Tetrahedron 65 (2009) 9116–9124

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

New chiral building blocks of β-peptoid analogs

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ARTICLE INFO

Article history:
Received 27 June 2009
Received in revised form 8 September 2009
Accepted 10 September 2009
Available online 15 September 2009

Keywords:
Chiral allenes
β-Amino acids
β-Amino esters
β-Enamino esters
β-Peptoids
Asymmetric reduction

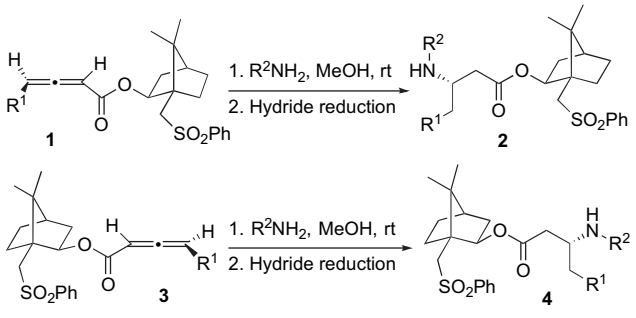
ABSTRACT

The synthesis of chiral functionalized β-amino esters via the hydride reductive amination of chiral allenes was explored. These compounds can be regarded as β-peptoids building blocks bearing a chiral side chain at the nitrogen and at the same time retaining the β-amino acid side chain. β-Enamino esters were obtained from the nucleophilic addition of α-amino esters (L-Ala, D-Ala, L-Phe, L-Leu, L-Trp and D-Trp methyl esters) to 2,3-allenoates bearing a chiral auxiliary, which determines the stereochemistry outcome of the subsequent reduction reaction. It was also demonstrated that in the reduction of β-enamino esters derived from L-Pro and D-Pro methyl esters the chirality of the new chiral center is controlled by the α-amino ester moiety.

1. Introduction

β-Amino acids are an important class of compounds due to their unique biological properties, their occurrence in natural products and their use as precursors of biologically and medicinally important molecules.[1] Some β-amino acids play an important role in the biological activity of complex molecules such as taxol, one of the most active antitumor agents. Therefore, the development of new synthetic methodologies for the asymmetric synthesis of β-amino acids is an important goal in organic synthesis.[2–7] On the other hand, the construction of new peptidomimetic backbone aiming to achieve new structural features and diverse biological activities is particularly interesting. In fact, distinct folding properties have been observed for several unnatural backbones such as β-amino acids and β-peptoids.[8]

We have recently described a highly selective two-step approach to chiral β-amino esters via the hydride reductive amination of chiral allenes (**1** and **3**). It was demonstrated that this route to chiral β-amino esters allows the control of the stereochemistry outcome by the selection of the chiral auxiliary (Scheme 1).[9]



Scheme 1.

In connection with our interest in the chemistry of amino-acid[10] and aminophosphonate[11] derivatives, we now describe a methodology to construct molecules with the general structure **5**, which can be regarded as β-peptoids building blocks bearing a chiral side chain at the nitrogen and at the same time retaining the β-amino acid side chain. These structures with specific spatial disposition of functional groups can lead to new peptidomimetics. Our approach was to carry out the reaction of chiral allenes with α-amino esters followed by reduction. It was also our aim to determine if the presence of an extra chiral center in the β-enamino ester moiety would influence the stereochemistry outcome of the hydride reduction.

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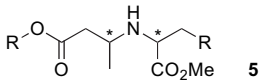
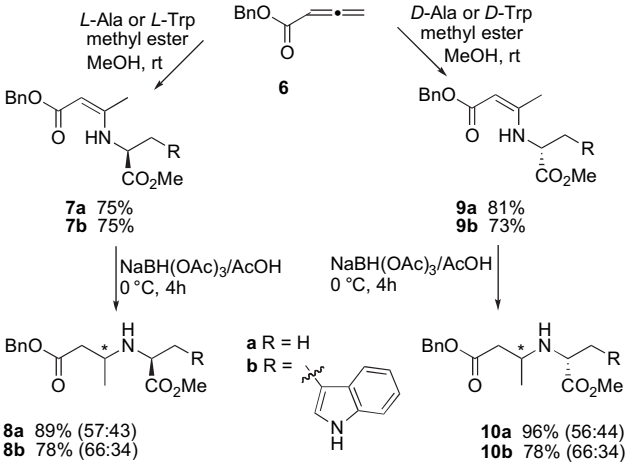
doi:10.1016/j.tet.2009.09.041



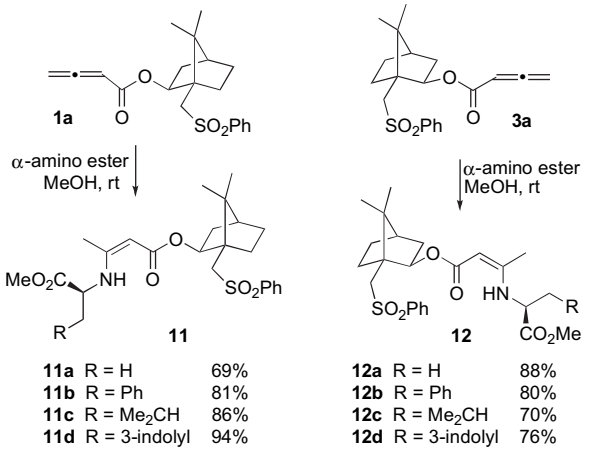
2. Results and discussion

Initially, the hydride reductive amination of an achiral allene was studied (Scheme 2). Thus, benzyl 2,3-butadienoate (**6**)[12] was reacted with L-Ala, D-Ala, L-Trp and D-Trp methyl esters followed by the subsequent reduction with sodium triacetoxyborohydride giving the corresponding β-amino esters in good yields. Mixtures of diastereoisomers were obtained as shown by the ^{1}H NMR and ^{13}C NMR spectra of the products. In fact, we observed that in the ^{1}H NMR spectrum of **8a** recorded at 120 °C is still clear the presence of a mixture of stereoisomers.



Scheme 2.

Aiming to achieve stereoselective synthesis of this type of functionalized β-amino esters, the hydride reductive amination of chiral allenes **1a**[13] and **3a**[13] with α-amino esters was carried out (Scheme 3). The reaction of chiral allenes **1a** and **3a** with methyl esters of L-alanine, L-phenylalanine, L-leucine and L-tryptophan gave the corresponding β-enamino esters (**11** and **12**), obtained in yields ranging from 69 to 94%. The reduction of chiral β-enamino esters **11a**–**11d** and **12a**–**12d** was carried out with sodium triacetoxyborohydride[9,14] in acetic acid giving the corresponding chiral β-amino esters stereoselectively and in good yields (Table 1). However, two rotamers are observed in the ^{1}H NMR and ^{13}C NMR spectra of some of these compounds recorded at ambient temperature but, as previously observed for β-amino esters **2** and **4**, the spectra are simpler at higher temperature.



Scheme 3.

The structure of (1*R*)-(−)-10-phenylsulfonylisobornyl (*S*)-3-[(1*S*)-1-methoxycarbonylethylamino]butanoate (**13a**) was determined by X-ray crystallography (Fig. 1). This allowed us to establish the *S* configuration to the new chiral center of β-amino esters **13**, the same configuration obtained from β-amino esters derived from achiral amines and chiral allenes **1**,[9] with (1*R*)-(−)-10-phenylsulfonylisobornyl group as the chiral auxiliary (Scheme 1). Thus, the stereoselectivity was again determined by the (1*R*)-(−)-10-phenylsulfonylisobornyl moiety.

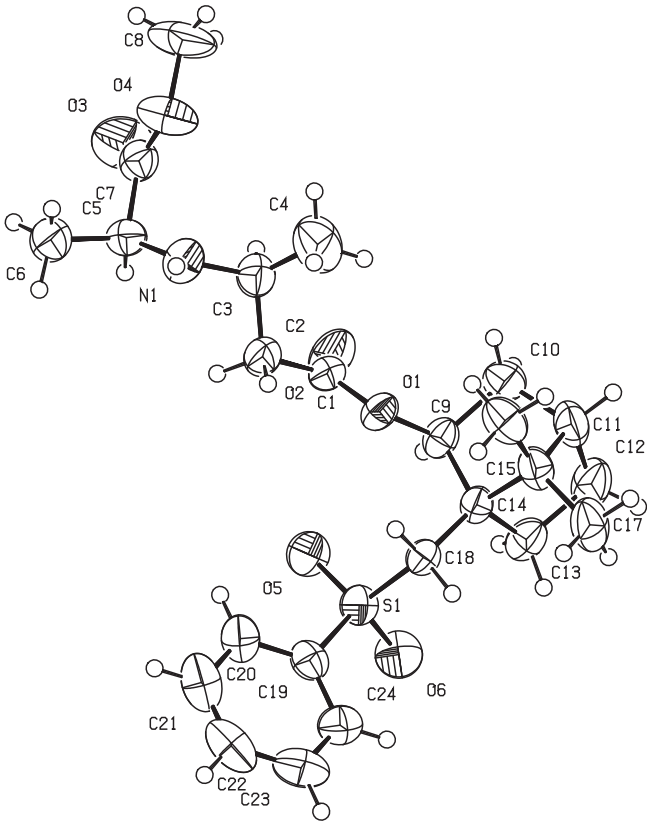
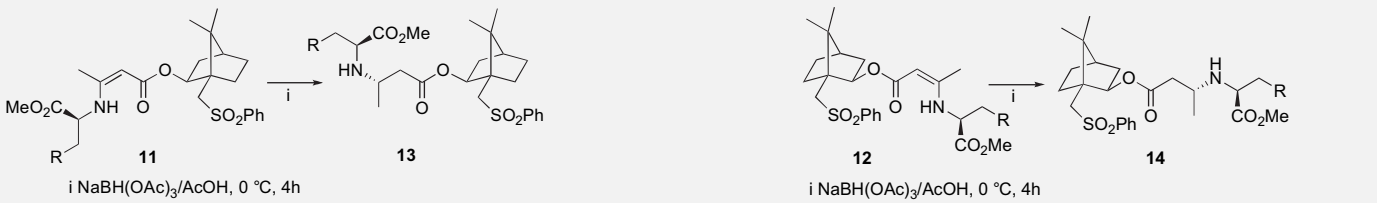


Figure 1. X-ray structure of (1*R*)-(−)-10-phenylsulfonylisobornyl (*S*)-3-[(1*S*)-1-methoxycarbonylethylamino]butanoate (**13a**).

These results indicate that the presence of the (1*R*)-(−)-10-phenylsulfonylisobornyl or (1*S*)-(+)-10-phenylsulfonylisobornyl unit of allenonates **1a** and **3a**, respectively, is a requirement to achieve the selective synthesis of the chiral β-amino esters.

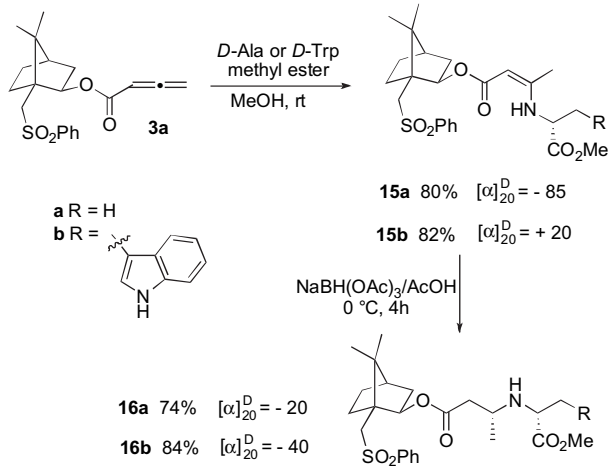
To confirm this observation we carried out the Michael addition of D-α-amino acids to chiral allene **3a** followed by reduction (Scheme 4). The β-amino esters **16a** and **16b** derived from D-alanine methyl ester and D-tryptophan methyl ester, respectively, were obtained selectively. The structure of (1*S*)-(+)-10-phenylsulfonylisobornyl (*R*)-3-[(1*R*)-1-methoxycarbonylethylamino]butanoate (**16a**) was determined by X-ray crystallography showing that the new chiral center has *R* configuration (Fig. 2). This is the expected configuration considering that the chirality was induced by the (1*S*)-(−)-10-phenylsulfonylisobornyl unit. In fact, compound **16a** is the enantiomer of β-amino ester **13a** showing opposite values for the optical rotation. In a similar way it was observed that a new chiral center with *R* configuration was created in the synthesis of **16b**. Compound **16b** is the enantiomer of β-amino ester **13d** as indicated also by the opposite value of the optical rotation.

Table 1
Reduction of β-Enamino Esters **11** and **12** to β-Amino Esters **13** and **14**



Entry	Product	R	Yield, %	$[\alpha]_{20}^{D}$	Entry	Product	R	Yield, %	$[\alpha]_{20}^{D}$
1	**13a**	H	88	+20	5	**14a**	H	88	−30
2	**13b**	Ph	98	+35	6	**14b**	Ph	95	−45
3	**13c**	Me_2CH	93	+30	7	**14c**	Me_2CH	95	−30
4	**13d**	3-Indolyl	75[a]	+40	8	**14d**	3-Indolyl	95[a]	−45

[a] Reaction time: 12 h.



Scheme 4.

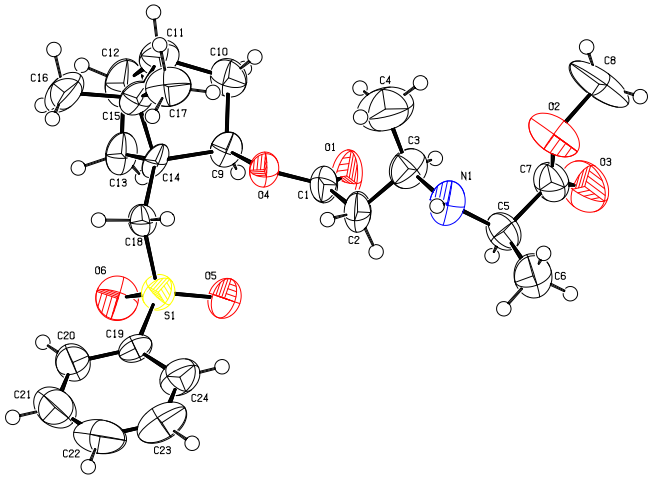
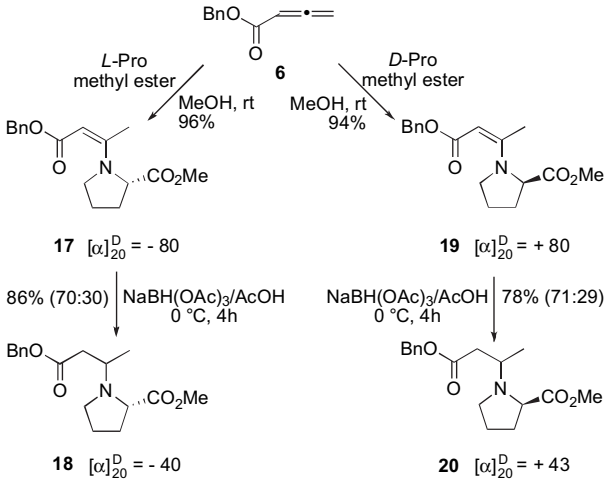


Figure 2. ORTEP diagram of (1*S*)-(+)-10-phenylsulfonylisobornyl (*R*)-3-[(1*R*)-1-methoxycarbonylethylamino]butanoate (**16a**).

These results support the conclusion that the chiral auxiliary in the ester moiety of the β-enamino esters is responsible for the chiral induction of the reduction reaction. We can therefore assert that a chiral center with *S* configuration was created in the synthesis of β-amino esters **13a**–**13d** whereas in the synthesis of β-amino esters **14a**–**14d** a chiral center with *R* configuration was created.

In order to get further insight into the role of both chiral auxiliaries, the 10-phenylsulfonylisobornyl unit and the α-amino ester moiety, the reduction of β-enamino esters derived from L-Pro and D-Pro methyl esters was also studied.

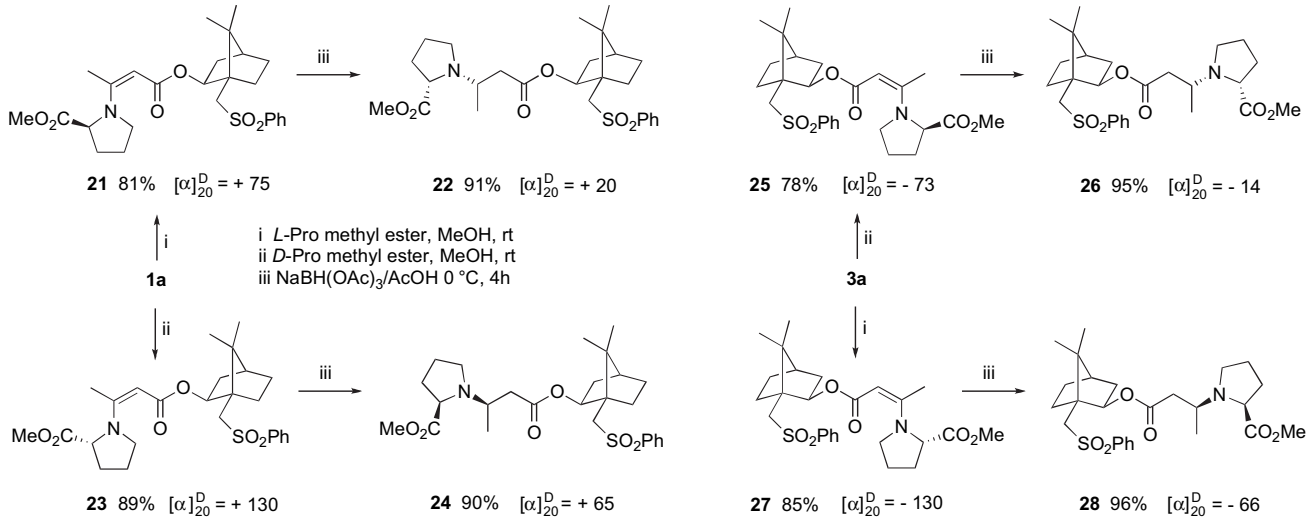
The reaction of benzyl 2,3-butadienoate with L-Pro and D-Pro methyl esters followed by reduction with triacetoxyborohydride was carried out (Scheme 5). The corresponding β-amino esters were obtained as mixtures of diastereoisomers in good yields. However, in this case the ^{1}H NMR and ^{13}C NMR spectra of the products **18** and **20** show clearly a major stereoisomer indicating that the α-amino esters act as a chiral auxiliary in the reduction reaction. The mixture of stereoisomers in the ^{1}H NMR spectrum of **18** recorded at 120 °C is still very clear.



Scheme 5.

The reductive amination of chiral allenes **1a** and **3a** using the α-amino methyl esters of L-Pro and D-Pro led to a different outcome (Scheme 6). The β-enamino esters **21**, **23**, **25** and **27** were obtained in yields ranging from 78% to 89% and its reduction led to the corresponding chiral β-amino esters as single stereoisomers in high yield. The structure of (1*S*)-(+)-10-phenylsulfonylisobornyl (*S*)-3-[(2*S*)-(2-methoxycarbonylpyrrolid-1-yl)]butanoate (**28**) was also determined by X-ray crystallography showing that the new chiral center has *S* configuration (Fig. 3).

If the stereochemistry outcome was controlled by the selection of the chiral auxiliary in the ester moiety, the (1*S*)-(+)-10-phenylsulfonylisobornyl unit in β-enamino ester **27** should induce the generation of a chiral center with *R* configuration. In fact, we also observed that β-amino ester **24**, with the (1*R*)-(−)-10-



Scheme 6.

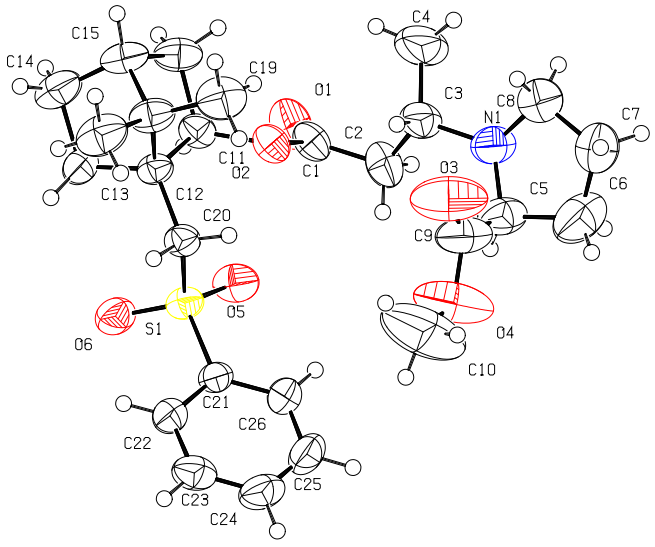


Figure 3. X-ray structure of (1*S*)-(+)-10-phenylsulfonylisobornyl (*S*)-3-[(2*S*)-(2-methoxycarbonylpyrrolid-1-yl)]butanoate (**28**).

phenylsulfonylisobornyl unit, showed opposite value for the optical rotation of the one of β-amino ester **28** indicating that they are indeed enantiomers. Therefore, the new chiral center of β-amino ester **24** has *R* configuration. In a similar way, we conclude that β-amino esters **22** and **26** are enantiomers.

These results show that in the case of β-enamino esters derived from L-proline and D-proline methyl esters the chirality of the α-amino ester influences the stereochemistry of the new chiral center leading to an inversion of the configuration. However, the presence of the α-amino ester moiety does not in itself justify the observed stereoselectivity in the formation of β-amino esters **22**, **24**, **26** and **28**. Therefore, we can conclude that to obtain the exclusive formation of β-amino esters derived from L-Pro and D-Pro methyl esters it is necessary the presence of both chiral auxiliaries, the 10-phenylsulfonylisobornyl unit and the α-amino ester.

3. Conclusion

Herein, we report the synthesis of new chiral β-peptoids building blocks via the reductive amination of chiral allenes with α-amino esters. The Michael addition of L-Ala, D-Ala, L-Phe, L-Leu, L-Trp and D-Trp methyl esters to chiral allenes followed by hydride reduction gave functionalized β-amino esters as single diastereoisomers. The nature of the chiral auxiliary in the ester moiety of the β-enamino esters determines the chirality of the β-amino esters, which are obtained exclusively: (1*R*)-(−)-10-phenylsulfonylisobornyl β-enamino esters gave β-amino esters with *S* configuration whereas the (1*S*)-(+)-10-phenylsulfonylisobornyl β-enamino esters led to β-amino esters with *R* configuration. However, in the reduction of β-enamino esters derived from L-Pro and D-Pro methyl esters, the chirality of the new chiral center is controlled by the α-amino ester moiety, although the presence of the 10-phenylsulfonylisobornyl unit is a requirement to ensure the formation of a single diastereoisomer. Reduction of β-enamino esters derived from L-Pro leads to β-amino esters with *S* configuration, whereas the configuration of the new chiral center of β-amino esters derived from D-Pro is *R*.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on a Bruker Avance III instrument operating at 400 MHz. ^{13}C NMR spectra were recorded on a Bruker Avance III instrument operating at 100 MHz. The solvent is deuteriochloroform except where indicated otherwise. IR spectra were recorded on a Perkin Elmer 1720X FTIR spectrometer. Mass spectra were recorded on a HP GC 6890/MSD5973 instrument under electron impact (EI) except where indicated otherwise. HRMS spectra were recorded on a Finnigan MAT95 S instrument. Optical rotations were measured on an Optical Activity AA-5 electrical polarimeter. Mp were recorded on a Reichert hot stage and are uncorrected. Flash column chromatography was performed with Merck 9385 silica as the stationary phase.

4.2. General procedure for the synthesis of β-enamino esters

The appropriated allene (5 mmol) was dissolved in dry methanol (50 mL) followed by the dropwise addition of the amino ester[15] (5 mmol). The reaction mixture was stirred overnight at room temperature. The solvent was evaporated off and the product crystallized.

4.2.1. Benzyl (Z)-3-[(S)-1-ethoxycarbonylethylamino]but-2-enoate ***7a***. Obtained as an oil (75%); IR (film) 1147, 1263, 1607, 1655 and 1745; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (3H, d, J=6.8 Hz), 1.89 (3H, s), 3.75 (3H, s), 4.15–4.23 (1H, m), 4.61 (1H, s), 5.12 (2H, br s), 7.26–7.35 (5H, m, Ar*H*), 8.75 (1H, br d, J=7.6 Hz, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 19.4, 51.4, 52.5, 64.5, 84.3, 127.7, 127.9, 128.4, 137.3, 160.4, 169.9, 173.2; MS (EI) m/z 277 (M^+, 34%), 218 (43), 186 (24), 143 (25), 110 (38), 91 (100); HRMS (EI) m/z 277.1316 ($C_{15}H_{19}NO_4$ [M^+], 277.1314). $[\alpha]_{20}^{D}$ +130 (c 1, CH_2Cl_2).

4.2.2. Benzyl (Z)-3-[(R)-1-ethoxycarbonylethylamino]but-2-enoate ***9a***. Obtained as an oil (81%); IR (film) 1147, 1263, 1607, 1654 and 1744; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (3H, d, J=7.2 Hz), 1.89 (3H, d, J=0.4 Hz), 3.75 (3H, s), 4.15–4.23 (1H, m), 4.61 (1H, d, J=0.4 Hz), 5.11 (2H, d, J=2.4 Hz), 7.25–7.38 (5H, m, Ar*H*), 8.75 (1H, br d, J=8.4 Hz, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 19.4, 51.4, 52.5, 64.4, 84.3, 127.7, 127.9, 128.4, 137.3, 160.4, 169.9, 173.2; MS (EI) m/z 277 (M^+, 27%), 218 (35), 186 (20), 143 (22), 110 (42), 91 (100), 84 (24); HRMS (EI) m/z 277.1322 ($C_{15}H_{19}NO_4$ [M^+], 277.1314). $[\alpha]_{20}^{D}$ −130 (c 1, CH_2Cl_2).

4.2.3. Benzyl (Z)-3-[(S)-1-ethoxycarbonyl-2-(1H-indol-3-yl)ethylamino]but-2-enoate ***7b***. Obtained as an oil (75%); IR (film) 1167, 1263, 1603, 1649, 1741 and 3414; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65 (3H, s), 3.19 (1H, dd, J_1=8.0 Hz and J_2=14.4 Hz), 3.35 (1H, dd, J_1=4.8 Hz and J_2=14.4 Hz), 3.68 (3H, s), 4.37–4.43 (1H, m), 4.52 (1H, s), 5.09 (1H, d, J=12.8 Hz), 5.13 (1H, d, J=12.4 Hz), 7.07–7.36 (9H, m, Ar*H*), 7.56 (1H, d, J=8.0 Hz, Ar*H*), 8.10 (1H, br s, N*H*), 8.93 (1H, bd, J=9.2 Hz, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 29.8, 52.5, 56.7, 64.4, 84.2, 109.9, 111.3, 118.3, 119.6, 122.2, 123.6, 127.1, 127.7, 127.9, 128.4, 136.1, 137.3, 160.5, 169.9, 172.6; MS (ES) m/z 393 ([MH^+], 100%); HRMS (ES) m/z 393.18088 ($C_{23}H_{25}N_2O_4$ [MH^+], 393.18143). $[\alpha]_{20}^{D}$ −105 (c 1, CH_2Cl_2).

4.2.4. Benzyl (Z)-3-[(R)-1-ethoxycarbonyl-2-(1H-indol-3-yl)ethylamino]but-2-enoate ***9b***. Obtained as an oil (73%); IR (film) 1167, 1263, 1603, 1649, 1741 and 3414; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65 (3H, s), 3.19 (1H, dd, J_1=8.0 Hz and J_2=14.4 Hz), 3.35 (1H, dd, J_1=4.8 Hz and J_2=14.4 Hz), 3.68 (3H, s), 4.37–4.43 (1H, m), 4.52 (1H, s), 5.09 (1H, d, J=12.8 Hz), 5.13 (1H, d, J=12.4 Hz), 7.07–7.36 (9H, m, Ar*H*), 7.56 (1H, d, J=8.0 Hz, Ar*H*), 8.10 (1H, br s, N*H*), 8.93 (1H, br d, J=9.2 Hz, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 29.8, 52.5, 56.7, 64.4, 84.2, 109.9, 111.3, 118.3, 119.6, 122.2, 123.6, 127.1, 127.7, 127.9, 128.4, 136.1, 137.3, 160.5, 169.9, 172.6; MS (ES) m/z 393 (MH^+, 100%); HRMS (ES) m/z 393.18088 ($C_{23}H_{25}N_2O_4$ [MH^+], 393.18143). $[\alpha]_{20}^{D}$ +105 (c 1, CH_2Cl_2).

4.2.5. (1R)-(−)-10-Phenylsulfonylisobornyl (Z)-3-[(1S)-1-methoxycarbonylethylamino]but-2-enoate ***11a***. Obtained as a white solid (69%), mp 51.8–53.1 °C (from ethanol). IR (KBr) 1611, 1655, 1744, 2956 cm^{-1}; ^{1}H NMR δ 0.88 (3H, s), 0.93 (3H, s), 1.14–1.21 (1H, m), 1.48 (3H, d, J=7.0 Hz), 1.56–2.05 (6H, m), 1.89 (3H, s), 3.00 (1H, d, J=14.4 Hz), 3.73 (1H, d, J=14.4 Hz), 3.80 (3H, s), 4.19 (1H, q, J=7.0 Hz), 4.27 (1H, dd, J=3.0 and 7.8 Hz), 4.38 (1H, s), 7.49–7.66 (3H, m, Ar-H), 7.87–7.94 (2H, m, Ar-H), 8.58 (1H, br d, J=8.6 Hz, NH); ^{13}C NMR 19.2, 19.3, 19.9, 20.4, 27.1, 29.4, 39.9, 44.1, 48.8, 49.9, 51.3, 52.5, 55.1, 75.3, 84.6, 127.8, 129.2, 133.5, 140.5, 159.8, 168.6, 173.3; MS (CI) m/z 464 (MH^+, 94), 277 (97), 170 (100); HRMS (CI) m/z 463.2027 ($C_{24}H_{33}NO_6S$ [M^+], 463.2028). $[\alpha]_{20}^{D}$ +85 (c 1, CH_2Cl_2).

4.2.6. (1R)-(−)-10-Phenylsulfonylisobornyl (Z)-3-[(1S)-2-phenyl-1-methoxycarbonylethylamino]but-2-enoate ***11b***. Obtained as an oil (81%). IR (KBr) 1612, 1654, 1746, 2959 cm^{-1}; ^{1}H NMR δ 0.87 (3H, s), 0.93 (3H, s), 1.14–1.21 (1H, m), 1.56–2.05 (6H, m), 1.66 (3H, s), 2.94–3.01 (2H, m), 3.17 (1H, dd, J=5.3 and 13.6 Hz), 3.71 (1H, d, J=14.3 Hz), 3.77 (3H, s), 4.25–4.33 (2H, m), 4.30 (1H, s), 7.19–7.32 (5H, m, Ar-H), 7.43–7.60 (3H, m, Ar-H), 7.85–7.93 (2H, m, Ar-H), 8.75 (1H, br d, J=9.4 Hz, NH); ^{13}C NMR 19.2, 19.9, 20.3, 27.1, 29.3, 39.9, 40.0, 44.1, 48.8, 49.9, 52.4, 55.1, 57.9, 75.3, 84.8, 127.0, 127.8, 128.6, 129.1, 129.3, 133.5, 136.2, 140.5, 159.5, 168.4, 172.0; MS (CI) m/z 540 (MH^+, 82), 277 (37), 246 (100); HRMS (CI) m/z 540.2415 ($C_{30}H_{38}NO_6S$ [MH^+], 540.2419). $[\alpha]_{20}^{D}$ −50 (c 1, CH_2Cl_2).

4.2.7. (1R)-(−)-10-Phenylsulfonylisobornyl (Z)-3-[(1S)-3-methyl-1-methoxycarbonylbutylamino]but-2-enoate ***11c***. Obtained as an oil (86%). IR (KBr) 1613, 1660, 1750, 2964 cm^{-1}; ^{1}H NMR δ 0.84–0.96 (12H, m), 1.14–1.25 (2H, m), 1.54–2.02 (6H, m), 1.88 (3H, s), 3.00 (1H, d, J=14.4 Hz), 3.73 (1H, d, J=14.4 Hz), 3.79 (3H, s), 4.10–4.12 (1H, m), 4.21 (1H, dd, J=3.2 and 7.7 Hz), 4.37 (1H, s), 7.48–7.65 (3H, m, Ar-H), 7.86–7.93 (2H, m, Ar-H), 8.51 (1H, br d, J=8.9 Hz, NH); ^{13}C NMR 19.4, 19.9, 20.4, 21.7, 22.7, 24.5, 27.1, 29.3, 39.9, 41.9, 44.1, 48.8, 49.9, 52.4, 54.3, 55.1, 75.2, 84.6, 127.9, 129.2, 133.6, 140.5, 160.1, 168.5, 173.3; MS (CI) m/z 506 (MH^+, 94), 277 (99), 212 (100); HRMS (CI) m/z 506.2578 ($C_{27}H_{40}NO_6S$ [MH^+], 506.2576). $[\alpha]_{20}^{D}$ +70 (c 1, CH_2Cl_2).

4.2.8. (1R)-(−)-10-Phenylsulfonylisobornyl (Z)-3-[(1S)-2-(1H-indol-3-yl)-1-methoxycarbonylethylamino]but-2-enoate ***11d***. Obtained as an oil (94%). IR (KBr) 1607, 1647, 1740, 2969 cm^{-1}; ^{1}H NMR δ 0.84 (3 h, s), 0.94 (3H, s), 1.14–1.21 (1H, m), 1.63 (3H, s), 1.67–1.99 (6H, m), 2.95 (1H, d, J=13.9 Hz), 3.21 (1H, dd, J=7.7 and 14.4 Hz), 3.34 (1H, dd, J=5.1 and 14.4 Hz), 3.48 (1H, d, J=13.9 Hz), 3.74 (3H, s), 4.26–4.30 (1H, m), 4.29 (1H, s), 4.35–4.45 (1H, m), 4.97–5.01 (1H, m), 7.11–7.20 (3H, m, Ar-H), 7.35–7.66 (5H, m, Ar-H), 7.84–7.94 (2H, m, Ar-H), 8.17 (1H, br s, NH), 8.77 (1H, br d, J=9.2 Hz, NH); ^{13}C NMR 19.3, 19.8, 20.2, 27.1, 29.3, 29.9, 39.4, 44.0, 49.5, 49.9, 52.5, 55.0, 56.6, 75.2, 84.5, 109.9, 111.2, 118.3, 119.6, 122.1, 123.6, 127.0, 127.7, 129.3, 133.6, 136.1, 140.5, 159.8, 168.4, 172.5; MS (CI) m/z 579 (MH^+, 54), 277 (77), 135 (100); HRMS (CI) m/z 579.2644 ($C_{32}H_{39}N_2O_6S$ [MH^+], 579.2654). $[\alpha]_{20}^{D}$ −20 (c 1, CH_2Cl_2).

4.2.9. (1S)-(+)-10-Phenylsulfonylisobornyl (Z)-3-[(1S)-1-methoxycarbonylethylamino]but-2-enoate ***12a***. Obtained as an oil (88%). IR (KBr) 1615, 1661, 1748, 2960 cm^{-1}; ^{1}H NMR δ 0.86 (3H, s), 0.95 (3H, s), 1.14–1.21 (1H, m), 1.56 (3H, d, J=7.1 Hz), 1.56–1.98 (6H, m), 1.90 (3H, s), 2.98 (1H, d, J=14.1 Hz), 3.67 (1H, d, J=14.1 Hz), 3.75 (3H, s), 4.20 (1H, d, J=7.1 Hz), 4.44 (1H, s), 4.58–4.61 (1H, m), 7.46–7.58 (3H, m, Ar-H), 7.89–7.91 (2H, m, Ar-H), 8.69 (1H, br d, J=8.5 Hz, NH); ^{13}C NMR 19.1, 19.2, 19.9, 20.3, 27.1, 29.4, 39.8, 44.0, 49.0, 49.7, 51.2, 52.4, 55.0, 75.5, 84.5, 127.7, 129.0, 133.1, 141.1, 159.7, 168.7, 173.2; MS (CI) m/z 464 (MH^+, 83), 277 (70), 170 (100); HRMS (CI) m/z 463.2025 ($C_{24}H_{33}NO_6S$ [M^+], 463.2028). $[\alpha]_{20}^{D}$ +40 (c 1, CH_2Cl_2).

4.2.10. (1S)-(+)-10-Phenylsulfonylisobornyl (Z)-3-[(1S)-2-phenyl-1-methoxycarbonylethylamino]but-2-enoate ***12b***. Obtained as an oil (80%). IR (KBr) 1611, 1655, 1743, 2960 cm^{-1}; ^{1}H NMR δ 0.86 (3H, s), 0.93 (3H, s), 1.14–1.21 (1H, m), 1.56–2.05 (6H, m), 1.67 (3H, s), 2.93–3.00 (2H, m), 3.21 (1H, dd, J=4.9 and 13.7 Hz), 3.67 (1H, d, J=14.2 Hz), 3.72 (3H, s), 4.29–4.32 (1H, m), 4.31 (1H, s), 4.59 (1H, dd, J=2.8 and 7.7 Hz), 7.24–7.44 (7H, m, Ar-H), 7.57–7.66 (1H, m, Ar-H), 7.85–7.94 (2H, m, Ar-H), 8.81 (1H, br d, J=9.6 Hz, NH); ^{13}C NMR 19.2, 19.9, 20.3, 27.1, 29.4, 39.3, 40.0, 44.0, 49.1, 49.8, 52.4, 55.1, 57.8, 75.6, 84.9, 127.0, 127.6, 128.7, 129.0, 129.2, 133.1, 136.3, 141.1, 159.5, 168.6, 171.9; MS (CI) m/z 540 (MH^+, 82), 277 (95), 246 (100); HRMS (CI) m/z 540.2406 ($C_{30}H_{38}NO_6S$ [MH^+], 540.2419). $[\alpha]_{20}^{D}$ −70 (c 1, CH_2Cl_2).

4.2.11. (1S)-(+)-10-Phenylsulfonylisobornyl (Z)-3-[(1S)-3-methyl-1-methoxycarbonylbutylamino]but-2-enoate ***12c***. Obtained as an oil (70%). IR (KBr) 1612, 1654, 1744, 2957 cm^{-1}; ^{1}H NMR δ 0.86 (3H, s), 0.94 (3H, s), 0.98 and 1.00 (6H, d, J=8.8 Hz), 1.16–1.26 (2H, m), 1.58–1.98 (6H, m), 1.89 (3H, s), 2.99 (1H, d, J=14.1 Hz), 3.70 (1H, d, J=14.1 Hz), 3.73 (3H, s), 4.10–4.16 (1H, m), 4.41 (1H, s), 4.44–4.47 (1H, m), 7.44–7.58 (3H, m, Ar-H), 7.88–7.93 (2H, m, Ar-H), 8.58 (1H,

br d, J=9.8 Hz, NH); ^{13}C NMR 19.4, 19.9, 20.3, 21.6, 22.9, 24.5, 27.2, 29.4, 39.9, 41.8, 44.1, 49.0, 49.9, 52.3, 53.3, 55.0, 75.6, 84.6, 127.7, 129.2, 133.1, 141.1, 160.0, 168.7, 173.3; MS (CI) m/z 506 (MH^+, 72), 277 (100), 212 (89); HRMS (CI) m/z 506.2583 ($C_{27}H_{40}NO_6S$ [MH^+], 506.2576). $[\alpha]_{20}^{D}$ +10 (c 1, CH_2Cl_2).

4.2.12. (1S)-(+)-10-Phenylsulfonylisobornyl (Z)-3-[(1S)-2-(1H-indol-3-yl)-1-methoxycarbonylethylamino]but-2-enoate ***12d***. Obtained as an oil (76%). IR (KBr) 1663, 1741, 2966 cm^{-1}; ^{1}H NMR δ 0.84 (3H, s), 0.94 (3H, s), 1.14–1.21 (1H, m), 1.54 (3H, s), 1.67–1.99 (6H, m), 2.99 (1H, d, J=14.0 Hz), 3.16 (1H, dd, J=9.2 and 14.4 Hz), 3.41 (1H, dd, J=4.2 and 14.4 Hz), 3.63 (1H, d, J=14.0 Hz), 3.73 (3H, s), 4.34 (1H, s), 4.34–4.42 (1H, m), 4.98–5.02 (1H, m), 7.08–7.27 (4H, m, Ar-H), 7.41–7.60 (5H, m, Ar-H), 7.87–7.94 (2H, m, Ar-H), 8.46 (1H, br s, NH), 8.86 (NH, br d, J=9.9 Hz); ^{13}C NMR 19.3, 19.9, 20.3, 27.2, 29.5, 30.1, 39.7, 44.2, 49.5, 49.8, 52.5, 55.2, 56.4, 75.5, 84.7, 108.7, 111.5, 117.8, 119.3, 121.6, 125.3, 127.0, 127.6, 129.2, 133.3, 136.0, 141.5, 160.4, 168.9, 172.3; MS (CI) m/z 579 (MH^+, 100), 277 (87), 135 (93); HRMS (CI) m/z 580.2610 ($C_{32}H_{40}N_2O_6S$ [MH_2^+], 580.2607). $[\alpha]_{20}^{D}$ −90 (c 1, CH_2Cl_2).

4.2.13. (1S)-(+)-10-Phenylsulfonylisobornyl (Z)-3-[(1R)-1-methoxycarbonylethylamino]but-2-enoate ***15a***. Obtained as an oil (80%). IR (film) 1610, 1658, 1745, 2958 cm^{-1}; ^{1}H NMR δ 0.86 (3H, s), 0.93 (3H, s), 1.14–1.21 (1H, m), 1.48 (3H, d, J=7.1 Hz), 1.69–2.05 (7H, m), 1.89 (3H, s), 3.00 (1H, d, J=14.3 Hz), 3.73 (1H, d, J=14.3 Hz), 3.70–3.76 (1H, m), 3.80 (3H, s), 4.17–4.27 (1H, m), 4.39 (1H, s), 7.48–7.66 (3H, m, Ar-H), 7.87–7.94 (2H, m, Ar-H), 8.54 (1H, br d, NH); ^{13}C NMR 19.2, 19.3, 20.0, 20.4, 27.2, 29.4, 40.0, 44.1, 48.9, 49.9, 51.3, 52.5, 55.2, 75.4, 84.6, 127.9, 129.2, 133.5, 140.6, 159.8, 168.6, 173.0; MS (CI) m/z 464 (MH^+, 46), 277 (87), 236 (82), 135 (96); HRMS (CI) m/z 464.2107 ($C_{24}H_{33}NO_6S$ [MH^+], 464.2108). $[\alpha]_{20}^{D}$ −85 (c 1, CH_2Cl_2).

4.2.14. (1S)-(−)-10-Phenylsulfonylisobornyl (Z)-3-[(1R)-2-(1H-indol-3-yl)-1-methoxycarbonylethylamino]but-2-enoate ***15b***. Crystallized as a solid (82%), mp 65.2–67.8 °C (from ethyl acetate–hexane). IR (KBr) 1610, 1653, 1742, 2954 cm^{-1}; ^{1}H NMR δ 0.87 (3H, s), 0.93 (3H, s), 1.14–1.21 (1H, m), 1.69 (3H, s), 1.67–1.99 (6H, m), 2.99 (1H, d, J=14.3 Hz), 3.20 (1H, dd, J=7.6 and 14.4 Hz), 3.33 (1H, dd, J=5.1 and 14.4 Hz), 3.70 (1H, d, J=14.3 Hz), 3.73 (3H, s), 4.28–4.30 (1H, m), 4.29 (1H, bs), 4.31–4.42 (1H, m), 7.09–7.21 (3H, m, Ar-H), 7.34–7.60 (5H, m, Ar-H), 7.84–7.93 (2H, m, Ar-H), 8.26 (1H, br s, J=8.5 Hz NH), 8.78 (1H, br d, J=9.2 Hz, NH); ^{13}C NMR 19.3, 19.9, 20.4, 27.2, 29.3, 29.6, 39.9, 44.1, 48.9, 49.9, 52.4, 55.1, 56.6, 75.2, 84.5, 109.8, 111.3, 118.3, 119.5, 122.1, 123.6, 127.0, 127.8, 129.1, 133.5, 136.1, 140.5, 159.8, 168.5, 172.4; MS (CI) m/z 579 (MH^+, 15), 277 (66), 236 (82), 130 (100); HRMS (CI) m/z 579.2528 ($C_{32}H_{39}N_2O_6S$ [MH^+], 579.2520). $[\alpha]_{20}^{D}$ +20 (c 1, CH_2Cl_2).

4.2.15. (S,Z)-Methyl 1-(4-(benzyloxy)-4-oxobut-2-en-2-yl)pyrrolidine-2-carboxylate ***17***. Obtained as an oil (96%); IR (film) 1122, 1414, 1562, 1679, 1739 and 2949 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.96–2.28 (4H, m), 2.44 (3H, s), 3.36 (bs, 1H), 3.50 (br s, 1H), 3.74 (s, 3H), 4.35 (br s, 1H), 4.59 (br s, 1H), 5.06 (d, 1H, J=12.6 Hz), 5.13 (d, 1H, J=12.6 Hz), 7.25–7.40 (m, 5H, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8, 23.5, 30.8, 48.8, 52.7, 60.7, 64.6, 85.8, 127.8, 128.2, 128.6, 137.9, 159.4, 168.9, 173.3; MS (EI) m/z 303 (M^+, 19%), 244 (100), 212 (46), 196 (26), 169 (57); HRMS (EI) m/z 303.1465 ($C_{17}H_{21}NO_4$ [M^+], 303.1471). $[\alpha]_{20}^{D}$ −80 (c 1, CH_2Cl_2).

4.2.16. (R,Z)-Methyl 1-(4-(benzyloxy)-4-oxobut-2-en-2-yl)pyrrolidine-2-carboxylate ***19***. Obtained as an oil (94%); IR (film) 1124, 1422, 1566, 1681, 1737 and 2951 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.96–2.25 (4H, m), 2.43 (3H, s), 3.35 (br s, 1H), 3.49 (br s, 1H), 3.73 (s, 3H), 4.34 (br s, 1H), 4.59 (br s, 1H), 5.05 (d, 1H, J=12.6 Hz), 5.11 (d, 1H, J=12.6 Hz), 7.25–7.38 (m, 5H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.5, 23.1, 30.5, 48.5, 52.4, 60.4, 64.3, 85.6, 127.5, 127.9, 128.3, 137.6, 159.1, 168.6, 173.0; MS (EI) m/z 303 (M^+, 26%), 244 (82), 212 (100), 196 (24), 167 (45); HRMS (EI) m/z 303.1469 ($C_{17}H_{21}NO_4$ [M^+], 303.1471). $[\alpha]_{20}^{D}$ +80 (c 1, CH_2Cl_2).

4.2.17. (1R)-(−)-10-Phenylsulfonylisobornyl (Z)-3-[(2S)-(2-methoxycarbonylpyrrolid-1-yl)]but-2-enoate ***21***. Obtained as a yellow oil (81%). IR (KBr) 1691, 1742, 1749, 2870 cm^{-1}; ^{1}H NMR δ 0.84 and 0.86 (3H, s), 0.94 and 0.96 (3H,s), 1.14–1.21 (1H, m), 1.69–2.04 (10H, m), 2.98 (1H, d, J=14.1 Hz), 3.14–3.50 (2H, m), 3.71 (1H, d, J=14.1 Hz), 3.77 (3H, s), 4.33–4.38 (2H, m), 7.49–7.61 (3H, m, Ar-H), 7.86–7.88 (2H, m, Ar-H); ^{13}C NMR 16.4, 20.1, 20.4, 23.3, 27.2, 29.5, 31.0, 40.1, 44.1, 48.5, 48.9, 52.5, 55.2, 60.4, 75.5, 86.1, 127.7, 129.1, 133.2, 140.9, 158.4, 167.2, 173.3; MS (ESI) m/z 490 (MH^+, 11), 417 (100), 277 (35); HRMS (CI) m/z 490.2258 ($C_{26}H_{36}NO_6S$ [MH^+], 490.2263). $[\alpha]_{20}^{D}$ +75 (c 1, CH_2Cl_2).

4.2.18. (1R)-(−)-10-Phenylsulfonylisobornyl (Z)-3-[(2R)-(2-methoxycarbonylpyrrolid-1-yl)]but-2-enoate ***23***. Obtained as a white solid (89%), mp 165.0–166.2 °C (from Ethyl Acetate/Hexane); IR (film) 1136, 1567, 1685, 1739 and 2930; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (3H, s), 0.94 (3H, s), 1.11–1.20 (1H, m), 1.55–2.27 (10H, m), 2.33 (3H, s), 3.00 (1H, d, J=14.1 Hz), 3.32 (1H, br s), 3.45 (1H, br s), 3.71 (1H, d, J=14.0 Hz), 3.74 (3H, s), 4.24 (1H, br s), 4.30–4.42 (2H, m), 7.47–7.60 (3H, m, Ar*H*), 7.88–7.91 (2H, m, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.3, 20.0, 20.4, 23.2, 27.2, 29.5, 30.5, 40.0, 44.2, 48.5, 49.0, 49.9, 52.4, 55.4, 60.4, 75.4, 86.2, 127.9, 129.1, 133.3, 141.1, 158.3, 167.1, 173.3; MS (EI) m/z 489 (M^+, 16), 467 (35), 443 (55), 430 (53), 393 (58), 381 (56), 231 (51), 212 (42), 181 (84), 118 (100); HRMS (EI) m/z 489.2191 ($C_{26}H_{35}NO_6S$ [M^+], 489.2185). $[\alpha]_{20}^{D}$ +130 (c 1, CH_2Cl_2).

4.2.19. (1S)-(+)-10-phenylsulfonylisobornyl (Z)-3-[(2R)-(2-methoxycarbonylpyrrolid-1-yl)]but-2-enoate ***25***. Obtained as an oil (78%); IR (film) 1128, 1568, 1682, 1739 and 2955 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, s), 0.96 (3H, s), 1.12–1.20 (1H, m), 1.50–2.33 (10H, m), 2.37 (3H, s), 2.98 (1H, d, J=14.1 Hz), 3.36–3.42 (1H, m), 3.52 (1H, bs), 3.71 (1H, d, J=14.0 Hz), 3.76 (3H, s), 4.31–4.37 (3H, m), 7.46–7.60 (3H, m, Ar*H*), 7.86–7.89 (2H, m, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.6, 20.3, 20.6, 23.5, 27.4, 29.7, 30.8, 40.3, 44.4, 48.8, 49.2, 50.1, 52.7, 55.5, 60.6, 75.8, 86.5, 128.2, 129.3, 133.4, 141.3, 158.7, 167.4, 173.5; MS (EI) m/z 489 (M^+, 12%), 292 (17), 219 (20), 212 (30), 196 (100), 169 (62); HRMS (EI) m/z 489.2188 ($C_{26}H_{35}NO_6S$ [M^+], 489.2185). $[\alpha]_{20}^{D}$ −73 (c 1, CH_2Cl_2).

4.2.20. (1S)-(+)-10-phenylsulfonylisobornyl (Z)-3-[(2S)-(2-methoxycarbonylpyrrolid-1-yl)]but-2-enoate ***27***. Obtained as a white solid (85%), mp 125.3–126.9 °C (from ethanol). IR (KBr) 1686, 1740, 1747, 2865 cm^{-1}; ^{1}H NMR δ 0.87 (3H, s), 0.94 (3H, s), 1.14–1.25 (1H, m), 1.56–2.31 (10H, m), 2.34 (3H, s), 3.01 (1H, d, J=14.3 Hz), 3.34–3.50 (2H, m), 3.74 (1H, d, J=14.3 Hz), 3.76 (3H, s), 4.31 (1H, s), 4.36–4.41 (2H, m), 7.48–7.59 (3H, m, Ar-H), 7.89–7.92 (2H, m, Ar-H); ^{13}C NMR 16.3, 19.9, 20.4, 23.2, 27.1, 29.5, 30.5, 39.9, 44.1, 48.4, 48.9, 49.8, 52.4, 55.3, 60.3, 75.3, 86.1, 127.8, 129.1, 133.2, 141.0, 158.3, 167.1, 173.2; MS (CI) m/z 490 (MH^+, 88), 277 (50), 196 (100); HRMS (CI) m/z 490.2266 ($C_{26}H_{36}NO_6S$ [MH^+], 490.2263). $[\alpha]_{20}^{D}$ −130 (c 1, CH_2Cl_2).

4.3. General procedure for the reduction of β-enamino esters[9]

A solution of $NaBH(OAc)_3$ was prepared by adding $NaBH_4$ (0.34 g, 9.0 mmol) in glacial acetic acid (5 mL) while keeping the temperature between 10 and 20 °C. After the H_2 evolution ceased (1 h), acetonitrile (5 mL) was added and the solution was cooled to 0 °C. The β-enamino ester (3.0 mmol) was added in one portion and the reaction stirred for 4 h at 0 °C. The acetic acid and acetonitrile were evaporated off and the residue dissolved in CH_2Cl_2 and the combined organic layers were washed with saturated aqueous

solution of Na_2CO_3 and dried over magnesium sulfate affording the β-amino ester after removal of the solvent.

4.3.1. Benzyl 3-[(S)-1-ethoxycarbonylethylamino]butanoate ***8a***. Mixture of diastereoisomers (57:43) was obtained as an oil (89%); IR (film) 1169, 1456, 1735 and 2974; ^{1}H NMR (400 MHz, $CDCl_3$) Major component: δ 1.08 (3H, d, *J*=6.0 Hz), 1.27 (3H, d, *J*=6.8 Hz), 2.33–2.52 (2H, m), 3.07–3.12 (1H, m), 3.39–3.49 (1H, m), 3.69 (3H, s), 5.13 (2H, s), 7.27–7.35 (5H, m, Ar*H*); Minor Component: δ 1.11 (3H, d, *J*=6.4 Hz), 1.23 (3H, d, *J*=6.8 Hz), 2.33–2.52 (2H, m), 3.07–3.12 (1H, m), 3.39–3.49 (1H, m), 3.70 (3H, s), 5.12 (2H, s), 7.27–7.35 (5H, m, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) Major Component: δ 19.6, 20.2, 42.2, 48.3, 51.8, 53.6, 66.3, 128.2, 128.3, 128.6, 135.9, 171.7, 176.1; Minor Component: δ 19.5, 21.2, 41.8, 49.1, 51.9, 54.4, 128.2, 128.3, 128.6, 135.9, 171.9, 176.5; MS (ES) *m*/*z* 280 (MH^+, 100%); HRMS (ES) *m*/*z* 280.15433 ($C_{15}H_{22}NO_4$ [MH^+], 280.15488). $[\alpha]_{20}^{D}$ −35 (*c* 1, CH_2Cl_2).

4.3.2. Benzyl 3-[(R)-1-ethoxycarbonylethylamino]butanoate ***10a***. Mixture of diastereoisomers (56:44) obtained as an oil (96%); IR (film) 1169, 1455, 1735 and 2974; ^{1}H NMR (400 MHz, $CDCl_3$) Major component: δ 1.08 (3H, d, *J*=6.4 Hz), 1.28 (3H, d, *J*=6.8 Hz), 2.33–2.52 (2H, m), 3.05–3.14 (1H, m), 3.39–3.49 (1H, m), 3.69 (3H, s), 5.13 (2H, s), 7.27–7.35 (5H, m, Ar*H*); Minor Component: δ 1.11 (3H, d, *J*=6.4 Hz), 1.23 (3H, d, *J*=6.8 Hz), 2.33–2.52 (2H, m), 3.05–3.14 (1H, m), 3.39–3.49 (1H, m), 3.70 (3H, s), 5.12 (2H, s), 7.27–7.35 (5H, m, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) Major Component: δ 19.6, 20.2, 42.2, 48.3, 51.8, 53.6, 66.3, 128.2, 128.3, 128.6, 135.9, 171.7, 176.1; Minor Component: δ 19.5, 21.2, 41.8, 49.1, 51.9, 54.4, 128.2, 128.3, 128.6, 135.9, 171.9, 176.5; MS (ES) *m*/*z* 280 (MH^+, 100%), 213 (3), 197 (14); HRMS (ES) *m*/*z* 280.15433 ($C_{15}H_{22}NO_4$ [MH^+], 280.15488). $[\alpha]_{20}^{D}$ +15 (*c* 1, CH_2Cl_2).

4.3.3. Benzyl 3-[(S)-1-ethoxycarbonyl-2-(1H-indol-3-yl)ethylamino]-butanoate ***8b***. Mixture of diastereoisomers (66:34) obtained as a white solid (78%), mp 45.2–46.6 °C (from ethyl acetate/hexane); IR (KBr) 743, 1209, 1455, 1728, 2963 and 3280; ^{1}H NMR (400 MHz, $CDCl_3$) Major component: δ 1.01 (3H, d, *J*=6.0 Hz), 2.38–2.48 (2H, m), 3.01–3.16 (2H, m), 3.58 (3H, s), 3.73 (1H, t, *J*=6.4 Hz), 5.07 (2H, s), 7.02–7.33 (10H, m), 7.58 (1H, t, *J*=7.6 Hz, N*H*), 8.01 (1H, s, N*H*); Minor Component: δ 1.08 (3H, d, *J*=6.0 Hz), 2.27–2.35 (2H, m), 3.01–3.16 (2H, m), 3.60 (3H, s), 3.68 (1H, t, *J*=6.4 Hz), 4.96 (1H, d, *J*=12.4 Hz), 5.02 (1H, d, *J*=12.4 Hz), 7.02–7.33 (10H, m, Ar*H*), 7.58 (1H, t, *J*=7.6 Hz, N*H*), 8.01 (1H, s, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$) Major Component: δ 20.0, 29.6, 42.3, 48.6, 51.7, 59.2, 66.2, 111.1, 111.3, 118.7, 119.4, 122.1, 122.8, 128.2, 128.3, 128.5, 136.1, 171.7, 175.4; Minor Component: δ 21.3, 29.5, 41.6, 49.5, 51.8, 60.0, 66.1, 111.2, 111.3, 118.7, 119.4, 122.0, 122.9, 127.5, 128.3, 135.9, 171.8, 175.8; MS MS (ES) *m*/*z* 395 (MH^+, 100%); HRMS (ES) *m*/*z* 395.19653 ($C_{23}H_{27}N_2O_4$ [MH^+], 395.19708). $[\alpha]_{20}^{D}$ −5 (*c* 1, CH_2Cl_2).

4.3.4. Benzyl 3-[(R)-1-ethoxycarbonyl-2-(1H-indol-3-yl)ethylamino]-butanoate ***10b***. Mixture of diastereoisomers (66:34) obtained as a white solid (78%), mp 45.0–46.8 °C (from ethyl acetate/hexane); IR (KBr) 743, 1209, 1455, 1728, 2963 and 3280; ^{1}H NMR (400 MHz, $CDCl_3$) Major component: δ 1.01 (3H, d, *J*=6.4 Hz), 2.38–2.48 (2H, m), 3.01–3.16 (2H, m), 3.58 (3H, s), 3.73 (1H, t, *J*=6.8 Hz), 5.08 (2H, s), 7.03 (1H, br s, Ar*H*), 7.08–7.12 (1H, m, Ar*H*), 7.28–7.37 (8H, m, Ar*H*), 7.58 (1H, t, *J*=7.6 Hz, N*H*), 7.97 (1H, bs, N*H*); Minor Component: δ 1.09 (3H, d, *J*=6.4 Hz), 2.27–2.35 (2H, m), 3.01–3.16 (2H, m), 3.60 (3H, s), 3.68 (1H, t, *J*=6.8 Hz), 4.96 (1H, d, *J*=12.0 Hz), 5.02 (1H, d, *J*=12.4 Hz), 7.03 (1H, br s, Ar*H*), 7.16–7.19 (1H, m, Ar*H*), 7.28–7.37 (8H, m, Ar*H*), 7.58 (1H, t, *J*=7.6 Hz, N*H*), 7.97 (1H, s, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$) Major Component: δ 20.0, 29.7, 42.3, 48.6, 51.7, 59.2, 66.2, 111.1, 111.4, 118.8, 119.5, 122.1, 122.7, 128.2, 128.5, 136.2, 171.7, 175.4; Minor Component: δ 21.3, 29.6, 41.7, 49.6, 51.8, 60.0, 66.1, 111.3, 111.4, 118.8, 119.4, 122.1, 122.8, 127.5, 128.3, 128.5, 136.0, 171.8, 175.8; MS (ES) *m*/*z* 395 (MH^+, 100%), 213 (6), 197 (18); HRMS (ES) *m*/*z* 395.19653 ($C_{23}H_{27}N_2O_4$ [MH^+], 395.19708). $[\alpha]_{20}^{D}$ −5 (*c* 1, CH_2Cl_2).

4.3.5. (1R)-(−)-10-Phenylsulfonylisobornyl (S)-3-[(1S)-1-methoxy carbonylethylamino]butanoate ***13a***. Obtained as a white solid (88%), mp 84.3–85.6 °C (from ethanol). IR (film) 1447, 1732, 2967 cm^{-1}; ^{1}H NMR δ 0.85 (3H, s), 0.96 (3H, s), 1.12 (3H, d, *J*=6.3 Hz) and 1.13 (3H, d, *J*=6.3 Hz), 1.14–1.21 (1H, m), 1.28 and 1.29 (3H, d, *J*=4.3 Hz), 1.56–1.97 (6H, m), 2.18–2.48 (2H, m), 2.97 and 2.98 (1H, d, *J*=14.0 Hz), 3.00–3.10 (1H, m), 3.43–3.56 (2H, m), 3.71 and 3.72 (3H, s), 4.88–4.91 (1H, m), 7.56–7.66 (3H, m, Ar-H), 7.89–7.94 (2H, m, Ar-H); ^{13}C NMR 19.5, 19.9, 20.3, 21.1, 27.1, 29.8, 39.6, 41.9, 44.0, 48.1, 49.3, 49.9, 51.9, 54.4, 55.0, 77.8, 127.7, 129.3, 133.5, 141.3, 170.5, 176.5; MS (CI) *m*/*z* 466 (MH^+, 100), 406 (89), 277 (75), 190 (90); HRMS (CI) *m*/*z* 466.2251 ($C_{24}H_{36}NO_6S$ [MH^+], 466.2263). $[\alpha]_{20}^{D}$ +20 (*c* 1, CH_2Cl_2).

4.3.6. (1R)-(−)-10-Phenylsulfonylisobornyl (S)-3-[(1S)-2-phenyl-1-methoxycarbonylethylamino]butanoate ***13b***. Obtained as an oil (98%). IR (film) 1447, 1734, 2956 cm^{-1}; ^{1}H NMR δ 0.85 (3H, s), 0.94 and 0.95 (3H, s), 1.05 and 1.10 (3H, d, *J*=6.3 Hz), 1.14–1.21 (1H, m), 1.56–2.07 (7H, m), 2.08–2.18 (2H, m), 2.89–2.95 (3H, m), 3.00–3.06 (1H, m), 3.47–3.65 (2H, m), 3.60 and 3.62 (3H, s), 4.85–4.88 (1H, m), 7.15–7.31 (5H, m, Ar-H), 7.52–7.67 (3H, m, Ar-H), 7.88–7.92 (2H, m, Ar-H); ^{13}C NMR 19.9, 20.0, 20.3, 21.2, 27.1, 29.8, 39.6, 40.0, 42.4, 44.0, 48.4, 49.3, 49.9, 51.7, 55.1, 60.4, 77.8, 126.7, 127.7, 128.4, 129.1, 129.3, 133.5, 137.2, 141.3, 170.4, 174.8; MS (CI) *m*/*z* 542 (MH^+, 100), 450 (37), 277 (76), 135 (71); HRMS (CI) *m*/*z* 542.2575 ($C_{30}H_{40}NO_6S$ [MH^+], 542.2576). $[\alpha]_{20}^{D}$ +35 (*c* 1, CH_2Cl_2).

4.3.7. (1R)-(−)-10-Phenylsulfonylisobornyl (S)-3-[(1S)-3-methyl-1-methoxycarbonylbutylamino]butanoate ***13c***. Obtained as an oil (93%). IR (film) 1447, 1733, 2957 cm^{-1}; ^{1}H NMR δ 0.85–0.96 (12H, m), 1.10 and 1.11 (3H, d *J*=6.3 Hz), 1.14–1.21 (1H, m), 1.26–1.98 (7H, m), 2.05–2.43 (2H, m), 2.96–3.04 (2H, m), 3.30–3.42 (1H, m), 3.51 and 3.54 (1H, d, *J*=14.0 Hz), 3.70 and 3.71 (3H, s), 4.86–4.90 (1H, m), 7.57–7.65 (3H, m, Ar-H), 7.89–7.93 (2H, m, Ar-H); ^{13}C NMR 19.9, 20.0, 20.3, 22.4, 22.7, 24.8, 27.1, 29.8, 39.6, 41.9, 43.1, 44.0, 48.3, 49.3, 49.9, 51.7, 55.1, 77.7, 127.7, 129.3, 133.5, 141.3, 170.5, 176.2; MS (CI) *m*/*z* 508 (MH^+, 100), 448 (98), 277 (94), 135 (83); HRMS (CI) *m*/*z* 508.2735 ($C_{27}H_{42}NO_6S$ [MH^+], 508.2733). $[\alpha]_{20}^{D}$ +30 (*c* 1, CH_2Cl_2).

4.3.8. (1R)-(−)-10-Phenylsulfonylisobornyl (S)-3-[(1S)-2-(1H-indol-3-yl)-1-methoxycarbonylethylamino]butanoate ***13d***. Obtained as an oil (75%). IR (film) 1479, 1732, 2956 cm^{-1}; ^{1}H NMR δ 0.84 (3H, s), 0.90 and 0.92 (3H, s), 1.05 and 1.10 (3H, d, *J*=6.3 Hz), 1.14–1.21 (1H, m), 1.56–1.96 (7H, m), 2.08–2.27 (1H, m), 2.33–2.40 (1H, m), 2.96 (1H, d, *J*=14.0 Hz), 3.03–3.19 (3H, m), 3.49 and 3.51 (1H, d, *J*=14.0 Hz), 3.60 and 3.61 (3H, s), 3.68–3.76 (1H, m), 4.82–4.87 (1H, m), 7.06–7.20 (3H, m, Ar-H), 7.33–7.36 (1H, m, Ar-H), 7.47–7.65 (4H, m, Ar-H), 7.87–7.90 (2H, m, Ar-H), 8.06 and 8.13 (1H, br s, NH); ^{13}C NMR 19.9, 20.3, 21.2, 27.1, 29.6, 29.8, 30.9, 39.6, 41.9, 44.0, 49.3, 49.9, 51.8, 55.1, 59.3, 60.0, 77.8, 111.0, 111.2, 118.7, 119.4, 122.0, 122.7, 123.1, 127.4, 127.6, 133.5, 136.1, 141.3, 170.4, 175.3; MS (CI) *m*/*z* 581 (MH^+, 100), 450 (46), 277 (81), 135 (71); HRMS (CI) *m*/*z* 581.2687 ($C_{32}H_{41}N_2O_6S$ [MH^+], 581.2685). $[\alpha]_{20}^{D}$ +40 (*c* 1, CH_2Cl_2).

4.3.9. (1S)-(+)-10-phenylsulfonylisobornyl (R)-3-[(1S)-1-methoxy-carbonylethylamino]butanoate ***14a***. Obtained as an oil (88%). IR (film) 1448, 1733, 2960 cm^{-1}; ^{1}H NMR δ 0.85 (3H, s), 0.96 (3H, s), 1.10 (3H, d, *J*=6.3 Hz) and 1.14 (3H, d, *J*=6.3 Hz), 1.14–1.21 (1H, m), 1.27 and 1.29 (3H, d, *J*=6.9 Hz), 1.61–2.05 (6H, m), 2.22–2.42 (2H, m), 2.97 (1H, d, *J*=14.0 Hz), 3.06–3.10 (1H, m), 3.42–3.57 (2H, m), 3.71 (3H, s), 4.86–4.89 (1H, m), 7.54–7.67 (3H, m, Ar-H), 7.89–7.94 (2H, m, Ar-H); ^{13}C NMR 19.5, 19.9, 20.3, 21.1, 27.1, 29.8, 39.6, 42.3, 44.0, 48.0, 49.3, 49.9, 51.8, 53.5, 55.1, 77.8, 127.7, 129.3, 133.5, 141.3, 170.3, 176.1; MS (CI) *m*/*z* 466 (MH^+, 63), 277 (92), 135 (100); HRMS

(CI) *m*/*z* 465.2140 ($C_{24}H_{35}NO_6S$ [M^+], 465.2162). $[\alpha]_{20}^{D}$ −30 (*c* 1 CH_2Cl_2).

4.3.10. (1S)-(+)-10-Phenylsulfonylisobornyl (R)-3-[(1S)-2-phenyl-1-methoxycarbonylethylamino]butanoate ***14b***. Obtained as an oil (95%). IR (film) IR (film) 1447, 1733, 2961 cm^{-1}; ^1H NMR δ 0.85 (3H, s), 0.94 (3H, s), 1.03 and 1.11 (3H, d, *J*=6.3 Hz), 1.14–1.21 (1H, m), 1.56–2.05 (7H, m), 2.23 (1H, dd, *J*=6.4 Hz and 15.1 Hz), 2.37 (1H, dd, *J*=6.7 Hz and 15.1 Hz), 2.88–2.95 (3H, m), 2.99–3.08 (1H, m), 3.48–3.66 (4H, m), 4.84–4.88 (1H, m), 7.16–7.27 (5H, m, Ar-H), 7.53–7.64 (3H, m, Ar-H), 7.90–7.92 (2H, m, Ar-H); ^{13}C NMR 19.8, 19.9, 20.2, 27.1, 29.8, 30.9, 39.6, 40.0, 42.4, 44.0, 48.3, 49.3, 49.9, 51.6, 55.1, 60.2, 77.8, 126.6, 127.7, 128.3, 129.1, 129.2, 133.5, 137.2, 141.3, 170.3, 174.9; MS (CI) *m*/*z* 542 (MH^+, 86), 450 (63), 277 (86), 135 (100); HRMS (CI) *m*/*z* 541.2453 ($C_{30}H_{39}NO_6S$ [MH^+], 541.2454). $[\alpha]_{20}^{D}$ −45 (*c* 1, CH_2Cl_2).

4.3.11. (1S)-(+)-10-Phenylsulfonylisobornyl (R)-3-[(1S)-3-methyl-1-methoxycarbonylbutylamino]butanoate ***14c***. Obtained as an oil (95%). IR (film) 1446, 1731, 2960 cm^{-1}; ^1H NMR δ 0.85–0.97 (12H, m), 1.08 and 1.11 (3H, d *J*=6.3 Hz), 1.14–1.21 (1H, m), 1.40–1.46 (1H, m), 1.56–1.96 (6H, m), 1.98–2.36 (2H, m), 2.95–3.03 (2H, m), 3.33–3.42 (1H, m), 3.50–3.57 (1H, m), 3.70 (3H, s), 4.82–4.89 (1H, m), 7.57–7.65 (3H, m, Ar-H), 7.91–7.94 (2H, m, Ar-H); ^{13}C NMR 19.8, 19.9, 20.3, 22.2, 22.7, 24.8, 27.1, 29.8, 39.6, 42.6, 43.0, 44.0, 48.2, 49.3, 49.9, 51.6, 55.1, 77.8, 127.7, 129.3, 133.5, 141.3, 170.3, 176.3; MS (CI) *m*/*z* 508 (MH^+, 100), 448 (15), 277 (19), 135 (16); HRMS (CI) *m*/*z* 508.2744 ($C_{27}H_{42}NO_6S$ [MH^+], 508.2733). $[\alpha]_{20}^{D}$ −30 (*c* 1, CH_2Cl_2).

4.3.12. (1S)-(+)-10-Phenylsulfonylisobornyl (R)-3-[(1S)-2-(1H-indol-3-yl)-1-methoxycarbonylethylamino]butanoate ***14d***. Obtained as an oil (95%). IR (film) 1448, 1456, 1730, 2958 cm^{-1}; ^1H NMR δ 0.83 and 0.84 (3H, s), 0.88 and 0.92 (3H, s), 1.04 and 1.10 (3H, d, *J*=6.3 Hz), 1.19–1.24 (1H, m), 1.61–1.96 (7H, m), 2.24 (1H, dd, *J*=6.7 and 15.1 Hz), 2.39 (1H, dd, *J*=6.7 and 15.1 Hz), 2.96 (1H, d, *J*=14.0 Hz), 3.05–3.14 (3H, m), 3.51 (1H, d, *J*=14.0 Hz), 3.59 (3H, s), 3.75 (1H, approx. t, *J*=6.7 Hz), 4.83–4.87 (1H, m), 7.07–7.20 (3H, m, Ar-H), 7.33–7.37 (1H, m, Ar-H), 7.50–7.64 (4H, m, Ar-H), 7.85–7.91 (2H, m, Ar-H), 8.09 (1H, br s, NH);^{13}C NMR 19.8, 19.9, 21.1, 27.1, 29.5, 29.8, 39.6, 42.4, 44.0, 48.3, 49.3, 49.9, 51.7, 55.1, 59.1, 77.8, 111.1, 111.2, 118.7, 119.3, 122.0, 122.8, 127.4, 127.7, 129.3, 133.5, 136.1, 141.2, 170.4, 175.3; MS (CI) *m*/*z* 581 (MH^+, 100), 450 (71), 277 (69), 135 (80); HRMS (CI) *m*/*z* 581.2680 ($C_{32}H_{41}N_2O_6S$ [MH^+], 581.2685). $[\alpha]_{20}^{D}$ −45 (*c* 1, CH_2Cl_2).

4.3.13. (1S)-(+)-10-phenylsulfonylisobornyl (R)-3-[(1R)-1-methoxycarbonylethylamino]butanoate ***16a***. Prepared from the reduction of **15a** and was obtained as an oil (74%). IR (film) 1652, 1443, 1731, 2959 cm^{-1}; ^1H NMR δ 0.85 (3H, s), 0.96 (3H, s), 1.04 (3H, d, *J*=6.0 Hz), 1.14–1.21 (1H, m), 1.17 (3H, d, *J*=6.8 Hz), 1.57–2.05 (6H, m), 2.18–2.43 (2H, m), 2.97 (1H, d, *J*=13.9 Hz), 3.00–3.10 (1H, m), 3.43–3.56 (2H, m), 3.63 (3H, s), 4.88–4.91 (1H, m), 7.55–7.66 (3H, m, Ar-H), 7.89–7.94 (2H, m, Ar-H); ^{13}C NMR 19.5, 19.9, 20.2, 21.1, 27.1, 29.8, 39.6, 41.9, 42.3, 44.0, 48.1, 49.3, 49.8, 51.9, 53.6, 54.4, 55.0, 77.9, 127.7, 129.2, 133.5, 141.3, 170.5, 176.5; MS (CI) *m*/*z* 466 (MH^+, 55), 277 (87), 277 (46), 135 (82), 111 (100); HRMS (CI) *m*/*z* 466.2263 ($C_{24}H_{33}NO_6S$ [MH^+], 466.2267). $[\alpha]_{20}^{D}$ −20 (*c* 1, CH_2Cl_2).

4.3.14. (1S)-(+)-10-Phenylsulfonylisobornyl (R)-3-[(1R)-2-(1H-indol-3-yl)-1-methoxycarbonylethylamino]butanoate ***16b***. Prepared from the reduction of **15b** and was obtained as an oil (84%). IR (film) 1447, 1457, 1732, 2958 cm^{-1}; ^1H NMR δ 0.84 (3H, s), 0.90 and 0.92 (3H, s), 1.05 and 1.10 (3H, d, *J*=6.3 Hz), 1.17–1.25 (1H, m), 1.57–1.90 (6H, m), 2.25–2.35 (2H, m), 2.96 (1H, d, *J*=14.0 Hz), 3.05–3.14 (3H, m), 3.49 and 3.51 (1H, d, *J*=14.0 Hz), 3.60 (3H, s), 3.68–3.74 (1H, m), 4.82–4.87 (1H, m), 7.05–7.18 (3H, m, Ar-H), 7.33–7.36 (1H, m), 7.47–7.62 (4H, m), 7.87–7.90 (2H, m), 8.15 (1H, br d, NH); ^{13}C NMR 19.9, 20.3, 21.2, 27.1, 29.5, 29.9, 39.6, 42.4, 44.0, 48.6, 49.3, 49.9, 51.8, 55.1, 59.4, 77.8, 111.0, 111.2, 118.7, 119.4, 122.0, 128.8, 127.4, 129.3, 133.6, 136.2, 141.3, 170.5, 175.8; MS (CI) *m*/*z* 581 (MH^+, 40), 305 (42), 277 (35), 111 (100); HRMS (CI) *m*/*z* 581.2685 ($C_{32}H_{41}N_2O_6S$ [MH^+], 581.2673). $[\alpha]_{20}^{D}$ −40 (*c* 1, CH_2Cl_2).

4.3.15. Methyl 1-[(S)-4-(benzyloxy)-4-oxobutan-2-yl]pyrrolidine-2-carboxylate ***18***. Mixture of diastereoisomers (70:30) was obtained as an oil (86%); IR (film) 1166, 1195, 1727 and 2949 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *Major component*: δ 1.12 (3H, d, *J*=6.6 Hz), 1.69–2.07 (4H, m), 2.26–2.39 (1H, m), 2.55–2.68 (2H, m), 3.02–3.10 (1H, m), 3.26–3.48 (2H, m), 3.67 (3H, s), 5.04–5.18 (2H, m), 7.27–7.35 (5H, m, Ar*H*); Minor Component: δ 1.05 (3H, d, *J*=6.3 Hz), 1.69–2.07 (4H, m), 2.26–2.39 (1H, m), 2.56–2.68 (2H, m), 2.96–3.10 (1H, m), 3.26–3.48 (2H, m), 3.66 (3H, s), 5.04–5.18 (2H, m), 7.27–7.35 (5H, m, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) Major Component: δ 18.5, 23.9, 30.4, 38.8, 49.2, 52.1, 53.2, 61.9, 66.5, 128.3, 128.4, 128.4, 128.7, 136.2, 172.3, 175.7; Minor Component: δ 15.7, 24.1, 30.2, 40.7, 48.0, 52.8, 62.0, 66.4, 128.3, 128.4, 128.4, 128.7, 136.3, 172.2, 175.6; MS (EI) *m*/*z* 305 (M^+, 1%), 246 (100), 156 (31); HRMS (EI) *m*/*z* 305.1632 ($C_{17}H_{23}NO_4$ [M^+], 305.1627). $[\alpha]_{20}^{D}$ −40 (*c* 1, CH_2Cl_2).

4.3.16. Methyl 1-[(R)-4-(benzyloxy)-4-oxobutan-2-yl]pyrrolidine-2-carboxylate ***20***. Mixture of diastereoisomers (71:29) was obtained as an oil (78%); IR (film) 1163, 1192, 1727 and 2952 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) Major component: δ 1.12 (3H, d, *J*=6.6 Hz), 1.83–2.07 (4H, m), 2.26–2.40 (1H, m), 2.56–2.68 (2H, m), 3.03–3.10 (1H, m), 3.26–3.40 (1H, m), 3.44–3.48 (1H, m), 3.67 (3H, s), 5.0–5.19 (2H, m), 7.27–7.37 (5H, m, Ar*H*); Minor Component: δ 1.05 (3H, d, *J*=6.3 Hz), 1.69–1.81 (4H, m), 2.26–2.40 (1H, m), 2.56–2.68 (2H, m), 2.97–3.02 (1H, m), 3.26–3.40 (1H, m), 3.44–3.48 (1H, m), 3.66 (3H, s), 5.05–5.18 (2H, m), 7.27–7.57 (5H, m, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) Major Component: δ 18.5, 23.9, 30.3, 38.9, 49.1, 52.0, 53.2, 61.9, 66.4, 128.3, 128.3, 128.4, 128.5, 128.7, 136.2, 172.3, 175.7; Minor Component: δ 15.7, 24.1, 30.1, 40.7, 47.9, 51.9, 52.8, 62.0, 66.3, 128.3, 128.3, 128.4, 128.5, 128.7, 136.3, 172.1, 175.6; MS (EI) *m*/*z* 305 (M^+, 1%), 247 (16), 246 (100), 156 (10); HRMS (EI) *m*/*z* 305.1628 ($C_{17}H_{23}NO_4$ [M^+], 305.1627). $[\alpha]_{20}^{D}$ +43 (*c* 1, CH_2Cl_2).

4.3.17. (1R)-(−)-10-Phenylsulfonylisobornyl (S)-3-[(2S)-(2-methoxycarbonylpyrrolid-1-yl)]butanoate ***22***. Obtained as an oil (91%). IR (film) 1147, 1447, 1334, 2955 cm^{-1}; ^1H NMR δ 0.85 (3H, s), 0.95 and 0.96 (3H, s), 1.10 and 1.15 (3H, d, *J*=6.3 Hz), 1.14–1.21 (1H, m), 1.60–2.23 (11H, m), 2.57–2.63 (2H, m), 2.98 (1H, d, *J*=14.0 Hz), 3.01–3.27 (2H, m), 3.45–3.54 (2H, m), 3.69 (3H, s), 4.87–4.91 (1H, m), 7.57–7.64 (3H, m, Ar-H), 7.89–7.92 (2H, m, Ar-H); ^{13}C NMR 18.2, 19.8, 20.2, 23.7, 27.1, 29.8, 30.1, 39.1, 39.6, 44.0, 49.2, 49.4, 49.8, 51.8, 53.5, 55.0, 61.7, 77.9, 127.6, 129.2, 133.5, 141.3, 170.6, 175.5; MS (CI) *m*/*z* 492 (MH^+, 96), 432 (47), 277 (84), 156 (100); HRMS (CI) *m*/*z* 492.2419 ($C_{26}H_{38}NO_6S$ [MH^+], 492.2411). $[\alpha]_{20}^{D}$ +20 (*c* 1, CH_2Cl_2).

4.3.18. (1R)-(−)-10-Phenylsulfonylisobornyl (R)-3-[(2R)-(2-methoxycarbonylpyrrolid-1-yl)]butanoate ***24***. Obtained as a white solid (90%), mp 94.3–95.5 °C (from Ethyl Acetate/Hexane); IR (film) 1138, 1312, 1720 and 2958; ^1H NMR (400 MHz, $CDCl_3$) δ 0.82 (3H, s), 0.91 and 0.93 (3H, s), 1.07 and 1.15 (3H, d, *J*=6.8 Hz), 1.55–2.07 (11H, m), 2.13–2.23 (1H, m), 2.52–2.58 (2H, m), 2.95 (1H, d, *J*=14.0 Hz), 3.05–3.12 (1H, m), 3.19–3.29 (1H, m), 3.40–3.51 (2H, m), 3.67 (3H, s), 4.78–4.81 and 4.84–4.87 (1H, m), 7.52–7.57 (2H, m, Ar*H*), 7.60–7.64 (1H, m, Ar*H*), 7.84–7.86 (2H, m, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6, 19.9, 20.3, 23.6, 27.1, 29.8, 30.1, 38.7, 39.5, 44.0, 49.0, 49.3, 49.8, 51.8, 52.9, 55.0, 61.9, 127.6, 129.2, 133.5, 141.4, 170.7, 175.4; MS

(EI) *m*/*z* 491 (M^+, 1%), 432 (100); HRMS (EI) *m*/*z* 491.2341 ($C_{26}H_{37}NO_6S$ [M^+], 491.2342). $[\alpha]_{20}^{D}$ +65 (*c* 1, CH_2Cl_2).

4.3.19. (1S)-(+)-10-Phenylsulfonylisobornyl (R)-3-[(2R)-(2-methoxycarbonylpyrrolid-1-yl)]butanoate ***26***. Obtained as a white solid (95%), mp 98.4–99.8 °C (from Ethyl Acetate/Hexane); IR (film) 1136, 1301, 1716, 1740 and 2963; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (3H, s), 0.89 and 0.91 (3H, s), 1.04 and 1.10 (3H, d, *J*=6.5 Hz), 1.13–1.20 (1H, m), 1.53–2.06 (10H, m), 2.11–2.18 (1H, m), 2.43–2.60 (2H, m), 2.93 (1H, d, *J*=14.0 Hz), 3.04–3.09 (1H, m), 3.18–3.28 (1H, m), 3.36–3.45 (2H, m), 3.48 (3H, s), 4.75–4.77 and 4.80–4.83 (1H, m), 7.50–7.62 (3H, m, Ar*H*), 7.84–7.86 (2H, m, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2, 19.8, 20.2, 23.7, 27.0, 29.7, 30.1, 39.1, 39.6, 43.9, 49.2, 49.8, 51.8, 53.4, 54.9, 61.6, 127.5, 129.2, 133.5, 141.3, 170.5, 175.5; MS (EI) *m*/*z* 491 (M^+, 2%), 432 (100), 156 (19), 135 (14); HRMS (EI) *m*/*z* 491.2340 ($C_{26}H_{37}NO_6S$ [M^+], 491.2342). $[\alpha]_{20}^{D}$ −14 (*c* 1, CH_2Cl_2).

4.3.20. (1S)-(+)-10-Phenylsulfonylisobornyl (S)-3-[(2S)-(2-methoxycarbonylpyrrolid-1-yl)]butanoate ***28***. Obtained as a white solid (96%), mp 98.4–100.2 °C (from ethanol). IR (KBr) 1160, 1317, 1727, 2960 cm^{-1}; ^{1}H NMR δ 0.85 (3H, s), 0.95 and 0.96 (3H, s), 1.10 and 1.18 (3H, d, *J*=6.5 Hz), 1.14–1.21 (1H, m), 1.56–2.27 (11H, m), 2.57–2.62 (2H, m), 2.98 (1H, d, *J*=14.0 Hz), 3.01–3.14 (1H, m), 3.20–3.30 (1H, m), 3.46 (1H, dd, *J*=4.5 and 9.0 Hz), 3.52 and 3.53 (1H, d, *J*=14.0 Hz), 3.70 (3H, s), 4.82 and 4.89 (1H, dd, *J*=3.0 and 8.0 Hz), 7.54–7.65 (3H, m, Ar-H), 7.89–7.93 (2H, m, Ar-H); ^{13}C NMR 18.6, 19.9, 20.3, 23.6, 27.1, 29.8, 30.1, 38.7, 39.5, 44.0, 49.1, 49.3, 49.9, 51.9, 53.0, 55.0, 62.0, 77.7, 127.6, 129.2, 133.5, 141.3, 170.7, 175.5; MS (CI) *m*/*z* 492 (MH^+, 99), 432 (100), 277 (57), 156 (99); HRMS (CI) *m*/*z* 492.2416 ($C_{26}H_{38}NO_6S$ [MH^+], 492.2419). $[\alpha]_{20}^{D}$ −66 (*c* 1, CH_2Cl_2).

4.4. Crystal data for (1*R*)-(−)-10-phenylsulfonylisobornyl (*S*)-3-[(1*S*)-1-methoxycarbonylethylamino]butanoate 13a

The X-ray data were collected on a Bruker Apex II single crystal diffractometer at room temperature. The structure of this compound was determined using a transparent thin rectangular plate single crystal with dimensions 0.24×0.12×0.05 mm ($P2_12_12_1$) with unit cell, *a*=8.0876(4) Å, *b*=17.3058(12) Å, *c*=17.6137(12) Å and *V*=2465.2(3) $Å^3$. It contains four molecules/unit cell. r_{calcd}=1.254 g cm^{-3}, *m*=0.169 mm^{-1}. MoK_α radiation was used (0.71073 Å). A total of 2479 reflections with $I>2\sigma(I)$ were used. *R*=0.0479.

4.5. Crystal data for (1*S*)-(+)-10-phenylsulfonylisobornyl (*R*)-3-[(2*R*)-(2-methoxycarbonylpyrrolid-1-yl)]butanoate 28

The X-ray data were collected on a Bruker Apex II single crystal diffractometer at room temperature. The structure of this compound was determined using a transparent thin rectangular plate single crystal with dimensions 0.20×0.10×0.03 mm ($P2_1$) with unit cell, *a*=7.9904(3) Å, *b*=12.0055(5) Å, *c*=13.9100(5) Å, β=98.177(2) and *V*=1320.8(9) $Å^3$. It contains two molecules/unit cell. r_{calcd}=1.171 g cm^{-3}, *m*=0.158 mm^{-1}. MoK_α radiation was used (0.71073 Å). A total of 3329 reflections with $I>2\sigma(I)$ were used. *R*=0.0531.

4.6. Crystal data for (1*S*)-(+)-10-Phenylsulfonylisobornyl (*R*)-3-[(1*R*)-1-methoxycarbonylethylamino]butanoate 16a

The X-ray data were collected on an Enraf-nonius Mach-3 single crystal diffractometer, at 298(3) K, using graphite-monochromated Cu K_α radiation (λ=1.5418 Å). Intensities were recorded as full profiles of ω–θ scans. The structures were solved by direct methods as implemented in SHELXS97[a] and refined by full-matrix least-squares using SHELXL97[a].[16]

$C_{24}H_{35}NO_6S$, *M*=465.59, orthorhombic, $P2_12_12_1$ with unit cell, *a*=8.0614(17) Å, *b*=17.596(3) Å, *c*=17.318(2) Å, $\alpha=\beta=\gamma=90°$, *V*=2456.5(7) $Å^3$. It contains four molecules/unit cell. ρ_{calcd}=1.256 g cm^{-3}, *Z*=4, μ=1.489 mm^{-1}. *R* ($I>2\sigma(I)$)=0.0358 and R_w=0.0732 for 2042 independent reflections. H atoms were placed at calculated positions and refined as riding on their parent atoms. The Flack parameter refined to 0.0(2).[17]

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 739375–739377. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336 033 or e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgements

Thanks are due to FCT (Project: PTDC/QUI/64470/2006; Grants: SFRH/BPD/34569/2007 and SFRH/BD/45128/2008) as well as the Departamento de Educación, Universidades e Investigación del Gobierno Vasco (GV, IT-277/07 and UPV, GIU 06/51), the Dirección General de Investigación del Ministerio de Ciencia y Tecnología (MCYT, Madrid DGI, CTQ2006-09323) and FEDER for financial support. We acknowledge the Nuclear Magnetic Resonance Laboratory of the Coimbra Chemical Centre (www.nmrccc.uc.pt), University of Coimbra for obtaining the NMR data.

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