Diastereoselective Anomeric Oxygen to Carbon Rearrangements of Silyl Enol Ether Derivatives of Lactols.

Darren J. Dixon, Steven V. Ley* and Edward W. Tate.

Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, U.K.

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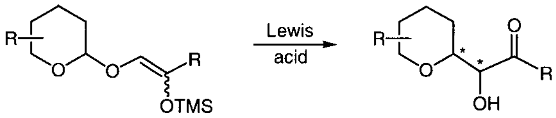
Abstract: Lewis acid promoted oxygen to carbon rearrangement of anomerically linked silyl enol ethers gives a new and diastereoselective route to the corresponding 2-α-hydroxyketone substituted products.

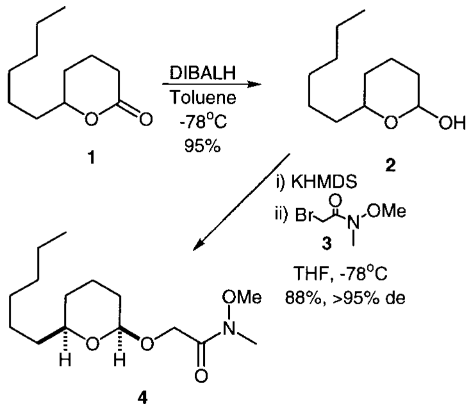
Of the many pyran and furan ring systems commonly found in natural products, the vast majority contain carbon-linked substituents adjacent to oxygen atoms. The problem of constructing these systems efficiently and stereoselectively represents a significant challenge for synthetic chemists, and a variety of different methods for direct introduction of such functionality have been developed.[1] In the previous communication we described a new route to 2-alkyl substituted pyran ring systems *via* anomeric oxygen to carbon rearrangement of alkynyl tributylstannanes.[2] Here we wish to report a further extension of this anomeric rearrangement method to encompass silyl enol ethers as the anomerically-linked carbon nucleophile.

The reactivity of silyl enol ethers towards oxonium ion intermediates combined with the potential for further elaboration has lead to their use for intermolecular displacement of anomeric leaving groups in pyran ring systems.[3] These features also make them attractive nucleophiles for use in the anomeric rearrangement strategy, with the further possibility for control at two new stereogenic centres (Scheme 1).



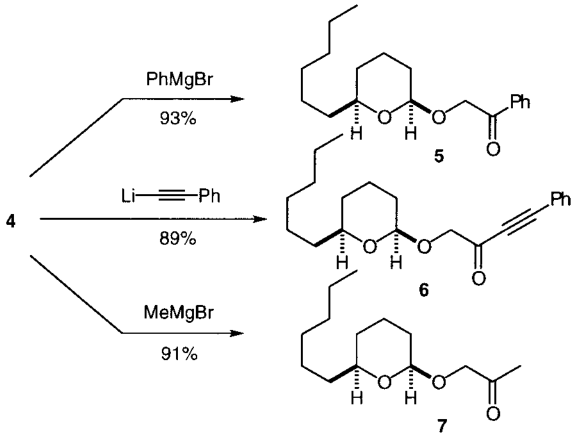
Scheme 1

In order to prepare the anomeric silyl enol ethers utilised in this work, we have designed a rapid and flexible route into these starting materials. This proceeds *via* initial quantitative reduction of a readily available δ-lactone such as **1**. Deprotonation of the product lactol **2** with potassium bis(trimethyl)silylamide at –78°C in tetrahydrofuran, followed by alkylation with α-bromo amide **3**, affords the *cis* product **4** as a single diastereoisomer (>95% de) in 88% isolated yield (Scheme 2).



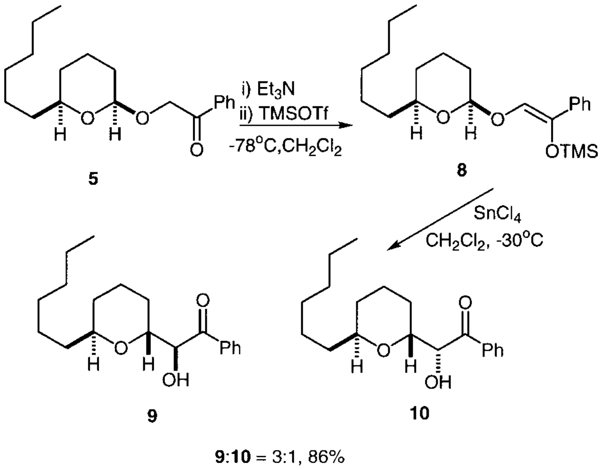
Scheme 2

Compound **4** allows access to a wide range of anomerically-linked carbonyl containing compounds, following the Weinreb protocol.[4] Thus the majority of the starting materials used in this study were simply prepared by the addition of alkyllithium or Grignard reagents to **4** at lowered temperature (-30°C) in tetrahydrofuran, in high isolated yield (Scheme 3).



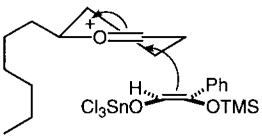
Scheme 3

In the first rearrangement study the phenyl ketone **5** was treated with an excess of triethylamine and trimethylsilyl trifluoromethanesulfonate at –78°C to give, after aqueous work-up, the silyl enol ether **8**, which was used directly in the subsequent step. The *cis-Z* configuration of **8** was unambiguously determined by ^{1}H nmr spectroscopy and nOe experiments. Treatment of silyl enol ether **8** with an excess of tin tetrachloride at –30°C resulted in a rapid rearrangement to a 3:1 separable pair of carbon linked products **9**[5] and **10** in 86% combined yield from **5** (Scheme 4).



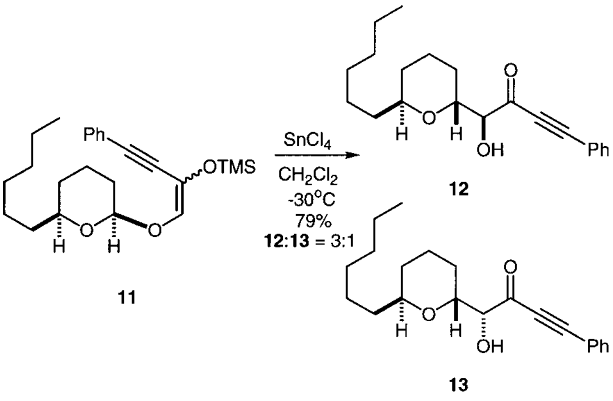
Scheme 4

Furthermore, it was also possible to achieve an improved selectivity of 4:1 using trimethylsilyl trifluoromethanesulfonate (10 mol%) as the catalyst in dichloromethane at –30°C. Additional experiments established that the rearrangement proceeds with slightly improved selectivity at temperatures below –30°C, but that the yield was reduced due to some decomposition of the starting material. Interestingly, only two of the possible four diastereoisomeric products are formed in this reaction, and just one (**9**) predominates. A combination of single crystal X-ray crystallography and nOe studies allowed the unambiguous assignment of all three stereocentres in each of the products. Complete control (>95% de) at the ring junction is observed in both products due to presumed preferential axial attack on a cyclic oxonium intermediate species. We would suggest that the major product is formed by a process under kinetic control, whereby the oxygen bearing the Lewis acid is directed away from the bulk of the ring (Scheme 5).[6]



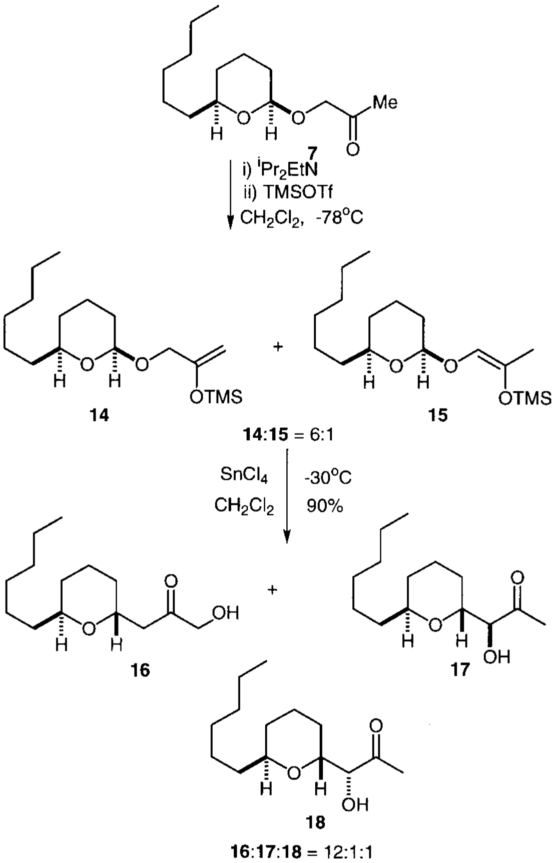
Scheme 5

We have also shown that effective rearrangements can be achieved with more complex silyl enol ethers. For example, silyl enol ether **11**, formed from phenylethynyl ketone **6** under the same conditions described above, undergoes facile rearrangement on treatment with excess tin tetrachloride at –30°C, to give a 3:1 separable ratio of two diastereoisomers **12** and **13** in 79% combined yield (Scheme 6).



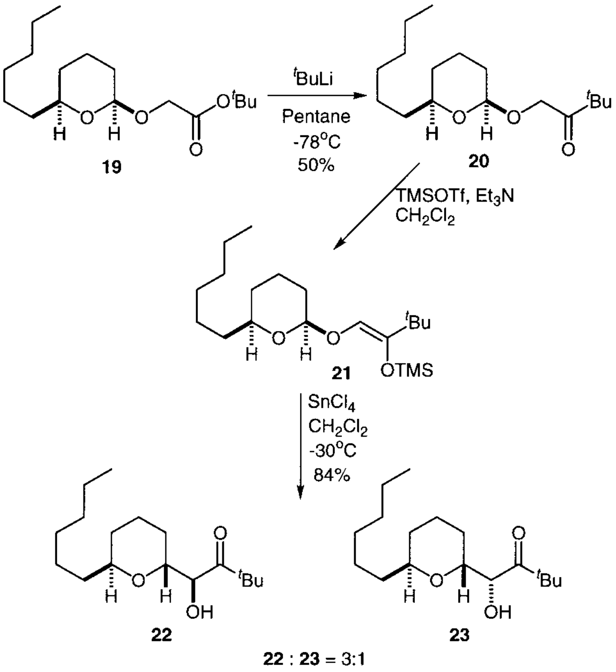
Scheme 6

The methyl ketone silyl enol ether precursor **7** was then investigated in the rearrangement sequence. Treatment of **7** with Hünig's base and trimethylsilyl trifluoromethanesulfonate in dichloromethane at -78°C afforded a mixture of *exo* and *endo* silyl enol ethers, with the kinetic *exo* product **14** dominant (**14**:**15**, 6:1). This mixture underwent a synthetically useful rearrangement with excess tin tetrachloride at –30°C to give an easily separable mixture of primary alcohol **16** and secondary alcohols **17** and **18** in 90% combined yield. The primary/secondary alcohol ratio mirrors the *exo*/*endo* ratio, indicating that no significant isomerisation has occurred under the rearrangement conditions (Scheme 7).



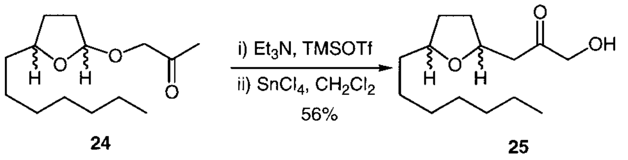
Scheme 7

For the final example involving rearrangement on a pyran ring system, the *tert*-butyl ketone **20** was synthesised in 50% yield by treatment of ester **19** with *tert*-butyl lithium in pentane at –78°C. Formation of enol ether **21** by the usual protocol followed by exposure to the standard rearrangement conditions gave the corresponding α-hydroxyketones **22** and **23** as a 3:1 mixture of diastereoisomers, in a combined yield of 84% (Scheme 8).



Scheme 8

This new rearrangement is not restricted to pyran ring systems. We have extended the method to also encompass furan ring systems. Thus the methyl ketone **24** was formed from the lactone by the reduction/alkylation and Grignard addition route, in a similar manner to the pyran systems described above. Following the same protocol as before, **24** is converted to predominantly the *exo* silyl enol ether, and subjected to the standard rearrangement conditions to give the two diastereoisomers of primary alcohol **25** in a 1:1 ratio and in 56% combined yield (Scheme 9).[7]



Scheme 9

We believe that the methodology described above represents a significant extension of our original concept of anomeric oxygen to carbon rearrangements, being the first reported example of using anomerically linked silyl enol ethers to effect *C*-glycosidation. Furthermore, the formation of the carbon-carbon bonds at the anomeric position occurs with concurrent stereocontrol at one or more stereogenic centres.

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References and Notes

(1) Levy, D.; Tang, C. *The Chemistry of C-Glycosides*, Pergamon, **1995**, and references cited therein.

(2) See also Buffet, M. B.; Dixon, D. J.; Edwards, G. L.; Ley, S. V.; Tate, E. W. *Synlett*, **1997**, 1055.

(3) For some related examples see: i) Reetz, M. T.; Mallerstarke, H. *Ann. Chem.*, **1983**, *10*, 1726; ii) Toshima, K.; Miyamoto, N.; Matsuo, G.; Nakata, M.; Matsumura, S. *J. Chem. Soc. Chem. Commun.*, **1996**, 1379; iii) Uenishi, J.; Sohma, A.; Yonemitsu, O. *Chem. Lett.*, **1996**, 595; iv) Craig, D.; Tierney, J. P.; Williamson, C. *Tetrahedron Lett.*, **1997**, *38*, 4153; and references cited therein.

(4) Weinreb, S. M.; Nahm, S. *Tetrahedron Lett.*, **1981**, *22*, 3815.

(5) Selected spectroscopic data for **9**: ^{1}H NMR (600MHz, $CDCl_3$): 7.89-7.94 (m, 2H, Ph), 7.44-7.64 (m, 3H, Ph), 4.94 (dd, J = 6.7, 2.7 Hz, 1H, $\mathrm{C\underline{H}OH}$), 3.98-4.05 (m, 1H, $\mathrm{OC\underline{H}CHOH}$), 3.74-3.79 (m, 2H, $\mathrm{O\underline{H}}$ and $\mathrm{CH_2C\underline{H}(CH_2)O}$), 0.79-1.89 (m, 19H, $\mathrm{C\underline{H}_3}$ and $\mathrm{8xC\underline{H}_2}$); ^{13}C NMR (150MHz, $CDCl_3$): 199.9 ($\mathrm{\underline{C}{=}O}$), 134.5, 133.5, 128.7, 128.5 ($\mathrm{Ph\text{-}\underline{C}}$), 76.3 ($\mathrm{\underline{C}HOH}$), 73.3 ($\mathrm{CH_2\underline{C}H(CH_2)O}$), 70.9 ($\mathrm{O\underline{C}HCHOH}$), 31.6, 30.3, 29.1, 28.3, 27.0, 25.5, 22.7, 18.4 ($\mathrm{8x\underline{C}H_2}$), 14.0 ($\mathrm{\underline{C}H_3}$).

(6) Re-exposure of a single diastereoisomer to identical rearrangement conditions shows no evidence of equilibration to the other diastereoisomer over an extended period, indicating that the rearrangement proceeds under kinetic control.

(7) The minor side products observed in this reaction were tentatively assigned as the rearrangement products of the *endo* enol ether.