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TETRAHEDRON: *ASYMMETRY*

Stereoselective synthesis of β-amino-γ-butyrolactones†

Jürgen Roos‡ and Franz Effenberger*

Institut für Organische Chemie der Universität Stuttgart, Pfaffenwaldring 55, D-70569 Stuttgart, Germany

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Abstract—A novel synthesis of optically active β-amino-γ-butyrolactones is described. *O*-Silylated (*R*)-cyanohydrins (*R*)-**3** (derived from aldehydes **1** by (*R*)-hydroxynitrile lyase ((*R*)-PaHNL)-catalyzed addition of HCN) were reacted with allyl Grignard to give amino alcohols (4*R*,5*S*)-**5** after reduction. In the addition of crotyl Grignard reagent, workup conditions are decisive for the formation of amino alcohol **8**, which was isolated as a diastereoisomeric mixture; the acetylated main diastereoisomer (3*S*,4*R*,5*R*)-**10** was separated. Ozonolysis of the acetylated amino alcohols (4*S*,5*R*)-**7a**,**b** and (3*S*,4*S*,5*R*)-**10** affords the aldehydes **12a**–**c**, which were directly oxidized with CrO_3 in dilute H_2SO_4 to yield the β-acetamido-γ-acetoxycarboxylic acids (3*S*,4*R*)-**13a**,**b** and (2*R*,3*S*,4*R*)-**13c**. Compounds **13** cyclized spontaneously under acidic conditions to afford β-acetamido-γ-butyrolactones (4*S*,5*R*)-**14a**,**b** and (3*R*,4*S*,5*R*)-**14c**.

1. Introduction

β-Amino-γ-butyrolactones and the corresponding open-chain β-amino-γ-hydroxycarboxylic acids, respectively, are known as components of many biologically active natural products and pharmaceuticals. Thus, this structural unit has been found in antifungal or antibiotic peptides,[2,3] in antimalarial alkaloids,[4] gastroprotective drugs,[5] as well as in new inhibitors of phosphodiesterase[6] and HIV-1 protease.[7] Furthermore, β-amino-γ-butyrolactones are important intermediates in the preparation of a variety of interesting β-amino acids[8] and β-lactam antibiotics.[9]

Only few generally applicable stereoselective syntheses for β-amino-γ-butyrolactones have been described in the literature until now. In general, optically active compounds derived from the 'chiral pool' serve as starting materials. For example, optically active 2-substituted β-amino-γ-lactones have been prepared from aspartic acid with relatively high diastereoselectivity and conservation of the configuration at the stereogenic α-C center of aspartic acid.[8,9a,c,10] Further approaches to specially substituted β-amino-γ-lactones start from α,β-unsaturated γ-hydroxycarboxylates or lactones derived from carbohydrates.[9d,11]

Optically active cyanohydrins, which are readily available using enzymes as catalysts,[12] offer an access to β-amino-γ-butyrolactones independent of the limited compounds of the 'chiral pool'. A methodology already developed[13] involves Reformatsky reaction of *O*-protected cyanohydrins to enamino esters, subsequent reduction with $NaBH_3CN$ to β-amino-γ-hydroxycarboxylates and acid-catalyzed ring closure to give 2-substituted β-amino-γ-butyrolactones in relatively good yields. Although the reduction of optically active enamino esters to β-amino-γ-hydroxycarboxylates occurs without racemization, the achieved diastereomeric ratios for the hydroxycarboxylates were not satisfying.[13] Therefore the reaction of optically active *O*-silylated cyanohydrins with allyl Grignard reagent has been investigated in this respect. The resultant addition products—unsaturated amino alcohols—should be converted to the corresponding β-amino-γ-hydroxycarboxylic acids, affording a generally applicable, stereoselective synthetic route to β-amino-γ-butyrolactones.

2. Results and discussion

2.1. Addition of Grignard reagents to *O*-silylated cyanohydrins (*R*)-3

The synthesis of chiral β-amino-γ-butyrolactones **14** starting from optically active cyanohydrins (*R*)-**2** is outlined in Scheme 1.

* Corresponding author. E-mail: franz.effenberger@po.uni-stuttgart.de

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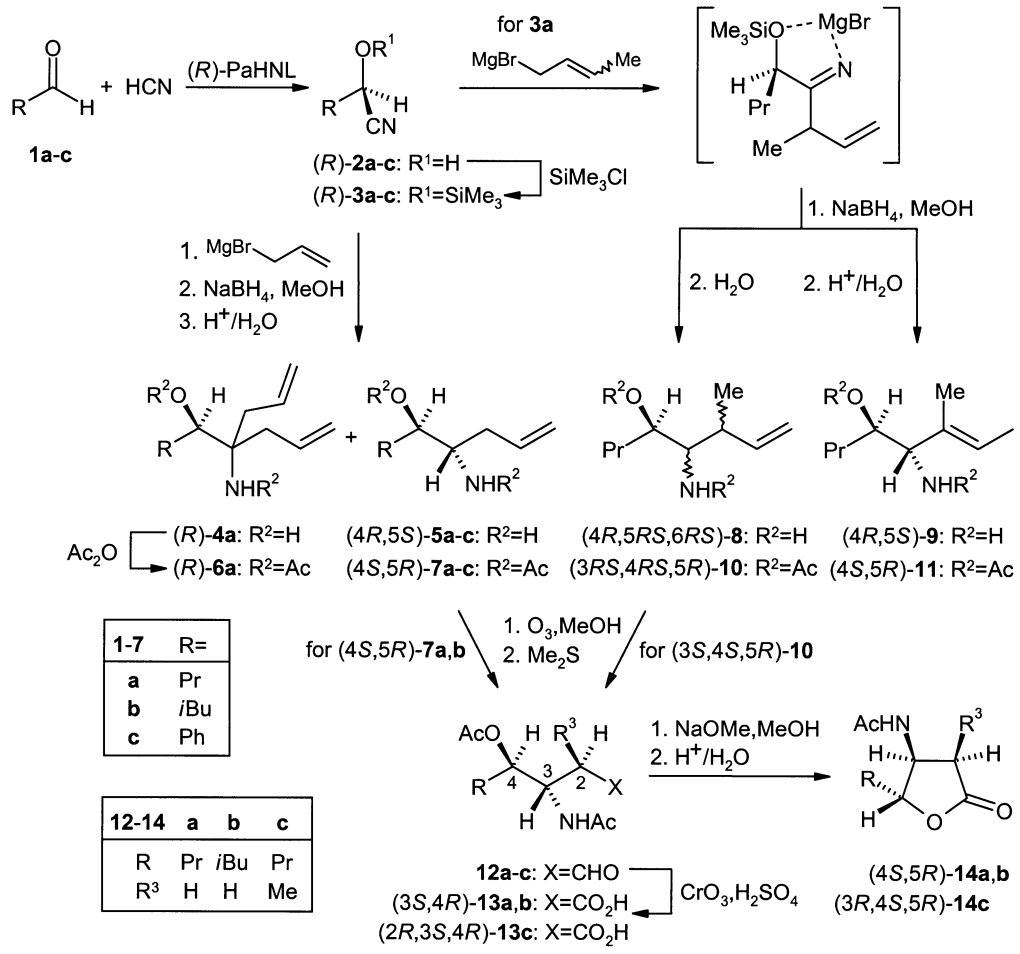


Scheme 1.

The (*R*)-cyanohydrins (*R*)-**2a**–**c**, easily accessible by (*R*)-PaHNL-catalyzed addition of HCN to aldehydes **1a**–**c**, were silylated with trimethylchlorosilane in the presence of pyridine[14] to give the *O*-trimethylsilylated cyanohydrins (*R*)-**3a**–**c** with 90–99% ee (Table 1). As described in a recent publication,[15] the 'CH_2CHO' moiety was introduced by reacting compounds (*R*)-**3a**–**c** with allyl Grignard. The resulting imino intermediates were hydrogenated in situ with $NaBH_4$ giving the amino alcohols (4*R*,5*S*)-**5a**–**c** with diastereomeric excesses of 75–99% (Table 1). Compounds (4*R*,5*S*)-**5a**–**c** were converted without further purification by treatment with acetic anhydride and catalytic amounts of DMAP in pyridine to yield the 4-acetamido-5-acetoxyalkenes (4*S*,5*R*)-**7a**–**c**. The diastereomeric excess of (4*S*,5*R*)-**7a** and (4*S*,5*R*)-**7b** could be improved from 89 and 70%, respectively, to 94 and 96% by recrystallization (Table 1). Because the Grignard reagent prepared from allyl bromide is very reactive,[15,16] a second mole of Grignard reagent reacted with the imino intermedi-

Table 1. Addition of allyl Grignard to silylated cyanohydrins (*R*)-**3**, reduction of the imino intermediates to amino alcohols (4*R*,5*S*)-**5** and subsequent acetylation to give 4-acetamido-5-acetoxyalkenes (4*S*,5*R*)-**7**

(*R*)-**3**		R.-time	Amino alcohols (4*R*,5*S*)-**5**			Acetamido-acetoxyalkenes (4*S*,5*R*)-**7**			
	ee (%)	(h)		Crude yield (%)	de (%)		Yield (%)	de (%)	$[\alpha]_D^{20}$ (*c* in $CHCl_3$)
3a	90	3	**5a**	81[a]	89	**7a**	78[b]	94[c]	+27.4 (1.0)
3b	94	4	**5b**	70	75	**7b**	79	96[d]	+14.0 (1.67)
3c	99	1.5	**5c**	87	99	**7c**	58	99	−49.6 (0.5)

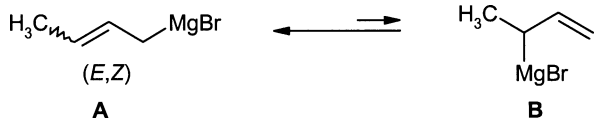
[a] As a mixture with (*R*)-**4a**.
[b] Acetylated carbinamine derivative (*R*)-**6a** was separated in 15% yield.
[c] After recrystallization from diisopropyl ether; 90% ee, $[\alpha]_D^{20} = +10.5$ (*c* 1.3, $CHCl_3$).
[d] After recrystallization from diisopropyl ether/petroleum ether.

ate derived of (*R*)-**3a**[15,17] to give the carbinamine derivative (*R*)-**4a** as a by-product in 15% yield. (*R*)-**4a** could be separated after acetylation to (*R*)-**6a** by recrystallization from diisopropyl ether (Table 1).

Although crotyl Grignard reagent, resembling the allyl Grignard in reactivity, exists in an equilibrium in favor of form **A**[18] (Scheme 2), the α-methylallyl product, resulting from reaction of isomer **B**, is formed almost exclusively in the addition to carbonyl compounds.[16,19]

The addition of the crotyl Grignard reagent to (*R*)-**3a** follows that of allyl Grignard, giving the corresponding imino intermediate (Scheme 1). The formation of amino alcohols **8** or (4*R*,5*S*)-**9** after diastereoselective reduction with $NaBH_4$ depends on the workup conditions. Under acidic conditions the terminal double bond isomerizes to give compound (4*R*,5*S*)-**9** exclusively in 79% yield. Acetylation and recrystallization afforded diastereomerically pure (4*S*,5*R*)-**11**. In basic medium, however, the amino alcohol (4*R*,5*RS*,6*RS*)-**8** was isolated in 81% yield as a diastereoisomeric mixture in a ratio of 62:21:11:6. After acetylation of **8**, the main diastereoisomer of **10** could be separated by chromatography on silica gel. The newly generated stereogenic center at C-3 was determined by X-ray crystallographic analysis[20] to be (*S*)-configured (Fig. 1). The main diastereoisomer therefore is (3*S*,4*S*,5*R*)-**10**.

Thus, the diastereoisomers could be assigned as follows: (3*S*,4*S*,5*R*)-**10**:(3*R*,4*S*,5*R*)-**10**:(3*S*,4*R*,5*R*)-**10**:(3*R*,4*R*,5*R*)-**10** = 62:21:11:6. Surprisingly, the (*S*)-configuration at C-3 is generated with relatively high selectivity[21] of 73:27, indicating an influence of the cyanohydrin configuration on the addition of the Grignard reagent. A prerequisite for an asymmetric induction is the coordination of magnesium to both the N- and O-atom, resulting in four possible transition states,[19b,21,22] from which the sterically favored state affords the two major diastereoisomers.



Scheme 2.

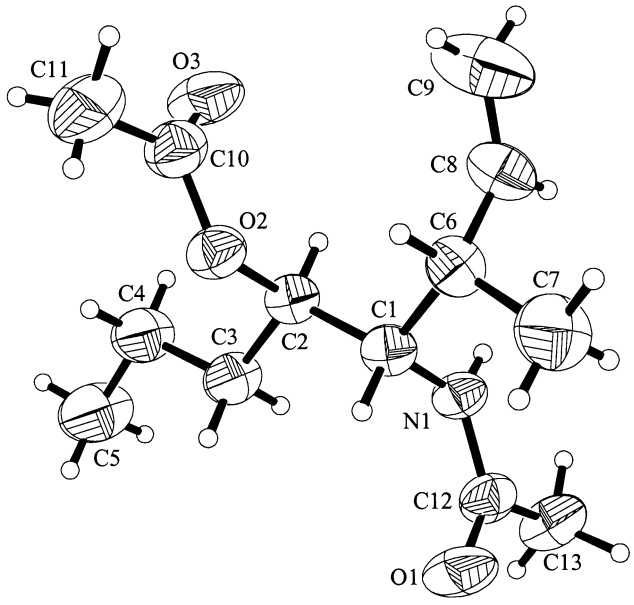


Figure 1. ORTEP view of the main diastereoisomer (3*S*,4*S*,5*R*)-**10**.

2.2. Ozonolysis, oxidation and cyclization of 4-acetamido-5-acetoxyalkenes 7a,b and 10 to β-acetamido-γ-butyrolactones 14

Oxidative cleavage of the terminal double bond in (4*S*,5*R*)-**7a**,**b** and (3*S*,4*S*,5*R*)-**10** was performed by ozonolysis to give the corresponding aldehydes (3*S*,4*R*)-**12a**,**b** and (2*R*,3*S*,4*R*)-**12c**. Crude aldehydes **12**—with the exception of (3*S*,4*R*)-**12a**, which was isolated in 87% yield—were oxidized without further purification with CrO_3 in dilute H_2SO_4,[23] yielding the β-acetamido-γ-acetoxycarboxylic acids (3*S*,4*R*)-**13a**,**b** and (2*R*,3*S*,4*R*)-**13c** (Scheme 1, Table 2). Other oxidants such as H_2O_2/formic acid[24] or $KMnO_4$[25] afforded either product mixtures or the oxidation reaction proceeded very slowly.

Selective cleavage of the ester function in the β-acetamido-γ-acetoxycarboxylic acids **13** with a solution of NaOMe/MeOH followed by spontaneous cyclization

Table 2. Oxidation of (4*S*,5*R*)-**7a**,**b** and (3*S*,4*S*,5*R*)-**10** to γ-acetoxycarboxylic acids (3*S*,4*R*)-**13a**,**b** and (2*R*,3*S*,4*R*)-**13c** followed by cyclization to β-acetamido-γ-butyrolactones (4*S*,5*R*)-**14a**,**b** and (3*R*,4*S*,5*R*)-**14c**

7, **10**		(3*S*,4*R*)- and (2*R*,3*S*,4*R*)-Carboxylic acids **13**				(4*S*,5*R*)- and (3*R*,4*S*,5*R*)-Butyrolactones **14**			
	de (%)		Yield (%)	de (%)[a]	$[\alpha]_D^{20}$ (*c* in solvent)		Yield (%)	de (%)[a]	$[\alpha]_D^{20}$ (*c* in $CHCl_3$)
7a	95	**13a**	54[b]	95[c]	+11.1 (0.36, $CHCl_3$)	**14a**	61	>95[c]	−14.4 (0.93)
7b	75	**13b**	67	75	+15.0 (0.5, $CHCl_3$)	**14b**	84	75	–
10	>99	**13c**	28	>95[c]	−7.25 (0.4, MeOH)	**14c**	83	>95[c]	+31.5 (0.4)

[a] Determined from ^1H NMR spectra.
[b] Referred to aldehyde (3*S*,4*R*)-**12a**, isolated in 87% yield.
[c] Only one diastereoisomer was detected by ^1H NMR and gas chromatography.

under acidic workup conditions afforded the β-acetamido-γ-butyrolactones (4*S*,5*R*)-**14a**,**b** and (3*R*,4*S*,5*R*)-**14c** (Scheme 1, Table 2). The configuration of the butyrolactones **14** could be confirmed by X-ray crystallographic analysis[20] of (4*S*,5*R*)-**14a** (Fig. 2).

3. Experimental

3.1. Materials and methods

Melting points were determined on a Büchi SMP-20 and are uncorrected. Unless otherwise stated, ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 250 F (250 MHz) and ARX 500 (500 MHz) in $CDCl_3$ with TMS as internal standard. Optical rotations were measured with a Perkin–Elmer polarimeter 241 LC in a thermostated glass cuvette ($l=10$ cm). Chromatography was performed using silica gel S (Riedel-de Haen), grain size 0.032–0.063 mm. Diastereomeric excess: GC separations were conducted using (a) capillary glass columns (20 m) with OV 1701 or PS086 with 10% permethylated β-cyclodextrin or Bondex-un-5,5-Et-105, carrier gas 0.4–0.5 bar hydrogen; (b) a Chiraldex B-TA (ICT) column (30 m×0.32 mm), carrier gas hydrogen. All solvents were dried and distilled.

3.2. Preparation of (*R*)-cyanohydrins, (*R*)-2

(*R*)-Cyanohydrins (*R*)-**2** were prepared according to Effenberger et al.,[26] but citrate buffer (pH 3.3) was used, and stirring at 4°C for 5–13 h.

3.3. Silylation of (*R*)-2 to (*R*)-3

Silylation was performed according to Effenberger et al.[14] (*R*)-4-methyl-2-trimethylsilyloxypentanenitrile (*R*)-**3b**: yield: 68%; bp 65°C/13 torr; $[\alpha]_D^{20}=+60.5$ (*c* 1.1, $CHCl_3$), 94% ee. ^{1}H NMR (250 MHz): δ 0.21 (s, 9H, $(CH_3)_3Si$), 0.94 (d, $J=6.3$ Hz, 3H, CH_3), 0.96 (d, $J=6.4$ Hz, 3H, CH_3), 1.58–1.92 (m, 3H, CH_2, 4-CH), 4.43 (dd, $J_1=6.3$ Hz, $J_2=7.8$ Hz, 1H, 2-CH). ^{13}C NMR (63 MHz): δ −0.36 ($Si(CH_3)_3$), 21.93, 22.53 (CH_3), 24.12 (C-4), 44.96 (C-3), 59.98 (C-2), 120.33 (CN). Anal. calcd for $C_9H_{19}NOSi$ (185.3): C, 58.32; H, 10.33; N, 7.56. Found: C, 57.90; H, 10.17; N, 7.33%.

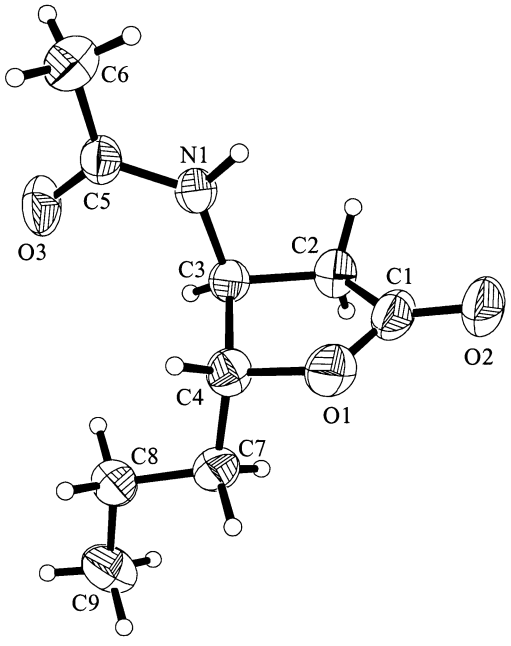


Figure 2. ORTEP view of 4-acetamido-5-propyltetrahydro-2-furanone (4*S*,5*R*)-**14a**.

3.4. Preparation of (4*R*,5*S*)-amino alcohols, (4*R*,5*S*)-5; general procedure

According to the method of Effenberger et al.[15] to a solution of allyl Grignard reagent in diethyl ether [prepared by slow addition of allyl bromide (59.1 mmol for **3a**, 61.5 mmol for **3b**, 81.8 mmol for **3c**) to equimolar amounts of Mg in diethyl ether] was added dropwise compound **3a**–**c** (27.3–30.2 mmol) over 15 min. After stirring for the time given in Table 1 (TLC control), the reaction mixture was cooled to −78°C. Methanol (40 mL for **3b**,**c**, 90 mL for **3a**) was added followed by $NaBH_4$ (ca. 2 equiv. referred to **3a**,**c**, 1 equiv. referred to **3b**) in three portions. The reaction mixture was allowed to warm to room temperature (12 h), and hydrolyzed with water (50 mL). The aqueous layer was adjusted to pH 2 with 1 M HCl and separated. The organic layer was extracted with dilute HCl (pH 2, 2×20 mL). The combined aqueous layers were adjusted to pH 10 with NaOH, and extracted with ethyl acetate (3×50 mL). The combined extracts were dried (Na_2SO_4), and concentrated.

3.4.1. (4*R*,5*S*)-5-Amino-7-octen-4-ol, (4*R*,5*S*)-5a. Mp 67–69°C; $[\alpha]_D^{20}=+24.3$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (250 MHz): δ 0.95 (t, $J=6.9$ Hz, 3H, CH_3), 1.25–2.35 (m, 9H, $(CH_2)_2$, 6-CH_2, OH, NH_2), 2.84 (dt, $J=3.7$ Hz, 1H, 5-CH), 3.53 (dt, $J_1=7.9$ Hz, $J_2=4.0$ Hz, 1H, 4-CH), 5.13–5.16 (m, 2H, =CH_2), 5.71–5.88 (m, 1H, CH=). ^{13}C NMR (63 MHz): δ 14.18 (CH_3), 19.36 (C-2), 34.26 (C-3), 36.22 (C-6), 54.35 (C-5), 73.79 (C-4), 117.63 (=CH_2), 136.03 (CH=).

3.4.2. (4*R*,5*S*)-5-Amino-2-methyl-7-octen-4-ol, (4*R*,5*S*)-5b. $[\alpha]_D^{20}=+28.6$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (250 MHz): δ 0.92 (d, $J=6.6$ Hz, 3H, CH_3), 0.96 (d, $J=6.7$ Hz, 3H, CH_3), 1.09–1.46 (m, 2H, 3-CH_2), 1.74–1.90 (m, 1H, 2-CH), 1.94–2.33 (m, 5H, 6-CH_2, OH, NH_2), 2.85 (dt, $J=3.7$ Hz, $J=9.6$ Hz, 1H, 5-CH), 3.64 (dt, $J=3.3$ Hz, 1H, 4-CH), 5.09–5.16 (m, 2H, =CH_2), 5.70–5.87 (m, 1H, CH=). ^{13}C NMR (63 MHz): δ 21.83, 23.81 (CH_3), 24.72 (C-2), 36.13 (C-6), 41.04 (C-3), 54.77 (C-5), 71.72 (C-4), 117.75 (=CH_2), 135.83 (CH=).

3.5. Acetylation of amino alcohols (*R*)-4a and (4*R*,5*S*)-5 to (*R*)-6a and (4*S*,5*R*)-7; general procedure

According to Effenberger et al.,[15] but purification either by chromatography on silica gel with ethyl acetate (**7c**) or recrystallization from diisopropyl ether (**7a**) or diisopropyl ether/petroleum ether (**7b**).

3.5.1. (*R*)-4-Acetamido-4-(2-acetoxybutyl)-1,6-heptadiene, (*R*)-6. ^{1}H NMR (500 MHz): δ 0.91 (t, $J=7.3$ Hz, 3H, 4′-CH_3), 1.20–1.38 (m, 2H, 3′-CH_2), 1.56–1.61 (m, 2H, 2′-CH_2), 1.92 (s, 3H, CH_3CON), 2.08 (s, 3H, CH_3COO), 2.49–2.73 (m, 4H, 3,5-CH_2), 5.08–5.15 (m, 4H, =CH_2), 5.24–5.26 (m, 1H, 1′-CH), 5.59 (s, 1H, NH), 5.75–5.89 (m, 2H, CH=). ^{13}C NMR (126 MHz): δ 13.85 (4′-CH_3), 19.29 (3′-CH_3), 21.07, 24.40 (CH_3CO), 31.40 (C-2′), 38.15, 38.77 (C-3,5), 61.03 (C-4), 77.22 (C-1′), 118.35, 118.94 (=CH_2), 133.16, 133.92 (CH=), 169.76, 171.37 (CO). Anal. calcd for $C_{15}H_{25}NO_3$ (267.4): C, 67.38; H, 9.43; N, 5.24. Found: C, 66.98; H, 9.46; N, 5.06%.

3.5.2. (4*S*,5*R*)-4-Acetamido-5-acetoxy-1-octene, (4*S*,5*R*)-7a. Mp 75°C. ^{1}H NMR (250 MHz): δ 0.91 (t, $J=7.2$ Hz, 3H, CH_3), 1.22–1.62 (m, 4H, $(CH_2)_2$), 1.97 (s, 3H, CH_3CON), 1.99–2.39 (m, 2H, 3-CH_2), 2.08 (s, 3H, CH_3COO), 4.17–4.27 (m, 1H, 4-CH), 4.89 (dt, $J_1=4.4$ Hz, $J_2=8.5$ Hz, 1H, 5-CH), 5.04–5.17 (m, 2H, =CH_2), 5.62 (d, $J=9.1$ Hz, 1H, NH), 5.68–5.84 (m, 1H, CH=). ^{13}C NMR (63 MHz): δ 13.85 (CH_3), 18.79 (C-7), 21.11, 23.39 (CH_3CO), 33.08 (C-6), 34.45 (C-3), 50.61 (C-4), 75.61 (C-5), 117.79 (=CH_2), 134.25 (CH=), 169.69, 171.07 (CO). Anal. calcd for $C_{12}H_{21}NO_3$ (227.3): C, 63.41; H, 9.31; N, 6.16. Found: C, 63.33; H, 9.35; N, 6.08%.

3.5.3. (4*S*,5*R*)-4-Acetamido-5-acetoxy-7-methyl-1-octene, (4*S*,5*R*)-7b. Mp 63–64°C. ^{1}H NMR (250 MHz): δ 0.89, 0.93 (d each, $J=6.5$ Hz, 3H, CH_3), 1.25–1.67 (m, 3H, CH_2, 7-CH), 1.97 (s, 3H, CH_3CON), 2.07 (s, 3H, CH_3COO), 2.08–2.38 (m, 2H, 3-CH_2), 4.16–4.26 (m, 1H, 4-CH), 4.98 (dt, $J_1=3.9$ Hz, $J_2=9.6$ Hz, 1H, 5-CH), 5.04–5.11 (m, 2H, =CH_2), 5.57 (d, $J=9.0$ Hz, 1H, NH), 5.68–5.84 (m, 1H, CH=). ^{13}C NMR (63 MHz): δ 21.14 (CH_3CO), 21.88, 23.26 (CH_3), 23.41 (CH_3CO), 24.62 (C-7), 34.47 (C-3), 39.73 (C-6), 50.89 (C-4), 74.19 (C-5), 117.75 (=CH_2), 134.27 (CH=), 169.66, 171.06 (CO). Anal. calcd for $C_{13}H_{23}NO_3$ (241.3): C, 64.70; H, 9.61; N, 5.80. Found: C, 64.47; H, 9.71; N, 5.72%.

3.5.4. (4*S*,5*R*)-4-Acetamido-5-acetoxy-5-phenyl-1-pentene, (4*S*,5*R*)-7c. Mp 93°C. ^{1}H NMR (500 MHz): δ 1.93 (s, 3H, CH_3CON), 2.04–2.32 (m, 2H, 3-CH_2), 2.13 (s, 3H, CH_3COO), 4.47–4.52 (m, 1H, 4-CH), 5.04–5.08 (m, 2H, =CH_2), 5.31 (d, $J=9.2$ Hz, 1H, NH), 5.68–5.76 (m, 1H, CH=), 5.88 (d, $J=4.4$ Hz, 1H, 5-CH), 7.29–7.38 (m, 5H, Ph). ^{13}C NMR (63 MHz): δ 21.15, 23.34 (CH_3CO), 34.35 (C-3), 51.73 (C-4), 76.56 (C-5), 118.05 (=CH_2), 126.69, 128.25, 128.50, 136.82 (Ph), 134.02 (CH=), 169.62, 170.05 (CO). Anal. calcd for $C_{15}H_{19}NO_3$ (261.3): C, 68.94; H, 7.33; N, 5.36. Found: C, 69.11; H, 7.43; N, 5.30%.

3.6. Addition of the crotyl Grignard reagent to (*R*)-3a

3.6.1. (4*R*,5*S*)-5-Amino-6-methyl-6-octen-4-ol, (4*R*,5*S*)-9. As described in Section 3.4, from (*R*)-**3a** (5 g, 29.2 mmol), Mg (1.42 g, 58.4 mmol), crotyl bromide (6 mL, 59.6 mmol), diethyl ether (130 mL), methanol (90 mL) and $NaBH_4$ (2.2 g, 58.2 mmol); yield: 61%, bp 69°C/0.01 torr; 79% de. ^{1}H NMR (250 MHz): δ 0.93 (t, $J=7.0$ Hz, 3H, CH_3), 1.18–1.73 (m, 13H, $(CH_2)_2$, 6,8-CH_3, OH, NH_2), 3.20 (d, $J=6.1$ Hz, 1H, 5-CH), 3.51–3.58 (m, 1H, 4-CH), 5.42–5.51 (m, 1H, CH=). ^{13}C NMR (63 MHz): δ 12.70, 13.16, 14.19 (CH_3), 19.19 (C-2), 34.69 (C-3), 63.41 (C-5), 72.32 (C-4), 121.71 (CH=), 136.56 (C-6).

3.6.2. (4*S*,5*R*)-4-Acetamido-5-acetoxy-3-methyl-2-octene, (4*S*,5*R*)-11. As described in Section 3.5, from (4*R*,5*S*)-**9** (0.7 g, 4.45 mmol), acetic anhydride (1.3 mL, 13.75 mmol), DMAP (40 mg, 0.33 mmol) in pyridine (5 mL); yield: 77%, mp 83°C (diisopropyl ether); $[\alpha]_D^{20}=+29.5$ (*c* 0.6, $CHCl_3$), >99% de. ^{1}H NMR (500 MHz): δ 0.90 (t, $J=7.3$ Hz, 3H, CH_3), 1.24–1.44 (m, 2H, 7-CH_2), 1.45–1.58 (m, 2H, 6-CH_2), 1.61 (d, $J=5.8$ Hz, 3H, 1-CH_3), 1.61 (s, 3H, 6-CH_3), 2.00 (s, 3H, CH_3CON), 2.04 (s, 3H, CH_3COO), 4.52 (dd, $J=5.1$ Hz, 1H, 4-CH), 4.94–4.98 (m, 1H, 5-CH), 5.45–5.47 (m, 1H, CH=), 5.97 (d, $J=8.6$ Hz, 1H, NH). ^{13}C NMR (63 MHz): δ 13.26, 13.46, 13.84 (CH_3), 18.89 (C-7), 21.08, 23.51 (CH_3CO), 32.88 (C-6), 58.42 (C-4), 74.65 (C-5), 123.24 (CH=), 131.63 (C-3), 169.30, 171.16 (CO). Anal. calcd for $C_{13}H_{23}NO_3$ (241.3): C, 64.70; H, 9.61; N, 5.80. Found: C, 64.88; H, 9.56; N, 5.66%.

3.6.3. 5-Amino-6-methyl-7-octen-4-ol, 8. As described in Section 3.4, from (*R*)-**3a** (5 g, 29.2 mmol), but modified workup: after reduction with $NaBH_4$, the reaction mixture was hydrolyzed with water. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3×65 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was taken up in methanol (2×70 mL) and again concentrated to give 3.72 g (81%) of **8** as a diastereoisomeric mixture of 62:21:11:6.

3.6.4. (3*S*,4*S*,5*R*)-4-Acetamido-5-acetoxy-3-methyl-1-octene, (3*S*,4*S*,5*R*)-10. The diastereoisomeric mixture of **8** was acetylated as described in Section 3.5. Chromatography on silica gel with petroleum ether:ethyl acetate (2:1) gave 1.9 g (33%) of (3*S*,4*S*,5*R*)-**10**; mp 83°C (diisopropyl ether); $[\alpha]_D^{20}=+16.4$ (*c* 2.3, $CHCl_3$). ^{1}H NMR (250 MHz): δ 0.90 (t, $J=7.2$ Hz, 3H, CH_3), 1.05 (d, $J=6.9$ Hz, 3H, 3-CH_3), 1.23–1.64 (m, 4H, $(CH_2)_2$), 2.00 (s, 3H, CH_3CON), 2.07 (s, 3H, CH_3COO), 2.44–2.52 (m, 1H, 3-CH), 4.08–4.17 (m, 1H, 4-CH), 4.84–4.91 (m, 1H, 5-CH), 5.02–5.17 (m, 2H, =CH_2), 5.30 (d, $J=9.8$ Hz, 1H, NH), 5.76–5.90 (m, 1H, CH=). ^{13}C NMR (63 MHz): δ 13.86, 16.64 (CH_3), 18.53 (C-7), 21.03, 23.33 (CH_3CO), 32.95 (C-6), 36.91 (C-3), 54.55 (C-4), 73.81 (C-5), 116.50 (=CH_2), 138.47 (CH=), 169.95, 170.75 (CO). Anal. calcd for $C_{13}H_{23}NO_3$ (241.3): C, 64.70; H, 9.61; N, 5.80. Found: C, 64.84; H, 9.54; N, 5.80%.

3.7. Ozonolysis of 4-acetamido-5-acetoxy-1-octenes (4*S*,5*R*)-7a,b and (3*S*,4*S*,5*R*)-10 and subsequent oxidation with CrO_3; general procedure

(a) Ozone (40 L/h) was passed through a solution of **7** (1 mmol **7a**, 12.4 mmol **7b**) or **10** (3.1 mmol) in methanol (20 mL for **7a**, 150 mL for **7b**, 35 mL for **10**)

at −78°C over 10 min, and subsequently O_2 was passed through for 5 min to remove excess O_3. Then dimethylsulfide (ca. 3 equiv. referred to **7**, **10**) was added, and the reaction mixture was allowed to warm to room temperature (12 h). The reaction mixture was concentrated, and crude aldehydes **12** were dried under high vacuum.

(b) To a solution of crude **12** (3.1–12.4 mmol) in acetone (40 mL for **12a**, 100 mL for **12b**, 25 mL for **12c**) at 0°C was added dropwise a solution of CrO_3 in H_2SO_4 [prepared by dissolving CrO_3 (22 g, 0.22 mol) in dilute H_2SO_4 (65 mL)] (20 mL for **7a**, 65 mL for **7b**, 15 mL for **10**) over 30 min, and the reaction mixture was stirred at 0°C for a further 30 min. Then isopropanol (12–50 mL) was added followed by addition of water (25–100 mL) after 1 h. The reaction mixture was extracted with $CHCl_3$ (3×65 mL). The combined organic layers were extracted with a solution of $NaHCO_3$ (10%) (2×70 mL). The combined aqueous layers were adjusted to pH 2 with conc. HCl and extracted with $CHCl_3$ (3×50 mL). The combined extracts were dried (Na_2SO_4), and concentrated. Recrystallization from diethyl ether gave acids **13**.

3.7.1. (3*S*,4*R*)-3-Acetamido-4-acetoxyheptanal, (3*S*,4*R*)-12a. Yield: 87%, mp 63–64°C; $[\alpha]_D^{20}=+42.6$ (*c* 1.0, $CHCl_3$), 94% de. ^{1}H NMR (250 MHz): δ 0.92 (t, $J=7.2$ Hz, 3H, CH_3), 1.22–1.62 (m, 4H, $(CH_2)_2$), 1.98 (s, 3H, CH_3CON), 2.08 (s, 3H, CH_3COO), 2.51–2.63 (m, 2H, CH_2), 4.49–4.59 (m, 1H, 3-CH), 4.94–5.06 (m, 1H, 4-CH), 6.41 (d, $J=8.5$ Hz, 1H, NH), 9.73 (t, $J=2.0$ Hz, 1H, CHO). ^{13}C NMR (63 MHz): δ 13.77 (CH_3), 18.65 (C-6), 21.02, 23.26 (CH_3CO), 33.57 (C-5), 43.64 (C-2), 47.91 (C-3), 75.30 (C-4), 169.99, 171.23 (CO), 200.59 (CHO). Anal. calcd for $C_{11}H_{19}NO_4$ (229.3): C, 57.63; H, 8.35; N, 6.11. Found: C, 57.54; H, 8.38; N, 5.92%.

3.7.2. (3*S*,4*R*)-3-Acetamido-4-acetoxyheptanoic acid, (3*S*,4*R*)-13a. Mp 129°C. ^{1}H NMR (500 MHz): δ 0.83 (t, $J=7.3$ Hz, 3H, CH_3), 1.13–1.54 (m, 4H, $(CH_2)_2$), 1.93 (s, 3H, CH_3CON), 2.00 (s, 3H, CH_3COO), 2.41–2.53 (m, 2H, CH_2), 4.35–4.40 (m, 1H, 3-CH), 4.94 (ddd, $J_1=5.1$ Hz, $J_2=8.2$ Hz, 1H, 4-CH), 6.74 (d, $J=9.0$ Hz, 1H, NH), 8.74 (br s, 1H, CO_2H). ^{13}C NMR (126 MHz): δ 13.80 (CH_3), 18.58 (C-6), 20.94, 23.11 (CH_3CO), 33.45 (C-5), 34.32 (C-2), 48.93 (C-3), 74.84 (C-4), 170.93, 171.21 (CO), 175.01 (CO_2H). Anal. calcd for $C_{11}H_{19}NO_5$ (245.3): C, 53.87; H, 7.81; N, 5.71. Found: C, 53.63; H, 7.83; N, 5.62%.

3.7.3. (3*S*,4*R*)-3-Acetamido-4-acetoxy-6-methylheptanoic acid, (3*S*,4*R*)-13b. Mp 122–125°C. ^{1}H NMR (500 MHz): δ 0.90, 0.93 (d each, $J=6.4$ Hz, 3H, CH_3), 1.32–1.63 (m, 3H, CH_2, 6-CH), 2.00 (s, 3H, CH_3CON), 2.07 (s, 3H, CH_3COO), 2.47–2.59 (m, 2H, CH_2), 4.39–4.43 (m, 1H, 3-CH), 5.08–5.11 (m, 1H, 4-CH), 6.78 (d, $J=8.8$ Hz, 1H, NH), 9.45 (br s, 1H, CO_2H). ^{13}C NMR (126 MHz): δ 20.97, 23.15 (CH_3CO), 21.89, 23.17 (CH_3), 24.60 (C-6), 34.21, 40.37 (C-2,5), 49.43 (C-3), 73.61 (C-4), 170.88, 171.25 (CO), 175.08 (CO_2H). Anal. calcd for $C_{12}H_{21}NO_5$ (259.3): C, 55.58; H, 8.16; N, 5.40. Found: C, 55.62; H, 8.12; N, 5.30%.

3.7.4. (2*R*,3*S*,4*R*)-3-Acetamido-4-acetoxy-2-methylheptanoic acid, (2*R*,3*S*,4*R*)-13c. Mp 156–157°C. ^{1}H NMR (500 MHz, acetone): δ 0.87 (t, $J=7.4$ Hz, 3H, CH_3), 1.16 (d, $J=7.2$ Hz, 3H, 2-CH_3), 1.19–1.65 (m, 4H, $(CH_2)_2$), 1.94 (s, 3H, CH_3CON), 1.97 (s, 3H, CH_3COO), 2.77 (dq, $J=4.1$ Hz, 1H, 2-CH), 4.32 (ddd, $J_1=7.8$ Hz, $J_2=10.0$ Hz, 1H, 3-CH), 4.96–5.00 (m, 1H, 4-CH), 7.07 (d, 1H, NH), 10.92 (br s, 1H, CO_2H). ^{13}C NMR (126 MHz, acetone): δ 14.60, 15.01 (CH_3), 19.36 (C-6), 21.26, 23.41 (CH_3CO), 34.40 (C-5), 39.87 (C-2), 54.28 (C-3), 74.14 (C-4), 170.51, 170.98 (CO), 176.92 (CO_2H). Anal. calcd for $C_{12}H_{21}NO_5$ (259.3): C, 55.58; H, 8.16; N, 5.40. Found: C, 55.61; H, 8.20; N, 5.27%.

3.8. Cyclization of heptanoic acids (3*S*,4*R*)-13a,b and (2*R*,3*S*,4*R*)-13c to the corresponding lactones (4*S*,5*R*)-14a,b and (3*R*,4*S*,5*R*)-14c; general procedure

Acid **13** (0.8–3.7 mmol) in a 0.5 M solution of NaOMe in methanol (20 mL for **13a**,**c**, 10 mL for **13b**) was stirred for 2 h at room temperature. Then dichloromethane (50 mL) and a 1.5-fold volume of HCl (10%) (referred to NaOMe/MeOH) were added, and the reaction mixture was stirred for a further 5 min. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3×25 mL). The combined organic layers were dried (Na_2SO_4), and concentrated. The residue was recrystallized from diethyl ether to give lactones **14**.

3.8.1. (4*S*,5*R*)-4-Acetamido-5-propyltetrahydro-2-furanone, (4*S*,5*R*)-14a. Mp 104–105°C. ^{1}H NMR (500 MHz, acetone): δ 0.94 (t, $J=7.4$ Hz, 3H, CH_3), 1.38–1.76 (m, 4H, $(CH_2)_2$), 1.89 (s, 3H, CH_3CON), 2.44 (dd, $J_1=5.7$ Hz, $J_2=17.7$ Hz, 1H, 3-CH_2), 2.90 (dd, $J=8.3$ Hz, 1H, 3-CH_2), 4.27–4.36 (m, 2H, 4,5-CH), 7.57 (br s, 1H, NH). ^{13}C NMR (126 MHz, acetone): δ 14.45 (CH_3), 19.71 (CH_2), 23.23 (CH_3CO), 35.28 (CH_2), 36.85 (C-3), 51.80 (C-4), 86.32 (C-5), 170.52 (CO), 175.38 (C-2). Anal. calcd for $C_9H_{15}NO_3$ (185.2): C, 58.36; H, 8.16; N, 7.56. Found: C, 58.48; H, 8.21; N, 7.52%.

3.8.2. (4*S*,5*R*)-4-Acetamido-5-(2-methylpropyl)tetrahydro-2-furanone, (4*S*,5*R*)-14b. Mp 91°C. ^{1}H NMR (500 MHz, acetone): δ 0.93 (d, $J=6.8$ Hz, 3H, CH_3), 0.95 (d, $J=6.8$ Hz, 3H, CH_3), 1.54–1.59 (m, 2H, CH_2), 1.77–1.84 (m, 1H, CH), 1.90 (s, 3H, CH_3CON), 2.44 (dd, $J_1=5.8$ Hz, $J_2=17.7$ Hz, 1H, 3-CH_2), 2.90 (dd, $J=8.3$ Hz, 1H, 3-CH_2), 4.28–4.33 (m, 1H, 4-CH), 4.36–4.39 (m, 1H, 5-CH), 7.59 (br s, 1H, NH). ^{13}C NMR (126 MHz, acetone): δ 22.16 (CH_3), 22.84 (CH_3CO), 23.35 (CH_3), 25.66 (CH), 34.78 (CH_2), 43.38 (C-3), 51.91 (C-4), 84.48 (C-5), 170.25 (CO), 174.97 (C-2). Anal. calcd for $C_{10}H_{17}NO_3$ (199.3): C, 60.28; H, 8.60; N, 7.03. Found: C, 60.28; H, 8.63; N, 6.95%.

3.8.3. (3*R*,4*S*,5*R*)-4-Acetamido-3-methyl-5-propyltetrahydro-2-furanone, (3*R*,4*S*,5*R*)-14c. Mp 119–120°C. ^{1}H NMR (500 MHz, acetone): δ 0.95 (t, $J=7.4$ Hz, 3H, CH_3), 1.09 (d, $J=7.5$ Hz, 3H, 3-CH_3), 1.39–1.70 (m, 4H, $(CH_2)_2$), 1.93 (s, 3H, CH_3CON), 2.94 (dq, $J=7.6$ Hz, 1H, 3-CH), 4.21–4.25 (m, 1H, 4-CH), 4.45–4.49 (m,

1H, 5-CH), 7.47 (s, 1H, NH). ^{13}C NMR (126 MHz, acetone): δ 9.71, 14.00 (CH_3), 19.49 (CH_2), 22.69 (CH_3CO), 36.20 (CH_2), 37.43 (C-3), 53.90 (C-4), 84.29 (C-5), 170.14 (CO), 178.09 (C-2). Anal. calcd for $C_{10}H_{17}NO_3$ (199.3): C, 60.28; H, 8.60; N, 7.03. Found: C, 60.51; H, 8.68; N, 7.01%.

3.9. Crystallography

Compound (3*S*,4*S*,5*R*)-**10** was recrystallized from diisopropyl ether, compound (4*S*,5*R*)-**14a** from diethyl ether to obtain single crystals for X-ray analysis. Intensity data were collected on a Nicolet P3 diffractometer with ω-scan technique (graphite-monochromated Mo Kα radiation, $\lambda = 0.71073$ Å) at 293 K. The structures were solved by direct methods and refined[27] against F^2. Crystal data for **10**: formula, $C_{13}H_{23}NO_3$ (241.3); crystal size, 1.0×1.0×0.6 mm; $F(000) = 1056$; crystal system, tetragonal, space group, $P4_1$; $Z = 4$; $a = 9.3100(10)$, $b = 9.3100(10)$, $c = 35.052(5)$ Å; $V = 3038.2(6)$ Å^3; $D_{calcd} = 1.055$ g/cm^3; number of reflections = 2452; number of independent reflections (with 2θ in the range of 4.4–46.0°) = 2155; number of reflections having $I > 2\sigma(I) = 1840$; GooF = 1.065; $R_1 = 0.0411$; $wR_2 = 0.1031$. Crystal data for **14a**: formula, $C_9H_{15}NO_3$ (185.2); crystal size, 0.8×0.4×0.35 mm; $F(000) = 400$; crystal system, tetragonal, space group, $P4_1$; $Z = 4$; $a = 7.3938(4)$, $b = 7.3938(4)$, $c = 18.541(2)$ Å; $V = 1013.58(13)$ Å^3; $D_{calcd} = 1.214$ g/cm^3; number of reflections = 1379; number of independent reflections (with 2θ in the range of 5.5–50.0°) = 1206; number of reflections having $I > 2\sigma(I) = 1022$; GooF = 1.053; $R_1 = 0.0365$; $wR_2 = 0.0776$.

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