2-Alkoxy-3-oxoalkyl-tetrahydropyrans and -tetrahydrofurans: versatile intermediates in heterocyclic synthesis

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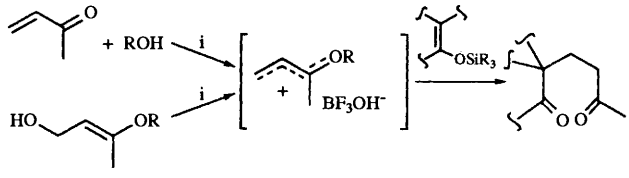
A new Lewis acid-catalysed Michael-type addition of heterocyclic enol ethers to hemiacetal vinylogues **1** or to enones in the presence of a hydroxylic compound is described. The 1,5-keto acetals **3** so obtained have been studied with a view to synthetic applications. Acidic hydrolysis of compounds **3** leads in most cases to annulation products **9** in a stereocontrolled manner. Organometallic addition, hydride reduction or reductive amination of 1,5-keto acetals **3** afford, in good yields, the hydroxy acetals **12** (and cyclisation products **13**) and amino acetals **18**, respectively. Acidic treatment of these compounds gave access to oxa- and aza-annulation products **13**, **17** and **19** by an efficient kinetically controlled heterocyclisation process. These products can be obtained with high *cis*-junction selectivities as established by NMR spectroscopy and confirmed by equilibration studies.

Introduction

1,5-Dicarbonyl compounds[1,2] are useful intermediates in organic synthesis, especially when further cyclisation can occur, leading to cyclohexenonic skeletons of great value in terpenic,[3] steroidal[4] and carbohydrate[5] syntheses. We recently proposed a general method of preparation of such compounds by cationic Michael-type reaction, catalysed by boron trifluoride–diethyl ether, between a silyl enol ether and a hemiacetal vinylogue **1** †,[6] or its synthetic equivalent: methyl vinyl ketone (MVK) in the presence of a stoichiometric amount of a hydroxylic compound[7] (Scheme 1). This reaction, involving formation of a delocalised-double-bond carbocation, proved to be effective in the preparation of Robinson annulation-type products in high total yield even with hindered substrates, while ensuring regio- and diastereo-control.[8]

With heterocyclic enol ethers **2**, only a few examples of Michael reaction-type products have been reported,[9,10] because of the temperature conditions used; Diels–Alder cycloaddition can compete[9] or indeed mainly occurs.[10] As for silyl enol ethers, we have shown that a Lewis acid-catalysed Michael-type addition took place between compounds **2** and the hemiacetal vinylogues **1a–d**, leading chemioselectively to 1,5-keto acetals **3**[11] (Scheme 2).

The results reported here concern the scope of this reaction, subsequent acidic hydrolysis and synthetic developments due to the aptitude of compounds **3** to undergo modifications of the carbonyl group while still maintaining an intact acetal moiety. As examples, ready conversions into various hydroxy and amino acetals and subsequent cyclisation are reported. Otherwise, *cis–trans* isomerism of Michael adducts **3** and of derived bicyclic products **9**, **13**, **17**, **19** has been elucidated by spectroscopic studies.



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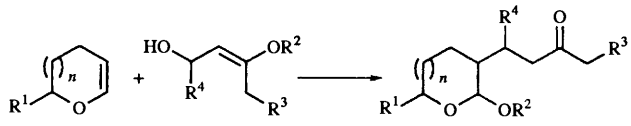
Scheme 1 *Reagents:* i, BF_3·Et_2O



2 **1a–d** **3**

Scheme 2 *Reagents:* BF_3·Et_2O, $MeNO_2$. Groups R^1–R^4 are defined in Table 1.

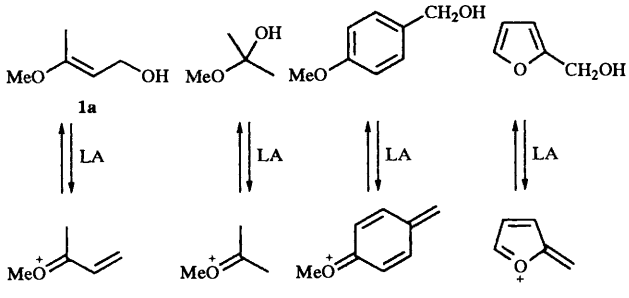
Results and discussion

1,5-keto acetal synthesis

The Lewis acid-catalysed reaction between a hemiacetal vinylogue **1** (equivalent to an α,β-unsaturated ketone) and a heterocyclic enol ether **2** (equivalent to an aldehyde) generally gives access to keto acetals **3** in moderate yields in the presence of 0.25 mol equiv. of BF_3·OEt_2 (Table 1).

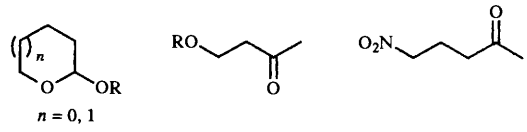
Experiments showed significant improvements of the yields when 2 mole equivalents of vinylogue hemiacetal **1** were used (Table 1, entries 5, 7).‡ The use of 1 mole equivalent of reagent **1a** with 1 mole equivalent of alcohol R^2OH also

† Hemiacetal vinylogues **1** present some analogies with hemiacetals, hemiacetal phenylogues and furfuryl alcohol in the presence of a Lewis acid (LA).



1a

‡ Two side-reactions are observed: tetrahydropyranyl or tetrahydrofuranyl alcohol protection (**5**) and hetero-Michael addition of alcohol on the electrophile (**20**). In some cases, solvolysis product **21** can compete slightly with the major Michael reaction product **3**.



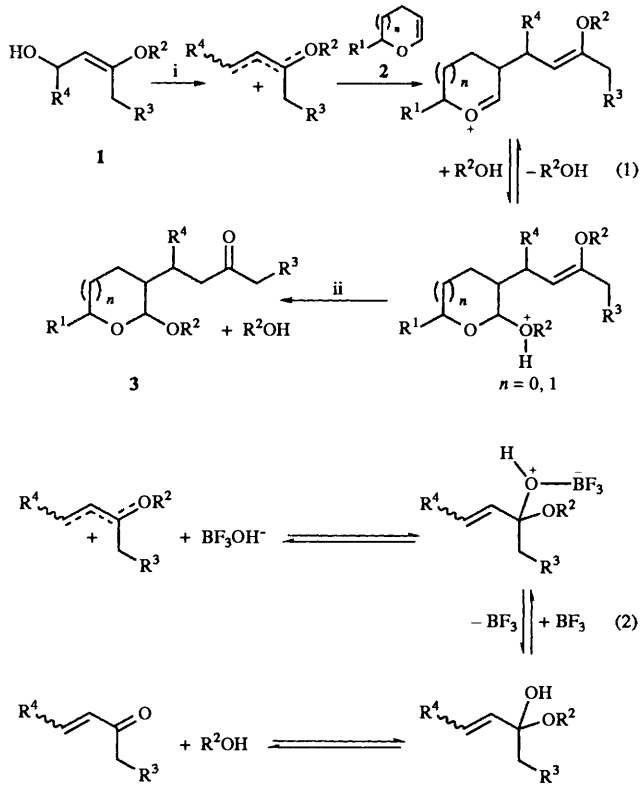
n = 0, 1

5 **20** **21**

Table 1 Preparation of keto acetals **3** with the hemiacetal vinylogue **1**

	Enol ether			Hemiacetal vinylogue					Product	
Entry	**2**	*n*	R^1	**1**[b]	R^2	R^3	R^4	Reaction time (*t*/h)[a]	**3**	Yield (%)[c]
1	**2a**	0	H	**1a**	Me	H	H	1	**3a**	50
2	**2a**	0	H	**1b**	Et	H	H	0.5	**3b**	35
3	**2a**	0	H	**1c**	Me	Et	H	3	**3c**	42
4	**2a**	0	H	**1d**	Me	H	Me	1	**3d**	30
5	**2b**	1	H	**1a**[d]	Me	H	H	0.5	**3e**	25
6	**2b**	1	H	**1a**[e]	Me	H	H	0.5	**3e**	36
7	**2b**	1	H	**1a**	Me	H	H	0.5	**3e**	57
8	**2b**	1	H	**1b**	Et	H	H	0.5	**3f**	35
9	**2b**	1	H	**1c**	Me	Et	H	3	**3g**	35
10	**2c**	1	OMe	**1a**	Me	H	H	0.5	**3h**	56
11	**2c**	1	OMe	**1c**	Me	Et	H	3	**3i**	40

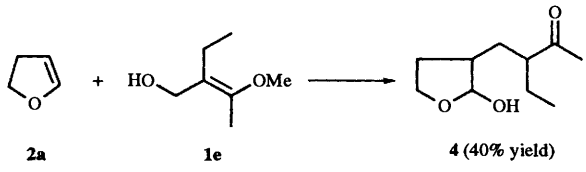
[a] −20 °C, $MeNO_2$, BF_3·OEt_2, 0.25 mol equiv. [b] 2 Mol equiv. unless otherwise noted. [c] Yield of product **3** purified by flash chromatography. [d] 1 Mol equiv. [e] 1 Mol equiv. and 1 mol equiv. of anhydrous methanol.



Scheme 3 *Reagents*: i, BF_3·Et_2O; ii, water

caused an increase in the yield of keto acetal **3e** (Table 1, entries 5, 6). Nevertheless, this improvement (25 to 36%) is lower than those obtained with 2 mole equivalents of reagent **1a** because of the competitive formation of a tetrahydropyranyl derivative under the reaction conditions used. These results may suggest the following mechanistic process, in which 2 mole equivalents of hemiacetal vinylogue **1** are required for the formation of keto acetal **3**: one for carbon–carbon bond formation [Scheme 3, equilibrium (1)] and another for generating the alcohol R^2OH [Scheme 3, equilibrium (2)] needed in the last step for the nucleophilic attack of the intermediate oxonium.

With the use of a tetrasubstituted double-bond-vinylogue hemiacetal **1e** (2 mol equiv.), the major addition product became the keto hemiacetal **4** instead of the corresponding keto acetal **3**, possibly due to steric hindrance (Scheme 4).



Scheme 4 *Reagents*: BF_3·Et_2O, $MeNO_2$

To the best of our knowledge the synthesis of only the keto acetals **3a** and **3e** has been described. They were prepared by Giese,[12] and this involved the condensation of MVK with an intermediate radical obtained by reduction of the solvomercuriated product of ethers **2a** and **2b**, respectively. This carbon–carbon bond formation exhibits *trans* selectivity whatever the ring size.

The cationic process described here led mainly to *trans* products for five-membered rings [diastereoisomeric excess (de) > 30%] and to *cis* products for six-membered rings (de = 30%) as shown by ^1H NMR spectra. The stereochemical analysis§ of these compounds was based on the value of the coupling constant of the acetalic proton 2-H. For the tetrahydropyranic derivatives, a high value of this constant ($J_{2,3}$ 6 Hz) is in good agreement with a *trans* junction for the minor isomer (ring junction equatorial–equatorial) and a weaker value (< 3 Hz) is consistent with a *cis* junction for the major isomer (ring junction axial–equatorial). As established by Giese,[12] a *trans* configuration may be attributed to the tetrahydrofuranic acetal of lowest $J_{2,3}$ value (1.5 Hz), which coincides with the major isomer in the present case (4 Hz for the other isomer). For all the compounds studied, the proton 2-H of the *cis* stereoisomer was always displaced more downfield than that for the *trans* stereoisomer. The relative configuration obtained follows upon the oxygen–carbon bond formation and may allow the opposite selectivity to that observed by Giese[12] in the tetrahydropyran series.

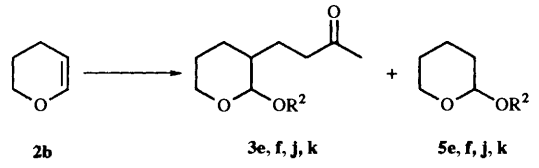
We have also shown that the hemiacetal vinylogues **1a** and **b** could be replaced by a mixture: MVK–alcohol (R^2OH) (Scheme 5 and Table 2). Without the alcohol no keto hemiacetal (**3**, R^2 = H) was detected. Use of primary alcohols (entries 1, 2) gave low yields, because of the competitive formation of tetrahydropyranyl derivatives **5** but this side reaction may be restricted with the use of *sec*-butyl alcohol (entry 3). So, keto acetals **3** are now available from cheap material on a large scale (up to 50 mmol) and in a one-step procedure.

§ Diastereoisomeric ratios were determined by ^1H NMR (400 or 500 MHz) spectroscopy.

Table 2 Keto acetals **3** prepared by the enone alcohol procedure on enone **2b** (Scheme 3 refers)

Entry	R^2OH	Reaction time (t/h)[a]	Product 3	Yield (%)[b]
1	MeOH	1	**3e**	21
2	EtOH	0.5	**3f**	33
3	Bu^{t}OH	1	**3j**	40
4	Pr^{i}OH	1	**3k**	30

[a] MVK 2 mol equiv., R^2OH 2 mol equiv., BF_3·OEt_2 0.25 mol equiv., $MeNO_2$, −20 °C. [b] Yield of product purified by flash chromatography.



Scheme 5 *Reagents:* MVK, R^2OH

With hemiacetal vinylogue **1f**, the synthetic equivalent of crotonaldehyde, the aldolisation product **6** was mainly obtained according to previous results,[13] together with aldehyde **3l** in low yield (Scheme 6).

1,5-Keto acetal hydrolysis

Keto acetals **3** are obvious precursors of 1,5-keto aldehydes.¶ Treatment of compounds **3** in aq. acidic medium led to different cyclisation products according to the functionality initially borne by the heterocyclic ring (Scheme 7).

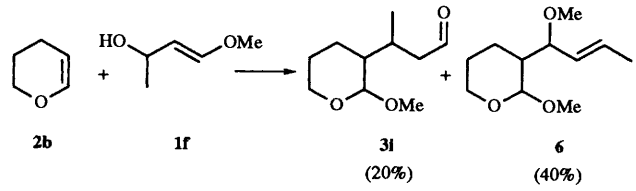
Acetals **3a–g**, **j**, heated in an acidic medium, led to bicyclic keto ethers **9a**, **d**, **e**, **g** (Table 3, entries 1, 2, 4, 6–9) or their monocyclic enone precursors **10** (Table 3, entry 3). In the first step, keto hemiacetal **7** was obtained and could be isolated (Table 3, entry 5) if acidic treatment was performed at room temperature. After reflux, the intermediate 1,5-dicarbonyl compound **8**, produced by hydrolysis of keto hemiacetal **7** underwent intramolecular annulation followed by dehydration. In most cases, the cyclohexenone **10** so obtained was finally converted by intramolecular hetero-Michael addition into adduct **9**.

This expeditious synthesis of bicyclic heterocycles **9** bearing a carbonyl function offered the main advantage of ensuring high stereocontrol of the ring junction (de > 95%). ^1H NMR analysis§ has unambiguously established a *trans* junction in the octahydrobenzopyran series (**9e**, **g**) and a *cis* junction for its hexahydrobenzofuran homologue (**9a**, **d**). A study of 1D and 2D homonuclear chemical-shift correlation (COSY) $^1H/^1H$ spectra for compounds **9a** and **9e** has allowed the identification of each proton and the determination of the nature of the ring junction from the coupling constants (7a-H and 8a-H protons).

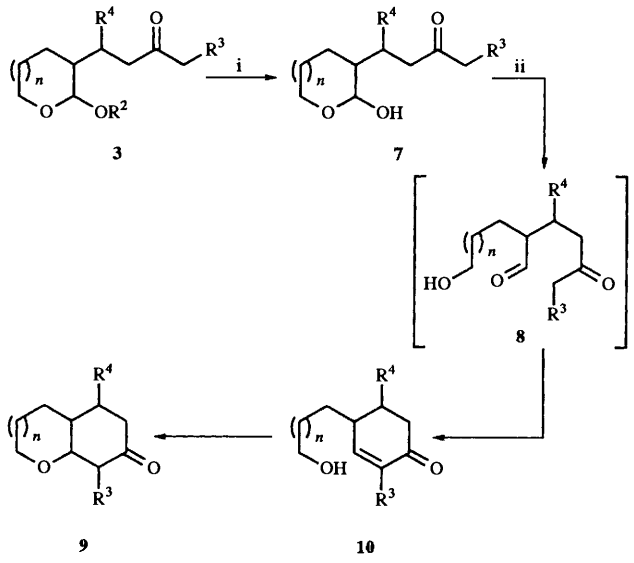
For compound **9e**, the 8a-H proton reveals two high-value coupling constants: one with the axial proton 8-H ($J_{8a,8}$ 12.1 Hz) and the other with the junction proton 4a-H ($J_{8a,4a}$ 9.7 Hz). This result attests that the protons 8a-H and 4a-H are in a *trans* diaxial relationship, so the ring junction is *trans*, whereas Birch[14] reported a lower values of $J_{8a,4a}$ (~3 Hz) for a *cis* analogue of compound **9e**. For compound **9a**, the multiplicity of the signal given by the proton 7a-H showed a weak coupling constant with the equatorial proton 7-H ($J_{7a,7}$ 4.5 Hz) and also with the junction proton 3a-H ($J_{7a,3a}$ 6.6 Hz) as well as a moderate one with the axial proton 7-H. This spectroscopic analysis established an equatorial position for 7a-H and an axial position for 3a-H; according to these values, the ring junction is *cis*. ^1H NMR spectra of compounds **9d** and **9g** exhibited the same ring junction as for compounds **9a** and **9e**, respectively. The presence of two epimers is to be noted; this is due to the third asymmetric centre. Reaction conditions and results concerning ring-junction geometry of carbocyclic analogues suggest that the formation of compounds **9** is under thermodynamic control.

Compared with the sole method proposed in the literature for the preparation of hexahydrochroman-7-one **9e**[15] from a resorcinol derivative in six steps, the route proposed here is considerably shorter (two steps) and can be applied to the synthesis of substituted analogues such as compound **9g**. In the octahydrobenzofuran field, no general method has really been described, although the preparation of compound **9a**, substituted by a carboxylic moiety, from methoxytyrosine was briefly mentioned.[16] So, we suggest that the synthetic route for the preparation of compounds **9** and **10** reported here could be applied to the synthesis of natural products such as lycoramine[17] or juvabione.[14]

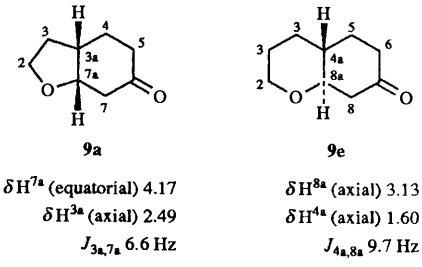
Acidic treatment of keto acetals **3h** and **i** follows a different cyclisation process. Dicarbonylated cyclohexenes **11** are



Scheme 6 *Reagents:* BF_3·Et_2O, $MeNO_2$



Scheme 7 *Reagents and conditions:* i, 3 mol dm^{-3} HCl; ii, heat. Groups R^2–R^4 are given in Table 3.

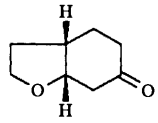
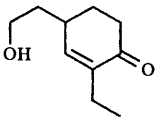
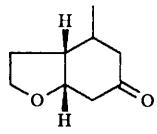
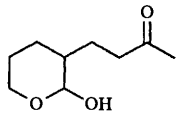
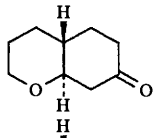
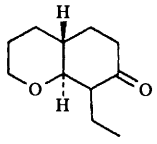


δH^{7a} (equatorial) 4.17
δH^{3a} (axial) 2.49
$J_{3a,7a}$ 6.6 Hz

δH^{8a} (axial) 3.13
δH^{4a} (axial) 1.60
$J_{4a,8a}$ 9.7 Hz

¶ Attempts to prepare monoprotected 1,5-diketones from compound **1a** and 2-methyldihydrofuran gave only hydrolysis of the starting materials and formation of methoxy ketone **20**.

Table 3 Acidic treatment of keto acetals **3**

Entry	Keto acetal	*n*	R^2	R^3	R^4	Product[a]		Yield (%)[b]
1	**3a**	0	Me	H	H		**9a**	50
2	**3b**	0	Et	H	H			50
3	**3c**	0	Me	Et	H		**10c**	54
4	**3d**	0	Me	H	Me		**9d**	50
5	**3e**	1	Me	H	H		**7e**[c]	48
6	**3e**	1	Me	H	H		**9e**	55
7	**3f**	1	Et	H	H			55
8	**3j**	1	Bu^t	H	H			48
9	**3g**	1	Me	Et	H		**9g**	38

[a] HCl 3 mol dm^{-3}, reflux for 1 h unless otherwise noted. [b] Yield of product purified by flash chromatography. [c] HCl 3 mol dm^{-3}, 20 °C, 0.5 h.

Table 4 Acidic cyclisation of hydroxy acetal **12** into compound **13**

Entry	Acidic medium	Time (*t*/h)	Conversion rate (%)[a]	*cis*:*trans* ratio (%)[b]
1	HCl,[c] THF, 20 °C	0.16	85[d]	95:5
2	HCl,[c] THF, 20 °C	96	100	36:64
3	PTSA, MeOH, 20 °C	1	67	80:20
4	PTSA, MeOH, 20 °C	40	67	33:67
5	PTSA, MeOH, reflux	18	65	31:69

[a] By GLC analysis. [b] By GLC and 1H NMR analysis. [c] 3 mol dm^{-3}. [d] Isolated yield: 70%.

specifically obtained in good yields after heating of compounds **3h** and **i** in 3 mol dm^{-3} hydrochloric acid (Scheme 8).

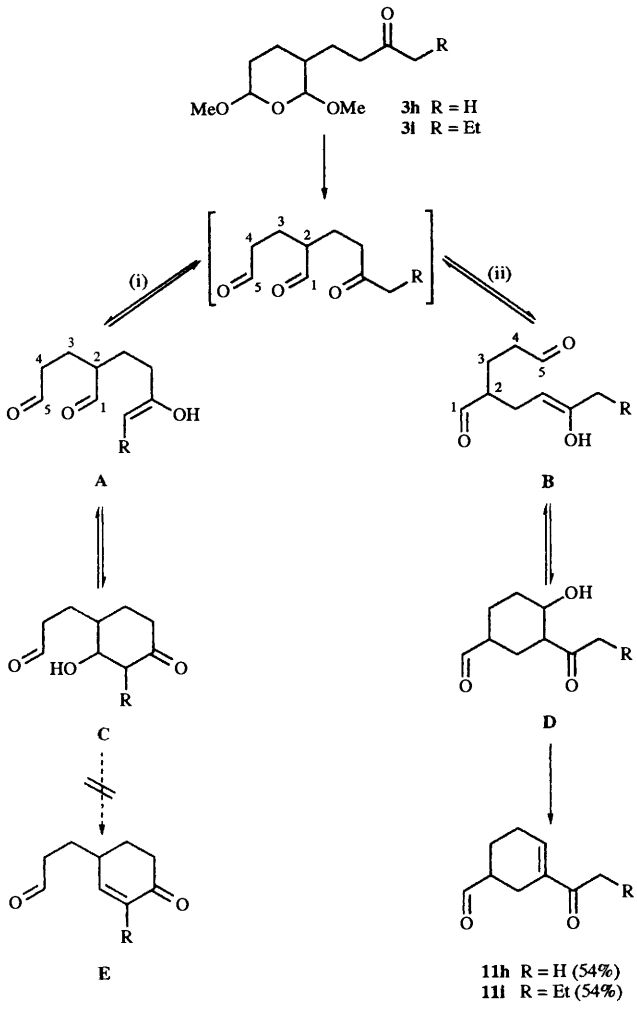
Baldwin's empirical rules[18] should allow two different processes: (i) 6-*exo* alkylation consisting in an *exo*-attack of the ketonic enol on the C-1 aldehyde function and (ii) 6-*endo* alkylation involving *endo*-attack of its regioisomer on the C-5 aldehyde function. If the formation of an intermediate keto dialdehyde can be reasonably presumed, regioselective intramolecular aldolisation of the keto dialdehyde and subsequent dehydration by pathway (ii) may therefore be a consequence of: (a) selective attack of the enol **B** on the less hindered aldehyde (C-5); (b) steric inability of aldol **C** to take the convenient OH-axial conformation for subsequent dehydration; (c) higher ability of aldol **D** to have an OH group in an axial position due to the presence of two epimerisable substituents allowing easy dehydration.

1,5-Hydroxy acetals: synthesis and hydrolysis

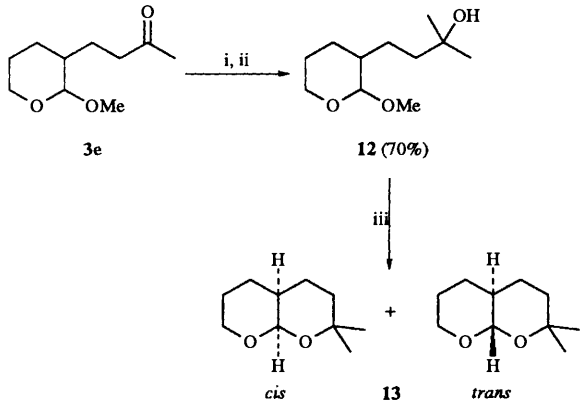
Acetal protection may allow numerous modifications of the unprotected carbonyl moiety in compounds **3**. As a first example, condensation of keto acetal **3e** with methylmagnesium iodide yielded hydroxy acetal **12** in good unoptimised yield (Scheme 9 and Table 4).

Short acidic treatment, with 3 mol dm^{-3} hydrochloric acid at room temperature, of the tertiary hydroxy acetal **12** so obtained yielded dimethylhexahydropyranopyran **13** in a highly stereocontrolled manner (de 90%). For the major isomer, easily isolable from its epimer by flash chromatography, the ^1H NMR coupling constant of the ring-junction ($J_{8a,4a}$ 1.7 Hz) was fully compatible with a *cis* junction, while the *trans* geometry of the minor isomer was established by a higher value of $J_{8a,4a}$ (~ 7.5 Hz) and a lower downfield displacement of the anomeric proton (δ_{trans} 4.30, δ_{cis} 4.88).

Stereoelectronic effects can explain this diastereocontrol if, like Deslongchamps,[19] we accept that acetal formation will take place with minimum energy, only when the intermediate oxonium ion can develop an electron pair which becomes antiperiplanar to the newly formed C–O bond in the final product. Under these conditions, attack on the oxonium with stereoelectronic control cannot yield the *trans* acetal directly in



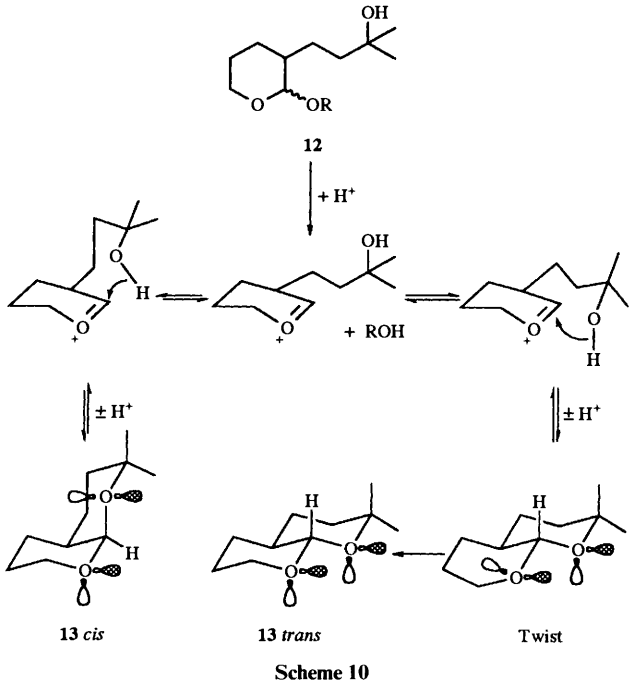
Scheme 8 *Reagents and conditions*: 3 mol dm^{-3} HCl, THF, reflux



Scheme 9 *Reagents and conditions*: i, MeMgI, Et_2O, 1 h, 20 °C; ii, water; iii, H^+

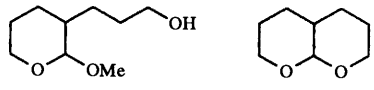
its more stable conformation, but must provide a disfavoured twist conformation, contrary to the *cis* acetal formation process (Scheme 10).

The highly selective conversion of hydroxy acetal **12** into *cis* bicyclic acetal **13** under these experimental conditions (room temp.; 3 mol dm^{-3} hydrochloric acid; 10 min) upholds the hypothesis of a kinetically controlled reaction (Table 4, entry 1). Prolongation of this acidic treatment caused a slow but intensive epimerisation of the acetal function (de 28% in favour of *trans* form) (entry 2).



Scheme 10

By treatment of 2-methoxy-3-(3-hydroxypropyl)tetrahydropyran **14** with toluene-*p*-sulfonic acid (PTSA) in methanol (20 °C; 120 h), Deslongchamps and co-workers[19] obtained hexahydropyranopyran **15** as an equilibrium mixture in a 55 : 45 *cis* : *trans* ratio.



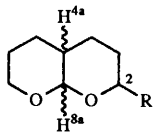
Applying the same conditions for transacetalisation of compound **12** showed that this protocol did not allow kinetic control, even with a short reaction time, together with full conversion (Table 4, entry 3). Prolongation (entry 4) or reflux (entry 5) led to quite the same equilibrium mixture revealing a weak *trans* selectivity (de 34–38%). These equilibration studies showed that, at 65 °C, *cis* acetal **13** (31%) is less stable than the *trans* isomer (69%) by 0.52 kcal mol^{-1}.‖ If classical values[19] are taken for the steric interaction (one *gauche* interaction = 0.85 kcal mol^{-1} and one interaction for an axial OR group = 0.8 kcal mol^{-1}), the *cis* acetal **13** should be less stable than the *trans* isomer by 1.65 kcal mol^{-1}. The anomeric effect can therefore be evaluated to be ~ 1.13 kcal mol^{-1} in this present case. If we consider that there is no entropy factor (nearly 0.4 kcal mol^{-1})[20] in favour of the *cis* form in the present case (1,3-diaxial interaction between the methyl group and the C–O bond strongly disfavouring one of the two *cis* conformers), this result is in agreement with the previous values of the anomeric effect estimated for unmethylated analogues (1.4–1.5 kcal mol^{-1}).[19,21]

As a second example, we have reduced keto acetals **3a**, **e** and **j** to hydroxy acetals **16** in good to quantitative yields (Scheme 11). The reduction showed no selectivity, the diastereoisomeric mixture consisting of two couples of equimolar OH-epimers. *cis–trans* Ratio was the same as for precursor **3**.

Like the tertiary analogue **12**, secondary hydroxy acetals **16a**, **e** and **j** underwent a rapid intramolecular sequence reaction

‖ 1 cal = 4.184 J.

Table 5 Spectral data of bicyclic compounds **17e** and **15**

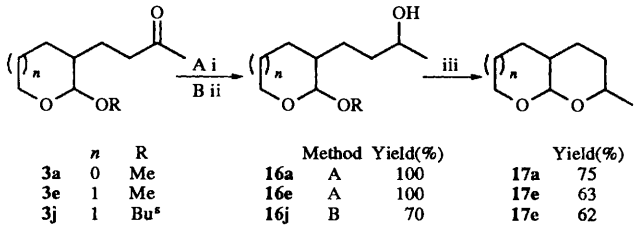
		17e Isomers					
	Spectral data	**I**	**II**	**III**	**IV**	**15** *cis*	**15** *trans*
 **17e** R = Me **15** R = H	δ H^{8a} (ppm)	4.74	4.77	4.08		4.6,[21] 4.7[19]	3.86[21]
	J H^{4a-8a} (Hz)	2.0	2.2	7.4		3.0[19]	7.0,[21] 10.0[19]
	δ C^{8a} (ppm)	97.9	98.6	105.0		98.0[19]	105.4[19]
	Relative abundance[a]	51	44	4	1		

[a] By GLC analysis.

Table 6 Acidic cyclisation of hydroxy acetal **16e**

				Crude product **17e** composition (%)					
Entry	Acidic medium	Time (t/h)	Conversion rate (%)	**I**	**II**	**III**	**IV**	**II**:**III**	*cis*:*trans* ratio (%)
1	HCl,[a] THF, 20 °C	0.16	100	51	44	4	1	92:8	95:5
2	HCl,[a] THF, 20 °C	24	100	49	21	29	1	42:58	70:30
3	PTSA, MeOH, 20 °C	0.25	37	43	38	13	5	74:26	80:20
4	PTSA, MeOH, reflux	24	100	40	25	34	1	42:58	65:35

[a] 3 mol dm^{-3}



	n	R		Method	Yield(%)		Yield(%)
3a	0	Me	**16a**	A	100	**17a**	75
3e	1	Me	**16e**	A	100	**17e**	63
3j	1	Bu^s	**16j**	B	70	**17e**	62

Scheme 11 *Reagents and conditions*: i, $LiAlH_4$, 3 h; ii, $NaBH_4$, 3 h; iii, 3 mol dm^{-3}, 20 °C, 10–15 min

under acidic conditions, leading to bisheterocyclic compounds **17** (Scheme 11).

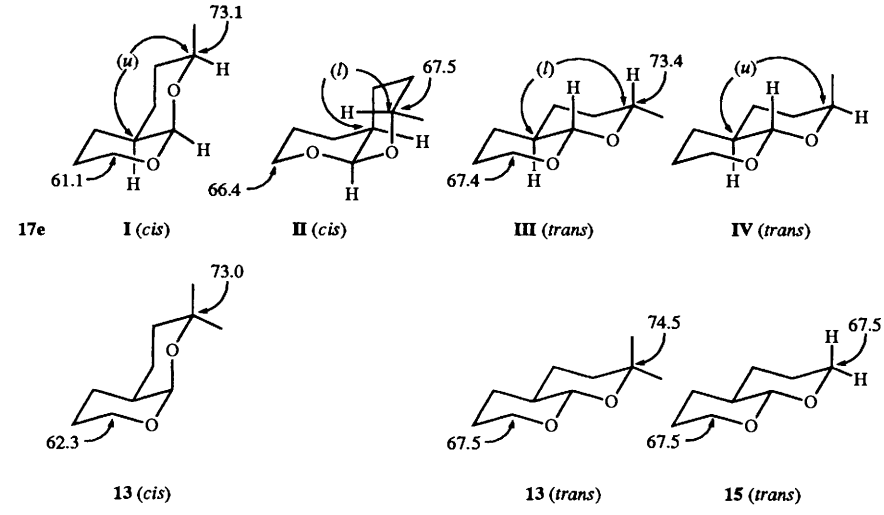
From tetrahydrofuranyl hydroxy acetal **16a**, acidic hydrolysis with 3 mol dm^{-3} hydrochloric acid at room temp. furnished bicycle **17a** as the sole equimolar couple of diastereoisomers. Each isomer of product **17a** exhibited a ^1H NMR coupling constant ($J_{7a,3a}$ 3.5 and 2.6 Hz, respectively) consistent with a *cis* ring-junction, according to spectral data of previous *cis* bicyclic analogues ($J_{7a,3a}$ 3.4,[22] 3.5 and 2.6,[23] 4.1[24]).

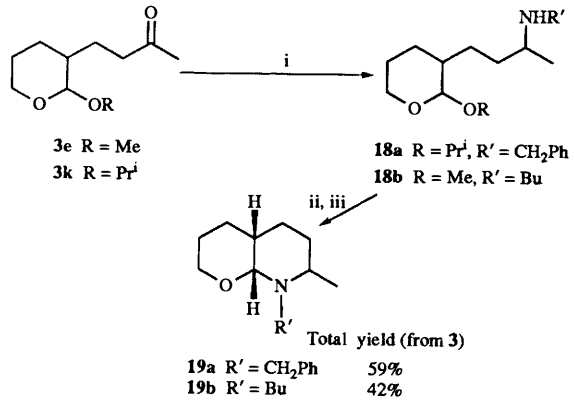
Kinetically controlled transacetalisation (3 mol dm^{-3} hydrochloric acid; 20 °C; 10 min) in the tetrahydropyran series (**16e** and **j**) provided *cis* products in the same way with high selectivity (de 90%). Indeed, ^1H and ^{13}C NMR spectra of compound **17e** showed that the isolated couple of the two major stereoisomers **I** and **II** (51% and 44% each of the total yield) exhibited the same *cis* junction and spectral data in accord with *cis* **13** and the well known *cis*-hexahydropyranopyran **15**[19,21] while spectral data of the isolated minor stereoisomers **III** and **IV** (4% and 1% each of the total yield) agree with *trans*-hexahydropyranopyran geometry[19,21] (Table 5 and Table 6, entry 1). In particular, ^1H NMR spectroscopy of the mixture of the two major isomers of compound **17e** gave, for the junction proton 8a-H, two signals displaced very downfield (~ 4.74 and 4.77) with a characteristically weak coupling constant ($J_{8a,4a}$ 2.0 and 2.2 Hz, respectively).

Prolongation of this acidic treatment led, through a slow but significant and selective epimerisation of *cis*-isomer **II** into *trans*-isomer **III**, to a final 70:30 *cis*:*trans* ratio (Table 6, entry 2). Every time, GLC analysis of the crude product showed complete conversion of the starting product **16e**. This result can be rationalised if we consider that (i) equilibration on the acetalic position occurs in total respect of initial relative configurations at C-2 and C-4a centres, referred to (*u*) as ('*unlike*' = R*S*) and (*l*) as ('*like*' = R*R*) in the following discussion. Therefore *cis*-**II** and *trans*-**III** forms (reasonably produced from the same oxonium) can equilibrate independantly from *cis*-**I** and *trans*-**IV** forms, coming from the epimeric oxonium; and (ii) conformationally mobile *cis* forms **I** and **II** can together lead to the more stable conformation with the methyl group in the equatorial position, in contrast with conformationally rigid *trans* isomers for which this same position is only assumed by the sole form issued from the (*l*) oxonium.

For the *cis*-**II**–*trans*-**III** couple, the equilibrium ratio (42:58) indicates a low *trans* selectivity, as for compound **13**, consistent with a non-destabilising position of the methyl group in *trans*-**III** isomer. So, these thermodynamic results are fully explained if we attribute the (*l*) configuration to the precursor oxonium of forms **II** and **III**. The absence of isomerisation of *cis*-**I** in favour of *trans*-**IV** is clearly the consequence of a large destabilisation ('reverse anomeric-effect'[25]) of the conformationally rigid *trans*-**IV** isomer, assuming an axial position of the methyl group. So, the (*u*) configuration may be attributed unambiguously to the precursor oxonium of **I** and **IV** forms.

Confirmations of these attributions are given by ^{13}C NMR spectral data at C-2 and C-7 centres for **I**, **II** and **III** isomeric forms of compounds **17e**. According to the conformations established above, a lesser downfield C-7 displacement (δ_C 61.1) for the sole **I** isomer is consistent with an axial position of the β-OR group[26] on the unmethylated ring, like *cis* dimethylated **13** (δ_C 62.3) in its more stable conformation, avoiding 1,3-diaxial interaction. On the other hand, higher C-7 displacement in the form **II** of compound **17e** (δ_C 66.4) agrees with an equatorial position of the β-OR group on the unmethylated ring, as noted for *trans*-form **III** (67.4) and *trans* analogues **13** (δ_C 67.5) and **15** (δ_C 67.5). A similar and concordant discrimination is focused at the C-2 centre by the influence of the β-OR group substitution on the methylated ring: a higher downfield C-2 displacement for **I** (δ_C 73.1) than for **II** isomer (δ_C 67.5) agrees with an equatorial





Scheme 12 *Reagents and conditions*: i, $R'NH_2$, $NaBH(OAc)_3$; ii, 3 mol dm^{-3} HCl, aq. THF, 20 °C, 2 h; iii, Na_2CO_3

position of the β-OR group for **I** and an axial position of the β-OR group for **II** on their respective methylated rings.[27] Finally, an analogy between C-2 displacements of *trans*-**III** form (δ_C 73.4) and *cis*-**I** (δ_C 73.1) agrees with our explanations.

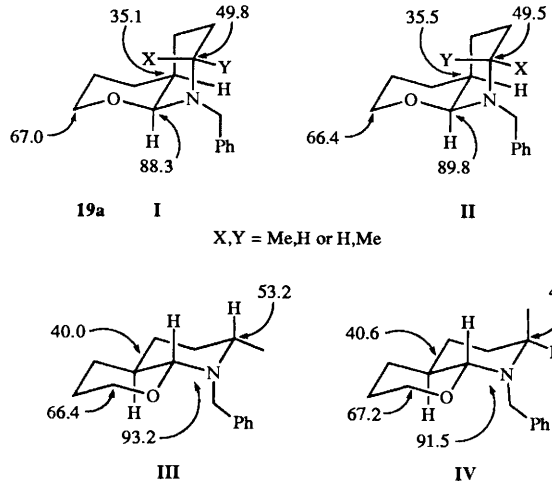
Applying Deslongchamps' conditions (PTSA, methanol; 20 °C) for transacetalisation of compound **16e** led us to observe a slower conversion than with 3 mol dm^{-3} hydrochloric acid and the constant presence of a significant amount of *trans*-isomer **III** (Table 6, entry 3). Reflux seems to cause overall isomerisation (Table 6, entry 4).

For all the hydroxy acetals studied, the results reported here constitute strong experimental evidence that the acidic conditions described (3 mol dm^{-3} hydrochloric acid; 20 °C; 15 min) gave ready access to *cis* fused-bicyclic acetals *via* an efficient kinetic control.

1,5-Amino acetals: synthesis and hydrolysis

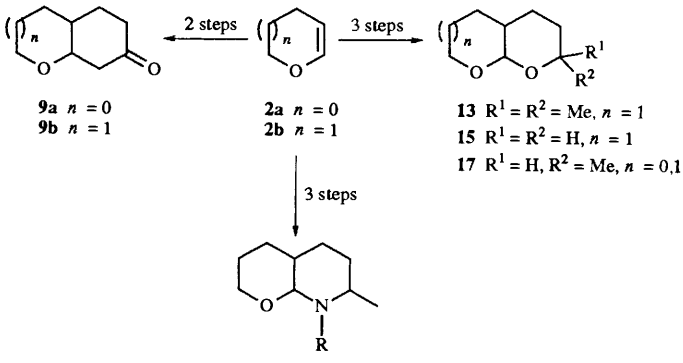
Aza analogues **19** of hexahydropyranopyrans **17**, bearing a hemiaminal function, also attracted our attention. To our knowledge, no preparative method of this type of compound is mentioned in the literature: in particular, [4 + 2] cycloaddition of unactivated 1-azabuta-1,3-dienes with enol ethers is known to fail.[10] We have prepared the required amino acetals **18** by reductive amination of keto acetals **3** using sodium triacetoxyboranuide.[28] This sequence has been successfully carried out with benzylamine and butylamine, to give compounds **18a** and **18b**, respectively (Scheme 12).

Then, acidic cyclisation was investigated under the conditions described above in the oxygen series: amino acetals **18a** and **b** led to hemiaminals **19a** and **b** after treatment with 3 mol dm^{-3} hydrochloric acid in water–tetrahydrofuran (THF) at room temperature in good total yields. The cyclisation process works with an efficient *cis* selectivity (*cis*:*trans* 90:10). Indeed, for the two products **19a** and **19b**, the four inseparable isomers are detected in the NMR spectra in the relevant proportions *cis*-**I**:*cis*-**II**:*trans*-**III**:*trans*-**IV** = 65:25:9:1. A *cis*-junction in the major isomers is attested by weak coupling constants $J_{4a,8a}$ [1.8 (**I**) and 2.2 Hz (**II**) for **19a**, 2.0 (**I**) and 2.5 Hz (**II**) for **19b**] and by lowfield displacement of the anomeric proton (δ 8a-H > 4.1), fully compatible with its equatorial position on the oxygen ring. *trans*-Isomers revealed a higher value of the coupling constant $J_{4a,8a}$ (> 7 Hz) and a highfield position for the (axial) 8a-H proton (δ < 3.3). ^{13}C Data of the junction carbon atoms agreed with these attributions, indicating a lower field for C-8a and C-4a in minor (*trans*) forms.



Contrary to the tetrahydropyranopyran spectral data, equal displacements at C-7 for the two *cis* isomers suggest the same equatorial position of the nitrogen atom on the tetrahydropyran ring in the two cases. So, one of the two would suggest an axial methyl group on the piperidine ring in its more stable conformation. This result can be rationalised if we consider a strong steric interaction between the *N*-butyl or *N*-benzyl group and the oxygenated ring when the nitrogen atom is in axial position.

Thus, keto acetals of type **3** have been shown to be efficient intermediates in the synthesis of rare mixed O–N–bisheterobicycles **19** with respect to *cis*-junction selectivity.



Scheme 13

Conclusions

We have demonstrated the easy access and the synthetic utility of keto acetals **3** and monoprotected 1,5-dicarbonyl compounds, mostly previously undescribed species. By this method, we have developed several two- or three-step annulation processes applicable to various cyclic enol ethers (Scheme 13). These methods allow large-scale access, with good total yields and high diastereocontrol, to numerous heterobicyclic skeletons of great interest in natural product synthesis.

Experimental

General

IR spectra were recorded on a Perkin-Elmer 377 IR spectrophotometer for samples as pure liquid films, or in $CHCl_3$ or CCl_4 solution. ^1H NMR spectra were obtained with a Bruker AW 80 (80 MHz) or AM 400 (400 MHz) or WM 500 (500 MHz) spectrometer for $CDCl_3$ solutions, with $SiMe_4$ as internal standard, unless otherwise noted. *J* Values are given in Hz. ^{13}C NMR spectra were recorded on a Varian CFT 20 (20 MHz) or a Bruker AM 400 (100 MHz) spectrometer for $CDCl_3$ solutions unless otherwise noted. Mass spectra were recorded on a JEOL JMS AX 500 mass spectrophotometer (EI: electronic impact; CI: chemical ionisation with CH_4). GLC analyses were performed on a Hewlett Packard 5890 gas chromatograph, using an H.-P.-5.1 column [16 ft, 1/50 in (i.d.)]. Flash chromatography was performed with Merck Kieselgel 60 (230–400 mesh ASTM) support with light petroleum (distillation temp. < 60 °C)–diethyl ether mixtures as eluent. Microanalyses were performed by INSA Laboratories, Rouen. All reactions involving heterocyclic enol ethers were conducted under dry argon. The progress of reactions was monitored in each case by TLC (Et_2O–light petroleum; 50:50).

Reagents and solvents

Hemiacetal vinylogues **1** were prepared by literature procedures.[6] Others reagents were commercial products and were distilled prior to use. Nitromethane, stored over molecular sieves 4 Å, was distilled prior to use.

General preparation of keto acetals 3

(a) Using hemiacetal vinylogue 1. To a solution of heterocyclic enol ether **2** (10 mmol) in nitromethane (10 cm^3) in a two-necked, round-bottom flask were added, at −20 °C, a solution of hemiacetal vinylogue **1** (20 mmol) in nitromethane (10 cm^3), then also at −20 °C boron trifluoride–diethyl ether (0.50 cm^3) as a solution in diethyl ether (0.125 cm^3). Stirring of the mixture was continued for 1 h. Then saturated aq. $NaHCO_3$ (10 cm^3) was added at 0 °C. After return to room temperature, the crude product was extracted with CH_2Cl_2, and the extract was dried over $MgSO_4$, filtered, and evaporated. Purification was performed by flash chromatography, and gave pure keto acetal **3** (eluent: Et_2O–light petroleum; 1:6).

(b) Using α,β-ethylenic ketone and alcohol. The same procedure as above was applied with the following modifications: a compound **1** was replaced by MVK (20 mmol). Then, at −20 °C, the same catalyst mixed with a hydroxylic compound (20 mmol) was added (no diethyl ether was used in this case) or EtOH (20 mmol), followed by boron trifluoride–diethyl ether for compound **3e**. Further operations and purification were accomplished as described above. In this case, chromatographed compound **3** may be contaminated by traces of nitro ketone **21**.‡

4-(2-*Methoxytetrahydrofuran*-3-*yl*)*butan*-2-*one* **3a**.[12]—2,3-Dihydrofuran **2a** (0.70 g, 10 mmol) and vinylogue **1a** (2.04 g, 20 mmol) gave keto acetal **3a** (0.86 g, 50%) as a mixture of two diastereoisomers distinguishable by TLC [R_f *cis* < R_f *trans*; $\Delta(R_f)$ 0.07] and partially isolable from each other after flash chromatography (diastereoisomeric ratio: *trans*:*cis* = 65:35) (Found: C, 62.8; H, 9.7. Calc. for $C_9H_{16}O_3$: C, 62.76; H, 9.36%). Distillation of the crude product gave compound **3a** (1.17 g, 69%) with a state of purity reaching 90%; δ_H(80 MHz; CCl_4) *trans*-isomer 1.3–2.0 (5 H, m), 2.14 (3 H, s), 2.44 (2 H, t, *J* 7.4), 3.30 (3 H, s), 3.84 (2 H, m) and 4.60 (1 H, d, *J* 1.5); *cis*-isomer 1.22 (1 H, m), 1.5–2.0 (4 H, m), 2.14 (3 H, s), 2.46 (2 H, t, *J* 7.4), 3.30 (3 H, s), 3.89 (2 H, m) and 4.70 (1 H, d, *J* 4); δ_C(20 MHz; $CDCl_3$) *trans*-isomer 26.1, 29.8, 30.6, 41.7, 44.8, 54.6, 66.4, 109.4 and 207.8; ν_{max}(neat)/cm^{-1} 1715 (C=O).

4-(2-*Ethoxytetrahydrofuran*-3-*yl*)*butan*-2-*one* **3b**.—Reaction of the dihydrofuran **2a** (0.70 g, 10 mmol) and vinylogue **1b** (2.32 g, 20 mmol) led to pure *keto acetal* **3b** (0.65 g, 35%) as a mixture of two diastereoisomers (diastereoisomeric ratio: *trans*:*cis* = 65:35) (HRMS: Found: M^+, 186.1269. $C_{10}H_{18}O_3$ requires *M*, 186.1256); δ_H(400 MHz; $CDCl_3$) 1.20 (3 H, t), 1.4–1.85 (3 H, m), 1.95–2.20 (2 H, m), 2.17 (3 H, s), 2.48 (2 H, t), 3.42 (1 H, m), 3.72 (1 H, m), 3.80–4.00 (2 H, m) and 4.76 (0.65 H, d, *J* 1.6, 2-H *trans*-isomer) and 4.90 (0.35 H, d, *J* 4.3, 2-H *cis*-isomer); δ_C(100 MHz; $CDCl_3$) *trans*-isomer 15.5, 26.6, 30.1, 30.8, 42.1, 45.2, 63.1, 66.7, 108.5 and 208.3; *cis*-isomer 15.5, 23.1, 29.5, 29.9, 42.7, 43.7, 62.7, 66.7, 103.3 and 209.0; ν_{max}(neat)/cm^{-1} 1720 (C=O); *m*/*z* (EI) 186 (M^+), 141, 112 and 83.

1-(2-*Methoxytetrahydrofuran*-3-*yl*)*hexan*-3-*one* **3c**.—Reaction of the dihydrofuran **2a** (0.70 g, 10 mmol) and vinylogue **1c** (2.60 g, 20 mmol) gave pure keto acetal **3c** (0.84 g, 42%) as a mixture of two diastereoisomers distinguishable by TLC [R_f *cis* < R_f *trans*; $\Delta(R_f)$ 0.05] (diastereoisomeric ratio: *trans*:*cis* = 65:35) (HRMS: Found: M^+, 200.1408. $C_{11}H_{20}O_3$ requires *M*, 200.1412); δ_H(400 MHz; $CDCl_3$) *trans*-isomer 0.93 (3 H, t, *J* 8.4), 1.45–1.75 (3 H, m), 1.62 (2 H, q, *J* 7.6), 2.08 (2 H, m), 2.39 (2 H, t, *J* 7.4), 2.44 (2 H, t, *J* 7.8), 3.33 (3 H, s), 3.87 (1 H, m), 3.94 (1 H, td, *J* 8.2 and 4.1) and 4.67 (1 H, d, *J* 1.8); *cis*-isomer 0.92 (3 H, t, *J* 8.4), 1.55–1.85 (3 H, m), 1.61 (2 H, q, *J* 7.4), 2.00 (2 H, m), 2.38 (2 H, t, *J* 7.6), 2.42 (2 H, t, *J* 7.6), 3.31 (3 H, s), 3.85 (1 H, m), 3.97 (1 H, td, *J* 8.5 and 2.8) and 4.77 (1 H, d, *J* 4.2); δ_C(20 MHz; $CDCl_3$) *trans*-isomer 13.1, 16.7, 25.7, 29.9, 40.3, 44.1, 44.4, 54.1, 65.9, 109.0 and 209.5; *cis*-isomer 13.1, 16.7, 22.2, 28.7, 40.8, 43.0, 43.9, 53.7, 65.9, 103.9 and 210.0; ν_{max}(neat)/cm^{-1} 1720 (C=O).

4-(2-*Methoxytetrahydrofuran*-3-*yl*)*pentan*-2-*one* **3d**.—Dihydrofuran **2a** (0.70 g, 10 mmol) and vinylogue **1d** (2.32 g, 20 mmol) gave pure *keto acetal* **3d** (0.56 g, 30%) as a mixture of two diastereoisomers distinguishable by TLC [R_f *cis* > R_f *trans*; $\Delta(R_f)$ 0.07], (diastereoisomeric ratio: *trans*:*cis* = 60:40) (Found: C, 64.1; H, 9.9. $C_{10}H_{18}O_3$ requires C, 64.5; H, 9.91%); δ_H(80 MHz; $CDCl_3$) *trans*-isomer 0.95 (3 H, d, *J* 5), 1.0–2.0 (4 H, m), 2.13 (3 H, s), 2.2–2.7 (2 H, m), 3.31 (3 H, s), 3.88 (2 H, m) and 4.70 (1 H, d, *J* 1.5); *cis*-isomer 0.95 (3 H, d, *J* 5), 1.0–2.0 (4 H, m), 2.13 (3 H, s), 2.2–2.7 (2 H, m), 3.31 (3 H, s), 3.85 (2 H, m) and 4.76 (1 H, d, *J* 3); δ_C(20 MHz; $CDCl_3$) *trans*-isomer 18.2, 29.3, 30.0, 31.0, 48.7, 51.4, 54.5, 66.7, 108.8 and 205.8; *cis*-

‡ See footnote on p. 2103.

isomer 19.1, 27.9, 28.0, 29.7, 49.7, 50.8, 54.1, 66.8, 104.3 and 206.4; ν_{max}(neat)/cm^{-1} 1715 (C=O); *m*/*z* (70 eV, CI) 187 (M^+ + 1), 169, 155, 97, 85 and 59.

4-(2-Methoxytetrahydropyran-3-yl)butan-2-one **3e**.[12]—Reaction of the dihydropyran **2b** (0.84 g, 10 mmol) and vinylogue **1a** (2.04 g, 20 mmol) led to pure keto acetal **3e** (1.06 g, 57%) as a mixture of two diastereoisomers distinguishable by TLC [R_f *cis* > R_f *trans*; $\Delta(R_f) \geqslant 0.07$] and partially isolable from each other after flash chromatography (diastereoisomeric ratio: *trans*:*cis* = 35:65); δ_H(500 MHz; $CDCl_3$) *cis*-isomer 1.4–1.65 (7 H, m), 2.11 (3 H, s), 2.38 (1 H, ddd), 2.45 (1 H, m), 3.32 (3 H, s), 3.50 (1 H, m), 3.65 (1 H, dt, *J* 2.8 and 12) and 4.45 (1 H, d, *J* 2.5); *trans*-isomer 1.20 (1 H, m), 1.38 (1 H, m), 1.4–1.65 (3 H, m), 1.8 (1 H, m), 1.86 (1 H, m), 2.11 (3 H, s), 2.34 (1 H, m), 2.46 (1 H, m), 3.39 (3 H, s), 3.42 (1 H, m), 3.90 (1 H, m) and 4.01 (1 H, d, *J* 6.2); δ_C(20 MHz; $CDCl_3$) *cis*-isomer 24.5, 25.8, 25.9, 29.7, 39.3, 40.8, 54.7, 59.3, 100.2 and 208.6; *trans*-isomer 24.2, 25.2, 26.8, 29.7, 39.6, 41.6, 55.5, 64.1, 105.4 and 207.8; ν_{max}(neat)/cm^{-1} 1715 (C=O).

4-(2-Ethoxytetrahydropyran-3-yl)butan-2-one **3f**.—Dihydropyran **2b** (0.84 g, 10 mmol) and vinylogue **1b** (2.32 g, 20 mmol) gave pure *keto acetal* **3f** (0.70 g, 35%) as a mixture of two diastereoisomers distinguishable by TLC [R_f *cis* > R_f *trans*; $\Delta(R_f)$ 0.06] (diastereoisomeric ratio: *trans*:*cis* = 35:65) (HRMS: Found: M^+, 200.1427. $C_{11}H_{20}O_3$ requires *M*, 200.1412); δ_H(400 MHz; $CDCl_3$) 1.20 (3 H, t), 1.35–1.70 (6 H, m), 1.85 (1 H, m), 2.16 (3 H, s), 2.40 (1 H, m), 2.54 (1 H, m), 3.40–3.55 (2 H, m), 3.70 (1 H, m), 3.88 (1 H, m) and 4.12 (0.35 H, d, *J* 6.4, 2-H *trans* isomer) and 4.62 (0.65 H, d, 2-H *J* 2.6, *cis*-isomer); δ_C(100 MHz; $CDCl_3$) *cis*-isomer 14.8, 23.9, 25.3, 25.5, 29.5, 39.0, 40.7, 59.3, 62.3, 98.5 and 208.7; *trans*-isomer 14.1, 24.1, 25.1, 27.0, 29.5, 39.4, 41.3, 63.6, 64.3, 104.4 and 208.7; ν_{max}(neat)/cm^{-1} 1715 (C=O); *m*/*z* (EI) 200 (M^+), 154 and 97.

1-(2-Methoxytetrahydropyran-3-yl)hexan-3-one **3g**.—Dihydropyran **2b** (0.84 g, 10 mmol) and vinylogue **1c** (2.60 g, 20 mmol) gave pure *keto acetal* **3g** (0.75 g, 35%) as a mixture of two diastereoisomers (diastereoisomeric ratio: *trans*:*cis* = 35:65) (HRMS: Found: M^+, 214.1573. $C_{12}H_{22}O_3$ requires *M*, 214.1569); δ_H(400 MHz; $CDCl_3$) *cis*-isomer 0.92 (3 H, t, *J* 7.4), 1.15–1.95 (9 H, m), 2.37 (2 H, t), 2.44 (2 H, q), 3.37 (3 H, s), 3.53 (1 H, m), 3.67 (1 H, dd) and 4.47 (1 H, d, *J* 1.9); *trans*-isomer 0.93 (3 H, t, *J* 7.4), 1.95 (9 H, m), 2.35 (2 H, m), 2.67 (2 H, m), 3.42 (3 H, s), 3.70 (1 H, m), 3.93 (1 H, dt) and 4.04 (1 H, d, *J* 6.1); δ_C(100 MHz; $CDCl_3$) *cis*-isomer 13.8, 17.3, 24.2, 25.4, 25.8, 39.3, 39.9, 44.6, 54.8, 59.4, 100.3 and 210.8; *trans*-isomer 13.7, 17.0, 24.1, 25.1, 25.4, 39.5, 42.7, 44.7, 55.7, 64.2, 105.7 and 209.6; ν_{max}(neat)/cm^{-1} 1715 (C=O).

4-(2,6-Dimethoxytetrahydropyran-3-yl)butan-2-one **3h**.—2-Methoxydihydropyran **2c** (1.14 g, 10 mmol) and vinylogue **1a** (2.04 g, 20 mmol) gave pure *keto acetal* **3h** (1.37 g, 56%) as a mixture of four diastereoisomers (Found: C, 60.6; H, 9.6. $C_{11}H_{20}O_4$ requires C, 61.0; H, 9.3%); δ_H(500 MHz; $CDCl_3$) 1.25–2.0 (7 H, m), 2.16 (3 H, s), 2.66 (2 H, t), 3.50 and 3.54 (6 H, 2 s) and 4.4–5.0 (2 H, m); δ_C(20 MHz; $CDCl_3$) 23.5, 24.7/25.4, 29.6, 30.5/29.3, 39.4/38.6, 41.1/40.9, 54.6/54.7, 55.5, 99.0/97.3, 101.5/101.3 and 207.3; ν_{max}(neat)/cm^{-1} 1715 (C=O).

1-(2,6-Dimethoxytetrahydropyran-3-yl)hexan-3-one **3i**.—2-Methoxydihydropyran **2c** (1.14 g, 10 mmol) and vinylogue **1c** (2.04 g, 20 mmol) gave pure *keto acetal* **3i** (1.04 g, 40%) as a mixture of four diastereoisomers (Found: C, 63.1; H, 10.1. $C_{13}H_{24}O_4$ requires C, 63.4; H, 9.75%); δ_H(80 MHz; $CDCl_3$) 0.7–2.0 (12 H, m), 2.2–2.9 (4 H, m), 3.32 and 3.52 (6 H, 2 s) and 4.0–5.0 (2 H, m); ν_{max}(neat)/cm^{-1} 1715 (C=O).

4-(2-sec-Butoxytetrahydropyran-3-yl)butan-2-one **3j**.—Dihydropyran **2b** (0.84 g, 10 mmol), MVK (1.40 g, 20 mmol) and *sec*-butyl alcohol (1.48 g, 20 mmol) gave pure *keto acetal* **3j** (0.92 g, 40%) as a mixture of two diastereoisomers distinguishable by TLC [R_f *cis* > R_f *trans*; $\Delta(R_f)$ 0.08] (diastereoisomeric ratio: *trans*:*cis* = 47:53) (Found: C, 68.6; H, 10.7. $C_{13}H_{24}O_3$ requires C, 68.42; H, 10.52%); δ_H(80 MHz; $CDCl_3$) 0.7–1.1 (5 H, m), 1.15 (3 H, t), 1.52 (7 H, m), 2.12 (3 H, s), 2.50 (2 H, m), 3.2–4.0 (3 H, m), 4.18 (*trans*) and 4.70 (*cis*) together (1 H, d, J_{trans} 6, J_{cis} 3); δ_C(20 MHz; $CDCl_3$; selected carbons) 58.9 (*cis*) and 63.8 (*trans*) (C-6), 71.1 and 73.8 (*cis*) and 72.9 and 75.0 (*trans*) (CHO), 95.0 and 97.6 (*cis*), 101.6 and 103.6 (*trans*) (C-2), 207.7 (*cis*) and 208.7 (*trans*) (C=O); ν_{max}(neat)/cm^{-1} 1715 (C=O).

4-(2-Isopropoxytetrahydropyran-3-yl)butan-2-one **3k**.—Dihydropyran **2b** (0.84 g, 10 mmol), MVK (1.40 g, 20 mmol) and propan-2-ol (1.20 g, 20 mmol) gave pure *keto acetal* **3k** (0.64 g, 30%) as a mixture of two diastereoisomers (diastereoisomeric ratio: *trans*:*cis* = 42:58) (Found: C, 66.7; H, 10.3. $C_{12}H_{22}O_3$ requires C, 67.2; H, 10.3%); δ_H(200 MHz; $CDCl_3$) 1.1 (6 H, m), 1.45 (6 H, m), 1.75 (1 H, m), 2.05 (3 H, s), 2.4 (2 H, m), 3.35 (1 H, m), 3.8 (2 H, m) and 4.1 (0.42 H *trans*, d, *J* 6, 2-H *trans*) and 4.6 (0.58 H, d, *J* 6, 2-H *cis*); δ_C(50 MHz; $CDCl_3$); *cis*-isomer 21.3, 23.3, 23.9, 25.2, 25.5, 29.7, 39.9, 40.7, 59.4, 67.8, 96.7 and 209.0; *trans*-isomer 21.5, 23.5, 24.5, 25.6, 27.5, 29.7, 39.7, 41.4, 64.7, 69.5, 103 and 209.0; ν_{max}(neat)/cm^{-1} 1714 (C=O).

3-[(2-Hydroxytetrahydrofuran-3-yl)methyl]pentan-2-one **4**.—Dihydrofuran **2a** (0.70 g, 10 mmol) and vinylogue **1e** (2.60 g, 20 mmol) gave pure keto hemiacetal **4** (0.80 g, 40%) as a mixture of diastereoisomers; δ_H(80 MHz; $CDCl_3$) 0.7–2.0 (10 H, m), 2.20 (3 H, s), 2.68 (1 H, m), 3.54 (1 H mobile, large s, OH), 3.4–4.2 (2 H, m), 4.62 and 4.68 (1 H, d); ν_{max}(neat)/cm^{-1} 3420 (OH) and 1710 (C=O).

2-Methoxy-3-(1-methoxybut-2-enyl)tetrahydropyran **6**.—Dihydropyran **2b** (0.84 g, 10 mmol) and vinylogue **1f** (1.76 g, 20 mmol) gave a mixture of allylic ether **6** (0.80 g, 40%, mixture of diastereoisomers) and aldehyde **3l** (20%, two diastereoisomers). Compound **6**; δ_H(400 MHz; $CDCl_3$) 1.0–2.0 (5 H, m), 1.5–1.8 (3 H, d), 3.2–3.5 (6 H, 2 s), 3.3–4.0 (3 H, m), 4.2–4.8 (1 H, m) and 5.0–6.0 (2 H, m); ν_{max}(neat)/cm^{-1} 1630–1660 (C=C). The aldehyde **3l** was detected by the following signals: δ_H(400 MHz; $CDCl_3$) 9.5 and 9.8 (1 H); δ_C(100 MHz; $CDCl_3$) 199.5 and 203.3; ν_{max}(neat)/cm^{-1} 1727 (C=O).

Acidic hydrolysis of keto acetals 3

To a keto acetal **3** (2 mmol) was added, at room temp., 3 mol dm^{-3} hydrochloric acid (5 cm^3) mixed with THF (1 cm^3). After stirring of the mixture for 1 h (complete conversion of **3** being observed by TLC) at room temp. (Method A) or reflux (Method B), CH_2Cl_2 (10 cm^3) was added, followed by decantation and extraction of the aqueous layer (4 × 10 cm^3 of CH_2Cl_2). The mixed organic layers were dried ($MgSO_4$) and concentrated. Purification of the hydrolysis product was performed by flash chromatography [eluent for keto hemiacetal **7e**: diethyl ether–light petroleum (1:2.5); for keto ethers **9**: diethyl ether–light petroleum (1:9); for hydroxy enone **10c**: diethyl ether–light petroleum (1:4)].

4-(2-Hydroxytetrahydropyran-3-yl)butan-2-one 7e. *Method A*. From keto acetal **3e** (0.372 g, 2 mmol) was obtained pure *keto hemiacetal* **7e** (0.21 g, 48%) as a mixture of diastereoisomers (HRMS: Found: M^+, 172.1104. $C_9H_{16}O_3$ requires *M*, 172.1099); δ_H(400 MHz; $CDCl_3$) 1.1–1.8 (6 H, m), 1.88 (1 H, m), 2.15 (3 H, s), 2.48 (1 H, m), 2.53 (1 H, t), 2.70 and 3.20 (1 H mobile, br s, *cis* and *trans* isomers), 3.40–3.60 (1 H, m), 3.96 (1 H, m) and 4.40 (0.4 H, d, *J* 7.2, 2-H *trans*-isomer) and 5.03 (0.6 H, d, *J* < 1, 2-H *cis*-isomer); δ_C(100 MHz; $CDCl_3$) *cis*-isomer 23.2, 24.7, 25.0, 29.4, 40.5, 40.9, 59.4, 93.1 and 208.7; *trans*-isomer 24.4, 24.9, 27.4, 29.5, 38.7, 40.9, 65.0, 99.3 and 208.8; ν_{max}(neat)/cm^{-1} 3450 (OH) and 1710 (C=O); *m*/*z* (EI) 172 (M^+), 154, 97, 69 and 58.

***cis*-Octahydrobenzofuran-6-one 9a.** *Method B*. From keto acetal **3a** (0.344 g, 2 mmol) was obtained pure cis-*keto ether* **9a** (0.140 g, 48%) (HRMS: Found: M^+, 140.0837. $C_8H_{12}O_2$ requires *M*, 140.0835); δ_H(400 MHz; $CDCl_3$; 1D and 2D COSY)

1.72 (2 H, m, 3- and 4-H^{ax}), 1.95 (1 H, m, 4-H^{eq}), 2.19 (1 H, m, 3-H), 2.25 (1 H, ddd, 5-H^{ax}), 2.34 (1 H, ddd, 5-H^{eq}), 2.49 (1 H, sext, 3a-H^{ax}), 2.62 (2 H, ddd, 7-H), 3.63 (1 H, q, *J* 7.7, 2-H), 3.96 (1 H, dt, *J* 8.3, 8.3 and 4.8, 2-H) and 4.17 (1 H, dt, *J* 6.6, 4.5 and 4.5, 7a-H^{eq}); δ_C(20 MHz; $CDCl_3$) 25.7, 31.8, 35.4, 36.7, 42.5, 66.2, 77.1 and 210.0; ν_{max}(neat)/cm^{-1} 1720 (C=O); *m*/*z* (70 eV, CI) 141 (M^+ + 1), 123, 95 and 85.

4-Methyloctahydrobenzofuran-6-one 9d. *Method B.* From keto acetal **3d** (0.372 g, 2 mmol) was obtained pure keto ether **9d** (0.154 g, 50%) as a couple of two diastereoisomers distinguishable by GLC [120 °C; 10 cm^3 min^{-1}: 2.8 min (65%), 3.2 min (35%)] (HRMS: Found: M^+, 154.0994. $C_9H_{14}O_2$ requires *M*, 154.1022); δ_H(80 MHz; $CDCl_3$) 1.04 (3 H, d), 1.6–2.3 (4 H, m), 2.02 (2 H, d), 2.43 (65%) and 2.48 (35%) (together 2 H, d, *J* 4 and 5) and 3.2–4.4 (3 H, m); δ_C(20 MHz; $CDCl_3$) major isomer 19.3, 29.9, 31.6, 42.6, 43.9, 45.8, 65.5, 76.9 and 209.2; minor isomer 17.3, 24.8, 27.9, 39.9, 41.1, 41.8, 66.0, 75.9 and 209.5; ν_{max}(neat)/cm^{-1} 1720 (C=O); *m*/*z* (70 eV, CI) 155 (M^+ + 1), 130, 97 and 85.

***trans*-Octahydrobenzopyran-7-(2*H*)-one 9e.**[15] *Method B.* From keto acetal **3e** (0.372 g, 2 mmol) was obtained pure *trans*-keto ether **9e** (0.169 g, 55%) (HRMS: Found: M^+, 154.0994. $C_9H_{14}O_2$ requires *M*, 154.1022.); δ_H(400 MHz; $CDCl_3$, 1D and 2D COSY) 1.60 (1 H, m, 4a-H^{ax}), 1.70 (1 H, m, 3-H), 1.80 (1 H, m, 3-H), 1.1–2.0 (4 H, m, 4-H_2 and 5-H_2), 2.2–2.4 (2 H, m, 6-H_2), 2.39 (1 H, t, *J* 12.1, 8-H^{ax}), 2.68 (1 H, ddd, *J* 12, 4.9 and 2.1, 8-H^{eq}), 3.13 (1 H, ddd, *J* 12.1, 4.9 and 9.7, 8a-H^{ax}), 3.43 (1 H, td, *J* 12.0 and 2.5, 2-H^{ax}) and 3.99 (1 H, ddd, *J* 1.2, 11.5 and 4.7, 2-H^{eq}); ν_{max}(neat)/cm^{-1} 1715 (C=O); *m*/*z* (70 eV, CI) 155 (M^+ + 1) and 85.

8-Ethyloctahydrobenzopyran-7-(2*H*)-one 9g. *Method B.* From keto acetal **3g** (0.428 g, 2 mmol) was obtained pure keto ether **9g** (0.128 g, 38%) as a couple of paired diastereoisomers; δ_H(400 MHz; $CDCl_3$) 0.90 (3 H, t, *J* 8.0), 1.0–2.1 (9 H, m), 2.2–2.5 (3 H, m), 2.84 (1 H, dd, *J* 9.8 and 11), 3.38 (1 H, dt, *J* 2.5 and 11.8) and 4.04 (1 H, ddt, *J* 1.5, 4.7 and 11.8); ν_{max}(neat)/cm^{-1} 1720 (C=O).

2-Ethyl-4-(2-hydroxyethyl)cyclohex-2-enone 10c. *Method B.* From keto acetal **3c** (0.400 g, 2 mmol) was obtained pure *hydroxy enone* **10c** (0.181 g, 54%) (HRMS: Found: M^+, 168.1152. $C_{10}H_{16}O_2$ requires *M*, 168.1150); δ_H(80 MHz; $CDCl_3$) 1.04 (3 H, t), 1.3–2.7 (9 H, m), 2.8 (1 H mobile, large s, OH), 3.86 (2 H, t) and 6.73 (1 H, m); δ_C(20 MHz; $CDCl_3$) 12.6, 22.2, 28.7, 32.9, 37.1, 37.4, 59.8, 140.1, 148.4 and 199.6; ν_{max}(neat)/cm^{-1} 3470 (OH), 1705 (C=O conj.) and 1660 (C=C); *m*/*z* (70 eV, CI) 169 (M^+ + 1).

3-Acetylcyclohex-3-enecarbaldehyde 11h. *Method B.* From keto acetal **3h** (0.488 g, 2 mmol) was obtained the pure *cyclohexene* **11h** (0.164 g, 54%) (HRMS: Found: M^+, 152.0837. $C_9H_{12}O_2$ requires *M*, 152.0837); δ_H(80 MHz; $CDCl_3$) 1.5–2.1 (2 H, m), 2.30 (3 H, s), 2.18–2.70 (5 H, m), 6.97 (1 H, t) and 9.23 (1 H, s); ν_{max}(neat)/cm^{-1} 1720 (HC=O), 1665 (C=O conj.) and 1640 (C=C); δ_C(20 MHz; C_6D_6) 21.0, 22.6, 24.5, 24.9, 45.4, 137.6, 139.6, 197.2 and 202.7; *m*/*z* (70 eV, CI) 153 (M^+ + 1), 135, 123 and 107.

3-Butyrylcyclohex-3-enecarbaldehyde 11i. *Method B.* From keto acetal **3h** (0.532 g, 2 mmol) was obtained the pure cyclohexene **11i** (0.194 g, 54%); δ_H(80 MHz; $CDCl_3$) 0.93 (3 H, t, *J* 6.5), 1.15–2.9 (11 H, m), 6.95 (1 H, m) and 9.70 (1 H, s); ν_{max}(neat)/cm^{-1} 1720 (CH=O) and 1665–1640 (C=O conj. and C=C); *m*/*z* (70 eV, CI) 181 (M^+ + 1), 149, 137 and 111.

4-(2-Methoxytetrahydropyran-3-yl)-2-methylbutan-2-ol 12

To a solution of methylmagnesium iodide (2.25 mmol, 1.5 mol equiv.) in dry diethyl ether (3 cm^3) was added dropwise a solution of keto acetal **3e** (0.28 g, 1.5 mmol) in dry diethyl ether (7 cm^3). After stirring of this suspension at room temp. for 1 h, saturated aq. NH_4Cl was added. After decantation and extraction (Et_2O), the organic layers were washed with saturated aq. NH_4Cl, dried ($MgSO_4$), and concentrated. Purification of the hydroxymethylation product by flash chromatography yielded compound **12** (0.21 g, 70%) as a mixture of two diastereoisomers distinguishable by TLC [R_f *cis* > R_f *trans*; $\Delta(R_f)$ 0.05] and partially isolable from each other after flash chromatography (diastereoisomeric ratio: *trans*:*cis* = 35:65); δ_H(400 MHz; $CDCl_3$) 1.21 (6 H, s), 1.1–1.7 (9 H, m), 3.38 (*cis*) and 3.45 (*trans*) (3 H, s), 3.4–3.95 (3 H, m) and 4.11 (*trans*) and 4.52 (*cis*) (1 H, d, J_{trans} 6.0, J_{cis} 2.65); δ_C(100 MHz; C_6D_6) *cis*-isomer 24.9, 26.1, 26.8, 29.0 (2 C), 40.9, 41.2, 54.5, 59.4, 70.1 and 100.8; *trans*-isomer 23.7, 25.5, 25.9, 29.4 (2 C), 40.0, 41.4, 55.1, 63.0, 70.1 and 105.0; ν_{max}(neat)/cm^{-1} 3450 (OH); *m*/*z* (70 eV, CI, NH_3) 220 (MNH_4^+) and 184 (M − H_2O).

Reduction of keto acetals 3

To $LiAlH_4$ (0.28 g) in suspension in dry diethyl ether (25 cm^3) was added dropwise a solution of a keto acetal **3** (10 mmol) in dry diethyl ether (5 cm^3). After stirring of this suspension at room temp. during 3 h, hydrolysis was accomplished at 4 °C by addition of saturated aq. Na_2SO_4 (1.25 cm^3). After a few minutes at room temperature, the ethereal layers were filtered, dried ($MgSO_4$), and concentrated. The hydroxy acetal **16** was purified by flash chromatography yield [eluent: diethyl ether–light petroleum (1:3)].

4-(2-Methoxytetrahydrofuran-3-yl)butan-2-ol 16a. From keto acetal **3a** (1.72 g, 10 mmol) was obtained pure hydroxy acetal **16a** (1.74 g, 100%) as a mixture of two pairs of diastereoisomers; δ_H(80 MHz; $CDCl_3$) 1.12 (3 H, d, *J* 6), 1.2–2.2 (7 H, m), 2.58 (1 H mobile, large s, OH), 3.30 (3 H, s), 3.30–4.10 (3 H, m) and 4.62 (*trans*) and 4.72 (*cis*) (1 H, d); δ_C(20 MHz; $CDCl_3$) *trans*-isomer 23.4, 29.0, 30.7, 37.7, 45.7, 54.6, 65.8 and 67.6, 66.6 and 110.0; *cis*-isomer 25.0, 29.5, 30.6, 38.3, 44.6, 54.6, 65.3 and 67.9, 67.3 and 105.0; ν_{max}(neat)/cm^{-1} 3400 (OH).

4-(2-Methoxytetrahydropyran-3-yl)butan-2-ol 16e. From keto acetal **3e** (1.86 g, 10 mmol) was obtained pure hydroxy acetal **16e** (1.88 g, 100%) as a mixture of two pairs of diastereoisomers; δ_H(80 MHz; $CDCl_3$) 1.12 (3 H, d, *J* 6), 1.0–2.0 (9 H, m), 3.50 (1 H mobile, large s, OH) 3.30 (*cis*) and 3.36 (*trans*) (3 H, s), 3.2–4.0 (3 H, m) and 4.05 (*trans*) and 4.46 (*cis*) (1 H, d); δ_C(20 MHz; $CDCl_3$) *cis*-isomer 22.8, 23.8, 25.0, 27.3, 35.8, 39.4, 54.2, 58.8, 67.2 and 100.2; *trans*-isomer 22.0, 23.1, 25.4, 26.3, 37.8 and 37.9, 38.9, 55.0, 63.0, 65.1 and 65.8 and 104.6; ν_{max}(neat)/cm^{-1} 3400 (OH); *m*/*z* (70 eV, CI) 173 (M^+ − CH_3).

Kinetically controlled acidic hydrolysis of hydroxy acetals 12 and 16

To 2 mmol of hydroxy acetal in solution in THF (5 cm^3) was added, at room temp., 3 mol dm^{-3} hydrochloric acid (5 cm^3). After stirring of the mixture for 10 min at room temp., CH_2Cl_2 (10 cm^3) was added, followed by decantation, and extraction of the aqueous layer (4 × 10 cm^3 of CH_2Cl_2). The organic layers were dried ($MgSO_4$) and concentrated. *cis*-Cyclisation product(s) (**13** or **17**) was/were obtained after flash chromatography (eluent: light petroleum), free from its *trans*-isomer or, if mentioned, separated one from the other.

2,2-Dimethylhexahydro-2*H*,5*H*-pyrano[2,3-*b*]pyran 13. From hydroxy acetal **12** (1.01 g, 5 mmol) was obtained pure *compound cis*-**13** (0.57 g, 67%), isolated from *trans*-**13** (0.03 g, 3%) (diastereoisomeric ratio: *cis*:*trans* = 95:5) (Found: C, 70.4; H, 10.5. $C_{10}H_{18}O_2$ requires C, 70.55; H, 10.66%); δ_H(400 MHz; $CDCl_3$) *cis*-isomer 1.20 (3 H, s, Me), 1.30 (3 H, s, Me), 1.30–1.90 (9 H, m), 3.55 (1 H, ddt, 7-H^{ax}), 3.90 (1 H, m, 7-H^{eq}) and 4.88 (1 H, d, *J* 1.7, 8a-H); *trans*-isomer 1.28 (3 H, s, Me), 1.32 (3 H, s, Me), 0.8–1.8 (9 H, m), 3.58 (1 H, dt, 7-H^{ax}), 4.07 (1 H, ddd, 7-H^{eq}), 4.30 (1 H, d, *J* 7.5, 8a-H); δ_C(100 MHz; $CDCl_3$) *cis*-isomer 23.7, 24.1, 25.4, 30.6, 32.6, 34.4 (C-4a), 62.3 (C-7),

73.5 (C-2) and 94.9 (C-8a); *trans*-isomer 22.6, 25.6, 26.1, 28.5, 31.5, 36.4, 40.8 (C-4a), 67.5 (C-7), 74.6 (C-2) and 100.6 (C-8a); *m/z* (70 eV, CI, Bu^{i}H) 253 ($MBu^iH_2^+$).

6-Methylhexahydro-4*H*-furo[2,3-*b*]pyran 17a. From hydroxy acetal **16a** (0.87 g, 5 mmol) was obtained pure *compound* **17a** (0.53 g, 75%) as a pair (50/50) of paired *cis*-isomers isolable one from each other (Found: C, 67.9; H, 9.5. $C_8H_{14}O_2$ requires C, 67.6; H, 9.9%); δ_H(200 MHz; $CDCl_3$) Isomer A 1.08 (3 H, d, *J* 6.3), 1.2–2.2 (7 H, m), 3.5–4.2 (3 H, m), 5.20 (1 H, d, *J* 3.5, 7a-H); Isomer B 1.08 (3 H, d, *J* 5.7), 1.0–1.5 (3 H, m), 1.5–2.3 (4 H, m), 3.0–3.6 (1 H, sext), 3.6–4.3 (2 H, m) and 4.90 (1 H, d, *J* 2.6); δ_C(20 MHz; $CDCl_3$) Isomer A 21.1, 24.2, 30.0 (2 C), 33.1, 64.5, 65.8 and 101.8; Isomer B 21.5, 23.0, 25.5, 27.1, 37.4, 68.2, 70.3 and 101.2.

2-Methylhexahydro-2*H*,5*H*-pyrano[2,3-*b*]pyran 17e. From hydroxy acetal **16e** (0.94 g, 5 mmol) was obtained pure compound *cis*-**17e** (0.58 g, 60%) as a couple of two *cis*-isomers (*u*/*l* 53/47), and pure compound *trans*-**17e** (0.03 g, 3%) (diastereoisomeric ratio: *cis*/*trans* = 95:5) (HRMS: Found: M^+, 156.1140. $C_9H_{16}O_2$ requires M, 156.1150); δ_H(400 MHz; $CDCl_3$) *cis*-isomers 1.13 (*u*) and 1.23 (*l*) (3 H, d, *J* 6.2, Me), 1.25–1.42 (3 H, m), 1.52–1.8 (5 H, m), 1.84 (*l*) and 1.92 (*u*) (1 H, dt), 3.49 (*u*) and 3.86 (*l*) (1 H, dt, 7-H^{ax}), 3.55 (*l*) and 3.95 (*u*) (1 H, m, 2-H^{ax}), 3.63 (*l*) and 4.02 (*u*) (1 H, m, 7-H^{eq}), 4.74 (*u*) and 4.77 (*l*) [1 H, d, *J* 2.0 (*u*) and 2.2 (*l*, 8a-H)]; *trans*-Isomer (*l*) 1.20 (3 H, d, *J* 6.5, Me), 1.0–1.35 (4 H, m), 1.50 (2 H, m), 1.65 (3 H, m), 3.50 (1 H, dt, 7-H^{ax}), 3.59 (1 H, m, 2-H^{ax}), 4.00 (1 H, m, 7-H^{eq}) and 4.08 (1 H, d, *J* 7.4, 8a-H); δ_C(100 MHz; $CDCl_3$) *cis*-isomer (*u*) 21.8, 22.3, 25.5, 27.9, 28.1, 33.7 (C-4a), 61.1 (C-7), 73.1 (C-2) and 97.9 (C-8a); *cis*-isomer (*l*) 20.6, 21.7, 22.6, 28.0, 32.8, 34.1 (C-4a), 66.4 and 67.5 (C-2 and -7) and 98.6 (C-8a); *trans*-isomer (*l*) 21.5, 26.0, 28.5, 28.6, 33.4, 39.9 (C-4a), 67.4 (C-7), 73.4 (C-2) and 105.0 (C-8a).

Reductive amination of keto acetal 3 into compound 18 and cyclisation into compound 19

To a solution of a keto acetal **3** (10 mmol) was added, at room temp., the appropriate primary amine (11 mmol) in 1,2-dichloroethane (30 cm^3), then, portionwise, sodium triacetoxyboranuide (15 mmol) and acetic acid (10 mmol) *via* syringe. The mixture was stirred at room temp. overnight. After evaporation, the residue was treated by water (10 cm^3). Then Na_2CO_3 was added (until pH 12). The solution was then extracted with CH_2Cl_2 (4 × 25 cm^3). The extract was dried over $MgSO_4$ and evaporated under reduced pressure, to give crude amino acetal identified as follows:

3-(3-Benzylaminobutyl)-2-isopropoxytetrahydropyran 18a. (2 pairs of diastereoisomers, diastereoisomeric ratio: *cis*/*trans* 57/43); δ_H(200 MHz; $CDCl_3$) 1.0–2.0 (17 H, m), 2.60 (1 H, m), 3.45 (1 H, m), 3.6–4.0 (4 H, m), 4.16 (1 H, dd, *J* 6.4 and 2.3, 2-H *trans*), 4.68 (1 H, d, *J* < 2, 2-H *cis*), 7.3 (5 H, m); δ_C(50 MHz; $CDCl_3$) *cis*-isomers 20.2, 21.5, 23.4, 24.3, 25.7, 27.0, 33.7 and 34.0, 40.0, 51.3, 52.7, 59.5 (C-6), 68.1 (C-2′), 97.1 and 97.2 (C-2), 126.7, 128.0 (2 C), 128.3 (2 C) and 140.7; *trans*-isomers 20.2, 21.5, 23.5, 24.3, 25.7, 27.0, 27.8 and 28.2, 40.0, 51.3, 52.7, 64.5 (C-6), 69.5 (C-2′), 102.7 and 102.8 (C-2), 126.7, 128.0 (2 C), 128.3 (2 C) and 140.7; ν_{max}(neat)/cm^{-1} 1603.

3-(3-Butylaminobutyl)-2-methoxytetrahydropyran 18b. This compound was used as a crude product and was characterised only by its mass spectrum: **18b**; *m/z* (70 eV, CI, NH_3) 244 (MH^+, 100).

In each case, a solution of the crude product **18** in THF (5 cm^3) was treated by 3 mol dm^{-3} hydrochloric acid (25 cm^3) at room temp. for 2 h while being stirred. The solution was basified by Na_2CO_3, then was extracted with diethyl ether (4 × 25 cm^3). The extract was dried over $MgSO_4$ and evaporated under reduced pressure. The product was purified by flash chromatography [eluent: diethyl ether–light petroleum (10:100)] leading to pure compounds **19**. Compound **19a** (1.45 g, 59% from **3k**) as a mixture of four isomers (*cis*-**I**/*cis*-**II**/*trans*-**III**/*trans*-**IV**: 65/25/9/1, diastereoisomeric ratio: *cis*:*trans* = 90:10) (Found: C, 78.0; H, 9.1; N, 5.5. $C_{16}H_{23}NO$ requires C, 78.3; H, 9.4; N, 5.7%); δ_H(400 MHz; $CDCl_3$) *cis*-**I** 1.04 (3 H, d, *J* 6.1, Me), 1.0–2.05 (8 H, m), 1.68 (1 H, m, 4a-H), 2.92 (1 H, m, 7-H), 3.19 (1 H, td, *J* 12.4 and 2.5, 2-H^{ax}), 3.77 and 3.91 (1 + 1 H, 2 d, AB system, *J* 13.7, CH_2Ph), 3.81 (1 H, d, *J* 1.8, 8a-H), 3.93 (1 H, m, 2-H^{eq}) and 7.15–7.4 (5 H, m); *cis*-**II** 1.16 (3 H, d, *J* 6.8, Me), 1.0–2.05 (8 H, m), 1.68 (1 H, m, 4a-H), 2.91 (1 H, m, 7-H), 3.21 (1 H, td, *J* 11.3 and 2.3, 2-H^{ax}), 3.85 and 3.97 (1 + 1 H, 2 d, AB system, *J* 14.3, CH_2Ph), 3.91 (1 H, m, 2-H^{eq}), 4.14 (1 H, d, *J* 2.2, 8a-H) and 7.15–7.4 (5 H, m); *trans*-**III** 1.22 (3 H, d, *J* 6.1, Me), 1.0–2.05 (8 H, m), 1.40 (1 H, m, 4a-H), 2.43 (1 H, m, 7-H), 3.12 (1 H, d, *J* 8.2, 8a-H), 3.47 (1 H, td, *J* 11.7 and 2.4, 2-H^{ax}), 3.98 and 4.12 (1 + 1 H, 2 d, AB system, *J* 14.9, CH_2Ph), 4.05 (1 H, m, 2-H^{eq}) and 7.15–7.4 (5 H, m), *trans*-**IV** detected by: 0.97 (3 H, d, *J* 6.8, Me), 3.68 (1 H, d, *J* 8.0, 8a-H) and 3.54 (1 H, td, 2-H^{ax}); δ_C(100 MHz; $CDCl_3$) *cis*-**I** 20.9 (7-Me), 21.5, 23.1, 28.7, 34.8, 35.1 (C-4a), 49.8 (C-7), 52.7 (*C*H$_2$Ph), 67.0 (C-2), 88.3 (C-8a) and 126–130 (C-Ar); *cis*-**II** 21.4 (7-Me), 21.3, 29.0, 29.5, 31.4, 35.5 (C-4a), 49.5 (C-7), 54.7 (*C*H$_2$Ph), 66.4 (C-2), 89.8 (C-8a) and 126–130 (C-Ar); *trans*-**III** 16.2 (7-Me), 18.9, 25.8, 28.6, 29.8, 40.0 (C-4a), 49.4 (*C*H$_2$Ph), 53.2 (C-7), 66.4 (C-2), 93.2 (C-8a) and 126–130 (C-Ar); *trans*-**IV** detected by: 40.6 (C-4a), 50.3 (*C*H$_2$Ph), 49.0 (C-7), 67.2 (C-2) and 91.5 (C-8a).

Compound **19b** (0.89 g, 42%) (*cis*-**I**/*cis*-**II**/*trans*-**III**/*trans*-**IV** 65/25/9/1, diastereoisomeric ratio *cis*:*trans* = 90:10) (Found: C, 73.8; H, 11.9; N, 6.7. $C_{13}H_{25}NO$ requires C, 73.61; H, 12.23; N, 6.84%) (HRMS: Found: M^+, 211.1959. $C_{13}H_{25}NO$ requires M, 211.1936); δ_H(400 MHz; $CDCl_3$) *cis*-**I** 0.88 (3 H, t, *J* 7.2), 1.00 (3 H, d, *J* 6.3), 1.1–2.0 (13 H, m), 2.63 (2 H, ddd, 1′-H), 2.78 (1 H, m, 7-H), 3.33 (1 H, td, *J* 11.7 and 2.6, 2-H^{ax}), 3.93 (1 H, m, 2-H^{eq}), 4.10 (1 H, d, *J* 2.0, 8a-H); *cis*-**II** 0.86 (3 H, t, *J* 7.2), 1.07 (3 H, d, *J* 6.7), 1.1–2.0 (13 H, m) 2.55–2.7 (2 H, ddd, 1′-H), 2.94 (1 H, m, 7-H), 3.35 (1 H, td, 2-H^{ax}), 3.89 (1 H, m, 2-H^{eq}) and 4.07 (1 H, d, *J* 2.5, 8a-H); *trans*-**III** 0.87 (3 H, t, *J* 7.2), 1.08 (3 H, d, *J* 6.1), 1.1–2.0 (13 H, m), 2.44 (1 H, m, 7-H), 2.55–2.7 (2 H, ddd, 1′-H), 3.24 (1 H, d, *J* 8.2, 8a-H), 3.42 (1 H, td, *J* 11.8 and 2.7, 2-H^{ax}) and 3.98 (1 H, m, 2-H^{eq}); *trans*-**IV** detected by: 0.93 (3 H, d, *J* 6.9); δ_C(100 MHz; $CDCl_3$) *cis*-**I** 13.8 (3′-Me), 20.6, 20.9, 21.2 (7-Me), 23.1, 29.0, 30.5, 34.8, 35.5 (C-4a), 49.1 (C-7), 49.7 (C-1′) 67.3 (C-2) and 89.5 (C-8a); *cis*-**II** 13.8 (3′-Me), 16.1 (7-Me), 19–35 (6 C), 35.6 (C-4a), 49.4 (C-7), 49.9 (C-1′), 66.5 (C-2) and 89.8 (C-8a); *trans*-**III** 13.8 (3′-Me), 21.0 (7-Me), 40.1 (C-4a), 47.0 (C-1′), 54.2 (C-7), 66.9 (C-2) and 94.9 (C-8a); *trans*-**IV** detected by: 40.8 (C-4a), 46.9 (C-1′) and 92.1 (C-8a). All the signals were attributed after a 2D ^{13}C, ^1H NMR correlation.

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