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Silver acetate-catalysed asymmetric 1,3-dipolar cycloadditions of imines and chiral acrylamides

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Abstract—*N*-Metallated azomethine ylides were generated by the reaction of arylidene glycine imines with AgOAc and triethylamine. These azomethine ylides undergo cycloaddition to chiral acrylamides with excellent diastereoselectivity. The configuration of two of the cycloadducts was confirmed by X-ray crystallography.

1. Introduction

1,3-Dipolar cycloadditions are very important tools for the construction of five membered heterocycles.[1] The ease of generation of 1,3-dipoles, coupled with the highly regio-, and stereoselective nature of their cycloaddition reactions, has resulted in a number of syntheses which utilize such a reaction as a key step.[2] One of the major challenges now for 1,3-dipolar cycloadditions is the preparation of optically active compounds.[3]

The proline structure is present in many compounds with interesting biological features. The most direct strategy for the synthesis of functionalized proline derivatives is the 1,3-dipolar cycloaddition reaction of in situ generated carboxy-stabilized azomethine ylide and a dipolarophile. The asymmetric version of this reaction allows the synthesis of enantiomerically enriched prolines with the simultaneous creation of up to four stereochemically defined centers. Chiral acrylate esters and amides, have been widely evaluated as chirality sources in asymmetric Diels–Alder reactions.[4] In contrast fewer examples of chiral inductions in the 1,3-dipolar cycloadditions of azomethine ylides have been reported. To date, most attention has been devoted to the use of chiral esters (mainly menthyl-esters,[5] or those with a chiral controller at the β-position[6]), chiral α,β-unsaturated ketones,[7] and bicyclic lactams,[8] with use of *N*-acryloyl-(*S*)-proline esters as the only chiral alkenes.[9] Thus, the wide range of easily available and cheap chiral amines[10] and amino acids still remained unexplored as chiral auxiliaries in cycloadditions reactions. In this paper[11] we demonstrate the utilization of these chiral elements in the 1,3-dipolar cycloadditions of azomethine ylides to acrylamides.

2. Results and discussion

Starting from the corresponding amines,[12] acrylamides **2a**,[13] **2b**,[14] **2c**,[15] **2d**,[12b] were prepared by simple acylation with acryloyl chloride in dichloromethane in the presence of triethylamine. The acrylamide **2e** was prepared by the modification of a literature procedure[16] since, in this case, the simple acylation of ephedrine (**1**) with acryloyl chloride, led to a mixture of the *N*-acylated **2e** and *N*,*O*-diacylated product (**2f**). When acrylic acid was activated by ethyl chloroformate, however, the secondary nitrogen of the intermediate was acylated selectively, to give **2e** as a single product (Scheme 1).

These alkenes were then reacted with azomethine ylides, derived from arylidene glycine imines **3** in the presence of AgOAc and triethylamine at room temperature, employing

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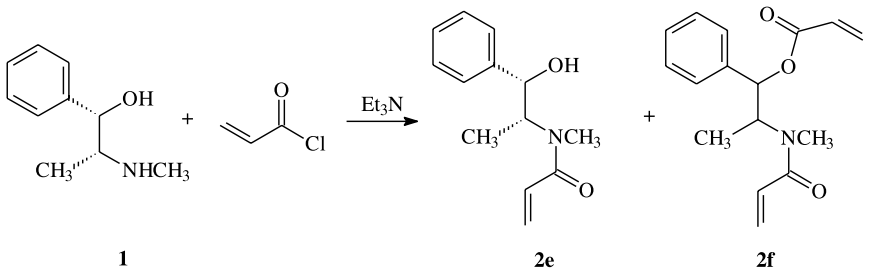
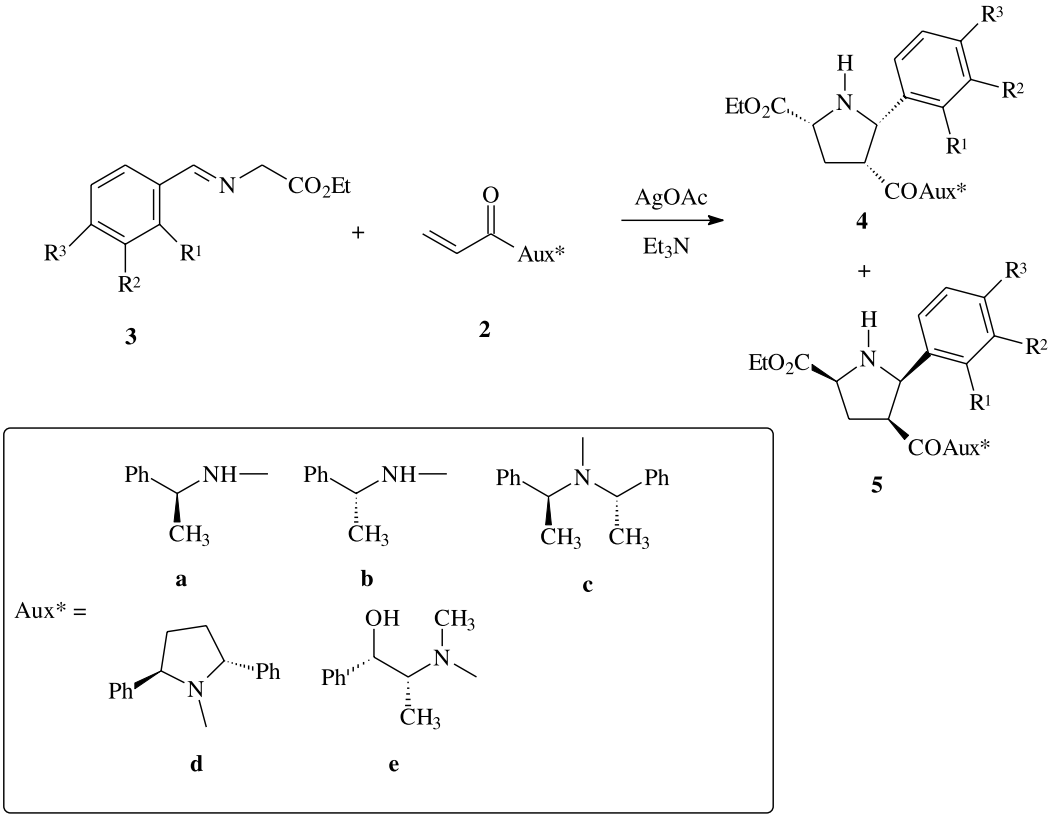


1 2e 2f

Scheme 1.



3 2 4 5 a b c d e

Scheme 2.

dry toluene as the solvent (Scheme 2). In accordance with previous results,[5a] this metallo-azomethine ylide cycloaddition exhibited regio- and stereospecific formation of the expected *syn-endo* cycloadducts, but the diastereoselectivities and yields varied depending upon the nature of the chiral auxillary and the substituents on the aryl group (Table 1).

The acrylamides **2a** and **2b**, derived from the corresponding α-phenylethylamine reacted only with moderate diastereoselectivity (entry 1–4), but in most cases both pyrrolidine isomers were readily obtained, in pure form, from these cycloadduct mixtures after repeated recrystallisations. The chiral dipolarophile **2c** based on (*R*,*R*)-*bis*-α-phenylethylamine as the chiral auxillary also resulted in the formation of diastereoisomeric mixtures. In contrast, the cyclic C_2-symmetric pyrrolidine derivative **2d** (R=H) showed complete diastereoselectivity in all cases.

The most promising results were achieved using (1*R*,2*S*)-(−)-ephedrine as the chiral element: the corresponding alkene **2e** gave, in most of the cycloadditions studied, a single diastereoisomer in good yield.

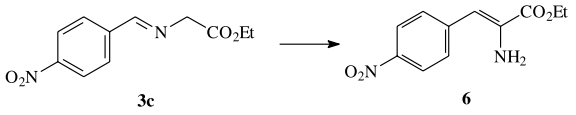
In the case of imine **3c** in all cases, depending on the reaction time a small amount of didehydroaminoacid **6** was always isolated from the reaction mixture. The formation of this compound has been observed and explained in our earlier papers (Scheme 3).[17]

The relative configuration of the cycloadducts of series **4** and **5** were determined by NOE studies of representative examples. The all-*cis* configuration of these pyrrolidines in all cases has been confirmed by the observed NOE effects between H-2 and H-5 (2–4%) and H-5 and H-4 (3–6%). The absolute configuration of two cycloadducts (**4a$_1$** and **4c$_1$**) has been established by X-ray crystallography. To compare

Table 1. Synthesis of pyrrolidines **3** and **4** from acrylamides **2** and glycine imines **1**

Entry	Acrylamide	Imine	R^1	R^2	R^3	Products	Reaction time	Yield (%)	Ratio (**4**:**5**)
1	**2a**	**3a**	H	H	H	**4a$_1$**, **5a$_1$**	48 h	77[a]	1.8:1
2	**2b**	**3a**	H	H	H	**4b$_1$**, **5b$_1$**	48 h	74[a]	1:1.8
3	**2b**	**3b**	Cl	H	Cl	**4b$_2$**, **5b$_2$**	36 h	70[a]	1:1.5
4	**2b**	**3c**	H	H	NO_2	**4b$_3$**, **5b$_3$**	24 h	82[a]	1:1
5	**2b**	**3d**	H	MeO	MeO	**4b$_4$**, **5b$_4$**	24 h	71[a]	1:1.2
6	**2c**	**3a**	H	H	H	**4c$_1$**, **5c$_1$**	36 h	65[a]	1:1
7	**2c**	**3b**	Cl	H	Cl	**4c$_2$**, **5c$_2$**	80 h	51[a]	1:2
8	**2c**	**3c**	H	H	NO_2	**4c$_3$**, **5c$_3$**	24 h	67[a]	1:1.7
9	**2d**	**3a**	H	H	H	**4d$_1$**, **5d$_1$**	24 h	78[b]	1:0
10	**2d**	**3b**	Cl	H	Cl	**4d$_2$**, **5d$_2$**	48 h	66[a]	1:0
11	**2d**	**3c**	H	H	NO_2	**4d$_3$**, **5d$_3$**	24 h	85[b]	1:0
12	**2e**	**3a**	H	H	H	**4e$_1$**, **5e$_1$**	24 h	76[b]	1:0
13	**2e**	**3b**	Cl	H	Cl	**4e$_2$**, **5e$_2$**	48 h	57[b]	10:1
14	**2e**	**3e**	H	H	MeO	**4e$_3$**, **5e$_3$**	24 h	75[b]	1:0
15	**2e**	**3d**	H	MeO	MeO	**4e$_4$**, **5e$_4$**	24 h	81[b]	1:0

[a] Isolated yield after flash chromatography.
[b] Isolated yield after recrystallisation.

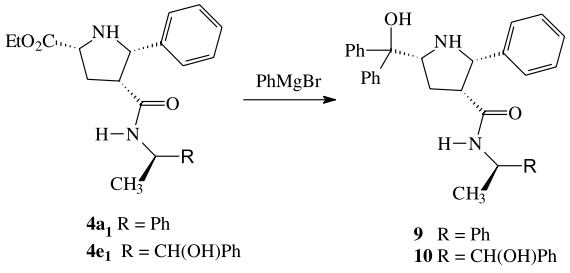


Scheme 3.

the configurations of the other products to those of these configurations, the cycloadducts were hydrolysed to the diacids **6** by ethanolic hydrochloric acid and re-esterified by the means of thionyl chloride in dry EtOH. The diesters **7** were then purified by chromatography and the optical rotations were compared (Scheme 4).

In an earlier attempt for the comparison of the absolute stereochemistry of the resulted cycloadducts, the reaction of **4a$_1$** and **4e$_1$** with PhLi and PhMgBr was attempted. To our surprise in spite of the large excess of organometallic reagents (PhMgCl or PhLi) the amide functions remained intact and in both cases, only transformation of the carbethoxy functionality was observed (Scheme 5).

In summary, *N*-metallated azomethine ylides were generated by the reaction of arylidene glycine imines **3** with AgOAc and triethylamine. These azomethine ylides undergo cycloaddition to chiral acrylamides **2** to give chiral pyrrolidines, **4** and **5**, with excellent diastereoselectivity. Single diastereoisomers were obtained from the reaction of the ylides with the dipolarophiles **2d** and **2e** (Figs. 1 and 2).



Scheme 5.

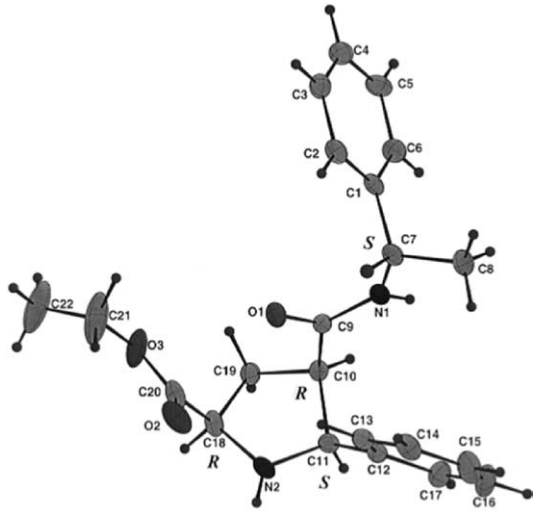
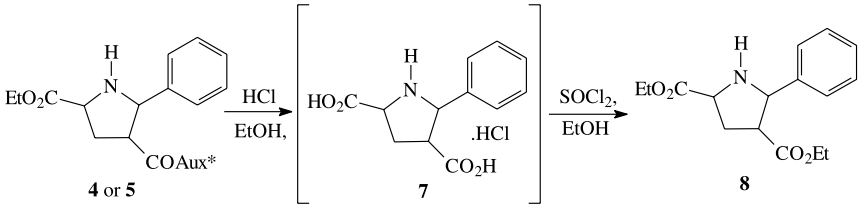


Figure 1. Crystal structure of **4a$_1$**.



Scheme 4.

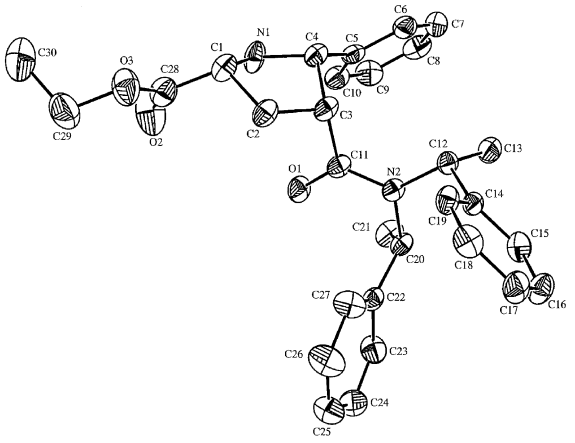


Figure 2. Crystal structure of $\mathbf{4c_1}$.

3. Experimental

3.1. General

Melting points were determined on a Gallenkamp apparatus and are uncorrected. Elemental analyses were performed on a Perkin–Elmer 240 °C or Carlo Erba 1106 Elemental Analyser. IR spectra were recorded on a Perkin–Elmer 1600 series FTIR or Unicam research series FTIR spectrophotometer using sodium chloride plates. ^{1}H NMR spectra were acquired on a Jeol GSX 270 FT NMR at 270 MHz. Coupling constants are given in Hz and all chemical shifts are relative to an internal standard of tetramethylsilane. ^{13}C NMR spectra were obtained on a Jeol GFX 270 FT NMR (68 MHz) spectrometer. Low resolution electron impact mass spectra were obtained on a Trio 2000 VG. High resolution spectra were obtained on a VG ZAB-E spectrometer (E.P.S.R.C. Mass Spectrometry Service Centre, Swansea). Thin layer chromatography was performed on Merck silica gel $60F_{254}$. All solvents were purified according to standard procedures.

3.1.1. *S*-(*R,*R**)]-(−)-*N*,*N*-Bis-(1-phenyl-ethyl)-acrylamide (2c).** [*S*-(*R**,*R**)]-(−)-*bis*-(α-Phenyl-ethyl)-amine (0.50 g, 1.90 mM) has been dissolved in dry CH_2Cl_2 (10 mL) and at 0 °C triethylamine (0.70 mL, 5 mmol) was added. After 5 min acroyl chloride (0.25 g, 0.23 mL, 2.8 mM) was added dropwise. After 12 h stirring at room temperature the mixture was washed with saturated sodium hydrocarbonate solution (2×5 mL), water (5 mL), brine (5 mL) and dried over magnesium sulfate. The evaporation yielded a colourless oil (0.49 g, 92%); $[\alpha]_D^{23} = +213$ (*c* 1, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): 7.2 (m, 10H, Ph), 6.28 (dd, 1H, *J*=2.6, 16.5 Hz, CH_2=), 6.11 (dd, 1H, *J*=9.9, 16.5 Hz, CH_2=), 5.97 (br s, 1H, CH), 5.40 (dd, 1H, *J*=2.6, 9.9 Hz, CH=), 4.98 (br s, 1H, CH), 1.74 (br d, 6H, *J*=6.6 Hz, 2×CH_3), ^{13}C NMR: 166.7 (C=O), 141.1 (CH), 130.6 (2×q), 128.3 (overlapping CHs), 127.6 (overlapping CHs), 126.7 (overlapping CHs), 55.2 (CH), 20 (broad, CH_3); IR (film, cm^{-1}): 3058, 3037, 2976, 2936, 1642, 1601, 1428, 1303, 1246, 1204, 1163, 1086, 1059; CIMS (*m*/*z*, rel intensity %): 280 (M^{+1}, 3), 174 (83), 120 (51), 105 (100), 55 (49); HRMS: Calcd: 279.1623 for $C_{19}H_{21}NO$; Found: 279.1628.

3.1.2. (*R*,*R*)-2,5-Diphenyl-1-acroyl-pyrrolidine (2d, R=H). (*R*,*R*)-2,5-Diphenyl-pyrrolidine (0.30 g, 1.35 mmol) has been dissolved in dry CH_2Cl_2 (10 mL) and at 0 °C triethylamine (0.28 mL, 2 mmol) was added. After 5 min acroyl chloride (0.24 g, 0.22 mL, 2.7 mM) was added dropwise. After 12 h stirring at room temperature the mixture was washed with saturated sodium hydrocarbonate solution (2×5 mL), water (5 mL), brine (5 mL) and dried over magnesium sulfate. The evaporation of the solvent followed by flash chromatography has yielded the product as a white solid (0.35 g, 93%). Mp 111–2 °C; $[\alpha]_D^{23} = +106$ (*c* 0.83, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): 7.20–6.85 (m, 10H, Ph), 6.00 (m, 2H, CH=), 5.35 (d, 1H, *J*=7.9 Hz, CH=), 5.17 (t, 2H, *J*=9.9 Hz, C*H*-Ph), 2.34 (m, 1H, CH_2), 2.13 (m, 1H, CH_2), 1.56 (m, 2H, CH_2); ^{13}C NMR: 165.0, 143.7, 142.8, 128.8 (3×C), 128.4 (2×C), 128.0, 127.4, 126.7, 125.4 (2×CH), 125.3 (2×CH), 62.2, 62.1, 33.1, 30.3; IR (KBr, cm^{-1}): 3061, 2986, 2929, 1651, 1609, 1391, 1306, 1074; CIMS (*m*/*z*, rel intensity %): 278 (M^{+1}, 100), 146 (10), 73 (10); HRMS: Calcd: 277.1467 for $C_{19}H_{19}NO$; Found: 277.1470.

3.1.3. (1*R*,2*S*)-*N*-(2-Hydroxy-1-methyl-2-phenyl-ethyl)-*N*-methyl-acrylamide (2e) and (1*R*,2*S*)-*N*-(2-acroyloxy-1-methyl-2-phenyl-ethyl)-*N*-methyl-acrylamide (2f). *Method A*. (−)-Ephedrine hydrochloride (4.0 g, 20 mmol) was suspended in dry dichlormethane (50 mL) and triethylamine (4.22 g, 5.8 mL) was added in one portion. After 10 min stirring the mixture was cooled down to 0 °C and acryloyl chloride (2.64 g, 2.81 mL, 21 mM) was added dropwise. The reaction mixture was allowed to warm up to room temperature and it was stirred for 5 h. Then it was washed with water (25 mL), saturated $NaHCO_3$ solution (25 mL), brine (25 mL), dried over magnesium sulfate and evaporated to yield an oil which is a mixture of **2e** and **2f**. These products were separated by column chromatography (eluent: petrolether–ethyl acetate 1:1) to yield **2e** (1.38 g, 31.5%), and **2f** (2.18 g, 40%).

Method B. Acrylic acid (6.30 g, 6.0 mL, 87.5 mM) was dissolved in dry CH_2Cl_2 (30 mL) and triethylamine (8.8 g, 12.5 mL) was added. The mixture was cooled down to 0 °C and methyl chlorofomate (9.5 g, 8.4 mL) was added dropwise. After an hour stirring at 0 °C this mixture was slowly transferred to a flask containing (−)-ephedrine hydrochloride (8.0 g, 39.8 mM) and triethylamine (5.7 mL) in dry CH_2Cl_2 (50 mL). The reaction mixture was stirred at room temperature overnight and then washed with 2% aqueous NaOH (40 mL), water (30 mL) and brine (30 mL). The organic phase was dried over magnesium sulfate, evaporated to yield a yellow oil which was purified by flash chromatography to yield the product (**2e** only) as a colourless oil (7.67 g, 88%).

Compound **2e**. Colourless oil; $[\alpha]_D^{23} = -162$ (*c* 2.4, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): 7.37–7.21 (m, 5H, Ph), 6.48 (dd, 1H, *J*=10.5, 16.5 Hz,=CH_2-trans), 6.29 (dd, 1H, *J*=2.6, 16.5 Hz, CH=), 5.88 (dd, 1H, *J*=2.6, 10.5 Hz,=CH_2-*cis*), 4.88 (d, 1H, *J*=3.3 Hz, H-2), 4.50 (dq, 1H, *J*=3.3, 7.3 Hz, H-1), 2.79 (s, 3H, NMe), 1.20 (d, 1H, *J*=7.3 Hz, CH_3); ^{13}C NMR: 168.0 (C=O), 141.8 (Ph-1′C), 128.2 and 128.1 (overlapping, 4×CH), 127.4 (CH), 126.2 (2×CH), 76.5 (C-2), 58.1 (NMe), 33.1 (C-1), 11.7 (CH_3); IR (film,

cm^{-1}): 3386 (br, OH), 3035, 2982, 2942, 1639, 1588, 1480, 1450, 1412, 1334, 1275, 1250, 1125, 1042; CIMS (*m/z*, rel intensity %): 220 (M^{+1}, 38), 202 (base peak), 148 (17), 112 (12); HRMS: Calcd: 219.1259 for $C_{13}H_{17}NO_2$; Found: 219.1257.

Compound **2f**. Colourless oil; $[\alpha]_D^{23}=-198$ (*c* 2.0, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): 7.40–7.26 (m, 5H, Ph), 6.51–5.70 (m, 7H), 5.60 (dd, 1H, *J*=2, 10 Hz), 5.12 (m, 1H, CH), 2.90 (s, 3H, NMe), 1.25 (d, 3H, *J*=7 Hz, CH_3); ^{13}C NMR: 166.7, 165.0, 137.7, 131.7, 131.3, 128.6, 128.3, 128.1, 127.8, 126.7, 56.5, 52.5, 30.8, 12.8; IR (film, cm^{-1}): 3480, 3034, 2904, 2910, 1726, 1646, 1611, 1478, 1437, 1412, 1266, 1187, 1046, 979; CIMS (*m/z*, rel intensity %): 274 (M^{+1},18), 230 (10), 202 (base peak), 148 (10), 112 (22); HRMS: Calcd: 273.1365 for $C_{16}H_{19}NO_3$; Found: 273.1360.

3.2. AgOAc catalysed cycloaddition reactions—general procedure

A mixture of imine (1.2 equiv) AgOAc (1.5 equiv), appropriate dipolarophile (1 equiv) and Et_3N (1.1 equiv) in dry toluene (5 mL for 1 mmol of imine) protected from the light with aluminium was stirred at room temperature for 12–48 h. The reaction was then quenched by addition of saturated aqueous ammonium chloride solution and ether. The mixture was filtered through a pad of Celite. The organic layer was separated, washed with water, brine and dried over magnesium sulfate, filtered and the solvent evaporated. The residue was purified by flash chromatography and/or recrystallisation to afford the cycloadducts.

3.2.1. Ethyl,5-phenyl-4-[(1′-phenylethyl)carbamoyl]-pyrrolidine-2-carboxylate ($4a_1$ and $5b_1$). Colourless crystals; ^{1}H NMR (270 MHz, $CDCl_3$): 7.27–7.15 (m, 8H, Ph), 6.95—6.92 (m, 2H, Ph), 6.58 (broad d, 1H, *J*=7.3 Hz, N*H*CO), 4.71 (m, 1H, CH_3CH), 4.41 (d, 1H, *J*=5.9 Hz, H-5), 4.27 (dq, 2H, OCH_2), 3.98 (dd, 1H, *J*=6.0, 9.9 Hz, H-2), 3.06 (ddd, 1H, *J*=2.6, 5.9, 6.6 Hz, H-4), 2.76 (broad s, 1H, NH), 2.60 (ddd, 1H, *J*=6.6, 9.9, 13.9 Hz, H_2-3), 2.38 (ddd, 1H, *J*=2.6, 6.0, 13.9 Hz, H_2-3), 1.32 (t, 3H, *J*=7.3 Hz, Me), 1.11 (d, 1H, *J*=7.3 Hz, Me); ^{13}C NMR: 173.5 (C=O), 171.7 (C=O), 143.2 (Ph-1′C), 138.2 (Ph-1′C), 128.4 (4×CH), 127.3 (CH), 128.8 (CH), 126.4 (2×CH), 126.2 (2×CH), 65.1, 61.1, 58.1, 50.0, 48.3, 33.8, 21.3, 14.2; CIMS (*m/z*, rel intensity %): 367 (M^+, base peak), 293 (12), 246 (8), 105 (10); IR (nujol, cm^{-1}): 3322, 1737, 1648, 1526, 1214, 1059, 1009.

(*R*,*R*,*R*,*S*)-**$4a_1$**. Mp 145–6 °C; $[\alpha]_D^{23}=-100$ (*c* 1.0, $CHCl_3$) HRMS: Calcd: 366.1943 for $C_{22}H_{26}N_2O_3$; Found: 366.1933.

(*S*,*S*,*S*,*R*)-**$5b_1$**: Mp 143–4 °C; $[\alpha]_D^{23}=+100$ (*c* 1.0, $CHCl_3$); HRMS: Calcd: 366.1943 for $C_{22}H_{26}N_2O_3$; Found: 366.2074.

3.2.2. (*R*,*R*,*R*,*R*)-Ethyl,5-phenyl-4-[(1′-phenylethyl)carbamoyl]-pyrrolidine-2-carboxylate ($4b_1$). White powder; mp 151–2 °C; $[\alpha]_D^{23}=+130$ (*c* 1.7, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): 7.39—7.17 (m, 8H, Ph), 7.04 (dd, 2H, *J*=1.4, 7.5 Hz, Ph), 6.81 (broad d, 1H, *J*=7.9 Hz, N*H*CO), 4.71 (m, 1H, CH_3CH), 4.45 (d, 1H, *J*=6.6 Hz, H-5), 4.15 (q, *J*=7.3 Hz, 2H, OCH_2), 3.99 (dd, 1H, *J*=6.6, 9.9 Hz, H-2), 3.10 (ddd, 1H, *J*=3.3, 5.9, 6.6 Hz, H-4), 2.76 (broad s, 1H, NH), 2.61 (ddd, 1H, *J*=6.6, 9.9, 13.9 Hz, H_2-3), 2.29 (ddd, 1H, *J*=3.3, 6.6, 13.9 Hz, H_2-3), 1.32 (t, 3H, *J*=7.3 Hz, Me), 1.11 (d, 1H, *J*=7.3 Hz, Me); ^{13}C NMR: 173.4 (C=O), 171.9 (C=O), 143.5 (Ph-1′C), 138.3 (Ph-1′C), 127.4 (4×CH), 126.8 (CH), 126.4 (CH), 126.2 (2×CH), 126.1 (2×CH), 64.7, 61.1, 58.0, 49.9, 48.1, 33.5, 21.5, 14.1; CIMS (*m/z*, rel intensity %): 367 (M^+, base peak), 293 (19), 105 (20); IR (nujol, cm^{-1}): 3332, 1738, 1648, 1527, 1214, 1059, 1011; HRMS: Calcd: 366.1943 for $C_{22}H_{26}N_2O_3$; Found: 366.2015.

3.2.3. (*S*,*S*,*S*,*R*)-Ethyl,5-(2,4-dichlorophenyl)-4-[(1′-phenylethyl)carbamoyl]-pyrrolidine-2-carboxylate ($5b_2$). White powder; mp 171–2 °C; $[\alpha]_D^{23}=+116$ (*c* 1.2, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): 7.51 (d, 1H, *J*=7.9 Hz, Ar), 7.33–7.12 (m, 5H, Ar), 6.93 (dd, 1H, *J*=1.8, 7.9 Hz, Ar), 6.42 (d, 1H, *J*=7.9 Hz, Ar), 4.73 (m, 1H, C*H*CH_3), 4.57 (d, 1H, *J*=6.0 Hz, H-5), 4.29 (q, 2H, *J*=7.3 Hz, OCH_2), 3.96 (dd, 1H, *J*=6.1, 9.5 Hz, H-2), 3.35 (ddd, 1H, *J*=3.2, 6.0, 6.7 Hz, H-4), 2.70 (br s, 1H, NH), 2.53 (ddd, 1H, *J*=6.7, 9.5, 13.8 Hz, H_2-3), 2.35 (ddd, 1H, *J*=3.2, 6.1, 13.8 Hz, H_2-3), 1.29 (t, 3H, *J*=7.3 Hz, Me), 1.08 (d, 3H, *J*=8.6 Hz, Me); ^{13}C NMR: 173.4 (C=O), 170.9 (C=O), 143.0 (q), 134.5 (q), 133.8 (q), 133.3 (q), 129.1 (2×CH), 128.6 (2×CH), 127.6 (CH), 127.6 (CH), 126.4 (CH), 125.9 (CH), 62.6, 61.2, 58.1, 47.3, 33.6, 21.0, 14.2; IR (nujol, cm^{-1}): 3306, 1734, 1644, 1527, 1213, 1123, 1090, 1050, 1019; CIMS (*m/z*, rel intensity %): 477 (M^+, 4), 463 (12), 435 (base peak), 401 (15), 361 (14), 262 (17), 140 (20), 105 (34); HRMS: Calcd: 434.1164 for $C_{22}H_{24}Cl_2N_2O_3$; Found: 434.1152.

3.2.4. (*R*,*R*,*R*,*R*)-Ethyl,5-(2,4-dichlorophenyl)-4-[(1′-phenylethyl)carbamoyl]-pyrrolidine-2-carboxylate ($4b_2$). White powder; mp 162–3 °C; $[\alpha]_D^{23}=+78$ (*c* 0.8, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): 7.52 (d, 1H, *J*=7.9 Hz, Ar), 7.37–7.10 (m, 5H, Ar), 6.94 (dd, 1H, *J*=1.9, 7.9 Hz, Ar), 6.27 (d, 1H, *J*=7.9 Hz, Ar), 4.73 (quintet, 1H, C*H*CH_3), 4.52 (d, 1H, *J*=6.0 Hz, H-5), 4.31 (q, 2H, *J*=7.3 Hz, OCH_2), 3.98 (dd, 1H, *J*=6.5, 9.8 Hz, H-2), 3.31 (ddd, 1H, *J*=3.2, 6.0, 6.7 Hz, H-4), 2.70 (br s, 1H, NH), 2.55 (ddd, 1H, *J*=6.7, 9.8, 13.9 Hz, H_2-3), 2.39 (ddd, 1H, *J*=3.2, 6.5, 13.9 Hz, H_2-3), 1.34 (t, 3H, *J*=7.3 Hz, Me), 1.30 (d, 3H, *J*=8.6 Hz, Me); ^{13}C NMR: 173.3 (C=O), 171.1 (C=O), 143.0 (q), 134.5 (q), 133.6 (q), 133.3 (q), 128.9 (2×CH), 128.4 (2×CH), 127.7 (CH), 127.5 (CH), 126.4 (CH), 125.9 (CH), 62.4, 61.2, 58.4, 47.4, 33.8, 21.8, 14.2; CIMS (*m/z*, rel intensity %): 477 (M^+, 14), 435 (base peak), 401 (5), 361 (24), 262 (37); HRMS: Calcd: 434.1164 for $C_{22}H_{24}Cl_2N_2O_3$; Found: 434.1174.

3.2.5. (*S*,*S*,*S*,*R*)-Ethyl,5-(4-nitrophenyl)-4-[(1′-phenylethyl)carbamoyl]-pyrrolidine-2-carboxylate ($5b_3$). White needles; mp 189–90 °C; $[\alpha]_D^{23}=+148$ (*c* 1.5, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): 7.87 (d, 1H, *J*=8.6 Hz, Ar-3′H and 5′H), 7.31 (d, 1H, *J*=8.6 Hz, Ar-2′H and 6′H), 7.21 (m, 3H, Ph), 7.03 (m, 2H, Ph), 4.78 (sextett, 1H, PhCH), 4.51 (d, 1H, *J*=6.6 Hz, H-5), 4.29 (dq, 2H, OCH_2), 4.05 (dd, 1H, *J*=5.9, 10.6 Hz, H-2), 3.17 (ddd, 1H, *J*=2.5, 6.6, 8.6 Hz, H-4), 2.71 (ddd, 1H, *J*=5.9, 8.6, 14 Hz, H_2-3), 2.35 (ddd, 1H, *J*=2.5, 5.9, 14 Hz, H_2-3), 1.35 (t,

3H, J=6.6 Hz, CH_3), 1.26 (d, 3H, J=6.6 Hz, CH_3); ^{13}C NMR: 173.8 (C=O), 170.7 (C=O), 145.7 (Ar-1′H), 132.0 (Ph-1′C), 128.4 (2×CH), 127.3 (3×CH), 126.4 (2×CH), 123.3 (2×CH), 64.2, 61.5, 57.6, 50.1, 48.2, 33.5, 21.1 (Me), 14.2 (Me); IR (nujol, cm^{-1}): 3290, 1726, 1642, 1548, 1521, 1343, 1262, 1203, 1106, 1021; CIMS (*m/z*, rel intensity %): 412 (M^+, base peak), 382 (29), 338 (7), 289 (10), 167 (10), 105 (13); HRMS: Calcd: 411.1794 for $C_{22}H_{25}N_3O_5$; Found: 411.1808.

3.2.6. (*R*,*R*,*R*,*R*,*R*)-Ethyl,5-phenyl-4-[[*bis*(1′-phenylethyl)]carbamoyl]-pyrrolidine-2-carboxylate (4c$_1$). Colourless needles; mp 172–3 °C; $[\alpha]_D^{23}=-158$ (*c* 0.96, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): 7.31–7.02 (m, 11H, Ph), 6.77–6.71 (m, 4H, Ph), 5.31 (broad d, 1H, J=6.6 Hz, PhC*H*), 4.70 (q, 1H, J=7.3 Hz, PhC*H*), 4.23 (dq, 2H, OCH_2), 3.95 (d, 1H, J=7.3 Hz, H-5), 3.87 (t, 1H, J=8.6 Hz, H-2), 3.43 (dd, 1H, J=5.3, 7.3 Hz, H-4), 2.53–2.02 (m, 2H, H_2-3), 1.46 (d, 3H, J=7.3 Hz, CH_3), 1.42 (d, 3H, J=7.3 Hz, CH_3), 1.29 (t, 3H, J=7.3 Hz, CH_3); ^{13}C NMR: 173.9 (C=O), 173.1 (C=O), 141.1 (2×Ph-1′C), 138.7 (Ph-1′C), 128.4, 128.3, 128.0, 127.8, 127.2, 126.9 (15×CH, overlapping), 67.4, 61.0, 52.4, 52.1, 47.2, 36.9, 30.0, 19.5, 16.9, 14.3; IR (nujol, cm^{-1}): 1737, 1627, 1604, 1453, 1293, 1262, 1195, 1177, 1102, 1025, 949; CIMS (*m/z*, rel intensity %): 471 (M^+, base peak), 397 (10), 367 (15), 280 (12), 246 (9), 105 (22); HRMS: Calcd: 470.2569 for $C_{30}H_{34}N_2O_3$; Found: 470.2573.

3.2.7. (*S*,*S*,*S*,*R*,*R*)-Ethyl,5-phenyl-4-[[*bis*(1′-phenylethyl)]carbamoyl]-pyrrolidine-2-carboxylate (5c$_1$). White powder; mp 156–8 °C; $[\alpha]_D^{23}=-121$ (*c* 0.42, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): 7.35–7.12 (m, 11H, Ph), 6.78–6.73 (m, 4H, Ph), 5.38 (broad d, 1H, J=6.9 Hz, PhC*H*), 4.66 (q, 1H, J=6.8 Hz, PhC*H*), 4.27 (dq, 2H, OCH_2), 3.98 (d, 1H, J=7.6 Hz, H-5), 3.91 (t, 1H, J=8.6 Hz, H-2), 3.48 (dd, 1H, J=5.1, 7.6 Hz, H-4), 2.35–2.22 (m, 2H, H_2-3), 1.47 (d, 3H, J=6.8 Hz, CH_3), 1.41 (d, 3H, J=6.8 Hz, CH_3), 1.31 (t, 3H, J=7.5 Hz, CH_3); ^{13}C NMR: 174.8, 172.9, 141.8, 140.9, 138.1, 129.1, 128.1, 127.9, 127.6, 127.4, 127.1, 126.8, 126.3, 125.9, 68.0, 51.7, 50.7, 48.6, 35.8, 30.1, 21.0, 17.4, 14.2; IR (nujol, cm^{-1}): 1739, 1625, 1604, 1452, 1296, 1197, 1109, 1027, 949; CIMS (*m/z*, rel intensity %): 471 (M^+, base peak), 397 (15), 367 (25), 105 (36); HRMS: Calcd: 470.2569 for $C_{30}H_{34}N_2O_3$; Found: 470.2573.

3.2.8. (*S*,*S*,*S*,*R*,*R*)-Ethyl,5-(2,4-dichlorophenyl)-4-[[*bis*(1′-phenylethyl)]carbamoyl]-pyrrolidine-2-carboxylate (5c$_2$). White powder; mp 184–6 °C; $[\alpha]_D^{23}=-102$ (*c* 0.88, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): 7.61 (d, 1H, J=8.6 Hz, Ar), 7.39—7.03 (m, 8H, Ar), 6.78–6.77 (m, 4H, Ar), 5.64 (br s, 1H, PhC*H*), 4.90 (q, 1H, J=6.6 Hz, PhC*H*), 4.48 (d, 1H, J=6.0 Hz, H-5), 4.25 (dq, 2H, OCH_2), 3.70 (br dd, 1H, H-2), 3.42 (br s, 1H, H-4), 1.90 (broad ddd, 1H, H_2-3), 1.75 (broad ddd, 1H, H_2-3), 1.54 (d, 3H, J=6.6 Hz, Me), 1.30 (t, 3H, J=7.2 Hz, Me), 1.22 (d, 3H, J=6.6 Hz, Me); ^{13}C NMR: 173.6 (C=O), 172.7 (C=O), 141.3 (q), 141.1 (q), 134.8 (q), 133.5, 133.1, 128.9, 128.4, 128.0, 127.7, 127.3, 126.8, 126.7 (15×C, overlapping), 66.9, 61.1, 51.9, 47.6, 36.3, 29.6, 20.5, 17.8, 14.3; CIMS (*m/z*, rel intensity %): 539 (M^+, base peak), 505 (10), 435 (12), 280 (30), 105 (70); IR (film, cm^{-1}): 2976, 2931, 1738, 1629, 1445, 1378, 1279, 1201, 1178, 1102; HRMS: Calcd 538.1790 for $C_{30}H_{32}Cl_2N_2O_3$; Found: 538.1791.

3.2.9. (*S*,*S*,*S*,*R*,*R*)-Ethyl,5-(2,4-dichlorophenyl)-4-[[*bis*(1′-phenylethyl)]carbamoyl]-pyrrolidine-2-carboxylate (4c$_2$). White powder; mp 170 °C; $[\alpha]_D^{23}=-95$ (*c* 0.25, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): 7.56 (d, 1H, J=8.5 Hz, Ar), 7.33–7.01 (m, 8H, Ar), 6.75–6.71 (m, 4H, Ar), 4.99 (br s, 1H, PhC*H*), 4.65 (q, 1H, J=6.6 Hz, PhC*H*), 4.48 (d, 1H, J=6.0 Hz, H-5), 4.23 (dq, 2H, OCH_2), 3.89 (dd, 1H, J=7.3, 9.3 Hz, H-2), 3.10 (br s, 1H, H-4), 2.51 (ddd, 1H, J=7.9, 9.3, 13.2 Hz, H_2-3), 2.27 (ddd, 1H, J=4.0, 7.3, 13.2 Hz, H_2-3), 1.38 (d, 3H, J=6.6 Hz, Me), 1.34 (t, 3H, J=7.3 Hz, Me), 1.25 (d, 3H, J=6.6 Hz, Me); ^{13}C NMR: 173.5 (C=O), 172.5 (C=O), 141.4 (q), 141.1 (q), 134.7 (q), 133.9, 133.4, 129.0, 128.7, 128.0, 127.7, 127.5, 127.1, 126.8, 126.6 (15×C, overlapping), 66.7, 61.3, 51.9, 47.7, 36.6, 31.2, 20.5, 17.9, 14.1; CIMS (*m/z*, rel intensity %): 539 (M^+, base peak), 105 (80); IR (film, cm^{-1}): 2979, 2938, 1737, 1626, 1452, 1377, 1211, 1109; HRMS: Calcd 538.1790 for $C_{30}H_{32}Cl_2N_2O_3$; Found: 538.1786.

3.2.10. (*S*,*S*,*S*,*R*,*R*)-Ethyl,5-(4-nitrophenyl)-4-[[*bis*(1′-phenylethyl)]carbamoyl]-pyrrolidine-2-carboxylate (5c$_3$). White powder; mp 212–3 °C; $[\alpha]_D^{23}=-179$ (*c* 1.2, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): 8.03 (d, 2H, J=8.6 Hz, Ar), 7.25–7.04 (m, 10H, Ph), 6.49 (d, 2H, J=8.6 Hz, Ar), 5.82 (broad q, 1H, J=6.6 Hz, C*H*Ph), 4.65 (q, 1H, J=7.2 Hz, C*H*Ph), 4.25 (dq, 2H, OCH_2), 3.90 (t, 1H, J=8.6 Hz, H-2), 3.79 (d, 1H, J=7.9 Hz, H-5), 3.42 (ddd, 1H, J=1.4, 5.3, 7.9 Hz, H-4), 2.57 (ddd, 1H, J=5.3, 8.6, 13.5 Hz, H_2-3), 2.32 (ddd, 1H, J=1.4, 8.6, 13.5 Hz, H_2-3), 1.68 (d, 3H, J=6.5 Hz, Me), 1.47 (d, 3H, J=6.5 Hz, Me), 1.31 (t, 3H, J=7.3 Hz, Me); ^{13}C NMR: 173.8 (C=O), 172.7 (C=O), 146.8 (q), 141.0 (q), 140.7 (q), 128.7, 128.6, 128.5, 128.3, 128.2, 127.8, 127.6 (overlapping CHs), 127.2 (CH), 122.8 (CH), 66.1, 61.1, 51.6, 51.0, 48.6, 37.0, 29.6, 20.1, 16.4, 14.2; IR (KBr, cm^{-1}): 2977, 2933, 1734, 1626, 1517, 1494, 1442, 1345, 1240, 1201, 1105, 1035, 841; CIMS (*m/z*, rel intensity %): 516 (M^{+1}, 100), 486 (10), 412 (9), 280 (10), 105 (30); HRMS: Calcd 515.2402 for $C_{30}H_{33}N_3O_5$; Found: 515.2407.

3.2.11. (*R*,*R*,*R*,*R*,*R*)-Ethyl,5-(4-nitrophenyl)-4-[[*bis*(1′-phenylethyl)]carbamoyl]-pyrrolidine-2-carboxylate (4c$_3$). White powder; mp 201–3 °C; $[\alpha]_D^{23}=-142$ (*c* 0.34, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): 8.14 (d, 2H, J=8.6 Hz, Ar), 7.29–7.02 (m, 10H, Ph), 6.73 (d, 2H, J=8.6 Hz, Ar), 5.70 (broad s, 1H, C*H*Ph), 4.65 (q, 1H, J=7.2 Hz, C*H*Ph), 4.27 (dq, 2H, OCH_2), 3.70 (t, 1H, J=8.6 Hz, H-2), 3.76 (d, 1H, J=7.0 Hz, H-5), 3.05 (broad q, 1H, H-4), 1.97 (broad m, 1H, H_2-3), 1.72 (broad m, 1H, H_2-3), 1.59 (d, 3H, Me), 1.32 (d, 3H, Me), 1.29 (t, 3H, J=6.9 Hz, Me); ^{13}C NMR: 173.8 (C=O), 172.6 (C=O), 146.8 (q), 141.1 (q), 140.6 (q), 128.7, 128.6, 128.4, 128.3, 128.2, 127.9 (overlapping CHs), 126.1 (CH), 123.0 (CH), 66.8, 61.2, 51.6, 51.3, 47.4, 35.6, 29.9, 21.2, 17.7, 14.2; CIMS (*m/z*, rel intensity %): 516 (M^{+1}, 100), 412 (13), 105 (30); HRMS: Calcd 515.24022 for $C_{30}H_{33}N_3O_5$; Found: 515.240545.

3.2.12. (*R*,*R*,*R*,*R*,*R*)-Ethyl,4-[(2′,5′-*trans*-diphenylpyrrolidinyl)-1-carbonyl]-5-phenyl-pyrrolidine-2-carboxylate (4d$_1$). White powder; mp 203 °C; $[\alpha]_D^{23}=+262$ (*c* 2.2,

$CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): 7.39 (m, 10H, Ph), 7.20 (d, 1H, $J=7.2$ Hz, Ph), 7.02 (m, 2H, Ph), 6.28 (d, 2H, $J=7.8$ Hz, Ph), 5.26 (d, 1H, $J=7.9$ Hz) and 5.17 (d, 1H, $J=7.9$ Hz, H-2′ and H-5′), 4.20 (q, 2H, $J=6.6$ Hz, OCH_2), 4.19 (d, 1H, $J=7.3$ Hz, H-5), 3.70 (t, 1H, $J=8.6$ Hz, H-2), 3.20 (dt, 1H, $J=4.5$, 7.9 Hz, H-4), 2.24 (m, 2H, CH_2), 2.11 (m, 1H, CH_2), 1.90 (m, 1H, CH_2), 1.67 (d, 1H, $J=6.6$ Hz, CH_2), 1.50 (d, 1H, $J=6.6$ Hz, CH_2), 1.25 (t, 3H, $J=6.6$ Hz, CH_3); ^{13}C NMR: 173.4 (C=O), 172.5 (C=O), 143.6 (Ph-1′C), 142.6 (Ph-1′C), 138.5 (Ph-1′C), 128.9 (2×CH), 128.7 (2×CH), 128.5 (2×CH), 127.4 (CH), 127.3 (CH), 126.9 (2×CH), 125.9 (CH), 125.4 (2×CH), 124.8 (2×CH), 66.5, 62.9, 62.0, 60.9, 60.1, 47.8, 36.5, 32.7, 30.4, 14.1 (CH_3); IR (nujol, cm^{-1}): 1737, 1622, 1424, 1318, 1260, 1169, 1090, 1031; CIMS (*m/z*, rel intensity %): 469 (M^{+1}, base peak), 395 (10), 278 (12), 192 (10); HRMS: Calcd: 468.2413 for $C_{30}H_{32}N_2O_3$; Found: 468.2400.

3.2.13. (*R*,*R*,*R*,*R*,*R*)-Ethyl,5-(2,4-dichlorophenyl)-4-[(2′,5′-*trans*-diphenylpyrrolidinyl)-1-carbonyl]-pyrrolidine-2-carboxylate (4d$_2$). White powder; mp 211 °C; $[\alpha]_D^{23}=+47$ (*c* 0.2, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): 7.52 (d, 1H, $J=2.6$ Hz, Ar), 7.51–7.01 (m, 10H, Ar), 6.42 (dd, 2H, $J=2.0$, 8.2 Hz, Ar), 5.31 (d, 1H, $J=7.2$ Hz, NC*H*Ph), 5.27 (d, 1H, $J=7.2$ Hz, *NCH*Ph), 4.20 (d, 1H, $J=7.2$ Hz, H-5), 4.19 (q, 2H, $J=7.0$ Hz, OCH_2), 3.65 (t, 1H, $J=8.6$ Hz, H-2), 3.47 (ddd, 1H, $J=1.9$, 3.7, 7.2 Hz, H-4), 2.33 (m, 2H, CH_2), 1.93 (m, 1H, CH_2), 1.81 (m, 1H, CH_2), 1.70 (m, 1H, CH_2), 1.55 (m, 1H, CH_2), 1.26 (t, 3H, $J=7.0$ Hz, CH_3); ^{13}C NMR: 173.2 (C=O), 172.7 (C=O), 143.5 (q), 142.8 (q), 133.3, 132.9, 129.2, 128.8, 128.7, 128.6, 127.5, 127.4, 127.0, 125.8, 124.9 (16×C, overlapping), 66.3, 63.0, 62.1, 61.0, 60.1, 47.9, 36.4, 32.8, 30.2, 14.1; IR (nujol, cm^{-1}): 1735, 1624, 1427, 1269, 1204, 1178, 1095, 1031; CIMS (*m/z*, rel intensity %): 537 (M^+, 100), 503/501 (14), 278 (38), 205 (17), 149 (60), 85 (99); HRMS: Calcd: 536.1633 for $C_{30}H_{30}Cl_2N_2O_3$; Found: 536.1636.

3.2.14. (*R*,*R*,*R*,*R*,*R*)-Ethyl,5-(4-nitrophenyl)-4-[(2′,5′-*trans*-diphenylpyrrolidinyl)-1-carbonyl]-pyrrolidine-2-carboxylate (4d$_3$). White powder; mp 222–3 °C; $[\alpha]_D^{23}=+34$ (*c* 0.17, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): 8.09 (d, 2H, $J=8.6$ Hz, Ar), 7.44–7.31 (m, 5H, Ar), 7.18 (d, 2H, $J=6.6$ Hz, Ar), 7.07 (t, 1H, $J=7.3$ Hz, Ar), 6.95 (t, 2H, $J=7.3$ Hz, Ar), 6.52 (d, 2H, $J=7.3$ Hz, Ar), 5.25 (d, 1H, $J=7.3$ Hz, C*H*Ph), 5.16 (d, 1H, $J=7.3$ Hz, C*H*Ph), 4.24 (d, 1H, $J=7.3$ Hz, H-5), 4.20 (q, 2H, $J=7.3$ Hz, OCH_2), 3.69 (t, 1H, $J=8.6$ Hz, H-2), 3.25 (ddd, 1H, $J=3.3$, 4.6, 7.9 Hz, H-4), 2.51–2.19 (m, 2H, CH_2), 2.01 (ddd, 1H, $J=4.6$, 7.3, 13.2 Hz, H_2-3), 1.88–1.72 (m, 2H, CH_2), 1.58 (dd, 1H, $J=5.3$, 11.9 Hz, CH_2), 1.27 (t, 3H, $J=7.3$ Hz, CH_3); ^{13}C NMR:172.9 (C=O), 172.2 (C=O), 147.1 (q), 146.2 (q), 143.6 (q), 142.6 (q), 129.0 (2×CH), 127.9 (2×CH), 127.8 (2×CH), 127.7 (2×CH), 126.6 (CH), 125.4 (2×CH), 125.1 (2×CH), 123.6 (2×CH), 66.1, 63.2, 62.0, 61.1, 60.2, 47.8, 36.3, 33.4, 30.0, 14.2; IR (nujol, cm^{-1}): 1736, 1611, 1511, 1416, 1353, 1309, 1272, 1187, 1171, 1063, 1028; CIMS (*m/z*, rel intensity %): 514 (M^{+1}, base peak), 484 (12), 440 (8), 278 (10), 237 (12); HRMS: Calcd: 513.2264 for $C_{30}H_{31}N_3O_5$; Found: 513.2259.

3.2.15. (*R*,*R*,*R*,*R*,*S*)-Ethyl,4-[(2′-hydroxy-1′-methyl-2′-phenyl-ethyl)carbamoyl]-5-(2,4-dichlorophenyl)-pyrrolidine-2-carboxylate (4e$_1$). White powder; mp 182–3 °C; $[\alpha]_D^{23}=-101$ (*c* 1.0, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): 7.40–7.15 (m, 8H, Ar), 4.61 (d, 1H, $J=6.6$ Hz, C*H*OH), 4.40 (d, 1H, $J=4.0$ Hz, H-5), 4.27 (dq, 2H, OCH_2), 4.10 (broad m, 2H, OH + C*H*-CH_3), 3.84 (t, 1H, $J=7.9$ Hz, H-2), 3.57 (ddd, 1H, $J=4.0$, 7.3, 10.7 Hz, H-4), 2.80 (m, 1H, H_2-3), 2.47 (s, 3H, NMe), 2.35 (m, 1H, H_2-3), 1.33 (t, 3H, $J=7.1$ Hz, CH_3), 0.72 (d, 3H, $J=7.3$ Hz, CH_3); ^{13}C NMR: 173.6 (C=O), 172.8 (C=O), 141.7, 134.7, 133.7, 133.2, 129.2, 128.5, 127.9 (2×CH), 127.3, 127.1, 126.1 (2×CH), 76.5, 62.3, 59.8, 56.8, 43.5, 34.8, 32.5, 14.2, 11.4; IR (KBr, cm^{-1}): 3377, 2987, 1736, 1621, 1476, 1449, 1413, 1374, 1206, 1104, 1048; CIMS (*m/z*, rel intensity %): 479 (M^+, base peak), 463 (20), 314 (31), 280 (15), 176 (10), 148 (52), 135 (22), 107 (25); HRMS: Calcd: 478.1426 for $C_{24}H_{28}Cl_2N_2O_4$; Found: 478.1409.

3.2.16. (*R*,*R*,*R*,*R*,*S*)-Ethyl,4-[(2′-hydroxy-1′-methyl-2′-phenyl-ethyl)carbamoyl]-5-(2,4-dichlorophenyl)-pyrrolidine-2-carboxylate (4e$_2$). White powder; mp 182–3 °C; $[\alpha]_D^{23}=-101$ (*c* 1.0, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): 7.40–7.15 (m, 8H, Ar), 4.61 (d, 1H, $J=6.6$ Hz, C*H*OH), 4.40 (d, 1H, $J=4.0$ Hz, H-5), 4.27 (dq, 2H, OCH_2), 4.10 (broad m, 2H, OH+C*H*–CH_3), 3.84 (t, 1H, $J=7.9$ Hz, H-2), 3.57 (ddd, 1H, $J=4.0$, 7.3, 10.7 Hz, H-4), 2.80 (m, 1H, H_2-3), 2.47 (s, 3H, NMe), 2.35 (m, 1H, H_2-3), 1.33 (t, 3H, $J=7.1$ Hz, CH_3), 0.72 (d, 3H, $J=7.3$ Hz, CH_3); ^{13}C NMR: 173.6 (C=O), 172.8 (C=O), 141.7, 134.7, 133.7, 133.2, 129.2, 128.5, 127.9 (2×CH), 127.3, 127.1, 126.1 (2×CH), 76.5, 62.3, 59.8, 56.8, 43.5, 34.8, 32.5, 14.2, 11.4; IR (film, cm^{-1}): 3377, 2987, 1736, 1621, 1476, 1449, 1413, 1374, 1206, 1104, 1048; CIMS (*m/z*, rel intensity %): 479 (M^+, base peak), 463 (20), 314 (31), 280 (15), 176 (10), 148 (52), 135 (22), 107 (25); HRMS: Calcd: 478.1426 for $C_{24}H_{28}Cl_2N_2O_4$; Found: 478.1419.

3.2.17. (*R*,*R*,*R*,*R*,*S*)-Ethyl,5-(4-methoxyphenyl)-4-[(2′-hydroxy-1′-methyl-2′-phenyl-ethyl)carbamoyl]-pyrrolidine-2-carboxylate (4e$_3$). White needles, mp. 134–5 °C; $[\alpha]_D^{23}=-59$ (*c*, 1.3, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): 7.28–7.14 (m, 7H, Ar), 6.80 (d, 2H, $J=7.5$ Hz, Ar), 4.55 (br s, 1H, OH), 4.41 (d, 1H, $J=4$ Hz, H-5), 4.28 (m, 3H, C*H*OH and, CH_2CH_3), 4.11 (m, 1H, $CHCH_3$), 3.81 (t, 1H, $J=8.0$ Hz, H-2), 3.73 (s, 3H, OMe), 3.33 (dd, 1H, $J=7$, 13 Hz, H-4), 2.75 (br s, 1H, NH), 2.45 (m, 1H, H_2-3), 2.35 (s, 3H, NCH_3), 2.27 (m, 1H, H_2-3), 1.33 (t, 3H, $J=8.7$ Hz, CH_3), 0.72 (d, 3H, $J=$Hz, CH_3); ^{13}C NMR: 173.4 (q), 173.3 (q), 159.1 (q), 141.9 (q), 130.6 (q), 128.2 (2×CH), 127.9 (2×CH), 127.1 (CH), 126.1 (2×CH), 113.5 (2×CH), 76.5, 65.6, 60.9, 59.9, 57.0, 55.2, 46.6, 34.6, 32.4, 14.1, 11.0; IR (nujol, cm^{-1}): 3184, 1739, 1609, 1521, 1402, 1259, 1231, 1104, 1027; EIMS (*m/z*, rel intensity %): 441 (M^{+1}, 6), 367 (10), 333 (10), 307 (19), 276 (base peak), 174 (34), 147 (49), 105 (38); HRMS: Calcd: 442.2467 for $C_{25}H_{34}N_2O_5$; Found: 442.2463.

3.2.18. (*R*,*R*,*R*,*R*,*S*)-Ethyl,5-(3,4-dimethoxyphenyl)-4-[(2′-hydroxy-1′-methyl-2′-phenyl-ethyl)carbamoyl]-pyrrolidine-2-carboxylate (4e$_4$). White needles, mp. 155 °C; $[\alpha]_D^{23}=-46$ (*c*, 1.5, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): 7.29–7.18 (m, 5H, Ph), 6.87 (d, 1H, $J=2.0$ Hz, Ar-2′H), 6.82 (dd, 1H, $J=2.0$, 8.0 Hz, Ar-6′H), 6.76 (d, 1H, $J=8.0$ Hz, Ar-5′H), 4.47 (d, 1H, $J=3.3$ Hz, C*H*OH), 4.37–4.22

(m, 4H, OCH_2, H-2 and H-4), 4.11 (dq, 1H, $J=3.3$, 7.3 Hz, C*H*–CH_3), 3.85 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.38 (ddd, 1H, $J=2.0$, 5.3, 7.9 Hz, H-4), 2.39 (ddd, 1H, $J=2.0$, 7.9, 13.2 Hz, H_2-3), 2.34 (s, 3H, NMe), 2.32 (ddd, 1H, $J=5.3$, 8.6, 13.2 Hz, H_2-3), 1.34 (t, 3H, $J=7.3$ Hz, CH_3), 0.78 (d, 3H, $J=7.3$ Hz, CH_3); ^{13}C NMR: 173.9 (C═O), 173.4 (C═O), 148.8 (2×q), 141.8 (q), 131.6 (q), 128.0 (2×CH), 127.4 (CH), 126.2 (2×CH), 119.5 (CH), 110.8 (CH), 110.5 (CH), 76.9 (*C*HOH), 66.1, 61.0, 60.1, 57.9, 55.9 (2×MeO), 46.8, 34.8, 32.9, 14.2, 11.4; IR (nujol, cm^{-1}): 3181, 1737, 1608, 1519, 1402, 1305, 1256, 1238, 1195, 1141, 1104, 1023; CIMS (*m*/*z*, rel intensity %): 471 (M^{+1}, base peak), 453 (18), 397 (8), 337 (10), 306 (28), 252 (12), 202 (18), 166 (20), 148 (42), 107 (13);HRMS: Calcd: 470.2417 for $C_{26}H_{34}N_2O_6$; Found: 470.2415.

3.2.19. (*R*,*R*,*R*)- or (*S*,*S*,*S*)-Diethyl, 5-phenyl-pyrrolidine-2,4-dicarboxylate (8). *Preparation from homochiral cycloadducts—General procedure*. The corresponding cycloadduct (**3** or **4**, 1.0 mM) was dissolved in ethanol (20 mL) and concentrated hydrochloric acid (3 mL) was added. The reaction mixture was refluxed overnight, then all the solvents were removed, and the residue was dried in vacuo. The obtained white powder was suspended in dry ethanol (10 mL) and thionyl chloride was added (0.2 mL). After 1 h reflux, when all the solids dissolved again the solvents were removed in vacuo and the residue was redissolved in ether–triethylamine mixture (25 mL/1 mL). This solution was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The remaining oil was purified by column chromatography to yield the corresponding enantiomer of the title diester as a colurless oil; $[\alpha]_D^{23}=\pm 88$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): 7.30 (m, 5H, Ph), 4.54 (d, 1H, $J=7.9$ Hz, H-5), 4.29 (q, 2H, $J=6.6$ Hz, OCH_2), 3.96 (t, 1H, $J=7.9$ Hz, H-2), 3.70 (dq, 2H, OCH_2), 3.31 (dd, 1H, $J=7.3$, 13.8 Hz, H-4), 2.78 (br s, 1H, NH), 2.41 (m, 2H, H_2-3), 1.33 (t, 3H, CH_3), 0.82 (t, 3H, $J=6.6$ Hz, CH_3); ^{13}C NMR: 173.3 (C═O), 172.6 (C═O), 139.2 (Ph-1′C), 128.1 (2×CH), 127.5 (Ph-4′C), 126.9 (2×CH), 65.9, 61.2, 60.2, 60.1, 49.7, 33.6, 14.2, 13.6; IR (film, cm^{-1}): 3351, 2980, 2905, 1732, 1451, 1378, 1198, 1166, 1111, 1037; CIMS (*m*/*z*, rel intensity %): 292 (M+1, 100), 246 (22), 218 (55), 191 (13), 144 (10), 117 (9), 29 (41); HRMS: Calcd: 291.1470 for $C_{16}H_{21}NO_4$; Found: 291.1463.

3.3. Grignard reaction

A Grignard reagent, freshly prepared from the addition of Mg (0.52 g, 21.6 mmol) to benzyl bromide (2.6 mL, 21.6 mmol) in anhyd Et_2O (50 mL) at room temperature for 1 h, was transferred to a solution of **4a$_1$** (0.73 g, 2 mmol) or **4e$_1$** (0.79 g, 2 mmol) in anhyd Et_2O (25 mL) at 0 °C via a cannula. The reaction mixture was refluxed under N_2 for 2 h, quenched by H_2O (15 mL). The organic layer was washed with H_2O (50 mL) brine (50 mL), dried ($MgSO_4$) and rotary evaporated to give a crude product which was purified by column chromatography (30% EtOAc/petroleum ether).

3.3.1. 2-(Diphenyl-hydroxy-methyl)-5-phenyl-4-[(1′-phenylethyl)carbamoyl]-pyrrolidine (9). Yield: 0.79 g, (84%); white powder; mp 219–20 °C; $[\alpha]_D^{23}=-22$ (*c* 0.16, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): 7.67 (d, 2H, $J=$ 7.3 Hz, Ph), 7.61 (d, 2H, $J=7.3$ Hz, Ph), 7.35–7.12 (m, 14H, Ph), 7.03 (d, 2H, $J=7.9$ Hz, Ph), 5.78 (s, 1H, NHCO), 5.21 (d, 1H, $J=7.9$ Hz, H-5), 4.68 (quintet, 1H, CH_3CH), 4.49 (t, 1H, $J=7.0$ Hz, H-2), 2.84 (ddd, 1H, $J=2.6$, 7.9, 9.2 Hz, H-4), 2.27 (ddd, 1H, $J=2.6$, 7.0, 14.5, H_2-3), 2.00 (ddd, 1H, $J=7.0$, 9.2, 14.5 Hz, H_2-3), 0.82 (d, 1H, $J=$ 6.6 Hz, Me), ^{13}C NMR: 172.3 (C═O), 147.5 (Ph-1′C), 146.4 (Ph-1′C), 142.9 (Ph-1′C), 139.2 (Ph-1′C), 128.4, 128.2, 127.7, 127.2, 126.9, 126.4, 126.1, 126.0, 125.8, (overlapping CHs), 112.1, 76.2, 65.8, 63.6, 50.4, 48.4, 37.3, 29.7, 20.6; IR (nujol, cm^{-1}): 3152, 1591, 1301, 1259, 1203, 1128, 1035; CIMS (*m*/*z*, rel intensity %): 477 (M^{+1},3), 459 (6), 293 (10), 257 (18), 229 (18), 183 (90), 159 (50), 85 (87), 57 (100); HRMS: Calcd: 476.2464 for $C_{32}H_{32}N_2O_2$; Found: 476.2467.

3.3.2. 2-(Diphenyl-hydroxy-methyl)-4-[(2′-hydroxy-1′-methyl-2′-phenyl-ethyl)carbamoyl]-5-phenyl-pyrrolidine (10). Yield: 0.92 g (91%); white powder; mp 232 °C; $[\alpha]_D^{23}=-15$ (*c* 0.26, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): 7.65 (d, 2H, $J=6.6$ Hz, Ph), 7.63 (d, 2H, $J=7.3$ Hz, Ph), 7.37–7.10 (m, 16H, Ph), 6.14 (br s, 1H, OH), 4.49–4.43 (m, 3H, H-2, H-5 and C*H*OH), 4.05 (br m, 1H, CH_3CH), 3.40 (dt, 1H, $J=4.0$, 7.9 Hz, H-4), 2.35 (ddd, 1H, $J=4.0$, 7.3, 13.9 Hz, H_2-3), 2.21 (s, 3H, NMe), 1.91 (ddd, 1H, $J=7.3$, 8.0, 13.9, H_2-3), 0.63 (d, 2H, $J=6.8$ Hz, CH_3); ^{13}C NMR: 175.3 (C═O), 147.5 (q), 146.7 (q), 141.7 (q), 139.1 (q), 128.1, 127.5, 127.0, 126.4, 126.1, (overlapping CHs), 77.7, 65.9, 63.9, 58.2, 45.6, 33.0, 30.6, 11.0; IR (nujol, cm^{-1}): 3164, 1594, 1309, 1253, 1203, 1128, 1024; CIMS (*m*/*z*, rel intensity %): 521 (M^+,2), 337 (4), 319 (5), 211 (7), 183 (base peak), 148 (32), 105 (27); HRMS: Calcd MH^+: 521.2804 for $C_{34}H_{37}N_2O_3$; Found: MH^+ 521.2805.

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