Synthesis of novel pipecolic acid derivatives. Part 2.[1] Addition of trimethylsilyl cyanide to 3,4,5,6-tetrahydropyridines

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The synthesis of alkyl- and aryl-substituted derivatives of pipecolic acid (piperidine-2-carboxylic acid) by a modified Strecker protocol is described. Addition of trimethylsilyl cyanide (TMSCN) to various tetrahydropyridines **1** and subsequent hydrolysis of the obtained α-amino nitriles **2** yielded pipecolic acid derivatives **3**. Addition of TMSCN to cyclic imines **1** proceeded rapidly and led to α-amino nitriles in excellent yields without any necessary further purification. Almost quantitative diastereoselectivity for the formation of 2,6-*trans*-substituted amino nitrile **2g** was observed at low temperature, when chiral imine **1g** was used as reactant. Acidic hydrolysis of α-amino nitriles **2** yielded the corresponding amino acids **3** in good to excellent yields. Furthermore, an efficient protocol for the optical resolution of *N*-formylated derivatives of pipecolic acid by separation of diastereomeric norephedrinium salts is described.

Application of unnatural, conformationally constrained amino acids to peptide synthesis is an important tool to develop peptide-derived pharmaceutical agents[2,3] and is of particular interest in studying peptide conformations.[4] In particular, cyclic amino acids such as proline and its higher homologue pipecolic acid are often used in this context.[5] Incorporation of pipecolic acid, also called homoproline, instead of proline into peptides is reported to induce significant changes in bioactivity and leads to interesting model compounds for studies on peptide conformations,[6] where derivatives of pipecolic acid also find a role as β-turn mimics.[7] The non-proteinogenic pipecolic acid is furthermore an important precursor to numerous bioactive compounds such as synthetic peptides,[8] local anesthetics,[9] or potential enzyme inhibitors[10] and is a component of biologically important natural products such as the immunomodulators rapamycin and demethoxyrapamycin,[11] the immunosuppressant FK506,[12] and the antitumor antibiotic sandramycin.[13] Recently, substituted derivatives of pipecolic acid attracted considerable attention as precursors for natural product synthesis[14] and rigid analogues of prolyl amide bonds in peptides.[15] As part of our studies directed towards the development of *cis*- and *trans*-proline analogues[16] we became interested in synthetic protocols applicable to large-scale preparation of multisubstituted pipecolic acids. Among known methods for the preparation of pipecolic acids are enantio- and diastereoselective[17] as well as racemic approaches[18] with subsequent resolution of racemic products by enzymatic[19] methods or by diastereomeric salt formation.[20] Most of these methods are multistep protocols that suffer from low overall yields or complex work-up procedures, involve cyclisation steps with expensive reactants, or restrict the substitution pattern of the six-membered ring rigorously. Herein, we would like to report an efficient two-step approach to pipecolic acid derivatives from 3,4,5,6-tetrahydropyridines *via* addition of trimethylsilyl cyanide and subsequent acidic hydrolysis of the obtained α-amino nitriles. Subsequent optical resolution of *N*-formylated cyclic amino acids by separation of their diastereomeric norephedrinium salts allows the preparation of enantiomeric pure pipecolic acids.

Results and discussion

Recently, we reported an efficient approach to alkyl- and aryl-substituted tetrahydropyridines **1a**–**i**.[1,21] These imines can be prepared easily and on a large scale according to a modified protocol of Zondler and Pfleiderer[22] and can be stored under nitrogen at −18 °C without any decomposition for several months. These reactive cyclic imines have already been demonstrated to be versatile precursors for the preparation of *N*-protected pipecolic acid derivatives and small peptides in high yields by using a multicomponent approach.[1,16] However, development of a simple synthesis applicable to large-scale preparation of pipecolic acids would be desirable.

One of the most efficient methods of synthesis of α-amino acids starting from imines is the modified Strecker reaction using hydrocyanic acid or the less toxic form trimethylsilyl cyanide (TMSCN) followed by hydrolysis of the obtained α-amino nitriles. Böhme *et al.*[23] reported on a method to generate racemic pipecolic acid by addition of hydrocyanic acid to the trimeric α-tripiperideine (dodecahydro-1*H*,6*H*,11*H*-tripyrido[1,2-*a*:1′,2′-*c*:1″,2″-*e*][1,3,5]triazine) and subsequent heating of the obtained α-amino nitrile with barium hydroxide. In order to extend this approach to substituted pipecolic acid derivatives we investigated the addition of TMSCN to 3,4,5,6-tetrahydropyridines **1**. Typical protocols[24] for the addition of TMSCN to cyclic imines require addition of a Lewis base in order to activate the C=N double bond. In our hands tetrahydropyridines **1** readily reacted under TMSCN-addition without previous activation to give the desired α-amino nitriles **2** in high yields as shown in Table 1. Usually monitoring by TLC indicated complete consumption of the starting material in the strongly exothermic reaction within 10 minutes when TMSCN was added to a solution of 3,4,5,6-tetrahydropyridines **1** in dichloromethane. Analytically pure α-amino nitriles **2** were isolated by adding water to the reaction mixture and subsequent extraction with dichloromethane (Table 1). The α-amino nitriles **2** were obtained as yellow oils (**2a**–**f**,**h**,**i**) or as yellow solids (**2g**).

The addition of TMSCN to a prochiral C=N double bond

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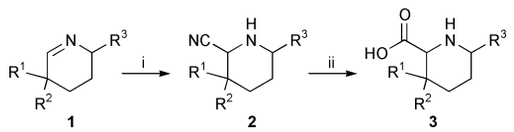
Table 1 Preparation of amino nitriles **2** and pipecolic acids **3** according to **GP1** and **GP2** (see Experimental section)



Imine	α-Amino nitrile	Yield (%)	dr[a]	α-Amino acid	Yield (%)	dr[a]	R^1	R^2	R^3
1a	**2a**	92	—	**3a**[1]	100	—	Me	Me	H
1b	**2b**	97	—	**3b**[1]	92	—	Et	Et	H
1c	**2c**	96	—	**3c**[1]	99	—	$-(CH_2)_5-$		H
1d	**2d**	100	58:42	**3d**	91	58:42	Me	Me	Me
1e	**2e**	100	63:37	**3e**	80	65:35	Me	Me	Et
1f	**2f**	92	85:15[b]	—	—	—	Me	Me	Ph
1g	**2g**	100	76:24	**3g**	61	81:19	$-(CH_2)_5-$		Me
1h	**2h**	93	—[c]	—	—	—	$-(CH_2)_5-$		Ph
1i	**2i**	95	53:47	**3i**	82	53:47	Me	Pr	H

Reagents and conditions: (i), DCM, TMSCN, RT, 10 min; (ii), conc. aq. HCL, reflux, 4 d. [a] Diastereomeric ratio (dr) determined by ^{1}H NMR spectra of the crude products. [b] dr at 0 °C ≥95:5. [c] dr (diastereomeric ratio) not determinable.

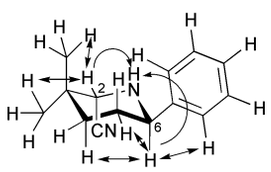


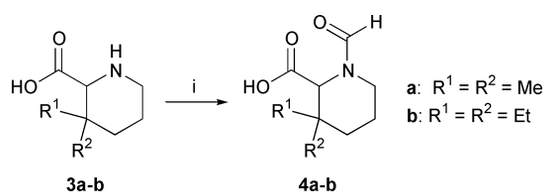
Fig. 1 Strong NOEs of hydrogen at C-2 and C-6 observed in the 2s-NOESY experiments on **2f**.

generates a new stereogenic center at the α-position of amino nitriles **2**. Thus, we tried to control the stereochemistry by using chiral tetrahydropyridines **1d**–**i** but only moderate diastereoselectivities were observed for the formation of α-amino nitriles **2d**–**i** at room temperature, although increasing the size of substituents R^3 attached to C-6 of the cyclic imines from methyl in **1d** to phenyl in **1f** resulted in an increase of the diastereoselectivity from dr 58:42 up to 85:15 (Table 1). However, a significant improvement of the stereoselectivity could be achieved by lowering the reaction temperature to 0 °C. In the case of **2f**, for example, the diastereomeric ratio was improved to ≥95:5 without diminishing the yield. The relative configuration of substituents attached to C-2 and C-6 in diastereomerically pure α-amino nitrile **2f** was found to be *trans* with the nitrile group adopting an axial position,[25] as confirmed by 1D-gradient-selective-NOESY-NMR (Fig. 1).

Acidic hydrolysis of α-amino nitriles

The previously mentioned protocol for the hydrolysis of piperidine-2-carbonitrile using barium hydroxide[23] failed in our hands when we applied it to nitriles **2** and led to decomposition of, *e.g.*, compound **2a**, indicated by a change in colour from a yellow to a dark brown solution. However, acidic hydrolysis of cyclic nitriles **2a**–**e**,**g**,**i** in refluxing conc. aq. HCl gave the desired pipecolic acid derivatives **3a**–**e**,**g**,**i** in good to excellent yields (Table 1). Although the cyclic nitriles proved to be rather stable in acidic media, making prolonged reaction times of 4 days necessary to obtain pipecolic acid derivatives **3** and not only the corresponding primary amides which could be isolated after 24 h reaction time (as indicated by mass spectra of the crude product), it should be noticed that this is the method of choice because of the very simple work-up. After simple evaporation of the solvent and dissolution of the residue in methanol followed by neutralization with alkaline ion exchange resign Lewatit MP 62 analytically pure pipecolic acid derivatives **3a**–**e**,**g**,**i** were isolated as crystalline compounds just by adding acetone or dichloromethane, stirring in the appropriate solvent for 10 min and subsequent filtration.

N-Formylation of amino acids **3a** and **3b** was achieved by using the mixed anhydride method with formic acid and acetic anhydride[26] and gave *N*-formyl protected amino acids **4a**,**b** in moderate yields that can be improved by recycling of unconsumed amino acids (see Experimental details) (Scheme 1).

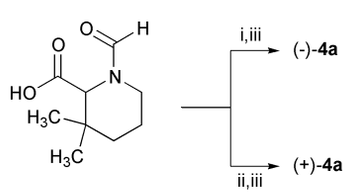


Scheme 1 *Reagents and conditions*: (i), HCOOH, acetic anhydride, 0 °C, 12 h.

Resolution of pipecolic acids

As mentioned before, amino acid derivatives **3** were obtained as racemic compounds. 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. An efficient method for the separation of *N*-benzoyl-protected pipecolic acid derivative **3a** into its optical antipodes *via* diastereomeric norephedrinium salt formation has previously been described by us.[1] In order to extend this methodology we chose racemic *N*-formylated (±)-**4a** as a model compound for resolution. The resolution of (±)-**4a** was achieved by formation of its diastereomeric salts with 0.5 equivalents of (−)-norephedrine or (+)-norephedrine. The norephedrinium salt of (−)-**4a** was prepared from (±)-**4a** with (−)-norephedrine and precipitated from ethyl acetate upon cooling. Acidic treatment after recrystallization of this salt gave the desired enantiomerically pure *N*-formylated amino acid (−)-**4a**. The corresponding enantiomer (+)-**4a** was obtained from the filtrate by repeating the procedure described above with (+)-norephedrine (Scheme 2).

Unfortunately, we were not able to get suitable crystals of the norephedrinium salts for X-ray analysis. Thus we



Scheme 2 *Reagents and conditions*: (i), 0.5 eq. (−)-norephedrine, ethyl acetate; (ii), 0.5 eq. (+)-norephedrine, ethyl acetate; (iii), aq. HCl.

could not determine the absolute configuration of (−)-**4a** and (+)-**4a**.

Conclusions

An efficient and simple synthesis of pipecolic acid derivatives *via* addition of trimethylsilyl cyanide to the C=N double bond of cyclic imines **1a**–**i** and subsequent acidic hydrolysis of the obtained α-amino nitriles **2a**–**i** was developed. The use of chiral imines **1d**–**i** resulted in highly diastereoselective formation of α-amino nitriles **2d**–**i** at low reaction temperatures. Simple work-up procedures allowed large-scale preparation of cyclic amino acids. Furthermore, an efficient resolution of *N*-formylated racemic α-amino acid **4a** into its optical antipodes *via* diastereomeric salt formation using norephedrine was achieved.

Experimental

General remarks

If indicated with 'abs.', dichloromethane was distilled from $CaCl_2$ prior to use. Thin-layer chromatography (TLC) analyses were performed on silica gel Polygram® plates using a fluorescence indicator from Macherey Nagel and Co., Düren. Lewatit MP 62 was a gift from Bayer AG, Leverkusen. Mps were determined in open capillaries in a Dr Lindström instrument and are not corrected. Specific optical rotations $[\alpha]_D$ were determined with a Perkin-Elmer polarimeter (241 MC), at 21 °C, and are given in units of 10^{-1} deg cm² g^{-1}. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 300 or an Avance 300 spectrometer (300.1 MHz/75 MHz). 1D-gradient-selective-NOESY-spectra were recorded on a Bruker Avance 500 spectrometer (500.1 MHz). ^{1}H NMR chemical shifts are reported on the δ-scale (ppm) relative to residual nondeuterated solvent or tetramethylsilane (TMS) as internal standards in $CDCl_3$, D_2O or [D_6]DMSO. ^{13}C NMR chemical shifts are reported on the δ-scale (ppm) relative to deuterated solvent or tetramethylsilane (TMS) in $CDCl_3$ and [D_6]DMSO, or acetone in D_2O as internal standards. Coupling constants, *J*, are given in Hz. Mass spectra were taken on a Finnegan-MAT 212 instrument in CI mode with isobutane as reactant gas. Elemental analyses were performed with a C, H, N-Analyser EA 1108 from Fisons Instruments. Abbreviations: mi: minor isomer; ma: major isomer. Cyclic imines **1a**–**i** were prepared according to literature procedures.[1,16,27] Diastereomeric ratios (dr) were determined by analysis of the ^{1}H NMR spectra of the crude products.

General procedures (GPs)

Preparation of cyclic α-amino nitriles 2a–i (GP1). 5 mmol of cyclic imine **1a**–**i** were dissolved in 20 ml abs. dichloromethane. Upon stirring an equimolar amount of trimethylsilyl cyanide was added *via* a syringe at room temperature. After TLC indicated the absence of starting material (generally after 10 minutes) the reaction mixture was quenched with 10 ml water. Separation of phases and two-fold extraction of the aqueous phase with dichloromethane, drying of combined organic phases and finally evaporation of the solvent under reduced pressure gave the pure product.

Preparation of pipecolic acids 3a–e,g,i (GP2). The α-amino nitrile **2a**–**e**,**g**,**i** was dissolved in 50 ml conc. aq. HCl and heated to reflux for 4 d. The solvent was evaporated under reduced pressure and the residue was dissolved in 30 ml methanol. 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 product. Acetone or dichloromethane was added to the solid and after stirring for 10 minutes pure product was obtained after filtration and drying.[1]

General procedure for *N*-formylation of cyclic amino acids 3a,b (GP3). 10 mmol of cyclic amino acid **3a**,**b** were dissolved in 30 ml of formic acid and cooled to 0 °C with stirring. 15 ml of acetic anhydride were slowly added *via* a dropping funnel maintaining the temperature below 5 °C. The solution was stirred overnight at room temperature. Addition of 30 ml water followed by evaporation of the solvent under reduced pressure gave the crude product as a colourless solid which was suspended in 100 ml ethyl acetate and stirred for an additional 10 minutes. Filtration and evaporation of the filtrate under reduced pressure gave the pure product. In ethyl acetate insoluble solids proved to be the unreacted pure α-amino acids **3**. Repeating the above procedure with these recycled amino acids improved the given yields significantly.

***rac*-3,3-Dimethylpiperidine-2-carbonitrile 2a.** The title compound was prepared according to **GP1** using 1.48 g (13.3 mmol) of 3,3-dimethyl-3,4,5,6-tetrahydropyridine† [16] **1a** and 1.68 ml (13.3 mmol) trimethylsilyl cyanide as starting materials. The product **2a** (1.70 g, 92%) was obtained as a yellow liquid, R_f: 0.27 (*n*-hexane–ethyl acetate, 7:3) [Found: C, 69.63; H, 10.22; N, 20.13. $C_8H_{14}N_2$ (138.22) requires C, 69.52; H, 10.21; N, 20.27%]; δ_H ($CDCl_3$) 1.03 [3H, s, $C(CH_3)_2$], 1.05 [3H, s, $C(CH_3)_2$], 1.27–1.61 [4H, m, CH_2], 1.98 [1H, br s, NH], 2.69–2.97 [2H, m, NHCH_2], 3.46 [1H, s, C*H*CN]; δ_C ($CDCl_3$) 21.43, 25.38, 25.92, 32.49, 35.11, 43.46, 57.42, 118.98; *m*/*z* (CI-isobutane) 139 (100%) [MH^+].

***rac*-3,3-Diethylpiperidine-2-carbonitrile 2b.** The title compound was prepared according to **GP1** using 0.70 g (5 mmol) of 3,3-diethyl-3,4,5,6-tetrahydropyridine† [16] **1b** and 0.63 ml (5 mmol) trimethylsilyl cyanide as starting materials. The product **2b** (0.81 g, 97%) was obtained as an orange liquid, R_f: 0.74 (*n*-hexane–ethyl acetate, 7:3) [Found: C, 72.19; H, 10.80; N, 16.90. $C_{10}H_{18}N_2$ (166.27) requires C, 72.24; H, 10.91; N, 16.85%]; δ_H ($CDCl_3$) 0.81 [6H, m, CH_3], 1.29–1.83 [8H, m, CH_2], 1.89 [1H, br s, NH], 2.93 [2H, m, NHCH_2], 3.70 [1H, s, C*H*CN]; δ_C ($CDCl_3$) 6.56, 7.07, 20.72, 22.50, 28.50, 30.17, 37.13, 42.80, 54.64, 119.09; *m*/*z* (CI-isobutane) 167 (100%) [MH^+].

***rac*-2-Azaspiro[5.5]undecane-1-carbonitrile 2c.** The title compound was prepared according to **GP1** using 0.76 g (5 mmol) of 2-azaspiro[5.5]undec-1-ene [27] **1c** and 0.63 ml (5 mmol) trimethylsilyl cyanide as starting materials. The product **2c** (0.86 g, 96%) was obtained as a green liquid, R_f: 0.68 (*n*-hexane–ethyl acetate, 7:3) [Found: C, 74.22; H, 10.10; N, 15.87. $C_{11}H_{18}N_2$ (178.28) requires C, 74.11; H, 10.18; N, 15.71%]; δ_H ($CDCl_3$) 1.02–1.72 [15H, m, CH_2, NH], 2.81 [2H, m, NHCH_2], 3.69 [1H, s, C*H*CN]; δ_C ($CDCl_3$) 20.55, 20.92, 21.14, 26.16, 31.44, 31.90, 34.73, 36.19, 43.18, 55.50, 119.09; *m*/*z* (CI-isobutane) 179 (100%) [MH^+].

(2*RS*,6*RS*)-3,3,6-Trimethylpiperidine-2-carbonitrile 2d. The title compound was prepared according to **GP1** using 0.63 g (5 mmol) of *rac*-3,3,6-trimethyl-3,4,5,6-tetrahydropyridine† [16] **1d** and 0.63 ml (5 mmol) trimethylsilyl cyanide as starting materials. The product **2d** (0.76 g, 100%) was obtained as a yellow liquid as a 58:42 mixture of racemic diastereomers, R_f: 0.41 (*n*-hexane–ethyl acetate, 7:3) [Found: C, 70.93; H, 10.60; N, 18.32. $C_9H_{16}N_2$ (152.24) requires C, 71.01; H, 10.59; N, 18.40%]; δ_H ($CDCl_3$) 1.09, 1.11, 1.13, 1.15, 1.17, 1.18 [9H, 6s, CH_3], 1.27–1.73 [5H, m, CH_2, NH], 2.64 [0.42H, m, NHC*H*], 3.01 [0.58H, m, NHC*H*], 3.47 [0.42H, s, C*H*CN], 3.60 [0.58H, s, C*H*CN]; δ_C ($CDCl_3$) 20.06, 22.04, 22.11, 24.14, 28.28, 28.57, 29.61, 29.93, 32.14 (ma), 32.37 (mi), 34.29 (ma), 37.88 (mi),

† Non-systematic name.

47.75 (ma), 52.57 (mi), 57.53 (ma), 58.31 (mi), 118.94 (mi), 119.51 (ma); *m*/*z* (CI-isobutane) 153 (100%) [MH^+].

(2*RS*,6*RS*)-3,3-Dimethyl-6-ethylpiperidine-2-carbonitrile 2e. The title compound was prepared according to **GP1** using 0.70 g (5 mmol) of *rac*-3,3-dimethyl-6-ethyl-3,4,5,6-tetrahydropyridine† [16] **1e** and 0.63 ml (5 mmol) trimethylsilyl cyanide as starting materials. The product **2e** (0.83 g, 100%) was obtained as a yellow liquid as a 63 : 37 mixture of racemic diastereomers, R_f: 0.56 (*n*-hexane–ethyl acetate, 7 : 3) [Found: C, 72.21; H, 10.91; N, 16.79. $C_{10}H_{18}N_2$ (166.27) requires C, 72.24; H, 10.91; N, 16.85%]; δ_H ($CDCl_3$) 0.93 [3H, m, CH_2CH_3], 1.00–1.98 [13H, m, CH_2, CH_3, NH], 1.09, 1.11, 1.13, 1.15, 1.17, 1.18 [9H, 6s, CH_3], 1.27–1.73 [5H, m, CH_2, NH], 2.78 [0.37H, m, NHC*H*], 2.97 [0.63H, m, NHC*H*], 3.42 [0.37H, s, C*H*CN], 3.60 [0.63H, s, C*H*CN]; δ_C ($CDCl_3$) 9.88 (ma), 10.10 (mi), 20.04 (mi), 24.06 (ma), 27.18, 27.55, 28.25, 28.53, 29.08, 29.22, 32.45 (ma), 32.75 (mi), 34.15 (ma), 37.77 (mi), 53.58 (ma), 57.48 (ma), 58.32 (mi), 58.43 (mi), 119.05 (mi), 119.49 (ma); *m*/*z* (CI-isobutane) 167 (100%) [MH^+].

(2*RS*,6*RS*)-3,3-Dimethyl-6-phenylpiperidine-2-carbonitrile 2f. The title compound was prepared according to **GP1** using 0.94 g (5 mmol) of *rac*-3,3-dimethyl-6-phenyl-3,4,5,6-tetrahydropyridine† [16] **1f** and 0.63 ml (5 mmol) trimethylsilyl cyanide as starting materials. The product **2f** (0.99 g, 92%) was obtained as an orange oil, which started to crystallize on standing after a few days. It was obtained as an 85 : 15 mixture of racemic diastereomers. The diastereomeric ratio was improved by cooling to 0 °C while adding cyanide to dr ≥95 : 5, mp 85 °C (dr ≥95 : 5); R_f: 0.77 (*n*-hexane–ethyl acetate, 7 : 3) [Found: C, 78.50; H, 8.41; N, 12.93. $C_{14}H_{18}N_2$ (214.31) requires C, 78.46; H, 8.47; N, 13.07%]; δ_H ($CDCl_3$) (only one diastereomer is shown) 1.07, 1.20 [6H, 2s, CH_3], 1.42–1.64 [5H, m, NH, CH_2], 3.62 [1H, s, C*H*CN], 3.88 [1H, m, NHC*H*], 7.12–7.38 [5H, m, ArH]; δ_C ($CDCl_3$) 24.09, 28.57, 30.64, 34.60, 32.10, 57.38, 57.57, 119.27, 126.73, 127.50, 128.46, 143.78; *m*/*z* (CI-isobutane) 215 (100%) [MH^+].

(1*RS*,3*RS*)-3-Methyl-2-azaspiro[5.5]undecane-1-carbonitrile 2g. The title compound was prepared according to **GP1** using 0.83 g (5 mmol) of *rac*-3-methyl-2-azaspiro[5.5]undec-1-ene [1] **1g** and 0.63 ml (5 mmol) trimethylsilyl cyanide as starting materials. The product **2g** (0.98 g, 100%) was obtained as a yellow liquid as a 76 : 24 mixture of racemic diastereomers, R_f: 0.76 (*n*-hexane–ethyl acetate, 7 : 3) [Found: C, 74.87; H, 10.54; N, 14.65. $C_{12}H_{20}N_2$ (192.30) requires C, 74.95; H, 10.48; N, 14.57%]; δ_H ($CDCl_3$) 0.85–1.80 [17H, m, CH_3, CH_2], 2.09, 2.27 [1H, 2m, NH], 2.57 [0.24H, m, NHC*H*], 3.03 [0.76H, m, NHC*H*], 3.49 [0.24H, s, CHCN], 3.94 [0.76H, s, CHCN]; δ_C ($CDCl_3$) 20.95, 21.17, 21.31, 22.12, 26.22, 26.98, 28.79, 29.02, 30.27, 31.35, 31.94, 34.36, 34.65, 36.25, 36.65, 37.23, 43.23, 48.32 (ma), 52.88 (mi), 55.12 (ma), 60.02 (mi), 118.94 (mi), 119.34 (ma); *m*/*z* (CI-isobutane) 193 (100%) [MH^+].

(1*RS*,3*RS*)-3-Phenyl-2-azaspiro[5.5]undecane-1-carbonitrile 2h. The title compound was prepared according to **GP1** using 1.14 g (5 mmol) of *rac*-3-phenyl-2-azaspiro[5.5]undec-1-ene [1] **1h** and 0.63 ml (5 mmol) trimethylsilyl cyanide as starting materials. The product **2h** (1.18 g, 93%) was obtained as an orange oil, the determination of the diastereomeric ratio from the ^1H NMR spectrum was not possible due to severe signal crowding, R_f: 0.88 (*n*-hexane–ethyl acetate, 7 : 3) [Found: C, 80.20; H, 8.82; N, 10.99. $C_{17}H_{22}N_2$ (254.37) requires C, 80.27; H, 8.72; N, 11.01%]; δ_H ($CDCl_3$) 0.93–1.74 [14H, m, CH_2], 1.81 [1H, m, NH], 3.90 [2H, m, C*H*CN, NHC*H*], 7.15–7.52 [5H, m, ArH]; δ_C ($CDCl_3$) 21.17, 21.35, 26.22, 29.81, 30.74, 31.36, 32.23, 37.20, 34.35, 55.27, 57.96, 119.17, 126.73, 127.49, 128.44, 143.91; *m*/*z* (CI-isobutane) 255 (100%) [MH^+].

(2*RS*,3*RS*)-3-Methyl-3-propylpiperidine-2-carbonitrile 2i. The title compound was prepared according to **GP1** using 0.70 g (5 mmol) of *rac*-3-methyl-3-propyl-3,4,5,6-tetrahydropyridine† [16] **1i** and 0.63 ml (5 mmol) trimethylsilyl cyanide as starting materials. The product **2i** (0.74 g, 95%) was obtained as a green liquid as a 53 : 47 mixture of racemic diastereomers, R_f: 0.75, 0.86 (*n*-hexane–ethyl acetate, 7 : 3) [Found: C, 78.50; H, 8.41; N, 12.93. $C_{10}H_{18}N_2$ (166.27) requires C, 72.24; H, 10.91; N, 16.85%]; δ_H ($CDCl_3$) 0.98 [3H, t, CH_3-CH_2-CH_2, ^3J 6.6], 1.02 [1.41H, s, CH_3], 1.09 [1.59H, s, CH_3], 1.17–1.71 [8H, m, CH_2], 1.89 [1H, br s, NH], 2.87 [2H, m, NHCH_2], 3.58 [1H, s, C*H*CN]; δ_C ($CDCl_3$) 14.78, 16.00 (mi), 16.43 (ma), 21.19, 21.27, 21.39, 23.52, 32.83, 33.43, 35.16 (ma), 35.23 (mi), 39.28, 43.39, 56.50 (mi), 56.74 (ma), 119.05 (mi), 119.26 (ma); *m*/*z* (CI-isobutane) 167 (100%) [MH^+].

***rac*-3,3-Dimethylpiperidine-2-carboxylic acid 3a.** [1] The title compound was prepared according to **GP2** using 1.70 g (12.3 mmol) of **2a** as starting material. Stirring in acetone gave the pure product in 100% yield (1.93 g). The analytical data correspond with literature data; [1] mp 267 °C (decomp.) [lit.[1]: >260 °C].

***rac*-3,3-Diethylpiperidine-2-carboxylic acid 3b.** [1] The title compound was prepared according to **GP2** using 0.70 g (4.21 mmol) of **2b** as starting material. Stirring in acetone gave the pure product. Yield 0.72 g, 92%. The analytical data correspond with literature data; [1] mp 293 °C (decomp.) [lit.[1]: >260 °C].

***rac*-2-Azaspiro[5.5]undecane-1-carboxylic acid 3c.** [1] The title compound was prepared according to **GP2** using 0.79 g (4.41 mmol) of **2c** as starting material. Stirring in acetone gave the pure product. Yield 0.86 g, 99%. The analytical data correspond with the literature data; [1] mp 264 °C (decomp.) [lit.[1]: >260 °C].

(3*RS*,6*RS*)-3,3,6-Trimethylpiperidine-2-carboxylic acid 3d. The title compound was prepared according to **GP2** using 0.76 g (5 mmol) of **2d** as starting material. Stirring in acetone gave the pure product. The product **3d** (0.78 g, 91%) was obtained as a colourless solid as a 58 : 42 mixture of racemic diastereomers, mp > 325 °C [Found: C, 63.13; H, 9.91; N, 8.17. $C_9H_{17}NO_2$ (171.24) requires C, 63.13; H, 10.00; N, 8.18%]; δ_H (D_2O) 0.87, 1.09 [6H, 2s, CH_3], 1.25 [3H, d, CHCH_3, ^3J 6.9], 1.33–1.91 [5H, m, CH_2, NH], 3.10 [0.42H, m, NHC*H*], 3.31 [0.42H, s, C*H*COOH], 3.43 [0.58H, s, C*H*COOH], 3.70 [0.58H, m, NHC*H*]; δ_C (D_2O) 14.34 (ma), 18.36 (mi), 19.70 (mi), 20.36 (ma), 23.61 (ma), 26.77 (mi), 28.60 (ma), 28.69 (mi), 31.40 (mi), 31.60, 37.77 (ma), 48.41 (ma), 53.10 (mi), 61.60 (ma), 68.25 (mi), 173.16; *m*/*z* (CI-isobutane) 172 (100%) [MH^+].

(3*RS*,6*RS*)-3,3-Dimethyl-6-ethylpiperidine-2-carboxylic acid 3e. The title compound was prepared according to **GP2** using 0.80 g (4.81 mmol) of **2e** as starting material. Stirring in dichloromethane gave the pure product. The product **3e** (0.69 g, 80%) was obtained as a colourless solid as a 65 : 35 mixture of racemic diastereomers, mp >325 °C [Found: C, 64.84; H, 10.39; N, 7.65. $C_{10}H_{19}NO_2$ (185.27) requires C, 64.83; H, 10.34; N, 7.56%]; δ_H (D_2O) 0.98 [6H, m, CH_2CH_3, CH_3], 1.17 [3H, s, CH_3], 1.31–1.98 [7H, m, NH, CH_2], 2.92 [0.65H, m, NHC*H*], 3.30 [0.65H, s, C*H*COOH], 3.42 [0.7H, m, NHC*H*, C*H*COOH]; δ_C (D_2O) 9.36 (ma), 10.12 (mi), 19.86 (ma), 20.54 (mi), 20.97 (mi), 21.41 (ma), 24.52 (ma), 26.37 (mi), 28.57 (mi), 28.88 (ma), 37.76, 31.65 (mi), 31.80 (ma), 54.51 (mi), 58.67 (ma), 62.54 (mi), 68.55 (ma), 173.26; *m*/*z* (CI-isobutane) 186 (100%) [MH^+].

(1*RS*,3*RS*)-3-Methyl-2-azaspiro[5.5]undecane-1-carboxylic acid 3g. The title compound was prepared according to **GP2** using 0.97 g (4.41 mmol) of **2g** as starting material. Stirring in

dichloromethane gave the pure product. The product **3g** (0.57 g, 61%) was obtained as a colourless solid as an 81 : 19 mixture of racemic diastereomers, mp >325 °C [Found: C, 68.24; H, 10.00; N, 6.76. $C_{12}H_{21}NO_2$ (211.30) requires C, 68.21; H, 10.02; N, 6.63%]; δ_H (D_2O) 0.92–1.85 [17H, m, CH_2, CH_3], 2.15 [1H, br s, NH], 2.92 [0.81H, m, NHC*H*], 3.11 [0.81H, s, C*H*COOH], 3.49 [0.19H, s, C*H*COOH], 3.87 [0.19H, m, NHC*H*]; δ_C (D_2O) 18.55, 20.54, 20.70, 25.92, 26.03, 26.65, 29.53, 35.80, 34.66, 53.27, 68.99, 169.13; *m*/*z* (CI-isobutane) 212 (100%) [MH^+].

(2*RS*,3*RS*)-3-Methyl-3-propylpiperidine-2-carboxylic acid 3i. The title compound was prepared according to **GP2** using 0.71 g (5 mmol) of **2i** as starting material. Stirring in acetone gave the pure product. The product **3i** (0.65 g, 82%) was obtained as a colourless solid as a 53 : 47 mixture of racemic diastereomers, mp 305 °C (decomp.) [Found: C, 64.89; H, 10.31; N, 7.53. $C_{10}H_{19}NO_2$ (185.27) requires C, 64.83; H, 10.34; N, 7.56%]; δ_H ([D_6]DMSO–D_2O) 0.93–1.89 [15H, m, CH_2, CH_3, NH], 2.93 [1H, m, NHCH_2], 3.37 [1H, m, NHCH_2], 3.67 [0.53H, s, C*H*COOH], 3.72 [0.47H, s, C*H*COOH]; δ_C ([D_6]DMSO–D_2O) 15.74, 16.86, 16.98, 19.11, 19.94, 26.50, 33.69, 33.96, 34.51, 36.03, 36.15, 44.00 (mi), 44.66 (ma), 64.96 (mi), 67.17 (ma), 171.66; *m*/*z* (CI-isobutane) 186 (100%) [MH^+].

***rac*-1-Formyl-3,3-dimethylpiperidine-2-carboxylic acid 4a.** The title compound was prepared according to **GP3** using 1.57 g (10 mmol) of **3a** as starting material. The product **4a** (1.13 g, 61%) was obtained as a colourless solid. Due to the hindered rotation around the amidic N–C bond two rotamers in a 68 : 32 ratio were observed in the ^{1}H NMR spectrum, mp 155 °C [Found: C, 58.33; H, 8.15; N, 7.57. $C_9H_{15}NO_3$ (185.22) requires C, 58.36; H, 8.16; N, 7.56%]; δ_H ([D_6]DMSO–$CDCl_3$) 0.98, 1.02, 1.08 [6H, 3s, CH_3], 1.30–2.12 [4H, m, CH_2], 3.18 [0.32H, m, NCH_2], 3.48 [0.68H, m, NCH_2], 3.71 [0.32H, s, C*H*COOH], 3.73 [0.68H, m, NCH_2], 4.17 [0.32H, m, NCH_2], 4.53 [0.68H, s, C*H*COOH], 7.98 [0.32H, s, COH], 8.11 [0.68H, s, COH]; δ_C ([D_6]DMSO–$CDCl_3$) 18.55 (mi), 19.91 (ma), 24.13 (mi), 24.38 (ma), 26.07 (mi), 26.42 (ma), 30.35 (mi), 30.54 (mi), 31.69 (ma), 32.23 (ma), 34.92 (mi), 41.25 (ma), 57.58 (ma), 64.20 (mi), 160.82, 170.14 (mi), 170.38 (ma); *m*/*z* (CI-isobutane) 186 (100%) [MH^+].

***rac*-1-Formyl-3,3-diethylpiperidine-2-carboxylic acid 4b.** The title compound was prepared according to **GP3** using 1.85 g (10 mmol) of **3b** as starting material. The product **4b** (1.30 g, 61%) was obtained as a colourless solid. Due to the hindered rotation around the the amidic N–C bond two rotamers in a 60 : 40 ratio were observed in the ^{1}H NMR spectrum, mp 142 °C [Found: C, 62.04; H, 8.90; N, 6.57. $C_{11}H_{19}NO_3$ (213.28) requires C, 61.95; H, 8.97; N, 6.57%]; δ_H ($CDCl_3$) 0.69–0.83 [6H, m, CH_3], 1.24–1.64 [8H, m, CH_2], 3.11 [0.4H, m, NCH_2], 3.38 [0.60H, m, NCH_2], 3.73 [0.60H, m, NCH_2], 3.80 [0.40H, s, C*H*COOH], 4.21 [0.40H, m, NCH_2], 4.81 [0.60H, s, C*H*COOH], 7.97 [0.40H, s, COH], 8.08 [0.60H, s, COH]; δ_C ($CDCl_3$) 6.72 (mi), 7.00, 7.12 (ma), 19.02 (mi), 20.39 (ma), 22.91 (mi), 23.12 (ma), 27.56 (mi), 27.76 (ma), 28.48 (mi), 28.97 (ma), 37.00 (mi), 37.37 (mi), 37.47 (ma), 43.38 (ma), 56.91 (ma), 63.84 (mi), 163.12 (ma), 163.84 (mi), 173.22 (mi), 173.75 (ma); *m*/*z* (CI-isobutane) 214 (100%) [MH^+].

(−)-1-Formyl-3,3-dimethylpiperidine-2-carboxylic acid (−)-4a. 3.83 g (20.68 mmol) of *N*-formylated amino acid (±)-**4a** were dissolved in 200 ml ethyl acetate and heated to reflux. 1.56 g (10.34 mmol) (−)-norephedrine were added to the hot solution and the mixture was heated to reflux for an additional 15 min. Colourless crystals separated from the solution upon slow cooling to room temperature. The solid was filtered off, and recrystallized from ethyl acetate (200 ml) to yield the (−)-norephedrinium salt of (−)-**4a** (2.18 g, 63%) as a colourless, voluminous and flocculent solid. Due to hindered rotation around the amidic N–C bond two rotamers in a 61 : 39 ratio were observed in the ^{1}H NMR spectrum, [α_D] −66.4 (*c* 1, methanol), mp 160 °C [Found: C, 64.18; H, 8.31; N, 8.39. $C_{18}H_{28}N_2O_4$ (336.43) requires C, 64.26; H, 8.39; N, 8.33%]; δ_H ([D_6]DMSO) 0.88 [6H, m, CH_3], 1.01 [3H, s, CH_3], 1.17, 1.44, 1.92, 2.08 [4H, 4m, CH_2], 3.36 [2H, m, NCH_2], 3.49 [0.61H, s, C*H*COOH], 3.96 [1H, m, H_3CC*H*NH], 4.24 [0.39H, s, C*H*COOH], 4.94 [1H, m, PhCHOH], 7.32 [5H, m, ArH], 7.92 [0.61H, s, COH], 8.04 [0.39H, s, COH]; δ_C ([D_6]DMSO) 12.07, 20.19 (ma), 21.59 (mi), 25.69 (ma), 25.95 (mi), 27.86 (ma), 28.49 (mi), 31.35 (mi), 31.50 (ma), 33.15 (ma), 33.68 (mi), 35.84, 42.16, 51.70 (ma), 61.64 (mi), 68.50 (mi), 71.56 (ma), 125.90, 126.97, 128.02, 141.89, 161.57 (mi), 161.80 (ma), 173.91.

The (−)-norephedrinium salt of (−)-**4a** (0.78 g, 2.32 mmol) was dissolved in 50 ml water and treated with 1 ml of conc. HCl. The mixture was extracted with 50 ml of ethyl acetate three times. After drying of the combined organics over $MgSO_4$ the solvent was removed under reduced pressure to give the enantiomerically pure *N*-formylated α-amino acid (−)-**4a** (0.43 g, 100%) as a colourless solid, [α_D] −68.9 (*c* 1, methanol).

(+)-1-Formyl-3,3-dimethylpiperidine-2-carboxylic acid (+)-4a. The filtrate of the (−)-norephedrinium–(−)-**4a** salt formation described above was evaporated under reduced pressure. The residue was dissolved in 50 ml water and treated with 1 ml of conc. HCl. The mixture was extracted with 50 ml of ethyl acetate three times. The combined organics were dried over $MgSO_4$ and filtered. After the addition of 50 ml ethyl acetate the solution was heated to reflux. 1.56 g (10.34 mmol) of (+)-norephedrine were added to the hot solution and the mixture was heated to reflux for an additional 15 min. A colourless solid separated from the solution upon slow cooling to room temperature. The solid was filtered off, and recrystallized from ethyl acetate (200 ml) to yield the (+)-norephedrinium salt of (+)-**4a** (1.77 g, 51%) as a colourless, voluminous and flocculent solid, mp 160 °C; [α_D] +65.8 (*c* 1, methanol).

The (+)-norephedrinium salt of (+)-**4a** (0.85 g, 2.54 mmol) was dissolved in 50 ml water and treated with 1 ml of conc. HCl. The mixture was extracted with 50 ml of ethyl acetate three times. After drying of the combined organics over $MgSO_4$ the solvent was removed under reduced pressure to give the enantiomerically pure *N*-formylated α-amino acid (+)-**4a** (0.47 g, 100%) as a colourless solid, [α_D] +68.2 (*c* 1, methanol).

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