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# Reaction of aspartic acid derivatives with Grignard reagents—synthesis of γ,γ-disubstituted α- and β-amino-butyrolactones

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**Abstract**

A series of γ,γ-dimethyl and γ,γ-diphenyl substituted α- and β-amino-butyrolactones have been prepared in enantiomerically pure form using L-aspartic acid as a chiral building block. For the final Grignard reaction the difference in chemical reactivity between the carboxyl groups of aspartic acid was increased or inverted by preparing the corresponding semiesters, diesters and anhydrides. The resulting hydroxyacids and hydroxyesters lactonised in most cases during work up. Thus, (2*S*)-2-ethoxycarbonylamino-succinic acid-4-methylester **1** reacted with methylmagnesium iodide to form (3*S*)-3-ethoxycarbonylamino-5,5-dimethyl-tetrahydrofuran-2-one **2b**. Two interesting side products were obtained and were found to result from attack at the C-1 carboxylic acid rather than the C-4 carboxylic ester group leading to (3*S*)-3-ethoxycarbonylamino-4-oxo-pentanoic acid methylester **3** and (4*S*)-4-ethoxycarbonylamino-5,5-dimethyl-tetrahydrofuran-2-one **5a**. 

## 1. Introduction

Non-proteinogenic α-amino acids are interesting target molecules in their own right due to the biological and toxicological properties displayed by many of these compounds.[1,2] Furthermore, they are often used as chiral starting materials for the synthesis of natural products and chiral auxiliaries.[3] For example, L-homoserine lactone can be synthesised from L-α-amino acids,[4] but the synthesis of substituted L-homoserine lactones, which are α-amino-γ-butyrolactones, has only been rarely explored. A potential preparation starts from the inexpensive L-aspartic acid. The *tert*-alcohol function can be introduced by addition of a Grignard reagent. However, one has to direct the reaction to the 4- rather than to the 1-carboxyl group, which can be achieved

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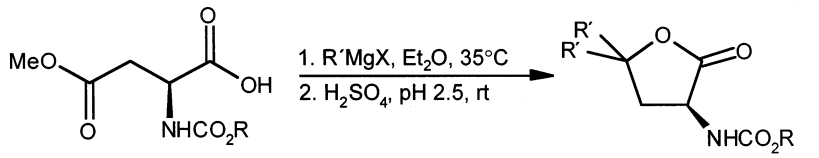
by selective monoesterification of the acid functionality in the 4-position. Having established a highly efficient route to *N*-protected aspartic acid semiesters **1**,[4] we now describe a straightforward synthesis of substituted L-homoserine lactones by their reaction with Grignard reagents.

## 2. Results and discussion

In a first attempt, methyl magnesium iodide was allowed to react with the semiesters **1a–c**. At least a fourfold excess of the methyl Grignard reagent is necessary: two equivalents for the acidic protons and two more for the addition to the ester group. However, in the course of our attempts to improve the synthesis, a 10-fold excess proved to be most useful giving the desired lactones **2a–c** in moderate yields (14–24%). The reaction of the semiester **2b** with a fivefold excess of phenylmagnesium bromide led to the corresponding diphenyl-substituted product **2d**. The free hydroxyacids could not be isolated because of their tendency to undergo ring closure during work up (Scheme 1).




**1a**: R = Me
**1b**: R = Et
**1c**: R = $^t$Bu

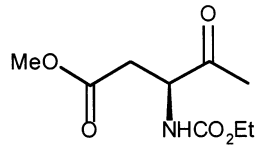
**2a**: R, R´ = Me (16%)
**2b**: R = Et, R´= Me (24%)
**2c**: R = $^t$Bu, R´= Me (14%)
**2d**: R = Et, R´= Ph (16%)

Scheme 1.

The lactones **2a–c** are derivatives of L-γ-hydroxyleucines, which represent an important class of non-proteinogenic amino acids occurring naturally as constituents of the phallotoxines, toxic compounds from *Amanita phalloides*, the death cap mushroom.[5] *N*-Protected L-γ-hydroxyleucine lactones had formerly been prepared by the photochlorination of leucine[6] followed by derivatisation of the amino group,[7] by oxidation of *N*-benzyloxycarbonyl-leucine-1-methylester with 3,3-dimethyldioxirane,[8] and by Grignard reaction of an *N*-protected aspartic acid derivative, in which the 1-carboxy group had been transformed to an orthoester.[9] In comparison to the last preparation, our method involves fewer steps leading to nearly the same yields.

While we tried to optimise the reaction conditions for the synthesis of the ethoxycarbonyl-amino substituted lactone **2b**, we always observed the formation of constant amounts of two minor by-products, irrespective of the mode of addition, the excess of organometallic reagent, the solvents, concentrations and the reaction temperatures. Since the main product **2b** could be crystallised, the by-products were accumulated in the mother liquors, which we studied by NMR spectroscopy. A singlet at $\delta$ 2.21 in the $^1$H NMR and a signal at $\delta$ 205.8 in the $^{13}$C NMR pointed to a methyl ketone. This was temporarily thought to be the presumable intermediate (2*S*)-2-ethoxycarbonyl-amino-4-oxo-pentanoic acid, formed after the first Grignard addition to the methylester group. However, after the compounds had been separated by silica gel chromatography, the structure was unambiguously assigned as the ketoester **3** by an INADEQUATE experiment. The $^1$H and $^{13}$C NMR spectra of the second by-product closely resembld the ones of the lactone **2b**. After further NMR experiments (C,H long range correlation, NOE) we identified the product as the

regioisomeric inverse lactone **5a**, which is a β-amino-γ-butyrolactone. In the reaction of the semiester **2b** with phenylmagnesium bromide we found the corresponding by-product, that is the inverse lactone **5b** (Scheme 2).

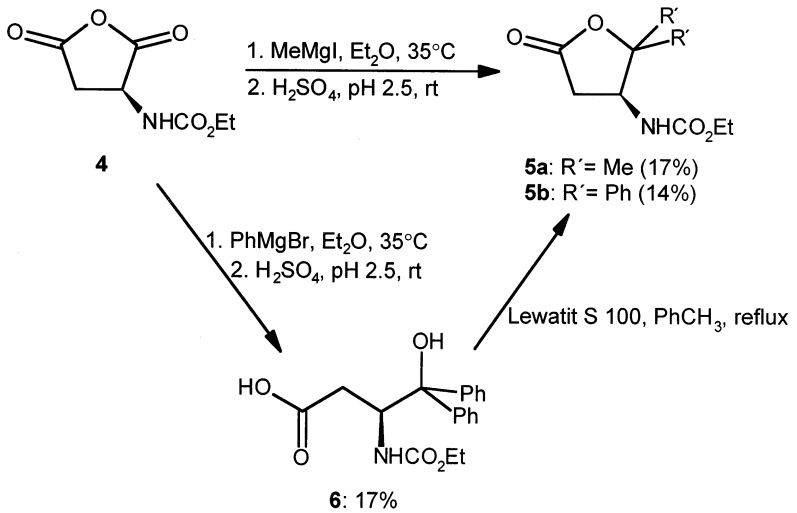



**3**

Scheme 2.

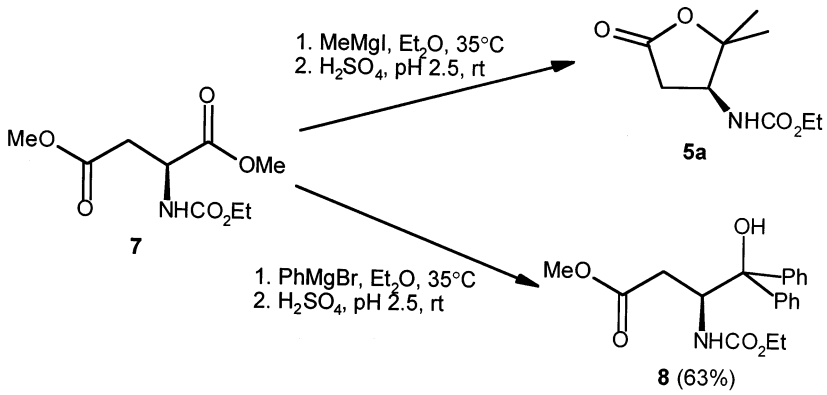
Obviously, the by-products originate from an addition to the less reactive C-1 acid functionality which should be even more inactivated by deprotonation to the carboxylate anion. However, the electron-withdrawing effect of the carbamate group might be counteracting and favouring the nucleophilic attack at C-1. Examples for the addition of Grignard reagents to the carboxylic acid group of amino acids can be found in the literature.[10] On the other hand, we did not find any formation of products derived from attack at the carbamate protecting group, indicating that this is at least sufficiently deactivated during the reaction.

The β-amino-γ-butyrolactones **5** could be synthesised by shifting the regioselectivity of the Grignard addition, which was achieved by employing the aspartic acid anhydride **4** as starting material. The electron-withdrawing carbamate group activated the C-1 carbon, which was therefore preferentially attacked. Under optimised conditions we were able to synthesise the β-amino substituted lactones **5** in 14–17% overall yield. While the dimethyl substituted product lactonised during work up, the diphenyl substituted hydroxyacid **6** had to be heated to reflux with a strong acid resin to close the lactone ring (Scheme 3).

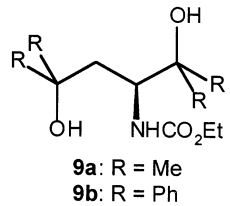



Scheme 3.

The same reactivity was found in the reaction of the diester **7**. As in the case of the anhydride, the dimethyl-substituted hydroxyester lactonised during work up giving the lactone **5a**, while the corresponding diphenyl-substituted hydroxyester **8** could be isolated. The diols **9a** and **9b** which result from the attack of the Grignard reagent to both carbonyl groups were found as by-products of the reaction (Schemes 4 and 5).




Scheme 4.




Scheme 5.

The strongly basic reaction conditions necessitate a check of the enantiomeric purity of the products which might well be lost due to deprotonation of the α-H. Nevertheless, all isolated products were optically active and the observed molar rotation of the α-amino-γ-butyrolactone **2c** is in good agreement with literature data.[7]

## 3. Conclusion

In the reaction of *N*-protected aspartic acid semiesters **1** with Grignard reagents moderate yields of γ,γ-disubstituted α-amino-γ-butyrolactones **2** were obtained. The carboxylic acid functional group of **1** appeared to be not as inert as expected, giving rise to two minor by-products, a methyl ketone **3** and the inverse lactone **5a**, a product of a subsequent reaction. It can be reasoned that these unexpected side reactions might be induced by the activating neighbouring carbamate group. Employing the *N*-protected aspartic acid anhydride **4** and diester **7**, the regioselectivitiy of the reaction could be inverted giving γ,γ-disubstituted β-amino-γ-butyrolactones **5** in moderate yields. The carbamate *N*-protecting group was found to be stable under the reaction conditions, as was the configuration at the C-2 stereogenic centre.

## 4. Experimental

### 4.1. General information

The reactions involving Grignard reagents were carried out under argon in anhydrous solvent. Silica gel from Merck (0.2–0.5 mm; 0.040–0.063 mm) was used for column and flash chromatography, respectively. TLC was performed on Polygram Sil $G/UV_{254}$ plates (Macherey–Nagel, 40×80 mm; 0.25 mm layer thickness). Melting points were determined on a Büchi 510 apparatus and are uncorrected. Optical rotations were measured with a Technolab AA 1000 instrument. IR spectra were recorded on a Perkin–Elmer FTIR 1750. $^1H$ and $^{13}C$ NMR spectra were obtained on a Bruker AC 200 spectrometer at 200 and 50 MHz, respectively. Mass spectra were measured in the EI mode at 70 eV with a Quadrupol-MS (HP59824a) instrument. Combustion analyses were performed by Beller Mikroanalytisches Laboratorium, Göttingen (Germany). HRMS were obtained on a Finnigan MAT 8400 instrument with chemical ionisation.

### 4.2. Starting materials

#### 4.2.1. (2S)-2-Alkoxycarbonylamino-succinic acid-4-methylesters **1**

Previously, we have described the preparation of (2*S*)-2-alkoxycarbonylamino-succinic acid-4-methylester dicyclohexylammonium salts.[4] After selective monoesterification of L-aspartic acid in acidic methanol followed by *N*-protection, we separated the monoester from the diester by precipitation of the dicyclohexylammonium salts. The salt (20.0 g, 51.7 mmol methoxy derivative, 49.9 mmol ethoxy derivative, and 46.7 mmol *tert*-butoxy derivative) and $NaHCO_3$ (20.0 g) were then dissolved in water (200 mL). The resulting solutions were adjusted to pH 10 with NaOH and extracted with diethyl ether (100 mL) to remove the dicyclohexylamine. The aqueous phases were then acidified with 50% $H_2SO_4$ to pH 2.5 and extracted with diethyl ether (3×100 mL). After washing the ethereal phases with water (10 mL) the solvent was removed under reduced pressure to give the semiesters **1** as thick colourless oils.

**1a** (4.24 g, 20.7 mmol, 40%). $^1H$ NMR ($CDCl_3$) $\delta$ 2.84 (dd, $J=17.3$, 4.7 Hz, 1H), 3.02 (dd, $J=17.3$, 4.6 Hz, 1H), 3.67 (s, 6H), 4.52–4.70 (m, 1H), 5.87 (d, $J=8.6$ Hz, 1H), 9.88 (s, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 36.2, 50.1, 52.1, 52.6, 156.8, 171.5, 174.8.

**1b** (5.91 g, 27.0 mmol, 54%). $^1H$ NMR ($CDCl_3$) $\delta$ 1.24 (t, $J=7.1$ Hz, 3H), 2.85 (dd, $J=17.4$, 4.8 Hz, 1H), 3.05 (dd, $J=17.4$, 4.5 Hz, 1H), 3.69 (s, 3H), 4.12 (q, $J=7.1$ Hz, 2H), 4.55–4.73 (m, 1H), 5.74 (d, $J=8.4$ Hz, 1H), 7.99 (s, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 14.4, 36.3, 50.0, 52.2, 61.6, 156.4, 171.5, 175.1.

**1c** (9.12 g, 36.9 mmol, 79%). $^1H$ NMR ($CDCl_3$) $\delta$ 1.41 (s, 9H), 2.81 (dd, $J=17.2$, 4.9 Hz, 1H), 3.01 (dd, $J=17.2$, 4.4 Hz, 1H), 3.68 (s, 3H), 4.50–4.68 (m, 1H), 5.61 (d, $J=8.6$ Hz, 1H), 10.23 (s, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 28.2, 36.4, 49.7, 52.1, 80.5, 155.6, 171.6, 175.6.

#### 4.2.2. (2S)-2-Ethoxycarbonylamino-succinic acid anhydride **4**

A solution of 88.0 g (429 mmol) of (2*S*)-2-ethoxycarbonylamino-succinic acid (synthesised from L-aspartic acid according to Vernsten and Moore[11]) in acetic anhydride (500 mL) was heated to reflux and stirred for 1 h at room temperature following a procedure of Lutz et al.[12] for the preparation of (2*S*)-2-benzoxycarbonylamino-succinic acid anhydride. After removal of the solvent under reduced pressure, the crude product crystallised overnight. It was washed with diethyl ether:hexane (1:1) (2×100 mL), and the crystals were dried in vacuo over KOH to give

44.4 g (237 mmol, 55%) of **4**. Mp 73°C; $[\alpha]_D^{20} = -3.0$ (*c* 2.6, THF); IR $\nu_{max}/cm^{-1}$ (KBr) 3359, 1871, 1801, 1681, 1536, 1302, 1280, 1219, 1081, 1051, 1022, 980, 914; $^1H$ NMR ($CDCl_3$) $\delta$ 1.22 (t, $J = 7.1$ Hz, 3H), 3.00–3.33 (m, 2H), 4.11 (q, $J = 7.1$ Hz, 2H), 4.44–4.62 (m, 1H), 5.91 (d, $J = 7.1$ Hz, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 14.3, 34.8, 50.8, 62.3, 156.2, 168.1, 170.8.

#### *4.2.3. (2S)-2-Ethoxycarbonylamino-succinic acid dimethylester* **7**

L-Aspartic acid (20.0 g, 150 mmol) was dissolved in a mixture of methanol (200 mL), trimethyl orthoformate (50 mL) and sulfuric acid (10 mL). After 20 h at room temperature the diester was derivatised with ethylchloroformate[4] to give 20.6 g (88.5 mmol, 59%) of **7**. $^1H$ NMR ($CDCl_3$) $\delta$ 1.08 (t, $J = 7.1$ Hz, 3H), 2.64–2.90 (m, 2H), 3.53 (s, 3H), 3.60 (s, 3H), 3.96 (q, $J = 7.1$ Hz, 2H), 4.38–4.56 (m, 1H), 5.73 (d, $J = 8.2$ Hz, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 14.1, 36.1, 49.9, 51.6, 52.3, 60.9, 155.8, 170.9, 171.0.

### *4.3. Reactions of aspartic acid derivatives with Grignard reagents*

#### *4.3.1. Reactions of (2S)-2-alkoxycarbonylamino-succinic acid-4-methylesters* ***1***

*4.3.1.1. (3S)-3-Alkoxycarbonylamino-5,5-dimethyl-tetrahydrofuran-2-one* ***2***. The Grignard reagent was prepared from 5.00 g (206 mmol) of magnesium suspended in 25 mL diethyl ether by dropwise addition within 1 h of 26.3 g (185 mmol) of methyl iodide dissolved in 50 mL diethyl ether. To complete the reaction, the mixture was heated to reflux and stirred for an additional 0.5 h. Under vigorous stirring and cooling with an ice bath, the semiester **1** (18.5 mmol; **a**: 3.80 g; **b**: 4.06 g; **c**: 4.58 g) dissolved in 100 mL diethyl ether was then added within 1.5 h to the suspension. Afterwards, stirring of the mixture was continued for 2 h. The remaining Grignard reagent was hydrolysed by cautious addition of 50 g ice and 100 mL water, and the aqueous phase was acidified to pH 2.5 with $H_2SO_4$ (50%). The ethereal phase was separated and the aqueous one was extracted with diethyl ether (3×100 mL). The combined ethereal solutions were washed with 20 mL of water and dried with $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was recrystallised from diethyl ether to give white crystals of the lactone **2**.

**2a** (0.554 g, 2.96 mmol, 16%). Mp 112°C; $[\alpha]_D^{20} = -36.9$ (*c* 1.0, MeOH); IR $\nu_{max}/cm^{-1}$ (KBr) 3332, 2986, 1761, 1721, 1535, 1380, 1258, 1160; $^1H$ NMR $\delta$ 1.44 (s, 3H), 1.51 (s, 3H), 2.02 (t, $J = 12.4$ Hz, 1H), 2.63 (dd, $J = 12.4$, 9.0 Hz, 1H), 3.71 (s, 3H), 4.50–4.72 (m, 1H), 5.46 (d, $J = 5.1$ Hz, 1H); $^{13}C$ NMR $\delta$ 26.9, 28.9, 42.1, 51.6, 52.5, 82.8, 157.1, 174.4. Anal. calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48; O, 34.19. Found: C, 51.04; H, 7.00.

**2b** (0.893 g, 4.44 mmol, 24%). Mp 115–116°C [lit. 112–114°C for racemate[13]]; $[\alpha]_D^{20} = -33.8$ (*c* 1.0, MeOH); IR $\nu_{max}/cm^{-1}$ (KBr) 3329, 2980, 1760, 1713, 1537, 1377, 1258, 1106; $^1H$ NMR ($CDCl_3$) $\delta$ 1.21 (t, $J = 7.1$ Hz, 3H), 1.39 (s, 3H), 1.46 (s, 3H), 1.99 (t, $J = 12.4$ Hz, 1H), 2.57 (dd, $J = 12.4$, 8.9 Hz, 1H), 4.10 (q, $J = 7.1$ Hz, 2H), 4.45–4.67 (m, 1H), 5.44 (d, $J = 5.4$ Hz, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 14.4, 26.9, 28.9, 42.0, 51.4, 61.4, 82.3, 156.2, 174.4. Anal. calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96; O, 31.80. Found: C, 53.49; H, 7.75.

**2c** (0.594 g, 2.59 mmol, 14%). Mp 145–146°C [lit. 145°C[7]]; $[\alpha]_D^{20} = -24.5$ (*c* 0.99, MeOH) [lit. −28.0 (*c* 1, MeOH),[7] +13.0 (*c* 1.0, $CHCl_3$)[8]]; IR $\nu_{max}/cm^{-1}$ (KBr) 3321, 2981, 1756, 1707, 1529, 1376, 1272, 1158, 1109; $^1H$ NMR ($CDCl_3$) $\delta$ 1.39 (s, 3H), 1.42 (s, 9H), 1.46 (s, 3H), 1.94 (t, $J = 12.0$ Hz, 1H), 2.61 (dd, $J = 12.0$, 9.3 Hz, 1H), 4.44–4.62 (m, 1H), 5.12 (d, $J = 4.4$ Hz, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 26.8, 28.2, 28.9, 42.4, 51.2, 80.4, 82.3, 155.4, 174.5. Anal. calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11; O, 27.91. Found: C, 57.52; H, 8.25.

The combined mother liquors of different experiments for the synthesis of the ethoxycarbonylamino substituted lactone **2b** were evaporated under reduced pressure. The residue (600 mg) was purified under ambient pressure on a silica gel column using a step gradient of diethyl ether:*n*-pentane (start 1:1, end 2:1). Three fractions were obtained and evaporated in vacuo to give 50 mg of the ketoester **3** as a yellowish oil, 40 mg of the lactone **2b** as colourless needles and 40 mg of the inverse lactone **5a** as a colourless oil.

(3*S*)-3-Ethoxycarbonylamino-4-oxo-pentanoic acid methylester **3**. $^1$H NMR ($CDCl_3$) $\delta$ 1.20 (t, $J=7.1$ Hz, 3H), 2.21 (s, 3H), 2.74 (dd, $J=17.2$, 4.9 Hz, 1H), 2.93 (dd, $J=17.2$, 4.7 Hz, 1H), 3.62 (s, 3H), 4.09 (q, $J=7.1$ Hz, 2H), 4.35–4.50 (m, 1H), 5.85 (d, $J=8.1$ Hz, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.2, 26.4, 35.1, 51.7, 56.4, 61.1, 156.0, 171.5, 205.8. HRMS (CI) calcd for $C_9H_{15}NO_5$: 217.09502. Found: 217.09555.

Data for **5a**: see Section 4.3.2.1.

*4.3.1.2. (3*S*)-3-Ethoxycarbonylamino-5,5-diphenyl-tetrahydrofuran-2-one **2d**.* Bromobenzene (70.7 g, 450 mmol) dissolved in 50 mL diethyl ether was added within 15 min to 10.9 g (448 mmol) of magnesium suspended in 60 mL diethyl ether. After refluxing for 30 min the reaction mixture was transferred into a dropping funnel and added at 0°C within 1 h to a solution of 19.5 g (89.0 mmol) of the semiester **1** in 140 mL diethyl ether. The suspension was refluxed for 3 h, hydrolysed with 30 mL water and acidified with sulfuric acid (50%) to pH 2.5. The organic layer was separated and the residual aqueous layer was extracted with diethyl ether (3×30 mL) and ethyl acetate (4×30 mL). The combined organic phases were washed with water (2×20 mL), dried over $Na_2SO_4$, and the solvent was removed in vacuo to yield 23.9 g of a reddish oil. **5** was purified by flash chromatography using toluene:ethyl acetate:acetic acid (100:11:0.1; $R_f=0.22$). The resulting colourless crystals were washed with diethyl ether and dried in vacuo to give 4.62 g of **2d** (14.2 mmol, 16%). Mp 139°C; $[\alpha]_D^{20}=+25.7$ (*c* 0.86, $CHCl_3$); IR $\nu_{max}/cm^{-1}$ (KBr) 3351, 1793, 1703, 1544, 1450, 1298, 1265, 1228, 1188, 1057, 963, 764, 708; $^1$H NMR ($CDCl_3$) $\delta$ 1.06 (t, $J=7.1$ Hz, 3H), 2.57 (t, $J=12.3$ Hz, 1H), 3.44 (dd, $J=12.3$, 7.9 Hz, 1H), 3.95 (q, $J=7.1$ Hz, 2H), 4.17–4.35 (m, 1H), 5.20 (d, $J=5.7$ Hz, 1H), 7.09–7.31 (m, 10H); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.4, 42.6, 51.3, 61.6, 87.3, 125.2, 125.4, 128.0, 128.2, 128.5, 128.8, 141.2, 143.1, 156.1, 173.8; MS (EI), *m*/*z* 193 (16.8), 192 (100.0), 191 (29.8), 165 (10.7), 105 (17.6), 103 (14.0), 90 (17.4), 77 (23.2), 29 (14.9). Anal. calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30; O, 19.67. Found: C, 70.48; H, 5.88; N, 4.28.

### *4.3.2. Reactions of (2*S*)-2-ethoxycarbonylamino-succinic acid anhydride **4***

*4.3.2.1. (4*S*)-4-Ethoxycarbonylamino-5,5-dimethyl-tetrahydrofuran-2-one **5a**.* The Grignard reaction was performed as described in Section 4.3.1.2 using a solution of 42.5 g (299 mmol) methyl iodide in 45 mL of diethyl ether, a suspension of 7.28 g (299 mmol) magnesium in 45 mL diethyl ether, and a solution of 15.9 g (85.0 mmol) anhydride **4** in 100 mL diethyl ether. After hydrolysis, extraction and evaporation of the solvent, a black oil was obtained that was purified by flash chromatography with ethyl acetate:hexane (50:40; $R_f=0.45$) to give 2.91 g (14.5 mmol, 17%) of the inverse lactone **5a** as a colourless oil that crystallised after 2 weeks. Mp 63°C; $[\alpha]_D^{20}=+11.3$ (*c* 4.2, $CH_3CO_2C_2H_5$); IR $\nu_{max}/cm^{-1}$ (KBr) 3359, 2977, 1764, 1709, 1682, 1532, 1259, 1123, 1048; $^1$H NMR ($CDCl_3$) $\delta$ 1.13 (t, $J=7.1$ Hz, 3H), 1.26 (s, 3H), 1.36 (s, 3H), 2.39 (dd, $J=18.1$, 5.4 Hz, 1H), 2.89 (dd, $J=18.1$, 8.4 Hz, 1H), 4.01 (q, $J=7.1$ Hz, 2H), 4.16–4.30 (m, 1H), 5.71 (d, $J=8.9$ Hz, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.3, 21.6, 26.8, 35.2, 54.8, 61.1, 87.2, 156.2, 174.3;

MS (EI), *m*/*z* (%) 115 (79.3), 56 (36.6), 43 (100), 42 (25.5), 41 (15.9), 29 (27.7), 28 (13.5), 27 (18.3). Anal. calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96; O, 31.80. Found: C, 54.25; H, 7.23; N, 6.75.

*4.3.2.2. (4*S*)-4-Ethoxycarbonylamino-5,5-diphenyl-tetrahydrofuran-2-one* ***5b***. The Grignard reaction was performed as described in Section 4.3.1.2 using a solution of 10.4 g (66.2 mmol) of bromobenzene in 20 mL of diethyl ether, a suspension of 1.60 g (65.8 mmol) magnesium in 15 mL diethyl ether, and a solution of 3.74 g (20.0 mmol) anhydride **4** in 80 mL diethyl ether. After hydrolysis, extraction, and evaporation of the solvent, the yellowish, oily product was allowed to crystallise overnight. The colourless crystals were filtrated, washed with diethyl ether and dried in vacuo to give 1.17 g (3.41 mmol, 17%) of (3*S*)-3-ethoxycarbonylamino-4-hydroxy-4,4-diphenylbutanoic acid **6**. Mp 139°C; $[\alpha]_D^{20}=-33.9$ (*c* 3.5, $CH_3CO_2C_2H_5$); IR $\nu_{max}/cm^{-1}$ (KBr) 3500–3300, 1726, 1707, 1537, 1448, 1241, 1062; $^1$H NMR (acetone-$d_6$) $\delta$ 1.10 (t, $J=7.0$ Hz, 3H), 2.46–2.83 (m, 2H), 3.97 (q, $J=7.0$ Hz, 2H), 5.15–5.33 (m, 1H), 5.64 (s, 1H), 6.34 (d, $J=9.1$ Hz, 1H), 7.19–7.80 (m, 10H), 10.83 (s, 1H); $^{13}$C NMR (acetone-$d_6$) $\delta$ 15.7, 36.8, 56.9, 61.9, 82.2, 127.3, 127.8, 128.2, 128.4, 129.5, 129.9, 147.3, 147.8, 158.3, 174.2; MS (EI), *m*/*z* (%) 208 (17.4), 183 (25.2), 115 (100.0), 105 (38.4), 77 (22.7). Anal. calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08; O, 23.30. Found: C, 66.62; H, 5.79; N 3.88.

Lewatit S 100 (1.00 g, strong acidic ion-exchange resin) was added to 1.00 g (2.91 mmol) (3*S*)-3-ethoxycarbonylamino-4-hydroxy-4,4-diphenylbutanoic acid **6** dissolved in 60 mL toluene and heated to reflux for 1 h, the formed water being removed by aceotropic distillation. Afterwards, the hot suspension was filtered and the solvent was removed under reduced pressure to a residual volume of 15 mL. Overnight crystallisation gave 0.780 g (2.40 mmol, 82%) of (4*S*)-4-ethoxycarbonylamino-5,5-diphenyl-tetrahydrofuran-2-one **5b** as colourless crystals. Mp 170°C; $[\alpha]_D^{20}=+0.7$ (*c* 4.9, $CHCl_3$); IR $\nu_{max}/cm^{-1}$ (KBr) 3379, 1775, 1713, 1528, 1246, 1207, 1058, 976, 703; $^1$H NMR ($CDCl_3$) $\delta$ 0.94 (t, $J=7.0$ Hz, 3H), 2.43 (dd, $J=17.7$, 3.7 Hz, 1H), 2.72 (dd, $J=17.7$, 7.0 Hz, 1H), 3.84 (q, $J=7.0$ Hz, 2H), 4.88 (d, $J=9.0$ Hz, 1H), 5.13–5.31 (m, 1H), 7.09–7.45 (m, 10H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 14.4, 36.4, 54.8, 61.3, 92.0, 125.7, 125.8, 128.0, 128.0, 128.4, 128.7, 138.5, 141.1, 155.6, 173.9; MS (EI), *m*/*z* (%) 208 (13.8), 183 (22.4), 115 (100.0), 105 (49.5), 77 (42.2), 56 (14.7), 43 (31.2), 29 (44.2). Anal. calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30; O, 19.67. Found: C, 70.17; H, 5.55; N, 4.20.

*4.3.3. Reactions of (2*S*)-2-ethoxycarbonylamino-succinic acid dimethylester* **7**

*4.3.3.1. (4*S*)-4-Ethoxycarbonylamino-5,5-dimethyl-tetrahydrofuran-2-one* ***5a***. The Grignard reaction was performed as described in Section 4.3.1.2 using 19.9 g (140 mmol) methyl iodide dissolved in 30 mL diethyl ether, a suspension of 3.40 g (140 mmol) magnesium in 20 mL of diethyl ether, and a solution of 9.30 g (39.9 mmol) of the diester **7** in 60 mL diethyl ether gave 10.1 g of a brown oil. The NMR signals could be fully attributed to the diester **7** (39%) and the lactone **5a** (61%). No efforts were made to purify the product.

For data for **5a**: see section Section 4.3.2.1.

*4.3.3.2. (3*S*)-3-Ethoxycarbonylamino-2,4-dimethylhexane-2,4-diol* ***9a***. The Grignard reaction was performed as described in Section 4.3.1.1 using 15.7 g (111 mmol) methyl iodide dissolved in 15 mL diethyl ether, a suspension of 2.70 g (111 mmol) magnesium in 10 mL diethyl ether, and a solution of 4.70 g (202 mmol) of the diester **7** in 25 mL diethyl ether. After hydrolysis,

extraction, and evaporation of the solvent, a crude black oil was obtained which was purified by flash chromatography with ethyl acetate:hexane (50:40; $R_f = 0.43$) to give 0.250 g (1.07 mmol, 0.5%) of (3*S*)-3-ethoxycarbonylamino-2,4-dimethylhexane-2,4-diol **9a**. $^1$H NMR ($CDCl_3$) $\delta$ 1.10 (t, $J = 7.1$ Hz, 3H), 1.15 (s, 12H), 1.35 (dd, $J = 19.5$, 3.3 Hz, 1H), 1.80 (dd, $J = 19.5$, 3.3 Hz, 1H), 3.54–3.74 (m, 1H), 4.05 (q, $J = 7.1$ Hz, 2H), 4.45 (s, 2H), 5.38 (d, $J = 9.5$ Hz, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.6, 26.3, 29.6, 29.8, 43.0, 56.5, 61.1, 70.4, 73.3, 157.6.

*4.3.3.3. (3*S*)-3-Ethoxycarbonylamino-4-hydroxy-4,4-diphenylbutanoic acid methylester **8**.* The Grignard reaction was performed as described in Section 4.3.1.2 using 10.4 g (66.2 mmol) bromobenzene dissolved in 20 mL diethyl ether, a suspension of 1.60 g (65.8 mmol) of magnesium in 15 mL diethyl ether, and a solution of 4.70 g (20.2 mmol) diester **7** in 80 mL diethyl ether. After hydrolysis, extraction and evaporation of the solvent, the product crystallised overnight to give 4.55 g (12.7 mmol, 63%) of (3*S*)-3-ethoxycarbonylamino-4-hydroxy-4,4-diphenylbutanoic acid methylester **8**, which was recrystallised from toluene. Mp 156–157°C; $[\alpha]_D^{20} = -46.6$ (*c* 7.2, $CHCl_3$); IR $\nu_{max}/cm^{-1}$ (KBr) 3491, 3436, 3388, 3340, 1727, 1693, 1544, 1450, 1258, 1052, 762, 750, 708; $^1$H NMR (acetone-$d_6$) $\delta$ 1.12 (t, $J = 7.1$ Hz, 3H), 2.47 (dd, $J = 14.9$, 9.9 Hz, 1H), 2.72 (dd, $J = 14.9$, 3.2 Hz, 1H), 3.63 (s, 3H), 3.98 (q, $J = 7.1$ Hz, 2H), 5.18–5.29 (m, 1H), 5.49 (s, 1H), 6.27 (d, $J = 9.5$ Hz, 1H), 7.20–7.73 (m, 10H); $^{13}$C NMR (acetone-$d_6$) $\delta$ 15.7, 37.2, 52.6, 56.9, 61.9, 82.1, 127.2, 127.7, 128.3, 128.4, 129.5, 129.9, 147.0, 147.7, 158.1, 173.4; MS (EI), *m*/*z* (%) 208 (15.0), 183 (23.4), 115 (100.0), 105 (39.8), 77 (25.5). Anal. calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92; O, 22.38. Found: C, 67.72; H, 6.11; N, 3.79.

*4.3.3.4. (2*S*)-2-Ethoxycarbonylamino-1,1,4,4-tetraphenylbutane-1,4-diol **9b**.* The Grignard reaction was performed as described in Section 4.3.1.2 using 21.9 g (139 mmol) of bromobenzene dissolved in 20 mL diethyl ether, a suspension of 3.40 g (140 mmol) magnesium in 15 mL diethyl ether, and a solution of 4.70 g (20.2 mmol) diester **7** in 20 mL diethyl ether. After hydrolysis, extraction and evaporation of the solvent, the product crystallised overnight to give 3.54 g (7.35 mmol, 36%) of (2*S*)-2-ethoxycarbonylamino-1,1,4,4-tetraphenylbutane-1,4-diol **9b**, which was recrystallised from toluene. Mp 175°C; $[\alpha]_D^{20} = -100.8$ (*c* 0.32, ethyl acetate); IR $\nu_{max}/cm^{-1}$ (KBr) 3426, 1681, 1527, 1448, 1239, 1156, 1056, 696; $^1$H NMR (acetone-$d_6$) $\delta$ 0.94 (t, $J = 7.1$ Hz, 3H), 2.31 (dd, $J = 14.7$, 1.5 Hz, 1H), 2.97 (s, 1H), 3.19 (dd, $J = 14.7$, 10.8 Hz, 1H), 3.70 (q, $J = 7.1$ Hz, 2H), 5.05–5.25 (m, 1H), 5.42 (s, 1H), 5.77 (d, $J = 9.5$ Hz, 1H), 7.15–7.64 (m, 20H); $^{13}$C NMR (acetone-$d_6$) $\delta$ 15.4, 42.1, 55.6, 62.2, 77.9, 82.8, 127.0, 127.2, 127.4, 127.4, 127.6, 128.1, 128.1, 129.3, 129.5, 129.6, 129.9, 147.2, 148.3, 150.0, 150.7, 159.0; MS (EI), *m*/*z* (%) 192 (26.4), 184 (15.1), 183 (100.0), 116 (14.6), 105 (92.5), 77 (41.7). Anal. calcd for $C_{31}H_{31}NO_4$: C, 77.32; H, 6.49; N, 2.91; O, 13.29. Found: C, 77.37; H, 6.32; N, 2.88.

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