 3.2-3.4 (4H, m, CHCH), 3.75 (3H, s, OCH_3), 5.06 (1H, dd *J* 9.0, 6.4Hz, NCH), 6.2-6.3 (2H, m, =CH); δ_C 34.96 (t, CH_2S), 42.95 (t, CH_2-bridge), 45.36, 45.53, 47.70, and 47.82 (4xd, CHCH), 51.16 (d, NCH), 53.09 (q, OCH_3), 137.96, and 138.02 (2xd, =CH), 168.17 (s, CO_2), 177.19, and 177.34 (2xs, CON); other data as reported for (**6o**) prepared by the high temperature route.

Racemisation Studies on N-(Exo-Himoyl)-(R)-Cystine Methyl Ester (5o)

To compound (**5o**) (0.5g, 0.9mmol) dissolved in toluene (10ml) was added the appropriate amount of triethylamine (0.5ml, 0.2ml, or 0ml), and the resulting homogenous solution was heated at reflux. At various intervals, a 0.5ml sample of the solution was withdrawn and its optical rotation measured. The sample was then returned to the reaction flask.

N-(Endo-Himoyl)-glycine (9a)

To *endo*-himic anhydride (43.7g, 266mmol) dissolved in dry DMF (90ml) was added glycine (20.0g, 266mmol). The reaction mixture was heated at reflux for 18hours, cooled to room temperature, diluted with ethyl acetate (100ml), and washed with saturated aqueous ammonium chloride solution (6 x 70ml). The organic phase was dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The residue was recrystallised twice from ethyl acetate giving compound (**9a**) as a white crystalline solid. Yield 29g (49%); mp 147-148°C; Found C,59.0; H,5.15; N,6.4. $C_{11}H_{11}NO_4.0.2(H_2O)$ requires: C,58.8; H,5.1; N,6.2.; υ_{max} ($CHCl_3$) 3456 br, 1708 s, 1327 s, 1215 s, and 754cm^{-1} s; δ_H 1.63 (1H, d *J* 7.6Hz, CH_2-bridge), 1.82 (1H, d *J* 7.6Hz, CH_2-bridge), 3.4-3.5 (4H, m, CHCH), 4.15 (2H, s, NCH_2), 6.1-6.2 (2H, m, =CH), 9.59 (1H, br, OH); δ_C 38.86 (t, CH_2), 44.95, and 46.14 (2xd, CHCH), 52.26 (t, CH_2N), 134.52 (d, =CH), 171.31 (s, CO_2), 177.08 (s, NCO); m/z (CI) 239 (bp, $M+NH_4^+$), 222 (30, MH^+).

*N-(Exo-Himoyl)-glycine (**10a**)*

To *exo*-himic anhydride (2.8g, 17mmol) dissolved in dry DMF (10ml) was added glycine (1.4g, 19mmol). The reaction mixture was heated at reflux for 19hours, cooled to room temperature, diluted with ethyl acetate (50ml), and washed with saturated aqueous ammonium chloride solution (2 x 20ml). The organic phase was dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The residue was recrystallised twice from ethyl acetate giving compound (**9a**) as a cream crystalline solid. Yield 2.5g (66%); mp 149-150°C; Found C,59.15; H,4.8; N,6.2. $C_{11}H_{11}NO_4.0.2(H_2O)$ requires: C,58.8; H,5.1; N,6.2.; υ_{max} ($CHCl_3$) 3437 br, 1707 s, 1415 m, 1216 s, and 772cm^{-1} s; δ_H 1.53 (1H, d *J* 10.0Hz, CH_2-bridge), 1.65 (1H, d *J* 9.9Hz, CH_2-bridge), 2.7-2.8 (2H, m, CHCO), 3.3-3.4 (2H, m, =CCH), 4.30 (2H, s, NCH_2), 6.3-6.4 (2H, m, =CH), 8.40 (1H, br, OH); δ_C 39.11 (t, CH_2), 42.76 (t, NCH_2), 45.33, and 47.95 (2xd, CHCH), 137.91 (d, =CH), 171.46 (s, CO_2), 177.34 (s, NCO); m/z (EI) 221 (12, M^+), 175 (9), 158 (50), 139 (30), 112 (45), 94 (70), 70 (bp).

*N-(Endo-Himoyl)-(S)-alanine (**9b**)*

To *endo*-himic anhydride (2.0g, 12.1mmol) dissolved in DMF (20ml) was added (S)-alanine (1.0g, 11mmol), and anhydrous magnesium sulphate (4g). The resulting mixture was heated at reflux for 18hours, diluted with dichloromethane (100ml) and washed with 10% hydrochloric acid (2 x 100ml), and water (4 x 100ml). The organic layer was dried ($MgSO_4$), and evaporated *in vacuo*., to leave a yellow oil which was crystallised from ether by the addition of petrol, giving compound (**9b**), as a white solid. Yield 1.5g (58%); mp 136-137°C; $[\alpha]_D^{20}$ -19.8° (c=1.0, $CHCl_3$); Found C,58.3; H,5.8; N,5.8. $3xC_{12}H_{13}NO_4.2xH_2O$ requires: C,58.3; H,5.8; N,5.7.; υ_{max} (Nujol) 2500-3500 br, 1743 m, and 1674cm^{-1} m; δ_H 1.40 (3H, d *J* 7.2Hz, CH_3), 1.52 (1H, d *J* 8.8Hz, CH_2-bridge), 1.71 (1H, dt *J* 9.2, 1.6Hz, CH_2-bridge), 3.2-3.3 (2H, m, CHCH), 3.3-3.4 (2H, m, CHCH), 4.65 (1H, q *J* 7.2Hz, NCH), 6.0-6.1 (2H, m, =CH), 8.03 (1H, br, OH); δ_C 14.29 (q, CH_3), 45.04, 45.22, 45.70, and 45.86 (4xd, CHCH), 47.31 (t, CH_2), 52.18 (d, NCH), 134.30, and 134.55 (2xd, =CH), 174.13 (s, CO_2); 176.63, and 176.71 (2xd, CON); m/z (CI) 253 (bp, $M+NH_4^+$), 236 (95, MH^+).

*N-(Exo-Himoyl)-(S)-alanine (**10b**)*

To *exo*-himic anhydride (4.9g, 30mmol) dissolved in dry DMF (20ml) was added (S)-alanine (2.7g, 30mmol). The resulting mixture was heated at reflux for 48hours, cooled to room temperature, diluted with ethyl acetate (60ml), and washed with saturated aqueous ammonium chloride solution (7 x 40ml), followed by water (2 x 50ml). The organic layer was dried ($MgSO_4$), filtered, and evaporated *in vacuo*., leaving a residue which was recrystallised three times from ethyl acetate to give compound (**10b**) as a cream coloured powder. Yield 5.7g (81%); mp 154.5°C; $[\alpha]_D^{20}$ -3.8° (c=1.0, $CHCl_3$); Found C,58.5; H,5.6; N,5.5. $3xC_{12}H_{13}NO_4.2xH_2O$ requires: C,58.3; H,5.8; N,5.7.; υ_{max} ($CHCl_3$) 3436 br, 1730 s, 1704 s, 1642 m, 1389 m, 1215 s, 764 s, and 669cm^{-1} s; δ_H 1.52 (2H, s, CH_2-bridge), 1.59 (3H, d *J* 7.3Hz, CH_3), 2.75 (2H, s, =CCH), 3.33 (2H, s, CHCO), 4.86 (1H, q *J* 7.3Hz, NCH), 6.3-6.4 (2H, m, =CH), 8.0 (1H, br, OH); δ_C 14.07 (q, CH_3), 42.77 (t, CH_2), 45.40, 45.54, 47.57, 47.69, and 47.88 (5xd, CHCH + NCH), 138.02 (d, =CH), 174.65 (s, CO_2), 177.06, and 177.19 (2xs, NCO); m/z (CI) 253 (bp, $M+NH_4^+$), 236 (40, MH^+).

*N-(Endo-Himoyl)-(**RS**)-alanine (**9c**)*

To *endo*-himic anhydride (53.3g, 325mmol) dissolved in dry DMF (140ml) was added (**RS**)-alanine (28.9g, 325mmol). The resulting mixture was heated at reflux for 14hours, cooled, and diluted with ethyl acetate (150ml) and washed with saturated aqueous ammonium chloride solution (100ml). The aqueous layer was back extracted with ethyl acetate (30ml), and the combined organic layers washed with saturated aqueous ammonium chloride solution (3 x 100ml). The organic layer was dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The residue was recrystallised four times from ethyl acetate/ 40-60petrol to give compound (**9c**), as a white crystalline solid. Yield 33g (43%); mp 95-97°C; Found C,57.3; H,5.6; N,5.2. $C_{12}H_{13}NO_4.H_2O$ requires: C,56.9; H,6.0; N,5.5.; m/z (CI) 253 (50, $M+NH_4^+$), 236 (40, MH^+), 189 (40); other data as reported for compound (**9b**).

N-(Exo-Himoyl)-(RS)-alanine (10c)

To *exo*-himic anhydride (6.9g, 42mmol) dissolved in dry DMF (20ml) was added (**RS**)-alanine (3.8g, 43mmol). The resulting mixture was heated at reflux for 15hours, cooled to room temperature, diluted with ethyl acetate (20ml), and washed with saturated aqueous ammonium chloride solution (20ml). The aqueous layer was back extracted with ethyl acetate (10ml), and the combined organic layers washed with saturated aqueous ammonium chloride solution (6 x 20ml). The organic layer was dried ($MgSO_4$), filtered, and evaporated *in vacuo*., leaving a residue which was recrystallised twice from ethyl acetate to give compound (**10c**) as a white solid. Yield 6.0g (61%); mp 154-155°C; other data as reported for compound (**10b**).

N-(Endo-Himoyl)-(S)-alanine Methyl Ester (5b) from N-(Endo-Himoyl)-(S)-alanine (9b)

Acetyl chloride (0.5ml) was added to methanol (10ml), and to this solution was added N-(*endo*-himoyl)-(**S**)-alanine (**9b**) (130mg, 0.55mmol). The resulting solution was stirred at room temperature for 18hours, and the solvents were evaporated *in vacuo*., leaving compound (**5b**) as a white solid. Yield 120mg (88%); $[\alpha]_D^{20}$ -25.5° (c=1.0, $CHCl_3$); other data as reported for the high temperature route.

N-(Exo-7-Oxo-himoyl)-(S)-alanine Methyl Ester (11)

To a solution of *exo*-7-oxo-himic anhydride (0.6g, 3.6mmol) and triethylamine (3ml, 24mmol) dissolved in dichloromethane (40ml) was added (**S**)-alanine methyl ester hydrochloride (0.5g, 3.6mmol), and the resulting solution was stirred at room temperature for 18 hours. The solution was evaporated *in vacuo*., and the residue added to a solution of acetyl chloride (5ml) in methanol (50ml) and stirred at room temperature for 18 hours. The solution was evaporated *in vacuo*., the residue redissolved in ethyl acetate (50ml), washed with 10% hydrochloric acid (2 x 50ml) and water (2 x 50ml), dried ($MgSO_4$), and evaporated to leave compound (**11**) as a colourless oil which solidified to a white solid on standing. Yield 0.23g (25%); mp 63-65°C; $[\alpha]_D^{20}$ -12.8° (c=1, $CHCl_3$); υ_{max} (Nujol) 1740 m, and 1700cm^{-1} s; δ_H 1.52 (3H, d *J* 7.4Hz, CH_3), 2.8-2.9 (2H, m, CHCO), 3.73 (3H, s, OCH_3), 4.72 (1H, q *J* 7.4Hz, NCH), 5.28 (2H, s, OCH), 6.52 (2H, s, =CH); δ_C 14.28 (q, CH_3), 47.27, and 47.53 (2xd, CHCO), 47.53 (d, NCH), 52.67 (q, OCH_3), 81.02 (d, OCH), 136.65 (d, =CH), 169.48 (CO_2), 175.24 (NCO); m/z (CI) 269 (10, M+NH_4^+), 233 (30), 216 (bp); Found 269.1137 ($C_{12}H_{13}NO_5.NH_4$ requires 269.1137).

N-Maleonyl-(S)-alanine Methyl Ester (12)

Maleic anhydride (7.7g, 79mmol) and (**S**)-alanine methyl ester hydrochloride (10.0g, 72mmol) were dissolved in toluene (50 ml), and triethylamine (12ml, 160mmol) was added. The solution was stirred at 70°C for 18 hours, then allowed to cool to room temperature. Ethyl acetate (100 ml) was added, and the solution was washed with dilute HCl (3 x 100ml), dried over $MgSO_4$, and evaporated *in vacuo*. The resulting white solid was dissolved in dichloromethane (50ml), and oxalyl chloride (5.4g, 43mmol) was added followed by DMF (1 drop). The solution was stirred at room temperature for one hour, after which time triethylamine (10ml, excess) was added and the solution was stirred at room temperature for 18 hours. The solution was washed with dilute hydrochloric acid (3 x 50ml), saturated aqueous sodium carbonate solution (3 x 50ml), and water (50ml), then evaporated *in vacuo* to leave an oil which was purified by flash chromatography (CH_2Cl_2), giving compound (**12**) as a white solid. Yield 1.2g (8%); υ_{max} (Nujol) 1756 s, and 1724cm^{-1} s; δ_H 1.56 (3H, d *J* 7.5Hz, CH_3), 3.74 (3H, s, OCH_3), 4.78 (1H, q *J* 7.5Hz, NCH), 6.73 (2H, s, =CH); δ_C 15.21 (q, CH_3); 47.41 (d, NCH); 52.80 (q, OCH_3); 134.34 (d, =CH); 156.38 (s, CO_2); 169.84, and 170.11 (2xs, CON); m/z (CI) 201 (bp, M+NH_4^+), 184 (22, MH^+).

N-(Norborn-2-en-5-oyl)-(S)-phenylalanine Methyl Ester (14)

To a solution of *N*-acryloyl-(**S**)-phenylalanine methyl ester[7] (1.1g, 4.6mmol) in toluene (40ml) was added freshly distilled cyclopentadiene (0.7ml, 50mmol). The resulting solution was heated at 70°C for 18hours, then the solvents were evaporated *in vacuo*. The residue was purified by flash chromatography (2%Et_2O/ CH_2Cl_2), giving the four stereoisomers of compound (**14**) as two separated fractions. Combined

yield 0.4g (29%). Data for fraction A: (oil); υ_{max} (neat) 3309 s, 3058 m, 2972 s, 1746 s, and 1652cm^{-1} s; δ_H 1.2-1.4 (2H, m, CH_2-bridge), 1.6-1.7 (1H, m, CHCO), 1.8-2.0 (1H, m, CH_2CHCO), 2.0-2.1 (1H, m, CH_2CHCO), 2.8-3.0 (2H, m, CHC=), 3.0-3.3 (2H, m, PhCH_2), 3.72 (3H, s, OCH_3), 4.8-5.0 (1H, m, NCH), 6.0-6.1 (3H, m, NH + =CHCH=), 7.0-7.4 (5H, m, ArH) (peak assignments were confirmed by a ^{1}H-^{1}H COSY spectrum); δ_C 30.01, and 30.33 (2xt, CH_2Ph), 37.77, and 37.84 (2xt, CH_2CHCO), 41.37, and 41.43 (2xd, CHC=), 44.32, and 44.36 (2xd, CHC=), 46.07, and 46.20 (2xt, CH_2-bridge), 46.76, and 47.04 (2xd, NCH), 52.13, and 52.90 (2xq, OCH_3), 126.92, 128.37, and 129.14 (3xd, ArCH), 135.64 (s, ArC), 135.85, and 135.88 (2xd, =CH), 138.00, and 138.21 (2xd, =CH), 172.19, and 172.22 (2xs, CO_2), 174.91, and 175.09 (2xs, CON); m/z (CI) 300 (bp, MH$^+$), 268 (20), 234 (20); Found 300.1600 ($C_{18}H_{22}NO_3$ requires 300.1600).
Data for fraction B: mp 45-47°C; υ_{max} (Nujol) 3356 m, 1747 s, and 1651cm^{-1} s; δ_H 1.2-1.5 (3H, m, CH_2-bridge + CH_2CHCO), 1.8-2.0 (1H, m, CH_2CHCO), 2.8-2.9 (2H, m, CHC=), 3.0-3.2 (3H, m, CH_2Ph + CHCO), 3.73 (3H, s, OCH_3), 4.8-4.9 (1H, m, NCH), 5.65-5.75 (1H, m, =CH), 5.7-5.8 (1H, m, NH), 6.1-6.2 (1H, m, =CH), 7.0-7.3 (5H, m, ArH) (peak assignments were confirmed by a ^{1}H-^{1}H COSY spectrum); δ_C 29.66, and 29.87 (2xt, CH_2Ph), 37.68, and 37.91 (2xt, CH_2CHCO), 42.61, and 42.64 (2xd, CHC=), 44.60, and 44.76 (2xd, CHC=), 45.95, and 46.28 (2xd, NCH), 49.84, and 50.03 (2xt, CH_2-bridge), 52.22, and 52.77 (2xq, OCH_3), 127.06, 128.52, and 129.19 (3xd, ArCH), 131.90, and 132.42 (2xd, =CH), 135.91, and 135.98 (2xs, ArC), 137.59, and 137.82 (2xd, =CH), 172.22, and 172.31 (2xs, CO_2), 173.87 (s, CON); m/z (CI) 300 (bp, MH$^+$), 234 (80); Found 300.1600 ($C_{18}H_{22}NO_3$ requires 300.1600).

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