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α-Bromo-β,γ-unsaturated ketenes for the synthesis of α-benzylamino-β,γ-unsaturated acids

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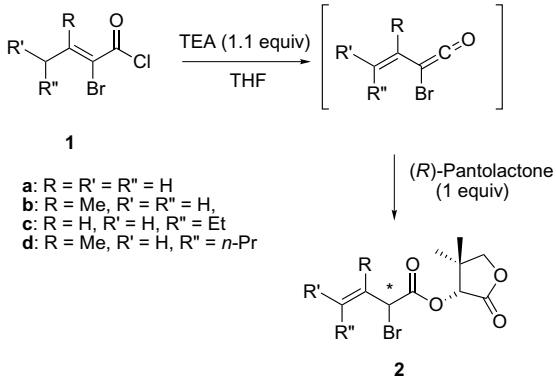
Abstract—The synthesis of α-benzylamino-β,γ-unsaturated acids has been developed starting from α-bromo-α,β-unsaturated chlorides. Via treatment of the acyl chlorides with (*R*)-pantolactone in the presence of TEA, the in situ formation of the deconjugated ketenes and their direct transformation into chiral esters was performed. The substitution of bromine with benzylamine, followed by acid hydrolysis, allowed to us obtain enantiomerically enriched α-benzylamino-β,γ-unsaturated acids.

1. Introduction

Over the last few years, extensive studies have been undertaken regarding the synthesis of unusual amino acids.[1] Among them α,β-unsaturated amino acids have attracted high interest as valuable intermediates in the synthesis of bioactive dehydropeptides and as starting materials for the synthesis of uncommon enantiomerically pure amino acids.[2] Synthetic and naturally occurring β,γ-unsaturated amino acids[3] are known to function as specific enzyme inhibitors of pyridoxal phosphate-dependent enzymes.[4] In addition, it has been demonstrated that the introduction of alkyl, alkenyl or aryl groups in the backbone or at the nitrogen of amino acid residues, allows the synthesis of conformationally constrained peptides with a rigidified secondary structure and an improved bioactivity and selectivity.[5]

As part of a program directed to preparing β,γ-unsaturated amino acids, we envisaged starting from α-bromo-β,γ-unsaturated ketenes,[6] which are well known as intermediates in the synthesis of organic molecules and have been widely employed for the preparation of diastereomeric esters.[7] The generation of saturated α-halogenated ketenes from α-halo acid halides, as precursors of α-amino acids, has already been reported.[8] The in situ preparation of the labile ketene and its treatment with an enantiomerically pure alcohol, afforded α-bromo ester in high yield and selectivity. In a similar way, we treated the α,β-unsaturated α-bromo acyl chlorides with triethylamine in order to obtain the simultaneous deconjugation of the double bond and the formation of the ketenes[9] that were in turn trapped by (*R*)-pantolactone. The unsaturated α-halo esters were obtained in good yield and good to excellent diastereomeric excess (Scheme 1).



Scheme 1. Diastereoselective synthesis of α-bromo ester **2**.

2. Results and discussion

The preparation of chloride **1** involved simple treatment of the α,β-dibromo acid with piperidine to obtain the monobromo unsaturated derivative.[10] The α-bromo acid

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Table 1. Synthesis of α-bromo-β,γ-unsaturated esters **2a–d**

Entry	Acyl chloride **1**	TEA (equiv)	*T* (°C)	Time (h)	Yield of **2** (%)	Ratio of diastereomers[a] 2*R*/2*S*	Ee (%)
1	**1a**	1.1	−70 °C → −40 °C	2	60	85:15	70
2	**1a**	1.1	−70 °C	2	60	92:8	84
3	**1b**	1.1	−70 °C	2.5	50	>95:5	>90
4	**1b**	2	−50 °C → −20 °C	2.5	85	92:8	84
5	**1c**	1.1	−50 °C → −20 °C	3	65[b]	72:28	44
6	**1d**	1.1	−50 °C → −20 °C	7	60	>95:5	>90
7	**1d**	1.1	−50 °C → −r.t.	14	60	50:50	0

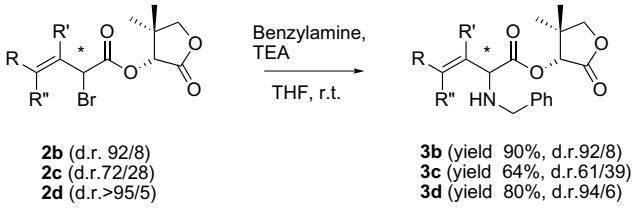
[a] Determined on the basis of ^{1}H NMR signals.
[b] A 15% amount of the conjugated bromo ester was observed in the crude mixture.

was then converted to the corresponding acid halide, which was purified by distillation under reduced pressure.

The subsequent reaction was performed by adding dropwise the α-bromo halide **1** in dry THF and a solution of triethylamine in THF, to a stirred solution of chiral alcohol for two hours at low temperatures. The reaction proceeded with good to excellent diastereoselectivity in the presence of (*R*)-pantolactone. However, using either ethyl lactate or (1*S*,2*R*)-*N*-Ts-ephedrine as the chiral source, lowered the diastereomeric excess.[6a] Some selected results of the reaction performed with pantolactone are given in Table 1.

The reaction of **1a** with 1.1 equiv of TEA, from −70 to −40 °C for 2 h, afforded **2a** with good yield and 85/15 d.r. (entry 1). Increased diastereoselectivity (92:8) was observed while maintaining the temperature at −70 °C (entry 2). When the reaction was performed with 2 equiv of TEA, the exclusive formation of the α-bromo-crotonyl ester was observed. For 2-bromo-3-methyl-but-2-enoyl chloride **1b**, high diastereoselectivity and moderate yield were obtained at −70 °C with 1.1 equiv of TEA (entry 3), while the use of 2 equiv of base at higher temperatures showed an increase in yield while still maintaining a good d.r. (entry 4). In the same temperature range, the reaction performed with 2-bromo-hex-2-enoyl chloride **1c** and an equimolar amount of base, furnished **2c** with good diastereoselectivity, although 15% of the corresponding conjugate bromo-ester was detected (entry 5). Under the same reaction conditions, compound **2d** was obtained in 60% yield as a single diastereoisomer from the reaction performed on 2-bromo-3-methyl-hex-2-enoyl chloride **1d** (entry 6). On warming the reaction mixture at r.t. overnight, complete epimerisation was observed (entry 7). The diastereomeric ratios of α-bromo esters **2a–d** were determined through the ^{1}H NMR spectrum of the crude mixture, based on the signal of the proton at the stereogenic centre of pantolactone.[7a]

The unsaturated esters **2** were quite stable at low temperature. However, slow racemisation was observed when the temperature was raised to room temperature. Furthermore, during the purification by flash chromatography on silica gel, some epimerisation occurred. For this reason the substitution of the bromine was performed on the crude diastereomeric mixture by treating the ester **2** with benzylamine and triethylamine in THF (Scheme 2).

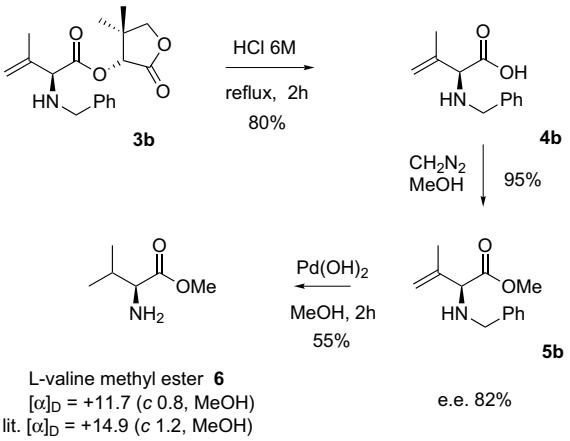


Scheme 2. Substitution with benzylamine on bromo derivative **2**.

The displacement of bromine occurred easily on **2b** affording the corresponding benzylamino derivatives **3b** in 92:8 d.r., as determined from the ^{1}H NMR signals of the C3′ pantolactone proton (5.45 ppm for the major isomer, 5.41 ppm for the minor one) and by GC–MS analysis. In a similar way, **2d** gave **3d** in 94:6 d.r., established on the ^{1}H NMR signals at 5.48 ppm (major) and 5.43 ppm (minor). The substitution of the benzylamine on the bromoderivative **2c** afforded **3c** with 61:39 d.r. Therefore the reaction occurred with appreciable epimerisation. On the other hand, treatment of **2a** under the same conditions afforded a mixture of compounds deriving both from the substitution and the 1,4-addition of benzylamine on the reconjugated derivative.

The configuration of the newly generated stereogenic centre in the predominant isomer of **3b**, was easily proven by conversion to valine methyl ester **6** (Scheme 3). Compound **3b** was refluxed in 6 M HCl for 2 h. (*R*)-pantolactone was recovered after purification of the unsaturated benzyl amino acid **4b** with a cation exchange resin. Acid **4b** was then treated with CH_2N_2/Et_2O to give the corresponding methyl ester **5b** in a quantitative yield. Compound **5b** was purified by flash chromatography with HPLC analysis on chiral column showing the same enantiomeric excess as the diastereomeric excess of the starting pantolactone ester **3b**.

The absolute configuration was established by reduction of **5b** with $Pd(OH)_2$ in methanol for two hours. Under these conditions the removal of the benzyl group and the reduction of the double bond furnished valine methyl ester **6** in quantitative yield. The specific rotation $\{[\alpha]_D = 11.7, (c = 0.8, \text{MeOH})\}$ compared with the data in literature[11] allowed us to assign an (*S*) absolute

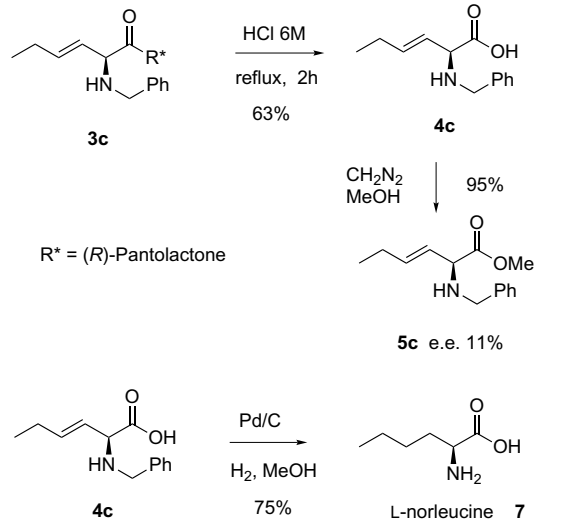


Scheme 3. Conversion of **3b** into L-valine methyl ester.

configuration to the major isomer. On the basis of these results we could attribute an (*R*)-configuration to the major isomer of the starting α-bromo panctolactone ester **2b**.

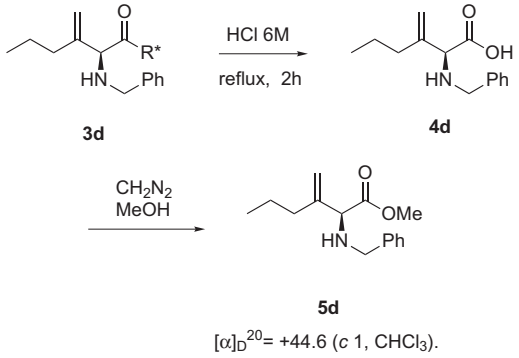
Since the comparison of the ^{1}H NMR spectra of the bromoderivatives **2a–d** showed the same trend of chemical shifts for the hydrogens on C2 and C3′, we assigned the (*R*)-configuration to the major isomers of the other bromo derivatives.

To obtain 2-benzylamino-hex-3-enoic acid **4c**, **3c** was hydrolysed by treatment with HCl (6 M) at reflux. Unfortunately, the HPLC analysis of the corresponding methyl ester **5c** showed a decreased enantiomeric excess (11%). The reduction of **4c** with H_2 in the presence of Pd/C catalyst allowed the removal of the benzylic protecting group and the reduction of the double bond, to afford norleucine **7** in 75% yield. The HPLC analysis, in comparison with the commercially available L-norleucine, confirmed the enantiomeric excess (11%) and the (2*S*)-configuration of the major isomer (Scheme 4).



Scheme 4. Conversion of **3c** into 2-benzylamino-hex-3-enoic acid **4c** and L-norleucine **7**.

Finally, the hydrolysis of **3d** gave the *N*-benzyl-β,γ-unsaturated amino acid **4d** in 88% ee, as established by the HPLC analysis of the corresponding methyl ester **5d** (Scheme 5).



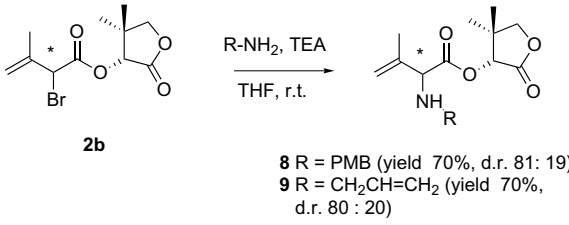
Scheme 5. Transformation of **3d** into α-benzylamino-β,γ-unsaturated ester **5d**.

Interesting papers by Koh, Ben and Durst demonstrated that starting from 1:1 diastereomeric mixtures of (*S*,*R*) and (*R*,*R*) α-haloesters, the synthesis of enriched α-amino esters can be achieved via treatment with benzylamine through a dynamic kinetic resolution. The enhanced yield of one diastereomer was attributed to a dynamic process, in which the (*R*,*R*) isomer reacted more quickly with the amine than the (*S*,*R*) isomer with the released bromide isomerising the slower to the faster reacting isomer.

In a similar way, we treated a 1:1 diastereomeric mixture of **2b**, **2c** or **2d** with benzylamine. The reaction performed on **2b** afforded **3b** in 62:38 d.r. while **3d** was obtained in 78:22 d.r. starting from **2d**. For **3c**, the d.r. observed at the equilibrium is the same obtained starting from a mixture of **2c** with 72:28 d.r. (see Scheme 2), suggesting that an epimerisation at the C2 stereogenic centre occurred during the substitution. However, for **3b** and **3d**, the diastereomeric ratios at the equilibrium were lower than the ones observed starting from diastereomerically enriched derivatives. These results seem to indicate that 3,3-disubtituted-α-bromo-esters are more stable during the substitution reaction with benzylamine, than the corresponding hexenoyl or crotonyl derivatives.

With the aim of extending this methodology to the synthesis of *N*-unsubstituted unsaturated amino acids, we performed the bromine displacement with other nitrogen nucleophiles, such as *p*-MeO-benzylamine and allylamine, whose dealkylation occurs under non-hydrogenolytic conditions (Scheme 6). The substitution reactions were performed under the conditions reported above for benzylamine.

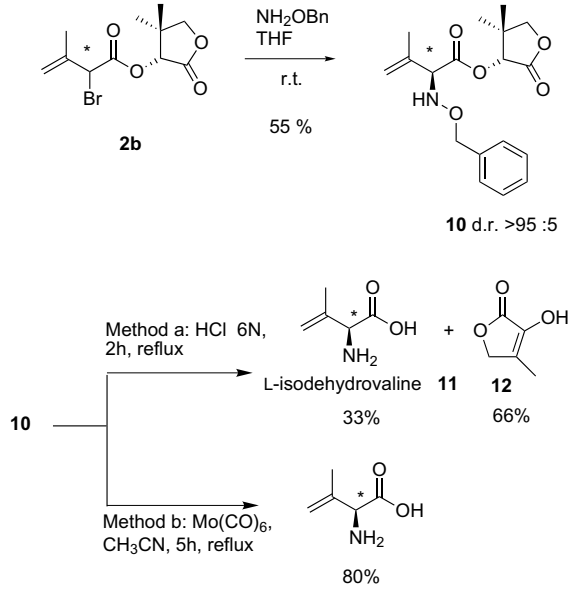
Although the substitution reactions gave excellent results in yields and good diastereomeric ratios, the



Scheme 6. Substitution on bromo derivative **2b** with *p*-MeO-benzylamine and allylamine.

transformation of the adducts **8** and **9** into the corresponding unsaturated amino acids proved troublesome with any attempt to remove the amine protection with previously reported methods failed.[12]

When the bromine displacement was performed with *O*-benzylhydroxylamine, starting either from a 1:1 diastereomeric mixture or from an enriched one, compound **10** was obtained as a single diastereoisomer in 55% yield (Scheme 7). In the literature, several methods for the reduction of hydroxylamine N–O bond have been reported.[13] We envisaged the $Mo(CO)_6$ method[13a,b] to be the more suitable for our purposes, since it does not affect double bonds. When we submitted **10** to acidic conditions, in order to remove the chiral auxiliary, we obtained directly the unsaturated amino acid L-isodehydrovaline **11** in 33% yield,[14] together with compound **12**,[15] deriving from the rearrangement of an α-imino intermediate. Better results were observed in the $Mo(CO)_6$ reaction on **10**, which allowed us to simultaneously remove the pantolactone with cleavage of the N–O bond, affording isodehydrovaline **11** in 80% yield. The comparison of the analytical data of **11** and of the corresponding BOC derivative, with the data reported in the literature[14c,16] allowed us to assign an (*S*) configuration to the stereogenic centre in position 2.



Scheme 7. Synthesis of L-isodehydrovaline.

3. Conclusion

The asymmetric synthesis of β,γ-unsaturated α-benzylamino acids **4** has been reported starting from α-bromo-α,β-unsaturated chlorides **1**. The treatment of the acyl chlorides with (*R*)-pantolactone in the presence of TEA, allowed the in situ formation of the deconjugated ketenes and their direct transformation into chiral esters **2**. The reactions occurred with good yields and high diastereomeric ratios. The substitution of bromine with benzylamine, followed by acid hydrolysis, allowed us to synthesise enantiomerically enriched α-benzylamino-β,γ-unsaturated acids **4**. The displacement of the bromine with other nitrogen nucleophiles also allowed us to synthesise *N*-unsubstituted-β,γ-unsaturated amino acids in good yield with complete diastereoselectivity.

4. Experimental

4.1. General procedures

Unless stated otherwise, chemicals were obtained from commercial sources and used without further purification. Flash chromatography was performed on Merck silica gel 60 (230–400 mesh). NMR spectra were recorded with a INOVA Varian spectrometer 300 MHz or with a Gemini Varian spectrometer 200 MHz. Chemical shifts are reported as δ values relative to the solvent peak of $CDCl_3$ set at $\delta = 7.27$ (^{1}H NMR) or $\delta = 77.0$ (^{13}C NMR). GC–MS analysis were performed on HP5890 series II chromatograph with HP5971 mass detector, HP-5 column (ultra low-bleed 5%-phenyl column based on diphenyl methylsiloxane chemistry), 50–250 °C programmed analysis. Optical rotations were recorded with Perkin Elmer Polarimeter 343. HPLC analysis of *N*-benzyl methyl esters 5 were performed on HP1090 liquid chromatograph equipped with UV detector, CHIRALCEL-OD chiral column, isocratic analysis with 90:10 hexane/isopropanol as eluent, 0.5 mL/min solvent flow, UV detector at 214.4 and 220.4 nm. HPLC analysis of norleucine **7** was performed on HP1090 liquid chromatograph equipped with UV detector, CHIROBIOT chiral column, isocratic analysis with 95:5 water/methanol as eluent, 0.5 mL/min solvent flow. MS analyses were performed with a HP1100 series mass spectrometer single quadrupole electrospray ionisation interface (ESI).

4.1.1. General procedure for the preparation of α-bromo-α,β-unsaturated chlorides 1a–c from α,β-unsaturated acids. To a stirred solution of α,β-unsaturated acid (10 mmol) in CH_2Cl_2 (10 mL), bromine (11 mmol, 0.56 mL) was added dropwise at 0 °C. The mixture was stirred overnight and then washed with a saturated solution of $Na_2S_2O_3$ to remove unreacted bromine. The organic layer was dried over Na_2SO_4 and concentrated to give the dibromo acid as a white powder. The product was dissolved in THF (10 mL) after which piperidine (40 mmol, 3.9 mL) was added in one portion at 0 °C. The

solution was stirred for 24 h at room temperature and then quenched with HCl 6 M (10 mL). After removing THF under reduced pressure, the aqueous acid layer was extracted twice with EtOAc (20 mL). The collected organic layers were dried over Na_2SO_4 and concentrated to give the α-bromo acid as a white powder. $SOCl_2$ (60 mmol, 4.4 mL) was then added to the neat product at 0 °C and the mixture then refluxed for 2 h. The α-bromo-α,β-unsaturated chlorides **1a–c** were isolated as *E*/*Z* unseparable mixtures by stilling under reduced pressure.

4.1.1.1. 2-Bromo-but-2-enoyl chloride 1a. Yield 82% (major isomer) ^{1}H NMR ($CDCl_3$) δ 2.05 (d, 3H, $J = 7.8$ Hz), 6.80 (q, 1H, $J = 7.8$ Hz). (minor isomer) ^{1}H NMR ($CDCl_3$) δ 2.13 (d, 3H, $J = 6.9$ Hz), 7.89 (q, 1H, $J = 6.9$ Hz).

4.1.1.2. 2-Bromo-3-methyl-but-2-enoyl chloride 1b. Yield 55% ^{1}H NMR ($CDCl_3$) δ 2.11 (s, 3H), 2.13 (s, 3H).

4.1.1.3. 2-Bromo-hex-2-enoyl chloride 1c. Yield 49% (major isomer) ^{1}H NMR ($CDCl_3$) δ 1.02 (t, 3H, $J = 7.2$ Hz), 1.58–1.68 (m, 2H), 2.47 (m, 2H), 7.8 (t, 1H, $J = 6.9$ Hz). (minor isomer) ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3H, $J = 7.2$ Hz), 1.48–1.57 (m, 2H), 2.40 (m, 2H), 6.68 (t, 1H, $J = 7.8$ Hz).

4.1.2. Preparation of α-bromo-α,β-unsaturated chlorides 1d from ethyl 3-methyl-hex-2-enoate. To a stirred solution of ethyl 3-methyl-hex-2-enoate (10 mmol) in CH_2Cl_2 (10 mL) at 0 °C, bromine (11 mmol, 0.56 mL) was added dropwise. The mixture was stirred overnight and then washed with a saturated solution of $Na_2S_2O_3$ to remove unreacted bromine. The organic layer was dried over Na_2SO_4 and concentrated to give the dibromo ester as a yellow oil. The product was dissolved in THF (10 mL) and then piperidine (40 mmol, 3.9 mL) added in one portion at 0 °C. The solution was stirred for 24 h at room temperature and then quenched with HCl 6 M (10 mL). After removing THF under reduced pressure, the acid aqueous layer was extracted twice with EtOAc (20 mL). The collected organic layers were dried over Na_2SO_4 and concentrated to give the α-bromo ester as a yellow oil. The product was refluxed in a 1:1 solution of 1 M NaOH/MeOH (10 mL) for 3 h and then, after removing methanol under reduced pressure, 1 M HCl was added to the aqueous residue to pH = 3. The solution was extracted twice in EtOAc (20 mL), the collected organic layers dried over Na_2SO_4 and concentrated to give the α-bromo acid as a white powder. $SOCl_2$ (60 mmol, 4.4 mL) was then added to the neat product at 0 °C and the solution then refluxed for 2 h. The α-bromo-α,β-unsaturated chloride **1d** was distilled under reduced pressure.

4.1.2.1. 2-Bromo-3-methyl-hex-2-enoyl chloride 1d. Yield 49% (major isomer) ^{1}H NMR ($CDCl_3$) δ 0.99 (t, 3H, $J = 7.5$ Hz), 1.50–1.60 (m, 2H), 2.08 (s, 3H), 2.40 (m, 2H). (minor isomer) ^{1}H NMR ($CDCl_3$) δ 0.94 (t, 3H, $J = 7.2$ Hz), 1.50–1.60 (m, 2H), 2.05 (s, 3H) 2.40 (m, 2H).

4.1.3. General procedure for the preparation of α-bromo-β,γ-unsaturated esters 2a–d from α,β-unsaturated chlorides 1a–d. To a stirred solution of (*R*)-pantolactone (2 mmol, 260 mg) in dry THF (10 mL), chloride **1** (2.1 mmol) in THF (1 mL) and TEA (1.1 or 2 equiv, see Table 1) in THF (1 mL) were added dropwise separately but simultaneously, at low temperatures under inert atmosphere. The mixture was stirred at the temperature and the time as reported in Table 1, with the exclusion of light. The reaction was quenched with a saturated solution of NH_4Cl (5 mL) and THF then removed under reduced pressure. The residue was diluted with Et_2O (20 mL) and washed twice with water. The organic layer was dried over Na_2SO_4 and solvent removed under reduced pressure. The crude reaction was analysed by ^{1}H NMR with the α-bromo-β,γ-unsaturated ester utilised without further purification.

4.1.3.1. 2-Bromo-but-3-enoic acid 4,4-dimethyl-2-oxo-tetrahydro-furan-3-yl ester 2a. (2*R*,3′*R*): ^{1}H NMR ($CDCl_3$) δ 1.18 (s, 3H), 1.25 (s, 3H), 4.10 (s, 2H), 4.94 (d, 1H, $J = 9.3$ Hz), 5.41 (s, 1H), 5.38–5.57 (m, 2H), 6.22 (dt, 1H, $J = 16.2$ Hz, 9.3 Hz).

(2*S*,3′*R*): ^{1}H NMR ($CDCl_3$) δ 1.19 (s, 3H), 1.26 (s, 3H), 4.10 (s, 2H), 4.99 (d, 1H, $J = 9.3$ Hz), 5.41 (s, 1H), 5.38–5.57 (m, 2H), 6.22 (dt, 1H, $J = 16.2$ Hz, 9.3 Hz).

4.1.3.2. 2-Bromo-3-methyl-but-3-enoic acid 4,4-dimethyl-2-oxo-tetrahydro-furan-3-yl ester 2b. (2*R*,3′*R*): ^{1}H NMR ($CDCl_3$) δ 1.15 (s, 3H), 1.28 (s, 3H), 2.02 (s, 3H), 4.07 (s, 2H), 5.07 (d, 1H, $J = 1$ Hz), 5.17 (m, 1H), 5.33 (s, 1H), 5.38 (s, 1H).

(2*S*,3′*R*): ^{1}H NMR ($CDCl_3$) δ 1.15 (s, 3H), 1.28 (s, 3H), 1.99 (s, 3H), 4.07 (s, 2H), 5.07 (d, 1H, $J = 1$ Hz), 5.17 (m, 1H), 5.31 (s, 1H), 5.40 (s, 1H).

4.1.3.3. 2-Bromo-hex-3-enoic acid 4,4-dimethyl-2-oxo-tetrahydro-furan-3-yl ester 2c. (2*R*,3′*R*): ^{1}H NMR ($CDCl_3$) δ 1.04 (t, 3H, $J = 9.5$ Hz), 1.20 (s, 3H), 1.25 (s, 3H), 2.23 (br t, 2H, $J = 9.6$ Hz), 4.18 (s, 2H), 4.93 (d, 1H, $J = 9.6$ Hz), 5.36 (s, 1H), 5.76–6.05 (m,2H).

(2*S*,3′*R*): ^{1}H NMR ($CDCl_3$) δ 1.04 (t, 3H, $J = 9.5$ Hz), 1.20 (s, 3H), 1.25 (s, 3H), 2.23 (br t, 2H, $J = 9.6$ Hz), 4.18 (s, 2H), 4.97 (d, 1H, $J = 9.6$ Hz), 5.39 (s, 1H), 5.76–6.05 (m, 2H).

4.1.3.4. 2-Bromo-3-methyl-hex-3-enoic acid 4,4-dimethyl-2-oxo-tetrahydro-furan-3-yl ester 2d. (2*R*,3′*R*): ^{1}H NMR ($CDCl_3$) δ 0.84 (t, 3H, $J = 7.8$ Hz), 1.18 (s, 3H), 1.24 (s, 3H), 1.55–1.62 (m, 2H), 2.22–2.36 (m, 2H), 4.07 (s, 2H), 5.03 (br s, 1H), 5.20 (br s, 1H), 5.37 (s, 1H), 5.45 (s, 1H).

(2*S*,3′*R*): ^{1}H NMR ($CDCl_3$) δ 0.84 (t, 3H, $J = 7.8$ Hz), 1.18 (s, 3H), 1.24 (s, 3H), 1.55–1.62 (m, 2H), 2.22–2.36

(m, 2H), 4.07 (s, 2H), 5.03 (br s, 1H), 5.20 (br s, 1H), 5.40 (s, 1H), 5.45 (s, 1H).

4.1.4. General procedure for the preparation of α-benzylamino-β,γ-unsaturated esters 3a–d from α-bromo-β,γ-unsaturated esters 2a–d. A solution of **2** (2 mmol), TEA (2.2 mmol, 0.3 mL) and benzylamine (2.4 mmol, 0.26 mL) in dry THF (10 mL) was stirred overnight at room temperature. After removing THF under reduced pressure, the residue was diluted with EtOAc (20 mL) and washed twice with water (10 mL). Compound **3** was isolated pure by flash chromatography on silica gel (cyclohexane/EtOAc, 8:2).

4.1.4.1. 2-Benzylamino-3-methyl-but-4-enoic acid 4,4-dimethyl-2-oxo-tetrahydro-furan-3-yl ester 3b. (2*S*,3′*R*): ^{1}H NMR ($CDCl_3$) δ 1.09 (s, 3H), 1.20 (s, 3H), 1.83 (s, 3H), 3.77 (s, 2H), 4.03 (s, 1H), 4.06 (s, 2H), 5.10 (m, 2H), 5.45 (s, 1H), 7.20–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 18.9, 19.6, 22.9, 40.4, 65.7, 75.1, 76.4, 115.5, 126.9, 128.1, 128.2, 139.2, 141.0, 171.7; GC–MS r.t. 24.76 min, *m*/*z* 317 (1), 204 (2), 160 (100), 91 (58), 65 (6).

(2*R*,3′*R*): ^{1}H NMR ($CDCl_3$) δ 1.09 (s, 3H), 1.20 (s, 3H), 1.86 (s, 3H), 3.77 (s, 2H), 3.97 (s, 1H), 4.06 (s, 2H), 5.10 (m, 2H), 5.41 (s, 1H), 7.20–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 18.9, 19.7, 22.9, 40.1, 65.8, 75.2, 76.4, 115.2, 126.9, 128.1, 128.2, 139.2, 140.9, 171.3; GC–MS r.t. 24.58 min, *m*/*z* 317 (2), 204 (2), 160 (100), 91 (100), 65 (8). $[\alpha]_D^{20} = +30.7$ (*c* 1; $CHCl_3$).

4.1.4.2. 2-Benzylamino-hex-3-enoic acid 4,4-dimethyl-2-oxo-tetrahydro-furan-3-yl ester 3c. (2*S*,3′*R*): ^{1}H NMR ($CDCl_3$) δ 1.01 (t, 3H, $J = 7.6$ Hz), 1.11 (s, 3H), 1.21 (s, 3H), *c* 3.76 (d, 1H, $J = 12.8$ Hz), 3.88 (d, 1H, $J = 12.8$ Hz), 4.01 (s, 1H), 4.07 (s, 2H), 5.44 (s, 1H), 5.46–5.56 (m, 1H), 5.86 (dt, 1H, $J = 6$ Hz, 13 Hz), 7.28–7.37 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 14.1, 20.8, 26.3, 41.3, 52.3, 63.5, 76.2, 77.1, 125.6, 128.1, 129.3, 129.4, 137.8, 140.4, 172.9, 173.5; GC–MS r.t. 38.63 min, *m*/*z* 331 (1), 218 (2), 174 (100), 91 (62), 65 (5).

(2*R*,3′*R*): ^{1}H NMR ($CDCl_3$) δ 1.01 (t, 3H, $J = 7.6$ Hz), 1.13 (s, 3H), 1.25 (s, 3H), 2.03–2.19 (m, 2H), 3.76 (d, 1H, $J = 12.8$ Hz), 3.88 (d, 1H, $J = 12.8$ Hz), 4.01 (s, 1H), 4.07 (s, 2H), 5.42 (s, 1H), 5.46–5.56 (m, 1H), 5.94 (dt, 1H, $J = 6$ Hz, 13 Hz), 7.28–7.37 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 14.1, 20.6, 26.3, 41.0, 52.1, 63.1, 76.2, 77.1, 126.0, 128.1, 129.3, 129.4, 138.3, 140.4, 172.8, 173.4; GC–MS r.t. 38.21 min, *m*/*z* 331 (3), 218 (13), 174 (4), 91 (100), 65 (5). $[\alpha]_D^{20} = +4.8$ (*c* 1; $CHCl_3$).

4.1.4.3. 2-Benzylamino-3-methyl-hex-2-enoic acid 4,4-dimethyl-2-oxo-tetrahydro-furan-3-yl ester 3d. (2*S*,3′*R*): ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 3H, $J = 7.8$ Hz), 1.11 (s, 3H), 1.23 (s, 3H), 1.47–1.58 (m, 2H), 2.04 (br s, 1H), 2.05–2.27 (m, 2H), 3.77 (d, 1H, $J = 12.8$ Hz), 3.84 (d, 1H, $J = 12.8$ Hz), 4.02 (s, 1H), 4.07 (s, 2H), 5.06 (d, 1H, $J = 1$ Hz), 5.14 (d, 1H, $J = 1$ Hz), 5.48 (s, 1H), 7.24–7.31 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 13.8, 19.7, 20.7, 23.0, 35.4, 40.4, 51.5, 64.9, 75.2, 76.1, 113.3, 127.1, 128.3, 128.4, 139.5, 146.0, 171.9, 172.4.

(2*R*,3′*R*): ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 3H, $J = 7.8$ Hz), 1.13 (s, 3H), 1.25 (s, 3H), 1.47–1.58 (m, 2H), 2.04 (br s, 1H), 2.05–2.27 (m, 2H), 3.77 (d, 1H, $J = 12.8$ Hz), 3.84 (d, 1H, $J = 12.8$ Hz), 4.00 (s, 1H), 4.07 (s, 2H), 5.09 (d, 1H, $J = 1$ Hz), 5.17 (d, 1H, $J = 1$ Hz), 5.43 (s, 1H), 7.24–7.31 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 13.8, 19.8, 20.7, 23.0, 35.1, 40.2, 51.4, 65.2, 75.3, 76.1, 113.2, 127.1, 128.3, 128.4, 139.5, 145.2, 171.6, 172.4. $[\alpha]_D^{20} = +17.2$ (*c* 0.8; $CHCl_3$).

4.1.5. Transformation of ester 3b into L-Valine methyl ester 6. A solution of **3b** (1 mmol, 317 mg) in HCl 6 M (5 mL) was refluxed for 2 h. After cooling to r.t., the aqueous mixture was concentrated and the residue dissolved in methanol (1 mL). The solution was adsorbed on a cation exchange resin (Dowex 50). (*R*)-pantolactone was recovered from the methanol eluate in almost quantitative yield. The resin was washed with distilled water until the washing came out neutral, then with 1.5 M NH_4OH. After evaporation of the aqueous solution, **4b** was isolated in 80% yield. The product was then diluted in MeOH and treated with an ethereal solution of CH_2N_2 until persistence of a yellow colour. Elimination of the solvents under reduced pressure allowed us to obtain **5b** in 95% yield. $Pd(OH)_2$ (40 mg) was added to a solution of **5b** in MeOH (15 mL). The reaction flask was evacuated, purged with hydrogen five times, and then stirred under a hydrogen atmosphere (40 psi) for 2 h. The solution was filtered over celite and concentrated to give L-valine methyl ester **6** in 55% yield.

4.1.5.1. (2*S*)-2-Benzylamino-3-methyl-but-4-enoic acid 4b. ^{1}H NMR (D_2O) δ 1.77 (s, 3H), 3.93 (s, 1H), 3.96 (d, 1H, $J = 13.5$ Hz), 4.01(d, 1H, $J = 13.5$ Hz), 5.01 (br s, 1H), 5.09 (br s, 1H), 7.26 (br s, 5H). ^{13}C NMR (D_2O) δ 19.4, 51.2, 65.8, 122.4, 129.8, 130.7, 131.8, 136.5, 137.5, 169.3; $[\alpha]_D^{20} = +44$ (*c* 1.4; H_2O).

4.1.6. (2*S*)-Methyl 2-benzylamino-3-methyl-but-4-enoate 5b. ^{1}H NMR ($CDCl_3$) δ 1.81 (s, 3H), 2.16 (br s, 1H), 3.74–3.76 (m, 5H), 3.88 (s, 1H), 5.05–5.07 (m, 2H), 7.31–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 18.7, 51.0, 51.9, 66.0, 115.0, 127.0, 128.2, 128.4, 139.5, 141.4, 173.0; GC–MS r.t. 16.7 min, *m*/*z* 219 (1), 160 (51), 128 (3), 91 (100), 65 (6); HPLC (isocratic 9:1 hexane/isopropanol) ee 82%, r.t. major enantiomer: 8.36 min, r.t. minor enantiomer: 9.12 min; $[\alpha]_D^{20} = +41$ (*c* 1; $CHCl_3$).

4.1.7. L-Valine methyl ester. ^{1}H NMR ($CDCl_3$) δ 1.11 (d, 3H, $J = 5.4$ Hz), 1.13 (d, 3H, $J = 5.4$ Hz), 2.40 (m, 1H), 3.81 (s, 3H), 3.94 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 18.3, 18.7, 30.1, 52.8, 58.6, 169.1; GC–MS r.t. 7.2 min, *m*/*z* 131 (1), 88 (36), 72 (100), 55(24); $[\alpha]_D^{20} = +11.7$ (*c* 0.8; $CHCl_3$).

4.1.8. Transformation of ester 3c into 5c. A solution of **3c** (1 mmol, 0.33 g) in HCl 6 M (5 mL) was refluxed for 2 h. The aqueous reaction mixture was concentrated and the residue dissolved in methanol (1 mL). The solution was adsorbed on cation exchange resin (Dowex 50) and (*R*)-pantolactone was recovered from the methanol layer in quantitative yield. The resin was washed with distilled water until the washing came out neutral, then with 1.5 M NH_4OH. **4c** was isolated after evaporation of the aqueous solution in 63% yield and then diluted in MeOH and treated with an ethereal solution of CH_2N_2 until persistence of the yellow colour. Elimination of the solvents under reduced pressure allowed to isolate **5c** in 95% yield.

4.1.8.1. (2*S*)-2-Benzylamino-hex-3-enoic acid 4c. ^{1}H NMR (D_2O) δ 0.85 (t, 3H, $J = 7.2$ Hz), 1.93–2.03 (m, 2H), 5.29–5.37 (m, 1H), 5.93 (br t, 1H, $J = 6.3$ Hz, 13.5 Hz), 7.31 (br s, 5H). ^{13}C NMR (D_2O) δ 11.7, 24.6, 48.6, 63.4, 118.4, 128.3, 128.7, 129.3, 130.3, 143.9, 172.2; $[\alpha]_D^{20} = +9.9$ (*c* 1.9; H_2O).

4.1.8.2. (2*S*)-Methyl 2-benzylamino-hex-3-enoate 5c. ^{1}H NMR ($CDCl_3$) δ 1.03 (t, 3H, $J = 6.5$ Hz), 1.90 (br s, 1H), 2.10 (dr t, 2H, $J = 6.1$ Hz, 6.5 Hz), 3.75 (s, 2H), 3.77 (s, 3H), 3.85 (d, 1H, $J = 7.5$ Hz), 5.45 (dd, 1H, $J = 7.5$ Hz, 15.3 Hz), 5.81 (dr t, 1H, $J = 15.3$ Hz, 6.1 Hz), 7.25–7.37 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 13.1, 25.3, 51.3, 51.9, 62.6, 125.2, 127.0, 128.3, 128.4, 136.7, 139.6, 173.9; GC–MS r.t. 16.7 min, *m*/*z* 233 (1), 188 (14), 174 (49), 91 (100), 65 (11); HPLC (isocratic 95:5 hexane/isopropanol) ee 11%, r.t. major enantiomer: 9.99 min, r.t. minor enantiomer: 11.65 min.

4.1.9. Transformation of acid 4c into norleucine 7. Pd/C (10%, 50 mg) was added to a solution of **4c** (1 mmol, 0.219 g) in MeOH (15 mL). The reaction flask was evacuated, purged with hydrogen five times, and then stirred under a hydrogen atmosphere (40 psi) for 2 h. The solution was filtered over celite and concentrated to give L-norleucine **7** in 75% yield.

4.1.9.1. L-norleucine 7. ^{1}H NMR (D_2O) δ 0.75 (t, 3H, $J = 7.5$ Hz), 1.21–1.26 (m, 4H), 1.71–1.78 (m, 2H), 3.76 (t, 1H, $J = 6.6$ Hz). ^{13}C NMR (D_2O) δ 12.7, 21.3, 26.0, 29.7, 54.4, 174.9. HPLC (isocratic 95:5 water/methanol) ee 11%, r.t. major enantiomer: 4.78 min, r.t. minor enantiomer: 5.51 min.

4.1.10. Transformation of ester 3d into 5d. A solution of **3d** (1 mmol, 0.319 g) in HCl 6 M (5 mL) was refluxed for 2 h. The aqueous reaction mixture was concentrated and the residue dissolved in methanol (1 mL). The solution was absorbed on a cation exchange resin (Dowex 50) and (*R*)-pantolactone recovered from the methanol layer in a quantitative yield. The resin was washed with distilled water until the washing came out neutral, then with 1.5 M NH_4OH. **4d** was isolated after evaporation of the aqueous solution in 76% yield, then diluted in MeOH and treated with an ethereal solution of CH_2N_2 until persistence of a yellow colour. Elimination of the solvents under reduced pressure allowed us to isolate **5d** in 95% yield.

4.1.10.1. (2*S*)-2-Benzylamino-3-methyl-hex-2-enoic acid 4d. ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 3H, $J = 7.2$ Hz), 1.45–1.55 (m, 2H), 2.09–2.13 (m, 2H), 3.71 (s, 1H), 3.76 (s, 2H), 5.04 (br s, 1H), 5.08 (br s, 1H), 7.31–7.37 (br s, 5H). ^{13}C NMR ($CDCl_3$) δ 13.9, 20.7, 34.6, 52.0, 67.4, 113.4, 127.3, 128.1, 128.5, 130.0, 146.9, 174.6; $[\alpha]_D^{20} = +13.1$ (*c* 0.7; $CHCl_3$).

4.1.10.2. (2*S*)-Methyl 2-benzylamino-3-methyl-hex-2-enoate 5d. ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3H, $J = 7.5$ Hz), 1.45–1.54 (m, 2H), 1.99–2.17 (m, 3H), 3.75 (s, 5H), 3.85 (s, 1H), 5.04 (br s, 1H), 5.08 (br s, 1H), 7.31–7.37 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 13.8, 20.7, 34.9, 51.4, 52.0, 65.4, 113.1, 127.0, 128.3, 128.4, 139.6, 145.9, 173.5; GC–MS r.t. 18.6 min, *m*/*z* 247 (2), 188 (60), 91 (100), 65 (9); HPLC (isocratic 95:5 hexane/isopropanol) ee 88%, r.t. major enantiomer: 8.75 min, r.t. minor enantiomer: 10.12 min; $[\alpha]_D^{20} = +44.6$ (*c* 1; $CHCl_3$).

4.1.11. Preparation of compounds 8 and 9 from α-bromo-β,γ-unsaturated ester 2b. A solution of **2b** (2 mmol, 0.58 g), TEA (2.2 mmol, 0.3 mL) and amine (2.4 mmol) in dry THF (10 mL) was stirred overnight at room temperature. After removing THF under reduced pressure, the residue was diluted with EtOAc (20 mL) and washed twice with water (10 mL). Compounds **8** and **9** were isolated pure by flash chromatography on silica gel (cyclohexane/EtOAc, 8:2).

4.1.11.1. 2-(*p*-Methoxy)benzylamino-3-methyl-but-4-enoic acid 4,4-dimethyl-2-oxo-tetrahydro-furan-3-yl ester 8. (2*S*,3′*R*): ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 3H), 1.19 (s, 3H), 1.81 (s, 3H), 3.70 (s, 2H), 3.80 (s, 3H), 4.00 (s, 1H), 4.04 (br s, 2H), 5.01–5.04 (m, 2H), 5.43 (s, 1H), 6.84–6.89 (m, 2H), 7.25–7.29 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 19.0, 19.7, 23.0, 40.5, 50.5, 55.2, 65.6, 75.1, 76.4, 113.7, 115.5, 129.5, 131.3, 141.2, 171.8; GC–MS r.t. 27.86 min, *m*/*z* 347 (2), 189 (24), 121 (100), 77 (8).

(2*R*,3′*R*): ^{1}H NMR ($CDCl_3$) δ 1.10 (s, 3H), 1.21 (s, 3H), 1.84 (s, 3H), 3.70 (s, 2H), 3.82 (s, 3H), 3.94 (s, 1H), 4.05 (br s, 2H), 5.01–5.04 (m, 2H), 5.40 (s, 1H), 6.84–6.89 (m, 2H), 7.25–7.29 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 19.0, 19.8, 23.2, 40.4, 50.7, 55.2, 65.7, 75.1, 76.0, 113.8, 115.5, 129.4, 131.2, 141.2, 171.6; GC–MS r.t. 27.89 min, *m*/*z* 347 (2), 189 (21), 121 (100), 77 (6). $[\alpha]_D^{20} = +30.8$ (d.r. 81/19, *c* 1; $CHCl_3$).

4.1.11.2. 2-Allylamino-3-methyl-but-4-enoic acid 4,4-dimethyl-2-oxo-tetrahydro-furan-3-yl ester 9. (2*S*,3′*R*): ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 3H), 1.18 (s, 3H), 1.80 (s, 3H), 3.21 (dd, 2H, $J = 7.2$, 1.6 Hz), 4.02–4.04 (m, 1H);

4.03 (br s, 2H), 5.04–5.14 (m, 4H), 5.42 (s, 1H), 5.81–5.99 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 18.8, 19.6, 22.8, 40.3, 49.7, 65.7, 75.1, 76.0, 115.5, 116.7, 135.8, 141.2, 171.9; GC–MS r.t. 19.98 min, m/z 267 (2), 110 (100).

(2*R*,3′*R*): ^{1}H NMR ($CDCl_3$) δ 1.12 (s, 3H), 1.22 (s, 3H), 1.86 (s, 3H), 3.21 (dd, 2H, $J = 7.2$, 1.6 Hz), 4.02–4.04 (m, 1H); 4.03 (br s, 2H), 5.04–5.14 (m, 4H), 5.41 (s, 1H), 5.81–5.99 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 18.8, 19.8, 22.8, 40.1, 49.7, 65.8, 75.3, 76.0, 115.1, 116.7, 135.9, 140.9, 172.6; GC–MS r.t. 19.82 min, m/z 267 (3), 110 (100). $[\alpha]_D^{20} = +28.5$ (c 1; $CHCl_3$).

4.1.12. Preparation of compound 10 from α-bromo-β,γ-unsaturated ester 2b. A solution of **2b** (2 mmol, 0.58 g), and *O*-benzylhydroxylamine (2 equiv, 4 mmol, 8 mL of solution 0.5 M in CH_2Cl_2) in dry THF (20 mL), was stirred at room temperature for 40 h. After removing THF under reduced pressure, the residue was diluted with CH_2CL_2 (20 mL) and washed twice with water (10 mL). Compound **10** was isolated pure by flash chromatography on silica gel (cyclohexane/EtOAc, 8:2).

4.1.12.1. 2-Benzyoxylamino-3-methyl-but-4-enoic acid 4,4-dimethyl-2-oxo-tetrahydro-furan-3-yl ester 10. (2*S*,3′*R*): ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 3H), 1.18 (s, 3H), 1.82 (s, 3H), 4.05 (s, 2H), 4.30 (s, 1H), 4.74 (s, 2H), 5.06 (br s, 2H), 5.46 (s, 1H), 5.96 (br s, 1H), 7.29–7.35 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 19.6, 20.6, 22.9, 40.6, 60.3, 68.8, 75.2, 75.6, 116.0, 127.8, 128.2, 128.5, 137.4, 138.2, 170.5, 171.8; GC–MS r.t. 17.84 min, m/z 225 (2), 114 (36), 99 (100), 68 (48), 55 (20). $[\alpha]_D^{20} = +30.9$ (c 0.9; $CHCl_3$).

4.1.13. Transformation of compound 10 into (L)-isodehydrovaline 11. *Method a*: A solution of **10** (1 mmol, 0.33 g) in HCl 6 M (5 mL) was refluxed for 2 h. The aqueous reaction mixture was concentrated and the residue dissolved in methanol (1 mL). The solution was absorbed on a cation exchange resin (Dowex 50). (*R*)-pantolactone, benzyl alcohol and compound **12** were recovered from the methanol layer in quantitative yield. The resin was washed with distilled water until the washing came out neutral, then eluted with 1.5 M NH_4OH. L-isodehydrovaline **11** was isolated after evaporation of the ammonia solution in 33% yield (>95% ee). The spectroscopic data was then compared with the literature values.[14c]

The transformation into an *N*-BOC derivative following a known procedure and the comparison with literature data for this compound,[16b] further confirmed the attribution.

Method b: A solution of **10** (1 mmol, 0.33 g) in H_2O (5 mL) and CH_3CN (0.3 mL) was refluxed for 5 h. The reaction mixture was diluted with MeOH (5 mL) and filtered over celite. The solution was concentrated and the residue dissolved in methanol (1 mL). The solution was absorbed on a cation exchange resin (Dowex 50). (*R*)-pantolactone and benzyl alcohol were recovered from the methanol layer in a quantitative yield. The resin was washed with distilled water until the washing came out neutral, then eluted with 1.5 M NH_4OH. L-isodehydrovaline **11** was isolated after evaporation of the ammonia solution in 80% yield (>95% ee). The spectroscopic data was then compared with literature values.[14c]

The transformation into the *N*-BOC derivative following a known procedure and the comparison with literature data for this compound,[16] further confirmed the attribution.

L-isodehydrovaline **11**. $[\alpha]_D^{20} = +110.7$ (c 0.8 H_2O). {Lit.[14c] $[\alpha]_D^{20} = +113$ (c 3.64 H_2O)}.

L-*N*(-*tert*-Butyloxycarbonyl)isodehydrovaline $[\alpha]_D^{20} = +53.7$ (c 0.8 MeOH). {Lit.[16b] $[\alpha]_D^{20} = +56.2$ (c 1.0 MeOH)}.

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