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Iodolactonization of 3-amino-4-pentenoic acid: a stereoselective synthesis of *syn*-γ-hydroxy-β-amino acids

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Abstract

The reaction of (*S*)-3-*N*-Cbz-4-pentenoic acid with iodine in acetonitrile in the presence of AgOTf gave the *cis*-iodo-lactone **6** in excellent yield and in a highly diastereoselective manner. The substitutions of the iodine in **6** by different Grignard reagents in the presence of CuI and the subsequent conversions into the functionalized *syn*-γ-hydroxy-β-amino acids have been investigated. By the above reaction sequence, (3*S*,4*S*)-3-amino-4-hydroxy-5-cyclohexyl pentanoic acid was synthesized with high enantioselectivity.

1. Introduction

β-Amino acids are emerging as an important topic in organic chemistry and as an interesting class of compounds in medicinal chemistry. They are found in humans, animals, micro-organisms and plants, either in the free form or as components of peptides or depsipeptides,[1] with antibiotic,[1] antifungal,[2] cytotoxic,[3] anticancer[4] etc. activities. Natural or synthetic enzyme inhibitors, such as bestatin and amastatin, contain β-amino acids as key components.[1] Peptides that contain β-amino acids are generally more stable to enzymatic hydrolysis, because the enzyme is not able to recognize the amide bonds.[1,5] Moreover, the ability of short β-peptide oligomers to form well defined, remarkably stable secondary structures[6] has enhanced the potential of these compounds as mimics of α-peptides.

In view of the importance and utility of β-amino acids a number of synthetic methods,[7] based mainly on the stereoselective formation of the C–N bond or on the transformation of α-amino acids, have been developed.

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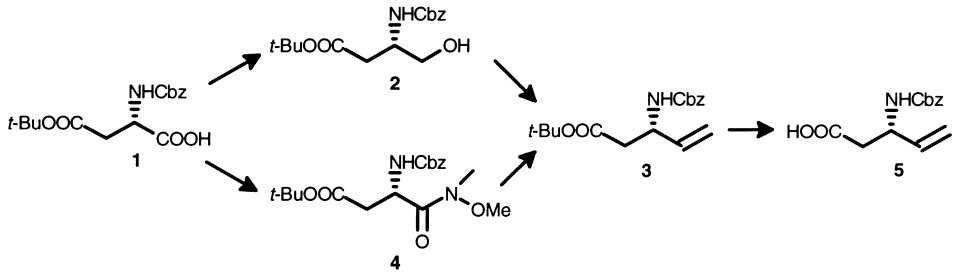
The Michael addition of 'chiral ammonia' equivalent to achiral α,β-unsaturated esters[8] or amines to chiral α,β-unsaturated esters,[9] as well as the stereoselective addition of metal acetate to chiral imines,[10] have been extensively studied. The stereoselective formation of 6-substituted perhydropyrimidin-4-ones,[11] the C-4 alkylation and arylation of enantiomerically pure dihydropyrimidones[12] and the use of β-lactams as acylating agents[13] in β-peptide synthesis have also been considered.

The Arndt–Eistert homologation of α-amino acids[14] is a versatile method for the preparation of enantiomerically pure β-amino acids with the same substituent as the proteinogenic α-amino acids. Moreover, in a different approach, the carboxylic group at C-1 of L-aspartic acid and L-asparagine has been transformed into the desired alkyl or aryl substituent[15] without altering the β-amino acid backbone. By contrast, insufficient consideration has been given to the synthesis of functionalized α-unsubstituted γ-hydroxy-β-amino acids, although they are components of antibiotic peptides, such as tuberactinomycins A and N,[16] or gastroprotective natural products such as Amicoumacin C and AI-77-B.[17] On the other hand, electrophilic mediated lactonization[18] of 4-pentenoic acid is a powerful method to introduce a γ-hydroxy function, and in the case of chiral 3-substituted 4-pentenoic acids, high levels of 1,2 stereochemical induction have been observed. However, whereas 3-hydroxy-, 3-alkoxy- and 3-alkyl-4-pentenoic acids have been extensively studied, little attention has been paid to 3-amino-4-pentenoic acid, in spite of its electronic characteristics.

Following our studies[19] on the stereoselective synthesis of non-proteinaceous amino acids via electrophilic functionalization of chiral allyl amines, we report here our results on the stereoselective, iodine mediated, lactonization reaction of (*S*)-3-*N*-benzyloxycarbonyl-4-pentenoic acid, as the key step for the preparation of γ-substituted *syn*-β-amino-γ-hydroxy acids.

2. Results and discussion

The (*S*)-3-*N*-benzyloxycarbonyl-4-pentenoic acid **5** was prepared in line with the two synthetic pathways depicted in Scheme 1.

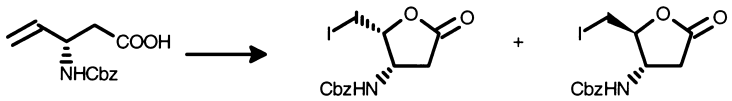


Scheme 1.

In the first approach, *N*-Cbz γ-*tert*-butyl L-aspartic acid[20] **1** was converted into the amino alcohol[15a,21] **2** by activation (EtOCOCl, Et_3N, THF, −15°C) of the acid function as a mixed anhydride followed by reduction with $NaBH_4$/MeOH, according to Kokotos.[22] The amino alcohol **2** was obtained in 89% yield and converted under Swern conditions ($COCl_2$/DMSO, −63°C, then DIPEA) into the corresponding α-amino aldehyde, which in turn, by Wittig methylation ($Ph_3P^+CH_3\ Br^-$/KHMDS, −78°C→rt), gave **3** in 80% yield. In the second pathway, the

conversion of the partially protected L-aspartic acid **1** into the Weinreb amide[23] **4** (MeNHOMe, EDC, 90%) was followed by treatment with $LiAlH_4$[24] (1 M THF, −5°C) to give the corresponding α-amino aldehyde, which was then subjected to the Wittig olefination reaction as above. The allyl amine **3** was obtained in 78% yield from **4** and in 70% yield from **1**. Although comparable yields were obtained by the two methods, the second was chosen because it requires less technically demanding transformations. The *tert*-butyl ester **3** was converted into the free acid **5** in quantitative yield by treatment with CF_3COOH in CH_2Cl_2.

The iodine mediated lactonization reaction of (*S*)-3-*N*-Cbz-4-pentenoic acid **5** (Scheme 2) was then studied under different conditions, and the results are reported in Table 1. Diastereomeric ratios were determined on the crude mixture by integration of non-overlapping signals in the ^1H NMR spectra and of chromatographic peaks in HPLC profiles. Under all conditions the major product was the *cis*-lactone **6**, although with different chemical yields and stereoselectivities.



5 **6** **7**

Scheme 2.

Table 1
Iodonium ion promoted lactonization of (*S*)-3-benzyloxycarbonylamino-4-pentenoic acid

run	reaction conditions[a]	T (°C)	time (h)	Yield (%)	*cis*/*trans* ratio
1	I_2/Et_2O-$NaHCO_3$[b]	−5	5	84	8:1
2	I_2/CH_2Cl_2	r.t.	5	42	6:1
3	I_2/CCl_4	−5	8	16	8:1
4	I_2/CH_3CN	−5	4	65	11:1
5	I_2/CH_3CN	−5	24	71	11:1
6	I_2/CH_3CN	−40	2	25	15:1
7	I_2/CH_3CN	−40	7	29	15:1
8	I_2/ CH_3CN/$NaHCO_3$	−40	2	25	12:1
9	I_2/ CH_3CN/Pyridine	−40	5	28	7:1
10	I_2/ AgOTf[c]/ CH_3CN	−40	3.5	97	15:1

a) 3 eq. of I_2 were used in each experiment. b) Satd. solution was used. c) 1.0 eq. was used.

Initial attempts to achieve the iodolactonization reaction[18] of **5**, in a biphasic system H_2O/Et_2O (entry 1) in the presence of sat. aqueous $NaHCO_3$ at −5°C, gave the two iodo-lactones **6** and **7** in good chemical yield (84%) but in a moderate ratio (8:1). On the other hand, reactions carried out in CH_2Cl_2 or CCl_4 (entries 2, 3) gave a mixture of products, where compounds **6** and **7** occurred in low yields and poor ratios. A cleaner reaction occurred in acetonitrile (entries 4 and 5) at −5°C, to give the diastereomeric mixture of iodo-lactones **6**/**7** in 65–70% overall yield and 11:1 ratio. A better diastereoselectivity (15:1, entry 6) was observed when the reaction was performed at −40°C[25] in CH_3CN, but with lower yields. A prolonged reaction time (entry 7) did not improve

the yield. The use of bases ($NaHCO_3$, pyridine, entries 8 and 9), in the same solvent, was also investigated, but the results were no better. However, a dramatic rate enhancement was observed when the reaction was carried out in the presence (1.0 equiv., entry 10) of AgOTf.[26] Within 3.5 h the starting material was consumed to give the iodo-lactones **6**/**7** in 97% yield and 15:1 ratio. The ^1H and ^{13}C NMR spectral data of diastereoisomers **6** and **7** are reported in Table 2.

Table 2
^1H and ^{13}C NMR spectroscopic data[a] for the iodo-lactones **6** and **7**

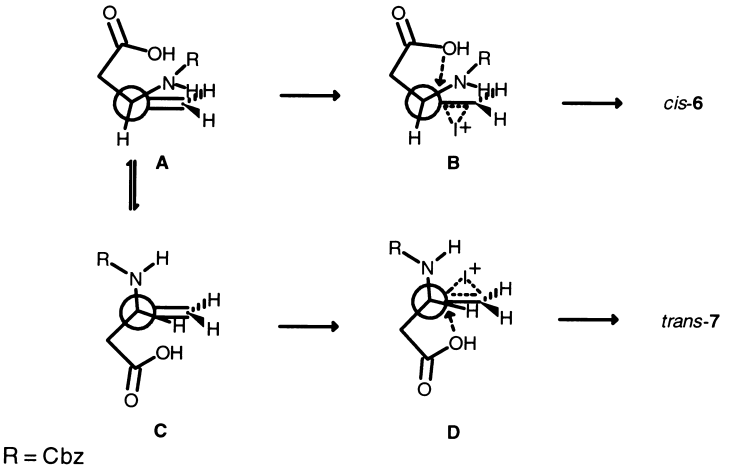
Position	**6**		**7**	
	δ_C	δ_H, mult., (J in Hz)	δ_C	δ_H, mult., (J in Hz)
C-5	174.03	-	173.56	
N-CO	155.88	-	155.67	
1'-C_6H_5	135.80	7.40-7.30, m	135.70	7.40-7.30, m
2',6'-C_6H_5	128.60		128.64	
4'-C_6H_5	128.40		128.46	
3',5'-C_6H_5	128.13		128.25	
C-2	82.18	4.88, dt (8.0, 5.5)	83.60	4.43, q (5.0)
OCH_2	67.41	5.11, s	67.32	5.10, s
C-3	50.25	4.71, tdd (8.5, 5.5, 3.5)	52.76	4.30, dtd (9.0, 7.0, 5.0)
C-4	36.59	3.09, dd (17.5, 8.5) 2.60, dd (17.5, 3.5)	35.08	3.05, dd (17.0, 9.0) 2.68, dd (17.0, 7.0)
CH_2I	-0.08	3.44, dd (11.0, 5.5) 3.38, dd (11.0, 8.0)	5.68	3.67, dd (11.0, 4.0) 3.56, dd (11.0, 6.0)
NH	--	7.06, brd (8.5)	--	7.09, brd (7.0)

a) Run in CD_3COCD_3. The signals showed the appropriate integration intensities. Assignments were confirmed by COSY and HECTOR experiments.

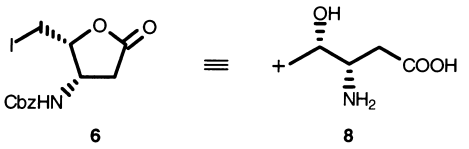
In the ^1H NMR spectra of compound **7** the signal of the H-2 proton appeared at higher field than that of compound **6**, as required for *trans* isomers.[27] On the other hand, in the ^{13}C NMR spectra the signals attributed to C-2, C-3 (82.18, 50.25 ppm) and CH_2I (−0.88 ppm) for the *cis* isomer **6** were upfield[27] from the corresponding signals (83.60, 52.76 and 5.68 ppm, respectively) of the *trans* isomer **7**. Finally, a DIFNOE (3.5%) between the NH and CH_2I confirmed the *cis*-relationship between the two groups. A single crystallization gave **6** in 73% yield and 97.5% d.e.[28] The stereochemical outcome may be rationalized on the basis of electronic and steric effects (Scheme 3).

The *trans*-product **7** is expected to arise from the transition state **D**, since the conformer **C** is sterically less hindered than the conformer **A**. On the other hand, electronic effects[29] activate the double bond in the conformer **A** for electrophilic addition towards the transition state **B** to give the predominant *cis*-form **6**.

Given that the iodo-lactone **6** can be considered equivalent, from a synthetic point of view, to the electrophilic synthon **8** (Scheme 4), the nucleophilic substitution of the iodine was investigated to obtain γ-functionalized *syn*-β-amino-γ-hydroxy acids.



Scheme 3.



Scheme 4.

Therefore, the nucleophilic displacement of the iodine in **6** by different Grignard reagents in the presence of CuI salts[30] was considered. Reactions were performed by addition of compound **6** in THF to a mixture of the Grignard reagent and CuI in dry THF at −50°C for 1.5 h. Fair results (Table 3) were obtained when both primary and secondary alkyl Grignard reagents were employed, whereas phenyl failed to give the substitution product in acceptable yield under all conditions tested.

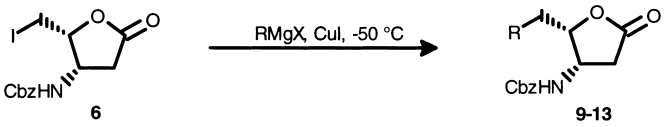
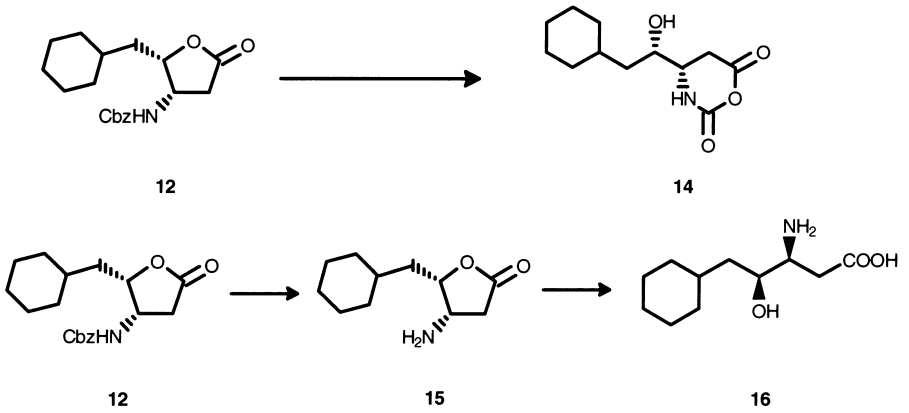


Table 3
CuI mediated cross-coupling of iodo-lactone **6** with different Grignard reagents

Compound	R	Nucleophile	Isolated yield (%)
9	Ethyl	C_2H_5MgBr/CuI	69
10	Dodecyl	$C_{12}H_{25}MgBr/CuI$	72
11	Isopropyl	C_3H_7Mg/CuI	61
12	Cyclohexyl	$C_6H_{11}MgBr/CuI$	75
13	Phenyl	C_6H_5MgBr/CuI	<15

The synthesis of (3*S*,4*S*)-5-cyclohexyl 4-hydroxy 3-amino pentanoic acid, an isomeric analogue of the biologically relevant (3*S*,4*S*)-cyclohexylstatine,[31] was then carried out (Scheme 5). First, we chose to open the lactone moiety under basic conditions and then to remove, by hydrogenolysis, the Cbz protecting group. However, treatment of **12** under alkaline conditions (K_2CO_3, NaOH) either in MeOH/H_2O or acetone/H_2O gave a mixture of products. The major product was assigned the structure 1,3-oxazinane-2,6 dione derivative **14,** based on ^1H and ^{13}C NMR and mass spectral data. Notably, the reaction performed with KOH (3 equiv.) in MeOH at 40°C afforded **14** in almost quantitative yield within 30 min. Ring opening of the lactone might have occurred by intramolecular attack of the carbamate followed by elimination of the benzyl group as benzyl alcohol, which was actually present in the reaction mixture. To circumvent this unwanted result we changed the sequence of reactions. The free amine **15** was thus obtained by hydrogenolysis (1 atm, 10% Pd/C, AcOEt) of the *N*-protected lactone **12** in quantitative yield, and was converted into the free amino acid **16** under alkaline conditions (0.1N NaOH, pH 9) in 74% yield.



Scheme 5.

In conclusion we have developed a convenient route to α-unsubstituted γ-functionalized *syn*-β-amino-γ-hydroxy amino acids by the combination of the stereoselective iodolactonization of (*S*)-3-*N*-benzyloxycarbonyl 4-pentenoic acid, and the replacement of the iodide in the compound **6** by CuI mediated cross-coupling addition of Grignard reagents. The feasibility of this approach was demonstrated by the synthesis of the (3*S*,4*S*)-3-amino-4-hydroxy-5-cyclohexyl pentanoic acid. Further use of the iodo-lactone **6** as a key intermediate for the total synthesis of biologically active natural products is at present under investigation.

3. Experimental

Melting points were determined in open capillaries using a Büchi apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were run on a Varian Gemini 300 spectrometer at 300 and 75 MHz, respectively, in $CDCl_3$, unless otherwise reported. Chemical shifts (δ scale) are relative to TMS as internal reference. The proton chemical-shifts in ^1H NMR spectra were confirmed by COSY and HETCOR experiments. MS spectra for **14** were recorded with a Hewlett–Packard HP 5980A spectrometer equipped with a Data System 5934 A. Optical rotations were determined on

a Perkin–Elmer 243 polarimeter at 23°C (concentration g/100 ml). All solvents were dried prior to use.[32] Thin layer chromatography was performed on Merck silica gel 60 F_{254} glass plates.

3.1. tert-*Butyl-(3*S*)-3-{[(benzyloxy)carbonyl]amino}-4-hydroxy-butanoate **2**

To a stirred solution of *Z*-L-aspartic 4-*tert*-butyl ester **1**[20] (6.47 g, 20 mmol) in THF (100 ml) at −15°C (ice + NaCl), *N*-methylmorpholine (2.2 ml, 20 mmol) was added followed by ethyl chloroformate (1.91 ml, 20 mmol). The reaction mixture was stirred at the same temperature for 15 min, and $NaBH_4$ (2.26 g, 60 mmol) was added followed by addition of MeOH (200 ml) over a period of 30 min at −15°C. The solution was stirred for 15 min and neutralized with 1N HCl. The organic solvents were evaporated under reduced pressure and the residue was extracted with EtOAc (3×150 ml). The combined organic phase was washed with 1N HCl (100 ml), H_2O (2×100 ml), 5% aqueous $NaHCO_3$ (2×100 ml), dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc:*n*-hexane 1:1) to give the amino alcohol **2** (5.51 g, 89%) as an oil; $[\alpha]_D = -19.6$ (c = 1.2, $CHCl_3$); $[\alpha]_D$[15a] = −19.3 (c = 2.03, $CHCl_3$); ^{1}H NMR spectra as reported.[15a,21]

3.2. tert-*Butyl-(3*S*)-3-{[(benzyloxy)carbonyl]amino}-4-pentenoate **3**

Oxalyl chloride (3 ml, 33 mmol) was dissolved in CH_2Cl_2 (50 ml), the mixture was cooled to −63°C and a solution of dry DMSO (5.61 ml, 66 mmol) in CH_2Cl_2 (10 ml) was added dropwise during 15 min.

The amino alcohol **2** (6.18 g, 20.0 mmol) in CH_2Cl_2 (20 ml) was added dropwise during 10 min, the resulting solution was stirred for 10 min at −63°C, and a solution of *N*,*N*-diisopropyl ethyl amine (20.9 g, 0.12 mol) in CH_2Cl_2 (50 ml) was added dropwise during 15 min. After 20 min water (5.0 ml) was added to the vigorously stirred solution at −63°C. The resulting slurry was poured in Et_2O (300 ml) and washed with 20% aqueous $KHSO_4$ (2×100 ml), the layers were separated and the aqueous layer was back-extracted with Et_2O (2×100 ml). The combined organic layers were washed with brine solution (2×50 ml), dried over Na_2SO_4 and the solvent was removed under reduced pressure (T = 20°C) to afford the crude aldehyde, which was immediately used in the next reaction without any further purification.

Methyl triphenylphosphonium bromide (12.52 g, 35 mmol) was suspended in dry THF (300 ml) at room temperature and KHMDS (0.5 M in toluene, 67.2 ml, 33.6 mmol) was added. The resultant yellow solution was stirred at room temperature for 1 h, then cooled to −78°C and a solution of the above aldehyde in dry THF (20 ml) was added dropwise. The temperature of the cooling bath was slowly increased to room temperature over 1 h and then stirred for a further 2 h. The reaction was quenched with MeOH (30 ml) and the resulting mixture was poured into a mixture of sat. potassium sodium tartrate and water (1:1, 500 ml). Extraction with Et_2O (3×250 ml), drying over Na_2SO_4 and evaporation under reduced pressure gave the crude olefin. The residue was purified by silica gel chromatography using EtOAc:*n*-hexane (20:80) as eluent to give **3** (4.9 g, 80%) as an oil; $[\alpha]_D = +26.8$ (c = 3.3, $CHCl_3$); ^{1}H NMR δ: 7.35 (5H, s, C_6H_5), 5.85 (1H, ddd, J = 17.0, 10.0 and 5.0 Hz, CH=), 5.54 (1H, br d, J = 8.0 Hz, NH), 5.22 (1H, br d, J = 17.0 Hz, =CH_AH$_B$), 5.14 (1H, br d, J = 10.0 Hz, =CH$_A$$H_B$), 5.11 (1H, s, OCH_2), 4.55 (1H, dq, J = 8.0 and 6.0 Hz, CHN), 2.56 (1H, dd, J = 15.0 and 6.0 Hz, CH_CH$_D$), 2.50 (1H, dd, J = 15.0 and 6.0 Hz, CH$_C$$H_D$), 1.43 [9H, s, $(CH_3)_3C$]; ^{13}C NMR δ: 170.31 (s, COO), 155.61 (s, CON), 136.99 (d, CH=), 136.49 (s, C_6H_5), 128.48 (4×d, C_6H_5), 128.06 (d, C_6H_5), 115.44

(d, $=CH_2$), 81.33 [s, $(CH_3)_3CO$], 66.72 (t, OCH_2), 50.01 (d, CHN), 40.09 (t, CH_2), 28.03 [q, $(CH_3)_3C$]. Anal. calcd for $C_{17}H_{23}NO_4$: C = 66.86, H = 7.59, N = 4.59; found: C = 66.90, H = 7.60, N = 4.57.

3.3. tert-*Butyl-(3*S*)-3-{[(benzyloxy)carbonyl]amino}-4-[methoxy(methyl)amino]-4-oxobutanoate **4**

A solution of acid **1**[20] (1.94 g, 6 mmol) in CH_2Cl_2 (25 ml) was cooled to −15°C and *N*,*O*-dimethyl hydroxyl amine hydrochloride (0.6 g, 6.15 mmol), *N*-methylmorpholine (0.68 ml, 6.15 mmol) were added, followed by *N*-(3-dimethylamino propyl)-*N*-ethylcarbodiimide hydrochloride (1.18 g, 6.15 mmol) in small portions. The reaction was stirred for 1 h at room temperature and then ice cooled 1 M HCl (8 ml) was added. The aqueous layer was extracted with CH_2Cl_2 (2×25 ml) and the combined organic layers were washed with H_2O (50 ml), sat. $NaHCO_3$ (25 ml) dried over Na_2SO_4 and concentrated under reduced pressure to give **4** as a colourless solid (1.98 g, 90%), which was used without any further purification. An analytical sample of hydroxamate was obtained by crystallization in an EtOAc/*n*-hexane mixture; m.p. 75°C; $[\alpha]_D = -19.4$ (c = 2.27, MeOH); ^{1}H NMR δ: 7.34 (5H, s, C_6H_5), 5.54 (1H, br d, J = 8.0 Hz, NH), 5.13 (1H, d, J = 12.0 Hz, OCH_AH_B) 5.08 (1H, d, J = 12.0 Hz, OCH_AH_B), 5.03 (1H, ddd, J = 9.0, 7.0 and 5.0 Hz, CHN), 3.78 (3H, s, OCH_3), 3.22 (s, NCH_3), 2.71 (1H, dd, J = 15.0 and 5.0 Hz, CH_CH_DCO), 2.55 (1H, dd, J = 15.0 and 7.0 Hz, CH_CH_DCO), 1.42 [9H, s, $(CH_3)_3C$]; ^{13}C NMR δ: 169.20 (s, COO), 155.70 (s, CON), 136.32 (s, C_6H_5) 128.45 (2×d, C_6H_5), 128.07 (2×d, C_6H_5), 127.99 (d, C_6H_5), 81.38 [s, $(CH_3)_3CO$], 66.89 (t, OCH_2), 61.59 (q, OCH_3), 48.44 (d, CHN), 38.35 (t, CH_2CO), 32.38 (q, NCH_3), 27.97 [q, $(CH_3)_3C$]. Anal. calcd for $C_{18}H_{26}NO_6$: C = 61.35, H = 7.44, N = 3.97; found: C = 61.38, H = 7.45, N = 3.97.

3.4. *Preparation of (3*S*)-*tert*-Butyl-3(*S*)-{[(benzyloxy)carbonyl]amino}-4-pentenoate **3** from the hydroxamate **4**

Hydroxamate **4** (1.83 g, 5 mmol), in dry THF (20 ml), was cooled (−5°C, ice + NaCl) and a solution of $LiAlH_4$ (1.0 M in THF, 2.5 ml, 2.5 mmol) was added dropwise over 10 min. The mixture was stirred for 30 min at the same temperature, then the reaction was cooled to −15°C and sat. aqueous $KHSO_4$ (15 ml) was added carefully followed by addition of Et_2O (50 ml). The mixture was stirred for additional 15 min and the organic layer separated, dried over Na_2SO_4 and concentrated under vacuum to give the corresponding α-amino aldehyde, which was immediately used without any further purification. The amino aldehyde was subjected to the Wittig methylation reaction following the above procedure to give **3** (1.3 g, 78%) as an oil.

3.5. *(3*S*)-3-{[(Benzyloxy)carbonyl]amino}-4-pentenoic acid **5***

To a solution of the *tert*-butyl ester **3** (3.97 g, 13 mmol) in CH_2Cl_2 (80 ml) at 0°C was added CF_3COOH (6.5 ml) and the reaction mixture was stirred at room temperature until the starting material was consumed. The mixture was then concentrated under reduced pressure, the residue was treated with Et_2O (50 ml) and concentrated under vacuum to give the acid **5** (3.23 g, 99%) as a colourless solid. M.p. 108–109°C; $[\alpha]_D = +12.0$ (c = 1.7, MeOH). ^{1}H NMR (T = 55°C) δ: 7.33 (5H, s, C_6H_5), 5.85 (1H, ddd, J = 17.0, 10.0 and 5.5 Hz, CH=), 5.48 (1H, br d, J = 8.0 Hz, NH), 5.22 (1H, br d, J = 17.0 Hz, $=CH_AH_B$), 5.14 (1H, br d, J = 10.0 Hz, $=CH_AH_B$), 5.11 (2H, s, OCH_2), 4.57 (1H, dq, J = 8.0 and 5.5 Hz, CHN), 2.66 (2H, dd, J = 5.5 Hz, CH_2); ^{13}C NMR δ: 175.83 (s, COO), 155.83 (s, CON), 136.53 (d, CH=), 136.23 (s, C_6H_5) 128.53 (2×d, C_6H_5), 128.18

(2×d, C_6H_5), 128.08 (d, C_6H_5), 116.03 (t, $=CH_2$), 67.03 (t, OCH_2), 49.68 (d, CHN), 38.82 (t, CH_2). Anal. calcd for $C_{13}H_{15}NO_4$: C = 62.64, H = 6.07, N = 5.62; found: C = 62.67, H = 6.09, N = 5.61.

3.6. *Benzyl (2R,3S)-2-(iodomethyl)-5-oxotetrahydrofuran-3-ylcarbamate* **6**

A solution of the unsaturated acid **5** (1.25 g, 5 mmol) and AgOTf (1.29 g, 5 mmol) in dry CH_3CN (18 ml) was cooled to −40 °C and I_2 (4.75 g, 15 mmol) was added in small portions. The reaction mixture was stirred at the same temperature for 3.5 h in the dark, then diluted with $CHCl_3$ (100 ml) and extracted with aqueous $Na_2S_2O_3$ (0.25 M, 3×50 ml). The aqueous solution was extracted with $CHCl_3$ (2×50 ml) and the combined organic extracts were washed with H_2O (2×100 ml), sat. aqueous $NaHCO_3$ (2×50 ml), H_2O (100 ml), dried over Na_2SO_4 and concentrated under reduced pressure to give **6** and **7** (1.82 g, 97%) as a 15:1 diastereomeric mixture, as judged by ^1H NMR and HPLC [column: SiO_2 LiChrosorb Si 60, 250×4 mm ID; eluent: $CHCl_3$:*n*-hexane 60:40 + 0.3% MeOH; T = 30°C, t_R (min) **6** = 7.3, $K'_6 = 2.32$; t_R (min) **7** = 8.3, $K'_7 = 2.77$]. A single crystallization (AcOEt:*n*-hexane 1:2.5) gave compound **6** (73% yield from **5**) as a colourless solid in a d.e. = 97.5% as judged by HPLC. M.p. 131–132°C; $[\alpha]_D = -43.6$ (c = 1.3, $CHCl_3$); ^1H NMR and ^{13}C NMR are reported in the text. Anal. calcd for $C_{13}H_{14}NO_4I$: C = 41.62, H = 3.76, N = 3.73; found: C = 41.61, H = 3.76, N = 3.74.

3.7. *General procedure for nucleophilic displacement using Grignard reagents/CuI*

CuI (1.5 mmol) was placed in a flame dried, round-bottomed flask which was flushed with nitrogen and charged with dry THF (10 ml). The suspension was cooled to −50°C (CO_2 + acetone) and the Grignard reagent (3 mmol) was added over 10 min. The mixture was stirred at the same temperature for 1 h then iodo-lactone **6** (0.376 g, 1 mmol) in THF (4 ml) was added dropwise over 5 min. The mixture was stirred at −50°C for 1.5 h, quenched by adding satd. NH_4Cl, stirred for additional 10 min and extracted with AcOEt (3×50 ml). The combined extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography using AcOEt:*n*-hexane (7:3) as solvent.

3.8. *Benzyl (2S,3S)-2-propyl-5-oxotetrahydrofuran-3-ylcarbamate* **9**

M.p. 97–98°C; $[\alpha]_D = -47.1$ (c = 1.2, $CHCl_3$); ^1H NMR δ: 7.35 (5H, s, C_6H_5), 5.23 (1H, br d, $J = 8.0$ Hz, NH), 5.12 (2H, s, OCH_2), 4.67 (1H, tdd, $J = 8.0$, 4.5 and 3.0 Hz, CHN), 4.50 (1H, dt, $J = 9.0$ and 4.5 Hz, CHO), 2.89 (1H, dd, $J = 17.0$ and 8.0 Hz, CH_AH_BCO), 2.47 (1H, dd, $J = 17.0$ and 3.0 Hz, CH_AH_BCO), 1.73–1.35 (4H, m, 2×CH_2), 0.94 (3H, t, $J = 7.0$ Hz, CH_3); ^{13}C NMR δ: 174.75 (s, COO), 155.79 (s, NCO), 135.99 (s, C_6H_5), 128.61, 128.38, 128.14 (2×d, 2×d, d, C_6H_5), 83.15 (d, CHO), 67.27 (t, OCH_2), 50.64 (d, CHN), 36.85 (t, CH_2CO), 31.21 (t, CH_2), 18.94 (t, CH_2), 13.81 (q, CH_3). Anal. calcd. for $C_{15}H_{19}NO_4$: C = 64.97, H = 6.91, N = 5.05; found: C = 65.00, H = 6.93, N = 5.04.

3.9. *Benzyl (2S,3S)-2-tridecyl-5-oxotetrahydrofuran-3-ylcarbamate* **10**

M.p. 83–84°C; $[\alpha]_D = -25$ (c = 1.7, $CHCl_3$); ^1H NMR δ: 7.35 (5H, s, C_6H_5), 5.22 (1H, br d, $J = 8.0$ Hz, NH), 5.11 (2H, s, OCH_2), 4.57 (1H, m, $J = 23.0$ Hz, CHN), 4.50 (1H, dt, $J = 8.0$ and 4.5 Hz, CHO), 2.89 (1H, dd, $J = 17.5$ and 7.5 Hz, CH_AH_BCO), 2.47 (1H, dd, $J = 17.0$ and 2.5 Hz, CH_AH_BCO), 1.64–1.26 (24H, m, 12×CH_2), 0.88 (3H, t, $J = 7.0$ Hz, CH_3); ^{13}C NMR δ: 174.76 (s,

COO), 155.76 (s, NCO), 135.98 (s, C_6H_5), 128.58, 128.36, 128.12 (2×d, 2×d, d, C_6H_5), 83.36 (d, CHO), 67.27 (t, OCH_2), 50.61 (d, CHN), 36.88 (t, CH_2CO), 31.92, 29.68, 29.64, 29.61, 29.52, 29.38, 29.34, 29.18, 25.57, 22.67 (t, t, 2×t, t, t, t, 2×t, t, t, t, 12×CH_2), 14.10 (t, CH_3). Anal. calcd for $C_{25}H_{39}NO_4$: C = 71.91, H = 9.41, N = 3.35; found: C = 71.90, H = 9.40, N = 3.33.

3.10. *Benzyl (2S,3S)-2-isobutyl-5-oxotetrahydrofuran-3-ylcarbamate* **11**

M.p. 90°C; $[\alpha]_D = -59.7$ (c = 0.72, $CHCl_3$); ^{1}H NMR (CD_3COCD_3) δ: 7.39–7.29 (5H, s, C_6H_5), 7.01 (1H, br s, NH), 5.13 (1H, d, J = 12 Hz, CH_AH$_B$OCO), 5.07 (1H, d, J = 12 Hz, CH$_A$$H_B$OCO), 4.69 (1H, dt, J = 8.0 and 5.0 Hz, CHO), 4.56 (1H, tdd, J = 8.0, 5.0 and 3.0 Hz, CHN), 3.01 (1H, dd, J = 17.0 and 8.0 Hz, CH_CH$_D$CO), 2.42 (1H, dd, J = 17.0 and 3.0 Hz, CH$_C$$H_D$CO), 1.77 (1H, m, ΣJ = 56 Hz, CH), 1.62 (1H, ddd, J = 14.0, 9.0 and 5.0 Hz, CH_EH$_F$), 1.43 (1H, ddd, J = 14.0, 8.0 and 4.0 Hz, CH$_E$$H_F$), 0.93 (3H, J = 6.5, CH_3), 0.91 (3H, d, J = 6.5 Hz, CH_3); ^{13}C NMR δ: 175.59 (s, COO), 155.93 (s, NCO), 136.98 (s, C_6H_5), 129.19, 128.65, 128.53 (2×d, 2×d, d, C_6H_5), 82.02 (d, CHO), 66.72 (t, OCH_2), 51.57 (d, CHN), 38.72 (t, CH_2CO), 36.38 (t, CH_2), 25.63 (q, CH_3), 23.47 (d, CH), 22.26 (q, CH_3). Anal. calcd for $C_{16}H_{21}NO_4$: C = 65.96, H = 7.27, N = 4.81; found: C = 65.98, H = 7.28, N = 4.80.

3.11. *Benzyl (2S,3S)-2-cyclohexylmethyl-5-oxotetrahydrofuran-3-ylcarbamate* **12**

M.p. 112°C; $[\alpha]_D = -46.9$ (c = 3.1, $CHCl_3$); ^{1}H NMR δ: 7.35 (5H, s, C_6H_5), 5.37 (1H, br d, J = 8.0 Hz, NH), 5.13 (H, d, J = 12 Hz OCH_AH$_B$), 5.08 (H, d, J = 12.0 Hz OCH$_A$$H_B$), 4.62 (1H, td, J = 7.0 and 4.0 Hz, CHO), 4.54 (1H, tt, J = 8.0 and 3.5 Hz, CHN), 2.87 (1H, dd, J = 17.0 and 8.0 Hz, CH_CH$_D$CO), 2.47 (1H, dd, J = 17.0 and 3.0 Hz, CH$_C$$H_D$CO), 1.61, 1.39 (1H each, m, CH_2), 1.41 (1H, m, CH), 1.69, 1.62, 0.86, 0.79 (1H each, m, 2×α-CH_2), 1.54, 1.28 (1H each, m, γ-CH_2), 1.65, 1.60, 1.17, 1.09 (1H each, m, 2×β-CH_2); ^{13}C NMR δ: 175.07 (s, COO), 155.82 (s, NCO), 136.04 (s,C_6H_5), 128.57, 128.31, 128.08 (2×d, 2×d, d, C_6H_5), 81.25 (d, CHO), 67.16 (t, OCH_2), 50.93 (d, CHN), 36.83 (t, CH_2CO), 36.54 (t, CH_2), 34.09 (d, CH), 33.90, 32.56 (t each, 2×α-CH_2), 26.33 (t, γ-CH_2), 26.10, 25.97 (t each, 2×β-CH_2). Anal. calcd for $C_{19}H_{25}NO_4$: C = 68.86, H = 7.60, N = 4.23; found: C = 68.87, H = 7.62, N = 4.21.

3.12. *Benzyl (2S,3S)-2-benzyl-5-oxotetrahydrofuran-3-ylcarbamate* **13**

M.p. = 54–55°C; $[\alpha]_D = -56.2$ (c = 0.3, $CHCl_3$); ^{1}H NMR δ: 7.97–7.33 (10H, m, 2×C_6H_5), 5.52 (1H, br d, J = 8.0 Hz, NH), 5.10 (1H, d, J = 12 Hz, OCH_AH$_B$), 5.07 (1H, d, J = 12 Hz, OCH$_A$$H_B$), 4.43 (1H, dt, J = 8.0 and 3.5 Hz, CHO), 3.97 (1H, m, CHN), 2.97 (1H, dd, J = 17.0 and 8.0 Hz, CH_AH$_B$CO), 2.85 (1H dd, J = 14.0 and 9.0 Hz, CH_CH$_D$C$_6$H$_5$), 2.68 (1H, dd, J = 14.0 and 5.0 Hz, CH$_C$H$_D$C$_6$H$_5$), 2.35 (1H, dd, J = 17.0 and 3.0 Hz, CH$_A$$H_B$CO); ^{13}C NMR δ: 175.80 (s, OCO), 155.11 (s, NCO), 137.62, 136.84 (s each, 2×C_6H_5), 128.76, 128.58, 128.28, 128.21, 128.06 (2×d each, 2×C_6H_5), 82.37 (d, CHO), 67.25 (t, OCH_2), 50.72 (d, CHN), 40.78 (t, CH_2CO), 32.83 (t, $CH_2C_6H_5$). Anal. calcd for $C_{19}H_{19}NO_4$: C = 70.14, H = 5.89, N = 4.30; found: C = 70.20, H = 5.92, N = 4.31.

3.13. *(4S)-4-[(1S)-2-Cyclohexyl-1-hydroxyethyl]1,3-oxazinane-2,6-dione* **14**

To a stirred solution of lactone **12** (0.124 g, 0.38 mmol) in methanol (6 ml) was added solid KOH (64 mg, 1.14 mmol) and the mixture was stirred at 40°C for 30 min. The solvent was

removed under reduced pressure, the residue was dissolved in H_2O, extracted with CH_2Cl_2 (2×5 ml) and acidified at pH 4 with acetic acid. The aqueous solution was extracted with CH_2Cl_2 (3×20 ml), washed with H_2O (10 ml), sat. NaCl (20 ml), H_2O (10 ml) and dried over Na_2SO_4. Removal of the solvent under reduced pressure afforded the 1,3-oxazinane-2,6-dione **14** (88 mg, 96%). M.p. 119–120°C; $[\alpha]_D = -82$ (c = 1.4, $CHCl_3$); ^{1}H NMR δ: 4.32 (1H, p, J = 5.0 Hz, CHO), 3.81 (1H, dt, J = 9.0 and 5.0 Hz, CHN), 2.65 (1H, dd, J = 17.0 and 5.0 Hz, CH_AH$_B$CO), 2.60 (1H, dd, J = 17.0 and 9.0 Hz, CH$_A$$H_B$CO), 1.62, 1.40 (1H each, m, CH_2), 1.68, 1.57, 0.93, 0.84 (1H each, m, 2×α-CH_2), 1.67, 1.63, 1.22, 1.10 (1H each, m, 2×β-CH_2), 1.42 (1H, m, CH), 1.40, 1.13 (1H each, m, γ-CH_2); ^{13}C NMR δ: 174.08 (s, OCO), 160.33 (s, NCO), 80.17 (d, CHO), 54.95 (d, CHN), 42.12 (t, CH_2), 39.17 (t, CH$_2$CO), 33.82 (d, CH), 33.69, 32.72 (t, 2×α-CH_2), 26.32 (t, γ-CH_2), 26.08, 25.97 (t each, 2×β-CH_2).

MS (CI, CH_4) m/z (relative intensity): 242 $[MH]^+$ (100), 198 $[MH-CO_2]$ (52), 181 $[198-NH_3]^+$ (49), 163 $[183-H_2O]^+$ (44), 135 [163−CO] (17), 121 $[M/2]^{2+}$ (72). Anal. calcd for $C_{12}H_{19}NO_4$: C = 59.73, H = 7.94, N = 5.80; found: C = 59.74, H = 7.96, N = 5.81.

3.14. (4S,5S)-4-Amino-5-(cyclohexylmethyl)-dihydrofuran-2(3H)-one **15**

To a well stirred solution of the compound **12** (110 mg, 0.33 mmol) in dry AcOEt (4 ml) was added 10% Pd/C (15 mg) and the solution was stirred under H_2 (1 atm) until the TLC showed no remaining starting material. The mixture was filtered through a short pad of Celite and concentrated under reduced pressure to give the amine **15** (64 mg, 98%) as a colourless solid. M.p. 39°C; $[\alpha]_D = -86.9$ (c = 1.2, $CHCl_3$); ^{1}H NMR δ: 4.59 (1H, dt, J = 9.5 and 4.0 Hz, CHO), 3.71 (1H, ddd, J = 6.0, 4.5 and 2.0 Hz, CHN), 2.80 (1H, dd, J = 18.0 and 6.0 Hz, CH_AH$_B$CO), 2.34 (1H, dd, J = 18.0 and 2.0 Hz, CH$_A$$H_B$CO), 1.63, 1.39 (1H each, m, CH_2), 1.46 (1H, m, CH), 1.77, 1.60, 0.95, 0.85 (1H each, m, 2×α-CH_2), 1.45, 1.10 (1H, m, γ-CH_2), 1.66, 1.63, 1.23, 1.11 (1H each, m, 2×β-CH_2); ^{13}C NMR δ: 175.96 (s, OCO), 81.90 (d, CHO), 50.90 (d, CHN), 39.57 (t, CH$_2$CO), 36.27 (t, CH_2), 34.34 (d, CH), 33.99, 32.87 (t each, 2×α-CH_2), 26.38 (t, γ-CH_2), 26.17, 26.06 (t each, 2×β-CH_2). Anal. calcd for $C_{11}H_{19}NO_2$: C = 66.97, H = 9.71, N = 7.10; found: C = 66.96, H = 9.71, N = 7.11.

3.15. (3S,4S)-3-Amino-4-hydroxy-5-cyclohexyl pentanoic acid **16**

A solution of the γ-lactone **15** (50 mg, 0.255 mmol) in methanol (5 ml) was taken to pH 9 by adding 0.1N NaOH solution. The mixture was stirred at this pH by addition of 0.1N NaOH solution until TLC showed no remaining starting material (approx. 5 h). The mixture was then acidified to pH 6.5 with 0.1N HCl before removing the methanol. The aqueous solution was purified by passing through a column of Amberlite XAD-2 resin, eluting first with water, followed by methanol. Fractions containing the acid were combined and concentrated under reduced pressure to give **16** (40 mg, 74%) as a colourless solid. M.p. 208–210°C; $[\alpha]_D = -51.1$ (c = 0.45, MeOH); ^{1}H NMR (CD_3OD, T = 55°C) δ: 3.69 (1H, ddd, J = 8.0, 6.0 and 5.0 Hz, CHO), 3.17 (1H, dt, J = 9.0 and 5.0 Hz, CHN), 2.45 (1H, dd, J = 16.0 and 5.0 Hz, CH_AH$_B$CO), 2.36 (1H, dd, J = 16.0 and 9.0 Hz, CH$_A$$H_B$CO), 1.85, 1.67, 1.03, 0.91 (1H each, m, 2×α-CH_2), 1.75, 1.70, 1.28, 1.26 (1H each, m, 2×β-CH_2), 1.69, 1.35 (1H each, m, CH_2), 1.54 (1H, m, CH), 1.34, 1.20 (1H each, m, γ-CH_2); ^{13}CNMR δ: 168.54 (s, COOH), 70.06 (d, CHO), 56.56 (d, CHN), 43.02 (t, CH$_2$CO), 37.82 (t, CH_2), 35.97, 34.01 (t each, 2×α-CH_2), 35.55 (d, CH), 28.13 (t, γ-CH_2), 27.92, 27.67 (t each, 2×β-CH_2). Anal. calcd for $C_{11}H_{21}NO_3$: C = 61.37, H = 9.83, N = 6.51; found: C = 61.36, H = 9.81, N = 6.50.

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