Reductive Ring Cleavage of 1-Alkyl-4-benzoylamino-5-phenyl-3-pyrazolidinones with Raney-Nickel Alloy. Synthesis of *N*-Benzoyl-3-alkylamino-3-phenylalanine Amides from *rel*-(4*R*,5*R*)-4-Benzoylamino-5-phenyl-3-pyrazolidinone

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rel-(4*R*,5*R*)-4-Benzoylamino-5-phenyl-3-pyrazolidinone (**1**) was alkylated at position 1 with carbonyl compounds **2a-g**. The corresponding *rel*-(4*R*,5*R*)-4-benzoylamino-5-phenyl-3-pyrazolidinone-1-azomethine imines **3a-g**, were treated with sodium borohydride to give *rel*-(4*R*,5*R*)-1-alkyl-4-benzoylamino-5-phenyl-3-pyrazolidinones **4a-g**. Reduction of pyrazolidinones **4a-g** with Raney-nickel alloy in methanolic potassium hydroxide furnished *rel*-(4*R*,5*R*)-*N*-benzoyl-3-alkylamino-3-phenylalanine amides **5a-f**.

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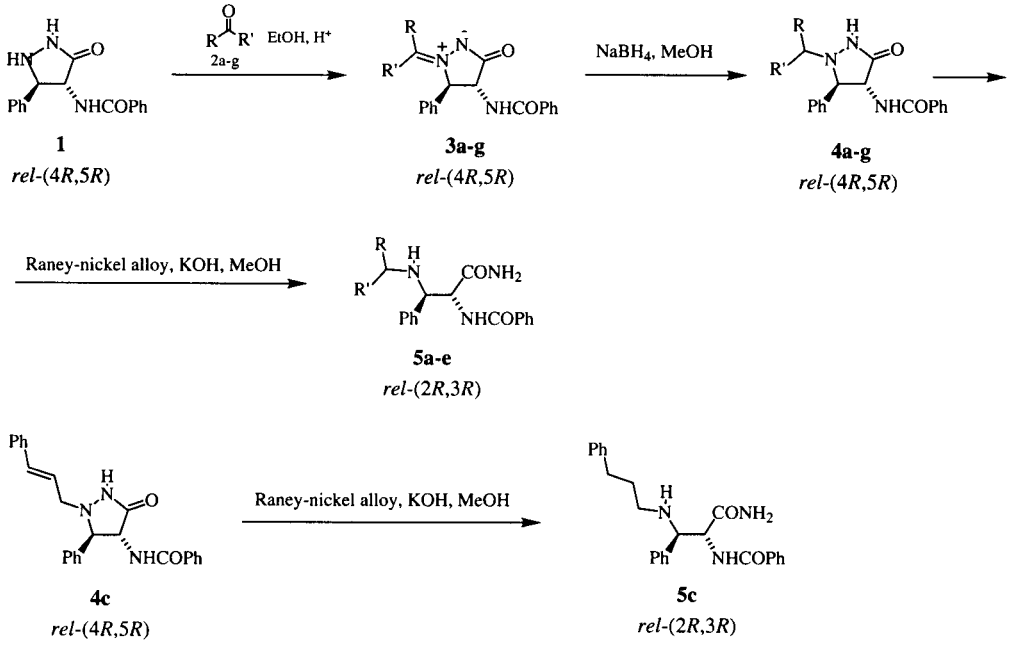
Since β-aminoalanines are non-proteinogenic amino acids widely found in nature, several synthetic methods for their preparation have been reported [1-6]. In continuation of our work in the field of the synthesis and transformation of substituted 3-pyrazolidinones [7] we report on a three step preparation of 3-alkylamino substituted 3-phenylalanine amides **5a-e** from *rel*-(4*R*,5*R*)-4-benzoylamino-5-phenyl-3-pyrazolidinone (**1**) *via* reduction of its azomethine imines **3a-e** followed by reductive N-N bond cleavage of *rel*-(4*R*,5*R*)-1-alkyl-4-benzoylamino-5-phenyl-3-pyrazolidinones **4a-e**.



1 *rel*-(4*R*,5*R*)

3a-g *rel*-(4*R*,5*R*)

4a-g *rel*-(4*R*,5*R*)

5a-e *rel*-(2*R*,3*R*)

4c *rel*-(4*R*,5*R*)

5c *rel*-(2*R*,3*R*)

Compounds **2-5**	R	R'
2a, 3a, 4a, 5a	phenyl	H
2b, 3b, 4b, 5b	4-methylphenyl	H
2c, 3c, 4c	2-phenylethenyl-1	H
5c	2-phenylethyl-1	H
2d, 3d, 4d, 5d	ethyl	H
2e, 3e, 4e, 5e	methyl	methyl
2f, 3f	cyclopentylidene	
4f	cyclopentyl	
2g, 3g, 4g	furyl-2	H

Formation of stable azomethine imines from 3-pyrazolidinones and carbonyl compounds is a general reaction which usually proceeds in high yields giving the corresponding 1,3-dipoles with *Z*-configuration around the exocyclic C=N double bond [7,8]. Catalytic hydrogenation of 3-pyrazolidinone-1-azomethine imines, which results in the saturation of a 1,3-dipole, have also been reported previously [8]. For our purpose, we started from *rel*-(4*R*,5*R*)-4-benzoylamino-5-phenyl-3-pyrazolidinone (**1**) [7] which was treated with the following carbonyl compounds: benzaldehyde (**2a**), 4-methylbenzaldehyde (**2b**), 3-phenylacrolein (**2c**), propionaldehyde (**2d**), acetone (**2e**), cyclopentanone (**2f**), and furfural (**2g**), to give the corresponding azomethine imines **3a-g**. Azomethine imines **3d-f** were not isolated in analytically pure form and were used subsequently for further transformations. Instead of catalytic hydrogenation, we chose sodium borohydride as the reducing reagent. Thus, treatment of azomethine imines **3a-g** with sodium borohydride in methanol afforded *rel*-(4*R*,5*R*)-1-alkyl-4-benzoylamino-5-phenyl-3-pyrazolidinones **4a-g** in 50-95% yields. Retention of relative configuration at the positions 4 and 5 in compounds **4a-g** was confirmed by nmr. The coupling constant between the protons at the positions 4 and 5 (J_{H4H5} = 10-11 Hz) clearly indicates that they are *trans*-oriented [7]. Treatment of 1-alkyl-3-pyrazolidinones **4a-e** with Raney-nickel alloy in 1*M* methanolic potassium hydroxide furnished the corresponding *N*-benzoyl-3-alkylamino-3-

Table 1

Experimental and Analytical Data

Compound	yield (%)	mp°C	Molecular Formula Analyses
3c	95	249-250 (from ethanol)	$C_{25}H_{21}N_3O_2$ Calcd.: C, 75.93; H, 5.35; N, 10.63 Found: C, 75.61; H, 5.30; N, 10.50
3g	88	242-243 (from ethanol)	$C_{21}H_{17}N_3O_3$ Calcd.: C, 70.18; H, 4.77; N, 11.69 Found: C, 70.26; H, 4.61; N, 11.77
4a	87	224-226 (from methanol)	$C_{23}H_{21}N_3O_2$ Calcd.: C, 74.37; H, 5.70; N, 11.31 Found: C, 74.50; H, 5.63; N, 11.42
4b	95	246-247 (from methanol)	$C_{24}H_{23}N_3O_2$ Calcd.: C, 74.78; H, 6.01; N, 10.90 Found: C, 74.82; H, 5.98; N, 10.93
4c	85	237-239 (from methanol)	$C_{25}H_{23}N_3O_2$ Calcd.: C, 75.55; H, 5.83; N, 10.57 Found: C, 75.49; H, 5.80; N, 10.54
4d	50	227-228 (from methanol)	$C_{19}H_{21}N_3O_2$ Calcd.: C, 70.57; H, 6.55; N, 12.99 Found: C, 70.67; H, 6.55; N, 13.01
4e	81	267-269 (from methanol)	$C_{19}H_{21}N_3O_2$ Calcd.: C, 70.57; H, 6.55; N, 12.99 Found: C, 70.85; H, 6.43; N, 13.12
4f	87	240-243 (from methanol)	$C_{21}H_{23}N_3O_2$ Calcd.: C, 72.18; H, 6.63; N, 12.03 Found: C, 72.04; H, 6.62; N, 11.72
4g	82	187-188 (from methanol)	$C_{21}H_{19}N_3O_3$ Calcd.: C, 69.79; H, 5.30; N, 11.63 Found: C, 70.04; H, 5.15; N, 11.86
5a	56	201-203 (from methanol/water)	$C_{23}H_{23}N_3O_2$ Calcd.: C, 73.97; H, 6.21; N, 11.25 Found: C, 73.73; H, 6.07; N, 11.35
5b	67	190-193 (from methanol/water)	$C_{24}H_{25}N_3O_2$ Calcd.: C, 74.39; H, 6.50; N, 10.84 Found: C, 74.10; H, 6.47; N, 10.68
5c	56	204-205 (from toluene)	$C_{25}H_{27}N_3O_2$ Calcd.: C, 74.79; H, 6.78; N, 10.46 Found: C, 74.46; H, 6.72; N, 10.79
5d	40	197-199 (from toluene)	$C_{19}H_{23}N_3O_2$ Calcd.: C, 70.13; H, 7.12; N, 12.91 Found: C, 70.45; H, 7.00; N, 12.82
5e	71	204-206 (from methanol)	$C_{19}H_{23}N_3O_2$ Calcd.: C, 70.13; H, 7.12; N, 12.91 Found: C, 70.14; H, 6.99; N, 13.07

phenylalanine amides **4a-e**. Ring cleavage of *rel*-(4*R*,5*R*)-4-benzoylamino-5-phenyl-1-(3-phenyl-2-propenyl-1)-3-pyrazolidinone (**4c**) was also accompanied by saturation of the 2-propenyl-1 residue at the position 1, giving *rel*-(2*R*,3*R*)-*N*-benzoyl-3-phenyl-3-[(3-phenylpropyl-1)amino]alanine amide (**5c**) as product (Scheme 1).

Structures of compounds **4a-g** and **5a-e** were confirmed by spectral characterisations and elemental analyses.

Table 2

^{1}H Nmr Data

Compound	^{1}H NMR (δ - Tetramethylsilane)
3c	4.73 (1H, dd, 4-H), 5.67 (1H, d, 5-H), 7.50 (18H, m, 15H-Ph, C*H*=C*H*-C*H*=), 9.30 (1H, d, NH), J_{H4H5} = 6.0 Hz, J_{CHNH} = 7.5 Hz
3g	4.73 (1H, dd, 4-H), 5.77 (1H, d, 5-H), 6.73 (1H, dd, 4'-H), 7.73 (13H, m, 10H-Ph, 3'-H, 5'-H, C*H*=N$^+$), 9.30 (1H, d, NH), J_{H4H5} = 5.0 Hz, J_{CHNH} = 8.0 Hz
4a	3.67 (1H, d, CH_2-Ha), 4.00 (1H, d, CH_2-Hb), 4.17 (1H, d, 5-H), 4.70 (1H, dd, 4-H), 7.50 (13H, m, 13H-Ph), 7.90 (2H, m, 2H-Ph), 9.03 (1H, d, N*H*COPh), 9.93 (1H, s, 2-H), $J_{CH2\ (gem)}$ = 14.2 Hz, J_{H4H5} = 10.3 Hz, J_{CHNH} = 8.0 Hz
4b	2.27 (3H, s, 4'-CH_3), 3.63 (1H, d, CH_2-Ha), 3.97 (1H, d, CH_2-Hb), 4.13 (1H, d, 5-H), 4.67 (1H, dd, 4-H), 7.53 (14H, m, 14H-Ph), 9.00 (1H, d, N*H*COPh), 9.90 (1H, s, 2-H), $J_{CH2\ (gem)}$ = 14.0 Hz, J_{H4H5} = 10.0 Hz, J_{CHNH} = 8.2 Hz
4c	3.47 (2H, br s, CH_2), 4.20 (1H, d, 5-H), 4.70 (1H, dd, 4-H), 6.47 (2H, m, C*H*=C*H*), 7.57 (15H, m, 15H-Ph), 9.00 (1H, d, N*H*COPh), 10.01 (1H, s, 2-H), J_{H4H5} = 11.0 Hz, J_{CHNH} = 9.0 Hz
4d	0.77 (3H, t, CH_3CH_2), 1.40 (2H, m, CH_2CH_3), 2.45 (2H, m CH_2N), 3.97 (1H, d, 5-H), 4.57 (1H, dd, 4-H), 7.40 (8H, m, 8H-Ph), 7.83 (2H, m, 2H-Ph), 8.93 (1H, d, N*H*COPh), 9.77 (1H, s, 2-H), J_{CH3CH2} = 6.0 Hz, J_{H4H5} = 11.0 Hz, J_{CHNH} = 8.0 Hz
4e	1.00 (6H, d, $(CH_3)_2$CH), 2.70 (1H, m, C*H*$(CH_3)_2$), 4.20 (1H, d, 5-H), 4.50 (1H, dd, 4-H), 7.47 (8H, m, 8H-Ph), 7.90 (2H, m, 2H-Ph), 8.93 (1H, d, N*H*COPh), 9.77 (1H, s, 2-H), J_{CH3CH} = 6.4 Hz, J_{H4H5} = 10.1 Hz, J_{CHNH} = 7.9 Hz
4f	1.50 (8H, m, 4CH_2-cyclopentyl), 3.07 (1H, m, C*H*,-cyclopentyl) 4.13 (1H, d, 5-H), 4.47 (1H, dd, 4-H), 7.45 (8H, m, 8H-Ph), 7.92 (2H, m, 2H-Ph), 9.03 (1H, d, N*H*COPh), 9.80 (1H, s, 2-H), J_{H4H5} = 10.0 Hz, J_{CHNH} = 8.0 Hz
4g	3.73 (1H, d, CH_2-Ha), 3.97 (1H, d, CH_2-Hb), 4.17 (1H, d, 5-H), 4.67 (1H, dd, 4-H), 6.33 (2H, m, 3'-H, 4'-H), 7.47 (9H, m, 8H-Ph, 5'-H), 7.93 (2H, m, 2H-Ph), 9.00 (1H, d, N*H*COPh), 9.93 (1H, s, 2-H), $J_{CH2(gem.)}$ = 15.0 Hz, J_{H4H5} = 10.5 Hz, J_{CHNH} = 8.5 Hz
5a	2.73 (1H, m, N*H*CH_2Ph), 3.48 (2H, m, CH_2Ph), 4.03 (1H, dd, 3-H), 4.70 (1H, dd, 2-H), 7.33 (17H, m, 15H-Ph, $CONH_2$), 8.17 (1H, d, N*H*COPh), J_{H2H3} = 8.0 Hz, $J_{CHNHCOPh}$ = 8.2 Hz, $J_{CHNHCH2Ph}$ = 7.2 Hz
5b	2.25 (3H, s, 4'-CH_3), 2.90 (1H, m, N*H*CH_2Ar), 3.43 (2H, m, CH_2Ph), 4.17 (1H, m, 3-H), 4.67 (1H, m, 2-H), 7.40 (16H, m, 10H-Ph, 4H-Ar, $CONH_2$), 8.17 (1H, d, N*H*COPh), $J_{CHNHCOPh}$ = 8.1 Hz
5c	1.67 (2H, m, Ph$CH_2CH_2CH_2$NH), 2.47 (5H, m, Ph$CH_2CH_2CH_2$N*H*), 4.00 (1H, m, 3-H), 4.67 (1H, dd, 2-H), 7.40 (17H, m, 15H-Ph, $CONH_2$), 8.20 (1H, d, N*H*COPh), J_{H2H3} = 9.5 Hz, $J_{CHNHCOPh}$ = 9.0 Hz
5d	0.80 (3H, t, CH_3CH_2), 1.10 (2H, m, CH_2CH_3), 2.27 (3H, m, N*H*CH_2), 4.00 (1H, m, 3-H), 4.60 (1H, dd, 2-H), 7.43 (12H, m, 10H-Ph, $CONH_2$), 8.20 (1H, d, N*H*COPh), J_{CH2CH3} = 6.0 Hz, J_{H2H3} = 8.0 Hz, $J_{CHNHCOPh}$ = 8.2 Hz
5e	0.90 (6H, d, $(CH_3)_2$CH), 2.30 (2H, m, $(CH_3)_2$C*H*N*H*), 4.08 (1H, m, 3-H), 4.63 (1H, dd, 2-H), 7.43 (12H, m, 10H-Ph, $CONH_2$), 8.17 (1H, d, N*H*COPh), J_{CHCH3} = J_{H2H3} = 6.0 Hz, $J_{CHNHCOPh}$ = 8.2 Hz

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^{1}H nmr spectra were obtained on a Varian E-360 (60 MHz) spectrometer with dimethyl-d_6 sulfoxide as the solvent and tetramethylsilane as internal standard. The microanalyses for C, H, and N were obtained on a Perkin-Elmer CHN Analyser 2400. *rel*-(4*R*,5*R*)-4-Benzoylamino-5-phenyl-3-pyrazolidinone (**1**), (1*Z*)-*rel*-(4*R*,5*R*)-1-benzylidene-4-benzoylamino-5-phenyl-3-pyrazolidinone-1-azomethine imine (**3a**), and (1*Z*)-*rel*-(4*R*,5*R*)-1-[(4-methylphenyl)methylidene]-4-benzoylamino-5-phenyl-3-pyrazolidinone-1-azomethine imine (**3b**) were prepared according to the procedures described in the literature [7]. The following compounds, (1*Z*)-*rel*-(4*R*,5*R*)-4-benzoylamino-5-phenyl-1-[(2-phenylethenyl-1)methylene]-3-pyrazolidinone-1-azomethine imine (**3c**) and (1*Z*)-*rel*-(4*R*,5*R*)-4-benzoylamino-1-(furyl-2)methylene-5-phenyl-3-pyrazolidinone-1-azomethine imine (**3g**), were prepared according to the same procedure.

(1*Z*)-*rel*-(4*R*,5*R*)-4-Benzoylamino-5-phenyl-1-[(2-phenylethenyl-1)methylene]-3-pyrazolidinone-1-azomethine imine (**3c**).

This compound was prepared from *rel*-(4*R*,5*R*)-4-benzoylamino-5-phenyl-3-pyrazolidinone (**1**, 1.405 g, 0.05 mole), anhydrous ethanol (20 ml), 3-phenylacrolein (**2c**, 0.792 g, 0.006 mole), and trifluoroacetic acid (5 drops). Analytical and spectral data for compound **3c** are given in Tables 1 and 2.

(1*Z*)-*rel*-(4*R*,5*R*)-4-Benzoylamino-1-(furyl-2)methylene-5-phenyl-3-pyrazolidinone-1-azomethine Imine (**3g**).

This compound was prepared from *rel*-(4*R*,5*R*)-4-benzoylamino-5-phenyl-3-pyrazolidinone (**1**, 1.405 g, 0.05 mole), anhydrous ethanol (25 ml), furfural (**2g**, 0.660 g, 0.006 mole), and trifluoroacetic acid (10 drops). Analytical and spectral data for compound **3g** are given in Tables 1 and 2.

rel-(4*R*,5*R*)-1-Alkyl-4-benzoylamino-5-phenyl-3-pyrazolidinones (**4a-c, g**).

General Procedure.

Sodium borohydride (0.190 g, 0.005 mole) was added in small portions to a stirred mixture of azomethine imines **3a-c, g** (0.005 mole) and methanol (25 ml). Stirring at room temperature was continued for 1 hour, the precipitate collected by filtration, and washed with ether to give pyrazolidinone **4a-c, g**. Analytical and spectral data for compounds **4a-c, g** are given in Tables 1 and 2.

rel-(4*R*,5*R*)-4-Benzoylamino-1-(propyl-1)-5-phenyl-3-pyrazolidinone (**4d**).

A mixture of *rel*-(4*R*,5*R*)-4-benzoylamino-5-phenyl-3-pyrazolidinone (**1**, 1.405 g, 0.05 mole), anhydrous ethanol (20 ml), and propionaldehyde (**2d**, 2.4 ml) was heated at reflux for 1 hour.

The resulting solution was cooled, sodium borohydride (0.380 g, 0.01 mole) added, the mixture heated at reflux temperature for 1 hour, and cooled again. The precipitate was collected by filtration, and washed with ether to give **4d**. Analytical and spectral data for compound **4d** are given in Tables 1 and 2.

rel-(4*R*,5*R*)-4-Benzoylamino-1-(propyl-2)-5-phenyl-3-pyrazolidinone (**4e**).

A mixture of *rel*-(4*R*,5*R*)-4-benzoylamino-5-phenyl-3-pyrazolidinone (**1**, 1.405 g, 0.05 mole), anhydrous ethanol (20 ml), acetone (**2e**, 20 ml), and trifluoroacetic acid (5 drops) was heated at reflux temperature for 30 minutes, cooled, and the precipitate collected by filtration to give a crude azomethine imine **3e**. The precipitate (**3e**, 3.105 g, "0.0048 mole") was suspended in methanol (25 ml) and, while stirring at room temperature, sodium borohydride (0.228 g, 0.006 mole) was added in small portions. The mixture was stirred for 1 hour, the precipitate collected by filtration, and washed with ether to give **4e**. Analytical and spectral data for compound **4e** are given in Tables 1 and 2.

rel-(4*R*,5*R*)-1-Cyclopentyl-4-benzoylamino-5-phenyl-3-pyrazolidinone (**4f**).

A mixture of *rel*-(4*R*,5*R*)-4-benzoylamino-5-phenyl-3-pyrazolidinone (**1**, 1.405 g, 0.05 mole), anhydrous ethanol (15 ml), cyclopentanone (**2f**, 5 ml), and trifluoroacetic acid (5 drops) was heated at reflux temperature for 1 hour, cooled, and the precipitate collected by filtration to give a crude azomethine imine **3f**. The precipitate (**3f**, 1.385 g, "0.004 mole") was suspended in methanol (20 ml) and, while stirring at room temperature, sodium borohydride (0.152 g, 0.004 mole) was added in small portions. The mixture was stirred for 1 hour, the precipitate collected by filtration, and washed with ether to give **4f**. Analytical and spectral data for compound **4f** are given in Tables 1 and 2.

rel-(2*R*,3*R*)-*N*-Benzoyl-3-alkylamino-3-phenylalanine amides (**5a-e**).

General Procedure.

1-Substituted-3-pyrazolidinone (**4a-e**, 0.005 mole) was dissolved in a stirred solution of potassium hydroxide (85%, 6.59 g, 0.1 mole) in a mixture of methanol (75 ml) and water (25 ml). Raney-nickel alloy (50%Al/50%Ni, 4 g) was added to the solution, stirred at room temperature for 3 hours, and undissolved material carefully removed by filtration [9]. Water (100 ml) was added to the filtrate and the precipitate collected by filtration to give **5a-e**. Analytical and spectral data for compounds **5a-e** are given in Tables 1 and 2.

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[9] Undissolved material consists mostly of Raney-nickel, which is pyrophoric. Care must be taken during filtration; nickel precipitate must always be kept wet and must not be allowed to dry!