Synthesis, structure and reactions of the most twisted amide

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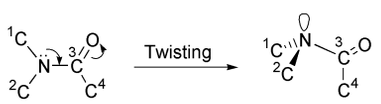
Received (in Cambridge, UK) 13th October 2000, Accepted 19th February 2001
First published as an Advance Article on the web 12th March 2001

Details are reported of the synthesis, properties and reactions of 3,5,7-trimethyl-1-azatricyclo[3.3.1.1^{3,7}]decan-2-one, **7** (the "most twisted amide"). Its spectroscopic properties show clearly that **7** is a ketone rather than an amide, albeit a ketone with a tertiary amino group directly attached to the carbonyl carbon. The amino group is basic (pK_a ~ 5.2) and nucleophilic, while the C=O group reacts normally as a ketone, giving the corresponding twisted enamine with the methylene Wittig reagent and acetals under standard conditions. As expected, **7** is rapidly hydrolysed to the bicyclic amino acid **15**, but, remarkably, hydrolysis is readily reversible under mild acidic conditions, and in methanol the amino acid is converted to the twisted amide in 80% yield. This cyclisation of the amino acid is an extraordinarily efficient intramolecular reaction: the effective molarity of the amine nucleophile is estimated at 10^{12} M: the carboxylate anion thus acting as an efficient acylating agent for both secondary and tertiary amine groups. The hydrate of the conjugate acid, typically a high-energy intermediate in amide hydrolysis, is stable in dilute aqueous acid and as the crystalline hydrochloride.

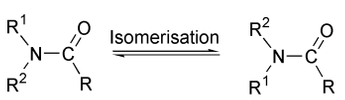
Introduction

The amide group prefers to be planar.[1] Exactly how planar is a subject of some theoretical interest[2] but the collected evidence from many thousands of crystal structures is clear-cut. Average atomic positions lie overwhelmingly in-plane (Fig. 1, data for tertiary amides), though small distortions are not uncommon, consistent with a locally shallow energy minimum favouring the planar conformation **1** (the twist angle $\tau = (\omega_{C4-C3-N-C2} + \omega_{O-C3-N-C1})/2$).



1 (τ = 0, ±180°) **2** (τ = ±90°)

Twisting is not a simple, single process because it is accompanied by pyramidalisation at nitrogen as n–$\pi^*_{C=O}$-delocalisation is progressively turned off, until it disappears completely at a twist angle of 90° (**2**), when the lone pair lies in the nodal plane of the π-system of the carbonyl group. The nitrogen centre in **2** is expected to be tetrahedral and relatively basic. However, the 90° conformation is not observed for normal amides or lactams, and **2** represents a high-energy conformation, marking the transition state for *E*–*Z* isomerisation (**3**–**4**): free energies of activation for this (180° twisting) reaction are of the order of 80–90 kJ mol^{-1}.[3]



3 **4**

Very few examples of highly twisted amides are described in the literature. Most, like compounds **5**[4] and **6**[5] are based on the quinuclidine skeleton, which retains a certain amount of flexibility. No structural information is available for these quinuclidinone derivatives, though calculations suggest[6] that the twist angle in such compounds could approach 90°.

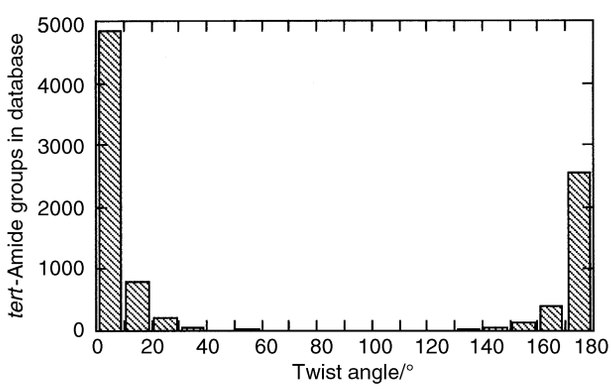
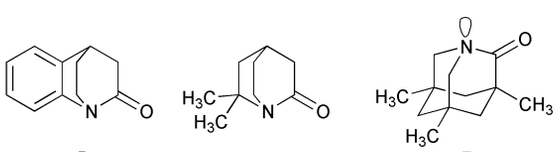


Fig. 1 Twist-angle distribution of tertiary amides in the Cambridge Crystallographic Database (CCDB) on 20th September 2000. Data for 9098 groups from 5641 accurate (r < 5%) structures.



5 **6** **7**

In the course of our work on the reverse anomeric effect[7] we prepared the twisted amide **7**, which, though constrained into the 90° conformation, turns out to be remarkably stable. We report details of the preparation of **7** and its structure and spectroscopic properties, and describe its chemical reactivity as an unusual amine, an extraordinary ketone, and as an amide manqué. (Preliminary communications are found in refs. 8 and 9.)

Results and discussion

Synthesis

Compound **7** was prepared by the series of eleven functional group transformations summarised in Scheme 1 from the

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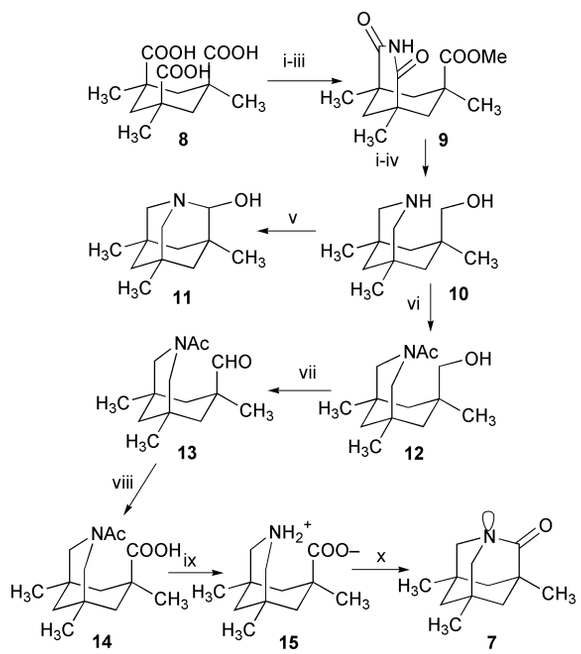
 DOI: 10.1039/b008270h

Table 1 Structural parameters and spectroscopic properties of **7** and 1-methyl-2-piperidone

Compound	Selected structural parameters					Selected spectroscopic parameters			
	Twist angle τ/°	Sum of bond angles at N/°	Sum of bond angles at C=O/°	Bond length C–N/Å	Bond length C=O/Å	δ ^{13}C C=O (ppm)	IR $\nu_{C=O}$/ cm^{-1}	100% peak in EI-MS	First IP/ eV
7	90.5	325.7	359.9	1.475	1.196	200.0	1732	$(M - CO)^+$	8.30 n(N)
	2.5	358.9	359.9	1.325	1.233	165	1653	$CH_2{=}NMe^+$	9.36 n(O)



Scheme 1 *Reagents and conditions*: i, sublimation [10] (190 °C, 0.01 mmHg); ii, 25% aq. NH_3, dimethylaminopyridine (cat.), reflux 24 h;[10] iii, $SOCl_2$, reflux 4 h, then evaporation and MeOH, 24 h;[10] iv, $LiAlH_4$ in Et_2O, reflux 24 h (81.6% from **8**); v, Jones reagent, 3 h (67.4%); vi, Ac_2O–MeOH, 8 h or pentafluorophenyl acetate, DMF, 20 h (82%); vii, CrO_3·2Py, CH_2Cl_2, 30 min (74.3%); viii, $KMnO_4$, H_2O–acetone, 30 min (86.3%); ix, 1.5 M HCl, reflux 24 h, then pH adjusted to 7.45 by 1 M NaOH (84.6% from **13**); x, sublimation (80 °C, 0.01 mmHg); 100%.

commercially available Kemp triacid **8**, which provides the complete carbon skeleton. The known imide ester **9** [10] could be reduced to the amino alcohol **10** under vigorous conditions: but at this stage the close proximity of the functional groups proved a disadvantage: direct oxidation of the amino alcohol **10** gave tricyclic compound **11**, resulting from the addition of the amine nitrogen to the aldehyde group initially formed (Scheme 1). The amine nitrogen had to be protected to permit further, careful oxidation of the CH_2OH fragment. Then proximity favoured the final step, and **15** was cyclised simply on evaporation of the aqueous solution and subsequent sublimation.

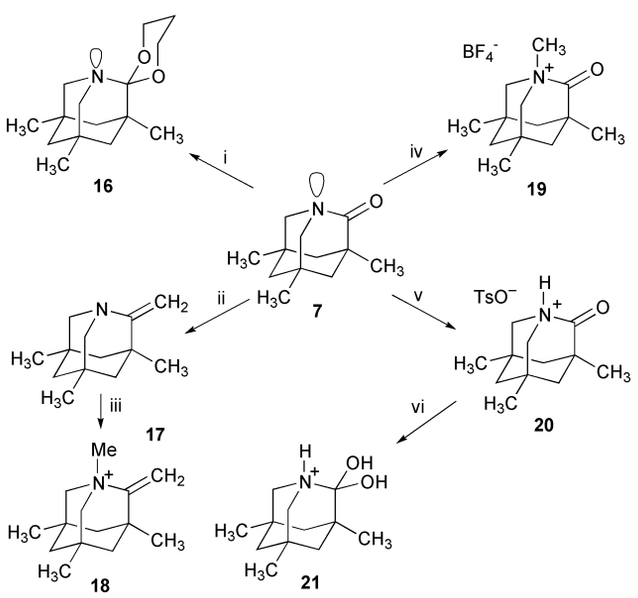
Structure and spectroscopic properties

Recrystallisation of **7** from toluene gave crystals suitable for X-ray analysis.[8] The twist angle τ is 90.5° (the deviation from 90° is assumed to result from packing forces). The carbonyl group is accurately planar, and the amine nitrogen, as expected, tetrahedral. The most relevant structural parameters are compared in Table 1 with those of 1-methyl-2-piperidone, as a representative δ-lactam with a planar amide group. (The lactam is not crystalline so its structural data are calculated.[11]) Particularly noteworthy are the N–C(=O) and C=O bond lengths of 1.475 and 1.196 Å, values characteristic of (amine) C–N single and (aldehyde) C=O double bonds, respectively.

The spectroscopic properties for **7** also differ markedly from those for the unconstrained δ-lactam, showing clearly that **7** is a ketone rather than an amide—albeit a ketone with a tertiary amino group directly attached to the carbonyl carbon. Thus the ^{13}C-NMR shift at 200 ppm falls in the region expected for an aldehyde, and easy fragmentation of the molecular ion on electron impact, with the loss of CO, gives a base peak at (M − 28). The first ionisation potential in the photoelectron spectrum corresponds to the removal of an electron from the nitrogen lone pair MO (n(N)): the much higher first ionisation of *N*-methylpiperidone involves an n(O) lone pair electron.[11]

Chemical behaviour

As expected, the twisted amide group in **7** reacts as both a ketone and an amine, rather than an amide. Some definitive reactions are summarised in Scheme 2. Thus, **7** reacts normally



Scheme 2 *Reagents and conditions*: i, $HO(CH_2)_3OH$, benzene, TsOH (cat.), reflux, 48 h (55.9%); ii, $Ph_3P{=}CH_2$, Et_2O, reflux 8 h (64.3%); iii, CH_3I in benzene (94%); iv, $(CH_3)_3O^+BF_4^-$, CH_2Cl_2 (quantitative); v, TsOH in dry CD_3CN; vi, evaporate solution in 0.1 M HCl (89% from **7**).

as a ketone with propane-1,3-diol, under standard conditions for acetal formation, to form the hemiaminal **16**.[8] Compound **7** also undergoes the Wittig reaction, reacting with the simple phosphorus ylide $Ph_3P{=}CH_2$ to give "the most twisted enamine" **17**.[8] The highly volatile **17** could be alkylated on nitrogen, and the stable *N*-methyl derivative **18** was produced and characterised by a crystal structure determination (see Fig. 2 below). Compound **7** could also be alkylated on nitrogen to give the *N*-methyl compound **19**. Meerwein's reagent was necessary in this case because the product **19** is extremely sensitive to traces of moisture, which were taken care of by the reagent (acting as an expensive but efficient drying agent).

The twisted amide **7** was protonated, also on nitrogen, by HCl in dry ether, to give the conjugate acid **7H**$^+$ (as the chloride **20**). Amides of course are normally protonated on oxygen.[12–14] Compound **20** was not isolated, but readily scavenged water to give the stable, protonated hydrate **21**.[9]

Amine basicity

The basicity of the "amide" nitrogen of **7** is of interest *per se*, and relevant also to the mechanism of action of the proline *cis–trans* isomerases, which play a key role in controlling protein conformation. These enzymes are thought to act by a simple twisting mechanism,[15] and it has been suggested that the reaction could be catalysed by a general acid group, possibly protonating, or hydrogen bonding to the developing lone pair on nitrogen.[16,17] The only literature value for the pK_a of a twisted amide is 5.33 for compound **6**.[18] We were initially sceptical about this figure, because of our difficulties in methylating **7**, and because we found it impossible to measure the pK_a of **7** by the method described for **6**. Compound **7** is hydrolysed effectively instantaneously in water: even in solution in neutral D_2O no signals for the twisted amide **7** were detectable in ^{1}H-NMR spectra taken within ~50 s, and its disappearance is certainly acid-catalysed. Pracejus' compound **6** was also hydrolysed in water, but much more slowly: he obtained the figure of 5.33 by the method of half-neutralisation, extrapolating the measured pH of a 50% neutralised solution of **6** back to zero time.[18]

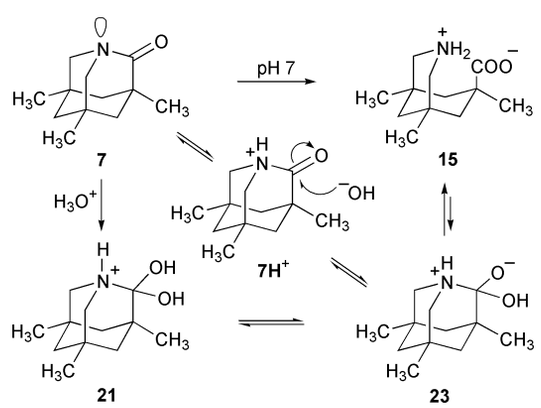
We were eventually able to estimate a pK_a value for **7** using a stopped-flow indicator method.[19] Separate solutions, of **7** in acetonitrile and aqueous HCl, were mixed on injection into a stopped-flow spectrophotometer to produce a 1 : 1 mixture of free base **7** and its conjugate acid **7H**$^+$, at 20 °C in 50% v/v water–CH_3CN. The hydrolysis of **7** was followed by monitoring the change in pH using the indicator Bromophenol Blue (dissolved initially in the HCl solution). The exponential fit of the pH–time curve thus obtained gave the pseudo-first order rate constant k_{obs} = 2.3 s^{-1} (half life 0.3 s) for the disappearance of **7**, and extrapolation of the pH to zero time gave an apparent pK_a value of 4.8 (water–acetonitrile 1 : 1, 20 °C). This value, corrected for the mixed solvent, is consistent with a value in pure water of about 5.2, closely similar to the pK_a obtained for **6**. This result confirms the relatively high basicity of simple twisted amides. Their decreased basicity compared with aliphatic tertiary amines (they are similar in pK_a to pyridine) is no doubt a consequence of the electron-withdrawing effect of the adjacent carbonyl group. Interestingly this effect appears to be substantially greater for **7** (and **6**) than for twisted anilides such as **5**. The measured (kinetic) pK_a for the conjugate acid of **5** is 3.7, less than 1.4 units lower than that of *N*,*N*-dimethylaniline, whereas **6** and **7** are less basic by some 5 pK units than typical tertiary amines.

These are both apparent pK_as for the conjugate acid **7H**$^+$, and we cannot rigorously rule out the possibility that we are measuring a pK_a (of the NH$^+$ or of an OH group) of the hydrate **21**, which we know is rapidly formed from **7** in water. However, the close similarity of the values for **6** and **7**, despite the much slower hydrolysis of **6** (see below), gives us some confidence in our assignment.

Hydrolysis

Normal (planar) amides are remarkably stable to hydrolysis, with half-lives of hundreds of years in the absence of acid or base,[20,21] and it has often been suggested that binding an amide (peptide) substrate in a non-planar conformation in an enzyme active site would increase its basic reactivity.[5,22] Current thinking is cool on this idea,[23] but there is no doubt that compounds like **6** and **7** with a 90° twist are exceedingly reactive towards hydrolysis. Thus, the neutral hydrolysis of **7** is at least 10^{10} times faster than that of a typical amide. Pracejus' compound **6** had a half-life of several minutes under the conditions of his pK_a measurements near pH 5, and so is hundreds of times less reactive than **7** (measured half-life 0.3 s under similar conditions). Addition to the C=O group of **6** is expected to be hindered sterically by the adjacent *gem*-dimethyl group.

At pH 7 the product of hydrolysis is the expected zwitterionic amino acid **15** (Scheme 3). The mechanism of the spontaneous (neutral) hydrolysis has been discussed for the corresponding



Scheme 3

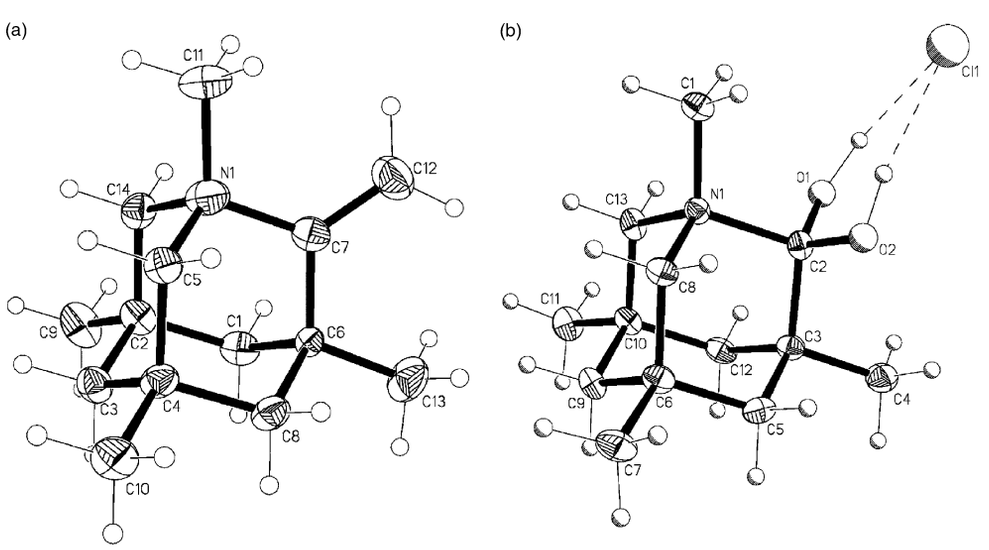


Fig. 2 Molecular structures of (a) **18** (cation only: the iodide anion and the water of crystallisation are omitted) and (b) **22** (ORTEP: ellipsoids are drawn at the 30% probability level. Hydrogen atoms are represented as spheres of radius 0.12 Å. For details see Experimental.)

reaction of **5** by Somayaji and Brown, who favoured the rate determining attack of water on the neutral aminoketone, largely because of the extensive ^{18}O-exchange reaction they observed with labelled water.[5] For the reaction of (the more basic) **7**, at least, we prefer the kinetically equivalent addition of hydroxide to the conjugate acid **7H$^+$**: in part, because we know from the pK_a that this species is present in kinetically significant amounts at pH 7, but in particular because of our evidence that **21**, the hydrate of **7H$^+$**, is a stable species, which could account for any isotopic exchange. In dilute acid (pH < 4) **7** is converted quantitatively to **21** (Scheme 3).

Such structures are high-energy intermediates in normal amide hydrolysis, but the tricyclic structure is stabilised in **21** by the same factors stabilising the twisted amide, as well as being stabilised chemically relative to the highly electrophilic **7H$^+$**. Remarkably we were able to isolate, crystallise and obtain X-ray structures of both **21** (as the chloride),[9] and its *N*-methyl analogue **22** (easily formed from the corresponding *N*-methylated amino acid: see below). The (O)C–N$^+$ bonds in these structures are among the longest known (1.552 Å in **22**), and the C–O bonds unusually short (1.382 Å in **22**), as expected for a strong normal anomeric effect.[7] The conformation about the C–O bonds is also consistent with the anomeric effect,[24] with the O–H and C–N bonds *gauche* to each other; although the main driving force in this case is likely to be crystal packing, and in particular the formation of hydrogen bonds to the (chloride) anion (Fig. 2).

Hydrolysis is reversible

Not the least remarkable property of the system summarised in Scheme 3 is that the hydrolysis of **7**, with its high-energy twisted-amide conformation, to the zwitterionic amino acid **15**, is readily reversible. When a solution of **15** at 25 °C is acidified to pH ~ 4 the ^{1}H- and ^{13}C-NMR spectra are those expected for an equilibrium mixture of **15** and **21**. On warming the solution corresponding peaks in the proton spectrum broaden then coalesce, and dynamic NMR studies allow an estimate of the rate of the cyclization of the amino acid. This proves to be extraordinarily high, at 280 s^{-1} at 60 °C, corresponding to an effective molarity (EM) for the amino group of **15** of the order of 10^{12} M.[9] The key intermediate in all these reactions is most likely the tetrahedral zwitterion **23** (Scheme 3): the zwitterion would be formed directly by the cyclisation of the neutral amino acid, is necessary for C–N cleavage in the hydrolysis direction, and could lose hydroxide to enable ^{18}O exchange.

The evidently low equilibrium concentration of the twisted amide **7** is not detectable by NMR in water, but the compound is readily observed when the same experiment is conducted in methanol-d_4. A series of ^{1}H-NMR spectra of a solution of the amino acid **15** dissolved in CD_3OD show **15** disappearing, with a half-life of about 30 minutes, to give the twisted amide **7** (~80%) plus some 20% of a new compound, probably the tricyclic methanol adduct **24** (Fig. 3).

Even the (even more reactive) *N*$^+$-methyl twisted amide **19** is formed under these conditions from its hydrolysis product, the *N*-methylated amino acid **25** (Scheme 4). When **25** (or its methyl ester **26**) is dissolved in CD_3OD it is slowly converted to the deuteriated ester **26**-d_3, with a half life of 10–15 hours at 20 °C. In these cyclisation reactions the amino group is acylated, in water, by carboxy/carboxylate to form the twisted amide, which must be the immediate acylating agent.

Mechanism and reactivity

The spontaneous formation of the twisted amide **7** from the amino acid is unique. The formation of lactams from amino acids under forcing conditions is a known reaction in synthetic heterocyclic chemistry,[25] but the evidence indicates that the mechanisms involved are different. Thus, the much slower cyclisation of an amino acid anion to form a stable planar

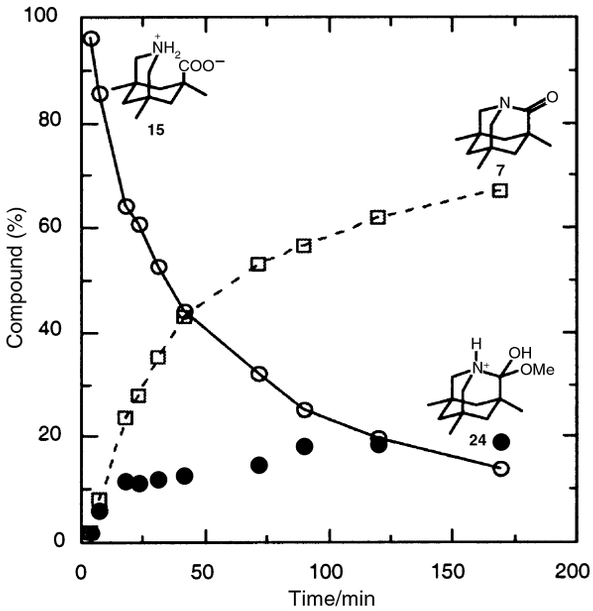
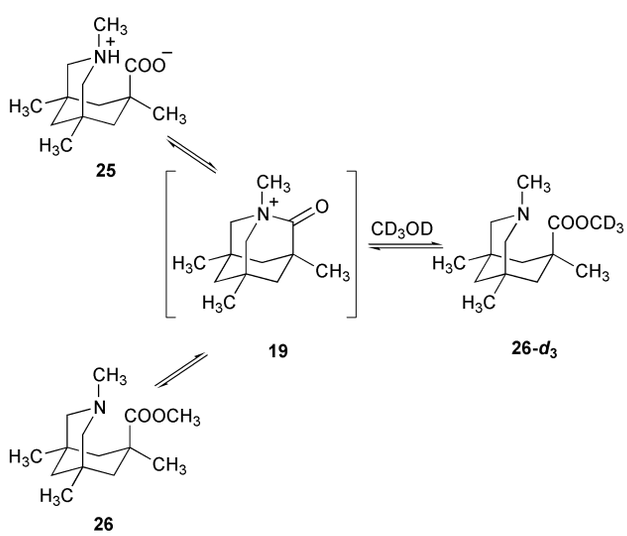


Fig. 3 Spontaneous formation of twisted amide **7** from a solution of the amino acid **15** in solution in CD_3OD (^{1}H-NMR measurements at 20 °C, ~10^{-2} M solutions).



Scheme 4

γ-lactam is observed at high pH,[26] and is thought to involve the rate determining attack of amine nitrogen on carboxylate. The cyclisation of **15** is observed near neutrality (pH 4–7) and may be presumed to involve the relatively rapid attack of the neutral amine on the COOH group. Here the breakdown to twisted amide of the tetrahedral intermediate **21** (which is observed to accumulate) is, not surprisingly, rate determining, and the thermodynamic driving force for cyclisation particularly favours the tetrahedral species. We speculate that this effect stems from the thermodynamic stability of the extended diamond-lattice framework, which can be considered as a "thermodynamic trap" for these usually very reactive intermediates.

Experimental

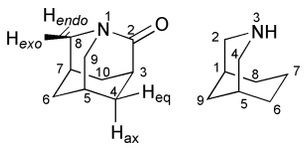
General procedures

One-dimensional NMR spectra and experiments (APT, NOE, dynamic NMR) were performed using a Bruker WM-400 (400 MHz for protons) instrument. Two-dimensional experiments

were done on a Bruker WM-500 (500 MHz for protons). Residual solvent peaks were used as reference. Infrared spectra were recorded on a Perkin-Elmer 1310 spectrometer. The samples were prepared as solutions in indicated solvents. Mass spectra were recorded in the University Chemical Laboratory, Cambridge. Microanalyses were carried out by the staff of the University Chemical Laboratory Microanalytical Department. Melting points were determined using a Büchi 510 melting point apparatus and are uncorrected. Analytical thin layer chromatography (TLC) was carried out on pre-coated 0.25 mm thick Merck 60 silica gel plates. Visualization was made by iodine vapours. Reagents were purified and dried where necessary by standard techniques.[27]

Synthetic procedures

Assignments of ^{1}H- and ^{13}C-NMR resonances were made using APT, H,H-COSY, HMBC, HMQC; enantiotopic hydrogens are distinguished as indicated in Scheme 5. The (different)



Scheme 5

systematic numbering of the 1-azatricyclo[3.3.1.1^{3,7}]decane and 3-azabicyclo[3.3.1]nonane systems is also shown.

(1,5,7-Trimethyl-3-azabicyclo[3.3.1]nonan-7-yl)methanol (10). Imine ester **9** (1.8 g, 7.1 mmol) was carefully added in small portions to a stirred suspension of $LiAlH_4$ (0.9 g, 23.7 mmol) in diethyl ether (80 mL). The reaction mixture was refluxed for 24 h, then cooled in an ice bath, and water (~10 mL) was added to quench the excess of the reducing agent (carefully, vigorous evolution of hydrogen). The organic layer was decanted and product extracted with ether (4 × 30 mL) from the aqueous layer. The amino alcohol **10** was then re-extracted from the combined ether solutions with 10% aqueous hydrochloric acid, the HCl solution washed twice with diethyl ether (20 mL), and the aqueous layer adjusted with 10% NaOH to pH ~ 9. Finally the amino alcohol was extracted from the alkaline solution with CH_2Cl_2, dried (Na_2SO_4) and evaporated to give **10** (1.2 g, 81.6% based on Kemp triacid) as a colourless oil, which crystallised on standing; mp 165–169 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.8 (broad s, 2H, NH + OH), 3.28 (s, 2H, OCH_2), 2.71 (d, J 10.2 Hz, 2H, N-CH_2), 2.30 (d, J 10.2 Hz, 2H, N-CH_2), 1.78 (d, J 14.9 Hz, 2H, 6,8-H(eq)), 1.23 (d, J 14.9 Hz, 2H, 6,8-H(ax)), 1.09 (d, J 11.8 Hz, 1H, 9-H(eq)), 0.91 (d, J 11.8 Hz, 1H, 9-H(ax)), 0.83 (s, 9H, 1,5,7-CH_3); ^{13}C-NMR (100.59 MHz, $CDCl_3$) δ: 76.92 (O-CH_2), 58.34 (N-CH_2), 46.91 (C), 45.17 (C), 36.54 (CH_3), 33.79 (CH_2), 31.31 (CH_2), 30.34 (CH_3); IR ν/cm^{-1}: 3550 (OH), 3080 (NH), 2908, 2230, 1651.8; MS (EI) m/z (%): 197 (22, M$^+$), 182 (40), 179 (45), 166 (68), 58 (100). HRMS: calc. for $C_{12}H_{23}NO$ 197.17795; found 197.1780.

3,5,7-Trimethyl-1-azatricyclo[3.3.1.1^{3,7}]decan-2-ol (11). The amino alcohol **10** (80 mg, 0.41 mmol) was dissolved in acetone (3 mL) and Jones reagent (prepared from 95 mg CrO_3, 0.09 mL H_2SO_4 and 0.18 mL H_2O) added. The mixture was stirred for 3 h at room temperature. Water (8 mL) was added, then i-PrOH (2 mL) to destroy excess oxidant. After stirring for 0.5 h, the saturated solution of Na_2CO_3 was added (carefully!) to bring the pH to ~9. The resulting mixture was evaporated and the product sublimed from the remaining solid (80 °C, 0.05 mm), then resublimed to obtain **11** (53.4 mg, 67.4% yield) as white crystals with a camphor-like smell; mp 139–140 °C. The compound can also be purified by column chromatography (SiO_2, CH_2Cl_2–MeOH, 9 : 1, R_f = 0.10). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.67 (broad s, 1H, OH), 3.95 (s, 1H, 2-H), 3.09 (dd, J 12.71 and 2.05 Hz, 1H), 2.65 (s, 2H), 2.23 (dd, J 12.71 and 2.77 Hz, 1H) (8,9-CH_2), 1.69 (dt, J 12.42 and 2.06 Hz, 1H, 6-H(eq)), 1.24 (dd, J 12.42 and 2.77 Hz, 2H), 1.18 (d, J 12.42 Hz, 1H), 0.87 (dd, J 12.42 and 2.77 Hz, 1H) (4,10-CH_2), 1.15 (dt, J 12.42 and 2.06 Hz, 1H, 6-H(ax)), 0.76 (s, 3H, 3-CH_3), 0.72 (s, 6H, 5,7-CH_3); ^{13}C-NMR (100.59 MHz, $CDCl_3$) δ: 88.15 (2-CH), 61.47 (N-CH_2), 54.07 (N-CH_2), 50.09 (C), 49.90 (C), 42.91 (C), 33.05 (CH_2), 29.63 (CH_2), 29.00 (CH_2), 26.94 (CH_3), 26.41 (CH_3), 25.31 (CH_3); IR ν/cm^{-1}: 3583 (OH), 1120 (C–O); MS (EI) m/z (%): 195 (100, M$^+$), 180 (27), 138 (48). Anal. calc. for $C_{12}H_{21}NO$: C, 73.80, H, 10.84, N, 7.17; found: C, 73.76, H, 10.98, N, 7.19%; HRMS: calc. 195.1623, found 195.1630.

1-[7-(Hydroxymethyl)-1,5,7-trimethyl-3-azabicyclo[3.3.1]-nonan-3-yl]ethan-1-one (12). *Method A.* Amino alcohol **10** (1.323 g, 6.7 mmol) was dissolved in methanol (50 mL), and acetic anhydride (2.9 mL, 30.7 mmol) added in one portion. The mixture was left to stand overnight at ambient temperature. Volatile products were removed *in vacuo* (temperature of the heating bath maintained at 40 °C), and the resulting oil chromatographed (SiO_2, CH_2Cl_2–MeOH, 9 : 1, R_f = 0.5) to give **12** as a white crystalline solid (1.33 g, 82.8% yield).

Method B. The amino alcohol **10** (1.2 g, 6.08 mmol) was dissolved in DMF and pentafluorophenyl acetate (gently melted, 4.12 g, 18.2 mmol) added dropwise to a stirred solution under an argon atmosphere. The mixture was left to stand for 20 h. The solvent was removed *in vacuo* (40–50 °C) and the remaining oil dissolved in CH_2Cl_2 (60 mL), washed with cold (ice bath) aqueous NaOH solution (5%, 20 mL), followed by ice-cold water (2 × 20 mL), dried (Na_2SO_4), and evaporated. The amorphous solid was dissolved in diethyl ether (~3 mL), and hexane added (~10 mL). Crystallisation was initiated by scratching with a glass rod, with the flask immersed in an ice bath. After 30 min the white crystals of **12** formed were filtered, washed with hexane and dried in air (0.82 g). The filtrate and washings were evaporated and the residue subjected to a column (SiO_2, CH_2Cl_2–MeOH, 9:1, R_f = 0.5) to give an additional portion of the product. The combined yield was 1.12 g (77%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.12 (d, J 13 Hz, 1H), 2.14 (d, J 13 Hz, 1H) (N-CH_2), 3.32 (d, J 12.44 Hz, 1H), 2.64 (d, J 12.44 Hz, 1H) (N-CH_2), 3.16 (dd, J 10.5 and 5.2 Hz, 1H), 3.11 (dd, J 10.5 and 5.2 Hz, 1H) (O-CH_2), 2.08 (s, 3H, $COCH_3$), 1.58 (dd, J 14.7 and 2.1 Hz, 1H), 1.42 (d, J 14.7 and 2.1 Hz, 1H) (6,8(eq)-CH), 1.53 (dt, J 12.9 and 2.1 Hz, 1H, 9-H(eq)), 1.01 (d, J 12.9 Hz, 1H, 9-H(ax)), 2.38 (t, J 5.2 Hz, 1H, OH), 1.03 (d, J 14.07 Hz, 1H), 1.08 (d, J 14.07 Hz, 1H) (6,8-H(a)), 0.94 (s, 9H, 1,5,7-CH_3); ^{13}C-NMR (100.59 MHz, $CDCl_3$) δ: 170.6 (C=O), 71.89 (O-CH_2), 58.77 (N-CH_2), 53.78 (N-CH_2), 44.82 (CH_2), 42.96 (CH_2), 42.77 (CH_2), 34.69 (C), 31.77 (C), 31.16 (CH_3), 31.04 (C), 29.85 (CH_3, two signals overlapped), 22.10 (CH_3); IR ν/cm^{-1}: 3408 (OH), 2956, 1633 (C=O), 1438; MS (EI) m/z (%): 239 (42, M$^+$), 221 (80, M − H_2O), 208 (100), 196 (73), 135 (80), 107 (88), 44 (84); HRMS: calc. for $C_{14}H_{25}NO_2$ 239.1885164; found 239.1886.

3-Acetyl-1,5,7-trimethyl-3-azabicyclo[3.3.1]nonane-7-carbaldehyde (13). A solution of the amide alcohol **12** (190 mg, 0.79 mmol) in dry CH_2Cl_2 (5 mL) was added to a magnetically stirred solution of the freshly prepared CrO_3·2Py complex [prepared from 474 mg (4.74 mmol) of CrO_3 and 0.77 mL (9.48 mmol) of pyridine in 20 mL of dichloromethane]. The mixture was stirred for 30 min at ambient temperature (a black deposit formed). The mixture was then diluted with diethyl ether (50 mL). The solution was decanted from the deposit, which was washed with ether (3 × 20 mL) by decantation. The combined decanted solutions were transferred to a separating funnel and washed successively with 2% NaOH (20 mL), 2% HCl

(20 mL), saturated $NaHCO_3$ (20 mL) and brine (10 mL), then dried over Na_2SO_4. Evaporation and column chromatography (SiO_2, CH_2Cl_2–CH_3OH, 9 : 1, $R_f = 0.54$) yielded 140 mg (74.3%) of aldehyde **13**, as colourless crystals; mp 91–92 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 9.15 (s, 1H, CHO), 4.11 (d, *J* 13.4 Hz, 1H), 2.02 (d, *J* 13.4 Hz, 1H) (N-CH_2), 3.23 (d, *J* 12.1 Hz, 1H), 2.56 (d, *J* 12.1 Hz, 1H) (N-CH_2), 2.23 (m, 2H, 6,8-H), 1.90 (s, 3H, CH_3CO), 1.20 (d, *J* 14.8 Hz, 1H, 9-H), 1.02 (d, *J* 14.8 Hz, 1H, 9-H), 1.15 (m, 2H, 6,8-H), 0.92 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 0.84 (s, 3H, CH_3); ^{13}C-NMR (100.59 MHz, $CDCl_3$) δ: 203.40 (CHO), 173.19 (NC=O), 55.07 (N-CH_2), 51.80 (N-CH_2), 47.20, 46.05, 45.23, 42.89, 31.27, 31.03, 28.92, 28.67, 22.95; IR ν/cm^{-1}: 2958, 2246, 1708, 1635, 1459; MS (EI) *m*/*z* (%): 237 (6, M^+), 209 (100, $M^+ - CO$), 194 (30), 166 (18), 123 (28), 110 (20), 70 (15), 50 (22); HRMS: calc. for $C_{14}H_{23}NO_2$ 237.1728672; found 237.1725.

3-Acetyl-1,5,7-trimethyl-3-azabicyclo[3.3.1]nonane-7-carboxylic acid (14). The aldehyde **13** (260 mg, 1.1 mmol) was dissolved in aqueous acetone (1 : 2, 30 mL), and finely ground $KMnO_4$ (260 mg, 1.65 mmol) added in one portion to the stirred solution. The mixture was stirred for 30 min at ambient temperature, by which time no starting aldehyde could be detected by TLC (SiO_2, CH_2Cl_2–CH_3OH, 9 : 1). The excess oxidant was destroyed with Na_2SO_3 (~0.5 mL of saturated aqueous solution). The mixture was filtered through a Celite pad, which was then washed with methanol and the combined filtrate and washings evaporated. The syrup-like residue was dissolved in water (20 mL) acidified to pH ~ 1 with conc. HCl. The white precipitate formed was filtered and washed with cold water, then dried in a vacuum desiccator (239.6 mg, 86.3%). The product **14** was used for the next transformation without further purification, though it could be purified further by column chromatography (SiO_2, CH_2Cl_2–CH_3OH, 9 : 1), $R_f = 0.5$. White powder, mp 232–235 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.30 (d, *J* 13.1 Hz, 1H), 2.49 (d, *J* 13.1 Hz, 1H) (N-CH_2), 3.51 (d, *J* 12.0 Hz, 1H), 2.64 (d, *J* 12.0 Hz, 1H) (N-CH_2), 2.53 (d, *J* 14.5 Hz, 1H), 2.23 (d, *J* 14.5 Hz, 1H) (6,8-H), 2.21 (s, 3H, CH_3C=O), 1.13 (d, *J* 14.5 Hz, 1H), 0.95 (d, *J* 14.5 Hz, 1H) (9-CH_2), 1.09 (d, *J* 14.5 Hz, 1H), 1.01 (d, *J* 14.5 Hz, 1H) (6,8-H), 1.16 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 0.91 (s, 3H, CH_3); ^{13}C-NMR (100.59 MHz, $CDCl_3$) δ: 179.02 (COOH), 174.04 (NC=O), 54.99 (N-CH_2), 50.90 (N-CH_2), 47.36, 45.71, 45.54, 41.47, 32.63, 31.65, 31.04, 28.67, 21.95; IR ν/cm^{-1}: 3760, 2957, 1700, 1601, 1458, 1432; HRMS (ISI): calc. for M + H ($C_{14}H_{24}NO_3$) 254.1756059; found 254.17628.

3,5,7-Trimethyl-1-azatricyclo[3.3.1.1^{3,7}]decan-2-one (7). Compound **14** (from 260 mg of **13**) was suspended in a 1.5 M HCl solution (~30 mL), and the mixture brought to reflux for 24 h. At the end of this period all the precipitate had dissolved. The solution was evaporated and dried in a vacuum desiccator. The product was extracted from the residual solid with methanol and the methanol extract evaporated. The product obtained was dissolved in water and the pH adjusted to 7.45 using 1 M NaOH. Then the solution was evaporated to dryness on a rotary evaporator and **7** sublimed from the solid obtained, then resublimed (60 °C/0.2 mmHg) to give white crystals of **7**, 179 mg (84.6% yield from the aldehyde **13**), mp 114–115 °C,[8] with a strong camphor-like smell. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.98 (dd, *J* 13.4 and 2.3 Hz, 2H, 8,9-H(*exo*)), 2.93 (dd, *J* 13.4 and 4.1 Hz, 2H, 8,9-H(*endo*)), 1.73 (d, *J* 12.3 Hz, 2H, 4,10-H(eq)), 1.61 (dt, *J* 12.6 and 2.3 Hz, 1H, 6-H(eq)), 1.52 (m, 3H, 6,4,10-H(ax)), 1.03 (s, 3H, 3-CH_3), 0.82 (s, 6H, 5,7-CH_3); ^{13}C-NMR (62.8 MHz, $CDCl_3$) δ: 200.0 (C=O), 65.97 (N-CH_2), 52.2 (10-, 4-CH_2), 48.6 (6-CH_2), 43.5 (3-C), 30.47 (5-, 7-C), 27.46 (5-, 7-CH_3), 23.2 (3-CH_3); IR ν/cm^{-1}: 2950, 2228, 1732, 1455; MS (EI) *m*/*z* (%): 193 (17, M^+), 165 (35, $M^+ - CO$), 150 (20), 110 (100), 41 (14); MS (FAB) 194 (94%, $M^+ + H$); HRMS (EI): calc. for $C_{12}H_{19}NO$ 193.1466547; found 193.1465.

The conjugate acid $\mathbf{7H^+}$ could be prepared as the chloride (**20**) by dissolving the twisted amide **7** in dry ether saturated with HCl, but even the carefully dried solvent was not dry enough to allow its isolation: $\mathbf{7H^+}$ (acting like **19** as a superior drying agent) could not be separated from its hydrolysis product. Reaction with one equivalent of carefully dried toluene-*p*-sulfonic acid in spectroscopic grade $CDCl_3$ gave spectra clean enough to identify the cation (present as the toluene-*p*-sulfonate) as the *N*-protonated (rather than the *O*-protonated) form. Thus the chemical shift of the C=O carbon is close to 179 ppm in both $\mathbf{7H^+}$ and the *N*-methylated compound **19**, compared with 200 ppm in neutral **7**: the ^{13}C and ^{1}H resonances of the (CH_2)N groups are shifted downfield by similar amounts on methylation and protonation; and $\nu_{C=O}$ is raised rather than lowered on protonation (from 1732 to 1818 cm^{-1}). (This latter figure is extremely sensitive to tiny traces of moisture, and can reasonably be regarded as a minimum.) Spectra: (only the $\mathbf{7H^+}$ signals are listed) ^{1}H-NMR (400 MHz, CD_3CN) δ: 8.9 (broad s, 1H, N^+H), 3.55 (d, *J* 12.5 Hz, 2H, 8,9-H), 3.37 (dd, *J* 12.5 and 2.5 Hz, 2H, 8,8-H), 2.00 (d, *J* 13 Hz, 2H, 4,10-H(eq)), 1.72 (m, 3H, 4,10-H(ax) + 6-H(eq)), 1.63 (d, *J* 13 Hz, 1H, 6-H(ax)), 1.13 (s, 3H, 3-CH_3), 0.97 (s, 6H, 5,7-CH_3); ^{13}C-NMR (100 MHz, CD_3CN) δ: 179.1 (C=O), 62.2 (N-CH_2), 48.2 (CH_2), 44.4 (CH_2), 43.5 (C), 29.8 (C), 22.9 (CH_3), 20.6 (CH_3); IR ν/cm^{-1}(C_6H_6): 1818.

Propane-1,3-diol acetal (16) of 7. Twisted amide **7** (55 mg, 0.28 mmol) was dissolved in benzene (20 mL) and propane-1,3-diol (350 mg, 4.60 mmol) and toluene-*p*-sulfonic acid (2 mg) were added to the solution. The reaction mixture was refluxed using a micro Dean–Stark adapter packed with 4 Å molecular sieves. The reaction could be followed by IR, with the $\nu_{C=O}$ band of the starting "amide" (1732 cm^{-1}) disappearing after 48 h of reflux. The molecular sieves in the adapter were replaced every 5 h. After the reaction was complete the mixture was cooled, diluted with ether (10 mL), poured into ~10 mL of a saturated $NaHCO_3$ solution, washed twice with water, dried (Na_2SO_4) and evaporated. The residue was sublimed (80 °C/0.2 mmHg) to give **16** (40 mg, 55.9% yield) as white crystals with a strong camphor-like smell; mp 46–47 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.16 (ddd, *J* 2.74, 10.08 and 10.21 Hz, 2H, 3′,5′-H(ax)), 3.60 (ddd, *J* 1.1, 5.44 and 10.21 Hz, 2H, 3′,5′-H(eq)), 2.83 (dd, *J* 2.52, 12.34 Hz, 2H, 8,9-H(eq)), 2.37 (dd, *J* 3.05 and 12.34 Hz, 2H, 8,9-H(ax)), 2.01 (dtt, *J* 5.44, 10.08 and 14.14 Hz, 1H, 4′-H(ax)), 1.73 (dd, *J* 12.21, 2.13 Hz, 2H, 4,10-H(eq)), 1.31 (dtt, *J* 13.14, 2.74 and 1.1 Hz, 1H, 4′-H(eq)), 1.26 (dt, *J* 12.08 and 2.13 Hz, 1H, 6-H(eq)), 1.20 (dt, *J* 12.08 and 2.52 Hz, 1H, 6-H(ax)), 0.91 (dd, *J* 12.21 and 3.05 Hz, 2H, 4,10-H(ax)), 0.85 (s, 3H, 3-CH_3), 0.71 (s, 6H, 5,7-CH_3); ^{13}C-NMR (100.59 MHz, $CDCl_3$) δ: 105.13 (2-C), 58.66 (N-CH_2), 57.92 (O-CH_2), 50.52 (6-CH_2), 46.44 (4,10-CH_2), 36.31 (3-C), 29.56 (5,7-C), 26.42 (5,7-CH_3), 24.91 (4′-CH_2), 22.38 (3-CH_3) (Coupling constants for protons of the dioxane ring were obtained by gNMR spectrum simulation.) IR ν/cm^{-1}: no carbonyl absorption. HRMS (ESI): calc. for $C_{15}H_{26}NO_2$ (M + H) 252.196341; found 252.19680.

2-Methylene-3,5,7-trimethyl-1-azatricyclo[3.3.1.1^{3,7}]decane (17). The reaction was carried out in a flame-dried flask under an argon atmosphere. To a stirred solution of *n*-BuLi (0.48 mL of a 15% (1.6 M) solution in hexane, 0.77 mmol) triphenylphosphonium bromide (268 mg, 0.75 mmol) was added cautiously. Stirring was continued for 4 h at room temperature, then a solution of the twisted amide **7** (50 mg, 0.26 mmol) in dry diethyl ether (2 mL) was added dropwise. The mixture was refluxed for 8 h, then allowed to cool to room temperature, diluted with diethyl ether (50 mL), filtered,

then evaporated on a rotary evaporator. The product is highly volatile, so it is very important not to heat the solution higher than to 20 °C during evaporation. Twisted enamine **17** was distilled from this crude material (60 °C/0.1 mmHg) into a liquid nitrogen trap. Colourless liquid (32 mg, 64.3% yield) with a strong adamantane-like smell, still contained traces of ether (^{1}H-NMR). It was alkylated with MeI without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.82 (s, 1H, C=CH), 4.55 (s, 1H, C=CH), 2.78 (dd, *J* 3.0 and 12.5 Hz, 2H, 8,9-H), 2.69 (dd, *J* 2.5 and 12.5 Hz, 2H, 8,9-H), 1.12–1.48 (m, 6H, 4,6,10-CH_2), 0.99 (s, 3H, 3-CH_3), 0.74 (s, 6H, 5,7-CH_3); ^{13}C-NMR (100.59 MHz, $CDCl_3$) δ: 128.4 (2-C), 101.3 (=CH_2), 66.1 (N-CH_2), 51.8 (N-CH_2), 49.3 (C), 35.3 (CH_2), 30.4 (C), 26.4 (CH_3), 26.2 (CH_3); IR ν/cm^{-1}: 1602 (=CH_2).

2-Methylene-1,3,5,7-tetramethyl-1-azoniatricyclo[3.3.1.1^{3,7}]-decane iodide (18). Twisted enamine **17** (30 mg, 0.16 mmol), was dissolved in $CDCl_3$ (0.5 mL), and iodomethane (0.1 mL) added. The course of the reaction was monitored by ^{1}H-NMR: after 24 h at ambient temperature no starting material could be observed. The reaction mixture was evaporated *in vacuo*, the residue dissolved in CH_2Cl_2 (0.1 mL) and diluted with diethyl ether (2 mL). Pale yellow crystals of the alkylated product (**18**), suitable for X-ray analysis (see Fig. 2, above),§ were formed in ~24 h. Microanalysis of the crystals, as well as their X-ray structure, showed that the product crystallised with one molecule of water, which could not be removed even after heating *in vacuo* (0.1 mmHg) at 100 °C for 10 h. Yield: 50 mg, 94%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.42 (d, *J* 4.2 Hz, 1H, C=CH), 5.19 (broad d, *J* 4.2 Hz, 1H, C=CH), 4.58 (d, *J* 11.6 Hz, 2H, 8,9-H), 3.60 (s, 3H, N-CH_3), 3.04 (d, *J* 11.6 Hz, 2H, N-CH_2), 2.11 (dt, *J* 13.0 and 2.0 Hz, 1H, 6-H(eq)), 1.53 (dd, *J* 14.0 and 2.0 Hz, 2H, 4,10-H(eq)), 1.46 (d, *J* 14.0 Hz, 2H, 4,10-H(ax)), 1.38 (d, *J* 13.0, 1H, 6-H(ax)), 1.21 (s, 3H, 3-CH_3), 1.05 (s, 6H, 5,7-CH_3); ^{13}C-NMR (100.59 MHz, $CDCl_3$) δ: 156.1 (2-C), 104.3 (=CH_2), 72.2 (N-CH_2), 52.1, 49.1 (N-CH_3), 43.9, 37.4, 31.7, 26.4, 24.7; IR ν/cm^{-1}: 1602 (C=CH_2). Anal. calc. for $C_{14}H_{24}NI{\cdot}H_2O$: C, 47.87; H, 7.46; N, 3.99; found: C, 47.79; H, 7.16; N, 3.93%.

1,5,7-Trimethyl-3-azabicyclo[3.3.1]nonane-7-carboxylic acid (15). The twisted amide **7** (50 mg, 0.26 mmol) was dissolved in a mixture of water–acetonitrile (3 : 1), and the solution was left to stand for 3 h at ambient temperature. Then it was evaporated under high vacuum (0.1 mmHg), not heating above 30 °C, and the residue dried in a desiccator over P_2O_5. The colourless crystals produced (**15**, 54 mg, 100%) had ^{1}H-NMR (400 MHz, D_2O–CD_3CN) δ: 2.90 (d, *J* 12.5 Hz, 2H, 2,4-H(eq)), 2.53 (dd, *J* 12.5 and 2.5 Hz, 2H, 2,4-H(ax)), 2.02 (d, *J* 14.0 Hz, 2H, 6,8-H(eq)), 1.26 (dd, *J* 14.0 and 2.5 Hz, 2H, 6,8-H(ax)), 1.21 (s, 2H, 9-CH_2), 1.10 (s, 3H), 0.87 (s, 6H, 1,5-CH_3); ^{13}C-NMR (100.59 MHz, D_2O–CD_3CN) δ: 190.0 (COO), 52.5 (N-CH_2), 47.2 (C), 44.3 (C), 43.0 (CH_2), 34.3 (CH_2), 30.8 (CH_3), 28.9 (CH_3).

1,3,5,7-Tetramethyl-2-oxo-1-azoniatricyclo[3.3.1.1^{3,7}]decane tetrafluoroborate (19). The twisted amide **7** (57 mg, 0.29 mmol) was added to a stirred mixture of $(CH_3)_3O^+BF_4^-$ (43.6 mg, 0.29 mmol) and dry CH_2Cl_2 (2 mL). Stirring was continued for 1 h, during which time the alkylating reagent dissolved completely. Dry diethyl ether was added, and the precipitate was filtered and washed with ether with careful exclusion of moisture, then dried *in vacuo* to give **19** as a white powder. ^{1}H-NMR (400 MHz, CD_2Cl_2) δ: 3.62 (dd, *J* 3.8 and 12.3 Hz, 2H, 8,9-H(*endo*)), 3.59 (dd, *J* 2.0 and 12.3 Hz, 2H, 8,9-H(*exo*)), 3.08 (s, 3H, N-CH_3), 2.12 (dd, *J* 2.0 and 12.5 Hz, 2H, 4,10-H(eq)), 1.96 (dt, *J* 2.0 and 13.3 Hz, 1H, 6-H(eq)), 1.79 (dd, *J* 3.8 and 12.5 Hz, 2H, 4,10-H(ax)), 1.64 (dt, *J* 2.0 and 13.3 Hz, 1H, 6-H(ax)), 1.31 (s, 3H, 3-CH_3), 1.12 (s, 6H, 5,7-CH_3); ^{13}C-NMR (100.59 MHz, CD_2Cl_2) δ: 178.6 (C=O), 72.3, 49.5, 46.4, 44.8, 44.3, 31.7, 25.3, 23.9. Anal. calc. for $C_{13}H_{22}F_4BNO$: C, 52.91; H, 7.51; N, 4.75; found: C, 52.92; H, 7.24; N, 4.68%.

2,2-Dihydroxy-3,5,7-trimethyl-1-azoniatricyclo[3.3.1.1^{3,7}]-decane chloride (21). Twisted amide **7** (50 mg, 0.26 mmol) was dissolved in 0.1 M HCl (2 mL), the solution was evaporated to dryness and the residue (compound **21**) dried in a desiccator over P_2O_5 for 24 h. The compound was purified by crystallisation from ether–dichloromethane (1 : 1). Slow crystallisation from this mixture gave crystals suitable for X-ray analysis. Colourless crystals, 57.3 mg (89% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 9.4 (broad s, 1H, NH), 6.84 (broad s, 2H, OH), 3.58 (d, *J* 12.0 Hz, 2H, 8,9-H), 2.81 (d, *J* 12.0 Hz, 2H, 8,9-H), 1.94 (d, *J* 13.1 Hz, 2H, 4,10-H(eq)), 1.40 (d, *J* 12.9 Hz, 1H, 6-H(eq)), 1.34 (d, *J* 12.9 Hz, 1H, 6-H(ax)), 1.11 (d, *J* 13.1 Hz, 2H, 4,10-H(ax)), 1.02 (s, 3H, 3-CH_3), 0.93 (s, 6H, 5,7-CH_3); ^{13}C-NMR (100.59 MHz, $CDCl_3$) δ: 107.46 (2-C), 57.14 (N-CH_2), 47.92, 44.27, 38.06, 29.60, 25.61, 21.62; IR ν/cm^{-1}($CDCl_3$): no carbonyl absorption, 3216, 2960, 2233, 1534, 1459, 1380, 1315. Anal. calc. for $C_{12}H_{22}ClNO_2$: C, 58.17; H, 8.95; N, 5.65; found: C, 57.94; H, 8.93; N, 5.61%.

Methyl 1,3,5,7-tetramethyl-3-azabicyclo[3.3.1]nonane-7-carboxylate (26). Compound **19** (50 mg, 0.17 mmol) was dissolved in dry methanol (5 mL). After standing for 5 h at ambient temperature the solution was evaporated and the residue dissolved in CH_2Cl_2 (50 mL), washed with water (2 × 10 mL), dried (Na_2SO_4) and evaporated to give **26** as a colourless oil (38 mg, 93.4% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.59 (s, 3H, O-CH_3), 2.46 (d, *J* 10.9 Hz, 2H, 2,4-H), 2.41 (d, *J* 14.1 Hz, 2H, 6,8-H(eq)), 1.87 (s, 3H, N-CH_3), 1.59 (d, *J* 10.9 Hz, 2H, 2,4-H), 1.00 (s, 3H, 7-CH_3), 0.97 (AB q, 2H, 9-CH_2), 0.90 (d, *J* 14.1 Hz, 2H, 6,8-H(ax)), 0.79 (s, 6H); ^{13}C-NMR (100.59 MHz, $CDCl_3$) δ: 175.2 (COO), 65.0, 51.3, 48.4, 46.2, 44.1, 43.2, 31.9, 31.8, 28.2; IR ν/cm^{-1}($CDCl_3$): 2928, 2784, 1702 (C=O), 1457, 1187.

1,3,5,7-Tetramethyl-3-azabicyclo[3.3.1]nonane-7-carboxylic acid (25). Water (2 mL) was added to methyl 1,3,5,7-tetramethyl-3-azabicyclo[3.3.1]nonane-7-carboxylate **26** (20 mg) and the mixture was refluxed for 0.5 h. Then it was cooled, evaporated, and dried in a desiccator over P_2O_5 to give **25** as colourless crystals, 18.8 mg (99%). ^{1}H-NMR (400 MHz, D_2O–CD_3CN) δ: 2.95 (d, *J* 12.5 Hz, 2H, 2,4-H), 2.58 (s, 3H, N-CH_3), 2.44 (d, *J* 12.5 Hz, 2H, 2,4-H), 1.89 (d, *J* 14.0 Hz, 2H, 6,8-H(eq)), 1.33 (d, *J* 14.0 Hz, 2H, 6,8-H(ax)), 1.24 (d, *J* 13.5 Hz, 1H, 9-H(eq)), 1.18 (d, *J* 13.5 Hz, 1H, 9-H(ax)), 1.08 (s, 3H, 7-CH_3), 0.84 (s, 6H, 1,5-CH_3); ^{13}C-NMR (100.59 MHz, D_2O–CD_3CN) δ: 190.0 (COO), 63.10, 46.43, 43.20, 43.10, 42.06, 34.87, 32.20, 28.90.

2,2-Dihydroxy-1,3,5,7-tetramethyl-1-azoniatricyclo[3.3.1.1^{3,7}]-decane chloride (22). Amino acid **25** (50 mg) was dissolved in 0.1 M HCl (2 mL), the solution was evaporated and the residue (compound **22**) dried in a desiccator over P_2O_5 for 24 h. The compound was purified by crystallisation from ether–dichloromethane (1 : 1). Slow crystallisation from this mixture

§ Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. CCDC reference number 188/287. See http://www.rsc.org/suppdata/p2/b0/b008270h/ for crystallographic files in .cif format. Crystal data, analysis and refinement for **18**: empirical formula $C_{13}H_{24}INO{\cdot}H_2O$; formula weight (*M*) 351.26; temperature 150(2) K; crystal system monoclinic; space group $P2_1/n$; unit cell dimensions a = 12.130(11), b = 8.810(7), c = 14.747(12) Å, β = 101.76(7)°; volume 1543(2) Å^3; Z = 4; μ = 2.064 mm^{-1}; reflections collected (Rigaku RAXIS-IIC image plate) 10426; independent reflections 2615 (R_{int} = 0.074); final R indices [$I > 2\sigma(I)$], R_1 = 0.087, wR_2 = 0.147.

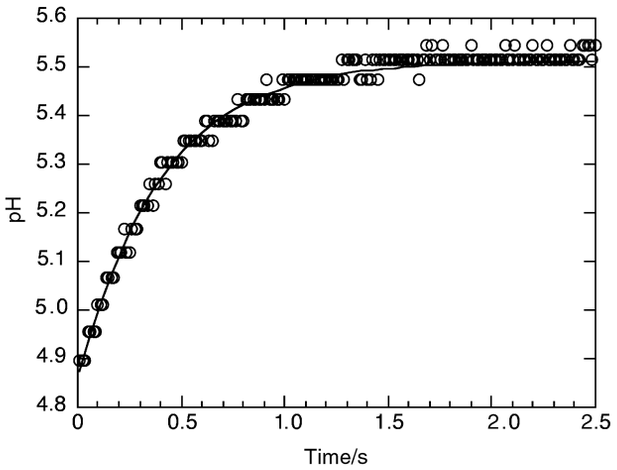


Fig. 4 pH *vs*. time curve for **7**, obtained by a stopped-flow indicator method (half-protonated free base, water–acetonitrile 1 : 1, 20 °C). See text.

gave crystals suitable for X-ray analysis (see Fig. 2).¶ Colourless crystals, 48.8 mg (84% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.7 (broad s, 2H, OH), 3.40 (d, *J* 12.5 Hz, 2H, 8,9-H(*endo*)), 2.86 (s, 3H, N-CH_3), 2.56 (dd, *J* 12.5 and 2.5 Hz, 2H, 8,9-H(*exo*)), 1.97 (d, *J* 13.5 Hz, 2H, 4,10-H(eq)), 1.36 (dt, *J* 12.5 and 2.5 Hz, 1H, 6-H(eq)), 1.33 (dt, *J* 12.5 and 2.5 Hz, 1H, 6-H(ax)), 1.13 (dd, *J* 13.5 and 2.5 Hz, 2H, 4,10-H(ax)), 1.07 (s, 3H, 3-CH_3), 0.95 (s, 6H, 5,7-CH_3); ^{13}C-NMR (100.59 MHz, $CDCl_3$) δ: 114.7 (2-C), 66.4, 46.8, 44.9, 43.7, 39.9, 30.7, 25.5, 23.0; IR ν/cm^{-1}($CDCl_3$): no carbonyl absorption, 3500, 3204, 2950, 1457, 1115. Anal. calc. for $C_{13}H_{24}ClNO_2$: C, 59.64; H, 9.24; N, 5.35; found: C, 58.68; H, 9.22; N, 5.35%.

Stopped-flow pK_a measurements

A stock solution of 10.4 mM aq. HCl was prepared containing the acid–base indicator, Bromophenol Blue (*ca*. 0.1 mM). This indicator has a pH transition interval from 3.0 (yellow, λ_{max} 422 nm) to 4.4 (blue). The stock solution was filtered. To obtain a calibration curve, NaOH solution was added to aliquots of the stock HCl, which were diluted with equal volumes of acetonitrile to give a series of solutions of varying pH (measured by pH meter) in the range 2.3–6.8. These solutions were injected into the stopped-flow instrument from both syringes, and the corresponding absorbance values measured. A polynomial curve fit of pH *vs*. absorbance gave the numerical equation that was used to convert absorbance into pH in the pK_a measurements. The measurements involved injecting into the stopped-flow instrument the stock solution of HCl from one syringe, and an equal volume of a solution of twisted amide **7** (20.8 mM) in acetonitrile from the other. A trace of a typical run is reproduced in Fig. 4.

¶ Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. CCDC reference number 188/287. See http://www.rsc.org/suppdata/p2/b0/b008270h/ for crystallographic files in .cif format. Crystal data, analysis and refinement for **22**: empirical formula $C_{13}H_{24}ClNO_2$; formula weight (*M*) 261.78; temperature 180(2) K; crystal system triclinic; space group $P\bar{1}$; unit cell dimensions a = 12.527(8), b = 14.498, c = 7.796(2) Å, α = 90.05(2)°, β = 90.45(4)°, γ = 86.77(4)°; volume 1413.6(10) Å^3; Z = 4; μ = 0.262 mm^{-1}; reflections collected (Rigaku AFC7R diffractometer) 5615; independent reflections 4987 (R_{int} = 0.088); final R indices [$I > 2\sigma(I)$], R_1 = 0.076, wR_2 = 0.166.

Acknowledgements

IVK is grateful for a NATO–Royal Society Postdoctoral Fellowship, and to the Royal Society of Chemistry for a Journals Grant for International Authors. We thank EPSRC for help with the purchase of the diffractometer and image plate system.

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