Stereoelectronic effects on reactivity. Crystal-structure–reactivity correlations for acetals with synperiplanar lone pairs

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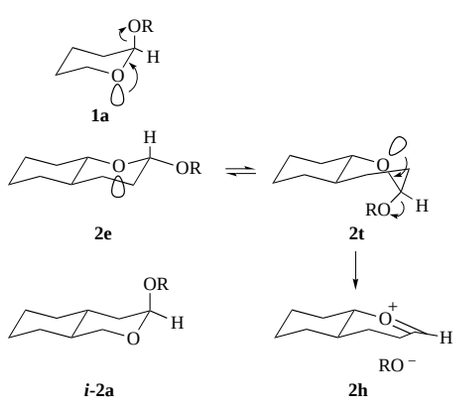
The synthesis and five crystal structures are reported for a series of tetrahydropyranyl acetals 3, in which the tetrahydropyranyl ring is fixed in the symmetrical boat conformation. The spontaneous hydrolysis of four aryl acetals 3 is a few times faster than that of corresponding compounds in which the tetrahydropyran ring is conformationally mobile and thus free to adopt the chair conformation. There appears to be no stereoelectronic barrier to participation by synperiplanar (sp) as compared with antiperiplanar (ap) lone pairs in the acetal cleavage reaction. However, at least part of this increased reactivity towards hydrolysis must derive from the higher ground state energy of the boat conformation, and a careful examination of a series of compounds 3 reveals intriguing and systematic differences between the two systems. The spontaneous hydrolysis of the synperiplanar series shows extraordinarily high sensitivity to the leaving group (β_{LG} = 1.4), compared with the already high value known for axial tetrahydropyranyl acetals with antiperiplanar lone pairs. In contrast, bond length correlations show a reduced sensitivity. The results suggest that the n–σ*$_{C-O}$ interaction (endocyclic anomeric effect) is weaker in the ground state in the sp geometry.

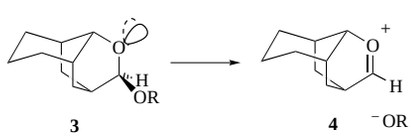
Acetal cleavage depends on n_O–σ*$_{C-O}$ overlap between the lone pair electrons on one donor oxygen and the σ* antibonding orbital of the C–OR bond to the leaving group. The strength of this interaction depends on geometry, and can control both conformation and reactivity. Thus tetrahydropyranyl acetals prefer the axial conformation **1a** (the anomeric effect[1]), in part



at least because of its ground-state stabilising effect, thought to be optimal when the overlap geometry is antiperiplanar. Reactivity, on the other hand, depends on the conformation only if this is firmly fixed. Thus equatorial systems **2e** (R = *p*-nitrophenyl[2]) are hydrolysed at least as fast as the axial anomers, even though they have only ring bonds antiperiplanar to the bond to the equatorial leaving group: they have higher ground state energies and ready access to non-chair conformations (*e.g.* the twist-boat **2t**) where overlap is possible.

This work examines the structure and reactivity of acetals with lone pairs synperiplanar to the C–OR bond of the leaving group. Calculations[1,3,4] suggest that the electronic effects of syn- and anti-periplanar lone pairs should be energetically similar. However, the syn relationship is not normally observed because eclipsed conformations are energetically unfavourable and a conformationally-fixed system is required to establish the synperiplanar geometry.

We report results of a series of acetals **3**, in which the tetra-



hydropyran ring is fixed in the symmetrical boat conformation by the three-carbon bridge (the simple [2,2,2]-system retains considerable flexibility). The fixed geometry allows an examination of the stereoelectronic effects of synperiplanar lone pairs on structure and reactivity uncomplicated by steric effects. The symmetry is confirmed by X-ray crystal structure determinations of five derivatives, which provide data for new crystal structure correlations.

Results

Acetals **3** were prepared from the known bicyclic keto ester **5**[5] *via* the lactol **3** (R = H), by the sequence outlined in Scheme 1. Reduction of **5** with sodium borohydride gave an inseparable mixture of hydroxy esters **6** and **7** in a 2:3 ratio. Treatment of this mixture with sodium methoxide in methanol at reflux gave a mixture of **7** and **8** which were separated by chromatography on silica gel. Reduction of lactone **8** with diisobutylaluminium hydride (DIBAL) provided the crystalline (racemic) lactol **9** which was transformed into the desired bicyclic acetal **3** (R = Me) by acid catalysed exchange with methanol. Other acetals were prepared *via* the acetate **10** (not isolated) by exchange of the acetoxy group for the phenol or alcohol.

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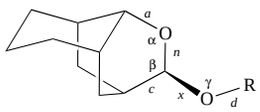
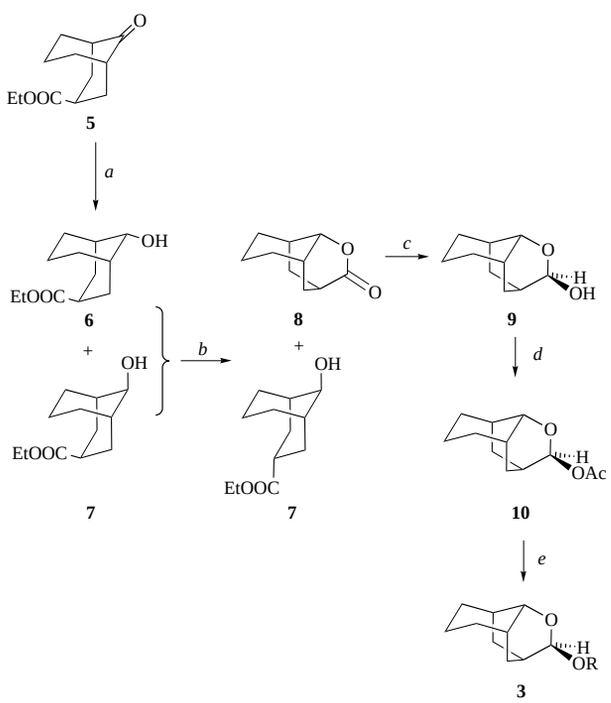
Table 1 Geometry at the acetal centre of compounds **3*** [a]



3*

		Bond lengths [b]/Å				Bond angles [b]/°			Torsion angles/°	
R	pK_a of ROH	*a*	*n*	*x*	*d*	*α*	*β*	*γ*	*anx*	*nxd*
CH_2CHAr_2	15.5	1.442	1.419	1.411(2)	1.420	113.1	110.1(1)	112.4	117.2	65.5
4-Chlorophenyl	9.38	1.447	1.410	1.428(2)	1.371	112.8	109.8(1)	117.2	114.4	75.84
4-Cyanophenyl	7.95	1.451	1.411	1.432(2)	1.362	112.7	109.8(1)	118.4	116.8	68.3
4-Nitrophenyl [c]	7.14	1.451	1.404	1.439(2)	1.354	112.7	109.2(1)	118.3	112.6	65.31
4-Nitrophenyl [c]	7.14	1.451	1.407	1.433(2)	1.355	112.5	109.9(1)	118.7	113.1	68.5
COPh [c]	4.20	1.442	1.398	1.468(4)	1.348	113.0	107.5(2)	117.0	112.7	90.7
COPh [c]	4.20	1.425	1.394	1.475(4)	1.342	112.7	107.8(2)	116.7	115.6	95.8

[a] Measurements at 143 K, except for the benzoate (173 K). For details of structure determinations see the Experimental section. [b] Typical standard errors (in brackets, for the last digit quoted) are given for bond *x* and angle *β*. [c] Two molecules in the asymmetric unit.



Scheme 1 *Reagents and conditions:* i, $NaBH_4$, CH_3OH, 1 h, 87%; ii, CH_3ONa, CH_3OH, reflux, 16 h; chromatography separates 20% of **7** from 57% of **8**; iii, DIBAL, CH_2Cl_2, −78 °C, 2 h, 92%; iv, CH_3OH, $(CH_3O)_3CH$, toluene-*p*-sulfonic acid, 24 h, room temp., 90%; v, Ac_2O, pyridine; vi, ROH, overnight reflux in THF

X-Ray crystal structure determinations of five derivatives **3**, with the exocyclic OR group being an alkoxy [R = 2,2-bis(4-chlorophenyl)ethyl], aryloxy (R = 4-chlorophenyl, 4-cyanophenyl and 4-nitrophenyl) or benzoate (R = COPh) group, provide accurate data (summarised in Table 1) for crystal-structure–reactivity correlations. The pattern of bond lengths at the anomeric centre depends on the basicity of the leaving group, qualitatively as observed previously in other acetals[6] with a marked lengthening of the exocyclic C–OR bond accompanied by a corresponding shortening of the endocyclic C–O bond for better leaving groups. Structural parameters for the tricyclic skeleton (not included in Table 1) do not change significantly over the series. In particular, the maximum divergence from zero (the perfectly eclipsed conformation, illustrated in Fig. 1 by the structure of **3**, R = 4-chlorophenyl) of the torsion angle *anc* in any of the seven individual structures **3*** (Table 1) is 5.9° (mean 4.3 ± 1.5°). (Torsion angles about the corresponding C–C bonds of the [2,2,2]-system diverge even less from zero.)

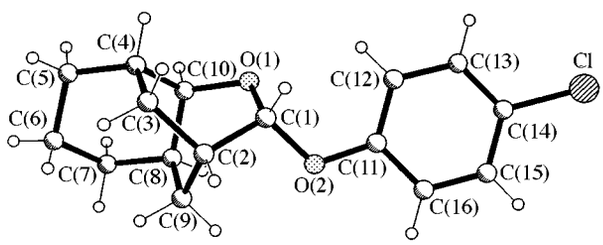


Fig. 1 Molecular structure of **3** (R = 4-chlorophenyl: crystallographic atom numbering scheme)

Kinetics

Rates of spontaneous hydrolysis for four aryl acetals **3** were measured in 10% dioxane–water at 39.2 °C by following the release of aryloxide anion, at four concentrations of KOH between 10^{-3} and 0.04 M. The rate was shown to be pH independent for the 4-nitrophenyl acetal, and independent of (TRIS and hydrogen carbonate) buffer concentration, at six different pH values down to pH 7.6. A logarithmic plot of these rate constants for spontaneous cleavage (included in Table 2) against the pK_a of the conjugate acid of the leaving group defines a good linear free energy relationship, with slope [the Brønsted (leaving group) parameter] $\beta_{LG} = -1.37 \pm 0.04$ (correlation coefficient 0.999). Rate constants were measured also for the acid-catalysed hydrolysis of two alkyl acetals **1a** and **3** [R = $(4\text{-Cl-}C_6H_4)_2CHCH_2$], by HPLC in 50% acetonitrile–water at 25 °C (ionic strength 0.5 M). These latter reactions were specific acid-catalysed: catalysis by formic acid–formate buffers was not detectable.

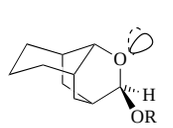
Discussion

Aryl acetals **3** are hydrolysed several times faster than the corresponding axial tetrahydropyranyl acetals **1a**, with the lone pairs antiperiplanar to the exocyclic C–O bond (Table 2). This is evidence that n_O–σ^*_{C-O} overlap involving sp and ap lone pairs is of broadly comparable efficiency, as predicted by calculations. However, detailed analysis of all the data reveals a series of differences between the two systems indicating that sp n_O–σ^*_{C-O} overlap is significantly weaker in the ground state.

Reactivity

Relative rates for various tetrahydropyranyl acetal systems are compared in Table 2. Note first the considerable differences in reactivity between axial tetrahydropyranyl derivatives **1a** and the corresponding oxadecalin acetals **2a**. These reflect the reduced flexibility imposed by the *trans* ring junction, resulting in increased torsional resistance to the formation of the half-chair conformation **2h** of the oxocarbocation in the bicyclic

Table 2 Relative rates of hydrolysis for tetrahydropyranyl acetals



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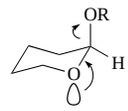
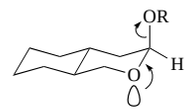


1a

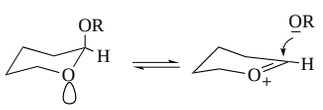


***i*-2a**

Leaving group OR	Relative rate,[a] k/M^{-1} s^{-1} **3**	**1a**	***i*-2a**
MeO/H^{+} [b]	0.21 [c,d] (≡1)	0.226 [e]	1/25 [d]
Ar_2CHCH_2O/H^{+} [f,g]	0.108 ± 0.001	0.10 ± 0.01	—
	k/s^{-1} (spontaneous reaction, 39 °C)		
ArO^{-}	**3** [h,i]	**1a** [j,k]	***i*-2a** [l,m]
m-NO_2	2.85×10^{-5} (≡1)	1/2.7	—
p-CN	1.23×10^{-4} (≡1)	1/3	—
p-NO_2	1.32×10^{-3} (≡1)	1/3.6	1/38
3-Cl-4-NO_2	4.25×10^{-3}	—	—

[a] Rates are given relative to the value for **3**. [b] 25 °C. [c] Ref. 8. [d] 4:5 acetone–water. [e] Water. [f] J. L. Jensen and W. B. Wuhrman, *J. Org. Chem.*, 1980, **48**, 4686. [g] 25 °C, 50% MeCN–water. [h] This work. Ar = 4-chlorophenyl. [i] 10% dioxane–water. [j] Ref. 9. [k] Water. [l] Ref. 7. [m] 30% dioxane–water.

system. (An oxasteroid derivative, with two *trans* ring junctions, is hydrolysed several hundred times more slowly than the corresponding acetal **1a**.[7]) No comparable conformation change is involved in the cleavage of the tricyclic acetals **3**, where the conversion to the oxocarbocation **4** involves only the changes in bonding at the acetal centre common to all such reactions. So the most appropriate comparisons for the reactivity of the tricyclic system are with the simple tetrahydropyranyl acetals **1a**,



1a **11**

where the torsional resistance to the formation of the oxocarbenium ion (**11**) is smallest.

Alkyl acetals **1a** and **3** are hydrolysed in acid at very similar rates. This appears to be true for the methyl acetals **1a** and **3** (R = Me; Table 2), though the published data[8] involve different solvents, and is confirmed by careful measurements of the rates of acid-catalysed hydrolysis of **1a** and **3** [R = $(4\text{-Cl-}C_6H_4)_2$-$CHCH_2$]. The spontaneous hydrolysis of the corresponding aryl derivatives **3** (R = Ar) is a few times faster than that of the corresponding THP acetals.[9] The difference is greater for better leaving groups, and thus expected to disappear for alkyl derivatives. The divergence is quantified by the good linear free energy relationships shown in Fig. 2: the Brønsted (leaving group) parameter β_{LG} is already high, at -1.10 ± 0.06 for the THP derivatives (properly interpreted as evidence for a late transition state, with C–OR bond breaking well advanced[9]), but higher still for the tricyclic acetals **3** (R = Ar), for which $\beta_{LG} = -1.37 \pm 0.04$. β_{LG} is formally a measure of the increase in negative charge on the leaving group in the transition state compared with the acetal ground state.[10] Since complete C–OR bond cleavage generates the RO^{-} anion, with (by definition) unit negative charge, the observed $\beta_{LG} > 1$ indicates either greater than unit charge on the developing oxyanion in the transition state (hard to imagine in this system), or a net positive charge on the OR group in the ground state. The difference in β_{LG} between the two systems clearly supports the second explanation.

Consider for simplicity the reverse reactions (**4**→**3**, **11**→**1a**). It is unlikely that the transition states for the addition of the same oxyanion RO^{-} to the oxocarbenium ions **4** and **11** will be very different, in either extent of bond-making or degree of solvation of the nucleophilic oxygen, and it is certain that some decrease in negative charge will result. So the higher β_{LG} for the cleavage of the tricyclic acetals **3** must represent primarily a ground state effect, with less negative charge density on the leaving group oxygen when the C–OR bond is synperiplanar to a lone pair on the ring oxygen. This is consistent with the synperiplanar lone pair being a less efficient donor in the key n_O–$\sigma^*_{C\text{–}O}$ interaction in the ground state. If this is true we would expect a parallel effect on C–OR bond lengths.

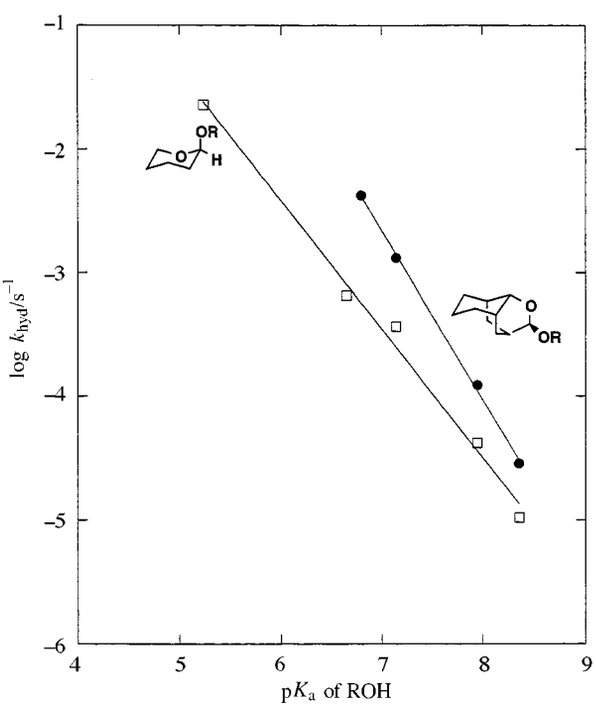


Fig. 2 Linear free energy relationships for the spontaneous hydrolysis of acetals **3** (data taken from Table 1) and for the same reaction of simple aryl tetrahydropyranyl acetals **1a** (data from ref. 9). Least squares slopes give values of $\beta_{LG} = -1.37 \pm 0.04$ (correlation coefficient 0.999) and 1.10 ± 0.06, respectively.

Bond-length correlations

The lengths of the central C–O bonds of acetals are particularly sensitive to the electronegativity of the two oxygens. For series

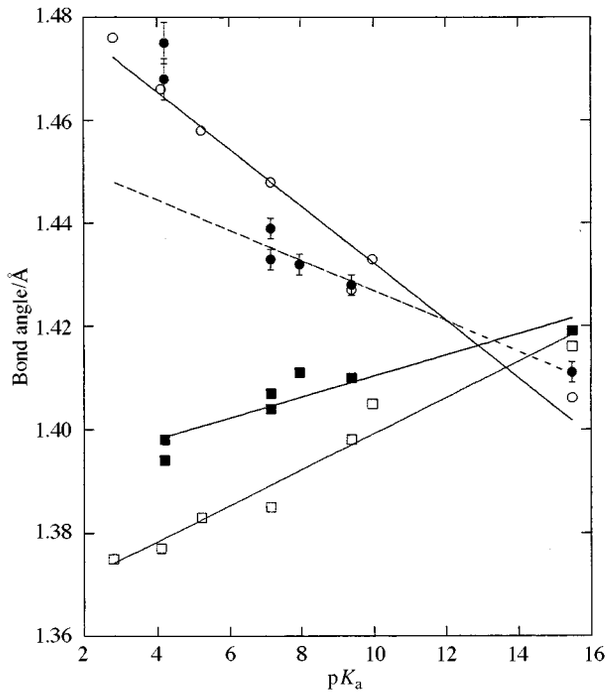
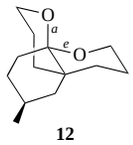


Fig. 3 Plots of bond lengths at the acetal centre for synperiplanar **3** (closed symbols) and antiperiplanar (open symbols) tetrahydropyranyl acetals. Circles represent exocyclic, squares endocyclic C–O bonds (*x* and *n*, respectively, in **13**). The (least squares) lines are calculated, using all points except in the case of sp bond *x* (●), where the two points for the benzoate (pK_a 4.2) have been omitted from the correlation (see the text).

of derivatives, such as **1a**, with the same conformation, these bond lengths show good linear relationships with reactivity (conveniently expressed in terms of the basicity, pK_a, of the leaving group RO^-).[6,11]

The two C–O bond lengths at the acetal centre of a series of acetals **3** are compared with those for axial tetrahydropyranyl acetals **1a** (and **2a**) in Fig. 3. Although they are cleaved faster, the exocyclic C–OR bonds *x* (filled circles) are generally shorter (and the corresponding endocyclic bonds longer) for the tricyclic acetals **3**. This is highly unusual,[6] but consistent with different steric and stereoelectronic effects on extending this C–OR bond in the ground and transition states. Some torsional strain is generated in the transition from chair to half-chair as **1a** is cleaved to give **11**, but no strain is generated in forming the oxocarbenium ion **4**, therefore acetals **3** react faster. However, the conformation does not change appreciably in either series of ground state structures (the in-ring torsion angles in THP acetals **1a** do not vary significantly in the series from R = alkyl to R = *p*-nitrophenyl), so the observed bond-length changes are a more or less uncomplicated measure of stereoelectronic effects. The smaller differences in length between C–O bonds *x* and *n* and the reduced sensitivity to the leaving group (Fig. 3) both confirm that n_O–σ^*_{C-O} donation from the sp lone pairs of the ring oxygen of **3** is weaker than from the ap lone pair of **1a**.

A measure of the difference between syn- and anti-periplanar n_O–σ^*_{C-O} overlap is the difference in the lengths of the endo- and exo-cyclic acetal C–O bonds in systems like **3** [R = 2,2-bis(4-chlorophenyl)ethyl], which have two oxygens of similar intrinsic basicity but are stereoelectronically unsymmetrical because the exocyclic oxygen has a lone pair antiperiplanar to the endocyclic C–O bond. The difference (0.008 Å) in this case is small, and significant only because it is supported by correlations with other derivatives (Fig. 3), which predict that the exocyclic bond *x* will be shorter than the endocyclic bond *n* for leaving groups derived from alcohols ROH with pK_a > 12.1. For comparison, the difference in the two bond lengths is 0.028 Å for the tricyclic acetal **12**, which is stereoelectronically



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unsymmetrical because one of the two otherwise identical oxygens is axial, and the second equatorial, to the other tetrahydropyran ring, so the comparison is between antiperiplanar n_O–σ^*_{C-O} and σ_{C-C}–σ^*_{C-O} overlap.[12]

The bond length–pK_a correlation for the sp system **3** (Fig. 3) gives a good straight line for the points from the four poorer leaving groups (r = 0.977 for five data points), but the point(s) for the benzoate ester (**3**, R = COPh) show a marked positive deviation. The benzoate is a highly reactive system, with a predicted half-life of 42 ms in water, and falls in the particularly interesting region on the borderline of stability; we can speculate that this deviation may signify the expected onset of curvature in such correlations,[6] though too much significance should not be attached to a result for a single compound.

Conclusions

We conclude that synperiplanar n_O–σ^*_{C-O} overlap in acetals **3** is less efficient than in simple THP acetals **1a**, which have a lone pair antiperiplanar to the C–OR bond. This result is consistent with other comparisons of sp and ap through-bond orbital interactions: including three-bond coupling between vicinal protons in ^{1}H NMR spectroscopy, also slightly smaller for the sp compared with the ap arrangement, and E2 eliminations; where both sp and ap are possible ap geometry is clearly preferred.[13] In acetals **3** too the effect is significant, but not large.

Experimental

General

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 NMR chemical shifts were determined using residual non-deuterated solvent as an internal standard and are reported downfield from TMS in ppm. Coupling constants are reported in Hz. 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.

2-[2,2-Bis(4-chlorophenyl)ethoxy]tetrahydropyran 1a [R = (4-Cl-C_6H_4)$_2$CHCH$_2$)]

1a was prepared by the acid-catalysed addition of the alcohol to 3,4-dihydro-2*H*-pyran.[14] It was purified by column chromatography (eluent 4:1 hexane–ethyl acetate) as colourless prisms, mp 68–69 °C (Found: C, 64.86; H, 5.70. $C_{19}H_{20}Cl_2O_2$ requires 64.97; 5.74%); δ_H($CDCl_3$) 7.26–7.23 (4H, m), 7.17–7.13 (4H, m), 4.58 (1H, t, *J* 3.3), 4.24–4.19 (2H, m), 3.86–3.80 (1H, m), 3.61–3.56 (1H, m), 3.45–3.40 (1H, m), 1.69–1.44 (6H, m) [HRMS (ESI) 373.0736 (M^+ + Na^+); $C_{19}H_{20}Cl_2O_2$ requires 373.0738.]

Ethyl 9-hydroxybicyclo[3.3.1]nonane-3-carboxylate 6 and 7

To a stirred solution of ethyl 9-oxobicyclo[3.3.1]nonane-3-carboxylate **5**[5] (0.981 g, 5 mmol) in methanol (10 ml) was added

dropwise sodium borohydride (0.185 g, 5 mmol) during 10 min at 0 °C. The mixture was stirred for 1 h at room temperature. Diethyl ether (30 ml) was added and the resulting mixture washed with 1 M HCl (2 × 10 ml) and brine (2 × 10 ml). The organic layer was dried with magnesium sulfate, filtered and evaporated to yield a solid (0.864 g). This solid was shown to be a mixture of **6** and **7** in a 2:3 ratio by ^{13}C NMR spectroscopy. These two compounds are difficult to separate by column chromatography.

9-Oxatricyclo[5.3.1.0^{3,8}]undecan-10-one 8

The above mixture of **6** and **7** (0.198 g, 1 mmol) was added to a solution made from sodium (0.092 g, 4 mmol) dissolved in methanol (10 ml), and refluxed for 16 h. The reaction mixture was cooled and acidified with 2 M HCl, extracted with diethyl ether (4 × 25 ml), the organic phase dried over magnesium sulfate, filtered and evaporated to yield an oil (0.169 g). Separation by flash column chromatography on silica gel (hexane–ethyl acetate 7:3) from unreacted **7** (40 mg, 20%) gave **8** (95 mg, 57%).

9-Oxatricyclo[5.3.1.0^{3,8}]undecan-10-ol 9

To a solution of **8** (85 mg, 0.5 mmol) in anhydrous THF (2 ml) was added 1 M diisobutylaluminium hydride in CH_2Cl_2 (0.49 ml) at −78 °C. After 2 h the reaction mixture was warmed to room temperature and 20% aqueous acetic acid (5 ml) added slowly. It was then extracted with diethyl ether (3 × 15 ml), and the diethyl ether phase washed with 10% aqueous sodium hydrogen carbonate (2 × 10 ml) then brine (2 × 10 ml), dried over magnesium sulfate, filtered and evaporated to yield a colourless oil. Compounds **8** (15 mg, 18%) and **9** (65 mg, 74%) were separated by flash column chromatography (hexane–ethyl acetate 7:3). The lactol **9** had mp 54–56 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3600, 1025; $\delta_H(CDCl_3)$ 5.14 [1 H, br, anomeric C*H*(OH)], 4.00 (1H, d, *J* 3.9, OH), 3.39 [1H, t, 3.5 Hz, C*H*OCO(OH)], 2.25 (1H, m), 2.17 (2H, m), 1.80–1.10 (10H, m, CH_2); $\delta_C(CDCl_3)$ 94.30, 72.68, 31.12, 30.78, 29.98, 28.04, 29.39, 21.67, 14.17; *m*/*z* 168 (M^+), 151 ($M^+ - OH$).

Acetal 3 (R = CH_3)

Compound **9** (65 mg) was treated with anhydrous methanol (2 ml), trimethyl orthoformate (0.5 ml) and toluene-*p*-sulfonic acid (10 mg). After stirring for 23 h at room temperature, the solvent was evaporated *in vacuo* and hexane (15 ml) was added, the resulting solution was washed with saturated aqueous sodium hydrogen carbonate (2 × 7 ml) then brine (2 × 7 ml), dried over sodium sulfate, filtered and evaporated. The residue was purified by flash column chromatography (eluent hexane–ethyl acetate–triethylamine 80:20:0.5) to give the acetal (64 mg, 90%); ν_{max}(film)/cm^{-1} 2925, 1110; $\delta_H(C_6D_6)$ 4.63 (1H, dd, *J* 2.35, 0.90, anomeric H), 3.42 (3H, s, OMe), 3.37 (1H, t, *J* 3.80, CHOCOMe), 2.32 (2H, m), 2.03 (1H, m), 1.70–0.90 (1H, m, 10H, CH_2); $\delta_C(C_6D_6)$ 101.19, 72.12, 54.56, 31.83, 31.60, 30.25, 30.45, 28.45, 29.74, 23.01, 14.66; *m*/*z* 182 (M^+), 151 ($M^+ - OCH_3$).

Other acetals **3** used in this work were prepared *via* the acetate **10** (not isolated).

10-(4-Nitrophenoxy)-9-oxatricyclo[5.3.1.0^{3,8}]undecane (3, R = 4-nitrophenyl). To the lactol **9** (116 mg, 0.69 mmol) dissolved in dry pyridine (4 ml) was added acetic anhydride (0.2 ml, 2.1 mmol) and the solution was stirred for 2 h. Volatile liquids were removed by evaporation under reduced pressure at 70 °C, the residue dissolved in dry THF (4 ml) and a solution of 4-nitrophenol (220 mg, 1.6 mmol) in dry THF (10 ml) was added. The resulting solution was refluxed overnight, the solvent removed under reduced pressure and the residue dissolved in diethyl ether (30 ml). The solution was washed with 10% aqueous NaOH (3 × 5 ml), water (3 × 20 ml) and brine (3 × 20 ml), then the diethyl ether layer was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed (SiO_2, EtOAc–hexane 3:7) to give the acetal (47 mg, 0.28 mmol, 56%); R_f (EtOAc–hexane 3:7) 0.705; recrystallisation from CH_2Cl_2–hexane gave crystals, mp 137–138 °C (Found: C, 66.62; H, 6.37; N, 4.69. $C_{16}H_{19}NO_4$ requires C, 66.42; H, 6.62; N, 4.84%); δ_H(250 MHz; $CDCl_3$) 8.16 (2H, d, *J* 9.2, ArH), 7.07 (2H, d, *J* 9.2, ArH), 5.56 (1H, CHOAr), 3.52 (1H, t, *J* 3.7, CHOCOAr), 2.4–1.2 (13H, m, tricyclic skeleton); $\delta_C(CDCl_3)$ 162.6, 141.8, 125.8, 116.2, 98.8, 73.4, 31.0, 30.9, 29.8, 29.4, 29.2, 27.7, 22.4, 14.2. The structure was confirmed by X-ray structure determination.

10-(3-*Nitrophenoxy*)-9-*oxatricyclo*[5.3.1.0^{3,8}]*undecane* (**3**, *R* = 3-*nitrophenyl*).—Mp 79–80 °C (from CH_2Cl_2–hexane); δ_H(250 MHz; $CDCl_3$) 7.9–7.3 (4H, m, ArH), 5.53 (1H, CHOAr), 3.52 (1H, t, *J* 3.6, CHOCOAr), 2.4–1.2 (13H, m, tricyclic skeleton); $\delta_C(CDCl_3)$ 157.9, 149.2, 129.8, 123.0, 116.2, 111.4, 98.9, 73.3, 31.0, 30.9, 29.9, 29.4, 29.3, 27.8, 22.5, 14.2.

10-(4-*Chlorophenoxy*)-9-*oxatricyclo*[5.3.1.0^{3,8}]*undecane* (**3**, R = 4-*chlorophenyl*).—Mp 122–124 °C (from CH_2Cl_2–hexane); δ_H(250 MHz; $CDCl_3$) 7.23 (2H, d, *J* 9.7, ArH), 6.95 (2H, d, *J* 8.7, ArH), 5.42 (1H, CHOAr), 3.49 (1H, t, *J* 3.5, CHOCOAr), 2.4–1.2 (13H, m, tricyclic skeleton); $\delta_C(CDCl_3)$ 156.0, 129.3, 126.2, 117.8, 98.8, 73.1, 31.1, 31.0, 29.9, 29.7, 29.5, 29.4, 27.9, 22.5, 14.2. The structure was confirmed by X-ray structure determination.

10-(4-*Cyanophenoxy*)-9-*oxatricyclo*[5.3.1.0^{3,8}]*undecane* (**3**, *R* = 4-*cyanophenyl*).—Mp 160–162 °C (from CH_2Cl_2–hexane); δ_H(250 MH; $CDCl_3$) 7.57 (2H, d, *J* 8.9, ArH), 7.08 (2H, d, *J* 8.9, ArH), 5.52 (1H, CHOAr), 3.51 (1H, t, *J* 3.7, CHOC), 2.4–1.2 (13H, m, tricyclic skeleton); $\delta_C(CDCl_3)$ 160.7, 133.8, 119.2, 116.9, 98.4, 73.3, 31.0, 30.8, 29.8, 29.3, 29.2, 27.7, 22.4, 14.1. The structure was confirmed by X-ray structure determination.

10-(3-*Chloro*-4-*nitrophenoxy*)-9-*oxatricyclo*[5.3.1.0^{3,8}]*undecane* (**3**, *R* = 3-*chloro*-4-*nitrophenyl*).—Mp 109–111 °C (from CH_2Cl_2–hexane); δ_H(250 MH; $CDCl_3$) 7.97 [1H, d, *J* 9.1, ArH(5)], 7.18 [1H, d, *J* 2.6, ArH(2)], 6.99 [1H, dd, *J* 2.6, 9.1, ArH(6)], 5.52 (1H, CHOAr), 3.52 (1H, t, *J* 3.7, CHOCOAr), 2.4–1.2 (13H, m, tricyclic skeleton); $\delta_C(CDCl_3)$ 160.9, 130.9, 127.9, 122.2, 119.2, 99.1, 73.5, 31.0, 30.8, 29.8, 29.3, 29.2, 27.6, 22.4, 14.2.

10-[2,2-*Bis*(4-*chlorophenyl*)*ethoxy*]-9-*oxatricyclo*[5.3.1.0^{3,8}]-*undecane* [**3**, *R* = 2,2-*bis*(4-*chlorophenyl*)*ethyl*].— This was prepared in a similar manner, except that a crystal of toluene-*p*-sulfonic acid was added to catalyse the exchange reaction, mp 92–93 °C; δ_H(250 MHz; $CDCl_3$) 7.3–7.0 (4H, m, Ar), 4.75 (1H, anomeric H), 4.3 (2H, m, OCH_2), 3.8 (1H, dd, *J* 5.8, 9.1, $CHAr_2$), 3.36 (1H, t, *J* 3.8, CHOCOR), 2.1–1.1 (13H, m, tricyclic skeleton); $\delta_C(CDCl_3)$ 140.8, 140.6, 132.3, 132.2, 129.9, 129.8, 128.5, 128.4, 100.1, 72.5, 69.4, 49.8, 31.3, 31.0, 30.1, 29.54, 29.47, 28.0, 22.6, 14.3. The structure was confirmed by X-ray structure determination.

10-(*Benzoyloxy*)-9-*oxatricyclo*[5.3.1.0^{3,8}]*undecane* (**3**, *R* = *benzoyl*).—The lactol **9** (420 mg, 2.5 mmol) was dissolved in pyridine (4 ml) and a solution of benzoic anhydride (678 mg, 3 mmol) in pyridine (4 ml) was added with stirring. After standing overnight the solution was worked up as for the acetate **10** (above), and the residue chromatographed (SiO_2, EtOAc–hexane 3:7) to give the benzoate (555 mg, 2.0 mmol, 80%); δ_H(200 MHz; $CDCl_3$) 8.2–8.1 (2H, m, Ar), 7.1–7.6 (2H, m, Ar), 6.26 (1H, dd, *J* 1.2 and 2.3, anomeric H), 3.53 (1H, t, *J* 3.8, CHOCOR), 2.5–1.1 (13H, m, tricyclic skeleton). The structure was confirmed by X-ray structure determination.

Kinetic measurements

Stock solutions (5 mM in dioxane) of aryl acetals were injected into buffer solutions in 10% (v/v) dioxane–water (up to 0.4 M total buffer) made up with KCl to ionic strength 1.0 M. Rates of hydrolysis were measured by monitoring the appearance of the aryl oxide anion over time, at 39.2 °C; as described previously.[9]

The hydrolysis of the alkyl acetals **1a** and **3** [R = (4-Cl-

Table 3 Crystal data for five acetals **10** with synperiplanar lone pairs on oxygen

	Compound **10**, R =				
	2,2-Diarylethyl	4-Chlorophenyl	4-Cyanophenyl	4-Nitrophenyl	Benzoyl
Formula	$C_{24}H_{26}Cl_2O_2$	$C_{16}H_{19}ClO_2$	$C_{17}H_{19}NO_2$	$C_{16}H_{19}NO_4$	$C_{17}H_{20}O_3$
M_r	417.35	278.76	269.33	289.32	272.33
Crystal habit	Colourless prism	Colourless block	Colourless, irregular	Colourless tablet	Colourless, equidim.
Crystal size/mm	0.85 × 0.5 × 0.5	0.8 × 0.6 × 0.6	0.7 × 0.5 × 0.15	0.65 × 0.5 × 0.25	0.4 × 0.4 × 0.3
Crystal system	Monoclinic	Monoclinic	Monoclinic	Triclinic	Triclinic
Space group	$P2_1/c$	$P2_1/c$	$P2_1/n$	$P\bar{1}$	$P\bar{1}$
Cell constants:					
a/Å	14.415(2)	11.717(2)	12.636(3)	10.456(3)	10.190(2)
b/Å	15.963(2)	9.7731(11)	9.122(2)	12.478(4)	11.847(2)
c/Å	8.998(2)	12.306(2)	13.417(3)	13.060(3)	13.105(2)
α/°	90	90	90	117.53(2)	89.770(14)
β/°	94.937(12)	103.163(12)	117.32(2)	108.90(2)	70.055(12)
γ/°	90	90	90	92.80(2)	70.577(8)
V/Å^3	2062.7	1372.1	1374.1	1388.8	1391.8
Z	4	4	4	4	4
D_x/mg m^{-3}	1.344	1.349	1.302	1.384	1.300
μ/mm^{-1}	0.33	0.27	0.09	0.10	0.09
$F(000)$	632	592	576	616	584
T/°C	−130	−130	−130	−130	−100
$2\theta_{max}$/°	55	55	55	55	50
No. of reflections:					
measured	9520	3314	3316	6735	5978
unique	4765	3167	3165	6398	4832
R_{int}	0.029	0.011	0.020	0.012	0.031
Parameters	254	173	182	380	361
Restraints	0	0	0	0	388
$wR(F^2$, all refl.)	0.092	0.100	0.124	0.114	0.142
$R[F, >4\sigma(F)]$	0.035	0.037	0.048	0.046	0.056
S	1.04	1.03	1.07	1.05	0.85
max. Δ/σ	0.001	0.001	<0.001	0.001	<0.001
max. $\Delta\rho$/e Å^{-3}	0.31	0.31	0.28	0.29	0.46

$C_6H_4)_2CHCH_2$] in 50% acetonitrile–water at 25 °C and ionic strength 0.5 M (KCl), was followed by HPLC for two half-lives. Aliquots were removed, quenched with the calculated amount of base (phosphate buffer or NaOH) and chilled immediately with solid CO_2 before running on a Hichrom S50DS-3991 reversed phase column, eluent methanol–water (15 and 12% water, respectively for **1a** and **3**).

Crystal structure analyses

Crystal data for five compounds **3** are presented in Table 3.‡

Data collection. Data were collected with Mo-Kα radiation on a Stoe STADI-4 diffractometer equipped with a Siemens LT-2 low temperature device. Scan type ω/θ. Cell constants were refined from $\pm\omega$ angles of *ca*. 50 reflections in the 2θ range 20–23°. The exception to this was **3** (R = benzoyl), data for which were collected on a Siemens P4 diffractometer, and cell constants were refined from setting angles.

Structure solution and refinement. Direct methods. Anisotropic refinement on F[2,15] H atoms with a riding model. For the more weakly diffracting structure **10** (R = benzoyl) similarity restraints were applied to light-atom displacement parameters.

‡ Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 2*, available *via* the RSC Web pages (http://chemistry.rsc.org/rsc/p1pifa.htm). Any request to the CCDC for this material should quote the full literature citation and the reference number 188/107.

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