Aminoalkyl-Substituted α-Methylene-γ-butyrolactones from α-Amino Acids Using an Indium-Mediated Barbier Allyl Addition

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The indium-mediated reaction of Z-protected α-amino aldehydes **1**–**6** with 2-(bromomethyl)acrylates **8/9** in aqueous solvents has been investigated. The preference for the formation of *syn*-configured homoallyl alcohols **10**–**16** (diastereoselectivities ranging from 2:1 to 32:1, yields 68–93%) may be explained by a chelate-controlled reaction. No racemization occurred during the preparation and transformation of the amino aldehydes. Acid-catalyzed esterification (H_2SO_4 in Et_2O) led to α-methylene-γ-butyrolactones **17**–**22** with yields ranging from 89 to 97%. The configurations of all diastereoisomers were established by five X-ray crystallographic analyses and by comparision of the NMR spectra.

Introduction

The α-methylene-γ-butyrolactone ring is a central structural element in a plethora of natural products, most of them sesquiterpenoids.[1−4] Most of the 6000 known compounds exhibit various biological activities including antibiotical,[5][6] fungicidal,[7] anthelmintical,[8] and antitumoral properties.[6][8] Additionally, some of them are potent antiplatelet agents,[8] antifeedants[5] or antagonists against opioid receptors.[9] Furthermore, it is not only complex, polycyclic structures that show biological activity, as even the parent α-methylene-γ-butyrolactone (tulipaline A) and its hydroxylated derivative tulipaline B are effective fungicides.[10][11]

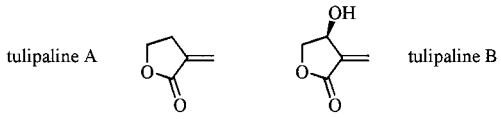

Figure 1. Tulipaline A and B − fungicidal α-methylene-γ-butyrolactones

Nevertheless, most α-methylene-γ-butyrolactones are too toxic for therapeutic utilization; consequently, there is a need for new, nontoxic compounds with this structural moiety. In addition to their biological activities, α-methylene-γ-butyrolactones are useful intermediates in organic synthesis; starting with such compounds peptide analogues or HIV-1 protease inhibitors have, for example, been prepared.[12−14]

α-Methylene-γ-butyrolactones can be prepared by cyclization of γ-hydroxy-α-methylene esters, which are accessible from aldehydes through allyl addition of 2-(bromomethyl)acrylates in a Barbier-type reaction.[15−18] Of all the metals employed in the Barbier reaction (Zn,[13,14,16,17,19,20] Sn,[16,17,19,20] Pb,[21] Cr,[22][23] Bi,[24] Sb,[25][26] Mn,[27] and In[19,23,28−43]), indium is especially important.[44][45] Since no activation by sonication or acid catalysis is necessary with indium, even acid-sensitive substrates like acetals can be allylated under these conditions. Indium has been reported to lead to better yields and diastereoselectivities,[19,23,28−35] especially in the allyl addition to hydroxy aldehydes, where drastic improvements were observed.[36−43] In addition, indium-mediated Barbier reactions can be favourably performed in water or in mixtures of water with organic solvents.[16,17,19,20] Though one might assume that water-sensitive species should be intermediates in these reactions, no hydrolysis of the organometallic compound occurs. The intermediacy of radical species might be responsible for this observation.[16][46] As both a hydroxy group and a C=C double bond are simultaneously introduced into a molecule, the allyl addition to carbonyl compounds is very interesting with respect to the possibility of further transformations of the resulting intermediates.

Only a few examples of indium-mediated allyl additions to amino aldehyde derivatives have been reported up to now.[47][48] In this paper we describe the utilization of α-amino acids for the preparation of γ-aminoalkyl-substituted α-methylene-γ-butyrolactones.

Results and Discussion

The intended reaction sequence for the preparation of the homoallyl alcohols is depicted in Scheme 1.

We started with different amino acids: alanine, phenylalanine, leucine, valine, isoleucine, and *tert*-leucine. We chose a Z protection of the amino functions to allow for an easier detection of the products during HPLC or MPLC separation. To establish the best method for the preparation of the respective amino aldehydes,[49] we tried several reaction sequences (Scheme 2): Swern[50][51] or Dess−Martin periodinane (DMP)[52][53] oxidation of the corresponding amino alcohols, reduction of *N*-methoxy-*N*-methyl carboxam-

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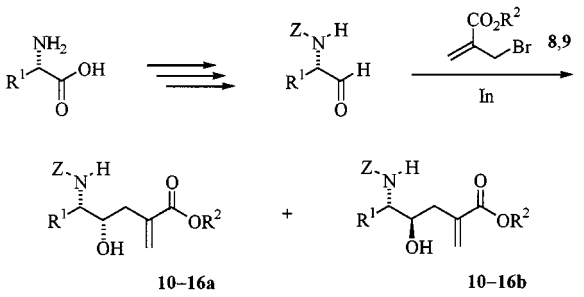
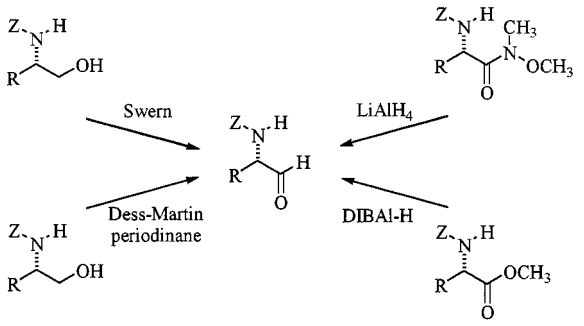


Scheme 1. Allyl addition of amino aldehydes **1**–**6** with 2-(bromomethyl)acrylates **8** or **9** (for specification of substituents see Table 1)

ides[54][55] (Weinreb amides[56]) with $LiAlH_4$ or reduction of methyl esters with DIBAl-H.[57] Since amino aldehydes should not be purified (vide infra) it is essential to have a clean and complete preparation method. DIBAl-H reduction led to considerable amounts of amino alcohols as side products. Contrary to published data,[58] we found it necessary to purify Weinreb amides before transformation to obtain a clean reduction. Amino aldehyde derivatives are not very stable[59] and racemization to a considerable extent has been observed during chromatography;[60] purification at this stage is, therefore, not profitable. It has been noticed before that reduction of Weinreb amides leads to a partial racemization during the reaction.[54] We checked this by NMR-spectroscopic analysis of amino aldehyde **4** by addition of a chiral shift reagent. Using 21 mol-% of tris{3-[(heptafluoropropyl)(hydroxy)methylene]-*d*-camphorato}-praseodym(III) [$Pr(hfc)_3$],[61] we found that reduction of Weinreb amides led to products with about 96% ee. Nevertheless, no racemization occurred when amino alcohols were oxidized with DMP. Since this method is, in addition, very easy to perform, we chose it for the preparation of all aldehydes used in this work. Minor amounts of side products were not removed, since the products of the allyl additions could be easily purified by chromatography.



Scheme 2. Preparation of amino aldehydes

The amino aldehydes generated in situ were immediately (within 1 h) allylated with methyl 2-(bromomethyl)acrylate (**8**). We used reaction conditions which we optimized for the allyl addition to Z-protected valinal **4** with the parent allyl bromide **7**.[62] We found that 1.7 equivalents allyl bromide and 1.1 equivalents of indium in ethanol/water (4:1, v/v) gave best results. No differences in diastereoselectivity and yield have been observed with THF/$NH_4Cl_{(aq.)}$ (5:1, v/v). The presence of water seems to be essential for a clean and fast reaction. With anhydrous THF or CH_2Cl_2, the reaction times increased drastically; the reaction was not complete even after 3 d. With DMF the reaction proceeded, but the diastereoselectivity dropped significantly. No salt effect[63] was observed when anhydrous lithium bromide was added to DMF. With allyl iodide, no diastereoselectivity was observed. We therefore used ethanol/water as the solvent for the following reactions. In the allyl addition to amino aldehydes **1**–**6** with 2-(bromomethyl)acrylates **8** or **9**, the homoallyl alcohols **10**–**16** were formed in yields ranging from 68 to 93%. Diastereoisomer ratios were determined by HPLC analysis of the crude isomer mixtures. The diastereoselectivities (67:33 up to 97:3) are essentially dependent on the bulkyness of the amino acid side chain; while with less demanding side chains (starting with alaninal or phenylalaninal, Table 1, entries 1–3) the diastereoselectivities are about 2:1, leucinal and valinal gave 3:1 and 5:1 ratios, respectively (entries 4, 5). Best diastereoselectivities could be obtained with isoleucinal (8:1, entry 6) and *tert*-leucinal (32:1, entry 7). No changes in yield or diastereoselectivity were observed, when the sterically more demanding *tert*-butyl 2-(bromomethyl)acrylate (**9**)[48][64] was used instead of the methyl ester **8** (entry 2). All isomers could be easily separated by MPLC.

Table 1. Allyl addition to amino aldehydes **1**–**6** with 2-(bromomethyl)acrylates **8** or **9** (see Scheme 1)

Entry	Aldehyde	R^1	R^2	Yield (%)	d.r.	Product
1	**1**	Me	Me	68	68:32	**10a/b**
2	**1**	Me	*t*Bu	72	67:33	**11a/b**
3	**2**	Bn	Me	73	68:32	**12a/b**
4	**3**	*i*Bu	Me	81	75:25	**13a/b**
5	**4**	*i*Pr	Me	84	82:18	**14a/b**
6	**5**	*s*Bu	Me	85	89:11	**15a/b**
7	**6**	*t*Bu	Me	93	97:3	**16a/b**

Chemical determination of the relative configuration of the newly formed stereogenic centres failed; a transformation to the corresponding oxazolidin-2-ones and subsequent measurement of the coupling constants could not be achieved.[47,65,66] Fortunately, the homoallyl alcohols **12a** and **16b** yielded crystals suitable for an X-ray crystallographic analysis (homoallyl alcohol **12a** is depicted in Figure 2).[67] The hydroxy and amino functions in this isomer turned out to be *syn*-arranged (2′*S*,3′*S*). By comparision of the NMR spectra, this configuration could be established for all the first eluted, major isomers **10a**–**16a**. The lower polarity of the *syn* isomers has already been mentioned for similar compounds.[47]

The results presented herein for the preparation of homoallyl alcohols are significantly better than those achieved in similar Barbier reactions. The allyl addition to Boc-valinal with ethyl 2-(bromomethyl)acrylate and $CrCl_2$ as reducing salt led to the corresponding homoallyl alcohol with a poor 55:45 diastereoselectivity and with 75% yield.[22]

2-(2-Hydroxyalkyl)propenoates usually cyclize easily to the corresponding α-methylene-γ-butyrolactones. The

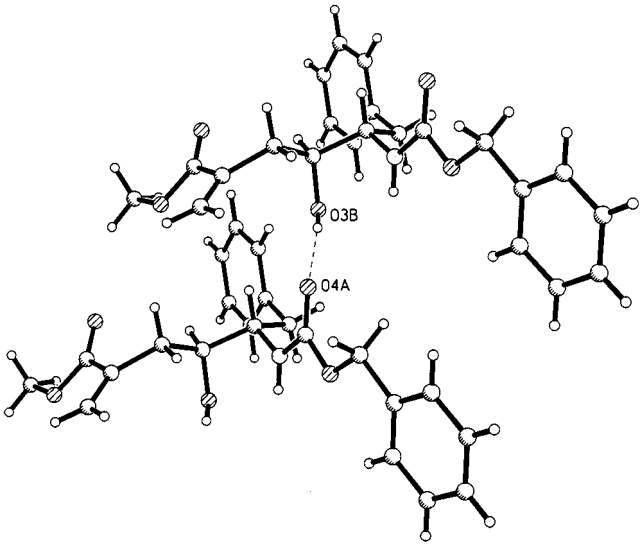
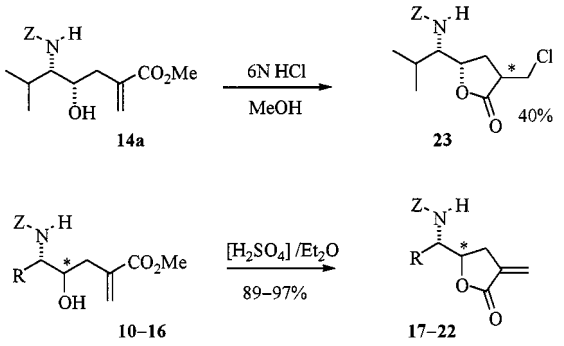


Figure 2. Molecular structure of the homoallyl alcohol **12a** as determined by X-ray crystallographic analysis

homoallyl alcohols presented herein turned out to be quite stable; we think that intramolecular hydrogen bonds (which are present in the crystal structure, too) might be responsible for this unusual stability. Whilst several methods for the lactonization of similar homoallyl alcohols are reported in the literature,[35] the first γ-hydroxy ester **14a** tested was neither cyclized by a catalytic amount of toluenesulfonic acid,[68] nor by addition of trifluoroacetic acid.[69] Addition of sodium hydride[22] led to decomposition of the starting material and thermal cyclization[70] gave very slow conversion. When we used 6 N hydrogen chloride in methanol as the solvent, lactonization proceeded quickly, but in addition formation of the chlorinated lactone **23** was observed (Scheme 3 and Table 2, entry 9). Obviously, a Michael addition of hydrogen chloride to the unsaturated lactone **20a** occurred. HPLC analysis showed that at the beginning of the reaction the lactone **20a** was formed, whose concentration decreased with longer reaction times at the benefit of the chlorinated lactone **23** (only one isomer was observed!). The amount and the rate of the chlorination was lower with 3 N HCl/MeOH and could be essentially suppressed with 1 N HCl/MeOH (careful HPLC monitoring is necessary). Nevertheless, under these conditions 15−25% of the starting materials were recovered (method A in Table 2). To avoid a conjugate addition of chloride, we used Dowex-H^+ as a strong, non-nucleophilic acid. No side product was observed, but complete reaction could not be obtained under these reaction conditions. About 20% starting material was isolated (method B). Best results were observed with 2 vol-% concd. sulfuric acid in ether (method C). After aqueous work up, the α-methylene-γ-butyrolactones **17**−**22** were isolated as pure compounds (elemental analysis within 0.3% boundaries without further purification!) with yields ranging from 89 to 97%.

The configuration of lactones **17a**, **19b**, and **20a** could be unambiguously determined by crystallographic analyses (lactone **17a** is depicted in Figure 3) giving again evidence



Scheme 3. Cyclization of homoallyl alcohols **10**−**16** to α-methylene-γ-butyrolactones **17**−**22** (for specification of substituents see Table 2)

Table 2. Cyclization of homoallyl alcohols **10**−**16** to α-methylene γ-butyrolactones **17**−**22** (see Scheme 3)

Entry	Homoallyl alcohol	R	Method[a]	Yield (%)	Lactone
1	**10a**	Me	A	61[b]	**17a**
2	**10b**	Me	B	61[b]	**17b**
3	**10a**	Me	C	95	**17a**
4	**12a**	Bn	B	61[b]	**18a**
5	**12b**	Bn	A	58[b]	**18b**
6	**13a**	*i*Bu	C	90	**19a**
7	**13b**	*i*Bu	C	89	**19b**
8	**14a**	*i*Pr	A	63[b]	**20a**
9	**14a**	*i*Pr	A[c]	17[d]	**20a**
10	**14a**	*i*Pr	C	97	**20a**
11	**14b**	*i*Pr	B	63[b]	**20b**
12	**15a**	*s*Bu	C	94	**21a**
13	**16a**	*t*Bu	C	96	**22a**

[a] See Experimental Section. − [b] 15−25% starting material could be recovered. − [c] 6 N HCl/MeOH. − [d] 20% starting material and 40% HCl adduct **23** were isolated.

for the configurations of the parent homoallyl alcohols.[67] The α-methylene-γ-butyrolactone ring turned out to be almost planar due to three sp^2-configured atoms O-1, C-2, and C-3, which is very advantageous for further diastereoselective reactions at the double bonds. One side of the molecule is effectively blocked by the aminoalkyl side chain.

To exclude racemization during the Barbier reaction, we checked the NMR spectra of the isoleucine-derived products **15a/b**. Since in these compounds an additional stereogenic centre is present, one should be able to observe signals of a second pair of diastereoisomers when epimerization occurred. Actually, no signals of a second pair of diastereoisomers could be detected. (Additional peaks in the spectra of **15a** and **15b** turned out to be due to rotamers; the peaks disappear completely at 60°C.)

In addition, we prepared the Mosher ester of the homoallyl alcohol **14a** by treatment with (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA-Cl).[71][72] Inspection of the (*Z*)-methylene proton signal (which is not superimposed by other signals) in the ^{1}H-NMR spectra showed no trace of the "false" diastereoisomer. Therefore, we esti-

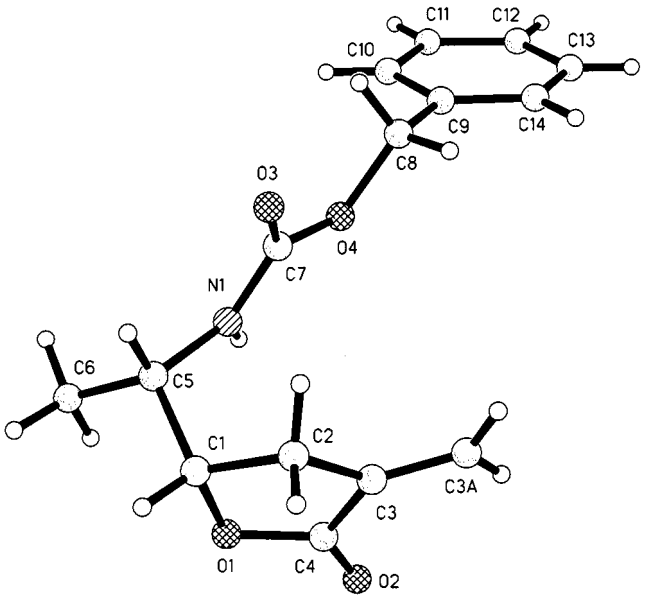
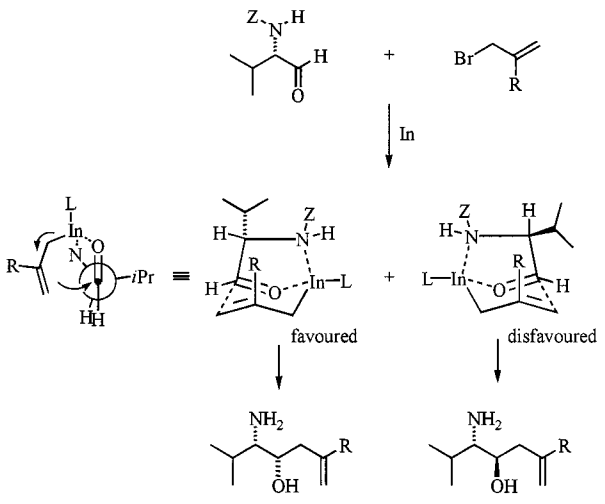


Figure 3. Molecular structure of lactone **17a** as determined by X-ray crystallographic analysis

mate the enantiopurity of the homoallyl alcohols to be greater than 98:2.

The observed stereochemistry might be explained by a Zimmerman−Traxler-like transition state[73] with additional complexation of the indium ion by the carbamate nitrogen atom (Scheme 4) or by the double-bonded carbamate oxygen atom (via a seven-membered ring[74]). Assuming that the bulky side chain in the amino aldehyde is opposite to the approaching allyl compound would explain the preference for the *syn*-configured product. This approach is equivalent to a model proposed by Felkin and Anh (Scheme 4, left hand).[75][76] Similar explanations have been given for allyl additions to α-hydroxy aldehydes.[47] Nevertheless, a boat-like conformation of the transition state could be assumed as well; again, this would explain, by similar arguments, the observed diastereoselectivity.



Scheme 4. A chelating model as a possible explanation for the observed diastereoselectivity in the formation of homoallyl alcohols

Conclusion

We have shown that α-amino aldehydes can be cleanly transformed into δ-amino-γ-hydroxy-α-methylenecarboxylic esters with high yields and without racemization by an indium-mediated Barbier reaction. The preference for the *syn*-configured products can be explained by a chelate model. The α-methylene lactones, which are effectively accessible by acid-catalyzed cyclization should be ideal starting materials for further transformations at the conjugate double bond. Work in this direction is ongoing in our laboratories.

Experimental Section

General: Solvents for chromatography and for work up, e.g. ethyl acetate (EA) and light petroleum ether (PE) were distilled prior to use; diethyl ether (ether) was distilled from KOH/$FeSO_4$. Ether and THF used for reactions were distilled from Na/benzophenone. Et_3N was distilled from CaH_2 and stored over molecular sieves (4 Å); $ClCO_2Et$ was distilled. Dowex 50 W X 8 (Fluka) was purified and acidified as published.[77] 2-(Bromomethyl)acrylates **8**[78−82] and **9**[64] were synthesized in accordance with published procedures, whilst amino acid derivatives were prepared by standard methods.[83][84] Amino aldehydes have been prepared as published [Swern oxidation,[50] periodinane oxidation (GP1),[53] reduction of methyl esters with DIBAl-H[57], reduction of Weinreb amides.[54]] Indium was purchased from Aldrich (powder, 100 mesh, 99.99%). Common amino acid abbreviations are used.[85] Moisture-sensitive reactions were performed in dried vessels (150°C, 24 h) under nitrogen using syringe techniques. − Flash column chromatography: Merck silica gel 60 (230−400 mesh). − TLC: Precoated sheets, Alugram SIL G/UV_{254} Macherey−Nagel; detection by UV extinction or by cerium molybdate solution [phosphomolybdic acid (25 g), $Ce(SO_4)_2 \cdot H_2O$ (10 g), concd. H_2SO_4 (60 mL), H_2O (940 mL)]. − MPLC: Detection with a UV detector. HPLC: Analyses of diastereoisomer distribution were carried out with a Pharmacia LKB, RSD 2140 apparatus with a Pharmacia LKB, RSD 2249 mixer and diode-array detection (Pharmacia RSD 2140) on a LiChrosorb Si 60, Merck (hexane/EA, flow: 2.0 mL/min) chromatographic column. − ^{1}H- and ^{13}C-NMR spectra were recorded with a Bruker ARX 500 spectrometer at room temp. in $CDCl_3$ unless otherwise indicated. Chemical shifts, δ, in ppm relative to internal TMS (δ = 0 or to resonances of the solvent (^{1}H: $CHCl_3$, δ = 7.24; ^{13}C: $CDCl_3$, δ = 77.0), *J* in Hz. − Mass spectra were recorded using a Finnigan MAT 95 [FAB or CI (CH_4 or NH_3) technique] or a Varian MAT 711 instrument (EI). − IR spectra were recorded with a Bruker IFS 28 or a Perkin−Elmer 283 instrument. − Elemental analyses were performed by the service of the Institut für Organische Chemie, Stuttgart. − Melting points are not corrected.

General Procedure for the Oxidation of Amino Alcohols with Dess−Martin Periodinane (GP1):[53] The Z-protected amino alcohol (1.00 mmol) in dry CH_2Cl_2 (2 mL) was added to a stirred solution of periodinane (530 mg, 1.25 mmol) in CH_2Cl_2 (5 mL) at 0°C and warmed to room temp. When the reaction was finished (as monitored by TLC; occasionally, addition of further DMP is necessary), excess of the oxidant was destroyed by addition of 1 N NaOH solution After 5 min of vigorous stirring, the mixture was diluted with Et_2O (10 mL), the organic layer was separated, and the aqueous layer was extracted twice with Et_2O. The organic layers were washed with brine, dried ($MgSO_4$), and the solvent was removed.

General Procedure for the Synthesis of Homoallyl Alcohols 10−16a/b (GP2): The Z-protected α-amino aldehyde (1.00 mmol) was dissolved in EtOH (8 mL) at room temp. After addition of water (2 mL), methyl 2-(bromomethyl)acrylate (1.70 mmol, 304 mg), and indium (1.10 mmol, 121 mg), the reaction mixture was stirred for 4 h at room temp. (monitored by TLC). 1 N HCl solution (5 mL) was added and the solution was extracted with EA (3 × 10 mL). The organic layers were combined, subsequently extracted with satd. $NaHCO_3$ solution (10 mL) and satd. NaCl solution (2 × 10 mL), dried ($MgSO_4$), and the solvents were removed in a rotatory evaporator yielding a crude product, which was dissolved in EA and filtered through a pad of silica gel (5 g). The diastereomeric ratio was determined by HPLC, separation of the isomers was achieved by MPLC.

(2′*S*,3′*S*)- and (2′*R*,3′*S*)-Methyl 2-[3-(Benzyloxycarbonylamino)-2-hydroxybutyl]propenoate (10a,b): Z-Ala-H (**1**, 820 mg, 3.96 mmol) was treated in accordance with GP2 yielding a crude mixture of isomers, whose isomeric ratio was determined to be **10a/b** = 68:32. Separation by MPLC (PE/EA = 4:1) led to the pure isomers **10a** (560 mg, 46%) and **10b** (270 mg, 22%). − **10a**: Colourless solid, m.p. 58−60°C. − t_R (HPLC; hexane/EA, 7:3) = 11.3 min. − $[\alpha]_D^{20} = -8.9$ (c = 1, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3480 cm^{-1} (O−H), 3320 (N−H), 2970, 2920 (C−H), 1680 (C=O), 1520 (C=C). − ^{1}H NMR (500 MHz; $CDCl_3$): δ = 1.22 (d, ^3J = 6.7 Hz, 3 H, 4′-H), 2.43 (dd, ^2J = 14.1 Hz, ^3J = 8.8 Hz, 1 H, 1′-H_A), 2.54 (dd, ^2J = 14.1 Hz, ^3J = 3.3 Hz, 1 H, 1′-H_B), 3.03 (d, ^3J = 3.9 Hz, 1 H, OH), 3.68 (m_c, 1 H, 2′-H), 3.75−3.80 (m, 1 H, 3′-H), 3.76 (s, 3 H, OCH_3), 5.10 (s, 2 H, CH_2Ph), 5.16 (d, ^3J = 8.9 Hz, 1 H, NH), 5.69 (s, 1 H, 3-H_E), 6.24 (s, 1 H, 3-H_Z), 7.29−7.39 (m, 5 H, C_6H_5). − ^{13}C NMR (125 MHz; $CDCl_3$): δ = 18.7 (C-4′), 38.1 (C-1′), 50.6 (C-3′), 52.2 (OCH_3), 66.7 (*C*H_2Ph), 73.4 (C-2′), 128.1, 128.5, 128.6 (C_6H_5, C-3, one signal covered), 136.5, 137.0 ($C_6H_{5\ ipso}$, C-2), 156.4 (N−C=O), 168.4 (C-1). − MS (FAB); *m*/*z* (%): 330 (6) [M^+ + Na], 308 (41) [M^+ + H], 276 (14) [$M^+ - CH_3O$], 178 (4) [$M^+ - CH_3OH - C_5H_5O_2$], 91 (100) [$C_7H_7^+$]. − $C_{16}H_{21}NO_5$ (307.3): calcd. C 62.53, H 6.89, N 4.56; found C 62.52, H 6.90, N 4.50. − **10b**: Colourless solid, m.p. 85−87°C. − t_R (HPLC; hexane/EA, 7:3) = 14.4 min. − $[\alpha]_D^{20} = -7.4$ (c = 1, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3300 cm^{-1} (br., O−H, N−H), 3040, 2920 (C−H), 1710 (C=O, ester), 1690 (C=O, carbamate), 1540 (C=C). − ^{1}H NMR (500 MHz; $CDCl_3$): δ = 1.16 (d, ^3J = 6.5 Hz, 3 H, 4′-H), 2.36 (dd, ^2J = 14.1 Hz, ^3J = 9.0 Hz, 1 H, 1′-H_A), 2.50 (dd, ^2J = 14.2 Hz, ^3J = 3.0 Hz, 1 H, 1′-H_B), 2.97 (d, ^3J = 3.7 Hz, 1 H, OH), 3.72−3.78 (m, 2 H, 2′-H, 3′-H), 3.76 (s, 3 H, OCH_3), 5.07 (d, ^2J = 12.2 Hz, 1 H, C$H_A$$H_B$Ph), 5.10 (d, ^2J = 12.2 Hz, 1 H, C$H_A$$H_B$Ph), 5.17 (d, ^3J = 8.9 Hz, 1 H, NH), 5.71 (s, 1 H, 3-H_E), 6.26 (d, J = 1.2 Hz, 1 H, 3-H_Z), 7.29−7.39 (m, 5 H, C_6H_5). − ^{13}C NMR (125 MHz; $CDCl_3$): δ = 14.7 (C-4′), 36.8 (C-1′), 51.1 (C-3′), 52.2 (OCH_3), 66.7 (*C*H_2Ph), 73.4 (C-2′), 128.1, 128.2, 128.5 (C_6H_5, C-3, one signal covered), 136.5, 137.0 ($C_6H_{5\ ipso}$, C-2), 156.1 (N−C=O), 168.3 (C-1). − MS (FAB); *m*/*z* (%): 330 (10) [M^+ + Na], 308 (100) [M^+ + H], 276 (7), [$M^+ - CH_3O$], 178 (8), [$M^+ - CH_3OH - C_5H_5O_2$], 97 (9) [$C_5H_5O_2^+$], 91 (81) [$C_7H_7^+$]. − $C_{16}H_{21}NO_5$ (307.3): calcd. C 62.53, H 6.89, N 4.56; found C 62.55, H 6.98, N 4.34.

(2′*S*,3′*S*)- and (2′*R*,3′*S*)-*tert*-Butyl 2-[3-(Benzyloxycarbonylamino)-2-hydroxybutyl]propenoate (11a,b): In slight variation of GP2 Z-Ala-H (**1**, 438 mg, 2.11 mmol) was treated with *tert*-butyl 2-(bromomethyl)propenoate (**9**) yielding a crude mixture of isomers, whose isomeric ratio was determined to be **11a/b** = 67:33. Separation by MPLC (PE/EA, 85:15) led to the pure isomers **11a** (359 mg, 49%) and **11b** (168 mg, 23%). − **11a**: M.p. 64−66°C. − t_R (HPLC; hexane/EA, 77:23) = 6.38 min. − $[\alpha]_D^{20} = -1.8$ (c = 1, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3430, 3300 cm^{-1} (N−H, O−H), 3020, 2980, 2930 (C−H), 1710 (C=O, ester), 1690 (C=O, carbamate), 1530 (C=C). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.23 (d, ^3J = 6.8 Hz, 3 H, 4′-H), 1.47 [s, 9 H, $C(CH_3)_3$], 2.42 (dd, ^2J = 14.1 Hz, ^3J = 8.9 Hz, 1 H, 1′-H_A), 2.47 (dd, ^2J = 14.1 Hz, ^3J = 2.8 Hz, 1 H, 1′-H_B), 3.26 (d, ^3J = 2.9 Hz, 1 H, OH), 3.65 (dddd, ^3J = 8.8 Hz, ^3J = ^3J = ^3J = 3.0 Hz, 1 H, 2′-H), 3.76 (m_c, 1 H, 3′-H), 5.09−5.13 (m, 3 H, NH, CH_2Ph), 5.61 (s, 1 H, 3-H_E), 6.13 (s, 1 H, 3-H_Z), 7.31−7.36 (m, 5 H, C_6H_5). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.8 (C-4′), 28.0 [C(*C*H_3)$_3$], 38.3 (C-1′), 50.9 (C-3′), 66.7 (*C*H_2Ph), 73.9 (C-2′), 81.6 [*C*$(CH_3)_3$], 127.5, 128.0, 128.1, 128.5 (C_6H_5, C-3), 136.6, 138.9 ($C_6H_{5\ ipso}$, C-2), 156.3 (N−C=O), 167.7 (C-1). − MS (CI, NH_3); *m*/*z* (%): 367 (17) [M^+ + NH_4], 350 (33) [M^+ + H], 178 (10), [$M^+ - (CH_3)_3COH - C_5H_5O_2$], 91 (100), [$C_7H_7^+$]. − $C_{19}H_{27}NO_5$ (349.4): calcd. C 65.31, H 7.79, N 4.01; found C 65.40, H 7.78, N 3.92. − **11b**: Colourless oil. − t_R (HPLC; hexane/EA, 77:23) = 7.75 min. − $[\alpha]_D^{20} = -5.7$ (c = 0.8, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3435, 3350 cm^{-1} (N−H, O−H), 3020, 2980, 2940 (C−H), 1715 (C=O, ester), 1695 (C=O, carbamate), 1535 (C=C). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.16 (d, ^3J = 6.6 Hz, 3 H, 4′-H), 1.49 [s, 9 H, $C(CH_3)_3$], 2.32 (dd, ^2J = 14.0 Hz, ^3J = 9.2 Hz, 1 H, 1′-H_A), 2.44 (dd, ^2J = 14.1 Hz, ^3J = 2.9 Hz, 1 H, 1′-H_B), 3.17 (d, ^3J = 3.1 Hz, 1 H, OH), 3.75 (m_c, 1 H, 2′-H), 3.78 (m_c, 1 H, 3′-H), 5.07−5.12 (m, 1 H, NH), 5.09 (s, 2 H, CH_2Ph), 5.62 (s, 1 H, 3-H_E), 6.16 (s, 1 H, 3-H_Z), 7.30−7.36 (m, 5 H, C_6H_5). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.6 (C-4′), 28.0 [C(*C*H_3)$_3$], 37.0 (C-1′), 51.2 (C-3′), 66.7 (*C*H_2Ph), 73.7 (C-2′), 81.6 [*C*$(CH_3)_3$], 127.1, 128.1, 128.5 (C_6H_5, C-3, one signal covered), 136.5, 138.9 ($C_6H_{5\ ipso}$, C-2), 156.1 (N−C=O), 167.4 (C-1). − MS (CI, NH_3); *m*/*z* (%): 372 (4) [M^+ + Na], 350 (40) [M^+ + H], 294 (64) [$M^+ - C_4H_7$], 276 (17) [$M^+ - (CH_3)_3CO$], 91 (100) [$C_7H_7^+$]. − $C_{19}H_{27}NO_5$ (349.4): calcd. C 65.31, H 7.79, N 4.01; found C 64.96, H 7.81, N 3.99.

(2′*S*,3′*S*)- and (2′*R*,3′*S*)-Methyl 2-[3-(Benzyloxycarbonylamino)-2-hydroxy-4-phenylbutyl]propenoate (12a,b): Z-Phe-H (**2**, 1.08 mg, 3.81 mmol) was treated in accordance with GP2 yielding a crude mixture of isomers, whose isomeric ratio was determined to be **12a/b** = 68:32. Separation by MPLC (PE/EA, 85:15) led to the pure isomers **12a** (716 mg, 49%) and **12b** (354 mg, 24%). − **12a**: Colourless solid, m.p. 62−64°C. − t_R (HPLC; hexane/EA, 7:3) = 7.3 min. − $[\alpha]_D^{20} = -27.9$ (c = 1, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3500 cm^{-1} (O−H), 3300 (N−H), 3010, 2930 (C−H), 1695 (C=O, ester), 1680 (C=O, carbamate), 1530 (C=C). − ^{1}H NMR (500 MHz; $CDCl_3$): δ = 2.47−2.48 (m, 2 H, 1′-H), 2.89 (dd, ^2J = 13.6 Hz, ^3J = 7.8 Hz, 1 H, 4′-H_A), 2.91 (dd, ^2J = 13.6 Hz, ^3J = 7.3 Hz, 1 H, 4′-H_B), 3.14 (d, ^3J = 3.5 Hz, 1 H, OH), 3.70 (s, 3 H, OCH_3), 3.72 (m_c, 1 H, 2′-H), 3.88 (dtd, ^3J = 9.6 Hz, ^3J = 7.7 Hz, ^3J = 1.8 Hz, 1 H, 3′-H), 5.05 (d, ^2J = 12.3 Hz, 1 H, OC$H_A$$H_B$Ph), 5.08 (d, ^2J = 12.3 Hz, 1 H, OC$H_A$$H_B$Ph), 5.20 (d, ^3J = 9.6 Hz, 1 H, NH), 5.63 (d, J = 1.2 Hz, 1 H, 3-H_E), 6.19 (d, J = 1.4 Hz, 1 H, 3-H_Z), 7.16−7.37 (m, 10 H, 2 C_6H_5). − ^{13}C NMR (125 MHz; $CDCl_3$): δ = 38.8 (C-1′), 39.4 (C-4′), 52.6 (OCH_3), 56.7 (C-3′), 67.1 (O*C*H_2Ph), 71.0 (C-2′), 126.8, 128.3, 128.5, 128.9, 129.1, 129.7 (2 C_6H_5, C-3, one signal covered), 137.0, 137.4, 138.5 (2 $C_6H_{5\ ipso}$, C-2), 156.8 (N−C=O), 169.0 (C-1). − MS (FAB); *m*/*z* (%): 384 (18) [M^+ + H], 352 (15) [$M^+ - CH_3O$], 292 (23) [$M^+ - C_7H_7$], 254 (20) [$M^+ - CH_3OH - C_5H_5O_2$], 91 (100) [$C_7H_7^+$]. − $C_{22}H_{25}NO_5$ (383.4): calcd. C 68.91, H 6.57, N 3.65; found C 69.00, H 6.65, N 3.68. − **12b**: Colourless solid, m.p. 110−112°C. − t_R (HPLC; hexane/EA, 4:1) = 10.8 min. − $[\alpha]_D^{24} = -26.5$ (c = 1, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3300 cm^{-1} (br., O−H, N−H), 3010, 2910, 2900 (C−H), 1725 (C=O, ester), 1690 (C=O, carbamate), 1540 (C=C). − ^{1}H NMR (500 MHz; $CDCl_3$): δ = 2.43 (dd, ^2J = 14.2 Hz, ^3J = 8.8 Hz, 1 H, 1′-H_A), 2.64 (ddd, ^2J = 14.2 Hz, ^3J = 3.1 Hz, ^4J = 1.2 Hz, 1 H,

1′-H_B), 2.84 (dd, ^2J = 14.1 Hz, ^3J = 9.1 Hz, 1 H, 4′-H_A), 3.00 (dd, ^2J = 14.1 Hz, ^3J = 4.7 Hz, 1 H, 4′-H_B), 3.28 (d, ^3J = 4.6 Hz, 1 H, OH), 3.77 (s, 3 H, OCH_3), 3.78 (m_c, 1 H, 2′-H), 3.93 (ddt, ^3J = ^3J = 9.2 Hz, ^3J = 4.7 Hz, 1 H, 3′-H), 4.87 (d, ^3J = 9.2 Hz, 1 H, NH), 5.02 (s, 2 H, OCH_2Ph), 5.71 (s, 1 H, 3-H_E), 6.27 (d, J = 1.2 Hz, 1 H, 3-H_Z), 7.19−7.35 (m, 10 H, 2 C_6H_5). − ^{13}C NMR (125 MHz; $CDCl_3$): δ = 35.6 (C-1′), 36.8 (C-4′), 52.3 (OCH_3), 56.7 (C-3′), 66.7 (OCH_2Ph), 72.8 (C-2′), 126.5, 127.9, 128.1, 128.5, 129.4 (2 C_6H_5, C-3, 2 signals covered), 136.4, 137.0, 137.7 (2 C_6H_5 ipso, C-2), 156.4 (N−C=O), 168.5 (C-1). − MS (FAB); *m/z* (%): 406 (16) [M^+ + Na], 384 (83) [M^+ + H], 352 (5), [M^+ − CH_3O], 254 (7) [M^+ − $HOCH_3$ − $C_5H_5O_2$], 97 (17) [$C_5H_5O_2^+$], 91 (100) [$C_7H_7^+$]. − $C_{22}H_{25}NO_5$ (383.4): calcd. C 68.91, H 6.57, N 3.65; found C 68.64, H 6.66, N 3.53.

(2′*S*,3′*S*)- and (2′*R*,3′*S*)-Methyl 2-[3-(Benzyloxycarbonylamino)-2-hydroxy-5-methylhexyl]propenoate (13a,b): Z-Leu-H (**3**, 616 mg, 2.47 mmol) was treated in accordance with GP2 yielding a crude mixture of isomers, whose isomeric ratio was determined to be **13a/b** = 75:25. Separation by MPLC (PE/EA, 85:15) led to the pure isomers **13a** (520 mg, 60%) and **13b** (181 mg, 21%). − **13a**: Colourless oil. − t_R (HPLC; hexane/EA, 77:23) = 6.53 min. − $[\alpha]_D^{20}$ = −21.6 (c = 0.5, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3380 cm^{-1} (br., O−H, N−H), 3033, 2955, 2870 (C−H), 1710 (C=O, ester), 1680 (C=O, carbamate), 1527 (C=C). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.91 [d, ^3J = 6.7 Hz, 3 H, CH(CH_3)$_2$], 0.93 [d, ^3J = 6.5 Hz, 3 H, CH(CH_3)$_2$], 1.32 (ddd, ^2J = 13.6 Hz, ^3J = 8.6 Hz, ^3J = 4.8 Hz, 1 H, 4′-H_A), 1.53 (ddd, ^2J = 13.9 Hz, ^3J = 9.6 Hz, ^3J = 5.5 Hz, 1 H, 4′-H_B), 1.65 (m_c, 1 H, 5′-H), 2.43 (dd, ^2J = 14.1 Hz, ^3J = 8.7 Hz, 1 H, 1′-H_A), 2.54 (dd, ^2J = 14.1 Hz, ^3J = 3.5 Hz, 1 H, 1′-H_B), 2.91 (d, ^3J = 3.7 Hz, 1 H, OH), 3.71 (m_c, 1 H, 2′-H), 3.76 (s, 3 H, OCH_3), 3.78 (m_c, 1 H, 3′-H), 5.00 (d, ^3J = 9.7 Hz, 1 H, NH), 5.10 (s, 2 H, CH_2Ph), 5.70 (s, 1 H, 3-H_E), 6.23 (s, 1 H, 3-H_Z), 7.29−7.36 (m, 5 H, C_6H_5). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.2, 23.1 [CH(CH_3)$_2$], 24.7 (C-5′), 38.3 (C-1′), 42.1 (C-4′), 52.2, 53.1 (C-3′, OCH_3), 66.7 (CH_2Ph), 72.8 (C-2′), 128.0, 128.1, 128.5, 128.6 (C-3, C_6H_5), 136.7, 137.2 (C_6H_5 ipso, C-2), 156.7 (N−C=O), 168.6 (C-1). − MS (FAB); *m/z* (%): 372 (3) [M^+ + Na], 350 (23) [M^+ + H], 306 (8) [M^+ − C_3H_8], 91 (100) [$C_7H_7^+$]. − $C_{19}H_{27}NO_5$ (349.4): calcd. C 65.31, H 7.79, N 4.01; found C 65.23, H 7.89, N 4.04. − **13b**: Colourless solid, m.p. 47−49°C. − t_R (HPLC; hexane/EA, 77:23) = 10.03 min. − $[\alpha]_D^{20}$ = −19.2 (c = 1.1, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3310 cm^{-1} (br., O−H, N−H), 3050, 3020, 2940, 2870 (C−H), 1725 (C=O, ester), 1690 (C=O, carbamate), 1540 (C=C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.93 [d, ^3J = 6.3 Hz, 3 H, CH(CH_3)$_2$], 0.94 [d, ^3J = 6.6 Hz, 3 H, CH(CH_3)$_2$], 1.37 (2 m_c, 2 H, 4′-H_A, 4′-H_B), 1.68 (m_c, 1 H, 5′-H), 2.35 (dd, ^2J = 14.3 Hz, ^3J = 9.4 Hz, 1 H, 1′-H_A), 2.51 (dd, ^2J = 14.1 Hz, ^3J = 2.9 Hz, 1 H, 1′-H_B), 3.01 (d, ^3J = 4.9 Hz, 1 H, OH), 3.72−3.80 (2 m, 2 H, 2′-H, 3′-H), 3.76 (s, 3 H, OCH_3), 4.89 (d, ^3J = 9.2 Hz, 1 H, NH), 5.09 (s, 2 H, CH_2Ph), 5.72 (s, 1 H, 3-H_E), 6.26 (s, 1 H, 3-H_Z), 7.29−7.37 (m, 5 H, C_6H_5). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.7, 23.7 [CH(CH_3)$_2$], 24.7 (C-5′), 36.4 (C-1′), 38.6 (C-4′), 52.2, 54.1 (C-3′, OCH_3), 66.9 (CH_2Ph), 73.8 (C-2′), 128.1 (C-3), 128.0, 128.2, 128.5 (C_6H_5), 136.4, 137.1 (C_6H_5 ipso, C-2), 156.7 (N−C=O), 168.3 (C-1). − MS (FAB); *m/z* (%): 699 (3) [2 M^+ + H], 372 (10), [M^+ + Na], 350 (100), [M^+ + H], 306 (16) [M^+ − C_3H_8], 91 (100) [$C_7H_7^+$]. − $C_{19}H_{27}NO_5$ (349.4): calcd. C 65.31, H 7.79, N 4.01; found C 65.30, H 7.79, N 3.98.

(2′*S*,3′*S*)- and (2′*R*,3′*S*)-Methyl 2-[3-(Benzyloxycarbonylamino)-2-hydroxy-4-methylpentyl]propenoate (14a,b): Z-Val-H (**4,** 710 mg, 3.02 mmol) was treated in accordance with GP2 yielding a crude mixture of isomers, whose isomeric ratio was determined to be **14a/b** = 82:18. Separation by MPLC (PE/EA, 85:15) led to the pure isomers **14a** (686 mg, 68%) and **14b** (164 mg, 16%). − **14a**: Colourless solid, m.p. 100−102°C. − t_R (HPLC; hexane/EA, 4:1) = 10.8 min. − $[\alpha]_D^{21}$ = −29.0 (c = 1, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3500 cm^{-1} (O−H), 3300 (N−H), 2940, 2860 (C−H), 1705 (C=O, ester), 1680 (C=O, carbamate), 1530 (C=C). − ^{1}H NMR (500 MHz; $CDCl_3$): δ = 0.95, 0.97 [2 d, ^3J = 6.9 Hz, ^3J = 6.7 Hz, 6 H, CH(CH_3)$_2$], 1.90 (dsept, ^3J = 8.5 Hz, ^3J = 6.7 Hz, 1 H, 4′-H), 2.44 (dd, ^2J = 14.0 Hz, ^3J = 8.5 Hz, 1 H, 1′-H_A), 2.50 (dd, ^2J = 14.0 Hz, ^3J = 3.7 Hz, 1 H, 1′-H_B), 2.92 (d, ^3J = 3.6 Hz, 1 H, OH), 3.30 (ddd, ^3J = 10.2 Hz, ^3J = 8.3 Hz, ^3J = 1.9 Hz, 1 H, 3′-H), 3.76 (s, 3 H, OCH_3), 3.94 (dtd, ^3J = 8.7 Hz, ^3J = 3.7 Hz, ^3J = 1.9 Hz, 1 H, 2′-H), 5.10 (d, ^2J = 12.3 Hz, 1 H, C$H_A$$H_B$Ph), 5.12 (d, ^2J = 12.3 Hz, 1 H, C$H_A$$H_B$Ph), 5.13 (d, ^3J = 10.2 Hz, 1 H, NH), 5.70 (s, 1 H, 3-H_E), 6.23 (s, 1 H, 3-H_Z), 7.29−7.37 (m, 5 H, C_6H_5). − ^{13}C NMR (125 MHz; $CDCl_3$): δ = 19.3, 19.7 [CH(CH_3)$_2$], 30.6 (C-4′), 38.9 (C-1′), 52.3 (OCH_3), 60.6 (C-3′), 66.7 (CH_2Ph), 70.2 (C-2′), 128.0, 128.1, 128.5, 128.7 (C_6H_5, C-3), 136.7, 137.2 (C_6H_5 ipso, C-2), 157.0 (N−C=O), 169.7 (C-1). − MS (EI, 70 eV); *m/z* (%): 335 (1) [M^+], 206 (9) [M^+ − CH_3OH − $C_5H_5O_2$], 162 (19) [M^+ − CH_3OH − $C_5H_5O_2$ − C_3H_8], 97 (7) [$C_5H_5O_2^+$], 91 (100) [$C_7H_7^+$]. − $C_{18}H_{25}NO_5$ (335.4): calcd. C 64.46, H 7.51, N 4.18; found C 64.76, H 7.52, N 4.26. − **14b**: Colourless oil. − t_R (HPLC; hexane/EA, 4:1) = 17.9 min. − $[\alpha]_D^{20}$ = −8.2 (c = 0.83, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3441 cm^{-1} (O−H), 3350 (N−H), 2959 (C−H), 1695 (C=O, ester), 1690 (C=O, carbamate), 1537 (C=C). − ^{1}H NMR (500 MHz; $CDCl_3$): δ = 0.90, 0.98 [2 d, ^3J = ^3J = 6.8 Hz, 6 H, CH(CH_3)$_2$], 1.90 (septd, ^3J = 6.8 Hz, ^3J = 5.2 Hz, 1 H, 4′-H), 2.29 (dd, ^2J = 14.0 Hz, ^3J = 9.5 Hz, 1 H, 1′-H_A), 2.65 (dd, ^2J = 14.1 Hz, ^3J = 2.6 Hz, 1 H, 1′-H_B), 2.80 (d, ^3J = 4.9 Hz, 1 H, OH), 3.60 (dd, ^3J = 9.9 Hz, ^3J = 5.2 Hz, 1 H, 3′-H), 3.73 (dddd, ^3J = 9.3 Hz, ^3J = ^3J = 4.9 Hz, ^3J = 2.6 Hz, 1 H, 2′-H), 3.76 (s, 3 H, OCH_3), 4.79 (d, ^3J = 9.8 Hz, 1 H, NH), 5.11 (s, 2 H, CH_2Ph), 5.70 (s, 1 H, 3-H_E), 6.26 (s, 1 H, 3-H_Z), 7.30−7.37 (m, 5 H, C_6H_5). − ^{13}C NMR (125 MHz; $CDCl_3$): δ = 17.5, 20.6 [CH(CH_3)$_2$], 28.6 (C-4′), 36.9 (C-1′), 52.6 (OCH_3), 60.9 (C-3′), 67.4 (CH_2Ph), 71.8 (C-2′), 128.5, 128.6, 128.9, 128.9 (C_6H_5, C-3), 136.8, 137.3 (C_6H_5 ipso, C-2), 157.5 (N−C=O), 168.7 (C-1). − MS (FAB); *m/z* (%): 358 (12) [M^+ + Na], 336 (61), [M^+ + H], 206 (8), [M^+ − CH_3OH − $C_5H_5O_2$], 162 (7), [M^+ − CH_3OH − $C_5H_5O_2$ − C_3H_8], 97 (8) [$C_5H_5O_2^+$], 91 (100) [$C_7H_7^+$]. − $C_{18}H_{25}NO_5$ (335.4): calcd. C 64.46, H 7.51, N 4.18; found C 64.53, H 7.64, N 3.96.

(*R*) Mosher Derivative of 14a: ^{1}H NMR (500 MHz; [D$_6$]DMSO; 333 K): δ = 5.99 (s, 1 H, =C$H_E$$H_Z$).

(*R*) Mosher Derivative of *ent*-14a: ^{1}H-NMR (500 MHz; [D$_6$]DMSO; 333 K): δ = 5.84 (s, 1 H, =C$H_E$$H_Z$).

(2′*S*,3′*S*,4′*S*)- and (2′*R*,3′*S*,4′*S*)-Methyl 2-[3-(Benzyloxycarbonylamino)-2-hydroxy-4-methylhexyl]propenoate (15a,b): Z-Ile-H (**5**, 463 mg, 1.86 mmol) was treated in accordance with GP2 yielding a crude mixture of isomers, whose isomeric ratio was determined to be **15a/b** = 89:11. Separation by MPLC (PE/EA, 85:15) led to the pure isomers **15a** (491 mg, 76%) and **15b** (58 mg, 9%). − **15a**: Colourless solid, m.p. 77−79°C. − t_R (HPLC; hexane/EA, 4:1) = 8.3 min. − $[\alpha]_D^{20}$ = −25.0 (c = 1.1, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3500, 3300 cm^{-1} (O−H, N−H), 3020, 2950, 2910 (C−H), 1695 (C=O, ester), 1680 (C=O, carbamate), 1530 (C=C). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, ^3J = 7.4 Hz, 3 H, 6′-H), 0.94 (d, ^3J = 6.7 Hz, 3 H, CHCH_3), 1.14 (ddq, ^2J = 13.5 Hz, ^3J = 8.9 Hz, ^3J = 7.4 Hz, 1 H, 5′-H_A), 1.56 (dqd, ^2J = 13.7 Hz, ^3J = 7.6 Hz, ^3J = 3.5 Hz, 1 H, 5′-H_B), 1.63 (m_c, 1 H, 4′-H), 2.45 (dd, ^2J = 14.0 Hz, ^3J = 8.4 Hz, 1 H, 1′-H_A), 2.50 (dd, ^2J = 14.0 Hz, ^3J = 3.7 Hz, 1 H, 1′-H_B), 2.91 (br. s, 1 H, OH), 3.37 (m_c, 1 H, 3′-H), 3.76 (s, 3 H, OCH_3), 3.96 (dddd, ^3J = 8.4 Hz, ^3J = ^3J = 3.6 Hz,

^3J = 1.6 Hz, 1 H, 2′-H), 5.11 (s, 2 H, CH_2Ph), 5.13 (d, ^3J = 10.4 Hz, 1 H, NH), 5.70 (s, 1 H, 3-H_E), 6.23 (s, 1 H, 3-H_Z), 7.29−7.36 (m, 5 H, C_6H_5). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.2 (C-6′), 15.7 (CH*C*H_3), 25.6 (C-5′), 36.9 (C-4′), 39.0 (C-1′), 52.3 (OCH_3), 59.1 (C-3′), 66.7 (*C*H_2Ph), 70.0 (C-2′), 128.0, 128.1 128.5 (C_6H_5), 128.7 (C-3), 136.7, 137.2 (C_6H_5 ipso, C-2), 156.9 (N−C=O), 168.7 (C-1). − MS (FAB); *m*/*z* (%): 372 (6) [M^+ + Na], 350 (53) [M^+ + H], 306 (15) [$M^+ - C_3H_7$], 91 (100) [$C_7H_7^+$]. − $C_{19}H_{27}NO_5$ (349.4): calcd. C 65.31, H 7.79, N 4.01; found C 65.17, H 7.79, N 4.00. − **15b**: Colourless oil. − t_R (HPLC; hexane/EA, 4:1) = 15.4 min. − $[\alpha]_D^{20}$ = −12.7 (*c* = 2.4, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3370, 3300 cm^{-1} (O−H, N−H), 3030, 2955, 2870 (C−H), 1710 (C=O, ester), 1690 (C=O, carbamate), 1530 (C=C). − ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.91 (t, ^3J = 7.4 Hz, 3 H, 6′-H), 0.98 (d, ^3J = 6.8 Hz, 3 H, CHCH_3), 1.05 (m_c, 1 H, 5′-H_A), 1.58 (m_c, 1 H, 5′-H_B), 1.73 (m_c, 1 H, 4′-H), 2.26 (dd, ^2J = 14.0 Hz, ^3J = 9.5 Hz, 1 H, 1′-H_A), 2.63 (dd, ^2J = 14.1 Hz, ^3J = 2.5 Hz, 1 H, 1′-H_B), 2.80 (d, ^3J = 5.1 Hz, 1 H, OH), 3.65 (ddd, ^3J = 9.7 Hz, ^3J = ^3J = 6.1 Hz, 1 H, 3′-H), 3.76 (s, 3 H, OCH_3), 3.96 (m_c, 1 H, 2′-H), 4.72 (d, ^3J = 9.7 Hz, 1 H, NH), 5.12 (s, 2 H, CH_2Ph), 5.71 (s, 1 H, 3-H_E), 6.26 (s, 1 H, 3-H_Z), 7.31−7.37 (m, 5 H, C_6H_5). − ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 11.5 (C-6′), 16.1 (CH*C*H_3), 24.1 (C-5′), 35.3, 36.2 (C-1′, C-4′), 52.1 (OCH_3), 60.4 (C-3′), 67.0 (*C*H_2Ph), 71.1 (C-2′), 128.1, 128.2 128.6 (C_6H_5), 128.5 (C-3), 136.4, 137.0 (C_6H_5 ipso, C-2), 157.3 (N−C=O), 168.3 (C-1). − MS (CI, CH_4); *m*/*z* (%): 350 (10) [M^+ + H], 318 (21) [$M^+ - CH_3O$], 306 (28) [$M^+ - C_3H_7$], 220 (28), [$M^+ - CH_3OH - C_5H_5O_2$], 176 (35) [$M^+ - CH_3OH - C_5H_5O_2 - C_3H_8$], 97 (7) [$C_5H_5O_2^+$], 91 (100) [$C_7H_7^+$]. − $C_{19}H_{27}NO_5$ (349.4): calcd. C 65.31, H 7.79, N 4.01; found C 65.08, H 7.79, N 4.00.

(2′*S*,3′*S*)- and (2′*R*,3′*S*)-Methyl 2-[3-(Benzyloxycarbonylamino)-2-hydroxy-4,4-dimethylpentyl]propenoate (16a,b): Z-Tle-H (**6**, 997 mg, 4.00 mmol) was treated in accordance with GP2 yielding a crude mixture of isomers, whose isomeric ratio was determined to be **16a**/**b** = 97:3. Separation by MPLC (PE/EA, 85:15) led to the pure isomers **16a** (1.23 g, 88%) and **16b** (64 mg, 5%). − **16a**: Colourless oil. − t_R (HPLC; hexane/EA, 77:23) = 4.4 min. − $[\alpha]_D^{20}$ = −25.0 (*c* = 1.1, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3440 cm^{-1} (br., O−H, N−H), 3034, 2956, 2870 (C−H), 1714 (C=O, ester), 1695 (C=O, carbamate), 1514 (C=C). − ^{1}H NMR (500 MHz; $CDCl_3$): δ = 0.95 [s, 9 H, C(CH_3)$_3$], 2.43 (dd, ^2J = 13.9 Hz, ^3J = 7.9 Hz, 1 H, 1′-H_A), 2.47 (dd, ^2J = 13.8 Hz, ^3J = 4.5 Hz, 1 H, 1′-H_B), 2.71 (d, ^3J = 3.8 Hz, 1 H, OH), 3.35 (dd, ^3J = 10.3 Hz, ^3J = 0.9 Hz, 1 H, 3′-H), 3.75 (s, 3 H, OCH_3), 4.10 (dddd, ^3J = 7.9 Hz, ^3J = 4.5 Hz, ^3J = 3.8 Hz, ^3J = 0.8 Hz 1 H, 2′-H), 5.11 (d, ^2J = 12.3 Hz, 1 H, CH_AH$_B$Ph), 5.13 (d, ^2J = 12.3 Hz, 1 H, CH$_A$$H_B$Ph), 5.26 (d, ^3J = 10.2 Hz, 1 H, NH), 5.70 (s, 1 H, 3-H_E), 6.23 (s, 1 H, 3-H_Z), 7.29−7.39 (m, 5 H, C_6H_5). − ^{13}C NMR (125 MHz; $CDCl_3$): δ = 27.0 [C(*C*H_3)$_3$], 35.2 (C-4′), 40.1 (C-1′), 52.3 (OCH_3), 61.5 (C-3′), 66.7 (*C*H_2Ph), 69.0 (C-2′), 128.0, 128.1, 128.5 (C_6H_5), 129.1 (C-3), 136.7, 136.8 (C_6H_5 ipso, C-2), 157.0 (N−C=O), 168.6 (C-1). − MS (FAB); *m*/*z* (%): 372 (6) [M^+ + Na], 350 (69) [M^+ + H], 318 (6) [$M^+ - CH_3O$], 306 (13) [$M^+ - C_3H_7$], 220 (6) [$M^+ - CH_3OH - C_5H_5O_2$], 91 (100) [$C_7H_7^+$]. − $C_{19}H_{27}NO_5$ (349.4): calcd. C 65.31, H 7.79, N 4.01; found C 65.18, H 7.82, N 3.97. − **16b**: Colourless solid, m.p. 88−90°C. − t_R (HPLC; hexane/EA, = 77:23) = 10.4 min. − $[\alpha]_D^{20}$ = −0.6 (*c* = 0.55, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3400 cm^{-1} (br., O−H), 3260 (N−H), 3060, 3010, 2940 (C−H), 1710 (C=O, ester), 1680 (C=O, carbamate), 1545 (C=C). − ^{1}H NMR (500 MHz; $CDCl_3$): δ = 1.03 [s, 9 H, C(CH_3)$_3$], 2.16 (dd, ^2J = 13.8 Hz, ^3J = 10.0 Hz, 1 H, 1′-H_A), 2.62 (dd, ^2J = 13.8 Hz, ^3J = 2.2 Hz, 1 H, 1′-H_B), 2.90 (d, ^3J = 7.2 Hz, 1 H, OH), 3.63 (dd, ^3J = 9.0 Hz, ^3J = 3.6 Hz, 1 H, 3′-H), 3.75 (s, 3 H, OCH_3), 3.91 (dddd, ^3J = 10.1 Hz, ^3J = 7.3 Hz, ^3J = 3.8 Hz, ^3J = 2.2 Hz, 1 H, 2′-H), 4.81 (d, ^3J = 9.0 Hz, 1 H, NH), 5.12 (d, ^2J = 12.2 Hz, 1 H, CH_AH$_B$Ph), 5.14 (d, ^2J = 12.1 Hz, 1 H, CH$_A$$H_B$Ph), 5.68 (s, 1 H, 3-$H_E$), 6.26 (d, *J* = 1.5 Hz, 1 H, 3-H_Z), 7.32−7.38 (m, 5 H, C_6H_5). − ^{13}C NMR (125 MHz; $CDCl_3$): δ = 27.3 [C(*C*H_3)$_3$], 34.0 (C-4′), 37.4 (C-1′), 52.0 (OCH_3), 65.2 (C-3′), 67.2 (*C*H_2Ph), 70.8 (C-2′), 128.4 (C-3), 128.2, 128.3, 128.6 (C_6H_5), 136.3, 136.9 (C_6H_5 ipso, C-2), 157.6 (N−C=O), 167.9 (C-1). − MS (FAB); *m*/*z* (%): 372 (6) [M^+ + Na], 350 (28) [M^+ + H], 318 (9) [$M^+ - CH_3O$], 220 (6), [$M^+ - CH_3OH - C_5H_5O_2$], 91 (100) [$C_7H_7^+$]. − $C_{19}H_{27}NO_5$ (349.4): calcd. C 65.31, H 7.79, N 4.01; found C C 65.18, H 7.70, N 3.89.

General Procedures for the Synthesis of α-Methylene-γ-butyrolactones 17−22 (See Table 2 for the Respective Method Used). − Method A: The homoallyl alcohol (0.5 mmol) was stirred in satd. methanolic HCl (16 mL) for 2 h at room temp. with careful monitoring by HPLC. The reaction mixture was poured in satd. $NaHCO_3$ solution (40 mL) and extracted with EA (3 × 50 mL). The combined organic layers were extracted with satd. $NaHCO_3$ solution (40 mL) and satd. NaCl solution (2 × 40 mL), dried ($MgSO_4$), and concentrated in a rotary evaporator. Purification by MPLC yielded the α-methylene-γ-butyrolactones. − **Method B:** The homoallyl alcohol (0.6 mmol) and ion-exchange resin Dowex-H^+ (400 mg) were stirred in EtOH (30 mL) for 3 d at 70°C. The cooled reaction mixture was filtered and concentrated in a rotary evaporator. Purification by MPLC yielded the α-methylene-γ-butyrolactones and about 15−25% of starting material. − **Method C:** The homoallyl alcohol (1.1 mmol) was stirred in Et_2O (16 mL) with concd. H_2SO_4 (0.3 mL) for 2 d at room temp. The reaction mixture was poured in satd. $NaHCO_3$ solution (25 mL) and extracted with Et_2O (3 × 45 mL). The combined organic layers were extracted with satd. $NaHCO_3$ solution (30 mL) and satd. NaCl solution (2 × 30 mL), dried ($MgSO_4$), and concentrated in a rotary evaporator.

(5*S*,1′*S*)-5-[1-(Benzyloxycarbonylamino)ethyl]-3-methylenedihydro-2(3*H*)-furanone (17a): Colourless solid, m.p. 117−119°C. − $[\alpha]_D^{20}$ = +4.8 (*c* = 0.83, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3280 cm^{-1} (N−H), 3040, 2960, 2910 (C−H), 1760 (C=O, lactone), 1680 (C=O, carbamate), 1540 (C=C). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31 (d, ^3J = 7.0 Hz, 3 H, 2′-H), 2.85 (ddt, ^2J = 17.5 Hz, ^3J = 8.1 Hz, ^4J = 2.6 Hz, 1 H, 4-H_A), 2.94 (ddt, ^2J = 17.5 Hz, ^3J = 5.7 Hz, ^4J = 2.9 Hz, 1 H, 4-H_B), 4.00 (m_c, 1 H, 1′-H), 4.51 (ddd, ^3J = 8.0 Hz, ^3J = 5.8 Hz, ^3J = 2.1 Hz, 1 H, 5-H), 4.83 (d, ^3J = 8.6 Hz, 1 H, NH), 5.07 (d, ^2J = 12.2 Hz, 1 H, CH_AH$_B$Ph), 5.09 (d, ^2J = 12.2, 1 H, CH$_A$$H_B$Ph), 5.54 (t, ^4J = 2.6 Hz, 1 H, 1′′-H_E), 6.16 (t, ^4J = 3.0 Hz, 1 H, 1′′-H_Z), 7.29−7.36 (m, 5 H, C_6H_5). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.4 (C-2′), 30.2 (C-4), 49.6 (C-1′), 67.0 (*C*H_2Ph), 79.4 (C-5), 122.2 (=CH_2), 128.0, 128.2, 128.5 (C_6H_5), 133.9, 136.2 (C_6H_5 ipso, C-3), 156.4 (N−C=O), 170.2 (C-2). − MS (FAB); *m*/*z* (%): 298 (3) [M^+ + Na], 276 (18) [M^+ + H], 91 (100) [$C_7H_7^+$]. − $C_{15}H_{17}NO_4$ (275.3): calcd. C 65.44, H 6.22, N 5.09; found C 65.63, H 6.30, N 5.06.

(5*R*,1′*S*)-5-[1-(Benzyloxycarbonylamino)ethyl]-3-methylenedihydro-2(3*H*)-furanone (17b): Colourless solid, m.p. 83−86°C. − $[\alpha]_D^{20}$ = −76.7 (*c* = 0.3, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3300 cm^{-1} (N−H), 3020, 2960, 2940 (C−H), 1750 (C=O, lactone), 1680 (C=O, carbamate), 1520 (C=C). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.15 (d, ^3J = 6.9 Hz, 3 H, 2′-H), 2.73 (ddt, ^2J = 17.6 Hz, ^3J = 5.6 Hz, ^4J = 2.8 Hz, 1 H, 4-H_A), 3.02 (ddt, ^2J = 17.7 Hz, ^3J = 8.4 Hz, ^4J = 2.5 Hz, 1 H, 4-H_B), 3.89 (m_c, 1 H, 1′-H), 4.57 (dt, ^3J = 8.6 Hz, ^3J = 4.7 Hz, 1 H, 5-H), 5.03 (d, ^3J = 7.1 Hz, 1 H, NH), 5.10 (s, 2 H, CH_2Ph), 5.66 (t, ^4J = 2.3 Hz, 1 H, 1′′-H_E), 6.25 (t, ^4J = 3.0 Hz, 1 H, 1′′-H_Z), 7.29−7.37 (m, 5 H, C_6H_5). −

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.3 (C-2′), 30.0 (C-4), 50.3 (C-1′), 66.9 (*C*H$_2$Ph), 79.0 (C-5), 122.9 (=CH$_2$), 128.1, 128.2, 128.6 (C$_6$H$_5$), 133.5, 136.2 (C$_6$H$_{5\ ipso}$, C-3), 155.7 (N−C=O), 170.0 (C-2). − MS (FAB); *m/z* (%): 298 (7) [M$^+$ + Na], 276 (17) [M$^+$ + H], 91 (100) [$C_7H_7^+$]. − $C_{15}H_{17}NO_4$ (275.3): calcd. C 65.44, H 6.22, N 5.09; found C 65.40, H 6.27, N 5.03.

(5*S*,1′*S*)-5-[1-(Benzyloxycarbonylamino)-2-phenylethyl]-3-methylenedihydro-2(3*H*)-furanone (18a): Colourless solid, m.p. 88−90°C. − $[\alpha]_D^{20}$ = +3.8 (*c* = 1.6, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3300 cm^{-1} (N−H), 3000, 2900 (C−H), 1765 (C=O, lactone), 1690 (C=O, carbamate), 1530 (C=C). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.84 (ddt, ^2J = 17.6 Hz, ^3J = 7.8 Hz, ^4J = 2.7 Hz, 1 H, 4-H$_A$), 2.87 (ddt, ^2J = 17.6 Hz, ^3J = 6.4 Hz, ^4J = 3.0 Hz, 1 H, 4-H$_B$), 2.95 (dd, ^2J = 13.7 Hz, ^3J = 8.4 Hz, 1 H, 2′-H$_A$), 2.97 (dd, ^2J = 13.7 Hz, ^3J = 7.5 Hz, 1 H, 2′-H$_B$), 4.11 (dddd, ^3J = 8.5 Hz, ^3J = ^3J = 7.4 Hz, ^3J = 1.6 Hz, 1 H, 1′-H), 4.51 (ddd, ^3J = 7.8 Hz, ^3J = 6.3 Hz, ^3J = 1.6 Hz, 1 H, 5-H), 4.98 (d, ^3J = 7.9 Hz, 1 H, NH), 5.04 (s, 2 H, OC*H*$_2$Ph), 5.51 (t, ^4J = 2.6 Hz, 1 H, 1′′-H$_E$), 6.15 (t, ^4J = 3.0 Hz, 1 H, 1′′-H$_Z$), 7.24−7.34 (m, 10 H, 2 C$_6$H$_5$). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 30.4 (C-4), 39.3 (C-2′), 55.6 (C-1′), 67.4 (O*C*H$_2$Ph), 76.9 (C-5), 122.6 (=CH$_2$), 127.3, 128.3, 128.6, 128.9, 129.1, 129.7 (2 C$_6$H$_5$), 134.3, 136.6, 137.3 (2 C$_6$H$_{5\ ipso}$, C-3), 157.0 (N−C=O), 170.7 (C-2). − MS (CI, CH_4); *m/z* (%): 352 (3) [M$^+$ + H], 260 (6) [M$^+$ − C_7H_7], 91 (100) [$C_7H_7^+$]. − $C_{21}H_{21}NO_4$ (351.4): calcd. C 71.78, H 6.02, N 3.99; found C 72.03, H 6.08, N 3.96.

(5*R*,1′*S*)-5-[1-(Benzyloxycarbonylamino)-2-phenylethyl]-3-methylenedihydro-2(3*H*)-furanone (18b): Colourless solid, m.p. 146−148°C. − $[\alpha]_D^{20}$ = −40.3 (*c* = 0.93, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3320 cm^{-1} (N−H), 3040, 2940, 2890 (C−H), 1760 (C=O, lactone), 1680 (C=O, carbamate), 1530 (C=C). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.77−2.82, 2.90−2.94 (2 m, 4 H, 4-H, 2′-H), 4.00 (m$_c$, 1 H, 1′-H), 4.40 (d, ^3J = 6.9 Hz, 1 H, 5-H), 4.69 (d, ^3J = 8.6 Hz, 1 H, NH), 4.97 (s, 2 H, OC*H*$_2$Ph), 5.59 (br. s, 1 H, 1′′-H$_E$), 6.20 (t, ^4J = 2.9 Hz, 1 H, 1′′-H$_Z$), 7.10−7.29 (m, 10 H, 2 C$_6$H$_5$). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.3, 34.7 (C-4, C-2′), 54.2 (C-1′), 66.0 (O*C*H$_2$Ph), 76.2 (C-5), 122.1 (=CH$_2$), 125.9, 126.9, 127.2, 127.5, 127.7, 128.4 (2 C$_6$H$_5$), 132.5, 135.0, 135.1 (2 C$_6$H$_{5\ ipso}$, C-3), 154.9 (N−C=O), 168.8 (C-2). − MS (CI, CH_4); *m/z* (%): 352 (26) [M$^+$ + H], 254 (9) [M$^+$ − $C_5H_5O_2$], 91 (100) [$C_7H_7^+$]. − $C_{21}H_{21}NO_4$ (351.4): calcd. C 71.78, H 6.02, N 3.99; found C 71.60, H 6.15, N 4.01.

(5*S*,1′*S*)-5-[1-(Benzyloxycarbonylamino)-3-methylbutyl]-3-methylenedihydro-2(3*H*)-furanone (19a): Colourless solid, m.p. 107−108°C. − $[\alpha]_D^{20}$ = −12.2 (*c* = 0.9, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3280 cm^{-1} (N−H), 3050, 2940, 2880 (C−H), 1760 (C=O, lactone), 1690 (C=O, carbamate), 1540 (C=C). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.93 [d, ^3J = 6.3 Hz, 6 H, CH(C*H*$_3$)$_2$], 1.39 (m$_c$, 1 H, 2′-H$_A$), 1.59−1.71 (m, 2 H, 2′-H$_B$, 3′-H), 2.86 (ddt, ^2J = 17.4 Hz, ^3J = 5.8 Hz, ^4J = 2.8 Hz, 1 H, 4-H$_A$), 2.94 (ddt, ^2J = 17.5 Hz, ^3J = 7.9 Hz, ^4J = 2.7 Hz, 1 H, 4-H$_B$), 3.95 (dddd, ^3J = ^3J = 9.7 Hz, ^3J = 5.1 Hz, ^3J = 1.7 Hz, 1 H, 1′-H), 4.54 (ddd, ^3J = 7.8 Hz, ^3J = 5.7 Hz, ^3J = 1.8 Hz, 1 H, 5-H), 4.61 (d, ^3J = 9.6 Hz, 1 H, NH), 5.06 (d, ^2J = 12.3 Hz, 1 H, C*H*$_A$H$_B$Ph), 5.11 (d, ^2J = 12.5 Hz, 1 H, CH$_A$*H*$_B$Ph), 5.52 (t, ^4J = 2.6 Hz, 1 H, 1′′-H$_E$), 6.15 (t, ^4J = 2.6 Hz, 1 H, 1′′-H$_Z$), 7.30−7.36 (m, 5 H, C$_6$H$_5$). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.9, 23.0 [CH(*C*H$_3$)$_2$], 24.7 (C-3′), 30.2 (C-4), 41.7 (C-2′), 52.2 (C-1′), 67.0 (*C*H$_2$Ph), 78.8 (C-5), 122.0 (=CH$_2$), 127.9, 128.2, 128.5 (C$_6$H$_5$), 134.0, 136.3 (C$_6$H$_{5\ ipso}$, C-3), 156.7 (N−C=O), 170.3 (C-2). − MS (EI, 70 eV); *m/z* (%): 317 (6) [M$^+$], 220 (38) [M$^+$ − $C_5H_5O_2$], 176 (41) [M$^+$ − $C_5H_5O_2$ − C_3H_8], 97 (6) [$C_5H_5O_2^+$], 91 (100) [$C_7H_7^+$]. − $C_{18}H_{23}NO_4$ (317.4): calcd. C 68.12, H 7.30, N 4.41; found C 67.95, H 7.28, N 4.42.

(5*R*,1′*S*)-5-[1-(Benzyloxycarbonylamino)-3-methylbutyl]-3-methylenedihydro-2(3*H*)-furanone (19b): Colourless solid, m.p. 89−91°C. − $[\alpha]_D^{20}$ = −86.3 (*c* = 0.9, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3310 cm^{-1} (N−H), 3050, 2940, 2860 (C−H), 1760 (C=O, lactone), 1680 (C=O, carbamate), 1540 (C=C). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.92 [d, ^3J = 6.6 Hz, 6 H, CH(C*H*$_3$)$_2$], 1.26, 1.33 (2 m$_c$, 2 H, 2′-H$_A$, 2′-H$_B$), 1.70 (sept, ^3J = 6.7 Hz, 1 H, 3′-H), 2.75 (d, ^2J = 17.2 Hz, 1 H, 4-H$_A$), 3.01 (dd, ^2J = 17.5 Hz, ^3J = 8.7 Hz, 1 H, 4-H$_B$), 3.84 (m$_c$, 1 H, 1′-H), 4.54 (m$_c$, 1 H, 5-H), 4.78 (d, ^3J = 8.7 Hz, 1 H, NH), 5.10 (d, ^2J = 12.3 Hz, 1 H, C*H*$_A$H$_B$Ph), 5.12 (d, ^2J = 12.3 Hz, 1 H, CH$_A$*H*$_B$Ph), 5.66 (s, 1 H, 1′′-H$_E$), 6.25 (t, ^4J = 2.8 Hz, 1 H, 1′′-H$_Z$), 7.30−7.38 (m, 5 H, C$_6$H$_5$). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.4, 23.7 [CH(*C*H$_3$)$_2$], 24.5 (C-3′), 30.0 (C-4), 37.8 (C-2′), 52.9 (C-1′), 67.0 (*C*H$_2$Ph), 79.2 (C-5), 122.9 (=CH$_2$), 128.0, 128.2, 128.6 (C$_6$H$_5$), 133.6, 136.2 (C$_6$H$_{5\ ipso}$, C-3), 156.1 (N−C=O), 169.9 (C-2). − MS (EI, 70 eV); *m/z* (%): 317 (2) [M$^+$], 220 (26) [M$^+$ − $C_5H_5O_2$], 176 (32) [M$^+$ − $C_5H_5O_2$ − C_3H_8], 97 (35) [$C_5H_5O_2^+$], 91 (100) [$C_7H_7^+$]. − $C_{18}H_{23}NO_4$ (317.4): calcd. C 68.12, H 7.30, N 4.41; found C 68.11, H 7.27, N 4.45.

(5*S*,1′*S*)-5-[1-(Benzyloxycarbonylamino)-2-methylpropyl]-3-methylenedihydro-2(3*H*)-furanone (20a): Colourless solid, m.p. 58−60°C. − $[\alpha]_D^{20}$ = −19.0 (*c* = 0.83, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3300 cm^{-1} (N−H), 2960, 2940 (C−H), 1755 (C=O, lactone), 1685 (C=O, carbamate), 1530 (C=C). − ^{1}H NMR (500 MHz; $CDCl_3$): δ = 0.98, 1.04 [2 d, ^3J = 6.8 Hz, ^3J = 6.7 Hz, 6 H, CH(C*H*$_3$)$_2$], 1.90 (dsept, ^3J = 8.7 Hz, ^3J = 6.7 Hz, 1 H, 2′-H), 2.81 (ddt, ^2J = 17.5 Hz, ^3J = 5.8 Hz, ^4J = 2.9 Hz, 1 H, 4-H$_A$), 2.94 (ddt, ^2J = 17.5 Hz, ^3J = 8.1 Hz, ^4J = 2.7 Hz, 1 H, 4-H$_B$), 3.53 (dd, ^3J = 10.2 Hz, ^3J = 8.6 Hz, 1 H, 1′-H), 4.78 (dd, ^3J = 7.5 Hz, ^3J = 5.9 Hz, 1 H, 5-H), 4.84 (d, ^3J = 10.2 Hz, 1 H, NH), 5.08 (d, ^2J = 12.3 Hz, 1 H, C*H*$_A$H$_B$Ph), 5.10 (d, ^2J = 12.3 Hz, 1 H, CH$_A$*H*$_B$Ph), 5.52 (t, ^4J = 2.6 Hz, 1 H, 1′′-H$_E$), 6.15 (t, ^4J = 3.0 Hz, 1 H, 1′′-H$_Z$), 7.28−7.36 (m, 5 H, C$_6$H$_5$). − ^{13}C NMR (125 MHz; $CDCl_3$): δ = 18.4, 18.7 [CH(*C*H$_3$)$_2$], 29.6 (C-4), 29.8 (C-2′), 58.7 (C-1′), 66.0 (*C*H$_2$Ph), 75.2 (C-5), 121.0 (=CH$_2$), 126.9, 127.1, 127.5 (C$_6$H$_5$), 133.0, 135.3 (C$_6$H$_{5\ ipso}$, C-3), 156.0 (N−C=O), 169.4 (C-2). − MS (EI, 70 eV); *m/z* (%): 303 (1) [M$^+$], 206 (30) [M$^+$ − $C_5H_5O_2$], 162 (30) [M$^+$ − $C_5H_5O_2$ − C_3H_8], 97 (20) [$C_5H_5O_2^+$], 91 (100) [$C_7H_7^+$]. − $C_{17}H_{21}NO_4$ (303.4): calcd. C 67.31, H 6.98, N 4.62; found C 67.28, H 7.05, N 4.62.

(5*R*,1′*S*)-5-[1-(Benzyloxycarbonylamino)-2-methylpropyl]-3-methylenedihydro-2(3*H*)-furanone (20b): Colourless solid, m.p. 63−65°C. − $[\alpha]_D^{20}$ = −16.7 (*c* = 1.1, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3340 cm^{-1} (N−H), 3020, 2940 (C−H), 1770 (C=O, lactone), 1690 (C=O, carbamate), 1530 (C=C). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.90 [2 d, ^3J = ^{3}J = 6.9 Hz, 6 H, CH(C*H*$_3$)$_2$], 2.18 (dsept, ^3J = 9.4 Hz, ^3J = 6.7 Hz, 1 H, 2′-H), 2.86 (ddt, ^2J = 17.4 Hz, ^3J = 5.6 Hz, ^4J = 2.8 Hz, 1 H, 4-H$_A$), 2.99 (ddt, ^2J = 17.4 Hz, ^3J = 8.0 Hz, ^4J = 2.6 Hz, 1 H, 4-H$_B$), 3.70−3.76 (m, 1 H, 1′-H), 4.39 (td, ^3J = 8.4 Hz, ^3J = 5.7 Hz, 1 H, 5-H), 4.70 (d, ^3J = 10.2 Hz, 1 H, NH), 5.11 (m$_c$, 2 H, C*H*$_2$Ph), 5.65 (t, ^4J = 2.6 Hz, 1 H, 1′′-H$_E$), 6.23 (m$_c$, 1 H, 1′′-H$_Z$), 7.31−7.39 (m, 5 H, C$_6$H$_5$). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.7, 19.8 [CH(*C*H$_3$)$_2$], 27.8 (C-2′), 30.9 (C-4), 59.1 (C-1′), 67.2 (*C*H$_2$Ph), 76.3 (C-5), 122.9 (=CH$_2$), 128.1, 128.4, 128.6 (C$_6$H$_5$), 133.6, 136.1 (C$_6$H$_{5\ ipso}$, C-3), 156.7 (N−C=O), 169.9 (C-2). − MS (CI, CH_4); *m/z* (%): 304 (31) [M$^+$ + H], 206 (43) [M$^+$ − $C_5H_5O_2$], 162 (26) [M$^+$ − $C_5H_5O_2$ − C_3H_8], 97 (6) [$C_5H_5O_2^+$], 91 (100) [$C_7H_7^+$]. − $C_{17}H_{21}NO_4$ (303.4): calcd. C 67.31, H 6.98, N 4.62; found C 67.06, H 7.02, N 4.54.

(5*S*,1′*S*,2′*S*)-5-[1-(Benzyloxycarbonylamino)-2-methylbutyl]-3-methylenedihydro-2(3*H*)-furanone (21a): Colourless oil. − $[\alpha]_D^{20}$ =

−13.1 (c = 1, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3310 cm^{-1} (O−H, N−H), 3020, 2970, 2930 (C−H), 1760 (C=O, lactone), 1695 (C=O, carbamate), 1540 (C=C). − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.89 (t, ^3J = 7.4 Hz, 3 H, 4′-H), 1.02 (d, ^3J = 6.7 Hz, 3 H, $CHCH_3$), 1.18 (dqd, ^2J = 13.9 Hz, ^3J = 8.7 Hz, ^3J = 7.3 Hz, 1 H, 3′-H_A), 1.57 (dqd, ^2J = 13.7 Hz, ^3J = 7.6 Hz, ^3J = 3.5 Hz, 1 H, 3′-H_B), 1.67 (m_c, 1 H, 2′-H), 2.82 (ddt, ^2J = 17.8 Hz, ^3J = 5.6 Hz, ^4J = 3.0 Hz, 1 H, 4-H_A), 2.94 (ddt, ^2J = 17.6 Hz, ^3J = 8.2 Hz, ^4J = 2.6 Hz, 1 H, 4-H_B), 3.60 (dd, ^3J = ^3J = 9.4 Hz, 1 H, 1′-H), 4.75 (d, ^3J = 9.8 Hz, 1 H, NH), 4.80 (m_c, 1 H, 5-H), 5.07 (d, ^2J = 12.3 Hz, 1 H, CH_AH_BPh), 5.11 (d, ^2J = 12.3 Hz, 1 H, CH_AH_BPh), 5.51 (t, ^4J = 2.5 Hz, 1 H, 1′′-H_E), 6.15 (t, ^4J = 2.9 Hz, 1 H, 1′′-H_Z), 7.30−7.35 (m, 5 H, C_6H_5). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.8 (C-4′), 15.8 ($CHCH_3$), 25.6 (C-3′), 30.6 (C-4), 37.0 (C-2′), 58.2 (C-1′), 67.0 (CH_2Ph), 122.0 (=CH_2), 127.9, 128.2 128.5 (C_6H_5), 134.0, 136.3 ($C_{6}H_{5\ ipso}$, C-3), 157.0 (N−C=O), 170.4 (C-2). − MS (FAB); m/z (%): 340 (3) [M^+ + Na], 318 (19) [M^+ + H], 91 (100) [$C_7H_7^+$]. − $C_{18}H_{23}NO_4$ (317.4): calcd. C 68.12, H 7.30, N 4.41; found C 67.89, H 7.34, N 4.37.

(5*S*,1′*S*)-5-[1-(Benzyloxycarbonylamino)-2,2-dimethylpropyl]-3-methylenedihydro-2(3*H*)-furanone (22a): Colourless oil. − $[\alpha]_D^{20}$ = −20.3 (c = 0.8, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3333 cm^{-1} (N−H), 3034, 2964, 2874 (C−H), 1767 (C=O, lactone), 1696 (C=O, carbamate), 1531 (C=C). − ^1H NMR (500 MHz; $CDCl_3$): δ = 1.01 [s, 9 H, $C(CH_3)_3$], 2.75 (ddt, ^2J = 17.4 Hz, ^3J = 6.4 Hz, ^4J = 3.0 Hz, 1 H, 4-H_A), 2.97 (ddt, ^2J = 17.4 Hz, ^3J = 8.0 Hz, ^4J = 2.6 Hz, 1 H, 4-H_B), 3.57 (d, ^3J = 10.7 Hz, 1 H, 1′-H), 4.87 (dd, ^3J = 8.0 Hz, ^3J = 6.4 Hz, 1 H, 5-H), 4.94 (d, ^3J = 10.4 Hz, 1 H, NH), 5.09 (d, ^2J = 12.4 Hz, 1 H, CH_AH_BPh), 5.10 (d, ^2J = 12.2 Hz, 1 H, CH_AH_BPh), 5.54 (t, ^4J = 2.6 Hz, 1 H, 1′′-H_E), 6.16 (t, ^4J = 2.9 Hz, 1 H, 1′′-H_Z), 7.31−7.37 (m, 5 H, C_6H_5). − ^{13}C NMR (125 MHz; $CDCl_3$): δ = 27.1 [$C(CH_3)_3$], 31.7 (C-4), 35.0 (C-2′), 61.8 (C-1′), 67.1 (CH_2Ph), 75.0 (C-5), 122.0 (=CH_2), 128.0, 128.2, 128.5 (C_6H_5), 133.7, 136.2 ($C_{6}H_{5\ ipso}$, C-3), 157.1 (N−C=O), 170.4 (C-2). − MS (FAB); m/z (%): 340 (3) [M^+ + Na], 318 (38) [M^+ + H], 220 (3) [M^+ − $C_5H_5O_2$], 97 (8) [$C_5H_5O_2^+$], 91 (100) [$C_7H_7^+$]. − $C_{18}H_{23}NO_4$ (317.4): calcd. C 68.12, H 7.30, N 4.41; found C 67.96, H 7.35, N 4.45.

(5*S*,1′*S*)-5-[1-(Benzyloxycarbonylamino)-2-methylpropyl]-3-(chloromethyl)dihydro-2(3*H*)-furanone (23): In the lactonization of the valine-derived homoallyl alcohol **14a** in 6 N HCl/MeOH, the chlorinated lactone **23** was formed as a side product (40%), which was isolated by MPLC (PE/EA, 85:15) and recrystallized from ether: colourless solid, m.p. 92−94°C. − t_R (HPLC; hexane/EA, 7:3) = 8.5 min. − $[\alpha]_D^{20}$ = −20.1 (c = 1, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3360 cm^{-1} (N−H), 2940 (C−H), 1770 (C=O, lactone), 1715 (C=O, carbamate), 1510 (C=C). − ^1H NMR (500 MHz; $CDCl_3$): δ = 0.99, 1.02 [2 d, ^3J = 6.8 Hz, ^3J = 6.7 Hz, 6 H, $CH(CH_3)_2$], 1.89 (dsept, ^3J = 8.0 Hz, ^3J = 6.8 Hz, 1 H, 2′-H), 2.19 (ddd, ^2J = 12.9 Hz, ^3J = 11.6 Hz, ^3J = 10.2 Hz, 1 H, 4-H_A), 2.39 (ddd, ^2J = 13.0 Hz, ^3J = 9.2 Hz, ^3J = 6.2 Hz, 1 H, 4-H_B), 3.06 (m_c, 1 H, 3-H), 3.59 (ddd, ^3J = 10.2 Hz, ^3J = 8.0 Hz, ^3J = 1.5 Hz, 1 H, 1′-H), 3.74 (m_c, 2 H, 1′′-H), 4.68 (ddd, ^3J = 10.2 Hz, ^3J = 6.2 Hz, ^3J = 1.5 Hz, 1 H, 5-H), 4.90 (d, ^3J = 10.2 Hz, 1 H, NH), 5.09 (d, ^2J = 11.6 Hz, 1 H, CH_AH_BPh), 5.15 (d, ^2J = 11.6 Hz, 1 H, CH_AH_BPh), 7.30−7.37 (m, 5 H, C_6H_5). − ^{13}C NMR (125 MHz; $CDCl_3$): δ = 19.3, 19.7 [$CH(CH_3)_2$], 28.6 (C-4), 31.4 (C-2′), 42.7 (C-1′′), 58.1 (C-1′), 67.1 (CH_2Ph), 77.6 (C-5), 127.1, 128.2, 128.6 (C_6H_5), 136.3 ($C_{6}H_{5\ ipso}$), 157.0 (N−C=O), 175.0 (C-2). − MS (FAB); m/z (%): 362 (4) [M^+ + Na], 340 (39) [M^+ + H], 91 (100) [$C_7H_7^+$]. $C_{17}H_{22}ClNO_4$ (339.8): calcd. C 60.09, H 6.53, Cl 10.43, N 4.12; found C 60.12, H 6.55, Cl 10.73, N 4.07.

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