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SYNTHESIS OF THE FOUR DL-PAIRS OF 2-AMINO-3-PHENYLNORBORNANE-2-CARBOXYLIC ACIDS

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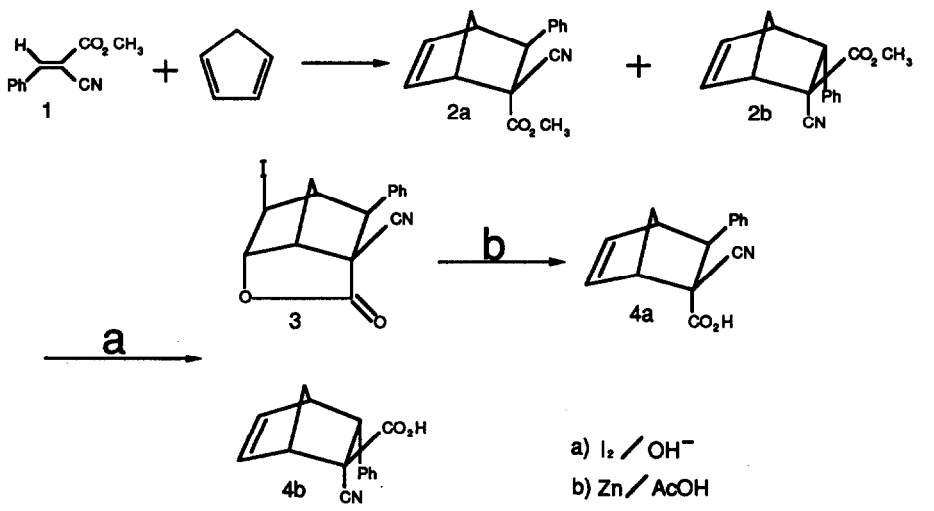
SUMMARY: The Diels-Alder reaction between methyl α-cyanocinnamate and cyclopentadiene, as a key step in the synthesis of 2-amino-3-phenylnorbornane-2-carboxylic acids, is studied. The cycloadducts can be easily separated and converted into the aminoacids through simple reactions.

Whereas the synthesis of α-aminoacids is a subject of great interest[1], the synthesis of cycloaliphatic aminoacids, such as those with a norbornane skeleton, which have noticeable biological activities[2], has been little studied. The parent compounds, 2-aminonorbornane-2-carboxylic acids, can be obtained by Diels-Alder reaction between N-acyl-α,β-dehydroalaninates and cyclopentadiene[3]. Nevertheless, the Diels-Alder reaction between cyclopentadiene and N-acyl-α,β-dehydrophenylalaninates does not lead to the corresponding aminoacids. Furthermore, the use as dienophiles of α-nitrocinnamates does not allow the unequivocal synthesis of these aminoacids, due in part to the isomerization of the dienophile under the reaction conditions[4]. We have therefore directed our attention to the development of an unequivocal synthesis of the four dl-pairs of the 2-amino-3-phenylnorbornane-2-carboxylic acids(14,15). This synthesis is based on the use of E-methyl α-cyanocinnamate[5](1) as dienophile, and the subsequent transformations of cyano and methoxycarbonyl substituents into amino and carboxylic acid groups.

RESULTS AND DISCUSSION

Schemes 1 and 2 shows the synthetic route leading to the four aminoacids (14,15). Table 1 shows the results obtained in the Diels-Alder reaction



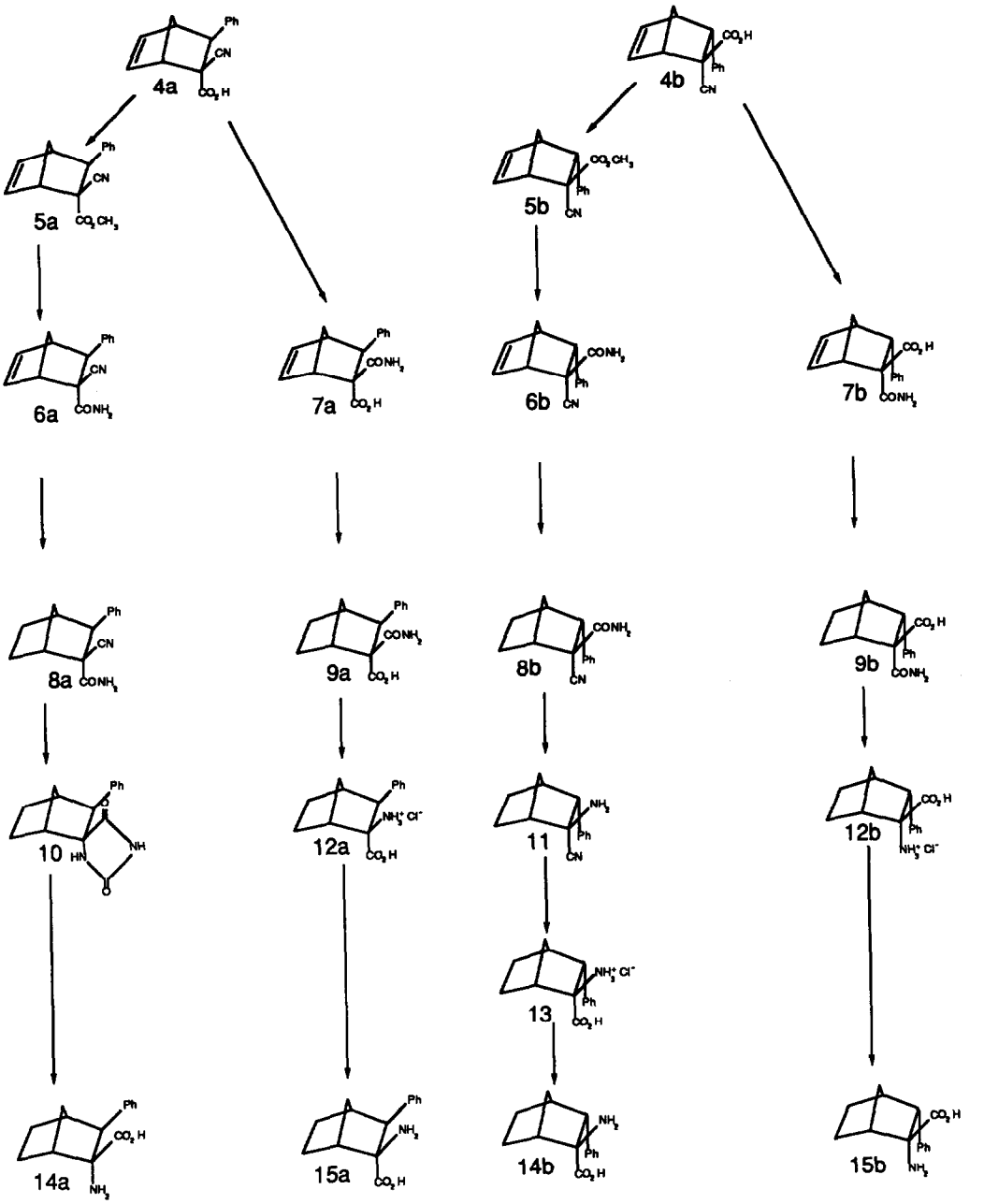
Scheme 1

Table 1. Diels-Alder reaction between E-methyl α-cyanocinnamate(1) and cyclopentadiene.

Lewis acid	Solvent	Diene/Dienophile	t(h)	T(°C)	%Conversion	ratio of 2a/2b[a]
--	1,4-dioxane	3:1	24	20	30	1.68:1
--	1,4-dioxane	3:1	24	60	83	1.59:1
--	1,4-dioxane	3:1	24	90	59	1.07:1
--	MeOH	3:1	24	60	94	1.60:1
--	H_2O[b]	3:1	7.5	25	100	1.68:1
$AlCl_3$	CH_2Cl_2	10:1	1	-30	83	3.31:1
$AlCl_3$	CH_2Cl_2	10:1	1	-78	74	24.50:1
$ZnCl_2$	CH_2Cl_2	10:1	48	25	89	2.90:1
$ZnCl_2$	CH_2Cl_2	10:1	48	0	73	2.71:1
ZnI_2	CH_2Cl_2	10:1	48	25	93	2.46:1
ZnI_2	CH_2Cl_2	10:1	48	0	91	2.59:1

a. Determined by HPLC. Column: 5 μm Hypersil[R] MOS(C_8). Eluent: MeOH:H_2O; 60% of MeOH 1 min.;gradient 60 to 75% of MeOH 1 min.; 75% of MeOH. Flow rate 2 ml/min. Detection 210 nm $\varepsilon_{\underline{1}}:\varepsilon_{\underline{2a}};\varepsilon_{\underline{2b}}$ = 1.217:1.137:1.000.

b. Because of the low solubility a suspension of both diene and dienophile in water was used.



Scheme 2

between cyclopentadiene and E-methyl α-cyanocinnamate(1); as can be seen, high levels of conversion can be achieved under several conditions. Reaction temperatures of over 60°C led to worse chemical yield and endo/exo selectivity, due to the reversibility of the reaction. Several authors have reported that the use of water greatly increases the rate of Diels-Alder reactions[6]; together with this effect an increase in endo/exo selectivity is sometimes observed. In our case the use of water noticeably increased the reaction rate, but only a small modification in the ratio of cycloadducts(2a:2b) was obtained. The use of a Lewis acid increased both the reaction rate and endo/exo selectivity, but high ratios of 2a:2b were only obtained when low reaction temperatures could be used.

Cycloadducts 2a and 2b, whose oustanding difference is the position of the phenyl group, were converted into the acids 4a and 4b, which were easily separated by means of the iodolactone transformation[7]. 4a and 4b were converted into the aminoacids by means of simple reactions, including selective transformation of the cyano or carboxyl group into an amide, followed by Hofmann rearrangement, but some difficulties stemming from the low reactivity of the groups placed at the endo position appeared[8]. The hydration of the nitrile group in polyphosphoric acid[9] led to a complex mixture of products, so hydrogen peroxide in alkaline medium[10] was used; when the hydration of the nitrile group of 4b was carried out under the conditions used with 4a(55°C,3 days) an equimolecular mixture of 4b and 7b was obtained, which was treated again under the same conditions to obtain 7b with a total yield of 56% with respect to the initial amount of 4b.

The Hofmann rearrangement has been the subject of many reviews[11] and the results obtained are strongly dependent on the nature of the starting amide. Under the conditions used amide 8a yielded spirohydantoin 10 probably due to the low intermolecular reactivity of the intermediate isocyanate.

The hydrolysis of this spirohydantoin ring is difficult because position 5 of the hydantoin ring is completely substituted, whereas position 3 is unsubstituted[12]. Hydrolysis was achieved by heating spirohydantoin 10 with aqueous $Ba(OH)_2$ at 140°C in a closed flask for three days.

Finally the transformation of aminonitrile 11 into aminoacid hydrochloride 13 is again made difficult by the low reactivity of the nitrile group at the endo position. The transformation was made by heating aminonitrile 11 with HCl 6N at 125°C in a closed flask for fifteen hours.

Following this synthetic route the four aminoacids were obtained with the following overall yields with respect to the initial amount of 4a or 4b: 14a, 21%; 15a, 61%; 14b, 40%; 15b, 41%.

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EXPERIMENTAL

^{1}H-NMR spectra were recorded on a Varian XL-200. Deuterochloroform, DMSO-d_6 and acetone-d_6 were used as solvents with tetramethylsilane as the internal standard(the chemical shifts are reported in ppm on the δ scale, coupling constants in Hz). Infrared spectra were obtained on a Perkin-Elmer 883 infrared spectrometer. Melting points were determined on a Büchi SMP-20 and 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 4.6x100 mm column Hypersil MOS(C_8) 5 μm and monitored using diode array detector.

E-methyl α-cyanocinnamate(1)

Prepared in accordance with the method described in the literature[13].

(2a) and (2b)

A) Without a catalyst: General procedure

Cyclopentadiene freshly distilled(7.92 g, 120 mmol) was added to a solution of methyl α-cyanocinnamate(1)(7.48 g, 40 mmol) in 1,4-dioxane(50 ml) and water(15 ml). After 7 h at 60°C, the solvent was evaporated under reduced pressure to afford a viscous oily product, which was recrystallised from hexane to give 8.40 g of a mixture of **2a** and **2b** as a white solid(yield:83%).

B) With a catalyst: General procedure

To a solution of **(1)**(94 mg, 0.5 mmol) in anhydrous CH_2Cl_2(7 ml), the catalyst(0.5 mmol) was added. After 1 h stirring at corresponding work temperature, a solution of cyclopentadiene freshly distilled(330 mg, 5 mmol) in CH_2Cl_2(3 ml) was added dropwise and the reaction was left under the conditions reported in Table 1. The mixture was treated with 2N HCl, extracted with diethyl ether, dried over Na_2SO_4 and analysed by HPLC(see Table 1).

Iodolactone(3)

A solution of a mixture of **2a** and **2b**(6.07 g, 24 mmol) in methanol(50 ml) and aqueous 10% NaOH(15 ml) was stirred at room temperature. After 24 h,

the solution was concentrated in vacuo(1/3 volume) and then diluted with water(100 ml). The resulting solution was extracted with diethyl ether (2x20 ml) and the aqueous layer was acidified with conc. HCl and again extracted with ether(3x25 ml). The ether solution was dried over Na_2SO_4 and evaporated in vacuo to yield an oily product(acid adducts **4a** and **4b**), which was dissolved in methanol(20 ml), neutralized with 10% NaOH and a solution of 5% $NaHCO_3$(100 ml) was added. It was then treated with an excess of iodine stock solution(5 g I_2, 10 g KI, 30 ml of water) and allowed to stand for 1 h. The precipitated iodolactone was collected by filtration, washed successively with 5% sodium thiosulfate solution(2x15 ml) and water(2x20 ml), dried and weighed(3.45 g). An analytical sample was recrystallised from methanol. mp 153-154°C. ir(nujol): 1792,2244 cm^{-1}. ^{1}H-NMR(Acetone-d_6): δ= 2.66-2.68(m,2H); 3.21(s,1H); 3.81(s,1H); 3.90(d,1H,J=5.1); 4.40(d,1H, J=1.9); 5.40(d,1H,J=5.1); 7.26-7.35(m,5H). Anal.Calc. for $C_{15}H_{12}INO_2$ C:49.33, H:3.31, N:3.83; found C:48.98, H:3.54, N:3.79.

2-exo-cyano-3-exo-phenylbicyclo[2.2.1]hept-5-ene-2-endo-carboxylic acid(4a)
The pure "endo" adduct **4a** was obtained by adding zinc dust(8 g) slowly to a solution of iodolactone(**3**)(3.65 g, 10 mmol) in glacial acetic acid(50 ml). After 6 h, the mixture was filtered and the solid was washed with diethyl ether(2x20 ml). The combined mother liquors and filtrate were evaporated to afford an oily residue which was taken up in diethyl ether(50 ml) and extracted with 5% $NaHCO_3$ solution(3x20 ml). After acidifying, the aqueous solution was extracted with ether(3x20 ml), dried over Na_2SO_4 and, finally, evaporated to afford an oily product which was recrystallised from methanol/water to yield 1.67 g of **4a**(yield:70%). mp 106-108°C(d). ir(nujol): 1772,2239 cm^{-1}. ^{1}H-NMR($CDCl_3$): δ = 1.95(d,1H,J=9.6); 2.35(d,1H,J=9.6); 3.32(s,1H); 3.58(d,1H,J=1.8); 3.71(s,1H); 6.17(dd,1H,J=5.6,2.7); 6.61(dd, 1H,J=5.6,3.3); 7.27-7.44(m,5H). Anal.Calc. for $C_{15}H_{13}NO_2$ C:75.29, H:5.47, N:5.85; found C:75.02, H:5.56, N:5.97.

2-endo-cyano-3-endo-phenylbicyclo[2.2.1]hept-5-ene-2-exo-carboxylic acid (4b)
The "exo" isomer **4b** was isolated from the filtrate of the iodolactonization. This filtrate was treated with 10% $Na_2S_2O_3$ solution to reduce the excess iodine, then acidified with conc. HCl. After extraction with ether(3x30 ml), the organic layer was washed with water(2x20 ml), then dried over Na_2SO_4 and evaporated in vacuo to afford an oily product which crystallised on standing. An analytical sample was recrystallised from methanol/water. mp 110-112°C(d). ir(nujol): 1711,2245 cm^{-1}. ^{1}H-NMR($CDCl_3$): δ= 1.76(d,1H, J=9.2); 1.98(d,1H,J=9.2); 3.39(s,1H); 3.60(s,1H); 4.16(d,1H,J=2.6);

6.40(s,1H); 6.53(dd,1H,J=5.6,3.1); 6.72(dd,1H,J=5.6,2.9); 7.26-7.35(m,5H). Anal.Calc. for $C_{15}H_{13}NO_2$ C:75.29, H:5.47, N:5.85; found C:74.97, H:5.56, N:5.75.

Methyl 2-exo-cyano-3-exo-phenylbicyclo[2.2.1]hept-5-ene-2-endo-carboxylate (5a)

To an ether solution(20 ml) of acid **4a**(2.39 g, 10 mmol) was added dropwise, at room temperature, a slight excess of a solution of diazomethane in ether. After a few minutes, the excess was eliminated with acetic acid and the evaporation of the solvent under reduced pressure afforded 2.50 g(quantitative yield) of **5a** as a white solid which was recrystallised from hexane. mp 73-75°C. ir(nujol): 1738,2236 cm^{-1}. ^{1}H-NMR($CDCl_3$): δ= 1.91(dd,1H, J=9.6,2.0); 2.33(d,1H,J=9.6); 3.29(s,1H); 3.61(d,1H,J=2.0); 3.65(s,1H); 3.84(s,3H); 6.06(dd,1H,J=5.6,2.8); 6.57(dd,1H,J=5.6,3.2); 7.28-7.42(m,5H). Anal.Calc. for $C_{16}H_{15}NO_2$ C:75.87, H:5.97, N:5.53; found C:76.44, H:6.11, N:5.73.

Methyl 2-endo-cyano-3-endo-phenylbicyclo[2.2.1]hept-5-ene-2-exo-carboxylate (5b)

The reaction was performed using the same conditions described for **5a**. Starting from **4b**(2.39 g, 10 mmol), 2.52 g(quantitative yield) of **5b** were obtained, which was recrystallised from hexane. mp 88-90°C. ir(nujol): 1741,2240 cm^{-1}. ^{1}H-NMR($CDCl_3$): δ= 1.72(d,1H,J=9.2); 1.94(d,1H,J=9.2); 3.34(s,1H); 3.52(s,1H); 3.90(s,3H); 4.14(d,1H,J=2.7); 6.50(dd,1H,J=5.5,3.2); 6.69(dd,1H,J=5.5,3.0); 7.23-7.32(m,5H). Anal.Calc. for $C_{16}H_{15}NO_2$ C:75.87, H:5.97, N:5.53; found C:76.64, H: 6.13, N:5.44.

2-exo-cyano-3-exo-phenylbicyclo[2.2.1]hept-5-ene-2-endo-carboamide(6a)

Ammonia was bubbled through a methanol solution(40 ml) of **5a**(1.05 g, 4 mmol) until the solution was saturated. After stirring at room temperature for 48 h(the reaction was followed by t.l.c.), the solution was evaporated and the residue was suspended in boliling hexane(20 ml). Hot filtration of the suspension gave a white solid, which was purified by recrystallisation from isopropyl alcohol/water to yield 756 mg of **6a**(yield: 79%). mp 139-141°C. ir(nujol): 1698,2236,3190,3408 cm^{-1}. ^{1}H-NMR($CDCl_3$): δ= 1.93 (d,1H,J=8.5); 2.36(d,1H,J=8.5); 3.29(s,1H); 3.52(s,1H); 3.70(d,1H,J=2.0); 5.58-5.72(s,broad,1H); 6.02-6.16(s,broad,1H); 6.08(dd,1H,J=5.5,2.8); 6.59 (dd,1H,J=5.5,3.4); 7.26-7.39(m,5H). Anal.Calc. for $C_{15}H_{14}N_2O$ C:75.60, H:5.92, N:11.75; found C:75.64, H:6.02, N:11.84.

2-endo-cyano-3-endo-phenylbicyclo[2.2.1]hept-5-ene-2-exo-carboamide(6b)

The reaction was carried out as described for **6a**. Starting from **5b**(1.05 g, 4 mmol), 822 mg of **6b**(yield:86%) were obtained. mp 148-150°C(d). ir(nujol): 1692,2237,3191,3409 cm^{-1}. ^{1}H-NMR($CDCl_3$): δ= 1.68(d,1H,J=9.0); 2.21(d,1H, J=9.0); 3.30(s,1H); 3.40(s,1H); 4.18(d,1H,J=2.7); 5.70-5.84(s,broad,1H); 6.33-6.47(s,broad,1H); 6.53(dd,1H,J=4.6,3.2); 6.73(dd,1H,J=4.6,2.9); 7.20-7.34(m,5H). Anal.Calc. for $C_{15}H_{14}N_2O$ C:75.60, H:5.92, N:11.78; found C:75.76, H:6.01, N:11.78.

2-exo-aminocarbonyl-3-exo-phenylbicyclo[2.2.1]hept-5-ene-2-endo-carboxylic acid(7a)

Hydrogen peroxide(30%, 8 ml) was added to a solution of **4a**(600 mg, 2.5 mmol) in 1N NaOH(3 ml). Aqueous 10% NaOH(4 ml) was then added slowly and the reaction mixture was stirred at 55°C. After 3 days, the resulting solution was cooled and acidified to afford a solid which after recrystallisation from aqueous methanol gave **7a** as a white solid(522 mg, 81%). mp 150-151°C(d). ir(nujol): 1648,1719,3338,3446 cm^{-1}. ^{1}H-NMR(DMSO-d_6): δ= 1.59(d, 1H,J=8.8); 2.39(d,1H,J=8.8); 2.80(s,1H); 3.27(s,1H); 3.42(s,1H); 6.10(m, 2H); 6.47(m,1H); 6.80(s,1H); 7.15-7.23(m,5H). Anal.Calc. for $C_{15}H_{15}NO_3$ C: 70.02, H:5.87, N:5.44; found C:70.34, H:5.68, N:5.51.

2-endo-aminocarbonyl-3-endo-phenylbicyclo[2.2.1]hept-5-ene-2-exo-carboxylic acid(7b)

7b was prepared from acid **4b**(1.29 g, 5 mmol) by the same procedure as isomer **7a**, to give a solid(955 mg) which was shown to be a mixture of starting material and amide **7b** in a 1:1 ratio. The reaction was repeated using the above-mentioned mixture as the starting material. When the reaction had finished, the solution was acidified to afford(730 mg, 56%) **7b** as a white solid, which was recrystallised from methanol/water. mp 123°C(d). ir(nujol): 1629,1725,3370,3489 cm^{-1}. ^{1}H-NMR(Acetone-d_6): δ= 1.53(m,2H); 3.02(s, 1H); 3.61(s,1H); 4.34(d,1H,J=3.4); 5.20-5.38(s,broad,1H); 6.00-6.18(s, broad,1H); 6.23(m,1H); 6.74(m,1H); 7.24-7.27(m,5H). Anal.Calc. for $C_{15}H_{15}NO_3$ C:70.02, H:5.87, N:5.44; found C:70.18, H:5.92, N:5.34.

2-exo-cyano-3-exo-phenylbicyclo[2.2.1]heptane-2-endo-carboamide(8a)

A solution of compound **6a**(1.19 g, 5 mmol) in methanol(50 ml) was hydrogenated at atmospheric pressure with 10% palladium-carbon(100 mg) as a catalyst. Removal of the catalyst and the solvent gave the required compound **8a** (1.06 g, 88%) as a white solid, which was recrystallised from isopropyl alcohol/water. mp 178°C(d). ir(nujol): 1698,2237,3166,3400 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ= 1.58-1.71(m,5H); 2.35(d,1H,J=10.1); 2.75(s,1H); 2.84(s,1H);

3.83(d,1H,J=1.5); 5.64-5.80(s,broad,1H); 6.04-6.20(s,broad,1H); 7.21-7.38 (m,5H). Anal.Calc. for $C_{15}H_{16}N_2O$ C:74.97, H:6.71, N:11.66; found C:74.38, H:6.74, N:11.43.

2-endo-cyano-3-endo-phenylbicyclo[2.2.1]heptane-2-exo-carboamide(8b)

In the same way, compound **6b**(1.19 g, 5 mmol) was hydrogenated to give 1.10 g of **8b**(yield:89%). mp 175°C(d). ir(nujol): 1699,2237,3166,3401 cm^{-1}. ^{1}H-NMR($CDCl_3$): δ = 1.51-2.12(m,6H); 2.75(s,1H); 2.79(s,1H); 4.08(d,1H, J=1.6); 5.87-6.08(s,broad,1H); 6.36-6.58(s,broad,1H); 7.20-7.40(m,5H). Anal.Calc. for $C_{15}H_{16}N_2O$ C:74.97, H:6.71, N:11.66; found C:74.80, H:6.97, N:11.43.

2-exo-aminocarbonyl-3-exo-phenylbicyclo[2.2.1]heptane-2-endo-carboxylic acid (9a)

In a similar way, compound **7a** (717 mg, 3 mmol) was hydrogenated to give 684 mg of **9a** as a white solid, which was recrystallised from methanol/water (yield:94%). mp 147-148°C(d). ir(nujol): 1652,1705,3342,3454 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 1.24(m,2H); 1.50-1.54(m,3H); 2.23(s,1H); 2.34(m,1H); 2.69(s, 1H); 3.54(s,1H); 6.09(s,1H); 6.66(s,1H); 7.11-7.19(m,5H). Anal.Calc. for $C_{15}H_{17}NO_3$ C:69.48, H:6.61, N:5.40; found C:69.51, H:6.54, N:5.36.

2-endo-aminocarbonyl-3-endo-phenylbicyclo[2.2.1]heptane-2-exo-carboxylic acid(9b)

In a similar way, compound **7b**(717 mg, 3 mmol) was hydrogenated to give 690 mg of **9b**(yield:95%). mp 145°C(d). ir(nujol): 1670,1715,3133,3461 cm^{-1}. ^{1}H-NMR(DMSO-d_6): δ = 1.49-1.68(m,5H); 2.17(m,1H); 2.51(s,1H); 3.10(s,1H); 3.99(s,1H); 4.80-5.00(s,broad,1H); 5.00-5.30(s,broad,1H); 7.29-7.32(m,5H). Anal.Calc. for $C_{15}H_{17}NO_3$ C:69.48, H:6.61, N:5.40; found C:69.60, H:6.59, N:5.39.

3-exo-phenylbicyclo[2.2.1]heptane-2-spiro-5'-hydantoin(10)

Compound **8a**(880 mg, 3.66 mmol) was added at 0°C to a sodium hypobromite solution, prepared from NaOH(1.47 g, 37 mmol) and Br_2(630 mg, 4 mmol) in water(50 ml) and the mixture was stirred at the same temperature for 1 h. The reaction mixture was then heated at 85-90°C for 90 min. After cooling, the mixture was extracted with ether(2x15 ml) and the aqueous layer was made acidic by adding 10% HCl. The precipitate was collected by filtration, washed with water and then recrystallised from methanol/water to give 450 mg of compound **10**(yield:48%). mp 271-273°C(d). ir(nujol): 1719,1739, 3275,3421,3495 cm^{-1}. ^{1}H-NMR(DMSO-d_6): δ = 1.39-1.78(m,5H); 2.27(s,1H); 2.70

(d,1H,J=10.6); 2.86(s,1H); 3.33(s,1H); 7.03-7.26(m,5H); 8.36(s,1H); 10.18 (s,1H). Anal.Calc. for $C_{15}H_{16}N_2O_2$ C:70.29, H:6.29, N:10.93; found C:69.82, H:6.41, N:10.64.

2-exo-amino-2-endo-cyano-3-endo-phenylbicyclo[2.2.1]heptane(11)

Similarly, to a sodium hypobromite solution(30 ml), prepared from NaOH (1.6 g, 40 mmol) and Br_2(785 mg, 5 mmol), amide **8b**(960 mg, 4 mmol) was added at 0°C. After stirring at the same temperature for 1 h, the mixture was heated at 85-90°C for 90 min. After cooling, the reaction mixture was made acidic by adding 10% HCl and extracted with ether(3x15 ml). The aqueous layer was made basic by adding 10% NaOH, then extracted with ether (3x20 ml) and the organic layer was separated and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave 460 mg of compound **11** as a white solid, which was recrystallised from hexane(yield:54%). mp 72-74°C. ir(nujol): 2233,3347,3376 cm^{-1}. ^{1}H-NMR($CDCl_3$): δ= 1.50-1.81(m,5H); 2.10(d,1H,J=10.2); 2.43(s,1H); 2.64(s,1H); 2.45-2.70(s,broad,2H); 3.09(s, 1H); 7.26-7.37(m,5H). Anal.Calc. for $C_{14}H_{16}N_2$ C:79.20, H:7.59, N:13.19; found C:79.30, H:7.30, N:13.33.

2-exo-amino-3-exo-phenylbicyclo[2.2.1]heptane-2-endo-carboxylic acid hydrochloride(12a)

To a sodium hypobromite solution(20 ml), prepared from NaOH(0.8 g, 20 mmol) and Br_2(392 mg, 2.5 mmol), compound **9a**(518 mg, 2 mmol) was added at 0°C. After stirring at the same temperature for 1 h, the mixture was heated at 85-90°C for 90 min. After cooling, the reaction mixture was extracted with ether(2x15 ml) and the aqueous layer was then made acidic with 10% HCl and again extracted with ether(2x15 ml). Evaporation in vacuo of the aqueous layer and the addition of water to the residue were repeated several times. The residue was thoroughly extracted with methanol/ether(1:1); the solvent was eliminated and the remaining solid was suspended in acetone and then filtered to give 462 mg of **12a**(yield:86%). ir(nujol): 1723 cm^{-1}.

2-endo-amino-3-endo-phenylbicyclo 2.2.1 heptane-2-exo-carboxylic acid hydrochloride(12b)

12b(412 mg, 77%) was similarly prepared from **9b**(518 mg, 2 mmol). ir(nujol): 1739 cm^{-1}.

2-exo-amino-3-endo-phenylbicyclo 2.2.1 heptane-2-endo-carboxylic acid hydrochloride(13)

Aminonitrile **11**(424 mg, 2 mmol) was dissolved in 6N HCl(20 ml) and the solution was heated at 125°C for 15 h in a sealed tube. After cooling, the

reaction mixture was filtered off, evaporated and the residue was suspended in acetone(10 ml) and then filtered to give compound **13**(442 mg, 82%) as a white solid. ir(nujol): 1725 cm^{-1}.

2-endo-amino-3-exo-phenylbicyclo[2.2.1]heptane-2-exo-carboxylic acid(14a) Spirohydantoin **10**(256 mg, 1 mmol) was dissolved in an alkaline solution prepared from $Ba(OH)_2$(1.5 g, 8.75 mmol) in water(25 ml) and the mixture was heated in a sealed tube at 140°C for 3 days. After cooling, the alkaline solution was filtered off and the filtrate was saturated with CO_2 gas until no further precipitation occurred. After removal of the precipitate, the filtrate was concentrated to dryness under reduced pressure to afford 150 mg of **14a**(yield:64%). ^{1}H-NMR(D_2O): δ = 1.44-1.74(m,5H); 2.55(s,2H); 2.70 (m,1H); 2.84(s,1H); 7.19-7.23(m,5H). Anal.Calc. for $C_{14}H_{17}NO_2$ C:72.70, H:7.41, N:6.06; found C:72.71, H:7.49, N:6.18.

2-exo-amino-3-endo-phenylbicyclo[2.2.1]heptane-2-endo-carboxylic acid(14b) 300 mg of the aminoacid hydrochloride **13** were dissolved in water(50 ml) and this solution was passed through a Dowex column 50x8(25 g, H^+ form). The column was washed with water until the eluates were neutral and aminoacid **14b** was eluted from the column using aqueous ammonia(1N; 300 ml). After evaporation of combined eluates, the remaining residue was recrystallised from water. ^{1}H-NMR(D_2O): δ = 1.43-1.80(m,5H); 2.39(m,1H); 2.63(s,1H); 2.78 (s,1H); 3.20(d,1H,J=2.0); 7.05-7.34(m,5H). Anal.Calc. for $C_{14}H_{17}NO_2$ C:72.70, H:7.41, N:6.06; found C:72.85, H:7.28, N:6.11.

2-exo-amino-3-exo-phenylbicyclo[2.2.1]heptane-2-endo-carboxylic acid(15a) 300 mg of the aminoacid hydrochloride **12a** were dissolved in water(50 ml) and this solution was passed through a Dowex column 50x8(25 g, H^+ form). The column was washed with water until the eluates were neutral and amino-acid **15a** was eluted from the column using aqueous ammonia(1N; 300 ml). After evaporation of combined eluates, the remaining residue was recrystallised from water. ^{1}H-NMR(D_2O): δ= 1.51-1.58(m,5H); 1.86(m,1H); 2.37(s,1H); 2.65(s,1H); 3.10(s,1H); 7.35-7.38(s,5H). Anal.Calc. for $C_{14}H_{17}NO_2$ C:72.70, H:7.41, N:6.06; found C:72.64, H:7.33, N:6.12.

2-endo-amino-3-endo-phenylbicyclo[2.2.1]heptane-2-exo-carboxylic acid(15b) 300 mg of the aminoacid hydrochloride **12b** were dissolved in water(50 ml) and this solution was passed through a Dowex column 50x8(25 g, H^+ form). The column was washed with water until the eluates were neutral and amino-acid **15b** was eluted from the column using aqueous ammonia(1N, 300 ml). After evaporation of combined eluates, the remaining residue was recrystalli-

sed from water. ^{1}H-NMR(D_2O): δ= 1.39-1.64(m,5H); 2.01(m,1H); 2.48(s,1H); 2.65(s,1H); 3.53(d,1H,J=2.0); 7.16-7.29(m,5H). Anal.Calc. for $C_{14}H_{17}NO_2$ C:72.70, H:7.41, N:6.06; found C:72.80, H:7.30, N:6.13.

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