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Enantioselective synthesis of non-proteinogenic 2-arylallyl-α-amino acids via Pd/In catalytic cascades

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Abstract—An efficient synthesis of both *R*- and *S*-enantiomers of 2-arylallyl-α-amino acids via a diastereoselective Pd/In mediated catalytic allylation of chiral *N*-sulfinyl-α-imino esters is described. The potential for further enhancement of molecular complexity and creating contiguous chiral centres by interfacing these processes with catalytic cyclisation–anion capture methodology is demonstrated.

1. Introduction

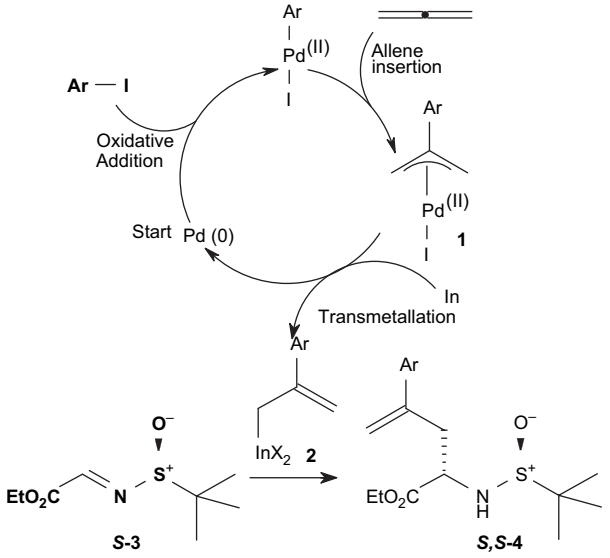
The synthesis of peptides and proteins containing non-natural α-amino acids vastly increases the structural and chemical diversity of polypeptides.

Novel α-amino acid side-chains and the availability of both *R*- and *S*-stereoisomers enable tuning of pharmacokinetics, formation of β-sheets and other peptide structural motifs that effect biological activity and structural properties.

The synthesis of 'designer' peptidomimetics, incorporating and/or modifying the beneficial aspects of the parent polypeptides whilst also possessing enhanced metabolic stability and/or improved pharmacokinetics, is an area of burgeoning interest.[1–3]

The asymmetric alkylation of glycine cation equivalents is a general, efficient route to non-proteinogenic α-amino acid derivatives. Previously, our group reported highly regio- and diastereoselective Pd/In mediated cascade allylations of carbonyl compounds including a highly stereoselective allylation of chiral *N*-sulfinyl aldimines.[4–10] We now report further applications of the *tert*-butyl sulfinyl chiral auxilliary, which has been widely used in the synthesis of chiral amines including 1,2-amino alcohols and α- and β-amino acids,[11–13] to a new approach to unusual α-amino acids.

The Pd/In bimetallic cascade process involves generation of an electrophilic π-allyl palladium species **1** that undergoes transmetallation in the presence of indium, furnishing nucleophilic η^1-allyl indium species **2**. Allylation of the enantiopure *N*-sulfinyl-α-imino ester **3**, affords *N*-sulfinyl-α-alkyl-α-amino esters **4** as single diastereoisomer (Scheme 1). Initial experiments employing iodobenzene and a catalyst system comprising of 10 mol % $Pd(OAc)_2$, 20 mol % tris-2-furyl phosphine and 20 mol % CuI in DMF at 40 °C confirmed these expectations (Table 1, entry 1).



Scheme 1. Reaction mechanism. Reagents and conditions: (i) ArI (0.75 mmol), allene (1 atm), In (0.75 mmol), $Pd(OAc)_2$ (10 mol %), tri-2-furyl phosphine (20 mol %), CuI (20 mol %), piperidine (0.5 mmol), DMF (20 ml/mmol), 40 °C, 24 h; (ii) 4 M HCl/dioxane (5 mol equiv), EtOH (10 ml/mmol), 30 min, rt, NaOH (2 mol equiv), 1:1 v/v EtOH/H_2O (10 ml/mmol) reflux, 2 h.

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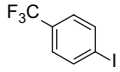
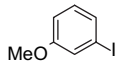
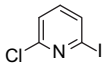
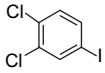
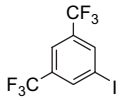
Table 1. Bimetallic cascade synthesis of chiral **4a–h** and **5a–h**[a]

Entry	ArI	Cascade product		Amino acid	
		Configuration	Yield (%)[b]	Configuration	Yield (%)[c]
1		*S,S*-**4a**	92	*S*-**5a**	100
		R,R-**4a**	80	*R*-**5a**	100
2		*S,S*-**4b**	69	*S*-**5b**	—
		R,R-**4b**	55	*R*-**5b**	100
3		*S,S*-**4c**	68	*S*-**5c**	50
		R,R-**4c**	68	*R*-**5c**	54
4		*S,S*-**4d**	54	*S*-**5d**	99
		R,R-**4d**	49	*R*-**5d**	99
5		*S,S*-**4e**	72	*S*-**5e**	97
		R,R-**4e**	67	*R*-**5e**	80
6		*S,S*-**4f**	52	*S*-**5f**	85
		R,R-**4f**	69	*R*-**5f**	79
7		*S,S*-**4g**	73	*S*-**5g**	73
		R,R-**4g**	74	*R*-**5g**	82
8		*S,S*-**4h**	69	*S*-**5h**	89
		R,R-**4h**	76	*R*-**5h**	68

[a] Conditions as for Scheme 1.
[b] Isolated yield.
[c] Isolated overall yield for the two-step deprotection.

The scope of the reaction was explored through a series of aryl iodides (Table 1). X-ray crystal structures of one such pair *S,S*-**6** and *R,R*-**6** (Fig. 1), derived by partial deprotection of *S,S*-**4g** and *R,R*-**4g**, established that the *S*-sulfinimine engenders *S* stereochemistry at the new chiral centre and the *R*-sulfinimine provides *R* stereochemistry at the new chiral centre.[14] Non-proteinogenic α-amino acids **5** are obtained in good to excellent yield (Table 1) from **4** via a two-step deprotection process (Scheme 2).

A rationale for the stereochemical outcome of the cascade **3**→**4** is summarised in Figure 2. The four possible Zimmerman–Traxler, chair-like transition states **7–10** have been modelled using semi-empirical calculations.[15] These correspond to additions of the allyl indium intermediate to either the *re* or *si* face of the *S*-sulfoximine, each of which can

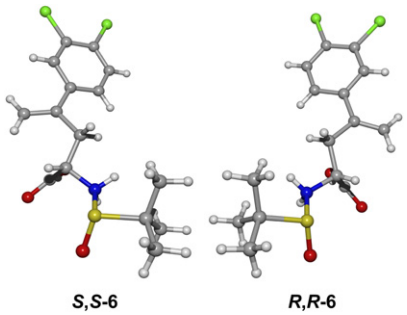
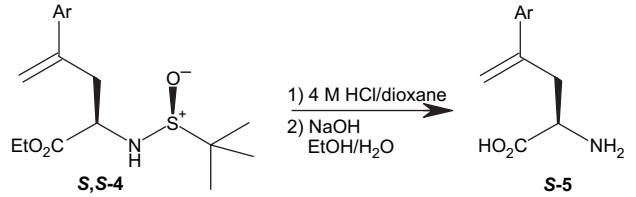


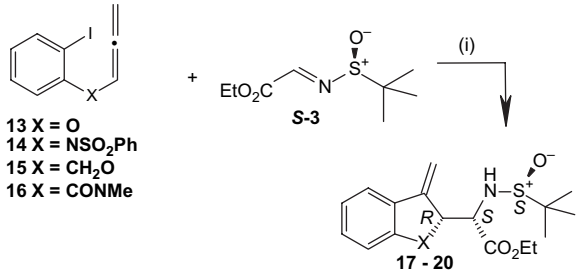
Figure 1. X-ray crystal structures of a matched pair of enantiomers.



Scheme 2. Deprotection of *N*-sulfinyl esters. Cleavage of the chiral sulfinyl auxilliary is carried out first by treatment with 4 M HCl in dioxane (5 mol equiv) for 30 min. Following the removal of the solvent the crude material is treated with 1 M aqueous NaOH solution (2 mol equiv) in a 1:1 v/v EtOH/H_2O under reflux for 2 h. The amino acids **5a–h** are isolated using an Amberlyst H^+ ion exchange resin (Table 1).

involve two possible chair-like arrangements. The heat of formation (ΔH_f) and imaginary vibrational frequencies (ν_i) for transition states corresponding to additions to the *S*-sulfoximine indicate a marked preference for transition state **10**, which locates the ester moiety axially. Closer inspection of this transition state reveals that the ester carbonyl oxygen is located near to the indium atom (O–In distance of 2.80 Å) indicating coordination to the indium atom. This transition state leads to the product possessing *S* stereochemistry at the newly created chiral centre. Interestingly, transition state **10** also locates the sulfoxide oxygen near to the metal centre (at a distance of 2.75 Å) and this, although now involves a four-membered ring, may also further stabilise the transition state. This type of chelation appears to be energetically important as the next most favourable transition state **8** locates the sulfoxide oxygen close to the metal centre at a distance of 2.75 Å. (Note: the calculations employed parameters for In(III) although the valence state of the In in this chemistry is not yet established.)

To further extend the scope of our chemistry, we have utilised bifunctional aryl iodide/allenes **13–16** (Scheme 3) allowing access to our catalytic cyclisation-anion capture methodology.[16] The cyclisation–allylation reaction is entirely regio- and diastereoselective generating two contiguous chiral centres with complete stereocontrol, affording **17–20** in moderate to good yield (Table 2).



Scheme 3. Tandem cyclisation–imine capture cascade. Reagents and conditions: (i) ArI (0.75 mmol), In (0.75 mmol), $Pd(OAc)_2$ (10 mol %), tri-2-furyl phosphine (20 mol %), CuI (20 mol %), piperidine (0.5 mmol), DMF (20 ml/mmol), 80 °C, 24 h.

A matched pair of X-ray crystal structures *S,S,R*-**18** and *R,R,S*-**18**[14] established that the *R*-sulfinimine engenders *R* stereochemistry at the 5-position and *S* stereochemistry at the 6-position (Table 2, entries 3 and 4, Fig. 3). Semi-empirical calculations reveal a similar trend to those described above. In this case, four chair-like transition states

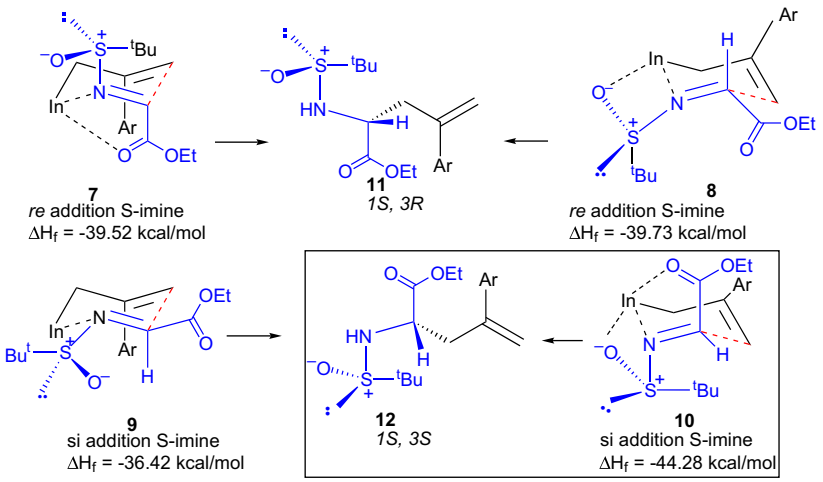
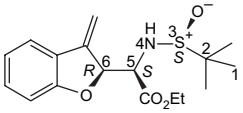
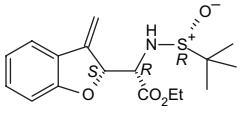
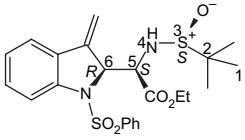
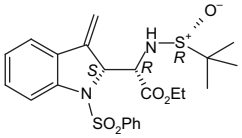
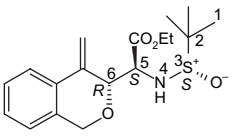
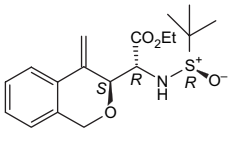


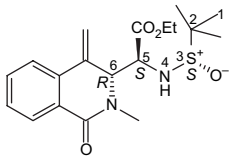
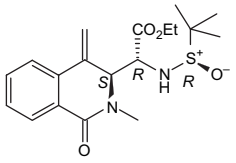
Figure 2. Stereochemical rationale for Scheme 2.

Table 2. Tandem cyclisation–allylation cascades[a]

Entry	Allene	Imine	Product	Yield (%)[b]
1	**13**	*S*-**3**	 ***S,S,R*-17**	64
2	**13**	*R*-**3**	 ***R,R,S*-17**	62
3	**14**	*S*-**3**	 ***S,S,R*-18**	44
4	**14**	*R*-**3**	 ***R,R,S*-18**	48
5	**15**	*S*-**3**	 ***S,S,R*-19**	62
6	**15**	*R*-**3**	 ***R,R,S*-19**	64

(*continued*)

Table 2. (*continued*)

Entry	Allene	Imine	Product	Yield (%)[b]
7	**16**	*S*-**3**	 ***S,S,R*-20**	28
8	**16**	*R*-**3**	 ***R,R,S*-20**	32

[a] General conditions as for Scheme 3.
[b] Isolated yield.

are possible giving rise to four possible diastereoisomeric products.

The most energetically favourable transition state **21** leads to the formation of **18**. As in the case of **10** (Fig. 2), this transition state appears to be stabilised by coordination to the indium involving both the sulfoxide and ester (Fig. 4). This transition state is calculated to be nearly 8 kcal/mol lower in energy than the next most energetically favoured transition state, thus accounting for the observed stereochemical preference in this reaction.

In conclusion, we have described a short, efficient, diastereoselective synthesis of 2-arylallyl-α-amino acids as single enantiomers with either *R* or *S* stereochemistry. Application of bifunctional allene/aryl iodides as substrates furnishes enantiopure *N*-sulfinyl-α-amino esters with two contiguous chiral centres via a regioselective process. The stereochemical outcome of both types of process has been modelled by semi-empirical calculations, which highlight the key transition state influence of chelation to indium by both the sulfoxide and carbonyl oxygen atoms.

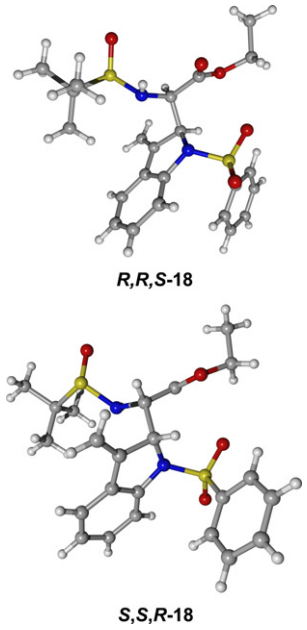


Figure 3. X-ray crystal structures of *R*,*R*,*S*-**18** and S,*S*,*R*-**18**.

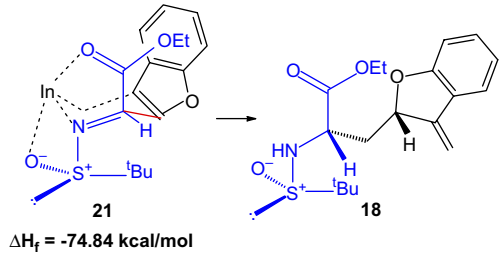


Figure 4. Stereochemical rationale for Scheme 3.

2. Experimental

2.1. General

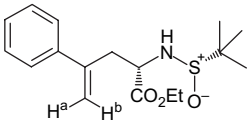
Unless otherwise noted all reagents were obtained from commercial suppliers and used without further purification. All solvents were dried or purified by literature procedures. Chromatography columns were prepared using Fisher chemicals 60A 35–70 μm silica gel. Nuclear magnetic resonance spectra were recorded using Bruker DPX300 and DRX500 MHz spectrometers. Chemical shifts are reported in parts per million (δ) downfield relative to the internal reference tetramethylsilane. Unless otherwise specified NMR spectra were recorded in deuterochloroform at room temperature. Abbreviations used: Ar=aromatic, d=doublet, dd=doublet of doublets, dq=doublet of quartets, dt=doublet of triplets, m=multiplet, q=quartet, s=singlet, t=triplet. Mass spectra were recorded using a micromass ZMD 2000 spectrometer employing the electrospray (ES^+) ionisation technique. Accurate molecular masses were obtained from the EPSRC Swansea Mass Spectroscopy service using perfluorotributylamine or polyethylenimine as an internal standard. Infrared spectra were recorded using a Perkin–Elmer FTIR spectrometer. IR spectra of liquids were recorded as thin films on sodium chloride plates. IR spectra of solids were recorded using the 'golden gate' apparatus. Optical rotations were measured on an Optical Activity AA-1000 polarimeter.

Rotations are quoted in 10^{-1} deg cm^2/g and the concentration (c) is expressed in grams per 100 ml. Unless otherwise stated chloroform was the solvent. Microanalysis was performed using a Carlo-Erber 1108 elemental analyser and, for sulfur, by titration against barium perchlorate.

2.2. General procedure for the synthesis of *N*-sulfinylamino esters 4a–h

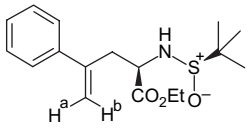
Aryl iodide (0.75 mmol) was added to a suspension of chiral α-imino ester **3** (0.5 mmol), indium metal powder (0.088 g, 0.75 mmol), $Pd(OAc)_2$ (0.011 g, 0.05 mmol), tri-2-furyl phosphine (0.024 g, 0.1 mmol), CuI (0.019 g, 0.1 mmol) and piperidine (0.05 ml, 0.5 mmol) in DMF (10 ml) in a Schlenk tube. The mixture was subjected to two freeze–pump–thaw cycles and then charged, using standard Schlenk techniques, with allene gas (0.5 bar). The mixture was stirred and heated to 40 °C (oil bath temperature) for 24 h, left to cool and vented. Ethyl acetate (20 ml) and 5% HCl aqueous solution (10 ml) was added and the mixture stirred for 20 min. The phases were separated and the aqueous layer extracted with ethyl acetate (20 ml). The organic extracts were combined and washed with water (3×40 ml), dried over magnesium sulfate, filtered and the filtrate concentrated in vacuo. The residue was purified by flash chromatography to give the *N*-sulfinylamino esters.

2.2.1. Ethyl 2*S*,4*S*-(2-methyl-propane-2-sulfinylamino)-4-phenyl-pent-4-enoate (*S*,*S*-4a).



Obtained as a pale yellow oil (0.149 g, 92%) after flash chromatography (9:1 v/v diethyl ether/hexane); R_f 0.43 (diethyl ether); $[\alpha]_D^{20}$ +81.4 (c 1.2); Found: C, 62.90; H, 7.80; N, 4.35; S, 9.90, $C_{17}H_{25}NO_3S$ requires: C, 63.13; H, 7.79; N, 4.33; S, 9.91%; ν_{max}/cm^{-1}: 3294, 2983, 2253, 1794, 1732, 1630; δ_H (500 MHz, $CDCl_3$): 7.37–7.34 (3H, m, ArH), 7.29–7.27 (2H, m, ArH), 5.34 (1H, s, $=CH^a$), 5.12 (1H, s, $=CH^b$), 4.10–4.01 (4H, m, OCH_2CH_3, N*HCH*), 3.04 (1H, dd, NCHC*H*, J=1.0, 2.9 Hz), 2.85 (1H, dd, NCHC*H*, J=1.0, 3.2 Hz), 1.26 (3H, t, OCH_2CH_3, J=7.1 Hz), 1.16 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$): 173.3 (*C*O), 144.1 ($H_2C=$*C*), 140.5 (Ar), 128.9 (Ar), 128.2 (Ar), 126.6 (Ar), 117.0 ($=CH_2$), 62.1 (OC), 57.3 (NC), 56.5 (S*C*), 40.8 (NC*C*), 23.0 ($SC(CH_3)_3$), 14.5 (OC*C*); m/z (ES^+): 324 (MH^+).

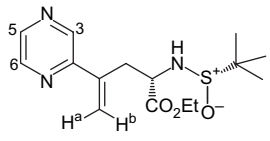
2.2.2. Ethyl 2*R*,4*R*-(2-methyl-propane-2-sulfinylamino)-4-phenyl-pent-4-enoate (*R*,*R*-4a).



Obtained as a pale yellow oil (0.130 g, 80%) after flash chromatography (9:1 v/v diethyl ether/hexane); R_f 0.43 (diethyl

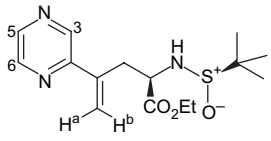
ether); $[\alpha]_D^{20}$ −79.9 (*c* 1.6); Found: C, 63.00; H, 7.80; N, 4.40; S, 9.90, $C_{17}H_{25}NO_3S$ requires: C, 63.13; H, 7.79; N, 4.33; S, 9.91%; ν_{max}/cm^{-1}: 3294, 2983, 2253, 1794, 1732, 1630; δ_H (500 MHz, $CDCl_3$): 7.37–7.34 (3H, m, ArH), 7.29–7.27 (2H, m, ArH), 5.34 (1H, s, =CH^a), 5.12 (1H, s, =CH^b), 4.10–4.01 (4H, m, OCH_2CH$_3$, NHC*H*), 3.04 (1H, dd, NCHC*H*, *J*=1.0, 2.9 Hz), 2.85 (1H, dd, NCHC*H*, *J*=1.0, 3.2 Hz), 1.26 (3H, t, OCH$_2$CH_3, *J*=7.1 Hz), 1.16 (9H, s, C(CH$_3$)$_3$); δ_c (75 MHz, $CDCl_3$): 173.3 (*C*O), 144.1 (H$_2$C=*C*), 140.5 (Ar), 128.9 (Ar), 128.2 (Ar), 126.6 (Ar), 117.0 (=*C*H$_2$), 62.1 (OC), 57.3 (NC), 56.5 (SC), 40.8 (NC*C*), 23.0 (SC(*C*H$_3$)$_3$), 14.5 (OC*C*); *m*/*z* (ES$^+$): 324 (MH$^+$).

2.2.3. Ethyl 2*S*,4*S*-(2-methyl-propane-2-sulfinylamino)-4-pyrazin-2-yl-pent-4-enoate (*S*,*S*-4b).



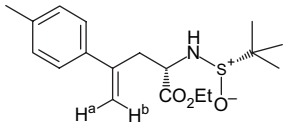
Obtained as a pale yellow oil (0.112 g, 69%) after flash chromatography (ethyl acetate); R_f 0.37 (ethyl acetate); $[\alpha]_D^{20}$ +63.5 (*c* 0.9); Found: C, 54.40; H, 6.90; N, 12.70, $C_{15}H_{23}N_3O_3S\cdot 0.25$ M H_2O requires: C, 54.61; H, 7.18; N, 12.74%; ν_{max}/cm^{-1}: 3584, 3436 (NH), 3289, 2982, 2963, 2240, 1734 (C=O), 1468, 1367, 1067; δ_H (500 MHz, $CDCl_3$): 8.74 (1H, s, pyrazinyl-3H), 8.47 (1H, d, pyrazinyl-6H, *J*=1.3 Hz), 8.39 (1H, d, pyrazinyl-5H, *J*=1.3 Hz), 5.81 (1H, s, =CH^a), 5.42 (1H, s, =CH^b), 4.14–4.04 (4H, br m, OCH_2, NHC*H*), 3.05 (1H, dd, NCHC*H*, *J*=5.3, 14.3 Hz), 2.93 (1H, dd, NHCHC*H*, *J*=8.2, 14.3 Hz), 1.18 (3H, t, OCH$_2$CH_3, *J*=7.2 Hz), 1.08 (9H, s, C(CH$_3$)$_3$); δ_C (75 MHz, $CDCl_3$): 172.00 (CO), 152.02 (H$_2$C=*C*), 142.29 (Ar), 141.91 (Ar), 141.22 (Ar), 140.08 (Ar), 119.35 (=*C*H$_2$), 60.69 (O*C*), 55.82 (NC), 55.13 (SC), 37.13 (NC*C*), 21.54 (C(*C*H$_3$)$_3$), 13.08 (OC*C*); *m*/*z* (ES$^+$): 326 (MH$^+$).

2.2.4. Ethyl 2*R*,4*R*-(2-methyl-propane-2-sulfinylamino)-4-pyrazin-2-yl-pent-4-enoate (*R*,*R*-4b).



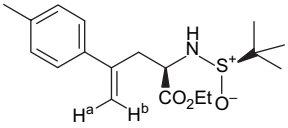
Obtained as a pale yellow oil (0.169 g, 35%) after flash chromatography (ethyl acetate); R_f 0.37 (ethyl acetate); $[\alpha]_D^{20}$ −63.6 (*c* 1.1); Found: C, 54.40; H, 6.85; N, 12.65, $C_{15}H_{23}N_3O_3S\cdot 0.25$ M H_2O requires: C, 54.61; H, 7.18; N, 12.74%; ν_{max}/cm^{-1}: 3447, 2981, 1734, 1633, 1519, 1469; δ_H (500 MHz, $CDCl_3$): 8.75 (1H, s, pyrazinyl-3H), 8.46 (1H, d, pyrazinyl-6H, *J*=1.3 Hz), 8.39 (1H, d, pyrazinyl-5H, *J*=1.3 Hz), 5.81 (1H, s, =CH^a), 5.42 (1H, s, =CH^b), 4.17–4.04 (4H, br m, OCH_2, NHC*H*), 3.05 (1H, dd, NCHC*H*, *J*=5.3 Hz, 14.3 Hz), 2.93 (1H, dd, NCHC*H*, *J*=8.2 Hz, 14.3 Hz), 1.18 (3H, t, OCH$_2$CH_3, *J*=7.2 Hz), 1.08 (9H, s, C(CH$_3$)$_3$); δ_C (75 MHz, $CDCl_3$): 171.95 (CO), 152.02 (H$_2$C=*C*), 142.32 (Ar), 141.89 (Ar), 141.19 (Ar), 140.57 (Ar), 119.35 (=*C*H$_2$), 60.63 (O*C*), 55.85 (NC), 55.19 (SC), 37.09 (NC*C*), 21.76 (C(*C*H$_3$)$_3$), 13.08 (OC*C*); *m*/*z* (ES$^+$): 326 (MH$^+$).

2.2.5. Ethyl 2*S*,4*S*-(2-methyl-propane-2-sulfinylamino)-4-*p*-tolyl-pent-4-enoate (*S*,*S*-4c).



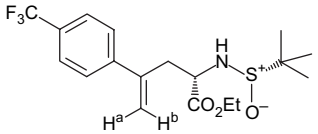
Obtained as a colourless oil (0.230 g, 68%) after flash chromatography (8:1 v/v Et_2O/hexane); R_f 0.53 (8:1 v/v Et_2O/hexane); $[\alpha]_D^{20}$ +87.2 (*c* 2.4); Found: C, 63.90; H, 8.40; N, 3.90; S, 9.40, $C_{18}H_{27}NO_3S$ requires: C, 64.06; H, 8.06; N, 4.15; S, 9.50%; ν_{max}/cm^{-1}: 3456, 3280 (NH), 3082, 1733 (CO), 1626, 1563, 1511; δ_H (500 MHz, $CDCl_3$): 7.25 (2H, d, ArH, *J*=7.9 Hz), 7.14 (2H, d, ArH, *J*=7.9 Hz), 5.31 (1H, s, =CH^a), 5.07 (1H, s, =CH^b), 4.12 (2H, q, OCH_2, *J*=7.1 Hz), 4.03 (1H, d, NH, *J*=8.3 Hz), 4.02–3.91 (1H, m, NCH), 3.00 (1H, dd, NCHC*H*, *J*=5.4, 14.3 Hz), 2.80 (1H, dd, NCHC*H*, *J*=7.6, 14.3 Hz), 2.35 (3H, s, ArCH$_3$), 1.25 (3H, t, OCH$_2$CH_3, *J*=7.1 Hz), 1.17 (9H, s, C(CH$_3$)$_3$); δ_C (75 MHz, $CDCl_3$): 171.29 (CO), 142.42 (H$_2$C=*C*), 136.50 (Ar), 136.05 (Ar), 128.11 (Ar), 125.21 (Ar), 114.65 (=*C*H$_2$), 60.54 (O*C*), 55.87 (NC), 55.08 (SC), 39.41 (NC*C*), 21.52 (C(*C*H$_3$)$_3$), 20.05 (OC*C*), 13.05 (Ar*C*H$_3$); *m*/*z* (ES$^+$): 338 (MH$^+$).

2.2.6. Ethyl 2*R*,4*R*-(2-methyl-propane-2-sulfinylamino)-4-*p*-tolyl-pent-4-enoate (*R*,*R*-4c).



Obtained as a colourless oil (0.233 g, 68%) after flash chromatography (8:1 v/v Et_2O/hexane); R_f 0.53 (8:1 v/v Et_2O/hexane); $[\alpha]_D^{20}$ −88.6 (*c* 1.5); Found: C, 64.00; H, 8.40; N, 4.10; S, 9.40, $C_{18}H_{27}NO_3S$ requires: C, 64.06; H, 8.06; N, 4.15; S, 9.50%; ν_{max}/cm^{-1}: 3276, 3085, 2980, 2958, 2926, 2869, 1737; δ_H (500 MHz, $CDCl_3$): 7.25 (2H, d, ArH, *J*=7.9 Hz), 7.14 (2H, d, ArH, *J*=7.9 Hz), 5.30 (1H, s, =CH^a), 5.07 (1H, s, =CH^b), 4.14–4.10 (2H, q, OCH$_2$, *J*=7.1 Hz), 4.03 (1H, d, NH, *J*=8.3 Hz), 4.0–3.9 (1H, m, NCH), 3.00 (1H, dd, NCHC*H*, *J*=5.4, 14.3 Hz), 2.80 (1H, dd, NCHC*H*, *J*=7.6, 14.3 Hz), 2.35 (3H, s, ArCH$_3$), 1.24 (3H, t, OCH$_2$CH_3, *J*=7.1 Hz), 1.16 (9H, s, C(CH$_3$)$_3$); δ_C (75 MHz, $CDCl_3$): 173.34 (CO), 143.84 (H$_2$C=*C*), 137.96 (Ar), 137.48 (Ar), 129.54 (Ar), 126.63 (Ar), 116.09 (=*C*H$_2$), 61.99 (O*C*), 57.28 (NC), 56.52 (SC), 40.85 (NC*C*), 22.96 (C(*C*H$_3$)$_3$), 21.48 (OC*C*), 14.47 (Ar*C*H$_3$); *m*/*z* (ES$^+$): 338 (MH$^+$).

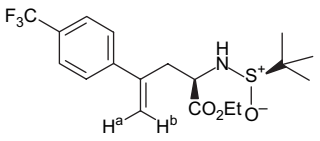
2.2.7. Ethyl 2*S*,4*S*-(2-methyl-propane-2-sulfinylamino)-4-(4-trifluoromethyl-phenyl)-pent-4-enoate (*S*,*S*-4d).



Obtained as a colourless oil (0.422 g, 54%) after flash chromatography (Et_2O); R_f 0.16 (Et_2O); $[\alpha]_D^{20}$ +82.2 (*c* 1.1);

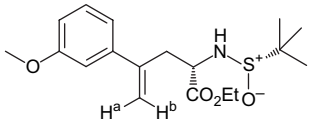
Found: C, 55.00; H, 6.30; N, 3.60; S, 8.10, $C_{18}H_{24}NSO_4F_3$ requires: C, 55.23; H, 6.18; N, 3.58; S, 8.19; F, 14.56%; ν_{max}/cm^{-1}: 3453, 3283 (NH), 3088, 2982, 2961, 2907, 2871, 1738 (CO), 1616; δ_H (500 MHz, $CDCl_3$): 7.60 (2H, ArH, d, J=8.2 Hz), 7.47 (2H, ArH, d, J=8.2 Hz), 5.41 (1H, s, =CH^a), 5.23 (1H, s, =CH^b), 4.12 (2H, m, OCH_2), 4.04 (1H, d, NH, 7.5 Hz), 3.97 (1H, dt, NCH, J=5.6, 7.5 Hz), 3.05 (1H, dd, NCHCH, J=5.6, 14.3 Hz), 2.86 (1H, dd, NCHCH, J=7.5, 14.3 Hz), 1.25 (3H, t, OCH_2CH_3, J=7.2 Hz), 1.16 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$): 172.99 (CO), 149.37 (Ar), 143.13 (H_2C=C), 130.17 (q, CF_3, J=32.39 Hz), 127.16 (Ar), 126.85 (Ar), 125.86 (q, F_3CC, 4.06 Hz), 118.89 (=CH_2), 62.20 (OC), 57.02 (NC), 56.52 (SC), 40.54 (NCC), 22.89 ($C(CH_3)_3$), 14.44 (OCC); m/z (ES$^+$): 392 (MH$^+$).

2.2.8. Ethyl 2*R*,4*R*-(2-methyl-propane-2-sulfinylamino)-4-(4-trifluoromethyl-phenyl)-pent-4-enoate (*R*,*R*-4d).



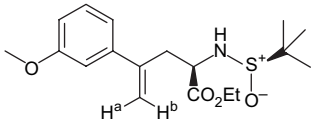
Obtained as a colourless oil (0.385 g, 49%) after flash chromatography (Et_2O); R_f 0.16 (Et_2O); $[\alpha]_D^{20}$ −80.4 (c 0.7); Found: C, 55.00; H, 6.20; N, 3.70; S, 8.30, $C_{18}H_{24}NSO_4F_3$ requires: C, 55.23; H, 6.18; N, 3.58; S, 8.19; F, 14.56%; ν_{max}/cm^{-1}: 3459, 3282 (NH), 2982, 3088, 2982, 2961, 2907, 2871, 1738 (CO), 1616, 1573; δ_H (500 MHz, $CDCl_3$): 7.60 (2H, ArH, d, J=8.2 Hz), 7.47 (2H, ArH, d, J=8.2 Hz), 5.41 (1H, s, =CH^a), 5.23 (1H, s, =CH^b), 4.19–4.06 (2H, m, OCH_2), 4.03 (1H, d, NH, J=7.5 Hz), 3.97 (1H, dt, NCH, J=5.6, 7.5 Hz), 3.04 (1H, dd, NCCH, J=5.6, 14.3 Hz), 2.87 (1H, dd, NCCH, J=7.5, 14.3 Hz); 1.25 (3H, t, OCH_2CH_3, J=7.19), 1.16 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$): 172.99 (CO), 149.37 (Ar), 143.13 (H_2C=C), 130.17 (q, CF_3, J=32.39 Hz), 127.16 (Ar), 126.85 (Ar), 125.86 (q, F_3CC, 4.06 Hz), 118.89 (=CH_2), 62.20 (OC), 57.02 (NC), 56.52 (SC), 40.54 (NCC), 22.89 ($C(CH_3)_3$), 14.44 (OCC); m/z (ES$^+$): 392 (MH$^+$).

2.2.9. Ethyl 2*S*,4*S*-(3-methoxy-phenyl)-2-(2-methyl-propane-2-sulfinylamino)-pent-4-enoate (*S*,*S*-4e).



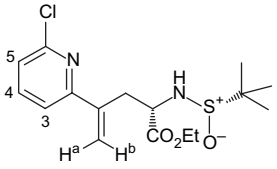
Obtained as a pale yellow oil (0.130 g, 72%) after flash chromatography (9:1 v/v diethyl ether/hexane); R_f 0.47 (3:1 v/v ethyl acetate/hexane); $[\alpha]_D^{20}$ +78.3 (c 2.1); Found: C, 60.40; H, 7.80; N, 3.70, $C_{18}H_{27}NO_4S\cdot0.25$ M H_2O requires: C, 60.39; H, 7.74; N, 3.91%; Found: 376.1552, $C_{18}H_{27}NO_4S\cdot Na$ requires: 376.1559; ν_{max}/cm^{-1}: 3583, 3453 (NH), 3283, 2978, 2836, 1736 (CO), 1628; δ_H (500 MHz, $CDCl_3$): 7.19 (1H, t, Ar-5H, J=7.7 Hz), 6.87 (1H, s, Ar-2H), 6.82 (1H, d, Ar-4H, J=7.7 Hz), 6.75 (1H, d, Ar-6H, J=7.7 Hz), 5.27 (1H, s, =CH^a), 5.04 (1H, s, =CH^b), 4.07–4.03 (2H, m, OCH_2), 3.97–3.92 (2H, m, NHCH), 3.74 (3H, s, OCH_3), 2.93 (1H, dd, NCCH, J=5.3, 14.0 Hz), 2.74 (1H, dd, NCCH, J=7.5, 14.0 Hz), 1.17 (3H, t, OCH_2CH_3, J=4.8 Hz), 1.09 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$): 171.85 (CO), 158.60 (H_2C=C), 150.48 (Ar), 142.52 (Ar), 140.55 (Ar), 134.76 (Ar), 117.83 (Ar), 115.61 (=CH_2), 111.91 (Ar), 60.72 (NCC), 55.85 (ArOC), 55.09 (NC), 54.19 (SC), 21.61 ($C(CH_3)_3$), 13.15 (OCC); m/z (ES$^+$): 354 (MH$^+$).

2.2.10. Ethyl 2*R*,4*R*-(3-methoxy-phenyl)-2-(2-methyl-propane-2-sulfinylamino)-pent-4-enoate (*R*,*R*-4e).



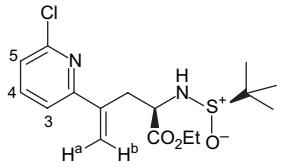
Obtained as a pale yellow oil (0.119 g, 67%) after flash chromatography (9:1 v/v diethyl ether/hexane); R_f 0.47 (3:1 v/v ethyl acetate/hexane); $[\alpha]_D^{20}$ −77.1 (c 1.2); Found: C, 61.30; H, 7.80; N, 4.00; S, 9.20, $C_{18}H_{27}NO_4S$ requires: C, 61.16; H, 7.70; N, 3.96; S, 9.07%; ν_{max}/cm^{-1}: 3282, 3082, 2980, 2958, 2907, 2869, 2836, 1737 (CO), 1627, 1598, 1577; δ_H (500 MHz, $CDCl_3$): 7.18 (1H, t, Ar-5H, J=7.9 Hz), 6.87 (1H, d, Ar-2H, 7.9 Hz), 6.82 (1H, s, Ar-4H), 6.76 (1H, d, Ar-6H, J=7.9 Hz), 5.27 (1H, s, =CH^a), 5.04 (1H, s, =CH^b), 4.07–4.03 (2H, m, OCH_2), 3.97–3.92 (2H, m, NHCH), 3.74 (3H, s, OCH_3), 2.93 (1H, dd, NCCH, J=5.3, 14.0 Hz), 2.74 (1H, dd, NCCH, J=7.5, 14.0 Hz), 1.17 (3H, t, OCH_2CH_3, J=7.1 Hz), 1.09 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$): 171.85 (CO), 158.61 (H_2C=C), 142.22 (Ar), 140.55 (Ar), 128.44 (Ar), 117.43 (Ar), 115.61 (=CH_2), 111.92 (Ar), 111.42 (Ar), 60.62 (OC), 55.87 (OCH_3), 55.10 (SC), 54.19 (NC), (NCC), 21.55 ($C(CH_3)_3$), 13.05 (OCC); m/z (ES$^+$): 354 (MH$^+$).

2.2.11. Ethyl 2*S*,4*S*-(6-chloro-pyridin-2-yl)-2-(2-methyl-propane-2-sulfinylamino)-pent-4-enoate (*S*,*S*-4f).



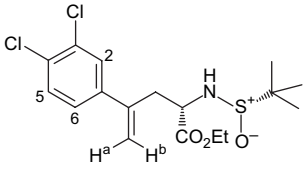
Obtained as a pale yellow oil (0.187 g, 52%) after flash chromatography (6:1 v/v ethyl acetate/hexane); R_f 0.41 (6:1 v/v ethyl acetate/hexane); $[\alpha]_D^{20}$ +86.7 (c 1.8); Found: C, 53.30; H, 6.60; N, 7.80; S, 9.00, $C_{16}H_{23}ClN_2O_3S$ requires: C, 53.55; H, 6.46; Cl, 9.88; N, 7.81; S, 8.93%; ν_{max}/cm^{-1}: 3417, 3209, 2981, 2961, 1737 (CO); δ_H (500 MHz, $CDCl_3$): 8.40 (1H, d, pyridyl-5H, J=2.3 Hz), 7.63 (1H, d, pyridyl-3H, J=8.4 Hz), 7.32 (1H, dd, pyridyl-4H, J=2.3, 8.4 Hz), 5.41 (1H, s, =CH^a), 5.27 (1H, s, =CH^b), 4.17–4.09 (3H, br m, NH, OCH_2), 3.96 (1H, m, NHCH), 3.00 (1H, dd, NCCH, 0.6, 5.0 Hz), 2.86 (1H, dd, H_2C=CCH, J=0.6, 7.7 Hz), 1.26 (3H, t, OCH_2CH_3, J=7.2 Hz), 1.18 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$): 172.82 (CO), 151.06 (H_2C=C), 147.96 (Ar), 140.11 (Ar), 136.86 (Ar), 135.10 (Ar), 124.36 (Ar), 119.32 (=CH_2), 62.36 (OC), 56.74 (NC), 56.61 (SC), 22.95 ($C(CH_3)_3$), 14.48 (O_2CC); m/z (ES$^+$): 359 (^{35}Cl MH$^+$), 361 (^{37}Cl MH$^+$).

2.2.12. Ethyl 2*R*,4*R*-(6-chloro-pyridin-2-yl)-2-(2-methyl-propane-2-sulfinylamino)-pent-4-enoate (*R*,*R*-4f).



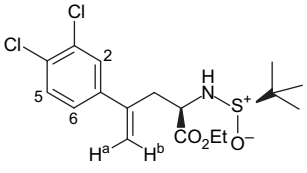
Obtained as a pale yellow oil (0.088 g, 49%) after flash chromatography (6:1 v/v ethyl acetate/hexane); R_f 0.41 (6:1 v/v ethyl acetate/hexane); $[\alpha]_D^{20}$ −84.9 (*c* 2.5); Found: C, 53.50; H, 7.00; Cl, 9.70; N, 7.70; S, 8.80, $C_{16}H_{23}ClN_2O_3S$ requires: C, 53.55; H, 6.46; Cl, 9.88; N, 7.81; S, 8.93%; ν_{max}/cm^{-1}: 3448, 3429, 2983, 1737 (CO), 1461, 1366; δ_H (500 MHz, $CDCl_3$): 8.32 (1H, d, pyridyl-5H, *J*=2.5 Hz), 7.57 (1H, dd, pyridyl-3H, *J*=2.5, 8.3 Hz), 7.25 (1H, d, pyridyl-4H, *J*=8.3 Hz), 5.34 (1H, s, =CH^a), 5.19 (1H, s, =CH^b), 4.06–4.01 (3H, br m, NH, OCH_2), 3.89 (1H, dd, NC*H*, *J*=5.0, 7.7 Hz), 2.92 (1H, dd, NCC*H*, *J*=0.6, 5.0 Hz), 2.78 (1H, dd, NCC*H*, *J*=0.6, 7.7 Hz), 1.19 (3H, t, OCH_2CH_3, *J*=7.2 Hz), 1.10 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$): 171.39 (CO), 149.61 (H_2C=*C*), 146.53 (Ar), 138.68 (Ar), 135.47 (Ar), 133.69 (Ar), 117.92 (=*C*H_2), 60.72 (O*C*), 55.35 (N*C*), 54.94 (SC), 38.81 (NC*C*), 21.61 ($C(CH_3)_3$), 13.06 (OC*C*); *m*/*z* (ES$^+$): 359 (^{35}Cl MH$^+$), 361 (^{37}Cl MH$^+$).

2.2.13. Ethyl 2*S*,4*S*-(3,4-dichloro-phenyl)-2-(2-methyl-propane-2-sulfinylamino)-pent-4-enoate (*S*,*S*-4g).



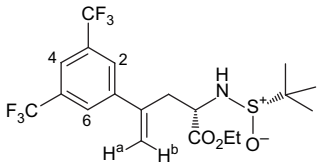
Obtained as a pale yellow oil (0.144 g, 73%) after flash chromatography (9:1 v/v diethyl ether/hexane); R_f 0.22 (9:1 v/v diethyl ether/hexane); $[\alpha]_D^{20}$ +68.3 (*c* 1.1); Found: C, 52.20; H, 6.10; Cl, 17.80; N, 3.60; S, 7.90, $C_{17}H_{23}Cl_2NO_3S$ requires: C, 52.04; H, 5.91; Cl, 18.07; N, 3.57; S, 8.17%; ν_{max}/cm^{-1}: 3583, 3450 (NH), 3282, 2981, 2960, 1736 (CO), 1474, 1367, 1074; δ_H (500 MHz, $CDCl_3$): 7.37 (1H, s, Ar-2H), 7.33 (1H, d, Ar-5H, *J*=8.3 Hz), 7.12 (1H, d, Ar-6H, *J*=8.3 Hz), 5.29 (1H, s, =CH^a), 5.11 (1H, s, =CH^b), 4.06 (2H, dq, OCH_2, *J*=7.2, 13.1 Hz), 3.89 (1H, dd, NC*H*, *J*=7.7, 6.2 Hz), 2.90 (1H, dd, NCHC*H*, *J*=6.2, 14.5 Hz), 2.75 (1H, dd, NCHC*H*, *J*=7.7, 14.5 Hz), 1.18 (3H, t, OCH_2CH_3, *J*=7.2 Hz), 1.10 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$): 171.51 (CO), 140.68 (*C*=CH_2), 131.57 (Ar), 130.73 (Ar), 129.87 (Ar), 128.87 (Ar), 127.77 (Ar), 124.67 (Ar), 117.79 (=*C*H_2), 60.58 (O*C*), 55.55 (N*C*), 55.14 (SC), 38.96 (NC*C*), 21.62 ($C(CH_3)_3$), 13.05 (OC*C*); *m*/*z* (ES$^+$): 393 ($^{35/35}$Cl MH$^+$), 395 ($^{35/37}$Cl MH$^+$), 397 ($^{37/37}$Cl MH$^+$).

2.2.14. Ethyl 2*R*,4*R*-(3,4-dichloro-phenyl)-2-(2-methyl-propane-2-sulfinylamino)-pent-4-enoate (*R*,*R*-4g).



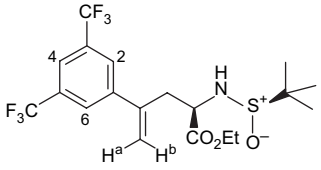
Obtained as a pale yellow oil (0.146 g, 74%) after flash chromatography (9:1 v/v diethyl ether/hexane); R_f 0.22 (9:1 v/v diethyl ether/hexane); $[\alpha]_D^{20}$ −70.8 (*c* 1.2); Found: C, 52.04; H, 5.91; Cl, 18.07; N, 3.57; S, 8.17, $C_{17}H_{23}Cl_2NO_3S$ requires: C, 52.00; H, 5.90; Cl, 18.10; N, 3.60; S, 8.20%; ν_{max}/cm^{-1}: 3583, 3450 (NH), 3274, 2978, 2956, 1736 (CO), 1473, 1366, 1070; δ_H (500 MHz, $CDCl_3$): 7.37 (1H, d, Ar-2H, *J*=2.0 Hz), 7.33 (1H, d, Ar-5H, *J*=8.3 Hz), 7.13 (1H, dd, Ar-6H, *J*=2, 8.3 Hz), 5.29 (1H, s, =CH^a), 5.11 (1H, s, =CH^b), 4.06 (2H, dq, OCH_2, *J*=7.6, 10.7 Hz), 3.89 (1H, dd, NC*H*, *J*=5.5, 7.4 Hz), 2.90 (1H, dd, NCHC*H*, *J*=5.5, 14.5 Hz), 2.73 (1H, dd, NCHC*H*, *J*=7.4, 14.5 Hz), 1.19 (3H, t, OCH_2CH_3, *J*=7.2 Hz), 1.10 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$): 171.50 (CO), 140.68 (*C*=CH_2), 131.55 (Ar), 130.71 (Ar), 129.39 (Ar), 128.87 (Ar), 127.35 (Ar), 124.68 (Ar), 117.02 (=*C*H_2), 60.82 (O*C*), 55.55 (N*C*), 55.13 (SC), 38.95 (NC*C*), 21.51 ($C(CH_3)_3$), 13.05 (OC*C*); *m*/*z* (ES$^+$): 393 ($^{35/35}$Cl MH$^+$), 395 ($^{35/37}$Cl MH$^+$), 397 ($^{37/37}$Cl MH$^+$).

2.2.15. Ethyl 2*S*,4*S*-(3,5-bis-trifluoromethyl-phenyl)-2-(2-methyl-propane-2-sulfinylamino)-pent-4-enoate (*S*,*S*-4h).



Obtained as a pale yellow oil (0.159 g, 69%) after flash chromatography (3:1–6:1 v/v ethyl acetate/hexane); R_f 0.58 (3:1 v/v ethyl acetate/hexane); $[\alpha]_D^{20}$ +55.2 (*c* 3.2); Found: C, 49.50; H, 5.00; N, 3.00; S, 6.80, $C_{19}H_{23}F_6NO_3S$ requires: C, 49.67; H, 5.05; F, 24.81; N, 3.05; S, 6.98%; ν_{max}/cm^{-1}: 3583, 3454 (NH), 2983, 2963, 1739 (CO), 1632, 1378, 1279, 1180, 1136, 1078; δ_H (500 MHz, $CDCl_3$): 7.72 (3H, s, ArH), 5.41 (1H, s, =CH^a), 5.28 (1H, s, =CH^b), 4.13–4.01 (3H, br m, OCH_2, NH), 3.91–3.88 (1H, m, NCH), 3.07 (1H, dd, NCHC*H*, *J*=5.1, 14.5 Hz), 2.93 (1H, dd, NCHC*H*, *J*=7.3, 14.5 Hz), 1.18 (3H, t, OCH_2CH_3, *J*=7.2 Hz), 1.07 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$): 171.35 (CO), 141.74 (H_2C=*C*), 140.72 (Ar), 130.90 (q, Ar, *J*=33.3 Hz), 125.86 (Ar), 122.2 (q, CF_3, *J*=272.8 Hz), 119.94 (Ar), 118.75 (=*C*H_2), 60.98 (O*C*), 55.93 (NC), 55.12 (SC), 38.76 (NC*C*), 21.43 ($C(CH_3)_3$), 12.93 (OC*C*); *m*/*z* (ES$^+$): 460 (MH$^+$).

2.2.16. Ethyl 2*R*,4*R*-(3,5-bis-trifluoromethyl-phenyl)-2-(2-methyl-propane-2-sulfinylamino)-pent-4-enoate (*R*,*R*-4h).



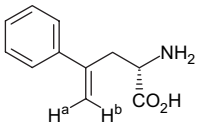
Obtained as a pale yellow oil (0.151 g, 66%) after flash chromatography (3:1–6:1 v/v ethyl acetate/hexane); R_f 0.58 (3:1 v/v ethyl acetate/hexane); $[\alpha]_D^{20}$ −53.0 (*c* 1.1); Found: C, 49.60; H, 5.10; N, 3.10; S, 6.80, $C_{19}H_{23}F_6NO_3S$ requires:

C, 49.67; H, 5.05; F, 24.81; N, 3.05; S, 6.98%; ν_{max}/cm^{-1}: 3450 (NH), 2978, 1739 (CO), 1629, 1374, 1278; δ_H (500 MHz, $CDCl_3$): 7.72 (3H, s, ArH), 5.41 (1H, s, =CH^a), 5.28 (1H, s, =CH^b), 4.13–4.02 (3H, br m, OCH_2, NH), 3.91–3.88 (1H, m, NC*H*), 3.07 (1H, dd, NCHC*H*, *J*=5.1, 14.5 Hz), 2.93 (1H, dd, NCHC*H*, *J*=7.3, 14.5 Hz), 1.18 (3H, t, OCH_2CH_3, *J*=7.2 Hz), 1.07 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$): 171.34 (CO), 141.75 (H_2C=*C*), 140.72 (Ar), 130.90 (q, Ar, *J*=33.3 Hz), 125.54 (Ar), 122.23 (q, CF_3, *J*=272.8 Hz), 119.94 (Ar), 118.75 (=CH_2), 60.98 (O*C*), 55.93 (NC), 55.12 (SC), 38.76 (NC*C*), 21.43 ($C(CH_3)_3$), 12.93 (OC*C*); *m*/*z* (ES$^+$): 460 (MH^+).

2.3. General procedure for the synthesis of α-amino acids 5a–h

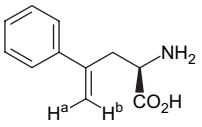
HCl (4 M) in dioxane (5 equiv) was added to a 0.1 M solution of the *N*-sulfinyl-α-amino ester in EtOH. The solution was stirred at room temperature for 2 h and the solvent removed in vacuo. NaOH solution (1 M, 2 equiv) was added to a 0.1 M solution of the ester in a 1:1 v/v H_2O/EtOH solvent system and the mixture stirred and heated to reflux (80 °C oil bath temperature) for 4 h. The solution was left to cool to room temperature and the solvent removed in vacuo. The residue was dissolved in deionised water and applied to the top of an Amberlyst 15H$^+$ form, 20–50 mesh ion exchange column and eluted with distilled water followed by a 1% NH_3 solution in deionised water. The ammonia fractions were visualised under UV light and the UV active fractions were collected and concentrated in vacuo to give the *amino acid products* as pale yellow to colourless solids.

2.3.1. 2-(*S*)-2-Amino-4-phenyl-pent-4-enoic acid (*S*-5a).



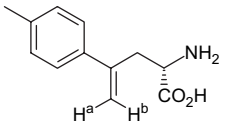
Obtained as colourless prisms (0.156 g, 100%) after ion exchange chromatography. Mp 130–132 °C; $[\alpha]_D^{20}$ +26.4 (*c* 0.3, MeOH); Found: 192.1021, $C_{11}H_{13}NO_2$ requires: 192.1019; ν_{max}/cm^{-1}: 3030 (br, OH), 2065, 1590 (CO), 1395, 1340; δ_H (500 MHz, D_2O): 6.90 (2H, d, ArH, 7.8 Hz), 6.85–6.75 (3H, m, ArH), 4.98 (1H, s, =CH^a), 4.73 (1H, s, =CH^b), 3.45 (1H, dd, NCH, *J*=5.1, 8.6 Hz), 2.76 (1H, dd, NCCH, *J*=5.1, 15.4 Hz), 2.47 (1H, dd, NCCH, *J*=8.6, 15.4 Hz); δ_C (75 MHz, D_2O): 171.00 (CO), 140.85 (H_2C=*C*), 137.72 (Ar), 128.62 (Ar), 128.36 (Ar), 126.12 (Ar), 118.04 (=CH_2), 51.23 (NC), 35.55 (NC*C*); *m*/*z* (ES$^+$): 192 (MH^+).

2.3.2. 2-(*R*)-2-Amino-4-phenyl-pent-4-enoic acid (*R*-5a).



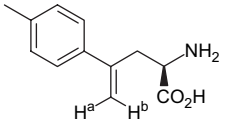
Obtained as colourless prisms (0.095 g, 100%) after ion exchange chromatography. Mp 138–140 °C; $[\alpha]_D^{20}$ −26.2 (*c* 0.6, MeOH); Found: C, 66.70; H, 6.65; N, 6.95, $C_{11}H_{13}NO_2 \cdot 0.33$ M H_2O requires: C, 66.99; H, 6.98; N, 7.10%; Found: 192.1022, $C_{11}H_{14}NO_2$ requires: 192.1025; ν_{max}/cm^{-1}: 3024 (br, OH), 2075, 1822, 1668, 1594 (CO), 1524, 1443, 1400, 1359; δ_H (500 MHz, D_2O): 7.15 (2H, d, ArH, 8.1 Hz), 7.09–6.98 (3H, m, ArH), 5.21 (1H, s, =CH^a), 4.95 (1H, s, =CH^b), 3.69 (1H, dd, NCH, *J*=5.1, 8.6 Hz), 2.98 (1H, dd, NCC*H*, *J*=5.1, 15.4 Hz), 2.71 (1H, dd, NCC*H*, *J*=8.6, 15.4 Hz); δ_C (75 MHz, D_2O): 171.31 (CO), 141.18 (H_2C=*C*), 138.08 (Ar), 128.93 (Ar), 128.67 (Ar), 126.47 (Ar), 118.40 (=CH_2), 51.44 (NCH), 35.80 (NC*C*); *m*/*z* (ES$^+$): 192 (MH^+).

2.3.3. 2-(*S*)-2-Amino-4-*p*-tolyl-pent-4-enoic acid (*S*-5c).



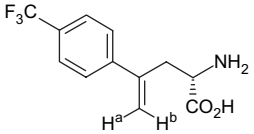
Obtained as colourless prisms (0.073 g, 61%) after ion exchange chromatography. Mp 165–167 °C; $[\alpha]_D^{20}$ +10.8 (*c* 0.2, MeOH); Found: C, 68.70; H, 7.20; N, 6.60, $C_{12}H_{15}NO_2 \cdot 0.25$ M H_2O requires: C, 68.71; H, 7.45; N, 6.68%; Found: 205.1097, $C_{12}H_{15}NO_2$ requires: 205.1097; ν_{max}/cm^{-1}: 3034 (br, OH), 2089, 1912, 1818, 1671 (CO), 1594, 1518, 1450, 1400, 1359; δ_H (300 MHz, D_2O): 7.24 (2H, ArH, d, *J*=8.0 Hz), 7.07 (2H, ArH, d, *J*=8.0 Hz), 5.37 (1H, s, =CH^a), 5.10 (1H, s, =CH^b), 3.88 (1H, dd, NCH, *J*=5.0, 8.7 Hz), 3.16 (1H, dd, NCCH, *J*=5.0, 14.9 Hz), 2.87 (1H, dd, NCCH, *J*=8.7, 14.9 Hz), 2.14 (3H, s, $ArCH_3$); δ_C (75 MHz, D_2O): 171.60 (CO), 141.2 (H_2C=*C*), 139.4 (Ar), 135.2 (Ar), 129.7 (Ar), 126.6 (Ar), 117.8 (=CH_2), 51.7 (ArCH_3), 36.0 (NC), 20.4 (NC*C*); *m*/*z* (ES): 206 (MH^+).

2.3.4. 2-(*R*)-2-Amino-4-*p*-tolyl-pent-4-enoic acid (*R*-5c).



Obtained as colourless prisms (0.084 g, 51%) after ion exchange chromatography. Mp 165–167 °C; $[\alpha]_D^{20}$ −10.6 (*c* 0.3, MeOH); Found: 205.1099, $C_{12}H_{15}NO_2$ requires: 205.1097; ν_{max}/cm^{-1}: 3030 (br, OH), 2087, 1818, 1670 (CO), 1594, 1518, 1450, 1401, 1359; δ_H (300 MHz, D_2O): 7.30 (2H, ArH, d, *J*=8.0 Hz), 7.13 (2H, ArH, d, *J*=8.0 Hz), 5.43 (1H, s, =CH^a), 5.16 (1H, s, =CH^b), 3.93 (1H, dd, NCH, *J*=5.0, 8.7 Hz), 3.22 (1H, dd, NCCH, *J*=5.0, 14.9 Hz), 2.92 (1H, dd, NCCH, *J*=8.7, 14.9 Hz), 2.20 (3H, s, $ArCH_3$); δ_C (75 MHz, D_2O): 171.66 (CO), 141.2 (H_2C=*C*), 139.4 (Ar), 135.3 (Ar), 129.8 (Ar), 126.6 (Ar), 117.8 (=CH_2), 51.7 (ArMe), 36.1 (NC), 20.5 (NC*C*); *m*/*z* (ES$^+$): 206 (MH^+).

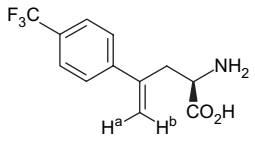
2.3.5. 2-(*S*)-2-Amino-4-(4-trifluoromethyl-phenyl)-pent-4-enoic acid (*S*-5d).



Obtained as colourless prisms (0.223 g, 99%) after ion exchange chromatography. Mp 141–143 °C; $[\alpha]_D^{20}$ +31.1

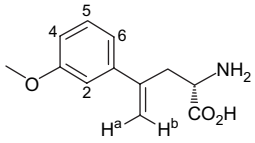
(*c* 0.6, MeOH), Found: C, 55.50; H, 4.80; N, 5.30, $C_{12}H_{13}NO_2F_3$ requires: C, 55.60; H, 4.67; N, 5.40%; ν_{max}/cm^{-1}: 3007 (br, OH), 2128, 1831, 1614 (CO), 1508, 1455, 1427, 1406, 1328; δ_H (500 MHz, CD_3OD): 7.95 (2H, d, ArH, *J*=8.3 Hz), 7.88 (2H, d, ArH, *J*=8.3 Hz), 5.86 (1H, s, =CH^a), 5.62 (1H, s, =CH^b), 3.73 (1H, dd, NC*H*, *J*=3.6, 10.5 Hz), 3.66 (1H, dd, NCC*H*, *J*=5.0, 15.1 Hz), 3.00 (1H, dd, NCC*H*, *J*=10.5, 15.1 Hz); δ_C (75 MHz, D_2O): 171.25 (CO), 162.45 (q, CF_3, *J*=36.8 Hz), 141.82 (H_2C=*C*), 129.32 (q, F_3C*C*, *J*=32.25 Hz), 126.83 (Ar), 125.64 (Ar), 121.95 (Ar), 114.26 (=CH_2), 51.44 (NC), 35.70 (NC*C*); *m*/*z* (ES$^+$): 260 (MH$^+$).

2.3.6. 2-(*R*)-2-Amino-4-(4-trifluoromethyl-phenyl)-pent-4-enoic acid (*R*-5d).



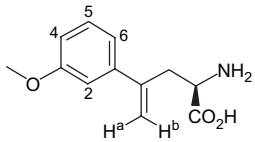
Obtained as colourless prisms (0.193 g, 99%) after ion exchange chromatography. Mp 141–143 °C; $[\alpha]_D^{20}$ −32.7 (*c* 0.5, MeOH); Found: C, 54.80; H, 4.80; N, 5.20, $C_{12}H_{13}NO_2F_3 \cdot 0.25$ M H_2O requires: C, 54.65; H, 4.78; F, 21.61; N, 5.31%; Found: 260.0887, $C_{12}H_{13}NO_2F_3$ requires: 260.0898; δ_H (500 MHz, CD_3OD): 6.84 (2H, d, ArH, *J*=8.3 Hz), 6.80 (2H, d, ArH, *J*=8.3 Hz), 4.86 (1H, s, =CH^a), 4.66 (1H, s, =CH^b), 3.26 (1H, dd, NC*H*, *J*=5.0, 9.1 Hz), 2.60 (1H, dd, NCC*H*, *J*=5.0, 15.1 Hz), 2.30 (1H, dd, NCC*H*, *J*=9.1, 15.1 Hz); δ_C (75 MHz, D_2O): 171.25 (CO), 162.45 (q, CF_3, *J*=36.8 Hz), 141.82 (H_2C=*C*), 129.32 (q, F_3C*C*, *J*=32.25 Hz), 126.83 (Ar), 125.64 (Ar), 121.95 (Ar), 114.26 (=CH_2), 51.44 (NC), 35.70 (NC*C*); *m*/*z* (ES$^+$): 260 (MH$^+$).

2.3.7. 2-(*S*)-2-Amino-4-(3-methoxy-phenyl)-pent-4-enoic acid (*S*-5e).



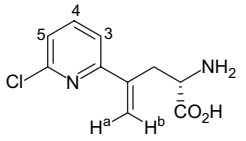
Obtained as colourless prisms (0.088 g, 97%) after ion exchange chromatography. Mp 144–147 °C; $[\alpha]_D^{20}$ +10.9 (*c* 0.2, MeOH); Found: 222.1126, $C_{12}H_{15}NO_3$ requires: 222.1125; ν_{max}/cm^{-1}: 3009 (br, OH), 2593, 2288, 2085, 1843, 1576 (CO), 1491, 1457, 1398; δ_H (500 MHz, D_2O): 7.22 (1H, dd, Ar-5H, *J*=7.7, 8.1 Hz), 6.99 (1H, d, Ar-4H, *J*=7.7 Hz), 6.94 (1H, s, Ar-2H), 6.84 (1H, d, Ar-6H, *J*=8.1 Hz), 5.45 (1H, s, =CH^a), 5.20 (1H, s, =CH^b), 3.93 (1H, dd, NCH, *J*=5.1, 8.1 Hz), 3.69 (3H, s, OCH_3), 3.18 (1H, dd, NCC*H*, *J*=5.1, 15.4 Hz), 2.96 (1H, dd, NCC*H*, *J*=8.1, 15.4 Hz); δ_C (75 MHz, D_2O): 171.57 (CO), 159.40 (H_2C=*C*), 141.21 (Ar), 140.10 (Ar), 130.41 (Ar), 119.67 (Ar), 119.05 (=CH_2), 114.96 (Ar), 112.57 (Ar), 55.70 (OCH_3), 51.70 (NC), 36.09 (NC*C*); *m*/*z* (ES$^+$): 222 (MH$^+$).

2.3.8. 2-(*R*)-2-Amino-4-(3-methoxy-phenyl)-pent-4-enoic acid (*R*-5e).



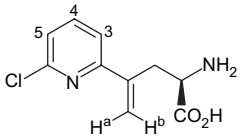
Obtained as colourless prisms (0.115 g, 80%) after ion exchange chromatography. Mp 147–149 °C; $[\alpha]_D^{20}$ −9.5 (*c* 0.3, MeOH); Found: C, 63.60; H, 6.80; N, 6.30, $C_{12}H_{15}NO_3 \cdot 0.25$ M H_2O requires: C, 63.84; H, 6.92; N, 6.20%; Found: 222.1130, $C_{12}H_{15}NO_3$ requires: 222.1120; ν_{max}/cm^{-1}: 3009 (br, OH), 2593, 2086, 1818, 1668, 1575 (CO), 1525, 1493; δ_H (500 MHz, CD_3OD): 7.18 (1H, t, Ar-5H, *J*=8.1 Hz), 7.01 (1H, d, Ar-4H, *J*=7.7 Hz), 6.99 (1H, d, Ar-2H, *J*=2.1 Hz), 6.77 (1H, dd, Ar-6H, *J*=8.1 Hz), 5.41 (1H, s, =CH^a), 5.17 (1H, s, =CH^b), 3.71 (3H, s, OCH_3), 3.44 (1H, dd, NCH, *J*=10.7, 11.1 Hz), 3.34 (1H, dd, NCCH, *J*=10.7, 15.2 Hz), 2.61 (1H, dd, NCCH, *J*=11.1, 15.2 Hz); δ_C (75 MHz, D_2O): 174.37 (CO), 159.51 (H_2C=*C*), 142.38 (Ar), 140.55 (Ar), 130.48 (Ar), 119.65 (Ar), 118.16 (=CH_2), 114.26 (Ar), 112.57 (Ar), 55.79 (OCH_3), 53.67 (NC), 36.96 (NC*C*); *m*/*z* (ES$^+$): 222 (MH$^+$).

2.3.9. 2-(*S*)-2-Amino-4-(6-chloro-pyridin-2-yl)-pent-4-enoic acid (*S*-5f).



Obtained as colourless prisms (0.066 g, 79%) after ion exchange chromatography. Mp 193–195 °C; $[\alpha]_D^{20}$ +31.7 (*c* 0.1, MeOH); Found: C, 52.00; H, 5.00; N, 11.70, $C_{10}H_{11}ClN_2O_2 \cdot 0.25$ M H_2O requires: C, 51.96; H, 5.01; N, 12.12%; Found: 227.0579, $C_{10}H_{11}ClN_2O_2$ requires: 227.0587; ν_{max}/cm^{-1}: 3456, (br, OH), 3049, 2929, 1854, 1630 (CO), 1523; δ_H (500 MHz, D_2O): 8.43 (1H, d, pyridyl-5H, *J*=2.1 Hz), 7.97 (1H, dd, pyridyl-4H, *J*=2.1, 8.3 Hz), 7.51 (1H, d, pyridyl-3H, *J*=8.3 Hz), 5.61 (1H, s, =CH^a), 5.43 (1H, s, =CH^b), 4.03 (1H, dd, NCH *J*=6.0, 7.7 Hz), 3.21 (1H, dd, NCC*H*, *J*=6.0, 15.4 Hz), 3.11 (1H, dd, NCC*H*, *J*=7.7, 15.4 Hz); δ_C (75 MHz, D_2O): 174.32 (CO), 142.57 (H_2C=*C*), 138.76 (Ar), 129.28 (Ar), 128.55 (Ar), 126.72 (Ar), 125.77 (Ar), 117.75 (=CH_2), 52.97 (NC), 36.87 (NC*C*); *m*/*z* (ES$^+$): 227 (^{35}Cl MH$^+$), 229 (^{37}Cl MH$^+$).

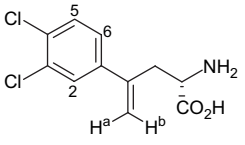
2.3.10. 2-(*R*)-2-Amino-4-(6-chloro-pyridin-2-yl)-pent-4-enoic acid (*R*-5f).



Obtained as colourless prisms (0.123 g, 79%) after ion exchange chromatography. Mp 196–198 °C; $[\alpha]_D^{20}$ −32.1

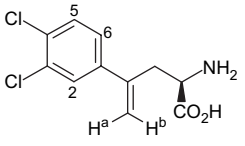
(*c* 0.3, MeOH); Found: 227.0583, $C_{10}H_{11}ClN_2O_2$ requires: 227.0587; ν_{max}/cm^{-1}: 3051 (br, OH), 2093, 1893, 1607 (CO), 1555, 1474, 1454, 1410; δ_H (500 MHz, D_2O): 8.17 (1H, d, pyridyl-5H, *J*=2.4 Hz), 7.89 (1H, dd, pyridyl-4H, *J*=2.4, 8.8 Hz), 7.89 (1H, d, pyridyl-3H, *J*=8.8 Hz), 5.23 (1H, s, =CH^a), 5.09 (1H, s, =CH^b), 3.54 (1H, dd, NCH, *J*=6.2, 7.7 Hz), 2.74 (1H, dd, NCC*H*, *J*=6.2, 15.5 Hz), 2.64 (1H, dd, NCC*H*, *J*=7.7, 15.5 Hz); δ_C (75 MHz, D_2O): 174.19 (CO), 150.06 (H_2C=*C*), 147.16 (Ar), 138.55 (Ar), 138.20 (Ar), 134.25 (Ar), 124.83 (Ar), 120.16 (=CH_2), 53.47 (NC), 36.45 (NC*C*); *m*/*z* (ES$^+$): 227 (^{35}Cl MH$^+$), 229 (^{37}Cl MH$^+$).

2.3.11. 2-(*S*)-2-Amino-4-(3,4-dichloro-phenyl)-pent-4-enoic acid (*S*-5g).



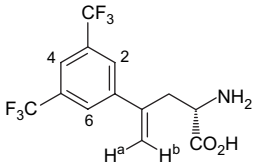
Obtained as colourless prisms (0.107 g, 82%) after ion exchange chromatography. Mp 147–148 °C; $[\alpha]_D^{20}$ +33.1 (*c* 0.4, MeOH); Found: C, 50.80; H, 4.50; Cl, 27.40; N, 5.30, $C_{11}H_{11}Cl_2NO_2$ requires: C, 50.79; H, 4.26; Cl, 27.26; N, 5.38%; ν_{max}/cm^{-1}: 3025 (br OH), 2064, 1899, 1840, 1761, 1670, 1579, 1517; δ_H (500 MHz, D_2O): 7.54 (1H, s, Ar-2H), 7.40 (1H, d, Ar-5H, *J*=8.4 Hz), 7.26 (1H, d, Ar-6H, *J*=8.4 Hz), 5.48 (1H, s, =CH^a), 5.26 (1H, s, =CH^b), 3.96 (1H, dd, NC*H*, *J*=5.1, 5.5 Hz), 3.15 (1H, dd, NCC*H*, *J*=5.5, 13.2 Hz), 2.98 (1H, dd, NCC*H*, *J*=5.1, 13.2 Hz); δ_C (75 MHz, D_2O): 165.14 (CO), 142.0 (H_2C=*C*), 141.14 (Ar), 134.78 (Ar), 134.39 (Ar), 133.30 (Ar), 131.07 (Ar), 128.91 (Ar), 120.84 (=CH_2), 54.02 (NC), 38.21 (NC*C*); *m*/*z* (ES$^+$): 260 ($^{35/35}$Cl MH$^+$), 262 ($^{35/37}$Cl MH$^+$), 264 ($^{37/37}$Cl MH$^+$).

2.3.12. 2-(*R*)-2-Amino-4-(3,4-dichloro-phenyl)-pent-4-enoic acid (*R*-5g).



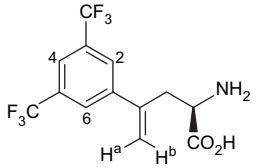
Obtained as colourless prisms (0.094 g, 73%) after ion exchange chromatography. Mp 146–148 °C $[\alpha]_D^{20}$ −31.4 (*c* 0.1, MeOH); Found: C, 49.30; H, 4.60; N, 4.70, $C_{11}H_{11}Cl_2NO_2 \cdot 0.5$ M H_2O requires: C, 49.09; H, 4.49; N, 5.20%; Found: 259.0164, $C_{11}H_{11}Cl_2NO_2$ requires: 259.0161; ν_{max}/cm^{-1}: 3033 (br, OH), 1669, 1576, 1516; δ_H (500 MHz, D_2O): 7.54 (1H, s, Ar-2H), 7.40 (1H, d, Ar-5H, *J*=8.4 Hz), 7.26 (1H, d, Ar-6H, *J*=8.4 Hz), 5.48 (1H, s, =CH^a), 5.26 (1H, s, =CH^b), 3.96 (1H, dd, NC*H*, *J*=5.1, 5.5 Hz), 3.15 (1H, dd, NCC*H*, *J*=5.5, 13.2 Hz), 2.98 (1H, dd, NCC*H*, *J*=5.1, 13.2 Hz); δ_C (75 MHz, D_2O): 171.48 (CO), 142.0 (H_2C=*C*), 141.14 (Ar), 134.78 (Ar), 134.39 (Ar), 133.30 (Ar), 131.07 (Ar), 128.91 (Ar), 120.84 (=CH_2), 54.02 (NC), 38.21 (NC*C*); *m*/*z* (ES$^+$): 260 ($^{35/35}$Cl MH$^+$), 262 ($^{35/37}$Cl MH$^+$), 264 ($^{37/37}$Cl MH$^+$).

2.3.13. 2-(*S*)-2-Amino-4-(3,5-bis-trifluoromethyl-phenyl)-pent-4-enoic acid (*S*-5h).



Obtained as colourless prisms (0.178 g, 89%) after ion exchange chromatography. Mp 152–155 °C; $[\alpha]_D^{20}$ +10.9 (*c* 0.5, MeOH); Found: C, 47.65; H, 3.30; N, 4.05, $C_{13}H_{11}F_6NO_2$ requires: C, 47.72; H, 3.39; N, 4.28%; Found: 328.0765, $C_{13}H_{11}F_6NO_2$ requires: 328.0767; ν_{max}/cm^{-1}: 3456 (NH), 3049 (br, OH), 2929, 1854, 1622 (CO), 1524, 1398, 1334, 1277; δ_H (500 MHz, CD_3OD): 8.01 (2H, s, Ar-2H, Ar-6H), 7.83 (1H, s, Ar-4H), 5.55 (1H, s, =CH^a), 5.40 (1H, s, =CH^b), 3.40 (1H, dd, NCH, *J*=4.1, 9.7 Hz), 3.33 (1H, dd, NCC*H*, *J*=4.1, 15.4 Hz), 2.79 (1H, dd, NCC*H*, *J*=9.7, 15.4 Hz); δ_C (75 MHz, CD_3OD): 173.70 (CO), 143.83 (H_2C=*C*), 143.11 (Ar), 133.42 (q, F_3CC, *J*=33.25 Hz), 128.64 (Ar), 125.14 (q, CF_3, *J*=271.82 Hz), 122.96 (Ar), 121.14 (=CH_2), 54.63 (NC), 38.29 (NC*C*); *m*/*z* (ES$^+$): 328 (MH$^+$).

2.3.14. 2-(*R*)-2-Amino-4-(3,5-bis-trifluoromethyl-phenyl)-pent-4-enoic acid (*R*-5h).



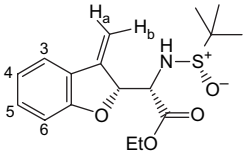
Obtained as colourless prisms (0.167 g, 68%) after ion exchange chromatography. Mp 153–156 °C; $[\alpha]_D^{20}$ −9.5 (*c* 0.6, MeOH); Found: C, 47.50; H, 3.30; N, 4.20, $C_{13}H_{11}F_6NO_2$ requires: C, 47.72; H, 3.39; N, 4.28%; ν_{max}/cm^{-1}: 3683, 2929 (br, OH), 2065, 1832, 1634 (CO), 1510, 1444; δ_H (500 MHz, D_2O): 7.40 (2H, s, Ar-2H, Ar-6H), 7.36 (1H, s, Ar-4H), 5.12 (1H, s, =CH^a), 4.95 (1H, s, =CH^b), 3.48 (1H, dd, NCH, *J*=5.5, 8.0 Hz), 2.78 (1H, dd, NCC*H*, *J*=5.5, 15.3 Hz), 2.79 (1H, dd, NCC*H*, *J*=8.0, 15.4 Hz); δ_C (75 MHz, CD_3OD): 173.65 (CO), 143.64 (H_2C=*C*), 142.96 (Ar), 133.22 (q, F_3CC, *J*=33.25 Hz), 128.56 (Ar), 125.14 (q, CF_3, *J*=271.82 Hz), 122.94 (Ar), 121.15 (=CH_2), 54.46 (NC), 38.17 (NC*C*); *m*/*z* (ES$^+$): 328 (MH$^+$).

2.4. General procedure for the synthesis of *N*-sulfinyl-α-amino esters 17–20

Bifunctional aryl iodide/allene (0.75 mmol) was added to a suspension of chiral α-imino ester (0.5 mmol), indium metal powder (0.088 g, 0.75 mmol), $Pd(OAc)_2$ (0.011 g, 0.05 mmol), tri-2-furyl phosphine (0.024 g, 0.1 mmol), CuI (0.019 g, 0.1 mmol) and piperidine (0.05 ml, 0.5 mmol) in DMF (10 ml) in a Schlenk tube. The mixture was stirred and heated to 60 °C (oil bath temperature) for 24 h, left to cool and vented. Ethyl acetate (20 ml) and 5% HCl solution (10 ml) was added and the mixture

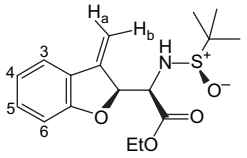
stirred for 20 min. The phases were separated and the aqueous layer extracted with ethyl acetate (20 ml). The organic extracts were combined and washed with water (3×100 ml), dried over magnesium sulfate, filtered and the filtrate concentrated in vacuo. The residue was purified by flash chromatography to give the *N*-sulfinylamino esters.

2.4.1. Ethyl 2*S*,5*S*,6*R*-(3-methylene-2,3-dihydro-benzofuran-2-yl)-(2-methyl-propane-2-sulfinylamino)acetate (*S*,*S*,*R*-17).



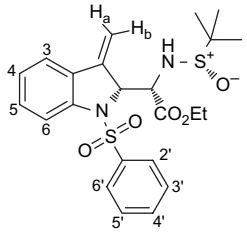
Obtained as a pale yellow oil (0.110 g, 64%) after flash chromatography (Et_2O); R_f 0.11 (Et_2O); $[\alpha]_D^{20}$ −42.2 (*c* 1.1); Found: C, 58.60; H, 7.20; N, 4.10, $C_{17}H_{23}NO_4S\cdot 0.5$ M H_2O requires: C, 58.94; H, 6.98; N, 4.04%; ν_{max}/cm^{-1}: 3286, 3078, 2984, 2968, 2869, 2836, 1739 (CO), 1634; δ_H (500 MHz, $CDCl_3$): 7.33 (1H, d, Ar-6H, *J*=7.6 Hz), 7.19 (1H, t, Ar-5H, *J*=7.6 Hz), 6.87 (1H, t, Ar-4H, *J*=7.6 Hz), 6.84 (1H, d, Ar-3H, *J*=7.6 Hz), 5.54 (2H, m, NCH, =CH^a), 5.09 (1H, s, =CH^b), 4.32 (2H, q, OCH_2, *J*=7.3 Hz), 4.21 (2H, m, NCH, OCH), 1.32 (3H, t, OCH_2CH_3, *J*=7.3 Hz); δ_C (75 MHz, $CDCl_3$): 170.45 (CO), 163.13 (Ar), 144.48 (Ar), 131.14 (Ar), 126.52 (Ar), 124.27 (Ar), 121.39 (Ar), 121.11 (Ar), 110.67 (Ar), 102.69 (=CH_2), 85.78 (OCH), 62.99 (OCH_2), 62.65 (NC), 56.73 (S*C*), 22.57 ($C(CH_3)_3$), 14.50 (OCH_2CH_3); *m*/*z* (ES^+): 338 (MH^+).

2.4.2. Ethyl 2*R*,5*R*,6*S*-(3-methylene-2,3-dihydro-benzofuran-2-yl)-(2-methyl-propane-2-sulfinylamino)acetate (*R*,*R*,*S*-17).



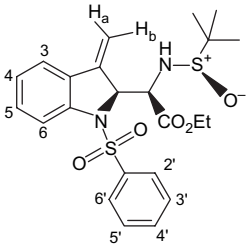
Obtained as a pale yellow oil (0.108 g, 64%) after flash chromatography (Et_2O); R_f 0.11 (Et_2O); $[\alpha]_D^{20}$ +39.7 (*c* 0.5); Found: C, 59.60; H, 6.85; N, 4.25, $C_{17}H_{23}NO_4S\cdot 0.25$ M H_2O requires: C, 59.71; H, 6.93; N, 4.10%; ν_{max}/cm^{-1}: 3281, 3077, 2959, 2869, 2836, 1737 (CO), 1634; δ_H (500 MHz, $CDCl_3$): 7.33 (1H, d, Ar-6H, *J*=7.6 Hz), 7.19 (1H, t, Ar-5H, *J*=7.6 Hz), 6.87 (1H, t, Ar-4H, *J*=7.6 Hz), 6.84 (1H, d, Ar-3H, *J*=7.6 Hz), 5.54 (2H, m, NCH, =CH^a), 5.09 (1H, s, =CH^b), 4.32 (2H, q, OCH_2, *J*=7.3 Hz), 4.21 (2H, m, NCH, OCH), 1.32 (3H, t, OCH_2CH_3, *J*=7.3 Hz); δ_C (75 MHz, $CDCl_3$): 170.43 (CO), 163.12 (Ar*C*), 144.46 (Ar), 131.12 (Ar), 126.51 (Ar), 121.37 (Ar), 121.10 (Ar), 110.67 (Ar), 102.64 (=CH_2), 85.76 (OCH), 62.94 (OCH_2), 62.62 (NC), 56.68 (S*C*), 22.65 ($C(CH_3)_3$), 14.49 (OCH_2CH_3); *m*/*z* (ES^+): 338 (MH^+).

2.4.3. Ethyl 2*S*,5*S*,6*R*-(1-benzenesulfonyl-3-methylene-2,3-dihydro-1*H*-indol-2-yl)-(2-methyl-propane-2-sulfinylamino)acetate (*S*,*S*,*R*-18).



Obtained as colourless prisms (0.110 g, 46%) after flash chromatography (Et_2O). Mp 149–151 °C; R_f 0.14 (Et_2O); $[\alpha]_D^{20}$ −16.3 (*c* 0.6); Found: C, 57.85; H, 5.65; N, 5.80; S, 13.35, $C_{23}H_{28}N_2O_5S_2$ requires: C, 57.96; H, 5.92; N, 5.88; S, 13.45%; ν_{max}/cm^{-1}: 3294 (NH), 3085, 3014, 2985, 1732 (CO), 1648, 1600, 1584; δ_H (500 MHz, $CDCl_3$): 7.71 (1H, d, Ar-6H, *J*=8.1 Hz), 7.55 (2H, d, Ar-2′H, Ar-6′H, *J*=7.7 Hz), 7.49 (1H, d, Ar-3H, *J*=7.5 Hz), 7.34 (2H, t, Ar-3′H, Ar-5′H, *J*=7.7 Hz), 7.27–7.23 (2H, m, Ar-4H, Ar-5H), 7.05 (1H, t, Ar-4′H, *J*=7.7 Hz), 5.44 (1H, s, =CH^a), 5.08 (1H, s, =CH^b), 4.97 (1H, d, NH, *J*=1.6 Hz), 4.37 (1H, d, $PhSO_2NCH$, *J*=7.6 Hz), 4.33 (2H, m, OCH_2), 4.15 (1H, dd, SNC*H*, *J*=1.6, 7.6 Hz), 1.32 (3H, t, OCH_2CH_3, *J*=7.2 Hz), 0.91 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$): 170.09 (CO), 144.73 (H_2C=*C*), 143.14 (Ar), 136.75 (Ar), 133.91 (Ar), 131.61 (Ar), 130.57 (Ar), 129.44 (Ar), 127.61 (Ar), 121.19 (Ar), 118.02 (H_2C=C), 68.14 (SO_2NC), 64.46 (SC), 62.90 (SNC), 56.45 (OCH_2), 22.50 ($C(CH_3)_3$), 14.41 (OCH_2CH_3); *m*/*z* (ES^+): 477 (MH^+).

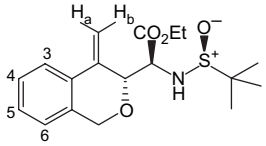
2.4.4. Ethyl 2*R*,5*R*,6*S*-(1-benzenesulfonyl-3-methylene-2,3-dihydro-1*H*-indol-2-yl)-(2-methyl-propane-2-sulfinylamino)acetate (*R*,*R*,*S*-18).



Obtained as colourless prisms (0.231 g, 48%) after flash chromatography (Et_2O). Mp 149–151 °C; R_f 0.14 (Et_2O); $[\alpha]_D^{20}$ +15.7 (*c* 0.8); Found: C, 58.0; H, 5.90; N, 5.90; S, 13.60, $C_{23}H_{28}N_2O_5S_2$ requires: C, 57.96; H, 5.92; N, 5.88; S, 13.45%; ν_{max}/cm^{-1}: 3294 (NH), 3085, 3014, 2985, 1732 (CO), 1648, 1600, 1584; δ_H (500 MHz, $CDCl_3$): 7.71 (1H, d, Ar-6H, *J*=8.1 Hz), 7.55 (2H, d, Ar-2′H, Ar-6′H, *J*=8.2 Hz), 7.49 (1H, d, Ar-3H, *J*=7.5 Hz), 7.34 (2H, t, Ar-3′H, Ar-5′H, *J*=7.9 Hz), 7.27–7.23 (2H, m, Ar-4H, Ar-5H), 7.05 (1H, t, Ar-4′H, *J*=7.5 Hz), 5.44 (1H, s, =CH^a), 5.08 (1H, s, =CH^b), 4.97 (1H, d, NH, *J*=1.6 Hz), 4.37 (1H, d, SO_2NCH, *J*=7.6 Hz), 4.33 (2H, m, OCH_2), 4.15 (1H, dd, NC*H*, *J*=1.6, 7.6 Hz), 1.32 (3H, t, OCH_2CH_3, *J*=7.2 Hz), 0.91 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$): 170.09 (CO), 144.73 (H_2C=*C*), 143.14 (Ar), 136.75 (Ar), 133.91 (Ar), 131.61 (Ar), 130.57 (Ar), 129.44 (Ar), 127.61 (Ar), 121.19 (Ar), 118.02 (H_2C=C), 68.14 (SO_2NC),

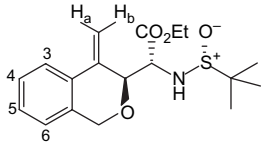
64.46 (SC), 62.90 (SNC), 56.45 (OC), 22.50 ($C(CH_3)_3$), 14.41 (OCH_2CH_3); *m*/*z* (ES^+): 477 (MH^+).

2.4.5. Ethyl 2*S*,5*S*,6*R*-(4-methylene-isochroman-3-yl)-(2-methyl-propane-2-sulfinylamino)acetate (*S*,*S*,*R*-19).



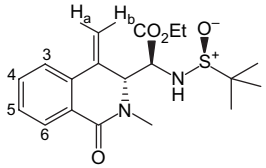
Obtained as a pale yellow oil (0.108 g, 62%) after flash chromatography (Et_2O); R_f 0.14 (Et_2O); $[\alpha]_D^{20}$ −41.0 (*c* 0.7); Found: C, 61.80; H, 7.00; N, 3.70; S, 9.20, $C_{18}H_{25}NO_4S$ requires: C, 61.51; H, 7.17; N, 3.99; S, 9.12%; ν_{max}/cm^{-1}: 3296 (NH), 3126, 2980, 2960, 2905, 2868, 2841, 1738 (CO), 1628; δ_H (500 MHz, $CDCl_3$): 7.57 (1H, d, Ar-6H, *J*=2.5 Hz), 7.25–7.22 (2H, m, Ar-4H, Ar-5H), 7.03 (1H, m, Ar-3H), 5.72 (1H, s, =CH^a), 5.11 (1H, s, =CH^b), 4.89 (1H, dd, OCH, *J*=1.7, 3.8 Hz), 4.75 (1H, d, ArCH, *J*=14.5 Hz), 4.62 (1H, d, ArCH, *J*=14.5 Hz), 4.32 (1H, dd, NCH, *J*=3.8, 8.6 Hz), 4.27 (2H, dq, CO_2CH_2, *J*=1.3, 7.3 Hz), 1.29 (3H, t, OCH_2CH_3, *J*=7.1 Hz), 1.09 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$): 171.49 (CO), 138.88 (=C), 134.58 (Ar), 132.32 (Ar), 128.33 (Ar), 127.83 (Ar), 124.89 (Ar), 124.14 (Ar), 110.09 (=CH_2), 79.17 (NC*C*), 66.91 (OCH_2), 62.40 (CO_2C), 62.06 (NC), 56.84 (SC), 22.96 ($C(CH_3)_3$), 14.51 (OCH_2CH_3); *m*/*z* (ES^+): 352 (MH^+).

2.4.6. Ethyl 2*R*,5*R*,6*S*-(4-methylene-isochroman-3-yl)-(2-methyl-propane-2-sulfinylamino)acetate (*R*,*R*,*S*-19).



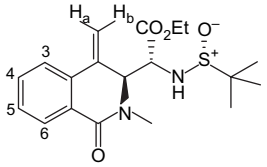
Obtained as a pale yellow oil (0.101 g, 58%) after flash chromatography (Et_2O); R_f 0.14 (Et_2O); $[\alpha]_D^{20}$ +41.5 (*c* 1.3); Found: 374.1402, $C_{18}H_{25}NO_4S{\cdot}Na$ requires: 374.1402; ν_{max}/cm^{-1}: 3450, 3297 (NH), 2959, 2868, 1738 (CO), 1628, 1576; δ_H (500 MHz, $CDCl_3$): 7.57 (1H, dd, Ar-6H, *J*=4.3, 9.0 Hz), 7.23 (2H, m, Ar-4H, Ar-5H), 7.03 (1H, dd, Ar-3H, *J*=4.3, 6.0 Hz), 5.72 (1H, s, =CH^a), 5.11 (1H, s, =CH^b), 4.89 (1H, m, NH), 4.75 (1H, d, OCH, *J*=14.5 Hz), 4.62 (1H, d, OCH, *J*=14.5 Hz), 4.32 (1H, dd, NCH, *J*=3.8, 8.6 Hz), 4.29–4.24 (3H, m, CO_2CH_2, OCH), 1.30 (3H, t, OCH_2CH_3, *J*=7.1 Hz), 1.09 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$): 170.08 (CO), 137.44 (=C), 133.15 (Ar), 130.89 (Ar), 126.90 (Ar), 126.40 (Ar), 123.46 (Ar), 122.71 (Ar), 108.66 (=CH_2), 77.74 (NC*C*), 65.48 (OCH_2), 60.98 (CO_2C), 60.92 (NC), 55.39 (SC), 21.53 ($C(CH_3)_3$), 13.09 (OCH_2CH_3); *m*/*z* (ES^+): 352 (MH^+).

2.4.7. Ethyl 2*S*,5*S*,6*R*-(2-methyl-4-methylene-1-oxo-1,2,3,4-tetrahydro-isoquinolin-3-yl)-(2-methyl-propane-2-sulfinylamino)acetate (*S*,*S*,*R*-20).



Obtained as a pale yellow oil (0.052 mg, 28%) after flash chromatography (EtOAc); R_f 0.10 (EtOAc); $[\alpha]_D^{20}$ −7.3 (*c* 0.4); Found: C, 60.20; H, 6.90; N, 7.10; S, 8.40, $C_{19}H_{26}N_2O_4S$ requires: C, 60.29; H, 6.92; N, 7.40; S, 8.47%; ν_{max}/cm^{-1}: 3459 (NH), 3274, 2961, 2239, 1739 (CO), 1648 (CO), 1602, 1573; δ_H (500 MHz, $CDCl_3$): 8.09 (1H, d, Ar-6H, *J*=7.7 Hz), 7.51 (1H, d, Ar-3H, *J*=7.7 Hz), 7.47 (1H, td, Ar-4H, *J*=0.9, 7.7 Hz), 7.40 (1H, td, Ar-5H, *J*=0.9, 7.7 Hz), 5.74 (1H, s, =CH^a), 5.31 (1H, s, =CH^b), 4.38 (1H, d, MeNC*H*, *J*=4.7 Hz), 4.27 (1H, d, NH, *J*=8.1 Hz), 4.11 (1H, dd, NCH, *J*=4.7, 8.1 Hz), 3.90 (1H, dq, OCH, *J*=7.3, 10.7 Hz), 3.54 (1H, dq, OCH, *J*=7.3, 10.7 Hz), 3.22 (3H, s, NCH_3), 1.15 (9H, s, $C(CH_3)_3$), 1.13 (3H, t, OCH_2CH_3, *J*=7.3 Hz); δ_C (75 MHz, $CDCl_3$): 170.53 (CO), 163.29 (NCO), 136.20 (=C), 134.46 (Ar), 132.19 (Ar), 128.10 (Ar), 127.83 (Ar), 127.27 (Ar), 123.68 (Ar), 115.76 (=CH_2), 68.33 (MeN*C*), 62.34 (OC), 59.54 (SNC), 56.22 (SC), 35.14 (NCH_3), 22.53 ($C(CH_3)_3$), 10.97 (OCH_2CH_3); *m*/*z* (ES^+): 379 (MH^+).

2.4.8. Ethyl (*R*)-((*S*)-2-methyl-4-methylene-1-oxo-1,2,3,4-tetrahydro-isoquinolin-3-yl)-((*R*)-2-methyl-propane-2-sulfinylamino)acetate (*R*,*R*,*S*-20).



Obtained as a pale yellow oil (0.130 g, 69%) after flash chromatography (EtOAc); R_f 0.10 (EtOAc); $[\alpha]_D^{20}$ +9.2 (*c* 0.6); Found: C, 60.50; H, 7.20; N, 7.40; S, 8.40, $C_{19}H_{26}N_2O_4S$ requires: C, 60.29; H, 6.92; N, 7.40; S, 8.47%; ν_{max}/cm^{-1}: 3459 (NH), 3274, 2964, 2239, 1744 (CO), 1658 (CO), 1602; δ_H (500 MHz, $CDCl_3$): 8.09 (1H, d, Ar-6H, *J*=7.8 Hz), 7.51 (1H, d, Ar-3H, *J*=7.7 Hz), 7.47 (1H, td, Ar-4H, *J*=0.9, 7.7 Hz), 7.40 (1H, td, Ar-4H, *J*=0.9, 7.7 Hz), 5.74 (1H, s, =CH^a), 5.31 (1H, s, =CH^b), 4.39 (1H, d, MeNC*H*, *J*=4.7 Hz), 4.27 (1H, d, NH, *J*=8.1 Hz), 4.14 (1H, dd, NCH, *J*=4.5, 8.1 Hz), 3.90 (1H, dq, OCH, *J*=7.3, 10.7 Hz), 3.54 (1H, dq, OCH, *J*=7.3, 10.7 Hz), 3.23 (3H, s, NCH_3), 1.15 (9H, s, $C(CH_3)_3$), 1.13 (3H, t, OCH_2CH_3, *J*=7.3 Hz); δ_C (75 MHz, $CDCl_3$): 170.53 (CO), 163.29 (NCO), 136.20 (=C), 134.46 (Ar), 132.19 (Ar), 128.10 (Ar), 127.83 (Ar), 127.27 (Ar), 123.68 (Ar), 115.76 (=CH_2), 68.33 (MeN*C*), 62.34 (OC), 59.54 (SNC), 56.22 (SC), 35.14 (NCH_3), 22.53 ($C(CH_3)_3$), 10.97 (OCH_2CH_3); *m*/*z* (ES^+): 379 (MH^+).

Acknowledgements

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14. Supplementary crystallographic data for *S*,*S*-**6** (CCDC 277090), *R*,*R*-**6** (CCDC 277091) and *R*,*R*,*S*-**18** (CCDC 277092) can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif.
15. Semi-empirical calculations were performed using MOPAC v7 by J. J. P. Stewart and the PM3 Hamiltonian. Approximate transition structures were located using the SADDLE routine within MOPAC following full conformational optimisation of the attached sub-structures (MM2). Transition structures were then fully optimised using the TS routine within MOPAC and these then characterised by observing them to have a single negative vibrational frequency following use of the FORCE calculation within MOPAC.
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