Synthesis of Highly Functionalized Amino Acid and Hydroxy Acid Derivatives from γ-Aminoalkyl-Substituted α-Methylene-γ-butyrolactones

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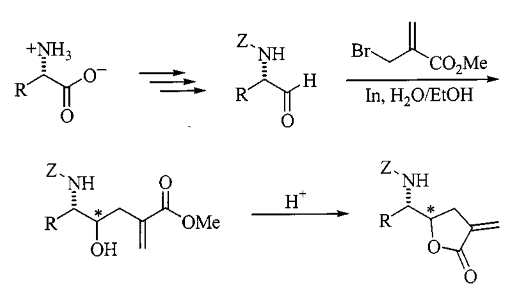
Dedicated to Günter Szeimies on the occasion of his 65th birthday

Keywords: Amino acids / Lactones / Michael additions / Synthetic methods / Radical reactions

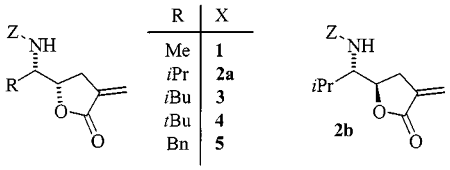
Addition of C-, S-, N- and O-nucleophiles to α-amino acid derived α-methylene-γ-butyrolactones provided the corresponding Michael adducts. Addition of cuprates or cyanide, respectively, could be achieved with excellent selectivities. Addition of malonate anion or methoxide could be performed with good yields, but with rather poor selectivities. Addition of *N*-nucleophiles was achieved with *N*-benzylhydroxylamine. Further reductive cleavage of the hydroxy and the benzyl groups under hydrogenolytic conditions afforded a diaminocarboxylic acid derivative. Addition of S-nucleophiles furnished the corresponding 1,4 adducts in excellent yields and with good selectivities, especially when a cysteine derivative was used as nucleophile. Hydrogenation of the α-methylene-γ-butyrolactones provided α-methyl-substituted lactones, and ozonolysis yielded the corresponding α,β-dicarbonyl compounds. An isomerization of the exocyclic double bond to an endocyclic double bond was achieved with rhodium chloride as catalyst. The configurations of all products were established by X-ray crystallographic analyses and NMR spectroscopy, including NOE experiments.

Introduction

α-Methylene-γ-butyrolactones are not only important because of their various biological activities, including antibiotic, fungicidal, anthelmintic and antitumor properties. Additionally, some of them are potent antiplatelet agents, antifeedants or antagonists against opioid receptors.[1,2] In addition they might be useful starting materials for the preparation of HIV-1 protease and renin inhibitors.[3−7] We have recently utilized a procedure developed by Schmidt et al.[8] and Dreiding et al.[9,10] for the diastereoselective preparation of α-amino acid derived γ-aminoalkyl-substituted α-methylene-γ-butyrolactones **1−5** (Scheme 1, Figure 1).[11] Inspection of several X-ray crystallographic analyses of these compounds showed that one side of the 5-membered ring (and consequently of the *exo*-methylene moiety) should be effectively blocked by the aminoalkyl substituent. This seems to be favourable for further diastereoselective transformations of the double bond.



Scheme 1. α-Methylene-γ-butyrolactones from α-amino acids[11]



R	X
Me	**1**
*i*Pr	**2a**
*i*Bu	**3**
*t*Bu	**4**
Bn	**5**

2b

Figure 1. Utilized α-methylene-γ-butyrolactones

Here we wish to present the conjugate additions of various C-, S-, N- and O-nucleophiles to α-amino acid derived α-methylene-γ-butyrolactones, together with radical additions and further transformations such as catalytic hydrogenation, ozonolysis and isomerization of the double bond.[12]

Results and Discussion

Addition of Cuprates

Cuprate- or copper-mediated Grignard additions to α,β-unsaturated carbonyl compounds are a frequently used tool for selective C−C couplings.[13] In the last few years, knowledge of the structures and properties of organocopper re-

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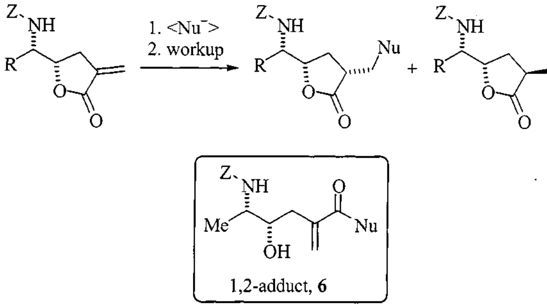
agents has increased substantially.[14−19] As well as classical Gilman cuprates prepared from copper(I) salts such as CuBr·DMS or CuI and 2 equiv. of an organolithium compound,[20−24] we also used cyanocuprates prepared in the same fashion from CuCN, which have been reported to show somewhat higher reactivity towards α,β-unsaturated carboxylic esters and amides.[25−27]

When we used CuBr·DMS/MeLi in the methyl cuprate addition to alanine-derived α-methylene-γ-butyrolactone **1** we observed exclusive 1,2-addition (21%, Scheme 2 and Table 1, Entry 1). Similar results were obtained with the valine-derived substrate **2a**. When we used CuCN as copper source together with the somewhat less reactive butyllithium, we isolated products **7a** and **7b**, resulting from conjugate addition, in 66% yield (Scheme 2 and Table 1, Entry 2). Nevertheless, the reaction times were somewhat longer and the isomers were obtained without selectivity (50:50).

Obviously, the intermediate enolate had been protonated unselectively during acidic workup. Nevertheless, no improvement of selectivities was observed when protolysis of the enolate was performed with bulky proton sources such as salicylic acid, pivalic acid[17] or collidinium trifluoroacetate.[28] When trimethylsilyl chloride (TMS−Cl) was added[22,29] after half of the reaction time, a silyl enol ether was formed, and this could be selectively cleaved with 1 N hydrochloric acid to afford an 86:14 mixture of isomers in favour of the *cis*-substituted butyrolactone **7a** (66%; Entry 3). Alternatively − in place of hydrolytic workup − the reaction mixture could be transferred onto a pad of silica gel and eluted with ethyl acetate, resulting in a comparable yield and a still further improved selectivity of 92:8 (Entry 4). Under these optimized conditions we attempted a conjugate addition of phenyl cuprate. With CuCN as the copper source we observed only biphenyl formation (Entry 5), but this was largely suppressed when we used CuI. However, products of a 1,4-addition were obtained in only moderate yields (37%, **8a/b** = 79:21, Entry 6). An attempted copper-catalysed Grignard addition of vinylmagnesium bromide with catalytic amounts of CuI as copper source did not produce a 1,4-addition. When we used stoichiometric amounts of CuI in the addition to α-methylene-γ-butyrolactone **2a**, we observed a conjugate addition, yielding isomers **9a** and **9b**. The timing of the addition of TMS−Cl seemed to be a crucial reaction parameter. When TMS−Cl was added − conventionally − after addition of lactone **2a**, a selectivity of **9a/b** = 89:11 was observed, with a yield of 37% (Entry 7). When lactone **2a** and TMS−Cl in THF were added to the cuprate at −78 °C, isomers **9a** and **9b** were isolated in 42% yield and with an inverted selectivity of 38:62 in favour of the *trans* isomer **9b** (Entry 8).



Scheme 2. Cuprate additions to α-methylene-γ-butyrolactones (for conditions and results, see Table 1)

Addition of Allyltrimethylsilane (Hosomi−Sakurai-Type Reaction)

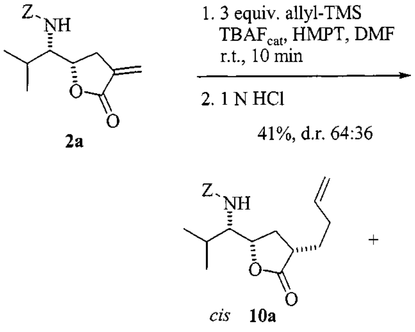
The usually Lewis-acid-catalysed, titanium-mediated addition of allylsilanes to carbonyl compounds (Hosomi−Sakurai reaction) has frequently been used for the introduction of allyl groups.[30,31] Majetich et al. re-

Table 1. Cuprate additions to α-methylene-γ-butyrolactones (cf. Scheme 2)

Entry	Starting material	R	Conditions	1,4-Addition Yield	1,4-Addition Selectivity	1,4-Addition Products	1,2-Addition Yield	1,2-Addition Product
1	**1**	Me	5 equiv. MeLi, 2.5 equiv. CuBr·DMS, Et_2O, −78 °C, 1.5 h; then NH_4Cl_{aq}				21%	**6**
2	**2a**	*i*Pr	4 equiv. *n*BuLi, 2 equiv. CuCN, −78 °C, 3 h; then NH_4Cl_{aq}	66%	50:50	**7a**,**b**		
3	**2a**	*i*Pr	4 equiv. *n*BuLi, 2 equiv. CuCN, 1.5 equiv. TMS−Cl, −78 to −50 °C, 3 h; then 1 N HCl	66%	86:14	**7a**,**b**		
4	**2a**	*i*Pr	4 equiv. *n*BuLi, 2 equiv. CuCN, 1.5 equiv. TMS−Cl, −78 to −50 °C, 3 h; then 5 g SiO_2, ethyl acetate	62%	92:8	**7a**,**b**		
5	**2a**	*i*Pr	6 equiv. PhLi, 3 equiv. CuCN, 3 equiv. TMS−Cl, −78 °C, 3 h; then 1 N HCl	[a]				
6	**2a**	*i*Pr	6 equiv. PhLi, 3 equiv. CuI, 3 equiv. TMSCl, −78 to −50 °C, 5 h; then 1 N HCl	37%	79:21	**8a**,**b**		
7	**2a**	*i*Pr	6 equiv. vinylMgBr, 3 equiv. CuI, 3 equiv. TMS−Cl[b], Et_2O, −78 to −50 °C, 5 h; then 1 N HCl	37%	89:11	**9a**,**b**		
8	**2a**	*i*Pr	6 equiv. vinylMgBr, 3 equiv. CuI, 3 equiv. TMS−Cl[c], Et_2O, −78 to −50 °C, 5 h; then 1 N HCl	42%	38:62	**9a**,**b**		

[a] Only biphenyl formation. [b] TMS−Cl was added after addition of lactone **2a** to the cuprate. [c] Treatment of the lactone **2a** with TMS−Cl before adding the mixture in THF to the cuprate.

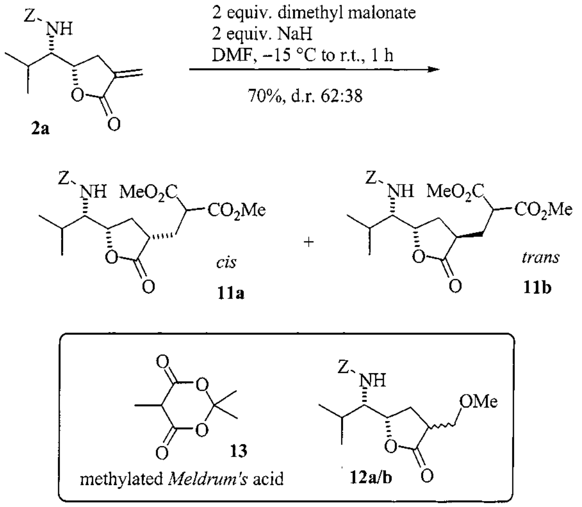
ported a variation of this reaction, permitting the 1,4-addition of allylsilane to α,β-unsaturated carbonyl compounds, although the yields are usually mediocre.[32] Here, titanium chloride is replaced by catalytic amounts of tetrabutylammonium fluoride (TBAF) to cleave the Si−C bond and thus generate an active allyl species. When we used these conditions in the allyl addition to α-methylene-γ-butyrolactone **2a**, we observed exclusive 1,4-addition, although yields and selectivities were fairly poor (**10a/b** = 64:36, 41%, Scheme 3). Selectivities could not be improved by protolysis with bulky acids or by addition of TMS−Cl (vide supra). Deprotonation with lithium diisopropylamide (LDA) and kinetic reprotonation at low temperature did not affect the diastereomeric ratio either. When we used the originally reported Hosomi−Sakurai reaction conditions ($TiCl_4$, allyl-TMS),[32] an unspecific reaction was observed without isolable products.



Scheme 3. Hosomi−Sakurai-type addition of allylsilane to α-methylene-γ-butyrolactone **2a**

Addition of Malonate

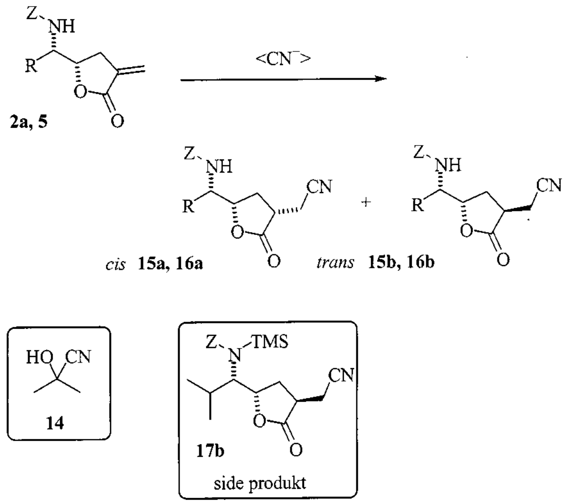
Malonates were the first reported nucleophiles subjected to 1,4-addition to α,β-unsaturated carbonyl compounds. We added dimethyl malonate, deprotonated with sodium methoxide in methanol, to the valine-derived α-methylene-γ-butyrolactone **2a**, resulting in the formation of the corresponding malonate adducts **11a** and **11b** (ca. 40%) and methoxide adducts **12a** and **12b** (ca. 30%). Utilization of sodium hydride in anhydrous dimethylformamide as base resulted in the clean formation of adducts **11a** and **11b** in a 70% yield, with a selectivity of 62:38 (Scheme 4). The rather acidic malonate α-proton, which is still present after the addition, was suspected to give rise to a nonspecific protonation of the intermediate enolate, which would explain the poor selectivity. Consequently, we tested a malonate derivative bearing only one acidic proton, using 2,2,5-trimethyl-1,3-dioxane-4,6-dione (**13**, methylated Meldrum's acid).[33] However, no addition of this substrate could be achieved.



Scheme 4. Addition of malonate and malonate derivatives to α-methylene-γ-butyrolactone **2a**

Addition of Cyanide

Addition of cyanide allows the introduction of a further functional group that can be easily modified to provide carboxylic acids, amides, ketones, aldehydes or amines. Cyanide additions to α,β-unsaturated carbonyl compounds have been reported previously; as well as HCN[34] or KCN,[35] acetone cyanohydrin[16,36,37] and trimethylsilyl cyanide (TMS−CN)[38−42] in the presence of Lewis acids have predominantly been used as cyanide sources. When we used acetone cyanohydrin **14** in the presence of a catalytic amount of potassium cyanide for cyanide additions to α-methylene-γ-butyrolactones **2a** and **5**, we isolated carbonitriles **15a** and **15b** and **16a** and **16b** in almost quantitative yields, but with only moderate selectivities of 69:31 and 73:27, respectively (Scheme 5, Table 2).



Scheme 5. Cyanide addition to α-methylene-γ-butyrolactones (for conditions and results, see Table 2)

These disappointing selectivities might be due to the protic reaction conditions, inevitable when acetone cyanohydrin is used as the cyanide source.

Better selectivities were obtained with TMS−CN in the presence of triethylaluminium; cyanide addition to lactones **2a** and **5** could now be achieved with high selectivities (< 5:95 and 14:86, respectively), though with poor yields (around 45%). It should be noted that the *trans* isomers were formed as major products under these reaction conditions. We again assume that a silyl enol ether is formed in-

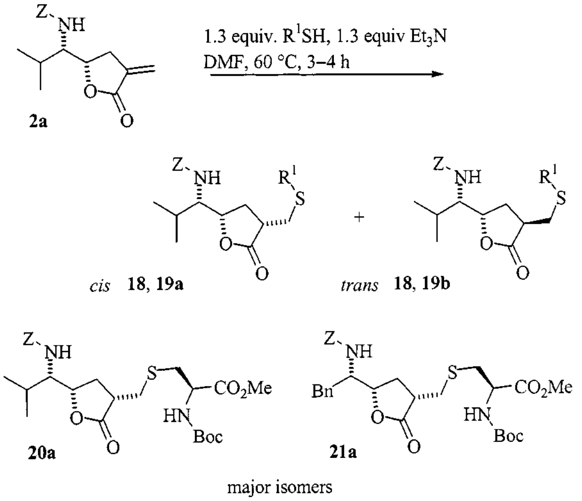
Table 2. Cyanide additions to α-methylene-γ-butyrolactones (cf. Scheme 5)

Entry	Starting material	R	Conditions	Yield	Selectivity	Products
1	**2a**	*i*Pr	4 equiv. **14**, KCN$_{cat.}$, DMSO, 30 °C, 4 h then NH$_4$Cl$_{aq}$	95%	73:27	**15a**,**b**
2	**5**	Bn	4 equiv. **14**, KCN$_{cat.}$, DMSO, 30 °C, 4 h then NH$_4$Cl$_{aq}$	99%	69:31	**16a**,**b**
3	**2a**	*i*Pr	2.5 equiv. TMS-CN, 2.5 equiv. AlEt$_3$, THF, 60 °C 24 h, then 1 N HCl$_{aq}$	43% (5%)	< 5:95	**15a**,**b**, **17b**
4	**5**	Bn	2.5 equiv. TMS-CN, 2.5 equiv. AlEt$_3$, THF, 60 °C 24 h, then 1 N HCl$_{aq}$	45%	14:86	**16a**,**b**

termediately and is then hydrolysed during the acidic workup. The inverted selectivity might be explained by a somewhat different and more rigid conformation of this intermediate, resulting from complexation with the Lewis acid AlEt$_3$. An intramolecular proton transfer of the enolate by the carbamate NH group might also be a possible explanation for the stereochemical course of the reaction. In one case we observed the *N*-silylated substance **17b** as a side product, which indicates the participation of the carbamate NH group during the reaction. The exact mechanism, however, is still unclear.

Addition of *S*-Nucleophiles

Thiols have frequently been added to naturally occurring, sesquiterpenoid α-methylene-γ-butyrolactones;[43–47] in particular, the use of this reaction for masking of the reactive double bond has been recognized by Kupchan et al.[43] For the addition to α-methylene-γ-butyrolactone **2a**, we first chose benzylmercaptan and thiophenol. The addition was accomplished under basic conditions (NEt$_3$), affording the stable and separable thioethers **18a** and **18b** and **19a** and **19b**, in yields of 79 and 80% and diastereomeric ratios of 71:29 and 82:18, respectively, in favour of the *cis* isomers (Scheme 6, Table 3).



Scheme 6. Addition of thiols to α-methylene-γ-butyrolactones (for results, see Table 3)

Table 3. Addition of S-nucleophiles to α-methylene-γ-butyrolactones (cf. Scheme 6)

Entry	Starting material	R^{1}SH	Yield	Selectivity	Products
1	**2a**	BnSH	90%	82:18	**18a**,**b**
2	**2a**	PhSH	87%	74:26	**19a**,**b**
3	**2a**	Boc-Cys-OMe	98%	78:22	**20a**,**b**
4	**5**	Boc-Cys-OMe	95%	76:24	**21a**,**b**

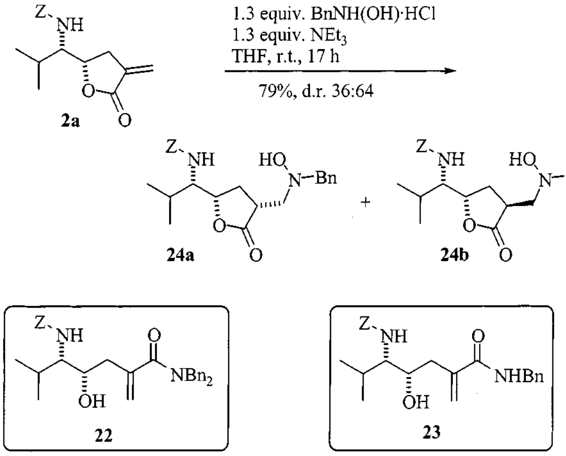
A reduction in the reaction temperature affected neither yields nor selectivities. Aprotic reaction conditions (with NaH as a base instead of Et$_3$N) and the addition of trimethylsilyl chloride (in order to trap the intermediate enolate) resulted only in reduced yields, but comparable selectivities.

In analogy to the biological mode of action of most sesquiterpenoid α-methylene-γ-butyrolactones,[2] we added Boc-protected cysteine methyl ester (Boc−Cys−OMe) to lactones **2a** and **5**. Under the same reaction conditions, the corresponding 1,4-addition products **20a** and **20b** and **21a** and **21b** were obtained in excellent yields and with good selectivities (Scheme 6, Table 3).

Addition of *N*-Nucleophiles

1,4-Addition of nitrogen nucleophiles has often been used for the synthesis of β-amino acid derivatives. Especially noteworthy is the addition of chiral lithium amides, which can be performed with excellent diastereoselectivities.[48–56] A variation has been published by Sewald et al., who used amido cuprates for a conjugate addition.[57] The addition of benzylamine was reported to produce low yields and mixtures of 1,2- and 1,4-addition.[58] When we treated the valine-derived α-methylene-γ-butyrolactone **2a** with lithium dibenzylamide at −78 °C, we observed exclusive 1,2-addition, affording a ring-opened substrate **22** (44%) together with 42% of the starting material (Scheme 7). A similar 1,2-addition was observed when we used an amido cuprate derived from benzyltrimethylsilylamine.[57] Under these reaction conditions, only 21% of the homoallyl alcohol **23** was obtained, whilst no starting material could be recovered.

A frequently applied method for conjugate additions of N-nucleophiles is the use of *N*-benzylhydroxylamines.[58–60] We were able to perform a 1,4-addition to methylene lactone **2a** successfully when we treated it with *N*-benzylhydroxylamine hydrochloride in the presence of triethylamine. β-Amino acid derivatives **24a** and **24b** were isolated in 79% yield, though with a poor selectivity of 36:64 (Scheme 7). Surprisingly, the main product was the *trans* isomer **24b**, which might be explained by an intramolecular proton transfer from the carbamate-NH to the intermediate enol-



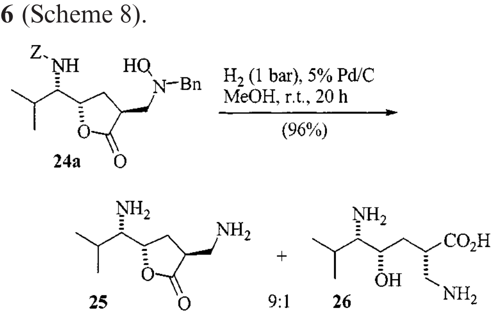
Scheme 7. Addition of N-nucleophiles to α-methylene-γ-butyrolactone **2a**

ate. Consequently, the proton would approach from the hindered face of the ring. When the *N*-benzylhydroxylamine was liberated from the hydrochloride before use, the addition of triethylamine was not necessary; essentially identical results were obtained.

Compounds **24a** and **24b** were obtained in analytically pure form, but proved to be rather unstable. Unspecified decomposition was observed, especially when they were left in chloroform (NMR sample).

No addition product was obtained when we used *O*-benzylhydroxylamine, even after several days of treatment. A Lewis acid catalysed reaction to afford isoxazolidinones, as has been reported for similar compounds, could not be achieved.[58]

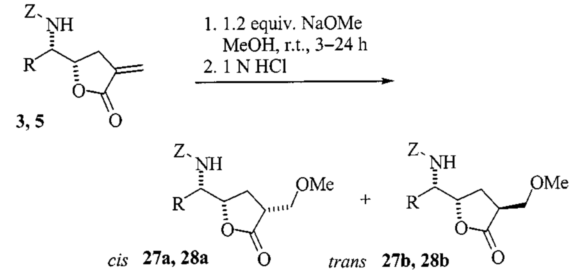
The cleavage of the hydroxy and the benzyl groups was performed under hydrogenolytic conditions, cleaving the carboxybenzyl (Z) group. The product **25** – a formal adduct of ammonia to the methylene lactone **2a** – could not be obtained in analytically pure form; it contained about 10% of the corresponding ring-opened β-amino acid derivative **26** (Scheme 8).



Scheme 8. Cleavage of the hydroxy and the benzyl groups in the hydroxylamine adduct **24a**

Addition of *O*-Nucleophiles

The observation of the methoxide adducts **12a** and **12b** as side-products in the addition of malonate (deprotonated with sodium methoxide, vide supra) prompted us to investigate a directed utilisation of O-nucleophiles. When we treated phenylalanine- and leucine-derived lactones **3** and **5** with sodium methoxide in methanol, we isolated methyl ethers **27a** and **27b** and **28a** and **28b** in satisfactory yields (81 and 71%, respectively). Unfortunately, selectivities were poor, not exceeding 55:45 (Scheme 9). We assumed that the selectivities would not be improvable under these protic conditions and consequently used anhydrous tetrahydrofuran and dimethylformamide, respectively, as solvents, but no reaction occurred even at elevated temperature. A kinetic epimerization of isomers **28a** and **28b** (53:47 mixture) by deprotonation with LDA at −78 °C and subsequent reprotonation with collidinium trifluoroacetate[61] resulted in an inverted but similarly poor ratio (45:55) in favour of the *trans* isomer **28b** together with various unidentified side-products formed during this isomerization.



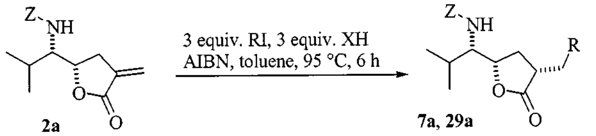
3: R = *i*Bu: 81%, d.r. = 55:45, **27a,b**
5: R = Bn: 71%, d.r. = 53:47, **28a,b**

Scheme 9. Methoxide addition to α-methylene-γ-butyrolactones **3** and **5**

Attempts to add phenylmethoxide or *tert*-butoxide as O-nucleophiles were unsuccessful. In the former case, starting material was isolated quantitatively, in the latter reaction decomposition of the lactone was observed. The relative configurations of lactones **27a** and **27b** were unambiguously proven by X-ray crystallographic analyses. Their respective structures were the foundation for the determination of all addition products by NMR spectroscopy (vide supra).[12]

Addition of Radicals

Additions of radicals to α-methylene-γ-butyrolactones[62] and α-methylenecarboxylic esters[63] have been reported occasionally. We tested whether the α-methylene-γ-butyrolactones presented here could be used in similar reactions. For this we subjected lactone **2a** to the presence of *n*-butyl iodide and of *tert*-butyl iodide, together with tributyltin hydride as hydrogen donor and a chain initiator (AIBN) at 95 °C. Under these reaction conditions, only *n*-butyl iodide gave a radical addition; product **7a** could be isolated in 30% yield (Scheme 10). When, however, we used the less toxic



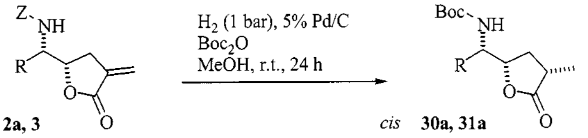
7a: R = *n*Bu, XH = Bu$_3$SnH, 30%, d.r. > 95:5
29a: R = *t*Bu, XH = (Me$_3$Si)$_3$SiH, 31%, d.r. > 95:5

Scheme 10. Radical addition to α-methylene-γ-butyrolactone **2a**

$(Me_3Si)_3SiH$[64] as hydrogen donor, addition of *tert*-butyl iodide did prove possible, resulting in lactone **29a** in 31% yield. The poor yields could not be further improved, although we added the reagents slowly by syringe pump and monitored the reaction temperature carefully. Only one isomer could be isolated in these radical additions; this is not surprising since the approach of the bulky hydrogen donor (the diastereoselective step in the reaction sequence) is effectively hindered at one side of the lactone ring. Consequently, only the *cis*-substituted products were obtained.

Hydrogenation of the Double Bond

Since one side of the α-methylene-γ-butyrolactones is effectively shielded by the side-chain, we expected hydrogenation of the double bond to occur with high selectivity. Actually, when we subjected substrates **2a** and **3** to hydrogen in the presence of palladium on charcoal (5%), the reduction could be achieved with a selectivity better than 10:1; when leucine-derived substrate **3** was hydrogenated, no second isomer could be detected in the NMR spectra of the crude product (Scheme 11). Under hydrogenolytic reaction conditions, the carbamate protection group (Z) was cleaved; in the presence of di-*tert*-butyl dicarbonate (Boc_2O) the amino function was reprotected with the Boc group in situ.[65,66] The α-methyl-γ-butyrolactones **30a** and **30b** and **31a** were formed in 93% and 80% yields, respectively. The relative configuration of **31a** was unambiguously determined by X-ray crystallographic analysis.[12]

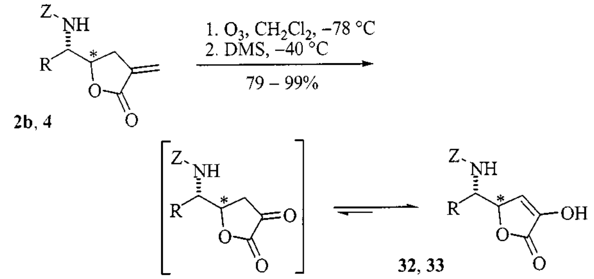


2a: R = *i*Pr: 93%, d.r. = 91:9, **30a/b**
3: R = *i*Bu: 80%, d.r. > 95:5, **31a**

Scheme 11. Hydrogenation of the exocyclic double bond in α-methylene-γ-butyrolactones with concomitant protection group interchange

Ozonolysis of the Double Bond

Ozonolysis of α-methylene-γ-butyrolactones has often been used,[67,68] especially in the synthesis of sialylic acids from carbohydrate-derived substrates.[69–71] We degraded the double bonds of lactones **2b** and **4** in anhydrous dichloromethane at −78 °C by introduction of an ozone/oxygen mixture and subsequent reductive workup with dimethyl sulfide. The α,β-dicarbonyl compounds **32** and **33**, which are in fact – from NMR spectroscopic investigations – exclusively enol tautomers, could be isolated in 99% and 79% yields, respectively (Scheme 12).

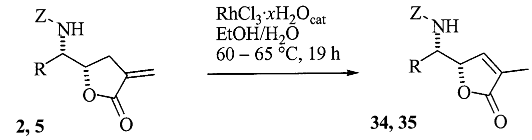


2b: R = *i*Pr, (5*R*): 99%, **32**
4: R = *t*Bu, (5*S*): 79%, **33**

Scheme 12. Ozonolysis of the exocyclic double bond in α-methylene-γ-butyrolactones

Isomerization of the Double Bond

The entropically and energetically favoured isomerization of the *exo* double bond should provide compounds with the potential for further substitutions in position C-4. Similar reactions have been performed with $RhCl_3$ [72–75] or acid catalysis.[76] We accomplished isomerizations of the double bonds in methylenelactones **2a** and **5** by using catalytic amounts of $RhCl_3{\cdot}xH_2O$ in $EtOH/H_2O$ (10:1) at 60–65 °C. The endocyclic α,β-unsaturated butyrolactones **34** and **35** could be isolated after 19 h in 88 and 99% yields, respectively (Scheme 13).



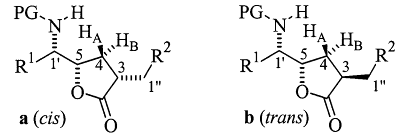
2a: R = *i*Pr: 88%, **34**
5: R = Bn: 99%, **35**

Scheme 13. Isomerization of the double bond in α-methylene-γ-butyrolactones

Conclusion

The diastereoisomers obtained in these reactions could in general be separated by medium pressure liquid chromatography (MPLC) and were obtained and characterized in analytically pure form. The configurations of the isomers were determined from the X-ray crystallographic data obtained for methanol adducts **27a** and **27b** and for the hydrogenated α-methylene-γ-butyrolactone **31a**.[12] NMR spectroscopy (including NOE experiments) and comparison of significant shifts and coupling constants (Table 4) revealed the configuration of the remaining isomers. Couplings and shifts of the protons at position C-4 proved to be most informative. The tendencies – as derived from the spectroscopic data for the adducts **6–31** – are summarized in Table 4.

Table 4. Spectroscopic data of the adducts **6−31**



a (*cis*) **b** (*trans*)

Isomer	Proton	δ [ppm]	$^3J_{(3H,4H)}$ [Hz]	$^3J_{(4H,5H)}$ [Hz]
a	4-H_A	2.16−2.70	8.3−9.8	5.3−6.9
	4-H_B	1.65−2.19	10.9−12.6	9.6−10.8
b	4-H_A	1.97−2.40	5.2−9.7	4.6−9.2
	4-H_B	2.12−2.53	6.8−10.2	3.4−8.0

Comparison of the results presented here suggests that the selectivities are too irregular and in some cases too poor to allow for a uniform interpretation. Rather than offering explanations, we shall discuss possible reasons for the observed selectivities (Figure 2). It should be kept in mind that the selectivities are governed not by the direction of the nucleophilic attack, but by the subsequent diastereoselective protonation of the intermediate enolate.[77,78] It turned out that formation of a silyl enol ether (in cuprate and cyanide additions) during the reaction and hydrolysis under mildly acidic conditions resulted in significantly improved selectivities. Several modes of reaction for the protonation step (either of the enolate or the enol ether) are possible, though they cannot be clearly predicted or distinguished. Besides the predominant protonation by way of the sterically less hindered face of the molecule (Figure 2, reaction path I, formation of the predominantly formed *cis* product), which is obvious in the presence of protic solvents or reagents, intramolecular protonation should be considered as well. The carbamate proton (which reaches into the vicinity of the enolate) might be transferred, especially under aprotic conditions (reaction path II). Obviously, this intramolecular protonation is not possible when strongly basic conditions result in the deprotonation of the carbamate (cuprate additions, for example). The participation of the counterion (copper, for example), possibly chelated by the carbamate, might also influence the stereochemical outcome, though no general difference between metal-based and nonmetallic additions (such as thiol additions) was observed.[79] A third modus reactandi is possible when acidic protons are present in the introduced nucleophile. This is true for the malonate addition (though the α-proton is possibly not suitably oriented for an intramolecular protonation of the enolate) or for the hydroxylamine addition (reaction path III). Whether, in all of these scenarios, protonation of the carbon or oxygen atom (producing an enol with subsequent tautomerization) takes place[80] should be irrelevant, since all these reasons should be applicable for both alternatives.

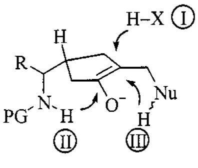
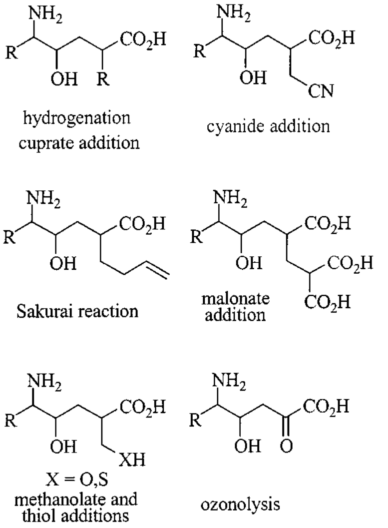


Figure 2. Modes of inter- and intramolecular stereoselective protonation giving rise to a stereogenic centre



hydrogenation cuprate addition

cyanide addition

Sakurai reaction

malonate addition

X = O,S methanolate and thiol additions

ozonolysis

Figure 3. Accessible substance classes depicted schematically without protecting groups

We have presented a variety of nucleophilic additions to amino acid derived α-methylene-γ-butyrolactones, which provide a plethora of amino acid derivatives bearing several functionalities and stereogenic centres in a minimum of space, therefore being useful intermediates for organic synthesis. The substance classes accessible in this manner are schematically depicted in Figure 3.

Experimental Section

General Remarks: Solvents for chromatography and for workup: 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). α-Methylene-γ-butyrolactones **1−5** were prepared as published.[11] Common amino acid abbreviations are used.[81] 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), conc. H_2SO_4 (60 mL), H_2O (940 mL)]. Medium pressure liquid chromatography (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. ^1H and ^{13}C NMR spectra were recorded with a Bruker ARX 500 spectrometer at room temp. in $CDCl_3$ unless otherwise indicated; δ in ppm relative to internal TMS (δ = 0) or to solvent resonances (^1H: $CHCl_3$, δ = 7.24; ^{13}C: $CDCl_3$, δ = 77.0), *J* in Hz. Mass spectra were recorded with 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.

(3*S*,5*S*,1′*S*)- and (3*R*,5*S*,1′*S*)-5-[-1-(Benzyloxycarbonylamino)-2-methylpropyl]-3-pentyl-4,5-dihydro-2(3*H*)furanone (7a and 7b). − a) CuCN (59 mg, 0.66 mmol) was placed in a flame-dried flask, and residual H_2O was removed azeotropically with anhydrous toluene in vacuo. Anhydrous Et_2O (0.7 mL) was added under Ar and the suspension was cooled to −78 °C. An *n*BuLi solution (15% in hexane, 805 μL, 1.32 mmol) was added, the temperature was allowed to rise to 0 °C and stirring was continued until the solution became homogenous. After this mixture had again been cooled to −78 °C, lactone **2a** (100 mg, 330 μmol) was added, and the solution was stirred for 3 h at −55 °C and hydrolysed at that temperature with saturated NH_4Cl solution (5 mL). The aqueous layer was extracted with Et_2O (3×10 mL) and the combined extracts were washed with 1 N HCl, saturated $NaHCO_3$ and brine (10 mL each) and dried ($MgSO_4$). The solvents were removed in a rotary evaporator, yielding a yellowish oil. After filtration through an SiO_2 pad, the diastereomeric ratio was determined by HPLC (hexane/EA, 80:20) to be **7a/7b** = 50:50. Separation by MPLC (PE/EA, 85:15) afforded lactones **7a** (40 mg, 34%) and **7b** (38 mg, 32%). − **b)** Scavenging as silyl enol ether: The experiment was started as described above. After addition of the lactone **2a** (76 mg, 251 μmol) the mixture was stirred at −78 °C for 1.5 h. TMS−Cl (1.5 equiv.) was added and stirring was continued at that temperature for a further 1.5 h. The mixture was hydrolysed at −78 °C with 1 N HCl, warmed to room temp. and worked up as described above. The isomers (**7a/7b** = 86:14) were separated by MPLC (PE/EA, 85:15) to afford lactones **7a** (52 mg, 57%) and **7b** (10 mg, 11%). − **c)** Alternative workup: The reaction was performed as described in b) (100 mg, 330 μmol of lactone **2a**). Instead of an aqueous workup, the mixture was applied (without hydrolysis) to a column filled with SiO_2 (5 g) and eluted with EA. Subsequent purification by MPLC (PE/EA, 85:15) afforded lactones **7a** (68 mg, 57%) and **7b** (6 mg, 5%) (*dr* = 92:8). **7a:** Colourless oil. $[\alpha]_D^{20} = -25.6$ ($c = 1.04$, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3315 cm^{-1} (N−H), 3010, 2930, 2850 (C−H), 1769 (C=O, lactone), 1714 (C=O, urethane), 1531 (C=C). ^{1}H NMR: δ = 0.88 (t, ^3J = 6.5, 3 H, 5′′-H), 0.98 [d, ^3J = 6.7, 3 H, $CH(CH_3)_2$], 1.02 [d, ^3J = 6.7, 3 H, $CH(CH_3)_2$], 1.22−1.37 (m, 7 H, 1′′-H_A, 2′′-H, 3′′-H, 4′′-H), 1.65 (ddd, ^2J = 12.3, ^3J = 12.3, ^3J = 10.4, 1 H, 4-H_B), 1.86 (m_c, 1 H, 1′′-H_B), 1.89 (dsept, ^3J = 7.9, ^3J = 6.8, 1 H, 2′-H), 2.31 (ddd, ^2J = 12.7, ^3J = 8.9, ^3J = 5.9, 1 H, 4-H_A), 2.57 (dddd, ^3J = 11.9, ^3J = ^3J = 8.9, ^3J = 4.3, 1 H, 3-H), 3.54 (ddd, ^3J = 9.7, ^3J = 7.9, ^3J = 1.5, 1 H, 1′-H), 4.59 (ddd, ^3J = 10.4, ^3J = 5.9, ^3J = 1.5, 1 H, 5-H), 4.83 (d, ^3J = 10.3, 1 H, NH), 5.11 (d, ^2J = 12.3, 1 H, OCH_AH_BPh), 5.13 (d, ^2J = 12.3, 1 H, OCH_AH_BPh), 7.29−7.39 (m, 5 H, C_6H_5). ^{13}C NMR: δ = 14.0 (C-5′′), 19.3, 19.7 [$CH(CH_3)_2$], 22.5 (C-4′′), 26.9 (C-3′′), 30.1 (C-2′′), 31.4 (C-2′), 31.5, 31.5 (C-1′′, C-4), 40.3 (C-3), 58.2 (C-1′), 67.0 (OCH_2Ph), 77.4 (C-5), 127.9, 128.2, 128.6 (C_6H_5), 136.3 (C_6H_5 *ipso*), 157.0 (C=O, urethane), 178.8 (C-2). MS (FAB): *m/z* (%) = 723 (3, [2 M + H]$^+$), 384 (6, [M + Na]$^+$), 362 (54, [M + H]$^+$), 91 (100 [$C_7H_7^+$]). $C_{21}H_{31}NO_4$ (361.5): calcd. C 69.78, H 8.64, N 3.87; found C 69.68, H 8.71, N 3.81. **7b:** Colourless oil. $[\alpha]_D^{20} = -23.6$ ($c = 1.25$, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3308 cm^{-1} (N−H), 3010, 2960, 2850 (C−H), 1767 (C=O, lactone), 1713 (C=O, urethane), 1531 (C=C). ^{1}H NMR: δ = 0.89 (t, ^3J = 6.8, 3 H, 5′′-H), 0.97 [d, ^3J = 6.7, 3 H, $CH(CH_3)_2$], 1.02 [d, ^3J = 6.8, 3 H, $CH(CH_3)_2$], 1.22−1.38 (m, 6 H, 2′′-H, 3′′-H, 4′′-H), 1.43 (m_c, 1 H, 1′′-H_A), 1.75 (m_c, 1 H, 1′′-H_B), 1.86 (dsept, ^3J = 8.2, ^3J = 6.7, 1 H, 2′-H), 1.97 (ddd, ^2J = 13.7, ^3J = 8.0, ^3J = 6.0, 1 H, 4-H_A), 2.24 (ddd, ^2J = 13.2, ^3J = 9.9, ^3J = 6.2, 1 H, 4-H_B), 2.51 (dddd, ^3J = 11.2, ^3J = 9.7, ^3J = ^3J = 5.7, 1 H, 3-H), 3.51 (ddd, ^3J = 10.1, ^3J = 8.2, ^3J = 1.7, 1 H, 1′-H), 4.71 (ddd, ^3J = 8.0, ^3J = 6.2, ^3J = 1.7, 1 H, 5-H), 4.79 (d, ^3J = 10.2, 1 H, NH), 5.11 (d, ^2J = 12.3, 1 H, OCH_AH_BPh), 5.13 (d, ^2J = 12.3, 1 H, OCH_AH_BPh), 7.30−7.38 (m, 5 H, C_6H_5). ^{13}C NMR: δ = 14.0 (C-5′′), 19.3, 19.8 [$CH(CH_3)_2$], 22.4 (C-4′′), 26.9 (C-3′′), 30.8 (C-4), 31.1 (C-2′), 31.4, 31.4 (C-1′′, C-2′′), 39.5 (C-3), 59.7 (C-1′), 67.1 (OCH_2Ph), 77.7 (C-5), 128.0, 128.2, 128.6 (C_6H_5), 136.3 (C_6H_5 *ipso*), 157.0 (C=O, urethane), 179.7 (C-2). MS (FAB): *m/z* (%) = 723 (4, [2 M + H]$^+$), 384 (3, [M + Na]$^+$), 362 (28, [M + H]$^+$), 91 (100, $C_7H_7^+$). $C_{21}H_{31}NO_4$ (361.5): calcd. C 69.78, H 8.64, N 3.87; found C 69.92, H 8.64, N 3.89.

(3*S*,5*S*,1′*S*)- and (3*R*,5*S*,1′*S*)-3-Benzyl-5-[-1-(benzyloxycarbonylamino)-2-methylpropyl]-4,5-dihydro-2(3*H*)furanone (8a and 8b): CuI (188 mg, 990 μmol) was placed in a flame-dried flask, and residual H_2O was removed azeotropically with anhydrous toluene in vacuo. Anhydrous Et_2O (2 mL) was added under Ar and the suspension was cooled to −78 °C. A PhLi solution (1.10 mL, 1.98 mmol) was added, the temperature was allowed to rise to 0 °C and stirring was continued until the solution became homogenous. After recooling to −78 °C, a mixture of lactone **2a** (100 mg, 330 μmol) and TMS−Cl (125 μL, 990 μmol) in anhydrous THF (1 mL) was added. The solution was stirred for 5 h at −50 °C and hydrolysed at that temperature with 1 N HCl (2 mL). The aqueous layer was extracted with Et_2O (3×10 mL) and the combined extracts were washed with saturated $NaHCO_3$ and brine (10 mL each) and dried ($MgSO_4$). The solvents were removed in a rotary evaporator, yielding a yellowish oil. After filtration through an SiO_2 pad, the diastereomeric ratio was determined by HPLC (hexane/EA, 85:15) to be **8a/8b** = 79:21. Separation by MPLC (PE/EA, 89:11) afforded lactones **8a** (39 mg, 31%) and **8b** (7 mg, 6%). **8a:** Colourless oil. $[\alpha]_D^{20} = +48.1$ ($c = 1.04$, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3320 cm^{-1} (N−H), 3030, 2960, 2850 (C−H), 1770 (C=O, lactone), 1715 (C=O, urethane), 1530 (C=C). ^{1}H NMR: δ = 0.95 [d, ^3J = 6.8, 3 H, $CH(CH_3)_2$], 0.99 [d, ^3J = 6.8, 3 H, $CH(CH_3)_2$], 1.73 (ddd, ^2J = 12.9, ^3J = 12.1, ^3J = 10.4, 1 H, 4-H_B), 1.85 (dsept, ^3J = 7.8, ^3J = 6.8, 1 H, 2′-H), 2.16 (ddd, ^2J = 12.8, ^3J = 8.8, ^3J = 5.8, 1 H, 4-H_A), 2.62 (dd, ^2J = 13.9, ^3J = 9.7, 1 H, 1′′-H_A), 2.85 (dddd, ^3J = 12.1, ^3J = 9.7, ^3J = 8.8, ^3J = 4.1, 1 H, 3-H), 3.22 (dd, ^2J = 13.9, ^3J = 4.1, 1 H, 1′′-H_B), 3.48 (ddd, ^3J = 10.3, ^3J = 7.9, ^3J = 1.6, 1 H, 1′-H), 4.55 (ddd, ^3J = 10.4, ^3J = 5.8, ^3J = 1.6, 1 H, 5-H), 4.81 (d, ^3J = 10.3, 1 H, NH), 5.10 (s, 2 H, OCH_2Ph), 7.09−7.39 (m, 10 H, 2 C_6H_5). ^{13}C NMR: δ = 19.2, 19.7 [$CH(CH_3)_2$], 31.2 (C-4), 31.4 (C-2′), 36.0 (C-1′′), 42.3 (C-3), 58.1 (C-1′), 67.0 (OCH_2Ph), 77.6 (C-5), 126.7, 128.0, 128.2, 128.6, 128.6, 128.8, (2 C_6H_5), 136.4, 138.3 (2 C_6H_5 *ipso*), 156.8 (C=O, urethane), 177.8 (C-2). MS (EI, 70 eV): *m/z* (%) = 381 (3) [M$^+$], 206 (14, [M − C_6H_6 − $C_5H_5O_2$]$^+$), 162 (26, [M − C_6H_6 − $C_5H_5O_2$ − CO_2]$^+$), 91 (100, [$C_7H_7^+$]). $C_{23}H_{27}NO_4$ (381.5): calcd. C 72.42, H 7.13, N 3.67; found C 72.32, H 7.12, N 3.63. **8b:** Colourless oil. $[\alpha]_D^{20} = -6.8$ ($c = 0.35$, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3320 cm^{-1} (N−H), 3030, 2960, 2875 (C−H), 1770 (C=O, lactone), 1715 (C=O, urethane), 1530 (C=C). ^{1}H NMR: δ = 0.91 [d, ^3J = 6.7, 3 H, $CH(CH_3)_2$], 0.92 [d, ^3J = 6.7, 3 H, $CH(CH_3)_2$], 1.78 (dsept, ^3J = 8.2, ^3J = 6.8, 1 H, 2′-H), 2.02 (ddd, ^2J = 13.2, ^3J = 7.8, ^3J = 5.2, 1 H, 4-H_A), 2.12 (ddd, ^2J = 13.4, ^3J = 9.6, ^3J = 6.7, 1 H, 4-H_B), 2.84 (dd, ^2J = 13.2, ^3J = 8.5, 1 H, 1′′-H_A), 2.89 (dddd, ^3J = 9.8, ^3J = 8.4, ^3J = 5.5, ^3J = 4.4, 1 H, 3-H), 3.06 (dd, ^2J = 13.1, ^3J = 4.2, 1 H, 1′′-H_B), 3.42 (ddd, ^3J = 10.1, ^3J = 8.2, ^3J = 1.8, 1 H, 1′-H), 4.35 (ddd, ^3J = 8.1, ^3J = 6.7, ^3J = 1.9, 1 H, 5-H), 4.71 (d, ^3J = 10.2, 1 H, NH), 5.09 (s, 2 H, OCH_2Ph), 7.13−7.39 (m, 10 H, 2 C_6H_5). ^{13}C NMR: δ = 19.5, 20.0 [$CH(CH_3)_2$], 30.0 (C-4), 31.4 (C-2′), 37.2 (C-1′′), 41.5 (C-3), 59.8 (C-1′), 67.5 (OCH_2Ph), 78.3 (C-5), 127.4, 128.4, 128.7, 129.0, 129.1, 129.4, (2 C_6H_5), 136.6, 138.1 (2 C_6H_5 *ipso*), 157.3 (C=O, urethane), 179.4 (C-2). MS

(FAB): m/z (%) = 763 (2, [2 M + H]$^+$), 404 (3, [M + Na]$^+$), 382 (23, [M + H]$^+$), 206 (7, [M − C_6H_6 − $C_5H_5O_2$]$^+$), 162 (6, [M − C_6H_6 − $C_5H_5O_2$ − CO_2]$^+$), 91 (100, $C_7H_7^+$). $C_{23}H_{27}NO_4$ (381.5): calcd. C 72.42, H 7.13, N 3.67; found C 72.96 H 6.99 N 3.24. HRMS (FAB, NBA): calcd. 382.2018 amu; found 382.2022 amu.

(3*S*,5*S*,1′*S*)- and (3*R*,5*S*,1′*S*)-5-[-1-(Benzyloxycarbonylamino)-2-methylpropyl]-3-prop-2-enyl-4,5-dihydro-2(3*H*)furanone (9a and 9b). − a) CuI (188 mg, 990 μmol) was placed in a flame-dried flask and dried in vacuo. Anhydrous Et_2O (1 mL) was added under Ar and the suspension was cooled to −78 °C. A 1 M solution of vinylmagnesium bromide in THF (1.98 mL, 1.98 mmol) was added, the temperature was allowed to rise to 0 °C and stirring was continued until the solution became homogenous. After the mixture had again been cooled to −78 °C, lactone **2a** (100 mg, 330 μmol) in anhydrous THF (1 mL) and then, after 30 min, TMS−Cl (125 μL, 990 μmol) were added. The solution was stirred for 5 h at −50 °C and hydrolysed at that temperature with 1 N HCl (2 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined extracts were washed with saturated $NaHCO_3$ and brine (10 mL each) and dried ($MgSO_4$). The solvents were removed in a rotary evaporator, yielding a yellowish oil. After filtration through an SiO_2 pad, the diastereomeric ratio was determined by HPLC (hexane/EA, 75:25) to be **9a/9b** = 89:11. Separation by MPLC (PE/EA, 80:20) afforded lactones **9a** (39 mg, 32%) and **9b** (5 mg, 5%). − **b)** When, in an analogous reaction, TMS−Cl was added before addition of the lactone, a diastereomeric ratio of **9a/9b** = 38:62 was observed. Separation by MPLC (PE/EA, 80:20) afforded lactones **9a** (14 mg, 13%) and **9b** (32 mg, 29%). **9a:** Colourless solid, m.p. 92−94 °C. $[\alpha]_D^{20}$ = −0.2 (c = 0.62, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3360 cm^{-1} (N−H), 3040, 2940, 2850 (C−H), 1770 (C=O, lactone), 1700 (C=O, urethane), 1510 (C=C). ^1H NMR: δ = 0.98 [d, ^3J = 6.7, 3 H, CH(CH_3)$_2$], 1.02 [d, ^3J = 6.6, 3 H, CH(CH_3)$_2$], 1.75 (ddd, ^2J = 12.9, ^3J = 12.0, ^3J = 10.3, 1 H, 4-H_B), 1.88 (dsept, ^3J = 7.9, ^3J = 6.8, 1 H, 2′-H), 2.19 (dddt, ^2J = 14.4, ^3J = 8.5, ^3J = 7.1, $^4J_{allyl.}$ = 1.3, 1 H, 1′′-H_A), 2.29 (ddd, ^2J = 12.9, ^3J = 9.1, ^3J = 6.1, 1 H, 4-H_A), 2.55 (dddt, ^2J = 14.4, ^3J = 7.0, ^3J = 4.4, $^4J_{allyl.}$ = 1.3, 1 H, 1′′-H_B), 2.70 (dddd, ^3J = 11.9, ^3J = ^3J = 8.8, ^3J = 4.4, 1 H, 3-H), 3.53 (ddd, ^3J = 10.2, ^3J = 7.9, ^3J = 1.6, 1 H, 1′-H), 4.61 (ddd, ^3J = 10.3, ^3J = 6.1, ^3J = 1.6, 1 H, 5-H), 4.82 (d, ^3J = 10.3, 1 H, NH), 5.02 (ddd, ^3J = 10.5, ^2J = $^4J_{allyl.}$ = 1.6, 1 H, 3′′-H_E), 5.12 (ddd, ^3J = 17.1, ^2J = $^4J_{allyl.}$ = 1.6, 1 H, 3′′-H_Z), 5.10 (d, ^2J = 12.3, 1 H, OC$H_A$$H_B$Ph), 5.14 (d, ^2J = 12.3, 1 H, OC$H_A$$H_B$Ph), 5.70 (dddd, ^3J = 17.1, ^3J = 10.2, ^3J = ^3J = 7.0, 1 H, 2′′-H), 7.30−7.38 (m, 5 H, C_6H_5). ^{13}C NMR: δ = 19.6, 20.1 [CH(CH_3)$_2$], 31.0 (C-4), 31.8 (C-2′), 34.4 (C-1′′), 40.3 (C-3), 58.6 (C-1′), 67.4 (OCH_2Ph), 78.0 (C-5), 118.2 (C-3′′), 128.4, 128.6, 129.0 (C_6H_5), 134.5 (C-2′′), 136.7 (C_6H_5 *ipso*), 157.3 (C=O, urethane), 178.4 (C-2). MS (EI, 70 eV): m/z (%) = 331 (1) [M$^+$], 206 (18, [M − C_2H_4 − $C_5H_5O_2$]$^+$), 162 (19, [M − C_2H_4 − $C_5H_5O_2$ − CO_2]$^+$), 91 (100, $C_7H_7^+$). $C_{19}H_{25}NO_4$ (331.4): calcd. C 68.86, H 7.60, N 4.23; found C 68.77, H 7.64, N 4.09. **9b:** Colourless oil. $[\alpha]_D^{20}$ = −24.6 (c = 0.67, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3310 cm^{-1} (N−H), 3030, 2960, 2875 (C−H), 1765 (C=O, lactone), 1720 (C=O, urethane), 1530 (C=C). ^1H NMR: δ = 0.96 [d, ^3J = 6.8, 3 H, CH(CH_3)$_2$], 1.02 [d, ^3J = 6.8, 3 H, CH(CH_3)$_2$], 1.85 (dsept, ^3J = 8.3, ^3J = 6.8, 1 H, 2′-H), 2.03 (ddd, ^2J = 13.4, ^3J = 7.8, ^3J = 6.2, 1 H, 4-H_A), 2.21 (ddd, ^2J = 13.5, ^3J = 10.0, ^3J = 5.9, 1 H, 4-H_B), 2.26 (dddt, ^2J = 14.6, ^3J = 8.7, ^3J = 7.3, $^4J_{allyl.}$ = 1.2, 1 H, 1′′-H_A), 2.47 (dddt, ^2J = 14.3, ^3J = 6.6, ^3J = 4.8, $^4J_{allyl.}$ = 1.4, 1 H, 1′′-H_B), 2.64 (dddd, ^3J = 10.5, ^3J = 8.8, ^3J = 6.2, ^3J = 4.7, 1 H, 3-H), 3.51 (ddd, ^3J = 10.1, ^3J = 8.2, ^3J = 1.8, 1 H, 1′-H), 4.70 (ddd, ^3J = 8.0, ^3J = 5.9, ^3J = 1.8, 1 H, 5-H), 4.83 (d, ^3J = 10.2, 1 H, NH), 5.08−5.12 (m, 2 H, 3′′-H), 5.10 (d, ^2J = 12.3, 1 H, OC$H_A$$H_B$Ph), 5.12 (d, ^2J = 12.4, 1 H, OC$H_A$$H_B$Ph), 5.70 (dddd, ^3J = 13.8, ^3J = 9.5, ^3J = ^3J = 6.9, 1 H, 2′′-H), 7.29−7.38 (m, 5 H, C_6H_5). ^{13}C NMR: δ = 19.6, 20.2 [CH(CH_3)$_2$], 30.2 (C-4), 31.4 (C-2′), 35.7 (C-1′′), 39.4 (C-3), 60.2 (C-1′), 67.5 (OCH_2Ph), 78.3 (C-5), 118.5 (C-3′′), 128.4, 128.6, 129.0 (C_6H_5), 134.5 (C-2′′), 136.7 (C_6H_5 *ipso*), 157.4 (C=O, urethane), 179.4 (C-2). MS (EI, 70 eV): m/z (%) = 331 (1) [M$^+$], 206 (32, [M − C_2H_4 − $C_5H_5O_2$]$^+$), 162 (37, [M − C_2H_4 − $C_5H_5O_2$ − CO_2]$^+$), 91 (100, $C_7H_7^+$). $C_{19}H_{25}NO_4$ (331.4): calcd. C 68.86, H 7.60, N 4.23; found C 68.74, H 7.60, N 4.16.

(3*S*,5*S*,1′*S*)- and (3*R*,5*S*,1′*S*)-5-[1-(Benzyloxycarbonylamino)-2-methylpropyl]-3-but-3-en-1-yl-4,5-dihydro-2(3*H*)furanone (10a and 10b): $nBu_4NF{\cdot}xH_2O$ (30 mg, 0.12 mmol) was placed in a flask and H_2O was removed over 30 min in vacuo. Anhydrous DMF (2 mL) was added and the solution was transferred under N_2 into a flask containing molecular sieves (4 Å, dried by heating in vacuo, 300 mg) and stirred for 30 min. The supernatant solution was transferred into a further flask containing similarly prepared molecular sieves (100 mg). Lactone **2a** (100 mg, 330 μmol) was added under N_2, and allyltrimethylsilane (157 μL, 989 μmol) and HMPA (173 μL, 989 μmol) in anhydrous DMF (2 mL) were added through a funnel. The reaction mixture was hydrolysed after 10 min (as monitored with TLC) by stirring with 1 N HCl (10 mL) for 10 min. The aqueous phase was extracted with EA (3×10 mL) and the combined extracts were washed with saturated $NaHCO_3$ solution and brine (10 mL each). The solution was dried ($MgSO_4$). The solvents were removed in a rotary evaporator to leave a yellow oil. After filtration through an SiO_2 pad, the diastereomeric ratio was determined by HPLC (hexane/EA, 80:20) to be **10a/10b** = 64:36. Separation by MPLC (PE/EA, 85:15) afforded lactones **10a** (31 mg, 27%) and **10b** (16 mg, 14%). **10a:** Colourless oil. $[\alpha]_D^{20}$ = −15.3 (c = 0.36, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3315 cm^{-1} (N−H), 3010, 3000, 2960, 2875 (C−H), 1770 (C=O, lactone), 1715 (C=O, urethane). ^1H NMR: δ = 0.98 [d, ^3J = 6.8, 3 H, CH(CH_3)$_2$], 1.01 [d, ^3J = 6.8, 3 H, CH(CH_3)$_2$], 1.44 (dddd, ^2J = 13.5, ^3J = 9.4, ^3J = 8.0, ^3J = 5.4, 1 H, 1′′-H_A), 1.65 (ddd, ^2J = 12.3, ^3J = 12.3, ^3J = 10.4, 1 H, 4-H_B), 1.88 (dsept, ^3J = 8.1, ^3J = 6.8, 1 H, 2′-H), 1.97 (dddd, ^2J = 13.4, ^3J = 8.7, ^3J = 7.3, ^3J = 4.5, 1 H, 1′′-H_B), 2.05 (ddddt, ^2J = 14.3, ^3J = 8.5, ^3J = ^3J = 7.6, $^4J_{allyl.}$ = 1.4, 1 H, 2′′-H_A), 2.16 (ddddt, ^2J = 14.5, ^3J = 8.8, ^3J = ^3J = 5.9, $^4J_{allyl.}$ = 1.5, 1 H, 2′′-H_B), 2.31 (ddd, ^2J = 12.7, ^3J = 8.9, ^3J = 5.9, 1 H, 4-H_A), 2.59 (dddd, ^3J = 12.0, ^3J = ^3J = 9.2, ^3J = 4.5, 1 H, 3-H), 3.53 (ddd, ^3J = 10.4, ^3J = 8.0, ^3J = 1.5, 1 H, 1′-H), 4.60 (ddd, ^3J = 10.3, ^3J = 5.9, ^3J = 1.5, 1 H, 5-H), 4.85 (d, ^3J = 10.3, 1 H, NH), 5.00 (ddt, ^3J = 11.7, ^2J = 3.1, J = 1.4, 1 H, 4′′-H_Z), 5.05 (ddt, ^3J = 17.1, ^2J = 3.2, J = 1.5, 1 H, 4′′-H_E), 5.11 (d, ^2J = 12.3, 1 H, OC$H_A$$H_B$Ph), 5.15 (d, ^2J = 12.3, 1 H, OC$H_A$$H_B$Ph), 5.74 (dddd, ^3J = 17.1, ^3J = 11.6, ^3J = 7.1, ^3J = 6.1, 1 H, 3′′-H), 7.30−7.39 (m, 5 H, C_6H_5). ^{13}C NMR: δ = 19.3, 19.7 [CH(CH_3)$_2$], 29.2 (C-1′′), 31.2 (C-2′′), 31.4 (C-2′), 31.5 (C-4), 39.5 (C-3), 58.1 (C-1′), 67.0 (OCH_2Ph), 77.5 (C-5), 115.8 (C-4′′), 128.0, 128.2, 128.6 (C_6H_5), 136.3 (C_6H_5 *ipso*), 137.1 (C-3′′), 156.9 (C=O, urethane), 178.7 (C-2). MS (CI, NH_3): m/z (%) = 708 (4, [2 M + NH_4]$^+$), 691 (8, [2 M + H]$^+$), 363 (78, [M + NH_4]$^+$), 346 (45, [M + H]$^+$), 206 (69, [M − C_3H_6 − $C_5H_5O_2$]$^+$), 162 (63, [M − C_3H_6 − $C_5H_5O_2$ − CO_2]$^+$), 91 (100, $C_7H_7^+$). $C_{20}H_{27}NO_4$ (345.4): calcd. C 69.54, H 7.88, N 4.05; found C 69.33, H 7.91, N 3.99. **10b**: Colourless oil. $[\alpha]_D^{20}$ = −22.6 (c = 0.43, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3320 cm^{-1} (N−H), 3020, 3000, 2960, 2875 (C−H), 1770 (C=O, lactone), 1715 (C=O, urethane). ^1H NMR: δ = 0.97 [d, ^3J = 6.8, 3 H, CH(CH_3)$_2$], 1.02 [d, ^3J = 6.6, 3 H, CH(CH_3)$_2$], 1.53 (dddd, ^2J = 13.6, ^3J = ^3J = 8.9, ^3J = 5.7, 1 H, 1′′-H_A), 1.82−1.91 (2m, 2 H, 1′′-H_B, 2′-H), 1.97 (ddd, ^2J = 13.2, ^3J = 8.1, ^3J = 6.3, 1 H, 4-H_A), 2.08 (ddddt, ^2J = ^3J = 13.6, ^3J = 8.7, ^3J = 6.6, $^4J_{allyl.}$ = 1.5, 1 H, 2′′-H_A), 2.17 (m_c, 1 H, 2′′-H_B), 2.27 (ddd, ^{2}J = 13.3, ^{3}J = 9.9, ^{3}J = 5.7, 1 H, 4-H$_B$), 2.55 (dddd, ^{3}J = ^{3}J = 9.5, ^{3}J = 6.3, ^{3}J = 5.5, 1 H, 3-H), 3.51 (ddd, ^{3}J = 9.9, ^{3}J = 8.3, ^{3}J = 1.7, 1 H, 1′-H), 4.73 (ddd, ^{3}J = 7.8, ^{3}J = 5.9, ^{3}J = 1.7, 1 H, 5-H), 4.77 (d, ^{3}J = 10.2, 1 H, NH), 5.00 (ddt, ^{3}J = 10.2, ^{2}J = 3.1, ^{4}J = 1.3, 1 H, 4′′-H$_Z$), 5.06 (ddt, ^{3}J = 17.1, ^{2}J = 3.3, ^{4}J = 1.6, 1 H, 4′′-H$_E$), 5.11 (s, 2 H, OC*H*$_2$Ph), 5.75 (dddd, ^{3}J = 17.0, ^{3}J = 13.3, ^{3}J = 10.2, ^{3}J = 6.6, 1 H, 3′′-H), 7.31−7.39 (m, 5 H, C_6H_5). ^{13}C NMR: δ = 19.3, 19.8 [CH(*C*H$_3$)$_2$], 30.5 (C-1′′), 30.8 (C-4), 31.0 (C-2′), 31.2 (C-2′′), 38.7 (C-3), 59.7 (C-1′), 67.1 (O*C*H$_2$Ph), 77.7 (C-5), 115.9 (C-4′′), 128.0, 128.3, 128.6 (C_6H_5), 136.3 (C_6H_5 *ipso*), 136.9 (C-3′′), 157.0 (C=O, urethane), 179.5 (C-2). MS (CI, NH$_3$): *m*/*z* (%) = 363 (10, [M + NH$_4$]$^+$), 346 (10, [M + H]$^+$), 206 (70, [M − C_3H_6 − $C_5H_5O_2$]$^+$), 162 (43, [M − C_3H_6 − $C_5H_5O_2$ − CO$_2$]$^+$), 91 (100, $C_7H_7^+$). $C_{20}H_{27}NO_4$ (345.4): calcd. C 69.54, H 7.88, N 4.05; found C 69.48, H 7.90, N 3.88.

Dimethyl (3′′*S*,5′′*S*,1′′′*S*)- and (3′′*R*,5′′*S*,1′′′S)-({5-[1-(Benzyloxycarbonylamino)-2-methylpropyl]-4,5-dihydro-2-oxo-(3*H*)fur-3-yl}-methyl)malonate (11a and 11b): Dimethyl malonate (76 µL, 0.67 mmol) in anhydrous DMF (3 mL) was placed in a flask under N$_2$, cooled to −15 °C, and NaH (10 mg, 666 µmol) was added. After 5 min, lactone **2a** (101 mg, 333 µmol) in anhydrous DMF (4 mL) was added by syringe. The mixture was warmed to room temp., stirred for 2 h at this temp. and hydrolysed with 1 N hydrochloric acid (2 mL). The aqueous phase was extracted with Et$_2$O (3×15 mL) and the combined extracts were washed with saturated NaHCO$_3$ solution (10 mL) and brine (2×10 mL). The solution was dried (MgSO$_4$). The solvents were removed in a rotary evaporator to leave a colourless oil. After filtration through an SiO$_2$ pad, the diastereomeric ratio was determined by HPLC (hexane/EA, 75:25) to be **11a/11b** = 62:38. Separation by MPLC (PE/EA, 80:20) afforded lactones **11a** (65 mg, 45%) and **11b** (38 mg, 25%). **11a:** Colourless oil. $[\alpha]_D^{20}$ = −23.8 (*c* = 1.16, CHCl$_3$). IR (film): $\tilde{\nu}$ = 3327 cm^{-1} (N−H), 3014, 2957 (C−H), 1731 (br, C=O), 1539 (C=C). ^{1}H NMR: δ = 0.99 [d, ^{3}J = 6.8, 3 H, CH(C*H*$_3$)$_2$], 1.01 [d, ^{3}J = 6.8, 3 H, CH(C*H*$_3$)$_2$], 1.70 (ddd, ^{2}J = 12.5, ^{3}J = 12.5, ^{3}J = 10.4, 1 H, 4′′-H$_B$), 1.85 (dsept, ^{3}J = 7.9, ^{3}J = 6.8, 1 H, 2′′′-H), 2.03 (ddd, ^{2}J = 14.2, ^{3}J = 8.0, ^{3}J = 8.0, 1 H, 1′-H$_A$), 2.33 (ddd, ^{2}J = 12.6, ^{3}J = 8.9, ^{3}J = 5.7, 1 H, 4′′-H$_A$), 2.35 (ddd, ^{2}J = 14.1, ^{3}J = 10.2, ^{3}J = 7.0, 1 H, 1′-H$_B$), 2.69 (dddd, ^{3}J = 12.2, ^{3}J = 8.7, ^{3}J = 7.9, ^{3}J = 6.9, 1 H, 3′′-H), 3.52 (ddd, ^{3}J = 9.9, ^{3}J = 8.0, ^{3}J = 1.6, 1 H, 1′′′-H), 3.74 (m$_c$, 1 H, 2-H), 3.74 (s, 3 H, -OCH$_3$), 3.75 (s, 3 H, OCH$_3$), 4.59 (ddd, ^{3}J = 10.4, ^{3}J = 5.7, ^{3}J = 1.6, 1 H, 5′′-H), 4.84 (d, ^{3}J = 10.3, 1 H, NH), 5.12 (d, ^{2}J = 12.3, 1 H, OC*H*$_A$H$_B$Ph), 5.13 (d, ^{2}J = 12.3, 1 H, OCH$_A$*H*$_B$Ph), 7.30−7.38 (m, 5 H, C_6H_5). ^{13}C NMR: δ = 19.3, 19.7 [CH(*C*H$_3$)$_2$], 29.2 (C-1′), 31.4 (C-2′′′), 31.8 (C-4′′), 37.9 (C-3′′), 49.1 (C-2), 52.7 (2 OCH$_3$), 57.9 (C-1′′′), 67.1 (O*C*H$_2$Ph), 77.5 (C-5′′), 128.0, 128.2, 128.6 (C_6H_5), 136.S3 (C_6H_5 *ipso*), 156.9 (C=O, urethane), 169.1, 169.3 (C-1, C-3), 177.5 (C-2′′). MS (FAB): *m*/*z* (%) = 458 (8, [M + Na]$^+$), 436 (81, [M + H]$^+$), 392 (14, [M − CO$_2$ + H]$^+$), 91 (100, $C_7H_7^+$). $C_{22}H_{29}NO_8$ (435.5): calcd, C 60.68, H 6.71, N 3.22; found C 60.63, H 6.76, N 3.14. **11b**: Colourless oil. $[\alpha]_D^{20}$ = −14.1 (*c* = 0.57, CHCl$_3$). IR (film): $\tilde{\nu}$ = 3324 cm^{-1} (N−H), 3010, 2958 (C−H), 1715 (br, C=O), 1539 (C=C). ^{1}H NMR: δ = 0.96 [d, ^{3}J = 6.7, 3 H, CH(C*H*$_3$)$_2$], 1.02 [d, ^{3}J = 6.7, 3 H, CH(C*H*$_3$)$_2$], 1.85 (dsept, ^{3}J = 8.2, ^{3}J = 6.8, 1 H, 2′′′-H), 1.98 (ddd, ^{2}J = 13.3, ^{3}J = 8.1, ^{3}J = 6.5, 1 H, 4′′-H$_A$), 2.11 (ddd, ^{2}J = 16.2, ^{3}J = 8.5, ^{3}J = 7.6, 1 H, 1′-H$_A$), 2.29 (ddd, ^{2}J = 16.0, ^{3}J = 8.2, ^{3}J = 6.4, 1 H, 1′-H$_B$), 2.34 (ddd, ^{2}J = 13.3, ^{3}J = 9.9, ^{3}J = 5.9, 1 H, 4′′-H$_B$), 2.65 (dddd, ^{3}J = 9.8, ^{3}J = ^{3}J = 7.9, ^{3}J = 6.4, 1 H, 3′′-H), 3.52 (ddd, ^{3}J = 10.1, ^{3}J = 8.2, ^{3}J = 1.8, 1 H, 1′′′-H), 3.69 (dd, ^{3}J = 8.6, ^{3}J = 6.4, 1 H, 2-H), 3.73 (s, 3 H, OCH$_3$), 3.74 (s, 3 H, OCH$_3$), 4.71 (d, ^{3}J = 10.2, 1 H, NH), 4.75 (ddd, ^{3}J = 7.9, ^{3}J = 5.8, ^{3}J = 1.8, 1 H, 5′′-H), 5.10 (d, ^{2}J = 12.2, 1 H, OC*H*$_A$H$_B$Ph), 5.13 (d, ^{2}J = 12.2, 1 H, OCH$_A$*H*$_B$Ph), 7.30−7.39 (m, 5 H, C_6H_5). ^{13}C NMR: δ = 19.2, 19.8 [CH(*C*H$_3$)$_2$], 30.3 (C-1′), 31.0 (C-2′′′), 31.2 (C-4′′), 37.2 (C-3′′), 49.1 (C-2), 52.8 (2 OCH$_3$), 59.6 (C-1′′′), 67.2 (O*C*H$_2$Ph), 77.8 (C-5′′), 128.0, 128.3, 128.6 (C_6H_5), 136.2 (C_6H_5 *ipso*), 157.0 (C=O, urethane), 169.0, 169.2 (C-1, C-3), 178.2 (C-2′′). MS (FAB): *m*/*z* (%) = 458 (8, [M + Na]$^+$), 436 (76, [M + H]$^+$), 392 (8, [M − CO$_2$ + H]$^+$), 91 (100, $C_7H_7^+$). $C_{22}H_{29}NO_8$ (435.5): calcd. C 60.68, H 6.71, N 3.22; found C 60.51, H 6.69, N 3.16.

(3′*S*,5′*S*,1′′*S*)- and (3′*R*,5′*S*,1′′*S*)-2-{5-[1-(Benzyloxycarbonylamino)-2-methylpropyl]-2-(4,5-dihydro-2-oxo-(3*H*)fur-3-yl)}ethanenitrile (15a and 15b). − a) Acetone cyanohydrin (**14**; 97 µL, 1.1 mmol) was added, at 50 °C under N$_2$, to lactone **2a** (80 mg, 0.26 mmol) in anhydrous DMSO (2 mL), followed by KCN (4 mg, 0.07 mmol). The mixture was allowed to cool to 30 °C, stirred for 4 h, allowed to cool to room temp. and quenched with saturated NH$_4$Cl solution (10 mL). The solution was extracted with EA (3×10 mL) and the combined extracts were washed with saturated NaHCO$_3$ solution and brine (15 mL each) and dried (MgSO$_4$). The solvents were removed in a rotary evaporator to leave a yellowish oil. After filtration through an SiO$_2$ pad, the diastereomeric ratio was determined by HPLC (hexane/EA, 60:40) to be **15a/15b** = 73:27. Separation by MPLC (PE/EA, 60:40) afforded lactones **15a** (61 mg, 70%) and **15b** (22 mg, 25%). − **b)** Lactone **2a** (100 mg, 330 µmol) was added at room temp. to a mixture of TMS−CN (91 µL, 0.73 mmol) and a 15% AlEt$_3$ solution in *n*-hexane (802 µL, 725 µmol) in anhydrous THF (3 mL). The solution was heated for 24 h at 60 °C, and hydrolysed after cooling to room temp. by stirring with 1 N HCl (5 mL) for 45 min. The aqueous phase was extracted with EA (3×10 mL) and the combined extracts were washed with 1 N HCl, saturated NaHCO$_3$ solution and brine (15 mL each) and dried (MgSO$_4$). The solvents were removed in a rotary evaporator to leave a yellow oil. The residue was purified by MPLC (PE/EA, 75:25) to afford nitrile **15b** (47 mg, 43%) and the *N*-silylated lactone **17b** (6 mg, 5%). **15a:** Colourless solid, m.p. 89−91 °C. $[\alpha]_D^{20}$ = −7.7 (*c* = 0.59, CHCl$_3$). IR (KBr): $\tilde{\nu}$ = 3320 cm^{-1} (N−H), 3010, 2950, 2860 (C−H), 2220 (C≡N), 1770 (C=O, lactone), 1690 (C=O, urethane), 1520 (C=C). ^{1}H NMR: δ = 0.99 [d, ^{3}J = 6.8, 3 H, CH(C*H*$_3$)$_2$], 1.02 [d, ^{3}J = 6.7, 3 H, CH(C*H*$_3$)$_2$], 1.89 (dsept, ^{3}J = 7.9, ^{3}J = 6.8, 1 H, 2′′-H), 1.95 (ddd, ^{2}J = 12.6, ^{3}J = 12.6, ^{3}J = 10.3, 1 H, 4′-H$_B$), 2.48 (dd, ^{2}J = 17.2, ^{3}J = 8.2, 1 H, 2-H$_A$), 2.51 (ddd, ^{2}J = 12.9, ^{3}J = 9.0, ^{3}J = 5.8, 1 H, 4′-H$_A$), 2.75 (dd, ^{2}J = 17.1, ^{3}J = 4.8, 1 H, 2-H$_B$), 2.92 (dddd, ^{3}J = 12.3, ^{3}J = 8.9, ^{3}J = 8.2, ^{3}J = 4.8, 1 H, 3′-H), 3.58 (ddd, ^{3}J = 9.9, ^{3}J = 8.0, ^{3}J = 1.6, 1 H, 1′′-H), 4.68 (ddd, ^{3}J = 10.3, ^{3}J = 5.8, ^{3}J = 1.6, 1 H, 5′-H), 4.95 (d, ^{3}J = 10.3, 1 H, NH), 5.11 (d, ^{2}J = 12.1, 1 H, OC*H*$_A$H$_B$Ph), 5.12 (d, ^{2}J = 12.1, 1 H, OCH$_A$*H*$_B$Ph), 7.30−7.38 (m, 5 H, C_6H_5). ^{13}C NMR: δ = 18.3 (C-2), 19.2, 19.7 [CH(*C*H$_3$)$_2$], 30.7 (C-4′), 31.2 (C-2′′), 37.4 (C-3′), 58.0 (C-1′′), 67.2 (O*C*H$_2$Ph), 78.0 (C-5′), 116.8 (CN), 128.2, 128.3, 128.6 (C_6H_5), 136.2 (C_6H_5 *ipso*), 157.0 (C=O, urethane), 175.0 (C-2′). MS (FAB): *m*/*z* (%) = 661 (10, [2 M + H]$^+$), 353 (8, [M + Na]$^+$), 331 (82, [M + H]$^+$), 91 (100, $C_7H_7^+$). $C_{18}H_{22}N_2O_4$ (330.4): calcd. C 65.44, H 6.71, N 8.48; found C 65.25, H 6.67, N 8.41. **15b:** Colourless oil. $[\alpha]_D^{20}$ = −15.1 (*c* = 0.49, CHCl$_3$). IR (film): $\tilde{\nu}$ = 3320 cm^{-1} (N−H), 3030, 2960, 2875 (C−H), 2250 (C≡N), 1770 (C=O, lactone), 1690 (C=O, urethane), 1540 (C=C). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.97 [d, ^{3}J = 6.7, 3 H, CH(C*H*$_3$)$_2$], 1.03 [d, ^{3}J = 6.7, 3 H, CH(C*H*$_3$)$_2$], 1.85 (dsept, ^{3}J = 8.4, ^{3}J = 6.7, 1 H, 2′′-H), 2.25 (ddd, ^{2}J = 13.5, ^{3}J = ^{3}J = 8.9, 1 H, 4′-H$_A$), 2.50 (ddd, ^{2}J = 13.7, ^{3}J = 10.1, ^{3}J = 3.6, 1 H, 4′-H$_B$), 2.62 (m$_c$, 2 H, 2-H), 2.79 (dddd, ^{3}J = 10.2, ^{3}J = 9.0, ^{3}J = 6.9, ^{3}J = 5.4, 1 H, 3′-H), 3.56 (ddd, ^{3}J = 10.1, ^{3}J = 8.4, ^{3}J = 1.9, 1 H, 1′′-H), 4.82−4.85 (2m, 2 H, 5′-H, NH), 5.09 (d, ^{2}J = 12.2, 1

H, OCH_AH$_B$Ph), 5.15 (d, ^2J = 12.2, 1 H, OCH$_A$$H_B$Ph), 7.32−7.40 (m, 5 H, C$_6$H$_5$). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 19.2, 19.8 [CH(*C*H$_3$)$_2$], 19.3 (C-2), 29.8 (C-4′), 30.7 (C-2′′), 36.0 (C-3′), 60.2 (C-1′′), 67.3 (O*C*H$_2$Ph), 78.1 (C-5′), 116.7 (CN), 128.2, 128.4, 128.6 (C$_6$H$_5$), 136.2 (C$_6$H$_5$ *ipso*), 157.0 (C=O, urethane), 176.0 (C-2′). MS (FAB): *m*/*z* (%) = 353 (4, [M + Na]$^+$), 331 (62, [M + H]$^+$), 91 (100, C$_7$H$_7$$^+$). C$_{18}H_{22}N_2O_4$ (330.4): calcd. C 65.44, H 6.71, N 8.48; found C 65.34, H 6.82, N 8.36. **17b:** Slightly yellowish oil. ^{1}H NMR: δ = 0.11 [s, 9 H, NSi(CH$_3$)$_3$], 0.82 [d, ^3J = 7.0, 3 H, CH(CH_3)$_2$], 1.06 [d, ^3J = 6.7, 3 H, CH(CH_3)$_2$], 2.00−2.15 (2m, 3 H, 2′′-H, 4′-H), 2.68 (m$_c$, 1 H, 2-H$_A$), 2.73−2.83 (2m, 2 H, 2-H$_B$, 3′-H), 4.02 (dd, ^3J = 7.9, ^3J = 1.2, 1 H, 1′′-H), 4.16 (m$_c$, 1 H, 5′-H), 5.17 (d, ^2J = 12.3, 1 H, OCH_AH$_B$Ph), 5.24 (d, ^2J = 12.3, 1 H, OCH$_A$$H_B$Ph), 7.24−7.38 (m, 5 H, C$_6$H$_5$). ^{13}C NMR: δ = 0.1 [NSi(CH$_3$)$_3$], 19.6 (C-2), 19.9, 22.9 [CH(*C*H$_3$)$_2$], 29.2 (C-2′′), 32.8 (C-4′), 39.9 (C-3′), 64.4 (C-1′′), 68.3 (C-5′), 68.9 (O*C*H$_2$Ph), 117.6 (CN), 128.2, 128.5, 128.7 (C$_6$H$_5$), 135.3 (C$_6$H$_5$ *ipso*), 154.2 (C=O, urethane), 171.4 (C-2′). MS (EI, 70 eV): *m*/*z* (%) = 402 (10) [M$^+$], 91 (100, C$_7$H$_7$$^+$), 73 (21, C$_3H_9Si^+$).

(3′*S*,5′*S*,1′′*S*)- and (3′*R*,5′*S*,1′′*S*)-2-{5-[1-(Benzyloxycarbonylamino)-2-phenylethyl]-4,5-dihydro-2-oxo-(3*H*)fur-3-yl}ethanenitrile (16a and 16b). − a) Acetone cyanohydrin (**14**; 0.10 mL, 1.1 mmol) was added at 50 °C under N$_2$ to lactone **5** (100 mg, 285 μmol) in anhydrous DMSO (3.5 mL), followed by KCN (5 mg, 0.07 mmol). The mixture was allowed to cool to 30 °C, stirred for 4 h, allowed to cool to room temp. and quenched with saturated NH$_4$Cl solution (10 mL). The solution was extracted with EA (3×10 mL) and the combined extracts were washed with saturated NaHCO$_3$ solution and brine (15 mL each) and dried (MgSO$_4$). The solvents were removed in a rotary evaporator to leave a yellowish oil. After filtration through an SiO$_2$ pad, the diastereomeric ratio was determined by HPLC (hexane/EA, 60:40) to be **16a**/**16b** = 69:31. Separation by MPLC (PE/EA, 65:35) afforded lactones **16a** (77 mg, 70%) and **16b** (31 mg, 29%). − **b)** Lactone **5** (100 mg, 285 μmol) was added at room temp. to a mixture of TMS−CN (0.11 mL, 0.86 mmol) and a 15% AlEt$_3$ solution in *n*-hexane (935 μL, 857 μmol) in anhydrous THF (2 mL). The solution was heated for 5 h to 60 °C and, after cooling to room temp., hydrolysed by stirring with 1 N HCl (2 mL) for 45 min. The aqueous phase was extracted with EA (3×10 mL) and the combined extracts were washed with 1 N HCl, saturated NaHCO$_3$ solution and brine (15 mL each) and dried (MgSO$_4$). The solvents were removed in a rotary evaporator to leave a yellow oil. After filtration through an SiO$_2$ pad, the diastereomeric ratio was determined by HPLC (hexane/EA, 60:40) to be **16a**/**16b** = 14:86. Separation by MPLC (PE/EA, 75:25) afforded nitrile **16b** (49 mg, 45%), but isomer **16a** could not be obtained in pure form. **16a**: Colourless solid, m.p. 132−134 °C. $[\alpha]_D^{20}$ = +6.4 (*c* = 0.66, CHCl$_3$). IR (KBr): $\tilde{\nu}$ = 3300 cm^{-1} (N−H), 3040, 3010, 2900 (C−H), 2220 (C≡N), 1750 (C=O, lactone), 1690 (C=O, urethane), 1530 (C=C). ^{1}H NMR: δ = 1.99 (ddd, ^2J = 12.6, ^3J = 12.6, ^3J = 10.3, 1 H, 4′-H$_B$), 2.43 (ddd, ^2J = 13.0, ^3J = 9.0, ^3J = 5.8, 1 H, 4′-H$_A$), 2.51 (dd, ^2J = 17.1, ^3J = 8.1, 1 H, 2-H$_A$), 2.75 (dd, ^2J = 17.3, ^3J = 5.0, 1 H, 2-H$_B$), 2.88 (dddd, ^3J = 12.2, ^3J = 8.9, ^3J = 8.1, ^3J = 4.8, 1 H, 3′-H), 2.91 (dd, ^2J = 13.8, ^3J = 8.9, 1 H, 2′′-H$_A$), 3.02 (dd, ^2J = 13.6, ^3J = 7.1, 1 H, 2′′-H$_B$), 4.12 (m$_c$, 1 H, 1′′-H), 4.44 (ddd, ^3J = 10.3, ^3J = 5.8, ^3J = 1.5, 1 H, 5′-H), 4.99 (d, ^3J = 9.8, 1 H, NH), 5.07 (d, ^2J = 12.2, 1 H, OCH_AH$_B$Ph), 5.08 (d, ^2J = 12.2, 1 H, OCH$_A$$H_B$Ph), 7.17−7.38 (m, 10 H, 2 C$_6$H$_5$). ^{13}C NMR: δ = 18.3 (C-2), 30.1 (C-4′), 37.6 (C-3′), 39.1 (C-2′′), 53.7 (C-1′′), 67.2 (O*C*H$_2$Ph), 77.9 (C-5′), 116.6 (CN), 127.0, 128.2, 128.3, 128.6, 128.8, 129.3 (2 C$_6$H$_5$), 136.1, 136.6 (2 C$_6$H$_5$ *ipso*), 156.5 (C=O, urethane), 174.8 (C-2′). MS (EI, 70 eV): *m*/*z* (%) = 378 (3) [M$^+$], 287 (6, [M − C$_7$H$_7$]$^+$), 243 (13, [M − C$_7$H$_7$ − CO$_2$]$^+$), 91 (100, C$_7$H$_7$$^+$). C$_{22}H_{22}N_2O_4$ (378.4): calcd. C 69.83, H 5.86, N 7.40; found C 69.65, H 5.95, N 7.27. **16b**: Colourless, glass-like solid, softening range 60−65 °C. $[\alpha]_D^{20}$ = +3.9 (*c* = 1.04, CHCl$_3$). IR (film): $\tilde{\nu}$ = 3320 cm^{-1} (N−H), 3020, 2940, 2880 (C−H), 2220 (C≡N), 1770 (C=O, lactone), 1690 (C=O, urethane), 1530 (C=C). ^{1}H NMR: δ = 2.18 (ddd, ^2J = 13.6, ^3J = ^3J = 9.2, 1 H, 4′-H$_A$), 2.53 (ddd, ^2J = 13.6, ^3J = 10.2, ^3J = 3.4, 1 H, 4′-H$_B$), 2.57 (dd, ^2J = 17.1, ^3J = 7.1, 1 H, 2-H$_A$), 2.62 (dd, ^2J = 17.1, ^3J = 5.4, 1 H, 2-H$_B$), 2.82 (dddd, ^3J = 10.0, ^3J = 9.2, ^3J = 7.1, ^3J = 5.3, 1 H, 3′-H), 2.92 (m$_c$, 2 H, 2′′-H), 4.15 (dddd, ^3J = ^3J = 9.7, ^3J = 8.1, ^3J = 1.7, 1 H, 1′′-H), 4.59 (ddd, ^3J = 9.1, ^3J = 3.3, ^3J = 1.8, 1 H, 5′-H), 5.02−5.07 (m, 3 H, OCH_2Ph, NH), 7.14−7.40 (m, 10 H, 2 C$_6$H$_5$). ^{13}C NMR: δ = 19.3 (C-2), 29.4 (C-4′), 36.1 (C-3′), 38.7 (C-2′′), 55.8 (C-1′′), 67.2 (O*C*H$_2$Ph), 78.5 (C-5′), 116.6 (CN), 127.1, 128.1, 128.4, 128.6, 128.8, 129.2 (2 C$_6$H$_5$), 136.1, 136.5 (2 C$_6$H$_5$ *ipso*), 156.6 (C=O, urethane), 176.0 (C-2′). MS (FAB): *m*/*z* (%) = 757 (5, [2 M + H]$^+$), 401 (9, [M + Na]$^+$), 379 (70, [M + H]$^+$), 91 (100, C$_7$H$_7$$^+$). C$_{22}H_{22}N_2O_4$ (378.4): calcd. C 69.83, H 5.86, N 7.40; found C 69.44, H 5.87, N 7.20.

(3*S*,5*S*,1′*S*)- and (3*R*,5*S*,1′*S*)-5-[1-(Benzyloxycarbonylamino)-2-methylpropyl]-3-(benzylthiomethyl)-4,5-dihydro-2(3*H*)furanone (18a and 18b): Lactone **2a** (100 mg, 330 μmol), BnSH (50 μL, 0.43 mmol) and NEt$_3$ (60 μL, 0.43 mmol) in anhydrous DMF (3 mL) were heated under N$_2$ to 60 °C for 4 h. HCl (1 N, 2 mL) was added, the aqueous phase was extracted with EA (3×10 mL), and the combined extracts were washed with saturated NaHCO$_3$ solution (2×10 mL) and brine (10 mL). The solution was dried (MgSO$_4$) and the solvents were removed in a rotary evaporator to leave a slightly yellow oil. After filtration through an SiO$_2$ pad, the diastereomeric ratio was determined by HPLC (hexane/EA, 75:25) to be **18a**/**18b** = 82:18. Separation by MPLC (PE/EA, 85:15) afforded lactones **18a** (98 mg, 70%) and **18b** (28 mg, 20%). **18a:** Colourless oil. $[\alpha]_D^{20}$ = −13.7 (*c* = 0.61, CHCl$_3$). IR (film): $\tilde{\nu}$ = 3320 cm^{-1} (N−H), 3030, 2960, 2875 (C−H), 1770 (C=O, lactone), 1715 (C=O, urethane). ^{1}H NMR: δ = 0.97 [d, ^3J = 6.8, 3 H, CH(CH_3)$_2$], 1.01 [d, ^3J = 6.8, 3 H, CH(CH_3)$_2$], 1.86 (dsept, ^3J = 7.8, ^3J = 6.7, 1 H, 2′-H), 1.91 (ddd, ^2J = 12.8, ^3J = 12.8, ^3J = 10.8, 1 H, 4-H$_B$), 2.32 (ddd, ^2J = 12.9, ^3J = 8.8, ^3J = 5.9, 1 H, 4-H$_A$), 2.54 (dd, ^2J = 13.3, ^3J = 8.3, 1 H, 1′′-H$_A$), 2.78 (dddd, ^3J = 13.0, ^3J = 8.4, ^3J = 8.2, ^3J = 4.2, 1 H, 3-H), 2.87 (dd, ^2J = 13.3, ^3J = 4.1, 1 H, 1′′-H$_B$), 3.55 (ddd, ^3J = 10.4, ^3J = 7.8, ^3J = 1.7, 1 H, 1′-H), 3.68 (d, ^2J = 13.5, 1 H, SCH_AH$_B$Ph), 3.70 (d, ^2J = 13.5, 1 H, SCH$_A$$H_B$Ph), 4.57 (ddd, ^3J = 10.4, ^3J = 5.9, ^3J = 1.7, 1 H, 5-H), 4.84 (d, ^3J = 10.3, 1 H, NH), 5.11 (s, 2 H, OCH_2Ph), 7.22−7.38 (m, 10 H, 2 C$_6$H$_5$). ^{13}C NMR: δ = 19.2, 19.7 [CH(*C*H$_3$)$_2$], 30.3 (C-1′′), 31.3 (C-4), 31.4 (C-2′), 37.2 (S*C*H$_2$Ph), 41.0 (C-3), 58.0 (C-1′), 67.0 (O*C*H$_2$Ph), 77.7 (C-5), 127.2, 128.0, 128.2, 128.6, 128.6, 128.9 (2 C$_6$H$_5$), 136.3, 138.0 (2 C$_6$H$_5$ *ipso*), 156.9 (C=O, urethane), 176.9 (C-2). MS (EI, 70 eV): *m*/*z* (%) = 427 (1) [M$^+$], 336 (65, [M − C$_7$H$_7$]$^+$), 206 (6, [M − C$_7$H$_7$SH − C$_5$H$_5$O$_2$]$^+$), 162 (11, [M − C$_7$H$_7$SH − C$_5$H$_5$O$_2$ − CO$_2$]$^+$), 91 (100, C$_7$H$_7$$^+$). C$_{24}H_{29}NO_4$S (427.6): calcd. C 67.42, H 6.84, N 3.28, S 7.50; found C 67.26, H 6.85, N 3.29, S 7.62. **18b:** Colourless oil. $[\alpha]_D^{20}$ = −12.7 (*c* = 0.35, CHCl$_3$). IR (film): $\tilde{\nu}$ = 3320 cm^{-1} (N−H), 3030, 2960, 2875 (C−H), 1770 (C=O, lactone), 1715 (C=O, urethane). ^{1}H NMR: δ = 0.95 [d, ^3J = 6.7, 3 H, CH(CH_3)$_2$], 1.01 [d, ^3J = 6.6, 3 H, CH(CH_3)$_2$], 1.84 (dsept, ^3J = 8.2, ^3J = 6.7, 1 H, 2′-H), 2.15 (ddd, ^2J = 12.7, ^3J = 8.2, ^3J = 6.2, 1 H, 4-H$_A$), 2.24 (ddd, ^2J = 13.3, ^3J = 9.6, ^3J = 5.9, 1 H, 4-H$_B$), 2.59 (dd, ^2J = 14.4, ^3J = 9.4, 1 H, 1′′-H$_A$), 2.75−2.81 (2m, 2 H, 1′′-H$_B$, 3-H), 3.50 (ddd, ^3J = 10.1, ^3J = 8.2, ^3J = 1.8, 1 H, 1′-H), 3.70 (d, ^2J = 13.5, 1 H, SCH_AH$_B$Ph), 3.72 (d, ^2J = 13.5, 1 H, SCH$_A$$H_B$Ph), 4.72 (ddd, ^3J = 8.0, ^3J = 5.9, ^3J = 1.8, 1 H, 5-H), 4.76 (d, ^3J = 10.2, 1 H, NH), 5.11 (s, 2

H, OC*H*$_2$Ph), 7.22−7.38 (m, 10 H, 2 C$_6$H$_5$). ^{13}C NMR: δ = 19.2, 19.8 [CH(*C*H$_3$)$_2$], 29.9 (C-4), 31.0 (C-2′), 32.3 (C-1′′), 36.8 (S*C*H$_2$Ph), 39.8 (C-3), 59.7 (C-1′), 67.1 (O*C*H$_2$Ph), 78.2 (C-5), 127.3, 128.0, 128.3, 128.6, 128.6, 128.9 (2 C$_6$H$_5$), 136.2, 137.7 (2 C$_6$H$_5$ *ipso*), 157.0 (C=O, urethane), 178.0 (C-2). MS (EI, 70 eV): *m*/*z* (%) = 427 (1) [M$^+$], 336 (45, [M − C$_7$H$_7$]$^+$), 206 (4, [M − C$_7$H$_7$SH − C$_5$H$_5$O$_2$]$^+$), 162 (12, [M − C$_7$H$_7$SH − C$_5$H$_5$O$_2$ − CO$_2$]$^+$), 91 (100, C$_7$H$_7^+$). C$_{24}$H$_{29}$NO$_4$S (427.6): calcd. C 67.42, H 6.84, N 3.28, S 7.50; found, C 67.49, H 6.90, N 3.27, S 7.45.

(3*S*,5*S*,1′*S*)- and (3*R*,5*S*,1′*S*)-5-[1-(Benzyloxycarbonylamino)-2-methylpropyl]-3-(phenylthiomethyl)-4,5-dihydro-2(3*H*)furanone (19a and 19b): Lactone **2a** (100 mg, 330 µmol), PhSH (44 µL, 0.43 mmol) and NEt$_3$ (60 µL, 0.43 mmol) in anhydrous DMF (3 mL) were heated under N$_2$ to 60 °C for 3 h. HCl (1 N, 2 mL) was added, the aqueous phase was extracted with Et$_2$O (3×10 mL), and the combined extracts were washed with saturated NaHCO$_3$ solution (2×10 mL) and brine (10 mL). The solution was dried (MgSO$_4$). The solvents were removed in a rotary evaporator to leave a slightly yellow oil. After filtration through an SiO$_2$ pad, the diastereomeric ratio was determined by HPLC (hexane/EA, 80:20) to be **19a**/**19b** = 74:26. Separation by MPLC (PE/EA, 85:15) afforded lactones **19a** (90 mg, 66%) and **19b** (29 mg, 21%). **19a:** Colourless oil. [α]$_D^{20}$ = +45.3 (*c* = 1.08, CHCl$_3$). IR (film): ν̃ = 3320 cm^{-1} (N−H), 3040, 2960, 2885 (C−H), 1770 (C=O, lactone), 1715 (C=O, urethane). ^{1}H NMR: δ = 0.97 [d, ^3J = 6.7, 3 H, CH(C*H*$_3$)$_2$], 1.00 [d, ^3J = 6.7, 3 H, CH(C*H*$_3$)$_2$], 1.82−1.90 (2 m, 2 H, 4-H$_B$, 2′-H), 2.41 (ddd, ^2J = 12.8, ^3J = 8.5, ^3J = 5.9, 1 H, 4-H$_A$), 2.77 (dd, ^2J = 13.4, ^3J = 9.5, 1 H, 1′′-H$_A$), 2.83 (dddd, ^3J = 12.0, ^3J = ^3J = 9.2, ^3J = 3.3, 1 H, 3-H), 3.50 (dd, ^2J = 13.0, ^3J = 3.3, 1 H, 1′′-H$_B$), 3.54 (ddd, ^3J = 9.7, ^3J = 7.9, ^3J = 1.6, 1 H, 1′-H), 4.58 (ddd, ^3J = 10.3, ^3J = 5.9, ^3J = 1.6, 1 H, 5-H), 4.83 (d, ^3J = 10.3, 1 H, NH), 5.10 (d, ^2J = 12.2, 1 H, OC*H*$_A$H$_B$Ph), 5.13 (d, ^2J = 12.2, 1 H, OCH$_A$*H*$_B$Ph), 7.20−7.39 (m, 10 H, 2 C$_6$H$_5$). ^{13}C NMR: δ = 19.2, 19.7 [CH(*C*H$_3$)$_2$], 31.3 (C-4), 31.4 (C-2′), 34.5 (C-1′′), 40.4 (C-3), 58.0 (C-1′), 67.1 (O*C*H$_2$Ph), 77.8 (C-5), 126.8, 128.0, 128.3, 128.6, 129.2, 130.1 (2 C$_6$H$_5$), 134.7, 136.3 (2 C$_6$H$_5$ *ipso*), 156.9 (C=O, urethane), 176.8 (C-2). MS (EI, 70eV): *m*/*z* (%) = 412 (34, [M − H]$^+$), 206 (12, [M − C$_6$H$_5$SH − C$_5$H$_5$O$_2$]$^+$), 162 (24, [M − C$_6$H$_5$SH − C$_5$H$_5$O$_2$ − CO$_2$]$^+$), 110 (9, C$_6$H$_5$SH$^+$), 91 (100, C$_7$H$_7^+$). C$_{23}$H$_{27}$NO$_4$S (413.5): calcd. C 66.80, H 6.58, N 3.39; found C 66.62, H 6.64, N 3.30. **19b:** Colourless oil. [α]$_D^{20}$ = −38.2 (*c* = 0.69, CHCl$_3$). IR (film): ν̃ = 3315 cm^{-1} (N−H), 3020, 2965, 2875 (C−H), 1770 (C=O, lactone), 1715 (C=O, urethane). ^{1}H NMR: δ = 0.95 [d, ^3J = 6.7, 3 H, CH(C*H*$_3$)$_2$], 1.01 [d, ^3J = 6.7, 3 H, CH(C*H*$_3$)$_2$], 1.84 (dsept, ^3J = 8.2, ^3J = 6.7, 1 H, 2′-H), 2.21−2.33 (2 m, 2 H, 4-H), 2.81 (dddd, ^3J = ^3J = 9.4, ^3J = 7.0, ^3J = 4.0, 1 H, 3-H), 2.93 (dd, ^2J = 13.4, ^3J = 9.5, 1 H, 1′′-H$_A$), 3.39 (dd, ^2J = 13.4, ^3J = 4.0, 1 H, 1′′-H$_B$), 3.51 (ddd, ^3J = 10.1, ^3J = 8.2, ^3J = 1.8, 1 H, 1′-H), 4.70 (d, ^3J = 10.1, 1 H, NH), 4.76 (ddd, ^3J = 7.9, ^3J = 6.2, ^3J = 1.8, 1 H, 5-H), 5.02 (d, ^2J = 12.2, 1 H, OC*H*$_A$H$_B$Ph), 5.10 (d, ^2J = 12.3, 1 H, OCH$_A$*H*$_B$Ph), 7.20−7.41 (m, 10 H, 2 C$_6$H$_5$). ^{13}C NMR: δ = 19.2, 19.8 [CH(*C*H$_3$)$_2$], 29.9 (C-4), 31.0 (C-2′), 35.5 (C-1′′), 39.7 (C-3), 59.7 (C-1′), 67.2 (O*C*H$_2$Ph), 78.1 (C-5), 127.1, 128.0, 128.3, 128.6, 129.2, 130.4 (2 C$_6$H$_5$), 134.4, 136.1 (2 C$_6$H$_5$ *ipso*), 156.9 (C=O, urethane), 177.7 (C-2). MS (CI): *m*/*z* (%) = 413 (32) [M$^+$], 304 (7, [M − C$_6$H$_5$S]$^+$), 206 (44, [M − C$_6$H$_5$SH − C$_5$H$_5$O$_2$]$^+$), 162 (39, [M − C$_6$H$_5$SH − C$_5$H$_5$O$_2$ − CO$_2$]$^+$), 110 (47, C$_6$H$_5$SH$^+$), 91 (100, C$_7$H$_7^+$). C$_{23}$H$_{27}$NO$_4$S (413.5): calcd. C 66.80, H 6.58, N 3.39, S 7.75; found C 66.64, H 6.65, N 3.31, S 7.95.

Methyl (2*R*,3′′*S*,5′′*S*,1′′′*S*)- and (2*R*,3′′*R*,5′′*S*,1′′′*S*)-3-({5-[1-(Benzyloxycarbonylamino)-2-methylpropyl]-4,5-dihydro-2-oxo-(3*H*)fur-3-yl}methylthio)-2-(*tert*-butyloxycarbonylamino)propanoate (20a and 20b): Lactone **2a** (100 mg, 330 µmol), Boc−Cys−OMe (101 mg, 429 µmol) and NEt$_3$ (60 µL, 43 µmol) were heated to 60 °C in DMF (3 mL) under N$_2$. After 4 h, the mixture was hydrolysed with saturated NH$_4$Cl solution (2 mL) and extracted with EA (3×10 mL). The organic layers were washed with saturated NaHCO$_3$ solution (2×10 mL) and brine (10 mL) and dried (MgSO$_4$), and the solvents were removed in a rotary evaporator to yield a slightly yellowish oil. After filtration through an SiO$_2$ pad, the diastereomeric ratio was determined by HPLC (hexane/EA, 70:30) to be **20a**/**20b** = 78:22. Separation by MPLC (PE/EA, 85:15) afforded lactones **20a** (143 mg, 80%) and **20b** (32 mg, 18%). **20a:** Colourless, glass-like solid. [α]$_D^{20}$ = +19.2 (*c* = 0.96, CHCl$_3$). IR (film): ν̃ = 3340 cm^{-1} (br, N−H), 3040, 2970, 2870 (C−H), 1700 (br, C=O). ^{1}H NMR: δ = 0.98 [d, ^3J = 6.7, 3 H, CH(C*H*$_3$)$_2$], 1.02 [d, ^3J = 6.7, 3 H, CH(C*H*$_3$)$_2$], 1.45 [s, 9 H, C(C*H*$_3$)$_3$], 1.84 − 1.93 (2m, 2 H, 4′′-H$_A$, 2′′′-H), 2.39 (ddd, ^2J = 12.9, ^3J = 8.9, ^3J = 5.9, 1 H, 4′′-H$_B$), 2.58 (dd, ^2J = 12.2, ^3J = 8.3, 1 H, 1′-H$_A$), 2.88 (m$_c$, 1 H, 3′′-H), 2.92 (dd, ^2J = 14.5, ^3J = 5.5, 1 H, 3-H$_A$), 2.98 − 3.03 (2m, 2 H, 3-H$_B$, 1′-H$_B$), 3.56 (ddd, ^3J = 9.9, ^3J = 7.9, ^3J = 1.6, 1 H, 1′′′-H), 3.75 (s, 3 H, OCH$_3$), 4.52 (m$_c$, 1 H, 2-H), 4.62 (ddd, ^3J = 10.3, ^3J = 5.9, ^3J = 1.6, 1 H, 5′′-H), 4.91 (d, ^3J = 10.1, 1 H, NH$_{Val}$), 5.13 (s, 2 H, OC*H*$_2$Ph), 5.32 (d, ^3J = 7.7, 1 H, NH$_{Cys}$), 7.30−7.38 (m, 5 H, C$_6$H$_5$). ^{13}C NMR: δ = 19.2, 19.7 [CH(*C*H$_3$)$_2$], 28.3 [C(*C*H$_3$)$_3$], 30.8 (C-4′′), 31.4 (C-2′′′), 32.7 (C-1′), 35.4 (C-3), 41.1 (C-3′′), 52.7 (OCH$_3$), 53.2 (C-2), 58.1 (C-1′′′), 67.0 (O*C*H$_2$Ph), 77.7 (C-5′′), 80.3 [*C*(CH$_3$)$_3$], 128.0, 128.2, 128.6 (C$_6$H$_5$), 136.3 (C$_6$H$_5$ *ipso*), 155.1, 156.9 (2 C=O, urethane), 171.4 (C-1), 176.6 (C-2′′). MS (FAB): *m*/*z* (%) = 561 (6, [M + Na]$^+$), 539 (22, [M + H]$^+$), 439 (100, [M − C$_4$H$_8$ − CO$_2$ + H]$^+$), 91 (45, C$_7$H$_7^+$), 57 (10, C$_4$H$_9^+$). C$_{26}$H$_{38}$N$_2$O$_8$S (538.6): calcd. C 57.97, H 7.11, N 5.20, S 5.95; found C 57.77, H 7.10, N 5.08, S 5.70. **20b:** Colourless, glass-like solid. [α]$_D^{20}$ = +4.3 (*c* = 1.39, CHCl$_3$). IR (film): ν̃ = 3325 cm^{-1} (N−H), 3060, 3035, 2970, 2875 (C−H), 1700 (br, C=O). ^{1}H NMR: δ = 0.96 [d, ^3J = 6.8, 3 H, CH(C*H*$_3$)$_2$], 1.02 [d, ^3J = 6.6, 3 H, CH(C*H*$_3$)$_2$], 1.45 [s, 9 H, C(C*H*$_3$)$_3$], 1.84 (dsept, ^3J = 8.2, ^3J = 6.7, 1 H, 2′′′-H), 2.22 (ddd, ^2J = 13.5, ^3J = 8.2, ^3J = 6.7, 1 H, 4′′-H$_A$), 2.28 (ddd, ^2J = 13.5, ^3J = 9.5, ^3J = 5.7, 1 H, 4′′-H$_B$), 2.74 (dd, ^2J = 12.4, ^3J = 8.2, 1 H, 1′-H$_A$), 2.80 (m$_c$, 1 H, 3′′-H), 2.90 (dd, ^2J = 12.3, ^3J = 3.8, 1 H, 1′-H$_B$), 2.95 (dd, ^2J = 13.8, ^3J = 5.6, 1 H, 3-H$_A$), 3.02 (dd, ^2J = 13.9, ^3J = 4.9, 1 H, 3-H$_B$), 3.52 (ddd, ^3J = 10.1, ^3J = 8.2, ^3J = 1.8, 1 H, 1′′′-H), 3.77 (s, 3 H, OCH$_3$), 4.54 (ddd, ^3J = 8.1, ^3J = ^3J = 5.2, 1 H, 2-H), 4.77 (d, ^3J = 10.1, 1 H, NH$_{Val}$), 4.78 (ddd, ^3J = 7.8, ^3J = 5.8, ^3J = 1.8, 1 H, 5′′-H), 5.12 (s, 2 H, OC*H*$_2$Ph), 5.35 (d, ^3J = 7.9, 1 H, NH$_{Cys}$), 7.32−7.38 (m, 5 H, C$_6$H$_5$). ^{13}C NMR: δ = 19.2, 19.8 [CH(*C*H$_3$)$_2$], 28.3 [C(*C*H$_3$)$_3$], 29.6 (C-4′′), 31.0 (C-2′′′), 33.9 (C-1′), 35.5 (C-3), 40.0 (C-3′′), 52.7 (OCH$_3$), 53.3 (C-2), 59.8 (C-1′′′), 67.2 (O*C*H$_2$Ph), 78.1 (C-5′′), 80.3 [*C*(CH$_3$)$_3$], 128.0, 128.3, 128.6 (C$_6$H$_5$), 136.2 (C$_6$H$_5$ *ipso*), 155.1, 157.0 (2 C=O, urethane), 171.3 (C-1), 177.6 (C-2′′). MS (FAB): *m*/*z* (%) = 561 (6, [M + Na]$^+$), 539 (4, [M + H]$^+$), 439 (93, [M − C$_4$H$_8$ − CO$_2$ + H]$^+$), 91 (100, C$_7$H$_7^+$), 57 (24, C$_4$H$_9^+$). C$_{26}$H$_{38}$N$_2$O$_8$S (538.6): calcd. C 57.97, H 7.11, N 5.20; found C 57.57, H 7.10, N 5.11. HRMS (FAB, NBA+NaI): calcd. 561.2247 amu; found 561.2250 amu.

Methyl (2*R*,3′′*S*,5′′*S*,1′′′*S*)- and (2*R*,3′′*R*,5′′*S*,1′′′*S*)-3-({5-[1-(Benzyloxycarbonylamino)-2-phenylethyl]-4,5-dihydro-2-oxo-(3*H*)fur-3-yl}methylthio)-2-(*tert*-butyloxycarbonylamino)propanoate (21a and 21b): Lactone **5** (100 mg, 285 µmol), Boc−Cys−OMe (87 mg, 37 µmol) and NEt$_3$ (52 µL, 37 µmol) in DMF (3 mL) were heated to 60 °C under N$_2$. After 4 h, the mixture was hydrolysed with saturated NH$_4$Cl solution (2 mL) and extracted with EA (3×10 mL). The organic layers were washed with saturated NaHCO$_3$ solution (2×10 mL) and brine (10 mL) and dried

($MgSO_4$), and the solvents were removed in a rotary evaporator to yield a slightly yellowish oil. After filtration through an SiO_2 pad, the diastereomeric ratio was determined by HPLC (hexane/EA, 70:30) to be **21a/21b** = 76:24. Separation by MPLC (PE/EA, 73:27) afforded lactones **21a** (121 mg, 72%) and **21b** (39 mg, 23%). **21a:** Colourless, glass-like solid. $[\alpha]_D^{20} = +22.8$ (*c* = 1.03, $CHCl_3$). IR (film): $\tilde{\nu} = 3320\ cm^{-1}$ (N−H), 3040, 2960 (C−H), 1770 (C=O, lactone), 1700 (br, C=O), 1530 (C=C). ^{1}H NMR: δ = 1.43 [s, 9 H, $C(CH_3)_3$], 1.93 (ddd, ^{2}J = 12.6, ^{3}J = 12.6, ^{3}J = 9.6, 1 H, 4′′-H_B), 2.29 (ddd, ^{2}J = 13.0, ^{3}J = 8.9, ^{3}J = 6.2, 1 H, 4′′-H_A), 2.60 (dd, ^{2}J = 11.4, ^{3}J = 8.6, 1 H, 1′-H_A), 2.86 (dddd, ^{3}J = 12.6, ^{3}J = ^{3}J = 8.7, ^{3}J = 4.1, 1 H, 3′′-H), 2.88−3.03 (m, 5 H, 3-H, 1′-H_B, 2′′′-H), 3.75 (s, 3 H, OCH_3), 4.08 (dddd, ^{3}J = 10.0, ^{3}J = 9.0, ^{3}J = 7.1, ^{3}J = 1.9, 1 H, 1′′′-H), 4.38 (ddd, ^{3}J = 10.1, ^{3}J = 5.9, ^{3}J = 1.7, 1 H, 5′′-H), 4.51 (m_c, 1 H, 2-H), 5.00 (d, ^{3}J = 9.7, 1 H, NH_{Phe}), 5.08 (d, ^{2}J = 12.4, 1 H, OCH_AH_BPh), 5.10 (d, ^{2}J = 12.3, 1 H, OCH_AH_BPh), 5.31 (d, ^{3}J = 7.6, 1 H, NH_{Cys}), 7.22−7.37 (m, 10 H, 2 C_6H_5). ^{13}C NMR: δ = 28.3 [$C(CH_3)_3$], 30.0 (C-4′′), 32.7 (C-1′), 35.4, 39.3 (C-3,C-2′′′), 41.3 (C-3′′), 52.7 (OCH_3), 53.2 (C-2), 53.9 (C-1′′′), 67.0 (OCH_2Ph), 77.6 (C-5′′), 80.3 [$C(CH_3)_3$], 126.9, 128.0, 128.2, 128.6, 128.8, 129.3 (2 C_6H_5), 136.2, 136.9 (2 C_6H_5 *ipso*), 155.1, 156.4 (2 C=O, urethane), 171.3 (C-1), 176.4 (C-2′′). MS (FAB): *m*/*z* (%) = 609 (8, $[M + Na]^+$), 587 (29, $[M + H]^+$), 487 (100, $[M - C_4H_8 - CO_2 + H]^+$), 91 (52, $C_7H_7^+$). $C_{30}H_{38}N_2O_8S$ (586.7): calcd. C 61.42, H 6.53, N 4.77, S 5.47; found C 61.32, H 6.49, N 4.64, S 5.75. **21b:** Colourless, glass-like solid. $[\alpha]_D^{20} = +16.2$ (*c* = 0.49, $CHCl_3$). IR (film): $\tilde{\nu} = 3320\ cm^{-1}$ (N−H), 3040, 2980, 2870 (C−H), 1770 (C=O, lactone), 1700 (br, C=O), 1535 (C=C). ^{1}H NMR: δ = 1.44 [s, 9 H, $C(CH_3)_3$], 2.16 (ddd, ^{2}J = 13.6, ^{3}J = 8.6, ^{3}J = 7.0, 1 H, 4′′-H_A), 2.32 (ddd, ^{2}J = 13.6, ^{3}J = 10.0, ^{3}J = 5.2, 1 H, 4′′-H_B), 2.70 (dd, ^{2}J = 12.7, ^{3}J = 8.0, 1 H, 1′-H_A), 2.82 (dddd, ^{3}J = 10.8, ^{3}J = 7.8, ^{3}J = 7.0, ^{3}J = 4.0, 1 H, 3′′-H), 2.89 (dd, ^{2}J = 12.7, ^{3}J = 4.2, 1 H, 1′-H_B), 2.91−3.02 (m, 4 H, 3-H, 2′′′-H), 3.75 (s, 3 H, OCH_3), 4.09 (dddd, ^{3}J = ^{3}J = 9.2, ^{3}J = 7.7, ^{3}J = 1.2, 1 H, 1′′′-H), 4.50−4.55 (2m, 2 H, 2-H, 5′′-H), 4.84 (d, ^{3}J = 9.7, 1 H, NH_{Phe}), 5.04 (d, ^{2}J = 12.4, 1 H, OCH_AH_BPh), 5.07 (d, ^{2}J = 12.3, 1 H, OCH_AH_BPh), 5.33 (d, ^{3}J = 8.2, 1 H, NH_{Cys}), 7.21−7.36 (m, 10 H, 2 C_6H_5). ^{13}C NMR: δ = 28.3 [$C(CH_3)_3$], 29.1 (C-4′′), 33.9 (C-1′), 35.4, 39.0 (C-3,C-2′′′), 40.0 (C-3′′), 52.7 (OCH_3), 53.3 (C-2), 55.5 (C-1′′′), 67.1 (OCH_2Ph), 78.4 (C-5′′), 80.3 [$C(CH_3)_3$], 126.9, 128.0, 128.2, 128.6, 128.8, 129.2 (2 C_6H_5), 136.1, 136.7 (2 C_6H_5 *ipso*), 155.1, 156.5 (2 C=O, urethane), 171.3 (C-1), 177.5 (C-2′′). MS (FAB): *m*/*z* (%) = 609 (5, $[M + Na]^+$), 587 (7, $[M + H]^+$), 487 (100, $[M - C_4H_8 - CO_2 + H]^+$), 91 (83, $C_7H_7^+$). $C_{30}H_{38}N_2O_8S$ (586.7): calcd. C 61.42, H 6.53, N 4.77, S 5.47; found C 61.27, H 6.53, N 4.73, S 5.71.

(2′*S*,3′*S*)-2-[3-(Benzyloxycarbonylamino)-2-hydroxy-4-methylpentyl]-*N*,*N*-dibenzylpropenamide (22): *n*BuLi (15% in *n*-hexane, 402 μL, 660 μmol) was added at −78 °C to a solution of Bn_2NH (127 μL, 660 μmol) in anhydrous Et_2O (1 mL). After 5 min, lactone **2a** (100 mg, 330 μmol) was added to the bright red solution, which was then allowed to come to −20 °C over 6 h. The mixture was hydrolysed by stirring with 1 N HCl (2 mL) for 15 min and the aqueous phase was extracted with EA (3×10 mL). The combined extracts were washed with saturated $NaHCO_3$ solution and brine (10 mL each) and dried ($MgSO_4$). The solvents were removed in a rotary evaporator to leave a yellowish oil. Separation by MPLC (PE/EA, 80:20) afforded homoallyl alcohol **22** (72 mg, 44%) and starting material **2a** (42 mg, 42%). **22**: Colourless oil. $[\alpha]_D^{20} = -14.1$ (*c* = 1.05, $CHCl_3$). IR (film): $\tilde{\nu} = 3350\ cm^{-1}$ (br, O−H, N−H), 3040, 3020, 2960, 2880 (C−H), 1715 (C=O, urethane), 1620 (C=O, amide). ^{1}H NMR: δ = 0.98 [d, ^{3}J = 6.7, 3 H, $CH(CH_3)_2$], 1.01 [d, ^{3}J = 6.6, 3 H, $CH(CH_3)_2$], 1.91 (dsept, ^{3}J = 8.4, ^{3}J = 6.7, 1 H, 4′-H), 2.30 (m_c, 2 H, 1′-H), 3.26 (m_c, 1 H, 3′-H), 4.06 (mc, 1 H, 2′-H), 4.48−4.64 (m, 4 H, NCH_2Ph), 4.75 (br. s, 1 H, OH), 5.09 (d, ^{2}J = 12.4, 1 H, OCH_AH_BPh), 5.13 (d, ^{2}J = 12.4, 1 H, OCH_AH_BPh), 5.23 (d, ^{3}J = 10.1, 1 H, NH), 5.30 (s, 1 H, 3-H_E), 5.34 (s, 1 H, 3-H_Z), 7.12−7.40 (m, 15 H, 3 C_6H_5). ^{13}C NMR: δ = 19.6, 19.8 [$CH(CH_3)_2$], 30.8 (C-4′), 41.0 (C-1′), 46.8, 51.4 (2 $-NCH_2Ph$), 60.9 (C-3′), 66.6 (OCH_2Ph), 71.1 (C-2′), 118.7 (C-3), 126.9, 127.8, 128.0, 128.2, 128.3, 128.4, 128.5, 128.8, 129.0 (3 C_6H_5), 136.0, 136.4, 136.8 (3 C_6H_5 *ipso*), 141.1 (C-2), 157.0 (C=O, urethane), 173.7 (C-1). MS (FAB): *m*/*z* (%) = 501 (48, $[M + H]^+$), 91 (100, $C_7H_7^+$). $C_{31}H_{36}N_2O_4$ (500.6): calcd. C 74.37, H 7.25, N 5.60; found C 73.89, H 7.25, N 5.45. HRMS (FAB): calcd. 501.2753 amu; found 501.2760 amu.

(2′*S*,3′*S*)-2-[3-(Benzyloxycarbonylamino)-2-hydroxy-4-methylpentyl]-*N*,*N*-dibenzylpropenamide (23): *n*BuLi (15% in *n*-hexane, 402 μL, 660 μmol) was added at −20 °C to a solution of benzyltrimethylsilylamine (131 μL, 660 μmol) in anhydrous Et_2O (2 mL). The solution was cooled to −78 °C and CuI (63 mg, 330 μmol) was added. After this had stirred for 15 min, $P(OEt)_3$ (40 μL, 0.23 mmol) and lactone **2a** (100 mg, 330 μmol) were added and stirring was continued for 1.5 h at that temp. The mixture was hydrolysed by stirring with saturated NH_4Cl solution (4 mL) for 15 min and concentrated in a rotary evaporator, and Et_2O (10 mL) was added. The mixture was stirred with 1 N HCl (5 mL) for 1 h at room temp. and the aqueous phase was extracted with Et_2O (3×10 mL). The combined extracts were washed with saturated $NaHCO_3$ solution and brine (10 mL each) and dried ($MgSO_4$). The solvents were removed in a rotary evaporator to leave a yellowish oil. Separation by MPLC (PE/EA, 72:18) afforded homoallyl alcohol **23** (29 mg, 21%). **23:** Colourless solid, m.p. 117−119 °C. IR (KBr): $\tilde{\nu} = 3350\ cm^{-1}$ (br, O−H, N−H), 3040, 2940, 2860 (C−H), 1680 (br, 2 C=O). ^{1}H NMR: δ = 0.95 [d, ^{3}J = 6.8, 3 H, $CH(CH_3)_2$], 0.98 [d, ^{3}J = 6.6, 3 H, $CH(CH_3)_2$], 1.86 (dsept, ^{3}J = 8.7, ^{3}J = 6.7, 1 H, 4′-H), 2.39 (dd, ^{2}J = 14.0, ^{3}J = 3.1, 1 H, 1′-H_A), 2.47 (dd, ^{2}J = 13.9, ^{3}J = 8.8, 1 H, 1′-H_B), 3.28 (ddd, ^{3}J = 10.2, ^{3}J = 8.8, ^{3}J = 1.5, 1 H, 3′-H), 3.91 (dddd, ^{3}J = 8.8, ^{3}J = ^{3}J = 2.8, ^{3}J = 1.7, 1 H, 2′-H), 4.44 (dd, ^{2}J = 14.8, ^{3}J = 5.7, 1 H, NCH_AH_BPh), 4.50 (dd, ^{2}J = 14.8, ^{3}J = 5.9, 1 H, NCH_AH_BPh), 5.02 (d, ^{3}J = 2.4, 1 H, OH), 5.08 (d, ^{2}J = 12.4, 1 H, OCH_AH_BPh), 5.10 (d, ^{2}J = 12.3, 1 H, OCH_AH_BPh), 5.22 (d, ^{3}J = 10.1, 1 H, NH_{Val}), 5.42 (s, 1 H, 3-H_E), 5.54 (s, 1 H, 3-H_Z), 6.39 (dd, ^{3}J = ^{3}J = 5.5, 1 H, NH_{amide}), 7.25−7.38 (m, 10 H, 2 C_6H_5). ^{13}C NMR: δ = 19.5, 19.8 [$CH(CH_3)_2$], 30.8 (C-4′), 39.8 (C-1′), 44.0 (NCH_2Ph), 61.1 (C-3′), 66.6 (OCH_2Ph), 71.7 (C-2′), 120.6 (C-3), 127.8, 127.8, 127.9, 128.0, 128.5, 128.9 (2 C_6H_5), 136.8, 137.5 (2 C_6H_5 *ipso*), 143.2 (C-2), 156.9 (C=O, urethane), 170.5 (C-1). MS (FAB): *m*/*z* (%) = 433 (2, $[M + Na]^+$), (31, $[M + H]^+$), 91 (100, $C_7H_7^+$). $C_{24}H_{30}N_2O_4$ (410.5): calcd. C 70.22, H 7.37, N 6.82; found C 69.59, H 7.35, N 6.55. HRMS (FAB): calcd. 411.2279 amu; found 411.2284 amu.

(3*R*,5*S*,1′*S*)- and (3*S*,5*S*,1′*S*)-3-(*N*-Benzyl-*N*-hydroxyamino)methyl-5-[1-(benzyloxycarbonylamino)-2-methylpropyl]-4,5-dihydro-2(3*H*)-furanone (24a and 24b): Lactone **2a** (100 mg, 330 μmol), BnNHOH·HCl (63 mg, 0.40 mmol) and NEt_3 (55 μL, 0.40 mmol) in anhydrous THF (3 mL) were stirred at room temp. under N_2 for 17 h. H_2O (2 mL) was added and the aqueous phase was extracted with EA (3×10 mL). The combined extracts were washed with brine (10 mL) and dried ($MgSO_4$). The solvents were removed in a rotary evaporator to leave a yellowish oil. After filtration through an SiO_2 pad, the diastereomeric ratio was determined by HPLC (hexane/EA, 75:25) to be **24a/24b** = 36:64. Separation by MPLC (PE/EA, 77:23) afforded lactones **24a** (41 mg, 29%) and **24b** (71 mg, 50%). **24a:** Colourless, glass-like solid, softening range 50−55

°C. $[\alpha]_D^{20}$ = +4.9 (*c* = 1.25, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3320 cm^{-1} (br, N−H, O−H), 3060, 2970, 2860 (C−H), 1770 (C=O, lactone), 1710 (C=O, urethane), 1530 (C=C). ^{1}H NMR: δ = 0.96 [d, ^3J = 6.7, 3 H, CH(CH_3)$_2$], 1.01 [d, ^3J = 6.8, 3 H, CH(CH_3)$_2$], 1.84 (br. s, 1 H, OH), 1.88 (dsept, ^3J = 8.6, ^3J = 6.8, 1 H, 2′′-H), 2.03 (ddd, ^2J = 12.8, ^3J = ^3J = 11.1, 1 H, 4-H_B), 2.38 (ddd, ^2J = 13.0, ^3J = 9.2, ^3J = 6.4, 1 H, 4-H_A), 2.86 (dd, ^2J = 12.9, ^3J = 7.1, 1 H, 1′-H_A), 2.90 (dddd, ^3J = 11.2, ^3J = 9.5, ^3J = 6.9, ^3J = 4.5, 1 H, 3-H), 3.15 (dd, ^2J = 12.8, ^3J = 4.9, 1 H, 1′-H_B), 3.58 (ddd, ^3J = 10.0, ^3J = 7.6, ^3J = 2.1, 1 H, 1′′-H), 3.81 (s, 2 H, NCH_2Ph), 4.60 (ddd, ^3J = 9.9, ^3J = 6.4, ^3J = 2.1, 1 H, 5-H), 4.88 (d, ^3J = 10.7, 1 H, NH), 5.10 (s, 2 H, OCH_2Ph), 7.24−7.48 (m, 10 H, 2 C_6H_5). ^{13}C NMR: δ = 19.0, 19.7 [CH(CH$_3$)$_2$], 30.1 (C-4), 31.2 (C-2′′), 39.5 (C-3), 58.3 (C-1′′), 58.9 (C-1′), 65.5 (NCH$_2$Ph), 67.0 (OCH$_2$Ph), 77.8 (C-5), 128.0, 128.2, 128.4, 128.6, 128.7, 129.5 (2 C_6H_5), 136.2, 137.0 (2 C_6H_5 *ipso*), 156.8 (C=O, urethane), 178.0 (C-2). MS (FAB): *m/z* (%) = 853 (2, [2 M + H]$^+$), 449 (4, [M + Na]$^+$), 427 (100, [M + H]$^+$), 409 (14, [M − OH]$^+$), 91 (91, $C_7H_7^+$). $C_{24}H_{30}N_2O_5$ (426.5): calcd. C 67.59, H 7.09, N 6.57; found C 67.58, H 7.04, N 6.45. Lactone **24b:** Colourless, glass-like solid, softening range 68−72 °C. $[\alpha]_D^{20}$ = −8.5 (*c* = 0.25, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3325 cm^{-1} (br, N−H, O−H), 3040, 3020, 2960, 2875 (C−H), 1770 (C=O, lactone), 1715 (C=O, urethane), 1535 (C=C). ^{1}H NMR: δ = 0.95 [d, ^3J = 6.8, 3 H, CH(CH_3)$_2$], 1.00 [d, ^3J = 6.6, 3 H, CH(CH_3)$_2$], 1.85 (dsept, ^3J = 8.3, ^3J = 6.8, 1 H, 2′′-H), 1.90 (br. s, 1 H, OH), 2.24 (ddd, ^2J = 13.4, ^3J = 9.7, ^3J = 6.0, 1 H, 4-H_A), 2.29 (ddd, ^2J = 13.4, ^3J = 7.8, ^3J = 6.8, 1 H, 4-H_B), 2.83 (dd, ^2J = 12.6, ^3J = 7.6, 1 H, 1′-H_A), 2.90 (dddd, ^3J = 9.7, ^3J = ^3J = 7.4, ^3J = 4.6, 1 H, 3-H), 3.04 (dd, ^2J = 12.6, ^3J = 4.8, 1 H, 1′-H_B), 3.50 (ddd, ^3J = 10.1, ^3J = 8.3, ^3J = 1.8, 1 H, 1′′-H), 3.80 (d, ^2J = 13.0, 1 H, NCH_AH$_B$Ph), 3.83 (d, ^2J = 12.9, 1 H, NCH$_A$$H_B$Ph), 4.72 (ddd, ^3J = 7.9, ^3J = 6.1, ^3J = 1.8, 1 H, 5-H), 4.93 (d, ^3J = 10.2, 1 H, NH), 5.08 (s, 2 H, OCH_2Ph), 7.26−7.47 (m, 10 H, 2 C_6H_5). ^{13}C NMR: δ = 19.2, 19.8 [CH(CH$_3$)$_2$], 29.5 (C-4), 31.0 (C-2′′), 38.9 (C-3), 59.8 (C-1′), 59.9 (C-1′′), 65.3 (NCH$_2$Ph), 67.1 (OCH$_2$Ph), 78.3 (C-5), 127.6, 128.0, 128.2, 128.4, 128.5, 129.4 (2 C_6H_5), 136.3, 136.9 (2 C_6H_5 *ipso*), 157.1 (C=O, urethane), 178.9 (C-2). MS (FAB): *m/z* (%) = 853 (2, [2 M + H]$^+$), 449 (4, [M + Na]$^+$), 427 (100, [M + H]$^+$), 91 (73, $C_7H_7^+$). $C_{24}H_{30}N_2O_5$ (426.5): calcd. C 67.59, H 7.09, N 6.57; found C 67.50, H 7.18, N 6.43.

(3*S*,5*S*,1′*S*)-3-Aminomethyl-5-(1-amino-2-methylpropyl)-4,5-dihydro-2(3*H*)furanone (25): Lactone **24b** (117 mg, 274 μmol) in MeOH (5 mL) was hydrogenated at normal pressure and room temp. with Pd/C (5%, 35 mg) for 20 h. The catalyst was filtered off and the solvent was removed in a rotary evaporator to leave lactone **25** as a slightly yellow oil (49 mg, 96%), which could not be further purified. (Approximately 10% of the product consisted of the ring-opened β-amino acid **26**, which could be detected by NMR and MS). **25:** Yellowish oil. IR (film): $\tilde{\nu}$ = 3200 cm^{-1} (br, N−H, O−H), 2960, 2870 (C−H), 1750 (C=O, lactone). ^{1}H NMR (300 MHz, D_3COD): δ = 0.95 [d, ^3J = 6.8, 3 H, CH(CH_3)$_2$], 1.01 [d, ^3J = 6.9, 3 H, CH(CH_3)$_2$], 1.51 (ddd, ^2J = 14.2, ^3J = 9.8, ^3J = 4.6, 1 H, 4-H_A), 1.81 (ddd, ^2J = 13.9, ^3J = 9.2, ^3J = 3.3, 1 H, 4-H_B), 1.90 (septd, ^3J = 6.9, ^3J = 5.5, 1 H, 2′′-H), 2.49−2.61 (2m, 2 H, 3-H, 1′′-H), 2.89 (dd, ^2J = 12.6, ^3J = 5.2, 1 H, 1′-H_A), 2.97 (dd, ^2J = 12.6, ^3J = 8.2, 1 H, 1′-H_B), 3.77 (ddd, ^3J = 9.8, ^3J = 5.3, ^3J = 3.3, 1 H, 5-H). ^{13}C NMR (75 MHz, D_3COD): δ = 18.3, 21.0 [CH(CH$_3$)$_2$], 30.8 (C-2′′), 37.1 (C-4), 44.9 (C-1′), 46.2 (C-3), 63.1 (C-1′′), 70.6 (C-5), 182.0 (C-2). MS (FAB): *m/z* (%) = 373 (8, [2M + H]$^+$), 187 (100, [M + H]$^+$). HRMS ($C_9H_{18}N_2O_2$, FAB): calcd. 187.1455 amu; found 187.1447 amu.

(3*R*,5*S*,1′*S*)- and (3*S*,5*S*,1′*S*)-5-[1-(Benzyloxycarbonylamino)-3-methylbutyl]-3-methoxymethyl-4,5-dihydro-2(3*H*)furanone (27a and 27b): Lactone **3** (77 mg, 0.24 mmol) in anhydrous MeOH (6 mL) was placed under N_2 in a flame-dried flask. NaOMe (16 mg, 0.30 mmol) was added at room temp. and the mixture was stirred for 3 h. After hydrolysis by stirring with 1 N HCl (10 mL) for 15 min, the aqueous layer was extracted with EA (3×10 mL). The combined extracts were washed with saturated $NaHCO_3$ solution (2×10 mL) and brine (10 mL) and dried ($MgSO_4$). The solvents were removed in a rotary evaporator to leave a colourless oil. After filtration through an SiO_2 pad, the diastereomeric ratio was determined by HPLC (hexane/EA, 75:25) to be **27a/27b** = 55:45. Separation by MPLC (PE/EA, 77:23) afforded lactones **27a** (37 mg, 44%) and **27b** (31 mg, 37%). **27a:** Colourless solid, m.p. 91−93 °C. $[\alpha]_D^{20}$ = −26.9 (*c* = 0.68, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3280 cm^{-1} (N−H), 3040, 2940, 2880 (C−H), 1770 (C=O, lactone), 1690 (C=O, urethane), 1540 (C=C). ^{1}H NMR: δ = 0.93 [d, ^3J = 5.0, 3 H, CH(CH_3)$_2$], 0.94 [d, ^3J = 4.9, 3 H, CH(CH_3)$_2$], 1.37 (ddd, ^2J = 13.7, ^3J = 8.7, ^3J = 4.8, 1 H, 2′-H_A), 1.58 (ddd, ^2J = 13.6, ^3J = 10.1, ^3J = 5.2, 1 H, 2′-H_B), 1.67 (m$_c$, 1 H, 3′-H), 2.09 (ddd, ^2J = 13.0, ^3J = 11.3, ^3J = 10.0, 1 H, 4-H_B), 2.33 (ddd, ^2J = 12.9, ^3J = 9.5, ^3J = 6.5, 1 H, 4-H_A), 2.85 (dddd, ^3J = 11.2, ^3J = 9.4, ^3J = 5.5, ^3J = 3.8, 1 H, 3-H), 3.28 (s, 3 H, OCH_3), 3.56 (dd, ^2J = 9.4, ^3J = 5.4, 1 H, 1′′-H_A), 3.59 (dd, ^2J = 9.4, ^3J = 3.8, 1 H, 1′′-H_B), 3.92 (dddd, ^3J = ^3J = 10.0, ^3J = 5.0, ^3J = 2.1, 1 H, 1′-H), 4.45 (ddd, ^3J = 10.0, ^3J = 6.5, ^3J = 2.1, 1 H, 5-H), 4.77 (d, ^3J = 10.0, 1 H, NH), 5.12 (d, ^2J = 12.3, 1 H, OCH_AH$_B$Ph), 5.14 (d, ^2J = 12.3, 1 H, OCH$_A$$H_B$Ph), 7.30−7.39 (m, 5 H, C_6H_5). ^{13}C NMR: δ = 21.9, 23.1 [CH(CH$_3$)$_2$], 24.7 (C-3′), 27.8 (C-4), 41.5 (C-3), 42.2 (C-2′), 51.0 (C-1′), 59.1 (OCH_3), 66.9 (OCH$_2$Ph), 70.6 (C-1′′), 80.2 (C-5), 127.9, 128.1, 128.5 (C_6H_5), 136.4 (C_6H_5 *ipso*), 156.6 (C=O, urethane), 176.7 (C-2). MS (FAB): *m/z* (%) = 372 (7, [M + Na]$^+$), 350 (47, [M + H]$^+$), 91 (100, $C_7H_7^+$). $C_{19}H_{27}NO_5$ (349.4): calcd. C 65.31, H 7.79, N 4.01; found C 65.15, H 7.82, N 3.97. Lactone **27b:** Colourless solid, m.p. 95 − 97 °C. $[\alpha]_D^{20}$ = −12.7 (*c* = 0.30, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3300 cm^{-1} (N−H), 3040, 2940, 2880 (C−H), 1760 (C=O, lactone), 1680 (C=O, urethane), 1535 (C=C). ^{1}H NMR: δ = 0.92 [d, ^3J = 6.6, 6 H, CH(CH_3)$_2$], 1.36 (ddd, ^2J = 13.8, ^3J = 8.9, ^3J = 4.7, 1 H, 2′-H_A), 1.58 (ddd, ^2J = 13.9, ^3J = 10.2, ^3J = 5.1, 1 H, 2′-H_B), 1.65 (m$_c$, 1 H, 3′-H), 2.21−2.29 (2 m, 2 H, 4-H), 2.69 (dddd, ^3J = 9.9, ^3J = 7.6, ^3J = 4.3, ^3J = 3.5, 1 H, 3-H), 3.33 (s, 3 H, OCH_3), 3.50 (dd, ^2J = 9.2, ^3J = 3.4, 1 H, 1′′-H_A), 3.66 (dd, ^2J = 9.2, ^3J = 4.3, 1 H, 1′′-H_B), 3.90 (dddd, ^3J = ^3J = 10.1, ^3J = 4.9, ^3J = 1.9, 1 H, 1′-H), 4.54 (ddd, ^3J = 8.6, ^3J = 6.7, ^3J = 1.9, 1 H, 5-H), 4.62 (d, ^3J = 9.8, 1 H, NH), 5.09 (d, ^2J = 12.3, 1 H, OCH_AH$_B$Ph), 5.11 (d, ^2J = 12.3, 1 H, OCH$_A$$H_B$Ph), 7.28−7.38 (m, 5 H, C_6H_5). ^{13}C NMR: δ = 21.8, 23.1 [CH(CH$_3$)$_2$], 24.7 (C-3′), 27.8 (C-4), 41.2 (C-3), 42.1 (C-2′), 52.1 (C-1′), 59.2 (OCH_3), 67.1 (OCH$_2$Ph), 71.9 (C-1′′), 81.3 (C-5), 128.0, 128.2, 128.6 (C_6H_5), 136.3 (C_6H_5 *ipso*), 156.7 (C=O, urethane), 178.0 (C-2). MS (FAB): *m/z* (%) = 372 (8, [M + Na]$^+$), 350 (66, [M + H]$^+$), 220 (6, [M − $C_6H_9O_3$]$^+$), 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 65.07, H 7.86, N 3.98.

(3*R*,5*S*,1′*S*)- and (3*S*,5*S*,1′*S*)-5-[1-(Benzyloxycarbonylamino)-2-phenylethyl]-3-methoxymethyl-4,5-dihydro-2(3*H*)furanone (28a and 28b): Lactone **5** (100 mg, 285 μmol) in anhydrous MeOH (3 mL) was placed in a flame-dried flask under N_2. NaOMe (19 mg, 0.34 mmol) was added at room temp. and the mixture was stirred for 24 h. After hydrolysis by stirring with 1 N HCl (3 mL) for 15 min, the aqueous layer was extracted with EA (3×10 mL). The combined extracts were washed with saturated $NaHCO_3$ solution (2×10 mL) and brine (10 mL) and dried ($MgSO_4$). The solvents were removed in a rotary evaporator to leave a colourless oil. After filtration through an SiO_2 pad, the diastereomeric ratio was determined by HPLC (hexane/EA, 75:25) to be **28a/28b** = 53:47. Separation by MPLC (PE/EA, 76:24) afforded lactones **28a** (42 mg, 38%) and **28b** (36 mg, 33%). **28a:** Colourless solid, m.p. 101−103 °C. [α]$^{20}_{D}$ = −13.4 (*c* = 0.95, CHCl$_3$). IR (KBr): ṽ = 3300 cm^{-1} (N−H), 3040, 3020, 2920, 2870 (C−H), 1770 (C=O, lactone), 1690 (C=O, urethane), 1540 (C=C). ^{1}H NMR: δ = 2.13 (ddd, ^2J = 13.0, ^3J = 10.9, ^3J = 9.7, 1 H, 4-H$_B$), 2.24 (ddd, ^2J = 13.0, ^3J = 9.8, ^3J = 6.9, 1 H, 4-H$_A$), 2.81 (dddd, ^3J = 10.8, ^3J = 9.7, ^3J = 5.2, ^3J = 3.5, 1 H, 3-H), 2.91 (dd, ^2J = 13.6, ^3J = 9.1, 1 H, 2′-H$_A$), 3.04 (dd, ^2J = 13.6, ^3J = 6.7, 1 H, 2′-H$_B$), 3.28 (s, 3 H, OCH$_3$), 3.57 (dd, ^2J = 9.4, ^3J = 3.6, 1 H, 1′′-H$_A$), 3.61 (dd, ^2J = 9.3, ^3J = 5.1, 1 H, 1′′-H$_B$), 4.04 (dddd, ^3J = ^3J = 9.1, ^3J = 6.7, ^3J = 1.9, 1 H, 1′-H), 4.41 (ddd, ^3J = 9.4, ^3J = 6.9, ^3J = 1.9, 1 H, 5-H), 5.08−5.11 (m, 3 H, OC*H*$_2$Ph, NH), 7.17−7.37 (m, 10 H, 2 C$_6$H$_5$). ^{13}C NMR: δ = 27.3 (C-4), 39.2 (C-2′), 41.5 (C-3), 54.4 (C-1′), 59.1 (OCH$_3$), 66.9 (O*C*H$_2$Ph), 70.7 (C-1′′), 77.3 (C-5), 126.8, 127.9, 128.1, 128.5, 128.7, 129.4 (2 C$_6$H$_5$), 136.3, 137.1 (2 C$_6$H$_5$ *ipso*), 156.4 (C=O, urethane), 176.6 (C-2). MS (EI, 70 eV): *m*/*z* (%) = 383 (3) [M$^+$], 292 (26, [M − C$_7$H$_7$]$^+$), 248 (21, [M − C$_7$H$_7$ − CO$_2$]$^+$), 91 (100, C$_7$H$_7$$^+$). C$_{22}H_{25}NO_5$ (383.4): calcd. C 68.91, H 6.57, N 3.65; found C 68.67, H 6.60, N 3.61. **28b:** Colourless oil. [α]$^{20}_{D}$ = −0.77 (*c* = 0.54, CHCl$_3$). IR (film): ṽ = 3320 cm^{-1} (N−H), 3060, 2960, 2875 (C−H), 1770 (C=O, lactone), 1690 (C=O, urethane), 1530 (C=C). ^{1}H NMR: δ = 2.19 (m$_c$, 1 H, 4-H$_A$), 2.24 (ddd, ^2J = 13.3, ^3J = 10.0, ^3J = 6.3, 1 H, 4-H$_B$), 2.73 (dddd, ^3J = 10.1, ^3J = 7.9, ^3J = ^3J = 3.7, 1 H, 3-H), 2.93 (d, ^3J = 7.9, 2 H, 2′-H), 3.30 (s, 3 H, OCH$_3$), 3.47 (dd, ^2J = 9.2, ^3J = 3.5, 1 H, 1′′-H$_A$), 3.63 (dd, ^2J = 9.2, ^3J = 4.4, 1 H, 1′′-H$_B$), 4.09 (dddd, ^3J = 9.7, ^3J = ^3J = 7.9, ^3J = 1.7, 1 H, 1′-H), 4.55 (ddd, ^3J = 8.0, ^3J = 6.2, ^3J = 1.8, 1 H, 5-H), 4.93 (d, ^3J = 9.7, 1 H, NH), 5.03 (d, ^2J = 12.3, 1 H, OC*H*$_A$H$_B$Ph), 5.06 (d, ^2J = 12.3, 1 H, OCH$_A$*H*$_B$Ph), 7.21−7.35 (m, 10 H, 2 C$_6$H$_5$). ^{13}C NMR: δ = 27.6 (C-4), 39.2 (C-2′), 41.1 (C-3), 55.4 (C-1′), 59.1 (OCH$_3$), 67.0 (O*C*H$_2$Ph), 71.7 (C-1′′), 79.0 (C-5), 126.8, 127.9, 128.2, 128.5, 128.7, 129.3 (2 C$_6$H$_5$), 136.2, 137.0 (2 C$_6$H$_5$ *ipso*), 156.6 (C=O, urethane), 178.0 (C-2). MS (EI, 70 eV): *m*/*z* (%) = 383 (6) [M$^+$], 292 (21, [M − C$_7$H$_7$]$^+$), 248 (18, [M − C$_7$H$_7$ − CO$_2$]$^+$), 91 (100, C$_7$H$_7$$^+$). C$_{22}H_{25}NO_5$ (383.4): calcd. C 68.91, H 6.57, N 3.65; found C 68.91, H 6.64, N 3.63.

(3*S*,5*S*,1′*S*)-5-[1-(Benzyloxycarbonylamino)-2-methylpropyl]-3-pentyl-4,5-dihydro-2(3*H*)furanone (7a): Lactone **2a** (50 mg, 0.17 mmol), *n*BuI (56 µL, 0.49 mmol), Bu$_3$SnH (131 µL, 494 µmol) and a small amount of AIBN in anhydrous toluene (3 mL) were heated to 95 °C for 6 h. The mixture was allowed to cool to room temp., 1 N HCl (3 mL) was added, and the aqueous layer was extracted with Et$_2$O (3×10 mL). The combined extracts were washed with 1 N HCl, saturated NaHCO$_3$ solution, and brine (10 mL each) and dried (MgSO$_4$). The solvents were removed in a rotary evaporator to leave a yellowish oil. After filtration through an SiO$_2$ pad, the crude product was analysed by HPLC and NMR and showed just one isomer, which was purified by MPLC (PE/EA, 90:10) to afford lactone **7a** (18 mg, 30%). **7a:** Colourless oil. [α]$^{20}_{D}$ = −25.3 (*c* = 0.85, CHCl$_3$). HRMS (C$_{21}$H$_{31}$NO$_4$, EI, 70 eV): calcd. 361.2258 amu; found 361.2253 amu. Further data were in full agreement with **7a** obtained from addition of butyl cuprate (vide supra).

(3*S*,5*S*,1′*S*)-5-[1-(Benzyloxycarbonylamino)-2-methylpropyl]-3-(2,2-dimethylpropyl)-4,5-dihydro-2(3*H*)furanone (29a): A solution of (Me$_3$Si)$_3$SiH (305 µL, 989 µmol) and a small amount of AIBN in anhydrous toluene (2 mL) was added by syringe pump at 85 °C over 3 h to a solution of lactone **2a** (98 mg, 0.32 mmol) and *t*BuI (118 µL, 989 µmol) in anhydrous toluene (2 mL) and heating was continued for 4 h. The mixture was allowed to cool to room temp., 1 N HCl (3 mL) was added, and the aqueous layer was extracted with Et$_2$O (3×10 mL). The combined extracts were washed with 1 N HCl, saturated NaHCO$_3$ solution and brine (10 mL each) and dried (MgSO$_4$). The solvents were removed in a rotary evaporator to leave a yellowish oil. After filtration through an SiO$_2$ pad, the crude product was analysed by HPLC and NMR, and showed just one isomer, which was purified by MPLC (PE/EA, 95:5) to afford lactone **29a** (36 mg, 31%). **29a:** Colourless solid, m.p. 122−124 °C. [α]$^{20}_{D}$ = −16.9 (*c* = 0.33, CHCl$_3$). IR (KBr): ṽ = 3400 cm^{-1} (br, N−H), 2940, 2900, 2850 (C−H), 1790 (C=O, lactone), 1710 (C=O, urethane). ^{1}H NMR: δ = 0.90 [s, 9 H, C(C*H*$_3$)$_3$], 0.98 [d, ^3J = 6.8, 3 H, CH(C*H*$_3$)$_2$], 1.01 [d, ^3J = 6.6, 3 H, CH(C*H*$_3$)$_2$], 1.15 (dd, ^2J = 14.1, ^3J = 9.8, 1 H, 1′′-H$_A$), 1.66 (ddd, ^2J = 12.6, ^3J = 11.8, ^3J = 10.4, 1 H, 4-H$_B$), 1.89 (dsept, ^3J = 8.0, ^3J = 6.7, 1 H, 2′-H), 1.99 (dd, ^2J = 14.1, ^3J = 2.3, 1 H, 1′′-H$_B$), 2.44 (ddd, ^2J = 12.6, ^3J = 8.9, ^3J = 5.8, 1 H, 4-H$_A$), 2.53 (dddd, ^3J = 11.4, ^3J = 9.9, ^3J = 8.8, ^3J = 2.3, 1 H, 3-H), 3.52 (ddd, ^3J = 10.4, ^3J = 7.9, ^3J = 1.6, 1 H, 1′-H), 4.57 (ddd, ^3J = 10.4, ^3J = 5.8, ^3J = 1.6, 1 H, 5-H), 4.85 (d, ^3J = 10.3, 1 H, NH), 5.08 (d, ^2J = 12.3, 1 H, OC*H*$_A$H$_B$Ph), 5.16 (d, ^2J = 12.3, 1 H, OCH$_A$*H*$_B$Ph), 7.31−7.36 (m, 5 H, C$_6$H$_5$). ^{13}C NMR: δ = 19.2, 19.7 [CH(*C*H$_3$)$_2$], 29.6 [C(*C*H$_3$)$_3$], 30.4 [*C*(CH$_3$)$_3$], 31.4 (C-2′), 34.5 (C-4), 37.6 (C-3), 45.0 (C-1′′), 58.0 (C-1′), 67.0 (O*C*H$_2$Ph), 77.2 (C-5), 127.9, 128.2, 128.6 (C$_6$H$_5$), 136.4 (C$_6$H$_5$ *ipso*), 156.9 (C=O, urethane), 179.7 (C-2). MS (EI, 70 eV): *m*/*z* (%) = 361 (7) [M$^+$], 206 (41, [M − C$_4$H$_{10}$ − C$_5$H$_5$O$_2$]$^+$), 162 (39, [M − C$_4$H$_{10}$ − C$_5$H$_5$O$_2$ − CO$_2$]$^+$), 91 (100, C$_7$H$_7$$^+$). C$_{21}H_{31}NO_4$ (361.5): calcd. C 69.78, H 8.64, N 3.87; found C 69.61, H 8.84, N 3.82.

(3*S*,5*S*,1′*S*)- and (3*R*,5*S*,1′*S*)-5-[1-(*tert*-Butyloxycarbonylamino)-2-methylpropyl]-4,5-dihydro-3-methyl-2(3*H*)furanone (30a and 30b): Lactone **2a** (100 mg, 330 µmol) in MeOH (5 mL) was hydrogenated in the presence of Boc$_2$O (106 mg, 486 µmol) and Pd/C (5%, 20 mg) for 24 h at room temp. and normal pressure. The catalyst was filtered off and the solvent was removed in a rotary evaporator, leaving an oily residue that was taken up in EA (50 mL). The solution was washed with brine (2×15 mL) and dried (MgSO$_4$). The solvent was removed in a rotary evaporator, leaving a colourless solid. Purification by chromatography (PE/EA, 83:17) afforded a mixture of lactones **30a** and **30b** (ratio 91:9, 83 mg, 93%). **30a/30b** (data are given for a 91:9 mixture of isomers, except for NMR spectra). Colourless solid, m.p. 98−100 °C. [α]$^{20}_{D}$ = −55.3 (*c* = 0.88, CHCl$_3$). IR (KBr): ṽ = 3320 cm^{-1} (N−H), 2960, 2910, 2860 (C−H), 1770 (C=O, lactone), 1685 (C=O, urethane), 1525 (N−H bending), 1360 (*tert*-butyl). MS (CI): *m*/*z* (%) = 543 (3, [2 M + H]$^+$), 294 (8, [M + Na]$^+$), 272 (5, [M + H]$^+$), 216 (100, [M − C$_4$H$_8$ + H]$^+$), 172 (50, [M − C$_5$H$_7$O$_2$]$^+$), 57 (57, C$_4$H$_9$$^+$). C$_{14}H_{25}NO_4$ (271.4): calcd. C 61.97, H 9.29, N 5.16; found C 61.95, H 9.38, N 5.12. **30a:** ^{1}H NMR: δ = 0.98 [d, ^3J = 6.8, 3 H, CH(C*H*$_3$)$_2$], 1.01 [d, ^3J = 6.8, 3 H, CH(C*H*$_3$)$_2$], 1.26 (d, ^3J = 7.1, 3 H, 1′-H), 1.44 [s, 9 H, C(CH$_3$)$_3$], 1.71 (ddd, ^2J = 12.7, ^3J = 12.0, ^3J = 10.2, 1 H, 4-H$_B$), 1.86 (dsept, ^3J = 8.0, ^3J = 6.8, 1 H, 2′′-H), 2.38 (ddd, ^2J = 12.8, ^3J = 9.0, ^3J = 6.0, 1 H, 4-H$_A$), 2.68 (ddq, ^3J = 11.9, ^3J = 9.0, ^3J = 7.1, 1 H, 3-H), 3.44 (ddd, ^3J = 10.3, ^3J = 8.0, ^3J = 1.4, 1 H, 1′′-H), 4.57 (d, ^3J = 10.2, 1 H, NH), 4.60 (ddd, ^3J = 10.2, ^3J = 6.0, ^3J = 1.4, 1 H, 5-H). ^{13}C NMR: δ = 15.2 (C-1′), 19.3, 19.7 [CH(*C*H$_3$)$_2$], 28.4 [C(*C*H$_3$)$_3$], 31.5 (C-2′′), 33.6 (C-4), 35.2 (C-3), 57.5 (C-1′′), 77.5 (C-5), 79.7 [*C*(CH$_3$)$_3$], 156.4 (C=O, urethane), 179.6 (C-2). **30b:** ^{13}C NMR: δ = 16.7 (C-1′), 19.3, 19.8 [CH(*C*H$_3$)$_2$], 28.4 [C(*C*H$_3$)$_3$], 31.2 (C-2′′), 32.9 (C-4), 34.3 (C-3), 59.0 (C-1′′), 77.7 (C-5), 79.8 [*C*(CH$_3$)$_3$], 156.4 (C=O, urethane), 180.6 (C-2).

(3*S*,5*S*,1′*S*)-5-[1-(*tert*-Butyloxycarbonylamino)-3-methylbutyl]-4,5-dihydro-3-methyl-2(3*H*)furanone (31a): Lactone **3** (78 mg, 0.25 mmol) in MeOH (4 mL) was hydrogenated in the presence of

Boc$_2$O (300 mg, 1.37 mmol) and Pd/C (5%, 22 mg) for 24 h at room temp. and normal pressure. The catalyst was filtered off and the solvent was removed in a rotary evaporator, leaving an oily residue that was taken up in EA (50 mL). The solution was washed with brine (2×15 mL) and dried (MgSO$_4$). The solvent was removed in a rotary evaporator, leaving a colourless solid. Purification by chromatography (PE/EA, 83:17) afforded lactone **31a** (56 mg, 80%). **31a:** Colourless solid, m.p. 110−112 °C. $[\alpha]_D^{20} = -40.7$ ($c = 0.77$, CHCl$_3$). IR (KBr): $\tilde{\nu} = 3320$ cm^{-1} (N−H), 2950, 2920, 2850 (C−H), 1765 (C=O, lactone), 1675 (C=O, urethane), 1520 (N−H bending), 1360 (*tert*-butyl). ^{1}H NMR: δ = 0.93 [d, ^3J = 6.3, 6 H, CH(C*H*$_3$)$_2$], 1.26 (d, ^3J = 7.1, 3 H, 1′-H), 1.36 (ddd, ^2J = 13.8, ^3J = 8.7, ^3J = 5.0, 1 H, 2′′-H$_A$), 1.44 [s, 9 H, C(CH$_3$)$_3$], 1.59 (ddd, ^2J = 13.9, ^3J = 9.4, ^3J = 5.5, 1 H, 2′′-H$_B$), 1.67 (m$_c$, 1 H, 3′′-H), 1.71 (ddd, ^2J = 12.8, ^3J = 11.9, ^3J = 10.2, 1 H, 4-H$_B$), 2.39 (ddd, ^2J = 12.8, ^3J = 9.0, ^3J = 5.9, 1 H, 4-H$_A$), 2.68 (ddq, ^3J = 11.8, ^3J = 9.1, ^3J = 7.1, 1 H, 3-H), 3.82 (dddd, ^3J = ^3J = 10.1, ^3J = 5.1, ^3J = 1.7, 1 H, 1′′-H), 4.39 (ddd, ^3J = 10.2, ^3J = 5.9, ^3J = 1.6, 1 H, 5-H), 4.45 (d, ^3J = 9.8, 1 H, NH). ^{13}C NMR: δ = 15.2 (C-1′), 21.9, 23.1 [CH(*C*H$_3$)$_2$], 24.8 (C-3′′), 28.3 [C(*C*H$_3$)$_3$], 32.9 (C-4), 35.4 (C-3), 42.3 (C-2′′), 50.1 (C-1′′), 79.7 [*C*(CH$_3$)$_3$], 80.2 (C-5), 156.0 (C=O, urethane), 179.6 (C-2). MS (CI): *m*/*z* (%) = 571 (34, [2 M + H]$^+$), 515 (23, [2 M − C$_4$H$_8$ + H]$^+$), 471 (81, [2 M − C$_5$H$_7$O$_2$]$^+$), 415 (16, [2 M − C$_5$H$_7$O$_2$ − C$_4$H$_8$]$^+$), 371 (74, [2 M − 2 C$_5$H$_7$O$_2$]$^+$), 286 (34, [M + H]$^+$), 230 (100, [M − C$_4$H$_8$ + H]$^+$), 186 (61, [M − C$_5$H$_7$O$_2$]$^+$), 130 (19, [M − C$_5$H$_7$O$_2$ − C$_4$H$_8$]$^+$). C$_{15}$H$_{27}$NO$_4$ (285.4): calcd. C 63.13, H 9.54, N 4.91; found C 63.07, H 9.56, N 4.81.

(5*R*,1′*S*)-5-[1-(Benzyloxycarbonylamino)-2-methylpropyl]-4,5-dihydro-3-hydroxy-2(3*H*)furanone (32): Lactone **2b** (76 mg, 0.25 mmol) in CH$_2$Cl$_2$ was cooled to −78 °C and O$_2$ was passed through the solution for 5 min. A mixture of O$_3$/O$_2$ (3.5 g O$_3$/h) was then passed through for 4 min, resulting in an intensive blue colour. Stirring was continued for 15 min at that temp. and Me$_2$S (63 µL, 0.86 mmol) was added. The mixture was allowed to warm to room temp. and stirred for 3 h at room temp. The volatile components were removed in a rotary evaporator, leaving a colourless solid that was recrystallized from CH$_2$Cl$_2$ to yield lactone **32** (60 mg, 79%). **32:** Colourless solid, m.p. 189−191 °C. $[\alpha]_D^{20} = +11.0$ ($c = 0.32$, CHCl$_3$/MeOH, 1:1). IR (KBr): $\tilde{\nu} = 3380$, 3080 cm^{-1} (br, N−H, O−H), 2950, 2850 (C−H), 1760 (C=O, lactone), 1690 (C=O, urethane), 1530 (C=C). ^{1}H NMR (500 MHz, D$_3$COD/CDCl$_3$): δ = 0.94 [d, ^3J = 6.8, 3 H, CH(C*H*$_3$)$_2$], 0.99 [d, ^3J = 6.9, 3 H, CH(C*H*$_3$)$_2$], 1.91 (dsept, ^3J = ^3J = 6.7, 1 H, 2′-H), 3.78 (m$_c$, 1 H, 1′-H), 4.97 (dd, ^3J = 6.0, ^3J = 2.0, 1 H, 5-H), 5.10 (s, 2 H, OC*H*$_2$Ph), 6.08 (d, ^3J = 2.1, 1 H, 4-H), 7.30−7.39 (m, 5 H, C$_6$H$_5$). ^{13}C NMR (125 MHz, D$_3$COD/CDCl$_3$): δ = 17.7, 20.1 [CH(*C*H$_3$)$_2$], 29.4 (C-2′), 58.1 (C-1′), 67.1 (O*C*H$_2$Ph), 78.9 (C-5), 115.4 (C-4), 128.0, 128.3, 128.6 (C$_6$H$_5$), 136.3 (C$_6$H$_5$ *ipso*), 144.5 (C-3), 156.8 (C=O, urethane), 169.7 (C-2). MS (FAB): *m*/*z* (%) = 306 (18, [M + H]$^+$), 91 (100, C$_7$H$_7$$^+$). C$_{16}H_{19}NO_5$ (305.3): calcd. C 62.94, H 6.27, N 4.59; found C 62.99, H 6.32, N 4.44.

(5*S*,1′*S*)-5-[1-(Benzyloxycarbonylamino)-2,2-dimethylpropyl]-4,5-dihydro-3-hydroxy-2(3*H*)furanone (33): Lactone **4** (79 mg, 0.25 mmol) in CH$_2$Cl$_2$ was cooled to −78 °C and O$_2$ was passed through the solution for 5 min. A mixture of O$_3$/O$_2$ (3.5 g O$_3$/h) was then passed through for 4 min, resulting in an intensive blue colour. Stirring was continued for 15 min at that temp. and Me$_2$S (63 µL, 0.86 mmol) was added. The mixture was allowed to warm to room temp. and stirred for 3 h at room temp. The volatile components were removed in a rotary evaporator, leaving a colourless solid that was recrystallized from Et$_2$O to yield lactone **33** (79 mg, 99%). **33:** Colourless solid, m.p. 166−168 °C. $[\alpha]_D^{20} = -116.5$ ($c = 1.07$, CHCl$_3$). IR (KBr): $\tilde{\nu} = 3380$, 3090 cm^{-1} (br, N−H, O−H), 2940, 2850 (C−H), 1760 (C=O, lactone), 1670 (C=O, urethane), 1530 (C=C). ^{1}H NMR (500 MHz, CDCl$_3$, two rotamers): δ = 0.98 {1.00} [s, 9 H, C(CH$_3$)$_3$], 3.52 {3.68} (dd, ^3J = 10.8 {10.6}, ^3J = 1.0 {1.2}, 1 H, 1′-H), 4.98 {6.69} (d, ^3J = 10.7 {10.8}, 1 H, NH), 5.01 {5.08} (s, 2 H, OC*H*$_2$Ph), 5.13 {5.18} (dd, ^3J = 2.1 {2.1}, ^3J = 1.0 {1.2}, 1 H, 5-H), 5.76 {6.06} (d, ^3J = 1.9 {1.9}, 1 H, 4-H), 6.21 {8.96} (s, 1 H, OH), 7.22−7.37 (m, 5 H, C$_6$H$_5$). ^{13}C NMR (125 MHz, CDCl$_3$ two rotamers): δ = 26.2 {26.3} [C(*C*H$_3$)$_3$], 33.7 {33.8} (C-2′), 58.6 {59.6} (C-1′), 66.0 {66.7} (O*C*H$_2$Ph), 76.4 {76.6} (C-5), 116.4 {117.0} (C-4), 126.8 {127.1}, 127.2 {127.4}, 127.5 {127.6} (C$_6$H$_5$), 134.9 {135.2} (C$_6$H$_5$ *ipso*), 141.4 {143.1} (C-3), 155.7 {156.8} (C=O, urethane), 169.0 {169.5} (C-2). MS (FAB): *m*/*z* (%) = 342 (2, [M + Na]$^+$), 320 (10, [M + H]$^+$), 91 (100, C$_7$H$_7$$^+$). C$_{17}H_{21}NO_5$ (319.4): calcd. C 63.94, H 6.63, N 4.39; found C 63.78, H 6.65, N 4.31.

(5*S*,1′*S*)-5-[1-(Benzyloxycarbonylamino)-2-methylpropyl]-4,5-dihydro-3-methyl-2(3*H*)furanone (34): Lactone **2a** (137 mg, 452 µmol), RhCl$_3$·*x*H$_2$O (12 mg), EtOH (1.5 mL) and H$_2$O (0.15 mL) were stirred for 19 h at 60−65 °C. The solution was allowed to cool to room temp., H$_2$O (2 mL) was added, and the aqueous phase was extracted with Et$_2$O (3×10 mL). The combined extracts were washed with brine (20 mL) and dried (MgSO$_4$), the solvents were removed in a rotary evaporator, and the residue was purified by MPLC (PE/EA, 75:25) to yield lactone **34** (120 mg, 88%). **34:** Colourless solid, m.p. 72−74 °C. $[\alpha]_D^{20} = -217$ ($c = 1.04$, CHCl$_3$). IR (KBr): $\tilde{\nu} = 3290$ cm^{-1} (N−H), 3040, 2940, 2860 (C−H), 1750 (C=O, lactone), 1690 (C=O, urethane), 1530 (C=C). ^{1}H NMR: δ = 1.02 (d, ^3J = 6.8, 3 H, CH(C*H*$_3$)$_2$], 1.09 (d, ^3J = 6.7, 3 H, CH(C*H*$_3$)$_2$], 1.79 (d, $^4J_{\text{allyl.}}$ = 1.6, 3 H, 1′′-H), 1.93 (dsept, ^3J = 8.7, ^3J = 6.7, 1 H, 2′-H), 3.69 (ddd, ^3J = 10.2, ^3J = 8.5, ^3J = 1.7, 1 H, 1′-H), 4.65 (d, ^3J = 9.9, 1 H, NH), 4.99 (d, ^2J = 12.4, 1 H, OC*H*$_A$H$_B$Ph), 5.10 (m$_c$, 1 H, 5-H), 5.11 (d, ^2J = 12.5, 1 H, OCH$_A$*H*$_B$Ph), 7.01 (s, 1 H, 4-H), 7.29−7.39 (m, 5 H, C$_6$H$_5$). ^{13}C NMR: δ = 10.4 (C-1′′), 19.6, 19.9 [CH(*C*H$_3$)$_2$], 30.9 (C-2′), 57.4 (C-1′), 66.8 (O*C*H$_2$Ph), 80.7 (C-5), 127.8, 128.2, 128.5 (C$_6$H$_5$), 130.5, 136.3 (C$_6$H$_5$ *ipso*, C-3), 156.4 (C=O, urethane), 174.4 (C-2). MS (EI, 70 eV): *m*/*z* (%) = 302 (2) [M$^+$], 206 (21, [M − C$_5$H$_5$O$_2$]$^+$), 162 (24, [M − C$_5$H$_5$O$_2$ − C$_3$H$_8$]$^+$), 97 (3, C$_5$H$_5$O$_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 67.03, H 7.08, N 4.58.

(5*S*,1′*S*)-5-[1-(Benzyloxycarbonylamino)-2-phenylethyl]-4,5-dihydro-3-methyl-2(3*H*)furanone (35): Lactone **5** (150 mg, 427 µmol), RhCl$_3$·xH$_2$O (11 mg), EtOH (1.5 mL) and H$_2$O (0.15 mL) were stirred for 19 h at 50 °C. The solution was allowed to cool to room temp., H$_2$O (2 mL) was added, and the aqueous phase was extracted with Et$_2$O (3×10 mL). The combined extracts were washed with brine (20 mL) and dried (MgSO$_4$), the solvents were removed in a rotary evaporator, and the residue was purified by MPLC (PE/EA, 76:24) to yield lactone **35** (148 mg, 99%). **35:** Colourless solid, m.p. 113−115 °C. $[\alpha]_D^{20} = -83.4$ ($c = 1.16$, CHCl$_3$). IR (KBr): $\tilde{\nu} = 3300$ cm^{-1} (N−H), 3040, 3000, 2900 (C−H), 1760 (C=O, lactone), 1690 (C=O, urethane), 1530 (C=C). ^{1}H NMR: − δ = 1.79 (s, 3 H, 1′′-H), 2.98 (dd, ^2J = 13.4, ^3J = 8.6, 1 H, 2′-H$_A$), 3.02 (dd, ^2J = 13.7, ^3J = 7.3, 1 H, 2′-H$_B$), 4.25 (dddd, ^3J = ^3J = 9.1, ^3J = 7.3, ^3J = 1.8, 1 H, 1′-H), 4.81 (d, ^3J = 9.5, 1 H, NH), 4.83 (m$_c$, 1 H, 5-H), 4.97 (d, ^2J = 12.4, 1 H, OC*H*$_A$H$_B$Ph), 5.05 (d, ^2J = 12.4, 1 H, OCH$_A$*H*$_B$Ph), 6.96 (s, 1 H, 4-H), 7.23−7.35 (m, 10 H, 2 C$_6$H$_5$). ^{13}C NMR: δ = 10.5 (C-1′′), 38.7 (C-2′), 53.2 (C-1′), 66.8 (O*C*H$_2$Ph), 80.7 (C-5), 127.0, 127.8, 128.2, 128.5, 128.8, 129.3 (2 C$_6$H$_5$), 130.7 (C-3), 136.2, 136.8 (2 C$_6$H$_5$ *ipso*), 146.9 (C-4), 156.0

(C=O, urethane), 174.2 (C-2). MS (EI, 70 eV): *m/z* (%) = 351 (1) [M^+], 254 (21, [$M - C_5H_5O_2]^+$), 210 (15, [$M - C_5H_5O_2 - CO_2]^+$), 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 71.95, H 6.10, N 3.99.

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