The synthesis of 3-amino-3-methylbicyclo[3.3.1]nonanes: *Endo*-selectivity in the Ritter reaction of 1,3,5,7α-tetramethylbicyclo[3.3.1]nonan-3-ol

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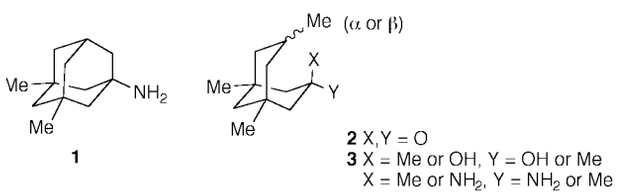
1,3,5,7α- and 1,3,5,7β-Tetramethylbicyclo[3.3.1]nonan-3-ols **3a** and **3b** were prepared from the corresponding ketones **2a** and **2b**. 7α-Methyl isomer **3a** gave selectively *endo*-3α-*N*-formylaminobicyclononane **10** in the Ritter reaction with trimethylsilyl cyanide. 7β-Methyl epimer **3b** suffered water elimination resulting in bicyclo[3.3.1]non-2-ene **12** under the same reaction conditions. The *endo*-amide structure was confirmed by X-ray analysis..

Introduction

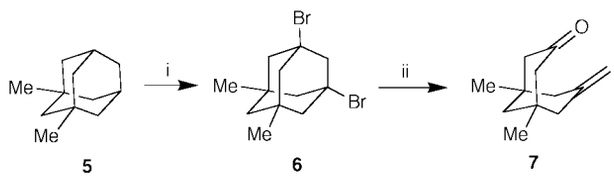
The therapeutic value of *N*-methyl-D-aspartate (NMDA) receptor antagonists for the treatment of central nervous system disorders has been discussed for many years.[1] The high-affinity NMDA receptor antagonists provoke undesirable side effects at therapeutic concentrations. However, Memantine **1** (1-amino-3,5-dimethyladamantane) possessing moderate receptor affinity, acts as an uncompetitive NMDA receptor antagonist and has been used for many years in the treatment of dementia.[1] Thus, clinical experience with Memantine **1** has shown that it is possible to develop NMDA receptor antagonists which do not activate receptors pathologically and retain their physiological activity. During the investigations of *N*-methyl-D-aspartate receptor ion channel blockers, Memantine **1** structural isomers, compounds of increased lipophilicity with shapes similar to Memantine **1**, have been sought.[2] Thus, it was necessary to develop a synthetic route toward 1,3,5,7-tetramethylbicyclo-[3.3.1]nonan-3-amine **4** isomers (X = CH_3, Y = NH_2 or *vice versa*).



Up to now the successful introduction of a nitrogen functionality at the tertiary C-3 carbon atom in bicyclo[3.3.1]nonane has not been reported. Moreover, nucleophilic additions to the carbonyl group in this system have been found to be quite difficult. Fortunately, recent studies of organocerium reagent addition to bicyclo[3.3.1]nonan-3-one demonstrated the possibility of developing the synthesis of the corresponding alcohols **3** from ketones **2**. Our synthetic efforts were, therefore, focussed on the Ritter reaction of tertiary alcohols **3**. Herein we report the first synthesis of 3-methyl-3-aminobicyclo[3.3.1]nonane derivatives and evidence that the Ritter reaction proceeds *endo*-selectively.

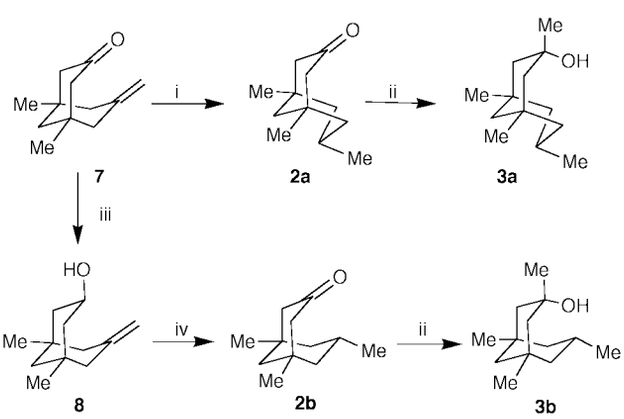
Results and discussion

7-Methylene-1,5-dimethylbicyclononan-3-one **7** can be obtained in two steps by bromination of 1,3-dimethyladamantane **5**[3] and by subsequent Grob fragmentation of 1,3-dibromo-5,7-dimethyladamantane **6**[4] (Scheme 1). Ketone **7** served as a starting material for the preparation of both 1,5,7α- and 1,5,7β-trimethylbicyclo[3.3.1]nonan-3-ones **2a** and **2b**.



Scheme 1 *Reagents and conditions*: i, Br_2, Fe, 83%; ii, NaOH, 79%.

Hydrogenation of unsaturated ketone **7** using a modified literature procedure[5] provided 1,5,7α-trimethylbicyclononan-3-one **2a** (Scheme 2). 3,5-Dimethyladamantan-1-ol was isolated as a by-product in this reaction. With a sample of isomeric ketone **2b** in hand we were able to estimate that the hydrogenation was highly selective, *i.e.* less than 2% of 7β-methyl isomer **2b** was detected by GC analysis. 1,5,7β-Trimethylbicyclononanone **2b** was obtained by the known procedure involving Meerwein–Pondorf–Verley reduction[6] of unsaturated ketone **7** and a subsequent acid catalyzed intramolecular proton transfer[7] in 7-methylene-1,5-dimethylbicyclo[3.3.1] nonan-3β-ol **8** (Scheme 2).



Scheme 2 *Reagents and conditions*: i, H_2, PtO_2, 34%; ii, "$MeCeCl_2$", 97% of both **3a** and **3b**; iii, $Al(OPr^i)_3$, 57%; iv, 75% H_2SO_4, 73%.

The next step involved the introduction of a methyl group at the C-3 position of bicyclononane. Bicyclo[3.3.1]nonan-3-one itself has been shown to be absolutely inert toward alkylmagnesium and -lithium reagents,[8] while organolanthanoid species were found to add to the carbonyl group more effi-

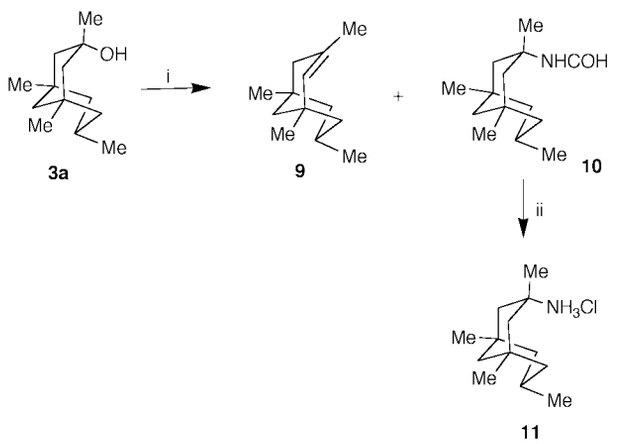
Table 1 Conversion of isomeric bicyclononanes **2** to tertiary alcohols **3** by organometallic reagents

Entry	Reaction conditions	Conversion to alcohols (%)[a]	
		3a	**3b**
1	$MeMgI/Et_2O$	50	9
2	MeLi/THF/cumene	70	40
3	$MeMgI/CeCl_3/THF$	100	100

[a] The conversion was determined from alcohol/ketone ratio by GC.

ciently.[9] 1,5,7-Trimethylbicyclononanones **2a** and **2b** displayed low to moderate conversion in reactions with methylmagnesium iodide and methyllithium, providing mixtures of the desired alcohols and starting ketones. Using the reagent prepared from methylmagnesium iodide and cerium trichloride, complete reaction was observed with both substances to give alcohols **3a** and **3b** in excellent yields (Table 1).

To introduce the amino group both alcohols **3a** and **3b** were used in the Ritter reaction with sulfuric acid and trimethylsilyl cyanide[10] as a hydrogen cyanide source (Scheme 3). Thus,



Scheme 3 *Reagents and conditions*: i, TMSCN, H_2SO_4, 34% of **9** and 55% of **10**; ii, H_3O^+, 71%.

1,3β,5,7α-tetramethylbicyclo[3.3.1]nonan-3α-ol **3a** gave 1,3,5,7β-tetramethylbicyclo[3.3.1]non-2-ene **9** and *N*-formyl-1,3,5,7-tetramethylbicyclo[3.3.1]nonan-3-amine **10** (34% of **9** and 55% of **10** by GC). The GC analysis of the reaction mixture indicated that only one amide isomer was formed. The other peaks registered with similar retention time were of negligible integral intensity (<1%). The ^1H NMR spectrum of the reaction product **10** was somewhat complicated due to the *cis–trans* isomerism of the formyl group, as could be seen from the different spin coupling constants of the formyl group protons. However, hydrolysis of formamide **10** undoubtedly gave one amine isomer **11** according to GC analysis, and ^1H and ^{13}C NMR spectra. As the correct stereochemical assignment of the formamido group could not be determined from simple ^1H NMR experiments due to the lack of any vicinal spin couplings, crystals of *N*-formyl derivative **10** were prepared for a single crystal X-ray analysis. This revealed two independent molecules (*a* and *b*) in the asymmetric unit cell (Fig. 1). These molecules differ in the orientation of the formylamino group. The torsion angles C5–C4–N3–C2 for the molecules *a* and *b* are −174.5(7) and 59.2(8)°, respectively. The bicyclo[3.3.1]nonane framework adopts a chair-boat conformation with the formamido group in the axial position of the chair.

There is little information in the literature about the stereochemistry of the Ritter reaction to explain the selective formation of **10**. Studies have been carried out only with 4-substituted cyclohexyl cations, showing the preference for axial nitrile

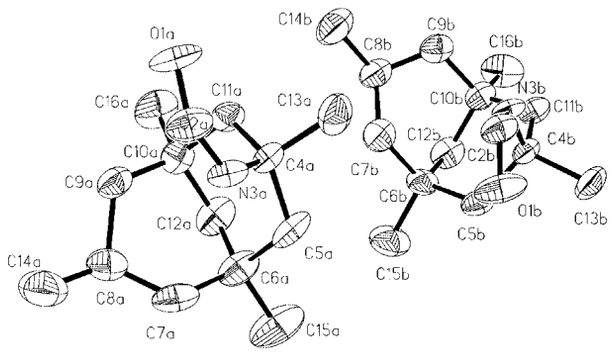


Fig. 1 Crystal structure of *N*-formyl-1,3,5,7β-tetramethylbicyclo-[3.3.1]nonan-3α-amine **10**.

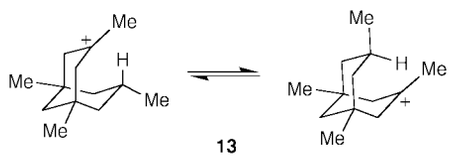
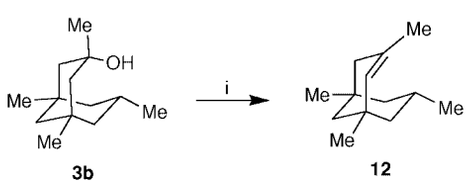


Fig. 2 Transannular hydride transfer in **13**.

attack.[11–13] Such a reaction course was explained by torsional strain caused by the 2,6-axial hydrogens, analogously to the nucleophilic addition to cyclohexanones.[11,12] Alternatively, Ichikawa suggested that the axial product resulted from the *trans*-antiparallel electrophilic addition of H^+ and CH_3CN to the olefinic bond.[13]

It is known that 3α-methylbicyclo[3.3.1]nonanone undergoes predominately *exo* attack of nucleophiles.[5] It is reasonable to assume that the capture of nitrile by the carbocation should also occur predominately from the *exo* face. Obviously, the selective *endo* product **10** formation cannot be explained by steric discrimination as the bicyclononyl cation should adopt the same conformation as the parent bicyclononanone. It is possible that *trans*-antiparallel addition as suggested by Ichikawa could be better rationalized as discrimination of the carbocation faces due to the differing C–C and C–H hyperconjugation.[14] The effect of hyperconjugation should thus override the steric factors. It is evident, however, that a more detailed investigation of the Ritter reaction stereochemistry should be carried out.

7β-Methylbicyclononanol **3b**, unlike its epimer **3a**, gave 1,3,5,7β-tetramethylbicyclo[3.3.1]non-2-ene **12** as sole product (93% by GC of the reaction mixture) and no formamide was isolated under the same Ritter reaction conditions (Scheme 4).



Scheme 4 *Reagents and conditions*: i, TMSCN, H_2SO_4, 66%.

It has been shown that the 7β-methylbicyclononan-3-yl cation **13** undergoes rapid transannular hydride transfer and exists in the double chair conformation (Fig. 2).[15] As a result of this, the *endo* face becomes inaccessible. The different reactivities of alcohols **3a** and **3b** provide additional evidence that amide formation from an obviously sterically unfavoured nitrile attack from the *endo* side of the carbocation is much more rapid than that from the *exo* side. This phenomenon requires an explanation which can be provided only on the basis of more extended studies. The results obtained for the Ritter reaction of both bicyclononanols **3a** and **3b** show that the stereoselectivity of

amide formation does not follow the rules of nucleophilic addition to the carbonyl group.[11]

Experimental

Melting points were determined in capillary tubes on a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 580B spectrometer. Mass spectra were registered on a Hewlett Packard HP 6890 Series GC system. Microanalyses were performed on a Carlo Erba Instrument EA1108. ^{1}H and ^{13}C NMR spectra were determined on a Varian Mercury 200BB spectrometer for solutions in $CDCl_3$ with TMS as internal standard. Chemical shifts are recorded as δ values in ppm. *J* Values are given in Hz. Reaction mixture analyses were made and the purity of all products were determined by GC analysis [MN-OV-1 (Fused Silica), 25 m × 0.53 mm, d_f = 1.0 μ, 50–270 °C (10 °C min^{-1})]. Preparative chromatography was carried out on Kieselgel 63–100 μm by the flash column method.[16] TLC analyses were performed on Kieselgel 60 F_{254} plates (Merck). Eluent: hexane–ethyl acetate, visualization agent: iodine vapors. Ether refers to diethyl ether. Petroleum ether refers to the fractions of bp 40–60 °C. Evaporation of solvent indicates evaporation under reduced pressure using a rotary evaporator. Tetrahydrofuran (THF) was distilled from sodium and benzophenone. Ether and acetonitrile (CH_3CN) were distilled from calcium hydride. Petroleum ether, methanol and ethyl acetate were distilled prior to use. Starting material 1,3-dimethyladamantane **5** and all the reagents were purchased from Aldrich.

1,3-Dibromo-5,7-dimethyladamantane 6

Iron powder (1.5 g) was added to bromine (65 ml) cooled in an ice bath. Neat 1,3-dimethyladamantane **5** (24.5 g, 150 mmol) was added dropwise to the reaction mixture during 1 h. The mixture was stirred for 1.5 h at room temperature then poured onto ice (0.5 kg) and carbon tetrachloride (250 ml) was added. Excess bromine was reduced with sodium metabisulfite. The organic layer was separated and the aqueous phase was extracted twice with chloroform (100 ml). The combined organic layers were washed with brine, saturated $NaHCO_3$ and dried ($CaCl_2$). Solvent evaporation gave a crude product which was treated with methanol (50 ml). Crystals were collected by filtration and washed with methanol to provide **6** (39.9 g; 83%), mp 106–107 °C (Found: C, 44.88; H, 5.55. $C_{12}H_{18}Br_2$ requires C, 44.75; H, 5.63%); *m/z* 241 (100%, $[M - Br]^+$); δ_H(200 MHz, $CDCl_3$) 0.92 (6H, s, 5,7-CH_3), 1.23 (2H, s, 6-H_2), 1.97 (8H, s, 4,8,9,10-H_2), 2.69 (2H, s, 2-H_2); δ_C(50 MHz, $CDCl_3$) 28.86, 38.51, 47.95, 50.67, 53.17, 57.35.

1,5-Dimethyl-7-methylenebicyclo[3.3.1]nonan-3-one 7[17]

1,3-Dibromo-5,7-dimethyladamantane **6** (21.6 g, 67 mmol) was heated in a mixture of dioxane (200 ml) and 1 M NaOH (200 ml) in a steel autoclave at 180 °C for 20 h. Water (200 ml) was added to the reaction mixture and the product was extracted with ether (3 × 150ml). The combined extracts were washed with brine (100ml) and dried ($CaCl_2$). Filtration and solvent evaporation gave an oily residue which was distilled at reduced pressure (113–116 °C/12 mmHg) to provide **7** (9.4 g, 79%) as an oil (Found: C, 81.04; H, 10.06. $C_{12}H_{18}O$ requires C, 80.85; H, 10.18%); *m/z* 178 (10%, $M^{+\bullet}$); δ_H(200 MHz, $CDCl_3$) 1.06 (6H, s, 1,5-CH_3), 1.50 (2H, td, *J* 13.2 and 2.0, 9-H), 1.62 (2H, td, *J* 13.2 and 2.0, 9-H), 1.97 (2H, m, 6,8-H_{ax}), 1.98 (2H, m, 2,4-H_{ax}), 2.10 (2H, dd, *J* 13.4 and 2.0, 6,8-H_{eq}), 2.20 (2H, dd, *J* 16.2 and 2.0, 2,4-H_{eq}), 4.74 (2H, t, *J* 1.4, $=CH_2$); δ_C(50 MHz, $CDCl_3$) 30.26, 34.78, 47.24, 47.78, 53.05, 113.94, 142.79, 210.93.

1,5,7α-Trimethylbicyclo[3.3.1]nonan-3-one 2a

A solution of unsaturated ketone **7** (0.7 g, 3.9 mmol) in acetic acid (7 ml) was hydrogenated (1 atm) over PtO_2 (70 mg) for 7 h. Catalyst was filtered off, water (20 ml) was added and the filtrate extracted with ether (30 ml). The organic phase was washed with saturated aqueous $NaHCO_3$ and dried ($MgSO_4$). After evaporation of ether the residue was purified by column chromatography eluting with 4% ethyl acetate in petroleum ether to give **2a** (0.24 g, 34%) as an oil (Found: C, 79.78; H, 11.15. $C_{12}H_{20}O$ requires C, 79.94; H, 11.18%); *m/z* 180 (8%, $M^{+\bullet}$); δ_H(200 MHz, $CDCl_3$) 0.80 (3H, d, *J* 7.4, 7-CH_3), 1.05 (6H, s, 1,5-CH_3), 0.7–1.9 (8H, m, 2,4-H_{ax}, 6,8,9-H_2), 1.9–2.4 (3H, m, 2,4-H_{eq}, 7-H); δ_C(50 MHz, $CDCl_3$) 24.75, 32.43, 33.82, 43.13, 44.8, 55.96; ν_{max}(thin film)/cm^{-1} 1709 (C=O).

Further elution with 30% ethyl acetate in petroleum ether gave 3,5-dimethyladamantan-1-ol (0.24 g) identical with an authentic sample.

1,5-Dimethyl-7-methylenebicyclo[3.3.1]nonan-3β-ol 8

The mixture of unsaturated ketone **7** (1g, 5.6 mmol) and aluminium triisopropoxide (2.64 g, 12.9 mmol) in toluene (20 ml) was refluxed for 17 h. Aqueous NaOH (10 ml of a 10% solution) was added and the resulting two phase mixture was stirred for 2 h at room temperature. The organic layer was separated, the aqueous layer extracted with ether (2 × 20 ml), and the combined extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent gave crude product which was purified by column chromatography eluting with 10% ethyl acetate and then with 20% ethyl acetate in petroleum ether to give **8** (0.57 g, 57%), mp 94–96 °C (Found: C, 79.81; H, 11.17. $C_{12}H_{20}O$ requires C, 79.94; H, 11.18%); *m/z* 180 (21%, $M^{+\bullet}$); δ_H(200 MHz, $CDCl_3$) 0.95 (6H, s, 1,5-CH_3), 0.8–1.20 (4H, m, 6,8-H_{ax} and 9-H_2), 1.24 (1H, s, OH), 1.7–2.1 (4H, m, 2,4-H_{ax} and 6,8-H_{eq}), 2.16 (2H, d, *J* 14.2, 2,4-H_{eq}), 4.45–4.7 (3H, m, $=CH_2$ and 3-H); δ_C(50 MHz, $CDCl_3$) 31.48, 34.57, 46.56, 47.79, 48.34, 48.63, 108.49, 148.32.

1,5,7β-Trimethylbicyclo[3.3.1]nonan-3-one 2b

Unsaturated alcohol **8** (0.45 g, 2.5 mmol) was stirred for 7 h in 75% H_2SO_4 (13 ml) at room temperature. Water (30 ml) was added and the mixture was extracted with hexane (50 ml and 25 ml). The organic layer was washed with saturated $NaHCO_3$ (25 ml) and water (25ml), and dried ($MgSO_4$). After evaporation of solvent the residue was passed through a short silica gel column eluting with 10% ethyl acetate in petroleum ether. Crystalline product **2b** (0.33g, 73%) was obtained, mp 48–50 °C (Found: C, 80.02; H, 11.11. $C_{12}H_{20}O$ requires C, 79.94; H, 11.18%); *m/z* 180 (11%, $M^{+\bullet}$); δ_H(200 MHz, $CDCl_3$) 0.81 (3H, d, *J* 5.8, 7-CH_3), 0.7–1.0 (2H, m, 9-H_2), 1.00 (6H, s, 1,5-CH_3), 1.2–1.35 (1H, m, 7-H), 1.4–1.6 (4H, m, 6,8-H_2), 2.01 (2H, d, *J* 15.4, 2,4-H_{ax}), 2.22 (2H, dd, *J* 16.3 and 2.0, 2,4-H_{eq}); δ_C(50 MHz, $CDCl_3$) 26.61, 30.96, 34.86, 47.27, 47.79, 47.71, 53.06; ν_{max}(Nujol)/cm^{-1} 1708 (C=O).

General procedure for synthesis of 1,3,5,7-tetramethylbicyclo-[3.3.1]nonan-3α-ols 3a and 3b

$CeCl_3 \cdot 7H_2O$ (4.0 mmol) was quickly powdered in a mortar and heated *in vacuo* (4 mmHg) while raising the temperature gradually to 140 °C, and then kept at this temperature for 2 h. After cooling under an argon atmosphere, THF (17 ml) was added and the suspension obtained was allowed to stir overnight at room temperature. The suspension was cooled to 3 °C and MeMgI (4.2 ml of a 0.95 M solution in ether, 4.0 mmol) was added. After the mixture had been stirred for 1 h at 3 °C, a solution of ketone **2a** or **2b** (2 mmol) in THF (5 ml) was added dropwise. After 15 min, saturated aq. NH_4Cl was added. The aqueous layer was extracted with ether (2 × 20 ml) and the combined extracts were washed with brine and dried over $MgSO_4$. The solution was filtered and the solvent evaporated. The residue was passed through a short silica gel column eluting with ether to give essentially pure **3a** or **3b**.

1,3β,5,7α-Tetramethylbicyclo[3.3.1]nonan-3α-ol 3a. Yield 97%; mp 87–89 °C (Found: C, 79.70; H, 12.26. $C_{13}H_{24}O$ requires C, 79.53; H, 12.32%); *m*/*z* 196 (0.1%, $M^{+\bullet}$), 181 (4, $[M - CH_3]^+$), 178 (5, $[M - H_2O]^+$); δ_H(200 MHz, $CDCl_3$) 0.52 (1H, d, *J* 12.6, 9-H), 0.81 (3H, d, *J* 5.8, 7-CH_3), 0.7–0.9 (1H, m, 9-H), 0.90 (6H, s, 1,5-CH_3), 1.15 (3H, s, 3-CH_3), 1.0–1.7 (10H, m, 2,4,6,8-H_2, 7-H and OH); δ_C(50 MHz, $CDCl_3$) 22.03, 26.01, 30.36, 34.01, 35.21, 40.74, 44.61, 53.17, 72.33.

1,3β,5,7β-Tetramethylbicyclo[3.3.1]nonan-3α-ol 3b. Yield 97%; mp 72–74 °C (Found: C, 79.64; H, 12.30. $C_{13}H_{24}O$ requires C, 79.53; H, 12.32%); *m*/*z* 196 (0.1%, $M^{+\bullet}$), 181 (14, $[M - CH_3]^+$), 178 (4, $[M - H_2O]^+$); δ_H(200 MHz, $CDCl_3$) 0.80 (3H, d, *J* 6.6, 7-CH_3), 0.86 (6H, s, 1,5-CH_3), 0.6–1.1 (4H, m, 9-H_2 and 6,8-H_{ax}), 1.06 (1H, s, OH), 1.24 (3H, s, 3-CH_3), 1.3–1.6 (6H, m, 2,4-H_2 and 6,8-H_{eq}), 2.75 (1H, m, 7-H); δ_C(50 MHz, $CDCl_3$) 23.68, 24.73, 30.36, 32.22, 33.48, 37.04, 47.77, 48.05, 51.30, 69.79.

Ritter reaction of 1,3,5,7-tetramethylbicyclo[3.3.1]nonan-3α-ols 3a and 3b

To the mixture of alcohol **3a** or **3b** (0.59 g, 3 mmol) and TMSCN (0.80 ml, 6 mmol) was added acetic acid (0.5 ml) and the mixture was cooled to 3 °C. Sulfuric acid (0.48 ml; 9 mmol) was added dropwise (25 min). The reaction mixture was allowed to warm to room temperature, stirred for 24 h and poured into ice water (20 ml). The resulting mixture was neutralized with 20% NaOH and extracted with ether (2 × 20 ml). The combined extracts were dried ($MgSO_4$) and the solvent evaporated. The reaction products were separated by column chromatography eluting with petroleum ether to give bicyclonene **9** or **12**, then with 30% ethyl acetate in petroleum ether to obtain amide **10**.

1,3,5,7α-Tetramethylbicyclo[3.3.1]non-2-ene 9. A volatile liquid (34%) (Found: C, 87.74; H, 12.35. $C_{13}H_{22}$ requires C, 87.56; H, 12.44%); *m*/*z* 178 (6%, $M^{+\bullet}$); δ_H(200 MHz, $CDCl_3$) 0.87 (3H, d, *J* 6.8, 7-CH_3), 0.92 and 0.94 (total 6H, both s, 1,5-CH_3), 1.57 (3H, br s, 3-CH_3), 0.8–1.9 (9H, m, ring protons), 5.15 (1H, br s, 2-H); δ_C(50 MHz, $CDCl_3$) 22.30, 23.37, 26.19, 30.42, 30.63, 32.03, 32.84, 43.00, 44.23, 45.09, 45.64, 131.84, 133.39.

***N*-Formyl-1,3β,5,7α-tetramethylbicyclo[3.3.1]nonan-3α-amine 10.** Yield 55%; mp 108–110 °C (Found: C, 75.31; H, 11.24; N, 6.23. $C_{14}H_{25}NO$ requires C, 75.28; H, 11.28; N, 6.27%); *m*/*z* 223 (2%, $M^{+\bullet}$); δ_H(200 MHz, $CDCl_3$) 0.93 and 0.94 (total 6H, both s, 1,5-CH_3), 0.57–2.2 (17H, m, ring protons and 3,7-CH_3), 5.2 and 5.6 (total 1H, both br s, NH), 8.03 and 8.33 (total 1H, both d, *J* 2.6 and 12.8, CHO); δ_C(50 MHz, $CDCl_3$) 21.83, 25.10, 25.68, 30.47, 31.54, 33.69, 36.00, 40.42, 40.53, 44.69, 49.99, 52.29, 54.82, 160.66, 160.84.

1,3,5,7β-Tetramethylbicyclo[3.3.1]non-2-ene 12. A volatile liquid (66%) (Found: C, 87.69; H, 12.38. $C_{13}H_{22}$ requires C, 87.56; H, 12.44%); *m*/*z* 178 (7%, $M^{+\bullet}$); δ_H(200 MHz, $CDCl_3$) 0.80 (3H, d, *J* 7.1, 7-CH_3), 0.91 and 0.94 (total 6H, both s, 1,5-CH_3), 0.55–1.6 (7H, m, 6,8,9-H_2 and 7-H), 1.63 (3H, br s, 3-CH_3), 1.63 and 1.80 (total 2H, both d, *J* 18, 4-H_2), 5.03 (1H, br s, 2-H); δ_C(50 MHz, $CDCl_3$) 22.21, 22.82, 26.82, 29.51, 31.67, 32.06, 32.16, 34.17, 44.25, 46.48, 47.24, 130.21, 134.58.

1,3β,5,7α-Tetramethylbicyclo[3.3.1]nonan-3α-amine hydrochloride 11

Formamide **10** (0.39 g, 1.75 mmol) was refluxed in 20% aqueous H_2SO_4 (4.2 ml) for 6 h. The reaction mixture was poured onto ice and neutralized with 20% NaOH. The product was extracted with ether (2 × 25 ml), and the combined extracts were dried over NaOH and filtered. To the filtrate was added HCl (1.5 ml of a 2 M solution in ether) and the solvent as well as the excess of HCl were removed *in vacuo*. The residue was treated with CH_3CN and filtered to provide **12** as white crystals (0.29 g, 71%), mp 284–285 °C (Found: C, 67.16; H, 11.39; N, 5.93. $C_{13}H_{25}N{\cdot}HCl$ requires C, 67.36; H, 11.31; N, 6.04%); *m*/*z* 195 (11%, $M^{+\bullet}$); δ_H(200 MHz, $CDCl_3$) 0.67 (1H, d, *J* 13, 9-H), 0.96 (6H, s, 1,5-CH_3), 1.03 (3H, d, *J* 6.5, 7-CH_3), 1.54 (3H, s, 3-CH_3), 0.8–1.9 (8H, m, 2,4-H_{ax}, 6,8-H_2, 7,9-H), 2.07 (2H, d, *J* 14.3, 2,4-H_{eq}), 8.2 (3H, br s, NH_3^+); δ_C(50 MHz, $CDCl_3$) 21.20, 26.18, 30.18, 32.15, 33.04, 42.43, 43.11, 49.48, 55.11.

Crystal structure determination for compound 10

$C_{14}H_{25}NO$, $M = 223.35$, triclinic, $a = 8.883(2)$, $b = 12.104(2)$, $c = 13.479(3)$ Å, $\alpha = 88.19(3)$, $\beta = 84.38(3)$, $\gamma = 85.53(3)°$, $V = 1437.5(5)$ Å^3, $D_x = 1.032$ g cm^{-3}, space group $P\bar{1}$, $Z = 4$, μ(Mo-Kα) = 0.064 mm^{-1}. Data were collected on a Syntex-P2$_1$ diffractometer using graphite monochromated Mo-Kα radiation at room temperature. Reflections collected/unique 2122/1980, R(int) = 0.034. The structure was solved by direct methods (SHELXS86)[18] and refined by the full-matrix least-squares method (SHELXL93).[19] Final R and R_w values were 0.0847 and 0.1848 [1980 $I > 2\sigma(I)$ reflections]. Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). CCDC referenece number 207/363. See http://www.rsc.rsc.org/suppdata/p1/1999/3527/ for crystallographic data in .cif format.

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