Intramolecular Prins cyclisations for the stereoselective synthesis of bicyclic tetrahydropyrans†

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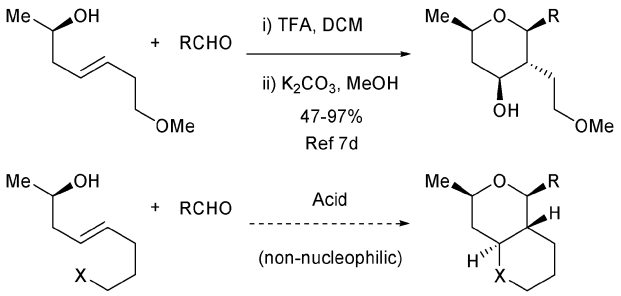
Methyl (4*E*,7*R*)-7-hydroxyoctanoate was prepared in 71% yield from ethyl (*R*)-3-hydroxybutanoate and on reaction with a series of aldehydes in the presence of TMSOTf gave bicyclic oxygen heterocycles in good yields and with the creation of three new stereogenic centres in a single pot.

Saturated oxygen containing heterocycles, of varying size, are common structural features of many biologically active natural products, for example the phorboxazoles[1] and bryostatins; often these compounds are isolated in only minute quantities.[2] In order to confirm their structures and gain sufficient material for full biological assessment of the natural products and analogues, the development of efficient methods for the synthesis of oxygen heterocycles remains an important goal.[3]

Whilst Prins cyclisations[4] have been used for the stereoselective assembly of functionalised tetrahydrofurans[5] and larger oxacycles,[6] they are more commonly employed for the synthesis of tetrahydropyrans.[7] The reaction involves the acid mediated *in situ* generation of a homoallylic oxycarbenium ion, which cyclises in the presence of a nucleophile to give the tetrahydropyran. In the majority of cases an intermolecular reaction between oxycarbenium ions and nucleophiles has been used[8] but we envisaged that by tethering a suitable nucleophilic functional group, novel bicyclic oxygen heterocycles may be prepared (Scheme 1). Oxygenated nucleophiles such as acetic acid or trifluoroacetic acid have been employed for intermolecular variants and consequently our investigations began with a homoallylic alcohol with a tethered carboxylic acid.

First, acetal **1** was treated with a catalytic amount of triflic acid in CH_2Cl_2 but none of the expected bicyclic product, **2**, was isolated. Indeed the only product obtained after column chromatography was the unsaturated lactone **3** (Table 1, Entry 1). Next acetal **1** was treated with catalytic $BF_3{\cdot}OEt_2$ in CH_2Cl_2 which mainly led to degradation and again the only product isolated was **3** in 18% yield (Table 1, Entry 2). We propose that lactone **3** was formed *via* an oxonia-Cope rearrangement of the initially formed oxycarbenium ion, **4**, to **5** followed by hydrolytic cleavage to the hydroxy acid and *in situ* lactonisation (Scheme 2).

It has been demonstrated that the mechanism of the Prins cyclisation is not simple and oxonia-Cope rearrangements and allyl transfer processes may occur depending on the stabilisation of the initially formed oxycarbenium ion compared with that subsequently generated *via* a [3,3]-sigmatropic rearrangement.[9] In the case illustrated in Scheme 2 the driving force behind the rearrangement is likely to be stabilisation of the oxycarbenium ion by the methyl group in **5** compared with the terminal oxycarbenium ion present in **4**.

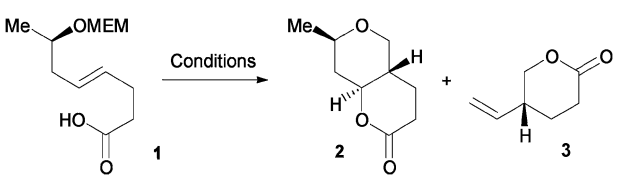


Scheme 1 Proposed intramolecular Prins cyclisation.

Rychnovsky and coworkers have illustrated that the reaction conditions also play an important role in controlling the participation of an oxonia-Cope rearrangement and as such the use of a non-polar solvent can minimise the production of any unwanted by-products.[9g] Therefore, acetal **1** was treated again with $BF_3{\cdot}OEt_2$ but instead of using CH_2Cl_2 the reaction was conducted in hexane. Encouragingly, lactone **3** was no longer detected in the mixture and only the desired tetrahydropyran **2** was isolated as a single diastereomer, albeit in only 41% yield (Table 1, Entry 3).

Whilst MEM acetal **1** was originally selected as a simple model to investigate the potential of Prins cyclisations for the

Table 1 Acid mediated cyclisation of homoallylic acetal **1**



Entry	Conditions	Yield[a] (%) 2	3
1	$TfOH_{(cat)}$, DCM, RT, 1 h	—	37
2	$BF_3{\cdot}OEt_{2(cat)}$, DCM, RT, 4 h	—	18
3	$BF_3{\cdot}OEt_2$, TMSOAc, Hexane, RT, 1 h	41	—

[a] Isolated yield.

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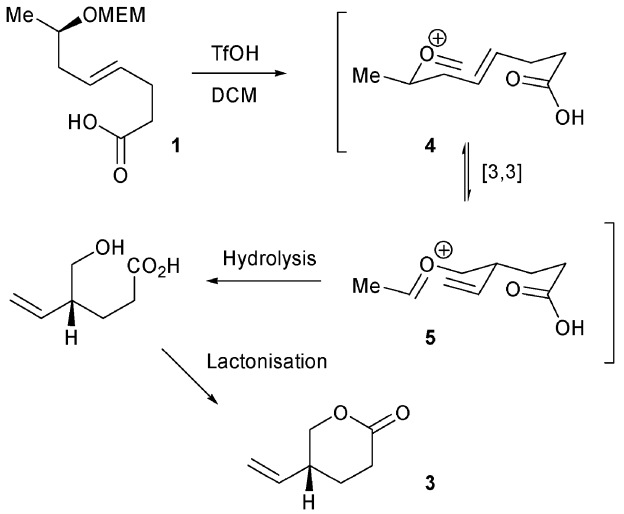
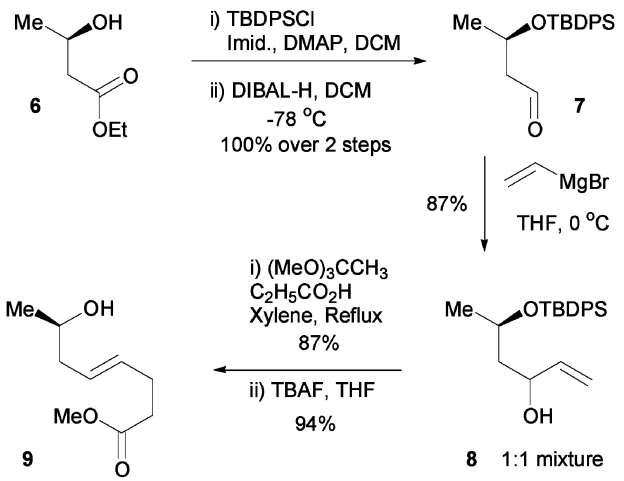


Scheme 2 Competing oxonia-Cope cascade.

synthesis of bicyclic targets, it is limited to the introduction of a methylene next to the oxygen in the tetrahydropyran ring and in the event led to poor yields of **2**. Ideally we required an approach that not only would give an improved yield but also allow greater structural variation in the target bicyclic oxygen heterocycles. An attractive option was to use a functionalised homoallylic alcohol which could react with an aldehyde to introduce a range of substituents at C-7 of the tetrahydropyran. We have previously found that on treatment of unsaturated α-hydroxy esters with iodine at room temperature cyclisation occurred to give lactones in good yields.[10] Hence we envisaged that tethering an ester onto the homoallylic alcohol would potentially facilitate the required cyclisation.

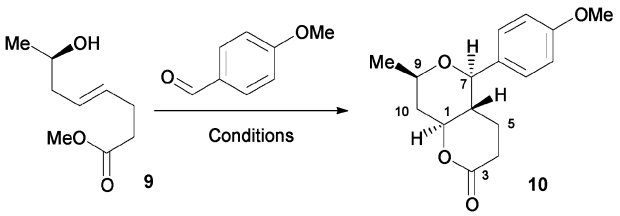
Homoallylic alcohol **9** was prepared in 71% yield from ethyl (*R*)-3-hydroxybutanoate **6** as shown in Scheme 3. The key steps were the addition of vinylmagnesium bromide to the known aldehyde **7**[11] to give **8**, which on reaction with trimethylorthoacetate in the presence of catalytic propionic acid underwent a Claisen rearrangement to give, after deprotection, the required (*E*)-unsaturated ester **9**.

Treatment of homoallylic alcohol **9** with anisaldehyde in the presence of TFA gave the novel tetrahydropyran **10** as a



Scheme 3 Synthesis of homoallylic alcohol **9**.

Table 2 Optimisation of the conversion of **9** to **10**



Entry	Conditions[a]	Yield[d] of **10** (%)
1[b]	TFA, DCM, RT, 5 h	29
2[c]	$MeSO_3H$, DCM, −10 °C → RT, 2.5 h	48
3	$BF_3{\cdot}OEt_2$, DCM, −78 °C → RT, 2.5 h	56
4	$Sc(OTf)_3$, DCM, −10 °C → RT, 2.5 h	83
5	TfOH, DCM, 0 °C → RT, 1.5 h	90
6	TMSOTf, DCM, −45 °C → RT, 2 h	93

[a] General procedure: acid (1.0 eq, 1.5 mmol) was added to **9** (1.5 mmol) and 4-anisaldehyde (1.1 eq, 1.65 mmol) in dry CH_2Cl_2 under N_2. [b] 5.0 eq of TFA was required. [c] 2.0 eq of $MeSO_3H$ was required. [d] Isolated yield.

crystalline solid but in just 29% yield (Table 2, entry 1). Different acids were screened as summarised in Table 2 and the optimised conditions proved to be the use of TMS triflate in CH_2Cl_2 to give the required product **10** in 93% yield.

It was clear from the spectral data of **10** that a single diastereomer had been formed with a *trans* ring junction and the two substituents on the tetrahydropyran ring in an equatorial position (Fig. 1). Hence in a single-pot process homoallylic alcohol **9** had been converted to lactone **10** in 93% yield, with the creation of 3 new stereogenic centres and the formation of two new heterocyclic rings.

Anisaldehyde was selected in these initial studies mainly because an electron-rich aromatic ring has been shown to stabilise an adjacent oxycarbenium ion,[9b,c] which removes the potential complication of a competing oxonia-Cope rearrangement. However, the next stage was to explore the scope of the reaction using a series of electrophiles. Accordingly, Table 3 illustrates that this variant on the Prins cyclisation may be used to prepare a wide range of bicyclic products with different substituents at C-7. For example, alcohol **9** reacts efficiently with either benzaldehyde or *p*-nitrobenzaldehyde to give the bicyclic lactones **11** and **12**, confirming that the electronic properties of the aromatic ring have little influence on the outcome of the reaction. Furthermore propanal, with a simple aliphatic side-chain, gave **14** in 72% yield (Entry 4) whilst in the case of a functionalised aldehyde such as acrolein

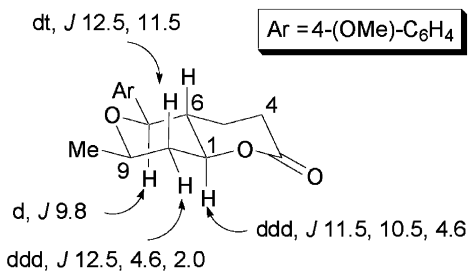
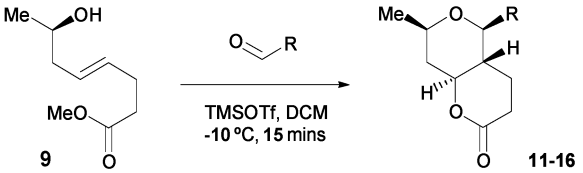
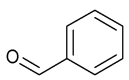
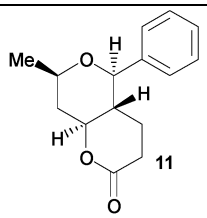
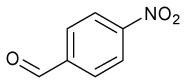
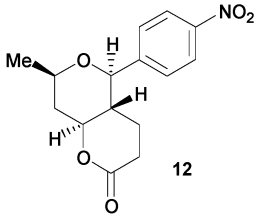
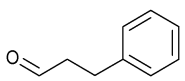
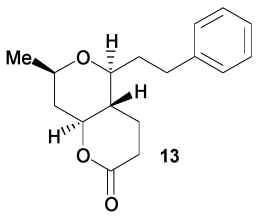
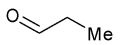
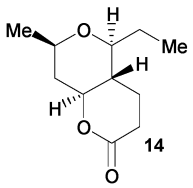
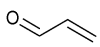
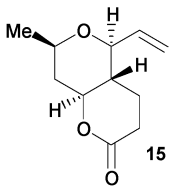
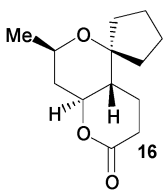


Fig. 1 Diagnostic coupling constants in the ^{1}H-NMR spectrum (400Mz, $CDCl_3$) of **10**.

Table 3 Reaction of alcohol **9** with a range of electrophiles



Entry[a]	Electrophile	Product	Yield[c] (%)
1		 **11**	81
2		 **12**	71
3		 **13**	73
4		 **14**	72
5		 **15**	84
6[b]		 **16**	63

[a] General procedure: TMSOTf (1.0 eq, 1.5 mmol) was added to **9** (1.5 mmol) and electrophile (1.1 eq, 1.65 mmol) in dry CH_2Cl_2 at −10 °C under N_2 and stirred for 15 min. [b] After 2 h at RT extra TMSOTf (0.5 eq) and cyclopentanone (0.5 eq) were added with stirring for a further 1.5 h. [c] Isolated yield.

(Entry 5) the product **15** was formed with an alkene side-chain, a useful handle for further manipulations. Interestingly, the reaction was also successful with a ketone (Entry 6) giving the spirocyclic product **16**; in this case a longer reaction time and extra equivalents of ketone and TMS triflate were required. Thus it is evident that this chemistry has widespread application for the synthesis of a series of novel bicyclic heterocycles.

In summary, an efficient method for the synthesis of methyl (4*E*,7*R*)-7-hydroxyoctanoate **9** is described from commercially available ethyl (*R*)-3-hydroxybutanoate **6** using a Claisen rearrangement to establish the *E*-double bond. Reaction of hydroxy ester **9** with various aldehydes in the presence of TMSOTf gave novel bicyclic products in good yield and with the creation of 3 new stereogenic centres in a single pot process. Furthermore a spirocyclic product **16** was isolated when cyclopentanone was used as the electrophile.

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