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A chemoenzymatic synthesis of optically active aza analogues of Quercus lactones

Fulvia Felluga,* Valentina Gombac, Michela Pavan, Giuliana Pitacco and Ennio Valentin

Dipartimento di Scienze Chimiche, Università di Trieste, via Licio Giorgieri 1, I-34127 Trieste, Italy

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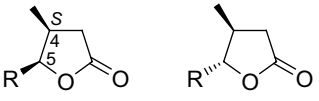
Abstract—The synthesis of optically active 4-methyl-5-*n*-butyl- and 5-*n*-pentylpyrrolidin-2-ones, aza analogues of the corresponding Quercus lactones, has been achieved by a chemoenzymatic procedure, involving in the enantiodifferentiating step the enzymatic kinetic resolution of the corresponding γ-ketoester precursors, followed by reductive amination and subsequent cyclization of the enantiomerically pure hydrolysis products. The effect of the reaction conditions as well as the influence of the structure of the substrates on the enzymatic hydrolyses were also studied.

1. Introduction

Quercus lactones are two pairs of diastereomeric γ-butyrolactones,[1] bearing a methyl group at C-4 and a linear aliphatic chain at C-5. In particular, (−)-*cis*- and (+)-*trans*-**1** and **2** (R = C_4H_9) are called whisky lactones,[1f,g] while (−)-*cis* and (+)-*trans*-**3** and **4** (R = C_5H_{11}) are called cognac lactones[1d–f] (Fig. 1). The absolute configuration at C-4 is *S* in all stereoisomers. They are naturally occurring compounds isolated from different types of wood[2] and are the key flavours of aged alcoholic beverages, such as whisky, brandy, wine and cognac.[1a–c]

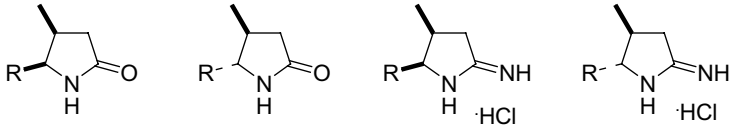


R = C_4H_9: (4*S*,5*S*)-(−)-**1** (4*S*,5*R*)-(+)-**2**
R = C_5H_{11}:(4*S*,5*S*)-(−)-**3** (4*S*,5*R*)-(+)-**4**

Figure 1.

Little is reported in the literature on the aza analogues of whisky and cognac lactones, namely the diastereomeric *cis*- and *trans*-5-*n*-butyl-4-methylpyrrolidin-2-ones **5** and **6** and *cis*- and *trans*-4-methyl-5-*n*-pentylpyrrolidin-2-ones **7** and **8** (Fig. 2).

To our knowledge, only one paper[3] has described the synthesis of racemic *trans*-**6**, as a single diastereomer, by Itoh radical cyclization[4] of an *N*-allyltrichloroacetamide, while both diastereomers **7** and **8** have been prepared by the same authors via reductive cyclization of the appropriate γ-nitroester precursor, synthesized by



R = C_4H_9:	**5**	**6**	**9**	**10**
R = C_5H_{11}:	**7**	**8**	**11**	**12**

Figure 2.

* Corresponding author. E-mail: felluga@dsch.univ.trieste.it

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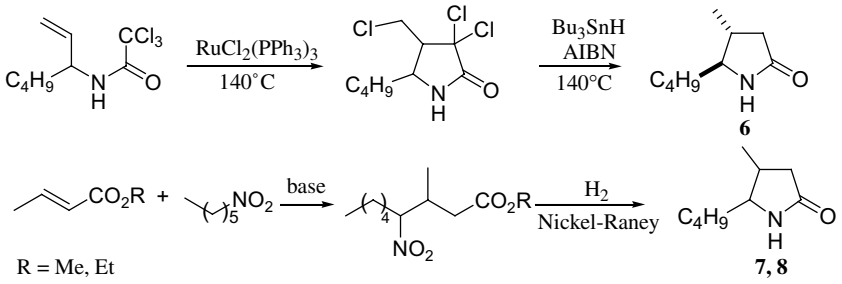


Scheme 1.

the Michael reaction of nitrohexane with crotonic ester (Scheme 1).

The same authors[3] also performed the resolution of *cis*-(±)-**7** via the formation of diasteromeric ureides[5] resulting in *cis*-(+)-**7** being isolated as a pure enantiomer, but whose absolute configuration could not be determined. The γ-lactams **5**–**8** are all precursors of the corresponding 4,5-disubstituted-2-iminopyrrolidines **9**–**12** (Fig. 2). Among them, compounds **10**–**12**, isolated as their respective hydrochlorides, were found to act as potent and selective inhibitors of the human inducible isoforms of nitric oxide synthase both in vitro and in vivo,[3] and therefore are likely to be potentially useful in the treatment of many diseases correlated with a harmful NO overproduction.[6] Interestingly, the biological activity exhibited by 4-methyl-5-*n*-pentyl-2-iminopyrrolidines **11** and **12** was found to be strongly affected by their stereochemical features. In fact, the potency and selectivity of the *cis* racemate **11** are remarkably higher than those observed for the corresponding *trans* diastereomer **12**. Furthermore, the optically active form *cis*-(+)-**11**, derived from the corresponding γ-lactam *cis*-(+)-**7**, was proved to be more active and selective than its enantiomer *cis*-(−)-**11**.[3] In spite of the potential biological activity exhibited by *cis*-**9**, especially in its optically active forms, this compound, together with its lactamic precursor *cis*-**7**, still remains undescribed.

In the frame of our research project, aimed at the synthesis of enantiomerically pure aza analogues of naturally occurring γ-butyrolactones,[7,8] we describe herein the synthesis of optically active diastereomeric *cis*- and *trans*-**5** and **6** and *cis*- and *trans*-**7** and **8** by the use of chemoenzymatic methods.

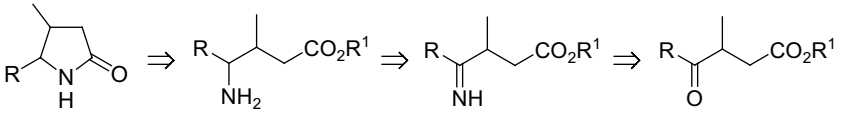
2. Results and discussion

2.1. Synthesis and kinetic resolution of γ-ketoesters 13–16

The γ-lactams **5**–**8** were prepared by reductive amination,[9] followed by cyclization, of the corresponding ethyl and cyanomethyl γ-ketoester precursors (Scheme 2). From the resulting diastereomeric mixtures thus obtained each γ-lactam was isolated as a single stereomer by flash chromatography.

The parent compounds, ethyl 3-methyl-4-oxooctanoate **13** and ethyl 3-methyl-4-oxononanoate **14** were prepared according to Günther and Mosandl,[10] while the corresponding cyanomethyl esters **15** and **16** were prepared following the procedure reported by Blanco et al.[11] (Scheme 3).

The resolution of the racemic γ-ketoesters **13**–**16** was performed by the use of the lipase PPL (*Porcine Pancreatic Lipase*). The kinetic resolution of **16** by PPL in water at pH 7.2 had already been previously described in

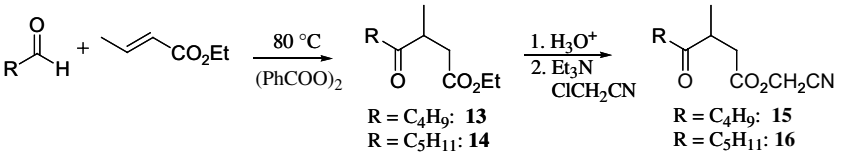


5, 6, 7, 8

$R = C_4H_9, C_5H_{11}$

$R^1 = C_2H_5, CH_2CN$

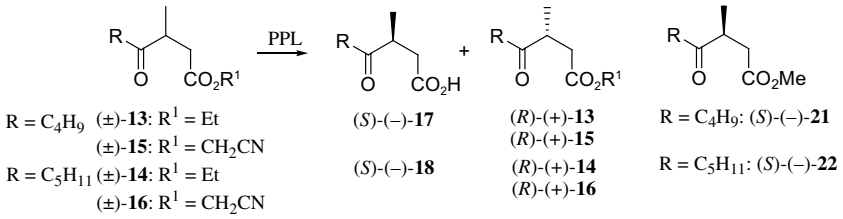
Scheme 2.



$R = C_4H_9$: **13**
$R = C_5H_{11}$: **14**

$R = C_4H_9$: **15**
$R = C_5H_{11}$: **16**

Scheme 3.



Scheme 4.

the literature[11] to give the unreacted γ-ketoester (*R*)-(+)-**16** with 98% ee and the γ-ketoacid (*S*)-(−)-**18** with 85% ee, at 49% conversion (Scheme 4). Later it was found[1e] that enzymic resolution of ethyl γ-ketoester **14** in a different medium (0.1 M phosphate buffer at pH 7.4) furnished the acid (*S*)-(−)-**18** with 98% ee, at 21% conversion. At this conversion value however the reaction did not proceed any further, thus preventing the isolation of the unreacted (*R*)-(+)-**14** with a high ee, unless six consecutive hydrolysis cycles were performed.

With the aim of preparing the desired aza analogues of Quercus lactones, we extended the study on the enzymatic hydrolysis of ethyl and cyanomethyl 3-methyl-4-oxooctanoate **13** and **15**, undescribed in the literature as yet, in both water and phosphate buffer. Moreover, the hydrolysis of **14** in water and that of **16** in phosphate buffer were also studied for a better understanding of the previously reported results.[1e,11]

The results for the enzymatic resolutions are summarized in Table 1. The best results were obtained for the cyanomethyl esters **15** and **16**, carrying out the hydrolyses in water, by analogy with what already found by Blanco for compound **16**.[11] Under these conditions, both substrates **15** and **16** were hydrolysed by PPL very rapidly and efficiently (*E* value[12] >100). At low conversion values, the γ-ketoacids (−)-**17** and (−)-**18** were isolated with 96% ee and 97% ee and in 20% and 25% yield, respectively, while at about 50% conversion, the unreacted esters (+)-**15** and (+)-**16** having ee's >99% were recovered.

In 0.1 M phosphate buffer, the ethyl esters **13** and **14** proved better substrates for PPL than the corresponding cyanomethyl esters **15** and **16**, resulting in higher enantiomeric ratio (*E*)[12] and hence in higher enantiomeric excesses for the respective acids.

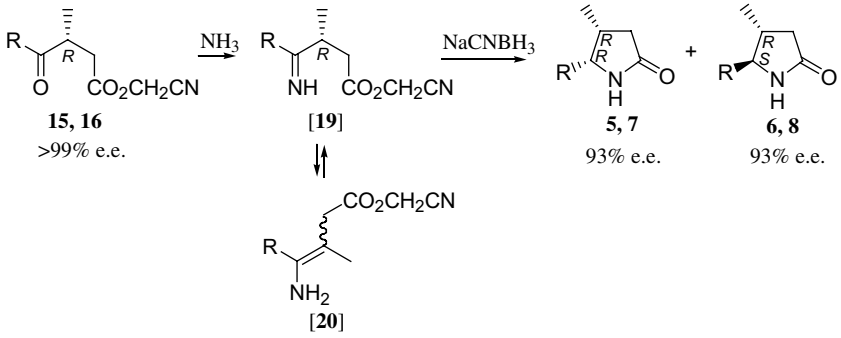
The hydrolysis rates for the activated esters **15** and **16** were higher than those observed for the corresponding ethyl esters **13** and **14** in both water and phosphate buffer, as it can be deduced from a comparison of the relative reaction times (Table 1). Such a strong effect on the reaction rate in the hydrolysis of polar alkyl esters with several microbial lipases had already been observed by Sih and co-workers[13] and by Blanco et al.,[11,14] thus suggesting that the acyl-enzyme formation is the rate-limiting step of the reaction. It is important to underline the strong influence of the reaction medium on the rate of the hydrolysis, which was in general much higher in water than in the phosphate buffer, with the exception of compound **14**.

The enantiopreference of PPL was the same in all the cases examined, as the enzyme always promoted

Table 1. Enzymatic resolution of γ-ketoesters **13**–**16**

Substrate	H_2O[a]					0.1 M phosphate buffer[b]				
	E	Conversion (%)	(*S*)-(−)-acid ee (%)[c] [yield (%)][d]	(*R*)-(+)-ester ee (%)[c] [yield (%)][d]	Reaction time	*E*	Conversion (%)	(*S*)-(−)-acid ee (%)[c] [yield (%)][d]	(*R*)-(+)-ester ee (%)[c] [yield (%)][d]	Reaction time
13	6	6	68 [5]	4 [82]	3 h	17	18	87 [10]	19 [76]	6 h
		50	52 [44]	50 [45]	7 h		50	75 [40]	61 [38]	48 h
		63	36 [60]	62 [26]	8 h		70	38 [65]	70 [27]	72 h
14	31	30	91 [13]	40 [70]	24 h	>100[1e]	21	98 [13]	26 [67]	10 h
							25	64 [18]	21 [72]	2 h
15	>100	38	96 [20]	89 [60]	10 min	6	50	49 [42]	60 [39]	140 min
		53	87 [35]	>99 [58]	2 h		69	38 [59]	85 [25]	3 h
16	>100	33	97 [25]	88 [65]	10 min	20	25	85 [19]	30 [73]	1 h
		54	85 [35]	>99 [63]	2 h		50	85 [49]	79 [35]	12 h

[a] Reaction conditions: 1.0 g substrate, 1.0 g enzyme, H_2O pH 7.2 (5 mL/mmol), room temperature.
[b] Reaction conditions: 1.0 g substrate, 1.0 g enzyme, 0.1 phosphate buffer at pH 7.4 (5 mL/mmol), room temperature.
[c] Enantiomeric excesses were determined by chiral HRGC.
[d] Yields in isolated products.



Scheme 5.

the cleavage of the (*S*)-enantiomers. Furthermore, the enantioselectivity of the hydrolyses, measured by the enantiomeric ratio *E*,[12] was found to increase with the length of the chain of the aliphatic substituent at the ketone function, as already evidenced by the experiments reported in the literature.[12,14]

2.2. Reductive amination of the optically active γ-ketoesters

The reductive amination reaction, performed with an ammonia source in the presence of sodium cyanoborohydride[9] on the enantiomerically pure γ-ketoesters (*R*)-(+)-**15** and (*R*)-(+)-**16** (>99% ee), led to 1:2 diastereomeric mixtures of *cis*-(+)- and *trans*-(−)-4,5-disubstituted-γ-lactams **5**, **6** and **7**, **8**, respectively. The geometry of the γ-lactams were determined by means of ^{13}C NMR spectroscopy. In the *cis*-isomers C-4, C-5, the methyl group and the first methylene group of the chain resonated upfield with respect to the corresponding shifts of the *trans*-isomers.

When ammonium acetate was used as the source of ammonia, a considerable decrease in the enantiomeric excess of the resulting lactams was observed. However, replacing ammonium acetate for ammonium formate limited the loss of enantiomeric purity to 6%, the desired diastereomeric lactams *cis*-(+)-**5**, *trans*-(−)-**6**, *cis*-(+)-**7** and *trans*-(−)-**8** all having 93% ee were isolated after chromatographic separation of their respective mixtures. The loss of enantiomeric purity occurred on the imine intermediate **19**, through its enamine tautomer **20** (Scheme 5). In fact, the optically active starting γ-ketoesters (*R*)-(+)-**15** and (*R*)-(+)-**16**, recovered in small amount from the respective reactions, showed no variation in the original enantiomeric excesses (>99%).

The aza analogues of natural Quercus lactones, namely *cis*-(−)-**5**, *trans*-(+)-**6** and *cis*-(−)-**7**, *trans*-(+)-**8**, the opposite enantiomers of the above described γ-lactams, were also prepared. The optically pure γ-ketoacids (*S*)-(−)-**17** (96% ee) and (*S*)-(−)-**18** (97% ee) were esterified with diazomethane to the corresponding methyl esters (*S*)-(−)-**21** and (*S*)-(−)-**22** (Scheme 4). These latter esters were then subjected to the above mentioned amination–reduction procedure, to furnish the desired γ-lactams (4*S*,5*S*)-(−)-**5**, (4*S*,5*R*)-(+)-**6**, (4*S*,5*S*)-(−)-**7**, and (4*S*,5*S*)-(+)-**8**, though unfortunately with some loss of enantiomeric purity (88% ee for **5**, **6** and 89% ee for **7**, **8**).

2.3. Absolute configuration of the products

The absolute configuration of the stereocentre in the cyanomethyl ester (+)-**16**, bearing the *n*-pentyl chain at C-4, is known to be *R*.[11] By a comparison of its CD spectrum with that of (+)-**15**, bearing the *n*-butyl chain at C-4, the same absolute configuration can be assigned to (+)-**15**. In fact both compounds show a positive Cotton effect at 284 nm (Fig. 3).

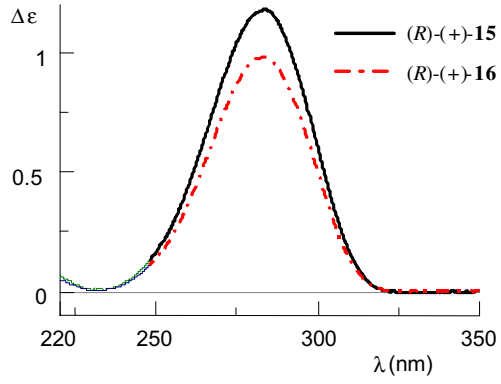


Figure 3.

As a consequence, the absolute configuration of C-4 in all the stereomeric γ-lactams **5**–**8** formed from the γ-ketoesters (+)-**15** and (+)-**16** by reductive amination is also *R*. Therefore, the absolute configurations of lactams *cis*-(+)-**5** and *cis*-(+)-**7** are (4*R*,5*R*) and those of *trans*-(−)-**6** and *trans*-(−)-**8** are (4*R*,5*S*). These assignments were also supported by the analysis of their CD spectra. In fact, the homologous *cis*-lactams **5** and **7** showed superimposable CD curves, as did the *trans* ones **6** and **8** (Figs. 4 and 5).

Finally, comparison between the CD spectra of these γ-lactams with the corresponding Quercus lactones deserves some comment. γ-Lactams are known to exhibit, for the 220 nm band, a Cotton effect whose sign

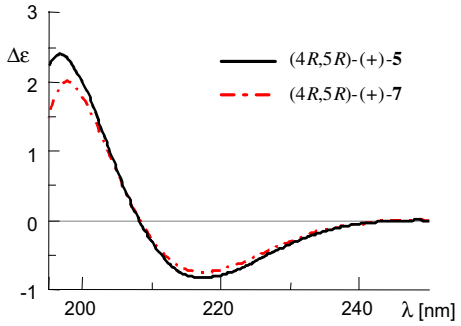


Figure 4.

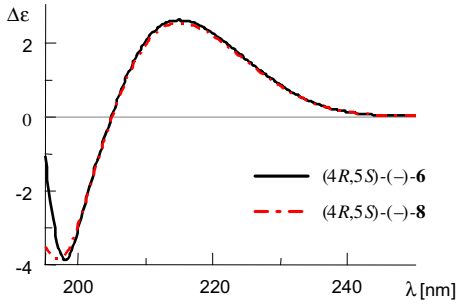


Figure 5.

is generally opposite to that of the corresponding dissymmetrically similar γ-lactones; this experimental evidence is supported by theoretical studies.[15] In the present case however, only the *trans* systems show CD curves, which are consistent with the general behaviour, whereas the *cis* derivatives deviate from it, as can be deduced from the data reported in Table 2, in which the observed values for the two counterparts are summarized. This particular behaviour of the *cis* diastereomeric lactams can be attributed to a higher conformational mobility of the ring, which can be seen by a marked solvent effect on the bisignate curves.

3. Conclusions

The chemoenzymatic methodology applied to the synthesis of these particular γ-lactams proved satisfactory both in terms of the enantiomeric purity of the products and the chemical yields obtained. The synthesis proposed can be easily and rapidly accomplished with the use of common reagents. Furthermore, in contrast to the chemical methods reported in the literature, which proved more selective, all stereoisomers of the aza analogues of Quercus lactones can be synthesized by the present method. The results concerning the enzymatic resolutions would indicate once more how important it is to evaluate of the parameters influencing the reaction. In the present case, an accurate choice of the ester moiety proved of paramount importance for the success of the enzymatic resolutions by lipases, as it was the ionic strength of the reaction medium.

4. Experimental part

4.1. General

IR spectra were recorded on a Jasco FT-IR 200 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were run on a Jeol EX-400 (400 MHz for proton), using deuteriochloroform as a solvent and tetramethylsilane as the internal standard. Optical rotations were determined on a Perkin Elmer Model 241 polarimeter, at 25 °C. CD spectra were obtained on a Jasco J-700A spectropolarimeter (0.1 cm cell) for methanol solutions. Mass spectra (EI, positive ions) were run on a VG 7070 spectrometer at 70 eV. ESI-MS spectra were obtained on a PE-API spectrometer at 5600 V by infusion of methanolic solutions. High resolution GLC analyses were obtained on a Carlo Erba GC 8000 instrument using an OV 1701 (25 m × 0.32 mm) column (carrier gas He, 180 kPa, split 1:50), and on a Shimadzu 14B apparatus, using a Chiraldex™ column, type G-TA, trifluoroacetyl-γ-cyclodextrin (40 m × 0.25 mm) (carrier gas He, 180 kPa, split 1:100). Enzymatic hydrolyses were performed using a pH-stat Controller PHM290 Radiometer, Copenhagen. M.p.s. were

Table 2. CD data for Quercus lactones in methanol and CD data for the aza analogues of Quercus lactams in various solvent (the values are reported for those enantiomers whose measurements were actually performed)

	Quercus lactones			Aza analogues of Quercus lactones						
		MeOH			MeOH		MeCN		Cyclohexane	
		λ (nm)	Δε		λ (nm)	Δε	λ (nm)	Δε	λ (nm)	Δε
cis	(4*S*,5*S*)-(−)-**1**[a]	208	+0.22	(4*R*,5*R*)-(+)-**5**	198 217	+2.01 −0.75	200 223	+1.08 −0.37	201 227	+0.05 −0.28
	(4*S*,5*S*)-(−)-**3**[b]	211	+0.24	(4*R*,5*R*)-(+)-**7**	197 217	+2.41 −0.83	200 223	+0.98 −0.34	201 225	−0.06 −0.46
trans	(4*S*,5*R*)-(−)-**2**[a]	205 227	−0.12 +0.03	(4*R*,5*S*)-(−)-**6**	215	+2.61	220	+2.21	224	+1.81
	(4*S*,5*R*)-(−)-**4**[b]	203 226	−0.16 +0.13	(4*R*,5*S*)-(−)-**8**	215	+2.52	220	+2.54	222	+2.01

[a] Ref. 16.
[b] Ref. 1e.

determined on a Büchi SHP-20 apparatus and are uncorrected. TLC's were performed on Polygram® Sil G/UV_{254} silica gel pre-coated plastic sheets (eluant: light petroleum–ethyl acetate). Flash chromatography was run on silica gel, 230–400 mesh ASTM (Kieselgel 60, Merck), using mixtures of light petroleum 40–70 °C and ethyl acetate as the eluant.

Porcine pancreatic lipase (PPL, Type II, crude, 42 U/mg) was supplied by Sigma.

4.2. Synthesis of the substrates

4.2.1. Ethyl 3-methyl-4-oxooctanoate 13. This was prepared following the procedure reported in the literature.[10] A mixture of ethyl crotonate (11.5 g, 0.1 mol) and pentanal (51.6 g, 0.6 mol) was stirred at 80 °C, under argon, in the presence of benzoyl peroxide (2.0 g, 8 mmol), for 6 h. During this time a further 2.0 g of benzoyl peroxide was added in portions at regular intervals. The mixture was then cooled down, washed with satd $NaHCO_3$, and the excess aldehyde distilled off at 15 mmHg. The residue so obtained was purified on column (eluent: petroleum ether–ethyl acetate 98:2 up to 90:10) to give the pure γ-ketoester (±)-**13** (80% yield). Oil, IR (neat), cm^{-1}: 1735 (s, OC=O), 1715 (s, CO), 1187 (s, C–O); ^1H NMR, δ, ppm: 0.89 (3H, t, CH_3CH$_2$), 1.10 (3H, d, CH_3CH), 1.19 (3H, t, CH_3CH$_2$O), 1.25 (2H, m, CH_2), 1.52 (2H, dt, $J = 7.32$ Hz, CH_2), 2.25 (1H, dd, $J = 16.5$, 5.5 Hz, H-2), 2.50 (2H, m, H-5), 2.74 (1H, dd, $J = 16.5$, 8.8 Hz, H-2), 2.96 (1H, m, H-3), 4.09 (2H, q, OCH_2CH$_3$); ^{13}C NMR, δ, ppm: 13.7 (q), 14.0 (q, CHCH_3), 16.6 (q), 22.2 (t), 25.5 (t), 36.8 (t, C-2), 40.7 (t, C-5), 41.8 (d, C-3), 60.3 (t), 179.3 (s, OC=O), 212.8 (s, C=O). ESI-MS (m/z): 201.0 $[M+H]^+$, 223.0 $[M+Na]^+$, 238.9 $[M+K]^+$.

4.2.2. Ethyl 3-methyl-4-oxononanoate 14. This was prepared as reported[1e] (80% yield). Spectroscopic data are in accordance with those reported in the literature.[1e]

4.2.3. 3-Methyl 4-oxooctanoic acid 17. The racemic ketoester **13** (1.0 g, 5.0 mmol) was refluxed in 100 mL of a 2:1 mixture of dioxane and 6 M HCl for 2 h. Evaporation of the solvent left the pure acid **17**, as a colourless oil, in quantitative yield. IR (neat), cm^{-1}: 3300–3000 (m, OH), 1745 (s, OC=O), 1720 (s, C=O), 1270 (s, C–O). ^1H NMR, δ, ppm: 0.89 (3H, t, CH_3CH$_2$), 1.16 (3H, d, CHCH_3), 1.28 (2H, m, CH_2), 1.52 (2H, dt, $J = 7.3$ Hz, CH_2), 2.30 (1H, dd, $J = 8.8$, 16.5 Hz, H-2), 2.53 (2H, m, H-5), 2.80 (1H, dd, $J = 5.7$, 16.5 Hz, H-2), 2.99 (1H, m, H-3), 10.08 (1H, br, OH); ^{13}C NMR, δ, ppm: 13.8 (q), 16.3 (CHCH_3, q), 22.2 (t), 25.2 (t), 35.6 (t, C-2), 41.0 (t, C-5), 41.7 (d, C-3), 179.8 (s, O–C=O), 212.9 (s, C=O). ESI-MS (m/z): 173 $[M+H]^+$, 195.0 $[M+Na]^+$.

4.2.4. Cyanomethyl 3-methyl-4-oxooctanoate 15. This was prepared as reported in the literature for **16**. A CH_2Cl_2 solution of the acid **17** (0.5 g, 2.9 mmol), chloroacetonitrile (0.74 g, 11.6 mmol) and Et_3N (1.05 mL, 8.7 mmol) was refluxed overnight. After cooling down the mixture, 0.1 N HCl was added and the organic phase separated. The aqueous system was extracted with CH_2Cl_2 twice, the combined organic layers dried and the oily residue obtained after evaporation of the solvent was chromatographed on column (petroleum ether–ethyl acetate 9:1) to give the pure ketoester **15** as an oil. IR (neat), cm^{-1}: 2960, 1756 (OC=O), 1712 (C=O); ^1H NMR ($CDCl_3$), δ, ppm: 0.90 (3H, t, CH_3CH$_2$), 1.18 (3H, d, CH_3CH), 1.22–1.42 (2H, m, CH_2), 1.48–1.70 (2H, m, CH_2), 2.39 (1H, dd, $J = 4.9$, 17.2 Hz, H-2), 2.39–2.68 (2H, m, H-5), 2.87 (1H, dd, $J = 9.1$, 17.2 Hz, H-2), 2.95–3.13 (1H, m, H-3), 4.64, 4.78 (2H, 2d, $J = 15.7$ Hz, CH_2CN); ^{13}C NMR, δ, ppm: 13.8 (q), 16.55 (q, CH_3CH), 22.2 (t), 23.2 (t), 35.75 (t, H-2), 40.7 (t, C-5), 41.75 (d, C-3), 48.3 (t, CH_2CN), 114.3 (s, CN), 170.9 (s, OC=O), 212. 2 (s, C=O). ESI-MS (m/z): 212.0 $[M+H]^+$, 234.0 $[M+Na]^+$, 250.0 $[M+K]^+$.

4.2.5. 3-Methyl-4-oxononanoic acid 18. This was prepared as in the literature.[1e] Spectroscopic data are in accordance with those reported.

4.2.6. Cyanomethyl 3-methyl-4-oxononanoate 16. This was prepared as in the literature. Spectroscopic data are in accordance with those reported.

4.3. Enzymatic hydrolysis of the substrates. General procedure

4.3.1. Enzymatic hydrolysis in H_2O. The racemic γ-ketoesters **13**–**16** (1.0 g), were suspended in distilled H_2O (5 mL/mmol). The pH was adjusted to 7.2 by the addition of 0.1 M NaOH with a microsyringe, after which PPL (1:1 w/w) was added at once under vigorous stirring. The pH was then continuously adjusted to the initial value with 1 M NaOH. At the desired conversion value, the unreacted ester was extracted from the suspension with diethyl ether (three times), using a centrifuge for the separation of the layers. The aqueous phase was acidified to pH 2 with 1 M HCl, and the acidic product extracted with diethyl ether (three times). The enantiomeric excesses of the unreacted esters and those of the acidic products were determined by chiral HRGC, after esterification of the carboxylic function in the latter compounds with diazomethane.

4.3.2. Enzymatic hydrolysis in phosphate buffer. The racemic γ-ketoesters (1.0 g) were suspended in 0.1 M KH_2PO_4–Na_2PO_4 buffer (5 mL/mmol), at pH 7.4. The same procedure as above was then followed.

4.3.2.1. (*S*)-(−)-3-Methyl-4-oxooctanoic acid 17. It was isolated from the hydrolysis of **15** in H_2O at 38% conversion (20% yield); 96% ee $[\alpha]_D^{25}$ −22.6 (*c* 0.4, MeOH), $\Delta\varepsilon_{282} = -0.80$ (MeOH).

4.3.2.2. Methyl (*S*)-(−)-3-methyl-4-oxooctanoate 21. It was obtained by esterification of (*S*)-(−)-**17** with diazomethane; 96% ee, $[\alpha]_D^{25}$ −21 (*c* 0.5, MeOH); IR (neat), cm^{-1}: 1736 (s, OC=O), 1712 (s, CO), 1187 (s, C–O); ^1H NMR, δ, ppm: 0.87 (3H, t, CH_3CH_2), 1.14 (3H, d, $CHCH_3$), 1.28 (2H, m, CH_2), 1.52 (2H, quint., CH_2), 2.29 (1H, dd, $J = 8.8, 16.5$ Hz, H-2), 2.51 (2H, m, H-5), 2.80 (1H, dd, $J = 5.7, 16.5$ Hz, H-2), 2.99 (1H, m, H-3), 4.07 (s, 3H, CH_3O); ^{13}C NMR, δ, ppm: 13.9 (q), 16.7 ($CHCH_3$, q), 22.4 (t), 25.7 (t), 36.9 (t, C-2), 41.0 (t, C-5), 41.9 (d, C-3), 51.6 (CH_3O), 172.4 (s, O–C=O), 213.1 (s, C=O). ESI-MS (*m*/*z*): 187 $[M+H]^+$.

4.3.2.3. Cyanomethyl (*R*)-(+)-3-methyl-4-oxooctanoate 15. This was isolated from the hydrolysis of **15** in H_2O, at 53% conv. (58% yield); >99% ee, $[\alpha]_D^{25}$ +15.2 (*c* 1, THF), $[\alpha]_D^{25}$ +15.7 (*c* 1, MeOH); $\Delta\varepsilon_{284} = +1.2$ (MeOH).

4.3.2.4. Ethyl (*R*)-(+)-3-methyl-4-oxooctanoate 13. This was isolated from the hydrolysis of **13** in phosphate buffer, at 70% conversion (27% yield); 70% ee $[\alpha]_D^{25}$ +8.8 (*c* 1, THF); $[\alpha]_D^{25}$ +9.2 (*c* 1, MeOH).

4.3.2.5. Cyanomethyl (*R*)-(+)-3-methyl-4-oxononanoate 16. This was isolated from the hydrolysis of **16** in H_2O at 54% conv. (63% yield); >99% ee $[\alpha]_D^{25}$ +15.0 (*c* 1.1, THF) {lit.:[11] $[\alpha]_D$ +22.5, (0.2, THF, 92% ee)}; $[\alpha]_D^{25}$ +15.9 (*c* 0.95, MeOH); $\Delta\varepsilon_{284} = +1.0$ (MeOH).

4.3.2.6. (*S*)-(−)-3-Methyl-4-oxononanoic acid 18. This was isolated from the hydrolysis of **16** in H_2O at 33% conv. (25% yield); 97% ee, $[\alpha]_D^{25}$ −30.0 (*c* 1.0, MeOH) {lit.[1e] $[\alpha]_D$ −32 (*c* 0.5, MeOH)}.

4.3.2.7. Methyl (*S*)-(−)-3-methyl-4-oxononanoate 22. This was obtained via esterification of (*S*)-(−)-**18** with diazomethane. Analytical and spectroscopic data are in accordance with the literature.[1e]

4.4. Reductive aminations of cyanomethyl (*R*)-(+)-3-methyl-4-oxooctanoate 15 and cyanomethyl (*R*)-(+)-3-methyl-4-oxononanoate 16

To a stirred solution of the γ-ketoesters (*R*)-(+)-**15** (1.05 g, 5 mmol) and (*R*)-(+)-**16** (1.15 g, 5 mmol), having 99% ee, in MeOH (15 mL), $HCOONH_4$ (50 mmol) and $NaBH_3CN$ (5 mmol) were added. The suspension was stirred overnight at rt, then the solvent evaporated in vacuo. Analysis of the crude mixtures showed the quantitative formation of the γ-lactams as 2:1 mixtures of *cis:trans* diastereomers, which were separated by flash chromatography (eluent *n*-hexane–ethyl acetate 80:20 up to 60:40) with 60% overall yield after chromatography.

4.4.1. (4*R*,5*R*)-(+)-4-Methyl-5-*n*-butylpyrrolidin-2-one 5. (0.150 g, 20% yield); 93% ee $[\alpha]_D^{25}$ +28.6 (*c* 0.5, $CHCl_3$); $[\alpha]_D^{25}$ +28.2 (*c* 0.5, MeOH); $\Delta\varepsilon_{216} = -0.8$ (MeOH). IR (neat), cm^{-1}: 3235 (NH), 1689 (NHCO); ^1H NMR, δ, ppm: 0.87 (3H, t, CH_3CH_2), 0.98 (3H, d, CH_3CH), 1.18–1.48 (6H, m, $(CH_2)_3$), 1.97 (1H, dd, $J = 6.6, 16.1$ Hz, H-3), 2.43 (1H, dd, $J = 16.1, 8.05$ Hz, H-3), 2.52 (1H, m, H-4) 3.51 (1H, m, H-5), 6.40 (1H, br, NH); ^{13}C NMR, δ, ppm: 13.9 (q, CH_3CH_2), 14.5 (q, CH_3CH), 22.6 (t), 28.5 (t), 30.1 (t), 32.6 (d, C-4), 38.6 (t, C-3), 57.6 (d, C-5), 177.9 (s, CO); ESI-MS (*m*/*z*): 156.1 $[M+H]^+$, 178.1 $[M+Na]^+$.

4.4.2. (4*R*,5*S*)-(−)-4-Methyl-5-*n*-butylpyrrolidin-2-one 6. (0.300 g, 40% yield), 93% ee; $[\alpha]_D^{25}$ −28.0 (*c* 1.3, $CHCl_3$); $[\alpha]_D^{25}$ −32 (*c* 0.5, MeOH); $\Delta\varepsilon_{214} = +2.6$ (MeOH). IR (neat), cm^{-1}: 3240 (NH), 1690 (NHCO); ^1H NMR, δ, ppm: 0.90 (3H, t, CH_3CH_2), 1.13 (3H, d, CH_3CH), 1.25–1.70 (6H, m, $(CH_2)_3$), 2.01 (1H, dd, $J = 7.5, 16.0$ Hz, H-3), 2.12 (1H, m, H-4), 2.54 (1H, dd, $J = 8.0, 16.0$ Hz, H-3), 3.16 (1H, m, H-5), 7.05 (1H, br, NH); ^{13}C NMR, δ, ppm: 13.8 (q, CH_3CH_2), 19.2 (q, CH_3CH), 22.6 (t), 28.3 (t), 35.2 (t), 35.5 (d, C-4), 38.7 (t, C-3), 62.1 (d, C-5), 177.6 (s, CO). ESI-MS (*m*/*z*): 156.1 $[M+H]^+$, 178.1 $[M+Na]^+$.

4.4.3. (4*R*,5*R*)-(+)-4-Methyl-5-pentylpyrrolidine-2-one 7. (0.160 g, 20% yield), 93% ee $[\alpha]_{D25}^{25}$ +25.0 (*c* 0.6, $CHCl_3$) {lit.:[3] $[\alpha]_D$ +29.6, $CHCl_3$}; $[\alpha]_D^{25}$ +28.0 (*c* 0.6, MeOH); $\Delta\varepsilon_{216} = -0.85$ (MeOH); IR (Nujol), cm^{-1}: 3230 (NH), 1695 (CONH); ^1H NMR, δ, ppm: 0.87 (3H, t, CH_3CH_2), 0.99 (3H, d, CH_3CH), 1.19–1.50 (8H, m, $(CH_2)_4$), 1.97 (1H, dd, $J = 6.6, 16.1$ Hz, H-3), 2.43 (1H, dd, $J = 16.1, 8.05$ Hz, H-3), 2.52 (1H, m, H-4), 3.54 (1H, m, H-5), 6.40 (1H, br s, NH); ^{13}C NMR, δ, ppm: 13.9 (q, CH_3CH_2), 14.4 (q, CH_3CH), 22.6 (t), 26.2 (t), 30.3 (t), 31.7 (t), 32.6 (d, C-4), 38.5 (t, C-3), 57.6 (d, C-5), 177.8 (s, CO); ESI-MS (*m*/*z*): 170.1 $[M+H]^+$, 192.1 $[M+Na]^+$, 208.0 $[M+K]^+$.

4.4.4. (4*R*,5*S*)-(−)-4-Methyl-5-pentylpyrrolidin-2-one 8. (0.320 g, 40% yield) 93% ee, $[\alpha]_D^{25}$ −36.3 (*c* 1.0, $CHCl_3$); $[\alpha]_D^{25}$ −39.0 (*c* 0.3, MeOH); $\Delta\varepsilon_{214} = 2.6$ (MeOH); IR (neat), cm^{-1}: 3228 (NH), 1690 (CONH); ^1H NMR, δ, ppm: 0.90 (3H, t, CH_3CH_2), 1.12 (3H, d, CH_3CH), 1.20–1.32 (6H, m, $(CH_2)_3$), 1.41 (1H, m, CH_2), 1.52 (1H, m, CH_2), 2.02 (1H, dd, $J = 16.5, 7.6$ Hz, H-3), 2.12 (1H, m, H-4), 2.54 (1H, dd, $J = 16.5, 8.0$ Hz, H-3), 3.17 (1H, m, H-5), 6.40 (1H, br s, NH); ^{13}C NMR, δ, ppm: 13.9 (q, CH_3CH_2), 19.2 (q, CH_3CH), 22.6 (t), 25.9 (t), 30.3 (t), 35.5 (t), 35.6 (d, C-4), 38.7 (t, C-3), 62.1 (d, C-5), 177.5 (s, CO); ESI-MS (*m*/*z*): 170.1 $[M+H]^+$, 192.1 $[M+Na]^+$, 208.0 $[M+K]^+$.

4.5. Reductive aminations of methyl (*S*)-(−)-3-methyl-4-oxooctanoate 21 and methyl-(*S*)-(−)-3-methyl-4-oxononanoate 22

Compounds **21** (96% ee) and **22** (97% ee) were subjected to reductive amination under the above described conditions.

4.5.1. (4*S*,5*S*)-(−)-4-Methyl-5-*n*-butylpyrrolidin-2-one 5. 89% ee; $[\alpha]_D^{25}$ −26.8 (*c* 0.9, MeOH).

4.5.2. (4*S*,5*R*)-(+)-4-Methyl-5-*n*-butylpyrrolidin-2-one 6. 89% ee; $[\alpha]_D^{25}$ +30 (*c* 0.5, MeOH).

4.5.3. (4*R*,5*R*)-(−)-4-Methyl-5-*n*-pentylpyrrolidin-2-one 7. 89% ee; $[\alpha]_D^{25}$ −26.2 (*c* 1, MeOH).

4.5.4. (4*S*,5*R*)-(+)-4-Methyl-5-*n*-pentylpyrrolidin-2-one 8. 89% ee; $[\alpha]_D^{25}$ +36 (*c* 0.6, MeOH).

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