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Synthesis of *exo*-3-amino-10-hydroxy-hexacyclo[10.2.1.$0^{2,11}$.$0^{4,10}$.$0^{4,14}$.$0^{9,13}$]-pentadecane-5,7-diene-*endo*-3-carboxyclic acid and *endo*-3-amino-10-hydroxy-hexacyclo[10.2.1.$0^{2,11}$.$0^{4,10}$.$0^{4,14}$.$0^{9,13}$]pentadecane-5,7-diene-*exo*-3-carboxylic acid

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ABSTRACT

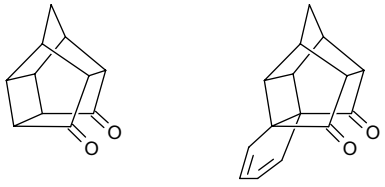
Treatment of hexacyclo[7.4.2.$0^{1,9}$.$0^{3,7}$.$0^{4,14}$.$0^{6,15}$]pentadecane-10,12-diene-2,8-dione with aqueous sodium cyanide produced 2,8-dihydroxy-hexacyclo[7.4.2.$0^{1,9}$.$0^{3,7}$.$0^{4,14}$.$0^{6,15}$]pentadecane-10,12-diene-2,8-lactam and with sodium cyanide, ammonium chloride and ammonium hydroxide, 2-amino-8-hydroxy-hexacyclo [7.4.2.$0^{1,9}$.$0^{3,7}$.$0^{4,14}$.$0^{6,15}$]pentadecane-10,12-diene-2,8-lactam was obtained. 10-Hydroxy-hexacyclo [10.2.1.$0^{2,11}$.$0^{4,10}$.$0^{4,14}$.$0^{9,13}$]pentadecane-5,7-diene-3-one was converted into the corresponding aminonitrile and hexacyclo[10.2.1.$0^{2,11}$.$0^{4,10}$.$0^{4,14}$.$0^{9,13}$]pentadecane-5,7-diene-10-hydroxy-3-spiro-5′-hydantoin. Treatment of the latter with barium hydroxide produced *exo*-3-amino-10-hydroxy-hexacyclo [10.2.1.$0^{2,11}$.$0^{4,10}$.$0^{4,14}$.$0^{9,13}$]pentadecane-5,7-diene-*endo*-3-carboxylic acid. The isomeric *endo*-3-amino-10-hydroxy-hexacyclo[10.2.1.$0^{2,11}$.$0^{4,10}$.$0^{4,14}$.$0^{9,13}$]pentadecane-5,7-diene-*exo*-3-carboxylic acid was obtained from 3-cyano-3-ureido-hexacyclo[10.2.1.$0^{2,11}$.$0^{4,10}$.$0^{4,14}$.$0^{9,13}$]pentadecane-5,7-diene-10-ol.

1. Introduction

It is well known that hydrocarbon moieties promote the transport of drugs across cell membranes and increase their affinity for lipophilic regions in receptor molecules.[1] The incorporation of cage carbon frameworks into drugs should have the added advantage that metabolic degradation should be retarded by the inherent stability and steric bulk of the cage skeleton thus prolonging the activity and reducing the frequency of drug administration. Areas in which the introduction of an adamantane moiety has been shown to result in longevity of drug action, increased drug potency, speed of action and receptor site specificity include antibacterial activity,[2] anabolic action,[3] analgesic activity[4] and antiviral activity.[5]

Amino acids are important building blocks for the synthesis of a large number of biologically important compounds and pharmaceutical drugs. However, a literature survey revealed that the synthesis of α-amino acids with cage carbon frameworks barely received any attention.

As part of a programme that is concerned with the synthesis and chemistry of amino acids with cage structures we have sought to synthesise novel α-amino acids by utilising polycyclic ketones with cage structures as substrates in Strecker reactions. It was previously shown[6–8] that the dione **1**[9] is not a suitable substrate to obtain amino acids via Strecker reactions due to the effect of transannular interactions. We decided to investigate the possible utilisation of **2**[10] (Fig. 1) as starting material for the synthesis of amino acids with rigid polycyclic carbon skeletons.



1 2

Figure 1. Cage compounds considered for amino acid synthesis.

2. Results and discussion

Since initial cyanohydrin and subsequent aminonitrile formation is an obvious route for a Strecker reaction, it was decided to investigate the reaction of the dione **2** with sodium cyanide in aqueous medium.

We found that the dione **2** produces the dihydroxy lactam derivative **3** upon treatment with 1 equiv of aqueous sodium cyanide. The dihydroxy lactam **3** is poorly soluble in conventional NMR

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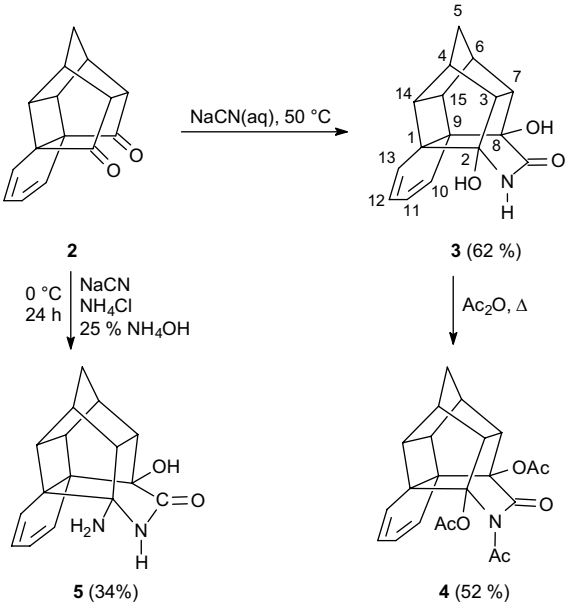
solvents. Compound **3** was characterised by conversion into the triacetate **4** (Scheme 1).



Scheme 1.

A ^{1}H and ^{13}C NMR investigation supported the allocated structure of **4**. NMR data of **4** are given in Experimental section.

Treatment of **2** with an aqueous mixture of 1 equiv sodium cyanide, ammonium chloride and an excess ammonium hydroxide (Strecker reagents) produced the lactam derivative **5**. Support for the correctness of the allocated structure of **5** was obtained from a SIMPLE (secondary isotope multiplets from partially labelled entities) experiment.[11] A proton noise decoupled ^{13}C NMR spectrum was recorded in $(CD_3)_2SO$, which was treated with two drops of a mixture of 60% D_2O and 40% H_2O to impose partial exchange of protons. As expected the quaternary carbon resonance at δ_C 80.58 (C-8) is registered as a double signal due to a β-effect of the OH/OD group where the second signal appears 0.1 ppm upfield. The carbonyl group of the lactam ring experience β- and γ-effects and is registered with signals appearing at 0.1 and 0.02 ppm upfield (effect of NH/ND and OH/OD groups). Amine protons are the most rapidly exchanging and as a result are also the most difficult to inhibit in the neutral state. The carbon resonance at δ_C 75.03 (C-2) suffers therefore only a β-effect from the nearby N–H group (second signal appears 0.1 ppm upfield). Upon forcing complete protonation of the NH_2-group in acidic medium a complex spectrum of signals is observed for C-2 due to the slower exchange in the NH_3^+-group.

Lactams can in many cases be hydrolysed to their corresponding amino acids. However, attempted hydrolysis of **3** and **5** under alkaline or acidic conditions only yielded starting material.

A suitable substrate for the synthesis of novel amino acids with cage structures could be derived from the dione **2** by reduction of the latter with zinc and acetic acid whereby the unsaturated ketol **6**[12] is obtained. Treatment of **6** with an aqueous solution of sodium cyanide containing acetic acid produced the cyanohydrin **7** (Scheme 2).

The cyanohydrin **7** and the hydroxy ketone **6** were both converted into the aminonitrile **8** by the treatment of **7** with ammonia or **6** with a mixture of sodium cyanide, ammonium chloride and ammonium hydroxide. These results are remarkable since no aminonitriles could previously[13] been isolated from similar reactions on the mono keto derivatives **9**, **10**, **11** and **12** (Fig. 2).

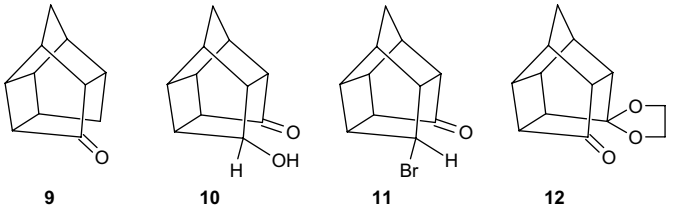


Figure 2. Keto derivatives, which produce labile aminonitriles.

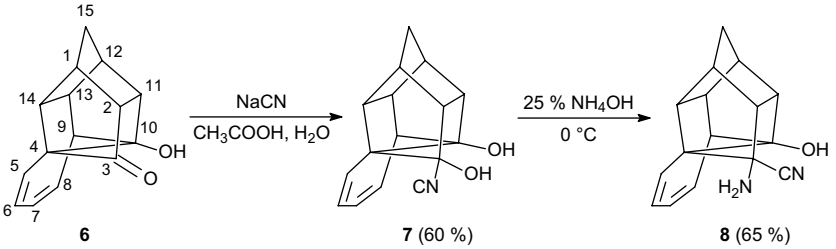
Attempted hydrolysis of the nitrile group of **8** in acidic or alkaline media failed and no amino acid could be obtained.

Hydantoin derivatives are established precursors for the synthesis of amino acids. Treatment of **8** with ammonium carbonate produced the hydantoin **13** as a precipitate. When **6** was treated with a mixture of sodium cyanide, ammonium chloride, ammonium hydroxide and ammonium carbonate the hydantoin **13** again precipitated from the reaction mixture (Scheme 3).

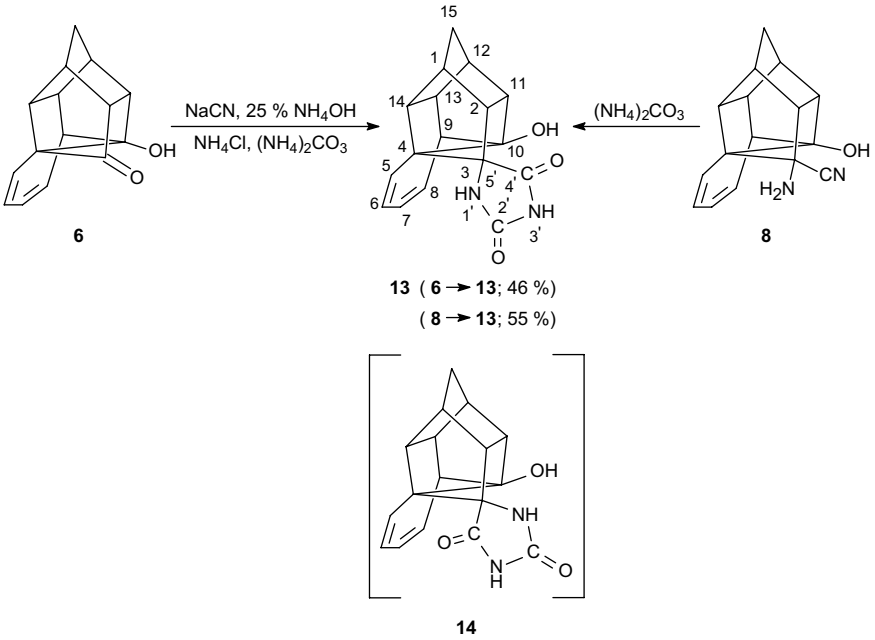
The 300 MHz ^{1}H NMR spectrum of **13** shows the presence of three deuterium exchangeable protons, which are registered at δ_H 7.63, δ_H 7.39 and δ_H 7.26. The resonance at δ_H 7.63 can be assigned to the 3′-nitrogen proton, which is shifted to lower field by the two adjacent carbonyl groups. The resonance at δ_H 7.39 can be associated with the 1′-nitrogen proton and the resonance at δ_H 7.26 with the OH proton. The latter experiences probably a strong deshielding by the diamagnetic anisotropy, which is induced by the nearby carbonyl group (4′-CO) of the hydantoin ring. The calculated[14] distance between the OH proton and the oxygen atom of the carbonyl group in **13** is 1.695 Å.

In order to discriminate between **13** and **14** as a possible structure for the hydantoin obtained as described above from **8** or **6** (Scheme 3) an NOE investigation was conducted. The calculated[14] distance between the proton of the 1′-nitrogen atom in **14** and the proton of the OH-group is 1.862 Å. These protons are close enough to experience a nuclear Overhauser effect (NOE).[15] A rotating frame Overhauser (ROESY) experiment[16] showed no NOE effect between the 1′-NH and the OH proton. This observation was verified by NOE-difference and NOESY experiments,[15] which rules **14** out as a possible structure for the hydantoin.

The isomer **14** should be obtained from cyclisation of the hydantoic acid derivative **16**. The latter was prepared (Scheme 4) from the hydrochloride salt of the aminonitrile **8** by the treatment



Scheme 2.



Scheme 3.

with potassium cyanate in glacial acetic acid whereby **15** was obtained. Hydrolysis of **15** with 20% hydrochloric acid at 60 °C produced the desired hydantoic acid derivative **16**.

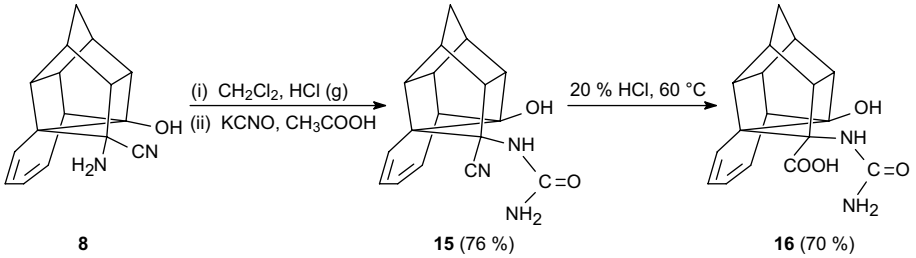
The ^{1}H NMR spectrum of **15** shows the presence of three deuterium exchangeable protons at δ_H 6.86 (OH), δ_H 6.07 (NH_2) and δ_H 5.99 (NH). In a NOESY-experiment nuclear Overhauser effects (NOEs) between the protons resonating at δ_H 6.86 (OH) and δ_H 6.07 (NH_2) as well as between δ_H 6.86 (OH) and δ_H 5.99 (NH) were observed. These observations confirm the close proximity between the OH-group and the $NHCONH_2$-group in **15** and unambiguously confirm the allocated structure of **15**.

Attempted cyclisation of **16** with 20% hydrochloric acid at 100 °C to produce **14** failed and only starting material was recovered. Normally quantitative conversion of **16** into **14** should be achieved under these reaction conditions.[17] Thermal cyclisation of **16** could also not be achieved and it was found to be stable up to its melting point.

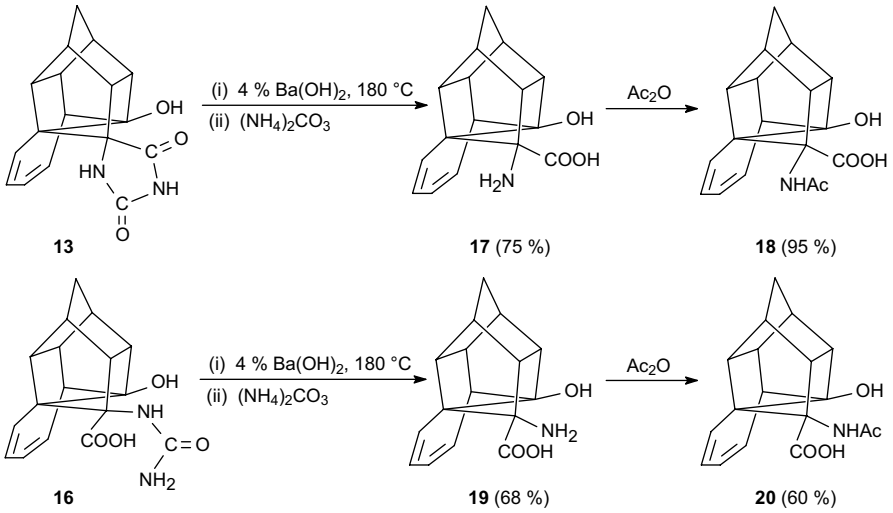
The hydantoin **13** and the hydantoic acid derivative **16** were both hydrolysed with barium hydroxide[18] to produce the desired novel amino acids **17** and **19,** respectively (Scheme 5). As **6** was derived from the *meso* dione **2** it is obvious that **17** as well as **19** are racemic mixtures of enantiomers.

As expected negative ion FABMS analysis of the amino acids **17** and **19** in sodium hydroxide containing glycerol matrices shows strong molecular ions at *m*/*z* 270 ($[M-H]^-$). Strong molecular ions are obtained at *m*/*z* 272 ($[M+H]^+$) for both **17** and **19** when hydrochloric acid containing glycerol matrices are used and recording is done in the positive ion mode. The infrared spectra of **17** and **19** are very similar except in the N–H and O–H stretching vibration region where a broad absorption peak is observed around 3427 cm^{-1} for **19** whereas broad absorption bands at 3350, 3445 and 3552 cm^{-1} are registered for **17**.

Further characterisation of the amino acids **17** and **19** was done by selective acetylation of the amino groups by the treatment with acetic anhydride at room temperature. The mono acetates **18** and **20** were obtained in high yield. The EI, MS, ^{1}H and ^{13}C NMR spectra supported mono acetylation. The IR spectra of **18** and **20** exhibit significant differences. The ^{1}H NMR spectra of **18** and **20** recorded in $(CD_3)_2SO$ both exhibit deuterium exchangeable protons at δ_H 7.84 (OH) and δ_H 4.62 (NH) integrating for one proton each. The carboxylic proton of **20** is registered at δ_H 12.19 as a broad signal (δ_H 12.06–12.32). The carboxylic proton of **18** is recorded at higher field and is observed as a much broader signal around δ_H 12.04 (δ_H 11.40–12.68). A NOESY-experiment performed on **20** revealed the close proximity between the OH and NHAc groups. An NOE effect is observed between the OH proton of C-10 and the NH and CH_3 protons of the nearby NHAc group. An NOE effect between the NH proton and the proton resonating at δ_H 2.49 (H-11) is also registered. The latter also shows an NOE effect with the OH proton, which in turn also experiences an NOE effect with the proton resonating at δ_H 2.18 (H-9). The calculated[14] distance between the OH proton and H-11 in **20** is 2.640 Å and between the NH proton and H-11 3.054 Å. The distance between the NH proton and H-2 is 3.398 Å and no NOE effect could be observed. A NOESY-experiment



Scheme 4.



Scheme 5.

performed on **18** showed an NOE effect between the NH proton and the proton resonating at δ_H 2.29 (H-1). The calculated[14] distance between H-1 and the NH proton of **18** is 2.462 Å. No NOE effect between the NH proton and other methine proton resonances could be observed. The assignment of the resonance at δ_H 2.29 to H-1 in **18** was verified by a COSY-experiment, which shows correlation peaks between the resonance signals of the AB spin system of the methylene protons on C-15 [d, δ_H 1.04 (J_{AB}=10.1 Hz); d, δ_H 1.17 (J_{AB}=10.1 Hz)] and the protons resonating at δ_H 2.29 (H-1) and δ_H 2.25 (H-12).

3. Conclusion

We have succeeded in synthesising racemic mixtures of enantiomers of *exo–endo* (**17**) as well as *endo–exo* (**19**) amino acid derivatives utilising the *meso* dione **2**. The latter was converted into the ketol **6**, which reacted in a remarkable stereoselective manner towards hydantoin (**13**) and hydantoic acid (**16**) formation. Hydrolysis of **13** and **16** produced the desired amino acids.

4. Experimental

4.1. 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. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Varian Gemini-300 spectrometer. Melting points are uncorrected.

4.2. 2.8-Dihydroxy-hexacyclo[7.4.2.0^{1,9}.0^{3,7}.0^{4,14}.0$^{6.15}$]pentadecane-10,12-diene-2,8-lactam (3)

A suspension of **2**[10] (1.5 g, 6.64 mmol) in water (60 cm^3) was stirred in an ice bath for 10 min. A solution of sodium cyanide (0.4 g, 8.16 mmol) in water (1 cm^3) was added drop wise over a period of 3 h and the reaction mixture stirred for a further 15 h at 50 °C. Evaporation to dryness on a water bath and extraction on a Soxhlet apparatus with ethyl acetate as extractant produced **3** (1.1 g, 4.09 mmol, mp 240 °C). IR (KBr-disc): ν_{max} 3395, 3360, 3165, 2950, 1680, 1365, 1290, 1180, 1080, 1075, 925 and 720 cm^{-1}. EIMS, *m*/*z* 269 (M^+). Calcd for $C_{16}H_{16}NO_3$: C, 71.44; H, 5.62; N, 5.21%. Found: C, 71.42; H, 5.60; N, 5.18%.

4.3. Acetylation of 3

A solution of **3** (0.5 g, 1.86 mmol) in acetic acid anhydride (20 cm^3) was refluxed for 2 h. The excess acetic anhydride was decomposed with ice water and the crystalline product **4** (0.38 g, 0.96 mmol, mp 207 °C) filtered off. IR (KBr-disc): ν_{max} 3200, 1770, 1740, 1720, 1380, 1340, 1245, 1235, 1220, 1165, 1040 and 720 cm^{-1}. EIMS, *m*/*z* 395 (M^+). Calcd for $C_{22}H_{21}NO_6$: C, 66.90; H, 5.36; N, 3.55%. Found: C, 66.86; H, 5.33; N, 3.52%. ^{13}C NMR ($CDCl_3$), δ_C 173.91 (s), 169.68 (s), 169.38 (s), 167.45 (s), 124.25 (d), 124.02 (d), 120.62 (d), 119.51 (d), 96.17 (s), 86.64 (s), 53.84 (d), 52.32 (s), 51.87 (s), 51.10 (d), 48.09 (d), 46.98 (d), 45.71 (d), 43.74 (d), 34.22 (t), 27.85 (q), 21.36 (q) and 21.19 (q). ^{1}H NMR ($CDCl_3$), δ_H 5.49–5.85 (m, 4×H), 3.36–3.48 (m, 2×H), 2.65–3.01 (m, 4×H), 2.40 (s, 3×H, CH_3), 2.12 (s, 3×H, CH_3), 2.04 (s, 3×H, CH_3), 1.60 (d, J_{AB}=10.6 Hz, $^1/_2$ ×CH_2) and 1.29 (d, J_{AB}=10.6 Hz, $^1/_2$ ×CH_2).

4.4. 2-Amino-8-hydroxy-hexacyclo[7.4.2.0^{1,9}.0^{3,7}.0^{4,14}.0$^{6.15}$]-pentadecane-10,12-diene-2,8-lactam (5)

To an ice cooled mixture of 25% ammonia solution (15 cm^3), sodium cyanide (0.4 g, 8.16 mmol) and ammonium chloride (0.4 g, 7.4 mmol) the dione **2** (1 g, 4.42 mmol) was added in one portion and the reaction mixture was stirred for 24 h in a sealed flask immersed in ice water. The reaction mixture was evaporated to dryness and the product (**5**, 0.4 g, 1.49 mmol, mp 220 °C) extracted on a Soxhlet apparatus with ethyl acetate as extractant and recrystallised from 1,4-dioxane. IR (KBr-disc): ν_{max} 3410, 3395, 3320, 3165, 3000, 1685, 1310, 1240, 1200, 1115, 1060, 920 and 720 cm^{-1}. FABMS (glycerol–HCl) *m*/*z* 269 $(M+H)^+$. Calcd for $C_{16}H_{17}N_2O_2$: C, 71.71; H, 6.02; N, 10.45%. Found: C, 71.67; H, 5.99; N, 10.41%. ^{13}C NMR [$(CD_3)_2SO$], δ_C 173.66 (s), 124.23 (d), 123.64 (d), 123.28 (d), 122.47 (d), 80.58 (s), 75.03 (s), 54.39 (d), 54.18 (d), 53.65 (d), 52.53 (s), 52.19 (s), 51.59 (d), 45.64 (d), 43.23 (d) and 34.59 (t). ^{1}H NMR [$(CD_3)_2SO$], δ_H 7.79 (s, 1×H, NH), 5.49–5.77 (m, 4×H), 4.73 (s, 1×H, OH), 2.62–2.79 (m, 5×H), 2.17–22.2 (m, 2×H), 2.10 (s, 2×H, NH_2), 1.52 (d, J_{AB}=9.4 Hz, $^1/_2$ ×CH_2) and 1.12 (d, J_{AB}=9.4 Hz, $^1/_2$ ×CH_2).

4.5. 3-Cyano-hexacyclo[10.2.1.0^{2,11}.0^{4,10}.0^{4,14}.0^{9,13}]pentadecane-5,7-diene-3,10-diol (7)

A solution of **6** (0.75 g, 3.3 mmol) in a mixture of water (15 cm^3) and acetic acid (2 cm^3) was stirred in an ice bath and a solution of

sodium cyanide (0.4 g, 8.16 mmol) in water (5 cm^3) was added drop wise. The reaction mixture was stirred for 48 h at room temperature. The product (**7**, 0.5 g, 1.98 mmol, mp 115 °C) was extracted with dichloromethane and recrystallised from chloroform. IR (KBr-disc): ν_{max} 3440, 3235, 3040, 3000, 2920, 2240, 1360, 1285, 1275, 1270, 1140, 1000, 935, 790, 745 and 695 cm^{-1}. EIMS, *m*/*z* 253 (M^+). Calcd for $C_{16}H_{15}NO_2$: C, 75.96; H, 5.98; N, 5.54%. Found: C, 75.91; H, 5.95; N, 5.51%. ^{13}C NMR ($CDCl_3$), δ_C 131.07 (d), 128.79 (d), 126.98 (d), 125.74 (d), 119.97 (s, C≡N), 82.57 (s), 81.76 (s), 62.08 (s), 56.29 (d), 56.26 (d), 53.84 (d), 50.99 (d), 50.98 (d), 46.21 (d), 44.21 (d), and 33.32 (t). ^1H NMR ($CDCl_3$), δ_H 7.27 (s, OH), 5.73–6.13 (m, 4×H), 4.83 (s, 1×H, OH), 2.39–2.64 (m, 7×H), 1.43 (d, J_{AB}=10.5 Hz, $^1/_2$ ×CH_2) and 1.24 (d, J_{AB}=10.5 Hz, $^1/_2$ ×CH_2).

4.6. 3-Amino-3-cyano-hexacyclo[10.2.1.$0^{2,11}$.$0^{4,10}$.$0^{4,14}$.$0^{9,13}$]-pentadecane-5,7-diene-10-ol (8)

A solution of **7** (1 g, 3.95 mmol) in methanol (20 cm^3) was cooled in an ice bath and cooled 25% ammonia (15 cm^3) added in small portions. The reaction mixture was stirred for 6 h in a sealed flask immersed in ice water. The crystalline product (**8**, 0.65 g, 2.58 mmol, mp 170 °C) was filtered off and recrystallised from chloroform.

A mixture of **6** (0.5 g, 2.2 mmol), sodium cyanide (0.4 g, 8.16 mmol), ammonium chloride (0.4 g, 7.4 mmol) and 25% ammonia (15 cm^3) was stirred in a sealed flask immersed in ice water for 48 h. The precipitated product (**8**, 0.39 g, 1.55 mmol, mp 170 °C) was filtered off and recrystallised from chloroform. IR (KBr-disc): ν_{max} 3340, 3320, 3300, 2840–3000, 2215, 1290, 1270, 1265, 1140, 860, 840, 730 and 670 cm^{-1}. EIMS, *m*/*z* 252 (M^+). Calcd for $C_{16}H_{16}N_2O$: C, 76.26; H, 6.39; N, 11.10%. Found: C, 76.18; H, 6.36; N, 11.09%. ^{13}C NMR ($CDCl_3$), δ_C 132.42 (d), 129.19 (d), 126.38 (d), 125.17 (d), 122.31 (s), 81.41 (s), 63.90 (s), 63.52 (s), 56.57 (d), 55.74 (d), 55.49 (d), 52.51 (d), 50.39 (d), 46.25 (d), 46.05 (d) and 33.04 (t). ^1H NMR ($CDCl_3$), δ_H 5.78–6.12 (m, 4×H), 5.28 (br, OH), 2.34–2.72 (m, 7×H), 2.22 (br, NH_2), 1.40 (d, J_{AB}=10.8 Hz, $^1/_2$ ×CH_2) and 1.23 (d, J_{AB}=10.8 Hz, $^1/_2$ ×CH_2).

4.7. Hexacyclo[10.2.1.$0^{2,11}$.$0^{4,10}$.$0^{4,14}$.$0^{9,13}$]pentadecane-5,7-diene-10-hydroxy-3-spiro-5′-hydantoin (13)

A mixture of **6** (0.5 g, 2.2 mmol), sodium cyanide (0.5 g, 10.2 mmol), ammonium chloride (0.5 g, 9.3 mmol), an excess ammonium carbonate (2 g, 20.8 mmol), 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 allowed to cool to room temperature and the precipitate (**13**, 0.3 g, 1.01 mmol, mp 310 °C dec) was filtered off and recrystallised from ethanol.

A mixture of **8** (0.5 g, 1.98 mmol), ammonium carbonate (2 g, 20.8 mmol), 50 cm^3 methanol and 30 cm^3 water was stirred at 40 °C for 15 h. Ammonium carbonate (2 g, 20.8 mmol) was added and stirring at 40 °C continued for 12 h. The reaction mixture was heated on a steam bath to decompose the excess ammonium carbonate. The reaction mixture was allowed to cool to room temperature and the precipitate (**13**, 0.32 g, 1.08 mmol, mp 310 °C dec) was filtered off and recrystallised from ethanol. Compound **13**, IR (KBr-disc): ν_{max} 3395, 3260, 3160, 2965, 2920, 1700, 1690, 1615, 1365, 765, 740 and 705 cm^{-1}. EIMS, *m*/*z* 296 (M^+). Calcd for $C_{17}H_{16}N_2O_3$: C, 68.98; H, 5.45; N, 9.46%. Found: C, 68.93; H, 5.42; N, 9.42%. ^{13}C NMR [$(CD_3)_2SO$], δ_C 170.18 (s), 152.12 (s), 130.58 (d), 128.06 (d), 127.87 (d), 125.04 (d), 82.05 (s), 72.75 (s), 58.43 (d), 55.49 (d), 54.10 (s), 52.22 (d), 51.01 (d), 46.89 (d), 44.73 (d), 44.22 (d) and 32.06 (t). ^1H NMR [$(CD_3)_2SO$], δ_H 7.63 (s, 1×H, 3′-NH), 7.39 (s, 1×H, 1′-NH), 7.26 (s, 1×H, OH), 5.87–5.94 (m, 1×H), 5.72–5.84 (m, 2×H), 5.62 (d, *J*=10.8 Hz, 1×H), 2.65–2.71 (m, 2×H), 2.48–2.53 (m, 3×H), 2.37–2.39 (m, 2×H), 1.22 (d, J_{AB}=9.7 Hz, $^1/_2$ ×CH_2) and 1.10 (d, J_{AB}=9.7 Hz, $^1/_2$ ×CH_2).

4.8. 3-Cyano-3-ureido-hexacyclo[10.2.1.$0^{2,11}$.$0^{4,10}$.$0^{4,14}$.$0^{9,13}$]-pentadecane-5,7-diene-10-ol (15)

A solution of **8** (0.5 g, 1.98 mmol) in dichloromethane (30 cm^3) was saturated with dry hydrogen chloride gas while cooled in ice and stirred for 12 h. The resulting precipitate was collected by filtration (0.52 g, 1.8 mmol) and dissolved in glacial acetic acid (10 cm^3). To this solution powdered potassium cyanate (0.3 g, 3.7 mmol) was added slowly in small portions. After the reaction mixture has been warmed for an hour at 60 °C, it was poured into five times its volume of cold water. The product (**15**, 0.47 g, 1.51 mmol, mp 255 °C) was filtered off and recrystallised from ethanol. IR (KBr-disc): ν_{max} 3460, 3355, 3207, 2975, 2237, 1655, 1615, 1525, 1290, 1260, 1255, 1230, 1120 and 730 cm^{-1}. EIMS, *m*/*z* 311 (M^+). Calcd for $C_{17}H_{17}N_3O_2$: C, 69.15; H, 5.76; N, 14.24%. Found: C, 69.11; H, 5.73; N, 14.21%. ^{13}C NMR [$(CD_3)_2SO$], δ_C 157.84 (s), 132.25 (d), 127.53 (d), 127.43 (d), 124.50 (d), 120.56 (s), 80.45 (s), 64.12 (s), 61.68 (s), 55.66 (d), 53.84 (d), 53.28 (d), 50.99 (d), 50.81 (d), 45.33 (d), 45.05 (d) and 32.44 (t). ^1H NMR [$(CD_3)_2SO$], δ_H 6.86 (s, 1×H, OH), 6.07 (s, 2×H, NH_2), 5.99 (s, 1×H, NH), 5.93–5.96 (m, 1×H), 5.74–5.85 (m, 3×H), 2.83–2.86 (m, 1×H), 2.48–2.53 (m, 2×H), 2.35–2.38 (m, 2×H), 2.26–2.31 (m, 2×H), 1.33 (d, J_{AB}=10.3 Hz, $^1/_2$ ×CH_2) and 1.14 (d, J_{AB}=10.3 Hz, $^1/_2$ ×CH_2).

4.9. Hexacyclo[10.2.1.$0^{2,11}$.$0^{4,10}$.$0^{4,14}$.$0^{9,13}$]pentadecane-5,7-diene-10-hydroxy-3-ureido-3-carboxylic acid (16)

A solution of **8** (0.5 g, 1.98 mmol) in dichloromethane (30 cm^3) was saturated with dry hydrogen chloride gas while cooled in ice and stirred for 12 h. The resulting precipitate was collected by filtration (0.52 g, 1.79 mmol) and dissolved in a mixture of glacial acetic acid (9 cm^3) and water (5 cm^3). After addition of potassium cyanate (1 g, 12.35 mmol) the reaction mixture was refluxed for 2 h. Hydrochloric acid (20%, 4.5 cm^3) was added and refluxing continued for 1 h. The reaction mixture was cooled to room temperature and crushed ice added until precipitation started. The product (**16**, 0.3 g, 1.0 mmol, mp 295 °C) was filtered off and recrystallised from ethanol. IR (KBr-disc): ν_{max} 3560, 3350, 3060, 2960, 1765, 1725, 1430, 1375, 1285, 1265, 1230, 1080, 790, 758 and 730 cm^{-1}. EIMS, *m*/*z* 296 (M^+-H_2O). Calcd for $C_{17}H_{18}N_2O_4$: C, 64.97; H, 5.73; N, 8.92%. Found: C, 64.91; H, 5.69; N, 8.89%. ^{13}C NMR [$(CD_3)_2SO$], δ_C 176.00 (s), 155.76 (s), 132.10 (d), 127.72 (d), 127.24 (d), 124.68 (d), 80.29 (s), 76.49 (s), 60.68 (s), 54.97 (d), 54.29 (d), 54.04 (d), 53.12 (d), 50.70 (d), 44.27 (d), 42.36 (d) and 42.46 (t). ^1H NMR [$(CD_3)_2SO$], δ_H 10.83 (br, COOH), 6.95 (s, 1×H, OH), 5.79–5.87 (m, 1×H), 5.81 (s, 1×H, NH), 5.68–5.75 (m, 2×H), 5.24 (d, *J*=11.02 Hz), 3.00–3.01 (m, 1×H), 2.40–2.49 (m, 3×H), 2.25–2.32 (m, 2×H), 2.19–2.21 (m, 1×H), 1.17 (d, J_{AB}=10.6 Hz, $^1/_2$ ×CH_2) and 1.09 (d, J_{AB}=10.6 Hz, $^1/_2$ ×CH_2).

4.10. Hydrolysis of 15

A mixture of **15** (1.0 g, 3.2 mmol) and 20% hydrochloric acid (10 cm^3) was heated at 60 °C for 1 h with stirring. The reaction mixture was evaporated to dryness on a steam bath and the residue washed with cold water and recrystallised from ethanol to produce **16** (0.8 g, 2.5 mmol).

4.11. *exo*-3-Amino-10-hydroxy-hexacyclo[10.2.1.$0^{2,11}$.$0^{4,10}$.$0^{4,14}$.$0^{9,13}$]pentadecane-5,7-diene-*endo*-3-carboxylic acid (17)

A mixture of **13** (1.0 g, 3.69 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

($250\ cm^3$) and an excess of ammonium carbonate (5 g) was added to the reaction mixture 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 ($4\ mol\ dm^{-3}$) and evaporated on a steam bath to a small volume ($\pm 5\ cm^3$) and the amino acid (**17**, 0.75 g, 2.77 mmol, mp 341 °C dec) filtered off as a colourless solid. IR (KBr-disc): ν_{max} 3552, 3445, 3350, 3018, 3003, 2975, 2942, 2894, 2870, 2780, 1620, 1574, 1494, 1331, 1368, 1295, 1242, 1224, 1012, and 729 cm^{-1}. FAB (glycerol+HCl matrix) MS (positive ion mode) *m*/*z* 272 ($[M+H]^+$). FAB (glycerol+NaOH matrix) MS (negative ion mode) *m*/*z* 270 ($[M-H\ ]^-$). Calcd for $C_{16}H_{17}NO_3$: C, 70.91; H, 6.32; N, 5.17%. Found: C, 70.88; H, 6.28; N, 5.15%.

4.12. *exo*-3-Acetylamino-10-hydroxy-hexacyclo[10.2.1.0^{2,11}.0^{4,10}.0^{4,14}.0^{9,13}]pentadecane-5,7-diene-*endo*-3-carboxylic acid (18)

A solution of **17** (0.5 g, 1.6 mmol) in a 2:1 mixture of acetic anhydride and glacial acetic acid ($20\ cm^3$) was stirred at room temperature for 3 h. Water ($100\ cm^3$) was added and the reaction mixture stirred for 5 h. The mono acetate (**18**, 0.48 g, 1.52 mmol, mp 218 °C) precipitated and was filtered off and recrystallised from ethanol. IR (KBr-disc): ν_{max} 3464, 3398, 3350, 3018, 2985, 2972, 2904, 1708, 1685, 1629, 1550, 1426, 1283, 1264, 1232, 1159 and 729 cm^{-1}. EIMS, *m*/*z* 313 (M^+). Calcd for $C_{18}H_{19}NO_4$: C, 69.01; H, 6.07; N, 4.47%. Found: C, 68.95; H, 6.04; N, 4.45%. ^{13}C NMR [$(CD_3)_2SO$], δ_C 172.43 (s), 169.59 (s), 132.76 (d), 130.57 (d), 124.92 (d), 124 .25 (d), 80.45 (s), 71.20 (s), 62.07 (s), 56.25 (d), 54.01 (d), 53.76 (d), 51.45 (d), 51.35 (d), 45.13 (d), 43.90 (d), 32.31 (t) and 22.75 (q). ^1H NMR [$(CD_3)_2SO$], δ_H 12.04 (br, 1×H, COOH), 7.84 (s, 1×H, OH), 6.35 (d, *J*=8.8 Hz, 1×H), 5.56–5.73 (m, 3×H), 4.62 (s, 1×H, NH), 2.42–2.50 (m, 2×H), 2.34–2.37 (m, 1×H), 2.28–2.30 (m, 1×H), 2.23–2.26 (m, 1×H), 2.16–2.19 (m, 1×H), 2.03–2.05 (m, 1×H), 1.79 (s, 3×H, CH_3), 1.17 (d, J_{AB}=10.1 Hz, $^1/_2$ ×CH_2) and 1.04 (d, J_{AB}=10.1 Hz, $^1/_2$ ×CH_2).

4.13. *endo*-3-Amino-10-hydroxy-hexacyclo[10.2.1.0^{2,11}.0^{4,10}.0^{4,14}.0^{9,13}]pentadecane-5,7-diene-*exo*-3-carboxylic acid (19)

A mixture of **16** (1.0 g, 3.69 mmol) and a 4% barium hydroxide ($60\ cm^3$) solution was stirred in an open beaker in an autoclave for 1 h at 180 °C. The reaction mixture was diluted with water ($250\ cm^3$) and an excess of ammonium carbonate (5 g) was added to the mixture 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 ($4\ mol\ dm^{-3}$) and evaporated on a steam bath to a small volume ($\pm 5\ cm^3$) and the amino acid (**19**, 0.68 g, 2.51 mmol, mp 350 °C dec) filtered off as a colourless solid. IR (KBr-disc): ν_{max} 3427, 3018, 3003, 2975, 2947, 2894, 2870, 2784, 1614, 1576, 1496, 1381, 1368, 1295, 1242, 1224, 1012 and 729 cm^{-1}. FAB (glycerol+HCl matrix) MS (positive ion mode) *m*/*z* 272 ($[M+H]^+$). FAB (glycerol+NaOH matrix) MS (negative ion mode) *m*/*z* 270 ($[M-H]^-$). Calcd for $C_{16}H_{17}NO_3$: C, 70.91; H, 6.32; N, 5.17%. Found: C, 70.85; H, 6.30; N, 5.14%.

4.14. *endo*-3-Acetylamino-10-hydroxy-hexacyclo[10.2.1.0^{2,11}.0^{4,10}.0^{4,14}.0^{9,13}]pentadecane-5,7-diene-*exo*-3-carboxylic acid (20)

A solution of **19** (0.5 g, 1.6 mmol) in a 2:1 mixture of acetic anhydride and glacial acetic acid ($20\ cm^3$) was stirred at 60 °C for 2 h. The reaction mixture was cooled to room temperature. Water ($100\ cm^3$) was added and the reaction mixture stirred for 5 h. The mono acetate (**20**, 0.3 g, 0.96 mmol, mp 207 °C) precipitated and was filtered off and recrystallised from ethanol. IR (KBr-disc): ν_{max} 3350, 3285, 2970, 2950, 2877, 1716, 1595, 1524, 1487, 1422, 1375, 1325, 1290, 1263, 1222 and 789 cm^{-1}. EIMS, *m*/*z* 313 (M^+). Calcd for $C_{18}H_{19}NO_4$: C, 69.01; H, 6.07; N, 4.47%. Found: C, 68.93; H, 6.05; N, 4.43%. ^{13}C NMR [$(CD_3)_2SO$], δ_C 172.41 (s), 169.57 (s), 132.76 (d), 130.55 (d), 124.91 (d), 124 .23 (d), 80.44 (s), 71.19 (s), 62.06 (s), 56.24 (d), 53.99 (d), 53.75 (d), 51.44 (d), 51.34 (d), 45.12 (d), 43.89 (d), 32.29 (t) and 22.74 (q). ^1H NMR [$(CD_3)_2SO$], δ_H 12.18 (br, 1×H, COOH), 7.84 (s, 1×H, OH), 6.35 (d, *J*=8.8 Hz, 1×H), 5.56–5.73 (m, 3×H), 4.62 (s, 1×H, NH), 2.42–2.49 (m, 2×H), 2.34–2.37 (m, 1×H), 2.29–2.32 (m, 1×H), 2.24–2.27 (m, 1×H), 2.17–2.19 (m, 1×H), 2.03–2.05 (m, 1×H), 1.79 (s, 3×H, CH_3), 1.17 (d, J_{AB}=10.1 Hz, $^1/_2$ ×CH_2) and 1.04 (d, J_{AB}=10.1 Hz, $^1/_2$ ×CH_2).

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