DIASTEREO- AND ENANTIOSELECTIVE SYNTHESIS OF γ- AND- δ-LACTAMS BEARING A PROPIONIC ACID α-SIDE-CHAIN *VIA* MICHAEL ADDITION OF *N*-DIALKYLAMINO LACTAMS TO ENOATES

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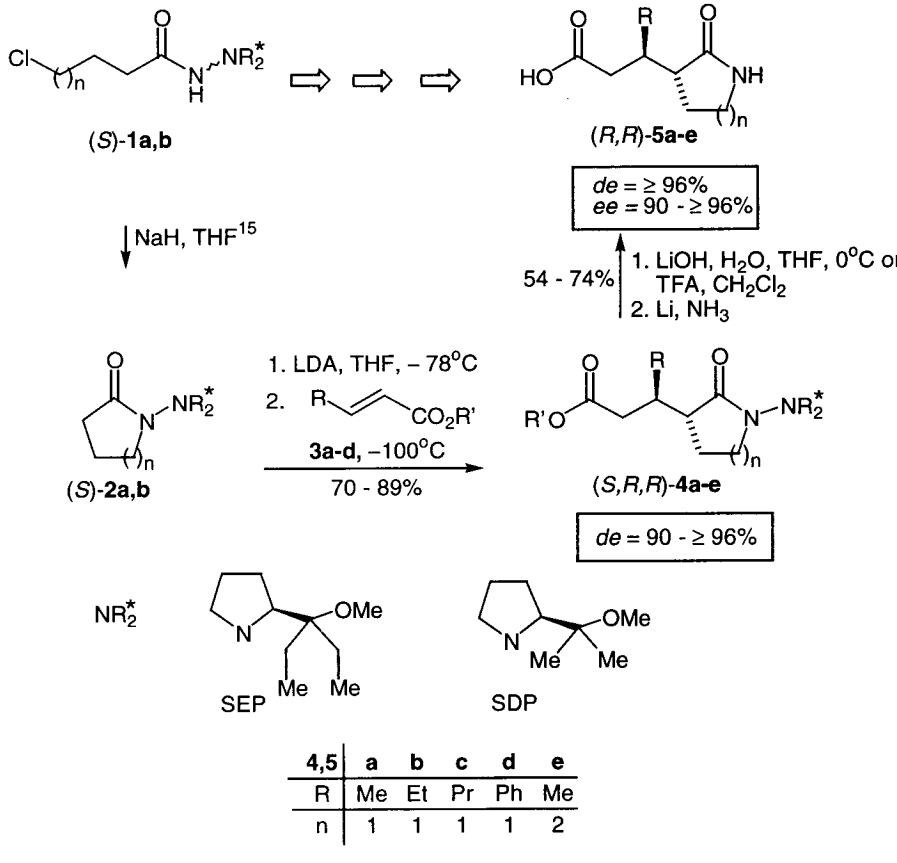
Abstract - γ- and- δ-Lactams [(*R,R*)-**5a-e**] bearing a propionic acid α-side-chain were synthesized in good overall yields (38 - 58 %, two steps) and diastereo- and enantiomeric excesses (*de* = ≥ 96%, *ee* = 90 - ≥ 96%) by 1,4-addition of metalated *N*-dialkylamino lactams [(*S*)-**2a,b**] to enoate Michael acceptors (**3**) followed by saponification of the ester group and subsequent removal of the chiral auxiliary by reductive cleavage of the N-N-bond with lithium in liquid ammonia.

The lactam moiety[1] is a commonly occurring structural feature of various biologically active compounds and natural products, and although most examples are represented by the large class of β-lactams,[2] γ- and δ-lactams are additionally of great interest, since many of them are biologically active.[3] In addition, they are useful building blocks for alkaloids[4] and as lactams are cyclic amides, they can be converted to their corresponding amino acids by ring opening. The class of γ-lactams is especially interesting as their derivatives, the γ-aminobutanoic acids (GABA), are of great importance in the regulation of neurological disorders.[5,6]

Recently various methods for the stereoselective synthesis of α-alkylated γ- and δ-lactams have been developed. Royer, Quirion and Husson *et al.* have carried out diastereoselective alkylations of γ- and δ-lactams derived from (*R*)-(−)-phenylglycinol.[7] Koga and Kobayashi *et al.* used chiral tetradentate ligands

Dedicated to Professor *Teruaki Mukaiyama* on the occasion of his 73rd birthday

for the enantioselective alkylation of lactam enolates.[8] Chung *et al.* reported the preparation of 3-alkyl-2-piperidones by asymmetric hydrogenation of an 3-alkylidene-2-piperidone.[9] Stevenson *et al.* employed a Meerwein-Eschenmoser [3,3] sigmatropic rearrangement to generate a stereogenic center adjacent to the lactam carbonylfunction.[10] In addition, the general bicyclic lactam methodology of Meyers *et al.*[11] must be mentioned. In 1996 we reported the enantioselective synthesis of α-alkylated lactams *via* alkylation of *N*-dialkylamino lactams bearing a chiral auxiliary as part of a hydrazine moiety and subsequent reductive removal of the auxiliary.[12] We now wish to report the stereoselective synthesis of γ- and- δ-lactams bearing a substituted propionic acid α-side-chain by asymmetric Michael addition of lithiated *N*-dialkylamino lactams (**2a,b**) to α,β-unsaturated carboxylic acid esters (**3a-d**) followed by saponification of the ester function and subsequent removal of the chiral auxiliary by reductive cleavage of the N-N bond with lithium in liquid ammonia[13] (Scheme 1).



Scheme 1. Diastereoselective 1,4-additions of lithiated lactams to α,β-unsaturated esters and removal of the auxiliary

For the Michael addition of lithiated 5-membered lactams, (*S*)-1-amino-[2-(1-ethyl-1-methoxypropyl]pyrrolidine (SAEP) as chiral auxiliary resulted in the highest diastereoselectivities, whereas for the addition of the six-membered lactam, (*S*)-1-amino-[2-(1-methyl-1-methoxyethyl]pyrrolidine SADP gave the best results.[14]

Lactams (**2a,b**) were synthesized by cyclization of the corresponding ω-chloroalkano hydrazides (**1a,b**) (n = 1,2) using NaH in THF.[15] Lactams (**2**) were lithiated by treatment with 1.2 equivalents of lithium diisopropylamide in THF at – 78 °C for 3-4 h, with subsequent addition of Michael acceptors (**3**) at – 100 °C, followed by further stirring at – 78 °C overnight. The reaction mixtures of the aliphatic Michael-adducts were quenched at – 30 °C. The Michael-adducts (**4 a-c**) were obtained in good yields (70 - 87%) and excellent diastereoselectivities (*de* ≥ 96%), **4e** was also obtained in good yield, although the *de* of the crude product was slightly lower (90%), and could be increased by flash chromatography (*de* ≥ 96%).

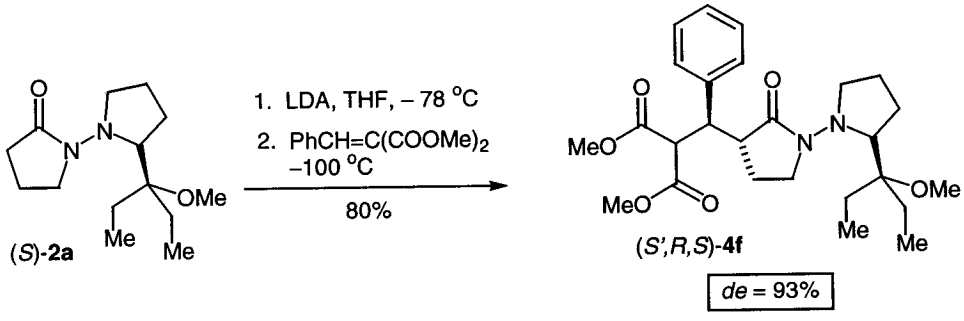
Initially, addition of lactam enolate (**2a**) to methyl cinnamate resulted in up to 40% of the 1,2 addition product with the desired product being obtained only in low yield (< 40%). By using *tert*-butyl cinnamate instead of the methyl ester, the formation of the 1,2 product could be avoided. The reaction mixture of the lithiated lactams (**2a**) with *tert*-butyl cinnamate was quenched at room temperature since quenching at lower temperatures resulted in lower yields. In this way Michael-product (**4d**) was obtained in good yield (77%) and diastereoselectivity (*de* = 90%).

Table 1. *N*-Dialkylamino lactam esters (**4**) prepared by Michael addition of metalated *N*-dialkylamino lactams [(*S*)-**2**] to (*E*)-enoates (**3**)

Product	NR_2*	n	R	R'	cy (%)	*de*[a] (%)	$[\alpha]_D^{23}$ (c, $CHCl_3$)[b]
(*S'*, *R*, *R*)-**4a**	SEP	1	Me	Me	84	≥ 96	– 25.4° (1.32)
(*S'*, *R*, *R*)-**4b**	SEP	1	Et	Me	89	91	– 22.1° (0.78)
(*S'*, *R*, *R*)-**4c**	SEP	1	Pr	Me	70	≥ 96	– 23.6° (0.85)
(*S'*, *R*, *R*)-**4d**	SEP	1	Ph	*t*-Bu	77	90	+ 14.8° (0.53)
(*S'*, *R*, *R*)-**4e**	SDP	2	Me	Me	70	90 (≥ 96)[c]	+ 21.5° (0.82)

[a] Determined by ^{1}H NMR and ^{13}C NMR spectroscopy. [b] All optical rotations were measured in Uvasol grade $CHCl_3$ at temperatures T = 23 °C ± 1 °C. [c] After column chromatography.

The addition of the lithiated lactam (**2a**) to the doubly activated Michael acceptor benzylidene-dimethylmalonate, afforded Michael adduct (**4f**) in good yield (80%) and good diastereoselectivity (93%, Scheme 2).



Scheme 2. Addition of lithiated lactam (**2a**) to a Knoevenagel acceptor

The *de*-values of the Michael products (**4**) were determined by ^{1}H- and ^{13}C-NMR spectroscopy.
The relative and absolute configuration of compound of **4f** was determined to be (*S',R,S*) by X-Ray structure analysis and thus confirmed the formation of the *anti*-isomers of **4**, (Figure). The configurations of the other compounds are based on the assumption of a uniform reaction pathway for the Michael addition.

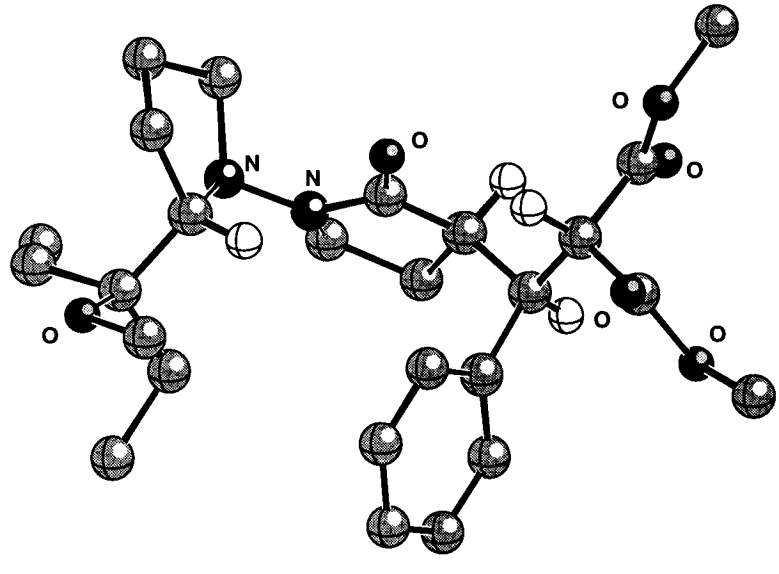


Figure. X-Ray structure of (2'*S*, *R*, *S*)-(**4f**)

The sense of asymmetric induction α- to the carbonyl is in agreement with that observed previously in the α-alkylation of *N*-dialkylamino lactams.[12] The relative configuration (*anti*) is the same as our findings for the formation of Michael adducts of enoates and lithiated SAMP hydrazones,[16] and corresponds with Heathcock's observations in Michael additions of α,β-unsaturated ketones to lithiated *N*-methyl-2-pyrrolidinone.[17]

Removal of the auxiliary was achieved by reductive cleavage of the N-N bond using lithium in liquid ammonia,[13] since this method has been succesfully employed for similar α-substituted lactams.[12] However, initial experiments indicated that when the esters (**4**) were used, mainly decomposition occurred. To avoid decomposition in the cleavage reaction, it was first necessary to generate the corresponding carboxylic acids.

The acids were prepared from the methyl esters (**4a, b, c, e**) by saponification with an aqueous 1M LiOH-solution at 0 °C or by removal of the *tert*-butyl group from the *tert*-butyl ester (**4d**) with trifluoroacetic acid. The acids were subjected to cleavage of the N-N bond without purification. Cleavage of the N-N bond was then carried out with 5 equivalents of lithium in liquid ammonia at – 33 °C to afford the lactam carboxylic acids (**5**) in moderate to good yields (54 - 74%). The lactam carboxylic acids (**5a-e**) were purified by recrystallization from Et_2O/MeOH to give colourless crystalline solids.

Table 2. Lactam carboxylic acids (**5**) prepared by saponification of the ester and subsequent reductive removal of the auxiliary

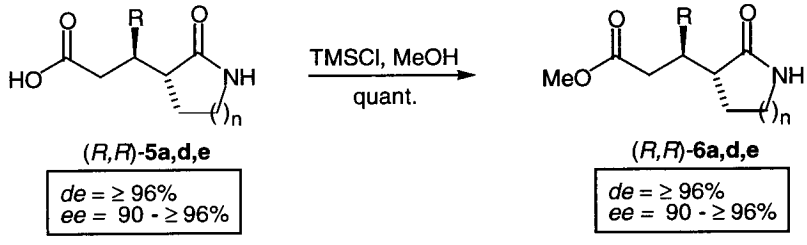
	n	R	cy[a](%)	*de* (%)[b]	*ee* (%)	$[\alpha]_D^{23}$ (c, MeOH)	mp (°C)
(*R*,*R*)-**5a**	1	Me	66	≥ 96	≥ 96[c]	+ 2.3° (0.66)	142 - 144
(*R*,*R*)-**5b**	1	Et	65	≥ 96	≥ 96[d]	+ 5.0° (0.79)	116 - 117
(*R*,*R*)-**5c**	1	Pr	54	≥ 96	≥ 96[d]	+ 8.2° (0.61)	122 - 123
(*R*,*R*)-**5d**	1	Ph	66	≥ 96	90[c]	+ 44.8° (0.35)	157 - 158
(*R*,*R*)-**5e**	2	Me	74	≥ 96	92[c]	+ 48.6° (0.75)	171 - 173

[a] Yield over two steps [b] Determined by ^{13}C-NMR-spectroscopy [c] Determined by ^{1}H-NMR shift experiment of the corresponding methyl ester using (*R*)-(–)-(9-anthryl)-2,2,2-trifluoroethanol [d] Determined by ^{1}H-NMR shift experiment of the acid using (*R*)-(–)-(9-anthryl)-2,2,2-trifluoroethanol

The *de*-values of compounds (**5**) were determined by ^{13}C-NMR spectroscopy, the *ee*-values of **5b, c** by ^{1}H-NMR shift experiments employing the chiral cosolvent (R)-(–)-9-anthryl-2,2,2-trifluoroethanol.[18] For the determination of the enantiomeric excesses of **5a, d, e** it was necessary to prepare the corresponding

methyl esters due to the low solubility of the compounds in $CDCl_3$. The *ee*-values of the esters (**6**), which were synthesized with trimethylsilyl chloride in methanol,[19] (Scheme 3) could also be determined using the chiral shift cosolvent (*R*)-(−)-9-anthryl-2,2,2-trifluoroethanol.

In all the cases the *ee*-values of **5** were identical with the *de*-values of **4**, indicating that no racemisation or epimerisation had occurred during saponification or N-N cleavage.



Scheme 3. Esterification of lactam carboxylic acids (**5**)

The auxiliary could be recycled in good yields by extracting the amine from the basic solution of the crude cleavage product with dichloromethane. The amines can be converted to the hydrazines according to the literature by nitrosation with *tert*-butyl nitrite and subsequent reduction of the nitrosamine by $LiAlH_4$.[20]

In summary, we have presented an efficient method for the diastereo- and enantioselective synthesis of α-substituted γ- and δ-lactams bearing a propionic acid side-chain, which represent interesting building blocks for natural product synthesis, by Michael addition of lithiated *N*-alkylamino lactams to enoates and reductive removal of the auxiliary by N-N bond cleavage.

EXPERIMENTAL

General : All reactions were carried out using standard Schlenk techniques. All reagents were of commercial quality used from freshly opened containers. Solvents were dried and purified by conventional methods prior to use. THF, Et_2O were freshly distilled from Na under Ar. *n*-Buli (1.6 N in hexane) was purchased from Merck, Darmstadt. Preparative column chromatography: Merck silica gel 60, particle size 0.040-0.063 mm (230-400 mesh, flash). Analytical TLC : silica gel 60 F_{254} plates, Merck, Darmstadt. *Apparatus.* All melting points (Büchi apparatus, system Dr. Tottoli) are uncorrected. Optical rotation values were measured using a Perkin-Elmer P 241 polarimeter, solvents used were of Merck UVASOL-quality. Analytical GC : Siemens Sichromat 2 or 3 equipped with Shimadzu Chromopac C-R3A, FID, using SE−54 capillary column (25 m x 0.25 mm), carrier gas : nitrogen. Preparative HPLC: GILSON Abimed; Merck. Lichrosorb®-column (25 cm x 25 mm, silica 60, particle size 0.007 mm), UV detection. Microanalyses were obtained with Elementar Vario EL element analyzer.

MS: Varian MAT 212 (EI 70 eV) with DIE ionisation. HRMS: Finnigan MAT, MAT95. IR spectra: Perkin-Elmer FT/IR 1750. ^{1}H-NMR spectra (300, 400 and 500 MHz), ^{13}C-NMR (75, 100 and 125 MHz): Varian VXR 300, Gemini 300, Varian Inova 400 or Varian Unity 500 , TMS was used as internal standard. - Chemical nomenclature was verified by the programme Autonom (version 1.1, Beilstein Informationssysteme GmbH, 1994).

(*S*)-(−)-5-Chloro-*N*-[2-(1-methyl-1-methoxyethyl]pyrrolidin-1-yl]pentanamide (1b). According to the general procedure[15] 5-chloropentanoyl chloride (1.55 g, 10 mmol) was treated with SADP (1.58 g, 10 mmol) and triethylamine (1.01 g, 10 mmol). After purification by flash chromatography (ethyl acetate/triethylamine = 99/1) 2.58 g (93 %) was obtained as a yellow oil. R_f = 0.36 (ethyl acetate/triethylamine = 99/1); $[\alpha]_D^{23}$ − 12.6° (c = 0.99, benzene); IR ($CHCl_3$): ν 3240 cm^{-1} (s, NH), 3060 (m), 2970, 2875, 2830 (s), 1655 (s), 550 (m), 1460, 1380, 1365 (s), 1305, 1285, 1240, 1180 (m), 1150, 1070 (s), 995, 930 (w), 730, 650 (m). ^{1}H-NMR (300 MHz, $CDCl_3$) : δ 1.11, 1.12, 1.16 [3s, 12 H, CH_3 (*E* and *Z*)], 1.56-2.00 [m, 16 H, $ClCH_2\underline{C}H_2\underline{C}H_2$, $NCH\underline{C}H_2\underline{C}H_2$, (*E* and *Z*)], 2.11 [t, *J* = 6.7 Hz, 2 H, $COC\underline{H}_2$], 2.57 - 2.71 [m, 3 H, $NC\underline{H}H$, $COC\underline{H}_2$, *E* or *Z*], 2.90 [m, 3 H, $NC\underline{H}_2$, *E* and *Z*], 3.10 [dd, *J* = 6.4, 6.8 Hz, 1 H, $NC\underline{H}$, *E* or *Z*,], 3.15, 3.19 [2s, 6 H, $OC\underline{H}_3$, *E* and *Z*], 3.32 [m, 1 H, $NC\underline{H}$, *E* or *Z*], 3.44, 3.57 [2t, *J* = 6.4 Hz, $ClC\underline{H}_2$, *E* and *Z*], 7.03, 7.45 [2s, 2 H, $N\underline{H}$, *E* and *Z*) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 20.59, 21.01, 21.77 [CH_3, (E/Z)], 22.03, 22.46, 22.82, 22.88, 26.02, 26.33 [$ClCH_2CH_2\underline{C}H_2$, $NCH\underline{C}H_2\underline{C}H_2$, (*E* and *Z*)], 30.86, 32.00, 32.44, 34.03 [$CO\underline{C}H_2$, $ClCH_2\underline{C}H_2CH_2$, (*E* and *Z*)], 33.60, 44.80 [$ClCH_2$, (*E* and *Z*)], 49.81, 49.09 [OCH_3, (*E* and *Z*)], 56.12, 59.31 [NCH_2, (*E* and *Z*)], 70.38, 71.76 [NCH, (*E* and *Z*)], 77.45, 77.92 [C, (*E* and *Z*)], 170.64, 176.78 [C=O, (*E* and *Z*)] ppm. MS (70 eV) : *m/z* (%) 278 (M^+ +2, 1), 277 (M^+ +1, 0.8), (M^+, 3), 2.5 (33), 204 (11), 203 (M^+ − $CH_3OC(CH_3)_2$, 100), 136 (6), 85 (51), 73 ($CH_3OC(CH_3)_2^+$, 12), 70 (11), 69 (6), 68 (28), 57 (13), 55 (13), 43 (8), 41 (14). Anal. Calcd for $C_{13}H_{24}N_2O_2Cl$: C, 56.41; H, 9.10; N, 10.12. Found : C, 56.91; H, 9.48; N, 9.67.

(*S*)-(−)-1-[2'-(1-Methyl-1-methoxyethyl)pyrrolidin-1-yl]piperidin-2-one (2b). According to the general procedure[15] 2.52 g (9.0 mmol) of SDP hydrazide (**1b**) were cyclised with 0.43 g (1.2 mmol) NaH (60 %), yielding 1.98 g of **2b** as a colourless oil after column chromatography (ether/pentane: 2/1+ 1 % Et_3N); Yield: 91%; R_f = 0.68 (ether/pentane: 2/1+ 1 % Et_3N); $[\alpha]_D^{23}$ − 18.6° (c = 1.21, $CHCl_3$); IR ($CHCl_3$): ν 2970 cm^{-1} (s), 2940, 2880, 2830 (s), 1685 (ν(C=O), s), 1590, 1550 (s), 1510 (m), 1460 (s), 1425 (m), 1380 (m), 1330, 1280 (m), 1240 (m), 1130 (s), 1005 (w), 910 (w). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.08, (2s, 6 H, $C\underline{H}_3$), 1.40 - 1.98 (m, 7 H, $NCHC\underline{H}_2C\underline{H}H$, $CONCH_2C\underline{H}_2C\underline{H}_2$), 2.10 (m, 1 H, $NCHCH_2C\underline{H}H$), 2.34 (b t, *J* = 6.4 Hz, $COC\underline{H}_2$), 3.13 (s, 3 H, $OC\underline{H}_3$), 3.16 (dd, *J* = 3.7, 6.5 Hz, $NC\underline{H}H$),

3.40 (m, 2 H, CONCHH, CONCHH), 3.68 (td, J = 5.7, 12.4 Hz, 1 H, NCHH), 3.99 (dd, J = 4.7, 9.4 Hz, 1 H, NCH) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 21.01, 23.72, 24.05, 27.25, ($NCHCH_2CHH$, $CONCH_2CH_2CH_2$), 21.31, 22.24 (2 CH_3), 33.96 ($COCH_2$)), 48.92 (OCH_3), 51.83, 52.29 (NCH_2, $CONCH_2$), 63.75 (NCH), 77.98 (C), 168.63 (C=O) ppm. MS (70 eV): *m/z* (%) 241 (M^+, 0.2), 168 (10), 167 ($M^+ - CH_3OC(CH_3)_2$, 100), 109 (8), 100 (33), 73 (11), 70 (8), 69 (6), 68 (24), 56 (10), 55 (10). Anal. Calcd for $C_{13}H_{24}N_2O_2$: C, 64.97; H, 10.06; N, 11.66. Found : C, 64.65; H, 10.15; N, 11.94.

General procedure 1 for the Michael addition with lithiated *N*-dialkylamino lactams :

To a solution of *N*-dialkylamino lactam (**2**) (1.5 mmol) in THF (7 mL) at – 78 °C was slowly added a solution of lithium diisopropylamide (1.8 mmol) in THF (15 mL) *via* double-ended needle. The mixture was stirred for 3-4 h at – 78 °C and then cooled to – 100 °C. The liquid Michael acceptors (**3**) (neat) were slowly added dropwise [solid Michael acceptors were dissolved in THF (1 mL)]. The mixture was stirred over night at – 78 °C and then warmed to – 30 °C (In case of the *tert*-butyl esters the reaction was quenched at rt). Then the reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (15 mL). The aqueous phase was extracted with CH_2Cl_2 (3x50 mL). The combined organic phases were washed with H_2O (25 mL) and dried over $MgSO_4$. After removal of the solvent, the residue was purified by flash chromatography (SiO_2; ether/pentane, 1:2) to afford the Michael adducts (**4**).

General procedure 2 for the preparation of the acids from esters (4):

The methyl esters (**4**) (1 mmol) were dissolved in THF (2 mL/mmol) and cooled to 0 °C. Then 1.5 - 3.0 mL of an aqueous 1 N LiOH solution were added. The reaction was monitored by TLC-control, after completion of the reaction 1-2 mL of 4 N HCl was added (pH 1-2) and the aqueous phase was extracted with CH_2Cl_2 (3x50 mL) and the combined organic phases were dried over $MgSO_4$. After removal of the solvent *in vacuo* (and high vacuum) the crude products were used in the next step without further purification.

General procedure 3 for the N-N bond cleavage:

Pieces of lithium wire (5 eq.) were added to liquid NH_3, which was placed in a three necked flask with dry-ice condenser. To the dark-blue solution the crude *N*-dialkylaminolactam acids (**4**) in anhydr. THF (10 mL/mmol) were added at – 78 °C. Then the cooling bath was removed and the solution was kept under reflux (– 33 °C) until the blue colour dissappeared (after 5-15 min). The reaction was quenched with solid NH_4Cl (12 eq.) and the NH_3 was evaporated at rt. The solid residue was dissolved in 5 mL/mmol of aqueous 1N LiOH (the flask was washed twice with 3 mL/mmol 1 N LiOH) and extracted twice with 10 mL of CH_2Cl_2 to remove the amine. The aqueous solution was cooled to 0°C under stirring

and a 4 N HCl solution was added until the pH was adjusted to 1-2, followed by extraction with CH_2Cl_2 (5 x 30 mL). The combined organic phases were dried over $MgSO_4$, concentrated *in vacuo* and purified by recrystallization (Et_2O/MeOH) to afford the final products (**5**).

(2'*S*,*R*,*R*)-(−)-3-[2'-(1-Ethyl-1-methoxypropyl-2-oxobipyrrolidinyl-3-yl)-3-butanoic Acid Methyl Ester (4a). Lactam (**2a**) (1.5 mmol, 382 mg) was metalated for 3 h according to general procedure 1 with 1.8 mmol of lithium diisopropylamide, then 1.8 mmol (180 mg) of methyl crotonate was added yielding 440 mg of **4a** as a colourless oil after column chromatography (silica gel, ether/pentane: 1/2);Yield : 84%; R_f = 0.24 (ether/pentane: 1/1); *de* ≥ 96%; $[\alpha]_D^{23}$ − 25.4° (c = 1.32, $CHCl_3$); IR ($CHCl_3$) ν 2970 cm^{-1} (s), 2880 (s), 2825 (m), 1740 (s, ν(C=O)), 1685 (s, ν(C=O)), 1460 (s), 1435 (s), 1380 (m), 1345 (w), 1310 (m), 1275, 1195, 1170 1080 (s), 1030, 1010, 945, 915, 880 (w). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.85, 0.87 (2t, *J* = 7.4 Hz, 6 H, $CH_2C\underline{H}_3$), 1.02 (d, *J* = 6.7 Hz, 3H, CH_3), 1.48 - 2.11 (m, 10 H, $C\underline{H}_2CH_3$, $NCH_2C\underline{H}_2C\underline{H}_2$, $CONCH_2C\underline{H}_2$), 2.25 – 2.41 (m, 2H, $CH_3C\underline{H}C\underline{H}$), 2.45 (dd, *J* = 8.5, 15.7 Hz, 1 H, $COC\underline{H}H$), 2.62 (dd, *J* = 8.5, 14.1 Hz, 1 H, $COCH\underline{H}$), 3.12 (m, 2H, $NNC\underline{H}_2$), 3.26 (s, 3 H, $OC\underline{H}_3$), 3.43 (m, 2H, $CONC\underline{H}_2$), 3.66 (s, 3H, $COOC\underline{H}_3$), 3.68 (br s, 1H, $NNC\underline{H}$) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 8.10, 8.58 ($CH_2\underline{C}H_3$), 16.25 (CH_3), 20.80, 24.03, 24.22, 26.21, 26.28 ($\underline{C}H_2CH_3$, $NCH_2\underline{C}H_2\underline{C}H_2$, $CONCH_2\underline{C}H_2$), 37.96 ($\underline{C}H_2COOCH_3$), 31.14, 44.88 ($\underline{C}H\underline{C}HCO$), 50.13 ($OCH_3$), 51.46 ($COO\underline{C}H_3$), 52.34 ($N\underline{C}H_2$), 65.15 ($N\underline{C}H$), 79.88 (C), 173.47, 173.24 (CON, $\underline{C}OOCH_3$) ppm. MS (70 eV); *m/z* (%) 354 (M^+, 1), 253 ($M^+ - CH_3OC(CH_2CH_3)_2$, 100), 101 ($CH_3OC(CH_2CH_3)_2^+$, 4). Anal. Calcd for $C_{19}H_{34}N_2O_4$: C, 64.38; H, 9.67; N, 7.90. Found C, 64.90; H, 9.85; N, 8.23.

(2'*S*,*R*,*R*)-(−)-3-[2'-(1-Ethyl-1-methoxypropyl-2-oxobipyrrolidinyl-3-yl)-3-pentanoic Acid Methyl Ester (4b). Lactam (**2a**) (1.5 mmol, 382 mg) was metalated for 3 h according to general procedure 1 with 1.8 mmol of lithium diisopropylamide, then 1.8 mmol (205 mg) of methyl pentenoate (**3b**) was added yielding 465 mg of **4b** as a colourless oil after column chromatography (silica gel, ether/pentane: 1/2); Yield : 84%; R_f = 0.47 (ether/pentane = 1/2); *de* ≥ 96% (^{13}C-NMR); $[\alpha]_D^{23}$ − 17.9° (c = 0.70, $CHCl_3$); IR ($CHCl_3$) : ν 2980 cm^{-1} (s), 2885 (s), 2830 (m), 1740 (s, ν(C=O)), 1690 (s, ν(C=O)), 1460 (s), 1435 (m), 1375 (m), 1320, 1310 (w), 1270 (m),1190, 1170 (m), 1140, 1110 (w), 1080 (m), 1020 (w), 920 (w). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.85, 0.88, 0.92 (3t, *J* = 7.3 Hz, 9 H, $CH_2C\underline{H}_3$), 1.30 - 2.06 (m, 12 H, $C\underline{H}_2CH_3$, $NCH_2C\underline{H}_2C\underline{H}_2$, $CONCH_2C\underline{H}_2$), 2.20 (dd, *J* = 8.5, 15.7 Hz, 1 H, $COC\underline{H}H$), 2.26 (m, 1 H, $CH_2C\underline{H}CH$), 2.54 (m, 2 H, $COCH\underline{H}$, $CH_2CHC\underline{H}$), 3.12 (m, 2H, $NNC\underline{H}_2$), 3.26 (s, 3 H, $OC\underline{H}_3$), 3.42 (m, 2H, $CONC\underline{H}_2$), 3.66 (s, 3H, $COOC\underline{H}_3$), 3.70 (br s, 1H, $NNC\underline{H}$) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 8.06, 8.63 ($CH_2\underline{C}H_3$), 11.73 (CH_3), 19.72, 23.95, 24.20, 26.23, 26.28 ($\underline{C}H_2CH_3$, $NCH_2\underline{C}H_2\underline{C}H_2$, $CONCH_2\underline{C}H_2$),

35.34 ($\underline{C}H_2COOCH_3$), 36.98, 42.70 ($\underline{C}H\underline{C}HCO$), 50.11 ($OCH_3$), 51.49 ($COO\underline{C}H_3$), 52.94 ($N\underline{C}H_2$), 65.21 ($N\underline{C}H$), 79.89 (C), 173.59, 173.68 (CON, $\underline{C}OOCH_3$) ppm - MS (70 eV); *m/z* (%) = 368 (M^+, 0.5), 267 ($M^+ - CH_3OC(CH_2CH_3)_2$, 100), 101 ($CH_3OC(CH_2CH_3)_2^+$, 5). Anal. Calcd for $C_{20}H_{36}N_2O_4$: C, 65.19; H, 9.85; N, 7.60. Found C, 64.82; H, 9.60; N, 7.69.

(2'*S*,*R*,*R*)-(−)-3-[2'-(1-Ethyl-1-methoxypropyl-2-oxobipyrrolidinyl-3-yl)-3-hexanoic Acid Methyl Ester (4c). Lactam (**2a**) (1.5 mmol, 382 mg) was metalated for 3 h according to general procedure 1 with 1.8 mmol of lithium diisopropylamide, then 1.8 mmol (230 mg) of methyl hexenoate (**3c**) was added yielding 395 mg of **4c** as a colourless oil after column chromatography (silica gel, ether/pentane: 1/2); Yield : 70%; R_f = 0.19 (ether/pentane: 1/2); *de* ≥ 96% (^{13}C-NMR); $[\alpha]_D^{23}$ − 23.6° (c = 0.85, $CHCl_3$); IR ($CHCl_3$): ν 2960 cm^{-1} (s), 2875 (s), 2830 (sh), 1740 (s, ν(C=O)), 1680 (s, ν(C=O)), 1455 (s), 1435 (m), 1380 (m), 1310 (m), 1275 (s),1190, 1170 (s), 1140, 1110 (m), 1080 (s), 1030 (m), 920 (m), 880 (m). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.87 (2t, *J* = 7.7 Hz, 6 H, $CH_2C\underline{H}_3$), 0.90 (t, *J* = 6.9 Hz, 3 H, $CH_2CH_2C\underline{H}_3$), 1.25 - 2.05 (m, 14 H, $C\underline{H}_2CH_3$, $CH_3C\underline{H}_2C\underline{H}_2$, $NCH_2C\underline{H}_2C\underline{H}_2$, $CONCH_2C\underline{H}_2$), 2.20 (dd, *J* = 8.2, 15.1 Hz, 1 H, $C\underline{H}HCOOCH_3$), 2.35 (m, 1 H, $CH_2C\underline{H}CHCO$), 2.55 (m, 2 H, $COCH\underline{H}$, $CH_2CHC\underline{H}CO$), 3.12 (m, 2H, $NC\underline{H}_2$), 3.26 (s, 3 H, $OC\underline{H}_3$), 3.41 (m, 2H, $CONC\underline{H}_2$), 3.67 (s, 3H, $COOC\underline{H}_3$), 3.67 (br s, 1H, $NNC\underline{H}$) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 8.06, 8.64 ($CH_2\underline{C}H_3$), 14.19 (CH_3), 19.89, 20.35, 24.11, 24.26, 26.28 ($\underline{C}H_2CH_3$, $NCH_2\underline{C}H_2CH_2$, $CONCH_2\underline{C}H_2$), 33.33 ($CH\underline{C}H_2CH_2$), 35.71 ($\underline{C}H_2COOCH_3$), 35.22, 43.06 ($\underline{C}H\underline{C}HCO$), 50.10 ($OCH_3$), 51.47 ($COO\underline{C}H_3$), 52.43 ($N\underline{C}H_2$), 65.21 ($N\underline{C}H$), 79.93, (C), 173.62 (CON, $\underline{C}OOCH_3$) ppm. MS (70 eV): *m/z* (%) 382 (M^+, 0.4), 295 (6), 282 (17), 281 ($M^+ - CH_3OC(CH_2CH_3)_2$, 100), 97 (5). Anal. Calcd for $C_{21}H_{38}N_2O_4$: C, 65.93, H. 10.01, N, 7.32; Found: C, 66.05, H, 10.24, N, 7.59.

(2'*S*,*R*,*R*)-(−)-3-[2'-(1-Ethyl-1-methoxypropyl-2-oxobipyrrolidinyl-3-yl)-3-phenylpropionic Acid *tert*-Butyl Ester (4d). Lactam (**2a**) (1.5 mmol, 382 mg) was metalated for 3 h according to general procedure 1 with 1.8 mmol of lithium diisopropylamide, then 1.8 mmol (368 mg) of cinnamic acid *tert*-butyl ester (**3c**) was added yielding 530 mg of **4d** as a colourless oil after column chromatography (silica gel, ether/pentane: 1/2). Yield : 77 %; R_f = 0.32 (ether/pentane: 1/1); *de* = 90 %; $[\alpha]_D^{23}$ + 14.8° (c = 0.53, $CHCl_3$); IR ($CHCl_3$): ν 2975 cm^{-1}(s), 2940, 2880 (s), 1725 (s, ν(C=O)), 1690 (s, ν(C=O)), 1605 (w), 1585 (w), 1495 (w), 1455 (w), 1415, 1395 (m), 1370 (m), 1275, 1255 (m), 1215 (m), 1140 (s), 1080 (m), 920 (w), 850 (w), 700 (m), 665 (w). ^{1}H-NMR (300 MHz, C_6D_6): δ 0.80, 0.88 (2t, *J* = 7.7 Hz, 9 H, $CH_2C\underline{H}_3$), 1.24 (s, 9 H, $C(C\underline{H}_3)_3$), 1.30 - 2.00 (m, 10 H, $C\underline{H}_2CH_3$, $NCH_2C\underline{H}_2C\underline{H}_2$, $CONCH_2C\underline{H}_2$), 2.48 (dt, *J* = 3.6, 9.6 Hz, 1 H, $CHC\underline{H}CO$), 2.73 (q, *J* = 8.0 Hz, 1 H, $NC\underline{H}H$), 2.83 (br s, 1 H, $NCH\underline{H}$), 2.93 (ddd, *J* = 4.4, 6.6, 8.5, 1 H, $CONC\underline{H}HCH_2$), 3.05 (s 3 H, $OC\underline{H}_3$), 3.05 (m, 1 H, $CONCH\underline{H}CH_2$), 3.11 (dd, *J* = 9.7, 15.6

Hz, CHHCOO), 3.28 (dd, J = 6.3, 15.7 Hz, CHHCOO), 3.57 (ddd, J = 3.6, 6.0, 9.6, 1 H, CHCHCO), 3.87 (br s, 1H, NNCH), 7.00 - 7.30 (m, 5 H, CH $_{arom}$) ppm. ^{13}C-NMR (100MHz, C_6D_6) : δ 8.43, 8.69 (CH_2CH_3), 21.16, 24.59, 24.68, 26.48, 26.58 ($CONCH_2CH_2$, $NCH_2CH_2CH_2$, CH_2CH_3), 27.93 ($C(CH_3)_3$), 37.81 (CH_2COO-*t*-Bu), 43.16, 45.41 (CHCHCO), 49.15 (OCH_3), 51.35 ($CONCH_2$, NCH_2), 65.48 (NCH), 79.64, 79.68 ($C(CH_3)_3$, $C(CH_3)_2$), 126.83, 128.62, 129.45 (CH $_{arom}$), 141.61 (C $_{arom}$), 171.52, 172.25 (COO-*t*-Bu, CON). MS (70 eV): *m/z* (%) : 458.6 ($M^{+\cdot}$, 0.1), 385 (6), 358 (23), 357 ($M^+ - CH_3OCEt_2$, 100), 302 (8), 301 (44), 216 (10), 152 (9), 131 (8), 101 ($CH_3OCEt_2^+$, 11), 97 (18), 70 (6), 69 (6), 68 (8), 59 (6), 57 (16). Anal. Calcd for $C_{27}H_{42}N_2O_4$: C, 70.71, H. 9.23, N, 6.11; Found: C, 70.69, H, 9.52, N, 6.40.

(2'*S*,*R*,*R*)-(−)-3-{1-[2-Methoxy-methylethyl)pyrrolidin-1-yl]-2-oxopiperidin-3-yl}butanoic Acid Methyl Ester (4e). Lactam (**2b**) (1.5 mmol, 360 mg) was metalated for 3 h according to general procedure 1 with 1.8 mmol of lithium diisopropylamide, then 1.8 mmol (230 mg) of methyl crotonate (**3a**) was added yielding 360 mg of **4e** as a colourless oil after column chromatography (silica gel, ether/pentane: 1/2). Yield : 65 %; R_f = 0.24 (ether/pentane: 1/1); *de* = 90 (≥ 96 %, after chromatography); $[\alpha]_D^{23}$ + 21.5° (c = 0.82, $CHCl_3$); IR ($CHCl_3$): ν = 2950 cm^{-1} (s), 2875, 1740 (s, ν(C=O)), 1640 (s, ν(C=O)), 1460, 1425, 1420 (s), 1380, 1360 (s), 1305 (s), 1265 (s), 1195, 1175, 1150 (s), 1090, 1075 (m), 1010 (m), 900 (w). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.99 (d, J = 7.4 Hz, 3 H, $CHCH_3$), 1.05, 1.10 (2s, 6 H, CH_3), 1.36 - 1.94 (m, 7 H, $NCHCH_2CH_2$, $CONCH_2CH_2CHH$), 2.13 (m, 1 H, $CONCH_2$, CH_2CHH), 2.23 (dd, J = 9.4, 14.7 Hz, 1 H, COOCHH), 2.29 (m, 1 H, CHCHCO), 2.61 (m, 2 H, CHCHCO, COOCHH), 3.14 (s, 3 H, OCH_3), 3.14 (m, 1 H, NCHH), 3.36 (m, 2 H, CONCHH, NCHH), 3.66 (s, 3 H, $COOCH_3$), 3.66 (m, 1 H, $COOCH_3$, CONCHH), 3.84 (dd, J = 4.7, 9.4 Hz, NCH) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 16.95 ($CHCH_3$), 20.43, 21.86 (CH_3), 23.14, 23.81, 28.00 ($NCHCH_2CH_2$, $CONCH_2CH_2CH_2$), 31.81 (CHCO), 38.33 (CH_2COOCH_3), 47.62 ($CHCH_3$), 48.94 (OCH_3), 51.36 ($COOCH_3$), 51.74, 52.21 ($NCOCH_2$, NCH_2), 65.41 (NCH), 78.07 (C), 170.05, 173.85 (CON, $COOCH_3$) ppm. MS (CI, Isobutane, 100 eV): *m/z* (% b.p.) = 342 (M^+ + 2, 20), 341 (M^+ + 1, 100), 309 (9), 267 (10). Anal. Calcd for $C_{18}H_{32}N_2O_4$: C, 63.50; H, 9.47; N, 8,23. Found C, 63.31; H, 9.69; N, 8.46.

(2'*S*,*R*,*S*)-(+)-2-{2'-[1-Ethyl-1-methoxypropyl)-2-oxobipyrrolidin-3-yl]phenylmethyl}malonic Acid Dimethyl Ester (4f). Lactam (**2a**) (1.5 mmol, 382 mg) was metalated for 3 h according to general procedure 1 with 1.8 mmol of lithium diisopropylamide, then 1.8 mmol (396 mg) of 2-benzylidene-malonic acid dimethylester was added yielding 570 mg of **4f** as a colourless solid after column chromatography (silica gel, ether/pentane: 1/2). Yield : 80%; R_f = 0.40 (ether/pentane = 1/2); *de* = 93 %

(^{1}H-NMR); mp : 77 - 79 °C; $[\alpha]_D^{23}$ + 78.5° (c = 1.04, $CHCl_3$); IR ($CHCl_3$) : ν 2970 cm^{-1}(s), 2955 (s), 2880 (m), 1755, 1735 (ν(C=O), s), 1680 (ν(C=O), s), 1455, 1435 (s), 1300, 1260 (s), 1200, 1180, 1150 (s), 1115 w), 1085 (m), 1030 (w), 920 (w), 880 (w), 755 (s), 700 (m), 670 (w). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.74, 0.77 (2 t, *J* = 7.1 Hz, 6 H, CH_2CH_3), 1.32 - 2.15 (m, 10 H, $NCH_2CH_2CH_2$, $CONCH_2CH_2$, CH_2CH_3), 2.69 (m, 2H, NCHH, CONCHH), 2.95 (m, 2 H, CONCHH, CHCO), 3.11 (br s, 3 H, OCH_3), 3.16 (br m, 1 H, NCHH), 3.32 (s, 3 H, $COOCH_3$), 3.40 (br s, 1 H, NCH), 3.53 (dd, *J* = 3.8, 11.5 Hz, 1 H, CHCHCO, 3.78 (s, 3 H, $COOCH_3$), 5.09 (d, *J* = 11.5 Hz, 1 H, $CH(COOCH_3)_2$), 7.26 -7.34 (m, 5H, CH_{arom}) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 8.54, 8.69 (CH_2CH_3), 22.17, 23.89, 24.41, 26.15, 26.64 ($NCH_2CH_2CH_2$, $CONCH_2CH_2$, CH_2CH_3), 42.10 (COCHCH), 46.63 (COCHCH), 50.58 ($CH(COOCH_3)_2$), 51.91 (NCH_2), 52.42, 53.06, 53.79 ($COCH_3$, $CH(COOCH_3)_2$), 65.40 (NCH), 80.29 (C), 127.89 (CH_{arom}), 128.68, 130.28 (CH_{arom}), 137.62 (C_{arom}), 169.14, 169.73 (COO), 172.97 (C=O) ppm. MS (70 eV): *m/z* (%) 474 (M^+, 0.1), 374 (24), 373 (M^+ – $CH_3OC(CH_2CH_3)_2$, 100), 242 (9), 174 (5), 131 (5), 117 (5), 101 ($CH_3OC(CH_2CH_3)_2^+$, 6), 97 (9). Anal. Calcd for $C_{26}H_{38}N_2O_6$: C, 65.80; H, 8.07; N, 5.90. Found C, 65.70; H, 8.03; N, 5.87.

Crystal data of lactam (**4f**) and experiment details: The compound was recrystallized after column chromatography from a 1/1 mixture of ether/pentane at – 24 °C. The compound crystallizes in monoclinic space group $P2_1$ (4), a =12.818(1), b = 8.445(2), c = 13.497(1) Å, β = 118.522(4)°. At Z = 2, V = 1283.7Å^3 and M_r = 474.6 the calculated density is ρ_{cal} = 1.228 g/cm^3. The structure was solved by means of direct methods as implemented in the program XTAL 3.4.[21] A total number of 6024 reflections were collected on a ENRAF-NONIUS CAD4 diffractometer at 150K. CuK_α radiation (λ = 1.54179 Å), μ = 6.7 cm^{-1}, no absorption correction. 4503 reflections with $I > 2\sigma(I)$ were used in the final full-matrix least-squares refinement process of 303 variables terminating at R = 0.082 (R_w = 0.091, $w = 1/\sigma^2$ (F)). Residual electron density ρ = – 0.32/+0.57 e Å^{-3}. Hydrogen positions were calculated and not refined. Their U's were fixed at 1.5 times U_{eq} of the relevant heavy atom prior to final refinement.

One of the ester groups at carbon C1 (C10, O2A,B O3A,B, C25A,B) is disordered over two positions with 0.65:0.35 occupancies. Both components could be refined isotropically with fixed site occupation parameters.

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CDDC-120341 . Copies of the data can be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, [fax: int. code +44(1223)336-033, e-mail: deposit@chemcrys.cam.ac.uk].

(*R,R*)-(+)-3-(2-Oxopyrrodinyl-3-yl)butanoic Acid (5a). Methyl ester (**4a**) (1.13 mmol, 400 mg) was converted into the acid according to general procedure 2 with 1.7 mL of 1.0 M LiOH solution. The crude acid (350 mg, 1.03 mmol) reacted with 36 mg (5.15 mmol) of Li in 100 mL of liquid ammonia according to general procedure 3 yielding 127 mg of **5a** as colourless crystals after recrystallization from Et_2O/MeOH. Yield : 66% (2 steps); *de* ≥ 96% (^{13}C-NMR); *ee* ≥ 96% (^{1}H-NMR shift experiment ($CDCl_3$) of the corresponding methyl ester[18] using (R)-(−)-9-anthryl-2,2,2-trifluoroethanol as chiral cosolvent). mp: 142 - 144 °C; $[\alpha]_D^{23}$ +2.3° (c = 0.66, CH_3OH).; IR (KBr) : ν 3350 cm^{-1} (s), 2965, 2865 (s), 2590 (w), 1720, 1660 (s, ν(C=O)), 1500 (m), 1470, 1440, 1410, 1380 (m), 1310 (m), 1285, 1260 (s), 1200 (s), 1155, 1095, 1055, 1025 (s), 935 (m), 805 (s), 740, 695 (s), 655 (m). ^{1}H-NMR (400 MHz, CD_3OD): δ 1.05 (d, *J* = 6.9 Hz, 3 H, C$\underline{H}_3$), 1.90 (m, 1 H, C$\underline{H}$HCH$_2$), 2.25 (m, 1H, CH$\underline{H}$CH$_2$), 2.25 (dd, *J* = 9.3, 14.6 Hz, 1 H, C$\underline{H}$HCOOH), 2.37 (m, 1 H, C$\underline{H}$CH$_3$), 2.43 (dd, *J* = 4.1, 15.0 Hz, CH$\underline{H}$COOH), 2.52 (dt, *J* = 4.1, 9.1 Hz, 1 H, CHC$\underline{H}$CON), 3.30 (m, 2 H, NC$\underline{H}_2$) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 18.50 (C$\underline{H}_3$), 22.67 (C$\underline{H}_2$CH$_2$NCO), 30.62 (C$\underline{H}$CHCO), 38.30, 41.07 (C$\underline{H}_2$COOH, NCH$_2$), 45.34 (CHC$\underline{H}$CO), 176.64, 180.38 (C=O, COOH) ppm. MS (70 eV): *m/z* (%) 171 (M^+, 0.7), 112 (18), 85 ($C_4H_7NO^+$, 100), 84 (42), 69 (14), 55 (20). Anal. Calcd for $C_8H_{13}NO_3$: C, 56.17, H. 8.42, N, 14.04; Found: C, 55.95, H, 8.51, N, 14.21.

(*R,R*)-(+)-3-(2-Oxopyrrodinyl-3-yl)pentanoic Acid (5b). Methyl ester (**4b**) (305 mg, 0.83 mmol) was converted according to general procedure 2 with 1.5 mL of 1.0 M LiOH solution into the acid. The crude acid (285 mg, 0.81 mmol) reacted with 29 mg (4.05 mmol) of Li in 50 mL of liquid ammonia according to general procedure 3 yielding 100 mg of **5b** as colourless crystals after recrystallization from Et_2O/MeOH. Yield : 65%; *de* ≥ 96% (^{13}C-NMR); *ee* ≥ 96% (^{1}H-NMR shift experiment ($CDCl_3$) using (R)-(−)-9-anthryl-2,2,2-trifluoroethanol as chiral cosolvent); mp: 117 - 118 °C; $[\alpha]_D^{23}$ +5.0° (c = 0.79, CH_3OH); IR (KBr) : ν 3240 cm^{-1} (m, br), 2955 (s), 2900, 2875 (m), 2420 (m), 2250 (m, br), 2080 (w), 1735, 1655 (s, ν(C=O)), 1495 (w), 1465 (m), 1415, 1385 (m), 1295 (s), 1275 (m), 1215, 1175, 1150 (m), 1055 (m), 925, 910 (w), 805 (w), 755 (w), 720 (m), 575 (m). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.96 (t, *J* = 7.4 Hz, 3 H, CH$_3$), 1.38/1.46 (2 sept, *J* = 7.2 Hz, 2 H, C$\underline{H}_2$CH$_3$), 1.96 (m, 1 H, C$\underline{H}$HCH$_2$), 2.15 (m, 1H, CH$\underline{H}$CH$_2$), 2.27 (dd, *J* = 8.3, 14.6 Hz, 1 H, C$\underline{H}$HCOOH), 2.34 (dd, *J* = 8.3, 14.6 Hz, CH$\underline{H}$COOH), 2.42 (m, 1 H, C$\underline{H}$CHCON), 2.68 (ddd, *J* = 3.3, 8.0, 9.9 Hz, CHC$\underline{H}$CO), 3.38 (m, 2 H, NC$\underline{H}_2$), 7.66 (br s, 1 H, N$\underline{H}$) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ 11.77 (C$\underline{H}_3$), 21.76, 24.36 (CH$_2$C$\underline{H}_2$CH$_3$, C$\underline{H}_2$CH$_2$N), 36.16 (C$\underline{H}$CHCO), 36.60, 43.42 (CH$_2$C$\underline{H}_2$N, C$\underline{H}_2$COOH), 41.24 (CHC$\underline{H}$CO), 177.37, 181.05 (C=O, COOH) ppm. MS (70 eV): *m/z* (%) 185 (M^+, 1), 156 (4), 138 (8), 126 (21), 123 (5), 110 (8), 86 (5), 85 ($C_4H_7NO^+$,

100), 84 (38), 71 (5), 70 (44), 69 (5), 67 (7), 56 (6), 55 (20), 53 (5). Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36, H, 8.10, N, 7.56. Found: C, 58.24, H, 8.17, N, 7.52.

(*R,R*)-(+)-3-(2-Oxopyrrodinyl-3-yl)hexanoic Acid (5c). Methyl ester (**4c**) (285 mg, 0.75 mmol) was converted according to general procedure 2 with 1.2 mL of 1.0 M LiOH solution into the acid. The crude acid (275 mg, 0.75 mmol) reacted with 26 mg (3.75 mmol) of Li in 50 mL of liquid ammonia according to general procedure 3 yielding 80 mg of **5c** as colourless crystals after recrystallization from Et_2O/MeOH. Yield : 54 %; *de* ≥ 96% (^{13}C-NMR); *ee* ≥ 96% (^{1}H-NMR shift experiment ($CDCl_3$) using (R)-(−)-9-anthryl-2,2,2-trifluoroethanol as chiral cosolvent); mp: 122 - 123 °C; $[\alpha]_D^{23}$ + 8.2° (c = 0.61, CH_3OH); IR (KBr) : ν 3240 cm^{-1} (m, br), 2955 (s), 2900, 2875 (m), 2420 (m), 2250 (m, br), 2080 (w), 1735, 1655 (s, ν(C=O)), 1495 (w), 1465 (m), 1415, 1385 (m), 1295 (s), 1275 (m), 1215, 1175, 1150 (m), 1055 (m), 925, 910 (w), 805 (w), 755 (w), 720 (m), 575 (m). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.93 (t, *J* = 6.7 Hz, 3 H,), 1.35 (m, 4 H, C<u>H</u>$_2$C<u>H</u>$_2$CH$_3$), 1.80 (m, 1 H, C<u>H</u>HCH$_2$), 2.14 (m, 1H, CH<u>H</u>CH$_2$), 2.28 (dd, *J* = 8.4, 14.7 Hz, 1 H, C<u>H</u>HCOOH), 2.34 (dd, *J* = 5.7, 14.4 Hz, CH<u>H</u>COOH), 2.53 (m, 1 H, C<u>H</u>CHCON), 2.65 (dt, *J* = 3.0, 9.1 Hz, CHC<u>H</u>CO), 3.37 (m, 2 H, NC<u>H</u>$_2$), 7.63 (br s, 1 H, N<u>H</u>) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.11 (<u>C</u>H$_3$), 20.27 (CH$_2$<u>C</u>H$_2$CH$_3$), 22.30 (<u>C</u>H$_2$CH$_2$N), 34.56 (<u>C</u>HCHCO), 34.62 (<u>C</u>H$_2$CH$_2$CH$_3$), 36.21, 41.07 (CH$_2$<u>C</u>H$_2$N, <u>C</u>H$_2$COOH), 43.54 (CH<u>C</u>HCO), 177.31, 181.04 (C=O, COOH) ppm. MS (70 eV): *m/z* (%) 199 (M^+, 3), 156 (6), 140 (31), 138 (9), 86 (5), 85 ($C_4H_7NO^+$, 100), 67 (5), 56 (5), 55 (5). Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28, H, 8.60, N, 7.03; Found: C, 59.81, H, 8.80, N, 6.91.

(*R,R*)-(+)-3-(2-oxopyrrolidin-3-yl)phenylpropionic Acid (5d). *tert*-Butyl ester (**4d**) (178 mg, 0.39 mmol, in 2 mL of CH_2Cl_2) was converted into the acid with 450 mg (3.9 mmol) of trifluoroacetic acid. After stirring over night at RT 20 mL of dichloromethane were added and this solution was washed twice with 10 mL of H_2O to remove the TFA. After drying over $MgSO_4$ the solvent was removed *in vacuo*. The crude product was used in the next step without further purification. The crude acid (136 mg, 0.34 mmol) reacted with 12 mg (1.72 mmol) of Li in 50 mL of liquid ammonia according to general procedure 3 yielding 50 mg of **5d** as colourless crystals after recrystallization from Et_2O/MeOH. Yield: 66%; *de* ≥ 96% (^{13}C-NMR); *ee* = 90% (^{1}H-NMR shift experiment ($CDCl_3$) of the corresponding methyl ester[19] using (R)-(−)-9-anthryl-2,2,2-trifluoroethanol as chiral cosolvent); mp : 157 – 158 °C; $[\alpha]_D^{23}$ + 44.8° (c = 0.35, CH_3OH); IR (KBr): ν 3555 cm^{-1} (m, br), 2910 (m), 2515 (m), 1890 (w), 1710 (s), 1690 (s), 1640 (s), 1490, 1455, 1435 (m), 1385 (m), 1295 (s), 1285 (s), 1230 (m), 1170 (w), 985 (m), 765 (m), 705 (s). ^{1}H NMR (400 MHz, CD_3OD): δ 1.96 (m, 1H, CHC<u>H</u>HCH$_2$), 2.10 (m, 1 H, CHCH$_2$C<u>H</u>H), 2.77 (ddd, *J* = 4.1, 7.7, 9.3 Hz, CHC<u>H</u>CO), 2.82 (m, 1 H, CONC<u>H</u>H), 2.86 (dd, *J* = 5.8, 15.9 Hz, 1 H, C<u>H</u>HCOOH), 2.96

(dd, J = 9.9, 16.2 Hz, CHHCOOH), 3.12 (ddd, J = 6.6, 8.2, 9.7 Hz, 1H, CONCHH), 3.55 (ddd, J = 4.1, 5.5, 9.9 Hz, 1H, CHCHCO), 7.18 - 7.32 (m, 5H, CH $_{arom}$) ppm. ^{13}C-NMR (75 MHz, CD_3OD): δ 23.35 (CH_2CH_2N), 36.95, 41.39 (CHCHCO), 43.45 (NCH_2), 47.59 (CH_2COOH), 127.96, 129.45, 129.35 (CH $_{arom}$), 142.56 (C $_{arom}$), 175.86, 180.72 (C=O, COOH) ppm. MS (70 eV): *m/z* (%) 233 (M^+, 10) 187 (14), 144 (38), 131 (20), 129 (26), 128 (12), 117 (25), 115 (20), 107 (14), 205 (9), 103 (20), 91 (35), 85 ($C_4H_6NO^+$, 100), 79 (27), 77 (23), 57 (10), 55 (10). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94, H, 6.48, N, 6.00; Found: C, 66.68, H, 6.65, N, 5.94.

(*R,R*)-(+)-3-(2-Oxopiperidin-3-yl)butanoic Acid (5e). Methyl ester (**4e**) (330 mg, 0.97 mmol) was converted according to general procedure 2 with 3 mL of 1.0 M LiOH solution into the acid. The crude acid (290 mg, 0.89 mmol) reacted with 31 mg (4.45 mmol) of Li in 50 mL of liquid ammonia according to general procedure 3 yielding 115 mg of **5e** as colourless crystals after recrystallization from Et_2O/MeOH. Yield : 64 %(two steps); *de* ≥ 96% (^{13}C-NMR); *ee* = 92% (^{1}H-NMR shift experiment ($CDCl_3$) of the corresponding methyl ester[18] using (R)-(−)-9-anthryl-2,2,2-trifluoroethanol as chiral cosolvent); mp : 171 - 173 °C; $[\alpha]_D^{23}$ + 48.6° (c = 0.75, CH_3OH); IR (KBr) : ν 3275 cm^{-1} (s, br), 3200 (s, br), 3020, 2960, 2905, 2885 (s), 2530 (m), 1950 (m, br), 1690, 1625 (s, ν(C=O)), 1495, 1470, 1450, 1420 (s), 1330, 1290 (m), 1270 (s), 1220, 1200, 1180 (s), 1125 (s), 1040, 1000, 980 (s), 940, 900 (s), 810 (s). ^{1}H-NMR (300 MHz, CD_3OD) : δ 1.17 (d, J = 7.0 Hz, 3 H, CH_3), 1.63 - 1.92 (m, 2 H, CHCHHCH$_2$ CHCH$_2$CHH), 2.01 - 2.13 (m, 2 H, CHCHHCH$_2$, CHCH$_2$CHH), 2.38 (dd, J = 9.7, 15.5 Hz, 1 H, CHHCOOH), 2.49 (m, 1 H, CHCHCO), 2.56 (dd, J = 4.4, 15.5 Hz, CHHCOOH), 2.75 (m, 1 H, $CHCH_3$), 3.30 - 3.46 (m, 2 H, $CONCH_2$) ppm. ^{13}C-NMR (75 MHz, CD_3OD): δ 17.82 (CH_3), 23.09, 24.75 ($CH_2CH_2CH_2N$), 33.07 ($CHCH_3$), 39.88, 43.68 (CH_2COOH, NCH_2), 47.49 (CHCON), 176.64, 177.60 (COOH, CON) ppm. MS (70 eV): *m/z* (%) 185 (M^+, 5) 126 (15), 99 ($C_5H_9NO^+$, 100), 98 (10). Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36, H, 8.16, N, 7.56; Found: C, 58.11, H, 7.99, N, 7.40.

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