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Stereocontrolled synthesis of 2,4,5-trisubstituted tetrahydropyrans

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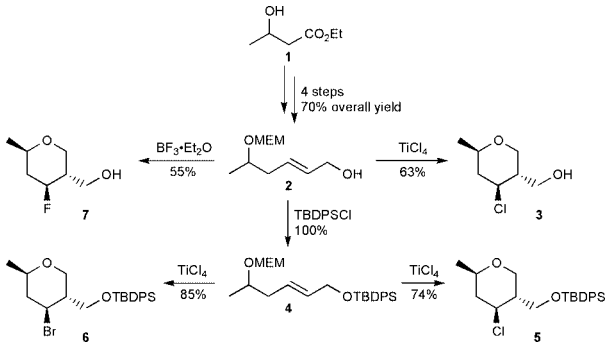
Cyclisation of homoallylic acetals under acidic conditions leads to the formation of 2,4,5-trisubstituted tetrahydropyrans with the creation of two new asymmetric centres with excellent stereocontrol. By varying the acid and the nucleophile, the reaction may be adapted for the preparation of 2,4,5-trisubstituted tetrahydropyrans with either a halide, alcohol, acetate or amide at C-4.

Substituted tetrahydropyrans are common features of many natural products and biologically active compounds and many strategies for their synthesis have been reported. One valuable approach to the preparation of tetrahydropyrans is a Prins type cyclisation in which treatment of a homoallylic acetal (or a mixture of a homoallylic alcohol and carbonyl compound) with acid leads to formation of an oxocarbenium cation intermediate which undergoes an intramolecular reaction with the alkene.[1] Upon cyclisation, the fate of the resulting carbocation intermediate is dependent upon the reaction conditions and substrates employed. Thus, Thompson and coworkers have shown that acetals derived from (*E*)- or (*Z*)-hex-3-en-1-ol cyclised in the presence of titanium tetrabromide or tetrachloride to give the *trans*- or *cis*-3-ethyl-4-halotetrahydropyrans respectively with good stereocontrol.[2] Prins type cyclisations have been widely used for the synthesis of 2,4,6-trisubstituted tetrahydropyrans[3] but examples of their use in the preparation of tetrahydropyrans with other substitution patterns has been rather more limited.[4] In this paper we describe a direct method for the preparation of 2,4,5-trisubstituted tetrahydropyrans from homoallylic acetals[5] which enables the creation of two asymmetric centres with excellent stereocontrol and in which a variety of functional groups may be introduced at C-4.

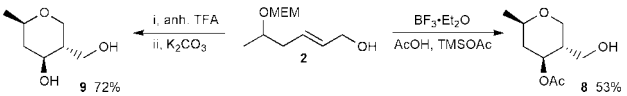
The substrate used for our initial cyclisation studies was the homoallylic acetal **2** which was readily prepared in 4 steps from ethyl 3-hydroxybutanoate **1** (readily available in both enantiomeric forms) by MEM (methoxyethoxymethyl) protection of the alcohol, DIBAL-H reduction to the aldehyde followed by Horner Wadsworth Emmons chain extension with triethyl phosphonoacetate and finally a further DIBAL-H reduction of the resultant (*E*)-α,β-unsaturated ester. In the first cyclisation study, homoallylic acetal **2** was treated with titanium tetrachloride in CH_2Cl_2 giving the 2,5-disubstituted 4-chlorotetrahydropyran **3** in 63% yield (Scheme 1). From the ^1H and ^{13}C-NMR spectra and NOE studies it was apparent that a single product had been isolated in which all three substituents were in an equatorial position.[6] When the primary alcohol of **2** was protected as the TBDPS ether **4**, the $TiCl_4$ mediated reaction gave an improved 74% yield of the cyclic product **5** again as a single diastereomer. By using other Lewis acids, further halides could be introduced at C-4 of the tetrahydropyran. Thus, treatment of **4** with titanium tetrabromide gave the 4-bromo derivative **6** in 85% yield and reaction of **2** with $BF_3{\cdot}Et_2O$ in CH_2Cl_2 gave a 55% yield of the 2,5-disubstituted 4-fluorotetrahydropyran **7**.

The synthetic utility of these cyclisations would be greatly extended if functional groups other than a halide could be introduced at C-4. Several methods have been reported for the introduction of oxygenated substituents at C-4 in Prins type



Scheme 1

cyclisations with varying success. These include the use of mercuric triflate,[7] scandium triflate,[8] $BF_3{\cdot}Et_2O$–AcOH,[3e,9] and TFAA–AcOH.[3f] We investigated a range of methods to cyclise homoallylic acetal **2** with the introduction of an oxygen nucleophile into C-4 of a tetrahydropyran. One of the more efficient procedures proved to be treatment of **2** with $BF_3{\cdot}Et_2O$ in the presence of AcOH as the nucleophile and TMSOAc to act as a fluoride trap to prevent competing formation of the 4-fluoro derivative **7**. Under these conditions, acetate **8** was obtained in 53% yield. Alternatively, treatment of **2** with anhydrous trifluoroacetic acid gave diol **9** in 72% yield after hydrolysis of the resultant 4-trifluoroacetate with potassium carbonate in MeOH, (Scheme 2). Again these reactions proceeded with good stereocontrol and only the all equatorial diastereomer was isolated.



Scheme 2

To further examine the use of TFA for the cyclisation of homoallylic acetals to give 2,4,5-trisubstituted tetrahydropyrans, a series of substrates with a *cis* double bond and a SEM, MEM or MOM group were prepared from pent-4-yn-2-ol **10** (Scheme 3). The hydroxy group of **10** was converted to the acetal prior to reaction of the alkyne with butyllithium, $BF_3{\cdot}Et_2O$ and propylene oxide giving a mixture of diastereomeric alcohols **11**. Catalytic hydrogenation of **11** in the presence of Lindlar's catalyst gave the (*Z*)-alkenols **12** and then oxidation under Swern conditions gave the three required homoallylic acetals **13**. Treatment of the SEM acetal **13** with aqueous TFAA gave three products in which the tetrahydropyran **14** was formed in only 18% yield. The major products were the diastereomeric tetrahydrofurans **15** and **16** formed *via* rearrangement of the double bond into conjugation, hydrolysis of the acetal and an intramolecular conjugate addition to the resultant enone.

However, treatment of each of the acetals **13** with anhydrous TFA in dichloromethane gave, after hydrolysis of the initially formed trifluoroacetate, the 2,5-disubstituted-4-hydroxytetra-

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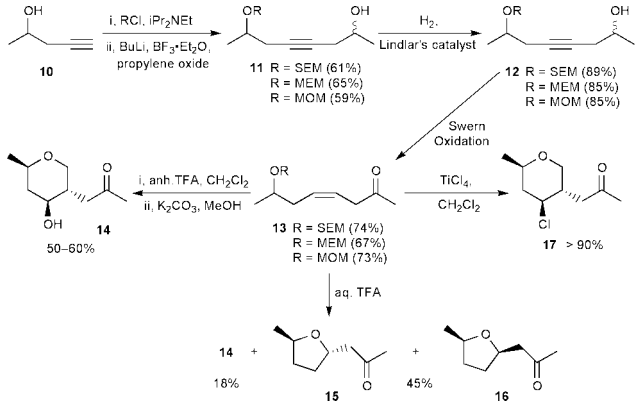
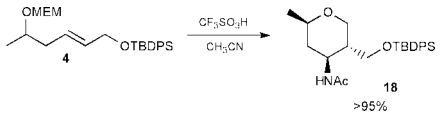


Scheme 3

hydropyran **14** in 50–60% yield with all three substituents again in an equatorial position. Interestingly the stereochemical outcome of this reaction differs from that reported for the cyclisation of MEM protected (*Z*)-hex-3-en-1-ol with $TiCl_4$ in which a *cis* relationship of the vicinal halide and alkyl group predominated.[2] In addition, Rychnovsky and co-workers have shown that although the $TiCl_4$ mediated cyclisation of an (*E*)-unsaturated homoallylic acetal gives an all equatorial 2,5,6-trisubstituted 4-chlorotetrahydropyran, the reaction on the analogous (*Z*)-isomer leads to a mixture of diastereomers in which the 4-chloro-5-alkyl substituents are *cis* in the major isomer.[9] Thus the MEM acetal **13** was cyclised using $TiCl_4$ and the product **17** was obtained in 92% yield again with all the substituents equatorial.

To the best of our knowledge Prins type cyclisations of homoallylic acetals to tetrahydropyrans have never been conducted in the presence of nitrogen nucleophiles although products from such reactions would be of great general value in synthesis. It would be expected that the acidic reaction conditions required for formation of the oxocarbenium cation would not be compatible with the use of amines as nucleophiles. Indeed we found this to be the case. However, on treatment of homoallylic acetal **4** with triflic acid in acetonitrile the 4-amido derivative **18** was obtained in excellent yield (Scheme 4).



Scheme 4

In conclusion, Prins type cyclisation of homoallylic acetals provides a versatile approach to the synthesis of 2,4,5-trisubstituted tetrahydropyrans. Our initial investigations indicate that excellent stereocontrol may be achieved with both *cis* and *trans* alkenes giving the all equatorial product and this merits further investigation. By varying the acid and nucleophile a halide (bromide, chloride or fluoride), oxygenated group (hydroxy, ether or ester) or a nitrogen containing substituent may be introduced at C-4 of the tetrahydropyran.

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6 All compounds were fully characterised, spectroscopic data for 4-chlorotetrahydropyran **3**: δ_H(300 MHz, $CDCl_3$) 1.22 (3H, d, *J* 6.3, 2-CH_3), 1.69 (1H, dt, *J* 13.0 and 11.5, 3-H_{ax}), 1.92 (1H, m, 5-H), 2.04 (1H, br s, OH), 2.21 (1H, ddd, *J* 13.0, 4.5 and 2.0, 3-H_{eq}), 3.40 (1H, t, *J* 12.0, 6-H_{ax}), 3.46 (1H, m, 2-H), 3.79 (2H, m, 5-CH_2OH), 4.03 (1H, dt, *J* 11.5 and 4.5, 4-H), 4.09 (1H, dd, *J* 12.0 and 4.5, 6-H_{eq}); δ_C(75 MHz, $CDCl_3$) 21.3 (2-CH_3), 44.2 (C-3), 47.0 (C-5), 57.6 (C-4), 61.0 (5-CH_2OH), 69.6 (C-6), 73.5 (C-2); *m*/*z* (CI) 167 and 165 (MH^+, 4 and 14%), 149 (5), 147 (15), 129 (75), 111 (48) and 85 (100). (Found: MH^+ 165.0685 $C_7H_{14}O_2Cl$ requires 165.0682).
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