Highly Selective Stereochemically Controlled Five- *versus* Six-membered Acetal Ring Cyclisation

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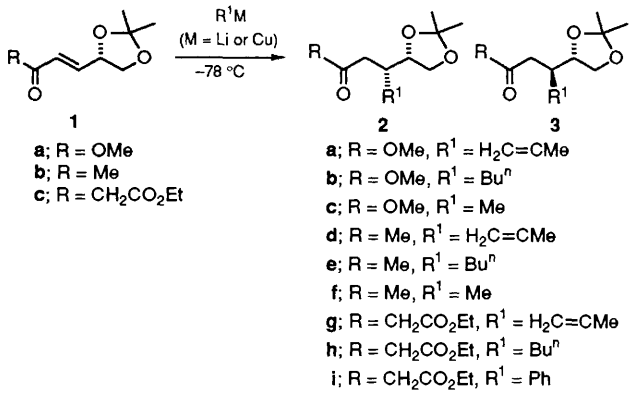
Cyclisations of 3-substituted-4,5-dihydroxy ketones, under acidic conditions, occur with high selectivity to give either tetrahydropyran or tetrahydrofuran acetals, the ring size being dependent on the relative stereochemistry between the substituents at C-3 and C-4.

In previous communications we have described the reactions of organolithium and organocopper reagents with γ-alkoxy enones and enoates derived from glyceraldehyde acetonide (*e.g.* **1a–c**).[1–3] It was interesting to discover that both types of organometallic reagent have a strong preference for conjugate addition to such systems and that, whereas the organocopper reagents react selectively *anti* to the γ-oxygen, lithium reagents usually react with *syn* selectivity (Scheme 1).

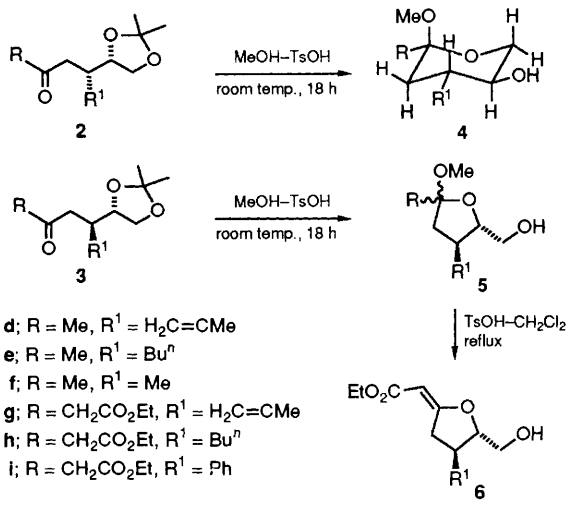
The relative stereochemistry of the substituents in acyclic compounds **2** and **3** was established by six-membered ring formation. For example, when **2d** was treated with toluene-*p*-sulfonic acid in methanol a spontaneous cyclisation of the deprotected diol occurred to give a single six-membered ring acetal **4d** and 1,3-dicarbonyl systems **2g–i** also cyclised cleanly to the tetrahydropyran acetals **4g–i** (Scheme 2). By chance the *syn* isomers were chosen for cyclisation in our early studies and these invariably cyclised cleanly to six-membered ring acetals under the reaction conditions. However, we have now carried out a systematic study of the cyclisation reactions of both *syn* and *anti* isomers and found a very interesting pattern in the outcome. Whereas each of the *syn* isomers **2** cyclises cleanly to a tetrahydropyran acetal **4**, as a single anomer, *anti* isomers **3** always cyclise cleanly to five-membered ring acetals **5**, generally as a 1:1 mixture of anomers. Tetrahydrofuran acetals **5g–i** are quite labile and on warming in acid or base they are converted to exocyclic unsaturated esters **6**.

For all the systems studied the cyclisations were remarkably selective, yields of the cyclic products were generally in the range 80–90%, and none of the alternative cyclisation products were ever isolated.† The more interesting cyclisations were those of the keto esters **2g–i** and **3g–i**. For example, when **2g** was treated with a catalytic quantity of toluene-*p*-sulfonic acid (TsOH) in methanol for 18 h, a single cyclic product **4g** was isolated in 80% yield which was characterised as its acetate. The ^{1}H NMR of the acetate of **4g** in deuteriobenzene was essentially first order and the all *trans-diaxial* arrangement of protons around a tetrahydropy-

† All yields are for isolated material and are not optimized. All new compounds were characterized by a full range of spectroscopic data, including 300 MHz ^{1}H NMR and high resolution mass spectrometry.

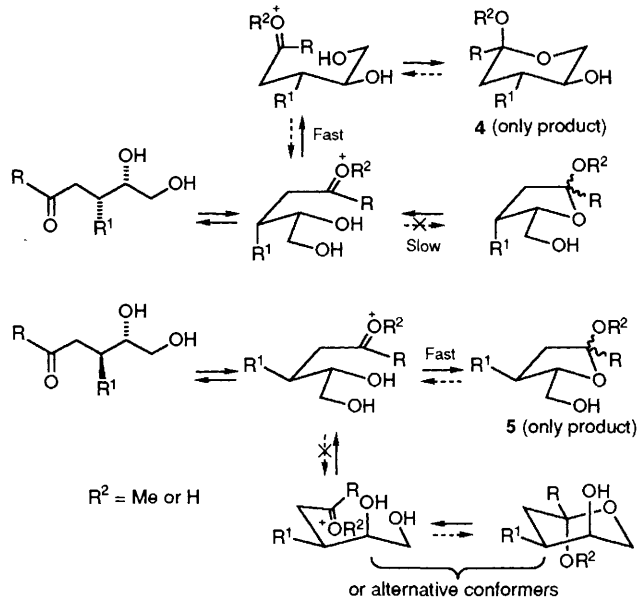


Scheme 1



Scheme 2

ran ring was clearly defined with the aid of decoupling experiments.‡ On the other hand **3g** cyclised under the same conditions to a 1:1 mixture of two anomeric products **5g**, obtained in 84% yield. The anomers of **5g** could be separated by flash chromatography and in each case the proton NMR coupling constants and chemical shifts were in accord with those expected for a five-membered ring acetal.§ On gentle



Scheme 3

warming in methylene chloride containing catalytic toluene-*p*-sulfonic acid, each anomer was initially converted to a mixture of geometric isomers of **6g**, but this quickly equilibrated to a single *E*-alkene under the same acidic conditions, 65% yield.¶ There was a characteristic exocyclic vinyl proton at δ 5.29 in the ^{1}H NMR spectrum of **6g** and acetylation caused a downfield shift of the exocyclic methylene protons adjacent to the hydroxy, but not the methyne, thus confirming the tetrahydrofuran structure. Reaction sequences similar to those described above were carried out for all the *syn* isomers **2d–i** and the *anti* isomers **3d–i**, all cyclisations followed the same pattern and yields were uniformly high.

It is generally assumed that carbohydrates cyclise kinetically to five-membered ring acetals, but slowly rearrange to six-membered ring acetals under thermodynamic conditions.[4–6] In this case acetonide cleavage with TsOH is quite slow and, because the reactions were so selective, it was difficult to determine whether any intermediates were involved. Reactions of **2d** and **3d** were therefore repeated using dry HCl–MeOH, which cleaves the acetonide rapidly, allowing us to monitor the cyclisation process more closely. Reaction of the *syn* isomer **2d** was monitored at one minute intervals and although formation of the tetrahydropyran product began immediately, no intermediate tetrahydrofuran could ever be detected. It is therefore likely that there is a kinetic as well as a thermodynamic preference for six-membered ring formation because of unfavourable interactions between 1,2-*cis* substituents in both the five-membered ring product and the transition state leading to it. Only five-membered ring acetals were ever observed during the cyclisations of *anti* isomer **3d**, even upon prolonged reaction times (up to 5 days). It therefore appears that *trans* five-membered ring acetals **5** are formed kinetically from *anti* isomers **3** and that they are also more thermodynamically stable than the alternative six-membered systems, which have unfavourable 1,3-diaxial interactions (Scheme 3).

The selective cyclisations seen here are in themselves interesting and such stereochemically controlled cyclisation

‡ (2*R*,4*S*,5*S*)-5-acetoxy-2-(ethoxycarbonyl)methyl-2-methoxy-4-isopropenyltetrahydropyran: δ_H (300 MHz, [^{2}H]benzene, *J*/Hz) 0.93 (3H, t, *J* 7, CH_2CH_3), 1.65 (3H, s, $COCH_3$) 1.95 (1H, ~t, $J_{3\alpha,3\beta}$ 13.5, $J_{3\alpha,4}$ 13, H-3α), 2.35 (1H, dd, $J_{3\alpha,3\beta}$ 13.5, $J_{3\beta,4}$ 4, H-3β), 2.50 (1H, d, *J* 14, CH_2CO_2Et), 2.76 (1H, d, *J* 14 CH_2CO_2Et), 3.00 (1H, ddd, $J_{3\alpha,4}$ 13, $J_{4,5}$ 10.5, $J_{3\beta,4}$ 4, H-4), 3.16 (3H, s, OCH_3), 3.42 (1H, t, $J_{6\alpha,6\beta}$ 10.5, $J_{6\beta,5}$ 10.5, H-6β), 3.83 (1H, dd, $J_{6\alpha,6\beta}$ 10.5, $J_{6\alpha,5}$ 5.5, H-6α), 3.93 (2H, 2 × overlapping q, CH_2CH_3), 4.80 (1H, m, $=CH_2$), 4.88 (1H, br s, $=CH_2$), 5.16 (1H, ~dt, $J_{5,4}$ 10.5, $J_{5,6\beta}$ 10.5, $J_{5,6\alpha}$ 5.5, H-5).

§ (2*R*/*S*,4*R*,5*S*)-2-(ethoxycarbonyl)methyl-5-hydroxymethyl-2-methoxy-4-isopropenyltetrahydrofuran: δ_H (300 MHz, $CDCl_3$, *J*/Hz), 1.25 (3H, t, *J* 7, CH_2CH_3), 1.72 (3H, s, $CH_2=CCH_3$), 2.25 (2H, m, H_2-3), 2.66 (1H, d, *J* 14, CH_2CO_2Et), 2.95 (1H, m, H-4), 2.95 (1H, d, *J* 14, CH_2CO_2Et), 3.30 (3H, s, OCH_3), 3.52 (1H, dd, *J* 12, 6, CH_2OH), 3.71 (1H, dd, *J* 12, 2.5, CH_2OH), 4.07 (1H, ddd, H-5), 4.14 (2H, ~q, *J* 7, CH_2CH_3), 4.80 (2H, ~s, $=CH_2$).

(2*R*/*S*,4*R*,5*S*)-2-(ethoxycarbonyl)methyl-5-hydroxymethyl-2-methoxy-4-isopropenyltetrahydrofuran: δ_H (300 MHz, $CDCl_3$, *J*/Hz) 1.25 (3H, t, *J* 7, CH_2CH_3), 1.73 (3H, s, $CH_2=CCH_3$), 2.07 (1H, dd, *J* 14, 8.5, H-3a), 2.44 (1H, dd, *J* 14, 10, H-3b), 2.77 (2H, ~s, CH_2CO_2Et), 2.92 (1H, ~q, H-4), 3.27 (3H, s, OCH_3), 3.49 (1H, m, CH_2OH), 3.83 (1H, dd, *J* 12, 2, CH_2OH), 3.98 (1H, ~dt, *J* 8, 3, 3, H-5), 4.14 (2H, 2 overlapping q, CH_2CH_3), 4.79–4.81 (2H, m, $=CH_2$).

¶ (4*R*,5*S*)-(*E*)-2-(ethoxycarbonyl)methylene-5-hydroxymethyl-4-isopropenyltetrahydrofuran: δ_H (300 MHz, $CDCl_3$, *J*/Hz) 1.24 (3H, t, *J* 7, CH_2CH_3), 1.74 (3H, s, $CH_2=CCH_3$) 2.9 (2H, m, H-3α, H-3β), 3.48 (1H, m, H-4), 3.63 (1H, dd, *J* 12, 5, H-6a), 3.87 (1H, dd, *J* 12, 2.5, H-6b), 4.11 (2H, q, *J* 7, CH_2CH_3), 4.31 (1H, m, *J* 8, 5, 3, H-5), 4.83 (1H, br s, $=CH_2$), 4.85 (1H, m, $=CH_2$), 5.29 (1H, m, *J* 2, $=CHCO_2Et$)

patterns may well be followed in other related systems. Substituted tetrahydrofurans and tetrahydropyrans are very important in nature[7] and this chemistry provides a useful method for preparing interesting substituted tetrahydropyrans and tetrahydrofurans stereoselectively, in high yield and in optically active form.

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