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Stereoselective synthesis of chiral β[2,3] – disubstituted – β - amino acid derivatives using Pd/In transmetallation cascade processes

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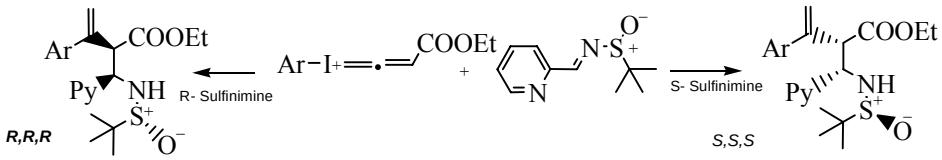

Pergamon

TETRAHEDRON

Stereoselective synthesis of chiral $\beta^{2,3}$-disubstituted-β-amino acid derivatives using Pd/In transmetallation cascade processes

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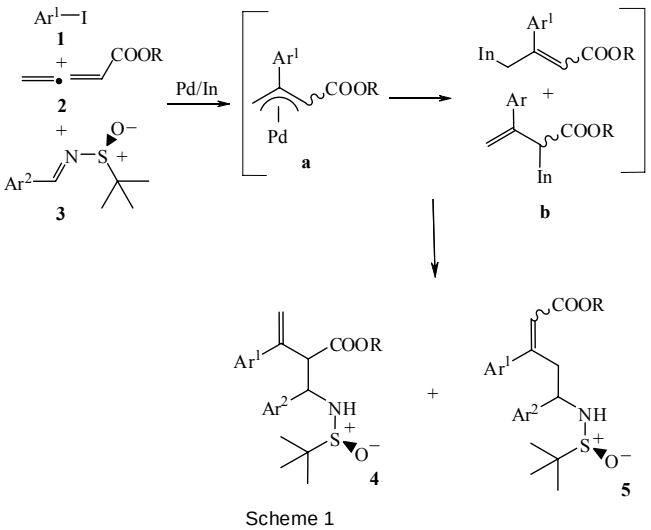
Abstract—A new, highly efficient synthesis of chiral $\beta^{2,3}$- disubstituted-β-amino acid derivatives has been developed, based on an allylation procedure employing allene and a catalytic Pd/In bimetallic process

Introduction

While α-amino acids are essential prerequisites for life, the β-amino isomers are far less common in living organisms. However, they are constituents of wide variety of natural products and various polypeptides with different biological properties[1] and have attracted growing interest.[2] These polypeptides have been shown to form secondary structures analogous to those of natural polypeptides, but are metabolically more stable than the α-amino acid equivalents.[3] This is particularly interesting from a medicinal chemistry point of view. Due to the increased interest in this area, β-amino acids have emerged as important synthetic targets and a range of methodologies have been developed for their preparation. The majority of these procedures are based on either the Mannich[4a-d] or aza-Michael[4e-g] reactions, although others methods are also known.[4h-j]

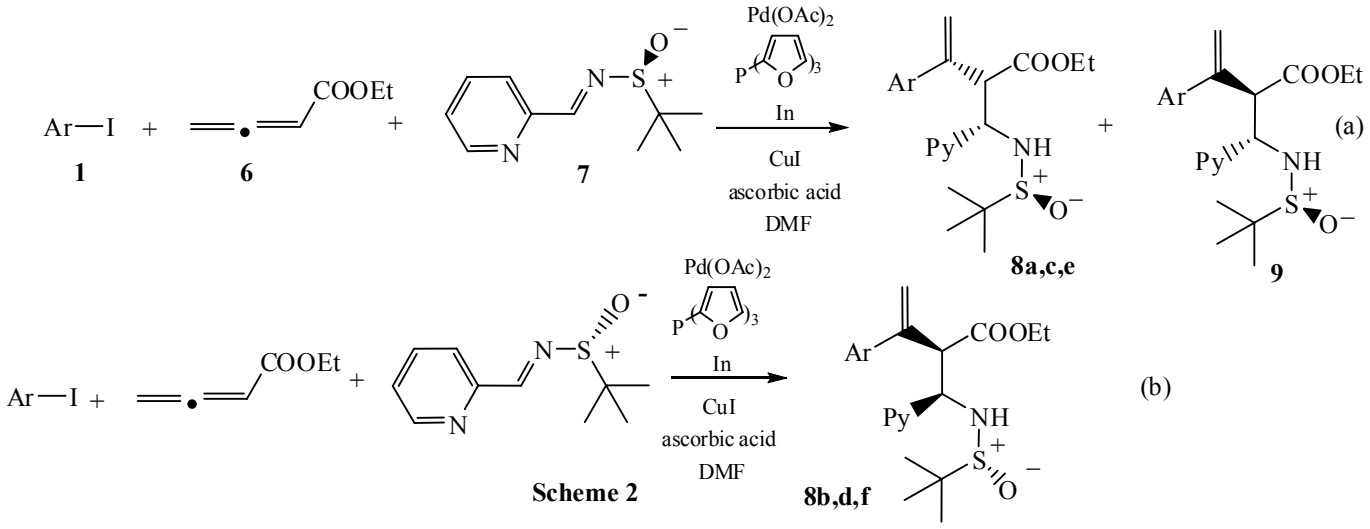
Results and Discussion

Our approach to the synthesis of β-amino acids is based on our Pd/In transmetallation process[5] involving allenes as key reactants. This methodology possesses significant synthetic diversity advantages in allowing access to a wide range of 2- and 2, 3-disubstituted allylic species. Others have developed analogous processes involving allylic acetates.[6] In recent years, the potential of this umpolung procedure, in which a nucleophilic In-species is generated from an electrophilic Pd-species, has been exemplified by the synthesis of a range of compounds,[7] including chiral non-natural α-amino acids.[8]



Scheme 1

* Corresponding author. Tel.:+44-113-343-6501; fax:=44-113-343-6501; e-mail:r.grigg@leeds.ac.uk.



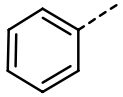
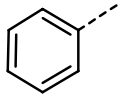
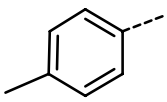
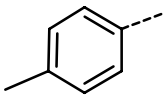
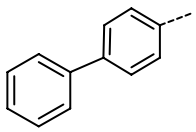
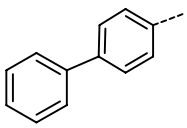
Scheme 2

Our strategy for the stereoselective synthesis of β-amino acid derivatives using our methodology is outlined in Scheme 1. The oxidative addition of the aryl iodide **1** to Pd(0) followed by reaction with allene **2** is expected to generate an allyl-Pd(II) species **a** which would then create a nucleophilic allyl-In species **b**, *via* a redox transmetallation process. Reaction of intermediate **b** with sulfinimine **3** would then afford the product. It was envisaged that the stereoselectivity of this process would be controlled by the chiral sulfinimine, which has been shown to be an efficient auxiliary in related transformations.[8,9] Although the cascade could afford two regioisomeric products, **4** and **5**, stereoelectronic factors were expected to control the regiochemistry leading to **4** as the sole or major product. Overall, this three component coupling would create two new bonds and two chiral centres.

In the event stirring and heating iodobenzene, allene **6** and imine (*S*)-**7** in DMF in the presence of $Pd(OAc)_2$, tri-2-furyl phosphine, In and additives[10] in a Schlenk flask at 40 ^{0}C afforded the expected product as a 15:1 mixture of separable diastereoisomers, **8** and **9**, in 69% yield (Scheme 2a, Table 1, entry 1). To our delight the regioisomeric product **5** (Scheme 1) was not observed.

When the reaction was carried out using the enantiomeric sulfinimine, (*R*)-**7** the results were identical apart from the sense of chiral induction (entry 1 vs entry 2, Table 1). Additional examples, performed with both enantiomeric sulfinimines **7** and 4-methyl- or 4-phenyliodobenzene, under the same conditions, afforded analogous products in good yield and with a high degree of diastereoselectivity, Table 1. Although the *para* substituent on the aryl iodide seems to influence the diastereoselectivity, the origin of this effect is not at present clear. It has been previously shown that the sulfoxy group can be easily removed[8,9] from *N*-atom. Hence, the process depicted by Scheme 2 is an efficient way to synthesise certain classes of β[2,3]-disubstituted-β-amino acids.

Table 1 Synthesis of chiral β-amino acid derivatives[a]

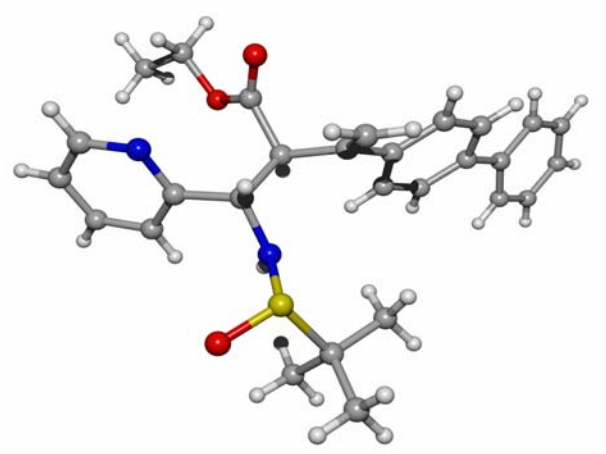
Entry	Ar(I)	Imine	Ratio 8:9[b]	Yield (%)[c]
1		*S*	15(*S,S,S*): 1(*S,S,R)*	60
2		*R*	15(*R,R,R*):1(*R,R,S*)	60
3		*S*	9(*S,S,S*):1(*S,S,R*)	60
4		*R*	19(*R,R,R*):1(*R,R,S*)	60
5		*S*	12(*S,S,S*):1(*S,S,R*)	69
6		*R*	12(*R,R,R*):1(*R,R,S)*	62

[a] Reaction conditions: ArI (0.75 mmol), iminoester (0.5 mmol), allene (0.75 mmol), $Pd(OAc)_2$ (0.05 mmol), phosphine (0.1 mmol), In (0.75 mmol), CuI (0.1 mmol), ascorbic acid (0.2 mmol), DMF (10 mL) in a Schlenk flask, 40 ^{o}C, 24 h.

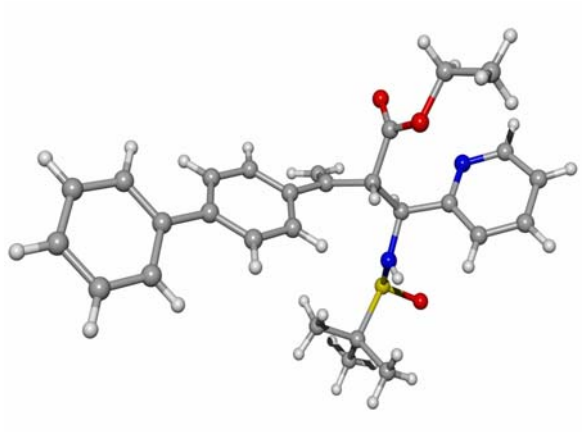
[b] Calculated by integration of the ^{1}H NMR spectra of the product mixtures

[c] Isolated yield

The absolute stereochemistries of the major products, **8e** and **8f,** were established by X-ray crystallography **(Figure 1).** These data demonstrate that (*S*)-**7** and (*R*)-**7** engender *S*- and *R*- stereochemistry on both newly formed chiral centres respectively.



(*S,S,S*)-**8e**



R,R,R)-**8f**

Figure 1

Based on the absolute stereochemistry of the products and our previous semi-empirical calculations using MOPAC v7 of related reactions forming α-amino acids,[7] the transition state leading to the major product was proposed (**Figure 2**). Compound **8e** is formed via a Zimmerman-Traxler chair - like transition state **A,** involving an In(I) species,[11] an *E*-allylindium species and addition to the *Si* face of the sulfinimine. This transition state may be further stabilised by the proximity of heteroatoms in the sulfinimine moieties and their ability to coordinate indium. An additional stabilisation factor is the potential π -π interactions between the electron deficient 2-pyridyl substituent and the electron rich aromatic substituents. The enantiomeric product **8f** is proposed to form via transition state **B** involving the *Z*-allylindium species. Although this transition state seems to be more stable due to *pseudo*equatorial orientation of the ester moiety, *Z*- and *E*-η^1-allylindium species are not expected to interconvert under these conditions[12] and their ratio is thus thought to reflect the ratio of the *syn*- and *anti*--allylpalladium(II) intermediates trapped out by indium.
This would accord with our previous experience involving π–allylpalladium species from monosubstituted allenes where the 1,2-disubstituted- *E*- isomer is the predominent or sole species. This in turn would indicate that transfer of the allyl moiety from palladium to indium occurs with retention of alkene geometry.

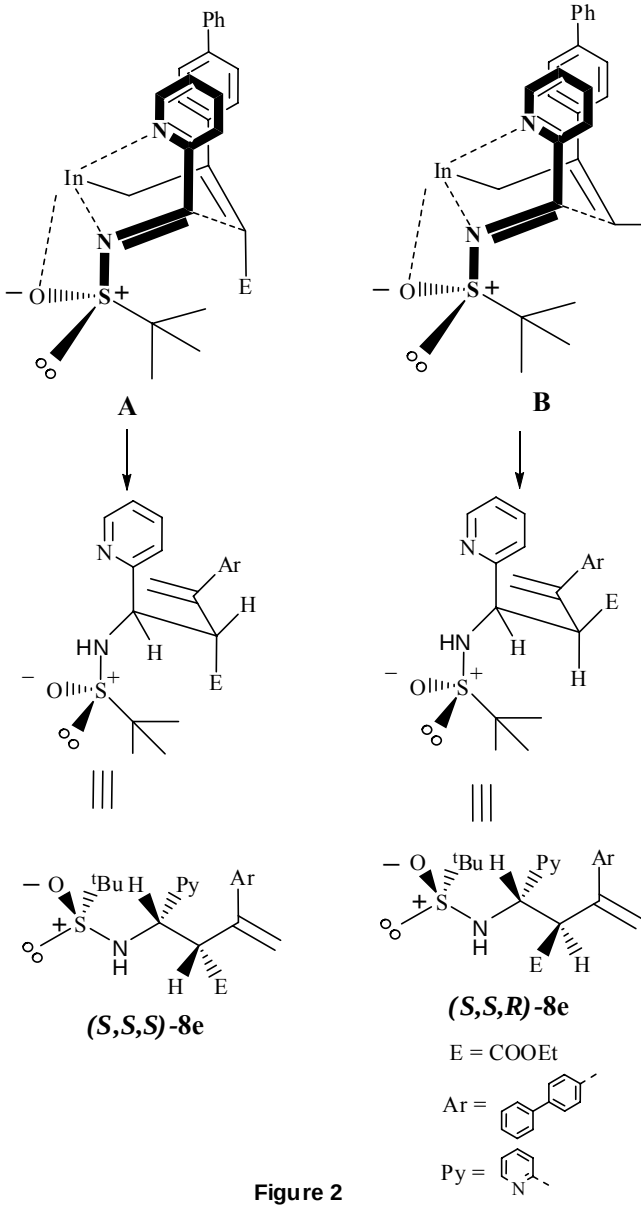


Figure 2

The mechanism of the reductive transmetallation proceeds via Pd-In bond formation or a pd-X-In bridged species[13] resulting in the delivery of indium to the same face of the allyl system as palladium. There is literature precedent for this in the both indium and zinc transmetallation with π - allyl Pd(II).[14]

An unresolved problem is that if indeed indium(I) allyl is the key allylation agent then two equivalents of In(0) are required for the reduction of Pd(II) and the nature of this process is unclear.[15] However, we employed only 1.5 mole equiv of In and yields/conversion were depressed in the absence of CuI[8] and ascorbic acid.

We believe a key role of the CuI additive is to promote formation of InI and hence facilitate transfer of indium from the solid to the solution phase. The formation of copper allyl species[16] may also be involved. The ascorbic acid was added to help recycle unproductive higher valency states of the Pd, Cu,[17] and In if present. It is undoubtedly benefical but its precise role(s) is unclear.

In conclusion, a short, diastereoselective synthesis of $\beta^{2,3}$-disubstituted-β–amino acid derivatives has been developed, employing Pd/In transmetallation processes. Under very mild conditions the three component coupling, forming two bonds and two chiral centres, afforded the products in good yield and with a high degree of diastereoselectivity. Further study of this process is underway.

Experimental

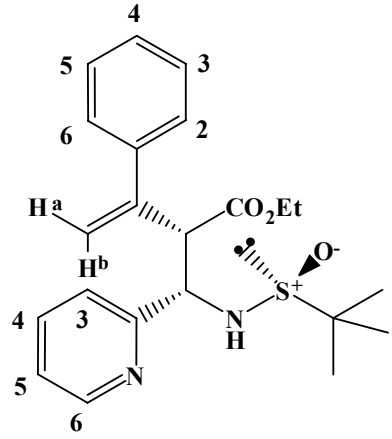
Unless otherwise noted all reagents were obtained from commercial suppliers and used without further purification. All solvents were dried or purified by literature procedures.[18] Chromatography columns were prepared using Fisher chemicals 60A 35 – 70 micron silica gel. Nuclear magnetic resonance spectra 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. Infra-red spectra were recorded using a Perkin-Elmer FT-IR 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^{-1} and the concentration (*c*) is expressed in g 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

General procedure for the synthesis of β-amino acid derivatives

Aryl iodide **1** (0.75 mmol) was added to a suspension of chiral sulfinimine **7** (0.5 mmol), ethyl 2,3-butadienoate **6** (0.75 mmol), indium metal powder (0.088 g, 0.75 mmol), $Pd(OAc)_2$ (0.011g, 0.05 mmol), tri-2-furyl phosphine (0.024 g, 0.1 mmol), CuI (0.019 g, 0.1 mmol) and ascorbic acid (0.0355 g, 0.2 mmol) in DMF (10 mL) in a Schlenk tube. The flask was flushed with nitrogen and sealed. The mixture was stirred and heated to 40 ^oC (oil bath temperature) for 24 h, left to cool and vented. Ethyl acetate (20 mL) and 5 % HCl aqueous solution (10 mL) were 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 x 40 mL), dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*.

The residue was purified by flash chromatography to give the *N* – sulfinyl - β - amino ester.

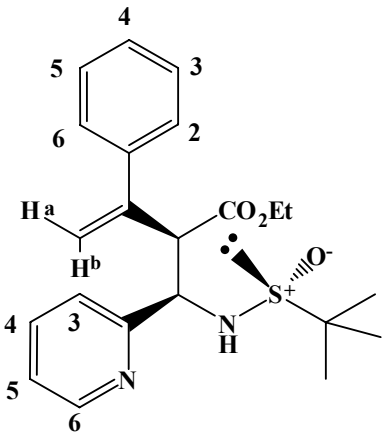
Ethyl (*S,S,S*) 2-[(2-methyl-propane-2-sulfinylamino)-pyridin-2-yl-methyl]-3-phenyl-but-3-enoate (*S,S,S*)-8a



Obtained as a pale yellow oil (0.120 g, 60 %) after flash chromatography (EtOAc); $R_{F;}$ 0.38 (EtOAc); $[a]_D^{20}$ – 14.4 (*c* 1.4); Found; C, 66.10; H, 7.30; N, 7.10; S, 7.80, $C_{22}H_{28}N_2O_3S$ requires; C, 65.97; H, 7.05; N, 6.99; S, 8.01 %; ν_{max}/cm^{-1}; 3453, 3254 (NH), 3063, 2947, 2321, 2219, 2136, 1954, 1832, 1732 (CO); δ_H (500 MHz, $CDCl_3$); 8.54

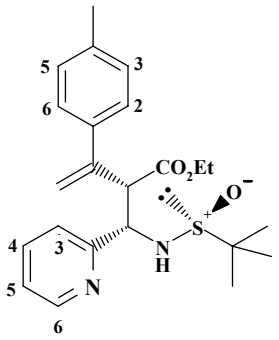
(1H, d, pyridyl-6H, *J* = 4.7 Hz), 7.61 (1H, t, Ar-4H, *J* = 7.7 Hz), 7.48 (1H, d, pyridyl-3H, *J* = 7.3 Hz), 7.42 (2H, d, Ar-2H, Ar-6H, *J* = 7.7 Hz), 7.34 (2H, t, Ar-3H, Ar-5H, *J* = 7.7 Hz), 7.28 (1H, t, pyridyl-4H, *J* = 7.3 Hz), 7.16 (1H, dd, pyridyl-5H, J = 4.7, 7.3 Hz), 5.63 (1H, s, =CH^{a}), 5.56 (1H, s, =CH^{b}), 4.97 (1H, t, NCH, *J* = 9.8 Hz), 4.41 (1H, d, NH, *J* = 9.8 Hz), 4.25 (1H, d, NCHC*H*, *J* = 9.8 Hz), 3.98 – 3.92 (2H, m, OCH_2), 1.06 (9H, s, $C(CH_3)_3$), 1.02 (3H, t, OCH_2CH_3, *J* = 7.3 Hz); δ_c (75 MHz, $CDCl_3$); 172.0 (CO), 160.3 (=C), 149.6 (Ar), 144.3 (Ar), 142.0 (Ar), 137.0 (Ar), 128.7 (Ar), 128.1 (Ar), 126.8 (Ar),126.7 (Ar), 124.1 (Ar), 123.2 (Ar), 117.2 (=CH_2), 63.7 (NC), 61.2 (OC), 56.6 (SC), 56.4 (NC*C*), 22.8 ($C(CH_3)_3$), 14.2 (OC*C*); m/z (ES^+); 401 (MH^+).

Ethyl (*R,R,R*) 2-[(2-methyl-propane-2-sulfinylamino)-pyridin-2-yl-methyl]-3-phenyl-but-3-enoate (*R,R,R*)-8b



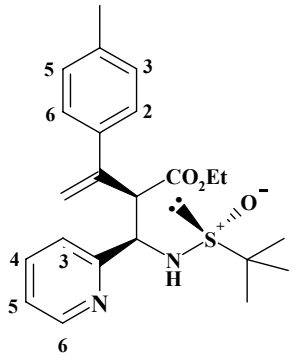
Obtained as a pale yellow oil (0.120 g, 60 %) after flash chromatography (EtOAc); $R_{F;}$ 0.38 (EtOAc); $[a]_D^{20}$ + 12.8 (*c* 1.9); Found; C, 66.10; H, 7.10; N, 7.20; S, 8.0, $C_{22}H_{28}N_2O_3S$ requires; C, 65.97; H, 7.05; N, 6.99; S, 8.01 %; ν_{max}/cm^{-1}; 3451, 3248 (NH), 3066, 2953, 2325, 2216, 2141, 1954, 1832, 1732 (CO); δ_H (500 MHz, $CDCl_3$); 8.54 (1H, d, pyridyl-6H, *J* = 4.7 Hz), 7.61 (1H, t, Ar-4H, *J* = 7.7 Hz), 7.48 (1H, d, pyridyl-3H, *J* = 7.3 Hz), 7.42 (2H, d, Ar-2H, Ar-6H, *J* = 7.7 Hz), 7.34 (2H, t, Ar-3H, Ar-5H, *J* = 7.7 Hz), 7.28 (1H, t, pyridyl-4H, *J* = 7.3 Hz), 7.16 (1H, dd, pyridyl-5H, 4.7, 7.3 Hz), 5.63 (1H, s, =CH^{a}), 5.56 (1H, s, =CH^{b}), 4.97 (1H, t, NCH, *J* = 9.8 Hz), 4.41 (1H, d, NH, *J* = 9.8 Hz), 4.25 (1H, d, NCHC*H*, *J* = 9.8 Hz), 3.98 – 3.92 (2H, m, OCH_2), 1.06 (9H, s, $C(CH_3)_3$), 1.02 (3H, t, OCH_2CH_3, *J* = 7.3 Hz), δ_c (75 MHz, $CDCl_3$); 172.0 (CO), 160.3 (=C), 149.8 (Ar), 144.3 (Ar), 142.0 (Ar), 137.1 (Ar), 128.7 (Ar), 128.1 (Ar), 126.9 (Ar), 126.7 (Ar), 124.1 (Ar), 123.3 (Ar), 117.3 (=CH_2), 63.9 (NC), 61.2 (OC), 56.7 (SC), 56.4 (NC*C*), 23.0 ($C(CH_3)_3$), 14.3 (OC*C*); m/z (ES^+); 401 (MH^+).

Ethyl (*S,S,S*) 2-[(2-methyl-propane-2-sulfinylamino)-pyridin-2-yl-methyl]-3-*p*-tolyl-but-3-enoate (*S,S,S*)-8c



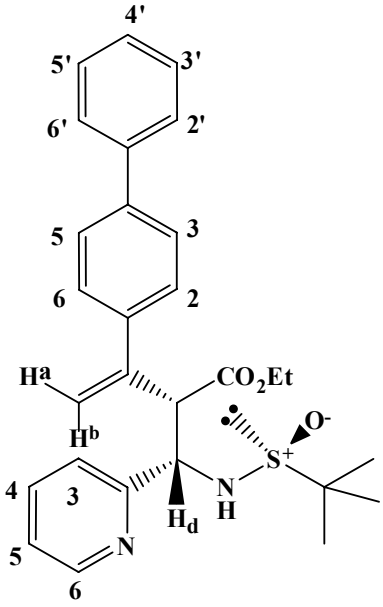
Obtained as colourless prisms (0.088 g, 60 %), mp 74-76 ^{o}C after flash chromatography (EtOAc); $R_{F;}$ 0.40 (EtOAc); $[a]_D^{20}$ – 20.3 (*c* 1.1); Found; 415.2069; $C_{23}H_{30}N_2O_3S$ requires 415.2055; ν_{max}/cm^{-1}; 3254 (NH), 3181, 3056, 2411, 2219, 2047, 1922, 1821, 1738 (CO); δ_H (500 MHz, $CDCl_3$); 8.54 (1H, d, pyridyl-6H, *J* = 4.5 Hz), 7.61 (1H, td, pyridyl-4H, *J* = 1.7, 7.7 Hz), 7.42 (1H, d, pyridyl-3H, *J* = 7.7 Hz), 7.38 (2H, d, Ar-3H, Ar-5H, *J* = 8.1 Hz), 7.15 (3H, m, Ar-2H, Ar-6H, pyridyl-5H), 5.59 (1H, s, =CH^{a}), 5.51 (1H, s, =CH^{b}), 4.95 (1H, t, NCH, *J* = 9.4 Hz), 4.40 (1H, d, NH, *J* = 9.4 Hz), 4.23 (1H, d, NCHC*H*, *J* = 9.4 Hz), 3.97 – 3.90 (2H, m, OCH_2), 1.06 (9H, s, $C(CH_3)_3$), 1.01 (3H, t, OCH_2CH_3, *J* = 7.3 Hz), δ_c (75 MHz, $CDCl_3$); 172.1 (CO), 160.3 (=C), 149.8 (Ar), 144.1 (Ar), 139.1 (Ar), 137.9 (Ar), 137.0 (Ar), 129.4 (Ar), 126.7 (Ar), 123.9 (Ar), 123.2 (Ar), 116.1 (=CH_2), 63.9 (NC), 61.2 (OC), 56.7 (SC), 56.4 (NC*C*), 23.0 ($C(CH_3)_3$), 21.5 (ArCH_3), 14.3 (OCH_2CH_3); m/z (ES^+); 415 (MH^+).

Ethyl (*R,R,R*) 2-[(2-methyl-propane-2-sulfinylamino)-pyridin-2-yl-methyl]-3-*p*-tolyl-but-3-enoate (*R,R,R*)-8d



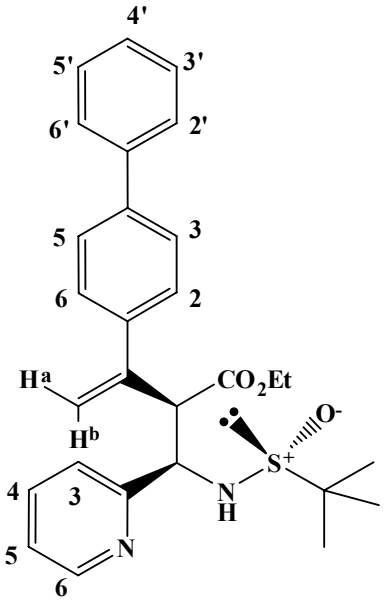
Obtained as colourless prisms (0.088 g, 60 %), mp 74-76 ^{o}C after flash chromatography (EtOAc); $R_{F;}$ 0.40 (EtOAc); $[a]_D^{20}$ + 18.9 (*c* 1.4); Found; C, 66.7; H, 7.40; N, 6.80; S, 7.80 %; $C_{23}H_{30}N_2O_3S$ requires; C, 66.64; H, 7.27; N, 6.76; S, 7.73 %; ν_{max}/cm^{-1}; 3254 (NH), 3181, 3056, 2411, 2219, 2051, 1926, 1823, 1738 (CO); δ_H (500 MHz, $CDCl_3$); 8.54 (1H, d, pyridyl-6H, *J* = 4.7 Hz), 7.61 (1H, td, pyridyl-4H, *J* = 1.7, 7.7 Hz), 7.42 (1H, d, pyridyl-3H, *J* = 7.7 Hz), 7.38 (2H, d, Ar-3H, Ar-5H, *J* = 8.1 Hz), 7.15 (3H, m, Ar-2H, Ar-6H, pyridyl-5H), 5.59 (1H, s, =CH^a), 5.51 (1H, s, =CH^b), 4.95 (1H, t, NCH, *J* = 9.4 Hz), 4.40 (1H, d, NH, *J* = 9.4 Hz), 4.23 (1H, d, NCHC*H*, *J* = 9.4 Hz), 3.97 – 3.90 (2H, m, OCH_2), 1.06 (9H, s, $C(CH_3)_3$), 1.01 (3H, t, OCH_2CH_3, *J* = 7.3 Hz), δ_c (75 MHz, $CDCl_3$); 172.1 (CO), 160.3 (=C), 149.8 (Ar), 144.1 (Ar), 139.1 (Ar), 137.9 (Ar), 137.0 (Ar), 129.4 (Ar), 126.7 (Ar), 123.9 (Ar), 123.2 (Ar), 116.1 (=CH_2), 63.9 (NC), 61.2 (OC), 56.7 (SC), 56.4 (NC*C*), 23.0 ($C(CH_3)_3$), 21.5 (ArCH_3), 14.3 (OCH_2CH_3); m/z (ES^+); 415 (MH^+).

Ethyl (*S,S,S*) 3-Biphenyl-4-yl-2-[(2-methyl-propane-2-sulfinylamino)-pyridin-2-yl-methyl]-but-3-enoate (*S,S,S*)-8e



Obtained as colourless prisms (0.164 g, 69 %), mp 64-67 ^{o}C, after flash chromatography (EtOAc); $R_{F;}$ 0.27 (EtOAc); $[a]_D^{20}$ + 32.6 (*c* 1.1); Found; 477.2214; $C_{28}H_{33}N_2O_3S$ requires; 477.2206; ν_{max}/cm^{-1}; 3443, 3254 (NH), 3034, 2960, 2309, 2217, 2060, 1963, 1834, 1731 (CO), 1623; δ_H (500 MHz, $CDCl_3$); 8.53 (1H, d, pyridyl-6H, *J* = 4.7 Hz), 7.62 (3H, m, ArH), 7.57 (4H, m, ArH), 7.43 (3H, m, ArH), 7.33 (1H, t, ArH, *J* = 7.3 Hz), 7.14 (1H, dd, pyridyl-5H, *J* = 4.7, 10.3 Hz), 5.69 (1H, s, =CH^a), 5.59 (1H, S, =CH^b), 5.00 (1H, t, NCH, *J* = 9.6 Hz), 4.44 (1H, d, NH, 9.6 Hz), 4.30 (1H, d, NCHC*H*, *J* = 9.6 Hz), 3.97 (2H, m, OCH_2,), 1.07 (9H, s, $C(CH_3)_3$), 1.02 (3H, t, $OCCH_3$, *J* 6.8 Hz); δ_c (75 MHz, $CDCl_3$); 172.5 (CO), 159.3 (Ar), 149.6 (H_2C=*C*), 140.9 (Ar), 140.7 (Ar), 136.8 (Ar), 129.3 (Ar), 128.0 (Ar), 127.4 (Ar), 127.3 (Ar), 127.2 (Ar), 127.2 (Ar), 124.1 (Ar), 123.9 (Ar), 123.3 (Ar), 116.9 (=CH_2), 63.9 (OC), 61.4 (NC), 56.7 (SC), 56.4 (NC*C*), 23.1 ($C(CH_3)_3$, 14.6 (OC*C*); m/z (ES^+); 478 (MH^+).

Ethyl (*R,R,R*) 3-Biphenyl-4-yl-2-[(2-methyl-propane-2-sulfinylamino)-pyridin-2-yl-methyl]-but-3-enoate (*R,R,R*)-8f



Obtained as colourless prisms (0.151 g, 62 %), mp 65-67 ^{o}C, after flash chromatography (EtOAc); $R_{F;}$ 0.27 (EtOAc); $[a]_D^{20}$ - 34.5 (*c* 0.6); Found; 477.2170; $C_{28}H_{33}N_2O_3S$ requires; 477.2206; ν_{max}/cm^{-1}; 3640, 3260 (NH), 2960, 2443, 2340, 2163, 2060, 1936, 1834, 1728 (CO), 1623; δ_H (500 MHz, $CDCl_3$); 8.53 (1H, d, pyridyl-6H, *J* = 4.7 Hz), 7.62 (3H, m, ArH), 7.57 (4H, m, ArH), 7.43 (3H, m, ArH), 7.33 (1H, t, ArH, *J* = 7.3 Hz), 7.14 (1H, dd, pyridyl-5H, *J* = 4.7, 10.3 Hz), 5.69 (1H, s, =CH^a), 5.59 (1H, S, =CH^b), 5.00 (1H, t, NCH, *J* = 9.6 Hz), 4.44 (1H, d, NH, 9.6 Hz), 4.30 (1H, d, NCHC*H*, *J* = 9.6 Hz), 3.97 (2H, m, OCH_2,), 1.07 (9H, s, $C(CH_3)_3$), 1.02 (3H, t, $OCCH_3$, *J* 6.8 Hz); δ_c (75 MHz, $CDCl_3$); 172.5 (CO), 159.3 (Ar), 149.6 (H_2C=*C*), 140.9 (Ar), 140.7 (Ar), 136.8 (Ar), 129.3 (Ar), 128.0 (Ar), 127.4 (Ar), 127.3 (Ar), 127.2 (Ar), 127.1 (Ar), 124.1 (Ar), 123.9 (Ar), 123.2 (Ar), 116.9 (=CH_2), 63.9 (OC), 61.4 (NC), 56.7 (SC), 56.4 (NC*C*), 23.1 ($C(CH_3)_3$, 14.6 (OC*C*); m/z (ES^+); 478 (MH^+).

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