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Copper-Catalysed *N*-Acyliminium Ion Cyclisation to 3-Azabicyclo[3.3.1]nonanes; Synthesis of 2,4-Disubstituted 1-Aza-adamantanes

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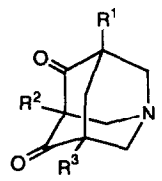
Abstract: An efficient Cu(bpy)Cl-catalysed *N*-acyliminium ion cyclisation to *N*-protected 3-azabicyclo[3.3.1]non-6-ene is reported. This compound has been demonstrated to be a valuable intermediate in the synthesis of 2,4-disubstituted 1-aza-adamantanes, and led to a stereoselective synthesis of 1-aza-adamantan-4-ol. This selectivity was also observed in the synthesis of two α-amino acid derivatives with the adamantane skeleton. An X-ray crystal structure of one of the cyclisation products is presented.

INTRODUCTION

1-Aza-adamantanes have explicitly been used as rigid models for studies on heterolytic fragmentation,[2-4] intramolecular charge transfer phenomena,[5,6] gas-phase basicity[7] and NMR studies.[8] The synthesis of functionalized 1-aza-adamantanes, however, has remained a relatively unexplored area thus far.[9,10] Recently, there is a growing interest in the synthesis of substituted 1-aza-adamantanes as conformationally restricted amines in the preparation of pharmacologically active agents.[11,12] For this purpose, Risch and co-workers[9,10] developed a procedure based on the work of Black,[13] which opened a route to 3,5,7-trisubstituted 1-aza-adamantanes. In a triple Mannich reaction of 1,3-cyclohexanediones with hexamethylenetetramine, various



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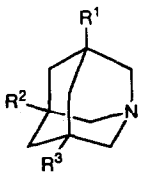

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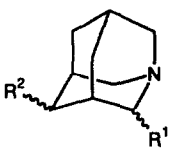
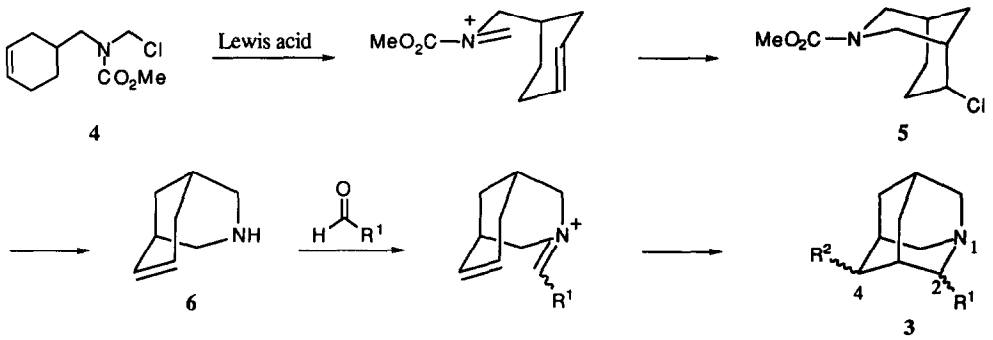


3

1-aza-adamantane-4,6-diones **1** were obtained, which gave 3,5,7-trisubstituted 1-aza-adamantanes **2** after deoxygenation. The synthesis of methylene-substituted 1-aza-adamantanes **3** is less straightforward and more elaborate.[14] In this paper the potential application of the Cu(bpy)Cl-complex as a Lewis acid catalyst for the synthesis of 3-azabicyclo[3.3.1]nonanes via *N*-acyliminium ion cyclisation will be discussed. It was envisioned[15-17] that the 3-azabicyclo[3.3.1]nonanes thus obtained might serve as useful precursors for the synthesis of 2,4-disubstituted 1-aza-adamantanes **3**. This approach is outlined in Scheme 1. Based on the results obtained from our earlier studies on copper-catalysed *N*-acyliminium ion cyclisations, it was anticipated that the ionic cyclisation of **4** to **5** could be catalysed by the Cu(bpy)Cl complex. This copper complex was shown to be effective for the ionic cyclisation of *N*-protected 2-aza-5-alkenyl chlorides.[18] It was expected[15-17] that after elimination of HCl and deprotection, 3-azabicyclo[3.3.1]non-6-ene **6** would cyclise to 2,4-disubstituted 1-aza-adamantanes **3** when treated with substituted aldehydes.

Scheme 1

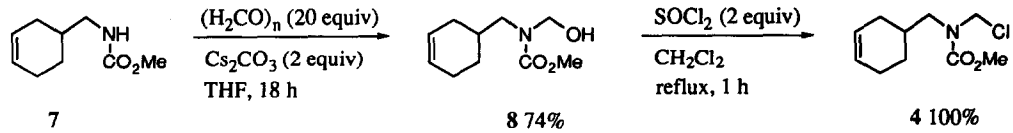


RESULTS AND DISCUSSION

Synthesis of N-protected 3-azabicyclo[3.3.1]non-6-ene

The precursor **4** for the *N*-methoxycarbonyliminium ion cyclisation to the 3-azabicyclo[3.3.1]nonane system was prepared as shown in Scheme 2. Carbamate **7** was prepared according to a literature procedure[19] and was obtained in 4 steps from 3-cyclohexenylmethanol in 69% yield. A methylol group was introduced via a procedure developed by Weinreb and co-workers.[20] Best results were obtained when 20 equiv of paraformaldehyde were used. In this way, **8** was obtained in 74% yield, along with 19% yield of starting material **9**. Treatment of **8** with thionyl chloride[21] gave chloride **4** quantitatively.

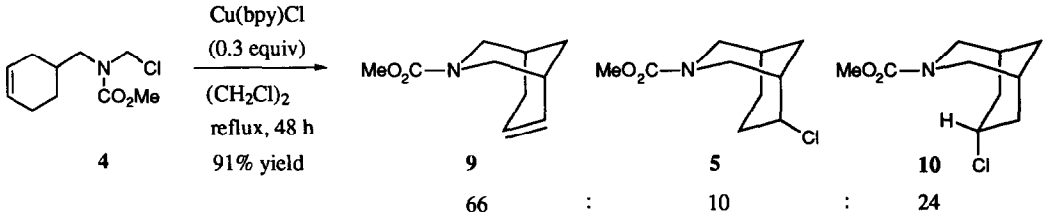
Scheme 2



7 8 74% 4 100%

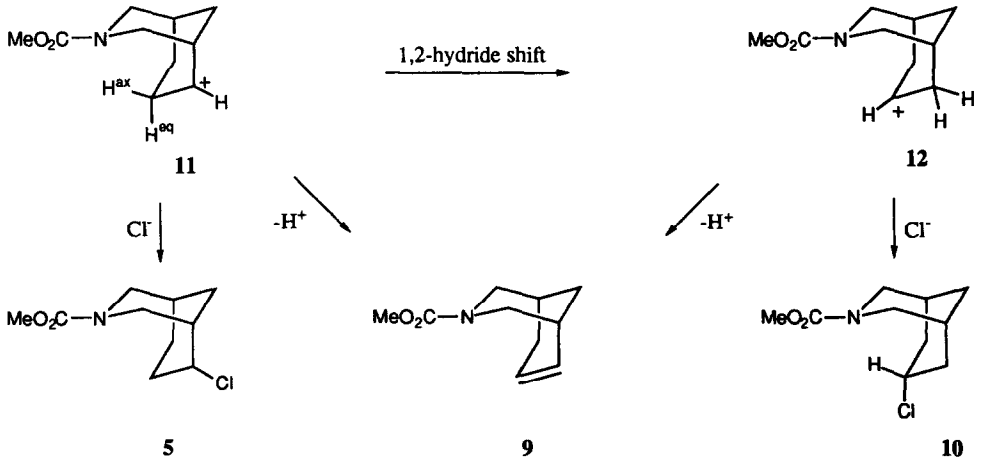
The cyclisation of **4** was performed in the presence of 0.3 equiv of Cu(bpy)Cl in refluxing 1,2-dichloroethane for 48 h to give in 91% yield the cyclisation products **5**, **9**, and **10** in the ratios indicated (Scheme 3). To check whether ionic cyclisation takes place at this temperature in the absence of a catalyst,[18] **4** was heated in 1,2-dichloroethane for 18 h. The need for a catalyst was clear, because only starting material **4** was obtained. Interestingly, the copper-catalysed cyclisation of **4** producedthe desired elimination product **9** as the major product. After flash chromatography, **9** was obtained pure in 48% yield together with **10** in 13%. Chloride **5** was present as a single diastereomer, but the stereochemistry of the chlorine substituent was not determined.

Scheme 3



The formation of a large amount of elimination product **9** agrees with earlier results in this type of ring closure[22] (Scheme 4). Due to steric interactions of H-7ax with the piperidine ring, the initial carbocation **11** rearranges via a 1,2-hydride shift to give **12**, which accounts for the formation of the symmetrical product **10** after capture of a chloride anion. The latter process is completely stereoselective, probably as a result of an effective shielding of the *endo* side of the carbocation **12** by the carbamate moiety. Elimination of a proton may proceed via both **11** and **12**, and relieves the steric interaction of H-7ax with the piperidine ring. The formation of **5** from **11** is also stereospecific, probably as a result of steric effects.

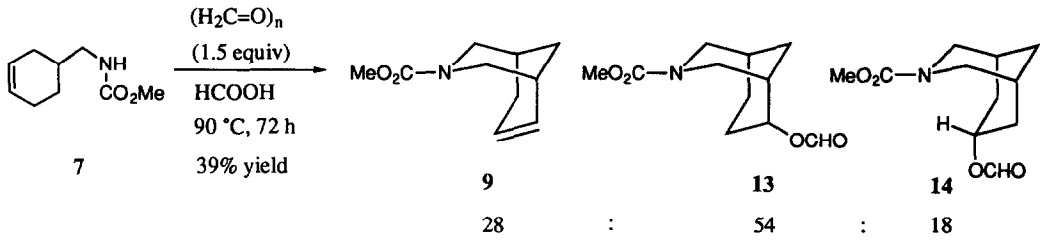
Scheme 4



In the formation of the desired alkene **9** via an *N*-methoxycarbonyl-iminium ion cyclisation, the concentration of nucleophiles such as Cl^- may be important as they may quench the carbocations **11** and **12** prior to elimination to **9**. In the Cu(bpy)Cl-catalysed cyclisation of **4**, the concentration of $[Cu(bpy)Cl_2]^-$ will be low during cyclisation, and a possible alternative source of chloride, i.e. the precursor **4** itself, is also present at rather low concentration (0.3 M).

To test the hypothesis that the chemoselectivity for this cationic cyclisation is depending on the concentration of nucleophiles, and to assess whether a shorter synthetic route to **9**, directly from **7**, would be possible, a formic acid-induced cyclisation of carbamate **7** was performed (Scheme 5). Thus, in the presence of 1.5 equiv of paraformaldehyde and with the solvent present as a nucleophile, **7** cyclised in 39% yield to give the expected products **9**, **13** and **14**.

Scheme 5



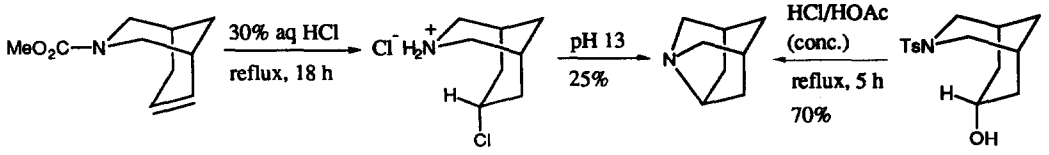
In comparison with the copper-catalysed cyclisation, the formic acid cyclisation is much less effective. More important, however, is the ratio of the cyclisation products. While the desired alkene **9** was the major product in the copper-catalysed cyclisation, the formates **13** and **14** are now the major products with the non-rearranged product **13** prevailing. This result is in agreement with the work of Schoemaker,[22] who described that the related acid-catalysed cyclisation of certain olefinic ω-ethoxylactams depends on both acid strength and solvent nucleophilicity, giving more of the rearranged product in stronger acid media. Thus, in order to obtain a good yield of **11**, the preferred method of catalysis is the use of Cu(bpy)Cl.

Attempts to eliminate HCl from **5** and **10**, in order to obtain **9**, failed. For example, heating of a mixture of chlorides **5** and **10** in toluene in the presence of DBU (5 equiv) for 18 h gave only starting material. These results further emphasize the beneficial role of the copper-catalyst for the construction of the 3-azabicyclo[3.3.1]non-6-ene system.

Deprotection of 3-azabicyclo[3.3.1]non-6-ene-3-carboxylic acid methyl ester

In order to remove the protecting methoxycarbonyl group in **9**, two methods were investigated. First, an acid-induced deprotection of **9** was studied (Scheme 6). When a solution of **9** in concentrated aqueous HCl was refluxed for 18 h, complete removal of the methoxycarbonyl group was established, but the alkene moiety was also affected and the HCl salt **15** was obtained quantitatively. Apparently, a regio- and stereospecific HCl-addition to the double bond occurred during acidic deprotection of the carbamate. The formation of **15** as a single product probably reflects similar steric interactions to those in the cyclisation of **4** via carbocations **11** and **12** (Scheme 4). Interestingly, when an aqueous solution of **15** was basified to pH 13 (Scheme 6), 3-aza-noradamantane[23] **16** was obtained in 25% yield. The formation of **16** confirms the equatorial orientation of

Scheme 6



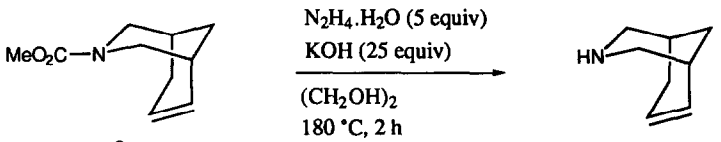
9 **15** 100% **16** **17**

H-7 in **15**, allowing an S_N2-substitution of the chloride by the free amine. 3-Aza-noradamantane is a highly volatile compound,[23] which may account for the low yield.

This synthesis of 3-aza-noradamantane **16** compares to our earlier synthesis of this heterocycle.[23] We reported that **16** formed spontaneously upon heating of the C-7-substituted N-tosyl-3-azabicyclo[3.3.1]nonane **17** in concentrated HCl/HOAc (Scheme 6). Both syntheses of **16** illustrate the facility of ring closure in this 3-azabicyclo[3.3.1]nonane system.

Next, a basic method was investigated for the deprotection of the amine **9** (Scheme 7). According to a procedure developed by Shono and co-workers,[24] **9** was treated with excess hydrazine hydrate and KOH pellets in ethylene glycol at 180 °C for 2 h, to give **6** in 90% yield, without affecting the double bond.

Scheme 7

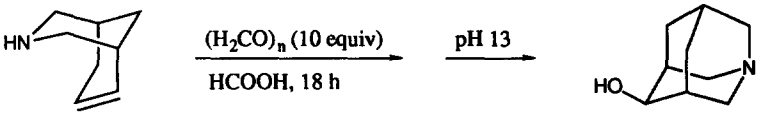


9 **6** 90%

Synthesis of 1-aza-adamantan-4-ol

With the desired precursor **6** for the adamantane skeleton in hand, the cyclisation of **6** with the introduction of a carbon-atom was performed using a Mannich-type reaction as shown in Scheme 8. Reaction of amine **6** with paraformaldehyde in formic acid, followed by basic workup, afforded the desired 1-aza-adamantan-4-ol **18** in 80% yield. Interestingly, alcohol **18** was obtained as a single diastereomer. The equatorial orientation[25] of the hydroxy group in **18** was established by comparison with literature data, as both equatorial and axial isomers of 1-aza-adamantanol are known compounds.[26-28] The high stereoselectivity in the cyclisation of alkene **6** may be explained as a result of steric interactions in the intermediate π-complex.[29]

Scheme 8



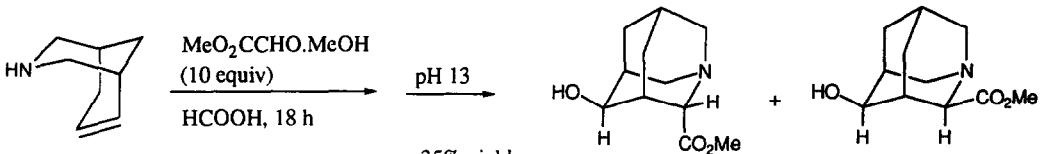
6 **18** 80%

Synthesis of 4-hydroxy-1-aza-adamantane-2-carboxylic acid methyl ester

For the introduction of a C-2 substituent in the 1-aza-adamantane, reaction of alkene **6** with an aldehyde, containing a substituent R as compared to paraformaldehyde, is required. The use of methyl glyoxylate would lead to the formation of a 1-aza-adamantane derivative substituted with an ester group on C-2. The introduction of an ester group would not only allow further modification of the molecule, but would also give a rigid α-amino acid derivative which might be of particular interest from a pharmacological point of view.

When amine **6** was treated with excess of methyl glyoxylate in formic acid (Scheme 9), the desired α-amino acid derivatives **19** and **20** were obtained in 35% yield after basic workup and flash-chromatography (Al_2O_3, CH_2Cl_2/MeOH). In this way, samples of both diastereomers **19** and **20** were obtained. The stereochemistry of the major product **19** was first established through NMR-experiments (C-H correlation, COSY and NOESY), and was confirmed after elucidation of its X-ray crystal structure (mp 143-144 °C).

Scheme 9



6 **19** 73 : 27 **20**

The X-ray structure of **19** is shown in Figure 1, and clearly shows the 1-aza-adamantane skeleton, containing an axial ester substituent on C-2 and an equatorial hydroxy group on C-4.

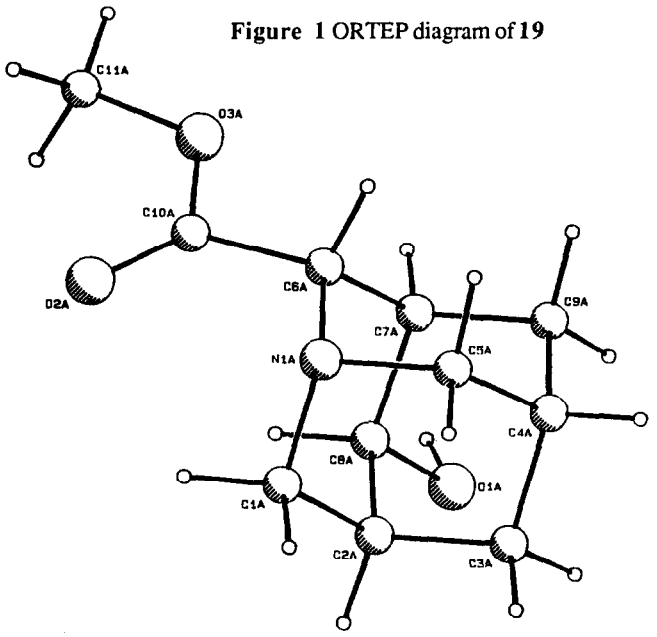


Figure 1 ORTEP diagram of **19**

The stereochemistry of the minor product **20** was established via NMR techniques and by comparison with **19**. The equatorial orientation of both the methyl ester and the hydroxy group in **20** was established via NOESY, showing good NOE effects of H-2 on H-4 (+6.6% NOE) and vice versa (+5.4% NOE). This effect was not found in **19**. Compared to the cyclisation with paraformaldehyde, the cyclisation with methyl glyoxylate gave a lower yield, probably due to the increase in steric hindrance in the latter case.

Interestingly, the stereoselectivity of cyclisation with respect to C-4 is similar for both aldehydes, leading exclusively to the formation of the equatorial alcohols. Apparently, the use of an aldehyde bearing an extra ester substituent as compared to formaldehyde, does not affect the stereoselectivity of cyclisation at C-4, and presumably a similar mechanism is operative. There is much less stereocontrol with respect to C-2, as a 73:27 mixture of C-2 isomers is obtained.

Conclusions

The application of the Cu(bpy)Cl-complex as a Lewis acid catalyst allows an efficient synthesis of 3-azabicyclonon-6-ene **6** via an *N*-acyliminium ion cyclisation. This compound has been demonstrated to be a valuable intermediate in a stereoselective synthesis of 1-aza-adamantan-4-ol **18**. This selectivity was also observed in the synthesis of 4-hydroxy-1-aza-adamantane-2-carboxylic acid methyl esters **19** and **20**. These rigid α-amino acid derivatives may be useful for further pharmacological studies.

EXPERIMENTAL

General information. Experimental techniques and analytical measurements were applied as previously described.[30] IR spectral data are reported in cm^{-1} and NMR chemical shifts in ppm with $CDCl_3$ as a solvent (unless stated otherwise). Methyl *N*-((3-cyclohexenyl)methyl)-carbamate (**7**) was prepared according to a literature procedure.[19] CuCl was purified according to a literature procedure.[31] In the case of **19** and **20**, neutral aluminium oxide-coated sheets (Merck 60 F_{254}, type E) were used for thin-layer chromatography, and aluminium oxide (Fluka type 5016A basic) was used for flash chromatography.

Methyl *N*-((3-cyclohexenyl)methyl)-*N*-(hydroxymethyl)carbamate (8). To a solution of methyl *N*-((3-cyclohexenyl)methyl)-carbamate (**7**) (3.00 g, 17.7 mmol) in 300 mL of tetrahydrofuran were added paraformaldehyde (10.65 g, 355 mmol) and Cs_2CO_3 (11.6 g, 35.5 mmol). The reaction mixture was stirred for 18 h and filtered on a glass funnel. After concentration of the filtrate in vacuo, the mixture was chromatographed to give two fractions. The first fraction consisted of **7** (563 mg, 3.3 mmol, 19%) as a colourless oil. R_f 0.55 (EtOAc/hexane 1:2). The second fraction consisted of **8** as a colourless oil (2.60 g, 13.1 mmol, 74%). R_f 0.25 (EtOAc/hexane 1:2). IR ($CHCl_3$) 3590, 3430 (broad), 3000, 2910, 1680, 1475. ^{1}H NMR (200 MHz) 1.10-1.35 (m, 1H), 1.55-2.15 (m, 6H), 3.15-3.35 (m, 2H), 3.50-3.70 (m, 1H), 3.71 (s, 3H, OCH_3), 4.76 (d, J = 7.8 Hz, 2H, NCH_2O), 5.55-5.70 (m, 2H, CH=CH).

Methyl *N*-((3-cyclohexenyl)methyl)-*N*-(chloromethyl)carbamate (4). To a solution of **8** (2.60 g, 13.1 mmol) in CH_2Cl_2 (13 mL) was added $SOCl_2$ (1.9 ml, 26 mmol). After heating under reflux for 1h, the volatiles were removed in vacuo to yield **4** as a colourless oil (2.84 g, 13.1 mmol, 100%). IR ($CHCl_3$) 3000, 2910, 1695, 1465, 1435. ^{1}H NMR (200 MHz) 1.10-1.40 (m, 1H), 1.60-2.20 (m, 6H), 3.30 (d, J = 7.1 Hz, 2H), 3.79 (s, 3H, OCH_3), 5.32 (s, 2H, CH_2Cl), 5.55-5.75 (m, 2H, CH=CH).

Cu(bpy)Cl-catalysed cyclisation of 4. To a solution of **4** (496 mg, 2.28 mmol) in 8 mL of 1,2-dichloroethane were added bpy (107 mg, 0.69 mmol) and CuCl (68 mg, 0.68 mmol). The reaction mixture was heated under reflux for 48 h. Flash chromatography gave three fractions. The first fraction consisted of **3-azabicyclo[3.3.1]non-6-ene-3-carboxylic acid**

methyl ester (9) as a colourless oil (197 mg, 1.09 mmol, 48%). R_f 0.37 (EtOAc/hexane 1:4). IR ($CHCl_3$) 3000, 2910, 2850, 1675, 1470, 1455, 1440. ^1H NMR (200 MHz) 1.55-1.80 (m, 2H), 1.80-2.10 (m, 2H), 2.15-2.35 (m, 2H), 2.70-3.00 (m, 2H, H-2 and H-4), 3.57 (s) and 3.59 (s, 3H, OCH_3 two rotamers), 3.73-4.21 (m, 2H, H-2 and H-4), 5.68-5.75 (m, 2H, CH=CH). ^{13}C NMR (50 MHz, some carbons show two peaks because of rotamers) 27.3 (C-1), 29.5 (C-5), 29.6, 30.8, 47.0 (C-2), 51.0 (C-4), 52.0 (OCH_3), 127.1, 127.5, 128.4 and 129.1 (CH=CH two rotamers) (C=O not observed). HRMS calculated for $C_{10}H_{15}NO_2$ 181.1103, found 181.1109. The second fraction consisted of a 40:30:30 mixture of **9**, **5** and **10** as a colourless oil (138 mg, 0.67 mmol, 29%). R_f 0.37 and 0.32 (EtOAc/hexane 1:4). IR ($CHCl_3$) 3000, 2910, 2850, 1675, 1470, 1455, 1440. Spectroscopic data derived derived from this mixture for **6-chloro-3-azabicyclo[3.3.1]nonane-3-carboxylic acid methyl ester (5)**: ^1H NMR (200 MHz, characteristic signals) 3.05-3.15 (m, 2H), 4.35-4.45 (m, 1H, H-6). ^{13}C NMR (50 MHz) 25.6, 26.0, 27.1 (C-1), 29.8, 35.5 (C-5), 47.4 (C-2), 49.3 (C-4), 52.5 (OCH_3), 62.6 (C-6), 156.1 (C=O). The third fraction consisted of **7-*exo*-chloro-3-azabicyclo[3.3.1]nonane-3-carboxylic acid methyl ester (10)** as a colourless oil (66 mg, 0.30 mmol, 13%). R_f 0.32 (EtOAc/hexane 1:4). IR ($CHCl_3$) 3000, 2910, 2850, 1675, 1470, 1455, 1440. ^1H NMR (200 MHz) 1.50-2.15 (m, 6H), 2.20-2.40 (m, 2H), 2.35-3.10 (m, 2H), 3.69 (s, 3H, OCH_3), 3.85-4.20 (m, 2H), 4.51 (tt, J = 11.9, 5.9 Hz, 1H, H-6). ^{13}C NMR (50 MHz) 30.4 (C-1 and C-5), 31.7 (C-9), 42.2 (C-6 and C-8), 48.6 (C-2 and C-4), 52.6 (OCH_3), 55.5 (C-7), 156.3 (C=O). HRMS calculated for $C_{10}H_{16}NO_2Cl$ 217.0870, found 217.0860.

Blank experiment. A solution of **4** (150 mg, 0.69 mmol) in 2.3 mL of 1,2-dichloroethane was refluxed for 18 h. Evaporation of the volatiles in vacuo gave **4** (150 mg, 0.69 mmol) as a colourless oil, pure according to ^1H NMR.

Formic acid-induced cyclisation of 7. To a solution of **7** (100.0 mg, 0.591 mmol) in 6 mL of formic acid was added paraformaldehyde (27 mg, 0.87 mmol) and the mixture was heated at 90 °C for 3 days. The reaction mixture was evaporated in vacuo, and was three times evaporated with benzene (5 mL). Flash chromatography gave two fractions. The first fraction consisted of **11** (12 mg, 0.066 mmol, 11%) as a colourless oil. R_f 0.35 (EtOAc/hexane 1:4). The second fraction consisted of a 25:75 mixture of **7-*exo*-formyloxy-3-azabicyclo[3.3.1]nonane-3-carboxylic acid methyl ester (14)** and **6-formyloxy-3-azabicyclo[3.3.1]nonane-3-carboxylic acid methyl ester (13)**, as a colourless oil (37.3 mg, 0.164 mmol, 28%). R_f 0.20 (EtOAc/hexane 1:4). IR ($CHCl_3$) 3000, 2920, 2850, 1715 (C=O), 1685 (NC=O), 1445, 1405. ^1H NMR (400 MHz) 1.47-2.20 (m, 8H), 2.90-3.10 (m, 2H, H-2 and H-4), 3.67 (s, **13**) and 3.70 (s, **14**, 3H, OCH_3), 3.95-4.15 (m, 2H, H-2 and H-4), 5.13 (broad s, 0.75H, **13** H-6), 5.35 (tt, J = 5.6, 11.2 Hz, 0.25H, **14** H-7), 7.95 (s, 0.25H, **14** HC=O), 8.04 (s, 0.75H, **13** HC=O). ^{13}C NMR (100 MHz) Data derived from this mixture for **14**: 29.37 (C-1 and C-4), 31.89 (C-9), 36.24 (C-6 and C-8), 48.73 (C-2 and C-4), 52.69 (OCH_3), 68.68 (C-7), 156.47 (NC=O), 160.44 (OC=O). Data derived from this mixture for **13**: 25.81, 26.31 and 26.55 (CH_2), 27.02 and 31.85 (C-1 and C-4), 46.04 and 49.19 (C-2 and C-4), 52.57 (OCH_3), 72.95 (C-6), 156.25 (NC=O), 160.32 (OC=O). HRMS calculated for $C_{11}H_{17}NO_4$ 227.1158, found 227.1170.

7-*Exo*-chloro-3-aza-bicyclo[3.3.1]nonane.HCl (15). A solution of **9** (187.9 mg, 1.037 mmol) in 10 mL of 30% aq. HCl was heated under reflux for 18 h. Evaporation of the volatiles in vacuo afforded **15** as a white powder (202.0 mg, 1.03 mmol, 100%). ^1H NMR (250 MHz, D_2O) 1.75-1.90 (m, 2H), 1.95-2.15 (m, 4H), 2.61 (broad s, 2H, H-1 and H-5), 3.34 (d, J = 10.3 Hz, 2H, H-2ax and H-4ax), 3.48 (d, J = 10.5 Hz, 2H, H-2eq and H-4 eq), 4.40-4.48 (m, 1H, H-7).

3-Aza-noradamantane (16). The salt **15** (151.8 mg, 0.774 mmol) was taken up in 10 mL of water, and an aq solution of 20% NaOH was added until the water layer was basified to pH 13. The water layer was three times extracted with toluene (10 mL), and the combined organic layers were concentrated in vacuo to give **16** as a white solid (23 mg, 0.193 mmol, 25%). ^1H NMR (400 MHz, benzene-d_6) 1.29 (d, J = 12.6 Hz, 1H), 1.45 (s, 1H), 1.48 (s, 1H), 1.52 (d quintet, J = 12.8, 2.5 Hz, 1H), 1.60-1.70 (m, 2H), 1.81 (s, 2H, H-1 and H-5), 2.78-2.85 (m, 4H, H-2 and H-4), 3.59 (t, J = 6.7 Hz, 1H, H-7). ^{13}C NMR (100 MHz, benzene-d_6) 34.57 (C-9), 37.61 (C-1 and C-5), 44.23 (C-6 and C-8), 61.06 (C-7), 69.00 (C-2 and C-4).

3-Aza-bicyclo[3.3.1]non-6-ene (6). To a solution of **9** (1.09 g, 6.04 mmol) in 40 mL of ethylene glycol were added

KOH pellets (8.47 g, 0.151 mol) and $N_2H_4.H_2O$ (1.47 mL, 30.2 mmol). The reaction mixture was heated at 180 °C for 2 h and poured into 140 mL of water. The water layer was five times extracted with 1,1,1-trichloroethane (60 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo, to give **6** as a yellow oil (670 mg, 5.45 mmol, 90%). IR ($CHCl_3$) 3660, 3000, 2920, 2850, 1440. ^{1}H NMR (400 MHz) 1.76-1.90 (m, 4H), 1.94 (dd, J = 2.5, 19.0 Hz, 1H), 2.18-2.25 (m, 1H), 2.34-2.41 (m, 1H), 2.57 (d, J = 13.0 Hz, 1H), 2.79 (dd, J = 2.4, 13.0 Hz, 1H), 2.85-2.88 (m, 2H), 5.66-5.71 (m, 1H), 6.01 (dt, J = 9.8, 3.4 Hz, 1H). ^{13}C NMR (100 MHz) 27.94 (CH), 30.16 (CH_2), 30.56 (CH), 31.86 (CH_2), 48.87 and 54.51 (C-2 and C-4), 129.19 and 130.53 (C-6 and C-7). HRMS calculated for $C_8H_{13}N$ 123.1048, found 123.1048.

1-Aza-adamantan-4-ol [4-OH$_{eq}$] (18). To a solution of **6** (131 mg, 1.07 mmol) in 10 mL of formic acid was added paraformaldehyde (217 mg, 10.6 mmol). The reaction mixture was stirred for 18 h and concentrated in vacuo. Toluene (5 mL) was added, and the mixture was concentrated in vacuo (this procedure was repeated three times). Water (5 mL) was added, and KOH pellets were added to basify the mixture to pH 13. The water layer was extracted six times with CH_2Cl_2 (10 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give **18** as a white solid (132 mg, 0.86 mmol, 80%). IR ($CHCl_3$) 3650, 3600, 3500-2200, 2990, 2930, 2850, 1445. ^{1}H NMR (400 MHz) 1.58 (s, 1H, H-7), 1.72 (d, J = 12.4 Hz, 2H), H-6 and H-10), 1.77 (s, 2H, H-3 and H-5), 2.26 (d, J = 12.4 Hz, 2H, H-6 and H-10), 2.99 (d, J = 12.9 Hz, 2H, H-2 and H-9), 3.08 (s, 2H, H-8), 3.24 (d, J = 12.8 Hz, 2H, H-2 and H-9), 3.98 (t, J = 3.0 Hz, 1H, H-4) (OH not observed). ^{13}C NMR (100 MHz) 26.56 (C-7), 29.74 (C-6 and C-10), 33.77 (C-3 and C-5), 57.44 (C-2 and C-9), 58.59 (C-8), 72.74 (C-4). HRMS calculated for $C_9H_{15}NO$ 153.1154, found 153.1152.

4-Hydroxy-1-aza-adamantane-2-carboxylic acid methyl ester [2-(CO$_2$Me)$_{ax}$, 4-OH$_{eq}$] (19) and 4-Hydroxy-1-aza-adamantane-2-carboxylic acid methyl ester [2-(CO$_2$Me)$_{eq}$, 4-OH$_{eq}$] (20). To a solution of **6** (84 mg, 0.68 mmol) in 7 mL of formic acid was added $MeO_2CCHO.MeOH$ (816 mg, 6.8 mmol). The reaction mixture was stirred for 18 h and concentrated in vacuo. Toluene (5 mL) was added, and the mixture was concentrated in vacuo (this procedure was repeated three times). Water (8 mL) was added, and the mixture was extracted two times with CH_2Cl_2 (8 mL). Then, KOH pellets were added to the water layer to basify the mixture to pH 13. The water layer was extracted six times with EtOAc (8 mL), and these last combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed (aluminium oxide, CH_2Cl_2/MeOH 1:99) to give three fractions. The first fraction consisted of **19** as a white solid (32 mg, 0.15 mmol, 22%). R_f 0.30 (CH_2Cl_2/MeOH 3:97). Recrystallization from CH_2Cl_2/diisopropylether gave white needles, mp 143-144 °C. IR 3600, 3500-2300, 2920, 2850, 1725, 1430. ^{1}H NMR (400 MHz) 1.60 (broad s, 2H, H-7 and OH), 1.70-1.75 (m, 3H, H-10, H-6 and H-5), 2.20-2.28 (m, 1H, H-6), 2.36 (s, 1H, H-3), 2.36-2.43 (m, 1H, H-10), 3.07-3.17 (m, 3H, H-8 and H-9), 3.26 (d, J = 13.3 Hz, 1H, H-8), 3.76 (s, 3H, OCH_3), 3.89 (s, 1H, H-2), 3.99 (s, 1H, H-4). ^{13}C NMR (100 MHz) 25.93 (C-7), 29.688 (C-6), 30.61 (C-10), 33.11 (C-5), 34.76 (C-3), 52.14 (OCH_3), 53.84 (C-9), 60.29 (C-8), 67.43 (C-2), 69.62 (C-4), 171.86 (C=O). HRMS calculated for $C_{11}H_{17}O_3N$ 211.1208, found 211.1187. The X-ray crystal structure of this major isomer was determined (see Figure 1).[32] The second fraction consisted of a 42:58 mixture of **19** and **20** as a colourless oil (12 mg, 0.06 mmol, 8%). The third fraction consisted of **20** as a colourless oil (7 mg, 0.03 mmol, 5%). R_f 0.15 (CH_2Cl_2/MeOH 3:97). IR ($CHCl_3$) 3600, 3500-2300, 2930, 2850, 1730, 1450, 1435. ^{1}H NMR (400 MHz) 1.52 (s, 1H, H-7), 1.68-1.75 (m, 3H, H-6, H-10 and OH), 1.79 (s, 1H, H-5), 2.15 (d, J = 13.2 Hz, 1H, H-10), 2.23-2.28 (m, 1H, H-6), 2.32 (s, 1H, H-3), 2.97 (d, J = 12.7 Hz, 1H, H-8), 3.01-3.05 (m, 1H, H-9), 3.20-3.24 (m, 1H, H-8), 3.38 (dd, J = 2.2, 13.5 Hz, 1H, H-9), 3.58 (s, 1H, H-2), 3.80 (s, 3H, OCH_3), 4.04 (t, J = 3.2 Hz, 1H, H-4). ^{13}C NMR (100 MHz) 25.71 (C-7), 26.15 (C-10), 29.66 (C-6), 33.02 (C-5), 34.80 (C-3), 52.17 (OCH_3), 54.42 (C-8), 58.46 (C-9), 65.80 (C-2), 73.42 (C-4), 171.54 (C=O). HRMS calculated for $C_{11}H_{17}O_3N$ 211.1208, found 211.1217.

Crystallographic data for **19**:

Triclinic, P-1, a = 8.2114(8) Å, b = 11.274(2) Å, c = 12.1181(8) Å; α = 87.62(1) °, β = 71.595(7) °, γ = 89.33(1) °; V = 1063.5(3) Å^3; Z = 4. CuK-α-radiation, λ = 1.5418 Å. Final R = 0.062 for 3395 observed reflections.[32]

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