# Unequivocal Synthesis of the Four *d,l*-Pairs of 3-Substituted 2-Aminonorbornane-2-carboxylic Acids

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**Synopsis.** 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 amino acids through simple reactions.

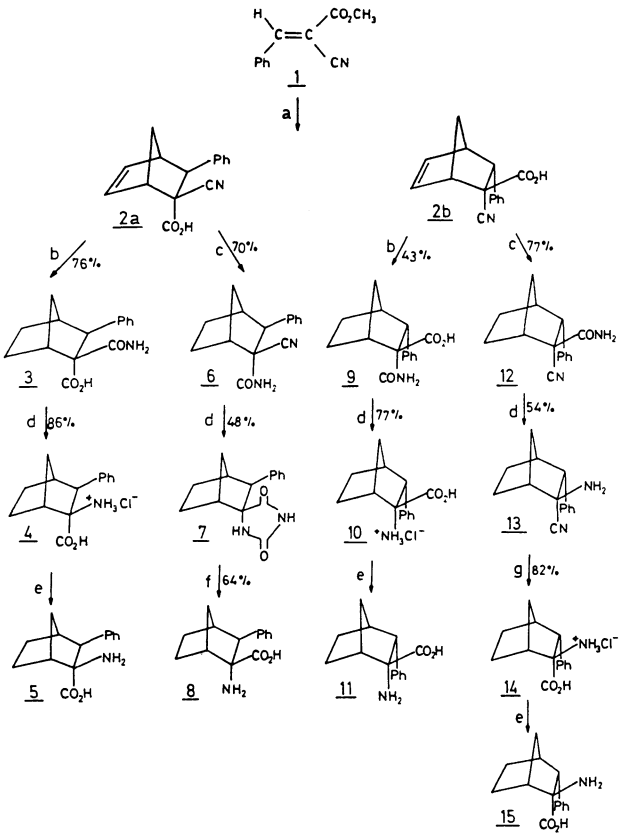
Alicyclic amino acids, such as those with a norbornane skeleton are of interest because of their noticeable biological activities.[1] The parent compounds, 2-aminonorbornane-2-carboxylic acids, can be obtained by Diels–Alder reaction between *N*-acyl-α,β-dehydroalaninates and cyclopentadiene.[2] Nevertheless, the Diels–Alder reaction between cyclopentadiene and *N*-acyl-α,β-dehydrophenylalaninates does not lead to the corresponding amino acids. Furthermore, the reaction of ethyl α-nitrocinnamate with cyclopentadiene followed by catalytic hydrogenation and hydrolysis leads to a mixture of diastereoisomers,[3] so we have directed our attention to the development of a new unequivocal synthesis of the four *d,l*-pairs of the 2-amino-3-phenylnorbornane-2-carboxylic acids (**5**, **8**, **11**, **15**). This synthesis is based on the use of a compound with well-defined stereochemistry and two withdrawing groups which are precursors of both, amino and carboxyl groups as a dienophile, the compound being methyl (*E*)-α-cyanocinnamate[4] (**1**).

## Experimental

Table 1 shows the conditions and proportions of the reagents used in the Diels–Alder reaction, together with the results obtained. Figure 1 shows the synthetic route leading to the four amino acids (**5**, **8**, **11**, **15**) and the yields obtained in each step. All products were characterized by elemental analysis and $^1$H NMR spectra. Microanalyses were carried out on a Perkin-Elmer 240-B analyser. $^1$H NMR spectra were recorded on a Varian XL-200. Deuterochloroform and $D_2O$ were used as solvents with TMS as the internal standard (the chemical shifts are reported in ppm on the δ scale, coupling constants in Hz).

**2a:** mp 73—75 °C. Found: C, 76.05; H, 6.08; N, 5.60%: Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53%: $^1$H NMR ($CDCl_3$): δ=1.91 (1H, dd, *J*=9.6, 2.0), 2.33 (1H, d, *J*=9.6), 3.29 (1H, s), 3.61 (1H, d, *J*=2.0), 3.65 (1H, s), 3.84 (3H, s), 6.06 (1H, dd, *J*=5.6, 2.8), 6.57 (1H, dd, *J*=5.6, 3.2), 7.28—7.42 (5H, m).

**2b:** mp 88—90 °C. Found: C, 76.10; H, 6,12; N, 5.40%:




a) i. cyclopentadiene, ii. $HO^-/H_2O$, iii. iodolactone sep. b) i. $H_2O_2/HO^-$, ii. $H_2$(Pd/C). c) i. $CH_2N_2/Et_2O$, ii. $NH_3$/MeOH, iii. $H_2$(Pd/C). d) $Br_2/HO^-$, Δ. e) Dowex 50W 20—50 mesh, $H^+$ form. f) $Ba(OH)_2/H_2O/\Delta$. g) 6 M HCl/Δ.

Fig. 1.

Table 1. Diels–Alder Reaction between Methyl (*E*)-α-Cyanocinnamate (**1**) and Cyclopentadiene

| Lewis acid | Solvent | Diene/dienophile | *t*/h | *T*/°C | Conversion[a]/% | Ratio[a] of **2a**/**2b** methyl esters |
|---|---|---|---|---|---|---|
| — | 1,4-Dioxane | 3:1 | 24 | 60 | 83 | 1.59:1 |
| — | MeOH | 3:1 | 24 | 60 | 94 | 1.60:1 |
| — | $H_2O$[b] | 3:1 | 7.5 | 25 | 100 | 1.68:1 |

a) Determined by HPLC. Column: 5 μm Hypersil RMOS ($C_8$). Eluent: MeOH: $H_2O$; 60% of MeOH 1 min; gradient 60 to 75% of MeOH 1 min; 75% of MeOH. Flow rate 2 ml $min^{-1}$. Detection 210 nm $\varepsilon_1:\varepsilon_{2a}:\varepsilon_{2b}$=1.217:1.137:1.00. b) Because of the low solubility a suspension of both diene and dienophile in water was used.

Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53%: $^1H$ NMR ($CDCl_3$): $\delta$=1.72 (1H, d, $J$=9.2), 1.94 (1H, d, $J$=9.2), 3.34 (1H, s), 3.52 (1H, s), 3.90 (3H, s), 4.14 (1H, d, $J$=2.7), 6.50 (1H, dd, $J$=5.5, 3.2), 6.69 (1H, dd, $J$=5.5, 3.0), 7.23—7.32 (5H, m).

**5**: mp>300 °C. Found: C, 72.64; H, 7.33; N, 6.12%: Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06%: $^1H$ NMR ($D_2O$): $\delta$=1.51—1.58 (5H, m), 1.86 (1H, m), 2.37 (1H, s), 2.65 (1H, s), 3.10 (1H, s), 7.35—7.38 (5H, m).

**8**: mp>300 °C. Found: C, 72.71; H, 7.49; N, 6.18%: Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06%: $^1H$ NMR ($D_2O$): $\delta$=1.44—1.74 (5H, m), 2.55 (2H, s), 2.70 (1H, m), 2.84 (1H, s), 7.19—7.23 (5H, m).

**11**: mp>300 °C. Found: C, 72.80; H, 7.30; N, 6.13%: Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06%: $^1H$ NMR ($D_2O$): $\delta$=1.39—1.64 (5H, m), 2.01 (1H, m), 2.48 (1H, s), 2.65 (1H, s), 3.53 (1H, d, $J$=2.0), 7.16—7.29 (5H, m).

**15**: mp>300 °C. Found: C, 72.85; H, 7.28; N, 6.11%: Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06%: $^1H$ NMR ($D_2O$): $\delta$=1.43—1.80, (5H, m), 2.39 (1H, m), 2.63 (1H, s), 2.78 (1H, s), 3.20 (1H, d, $J$=2.0), 7.05—7.34 (5H, m).

## Results and Discussion

Table 1 shows the results obtained in the Diels–Alder reaction between cyclopentadiene and methyl (*E*)-α-cyanocinnamate (**1**); as can be seen, high levels of conversion can be achieved under several conditions. Several authors have reported that the use of water greatly increases the rate of Diels–Alder reactions;[5] 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.

Cycloadducts **2a** and **2b** were easily separated and converted into the corresponding amino acids by means of simple reactions, but some difficulties stemming from the low reactivity of the groups placed at the endo position, appeared. So when the partial hydrolysis of the cyano group in **2b** was carried out under the conditions used with **2a** (55 °C, 3 days) an equimolecular mixture of **2b** and **9** was obtained, which was treated again under the same conditions to obtain **9** with a total yield of 70% with regard to the initial amount of cycloadduct **2b**.

The Hofmann rearrangement has been the object of several revisions[6] and the results obtained are strongly dependent on the nature of the starting amide. Under the conditions used amide **6** yielded spirohydantoin **7**, probably due to the low intermolecular reactivity of the intermediate isocyanate. The hydrolysis of this spirohydantoin is difficult because position 5 of the hydantoin ring is completely substituted, whereas position 3 is unsubstituted.[7] Hydrolysis was achieved by heating spirohydantoin **7** with aqueous $Ba(OH)_2$ at 140 °C in a closed flask for three days.

Finally the transformation of amino nitrile **13** into amino acid hydrochloride **14** is again made difficult by the low reactivity of the cyano group at the endo position. The transformation was made by heating amino nitrile **13** with 6M HCl (1 M=1 mol $dm^{-3}$) at 125 °C in a closed flask for fifteen hours.

To sum up, the described synthetic route constitutes a new way to the synthesis of these four amino acids through very simple reactions.

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