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# Enantioselective synthesis of amino acids from pentacyclo[5.4.0.0$^{2,6}$.0$^{3,10}$.0$^{5,9}$]undecane-8,11-dione

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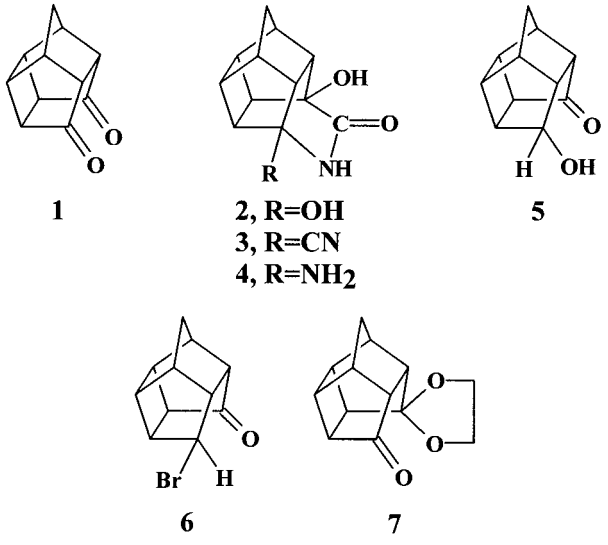
**Abstract**—Treatment of (+)-pentacyclo[5.4.0.0$^{2,6}$.0$^{3,10}$.0$^{5,9}$]undecane-8-one with sodium cyanide and ammonium carbonate produced an optically active hydantoin of which the 4′-carbonyl group of the hydantoin ring is in the less sterically hindered equatorial position. Hydrolysis of the latter with barium hydroxide produced (−)-8-amino-pentacyclo[5.4.0.0$^{2,6}$.0$^{3,10}$.0$^{5,9}$]undecane-8-carboxylic acid which has the 1*S*,2*R*,3*R*,5*R*,6*R*,7*S*,8*R*,9*R*,10*R* configuration. In a similar way, (+)-6-amino-tetracyclo-[6.2.0.0$^{4,11}$.0$^{5,9}$]undec-2-ene-6-carboxylic acid with 1*R*,4*R*,5*R*,6*R*,8*S*,9*S*,11*R* configuration was obtained from (−)-tetracyclo[6.3.0.0$^{4,11}$.0$^{5,9}$]undec-2-ene-6-one. The latter was obtained from (−)-11-hydroxy-pentacyclo[5.4.0.0$^{2,6}$.0$^{3,10}$.0$^{5,9}$]undecan-8-one. 

## 1. Introduction

As part of a programme that is concerned with the synthesis and chemistry of amino acids with cage carbon structures, we sought to synthesise novel unsymmetrical α-amino acids utilising pentacyclo[5.4.0.0$^{2,6}$.0$^{3,10}$,0$^{5,9}$]undecane-8,11-dione (**1**) and derivatives thereof. The dione (**1**) is easily obtained from the Diels–Alder adduct of cyclopentadiene and *p*-benzoquinone by intramolecular photocyclisation.[1] The Strecker reaction would be the obvious method of choice to convert polycyclic ketones into amino acids.

It was previously shown[2] that **1** produces the dihydroxy lactam derivative **2** upon treatment with one equivalent of aqueous sodium cyanide. With an excess of sodium cyanide the cyano hydroxy lactam derivative **3** is obtained,[3] whereas with Strecker reagents (mixture of ammonium chloride, sodium cyanide and ammonium hydroxide) the amino hydroxy lactam derivative **4** is produced.[3] Attempts[2,4] to convert the mono keto derivatives **5**, **6** and **7** into amino acids via amino nitrile derivatives failed.




**1** **2, R=OH** **3, R=CN** **4, R=NH$_2$** **5**

**6** **7**

## 2. Results and discussion

In order to minimise steric hindrance it was decided to investigate the utilisation of pentacyclo-[5.4.0.0$^{2,6}$.0$^{3,10}$.0$^{5,9}$]undecane-8-one (**10**) as the starting material for the synthesis of α-amino acids. The ketone **10** can be obtained readily from the dione **1** as a racemic mixture[5] or in the optically active form (+)-**10**[6] by enantioselective microbial asymmetric reduction of the dione **1** with Baker's yeast[7] or by horse liver alcohol dehydrogenase-catalysed (HLADH catalysed) reduction of **1**.[6] In the latter case (−)-**8** was reported[6] to form in 74% yield,

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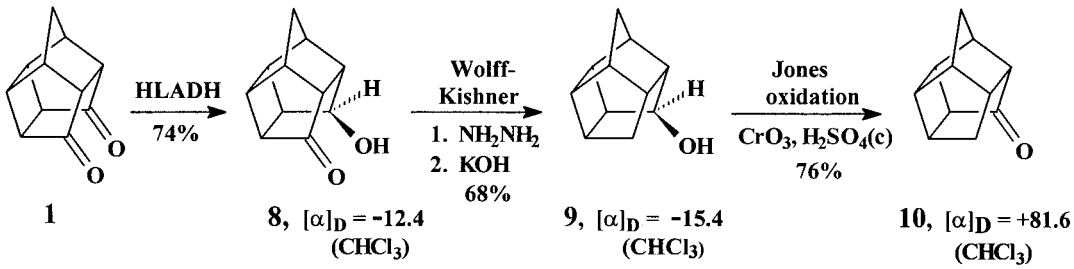


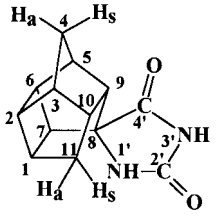

**Scheme 1.**

which was then converted into the optically active ketone (+)-**10** as outlined in Scheme 1.[6]

The efficiency of this conversion was improved to a great extent by using a more concentrated solution of reactants and extended reaction times. It was possible to increase the yield of **8** from the reported[6] 74% to a quantitative conversion (95%). Huang–Minlon reduction[8] of the latter produced the alcohol (−)-**9** in high yield (89%) compared to the 68% yield reported[6] for a Wolff–Kishner reduction of (−)-**8**. Chromium trioxide oxidation of (−)-**9** in acetic acid produced (+)-**10** as the sole product.

Although no amino nitrile could be isolated from a conventional Strecker reaction on the monoketone (+)-**10**, it was argued that the presence of ammonium carbonate could possibly trap the amino nitrile from the established equilibrium. In order to verify this possibility, a mixture of (+)-**10**, sodium cyanide, ammonium chloride, 25% ammonia (aq) and ammonium carbonate was kept at 40–60°C for 10 h in a sealed glass tube. Extraction with dichloromethane rendered a product of which the EI mass spectrum exhibits a molecular ion at *m/z* 230, confirming the desired hydantoin formation. The infrared spectrum also clearly shows the presence of two carbonylic absorption bands at 1760 and 1715 $cm^{-1}$ and two different N–H stretching vibration absorptions at 3280 and 3205 $cm^{-1}$ of a hydantoin ring. However, two possible orientations of the hydantoin ring can be obtained theoretically. The isomers differ in having the 4′-carbon atom of the hydantoin ring

**Table 1.** $^{1}H$ and $^{13}C$ NMR data of **11**




**11**

| Proton/carbon | $\delta_H$[a] (ppm) | *J* (Hz) | $\Delta^b$ $\delta_H$ (ppm) | $\delta_C$[a] (ppm) | $^1J$ (Hz) | $>^1J$ (Hz) | $\Delta^c$ $\delta_H$ (ppm) |
|---|---|---|---|---|---|---|---|
| 1 | 2.838 | | 0.45 | 35.40 Dm | 139.4 | | 0.13 |
| 2 | 2.652 q | 6.8 | 0.50 | 41.30 D | 145.0 | | 0.10 |
| 3 | 2.273 | | 0.29 | 46.00 Dm | 142.1 | | 0.09 |
| 4a | 1.243 d | 10.8 (a,s) | 0.28 | 33.82 T | 130.9 | | 0.08 |
| 4s | 1.640 d | 10.8 | 0.28 | | | | |
| 5 | 2.989 | | | 42.41 Dd | 139.1 | 8.4 | 0.16 |
| 6 | 2.752 q | 7.1 | 0.58 | 41.19 D | 145.0 | | 0.15 |
| 7 | 2.591 t | 6.6 | 0.64 | 41.40 D | 146.0 | | 0.30 |
| 8 | | | | 68.52 S(br) | | | 0.07 |
| 9 | 2.324 | | 0.80 | 48.15 Dm | 141.7 | | 0.28 |
| 10 | 2.528 | | 0.44 | 42.06 Dm | 140.2 | | 0.12 |
| 11a | 1.267 dt | 8.4, 3.4 | 0.44 | 28.35 DD | 127.1;132.7 | | 0.15 |
| 11s | 1.450 d | 13.7 (a,s) | 0.86 | | | | |
| 1′-NH | 7.566 | | | | | | |
| 3′-NH | 10.525 | | | | | | |
| 2′-CO | | | | 157.29 S | | | 1.00 |
| 4′-CO | | | | 178.70Sd | | 7.5 | 0.82 |

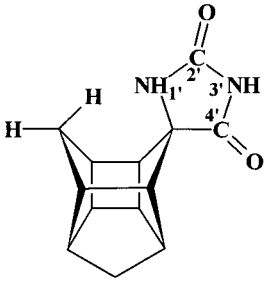
500 MHz for $^{1}H$ and 125 MHz for $^{13}C$.

[a] Solvent $CDCl_3$. Symbols in capital letters refer to patterns resulting from directly bonded protons and lower case letters refer to (C,H)- couplings over more than one bond. S=singlet, D or d=doublet, T or t=triplet, dt=doublet of triplets, q=quartet and m=multiplet. Where couplings are not specified complex coupling patterns are observed.

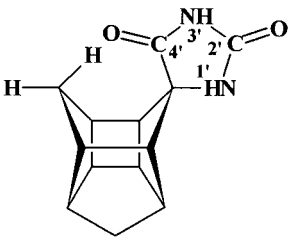
[b] Induced shift after addition of Eu(fod)$_3$-$d_{30}$ to the sample in $CDCl_3$. Values relative to that for H-5.

[c] Induced shifts after addition of Eu(fod)$_3$-$d_{30}$ relative to that of 2′ CO taken as 1.00.

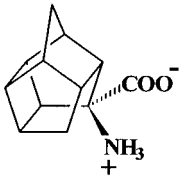
equatorial in one isomer (**11**) and the more sterically hindered axial orientation in the other (**12**), in reference to the boat cyclohexane ring.



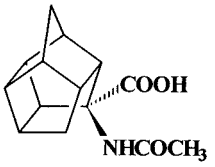
**11**, $[\alpha]_D = -3.5$ ($CH_3OH$)



**12**



**13**, $[\alpha]_D = -20.8$ (32% HCl)



**14**

The structure of the product (−)-**11** was elucidated from an extensive $^1$H and $^1$C NMR investigation. The $^1$H and $^{13}$C NMR data are collected in Table 1.

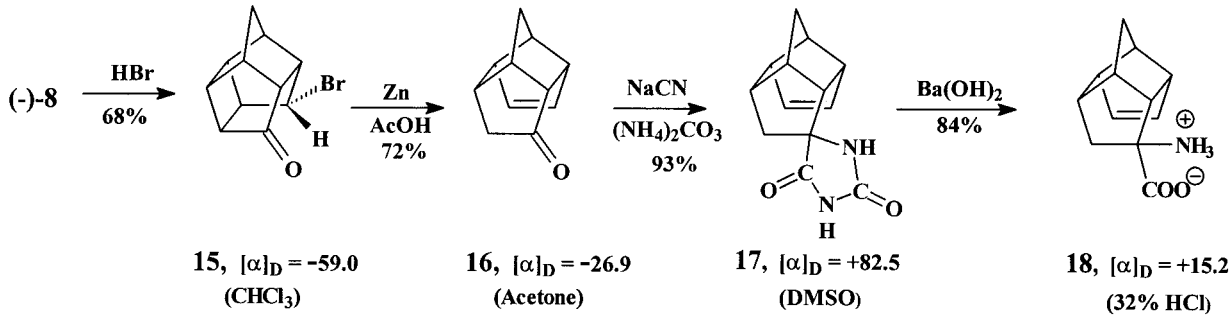
The 500 MHz $^1$H NMR spectrum of the hydantoin **11** recorded in deuterated dimethyl sulfoxide [$(CD_3)_2SO$] exhibits some resonance overlapping. Better resolved spectra were obtained in deuterated trichloromethane ($CDCl_3$). The cage protons resonate between $\delta_H$ 1.0 and $\delta_H$ 3.0 and are registered as a complex signal pattern. The spectrum shows two AX spin systems that appear at high field and are associated with two different methylene groups. In order to distinguish between the chemical shifts of the two methylene groups the geminal coupling constants ($^2J$ values) were compared. It was previously observed that the geminal coupling constants of the bridgehead methylene protons (H-4) of pentacyclo-undecane derivatives are in the order of 10 Hz.[2,3,4,9] It can therefore be concluded that the doublets at $\delta_H$ 1.243 and 1.640 ($J_{a,s}$=10.8 Hz) can be associated with the methylene protons on C-4 and that the high field chemical shifts at $\delta_H$ 1.267 (doublet of triplets; $J$=3.4 Hz) and $\delta_H$ 1.450 (doublet; $J_{a,s}$=13.7 Hz) can be attributed to the protons H-11$_a$ and H-11$_s$ of the methylene carbon atom C-11, respectively.

Two deuterium exchangeable protons are registered at $\delta_H$ 7.566 and $\delta_H$ 10.525. The sharp resonance signal at $\delta_H$ 7.566 can be assigned to the 1′-nitrogen proton and the broad signal registered at $\delta_H$ 10.525 to the 3′-nitrogen proton which is shifted to lower field by the two adjacent carbonyl groups. The $^{13}$C NMR spectrum of the hydantoin **11** exhibits two signals of carbonyl carbon atoms characteristic of a carbonyl group coupled to a NH-group at $\delta_C$ 178.70 and a carbonyl group bearing two NH-groups at $\delta_C$ 157.29. Two methylene carbon resonances are registered at $\delta_C$ 33.82 and $\delta_C$ 28.35 and a methine carbon resonance appears at $\delta_C$ 68.52. Some overlapping occurs for the methine carbon resonances that complicates assignment to certain nuclei. The assignments of the different resonance signals in the $^1$H and $^{13}$C spectra of the hydantoin **11** to certain nuclei were made from heteronuclear chemical shift correlation (HETCOR)[10] and proton–proton chemical shift correlation (COSY)[11] 2D-experiments assisted by hydrogen multiple quantum correlation (HMQC)[12] and hydrogen multiple bond correlation (HMBC)[12] experiments. The results of the HMBC experiments were used as cross references for the $^1$H assignments made from COSY and HMQC experiments, while identification of overlapping resonances in the $^{13}$C NMR spectrum followed from HMBC experiments. The assignments are given in Table 1. The assignments of the methine cage protons were made with COSY experiments starting from the methylene protons on C-4, which show correlation peaks with the H-3 and H-5 protons. H-3 shows cross correlation peaks with H-10 and the methylene protons on C-11. The assignment of the methine protons followed from these allocations.

It is not possible to distinguish between the structural isomers **11** and **12** from the $^1$H and $^{13}$C data given in Table 1. Force field calculations[13,14] showed that the hydantoin **11** is of lower steric energy than the hydantoin **12**. The calculated distance between the proton on the 1′-nitrogen atom in **11** and the H$_s$ proton on C-11 is 1.98 Å. These protons are close enough to experience a nuclear Overhauser effect (NOE).[15] Irradiation at the 1′-NH signal should stimulate absorption and emission processes for this proton, and this stimulation will be transferred through space to the relaxation mechanism of H$_s$-11. The spin–lattice relaxation of H$_s$-11 will be speeded up, leading to a net increase in the NMR absorption signal of H$_s$-11. A rotating frame Overhauser (ROESY) experiment[16] performed on a 300 MHz NMR instrument (mixing time 200 ms) indeed showed a strong NOE effect between 1′-NH and H$_s$-11. This observation was verified by an NOE difference experiment in which a proton is irradiated prior to detection of the spectrum. A second spectrum without pre-irradiation is subtracted from the first one, and the process is repeated until the weak difference peaks are clearly observed. A difference NOE experiment in which the 1′-NH proton was irradiated (irradiation time 1.5 s) showed a strong NOE with H$_s$-11, confirming the close proximity effect between these protons. A much weaker effect on H-9 and H-7 was observed. These observations unambiguously assign structure **11** to the hydantoin.

In no experiment could the presence of the hydantoin **12** be detected. Force field calculations on **12** showed an interatomic distance of 2.15 Å between the proton on 1′-NH and H-5, 2.94 Å between 1′-NH and H-7, 2.95 Å between 1′-NH and H-6 and 3.16 Å between 1′-NH and H-9. An NOE between 1′-NH and H-5 should be observed if **12** was present in detectable quantities.

The result of addition of Eu(fod)$_3$-d$_{30}$ to the $CDCl_3$ solution of the hydantoin **11** are also given in Table 1. Complexation on both the NH–CO-groups occur as evidenced by the large-induced $^{13}$C shifts observed for the carbonyl carbon atoms. No extra resonances, which could be associated with




**Scheme 2.**

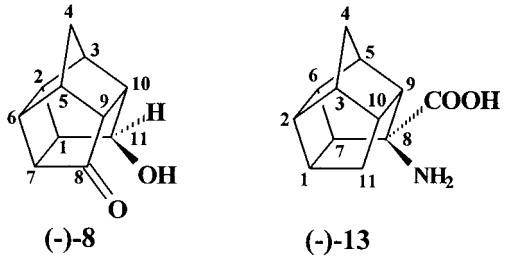
**12**, could be observed with the addition of Eu(fod)$_3$-d$_{30}$. The purity of **11** could be claimed confidently to be better than 95%.

Hydrolysis of the hydantoin **11** with barium hydroxide[17] produced the expected amino acid (−)-**13** in 67% yield. The p$K_a$ values of the amino acid was found to be p$K_{a1}$=3.7±0.1 and p$K_{a2}$=9.4±0.1. The amino acid was isolated at pH=6.5 and should therefore be in the zwitterionic form.

As expected a negative ion FAB MS analysis of the amino acid **13** in a sodium hydroxide containing glycerol matrix shows a strong molecular ion at *m/z* 204 ($[M-H]^-$). A strong molecular ion is obtained at *m/z* 206 ($[M+H]^+$) when a hydrochloric acid containing glycerol matrix is used and recording is done in the positive ion mode.

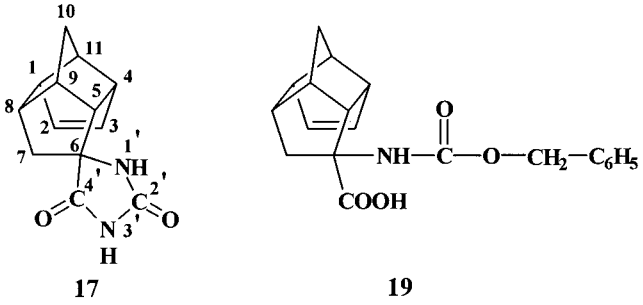
The infrared spectrum of the amino acid **13** exhibits a broad complex absorption pattern of peaks between 2345 and 3630 cm$^{-1}$ typical of amino acids. A strong carbonylic absorption peak appears at 1715 cm$^{-1}$. Further characterisation of amino acid **13** was done by acetylation with acetic anhydride and sodium acetate at room temperature whereby the *N*-acetyl derivative **14** was obtained.

The optically active keto alcohol (−)-**8** was assigned[6] the 1*R*,2*R*,3*R*,5*S*,6*S*,7*S*,9*R*,10*S*,11*R* configuration. It can thus be concluded that the amino acid (−)-**13** has the 1*S*,2*R*,3*R*,5*R*,6*R*,7*S*,8*R*,9*R*,10*R* configuration (referring to the skeletal numbering given below).




The selectivity of hydantoin formation in cage structures was also demonstrated for the enone **16**. The latter was obtained enantioselectively as shown in Scheme 2. Treatment of (−)-**8** with hydrobromic acid produced the bromoketone (−)-**15** in 68% yield. Since nucleophilic attack can only occur from the *exo*-face[2] no racemisation can occur and only the *exo*-bromo derivative (−)-**15** is obtained. Treatment of the latter with zinc in acetic acid produced the optically pure enone (−)-**16**. A racemic mixture of the two possible enantiomers of **16** was previously synthesised[18] from a racemic mixture of **15**. The latter was obtained from a different route.[18]

Treatment of (−)-**16** with a mixture of soduim cyanide, ammonium chloride, 25% ammonia (aq) and excess ammonium carbonate produced the hydantoin (+)-**17**. The assignments of $^1$H and $^{13}$C resonance signals to certain nuclei were made as described before and are given in Section 3. The calculated [13,14] distance between the proton on the 1′-nitrogen atom and H-3 for **17** is 2.10 Å and are close enough to experience an NOE effect.[15] Irradiation of the 1′-NH signal indeed showed a strong NOE with H-3 confirming the close proximity between these protons. No NOE with any of the protons H-7, H-5 and H-9 could be observed. An NOE between 1′-NH and H-9 (2.15 Å interatomic distance) should be observed if the 1′-NH group was in the *exo* position in any detectable quantities. No extra resonances, which should be associated with the latter isomer, could be observed with the addition of Eu(fod)$_3$-d$_{30}$. A similar regioselectivity was observed previously[19–22] for hydantoin formation on cyclohexanone derivatives in the chair conformation where the 4′-carbonyl group of the hydantoin ring is directed towards the less sterically hindered (equatorial) position when the ketone is treated with sodium cyanide and ammonium carbonate.




Hydrolysis of (+)-**17** in an autoclave at 180°C produced the amino acid (+)-**18** which was characterised by its FAB mass spectra in positive and negative ion mode as described above for **13** as well as conversion into the benzyloxycarbonyl derivative **19**. As (+)-**18** was derived from (−)-**8** with known configuration[6] a 1*R*,4*R*,5*R*,6*R*,8*S*,9*S*,11*R* configuration (referring to numbering in **17**) could be assigned to (+)-**18**.

## 3. Experimental

### 3.1. General

Infrared spectra (KBr-disc) were recorded on a Nicolet 550 Magna-IR-spectrometer. EI mass spectra were obtained at 70 eV on a Micromass Autospec-Tof mass spectrometer. FAB mass spectra were obtained by bombardment with a 1 mA beam of 8 keV accelerated neutral xenon atoms produced by an Ion-Tech FAB gun fitted to a VG 7070-E mass spectrometer. NMR spectra were recorded on a Brucker WM 500 FT and a Varian Gemini-300 spectrometer. Melting points are uncorrected.

**3.1.1. Improved synthesis of (−)-8.** The dione **1** (1.5 g, 8.6 mmol) in a Sörensen phosphate buffer[23] solution (100 $cm^3$, pH=7) containing the reduced form of β-nicotineamide-adenine dinucleotide (NADH, 0.1 g, Boehringer Manheim), ethanol (1 $cm^3$) and horse liver alcohol dehydrogenase (HLADH, 1 $cm^3$, Boehringer Manheim) was stirred at 25°C for 5 d. Extraction of the product with dichloromethane (40 $cm^3$), treatment with activated charcoal (0.2 g) and removal of the excess solvent (35 $cm^3$) by distillation under reduced pressure, produced the optically active hydroxyketone (−)-**8** (1.45 g, 95%, mp 230°C, $[\alpha]_D^{25}$= −12.4 in chloroform, lit.[6]: mp 230–232.5°C, $[\alpha]_D$= −12.4) as colourless crystals. The IR, MS and NMR data were identical to those of the corresponding racemate prepared according to the Dekker's procedures.[5]

**3.1.2. Huang–Minlon reduction of (−)-8.** A mixture of the hydroxyketone (−)-**8** (1 g, 5.68 mmol) and hydrazine hydrate (2 $cm^3$, 98%) in diethylene glycol (20 $cm^3$) was maintained at 120°C for 1.5 h. The mixture was allowed to cool down to 80°C after which potassium hydroxide (1 g, 25 mmol) was added. The excess hydrazine hydrate and water was removed from the reaction mixture by distillation. Distillation was terminated when the temperature reached 190°C. The reaction mixture was refluxed for 3 h at 190°C after which the product was separated from the reaction mixture by steam distillation utilising steam from an external source. The distillate was extracted with dichloromethane (2×25 $cm^3$). The organic layer was dried (anhydrous sodium sulfate), filtered and the excess solvent (40 $cm^3$) removed under reduced pressure to produce the alcohol (−)-**9** as colourless crystals (0.82 g, 89%, mp 208–210°C after sublimation, $[\alpha]_D^{25}$= −15.4 in chloroform, lit.[6]: mp 209–211°C, $[\alpha]_D$= −15.4). The IR, MS and NMR data were identical to those of the corresponding racemate prepared according to Dekker's procedures.[5]

**3.1.3. Oxidation of (−)-9.** A solution (−)-**9** (1.0 g, 6.2 mmol) in acetic acid (5 $cm^3$) was added dropwise over a period of 10 min with stirring to a mixture of chromium trioxide (1.2 g, 12 mmol), acetic acid (15 $cm^3$) and water (2 $cm^3$). The reaction mixture was stirred at 90°C for 4 h, cooled to room temperature and diluted with water (60 $cm^3$). The crude product was extracted with dichloromethane (3×20 $cm^3$). The dichloromethane extract was washed successively with water (2×25 $cm^3$), saturated aqueous sodium hydrogen carbonate (2×25 $cm^3$) and water (50 $cm^3$). Removal of the solvent under reduced pressure and recrystallisation from cyclohexane produced pure (+)-**10** as colourless needles (0.75 g, 76%, mp 194–195°C, $[\alpha]_D^{25}$=+81.5 in chloroform, lit.[6]: mp 196–197°C, $[\alpha]_D$=+81.6). The IR, MS and NMR data were identical to those of the corresponding racemate prepared according to the Dekker's procedures.[5]

**3.1.4. Synthesis of the hydantoin (−)-11.** A mixture of the monoketone (+)-**10** (1 g, 6.3 mmol), sodium cyanide (0.5 g, 10.2 mmol), ammonium chloride (0.5 g, 9.4 mmol), an excess of ammonium carbonate (2 g) and ammonia (10 $cm^3$) was sealed in a glass tube. The solution was stirred in a water bath at 40–60°C for 10 h. The mixture was poured into water (800 $cm^3$) and the solution boiled until no more ammonia vapours could be detected. The product was extracted with dichloromethane (3×20 $cm^3$). The organic layer was dried (anhydrous sodium sulfate), filtered and the excess solvent (50 $cm^3$) removed under reduced pressure. Upon cooling (0°C), the product **11** (1.2 g, 83%, mp 230°C, $[\alpha]_D^{25}$= −3.5 in methanol) was obtained as colourless crystals. IR (KBr-disc): $\nu_{max}$ 3280, 3205, 2968, 1760, 1715, 1417, 1278, 1261, and 769 $cm^{-1}$; EI MS: *m/z* 230 ($M^+$), 202 ($M^+$−CO). Calcd for $C_{13}H_{14}N_2O_2$: C, 67.83; H, 6.09, N, 12.17%. Found: C, 67.71; H, 6.02, N, 12.08%. See Table 1 for the NMR data of the hydantoin **11**.

**3.1.5. Synthesis of 8-amino-pentacyclo[5.4.0.0$^{2,6}$.0$^{3,10}$.0$^{5,9}$]-undecane-8-carboxylic acid (−)-13.** The optically active hydantoin (−)-**11** (1 g, 4.3 mmol) was added to a clear 4% aqueous solution of barium hydroxide (60 $cm^3$) and refluxed for 30 h.[16] A drying tube filled with soda lime was placed on the reflux condenser to prevent atmospheric carbon dioxide entering the reaction flask. The reaction mixture was transferred to a beaker and diluted with water (1000 $cm^3$). An excess of ammonium carbonate (5 g) was added to the solution and then heated to boiling point with stirring. The hot solution was filtered to remove the insoluble barium carbonate. The pH of the filtrate was adjusted to 6.5 by addition of hydrochloric acid (4 mol $dm^{-3}$). The aqueous solution was evaporated on a steam bath to a small volume (±5 $cm^3$) and the amino acid (**13**, 0.6 g, 67%, mp 325°C dec., $[\alpha]_D^{25}$= −20.8 in 32% HCl) filtered off as a white solid. IR (KBr-disc) $\nu_{max}$ 3460, 3402, 2959, 1713, 1630, 1606, 1540, 1458, 1409, 1368, 1261, 1196, 1114 and 794 $cm^{-1}$. FAB (glycerol+HCl matrix) MS (positive ion), *m/z* 206 ($[M+H]^+$). FAB (glycerol+NaOH matrix) MS (negative ion), *m/z* 204 ($[M-H]^-$). Calcd for $C_{12}H_{15}NO_2$: C, 70.24; H, 7.32; N, 6.83%. Found: C, 69.98; H, 7.23; N, 6.72%, p$K_{a1}$=3.7±0.1 and p$K_{a2}$=9.4±0.1 (determined from the pH titration curve obtained from the titration of the protonated acid form of **13** with sodium hydroxide). Due to poor solubility in conventional NMR solvents no NMR data was obtained.

**3.1.6. Synthesis of 8-acetylamino-pentacyclo-[5.4.0.0$^{2,6}$.0$^{3,10}$.0$^{5,9}$]undecane-8-carboxylic acid (14).** A solution of the amino acid **13** (0.5 g, 2.4 mmol) in acetic anhydride (10 $cm^3$) and sodium acetate (0.05 g, 0.6 mmol) was stirred for 3 h at room temperature. 100 $cm^3$ water was added and the reaction mixture stirred for 5 h. The monoacetate (**14**, 0.4 g, 66%, mp 181–183°C, $[\alpha]_D^{25}$= −15.2) precipitated and was filtered off. IR (KBr-disc) $\nu_{max}$ 3420, 2959, 1715, 1631, 1573, 1278 $cm^{-1}$. EI MS, *m/z* 247 ($M^+$), 202 ($M^+$−COOH). FAB (glycerol+HCl matrix) MS

(positive ion), *m/z* 248 ($[M+H]^+$). Calcd for $C_{14}H_{17}NO_3$: C, 68.02; H, 6.88; N, 5.67%. Found: C, 67.94; H, 6.80; N, 5.52%. $^{13}C$ NMR [$(CD_3)_2SO$, 75 MHz]: $\delta_C$ 174.59 (S, COOH), 169.03 (S, CO of $NHCOCH_3$), 64.10 (S, C-8), 47.56 (D, C-6), 46.22 (D, C-5), 42.39 (D, C-2), 42.28 (D, C-3), 42.02 (D, C-10), 40.97 (D, C-9), 37.86 (D, C-7), 35.13 (D, C-1), 33.51 (T, C-4), 28.14 (T, C-11) and 22.46 (Q, $CH_3$). $^1H$ NMR [$(CD_3)_2SO$, 300 MHz]: $\delta_H$ 11.80 (1H, COO*H*), 8.46 (1H, N*H*), 3.17 (1H, m, H-7), 2.58 (1H, m, H-1), 2.52 (1H, m, H-2), 2.51 (1H, m, H-9), 2.38 (1H, m, H-10), 2.37 (1H, m, H-6), 2.19 (1H, m, H-5), 2.09 (1H, d, $J$=11.3 Hz, H-$11_s$), 2.07 (1H, m, H-3), 1.78 (3H, s, C$H_3$), 1.62 (1H, d, $J$=9.9 Hz, H-$4_s$), 1.14 (1H, d, $J$=9.9 Hz, H-$4_a$), and 0.93 (1H, dt, $J$=9.4, 3.2 Hz, H-$11_a$).

**3.1.7. Synthesis of the bromoketone (−)-15.** The hydroxy ketone (−)-**8** (1 g, 5.68 mmol) was stirred for 3 h at 80°C in 48% hydrogen bromide (10 $cm^3$). The warm solution was poured over crushed ice and the precipitate filtered off, dissolved in acetone and treated with activated charcoal. After filtration the filtrate was concentrated under vacuo and the solid recrystallised from methanol to produce **15** (0.93 g, 68%, mp 84–85°C, lit.[18]: 84.5–85.3°C, $[\alpha]_D^{25}$= −59.0 in chloroform) as colourless crystals. The IR, MS and NMR data of (−)-**15** were identical to those of an authentic sample[18] of a racemic mixture.

**3.1.8. Synthesis of the enone(−)-16.** A mixture of the bromoketone (−)-**15** (1 g, 4.2 mmol), glacial acetic acid (12 $cm^3$) and an excess of zinc powder (1.6 g) was refluxed for 8 h. The reaction mixture was cooled and the residue filtered off and washed with diethyl ether (10 $cm^3$). The filtrate was neutralised with a saturated sodium bicarbonate solution and the crude product was extracted with diethyl ether (3×10 $cm^3$). After removal of the solvent under vacuo and chromatography with silica gel as stationary phase and 1:1 *n*-hexane–ethyl acetate mixture as eluant (−)-**16** (0.48 g, 72%, mp 190–191°C, lit.[18]: 192–193°C, $[\alpha]_D^{25}$= −26.9 in acetone) was obtained as colourless needles. The IR, MS and NMR data of (−)-**16** were identical to that of an authentic sample[18] of a racemic mixture.

**3.1.9. Synthesis of the hydantoin (−)-17.** A mixture of the enone (−)-**16** (1 g, 6.3 mmol), sodium cyanide (0.5 g, 10.2 mmol), ammonium chloride (0.5 g, 9.4 mmol), an excess of ammonium carbonate (2 g), and 25% ammonia (10 $cm^3$) and ethanol (5 $cm^3$) was sealed in a glass tube. The mixture was stirred in a water bath at 60°C for 24 h. The reaction mixture was poured into water (800 $cm^3$) and boiled until no more ammonia vapours could be detected. The reaction mixture was cooled to room temperature and the product extracted with dichloromethane (3×20 $cm^3$). The combined organic layers were washed with water, dried (anhydrous sodium sulfate), filtered and the filtrate concentrated in vacuo. The product **17** (1.33 g, 93%, mp 243°C, $[\alpha]_D$=+82.5° in dimethylsulphoxide) crystallised out as colourless needles. IR (KBr-disc): $\nu_{max}$ 3290, 3230, 3065, 2965, 2940, 1780, 1715, 1410, 1285 and 780 $cm^{-1;}$ EI MS: *m/z* 230. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.83; H, 6.09; N, 12.17%. Found: C, 67.75; H, 6.01; N, 12.09%. $^{13}C$ NMR. [$(CD_3)_2SO$, 75 MHz]: $\delta_C$ 180.73 (S, 4′ CO), 156.92 (S, 2′ CO), 140.28 (D, C-3), 138.80 (D, C-2), 70.71 (S, C-6), 58.75 (D, C-11), 55.02 (D, C-5), 51.24 (D, C-9), 46.87 (D, C-1), 46.80 (D, C-4), 41.85 (D, C-8), 39.22 (T, C-7) and 31.34 (T, C-10). $^1H$ NMR [$(CD_3)_2SO$, 300 MHz]: $\delta_H$ 10.5 (1H, br, 3′ N*H*), 7.13 (1H, S, 1′ N*H*), 6.45 (1H, m, H-3), 5.98 (1H, m, H-2), 3.04 (1H, m, H-9), 2.80 (1H, m, H-11), 2.47 (1H, m, H-1), 2.44 (1H, m, H-4), 2.14 (1H, m, H-8), 2.10 (1H, dt, $J$=8.4, 3.2 Hz, H-$7_b$), 2.05 (1H, m, H-5), 1.66 (1H, d, $J$=13.0 Hz, H-$7_a$), and 1.48 (1H, H-10).

**3.1.10. Synthesis of 6-amino-tetracyclo[6.3.0.0$^{4,11}$.0$^{5,9}$]-undec-2-ene-6-carboxylic acid (+)-18.** A mixture of (+)-**17** (1 g, 4.3 mmol) and a 4% barium hydroxide (60 $cm^3$) solution was stirred in an open beaker in an autoclave for 0.5 h at 180°C. The reaction mixture was diluted with water (1000 $cm^3$) and an excess of ammonium carbonate (5 g) was added to the mixture and which was then heated to boiling point with stirring. The hot solution was filtered to remove the insoluble barium carbonate. The pH of the filtrate was adjusted to 6.5 by addition of hydrochloric acid (4 mol $dm^{-3}$) and evaporated on a steam bath to a small volume (~5 $cm^3$) and the amino acid (**18**, 0.75 g, 84%, $[\alpha]_D^{25}$=+15.2 in 32% HCl) filtered off as a white solid. IR (KBr-disc) $\nu_{max}$ 3450, 2787, 2695, 2500, 1738, 1225, 1066, and 695 $cm^{-1}$. FAB (glycerol+HCl matrix) MS (positive ion), *m/z* 206 ($[M+H]^+$). FAB (glycerol+NaOH matrix) MS (negative ion), *m/z* 204 ($[M-H]^-$). Calcd for $C_{12}H_{15}NO_2$: C, 70.24; H, 7.32; N, 6.83%. Found: C, 69.94; H, 7.26; N, 6.77%, p$K_{a1}$=2.6±0.1 and p$K_{a2}$=10.4±0.1 (determined from the pH titration curve obtained from the titration of the protonated acid form of **18** with sodium hydroxide). Due to poor solubility in conventional solvents no NMR data was obtained.

**3.1.11. Synthesis of the benzyloxycarbonyl derivative 19.** A solution of benzyl chloroformate (0.418 g, 2.5 mmol) in toluene (4 $cm^3$) was added to a solution of **18** (0.5 g, 2.4 mmol) in 4 mol $dm^{-3}$ NaOH (20 $cm^3$). The reaction mixture was stirred for 0.5 h. Hydrochloric acid (20 $cm^3$, 4 mol $dm^{-3}$) was added and the precipitated white solid filtered off. Recrystallisation from ethanol produced **19** (0.43 g, 88%, mp 80–81°C) as colourless crystals (plates). IR (KBr-disc) $\nu_{max}$ 3420, 3330, 3270, 3195, 3035, 1690, 1695, 1620, 1610, 1445, 1403, 1344, 1092, 1070 and 730 $cm^{-1}$. FAB (glycerol+NaOH matrix) MS (negative ion), *m/z* 338 ($[M-H]^-$). Calcd for $C_{20}H_{21}NO_4$: C, 70.79; H, 6.20; N, 4.13%. Found: C, 70.45; H, 6.12; N, 4.05%. $^{13}C$ NMR [$(CD_3)_2SO$, 75 MHz]: $\delta_C$ 176.45 (S, COOH), 158.85 (S, CO of $NHCOOCH_2Ph$), 141.28 (D, C-3), 139.55 (D, C-2), 136.45 (S, Ph), 128.63 (D, Ph), 128 03 (D, Ph), 127.28 (D, Ph), 72.24 (T, *C*$H_2$Ph), 71.83 (S, C-6), 57.88 (D, C-11), 54.86 (D, C-5), 50.24 (D, C-9), 47.44 (D, C-1), 45.32 (D, C-4), 42.82 (D, C-8), 41.65 (T, C-7), 32.15 (T, C-10).). $^1H$ NMR [$(CD_3)_2SO$, 300 MHz]: $\delta_H$ 11.8 (br, COO*H*), 7.18–7.93 (5H, m, Ph), 6.45 (1H, m, H-3), 6.16 (1H, br, N*H*), 5.88 (1H, m, H-2), 4.18 (2H, s, C$H_2$Ph), 3.05 (1H, m, H-9), 2.83 (1H, m, H-11), 2.49 (1H, m, H-1), 2.41 (1H, m, H-4), 2.19 (1H, dt, $J$=8.2, 3.0 Hz, H-$7_b$), 2.05 (1H, m, H-8), 1.95 (1H, m, H-5), 1.75 (1H, d, $J$=13.0 Hz, H-$7_a$), 1.46 (2H, m, H-10).

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