CHAPTER 3

SYNTHESIS OF RELEVANT COMPOUNDS

For the synthesis of the compounds that will be tested for anti-apoptotic as well as MAO-B inhibiting activity, several experimental procedures and methods, both conventional and modern, were utilised. Each compound was synthesised to evaluate the effect of a certain functional group on the activity. Some of these groups include a terminal acetylene group, an acetylene group between two non-polar groups, a secondary propargylamine connected to a polycyclic cage and a tertiary propargylamine in an aza polycyclic structure.

1 Standard experimental procedures

1.1 Reagents and chemicals

Reagents used in the synthesis of the compounds, were obtained from Sigma-Aldrich (U.K. & U.S.A.) and Merck Chemicals (Germany). Reaction and chromatography solvents were purchased from various commercial sources.

1.2 Instrumental methods

Melting point (MP) determination: Melting points were measured with a Gallenkamp and Stuart SMP10 melting point apparatus.

Infrared (IR) absorption spectrophotometry: Infrared spectra were recorded on a Shimadzo IR prestige – 21 Fourier transform infrared spectrophotometer using KBr.

Mass spectrometry (MS): Mass spectra were recorded on an analytical VG 7070E mass spectrometer. Ionisation took place at 70 eV.

Nuclear magnetic resonance (NMR) spectrometry: ^{1}H and ^{13}C NMR spectra were acquired on a Bruker Avance III 600 MHz spectrometer, with the ^{1}H spectra recorded at a frequency of 600.170 MHz and the ^{13}C spectra at 150.913 MHz. Tetramethylsilane (TMS) was used as internal standard, with $CDCl_3$ as solvent. All chemical shifts are reported in parts per million (ppm), relative to the internal standard. The following abbreviations are used to indicate the multiplicities of the respective signals: s - singlet; br s - broad singlet; d - doublet; dd - doublet of doublets; t - triplet; m - multiplet; and AB-q - AB quartet. The multiplicity of the identified carbons was confirmed with DEPT-spectra.

Microwave synthesis system: Microwave synthesis was performed using a CEM Discover™ focused closed vessel microwave synthesis system.

1.3 Chromatographic methods

The mobile phases used for column and thin layer chromatography (TLC) were prepared on a volume-to-volume (v/v) basis, employing the Prism model (Nyiredy *et al.*, 1985).

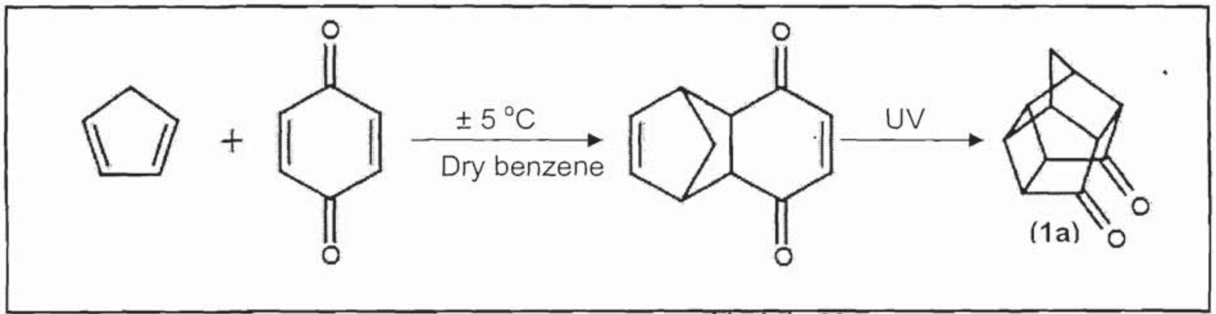
Thin layer chromatography (TLC): Thin layer chromatographic methods were used to monitor the progress of all chemical reactions. Visualisation of thin layer chromatography was achieved by making use of UV light at 254 nm and 360 nm, iodine vapours and heating the TLC plates after the application of ninhydrin 1.5%.

Column chromatography: Separation and purification of mixtures were carried out either by flash chromatography (Harwood *et al.*, 1999) with nitrogen gas on glass columns, packed with silica gel (0.063 – 0.200 mm), or by utilising a Versa Flash™ station with a VersaPak™ column (silica cartridge 40 x 75 mm).

2 Synthetic procedures

2.1 Synthesis of precursor compounds

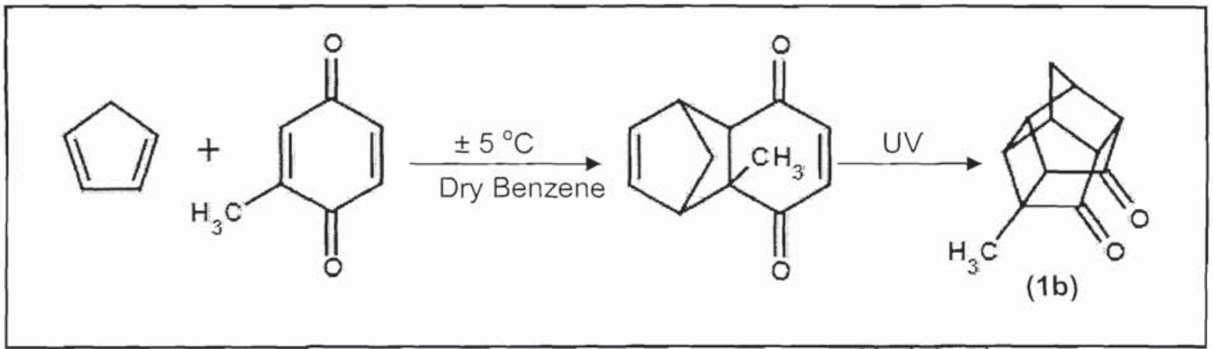
2.1.1 Synthesis of pentacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane-8-11-dione (1a)



Scheme 3.1 The synthetic route of pentacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane-8-11-dione

A stoichiometric volume of freshly monomerised cyclopentadiene (37.860 mL; 0.281 mol) was slowly added drop wise, in increments of 2 mL, to a solution of *p*-benzoquinone (30.400 g; 0.281 mol) in dry benzene (310 mL). The reaction mixture was maintained on an ice bath at a low temperature of ± 3 °C, to prevent the formation of the undesired Diels Alder di-adduct. The reaction mixture was protected from light and left to stir for 1 hour to reach completion, with the reaction progression being monitored by TLC. This was followed by the addition of activated charcoal (3 spatula scoops), and the mixture was stirred for a further 30–60 minutes. After filtration through Celite®, the solvent was removed under reduced pressure and the residue, a yellow syrupy oil, was allowed to remain overnight in a dark fume hood. This allowed the full evaporation of the benzene, affording the Diels Alder adduct as yellow crystals. The Diels Alder adduct was dissolved in acetone (± 4 g/100 mL) and irradiated for ± 6 hours in a photochemical reactor (1000 W medium pressure UV lamp, Phillips HPA 1000/20). Discolouration of the solution confirmed completion of the cyclisation of the adduct. The solvent was subsequently removed under reduced pressure to afford the impure pentacyclic dione as a beige/yellow residue. This residue was purified by Soxhlett extraction in cyclohexane to produce the pure diketone as a waxy, off-white precipitate (yield: 37.890 g; 0.218 mol; 77.58%). The data from the physical characterisation of the obtained compound correlates with that of the pentacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane-8-11-dione (174.2 g/mol) as described by Cookson *et al.* (1958). Therefore no spectral data for this compound is presented.

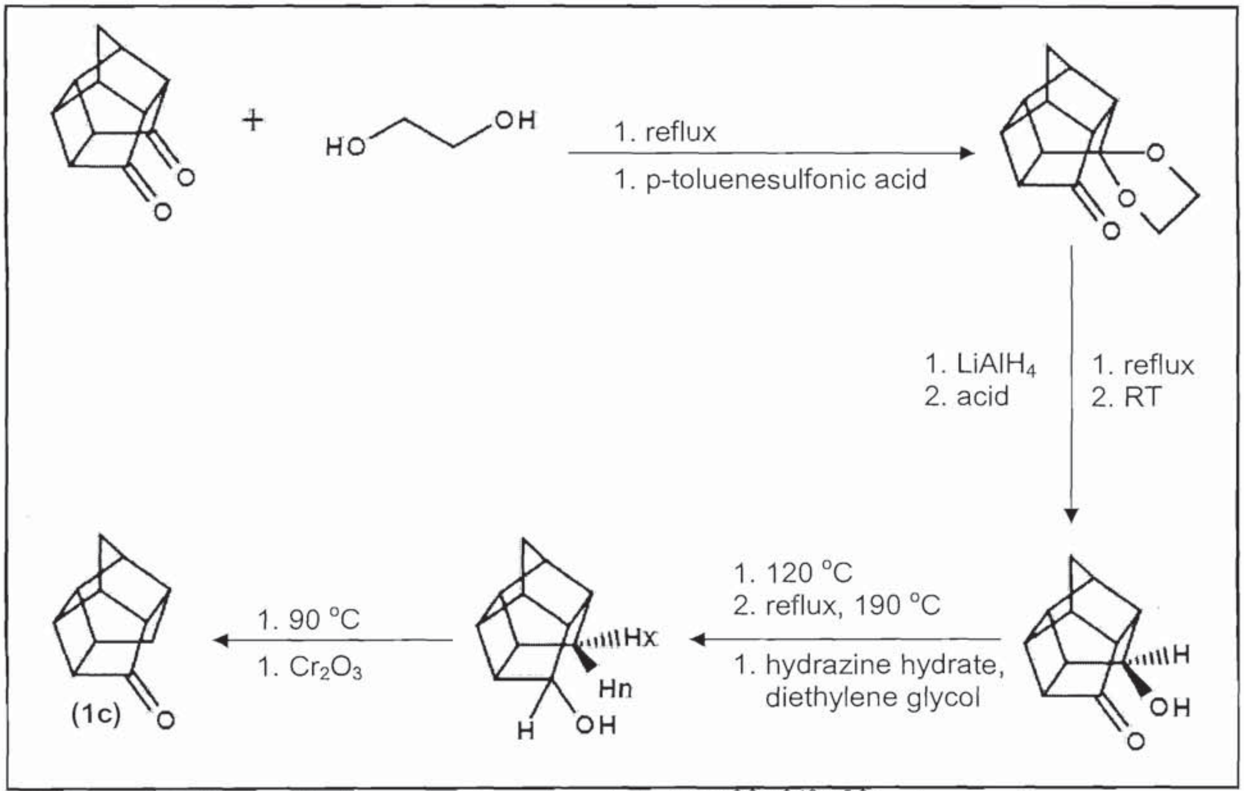
2.1.2 Synthesis of 1-methyl-pentacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane-8-11-dione (1b)



Scheme 3.2 The synthetic route of 1-methyl-pentacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane-8-11-dione

A stoichiometric volume of freshly monomerised cyclopentadiene (35.610 mL; 0.265 mol) was slowly added drop wise, in increments of 2 mL, to a solution of methyl-*p*-benzoquinone (32.300 g; 0.265 mol) in dry benzene (310 mL). The reaction mixture was maintained on an ice bath at a low temperature of ± 3 °C, to prevent the formation of the undesired Diels Alder di-adduct. The reaction mixture was protected from light and left to stir for 1 hour to reach completion, with the reaction progress being monitored by TLC. This was followed by the addition of activated charcoal (3 spatula scoops), and further stirring for 30–60 minutes. After filtration through Celite®, the solvent was removed under reduced pressure and the formed red/brown oil was allowed to remain overnight in a dark fume hood. This allowed the full evaporation of the benzene with the Diels Alder adduct remaining as oil. The Diels Alder adduct was dissolved in acetone (± 4 g/100 mL) and irradiated for ± 6 hours in a photochemical reactor (1000 W medium pressure UV lamp; Phillips HPA 1000/20). A reduction of the colour intensity of the solution confirmed completion of the cyclisation reaction. The solvent was subsequently removed under reduced pressure to afford the impure methyl-pentacyclic dione as an orange/brown oil. After several unsuccessful attempts of crystallisation of the product, it was purified by means of flash column chromatography on silica gel with ethyl acetate/petroleum ether/methylene chloride (1:1:1) as eluent, to afford the pure methyl-diketone as a yellow/brown oil (yield: 40.938 g; 0.217 mol; 82.23%). Data from the physical characterisation of the obtained compound correlates with that of the 1-methyl-pentacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane-8-11-dione (188.2 g/mol) as described by Marchand *et al.* (1984). Therefore no spectral data for this compound is presented.

2.1.3 Synthesis of pentacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane-8-one (1c)



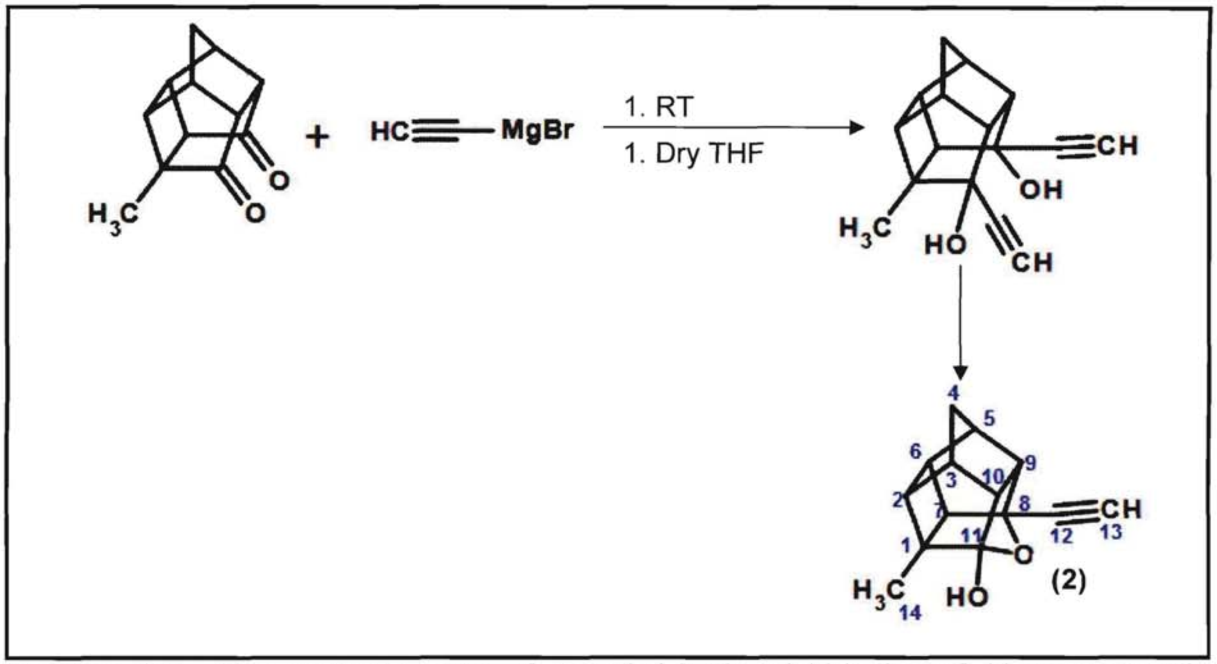
Scheme 3.3 The synthetic route of pentacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane-8-one

A mixture of pentacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane-8-11-dione (20.000 g; 0.115 mol), ethylene glycol (7.138 g; 0.115 mol) and *p*-toluenesulfonic acid (0.263 g; 0.001 mol) was prepared in 100 mL benzene and was refluxed under Dean-Stark conditions for 3½ hours with stirring. The reaction was then cooled and slowly poured into an ice cold aqueous sodium carbonate (Na_2CO_3) solution (100 mL, 10%). This was followed by extraction with methylene chloride (DCM) (4 x 50 mL). The organic phase was dried over magnesium sulphate ($MgSO_4$), and removal of the solvent under reduced pressure afforded the oxo-acetal as a white precipitate (yield: 23.800 g; 94.83%). A suspension of the oxo-acetal (ketal) (23.000 g; 0.105 mol) in dry ether (75 mL) was added to a stirred suspension of lithium aluminium hydride ($LiAlH_4$) (2.150 g; 0.057 mol) in dry ether (75 mL) over a period of 30 minutes. The reaction mixture was refluxed for 2 hours and then cooled to 0 °C. The excess $LiAlH_4$ was destroyed with aqueous ammonium chloride. The organic phase was concentrated under reduced pressure leaving a clear homogenous oil. The crude product was stirred in aqueous hydrochloric acid (400 mL, 6%) at room temperature (RT) for 2 hours. The reaction mixture was diluted with water (300 mL) and extracted to methylene chloride (4 x 100 mL). The organic phase was dried over $MgSO_4$, and removal of the solvent gave the hydroxy-ketone (yield: 11.353 g; 61.36%). A mixture of the hydroxy-ketone (11 g; 0.062 mol) and hydrazine hydrate (22.360 mL, 98%) in diethylene glycol (180 mL) was maintained at 120 °C for 1½ hours. Potassium hydroxide (5 g) was added and the excess hydrazine and water was distilled until the temperature reached 190 °C. The reaction mixture was refluxed for 3 hours at 190 °C and then steam distilled. Extraction of the distillate with methylene chloride afforded the alcohol (yield: 3.301 g; 32.60%). Chromium trioxide (CrO_3) (3.700 g; 0.037 mol) in water (6 mL) was added to the alcohol (3 g; 0.018 mol) in aqueous acetic acid (60 mL; 94%), and the mixture was stirred at 90 °C for 4 hours. The reaction mixture was cooled, diluted with water (300 mL) and extracted with methylene chloride (3 x 40 mL). The methylene chloride extract was washed consecutively with water (2 x 100 mL), saturated aqueous sodium hydrogen carbonate ($NaHCO_3$) (2 x 100 mL), and water (100 mL). The organic phase was dried over $MgSO_4$, and removal of the solvent under reduced pressure gave the monoketone (yield: 2.500 g; 0.016 mol; 84.38%). Data from the physical characterisation of the obtained compound correlates with that of the pentacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane-11-one (160.2 g/mol) as described by Dekker and Oliver (1979). Therefore no spectral data for this compound is presented.

2.2 Synthesis of test compounds

2.2.1 Synthesis of 1-methyl-8-ethynyl-11-hydroxy-8,11-oxapentacyclo [5.4.1.$0^{2,6}$.$0^{3,10}$. $0^{5,9}$]undecane (2)

A solution of methyl-pentacyclo-undecane dione (1.88 g; 10 mmol) in dry tetrahydrofuran (THF) (10 mL) was added to an excess of ethynyl magnesium bromide (1.0 M solution in THF) (2.838 mL; 22 mmol) under argon, whilst stirring. The resulting mixture was stirred at ambient temperature for 21 hours. The reaction mixture was poured over saturated aqueous ammonium chloride (NH_4Cl) solution (100 mL), and the resulting suspension was extracted with diethyl ether (3 x 25 mL). The combined organic extracts were washed sequentially with water (25 mL) and brine (25 mL). The solvent was dried (Na_2SO_4) and filtered, and the filtrate was concentrated under reduced pressure. The residue, pale yellow oil, was successfully purified by precipitation from a mixture of ethyl acetate/petroleum ether (1:3), over a period of 24 hours at ambient temperature. This yielded the pure product as a light brown powder (yield: 0.762 g; 3.170 mmol; 15.87%).



Scheme 3.4 The synthetic route of 1-methyl-8-ethynyl-11-hydroxy-8,11-oxapentacyclo $[5.4.1.0^{2,6}.0^{3,10}.\ 0^{5,9}]$undecane

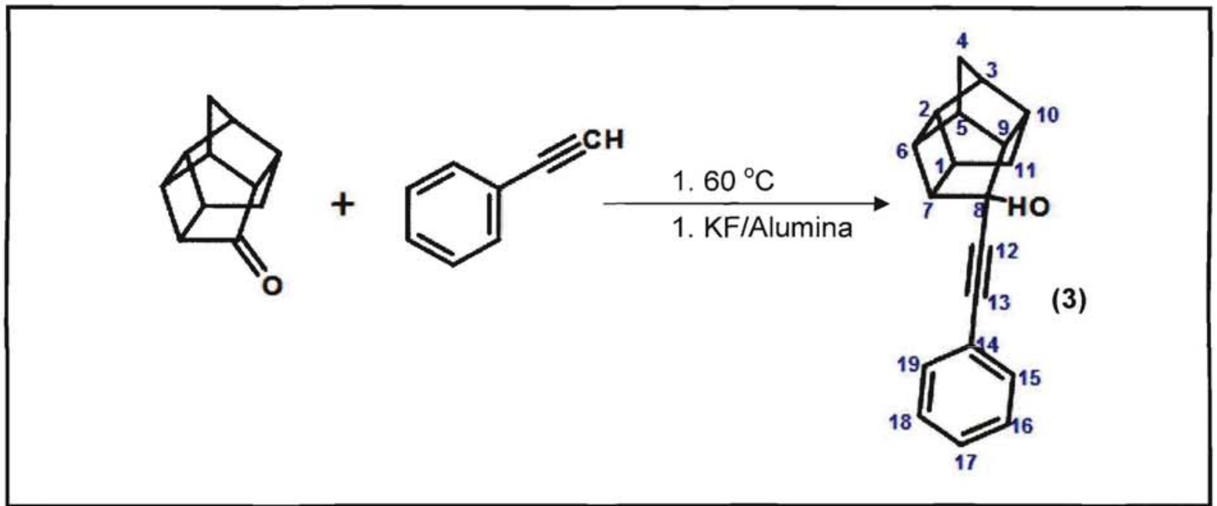
PHYSICAL DATA:

$C_{11}H_{10}O_2N_1$; MW, 214.3 g/mol; **mp.** 126 °C; **IR (KBr)** ν_{max} (Spectrum 1): 3260, 2125, 1211, 1031 cm^{-1}; **MS** (EI, 70 eV) m/z (Spectrum 9): 214 (M^+), 186, 169, 158, 116, 91, 77, 39; **^{1}H NMR** (600 MHz, $CDCl_3$) δ_H (Spectrum 17): 3.72 (s, OH), 3.12 - 2.37 (m, 7H, H-2,3,5,6,7,9,10), 2.31 (s, 1H, H-13), 1.88:1.54 (AB-q, 2H, J = 10.4 Hz, H-4a,4b), 1.10 (s, 3H, CH_3); **^{13}C NMR** (150 MHz, $CDCl_3$) δ_c (Spectrum 25): 116.87 (1C, C-11), 81.18 (1C, C-8), 75.30 (1C, C-12), 61.84 (1C, C-13), 57.24 (1C, C-9), 56.91 (1C, C-7), 50.75 (1C), 47.46 (1C), 45.22 (1C), 43.49 (1C, C-4), 41.56 (1C), 39.19 (1C, C-1), 15.29 (1C, C-14).

STRUCTURE ELUCIDATION:

Several characteristic groups, which include the oxa-group between carbon 8 and 11, the *ethynyl group* at carbon 8, the hydroxyl group at carbon 11, and the methyl group at carbon 1 of the cage as well as carbons 8, 11 and 4 were identified to confirm the structure. On the infrared spectrum the C-O bond (oxa-group) was present at 1031 cm^{-1}, the C-O bond (hydroxyl-group) at 1211 cm^{-1}, the C≡C bond (ethynyl group) at 2125 cm^{-1}, and the ≡C-H bond (ethynyl group) at 3260 cm^{-1}. On the ^{1}H NMR spectrum, the AB-q system of the protons on carbon 4 (1.88:1.54 ppm), the singulet of the methine proton (2.31 ppm), and the singulet integrating for the three protons of the methyl (1.10 ppm), as well as the hydrogen of the alcohol group (3.72) was identified. On the ^{13}C NMR spectrum the unsaturated and deshielded carbons are detectable downfield from the others and include carbons 8, 11, 12 and 13. The single methyl group (C-14) is also clearly present at 15.29 ppm. The molecular ion from the MS confirmed a mass of 214.

2.2.2 Synthesis of 8-phenylethynyl-8-hydroxy-pentacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}]undecane (3)



Scheme 3.5 The synthetic route of 8-phenylethynyl-8-hydroxy-pentacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}] undecane

Neutral alumina (60–80 mesh, 30 g) in water (150 mL) was added to a stirred solution of potassium fluoride (20 g) in water (150 mL). After 30 minutes the water was evaporated in a rotary evaporator at 80 °C. When most of the water had been removed, the remaining mixture was heated to, and maintained at 140–150 °C under vacuum (5 mmHg) overnight to afford 50 g of KF/alumina reagent.

Phenylacetylene (255.350 mg; 2.500 mmol), pentacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8-one (480,650 mg; 3 mmol), and KF/alumina (2.500 g) were mixed in a 25 mL flask at 60 °C . The progress of the reaction was monitored by TLC. After 12 hours the reaction mixture was washed with petroleum ether (PE), filtered, and the solvent was evaporated under vacuum affording a clear yellow oil. The residue was purified by means of column chromatography, by using a versa flash silica-gel column with petroleum ether/ethyl acetate (10:2) as eluent, to afford the product as a light yellow wax (yield: 480 mg; 1.830 mmol; 73.18%).

PHYSICAL DATA:

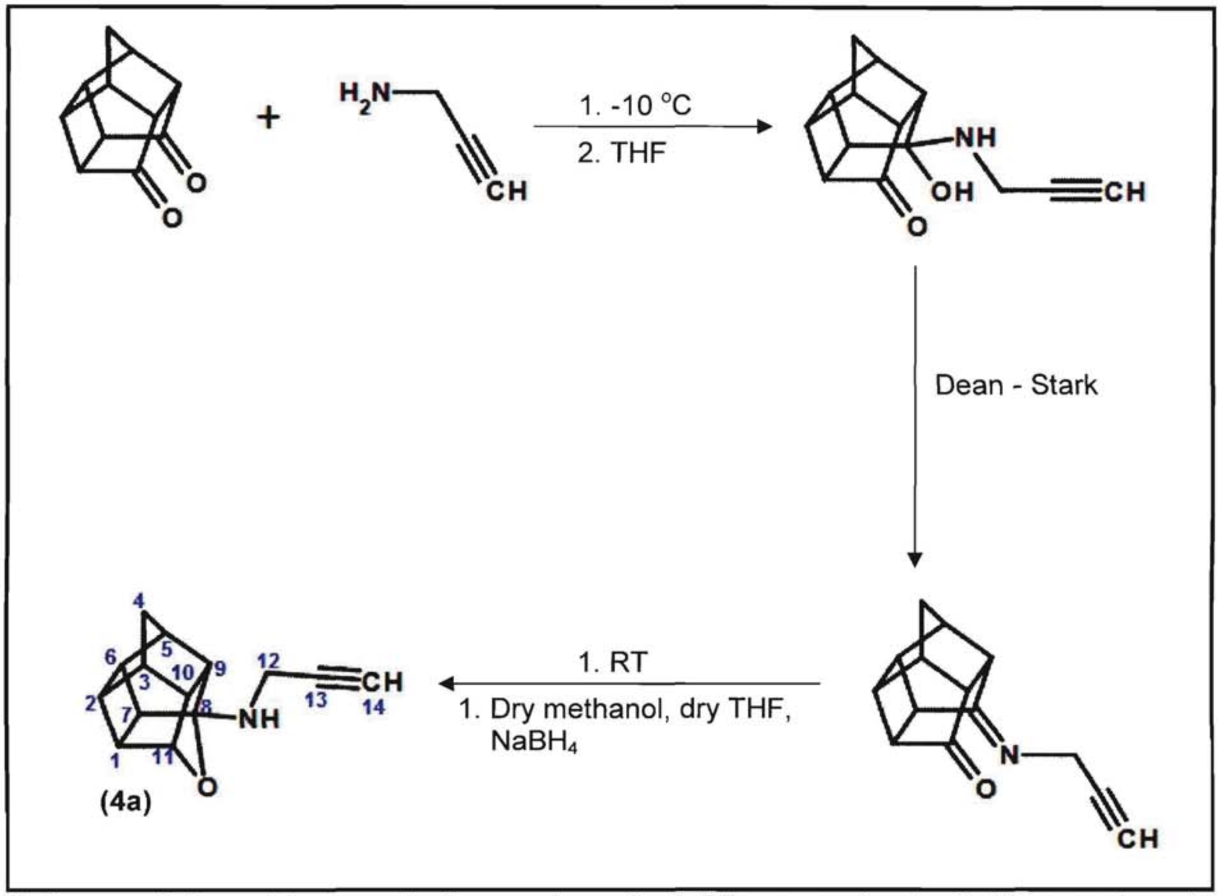
$C_{11}H_{10}O_2N_1$; MW, 262.4 g/mol; **mp.** 90 °C; **IR (KBr)** ν_{max} (Spectrum 2): 3069, 2225, 1599, 1491, 1125, 752 cm^{-1}; **MS** (EI, 70 eV) m/z (Spectrum 10): 262 (M$^+$), 196, 183, 165, 129, 115, 91, 77; **^1H NMR** (600 MHz, $CDCl_3$) δ_H (Spectrum 18): 7.36 – 7.13 (m, 5H, H-15,16,17,18,19), 2.77 – 2.28 (m, 8H, H-1,2,3,5,6,7,9,10), 1.93:1.60 (AB-q, 2H, H-11a,11b), 1.72:1.18 (AB-q, 2H, J = 10.4 Hz, H-4a,4b); ^{13}**C NMR** (150 MHz, $CDCl_3$) δ_c (Spectrum 26): 131.51 (1C, C-14), 128.23 (2C, C-15,19), 128.10 (2C, C-16,18), 123.02 (1C, C-17), 94.15 (1C, C-8), 83.21 (1C, C-13), 75.91 (1C, C-12), 51.50 (1C), 47.27 (1C), 45.20 (1C), 44.95 (1C), 42.73 (1C, C-4), 41.50 (1C), 40.61 (1C), 36.62 (1C), 34.73 (1C), 28.98 (1C, C-11).

STRUCTURE ELUCIDATION:

Several characteristic groups including the aromatic ring, the ethynyl group between the cage and the benzene, and the hydroxyl group on carbon 8, as well as carbons 8, 11 and 4 of the cage, were identified to confirm the structure. On the infrared spectrum the C-O bond (hydroxyl-group) is present at 1125 cm^{-1}, the C≡C bond (ethynyl group) at 2225 cm^{-1}, the C-H bonds (aromatic group) at 3069 cm^{-1} and 752 cm^{-1}, and the C=C bonds (aromatic group) at 1599 cm^{-1} and 1491 cm^{-1}. On the ^{1}H NMR spectrum, the AB-q system of the protons on carbon 4 (1.72:1.18 ppm) and 11 (1.93:1.60 ppm), and the aromatic hydrogens (7.36 – 7.13 ppm) were evident. On the ^{13}C NMR spectrum the aromatic and methine carbons, as well as those of the cage were identified. The molecular ion from the MS confirmed a mass of 262.

2.2.3 Synthesis of 8-(N)-propargylamino-8,11-oxapentacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}] undecane (4a)

Pentacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8-11-dione (5 g; 0,029 mol) was dissolved in tetrahydrofuran (THF) (50 mL) and cooled to ± -10 °C, while stirring on an external bath, containing an acetone/NaCl/ice mixture. Propargylamine (1.600 g; 0.029 mol) was added drop-wise, with continued stirring of the reaction mixture at lowered temperature. The carbinolamine started precipitating after approximately 15 minutes, but the reaction was allowed to stir for an additional 30 minutes to reach completion. The carbinolamine was isolated by filtration and washed with ice cold THF. Water was removed azeotropically by refluxing the material in dry benzene (60 mL), under Dean–Stark dehydrating conditions for 1 hour, or until no more water was collected in the trap. The benzene was removed under reduced pressure, which yielded the Schiff base as yellow oil. The Schiff base (imine) was then dissolved in a mixture of anhydrous methanol (MeOH) (30 mL) and anhydrous tetrahydrofuran (THF) (150 mL). Reduction was carried out by adding sodium borohydride ($NaBH_4$) (1.500 g; 0.040 mol) in excess, and stirring the mixture for 24 hours at room temperature. The solvents were removed under reduced pressure, the residue suspended in water (100 mL) and extracted with methylene chloride (DCM) (4 x 50 mL). The combined organic fractions were washed with water (2 x 100 mL), dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to yield milky yellowish oil.



Scheme 3.6 The synthetic route of 8-(N)-propargylamino-8,11-oxapentacyclo $[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}]$undecane

Purification of the product mixture was accomplished using column chromatography on silica gel, with ethyl acetate/methylene chloride/petroleum ether (1:1:1) as eluent. This yielded the desired amine as a light yellow precipitate. Recrystallisation from absolute ethanol rendered the final product as a colourless microcrystalline solid (yield: 600 mg; 2.827 mmol; 9.75%).

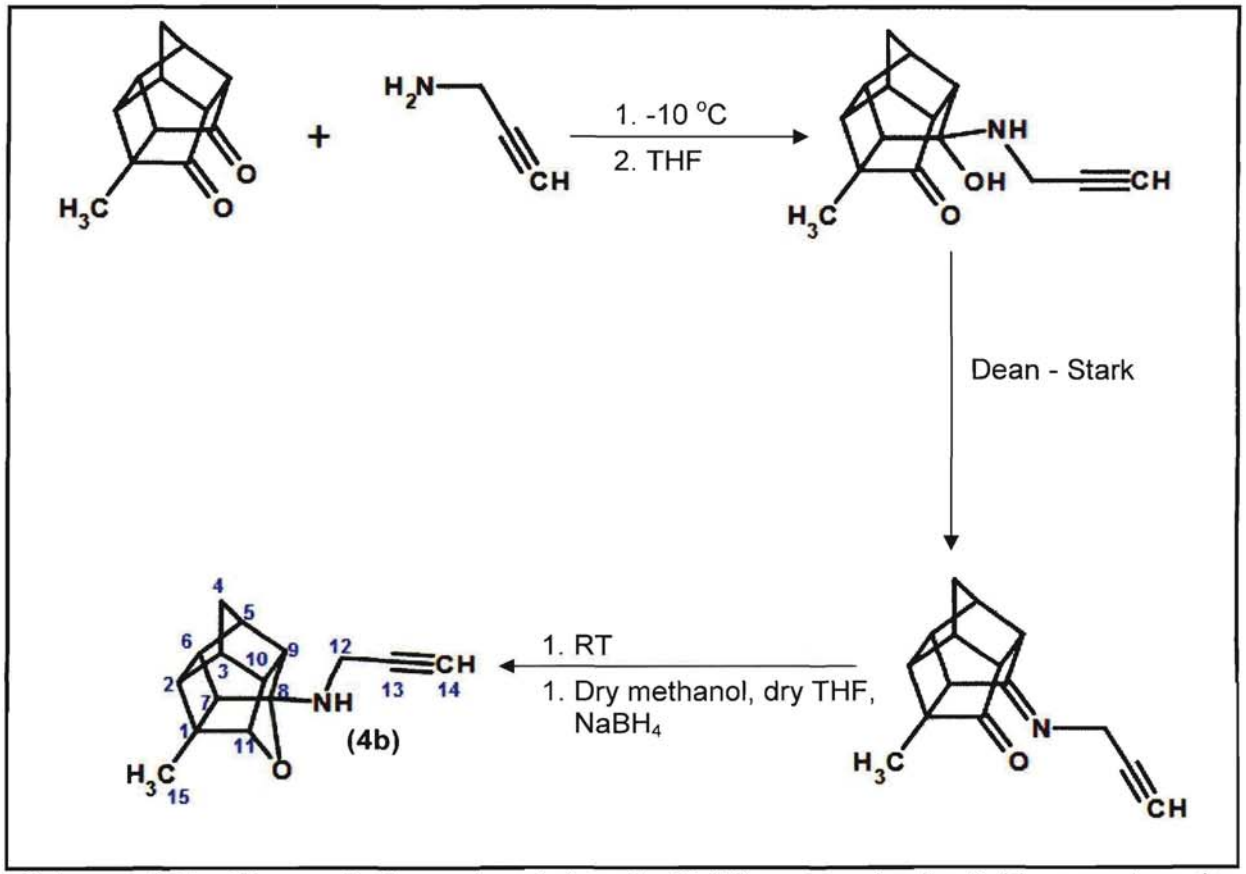
PHYSICAL DATA:

$C_{11}H_{10}O_2N_1$; MW, 212.3 g/mol; **mp.** 113 °C**; IR (KBr)** ν_{max} (Spectrum 3): 3306, 3238, 2124, 1485, 1153, 1000 cm^{-1}; **MS** (EI, 70 eV) m/z (Spectrum 11): 213 [$(M^+)+1$], 212 (M^+), 184, 134, 118, 91, 77, 39; **^{1}H NMR** (600 MHz, $CDCl_3$) δ_H (Spectrum 19): 4.63 (t, 1H, J = 5 Hz, H-11), 3.57:3.56 (dd, 2H, J = 2.5 Hz, H-12a,12b), 2.80 – 2.39 (m, 8H, H-1,2,3,5,6,7,9,10), 2.26 (br s, NH), 2.21 (s, 1H, H-14), 1.88:1.52 (AB-q, 2H, J = 10.4 Hz, H-4a,4b); **^{13}C NMR** (150 MHz, $CDCl_3$) δ_c (Spectrum 27): 108.98 (1C, C-8), 82.81 (1C, C-11), 82.76 (1C, C-13), 70.92 (1C, C-14), 55.46 (1C, C-7/9), 54.76 (1C, C-7/9), 44.84 (1C), 44.65 (1C), 44.54 (1C), 43.3 (1C), 43.07 (1C, C-12), 42.04 (1C), 41.54 (1C), 33.07 (1C).

STRUCTURE ELUCIDATION:

In confirming the structure of **4a**, several groups, which include the oxa-group between carbon 8 and 11, the ethynyl and amine group of the propargylamine moiety, as well as carbons, 8, 11 and 4 of the cage were identified. On the infrared spectrum the C-O bond (oxa-group) is present at 1000 cm^{-1}, the C≡C bond (propargylamine moiety) at 2124 cm^{-1}, the ≡C-H bond (propargylamine moiety) at 3238 cm^{-1}, the C-N bond (propargylamine moiety) at 1153 cm^{-1}, and the N-H bond (propargylamine moiety) at 1485 cm^{-1} and 3306 cm^{-1}. On the ^{1}H NMR spectrum, the AB-q system of the protons on carbon 4 (1.88:1.52 ppm), the triplet of carbon 11 (4.63 ppm) and the doublet of doublets of carbon 12 (3.57:3.56), the terminal hydrogen (2.21 ppm) of the acetylene group, as well as the nitrogen hydrogen (2.26 ppm) is evident of the structure of **4a**. The typical signals indicating C-8,11,13 and 14 were indicated on the ^{13}C NMR spectrum. The molecular ion from the MS confirmed a mass of 212.

2.2.4 Synthesis of 1-methyl-8-(N)-propargylamino-8,11-oxapentacyclo[5.4.1.0^{2,6}.0^{3,10}. 0^{5,9}]undecane (4b)



Scheme 3.7 The synthetic route of 1-methyl-8-(N)-propargylamino-8,11-oxapentacyclo [5.4.1.0^{2,6}.0^{3,10}. 0^{5,9}]undecane

1-Methyl-pentacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane-8-11-dione (5.460 g; 0.029 mol) was dissolved in tetrahydrofuran (THF) (50 mL) and cooled to ± -10 °C, while stirring on an external bath containing an acetone/NaCl/ice mixture. Propargylamine (1.600 g; 0.029 mol) was slowly added with continued stirring of the reaction mixture at lowered temperature. The reaction mixture was stirred for an additional 1½ hours to reach completion. The THF was removed under reduced pressure, affording the carbinolamine as red/brown oil. Water was removed azeotropically by refluxing this material in dry benzene (60 mL), under Dean–Stark dehydrating conditions for 1 hour, or until no more water was collected in the trap. The benzene was removed under reduced pressure, which yielded the Schiff base as brown oil. The Schiff base (imine) was dissolved in a mixture of anhydrous methanol (MeOH) (30 mL) and anhydrous THF (150 mL). Reduction was carried out by adding sodium borohydride (1.500 g; 0.040 mol) in excess and stirring the mixture for 24 hours at room temperature. The solvents were removed under reduced pressure, the residue suspended in water (100 mL) and extracted with methylene chloride (DCM) (4 x 50 mL). The combined organic fractions were washed with water (2 x 100 mL), dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to yield milky dark brown oil. Purification of the product mixture was accomplished using column chromatography, with ethyl acetate/methylene chloride/petroleum ether (1:1:1) as eluent, yielding the desired amine as a dark brown oil (Yield: 1.753 g; 7.746 mmol; 26.71%).

PHYSICAL DATA:

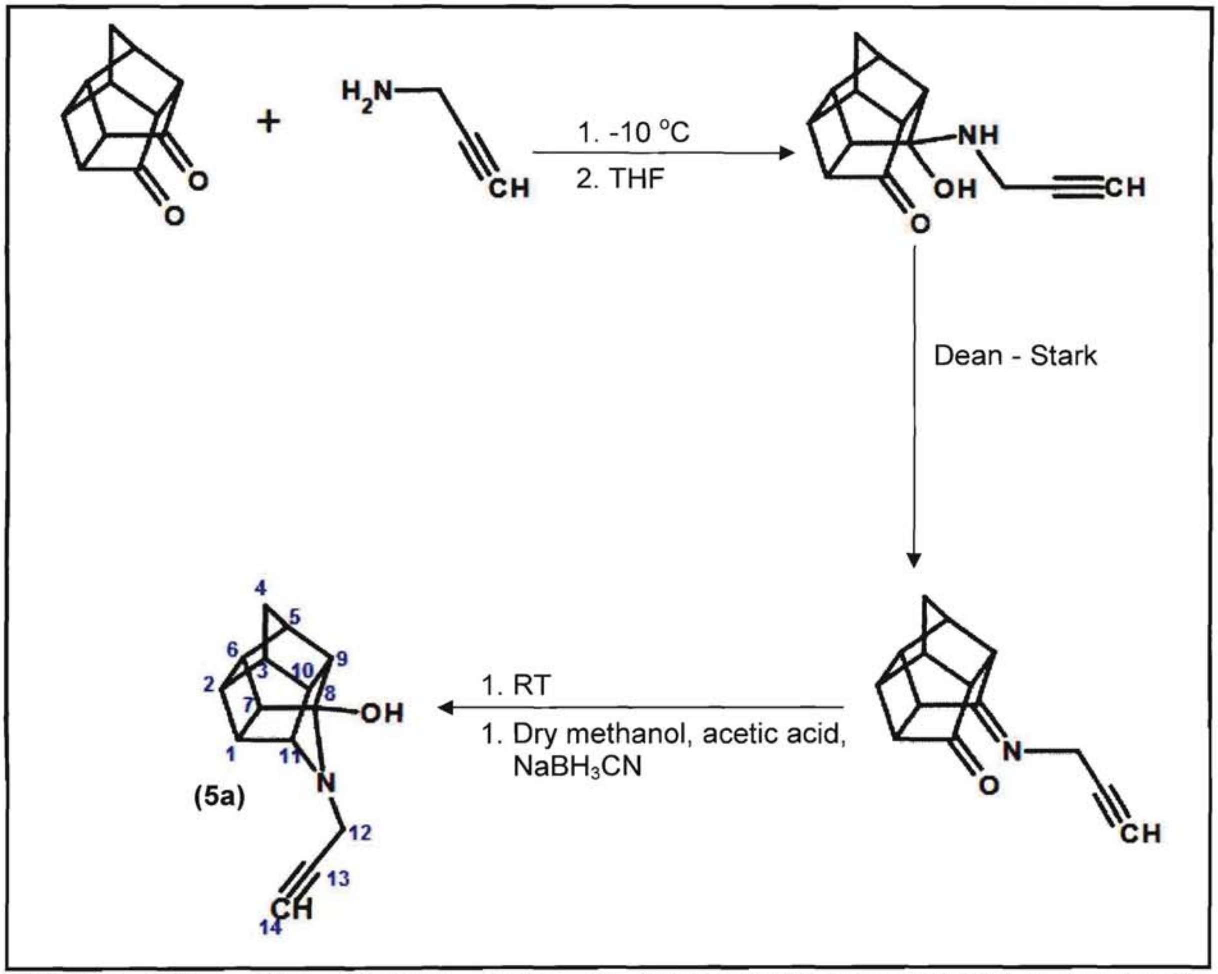
$C_{11}H_{10}O_2N_1$; MW, 226.3 g/mol; **IR (KBr)** v_{max} (Spectrum 4): 3310, 3250, 2100, 1452, 1153, 1007cm^{-1}; **MS** (EI, 70 eV) m/z (Spectrum 12): 227 [(M^+)+1], 226 (M^+), 212, 198, 184, 158, 145, 131, 91, 77, 39; **^{1}H NMR** (600 MHz, $CDCl_3$) δ_H (Spectrum 20): 4.08 (d, 1H, J = 4.4 Hz, H-11), 3.57 (m, 2H, H-12a,12b), 2.73 – 2.20 (m, 7H, H-2,3,5,6,7,9,10), 2.14 (br s, NH), 2.06 (d, 1H, J = 5.28 Hz, H-14), 1.86:1.51 (AB-q, 2H, J = 10.4 Hz, H-4a,4b), 1.15 (s, 3H, CH_3); **^{13}C NMR** (150 MHz, $CDCl_3$) δ_c (Spectrum 28): 109.73 (1C, C-8), 87.15 (1C, C-11), 82.65 (1C, C-13), 70.95 (1C, C-14), 54.97 (1C, C-9), 54.66 (1C, C-7), 50.74 (1C), 46.99 (1C), 43.58 (1C), 43.18 (1C), 38.91 (1C, C-1), 33.07 (1C, C-12), 19.85 (1C, C-15).

STRUCTURE ELUCIDATION:

In addition to the characteristic groups described under **4a**, the methyl signal was observed at 1.15 ppm on the ^{1}H NMR spectrum and at 19.85 ppm on the ^{13}C NMR spectrum. The proton signal for C-11 showed a slight shift to 4.08 ppm on the ^{1}H NMR spectrum. The molecular ion from the MS confirmed a mass of 226.

2.2.5 Synthesis of 8-hydroxy-(N)-propargyl-8,11-azapentacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$] undecane (5a)

Pentacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane-8-11-dione (5 g; 0.029 mol) was dissolved in tetrahydrofuran (THF) (50 mL) and cooled to ± -10 °C, while stirring on an external bath, containing an acetone/NaCl/ice mixture. Propargylamine (1,600 g; 0.029 mol) was added slowly with continued stirring of the reaction mixture at lowered temperature. The carbinolamine started precipitating after approximately 60 minutes, but the reaction was stirred for an additional 45 minutes to reach completion. This carbinolamine was isolated by filtration.



Scheme 3.8 The synthetic route of 8-hydroxy-(N)-propargyl-8,11-azapentacyclo [5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane

Water was removed azeotropically by refluxing this material in dry benzene (60 mL), under Dean–Stark dehydrating conditions for 1 hour, or until no more water was collected in the trap. The benzene was removed under reduced pressure and the Schiff base was used without further purification. It was dissolved in a solution of acetic acid (15 mL) and dry methanol (250 mL). To the resulting solution was added sodium cyanoborohydride

($NaBH_3CN$) (2.510 g; 40 mmol) portion wise, with stirring at room temperature over a period of 5 minutes. The resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was then concentrated under reduced pressure, and water (100 mL) was added to the residue. The resulting suspension was stirred and solid sodium bicarbonate was added portion wise until evolution of carbon dioxide ceased. Excess solid sodium bicarbonate (2.000 g) was added, and the aqueous suspension was extracted with methylene chloride (4 x 50 mL). The combined extracts were washed with water (2 x 100 mL), dried with anhydrous magnesium sulphate and filtered. The filtrate was concentrated under reduced pressure. A yellow solid was thereby obtained. Purification of the product mixture was accomplished using column chromatography on silica, with ethyl acetate/methylene chloride/ethanol (10:5:1) as eluent. The desired amine was obtained as an off-white powder. Recrystallisation from cyclohexane rendered the final product as an off-white microcrystalline solid (Yield: 960 mg; 4.501 mmol; 15.52%).

PHYSICAL DATA:

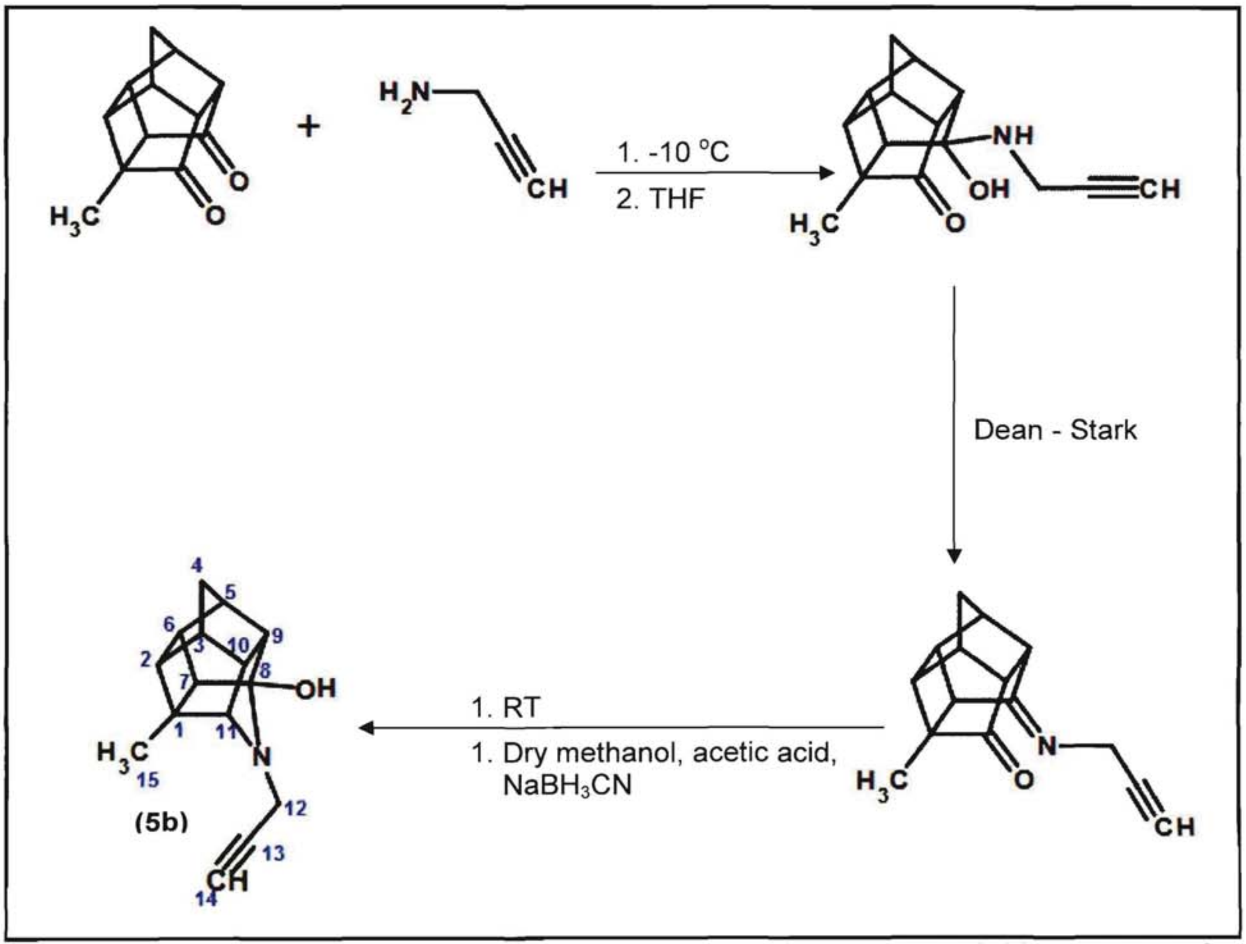
$C_{11}H_{10}O_2N_1$; MW, 213.3 g/mol; **mp.** 140 °C; **IR (KBr)** ν_{max} (Spectrum 5): 3225, 3100, 2114, 1120, 1070, cm^{-1}; **MS** (EI, 70 eV) m/z (Spectrum 13): 214 [(M^+)+1], 213 (M^+), 196, 174, 147, 134, 118, 91, 77, 39; **^{1}H NMR** (600 MHz, $CDCl_3$) δ_H (Spectrum 21): 3.71 (s, 1H, H-12), 3.35 (d, 1H, J = 16.5 Hz, H-11), 3.00 – 2.43 (m, 8H, H-1,2,3,5,6,7,9,10), 2.25 (s, 1H, H-14), 1.82:1.49 (AB-q, 2H, J = 10.4 Hz, H-4a,4b); **^{13}C NMR** (150 MHz, $CDCl_3$) δ_c (Spectrum 29): 125.53 (1C, C-8), 81.23 (1C, C-13), 71.37 (1C, C-14), 65.52 (1C, C-11), 45.62 (1C, C-7/9), 43.12 (1C, C-7/9), 41.74 (1C, C-4), 41.60 (1C), 36.79 (1C), 30.33 (1C, C-12).

STRUCTURE ELUCIDATION:

Groups, which deviate from those of the oxa compounds, are the aza-group between carbon 8 and 11 and hydroxyl group on carbon 8. The C-N bond is now present at 1120 cm^{-1} on the infrared spectrum. Instead of the N-H bond of compounds **4a** and **4b**, the aza compounds, **5a** and **5b**, have an O-H bond, which is present as a broad peak between 3600 and 2000 cm^{-1}. On the ^{1}H NMR spectrum, the hydrogen of carbon 11 is present as a doublet at 3.35 ppm, and the hydrogens connected to carbon 12 give a singlet at 3.71 ppm. On the ^{13}C NMR spectrum carbons 8, 11, 13 and 14 all lie downfield compared to the others. The molecular ion from the MS confirmed a mass of 213.

2.2.6 Synthesis of 1-methyl-8-hydroxy-(N)-propargyl-8,11-azapentacyclo [5.4.1.0^{2,6}. 0^{3,10}.0^{5,9}]undecane (5b)

1-Methyl-pentacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8-11-dione (10.658 g; 56.620 mmol) was dissolved in tetrahydrofuran (THF) (50 mL) and cooled to ± -10 °C, while stirring on an external bath containing an acetone/NaCl/ice mixture. Propargylamine (3.119 g; 56.620 mmol) was added drop wise with continued stirring of the reaction mixture at lowered temperature. The reaction mixture was stirred for 5½ hours to reach completion. The THF was removed under reduced pressure, affording red/brown oil, the carbinolamine. Water was removed azeotropically by refluxing this material in dry benzene (60 mL), under Dean–Stark dehydrating conditions for 1 hour, or until no more water was collected in the trap. The benzene was removed under reduced pressure, which yielded the Schiff base as dark brown oil. The Schiff base was used without further purification. It was dissolved in a solution of acetic acid (30 mL) in dry methanol (500 mL).



Scheme 3.9 The synthetic route of 1-methyl-8-hydroxy-(N)-propargyl-8,11-azapentacyclo [5.4.1.0^{2,6}. 0^{3,10}.0^{5,9}]undecane

To the resulting solution sodium cyanoborohydride (3.970 g; 63 mmol) was added portion wise with stirring at room temperature over a period of 5 minutes. The resulting mixture was stirred at room temperature for 14 hours.The reaction mixture was then concentrated under reduced pressure, and water (150 mL) was added to the residue. The resulting suspension was stirred, and solid sodium bicarbonate was added portion wise until evolution of carbon dioxide ceased. Excess solid sodium bicarbonate (3.000 g) was added, and the aqueous suspension was extracted with methylene chloride (4 x 50 mL). The combined extracts were washed with water (2 x 100 mL), dried with anhydrous magnesium sulphate, and filtered. The filtrate was concentrated under reduced pressure, leaving deep orange oil as residue. Purification of the product mixture was accomplished using column chromatography on silica, with ethyl acetate/tetrahydrofuran (5:1) as eluent. This yielded the desired amine as light yellow oil, which precipitated when ethanol was added. Recrystallisation from ethanol (EtOH) rendered the final product as a light yellow microcrystalline solid (Yield: 555 mg; 2.442 mmol; 4.31%).

PHYSICAL DATA:

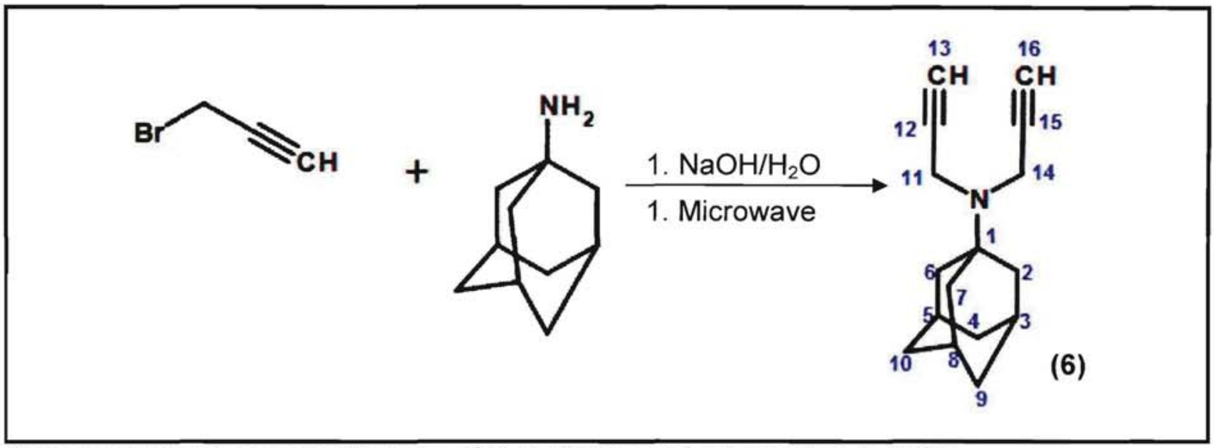
$C_{11}H_{10}O_2N_1$; MW, 227.3 g/mol; **mp.** 125 °C; **IR (KBr)** v_{max} (Spectrum 6): 3225, 3078, 2124, 1119, 1070 cm^{-1}; **MS** (EI, 70 eV) m/z (Spectrum 14): 228 [$(M^+)+1$], 227 (M^+), 188, 134, 118, 91, 77, 39; **^{1}H NMR** (600 MHz, $CDCl_3$) δ_H (Spectrum 22): 3.46 - 3.34 (m, 1H, H-11), 3.22:3.09 (d, 2H, J = 17.3 Hz, H-12a,12b), 2.57 – 2.09 (m, 8H, H-2,3,5,6,7,9,10,14), 1.60:1.06 (AB-q, 2H, J = 10.4 Hz, H-4a,4b), 1.19 (s, 3H, CH_3); **^{13}C NMR** (150 MHz, $CDCl_3$) δ_c (Spectrum 30): 125.53 (1C, C-8), 80.31 (1C, C-13), 72.68 (1C, C-14), 57.40 (1C, C-11), 46.62 (1C, C-9), 46.10 (1C, C-7), 45.09 (1C), 41.54 (1C, C-4), 37.63 (1C), 36.33 (1C), 34.52 (1C), 30.32 (1C, C-12), 21.98 (1C, C-15).

STRUCTURE ELUCIDATION:

Besides the characteristic groups described for **5a**, the methyl signal was observed at 1.19 ppm on the ^{1}H NMR spectrum and at 21.98 ppm on the ^{13}C NMR spectrum. The proton signal for C-11 showed a slight shift to 3.40 ppm on the ^{1}H NMR spectrum.

2.2.7 Synthesis of N,N-dipropargyl-adamantan-1-amine (6)

Excess propargylbromide (0.595 mL; 6.677 mmol), amantadine (302.49 mg; 2 mmol) and aqueous sodium hydroxide (NaOH) solution (180 mg in 6 mL water; 4.5 mmol) were placed in a round-bottom glass flask equipped with a condenser and a magnetic stirrer. The flask was placed in a CEM discover focused microwave synthesis system, and subjected to microwave irradiation at 80–100 °C (power 250 Watt) for 25 minutes.



Scheme 3.10 The synthetic route of N,N-dipropargyl-adamantan-1-amine

After completion of the reaction, the product was extracted into ethyl acetate. The solvent was then removed under reduced pressure. The unreacted amantadine was removed from the residue by adding acetone to the residue and collecting the amantadine by filtration. The acetone was then removed under reduced pressure from the filtrate, affording orange crystals which were recrystallised out of ethyl acetate (EtOAc) to afford the pure product as light yellow crystals (412 mg; 1.812 mmol; 90.61%).

PHYSICAL DATA:

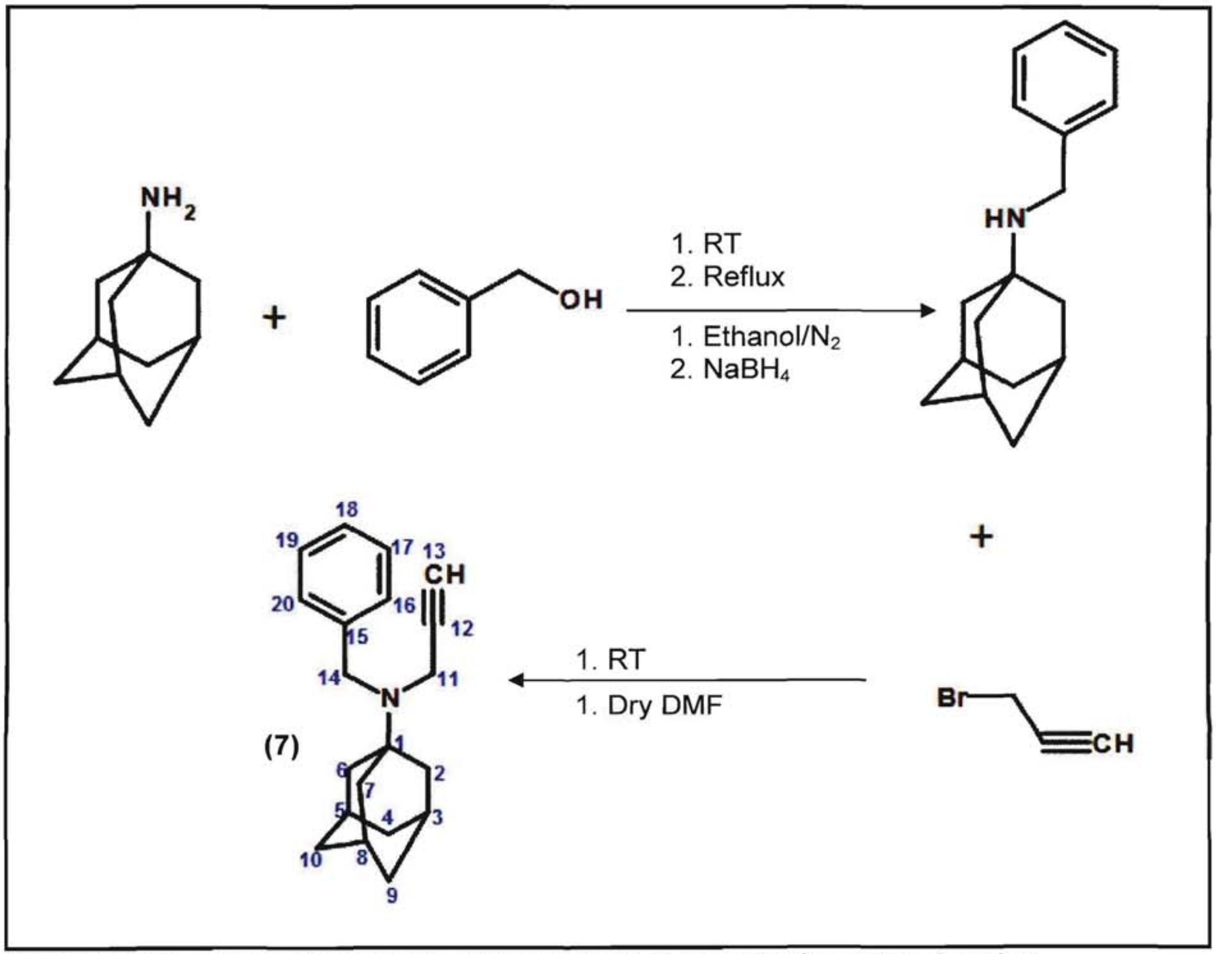
$C_{11}H_{10}O_2N_1$; MW, 227.35 g/mol; **mp.** 76 °C; **IR (KBr)** ν_{max} (Spectrum 7): 3237, 2099, 1119 cm^{-1}; **MS** (EI, 70 eV) m/z (Spectrum 15): 228 [(M$^+$)+1], 227 (M$^+$), 184, 144, 132, 91, 79, 53, 39; **^{1}H NMR** (600 MHz, $CDCl_3$) δ_H (Spectrum 23): 3.65 (s, 4H, H-11a,11b,14a,14b), 2.17 (s, 2H, H-13,16), 2.06 (s, 3H, H-3,5,8), 1.80 (s, 6H, H-2a,2b,6a,6b,7a,7b), 1.63 – 1.46 (m, 6H, H-4a,4b,9a,9b,10a,10b);**^{13}C NMR** (150 MHz, $CDCl_3$) δ_c (Spectrum 31): 82.12 (2C, C-12,15), 72.08 (2C, C-13,16), 55.45 (1C, C-1), 39.96 (3C, C-3,5,8), 36.54 (3C, C-2,6,7), 35.03 (2C, C-11,14), 29.70 (3C, C-4,9,10).

STRUCTURE ELUCIDATION:

Characteristic groups of compound **6** to be identified, include the ethynyl and amine group of the propargylamine moiety. On the ^{1}H NMR spectrum the protons of the propargyl group is evident, all lying more downfield than the protons of the amantadine cage. On the ^{13}C NMR spectrum the peaks of C-11, 12, 13, 14, 15 and 16 were present. The molecular ion from the MS confirmed a mass of 227.

2.2.8 Synthesis of N-propargyl-N-benzyl-adamantan-1-amine (7)

A solution of amantadine (5 g; 33.056 mmol) and benzaldehyde (3.51 g; 33.073 mmol) in ethanol (EtOH) (60 mL) was stirred for 4 days at ambient temperature under nitrogen atmosphere. Solid sodium borohydride ($NaBH_4$) (2.5 g; 66.085 mmol) was then added slowly in small portions over 30 minutes, and stirring of the resulting suspension was continued at room temperature for 30 minutes under nitrogen atmosphere. The reaction mixture was refluxed for 12 hours. After cooling to ambient temperature, the mixture was diluted with ethanol (EtOH) (60 mL), and the excess sodium borohydride was destroyed by adding aqueous hydrochloric acid (HCl) (10 mL, 5 M) drop wise. The reaction mixture was then made alkaline by adding aqueous sodium hydroxide (NaOH) solution, until the pH reached 12. Finally, the desired product was extracted to methylene chloride (DCM) (4 x 10 mL) and dried over anhydrous magnesium sulphate ($MgSO_4$). The solvent was evaporated under reduced pressure to afford the intermediate product, N-benzyl-adamantan-1-amine, as pure white crystals (yield: 4.757 g; 19.6 mmol; 59.29%). The intermediate product was used without any further purification.



Scheme 3.11 The synthetic route of N-propargyl-N-benzyl-adamantan-1-amine

A solution was made of N-benzyl-adamantan-1-amine (4.757 g; 19.6 mmol) and excess propargylbromide (2.3 ml; 25.81 mmol) in dry dimethylformamide (DMF) (30 mL), and left for 24 hours to stir at ambient temperature. After this period of time the mixture was diluted with water (50 mL), and an extraction was done in methylene chloride (DCM) (3 x 50 mL) and dried over anhydrous sodium sulphate (Na_2SO_4). The solvent was removed under reduced pressure to afford a dark orange syrupy fluid as residue. The desired product was precipitated out of the residue by the addition of chloroform (CCl_3) (30 mL), which allowed the collection of the final product by filtration as an off-white powder (yield: 1.352 g; 4.82 mmol; 24.59%).

PHYSICAL DATA:

$C_{11}H_{10}O_2N_1$; MW, 279.3 g/mol; **mp.** 81 °C; **IR (KBr)** v_{max} (Spectrum 8): 3210, 3062, 2091, 1495, 1130, 748cm^{-1}; **MS** (EI, 70 eV) m/z (Spectrum 16): 280 [(M^+)+1], 279 (M^+), 236, 222, 185, 135, 91; **^{1}H NMR** (600 MHz, $CDCl_3$) δ_H (Spectrum 24): 7.35-7.20 (m, 5H, H-16,17,18,19,20), 3.84 (s, 2H, H-14a,14b), 3.32 (s, 2H, H-11a,11b), 2.15 (s, 3H, H-3,5,8), 2.09 (s, 1H, H-13), 1.90 (s, 6H, H-2a,2b,6a,6b,7a,7b), 1.65 (s, 6H, H-4a,4b,9a,9b,10a,10b);**^{13}C NMR** (150 MHz, $CDCl_3$) δ_c (Spectrum 32): 141.11 (1C, C-15), 128.65 (2C, C-16,20), 128.18 (2C, C-17,19), 126.66 (1C, C-18), 83.22 (1C, C-12), 72.08 (1C, C-13), 55.05 (1C, C-1), 48.98 (1C, C-14), 40.53 (3C, C-3,5,8), 36.77 (3C, C-2,6,7), 34.79 (1C, C-11), 29.86 (3C, C-4,9,10).

STRUCTURE ELUCIDATION:

Characteristic groups evident of the structure of compound **6**, include the ethynyl and amine group of the propargylamine moiety, as well as the phenyl group. The only group making the structure of 7 different from that of 6 is the phenyl group. On the infrared spectrum the aromatic C=C bonds are present at 1495 cm^{-1}, and the aromatic C-H bonds at 3062 cm^{-1} and 748 cm^{-1}. The deshielded aromatic carbons and protons can also be identified on the ^{1}H and ^{13}C NMR spectrum, all lying much more downfield than the other signals. The molecular ion from the MS confirmed a mass of 279.

3 Concluding remarks

In this chapter the synthesis of 8 new polycyclic cage structures are described. The structures and purity of all the compounds were confirmed with IR, MS and NMR analysis.