The Synthesis of Novel Cyclic β-Amino Acids as Intermediates for the Preparation of Bicyclic β-Lactams

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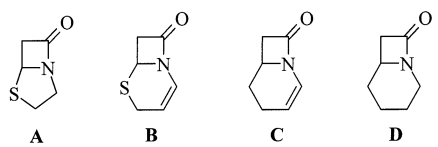
Several derivatives of homopipecolic acid are prepared by α-amino alkylation of malonic acid with cyclic imines **6** and **7**. These are prepared on a large scale and with different substitution patterns. The β-amino acids **8** and **9** were formed in high yield and with remarkable diastereoselectivity if chiral imines are used as starting materials. The diastereoselectivity of the amino alkylation leading to homopipecolic acid analogues is compared to those of thiazolidineacetic acids by epimerisation experiments. A method for resolution of the obtained racemic β-amino acids by diastereomeric salt formation is described. The β-amino acids **9** and **15** were converted into their corresponding carbacepham analogues **14** and isopenam **16**. The isopenam *endo*-**16** was selectively epimerised by mild basic treatment of the N/S-acetal to give an *exo*-configured precursor of isopenicillin G.

Introduction

Although β-amino acids play a minor role in nature relative to their α-amino acid analogues their synthesis has been extensively studied due to their outstanding importance as intermediates in synthetic chemistry as well as their interesting influence on the structures of novel peptides.[1] Of particular importance are cyclic derivatives which serve as precursors for the synthesis of natural products. Homopipecolic acid and its derivatives, for example, are versatile intermediates in the synthesis of several alkaloids and are themselves pharmacologically important.[2] In addition, extensive studies have been published on the synthesis of bicyclic β-lactams from heterocyclic β-amino acids, because of their outstanding importance as antibiotics.[3] In times of fast growing antibiotic resistance and the ongoing search for new active compounds much work has also been focussed on the preparation of nuclear analogues of penams **A** and 3-cephems **B** like **C** and **D**,[4] since some of these derivatives show a higher chemical stability than the analogous cephalosporines while they still exhibit high antibiotic activity.[5] 1-Carbacephams **D** serve as precursors for carbacephems and are also interesting model compounds to investigate the mode of action of β-lactam antibiotics.[6]



Scheme 1. Skeletons of some important β-lactam antibiotics

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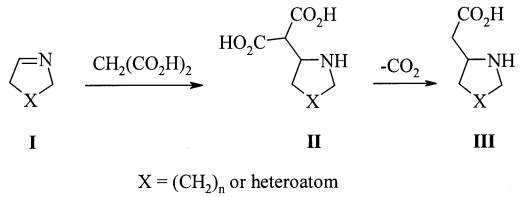
Herein we report on an efficient synthesis of previously unknown derivatives of piperidine-2-ylacetic acid and their conversion into bicyclic β-lactams, which constitute the backbone of carbacephames. The β-amino acids are prepared by highly diastereoselective addition of malonic acid to novel cyclic imines. Adapting recent protocols[7] we were also able to synthesise two new isopenames from β-homopenicillamine.

Results and Discussion

Synthesis of Piperidine-2-ylacetic Acids

Until now a lot of procedures have been developed for the preparation of β-amino acids.[8] One of the most efficient methods is the α-amino alkylation of malonic acid with imines. This reaction was first reported by Johnson et al. who used acyclic imines and was later extended to cyclic imines.[9]



Scheme 2. α-Amino alkylation of malonic acid using cyclic imines

As shown in Scheme 2 malonic acid serves as a carboxymethyl synthon. In some cases the dicarboxylic acid-adducts **II** were isolated but in most cases decarboxylation occurred spontaneously at room temperature to give the desired β-amino acids **III** or derivatives thereof.[10] This reaction also worked well for a number of heterocyclic imines and the trimers of piperidine and pyrroline.[7,9,11] Since we were previously able to obtain thiazolidineacetic acids from 3-thiazolines[7] in a very simple manner, we focussed our

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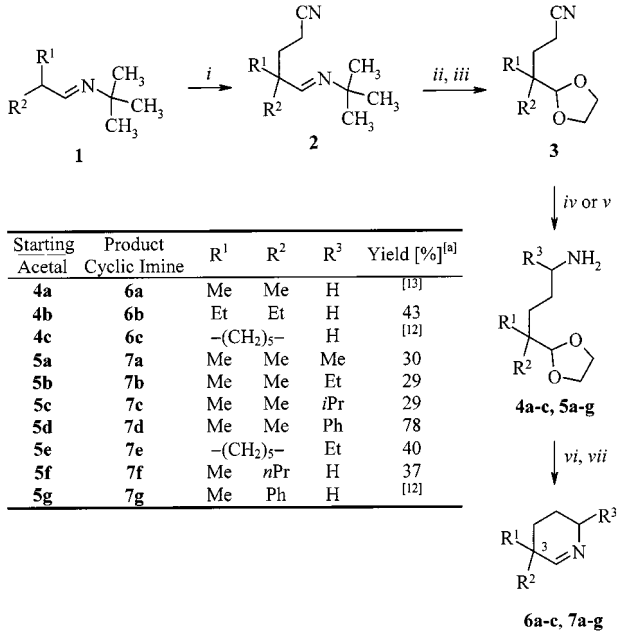
interest on the synthesis of piperidine-2-ylacetic acid derivatives from 3,4,5,6-tetrahydropyridine analogues. Due to the fact that only a limited number of 3,4,5,6-tetrahydropyridines are known it was our first task to find a practical approach to this type of compounds.[12] This was found by successful adaptation of a protocol by Zondler and Pfleiderer[13] which allowed the large scale preparation of several previously unknown cyclic imines depicted in Scheme 3.



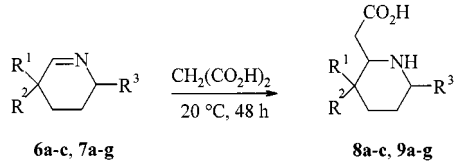
Starting Acetal	Product Cyclic Imine	R^1	R^2	R^3	Yield [%][a]
4a	**6a**	Me	Me	H	[13]
4b	**6b**	Et	Et	H	43
4c	**6c**	$-(CH_2)_5-$		H	[12]
5a	**7a**	Me	Me	Me	30
5b	**7b**	Me	Me	Et	29
5c	**7c**	Me	Me	*i*Pr	29
5d	**7d**	Me	Me	Ph	78
5e	**7e**	$-(CH_2)_5-$		Et	40
5f	**7f**	Me	*n*Pr	H	37
5g	**7g**	Me	Ph	H	[12]

Scheme 3. Preparation of 3,4,5,6-tetrahydropyridines. [a] Given yields calculated for the four-step reaction sequence with respect to the starting imines **1**. Reagents and conditions: (i) acrylonitrile, hydroquinone, reflux; (ii) HCl, H_2O; (iii) ethylene glycol, H_2SO_4; (iv) LiAlH4; (v) R^3MgX, $LiAlH_4$; (vi) HCl, H_2O; (vii) NaOH, H_2O

The cyano dioxolanes **3** were prepared in large amounts from the aldimines **1** and **2**. Subsequent reduction or Grignard-addition led to the amino dioxolanes **4** and **5**, respectively, in high yields and without necessity of any purification. Finally, hydrolysis of the acetal function followed by intramolecular imine formation under alkaline conditions gave the corresponding cyclic imines **6a–c** and **7a–g** in a one-pot process. All imines were obtained as colourless liquids of a characteristic sweetish odour. They are stable compounds and can be stored under argon at −18°C for several months.

The cyclic Schiff bases **6** and **7** were exposed to the above mentioned α-amino alkylation of malonic acid as outlined in Scheme 4. In most cases TLC indicated the absence of starting material after 48 hours. The precipitated raw product was collected by filtration and purified by recrystallisation or column chromatography to give the desired racemic β-amino acids **8** (from **6**) and **9** (from **7**).

Compared to related aminoalkylations of malonic acid using 3-thiazolines or other cyclic imines, the yields of piperidineacetic acids shown in Table 1 are very high.[7,9b–9c] A reason for the enhanced reactivity of tetrahydropyridines might be the loss of conformational strain during the course



Scheme 4. Preparation of β-amino acids from cyclic amines

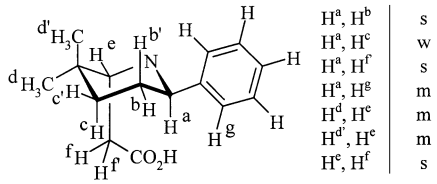
Table 1. Selected experimental data for β-amino acids

β-Amino acid	R^1	R^2	R^3	*dr*[a] *trans*:*cis*	Yield [%]
8a	Me	Me	H	–	92
8b	Et	Et	H	–	88
8c	$-(CH_2)_5-$		H	–	85
9a	Me	Me	Me	80:20[b]	98
9b	Me	Me	Et	> 95:5	72
9c	Me	Me	*i*Pr	> 95:5	98
9d	Me	Me	Ph	> 95:5	87
9e	$-(CH_2)_5-$		Et	> 95:5	77
9f	Me	*n*Pr	H	50:50[b]	71
9g	Me	Ph	H	50:50[b]	80

[a] The diastereomeric ratio (*dr*) was measured from the crude products using ^{1}H-NMR spectroscopy. – [b] Mixture of racemic diastereomers.

of the reaction from the unsaturated six-membered ring to the saturated one.

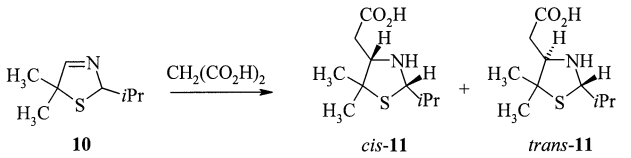
Addition of malonic acid to the prochiral C=N double bond leads to the formation of a stereogenic centre at the β-carbon atom of the cyclic amino acid. Thus, we were interested in the level of diastereomeric control in reactions with chiral imines **7a–g** as starting materials. Our recent studies showed a lower diastereomeric excess for α-amino alkylations of malonic acid from chiral 3-thiazolines.[7] In contrast chiral tetrahydropyridines **7a–e** with a stereogenic centre next to the nitrogen atom lead to a high excess of one diastereomer in the corresponding β-amino acids **9a–e** according to ^{1}H-NMR spectroscopy of the crude products. In contrast to their thiazolidine counterparts[14] all β-amino acids **9a–e** exhibit a preferred *trans* geometry of the alkyl or aryl substituents at their stereogenic centres as confirmed by 2D-NOESY-NMR studies.



Scheme 5. Structure of piperidineacetic acid **9d** and observed NOESY crosspeaks (s: strong, m: middle, w: weak)

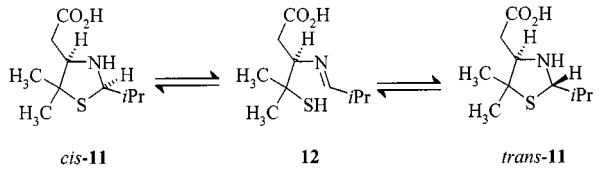
Observed NOESY crosspeaks indicate a *trans* arrangement of the phenyl and the carboxymethyl group in amino acid **9d**. A large axial, axial ^{3}J coupling constant of H_a and $H_{b'}$ of 11.5 Hz, is due to an equatorial arrangement of the phenyl residue. However, cyclic imines **7f** and **7g** with a ster-

eogenic centre in 3-position do not induce any diastereoselectivity in the formation of β-amino acids **9f** and **9g**.



Scheme 6. Synthesis of diastereomeric thiazolidineacetic acids (only one enantiomer of racemic compounds is shown)

The steric situation in 3-thiazolines, e.g. **10**, is different from the one in tetrahydropyridines, thus leading preferentially to *cis*-configured β-amino acids upon addition of malonic acid.[14] One reason for this discrepancy in diastereoselectivity is the fact that ring-chain epimerisation occurs in heterocycles like 3-thiazolidines,[15] e.g. **11** shown in Scheme 7, which obviously interferes with the diastereomeric ratio of amino alkylation products.

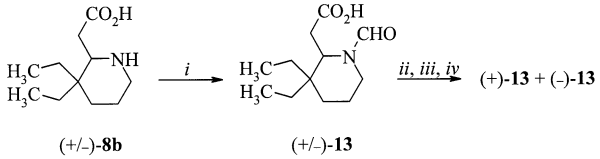


Scheme 7. Epimerisation of the N/S-acetal (only one enantiomer of racemic compounds is shown)

To get an idea of the influence of epimerisation in α-amino alkylations of malonic acid with 3-thiazolines the reaction depicted in Scheme 6 was performed at different temperatures in ethyl acetate. At 20°C the *cis*:*trans* ratio of **11**[7] is 87:13, whereas the ratio decreased to 75:25 at 50°C and finally reached 68:32 at 77°C (reflux). These data indicate a kinetically controlled addition of malonic acid to the chiral imine leading preferentially to the *cis*-adduct. The resulting *cis*:*trans* mixture (87:13) of **11** obtained after 48 hours at 20°C changed its composition in [D_6]DMSO after a few days to a constant composition of 66:34. The same ratio is achieved by heating **11** in [D_6]DMSO at 80°C for five minutes. These results clearly indicate a two-step process. First, kinetically controlled highly *cis*-stereoselective addition takes place followed by a thermodynamically controlled epimerisation leading to an increased portion of *trans*-**11** especially at higher temperatures. The intermediate **12** has not yet been detected but the analogous intermediate from the corresponding oxazolidines was identified by ^{1}H-NMR spectroscopy.[16]

Resolution of Piperidineacetic Acids

As mentioned before, the β-amino acids **8** and **9** were obtained as racemates. Since enantiomerically pure compounds are far more attractive as building blocks for β-peptide or natural product synthesis we concentrated our efforts on the resolution of these β-amino acids. Racemic amino acid **8b** was chosen as a model compound for resolution by diastereomeric salt formation. Therefore, **8b** was formylated first to give (±)-**13**.

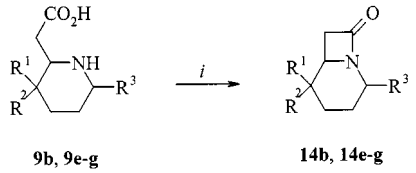


Scheme 8. Resolution of racemic β-amino acid **8b**. Reagents and conditions: (i) Ac_2O/HCO_2H; (ii) 1/2 equiv. (−)-norephedrine, Et_2O, 15 min. reflux, filtration; (iii) 1/2 equiv. (−)-norephedrine, Et_2O, 15 min. reflux; (iv) H_3O^+

Resolution of the racemic *N*-formylated amino acid (±)-**13** was achieved by formation of diastereomeric salts[17] with (−)-norephedrine. The norephedrinium salt of (−)-**13** precipitated upon cooling from diethyl ether. Acidic treatment of this norephedrine salt gave the desired enantiomerically pure *N*-formylated amino acid (−)-**13**. The corresponding enantiomer (+)-**13** was obtained from the filtrate by repeating the above described procedure. Final deformylation of compounds (+)-**13** and (−)-**13** should be possible according to known procedures.[18] The absolute configuration of enantiomerically pure *N*-formylated β-amino acids (+)-**13** and (−)-**13** has not been determined yet because we were not able to get suitable crystals for X-ray crystal structure analysis.

Synthesis of β-Lactams

The synthesis of β-lactams from β-amino acids requires the activation of the carboxyl group as well as working at low concentrations in order to suppress possible intermolecular side reactions.[19] Although quite a number of methods have been reported to give satisfying yields for special products many of these procedures for the intramolecular condensation of β-amino acids are not suitable for the preparation of carbacephams.[4b] In our hands, a method using Mukaiyama's reagent[20] proved to be the best for the synthesis of carbacepham analogues **14** from homopipecolic acid derivatives **9**.



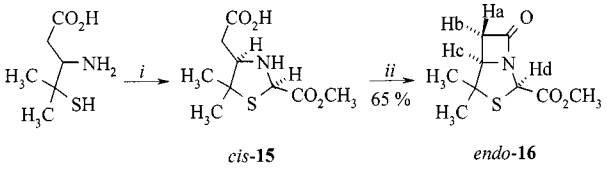
Scheme 9. Preparation of β-lactams from β-amino acids. Reagents and conditions: (i) 2-chloro-1-methylpyridinium iodide, Et_3N, reflux, 3 h

Table 2. Yields of β-lactams

β-lactam	R^1	R^2	R^3	Yield [%]
14b	Me	Me	Et	33
14e		$-(CH_2)_5-$	Et	19
14f	Me	*n*Pr	H	35
14g	Me	Ph	H	71

The 1-azabicyclo[4.2.0]octan-8-ones **14b** and **14e−g** were obtained in moderate to good yields after purification by column chromatography. As expected, the β-lactams **14** are obtained from the corresponding β-amino acids **9** without any change in the diastereomeric ratio, thus also exhibiting a *trans* arrangement of the substituents at their stereogenic centres.

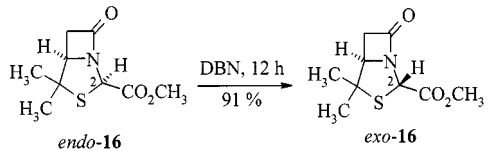
In order to evaluate the practical value of these compounds as building blocks we prepared two new isopenams as precursors of isopenicillin G starting from homopenicillamine.[7] This was converted into the thiazolidineacetic acid *cis*-**15** by treatment with methyl glyoxylate.



cis-**15** *endo*-**16**

Scheme 10. Two-step-synthesis of isopenam *endo*-**16** starting from homopenicillamine (only one enantiomer of racemic compounds is shown). Reagents and conditions: (i) methyl glyoxylate, MeOH, 30 min reflux; (ii) triphenylphosphane, bis(2-pyridyl) disulfide, acetonitrile, 5 h reflux

Subsequent treatment with bis(2-pyridyl) disulfide[21] furnished the β-lactam *endo*-**16**. The *endo* arrangement was confirmed by analysis of the H,H coupling constants. Besides a large, long range ^5J coupling constant of H_d and H_b (1.8 Hz), a small vicinal coupling constant of H_a and H_c (2.1 Hz) and a moderate vicinal coupling constant for H_b and H_c (4.3 Hz) were found. These data are consistent with a *trans*-arrangement of H_a, H_c and H_b, H_d occupying the *exo*-position in the bicyclic ring system.[22]



endo-**16** *exo*-**16**

Scheme 11. Basic epimerisation procedure for isopenams (only one enantiomer of racemic compounds is shown)

The stereogenic centre at C-2 is completely inverted within twelve hours by mild basic treatment with DBN to give *exo*-**16** which exhibits the right configuration for the synthesis of isopenicillin G.

Conclusion

We have described the synthesis of a number of previously unknown homopipecolic acid analogues by addition of malonic acid to tetrahydropyridine derivatives. The substitution pattern of cyclic Schiff bases was varied in a wide range to give achiral and chiral, racemic derivatives from which β-amino acids **9** can be prepared in high yields. Addition of malonic acid to chiral tetrahydropyridines **7a−d** yields, in a highly stereoselective manner, the *trans*-configured adducts. The reason for the remarkable decrease in diastereoselectivity observed in recent studies on the synthesis of thiazolidineacetic acids was found to be a competing thermodynamically controlled ring-chain epimerisation of the N/S-acetal as proved by epimerisation experiments with **11** at different temperatures.

The intramolecular condensation of cyclic β-amino acids yields novel carbacepham analogues **14** and isopenams **16** in moderate to good yields. The isopenam *endo*-**16** could be selectively epimerised to *exo*-**16**, which is a direct precursor of isopenicillin G.

We believe that our route is an attractive approach to new cyclic β-amino acids and bicyclic β-lactams

Experimental Section

General Remarks: Imines **1** were prepared by heating the appropriate aldehyde with an equimolar amount of *tert*-butylamine and a catalytic amount of ammonium chloride in toluene in a Dean-Stark apparatus for 24 hours. Removal of the solvent at reduced pressure gave the crude imines which were used without further purification. − If indicated with "abs." solvents were purified prior to use as follows: dichloromethane was distilled from $CaCl_2$, and THF and Et_2O were distilled from sodium and benzophenone. − Thin layer chromatography (TLC) analyses were performed on silica gel Polygram® plates and fluorescence indicator from Macherey−Nagel & Co., Düren. − For preparative chromatography Merck silica gel 60, 230−400 mesh was used. − Melting points were determined in open capillaries in a Dr. Lindström instrument and are uncorrected. − Optical rotations $[\alpha]_D$ were determined with a Perkin −Elmer polarimeter (241 MC), at 21°C, $c = 1$ in methanol unless otherwise indicated. − IR spectra were recorded with a Beckman spectrophotometer (IR 4220). − ^{1}H-NMR and ^{13}C-NMR spectra were recorded with a Bruker-Karlsruhe AM 300 spectrometer (300 MHz/75 MHz) or with a Bruker − Karlsruhe ARX 500 spectrometer (500 MHz). Chemical shifts, δ, are presented in parts per million (ppm) and coupling constants, *J*, in Hertz (Hz) from tetramethylsilane (TMS) as the internal standard in deuterated solvents such as D_2O, $CDCl_3$ or [D_6]DMSO. − Mass spectra were obtained with a Finnigan-MAT 212 instrument in a CI mode with isobutane as a reactant gas. − Elemental analyses were performed with a C, H, N-Analyser EA 1108 from Fisons Instrument.

General Procedures (GPs)

Preparation of ω-Cyano Dioxolanes 3 (GP1): The appropriate imine **1** (2 mol) was heated to reflux with 191.2 g (3.6 mol) of acrylonitrile and a catalytic amount of hydroquinone in 500 mL toluene for 48 hours. After cooling to room temperature the reaction mixture was washed with 250 mL of water. The layers were separated and the organic phase was dried with $MgSO_4$. Evaporation of the solvent under reduced pressure gave the desired cyano imine **2** as yellow oil. The crude product was treated with 300 mL 6 N HCl and stirred for three hours at room temperature. The acidic solution was extracted with 250 mL dichloromethane three times and the combined organic extracts were dried with $MgSO_4$. After evaporation of the solvent under reduced pressure the residue was dissolved in 500 mL toluene and refluxed with 136 g (2.2 mol) ethylene glycol and a catalytic amount of H_2SO_4 for twelve hours in a Dean-Stark apparatus. The resulting yellow solution was washed with water, saturated aqueous $NaHCO_3$ solution and brine. Drying of the organic phase with $MgSO_4$ and evaporation of the solvent under reduced pressure gave the desired cyano dioxolane **3** as a yellow oil.

Preparation of ω-Amino Dioxolanes 4 (GP2): A solution of 0.1 mol cyano dioxolane **3** in 100 mL abs. Et_2O was added dropwise to a

slurry of 2.3 g (0.06 mol) $LiAlH_4$ in 500 mL abs. Et_2O. After complete addition the reaction mixture was heated to reflux for 15 hours and subsequently hydrolysed by the careful addition of 5 mL water, 2 mL 20% aqueous NaOH and 20 mL water. The resulting white precipitate was filtered off after one hour of stirring at room temperature and the filtrate was dried with $MgSO_4$. The solvent was removed in vacuo to give the crude amino dioxolane **4** as a yellow oil which was used without further purification.

Preparation of δ-Amino Dioxolanes 5 (GP3): A solution of 0.1 mol cyano dioxolane **3** in 100 mL abs. Et_2O was added dropwise to 0.13 mol of the appropriate Grignard reagent in 200 mL abs. Et_2O. After addition of 50 mL abs. THF the solution was heated to reflux for three hours and 5 g (0.13 mol) $LiAlH_4$ is added carefully. The reaction mixture was heated to reflux for 13 hours and subsequently hydrolysed by the careful addition of 5 mL water, 2 mL 20% aqueous NaOH and 25 mL water. The resulting precipitate was filtered off after three hours of stirring at room temperature and the filtrate was dried with $MgSO_4$. The solvent was removed in vacuo to give the crude amino dioxolane **5** as a yellow oil which was used without further purification in *GP4*.

Preparation of Cyclic Imines 6 or 7 (GP4): The appropriate amino dioxolane **4** or **5**, prepared according to *GP2* or *GP3*, was dissolved in 50 mL water and 15 mL conc. HCl. After two hours of stirring at room temperature 10 g of solid NaOH were added accompanied by the addition of 50 g ice. The resulting red solution exhibited the typical sweetish odour of cyclic imines and was stirred at room temperature for one hour. After extraction three times with 150 mL $CHCl_3$ the organic extracts were dried with $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude imine as a red oil which was purified by distillation or chromatography.

Preparation of Cyclic β-Amino Acids 8 or 9 (GP5): Cyclic imine **6** or **7** was added to a solution of 1.3 molar equivalents malonic acid in the indicated solvent (see detailed description of the compounds). After 48 hours the solvent was evaporated in vacuo to give the crude amino acid **8** or **9** as a colourless solid which was purified by chromatography or recrystallised.

Preparation of Bicyclic β-Lactams 14 (GP6): The appropriate β-amino acid **9** (5 mmol) and 1.40 g (5.5 mmol) 2-chloro-1-methylpyridinium iodide were dissolved in 240 mL abs. dichloromethane and 11 mL Et_3N in 10 mL dichloromethane were added. The solution was heated to reflux for three hours. The solvent was removed under reduced pressure to give the crude β-lactam **14** as a yellow solid which was purified by chromatography.

3,3-Diethyl-3,4,5,6-tetrahydropyridine (6b): The title compound was prepared according to the sequence *GP1*, *GP2* and *GP4* from 310.6 g (2 mol) 2-ethylbutyraldehyde-*tert*-butylimine as starting material. The cyclic imine was purified by distillation in vacuo at 50°C (3.5 mbar) to yield 7.93 g (43%) of colourless liquid. − TLC (dichloromethane/methanol, 95:5): R_f = 0.57. − ^{1}H-NMR ($CDCl_3$): δ = 0.79 (t, 6 H, CH_3, ^3J = 7.3 Hz), 1.35 (2q, 4 H, ^3J = 7.3 Hz), 1.46 (m, 4 H), 3.39 (m, 2 H, N−CH_2), 7.38 (s, 1 H, CH=N). − ^{13}C−NMR ($CDCl_3$): δ = 7.92, 19.31, 27.22, 29.77, 39.31, 49.24, 170.18. − MS (CI, *iso*-butane): *m*/*z* (%) = 140 (100) [MH^+]. − $C_9H_{17}N$ (139.2): calcd. C 77.63, H 12.31, N 10.06; found C 77.59, H 12.37, N 10.05.

***rac*-3,3,6-Trimethyl-3,4,5,6-tetrahydropyridine (7a):** The title compound was prepared according to the sequence *GP1*, *GP3* and *GP4* from 253 g (2 mol) isobutyraldehyde-*tert*-butylimine as starting material. The cyclic imine was purified by distillation in vacuo at 80°C (25 mbar) to yield 3.80 g (30%) of colourless liquid. − ^{1}H-NMR ($CDCl_3$): δ = 1.00, 1.03 (2s, 6 H, CH_3), 1.21, 1.24 (2s, 3 H), 1.0−1.7 (m, 4 H, CH_2), 3.34 (m, 1 H, CH), 7.40 (s, 1 H, N=CH). − ^{13}C-NMR ($CDCl_3$): δ = 22.85, 26.07, 26.85, 27.30, 32.75, 33.17, 53.46, 169.22. − IR (NaCl): $\tilde{\nu}$ = 1640 cm^{-1} (N=CH). − MS (CI, *iso*-butane): *m*/*z* (%) = 126 (100) [MH^+]. − $C_8H_{15}N$ (125.2): calcd. C 76.74, H 12.07, N 11.19; found C 76.69, H 12.02, N 11.15.

***rac*-6-Ethyl-3,3-dimethyl-3,4,5,6-tetrahydropyridine (7b):** The title compound was prepared according to the sequence *GP1*, *GP3* and *GP4* from 253 g (2 mol) isobutyraldehyde-*tert*-butylimine as starting material. The cyclic imine was purified by distillation in vacuo at 54−58°C (15 mbar) to yield 4.09 g (29%) of colourless liquid. − IR (NaCl): $\tilde{\nu}$ = 3400, 3320 (C=N), 2920, 2860 (CH_3, CH_2), 1630 (C=N), 1450 (CH_2) cm^{-1}. − ^{1}H-NMR ($CDCl_3$): δ = 1.00 (s, 6 H, 2×CCH_3), 1.04 (s, 3 H), 1.20−1.36 (m, 2 H), 1.39−1.76 (m, 4 H), 3.14 (m, 1 H), 7.44 (s, 1 H). − ^{13}C-NMR ($CDCl_3$): δ = 10.42, 24.27, 25.84, 27.37, 29.82, 32.89, 33.33, 59.30, 169.32. − MS (CI, *iso*-butane): *m*/*z* (%) = 140.3 (100) [MH^+]. − $C_9H_{17}N$ (139.2): calcd. C 77.63, H 12.31, N 10.06; found C 77.89, H 12.19, N 9.88.

***rac*-6-Isopropyl-3,3-dimethyl-3,4,5,6-tetrahydropyridine (7c):** The title compound was prepared according to the sequence *GP1*, *GP3* and *GP4* from 253 g (2 mol) isobutyraldehyde-*tert*-butylimine as starting material. The cyclic imine was purified by distillation in vacuo at 75°C (5 mbar) to yield 3.50 g (29%) of colourless liquid. − ^{1}H-NMR ($CDCl_3$): δ = 0.93, 0.97 (2d, 6 H, ^3J = 7.1 Hz), 1.00, 1.05 (2s, 6 H, CH_3), 1.2−1.6 (m, 4 H, CH_2), 1.85 (m, 1 H), 3.03 (m, 1 H, CH), 7.48 (s, 1 H, N=CH). − ^{13}C-NMR ($CDCl_3$): δ = 18.41, 18.86, 21.11, 25.65, 27.78, 33.50, 33.35, 63.50, 33.61 33.70, 169.71. − MS (CI, *iso*-butane): *m*/*z* (%) = 154 (100) [MH^+]. − $C_{10}H_{19}N$ (153.3): calcd. C 78.37, H 12.50, N 9.14; found C 78.28, H 12.54, N 9.17.

***rac*-3,3-Dimethyl-6-phenyl-3,4,5,6-tetrahydropyridine (7d):** The title compound was prepared according to the sequence *GP1*, *GP3* and *GP4* from 253 g (2 mol) isobutyraldehyde-*tert*-butylimine as starting material to give the cyclic imine, without purification, as a colourless solid in 18.4 g (78%) yield, m.p. 41°C. − ^{1}H-NMR ($CDCl_3$): δ = 1.01, 1.05 (2s, 6 H, CH_3), 1.54−1.91 (m, 4 H, CH_2), 4.42 (m, 1 H, CH-phenyl), 7.16−7.28 (m, 5 H, arH), 7.59 (s, 1 H, N=CH). − ^{13}C-NMR ($CDCl_3$): δ = 25.99, 27.24, 28.13, 32.66, 33.41, 61.67, 126.35, 126.49, 127.01, 128.13, 144.42, 170.82. − IR (KBr): $\tilde{\nu}$ = 1650 cm^{-1} (N=CH). − MS (CI, *iso*-butane): *m*/*z* (%) = 188 (100) [MH^+]. − $C_{13}H_{17}N$ (187.3): calcd. C 83.37, H 9.15, N 7.48; found C 83.45, H 9.19, N 7.56.

***rac*-3-Ethyl-2-azaspiro[5.5]undec-1-ene (7e):** The title compound was prepared according to the sequence *GP1*, *GP3* and *GP4* from 335 g (2 mol) cyclohexanecarbaldehyde-*tert*-butylimine as starting material. The cyclic imine was purified by chromatography (dichloromethane/methanol, 95:5) to yield 8.80 g (40%) of colourless liquid. − TLC (dichloromethane/methanol, 95:5): R_f = 0.40. − IR (NaCl): $\tilde{\nu}$ = 3260, 3180 (C=N), 2910, 2840 (CH_3, CH_2), 1630 (C=N), 1440 (CH_2) cm^{-1}. − ^{1}H-NMR ($CDCl_3$, 500 MHz): δ = 0.93 (s, 3 H), 1.08−1.62 (m, 16 H), 3.07 (m, 1 H), 7.36 (s, 1 H). − ^{13}C-NMR ($CDCl_3$): δ = 10.50, 20.60, 20.75, 24.06, 25.67, 28.41, 29.95, 32.56, 35.82, 36.46, 60.09, 169.86. − MS (CI, *iso*-butane): *m*/*z* (%) = 180.3 (100) [MH^+]. − $C_{12}H_{21}N$ (179.3): calcd. C 80.38, H 11.80, N 7.81; found C 80.26, H 11.72, N 7.88.

***rac*-3-Methyl-3-propyl-3,4,5,6-tetrahydropyridine (7f):** The title compound was prepared according to the sequence *GP1*, *GP2* and *GP4* from 310 g (2 mol) *rac*-2-methyl-pentylaldehyde-*tert*-butylimine as starting material. The cyclic imine was purified by distillation in vacuo at 75°C (5 mbar) to yield 6.50 g (37%) of a colourless oil. − TLC (dichloromethane/methanol, 95:5): R_f = 0.55. − ^{1}H-NMR ($CDCl_3$): δ = 0.88 (t, 3 H, ^3J = 6.6 Hz), 0.98 (s, 3 H, CCH_3), 1.2−1.6 (m, 8 H, CH_2), 3.3−3.6 (m, 2 H, NCH_2), 7.40 (s, 1 H, N=

CH). − ^{13}C-NMR ($CDCl_3$): δ = 14.67, 16.87, 19.25, 24.41, 30.71, 36.54, 42.43, 49.30, 170.42. − MS (CI, *iso*-butane): *m*/*z* (%) = 140 (100) [MH^+]. − $C_9H_{17}N$ (139.2): calcd. C 77.63, H 12.31, N 10.06; found C 77.54, H 12.43, N 9.98.

***rac*-(3,3-Dimethylpiperidine-2-yl)acetic Acid (8a):** The α-amino alkylation of 0.68 g (6.5 mmol) malonic acid in 25 mL Et_2O with 0.56 g (5 mmol) cyclic imine **6a** was performed according to *GP5*. The β-amino acid was purified by recrystallisation from acetone/methanol to yield 0.79 g (92%) of a colourless solid, m.p. 272°C. − TLC (dichloromethane/methanol, 80:20): R_f = 0.42. − ^{1}H-NMR (D_2O): δ = 0.82, 0.86 (2s, 6 H, $C(CH_3)_2$), 1.2−1.7 (m, 4 H), 2.17 (dd, 1 H, C*H*$_2$COOH, ^{2}J = 17.6 Hz, ^{3}J = 10.4 Hz), 2.51 (dd, 1 H, C*H*$_2$COOH, ^{2}J = 17.6 Hz, ^{3}J = 3.3 Hz), 2.84 (m, 1 H, NCH_2), 3.08 (dd, 1 H, NCH, ^{3}J = 3.3 Hz, ^{3}J = 10.4 Hz), 3.23 (m, 1 H, NCH_2). − ^{13}C-NMR (D_2O): δ = 18.59, 18.85, 27.43, 32.03, 34.16, 36.62, 44.60, 62.17, 178.42. − MS (CI, *iso*-butane): *m*/*z* = 172 (100) [MH^+]. − $C_9H_{17}NO_2$ (171.2): calcd. C 63.13, H 10.01, N 8.18; found C 63.19, H 10.10, N 8.12.

***rac*-(3,3-Diethylpiperidine-2-yl)acetic Acid (8b):** The α-amino alkylation of 0.68 g (6.5 mmol) malonic acid in 25 mL Et_2O with 0.70 g (5 mmol) cyclic imine **6b** was performed according to *GP5*. The β-amino acid was purified by recrystallisation from acetone to yield 0.71 g (88%) of a colourless solid, m.p. 167°C. − TLC (dichloromethane/methanol, 80:20): R_f = 0.57. − ^{1}H-NMR (D_2O): δ = 0.68, 0.69 (2t, 6 H, ^{3}J = 7.7 Hz), 1.0−1.7 (m, 8 H), 2.24 (dd, 1 H, C*H*$_2$COOH, ^{2}J = 17.6 Hz, ^{3}J = 11.0 Hz), 2.42 (dd, 1 H, C*H*$_2$COOH, ^{2}J = 17.6 Hz, ^{3}J = 2.8 Hz), 2.88 (m, 1 H, NCH_2), 3.17 (m, 1 H, NCH_2), 3.28 (dd, 1 H, NCH, ^{3}J = 2.8 Hz, ^{3}J = 11.0 Hz). − ^{13}C-NMR (D_2O): δ = 6.32, 6.56, 18.21, 23.69, 26.95, 27.10, 32.72, 36.52, 43.35, 59.48, 178.61. − MS (CI, *iso*-butane): *m*/*z* (%) = 200 (100) [MH^+]. − $C_{11}H_{21}NO_2$ (199.3): calcd. C 66.29, H 10.62, N 7.03; found C 66.21, H 10.78, N 7.12.

***rac*-(2-Azaspiro[5.5]undec-1-yl)acetic Acid (8c):** The α-amino alkylation of 0.68 g (6.5 mmol) malonic acid in 25 mL Et_2O with 0.76 g (5 mmol) cyclic imine **6c** was performed according to *GP5*. The β-amino acid was purified by recrystallisation from acetone to yield 0.90 g (85%) of a colourless solid, m.p. 208°C. − TLC (dichloromethane/methanol, 80:20): R_f = 0.53. − ^{1}H-NMR (D_2O): δ = 1.0−2.0 (m, 14 H), 2.29 (dd, 1 H, C*H*$_2$COOH, ^{2}J = 17.6 Hz, ^{3}J = 11.0 Hz), 2.55 (dd, 1 H, C*H*$_2$COOH, ^{2}J = 17.6 Hz, ^{3}J = 3.3 Hz), 2.90 (m, 1 H, NCH_2), 3.13 (m, 1 H, NCH_2), 3.21 (dd, 1 H, NCH, ^{3}J = 3.3 Hz, ^{3}J = 11.0 Hz). − ^{13}C-NMR (D_2O): δ = 17.75, 20.34, 20.32, 25.62, 27.97, 28.21, 32.51, 33.76, 34.60, 42.74, 61.09, 178.78. − MS (CI, *iso*-butane): *m*/*z* = 212 (100) [MH^+]. − $C_{12}H_{21}NO_2$ (211.3): calcd. C 68.21, H 10.02, N 6.63; found C 68.41, H 10.12, N 6.71.

(3,3,6-Trimethylpiperidine-2-yl)acetic Acid (9a): The α-amino alkylation of 0.68 g (6.5 mmol) malonic acid in 25 mL Et_2O with 0.63 g (5 mmol) cyclic imine **7a** was performed according to *GP5*. The β-amino acid was purified by recrystallisation from acetone to yield 0.71 g (88%) of a colourless solid (88:12-mixture of racemic *trans:cis* diastereomers after recrystallisation). − TLC (dichloromethane/methanol, 80:20): R_f = 0.57. − ^{1}H-NMR (D_2O) (*trans*-diastereomer): δ = 0.86, 0.98 (2s, 6 H), 1.27 (d, 3 H), 1.3−1.9 (m, 4 H), 2.41 (dd, 1 H, C*H*$_2$COOH, ^{2}J = 17.7 Hz, ^{3}J = 10.4 Hz), 2.65 (dd, 1 H, C*H*$_2$COOH, ^{2}J = 17.7 Hz, ^{3}J = 3.6 Hz), 3.45 (m, 2 H). − ^{13}C-NMR (D_2O) (*trans*-diastereomer): δ = 16.11, 21.58, 24.89, 26.32, 31.07, 31.73, 32.52, 48.14, 57.12, 177.29. − MS (CI, *iso*-butane): *m*/*z* = 186 (100) [MH^+]. − $C_{10}H_{19}NO_2$ (185.3): calcd. C 64.83, H 10.34, N 7.56; found C 64.92, H 10.43, N 7.61.

(2*SR*,6*RS*)-(6-Ethyl-3,3-dimethylpiperidine-2-yl)acetic Acid (*trans*-9b): The α-amino alkylation of 2.36 g (20 mmol) malonic acid in 25 mL ethanol with 2.09 g (15 mmol) cyclic imine **7b** was performed according to *GP5*. The β-amino acid was purified by chromatography (dichloromethane/methanol, 70:30) to yield 2.10 g (72%) of a colourless solid, m.p. 186°C (dec.). − TLC (dichloromethane/methanol, 70:30): R_f = 0.62. − IR (KBr): ṽ = 3540, 3460 (NH_2), 2960, 2900, 2860 (CH_3, CH_2), 2300−2600 br. (COOH), 1560 (NH_2) cm^{-1}. − ^{1}H-NMR (CDCl3): δ = 1.00 (s, 6 H, CCH_3), 1.07 (t, 3 H, *J* = 7.7 Hz), 1.44−2.05 (m, 6 H), 2.46 (m, 2 H, C*H*$_2$COOH), 3.22−3.40 (m, 2 H). − ^{13}C-NMR ($CDCl_3$): δ = 10.25, 23.14, 23.52, 27.32, 31.78, 32.41, 51.63, 56.62, 176.31. − MS (CI, *iso*-butane): *m*/*z* (%) = 200 (100) [MH^+]. − $C_{11}H_{21}NO_2$ (199.3): calcd. C 66.29, H 10.62, N 7.03; found C 65.87, H 10.43, N 7.25.

(2*RS*,6*RS*)-(6-Isopropyl-3,3-dimethylpiperidine-2-yl)acetic Acid (*trans*-9c): The α-amino alkylation of 0.68 g (6.5 mmol) malonic acid in 25 mL Et_2O with 0.77 g (5 mmol) cyclic imine **7c** was performed according to *GP5*. The β-amino acid was purified by recrystallisation from acetone to yield 1.04 g (98%) of a colourless solid, m.p. 190°C (dec.) . − TLC (dichloromethane/methanol, 80:20): R_f = 0.69. − ^{1}H-NMR (D_2O): δ = 0.9−1.1 (m, 12 H), 1.2−2.0 (m, 5 H), 2.65 (m, 2 H), 2.89 (m, 1 H), 3.45 (dd, 1 H, NCH, ^{2}J = 10.3 Hz, ^{3}J = 4.3 Hz). − ^{13}C-NMR (D_2O): δ = 18.16, 18.42, 21.80, 23.56, 25.39, 25.67, 28.68, 30.83, 31.36, 57.41, 58.19, 177.82. − MS (CI, *iso*-butane): *m*/*z* = 214 (100) [MH^+]. − $C_{12}H_{23}NO_2$ (213.3): calcd. C 67.57, H 10.87, N 6.57; found C 67.62, H 10.95, N 6.63.

(2*RS*,6*RS*)-(3,3-Dimethyl-6-phenylpiperidine-2-yl)acetic Acid (*trans*-9d): The α-amino alkylation of 0.68 g (6.5 mmol) malonic acid in 25 mL ethanol with 0.94 g (5 mmol) cyclic imine **7d** was performed according to *GP5*. The β-amino acid was purified by recrystallisation from acetone to yield 1.08 g (87%) of a colourless solid, m.p. 99−100°C (dec.). − TLC (dichloromethane/methanol, 80:20): R_f = 0.72. − ^{1}H-NMR (D_2O): δ = 0.94, 1.10 (2s, 6 H, $C(CH_3)_2$), 1.5−2.3 (m, 4 H), 2.72 (d, 2 H, C*H*$_2$COOH, ^{3}J = 7.3 Hz), 3.48 (t, 1 H, NCH, ^{3}J = 7.3 Hz), 4.40 (dd, 1 H, NCH-phenyl, ^{2}J = 10.4 Hz, ^{3}J = 4.5 Hz), 7.3−7.5 (m, 5 H, ar.H). − ^{13}C-NMR (D_2O): δ = 14.34, 23.73, 25.50, 31.19, 31.45, 31.71, 54.20, 59.31, 127.61, 129.57, 129.66, 135.39, 177.44. − MS (CI, *iso*-butane): *m*/*z* = 248 (100) [MH^+]. − $C_{15}H_{21}NO_2$ (247.3): calcd. C 72.84, H 8.56, N 5.66; found C 72.96, H 8.73, N 5.82.

(1*SR*,3*RS*)-(3-Ethyl-2-azaspiro[5.5]undec-1-yl)acetic Acid (*trans*-9e): The α-amino alkylation of 2.36 g (20 mmol) malonic acid in 25 mL ethanol with 2.69 g (15 mmol) cyclic imine **7e** was performed according to *GP5*. The β-amino acid was purified by chromatography (dichloromethane/methanol, 70:30) to yield 2.76 g (77%) of a colourless solid, m.p. 110−111°C. − TLC (dichloromethane/methanol, 70:30): R_f = 0.71. − IR (KBr): ṽ = 3300−3500 br. (NH_2), 2930, 2840 (CH_3, CH_2), 2300−2600 br. (COOH), 1560 (NH_2) cm^{-1}. − ^{1}H-NMR ($CDCl_3$): δ = 1.01 (t, 3 H, CH_3, ^{3}J = 7.7 Hz), 1.14−1.89 (m, 10 H), 2.59 (d, 2 H, C*H*$_2$COOH, ^{3}J = 7.7 Hz), 2.99 (m, 1 H), 3.60 (m, 1 H, H1, ^{3}J = 7.7 Hz). − ^{13}C-NMR ($CDCl_3$): δ = 10.09, 20.85, 23.51, 25.85, 28.39, 29.80, 32.79, 33.83, 51.63, 55.52, 176.28. − MS (CI, *iso*-butane): *m*/*z* (%) = 240 (100) [MH^+]. − $C_{14}H_{25}NO_2$ (239.4): calcd. C 70.25, H 10.53, N 5.85; found C 70.03, H 10.14, N 5.45.

(3-Methyl-3-propylpiperidine-2-yl)acetic Acid (9f): The α-amino alkylation of 2.36 g (20 mmol) malonic acid in 25 mL ethanol with 2.09 g (15 mmol) cyclic imine **7f** was performed according to *GP5*. The β-amino acid was purified by chromatography (dichloromethane/methanol, 70:30) to yield 2.12 g (71%) of a colourless solid (50:50-mixture of racemic *cis*:*trans* diastereomers after chromatography). − TLC (dichloromethane/methanol, 70:30): R_f = 0.65. − IR (KBr): ṽ = 3400 br. (NH_2^+), 2960, 2860 (CH_3, CH_2),

2300−2600 br. (COOH), 1560 (NH_2^+) cm^{-1}. − ^{1}H-NMR (D_2O): δ = 0.70 (t, 1.5 H, ^{3}J = 7.2 Hz), 0.74 (t, 1.5 H, ^{3}J = 7.4 Hz), 0.78 (s, 1.5 H, CH_3C), 0.81 (s, 1.5 H, CH_3C), 0.93−1.72 (m, 8 H), 2.12 (dd, 0.5 H, C*H*$_2$COOH, ^{3}J = 11.0 Hz, ^{2}J = 17.6 Hz), 2.19 (dd, 0.5 H, C*H*$_2$COOH, ^{3}J = 11.0 Hz, ^{2}J = 17.6 Hz), 2.46 (dd, 0.5 H, C*H*$_2$COOH, ^{3}J = 4.4 Hz, ^{2}J = 17.6 Hz), 2.47 (dd, 0.5 H, C*H*$_2$COOH, ^{3}J = 4.4 Hz, ^{2}J = 17.6 Hz), 2.85 (m, 1 H, H6), 3.17 (m, 2 H, H2). − ^{13}C-NMR (D_2O): δ = 14.33, 14.37, 15.65, 15.82, 17.70, 18.53, 18.70, 23.96, 32.08, 32.95, 33.18, 33.81, 34.51, 34.65, 42.19, 44.20, 44.44, 60.94, 63.10, 178.39, 178.54. − MS (CI, *iso*-butane): *m*/*z* (%) = 200 (100) [MH^+]. − $C_{11}H_{21}NO_2$ (199.3): calcd. C 66.29, H 10.62, N 7.03; found C 66.21, H 10.52, N 7.18.

(3-Methyl-3-phenylpiperidine-2-yl)acetic Acid (9g): The α-amino alkylation of 2.36 g (20 mmol) malonic acid in 25 mL ethanol with 2.60 g (15 mmol) cyclic imine **7g** was performed according to *GP5*. The β-amino acid was purified by chromatography (dichloromethane/methanol, 70:30) to yield 2.81 g (80%) of a colourless solid (50:50-mixture of racemic *cis*:*trans* diastereomers after chromatography). − TLC (dichloromethane/methanol, 70:30): R_f = 0.65. − IR (KBr): ṽ = 3300−3500 br. (NH_2^+), 2940 (CH_3, CH_2), 2400−2600 br. (COOH), 1570 (NH_2^+), 1630, 1440 (ar.) cm^{-1}. − ^{1}H-NMR (D_2O): δ = 1.28 (s, 1.5 H, CH_3), 1.32 (s, 1.5 H, CH_3), 1.50−2.01 (m, 4 H), 2.12 (dd, 0.5 H, C*H*$_2$COOH, ^{3}J = 11.5 Hz, ^{2}J = 17.6 Hz), 2.33 (dd, 0.5 H, C*H*$_2$COOH, ^{3}J = 11.5 Hz, ^{2}J = 17.6 Hz), 2.88−3.14 (m, 2 H, H2), 3.34 (m, 1 H, C*H*$_2$COOH), 3.77 (dd, 0.5 H, H6, ^{3}J = 1.7 Hz, ^{2}J = 11.5 Hz), 3.85 (dd, 0.5 H, H6, ^{3}J = 1.7 Hz, ^{2}J = 11.5 Hz), 7.12−4.40 (m, 5 H, ar.H). − ^{13}C-NMR (D_2O): δ = 16.41, 18.07, 19.17, 25.53, 26.42, 31.93, 34.51, 37.29, 38.04, 38.58, 39.84, 44.62, 58.83, 60.87, 125.89, 126.27, 127.35, 127.54, 129.24, 145.00, 145.54, 177.92, 178.11. − MS (CI, *iso*-butane): *m*/*z* (%) = 234 (100) [MH^+]. − $C_{14}H_{19}NO_2$ (233.3): calcd. C 72.07, H 8.21, N 6.00; found C 72.21, H 8.07, N 6.16.

***rac*-(3,3-Diethyl-1-formylpiperidine-2-yl)acetic Acid [(±)-13]:** 2.0 g amino acid **8b** (10 mmol) was dissolved in 20 mL formic acid and 7 mL acetic anhydride was slowly added. The reaction mixture was stirred for twelve hours at room temperature and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane and washed twice with water. After removal of the solvent under reduced pressure the *N*-formylated β-amino acid (±)-**13** was obtained as a colourless oil in 1.86 g (82%) yield. − TLC (dichloromethane/methanol, 80:20): R_f = 0.19. − ^{1}H-NMR ($CDCl_3$, two rotamers in a 76:24 ratio): δ = 0.73, 0.81 (2 m, 6 H), 1.1−1.6 (m, 8 H), 2.48 (dd, 1 H, C*H*$_2$COOH, ^{2}J = 17.5 Hz, ^{3}J = 10.6 Hz), 2.74 (m, 1.76 H, NCH_2), 3.28 (m, 0.24 H, NCH_2), 3.37 (m, 0.24 H, C*H*$_2$COOH, ^{2}J = 17.5 Hz, ^{3}J = 3.0 Hz), 3.65 (dd, 0.76 H, C*H*$_2$COOH, ^{2}J = 17.5 Hz, ^{3}J = 3.0 Hz), 4.28 (dd, 0.76 H, NCH, ^{3}J = 3.0 Hz, ^{3}J = 10.6 Hz), 4.69 (dd, 0.24 H, NCH, ^{3}J = 3.0 Hz, ^{3}J = 10.6 Hz), 7.99 (s, 0.76 H, CHO), 8.10 (s, 0.24 H, CHO), 8.85 (br., 1 H, COOH). − ^{13}C-NMR ($CDCl_3$, major rotamer): δ = 6.46, 6.84, 19.53, 22.98, 27.15, 28.72, 32.32, 35.47, 37.56, 59.18, 163.83, 173.64. − MS (CI, *iso*-butane): *m*/*z* (%) = 228 (100) [MH^+]. − $C_{11}H_{21}NO_2$ (228.3): calcd. C 63.41, H 9.31, N 6.16; found C 63.98, H 9.29, N 6.32.

(−)-(3,3-Diethyl-1-formylpiperidine-2-yl)acetic Acid [(−)-13]: 1.30 g (5.7 mmol) *N*-formylated β-amino acid (±)-**13** was dissolved in diethyl ether and heated to reflux. 0.43 g (2.9 mmol) (−)-norephedrine were added to the hot solution and the mixture was heated for 15 min. at reflux. Colourless crystals separated from the solution after slowly cooling to room temperature. The solid was filtered off and purified by recrystallisation from dichloromethane to yield 0.86 g (80%) (−)-norephedrinium salt of (−)-**13** as a colourless solid, m.p. 129−130°C. − $[\alpha]_D$ = − 56.4 (*c* = 0.5 in methanol) − ^{1}H-NMR ([D_6]DMSO, two rotamers in a 85:15 ratio): δ = 0.61 (d, 0.45 H, CHC*H*$_3$, ^{3}J = 6.7 Hz), 0.69 (m, 6 H, CH$_2$C*H*$_3$), 0.84 (d, 2.55 H, CHC*H*$_3$), 1.0−1.4 (m, 8 H), 2.19 (dd, 1 H, C*H*$_2$COOH, ^{2}J = 17.5 Hz, ^{3}J = 11.0 Hz), 2.48 (dd, 1 H, C*H*$_2$COOH, ^{2}J = 17.5 Hz, ^{3}J = 3.0 Hz), 3.03 (m, 0.15 H, NCH_2), 3.20 (m, 1.7 H, NCH_2), 3.35 (m, 0.15 H, NCH_2), 3.57 (br., 1 H), 3.73 (m, 0.15 H, C*H*CH$_3$), 4.01 (br., 0.85 H), 4.56 (br., 0.15 H), 4.86 (br., 1 H), 6.4 (br., 3 H, NH_3^+), 7.25 (m, 5 H, ar H), 7.86 (s, 0.85 H, CHO), 7.90 (s, 0.15 H, CHO). − ^{13}C-NMR ([D_6]DMSO, major rotamer): δ = 6.81, 7.18, 13.40, 19.91, 22.92, 27.02, 29.09, 34.65, 37.27, 52.17, 58.79, 72.88, 126.35, 127.17, 128.24, 142.48, 162.27, 175.30. − $C_{21}H_{34}N_2O_4$ (378.5): calcd. C 66.64, H 9.05, N 7.40; found C 66.21, H 9.12, N 7.32.

The (−)-norephedrinium salt of (−)-**13** was dissolved in 50 mL water and treated with 1 mL conc. HCl. The mixture was extracted with 30 mL dichloromethane three times. After drying of the combined organic extracts with $MgSO_4$ the solvent was removed in vacuo to give the enantiomeric pure *N*-formylated β-amino acid (−)-**13** in 0.47 g (91%) yield as a colourless oil. − $[\alpha]_D$ = −27.6.

(+)-(3,3-Diethyl-1-formylpiperidine-2-yl)acetic Acid [(+)-13]: The filtrate of (−)-norephedrinium salt of (−)-**13** was heated to reflux and 0.43 g (2.9 mmol) (−)-norephedrine were added to the hot solution. The mixture was heated for 15 min. to reflux. Colourless crystals separated from the solution after slowly cooling to room temperature. The solid was filtered off and was purified by recrystallisation from dichloromethane to yield 0.72 g (67%) (−)-norephedrinium salt of (+)-**13** as a colourless solid, m.p. 97−98°C. − $[\alpha]_D$ = −17.7. − ^{1}H-NMR ([D_6]DMSO, two rotamers in a 85:15 ratio): δ = 0.69 (m, 6 H, CH$_2$C*H*$_3$), 0.84 (m, 3 H, CHC*H*$_3$), 1.0−1.4 (m, 8 H), 2.04 (dd, 1 H, C*H*$_2$COOH, ^{2}J = 17.5 Hz, ^{3}J = 10.8 Hz), 2.31 (dd, 1 H, C*H*$_2$COOH, ^{2}J = 17.5 Hz, ^{3}J = 3.0 Hz), 2.86 (m, 0.15 H, NCH_2), 3.12 (m, 1.7 H, NCH_2), 3.34 (m, 0.15 H, NCH_2), 3.61 (br., 1 H), 3.69 (m, 0.15 H, C*H*CH$_3$), 4.03 (br., 0.85 H), 4.47 (br., 0.15 H), 4.81 (br., 1 H), 6.5 (br., 3 H, NH_3^+), 7.31 (m, 5 H, ar H), 7.85 (s, 0.85 H, CHO), 7.92 (s, 0.15 H, CHO). − ^{13}C-NMR ([D_6]DMSO, major rotamer): δ = 6.95, 7.27, 13.68, 19.86, 22.98, 27.35, 29.58, 34.92, 36.13, 52.98, 58.16, 72.12, 126.76, 127.87, 128.56, 141.45, 163.45, 175.76. − $C_{21}H_{34}N_2O_4$ (378.5): calcd. C 66.64, H 9.05, N 7.40; found C 66.21, H 9.12, N 7.32.

The (−)-norephedrinium salt of (+)-**13** was dissolved in 50 mL water and treated with 1 mL conc. HCl. The mixture was extracted with 30 mL dichloromethane three times. After drying of the combined organic extracts with $MgSO_4$ the solvent was removed in vacuo to give the enantiomeric pure *N*-formylated β-amino acid (+)-**13** in 0.38 g (87%) yield as a colourless oil. − $[\alpha]_D$ = +27.9.

(2*SR*,6*RS*)-2-Ethyl-5,5-dimethyl-1-azabicyclo[4.2.0]octan-8-one (14b): The intramolecular lactam formation of 1.00 g (5 mmol) *trans*-**9b** was performed according to *GP6*. The β-lactam was purified by column chromatography (*n*-hexane/ethyl acetate, 50:50) to yield 0.30 g (33%) of a colourless liquid. − TLC (*n*-hexane/ethyl acetate, 50:50): R_f = 0.57. − IR (NaCl): ṽ = 2940, 2860 (CH_3, CH_2), 1730 (lactam) cm^{-1}. − ^{1}H-NMR ($CDCl_3$): δ = 0.92 (t, 3 H, ^{3}J = 6.6 Hz), 0.94 (s, 6 H, CCH_3), 1.31−1.96 (m, 6 H), 2.67 (dd, 1 H, CH_2CO, ^{3}J = 1.6 Hz, ^{2}J = 14.3 Hz), 2.82 (dd, 1 H, CH_2CO, ^{3}J = 4.4 Hz, ^{2}J = 14.3 Hz), 3.17 (dd, 1 H, H6, ^{3}J = 1.6 Hz, ^{3}J = 4.4 Hz), 3.68 (m 1 H, H2). − ^{13}C-NMR ($CDCl_3$): δ = 10.82, 18.20, 23.77, 24.57, 27.73, 30.96, 33.58, 38.17, 47.45, 52.99, 166.05. − MS (CI, *iso*-butane): *m*/*z* (%) = 182 (100) [MH^+]. − $C_{11}H_{19}NO$ (181.3): calcd. C 72.88, H 10.49, N 7.73; found C 72.39, H 10.72, N 7.60.

(2*SR*,6*RS*)-2-Ethyl-5-spirocyclohexyl-1-azabicyclo[4.2.0]octan-8-one (14e): The intramolecular lactam formation of 1.20 g (5 mmol) *trans*-**9e** was performed according to *GP6*. The β-lactam was puri-

fied by column chromatography (*n*-hexane/ethyl acetate, 60:40) to yield 0.21 g (19%) of a colourless liquid. − TLC (*n*-hexane/ethyl acetate, 60:40): R_f = 0.47. − IR (NaCl): $\tilde{\nu}$ = 2930, 2860 (CH_3, CH_2), 1740 (lactam) cm^{-1}. − ^{1}H-NMR ($CDCl_3$): δ = 0.92 (t, 3 H, ^{3}J = 7.7 Hz),1.06−2.02 (m, 16 H), 2.76 (dd, 1 H, CH_2CO, ^{3}J = 4.4 Hz, ^{2}J = 14.3 Hz), 2.88 (dd, 1 H, CH_2CO, ^{3}J = 2.2 Hz, ^{2}J = 14.3 Hz), 3.13 (dd, 1 H, H1, ^{3}J = 2.2 Hz, ^{3}J = 4.4 Hz), 3.63 (m, 1 H, H3). − ^{13}C-NMR ($CDCl_3$): δ = 10.80, 20.90, 22.73, 25.01, 25.50, 26.16, 26.34, 33.42, 36.06, 37.54, 47.55, 54.61, 166.02. − MS (CI, *iso*-butane): *m*/*z* (%) = 222 (100) [MH^+]. − $C_{14}H_{23}NO$ (221.3): calcd. C 75.97, H 10.47, N 6.33; found C 75.88, H 10.73, N 6.32.

5-Methyl-5-propyl-1-azabicyclo[4.2.0]octan-8-one (14f): The intramolecular lactam formation of 1.00 g (5 mmol) **9f** was performed according to *GP6*. The β-lactam was purified by column chromatography (*n*-hexane/ethyl acetate, 60:40) to yield 0.32 g (35%) of a colourless liquid (50:50-mixture of racemic *cis*:*trans* diastereomers after chromatography). − TLC (*n*-hexane/ethyl acetate, 60:40): R_f = 0.34. − IR (NaCl): $\tilde{\nu}$ = 2960, 2870 (CH_3, CH_2), 1750 (lactam) cm^{-1}. − ^{1}H-NMR ($CDCl_3$): δ = 0.90(s, 3 H, CH_3), 0.91 (t, 3 H, ^{3}J = 7.7 Hz), 1.02−1.80 (m, 8 H), 2.60−2.90 (m, 3 H), 3.14 (d, 1 H, CH_2CO, ^{3}J = 2.8 Hz), 3.74 (dd, 1 H, H6, ^{3}J = 6.1 Hz, ^{3}J = 13.2 Hz). − ^{13}C-NMR ($CDCl_3$): δ = 14.12, 15.45, 16.33, 16.60, 19.43, 19.71, 24.69, 31.86, 32.38, 33.02, 33.86, 35.81, 37.28, 37.40, 37.94, 39.83, 44.65, 54.67, 56.66, 165.47, 165.59. − MS (CI, *iso*-butane): *m*/*z* (%) = 182 (100) [MH^+]. − $C_{11}H_{19}NO$ (181.3): calcd. C 72.88, H 10.49, N 7.73; found C 72.99, H 10.63, N 7.66.

5-Methyl-5-phenyl-1-azabicyclo[4.2.0]octan-8-one (14g): The intramolecular lactam formation of 1.17 g (5 mmol) **9g** was performed according to *GP6*. The β-lactam was purified by column chromatography (*n*-hexane/ethyl acetate, 50:50) to yield 0.76 g (71%) of a colourless liquid (50:50-mixture of racemic *cis*:*trans* diastereomers after chromatography). − TLC (*n*-hexane/ethyl acetate, 50:50): R_f = 0.40. − IR (KBr): $\tilde{\nu}$ = 2930, 2860 (CH_3, CH_2), 1720 (lactam), 1590, 1390 (ar.) cm^{-1}. − ^{1}H-NMR ($CDCl_3$): δ = 1.29 (s, 1.5 H, CH_3), 1.43 (s, 1.5 H, CH_3), 1.54−2.20 (m, 4 H), 2.57 (dd, 0.5 H, CH_2CO, ^{3}J = 1.7 Hz, ^{2}J = 14.9 Hz), 2.75−3.02 (m, 2.5 H), 3.52 (dd, 0.5 H, CH_2CO, ^{3}J = 2.2 Hz, ^{2}J = 4.4 Hz), 3.60 (dd, 0.5 H, CH_2CO, ^{3}J = 2.2 Hz, ^{2}J = 3.8 Hz), 3.84 (m, 1 H, H6), 7.19−7.43 (m, 5 H, ar.H). − ^{13}C-NMR ($CDCl_3$): δ = 19.33, 19.80, 28.60, 34.54, 35.29, 37.03, 37.27, 37.79, 38.04, 40.52, 41.15, 54.39, 56.34, 124.88, 126.30, 126.39, 126.91, 128.21, 128.49, 143.75, 147.86, 165.10, 166.11. − MS (CI, *iso*-butane): *m*/*z* (%) = 216 (100) [MH^+]. − $C_{14}H_{17}NO$ (215.3): calcd. C 78.10, H 7.96, N 6.51; found C 77.84, H 7.89, N 6.60.

(2*RS*,5*RS*)-2-(Carboxymethyl)-5,5-dimethyl-3-thiazolidine-4-acetic Acid (*cis*-15): 4.90 g (30 mmol) *rac*-homopenicillamine was dissolved in 50 mL methanol and 3.96 g (45 mmol) glyoxylic acid methyl ester was added. The solution was heated to reflux for 30 minutes. The desired product separated in colourless crystals upon cooling from the reaction mixture. The solid was filtered off and washed with Et_2O to give 2.20 g (32%) of the title compound (*cis*-**15**), m.p. 158−159°C. − ^{1}H-NMR ([D_6]DMSO): δ = 1.15, 1.39 (2s, 6 H, CH_3), 2.36 (dd, 1 H, CH_2COOH, ^{2}J = 15.3 Hz, ^{3}J = 2.7 Hz), 3.14 (dd, 1 H, NCH, ^{3}J = 9.6 Hz, ^{3}J = 2.7 Hz), 3.31 (s, 1 H, NH), 3.69 (s, 3 H, OCH_3), 4.97 (s, 1 H, H2). − ^{13}C-NMR ([D_6]DMSO): δ = 26.15, 33.40, 52.52, 58.82, 62.35, 69.57, 171.40, 172.68. − $C_9H_{15}NO_4S$ (233.3): calcd. C 46.34, H 6.48, N 6.00; found C 46.37, H 6.44, N 6.03.

2-Methyl (2*RS*,5*RS*)-4,4-Dimethyl-7-oxo-3-thia-1-azabicyclo[3.2.0]-heptanecarboxylate (*endo*-16): 2.30 g (10 mmol) *cis*-**15**, 3.10 g (12 mmol) triphenylphosphane and 2.60 g (12 mmol) bis(2-pyridyl) disulfide were dissolved in acetonitrile and heated at reflux for five hours. The solvent was evaporated in vacuo and the residue was purified by column chromatography (dichloromethane/Et_2O, 50:50) to yield 0.35 g (65%) of a colourless oil. − ^{1}H-NMR ($CDCl_3$): δ = 1.52, 1.65 (2s, 6 H, CH_3), 2.76 (dd, 1 H, H_a, $^2J_{Ha,Hb}$ = 15.5 Hz, $^3J_{Ha,Hc}$ = 2.1 Hz), 3.89 (ddd, 1 H, H_b, $^2J_{Hb,Ha}$ = 15.5 Hz, $^3J_{Hb,Hc}$ = 4.3 Hz, $^5J_{Hb,Hd}$ = 1.8 Hz), 3.85 (s, 3 H, OCH_3), 3.97 (dd, 1 H, H_c, $^3J_{Hc,Hb}$ = 4.3 Hz, $^3J_{Hc,Ha}$ = 2.1 Hz), 4.90 (d, 1 H, H_d, $^5J_{Hd,Hb}$ = 1.8 Hz). − ^{13}C-NMR ($CDCl_3$): δ = 25.65, 25.83, 34.60, 54.76, 59.54, 64.99, 68.34, 165.74, 168.25. − $C_9H_{13}NO_3S$ (215.3): calcd. C 50.22, H 6.09, N 6.51; found C 50.01, H 5.98, N 6.66.

2-Methyl (2*RS*,5*SR*)-4,4-Dimethyl-7-oxo-3-thia-1-azabicyclo[3.2.0]-heptanecarboxylate (*exo*-16): 0.11 g (0.5 mmol) *endo*-**16** was dissolved in 10 mL abs. dichloromethane. A drop of diazabicylo-[4.3.0]non-5-ene (DBN) was added and the mixture was stirred under argon for twelve hours. After washing with saturated aqueous $NaHCO_3$ solution the organic phase was dried with $MgSO_4$ and the solvent was evaporated in vacuo to yield 0.10 g (91%) of a colourless oil. − ^{1}H-NMR ($CDCl_3$): δ = 1.55, 1.61 (2s, 6 H, CH_3), 2.70 (dd, 1 H, H_a, $^2J_{Ha,Hb}$ = 15.7 Hz, $^3J_{Ha,Hc}$ = 4.8 Hz), 3.11 (dd, 1 H, H_b, $^2J_{Hb,Ha}$ = 15.7 Hz, $^3J_{Hb,Hc}$ = 1.8 Hz), 3.80 (s, 3 H, OCH_3), 4.08 (dd, 1 H, H_c, $^3J_{Hc,Ha}$ = 4.8 Hz, $^3J_{Hc,Hb}$ = 1.8 Hz), 5.44 (s, 1 H, H_d).

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