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Synthesis of New Conformationally Rigid Phenylalanine Analogues.

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Abstract: *The reactivity of (Z)-2-phenyl-4-benzylidene-5(4H)-oxazolone* **1** *as dienophile in the Diels-Alder reaction with 1,3-butadiene and 2,3-dimethyl-1,3-butadiene is studied. The adducts obtained starting from the cycloaddition of* **1** *with both dienes are converted, through simple reactions, into the conformationally restricted cyclic amino acids cis-1-amino-2-phenylcyclohexanecarboxylic acid* **6** *and 1-amino-c-4,c-5-dimethyl-t-2-phenyl-r-1-cyclohexanecarboxylic acid* **10**, *analogues of phenylalanine.*

The interesting properties of α-amino acids with a conformational rigidity has attracted the attention of numerous research groups,[1] so the description of new products with these characteristics or new synthetic procedures to obtain these compounds is a subject of continuous interest. In particular the conformationally restricted cyclic amino acid analogues of phenylalanine (fig. 1) have proved to be useful for determining the importance of tyrosine conformation in the enkephalins on analgesic activity and receptor recognition.[2]

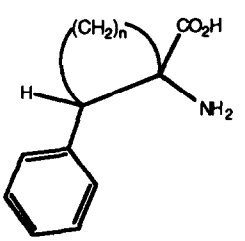
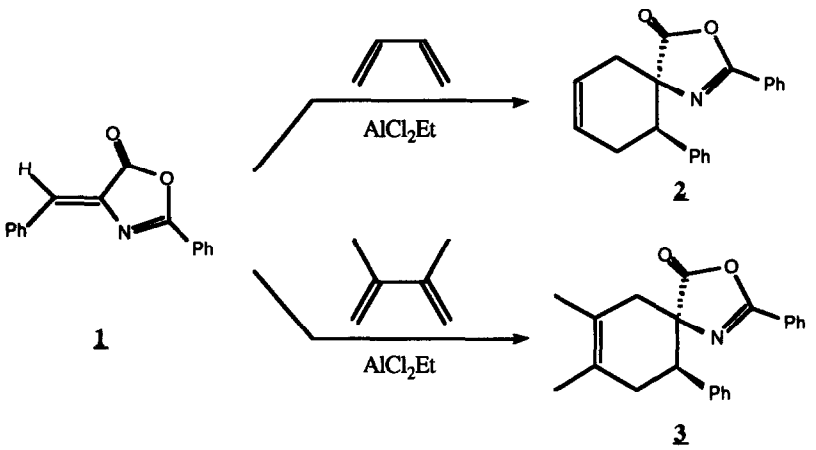


Fig. 1. Structure of conformationally rigid phenylalanine derivatives

In spite of the growing interest in these compounds only the corresponding cyclopropyl analogues (n=1) have received particular attention and the synthesis of each stereoisomer[3] as well as their asymmetric synthesis have been described.[4] Nevertheless, the corresponding six-membered derivatives have scarcely been considered, in spite of the fact they have been used to prepare some derivatives of cyclacillin with a view to studying their pharmacological activity[5] and to study the structural assignment of the stereoisomers of 1-amino-2-phenylcyclohexanecarboxylic acid.[6] Moreover, to the best of our knowledge, the title compounds have only been synthesized from 2-phenylcyclohexanone using the Bucherer[7] or the Strecker method.[8]

In the course of our research program on the synthesis of new conformationally-restricted cyclic amino acids of pharmacological interest, we have reported the reaction of 5(4H)-oxazolones as dienophiles and cyclopentadiene to describe the synthesis of new α-amino acid derivatives with a norbornane skeleton.[9] We would now like to report the study of the Diels-Alder reaction using other less reactive dienes such as 1,3-butadiene and 2,3-dimethyl-1,3-butadiene, which open the way to the synthesis of new 1-amino-2-phenylcyclohexanecarboxylic acid derivatives.



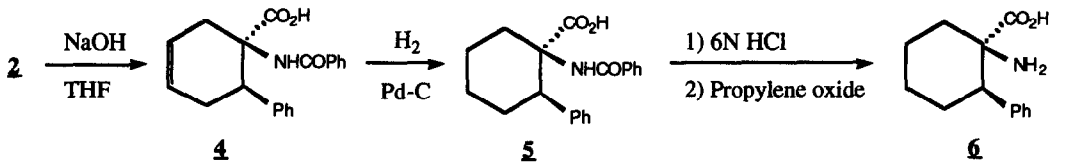
1 2 3

Scheme 1

Easily available (Z)-2-phenyl-4-benzylidene-5(4H)-oxazolone **1** was reacted with an excess of both dienes in dry methylene chloride using various Lewis acids as catalysts to give spiro-oxazolones **2** and **3**. It is well known that 1,3-butadiene is less reactive than 2,3-dimethyl-1,3-butadiene in Diels-Alder reactions with different dienophiles.[10] Thus, the 1,3-butadiene gave a 64% yield of adduct **2**, whereas the 2,3-dimethyl-1,3-butadiene gave adduct **3** in almost quantitative yield.

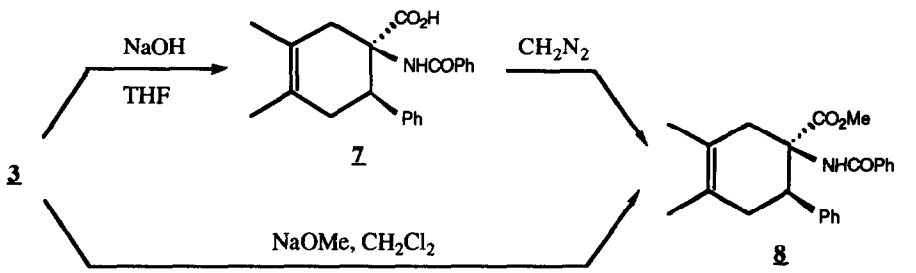
We have found that the Diels-Alder cycloaddition between oxazolone **1** and 2,3-dimethyl-1,3-butadiene was greatly accelerated by the use of aluminium ethyldichloride as a catalyst. So, when oxazolone **1**, 2,3-dimethyl-1,3-butadiene and aluminium ethyldichloride were used in a ratio 1:3:0.75 in methylene chloride solution, the yield of adduct **3** was quantitative in 48 h at -30° C. In similar conditions, a low yield of adduct **3** was obtained in the presence of other Lewis acids (titanium tetrachloride, aluminium trichloride...) as a catalyst. In the absence of a catalyst, no reaction took place.

In agreement with the previously reported results,[9] the stereospecific hydrolysis of the spiro-oxazolone-adduct **2** took place with excellent yield by treatment with a 5% aqueous solution of sodium hydroxide in tetrahydrofuran at room temperature to afford the N-benzoyl-α-amino acid **4**, which was hydrogenated, using 10% palladium-carbon as a catalyst to give quantitatively the corresponding N-benzoyl-α-amino acid **5**. This compound was hydrolysed in acid medium and the free α-amino acid **6** was obtained with propylene oxide using a typical procedure. (Scheme 2)



Scheme 2

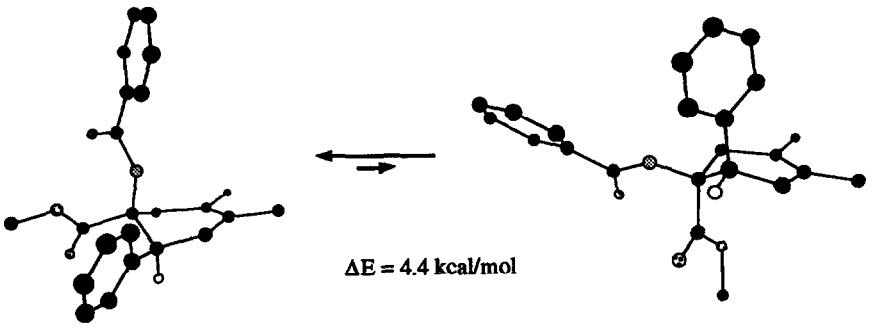
The stereospecific hydrolysis of the spiro-oxazolone-adduct **3** also took place with excellent yield to afford the N-benzoyl-α-amino acid **7**, but in this case as the hydrogenation of the double bond gave a mixture of two products which must be separated by column chromatography, we have preferred to obtain the methyl ester **8** favouring thus their separation. So, N-benzoyl-α-amino acid **7** was esterified with diazomethane to give quantitatively the corresponding methyl ester **8**. Similarly, compound **8** was obtained by the addition of sodium methoxide to a solution of spiro-oxazolone **3** in methylene chloride at room temperature. (Scheme 3)



Scheme 3

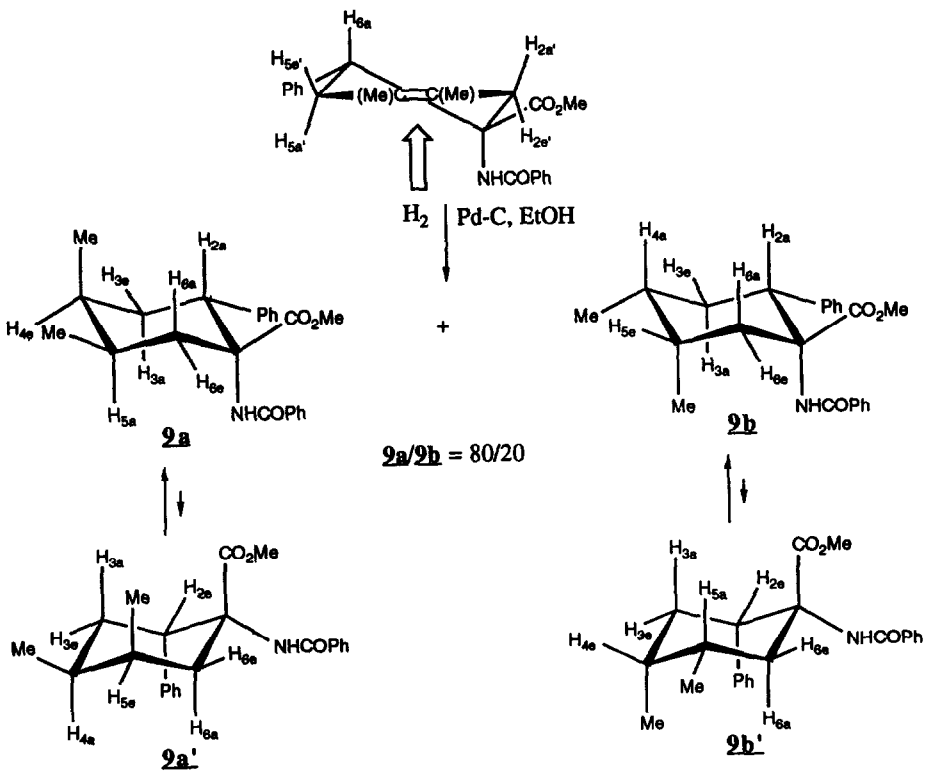
The heterogeneous hydrogenation of the double bond of compound **8** using 10% palladium-carbon as a catalyst did not occur at room temperature. It was necessary to heat at 50° C to obtain a mixture of two products in a ratio of 4:1 as determined by HPLC, which were separated by silica gel column chromatography. (Scheme 5)

In order to determine the stereochemistry of the hydrogenated products, several experiments and calculations were carried out. The lowest energy conformer of cycloadduct **8** was calculated by molecular mechanics, using the Chem 3D Plus™ program[11] and MM2 force field.[12] The geometry of the most favorable conformer of **8** was the half-chair conformation, where the phenyl and methyl ester groups adopted equatorial positions. This geometry is shown in Scheme 4.



Scheme 4

The addition of a hydrogen molecule to the double bond of product **8** can either take place on the same side of the benzamido group to give compound **9a** or on the opposite side to give compound **9b**. The geometries of the lowest energy conformers of both hydrogenated products **9a** and **9b**, calculated by Chem 3D Plus™ program, are the chair conformations where the phenyl group, the methyl ester group and one methyl group are in equatorial positions. These conformers are 5 kcal/mol more stable than the conformers that have the same groups in the axial positions, **9a'** and **9b'**. (Scheme 5).



Scheme 5

The geometry of products **2a** and **2b** was determined by consideration of their NMR spectral data. The aliphatic region of the ^{1}H-NMR spectrum corresponding to the protons attached to the cyclohexane ring of the major compound was comprised of six sets of distinct spin systems, one of which integrated for two protons while each of the other five integrated for one proton. The aliphatic region of the ^{1}H-NMR spectrum corresponding to the protons attached to the cyclohexane ring of the minor compound was composed of five sets of distinct spin systems, one of which integrated for three protons and each of the other four integrated for one proton. The assignment of all separate signals in the spectra was made on the basis of their coupling constants and irradiation experiments. The results are summarized in Table 1.

Protons (H_{6a}, H_{6e}, H_{3a}, H_{3e}, H_{2a}) are placed on the same spatial position in both cyclohexane structures **2a** and **2b**. However there are two important differences about the multiplicity and the value of the coupling constants of the H_{6a} and H_{3a} protons in both compounds. The H_{6a} proton, in the major compound, shows a doublet of doublets collapsed into a triplet system due to strong couplings with H_{6e} and H_{5a} protons ($J_{6a\text{-}6e} \approx J_{6a\text{-}5a}$ = 13.2 Hz) corresponding to the geminal coupling constant and to the axial-axial coupling constant, respectively. The H_{3a} proton shows a doublet of doublet of doublets collapsed into a triplet of doublets system. The large couplings observed in the triplet ($J_{3a\text{-}3e} \approx J_{3a\text{-}2a}$ = 13.8 Hz) show that the H_{3a} proton has an axial neighbour (H_{2a}) as well as a geminal partner (H_{3e}). Similarly, the weak coupling observed in the doublet ($J_{3a\text{-}4e}$ = 4.5 Hz) shows that the H_{3a} proton has an equatorial neighbour (H_{4e}), too. These results would only be explainable if the major product had the **2a** structure.

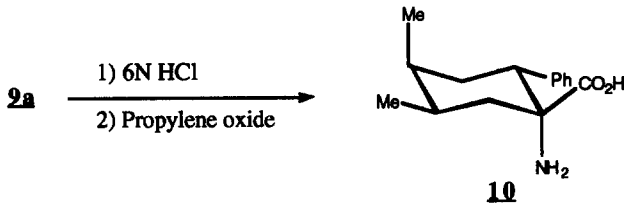
In order to confirm this stereochemistry, we have studied the ^{1}H-NMR spectrum of the minor compound and found that the H_{6a} proton showed a doublet of doublets system, strongly coupled with H_{6e} proton ($J_{geminal}$ = $J_{6a\text{-}6e}$ = 14.7 Hz) and more weakly with H_{5e} proton ($J_{axial\text{-}equatorial} = J_{6a\text{-}5e}$ = 5.1 Hz). So the minor compound has the **2b** structure.

Table 1. Selected ^{1}H-NMR Spectral Data for Major and Minor Hidrogenated Compounds.

	Major		Minor	
Proton	δ (ppm)	Coupling constants (Hz)	δ (ppm)	Coupling constants (Hz)
H_{2a}	3.41(dd)	$J_{2a\text{-}3e}$ = 2.4, $J_{2a\text{-}3a}$ = 13.8	3.28(dd)	$J_{2a\text{-}3e}$ = 4.5, $J_{2a\text{-}3a}$ = 12.0
H_{3a}	2.48(ddd)	$J_{3a\text{-}4e}$ = 4.5, $J_{3a\text{-}3e} \approx J_{3a\text{-}2a}$ = 13.8		
H_{3e}	1.68(ddd)	$J_{3e\text{-}4e} \approx J_{3e\text{-}2a}$ = 2.4, $J_{3e\text{-}3a}$ = 13.2		
H_{6a}	2.11(dd)	$J_{6a\text{-}6e} \approx J_{6a\text{-}5a}$=13.2	2.41(dd)	$J_{6a\text{-}5e}$ = 5.1, $J_{6a\text{-}6e}$ = 14.7
H_{6e}	2.93(dd)	$J_{6e\text{-}5a}$ = 3.0, $J_{6e\text{-}6a}$ = 13.2	3.29(dd)	$J_{6e\text{-}5e}$ = 2.1, $J_{6e\text{-}6a}$ = 14.7

We suppose that the remarkable stereochemical control in the hydrogenation is due to the presence of a coordinating function, the benzamido group, in the olefinic molecule which anchors itself on the catalyst surface in such a way that forces the addition of hydrogen to its own side of the molecule. There are many examples in the literature of this anchoring effect.[13]

The hydrolysis of the major hydrogenated product **2a** occurs without problems in acid medium and the isolation of free α-amino acid **10** takes place following the above-described procedure for α-amino acid **6**. (Scheme 6).



Scheme 6

In conclusion, two rigid amino acids analogues of phenylalanine were obtained starting from easily available (Z)-2-phenyl-4-benzylidene-5(4H)-oxazolone and further studies are in progress with a view to extending this new synthetic procedure to the synthesis of other rigid α-amino acids analogues of pharmacological interest.

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EXPERIMENTAL SECTION

Solvents were purified according to standard procedures. Analytical TLC was performed by using Kiesel 60 F_{254} plates. Column chromatography was performed by using Kiesel 60 (230-400 mesh) ^1H and ^{13}C-NMR spectra were recorded on a Varian UNITY 300. Deuteriochloroform was used as solvent with the solvent signal as the internal standard (the chemical shifts are reported in ppm on the δ scale). Melting points were determined on a Büchi SMP-20 melting point apparatus and are uncorrected. Microanalyses were carried out on a Perkin-Elmer 240-C analyser and were in good agreement with the calculated values. High Performance Liquid Chromatography (HPLC) was carried out with HP-1090 M equiped with 4.6 x 200mm column Hypersyl® C18 5 μm and monitored using a diode array detector.

***cis*-6-Phenylcyclohex-1-spiro-{4'[2'-phenyl-5'(4'H)oxazolone]}-3-ene. (2).**

A solution of 1 M $AlCl_2Et$ in hexane (0.75 mL) was added to a solution of oxazolone **1** (249 mg, 1 mmol) in dry CH_2Cl_2 (10 mL) kept under an inert atmosphere. After 1 h stirring at 0° C, a solution of 1,3-butadiene (594 mg, 11 mmol) in dry CH_2Cl_2 (5 mL), at the same temperature, was added dropwise and the mixture was stirred for a further 72 h at 0° C. The reaction was quenched by the addition of solid $Na_2CO_3 \cdot 10H_2O$, the precipitate was filtered and the solution was evaporated *in vacuo*. The residue was chromatographed on silicagel (hexane-ethyl acetate 9:1) to afford 194 mg (64%) of cycloadduct **2** as an oil.

Found: C: 79.24, H: 5.71, N: 4.51

Calc. for $C_{20}H_{17}NO_2$ C: 79.19, H: 5.65, N: 4.62

^1H-NMR($CDCl_3$): δ= 2.28-2.41 (m, 2H, $H_{5e'} + H_{5a'}$); 2.88-2.97 (m, 2H, $H_{2e'} + H_{2a'}$); 3.39(dd, 1H, $J_{6a\text{-}5e'}$ = 5.4 Hz, $J_{6a\text{-}5a'}$ = 11.8 Hz, H_{6a}); 5.84-5.87 (m, 1H, H_3); 6.00-6.03 (m, 1H, H_4); 7.11-7.22 (m, 5H, Ph-C_6); 7.40-7.57 (m, 3H, m,p-Ph-C=N); 7.88-7.94 (m, 2H, o-Ph-C=N). ^{13}C-NMR($CDCl_3$): δ= 28.8(C_5); 35.3(C_2); 46.3(C_6); 72.3(C_1); 122.0(C_3); 125.9(C_4); 127.1; 127.6; 127.9; 128.2; 128.6; 128.7; 132.5; 138.5(Arom.); 160.6(C=N); 179.9(CO).

***cis*-3,4-Dimethyl-6-phenylcyclohex-1-spiro-{4'[2'-phenyl-5'(4'H)oxazolone]}-3-ene. (3).**

A solution of 1 M $AlCl_2Et$ in hexane (6.6 mL) was added to a solution of oxazolone **1** (2 g, 8 mmol) in dry CH_2Cl_2 (40 mL) kept under an inert atmosphere. After 1 h stirring at -30° C, a solution of 2,3-dimethyl-1,3-butadiene (1.97 g, 24 mmol) in dry CH_2Cl_2 (5 mL), at the same temperature, was added dropwise and the mixture was stirred for a further 48 h at -30° C. The reaction was quenched by the addition of solid $Na_2CO_3 \cdot 10H_2O$, the precipitate was filtered and the solution was evaporated *in vacuo* to give cycloadduct **3**. Compound **3** was recrystallised from EtOH. Isolated yield 2.41 g (91%). Mp: 128-30° C.

Found: C: 79.84, H: 6.45, N: 4.33

Anal. Calc. for $C_{22}H_{21}NO_2$ C: 79.73, H: 6.39, N: 4.23

^{1}H-NMR($CDCl_3$): δ= 1.72 (s, 3H, Me); 1.78 (s, 3H, Me); 2.07-2.24 (m, 2H, $H_{5e'}$ + $H_{2e'}$); 2.81-2.96 (m, 2H, $H_{5a'}$ + $H_{2a'}$); 3.36 (dd, 1H, $J_{6a\text{-}5e'}$ = 4.8 Hz, $J_{6a\text{-}5a'}$ = 12.0 Hz, H_{6a}); 7.10-7.20 (m, 5H, Ph-C_6); 7.38-7.55 (m, 3H, m,p-Ph-C=N); 7.85-7.92 (m, 2H, o-Ph-C=N). ^{13}C-NMR($CDCl_3$): δ= 18.4(Me-C_4); 19.0(Me-C_3); 35.0(C_5); 41.2(C_2); 47.0(C_6); 73.2(C_1); 120.9(C_3); 125.9(C_4); 125.9; 127.5; 127.9; 128.1; 128.5; 128.6; 132.4; 138.5(Arom.); 160.4(C=N); 180.0(CO).

***cis*-1-Benzamido-6-phenyl-3-cyclohexen-1-carboxylic Acid. (4).**

To a solution of cycloadduct **2** (101 mg, 0.33 mmol) in THF (10 mL) was added 5% aq. NaOH (7.5 mL) and the mixture was stirred for 90 min at room temperature. THF was eliminated in vacuo and the aqueous layer was washed with ethyl ether (3 x 5 mL), acidified with 6 N HCl and extracted with ethyl ether (3 x 5 mL). The organic solution was dried over anhydrous Na_2SO_4 and the solvent evaporated *in vacuo* to afford cycloadduct acid **4**. Isolated yield 82 mg (77%).

Found: C: 74.68, H: 6.01, N: 4.30

Anal. Calc. for $C_{20}H_{19}NO_3$ C: 74.75, H: 5.96, N: 4.36

^{1}H-NMR(DMSO-d_6): δ= 2.26-2.40 (m, 2H, $H_{2a'}$ + $H_{2e'}$); 2.65-2.92 (m, 2H, $H_{5a'}$ + $H_{5e'}$); 3.63 (dd, 1H, $J_{6a\text{-}5e'}$ = 3.9 Hz, $J_{6a\text{-}5a'}$ = 6.6 Hz, H_{6a}); 5.62-5.70 (m, 1H, H_3); 5.72-5.80 (m, 1H, H_4); 6.31 (brs, 1H, NH); 7.08-7.43 (m, 10H, Arom.). ^{13}C-NMR(DMSO-d_6): δ= 29.2(C_5); 30.3(C_2); 42.4(C_6); 59.9(C_1); 123.7(C_3); 125.8(C_4); 126.6; 127.0; 128.0; 128.2; 128.3; 131.0; 134.3; 141.5(Arom.); 166.7(CONH); 173.6(CO).

***cis*-1-Benzamido-2-phenylcyclohexanecarboxylic Acid. (5).**

A solution of compound **4** (65 mg, 0.20 mmol) in absolute EtOH (15 mL) was hydrogenated at 30° C with 10% palladium-carbon (15 mg) as a catalyst, for 15 h. Removal of the catalyst and the solvent gave quantitatively the required compound **5** as an oil.

Found C: 73.98, H: 6.61, N: 4.28

Anal. Calc. for $C_{20}H_{21}NO_3$ C: 74.28, H: 6.55, N: 4.33

^{1}H-NMR($CDCl_3$): δ= 0.77-0.93 (m, 2H); 1.40-1.77 (m, 3H); 1.85-1.95 (m, 1H); 2.00-2.14 (m, 1H); 3.22 (m, 1H, H_{6e}); 3.43 (dd, 1H, $J_{2a\text{-}3e}$ = 3.3 Hz, $J_{2a\text{-}3a}$ = 12.9 Hz, H_{2a}); 6.31 (brs, 1H, NH); 7.24-7.56 (m, 8H, Arom.); 7.67-7.74 (m, 2H, Arom.). ^{13}C-NMR($CDCl_3$): δ= 25.4; 26.8; 29.4; 30.9(C_3, C_4, C_5, C_6); 48.1(C_2); 64.4(C_1); 126.7; 127.6; 127.7; 128.5; 128.8; 131.7; 134.3; 139.5(Arom.); 168.0(CONH); 175.5(CO).

***cis*-1-Amino-2-phenylcyclohexanecarboxylic Acid. (6).**

Compound **5** (55 mg, 0.17 mmol) was dissolved in 6 N HCl (10 mL) and refluxed for 48 h. The solvent was removed under reduced pressure. The residue of aminoacid hydrochloride was dissolved in EtOH (6 mL) and propylene oxide (2 mL) was added. The mixture was refluxed for 1 h and the precipitate was filtered to give 40 mg (83%) of amino acid **6** as a white solid.

Found C: 71.01, H: 7.91, N: 6.32

Anal. Calc. for $C_{13}H_{17}NO_2$ C: 71.21, H: 7.81, N: 6.39

^{1}H-NMR(D_2O/CF_3COOH): δ= 1.38-1.65 (m, 2H); 1.78-2.36 (m, 6H); 3.43 (dd, 1H, $J_{2a\text{-}3e}$ = 3.9 Hz, $J_{2a\text{-}3a}$ = 13.2 Hz, H_{2a}); 7.21-7.42 (m, 5H, Ph-C_2).

***cis*-1-Benzamido-3,4-dimethyl-6-phenyl-3-cyclohexen-1-carboxylic Acid. (7).**

To a solution of cycloadduct **3** (0.75 g, 2.27 mmol) in THF (30 mL) was added 5% aq. NaOH (20 mL) and the mixture was stirred for 90 min at room temperature. THF was eliminated in vacuo and the aqueous layer was washed with ethyl ether (3 x 15 mL), acidified with 6 N HCl and extracted with ethyl ether (3 x 15 mL). The organic solution was dried over anhydrous Na_2SO_4 and the solvent evaporated *in vacuo* to afford cycloadduct acid **7** Isolated yield 581 mg (73%). Mp: 167-9° C.

Found C: 75.69, H: 6.55, N: 4.15

Anal. Calc. for $C_{22}H_{23}NO_3$ C: 75.62, H: 6.63, N: 4.01

^{1}H-NMR(DMSO-d_6): δ= 1.65 (s, 6H, 2Me); 2.26 (d, 1H, $J_{2e'\text{-}2a'}$ = 17.5 Hz, $H_{2e'}$); 2.40 (d, 1H, $J_{2a'\text{-}2e'}$ = 17.5 Hz, $H_{2a'}$); 2.52 (d, 1H, $J_{5a'\text{-}5e'}$ = 15.6 Hz, $H_{5a'}$); 2.86 (dd, 1H, $J_{5e'\text{-}6a}$ = 5.0 Hz, $J_{5e'\text{-}5a'}$ = 15.6 Hz, $H_{5e'}$); 3.83 (d, 1H, $J_{6a\text{-}5e'}$ = 5.0 Hz, H_{6a}); 7.08-7.24 (m, 5H, Ph-C_6); 7.32-7.50 (m, 3H, m,p-Ph-C=N); 7.52-7.58 (m, 2H, o-Ph-C=N); 7.67 (brs, 1H, NH). ^{13}C-NMR(DMSO-d_6): δ= 18.3(Me-C_4); 19.1(Me-C_3); 36.3(C_5, C_2); 41.2(C_6); 60.2(C_1); 121.3(C_3); 125.2(C_4); 126.4; 127.4; 127.9; 128.0; 128.3; 131.0; 134.7; 143.4(Arom.); 166.7(CONH); 173.4(CO).

Methyl *cis*-1-Benzamido-3,4-dimethyl-6-phenyl-3-cyclohexen-1-carboxylate. (8).

Cycloadduct acid **7** was esterified as usual[9] with an excess of diazomethane in ethyl ether to give quantitatively the compound **8**, as a white solid. Mp: 172-4° C.

Found C: 75.89, H: 6.85, N: 3.95

Anal. Calc. for $C_{23}H_{25}NO_3$ C: 76.01, H: 6.93, N: 3.85

^{1}H-NMR($CDCl_3$): δ= 1.70 (s, 6H, 2Me); 2.31-2.40 (m, 1H, $H_{5e'}$); 2.44 (d, 1H, $J_{2e'\text{-}2a'}$ = 18.0 Hz, $H_{2e'}$); 2.57 (m, 1H, $H_{5a'}$); 2.96 (d, 1H, $J_{2a'\text{-}2e'}$ = 18.0 Hz, $H_{2a'}$); 3.57 (m, 1H, H_{6a}); 3.61 (s, 3H, CO_2Me); 6.17 (brs, 1H, NH); 7.24-7.58 (m, 10H, Arom.). ^{13}C-NMR($CDCl_3$): δ= 18.6(Me-C_4); 18.81(Me-C_3); 35.2(C_5); 36.8(C_2); 44.6(C_6); 52.3(CO_2Me); 61.0(C_1); 123.5(C_3); 123.7(C_4); 126.8; 127.6; 128.4; 128.5; 128.8; 131.5; 134.3; 141.1(Arom.); 166.7(CONH); 172.9(CO).

Methyl 1-Benzamido-*c*-4,*c*-5-dimethyl-*t*-2-phenyl-*r*-1-cyclohexanecarboxylate and Methyl 1-Benzamido-*t*-4,*t*-5-dimethyl-*t*-2-phenyl-*r*-1-cyclohexanecarboxylate. (9a) and (9b).

A solution of compound **8** (160 mg, 0.44 mmol) in absolute EtOH (60 mL) was hydrogenated at 50° C with 10% palladium-carbon (30 mg) as a catalyst, during 48 h. Removal of the catalyst and the solvent gave a mixture of compounds **9a** and **9b**. Conversion = 91%, ratio **9a**/**9b** = 80/20, determined by HPLC: retention time: **9a** = 4.9

min, **9b** = 6.2 min, **8** = 7.1 min. Column: 5 μm C18 Hypersil® Silica 200 x 4.6 mm. Eluent: hexane-^{t}butyl methyl ether (85:15). Flow rate: 2 mL/min. Detection UV at 200 nm. Three fractions were separated by silica gel column chromatography eluting with hexane-ethyl acetate (70:30), the first of all yielded 87 mg (55%) of compound **9a** as an oil, the second yielded 39 mg (25%) of a mixture of compounds **9a** and **9b** and the third yielded 14 mg (9%) of **9b** as an oil.

Compound **9a**:

Found C: 75.65, H: 7.49, N: 3.80

Anal. Calc. for $C_{23}H_{27}NO_3$ C: 75.59, H: 7.45, N: 3.83

^{1}H-NMR($CDCl_3$): δ= 0.91 (d, 3H, $J_{Me\text{-}4e}$ = 6.3 Hz, Me-C_4); 0.94-1.01 (m, 2H, H_{5a} + H_{4e}); 1.03 (d, 3H, $J_{Me\text{-}5a}$ = 7.2 Hz, Me-C_5); 1.68 (ddd, 1H, $J_{3e\text{-}4e} \approx J_{3e\text{-}2a}$ = 2.4 Hz, $J_{3e\text{-}3a}$ = 13.2 Hz, H_{3e}); 2.11 (dd, 1H, $J_{6a\text{-}6e} \approx J_{6a\text{-}5a}$ = 13.2 Hz, H_{6a}); 2.42 (ddd, 1H, $J_{3a\text{-}4e}$ = 4.5 Hz, $J_{3a\text{-}3e} \approx J_{3a\text{-}2a}$ = 13.8 Hz, H_{3a}); 2.93 (dd, 1H, $J_{6e\text{-}5a}$ = 3.0 Hz, $J_{6e\text{-}6a}$ = 13.2 Hz, H_{6e}); 3.41 (dd, 1H, $J_{2a\text{-}3e}$ = 2.4 Hz, $J_{2a\text{-}3a}$ = 13.8 Hz, H_{2a}); 3.50 (s, 3H, CO_2Me); 6.18 (brs, 1H, NH); 7.14-7.69 (m, 10H, Arom.). ^{13}C-NMR($CDCl_3$): δ= 11.6(Me-C_4); 19.0(Me-C_5); 29.1(C_3); 32.3(C_4); 32.4(C_6); 34.1(C_5); 43.2(C_2); 51.9(CO_2Me); 64.9(C_1); 126.8; 127.7; 128.6; 128.9; 131.4; 135.5; 139.8; 153.9(Arom.); 153.9(CONH); 173.4(CO).

Compound **9b**:

Found C: 75.67, H: 7.52, N: 3.89

Anal. Calc. for $C_{23}H_{27}NO_3$ C: 75.59, H: 7.45, N: 3.83

^{1}H-NMR($CDCl_3$): δ= 0.95 (d, 3H, $J_{Me\text{-}4a}$=1.8 Hz, Me-C_4); 0.89 (d, 3H, $J_{Me\text{-}5e}$=3.0 Hz, Me-C_5); 1.50-1.53 (m, 1H, H_{3e}); 1.90-2.10 (m, 3H, H_{5e} + H_{4a} + H_{3a}); 2.41 (dd, 1H, $J_{6a\text{-}5e}$ = 5.1 Hz, $J_{6a\text{-}6e}$ = 14.7 Hz, H_{6a}); 3.28 (dd, 1H, $J_{2a\text{-}3e}$ = 4.5 Hz, $J_{2a\text{-}3a}$ = 12.0 Hz, H_{2a}); 3.29 (dd, 1H, $J_{6e\text{-}5e}$ = 2.1 Hz, $J_{6a\text{-}6e}$ = 14.7 Hz, H_{6e}); 3.49 (s, 3H, CO_2Me); 6.19 (brs, 1H, NH); 7.13-7.20 (m, 2H, Arom.); 7.22-7.50 (m,6H, Arom.); 7.58-7.63(m, 2H, Arom.). ^{13}C-NMR($CDCl_3$): δ= 12.6(Me-C_4); 19.4(Me-C_5); 29.7(C_4); 31.6(C_3); 35.1(C_6); 36.0(C_5); 50.5(C_2); 52.0(CO_2Me); 63.3(C_1); 126.7; 127.5; 127.9; 128.6; 128.9; 131.4; 135.5; 140.0(Arom.); 153.9(CONH); 173.4(CO).

1-Amino-*c*-4,*c*-5-dimethyl-*t*-2-phenyl-*r*-1-cyclohexanecarboxylic Acid. (10).

Compound **6a** (56 mg, 0.15 mmol) was dissolved in 6 N HCl (10 mL) and refluxed for 48 h. The solvent was removed under reduced pressure. The residue of aminoacid hydrochloride was dissolved in EtOH (6 mL) and propylene oxide (2 mL) was added. The mixture was refluxed for 1 h and the precipitate was filtered to give 30 mg (80%) of amino acid **10** as a white solid.

Found C: 72.73, H: 8.49, N: 5.58

Anal. Calc. for $C_{15}H_{21}NO_2$ C: 72.84, H: 8.56, N: 5.66

^{1}H-NMR(D_2O/CF_3COOH): δ= 0.86 (d, 3H, $J_{Me\text{-}4e}$ = 7.2 Hz, Me-C_4); 0.89 (d, 3H, $J_{Me\text{-}5a}$ = 7.2 Hz, Me-C_5); 1.63 (d, 1H, $J_{3e\text{-}3a}$ = 14.4 Hz, H_{3e}); 1.71 (d, 1H, $J_{6e\text{-}6a}$ = 12.0 Hz, H_{6e}); 1.24-1.55 (m, 2H, H_{5a} + H_{4e}); 2.12 (dd, 1H, $J_{6a\text{-}6e} \approx J_{6a\text{-}5a}$ = 12.0 Hz, H_{6a}); 2.28 (ddd, 1H, $J_{3a\text{-}4e}$ = 3.9 Hz, $J_{3a\text{-}3e} \approx J_{3a\text{-}2a}$ = 14.4 Hz, H_{3a}); 3.35-3.48 (brs, 2H, NH_2); 3.52 (d, 1H, $J_{2a\text{-}3a}$ = 13.2 Hz, H_{2a}); 7.14-7.35 (m, 5H, Ph-C_2).

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