Mechanism of esterification of 1,3-dimethylamino alcohols by *N*-acetylimidazole in acetonitrile and the influence of alkyl and geminal dialkyl substitution upon the rate

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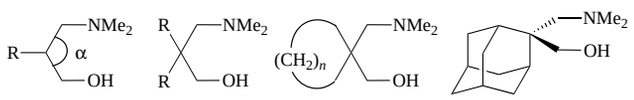
3-(Dimethylamino)propan-1-ol and seven derivatives with alkyl substituents at the 2-position have been prepared by conventional methods, and second-order rate constants for their esterification by *N*-acetylimidazole in acetonitrile have been measured under pseudo-first-order conditions both by ^{1}H NMR spectroscopy at a single temperature (23 °C) and by a UV spectroscopic method over the temperature range 25–65 °C. Evidence is presented that the intermolecular esterifications proceed *via* an initial rate-determining intramolecular general base catalysed formation of a cyclic tetrahedral intermediate. Effective molarities compared with the third-order reactions of simpler alcohols with acetylimidazole catalysed by triethylamine are estimated to be 13–14 mol dm^{-3}, but alkyl substitution at the 2-position of the amino alcohol has only a modest effect upon reaction rates. All reactions have substantial negative entropies of activation and only modest enthalpies of activation as expected for concerted bimolecular reactions with highly ordered transition structures. Three structurally related carbocyclic amino alcohols constitute a short isokinetic series with the isokinetic temperature very close to the experimental range. Along this series, decreasing enthalpies of activation are almost exactly balanced in their contributions to the overall free energy of activation near room temperature by increasingly negative entropies of activation.

Introduction

Recently, in the context of developing a non-enzymic catalyst for the cleavage of esters and amides, we studied the influence of anchoring substitution in 1,3-amino alcohols on the rate of esterification by *N*-acetylimidazole (AcIm) and by *p*-nitrophenyl acetate (PNPA) in acetonitrile.[1] We found that anchoring substitution (**1b** *vs.* **1a**) led to (*i*) a rate decrease in the esterification with PNPA, and (*ii*) a rate increase in the reaction with AcIm. We ascribed these effects to enforced intramolecular hydrogen bonding between the terminal dimethylamino and hydroxy groups in the case of the 2-*tert*-butyl substituted derivative, a nucleophilic catalysis mechanism for reaction with PNPA, and general base catalysis (GBC) for reaction with AcIm.[2]

In continuation of that study, we became interested in investigating the influence of various 2,2-*gem*-dialkyl substituents in the 3-(*N*,*N*-dimethylamino)propan-1-ol system upon esterification with AcIm. We were aware, for example, that alkyl substitution and, in particular, *gem*-dialkyl substitution have long been known to promote ring closure reactions.[3] Although no final ring closed products are formed in the present reactions, cyclic transition structures are involved in the intramolecular proton transfers of the GBC mechanism. Consequently, we sought to investigate how the rates of these reactions are influenced by the alkyl substitution pattern in the chain between the donor and acceptor of the intramolecular hydrogen bond. We now report fully our results obtained for the esterification of a series of 2,2-dialkyl-3-(*N*,*N*-dimethylamino)propan-1-ols (**1**–**7**) by AcIm in acetonitrile.



1a: R = H
1b: R = Bu^t

2: R = Me
3: R = Pr^n

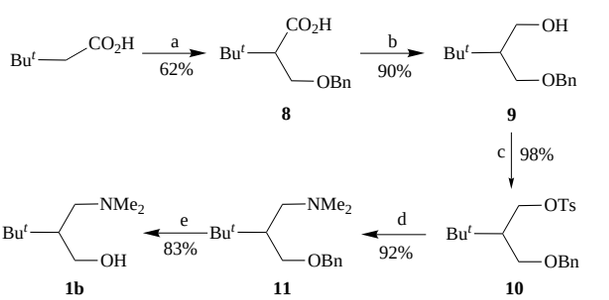
4: *n* = 1
5: *n* = 2
6: *n* = 3

7

Results and discussion

Syntheses

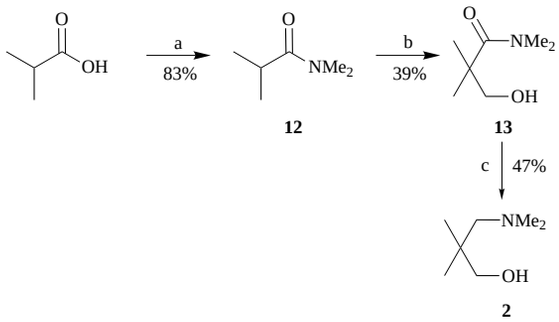
Compound **1a** was commercially available and the syntheses of the other amino alcohols investigated, **1b**–**7**, are given in Schemes 1–3. The synthetic route for the preparation of *N*,*N*,3,3-tetramethyl-2-(hydroxymethyl)butylamine **1b** is outlined in Scheme 1. Commercially available *tert*-butylacetic acid



Scheme 1 *Reagents*: (a) i NaH LDA, ii $ClCH_2OBn$; (b) LAH, THF; (c) TsCl, pyridine, DMAP, CH_2Cl_2; (d) Me_2NH (40% aq. sol.), THF, 100 °C; (e) H_2, Pd/C, EtOH

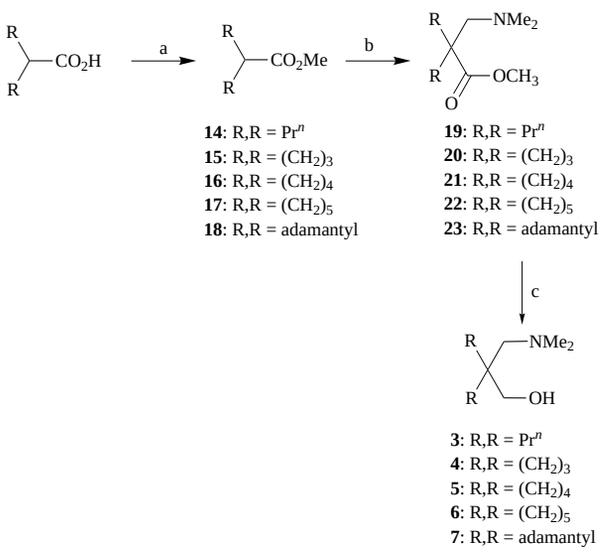
was alkylated with benzyl chloromethyl ether to give **8**. Subsequent reduction with lithium aluminium hydride followed by tosylation yielded **10**, which was treated with a 40% aqueous solution of dimethylamine. Finally, debenzylation of **11** led to the desired amino alcohol **1b**.

The synthesis of 3-(dimethylamino)-2,2-dimethylpropan-1-ol (Scheme 2) started from isobutyric acid. First, the acid was



Scheme 2 *Reagents*: (a) i DMF, $SOCl_2$, 0–80 °C, ii Me_2NH (40% aq. sol.), CH_2Cl_2, −70 °C–room temp. (b) i 2,2,6,6-tetramethylpiperidine, BuLi, THF–HMPA, ii $(CH_2O)_n$; (c) $BF_3{\cdot}Et_2O$, borane·dimethylsulfide, THF

transformed into amide **12**, then condensation with formaldehyde followed by reduction with borane gave the amino alcohol **2**. Amino alcohols **3**–**7** were prepared *via* essentially the same strategy starting from the commercially available dialkyl acids (Scheme 3). In the case of the adamantane derivative, the



Scheme 3 *Reagents*: (a) CH_2N_2, Et_2O; (b) LDA, *N*,*N*-dimethylmethyleneammonium iodide; (c) LAH, Et_2O

adamantane-2-carboxylic acid was prepared from adamantan-2-one *via* a three-step sequence according to a literature procedure.[4] Conversion of the acids into the methyl esters was followed by alkylation with *N*,*N*-dimethylmethyleneammonium iodide (Eschenmoser's salt).[5] The resulting amino esters were isolated as their hydrochlorides and subsequently transformed into the desired amino alcohols by lithium aluminium hydride reduction. Distillation resulted in pure amino alcohols (see Experimental section for detailed procedures and yields).

Kinetics

At first, half-lives for the esterification at 23 °C were determined by ^{1}H NMR spectroscopy using the amino alcohol in 10-fold excess over AcIm (Table 1). From these results we note the following four features. First, compounds show rate enhancements over the reactions of propan-1-ol and hexane-1,6-diol

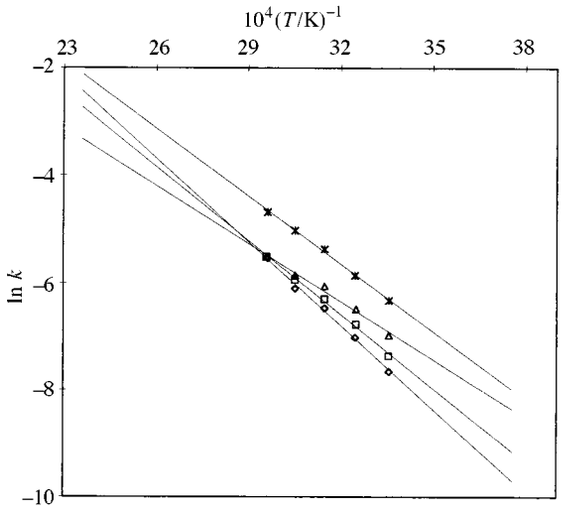


Fig. 1 Arrhenius plot (ln *k* *vs.* 1/*T*) obtained for the alcoholysis of AcIm by **4** (◇), **5** (□), **6** (△) and **7** (*) (lines for **1a**, **1b**, **2** and **3** are almost parellel with the line for **7**)

with AcIm catalysed by triethylamine, *i.e.* a system capable only of intermolecular general base catalysis.[6] Secondly, the total reactivity range for compounds **1**–**7** is narrow (four-fold) indicating only a small dependence of reactivity upon the alkyl substituents at the central carbon of the 1,3-amino alcohols. This is in line with the results from previous studies where the effect of structural variation on the efficiency of intramolecular general base catalysis was investigated.[7] Thirdly, the reactivity orders between the 2-alkyl and 2,2-dialkyl acyclic compounds, *i.e.* **1b** > **1a** and **3** > **2**, are as expected but the differences are small and there is no evident trend related to structure amongst these four compounds.[8] Fourthly, there is a (modest) structure-related trend in reactivity amongst the cyclic *gem*-dialkyl compounds, *i.e.* **7** > **6** > **5** > **4**, which follows the order of the magnitude of the internal bond angle *a* at the 2-position (Table 1). This suggested that the Thorpe–Ingold angle deformation could contribute to some degree to the relative reactivities within the series which,[9] although expected to be small,[10] should be reflected primarily in the enthalpies of activation.[11]

Seeking further insight into these relative reactivities, we measured the activation parameters for all members of the series. Reaction rates were measured in acetonitrile by monitoring the decrease in UV absorbance at 270 nm due to AcIm over at least five half-lives with the amino alcohol present in very large excess (160–1300-fold), and the rate constants were found to be strictly first-order in AcIm, the limiting reagent. By measuring the pseudo-first-order rate constants at different high concentrations of the amino alcohol, it was also established that the reactions are first-order in amino alcohol, and second-order rate constants (at least in duplicate) were measured for the esterification of compounds **1**–**7**. Activation enthalpies and entropies were obtained in the usual way from second-order rate constants at five different temperatures (at least) in the range of 25–65 °C using classical Eyring plots. Activation parameters are included in Table 1 along with second-order rate constants *k* calculated at 25 °C which differ slightly from those obtained by ^{1}H NMR spectroscopy (at 23 °C). In view of the pseudo-first-order requirements and the number of data involved in their determination, the former are considered to be more reliable; for **1a** and **1b**, somewhat different (and better) values were obtained than were reported originally.[1]

All the reactions have very substantial negative entropies of activation and modest enthalpies of activation as expected for concerted bimolecular reactions in general. Inspection of the activation parameters in Table 1 reveals, at least for some compounds, a tendency for compensation between enthalpies and entropies of activation suggesting that there could be an

Table 1 Half-lives (23 °C),[a] calculated internal bond angles,[b] activation enthalpies,[c] activation entropies,[d] and second-order rate constants (25 °C)[e] for the alcoholysis of Aclm by **1a**, **1b** and **2**–**7** in acetonitrile

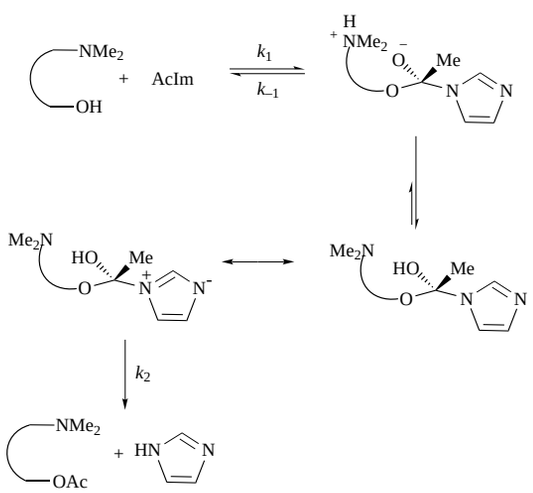
	$t_{\frac{1}{2}}$/min	a/°	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J K^{-1} mol^{-1}	k/10^{-4} dm^3 mol^{-1} s^{-1}
1a	721	113.9	33.1	−195	6.04
1b	198	110.3	35.3	−180	14.9
2	677	111.8	33.8	−196	4.26
3	462	109.8	33.5	−193	6.58
4	682	114.2	40.9	−171	4.76
5	473	111.7	35.6	−186	6.25
6	421	110.1	27.4	−210	9.28
7	169	106.7	32.5	−188	17.7

[a] Determined by NMR spectroscopy for the pseudo-first-order reaction (0.05 mol dm^{-3} amino alcohol; 10-fold excess over Aclm); for the reaction of Aclm with hexane-1,6-diol and triethylamine, the estimated pseudo-first-order half-life is 224 h at [hexane-1,6-diol] = [triethylamine] = 0.05 mol dm^{-3}. [b] In the intramolecular hydrogen bonded global minimum energy form. [c] Estimated maximum probable error, ±4 kJ mol^{-1}. [d] Estimated maximum probable error, ±14 J K^{-1} mol^{-1}. [e] Determined by UV spectroscopy (see text).

isokinetic series amongst our compounds.[12] In order to identify the compounds for which there is an isokinetic relationship (IKR), we applied the strictest statistical test that has been recently and convincingly advocated by Linert.[13] From inspection of Arrhenius plots (ln k *vs.* 1/T) for substrates **1a**–**7**, it was clear that only the closely related compounds **4**, **5** and **6** showed a common small area of intersection (Fig. 1) and hence could constitute an isokinetic series with an isokinetic temperature almost within the experimental range (69 °C). We observe that, along this series **4**, **5** and **6**, $\Delta H^{\ddagger}$ decreases appreciably (40.9, 35.6 and 27.4 kJ mol^{-1}), but that this trend is almost exactly counterbalanced by the corresponding trend in $\Delta S^{\ddagger}$ (−171, −186 and −210 J K^{-1} mol^{-1}). For the other compounds, including the two most reactive substrates investigated (**1b** and **7**), there are no trends in the activation parameters which are very similar ($\Delta H^{\ddagger}$ = 33.5 ± 2.0 kJ mol^{-1} and $\Delta S^{\ddagger}$ = −195 ± 15 J K^{-1} mol^{-1}).

Mechanism

Whereas it is generally accepted that the esterification of amino alcohols by AcIm involves intramolecular GBC (Scheme 4), it



Scheme 4

may not be immediately obvious whether the forward reaction of the tetrahedral intermediate to products (the k_2 process) is faster than the reverse breakdown to reactants (the k_{-1} process). The k_{-1} process, being the reverse of an intramolecular general base catalysed step, involves intramolecular general acid catalysis. This step involves partial proton transfer from the $-NMe_2H^+$ group to an uncharged oxygen, and departure of an incipient alcohol as nucleofuge. However, a minor conformational change allows a second and more favourable possibility, the complete proton transfer to the more strongly basic negatively charged oxygen of the zwitterionic tetrahedral intermediate to give the isomeric uncharged tetrahedral intermediate. Calculations indicate that the conformation required for proper alignment of proton donor and acceptor residues to allow a third possibility, efficient intramolecular general acid catalysis in a direct forward step from the zwitterionic tetrahedral intermediate with departure of imidazole, is too strained and may be dismissed.[14a] This leaves the formation of the uncharged tetrahedral intermediate as the most favourable process from the first-formed zwitterionic intermediate, and the thermodynamics of this step may cause it to be essentially irreversible in acetonitrile.

The pK_a values alone of the conjugate acids of the respective potential leaving groups within the uncharged tetrahedral intermediate may lead one to expect their departures to be competitive. However, molecular orbital calculations on *N*-acetylimidazole indicate that both N-1 and the carbonyl carbon bear a net positive charge, and N-3 possesses a net negative charge.[14b] This is in accord with the earlier finding by Fife that imidazole is a much more effective nucleofuge than is predicted solely on the basis of its pK_a value.[2c] Consequently, we expect this forward reaction from the uncharged tetrahedral intermediate to be faster than the alternatives; and hence, in the forward direction of the overall sequence, the initial GBC step is rate limiting.[15]

The remaining unresolved issue is the small size of the effect of 2-alkyl substitution in the 1,3-amino alcohols upon the rate constants. Our present working hypothesis is that, in acetonitrile, all the 1,3-amino alcohols react with the benefit of fully formed intramolecular hydrogen bonds in their initial states. Consequently, there is relatively little difference in reactivity between substrates **1**–**7** with different sizes or numbers of alkyl groups at carbon-2.

Experimental

General procedures

All reactions involving air and/or moisture sensitive materials were conducted under atmospheres of N_2 or Ar. All solvents were purified before use; diethyl ether and tetrahydrofuran were distilled from sodium benzophenone ketyl, triethylamine and diisopropylamine were distilled over calcium hydride and dichloromethane was distilled over phosphorus pentoxide. Analytical thin-layer chromatography was performed using glass plates precoated (0.25 mm layer) with silica gel 60 F_{254}. Flash chromatography was performed using Merck silica gel 60 (70–235 or 230–400 mesh). The ^{1}H NMR spectra were obtained at 500, 360 and 200 MHz, and ^{13}C NMR spectra at 50.3 MHz. Chemical shifts are reported in ppm downfield from TMS using residual $CHCl_3$ (7.27 ppm) as an internal standard; J values are given in Hz. Melting points are uncorrected. IR spectra were recorded on a FTIR spectrometer using KBr plates with film or in solution; mass spectra were recorded at 70 eV.

Kinetics measurements (UV)

Acetylimidazole was obtained from Aldrich and recrystallized from dichloromethane–diethyl ether. Acetonitrile (super gradient, far UV) was obtained from Lab Scan and stored under nitrogen. 3-(*N*,*N*-Dimethylamino)propan-1-ol was obtained from Aldrich and distilled. Stock solutions of amino alcohols (1 M) and acetylimidazole (3.3×10^{-6} M) were prepared and stored in the dark. New stock solutions were prepared for duplicate runs.

Rates of reactions were followed spectrophotometrically by measuring the disappearance of acetylimidazole at 270 nm using a Varian Cary 3E UV–VIS spectrophotometer equipped with a thermostatted multi-cell block. The temperature in the sample compartment was constantly checked using a temperature probe emersed in one of the cells (±0.1 °C). Stoppered semi-micro cuvettes (1.5 ml) were used. Reactions were initiated by adding a small volume of amino alcohol solution (30–150 µl) *via* a syringe to a cuvette containing the acetylimidazole solution which had been equilibrated for at least 20 min. Reactions were followed for at least five half-lives. Cary kinetics application software was employed to obtain pseudo-first-order rate constants using the recursive Marquardt non-linear curve fitting technique as described by Schwartz and Gelb.[16]

Plots of k_{obs} (for the pseudo-first-order reaction) *vs.* amino alcohol concentration were linear with a correlation of at least 0.997, *i.e.* the reactions are pure first-order in amino alcohol. All reactions were run at least in duplicate.

Kinetics measurements (^{1}H NMR)

Half-lives were obtained by this method by adding a small amount (0.1 equiv.) of acetylimidazole to an NMR tube containing the amino alcohol solution. The concentration of amino alcohol was 0.05 M. Spectra were then recorded at specific time intervals on a Bruker 500 MHz instrument thermostatted at 23 °C. The half-life was calculated using the integrations of acetylimidazole peaks in the NMR spectra in the following way. Acetylimidazole shows three peaks at characteristic δ-values of 7.0, 7.51 and 8.13, each integrating for one proton. The imidazole which is formed shows a peak at $\delta = 7.55$, integrating for one proton and another at $\delta = 6.95$ integrating for two protons. At each moment the ratio of the integration at $\delta \cong 8.13$ over the total integration at $\delta = 7.5$ reflects the ratio of the actual acetylimidazole concentration over the initial acetylimidazole concentration. Plotting the $\log_e$ of this ratio *vs.* time produces a straight line, showing the reaction to be first order in acetylimidazole.

Syntheses

***N*,*N*,3,3-Tetramethyl-2-(hydroxymethyl)butylamine (1b).** 2-2-(*Benzyloxymethyl*)-3,3-*dimethylbutanoic acid* (**8**).—*tert*-Butylacetic acid (81.6 ml, 0.63 mol) was added to a stirred suspension of sodium hydride in mineral oil (21.6 g of a 70% suspension, 0.63 mol) and diisopropylamine (88 ml, 0.63 mol) in tetrahydrofuran (630 ml) maintained below 10 °C by the use of an ice bath. The reaction mixture was then heated up to reflux temperature and stirred for a further 15 min. After the reaction mixture had then been cooled to 0 °C, *n*-butyllithium (252 ml of a 2.5 M solution in hexane, 0.63 mol) was added dropwise, care being taken not to exceed a reaction temperature of 10 °C. The reaction mixture was then warmed up to 30 °C and stirred for 45 min to complete the metallation, whereupon the suspension was cooled back down to 0 °C and a solution of benzyl chloromethyl ether (110 g, 0.7 mol) in tetrahydrofuran (100 ml) was added dropwise. During this addition, the internal temperature was kept below 20 °C. After being stirred overnight at room temperature, the reaction mixture was poured into ice water (1.5 l) and extracted with diethyl ether (4 × 300 ml). The aqueous phase was acidified almost to pH 1 with concentrated hydrochloric acid (37%) after which it was extracted again with diethyl ether. The combined organic layers were washed with saturated aqueous sodium chloride, dried over magnesium sulfate and filtered. The solvent was then evaporated under reduced pressure to yield the carboxylic acid **8** (92.8 g, 62%) pure enough for direct use in the next step; ν_{max}(KBr)/cm^{-1} 3730–2400, 3460, 3020, 2920, 1725, 1520, 1505, 1475, 1455, 1425, 1395, 1380, 1335, 1285, 1240; δ_H(500 MHz, $CDCl_3$) 1.01 (9 H, s,), 2.60 (1 H, dd, *J* 3.8 and 10.4), 3.66 (1 H, dd, *J* 3.8 and 9.0), 3.78 (1 H, dd, *J* 9.1 and 10.3), 4.54 (2 H, app. s), 7.34–7.25 (5 H, m); *m*/*z* 236 (M^+, 2%), 190 (2), 179 (2), 107 (50), 92 (100), 79 (10), 65 (12), 57 (24), 41 (19).

2-(*Benzyloxymethyl*)-3,3-*dimethylbutan*-1-*ol* (**9**).—A suspension of lithium aluminium hydride (11.4 g, 0.3 mol) in dry tetrahydrofuran (400 ml) was heated under reflux and a solution of the carboxylic acid **8** (35.4 g, 0.15 mol) in dry tetrahydrofuran (60 ml) was added dropwise to the boiling suspension over about 30 min. The reaction mixture was stirred for an additional 10 min at reflux temperature, then overnight at room temperature. Hydrochloric acid (10%, 200 ml) was then added dropwise to the suspension at 0 °C before the aqueous phase was extracted with dichloromethane. The combined organic layers were washed with saturated aqueous sodium chloride, dried over magnesium sulfate and filtered. The solvent was evaporated under reduced pressure to give the alcohol as a colourless oil (30 g, 90%); ν_{max}(KBr)/cm^{-1} 3440, 3080, 3056, 2960, 2856, 1496, 1472, 1452, 1370, 1116, 1076, 1040, 1026, 1008, 706, 700; δ_H(360 MHz, $CDCl_3$) 0.91 (9 H, s), 1.73 (1 H, m), 3.04 (1 H, dd, *J* 2.8 and 8.8), 3.60 (1 H, app. t, *J* 9.2), 3.71 (1 H, m), 3.89–3.81 (2 H, m), 4.55 (1 H, d, J_{AB} 11.9), 7.38–7.20 (5 H, m); *m*/*z* 222 (M^+, 2%), 221 (10), 204 (2), 159 (8), 145 (4), 144 (7), 91 (94), 79 (40), 70 (82), 69 (80), 57 (100), 56 (44), 38 (70).

2-(*Benzyloxymethyl*)-3,3-*dimethylbutyl toluene-p-sulfonate* (**10**).—A solution of alcohol **9** (9.60 g, 43.2 mmol), toluene-*p*-sulfonyl chloride (tosyl chloride) (9.26 g, 47.5 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (10 mg) in pyridine (10 ml) and dichloromethane (40 ml) was stirred at room temperature for 12 h. Ice water (about 10 ml) was added to the reaction mixture and the resulting solution was stirred for 30 min. Diethyl ether (100 ml) was then added and the separated organic phase was extracted with 5% hydrochloric acid then saturated aqueous sodium chloride, dried over magnesium sulfate, filtered and concentrated under reduced pressure; the crystallized toluene-*p*-sulfonate (tosylate) **10** (15.9 g, 98%) was pure enough to be used directly in the next step. Further purification of a sample was achieved by column chromatography on silica gel (diethyl ether : hexane, 5 : 95); (Found: C, 66.84; H, 7.47. Calc. for $C_{21}H_{24}O_4S$: C, 66.99; H, 7.50%); ν_{max}(KBr)/cm^{-1} 2960, 2870, 1490, 1470, 1355, 135, 1165, 960, 835, 735, 695; δ_H(360 MHz, $CDCl_3$) 0.92 (9 H, s), 1.63 (1 H, m), 2.38 (3 H, s), 3.47 (1 H, dd, *J* 6.7 and 9.5), 3.55 (1 H, dd, *J* 3.9 and 9.5), 4.21 (1 H, dd, *J* 5.8 and 9.6), 4.25 (1 H, dd, *J* 4.0 and 9.6), 4.34 (2 H, s), 7.20 (2 H, d, *J* 10.2), 7.29 (5 H, m), 7.27 (2 H, d, *J* 10.2); *m*/*z* 204 ($M^{\cdot+}$ − Ts, 2%), 159 (10), 147 (4), 107, 95 (100), 92 (51), 84 (24), 64 (59), 70 (40), 57 (60), 41 (50).

2-(*Benzyloxymethyl*)-*N*,*N*,3,3-*Tetramethylbutylamine* (**11**).—A solution of tosylate **10** (5.00 g, 13.3 mmol) and dimethylamine (13 ml of a 60% aqueous solution) in tetrahydrofuran (13 ml) was heated in a pressure vessel for 48 h at 100 °C. The reaction mixture was cooled to room temperature, treated with aqueous potassium hydroxide solution (10%, 50 ml) and then extracted with diethyl ether (3 × 50 ml). The combined ether layers were washed with saturated aqueous sodium chloride, dried over magnesium sulfate, filtered and concentrated under reduced pressure. Pure amine **11** (3.05 g, 92%) was obtained after Kugelrohr distillation (150 °C, 0.03 mmHg); ν_{max}(KBr)/cm^{-1} 3080, 3050, 3020, 2950, 2850, 2800, 2750, 1490, 1460, 1450, 1390, 1360, 1255, 1235, 1190, 1150, 1110, 1095, 1030, 940, 840, 730, 690; δ_H(500 MHz, C_6D_6) 1.01 (9 H, s), 1.45 (1 H, m), 2.08 (1 H, dd, *J* 3.6 and 12.2), 2.41 (1 H, dd, *J* 10 and 12.2), 3.56 (1 H, dd, *J* 3.3 and 9.3), 3.65 (1 H, dd, *J* 4.6 and 9.3), 4.35 (2 H, app. s), 7.07–7.32 (5 H, m); *m*/*z* 249 ($M^{\cdot+}$, 2%), 234

($M^{\cdot+} - CH_3$, 1), 219 (2), 192 ($M^{\cdot+} - Bu'$, 4), 158 (8), 91 (12), 58 (100).

N,*N*,3,3-*Tetramethyl*-2-(*hydroxymethyl*)*butylamine* (**1b**).—A solution of benzyl ether **11** (1.1 g, 4.5 mmol) and toluene-*p*-sulfonic acid (0.855 g, 4.5 mmol) in ethanol (5 ml) was added to a prehydrogenated suspension of palladium on carbon (350 mg, 10% Pd on C) in ethanol (2 ml). The reaction mixture was shaken for 48 h under hydrogen (4 bar). After the reaction mixture had been flushed with nitrogen to remove hydrogen, the catalyst was removed by filtration through celite. Aqueous potassium hydroxide solution (10%) was added to the filtrate which was then extracted with diethyl ether. The combined organic layers were washed with saturated aqueous sodium chloride, dried over magnesium sulfate, filtered and concentrated under reduced pressure. Finally, the amino alcohol (0.593 g, 83%) was obtained by Kugelrohr distillation (80 °C, 0.03 mmHg); (Found: C, 67.73; H, 13.09; N, 8.59. Calc. for $C_9H_{21}NO$: C, 67.87; H, 13.29; N, 8.79%); ν_{max}(KBr)/cm^{-1} 3426, 2956, 2867, 1467, 1396, 1366, 1290, 1238, 1194, 1164, 1098, 1048, 1009, 947, 839, 668; δ_H(360 MHz, CD_3OD) 0.91 (9 H, s), 1.61 (1 H, m), 2.26 (6 H, s), 2.47 (1 H, app. dt, *J* 2.8, 2.3 and 12.2), 2.56 (1 H, dd, *J* 12.2 and 12.2), 3.64 (1 H, dd, *J* 9.2 and 10.3), 3.84 (1 H, ddd, *J* 2.3, 3.8 and 10.3); δ_C(50.3 MHz, $CDCl_3$) 27.41, 30.61, 44.56, 45.13, 62.22, 66.02; *m*/*z* 159 ($M^{\cdot+}$, 7%), 112 (9), 102 (12), 84 (17), 69 (30), 58 (100).

3-(Dimethylamino)-2,2-dimethylpropan-1-ol (2). *N*,*N*-*Dimethyl*-2-*methylpropanamide* (**12**).—In a 500 ml flask fitted with a reflux condenser, stirring bar and gas trap, isobutyric acid (100 ml, 1.08 mol), *N*,*N*-dimethylformamide (0.5 ml) and thionyl chloride (80 ml, 1.10 mol, 1.01 equiv.) were cooled to 0 °C. The reaction mixture was then stirred for 1 h on a warm water bath as the temperature was gradually raised from 40 to 80 °C. Hydrogen chloride and the excess of thionyl chloride were removed by an air stream, then the acid chloride (85 ml) was distilled under reduced pressure from the residue (45–50 °C, 40 mmHg). A solution of the acid chloride in dichloromethane (200 ml) was cooled to −70 °C then added to an aqueous solution of dimethylamine (40%, 200 ml) at −30 °C. After 30 min, the mixture was warmed up to room temperature and more dichloromethane was added. The organic phase was separated, dried over magnesium sulfate, filtered and the solvent was evaporated under reduced pressure. The amide (103 g) was distilled from the residue (68–72 °C, 14 mmHg). Since the product still contained isobutyric acid (15%), it was dissolved in dichloromethane and stirred with solid potassium carbonate for 1 h. After filtration and evaporation of the solution, the product obtained was pure enough to be used directly in the next step; δ_H(200 MHz, $CDCl_3$) 1.10 (6 H, d, *J* 6.6), 2.81 (1 H, heptuplet, *J* 6.6), 2.92 (3 H, s), 3.02 (3 H, s).

N,*N*,2,2-*Tetramethyl*-3-*hydroxypropanamide* (**13**).—*n*-Butyllithium (44 ml of a 2.5 M solution in hexane, 0.11 mol) was added to a solution of 2,2,6,6-tetramethylpiperidine (16.8 ml, 0.1 mol, 1.05 equiv.) in dry tetrahydrofuran (120 ml) and hexamethylphosphoramide (12 ml) at −78 °C, and the resultant solution was stirred for 15 min. A solution of amide **12** (11 g, 0.096 mol) in tetrahydrofuran (20 ml) was then added and the mixture was stirred for 20 min at 0 °C then cooled to −40 °C. Solid paraformaldehyde (3.3 g, 0.11 mol) was added next, then the mixture was stirred at 10 °C for 15 min and at 45 °C for 30 min before being cooled to room temperature. Ice was then added and the reaction mixture was neutralized with hydrochloric acid (6 M). The tetrahydrofuran was removed under reduced pressure and the residual solution was extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and evaporated. The residue was dissolved in diethyl ether and percolated through silica gel to remove the hexamethylphosphoramide. The desired amide **13** (5.4 g, 39%) was isolated by column chromatography on silica gel (pentane : diethyl ether 1 : 1→diethyl ether) using the following procedure; a column of 4 cm diameter is filled to a height of 15 cm with silica (volume silica = 190 ml); the column is packed using pentane–diethyl ether (50 : 50); elution is performed successively with 100 ml of pentane–diethyl ether (50 : 50), 100 ml of pentane–diethyl ether (25 : 75), 100 ml of pentane–diethyl ether (12.5 : 87.5) and 100 ml of pure diethyl ether. The R_f value of the desired compound (eluent 70% ethyl acetate in toluene) = 0.24; δ_H(200 MHz, $CDCl_3$) 1.25 (6 H, s), 3.0 (6 H, s), 3.48 (2 H, s), 3.82 (1 H, br s).

3-(*Dimethylamino*)-2,2-*dimethylpropan*-1-*ol* (**2**).—Boron trifluoride–diethyl ether (6.00 ml, 48 mmol, 1.17 equiv.) followed by borane–dimethyl sulfide (10.5 ml, 105 mmol, 2.6 equiv.) were added to a solution of amide **13** (6.0 g, 41 mmol), in tetrahydrofuran (80 ml) at 0 °C. The reaction mixture was warmed to 45 °C over 30 min then cooled down before small pieces of ice were carefully added to destroy the excess borane (**caution**—exothermic reaction). Tetrahydrofuran was evaporated under reduced pressure, then the mixture was acidified with hydrochloric acid (6 M) and briefly warmed until a clear solution was obtained. The cooled reaction mixture was made alkaline with aqueous sodium hydroxide solution (4 M) then extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and slowly evaporated under reduced pressure. The residue was distilled (85 °C, 20 mmHg) to yield the amino alcohol (6.8 g, 47%); ν_{max}(KBr)/cm^{-1} 3357 (br, m), 2952 (s), 2830 (m), 2800 (m), 1463 (m), 1045 (s), 842 (w), 733 (m); δ_H(200 MHz, $CDCl_3$) 0.92 (6 H, s), 2.30 (6 H, s), 2.36 (2 H, s), 3.50 (2 H, s); δ_C(50.3 MHz, $CDCl_3$) 23.98, 35.26, 48.07, 71.74, 73.99; *m*/*z* (ESMS), 132, ($M^{\cdot+}$ + 1).

2-(*N*,*N*-Dimethylaminomethyl)-2-(hydroxymethyl)adamantane (7). *Adamantane*-2-*carbaldehyde*.—Sodium hydride (3.16 g, 79 mmol as a 60% dispersion in mineral oil) was washed three times with dry hexane, then dimethyl sulfoxide (120 ml, stored over molecular sieves) was added followed by trimethylsulfoxonium iodide (16.5 g, 75 mmol) over a 5 min period. Fifteen minutes after the gas evolution had ceased, the flask was cooled to room temperature and adamantanone (10 g, 67 mmol) was added over 3–5 min. The reaction mixture was stirred for 1 h at room temperature followed by 1.5 h at 55 °C, then poured into ice water (300 ml) which caused the epoxide to precipitate. The mixture was extracted twice with hexane, then the combined hexane solution was dried with magnesium sulfate, filtered and evaporated to give the crude epoxide (10.3 g, 95%). Boron trifluoride–diethyl ether (5.60 g, 39.5 mmol) was added to the crude epoxide dissolved in dry benzene, and the reaction mixture was stirred for 10 min then poured into ice water. The layers were separated and the benzene layer washed twice with water. The combined aqueous layers were re-extracted with benzene, then the combined benzene solution was dried with sodium sulfate, filtered and evaporated to give the unstable aldehyde (9.2 g, 90%); ν_{max}(KBr)/cm^{-1} 2903 (s), 2851 (s), 2697 (m), 1723 (s), 1451 (s), 1267 (w), 1082 (m), 939 (w), 739 (s); δ_H(200 MHz, $CDCl_3$) 1.62–1,92 (12 H, complex), 2.37–2.43 (3 H, complex), 9.73 (1 H, s); *m*/*z* 164 ($M^{\cdot+}$, 52%), 135 (98), 121 (12), 105 (56), 93 (56), 91 (50), 79 (100), 67 (66), 58 (80), 41 (68).

Adamantane-2-*carboxylic acid*.—Jones reagent (prepared by dissolving 50 g chromium(III) oxide and 41.5 ml concentrated sulfuric acid in 190 ml water) was added slowly to a solution of adamantane-2-carbaldehyde (9.2 g, 56 mmol) in diethyl ether (150 ml) over 1 h at 10 °C. The reaction mixture was then stirred for 2 h at 20 °C, poured into water, and the organic layer was separated. The aqueous phase was extracted with dichloromethane and the combined organic phase was washed with water, dried over magnesium sulfate, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (hexane : ethyl acetate 95 : 5→70 : 30) to give the carboxylic acid (8.5 g, 85%); ν_{max}(KBr)/cm^{-1} 3436 (br), 2903 (s), 2851 (s), 1682 (s), 1451 (s), 1415 (m), 1272 (s), 1103 (s), 939 (m); δ_H(500 MHz, $CDCl_3$) 1.63–1.66 (2 H, complex), 1.74–1.78 (4 H, complex), 1.85–1.93 (6 H, complex), 2.35 (2 H, br s), 2.67

(1 H, br s); *m/z* 180 ($M^{\cdot+}$, 22%), 162 (30), 137 (21), 134 (75), 120 (14), 105 (14), 91 (64), 79 (100), 67 (56), 41 (76).

Methyl adamantane-2-carboxylate (**18**).—A solution of diazomethane in diethyl ether was added dropwise to a solution of adamantane-2-carboxylic acid (8.4 g, 47 mmol) in dry diethyl ether (50 ml) at 0 °C until the reaction mixture became yellow; it was stirred for a further 30 min at room temperature. The excess of diazomethane was destroyed by the addition of a small amount of silica gel which was then removed by filtration. Evaporation of the solvent left a residue which was purified by column chromatography on silica gel (hexane : ethyl acetate 96 : 4) yielding the methyl ester (8.15 g, 90%); ν_{max}(KBr)/cm^{-1} 2913 (s), 2851 (s), 1732 (s), 1451 (m), 1339 (w), 1267 (m), 1200 (s), 1174 (s), 1097 (s), 1046 (m), 1010 (m); δ_H(500 MHz, $CDCl_3$) 1.59–1.61 (2 H, complex), 1.71–1.76 (4 H, complex), 1.80–1.88 (6 H, complex), 2.31 (2 H, br s), 2.58 (1 H, br s), 3.67 (3 H, s); *m/z* 193 ($M^{\cdot+} - 1$, 58%), 165 (8), 162 (18), 149 (16), 135 (50), 119 (20), 97 (24), 91 (42), 79 (50), 55 (72), 41 (100).

Methyl 2-(N,N-dimethylaminomethyl)adamantane-2-carboxylate (**23**).—*n*-Butyllithium (14.17 ml of a 1.6 M solution in hexane, 22.66 mmol, 1.1 equiv.) was added to a solution of diisopropylamine (2.97 ml, 22.66 mmol, 1.1 equiv.) in tetrahydrofuran (60 ml) at 0 °C. The reaction mixture was stirred for 30 min then cooled to −50 °C before a solution of methyl adamantane-2-carboxylate (4 g, 20.6 mmol) in tetrahydrofuran (10 ml) was added. After 30 min stirring, hexamethylphosphoramide (10 ml) was added and the mixture was cooled down to −78 °C before *N*,*N*-dimethylmethyleneammonium iodide (6.86 g, 37 mmol) was added in one portion, then the reaction mixture was stirred at −78 °C for 1 h and at room temperature for 4 h. After being poured into saturated aqueous sodium chloride, the reaction mixture was extracted with pentane (3 × 80 ml). The combined organic phase was washed with saturated aqueous sodium chloride then with water, dried over magnesium sulfate, filtered, and evaporated under reduced pressure to give a residue which was purified by column chromatography on silica gel (hexane : ethyl acetate 90 : 10→70 : 30). The desired product was obtained as a colourless oil (2.2 g, 43%); ν_{max}(KBr)/cm^{-1} 2913 (s), 2872 (s), 2769 (s), 1736 (s), 1456 (m), 1246 (s), 1205 (s), 1097 (s), 1072 (s), 1041 (m); δ_H(500 MHz, $CDCl_3$) 1.61–1.68 (7 H, complex), 1.80–1.82 (3 H, complex), 1.86–1.89 (2 H, complex), 1.95–1.97 (2 H, complex), 2.22 (6 H, s), 2.67 (2 H, s), 3.69 (3 H, s); *m/z* 151 (2), 135 (2), 114 (13), 91 (26), 77 (28), 67 (16), 58 (100).

2-(N,N-Dimethylaminomethyl)-2-hydroxymethyl)adamantane (**7**).—A solution of methyl 2-(*N*,*N*-dimethylaminomethyl)-adamantane-2-carboxylate (2.2 g, 8.76 mmol) in dry diethyl ether (10 ml) was added to a suspension of lithium aluminium hydride (832 mg, 21.9 mmol, 2.5 equiv.) in dry diethyl ether (30 ml) at 0 °C. After 30 min at 0 °C the reaction mixture was stirred overnight at room temperature. The excess of lithium aluminium hydride was destroyed by stirring with solid sodium sulfate decahydrate until a white crystalline solid was obtained. After removal of the solid by filtration and evaporation of the solvent under reduced pressure, the residue was purified by column chromatography [isooctane : acetone–ammonia (98 : 2) 6 : 4], to yield the amino alcohol (1.7 g, 87%); (Found: C, 75.15; H, 11.38; N, 6.16. Calc. for $C_{14}H_{25}NO$: C, 75.28; H, 11.28; N, 6.27%); ν_{max}(KBr)/cm^{-1} 3420 (br s), 2912 (s), 2865 (s), 2771 (s), 2668 (w), 1455 (s), 1248 (w), 1065 (m), 1032 (s); δ_H(500 MHz, $CDCl_3$) 1.49–1.55 (4 H, complex), 1.65 (2 H, app. br s), 1.73 (2 H, app. br s), 1.82 (1 H, m), 1.86 (1 H, m), 1.99 (2 H, complex), 2.06 (2 H, complex), 2.29 (6 H, s), 2.70 (2 H, s), 3.83 (2 H, s); δ_C(50.3 MHz, $CDCl_3$) 27.72, 28.44, 31.17, 32.57, 32.81, 39.42, 48.38, 68.18, 69.86; *m/z* 223 ($M^{\cdot+}$, 3%), 105 (7), 91 (31), 79 (35), 67 (18), 58 (100).

***N*,*N*-Dimethyl-2-hydroxymethyl-2-propylpentylamine (3).** *Methyl 2-propylpentanoate* (**14**).—2-Propylpentanoic acid (10.0 g, 69.3 mmol) was converted into its methyl ester using the procedure described above for **18**. The ester (10.2 g, 93%) was isolated by distillation (bp 85 °C, 20 mmHg): ν_{max}(KBr)/cm^{-1} 2958 (s), 2874 (s), 2256 (w), 1738 (s), 1466 (s), 1435 (s), 1379 (s), 1264 (m), 1240 (s), 1194 (s), 1170 (s), 1148 (s), 1106 (m), 1108 (m), 918 (s), 830 (m), 735 (s), 648 (w); δ_H(500 MHz, $CDCl_3$) 0.89 (6 H, t, *J* 7.20), 1.19–1.31 (4 H, m), 1.37–1.44 (2 H, m), 1.54–1.62 (2 H, m), 2.37 (1 H, tt, *J* 9.25 and 5.26), 3.68 (3 H, s); δ_C(50.3 MHz, $CDCl_3$) 13.74, 20.47, 34.51, 45.06, 50.98, 176.77; *m/z* 143 ($M^+ - CH_3$, 1%), 127 (5), 116 (50), 44 (100), 69 (4), 57 (51).

Methyl 2-(N,N-dimethylaminomethyl)-2-propylpentanoate hydrochloride (**19**).—After alkylation of the methyl ester **14** (4 g, 25.28 mmol) with Eschenmoser's salt as described above for compound **23** and isolation as the hydrochloride, the desired product was obtained (3.65 g, 57%): ν_{max}(KBr)/cm^{-1} 3043 (s), 2965 (s), 2875 (m), 2360 (s), 1723 (s), 1474 (s), 1464 (s), 1386 (m), 1229 (s), 1159 (s); δ_H(500 MHz, $CDCl_3$) 0.94 (6 H, t, *J* 7.2), 1.12–1.30 (4 H, m), 1.74 (4 H, m), 2.81 (6 H, d, *J* 3.9), 3.25 (2 H, d, *J* 4.6), 3.75 (3 H, s); δ_C(50.3 MHz, $CDCl_3$) 13.99, 16.67, 34.86, 45.77, 48.82, 52.51, 61.76, 77.14, 174.91.

N,N-Dimethyl-2-hydroxymethyl-2-propylpentylamine (**3**).—Lithium aluminium hydride reduction of amino ester **19** (1.18 g, 4.7 mmol) in the usual manner followed by distillation (bp 82 °C, 1 mmHg) gave the desired amino alcohol **3** (1.82 g, 66%); (Found: C, 70.60; H, 13.50; N, 7.51. Calc. for $C_{11}H_{25}NO$: C, 70.53; H, 13.45; N, 7.48%); ν_{max}(KBr)/cm^{-1} 3422 (m), 2956 (s), 2931 (s), 2870 (s), 2828 (s), 2778 (s), 1461 (s), 1376 (m), 1329 (m), 1254 (m), 1161 (m), 1098 (m), 1042 (s), 913 (m); δ_H(500 MHz, $CDCl_3$) 0.89 (6 H, t, *J* 6.9), 1.13–1.32 (8 H, m), 2.30 (6 H, s), 2.39 (2 H, s), 3.53 (2 H, s); δ_C(50.3 MHz, $CDCl_3$) 14.71, 15.87, 35.08, 39.88, 48.27, 66.98, 71.07; *m/z* 187 ($M^{\cdot+}$, 3%), 166 (3), 124 (3), 121 (9), 91 (3), 73 (3), 58 (100), 41 (15).

1-(*N*,*N*-Dimethylaminomethyl)-1-(hydroxymethyl)cyclobutane (4). *Methyl cyclobutanecarboxylate* (**15**).—Treatment of cyclobutanecarboxylic acid (2.9 g, 0.029 mmol) with diazomethane as described above, followed by distillation (bp 36 °C, 16 mmHg), yielded the methyl ester **15** (3.1 g, 94%): ν_{max}(KBr)/cm^{-1} 2985 (s), 2954 (s), 2872 (w), 1733 (s), 1436 (s), 1359 (s), 1251 (s), 1169 (s), 1056 (m); δ_H(500 MHz, $CDCl_3$) 1.79–1.87 (1 H, m), 1.89–1.96 (1 H, m), 2.10–2.16 (2 H, m), 2.19–2.27 (2 H, m), 3.08 (1 H, p, *J* 8.6), 3.61 (3 H, s); *m/z* 114 ($M^{\cdot+}$, 6%), 83 (20), 72 (10), 55 (100).

Methyl 1 (N,N-dimethylaminomethyl)cyclobutane-1-carboxylate hydrochloride (**20**).—After alkylation of ester **15** (3.00 g, 26.3 mmol) with Eschenmoser's salt as described above, the product was isolated as the hydrochloride (2.18 g, 40%): ν_{max}(KBr)/cm^{-1} 3415 (s), 2954 (s), 2667 (br, m), 2472 (m), 1731 (s), 1636 (w), 1467 (m), 1344 (w), 1287 (w), 1221 (s), 1159 (s), 1097 (m); δ_H(500 MHz, $CDCl_3$) 2.07–2.12 (2 H, m), 2.33–2.39 (2 H, m), 2.53–2.59 (2 H, m), 2.71 (6 H, s), 3.51 (2 H, s), 3.83 (3 H, s); *m/z* 84 (3%), 58 (100).

1-(N,N-Dimethylaminomethyl)-1-(hydroxymethyl)cyclobutane (**4**).— Lithium aluminium hydride reduction of amino ester **20** (1.4 g, 6.7 mmol) in the usual manner followed by recrystallization gave the desired amino alcohol **4** (1.82 g, 66%, mp 25–27 °C); ν_{max}(KBr)/cm^{-1} 3323 (br s), 3046 (m), 2944 (s), 2831 (s), 1598 (m), 1456 (m), 1262 (s), 1164 (m), 1031 (s), 733 (s); δ_H(500 MHz, $CDCl_3$) 1.76–1.86 (5 H, m), 1.90–2.01 (1 H, m), 2.22 (6 H, s), 2.47 (2 H, s), 3.38 (2 H, s), 5.96 (1 H, br s); *m/z* 142 ($M^{\cdot+} - 1$, 1%), 128 ($M^{\cdot+} - CH_3$, 2), 84 (3), 58 (100).

1-(*N*,*N*-Dimethylaminomethyl)-1-(hydroxymethyl)cyclopentane (5). *Methyl cyclopentanecarboxylate* (**16**).—Treatment of cyclopentanecarboxylic acid (10 g, 87 mmol) with diazomethane as described above, followed by distillation (bp 49 °C, 14 mmHg) gave the methyl ester **16** (10.6 g, 95%): ν_{max}(KBr)/cm^{-1} 2955 (s), 2872 (s), 1737 (s), 1431 (m), 1361 (m), 1196 (s), 1002 (w); δ_H(500 MHz, $CDCl_3$) 1.50–1.59 (2 H, m), 1.63–1.72 (2 H, m), 1.73–1.80 (2 H, m), 1.83–1.89 (2 H, m), 2.70 (1 H, p, *J* 8.0), 3.64 (3 H, s); *m/z* 128 ($M^{\cdot+}$, 6%), 100 (16), 97 (17), 87 (100), 69 (54), 67 (16), 55 (22), 41 (45).

Methyl 1-(N,N-dimethylaminomethyl)cyclopentane-1-carb-

oxylate hydrochloride (**21**).— Alkylation of the methyl ester **16** (4.0 g, 13 mmol) with Eschenmoser's salt as described above followed by purification on silica (1 : 1 hexane–ethyl acetate) and isolation as the hydrochloride gave compound **21** (2.0 g, 35%): ν_{max}(KBr)/cm^{-1} 3413 (br s), 3025 (w), 2955 (s), 2872 (w), 2649 (m), 1725 (s), 1633 (w), 1455 (m), 1267 (m), 1173 (s), 726 (s); δ_H(500 MHz, $CDCl_3$) 1.51 (1 H, m), 1.75–1.85 (4 H, m), 1.88–1.93 (2 H, m), 2.16–2.22 (2 H, m), 2.78 (6 H, d, *J* 4.9), 3.36 (2 H, d, *J* 5.8), 3.78 (3 H, s); *m*/*z* 186 ($M^{\bullet+}$ − Cl, 2%), 171 (2), 81 (3), 58 (100).

1-(*N*,*N*-*Dimethylaminomethyl*)-1-(*hydroxymethyl*)*cyclopentane* (**5**).—Lithium aluminium hydride reduction of the amino ester **21** (2.00 g, 10.8 mmol) in the usual way followed by distillation (bp 105 °C, 0.05 mmHg) gave amino alcohol **5** (1.18 g, 70%); (Found: C, 67.88; H, 12.13; N, 9.08. Calc. for $C_9H_{19}NO$: C, 68.74; H, 12.18; N, 8.91%); ν_{max}(KBr)/cm^{-1} 3413 (s), 2943 (s), 2861 (s), 2825 (s), 2778 (s), 1461 (s), 1255 (m), 1155 (m), 1038 (s); δ_H(500 MHz, $CDCl_3$) 1.20–1.26 (2 H, m), 1.56–1.61 (4 H, m), 1.62–1.68 (2 H, m), 2.27 (6 H, s), 2.48 (2 H, s), 3.49 (2 H, s), 6.31 (1 H, br s); *m*/*z* 157 ($M^{\bullet+}$; 2%), 126 (1), 58 (100).

1-(*N*,*N*-Dimethylaminomethyl)-1-(hydroxymethyl)cyclohexane (6). *Methyl cyclohexanecarboxylate* (**17**).—Treatment of cyclohexanecarboxylic acid (10 g, 78 mmol) with diazomethane as described above followed by distillation (bp 68 °C, 15 mmHg) gave the methyl ester (10.6 g, 96%): ν_{max}(KBr)/cm^{-1} 2933 (s), 2851 (s), 1737 (s), 1451 (m), 1246 (s), 1169 (s), 1041 (m); δ_H(500 MHz, $CDCl_3$) 1.16–1.30 (3 H, m), 1.34–1.46 (2 H, m), 1.60–1.64 (1 H, m), 1.72–1.76 (2 H, m), 1.86–1.90 (2 H, m), 2.28 (1 H, tt, *J* 11.1 and 3.64), 3.64 (3 H, s); *m*/*z* 142 ($M^{\bullet+}$, 20%), 127 ($M^{\bullet+}$ − CH_3, 8), 110 ($M^{\bullet+}$ − MeOH, 18), 87 (66), 74 (32), 55 (100).

Methyl 1-(*N*,*N*-*dimethylaminomethyl*)*cyclohexane*-1-*carboxylate hydrochloride* (**22**).—Alkylation of the methyl ester **17** (2.0 g, 10 mmol) with Eschenmoser's salt as described above was followed by isolation as the hydrochloride. After recrystallization from ethyl acetate, the amino ester hydrochloride (1.32 g, 40%) was obtained: ν_{max}(KBr)/cm^{-1} 3413 (br s), 2943 (s), 2849 (w), 1725 (s), 1455 (m), 1261 (m), 1161 (m), 738 (s); δ_H(500 MHz, $CDCl_3$) 1.39–1.41 (1 H, m), 1.50–1.64 (7 H, m), 2.10–2.13 (2 H, m), 2.78 (6 H, br s), 3.27 (2 H, br s), 3.79 (3 H, s); *m*/*z* 199 ($M^{\bullet+}$, HCl, 2%), 81 (4), 58 (100).

1-(*N*,*N*-*Dimethylaminomethyl*)-1-(*hydroxymethyl*)*cyclohexane* (**6**).—Lithium aluminium hydride reduction of the amino ester **22** (1.15 g, 4.9 mmol) in the normal manner followed by distillation (bp 180 °C, 0.05 mm Hg) yielded the amino alcohol **6** (0.62 g, 75%); (Found: C, 69.99; H, 12.53; N, 8.21. Calc. for $C_{10}H_{21}NO$: C, 70.12; H, 12.36; N, 8.18%); ν_{max}(KBr)/cm^{-1} 3417 (br s), 2925 (s), 2853 (s), 2781 (s), 1457 (s), 1252 (m), 1150 (m), 1042 (s), 1006 (m); δ_H(500 MHz, $CDCl_3$) 1.20–1.24 (2 H, m), 1.30–1.35 (1 H, m), 1.40–1.50 (7 H, m), 2.30 (6 H, s), 2.38 (2 H, s), 3.60 (2 H, s); *m*/*z* 126 (2), 96 (3), 81 (5), 67 (10), 58 (100), 42 (8).

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