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Carbocyclic α-amino acids: asymmetric Strecker synthesis of a series of 2-alkylated 1-aminocyclopentanecarboxylic acids

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Abstract

A series of 12 carbocyclic α-amino acids has been prepared from four different racemic 2-alkylated cyclopentanones and (*R*)-1-phenylethylamine as the chiral auxiliary by means of an asymmetric Strecker synthesis. The stereoselectivity was influenced by solvent, temperature and size of the substituent at the 2-position of the cyclopentanones. For the methyl and ethyl substituted amino acids all four possible stereoisomers could be obtained, whereas for the isopropyl and tertiary butyl compounds an unexpected side reaction prohibited the isolation of the *cis* configured amino acids. The 1,3-induction mechanism observed for the kinetically controlled α-amino nitrile formation in the 2-methyl and 2-ethyl series was overlayed by a 1,2-induction in the respective 2-isopropyl and 2-tertiary butyl series.

1. Introduction

In the last few years a variety of interesting biological properties of carbocyclic α-amino acids have been described. Ohfune et al. showed that cyclic threonine analogues when incorporated as building blocks into peptides (e.g. Leu-enkephalin) can alter their biological effects.[1] Moreover, 1-aminocyclopropane (ACPC), 1-aminocyclobutan (ACBC), and 1-aminocyclopentanecarboxylic acid are reported as partial agonists at the strychnine insensitive glycine binding site of the NMDA receptor complex.[2] Recently, it was shown that ACPC acts concurrently as a glycine site partial agonist and as a glutamate site antagonist,[3] thus protecting against neural cell death and exhibiting antipsychotic-like effects in animal models.[4] Finally, α-quaternary α-amino acids such as ACPC or α-methylaspartate are able to function as enzyme inhibitors by covalently binding to pyridoxal phosphate dependent enzymes such as decarboxylases[5a] and transaminases.[5b]

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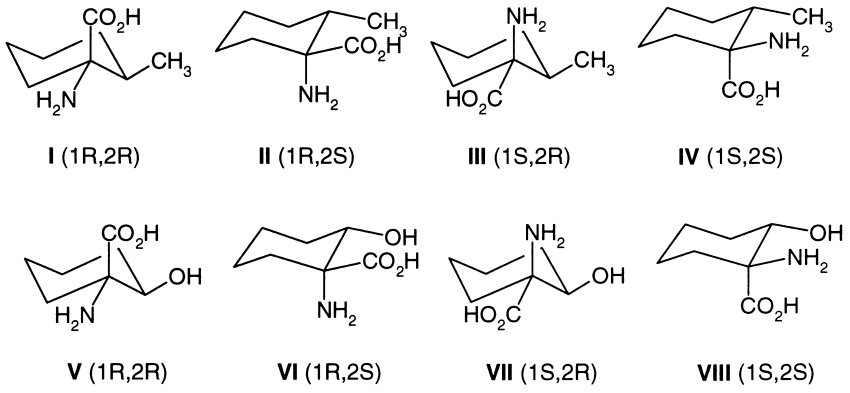
In the course of our work on asymmetric synthesis of cyclic analogues of naturally occurring α-amino acids we previously published the cyclohexane derived isoleucines[6] **I–IV** and threonines[7] **V–VIII**, respectively, (Scheme 1) by means of asymmetric Strecker reactions.[8,9]

In this paper we report on the preparation of a series of 12 homochiral 1-amino-2-alkylcyclopentanecarboxylic acids from the racemic cyclopentanones **1.1-4** and (*R*)-1-phenylethylamine[10] as the chiral auxiliary. For the methyl and ethyl substituted α-amino acids all four possible diastereo- and enantiomerically pure stereoisomers could be obtained, whereas in the isopropyl and tertiary butyl series only the two *trans* configured α-amino acids were accessible according to our experimental protocol.



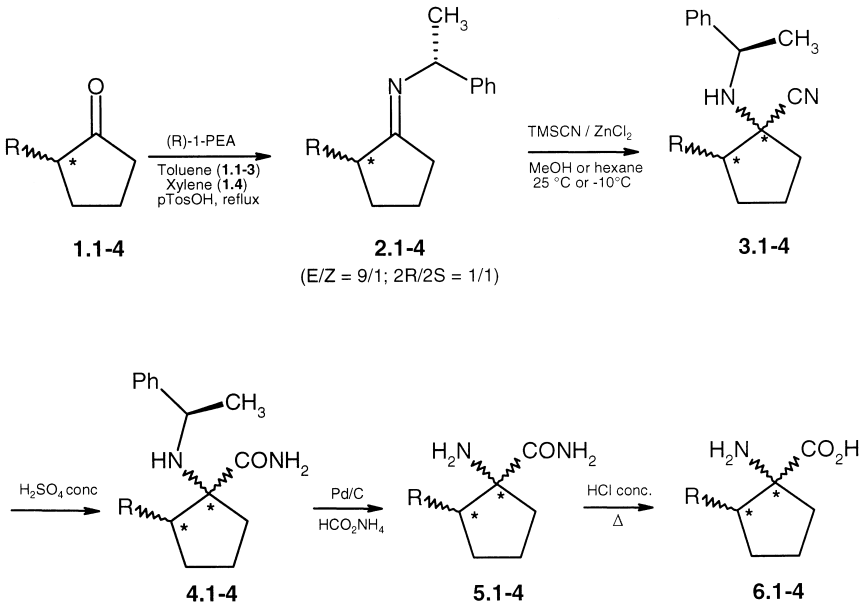
Scheme 1. Cyclic isoleucines **I–IV** and cyclic threonines **V–VIII**

2. Results

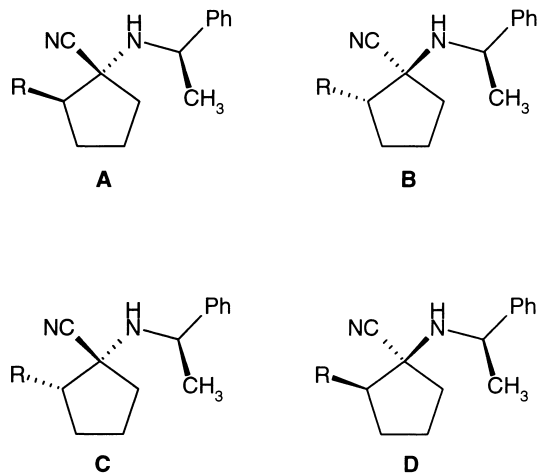
2.1. α-Amino nitrile synthesis

The racemic starting ketones **1.2-4** were prepared according to literature procedures,[11] while **1.1** is commercially available. For the synthesis of the α-amino nitriles **3.1-4** the 2-alkylated ketones **1.1-4** were subjected to a two-step procedure previously developed in our group[6,7] (Scheme 2) which includes azeotropic condensation with the chiral auxiliary (*R*)-1-phenylethylamine to the corresponding ketimin mixtures **2.1-4**[12] (each as a mixture of the *E*-α*R*,2*R*, *E*-α*R*,2*S*, *Z*-α*R*,2*R*, and *Z*-α*R*,2*S* stereoisomers) in the first step, followed by a Lewis-acid catalysed addition of trimethylsilylcyanide (TMSCN) to the C=N bond of the Schiff's bases yielding the α-amino nitriles **3.1-4**.

In this step, a new stereogenic centre is formed at C-1 of the cyclopentane skeleton. Since the stereochemistry of the chiral auxiliary is fixed, theoretically up to four diastereomeric α-amino nitriles can be obtained. In accordance with our earlier observations in the cyclohexane series,[6,7] TMSCN addition to the ketimines **2.1-4**. yielded oily mixtures of all four theoretically feasible diastereomers **A–D** of the α-aminocarbonitriles **3.1-4** (Scheme 3) even under different reaction conditions, each exhibiting four sets of signals in the ^{13}C NMR spectra. The relative proportions of the nitriles in the **3.1-4** mixtures were assigned by comparison of the intensities of corresponding ^{13}NMR signals, a method we have established previously.[6]



Scheme 2. Synthesis of the α-amino acids **6.1-4**



Scheme 3. The four theoretically feasible stereomers **A**–**D**

Although the selective synthesis of only a single α-amino nitrile failed, we could make interesting observations changing the solvent from methanol to hexane and running the formation of the amino nitriles **3.1-4** at 25°C and –10°C, respectively. The results of these investigations are summarised in Tables 1 and 2.

Table 1
Stereochemical composition **A**–**D** of the α-amino nitrile mixtures **3.1-4** obtained from reactions in MeOH

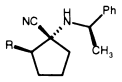
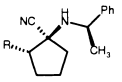
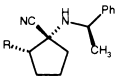
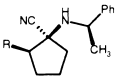
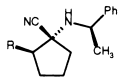
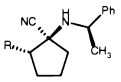
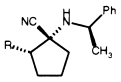
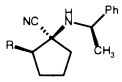
T [°C]	time [h/w*]	entry	R	A	B	C	D	yield [%]
								
				trans	*trans*	*cis*	*cis*	
25	24	**3.1**	CH_3	55	24	16	5	100
25	24	**3.2**	C_2H_5	57	23	14	6	98
25	24	**3.3**	$CH(CH_3)_2$	44	23	28	5	86
25	24	**3.4**	$C(CH_3)_3$	61	23	14	2	74
-10	3	**3.1**	CH_3	45	30	21	4	100
-10	3	**3.2**	C_2H_5	45	21	28	6	98
-10	3	**3.3**	$CH(CH_3)_2$	37	4	47	12	92
-10	3	**3.4**	$C(CH_3)_3$	26	0	59	15	36
-10	2*	**3.4**	$C(CH_3)_3$	55	6	32	7	100

Table 2
Stereochemical composition **A**–**D** of the α-amino nitrile mixtures **3.1-4** obtained from reactions in *n*-hexane

T [°C]	time [h/w*]	entry	R	A	B	C	D	yield [%]
								
				trans	*trans*	*cis*	*cis*	
25	24	**3.1**	CH_3	57	23	16	4	100
-10	3	**3.1**	CH_3	43	5	47	5	100
-10	3	**3.2**	C_2H_5	39	5	45	11	82
-10	3	**3.3**	$CH(CH_3)_2$	12	4	57	27	84
-10	3	**3.4**	$C(CH_3)_3$	5	1	66	28	37
-10	1*	**3.4**	$C(CH_3)_3$	7	1	59	33	83

It shows that, apart from the type of alkyl substituent at 2-position of the cyclopentane skeleton, after 24 h at 25°C in MeOH the *trans* configured α-amino nitrile **A** was obtained as the major reaction product in 44–61%, whereas the second *trans* compound **B** and the *cis* nitrile **C** was obtained in 23–24% and 14–28%, respectively. In all cases the second *cis* configured α-amino nitrile **D** was the minor product in only 2–5%. Neither heating these nitrile mixtures for 3 h in MeOH in a sealed tube nor refluxing them under the exact reaction conditions, i.e. in the presence of zinc chloride and 1-PEA changed their stereochemical composition, thus indicating that at 25°C the reaction is under thermodynamic control. However, after 3 h at –10°C in MeOH the stereochemical outcome of the reaction changes. For the methyl (**3.1**) and ethyl (**3.2**) substituted α-amino nitrile mixtures diastereomer **A** was still found as the major product (45%) along with increased amounts of the *cis* nitrile **C** (21–28%), which becomes the major reaction product (47 or 59%) in the isopropyl (**3.3**) and tertiary butyl (**3.4**) series. Similarly, the second *trans* nitrile **B** is either not formed at all (**3.4**) or only in negligible amounts of 4% for **3.3**. Hence, at –10°C in MeOH, the synthesis of the α-amino nitriles **3.1** and **3.2** still occurs with *trans*-diastereoselectivity, whereas those of the respective **3.3** and **3.4** series is switched to *cis*-diastereoselectivity. This reversal is in accordance with a decreased chemical yield of only 36%, i.e. 74% of the ketimine mixture **2.4** remains unreacted. Increasing the reaction time from 3 h to 2 weeks, quantitative yields of the tertiary butyl α-amino nitrile mixture can be obtained, and similarly the *trans* compound **A** becomes the major product (55%). Consequently, the *cis*-diastereoselectivity observed after 3 h in MeOH at –10°C in the **3.3** and **3.4** series is due to a kinetic resolution of the ketimine mixture **2.3** and **2.4** with the respective α*R*,2*R* configured imines reacting faster compared to the (α*R*,2*S*) configured ketimines.

As a model the use of hexane at 25°C was studied for the methyl series, revealing the same stereochemical composition (**A**:**B**:**C**:**D** = 57:23:16:4) as in MeOH, whereas after 3 h at –10°C in hexane we observed that for all four substituents the *cis* configured amino nitrile **C** becomes the major product in quantities (47–66%). Furthermore, the amount of **A** decreases with the size of the substituent from 43% for methyl to 5% for tertiary butyl. In parallel, the amount of the second *cis* nitrile **D** increases from 5% to 28%. Under these conditions the tertiary butyl substituted nitrile mixture was obtained in only 37%; however, after 1 week the yield increased to 83% with only small alterations in the stereochemical composition, i.e. the *cis* nitrile **C** remains the dominating product. Therefore, by the choice of the solvent, we are able to run the α-amino nitrile synthesis with either *trans*-diastereoselectivity (MeOH) or *cis*-diastereoselectivity (*n*-hexane) in good to quantitative yields.

In order to quantify the effect of the additional stereogenic centre we also studied the α-amino nitrile synthesis using benzylamine derived ketimines. As a result, we found that the *trans*/*cis*-diastereoselectivity of the reaction remained unchanged but of course both the *trans* as well as the *cis* amino nitriles were obtained as racemates. Hence, on the one side the use of 1-PEA influences the reaction in the sense that it proceeds with diastereo- and enantioselectivity and on the other side it allows us to separate the subsequent α-amino amide mixtures **4.1-4** under achiral conditions (vide infra).

2.2. Acidic hydrolysis

Subsequently, the α-amino nitrile mixtures **3.1-4** were subjected to hydrolysis, which was only successful with conc. sulfuric acid. Therefore, the mixtures obtained in methanol were added dropwise to precooled (–10°C) sulfuric acid (Procedure I), whereas to those stemming from

kinetically controlled reactions H_2SO_4 was added to the hexane solution without work-up at –10°C (Procedure II). The reactions were kept for 3 h at –10°C, 3 h at 0°C and finally for 1 week at 25°C yielding the α-amino carboxamides **4.1-4** each as a diastereomeric mixture in 20–68% chemical yield with essentially unchanged stereochemical distributions for the methyl and ethyl series (Table 3).

Table 3
Structural and stereochemical distribution of the products obtained from the α-amino nitrile mixtures **A**–**D** of **3.1-4** with H_2SO_4 conc.

Educt	Product(s)	R^1	R^2	R^3	A		B		C		D		ratio 4.x/5.x
3.1		CN	CH_3	$CH(CH_3)Ph$	**55**	*42*	**24**	*7*	**16**	*43*	**5**	*8*	
	4.1	$CONH_2$	CH_3	$CH(CH_3)Ph$	**54**	*50*	**21**	*8*	**15**	*34*	**10**	*8*	
3.2		CN	C_2H_5	$CH(CH_3)Ph$	**53**	*49*	**26**	*8*	**17**	*39*	**4**	*4*	
	4.2	$CONH_2$	C_2H_5	$CH(CH_3)Ph$	**55**	*47*	**31**	*5*	**9**	*38*	**5**	*10*	
3.3		CN	$CH(CH_3)_2$	$CH(CH_3)Ph$	**44**		**23**		**28**		**5**		
	4.3	$CONH_2$	$CH(CH_3)_2$	$CH(CH_3)Ph$	**52**		**48**		**0**		**0**		45
	5.3	$CONH_2$	$CH(CH_3)_2$	H	**39**				**61**				55
3.4		CN	$C(CH_3)_3$	$CH(CH_3)Ph$	**61**		**23**		**14**		**2**		
	4.4	$CONH_2$	$C(CH_3)_3$	$CH(CH_3)Ph$	**61**		**39**		**0**		**0**		36
	5.4	$CONH_2$	$C(CH_3)_3$	H	**83**				**17**				64

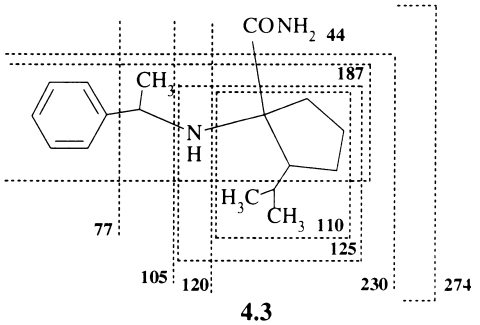
values in **bold**: from thermodynamically controlled reactions
values in *italics*: from kinetically controlled reactions

However, in the isopropyl and tertiary butyl series the outcome of the acidic hydrolysis differed completely. Hence, for example as shown in Fig. 1 for the isopropyl series **4.3**, GC–MS analysis of the crude product mixtures revealed four peaks (Fig. 1B) with retention times of 2.7, 3.0, 9.8, and 10.2 min, respectively. The mass peaks of *m*/*z* 230 (Fig. 1A), corresponding to M–44, for the latter two are in accordance with their expected α-amino carboxamide structures and can be explained with the spontaneous loss of the carboxamide functional group. The entities with retention times of 2.7 and 3.0 min, respectively, showed mass peaks of *m*/*z* 125 [M–44] (Fig. 1/C), corresponding to hydrogenolysed α-amino carboxamides, i.e. compounds with a primary α-amino group. Since this hydrogenolysis of the 1-phenylethyl moiety goes along with the loss of the third stereogenic centre the first two peaks consequently correspond to the *cis* and *trans* configured α-amino carboxamides **5.3**, each as non-racemic mixtures of two enantiomers, whereas the two peaks with higher retention times turned out to stem from the two *trans* configured α-amino carboxamides **4.3A** and **4.3B**, respectively.

Thus, it becomes evident that the acidic hydrolysis of the α-amino nitrile mixtures **3.3** and **3.4** runs in parallel with a *complete* hydrogenolysis of the *cis* configured diastereomers **C** and **D**, while the respective *trans* configured ones, **A** and **B**, are only cleaved to a certain degree (Table 3).

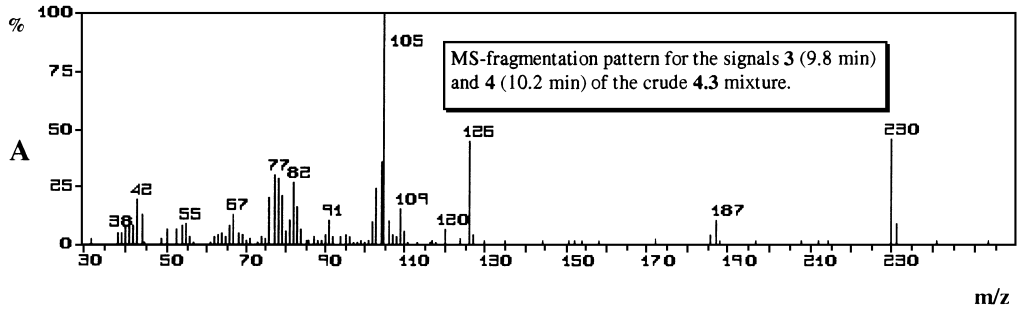
2.3. Separation of the α-aminocarboxamide mixtures *4.1-4*

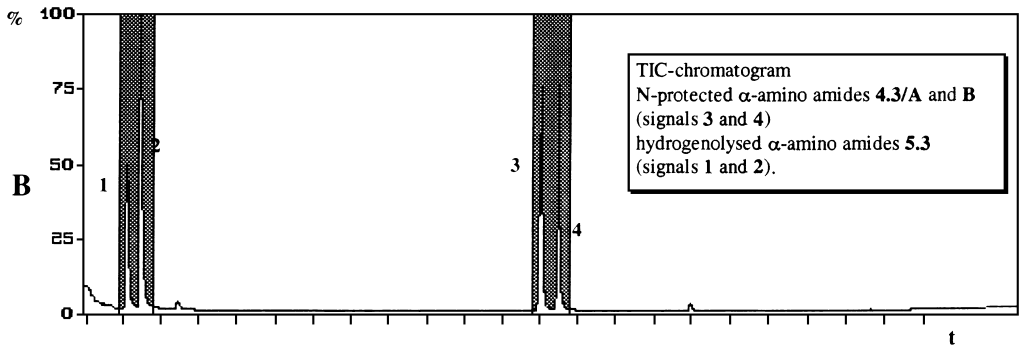
The α-aminocarboxamide mixtures **4.1-4** were separated into diastereomerically pure compounds by means of flash chromatography and preparative HPLC. For the **4.1** and **4.2** series



4.3

$C_{17}H_{26}N_2O$	274
$C_{16}H_{24}N$	230
$C_8H_{15}N$	125
C_8H_{14}	110
$C_{13}H_{17}N$	187
$C_8H_{10}N$	120
C_8H_9	105
C_6H_5	77
$CONH_2$	44





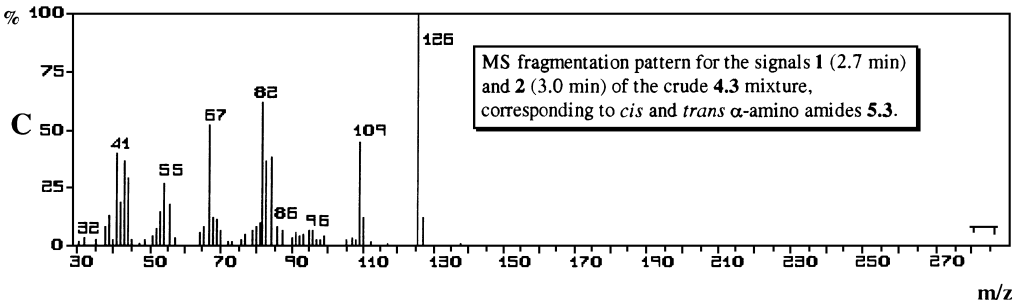


Figure 1. GC–MS analyses of the crude **4.3** mixture

flash chromatography yielded two combined fractions. The first one consisted of the stereomers **A** and **C**, whereas the second one was a mixture of **B** and **D**. Separation of the **A**/**C** mixture was achieved using HPLC in the reversed-phase mode, while the application of silica gel in normal-phase mode was successful for the separation of the **B**/**D** mixtures. In the case of the **4.3** and **4.4** mixtures, flash chromatography directly gave the two *trans* configured carboxamides **A** and **B** as diastereomerically pure compounds.

2.4. Hydrogenolysis and final hydrolysis

The diastereomerically pure α-amino carboxamides **4.1**/**A**–**D**, **4.2**/**A**–**D**, **4.3**/**A**–**B** and **4.4**/**A**–**B**, respectively, were subjected to catalytic transfer hydrogenolysis, using ammonium format and palladium on charcoal (10%). Refluxing for 1 h in methanol gave the corresponding α-amino amides **5.X** in 72–99% yield, which were finally hydrolysed with conc. HCl to the target α-amino acid hydrochlorides **6.X**·HCl. For the removal of NH_4Cl the crude products were chromatographed over a strong acidic cation exchange resin using 1 M ammonia as the eluent, yielding the 12 α-amino acids (zwitterionic form) **6.1**/**A**–**D**, **6.2**/**A**–**D**, **6.3**/**A**–**B** and **6.4**/**A**–**B** in 55–92% yield.

2.5. Absolute stereochemistry

The absolute stereochemistry of all synthesised compounds was deduced stepwise. First, compound **4.1A** was determined as *trans*-(α*R*,1*R*,2*R*)-2-methyl-1-(1-phenylethylamino)cyclopentanecarboxamide by X-ray analysis (three beam method[13]). Compound **4.1A** (α*R*,1*R*,2*R*) was hydrogenolysed to **5.1A** (1*R*,2*R*) which, according to NMR data and specific rotation values, turned out to be the enantiomer of **5.1B**. Hence, the (1*S*,2*S*)-configuration could be assigned to **5.1B** and (α*R*,1*S*,2*S*) to its chemical precursor **4.1B**. For the two *cis* configured compounds **4.1C** and **4.1D** the absolute configuration was derived in analogy to our previous observations, showing that in all cases the major product from kinetically controlled reactions (–10°C, hexane, 3 h) posesses the same configuration at C-1 as the chiral auxiliary used ('like-induction'). Thus, the (α*R*,1*R*,2*S*)-configuration was assigned to **4.1C** and finally (α*R*,1*S*,2*R*) to **4.1D**. The stereochemical assignments made for the methyl series **X.1** account also for the compounds of the ethyl (**X.2**), isopropyl (**X.3**) and tertiary butyl (**X.4**) series.

3. Conclusions

The asymmetric Strecker synthesis starting from the racemic 2-substituted cyclopentanones **1.1-4** and (*R*)-1-phenylethylamine gave mixtures of all four possible α-amino nitriles **3.1-4**/**A**–**D** the stereochemical composition of which was affected by the solvent, the temperature and the 2-alkyl substituent. Thus, the thermodynamically controlled reactions (MeOH or hexane, 25°C, 24 h) gave the *trans* configured α-amino nitriles **A** as major reaction products with *trans*/*cis* diastereoselectivities (**A+B**/**C+D**) ranging from 67:33 for the **3.3** series to 84:16 for the **3.4** series. In contrast, the kinetically controlled formations (–10°C, hexane, 3 h) yielded the *cis* configured nitriles **C** as the dominant products with *trans*/*cis* diastereoselectivities of 48:52 (**3.1**) to 6:94 (**3.4**) according to the spatial requirements of the respective alkyl substituents at 2-position. Therefore, regarding the nucleophilic attack of the cyanide to the ketimine mixtures **2.1-4** the following conclusions can be drawn.

In the methyl series **2.1** the *re*-face attack to the (*E*-α*R*,2*R*)- and to the (*E*-α*R*,2*S*)-configured ketimines is hindered by the phenyl group of the 1-phenylethyl moiety, whereas the pseudo-equatorial oriented methyl group at 2-position does not influence the cyanide addition, which therefore occurs with a high *si*-face selectivity (Fig. 2). The *si*-face attack to the (*E*-α*R*,2*R*)-imine leads to the *trans*-(α*R*,1*R*,2*R*)-α-amino nitrile **A** (43%), the *si*-face attack to the (*E*-α*R*,2*S*)-imine to the *cis*-(α*R*,1*R*,2*S*)-nitrile **C** (47%). In contrast, both the *Z*-configured ketimines are attacked from the *re*-face, since in the respective lowest energy conformers the phenyl group hampers a nucleophilic attack from the *si*-face (Fig. 3). The *re*-face attack on the (*Z*-α*R*,2*R*)-imine leads to the *cis*-(α*R*,1*S*,2*R*)-α-amino nitrile **D** (5%), while the corresponding attack on the (*Z*-α*R*,2*S*)-imine leads to the *trans* (α*R*,1*S*,2*S*)-nitrile **B** (5%).

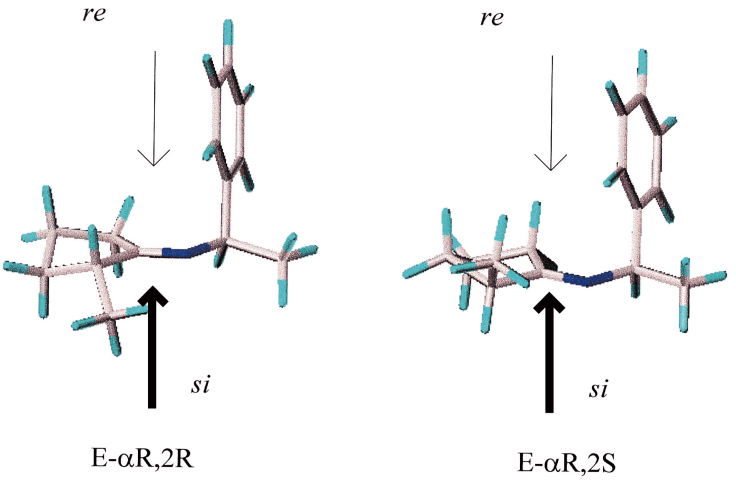


Figure 2. Proposed nucleophilic attack to the *E*-α*R*,2*R* and *E*-α*R*,2*S* ketimines **2.1**

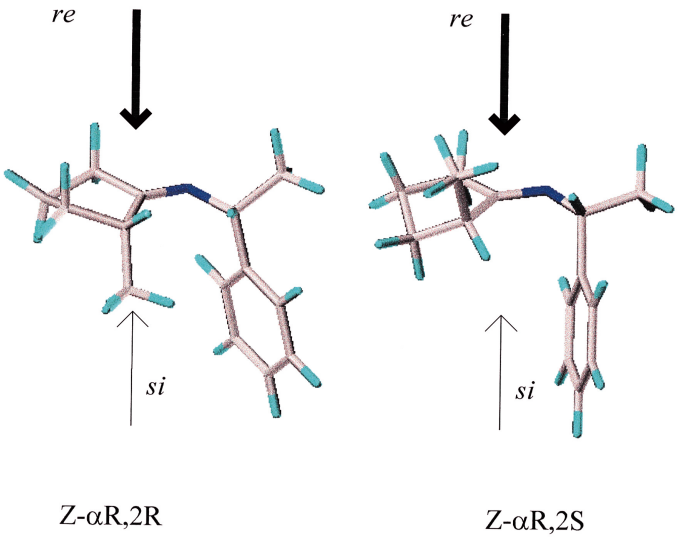


Figure 3. Proposed nucleophilic attack to the *Z*-α*R*,2*R* and *Z*-α*R*,2*S* ketimines **2.1**

In the tertiary butyl series **2.4**, as well as in the isopropyl series **2.3**, the *1,3-induction* mechanism from the **2.1** and **2.2** series is overlayed by a *1,2-induction* mechanism, e.g. the cyanide addition occurs *anti* to the bulky tertiary butyl group in all cases. For example, in the (*E*-α*R*,2*S*)-imine the tertiary butyl group hampers the nucleophilic *si*-face attack, thus leading to a moderate *re*-face selectivity of ≈6:1 (**D**:**A** = 28:5), while for the (*E*-α*R*,2*R*)-imine the *re*-face is completely blocked by both the tertiary butyl and the phenyl group of the 1-phenylethyl moiety (Fig. 4). This sterical hindrance induces the very high *si*-face selectivity of 66:1, reflected in the formation of the *cis* configured α*R*,1*R*,2*R* amino nitrile **C** as the predominating product.

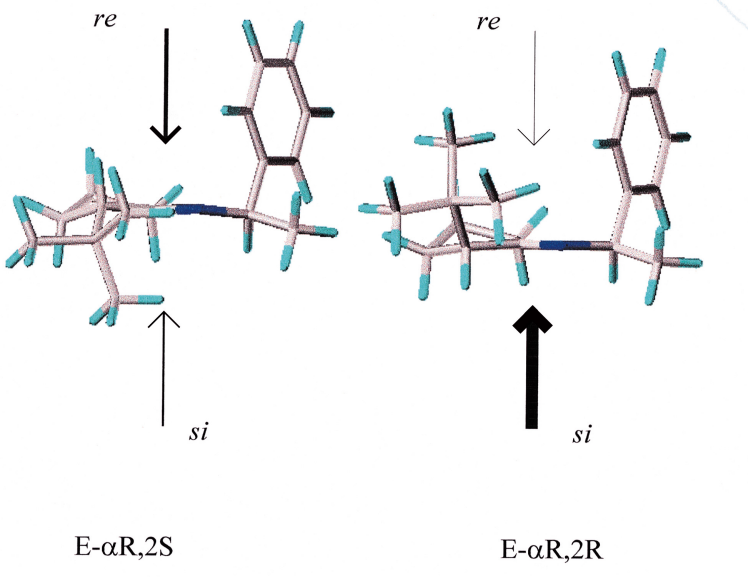


Figure 4. Proposed nucleophilic attack to the *E*-α*R*,2*S* and *E*-α*R*,2*R* ketimines **2.4**

Accordingly, the nucleophilic cyanide addition to the (*Z*-α*R*,2*R*)- and (*Z*-α*R*,2*S*)-imines gives rise to the amino nitriles **C** (originates from the *si* attack) and **D** (originates from the *re*-attack), respectively (Fig. 5).

In some cases, the original 1:1 ketimine mixtures **2.X** [(α*R*,2*R*):(α*R*,2*S*) = 50:50)] were converted to a 2(*R*):2(*S*)≈60:40 mixture of α-amino nitrile products **3.X**. This indicates that an inter-conversion, namely a C-2 epimerisation of the ketimines **2.X**, takes place during the cyanide addition step, although the epimerisation of about 5% is comparably low. Under the applied reaction conditions, this epimerisation at C-2 of the cyclopentane occurs most likely via an carbanion intermediate, since enamine intermediates could not be traced in the NMR spectra.

4. Experimental

Melting points were determined with a Reichert melting point apparatus and are uncorrected. Elemental analyses were obtained with a Perkin–Elmer elemental analyzer PE 240 at the Department of Biochemistry and Organic Chemistry, University of Freiburg. NMR experiments were carried out at 300 MHz (^{1}H) and 75.4 MHz (^{13}C), respectively, with a Varian Unity 300

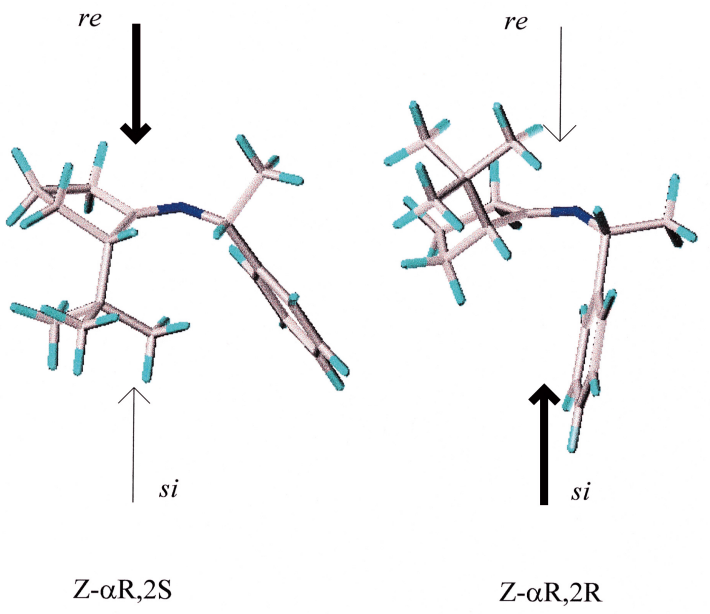


Figure 5. Proposed nucleophilic attack to the *Z*-α*R*,2*S* and *Z*-α*R*,2*R* ketimines **2.4**

spectrometer. Chemical shifts are reported as δ values using either TMS (^{1}H) or the solvent peak (^{13}C) as the reference. Infrared spectra were recorded with a Perkin–Elmer PE 841 spectrometer. Optical rotations values were measured in a 1 dm cell with a Perkin–Elmer 241 polarimeter. GC–MS analyses were carried out with a Perkin–Elmer QMASS 910 spectrometer using a RTX-35® column (Restek GmbH, Bad Soden, Germany). Flash chromatography was performed with silica gel (Si 60, 0.04–0.063 μm, Sigma–Aldrich Chemie GmbH). Analytical and preparative HPLC was carried out with Waters equipment, including photodiode-array detection, on silica gel columns (Si 60, Bischoff GmbH or Merck Eurolab GmbH) with *n*-hexane/ethyl acetate mixtures as mobile phase and on reversed phase columns (RP-18 select AB, Macherey & Nagel GmbH) using methanol/water mixtures as the eluent. Solvents were purified according to standard procedures. Starting materials were purchased from either Merck or Fluka companies and were used without further purification.

4.1. E/Z-*2-(*RS*)*-N-*[(*R*)-1-Phenylethyl]cyclopentylidenamines* **2.1-4** *(mixtures of four diastereomers)*

A mixture of 2-alkylated cyclopentanone **1.1-4** (0.1 mol), (*R*)-(+)-1-phenylethylamine (0.1 mol, 12.1 g) and a catalytic amount of *p*-toluenesulfonic acid was dissolved in toluene (**2.1-3**) and xylene (**2.4**), repectively, and refluxed for 24 h (**2.1**), 48 h (**2.2**), 72 h (**2.3**) and 240 h (**2.4**), respectively, using a Dean–Stark apparatus. The solvent was evaporated in vacuo. The residues of **2.1** and **2.2** were purified by destillation in vacuo.

4.1.1. E/Z-*2-(*RS*)*-N-*[(*R*)-1-Phenylethyl]-2-methylcyclopentylidenamine* **2.1**

$Bp_{0.3}$ = 72–78°C; IR (film): ν = 3083, 3061, 3027, 2963, 2930, 2866, 1675, 1601, 1491, 1448, 1418, 1368, 1179, 1068, 1008, 761, 700 cm^{-1}.

4.1.2. E/Z-*2(*RS*)*-N-*[(*R*)-1-Phenylethyl]*-2-ethylcyclopentylidenamine **2.2**

$Bp_{0.7}$ = 90–94°C; IR (film): ν = 3090, 3062, 3027, 2963, 2930, 2873, 1674, 1603, 1492, 1449, 1420, 1367, 1179, 1069, 1009, 762, 699 cm^{-1}.

4.1.3. E/Z-*2(*RS*)*-N-*[(*R*)-1-Phenylethyl]*-2-*(1-methylethyl)cyclopentylidenamine **2.3**

IR (film): ν = 3084, 3062, 3027, 2956, 2870, 1673, 1602, 1492, 1449, 1420, 1365, 1179, 1068, 1011, 761, 700 cm^{-1}.

4.1.4. E/Z-*2(*RS*)*-N-*[(*R*)-1-Phenylethyl]*-2-*(1,1-dimethylethyl)cyclopentylidenamine **2.4**

IR (film): ν = 3082, 3060, 3030, 2963, 2868, 1667, 1602, 1492, 1449, 1420, 1361, 1177, 1080, 1010, 760, 699 cm^{-1}.

*4.2. 2-Alkyl-1-(1-phenylethylamino)cyclopentanecarbonitrile mixtures **3.1-4***

4.2.1. Procedure I ('thermodynamic control')

To a solution of 10 mmol of the ketimine mixtures **2.1-4** and 75 mg of dry zinc chloride in 50 mL of methanol, 1.5 mL TMSCN (14 mmol) were added slowly at 0°C. The reaction mixture was either stirred for 3 h at 0°C and then for 21 h at 25°C or for 3 h at –10°C. The methanol was evaporated and the residue was dried in vacuo yielding the α-amino nitriles **3.1-4** each as a diastereomeric mixture of **A**–**D**.

4.2.2. Procedure II ('kinetic control')

To a solution of 10 mmol of the ketimine mixtures **2.1-4** and 75 mg of dry zinc chloride in 50 mL of *n*-hexane 1.5 mL TMSCN (14 mmol) were added dropwise at 25°C and –10°C, respectively. The resulting mixture was stirred for 24 h at 25°C or for 3 h at –10°C. The solvent was evaporated yielding diastereomeric mixtures of the α-amino nitriles **3.1-4** as pale yellow oils, which were dried in vacuo and analysed without further purification.

*4.2.3. 2-Methyl-1-(1-phenylethylamino)cyclopentanecarbonitriles **3.1**/**A**–**D***

IR (film): ν = 3329, 3083, 3061, 3028, 2964, 2872, 2220, 1672, 1603, 1492, 1451, 1371, 1314, 1277, 1205, 1028, 913, 846, 762, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.18 (**A**)/1.00 (**B**)/1.16 (**C**)/0.89 (**D**) (d, J = 6.3–6.8 Hz, 3H, 4×2-CH_3), 1.2–2.4 (**A**–**D**) (m, 8H, cycloaliphatic *H* and N*H*), 1.42 (**A**)/1.41 (**B**)/1.41 (**C**) (d, J = 6.6–6.7 Hz, 3H, 3×β-CH_3), 4.15 (**A**)/4.09 (**B**)/4.08 (**C**) (q, J = 6.7 Hz, 1H, 3×α-C*H*), 7.1–7.5 (**A**–**D**) (m, 5H, aromatic *H*); ^{13}C NMR ($CDCl_3$): 15.48 (**A**)/16.26 (**B**)/12.61 (**C**)/12.97 (**D**) (4×2-CH_3), 20.44 (**A**)/20.89 (**B**)/20.89 (**C**)/20.55 (**D**) (4×C-4), 25.78 (**A**)/25.35 (**B**)/26.23 (**C**)/25.05 (**D**) (4×β-CH_3), 30.22 (**A**)/30.83 (**B**)/30.25 (**C**)/30.34 (**D**) (4×C-3), 37.69 (**A**)/35.50 (**B**)/35.50 (**C**)/36.69 (**D**) (4×C-5), 44.87 (**A**)/43.28 (**B**)/45.21 (**C**)/44.51 (**D**) (4×C-2), 55.98 (**A**)/55.62 (**B**)/55.19 (**C**)/54.98 (**D**) (4×C-α), 67.08 (**A**)/66.05 (**B**)/63.36 (**C**)/62.30 (**D**) (4×C-1), 120.70 (**A**)/122.57 (**B**)/122.57 (**C**) (3×CN), 126.83 (**A**)/126.37 (**B**)/128.18 (**C**) (3×C-2′/6′), 127.00 (**A**)/127.11 (**B**)/126.76 (**C**) (3×C-4′), 128.22 (**A**)/128.44 (**B**)/128.22 (**C**) (3×C-3′/5′), 146.04 (**A**)/145.81 (**B**)/146.86 (**C**) (3×C-1′).

*4.2.4. 2-Ethyl-1-(1-phenylethylamino)cyclopentanecarbonitriles **3.2**/**A**–**D***

IR (film): ν = 3330, 3090, 3063, 3029, 2965, 2875, 2221, 1674, 1603, 1493, 1452, 1372, 1307, 1277, 1203, 1028, 912, 763, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.01 (**A**)/0.83 (**B**)/1.06 (**C**)/0.85 (**D**) (t, J = 7.3–7.5 Hz, 3H, 4×CH_2-CH_3), 1.2–2.4 (**A**–**D**) (m, 10H, cycloaliphatic *H*, CH_2-CH_3 and N*H*), 1.42 (**A**)/1.41 (**B**)/1.40 (**C**) (d, J = 6.6 Hz, 3H, 3×β-CH_3), 4.14 (**A**)/4.09 (**B**)/4.06 (**C**)/4.04 (**D**) (q,

J = 6.6 Hz, 1H, 4×α-C*H*), 7.1–7.5 (**A**–**D**) (m, 5H, aromatic *H*); ^{13}C NMR ($CDCl_3$): 12.52 (**A**)/12.40 (**B**)/12.60 (**C**)/12.32 (**D**) (4×CH_2-*C*H_3), 20.73 (**A**)/20.81 (**B**)/20.73 (**C**)/20.98 (**D**) (4×C-4), 24.33 (**A**)/24.62 (**B**)/24.33 (**C**)/24.62 (**D**) (4×*C*H_2-CH_3), 25.90 (**A**)/25.36 (**B**)/26.38 (**C**) (3×β-CH_3), 28.00 (**A**)/28.55 (**B**)/28.13 (**C**)/27.93 (**D**) (4×C-3), 38.51 (**A**)/40.16 (**B**)/36.04 (**C**)/37.27 (**D**) (4×C-5), 52.06 (**A**)/50.86 (**B**)/52.64 (**C**)/52.13 (**D**) (4×C-2), 56.03 (**A**)/55.76 (**B**)/55.18 (**C**)/54.92 (**D**) (4×C-α), 66.73 (**A**)/65.68 (**B**)/62.91 (**C**)/61.94 (**D**) (4×C-1), 121.23 (**A**)/121.11 (**B**)/123.04 (**C**) (3×CN), 126.76 (**A**)/126.36 (**B**)/126.05 (**C**) (3×C-2′/6′), 126.92 (**A**)/127.08 (**B**)/126.67 (**C**)/127.18 (**D**) (4×C-4′), 128.15 (**A**)/128.38 (**B**)/128.15 (**C**)/128.00 (**D**) (4×C-3′/5′), 146.18 (**A**)/145.69 (**B**)/147.02 (**C**) (3×C-1′).

*4.2.5. 2-(1-Methylethyl)-1-(1-phenylethylamino)cyclopentanecarbonitriles **3.3**/**A**–**D***

IR (film): ν = 3333, 3080, 3062, 3028, 2959, 2870, 2220, 1673, 1603, 1493, 1449, 1367, 1304, 1276, 1202, 1027, 912, 843, 762, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.00 (**A**)/0.92 (**B**)/1.00 (**C**)/1.07 (**D**) (d, J = 6.6 Hz, 3H, 4×CH(C*H*$_3$)$_2$), 1.16 (**A**)/0.92 (**B**)/1.26 (**C**)/0.92 (**D**) (d, J = 6.6 Hz, 3H, 4×CH(C*H*$_3$)$_2$), 1.3–2.5 (**A**–**D**) (m, 9H, cycloaliphatic *H*, C*H*(CH$_3$)$_2$ and N*H*), 1.41 (**A**)/1.41 (**B**)/1.42 (**C**) (d, J = 6.6 Hz, 3H, 3×β-C*H*$_3$), 4.16 (**A**)/4.09 (**B**)/4.10 (**C**)/4.03 (**D**) (q, J = 6.6 Hz, 1H, 4×α-C*H*), 7.1–7.5 (**A**–**D**) (m, 5H, aromatic *H*); ^{13}C NMR ($CDCl_3$): 21.34 (**A**)/20.73 (**B**)/20.65 (**C**)/21.06 (**D**) (4×CH(*C*H$_3$)$_2$), 21.76 (**A**)/21.76 (**B**)/21.55 (**C**)/21.48 (**D**) (4×C-4), 22.19 (**A**)/22.19 (**B**)/22.12 (**C**)/22.02 (**D**) (4×CH(*C*H$_3$)$_2$), 26.03 (**A**)/25.11 (**B**)/26.42 (**C**)/25.25 (**D**) (4×β-CH_3), 28.48 (**A**)/28.02 (**B**)/28.60 (**C**) (3×C-3), 31.14 (**A**)/30.67 (**B**)/28.69 (**C**)/28.85 (**D**) (4×*C*H(CH$_3$)$_2$), 40.10 (**A**)/41.45 (**B**)/37.67 (**C**)/38.84 (**D**) (4×C-5), 55.77 (**A**)/55.68 (**B**)/54.80 (**C**)/ 54.29 (**D**) (4×C-α), 57.29 (**A**)/56.36 (**B**)/57.42 (**C**)/57.71 (**D**) (4×C-2), 65.80 (**A**)/64.50 (**B**)/61.15 (**C**)/59.24 (**D**) (4×C-1), 121.51 (**A**)/121.16 (**B**)/123.45 (**C**)/123.10 (**D**) (4×CN), 126.64 (**A**)/126.64 (**B**)/125.99 (**C**) (3×C-2′/6′), 126.81 (**A**)/126.34 (**B**)/126.34 (**C**)/126.21 (**D**) (4×C-4′), 128.13 (**A**)/128.41 (**B**)/128.13 (**C**)/128.48 (**D**) (4×C-3′/5′), 146.35 (**A**)/145.42 (**B**)/147.02 (**C**)/145.10 (**D**) (4×C-1′).

*4.2.6. 2-(1,1-Dimethylethyl)-1-(1-phenylethylamino)cyclopentanecarbonitriles **3.4**/**A**–**D***

IR (film): ν = 3329, 3080, 3063, 3028, 2962, 2869, 2220, 1666, 1603, 1492, 1449, 1363, 1276, 1209, 1028, 910, 761, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.16 (**A**)/1.04 (**B**)/1.19/ (**C**) 1.12 (**D**) (s, 9H, 4xC(C*H*$_3$)$_3$), 1.3–2.6 (**A**–**D**) (m, 8H, cycloaliphatic *H* and N*H*), 1.40 (**A**)/1.41 (**B**)/1.42 (**C**)/1.40 (**D**) (d, J = 6.6–6.8 Hz, 3H, 4×β-C*H*$_3$), 4.17 (**A**)/4.15 (**B**)/4.06 (**C**)/3.98 (**D**) (q, J = 6.6–6.8 Hz, 1H, 4×α-C*H*), 7.1-7.5 (**A**–**D**) (m, 5H, aromatic *H*); ^{13}C NMR ($CDCl_3$): 22.16 (**A**)/22.41 (**B**)/20.24 (**C**)/20.70 (**D**) (4×C-4), 25.04 (**A**)/25.41 (**B**)/24.84 (**C**)/24.52 (**D**) (4×C-3), 26.62 (**A**)/26.41 (**B**)/26.66 (**C**)/25.74 (**D**) (4×β-CH_3), 28.41 (**A**)/28.27 (**B**)/29.91 (**C**)/29.66 (**D**) (q, 4×C(*C*H$_3$)$_3$), 32.72 (**A**)/32.67 (**B**)/32.67 (**C**)/33.32 (**D**) (4×*C*(CH$_3$)$_3$), 40.99 (**A**)/42.64 (**B**)/37.76 (**C**)/38.70 (**D**) (4×C-5), 55.27 (**A**)/55.23 (**B**)/55.23 (**C**)/55.07 (**D**) (4×C-α), 61.30 (**A**)/59.72 (**B**)/59.51 (**C**)/59.72 (**D**) (4×C-2), 63.06 (**A**)/61.94 (**C**)/62.80 (**D**) (3×C-1), 122.69 (**A**)/122.62 (**B**)/123.68 (**C**)/123.30 (**D**) (4×CN), 126.53 (**A**)/126.25 (**B**)/125.94 (**C**)/126.32 (**D**) (4×C-2′/6′), 126.70 (**A**)/126.98 (**B**)/126.62 (**C**)/126.68 (**D**) (4×C-4′), 128.14 (**A**)/128.41 (**B**)/128.18 (**C**)/128.47 (**D**) (4×C-3′/5′), 146.77 (**A**)/145.85 (**B**)/147.20 (**C**)/146.10 (**D**) (4×C-1′).

*4.3. 2-Alkyl-1-(1-phenylethylamino)cyclopentanecarboxamide mixtures **4.1-4***

4.3.1. Procedure I ('thermodynamic control')

Diastereomeric α-amino nitrile mixtures **3.1-4** (40 mmol) (obtained from reactions in methanol at 25°C) were dissolved in 80 mL of concentrated H_2SO_4 and stirred for 3 h at –10°C, 3 h at 0°C

and 168 h at 25°C. The mixture was poured onto ice (300 g) and filtered over silica gel. The filtrate was adjusted to pH 8 with concentrated NH_3 and extracted Et_2O (3×200 mL). The combined organic layers were washed with H_2O (2×200 mL), dried with Na_2SO_4, filtered, and the Et_2O was evaporated, yielding 67% of **4.1** (**A**:**B**:**C**:**D** = 54:21:15:10), 62% of **4.2** (**A**:**B**:**C**:**D** = 55:31:9:5), 20% of **4.3** (**A**:**B** = 52:48) and 21% of **4.4** (**A**:**B** = 61:39), respectively. The oily mixtures were separated into diastereomerically pure α-amino amides by flash chromatography followed by preparative HPLC.

4.3.2. Procedure II ('kinetic control')

To 40 mmol of the diastereomeric α-amino nitrile mixtures **3.1-2** (obtained from reactions in hexane at –10°C) dissolved in 200 mL of *n*-hexane, 80 mL of concentrated H_2SO_4 were added slowly at –10°C. The mixture was stirred for 3 h at –10°C, 3 h at 0°C and 168 h at 25°C, poured onto ice (300 g) and filtered over silica gel. The filtrate was adjusted to pH 8 with concentrated NH_3 and extracted with Et_2O (3×200 mL). The combined organic layers were washed with H_2O (2×200 mL), dried with Na_2SO_4, filtered, and the Et_2O was evaporated, yielding 62% of **4.1** (**A**:**B**:**C**:**D** = 50:8:34:8) and 68% of **4.2** (**A**:**B**:**C**:**D** = 47:5:38:10), respectively. The oily mixtures were separated into diastereomerically pure α-amino amides by flash chromatography followed by preparative HPLC.

*4.3.3. Flash chromatography of the α-aminocarboxamide mixtures **4.1** and **4.2***

Stationary phase: Si 60 (230–400 mesh); mobile phase: petrolether (40–60°C):ethyl acetate (60:40); compound:stationary phase = 1:100; fraction size = 100 mL; detection: TLC (Si 60 F254 plats) with ninhydrine reagent; recovery rates: **4.1**/**A** = 63–74%, **4.1**/**B** = 71–82%, **4.1**/**C** = 66–69%, **4.1**/**D** = 61–62%, **4.2**/**A** = 66–79%, **4.**2/**B** = 62–81%, **4.2**/**C** = 65–67%, **4.2**/**D** = 73–98%.

*4.3.4. Flash chromatography of the α-aminocarboxamide mixtures of **4.3** and **4.4***

Stationary phase: Si 60 (230–400 mesh); mobile phase: petrolether (40–60°C):ethyl acetate (70:30); compound:stationary phase = 1:100; fraction size = 100 mL; detection: TLC (Si 60 F254 plats) with ninhydrine reagent; recovery rates: **4.3**/**A** = 81%, **4.3**/**B** = 94%, **4.4**/**A** = 52%, **4.4**/**B** = 66%.

*4.3.5. Analytical HPLC of the α-aminocarboxamide mixtures **4.1A**/**C** and **4.2A**/**C***

Stationary phase: Nucleosil® RP-18 select AB (5 μm; 250–4); mobile phase: CH_3OH:H_2O (65:35); flow rate: 0.5 mL/min; detection: UV (254 nm).

*4.3.6. Analytical HPLC of the α-aminocarboxamide mixtures **4.1B**/**D** and **4.2B**/**D***

Stationary phase: LiChrosorb® Si 60 (5 μm, 250–4); mobile phase: *n*-hexane:ethyl acetate (50:50); flow rate: 0.6 mL/min; detection: UV (254 nm).

*4.3.7. Preparative HPLC of the α-aminocarboxamide mixtures **4.1A**/**C** and **4.2A**/**C***

Diastereomeric ratios: **4.1**: **A**:**C** = 81:19 (procedure I) and 57:43 (procedure II); **4.2**: **A**:**C** = 94:6 (procedure I) and 68:32 (procedure II); stationary phase: Nucleosil®RP-18 select AB (5 μm, 250–20); mobile phase: CH_3OH:H_2O (65:35); flow rate: 6 mL/min; detection: UV (254 nm); recovery rates: **4.1**/**A** = 89–93%, **4.1**/**C** = 69–81%, **4.2**/**A** = 65–66%, **4.2**/**C** = 45–68%.

*4.3.8. Preparative HPLC of the α-aminocarboxamide mixtures **4.1B**/**D** and **4.2B**/**D***

Diastereomeric ratios: **4.1**: **B**:**D** = 94:6 (procedure I) and 64:36 (procedure II); **4.2**: **B**:**D** = 87:13 (procedure I) and 55:45 (procedure II); stationary phase: LiChrosorb® Si 60 (5 μm, 250–10); mobile phase: *n*-hexane:ethyl acetate (50:50); flow rate: 3 mL/min; detection: UV (254 nm); recovery rates: **4.1**/**B** = 77–96%, **4.1**/**D** = 92–99%, **4.2**/**B** = 70–80%, **4.2**/**D** = 55–80%.

*4.3.9. (αR,1R,2R)-2-Methyl-1-(1-phenylethylamino)cyclopentanecarboxamide **4.1A***

Mp: 75°C; $[\alpha]_D^{25}$ = +18.6 (*c* 0.56, CH_3OH); IR: ν = 3473, 3023, 2962, 2869, 1650, 1608, 1494, 1452, 1379, 1305, 1274, 1208, 1142, 1100, 1026, 911, 763, 704 cm^{-1}; ^1H NMR ($CDCl_3$): 0.90 (d, *J* = 6.8 Hz, 3H, 2-C*H*$_3$), 1.30 (d, *J* = 6.8 Hz, 3H, β-C*H*$_3$), 1.36/1.85 (m, 2H, 3-C*H*$_2$), 1.43/1.74 (m, 2H, 4-C*H*$_2$), 1.62/2.14 (m, 2H, 5-C*H*$_2$), 1.76 (m, 1H, 2-*H*), 3.85 (q, *J* = 6.8 Hz, 1H, α-C*H*), 7.1–7.4 (m, 5H, aromatic *H*), 1.5 (s(b), 1H, N*H*(amine)), 5.6/7.2 (s(b), 2H, N*H*(amide)); ^{13}C NMR ($CDCl_3$): 16.78 (2-CH_3), 21.95 (C-4), 24.98 (β-CH_3), 29.73 (C-5), 31.75 (C-3), 46.25 (C-2), 54.74 (C-α), 72.67 (C-1), 126.20 (C-2′/6′), 126.89 (C-4′), 128.45 (C-3′/5′), 147.30 (C-1′) 178.74 (C-6); $C_{15}H_{22}N_2O$ (246.36) calcd: C, 73.13; H, 9.01; N, 11.36; found: C, 73.14; H, 8.91; N, 11.29.

*4.3.10. (αR,1S,2S)-2-Methyl-1-(1-phenylethylamino)cyclopentanecarboxamide **4.1B***

Colorless oil; $[\alpha]_D^{25}$ = +111.4 (*c* 0.6, CH_3OH); IR: ν = 3453, 2965, 2874, 1673, 1558, 1492, 1453, 1374, 1216, 1132, 757, 701 cm^{-1}; ^1H NMR ($CDCl_3$): 0.92 (d, *J* = 6.8 Hz, 3H, 2-C*H*$_3$), 1.23/1.61 (m, 2H, 4-C*H*$_2$), 1.25/1.86 (m, 2H, 3-C*H*$_2$), 1.35 (d, *J* = 6.8 Hz, 3H, β-C*H*$_3$), 1.85/2.20 (m, 2H, 5-C*H*$_2$), 2.14 (m, 1H, 2-*H*), 3.74 (q, *J* = 6.8 Hz, 1H, α-C*H*), 7.1–7.4 (m, 5H, aromatic *H*), 1.5 (s(b), 1H, N*H*(amine)), 5.1/6.5 (s(b), 2H, N*H* (amide)); ^{13}C NMR ($CDCl_3$): 16.28 (2-CH_3), 22.15 (C-4), 27.26 (β-CH_3), 31.95 (C-5), 32.09 (C-3), 46.46 (C-2), 54.35 (C-α), 73.43 (C-1), 126.11 (C-2′/6′), 126.59 (C-4′), 128.44 (C-3′/5′), 147.44 (C-1′), 177.33 (C-6); $C_{15}H_{22}N_2O$ (246.36) calcd: C, 73.13; H, 9.01; N, 11.36; found: C, 72.96; H, 8.90; N, 11.45.

*4.3.11. (αR,1R,2S)-2-Methyl-1-(1-phenylethylamino)cyclopentanecarboxamide **4.1C***

Colorless oil; $[\alpha]_D^{25}$ = +33.7 (*c* 0.4, CH_3OH); IR: ν = 3442, 2964, 2875, 1667, 1602, 1452, 1373, 1274, 1215, 1153, 1112, 1026, 911, 702 cm^{-1}; ^1H NMR ($CDCl_3$): 0.95 (d, *J* = 7.1 Hz, 3H, 2-C*H*$_3$), 1.25/1.62 (m, 2H, 4-C*H*$_2$), 1.31 (d, *J* = 6.6 Hz, 3H, β-C*H*$_3$), 1.35/1.87 (m, 2H, 3-C*H*$_2$), 1.85/2.21 (m, 2H, 5-C*H*$_2$), 2.15 (m, 1H, 2-*H*), 3.80 (q, *J* = 6.6 Hz, 1H, α-C*H*), 7.1–7.4 (m, 5H, aromatic *H*), 1.4 (s(b), 1H, N*H* (amine)), 6.5/7.4 (s(b), 2H, N*H* (amide)); ^{13}C NMR ($CDCl_3$): 12.80 (2-CH_3), 21.47 (C-4), 24.89 (β-CH_3), 30.26 (C-5), 31.82 (C-3), 45.05 (C-2), 54.17 (C-α), 70.47 (C-1), 126.09 (C-2′/6′), 126.98 (C-4′), 128.53 (C-3′/5′), 147.08 (C-1′), 180.15 (C-6); $C_{15}H_{22}N_2O$ (246.36) calcd: C, 73.13; H, 9.01; N, 11.36; found: C, 72.88; H, 8.98; N, 11.32.

*4.3.12. (αR,1S,2R)-2-Methyl-1-(1-phenylethylamino)cyclopentanecarboxamide **4.1.D***

Colorless oil; $[\alpha]_D^{25}$ = +90.0 (*c* 0.4, CH_3OH); IR: ν = 3445, 2965, 1674, 1453, 1372, 1203, 1104, 762, 702 cm^{-1}; ^1H NMR ($CDCl_3$): 0.94 (d, *J* = 6.9 Hz, 3H, 2-C*H*$_3$), 1.34 (d, *J* = 6.3 Hz, 3H, β-C*H*$_3$), 1.40/2.02 (m, 2H, 3-C*H*$_2$), 1.75/1.82 (m, 2H, 4-C*H*$_2$), 2.02/2.41 (m, 2H, 5-C*H*$_2$), 2.20 (m, 1H, 2-*H*), 3.73 (q, *J* = 6.7 Hz, 1H, α-C*H*), 7.1–7.4 (m, 5H, aromatic *H*), 5.3/6.6 (s(b), 2H, N*H* (amide)); ^{13}C NMR ($CDCl_3$): 12.97 (2-CH_3), 21.67 (C-4), 27.09 (β-CH_3), 31.53 (C-5), 32.11 (C-3), 44.66 (C-2), 53.57 (C-α), 71.85 (C-1), 126.10 (C-2′/6′), 126.68 (C-4′), 128.55 (C-3′/5′), 147.46 (C-1′), 178.85 (C-6); $C_{15}H_{22}N_2O$ (246.36) calcd: C, 73.13; H, 9.01; N, 11.36; found: C, 73.25; H, 9.06; N, 11.48.

4.3.13. (αR,1R,2R)-2-Ethyl-1-(1-phenylethylamino)cyclopentanecarboxamide ***4.2A***

Colorless oil; $[\alpha]_D^{25}$ = +2.8 (*c* 0.75, CH_3OH); IR: ν = 3446, 3340, 3026, 2962, 2875, 1670, 1601, 1451, 1373, 1275, 1202, 1137, 910, 762, 701 cm^{-1}; ^1H NMR ($CDCl_3$): 0.76 (t, *J* = 7.3 Hz, 3H, CH_2-C*H*$_3$), 1.02/1.48 (m, 2H, C*H*$_2$-CH_3), 1.28 (d, *J* = 6.3 Hz, 3H, β-C*H*$_3$), 1.36/1.83 (m, 2H, 3-C*H*$_2$), 1.44/1.74 (m, 2H, 4-C*H*$_2$), 1.50 (m, 1H, 2-*H*), 1.61/2.11 (m, 2H, 5-C*H*$_2$), 3.88 (q, *J* = 6.6 Hz, 1H, α-C*H*), 7.1–7.4 (m, 5H, aromatic *H*), 5.6/7.2 (s(b), 2H, N*H* (amide)); ^{13}C NMR ($CDCl_3$): 12.86 (CH_2-*C*H_3), 22.24 (C-4), 24.18 (*C*H_2-CH_3), 25.24 (β-CH_3), 28.79 (C-3), 31.22 (C-5), 53.72 (C-2), 54.74 (C-α), 72.66 (C-1), 126.25 (C-2′/6′), 126.95 (C-4′), 128.52 (C-3′/5′), 147.41 (C-1′), 178.79 (C-6); $C_{16}H_{24}N_2O$ (260.38) calcd: C, 73.20; H, 9.30; N, 10.75; found: C, 73.18; H, 9.18; N, 10.39.

4.3.14. (αR,1S,2S)-2-Ethyl-1-(1-phenylethylamino)cyclopentanecarboxamide ***4.2B***

Colorless oil; $[\alpha]_D^{25}$ = +87.5 (*c* 0.36, CH_3OH); IR: ν = 3450, 3330, 3030, 2962, 2873, 1679, 1556, 1492, 1450, 1372, 1275, 1200, 1131, 1028, 910, 762, 701 cm^{-1}; ^1H NMR ($CDCl_3$): 0.90 (t, *J* = 7.3 Hz, 3H, CH_2-C*H*$_3$), 1.11/1.56 (m, 2H, C*H*$_2$-CH_3), 1.38 (d, *J* = 6.8 Hz, 3H, β-C*H*$_3$), 1.41/1.94 (m, 2H, 3-C*H*$_2$), 1.58 (m, 1H, 2-*H*), 1.67/1.90 (m, 2H, 4-C*H*$_2$), 1.84/2.37 (m, 2H, 5-C*H*$_2$), 3.77 (q, *J* = 6.8 Hz, 1H, α-C*H*), 7.1–7.4 (m, 5H, aromatic *H*), 5.0/6.5 (s(b), 2H, N*H* (amide)); ^{13}C NMR ($CDCl_3$): 13.11 (CH_2-*C*H_3), 22.33 (C-4), 23.97 (*C*H_2-CH_3), 27.42 (β-CH_3), 29.31 (C-3), 33.05 (C-5), 54.16 (C-2), 54.37 (C-α), 73.36 (C-1), 126.07 (C-2′/6′), 126.59 (C-4′), 128.47 (C-3′/5′), 147.57 (C-1′), 177.60 (C-6); $C_{16}H_{24}N_2O$ (260.38) calcd: C, 73.20; H, 9.30; N, 10.75; found: C, 73.51; H, 9.46; N, 10.80.

4.3.15. (αR,1R,2S)-2-Ethyl-1-(1-phenylethylamino)cyclopentanecarboxamide ***4.2C***

Colorless oil; $[\alpha]_D^{25}$ = –2.2 (*c* 0.57, CH_3OH); IR: ν = 3442, 2963, 2864, 1674, 1453, 1372, 1205, 1111, 910, 763, 701 cm^{-1}; ^1H NMR ($CDCl_3$): 0.85 (t, *J* = 7.4 Hz, 3H, CH_2-C*H*$_3$), 1.10/1.23 (m, 2H, C*H*$_2$-CH_3), 1.20/1.94 (m, 2H, 3-C*H*$_2$), 1.29 (d, *J* = 6.6 Hz, 3H, β-C*H*$_3$), 1.60/1.60 (m, 2H, 4-C*H*$_2$), 1.88/2.21 (m, 2H, 5-C*H*$_2$), 1.94 (m, 1H, 2-*H*), 3.79 (q, *J* = 6.6 Hz, 1H, α-C*H*), 7.1–7.4 (m, 5H, aromatic *H*), 5.9/7.4 (s(b), 2H, N*H* (amide)); ^{13}C NMR ($CDCl_3$): 12.87 (CH_2-*C*H_3), 21.38 (C-4), 21.45 (*C*H_2-CH_3), 24.94 (β-CH_3), 29.25 (C-3), 30.27 (C-5), 52.57 (C-2), 54.14 (C-α), 70.75 (C-1), 126.09 (C-2′/6′), 127.01 (C-4′), 128.55 (C-3′/5′), 147.08 (C-1′), 180.10 (C-6); $C_{16}H_{24}N_2O$ (260.38) calcd: C, 73.20; H, 9.30; N, 10.75; found: C, 73.16; H, 9.20; N, 10.68.

4.3.16. (αR,1S,2R)-2-Ethyl-1-(1-phenylethylamino)cyclopentanecarboxamide ***4.2D***

Colorless oil; $[\alpha]_D^{25}$ = +38.2 (*c* 0.27, CH_3OH); IR: ν = 3445, 2962, 2877, 1672, 1556, 1453, 1371, 1274, 1206, 1105, 911, 756, 702 cm^{-1}; ^1H NMR ($CDCl_3$): 0.90 (t, *J* = 7.3 Hz, 3H, CH_2-C*H*$_3$), 1.26/1.58 (m, 2H, C*H*$_2$-CH_3), 1.36/2.08 (m, 2H, 3-C*H*$_2$), 1.37 (d, *J* = 6.8 Hz, 3H, β-C*H*$_3$), 1.73/1.85 (m, 2H, 4-C*H*$_2$), 2.02 (m, 1H, 2-*H*), 2.02/2.38 (m, 2H, 5-C*H*$_2$), 3.76 (q, *J* = 6.6 Hz, 1H, α-C*H*), 7.1–7.4 (m, 5H, aromatic *H*), 5.3/6.7 (s(b), 2H, N*H* (amide)); ^{13}C NMR ($CDCl_3$): 12.85 (CH_2-*C*H_3), 21.57 (C-4), 21.67 (*C*H_2-CH_3), 27.16 (β-CH_3), 29.60 (C-3), 31.97 (C-5), 52.09 (C-2), 53.53 (C-α), 72.05 (C-1), 126.05 (C-2′/6′), 126.67 (C-4′), 128.57 (C-3′/5′), 147.53 (C-1′), 178.98 (C-6); $C_{16}H_{24}N_2O$ (260.38) calcd: C, 73.20; H, 9.30; N, 10.75; found: C, 72.42; H, 9.09; N, 10.49.

4.3.17. (αR,1R,2S)-2-(1-Methylethyl)-1-(1-phenylethylamino)cyclopentanecarboxamide ***4.3A***

Colorless oil; $[\alpha]_D^{25}$ = +71.4 (*c* 0.65, CH_3OH), IR: ν = 3446, 2958, 2871, 1671, 1602, 1452, 1370, 1275, 1200, 1026, 760, 701 cm^{-1}; ^1H NMR ($CDCl_3$): 0.81 (d, *J* = 6.8 Hz, 3H, CH(C*H*$_3$)$_2$), 0.90 (d, *J* = 6.8 Hz, 3H, CH(C*H*$_3$)$_2$), 1.30 (d, *J* = 6.8 Hz, 3H, β-C*H*$_3$), 1.44/1.74 (m, 2H, 4-C*H*$_2$), 1.52/1.71 (m, 2H, 3-C*H*$_2$), 1.55 (m, 1H, 2-*H*), 1.65/2.13 (m, 2H, 5-C*H*$_2$), 1.78 (m, 1H, C*H*(CH$_3$)$_2$), 3.88 (q, *J* = 6.7 Hz, 1H, α-C*H*), 7.2–7.4 (m, 5H, aromatic *H*), 5.8/7.4 (s(b), 2H, N*H* (amide)); ^{13}C NMR

($CDCl_3$): 20.19 ($CH(CH_3)_2$), 22.30 (C-4), 23.69 ($CH(CH_3)_2$), 25.56 (β-CH_3), 26.58 (C-3), 28.44 ($CH(CH_3)_2$), 32.73 (C-5), 55.04 (C-α), 59.29 (C-2), 72.47 (C-1), 126.16 (C-2′/6′), 126.92 (C-4′), 128.56 (C-3′/5′), 147.48 (C-1′) 179.39 (C-6); $C_{17}H_{26}N_2O$ (274.41) calcd: C, 74.40; H, 9.56; N, 10.20; found: C, 73.89; H, 9.58; N, 10.16.

4.3.18. (αR,1S,2R)-2-(1-Methylethyl)-1-(1-phenylethylamino)cyclopentanecarboxamide ***4.3B***

Colorless oil; $[\alpha]_D^{25} = +3.8$ (*c* 0.61, CH_3OH); IR: $\nu = 3329$, 2960, 2870, 1673, 1608, 1561, 1449, 1383, 1275, 1201, 1130, 1026, 922, 760, 702 cm^{-1}; ^1H NMR ($CDCl_3$): 0.87 (d, $J = 6.6$ Hz, 3H, $CH(CH_3)_2$), 1.03 (d, $J = 6.6$ Hz, 3H, $CH(CH_3)_2$), 1.36 (d, $J = 6.8$ Hz, 3H, β-CH_3), 1.55 (m, 1H, 2-*H*), 1.58 (m, 1H, $CH(CH_3)_2$), 1.58/1.83 (m, 2H, 3-CH_2), 1.59/1.82 (m, 2H, 4-CH_2), 1.80/2.22 (m, 2H, 5-CH_2), 3.75 (q, $J = 6.8$ Hz, 1H, α-C*H*), 7.2–7.4 (m, 5H, aromatic *H*), 5.3/6.8 (s(b), 2H, N*H* (amide)); ^{13}C NMR ($CDCl_3$): 21.49 ($CH(CH_3)_2$), 22.58 (C-4), 23.44 ($CH(CH_3)_2$), 27.75 (β-CH_3), 28.74 (C-3), 28.83 ($CH(CH_3)_2$), 34.92 (C-5), 54.07 (C-α), 59.06 (C-2), 72.78 (C-1), 124.48 (C-3′/5′), 125.88 (C-2′/6′), 126.49 (C-4′), 147.98 (C-1′) 178.65 (C-6); $C_{17}H_{26}N_2O$ (274.41) calcd: C, 74.40; H, 9.56; N, 10.20; found: C, 74.56; H, 9.40; N, 9.82.

4.3.19. (αR,1R,2S)-2-(1,1-Dimethylethyl)-1-(1-phenylethylamino)cyclopentanecarboxamide ***4.4A***

Colorless oil; $[\alpha]_D^{25} = +65.7$ (*c* 0.33, CH_3OH); IR: $\nu = 3442$, 3252, 2961, 2870, 1673, 1563, 1450, 1368, 1313, 1216, 1132, 1024, 910, 759, 701 cm^{-1}; ^1H NMR ($CDCl_3$): 1.01 (s, 9H,$C(CH_3)_3$), 1.32 (d, $J = 6.8$ Hz, 3H, β-CH_3), 1.45/1.80 (m, 2H, 4-CH_2), 1.63/2.08 (m, 2H, 5-CH_2), 1.67 (m, 1H, 2-*H*), 1.77/1.77 (m, 2H, 3-CH_2), 3.87 (q, $J = 6.6$ Hz, 1H, α-C*H*), 7.1–7.4 (m, 5H, aromatic *H*), 5.9/7.5 (s(b), 2H, N*H* (amide)); ^{13}C NMR ($CDCl_3$): 21.30 (C-4), 26.19 (C-3), 26.19 (β-CH_3), 28.94 ($C(CH_3)_3$), 33.18 ($C(CH_3)_3$), 33.34 (C-5), 55.41 (C-α), 63.86 (C-2), 71.07 (C-1), 125.92 (C-2′/6′), 126.72 (C-4′), 128.54 (C-3′/5′), 147.98 (C-1′), 179.82 (C-6); $C_{18}H_{28}N_2O$ (288.44) calcd: C, 74.95; H, 9.79; N, 9.70; found: C, 74.96; H, 9.70; N, 9.15.

4.3.20. (αR,1S,2R)-2-(1,1-Dimethylethyl)-1-(1-phenylethylamino)cyclopentanecarboxamide ***4.4B***

Colorless oil; $[\alpha]_D^{25} = -6.2$ (*c* 0.66, CH_3OH); IR: $\nu = 3450$, 3336, 2960, 2870, 1678, 1552, 1450, 1369, 1313, 1201, 1130, 1027, 761, 701 cm^{-1}; ^1H NMR ($CDCl_3$): 1.03 (s, 9H, $C(CH_3)_3$), 1.37 (d, $J = 6.8$ Hz, 3H, β-CH_3), 1.67/1.94 (m, 2H, 4-CH_2), 1.71 (m, 1H, 2-*H*), 1.75/1.75 (m, 2H, 3-CH_2), 1.83/2.36 (m, 2H, 5-CH_2), 3.80 (q, $J = 6.8$ Hz, 1H, α-C*H*), 7.1–7.4 (m, 5H, aromatic *H*), 5.1/6.8 (s(b), 2H, N*H* (amide)); ^{13}C NMR ($CDCl_3$): 21.37 (C-4), 26.53 (C-3), 28.39 (β-CH_3), 29.20 ($C(CH_3)_3$), 33.03 ($C(CH_3)_3$), 36.96 (C-5), 54.75 (C-α), 63.40 (C-2), 71.64 (C-1), 125.83 (C-2′/6′), 126.47 (C-4′), 128.53 (C-3′/5′), 148.32 (C-1′), 178.83 (C-6); $C_{18}H_{28}N_2O$ (288.44) calcd: C, 74.95; H, 9.79; N, 9.70; found: C, 75.40; H, 9.93; N, 9.37.

4.4. 1-Amino-2-alkylcyclopentanecarboxamides ***5.1-4***

To a solution of 1 mmol of the diastereomerically pure α-amino carboxamides **4.1A**–**D**, **4.2A**–**D**, **4.3A**–**B** and **4.4A**–**B**, respectively, in 50 mL of CH_3OH, 280 mg of Pd/C (10%) and 510 mg of ammonium formiate were added and the mixture was refluxed for 1 h. The cooled solution was filtered over Celite and the solvent was evaporated yielding the oily α-amino amides which were dried in vacuo. For microanalysis the oily α-amino amides were converted into their hydrochloride salts using ether saturated with HCl gas.

4.4.1. (1R,2R)-1-Amino-2-methylcyclopentanecarboxamide ***5.1A***

Yield: 91%; colorless oil; $[\alpha]_D^{25} = -37.1$ (*c* 1.0, CH_3OH); IR: $\nu = 3336$, 2963, 2875, 1658, 1459, 1383, 1355, 1208, 1125 cm^{-1}; ^1H NMR ($CDCl_3$): 0.97 (d, $J = 6.8$ Hz, 3H, 2-CH_3), 1.47/2.46 (m, 2H, 5-CH_2), 1.52/1.88 (m, 2H, 3-CH_2), 1.70/1.83 (m, 2H, 4-CH_2), 1.73 (m, 1H, 2-*H*), 1.6 (s(b), 2H, N*H* (amine)), 5.7/7.2 (s(b), 2H, N*H* (amide)); ^{13}C NMR ($CDCl_3$): 15.63 (2-CH_3), 22.58 (C-4), 33.35 (C-3), 39.96 (C-5), 47.85 (C-2), 67.65 (C-1), 178.82 (C-6); $C_7H_{14}N_2O$ (142.20).

4.4.2. (1R,2R)-1-Amino-2-methylcyclopentanecarboxamide hydrochloride ***5.1A*** *× HCl*

Mp: 234°C; $C_7H_{15}N_2OCl$ (178.52) calcd: C, 47.09; H, 8.47; N, 15.68; found: C, 47.19; H, 8.57; N, 15.82.

4.4.3. (1S,2S)-1-Amino-2-methylcyclopentanecarboxamide ***5.1B***

Yield: 92%; colorless oil; $[\alpha]_D^{25} = +37.7$ (*c* 0.5, CH_3OH); IR, ^1H NMR and ^{13}C NMR data are identical with those of **5.1A**.

4.4.4. (1S,2S)-1-Amino-2-methylcyclopentanecarboxamide hydrochloride ***5.1B*** *× HCl*

Mp: 238°C; $C_7H_{15}N_2OCl$ (178.52) calcd: C, 47.09; H, 8.47; N, 15.68; found: C, 47.10; H, 8.46; N, 15.83.

4.4.5. (1R,2S)-1-Amino-2-methylcyclopentanecarboxamide ***5.1C***

Yield: 90%; colorless oil; $[\alpha]_D^{25} = +16.8$ (*c* 0.69, CH_3OH); IR: $\nu = 3324$, 2957, 2874, 1662, 1454, 1384, 1216, 1106 cm^{-1}; ^1H NMR ($CDCl_3$): 0.88 (d, $J = 6.8$ Hz, 3H, 2-CH_3), 1.29/1.90 (m, 2H, 3-CH_2), 1.55/2.25 (m, 2H, 5-CH_2), 1.6–1.8 (m, 2H, 4-CH_2), 2.49 (m, 1H, 2-*H*), 1.3 (s(b), 2H, N*H* (amine)), 5.9/7.5 (s(b), 2H, N*H* (amide)), ^{13}C NMR ($CDCl_3$): 12.83 (2-CH_3), 21.71 (C-4), 31.41 (C-3), 40.05 (C-5), 42.01 (C-2), 66.76 (C-1), 179.92 (C-6).

4.4.6. (1R,2S)-1-Amino-2-methylcyclopentanecarboxamide hydrochloride ***5.1C*** *× HCl*

Mp: 235°C; $C_7H_{15}N_2OCl$ (178.52) calcd: C, 47.09; H, 8.47; N, 15.68; found: C, 47.17; H, 8.57; N, 15.83.

4.4.7. (1S,2R)-1-Amino-2-methylcyclopentanecarboxamide ***5.1D***

Yield: 72%; colorless oil; $[\alpha]_D^{25} = -12.7$ (*c* 0.4, CH_3OH); IR, ^1H NMR and ^{13}C NMR data are identical with those of **5.1C**; $C_7H_{14}N_2O$ (142.20) calcd: C, 59.12; H, 9.93; N, 19.69; found: C, 58.87; H, 9.83; N, 19.42.

4.4.8. (1R,2R)-1-Amino-2-ethylcyclopentanecarboxamide ***5.2A***

Yield: 97%; oil; $[\alpha]_D^{25} = -44.8$ (*c* 1.0, CH_3OH); IR: $\nu = 3282$, 2959, 2869, 1677, 1456, 1384, 1201, 1119 cm^{-1}; ^1H NMR ($CDCl_3$): 0.82 (t, $J = 7.2$ Hz, 3H, CH_2-CH_3), 1.09/1.48 (m, 2H, CH_2-CH_3), 1.38/1.85 (m, 2H, 3-CH_2), 1.40 (m, 1H, 2-*H*), 1.42/2.30 (m, 2H, 5-CH_2), 1.62/1.72 (m, 2H, 4-CH_2), 1.9 (s(b), 2H, N*H* (amine)), 6.3/7.2 (s(b), 2H, N*H* (amide)); ^{13}C NMR ($CDCl_3$): 13.07 (CH_2-*C*H_3), 22.61 (C-4), 23.43 (*C*H_2-CH_3), 30.69 (C-3), 40.46 (C-5), 55.40 (C-2), 67.26 (C-1), 179.22 (C-6).

4.4.9. (1R,2R)-1-Amino-2-ethylcyclopentanecarboxamide hydrochloride ***5.2A*** *× HCl*

Mp: 244°C; $C_8H_{17}N_2OCl$ (192.68) calcd: C, 49.86; H, 8.90; N, 14.53; found: C, 49.73; H, 8.89; N, 14.61.

4.4.10. (1S,2S)-1-Amino-2-ethylcyclopentanecarboxamide ***5.2B***

Yield: 91%; oil; $[\alpha]_D^{25} = +47.9$ (*c* 1.0, CH_3OH), IR, ^1H NMR and ^{13}C NMR data are identical with those of **5.2A**.

4.4.11. (1S,2S)-1-Amino-2-ethylcyclopentanecarboxamide hydrochloride ***5.2B*** *× HCl*

Mp: 246°C; $C_8H_{17}N_2OCl$ (192.68) calcd: C, 49.86; H, 8.90; N, 14.53; found: C, 49.66; H, 8.90; N, 14.64.

4.4.12. (1R,2S)-1-Amino-2-ethylcyclopentanecarboxamide ***5.2C***

Yield: 93%; oil; $[\alpha]_D^{25} = +17.9$ (*c* 1.0, CH_3OH); IR: $\nu = 3301$, 2951, 2866, 1667, 1407, 1192, 1182 cm^{-1}; ^1H NMR ($CDCl_3$): 0.84 (t, $J = 7.3$ Hz, 3H, CH_2-CH_3), 1.11/1.30 (m, 2H, CH_2-CH_3), 1.20/1.91 (m, 2H, 3-CH_2), 1.48/2.15 (m, 2H, 5-CH_2), 1.69/1.69 (m, 2H, 4-CH_2), 2.26 (m, 1H, 2-*H*), 1.5 (s(b), 2H, N*H* (amine)), 6.3/7.5 (s(b), 2H, N*H* (amide)); ^{13}C NMR ($CDCl_3$): 12.62 (CH_2-*C*H_3), 21.47 (C-4), 22.00 (*C*H_2-CH_3), 29.08 (C-3), 40.34 (C-5), 49.06 (C-2), 66.31 (C-1), 180.39 (C-6).

4.4.13. (1R,2S)-1-Amino-2-ethylcyclopentanecarboxamide hydrochloride ***5.2C*** *× HCl*

Mp: 247°C; $C_8H_{17}N_2OCl$ (192.68) calcd: C, 49.86; H, 8.90; N, 14.53; found: C, 49.64; H, 8.88; N, 14.43.

4.4.14. (1S,2R)-1-Amino-2-ethylcyclopentanecarboxamide ***5.2D***

Yield: 89%; oil; $[\alpha]_D^{25} = -14.3$ (*c* 0.35, CH_3OH); IR, ^1H NMR and ^{13}C NMR data are identical with those of **5.2C**.

4.4.15. (1S,2R)-1-Amino-2-ethylcyclopentanecarboxamide hydrochloride ***5.2D*** *× HCl*

Mp: 243°C; $C_8H_{17}N_2OCl$ (192.68) calcd: C, 49.86; H, 8.90; N, 14.53; found: C, 49.73; H, 8.88; N, 14,70.

4.4.16. (1R,2S)-1-Amino-2-(1-methylethyl)cyclopentanecarboxamide ***5.3A***

Yield: 99%; oil; $[\alpha]_D^{25} = -10.0$ (*c* 1.0, CH_3OH); IR: $\nu = 3300$, 2960, 2871, 1665, 1469, 1385, 1366, 1204 cm^{-1}; ^1H NMR ($CDCl_3$): 0.72 (d, $J = 6.6$ Hz, 3H, $CH(CH_3)_2$), 0.84 (d, $J = 6.6$ Hz, 3H, $CH(CH_3)_2$), 1.36 (m, 1H, 2-*H*), 1.54/2.30 (m, 2H, 5-CH_2), 1.60/1.90 (m, 2H, 3-CH_2), 1.61/1.76 (m, 2H, 4-CH_2), 1.80 (m, 1H, C*H*(CH_3)$_2$), 2.5 (s(b), 2H, N*H* (amine)), 6.6/7.4 (s(b), 2H, N*H* (amide)); ^{13}C NMR ($CDCl_3$): 21.96 ($CH(CH_3)_2$), 22.49 ($CH(CH_3)_2$), 22.58 (C-4), 29.06 (C-1″), 31.42 (C-3), 42.78 (C-5), 61.72 (C-2), 66.42 (C-1), 179.85 (C-6).

4.4.17. (1R,2S)-1-Amino-2-(1-methylethyl)cyclopentanecarboxamide hydrochloride ***5.3A*** *× HCl*

Mp: 237°C; $C_9H_{19}N_2OCl$ (206.71) calcd: C, 52.29; H, 9.27; N, 13.54; found: C, 52.39; H, 9.80; N, 13.21.

4.4.18. (1S,2R)-1-Amino-2-(1-methylethyl)cyclopentanecarboxamide ***5.3B***

Yield: 97%; oil; $[\alpha]_D^{25} = +11.7$ (*c* 1.0, CH_3OH); IR, ^1H NMR and ^{13}C NMR data are identical with those of **5.3A**.

4.4.19. (1S,2R)-1-Amino-2-(1-methylethyl)cyclopentanecarboxamide hydrochloride ***5.3B*** *× HCl*

Mp: 236°C; $C_9H_{19}N_2OCl$ (206.71) calcd: C, 52.29; H, 9.27; N, 13.54; found: C, 52.28; H, 9.33; N, 13.47.

4.4.20. (1R,2S)-1-Amino-2-(1,1-dimethylethyl)cyclopentanecarboxamide ***5.4A***

Yield: 80%; mp: 68°C; $[\alpha]_D^{25} = -18.6$ (*c* 1.0, CH_3OH); IR: $\nu = 3438$, 2957, 1668, 1477, 1397, 1368, 1215, 755 cm^{-1}; ^1H NMR ($CDCl_3$): 0.94 (s, 9H, C(CH_3)$_3$), 1.56/2.32 (m, 2H, 5-CH_2), 1.65 (m, 1H, 2-*H*), 1.68/1.86 (m, 2H, 4-CH_2), 1.86/1.96 (m, 2H, 3-CH_2), 2.2 (s(b), 2H, N*H* (amine)), 6.3/7.4 (s(b), 2H, N*H* (amide)); ^{13}C NMR ($CDCl_3$): 21.27 (C-4), 27.60 (C-3), 28.95 (C(CH_3)$_3$), 32.73 ($C(CH_3)_3$), 44.50 (C-5), 63.79 (C-2), 65.49 (C-1), 180.13 (C-6); $C_{10}H_{20}N_2O$ (184.28) calcd: C, 65.18; H, 10.95; N, 15.19; found: C, 65.04; H, 10.79; N, 14.76.

4.4.21. (1S,2R)-1-Amino-2-(1,1-dimethylethyl)cyclopentanecarboxamide ***5.4B***

Yield: 82%; mp: 65°C; $[\alpha]_D^{25} = +19.8$ (*c* 1.0, CH_3OH); IR, ^1H NMR and ^{13}C NMR data are identical with those of **5.4A**; $C_{10}H_{20}N_2O$ (184.28) calcd: C, 65.18; H, 10.95; N, 15.19; found: C, 65.21; H, 10.98; N, 15.08.

4.5. 1-Amino-2-alkylcyclopentanecarboxylic acids ***6.1-4***

An amount of 1 mmol of the stereomerically pure α-amino carboxamides **5.1A**–**D**, **5.2A**–**D**, **5.3A**–**B**, and **5.4A**–**B**, respectively, were dissolved in 10 mL of concentrated hydrochloric acid and refluxed at 80°C for 10 h. The solution was evaporated to dryness, the residue was dissolved in water and chromatographed using strong acid ion exchang resin (Merck Eurolab GmbH Art. 4765) and 1 M ammonia as the eluent. The combined fractions were concentrated in vacuo yielding the α-amino acids **6.1A**–**D**, **6.2A**–**D**, 6.**3A**–**B**, and **6.4A**–**B** in the zwitterionic form.

4.5.1. (1R,2R)-1-Amino-2-methylcyclopentanecarboxylic acid ***6.1A***

Yield: 92%; mp: 280°C (decomp); $[\alpha]_D^{25} = -16.3$ (*c* 0.63, CH_3OH); ^1H NMR (CD_3OD) 1.08 (d, $J = 6.7$ Hz, 3H, 2-CH_3), 1.69/1.89 (m, 2H, 3-CH_2), 1.76/1.87 (m, 2H, 4-CH_2), 1.78/2.46 (m, 2H, 5-CH_2), 2.00 (m, 1H, 2-*H*); ^{13}C NMR (CD_3OD): 15.06 (2-CH_3), 24.35 (C-4), 34.96 (C-3), 36.29 (C-5), 45.33 (C-2), 70.55 (C-1), 175.88 (C-6); $C_7H_{13}NO_2$ (143.18) calcd: C, 58.72; H, 9.16; N, 9.77; found: C, 58.61; H, 9.16; N, 9.72.

4.5.2. (1S,2S)-1-Amino-2-methylcyclopentanecarboxylic acid ***6.1B***

Yield: 91%; mp: 275°C (decomp); $[\alpha]_D^{25} = +20.1$ (*c* 0.47, CH_3OH); ^1H NMR and ^{13}C NMR data are identical with those of **6.1A**; $C_7H_{13}NO_2$ (143.18) calcd: C, 58.72; H, 9.16; N, 9.77; found: C, 58.53; H, 9.55; N, 9.85.

4.5.3. (1R,2S)-1-Amino-2-methylcyclopentanecarboxylic acid ***6.1C***

Yield: 91%; mp: 277°C (decomp); $[\alpha]_D^{25} = -17.4$ (c 0.49, CH_3OH); ^1H NMR (CD_3OD): 1.00 (d, $J = 7.2$ Hz, 3H, 2-CH_3), 1.40/1.98 (m, 2H, 3-CH_2), 1.79/1.79 (m, 2H, 4-CH_2), 1.82/2.39 (m, 2H, 5-CH_2), 2.50 (m, 1H, 2-*H*); ^{13}C NMR (CD_3OD): 13.25 (2-CH_3), 23.50 (C-4), 33.06 (C-3), 37.17 (C-5), 43.49 (C-2), 71.20 (C-1), 176.20 (C-6); $C_7H_{13}NO_2$ (143.18) calcd: C, 58.72; H, 9.16; N, 9.77; found: C, 58.62; H, 9.16; N, 9.61.

4.5.4. (1S,2R)-1-Amino-2-methylcyclopentanecarboxylic acid ***6.1D***

Yield: 87%; mp: 269°C (decomp); $[\alpha]_D^{25} = +20.5$ (*c* 0.49, CH_3OH); ^1H NMR and ^{13}C NMR data are identical with those of **6.1C**; $C_7H_{13}NO_2$ (143.18) calcd: C, 58.72; H, 9.16; N, 9.77; found: C, 58.59; H, 9.16; N, 9.58.

4.5.5. (1R,2R)-1-Amino-2-ethylcyclopentanecarboxylic acid ***6.2A***

Yield: 88%; mp: 267°C (decomp); $[\alpha]_D^{25} = -20.9$ (*c* 1.0, CH_3OH); ^1H NMR (CD_3OD): 0.92 (t, $J = 7.4$ Hz, 3H, CH_2-CH_3), 1.29/1.67 (m, 2H, CH_2-CH_3), 1.59/1.98 (m, 2H, 3-CH_2), 1.74/1.90 (m, 2H, 4-CH_2), 1.78 (m, 1H, 2-*H*), 1.79/2.42 (m, 2H, 5-CH_2); ^{13}C NMR (CD_3OD): 13.37 (CH_2-*C*H_3), 24.19 (*C*H_2-CH_3), 24.22 (C-4), 32.08 (C-3), 36.63 (C-5), 52.84 (C-2), 70.60 (C-1), 175.81 (C-6); $C_8H_{15}NO_2$ (157.21) calcd: C, 61.12; H, 9.62; N, 8.90; found: C, 60.67; H, 9.49; N, 8.72.

4.5.6. (1S,2S)-1-Amino-2-ethylcyclopentanecarboxylic acid ***6.2B***

Yield: 84%; mp: 269°C (decomp); $[\alpha]_D^{25} = +17.1$ (*c* 0.51, CH_3OH); ^1H NMR and ^{13}C NMR data are identical with those of **6.2A**; $C_8H_{15}NO_2$ (157.21) calcd: C, 61.12; H, 9.62; N, 8.90; found: C, 60.57; H, 9.27; N, 8.67.

4.5.7. (1R,2S)-1-Amino-2-ethylcyclopentanecarboxylic acid ***6.2C***

Yield: 81%; mp: 271°C (decomp); $[\alpha]_D^{25} = -22.7$ (*c* 0.52, CH_3OH); ^1H NMR (CD_3OD): 0.96 (t, $J = 7.4$ Hz, 3H, CH_2-CH_3), 1.22/1.54 (m, 2H, CH_2-CH_3), 1.35/2.08 (m, 2H, 3-CH_2), 1.81/1.81 (m, 2H, 4-CH_2), 1.82/2.38 (m, 2H, 5-CH_2), 2.35 (m, 1H, 2-*H*); ^{13}C NMR (CD_3OD): 13.32 (CH_2-*C*H_3), 22.96 (*C*H_2-CH_3), 23.17 (C-4), 30.49 (C-3), 37.47 (C-5), 50.65 (C-2), 71.01 (C-1), 177.00 (C-6); $C_8H_{15}NO_2$ (157.21) calcd: C, 61.12; H, 9.62; N, 8.90; found: C, 60.58; H, 9.43; N, 8.73.

4.5.8. (1S,2R)-1-Amino-2-ethylcyclopentanecarboxylic acid ***6.2D***

Yield: 80%; mp: 273°C (decomp); $[\alpha]_D^{25} = -20.1$ (*c* 0.63, CH_3OH); ^1H NMR and ^{13}C NMR data are identical with those of **6.2C**; $C_8H_{15}NO_2$ (157.21) calcd: C, 61.12; H, 9.62; N, 8.90; found: C, 60.46; H, 9.42; N, 8.62.

4.5.9. (1R,2S)-1-Amino-2-(1-methylethyl)cyclopentanecarboxylic acid ***6.3A***

Yield: 80%; mp: 254°C (decomp); $[\alpha]_D^{25} = -19.9$ (*c* 0.1, CH_3OH); ^1H NMR (CD_3OD): 0.92 (d, $J = 6.6$ Hz, 3H, $CH(CH_3)_2$), 1.02 (d, $J = 6.6$ Hz, 3H, $CH(CH_3)_2$), 1.62 (m, 1H, 2-*H*), 1.71/1.90 (m, 2H, 4-CH_2), 1.72/1.96 (m, 2H, 3-CH_2), 1.82/2.42 (m, 2H, 5-CH_2), 1.89 (m, 2H, C*H*$(CH_3)_2$); ^{13}C NMR (CD_3OD): 22.35 ($CH(CH_3)_2$), 23.13 ($CH(CH_3)_2$), 23.95 (C-4), 30.48 (*C*$H(CH_3)_2$), 32.25 (C-3), 38.45 (C-5), 58.63 (C-2), 69.84 (C-1), 176.27 (C-6); $C_9H_{17}NO_2 \times 0.5\ H_2O$ (180.24) calcd: C, 59,97; H, 10.07; N, 7.76; found: C, 59.80; H, 9.56; N, 7.78.

4.5.10. (1S,2R)-1-Amino-2-(1-methylethyl)cyclopentanecarboxylic acid ***6.3B***

Yield: 66%; mp: 257°C (decomp); $[\alpha]_D^{25} = +17.3$ (*c* 0.22, CH_3OH); ^1H NMR and ^{13}C NMR data are identical with those of **6.3A**; $C_9H_{17}NO_2$ (171.24) calcd: C, 63.12; H, 10.01; N, 8.17; found: C, 62.93; H, 9.88; N, 7.98.

4.5.11. (1R,2S)-1-Amino-2-(1,1-dimethylethyl)cyclopentanecarboxylic acid ***6.4A***

Yield: 55%; mp: 259°C (decomp); $[\alpha]_D^{25} = -22.1$ (*c* 0.5, CH_3OH); ^1H NMR (CD_3OD): 1.01 (s, 9H, C(CH_3)$_3$), 1.74/2.25 (m, 2H, 5-CH_2), 1.76/1.85 (m, 2H, 4-CH_2), 1.85 (m, 1H, 2-*H*), 1.91/1.91 (m, 2H, 3-CH_2); ^{13}C NMR (CD_3OD): 22.46 (C-4), 29.13 (C-3), 29.86 (C(*C*H_3)$_3$), 34.08 (*C*$(CH_3)_3$), 42.95 (C-5), 64.41 (C-2), 67.62 (C-1), 181.69 (C-6); $C_{10}H_{19}NO_2$ (185.26) calcd: C, 64.84; H, 10.35; N, 7.55; found: C, 64.19; H, 9.92; N, 7.23.

*4.5.12. (1S,2R)-1-Amino-2-(1,1-dimethylethyl)cyclopentanecarboxylic acid **6.4B***

Yield: 70%; mp: 255°C (decomp); $[\alpha]_D^{25} = +19.6$ (*c* 0.26, CH_3OH); ^1H NMR and ^{13}C NMR data are identical with those of **6.4A**; $C_{10}H_{19}NO_2$ (185.26) calcd: C, 64.84; H, 10.35; N, 7.55; found: C, H, N.

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