Tetrahedron Vol. 49, No 3, pp 677-684, 1993
Printed in Great Britain

0040-4020/93 $5 00+ 00

Synthesis of the Four d,l-Pairs of 2-Amino-3-phenylnorbornane-2-carboxylic acids II. The Use of 5(4H)-Oxazolones as Dienophiles.

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(*Received in UK* 14 *September* 1992)

Key Words (E)- and (Z)-oxazolones, Diels-Alder cycloaddition, α-aminoacids

Abstract *The Diels-Alder reaction between both geometric isomers (Z)- or (E)-2-phenyl-4-benzylidene-5(4H)-oxazolone and cyclopentadiene is studied. The cycloadducts are converted into the aminoacids through simple reactions allowing the synthesis of the four d,l-pairs of 2-amino-3-phenylnorbornane-2-carboxylic acids*

Whereas the synthesis of α-aminoacids is a matter of continual interest[1], the synthesis of cycloaliphatic aminoacids, especially those with a norbornane skeleton, which have noticeable biological activities[2], has scarcely been studied The parent compounds, 2-aminonorbornane-2-carboxylic acids, can be obtained by the Diels-Alder reaction between N-acyl-α,β-didehydroalaninates and cyclopentadiene[3], and using this strategy and the appropriate chiral auxiliary, the asymmetric synthesis of these compounds has recently been published[4] Nevertheless, the Diels-Alder reaction between cyclopentadiene and N-acyl-α,β-didehydrophenylalaninates does not lead to the corresponding 3-substituted aminoacids, so an alternative and unequivocal synthesis of the four d,l-pairs of 2-amino-3-phenylnorbornane-2-carboxylic acids has been published[5] based on the use of the easily available methyl (E)-2-cyanocinnamate as a dienophile and the subsequent transformations of the cyano and methoxycarbonyl groups of the cycloadducts into amino and carboxylic groups through well-established reactions which have controlled stereochemistry but involve several steps which decrease the total yield of the synthetic route

In this paper we would like to report the use of the available geometric (Z)- or (E)-2-phenyl-4-benzylidene-5(4H)-oxazolones as dienophiles completing in this way the first results previously reported[6] to describe an easy and unequivocal synthesis of the four d,l-pairs of the titled compounds

RESULTS AND DISCUSSION

Although the reactivity of 5(4H)-oxazolones is very well-known[7] and that these compounds have proved to be very important intermediates in the synthesis of α-aminoacid derivatives very little has been reported about their behaviour as dienophiles To the best of our knowledge, apart from our preliminary results[6], only the reaction of 2-phenyl-4-(3,4-methylenedioxybenzylidene)-5-(4H)-oxazolone with Danishefsky's diene and related dienes has been reported[8] and it is important to point out that this reaction took place at high temperatures with low yields and stereochemical results were not determined Both (Z)- and (E)-stereoisomers of 2-phenyl-4-benzylidene-5(4H)-oxazolones are easily available[7]. The former is obtained from benzaldehyde and hippuric acid and the latter from the (Z)-isomer through an isomerization reaction using hydrogen bromide From these starting compounds the desired aminoacids were obtained using the reactions summarized in Scheme 1

(Z)-2-Phenyl-4-benzylidene-5(4H)-oxazolone reacts with cyclopentadiene in the presence of the corresponding amount of Lewis acid to give a mixture of spiroxazolones (for example, using a ratio cyclopentadiene/dienophile/Lewis acid of 3/1/0 5 and working at -25° C, 95% of spiroxazolones was obtained after 2 h with a endo/exo ratio of 0 87) that could be hydrolyzed and the corresponding exo- and endo-N-benzoyl-α-aminoacids **8a** and **8b** were separated through a typical iodolactonization procedure

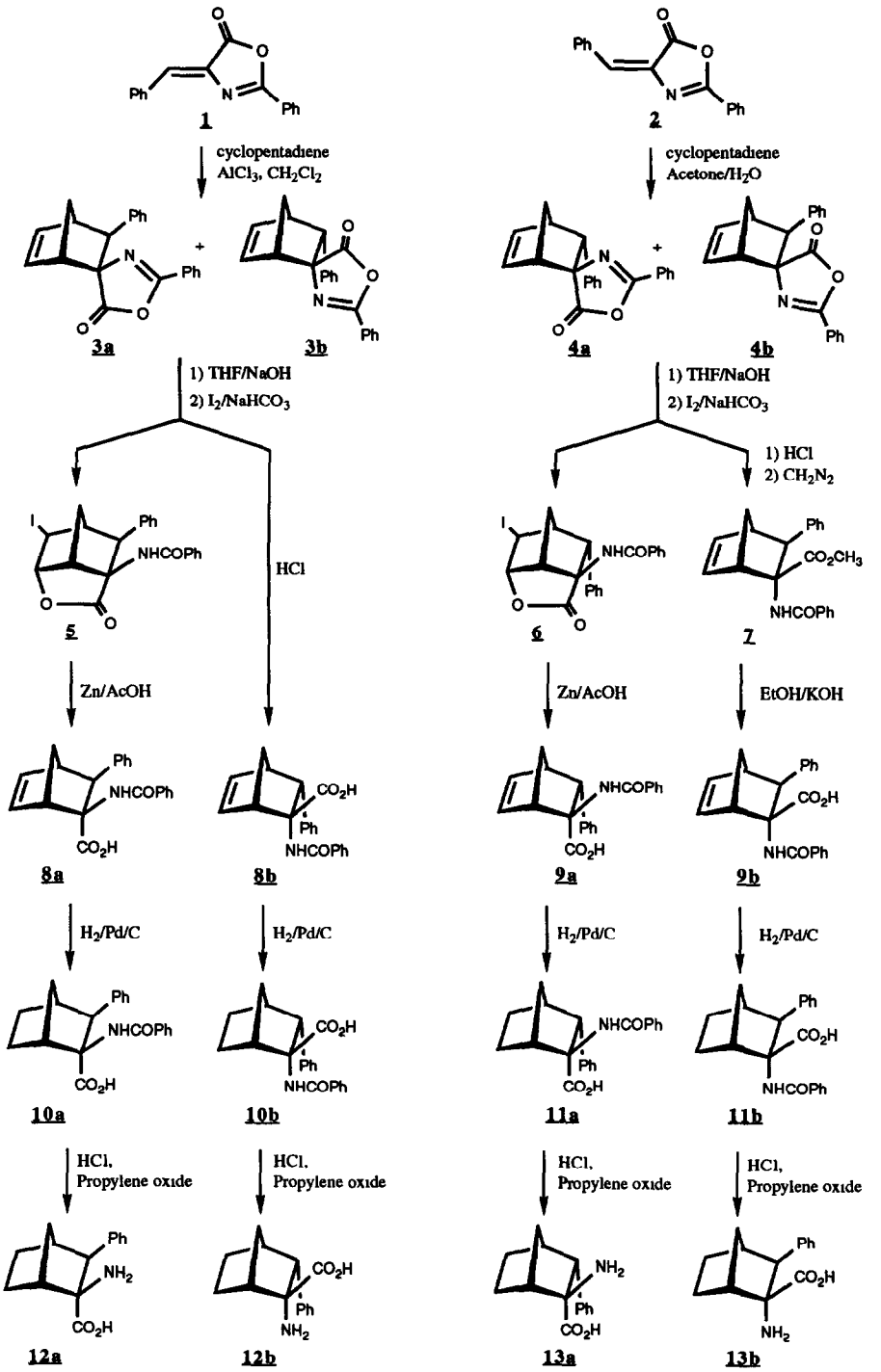
On the other hand, all attempts at using the same methodology with (E)-2-phenyl-4-benzylidene-5(4H)-oxazolone to obtain the other stereoisomers repeating the sequence of reactions were unsuccessful since in the presence of Lewis acids the partial isomerization of the (E)-5(4H)-oxazolone to the thermodynamically more stable (Z)-5(4H)-oxazolone takes place and the mixture of all spiroxazolones was always obtained Moreover, without a catalyst the Diels-Alder reaction does not occur

Several authors have reported that the use of water greatly increases the rate of Diels-Alder reactions[9] and, together with this effect, an increase in endo/exo selectivity is sometimes observed In our case, although the reaction is very slow, (E)-5(4H)-oxazolone reacted with cyclopentadiene in the presence of water and, after six days at room temperature, a mixture of the corresponding spiroxazolones **4a**, **4b** (yield 95%, see experimental section) was obtained together with a 5% of the starting dienophile which could not be separated N-benzoyl-α-aminoacid **9a** was separated through a typical iodolactonization procedure but, in the filtrate, a mixture of **9b** and (E)-benzamidocinnamic acid, from the opening of the unreacted (E)-5(4H)-oxazolone, was obtained, from which purification of the desired product in a large quantity was difficult Alternatively, the mixture of acids was quantitatively esterified with diazomethane and the resulting methyl esters were chromatographied, thus allowing the obtention of compound **7**, which was then hydrolyzed to obtain pure **9b**

The hydrolysis of the amide group of the four d,l-pairs of 2-benzamido-3-phenylbicyclo[2 2 1]hept-5-ene-2-carboxylic acids (**8a**, **8b**, **9a**, **9b**) does not occur in alkaline medium and if the typical acid conditions are used rearrangement of the bicyclic ring takes place Therefore it is necessary first of all to obtain the corresponding saturated compounds through heterogeneous hydrogenation using Pd/C as a catalyst. Once this has been done the hydrolysis of the benzamido group occurs without problems in acid medium and the obtention of free α-aminoacids takes place with propylene oxide using a typical procedure

In conclusion, following this synthetic route the four d,l-pairs of 2-amino-3-phenylnorbornane-2-carboxylic acids were obtained starting from the easily available stereoisomers of 2-phenyl-4-benzylidene-5(4H)-oxazolones and opening the way to a general procedure for the synthesis of 3-substituted 2-aminonorbornane-2-carboxylic acids

Scheme 1


1
2
cyclopentadiene
AlCl3, CH2Cl2
cyclopentadiene
Acetone/H2O
3a
3b
4a
4b
1) THF/NaOH
2) I2/NaHCO3
1) THF/NaOH
2) I2/NaHCO3
1) HCl
2) CH2N2
HCl
5
6
7
Zn/AcOH
Zn/AcOH
EtOH/KOH
8a
8b
9a
9b
H2/Pd/C
H2/Pd/C
H2/Pd/C
H2/Pd/C
10a
10b
11a
11b
HCl,
Propylene oxide
HCl,
Propylene oxide
HCl,
Propylene oxide
HCl,
Propylene oxide
12a
12b
13a
13b

Acknowledgements We are indebted to the generous support of the Dirección General de Investigación Científica y Técnica, projects PB88-0038 and PB91-0696 We would like to express our gratitude to the Instituto de Estudios Riojanos for a grant.

EXPERIMENTAL SECTION

Solvents were purified according to standard procedures Analytical TLC was performed by using Kieselgel 60 F_{254} plates Column chromatography was performed by using Kieselgel 60 (230-400 mesh) ^1H and ^{13}C-NMR spectra were recorded on a Varian Unity-300 in $CDCl_3$ or DMSO-d_6 with TMS as the internal standard (the chemical shifts are reported in ppm on the δ scale, coupling constants in Hz) Melting points are uncorrected Microanalyses were carried out on a Perkin-Elmer 240-B analyser and were in good agreement with the calculated values High Performance Liquid Chromatography (HPLC) was carried out with HP-1090 M equipped with 4 6 x 200mm column Hypersil C18 5 μm and monitored using a diode array detector. Compounds **5**, **8a**, and **8b** have been previously described[6]

endo-3-Phenylbicyclo[2.2.1]hept-2-spiro-{4'[2'-phenyl-5'(4'H)oxazolone]}-5-ene (4a) and exo-3-Phenylbicyclo[2.2.1]hept-2-spiro-{4'[2'-phenyl-5'(4'H)oxazolone]}-5-ene (4b).
Freshly distilled cyclopentadiene (1 30 g, 20 mmol) was added to a solution of oxazolone **2** (1 00 g, 4 mmol) in acetone/H_2O (3/1) (80ml) After stirring for 6 days at room temperature, the solution was evaporated under reduced pressure and MeOH was added to the mixture The residue (polymers of cyclopentadiene) was filtered off and the filtrate was evaporated to give the crude products **4a** and **4b** (ratio **4a**/**4b** = 80/20) as a slightly yellowish solid which was used in the next-step without purification, yield 1 20 g (95%).
^1H-RMN ($CDCl_3$, δ) 1 80-1 90(m, 2H, H_{7s} **4a** + H_{7s} **4b**), 2 42(d, 1H, $J_{7a\text{-}7s}$=9 0, H_{7a} **4a**), 2 86(d, 1H, $J_{7a\text{-}7s}$=9 0, H_{7a} **4b**), 3 04(s, 1H, H_4 **4a**); 3 16(s, 1H, H_4 **4b**), 3 28-3 34(m, 2H, H_1 **4b**+ H_{3n} **4b**), 3 42(s, 1H, H_1 **4a**), 4 13(d, 1H, $J_{3x\text{-}4}$=2.8, H_{3x} **4a**), 6 37-6 45(m, 2H, H_6 **4a** + H_6 **4b**), 6 73-6 78(dd, 1H, $J_{5\text{-}6}$=5 6, $J_{5\text{-}4}$=3 0, H_5 **4b**), 6 80-6 83(dd, 1H, $J_{5\text{-}6}$=5 5, $J_{5\text{-}4}$=3 1, H_5 **4a**), 7 05- 7 65(m, 16H, Arom), 7 88-8 10(m, 2H, o-Ph-C=N **4a**), 8 19-8 26(m, 2H, o-Ph-C=N **4b**)

exo-2-Benzamido-exo-5-iodo-exo-3-phenyl-endo-6-hydroxybicyclo[2.2.1]heptane-endo-2-carboxylic Acid Lactone (5).
^{13}C-NMR($CDCl_3$, δ)· 29 6(C_5), 35 7(C_7), 47 7(C_3), 50 6(C_4), 55 1(C_1), 62 0(C_2), 86 2(C_6), 126 6, 128 5, 128 7, 128 8, 129.5, 132 0, 132 7, 134 0(Arom), 165.9(CONH), 175.0(CO)

exo-2-Benzamido-exo-5-iodo-endo-3-phenyl-endo-6-hydroxybicyclo[2.2.1]heptane-endo-2-carboxylic Acid Lactone (6).
To a solution of the crude mixture of **4a,b** (from 4 mmol of **2**) in THF (30 ml) was added 5% aq NaOH (20 ml) and the mixture was stirred for 30 min at room temperature After evaporation, the residue was taken up in MeOH (10 ml) and an aqueous solution of 5% $NaHCO_3$ (75 ml) was added It was then treated with an excess of a stock solution of I_2 [prepared from I_2 (5 g) and KI (10 g) in H_2O (30 ml)] and allowed to stand for 1 h The precipitate was collected by filtration, washed with cold MeOH (15 ml) and dried to afford iodolactone **6**, yield 0 80 g (46% from **2**) mp 211-213 °C (MeOH)

Found C. 54.82, H 3 88, N. 2 92, I 27 70
Calc for $C_{21}H_{18}O_3NI$ C 54 92, H 3.95, N 3.05, I 27 63
^{1}H-RMN ($CDCl_3$, δ) 2.55(d, 1H, J_{7s-7a}=11 4, H_{7s}), 2 92(d, 1H, J_{7a-7s}=11 7, H_{7a}), 3 17(s, 1H, H_4), 3.64(d, 1H, J_{5n-6x}=5 1, H_{5n}), 3.97-3 99(m, 1H, H_1), 4 36(d, 1H, J_{3x-4}=2.4, H_{3x}), 5 18(d, 1H, J_{6x-5n}=5 1, H_{6x}), 6 85(br s, 1H, NH); 7 23-7.31(m, 5H, Ph-C_3), 7 40-7 46(m, 3H, m,p-Ph-CO), 7 77-7 80(m, 2H, o-Ph-CO)
^{13}C-NMR($CDCl_3$, δ) 25 1(C_5); 36 4(C_7), 50 7(C_4), 53.0(C_1), 55 4(C_3), 63 7(C_2), 87 2(C_6), 127 0, 127 7, 127 9, 128 8, 132 2, 133 5, 134 2(Arom), 166 9(CONH); 174 7(CO)

Methyl endo-2-Benzamido-exo-3-phenylbicyclo[2.2.1]hept-5-ene-exo-2-carboxylate (7).
Compound **7** was prepared from the filtrate of the iodolactone **6** The filtrate was acidified with conc HCl and extracted with Et_2O (3 x 30 ml) The organic layer was washed successively with 10% $Na_2S_2O_3$ solution (2 x 15 ml), H_2O (2 x 25 ml) and dried ($MgSO_4$) After evaporating the solvent, the residue (0 28 g) was dissolved in Et_2O (40 ml) and esterified with an excess of diazomethane in Et_2O The excess of diazomethane was destroyed with $CaCl_2$, the solution filtered, the solvent eliminated under reduced pressure and **7** purified by column chromatography on silicagel (n-hexane/AcOEt = 8/2 as eluent) to afford **7** as an oil, yield 140 mg (10% from **2**)
Found C 75.90, H 6 00, N 3 90
Calc for $C_{22}H_{21}O_3N$ C 76 06, H 6 09, N 4 03
^{1}H-RMN ($CDCl_3$, δ) 1 89-1 94(m, 1H, H_{7s}), 2 76-2 80(m, 2H, H_{7a} + H_{3n}), 3 03(s, 3H, $COOCH_3$), 3.06(m, 1H, H_4), 4 00(s, 1H, H_1), 6 20(dd, 1H, J_{6-5}=5 6, J_{6-1}=3 2, H_6), 6 57(dd, 1H, J_{5-6}=5 6, J_{5-4}=3 0, H_5), 6.68(br s, 1H, NH), 7 18-7.29(m, 5H, Ph-C_3), 7 38-7 52(m, 3H, m,p-Ph-CO), 7.73-7 77(m, 2H, o-Ph-CO)
^{13}C-NMR($CDCl_3$, δ)· 47 1, 48.3, 49 4(C_4, C_7, C_3), 51 5(C_1), 59 8($COOCH_3$), 70 7(C_2), 126 9, 127 0, 127 9, 128 5, 128 6, 131 6, 134 0, 138 9(Arom), 137.2(C_6), 140 6(C_5), 167.3(CONH), 171 8(CO).

exo-2-Benzamido-exo-3-phenylbicyclo[2.2.1]hept-5-ene-endo-2-carboxylic Acid (8a).
^{13}C-NMR($CDCl_3$, δ) 45 8(C_4), 47 3(C_7), 48 2(C_3), 52 0(C_1), 68 4(C_2), 126 8, 128 2, 128 6, 128 8, 129 6; 132 6, 133 8, 138 0(Arom), 141 7(C_5 + C_6), 169.0(CONH), 172 5(CO).

endo-2-Benzamido-endo-3-phenylbicyclo[2.2.1]hept-5-ene-exo-2-carboxylic Acid (8b).
^{13}C-NMR($CDCl_3$, δ) 46 6(C_4), 48 6(C_7), 50 9(C_3), 54 5(C_1), 67 9(C_2), 126 9, 128 0, 128 7, 129 2, 129 6, 132 3, 132 5, 137 1(Arom), 135 3(C_6), 138 0(C_5), 168 9(CONH), 175 6(CO)

exo-2-Benzamido-endo-3-phenylbicyclo[2.2.1]hept-5-ene-endo-2-carboxylic Acid (9a).
Zinc dust (6 g) was slowly added to a solution of iodolactone **6** (0 80 g, 1 7 mmol) in glacial AcOH (50 ml) The mixture was allowed to react at room temperature for 6 h, then filtered and the solid was washed with Et_2O (2 x 25 ml). The combined mother liquors and filtrate were evaporated to afford an oil, which was taken up in Et_2O (50 ml) and extracted with 5% $NaHCO_3$ solution (2 x 30 ml) After acidifying with conc HCl, the aqueous solution was extracted with Et_2O (3 x 25 ml), dried ($MgSO_4$) and evaporated under vacuum to give **9a**, yield 0 55 g (92 %) mp 175-177 °C (dec) (MeOH)
Found C. 75 60, H 5 79, N 4 12
Calc for $C_{21}H_{19}O_3N$ C 75 66, H. 5 74, N 4 20
^{1}H-RMN (DMSO-d_6, δ) 1.23(d, 1H, J_{7s-7a}=7 6, H_{7s}), 1.56(d, 1H, J_{7a-7s}=7 6, H_{7a}), 2 53(m, 1H, H_4), 3.29(m, 1H, H_1), 3 41(d, 1H, J_{3x-4}=3.4, H_{3x}), 5 00(s, 1H, NH), 5 82(dd, 1H, J_{6-5}=5 4, J_{6-1}=2 9, H_6),

6.34(dd, 1H, J_{5-6}=5.4, J_{5-4}=3 4, H_5), 6 78-6 91(m, 5H, Ph-C_3); 7 01-7 24(m, 3H, m,p-Ph-CO), 7 48-7 51(m, 2H, o-Ph-CO), 8 30(br s, 1H, COOH)

^{13}C-NMR(DMSO-d_6, δ). 47.9, 48 2, 50.6(C_4, C_7, C_3), 58.1(C_1), 73 0(C_2), 125 6; 126 7, 127 1, 127 2, 128 4; 130 6, 133.0, 133.7(Arom.); 137 3(C_6); 140 3(C_5), 167 4(CONH), 171 8(CO)

endo-2-Benzamido-exo-3-phenylbicyclo[2.2.1]hept-5-ene-exo-2-carboxylic Acid (9b).

Ester **7** (70 mg, 0 2 mmol) was refluxed with 10% KOH/EtOH (10 ml) for 6 h The solvent was eliminated under reduced pressure The residue was diluted with H_2O (5 ml) extracted with Et_2O (3 x 10 ml), the aqueous layer acidified with conc HCl and extracted with Et_2O (3 x 10 ml) The organic solution was dried over anhydrous Na_2SO_4 and the solvent evaporated under vacuum to give acid **9b** as an oil, yield 57 mg (85%)

Found· C 75 58, H: 5 69, N: 4 23

Calc for $C_{21}H_{19}O_3N$ C 75.66, H: 5 74, N 4 20

^{1}H-RMN (DMSO-d_6, δ)· 2 16-2 24(m, 1H, H_{7s}), 3 06-3 13(d, 1H, J_{7a-7s}=9 0, H_{7a}), 3 29(s, 1H, H_{3n}), 3 35-3 37(m, 1H, H_4), 4 30-4 31(m, 1H, H_1), 6 54-6 58(m, 1H, H_6), 6 85-6 89(m, 1H, H_5), 7 55-7 86(m, 9H, Arom + NH), 8 08-8 12(m, 2H, o-Ph-CO)

^{13}C-NMR(DMSO-d_6, δ) 47 3, 48 0, 49 5(C_4, C_7, C_3), 58 5(C_1), 70 6(C_2), 127 2, 127 7, 128 1, 128 8, 129 0, 132 4, 134 1, 134 7(Arom), 137 0(C_6), 140 2(C_5), 167 8(CONH), 173 4(CO)

exo-2-Benzamido-exo-3-phenylbicyclo[2.2.1]heptane-endo-2-carboxylic Acid (10a).

A solution of compound **8a** (50 mg, 0 16 mmol) in dry CH_2Cl_2 (10 ml) was hydrogenated at atmospheric pressure with 10% palladium-carbon (10 mg) as a catalyst Removal of the catalyst and the solvent gave the required compound **10a** as a white solid, yield 48 mg (90%) mp 187-189 °C (dec)

Found C 75 26, H 6 38, N 4 21

Calc for $C_{21}H_{21}O_3N$ C 75 20, H 6 31, N 4 18

^{1}H-RMN ($CDCl_3$, δ) 1 68-180(m, 5H, $2H_5$ + $2H_6$ + H_{7s}), 1 99(d, 1H, J_{7a-7s}=10 8, H_{7a}), 2 69(s, 1H, H_4), 3 43(m, 1H, H_1), 4.17(d, 1H, J_{3n-7s}=1 8, H_{3n}), 5 92(br s, 1H, NH), 7 14-7 19(m, 2H, Arom), 7.23-7 31(m, 2H, Arom.), 7 32-7 48(m, 6H, Arom)

^{13}C-NMR($CDCl_3$, δ) 23 4; 29 8(C_5, C_6), 38 0, 40 6, 42 0(C_4, C_7, C_3), 53 5(C_1), 73 5(C_2), 126 8, 128 0, 128 8, 129 5, 132 0, 132.8, 132 8, 137 5(Arom.); 169 6(CONH), 171 8(CO)

endo-2-Benzamido-endo-3-phenylbicyclo[2.2.1]heptane-exo-2-carboxylic Acid (10b).

In a similar way to compound **10a**, acid **8b** (50 mg, 0 16 mmol) was hydrogenated to give compound **10b** as a white solid, yield: 45 mg (84 %) mp 191-193 ° C (dec)

Found C 75 29, H 6 37, N 4 26

Calc for $C_{21}H_{21}O_3N$ C 75 20, H 6 31, N 4 18

^{1}H-RMN ($CDCl_3$, δ) 1 30-1 80(m, 5H, $2H_5$ + $2H_6$ + H_{7s}), 1 97(d, 1H, J_{7a-7s}=9 7, H_{7a}), 2 81(s, 1H, H_4), 3 42(m, 1H, H_1), 4 13(m, 1H, H_{3x}), 6.45(br s, 1H, NH), 7 28-7 49(m, 10H, Arom)

^{13}C-NMR($CDCl_3$, δ) 21 9, 24 5(C_5, C_6), 37 8, 38 6, 45 7(C_4, C_7, C_3), 51 9(C_1), 65 9(C_2), 126 8, 127 5, 128 8, 129 1, 129 6, 132 3, 132 5, 135 8(Arom), 169 5(CONH), 175 6(CO)

exo-2-Benzamido-endo-3-phenylbicyclo[2.2.1]heptane-endo-2-carboxylic Acid (11a).
In a similar way, acid **9a** (50 mg, 0.16 mmol) was hydrogenated to give compound **11a** as a white solid, yield 52 mg (97 %) mp 198-200 °C (dec)
Found: C 75 15, H 6 27, N 4 11
Calc for $C_{21}H_{21}O_3N$ C: 75 20, H: 6 31, N: 4.18
^{1}H-RMN ($CDCl_3$, δ) 1 26-1 42(m, 2H), 1 60-1 82(m, 3H, $2H_5 + 2H_6 + H_{7s}$), 2 10(d, 1H, $J_{7a\text{-}7s}$=9 9, H_{7a}), 2 47(d, 1H, $J_{4\text{-}5x}$=3 9, H_4), 2 79(d, 1H, $J_{1\text{-}6x}$=4 5, H_1), 3 54(d, 1H, $J_{3x\text{-}4}$=4 8, H_{3x}), 6 87(br s, 1H, NH), 7 17-7 21(m, 2H, Arom.), 7 22-7 39(m, 3H, Arom), 7 44-7.56(m, 2H, Arom), 7 58-7 63(m, 1H, Arom), 7 79-7.84(m, 2H, Arom).
^{13}C-NMR($CDCl_3$, δ) 22 1, 22 8(C_5, C_6), 37 9, 44 1, 47 5(C_4, C_7, C_3), 57 8(C_1), 70 9(C_2), 126 8, 127 5, 128 1, 128.9, 129 2, 132 6, 132 9, 138 1(Arom), 170 1(CONH), 170 8(CO)

endo-2-Benzamido-exo-3-phenylbicyclo[2.2.1]heptane-exo-2-carboxylic Acid (11b).
In a similar way, acid **9b** (50 mg, 0 16 mmol) was hydrogenated to give compound **11b** as an oil, yield 46 mg (86 %)
Found C 75 17, H 6 21, N 4 15
Calc for $C_{21}H_{21}O_3N$ C 75 20, H 6 31, N 4 18
^{1}H-RMN ($CDCl_3$, δ) 1 38-1.85(m, 5H, $2H_5 + 2H_6 + H_{7s}$), 2 47(d, 1H, $J_{4\text{-}5x}$=3 0, H_4), 2 70(d, 1H, $J_{7a\text{-}7s}$=10 8, H_{7a}), 2 78(d, 1H, $J_{3n\text{-}7a}$=2 1, H_{3n}), 3 26(d, 1H, $J_{1\text{-}6x}$=3 0, H_1), 6 78(br s, 1H, NH), 7 16-7 31(m, 5H, Ph-C_3), 7 42-7 58(m, 3H, m,p-Ph-CO), 7 75-7 81(m, 2H, o-Ph-CO)
^{13}C-NMR($CDCl_3$, δ) 23 3, 30 9(C_5, C_6), 39 2, 42 9, 44 6(C_4, C_7, C_3), 62 7(C_1), 72 9(C_2), 127 2, 128 3, 128 4, 128.8, 132 3, 133 4, 140 3, 153 9(Arom), 169 3(CONH), 172 3(CO)

exo-2-Amino-exo-3-phenylbicyclo[2.2.1]heptane-endo-2-carboxylic Acid (12a).
Compound **10a** (40 mg, 0 12 mmol) was dissolved in HCl 6N (10 ml) and refluxed for 72 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 30 min and the solvent evaporated to give aminoacid **12a**, yield 22 mg (81 %)

endo-2-Amino-endo-3-phenylbicyclo[2.2.1]heptane-exo-2-carboxylic Acid (12b).
In a similar way, aminoacid **12b** was prepared from acid **10b** (40 mg, 0 12 mmol), yield. 24 mg (88 %)

exo-2-Amino-endo-3-phenylbicyclo[2.2.1]heptane-endo-2-carboxylic Acid (13a).
In a similar way, aminoacid **13a** was prepared from acid **11a** (40 mg, 0 12 mmol), yield 26 mg (96 %)

endo-2-Amino-exo-3-phenylbicyclo[2.2.1]heptane-exo-2-carboxylic Acid (13b).
In a similar way, aminoacid **13b** was prepared from acid **11b** (40 mg, 0 12 mmol), yield 18 mg (66 %)

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