Synthesis of novel pipecolic acid derivatives: a multicomponent approach from 3,4,5,6-tetrahydropyridines

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A simple approach to several derivatives of pipecolic acid is *via* a multicomponent reaction starting from cyclic imines **2**, which are synthesized on a large scale and with different substitution patterns. The protected amino acids **3** are formed in high yields. In cases where chiral imines are used the target compounds are obtained with remarkable diastereoselectivity. Bisamides **3** serve as versatile precursors for the preparation of a wide range of amino acid derivatives. Different methods of hydrolysis of **3** lead to the free pipecolic acids or its derivatives. Employment of methanol or ethanethiol as a nucleophile in the acid-mediated conversion of enamides **3** results in *N*-acylated amino acid esters **5**. Furthermore a method for the resolution of the obtained racemic α-amino acids *via* diastereomeric salt formation is described.

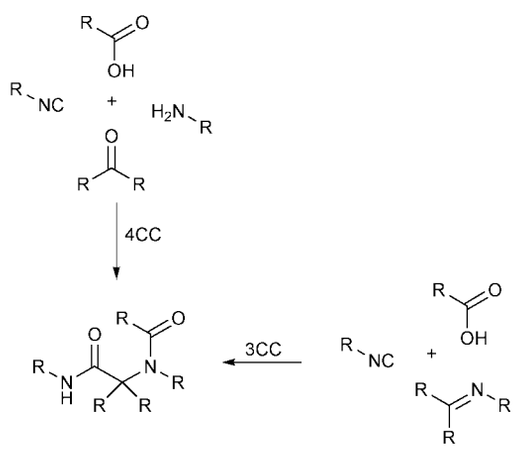
Introduction

Growing interest is focussed on the synthesis of unnatural non-proteinogenic α-amino acids since they became a more-and-more important factor in peptide chemistry. Their incorporation into biologically relevant peptides may influence their properties dramatically. In some cases increasing binding affinity to receptors or improvement of metabolic stability is the consequence of such incorporation.[1] In addition, non-proteinogenic α-amino acids are interesting compounds with regard to the study of peptide conformations.[2] In this context conformationally restricted amino acid derivatives are of particular interest. In particular, cyclic amino acids related to proline exhibit remarkable effects.[3] The noncoded α-amino acid pipecolic acid, also called homoproline, is a proline homologue with a six-membered hexahydropyridine ring. Pipecolic acid is abundant in many natural products such as immunosuppressants or cyclic peptides with antifungal activity. Many applications of homoproline as a precursor in organic chemistry have been reported, including the synthesis of alkaloids and a lot of pharmaceutically important compounds such as antipsychotica, anticonvulsants, local anaesthetics or analgesics.[4] Replacement of proline by its higher homologue in peptides is reported to produce a significant change in bioactivity and leads to interesting model compounds for studies on peptide conformations,[5] where derivatives of pipecolic acid often find a role as β-turn mimics.[6] Comparing investigations of pipecolic acid residues to other cyclic amino acids incorporated in peptides gives detailed insight into local mechanisms relevant for peptide-folding processes in relation to ring size.[7]

Taking these remarkable properties of pipecolic acid derivatives into account only a few methods for the synthesis of these compounds were known until now.[8] Most of them require several steps for the preparation and on top of that also restrict the substitution pattern rigorously. Herein we would like to report on a versatile, one-pot approach to totally protected pipecolic acid derivatives with variable substitution patterns from 3,4,5,6-tetrahydropyridines *via* Ugi Three-Component Condensation (Ugi 3CC). Furthermore, an efficient method for the optical resolution of N-protected homoprolines leading to enantiomerically pure pipecolic acid derivatives is described.

Results and discussion

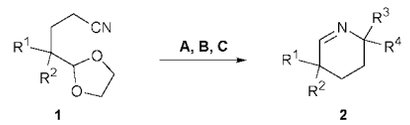
Among the methods for the multicomponent synthesis of peptides or amino acids, the Ugi 4CC is one of the most popular.[9] This versatile α-amido alkylation leads to the synthesis of several amino acid derivatives and peptides in a simple, one-pot procedure. Reaction of an isocyanide, an oxo compound, a carboxylic acid, and an amine generates bisamides which contain a totally protected α-amino acid skeleton (4CC, Scheme 1). In some cases substitution of the oxo and amine component by the corresponding imine is advantageous, resulting in a three-component condensation (3CC, Scheme 1).



Scheme 1

Recently we demonstrated the use of Ugi 3CC for the preparation of small peptides including heterocyclic amino acids from 3-thiazolines and 3-oxazolines.[10] However, the synthesis of amino acids *via* Ugi reaction suffers from a severe problem since the generated amides 'protecting' the carboxylic function within the cyclic amino acids are difficult to cleave in general.[11] A few methods[12] to circumvent these problems have been reported but most of them require harsh conditions and are incompatible with additional functional groups within the same molecule.[13] In this context Ugi and, later, Armstrong,

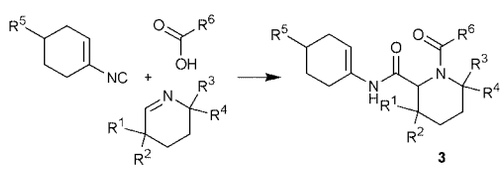
Table 1 Synthesis of tetrahydropyridines



Educt	Imine	Method[a]	R^1	R^2	R^3	R^4	Yield (%)
1a[15]	**2a**	**A**	Me	Me	H	H	[21]
1b[15]	**2b**	**A**	Et	Et	H	H	[15]
1c[15]	**2c**	**A**	$-(CH_2)_5-$		H	H	[22]
1c[15]	**2d**	**A**	Me	Pr	H	H	[15]
1d[15]	**2e**	**A**	Me	Ph	H	H	[22]
1e[15]	**2f**	**B**	Me	Me	Ph	H	[15]
1a	*cis*-**2g**	**B**	Me	Ph	Ph	H	36[b]
1e	*trans*-**2g**	**B**	Me	Ph	Ph	H	53[b]
1c	**2h**	**B**	$-(CH_2)_5-$		Me	H	49
1c	**2i**	**B**	$-(CH_2)_5-$		Et	H	[15]
1c	**2j**	**B**	$-(CH_2)_5-$		Pr^i	H	40
1c	**2k**	**B**	$-(CH_2)_5-$		Ph	H	92
1a	**2l**	**C**	Me	Me	Me	Me	44
1a	**2m**	**C**	Me	Me	Ph	Ph	73

[a] **A**: 1. $LiAlH_4$, Et_2O–THF; 2. HCl, H_2O; 3. NaOH. **B** (GP1): 1. R^3MgX, Et_2O (X = Cl, Br or I); 2. $LiAlH_4$, Et_2O–THF; 3. HCl, H_2O; 4. NaOH. **C** (GP2): 1. $CeCl_3 \cdot 7H_2O$, R^3Li, abs. THF; 2. HCl, H_2O; 3. NaOH. [b] *cis*- and *trans*-**2g** were obtained from the diastereomeric mixture of **2g** by column chromatography.

Table 2 Preparation of protected pipecolic acids **3** according to GP3 (see Experimental section)



	R^1	R^2	R^3	R^4	R^5	R^6	Yield (%)	dr[a]
3a	Me	Me	H	H	*t*-Bu	Ph	89	[b]
3b	Me	Me	H	H	*t*-Bu	CH_2Cl	98	50:50[b]
3c	Me	Me	H	H	Ph	2-NPh[c]	93	50:50[b]
3d	Me	Me	H	H	Ph	2,4-DPh[d]	100	50:50[b]
3e	Me	Me	H	H	H	Pr^i	91	
3f	Me	Me	Ph	H	H	CH_3	100	>95:5
3g	Me	Ph	Ph	H	H	CH_3	83	>95:5
3h	Et	Et	H	H	H	Pr^i	91	
3i	$-(CH_2)_5-$		H	H	H	Pr^i	96	
3j	Me	Me	Me	Me	H	Pr^i	42	
3k	Me	Me	Ph	Ph	H	Pr^i	85	

[a] Diastereomeric ratio (*trans*:*cis*) of the crude reaction products, measured by ^{1}H-NMR spectroscopy. [b] As expected, chiral isocyanides had no effect on the diastereomeric course of the reaction. However, the employed chiral isocyanides are easy to handle and therefore useful precursors for the synthesis of bisamides **3**. The diastereomeric ratio of **3a** could not be unambiguously determined from the ^{1}H-NMR spectrum. [c] 2-NPh: 2-nitrophenyl. [d] 2,4-DPh: 2,4-dimethoxyphenyl.

reported on the use of cyclohexenyl isocyanide as a suitable isocyanide in the Ugi 4CC.[14] The generated bisamides contain a vinylic amide comprising a carboxy-protecting group which can be cleaved selectively under mild acidic conditions to yield N-protected α-amino acids or derivatives thereof. Our aim was to extend this methodology to the synthesis of cyclic amino acid derivatives. The preparation of pipecolic acid derivatives *via* Ugi 3CC requires the synthesis of corresponding 3,4,5,6-tetrahydropyridines **2** as imino compounds.

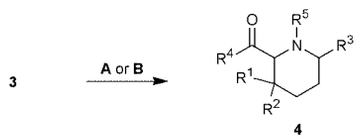
The cyclic imines **2a**–**k** were prepared from cyanodioxolanes **1** on a large scale according to methods **A** and **B** (defined in Table 1), which were recently described by us.[15] The new tetrahydropyridines **2g**,**h** and **2j**,**k** are obtained as colourless liquids of a characteristic sweetish odour in moderate to good yields. As an extension of this work we developed a route to tetrasubstituted achiral imines **2l**,**m** (method **C** in Table 1). These were prepared by reaction of cyanodioxolane **1a**[15] with cerium organyls. Subsequent hydrolysis of the acetal and intramolecular imine formation led to the cyclic imines **2l**,**m** which were obtained in moderate to good yields.

Synthesis of convertible protected derivatives of pipecolic acid

Together with a cyclohexenyl isocyanide derivative and a carboxylic acid the cyclic imines **2** were applied to Ugi 3CC to give the totally protected homoproline analogues **3** in high yields (see Table 2).

Both cyclohexenyl isocyanides and tetrahydropyridines **2** show an extraordinary high reactivity in the Ugi reaction, resulting in a desirable short reaction time but also in a con-

Table 3 Hydrolysis of enamides **3**



Educt	Product	Method[a]	R^1	R^2	R^3	R^4	R^5	Yield (%)
3e	**4a**	**A**	Me	Me	H	OH	H	78
3h	**4b**	**A**	Et	Et	H	OH	H	76
3i	**4c**	**A**	-$(CH_2)_5$-		H	OH	H	67
3g	**4d**	**A**	Me	Ph	Ph	OH	H	70
3e	**4e**	**B**	Me	Me	H	OH	Ib[b]	94
3f	**4f**	**B**	Me	Me	Ph	OH	Ac	87
3d	**4g**	**B**	Me	Me	H	OH	2,4-DB[c]	100
3a	**4h**	**B**	Me	Me	H	OH	Bz	65
3b	**4i**	**B**	Me	Me	H	NH_2	ClAc[d]	100
3a	**4j**	**B**	Me	Me	H	NH_2	Bz	31
3c	**4k**	**B**	Me	Me	H	NH_2	2-NB[e]	61

[a] **A** (GP5): 1. 10% conc. HCl in THF, 2. 4 M HCl, reflux, 3 h; **B** (GP4): 10% HCl in THF. [b] Ib: isobutyryl. [c] 2,4-DB: 2,4-Dimethoxybenzoyl. [d] ClAc: 2-chloroacetyl. [e] 2-NB: 2-nitrobenzoyl.

siderable evolution of heat while the isocyanide is being added to the reaction mixture. TLC usually indicated the absence of the starting materials after 30 min to 1 h. Bisamides **3** were obtained in high yields after purification by chromatography or crystallization. We used different carboxylic acids in the Ugi reaction to obtain *N*-acyl-protected bisamides **3**. It should be noted that this methodology may be extended to carbamate-protected derivatives by using CO_2 and alcohols as previously described in the synthesis of other amino acids *via* a Five-Component Condensation.[16]

Ugi reactions of tetrahydropyridines **2** with a prochiral C=N double bond led to the formation of a stereogenic centre at the α-carbon atom of the totally protected cyclic amino acids **3**. During the course of our investigations we focussed our efforts to find a way to control the diastereoselectivity of the reaction using chiral imines **2f**,**g** as reactants. Recent studies showed a low diastereomeric excess for Ugi reactions using chiral reactants in most cases.[9b] However, in our hands chiral tetrahydropyridines **2f**,**g** with a stereogenic centre next to the nitrogen atom led to a high excess of one diastereomer in the corresponding bisamides **3f**,**g** according to ^{1}H-NMR spectroscopy of the crude products. The bisamides **3f**,**g** exhibit preferentially a *trans* geometry of alkyl or aryl substituents at C-2 and C-6, as confirmed by 2D-NOESY-NMR studies of compound **4f** (see Fig. 1, *vide infra*).

Conversion of Ugi-adducts

The totally protected derivatives of pipecolic acid **3** serve as versatile precursors for the synthesis of cyclic amino acids or further derivatives thereof. Recently, Keating and Armstrong reported on several acid-mediated conversions of cyclohexenyl-amides.[14b] Therefore, we also treated our Ugi adducts **3** with different nucleophiles under acidic conditions.

Employment of water as a nucleophile under mildly acidic conditions (method **B** in Table 3) led to *N*-acylated amino acids **4e**–**h** in good yields. Compound **4f** was synthesized from **3f** in diastereomerically pure form without changing the configuration.

A second method for hydrolysis requiring a larger excess of hydrochloric acid (method **A** in Table 3) led to novel amino acids **4a**–**d** in a one-pot process. Several new derivatives of pipecolic acid were synthesized in this way. Again amino acid **4d** was formed, without changing the configuration of the starting bisamide **3g**, in diastereomerically pure form. All products **4e**–**k** and **5** seem to prefer an axial arrangement of

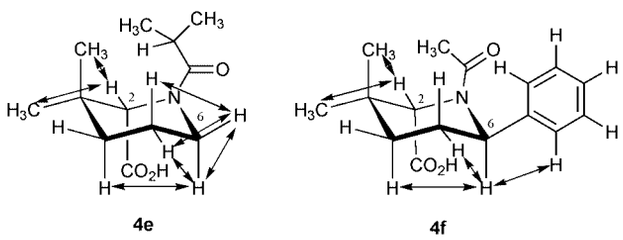


Fig. 1 Strong NOEs of hydrogens at C-2 and C-6 observed in the 2D-NOESY experiments of **4e** and **4f**.

the amino acid carboxy group as confirmed by 2D-NOESY-NMR investigations for **4e** and **4f** (Fig. 1).

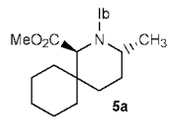
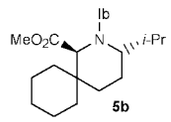
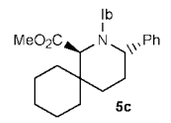
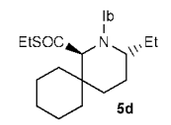
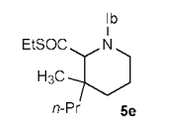
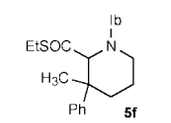
Unfortunately the *cis*- or *trans*-geometry of the *N*-acyl side chain could not be determined unambiguously by the 2D-NOESY experiments because either the spectra were taken at temperatures above coalescence as in the case of **4f**, or the signals of the *cis*- and the *trans*-form for the single hydrogen in the *N*-isobutyryl residue happened to be isochronic, thus leading to NOEs of these signals to both hydrogens at C-2 and C-6. Therefore, these NOEs are omitted in the scheme above since they do not contribute to the elucidation of the stereochemical substitution pattern of the piperidine ring. However, the *cis*- and *trans*-geometry *can* be revealed by analysis of the chemical shifts of the hydrogens at C-2 and C-6 in cases where the spectra were taken at temperatures beneath coalescence.

The stereogenically unfavourable axial arrangement of the carboxy group is imposed by the presence of the *N*-acyl group attached to the six-membered ring system. Such configurations are known to cause excessive 1,3-allylic strain in the case of neighbouring equatorial carboxylic functions.[17]

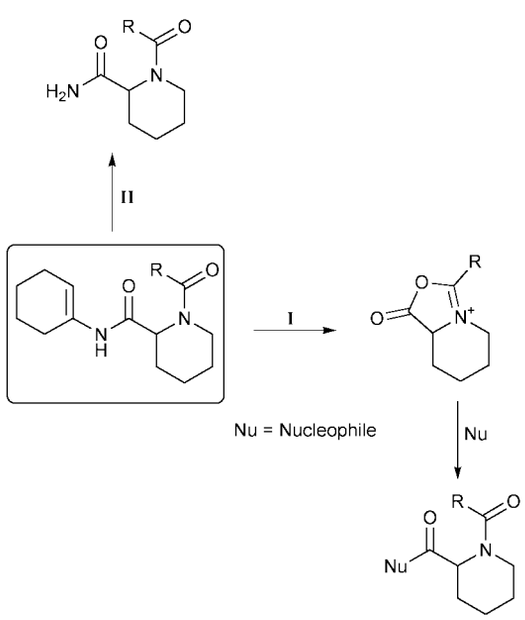
Surprisingly, acidic hydrolysis of Ugi adducts **3b**,**c** did not yield the expected corresponding carboxylic acid derivatives (pathway **I**, Scheme 2). Instead the primary amides **4i**,**k** were observed as main products. A significant amount of primary amide **4j** was also obtained as a second reaction product in the hydrolysis of **3a** to give **4h**. Keeping these observations in mind we believe that properties of bisamides **3** with regard to hydrolysis may be modulated by the nature of the carboxylic acid derivatives employed in the Ugi 3CC.

The mechanism of the acidic conversion of cyclohexenamides to carboxylic acids or esters like **4a**–**h** and **5** is supposed to involve a reactive münchnone species as an intermediate (pathway **I**, Scheme 2).[14b] Electron-withdrawing groups attached to

Table 4 Ugi 3CC and *in situ* conversion of enamides according to GP6 (see Experimental section)

Educts	Product[a]	dr[b]	Yield (%)
2h, 4-phenylcyclohex-1-enyl isocyanide, isobutyric acid, methanol	 **5a**	78 : 22	60
2j, 4-*tert*-butylcyclohex-1-enyl isocyanide, isobutyric acid, methanol	 **5b**	>95 : 5	67
2k, 4-phenylcyclohex-1-enyl isocyanide, isobutyric acid, methanol	 **5c**	>95 : 5	44
2i, 4-*tert*-butylcyclohex-1-enyl isocyanide, isobutyric acid, ethanethiol	 **5d**	>95 : 5	29
2d, 4-*tert*-butylcyclohex-1-enyl isocyanide, isobutyric acid, ethanethiol	 **5e**	50 : 50	54
2e, 4-*tert*-butylcyclohex-1-enyl isocyanide, isobutyric acid, ethanethiol	 **5f**	50 : 50	53

[a] **5a**: main diastereomer is shown; one enantiomer of racemic **5a**–**d** is shown; Ib: isobutyryl. [b] Diastereomeric ratio (*trans* : *cis*) of the crude reaction products, measured by ^{1}H-NMR spectroscopy.



Scheme 2

R (Scheme 2) destabilize the reactive intermediate, resulting in hydrolysis of bisamides **3b**,**c** to primary amides **4i**,**k** and a cyclohexanone derivative (pathway **II**, Scheme 2).

Different esters and thioesters can be prepared if alcohols or thiols, respectively, are employed as nucleophiles instead of water, *e.g*. methyl esters **5a**–**c** resulted from an acid-mediated *in situ* conversion of 3CC products using methanol, whereas utilization of ethanethiol gave thioesters **5d**–**f**. Given yields (Table 4) include the two steps of Ugi reaction and hydrolysis of enamides to carboxylic esters **5**.

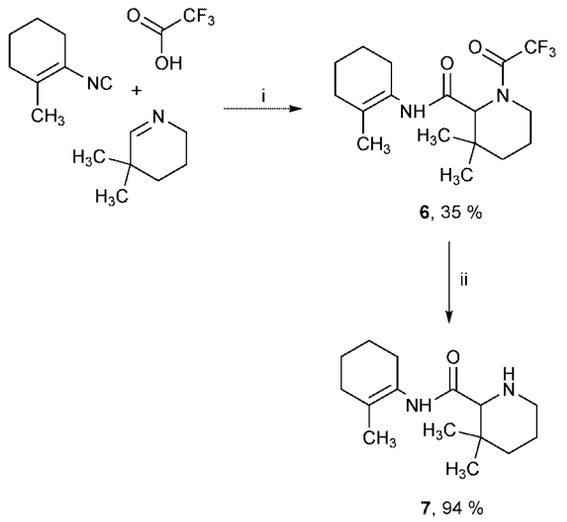
Derivatives **5b**–**d** were obtained in diastereomerically pure form from cyclic imines **2i**–**k**. Due to the diastereomeric ratios of the crude carboxylic esters Ugi reactions proceeded with high diastereoselectivity even with small substituents R^3 (see Table 1) in cyclic imines **2**. Employment of imines **2d**,**e** with a stereogenic centre in 3-position in the Ugi 3CC resulted in no diastereoselection in products **5e**,**f**. However, diastereomeric mixtures of **5e**,**f** were easily separated by chromatography to yield diastereomerically pure compounds.

Acyl residues R such as the trifluoroacetamide in bisamide **6** could also be selectively removed as illustrated in Scheme 3.

The trifluoroacyl group of **6** was cleaved under mild alkaline conditions in the presence of the cyclohexenyl amide to give the N-deprotected amino acid **7**, which is now available for further modifications at the N-terminus. The somewhat lower yield of the trifluoroacetamide **6** in comparison to other Ugi adducts **3** is due to a TFA-mediated cleavage of the cyclohexenyl amide. As a consequence reaction conditions have to be controlled carefully.

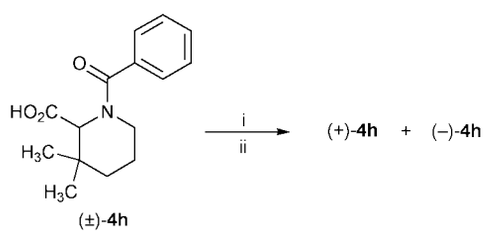
Resolution of pipecolic acids

As mentioned before, amino acid derivatives **3**, **4** and **5** were obtained as racemates. Since enantiomerically pure compounds are far more attractive as building blocks for peptide or natural product synthesis we finally concentrated our efforts on the resolution of these amino acids. Racemic *N*-acylated amino acid **4h** was chosen as a model compound for the resolution *via* diastereomeric salt formation. Resolution of the



Scheme 3 *Reagents and conditions*: i, dichloromethane, 1 h; ii, K_2CO_3, aq. MeOH.

N-benzoylated amino acid (±)-**4h** was achieved by formation of its diastereomeric salts[18] with (−)-norephedrine. The norephedrinium salt of (−)-**4h** precipitated from diethyl ether upon cooling. Acidic treatment of this norephedrine salt gave the desired enantiomerically pure *N*-benzoylated amino acid (−)-**4h** (Scheme 4). The corresponding enantiomer (+)-**4h** was



Scheme 4 *Reagents and conditions*: i, (−)-norephedrine, Et_2O, ii, aq. HCl.

obtained from the filtrate by repeating the procedure described above. Finally, deprotection of compounds (+)-**4h** and (−)-**4h** should be possible in an analogous manner to the hydrolysis of compounds **3e**,**g**–**i**. Unfortunately we have not yet been able to determine the absolute configuration of the enantiomerically pure *N*-benzoylated α-amino acids (+)-**4h** and (−)-**4h** because we have not been able to obtain suitable crystals from their norephedrinium salts for X-ray crystal-structure analysis.

Conclusions

The synthesis of new pipecolic acid analogues from cyclic imines **2** *via* Ugi multicomponent condensation has been described. Several previously unknown 3,4,5,6-tetrahydropyridines **2** were prepared and used as imine components in the Ugi 3CC to yield totally protected derivatives of cyclic amino acids. Chiral tetrahydropyridines **2f**–**k** led to the diastereoselective formation of Ugi products **3f**,**g**, hydrolysis products **4d**,**f** and *N*-acylated amino acid esters **5a**–**d**. The obtained bisamides **3** serve as versatile precursors for a wide range of amino acid derivatives. An acid-mediated nucleophilic conversion of Ugi adducts yielded carboxylic esters **5a**–**c**, thioesters **5d**–**f**, N-protected amino acids **4e**–**h**, and the free amino acids **4a**–**d**. It was found that electron-rich substituents as in **3d** gave rise to carboxylic acid derivatives such as **4g**, whereas electron-withdrawing substituents present in **3b**,**c** led to primary amides such as **4i**,**k** when exposed to otherwise identical acidic hydrolysis conditions.

The synthesis of enantiomerically pure amino acid derivatives (−)-**4h** and (+)-**4h** was achieved *via* an efficient resolution procedure employing (−)-norephedrine.

In conclusion we were able to present a highly diastereoselective multicomponent approach to novel pipecolic acid derivatives which were converted to enantiomerically pure compounds *via* diastereoselective salt formation with norephedrine. We are currently investigating the incorporation of these new amino acids into small peptides in order to study their effects on the structural properties of these compounds. The results of these investigations will be reported in due course.

Experimental

General remarks

If indicated with 'abs.', solvents were purified prior to use as follows: dichloromethane was distilled from $CaCl_2$; THF and Et_2O were distilled from sodium and benzophenone. $CeCl_3 \cdot 7H_2O$ was dried prior to use at 150 °C for 3 h. Thin-layer chromatography (TLC) analyses were performed on silica gel Polygram® plates and fluorescence indicator from Macherey Nagel and Co., Düren. For preparative chromatography Merck silica gel 60, 230–400 mesh, was used. Lewatit MP 62 was a gift from Bayer AG Leverkusen. Mps were determined in open capillaries in a Dr Lindström instrument and are uncorrected. Specific optical rotations $[a]_D$ were determined with a Perkin-Elmer polarimeter (241 MC), at 21 °C, and are given in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded on a Beckmann spectrophotometer (IR 4220). ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker-Karlsruhe AM 300 or an Avance 300 spectrometer (300.1 MHz/75 MHz). 2D-NOESY-spectra were recorded on a Bruker-Karlsruhe Avance 500 spectrometer (500.1 MHz). Chemical shifts are reported on the δ-scale (ppm) relative to residual nondeuterated solvent or tetramethylsilane (TMS) in [D_3]MeOD, D_2O, $CDCl_3$, or [D_6]DMSO. Coupling constants, J, are given in Hz. Mass spectra were taken on a Finnigan-MAT 212 instrument in CI mode with isobutane or NH_3 as reactant gas. Elemental analyses were performed with a C, H, N-Analyser EA 1108 from Fisons Instrument. Abbreviations: mi: minor isomer; ma: major isomer.

General procedures (GPs)

Preparation of cyclic imines 2f–k (GP1). A solution of 0.1 mol of cyanodioxolane **1** in 100 ml of abs. Et_2O was added dropwise to 0.13 mol of the appropriate Grignard reagent in 200 ml of abs. Et_2O. After addition of 50 ml of abs. THF the solution was heated to reflux for 3 h and 5 g (0.13 mol) of $LiAlH_4$ were added carefully. The reaction mixture was heated to reflux for 13 h and subsequently hydrolysed by careful addition of 5 ml of water, 2 ml of 20% aq. NaOH, and 25 ml of water. The resulting precipitate was filtered off after 3 h of stirring at room temperature and the filtrate was dried over $MgSO_4$. The solvent was removed *in vacuo* to give a crude amino dioxolane as a yellow oil, which was dissolved in a mixture of 50 ml of water and 15 ml of conc. HCl. After 2 h of stirring at room temperature, 10 g of solid NaOH were added accompanied by 50 g of ice. The resulting red solution exhibited the typical sweetish odour of cyclic imines **2** and was stirred at room temperature for 1 h. After three-fold extraction with 150 ml of $CHCl_3$ each time the organic layer was dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude imine as a red oil, which was further purified by distillation or chromatography.

Preparation of cyclic imines 2l,m (GP2). 15 g (40.2 mmol) of $CeCl_3 \cdot 7H_2O$ were suspended in 80 ml of abs. THF and the mixture was stirred for 2 h at room temperature. After the suspension was cooled to −50 °C the appropriate organic

Li-compound was added and the resulting solution was stirred for 30 min under argon. 2.20 g (13 mmol) of cyanodioxolane **1a**[14] were added at −65 °C and the reaction mixture was stirred for 2 h. After warming to −40 °C, 25 ml of saturated aq. NH_4Cl were added carefully and the suspension was filtered through Celite. After evaporation of the solvent *in vacuo* the residue was dissolved in 30 ml of toluene, treated with 30 ml of H_3PO_4 (3%, aq.), and the solution stirred for 15 min. The organic phase was extracted three times with 10 ml of water each and the combined aqueous extracts were treated with 2 M NaOH until they were slightly alkaline. Three-fold extraction with 30 ml of dichloromethane each, drying of the organics over $MgSO_4$, and evaporation of the solvent gave a yellow oil, which was treated with 15 ml of water and 2 ml of conc. HCl. After the solution was stirred for 2 h it was treated with 1.5 g of solid NaOH and extracted three times with 30 ml of $CHCl_3$ each. Drying over $MgSO_4$ and evaporation of the solvent *in vacuo* led to the cyclic imine, which was further purified by column chromatography on silica gel (dichloromethane–methanol, 9 : 1).

General procedure for the preparation of totally protected pipecolic acids 3 (GP3). The appropriate imine **2** (2 mmol) and the carboxylic acid (2 mmol) were dissolved in 7 ml of abs. MeOH. The isocyanide (2.0 mmol) was added and the solution was stirred for 1 h at room temperature. The solvent was removed *in vacuo* and the resulting crude enamide **3** was purified by column chromatography or crystallized from a suitable solvent.

General procedure for hydrolysis of enamides 3 to carboxylic acids 4e–h and primary amides 4i–k (GP4). The appropriate enamide **3** (1–2 mmol) was dissolved in a stock solution of 1 ml of conc. HCl and 9 ml of THF. The solution was stirred for 12 h at room temperature. Solid Na_2CO_3 was added for neutralization and the solution was filtered. The filtrate was evaporated to dryness *in vacuo* and the residue dissolved in 10 ml of dichloromethane. The solution was extracted three times with 10 ml of pH 10 water each. The combined aqueous phases were acidified with 4 M HCl (pH 1) and extracted three times with 20 ml of dichloromethane each. After drying of the organics over $MgSO_4$ and evaporation of the solvent under reduced pressure the desired carboxylic acids **4e**–**h** were obtained. In some cases the obtained products were further purified by column chromatography on silica gel.

General procedure for hydrolysis of enamides 3 to amino acids 4a–d (GP5). The appropriate enamide **3** (1–2 mmol) was dissolved in a stock solution of 1 ml of conc. HCl and 9 ml of THF. The solution was stirred for 12 h at room temperature. After removal of the solvent under reduced pressure 20 ml of 4 M aq. HCl was added and the solution was heated to reflux for 3 h. Water was evaporated *in vacuo* and the residue was dissolved in MeOH. The solution was treated with Lewatit MP 62 until it was slightly alkaline. Subsequent filtration and evaporation of the solvent *in vacuo* gave the crude amino acids, which were crystallized from acetone to give the pure cyclic amino acids.

General procedure for *in situ* conversions of Ugi adducts to carboxylic esters 5a–c and thioesters 5d–f (GP6). The appropriate imine **2** (2 mmol) and the carboxylic acid (2 mmol) were dissolved in 7 ml of abs. MeOH. The isocyanide (2.0 mmol) was added and the solution was stirred for 1 h at room temperature. The solvent was removed *in vacuo* and the residue was dissolved in 20 ml of MeOH or ethanethiol. 10 mol equiv. of acetyl chloride were added and the solution was heated to reflux for 3 h. The solvent was removed under reduced pressure and the residue was taken up in 20 ml of dichloromethane. After filtration the solvent was removed *in vacuo*. The resulting crude ester was purified by column chromatography on silica gel with a 0–2% methanol in dichloromethane gradient.

*3-Methyl-3,6-diphenyl-3,4,5,6-tetrahydropyridine† cis/trans-**2g***.—The title compound was prepared according to **GP1** using 23.1 g (0.1 mol) cyanodioxolane **1e**[15] as starting material. The *cyclic imine* **2g** (22.70 g, 92%) was obtained as a yellow oil without any purification. The crude diastereomeric mixture (60 : 40) was separated into the *cis* and *trans* racemates by column chromatography on silica gel with a Et_2O–CH_2Cl_2–*n*-hexane (10 : 5 : 5) gradient with *cis*-**2g** eluting as the first fraction.

*(3SR,6RS)-3-Methyl-3,6-diphenyl-3,4,5,6-tetrahydropyridine† cis-**2g***.—Yield: 9.01 g (36%); R_f 0.82 (Et_2O–CH_2Cl_2–*n*-hexane, 10 : 5 : 5) [Found: C, 87.02; H, 7.70; N, 5.62. $C_{18}H_{19}N$ (249.4) requires C, 86.70; H, 7.68; N, 5.62%]; δ_H ($CDCl_3$) 1.45 (3H, s, CH_3), 1.5–2.0 (4H, m, CH_2CH_2), 4.59 (1H, m, NCH), 7.2–7.4 (10H, m, ArH), 7.88 (1H, s, N=CH); δ_C ($CDCl_3$) 24.26, 28.17, 34.77, 41.71, 61.52, 126.22, 126.65, 127.11, 128.33, 128.52, 128.68, 144.32, 145.91, 168.47; *m*/*z* (CI-isobutane) 250 (100%) [MH^+].

*(3SR,6SR)-3-Methyl-3,6-diphenyl-3,4,5,6-tetrahydropyridine† trans-**2g***.—Yield: 13.16 g (53%); R_f 0.71 (Et_2O–CH_2Cl_2–*n*-hexane, 10 : 5 : 5) (Found: C, 86.65; H, 7.59; N, 5.51%); δ_H ($CDCl_3$) 1.4–2.1 (4H, m, CH_2CH_2), 1.45 (3H, s, CH_3), 4.49 (1H, m, NCH), 7.1–7.3 (10H, m, ArH), 7.92 (1H, s, N=CH); δ_C ($CDCl_3$) 26.91, 27.38, 35.19, 41.30, 62.27, 126.17, 126.37, 126.47, 127.94, 128.32, 128.50, 144.40, 145.47, 168.10; *m*/*z* (CI-isobutane) 250 (100%) [MH^+].

*rac-3-Methyl-2-azaspiro[5.5]undec-1-ene **2h***.—The title compound was prepared according to **GP1** starting from 21.0 g (0.1 mol) of cyanodioxolane **1c**.[15] The cyclic imine was purified by distillation *in vacuo* at 75 °C (0.05 mbar‡) to give **2h** (8.10 g, 49%) as a *colourless liquid*, R_f 0.54 (dichloromethane–methanol, 95 : 5) [Found: C, 80.26; H, 11.62; N, 8.51. $C_{11}H_{19}N$ (165.3) requires C, 79.94; H, 11.59; N, 8.47%]; ν_{max}(film)/cm^{-1} 1630; δ_H ($CDCl_3$) 1.0–1.8 (14H, m, CH_2), 1.18 (3H, d, CH_3, ^3J 7.2), 3.32 (1H, m, CH), 7.34 (1H, s, N=CH); δ_C ($CDCl_3$) 20.62, 20.78, 22.96, 25.70, 26.61, 28.25, 32.84, 35.62, 54.21, 169.81; *m*/*z* (CI-isobutane) 166 (100%) [MH^+].

*rac-3-Isopropyl-2-azaspiro[5.5]undec-1-ene **2j***.—The title compound was prepared from 21.0 g (0.1 mol) of cyanodioxolane **1c**[15] according to **GP1**. The cyclic imine was purified by distillation *in vacuo* at 125 °C (0.05 mbar) to give **2j** (7.72 g, 40%) as a *colourless liquid*, R_f 0.72 (dichloromethane–methanol, 95 : 5) [Found: C, 80.49; H, 11.87; N, 7.23. $C_{13}H_{23}N$ (193.3) requires C, 80.76; H, 11.99; N, 7.24%]; ν_{max}(film)/cm^{-1} 1635; δ_H ($CDCl_3$) 0.90 and 0.95 [6H, 2d, $CH(CH_3)_2$, ^3J 6.6], 1.0–1.7 [15 H, m, CH_2 + $CH(CH_3)_2$], 3.03 (1H, m, NCH), 7.47 (1H, s, N=CH); δ_C ($CDCl_3$) 18.48, 18.90, 20.72, 20.91, 25.81, 29.03, 32.16, 33.44, 36.47, 64.26, 170.21; *m*/*z* (CI-isobutane) 194 (100%) [MH^+].

*rac-3-Phenyl-2-azaspiro[5.5]undec-1-ene **2k***.—The title compound was prepared according to **GP1** using 21.0 g (0.1 mol) of cyanodioxolane **1c**[15] as starting material. The *cyclic imine* **2k** (20.91 g, 92%) was obtained without any purification, R_f 0.84 (dichloromethane–methanol, 95 : 5) [Found: C, 85.16; H, 9.30; N, 6.32. $C_{16}H_{21}N$ (227.3) requires C, 84.53; H, 9.31; N, 6.16%]; ν_{max}(film)/cm^{-1} 1635; δ_H ($CDCl_3$) 1.2–2.1 (14H, m, CH_2), 4.44 (1H, m, CH), 7.1–7.3 (5H, m, ArH), 7.59 (1H, s, N=CH); δ_C ($CDCl_3$) 20.64, 20.84, 25.74, 27.90, 28.15, 32.96, 35.41, 36.48, 62.46, 126.39, 126.59, 127.06, 128.18, 144.56, 171.48; *m*/*z* (CI-isobutane) 228 (100%) [MH^+].

*3,3,6,6-Tetramethyl-3,4,5,6-tetrahydropyridine† **2l***.—The title compound was prepared according to **GP2** using 40 mmol of MeLi. The *cyclic imine* **2l** (0.80 g, 44%) was obtained as a

† Non-systematic name.
‡ 1 bar = 10^5 Pa.

colourless oil, R_f 0.57 (dichloromethane–methanol, 9:1) [Found: C, 77.91; H, 12.34; N, 10.13. $C_9H_{17}N$ (139.2) requires C, 77.63; H, 12.31; N, 10.06%]; δ_H ($CDCl_3$) 1.02 (6H, s, CH_3), 1.18 (6H, s, CH_3), 1.53 (4H, m, CH_2), 7.34 (1H, s, NCH); δ_C ($CDCl_3$) 26.68, 29.89, 30.67, 31.58, 32.84, 53.99, 167.66; *m/z* (CI-isobutane) 140 (100%) [MH^+].

3,3-Dimethyl-6,6-diphenyl-3,4,5,6-tetrahydropyridine† ***2m***.—The title compound was prepared according to **GP2** using 40 mmol of PhLi. The *cyclic imine* **2m** (2.50 g, 73%) was obtained as a colourless solid without purification, mp 84 °C [Found: C, 86.79; H, 8.06; N, 5.41. $C_{19}H_{21}N$ (263.4) requires C, 86.65; H, 8.04; N, 5.32%]; δ_H ($CDCl_3$) 1.01 (6H, s, CH_3), 1.42 (2H, m, CH_2), 2.31 (2H, m, CH_2), 7.1–7.4 (10H, m, ArH), 7.78 (1H, s, NCH); δ_C ($CDCl_3$) 26.29, 30.27, 31.14, 33.63, 65.87, 126.12, 126.53, 126.94, 127.97, 147.75, 169.92; *m/z* (CI-isobutane) 264 (100%) [MH^+].

1-Benzoyl-3,3-dimethylpiperidine-2-carboxylic acid (4-tert-butylcyclohex-1-enyl)amide ***3a***.—The title compound was prepared according to **GP3** starting from 3.93 g (35 mmol) of **2a**, 5.72 g (35 mmol) of 4-*tert*-butylcyclohex-1-enyl isocyanide,[19] and 4.27 g (35 mmol) of benzoic acid. The *enamide* **3a** (12.38 g, 89%) was obtained as a mixture of racemic diastereomers. However, the diastereomeric ratio could not unambiguously be determined from the ^{1}H-NMR spectrum. R_f 0.45 (dichloromethane) [Found: C, 75.91; H, 9.16; N, 7.19. $C_{25}H_{36}N_2O_2$ (396.6) requires C, 75.72; H, 9.15; N, 7.06%]; δ_H ($CDCl_3$) 0.84 [9H, s, $C(CH_3)_3$], 1.06, 1.10 [6H, 2s, $C(CH_3)_2$], 1.2–2.4 (11H, m), 3.54 (2H, m, NCH_2), 4.77 (1H, s, CHN), 6.12 (1H, m, CH=C), 7.39 (5H, m, ArH), 7.90 (1H, s, NH); δ_C ($CDCl_3$, two diastereomers) 21.46, 23.57, 23.62, 25.34, 26.36, 27.10, 27.49, 29.17, 29.33, 32.00, 32.33, 32.54, 43.49, 44.68, 61.28, 112.55, 112.79, 126.90, 128.33, 129.78, 132.46, 132.54, 135.77, 168.10, 168.21, 172.02; *m/z* (CI-NH_3) 244 (100%) [MH^+ − 4-*tert*-butylcyclohexylideneamine].

1-Chloroacetyl-3,3-dimethylpiperidine-2-carboxylic acid (4-tert-butylcyclohex-1-enyl)amide ***3b***.—The title compound was prepared according to **GP3** using 0.22 g (2 mmol) of **2a**, 0.33 g (2 mmol) of 4-*tert*-butylcyclohex-1-enyl isocyanide,[19] and 0.19 g (2 mmol) of chloroacetic acid as starting materials. The *enamide* **3b** (0.72 g, 98%) was obtained as a 50:50 mixture of racemic diastereomers. R_f 0.56 (dichloromethane–methanol, 99:1) [Found: C, 65.63; H, 9.15; N, 7.63. $C_{20}H_{33}ClN_2O_2$ (368.9) requires C, 65.11; H, 9.02; N, 7.59%]; δ_H ($CDCl_3$) 0.84 (mi), 0.92 (ma) [9H, s, $C(CH_3)_3$], 0.99 (mi), 1.03 (ma) [3H, s, $C(CH_3)_2$], 1.14 (mi), 1.19 (ma) [3H, s, $C(CH_3)_2$], 1.2–2.4 (11H, m), 3.55–3.72 (2H, m, NCH_2), 4.17 (1H, d, $ClCH_2$, ^2J 16.0), 4.20 (1H, d, $ClCH_2$, ^2J 16.0), 4.50 (mi), 4.59 (ma) (1H, s, NCH), 5.81 (mi), 6.17 (ma) (1H, m, C=CH); δ_C ($CDCl_3$, two diastereomers) 21.19, 23.37, 25.85, 25.94, 27.32, 27.47, 32.17, 32.34, 35.67, 41.44, 42.98, 43.15, 46.58, 46.96, 59.86, 60.23, 113.15, 113.35, 132.35, 166.91, 167.11, 169.21, 171.61; *m/z* (CI-NH_3) 216 (100%) [MH^+ − 4-*tert*-butylcyclohexylideneamine].

3,3-Dimethyl-1-(2-nitrobenzoyl)piperidine-2-carboxylic acid (4-phenylcyclohex-1-enyl)amide ***3c***.—The title compound was prepared from 0.22 g (2 mmol) of **2a**, 0.37 g (2 mmol) of 4-phenylcyclohex-1-enyl isocyanide,[19] and 0.33 g (2 mmol) of 2-nitrobenzoic acid according to **GP3**. The enamide **3c** (0.86 g, 93%) was obtained as a 50:50 mixture of racemic diastereomers. Several signals in the ^{1}H-NMR spectrum were extremely broadened. R_f 0.66 (dichloromethane–methanol, 99:1) [Found: C, 70.41; H, 6.87; N, 9.29. $C_{27}H_{31}N_3O_4$ (461.6) requires C, 70.26; H, 6.77; N, 9.10%]; δ_H ($CDCl_3$) 1.08 (mi), 1.13 (ma) [3H, s, $C(CH_3)_2$], 1.24 (ma), 1.30 (mi) [3H, s, $C(CH_3)_2$], 1.3–2.9 (11H, m), 3.25 (1H, m, NCH_2), 3.46 (mi), 3.91 (ma) (1H, m, NCH_2), 4.78 (ma), 5.14 (mi) (1H, br, NCH), 6.23 (ma), 6.27 (mi) (1H, m, C=CH), 7.1–8.3 (10H, m, 9 ArH + NH); δ_C ($CDCl_3$, two diastereomers) 20.93, 21.31, 26.01, 26.43, 26.88, 27.59, 28.10, 28.36, 29.16, 31.99, 32.31, 32.47, 32.60, 33.80, 39.51, 41.22, 43.69, 45.04, 60.76, 111.96, 112.65, 124.63, 135.94, 126.42, 126.54, 126.68, 127.29, 127.91, 128.23, 128.44, 129.63, 129.94, 132.40, 133.97, 134.45, 145.10, 146.33, 146.52, 166.52, 167.31, 168.33, 168.81; *m/z* (CI-NH_3) 290 (100%) [MH^+ − 4-phenylcyclohexylideneamine].

1-(2,4-Dimethoxybenzoyl)-3,3-dimethylpiperidine-2-carboxylic acid (4-phenylcyclohex-1-enyl)amide ***3d***.—The title compound was prepared according to **GP3** using 0.22 g (2 mmol) of **2a**, 0.37 g (2 mmol) of 4-phenylcyclohex-1-enyl isocyanide,[19] and 0.36 g (2 mmol) of 2,4-dimethoxybenzoic acid as starting materials. The *enamide* **3d** (0.95 g, 100%) was obtained as a 50:50 mixture of racemic diastereomers. R_f 0.48 (dichloromethane–methanol, 99:1) [Found: C, 73.12; H, 8.02; N, 5.94. $C_{29}H_{36}N_2O_4$ (476.6) requires C, 73.08; H, 7.61; N, 5.88%]; δ_H ($CDCl_3$) 1.07 (mi), 1.12 (ma) [3H, s, $C(CH_3)_2$], 1.16 (ma), 1.21 (mi) [3H, s, $C(CH_3)_2$], 1.2–2.9 (11H, m), 3.4–3.7 (2H, m, NCH_2), 3.81 (6H, s, OMe), 4.69 (ma), 4.91 (mi) (1H, s, NCH), 6.23 (1H, m, C=CH), 6.4–6.5 (2H, m), 7.1–7.4 (6H, m), 7.68 (mi), 7.96 (ma) (1H, br, NH); δ_C ($CDCl_3$, two diastereomers) 21.19, 26.13, 27.08, 28.48, 29.26, 32.25, 32.34, 39.57, 43.44, 44.44, 55.12, 55.29, 60.42, 61.16, 97.99, 98.42, 104.70, 111.72, 111.92, 118.28, 125.94, 126.65, 127.87, 128.21, 130.02, 132.42, 132.56, 135.25, 146.37, 156.24, 156.97, 161.61, 161.75, 167.79, 168.35, 168.44, 169.25; *m/z* (CI-NH_3) 305 (100%) [MH^+ − 4-phenylcyclohexylideneamine], 322 (80) [MH^+ + NH_3 − 4-phenylcyclohexylideneamine].

rac-1-Isobutyryl-3,3-dimethylpiperidine-2-carboxylic acid cyclohex-1-enylamide ***3e***.—According to **GP3** the title compound was prepared starting from 0.22 g (2 mmol) of **2a**, 0.21 g (2 mmol) of cyclohex-1-enyl isocyanide,[19] and 0.18 g (2 mmol) of isobutyric acid. The *enamide* **3e** (0.56 g, 91%) was obtained as a colourless solid, mp 149–150 °C; R_f 0.61 (dichloromethane–methanol, 99:1) [Found: C, 70.72; H, 10.02; N, 9.19. $C_{18}H_{30}N_2O_2$ (306.4) requires C, 70.55; H, 9.87; N, 9.14%]; δ_H ($CDCl_3$) 0.92 [3H, s, $C(CH_3)_2$], 1.08 [3H, d, CH-$(CH_3)_2$, ^3J 6.6], 1.10 [3H, s, $C(CH_3)_2$], 1.17 [3H, d, $CH(CH_3)_2$, ^3J 6.6], 1.26–1.69 (7H, m, CH_2), 2.1 (4H, m, CH_2), 2.34 [1H, m, $CH_2C(CH_3)_2$, ^2J 13.2, ^3J 4.4], 2.86 [1H, m, $CH(CH_3)_2$, ^3J 6.6], 3.42 [1H, m, NCH_2, ^2J 13.2, ^3J 3.9], 3.77 [1H, d, NCH_2, ^2J 13.2], 4.60 (1H, s, NCH), 6.04 (1H, m, C=CH), 7.24 (1H, br, NH); δ_C ($CDCl_3$, two diastereomers) 18.85, 19.80, 21.69, 26.27, 27.23, 28.53, 28.68, 29.37, 30.58, 32.15, 32.30, 39.68, 42.23, 60.77, 112.26, 132.43, 168.75, 177.55; *m/z* (CI-NH_3) 210 (100%) [MH^+ − cyclohexylideneamine].

(2RS,6RS)-1-Acetyl-3,3-dimethyl-6-phenylpiperidine-2-carboxylic acid cyclohex-1-enylamide ***3f***.—The title compound was prepared from 1.87 g (10 mmol) of **2f**, 1.07 g (10 mmol) cyclohex-1-enyl isocyanide,[19] and 0.60 g (10 mmol) of acetic acid according to **GP3**. The *enamide* **3f** (3.54 g, 100%) was obtained as a colourless solid, mp 149–150 °C [Found: C, 74.19; H, 8.51; N, 8.03. $C_{22}H_{30}N_2O_2$ (354.5) requires C, 74.54; H, 8.53; N, 7.90%]; δ_H ($CDCl_3$) 1.14 [3H, s, $C(CH_3)_2$], 1.19 [3H, s, $C(CH_3)_2$], 1.2–2.3 (12H, m, CH_2), 1.65 (3H, s, $COCH_3$), 4.69 (1H, s, NCH), 5.08 (1H, m, NC*H*Ph), 6.09 (1H, m, C=CH), 7.2–7.4 (5H, m, ArH), 7.61 (1H, br, NH); δ_C ($CDCl_3$) 21.92, 22.44, 23.91, 25.25, 27.67, 27.78, 28.77, 30.93, 31.20, 32.30, 58.44, 65.76, 112.43, 126.03, 126.83, 128.79, 132.60, 145.38, 170.23, 175.93; *m/z* (CI-NH_3) 258 (100%) [MH^+ − cyclohexylideneamine].

(2RS,3SR,6RS)-1-Acetyl-3-methyl-3,6-diphenylpiperidine-2-carboxylic acid cyclohex-1-enylamide ***3g***.—According to **GP3** the title compound was obtained from 1.25 g (5 mmol) of *cis*-**2g**, 0.54 g (5 mmol) of cyclohex-1-enyl isocyanide,[19] and 0.30 g (5 mmol) of acetic acid. The *enamide* **3g** (1.72 g, 83%) was obtained as a colourless solid, mp 203–204 °C [Found: C, 77.92; H, 7.76; N, 6.81. $C_{27}H_{32}N_2O_2$ (416.6) requires C, 77.85; H, 7.74; N, 6.72%]; δ_H ($CDCl_3$) 1.44 (3H, s, CCH_3), 1.4–1.7 (5H, m, CH_2), 1.54 (3H, s, $COCH_3$), 2.03 (6H, m, CH_2), 2.40 (1H, m, CH_2), 5.06 (1H, m, NC*H*Ph), 5.83 (1H, s, NCH), 6.20 (1H, m, C=CH), 6.9–7.5 (10H, m, ArH), 7.85 (1H, br, NH); δ_C ($CDCl_3$) 21.93, 22.47, 23.99, 26.12, 27.70, 29.29, 30.41, 32.84, 39.93,

58.83, 62.78, 112.25, 126.03, 126.07, 126.26, 126.64, 128.65, 128.72, 132.59, 146.38, 146.49, 170.35, 176.38; *m/z* (CI-NH_3) 320 (100%) [MH^+ − cyclohexylideneamine].

3,3-Diethyl rac-1-isobutyrylpiperidine-2-carboxylic acid cyclohex-1-enylamide ***3h***.—The title compound was prepared according to **GP3** using 0.70 g (5 mmol) of **2b**, 0.53 g (5 mmol) of cyclohex-1-enyl isocyanide,[19] and 0.44 g (5 mmol) of isobutyric acid as starting materials. The *enamide* **3h** (1.53 g, 91%) was obtained as a colourless solid, mp 115–116 °C; R_f 0.48 (dichloromethane–methanol, 99 : 1) [Found: C, 71.69; H, 10.21; N, 8.39. $C_{20}H_{34}N_2O_2$ (334.5) requires C, 71.81; H, 10.25; N, 8.37%]; δ_H ($CDCl_3$) 0.66 and 0.75 (6H, 2t, CH_3CH_2, ^3J 7.7), 1.01 and 1.09 [6H, 2d, $CH(CH_3)_2$, ^3J 6.6], 1.2–1.7 (11H, m, CH_2), 2.02 (5H, m, CH_2), 2.78 [1H, m, $CH(CH_3)_2$, ^3J 6.6], 3.40 [1H, dt, NCH_2, ^2J 12.7, ^3J 3.9], 3.68 [1H, d, NCH_2, ^2J 12.7], 4.68 (1H, s, CHN), 5.96 (1H, s, CH=C), 7.39 (1H, s, NH); δ_C ($CDCl_3$) 6.99, 7.10, 18.79, 19.64, 20.99, 21.91, 22.41, 23.53, 23.91, 26.74, 27.77, 27.95, 30.56, 37.22, 42.31, 58.14, 113.25, 132.66, 168.15, 177.37; *m/z* (CI-NH_3) 238 (100%) [MH^+ − cyclohexylideneamine].

rac-2-Isobutyryl-2-azaspiro[5.5]undecane-1-carboxylic acid cyclohex-1-enylamide ***3i***.—The title compound was prepared using 0.91 g (6 mmol) of **2c**, 63 g (6 mmol) of cyclohex-1-enyl isocyanide,[19] and 0.54 g (6 mmol) of isobutyric acid as starting materials according to **GP3**. The *enamide* **3i** (2.00 g, 96%) was obtained as a colourless solid, mp 135–136 °C; R_f 0.69 (dichloromethane–methanol, 99 : 1) [Found: C, 72.71; H, 9.86; N, 8.12. $C_{21}H_{34}N_2O_2$ (346.5) requires C, 72.79; H, 9.89; N, 8.08%]; δ_H ($CDCl_3$) 1.02 [3H, d, $CH(CH_3)_2$, ^3J 6.6], 1.10 [3H, d, $CH(CH_3)_2$, ^3J 6.6], 1.2–2.2 (22H, m, CH_2), 2.80 [1H, m, $CH(CH_3)_2$, ^3J 6.6], 3.55 [1H, dt, NCH_2, ^2J 13.6, ^3J 2.2], 3.70 [1H, dd, NCH_2, ^2J 13.6, ^3J 6.4], 4.91 (1H, s, NCH), 6.00 (1H, s, cyclohexenyl-C=CH), 7.58 (1H, br, NH); δ_C ($CDCl_3$) 18.77, 19.67, 20.53, 20.71, 21.21, 21.86, 22.35, 23.85, 26.20, 27.85, 28.37, 30.49, 32.72, 34.65, 35.28, 42.37, 59.06, 113.03, 132.66, 168.22, 177.15; *m/z* (CI-Isobutane) 250 (100%) [MH^+ − cyclohexylideneamine].

rac-1-Isobutyryl-3,3,6,6-tetramethylpiperidine-2-carboxylic acid cyclohex-1-enylamide ***3j***.—The title compound was prepared according to **GP3** starting from 0.28 g (2 mmol) of **2l**, 0.21 g (2 mmol) of cyclohex-1-enyl isocyanide,[19] and 0.18 g (1.7 mmol) of isobutyric acid. The *enamide* **3j** (0.28 g, 42%) was obtained as a colourless solid, mp 110–113 °C; R_f 0.47 (dichloromethane–methanol, 99 : 1) [Found: C, 71.93; H, 10.26; N, 8.51. $C_{20}H_{34}N_2O_2$ (334.5) requires C, 71.81; H, 10.25; N, 8.37%]; δ_H ($CDCl_3$) 1.09 [3H, s, $C(CH_3)_2$], 1.18 [6H, d, $CH(CH_3)_2$, ^3J 7.2], 1.24 [3H, s, $C(CH_3)_2$], 1.3–2.5 (12H, m, CH_2), 1.46 [3H, s, $C(CH_3)_2$], 1.53 [3H, s, $C(CH_3)_2$], 3.09 [1H, m, $CH(CH_3)_2$, ^3J 7.2], 4.68 (1H, s, NCH), 6.03 (1H, m, C=CH), 7.75 (1H, br, NH); δ_C ($CDCl_3$) 20.01, 20.46, 21.98, 22.48, 23.93, 27.79, 28.04, 28.88, 30.14, 31.37, 32.34, 32.46, 33.51, 38.08, 54.85, 63.45, 112.71, 132.62, 170.24, 181.77; *m/z* (CI-NH_3) 335 (100%) [MH^+ − cyclohexylideneamine].

rac-1-Isobutyryl-3,3-dimethyl-6,6-diphenylpiperidine-2-carboxylic acid cyclohex-1-enylamide ***3k***.—According to **GP3** the title compound was obtained from 0.45 g (1.7 mmol) of **2l**, 0.18 g (1.7 mmol) of cyclohex-1-enyl isocyanide,[19] and 0.15 g (1.7 mmol) of isobutyric acid. The *enamide* **3k** (0.66 g, 85%) was obtained as a colourless solid, mp 52 °C; R_f 0.41 (dichloromethane–methanol, 99 : 1) [Found: C, 78.91; H, 8.37; N, 6.24. $C_{30}H_{38}N_2O_2$ (458.7) requires C, 78.56; H, 8.35; N, 6.11%]; δ_H ($CDCl_3$) 0.91 [3H, s, $C(CH_3)_2$], 1.04 [3H, s, $C(CH_3)_2$], 1.12 [3H, d, $CH(CH_3)_2$, ^3J 7.2], 1.23 [3H, d, $CH(CH_3)_2$, ^3J 7.2], 1.3–2.7 (12H, m, CH_2), 3.09 [1H, m, $CH(CH_3)_2$, ^3J 7.2], 3.92 (1H, s, NCH), 5.68 (1H, m, C=CH), 7.1–7.6 (11H, m, ArH + NH); δ_C ($CDCl_3$) 19.99, 20.81, 21.38, 21.63, 23.00, 25.37, 29.00, 29.61, 31.47, 32.92, 36.00, 38.00, 60.97, 63.12, 125.52, 126.60, 126.72, 127.44, 128.69, 128.89, 129.05, 136.96, 144.48, 150.02, 176.78, 181.97; *m/z* (CI-NH_3) 459 (100%) [MH^+ − cyclohexylideneamine].

rac-3,3-Dimethylpiperidine-2-carboxylic acid ***4a***.—Following **GP5** the title compound was prepared from 0.28 g (0.90 mmol) of **3e**. The *amino acid* **4a** (0.11 g, 78%) was obtained as a colourless solid after crystallization from acetone, mp >260 °C [Found: C, 61.02; H, 9.67; N, 8.95. $C_8H_{15}NO_2$ (157.2) requires C, 61.12; H, 9.62; N, 8.91%]; δ_H (D_2O) 0.81 [3H, s, $C(CH_3)_2$], 0.99 [3H, s, $C(CH_3)_2$], 1.3–1.7 (4H, m, CH_2), 2.73 (1H, m, NCH_2), 3.19 (1H, s, NCH_2), 3.21 (1H, s, NCH); δ_C (D_2O) 18.34, 19.52, 28.73, 31.64, 36.98, 43.52, 67.28, 173.12; *m/z* (CI-isobutane) 158 (100%) [MH^+].

rac-3,3-Diethylpiperidine-2-carboxylic acid ***4b***.—Standard hydrolysis, following **GP5**, of 0.88 g (2.64 mmol) of **3h** gave the title compound. The *amino acid* **4b** (0.37 g, 76%) was obtained as a colourless solid after crystallization from acetone, mp >260 °C [Found: C, 65.19; H, 10.26; N, 7.58. $C_{10}H_{19}NO_2$ (185.3) requires C, 64.83; H, 10.34; N, 7.56%]; δ_H (D_2O) 0.76 (3H, t, CH_2CH_3, ^3J 7.2), 0.88 (3H, t, CH_2CH_3, ^3J 7.2), 1.1–1.7 (8H, m, CH_2), 2.80 (1H, m, NCH_2), 3.24 (1H, s, NCH_2), 3.43 (1H, s, NCH); δ_C (D_2O) 8.31, 8.68, 19.05, 25.35, 29.74, 29.83, 38.27, 44.62, 65.80, 173.73; *m/z* (CI-isobutane) 186 (100%) [MH^+].

rac-2-Azaspiro[5.5]undecane-1-carboxylic acid ***4c***.—The title compound was prepared according to **GP5** using 1.02 g (2.93 mmol) of **3i** as starting material. The *amino acid* **4c** (0.39 g, 67%) was obtained as a colourless solid after crystallization from acetone, mp >260 °C [Found: C, 66.81; H, 9.70; N, 7.10. $C_{11}H_{19}NO_2$ (197.3) requires C, 66.97; H, 9.71; N, 7.10%]; δ_H (D_2O) 1.1–1.9 (13H, m, CH_2), 2.34 (1H, m), 2.85 (1H, m, NCH_2), 3.22 (1H, s, NCH), 3.28 (1H, m, NCH_2); δ_C (D_2O) 18.68, 21.58, 26.99, 27.75, 29.86, 35.89, 36.61, 44.67, 69.75, 172.69; *m/z* (CI-isobutane) 198 (100%) [MH^+].

(2RS,3SR,6RS)-3-Methyl-3,6-diphenylpiperidine-2-carboxylic acid ***4d***.—According to **GP5** the title compound was obtained from 0.36 g (0.86 mmol) of **3g**. The racemic *amino acid* **4d** (0.18 g, 70%) was obtained as a colourless solid after crystallization from acetone, mp 193–194 °C [Found: C, 77.09; H, 7.12; N, 4.81. $C_{19}H_{21}NO_2$ (295.4) requires C, 77.26; H, 7.17; N, 4.74%]; δ_H ([D_3]MeOD) 1.43 (3H, s, CCH_3), 2.1–2.5 (4H, m, $NCHPhCH_2CH_2$), 4.46 (1H, s, $NCHCOOH$), 5.54 (1H, s, $NCHPh$), 7.3–7.6 (10H, m, ArH); δ_C ([D_3]MeOD) 26.79, 30.96, 31.51, 39.70, 56.24, 65.94, 127.62, 127.86, 128.75, 130.10, 130.19, 138.00, 145.68, 172.64; *m/z* (CI-isobutane) 296 (100%) [MH^+].

rac-1-Isobutyryl-3,3-dimethylpiperidine-2-carboxylic acid ***4e***.—The title compound was prepared according to **GP4** starting from 0.56 g (1.83 mmol) of **3e**. The *carboxylic acid* **4e** (0.39 g, 94%) was obtained as a colourless solid after crystallization from dichloromethane (two rotamers in a 79 : 21 ratio were observed in the ^{1}H-NMR spectrum in $CDCl_3$ at room temperature), mp 122–123 °C; R_f 0.38 (dichloromethane–methanol, 98 : 2) [Found: C, 62.92; H, 9.26; N, 6.38. $C_{12}H_{21}NO_3$ (227.3) requires C, 63.41; H, 9.31; N, 6.16%]; δ_H ($CDCl_3$) 1.00 [2.4H, s, $C(CH_3)_2$], 1.10 [2.4H, d, $CH(CH_3)_2$, ^3J 6.6], 1.12 [2.4H, s, $C(CH_3)_2$], 1.60 [2.4H, d, $CH(CH_3)_2$, ^3J 6.6], 1.1–1.9 (6.4H, m), 2.88 [0.79H, m, $CH(CH_3)_2$, ^3J 6.6], 2.90 [0.21H, m, $CH(CH_3)_2$, ^3J 6.6], 3.12 (0.21H, m, NCH_2), 3.61 (0.79H, dt, NCH_2, ^2J 12.5, ^3J 4.4), 3.81 (0.79H, d, NCH_2, ^2J 12.5), 4.20 (0.21H, s, NCH), 4.61 (0.21H, m, NCH_2), 4.98 (0.79H, s, NCH), 8.81 (1H, br, COOH); δ_C ($CDCl_3$) 18.51 (ma), 19.21 (mi), 19.38 (ma), 19.75 (mi), 20.21 (mi), 21.15 (ma), 25.78 (ma), 26.05 (mi), 27.56 (mi), 27.76 (ma), 29.84 (mi), 30.56 (ma), 32.12 (ma), 32.26 (mi), 32.35 (mi), 32.75 (ma), 37.76 (mi), 41.76 (ma), 59.85 (ma), 64.35 (mi), 172.76 (mi), 174.41 (ma), 177.90 (ma), 178.01 (mi); *m/z* (CI-isobutane) 328 (100%) [MH^+].

(2RS,6RS)-1-Acetyl-3,3-dimethyl-6-phenylpiperidine-2-carboxylic acid ***4f***.—The title compound was prepared according to **GP4** starting from 3.50 g (9.87 mmol) of **3f**. The *carboxylic acid* **4f** (2.37 g, 87%) was obtained as a colourless solid after crystallization from dichloromethane, mp 125 °C [Found: C, 69.91; H, 7.71; N, 5.04. $C_{16}H_{21}NO_3$ (275.2) requires

C, 69.79; H, 7.69; N, 5.09%]; δ_H ($CDCl_3$) 1.11 [3H, s, $C(CH_3)_2$], 1.14 [3H, s, $C(CH_3)_2$], 1.3–1.5 (2H, m, CH_2), 1.98 (3H, s, Ac), 2.0–2.3 (2H, m, CH_2), 3.83 (1H, s, 2-H), 5.06 (1H, m, 6-H), 7.2–7.4 (5H, m, ArH), 10.10 (1H, br, COOH); δ_C ($CDCl_3$) 22.52, 26.97, 28.43, 32.38, 33.15, 34.19, 57.98, 63.26, 125.86, 127.15, 129.00, 141.39, 173.43, 173.73; *m/z* (CI-isobutane) 276 (100%) [MH^+].

rac-1-(2,4-Dimethoxybenzoyl)-3,3-dimethylpiperidine-2-carboxylic acid ***4g***.—The title compound was prepared according to **GP4** starting from 0.83 g (1.74 mmol) of **3d**. The *carboxylic acid* **4g** (0.58 g, 100%) was obtained as a colourless oil. Due to hindered rotation around the amidic N–C-bond two rotamers in a 65:35 ratio were observed in the ^{1}H-NMR spectrum. R_f 0.24 (dichloromethane–methanol, 95:5) [Found: C, 63.19; H, 7.38; N, 4.41. $C_{17}H_{23}NO_5$ (321.4) requires C, 63.54; H, 7.21; N, 4.36%]; δ_H ($CDCl_3$) 0.87 (ma), 0.90 (mi) [3H, s, $C(CH_3)_2$], 1.12 (ma), 1.16 (mi) [3H, s, $C(CH_3)_2$], 1.2–1.8 (4H, m, $NCH_2CH_2CH_2$), 3.49 (1H, m, NCH_2), 3.7–3.8 (6H, 4s, OMe), 4.69 (1H, m, NCH_2), 4.99 (ma), 5.10 (mi) (1H, s, NCH), 6.3–6.5 (2H, m, ArH), 7.1–7.2 (1H, m, ArH); δ_C ($CDCl_3$) 20.17 (mi), 20.95 (ma), 25.24 (mi), 25.76 (ma), 27.76 (ma), 32.27 (mi), 32.53 (mi), 32.85 (ma), 33.18 (ma), 37.82 (mi), 44.21 (ma + mi), 54.46 (mi), 55.06 (mi), 55.25 (ma), 55.31 (ma), 60.52 (mi), 65.48 (ma), 97.63 (mi), 98.06 (ma), 104.76 (ma), 104.89 (mi), 117.35 (mi), 117.87 (ma), 129.20 (ma), 129.80 (mi), 156.19 (mi), 156.29 (ma), 161.77 (ma + mi), 169.79 (ma), 170.06 (mi), 173.99 (ma), 174.20 (mi); *m/z* (CI-isobutane) 322 (100%) [MH^+].

rac-1-Benzoyl-3,3-dimethylpiperidine-2-carboxylic acid ***4h***.—According to **GP4**, hydrolysis of 13.00 g (33 mmol) of **3a** gave the title compound. The *carboxylic acid* **4h** (5.60 g, 65%) was obtained as a colourless solid, mp 47–49 °C. Due to hindered rotation around the amidic NC-bond two rotamers in a 68:32 ratio were observed in the ^{1}H-NMR spectrum. R_f 0.60 (dichloromethane–methanol, 9:1) [Found: C, 68.82; H, 7.46; N, 5.72. $C_{15}H_{19}NO_3$ (261.3) requires C, 68.94; H, 7.33; N, 5.36%]; δ_H ($CDCl_3$) 0.92 (ma), 0.94 (mi) [3H, s, $C(CH_3)_2$], 1.14 (mi), 1.16 (ma) [3H, s, $C(CH_3)_2$], 1.2–2.0 (4H, m, $NCH_2CH_2CH_2$), 3.36 (mi), 3.58 (ma), 3.80 (mi) (2H, m, NCH_2), 4.66 (mi), 5.04 (ma) (1H, s, NCH), 7.41 (5H, m, ArH), 10.17 (1H, br, COOH); δ_C ($CDCl_3$) 20.20 (mi), 21.05 (ma), 25.65 (mi), 26.16 (ma), 27.49 (mi), 27.87 (ma), 32.56 (mi), 33.06 (ma), 38.33 (ma), 39.65 (mi), 44.57 (ma + mi), 60.57 (ma), 66.39 (mi), 126.60 (mi), 126.86 (ma), 128.40 (ma + mi), 129.83 (mi), 130.02 (ma), 133.53 (ma), 135.53 (mi), 171.25 (mi), 172.72 (ma), 174.50 (ma + mi); *m/z* (CI-isobutane) 262 (100%) [MH^+].

(+)-1-Benzoyl-3,3-dimethylpiperidine-2-carboxylic acid (+)- ***4h***.—5.50 g (21 mmol) of *N*-acylated α-amino acid (±)-**4h** were dissolved in diethyl ether and heated to reflux. 1.59 g (10.5 mmol) of (−)-norephedrine were added to the hot solution and the mixture was heated to reflux for 15 min. Colourless crystals separated from the solution upon slow cooling to room temperature. The solid was filtered off, and crystallized from diethyl ether–dichloromethane to yield the (−)-norephedrinium salt of (+)-**4h** (3.90 g, 89%) as a colourless solid, mp 158–159 °C [Found: C, 69.59; H, 7.57; N, 6.92. $C_{24}H_{32}N_2O_4$ (412.6) requires C, 69.87; H, 7.82; N, 6.79%]; δ_H ([D_6]DMSO–$CDCl_3$, two rotamers in a 68:32 ratio) 0.84, 0.91 [3H, 2s, $C(CH_3)_2$], 0.96 (3H, d, CH_3CH, ^3J 6.7), 1.03, 1.09 [3H, 2s, $C(CH_3)_2$], 1.0–2.0 (4H, m, CH_2), 3.2–3.9 (3H, m), 4.48 (mi) (1H, m, NCH_2), 4.69 (mi), 5.06 (1H, s, NCHCOO), 7.1–7.4 (10H, m, ArH); δ_C ([D_6]DMSO–$CDCl_3$, mixture of rotamers) 10.74, 19.41, 20.24, 24.87, 25.24, 27.16, 27.39, 30.86, 31.61, 31.96, 33.12, 36.66, 42.78, 51.22, 61.99, 67.95, 70.49, 124.66, 125.20, 125.43, 125.74, 126.73, 126.98, 127.47, 127.77, 136.06, 140.11, 169.70, 169.95, 173.91.

The (−)-norephedrinium salt of (+)-**4h** was dissolved in 50 ml of water and treated with 1 ml of conc. HCl. The mixture was extracted with 30 ml of dichloromethane three times. After drying of the combined organics over $MgSO_4$ the solvent was removed *in vacuo* to give the enantiomerically pure *N*-acylated α-amino acid (+)-**4h** (2.01 g, 73%) as a colourless solid. $[\alpha]_D$ +44.2 (*c* 1, $CHCl_3$).

(−)-1-Benzoyl-3,3-dimethylpiperidine-2-carboxylic acid (−)- ***4h***.—The filtrate of the (−)-norephedrinium-(+)-**4h** salt formation described above was heated to reflux and an additional 1.59 g (10.5 mmol) of (−)-norephedrine were added to the hot solution. The mixture was heated for 15 min at reflux. Colourless crystals separated from the solution upon slow cooling to room temperature. The solid was filtered off and further purified by recrystallization from dichloromethane to yield the (−)-norephedrinium salt of (−)-**4h** (3.65 g, 84%) as a colourless solid, mp 146–147 °C (Found: C, 70.24; H, 7.90; N, 6.86%); δ_H ([D_6]DMSO, two rotamers in a 64:36 ratio) 0.80 [3H, s, $C(CH_3)_2$], 0.86 (3H, d, CH_3CH, ^3J 6.7), 1.00, 1.07 [3H, 2s, $C(CH_3)_2$], 1.0–2.0 (4H, m, CH_2), 3.2–3.6 (3H, m), 3.94 (mi), 4.38 (mi) (1H, m, NCH_2), 4.61 (mi), 4.96 (1H, s, NCHCOO), 7.1–7.5 (10H, m, ArH); δ_C ([D_6]DMSO, mixture of rotamers) 12.09, 20.58, 21.31, 26.16, 26.42, 28.45, 28.85, 32.03, 32.65, 33.03, 33.22, 37.48, 43.54, 51.75, 62.79, 69.11, 71.60, 125.91, 126.31, 126.73, 126.96, 128.02, 128.39, 128.68, 128.89, 137.51, 141.96, 169.83, 170.23, 173.84, 174.20.

The (−)-norephedrinium salt of (−)-**4h** was dissolved in 50 ml of water and treated with 1 ml of conc. HCl. The mixture was extracted with 30 ml of dichloromethane three times. After drying of the combined organics over $MgSO_4$ the solvent was removed *in vacuo* to give the enantiomerically pure *N*-acylated α-amino acid (−)-**4h** (1.72 g, 63%) as a colourless solid, $[\alpha]_D$ −43.8 (*c* 1, $CHCl_3$).

rac-1-Chloroacetyl-3,3-dimethylpiperidine-2-carboxamide ***4i***.—The title compound was prepared according to **GP4** using 0.25 g (0.68 mmol) of **3b** as starting material. The *carboxamide* **4i** (0.17 g, 100%) was isolated from the dichloromethane extracts which resulted from extraction of the alkaline aqueous phase as a colourless solid; R_f 0.30 (dichloromethane–methanol, 95:5) [Found: C, 51.92; H, 7.42; N, 12.09. $C_{10}H_{17}ClN_2O_2$ (232.7) requires C, 51.61; H, 7.36; N, 12.04%]; δ_H ($CDCl_3$) 0.97 [3H, s, $C(CH_3)_2$], 1.10 [3H, s, $C(CH_3)_2$], 1.2–2.4 (4H, m, $NCH_2CH_2CH_2$), 3.68 (2H, m, NCH_2), 4.09 (1H, d, $ClCH_2$, ^2J 15.9), 4.18 (1H, d, $ClCH_2$, ^2J 15.9), 4.64 (1H, s, NCH), 6.03 (1H, s, NH_2), 6.52 (1H, s, NH_2); δ_C ($CDCl_3$) 21.21, 25.98, 27.18, 31.68, 32.12, 41.45, 43.04, 59.94, 167.11, 171.93; *m/z* (CI-isobutane) 234 (100%) [MH^+].

rac-1-Benzoyl-3,3-dimethylpiperidine-2-carboxamide ***4j***.—The title compound was prepared according to **GP4** using 13.00 g (33 mmol) of **3a** as starting material. The *carboxamide* **4f** was isolated from the dichloromethane extracts from the extraction of the alkaline aqueous phase. It was crystallized from diethyl ether to give **4j** (2.7 g, 31%) as a colourless solid, mp 154–155 °C [Found: C, 69.39; H, 7.58; N, 10.81. $C_{15}H_{20}N_2O_2$ (260.3) requires C, 69.20; H, 7.74; N, 10.76%]; δ_H ($CDCl_3$) 1.06, 1.10 [6H, 2s, $C(CH_3)_2$], 1.2–2.2 (4H, m, $NCH_2CH_2CH_2$), 3.53 (2H, m, NCH_2), 4.77 (1H, s, NCH), 6.08 (1H, s, NH_2), 6.87 (1H, s, NH_2), 7.38 (5H, m, ArH); δ_C ($CDCl_3$) 21.40, 26.22, 27.20, 32.15, 44.43, 59.86, 126.72, 128.36, 129.72, 135.75, 171.85, 174.50; *m/z* (CI-isobutane) 261 (100%) [MH^+].

rac-3,3-Dimethyl-1-(2-nitrobenzoyl)piperidine-2-carboxamide ***4k***.—The title compound was prepared from 0.69 g (1.49 mmol) of **3c** according to **GP4**. The *carboxamide* **4k** (0.28 g, 61%) was isolated from the dichloromethane extracts from the extraction of the alkaline aqueous phase as a colourless solid, mp 163–164 °C. Due to hindered rotation around the amidic NC-bond two rotamers in a 58:42 ratio were observed in the ^{1}H-NMR spectrum [Found: C, 59.28; H, 6.34; N, 13.80. $C_{15}H_{19}N_3O_4$ (305.3) requires C, 59.01; H, 6.27; N, 13.76%]; δ_H ($CDCl_3$) 1.09 [3H, s, $C(CH_3)_2$], 1.21 (ma), 1.26 (mi) [3H, s, $C(CH_3)_2$], 1.2–2.4 (4H, m, $NCH_2CH_2CH_2$), 3.16 (1H, m, NCH_2), 3.41 (mi), 3.69 (ma) (1H, m, NCH_2), 4.74 (ma), 4.99 (mi) (1H, s, NCH), 5.85 (mi), 5.97 (ma) (1H, s, NH_2), 6.44 (mi), 6.82 (ma) (1H, s, NH_2), 7.3–8.2 (4H, m, ArH); δ_C ($CDCl_3$) 20.91 (ma), 21.26 (mi), 26.05 (mi), 26.31 (ma), 26.92 (ma), 27.57 (mi),

32.00 (mi), 32.09 (ma + mi), 32.30 (ma), 43.54 (ma), 44.69 (mi), 59.45 (ma + mi), 124.63 (mi), 124.74 (ma), 127.37 (mi), 128.01 (ma), 129.68 (mi), 129.92 (ma), 132.73 (ma), 132.97 (mi), 134.32 (mi), 134.54 (ma), 144.81 (ma + mi), 167.42 (mi), 168.12 (ma), 170.52 (ma), 172.14 (mi); *m*/*z* (CI-isobutane) 306 (100%) [MH^+].

2-Isobutyryl-3-methyl-2-azaspiro[5,5]undecane-1-carboxylic acid methyl ester ***5a***.—The title compound was prepared according to **GP6** using 0.33 g (2 mmol) of **2h**, 0.37 g (2 mmol) of 4-phenylcyclohex-1-enyl isocyanide,[19] and 0.18 g (2 mmol) of isobutyric acid as starting materials. The *methyl ester* **5a** (0.35 g, 60%) was obtained as a 78:22 (*trans*:*cis*) mixture of two racemic diastereomers as a colourless oil. R_f 0.80 (dichloromethane–methanol, 98:2) [Found: C, 68.91; H, 10.01; N, 4.82. $C_{17}H_{29}NO_3$ (295.3) requires C, 69.12; H, 9.89; N, 4.74%]; δ_H ($CDCl_3$) 1.11 [3H, d, $CH(CH_3)_2$, ^3J 6.6], 1.17 [3H, d, $CH(CH_3)_2$, ^3J 6.6], 1.31 [3H, d, $CHCH_3$, ^3J 7.2], 1.3–2.0 (14H, m, CH_2), 2.84 (ma), 3.00 (mi) [1H, m, $CH(CH_3)_2$, ^3J 6.6], 3.64 (ma), 3.66 (mi) (3H, s, OCH_3), 4.18 (ma), 4.77 (mi) (1H, m, CH_3CHN), 5.21 (ma), 5.35 (mi) (1H, s, NCH); δ_C ($CDCl_3$, two diastereomers) 19.23, 19.56, 20.44, 21.14, 21.33, 23.59, 24.04, 24.49, 24.91, 26.07, 27.44, 29.87, 30.60, 33.31, 33.59, 34.48, 35.45, 44.17, 47.34, 51.12, 51.38, 57.08, 62.08, 170.60, 172.41, 177.86, 178.31; *m*/*z* (CI-isobutane) 296 (100%) [MH^+].

(1RS,3RS)-2-Isobutyryl-3-isopropyl-2-azaspiro[5,5]undecane-1-carboxylic acid methyl ester ***5b***.—According to **GP6** the title compound was obtained from 0.39 g (2 mmol) of **2j**, 0.33 g (2 mmol) of 4-*tert*-butylcyclohex-1-enyl isocyanide,[19] and 0.18 g (2 mmol) of isobutyric acid. The *methyl ester* **5b** (0.43 g, 67%) was obtained as a colourless oil, R_f 0.82 (dichloromethane–methanol, 98:2) [Found: C, 70.82; H, 10.19; N, 4.35. $C_{19}H_{33}NO_3$ (323.5) requires C, 70.55; H, 10.28; N, 4.33%]; δ_H ($CDCl_3$) 0.99 [3H, d, $CHCH(CH_3)_2$, ^3J 6.6], 1.02 [3H, d, $CHCH(CH_3)_2$, ^3J 6.6], 1.09 [3H, d, $O{=}CCH(CH_3)_2$, ^3J 6.6], 1.13 [3H, d, $O{=}CCH(CH_3)_2$, ^3J 6.6], 1.2–1.9 (15H, m, $NCHCH + 7 \times CH_2$), 2.82 [1H, m, $O{=}CCH(CH_3)_2$, ^3J 6.6], 3.52 (1H, m, $NCHCH$), 3.65 (3H, s, OCH_3), 5.38 (1H, s, CHN); δ_C ($CDCl_3$) 18.89, 19.12, 19.28, 19.37, 21.26, 23.18, 25.85, 26.76, 27.09, 28.08, 28.36, 30.27, 33.12, 37.65, 50.91, 60.34, 60.74, 169.00, 176.30; *m*/*z* (CI-isobutane) 324 (100%) [MH^+].

(1RS,3RS)-2-Isobutyryl-3-phenyl-2-azaspiro[5,5]undecane-1-carboxylic acid methyl ester ***5c***. The title compound was prepared according to **GP6** using 0.45 g (2 mmol) of **2k**, 0.37 g (2 mmol) of 4-phenylcyclohex-1-enyl isocyanide,[19] and 0.18 g (2 mmol) of isobutyric acid as starting materials. The *methyl ester* **5c** (0.31 g, 44%) was obtained as a colourless oil, R_f 0.66 (dichloromethane–methanol, 98:2) [Found: C, 74.02; H, 8.69; N, 3.90. $C_{22}H_{31}NO_3$ (357.5) requires C, 73.92; H, 8.74; N, 3.92%]; δ_H ($CDCl_3$) 0.86 [3H, d, $O{=}CCH(CH_3)_2$, ^3J 6.6], 1.05 [3H, d, $O{=}CCH(CH_3)_2$, ^3J 6.6], 1.2–2.4 (14H, m, $7 \times CH_2$), 2.56 [1H, m, $O{=}CCH(CH_3)_2$, ^3J 6.6], 3.66 (3H, s, OCH_3), 4.18 (1H, s, CHN), 5.05 [1H, dd, $NCHPh$, ^3J 6.1 and 6.6], 7.1–7.4 (5H, m, ArH); δ_C ($CDCl_3$) 18.71, 19.84, 21.34, 21.48, 25.81, 26.74, 27.56, 31.39, 32.41, 35.41, 36.05, 51.34, 57.05, 63.74, 125.36, 126.71, 128.42, 143.84, 171.48, 179.03; *m*/*z* (CI-isobutane) 358 (100%) [MH^+].

(1RS,3SR)-3-Ethyl-2-isobutyryl-2-azaspiro[5.5]undecane-1-thiocarboxylic acid S-ethyl ester ***5d***. Starting from 0.36 g (2 mmol) of **2i**, 0.33 g (2 mmol) of 4-*tert*-butylcyclohex-1-enyl isocyanide,[19] and 0.18 g (2 mmol) of isobutyric acid the title compound was prepared according to **GP6**. The *S-ethyl ester* **5d** (0.20 g, 29%) was obtained as an orange oil, R_f 0.25 (*n*-hexane–MeOBu^t, 9:1) [Found: C, 67.44; H, 9.83; N, 4.19. $C_{19}H_{33}NO_2S$ (339.5) requires C, 67.21; H, 9.80; N, 4.13%]; δ_H ($CDCl_3$) 0.84 (3H, t, ^3J 7.7, CH_3CH_2C), 1.14 [3H, d, ^3J 6.6, $CH(CH_3)_2$], 1.18 [3H, d, ^3J 6.6, $CH(CH_3)_2$], 1.21 (3H, t, ^3J 7.7, CH_3CH_2S), 1.33–2.47 (16H, m), 2.82 [3H, m, ^3J 6.6, ^3J 7.7, $CH(CH_3)_2$, CH_3CH_2S], 3.84 (1H, dd, ^3J 6.6, ^2J 13.2, $NCHCH_2$), 5.50 (1H, s, NCH); δ_C ($CDCl_3$) 11.59, 14.24, 19.23, 20.35, 21.35, 22.60, 23.25, 25.36, 26.20, 27.56, 30.87, 33.04, 35.21, 41.25, 46.37, 54.16, 61.57, 177.52, 198.88; *m*/*z* (CI-isobutane) 358 (100) [MH^+].

1-Isobutyryl-3-methyl-3-propylpiperidine-2-thiocarboxylic acid S-ethyl ester ***5e***.—The title compound was prepared according to **GP6** starting from 0.28 g (2 mmol) of **2d**, 0.33 g (2 mmol) of 4-*tert*-butylcyclohex-1-enyl isocyanide,[19] and 0.18 g (2 mmol) of isobutyric acid. The *S-ethyl ester* **5e** (0.32 g, 54%) was obtained as a 50:50 (*trans*:*cis*) mixture of two racemic diastereomers as a colourless oil. The diastereomers were separated by column chromatography (*n*-hexane–ethyl acetate 9:1).

First fraction: 0.16 g (27%) yield; R_f 0.33 (*n*-hexane–ethyl acetate 9:1) [Found: C, 64.52; H, 9.81; N, 4.70. $C_{16}H_{29}NO_2S$ (299.5) requires C, 64.17; H, 9.76; N, 4.68%]; δ_H (C–N rotamers in a 87:13 ratio, $CDCl_3$) 0.92 (3H, m, $CH_3CH_2CH_2$), 1.00 (3H, s, CH_3C), 1.11 [3H, d, ^3J 6.6, $CH(CH_3)_2$], 1.16 [3H, d, ^3J 6.6, $CH(CH_3)_2$], 1.23 (3H, t, ^3J 7.4, CH_3CH_2S), 1.39–1.73 (6H, m, CH_2), 1.90 (1H, dt, ^3J 4.9, ^2J 12.9, 4-H), 2.38 (1H, m, ^2J 13.2, 4-H), 2.91 [3H, m, ^3J 6.6, ^3J 7.4, CH_3CH_2S, $CH(CH_3)_2$], 3.42 (1H, dt, ^3J 4.4, ^2J 12.9, NCH_2), 3.80 (ma), 4.63 (mi) (1H, d, ^2J 13.2, NCH_2), 4.22 (mi), 5.14 (ma) (1H, s, NCH); δ_C ($CDCl_3$, two rotamers) 14.27, 14.69, 16.29, 18.75, 19.47, 19.76, 20.18, 21.28, 23.25, 23.90, 27.49, 29.91, 30.21, 30.55, 32.34, 39.36, 41.21, 42.01, 46.16, 63.97, 176.20, 197.68; *m*/*z* (CI-isobutane) 335 (100%) [MH^+].

Second fraction: 0.16 g (27%) yield; R_f 0.25 (*n*-hexane–ethyl acetate 9:1) (Found: C, 64.40; H, 9.69; N, 4.74%); δ_H (C–N rotamers in a 89:11 ratio, $CDCl_3$) 0.88 (3H, m, $CH_3CH_2CH_2$), 0.91 (3H, s, CH_3C), 1.12 [3H, d, ^3J 6.6, $CH(CH_3)_2$], 1.17 [3H, d, ^3J 6.6, $CH(CH_3)_2$], 1.23 (3H, t, ^3J 7.7, CH_3CH_2S), 1.31–1.80 (6H, m, CH_2), 1.96 (1H, dt, ^3J 4.9, ^2J 13.2, 4-H), 2.86 [3H, m, ^3J 6.6, ^3J 7.7, CH_3CH_2S, $CH(CH_3)_2$], 3.42 (1H, dt, ^3J 3.9, ^2J 13.2, NCH_2), 3.81 (ma), 4.62 (mi) (1H, d, ^3J 13.2, NCH_2), 4.24 (mi), 5.18 (ma) (1H, s, NCH); δ_C ($CDCl_3$, two rotamers) 14.38, 14.75, 16.34, 18.83, 19.46, 19.70, 20.25, 21.55, 21.98, 22.67, 23.17, 23.65, 27.52, 29.63, 30.52, 31.29, 31.66, 38.41, 41.24, 42.20, 42.45, 63.97, 69.58, 176.04, 197.21; *m*/*z* (CI-isobutane) 301 (100%) [MH^+].

1-Isobutyryl-3-methyl-3-phenyl-piperidine-2-thiocarboxylic acid ***5f***. According to **GP6** the title compound was prepared using 0.35 g (2 mmol) of **2e**, 0.33 g (2 mmol) of 4-*tert*-butylcyclohex-1-enyl isocyanide,[19] and 0.18 g (2 mmol) of isobutyric acid as starting materials. The *S-ethyl ester* **5f** (0.35 g, 53%) was obtained as a 50:50 (*trans*:*cis*) mixture of two racemic diastereomers as a colourless oil. The diastereomers were separated by column chromatography (*n*-hexane–ethyl acetate 9:1).

First fraction: 0.12 g (18%) yield; R_f 0.26 (*n*-hexane–ethyl acetate 9:1) [Found: C, 68.54; H, 8.23; N, 4.02. $C_{19}H_{27}NO_2S$ (333.5) requires C, 68.43; H, 8.16; N, 4.20%]; δ_H ($CDCl_3$) 0.96 [3H, d, ^3J 6.7, $CH(CH_3)_2$], 1.09 [3H, d, ^3J 6.7, $CH(CH_3)_2$], 1.27 (3H, t, ^3J 7.3, CH_3CH_2S), 1.32 (3H, s, CH_3C), 1.56 (1H, dd, ^3J 2.4, ^2J 13.4, 4-H), 2.08–2.26 (2H, m, 2×5-H), 2.35 (1H, dt, ^3J 3.7, ^2J 13.4, 4-H), 2.72 [1H, m, ^3J 6.7, $CH(CH_3)_2$], 2.79–3.02 (2H, m, ^3J 7.3, CH_2S), 3.53 (1H, dt, ^3J 3.7, ^2J 13.0, NCH_2), 3.71 (1H, dd, ^3J 4.3, ^2J 13.0, NCH_2), 5.96 (1H, s, NCH), 7.15–7.35 (5H, m, ArH); δ_C ($CDCl_3$) 14.24, 18.49, 19.26, 21.59, 23.63, 29.73, 30.58, 31.87, 41.17, 42.34, 62.21, 125.60, 126.01, 128.40, 145.58, 175.99, 197.86; *m*/*z* (CI-isobutane) 335 (100%) [MH^+].

Second fraction: 0.17 g (26%) yield; R_f 0.17 (*n*-hexane–ethyl acetate 9:1) (Found: C, 68.31; H, 8.10; N, 4.23%); δ_H (C–N rotamers in a 88:12 ratio, $CDCl_3$) 0.95 (3H, t, ^3J 7.3, CH_3CH_2S), 1.18 [3H, d, ^3J 6.7, $CH(CH_3)_2$], 1.24 [3H, d, ^3J 6.7, $CH(CH_3)_2$], 1.27 (3H, s, CH_3C), 1.79–2.02 (3H, m, CH_2), 2.47–2.73 (3H, m, ^3J 7.3, CH_2S, 4-H), 2.93 [1H, m, ^3J 6.7, $CH(CH_3)_2$], 3.25 (1H, t, NCH_2), 3.90 (ma), 4.72 (mi) (1H, d, ^2J 14.0, NCH_2), 4.88 (mi), 5.90 (ma) (1H, s, NCH), 7.15–7.50 (5H, m, ArH); δ_C ($CDCl_3$, two rotamers) 14.24, 18.81, 19.41, 19.76, 20.18, 21.54, 22.74, 23.26, 26.54, 26.85, 29.21, 29.65, 30.46, 30.78, 39.27, 41.86, 64.54, 70.08, 125.21, 125.44, 126.05, 126.41,

128.40, 145.58, 176.19, 196.37; *m/z* (CI-isobutane) 335 (100%) [MH^+].

rac-3,3-Dimethyl-1-(trifluoroacetyl)piperidine-2-carboxylic acid (2-methylcyclohex-1-enyl)amide ***6***. Reaction of 0.55 g (5 mmol) of **2a**, 0.61 g (5 mmol) of 2-methylcyclohex-1-enyl isocyanide,[20] and 0.70 g (5 mmol) of trifluoroacetic acid according to **GP3** gave the title compound. Dichloromethane was substituted for methanol as a solvent. The *enamide* **6** (0.61 g, 35%) was obtained as a colourless solid after crystallization from diethyl ether, mp 154–156 °C; R_f 0.88 (dichloromethane–MeOH, 99 : 1) [Found: C, 59.06; H, 7.23; N, 8.15. $C_{17}H_{25}F_3N_2O_2$ (346.4) requires C, 58.95; H, 7.27; N, 8.09%]; δ_H ($CDCl_3$) 0.94, 1.08 [6H, 2s, $C(CH_3)_2$], 1.2–2.6 (12H, m, cyclohexenyl-CH_2 + $NCH_2CH_2CH_2$), 3.80 (2H, m, NCH_2), 4.55 (1H, s, CHN), 7.24 (1H, br, NH); δ_C ($CDCl_3$) 18.18, 21.18, 22.40, 22.83, 25.86, 27.08, 28.27, 31.68, 32.55, 45.29, 61.85, 116.50 (q, CF_3, $^1J_{CF}$ 287.7), 126.10, 127.44, 157.31 (q, CF_3C=O, $^2J_{CF}$ 37.1), 166.64; *m/z* (CI-NH_3) 347 (80%) [MH^+], 236 (100) [MH^+ − 2-methylcyclohexylideneamine].

rac-3,3-Dimethylpiperidine-2-carboxylic acid (2-methylcyclohex-1-enyl)amide ***7***. Trifluoroacetamide **6** (0.39 g, 1.10 mmol) was dissolved in 5 ml of MeOH and 5 ml of saturated aq. K_2CO_3. The solution was stirred for 24 h at room temperature and extracted three times with 10 ml of dichloromethane each. After drying of the organics over $MgSO_4$ and evaporation of the solvent *in vacuo* the crude product was crystallized from dichloromethane–diethyl ether to give the *N-deprotected amino acid* **7** (0.26 g, 94%) as a colourless solid [Found: C, 71.72; H, 10.51; N, 11.23. $C_{15}H_{26}N_2O$ (250.4) requires C, 71.96; H, 10.47; N, 11.19%]; δ_H ($CDCl_3$) 0.93, 1.06 [6H, 2s, $C(CH_3)_2$], 1.2–2.6 (13H, m, CH_2 + NH), 1.59 (3H, s, CH_3), 3.67 (2H, m, NCH_2), 4.26 (1H, s, CHN), 7.01 (1H, br, NH); δ_C ($CDCl_3$) 18.22, 21.22, 22.44, 22.87, 25.98, 27.09, 28.34, 30.70, 31.67, 32.55, 42.55, 61.92, 126.81, 127.25, 166.39; *m/z* (CI-NH_3) 251 (70%) [MH^+], 140 (100) [MH^+ − 2-methylcyclohexylideneamine].

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