Efficiency of proton transfer catalysis. Intramolecular general acid catalysis of the hydrolysis of dialkyl acetals of benzaldehyde

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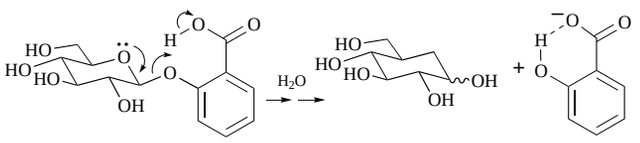
Intramolecular general acid catalysis is demonstrated for the first time for the hydrolysis of dialkyl acetals of benzaldehyde.† Effective molarities (EM) ranging from 810 to over 10^4 mol dm^{-3} are observed for the hydrolysis of the carboxylic acid 4 and for the three dimethylammonium systems $5{\cdot}H^+$–$7{\cdot}H^+$, which show pH–rate profile plateaux extending as far as pH 7–9. Reactivity is shown to depend significantly on the strength of the general acid involved. Efficient catalysis depends on the development of a strong hydrogen bond in the transition state for the reaction, but efficiency is reduced when significant intramolecular hydrogen bonding is present in the ground state. The most reactive acetal, the carboxylic acid 4, is hydrolysed with a halflife of 1.15 s at 20 °C, fast enough to become complicated kinetically by the build up of the hemiacetal intermediate (Scheme 2). It does not, however, show the highest EM.

General acid catalysis is an essential part of the mechanism of action of many—perhaps most—enzymes. It is particularly clearly defined in the large class of glycosyl transferases, which use an active site COOH group as the general acid.[1] Typical glycoside substrates are extremely unreactive near pH 7, so this catalysis must be highly efficient; an unsolved question is whether this can be accounted for by general acid catalysis alone, operating in the special microenvironment of an active site. The activity of many glycohydrolases depends on a second active site carboxyl, active in the ionised, COO^-, form, which plays an essential role. This acts in some cases at least as a nucleophilic catalyst, the resulting double displacement mechanism accounting for the observed retention of configuration at the anomeric centre. However, a second carboxyl is not an absolute requirement: it is not present in some (inverting) enzymes, where a molecule of water presumably acts as the primary nucleophile;[1] and in one mutant can be replaced rather effectively by formate anion from solution,[2] suggesting that its 'tight'[3] positioning is not crucial. This is consistent with another mutagenesis experiment, with a retaining glycosidase, in which replacement of the active site glutamate by aspartate did not change the mechanism and reduced activity a relatively modest 2500-fold.[4]

We are exploring the limits of efficiency of general acid catalysis in intramolecular model systems, in the presence and absence of potential nucleophilic assistance.[5,6] Intramolecular general acid catalysis is intrinsically inefficient:[7] it is often not detectable in the hydrolysis of acetals with neighbouring carboxy groups,[8] and even the most efficient classical model (salicyl β-D-glucopyranoside **1**) had to be studied at elevated temperature (91.3 °C),[9] despite the good, phenolic leaving group, and even though it takes advantage of the formation of a strong intramolecular hydrogen-bond in the salicylate anion (**2**) produced.

We have identified the development of such strong hydrogen bonds as the key to efficient intramolecular general acid catalysis,[5,6] and believe they are likely to be key features of general acid-base catalysis in enzyme reactions. In biological glycosyl transfers this would involve the formation of a strong hydrogen bond from COOH to a developing alkoxide anion.We report results with three structurally unrelated model systems, based on three different general acids, which confirm that such



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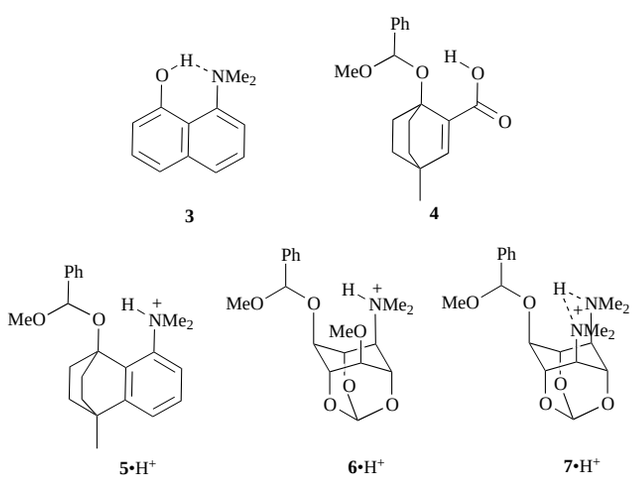
interactions can lead to efficient general acid catalysis of the hydrolysis of dialkyl acetals.

Strong intramolecular hydrogen bonds are rarely observed in water, the groups concerned being generally solvated better by H-bonding to the solvent than to each other. The design of our test systems is based on two structures known to retain strong intramolecular hydrogen bonds in aqueous solution. These are the salicylate anion (**2**) and the peri-hydroxynaphthalene system **3**, related to proton sponge. The rates of reactions like **1**



3 **4**

5•H^+ **6**•H^+ **7**•H^+

(arrows) are known to be sensitive to the basicity of the leaving group,[10] so one predictable result of making the leaving group an alkoxide will be a sharp decrease in reactivity. To compensate we use reactive benzaldehyde acetals. The resulting systems **4** and $5{\cdot}H^+$ retain the eclipsed geometry of the all-aromatic systems, so can form hydrogen bonds within planar six-membered rings; but the detailed geometry of the ring is modified, by the introduction of one single sp^3C–sp^2C bond in each case. In the third test compound, based on inositol, the basic planar geometry of the cyclic hydrogen-bonding system is

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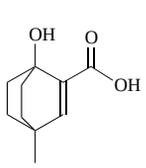
retained in the conjugate acid (**6**·$\mathbf{H}^+$), but the system is now all-aliphatic: both framework C–C bonds connect sp^3-centres, and should be slightly longer than in **3** or **4**. Finally, we have briefly investigated the diamine **7**, of interest because its geometry favours bifurcate hydrogen-bonding between the leaving group oxygen and the two amino groups.

All of these systems are new, and their syntheses far from trivial. Since this work is concerned primarily with their reactivity, the successful synthetic routes are summarised, and syntheses described in detail, in the Experimental section.

Kinetic methods and results

Reactions were followed under pseudo first order conditions, in aqueous solution at a constant ionic strength of 1 mol dm^{-3} (KCl), at 20 °C for **4** and **5**, and at 80 °C for the much less reactive **6** and **7**. The appearance of benzaldehyde was monitored at 248 nm in all cases, generally in the thermostatted cell compartment of a UV–VIS spectrophotometer. The systems used in this work have in common the PhCH(OMe)–O structure of the benzaldehyde acetal system, and a neighbouring Brønsted acid–base group. All are hydrolysed to benzaldehyde, methanol and the parent alcohol (**8–11**, respectively), but their



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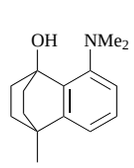

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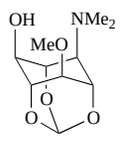

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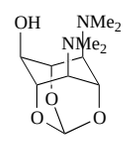

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reactivities are very different. Their reactions are described separately.

The bicyclic acetal acid **4** is highly reactive, and its hydrolysis was followed at 20 °C. For runs above pH 6.5 the reaction was followed in the spectrophotometer and showed simple first-order kinetics, but in the pH range 0–6.5, where the halflife was of the order of 1 s, measurements required the stopped-flow method. These latter experiments showed marked deviations from first-order kinetics: a reproducible induction period was observed, after which the data could be fitted to a first-order equation. Such an induction period is typical for consecutive reactions $\mathbf{A} \xrightarrow{k_1} \mathbf{B} \xrightarrow{k_2} \mathbf{C}$ [11] in which an intermediate **B** builds up to a (steady) finite concentration, after which point the formation of the final product **C** shows first-order behaviour. The rate law for the appearance of **C** is then expressed as eqn. (1).

$$[\mathbf{C}]_t = [\mathbf{C}]_0 - [\mathbf{C}]_\infty \left\{ \frac{(k_1 e^{-k_2 t} - k_2 e^{-k_1 t}}{k_1 - k_2} \right\} \qquad (1)$$

The kinetic measurements (of absorbance *vs.* time) produced a good fit to eqn. (1), giving rise to two sets of rate constants (supplementary Table S1; see Table 1). These correspond to k_1 and k_2, but because of the symmetry of the equation cannot directly be identified with the first and second steps of the reaction. In supplementary Table 2 they are labelled simply k_{fast} and k_{slow}, according to their relative magnitudes. These can be identified with two slow steps of the mechanism as follows.

One of the two sets shows a well-defined linear dependence on the concentration of the buffer. The other set varies little and apparently randomly with buffer concentration. Such kinetic behaviour has been observed previously by Jensen,[12] especially for the hydrolysis of reactive dialkyl acetals of benzaldehyde.[13] It was established that the hemiacetal **12** was an intermediate, which accumulated during the hydrolysis reaction. Two slow kinetic steps were observed (Scheme 1). In the first of these the acetal is cleaved in a H_3O^+-catalysed reaction to an alcohol and an oxocarbenium ion, which has a short

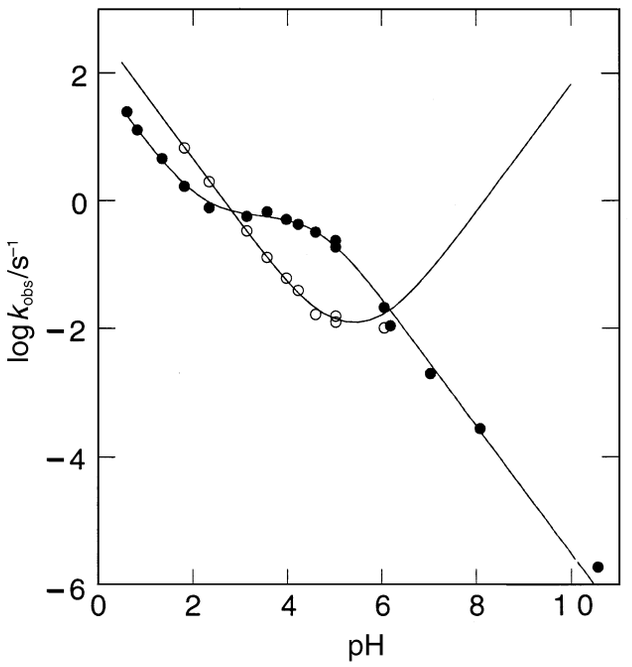
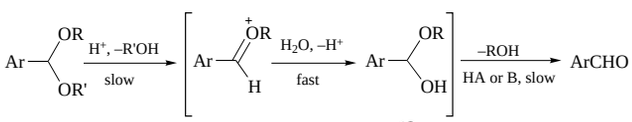


Fig. 1 pH–rate profiles for the two consecutive reactions observed in the hydrolysis of acetal **4**. Closed circles represent the rate of disappearance of **4**, open circles that of the hydrolysis of the hemiacetal **11**. The curves are calculated, using for the reaction of **3** the rate and dissociation constants shown in Table 2: and for the hydrolysis of **11** k_{H^+} 460 and k_{OH} 1.2 × 10^6 dm^3 mol^{-1} s^{-1}, respectively.



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Scheme 1

lifetime in water[14] and is rapidly hydrated to give the hemiacetal **12**, which accumulates. In the second slow step the hemiacetal is hydrolysed to benzaldehyde and a second molecule of alcohol. In these reactions hemiacetal hydrolysis is generally faster than acetal cleavage, and is general acid–base catalysed.

The hydrolysis of the unsymmetrical dialkyl acetal **4** behaves similarly, though it is somewhat more complicated in that two alternative hemiacetals can be formed. The ambiguities are simply resolved by considering the pH–rate profiles for the two consecutive reactions. The open circles of Fig. 1 represent rate constants for the step showing significant buffer catalysis, obtained by extrapolating to zero buffer concentration. The initial cleavage of the acetal **4** is not expected to show catalysis by external general acids, and certainly not by general bases, so the inference is clear that this step is the hydrolysis of the hemiacetal, and thus necessarily the second step of the reaction. This conclusion is confirmed by comparing the rate constants obtained with published data for the hydrolysis of benzaldehyde hemiacetals (Table 1). The comparison makes clear that the methyl hemiacetal is involved. Capon *et al.*[15] have published the pH–rate profile for the hydrolysis of benzaldehyde methyl hemiacetal (**12**, Ar = Ph, R = Me) over the pH range 3.7–6.3 at 15 °C. The reaction is catalysed by specific and general acids and bases and so shows a U-shaped pH rate profile. The U-shaped curve drawn in Fig. 1 is the calculated pH–rate profile for the hydrolysis of PhCH(OH)OMe under our conditions, based on a short extrapolation of the Capon data to 20 °C.[16] It fits our data well, whereas Jensen's data for the hydrolysis of PhCH(OH)OBu^t show that a derivative of a tertiary alcohol would be hydrolysed faster.

If the intermediate is benzaldehyde methyl hemiacetal the initial acetal cleavage must involve breaking the bond to the

bicyclic alcohol oxygen, so that the set of data points identified as k_1 represents the pH–rate profile for this reaction (Scheme 2). The feature of interest for this work is the plateau which extends from pH 2.5–4.5. This represents the spontaneous hydrolysis of the free acid form of **4**: at pH < 2.5 its H_3O^+-catalysed reaction is observed (k_H is comparable to values observed for similar dialkyl acetals of benzaldehyde[17]), while at higher pH the rate falls off exponentially as the acid is converted to the anion.

The data for this reaction were fitted to eqn. (2).

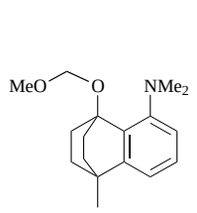
$$k_1 = (k_0 + k_H a_H)\left[\frac{a_H}{a_H + K_a}\right] \quad (2)$$

The rate and dissociation constants obtained are summarised in Table 2. The apparent pK_a of 4.6 is consistent with the ionisation of an acrylic acid.[18]

The tricyclic acetal **5** could not be purified to homogeneity because the acetal functional group was unstable to chromatography (see the Experimental section). It could however be prepared without major impurity apart from the dimethylaminoalcohol **9**. Since this is a hydrolysis product it did not interfere with our kinetic measurements.

The hydrolysis of **5** also measured at 20 °C, obeys first-order kinetics over the pH range 1–6.5. Above pH 6.5 the reaction is slower, but no longer follows first-order kinetics. This behaviour, which prevents precise measurement of the kinetic pK_a of **5**, is not well-defined and is as yet unexplained; but it is unlikely to be relevant to the present discussion. Over the pH range 1–6 of interest the rate was effectively constant with a halflife of *ca.* 10 min (Fig. 2), and no significant buffer catalysis was apparent. This plateau represents the rate constant for the hydrolysis of the acetal conjugate acid (**5**·$\mathbf{H}^+$), in which the dimethylammonium group is available for intramolecular general acid catalysis (Scheme 3). The H_3O^+-catalysed reaction is too slow to be observed above pH 1, either because it is unusually slow or because the intramolecular reaction is particularly fast—or both. The rate constant for the hydronium ion catalysed reaction of the protonated acetal (Scheme 3) is expected to be slow because reaction through a dication will suffer from unfavourable electrostatic effects.

It is possible to fit the pH–rate data to the eqn. (2) used above for the data for the hydrolysis of **4**. The fit (Fig. 2) has a poor correlation coefficient because of the minimal contribution from k_H and the poor quality of the data above pH 6, but gives a good value for k_0 and sensible values for k_H and K_a (Table 2). The estimated pK_a of 6.9 ± 0.2 is the same as that measured for the corresponding formaldehyde acetal **13**.



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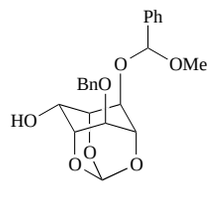

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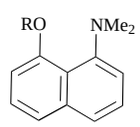

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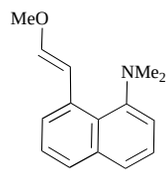

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The inositol-based acetals **6** and **7** are much less reactive than **4** or **5**, and their reactions were followed at 80 °C. For comparison we measured also the hydrolysis of the compound **14**, lacking a catalytic group, under the same conditions. The acetals were hydrolysed cleanly at this temperature to methanol, benzaldehyde and the parent alcohol, with no sign of hydrolysis of the

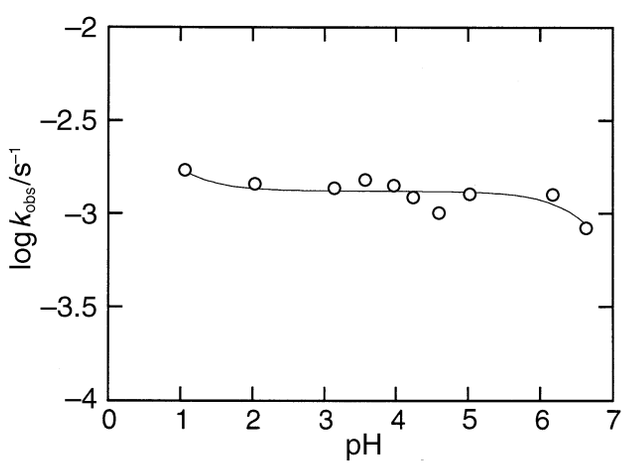


Fig. 2 pH–rate profile for the hydrolysis of the acetal group of **5**, at 20 °C and ionic strength 1.0 mol dm^{-3}. The points are experimental, the curve calculated using the rate and dissociation constants shown in Table 2.

Table 1 Hydrolysis data for hemiacetals PhCH(R)OH[13,15]

R	*T*/°C	k_{H^+}/ dm^3 mol^{-1} s^{-1}	k_{H_2O}/s^{-1}	k_{OH^-}/ dm^3 mol^{-1} s^{-1}
? (This work)	20	460 ± 24	0.008 ± 0.001	2.01 ± 0.4 10^6
Me	15	261	0.005 18	6.87 × 10^5
Bu^t	25	2600		

Table 2 Kinetic parameters for the hydrolysis of acetals **4**–**7** and **14**[a]

	4 (at 20 °C)	**5** (at 20 °C)	**6** (at 80 °C)	**7** (at 80 °C)	**14** (at 80 °C)
k_0/s^{-1} [Extrapolated to 20 °C]	0.6 ± 0.1	1.32 ± 0.07 × 10^{-3}	9.9 ± 0.4 × 10^{-4} [3.5 × 10^{-7}]	1.6 ± 0.1 × 10^{-4} [5.7 × 10^{-8}]	—
$k_0(H_2O)/k_0(D_2O)$	1.4 ± 0.3	—	2.1 ± 0.2	2.0 ± 0.2	—
k_H/dm^3 mol^{-1} s^{-1}	83 ± 13	4.2 ± 2.6 × 10^{-3}	0.24 ± 0.03	1.5 ± 0.2	93 ± 11
K_a/mol dm^{-3}	2.8 ± 0.6 × 10^{-5}	1.2 ± 0.5 × 10^{-7}	1.4 ± 0.2 × 10^{-9}	1.9 ± 0.5 × 10^{-10}	—
Corrln. coefficient *r*	0.997	0.823	0.996	0.994	0.989
k_{rel} (at 20 °C)	1	2.2 × 10^{-3}	5.8 × 10^{-7}	9.5 × 10^{-8}	—
k_0/k_HK_a	258	2.6 × 10^6	2.9 × 10^6	5.6 × 10^5	—
EM (see text)	2880	810	10 800	9500	—
$\Delta H^‡$/kJ mol^{-1}	—	82 ± 5	111 ± 4	111 ± 2	—
$\Delta S^‡_{298}$/J K^{-1} mol^{-1}	—	−20 ± 17	13 ± 8	−3.9 ± 2.5	—

[a] The following Supplementary Data are available from the British Library (Suppl. S7237, pp. 9). Table S1 Primary kinetic data for the hydrolysis of acetal **4**. Table S2 Primary kinetic data for the hydrolysis of acetal **5**. Table S3. Primary kinetic data for the hydrolysis of the inositol systems **6** and **7**. For details of the Supplementary Publications Scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 2*, Issue 1, 1997.

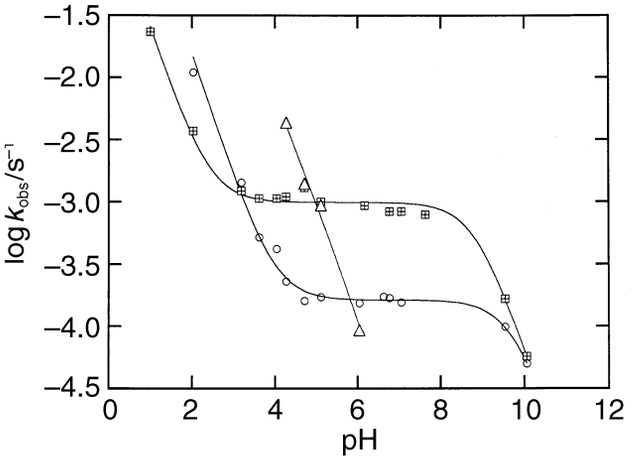


Fig. 3 pH–rate profiles, measured at 80 °C and ionic strength 1.0 mol dm^{-3}, for the hydrolysis of the acetal groups of **6** (squares) and **7** (circles), compared with the specific acid catalysed hydrolysis of the acetal **14** with no catalytic general acid (triangles). The points are experimental, the curves calculated using the rate and dissociation constants shown in Table 2.

orthoformate system in product studies in the plateau regions of the pH–rate profiles for **6** and **7**. These compounds are mixtures of epimers at the acetal centre, but clean first-order kinetics were observed under all conditions used, indicating that the two diastereoisomers have similar reactivity.

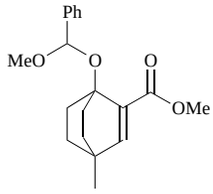
pH–rate profiles for the hydrolysis of **6** and **7** are compared with that for **14** in Fig. 3, in which the data (Tables S2 and S3) are once again fitted to eqn. (2). The points represent extrapolations to zero buffer concentration where appropriate. No significant dependence on buffer concentration was observed for the hydrolysis of **6**. The rates of the reactions of **7** and the comparison compound **14** varied to some extent with buffer concentration in some cases, but not systematically. It is not likely that this represents buffer catalysis.

pK_a Measurements. The pK_a of the formaldehyde acetal **13** was measured as 6.93 ± 0.04 at 20 °C from the variation of its UV spectrum over the appropriate pH range. Comparison with the dimethylaminonaphthalene acetal **15**, R = MeOCH$_2$ and ether **15**, R = Me, which have pK_a values of 7.4 at 65 °C and 7.75 at 25 °C, respectively,[5,19] shows that the deviation from a normal aniline pK_a is slightly reduced.

The pK_a of the (conjugate acid of) the dimethylamino alcohol **9** was measured as 5.8 by the same technique.

Calculation of effective molarities (EM). An efficient intramolecular reaction precludes the observation of competing intermolecular catalysis under the same conditions, so to estimate the rate of the intermolecular reaction a control system is needed. We tried to characterise buffer catalysis of the hydrolysis of the methyl ester **17** of **4**, and of the inositol derivative **14**. Individual preliminary experiments were consistent with some catalysis by acetate and formate buffers, but the data were of poor quality and acceptable second-order plots could not be obtained. This is not entirely unexpected: general acid catalysis in these systems is close to the limits of detectability against the background H_3O^+ catalysis, with Brønsted coefficients α of the order of 0.9.[20] However, Jensen's work has defined the (weak) leaving-group dependence of α, and has shown that the points for the H_3O^+-catalysed reactions fall on the Brønsted plot correlating catalysis by other general acids.[20] Thus, we can use k_H for the compound itself as the anchor point for an estimate of k_H for the compound itself as the anchor point for an estimate of k_{HA} for a general acid of the same pK_a as the intramolecular catalytic group. The resulting EM values should be reasonably accurate, certainly to better than an order of magnitude.

The measured k_H for the hydrolysis of the bicyclic acetal **4** (pK_a 4.55) is 83 dm^3 mol^{-1} s^{-1} (Table 2). The Brønsted α



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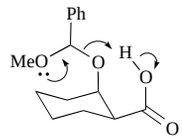

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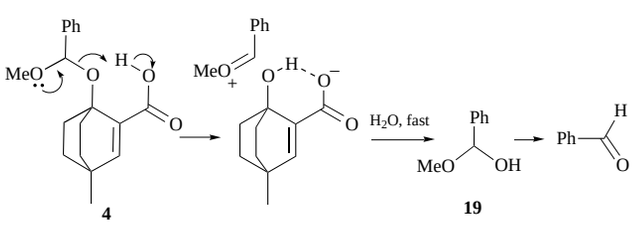
for catalysis by general acids of the hydrolysis of PhCH(OMe)OEt [the closest equivalent available to our acetal **4**, PhCH(OMe)OR, where ROH is a tertiary alcohol with electron-withdrawal in one substituent group] is 0.89 (in any case this figure varies little with R[20]). Thus we can estimate k_{HA} for an intermolecular general acid of pK_a 4.55 as $83 \times 10^{0.89(-1.74-4.55)} = 2.08 \times 10^{-4}$ dm^3 mol^{-1} s^{-1}, giving an estimated EM of 2880 mol dm^{-3} (Table 2). The estimated rate constant tells us that 1 mol dm^{-3} of such a general acid, at a pH equal to its pK_a, would increase the observed rate for the hydrolysis of **17** over that of the background H_3O^+ reaction by just 8.9%, explaining why we could not measure catalysis by external general acids accurately (using up to 0.14 mol dm^{-3} carboxylic acid).

We use the same values of k_H and Brønsted α for the calculation of EM for the reaction of **5**·**H**$^+$. Neutral **4** and **5** are similar enough structurally that the estimate of α (depending very little on the leaving group) is reasonable: but k_H observed for the hydrolysis of **5** is much smaller than for the hydrolysis of **4**, and not an appropriate anchor point for an estimate of k_{HA} for catalysis of the hydrolysis of **5** by an intermolecular general acid. This is because the reaction involves the H_3O^+-catalysed reaction of the cation **5**·H$^+$ and is thus subject to significant electrostatic retardation, as discussed below. The calculation using $k_H = 83$ dm^3 mol^{-1} gives an estimate of 810 for the effective molarity of the dimethylammonium group of **5**·**H**$^+$.

Slightly different parameters are appropriate for the reactions of **6** and **7**. For a measure of k_H undistorted by electrostatic retardation in a closely related inositol system we measured the rate of hydrolysis of the acetal **14** under the same conditions, between pH 4.2–6 (Fig. 3, triangles: the comparison with the pH–rate profile for the hydrolysis of **5**·**H**$^+$ shows clearly the electrostatic effect on k_H of the neighbouring NH$^+$ group). k_H for the hydrolysis of **14** (93 dm^3 mol^{-1} s^{-1} at 80 °C, see Table 2) is very similar to the value measured for **4** at 20 °C. We estimate the Brønsted coefficient α for general acid catalysis of the hydrolysis of the inositol acetals to be 0.85 (using an estimate of 0.3 for ρ* for the inositol group.[16] The estimated effective, molarities are closely similar, at 10 800 and 9500, respectively, for the dimethylammonium groups of **6** and **7**.

Discussion

The hydrolyses of all four acetals (**4**, **5**·**H**$^+$, **6**·**H**$^+$ and **7**·**H**$^+$) with neighbouring general acid groups studied in this work show sigmoid pH–rate profiles (Fig. 1–3), consistent with significant intramolecular general acid catalysis of the reaction (as shown in Schemes 2–4). The plateau region is more or less prominent



4 **19**

Scheme 2

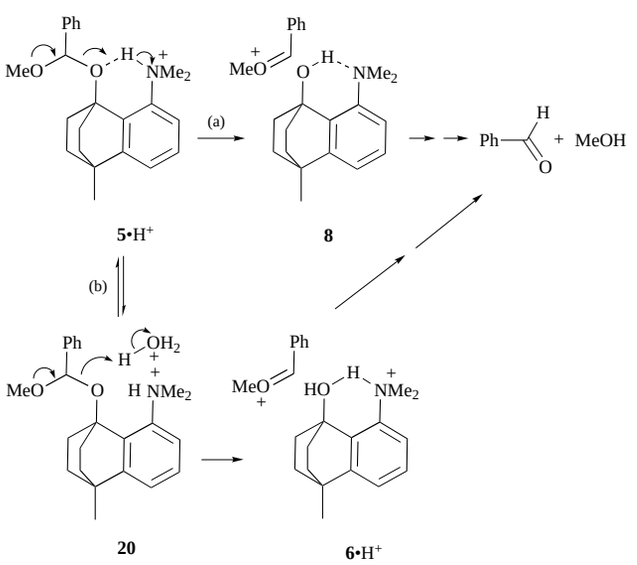
depending on the efficiency of intramolecular relative to H_3O^+ catalysis, and in the case of the dimethylamines **5**–**7** extends up

to pH 7 and beyond. All our evidence, particularly the significant solvent deuterium isotope effects (Table 2) and the original design of these systems, supports the interpretation in terms of intramolecular general acid catalysis, and this forms the basis of our discussion of reactivity. The alternative explanation, in terms of the kinetically equivalent H_3O^+-catalysis of the hydrolysis of the anion **4**$^-$ enhanced by the electrostatic effect of the neighbouring carboxylate group, has been ruled out in many related systems in the past, and is not in any case relevant to the reactions of **5**–**7**.

These are the first observed cases of intramolecular general acid catalysis of the hydrolysis of dialkyl acetals of benzaldehyde.[21] Fife and Przystas[22] found no significant catalysis by the neighbouring COOH group of the acetal **18** (above) though catalysis was observed for two such acetals derived from benzaldehydes with electron-withdrawing substituents. They estimated an upper limit for the rate constant for the reaction shown (**18**, arrows) of 2.3×10^{-5} s^{-1} (at 50 °C in 50% aqueous dioxane). For comparison, our measured rate constant for the reaction of **4** is 0.6 ± 0.1 s^{-1}. This is 26 000 times faster at 20 °C, and thus some 10^5 times faster if the difference in temperature is allowed for. Catalysis is clearly exceptionally efficient in the reaction of **4**.

The hydrolysis of **4** below pH 7 is fast enough to become complicated kinetically by the build up of the hemiacetal intermediate **19** (Scheme 2), which is hydrolysed at a comparable rate in this region. When the rate constants for the two consecutive reactions are disentangled as described above the pH–rate profile for the initial acetal cleavage is revealed (Fig. 1, filled circles). In the plateau region between pH 2.5–4.5 the halflife of **4** is 1.15 s, and the solvent deuterium isotope effect (reflecting mainly a primary kinetic isotope effect in this reaction) is 1.4 ± 0.3. This is comparable with the low values, between 1–1.6, obtained for salicylic acid derivatives hydrolysing by the same mechanism.[10,23] The acceleration relative to the H_3O^+-catalysed reaction (measured conveniently as $k_0k_HK_a$ [the ratio at the pK_a of the general acid: it is greater at higher pH] is 258-fold, and the EM of the COOH group of **4** is estimated to be 2880 mol dm^{-3}.

The pH–rate profile for the hydrolysis of **5** (Fig. 2) shows a more extended plateau region, accounted for by the combination of efficient catalysis by the dimethylammonium group (Scheme 3) and less efficient H_3O^+-catalysis of the hydrolysis of **5**·**H**$^+$. k_0 is 450 times slower than for the hydrolysis of **4** (the dimethylammonium group is the weaker acid by 2.4 units), but k_H is some 20 000 times slower. Though only the plateau region is well-defined, the mechanistic interpretation is straightforward (Scheme 3).

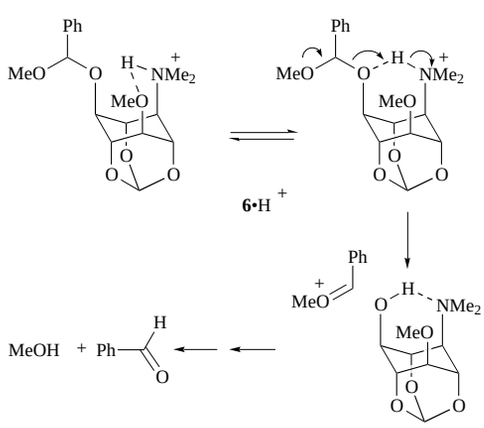


Scheme 3

The conjugate acid **5**·**H**$^+$ evidently has a hydrogen bond in the ground state strong enough to raise the pK_a of the dimethylammonium group by 2–3 units (from 4–5 to 6.92). Intramolecular general acid catalysis involves transfer of the proton concerned to the leaving group oxygen concerted with C–O bond breaking (Scheme 3, path a). The binding of the proton in the transition state for this reaction—a sort of enhanced hydrogen-bonding, which we have termed dynamic molecular recognition[3,24]—must be considerably stronger, since intramolecular catalysis is relatively efficient. However, to the extent that the ground state is stabilised by intramolecular hydrogen-bonding its reactivity, and in particular the EM for intramolecular catalysis, will be reduced. This accounts for the relatively low EM (810 mol dm^{-3}) estimated for the dimethylammonium group of **5**·**H**$^+$.

This ground state stabilisation must also reduce the reactivity of **5**·**H**$^+$ towards catalysis by H_3O^+, but the effect is reinforced by the electrostatic repulsion involved in a reaction involving a dicationic transition state (Scheme 3, **20**). As a result the parameter k_0/k_HK_a (the acceleration relative to the H_3O^+-catalysed reaction at the pK_a of the general acid) at 2.6×10^6 is far greater than for **4** (Table 2). We assume in Scheme 3 that H_3O^+ acts as a general acid in this reaction: there is good evidence that this is the case for dialkyl acetals of benzaldehyde, and the less stable is the protonated-oxygen form the less likely the specific acid catalysis mechanism becomes.[20] It is less clear which C–O bond will be broken in the H_3O^+-catalysed reaction. Structure **20** is drawn with the proton being transferred to the oxygen which is already involved in the intramolecular H-bond, but both acetal oxygens develop significant positive charge in the transition state for the cleavage reaction, and it is not obvious which is the more likely leaving group. If the other (C–OMe) bond is in fact broken in the H_3O^+-catalysed reaction the observed acceleration by intramolecular general acid catalysis will be correspondingly greater.

Ground state stabilisation by intramolecular hydrogen bonding is less important in the reactions of the inositol derivative **6**, partly at least because two axial oxygen atoms are available as acceptors for intramolecular hydrogen-bonds in **6H**$^+$, of which only one has a stabilising effect on the acetal group (Scheme 4). Catalysis is correspondingly more efficient.

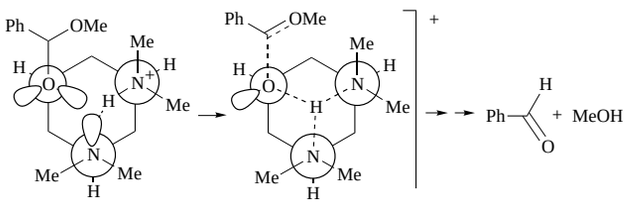


Scheme 4

Fig. 3 compares pH–rate profiles for the hydrolysis of **6** and the bis-dimethylamino-derivative **7** with that for the model compound **14**, which has an equatorial OH group in place of the dimethylamino-group of **6**. The kinetic pK_a of **6** is 8.85, higher by less than one pK_a unit than might be expected for a dimethyl tertiary amine with the same substituent pattern but lacking intramolecular H-bonding (no closer comparison compound is available). So the low value of k_H, indicated by the position of the linear plot of this parameter for the reaction of **14**, results mainly from the electrostatic effect of the dimethylammonium cation on the H_3O^+-catalysed reaction of **6**. The

combined effects contribute to a value of k_0/k_HK_a (the acceleration relative to the H_3O^+-catalysed reaction at the pK_a of the general acid) of 2.9×10^6 (Table 2), much the same as for **5**: but when we allow for the electrostatic effect (here using k_H measured for the hydrolysis of **14**, rather than that for **6**, in the calculation) the estimated EM is considerably greater, at 10 800.

Finally, we introduced a second dimethylamino-group into the inositol-derived system, to give **7**. The objective was to test the possibility that the transition state for the proton transfer part of the intramolecular general acid catalysed hydrolysis of the acetal group would be stabilised significantly more than the ground state by bifurcate hydrogen bonding, as in **7H$^+$(TS)** (Scheme 5). The ground state pK_a is raised in **7H$^+$** by almost



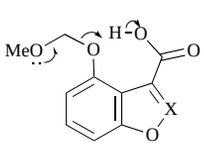
7•H$^+$ **7**•H$^+$ (TS)

Scheme 5

one unit with respect to **6H$^+$**, reflecting the presence of a stronger intramolecular (N–H···N) hydrogen bond (reinforcing the statistical effect of the second basic group). k_H is six-fold greater, as the electrostatic effect is reduced somewhat by 'delocalisation' of the positive charge, but there is no significant effect on catalytic efficiency. k_0 is a few times smaller than for **6H$^+$**, but this reflects no more than the weaker acidity of the dimethylammonium group, since the estimated EM is the same within experimental error (Table 2).

Structure and reactivity

It may seem obvious that intramolecular general acid catalysis should be more effective the stronger the general acid concerned, but there is little evidence available to support this proposition. The only systematic studies involve substituted salicylic acid derivatives, where in each case reactivity is more or less completely insensitive to the pK_a of the neighbouring COOH group.[10,23,25] Derivatives of **3** are clearly less reactive, as might be expected, but because both the gross structure and the general acid have changed we cannot ascribe this with confidence to the higher pK_a of the catalytic group. The best evidence for a significant dependence of reactivity on the pK_a of the neighbouring general acid comes from the comparison of two closely related heterocyclic systems, **21** (X = N and CH).[6]



21

Here, the acetal group is the same and the geometry change, from the benzisoxazole to the benzofuran, minimal. The hydrolysis of the benzisoxazole derivative (**21**, X = N, pK_a 1.55) catalysed by the neighbouring carboxyl group is the fastest known for a methoxymethyl acetal, and six times faster than that of the benzofuran (**21**, X = CH, pK_a 3.84): giving a two-point Brønsted coefficient α of 0.4.

In the series **4**–**7** the last three involve the same type of general acid, and reactivity falls off so dramatically [relative rates at 20 °C (Table 2) are of the order of $1 : 10^{-3} : 10^{-6} : 10^{-7}$, respectively] that there can be little doubt that acid strength is a significant factor. Log k_{rel} shows (presumably fortuitously in this case) a good linear dependence on the pK_a of the general acid (correlation coefficient $r = 0.994$ for the four data points), with the extraordinarily high slope of -1.41 ± 0.11 (Fig. 4). This Brønsted-type behaviour must include the response to changing geometry, and there is no obvious way of partitioning it: the high Brønsted α near 0.9 observed for general acid catalysis of the hydrolysis of benzaldehyde dialkyl acetals by H_3O^+[20] does not apply in any case to unsymmetrical systems with better leaving groups, which are likely to be hydrolysed by the classical concerted mechanism, with the C–O cleavage step rather than diffusional separation rate determining. This certainly seems to be the case for our acetals **4**, **6** and **7** (and no doubt also for **5**), which show significant solvent deuterium isotope effects (Table 2).

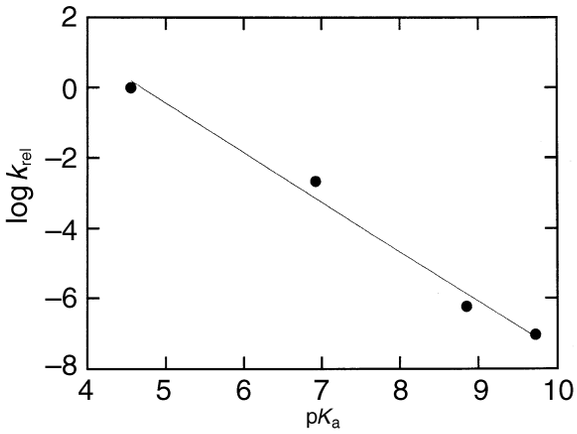


Fig. 4 Linear free energy relationship between the rate of hydrolysis of benzaldehyde acetals **4** and **5**·**H**$^+$–**7**·**H**$^+$ and the pK_a of the intramolecular general acid involved

The low Brønsted coefficient α for the reactions of **21** (X = N and CH), and the significant solvent deuterium isotope effects for the hydrolyses of **6** and **7** suggest that the sensitivity to the pK_a of the general acid is not likely to be greater than 0.4–0.6. The greater part of the observed sensitivity to pK_a of k_{rel} (apparent $\alpha = 1.4$) must therefore come from differences in intrinsic reactivity across the series, particularly from changing geometry.‡ Since the estimated EM, which measures the efficiency of catalysis, is actually slightly smaller for the more reactive systems **4** and **5**, this variation in intrinsic reactivity does not apparently include a major contribution from varying 'dynamic molecular recognition' of the in-flight proton.

Conclusions

The effective molarities, ranging from 810 to over 10^4, observed in this work extend the very limited range of systems for which efficient proton transfer catalysis has been observed to acetals of aliphatic alcohols. EM values are high for all four acetals we have studied, and the properties of each system tell us something different about this deceptively simple type of catalysis. Our most reactive acetal, the carboxylic acid **4**, does not show the highest EM, but absolute reactivity, as opposed to efficiency, does appear, to depend on the strength of the general acid. In water near pH 7 the optimum pK_a for the catalytic group is of course near **7**, as stronger acids will be present predominantly as their conjugate bases. In the special environment of an enzyme active site it is of course possible for the effective pK_a to be substantially modified in a bound transition state.

Efficient proton transfer catalysis depends on the formation

‡ We have not been able to grow useful crystals of the conjugate acids of **4**–**7**, and low-level structure calculations have given inconsistent results.

of a strong hydrogen bond in the transition state for the reaction. The simplest way to achieve this is to design a strong intramolecular hydrogen bond into the product. Efficiency is reduced if the hydrogen bond is present in the ground state. Thus, probably the most efficient system we have identified so far (EM of the order of 10^5 mol dm^{-3}) is the enol ether **16**:[26] in which case intramolecular general acid catalysis takes advantage of the desired strong intramolecular hydrogen bond in the transition state for hydrolysis of the conjugate acid, though the reactant alkene is not a significant H-bond acceptor. These simple but fundamental lessons can now be applied to the design of even more efficient model reactions: which we may expect to be increasingly closely related to key steps in enzyme catalysis.

Experimental

NMR spectra were recorded on Varian EM 390 (90 MHz), Bruker WM 250 (250 MHz), WM 200 (200 MHz) or DX400 (400 MHz) instruments. ^{1}H and ^{13}C chemical shifts were determined using residual nondeuteriated solvent as an internal standard and are reported downfield from $SiMe_4$ in ppm. Coupling constants are reported in Hz. For spectra of acetals in $CDCl_3$ the solvent was passed through a short plug of oven-dried alumina. ^{19}F spectra were measured at 235 MHz. In the ^{13}C NMR data + or − shows the result of an attached proton test: + signifies CH_3 or CH, − a quaternary carbon or a CH_2 group.

IR spectra were recorded on Perkin-Elmer 297, 1310 or 1600 (FT) spectrometers. Mass spectra were recorded on a Kratos MS 30 electron impact machine. Melting points were measured using a Reichart hot stage microscope and are uncorrected. TLC was performed using Merck silica gel 60 F254 pre-coated plates (0.25 mm) and the compounds visualised under UV light or with iodine. Microanalyses were carried out by the staff of the University Chemical Laboratories using Carlo Erba 1106 or Perkin-Elmer 240 automatic analysers.

Column chromatography was carried out on Merck silica gel 60 (70–230 mesh). The solvents used for chromatography were distilled before use. All solvents were dried before use by standard procedures.[27] When used under an argon atmosphere, glassware was dried by a hot air blower *in vacuo*, or assembled straight from the oven, allowed to cool *in vacuo* and flushed with argon several times. For reactions in liquid ammonia a potassium hydroxide drying tube was used.

Kinetic procedures

Kinetic runs were performed under pseudo-first-order conditions, for a minimum of three halflives, in the thermostatted cell holders of a Varian Cary 3 spectrophotometer or a Gilford 2600 spectrophotometer. Stock solutions were made by dissolving a sample of the substrate in anhydrous tetrahydrofuran (THF). For particularly reactive substrates a small amount of aqueous KOH solution was added. The stock solution concentration was such that adding 3–7 μl into 2 ml (or 1–3 μl into 300 μl) caused a total change in absorbance greater than 0.3 units. Runs showing simple first-order behaviour were fitted to the first-order exponential equation using KALEIDAGRAPH 3.0.2. Details of more complicated fits are described in the Results section.

For the hydrolysis of the most reactive system **4** in the pH range 0–6.5 measurements were made using a stopped flow apparatus, fitted with and Applied Photophysics stopped flow driver–mixer unit. The stock solution was a 2.5×10^{-5} mol dm^{-3} solution of the substrate in 1×10^{-3} mol dm^{-3} potassium hydroxide, with ionic strength 1 mol dm^{-3} (KCl). Data cited represent averages of at least five runs. In the case of stopped flow experiments pH data for buffer solutions were assumed to be the same as those measured at double the concentration. For HCl dilutions pH values were corrected for halving the concentration by adding 0.30. The effect of dilution on the pH of buffers should be minimal.

Buffers were used to control the pH at which the reaction was followed and the buffer concentration was varied to check for buffer catalysis (typical total buffer concentrations were 0.40, 0.32 and 0.16 mol dm^{-3}). Buffers were prepared using triply distilled and degassed water with AnalaR grade inorganic reagents. Buffer solutions in D_2O were prepared from 99.9% D_2O (Fluorochem) using a standard DCl solution (20% wt DCl, Aldrich 99+%) and organic salts. pHs were measured with a Russell CMAWL electrode and a Radiometer PHM82 pH meter (at the temperature of interest). pD values were obtained by adding 0.4 to the meter reading.[28]

pK_a Measurements

pK_a values were measured spectrophotometrically for the parent tricyclic alcohol **9** and the derived stable methoxymethyl acetal **13** by monitoring the changes in absorbance upon protonation of the dimethylamino group in various buffer solutions. Measurements were made on the Gilford spectrophotometer and corrections made for the absorbance due to the buffer solutions. The volume of the buffer (300 μl) and the substrate solutions (3 μl) were measured using microlitre syringes. Buffers were as used for the kinetic runs, with ionic strength 1 mol dm^{-3}. The two pK_a values of **11** were measured using an automatic titrator. Results appear in Table 2, above, and are given with the preparative details and other properties of the compounds concerned, below.

Product studies

Bicyclic acetal 4. The acetal was hydrolysed in 50% free base acetate buffer in D_2O [containing 20% $(CO_3)_2$] to give benzaldehyde, the bicyclic alcohol **8**, and methanol (Scheme 2). The products were identified by ^{1}H NMR, by comparison with a prepared solution of methanol and benzaldehyde under the same conditions. The bicyclic alcohol **8** was identified by comparison with a solution in methanol of an authentic sample of the alcohol.

Tricyclic acetal 5. In 50% free base formate buffer in D_2O at room temperature a kinetic sample (see below) of the benzaldehyde acetal **5** was hydrolysed to give the protonated dimethylamino alcohol **9**·$\mathbf{D}^+$, methanol and benzaldehyde as the only products (Scheme 3). This means that any impurities also hydrolyse to give benzaldehyde and methanol.

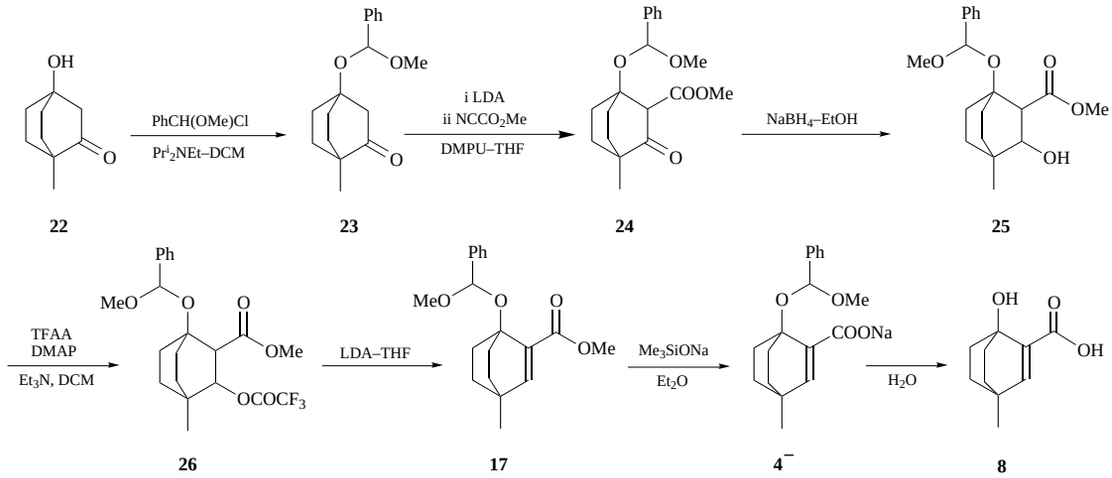
Inositol-derived acetal 6. Hydrolysis of the mono(dimethylamino) acetal **6** in D_2O, in 70% free base formate buffer at 80 °C, gave methanol, benzaldehyde and the alcohol **10**·$\mathbf{D}^+$ (Scheme 4), all of which were identified by ^{1}H NMR. Under these conditions there was no sign of hydrolysis of the orthoformate ring: the only reaction observed is the hydrolysis of the acetal.

Synthesis

The bicyclic acetal **4** was prepared, in its more stable carboxylate form $\mathbf{4}^-$, by the route shown in Scheme 6.

The benzaldehyde acetal **23** of the known[29] bicyclic hydroxyketone **22** was converted using Mander's reagent to the methyl esters **24**, which were reduced to a mixture of the four diastereoisomeric alcohols **25**. The diastereoisomers were not separated because two of the stereogenic centres disappear in the next, elimination step. This step was expected to go by an E1cb mechanism, and thus not to be stereospecific. In the event the elimination proved difficult (it is not stereoelectronically ideal at any stage in this rigid system), and various precedented routes to **17** from **24** were tried and proved unsuccessful before the LDA-catalysed elimination of trifluoroacetate was found to go in satisfactory yield.

Benzaldehyde methyl 4-methyl-3-oxobicyclo[2.2.2]octanyl acetal 23. α-Chlorobenzyl methyl ether[30] (81 mg, 0.52 mmol, **CAUTION Carcinogen**) in dichloromethane (1 cm^3) was added



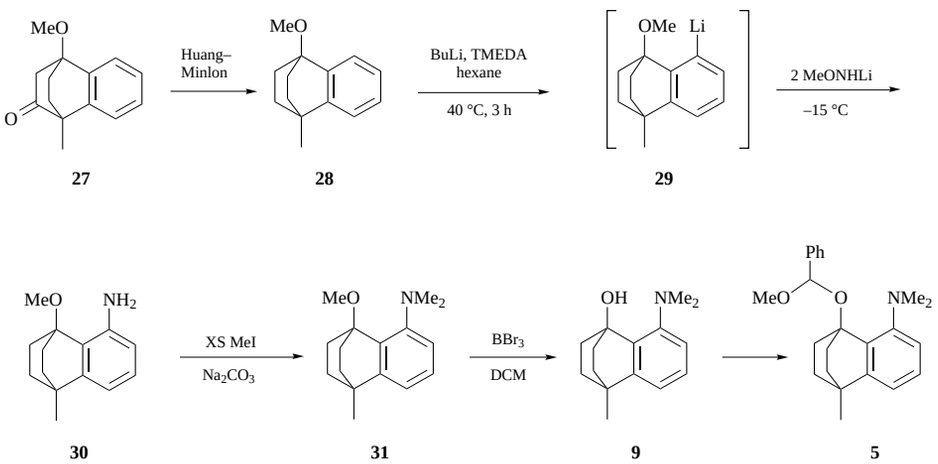
Scheme 6 DCM = dichloromethane, LDA = lithium diisopropylamide, DMPU = 1,3-dimethylimidazolidin-2-one, TFAA = trifluoroacetic anhydride, DMAP = 2-dimethylaminopyridine

to a solution of 1-hydroxy-4-methylbicyclo[2.2.2]octan-3-one **22**[29] (40 mg, 0.26 mmol) and diisopropylethylamine (67 mg, 90 ml, 0.52 mmol) in dichloromethane (1 cm^3) *via* a cannula under argon. The mixture was stirred at room temp. overnight, quenched with sodium hydroxide solution (10%, 2 cm^3) and extracted with dichloromethane (3 × 2 cm^3). The extract was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, hexane–Et_2O, 2:1) to give the acetal **23** (54 mg, 85%) as a colourless oil; R_f (hexane–Et_2O 2:1) 0.34; ν_{max}(CCl_4)/cm^{-1} 1726 (C=O) and 1452 (C=CAr); δ_H (250 MHz; $CDCl_3$), 7.46–7.26 (5 H, m, Ph), 5.74 [1 H, s, OCH(Ph)O], 3.13 (3 H, s, OMe), 2.59 (2 H, s, CH_2CO), 2.05–1.55 (8 H, m, CH_2CH_2) and 0.95 (3 H, CCH_3); δ_C($CDCl_3$) 213.5−, 139.2−, 128.7+, 128.4+, 126.6+, 96.7+, 75.3−, 50.6+, 49.4−, 42.6−, 30.9−, 30.6−, 30.2−, 30.4− and 19.3+; *m*/*z* 274 (1.2%, M$^+$) and 243 (6, M − Me) (Found: M$^+$, 274.1563. $C_{17}H_{22}O_3$ requires *M*, 274.1569).

Benzaldehyde methyl 4-methyl-2-(methoxycarbonyl)-3-oxobicyclo[2.2.2]octanyl acetal 24. Lithium bis(trimethylsilyl)amide (0.217 cm^3 of a 1 mol dm^{-3} solution in THF, 0.217 mmol) was diluted with THF (0.5 cm^3) and cooled to −78 °C under argon then a solution of benzaldehyde methyl 4-methyl-3-oxobicyclo-[2.2.2]octanyl acetal **23** (54 mg, 0.197 mmol) in THF (2 cm^3) added *via* a cannula.The solution was warmed to 0 °C, stirred for 1 h then cooled to −78 °C and DMPU (25 mg, 24 μl, 0.197 mmol) and methyl cyanoformate[31] (20 mg, 19 μl, 0.236 mmol) were added. The solution was stirred for 10 min then warmed to room temp. and sodium hydroxide solution (10%, 1 cm^3) added. The mixture was extracted with diethyl ether (3 × 2 cm^3), and the extract dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, hexane–Et_2O, 2:1) to give the ester **24** (47 mg, 73%, mixture of two diastereoisomers) as a colourless oil; R_f (hexane–Et_2O, 2:1) 0.20; ν_{max}($CDCl_3$)/cm^{-1} 1744 (C=O) and 1717 (C=O); δ_H(400 MHz; $CDCl_3$) (4:3 ratio of diastereoisomers A:B) 7.51–7.27 (5 H_A and 5 H_B, m, Ph), 5.89 [1 H_A, s, OCH(Ph)O], 5.82 [1 H_B, s, OCH(Ph)O], 3.73 (3 H_B, s, $COOCH_3$), 3.61–3.60 (1 H_A and 1 H_B, m, COCHCOOMe), 3.48 (3 H_A, s, $COOCH_3$), 3.07 [3 H_B, s, OCH(Ph)OCH_3], 3.03 [3 H_A, s, OCH(Ph)OCH_3], 2.5–1.64 (8 H_A and 8 H_B, m, CH_2CH_2), and 0.99 (3 H_A and 3 H_B, s, CCH_3); δ_C($CDCl_3$) 208.0−, 168.0−, 138.7−, 128.9+, 128.3+, 128.2+, 128.1+, 126.8+, 126.7+, 96.4+, 95.9−, 77.2+, 63.9+, 62.5+, 51.1+, 51.9+, 50.1+, 49.4+, 72.6−, 42.5−, 32.0−, 31.4−, 30.6−, 30.5−, 29.5−, 27.3−, 25.6− and 19.4+; *m*/*z* 332 (0.1%, M$^+$) and 301 (5, M − OMe) (Found: M$^+$, 332.1623. $C_{19}H_{24}O_5$ requires *M*, 332.1624).

Benzaldehyde methyl 3-hydroxy-2-(methoxycarbonyl)-4-methylbicyclo[2.2.2]octanyl acetal 25. Sodium borohydride (67 mg, 1.77 mmol) was added to a solution of benzaldehyde methyl 2-(methoxycarbonyl)-4-methyl-3-oxo-bicyclo[2.2.2]-octanyl acetal **24** (393 mg, 1.18 mmol) in ethanol (10 cm^3) at 0 °C and the mixture stirred for 2 h. The reaction was quenched with sodium hydroxide solution (5%, 20 cm^3) and extracted with ethyl acetate (6 × 10 cm^3). The extract was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, hexane–Et_2O, 1:2) to give the alcohol **25** (322 mg, 81%, mixture of four diastereoisomers, 25:20:6:5) as a colourless oil; R_f (hexane–Et_2O, 1:1) 0.21(A) and 0.17(B); ν_{max}($CDCl_3$)/cm^{-1} 3513 (br, OH) and 1712 (ester); ^{1}H NMR for two major diastereoisomers: (A) δ_H(400 MHz; $CDCl_3$) 7.39–7.25 (5 H, m, Ph), 5.83 [1 H, s, OCH(Ph)O], 3.73 (1 H, dt, *J* 1.7 and 9.2, C*H*OH), 3.47 (3 H, s, $COOCH_3$), 3.30 (1 H, dd, *J* 9.4 and 2.0, CHCOOMe), 3.26 (1 H, d, *J* 8.9, OH), 2.99 (3 H, s, $COCH_3$), 2.46–2.37 (1 H, m, CH*H*CH_2), 1.98–1.34 (7 H, m, CH_2CH_2) and 0.87 (3 H, s, CMe):(B) δ_H(250 MHz; $CDCl_3$) 7.44–7.24 (5 H, m, Ph), 5.76 [1 H, s, OCH(Ph)O], 3.77 (1 H, ddd, *J* 9.4, 8.8 and 1.7, C*H*OH), 3.66 (3 H, s, $COOCH_3$), 3.38 (1 H, dd, *J* 9.5 and 2.0, CHCOOMe), 3.04 (3 H, s, $COCH_3$), 2.94 (1 H, d, *J* 8.7, OH), 2.40–2.28 (1 H, m, CH*H*CH_2), 2.1–1.31 (7 H, m, CH_2CH_2) and 0.87 (3 H, s, CMe); ^{13}C for two major diastereoisomers: (A) δ_C($CDCl_3$) 172.5−, 139.3−, 128.1+, 128.0+, 126.8+, 52.4+, 76.8−, 73.1+, 51.6+, 51.5+, 49.2+, 32.7−, 31.3−, 31.1−, 27.0−, 26.6− and 23.5+: (B) δ_C($CDCl_3$) 172.5−, 139.2−,128.1+, 126.7+, 95.8+, 76.6+, 73.1+, 53.3+, 51.6+, 49.8+, 32.7−, 32.3−, 31.2−, 27.0−, 24.6− and 23.5+; *m*/*z* 303 (2%, M$^+$ − OMe) (Found: M − OMe, 303.1581. $C_{19}H_{23}O_4$ requires M − OMe, 303.1596).

Benzaldehyde methyl 2-(methoxycarbonyl)-4-methyl-3-trifluoroacetoxybicyclo[2.2.2]octanyl acetal 26. Trifluoroacetic anhydride (282 mg, 190 μl, 1.341 mmol) was added to a solution of benzaldehyde methyl 3-hydroxy-2-(methoxycarbonyl)-4-methylbicyclo[2.2.2]octanyl acetal **25** (283 mg, 0.847 mmol), triethylamine (0.181 g, 250 μl, 1.79 mmol) and DMAP (11 mg, 8.94 mmol) in dichloroethane (10 cm^3) at 0 °C and the mixture stirred for 3.5 h. The reaction was quenched with sodium hydroxide solution (10%, 15 cm^3) and extracted with dichloromethane (4 × 15 cm^3). The extract was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, hexane–Et_2O, 1:1) to give the trifluoroacetate **26** (290 mg, 80%, mixture of four diastereoisomers) as a very moisture sensitive colourless oil; R_f (hexane–Et_2O, 1:1) 0.45; ν_{max}($CDCl_3$)/cm^{-1} 1782 (CF_3C=O),1735 (COOMe) and 1601 (Ph); δ_H(250 MHz; $CDCl_3$) (4 diastereoisomers A:B:C:D, 26:20:7:5) 7.35–7.25 (5 H_A, 5 H_B, 5 H_C and 5 H_D, m, Ph), 5.87 [1 H_D, s, OCH(Ph)O], 5.81 [1 H_A, s, OCH(Ph)O], 5.80 [1 H_B, s, OCH(Ph)O], 5.73 [1 H_C, s, OCH(Ph)O], 5.19 (1 H_B, dd, *J* 9.6, 1.8, F_3COOCH), 5.09 (1 H_A, dd, 9.4, 1.7, F_3COOCH), 5.08–5.04 (1 H_C and 1 H_D, m, F_3COOCH), 3.74 (3 H_C, s, $COOCH_3$),



Scheme 7 TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine

3.57 (3 H_B, s, $COOCH_3$), 3.47 (3 H_A, s, $COOCH_3$), 3.42 (3 H_D, s, $COOCH_3$), 3.40–3.332 (1 H_A and 1 H_B, m, CHCOOMe), 3.06 (3 H_C, s, $CHOCH_3$), 3.05 (3 H_A, s, $CHOCH_3$), 3.03 (3 H_B, s, $CHOCH_3$), 2.96 (3 H_D, s, $CHOCH_3$), 2.90–2.85 (1 H_C and 1 H_D, m, CHCOOMe), 2.83–2.62 (1 H_A and 1 H_B, m, CH_aHCH_2), 2.12–1.40 (7 H_A, 7 H_B, 8 H_C and 8 H_D, m, CH_2CH_2), 0.89 (3 H_C, s, CCH_3), 0.88 (3 H_D, s, CCH_3) and 0.83 (3 H_A and H_B, s, CCH_3); $\delta_C(CDCl_3)$ 168.6−, 139.1−, 138.8−, 128.2+, 128.1+, 128.0+, 126.8+, 129.7+, 96.2+, 95.7+, 78.3+, 75.8−,75.6−, 56.2+, 51.5+, 49.9+, 49.7+, 32.1−, 32.1−, 31.9−, 31.1−, 10.8−, 30.7−, 29.7−, 28.0−, 25.9−, 24.5−, 23.2+ and 22.7+; $\delta_F(CDCl_3)$ −75.45 (D), −75.49 (C), −75.58 (B) and −75.59 (A); *m*/*z* 310 (M − PhCHOMe, 13%) and 279 (M − PhCHOMe − OMe, 10) (Found: M^+ − PhCHOMe 310.1034. $C_{13}H_{17}O_5F_3$ requires M, 310.1028).

Benzaldehyde methyl 2-(methoxycarbonyl)-4-methylbicyclo[2.2.2]oct-2-enyl acetal 17. Butyllithium (164 μl of a 1.5 mol dm^{-3} solution in hexane, 0.248 mmol) was added to a solution of diisopropylamine (25 mg, 35 μl, 0.248 mmol) in THF (6 cm^3) at −78 °C then stirred at 0 °C for 30 min. A solution of the trifluoroacetate ester acetal **25** (97 mg, 0.225 mmol) in THF (5 cm^3) was added to the lithium base at −78 °C and the solution stirred for 2 h. The mixture was warmed to room temp., quenched with sodium hydroxide solution (10%, 5 cm^3) and extracted with dichloromethane (4 × 10 cm^3). The extract was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, hexane–Et_2O, 1:1) to give the alkene **17** (49 mg, 73%) as a colourless oil; R_f (hexane–Et_2O, 1:1) 0.53; $\nu_{max}(CDCl_3)/cm^{-1}$ 1719 (C=O) and 1609 (Ar); δ_H(250 MHz; $CDCl_3$) 7.52–7.48 (2 H, m, Ph), 7.40–4.25 (3 H, m, Ph), 6.66 (1 H, s, C=CH), 5.89 [1 H, s, OCH(Ph)O], 3.46 (3 H, s, $COOCH_3$), 3.05 (3 H, s, $CHOCH_3$), 2.01 (2 H, dt, *J* 4.0 and 11.1, $OCCH_AH_BCH_2CMe$), 1.85–1.72 (2 H, m, $OCCH_AH_BCH_2CMe$), 1.63–1.51 (2 H,m, $OCCH_2CH_AH_B$), 1.40–1.27 (2 H, m, $OCCH_2CH_AH_B$) and 1.18 (3 H, s, CCH_3); $\delta_C(CDCl_3)$ 166.2−, 145.2+, 139.3−, 139.2−, 128.0+, 127.9+, 127.1+, 976.6+, 78.9−, 51.3+, 49.3+, 34.3−, 33.5−, 33.1−, 31.5− and 24.7+; *m*/*z* 316 (M^+, 0.4%) and 285 (M − OMe, 12) (Found: M^+, 316.1673. $C_{19}H_{24}O_4$ requires 316.1674) (Found: C, 72.1; H, 6.8. $C_{19}H_{24}O_4$ requires C, 72.1; H, 7.65%).

Sodium 1-(α-methoxybenzyloxy)-4-methylbicyclo[2.2.2]-oct-2-ene-3-carboxylate 4^-. A solution of the methyl ester acetal **17** (40 mg, 126 mmol) in diethyl ether (2 cm^3) was added to sodium trimethylsiloxide[32] (14.2 mg, 126 mmol) in diethyl ether (3 cm^3) and the mixture refluxed for 3 d. The mixture was filtered and was washed with diethyl ether to give the sodium salt 4^- as moisture sensitive colourless crystals; δ_H(400 MHz; D_2O) 7.50 (2 H, d, *J* 6.8, *ortho*-Ph), 7.44–7.40 (3 H, m, Ph), 5.91 (1 H, s, C=CH), 8.85 [1 H, s, OCH(O)Ph], 3.21 (3 H, s, OCH_3), 1.97–1.85 (2 H, m, $CH_AH_BCH_2$), 1.69–1.41 (4 H, m, $CH_AH_BCH_2$ and $CH_2CH_AH_B$), 1.31–1.23 (2 H, m, $CH_2CH_AH_B$) and 1.09 (3 H, s, CCH_3); $\delta_C(D_2O)$ 175.7−, 144.9−, 138.6−, 132.5+, 128.6+, 128.2+, 126.2+, 98.2+, 79.4−, 51.1+, 34.0−, 32.8−, 32.5−, 32.4−, 32.2−, 31.8−, 31.1− and 23.5+.

2-Carboxy-4-methylbicyclo[2.2.2]oct-2-en-1-ol 8. A solution of the acetal 4^- (24 mg, 7.4, mmol) in THF (0.5 cm^3) was added to aqueous hydrochloric acid (0.5 cm^3, 0.1 mol dm^{-3}) and the mixture stirred for 1 hour at room temperature. The mixture was extracted with diethyl ether (3 × 2 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, dichloromethane–methanol, 1:1) to give the acid **8** (6 mg, 44%) as a colourless solid; R_f (dichloromethane–methanol, 1:1) 0.08; δ_H(400 MHz; CD_3OD) 6.84 (1 H, s, C=CH), 1.7 (2 H, ddd, *J* 11.0, 9.9 and 3.7, $OCCH_AH_BCH_2CMe$), 1.54 (2 H, dt, *J* 10.9 and 3.6, $OCCH_AH_BCH_2CMe$), 1.46–1.40 (2 H, m, $OCCH_2CH_AH_BCMe$), 1.37–1.20 (2 H, m, $OCCH_2CH_AH_BCMe$) and 1.15 (3 H, s, CCH_3); $\delta_C(CD_3OD)$ 173.5−, 147.1+, 139.3−, 74.6−, 36.4−, 35.8− and 25.2+; *m*/*z* 182 (0.3%, M^+) and 167 (4, M − Me) (Found: M^+, 182.0943. $C_{10}H_{14}O_3$ requires M, 182.0941).

The tricyclic acetal **5** was prepared as shown in Scheme 7.

peri-Lithiation of the tricyclic ether **28** proceeded in acceptable yield [the reaction with MeI of the solution of the 8-lithio compound as prepared below gave 58% (isolated) of the 8-methyl derivative]. Electrophilic amination according to Beak and Kokko[33] eventually gave a low yield of the aniline **30**, which was readily methylated with methyl iodide. (Quaternisation of the hindered NMe_2 group was not expected to interfere, since methylation of the NMe_2 group of derivatives of **3** was known to be very difficult.[34]) The final step, the apparently simple alkylation of the tertiary alcohol OH of **9** with α-chlorobenzyl methyl ether, proved most troublesome. The product from the reaction using Hunig's base was unstable to chromatography, and initially unidentifiable; showing only one methyl singlet at δ 3.0 in the ^{1}H NMR (in $CDCl_3$). In fact this product was the desired acetal **5**. The *N*-methyl group signals were eventually identified as two broad humps, at δ 2.23 and 2.00, resulting no doubt from restricted rotation in the crowded *peri*-system. The singlet at δ 3.0 is then from the OMe group, presumably shifted upfield by the benzene ring of the acetal. This assignment was confirmed when the ^{1}H NMR spectrum was rerun in C_6D_6, to reveal a single peak for the NMe_2 group at δ 2.1 ppm. **5** was not stable to chromatography, and could not be separated from unreacted starting material **9**. Since this is also the product of hydrolysis, and rates were measured under pseudo-first-order conditions; this did not prevent accurate kinetic measurements.

1-Methoxy-4-methyl-1,2,3,4-tetrahydro-1,4-ethanonaphthalene 28. The known ketoether **27**[35] (6.2 g, 0.029 mol) was dissolved in triethylene glycol (30 cm^3) containing potassium hydroxide (4.88 g, 0.122 mol). After addition of hydrazine monohydrate (2.90 g, 2.81 cm^3, 0.0606 mol) the mixture was heated under reflux (120 °C) for 45 min.[36,37] Excess hydrazine

hydrate and water were distilled off (140 °C). The solution was heated under reflux again, now at 195 °C for 210 min. After the solution had cooled down to room temperature water was added (125 cm^3) and the product extracted with dichloromethane (5 × 50 cm^3). The combined organic extracts were washed with 10% hydrochloric acid (3 cm^3) and water (10 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was distilled to yield the ether **28** (5.06 g, 87%) as a colourless oil, bp 130 °C at 0.05 mmHg; R_f (EtOAc–hexane, 1:1) 0.68; δ_H(250 MHz; $CDCl_3$) 7.44–7.40 (1 H, m, aromatic CHCCO), 7.31–7.18 (3 H, m, aromatic), 3.52 (3 H, s, OCH_3), 2.02 (2 H, dt, *J* 2 and 10, twice MeOCCH_AH_B), 1.74 (2 H, dt, *J* 2 and 10, twice MeOCCH_AH_B), 1.53–1.31 (4 H, m, CH_2 envelope) and 1.34 (3 H, s, 4-CH_3).

8-Lithio-1-methoxy-4-methyl-1,2,3,4-tetrahydro-1,4-ethanonaphthalene 29. TMEDA (0.079 g, 0.103 cm^3, 0.68 mmol) was added to a stirred solution of butyllithium (0.45 cm^3 of a 1.6 mol dm^{-3} solution in hexane, 0.72 mmol) under an argon atmosphere and cooled to 0 °C (ice bath). The ether **27** [0.137 g, 0.68 mmol in hexane (2 cm^3)] was added and the solution stirred at 40 °C for 3 h. The resulting organolithium derivative **29** was reacted with various electrophiles.[16]

8-Amino-1-methoxy-4-methyl-1,2,3,4-tetrahydro-1,4-ethanonaphthalene 30. A solution of methyllithium (4.6 cm^3 of a 1.4 mol dm^{-3} solution in diethyl ether, 6.44 mmol) was cooled to −78 °C under an argon atmosphere and a solution of methoxylamine (distilled from DMF–sodium hydroxide–methoxylamine hydrochloride, 0.303 g, 6.44 mmol) in anhydrous hexane (6.5 cm^3) was added dropwise.[33] The organolithium compound **29** (3.22 mmol) was added *via* a cannula, then the solution was warmed to −15 °C and stirred for 2 h. The reaction mixture was quenched with water (0.5 cm^3), extracted with 10% hydrochloride acid, the extract cooled to 0 °C, neutralised with 10% sodium hydroxide and extracted with diethyl ether. The extract was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, Et_2O–hexane, 2:1) to yield the amine **30** (175 mg, 25%) as a colourless liquid (45% of starting material was also recovered); R_f (Et_2O–hexane, 2:1) 0.39; $\nu_{max}(CDCl_3)/cm^{-1}$ 3480, 3380 (N–H) and 1590 (aromatic); δ_H(250 MHz; $CDCl_3$) 7.00 (1 H, t, *J* 8, H-6), 6.58–6.48 (2 H, m, H-5,7), 4.64 (2 H, br s, NH_2), 3.44 (3 H, s, OCH_3), 2.19–2.09 (2 H, m, twice OCCH_AH_B), 1.73–1.25 (6 H, m, rest CH_2) and 1.30 (3 H, s, 4-CH_3); δ_C(100 MHz; $CDCl_3$) 146.4, 142.4, 126.7, 125.6, 115.6, 110.9, 80.5, 50.0, 34.0, 33.8, 29.3 and 23.5; *m*/*z* 217 (100%, M^+), 202 (18, M − Me), 189 (100, M − CNH_2) and 174 (85, M − MeOC) (Found: M^+, 217.1475. $C_{14}H_{19}NO$ requires M, 217.1466).

8-Dimethylamino-1-methoxy-4-methyl-1,2,3,4-tetrahydro-1,4-ethanonaphthalene 31. An excess of iodomethane (2.5 cm^3) was added to a mixture of the amine **30** (295 mg, 1.44 mmol) and sodium carbonate (399 mg, 2.88 mmol) and the mixture refluxed for 2 d. The excess of iodomethane was distilled off. 10% Sodium hydroxide solution (5 cm^3) was added and the mixture extracted with dichloromethane (5 × 4 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, hexane–Et_2O, 1:1) to give the tertiary amine **31** (278 mg, 80%) as a colourless oil; R_f (hexane–Et_2O, 1:1) 0.35; δ_H(250 MHz; $CDCl_3$) 7.18 (1 H, t, *J* 7.8, H6), 7.03 (1 H, dd, *J* 8.1 and 1, H5), 6.89 (1 H, dd, *J* 7.4 and 1, H7), 3.50 (3 H, s, OMe), 2.77 (6 H, s, NMe_2), 1.89–1.65 (6 H, m, CH_2), 1.38–1.26 (2 H, m, CH_2) and 1.35 (3 H, s, CMe); δ_C($CDCl_3$) 149.2−, 147.4−, 134.8−, 126.2+, 117.2+, 115.9+, 78.4−, 53.2+, 46.0−, 34.4−, 33.6−, 32.0− and 23.9+; *m*/*z* 245 (2.5%, M^+), 230 (2%, M − Me) and 215 (6%, M − 2Me) (Found: M^+, 245.1782. $C_{16}H_{23}NO$ requires M, 245.1781).

8-Dimethylamino-4-methyl-1,2,3,4-tetrahydro-1,4-ethanonaphthalen-1-ol 9. Boron tribromide[38] (5.4 cm^3 of a 1 mol dm^{-3} solution in dichloromethane, 5.4 mmol) was slowly added to a solution of the dimethylamine **31** (134 mg, 0.54 mmol) in dichloromethane (2 cm^3) at −78 °C. The solution was warmed to room temp. and stirred overnight. The solution was cooled to 0 °C (ice bath) and 10% sodium hydroxide (5 cm^3) added. The mixture was extracted with dichloromethane (5 × 4 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, hexane–Et_2O, 1:4) to give the alcohol **9** (102 mg, 80%) as white needles; R_f (hexane–diethyl ether, 1:4) 0.31; $\nu_{max}(CDCl_3)/cm^{-1}$ 3400–2500 (br, OH),1596 (aromatic) and 1584 (aromatic); δ_H(400 MHz; $CDCl_3$) 10.2 (1 H, br s, OH), 7.24 (2 H, 2 × d, *J* 3.7 and 4.9, 5 and 7-H),7.06 (1 H, dd, *J* 3.8 and 4.8, 6-H), 2.76 (6 H, s, NCH_3), 1.94 (2 H, dt, *J* 4 and 11.2, OCC$H_AH_B$$CH_2$CMe), 1.75–1.68 (2 H, m, OCC$H_AH_B$$CH_2$CMe), 1.63–1.55 (2 H, m, OCCH_2-CH_AH_BCMe), 1.32 (3 H, s, CCH_3) and 1.32–1.25 (2 H, m, OCCH_2CH_AH_BCMe); δ_C($CDCl_3$) 147.8−, 146.3−, 137.6−, 126.9+, 119.5+, 119.1+, 74.0−, 46.6+, 35.8−, 43.4−, 34.4− and 23.2+; *m*/*z* 231 (M^+, 34%) and 216 (M − Me, 6) (Found: M^+ 231.1625. $C_{15}H_{21}NO$ requires M, 231.1624).

The measured pK_a of **9** was 5.81 ± 0.05, at 20 °C and ionic strength 1 mol dm^{-3}.

Benzaldehyde methyl 8-dimethylamino-4-methyl-1,2,3,4-tetrahydro-1,4-ethanonaphthyl acetal 5. A solution of α-chlorobenzyl methyl ether (30 mg, 193 μmol, **CAUTION Carcinogen**) in dichloromethane (1.5 cm^3) was added *via* cannula to a solution of 8-dimethylamino-4-methyl-1,2,3,4-tetrahydro-1,4-ethanonaphthalen-1-ol **9** (21 mg, 97 μmol) and diisopropylethylamine (25 mg, 34 μl, 193 μmol) in dichloromethane under argon (2 cm^3). The mixture was stirred at 0 °C for 30 min, quenched with sodium hydroxide solution (10%, 2 cm^3) and extracted with dichloromethane (3 × 2 cm^3). The extract was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, hexane–Et_2O, 1:1) to give the acetal **5** (22 mg, 79%) in crude form as a colourless oil contaminated with possibly two other compounds; R_f (hexane–Et_2O, 4:1) 0.17 streaking and R_f (hexane–Et_2O, alumina, 4:1); δ_H(250 MHz; $CDCl_3$) 7.53–7.47 (2 H, m, H-Ph), 7.40–7.30 (3 H, m, H-Ph), 7.18 (1 H, dd, *J* 7.6 and 7.9, H-6), 7.01 (1 H, dd, *J* 1.1 and 8.2, H-5 or 7), 6.94 (1 H, dd, *J* 1.2 and 7.4), 5.98 [1 H, s, OCH(O)Ph], 3.05 (3 H, s, OCH_3), 2.23–1.68 (6 H, m, CH_2CH_2), 2.23 [3 H, br s, N(CH_3)CH_3], 2.00 [3 H, br s, N(CH_3)CH_3], 1.39–1.24 (2 H, m,$CH_2CH_AH_B$CMe) and 1.34 (3 H, s, CCH_3); δ_H(250 MHz; C_6D_6) 7.63–7.60 (3 H, m, H-Ph), 7.25–7.08 (3 H, m, 2-H-Ph and 6-H), 6.98–6.95 (2 H, m, 5 and 7-H), 6.17 [1 H, s, OCH(O)Ph], 3.04 (3 H, s, OCH_3), 2.24–2.09 (3 H, m, CH_2CH_2), 2.11 (6 H, s, NCH_3), 2.00–1.96 (1 H, m, CH_A-$H_B$$CH_2$), 1.57–1.47 (2 H, m, CH_2CH_AH_B) and 1.29–1.17 (2 H, m, $CH_2CH_AH_B$); δ_H(250 MHz; $CDCl_3$) for impurity(s) 5.94 (1 H, s) and 5.61 (1 H, s), 3.66 (3 H, s) and 3.19 (1 H, s); δ_C($CDCl_3$) 149.5−, 147.4−, 139.9−, 135.1−, 128.3+, 128.3+, 127.3+, 127.2+, 127.0+, 126.9+, 126.9+, 126.4+, 117.6+, 116.5+, 99.9+, 80.1−, 772−, 48.8+, 34.4−, 33.5−, 33.3−, 33.2− and 23.9+; *m*/*z* 351.2 (0.4%, M^+), 336.2 (0.8, M − Me), 320.2 (0.6, M − OMe), 230.2 (10, M − PhCHOMe) and 215.2 (21, M − Me, PhCHOMe) (Found: M^+ 351.2202. $C_{23}H_{20}O_2N$ requires M, 351.2198).

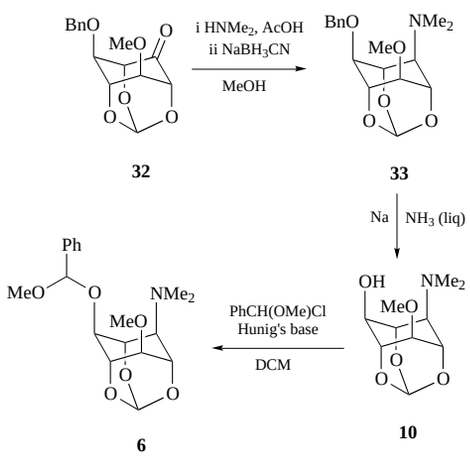
For kinetic experiments. A solution of α-chlorobenzyl methyl ether (8 mg, 52 μmol, **CAUTION Carcinogen**) in dichloromethane (1 cm^3) was added to a solution of 8-dimethylamino-4-methyl-1,2,3,4-tetrahydro-1,4-ethanonaphthen-1-ol **9** (11 mg, 48 μmol) and diisopropylethylamine (8 mg, 11 μl, 62 μmol) in dichloromethane (1 cm^3) *via* a cannula under argon. The mixture was stirred at 0 °C for 30 min, quenched with sodium hydroxide solution (10%, 2 cm^3) and extracted with dichloromethane (3 × 2 cm^3). The extract was dried ($MgSO_4$) and evaporated under reduced pressure.The sample was put on a high vacuum to remove any benzaldehyde giving a sample of the acetal **5** plus starting material (20 mg, 9:7), with spectroscopic properties as described above.

8-Dimethylamino-1-(methyoxymethoxy)-4-methyl-1,2,3,4-tetrahydro-1,4-ethanonaphthalene 13. α-Chloromethoxymethane (0.946 mmol, 0.22 cm^3 of a 4.3 mol dm^{-3} solution,

CAUTION Carcinogen) was added to a solution of 8-dimethylamino-4-methyl-1,2,3,4-tetrahydro-1,4-ethano-naphthalen-1-ol **9** (55 mg, 0.24 mmol) and diisopropylethylamine (96 mg, 137 μl, 0.946 mmol) in dichloromethane (3 cm^3). The solution was stirred overnight then sodium hydroxide solution (2 cm^3, 5%) was added and the mixture extracted with dichloromethane (3 × 3 cm^3). The extract was dried ($MgSO_4$) and evaporated under reduced pressure. Preparative plate chromatography (alumina, hexane–Et_2O, 2:1) gave the acetal **13** (51 mg, 78%) as colourless needles, mp 44–48 °C (from hexane); R_f (hexane–Et_2O, 1:1) 0.36 (streaking) and R_f (alumina, hexane–Et_2O, 1:1) 0.66; $\nu_{max}(CDCl_3)/cm^{-1}$ 3070–2780 (CH); δ_H(400 MHz; $CDCl_3$) 7.20 (1 H, t, *J* 8, CHCCN), 7.07 (1 H, d, *J* 8.1, CHCCCN), 6.94 (1 H, d, *J* 7.4, CHCN), 4.9 (2 H, s, OCH_2O), 3.45 (3 H, s, OCH_3), 3.71 (6 H, s, NCH_3), 1.98 (2 H, 1.98 dt, *J* 4 and 12, $CH_AH_BCH_2$), 1.89–1.181 (2 H, m, $CH_2CH_AH_B$), 1.73 (2 H, dt, *J* 3.8 and 12, $CH_AH_BCH_2$), 1.36 (3 H, s, CCH_3) and 1.36–1.28 (2 H, m, $CH_2CH_AH_B$); $\delta_C(CDCl_3)$ 149.6−, 147.4−, 134.9−, 126.4+, 117.7+, 116.5+, 94.8−, 79.3−, 54.8+, 45.9+, 34.4−, 33.4−, 33.4− and 23.8+; *m*/*z* 275 (M^+, 8.4%), 260 (M − Me, 5), 244 (M − OMe, 11) and 230 (M − CH_2OMe, 7) (Found: M^+, 275.1887. $C_{17}H_{25}NO_2$ requires M, 275.1885) (Found: C, 74.35; H, 9.2; N, 5.0. $C_{17}H_{25}NO_2$ requires C, 74.15; H, 9.15; N, 5.1%).

The measured pK_a of **13** was 6.93 ± 0.04, at 25 °C and ionic strength 1.0 mol dm^{-1}.

The aminoinositol derivative **6** was prepared as a mixture of diastereoisomers as shown in Scheme 8.



Scheme 8

The protected ketone **32**[39] was reductively aminated (stereospecifically axial), then the benzyl group removed selectively and the free hydroxy group alkylated as above with α-chlorobenzyl methyl ether. The two diastereoisomers of **6** were not separated: any difference in reactivity between them was not expected to be significant for the purposes of this work, and the hydrolysis of the mixture did not indeed show good first-order kinetics.

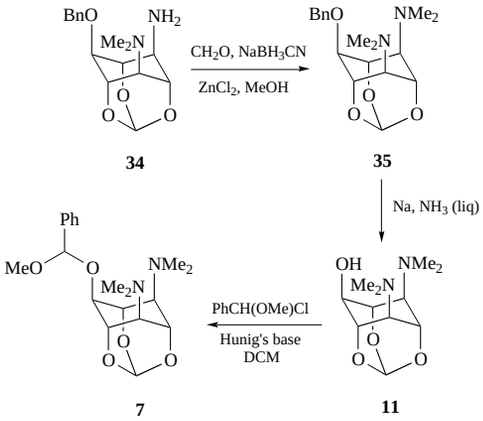
4-*O*-Benzyl-6-*O*-methyl-2-deoxy-2-(dimethylamino)-*scyllo*-inositol orthoformate 33. Dimethylamine (33% w/v in diethyl ether, 415 μl, 3.05 mmol) and acetic acid (40.3 mg, 38 μl, 0.671 mmol) were added to a solution of 4-*O*-benzyl-6-*O*-methyl-2-deoxy-2-oxo-*myo*-inositol orthoformate **32**[39] (178 mg, 0.61 mmol) in methanol (5 cm^3) and the solution stirred at 0 °C for 10 min. Sodium cyanoborohydride (60 mg, 0.915 mmol) was added and the solution stirred at room temp. for 3 d. The reaction was quenched by the addition of aqueous HCl (10%) and the solution extracted with diethyl ether. Potassium hydroxide pellets were added to the aqueous solution (until pH > 10), the solution extracted with diethyl ether (3 × 10 cm^3) and the extract evaporated to give the crude amine **33** (89 mg, 45%) as a colourless oil; R_f (ethyl acetate–methanol, 4:1) 0.07; $\nu_{max}(CDCl_3)/cm^{-1}$ 1602 (Ph); δ_H(400 MHz; $CDCl_3$) 7.41–7.25 (5 H, m, Ph), 5.46 [1 H, s, OCH(O)O], 4.69 (1 H, d, roofing, *J* 13, $PhCH_AH_B$), 4.65 (1 H, d roofing, *J* 13, $PhCH_AH_B$), 4.56 (1 H, br s, CHO), 4.42 (1 H, br s, CHO), 4.29 (1 H, br s, CHO), 4.41 (1 H, br s, CHO), 4.05 (1 H, br s, CHO), 3.53 (3 H, s, OCH_3), 2.91 (1 H, br s, CHN) and 2.35 [6 H, s, $N(CH_3)_2$]; $\delta_C(CDCl_3)$ 138.0−, 128.5+, 128.1+, 128.0+, 103.0+, 75.9+, 72.0−, 71.6+, 69.0+, 68.7+,67.9+, 65.0+, 59.0+ and 45.1+; *m z* 321 (22%, M^+) (Found: M^+, 321.1588. $C_{17}H_{23}NO_5$ requires M, 321.1576).

6-*O*-Methyl-2-deoxy-2-(dimethylamino)-*scyllo*-inositol orthoformate 10. A solution of 4-*O*-benzyl-6-*O*-methyl-2-deoxy-2-(dimethylamino)-*scyllo*-inositol orthoformate **33** (89 mg, 0.277 mmol) and 2-methylpropan-2-ol (20 mg, 25.6 μl, 0.277 mmol) in diethyl ether was added to a solution of sodium (enough to maintain a blue colour) in ammonia (20 cm^3) at −78 °C. The mixture was allowed to warm slowly to room temp. overnight (the ammonia evaporating). Sodium hydroxide solution (10%, 30 cm^3) was added to the mixture which was then extracted with ethyl acetate (6 × 20 cm^3). The extract was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, ethyl acetate–methanol, 10:1) to give the alcohol **10** (52 mg, 82%) as a solid form; R_f (ethyl acetate–methanol, 10:1) 0.45; $\nu_{max}(CDCl_3)/cm^{-1}$ 3265 (br, OH); δ_H(250 MHz; $CDCl_3$) 5.97 (1 H, br s, OH), 5.49 [1 H, s, OCH(O)O], 5.49–4.49 (2 H, m, CHO), 4.44–4.42 (1 H, m, CHO), 4.35–4.31 (1 H, m, CHO), 4.12–4.10 (1 H, m, CHO), 2.46 (3 H, s, OCH_3), 3.08–3.02 (1 H, m, CHN) and 2.31 [6 H, s, $N(CH_3)_2$]; $\delta_C(CDCl_3)$ 102.0+, 76.1+, 69.4+, 68.8+, 67.8+, 67.0+, 63.7+, 57.77+ and 44.0+; *m*/*z* 231 (M^+, 75%) and 200 (M − OMe, 21) (Found: M^+, 231.1101. $C_{10}H_{17}NO_5$ requires M, 231.1107).

4-*O*-(α-Methoxybenzyl)-6-*O*-methyl-2-deoxy-2-(dimethylamino)-*scyllo*-inositol orthoformate 6. A solution of α-chlorobenzyl methyl ether (13 mg, 0.083 mmol, **CAUTION Carcinogen**) in dichloromethane (1 cm^3) was added to a solution of 6-*O*-methyl-2-deoxy-2-*N*,*N*-dimethylamino-*scyllo*-inositol orthoformate **10** (16 mg, 0.069 mmol) and diisopropylethylamine (18 μl, 0.14 mmol) in dichloromethane (2 cm^3) *via* a cannula under argon. The mixture was stirred at room temp. for 2 h, quenched with sodium hydroxide solution (10%, 2 cm^3) and extracted with dichloromethane (3 × 2 cm^3). The extract was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed [SiO_2 (washed with triethylamine in diethyl ether), ethyl acetate–methanol, 4:1] to give the acetal **6** (15 mg, 62%, 2 diastereoisomers) as a colourless oil; R_f (ethyl acetate–methanol, 4:1) 0.14; $\nu_{max}(CDCl_3)/cm^{-1}$; δ_H(400 MHz; $CDCl_3$) (2 diastereoisomers A:B 10:9) 7.61–7.45 (2 H_A and 2 H_B, m, Ph), 7.38–7.30 (3 H_A and 3 H_B, m, Ph), 5.75 [1 H_A and 1 H_B, s, OCH(Ph)O], 5.44 [1 H_A, s, OCH(O)O], 5.43 [1 H_B, s, OCH(O)O], 4.58–4.99 (3 H_A and 2 H_B, m, CHO), 4.37 (1 H_B, br s, CHO), 4.06 (1 H_A, br s, CHO), 3.92 (1 H_B, br s, CHO), 3.83 (1 H_A, br s, CHO), 3.63 (1 H_B, br s, CHO), 3.52 (3 H_A, s, OMe), 3.50 (3 H_B, s, OMe), 3.48 (3 H_B, s, OMe), 3.46 (3 H_A, s, OMe), 2.92 (1 H_B, br s, CHN), 2.81 (1 H_A, br s, CHN) and (2.33 and 2.30) [6 H_A and 6 H_B, br s, $N(CH_3)_2$]; $\delta_C(CDCl_3)$ 138.0−, 128.7+, 128.2+, 127.2+, 127.0+, 102.9+, 102.0+, 101.7+, 77.2+, 75.8+, 75.6+, 69.9+, 69.3+, 68.5+, 66.9+, 66.2+, 65.0+, 59.0+, 58.7+, 55.1+, 54.7+ and 45.1+; *m*/*z* 351 (M^+, 11%), 336 (M − Me, 18) and 320 (Me − OMe, 16) (Found: M^+, 351.1685. $C_{18}H_{25}NO_6$ requires M, 351.1681).

The bis(dimethylamino) system 7. This was prepared according to Scheme 9. The diamine analogue of inositol was obtained by degradation of streptomycin. Its conversion to the orthoformate **33** is described by Beckmann.[40] Methylation with an excess of methyl iodide unexpectedly gave the pentamethylated mono-trimethylammonium compound rather than the expected bis-dimethylamino-derivative **35**, so reductive methylation was used for this step.

4-*O*-Benzyl-2,6-dideoxy-2,6-bis(dimethylamino)]-*scyllo*-inositol orthoformate 35. A solution of zinc chloride (608 g, 4.46 mmol) and sodium cyanoborohydride[41] (561 mg, 8.9 mmol) in



Scheme 9

methanol was prepared. This solution was added to a solution of 4-*O*-benzyl-2,6-dideoxy-2,6-diamino-*scyllo*-inositol orthoformate **34**[40] (207 mg, 0.744 mmol) and formaldehyde (2.17 cm^3 of a 37% w/v aqueous solution) in methanol (20 cm^3) and the mixture was stirred at room temp. for 5 d. The reaction was quenched with aqueous sodium hydroxide (20 cm^3, 10%) and extracted with dichloromethane. The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. Preparative plate chromatography (SiO_2, EtOAc–MeOH, 4:1) on the residue gave the bisdimethylamine **35** (85 mg, 34%) as colourless needles mp 144–145 °C (from methanol); R_f (EtOAc–MeOH, 4:1) 0.33 streaking; $\nu_{max}(CDCl_3)/cm^{-1}$ 3088–2792 (CH); δ_H(250 MHz; $CDCl_3$) 7.83–7.29 (2 H, m, Ph), 5.50 [1 H, s, OCH(O)O], 4.68 (2 H, s, CH_2Ph), 4.60 (1 H, br s, CHOBn), 4.43 (2 H, br s, 3,5-CHO), 4.18 (1 H, br t, *J* 3.4, 1-CHO), 3.05 (2 H, br s, CHN) and 2.42 (12 H, s, NCH_3); $\delta_C(CDCl_3)$ 137.4−, 128.7+, 128.35+, 128.3+, 128.1+, 103.0+, 72.4−, 71.4+, 68.4+, 68.0+, 65.4+ and 45.5; *m*/*z* 344.2 (M^+, 15%) (Found: M^+, 334.1898. $C_{18}H_{26}O_4N_2$ requires M, 334.1892) (Found: C, 64.5; H, 7.85; N, 8.4. $C_{18}H_{26}O_4N_2$ requires C, 64.65; H, 0.85; N, 8.4%).

2,6-Dideoxy-2,6-bis(dimethylamino)-*scyllo*-inositol orthoformate 11. Sodium (enough to maintain a blue colour) was added to a solution of 4-*O*-benzyl-2,6-dideoxy-2,6-bis(dimethylamino)-*scyllo*-inositol orthoformate **35** (24 mg, 71.8 μmol) in ammonia (5 cm^3) at −78 °C. The solution was stirred at −33 °C for 50 min then allowed to warm to room temp. overnight, the ammonia evaporating. Sodium hydroxide solution (10%, 4 cm^3) was added to the mixture which was then extracted with ethyl acetate (5 × 3 cm^3). The extract was dried ($MgSO_4$) and evaporated under reduced pressure. Preparative plate chromatography (SiO_2, EtOAc–MeOH, 4:1) of the residue gave the alcohol **11** (12 mg, 68%) as prisms, which sublime above 150 °C; R_f (ethyl acetate–methanol, 4:1) 0.14; $\nu_{max}(CDCl_3)/cm^{-1}$ 3241 (OH); δ_H(400 MHz; $CDCl_3$) 6.12 (1 H, br s, OH), 5.53 [1 H, s, OCH(O)O], 4.56 (1 H, br m, CHO), 4.52 (2 H, m, CHO), 4.34 (1 H, br m, C*H*OH), 3.07 (2 H, br m, CHN) and 2.34 (12 H, s, NCH_3); $\delta_C(CDCl_3)$ 102.4+, 169.1+, 69.1+, 66.4+, 65.2+ and 44.8+; *m*/*z* 244 (M^+, 43%) and 229 (M − Me) (Found: M^+, 244.1422. $C_{11}H_{20}O_4N_2$ requires M, 244.2423) (Found: C, 54.05; H, 8.35; N, 11.5. $C_{11}H_{20}O_4N_2$ requires C, 54.1; H, 8.25; N, 11.5%).

The ionisation constant of **11** was measured (by Claus Beckmann, private communication) using a Sirius Analytical Instruments PAC 1010 automatic titrator at SmithKline Beecham Pharmaceuticals laboratories at the Frythe, Welwyn. The pK_a values obtained were 8.819 ± 0.006 and 2.25 ± 25.3 °C, in water with a mean ionic strength of 0.116.

4-*O*-(α-Methoxybenzyl)-2,6-dideoxy-2,6-bis(dimethylamino)-*scyllo*-inositol orthoformate 7. A solution of α-chlorobenzyl methyl ether (**CAUTION Carcinogen**) (12 mg, 0.074 mmol) in dichloromethane (1 cm^3) was added to a solution of 2,6-dideoxy-2,6-bis(dimethylamino)-*scyllo*-inositol orthoformate **11** (12 mg, 0.049 mmol) and diisopropylethylamine (17 μl, 0.098 mmol) in dichloromethane (2 cm^3) *via* a cannula under argon. The mixture was stirred at room temp. for 4 d, quenched with sodium hydroxide solution (10%, 2 cm^3) and extracted with dichloromethane (3 × 2 cm^3). The extract was dried ($MgSO_4$) and evaporated under reduced pressure. Preparative plate chromatography (SiO_2, Et_2O) on the residue gave the acetal **7** (8 mg, 45%) as a colourless oil; R_f (dichloromethane–methanol, 9:1) 0.11; $\nu_{max}(CDCl_3)/cm^{-1}$ 3000–2775 (C–H) and 1601 (aromatic); δ_H(250 MHz; $CDCl_3$) 7.53–7.48 (2 H, m, Ph), 7.42–7.30 (3 H, m, Ph), 5.66 [1 H, s, OCH(O)Ph], 5.52 [1 H, s, OCH(O)O], 4.68–4.52 (3 H, m, CHO), 4.05 (1 H, br s, CHO), 3.39 (3 H, s, OCH_3), 3.13 (1 H, br s, CHN), 3.04 (1 H, br s, CHN) and 2.60–2.20 [12 H, br s and two s (2.42 and 3.39), NCH_3]; $\delta_C(CDCl_3)$ 129.2−, 128.5−, 127.0−, 102.9−, 69.7−, 69.2−, 65.2−, 54.8−, 45.5− and 44.8−; *m*/*z* 364 (2.3, M^+), 349 (9, M − Me), 333 (5, M − OMe) and 243 (50, M − PhCHOMe) (Found: M^+, 364.1993. $C_{19}H_{28}O_5N_2$ requires M, 364.1998).

6-Trimethylammonio-4-*O*-benzyl-2,6-dideoxy-2-dimethylamino-*scyllo*-inositol orthoformate iodide 36. Using the procedure of Chen and Benoit,[42] a mixture of 4-*O*-benzyl-2,6-dideoxy-2,6-diamino)-*scyllo*-inositol orthoformate **34**[40] (56 mg, 0.201 mmol) and sodium hydrogen carbonate (100 mg) in methanol (3 cm^3) and iodomethane (2 cm^3) was refluxed overnight. The reaction was quenched with sodium hydroxide solution (3 cm^3, 10%) and extracted with dichloromethane (5 × 5 cm^3). The extract was dried ($MgSO_4$) and evacuated under reduced pressure to give the ammonium salt **36** (43 mg, 45%) as colourless needles, mp > 250 °C (from methanol); R_f (dichloromethane–methanol, 9:1) 0.0; δ_H[250 MHz; $(CD_3)_2SO$] 7.43–7.29 (5 H, m, Ph), 5.78 [1 H, s, OCH(O)O], 5.19 (1 H, br s, CHO), 5.20 (1 H, br s, CHO), 4.87 (1 H, d, *J* 11.7, $PhCH_AH_B$), 4.80 (1 H, d, *J* 11.7, $PhCH_AH_B$), 4.72 (1 H, br s, CHO), 4.61 (1 H, br s, CHO), 4.28 (1 H, br t, *J* 3, CHN^+?), 3.31 (9 H, s, CH_3N^+), 2.99 (1 H, br s, CHN), 2.29 (3 H, br s, NCH_3Me) and 2.26 (3 H, br s, $NMeCH_3$); $\delta_C(CDCl_3)$ 137.1−, 128.8+, 128.0+, 127.8+, 72.6−, 72.4+, 67.4+, 67.3+, 66.8+, 61.8+, 55.1+, 45.0+ and 42.5+ (Found: C,48.0; H, 6.25: N, 5.8; I, 26.6. $C_{19}H_{24}N_2O_4I$ requires C, 47.9; H, 6.15; N, 5.9; I, 26.6).

Attempted demethylation of **36** using lithium propanethiolate[43] was unsuccessful.

4-*O*-Benzyl-6-*O*-(α-methoxybenzyl)-*myo*-inositol orthoformate 14. A solution of α-chlorobenzyl methyl ether (44 mg, 0.28 mmol, **CAUTION Carcinogen**) in dichloromethane (2 cm^3) was added to a solution of the protected ester 6-*O*-benzyl-2-*O*-(*p*-nitrobenzoyl)-*myo*-inositol orthoformate[44] (100 mg, 0.233 mmol) and diisopropylethylamine (45 mg, 61 μl, 0.35 mmol) in dichloromethane (5 cm^3) *via* a cannula under argon. The mixture was stirred at room temp. overnight. Methanol (5 cm^3) and aqueous sodium hydroxide (10%, 5 cm^3) were added and the mixture stirred for a further hour. The mixture was extracted with dichloromethane (3 × 2 cm^3), dried ($MgSO_4$), and the extract evaporated under reduced pressure. The residue was chromatographed (SiO_2, hexane–Et_2O, 1:1) to give the acetal **14** (67 mg, 72%, mixture of two diastereoisomers) as a colourless oil; R_f (hexane–Et_2O, 1:1) 0.11; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3569 (OH); δ_H(250 MHz; $CDCl_3$) (2 diastereoisomers A:B 13:17) 7.41–7.20 (10 H_A and 10 H_B, m, Ph), 5.67 [1 H_B, s, OCH(Ph)O], 5.59 [1 H_A, s, OCH(Ph)O], 5.47 [1 H_B, d, *J* 1.0, OCH(O)O], 5.46 [1 H_A, *J* 0.9, OCH(O)O], 4.75 (1 H_A, d, *J* 11.5, $PhCH_aH_b$), 4.62–4.55 (1 H_A and 3 H_B, m, $PhCH_{2(B)}$, $CHO_{(A)}$ and $CHO_{(B)}$), 4.61 (1 H_A, d, *J* 11.5, $PhCH_aH_b$), 4.42–4.49 (1 H_B, m, CHO), 4.48–4.33 (1 H_A and 1 H_B, m, CHO), 4.29–4.21 (3 H_A and 1 H_B, m, CHO), 4.21–4.17 (1 H_A and 1 H_B, m, CHO), 4.16–4.13 (1 H_B, m, CHO), 3.30 (3 H_A, s, OCH_3), 3.26 (1 H_B, d, *J* 12.1, OH, disappeared on D_2O shake), 3.25 (1 H_A, d, *J* 11.6, OH, disappeared on D_2O shake) and 3.21 (3 H_B, s, OCH_3); $\delta_C(CDCl_3)$ 137.5−, 137.4−,

137.3−, 128.9+, 128.6+, 128.5+, 128.3+, 128.3+, 128.0+, 127.7+, 127.6+, 126.8+, 103.3+, 103.3+, 102.3+, 102.1+, 77.3+, 73.9+, 73.8+, 73.6+, 73.4+, 72.9+, 72.9+, 71.8−, 71.5−, 70.6+, 69.9+, 68.7+, 68.2+, 61.5+, 61.5+, 53.1+, 53.1+ and 52.0+; *m*/*z* 400 (M^+, 0.4%) and 401 (M + H, 1) (Found: 400.1535. $C_{22}H_{24}O_7$ requires 400.1522) (Found: C, 66.0; H, 6.05. $C_{22}H_{24}O_7$ requires C, 66.0; H, 6.1%).

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References

1 M. L Sinnott, *Chem. Rev*., 1990, **90**, 1171.
2 Q. Wang, R. W. Graham, D. Trimbur, R. A. J. Warren and S. G. Withers, *J. Am. Chem. Soc*., 1994, **116**, 11 595–5.
3 A. J. Kirby, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 707.
4 S. G. Withers, K. Rupitz, D. Trimbur and R. A. J. Warren, *Biochemistry*, 1992, **31**, 9979.
5 A. J. Kirby and J. M. Percy, *J. Chem. Soc., Perkin Trans. 2*, 1989, 907.
6 A. J. Kirby and A. Parkinson, *J. Chem. Soc., Chem. Commun*., 1994, 707.
7 A. J. Kirby, *Adv. Phys. Org. Chem*., 1980, **17**, 183.
8 A. J. Kirby and A. R. Fersht, in *Intramolecular Catalysis*, eds. E. T. Kaiser and F. J. Kezdy, New York, 1971.
9 B. Capon, M. C. Smith, E. Anderson, R. H. Dahm and G. H. Sankey, *J. Chem. Soc., B*, 1969, 1038.
10 G.-A. Craze and A. J. Kirby, *J. Chem. Soc., Perkin Trans. 2*, 1974, 61.
11 A. A. Frost and R. G. Pearson, *Kinetics and Mechanism*, Wiley, 1961.
12 J. L. Jensen and P. A. Lenz, *J. Am. Chem. Soc*., 1978, **100**, 1291.
13 J. L. Jensen, A. B. Martinez and C. L. Shimazu, *J. Org. Chem*., 1983, **48**, 4175.
14 T. L. Amyes and W. P. Jencks, *J. Am. Chem. Soc*., 1989, **111**, 7888.
15 B. Capon, K. Nimmo and G. L. Reid, *J. Chem. Soc., Chem. Commun*., 1976, 871.
16 C. J. Brown, *Efficient Intramolecular General Acid Catalysis*, Thesis, Cambridge, 1995.
17 J. L. Jensen and K. S. Yamaguchi, *J. Org. Chem*., 1984, **49**, 2613.
18 W. P. Jencks and J. Regenstein, in *Ionisation Constants*, ed. H. A. Sober, Cleveland, Ohio, 1970.
19 A. Awwal and F. Hibbert, *J. Chem. Soc., Perkin Trans. 2*, 1977, 152.
20 A. J. Kirby and F. O'Carroll, *J. Chem. Soc., Perkin Trans. 2*, 1994, 649.
21 M. I. Page, personal communication.
22 J. L. Jensen, L. R. Herold, P. A. Lenz, S. Trusty, V. Sergi, K. Bell and P. Rogers, *J. Am. Chem. Soc*., 1979, **101**, 4672.
23 C. J. Brown and A. J. Kirby, *Chem. Commun*., 1996, 2355.
24 T. H. Fife and T. J. Przystas, *J. Am. Chem. Soc*., 1979, **101**, 1202.
25 R. H. Bromilow and A. J. Kirby, *J. Chem. Soc., B*, 1972, 149.
26 A. J. Kirby and D. H. Williams, *Phil. Trans. Roy. Soc.* (*London*), *Ser. A*, 1993, **345**, 1.
27 S. E. Barber and A. J. Kirby, *J. Chem. Soc., Chem. Commun*., 1987, 1775.
28 D. D. Perrin and W. F. Armarego, *Purification Methods*, Pergamon Press, 1988.
29 K. Glasoe and F. A. Long, *J. Phys. Chem*., 1960, **64**, 188.
30 J. Colonge and R. Vuillemet, *Bull. Soc. Chim. Fr*., 1961, 2235.
31 F. Straus and H. Heinze, *Liebigs Ann. Chem*., 1932, **292**, 191.
32 L. N. Mander and S. P. Sethi, *Tetrahedron Lett*., 1983, **24**, 5425.
33 E. D. Laganis and B. L. Chenard, *Tetrahedron Lett*., 1984, **25**, 5831.
34 P. Beak and B. J. Kokko, *J. Org. Chem*., 1982, **47**, 2822.
35 A. J. Kirby and J. M. Percy, *Tetrahedron*, 1988, **44**, 6919.
36 K.-I. Morita and T. Kobayashi, *J. Org. Chem*., 1966, **31**, 229.
37 Huang-Minlon, *J. Am. Chem. Soc.*, 1946, **68**, 2483.
38 M. Harwood and C. Moody, *Experimental Organic Chemistry*, Blackwell, 1989.
39 M. Demuynck, P. D. Clercq and M. Vandewalle, *J. Org. Chem*., 1979, **44**, 4863.
40 R. E. Marriott, *Accelerated Cleavage of Phosphate Esters*, Thesis, Cambridge, 1994.
41 C. Beckmann, *Built-in Polyamine Catalyst for Phosphate Transfer*, Thesis, Cambridge, 1997.
42 S. Kim, C. H. Oh, J. S. Ko, K. H. Ahn and V. J. Kim, *J. Org. Chem*., 1985, **50**, 1927.
43 F. C. M Chen and N. L. Benoit, *Can. J. Chem*., 1976, **54**, 3310.
44 R. O. Hutchins and F. J. Dux, *J. Org. Chem*., 1973, **38**, 1961.
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